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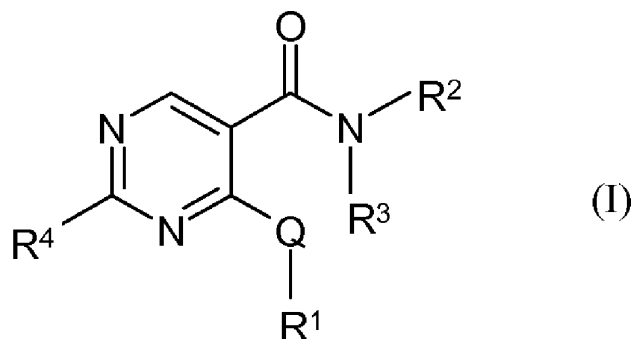
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(54) Title: SUBSTITUTED PYRIMIDIN-5-CARBOXAMIDES 281



(57) Abstract: A compound of formula (I) and pharmaceutically-acceptable salts thereof wherein the variable groups are defined within; their use in the inhibition of 11 β HSD1, processes for making them and pharmaceutical compositions comprising them are also described.

Substituted Pyrimidin-5-carboxamides 281

This invention relates to chemical compounds, or pharmaceutically-acceptable salts thereof. These compounds possess human 11- β -hydroxysteroid dehydrogenase type 1 enzyme (11 β HSD1) inhibitory activity and accordingly have value in the treatment of disease states including metabolic syndrome and are useful in methods of treatment of a warm-blooded animal, such as man. The invention also relates to processes for the manufacture of said compounds, to pharmaceutical compositions containing them and to their use in the manufacture of medicaments to inhibit 11 β HSD1 in a warm-blooded animal, such as man.

Glucocorticoids (cortisol in man, corticosterone in rodents) are counter regulatory hormones i.e. they oppose the actions of insulin (Dallman MF, Strack AM, Akana SF et al. 1993; Front Neuroendocrinol 14, 303-347). They regulate the expression of hepatic enzymes involved in gluconeogenesis and increase substrate supply by releasing glycerol from adipose tissue (increased lipolysis) and amino acids from muscle (decreased protein synthesis and increased protein degradation). Glucocorticoids are also important in the differentiation of pre-adipocytes into mature adipocytes which are able to store triglycerides (Bujalska IJ et al. 1999; Endocrinology 140, 3188-3196). This may be critical in disease states where glucocorticoids induced by "stress" are associated with central obesity which itself is a strong risk factor for type 2 diabetes, hypertension and cardiovascular disease (Bjorntorp P & Rosmond R 2000; Int. J. Obesity 24, S80-S85).

It is now well established that glucocorticoid activity is controlled not simply by secretion of cortisol but also at the tissue level by intracellular interconversion of active cortisol and inactive cortisone by the 11-beta hydroxysteroid dehydrogenases, 11 β HSD1 (which activates cortisone) and 11 β HSD2 (which inactivates cortisol) (Sandeep TC & Walker BR 2001 Trends in Endocrinol & Metab. 12, 446-453). That this mechanism may be important in man was initially shown using carbenoxolone (an anti-ulcer drug which inhibits both 11 β HSD1 and 2) treatment which (Walker BR et al. 1995; J. Clin. Endocrinol. Metab. 80, 3155-3159) leads to increased insulin sensitivity indicating that 11 β HSD1 may well be regulating the effects of insulin by decreasing tissue levels of active glucocorticoids (Walker BR et al. 1995; J. Clin. Endocrinol. Metab. 80, 3155-3159).

Clinically, Cushing's syndrome is associated with cortisol excess which in turn is associated with glucose intolerance, central obesity (caused by stimulation of pre-adipocyte differentiation in this depot), dyslipidaemia and hypertension. Cushing's syndrome shows a number of clear parallels with metabolic syndrome. Even though the metabolic syndrome is not generally associated with excess circulating cortisol levels (Jessop DS et al. 2001; J. Clin. Endocrinol. Metab. 86, 4109-4114) abnormally high 11 β HSD1 activity within tissues would be expected to have the same effect. In obese men it was shown that despite having similar or lower plasma cortisol levels than lean controls, 11 β HSD1 activity in subcutaneous fat was greatly enhanced (Rask E et al. 2001; J. Clin. Endocrinol. Metab. 1418-1421). Furthermore, the central fat, associated with the metabolic syndrome expresses much higher levels of 11 β HSD1 activity than subcutaneous fat (Bujalska IJ et al. 1997; Lancet 349, 1210-1213). Thus there appears to be a link between glucocorticoids, 11 β HSD1 and the metabolic syndrome.

11 β HSD1 knock-out mice show attenuated glucocorticoid-induced activation of gluconeogenic enzymes in response to fasting and lower plasma glucose levels in response to stress or obesity (Kotelevtsev Y et al. 1997; Proc. Natl. Acad. Sci USA 94, 14924-14929) indicating the utility of inhibition of 11 β HSD1 in lowering of plasma glucose and hepatic glucose output in type 2 diabetes. Furthermore, these mice express an anti-atherogenic lipoprotein profile, having low triglycerides, increased HDL cholesterol and increased apo-lipoprotein AI levels. (Morton NM et al. 2001; J. Biol. Chem. 276, 41293-41300). This phenotype is due to an increased hepatic expression of enzymes of fat catabolism and PPAR α . Again this indicates the utility of 11 β HSD1 inhibition in treatment of the dyslipidaemia of the metabolic syndrome.

The most convincing demonstration of a link between the metabolic syndrome and 11 β HSD1 comes from recent studies of transgenic mice over-expressing 11 β HSD1 (Masuzaki H et al. 2001; Science 294, 2166-2170). When expressed under the control of an adipose specific promoter, 11 β HSD1 transgenic mice have high adipose levels of corticosterone, central obesity, insulin resistant diabetes, hyperlipidaemia and hyperphagia. Most importantly, the increased levels of 11 β HSD1 activity in the fat of these mice are similar to those seen in obese subjects. Hepatic 11 β HSD1 activity and plasma corticosterone levels were normal, however, hepatic portal vein levels of corticosterone

were increased 3 fold and it is thought that this is the cause of the metabolic effects in liver.

Overall it is now clear that the complete metabolic syndrome can be mimicked in mice simply by overexpressing 11 β HSD1 in fat alone at levels similar to those in obese man.

11 β HSD1 tissue distribution is widespread and overlapping with that of the glucocorticoid receptor. Thus, 11 β HSD1 inhibition could potentially oppose the effects of glucocorticoids in a number of physiological/pathological roles. 11 β HSD1 is present in human skeletal muscle and glucocorticoid opposition to the anabolic effects of insulin on protein turnover and glucose metabolism are well documented (Whorwood CB et al. 2001; J. Clin. Endocrinol. Metab. 86, 2296-2308). Skeletal muscle must therefore be an important target for 11 β HSD1 based therapy.

Glucocorticoids also decrease insulin secretion and this could exacerbate the effects of glucocorticoid induced insulin resistance. Pancreatic islets express 11 β HSD1 and carbenoxolone can inhibit the effects of 11-dehydrocorticosterone on insulin release (Davani B et al. 2000; J. Biol. Chem. 275, 34841-34844). Thus in treatment of diabetes 11 β HSD1 inhibitors may not only act at the tissue level on insulin resistance but also increase insulin secretion itself.

Skeletal development and bone function is also regulated by glucocorticoid action. 11 β HSD1 is present in human bone osteoclasts and osteoblasts and treatment of healthy volunteers with carbenoxolone showed a decrease in bone resorption markers with no change in bone formation markers (Cooper MS et al 2000; Bone 27, 375-381). Inhibition of 11 β HSD1 activity in bone could be used as a protective mechanism in treatment of osteoporosis.

Glucocorticoids may also be involved in diseases of the eye such as glaucoma. 11 β HSD1 has been shown to affect intraocular pressure in man and inhibition of 11 β HSD1 may be expected to alleviate the increased intraocular pressure associated with glaucoma (Rauz S et al. 2001; Investigative Ophthalmology & Visual Science 42, 2037-2042).

There appears to be a convincing link between 11 β HSD1 and the metabolic syndrome both in rodents and in humans. Evidence suggests that a drug which specifically inhibits 11 β HSD1 in type 2 obese diabetic patients will lower blood glucose by reducing

hepatic gluconeogenesis, reduce central obesity, improve the atherogenic lipoprotein phenotype, lower blood pressure and reduce insulin resistance. Insulin effects in muscle will be enhanced and insulin secretion from the beta cells of the islet may also be increased.

5 Currently there are two main recognised definitions of metabolic syndrome.

1) The Adult Treatment Panel (ATP III 2001 JMA) definition of metabolic syndrome indicates that it is present if the patient has three or more of the following symptoms:

Waist measuring at least 40 inches (102 cm) for men, 35 inches (88 cm) for women;

Serum triglyceride levels of at least 150 mg/dl (1.69 mmol/l);

10 HDL cholesterol levels of less than 40 mg/dl (1.04 mmol/l) in men, less than 50 mg/dl

(1.29 mmol/l) in women;

Blood pressure of at least 135/80 mm Hg; and / or Blood sugar (serum glucose) of at least 110 mg/dl (6.1 mmol/l).

2) The WHO consultation has recommended the following definition which does not
15 imply causal relationships and is suggested as a working definition to be improved upon in due course:

The patient has at least one of the following conditions: glucose intolerance, impaired glucose tolerance (IGT) or diabetes mellitus and/or insulin resistance; together with two or more of the following:

20 Raised Arterial Pressure;

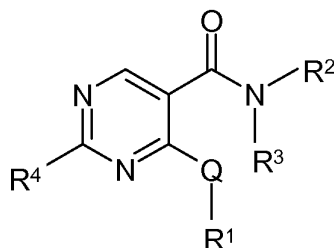
Raised plasma triglycerides

Central Obesity

Microalbuminuria

25 We have found that the compounds defined in the present invention, or a pharmaceutically-acceptable salt thereof, are effective 11 β HSD1 inhibitors, and accordingly have value in the treatment of disease states associated with metabolic syndrome.

Accordingly there is provided a compound of formula (1):



(I)

wherein:

Q is O, S, N(R⁸) or a single bond;

- 5 **R⁸** is selected from hydrogen, C₁₋₄alkyl, C₃₋₅cycloalkyl and C₃₋₅cycloalkylmethyl (each of which is optionally substituted by 1, 2 or 3 fluoro atoms);

- R¹** is selected from C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₇cycloalkyl, heterocyclyl, heteroaryl, aryl, arylC₁₋₃alkyl, heteroarylC₁₋₃alkyl, C₃₋₇cycloalkylC₁₋₃alkyl, heterocyclylC₁₋₃alkyl, C₃₋₇cycloalkylC₂₋₃alkenyl and C₃₋₇cycloalkylC₂₋₃alkynyl, [each of
10 which is optionally substituted, on available carbon atoms, by 1, 2 or 3 substituents independently selected from C₁₋₃alkyl, hydroxy, halo, oxo, cyano, trifluoromethyl, C₁₋₃alkoxy, C₁₋₃alkylS(O)_n- (wherein n is 0, 1, 2 or 3), R^{5'}CON(R^{5'})-, (R^{5'})(R^{5''})N-, (R^{5'})(R^{5''})NC(O)-, R^{5'}C(O)O-, R^{5'}OC(O)-, (R^{5'})(R^{5''})NC(O)N(R^{5'''})-, R^{5'}SO₂N(R^{5''})-, (R^{5'})(R^{5''})NSO₂- and C₁₋₂alkyl optionally substituted by 1, 2 or 3 substituents

- 15 independently selected from hydroxy, halo, carboxy and C₁₋₃alkoxy (wherein R⁵ is C₁₋₃alkyl optionally substituted by 1, 2 or 3 substituents independently selected from hydroxyl, halo and cyano; and

- R^{5'}, R^{5''} and R^{5'''} are independently selected from hydrogen and C₁₋₃alkyl optionally substituted by 1, 2 or 3 substituents independently selected from hydroxyl, halo, C₁₋₃alkoxy, carboxy and cyano or R^{5'} and R^{5''} together with the nitrogen atom to which they are attached form a 4-7 membered saturated ring) and optionally substituted, on an available nitrogen, by a substituent independently selected from C₁₋₄alkyl, C₂₋₄alkanoyl and C₁₋₄alkanesulphonyl each of which is optionally substituted by 1, 2 or 3 substituent independently selected from hydroxyl, halo, C₁₋₄alkoxy, carboxy and cyano]; or

- 25 R¹ and R⁸ together with the nitrogen atom to which they are attached form a saturated mono, bicyclic or bridged ring system optionally containing 1 or 2 additional ring heteroatoms independently selected from nitrogen, oxygen and sulphur and optionally fused to a saturated, partially saturated or unsaturated monocyclic ring wherein the

resulting ring system is optionally substituted, on available carbon atoms, by 1, 2, or 3 substituents independently selected from R^9 and optionally substituted, on an available nitrogen, by a substituent independently selected from C_{1-4} alkyl, C_{2-4} alkanoyl and C_{1-4} alkanesulphonyl each of which is optionally substituted by 1, 2 or 3 substituent

5 independently selected from hydroxyl, halo, C_{1-4} alkoxy, carboxy and cyano;

R^2 is selected from C_{3-7} cycloalkyl $(CH_2)_m$ -, and C_{6-12} polycycloalkyl $(CH_2)_m$ - (wherein m is 0, 1 or 2 and the rings optionally contain 1 or 2 ring atoms independently selected from nitrogen, oxygen and sulphur are optionally substituted, on available carbon atoms, by 1, 2 or 3 substituents independently selected from R^6 and optionally substituted, on an available
10 nitrogen, by a substituent independently selected from C_{1-4} alkyl, C_{2-4} alkanoyl and C_{1-4} alkanesulphonyl each of which is optionally substituted by 1, 2 or 3 substituent independently selected from hydroxyl, halo, C_{1-4} alkoxy, carboxy and cyano);

R^3 is selected from hydrogen, C_{1-4} alkyl, C_{3-5} cycloalkyl and C_{3-5} cycloalkylmethyl (each of which is optionally substituted by 1, 2 or 3 fluoro atoms);

15 R^2 and R^3 together with the nitrogen atom to which they are attached form a saturated mono, bicyclic or bridged ring system optionally containing 1 or 2 additional ring heteroatoms independently selected from nitrogen, oxygen and sulphur and optionally fused to a saturated, partially saturated or unsaturated monocyclic ring wherein the resulting ring system is optionally substituted, on available carbon atoms, by 1, 2, or 3
20 substituents independently selected from R^7 and optionally substituted, on an available nitrogen, by a substituent independently selected from C_{1-4} alkyl, C_{2-4} alkanoyl and C_{1-4} alkanesulphonyl each of which is optionally substituted by 1, 2 or 3 substituent independently selected from hydroxyl, halo, C_{1-4} alkoxy, carboxy and cyano;

R^4 is selected from hydrogen, R^{10} , $-OR^{10}$, $-SR^{10}$ and $-NR^{11}R^{12}$;

25 R^{10} is selected from C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-7} cycloalkyl, heterocyclyl, aryl C_{1-3} alkyl, heteroaryl C_{1-3} alkyl, heterocyclyl C_{1-3} alkyl, C_{3-7} cycloalkyl C_{1-3} alkyl, C_{3-7} cycloalkyl C_{2-3} alkenyl and C_{3-7} cycloalkyl C_{2-3} alkynyl, [each of which is optionally substituted, on available carbon atoms, by 1, 2 or 3 substituents independently selected from C_{1-3} alkyl, hydroxy, halo, oxo, cyano, trifluoromethyl, C_{1-3} alkoxy, C_{1-3} alkylS(O)_p-
30 (wherein p is 0, 1, 2 or 3), $R^{13}CON(R^{13'})$ -, $(R^{13'})(R^{13''})N$ -, $(R^{13'})(R^{13''})NC(O)$ -, $R^{13'}C(O)O$ -, $R^{13'}OC(O)$ -, $(R^{13'})(R^{13''})NC(O)N(R^{13'''})$ -, $R^{13}SO_2N(R^{13''})$ -, $(R^{13'})(R^{13''})NSO_2$ - and C_{1-2} alkyl optionally substituted by 1, 2 or 3 substituents independently selected from hydroxy, halo,

- carboxy and C₁₋₃alkoxy (wherein R¹³ is C₁₋₃alkyl optionally substituted by 1, 2 or 3 substituents selected from hydroxyl, halo and cyano; and R^{13'}, R^{13''} and R^{13'''} are independently selected from hydrogen and C₁₋₃alkyl optionally substituted by 1, 2 or 3 substituents independently selected from hydroxyl, halo,
- 5 C₁₋₃alkoxy, carboxy and cyano or R^{13'} and R^{13''} together with the nitrogen atom to which they are attached form a 4-7 membered saturated ring) and optionally substituted, on an available nitrogen, by a substituent independently selected from C₁₋₄alkyl, C₂₋₄alkanoyl and C₁₋₄alkanesulphonyl each of which is optionally substituted by 1, 2 or 3 substituent independently selected from hydroxyl, halo, C₁₋₄alkoxy, carboxy and cyano];
- 10 R¹¹ is selected from hydrogen, C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₇cycloalkyl, heterocyclyl, arylC₁₋₃alkyl, heteroarylC₁₋₃alkyl, heterocyclylC₁₋₃alkyl, C₃₋₇cycloalkylC₁₋₃alkyl, C₃₋₇cycloalkylC₂₋₃alkenyl and C₃₋₇cycloalkylC₂₋₃alkynyl, [each of which is optionally substituted, on available carbon atoms, by 1, 2 or 3 substituents independently selected from C₁₋₃alkyl, hydroxy, halo, oxo, cyano, trifluoromethyl,
- 15 C₁₋₃alkoxy, C₁₋₃alkylS(O)_q- (wherein q is 0, 1, 2 or 3), R¹⁴CON(R^{14'})-, (R^{14'})(R^{14''})NC(O)-, R^{14'}C(O)O-, R^{14'}OC(O)-, (R^{14'})(R^{14''})NC(O)N(R^{14'''})-, R¹⁴SO₂N(R^{14''})-, (R^{14'})(R^{14''})NSO₂- and C₁₋₂alkyl optionally substituted by 1, 2 or 3 substituents independently selected from hydroxy, halo, carboxy and C₁₋₃alkoxy (wherein R¹⁴ is C₁₋₃alkyl optionally substituted by 1, 2 or 3 substituents independently selected from hydroxyl, halo and cyano; and
- 20 R^{14'}, R^{14''} and R^{14'''} are independently selected from hydrogen and C₁₋₃alkyl optionally substituted by 1, 2 or 3 substituents independently selected from hydroxyl, halo, C₁₋₃alkoxy, carboxy and cyano or R^{14'} and R^{14''} together with the nitrogen atom to which they are attached form a 4-7 membered saturated ring) and optionally substituted, on an available nitrogen, by a substituent independently selected from C₁₋₄alkyl, C₂₋₄alkanoyl and
- 25 C₁₋₄alkanesulphonyl each of which is optionally substituted by 1, 2 or 3 substituent independently selected from hydroxyl, halo, C₁₋₄alkoxy, carboxy and cyano]; and R¹² is selected from hydrogen, C₁₋₄alkyl, C₃₋₅cycloalkyl and C₃₋₅cycloalkylmethyl (each of which is optionally substituted by 1, 2 or 3 fluoro atoms); or
- R¹¹ and R¹² together with the nitrogen atom to which they are attached form a saturated
- 30 mono, bicyclic or bridged ring system optionally containing 1 or 2 additional ring heteroatoms independently selected from nitrogen, oxygen and sulphur and optionally fused to a saturated, partially saturated or unsaturated monocyclic ring (optionally

containing 1 or 2 additional ring heteroatoms independently selected from nitrogen, oxygen and sulphur) wherein the resulting ring system is optionally substituted, on available carbon atoms, by 1, 2, or 3 substituents independently selected from R^{15} and optionally substituted on an available nitrogen by a substituent independently selected
 5 from C_{1-4} alkyl, C_{2-4} alkanoyl and C_{1-4} alkanesulphonyl each of which is optionally substituted by 1, 2 or 3 substituent independently selected from hydroxyl, halo, C_{1-4} alkoxy, carboxy and cyano;

R^6 , R^7 , R^9 and R^{15} are independently selected from hydroxyl, halo, oxo, carboxy, cyano, trifluoromethyl, R^{16} , $R^{16}O-$, $R^{16}CO-$, $R^{16}C(O)O-$, $R^{16}CON(R^{16'})-$, $(R^{16'})(R^{16''})NC(O)-$,
 10 $(R^{16'})(R^{16''})N-$, $R^{16}S(O)_a-$ wherein a is 0 to 2, $R^{16'}OC(O)-$, $(R^{16'})(R^{16''})NSO_2-$, $R^{16}SO_2N(R^{16''})-$, $(R^{16'})(R^{16''})NC(O)N(R^{16''''})-$, phenyl and heteroaryl [wherein the phenyl and heteroaryl groups are optionally fused to a phenyl, heteroaryl or a saturated or partially-saturated 5- or 6-membered ring optionally containing 1, 2 or 3 heteroatoms independently selected from nitrogen, oxygen and sulphur and the resulting ring system is
 15 optionally substituted, on available carbon atoms, by 1, 2 or 3 substituents independently selected from C_{1-4} alkyl, hydroxyl, cyano, trifluoromethyl, trifluoromethoxy, halo, C_{1-4} alkoxy, C_{1-4} alkoxy C_{1-4} alkyl, amino, N- C_{1-4} alkylamino, di-N,N-(C_{1-4} alkyl)amino, N- C_{1-4} alkylcarbonyl, di-N,N-(C_{1-4} alkyl)carbonyl, C_{1-4} alkylS(O)_r- and C_{1-4} alkylS(O)_r C_{1-4} alkyl (wherein r is independently selected 0, 1 and 2) and optionally
 20 substituted, on an available nitrogen, by a substituent independently selected from C_{1-4} alkyl, C_{2-4} alkanoyl and C_{1-4} alkanesulphonyl each of which is optionally substituted by 1, 2 or 3 substituent independently selected from hydroxyl, halo, C_{1-4} alkoxy, carboxy and cyano];

R^{16} is independently selected from, C_{1-3} alkyl optionally substituted by 1, 2 or 3
 25 substituents independently selected from hydroxyl, halo, C_{1-4} alkoxy, carboxy and cyano; $R^{16'}$, $R^{16''}$ and $R^{16'''}$ are independently selected from hydrogen and C_{1-3} alkyl optionally substituted by 1, 2, or 3 substituents independently selected from hydroxyl, halo, C_{1-4} alkoxy, carboxy and cyano);
 or a pharmaceutically-acceptable salt thereof, for use as a as a medicament for producing a
 30 11 β HSD1-inhibitory effect.

In another aspect the invention relates to a compound of the formula (1) as hereinabove defined or a pharmaceutically-acceptable salt thereof, for use as a medicament for treating diabetes.

In another aspect the invention relates to a compound of the formula (1) as
 5 hereinabove defined or a pharmaceutically-acceptable salt thereof, for use as a medicament for treating obesity.

In another aspect the invention relates to a compound of formula (1):
 wherein:

Q is O, S, N(R⁸) or a single bond;

10 R⁸ is selected from hydrogen, C₁₋₄alkyl, C₃₋₅cycloalkyl and C₃₋₅cycloalkylmethyl (each of which is optionally substituted by 1, 2 or 3 fluoro atoms);

R¹ is selected from C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₇cycloalkyl, heterocyclyl, heteroaryl, aryl, arylC₁₋₃alkyl, heteroarylC₁₋₃alkyl, C₃₋₇cycloalkylC₁₋₃alkyl, heterocyclylC₁₋₃alkyl, C₃₋₇cycloalkylC₂₋₃alkenyl and C₃₋₇cycloalkylC₂₋₃alkynyl, [each of
 15 which is optionally substituted, on available carbon atoms, by 1, 2 or 3 substituents independently selected from C₁₋₃alkyl, hydroxy, halo, oxo, cyano, trifluoromethyl, C₁₋₃alkoxy, C₁₋₃alkylS(O)_n- (wherein n is 0, 1, 2 or 3), R⁵CON(R^{5'})-, (R^{5'})(R^{5''})N-, (R^{5'})(R^{5''})NC(O)-, R^{5'}C(O)O-, R^{5'}OC(O)-, (R^{5'})(R^{5''})NC(O)N(R^{5'''})-, R⁵SO₂N(R^{5''})-, (R^{5'})(R^{5''})NSO₂- and C₁₋₂alkyl optionally substituted by 1, 2 or 3 substituents
 20 independently selected from hydroxy, halo, carboxy and C₁₋₃alkoxy (wherein R⁵ is C₁₋₃alkyl optionally substituted by 1, 2 or 3 substituents independently selected from hydroxyl, halo and cyano; and

R^{5'}, R^{5''} and R^{5'''} are independently selected from hydrogen and C₁₋₃alkyl optionally substituted by 1, 2 or 3 substituents independently selected from hydroxyl, halo,
 25 C₁₋₃alkoxy, carboxy and cyano or R^{5'} and R^{5''} together with the nitrogen atom to which they are attached form a 4-7 membered saturated ring) and optionally substituted, on an available nitrogen, by a substituent independently selected from C₁₋₄alkyl, C₂₋₄alkanoyl and C₁₋₄alkanesulphonyl each of which is optionally substituted by 1, 2 or 3 substituent independently selected from hydroxyl, halo, C₁₋₄alkoxy, carboxy and cyano]; or

30 R¹ and R⁸ together with the nitrogen atom to which they are attached form a saturated mono, bicyclic or bridged ring system optionally containing 1 or 2 additional ring heteroatoms independently selected from nitrogen, oxygen and sulphur and optionally

fused to a saturated, partially saturated or unsaturated monocyclic ring wherein the resulting ring system is optionally substituted, on available carbon atoms, by 1, 2, or 3 substituents independently selected from R^9 and optionally substituted, on an available nitrogen, by a substituent independently selected from C_{1-4} alkyl, C_{2-4} alkanoyl and C_{1-4} alkanesulphonyl each of which is optionally substituted by 1, 2 or 3 substituent independently selected from hydroxyl, halo, C_{1-4} alkoxy, carboxy and cyano;

R^2 is selected from adamantyl optionally substituted, on available carbon atoms, by 1 or substituents independently selected from R^6 ;

R^3 is hydrogen;

R^4 is selected from hydrogen, R^{10} , $-OR^{10}$, $-SR^{10}$ and $-NR^{11}R^{12}$;

R^{10} is selected from C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-7} cycloalkyl, heterocyclyl, aryl C_{1-3} alkyl, heteroaryl C_{1-3} alkyl, heterocyclyl C_{1-3} alkyl, C_{3-7} cycloalkyl C_{1-3} alkyl, C_{3-7} cycloalkyl C_{2-3} alkenyl and C_{3-7} cycloalkyl C_{2-3} alkynyl, [each of which is optionally substituted, on available carbon atoms, by 1, 2 or 3 substituents independently selected from C_{1-3} alkyl, hydroxy, halo, oxo, cyano, trifluoromethyl, C_{1-3} alkoxy, C_{1-3} alkylS(O)_p- (wherein p is 0, 1, 2 or 3), $R^{13}CON(R^{13'})$ -, $(R^{13'})(R^{13''})N$ -, $(R^{13'})(R^{13''})NC(O)$ -, $R^{13'}C(O)O$ -, $R^{13'}OC(O)$ -, $(R^{13'})(R^{13''})NC(O)N(R^{13'''})$ -, $R^{13}SO_2N(R^{13''})$ -, $(R^{13'})(R^{13''})NSO_2$ - and C_{1-2} alkyl optionally substituted by 1, 2 or 3 substituents independently selected from hydroxy, halo, carboxy and C_{1-3} alkoxy (wherein R^{13} is C_{1-3} alkyl optionally substituted by 1, 2 or 3 substituents selected from hydroxyl, halo and cyano; and

$R^{13'}$, $R^{13''}$ and $R^{13'''}$ are independently selected from hydrogen and C_{1-3} alkyl optionally substituted by 1, 2 or 3 substituents independently selected from hydroxyl, halo, C_{1-3} alkoxy, carboxy and cyano or $R^{13'}$ and $R^{13''}$ together with the nitrogen atom to which they are attached form a 4-7 membered saturated ring) and optionally substituted, on an available nitrogen, by a substituent independently selected from C_{1-4} alkyl, C_{2-4} alkanoyl and C_{1-4} alkanesulphonyl each of which is optionally substituted by 1, 2 or 3 substituent independently selected from hydroxyl, halo, C_{1-4} alkoxy, carboxy and cyano];

R^{11} is selected from hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-7} cycloalkyl, heterocyclyl, aryl C_{1-3} alkyl, heteroaryl C_{1-3} alkyl, heterocyclyl C_{1-3} alkyl, C_{3-7} cycloalkyl C_{1-3} alkyl, C_{3-7} cycloalkyl C_{2-3} alkenyl and C_{3-7} cycloalkyl C_{2-3} alkynyl, [each of which is optionally substituted, on available carbon atoms, by 1, 2 or 3 substituents independently selected from C_{1-3} alkyl, hydroxy, halo, oxo, cyano, trifluoromethyl,

C_{1-3} alkoxy, C_{1-3} alkylS(O)_q- (wherein q is 0, 1, 2 or 3), R^{14} CON($R^{14'}$)-, ($R^{14'}$)($R^{14''}$)NC(O)-, $R^{14'}$ C(O)O-, $R^{14'}$ OC(O)-, ($R^{14'}$)($R^{14''}$)NC(O)N($R^{14'''}$)-, R^{14} SO₂N($R^{14''}$)-, ($R^{14'}$)($R^{14''}$)NSO₂- and C_{1-2} alkyl optionally substituted by 1, 2 or 3 substituents independently selected from hydroxy, halo, carboxy and C_{1-3} alkoxy (wherein R^{14} is C_{1-3} alkyl optionally substituted by 1, 2 or 3 substituents independently selected from hydroxyl, halo and cyano; and $R^{14'}$, $R^{14''}$ and $R^{14'''}$ are independently selected from hydrogen and C_{1-3} alkyl optionally substituted by 1, 2 or 3 substituents independently selected from hydroxyl, halo, C_{1-3} alkoxy, carboxy and cyano or $R^{14'}$ and $R^{14''}$ together with the nitrogen atom to which they are attached form a 4-7 membered saturated ring) and optionally substituted, on an available nitrogen, by a substituent independently selected from C_{1-4} alkyl, C_{2-4} alkanoyl and C_{1-4} alkanesulphonyl each of which is optionally substituted by 1, 2 or 3 substituent independently selected from hydroxyl, halo, C_{1-4} alkoxy, carboxy and cyano]; and R^{12} is selected from hydrogen, C_{1-4} alkyl, C_{3-5} cycloalkyl and C_{3-5} cycloalkylmethyl (each of which is optionally substituted by 1, 2 or 3 fluoro atoms); or R^{11} and R^{12} together with the nitrogen atom to which they are attached form a saturated mono, bicyclic or bridged ring system optionally containing 1 or 2 additional ring heteroatoms independently selected from nitrogen, oxygen and sulphur and optionally fused to a saturated, partially saturated or unsaturated monocyclic ring (optionally containing 1 or 2 additional ring heteroatoms independently selected from nitrogen, oxygen and sulphur) wherein the resulting ring system is optionally substituted, on available carbon atoms, by 1, 2, or 3 substituents independently selected from R^{15} and optionally substituted on an available nitrogen by a substituent independently selected from C_{1-4} alkyl, C_{2-4} alkanoyl and C_{1-4} alkanesulphonyl each of which is optionally substituted by 1, 2 or 3 substituent independently selected from hydroxyl, halo, C_{1-4} alkoxy, carboxy and cyano; R^6 , R^7 , R^9 and R^{15} are independently selected from hydroxyl, halo, oxo, carboxy, cyano, trifluoromethyl, R^{16} , $R^{16}O$ -, $R^{16}CO$ -, $R^{16}C(O)O$ -, $R^{16}CON(R^{16'})$ -, ($R^{16'})(R^{16''})NC(O)$ -, ($R^{16'})(R^{16''})N$ -, $R^{16}S(O)_a$ - wherein a is 0 to 2, $R^{16'}OC(O)$ -, ($R^{16'})(R^{16''})NSO_2$ -, $R^{16}SO_2N(R^{16''})$ -, ($R^{16'})(R^{16''})NC(O)N(R^{16''''})$ -, phenyl and heteroaryl [wherein the phenyl and heteroaryl groups are optionally fused to a phenyl, heteroaryl or a saturated or partially-saturated 5- or 6-membered ring optionally containing 1, 2 or 3 heteroatoms independently selected from nitrogen, oxygen and sulphur and the resulting ring system is

- optionally substituted, on available carbon atoms, by 1, 2 or 3 substituents independently selected from C₁₋₄alkyl, hydroxyl, cyano, trifluoromethyl, trifluoromethoxy, halo, C₁₋₄alkoxy, C₁₋₄alkoxyC₁₋₄alkyl, amino, N-C₁₋₄alkylamino, di-N,N-(C₁₋₄alkyl)amino, N-C₁₋₄alkylcarbamoyl, di-N,N-(C₁₋₄alkyl)carbamoyl, C₁₋₄alkylS(O)_r- and
- 5 C₁₋₄alkylS(O)_rC₁₋₄alkyl (wherein r is independently selected 0, 1 and 2) and optionally substituted, on an available nitrogen, by a substituent independently selected from C₁₋₄alkyl, C₂₋₄alkanoyl and C₁₋₄alkanesulphonyl each of which is optionally substituted by 1, 2 or 3 substituent independently selected from hydroxyl, halo, C₁₋₄alkoxy, carboxy and cyano];
- 10 R¹⁶ is independently selected from, C₁₋₃alkyl optionally substituted by 1, 2 or 3 substituents independently selected from hydroxyl, halo, C₁₋₄alkoxy, carboxy and cyano; R^{16'}, R^{16''} and R^{16'''} are independently selected from hydrogen and C₁₋₃alkyl optionally substituted by 1, 2, or 3 substituents independently selected from hydroxyl, halo, C₁₋₄alkoxy, carboxy and cyano);
- 15 or a pharmaceutically-acceptable salt thereof.

In this specification the term “alkyl” includes both straight and branched chain alkyl groups but references to individual alkyl groups such as “propyl” are specific for the straight chain version only. For example, “C₁₋₄alkyl” includes propyl, isopropyl and *t*-butyl. However, references to individual alkyl groups such as ‘propyl’ are specific for the

20 straight chain version only and references to individual branched chain alkyl groups such as ‘isopropyl’ are specific for the branched chain version only. A similar convention applies to other radicals therefore “arylC₁₋₄alkyl” would include 1-arylpropyl, 2-arylethyl and 3-arylbutyl. The term “halo” refers to fluoro, chloro, bromo and iodo.

Where optional substituents are chosen from “one or more” groups it is to be

25 understood that this definition includes all substituents being chosen from one of the specified groups or the substituents being chosen from two or more of the specified groups.

A 4-7 membered saturated ring (for example formed between R^{5'} and R^{5''} and the nitrogen atom to which they are attached) is a monocyclic ring containing the nitrogen atom as the only ring atom.

30 “Heteroaryl”, unless otherwise specified, is a totally unsaturated, monocyclic ring containing 5 or 6 atoms of which at least 1, 2 or 3 ring atoms are independently chosen from nitrogen, sulphur or oxygen, which may, unless otherwise specified, be carbon-

linked. A ring nitrogen atom may be optionally oxidised to form the corresponding N-oxide. Examples and suitable values of the term “heteroaryl” are thienyl, furyl, thiazolyl, pyrazolyl, isoxazolyl, imidazolyl, pyrrolyl, thiadiazolyl, isothiazolyl, triazolyl, pyrimidyl, pyrazinyl, pyridazinyl and pyridyl. Particularly “heteroaryl” refers to thienyl, furyl,
5 thiazolyl, pyridyl, imidazolyl or pyrazolyl.

“Heterocyclcyl” is a 4-7 saturated, monocyclic ring having 1-3 ring heteroatoms independently selected from nitrogen, oxygen and sulphur. The ring sulphur may be optionally oxidised to SO or SO₂.

“Aryl” is an aromatic carbocyclic ring i.e. phenyl or naphthyl.

10 A C₃₋₇cycloalkyl ring is a saturated carbon ring containing from 3 to 7 ring atoms.

A C₆₋₁₂polycycloalkyl ring is a ring system in which either at least 2 rings are fused together (fused or bridged) or in which 2 ring have one ring atom in common (spiro). An example of a polycycloalkyl ring is adamantyl.

A “saturated mono, bicyclic or bridged ring system optionally containing 1 or 2
15 additional ring heteroatoms independently selected from nitrogen, oxygen and sulphur”, unless otherwise specified contains 4-14 ring atoms. Particularly a mono ring contains 4 – 7 ring atoms, a bicyclic ring 6-14 ring atoms and a bridged ring system 6-14 ring atoms. Examples of mono rings include piperidinyl, piperazinyl and morpholinyl. Examples of bicyclic rings include decalin and 2,3,3a,4,5,6,7,7a-octahydro-1H-indene.

20 Bridged ring systems are ring systems in which there are two or more bonds common to two or more constituent rings. Examples of bridged ring systems include 1,3,3-trimethyl-6-azabicyclo[3.2.1]octane, 2-aza-bicyclo[2.2.1]heptane and 7-azabicyclo(2,2,1)heptane, 1- and 2-adamantanyl.

A “saturated, partially saturated or unsaturated monocyclic ring” is, unless
25 otherwise specified, a 4-7 membered carbon ring. Examples include, cyclopropyl, cyclobutyl, cyclopentyl, cyclopentenyl, cyclohexyl, cyclohexenyl and phenyl.

Examples of “C₁₋₄alkoxy” include methoxy, ethoxy and propoxy. Examples of “C₁₋₄alkoxyC₁₋₄alkyl” include methoxymethyl, ethoxymethyl, propoxymethyl, 2-methoxyethyl, 2-ethoxyethyl and 2-propoxyethyl. Examples of “C₁₋₄alkylS(O)_n or p or q or r
30 wherein n or p or q or r is 0 to 2” include methylthio, ethylthio, methylsulphinyl, ethylsulphinyl, mesyl and ethylsulphonyl. Examples of “C₁₋₄alkylS(O)_rC₁₋₄alkyl” wherein r is 0 to 2” include methylthio, ethylthio, methylsulphinyl, ethylsulphinyl, mesyl,

ethylsulphonyl, methylthiomethyl, ethylthiomethyl, methylsulphinylmethyl, ethylsulphinylmethyl, mesylmethyl and ethylsulphonylmethyl. Examples of “C₁₋₄alkanoyl” include propionyl and acetyl. Examples of “N-(C₁₋₄alkyl)amino” include methylamino and ethylamino. Examples of “N,N-(C₁₋₄alkyl)₂amino” include N,N-dimethylamino, N,N-diethylamino and N-ethyl-N-methylamino. Examples of “C₂₋₄alkenyl” are vinyl, allyl and 1-propenyl. Examples of “C₂₋₄alkynyl” are ethynyl, 1-propynyl and 2-propynyl. Examples of “N-(C₁₋₄alkyl)carbamoyl” are methylaminocarbonyl and ethylaminocarbonyl. Examples of “N,N-(C₁₋₄alkyl)₂carbamoyl” are dimethylaminocarbonyl and methylethylaminocarbonyl. Examples of “C₃₋₇cycloalkylC₁₋₃alkyl” include cyclopropylmethyl, 2-cyclopropylethyl, cyclobutylmethyl, cyclopentylmethyl and cyclohexylmethyl. Examples of “C₃₋₇cycloalkylC₂₋₃alkenyl” include 2-cyclopropylethenyl, 2-cyclopentylethenyl and 2-cyclohexylethenyl. Examples of “C₃₋₇cycloalkylC₂₋₃alkynyl” include 2-cyclopropylethynyl, 2-cyclopentylethynyl and 2-cyclohexylethynyl.

Examples of “C₃₋₇cycloalkyl(CH₂)_m-” include cyclopropylmethyl, 2-cyclopropylethyl, cyclobutylmethyl, cyclopentylmethyl and cyclohexylmethyl. Examples of C₆₋₁₂polycycloalkyl(CH₂)_m- include norbornyl bicyclo[2.2.2]octane(CH₂)_m-, bicyclo[3.2.1]octane(CH₂)_m- and 1- and 2-adamantanyl(CH₂)_m-.

A suitable pharmaceutically-acceptable salt of a compound of the invention is, for example, an acid-addition salt of a compound of the invention which is sufficiently basic, for example, an acid-addition salt with, for example, an inorganic or organic acid, for example hydrochloric, hydrobromic, sulphuric, phosphoric, trifluoroacetic, citric or maleic acid. In addition a suitable pharmaceutically-acceptable salt of a compound of the invention which is sufficiently acidic is an alkali metal salt, for example a sodium or potassium salt, an alkaline earth metal salt, for example a calcium or magnesium salt, an ammonium salt or a salt with an organic base which affords a physiologically-acceptable cation, for example a salt with methylamine, dimethylamine, trimethylamine, piperidine, morpholine or tris-(2-hydroxyethyl)amine.

Some compounds of the formula (1) may have chiral centres and/or geometric isomeric centres (E- and Z- isomers), and it is to be understood that the invention encompasses all such optical, diastereoisomers and geometric isomers that possess 11βHSD1 inhibitory activity.

The invention relates to any and all tautomeric forms of the compounds of the formula (1) that possess 11 β HSD1 inhibitory activity.

It is also to be understood that certain compounds of the formula (1) can exist in solvated as well as unsolvated forms such as, for example, hydrated forms. It is to be understood
 5 that the invention encompasses all such solvated forms, which possess 11 β HSD1 inhibitory activity.

In another, there is provided a compound of formula (1) wherein:

Q is O, S, N(R⁸) or a single bond;

R⁸ is selected from hydrogen, C₁₋₄alkyl, C₃₋₅cycloalkyl and C₃₋₅cycloalkylmethyl (each of
 10 which is optionally substituted by 1, 2 or 3 fluoro atoms);

R¹ is selected from C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₇cycloalkyl, heterocyclyl, heteroaryl, aryl, arylC₁₋₃alkyl, heteroarylC₁₋₃alkyl, heterocyclylC₁₋₃alkyl, C₃₋₇cycloalkylC₁₋₃alkyl, C₃₋₇cycloalkylC₂₋₃alkenyl and C₃₋₇cycloalkylC₂₋₃alkynyl, [each of
 15 which is optionally substituted, on available carbon atoms, by 1, 2 or 3 substituents independently selected from C₁₋₃alkyl, hydroxy, halo, oxo, cyano, trifluoromethyl, C₁₋₃alkoxy, C₁₋₃alkylS(O)_n- (wherein n is 0, 1, 2 or 3), R^{5'}CON(R^{5'})-, (R^{5'})(R^{5''})N-, (R^{5'})(R^{5''})NC(O)-, R^{5'}C(O)O-, R^{5'}OC(O)-, (R^{5'})(R^{5''})NC(O)N(R^{5'''})-, R^{5'}SO₂N(R^{5''})-, (R^{5'})(R^{5''})NSO₂- and C₁₋₂alkyl optionally substituted by 1, 2 or 3 substituents

independently selected from hydroxy, halo, carboxy and C₁₋₃alkoxy (wherein R⁵ is

20 C₁₋₃alkyl optionally substituted by 1, 2 or 3 substituents independently selected from hydroxyl, halo and cyano; and

R^{5'}, R^{5''} and R^{5'''} are independently selected from hydrogen and C₁₋₃alkyl optionally substituted by 1, 2 or 3 substituents independently selected from hydroxyl, halo,

C₁₋₃alkoxy, carboxy and cyano or R^{5'} and R^{5''} together with the nitrogen atom to which

25 they are attached form a 4-7 membered saturated ring) and optionally substituted, on an

available nitrogen, by a substituent independently selected from C₁₋₄alkyl, C₂₋₄alkanoyl and C₁₋₄alkanesulphonyl]; or

R¹ and R⁸ together with the nitrogen atom to which they are attached form a saturated mono, bicyclic or bridged ring system optionally containing 1 or 2 additional ring

30 heteroatoms independently selected from nitrogen, oxygen and sulphur and optionally fused to a saturated, partially saturated or unsaturated monocyclic ring wherein the resulting ring system is optionally substituted, on available carbon atoms, by 1, 2, or 3

substituents independently selected from R^9 and optionally substituted, on an available nitrogen, by a substituent independently selected from C_{1-4} alkyl, C_{2-4} alkanoyl and C_{1-4} alkanesulphonyl;

R^2 is selected from C_{3-7} cycloalkyl $(CH_2)_m$ -, and C_{6-12} polycycloalkyl $(CH_2)_m$ - (wherein m is 0, 1 or 2 and the rings optionally contain 1 or 2 ring atoms independently selected from nitrogen, oxygen and sulphur are optionally substituted, on available carbon atoms, by 1, 2 or 3 substituents independently selected from R^6 and optionally substituted, on an available nitrogen, by a substituent independently selected from C_{1-4} alkyl, C_{2-4} alkanoyl and C_{1-4} alkanesulphonyl);

R^3 is selected from hydrogen, C_{1-4} alkyl, C_{3-5} cycloalkyl and C_{3-5} cycloalkylmethyl (each of which is optionally substituted by 1, 2 or 3 fluoro atoms);

R^2 and R^3 together with the nitrogen atom to which they are attached form a saturated mono, bicyclic or bridged ring system optionally containing 1 or 2 additional ring heteroatoms independently selected from nitrogen, oxygen and sulphur and optionally fused to a saturated, partially saturated or unsaturated monocyclic ring wherein the resulting ring system is optionally substituted, on available carbon atoms, by 1, 2, or 3 substituents independently selected from R^7 and optionally substituted, on an available nitrogen, by a substituent independently selected from C_{1-4} alkyl, C_{2-4} alkanoyl and C_{1-4} alkanesulphonyl;

R^4 is selected from hydrogen, R^{10} , $-OR^{10}$, $-SR^{10}$ and $-NR^{11}R^{12}$;

R^{10} is selected from C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-7} cycloalkyl, heterocyclyl, aryl C_{1-3} alkyl, heteroaryl C_{1-3} alkyl, C_{3-7} cycloalkyl C_{1-3} alkyl, C_{3-7} cycloalkyl C_{2-3} alkenyl and C_{3-7} cycloalkyl C_{2-3} alkynyl, [each of which is optionally substituted, on available carbon atoms, by 1, 2 or 3 substituents independently selected from C_{1-3} alkyl, hydroxy, halo, oxo, cyano, trifluoromethyl, C_{1-3} alkoxy, C_{1-3} alkylS(O) $_p$ - (wherein p is 0, 1, 2 or 3),

$R^{13}CON(R^{13'})$ -, $(R^{13'})(R^{13''})N$ -, $(R^{13'})(R^{13''})NC(O)$ -, $R^{13'}C(O)O$ -, $R^{13'}OC(O)$ -, $(R^{13'})(R^{13''})NC(O)N(R^{13'''})$ -, $R^{13}SO_2N(R^{13''})$ -, $(R^{13'})(R^{13''})NSO_2$ - and C_{1-2} alkyl optionally substituted by 1, 2 or 3 substituents independently selected from hydroxy, halo, carboxy and C_{1-3} alkoxy (wherein R^{13} is C_{1-3} alkyl optionally substituted by 1, 2 or 3 substituents selected from hydroxyl, halo and cyano; and

$R^{13'}$, $R^{13''}$ and $R^{13'''}$ are independently selected from hydrogen and C_{1-3} alkyl optionally substituted by 1, 2 or 3 substituents independently selected from hydroxyl, halo,

C₁₋₃alkoxy, carboxy and cyano or R^{13'} and R^{13''} together with the nitrogen atom to which they are attached form a 4-7 membered saturated ring) and optionally substituted, on an available nitrogen, by a substituent independently selected from C₁₋₄alkyl, C₂₋₄alkanoyl and C₁₋₄alkanesulphonyl];

5 R¹¹ is selected from hydrogen, C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₇cycloalkyl, heterocyclyl, arylC₁₋₃alkyl, heteroarylC₁₋₃alkyl, C₃₋₇cycloalkylC₁₋₃alkyl, C₃₋₇cycloalkylC₂₋₃alkenyl and C₃₋₇cycloalkylC₂₋₃alkynyl, [each of which is optionally substituted, on available carbon atoms, by 1, 2 or 3 substituents independently selected from C₁₋₃alkyl, hydroxy, halo, oxo, cyano, trifluoromethyl, C₁₋₃alkoxy, C₁₋₃alkylS(O)_q-
 10 (wherein q is 0, 1, 2 or 3), R¹⁴CON(R^{14'})-, (R^{14'})(R^{14''})NC(O)-, R^{14'}C(O)O-, R^{14'}OC(O)-, (R^{14'})(R^{14''})NC(O)N(R^{14'''})-, R¹⁴SO₂N(R^{14''})-, (R^{14'})(R^{14''})NSO₂- and C₁₋₂alkyl optionally substituted by 1, 2 or 3 substituents independently selected from hydroxy, halo, carboxy and C₁₋₃alkoxy (wherein R¹⁴ is C₁₋₃alkyl optionally substituted by 1, 2 or 3 substituents independently selected from hydroxyl, halo and cyano; and

15 R^{14'}, R^{14''} and R^{14'''} are independently selected from hydrogen and C₁₋₃alkyl optionally substituted by 1, 2 or 3 substituents independently selected from hydroxyl, halo, C₁₋₃alkoxy, carboxy and cyano or R^{14'} and R^{14''} together with the nitrogen atom to which they are attached form a 4-7 membered saturated ring) and optionally substituted, on an available nitrogen, by a substituent independently selected from C₁₋₄alkyl, C₂₋₄alkanoyl and
 20 C₁₋₄alkanesulphonyl]; and

R¹² is selected from hydrogen, C₁₋₄alkyl, C₃₋₅cycloalkyl and C₃₋₅cycloalkylmethyl (each of which is optionally substituted by 1, 2 or 3 fluoro atoms); or

R¹¹ and R¹² together with the nitrogen atom to which they are attached form a saturated mono, bicyclic or bridged ring system optionally containing 1 or 2 additional ring
 25 heteroatoms independently selected from nitrogen, oxygen and sulphur and optionally fused to a saturated, partially saturated or unsaturated monocyclic ring (optionally containing 1 or 2 additional ring heteroatoms independently selected from nitrogen, oxygen and sulphur) wherein the resulting ring system is optionally substituted, on available carbon atoms, by 1, 2, or 3 substituents independently selected from R¹⁵ and
 30 optionally substituted on an available nitrogen by a substituent independently selected from C₁₋₄alkyl, C₂₋₄alkanoyl and C₁₋₄alkanesulphonyl];

- R^6 , R^7 , R^9 and R^{15} are independently selected from hydroxyl, halo, oxo, carboxy, cyano, trifluoromethyl, R^{16} , $R^{16}O-$, $R^{16}CO-$, $R^{16}C(O)O-$, $R^{16}CON(R^{16'})-$, $(R^{16'})(R^{16''})NC(O)-$, $(R^{16'})(R^{16''})N-$, $R^{16}S(O)_a-$ wherein a is 0 to 2, $R^{16'}OC(O)-$, $(R^{16'})(R^{16''})NSO_2-$, $R^{16}SO_2N(R^{16''})-$, $(R^{16'})(R^{16''})NC(O)N(R^{16''''})-$, phenyl and heteroaryl [wherein the phenyl and heteroaryl groups are optionally fused to a phenyl, heteroaryl or a saturated or partially-saturated 5- or 6-membered ring optionally containing 1, 2 or 3 heteroatoms independently selected from nitrogen, oxygen and sulphur and the resulting ring system is optionally substituted, on available carbon atoms, by 1, 2 or 3 substituents independently selected from C_{1-4} alkyl, hydroxyl, cyano, trifluoromethyl, trifluoromethoxy, halo, C_{1-4} alkoxy, C_{1-4} alkoxy C_{1-4} alkyl, amino, $N-C_{1-4}$ alkylamino, di- N,N -(C_{1-4} alkyl)amino, $N-C_{1-4}$ alkylcarbamoyl, di- N,N -(C_{1-4} alkyl)carbamoyl, C_{1-4} alkylS(O) $_r$ - and C_{1-4} alkylS(O) $_rC_{1-4}$ alkyl (wherein r is independently selected 0, 1 and 2) and optionally substituted, on an available nitrogen, by a substituent independently selected from C_{1-4} alkyl, C_{2-4} alkanoyl and C_{1-4} alkanesulphonyl];
- R^{16} is independently selected from, C_{1-3} alkyl optionally substituted by 1, 2 or 3 substituents independently selected from hydroxyl, halo, C_{1-4} alkoxy, carboxy and cyano; $R^{16'}$, $R^{16''}$ and $R^{16'''}$ are independently selected from hydrogen and C_{1-3} alkyl optionally substituted by 1, 2, or 3 substituents independently selected from hydroxyl, halo, C_{1-4} alkoxy, carboxy and cyano);
- or a pharmaceutically-acceptable salt thereof ;
- provided that:
- when $-QR^1$ is N -(3-chloro-4-methoxybenzyl)amino then $-NR^2R^3$ is not N -(4-hydroxycyclohexyl)amino; and
 - when $-QR^1$ is 2-fluorophenyl, 4-cyanophenyl or 3-methylphenyl then R^4 is not morpholino, pyrrolidino, 4-methylpiperidino, cyclohexylmethylamino, 2-methoxyethylamino, 3-methoxypropylamino or cyclopropylmethylamino;
- and excluding:
- 2-[(2,4-dichlorophenyl)amino]- N -(tetrahydro-2H-pyran-4-yl)methyl]-4-(trifluoromethyl)-5-pyrimidinecarboxamide;
- 4-methyl- N -[2-(4-morpholinyl)ethyl]-2-(1-pyrrolidinyl)-5-pyrimidinecarboxamide;
- N -cycloheptyl-2-(dimethylamino)-4-methyl-5-pyrimidinecarboxamide;

- N-cyclopentyl-4-methyl-2-(4-morpholinyl)- 5-pyrimidinecarboxamide;
N-cyclohexyl-2-(dimethylamino)-4-methyl-5-pyrimidinecarboxamide;
N-cycloheptyl-4-methyl-2-(1-piperidinyl)- 5-pyrimidinecarboxamide;
N-cyclopropyl-4-methyl-2-(4-morpholinyl)- 5-pyrimidinecarboxamide;
5 N-cyclopentyl-2-(dimethylamino)-4-methyl-5-pyrimidinecarboxamide;
4-methyl-2-(4-morpholinyl)-N-[2-(4-morpholinyl)ethyl]- 5-pyrimidinecarboxamide;
N-cycloheptyl-4-methyl-2-(4-methyl-1-piperazinyl)- 5-pyrimidinecarboxamide;
2-(dimethylamino)-4-methyl-N-[2-(4-morpholinyl)ethyl]- 5-pyrimidinecarboxamide;
2-(4-ethyl-1-piperazinyl)-4-methyl-N-[2-(4-morpholinyl)ethyl]- 5-pyrimidinecarboxamide;
10 N-cyclohexyl-2-(4-ethyl-1-piperazinyl)-4-methyl-5-pyrimidinecarboxamide;
N-cyclopropyl-2-(4-ethyl-1-piperazinyl)-4-methyl-5-pyrimidinecarboxamide;
N-cyclohexyl-4-methyl-2-(4-methyl-1-piperazinyl)- 5-pyrimidinecarboxamide;
N-cyclohexyl-4-methyl-2-(4-morpholinyl)- 5-pyrimidinecarboxamide;
N-cyclopentyl-2-[[2-(methoxyphenyl)methyl]amino]-4-methyl-5-pyrimidinecarboxamide;
15 N-cyclohexyl-2-[[4-(methoxyphenyl)methyl]amino]-4-methyl-5-pyrimidinecarboxamide;
N-cycloheptyl-2-[[4-(methoxyphenyl)methyl]amino]-4-methyl-5-pyrimidinecarboxamide;
N-cyclopentyl-2-[[3-(methoxyphenyl)methyl]amino]-4-methyl-5-pyrimidinecarboxamide;
2-ethyl-4-methyl-N-[(tetrahydro-2-furanyl)methyl]- 5-pyrimidinecarboxamide;
N-cyclopentyl-2-[[4-(methoxyphenyl)methyl]amino]-4-methyl-5-pyrimidinecarboxamide;
20 N-cyclopropyl-2-ethyl-4-methyl-5-pyrimidinecarboxamide;
N-cyclohexyl-2-(methylthio)-4-propyl-5-pyrimidinecarboxamide;
N-cycloheptyl-4-ethyl-2-(methylthio)- 5-pyrimidinecarboxamide;
N-cycloheptyl-2-[[3-(methoxyphenyl)methyl]amino]-4-methyl-5-pyrimidinecarboxamide;
N-cyclopentyl-2-(4-ethyl-1-piperazinyl)-4-methyl-5-pyrimidinecarboxamide;
25 N-cyclohexyl-2-[[2-(methoxyphenyl)methyl]amino]-4-methyl-5-pyrimidinecarboxamide;
N-cycloheptyl-4-methyl-2-(4-morpholinyl)- 5-pyrimidinecarboxamide;
4-methyl-2-(4-morpholinyl)-N-[2-(1-pyrrolidinyl)ethyl]- 5-pyrimidinecarboxamide;
N-cyclopentyl-4-methyl-2-[(phenylmethyl)amino]- 5-pyrimidinecarboxamide;
N-cyclohexyl-2-[[3-(methoxyphenyl)methyl]amino]-4-methyl-5-pyrimidinecarboxamide;
30 N-cyclopropyl-2-(methylthio)-4-propyl-5-pyrimidinecarboxamide;
2-(2-benzoxazolylamino)-N-cyclohexyl-N,4-dimethyl-5-pyrimidinecarboxamide;
N-cyclohexyl-4-ethyl-2-(methylthio)- 5-pyrimidinecarboxamide;

- N-cyclohexyl-4-methyl-2-(methylthio)-5-pyrimidinecarboxamide;
N-cycloheptyl-4-methyl-2-(methylthio)- 5-pyrimidinecarboxamide;
N-cyclohexyl-2-(cyclohexylamino)-4-methyl-5-pyrimidinecarboxamide;
(3 α ,3 β ,5 α ,6 β ,6 β) 2-(dimethylamino)-4-methoxy-N-(octahydro-1-methyl-3,5-
5 methanocyclopenta[b]pyrrol-6-yl)-5-pyrimidinecarboxamide;
N-[(1-ethyl-2-pyrrolidinyl)methyl]-4-methoxy-2-(methylthio)- 5-pyrimidinecarboxamide;
N-[(1-ethyl-2-pyrrolidinyl)methyl]-4-methoxy-5-pyrimidinecarboxamide;
2-amino-4-methoxy-N-[(1-methyl-2-pyrrolidinyl)methyl]- 5-pyrimidinecarboxamide;
4-ethoxy-N-[(1-ethyl-2-pyrrolidinyl)methyl]-2-methyl-5-pyrimidinecarboxamide;
10 (3 α ,3 β ,5 α ,6 β ,6 β)-4-ethoxy-2-methyl-N-(octahydro-1-methyl-3,5-
methanocyclopenta[b]pyrrol-6-yl)-5-pyrimidinecarboxamide;
(R)-N-[(1-ethyl-2-pyrrolidinyl)methyl]-4-methoxy-2-methyl-5-pyrimidinecarboxamide;
N-[(1-ethyl-2-pyrrolidinyl)methyl]-2-methyl-4-(1-methylethoxy)- 5-
pyrimidinecarboxamide;
15 2-amino-N-(1-ethyl-3-pyrrolidinyl)-4-methoxy-5-pyrimidinecarboxamide;
exo-2-amino-N-8-azabicyclo[3.2.1]oct-3-yl-4-methoxy-5-pyrimidinecarboxamide;
(S)-4-ethoxy-N-[(1-ethyl-2-pyrrolidinyl)methyl]-2-methyl-5-pyrimidinecarboxamide;
N-[(1-ethyl-2-pyrrolidinyl)methyl]-4-methoxy-2-propyl-5-pyrimidinecarboxamide;
2-ethyl-N-[(1-ethyl-2-pyrrolidinyl)methyl]-4-methoxy-5-pyrimidinecarboxamide;
20 4-methoxy-2-methyl-N-[(1-propyl-2-pyrrolidinyl)methyl]- 5-pyrimidinecarboxamide;
N-[(1-butyl-2-pyrrolidinyl)methyl]-4-methoxy-2-methyl-5-pyrimidinecarboxamide;
4-ethoxy-2-ethyl-N-[(1-methyl-2-pyrrolidinyl)methyl]- 5-pyrimidinecarboxamide;
4-ethoxy-2-methyl-N-[(1-methyl-2-pyrrolidinyl)methyl]- 5-pyrimidinecarboxamide;
4-methoxy-2-methyl-N-[(1-methyl-2-pyrrolidinyl)methyl]- 5-pyrimidinecarboxamide;
25 N-[(1-ethyl-2-pyrrolidinyl)methyl]-4-methoxy-2-(1-methylethyl)- 5-
pyrimidinecarboxamide;
4-ethoxy-2-ethyl-N-[(1-ethyl-2-pyrrolidinyl)methyl]- 5-pyrimidinecarboxamide;
N-(N-ethylpyrrolidin-2-ylmethyl)-4-ethoxy-2-methyl-5-pyrimidinecarboxamide;
N-(N-ethylpyrrolidin-2-ylmethyl)-4-propoxy-2-methyl-5-pyrimidinecarboxamide;
30 N-(N-ethylpyrrolidin-2-ylmethyl)-4-isopropoxy-2-methyl-5-pyrimidinecarboxamide;
N-(N-ethylpyrrolidin-2-ylmethyl)-4-ethoxy-2-amino-5-pyrimidinecarboxamide;
N-(N-ethylpyrrolidin-2-ylmethyl)-4-propoxy-2-amino-5-pyrimidinecarboxamide;

- N-(N-ethylpyrrolidin-2-ylmethyl)-4-isopropoxy-2-amino-5-pyrimidinecarboxamide;
 N-(N-ethylpyrrolidin-2-ylmethyl)-4-methoxy-2-methylamino-5-pyrimidinecarboxamide;
 N-(cyclohexyl)-4-methyl-2-piperazin-1-yl-5-pyrimidinecarboxamide;
 N-cyclooctyl-2,4-dimethyl-5-pyrimidinecarboxamide;
 5 N-cycloheptyl-2,4-dimethyl-5-pyrimidinecarboxamide;
 N-cyclopropyl-2,4-dimethyl-5-pyrimidinecarboxamide;
 N-cyclopentyl-2,4-dimethyl-5-pyrimidinecarboxamide;
 N-cyclohexyl-2,4-dimethyl-5-pyrimidinecarboxamide;
 N-cyclopentyl-4-methyl-2-(1-pyrrolidinyl)-5-pyrimidinecarboxamide;
 10 N-cycloheptyl-4-methyl-2-(4-methyl-1-pyrrolidinyl)-5-pyrimidinecarboxamide;
 N-cycloheptyl-4-methyl-2-(1-pyrrolidinyl)-5-pyrimidinecarboxamide;
 N-cyclohexyl-2-(4-ethyl-1-piperazinyl)-4-methyl-5-pyrimidinecarboxamide;
 N-cyclohexyl-4-methyl-2-[(phenylmethyl)amino]-5-pyrimidinecarboxamide;
 N-cyclopentyl-2-[[2-(2-fluorophenyl)methyl]amino]-4-methyl-5-pyrimidinecarboxamide;
 15 N-cycloheptyl-2-(methylthio)-4-phenyl-5-pyrimidinecarboxamide;
 N-cycloheptyl-2-(methylthio)-4-propyl-5-pyrimidinecarboxamide;
 N-cyclohexyl-2-(methylthio)-4-phenyl-5-pyrimidinecarboxamide;
 N-cycloheptyl-4-methyl-2-[(phenylmethyl)amino]-5-pyrimidinecarboxamide;
 N-cycloheptyl-2-[[2-(2-fluorophenyl)methyl]amino]-4-methyl-5-pyrimidinecarboxamide;
 20 and
 N-cyclopropyl-2-(methylthio)-4-phenyl-5-pyrimidinecarboxamide.

In another aspect, there is provided a compound of formula (1):

wherein:

- 25 **Q** is O, S, N(R⁸) or a single bond;
 R⁸ is selected from hydrogen, C₁₋₄alkyl, C₃₋₅cycloalkyl and C₃₋₅cycloalkylmethyl (each of which is optionally substituted by 1, 2 or 3 fluoro atoms);
R¹ is selected from C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₇cycloalkyl, heterocyclyl, heteroaryl, aryl, arylC₁₋₃alkyl, heteroarylC₁₋₃alkyl, C₃₋₇cycloalkylC₁₋₃alkyl,
 30 heterocyclylC₁₋₃alkyl, C₃₋₇cycloalkylC₂₋₃alkenyl and C₃₋₇cycloalkylC₂₋₃alkynyl, [each of which is optionally substituted, on available carbon atoms, by 1, 2 or 3 substituents independently selected from C₁₋₃alkyl, hydroxy, halo, oxo, cyano, trifluoromethyl,

- C_{1-3} alkoxy, C_{1-3} alkylS(O)_n- (wherein n is 0, 1, 2 or 3), $R^5CON(R^{5'})$ -, $(R^{5'})(R^{5''})N$ -,
 $(R^{5'})(R^{5''})NC(O)$ -, $R^{5'}C(O)O$ -, $R^{5'}OC(O)$ -, $(R^{5'})(R^{5''})NC(O)N(R^{5'''})$ -, $R^5SO_2N(R^{5''})$ -,
 $(R^{5'})(R^{5''})NSO_2$ - and C_{1-2} alkyl optionally substituted by 1, 2 or 3 substituents
independently selected from hydroxy, halo, carboxy and C_{1-3} alkoxy (wherein R^5 is
5 C_{1-3} alkyl optionally substituted by 1, 2 or 3 substituents independently selected from
hydroxyl, halo and cyano; and
 $R^{5'}$, $R^{5''}$ and $R^{5'''}$ are independently selected from hydrogen and C_{1-3} alkyl optionally
substituted by 1, 2 or 3 substituents independently selected from hydroxyl, halo,
 C_{1-3} alkoxy, carboxy and cyano or $R^{5'}$ and $R^{5''}$ together with the nitrogen atom to which
10 they are attached form a 4-7 membered saturated ring) and optionally substituted, on an
available nitrogen, by a substituent independently selected from C_{1-4} alkyl, C_{2-4} alkanoyl and
 C_{1-4} alkanesulphonyl each of which is optionally substituted by 1, 2 or 3 substituent
independently selected from hydroxyl, halo, C_{1-4} alkoxy, carboxy and cyano] provided that
when Q is a single bond R^1 is not methyl; or
15 R^1 and R^8 together with the nitrogen atom to which they are attached form a saturated
mono, bicyclic or bridged ring system optionally containing 1 or 2 additional ring
heteroatoms independently selected from nitrogen, oxygen and sulphur and optionally
fused to a saturated, partially saturated or unsaturated monocyclic ring wherein the
resulting ring system is optionally substituted, on available carbon atoms, by 1, 2, or 3
20 substituents independently selected from R^9 and optionally substituted, on an available
nitrogen, by a substituent independently selected from C_{1-4} alkyl, C_{2-4} alkanoyl and C_{1-4}
alkanesulphonyl each of which is optionally substituted by 1, 2 or 3 substituent
independently selected from hydroxyl, halo, C_{1-4} alkoxy, carboxy and cyano;
 R^2 is selected from C_{3-7} cycloalkyl(CH₂)_m-, and C_{6-12} polycycloalkyl(CH₂)_m- (wherein m is
25 0, 1 or 2 and the rings are optionally substituted, on available carbon atoms, by 1, 2 or 3
substituents independently selected from R^6 and optionally substituted, on an available
nitrogen, by a substituent independently selected from C_{1-4} alkyl, C_{2-4} alkanoyl and C_{1-4}
alkanesulphonyl each of which is optionally substituted by 1, 2 or 3 substituent
independently selected from hydroxyl, halo, C_{1-4} alkoxy, carboxy and cyano);
30 R^3 is selected from hydrogen, C_{1-4} alkyl, C_{3-5} cycloalkyl and C_{3-5} cycloalkylmethyl (each of
which is optionally substituted by 1, 2 or 3 fluoro atoms);

R² and **R³** together with the nitrogen atom to which they are attached form a saturated mono, bicyclic or bridged ring system optionally containing 1 or 2 additional ring heteroatoms independently selected from nitrogen, oxygen and sulphur and optionally fused to a saturated, partially saturated or unsaturated monocyclic ring wherein the resulting ring system is optionally substituted, on available carbon atoms, by 1, 2, or 3 substituents independently selected from **R⁷** and optionally substituted, on an available nitrogen, by a substituent independently selected from C₁₋₄alkyl, C₂₋₄alkanoyl and C₁₋₄alkanesulphonyl each of which is optionally substituted by 1, 2 or 3 substituent independently selected from hydroxyl, halo, C₁₋₄alkoxy, carboxy and cyano;

R⁴ is selected from hydrogen, **R¹⁰**, -OR¹⁰ and -NR¹¹R¹²;

R¹⁰ is selected from C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₇cycloalkyl, heterocyclyl, arylC₁₋₃alkyl, heteroarylC₁₋₃alkyl, heterocyclylC₁₋₃alkyl, C₃₋₇cycloalkylC₁₋₃alkyl, C₃₋₇cycloalkylC₂₋₃alkenyl and C₃₋₇cycloalkylC₂₋₃alkynyl, [each of which is optionally substituted, on available carbon atoms, by 1, 2 or 3 substituents independently selected from C₁₋₃alkyl, hydroxy, halo, oxo, cyano, trifluoromethyl, C₁₋₃alkoxy, C₁₋₃alkylS(O)_p- (wherein p is 0, 1, 2 or 3), R¹³CON(R^{13'})-, (R^{13'})(R^{13''})N-, (R^{13'})(R^{13''})NC(O)-, R^{13'}C(O)O-, R^{13'}OC(O)-, (R^{13'})(R^{13''})NC(O)N(R^{13'''})-, R¹³SO₂N(R^{13''})-, (R^{13'})(R^{13''})NSO₂- and C₁₋₂alkyl optionally substituted by 1, 2 or 3 substituents independently selected from hydroxy, halo, carboxy and C₁₋₃alkoxy (wherein R¹³ is C₁₋₃alkyl optionally substituted by 1, 2 or 3 substituents selected from hydroxyl, halo and cyano; and

R^{13'}, **R^{13''}** and **R^{13'''}** are independently selected from hydrogen and C₁₋₃alkyl optionally substituted by 1, 2 or 3 substituents independently selected from hydroxyl, halo, C₁₋₃alkoxy, carboxy and cyano or **R^{13'}** and **R^{13''}** together with the nitrogen atom to which they are attached form a 4-7 membered saturated ring) and optionally substituted, on an available nitrogen, by a substituent independently selected from C₁₋₄alkyl, C₂₋₄alkanoyl and C₁₋₄alkanesulphonyl each of which is optionally substituted by 1, 2 or 3 substituent independently selected from hydroxyl, halo, C₁₋₄alkoxy, carboxy and cyano];

R¹¹ is selected from hydrogen, C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₇cycloalkyl, heterocyclyl, arylC₁₋₃alkyl, heteroarylC₁₋₃alkyl, heterocyclylC₁₋₃alkyl, C₃₋₇cycloalkylC₁₋₃alkyl, C₃₋₇cycloalkylC₂₋₃alkenyl and C₃₋₇cycloalkylC₂₋₃alkynyl, [each of which is optionally substituted, on available carbon atoms, by 1, 2 or 3 substituents independently selected from C₁₋₃alkyl, hydroxy, halo, oxo, cyano, trifluoromethyl,

C_{1-3} alkoxy, C_{1-3} alkylS(O)_q- (wherein q is 0, 1, 2 or 3), R^{14} CON(R^{14'})-, (R^{14'})(R^{14''})NC(O)-, $R^{14'}$ C(O)O-, $R^{14'}$ OC(O)-, (R^{14'})(R^{14''})NC(O)N(R^{14'''})-, R^{14} SO₂N(R^{14''})-, (R^{14'})(R^{14''})NSO₂- and C_{1-2} alkyl optionally substituted by 1, 2 or 3 substituents independently selected from hydroxy, halo, carboxy and C_{1-3} alkoxy (wherein R¹⁴ is C_{1-3} alkyl optionally substituted by 1, 2 or 3 substituents independently selected from hydroxyl, halo and cyano; and R^{14'}, R^{14''} and R^{14'''} are independently selected from hydrogen and C_{1-3} alkyl optionally substituted by 1, 2 or 3 substituents independently selected from hydroxyl, halo, C_{1-3} alkoxy, carboxy and cyano or R^{14'} and R^{14''} together with the nitrogen atom to which they are attached form a 4-7 membered saturated ring) and optionally substituted, on an available nitrogen, by a substituent independently selected from C_{1-4} alkyl, C_{2-4} alkanoyl and C_{1-4} alkanesulphonyl each of which is optionally substituted by 1, 2 or 3 substituent independently selected from hydroxyl, halo, C_{1-4} alkoxy, carboxy and cyano]; and R¹² is selected from hydrogen, C_{1-4} alkyl, C_{3-5} cycloalkyl and C_{3-5} cycloalkylmethyl (each of which is optionally substituted by 1, 2 or 3 fluoro atoms); or R¹¹ and R¹² together with the nitrogen atom to which they are attached form a saturated mono, bicyclic or bridged ring system optionally containing 1 or 2 additional ring heteroatoms independently selected from nitrogen, oxygen and sulphur and optionally fused to a saturated, partially saturated or unsaturated monocyclic ring (optionally containing 1 or 2 additional ring heteroatoms independently selected from nitrogen, oxygen and sulphur) wherein the resulting ring system is optionally substituted, on available carbon atoms, by 1, 2, or 3 substituents independently selected from R¹⁵ and optionally substituted on an available nitrogen by a substituent independently selected from C_{1-4} alkyl, C_{2-4} alkanoyl and C_{1-4} alkanesulphonyl each of which is optionally substituted by 1, 2 or 3 substituent independently selected from hydroxyl, halo, C_{1-4} alkoxy, carboxy and cyano; R⁶, R⁷, R⁹ and R¹⁵ are independently selected from hydroxyl, halo, oxo, carboxy, cyano, trifluoromethyl, R¹⁶, R¹⁶O-, R¹⁶CO-, R¹⁶C(O)O-, R¹⁶CON(R^{16'})-, (R^{16'})(R^{16''})NC(O)-, (R^{16'})(R^{16''})N-, R¹⁶S(O)_a- wherein a is 0 to 2, R^{16'}OC(O)-, (R^{16'})(R^{16''})NSO₂-, R¹⁶SO₂N(R^{16''})-, (R^{16'})(R^{16''})NC(O)N(R^{16'''})-, phenyl and heteroaryl [wherein the phenyl and heteroaryl groups are optionally fused to a phenyl, heteroaryl or a saturated or partially-saturated 5- or 6-membered ring optionally containing 1, 2 or 3 heteroatoms independently selected from nitrogen, oxygen and sulphur and the resulting ring system is

- optionally substituted, on available carbon atoms, by 1, 2 or 3 substituents independently selected from C₁₋₄alkyl, hydroxyl, cyano, trifluoromethyl, trifluoromethoxy, halo, C₁₋₄alkoxy, C₁₋₄alkoxyC₁₋₄alkyl, amino, N-C₁₋₄alkylamino, di-N,N-(C₁₋₄alkyl)amino, N-C₁₋₄alkylcarbamoyl, di-N,N-(C₁₋₄alkyl)carbamoyl, C₁₋₄alkylS(O)_r- and C₁₋₄alkylS(O)_rC₁₋₄alkyl (wherein r is independently selected 0, 1 and 2) and optionally substituted, on an available nitrogen, by a substituent independently selected from C₁₋₄alkyl, C₂₋₄alkanoyl and C₁₋₄alkanesulphonyl each of which is optionally substituted by 1, 2 or 3 substituent independently selected from hydroxyl, halo, C₁₋₄alkoxy, carboxy and cyano];
- 10 R¹⁶ is independently selected from, C₁₋₃alkyl optionally substituted by 1, 2 or 3 substituents independently selected from hydroxyl, halo, C₁₋₄alkoxy, carboxy and cyano; R^{16'}, R^{16''} and R^{16'''} are independently selected from hydrogen and C₁₋₃alkyl optionally substituted by 1, 2, or 3 substituents independently selected from hydroxyl, halo, C₁₋₄alkoxy, carboxy and cyano);
- 15 or a pharmaceutically-acceptable salt thereof; provided that:
- i) when -QR¹ is N-(3-chloro-4-methoxybenzyl)amino then -NR²R³ is not N-(4-hydroxycyclohexyl)amino; and
 - ii) when -QR¹ is 2-fluorophenyl, 4-cyanophenyl or 3-methylphenyl then R⁴ is not morpholino, pyrrolidino, 4-methylpiperidino, cyclohexylmethylamino, 2-methoxyethylamino, 3-methoxypropylamino or cyclopropylmethylamino.
- 20

In another aspect, there is provided a compound of formula **(1)**:

wherein:

- Q** is O, S, N(R⁸) or a single bond;
- 25 R⁸ is selected from hydrogen, C₁₋₄alkyl, C₃₋₅cycloalkyl and C₃₋₅cycloalkylmethyl (each of which is optionally substituted by 1, 2 or 3 fluoro atoms);
- R¹** is selected from C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₇cycloalkyl, heterocyclyl, heteroaryl, heteroarylC₁₋₃alkyl, C₃₋₇cycloalkylC₁₋₃alkyl, heterocyclylC₁₋₃alkyl, C₃₋₇cycloalkylC₂₋₃alkenyl and C₃₋₇cycloalkylC₂₋₃alkynyl, [each of which is optionally
- 30 substituted, on available carbon atoms, by 1, 2 or 3 substituents independently selected from C₁₋₃alkyl, hydroxy, halo, oxo, cyano, trifluoromethyl, C₁₋₃alkoxy, C₁₋₃alkylS(O)_n- (wherein n is 0, 1, 2 or 3), R⁵CON(R^{5'})-, (R^{5'})(R^{5''})N-, (R^{5'})(R^{5''})NC(O)-, R^{5'}C(O)O-,

- $R^{5'}OC(O)-$, $(R^{5'})(R^{5''})NC(O)N(R^{5'''})-$, $R^{5'}SO_2N(R^{5''})-$, $(R^{5'})(R^{5''})NSO_2-$ and C_{1-2} alkyl
 optionally substituted by 1, 2 or 3 substituents independently selected from hydroxy, halo,
 carboxy and C_{1-3} alkoxy (wherein R^5 is C_{1-3} alkyl optionally substituted by 1, 2 or 3
 substituents independently selected from hydroxyl, halo and cyano; and
 5 $R^{5'}$, $R^{5''}$ and $R^{5'''}$ are independently selected from hydrogen and C_{1-3} alkyl optionally
 substituted by 1, 2 or 3 substituents independently selected from hydroxyl, halo,
 C_{1-3} alkoxy, carboxy and cyano or $R^{5'}$ and $R^{5''}$ together with the nitrogen atom to which
 they are attached form a 4-7 membered saturated ring) and optionally substituted, on an
 available nitrogen, by a substituent independently selected from C_{1-4} alkyl, C_{2-4} alkanoyl and
 10 C_{1-4} alkanesulphonyl each of which is optionally substituted by 1, 2 or 3 substituent
 independently selected from hydroxyl, halo, C_{1-4} alkoxy, carboxy and cyano] provided that
 when Q is a single bond R^1 is not methyl; or
 R^1 and R^8 together with the nitrogen atom to which they are attached form a saturated
 mono, bicyclic or bridged ring system optionally containing 1 or 2 additional ring
 15 heteroatoms independently selected from nitrogen, oxygen and sulphur and optionally
 fused to a saturated, partially saturated or unsaturated monocyclic ring wherein the
 resulting ring system is optionally substituted, on available carbon atoms, by 1, 2, or 3
 substituents independently selected from R^9 and optionally substituted, on an available
 nitrogen, by a substituent independently selected from C_{1-4} alkyl, C_{2-4} alkanoyl and C_{1-}
 20 4 alkanesulphonyl each of which is optionally substituted by 1, 2 or 3 substituent
 independently selected from hydroxyl, halo, C_{1-4} alkoxy, carboxy and cyano;
 R^2 is selected from C_{3-7} cycloalkyl $(CH_2)_m-$, and C_{6-12} polycycloalkyl $(CH_2)_m-$ (wherein m is
 0, 1 or 2 and the rings are optionally substituted, on available carbon atoms, by 1, 2 or 3
 substituents independently selected from R^6 and optionally substituted, on an available
 25 nitrogen, by a substituent independently selected from C_{1-4} alkyl, C_{2-4} alkanoyl and C_{1-}
 4 alkanesulphonyl each of which is optionally substituted by 1, 2 or 3 substituent
 independently selected from hydroxyl, halo, C_{1-4} alkoxy, carboxy and cyano);
 R^3 is selected from hydrogen, C_{1-4} alkyl, C_{3-5} cycloalkyl and C_{3-5} cycloalkylmethyl (each of
 which is optionally substituted by 1, 2 or 3 fluoro atoms);
 30 R^2 and R^3 together with the nitrogen atom to which they are attached form a saturated
 mono, bicyclic or bridged ring system optionally containing 1 or 2 additional ring
 heteroatoms independently selected from nitrogen, oxygen and sulphur and optionally

- fused to a saturated, partially saturated or unsaturated monocyclic ring wherein the resulting ring system is optionally substituted, on available carbon atoms, by 1, 2, or 3 substituents independently selected from R^7 and optionally substituted, on an available nitrogen, by a substituent independently selected from C_{1-4} alkyl, C_{2-4} alkanoyl and C_{1-4} alkanesulphonyl each of which is optionally substituted by 1, 2 or 3 substituent independently selected from hydroxyl, halo, C_{1-4} alkoxy, carboxy and cyano;
- R^4 is selected from hydrogen, R^{10} , $-OR^{10}$ and $-NR^{11}R^{12}$;
- R^{10} is selected from C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-7} cycloalkyl, heterocyclyl, aryl C_{1-3} alkyl, heteroaryl C_{1-3} alkyl, heterocyclyl C_{1-3} alkyl, C_{3-7} cycloalkyl C_{1-3} alkyl, C_{3-7} cycloalkyl C_{2-3} alkenyl and C_{3-7} cycloalkyl C_{2-3} alkynyl, [each of which is optionally substituted, on available carbon atoms, by 1, 2 or 3 substituents independently selected from C_{1-3} alkyl, hydroxy, halo, oxo, cyano, trifluoromethyl, C_{1-3} alkoxy, C_{1-3} alkylS(O)_p- (wherein p is 0, 1, 2 or 3), $R^{13}CON(R^{13'})$ -, $(R^{13'})(R^{13''})N$ -, $(R^{13'})(R^{13''})NC(O)$ -, $R^{13'}C(O)O$ -, $R^{13'}OC(O)$ -, $(R^{13'})(R^{13''})NC(O)N(R^{13'''})$ -, $R^{13}SO_2N(R^{13''})$ -, $(R^{13'})(R^{13''})NSO_2$ - and C_{1-2} alkyl optionally substituted by 1, 2 or 3 substituents independently selected from hydroxy, halo, carboxy and C_{1-3} alkoxy (wherein R^{13} is C_{1-3} alkyl optionally substituted by 1, 2 or 3 substituents selected from hydroxyl, halo and cyano; and $R^{13'}$, $R^{13''}$ and $R^{13'''}$ are independently selected from hydrogen and C_{1-3} alkyl optionally substituted by 1, 2 or 3 substituents independently selected from hydroxyl, halo, C_{1-3} alkoxy, carboxy and cyano or $R^{13'}$ and $R^{13''}$ together with the nitrogen atom to which they are attached form a 4-7 membered saturated ring) and optionally substituted, on an available nitrogen, by a substituent independently selected from C_{1-4} alkyl, C_{2-4} alkanoyl and C_{1-4} alkanesulphonyl each of which is optionally substituted by 1, 2 or 3 substituent independently selected from hydroxyl, halo, C_{1-4} alkoxy, carboxy and cyano];
- R^{11} is selected from hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-7} cycloalkyl, heterocyclyl, aryl C_{1-3} alkyl, heteroaryl C_{1-3} alkyl, heterocyclyl C_{1-3} alkyl, C_{3-7} cycloalkyl C_{1-3} alkyl, C_{3-7} cycloalkyl C_{2-3} alkenyl and C_{3-7} cycloalkyl C_{2-3} alkynyl, [each of which is optionally substituted, on available carbon atoms, by 1, 2 or 3 substituents independently selected from C_{1-3} alkyl, hydroxy, halo, oxo, cyano, trifluoromethyl, C_{1-3} alkoxy, C_{1-3} alkylS(O)_q- (wherein q is 0, 1, 2 or 3), $R^{14}CON(R^{14'})$ -, $(R^{14'})(R^{14''})NC(O)$ -, $R^{14'}C(O)O$ -, $R^{14'}OC(O)$ -, $(R^{14'})(R^{14''})NC(O)N(R^{14'''})$ -, $R^{14}SO_2N(R^{14''})$ -, $(R^{14'})(R^{14''})NSO_2$ - and C_{1-2} alkyl optionally substituted by 1, 2 or 3 substituents independently selected from

hydroxy, halo, carboxy and C₁₋₃alkoxy (wherein R¹⁴ is C₁₋₃alkyl optionally substituted by 1, 2 or 3 substituents independently selected from hydroxyl, halo and cyano; and R^{14'}, R^{14''} and R^{14'''} are independently selected from hydrogen and C₁₋₃alkyl optionally substituted by 1, 2 or 3 substituents independently selected from hydroxyl, halo,

5 C₁₋₃alkoxy, carboxy and cyano or R^{14'} and R^{14''} together with the nitrogen atom to which they are attached form a 4-7 membered saturated ring) and optionally substituted, on an available nitrogen, by a substituent independently selected from C₁₋₄alkyl, C₂₋₄alkanoyl and C₁₋₄alkanesulphonyl each of which is optionally substituted by 1, 2 or 3 substituent independently selected from hydroxyl, halo, C₁₋₄alkoxy, carboxy and cyano]; and

10 R¹² is selected from hydrogen, C₁₋₄alkyl, C₃₋₅cycloalkyl and C₃₋₅cycloalkylmethyl (each of which is optionally substituted by 1, 2 or 3 fluoro atoms); or

R¹¹ and R¹² together with the nitrogen atom to which they are attached form a saturated mono, bicyclic or bridged ring system optionally containing 1 or 2 additional ring heteroatoms independently selected from nitrogen, oxygen and sulphur and optionally

15 fused to a saturated, partially saturated or unsaturated monocyclic ring (optionally containing 1 or 2 additional ring heteroatoms independently selected from nitrogen, oxygen and sulphur) wherein the resulting ring system is optionally substituted, on available carbon atoms, by 1, 2, or 3 substituents independently selected from R¹⁵ and optionally substituted on an available nitrogen by a substituent independently selected

20 from C₁₋₄alkyl, C₂₋₄alkanoyl and C₁₋₄alkanesulphonyl each of which is optionally substituted by 1, 2 or 3 substituent independently selected from hydroxyl, halo, C₁₋₄alkoxy, carboxy and cyano;

R⁶, R⁷, R⁹ and R¹⁵ are independently selected from hydroxyl, halo, oxo, carboxy, cyano, trifluoromethyl, R¹⁶, R¹⁶O-, R¹⁶CO-, R¹⁶C(O)O-, R¹⁶CON(R^{16'})-, (R^{16'})(R^{16''})NC(O)-, (R^{16'})(R^{16''})N-, R¹⁶S(O)_a- wherein a is 0 to 2, R^{16'}OC(O)-, (R^{16'})(R^{16''})NSO₂-,

25 R¹⁶SO₂N(R^{16''})-, (R^{16'})(R^{16''})NC(O)N(R^{16'''})-, phenyl and heteroaryl [wherein the phenyl and heteroaryl groups are optionally fused to a phenyl, heteroaryl or a saturated or partially-saturated 5- or 6-membered ring optionally containing 1, 2 or 3 heteroatoms independently selected from nitrogen, oxygen and sulphur and the resulting ring system is

30 optionally substituted, on available carbon atoms, by 1, 2 or 3 substituents independently selected from C₁₋₄alkyl, hydroxyl, cyano, trifluoromethyl, trifluoromethoxy, halo, C₁₋₄alkoxy, C₁₋₄alkoxyC₁₋₄alkyl, amino, N-C₁₋₄alkylamino, di-N,N-(C₁₋₄alkyl)amino,

N-C₁₋₄alkylcarbamoyl, di-N,N-(C₁₋₄alkyl)carbamoyl, C₁₋₄alkylS(O)_r- and C₁₋₄alkylS(O)_rC₁₋₄alkyl (wherein r is independently selected 0, 1 and 2) and optionally substituted, on an available nitrogen, by a substituent independently selected from C₁₋₄alkyl, C₂₋₄alkanoyl and C₁₋₄alkanesulphonyl each of which is optionally substituted by 1, 2 or 3 substituent independently selected from hydroxyl, halo, C₁₋₄alkoxy, carboxy and cyano];

R¹⁶ is independently selected from, C₁₋₃alkyl optionally substituted by 1, 2 or 3 substituents independently selected from hydroxyl, halo, C₁₋₄alkoxy, carboxy and cyano; R^{16'}, R^{16''} and R^{16'''} are independently selected from hydrogen and C₁₋₃alkyl optionally substituted by 1, 2, or 3 substituents independently selected from hydroxyl, halo, C₁₋₄alkoxy, carboxy and cyano); or a pharmaceutically-acceptable salt thereof.

The invention also relates to in vivo hydrolysable esters of a compound of the formula (I). In vivo hydrolysable esters are those esters that are broken down in the animal body to produce the parent carboxylic acid.

In one embodiment of the invention are provided compounds of formula (1). In an alternative embodiment are provided pharmaceutically-acceptable salts of compounds of formula (1).

Definition of Q

- a) In one aspect, the invention relates to a compound of the formula (I) as hereinabove defined wherein Q is O.
- b) In another aspect Q is S.
- c) In another aspect Q is a single bond.
- d) In another aspect Q is N(R⁸).

Definition of R¹

- a) In one aspect R¹ is C₃₋₆cycloalkyl optionally substituted by 1, 2 or 3 substituents independently selected from C₁₋₃alkyl, hydroxy, halo, oxo, cyano, fluoro, trifluoromethyl and C₁₋₃alkoxy.
- b) In another aspect R¹ is C₃₋₆cycloalkyl.
- c) In another aspect R¹ is C₃₋₆cycloalkylC₁₋₂alkyl optionally substituted by 1, 2 or 3 substituents independently selected from C₁₋₃alkyl, hydroxy, halo, oxo, cyano, fluoro, trifluoromethyl and C₁₋₃alkoxy.

- d) In another aspect R^1 is C_{3-4} cycloalkyl C_{1-2} alkyl.
- e) In another aspect R^1 is C_{1-4} alkyl optionally substituted by 1, 2 or 3 substituents independently selected from C_{1-3} alkyl, hydroxy, halo, oxo, cyano, trifluoromethyl and C_{1-3} alkoxy.
- 5 f) In another aspect R^1 is C_{1-4} alkyl.
- g) In yet another aspect R^1 is selected from C_{1-6} alkyl, C_{3-7} cycloalkyl, heterocyclyl, aryl C_{1-3} alkyl, heteroaryl C_{1-3} alkyl and C_{3-7} cycloalkyl C_{1-3} alkyl [each of which is optionally substituted, on available carbon atoms, by 1, 2 or 3 substituents independently selected from C_{1-3} alkyl, halo, cyano, trifluoromethyl, C_{1-3} alkoxy and C_{1-2} alkyl optionally
- 10 substituted by 1, 2 or 3 substituents independently selected from hydroxy, halo, carboxy and C_{1-3} alkoxy; and optionally substituted, on an available nitrogen, by a substituent independently selected from C_{1-4} alkyl and C_{2-4} alkanoyl.
- h) In yet another aspect R^1 is selected from C_{3-7} cycloalkyl and heterocyclyl [each of which is optionally substituted, on available carbon atoms, by 1, 2 or 3 substituents
- 15 independently selected from C_{1-3} alkyl, halo, cyano, trifluoromethyl, C_{1-3} alkoxy and C_{1-2} alkyl optionally substituted by 1, 2 or 3 substituents independently selected from hydroxy, halo, carboxy and C_{1-3} alkoxy; and optionally substituted, on an available nitrogen, by a substituent independently selected from C_{1-4} alkyl and C_{2-4} alkanoyl.
- i) In yet another aspect R^1 is selected from C_{3-7} cycloalkyl and heterocyclyl.

20

Definition of R^8

- a) In one aspect R^8 is selected from hydrogen, C_{1-3} alkyl, C_{3-5} cycloalkyl and C_{3-5} cycloalkylmethyl.
- b) In another aspect R^8 is selected from hydrogen, C_{1-3} alkyl, propyl and propylmethyl.
- 25 c) In another aspect R^8 is selected from hydrogen and methyl.
- d) In yet another aspect R^8 is hydrogen.

Definition of R^1 and R^8 together

- a) In another aspect, R^1 and R^8 together with the nitrogen atom to which they are attached form a saturated 5 or 6-membered mono, 6-12 membered bicyclic or 6-12
- 30 membered bridged ring system optionally containing 1 or 2 additional ring heteroatoms independently selected from nitrogen, oxygen and sulphur and which is optionally fused to a saturated, partially-saturated or aryl monocyclic ring wherein the resulting ring system is

optionally substituted, on available carbon atoms, by 1, 2, or 3 substituents independently selected from R^9 and optionally substituted, on an available nitrogen, by a substituent independently selected from C_{1-4} alkyl and C_{2-4} alkanoyl.

- b) In another aspect, R^1 and R^8 together with the nitrogen atom to which they are attached form a pyrrolidine ring optionally substituted, on available carbon atoms, by 1 or 2 substituents independently selected from R^9 and optionally substituted, on an available nitrogen, by a substituent independently selected from C_{1-4} alkyl and C_{2-4} alkanoyl.

Definition of R^2

- a) In one aspect, R^2 is selected from C_{3-7} cycloalkyl(CH_2) $_m$ -, and C_{6-12} polycycloalkyl(CH_2) $_m$ - (wherein m is 0, 1 or 2 and the rings are optionally substituted by 1, 2 or 3 substituents independently selected from R^6) wherein m is 0, 1 or 2.
- b) In another aspect, R^2 is selected from C_{5-7} cycloalkyl(CH_2) $_m$ - and C_{8-12} polycycloalkyl(CH_2) $_m$ - (wherein the rings are optionally substituted by 1, 2 or 3 substituents independently selected from R^6) and wherein m is 0, 1 or 2.
- c) In another aspect, R^2 is selected from C_{5-7} cycloalkyl(CH_2) $_m$ -, C_{7-10} bicycloalkyl(CH_2) $_m$ - and C_{10} tricycloalkyl(CH_2) $_m$ - (wherein the cycloalkyl, bicycloalkyl and tricycloalkyl rings are optionally substituted by 1, 2 or 3 substituents independently selected from R^6) and wherein m is 0, 1 or 2.
- d) In yet another aspect, R^2 is selected from C_{5-7} cycloalkyl(CH_2) $_m$ -, C_{7-10} bicycloalkyl(CH_2) $_m$ - and adamantyl (wherein the cycloalkyl, bicycloalkyl and tricycloalkyl rings are optionally substituted by 1, 2 or 3 substituents independently selected from R^6) and wherein m is 0, 1 or 2.
- e) In yet another aspect, R^2 is selected from adamantyl optionally substituted by 1 or 2 substituents independently selected from R^6 .
- f) In yet another aspect, R^2 is selected from adamantyl optionally substituted by 1 or 2 substituents independently selected from hydroxy and fluoro.
- g) In yet another aspect, R^2 is selected from adamantyl optionally substituted by 1 hydroxy group.
- h) In yet another aspect, R^2 is 5-hydroxy-2-adamantyl.
- i) In yet another aspect, R^2 is (2r,5s)-5-hydroxyadamantyl-2-yl.
- j) In yet another aspect R^2 is adamant-2-yl.
- k) In antoher aspect R^2 is adamant-1-yl.

l) In yet another aspect, R^2 is cyclohexyl.

Definition of m

a) In one aspect, m is 0 or 1.

Definition of R^3

- 5 a) In one aspect, R^3 is C_{1-4} alkyl.
 b) In another aspect, R^3 is hydrogen, methyl or ethyl.
 c) In another aspect, R^3 is hydrogen.
 d) In another aspect, R^3 is methyl.
 e) In another aspect, R^3 is ethyl.
 10 f) In another aspect, R^3 is cyclopropyl.

Definition of R^2 and R^3 together

- a) In another aspect, R^2 and R^3 together with the nitrogen atom to which they are attached form a saturated 5 or 6-membered mono, 6-12 membered bicyclic or 6-12 membered bridged ring system optionally containing 1 or 2 additional ring heteroatoms
 15 independently selected from nitrogen, oxygen and sulphur and which is optionally fused to a saturated, partially-saturated or aryl monocyclic ring wherein the resulting ring system is optionally substituted, on available carbon atoms, by 1, 2, or 3 substituents independently selected from R^7 and optionally substituted, on an available nitrogen, by a substituent independently selected from C_{1-4} alkyl and C_{2-4} alkanoyl.
 20 b) In another aspect, R^2 and R^3 together with the nitrogen atom to which they are attached form a pyrrolidine ring optionally substituted, on available carbon atoms, by 1 or 2 substituents independently selected from R^7 and optionally substituted, on an available nitrogen, by a substituent independently selected from C_{1-4} alkyl and C_{2-4} alkanoyl.

Definition of R^6

- 25 a) In one aspect, R^6 is independently selected from hydroxyl, $R^{16}O-$, $R^{16}CO-$ and $R^{16}C(O)O-$.
 b) In another aspect, R^6 is independently selected from hydroxyl, $R^{16}O-$, $R^{16}CO-$ and $R^{16}C(O)O-$
 wherein R^{16} is C_{1-3} alkyl optionally substituted by C_{1-4} alkoxy or carboxy.
 30 c) In another aspect, R^6 is independently selected from $R^{16}CON(R^{16'})-$, $R^{16}SO_2N(R^{16'})-$ and $(R^{16'})(R^{16''})NC(O)N(R^{16''})-$.

d) In another aspect, R^6 is independently selected from $R^{16}CON(R^{16'})$ -, $R^{16}SO_2N(R^{16'})$ - and $(R^{16'})(R^{16''})NC(O)N(R^{16'''})$ -;

R^{16} is C_{1-3} alkyl optionally substituted by C_{1-4} alkoxy or carboxy;

$R^{16'}$, $R^{16''}$ and $R^{16'''}$ are independently selected from hydrogen and C_{1-3} alkyl optionally substituted by C_{1-4} alkoxy or carboxy).

e) In another aspect, R^6 is independently selected from $(R^{16'})(R^{16''})NC(O)$ - and $(R^{16'})(R^{16''})N$ -.

f) In another aspect, R^6 is independently selected from $(R^{16'})(R^{16''})NC(O)$ - and $(R^{16'})(R^{16''})N$ -;

wherein $R^{16'}$ and $R^{16''}$ are independently selected from hydrogen and C_{1-3} alkyl optionally substituted by C_{1-4} alkoxy or carboxy.

g) In one aspect R^6 is independently selected from methyl, trifluoromethyl, chloro, fluoro, bromo, methoxy, ethoxy, trifluoromethoxy, methanesulfonyl, ethanesulfonyl, methylthio, ethylthio, amino, N-methylamino, N-ethylamino, N-propylamino,

N,N-dimethylamino, N,N-methylethylamino or N,N-diethylamino.

h) In another aspect, R^6 is optionally substituted phenyl, pyridyl or pyrimidyl.

i) In another aspect, R^6 is optionally substituted pyrid-2-yl, pyrid-3-yl or pyrid-4-yl.

Definition of R^7

a) In another aspect, R^7 is independently selected from hydroxyl, halo, oxo, cyano, trifluoromethyl, R^{16} and $R^{16}O$ -.

b) In another aspect, R^7 is independently selected from hydroxyl, halo, trifluoromethyl, R^{16} and $R^{16}O$ -.

Definition of R^9

a) In another aspect, R^9 is independently selected from hydroxyl, halo, oxo, cyano, trifluoromethyl, R^{16} and $R^{16}O$ -.

b) In another aspect, R^9 is independently selected from hydroxyl, halo, trifluoromethyl, R^{16} and $R^{16}O$ -.

Definition of R^{15}

a) In another aspect, R^{15} is independently selected from hydroxyl, halo, oxo, cyano, trifluoromethyl, R^{16} and $R^{16}O$ -.

b) In another aspect, R^{15} is independently selected from hydroxyl, halo, trifluoromethyl, R^{16} and $R^{16}O$ -.

Definition of R¹⁶

a) In one aspect, R¹⁶ is independently selected from C₁₋₃alkyl.

Definition of R^{16'}, R^{16''} and R^{16'''}

a) In one aspect, R^{16'}, R^{16''} and R^{16'''} are independently selected from hydrogen and
5 C₁₋₃alkyl.

Definition of R⁴

- a) In one aspect, the invention relates to a compound of the formula (I) as hereinabove defined wherein R⁴ is R¹⁰.
- b) In another aspect R⁴ is OR¹⁰.
- 10 c) In another aspect R⁴ is SR¹⁰.
- d) In another aspect R⁴ is -NR¹¹R¹².
- e) In another aspect R⁴ is -NHR¹¹.
- f) In another aspect R⁴ is hydrogen.

Definition of R¹⁰

- 15 a) In one aspect R¹⁰ is selected from C₁₋₆alkyl, C₃₋₇cycloalkyl, heterocyclyl, arylC₁₋₃alkyl, heteroarylC₁₋₃alkyl and C₃₋₇cycloalkylC₁₋₃alkyl [each of which is optionally substituted, on available carbon atoms, by 1, 2 or 3 substituents independently selected from C₁₋₃alkyl, hydroxy, halo, oxo, cyano, trifluoromethyl, C₁₋₃alkoxy, C₁₋₃alkylS(O)_p- (wherein p is 0, 1, 2 or 3), R¹³CON(R^{13'})-, (R^{13'})(R^{13''})N-, (R^{13'})(R^{13''})NC(O)-, R^{13'}C(O)O-,
20 R^{13'}OC(O)-, (R^{13'})(R^{13''})NC(O)N(R^{13'''})-, R¹³SO₂N(R^{13''})-, and (R^{13'})(R^{13''})NSO₂- (wherein R¹³ is C₁₋₃alkyl and R^{13'}, R^{13''} and R^{13'''} are independently selected from hydrogen and C₁₋₃alkyl) and optionally substituted, on an available nitrogen, by a substituent independently selected from C₁₋₄alkyl and C₂₋₄alkanoyl].
- 25 b) In another aspect R¹⁰ is selected from C₁₋₆alkyl, C₃₋₇cycloalkyl, heterocyclyl and C₃₋₇cycloalkylC₁₋₃alkyl [each of which is optionally substituted, on available carbon atoms, by 1, 2 or 3 substituents independently selected from C₁₋₃alkyl, hydroxy, halo, oxo, cyano, trifluoromethyl, C₁₋₃alkoxy, C₁₋₃alkylS(O)_p- (wherein p is 0, 1, 2 or 3) and R¹³CON(R^{13'})- (wherein R¹³ is C₁₋₃alkyl and
30 R^{13'}, R^{13''} and R^{13'''} are independently selected from hydrogen and C₁₋₃alkyl) and optionally substituted, on an available nitrogen, by a substituent independently selected from C₁₋₄alkyl and C₂₋₄alkanoyl].

c) In another aspect R^{10} is selected from C_{3-7} cycloalkyl and heterocyclyl [each of which is optionally substituted, on available carbon atoms, by 1, 2 or 3 substituents independently selected from C_{1-3} alkyl, hydroxy, halo, oxo, cyano, trifluoromethyl, C_{1-3} alkoxy, C_{1-3} alkylS(O)_p- (wherein p is 0, 1, 2 or 3) and R^{13} CON($R^{13'}$)- (wherein R^{13} is C_{1-3} alkyl and

$R^{13'}$, $R^{13''}$ and $R^{13'''}$ are independently selected from hydrogen and C_{1-3} alkyl) and optionally substituted, on an available nitrogen, by a substituent independently selected from C_{1-4} alkyl and C_{2-4} alkanoyl].

10 Definition of R^{11}

a) In one aspect R^{11} is selected from hydrogen, C_{1-6} alkyl, C_{3-7} cycloalkyl, heterocyclyl, aryl C_{1-3} alkyl, heteroaryl C_{1-3} alkyl, C_{3-7} cycloalkyl C_{1-3} alkyl and C_{3-7} cycloalkyl [each of which is optionally substituted, on available carbon atoms, by 1, 2 or 3 substituents independently selected from C_{1-3} alkyl, hydroxy, halo, oxo, cyano, trifluoromethyl, C_{1-3} alkoxy, C_{1-3} alkylS(O)_q- (wherein q is 0, 1, 2 or 3), R^{14} CON($R^{14'}$)-, ($R^{14'}$)($R^{14''}$)NC(O)-, $R^{14'}$ C(O)O-, $R^{14'}$ OC(O)-, ($R^{14'}$)($R^{14''}$)NC(O)N($R^{14'''}$)-, R^{14} SO₂N($R^{14''}$)-, and ($R^{14'}$)($R^{14''}$)NSO₂- (wherein R^{14} is C_{1-3} alkyl optionally substituted by 1, 2 or 3 substituents independently selected from hydroxyl, halo or cyano; and $R^{14'}$, $R^{14''}$ and $R^{14'''}$ are independently selected from hydrogen and C_{1-3} alkyl optionally substituted by 1, 2 or 3 substituents independently selected from hydroxyl, halo, C_{1-3} alkoxy, carboxy and cyano or $R^{14'}$ and $R^{14''}$ together with the nitrogen atom to which they are attached form a 4-7 membered saturated ring) and optionally substituted, on an available nitrogen, by a substituent independently selected from C_{1-4} alkyl and C_{2-4} alkanoyl].

b) In another aspect R^{11} is selected from C_{1-6} alkyl, C_{3-7} cycloalkyl, heterocyclyl, aryl C_{1-3} alkyl, heteroaryl C_{1-3} alkyl, C_{3-7} cycloalkyl C_{1-3} alkyl and C_{3-7} cycloalkyl [each of which is optionally substituted, on available carbon atoms, by 1, 2 or 3 substituents independently selected from C_{1-3} alkyl, hydroxy, halo, oxo, cyano, trifluoromethyl, C_{1-3} alkoxy, C_{1-3} alkylS(O)_q- (wherein q is 0, 1, 2 or 3), R^{14} CON($R^{14'}$)- and ($R^{14'}$)($R^{14''}$)NC(O)-, (wherein R^{14} is C_{1-3} alkyl and $R^{14'}$, $R^{14''}$ and $R^{14'''}$ are independently selected from hydrogen and C_{1-3} alkyl optionally substituted by 1, 2 or 3 substituents independently selected from hydroxyl, halo, C_{1-3} alkoxy, carboxy and cyano or $R^{14'}$ and $R^{14''}$ together with the nitrogen atom to which they are attached form a 4-7 membered saturated ring) and optionally substituted, on an available nitrogen, by a substituent independently selected from C_{1-4} alkyl and C_{2-4} alkanoyl].

alkoxy, carboxy and cyano or $R^{14'}$ and $R^{14''}$ together with the nitrogen atom to which they are attached form a 4-7 membered saturated ring) and optionally substituted, on an available nitrogen, by a substituent independently selected from C_{1-4} alkyl and C_{2-4} alkanoyl].

5 c) In another aspect R^{11} is selected from C_{3-7} cycloalkyl and heterocyclyl, [each of which is optionally substituted, on available carbon atoms, by 1, 2 or 3 substituents independently selected from C_{1-3} alkyl, hydroxy, halo, oxo, cyano, trifluoromethyl, C_{1-3} alkoxy, C_{1-3} alkylS(O)_q- (wherein q is 0, 1, 2 or 3), R^{14} CON($R^{14'}$)- and ($R^{14'}$)($R^{14''}$)NC(O)-, (wherein R^{14} is C_{1-3} alkyl and

10 $R^{14'}$, $R^{14''}$ and $R^{14'''}$ are independently selected from hydrogen and C_{1-3} alkyl optionally substituted by 1, 2 or 3 substituents independently selected from hydroxyl, halo, C_{1-3} alkoxy, carboxy and cyano or $R^{14'}$ and $R^{14''}$ together with the nitrogen atom to which they are attached form a 4-7 membered saturated ring) and optionally substituted, on an available nitrogen, by a substituent independently selected from C_{1-4} alkyl and C_{2-4} alkanoyl].

d) In another aspect R^{11} is selected from C_{3-7} cycloalkyl and heterocyclyl, [each of which is optionally substituted, on available carbon atoms, by 1 or 2 substituents independently selected from C_{1-3} alkyl, hydroxy, halo, oxo, cyano, trifluoromethyl and C_{1-3} alkoxy.

20 e) In another aspect R^{11} and R^{12} together with the nitrogen atom to which they are attached form a saturated mono, bicyclic or bridged ring system optionally containing 1 or 2 additional ring heteroatoms independently selected from nitrogen, oxygen and sulphur and optionally fused to a saturated, partially saturated or unsaturated monocyclic ring (optionally containing 1 or 2 additional ring heteroatoms independently selected from
25 nitrogen, oxygen and sulphur) wherein the resulting ring system is optionally substituted, on available carbon atoms, by 1, 2, or 3 substituents independently selected from R^{15} and optionally substituted, on an available nitrogen, by a substituent independently selected from C_{1-4} alkyl and C_{2-4} alkanoyl.

f) In another aspect R^{11} and R^{12} together with the nitrogen atom to which they are
30 attached form a saturated mono, bicyclic or bridged ring system optionally containing 1 or 2 additional ring heteroatoms independently selected from nitrogen, oxygen and sulphur.

g) In another aspect R^{11} and R^{12} together with the nitrogen atom to which they are attached form a heterocyclyl group which is optionally substituted by 1 or 2 substituents independently selected from R^{15} .

h) In another aspect R^{11} and R^{12} together with the nitrogen atom to which they are attached form a heterocyclyl group which is optionally substituted by 1 or 2 substituents independently selected from hydroxyl, halo, oxo, carboxy, cyano, trifluoromethyl, R^{16} , $R^{16}O-$, $R^{16}CO-$, $R^{16}C(O)O-$, $R^{16}CON(R^{16'})-$, $(R^{16'})(R^{16''})NC(O)-$, $(R^{16'})(R^{16''})N-$, $R^{16}S(O)_a-$ wherein a is 0 to 2, $R^{16'}OC(O)-$, $(R^{16'})(R^{16''})NSO_2-$, $R^{16}SO_2N(R^{16''})-$, $(R^{16'})(R^{16''})NC(O)N(R^{16''''})-$ wherein R^{16} is selected from hydrogen and C_{1-3} alkyl.

10

Definition of R^{12}

a) In one aspect R^{12} is selected from hydrogen, C_{1-3} alkyl, C_{3-5} cycloalkyl and C_{3-5} cycloalkylmethyl.

b) In another aspect R^{12} is selected from hydrogen, C_{1-3} alkyl, propyl and propylmethyl.

c) In another aspect R^{12} is selected from hydrogen and methyl.

d) In yet another aspect R^{12} is hydrogen.

In one aspect R^1 is optionally substituted by 0 substituents.

In one aspect R^1 is optionally substituted by 1 substituent.

20 In one aspect R^1 is optionally substituted by 2 substituents.

In one aspect R^1 is optionally substituted by 3 substituents.

In one aspect R^2 is optionally substituted by 0 substituents.

In one aspect R^2 is optionally substituted by 1 substituent.

In one aspect R^2 is optionally substituted by 2 substituents.

25 In one aspect R^2 is optionally substituted by 3 substituents.

In one aspect R^3 is optionally substituted by 0 substituents.

In one aspect R^3 is optionally substituted by 1 substituent.

In one aspect R^3 is optionally substituted by 2 substituents.

In one aspect R^3 is optionally substituted by 3 substituents.

30 In one aspect the group formed by R^2 and R^3 together is optionally substituted by 0 substituents.

In one aspect the group formed by R^2 and R^3 together is optionally substituted by 1 substituent.

In one aspect the group formed by R^2 and R^3 together is optionally substituted by 2 substituents.

- 5 In one aspect the group formed by R^2 and R^3 together is optionally substituted by 3 substituents.

In one aspect the phenyl and heteroaryl groups in R^6 and R^7 are independently optionally substituted by 0 substituents.

- 10 In one aspect the phenyl and heteroaryl groups in R^6 and R^7 are independently optionally substituted by 1 substituent.

In one aspect the phenyl and heteroaryl groups in R^6 and R^7 are independently are optionally substituted by 2 substituents.

In one aspect the phenyl and heteroaryl groups in R^6 and R^7 are independently are optionally substituted by 3 substituents.

- 15 Particular values of variable groups are as follows. Such values may be used where appropriate with any of the definitions, claims or embodiments defined hereinbefore or hereinafter, for compounds of formula (1).

- Particular classes of compounds of the present invention are disclosed in Table A using combinations of the definitions described hereinabove. For example, 'a' in the column
20 headed R^2 in the table refers to definition (a) given for R^2 hereinabove and '1' refers to the first definition given for the variables in the compound of formula (1) at the beginning of the description. The variables R^5 , $R^{5'}$, $R^{5''}$, $R^{5'''}$, R^{13} , $R^{13'}$, $R^{13''}$, $R^{13'''}$, R^{14} , $R^{14'}$, $R^{14''}$, $R^{14'''}$, R^{16} , $R^{16'}$, $R^{16''}$ and $R^{16'''}$ are as hereinabove defined.

Table A

Class	Q	R^1 and R^8	R^1	R^9	R^2	R^6	R^3	R^7	R^4	R^{10}	R^{11}	R^{12}	R^{15}
1	a	-	a	-	d	b	b	-	a	a	-	-	-
2	b	-	a	-	d	b	b	-	a	a	-	-	-
3	c	-	a	-	d	b	b	-	a	a	-	-	-
4	d	a	-	a	d	b	b	-	a	a	-	-	-

5	a	-	a	-	d	b	b	-	b	a	-	-	-
6	b	-	a	-	d	b	b	-	b	a	-	-	-
7	c	-	a	-	d	b	b	-	b	a	-	-	-
8	d	a	-	a	d	b	b	-	b	a	-	-	-
9	a	-	a	-	d	b	b	-	c	a	-	-	-
10	b	-	a	-	d	b	b	-	c	a	-	-	-
11	c	-	a	-	d	b	b	-	c	a	-	-	-
12	d	a	-	a	d	b	b	-	c	a	-	-	-
13	a	-	a	-	d	b	b	-	d	-	c	-	1
14	b	-	a	-	d	b	b	-	d	-	c	-	1
15	c	-	a	-	d	b	b	-	d	-	c	-	1
16	d	a	-	a	d	b	b	-	d	-	c	-	1
17	a	-	a	-	d	b	b	-	e	-	-	-	-
18	b	-	a	-	d	b	b	-	e	-	-	-	-
19	c	-	a	-	d	b	b	-	e	-	-	-	-
20	d	a	-	a	d	b	b	-	e	-	-	-	-

A particular class of compound is that of formula **(1)** wherein:

Q is O, S, N(R⁸) or a single bond;

R⁸ is selected from hydrogen, C₁₋₄alkyl, C₃₋₅cycloalkyl and C₃₋₅cycloalkylmethyl (each of which is optionally substituted by 1, 2 or 3 fluoro atoms);

R¹ is selected from C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₇cycloalkyl, heterocyclyl, arylC₁₋₃alkyl, heteroarylC₁₋₃alkyl, C₃₋₇cycloalkylC₁₋₃alkyl, C₃₋₇cycloalkylC₂₋₃alkenyl and C₃₋₇cycloalkylC₂₋₃alkynyl, [each of which is optionally substituted, on available carbon atoms, by 1, 2 or 3 substituents independently selected from C₁₋₃alkyl, hydroxy, halo, oxo, cyano, trifluoromethyl, C₁₋₃alkoxy, C₁₋₃alkylS(O)_n- (wherein n is 0, 1, 2 or 3) and C₁₋₂alkyl optionally substituted by 1, 2 or 3 substituents independently selected from hydroxy, halo, carboxy and C₁₋₃alkoxy; and optionally substituted, on an available nitrogen, by a substituent independently selected from C₁₋₄alkyl, C₂₋₄alkanoyl and C₁₋₄alkanesulphonyl; or

R^1 and R^8 together with the nitrogen atom to which they are attached form a saturated mono, bicyclic or bridged ring system optionally containing 1 or 2 additional ring heteroatoms independently selected from nitrogen, oxygen and sulphur and optionally fused to a saturated, partially saturated or unsaturated monocyclic ring wherein the
 5 resulting ring system is optionally substituted, on available carbon atoms, by 1, 2, or 3 substituents independently selected from R^9 and optionally substituted, on an available nitrogen, by a substituent independently selected from C_{1-4} alkyl, C_{2-4} alkanoyl and C_{1-4} alkanesulphonyl;

R^2 is selected from C_{3-7} cycloalkyl $(CH_2)_m$ -, and C_{6-12} polycycloalkyl $(CH_2)_m$ - (wherein m is
 10 0, 1 or 2 and the rings optionally contain 1 or 2 ring atoms independently selected from nitrogen, oxygen and sulphur are optionally substituted, on available carbon atoms, by 1, 2 or 3 substituents independently selected from R^6 and optionally substituted, on an available nitrogen, by a substituent independently selected from C_{1-4} alkyl, C_{2-4} alkanoyl and C_{1-4} alkanesulphonyl);

R^3 is selected from hydrogen, C_{1-4} alkyl, C_{3-5} cycloalkyl and C_{3-5} cycloalkylmethyl (each of which is optionally substituted by 1, 2 or 3 fluoro atoms);

R^2 and R^3 together with the nitrogen atom to which they are attached form a saturated mono, bicyclic or bridged ring system optionally containing 1 or 2 additional ring heteroatoms independently selected from nitrogen, oxygen and sulphur and optionally
 20 fused to a saturated, partially saturated or unsaturated monocyclic ring wherein the resulting ring system is optionally substituted, on available carbon atoms, by 1, 2, or 3 substituents independently selected from R^7 and optionally substituted, on an available nitrogen, by a substituent independently selected from C_{1-4} alkyl, C_{2-4} alkanoyl and C_{1-4} alkanesulphonyl;

R^4 is selected from hydrogen, R^{10} , $-OR^{10}$, $-SR^{10}$ and $-NR^{11}R^{12}$;

R^{10} is selected from C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-7} cycloalkyl, heterocyclyl, aryl C_{1-3} alkyl, heteroaryl C_{1-3} alkyl, C_{3-7} cycloalkyl C_{1-3} alkyl, C_{3-7} cycloalkyl C_{2-3} alkenyl and C_{3-7} cycloalkyl C_{2-3} alkynyl, [each of which is optionally substituted, on available carbon
 25 atoms, by 1, 2 or 3 substituents independently selected from C_{1-3} alkyl, hydroxy, halo, oxo, cyano, trifluoromethyl, C_{1-3} alkoxy, C_{1-3} alkylS(O)_p- (wherein p is 0, 1, 2 or 3)) and C_{1-2} alkyl optionally substituted by 1, 2 or 3 substituents independently selected from hydroxy, halo, carboxy and C_{1-3} alkoxy; and optionally substituted, on an available
 30

nitrogen, by a substituent independently selected from C₁₋₄alkyl, C₂₋₄alkanoyl and C₁₋₄alkanesulphonyl;

R¹¹ is selected from hydrogen, C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₇cycloalkyl, heterocyclyl, arylC₁₋₃alkyl, heteroarylC₁₋₃alkyl, C₃₋₇cycloalkylC₁₋₃alkyl,

5 C₃₋₇cycloalkylC₂₋₃alkenyl and C₃₋₇cycloalkylC₂₋₃alkynyl, [each of which is optionally substituted, on available carbon atoms, by 1, 2 or 3 substituents independently selected from C₁₋₃alkyl, hydroxy, halo, oxo, cyano, trifluoromethyl, C₁₋₃alkoxy, C₁₋₃alkylS(O)_q- (wherein q is 0, 1, 2 or 3), R¹⁴CON(R^{14'})-, (R^{14'})(R^{14''})NC(O)-, R^{14'}C(O)O-, R^{14'}OC(O)-, (R^{14'})(R^{14''})NC(O)N(R^{14'''})-, R¹⁴SO₂N(R^{14''})-, and (R^{14'})(R^{14''})NSO₂- (wherein R¹⁴ is

10 C₁₋₃alkyl optionally substituted by 1, 2 or 3 substituents independently selected from hydroxyl, halo and cyano; and

R^{14'}, R^{14''} and R^{14'''} are independently selected from hydrogen and C₁₋₃alkyl optionally substituted by 1, 2 or 3 substituents independently selected from hydroxyl, halo,

15 C₁₋₃alkoxy, carboxy and cyano or R^{14'} and R^{14''} together with the nitrogen atom to which they are attached form a 4-7 membered saturated ring) and optionally substituted, on an available nitrogen, by a substituent independently selected from C₁₋₄alkyl, C₂₋₄alkanoyl and C₁₋₄alkanesulphonyl]; and

R¹² is selected from hydrogen, C₁₋₄alkyl, C₃₋₅cycloalkyl and C₃₋₅cycloalkylmethyl (each of which is optionally substituted by 1, 2 or 3 fluoro atoms); or

20 R¹¹ and R¹² together with the nitrogen atom to which they are attached form a saturated mono, bicyclic or bridged ring system optionally containing 1 or 2 additional ring heteroatoms independently selected from nitrogen, oxygen and sulphur and optionally fused to a saturated, partially saturated or unsaturated monocyclic ring (optionally containing 1 or 2 additional ring heteroatoms independently selected from nitrogen, oxygen and sulphur) wherein the resulting ring system is optionally substituted, on available carbon atoms, by 1, 2, or 3 substituents independently selected from R¹⁵ and optionally substituted, on an available nitrogen, by a substituent independently selected from C₁₋₄alkyl, C₂₋₄alkanoyl and C₁₋₄alkanesulphonyl;

25 R⁶, R⁷, R⁹ and R¹⁵ are independently selected from hydroxyl, halo, oxo, carboxy, cyano, trifluoromethyl, R¹⁶, R¹⁶O-, R¹⁶CO-, R¹⁶C(O)O-, R¹⁶CON(R^{16'})-, (R^{16'})(R^{16''})NC(O)-, (R^{16'})(R^{16''})N-, R¹⁶S(O)_a- wherein a is 0 to 2, R^{16'}OC(O)-, (R^{16'})(R^{16''})NSO₂-, R¹⁶SO₂N(R^{16''})-, (R^{16'})(R^{16''})NC(O)N(R^{16'''})-, phenyl and heteroaryl [wherein the phenyl

and heteroaryl groups are optionally fused to a phenyl, heteroaryl or a saturated or partially-saturated 5- or 6-membered ring optionally containing 1, 2 or 3 heteroatoms independently selected from nitrogen, oxygen and sulphur and the resulting ring system is optionally substituted, on available carbon atoms, by 1, 2 or 3 substituents independently selected from C₁₋₄alkyl, hydroxyl, cyano, trifluoromethyl, trifluoromethoxy, halo, C₁₋₄alkoxy, C₁₋₄alkoxyC₁₋₄alkyl, amino, N-C₁₋₄alkylamino, di-N,N-(C₁₋₄alkyl)amino, N-C₁₋₄alkylcarbonyl, di-N,N-(C₁₋₄alkyl)carbonyl, C₁₋₄alkylS(O)_r- and C₁₋₄alkylS(O)_rC₁₋₄alkyl (wherein r is independently selected 0, 1 and 2) and optionally substituted, on an available nitrogen, by a substituent independently selected from C₁₋₄alkyl, C₂₋₄alkanoyl and C₁₋₄alkanesulphonyl];

R¹⁶ is independently selected from, C₁₋₃alkyl optionally substituted by 1, 2 or 3 substituents independently selected from hydroxyl, halo, C₁₋₄alkoxy, carboxy and cyano; R^{16'}, R^{16''} and R^{16'''} are independently selected from hydrogen and C₁₋₃alkyl optionally substituted by 1, 2, or 3 substituents independently selected from hydroxyl, halo, C₁₋₄alkoxy, carboxy and cyano);

or a pharmaceutically-acceptable salt thereof;

provided that:

when -QR¹ is N-(3-chloro-4-methoxybenzyl)amino then -NR²R³ is not N-(4-hydroxycyclohexyl)amino.

Another class of compound is that of formula **(I)** wherein:

Q is O, S, N(R⁸) or a single bond;

R⁸ is selected from hydrogen, C₁₋₄alkyl, C₃₋₅cycloalkyl and C₃₋₅cycloalkylmethyl (each of which is optionally substituted by 1, 2 or 3 fluoro atoms);

R¹ is selected from C₁₋₆alkyl, C₃₋₇cycloalkyl, heterocyclyl, arylC₁₋₃alkyl, heteroarylC₁₋₃alkyl and C₃₋₇cycloalkylC₁₋₃alkyl [each of which is optionally substituted, on available carbon atoms, by 1, 2 or 3 substituents independently selected from C₁₋₃alkyl, halo, cyano, trifluoromethyl, C₁₋₃alkoxy and C₁₋₂alkyl optionally substituted by 1, 2 or 3 substituents independently selected from hydroxy, halo, carboxy and C₁₋₃alkoxy; and optionally substituted, on an available nitrogen, by a substituent independently selected from C₁₋₄alkyl and C₂₋₄alkanoyl; or

R¹ and R⁸ together with the nitrogen atom to which they are attached form a saturated mono, bicyclic or bridged ring system optionally containing 1 or 2 additional ring

- heteroatoms independently selected from nitrogen, oxygen and sulphur and optionally fused to a saturated, partially saturated or unsaturated monocyclic ring wherein the resulting ring system is optionally substituted, on available carbon atoms, by 1, 2, or 3 substituents independently selected from R^9 and optionally substituted, on an available nitrogen, by a substituent independently selected from C_{1-4} alkyl and C_{2-4} alkanoyl;
- R^2 is selected from C_{3-7} cycloalkyl $(CH_2)_m$ -, and C_{6-12} polycycloalkyl $(CH_2)_m$ - (wherein m is 0, 1 or 2 and the rings optionally contain 1 or 2 ring atoms independently selected from nitrogen, oxygen and sulphur are optionally substituted by 1, 2 or 3 substituents independently selected from R^6);
- R^3 is selected from hydrogen, C_{1-4} alkyl, C_{3-5} cycloalkyl and C_{3-5} cycloalkylmethyl (each of which is optionally substituted by 1, 2 or 3 fluoro atoms);
- R^2 and R^3 together with the nitrogen atom to which they are attached form a saturated mono, bicyclic or bridged ring system optionally containing 1 or 2 additional ring heteroatoms independently selected from nitrogen, oxygen and sulphur and optionally fused to a saturated, partially saturated or unsaturated monocyclic ring wherein the resulting ring system is optionally substituted, on available carbon atoms, by 1, 2, or 3 substituents independently selected from R^7 and optionally substituted, on an available nitrogen, by a substituent independently selected from C_{1-4} alkyl and C_{2-4} alkanoyl;
- R^4 is selected from hydrogen, R^{10} , $-OR^{10}$ and $-NR^{11}R^{12}$;
- R^{10} is selected from C_{1-6} alkyl, C_{3-7} cycloalkyl, heterocyclyl, aryl C_{1-3} alkyl, heteroaryl C_{1-3} alkyl and C_{3-7} cycloalkyl C_{1-3} alkyl [each of which is optionally substituted, on available carbon atoms, by 1, 2 or 3 substituents independently selected from C_{1-3} alkyl, halo, cyano, trifluoromethyl, C_{1-3} alkoxy and C_{1-2} alkyl optionally substituted by 1, 2 or 3 substituents independently selected from hydroxy, halo, carboxy and C_{1-3} alkoxy; and optionally substituted, on an available nitrogen, by a substituent independently selected from C_{1-4} alkyl and C_{2-4} alkanoyl;
- R^{11} is selected from hydrogen, C_{1-6} alkyl, C_{3-7} cycloalkyl, heterocyclyl and C_{3-7} cycloalkyl C_{1-3} alkyl, C_{3-7} cycloalkyl C_{2-3} alkenyl and C_{3-7} cycloalkyl C_{2-3} alkynyl, [each of which is optionally substituted, on available carbon atoms, by 1, 2 or 3 substituents independently selected from C_{1-3} alkyl, hydroxy, halo, oxo, cyano, trifluoromethyl, C_{1-3} alkoxy, C_{1-3} alkyl $S(O)_q$ - (wherein q is 0, 1, 2 or 3), $R^{14}CON(R^{14'})$ -, $(R^{14'})(R^{14''})NC(O)$ -, $(R^{14'})(R^{14''})NC(O)N(R^{14'''})$ -, $R^{14}SO_2N(R^{14''})$ - and $(R^{14'})(R^{14''})NSO_2$ - (wherein R^{14} is

C₁₋₃alkyl optionally substituted by 1, 2 or 3 substituents independently selected from hydroxyl, halo and cyano; and

R^{14'}, R^{14''} and R^{14'''} are independently selected from hydrogen and C₁₋₃alkyl optionally substituted by 1, 2 or 3 substituents independently selected from hydroxyl, halo,

5 C₁₋₃alkoxy, carboxy and cyano or R^{14'} and R^{14''} together with the nitrogen atom to which they are attached form a 4-7 membered saturated ring) and optionally substituted, on an available nitrogen, by a substituent independently selected from C₁₋₄alkyl and C₂₋₄alkanoyl]; and

R¹² is selected from hydrogen, C₁₋₄alkyl, C₃₋₅cycloalkyl and C₃₋₅cycloalkylmethyl (each of which is optionally substituted by 1, 2 or 3 fluoro atoms); or

R¹¹ and R¹² together with the nitrogen atom to which they are attached form a saturated mono, bicyclic or bridged ring system optionally containing 1 or 2 additional ring heteroatoms independently selected from nitrogen, oxygen and sulphur and optionally fused to a saturated, partially saturated or unsaturated monocyclic ring (optionally containing 1 or 2 additional ring heteroatoms independently selected from nitrogen, oxygen and sulphur) wherein the resulting ring system is optionally substituted on available carbon atoms, by 1, 2, or 3 substituents independently selected from R¹⁵ and optionally substituted, on an available nitrogen, by a substituent independently selected from C₁₋₄alkyl and C₂₋₄alkanoyl;

20 R⁶, R⁷, R⁹ and R¹⁵ are independently selected from hydroxyl, halo, oxo, carboxy, cyano, trifluoromethyl, R¹⁶, R¹⁶O- and R¹⁶CO-,

R¹⁶ is independently selected from, C₁₋₃alkyl optionally substituted by 1, 2 or 3 substituents independently selected from hydroxyl, halo, C₁₋₄alkoxy, carboxy and cyano; or a pharmaceutically-acceptable salt thereof;

25 provided that:

when -QR¹ is N-(3-chloro-4-methoxybenzyl)amino then -NR²R³ is not N-(4-hydroxycyclohexyl)amino.

Another class of compound is that of formula **(1)** wherein:

30 Q is O, S, N(R⁸) or a single bond;

R⁸ is selected from hydrogen, C₁₋₄alkyl;

R¹ is selected from C₁₋₆alkyl, C₃₋₇cycloalkyl, heterocyclyl, arylC₁₋₃alkyl, heteroarylC₁₋₃alkyl and C₃₋₇cycloalkylC₁₋₃alkyl [each of which is optionally substituted, on available carbon atoms, by 1, 2 or 3 substituents independently selected from C₁₋₃alkyl, halo, cyano, trifluoromethyl, C₁₋₃alkoxy and C₁₋₂alkyl optionally substituted by 1, 2 or 3 substituents independently selected from hydroxy, halo, carboxy and C₁₋₃alkoxy; and optionally substituted, on an available nitrogen, by a substituent independently selected from C₁₋₄alkyl and C₂₋₄alkanoyl; provided that when Q is a single bond R¹ is not methyl; or
R¹ and **R⁸** together with the nitrogen atom to which they are attached form a saturated mono, bicyclic or bridged ring system optionally containing 1 or 2 additional ring heteroatoms independently selected from nitrogen, oxygen and sulphur and optionally fused to a saturated, partially saturated or unsaturated monocyclic ring wherein the resulting ring system is optionally substituted, on available carbon atoms, by 1, 2, or 3 substituents independently selected from R⁹ and optionally substituted, on an available nitrogen, by a substituent independently selected from C₁₋₄alkyl and C₂₋₄alkanoyl;
R² is selected from C₃₋₇cycloalkyl(CH₂)_m-, and C₆₋₁₂polycycloalkyl(CH₂)_m- (wherein the rings are optionally substituted by 1, 2 or 3 substituents independently selected from R⁶);
R³ is selected from hydrogen;
R⁴ is selected from hydrogen, R¹⁰, -OR¹⁰ and -NR¹¹R¹²;
R¹⁰ is selected from C₁₋₆alkyl, C₃₋₇cycloalkyl, heterocyclyl, arylC₁₋₃alkyl, heteroarylC₁₋₃alkyl and C₃₋₇cycloalkylC₁₋₃alkyl [each of which is optionally substituted, on available carbon atoms, by 1, 2 or 3 substituents independently selected from C₁₋₃alkyl, halo, cyano, trifluoromethyl, C₁₋₃alkoxy and C₁₋₂alkyl optionally substituted by 1, 2 or 3 substituents independently selected from hydroxy, halo, carboxy and C₁₋₃alkoxy; and optionally substituted, on an available nitrogen, by a substituent independently selected from C₁₋₄alkyl and C₂₋₄alkanoyl;
R¹¹ is selected from hydrogen, C₁₋₆alkyl, C₃₋₇cycloalkyl, heterocyclyl and C₃₋₇cycloalkylC₁₋₃alkyl, C₃₋₇cycloalkylC₂₋₃alkenyl and C₃₋₇cycloalkylC₂₋₃alkynyl, [each of which is optionally substituted, on available carbon atoms, by 1, 2 or 3 substituents independently selected from C₁₋₃alkyl, hydroxy, halo, oxo, cyano, trifluoromethyl, C₁₋₃alkoxy, C₁₋₃alkylS(O)_q- (wherein q is 0, 1, 2 or 3), R¹⁴CON(R^{14'})-, (R^{14'})(R^{14''})NC(O)-, (R^{14'})(R^{14''})NC(O)N(R^{14'''})-, R¹⁴SO₂N(R^{14''})- and (R^{14'})(R^{14''})NSO₂- (wherein R¹⁴ is

C₁₋₃alkyl optionally substituted by 1, 2 or 3 substituents independently selected from hydroxyl, halo and cyano; and

R^{14'}, R^{14''} and R^{14'''} are independently selected from hydrogen and C₁₋₃alkyl optionally substituted by 1, 2 or 3 substituents independently selected from hydroxyl, halo,

5 C₁₋₃alkoxy, carboxy and cyano or R^{14'} and R^{14''} together with the nitrogen atom to which they are attached form a 4-7 membered saturated ring) and optionally substituted, on an available nitrogen, by a substituent independently selected from C₁₋₄alkyl and C₂₋₄alkanoyl]; and

R¹² is selected from hydrogen, C₁₋₄alkyl, C₃₋₅cycloalkyl and C₃₋₅cycloalkylmethyl (each of which is optionally substituted by 1, 2 or 3 fluoro atoms); or

R¹¹ and R¹² together with the nitrogen atom to which they are attached form a saturated mono, bicyclic or bridged ring system optionally containing 1 or 2 additional ring heteroatoms independently selected from nitrogen, oxygen and sulphur and optionally fused to a saturated, partially saturated or unsaturated monocyclic ring (optionally containing 1 or 2 additional ring heteroatoms independently selected from nitrogen, oxygen and sulphur) wherein the resulting ring system is optionally substituted on available carbon atoms, by 1, 2, or 3 substituents independently selected from R¹⁵ and optionally substituted, on an available nitrogen, by a substituent independently selected from C₁₋₄alkyl and C₂₋₄alkanoyl;

20 R⁶, R⁷, R⁹ and R¹⁵ are independently selected from hydroxyl, halo, oxo, carboxy, cyano, trifluoromethyl, R¹⁶, R¹⁶O- and R¹⁶CO-,

R¹⁶ is independently selected from, C₁₋₃alkyl optionally substituted by 1, 2 or 3 substituents independently selected from hydroxyl, halo, C₁₋₄alkoxy, carboxy and cyano; or a pharmaceutically-acceptable salt thereof;

25 provided that:

when -QR¹ is N-(3-chloro-4-methoxybenzyl)amino then -NR²R³ is not N-(4-hydroxycyclohexyl)amino.

Yet another class of compound is that of formula **(1)** wherein:

Q is a single bond;

30 **R¹** is selected from C₁₋₆alkyl, C₃₋₇cycloalkyl, heterocyclyl, arylC₁₋₃alkyl, heteroarylC₁₋₃alkyl and C₃₋₇cycloalkylC₁₋₃alkyl [each of which is optionally substituted, on available carbon atoms, by 1, 2 or 3 substituents independently selected from C₁₋₃alkyl,

halo, cyano, trifluoromethyl, C₁₋₃alkoxy and C₁₋₂alkyl optionally substituted by 1, 2 or 3 substituents independently selected from hydroxy, halo, carboxy and C₁₋₃alkoxy; and optionally substituted, on an available nitrogen, by a substituent independently selected from C₁₋₄alkyl and C₂₋₄alkanoyl;

5 **R²** is adamantyl optionally substituted by 1, 2 or 3 substituents independently selected from R⁶;

R³ is hydrogen;

R⁴ is selected from hydrogen, R¹⁰, -SR¹⁰, -OR¹⁰ and -NR¹¹R¹²;

R¹⁰ is selected from C₁₋₆alkyl, C₃₋₇cycloalkyl, heterocyclyl, arylC₁₋₃alkyl,

10 heteroarylC₁₋₃alkyl and C₃₋₇cycloalkylC₁₋₃alkyl [each of which is optionally substituted, on available carbon atoms, by 1, 2 or 3 substituents independently selected from C₁₋₃alkyl, halo, cyano, trifluoromethyl, C₁₋₃alkoxy and C₁₋₂alkyl optionally substituted by 1, 2 or 3 substituents independently selected from hydroxy, halo, carboxy and C₁₋₃alkoxy; and optionally substituted, on an available nitrogen, by a substituent independently selected

15 from C₁₋₄alkyl and C₂₋₄alkanoyl;

R¹¹ is selected from hydrogen, C₁₋₆alkyl, C₃₋₇cycloalkyl, heterocyclyl and C₃₋

7cycloalkylC₁₋₃alkyl, C₃₋₇cycloalkylC₂₋₃alkenyl and C₃₋₇cycloalkylC₂₋₃alkynyl, [each of which is optionally substituted, on available carbon atoms, by 1, 2 or 3 substituents

independently selected from C₁₋₃alkyl, hydroxy, halo, oxo, cyano, trifluoromethyl,

20 C₁₋₃alkoxy, C₁₋₃alkylS(O)_q- (wherein q is 0, 1, 2 or 3), R¹⁴CON(R^{14'})-, (R^{14'})(R^{14''})NC(O)-, (R^{14'})(R^{14''})NC(O)N(R^{14'''})-, R¹⁴SO₂N(R^{14''})- and (R^{14'})(R^{14''})NSO₂- (wherein R¹⁴ is C₁₋₃alkyl optionally substituted by 1, 2 or 3 substituents independently selected from hydroxyl, halo and cyano; and

R^{14'}, R^{14''} and R^{14'''} are independently selected from hydrogen and C₁₋₃alkyl optionally

25 substituted by 1, 2 or 3 substituents independently selected from hydroxyl, halo,

C₁₋₃alkoxy, carboxy and cyano or R^{14'} and R^{14''} together with the nitrogen atom to which they are attached form a 4-7 membered saturated ring) and optionally substituted, on an available nitrogen, by a substituent independently selected from C₁₋₄alkyl and C₂₋₄alkanoyl]; and

30 R¹² is selected from hydrogen, C₁₋₄alkyl, C₃₋₅cycloalkyl and C₃₋₅cycloalkylmethyl (each of which is optionally substituted by 1, 2 or 3 fluoro atoms); or

R^{11} and R^{12} together with the nitrogen atom to which they are attached form a saturated mono, bicyclic or bridged ring system optionally containing 1 or 2 additional ring heteroatoms independently selected from nitrogen, oxygen and sulphur and optionally fused to a saturated, partially saturated or unsaturated monocyclic ring (optionally containing 1 or 2 additional ring heteroatoms independently selected from nitrogen, oxygen and sulphur) wherein the resulting ring system is optionally substituted on available carbon atoms, by 1, 2, or 3 substituents independently selected from R^{15} and optionally substituted, on an available nitrogen, by a substituent independently selected from C_{1-4} alkyl and C_{2-4} alkanoyl;

R^6 and R^{15} are independently selected from hydroxyl, halo, oxo, carboxy, cyano, trifluoromethyl, R^{16} , $R^{16}O^-$ and $R^{16}CO^-$,
 R^{16} is independently selected from, C_{1-3} alkyl optionally substituted by 1, 2 or 3 substituents independently selected from hydroxyl, halo, C_{1-4} alkoxy, carboxy and cyano; or a pharmaceutically-acceptable salt thereof.

Yet another class of compound is that of formula **(1)** wherein:

Q is a single bond;

R¹ is selected from C_{3-7} cycloalkyl and heterocyclyl [each of which is optionally substituted, on available carbon atoms, by 1, 2 or 3 substituents independently selected from C_{1-3} alkyl, halo, cyano, trifluoromethyl, C_{1-3} alkoxy and C_{1-2} alkyl optionally substituted by 1, 2 or 3 substituents independently selected from hydroxy, halo, carboxy and C_{1-3} alkoxy; and optionally substituted, on an available nitrogen, by a substituent independently selected from C_{1-4} alkyl and C_{2-4} alkanoyl;

R² is adamantyl optionally substituted by 1, 2 or 3 substituents independently selected from R^6 ;

R³ is hydrogen;

R⁴ is selected from R^{10} and $-NR^{11}R^{12}$;

R^{10} is selected from C_{1-6} alkyl, C_{3-7} cycloalkyl and heterocyclyl [each of which is optionally substituted, on available carbon atoms, by 1, 2 or 3 substituents independently selected from C_{1-3} alkyl, halo, cyano, trifluoromethyl, C_{1-3} alkoxy and C_{1-2} alkyl optionally substituted by 1, 2 or 3 substituents independently selected from hydroxy, halo, carboxy and C_{1-3} alkoxy; and optionally substituted, on an available nitrogen, by a substituent independently selected from C_{1-4} alkyl and C_{2-4} alkanoyl;

- R^{11} is selected from hydrogen, C_{1-6} alkyl, C_{3-7} cycloalkyl, heterocyclyl [each of which is optionally substituted, on available carbon atoms, by 1, 2 or 3 substituents independently selected from C_{1-3} alkyl, hydroxy, halo, oxo, cyano, trifluoromethyl, C_{1-3} alkoxy, C_{1-3} alkylS(O)_q- (wherein q is 0, 1, 2 or 3), $R^{14'}CON(R^{14'})$ -, $(R^{14'})(R^{14''})NC(O)$ -, $(R^{14'})(R^{14''})NC(O)N(R^{14'''})$ -, $R^{14'}SO_2N(R^{14'})$ - and $(R^{14'})(R^{14''})NSO_2$ - (wherein $R^{14'}$ is C_{1-3} alkyl optionally substituted by 1, 2 or 3 substituents independently selected from hydroxyl, halo and cyano; and $R^{14'}$, $R^{14''}$ and $R^{14'''}$ are independently selected from hydrogen and C_{1-3} alkyl optionally substituted by 1, 2 or 3 substituents independently selected from hydroxyl, halo, C_{1-3} alkoxy, carboxy and cyano or $R^{14'}$ and $R^{14''}$ together with the nitrogen atom to which they are attached form a 4-7 membered saturated ring) and optionally substituted, on an available nitrogen, by a substituent independently selected from C_{1-4} alkyl and C_{2-4} alkanoyl];
- R^{12} is selected from hydrogen and C_{1-3} alkyl; or
- R^{11} and R^{12} together with the nitrogen atom to which they are attached form a saturated monocyclic ring system optionally containing 1 or 2 additional ring heteroatoms independently selected from nitrogen, oxygen and sulphur and optionally fused to a saturated, partially saturated or unsaturated monocyclic ring (optionally containing 1 or 2 additional ring heteroatoms independently selected from nitrogen, oxygen and sulphur) wherein the resulting ring system is optionally substituted on available carbon atoms, by 1, 2, or 3 substituents independently selected from R^{15} and optionally substituted, on an available nitrogen, by a substituent independently selected from C_{1-4} alkyl and C_{2-4} alkanoyl; R^6 and R^{15} are independently selected from hydroxyl, halo, oxo, carboxy, cyano, trifluoromethyl, R^{16} , $R^{16}O$ - and $R^{16}CO$ -,
- R^{16} is independently selected from, C_{1-3} alkyl optionally substituted by 1, 2 or 3 substituents independently selected from hydroxyl, halo, C_{1-4} alkoxy, carboxy and cyano; or a pharmaceutically-acceptable salt thereof.

Yet another class of compound is that of formula **(1)** wherein:

- Q** is a single bond;
- R^1 is selected from C_{3-7} cycloalkyl and heterocyclyl [each of which is optionally substituted, on available carbon atoms, by 1, 2 or 3 substituents independently selected from C_{1-3} alkyl, halo, cyano, trifluoromethyl, C_{1-3} alkoxy and C_{1-2} alkyl optionally

substituted by 1, 2 or 3 substituents independently selected from hydroxy, halo, carboxy and C₁₋₃alkoxy; and optionally substituted, on an available nitrogen, by a substituent independently selected from C₁₋₄alkyl and C₂₋₄alkanoyl;

R² is adamantyl optionally substituted by 1, 2 or 3 substituents independently selected from R⁶;

R³ is hydrogen;

R⁴ is selected from R¹⁰ and -NR¹¹R¹²;

R¹⁰ is selected from C₁₋₆alkyl, C₃₋₇cycloalkyl and heterocyclyl [each of which is optionally substituted, on available carbon atoms, by 1, 2 or 3 substituents independently selected

from C₁₋₃alkyl, halo, cyano, trifluoromethyl, C₁₋₃alkoxy and C₁₋₂alkyl optionally substituted by 1, 2 or 3 substituents independently selected from hydroxy, halo, carboxy and C₁₋₃alkoxy; and optionally substituted, on an available nitrogen, by a substituent independently selected from C₁₋₄alkyl and C₂₋₄alkanoyl;

R¹¹ is selected from hydrogen, C₁₋₆alkyl, C₃₋₇cycloalkyl, heterocyclyl [each of which is optionally substituted, on available carbon atoms, by 1, 2 or 3 substituents independently selected from C₁₋₃alkyl, hydroxy, halo, oxo, cyano, trifluoromethyl, C₁₋₃alkoxy, C₁₋₃alkylS(O)_q- (wherein q is 0, 1, 2 or 3), R¹⁴CON(R^{14'})-, (R^{14'})(R^{14''})NC(O)-, (R^{14'})(R^{14''})NC(O)N(R^{14'''})-, R¹⁴SO₂N(R^{14''})- and (R^{14'})(R^{14''})NSO₂- (wherein R¹⁴ is C₁₋₃alkyl optionally substituted by 1, 2 or 3 substituents independently selected from

hydroxyl, halo and cyano; and

R^{14'}, R^{14''} and R^{14'''} are independently selected from hydrogen and C₁₋₃alkyl optionally substituted by 1, 2 or 3 substituents independently selected from hydroxyl, halo, C₁₋₃alkoxy, carboxy and cyano or R^{14'} and R^{14''} together with the nitrogen atom to which they are attached form a 4-7 membered saturated ring) and optionally substituted, on an available nitrogen, by a substituent independently selected from C₁₋₄alkyl and C₂₋₄alkanoyl];

R¹² is selected from hydrogen and C₁₋₃alkyl; or

R¹¹ and R¹² together with the nitrogen atom to which they are attached form a saturated monocyclic ring system optionally containing 1 or 2 additional ring heteroatoms independently selected from nitrogen, oxygen and sulphur and optionally fused to a saturated, partially saturated or unsaturated monocyclic ring (optionally containing 1 or 2 additional ring heteroatoms independently selected from nitrogen, oxygen and sulphur)

wherein the resulting ring system is optionally substituted on available carbon atoms, by 1, 2, or 3 substituents independently selected from R^{15} and optionally substituted, on an available nitrogen, by a substituent independently selected from C_{1-4} alkyl and C_{2-4} alkanoyl; R^6 and R^{15} are independently selected from hydroxyl, halo, oxo, carboxy, cyano, trifluoromethyl, R^{16} , $R^{16}O-$ and $R^{16}CO-$,
 5 R^{16} is independently selected from, C_{1-3} alkyl optionally substituted by 1, 2 or 3 substituents independently selected from hydroxyl, halo, C_{1-4} alkoxy, carboxy and cyano; or a pharmaceutically-acceptable salt thereof.

Yet another class of compound is that of formula **(1)** wherein:

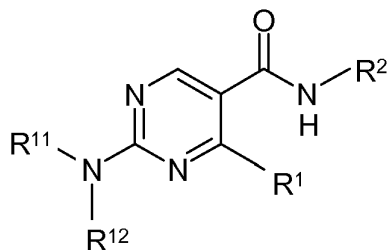
- 10 **Q** is a single bond;
R¹ is selected from C_{3-7} cycloalkyl and heterocyclcyl [each of which is optionally substituted, on available carbon atoms, by 1, 2 or 3 substituents independently selected from C_{1-3} alkyl, halo, cyano, trifluoromethyl, C_{1-3} alkoxy and C_{1-2} alkyl optionally substituted by 1, 2 or 3 substituents independently selected from hydroxy, halo, carboxy
 15 and C_{1-3} alkoxy; and optionally substituted, on an available nitrogen, by a substituent independently selected from C_{1-4} alkyl and C_{2-4} alkanoyl;
R² is adamantyl optionally substituted by 1 hydroxy group;
R³ is hydrogen;
R⁴ is $-NR^{11}R^{12}$;
 20 **R¹¹** is selected from hydrogen, C_{1-6} alkyl, C_{3-7} cycloalkyl, heterocyclcyl [each of which is optionally substituted, on available carbon atoms, by 1, 2 or 3 substituents independently selected from C_{1-3} alkyl, hydroxy, halo, oxo, cyano, trifluoromethyl, C_{1-3} alkoxy, C_{1-3} alkylS(O)_q- (wherein q is 0, 1, 2 or 3), $R^{14}CON(R^{14'})-$, $(R^{14'})(R^{14''})NC(O)-$, $(R^{14'})(R^{14''})NC(O)N(R^{14''''})-$, $R^{14}SO_2N(R^{14''})-$ and $(R^{14'})(R^{14''})NSO_2-$ (wherein R^{14} is
 25 C_{1-3} alkyl optionally substituted by 1, 2 or 3 substituents independently selected from hydroxyl, halo and cyano; and
R^{14'}, **R^{14''}** and **R^{14'''}** are independently selected from hydrogen and C_{1-3} alkyl optionally substituted by 1, 2 or 3 substituents independently selected from hydroxyl, halo, C_{1-3} alkoxy, carboxy and cyano) and optionally substituted, on an available nitrogen, by a
 30 substituent independently selected from C_{1-4} alkyl and C_{2-4} alkanoyl];
R¹² is hydrogen; or

R^{11} and R^{12} together with the nitrogen atom to which they are attached form a saturated monocyclic ring system optionally containing 1 or 2 additional ring heteroatoms independently selected from nitrogen, oxygen and sulphur and wherein the ring system is optionally substituted on available carbon atoms, by 1, 2, or 3 substituents independently selected from R^{15} and optionally substituted, on an available nitrogen, by a substituent

independently selected from C_{1-4} alkyl and C_{2-4} alkanoyl;
 R^6 and R^{15} are independently selected from hydroxyl, halo, oxo, carboxy, cyano, trifluoromethyl, R^{16} , $R^{16}O^-$ and $R^{16}CO^-$,

R^{16} is independently selected from, C_{1-3} alkyl optionally substituted by 1, 2 or 3 substituents independently selected from hydroxyl, halo, C_{1-4} alkoxy, carboxy and cyano; or a pharmaceutically-acceptable salt thereof.

In another aspect the invention relates to a compound of the formula (IA):



wherein R^2 is adamantyl optionally substituted by hydroxy and R^1 , R^{11} and R^{12} are as hereinabove defined.

In another aspect, the invention relates to a compound of the formula 1 as hereinabove defined or a pharmaceutically-acceptable salt thereof excluding any one of the Examples and pharmaceutically-acceptable salts thereof.

In another aspect of the invention, suitable compounds of the invention are any one or more of the Examples or a pharmaceutically-acceptable salt thereof.

In another aspect of the invention, suitable compounds of the invention are any one or more of the following or a pharmaceutically-acceptable salt thereof:

4-cyclopropyl-N-[(2s,5r)-5-hydroxyadamantan-2-yl]-2-morpholin-4-ylpyrimidine-5-carboxamide;

4-cyclopropyl-N-[(2r,5s)-5-hydroxyadamantan-2-yl]-2-methylpyrimidine-5-carboxamide;

4-cyclopropyl-N-[(2r,5s)-5-hydroxyadamantan-2-yl]pyrimidine-5-carboxamide;

4-tert-butyl-N-[(2r,5s)-5-hydroxyadamantan-2-yl]-2-morpholin-4-ylpyrimidine-5-carboxamide;

- N-[(2r,5s)-5-hydroxyadamantan-2-yl]-4-methyl-2-morpholin-4-ylpyrimidine-5-carboxamide;
- 4-tert-butyl-N-[(2r,5s)-5-hydroxyadamantan-2-yl]-2-methylpyrimidine-5-carboxamide;
- 4-tert-butyl-N-[(2r,5s)-5-hydroxyadamantan-2-yl]pyrimidine-5-carboxamide;
- 5 N-[(2r,5s)-5-hydroxyadamantan-2-yl]-2-morpholin-4-yl-4-propylsulfanyl-pyrimidine-5-carboxamide;
- N-[(2r,5s)-5-hydroxyadamantan-2-yl]-2-methyl-4-propylsulfanylpyrimidine-5-carboxamide;
- N-[(2r,5s)-5-hydroxyadamantan-2-yl]-4-propylsulfanylpyrimidine-5-carboxamide;
- 10 4-cyclopropyl-N-[(2r,5s)-5-hydroxyadamantan-2-yl]-2-methylsulfanyl-pyrimidine-5-carboxamide;
- N-(2-adamantyl)-4-cyclopropyl-2-methyl-pyrimidine-5-carboxamide;
- N-(2-adamantyl)-4-cyclopropyl-2-morpholino-pyrimidine-5-carboxamide;
- N-(2-adamantyl)-4-tert-butyl-2-morpholin-4-ylpyrimidine-5-carboxamide;
- 15 N-(2-adamantyl)-4-methyl-2-morpholin-4-ylpyrimidine-5-carboxamide;
- N-[(2r,5s)-5-hydroxyadamantan-2-yl]-2,4-bis(propylsulfanyl)pyrimidine-5-carboxamide;
- 2-dimethylamino-N-[(2r,5s)-5-hydroxyadamantan-2-yl]-4-propylsulfanylpyrimidine-5-carboxamide;
- 4-dimethylamino-N-[(2r,5s)-5-hydroxyadamantan-2-yl]-2-propylsulfanylpyrimidine-5-
- 20 carboxamide;
- {(3S)-1-[5-(cyclohexylcarbamoyl)-4-(propylthio)pyrimidin-2-yl]piperidin-3-yl}acetic acid;
- N-[(2r,5s)-5-hydroxyadamantan-2-yl]-2-methylamino-4-propylsulfanylpyrimidine-5-carboxamide;
- N-[(2r,5s)-5-hydroxyadamantan-2-yl]-4-methylamino-2-propylsulfanylpyrimidine-5-
- 25 carboxamide;
- 2-[(2S,6R)-2,6-dimethylmorpholin-4-yl]-N-[(2r,5s)-5-hydroxyadamantan-2-yl]-4-propylsulfanylpyrimidine-5-carboxamide;
- 4-[(2S,6R)-2,6-dimethylmorpholin-4-yl]-N-[(2r,5s)-5-hydroxyadamantan-2-yl]-2-propylsulfanylpyrimidine-5-carboxamide;
- 30 4-(4-acetylpiperazin-1-yl)-N-[(2r,5s)-5-hydroxyadamantan-2-yl]-2-propylsulfanylpyrimidine-5-carboxamide;

- 2-(4-acetylpiperazin-1-yl)-N-[(2r,5s)-5-hydroxyadamantan-2-yl]-4-propylsulfanylpurimidine-5-carboxamide;
- 2-(4-acetylpiperazin-1-yl)-N-(2-adamantyl)-4-propylsulfanyl-purimidine-5-carboxamide;
- N-(2-adamantyl)-2-(4-methylsulfonylpiperazin-1-yl)-4-propylsulfanyl-purimidine-5-
- 5 carboxamide;
- N-(2-adamantyl)-2-[4-(dimethylcarbamoyle)piperazin-1-yl]-4-propylsulfanyl-purimidine-5-carboxamide;
- 4-cyclopentyl-N-[(2s,5r)-5-hydroxyadamantan-2-yl]-2-morpholin-4-ylpurimidine-5-carboxamide;
- 10 N-[(2s,5r)-5-hydroxyadamantan-2-yl]-2-morpholin-4-yl-4-propoxypurimidine-5-carboxamide;
- 4-cyclopropyl-N-[(2r,5s)-5-hydroxyadamantan-2-yl]-2-[(3R)-oxolan-3-ylamino]purimidine-5-carboxamide;
- N-[(2r,5s)-5-hydroxyadamantan-2-yl] 4-cyclopropyl-2-[(3S)-oxolan-3-
- 15 yl]amino]purimidine-5-carboxamide;
- N-[(2s,5r)-5-hydroxyadamantan-2-yl]-2,4-dimorpholin-4-ylpurimidine-5-carboxamide;
- 4-cyclopropyl-N-[(2r,5s)-5-hydroxyadamantan-2-yl]-2-methoxypurimidine-5-carboxamide;
- 4-cyclopropyl-N-[(2r,5s)-5-hydroxyadamantan-2-yl]-2-methylaminopurimidine-5-
- 20 carboxamide;
- 4-cyclopropyl-N-[(2r,5s)-5-hydroxyadamantan-2-yl]-2-thiomorpholin-4-ylpurimidine-5-carboxamide
- 4-cyclopropyl-N-[(2r,5s)-5-hydroxyadamantan-2-yl]-2-(1-oxo-1,4-thiazinan-4-yl)purimidine-5-carboxamide;
- 25 4-cyclopropyl-2-(1,1-dioxo-1,4-thiazinan-4-yl)-N-[(2r,5s)-5-hydroxyadamantan-2-yl]purimidine-5-carboxamide;
- 4-cyclohexyl-N-[(2r,5s)-5-hydroxyadamantan-2-yl]-2-morpholin-4-ylpurimidine-5-carboxamide;
- 4-cyclopentyl-N-[(2r,5s)-5-hydroxyadamantan-2-yl]-2-methylpurimidine-5-carboxamide;
- 30 4-cyclobutyl-N-[(2r,5s)-5-hydroxyadamantan-2-yl]-2-morpholin-4-ylpurimidine-5-carboxamide;

- 4-cyclobutyl-N-[(2r,5s)-5-hydroxyadamantan-2-yl]-2-thiomorpholin-4-ylpyrimidine-5-carboxamide
- 4-cyclopropyl-2-(2,6-dimethylmorpholin-4-yl)-N-[(2r,5s)-5-hydroxyadamantan-2-yl]pyrimidine-5-carboxamide;
- 5 4-cyclopropyl-2-(3,3-difluoroazetidin-1-yl)-N-[(2r,5s)-5-hydroxyadamantan-2-yl]pyrimidine-5-carboxamide;
- 2-(azetidin-1-yl)-4-cyclopropyl-N-[(2r,5s)-5-hydroxyadamantan-2-yl]pyrimidine-5-carboxamide;
- 2-(cyclobutylamino)-4-cyclopropyl-N-[(2r,5s)-5-hydroxyadamantan-2-yl]pyrimidine-5-
- 10 carboxamide;
- 4-cyclopropyl-N-[(2r,5s)-5-hydroxyadamantan-2-yl]-2-[4-(2-methoxyethyl)piperazin-1-yl]pyrimidine-5-carboxamide;
- 4-cyclopropyl-2-(cyclopropylamino)-N-[(2r,5s)-5-hydroxyadamantan-2-yl]pyrimidine-5-carboxamide;
- 15 2-(cyclopentylamino)-4-cyclopropyl-N-[(2r,5s)-5-hydroxyadamantan-2-yl]pyrimidine-5-carboxamide;
- 4-cyclopropyl-N-[(2r,5s)-5-hydroxyadamantan-2-yl]-2-[(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl]pyrimidine-5-carboxamide;
- 4-cyclopropyl-N-[(2r,5s)-5-hydroxyadamantan-2-yl]-2-[2-(hydroxymethyl)morpholin-4-
- 20 yl]pyrimidine-5-carboxamide;
- 4-cyclopropyl-N-[(2r,5s)-5-hydroxyadamantan-2-yl]-2-[3-(hydroxymethyl)morpholin-4-yl]pyrimidine-5-carboxamide;
- 4-cyclopropyl-2-(dimethylamino)-N-[(2r,5s)-5-hydroxyadamantan-2-yl]pyrimidine-5-carboxamide;
- 25 4-cyclopropyl-2-[(3R,5S)-3,5-dimethylpiperazin-1-yl]-N-[(2r,5s)-5-hydroxyadamantan-2-yl]pyrimidine-5-carboxamide;
- 4-cyclopropyl-2-[(2R,6R)-2,6-dimethylmorpholin-4-yl]-N-[(2r,5s)-5-hydroxyadamantan-2-yl]pyrimidine-5-carboxamide;
- 4-cyclopropyl-N-[(2r,5s)-5-hydroxyadamantan-2-yl]-2-(isopropylamino)pyrimidine-5-
- 30 carboxamide;
- 4-cyclopropyl-N-[(2r,5s)-5-hydroxyadamantan-2-yl]-2-[(2-hydroxy-1,1-dimethylethyl)amino]pyrimidine-5-carboxamide;

- 4-cyclopropyl-N-[(2r,5s)-5-hydroxyadamantan-2-yl]-2-(tetrahydro-2H-pyran-4-ylamino)pyrimidine-5-carboxamide;
- 4-cyclopropyl-N-[(2r,5s)-5-hydroxyadamantan-2-yl]-2-[(2-hydroxy-2-methylpropyl)amino]pyrimidine-5-carboxamide;
- 5 4-cyclopropyl-2-[(1,1-dioxidotetrahydro-2H-thiopyran-4-yl)amino]-N-[(2r,5s)-5-hydroxyadamantan-2-yl]pyrimidine-5-carboxamide;
- 4-cyclopropyl-N-[(2r,5s)-5-hydroxyadamantan-2-yl]-2-[(2-hydroxyethyl)amino]pyrimidine-5-carboxamide;
- 4-cyclopropyl-N-[(2r,5s)-5-hydroxyadamantan-2-yl]-2-(4-methylsulfonylpiperazin-1-yl)pyrimidine-5-carboxamide;
- 10 4-cyclopropyl-N-[(2r,5s)-5-hydroxyadamantan-2-yl]-2-(oxetan-3-ylamino)pyrimidine-5-carboxamide;
- 4-cyclopropyl-N-[(2r,5s)-5-hydroxyadamantan-2-yl]-2-[(2-morpholin-4-ylethyl)amino]pyrimidine-5-carboxamide;
- 15 4-cyclopropyl-2-({2-[(2R,6S)-2,6-dimethylmorpholin-4-yl]ethyl}amino)-N-[(2r,5s)-5-hydroxyadamantan-2-yl]pyrimidine-5-carboxamide;
- 4-cyclopropyl-N-[(2r,5s)-5-hydroxyadamantan-2-yl]-2-{[2-(4-methylpiperazin-1-yl)ethyl]amino}pyrimidine-5-carboxamide;
- 2-(cyclobutyloxy)-4-cyclopropyl-N-[(2r,5s)-5-hydroxyadamantan-2-yl]pyrimidine-5-
- 20 carboxamide;
- 4-cyclopropyl-N-[(2r,5s)-5-hydroxyadamantan-2-yl]-2-isopropoxypyrimidine-5-carboxamide;
- 2-(cyclopentyloxy)-4-cyclopropyl-N-[(2r,5s)-5-hydroxyadamantan-2-yl]pyrimidine-5-carboxamide;
- 25 4-cyclopropyl-N-[(2r,5s)-5-hydroxyadamantan-2-yl]-2-(oxetan-3-yloxy)pyrimidine-5-carboxamide;
- (4-cyclopropyl-2-morpholinopyrimidin-5-yl)(3-(pyridin-3-yl)pyrrolidin-1-yl)methanone
- 1-(4-(4-cyclopropyl-5-(3-(pyridin-3-yl)pyrrolidine-1-carbonyl)pyrimidin-2-yl)piperazin-1-yl)ethanone;
- 30 (4-cyclopropyl-2-((2S,6R)-2,6-dimethylmorpholino)pyrimidin-5-yl)(3-(pyridin-3-yl)pyrrolidin-1-yl)methanone;
- 4-cyclobutyl-N-[(2r,5s)-5-hydroxyadamantan-2-yl]-2-(1-oxo-1,4-thiazinan-4-

- yl)pyrimidine-5-carboxamide;
4-cyclobutyl-2-(1,1-dioxo-1,4-thiazinan-4-yl)-N-[(2r,5s)-5-hydroxyadamantan-2-yl]pyrimidine-5-carboxamide;
2-amino-4-cyclobutyl-N-[(2r,5s)-5-hydroxyadamantan-2-yl]pyrimidine-5-carboxamide;
5 2-azetidin-1-yl-4-cyclobutyl-N-[(2r,5s)-5-hydroxyadamantan-2-yl]pyrimidine-5-carboxamide;
4-cyclobutyl-2-(dimethylamino)-N-[(2r,5s)-5-hydroxyadamantan-2-yl]pyrimidine-5-carboxamide;
4-cyclobutyl-N-[(2r,5s)-5-hydroxyadamantan-2-yl]-2-[4-(2-methoxyethyl)piperazin-1-yl]pyrimidine-5-carboxamide;
10 4-cyclobutyl-2-(cyclopropylamino)-N-[(2r,5s)-5-hydroxyadamantan-2-yl]pyrimidine-5-carboxamide;
4-cyclobutyl-2-(3,3-difluoroazetidin-1-yl)-N-[(2r,5s)-5-hydroxyadamantan-2-yl]pyrimidine-5-carboxamide;
15 4-cyclobutyl-N-[(2r,5s)-5-hydroxyadamantan-2-yl]-2-[3-(hydroxymethyl)morpholin-4-yl]pyrimidine-5-carboxamide;
4-cyclobutyl-N-[(2r,5s)-5-hydroxyadamantan-2-yl]-2-(methylamino)pyrimidine-5-carboxamide;
4-cyclobutyl-2-[(2R,6S)-2,6-dimethylmorpholin-4-yl]-N-[(2r,5s)-5-hydroxyadamantan-2-yl]pyrimidine-5-carboxamide;
20 4-cyclobutyl-N-[(2r,5s)-5-hydroxyadamantan-2-yl]-2-[2-(hydroxymethyl)morpholin-4-yl]pyrimidine-5-carboxamide;
4-cyclobutyl-N-[(2r,5s)-5-hydroxyadamantan-2-yl]-2-(isopropylamino)pyrimidine-5-carboxamide;
25 4-cyclobutyl-N-[(2r,5s)-5-hydroxyadamantan-2-yl]-2-[(2-hydroxy-1,1-dimethylethyl)amino]pyrimidine-5-carboxamide;
4-cyclobutyl-N-[(2r,5s)-5-hydroxyadamantan-2-yl]-2-(tetrahydro-2H-pyran-4-ylamino)pyrimidine-5-carboxamide;
4-cyclobutyl-N-[(2r,5s)-5-hydroxyadamantan-2-yl]-2-[(2-hydroxyethyl)amino]pyrimidine-5-carboxamide;
30 5-carboxamide;
N-[(2r,5s)-5-hydroxyadamantan-2-yl] 4-cyclobutyl-2-(cyclobutylamino) pyrimidine-5-carboxamide;

- 4-cyclobutyl-2-[(3R,5S)-3,5-dimethylpiperazin-1-yl]-N-[(2r,5s)-5-hydroxyadamantan-2-yl]pyrimidine-5-carboxamide;
- 4-cyclobutyl-N-[(2r,5s)-5-hydroxyadamantan-2-yl]-2-[(2-hydroxy-2-methylpropyl)amino]pyrimidine-5-carboxamide;
- 5 4-cyclobutyl-2-[(2R,6R)-2,6-dimethylmorpholin-4-yl]-N-[(2r,5s)-5-hydroxyadamantan-2-yl]pyrimidine-5-carboxamide;
- 4-cyclobutyl-2-(cyclopentylamino)-N-[(2r,5s)-5-hydroxyadamantan-2-yl]pyrimidine-5-carboxamide;
- 4-cyclobutyl-N-[(2r,5s)-5-hydroxyadamantan-2-yl]-2-[(1S,4S)-2-oxa-5-
- 10 azabicyclo[2.2.1]hept-5-yl]pyrimidine-5-carboxamide;
- 4-cyclobutyl-N-[(2r,5s)-5-hydroxyadamantan-2-yl]-2-(oxetan-3-ylamino)pyrimidine-5-carboxamide;
- 4-cyclobutyl-2-[(1,1-dioxidotetrahydro-2H-thiopyran-4-yl)amino]-N-[(2r,5s)-5-hydroxyadamantan-2-yl]pyrimidine-5-carboxamide;
- 15 4-cyclobutyl-2-(cyclopentyloxy)-N-[(2r,5s)-5-hydroxyadamantan-2-yl]pyrimidine-5-carboxamide;
- 4-cyclobutyl-N-[(2r,5s)-5-hydroxyadamantan-2-yl]-2-isopropoxypyrimidine-5-carboxamide;
- 4-cyclobutyl-2-(cyclobutyloxy)-N-[(2r,5s)-5-hydroxyadamantan-2-yl]pyrimidine-5-
- 20 carboxamide;
- 4-cyclobutyl-N-[(2r,5s)-5-hydroxyadamantan-2-yl]-2-(oxetan-3-yloxy)pyrimidine-5-carboxamide;
- 4-cyclopentyl-N-[(2r,5s)-5-hydroxyadamantan-2-yl]-2-propan-2-yloxypyrimidine-5-carboxamide;
- 25 2-cyclobutyloxy-4-cyclopentyl-N-[(2r,5s)-5-hydroxyadamantan-2-yl]pyrimidine-5-carboxamide;
- 4-cyclopentyl-2-cyclopentyloxy-N-[(2r,5s)-5-hydroxyadamantan-2-yl]pyrimidine-5-carboxamide;
- 4-cyclopentyl-N-[(2r,5s)-5-hydroxyadamantan-2-yl]-2-(oxetan-3-yloxy)pyrimidine-5-
- 30 carboxamide;
- 4-cyclopentyl-N-[(2s,5r)-5-hydroxyadamantan-2-yl]-2-thiomorpholin-4-ylpyrimidine-5-carboxamide;

- 4-cyclopentyl-N-[(2r,5s)-5-hydroxyadamantan-2-yl]-2-(1-oxo-1,4-thiazinan-4-yl)pyrimidine-5-carboxamide;
- 4-cyclopentyl-2-(1,1-dioxo-1,4-thiazinan-4-yl)-N-[(2r,5s)-5-hydroxyadamantan-2-yl]pyrimidine-5-carboxamide;
- 5 4-cyclopentyl-N-[(2r,5s)-5-hydroxyadamantan-2-yl]-2-methoxypyrimidine-5-carboxamide;
- 4-cyclopentyl-N-[(2r,5s)-5-hydroxyadamantan-2-yl]-2-methylaminopyrimidine-5-carboxamide;
- 4-cyclopentyl-2-[(2S,6R)-2,6-dimethylmorpholin-4-yl]-N-[(2r,5s)-5-hydroxyadamantan-2-yl]pyrimidine-5-carboxamide;
- 10 4-cyclopentyl-N-[(2r,5s)-5-hydroxyadamantan-2-yl]-2-[(1S,4S)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl]pyrimidine-5-carboxamide;
- 4-cyclopentyl-N-[(2r,5s)-5-hydroxyadamantan-2-yl]-2-(propan-2-ylamino)pyrimidine-5-carboxamide;
- 15 4-cyclopentyl-2-(cyclopropylamino)-N-[(2r,5s)-5-hydroxyadamantan-2-yl]pyrimidine-5-carboxamide;
- 4-cyclopentyl-N-[(2r,5s)-5-hydroxyadamantan-2-yl]-2-[(3S)-3-methylmorpholin-4-yl]pyrimidine-5-carboxamide;
- 4-cyclopentyl-2-[(2S,6S)-2,6-dimethylmorpholin-4-yl]-N-[(2r,5s)-5-hydroxyadamantan-2-yl]pyrimidine-5-carboxamide;
- 20 4-cyclopentyl-N-[(2r,5s)-5-hydroxyadamantan-2-yl]-2-[4-(2-methoxyethyl)piperazin-1-yl]pyrimidine-5-carboxamide;
- 2-(4-acetylpiperazin-1-yl)-4-cyclopentyl-N-[(2r,5s)-5-hydroxyadamantan-2-yl]pyrimidine-5-carboxamide;
- 25 4-cyclopentyl-N-[(2r,5s)-5-hydroxyadamantan-2-yl]-2-(3-oxo-4-propan-2-yl)piperazin-1-yl]pyrimidine-5-carboxamide;
- 4-cyclopentyl-N-[(2r,5s)-5-hydroxyadamantan-2-yl]-2-(4-methyl-3-oxopiperazin-1-yl)pyrimidine-5-carboxamide;
- 4-cyclopentyl-2-(cyclobutylamino)-N-[(2r,5s)-5-hydroxyadamantan-2-yl]pyrimidine-5-carboxamide;
- 30 4-cyclopentyl-2-(cyclopentylamino)-N-[(2r,5s)-5-hydroxyadamantan-2-yl]pyrimidine-5-carboxamide;

- 2-(azetidin-1-yl)-4-cyclopentyl-N-[(2r,5s)-5-hydroxyadamantan-2-yl]pyrimidine-5-carboxamide;
- 4-cyclopentyl-N-[(2r,5s)-5-hydroxyadamantan-2-yl]-2-(oxetan-3-ylamino)pyrimidine-5-carboxamide;
- 5 4-cyclopentyl-2-dimethylamino-N-[(2r,5s)-5-hydroxyadamantan-2-yl]pyrimidine-5-carboxamide;
- 4-cyclopentyl-2-[(3S,5R)-3,5-dimethylpiperazin-1-yl]-N-[(2r,5s)-5-hydroxyadamantan-2-yl]pyrimidine-5-carboxamide;
- 2-amino-4-cyclopentyl-N-[(2r,5s)-5-hydroxyadamantan-2-yl]pyrimidine-5-carboxamide;
- 10 4-cyclopentyl-2-[(1,1-dioxothian-4-yl)amino]-N-[(2r,5s)-5-hydroxyadamantan-2-yl]pyrimidine-5-carboxamide;
- 4-cyclopentyl-N-[(2r,5s)-5-hydroxyadamantan-2-yl]-2-[(2-hydroxy-2-methylpropyl)amino]pyrimidine-5-carboxamide;
- 4-cyclopentyl-N-[(2r,5s)-5-hydroxyadamantan-2-yl]-2-(2-hydroxyethylamino)pyrimidine-
- 15 5-carboxamide;
- 4-cyclopentyl-N-[(2r,5s)-5-hydroxyadamantan-2-yl]-2-[(1-hydroxy-2-methylpropan-2-yl)amino]pyrimidine-5-carboxamide;
- 4-cyclopentyl-N-[(2r,5s)-5-hydroxyadamantan-2-yl]-2-(oxan-4-ylamino)pyrimidine-5-carboxamide;
- 20 4-cyclopentyl-N-[(2r,5s)-5-hydroxyadamantan-2-yl]-2-[3-(hydroxymethyl)morpholin-4-yl]pyrimidine-5-carboxamide;
- 4-cyclopentyl-N-[(2r,5s)-5-hydroxyadamantan-2-yl]-2-[(3R)-oxolan-3-yl]amino]pyrimidine-5-carboxamide;
- 4-cyclopentyl-N-[(2r,5s)-5-hydroxyadamantan-2-yl]-2-(4-methylsulfonylpiperazin-1-
- 25 yl)pyrimidine-5-carboxamide;
- 4-cyclopentyl-N-[(2r,5s)-5-hydroxyadamantan-2-yl]-2-[(3S)-oxolan-3-yl]amino]pyrimidine-5-carboxamide;
- 4-cyclopentyl-N-[(2r,5s)-5-hydroxyadamantan-2-yl]-2-[2-(hydroxymethyl)morpholin-4-yl]pyrimidine-5-carboxamide;
- 30 4-cyclopentyl-2-(3,3-difluoroazetidin-1-yl)-N-[(2r,5s)-5-hydroxyadamantan-2-yl]pyrimidine-5-carboxamide;
- 4-cyclopentyl-N-[(2r,5s)-5-hydroxytricyclo[3.3.1.1^{3,7}]dec-2-yl]-2-[(2-morpholin-4-

- ylethyl)amino]pyrimidine-5-carboxamide;
- 4-cyclopentyl-2-({2-[(2R,6S)-2,6-dimethylmorpholin-4-yl]ethyl} amino)-N-[(2r,5s)-5-hydroxytricyclo[3.3.1.1^{3,7}]dec-2-yl]pyrimidine-5-carboxamide;
- 4-cyclopentyl-2-cyclopropyl-N-[(2r,5s)-5-hydroxyadamantan-2-yl]pyrimidine-5-
- 5 carboxamide;
- 4-cyclopentyl-N-[(2r,5s)-5-hydroxyadamantan-2-yl]-2-propan-2-ylpyrimidine-5-carboxamide-2-(1-aminocyclopropyl)-4-cyclopentyl-N-[(2r,5s)-5-hydroxyadamantan-2-yl]pyrimidine-5-carboxamide;
- 2-(aminomethyl)-4-cyclopentyl-N-[(2r,5s)-5-hydroxyadamantan-2-yl]pyrimidine-5-
- 10 carboxamide;
- 4-(3,3-difluorocyclobutyl)-N-[(2s,5r)-5-hydroxyadamantan-2-yl]-2-methylpyrimidine-5-carboxamide;
- 4-(3,3-difluorocyclobutyl)-N-[(2r,5s)-5-hydroxyadamantan-2-yl]-2-methylaminopyrimidine-5-carboxamide;
- 15 2-(cyclopropylamino)-4-(3,3-difluorocyclobutyl)-N-[(2r,5s)-5-hydroxyadamantan-2-yl]pyrimidine-5-carboxamide;
- 4-(3,3-difluorocyclobutyl)-2-[(2S,6R)-2,6-dimethylmorpholin-4-yl]-N-[(2r,5s)-5-hydroxyadamantan-2-yl]pyrimidine-5-carboxamide;
- 2-cyclobutyloxy-4-(3,3-difluorocyclobutyl)-N-[(2r,5s)-5-hydroxyadamantan-2-
- 20 yl]pyrimidine-5-carboxamide;
- N-[(2r,5s)-5-hydroxyadamantan-2-yl]-2-methyl-4-(oxolan-2-yl)pyrimidine-5-carboxamide;
- N-[(2r,5s)-5-hydroxyadamantan-2-yl]-4-(oxolan-2-yl)-2-(propan-2-ylamino)pyrimidine-5-carboxamide;
- 2-(cyclopropylamino)-N-[(2r,5s)-5-hydroxyadamantan-2-yl]-4-(oxolan-2-yl)pyrimidine-5-
- 25 carboxamide;
- N-[(2r,5s)-5-hydroxyadamantan-2-yl]-2-methylamino-4-(oxolan-2-yl)pyrimidine-5-carboxamide;
- 2-(cyclobutylamino)-N-[(2r,5s)-5-hydroxyadamantan-2-yl]-4-(oxolan-2-yl)pyrimidine-5-carboxamide;
- 30 2-[(2S,6R)-2,6-dimethylmorpholin-4-yl]-N-[(2r,5s)-5-hydroxyadamantan-2-yl]-4-(oxolan-2-yl)pyrimidine-5-carboxamide;
- N-[(2r,5s)-5-hydroxyadamantan-2-yl]-2-(oxetan-3-ylamino)-4-(oxolan-2-yl)pyrimidine-5-

carboxamide;

N-[(2r,5s)-5-hydroxyadamantan-2-yl]-4-(oxolan-2-yl)-2-propan-2-yloxy pyrimidine-5-carboxamide;

N-[(2r,5s)-5-hydroxyadamantan-2-yl]-2-methylsulfanyl-4-[(2R)-oxolan-2-yl]pyrimidine-5-carboxamide;

N-[(2r,5s)-5-hydroxyadamantan-2-yl]-2-methylamino-4-[(2R)-oxolan-2-yl]pyrimidine-5-carboxamide;

2-(cyclopropylamino)-N-[(2r,5s)-5-hydroxyadamantan-2-yl]-4-[(2R)-oxolan-2-yl]pyrimidine-5-carboxamide;

N-[(2r,5s)-5-hydroxyadamantan-2-yl]-4-[(2R)-oxolan-2-yl]-2-(propan-2-ylamino)pyrimidine-5-carboxamide;

2-[(3S,5R)-3,5-dimethylpiperazin-1-yl]-N-[(2r,5s)-5-hydroxyadamantan-2-yl]-4-[(2R)-oxolan-2-yl]pyrimidine-5-carboxamide;

N-[(2r,5s)-5-hydroxyadamantan-2-yl]-2-(oxetan-3-ylamino)-4-[(2R)-oxolan-2-yl]pyrimidine-5-carboxamide;

N-[(2r,5s)-5-hydroxyadamantan-2-yl]-2-(oxan-4-ylamino)-4-[(2R)-oxolan-2-yl]pyrimidine-5-carboxamide;

2-(cyclobutylamino)-N-[(2r,5s)-5-hydroxyadamantan-2-yl]-4-[(2R)-oxolan-2-yl]pyrimidine-5-carboxamide;

N-[(2r,5s)-5-hydroxyadamantan-2-yl]-4-[(2R)-oxolan-2-yl]-2-propan-2-yloxy pyrimidine-5-carboxamide;

N-[(2r,5s)-5-hydroxyadamantan-2-yl]-2-methylsulfanyl-4-[(2S)-oxolan-2-yl]pyrimidine-5-carboxamide;

N-[(2r,5s)-5-hydroxyadamantan-2-yl]-2-methylamino-4-[(2S)-oxolan-2-yl]pyrimidine-5-carboxamide;

N-[(2r,5s)-5-hydroxyadamantan-2-yl]-4-[(2S)-oxolan-2-yl]-2-(propan-2-ylamino)pyrimidine-5-carboxamide;

2-(cyclopropylamino)-N-[(2r,5s)-5-hydroxyadamantan-2-yl]-4-[(2S)-oxolan-2-yl]pyrimidine-5-carboxamide;

N-[(2r,5s)-5-hydroxyadamantan-2-yl]-4-[(2S)-oxolan-2-yl]-2-propan-2-yloxy pyrimidine-5-carboxamide;

2-[(2S,6R)-2,6-Dimethylmorpholin-4-yl]-N-[(2r,5s)-5-hydroxyadamantan-2-yl]-4-[(2R)-

- oxolan-2-yl]pyrimidine-5-carboxamide;
2-[(2S,6R)-2,6-Dimethylmorpholin-4-yl]-N-[(2r,5s)-5-hydroxyadamantan-2-yl]-4-[(2S)-oxolan-2-yl]pyrimidine-5-carboxamide;
4-(3,3-Difluorocyclopentyl)-N-[(2r,5s)-5-hydroxyadamantan-2-yl]-2-methylpyrimidine-5-
5 carboxamide;
N-[(2r,5s)-5-hydroxyadamantan-2-yl]-4-(1-methylcyclopropyl)-2-morpholin-4-ylpyrimidine-5-carboxamide;
N-[(2r,5s)-5-hydroxyadamantan-2-yl]-4-(1-methylcyclopropyl)-2-morpholin-4-ylpyrimidine-5-carboxamide;
10 (Z)-3-dimethylamino-2-(1-methylcyclopropanecarbonyl)-N-(5-phenylmethoxy-2-adamantyl)prop-2-enamide;
N-[(2r,5s)-5-hydroxyadamantan-2-yl]-2-methyl-4-phenylpyrimidine-5-carboxamide;
4-(2-Chlorophenyl)-N-[(2r,5s)-5-hydroxyadamantan-2-yl]-2-methylpyrimidine-5-carboxamide;
15 4-(cyclopentylmethyl)-N-[(2r,5s)-5-hydroxyadamantan-2-yl]-2-methylpyrimidine-5-carboxamide;
4-butyl-N-[(2r,5s)-5-hydroxyadamantan-2-yl]-2-methylpyrimidine-5-carboxamide;
N-[(2s,5r)-5-hydroxyadamantan-2-yl]-4-isobutyl-2-methylpyrimidine-5-carboxamide;
4-(2,2-dimethylpropyl)-N-[(2r,5s)-5-hydroxyadamantan-2-yl]-2-methylpyrimidine-5-
20 carboxamide;
4-(cyclopropylmethyl)-N-[(2r,5s)-5-hydroxyadamantan-2-yl]-2-methylpyrimidine-5-carboxamide
4-cyclohexyl-N-[(2r,5s)-5-hydroxyadamantan-2-yl]-2-(methylthio)pyrimidine-5-carboxamide;
25 4-cyclohexyl-N-[(2r,5s)-5-hydroxyadamantan-2-yl]-2-thiomorpholin-4-ylpyrimidine-5-carboxamide;
4-cyclohexyl-N-[(2r,5s)-5-hydroxyadamantan-2-yl]-2-(1-oxidothiomorpholin-4-yl)pyrimidine-5-carboxamide;
4-cyclohexyl-2-(1,1-dioxidothiomorpholin-4-yl)-N-[(2r,5s)-5-hydroxyadamantan-2-yl]pyrimidine-5-carboxamide;
30 2,4-bis(dimethylamino)-N-[(2r,5s)-5-hydroxyadamantan-2-yl]pyrimidine-5-carboxamide;

- 2,4-bis(3,3-difluoroazetidin-1-yl)-N-[(2r,5s)-5-hydroxyadamantan-2-yl]pyrimidine-5-carboxamide;
- 2,4-bis(azetidin-1-yl)-N-[(2r,5s)-5-hydroxyadamantan-2-yl]pyrimidine-5-carboxamide;
- N-[(2r,5s)-5-hydroxyadamantan-2-yl]-2-methyl-4-propan-2-yloxy pyrimidine-5-
- 5 carboxamide;
- 4-cyclobutyloxy-N-[(2r,5s)-5-hydroxyadamantan-2-yl]-2-methylpyrimidine-5-carboxamide;
- 4-cyclopentyloxy-N-[(2r,5s)-5-hydroxyadamantan-2-yl]-2-methylpyrimidine-5-carboxamide;
- 10 2-[(2R,6S)-2,6-Dimethylmorpholin-4-yl]-N-[(2r,5s)-5-hydroxytricyclo[3.3.1.1^{3,7}]dec-2-yl]-4-methoxypyrimidine-5-carboxamide;
- 2-(cyclopropylamino)-N-[(2r,5s)-5-hydroxytricyclo[3.3.1.1^{3,7}]dec-2-yl]-4-methoxypyrimidine-5-carboxamide;
- 2-(cyclobutylamino)-N-[(2r,5s)-5-hydroxytricyclo[3.3.1.1^{3,7}]dec-2-yl]-4-
- 15 methoxypyrimidine-5-carboxamide;
- 2-(cyclobutyloxy)-N-[(2r,5s)-5-hydroxytricyclo[3.3.1.1^{3,7}]dec-2-yl]-4-methoxypyrimidine-5-carboxamide;
- 2-[(2S,6R)-2,6-dimethylmorpholin-4-yl]-4-ethoxy-N-[(2r,5s)-5-hydroxyadamantan-2-yl]pyrimidine-5-carboxamide;
- 20 2-(cyclopropylamino)-4-ethoxy-N-[(2r,5s)-5-hydroxytricyclo[3.3.1.1^{3,7}]dec-2-yl]pyrimidine-5-carboxamide;
- 4-ethoxy-N-[(2r,5s)-5-hydroxytricyclo[3.3.1.1^{3,7}]dec-2-yl]-2-(oxetan-3-ylamino)pyrimidine-5-carboxamide;
- 2-(cyclobutylamino)-4-ethoxy-N-[(2r,5s)-5-hydroxytricyclo[3.3.1.1^{3,7}]dec-2-
- 25 yl]pyrimidine-5-carboxamide;
- 2-(cyclobutyloxy)-4-ethoxy-N-[(2r,5s)-5-hydroxytricyclo[3.3.1.1^{3,7}]dec-2-yl]pyrimidine-5-carboxamide;
- 2-[(2R,6S)-2,6-dimethylmorpholin-4-yl]-N-[(2r,5s)-5-hydroxytricyclo[3.3.1.1^{3,7}]dec-2-yl]-4-(1-methylethoxy)pyrimidine-5-carboxamide;
- 30 2-(cyclopropylamino)-N-[(2r,5s)-5-hydroxytricyclo[3.3.1.1^{3,7}]dec-2-yl]-4-(1-methylethoxy)pyrimidine-5-carboxamide;
- N-[(2r,5s)-5-hydroxytricyclo[3.3.1.1^{3,7}]dec-2-yl]-4-(1-methylethoxy)-2-(oxetan-3-

ylamino)pyrimidine-5-carboxamide;

2-(cyclobutylamino)-N-[(2r,5s)-5-hydroxytricyclo[3.3.1.1^{3,7}]dec-2-yl]-4-(1-methylethoxy)pyrimidine-5-carboxamide;

2-(cyclobutyloxy)-N-[(2r,5s)-5-hydroxytricyclo[3.3.1.1^{3,7}]dec-2-yl]-4-(1-methylethoxy)pyrimidine-5-carboxamide;

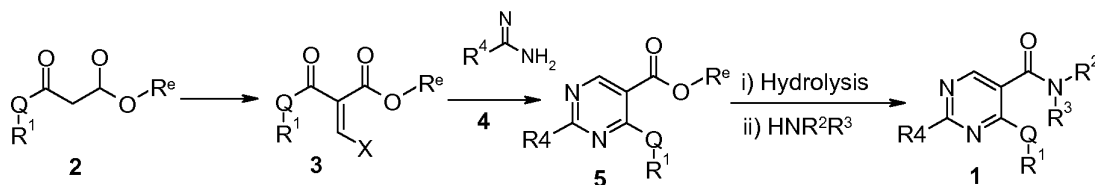
N-[(2r,5s)-5-hydroxyadamantan-2-yl] 2-[(2S,6R)-2,6-dimethylmorpholin-4-yl]-4-[(2R)-oxolan-2-yl]pyrimidine-5-carboxamide;

4-cyclopropyl-2-[(2S,6R)-2,6-dimethylmorpholin-4-yl]-N-[(2r,5s)-5-hydroxyadamantan-2-yl]pyrimidine-5-carboxamide; and

2-[(2S,6R)-2,6-dimethylmorpholin-4-yl]-N-[(2r,5s)-5-hydroxyadamantan-2-yl]-4-(methoxymethyl)pyrimidine-5-carboxamide.

Another aspect of the present invention provides a process for preparing a compound of formula **1** or a pharmaceutically acceptable salt thereof which process [wherein variable groups are, unless otherwise specified, as defined in formula **1**] comprises any one of the following processes;

a) suitable for when Q is a single bond linked to a carbon atom:



Scheme 1

According to this method, a β -ketoester of formula **2** is converted to a compound of formula **3** where X represents dialkylamino (e.g. dimethylamino) or lower alkoxy (e.g. ethoxy). The compound of formula **3** is then treated with an appropriately substituted amidine or guanidine of formula **4**. The ester protecting group in the compound of formula **5** is then cleaved and the resulting carboxylic acid is coupled with an amine of formula HNR^2R^3 to give the desired compound of formula **1**.

Methods for conversion of compounds of formula **2** to enamines of formula **3** (X is dialkylamino) are well known to the art and examples are described in the following references; *Tetrahedron Lett.*, **1984**, 25, 3743; *Synthesis*, **1983**, 566; *Synthesis*, **1990**, 70. When X=dimethylamino, the reaction typically involves treating a compound of formula **2**

with N,N-dimethylformamide dimethyl acetal in an inert solvent, typically 1,4-dioxane or toluene, at temperature between 50-100°C.

Methods for conversion of compounds of formula **2** to enol ethers of formula **3** (X is alkoxy) and well known to the art and examples are described in the following references; *Liebigs Ann. Chem.*, **1897**, 297, 1; *J. Chem. Soc., Perkin Trans. 1*, **1979**, 464; *J. Med. Chem.*, **2000**, 43, 3995; *Tetrahedron*, **2002**, 58, 8581; When X is ethoxy, the reaction typically involves treating a compound of formula **2** with triethylorthoformate in the presence of acetic anhydride at reflux.

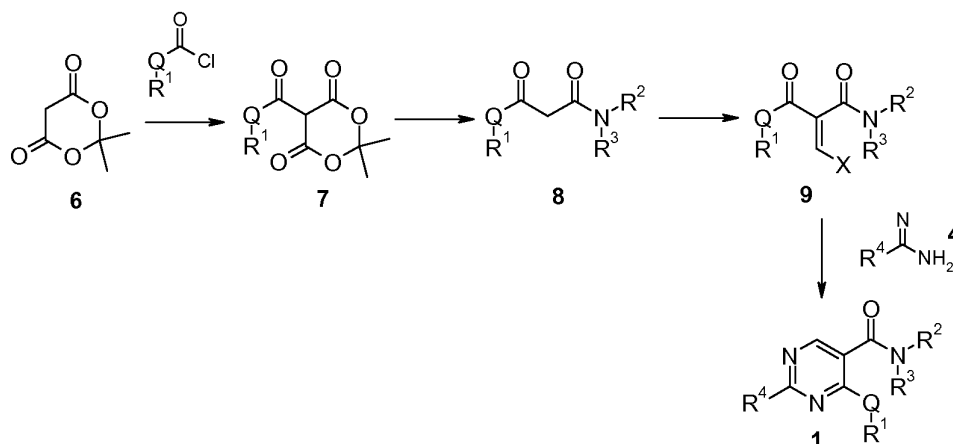
Methods for conversion of compounds of formula **3** to pyrimidines of formula **5** are well known in the art and examples are described in the following references; *Bioorg. Med. Chem. Lett.*, **2005**, 15, 4898; *Bioorg. Med. Chem. Lett.*, **2003**, 13, 567; US 2005096353. The compound of formula **3** is treated with an appropriate amidine or guanidine of formula **4** in an inert solvent (e.g. methanol, ethanol) with an appropriate base (e.g. sodium ethoxide) at temperatures ranging from 50-100°C, preferably at reflux.

Methods for conversion of compounds of formula **5** to pyrimidines of formula **1** are well known to the art. Cleavage of a compound of formula **5** to the corresponding carboxylic acid will be dependent on the nature of the ester group used and many procedures are outlined in the following reference; T.W. Green, *Protective Groups in Organic Synthesis*, John Wiley and Sons, 1991. For example, in the case where R^e represents lower alkoxy (e.g. methyl or ethyl), the reaction can be carried out by hydrolysis with a suitable base such as an alkaline metal hydroxide (e.g. sodium hydroxide, potassium hydroxide or lithium hydroxide) in a suitable solvent (e.g. methanol, THF, water) at temperatures ranging from 0-50°C but preferably at ambient temperature. In the case where R^e is an acid labile ester (e.g. *t*-butyl), the reaction may be carried out by treatment with an inorganic acid (e.g. hydrochloric acid) or an organic acid (e.g. trifluoroacetic acid) in a suitable solvent (e.g. dichloromethane) at temperatures ranging from 0-ambient but preferably at ambient temperature. In the case where R^e is an ester labile to hydrogenation (e.g. benzyl), the reaction may be carried out with a suitable catalyst (e.g. palladium-on-carbon) in the presence of an inert solvent (e.g. ethanol, methanol, toluene) typically at room temperature and a suitable pressure (typically atmospheric pressure). Formation of an amide from a carboxylic acid is a process well known to the art. Typical processes include, but are not limited to, formation of an acyl halide by treatment with a

suitable reagent (e.g. oxalyl chloride, POCl_3) in a suitable solvent such as dichloromethane or *N,N*-dimethylformamide for example at temperatures ranging from 0-50°C but preferably at ambient temperature. Alternatively, *in situ* conversion of the acid to an active ester derivative may be utilised with the addition of a suitable coupling agent (or
 5 combination of agents) to form an active ester such as HATU, 1-hydroxybenzotriazole (HOBT), and 1-ethyl-3-(3-dimethylaminopropyl)carbodi-imide hydrochloride (EDAC) for example, optionally in the presence of a suitable base such as triethylamine or *N,N*-di-*iso*-propylamine for example. Typically the reaction is carried out at temperatures ranging from 0-50°C but preferably at ambient temperature.

10 Direct conversions of esters to amides are known in the art with examples described in the following references; *J. Med. Chem.*, **2007**, *50*, 1675; *Heterocycles*, **2006**, *67*, 519 and typically involve heating of the two components, optionally in the presence of a suitable additive (e.g. AlMe_3). Typically reactions are carried out in inert solvents (e.g. toluene, benzene) at elevated temperatures (e.g. 50-150°C) achieved through conventional
 15 or microwave heating.

b) suitable for when Q is a single bond linked to a carbon atom:



Scheme 2

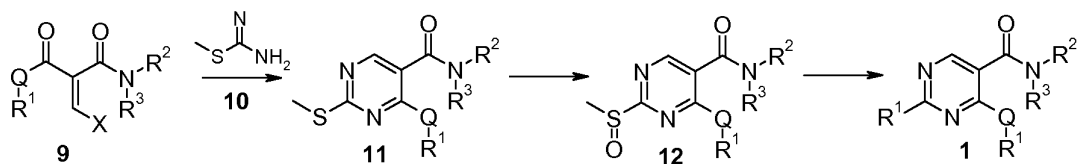
According to this method, Meldrum's acid of formula 6 is converted to a compound
 20 of formula 7. The compound of formula 7 is then treated with an amine of formula NHR^2R^3 to form a β-ketoamide of formula 8. This compound of formula 8 is then converted to a compound of formula 9 where X represents dialkylamino (e.g. dimethylamino) or lower alkoxy (e.g. ethoxy). The compound of formula 9 is then treated with an appropriately substituted amidine or guanidine of formula 4 to give the desired compound of formula 1.

Methods for conversion of compounds of formula **6** to compounds of formula **7** are well known in the art and examples are described in the following references; *J. Org. Chem.*, **2001**, 26, 6756; *J. Med. Chem.*, **1998**, 41, 3186. The Meldrum's acid is treated with an acyl chloride of formula R^1QCOCl in an anhydrous inert solvent (e.g. dichloromethane) in the presence of an organic base (e.g. pyridine, triethylamine, or N,N-diisopropylamine) at temperatures between 0-50°C, but preferably at 0°C to ambient temperature.

Methods for conversion of compounds of formula **7** to compounds of formula **8** are well known in the art and examples are described in the following reference; *Synthesis.*, **1992**, 1213. The compound of formula **7** is treated with a stoichiometric amount of amine of formula HNR^2R^3 in an inert solvent (e.g. toluene) at elevated temperature, preferably at reflux.

Methods for conversion of compounds of formula **8** to compounds of formula **9** are analogous to those previously outlined for the conversion of compounds of formula **2** to compounds of formula **3** described above. Methods for conversion of compounds of formula **9** to compounds of formula **1** are analogous to those previously outlined for the conversion of compounds of formula **3** to compounds of formula **5**.

c) suitable for when Q is a single bond linked to a carbon atom:



Scheme 3

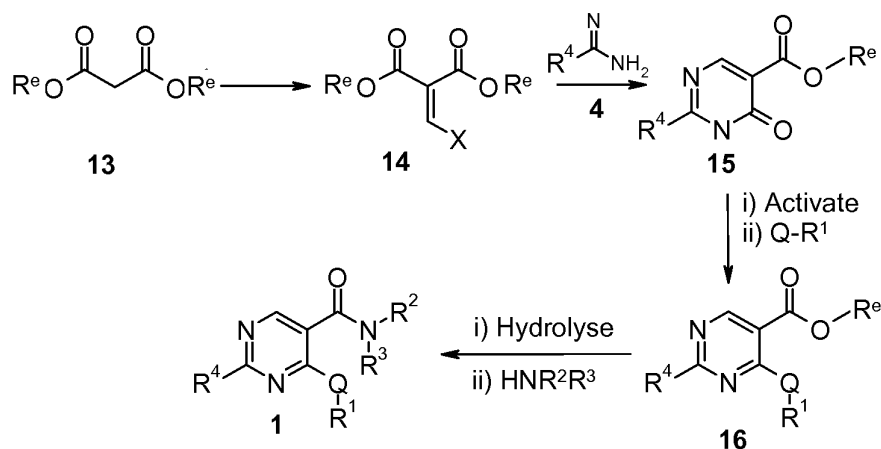
According to this method, a compound of formula **9** is converted to a compound of formula **11** by treatment with methylsulfonylformadine **10**. The compound of formula **11** is then oxidised to give a sulfoxide of formula **12** which is reacted with an appropriate nucleophile to give the desired compound of formula **1**.

Methods for conversion of compounds of formula **9** to pyrimidines of formula **11** are well known in the art and examples are described in the following patent reference; WO2006050476. The compound of formula **9** is treated with isothiurea sulphate **10** in an inert solvent (e.g. DMF) with an appropriate base (e.g. sodium acetate) and heated at temperatures of between 50-100°C, ideally at 80-90°C to give pyrimidines of formula **11**.

Methods for conversion of thioethers of formula **11** to sulphoxides of formula **12** are well known in the art and examples are described in the following patent reference; WO2006050476. The compound of formula **11** is treated with an appropriate oxidising agent (e.g. m-chloroperbenzoic acid) in an inert solvent (e.g. dichloromethane) at temperatures ranging from -78°C to ambient temperature, preferably at -10°C to ambient temperature. It will be appreciated by those skilled in the art that the potential to further oxidise the sulphur to the corresponding sulphoxide also exists and that these compounds would also be suitable for the activation of this group towards nucleophilic displacement in the subsequent step.

Methods for conversion of compounds of formula **12** to compounds of formula **1** are well known in the art and examples are described in the following references; WO2006050476, *Synth. Commun.*, **2007**, 37, 2231; *Bioorg. Med. Chem.*, **2005**, 13, 5717. The compound of formula **12** is treated with an appropriate nucleophilic reagent in an inert solvent (e.g. THF, DMF, 1,4-dioxane) at temperatures ranging from from ambient temperature to 100°C dependant of the nucleophilicity of the reagent.

d) suitable for when Q is O, S, N(R⁸) or a single bond linked to a heteroatom;



Scheme 4

According to this method, a malonate of formula **13** is converted to a compound of formula **14**. The compound of formula **14** is then treated with an appropriately substituted amidine or guanidine of formula **4** to give a pyrimidone of formula **15**. The pyrimidone is then converted to a suitably reactive species and treated with a nucleophile to give pyrimidines of formula **16**. The ester protecting group (R^e) in the compound of formula **16**

is then cleaved and the resulting carboxylic acid is coupled with an amine of formula NHR^2R^3 to give the desired compound of formula 1.

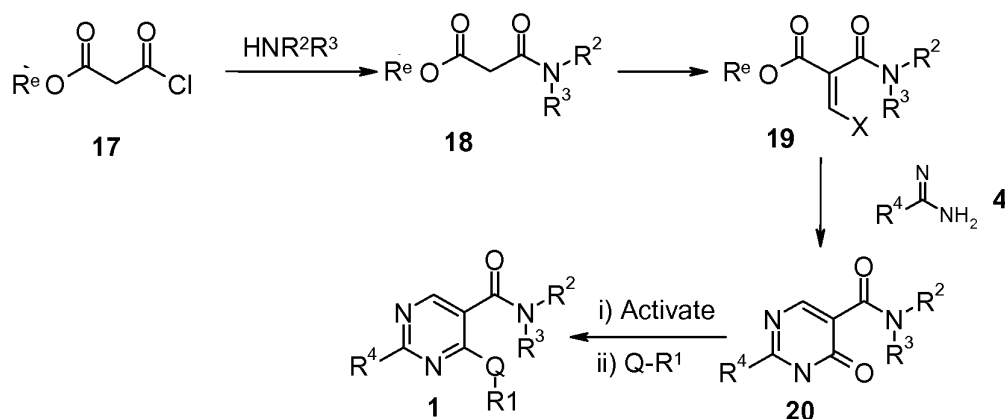
Methods for conversion of malonates of formula 13 to compounds of formula 14 where X represents dialkylamino (e.g. dimethylamino) or lower alkoxy (e.g. ethoxy) are well known in the art and examples are described in the following references; *J. Org. Chem.*, **1995**, 60, 1900; *Organic Synthesis*; J.Wiley & Sons: New York, **1996**: *Collect. Vol* 3, p395; EP 413918; EP 411417; WO 2002034710. When X is ethoxy, the reaction typically involves treating a compound of formula 13 with triethylorthoformate in the presence of acetic anhydride at reflux.

Methods for conversion of compounds of formula 14 to compounds of formula 15 are analogous to those previously outlined for the conversion of compounds of formula 3 to compounds of formula 5 described above.

Methods for conversion of compounds of formula 15 to pyrimidines of formula 16 are well known in the art and examples are described in the following references; *J. Med. Chem.*, **2007**, 50, 591. The compound of formula 15 is treated with a suitable halogenating system (e.g. $\text{POCl}_3/\text{PCl}_5$ or $\text{Cl}_2\text{P}(=\text{O})\text{OPh}$) in an inert solvent (e.g. DMF) or neat with an and heated at temperatures of between 50-190°C, ideally at reflux to give halo pyrimidines which are then displaced with appropriate nucleophiles in an inert solvent (e.g. DMF, butyronitrile, DMF) in the presence of an appropriate base (e.g. potassium carbonate, sodium carbonate) at temperatures ranging from ambient temperature to 100°C dependant of the nucleophilicity of the reagent to give compounds of formula 16. Optionally, the anion of the nucleophile may be prepared by treatment with a suitable base (e.g. sodium hydride, lithium hexamethyldisilazide).

Methods for conversion of compounds of formula 16 to compounds of formula 1 are analogous to those previously outlined for the conversion of compounds of formula 5 to compounds of formula 1 described above.

e) suitable for when Q is O, S, $\text{N}(\text{R}^8)$ or a single bond linked to a heteroatom;



Scheme 5

According to this method, an acid chloride of formula **17** is coupled with an amine of formula NHR^2R^3 and converted to an amide of formula **18**. The amide of formula **19** is then converted to a compound of formula **19** where X represents dialkylamino (e.g. dimethylamino) or lower alkoxy (e.g. ethoxy). The amide of formula **19** is then treated with an appropriately substituted amidine or guanidine of formula **4** to give a pyrimidone of formula **20**. The pyrimidone is then converted to a suitably reactive species and treated with a nucleophile to give the desired compound of formula **1**.

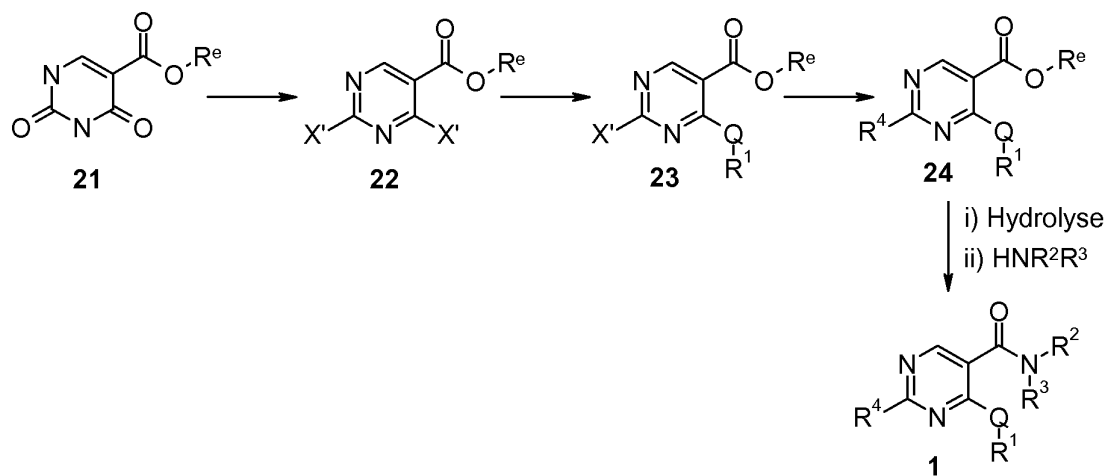
Methods for conversion of compounds of formula **17** to amides of formula **18** are well known in the art and examples are described in the following references; *J. Org. Chem.*, **2007**, 72, 7058; *Bioorg. Med. Chem. Lett.*, **2007**, 17, 1951. The compound of formula **17** is treated with an amine of formula NHR^2R^3 in the presence of a suitable base (e.g., triethylamine, pyridine) in a suitable solvent (e.g. dichloromethane) at temperatures of 0-50°C, typically at 0°C to ambient temperature.

Methods for conversion of compounds of formula **18** to compounds of formula **19** are analogous to those previously outlined for the conversion of compounds of formula **2** to compounds of formula **3** described above.

Methods for conversion of compounds of formula **19** to compounds of formula **20** are analogous to those previously outlined for the conversion of compounds of formula **3** to compounds of formula **5** described above.

Methods for conversion of compounds of formula **20** to compounds of formula **1** are analogous to those previously outlined for the conversion of compounds of formula **15** to compounds of formula **16** described above.

f) suitable for when Q is O, S, N(R⁸) or a single bond linked to a heteroatom;



Scheme 6

According to this method, a pyrimidinedione ester of formula **21** is halogenated to give a di-halo (or equivalent) compound of formula **22** wherein X' is halo. The compound is treated with a stoichiometric quantity of an appropriate nucleophile (Q-R^1) to give compounds of formula **23** and then reacted with another nucleophile (R^4) to give a pyrimidine of formula **24**. The ester protecting group (R^e) in the compound of formula **24** is then cleaved and the resulting carboxylic acid is coupled with an amine of formula NHR^2R^3 to give the desired compound of formula **1**.

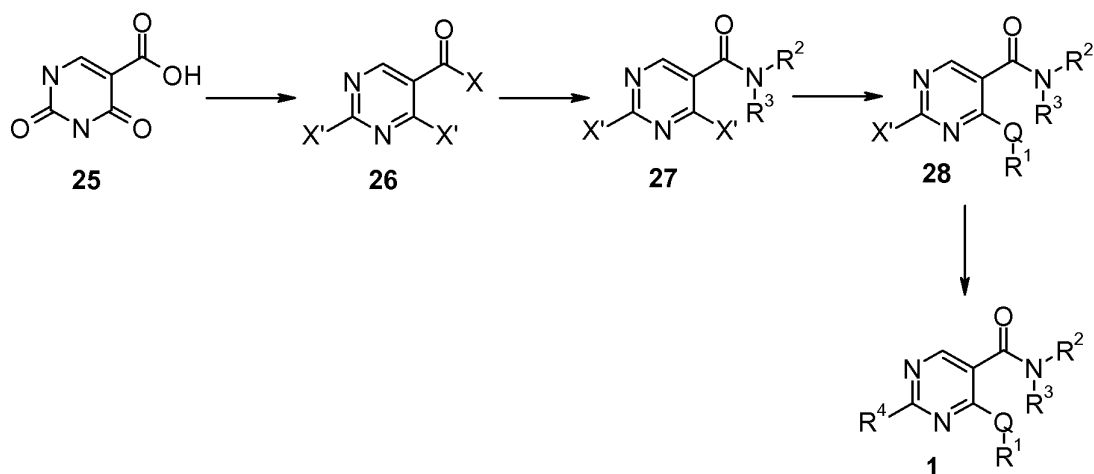
Methods for conversion of compounds of formula **21** to compounds of formula **22** are well known in the art and examples are described in the following references; *J. Med. Chem.*, **2007**, *50*, 591. The compound of formula **21** is treated with a suitable halogenating system (e.g. $\text{POCl}_3/\text{PCl}_5$ or $\text{Cl}_2\text{P}(=\text{O})\text{OPh}$) in an inert solvent (e.g. DMF) or neat and heated at temperatures of between 50-190°C, ideally at reflux to give halo pyrimidines. Methods for conversion of compounds of formula **22** to compounds of formula **23** are well known in the art and examples are described in the following references; *J. Med. Chem.*, **2007**, *50*, 591. Compounds of formula **22** are treated with appropriate nucleophiles in an inert solvent (e.g. DMF, butyronitrile, dichloromethane) in the presence of an appropriate base (e.g. potassium carbonate, sodium carbonate, N,N-diethylamine) at temperatures ranging from ambient temperature to 100°C dependant of the nucleophilicity of the reagent to give compounds of formula **23**. Optionally, the anion of the nucleophile may be prepared by treatment with a suitable base (e.g. sodium hydride, lithium

hexamethyldisilazide). It will be appreciated by those skilled in the art that regioisomeric mixtures may result in this reaction and that separation techniques may be required to obtain the desired regioisomer.

Methods for conversion of compounds of formula **23** to compounds of formula **24** are analogous to those previously outlined for the conversion of compounds of formula **22** to compounds of formula **23** described above.

Methods for conversion of compounds of formula **24** to compounds of formula **1** are analogous to those previously outlined for the conversion of compounds of formula **5** to compounds of formula **1** described above.

g) suitable for when Q is O, S, N(R⁸) or a single bond linked to a heteroatom;



Scheme 7

According to this method, a pyrimidinedione acid of formula **25** is halogenated to give a di-halo acyl halide (or equivalent) compound of formula **26** wherein X' is halo. The compound is treated with an amine of formula NHR²R³ to give compounds of formula **27**. The di-halo amide is then treated with a stoichiometric quantity of an appropriate nucleophile (Q-R¹) to give a compound of formula **28** and then reacted with another nucleophile (R⁴) to give the desired compound of formula **1**.

Methods for conversion of compounds of formula **25** to compounds of formula **26** are analogous to those previously outlined for the conversion of compounds of formula **21** to compounds of formula **22** described above.

Methods for conversion of compounds of formula **26** to compounds of formula **27** are analogous to those previously outlined for the conversion of compounds of formula **17** to compounds of formula **18** described above.

Methods for conversion of compounds of formula **27** to compounds of formula **28** are
5 compounds of formula **28** to compounds of formula **1** are analogous to those previously outlined for the conversion of compounds of formula **22** to compounds of formula **23** described above.

A significant number of β -ketoamides and β -ketoesters are commercially available as listed in the Available Chemicals Directory and a further number have been described in
10 the chemical literature. A listing of many of the methods suitable for preparation of β -ketoesters is contained within '*Comprehensive Organic Transformations; A Guide to Functional Group Preparations*', VCH Publishers, Inc, NY, **1989**, p685, 694 & 768]. Additional methods may be found in '*Advanced Organic Chemistry*', 3rd Ed, J. Wiley & Sons, Inc, NY, **1985** p437 & 823]. A sample method for the conversion of β -ketoesters to
15 β -ketoamides has been described above in the preparation of compounds of formula **8**.

A number of substituted amidines and guanidines are commercially available as listed in the Available Chemicals Directory and a further number have been described in the chemical literature. A listing of many of the methods suitable for preparation of amidines and guanidines is contained within '*Comprehensive Organic Functional Group
20 Transformations*'; Elsevier Publishers, Inc, Oxford, **1995**, vol 5, p741 and vol 6, p639]. Additional methods may be found in '*Advanced Organic Chemistry*', 4th Ed, J. Wiley & Sons, Inc, NY, **1991** p769 & 903]. A sample method for the conversion of amines to guanidines is given in patent WO1997045108.

It will be appreciated that certain of the various substituents in the compounds of
25 the present invention may be introduced by standard aromatic substitution reactions or generated by conventional functional group modifications either prior to or immediately following the processes mentioned above, and as such are included in the process aspect of the invention. Such reactions and modifications include, introduction of a substituent by means of an aromatic substitution reaction, reduction of substituents, oxidation of
30 substituents and alkylation of substituents, for example, alkylation reactions such as conversion of a secondary amide to a primary amide typically carried out using strong base (e.g. sodium hydride or lithium or potassium hexamethyldisilylazides) and a suitable

alkylating agent (e.g. methyl iodide). The reagents and reaction conditions for such procedures are well known in the chemical art. Particular examples of aromatic substitution reactions include the introduction of a nitro group using concentrated nitric acid, the introduction of an acyl group using, for example, an acyl halide and Lewis acid (e.g. aluminium trichloride) under Friedel Crafts conditions; the introduction of an alkyl
5 group using an alkyl halide and Lewis acid (e.g. aluminium trichloride) under Friedel Crafts conditions; and the introduction of a halogeno group. Particular examples of modifications include the reduction of a nitro group to an amino group by for example, catalytic hydrogenation with a nickel catalyst or treatment with iron in the presence of hydrochloric acid with heating; oxidation of alkylthio to alkylsulphinyl or alkylsulphonyl;
10 removal of alkylthio groups by reductive de-sulphurisation by for example treatment with a nickel catalyst.

It will also be appreciated that in some of the reactions mentioned herein it may be necessary/desirable to protect any sensitive groups in the compounds. The instances where protection is necessary or desirable and suitable methods for protection are known to those
15 skilled in the art. Conventional protecting groups may be used in accordance with standard practice (for illustration see T.W. Green, Protective Groups in Organic Synthesis, John Wiley and Sons, 1991). Thus, if reactants include groups such as amino, carboxy or hydroxy it may be desirable to protect the group in some of the reactions mentioned herein. A suitable protecting group for an amino or alkylamino group is, for example, an acyl
20 group, for example an alkanoyl group such as acetyl, an alkoxycarbonyl group, for example a methoxycarbonyl, ethoxycarbonyl or *t*-butoxycarbonyl group, an arylmethoxycarbonyl group, for example benzyloxycarbonyl, or an aroyl group, for example benzoyl. The deprotection conditions for the above protecting groups necessarily vary with the choice of protecting group. Thus, for example, an acyl group such as an
25 alkanoyl or alkoxycarbonyl group or an aroyl group may be removed for example, by hydrolysis with a suitable base such as an alkali metal hydroxide, for example lithium or sodium hydroxide. Alternatively an acyl group such as a *t*-butoxycarbonyl group may be removed, for example, by treatment with a suitable acid as hydrochloric, sulphuric or phosphoric acid or trifluoroacetic acid and an arylmethoxycarbonyl group such as a
30 benzyloxycarbonyl group may be removed, for example, by hydrogenation over a catalyst such as palladium-on-carbon, or by treatment with a Lewis acid for example boron

tris(trifluoroacetate). A suitable alternative protecting group for a primary amino group is, for example, a phthaloyl group which may be removed by treatment with an alkylamine, for example hydroxylamine, or with hydrazine.

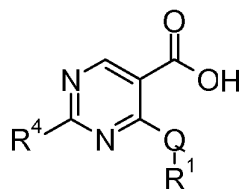
A suitable protecting group for a hydroxy group is, for example, an acyl group, for example an alkanoyl group such as acetyl, an aroyl group, for example benzoyl, or an arylmethyl group, for example benzyl. The deprotection conditions for the above protecting groups will necessarily vary with the choice of protecting group. Thus, for example, an acyl group such as an alkanoyl or an aroyl group may be removed, for example, by hydrolysis with a suitable base such as an alkali metal hydroxide, for example lithium or sodium hydroxide. Alternatively an arylmethyl group such as a benzyl group may be removed, for example, by hydrogenation over a catalyst such as palladium-on-carbon.

A suitable protecting group for a carboxy group is, for example, an esterifying group, for example a methyl or an ethyl group which may be removed, for example, by hydrolysis with a base such as sodium hydroxide, or for example a *t*-butyl group which may be removed, for example, by treatment with an acid, for example an organic acid such as trifluoroacetic acid, or for example a benzyl group which may be removed, for example, by hydrogenation over a catalyst such as palladium-on-carbon.

The protecting groups may be removed at any convenient stage in the synthesis using conventional techniques well known in the chemical art.

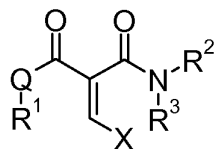
Accordingly, another aspect of the present invention provides a process for preparing a compound of formula (1) or a pharmaceutically acceptable salt thereof which process (wherein variable groups are, unless otherwise specified, as defined in formula (1)) comprises:

- i) reacting a compound of formula:



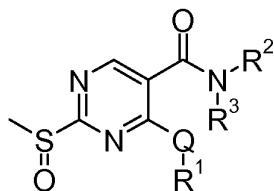
or a reactive derivative thereof with an amine of formula HNR^2R^3 ;

- ii) reacting together compounds of the formulae:



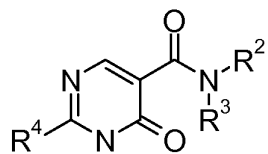
and $R^4-C(=N)NH_2$ wherein X is dialkylamino or lower alkoxy;

iii) when R^4 is $-SR^{10}$, reacting a compound of the formula:



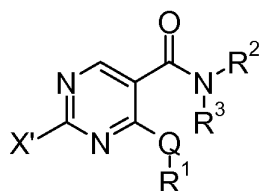
with the appropriate nucleophile to convert $-SOMe$ to $-R^4$;

iv) reacting an activated derivative of a compound of the formula:



with a nucleophile of the formula $Q-R^1$;

v) reacting a compound of the formula:



wherein X' is halo with a nucleophile R^4 ;

and thereafter if necessary or desirable:

i) converting a compound of the formula (1) into another compound of the formula (1);

ii) removing any protecting groups;

iii) resolving enantiomers;

iv) forming a pharmaceutically-acceptable salt thereof.

As stated hereinbefore the compounds defined in the present invention possess 11 β HSD1 inhibitory activity. These properties may be assessed using the following assay.

Assays

The conversion of cortisone to the active steroid cortisol by 11 β HSD1 oxo-reductase activity, can be measured using a competitive homogeneous time resolved fluorescence assay (HTRF) (CisBio International, R&D, Administration and Europe Office, In Vitro Technologies — HTRF® / Bioassays BP 84175, 30204 Bagnols/Cèze Cedex, France. Cortisol bulk HTRF kit: Cat No. 62CO2PEC).

The evaluation of compounds described herein was carried out using a baculovirus expressed N terminal 6-His tagged full length human 11 β HSD1 enzyme(*1). The enzyme was purified from a detergent solubilised cell lysate, using a copper chelate column.

Inhibitors of 11 β HSD1 reduce the conversion of cortisone to cortisol, which is identified by an increase in signal, in the above assay.

Compounds to be tested were dissolved in dimethyl sulphoxide (DMSO) to 10mM and diluted further in assay buffer containing 1% DMSO to 10 fold the final assay concentration. Diluted compounds were then plated into black 384 well plates (Matrix, Hudson NH, USA).

The assay was carried out in a total volume of 20 μ l consisting of cortisone (Sigma, Poole, Dorset, UK, 160nM), glucose-6-phosphate (Roche Diagnostics, 1mM), NADPH (Sigma, Poole, Dorset, 100 μ M), glucose-6-phosphate dehydrogenase (Roche Diagnostics, 12.5 μ g/ml), EDTA (Sigma, Poole, Dorset, UK, 1mM), assay buffer (K₂HPO₄/KH₂PO₄, 100mM) pH 7.5, recombinant 11 β HSD1 [using an appropriate dilution to give a viable assay window – an example of a suitable dilution may be 1 in 1000 dilution of stock enzyme] plus test compound. The assay plates were incubated for 25 minutes at 37°C after which time the reaction was stopped by the addition of 10 μ l of 0.5mM glycerolacetic acid plus conjugated cortisol(D2). 10 μ l of anti-cortisol Cryptate was then added and the plates sealed and incubated for 6 hours at room temperature. Fluorescence at 665nm and 620nm was measured and the 665nm:620nm ratio calculated using an Envision plate reader.

These data were then used to calculate IC₅₀ values for each compound (Origin 7.5, Microcal software, Northampton MA, USA) and/or the % inhibition at 30 μ M of compound.

*1 The Journal of Biological Chemistry, Vol. 26, No 25, pp16653 – 16658

Compounds of the present invention typically show an IC₅₀ of less than 30 μ M, and preferably less than 5 μ M.

For example, the following results were obtained:

Ex. No.	IC50 (uM)	Ex. No.	IC50 (uM)	Ex. No.	IC50 (uM)	Ex. No.	IC50 (uM)
3	0.370	12	0.045	18	0.003	30	0.019
9	0.017	13	0.014	19	0.014	32	0.220
10	0.005	16	0.002	20	0.002	33	0.033

11	0.070	17	0.330	29	0.013	38	0.041
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The following table displays %inhibition of human 11- β HSD at a test concentration of 30 μ M of compound

Example Number	% inhibition at 30 μ M	Example Number	% inhibition at 30 μ M	Example Number	% inhibition at 30 μ M
1	101.8	41	94.0	81	100.3
2	103.3	42	99.4	82	95.2
3	105.8	43	99.2	83	103.2
4	89.2	44	98.0	84	97.5
5	96.0	45	98.5	85	88.8
6	83.3	46	104.5	86	97.0
7	88.3	47	97.3	87	95.7
8	93.3	48	100.2	88	94.9
9	98.7	49	99.3	89	95.5
10	88.5	50	99.0	90	100.0
11	97.5	51	101.9	91	95.7
12	97.3	52	92.5	92	97.1
13	111.5	53	101.6	93	93.1
14	108.0	54	101.5	94	103.4
15	95.4	55	96.9	95	97.3
16	95.8	56	90.2	96	97.4
17	94.0	57	101.6	97	98.7
18	98.5	58	99.6	98	97.8
19	100.0	59	95.6	99	93.3
20	97.6	60	95.1	100	99.4
21	93.0	61	105.1	101	101.6
22	89.5	62	99.9	102	93.8
23	97.4	63	92.7	103	95.7
24	68.0	64	95.9	104	99.3
25	101.0	65	100.2	105	97.5
26	89.0	66	99.5	106	101.3
27	95.5	67	105.5	107	97.3
28	103.0	68	98.3	108	96.0
29	100.0	69	101.7	109	90.3
30	93.5	70	98.0	110	100.2
31	93.5	71	100.4	111	108.4
32	97.0	72	91.6	112	104.3
33	97.5	73	95.2	113	98.4
34	98.0	74	88.5	114	106.0
35	105.5	75	98.6	115	93.4

36	99.5	76	96.1	116	98.1
37	93.5	77	90.9	117	97.4
38	104.0	78	93.1	118	93.7
39	99.5	79	89.7	119	103.9
40	91.5	80	99.2	120	100.8

Example Number	% inhibition at 30 μ M	Example Number	% inhibition at 30 μ M	Example Number	% inhibition at 30 μ M
121	103.8	153	91.7	187	99.0
122	97.5	154	88.0	188	78.9
123	99.1	155	92.6	189	95.5
124	98.5	156	65.5	190	99.2
125	95.0	157	87.1	191	93.2
126	96.6	158	96.5	192	105.4
127	102.6	159	98.2	193	102.2
128	99.1	160	103.8	194	99.0
129	95.5	161	105.4	195	102.8
130	96.1	162	97.7	196	99.8
131	101.2	163	100.0	197	97.8
132	99.9	164	98.9	198	94.0
133	94.0	165	104.9	199	96.8
134	94.1	166	102.2	200	52.8
135	100.5	167	100.8	201	95.0
136	97.7	170	94.4	202	102.1
137	96.9	171	103.3	203	98.6
138	100.6	172	97.2	204	106.4
139	99.5	173	101.4	205	102.4
140	101.2	174	95.0	206	105.1
141	104.9	175	103.4	207	93.0
142	99.7	176	97.9	208	101.6
143	95.0	177	95.8	209	99.4
144	98.8	178	95.3	210	97.2
145	92.9	179	95.1	211	98.4
146	93.4	180	98.8	212	105.4
147	103.1	181	95.0	213	107.0
148	102.3	182	102.2	214	103.1
149	92.0	183	100.9	215	94.9
150	96.0	184	108.5	216	97.1
151	100.9	185	93.5	217	94.2
152	97.8	186	95.5	218	96.0
				219	98.6

According to a further aspect of the invention there is provided a pharmaceutical composition, which comprises a compound of the Examples, or a pharmaceutically-acceptable salt thereof, as defined hereinbefore in association with a pharmaceutically-acceptable diluent or carrier.

5 The compositions of the invention may be in a form suitable for oral use (for example as tablets, lozenges, hard or soft capsules, aqueous or oily suspensions, emulsions, dispersible powders or granules, syrups or elixirs), for topical use (for example as creams, ointments, gels, or aqueous or oily solutions or suspensions), for administration by inhalation (for example as a finely divided powder or a liquid aerosol), for administration
10 by insufflation (for example as a finely divided powder) or for parenteral administration (for example as a sterile aqueous or oily solution for intravenous, subcutaneous, intramuscular or intramuscular dosing or as a suppository for rectal dosing). In general, compositions in a form suitable for oral use are preferred.

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

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

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

 Aqueous suspensions generally contain the active ingredient in finely powdered form together with one or more suspending agents, such as sodium

carboxymethylcellulose, methylcellulose, hydroxypropylmethylcellulose, sodium alginate, polyvinyl-pyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents such as lecithin or condensation products of an alkylene oxide with fatty acids (for example polyoxethylene stearate), or condensation products of ethylene oxide with long chain
5 aliphatic alcohols, for example heptadecaethyleneoxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethyleneoxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as
10 polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, for example polyethylene sorbitan monooleate. The aqueous suspensions may also contain one or more preservatives (such as ethyl or propyl *p*-hydroxybenzoate, anti-oxidants (such as ascorbic acid), colouring agents, flavouring agents, and/or sweetening agents (such as sucrose,
15 saccharine or aspartame).

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

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

The pharmaceutical compositions of the invention may also be in the form of oil-in-water emulsions. The oily phase may be a vegetable oil, such as olive oil or arachis oil, or a mineral oil, such as for example liquid paraffin or a mixture of any of these.
30 Suitable emulsifying agents may be, for example, naturally-occurring gums such as gum acacia or gum tragacanth, naturally-occurring phosphatides such as soya bean, lecithin, an

esters or partial esters derived from fatty acids and hexitol anhydrides (for example sorbitan monooleate) and condensation products of the said partial esters with ethylene oxide such as polyoxyethylene sorbitan monooleate. The emulsions may also contain sweetening, flavouring and preservative agents.

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

 The pharmaceutical compositions may also be in the form of a sterile injectable aqueous or oily suspension, which may be formulated according to known procedures
10 using one or more of the appropriate dispersing or wetting agents and suspending agents, which have been mentioned above. A sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally-acceptable diluent or solvent, for example a solution in 1,3-butanediol.

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

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

 The amount of active ingredient that is combined with one or more excipients to produce a single dosage form will necessarily vary depending upon the host treated and the particular route of administration. For example, a formulation intended for oral
25 administration to humans will generally contain, for example, from 0.5 mg to 2 g of active agent compounded with an appropriate and convenient amount of excipients which may vary from about 5 to about 98 percent by weight of the total composition. Dosage unit forms will generally contain about 1 mg to about 500 mg of an active ingredient. For further information on Routes of Administration and Dosage Regimes the reader is referred
30 to Chapter 25.3 in Volume 5 of Comprehensive Medicinal Chemistry (Corwin Hansch; Chairman of Editorial Board), Pergamon Press 1990.

We have found that the compounds defined in the present invention, or a pharmaceutically-acceptable salt thereof, are effective 11 β HSD1 inhibitors, and accordingly have value in the treatment of disease states associated with metabolic syndrome.

5 It is to be understood that where the term “metabolic syndrome” is used herein, this relates to metabolic syndrome as defined in 1) and/or 2) or any other recognised definition of this syndrome. Synonyms for “metabolic syndrome” used in the art include Reaven’s Syndrome, Insulin Resistance Syndrome and Syndrome X. It is to be understood that where the term “metabolic syndrome” is used herein it also refers to Reaven’s Syndrome,
10 Insulin Resistance Syndrome and Syndrome X.

According to a further aspect of the present invention there is provided a compound of formula (1), or a pharmaceutically-acceptable salt thereof, as defined hereinbefore for use in a method of prophylactic or therapeutic treatment of a warm-blooded animal, such as man.

15 Thus according to this aspect of the invention there is provided a compound of formula (1), or a pharmaceutically-acceptable salt thereof, as defined hereinbefore for use as a medicament.

According to another feature of the invention there is provided the use of a compound of formula (1), or a pharmaceutically-acceptable salt thereof, as defined
20 hereinbefore in the manufacture of a medicament for use in the production of an 11 β HSD1 inhibitory effect in a warm-blooded animal, such as man.

Where production of or producing an 11 β HSD1 inhibitory effect is referred to suitably this refers to the treatment of metabolic syndrome. Alternatively, where production of an 11 β HSD1 inhibitory effect is referred to this refers to the treatment of
25 diabetes, obesity, hyperlipidaemia, hyperglycaemia, hyperinsulinemia or hypertension. In particularly where production of an 11 β HSD1 inhibitory effect is referred to this refers to the treatment of diabetes and obesity. In one aspect, type 2 diabetes. In another aspect, obesity. Alternatively, where production of an 11 β HSD1 inhibitory effect is referred to this refers to the treatment of glaucoma, osteoporosis, tuberculosis, dementia, cognitive
30 disorders or depression.

Alternatively, where production of an 11 β HSD1 inhibitory effect is referred to this refers to the treatment of cognitive disorders, such as improving the cognitive ability of an individual, for example by improvement of verbal fluency, verbal memory or logical memory, or for treatment of mild cognitive disorders. See for example WO03/086410 and
5 references contained therein, and Proceedings of National Academy of Sciences (PNAS), 2001, 98(8), 4717-4721.

Alternatively, where production of an 11 β HSD1 inhibitory effect is referred to this refers to the treatment of, delaying the onset of and/or reducing the risk of atherosclerosis – see for example J. Experimental Medicine, 2005, 202(4), 517-527.

10 Alternatively, where production of an 11 β HSD1 inhibitory effect is referred to this refers to the treatment of Alzheimers and/or neurodegenerative disorders.

According to a further feature of this aspect of the invention there is provided a method for producing an 11 β HSD1 inhibitory effect in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective
15 amount of a compound of formula (1), or a pharmaceutically-acceptable salt thereof.

In addition to their use in therapeutic medicine, the compounds of formula (1), or a pharmaceutically-salt thereof, are also useful as pharmacological tools in the development and standardisation of *in vitro* and *in vivo* test systems for the evaluation of the effects of inhibitors of 11 β HSD1 in laboratory animals such as cats, dogs, rabbits, monkeys, rats and
20 mice, as part of the search for new therapeutic agents.

The inhibition of 11 β HSD1 described herein may be applied as a sole therapy or may involve, in addition to the subject of the present invention, one or more other substances and/or treatments. Such conjoint treatment may be achieved by way of the simultaneous, sequential or separate administration of the individual components of the
25 treatment. Simultaneous treatment may be in a single tablet or in separate tablets. For example agents than might be co-administered with 11 β HSD1 inhibitors, particularly those of the present invention, may include the following main categories of treatment:

- 1) Insulin and insulin analogues;
- 2) Insulin secretagogues including sulphonylureas (for example glibenclamide,
30 glipizide), prandial glucose regulators (for example repaglinide, nateglinide), glucagon-

like peptide 1 agonist (GLP1 agonist) (for example exenatide, liraglutide) and dipeptidyl peptidase IV inhibitors (DPP-IV inhibitors);

3) Insulin sensitising agents including PPAR γ agonists (for example pioglitazone and rosiglitazone);

5 4) Agents that suppress hepatic glucose output (for example metformin);

5) Agents designed to reduce the absorption of glucose from the intestine (for example acarbose);

6) Agents designed to treat the complications of prolonged hyperglycaemia; e.g. aldose reductase inhibitors

10 7) Other anti-diabetic agents including phosphotyrosine phosphatase inhibitors, glucose 6 - phosphatase inhibitors, glucagon receptor antagonists, glucokinase activators, glycogen phosphorylase inhibitors, fructose 1,6 bisphosphatase inhibitors, glutamine:fructose -6-phosphate amidotransferase inhibitors

8) Anti-obesity agents (for example sibutramine and orlistat);

15 9) Anti- dyslipidaemia agents such as, HMG-CoA reductase inhibitors (statins, eg pravastatin); PPAR α agonists (fibrates, eg gemfibrozil); bile acid sequestrants (cholestyramine); cholesterol absorption inhibitors (plant stanols, synthetic inhibitors); ileal bile acid absorption inhibitors (IBATi), cholesterol ester transfer protein inhibitors and nicotinic acid and analogues (niacin and slow release formulations);

20 10) Antihypertensive agents such as, β blockers (eg atenolol, inderal); ACE inhibitors (eg lisinopril); calcium antagonists (eg. nifedipine); angiotensin receptor antagonists (eg candesartan), α antagonists and diuretic agents (eg. furosemide, benzthiazide);

11) Haemostasis modulators such as, antithrombotics, activators of fibrinolysis and antiplatelet agents; thrombin antagonists; factor Xa inhibitors; factor VIIa inhibitors;
25 antiplatelet agents (eg. aspirin, clopidogrel); anticoagulants (heparin and Low molecular weight analogues, hirudin) and warfarin;

12) Anti-inflammatory agents, such as non-steroidal anti-inflammatory drugs (eg. aspirin) and steroidal anti-inflammatory agents (eg. cortisone); and

13) Agents that prevent the reabsorption of glucose by the kidney (SGLT inhibitors).

30 In the above other pharmaceutical composition, process, method, use and medicament manufacture features, the alternative and preferred embodiments of the compounds of the invention described herein also apply.

Examples

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

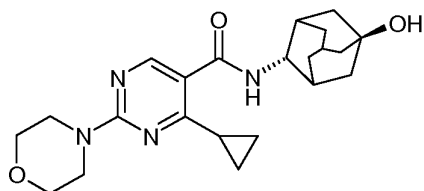
- (i) temperatures are given in degrees Celsius (°C); operations were carried out at room or ambient temperature, that is, at a temperature in the range of 18-25 °C and under an atmosphere of an inert gas such as argon;
- (ii) evaporation of solvent was carried out using a rotary evaporator under reduced pressure (600-4000 Pa; 4.5-30 mmHg) with a bath temperature of up to 60 °C;
- (iii) chromatography means flash chromatography on silica gel;
- (iv) in general, the course of reactions was followed by TLC and reaction times are given for illustration only;
- (v) yields are given for illustration only and are not necessarily those which can be obtained by diligent process development; preparations were repeated if more material was required;
- (vi) where given, NMR data (¹H) is in the form of delta values for major diagnostic protons, given in parts per million (ppm) relative to tetramethylsilane (TMS), determined at 300 or 400 MHz (unless otherwise stated) using perdeuterio dimethyl sulfoxide (DMSO-*d*₆) as solvent, unless otherwise stated; peak multiplicities are shown thus: s, singlet; d, doublet; dd, doublet of doublets; dt, doublet of triplets; dm, doublet of multiplets; t, triplet; m, multiplet; br, broad; protons attached to oxygen or nitrogen may give rise to very broad peaks which are not reported;
- (vii) chemical symbols have their usual meanings; SI units and symbols are used;
- (viii) solvent ratios are given in volume : volume (v/v) terms;
- (ix) mass spectra (MS) were run with an electron energy of 70 electron volts in the chemical ionisation (CI) mode using a direct exposure probe; where indicated ionisation was effected by electron impact (EI), fast atom bombardment (FAB) or electrospray (ESP); values for *m/z* are given; generally, only ions which indicate the parent mass are reported;
- (x) where examples are indicated by chemical name and/or structure to be an enantiomer, in some cases the product may contain a small amount of the other enantiomer;
- (xi) The following abbreviations may be used below or in the process section hereinbefore:

Et ₂ O	diethyl ether
DMF	dimethylformamide

	DCM	dichloromethane
	DME	1,2-dimethoxyethane
	MeOH	methanol
	EtOH	ethanol
5	H ₂ O	water
	TFA	trifluoroacetic acid
	THF	tetrahydrofuran
	DMSO	dimethylsulfoxide
	HOBt	1-hydroxybenzotriazole
10	EDCI (EDAC)	1-ethyl-3-(3-dimethylaminopropyl)carbodi-imide hydrochloride
	DIPEA	diisopropylethylamine
	DEAD	diethyl azodicarboxylate
	EtOAc	ethyl acetate
15	NaHCO ₃	sodium bicarbonate
	K ₃ PO ₄	potassium phosphate
	MgSO ₄	magnesium sulfate
	PS	polymer supported
	BINAP	2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
20	Dppf	1,1'-bis(diphenylphosphino)ferrocene
	dba	dibenzylideneacetone
	PS-CDI	polymer supported carbonyldiimidazole

Example 1

- 25 4-Cyclopropyl-N-[(2s,5r)-5-hydroxyadamantan-2-yl]-2-morpholin-4-ylpyrimidine-5-carboxamide



(1s,4r)-4-Aminoadamant-1-ol (335 mg, 2.01 mmol) was added in one portion to a mixture of 4-cyclopropyl-2-morpholinopyrimidine-5-carboxylic acid (Intermediate 3, 500 mg, 2.01

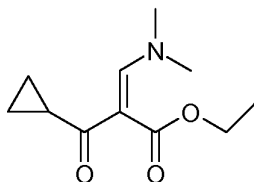
mmol), 1-hydroxybenzotriazole (298 mg, 2.21 mmol), 1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (461 mg, 2.41 mmol) and N,N-Diisopropylethylamine (1.22 mL, 7.02 mmol) in DMF (10 mL) under nitrogen. The resulting suspension was stirred at room temperature for 16 hours. The reaction mixture was diluted with water/ice
5 (50 mL) and the resulting precipitate was extracted with EtOAc (2x25 mL). The combined extracts were washed with brine (25 mL), dried over MgSO₄, filtered and evaporated to give crude product. The crude product was purified by flash silica (40 g) chromatography, elution gradient 0 to 100% 10%MeOH/EtOAc in EtOAc. Pure fractions were evaporated to dryness to afford 4-cyclopropyl-N-[(2s,5r)-5-hydroxyadamantan-2-yl]-2-morpholin-4-
10 ylpyrimidine-5-carboxamide (115 mg, 14%) as a white solid.

¹H NMR (400.13 MHz, DMSO-d₆) δ 0.91 - 0.98 (2H, m), 0.99 - 1.04 (2H, m), 1.32 (2H, d), 1.62 (4H, s), 1.71 (2H, s), 1.93 (2H, d), 1.99 (1H, s), 2.04 (2H, s), 2.41 - 2.46 (1H, m), 3.61 (4H, d), 3.67 (4H, t), 3.92 (1H, t), 4.37 (1H, s), 8.05 (1H, d), 8.23 (1H, t)
m/z (ESI+) (M+H)⁺ = 399; HPLC t_R = 1.64 min.

15

Intermediate 1

Ethyl 2-(cyclopropanecarbonyl)-3-(dimethylamino)acrylate

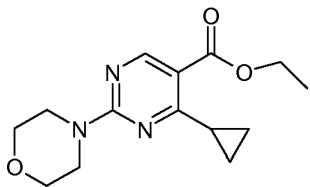


N,N-Dimethylformamide dimethyl acetal (4.26 mL, 32.01 mmol) was added in one portion
20 to ethyl 3-cyclopropyl-3-oxopropanoate (5.00 g, 32.01 mmol) in dioxane (50 mL) and warmed to 100°C over a period of 5 minutes under nitrogen. The resulting solution was stirred at this temperature for 4 hours. The resulting mixture was evaporated to dryness and the residue was azeotroped with toluene to afford crude ethyl 2-(cyclopropanecarbonyl)-3-(dimethylamino)acrylate (6.70 g, 99 %), which was used without further purification.

25 ¹H NMR (400.13 MHz, CDCl₃) δ 0.72 - 0.76 (2H, m), 0.92 - 0.98 (2H, m), 1.18 - 1.24 (3H, m), 2.31 (1H, s), 2.72 - 2.91 (6H, m), 4.16 (2H, q), 7.52 (1H, s)
m/z (ESI+) (M+H)⁺ = 212; HPLC t_R = 1.38 min.

Intermediate 2

Ethyl 4-cyclopropyl-2-morpholinopyrimidine-5-carboxylate

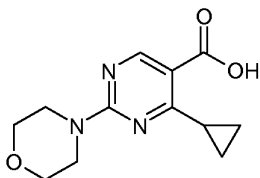


A solution of ethyl 2-(cyclopropanecarbonyl)-3-(dimethylamino)acrylate (Intermediate 1, 6.76 g, 32 mmol) in ethanol (25 mL) was added dropwise to a stirred suspension of morpholine-4-carboximidamide hydrochloride (5.30 g, 32.00 mmol) and sodium ethoxide (2.18 g, 32.00 mmol) in ethanol (75 mL) over a period of 5 minutes under nitrogen. The resulting suspension was stirred at room temperature for 16 hours. The reaction mixture was evaporated to dryness and redissolved in water/ice (150 mL). The precipitate was collected by filtration, washed with water (25 mL) and dried under vacuum to afford ethyl 4-cyclopropyl-2-morpholinopyrimidine-5-carboxylate (3.12 g, 35%) as a orange solid, which was used without further purification.

¹H NMR (400.13 MHz, DMSO-*d*₆) δ 1.01 - 1.06 (2H, m), 1.07 - 1.12 (2H, m), 1.30 (3H, t), 3.11 - 3.17 (1H, m), 3.64 (4H, d), 3.74 (4H, d), 4.26 (2H, q), 8.71 (1H, s)
m/z (ESI⁺) (M+H)⁺ = 278; HPLC *t*_R = 2.43 min.

Intermediate 3

4-cyclopropyl-2-morpholinopyrimidine-5-carboxylic acid



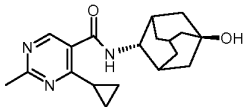
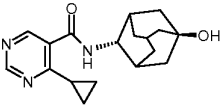
A solution of sodium hydroxide (9.01 mL, 18.03 mmol) was added in one portion to a stirred solution of ethyl 4-cyclopropyl-2-morpholinopyrimidine-5-carboxylate (Intermediate 2, 2.00 g, 7.21 mmol) in methanol (50 mL) and warmed to 100°C over a period of 5 minutes under air. The resulting solution was stirred at this temperature for 4 hours. The reaction mixture was evaporated to dryness and redissolved in water (20 mL) and acidified with 2M HCl. The precipitate was collected by filtration, washed with water (20 mL) and dried under vacuum to afford 4-cyclopropyl-2-morpholinopyrimidine-5-

carboxylic acid (1.70 g, 95%) as a cream solid, which was used without further purification.

^1H NMR (400.13 MHz, DMSO- d_6) δ 0.99 - 1.05 (2H, m), 1.07 - 1.10 (2H, m), 3.22 - 3.28 (1H, m), 3.62 - 3.67 (4H, m), 3.73 (4H, t), 8.71 (1H, s), 12.76 (1H, s)

5 m/z (ESI+) (M+H) $^+$ = 250; HPLC t_R = 1.64 min.

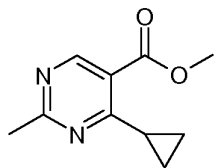
The following Examples were prepared in a similar manner to Example 1, using Intermediate 1 and an appropriate amidine or guanidine starting material:

Structure	Ex	Name	^1H NMR δ	MS m/e MH^+
	2	4-cyclopropyl-N-[(2r,5s)-5-hydroxyadamantan-2-yl]-2-methylpyrimidine-5-carboxamide	^1H NMR (400.132 MHz, CDCl $_3$) δ 1.05 - 1.12 (2H, m), 1.26 - 1.32 (2H, m), 1.59 (3H, d), 1.67 - 1.75 (2H, m), 1.78 - 1.86 (4H, m), 1.95 (2H, d), 2.19 (1H, s), 2.27 (2H, s), 2.35 - 2.42 (1H, m), 2.62 (3H, s), 4.25 (1H, d), 6.10 (1H, d), 8.53 (1H, s)	328; HPLC t_R = 1.33 min.
	3	4-cyclopropyl-N-[(2r,5s)-5-hydroxyadamantan-2-yl]pyrimidine-5-carboxamide	^1H NMR (400.132 MHz, CDCl $_3$) δ 1.11 - 1.17 (2H, m), 1.29 - 1.34 (2H, m), 1.60 (3H, d), 1.69 - 1.76 (2H, m), 1.78 - 1.86 (4H, m), 1.96 (2H, d), 2.19 (1H, s), 2.28 (2H, s), 2.40 (1H, septet), 4.27 (1H, d), 6.11 (1H, d), 8.61 (1H, s), 9.00 (1H, s)	314; HPLC t_R = 1.2 min.

The following intermediates were used and were prepared as described below.

Intermediate 4

Methyl 2-methyl-4-cyclopropylpyrimidine-5-carboxylate

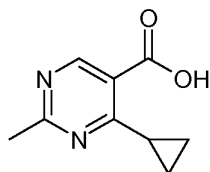


Prepared by the same process used for Intermediate 2 from methyl 2-(cyclopropanecarbonyl)-3-(dimethylamino)acrylate.

¹H NMR (400.13 MHz, DMSO-d₆) δ 1.09 - 1.17 (4H, m), 2.55 (3H, s), 2.96 - 3.02 (1H, m), 3.88 (3H, s), 8.88 (1H, s)
 m/z (ESI+) (M+H)⁺ = 193; HPLC t_R = 1.79 min.

Intermediate 5

2-Methyl-4-cyclopropylpyrimidine-5-carboxylic acid

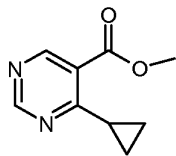


Prepared from methyl 2-methyl-4-cyclopropylpyrimidine-5-carboxylate (Intermediate 4) by the same process used for Intermediate 3.

¹H NMR (400.13 MHz, DMSO-d₆) δ 1.06 - 1.15 (4H, m), 2.54 (3H, s), 3.08 - 3.14 (1H, m), 8.87 (1H, s), 13.49 (1H, s)
 m/z (ESI+) (M+H)⁺ = 179; HPLC t_R = 1.07 min.

Intermediate 6

Methyl 4-cyclopropylpyrimidine-5-carboxylate

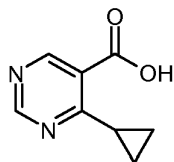


Prepared by the same process used for Intermediate 2 from methyl 2-(cyclopropanecarbonyl)-3-(dimethylamino)acrylate.

¹H NMR (400.132 MHz, CDCl₃) δ 1.15 - 1.20 (2H, m), 1.29 - 1.34 (2H, m), 3.12 (1H, septet), 3.97 (3H, s), 9.02 (2H, s)
 m/z (ESI+) (M+H)⁺ = 179; HPLC t_R = 1.46 min.

Intermediate 7

4-cyclopropylpyrimidine-5-carboxylic acid



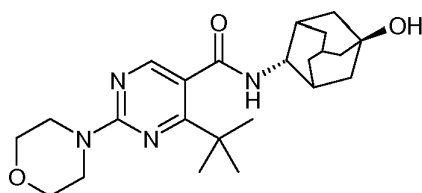
Prepared from methyl 4-cyclopropylpyrimidine-5-carboxylate (Intermediate 6) by the same process used for Intermediate 3.

¹H NMR (400.132 MHz, DMSO) δ 2.49 (4H, quintet), 3.09 (1H, quintet), 8.96 (1H, s), 9.05 (1H, s), 13.10 - 14.12 (1H, m)

m/z (ESI⁺) (M+H)⁺ = 165; HPLC t_R = 0.93 min.

Example 4

4-tert-Butyl-N-[(2r,5s)-5-hydroxyadamantan-2-yl]-2-morpholin-4-ylpyrimidine-5-carboxamide



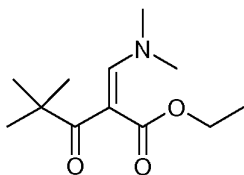
O-(7-Azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (456 mg, 1.20 mmol) was added in one portion to 4-tert-butyl-2-morpholinopyrimidine-5-carboxylic acid (Intermediate 10, 265 mg, 1.00 mmol), (1s,4r)-4-aminoadamantan-1-ol hydrochloride (203 mg, 1.00 mmol) and N-ethyl-diisopropylamine (0.518 mL, 3.00 mmol) in DMF (10 mL) at 20°C under nitrogen. The resulting suspension was stirred at 20 °C for 2 hours. The reaction mixture was diluted with EtOAc (100 mL), and washed sequentially with water (4x25 mL) and saturated brine (25 mL). The organic layer was dried over Na₂SO₄, filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 0 to 5% MeOH in EtOAc. Pure fractions were evaporated to dryness to afford 4-tert-butyl-N-[(2r,5s)-5-hydroxyadamantan-2-yl]-2-morpholin-4-ylpyrimidine-5-carboxamide (296 mg, 72%) as a white solid.

¹H NMR (300.13 MHz, DMSO-d₆) δ 1.28 - 1.35 (11H, m), 1.61 - 1.74 (6H, m), 1.89 - 2.02 (5H, m), 3.64 - 3.74 (8H, m), 3.88 - 3.95 (1H, m), 4.39 (1H, s), 8.09 (1H, s), 8.18 (1H, d)

m/z (ESI+) (M+H)+ = 415; HPLC t_R = 1.94 min.

Intermediate 8

Ethyl 2-((dimethylamino)methylene)-4,4-dimethyl-3-oxopentanoate



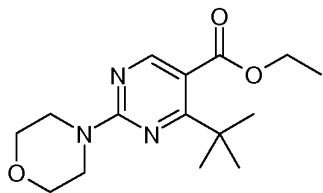
N,N-Dimethylformamide dimethyl acetal (3.86 mL, 29.03 mmol) was added to ethyl pivaloylacetate (5.21 mL, 29.03 mmol) in dioxane (40 mL) under nitrogen. The resulting solution was stirred at 100 °C for 9 hours. The reaction mixture was evaporated to afford the crude product as a yellow oil that was used in the following step without further purification.

^1H NMR (400.13 MHz, CDCl_3) δ 1.24 (9H, s), 1.26 - 1.30 (3H, m), 2.89 (6H, s), 4.18 (2H, q), 7.36 (1H, s)

m/z (ESI+) (M+H)+ = 228; HPLC t_R = 1.95 min.

Intermediate 9

Ethyl 4-tert-butyl-2-morpholinopyrimidine-5-carboxylate

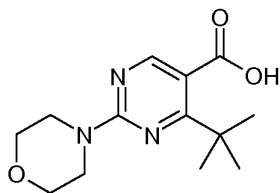


Morpholinoformamidinium hydrobromide (2.098 g, 9.99 mmol) was added to sodium methoxide (19.97 mL, 9.99 mmol). Ethyl 2-((dimethylamino)methylene)-4,4-dimethyl-3-oxopentanoate (Intermediate 8, 2.27 g, 9.99 mmol) was then added and the resulting mixture was stirred at 70 °C for 5 hours under nitrogen. The reaction mixture was diluted with EtOAc (100 mL), and washed sequentially with water (2x50 mL) and saturated brine (50 mL). The organic layer was dried over MgSO_4 , filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 0 to 20% EtOAc in isohexane. Pure fractions were evaporated to dryness to afford ethyl 4-tert-butyl-2-morpholinopyrimidine-5-carboxylate (1.310 g, 45%) as a colourless oil.

¹H NMR (400.13 MHz, DMSO-d₆) δ 1.28 (3H, t), 1.32 (9H, s), 3.64 - 3.67 (4H, m), 3.75 - 3.79 (4H, m), 4.25 (2H, q), 8.48 (1H, s)
m/z (ESI+) (M+H)⁺ = 294; HPLC t_R = 2.77 min.

5 Intermediate 10

4-tert-butyl-2-morpholinopyrimidine-5-carboxylic acid

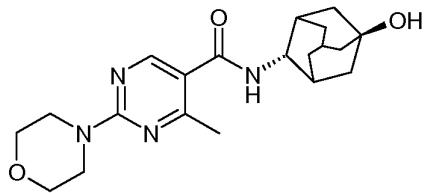


A solution of sodium hydroxide (11.16 mL, 22.33 mmol) was added to a stirred solution of ethyl 4-tert-butyl-2-morpholinopyrimidine-5-carboxylate (Intermediate 9, 1.31 g, 4.47 mmol) in methanol (20 mL) at 20°C. The resulting mixture was stirred at 100 °C for 24 hours. The reaction mixture was concentrated and diluted with water (100 mL) and washed with ether (50 mL). The reaction mixture was acidified with 2M HCl and extracted with EtOAc (2x50ml). The organic layers were combined and washed sequentially with water (50 mL) and saturated brine (50 mL). The organic layer was dried over MgSO₄, filtered and evaporated to afford desired product that was used without further purification.

¹H NMR (400.13 MHz, DMSO-d₆) δ 1.35 (9H, s), 3.64 - 3.66 (4H, m), 3.74 - 3.79 (4H, m), 8.51 (1H, s), 12.86 (1H, s)
m/z (ESI+) (M+H)⁺ = 266; HPLC t_R = 1.91 min.

20 Example 5

N-[(2r,5s)-5-hydroxyadamantan-2-yl]-4-methyl-2-morpholin-4-ylpyrimidine-5-carboxamide

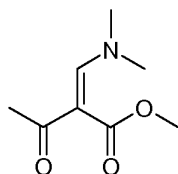


O-(7-Azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (456 mg, 1.20 mmol) was added in one portion to (1s,4r)-4-aminoadamantan-1-ol hydrochloride

(204 mg, 1.00 mmol), 4-methyl-2-morpholinopyrimidine-5-carboxylic acid (Intermediate 13, 223 mg, 1.00 mmol) and N-ethyldiisopropylamine (0.519 mL, 3.00 mmol) in DMF (10 mL) at 20°C under nitrogen. The resulting suspension was stirred at 20 °C for 2 hours. The reaction mixture was diluted with EtOAc (100 mL), and washed sequentially with water
5 (4x25 mL) and saturated brine (25 mL). The organic layer was dried over MgSO₄, filtered and evaporated to afford crude product. The crude product was purified by preparative HPLC (Phenomenex Gemini C18 110A (axia) column, 5μ silica, 30 mm diameter, 100 mm length), using decreasingly polar mixtures of water (containing 0.1% NH₃) and MeCN as eluents. Fractions containing the desired compound were evaporated to dryness to afford
10 N-[(2r,5s)-5-hydroxyadamantan-2-yl]-4-methyl-2-morpholin-4-ylpyrimidine-5-carboxamide (114 mg, 31%) as a white solid.
1H NMR (400.13 MHz, DMSO-d₆) δ 1.30 - 1.34 (2H, m), 1.60 - 1.63 (4H, m), 1.69 - 1.72 (2H, m), 1.92 (2H, d), 1.99 (1H, s), 2.03 (2H, s), 2.38 (3H, s), 3.62 - 3.64 (4H, m), 3.72 - 3.75 (4H, m), 3.90 (1H, t), 4.38 (1H, s), 7.96 - 7.98 (1H, m), 8.31 (1H, s)
15 m/z (ESI+) (M+H)+ = 373; HPLC t_R = 1.43 min.

Intermediate 11

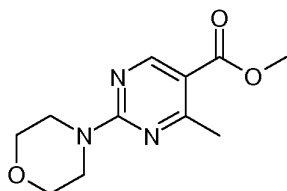
Methyl 2-((dimethylamino)methylene)-3-oxobutanoate



20 Prepared from methyl 3-oxobutanoate by the same process used for Intermediate 8.
1H NMR (400.13 MHz, DMSO-d₆) δ 2.13 (3H, s), 2.51 - 3.08 (6H, m), 3.63 (3H, s), 7.61 (1H, s)

Intermediate 12

25 Methyl 4-methyl-2-morpholinopyrimidine-5-carboxylate



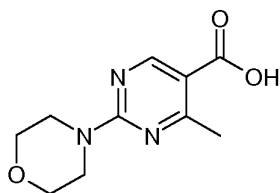
Prepared from methyl 2-((dimethylamino)methylene)-3-oxobutanoate (Intermediate 11) by the same process used for Intermediate 9.

¹H NMR (400.13 MHz, DMSO-d₆) δ 2.56 (3H, s), 3.62 - 3.66 (4H, m), 3.77 (3H, s), 3.80 - 3.82 (4H, m), 8.74 (1H, s)

5 m/z (ESI+) (M+H)⁺ = 238; HPLC t_R = 1.74 min.

Intermediate 13

4-methyl-2-morpholinopyrimidine-5-carboxylic acid



10 Prepared from methyl 4-methyl-2-morpholinopyrimidine-5-carboxylate (Intermediate 12) by the same process used for Intermediate 10.

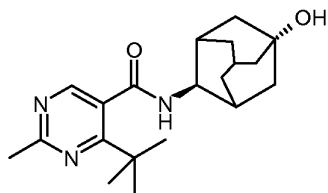
¹H NMR (400.13 MHz, DMSO-d₆) δ 2.56 (3H, s), 3.62 - 3.66 (4H, m), 3.79 - 3.81 (4H, m), 8.73 (1H, s), 12.63 (1H, s)

m/z (ESI+) (M+H)⁺ = 224; HPLC t_R = 1.3 min.

15

Example 6

4-tert-Butyl-N-[(2r,5s)-5-hydroxyadamantan-2-yl]-2-methylpyrimidine-5-carboxamide



Oxalyl chloride (0.337 mL, 3.86 mmol) was added to 4-tert-butyl-2-methylpyrimidine-5-carboxylic acid (Intermediate 15, 250 mg, 1.29 mmol) in CH₂Cl₂ (25 mL). One drop of DMF was added and the resulting suspension was stirred at 20 °C for 3 hours. The resulting mixture was evaporated to dryness and the residue was azeotroped with toluene to afford crude 4-tert-butyl-2-methylpyrimidine-5-carbonyl chloride, which was dissolved in DCM (2 mL) and added dropwise to a stirred suspension of (1s,4r)-4-aminoadamantan-1-ol hydrochloride (0.263 g, 1.29 mmol) and N-ethyldiisopropylamine (0.491 mL, 2.84 mmol) in THF (4 mL). The resulting solution was stirred at 20 °C for 3 hours. The reaction

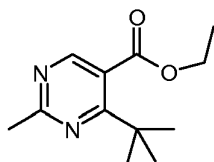
mixture was evaporated to dryness and redissolved in EtOAc (25 mL), and washed sequentially with water (5 mL), 1N citric acid (5 mL), saturated NaHCO₃ (5 mL) and saturated brine (5 mL). The organic layer was dried over MgSO₄, filtered and evaporated to afford crude product. The crude residue was triturated with Et₂O to give a solid which
 5 was collected by filtration and dried under vacuum to give 4-tert-butyl-N-[(2r,5s)-5-hydroxyadamantan-2-yl]-2-methylpyrimidine-5-carboxamide (0.240 g, 54%)

¹H NMR (400.132 MHz, CDCl₃) δ 1.42 (10H, s), 1.58 (2H, d), 1.64 - 1.72 (2H, m), 1.77 - 1.86 (4H, m), 1.95 (2H, d), 2.16 (1H, s), 2.26 (2H, s), 2.70 (3H, s), 4.22 (1H, d), 5.91 (1H, d), 8.41 (1H, s)

10 m/z (ESI+) (M+H)⁺ = 344; HPLC t_R = 1.63 min.

Intermediate 14

Ethyl 4-tert-butyl-2-methylpyrimidine-5-carboxylate



15 Prepared from ethyl 2-((dimethylamino)methylene)-4,4-dimethyl-3-oxopentanoate (Intermediate 8) by the same process used for Intermediate 9.

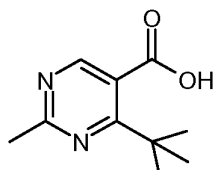
¹H NMR (400.132 MHz, CDCl₃) δ 1.39 (3H, t), 1.40 (9H, s), 2.71 (3H, s), 4.39 (2H, q), 8.54 (1H, s)

m/z (ESI+) (M+H)⁺ = 223; HPLC t_R = 2.36 min.

20

Intermediate 15

4-tert-butyl-2-methylpyrimidine-5-carboxylic acid



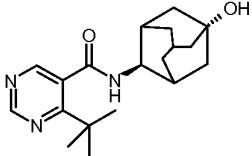
25 Prepared from ethyl 4-tert-butyl-2-methylpyrimidine-5-carboxylate (Intermediate 14) by the same process used for Intermediate 10.

¹H NMR (400.132 MHz, CDCl₃) δ 1.46 (9H, s), 2.77 (3H, s), 8.79 (1H, s)

m/z (ESI⁺) (M+H)⁺ = 195; HPLC t_R = 1.67 min.

The following Example was prepared in a similar manner to Example 6, using an appropriate carboxylic acid starting material (intermediate 17):

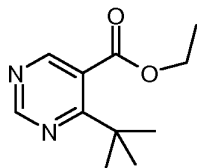
5

Structure	Ex	Name	¹ H NMR δ	MS m/e MH ⁺
	7	4-tert-butyl-N-[(2r,5s)-5-hydroxyadamantan-2-yl]pyrimidine-5-carboxamide	¹ H NMR (400.132 MHz, CDCl ₃) δ 1.41 (1H, s), 1.44 (9H, s), 1.59 (2H, d), 1.65 - 1.74 (2H, m), 1.78 - 1.86 (4H, m), 1.96 (2H, d), 2.18 (1H, s), 2.27 (2H, s), 4.24 (1H, d), 5.94 (1H, d), 8.52 (1H, s), 9.15 (1H, s)	330; HPLC t_R = 1.45 min.

The following intermediates were used and were prepared as described below.

Intermediate 16

10 Ethyl 4-tert-butylpyrimidine-5-carboxylate



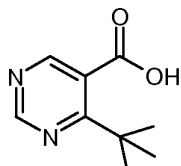
Prepared from Methyl 2-((dimethylamino)methylene)-3-oxobutanoate (Intermediate 11) by the same process used for Intermediate 12.

¹H NMR (400.132 MHz, CDCl₃) δ 1.41 (3H, t), 1.43 (9H, s), 4.41 (2H, q), 8.64 (1H, s),
15 9.15 (1H, s)

m/z (ESI⁺) (M+HOAc)⁺ = 269; HPLC t_R = 2.11 min.

Intermediate 17

4-tert-butylpyrimidine-5-carboxylic acid



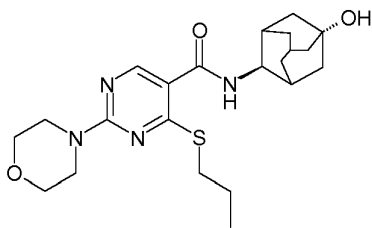
Prepared from ethyl 4-tert-butylpyrimidine-5-carboxylate (intermediate 16) by the same process used for Intermediate 10.

¹H NMR (400.132 MHz, CDCl₃) δ 1.48 (9H, s), 8.85 (1H, s), 9.23 (1H, s)

5 m/z (ESI⁺) (M+H)⁺ = 181; HPLC t_R = 1.07 min.

Example 8

N-[(2r,5s)-5-hydroxyadamantan-2-yl]-2-morpholin-4-yl-4-propylsulfanyl-pyrimidine-5-carboxamide



10

Oxalyl chloride (0.187 mL, 2.14 mmol) was added dropwise to a stirred solution of 2-morpholino-4-(propylthio)pyrimidine-5-carboxylic acid (Intermediate 21, 303 mg, 1.07 mmol) in dichloromethane (20 mL) cooled to 5°C, over a period of 5 minutes under air. The resulting solution was stirred at 20 °C for 1 hour until the gas evolution had stopped.

15 The solution was evaporated under reduced pressure and redissolved in DCM. It was then added to a suspension of (1s,4r)-4-aminoadamantan-1-ol (179 mg, 1.07 mmol) and N-ethyldiisopropylamine (0.559 mL, 3.21 mmol) in THF (10 mL) at room temperature over a period of 20 minutes under air. The resulting solution was stirred at room temperature for 2 days.

20 The reaction mixture was concentrated and diluted with EtOAc (75 mL), and washed sequentially with water (2 x 20 mL) and saturated brine (10 mL). The organic layer was dried over MgSO₄, filtered and evaporated to afford crude product.

The crude product was purified by flash silica chromatography eluting with 10% MeOH in DCM. Pure fractions were evaporated to dryness to afford N-[(2r,5s)-5-

25 hydroxyadamantan-2-yl]-2-morpholin-4-yl-4-propylsulfanyl-pyrimidine-5-carboxamide

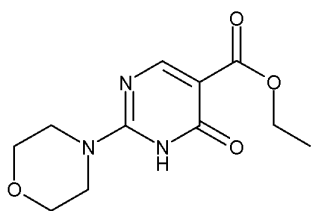
(127 mg, 28%) as a white solid.

¹H NMR (400.13 MHz, DMSO-d₆) δ 0.96 (3H, t), 1.32 (2H, d), 1.58 - 1.66 (6H, m), 1.71 (2H, d), 1.94 - 2.03 (5H, m), 3.01 (2H, t), 3.65 - 3.67 (4H, m), 3.75 - 3.79 (4H, m), 3.84 - 3.88 (1H, m), 4.44 (1H, s), 7.87 (1H, d), 8.32 (1H, s)

5 m/z (ESI+) (M+H)⁺ = 433; HPLC t_R = 1.94 min.

Intermediate 18

Ethyl 2-morpholino-6-oxo-1,6-dihydropyrimidine-5-carboxylate



10 Morpholinoformamidine hydrobromide (4.20 g, 20.0 mmol) was added portionwise to diethyl ethoxymethylenemalonate (4.04 mL, 20.0 mmol) and potassium carbonate (3.04 g, 22.0 mmol) in ethanol (80 mL) at room temperature and under air. The resulting suspension was stirred at 80°C for 2 hours causing formation of a white slurry. The reaction mixture was evaporated to dryness and acidified to pH 4-5. A white solid

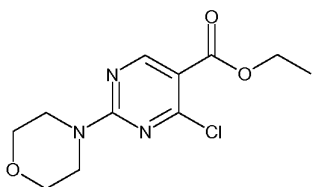
15 precipitated and was extracted with EtOAc (100 mL) and washed with saturated brine (20 mL). The organic layer was dried over MgSO₄, filtered and evaporated to afford ethyl 2-morpholino-6-oxo-1,6-dihydropyrimidine-5-carboxylate (2.13 g, 42%).

¹H NMR (400.13 MHz, DMSO-d₆) δ 1.24 (3H, t), 3.61 - 3.67 (4H, m), 3.69 - 3.74 (4H, m), 4.17 (2H, q), 8.45 (1H, s), 11.53 (1H, s)

20 m/z (ESI+) (M+H)⁺ = 254; HPLC t_R = 1.12 min.

Intermediate 19

Ethyl 4-chloro-2-morpholinopyrimidine-5-carboxylate



25 Phosphorus oxychloride (20 mL, 214 mmol) was added to ethyl 2-morpholino-6-oxo-1,6-dihydropyrimidine-5-carboxylate (Intermediate 18, 2.130 g, 8.41 mmol), and warmed to

100°C over a period of 5 minutes under nitrogen. The resulting suspension was stirred at 100 °C for 40 minutes and then allowed to cool down to room temperature. The reaction mixture was evaporated to dryness, redissolved in EtOAc (75 mL) and washed sequentially with water (15 mL) and saturated brine (10 mL). The organic layer was dried over MgSO₄,
5 filtered and evaporated to afford crude product.

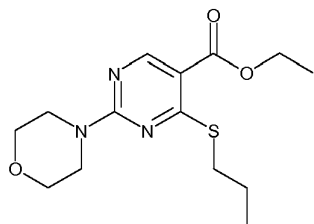
It was then purified by flash silica chromatography, elution gradient 0 to 50% EtOAc in isohexane. Pure fractions were evaporated to dryness to afford ethyl 4-chloro-2-morpholinopyrimidine-5-carboxylate (2.04 g, 89%) as a white solid.

¹H NMR (400.13 MHz, DMSO-d₆) δ 1.30 (3H, t), 3.67 - 3.68 (4H, m), 3.80 (4H, s), 4.27
10 (2H, q), 8.82 (1H, s)

m/z (ESI+) (M+H)⁺ = 272; HPLC t_R = 2.14 min.

Intermediate 20

ethyl 2-morpholino-4-(propylthio)pyrimidine-5-carboxylate



A solution of sodium bis(trimethylsilyl)amide (2.21 mL, 2.21 mmol) in THF (1M) was added to a stirred solution of 1-propanethiol (0.183 mL, 2.02 mmol) in DMF (10 mL) at room temperature, over a period of 3 minutes under air. The resulting suspension was stirred for 15 minutes and was added portionwise to a solution of ethyl 4-chloro-2-morpholinopyrimidine-5-carboxylate (Intermediate 19, 500 mg, 1.84 mmol) in DMF (5
20 mL). The resulting suspension was stirred at room temperature for 2 hours.

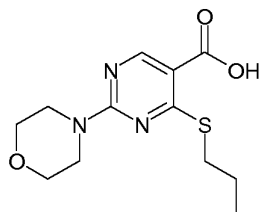
The reaction mixture was diluted with water (50 mL), extracted with DCM (100 mL) and washed with saturated brine (20 mL). The organic layer was dried over MgSO₄, filtered and evaporated to afford ethyl 2-morpholino-4-(propylthio)pyrimidine-5-carboxylate (529
25 mg, 92%).

¹H NMR (400.13 MHz, DMSO-d₆) δ 0.97 (3H, t), 1.28 (3H, t), 1.60 - 1.70 (2H, m), 3.03 (2H, t), 3.65 - 3.72 (4H, m), 3.80 - 3.87 (4H, m), 4.23 (2H, q), 8.64 (1H, s)

m/z (ESI+) (M+H)⁺ = 312; HPLC t_R = 2.60 min.

Intermediate 21

2-morpholino-4-(propylthio)pyrimidine-5-carboxylic acid



A solution of aqueous 2N sodium hydroxide (8.49 mL, 16.99 mmol) was added to a stirred suspension of ethyl 2-morpholino-4-(propylthio)pyrimidine-5-carboxylate (Intermediate 20, 529 mg, 1.70 mmol) in ethanol (15 mL). The resulting suspension was stirred at room temperature for 18 hours.

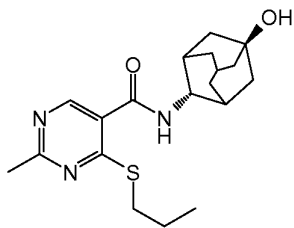
The reaction mixture was evaporated to dryness and redissolved in water (10 mL). It was then acidified with 2M HCl to pH 4-5, extracted with DCM (75 mL), and washed with saturated brine (10 mL). The organic layer was dried over MgSO₄, filtered and evaporated to afford 2-morpholino-4-(propylthio)pyrimidine-5-carboxylic acid (313 mg, 65%).

¹H NMR (400.13 MHz, DMSO-d₆) δ 0.97 (3H, t), 1.60 - 1.69 (2H, m), 3.01 (2H, t), 3.68 (4H, t), 3.83 (4H, t), 8.62 (1H, s), 12.76 (1H, s)

m/z (ESI⁺) (M+H)⁺ = 284; HPLC t_R = 1.91 min.

Example 9

N-[(2r,5s)-5-hydroxyadamantan-2-yl]-2-methyl-4-propylsulfanylpurimidine-5-carboxamide



Oxalyl chloride (0.20 mL, 2.36 mmol) was added dropwise to a suspension of 2-methyl-4-(propylthio)pyrimidine-5-carboxylic acid (Intermediate 24, 456 mg, 2.15 mmol) in DCM (20 mL) containing 3 drops of DMF at 20°C under nitrogen. The resulting mixture was stirred at 20 °C for 2 hours. The reaction mixture was evaporated, redissolved in DCM (10mL) and added dropwise to a suspension of 4-aminoadamantan-1-ol (359 mg, 2.15 mmol) and N,N-di-isopropylamine (1.10 mL, 6.44 mmol) in tetrahydrofuran (30 mL). The

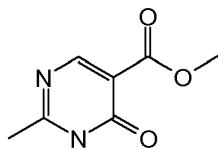
resulting mixture was stirred at 20 °C for 2 hours. The reaction mixture was diluted with EtOAc (100 mL), and then washed sequentially with water (2x100 mL). The organic layer was dried over MgSO₄, filtered and evaporated to afford the crude product. The crude product was purified by flash silica chromatography, elution gradient 0 to 10% MeOH in DCM. Pure fractions were evaporated to dryness to afford N-[(2r,5s)-5-hydroxyadamantan-2-yl]-2-methyl-4-propylsulfanylpurimidine-5-carboxamide (578 mg, 74%) as a yellow oil.

¹H NMR (400.13 MHz, CDCl₃) δ 0.99 (3H, t), 1.51 (2H, d), 1.65 - 1.74 (5H, m), 1.75 (2H, s), 1.74 - 1.79 (1H, m), 1.87 (2H, d), 2.13 (1H, s), 2.20 (2H, s), 2.62 (3H, s), 3.19 (2H, t), 4.14 - 4.19 (1H, m), 6.64 (1H, d), 8.61 (1H, s)

m/z (ESI⁺) (M+H)⁺ = 362; HPLC t_R = 1.79 min.

Intermediate 22

Methyl 2-methyl-4-oxo-3H-pyrimidine-5-carboxylate



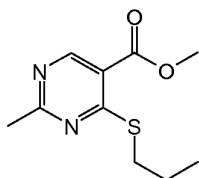
Diethyl 2-(ethoxymethylene)malonate (2.11 mL, 10.53 mmol) and acetimidamide (611 mg, 10.53 mmol) was added in one portion to sodium methoxide in methanol (0.5 M, 70 mL, 35 mmol) at room temperature. The resulting mixture was refluxed for 4 hours. The precipitate was collected by filtration, washed with MeOH (125 mL) and dried under vacuum to afford methyl 2-methyl-4-oxo-3H-pyrimidine-5-carboxylate (1.14 g, 64%), which was used without further purification.

¹H NMR (400.13 MHz, DMSO-d₆) δ 2.12 (3H, s), 3.16 (1H, s), 3.63 (3H, s), 8.27 (1H, s)

m/z (ESI⁺) (M+H)⁺ = 169; HPLC t_R = 0.60 min

Intermediate 23

Methyl 2-methyl-4-propylsulfanylpurimidine-5-carboxylate



Phosphorous oxychloride (15 mL, 6.78 mmol) was added to methyl 2-methyl-6-oxo-1,6-dihydropyrimidine-5-carboxylate (Intermediate 22, 1.14 g, 6.78 mmol). The insoluble mixture was refluxed for 3 hours. The excess POC_l3 was removed under vacuum. The mixture was evaporated to dryness and redissolved in EtOAc (100 mL) and washed sequentially with water (2x75 mL). The organic layer was dried over MgSO₄, filtered and evaporated to afford methyl 4-chloro-2-methylpyrimidine-5-carboxylate, which was used without further purification or characterisation.

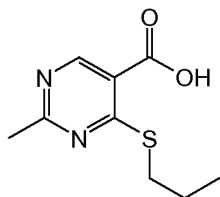
Sodium carbonate (819 mg, 7.73 mmol) was added to methyl 4-chloro-2-methylpyrimidine-5-carboxylate (490 mg, 2.63 mmol) and 1-propane thiol (0.24 mL, 2.63 mmol) in DMF (10 mL). The resulting solution was stirred at 60°C for 30 minutes. The reaction mixture was diluted with EtOAc (150 mL) and washed sequentially with water (2x100 mL). The organic layer was dried over MgSO₄, filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 10 to 50 % EtOAc in isohexane. Pure fractions were evaporated to dryness to afford methyl 2-methyl-4-(propylthio)pyrimidine-5-carboxylate (425 mg, 72%).

¹H NMR (400.13 MHz, CDCl₃) δ 0.98 (3H, t), 1.62 - 1.71 (2H, m), 2.62 (3H, s), 3.10 (2H, t), 3.85 (3H, s), 8.81 (1H, s)

m/z (ESI+) (M+H)⁺ = 227; HPLC t_R = 2.28 min

Intermediate 24

2-methyl-4-propylsulfanylpurimidine-5-carboxylic acid



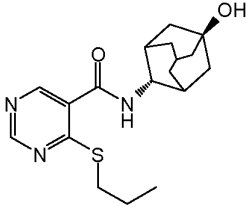
Prepared from methyl 2-methyl-4-propylsulfanylpurimidine-5-carboxylate (intermediate 23) by the same process used for Intermediate 21.

¹H NMR (400.13 MHz, CDCl₃) δ 1.00 (3H, t), 1.65 - 1.74 (2H, m), 2.72 (3H, s), 3.14 (2H, t), 7.19 (1H, s), 8.99 (1H, s)

m/z (ESI+) (M+H)⁺ = 213; HPLC t_R = 1.66 min.

The following Examples were prepared in a similar manner to Example 9, using (1s,4r)-4-

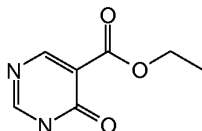
aminoadamantan-1-ol and an appropriate carboxylic acid starting material (intermediate 27):

Structure	Ex	Name	¹ H NMR δ	MS m/e MH ⁺
	10	N-[(2r,5s)-5-hydroxyadamantan-2-yl]-4-propylsulfanylpirimidine-5-carboxamide	¹ H NMR (400.13 MHz, CDCl ₃) δ 0.99 (3H, t), 1.51 (2H, d), 1.65 - 1.73 (5H, m), 1.76 (2H, s), 1.79 (1H, s), 1.86 - 1.89 (2H, m), 2.13 (1H, s), 2.20 (2H, s), 3.19 (2H, t), 4.14 - 4.20 (1H, m), 6.65 (1H, d), 8.65 (1H, s), 8.86 (1H, s)	348; HPLC t_R = 1.64 min

- 5 The following intermediates were used and were prepared as described below.

Intermediate 25

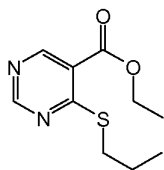
Ethyl 4-oxo-3H-pyrimidine-5-carboxylate



- 10 Prepared by the same process used for Intermediate 22.
¹H NMR (400.13 MHz, DMSO-d₆) δ 1.25 (3H, t), 3.52 (1H, s), 4.16 (2H, q), 8.27 (1H, s), 8.42 (1H, s)
 m/z (ESI⁺) (M+H)⁺ = 169; HPLC t_R = 0.50 min.

15 Intermediate 26

Ethyl 4-propylsulfanylpirimidine-5-carboxylate



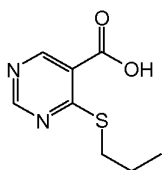
Prepared from ethyl 4-oxo-3H-pyrimidine-5-carboxylate (intermediate 25) by the same process used for Intermediate 23.

¹H NMR (400.13 MHz, CDCl₃) δ 0.77 (3H, t), 1.01 (3H, t), 1.67 (2H, q), 3.11 (2H, t), 4.35 (2H, q), 8.90 (1H, d), 8.92 (1H, d)

m/z (ESI+) (M+H)⁺ = 227; HPLC t_R = 2.30 min.

Intermediate 27

4-Propylsulfanylpurimidine-5-carboxylate

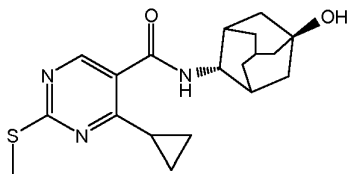


Prepared from ethyl 4-propylsulfanylpurimidine-5-carboxylate (intermediate 26) by the same process used for Intermediate 21.

m/z (ESI+) (M+H)⁺ = 199; HPLC t_R = 1.56 min.

Example 11

4-Cyclopropyl-N-[(2r,5s)-5-hydroxyadamantan-2-yl]-2-methylsulfanyl-pyrimidine-5-carboxamide



O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (458 mg, 1.21 mmol) was added to 4-cyclopropyl-2-(methylthio)pyrimidine-5-carboxylic acid (Intermediate 29, 230 mg, 1.09 mmol) and N,N-di-isopropylamine (0.375 mL, 2.19 mmol) in DMF (7 mL). The resulting solution was stirred at room temperature for 15 minutes then (1r,4s)-4-aminoadamantan-1-ol hydrochloride (268 mg, 1.32 mmol) was added and the reaction was allowed to stir at room temperature for 2 hours. The reaction mixture was

evaporated to dryness and redissolved in EtOAc (150 mL) and then washed sequentially with water (2x150 mL). The organic layer was dried over MgSO₄, filtered and evaporated to afford the crude product. The crude product was purified by flash silica chromatography, elution gradient 0 to 10% MeOH in DCM. Pure fractions were

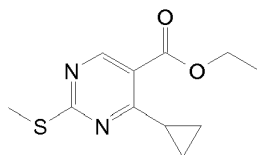
5 evaporated to dryness to afford 4-cyclopropyl-N-[(2r,5s)-5-hydroxyadamantan-2-yl]-2-methylsulfanyl-pyrimidine-5-carboxamide (311 mg, 79%) as a yellow oil.

¹H NMR (400.13 MHz, CDCl₃) δ 1.01 - 1.05 (2H, m), 1.20 - 1.22 (2H, m), 1.49 (2H, d), 1.68 - 1.75 (5H, m), 1.84 - 1.87 (2H, m), 2.08 (2H, s), 2.17 (2H, s), 2.31 - 2.37 (1H, m), 2.41 (3H, s), 4.13 - 4.18 (1H, m), 6.41 (1H, d), 8.29 (1H, s)

10 m/z (ESI+) (M+H)⁺ = 360; HPLC t_R = 1.89 min.

Intermediate 28

Ethyl 4-cyclopropyl-2-(methylthio)pyrimidine-5-carboxylate



15 Ethyl 2-(cyclopropanecarbonyl)-3-(dimethylamino)acrylate (Intermediate 1, 557 mg, 2.64 mmol) was dissolved in DMF (10 mL). To the solution was added 2-methyl-2-thiopseudourea sulfate (850 mg, 3.05 mmol) and sodium acetate (919 mg, 11.21 mmol). The reaction was heated at 80°C for 2 hours. Water was added to the cooled solution and the aqueous layer was washed sequentially with EtOAc (3x 200 mL). The combined

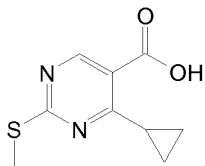
20 organic layers were washed with saturated aqueous NaHCO₃ (100mL). The organic layer was dried over MgSO₄, filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 0 to 10% EtOAc in isohexane. Pure fractions were evaporated to dryness to afford ethyl 4-cyclopropyl-2-(methylthio)pyrimidine-5-carboxylate (596 mg, 95%) as a colourless oil.

25 ¹H NMR (400.13 MHz, CDCl₃) δ 0.98 - 1.02 (2H, m), 1.15 - 1.19 (2H, m), 1.28 (3H, t), 2.39 (3H, s), 3.05 - 3.12 (1H, m), 4.27 (2H, q), 8.71 (1H, s)

m/z (ESI+) (M+H)⁺ = 239; HPLC t_R = 2.77 min.

Intermediate 29.

4-cyclopropyl-2-(methylthio)pyrimidine-5-carboxylic acid

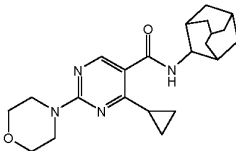


Ethyl 4-cyclopropyl-2-(methylthio)pyrimidine-5-carboxylate (Intermediate 28, 298 mg, 1.25 mmol) was dissolved in methanol (10 mL) and 2M aqueous sodium hydroxide (2mL) was added. The resulting solution was stirred at room temperature for 3 hours. The reaction mixture was evaporated to dryness and redissolved in water (100 mL) then was acidified to pH 4 with 2N HCl. The aqueous layer was washed sequentially with DCM (2 x 75 mL). The organic layer was dried over MgSO₄, filtered and evaporated to afford crude 4-cyclopropyl-2-(methylthio)pyrimidine-5-carboxylic acid (230 mg, 87 %) as a white solid, which was used without further purification and characterisation.

m/z (ESI+) (M+H)⁺ = 211; HPLC t_R = 1.96 min.

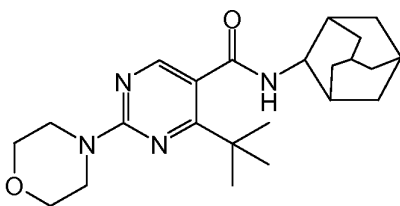
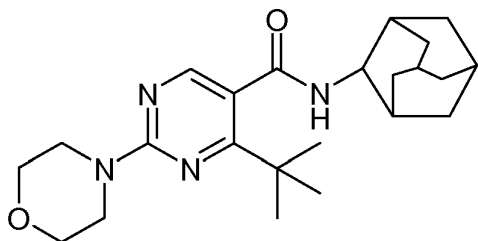
The following Examples were prepared in a similar manner to Example 1, using 2-adamantylamine and an appropriate carboxylic acid starting material (Intermediate 5 & Intermediate 3 respectively) as described previously:

Structure	Ex	Name	¹ H NMR δ	MS m/e MH ⁺
	12	N-(2-adamantyl)-4-cyclopropyl-2-methylpyrimidine-5-carboxamide	¹ H NMR (400.13 MHz, DMSO-d ₆) δ 1.01 - 1.08 (4H, m), 1.51 (2H, d), 1.70 (2H, s), 1.76 - 1.83 (5H, m), 1.84 (1H, s), 1.94 (2H, s), 2.04 (2H, d), 2.25 - 2.31 (1H, m), 2.52 (3H, s), 4.04 - 4.07 (1H, m), 8.41 (1H, s), 8.46 (1H, d)	312; HPLC t _R = 2.32 min.

	13	N-(2-adamantyl)-4-cyclopropyl-2-morpholino-pyrimidine-5-carboxamide	¹ H NMR (400.13 MHz, DMSO-d ₆) δ 0.92 - 0.97 (2H, m), 0.99 - 1.04 (2H, m), 1.50 (2H, d), 1.70 (2H, s), 1.76 - 1.81 (5H, m), 1.83 (1H, s), 1.92 (2H, s), 2.03 - 2.06 (2H, m), 2.43 - 2.47 (1H, m), 3.59 - 3.63 (4H, m), 3.64 - 3.68 (4H, m), 3.98 - 4.02 (1H, m), 8.10 (1H, d), 8.23 (1H, s)	383; HPLC t _R = 2.65 min.
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Example 14

N-(2-Adamantyl)-4-tert-butyl-2-morpholin-4-ylpyrimidine-5-carboxamide



5

Morpholine-4-carboximidamide hydrobromide (213 mg, 1.01 mmol) and N-(2-adamantyl)-2-(dimethylaminomethylidene)-4,4-dimethyl-3-oxopentanamide (Intermediate 30, 340 mg, 1.02 mmol) was added at room temperature to a solution of sodium methoxide (2.23 mL, 1.11 mmol) in methanol (10 mL). The mixture was refluxed for 3.5 hours. The reaction mixture was evaporated to dryness and redissolved in DCM (125 mL), and washed with saturated brine (2x75 mL). The organic layer was dried over MgSO₄, filtered and evaporated to afford the crude product. The crude product was purified by flash silica chromatography, elution gradient 10 to 40% EtOAc in isohexane. Pure fractions were evaporated to dryness to afford N-(2-adamantyl)-4-tert-butyl-2-morpholin-4-ylpyrimidine-

10

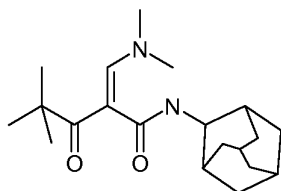
5-carboxamide (96 mg, 24 %) as a white solid.

¹H NMR (400.13 MHz, DMSO-d₆) δ 1.32 (9H, s), 1.49 (2H, d), 1.70 (2H, s), 1.76 (1H, s), 1.80 (3H, s), 1.84 (1H, s), 1.90 (3H, s), 2.04 (2H, s), 3.66 (4H, d), 3.71 - 3.73 (4H, m), 8.10 (1H, s), 8.27 (1H, d)

5 m/z (ESI+) M⁺ = 399; HPLC t_R = 3.00 min

Intermediate 30

N-(2-adamantyl)-2-(dimethylaminomethylidene)-4,4-dimethyl-3-oxo-pentanamide



10 A 1M solution of solution of lithium bis(trimethylsilyl)amide in THF (22.84 ml, 22.84 mmol) was added to THF (25mL) and cooled under nitrogen to -78°C. A solution of 3,3-dimethyl-2-butanone (2.287 g, 22.84 mmol) in THF (25mL) was added drop wise over a period of 5 minutes. The resulting solution was stirred at -78 °C under nitrogen for 15 minutes. A solution of 2-isocyanatoadamantane (prepared from 2-adamantylamine hydrochloride by the method of R. Reck & C. Jochims, *Chem. Ber.*, 1982, 115, 864) (3.68 g, 20.76 mmol) in THF (20mL) was added over a period of 5 minutes. The resulting solution was stirred at -78 °C for 1 hour and then allowed to warm to 20°C over 1h. The reaction mixture was poured into saturated NH₄Cl (150 mL) and extracted with EtOAc (2 x 100 mL), the organic layer was washed with water (50mL) and brine (50mL), dried over 20 MgSO₄, filtered and evaporated to afford a yellow oil. The crude product was purified by flash silica chromatography, elution gradient 0 to 50% EtOAc in isohexane. Pure fractions were evaporated to dryness to afford N-(2-adamantyl)-4,4-dimethyl-3-oxo-pentanamide (4.64 g, 81%) as a white solid.

25 ¹H NMR (400.13 MHz, DMSO-d₆) δ 1.08 - 1.09 (9H, m), 1.50 (2H, d), 1.66 - 1.89 (10H, m), 1.95 - 2.00 (2H, m), 3.53 (1.4H, s), 3.80 - 3.94 (1H, m), 5.30 (0.3H, s), 7.77- 7.87 (1H, m), 14.43 (0.3H, s) (2:1 mixture of keto and enol forms)

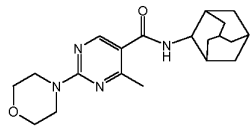
m/z (ESI+) (M+H)⁺ = 278

N,N-Dimethylformamide dimethyl acetal (3.02 mL, 22.71 mmol) was added to a stirred suspension of N-(2-adamantyl)-4,4-dimethyl-3-oxo-pentanamide (5.25 g, 18.93

mmol) in 1,4-dioxane (50 mL) under nitrogen. The resulting mixture was stirred at 100 °C for 2 hours. The reaction mixture was evaporated to dryness and the resulting pale cream solid was dried under vacuum to afford N-(2-adamantyl)-2-(dimethylaminomethylidene)-4,4-dimethyl-3-oxo-pentanamide (5.83 g, 93 %).

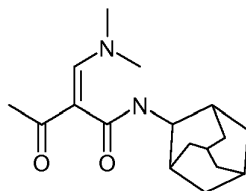
- 5 ¹H NMR (400.13 MHz, DMSO-d₆) δ 1.13 (9H, s), 1.47 (2H, d), 1.69 - 1.83 (10H, m), 2.03 (2H, d), 2.92 (6H, s), 3.90 (1H, d), 7.24 (1H, s), 7.94 (1H, d)
m/z (ESI+) (M+H)⁺ = 333

- The following Examples were prepared in a similar manner to Example 1, using 2-
10 adamantylamine and an appropriate carboxylic acid starting material:

Structure	Ex	Name	¹ H NMR δ	MS m/e MH ⁺
	15	N-(2-adamantyl)-4-methyl-2-morpholin-4-ylpyrimidine-5-carboxamide	¹ H NMR (400.13 MHz, DMSO-d ₆) δ 1.51 (2H, d), 1.71 (2H, s), 1.79 - 1.84 (6H, m), 1.92 (2H, s), 2.05 (2H, d), 2.40 (3H, s), 3.63 - 3.66 (4H, m), 3.74 - 3.76 (4H, m), 3.96 - 4.01 (1H, m), 8.07 (1H, d), 8.32 (1H, s)	357; HPLC t _R = 2.43 min

Intermediate 31

N-(2-adamantyl)-2-(dimethylaminomethylidene)-3-oxo-butanamide



- 15 2-Adamantanamine hydrochloride (23.70 g, 126.23 mmol) was added to 5-acetyl-2,2-dimethyl-1,3-dioxane-4,6-dione (23.5 g, 126.23 mmol) and N-Ethyldiisopropylamine (21.84 mL, 126.23 mmol) in toluene (300 mL). The resulting suspension was stirred at 110 °C for 2 hours. The reaction mixture was diluted with EtOAc (50 mL), and washed sequentially with 2M HCl (25 mL) and water (2x50 mL). The organic layer was dried over

MgSO₄, filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 50 to 80% EtOAc in isohexane. Pure fractions were evaporated to dryness to afford N-(2-adamantyl)-3-oxo-butanamide (15.80 g, 53%) as an orange oil which crystallised on standing.

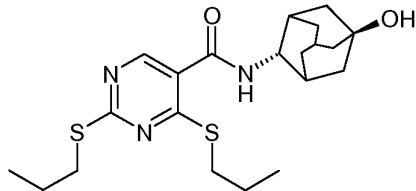
5 ¹H NMR (400.13 MHz, DMSO-d₆) δ 1.48 - 1.54 (2H, m), 1.69 - 1.85 (10H, m), 1.92-2.00 (2H, s), 2.13 (3H, s), 3.38 (2H, s), 3.84 (1H, d), 7.95 (1H, d)

N-(2-adamantyl)-2-(dimethylaminomethylidene)-3-oxo-butanamide was then prepared from ethyl N-(2-adamantyl)-3-oxo-butanamide by the same process used for Intermediate 30 described above.

10 ¹H NMR (400.13 MHz, DMSO-d₆) δ 1.46 - 1.52 (2H, m), 1.65-1.70 (2H, m), 1.72 - 1.85 (8H, m), 1.92-2.00 (2H, m), 2.04 (3H, s), 2.99 (6H, s), 3.91-3.96 (1H, m), 7.44 (1H, s), 8.35 (1H, d)

Example 16

15 N-[(2r,5s)-5-hydroxyadamantan-2-yl]-2,4-bis(propylsulfanyl)pyrimidine-5-carboxamide



O-(7-Azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (335 mg, 0.88 mmol) was added in one portion to 2,4-bis(propylthio)pyrimidine-5-carboxylic acid (Intermediate 36, 200 mg, 0.73 mmol), (1s,4r)-4-aminoadamantan-1-ol hydrochloride (150 mg, 0.73 mmol) and N-ethyl-diisopropylamine (0.384 mL, 2.20 mmol) in DMF (10 mL) at 25 °C under nitrogen. The resulting solution was stirred at 25 °C for 3 hours.

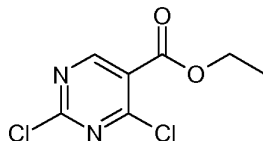
The reaction mixture was diluted with EtOAc (50 mL), and washed sequentially with saturated NaHCO₃ (25 mL), water (2x25 mL) and saturated brine (25 mL). The organic layer was dried over MgSO₄, filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 0 to 25% EtOAc in isohexane. Pure fractions were evaporated to dryness dried under high vacuum to afford N-[(2r,5s)-5-hydroxyadamantan-2-yl]-2,4-bis(propylsulfanyl)pyrimidine-5-carboxamide (229 mg, 74%) as a white solid foam.

¹H NMR (400.13 MHz, DMSO-d₆) δ 0.98 (6H, q), 1.32 (2H, d), 1.60 - 1.74 (10H, m), 1.92

- 2.04 (5H, m), 3.07 - 3.14 (4H, m), 3.88 (1H, t), 4.39 (1H, s), 8.20 (1H, d), 8.34 (1H, s)
m/z (ESI+) (M+H)+ = 422; HPLC t_R = 2.47 min.

Intermediate 32

5 Ethyl 2,4-dichloropyrimidine-5-carboxylate



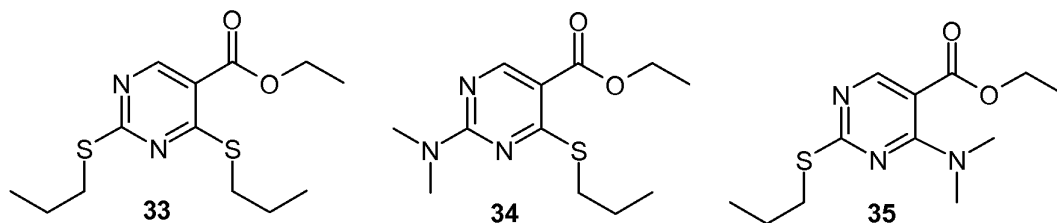
Ethyl 2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (5.0 g, 27.15 mmol) was added to phenyl phosphorodichloridate (32.4 ml, 217.21 mmol) under nitrogen. The resulting suspension was stirred at 180 °C for 1 hour. The reaction mixture was poured into
10 ice/water (500 mL) and adjusted to pH 7 with saturated NaHCO₃. The mixture was extracted with EtOAc (3x100mL). The organic layers were combined and washed with water (2x100 mL), dried over Na₂SO₄, filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 0 to 10% EtOAc in isohexane. Pure fractions were evaporated to dryness to afford ethyl 2,4-
15 dichloropyrimidine-5-carboxylate (4.22 g, 70%) as a colourless oil which crystallised on standing.

¹H NMR (400.13 MHz, DMSO-d₆) δ 1.33 (3H, t), 4.37 (2H, q), 9.15 (1H, s)

Intermediate 33: ethyl 2,4-bis(propylthio)pyrimidine-5-carboxylate,

20 **Intermediate 34:** ethyl 2-(dimethylamino)-4-(propylthio)pyrimidine-5-carboxylate and

Intermediate 35: ethyl 4-(dimethylamino)-2-(propylthio)pyrimidine-5-carboxylate



1-Propanethiol (0.408 mL, 4.51 mmol) was added in one portion to ethyl 2,4-
dichloropyrimidine-5-carboxylate (Intermediate 32, 997 mg, 4.51 mmol) and sodium
25 carbonate (1.434 g, 13.53 mmol) in DMF (10 mL) under nitrogen. The resulting suspension was stirred at 20 °C for 18 hours. The reaction mixture was diluted with EtOAc

(100 mL), and washed sequentially with water (2x25 mL) and saturated brine (20 mL). The organic layer was dried over MgSO₄, filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 0 to 20% EtOAc in isohexane. Pure fractions were evaporated to dryness to afford a clear colourless oil which was added to a 2M solution of dimethylamine (23.01 mL, 46.02 mmol) in THF. The resulting mixture was stirred at 22 °C for 2 hours. The reaction mixture was evaporated to dryness and redissolved in EtOAc (100 mL) and washed sequentially with water (2 x 50 mL) and saturated brine (50 mL). The organic layer was dried over MgSO₄, filtered and evaporated to afford a crude product containing three components. The crude product was purified by flash silica chromatography, elution gradient 0 to 25% EtOAc in isohexane. Pure fractions were evaporated to dryness to afford the following products as colourless oils.

Ethyl 2,4-bis(propylthio)pyrimidine-5-carboxylate (Intermediate 33, 410mg, 30%)

¹H NMR (400.13 MHz, CDCl₃) δ 0.98 (6H, t), 1.30 (3H, t), 1.64 - 1.73 (4H, m), 3.05 - 3.15 (4H, m), 4.25 (2H, q), 8.72 (1H, s)
m/z (ESI+) (M+H)⁺ = 301; HPLC t_R = 3.35 min.

Ethyl 2-(dimethylamino)-4-(propylthio)pyrimidine-5-carboxylate (Intermediate 34, 200mg, 17%)

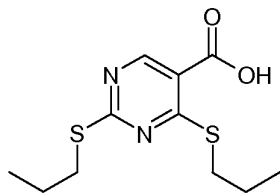
¹H NMR (400.13 MHz, CDCl₃) δ 0.98 (3H, t), 1.30 (3H, t), 1.64 - 1.73 (2H, m), 3.00 - 3.04 (2H, m), 3.22 (6H, s), 4.25 (2H, q), 8.64 (1H, s)
m/z (ESI+) (M+H)⁺ = 270; HPLC t_R = 2.88 min.

Ethyl 4-(dimethylamino)-2-(propylthio)pyrimidine-5-carboxylate (Intermediate 35, 306mg, 25%)

¹H NMR (400.13 MHz, CDCl₃) δ 1.04 - 1.10 (3H, m), 1.36 - 1.42 (3H, m), 1.74 - 1.83 (2H, m), 3.11 - 3.16 (8H, m), 4.31 - 4.40 (2H, m), 8.51 (1H, s)
m/z (ESI+) (M+H)⁺ = 270; HPLC t_R = 2.54 min.

Intermediate 36

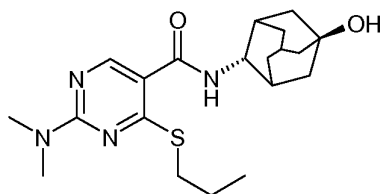
2,4-Bis(propylthio)pyrimidine-5-carboxylic acid



A solution of sodium hydroxide (3.41 mL, 6.82 mmol) was added to a stirred solution of ethyl 2,4-bis(propylthio)pyrimidine-5-carboxylate (Intermediate 33, 410 mg, 1.36 mmol) in MeOH (10 mL). The resulting mixture was stirred at 20 °C for 18 hours. The reaction mixture was concentrated and diluted with water (10 mL) and adjusted to pH4 with 2M HCl. The mixture was diluted with EtOAc (50 mL) and washed sequentially with water (2x25 mL) and saturated brine (25 mL). The organic layer was dried over MgSO₄, filtered and evaporated to afford 2,4-bis(propylthio)pyrimidine-5-carboxylic acid (312 mg, 84%).
¹H NMR (400.13 MHz, DMSO-d₆) δ 0.97 - 1.01 (6H, m), 1.63 - 1.75 (4H, m), 3.09 (2H, t), 3.14 (2H, t), 8.71 (1H, s)
 m/z (ESI+) (M+H)⁺ = 273; HPLC t_R = 1.54 min.

Example 17

2-Dimethylamino-N-[(2r,5s)-5-hydroxyadamantan-2-yl]-4-propylsulfanylpuridine-5-carboxamide



O-(7-Azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (248 mg, 0.65 mmol) was added in one portion to 2-(dimethylamino)-4-(propylthio)pyrimidine-5-carboxylic acid (Intermediate 37, 131 mg, 0.54 mmol), (1s,4r)-4-aminoadamantan-1-ol hydrochloride (111 mg, 0.54 mmol) and N-ethyldiisopropylamine (0.284 mL, 1.63 mmol) in DMF (5 mL) at 25 °C under nitrogen. The resulting solution was stirred at 25 °C for 3 hours.

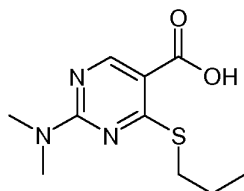
The reaction mixture was diluted with EtOAc (50 mL), and washed sequentially with saturated NaHCO₃ (25 mL), water (2x25 mL) and saturated brine (25 mL). The organic layer was dried over MgSO₄, filtered and evaporated to afford crude product. The crude

product was purified by flash silica chromatography, elution gradient 0 to 100% EtOAc in isohexane. Pure fractions were evaporated to dryness to afford 2-dimethylamino-N-[(2r,5s)-5-hydroxyadamantan-2-yl]-4-propylsulfanylpurimidine-5-carboxamide (145 mg, 68%) as a white solid foam.

- 5 ¹H NMR (400.13 MHz, DMSO-d₆) δ 0.96 (3H, t), 1.31 (2H, d), 1.57 - 1.71 (8H, m), 1.93 - 2.02 (5H, m), 2.98 - 3.04 (2H, m), 3.16 (6H, s), 3.85 (1H, t), 4.37 (1H, s), 7.75 (1H, d), 8.29 (1H, s)
m/z (ESI+) (M+H)⁺ = 391; HPLC t_R = 2.13 min.

10 Intermediate 37

2-(Dimethylamino)-4-(propylthio)pyrimidine-5-carboxylic acid

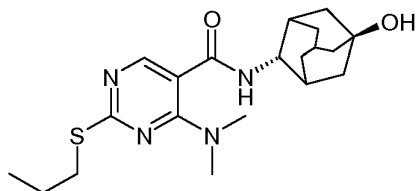


Prepared from ethyl 2-(dimethylamino)-4-(propylthio)pyrimidine-5-carboxylate (Intermediate 34) by the same process used for Intermediate 36.

- 15 ¹H NMR (400.13 MHz, DMSO-d₆) δ 0.97 (3H, t), 1.61 - 1.70 (2H, m), 3.00 - 3.04 (2H, m), 3.19 (6H, s), 8.58 (1H, s), 12.57 (1H, s)
m/z (ESI+) (M+H)⁺ = 242; HPLC t_R = 0.86 min.

Example 18

- 20 4-Dimethylamino-N-[(2r,5s)-5-hydroxyadamantan-2-yl]-2-propylsulfanylpurimidine-5-carboxamide



- O-(7-Azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (454 mg, 1.19 mmol) was added in one portion to 4-(dimethylamino)-2-(propylthio)pyrimidine-5-
25 carboxylic acid (Intermediate 38, 240 mg, 0.99 mmol), (1s,4r)-4-aminoadamantan-1-ol

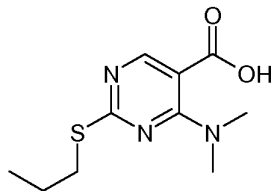
hydrochloride (203 mg, 0.99 mmol) and N-ethyldiisopropylamine (0.520 mL, 2.98 mmol) in DMF (10 mL) at 25 °C under nitrogen. The resulting solution was stirred at 25 °C for 3 hours.

The reaction mixture was diluted with EtOAc (50 mL), and washed sequentially with
5 saturated NaHCO₃ (25 mL), water (2x25 mL) and saturated brine (25 mL). The organic layer was dried over MgSO₄, filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 0 to 100% EtOAc in isohexane. Pure fractions were evaporated to dryness to afford 4-dimethylamino-N-
[(2r,5s)-5-hydroxyadamantan-2-yl]-2-propylsulfanylpurimidine-5-carboxamide (163 mg,
10 42%) as a white solid foam.

¹H NMR (400.13 MHz, DMSO-d₆) δ 0.96 (3H, t), 1.32 (2H, d), 1.60 - 1.71 (8H, m), 1.89 - 2.01 (5H, m), 3.00 - 3.04 (8H, m), 3.88 (1H, t), 4.38 (1H, s), 7.91 (1H, s), 8.27 (1H, d)
m/z (ESI+) (M+H)⁺ = 391; HPLC t_R = 1.87 min.

15 Intermediate 38

4-(Dimethylamino)-2-(propylthio)pyrimidine-5-carboxylic acid

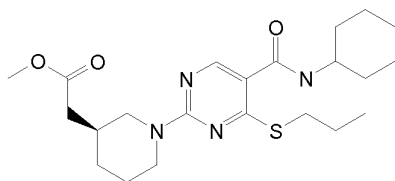


Prepared from ethyl 4-(dimethylamino)-2-(propylthio)pyrimidine-5-carboxylate
(Intermediate 35) by the same process used for Intermediate 36.

20 ¹H NMR (400.13 MHz, DMSO-d₆) δ 0.97 (3H, t), 1.63 - 1.70 (2H, m), 3.01 - 3.06 (8H, m), 8.34 (1H, s)
m/z (ESI+) (M+H)⁺ = 242; HPLC t_R = 0.71 min.

Example 19

25 (S)-Methyl 2-(1-(5-(cyclohexylcarbamoyl)-4-(propylthio)pyrimidin-2-yl)piperidin-3-yl)acetate

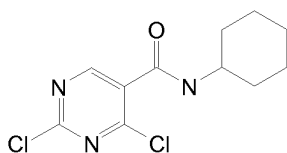


Potassium carbonate (0.363 g, 2.63 mmol) was added in one portion to 2-chloro-N-cyclohexyl-4-(propylthio)pyrimidine-5-carboxamide (Intermediate 40, 0.275 g, 0.88 mmol) and (S)-methyl 2-(piperidin-3-yl)acetate hydrochloride (0.170 g, 0.88 mmol) in butyronitrile (5 mL) at 20°C under nitrogen. The resulting suspension was stirred at 120°C for 24 hours. The reaction mixture was diluted with EtOAc (75 mL), and washed with saturated brine (20 mL). The organic layer was dried over MgSO₄, filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 0 to 50% EtOAc in DCM. Pure fractions were evaporated to dryness to afford (S)-methyl 2-(1-(5-(cyclohexylcarbamoyl)-4-(propylthio)pyrimidin-2-yl)piperidin-3-yl)acetate (0.351 g, 92%) as a white solid.

¹H NMR (400.13 MHz, DMSO-d₆) δ 0.95 (3H, t), 1.09 - 1.42 (7H, m), 1.55 - 1.90 (10H, m), 2.28 (2H, d), 2.84 - 3.09 (4H, m), 3.60 - 3.65 (4H, m), 4.41 - 4.49 (1H, m), 4.51 - 4.54 (1H, m), 7.89 (1H, d), 8.29 (1H, s).
m/z (ESI⁺) (M+H)⁺ = 435.36; HPLC t_R = 2.95 min.

Intermediate 39

2,4-dichloro-N-cyclohexylpyrimidine-5-carboxamide



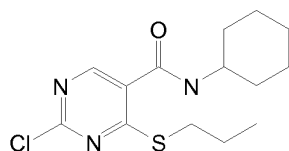
A solution of cyclohexylamine (0.951 mL, 8.32 mmol) and N-Ethyldiisopropylamine (1.44 mL, 8.32 mmol) in dichloromethane (5 mL) was added dropwise to a solution of 2,4-dichloropyrimidine-5-carbonyl chloride (CAS No. 2972-52-3; 1.76 g, 8.32 mmol) in DCM (20 mL) cooled to 0°C over a period of 5 minutes under nitrogen. The resulting suspension was stirred at 0°C for 2 hours then the temperature was increased to 20°C and the reaction mixture was stirred for a further 2 hours. The reaction mixture was diluted with DCM (200 mL) and washed with water (50 mL). The organic layer was dried over MgSO₄,

filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 0 to 10% EtOAc in DCM. Pure fractions were evaporated to dryness to afford 2,4-dichloro-N-cyclohexylpyrimidine-5-carboxamide (1.07 g, 47%) as a white solid.

- 5 ¹H NMR (400.13 MHz, DMSO-d₆) δ 1.12 - 1.37 (5H, m), 1.53 - 1.58 (1H, m), 1.68 - 1.72 (2H, m), 1.83 - 1.85 (2H, m), 3.69 - 3.77 (1H, m), 8.57 (1H, d), 8.84 (1H, s)
m/z (ESI-) (M-H)- = 272.13; HPLC t_R = 2.03 min.

Intermediate 40

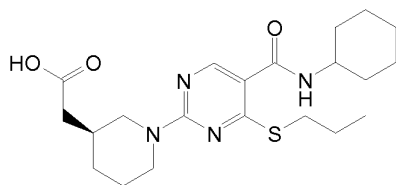
- 10 2-chloro-N-cyclohexyl-4-(propylthio)pyrimidine-5-carboxamide



- Sodium carbonate (0.199 g, 1.88 mmol) was added in one portion to 2,4-dichloro-N-cyclohexylpyrimidine-5-carboxamide (Intermediate 39, 0.515 g, 1.88 mmol) and 1-propanethiol (0.170 ml, 1.88 mmol) in DMF at 18°C under nitrogen. The resulting
15 suspension was stirred at 18°C for 18 hours. The reaction mixture was diluted with EtOAc (75 mL), and washed sequentially with water (20 mL) and saturated brine (20 mL). The organic layer was dried over MgSO₄, filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 0 to 10% EtOAc in DCM. Pure fractions were evaporated to dryness to afford 2-chloro-N-cyclohexyl-4-(propylthio)pyrimidine-5-carboxamide (0.551 g, 93%) as a white solid.
20 ¹H NMR (400.13 MHz, DMSO-d₆) δ 0.97 (3H, t), 1.09 - 1.35 (5H, m), 1.56 - 1.73 (5H, m), 1.80 - 1.83 (2H, m), 3.08 (2H, t), 3.65 - 3.73 (1H, m), 8.47 (1H, d), 8.50 (1H, s)
m/z (ESI+) (M+H)+ = 314.17; HPLC t_R = 2.60 min.

- 25 **Example 20**

{(3S)-1-[5-(Cyclohexylcarbamoyl)-4-(propylthio)pyrimidin-2-yl]piperidin-3-yl} acetic acid

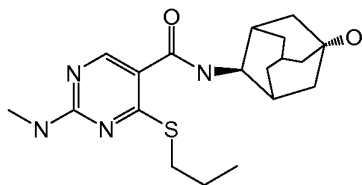


A solution of 2M sodium hydroxide (1.90 mL, 3.81 mmol) was added dropwise to a stirred solution of (S)-methyl 2-(1-(5-(cyclohexylcarbamoyl)-4-(propylthio)pyrimidin-2-yl)piperidin-3-yl)acetate (Example 19, 0.331 g, 0.76 mmol) in MeOH (5 mL) at ambient temperature and stirred for 18 hours. The reaction mixture was diluted with water (10 mL) then the pH was adjusted to ~ 4.5 with 1M HCl aq. The suspension was diluted with EtOAc (50 mL), and washed with saturated brine (20 mL). The organic layer was dried over MgSO₄, filtered and evaporated to afford crude product. The crude product was purified by preparative HPLC (Waters Xbridge column, 5μ silica, 50 mm diameter, 150 mm length), using decreasingly polar mixtures of water (containing 0.5% NH₃) and MeCN as eluents. Fractions containing the desired compound were evaporated combined and the bulk of the CH₃CN removed under reduced pressure. The clear colourless solution was acidified to ~ pH 4.5 with 1M HCl aq. and the white suspension extracted with EtOAc (50 mL). The organic layer was separated and dried over MgSO₄, filtered and evaporated to afford (S)-2-(1-(5-(cyclohexylcarbamoyl)-4-(propylthio)pyrimidin-2-yl)piperidin-3-yl)acetic acid (0.200 g, 62%) as a white solid.

¹H NMR (400.13 MHz, DMSO-d₆) δ 0.95 (3H, t), 1.07 - 1.45 (7H, m), 1.55 - 1.90 (10H, m), 2.14 - 2.21 (2H, m), 2.82 - 3.09 (4H, m), 3.60 - 3.67 (1H, m), 4.41 - 4.50 (1H, m), 4.52 - 4.60 (1H, m), 7.89 (1H, d), 8.28 (1H, s), 12.07 (1H, s)
m/z (ESI⁺) (M+H)⁺ = 421.24; HPLC t_R = 2.52 min.

Example 21

N-[(2r,5s)-5-hydroxyadamantan-2-yl]-2-methylamino-4-propylsulfanylpurimidine-5-carboxamide



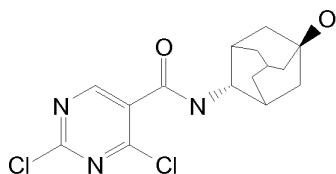
2-Chloro-N-[(2r,5s)-5-hydroxyadamantan-2-yl]-4-propylsulfanylpurimidine-5-

carboxamide (Intermediate 43, 383 mg, 1.00 mmol) was added to a solution of methylamine in ethanol (10.0 ml, 80.33 mmol). The resulting solution was stirred at 22 °C for 1 hour. The reaction mixture was evaporated to dryness to afford crude product that was purified by preparative HPLC (Waters XBridge Prep C18 OBD column, 5 μ silica, 50 mm diameter, 150 mm length), using decreasingly polar mixtures of water (containing 0.5% NH₃) and MeCN as eluents. Fractions containing the desired compound were evaporated to dryness to afford N-[(2r,5s)-5-hydroxyadamantan-2-yl]-2-methylamino-4-propylsulfanylpuridine-5-carboxamide (260 mg, 70%) as a white solid.

¹H NMR (400.13 MHz, DMSO-d₆) δ 0.96 (3H, t), 1.30 - 1.33 (2H, m), 1.60 - 1.71 (8H, m), 1.93 - 2.02 (5H, m), 2.84 (3H, d), 2.95 - 3.08 (2H, m), 3.85 (1H, t), 4.37 (1H, s), 7.31 - 7.52 (1H, m), 7.73 (1H, d), 8.23 (1H, s)
m/z (ESI+) (M+H)⁺ = 377; HPLC t_R = 1.89 min.

Intermediate 42

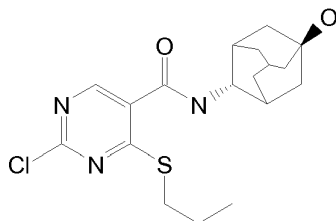
2,4-dichloro-N-[(2s,5r)-5-hydroxyadamantan-2-yl]pyrimidine-5-carboxamide



A suspension of (1r,4s)-4-aminoadamantan-1-ol .hydrochloride (2.89 g, 14.19 mmol) in THF (20 mL) was added drop wise to a stirred solution of 2,4-dichloropyrimidine-5-carbonyl chloride (3.0 g, 14.19 mmol) and N-ethyldiisopropylamine (4.91 mL, 28.38 mmol) in dichloromethane (20 mL) at -10 °C, over a period of 5 minutes under nitrogen. The resulting suspension was stirred at 0 °C for 4 hours. The reaction mixture was diluted with DCM (150 mL), and washed sequentially with 0.1M HCl (50 mL), water (50 mL) and saturated brine (75 mL). The organic layer was dried over MgSO₄, filtered and evaporated to afford the desired product. The crude solid was triturated with ice-cold DCM to give a solid which was collected by filtration and dried under vacuum to give 2,4-dichloro-N-[(2s,5r)-5-hydroxyadamantan-2-yl]pyrimidine-5-carboxamide (3.20 g, 66%) as a tan solid.
¹H NMR (400.13 MHz, DMSO-d₆) δ 1.36 (2H, d), 1.63 (4H, d), 1.71 - 1.77 (3H, m), 1.86 (2H, d), 1.98 - 2.00 (1H, m), 2.06 (2H, s), 3.95 (1H, t), 8.51 (1H, d), 8.83 - 8.85 (1H, m)
HPLC t_R = 1.44 min (no mass ion observed).

Intermediate 43

2-chloro-N-[(2s,5r)-5-hydroxyadamantan-2-yl]-4-(propylthio)pyrimidine-5-carboxamide.



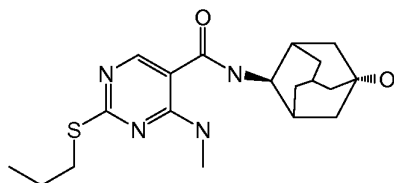
1-Propanethiol (0.151 mL, 1.67 mmol) was added in one portion to 2,4-dichloro-N-
 5 [(2s,5r)-5-hydroxyadamantan-2-yl]pyrimidine-5-carboxamide (Intermediate 42, 570 mg,
 1.67 mmol), and Sodium carbonate (0.070 mL, 1.67 mmol) in DMF (10 mL) under
 nitrogen. The resulting suspension was stirred at room temperature for 4 hours. The
 reaction mixture was diluted with EtOAc (100 mL), and washed sequentially with water
 (25 mL) and saturated brine (25 mL). The organic layer was dried over MgSO₄, filtered
 10 and evaporated to afford crude product. The crude product was purified by flash silica
 (40g) chromatography, elution gradient 50 to 100% EtOAc in isohexane. Pure fractions
 were evaporated to dryness to afford 2-chloro-N-[(2s,5r)-5-hydroxyadamantan-2-yl]-4-
 (propylthio)pyrimidine-5-carboxamide (310 mg, 49 %) as a white solid.

¹H NMR (400.13 MHz, DMSO-d₆) δ 0.97 (3H, t), 1.33 (2H, d), 1.62 (4H, d), 1.66 (2H, t),
 15 1.70 - 1.73 (2H, m), 1.92 (2H, d), 1.99 (1H, s), 2.05 (2H, s), 3.11 (2H, t), 3.91 (1H, t), 4.40
 (1H, s), 8.37 (1H, d), 8.47 (1H, s)

m/z (ESI⁺) (M+H)⁺ = 382; HPLC t_R = 2.1 min.

Example 22

20 N-[(2r,5s)-5-hydroxyadamantan-2-yl]-4-methylamino-2-propylsulfanylpurimidine-5-
 carboxamide



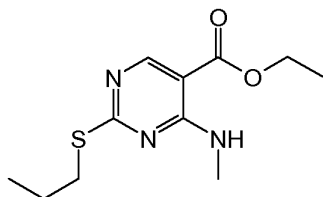
Prepared from 4-(methylamino)-2-(propylthio)pyrimidine-5-carboxylic acid (Intermediate
 45) by the same process used for Example 16.

25 ¹H NMR (400.13 MHz, DMSO-d₆) δ 0.97 (3H, t), 1.30 - 1.33 (2H, m), 1.60 - 1.73 (8H,

m), 1.94 - 1.98 (3H, m), 2.05 (2H, s), 2.89 (3H, d), 3.04 (2H, t), 3.89 (1H, t), 4.38 (1H, s), 7.91 - 7.92 (1H, m), 8.38 - 8.42 (2H, m)
 m/z (ESI+) (M+H)⁺ = 377; HPLC t_R = 2.18 min.

5 Intermediate 44

Ethyl 4-(methylamino)-2-(propylthio)pyrimidine-5-carboxylate

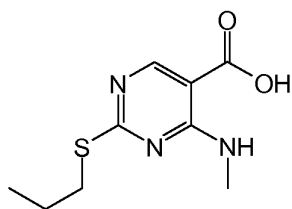


Prepared from ethyl 2,4-dichloropyrimidine-5-carboxylate (Intermediate 32) and methylamine by the same process used for Intermediate 35.

10 ^1H NMR (400.13 MHz, DMSO- d_6) δ 0.97 (3H, t), 1.29 (3H, t), 1.64 - 1.73 (2H, m), 2.96 - 2.97 (3H, m), 3.04 - 3.08 (2H, m), 4.27 (2H, q), 8.21 - 8.22 (1H, m), 8.51 (1H, s)
 m/z (ESI+) (M+H)⁺ = 256; HPLC t_R = 2.84 min.

Intermediate 45

15 4-methylamino-2-propylsulfanylpurimidine-5-carboxylic acid

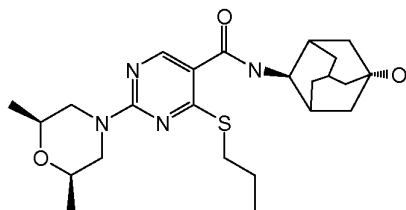


Prepared from ethyl 4-(methylamino)-2-(propylthio)pyrimidine-5-carboxylate (Intermediate 44) by the same process used for Intermediate 36.

1 ^1H NMR (400.13 MHz, DMSO- d_6) δ 0.97 (3H, t), 1.64 - 1.73 (2H, m), 2.96 (3H, d), 3.06 (2H, t), 8.32 - 8.33 (1H, m), 8.47 (1H, s), 13.09 (1H, s)
 20 m/z (ESI+) (M+H)⁺ = 228; HPLC t_R = 1.33 min.

Example 23

2-[(2s,6r)-2,6-Dimethylmorpholin-4-yl]-N-[(2r,5s)-5-hydroxyadamantan-2-yl]-4-propylsulfanylpurimidine-5-carboxamide
 25

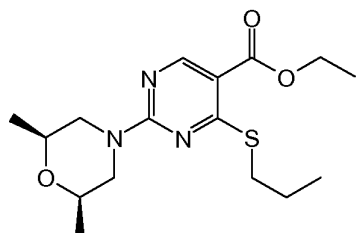


Prepared from 2-((2S,6R)-2,6-dimethylmorpholino)-4-(propylthio)pyrimidine-5-carboxylic acid (Intermediate 47) by the same process used for Example 16.

¹H NMR (400.13 MHz, DMSO-d₆) δ 0.96 (3H, t), 1.14 (6H, d), 1.31 (2H, d), 1.60 - 1.71 (8H, m), 1.92 - 2.02 (5H, m), 2.58 - 2.67 (2H, m), 2.99 (2H, t), 3.50 - 3.57 (2H, m), 3.85 (1H, t), 4.37 (1H, s), 4.52 - 4.55 (2H, m), 7.81 (1H, d), 8.28 (1H, s)
 m/z (ESI⁺) (M+H)⁺ = 461; HPLC t_R = 2.37 min.

Intermediate 46

10 Ethyl 2-((2S,6R)-2,6-dimethylmorpholino)-4-(propylthio)pyrimidine-5-carboxylate

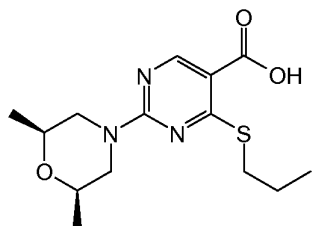


Prepared from ethyl 2,4-dichloropyrimidine-5-carboxylate (Intermediate 32) by the same process used for Intermediate 34.

¹H NMR (400.13 MHz, DMSO-d₆) δ 0.97 (3H, t), 1.15 (6H, s), 1.27 (3H, t), 1.60 - 1.69 (2H, m), 2.63 - 2.69 (2H, m), 3.00 - 3.01 (2H, m), 3.54 - 3.58 (2H, m), 4.22 (2H, q), 4.56 - 4.60 (2H, m), 8.62 (1H, s)
 m/z (ESI⁺) (M+H)⁺ = 340; HPLC t_R = 3.24 min.

Intermediate 47

20 2-((2S,6R)-2,6-dimethylmorpholino)-4-(propylthio)pyrimidine-5-carboxylic acid



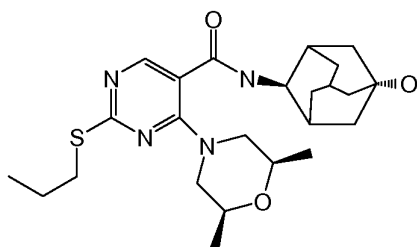
Prepared from ethyl 2-((2S,6R)-2,6-dimethylmorpholino)-4-(propylthio)pyrimidine-5-carboxylate (Intermediate 46) by the same process used for Intermediate 36.

¹H NMR (400.13 MHz, DMSO-d₆) δ 0.97 (3H, t), 1.14 (6H, d), 1.60 - 1.69 (2H, m), 2.62 - 2.67 (2H, m), 2.98 (2H, s), 3.54 - 3.58 (2H, m), 4.56 - 4.60 (2H, m), 8.59 (1H, s), 12.68 (1H, s)

m/z (ESI+) (M+H)⁺ = 312; HPLC t_R = 1.14 min.

Example 24

4-[(2S,6R)-2,6-Dimethylmorpholin-4-yl]-N-[(2r,5s)-5-hydroxyadamantan-2-yl]-2-propylsulfanylpurimidine-5-carboxamide



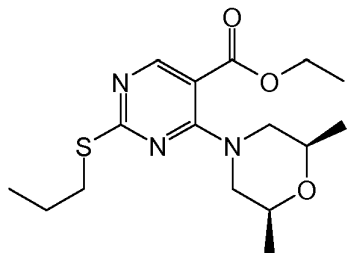
Prepared from 4-((2S,6R)-2,6-dimethylmorpholino)-2-(propylthio)pyrimidine-5-carboxylic acid (Intermediate 49) by the same process used for Example 16

¹H NMR (400.13 MHz, DMSO-d₆) δ 0.96 (3H, t), 1.07 (6H, d), 1.32 (2H, d), 1.60 - 1.72 (8H, m), 1.89 (2H, d), 2.00 (3H, d), 2.58 - 2.67 (2H, m), 3.00 (2H, t), 3.50 - 3.57 (2H, m), 3.85 - 3.87 (1H, m), 3.99 (2H, d), 4.40 (1H, s), 7.97 (1H, s), 8.35 (1H, d)

m/z (ESI+) (M+H)⁺ = 461; HPLC t_R = 2.13 min.

Intermediate 48

Ethyl 4-((2S,6R)-2,6-dimethylmorpholino)-2-(propylthio)pyrimidine-5-carboxylate



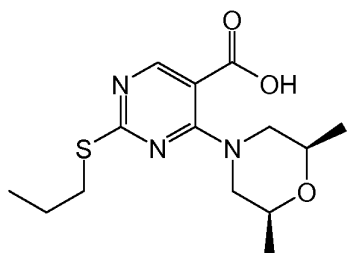
Prepared from ethyl 2,4-dichloropyrimidine-5-carboxylate (Intermediate 32) by the same process used for Intermediate 35

¹H NMR (400.13 MHz, DMSO-d₆) δ 0.97 (3H, t), 1.10 (6H, d), 1.28 (3H, t), 1.63 - 1.72 (2H, m), 2.66 - 2.75 (2H, m), 3.00 - 3.04 (2H, m), 3.54 - 3.62 (2H, m), 3.85 - 3.88 (2H, m), 4.25 (2H, q), 8.43 - 8.44 (1H, m)
m/z (ESI+) (M+H)⁺ = 340; HPLC t_R = 2.82 min.

5

Intermediate 49

4-((2S,6R)-2,6-dimethylmorpholino)-2-(propylthio)pyrimidine-5-carboxylic acid



prepared from ethyl 4-((2S,6R)-2,6-dimethylmorpholino)-2-(propylthio)pyrimidine-5-
carboxylate (Intermediate 48) by the same process used for Intermediate 36.

10

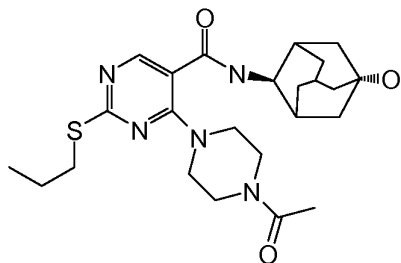
¹H NMR (400.13 MHz, DMSO-d₆) δ 0.97 (3H, t), 1.09 - 1.11 (6H, m), 1.63 - 1.72 (2H, m), 2.65 - 2.74 (2H, m), 3.00 - 3.03 (2H, m), 3.54 - 3.62 (2H, m), 3.92 - 3.95 (2H, m), 8.42 (1H, s), 13.02 (1H, s)

m/z (ESI+) (M+H)⁺ = 312; HPLC t_R = 1.03 min.

15

Example 25

4-(4-Acetylpiperazin-1-yl)-N-[(2r,5s)-5-hydroxyadamantan-2-yl]-2-propylsulfanylpurimidine-5-carboxamide



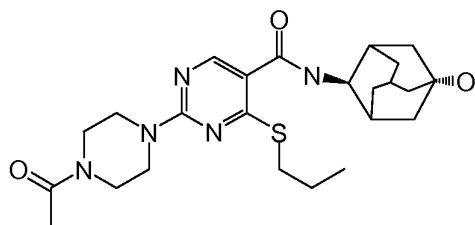
see below Example 26

20

Example 26

2-(4-Acetylpiperazin-1-yl)-N-[(2r,5s)-5-hydroxyadamantan-2-yl]-4-

propylsulfanylpurimidine-5-carboxamide



- O-(7-Azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (549 mg, 1.44 mmol) was added in one portion to a mixture of 2-(4-acetylpiperazin-1-yl)-4-(propylthio)pyrimidine-5-carboxylic acid and 4-(4-acetylpiperazin-1-yl)-2-(propylthio)pyrimidine-5-carboxylic acid (Intermediate 50) (390 mg, 0.60 mmol), (1s,4r)-4-aminoadamantan-1-ol hydrochloride (245 mg, 1.20 mmol) and N-ethyl-diisopropylamine (0.63 mL, 3.61 mmol) in DMF (10 mL) at 25 °C under nitrogen. The resulting solution was stirred at 25 °C for 3 hours.
- The reaction mixture was diluted with EtOAc (150 mL), and washed sequentially with saturated NaHCO₃ (50 mL), water (2x50 mL) and saturated brine (50 mL). The organic layer was dried over MgSO₄, filtered and evaporated to afford crude product containing two components. The crude product was purified and the products separated by preparative HPLC (Waters XBridge Prep C18 OBD column, 5 μ silica, 50 mm diameter, 150 mm length), using decreasingly polar mixtures of water (containing 0.1% NH₃) and MeCN as eluents. Fractions containing the desired compounds were evaporated to dryness to afford 2-(4-acetylpiperazin-1-yl)-N-[(2r,5s)-5-hydroxyadamantan-2-yl]-4-propylsulfanylpurimidine-5-carboxamide (76 mg, 27%) as a white solid and 4-(4-acetylpiperazin-1-yl)-N-[(2r,5s)-5-hydroxyadamantan-2-yl]-2-propylsulfanylpurimidine-5-carboxamide (45 mg, 16 %) as a white solid.

4-(4-acetylpiperazin-1-yl)-N-[(2r,5s)-5-hydroxyadamantan-2-yl]-2-propylsulfanylpurimidine-5-carboxamide (Example 25) :

- ¹H NMR (400.13 MHz, DMSO-d₆) δ 0.97 (3H, t), 1.33 (2H, d), 1.61 - 1.71 (8H, m), 1.85 - 2.04 (8H, m), 3.02 (2H, t), 3.50 - 3.58 (8H, m), 3.90 (1H, t), 4.39 (1H, s), 7.99 (1H, s), 8.32 (1H, d)

m/z (ESI⁺) (M+H)⁺ = 474; HPLC t_R = 1.75 min.

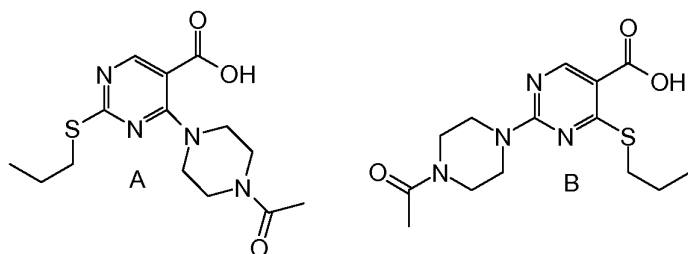
2-(4-acetylpiperazin-1-yl)-N-[(2r,5s)-5-hydroxyadamantan-2-yl]-4-propylsulfanylpuridine-5-carboxamide (Example 26) :

¹H NMR (400.13 MHz, DMSO-d₆) δ 0.97 (3H, t), 1.31 (2H, d), 1.60 - 1.71 (8H, m), 1.92 - 2.04 (8H, m), 3.01 (2H, t), 3.51 - 3.53 (4H, m), 3.76 - 3.78 (2H, m), 3.71 - 3.78 (3H, m),
 4.37 (1H, s), 7.82 (1H, d), 8.31 (1H, s)

m/z (ESI+) (M+H)⁺ = 474; HPLC t_R = 1.79 min

Intermediate 50

(a) 2-(4-acetylpiperazin-1-yl)-4-(propylthio)pyrimidine-5-carboxylic acid and (b) 4-(4-acetylpiperazin-1-yl)-2-(propylthio)pyrimidine-5-carboxylic acid



1-Propanethiol (1.73 mL, 19.09 mmol) was added in one portion to ethyl 2,4-dichloropyrimidine-5-carboxylate (4.22 g, 19.09 mmol) and sodium carbonate (6.07 g, 57.27 mmol) in DMF (40 mL) under nitrogen. The resulting suspension was stirred at 20 °C for 18 hours. The reaction mixture was diluted with EtOAc (300mL), and washed sequentially with water (3x100 mL) and saturated brine (50 mL). The organic layer was dried over MgSO₄, filtered and evaporated to afford crude product containing both possible regioisomers together with a quantity of the bis substituted product. The crude product was purified by flash silica chromatography, elution gradient 0 to 20% EtOAc in isohexane. Fractions were evaporated to dryness to afford a clear colourless oil (3.60 g).

1-Acetylpiperazine (418 mg, 3.26 mmol) and potassium carbonate (451 mg, 3.26 mmol) added to 850 mg of the above prepared mixture of chloro pyrimidines in butyronitrile (10 mL). The resulting mixture was stirred at 20 °C for 18 hours. The reaction mixture was diluted with EtOAc (50 mL), and washed sequentially with water (2x25 mL) and saturated brine (25 mL). The organic layer was dried over MgSO₄, filtered and evaporated to afford crude product that was purified by flash silica chromatography elution gradient 0 to 10% MeOH in EtOAc. Fractions were evaporated to dryness to afford a mixture of ethyl 2-(4-acetylpiperazin-1-yl)-4-(propylthio)pyrimidine-5-carboxylate and

ethyl 4-(4-acetylpiperazin-1-yl)-2-(propylthio)pyrimidine-5-carboxylate (818mg).

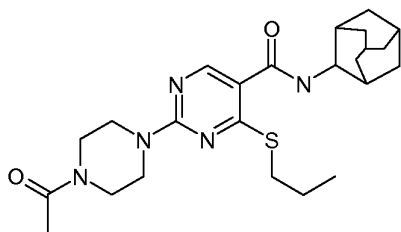
Sodium hydroxide (5.21 mL, 10.43 mmol) was added to the mixture of ethyl 2-(4-acetylpiperazin-1-yl)-4-(propylthio)pyrimidine-5-carboxylate compound with ethyl 4-(4-acetylpiperazin-1-yl)-2-(propylthio)pyrimidine-5-carboxylate (735 mg, 1.04 mmol) in
 5 methanol (20 mL). The resulting solution was stirred at 22 °C for 18 hours. The reaction mixture was concentrated and diluted with water (20 mL). The pH was adjusted to pH4 with 2M HCl and the mixture was extracted with EtOAc (2x25 mL). The combined extracts were washed sequentially with water (25 mL) and saturated brine (20 mL). The organic layer was dried over MgSO₄, filtered and evaporated to afford an inseparable
 10 mixture of 2-(4-acetylpiperazin-1-yl)-4-(propylthio)pyrimidine-5-carboxylic acid and 4-(4-acetylpiperazin-1-yl)-2-(propylthio)pyrimidine-5-carboxylic acid (399mg).

¹H NMR (400.13 MHz, DMSO-d₆) δ 0.96 - 1.00 (3H, m), 1.61 - 1.72 (2H, m), 2.02 (1H, s), 2.04 (2H, s), 2.99 - 3.06 (2H, m), 3.48 - 3.61 (5H, m), 3.75- 3.89 (3H, m), 8.46 (0.33H, s), 8.61 (0.66H, s), 12.56 (1H, s) (inseparable mixture)

15 m/z (ESI+) (M+H)⁺ = 325; t_R = 0.89 min. (inseparable mixture)

Example 27

2-(4-Acetylpiperazin-1-yl)-N-(2-adamantyl)-4-propylsulfanyl-pyrimidine-5-carboxamide



20 1-Acetylpiperazine (219 mg, 1.71 mmol), and N-adamantan-2-yl-2-chloro-4-(propylthio)pyrimidine-5-carboxamide (Intermediate 52, 250 mg, 0.68 mmol) were suspended in THF (3 mL) and sealed into a microwave tube. The reaction was heated using microwaves to 150 °C for 2 hours and then cooled to room temperature. The reaction mixture was diluted with EtOAc (25 mL) and washed sequentially with water (10 mL) and
 25 saturated brine (10 mL). The organic layer was dried over MgSO₄, filtered and evaporated to afford crude product. The crude solid was triturated with DMSO/CH₃CN/ water (7:2:1) (5 mL) to give a solid which was collected by filtration, washed with CH₃CN/water (2:1) and dried under vacuum to give 2-(4-acetylpiperazin-1-yl)-N-(2-adamantyl)-4-

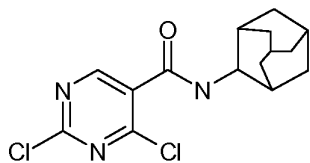
propylsulfanyl-pyrimidine-5-carboxamide (267 mg, 85 %) as a white solid.

¹H NMR (400.13 MHz, DMSO-d₆) δ 0.97 (3H, t), 1.48 - 1.51 (2H, m), 1.59 - 1.66 (2H, m), 1.69 (2H, d), 1.75 - 1.83 (6H, m), 1.90 (2H, s), 2.04 (4H, s), 2.07 (1H, s), 3.02 (2H, t), 3.52 (4H, t), 3.76 - 3.78 (2H, m), 3.84 (2H, t), 3.93 - 3.95 (1H, m), 7.86 (1H, d), 8.31 (1H, s)

m/z (ESI+) (M+H)⁺ = 458; HPLC t_R = 2.71 min.

Intermediate 51

N-adamantan-2-yl-2,4-dichloropyrimidine-5-carboxamide

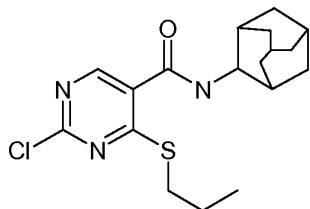


A suspension of 2-adamantanamine hydrochloride (1.776 g, 9.46 mmol) and N-ethyl-diisopropylamine (3.27 mL, 18.92 mmol) in THF (10.00 mL) was added dropwise to a stirred solution of 2,4-dichloropyrimidine-5-carbonyl chloride (2.00 g, 9.46 mmol) in dichloromethane (20 mL) at -10°C under an atmosphere of nitrogen. The resulting solution was stirred at 0°C for 1 hour. The reaction mixture was diluted with DCM (100 mL) and washed sequentially with 0.1M HCl (25 mL), saturated NaHCO₃ (25 mL) and saturated brine (25 mL). The organic layer was dried over MgSO₄, filtered and evaporated to afford crude product. The crude solid was triturated with isohexane to give a solid which was collected by filtration and dried under vacuum to give N-adamantan-2-yl-2,4-dichloropyrimidine-5-carboxamide (2.50 g, 81 %) as a yellow powder.

¹H NMR (400.13 MHz, DMSO-d₆) δ 1.53 (2H, d), 1.71 (2H, s), 1.81 (5H, d), 1.85 (1H, s), 1.94 - 1.96 (3H, m), 2.00 (1H, s), 4.02 - 4.04 (1H, m), 8.56 (1H, d), 8.84 - 8.86 (1H, m)
m/z (ESI+) (M+H)⁺ = 326; HPLC t_R = 2.65 min.

Intermediate 52

N-adamantan-2-yl-2-chloro-4-(propylthio)pyrimidine-5-carboxamide



Sodium carbonate (0.812 g, 7.66 mmol) was added in one portion to a mixture of N-adamantan-2-yl-2,4-dichloropyrimidine-5-carboxamide (Intermediate 51, 2.5 g, 7.66 mmol) and 1-Propanethiol (0.694 mL, 7.66 mmol) in DMF (15 mL) at room temperature under nitrogen. The resulting suspension was stirred at roomtemperature for 16 hours. The reaction mixture was diluted with EtOAc (150 mL) and washed sequentially with water (50 mL) and saturated brine (50 mL). The organic layer was dried over MgSO₄, filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 10 to 40% EtOAc in isohexane. Pure fractions were evaporated to dryness to afford N-adamantan-2-yl-2-chloro-4-(propylthio)pyrimidine-5-carboxamide (2.60 g, 93 %) as a white solid.

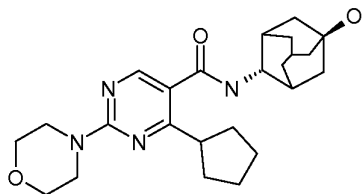
¹H NMR (400.13 MHz, DMSO-d₆) δ 0.97 (3H, t), 1.51 (2H, d), 1.64 (2H, q), 1.69 (1H, s), 1.80 - 1.84 (7H, m), 1.93 (2H, s), 2.04 (2H, d), 3.11 (2H, t), 4.00 (1H, t), 8.42 (1H, d), 8.47 (1H, s)
m/z (ESI⁺) (M+H)⁺ = 366; HPLC t_R = 3.19 min.

The following Examples were prepared in a similar manner to Example 27, using Intermediate 51 and an appropriate amine starting material:

Structure	Ex	Name	¹ H NMR δ	MS m/e MH ⁺
	28	N-(2-adamantyl)-2-(4-methylsulfonylpiperazin-1-yl)-4-propylsulfanylpirimidine-5-carboxamide	¹ H NMR (400.13 MHz, DMSO-d ₆) δ 0.97 (3H, t), 1.50 (2H, s), 1.59 - 1.66 (2H, m), 1.70 (2H, s), 1.75 - 1.83 (6H, m), 1.90 (2H, s), 2.04 - 2.07 (2H, m), 2.89 (3H, s), 3.02 (2H, t), 3.19 (4H, t), 3.91 - 3.95 (5H, m), 7.88 (1H, d), 8.32 (1H, s)	494; HPLC t _R = 3.04 min.
	29	N-(2-adamantyl)-2-[4-(dimethylcarbamoyl)piperazin-1-yl]-4-propylsulfanylpirimidine-5-carboxamide	¹ H NMR (400.13 MHz, DMSO-d ₆) δ 0.96 (3H, t), 1.49 (2H, s), 1.63 (2H, q), 1.69 (2H, d), 1.78 (4H, d), 1.75 - 1.83 (2H, m), 1.90 (2H, s), 2.04 - 2.07 (2H, m), 2.78 (6H, s), 3.01 (2H, t), 3.18 (4H, t), 3.80 - 3.82 (4H, m), 3.94 (1H, t), 7.85 (1H, d), 8.30 (1H, s)	487; HPLC t _R = 2.94 min.

Example 30

4-Cyclopentyl-N-[(2s,5r)-5-hydroxyadamantan-2-yl]-2-morpholin-4-ylpyrimidine-5-carboxamide



5

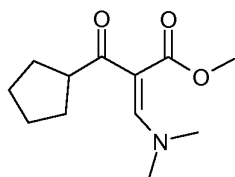
O-(7-Azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (0.456 g, 1.2 mmol) was added in one portion to 4-cyclopentyl-2-morpholinopyrimidine-5-

carboxylic acid (Intermediate 55, 0.277 g, 1.0 mmol) and N-ethyldiisopropylamine (0.523 ml, 3.00 mmol) in DMF (5.00 ml) at 25 °C under nitrogen. After stirring for 10 minutes (1r,4s)-4-aminoadamantan-1-ol (0.224 g, 1.10 mmol) was added and the solution was stirred at 25 °C for 3 hours. The reaction mixture was concentrated and diluted with DCM (100 mL) and washed sequentially with saturated NaHCO₃ (100 mL), saturated brine (100 mL) and water (100 mL). The organic layer was dried over MgSO₄, filtered and evaporated to afford crude product. The crude product was purified by preparative HPLC (Waters XBridge Prep C18 OBD column, 5 μ silica, 50 mm diameter, 150 mm length), using decreasingly polar mixtures of water (containing 0.5% NH₃) and MeCN as eluents. Fractions containing the desired compound were evaporated to dryness to afford 4-cyclopentyl-N-[(2s,5r)-5-hydroxyadamantan-2-yl]-2-morpholin-4-ylpyrimidine-5-carboxamide (0.224 g, 52%) as a white solid.

¹H NMR (400.13 MHz, DMSO-d₆) δ 1.30 - 1.33 (2H, m), 1.52 - 1.63 (6H, m), 1.69 - 1.78 (6H, m), 1.80 - 1.83 (1H, m), 1.83 - 1.87 (1H, m), 1.90 (1H, s), 1.93 (1H, s), 1.98 (1H, s), 2.02 (2H, s), 3.41 - 3.49 (1H, m), 3.65 (4H, q), 3.70 - 3.74 (4H, m), 3.90 (1H, t), 4.38 (1H, s), 8.04 - 8.06 (1H, m), 8.22 (1H, t)
m/z (ESI+) (M+H)⁺ = 427; HPLC t_R = 2.01 min.

Intermediate 53

Methyl 2-(cyclopentanecarbonyl)-3-(dimethylamino)acrylate



N,N-Dimethylformamide dimethyl acetal (3.28 mL, 24.68 mmol) was added in one portion to methyl 3-cyclopentyl-3-oxopropanoate (3.50 g, 20.56 mmol) in dioxane (40 mL) at room temperature under nitrogen. The resulting solution was stirred at 100 °C for 4 hours. The reaction mixture was evaporated to afford crude product. The crude product was purified by flash silica (120g) chromatography, elution gradient 50 to 80% EtOAc in isohexane. Pure fractions were evaporated to dryness to afford methyl 2-(cyclopentanecarbonyl)-3-(dimethylamino)acrylate (4.50 g, 97 %) as a yellow oil.

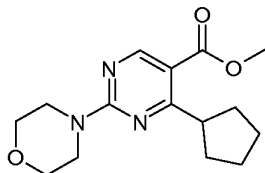
¹H NMR (400.13 MHz, DMSO-d₆) δ 1.45 - 1.73 (8H, m), 2.81 - 2.86 (1H, m), 2.95 (6H,

s), 3.62 (3H, s), 7.57 (1H, s)

m/z (ESI+) (M+H)⁺ = 226; HPLC t_R = 1.66 min.

Intermediate 54

5 Methyl 4-cyclopentyl-2-morpholinopyrimidine-5-carboxylate

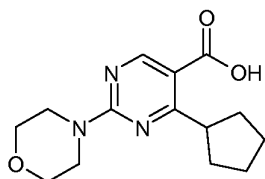


A solution of methyl 2-(cyclopentanecarbonyl)-3-(dimethylamino)acrylate (Intermediate 53, 1.50 g, 6.66 mmol) in methanol (5 mL) was added dropwise to a stirred suspension of morpholinoformamidine hydrobromide (1.399 g, 6.66 mmol) and sodium methoxide
10 (13.32 mL, 6.66 mmol) in methanol (25 mL) under nitrogen. The resulting solution was stirred at 80 °C for 6 hours then at room temperature for 16 hours. The reaction mixture was evaporated to dryness and then dissolved in DCM (50 mL) and washed sequentially with water (2x20 mL), and saturated brine (25 mL). The organic layer was dried over MgSO₄, filtered and evaporated to afford crude product. The crude product was purified
15 by flash silica (40g) chromatography, elution gradient 20 to 50% EtOAc in isohexane. Pure fractions were evaporated to dryness to afford methyl 4-cyclopentyl-2-morpholinopyrimidine-5-carboxylate (1.210 g, 62%) as a colourless oil which solidified on standing.

¹H NMR (400.13 MHz, DMSO-d₆) δ 1.58 - 1.66 (2H, m), 1.70 - 1.81 (4H, m), 1.86 - 1.93
20 (2H, m), 3.64 - 3.67 (4H, m), 3.77 (3H, s), 3.79 - 3.81 (4H, m), 3.96 (1H, q), 8.72 (1H, s)
m/z (ESI+) (M+H)⁺ = 292; HPLC t_R = 2.78 min.

Intermediate 55

4-cyclopentyl-2-morpholinopyrimidine-5-carboxylic acid



25

Sodium hydroxide (10.38 mL, 20.77 mmol) was added in one portion to methyl 4-

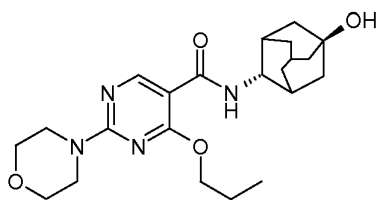
cyclopentyl-2-morpholinopyrimidine-5-carboxylate (Intermediate 54, 1.21 g, 4.15 mmol) in methanol (50 mL) under air. The resulting solution was stirred at 60 °C for 4 hours then at room temperature for 16 hours. The reaction mixture was concentrated and diluted with water (15 mL) and acidified with 2M HCl. The precipitate was collected by filtration,
5 washed with water (25 mL) and dried under vacuum to afford 4-cyclopentyl-2-morpholinopyrimidine-5-carboxylic acid (1.10 g, 96%) as a white solid that was used without further purification.

¹H NMR (400.13 MHz, DMSO-d₆) δ 1.55 - 1.65 (2H, m), 1.70 - 1.80 (4H, m), 1.84 - 1.93 (2H, m), 3.64 - 3.66 (4H, m), 3.78 - 3.80 (4H, m), 4.03 - 4.11 (1H, m), 8.72 (1H, s), 12.62
10 (1H, s)

m/z (ESI+) (M+H)⁺ = 278; HPLC t_R = 2.31 min.

Example 31

N-[(2s,5r)-5-Hydroxyadamantan-2-yl]-2-morpholin-4-yl-4-propoxypyrimidine-5-
15 carboxamide



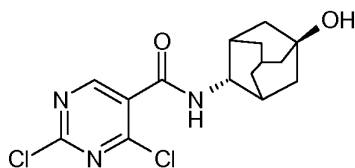
Morpholine (1.047 mL, 12.00 mmol) and 2-chloro-N-[(2s,5r)-5-hydroxyadamantan-2-yl]-4-propoxypyrimidine-5-carboxamide (Intermediate 57, 366 mg, 1.00 mmol) were suspended in THF (5 mL) and sealed into a microwave tube. The reaction was heated using
20 microwave heating to 100 °C for 30 minutes and then cooled to room temperature. The reaction mixture was diluted with DCM (50 mL) and washed sequentially with water (25 mL) and saturated brine (25 mL). The organic layer was dried over MgSO₄, filtered and evaporated to afford crude product. The crude product was purified by preparative HPLC (Waters XBridge Prep C18 OBD column, 5μ silica, 50 mm diameter, 150 mm length),
25 using decreasingly polar mixtures of water (containing 0.5% NH₃) and MeCN as eluents. Fractions containing the desired compound were evaporated to dryness to afford N-[(2s,5r)-5-hydroxyadamantan-2-yl]-2-morpholin-4-yl-4-propoxypyrimidine-5-carboxamide (140 mg, 34%)

¹H NMR (400.13 MHz, DMSO-d₆) δ 0.98 (3H, t), 1.43 - 1.46 (2H, m), 1.63 - 1.65 (4H,

m), 1.70 - 1.75 (4H, m), 1.77 - 1.82 (2H, m), 2.02 (3H, s), 3.63 - 3.66 (4H, m), 3.75 - 3.78 (4H, m), 3.97 (1H, t), 4.40 (2H, t), 4.42 (1H, s), 7.63 (1H, d), 8.65 (1H, s)
 m/z (ESI+) (M+H)+ = 417; HPLC t_R = 1.97 min.

5 Intermediate 56

2,4-dichloro-N-[(2s,5r)-5-hydroxyadamantan-2-yl]pyrimidine-5-carboxamide

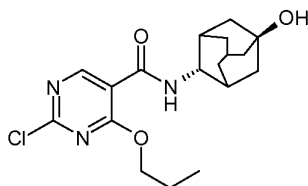


A suspension of (1r,4s)-4-aminoadamantan-1-ol .hydrochloride (2.89 g, 14.19 mmol) in THF (20.00 mL) was added dropwise to a stirred solution of 2,4-dichloropyrimidine-5-carbonyl chloride (3.00g, 14.19 mmol) and N-ethyldiisopropylamine (4.91 mL, 28.38 mmol) in dichloromethane (20 mL) at -10°C, over a period of 5 minutes under nitrogen. The resulting suspension was stirred at 0 °C for 4 hours. The reaction mixture was diluted with DCM (150 mL) and washed sequentially with 0.1M HCl (50 mL), water (50 mL) and saturated brine (75 mL). The organic layer was dried over MgSO₄, filtered and evaporated to afford desired product. The crude solid was triturated with ice-cold DCM to give a solid which was collected by filtration and dried under vacuum to give 2,4-dichloro-N-[(2s,5r)-5-hydroxyadamantan-2-yl]pyrimidine-5-carboxamide (3.20 g, 66%) as a tan solid.
 1H NMR (400.13 MHz, DMSO-d₆) δ 1.36 (2H, d), 1.63 (4H, d), 1.71 - 1.77 (3H, m), 1.86 (2H, d), 1.98 - 2.00 (1H, m), 2.06 (2H, s), 3.95 (1H, t), 8.51 (1H, d), 8.83 - 8.85 (1H, m)

m/z (ESI+) (M+H)+ = 342; HPLC t_R = 1.44 min.

Intermediate 57

2-chloro-N-[(2s,5r)-5-hydroxyadamantan-2-yl]-4-propoxypyrimidine-5-carboxamide

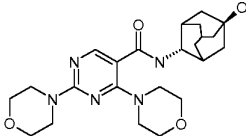


Sodium bis(trimethylsilyl)amide (1M solution in THF, 1.00 mL, 1.00 mmol) was added in

one portion to 1-propanol (0.075 mL, 1.00 mmol), in THF (1 mL) at room temperature under nitrogen. The resulting suspension was stirred at room temperature for 5 minutes. This suspension was added dropwise to 2,4-dichloro-N-[(2s,5r)-5-hydroxyadamantan-2-yl]pyrimidine-5-carboxamide (Intermediate 56, 0.342 g, 1 mmol) in THF (10mL) at room temperature under nitrogen. The resulting suspension was stirred for a further 4 hours. The reaction mixture was diluted with EtOAc (75 mL) and washed sequentially with 0.1M HCl (25 mL), water (25 mL) and saturated brine (25 mL). The organic layer was dried over MgSO₄, filtered and evaporated to afford crude product as yellow foam. Used directly in next stage.

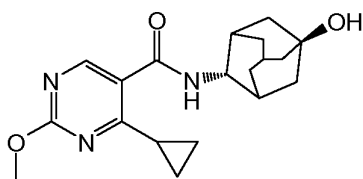
m/z (EI⁺) (M+H)⁺ = 366; HPLC t_R = 2.03 min.

The following Examples were prepared in a similar manner to Example 31, using Intermediate 57 and an appropriate amine starting material:

Structure	Ex	Name	¹ H NMR δ	MS m/e MH ⁺
	32	N-[(2s,5r)-5-hydroxyadamantan-2-yl]-2,4-dimorpholin-4-ylpyrimidine-5-carboxamide	¹ H NMR (400.13 MHz, DMSO-d ₆) δ 1.30 - 1.33 (2H, m), 1.59 - 1.62 (4H, m), 1.67 - 1.70 (2H, m), 1.90 (2H, d), 1.99 (3H, s), 3.43 (4H, t), 3.58 - 3.62 (8H, m), 3.64 - 3.66 (4H, m), 3.85 - 3.87 (1H, m), 4.37 (1H, s), 7.95 (1H, s), 8.04 (1H, d)	444; HPLC t _R = 1.40 min.

Example 33

4-Cyclopropyl-N-[(2r,5s)-5-hydroxyadamantan-2-yl]-2-methoxypyrimidine-5-carboxamide

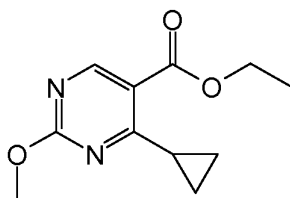


[Dimethylamino-(triazolo[5,4-b]pyridin-3-yloxy)methylidene]-dimethylazanium hexafluorophosphate (479 mg, 1.26 mmol) was added to 4-cyclopropyl-2-methoxypyrimidine-5-carboxylic acid (Intermediate 59, 155 mg, 0.80 mmol) and N-ethyl-N-propan-2-ylpropan-2-amine (0.274 mL, 1.60 mmol) in DMF (5 mL). The resulting solution was stirred at room temperature for 15 minutes. (1s,4r)-4-Aminoadamantan-1-ol hydrochloride (179 mg, 0.88 mmol) was added and the reaction mixture was stirred at room temperature for 2 hours. The reaction mixture was evaporated to dryness and redissolved in EtOAc (150 mL) and washed sequentially with water (2x150 mL). The organic layer was dried over MgSO₄, filtered and evaporated to afford the crude product. The crude product was purified by flash silica chromatography, elution gradient 0 to 10% MeOH in DCM. Pure fractions were evaporated to dryness to afford 4-cyclopropyl-N-[(2r,5s)-5-hydroxyadamantan-2-yl]-2-methoxypyrimidine-5-carboxamide (67mg, 24%) as a white solid.

¹H NMR (400.13 MHz, CDCl₃) δ 1.02 - 1.06 (2H, m), 1.22 - 1.25 (2H, m), 1.50 (2H, d), 1.67 (1H, s), 1.72 (3H, d), 1.75 (1H, s), 1.87 (2H, d), 1.97 (1H, s), 2.11 (1H, s), 2.19 (2H, s), 2.37 - 2.43 (1H, m), 3.89 (3H, s), 4.13 - 4.17 (1H, m), 6.26 (1H, d), 8.37 (1H, s)
m/z (ESI+) (M+H)⁺ = 344; HPLC t_R = 1.58 min.

Intermediate 58

Ethyl 4-cyclopropyl-2-methoxypyrimidine-5-carboxylate



Ethyl 2-(cyclopropanecarbonyl)-3-(dimethylamino)acrylate (499 mg, 2.36 mmol) was dissolved in DMF (10 mL). To this solution was added methyl carbamimidate hydrochloride (279 mg, 2.52 mmol) and sodium acetate (915 mg, 11.16 mmol). The reaction was heated at 85 °C for 8 hours and then allowed to cool to room temperature and water (50 mL) was added. The reaction mixture was diluted with EtOAc (100 mL) and washed sequentially with water (2x100 mL), saturated aqueous NaHCO₃ (100 mL) and water (100 mL). The organic layer was dried over MgSO₄, filtered and evaporated to afford the crude product. The crude product was purified by flash silica chromatography,

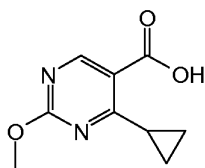
elution gradient 0 to 10% EtOAc in isohexane. Pure fractions were evaporated to dryness to afford ethyl 4-cyclopropyl-2-methoxypyrimidine-5-carboxylate (178 mg, 34 %) as a colourless oil.

¹H NMR (400.13 MHz, CDCl₃) δ 1.00 - 1.07 (2H, m), 1.17 - 1.24 (2H, m), 1.32 (3H, t),
3.12 - 3.19 (1H, m), 3.90 (3H, s), 4.30 (2H, q), 8.83 (1H, s)

m/z (ESI+) (M+H)⁺ = 223; HPLC t_R = 2.32 min.

Intermediate 59

4-cyclopropyl-2-methoxypyrimidine-5-carboxylic acid

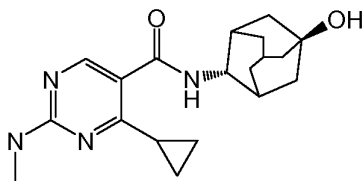


Ethyl 4-cyclopropyl-2-methoxypyrimidine-5-carboxylate (Intermediate 58, 178 mg, 0.80 mmol) was dissolved in methanol (5 mL) and 2M aqueous sodium hydroxide (2.0 mL, 4.0 mmol) was added. The resulting solution was stirred at room temperature for 3 hours. The reaction mixture was evaporated to dryness and then dissolved in water (50 mL) and then acidified to pH=4 with 2N HCl. The aqueous layer was washed sequentially with EtOAc (2x100 mL). The organic layer was dried over MgSO₄, filtered and evaporated to afford crude 4-cyclopropyl-2-methoxypyrimidine-5-carboxylic acid (107 mg, 69%) as a white solid, which was used without further purification.

m/z (ESI+) (M+H)⁺ = 195; HPLC t_R = 1.56 min.

Example 34

4-Cyclopropyl-N-[(2r,5s)-5-hydroxyadamantan-2-yl]-2-methylaminopyrimidine-5-carboxamide



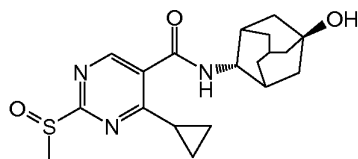
4-Cyclopropyl-N-[(2r,5s)-5-hydroxyadamantan-2-yl]-2-methylsulfonfylpyrimidine-5-carboxamide (Intermediate 60, 347 mg, 0.92 mmol) and 2M methylamine in THF (2.31

mL, 4.62 mmol) were dissolved in THF (2 mL) and sealed into a microwave tube. The reaction was heated to 110 °C for 30 min in the microwave reactor and then cooled to room temperature. The reaction mixture was evaporated to dryness and redissolved in EtOAc (75 mL) and washed sequentially with saturated brine (2x50 mL). The organic layer was dried over MgSO₄, filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 0 to 10 % MeOH in DCM. Pure fractions were evaporated to dryness to afford 4-cyclopropyl-N-[(2r,5s)-5-hydroxyadamantan-2-yl]-2-methylaminopyrimidine-5-carboxamide (137 mg, 43 %) as a white solid.

¹H NMR (400.13 MHz, CDCl₃) δ 0.91 - 0.96 (2H, m), 1.14 - 1.20 (2H, m), 1.49 (2H, d), 1.66 (2H, d), 1.71 (3H, s), 1.74 (1H, s), 1.86 (2H, d), 2.10 (1H, s), 2.17 (2H, s), 2.38 - 2.44 (1H, m), 2.89 (3H, d), 4.10 - 4.15 (1H, m), 5.31 (1H, s), 6.08 (1H, d), 8.24 (1H, s)
m/z (ESI+) (M+H)⁺ = 343; HPLC t_R = 1.60 min.

Intermediate 60

4-Cyclopropyl-N-[(2r,5s)-5-hydroxyadamantan-2-yl]-2-methylsulfinylpyrimidine-5-carboxamide

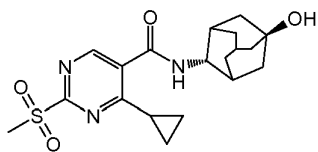


3-Chloroperoxybenzoic acid (88 mg, 0.36 mmol) was added as a solid to a cold (0°C) solution of 4-cyclopropyl-N-[(2r,5s)-5-hydroxyadamantan-2-yl]-2-methylsulfinylpyrimidine-5-carboxamide (Example 11, 107 mg, 0.30 mmol) in DCM (10 mL) under an atmosphere of nitrogen. After 30 minutes the reaction had gone to completion and saturated aqueous NaHCO₃ (50 mL) was added to quench the reaction. The organic layer was separated and the aqueous layer was washed sequentially with EtOAc (5x150 mL). The combined organic layers were dried over MgSO₄, filtered and evaporated to afford crude product as a colourless oil. The product was used in the next reaction step without further purification and characterisation.

m/z (ESI+) (M+H)⁺ = 376; HPLC t_R = 1.25 min.

Intermediate 80

4-cyclopropyl-N-[(2r,5s)-5-hydroxyadamantan-2-yl]-2-methylsulfonylpyrimidine-5-carboxamide



- 5 3-Chloroperoxybenzoic acid (70%) (19.20 g, 77.89 mmol) was added in one portion to 4-cyclopropyl-N-[(2r,5s)-5-hydroxyadamantan-2-yl]-2-methylsulfonylpyrimidine-5-carboxamide (Example 11, 14 g, 38.94 mmol) in DCM (450 mL) at 0°C. The resulting solution was stirred at 20 °C for 24 hours. The reaction mixture was diluted with DCM (300 mL), and washed sequentially with saturated NaHCO₃ (4x200 mL) and saturated
- 10 brine (200 mL). The organic layer was dried over MgSO₄, filtered and evaporated to afford 4-cyclopropyl-N-[(2r,5s)-5-hydroxyadamantan-2-yl]-2-methylsulfonylpyrimidine-5-carboxamide (12.10 g, 79 %) as a white solid.

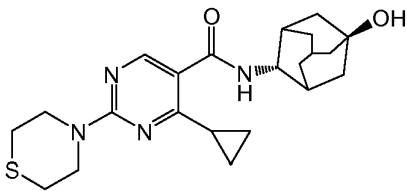
¹H NMR (400.132 MHz, CDCl₃) δ 1.28 - 1.31 (2H, m), 1.39 - 1.42 (2H, m), 1.56 - 1.62 (2H, m), 1.73 - 1.85 (7H, m), 1.94 - 1.97 (2H, m), 2.19 - 2.23 (1H, m), 2.28 - 2.32 (2H, m),

15 2.45 - 2.52 (1H, m), 3.27 (3H, s), 4.25 - 4.31 (1H, m), 6.37 (1H, d), 8.70 (1H, s)

m/z (ESI+) (M+H)⁺ = 392; HPLC t_R = 1.41 min.

Example 35

- 4-Cyclopropyl-N-[(2r,5s)-5-hydroxyadamantan-2-yl]-2-thiomorpholin-4-ylpyrimidine-5-
- 20 carboxamide



- 4-cyclopropyl-N-[(2r,5s)-5-hydroxyadamantan-2-yl]-2-methylsulfonylpyrimidine-5-carboxamide (Intermediate 60, 693 mg, 1.77 mmol) and thiomorpholine (2.00 mL, 21.09 mmol) were dissolved in THF (4 mL) and sealed into a microwave tube. The reaction was
- 25 heated to 150 °C for 10 hours in the microwave reactor and then cooled to room temperature. The reaction mixture was evaporated to dryness and redissolved in EtOAc (150 mL) and washed sequentially with saturated brine (2x75 mL). The organic layer was

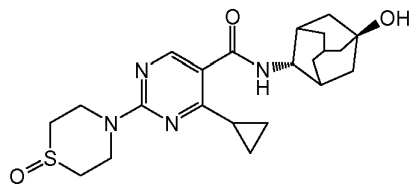
dried over MgSO₄, filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 0 to 7 % MeOH in DCM. Pure fractions were evaporated to dryness to afford 4-cyclopropyl-N-[(2r,5s)-5-hydroxyadamantan-2-yl]-2-thiomorpholin-4-ylpyrimidine-5-carboxamide (444 mg, 60 %) as a colourless oil which solidified on standing.

¹H NMR (400.13 MHz, DMSO-d₆) δ 0.93 - 0.96 (2H, m), 0.98 - 1.03 (2H, m), 1.32 (2H, d), 1.60 - 1.63 (4H, m), 1.69 - 1.72 (2H, m), 1.94 (2H, d), 1.99 - 1.99 (1H, m), 2.04 (2H, s), 2.20 (1H, s), 2.55 - 2.57 (4H, m), 3.16 (1H, d), 3.90 - 3.94 (1H, m), 4.01 - 4.04 (4H, m), 8.07 (1H, d), 8.23 (1H, s)

m/z (ESI+) (M+H)⁺ = 415; HPLC t_R = 2.18 min.

Example 36

4-Cyclopropyl-N-[(2r,5s)-5-hydroxyadamantan-2-yl]-2-(1-oxo-1,4-thiazinan-4-yl)pyrimidine-5-carboxamide



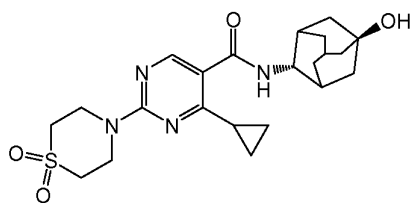
3-Chloroperoxybenzoic acid (153.1 mg, 0.62 mmol) was added as a solid to a cold (0°C) solution of 4-cyclopropyl-N-[(2r,5s)-5-hydroxyadamantan-2-yl]-2-thiomorpholin-4-ylpyrimidine-5-carboxamide (Example 35, 223.2 mg, 0.54 mmol) in dichloromethane (10 mL) and stirred for 15 minutes. Saturated aqueous NaHCO₃ (50 mL) was added to quench the reaction and the organic layer was separated. The aqueous layer was washed with EtOAc (3 x 100mL) and the combined organic layers were dried over MgSO₄, filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 0 to 20% MeOH in DCM. Pure fractions were evaporated to dryness to afford 4-cyclopropyl-N-[(2r,5s)-5-hydroxyadamantan-2-yl]-2-(1-oxo-1,4-thiazinan-4-yl)pyrimidine-5-carboxamide (74 mg, 32%) as a white solid.

¹H NMR (400.13 MHz, CDCl₃) δ 0.97 - 1.02 (2H, m), 1.11 - 1.15 (2H, m), 1.50 (2H, d), 1.67 (2H, d), 1.72 (3H, s), 1.75 (1H, s), 1.86 - 1.88 (2H, m), 2.10 (1H, s), 2.17 (2H, s), 2.41 - 2.47 (1H, m), 2.61 - 2.68 (2H, m), 2.72 - 2.77 (2H, m), 4.04 - 4.11 (2H, m), 4.11 - 4.16 (1H, m), 4.43 - 4.49 (2H, m), 6.13 (1H, d), 8.30 (1H, s)

m/z (ESI+) (M+H)+ = 431; HPLC t_R = 1.39 min.

Example 37

4-Cyclopropyl-2-(1,1-dioxo-1,4-thiazinan-4-yl)-N-[(2r,5s)-5-hydroxyadamantan-2-yl]pyrimidine-5-carboxamide

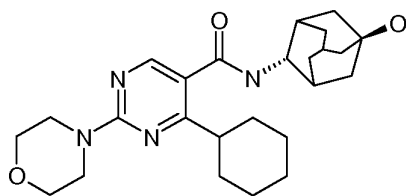


3-Chloroperoxybenzoic acid (606 mg, 2.46 mmol) was added as a solid to a cold (0°C) solution of 4-cyclopropyl-N-[(2r,5s)-5-hydroxyadamantan-2-yl]-2-thiomorpholin-4-ylpyrimidine-5-carboxamide (Example 35, 679 mg, 1.64 mmol) in dichloromethane (20 mL) and stirred for 20 minutes. Saturated aqueous NaHCO₃ (150 mL) was then added to quench the reaction. The organic layer was separated. The aqueous layer was washed with EtOAc (3 x 100mL) and the combined organic layers were dried over MgSO₄, filtered and evaporated to afford crude product. The crude product was purified by preparative HPLC (Phenomenex Gemini C18 110A (axia) column, 5μ silica, 30 mm diameter, 100 mm length), using decreasingly polar mixtures of water (containing 0.1% AcOH) and MeCN as eluents. Fractions containing the desired compound were evaporated to dryness to afford 4-cyclopropyl-2-(1,1-dioxo-1,4-thiazinan-4-yl)-N-[(2r,5s)-5-hydroxyadamantan-2-yl]pyrimidine-5-carboxamide (120 mg, 16%) as a white solid.

¹H NMR (400.13 MHz, CDCl₃) δ 1.00 - 1.04 (2H, m), 1.09 - 1.12 (2H, m), 1.51 (2H, d), 1.66 (2H, d), 1.72 (3H, s), 1.75 (1H, s), 1.86 - 1.89 (2H, m), 2.11 (1H, s), 2.18 (2H, s), 2.42 - 2.46 (1H, m), 2.94 (4H, t), 4.13 - 4.17 (1H, m), 4.27 (4H, t), 6.05 (1H, d), 8.31 (1H, s)
m/z (ESI+) (M+H)+ = 447; HPLC t_R = 1.70 min.

Example 38

4-Cyclohexyl-N-[(2r,5s)-5-hydroxyadamantan-2-yl]-2-morpholin-4-ylpyrimidine-5-carboxamide

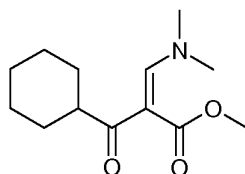


N-Ethyldiisopropylamine (0.285 mL, 1.65 mmol) was added in one portion to 4-aminoadamantan-1-ol hydrochloride (0.308 g, 1.51 mmol), 4-cyclohexyl-2-morpholinopyrimidine-5-carboxylic acid (Intermediate 63, 0.4 g, 1.37 mmol) and O-(7-Azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (0.626 g, 1.65 mmol) in DMF (8 mL) at 18 °C under nitrogen. The resulting suspension was stirred at 18 °C for 70 hours. The reaction was incomplete and further (1s,4r)-4-aminoadamantan-1-ol hydrochloride (0.308 g, 1.51 mmol) and N-ethyldiisopropylamine (0.57 mL, 3.30 mmol) was added in one portion and the suspension was stirred at 18 °C for a further 4 hours. The reaction mixture was diluted with EtOAc (75 mL), and washed sequentially with water (25 mL) and saturated brine (25 mL). The organic layer was dried over MgSO₄, filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography (40g column), elution gradient 0 to 100% EtOAc:MeOH (9:1) in DCM. Pure fractions were evaporated to dryness to afford 4-cyclohexyl-N-[(2R,5S)-5-hydroxyadamantan-2-yl]-2-morpholin-4-ylpyrimidine-5-carboxamide (0.402 g, 66%) as a white solid.

¹H NMR (400.13 MHz, DMSO-d₆) δ 1.15 - 1.34 (5H, m), 1.45 - 1.57 (2H, m), 1.60 - 1.75 (11H, m), 1.90 - 2.03 (5H, m), 2.97 - 3.03 (1H, m), 3.61 - 3.67 (4H, m), 3.69 - 3.76 (4H, m), 3.88 - 3.93 (1H, m), 4.38 (1H, s), 8.06 (1H, d), 8.22 (1H, s)
m/z (ESI+) (M+H)⁺ = 441; HPLC t_R = 2.12 min.

Intermediate 61

Methyl 2-(cyclohexanecarbonyl)-3-(dimethylamino)acrylate



N,N-Dimethylformamide dimethyl acetal (3.47 mL, 26.05 mmol) was added in one portion to methyl 3-cyclohexyl-3-oxopropanoate (4.0 g, 21.71 mmol) in dioxane (40 mL) under

nitrogen. The resulting solution was stirred at 105 °C for 6 hours. The reaction mixture was evaporated to give the product as a greenish-yellow oil. The crude product was purified by flash silica (120g) chromatography, elution gradient 60 to 100% EtOAc in isohexane. Pure fractions were evaporated to dryness to afford methyl 2-(cyclohexanecarbonyl)-3-

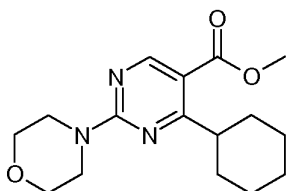
(dimethylamino)acrylate (4.99 g, 96%) as a yellow oil.

¹H NMR (400.13 MHz, DMSO-d₆) δ 1.07 - 1.27 (5H, m), 1.59 - 1.68 (5H, m), 2.78 - 2.98 (7H, m), 3.62 (3H, s), 7.57 (1H, s)

m/z (ESI+) (M+H)⁺ = 240; HPLC t_R = 1.83 min.

Intermediate 62

Methyl 4-cyclohexyl-2-morpholinopyrimidine-5-carboxylate



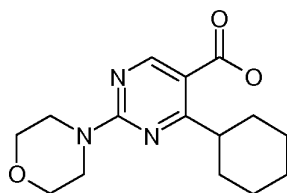
A solution of methyl 2-(cyclohexanecarbonyl)-3-(dimethylamino)acrylate (Intermediate 61, 1.61 g, 6.73 mmol) in MeOH (5 mL) was added dropwise to a stirred solution of morpholinoformamidinium hydrobromide (1.413 g, 6.73 mmol) and 0.5M Sodium Methoxide (13.46 mL, 6.73 mmol) at 18 °C, over a period of 3 minutes under nitrogen. The resulting solution was stirred at 80 °C for 6 hours then room temperature for 12 hours. The reaction mixture was quenched with saturated NH₄Cl aq. (10 mL) then diluted with DCM (50 mL) and washed with water (20 mL). The organic layer was dried over MgSO₄, filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 0 to 10% EtOAc in DCM. Pure fractions were evaporated to dryness to afford methyl 4-cyclohexyl-2-morpholinopyrimidine-5-carboxylate (1.610 g, 78%) as a white solid.

¹H NMR (400.13 MHz, DMSO-d₆) δ 1.18 - 1.38 (3H, m), 1.45 - 1.54 (2H, m), 1.67 - 1.78 (5H, m), 3.49 - 3.57 (1H, m), 3.63 - 3.67 (4H, m), 3.77 - 3.82 (7H, m), 8.73 (1H, s)

m/z (ESI+) (M+H)⁺ = 306; HPLC t_R = 2.98 min.

Intermediate 63

4-Cyclohexyl-2-morpholinopyrimidine-5-carboxylic acid



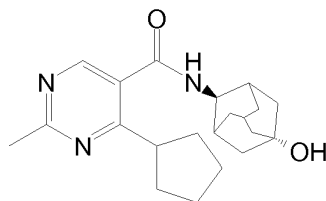
A 2M solution of sodium hydroxide in water (12.93 mL, 25.87 mmol) was added dropwise to a stirred suspension of methyl 4-cyclohexyl-2-morpholinopyrimidine-5-carboxylate (Intermediate 62, 1.58 g, 5.17 mmol) in MeOH (60 mL) at 18°C, over a period of 5 minutes. The resulting suspension was stirred at 18 °C for 18 hours. The reaction was incomplete so the temperature was increased to 60°C and the reaction mixture was stirred for a further 4 hours to give a clear colourless solution. The reaction mixture was acidified with 2M HCl to pH 4.5 and the white precipitate was filtered off and washed with water (3 x 20 mL). The combined aqueous washings and the mother liquors were extracted with DCM (3 x 20 mL) and the organic solution was combined with the original solid (DCM was used for this although the solid was only sparingly soluble in DCM). Evaporation gave a white solid that was azeotroped with toluene (30 mL) to afford 4-cyclohexyl-2-morpholinopyrimidine-5-carboxylic acid (1.430 g, 95%) as a white solid.

¹H NMR (400.13 MHz, DMSO-d₆) δ 1.15 - 1.37 (3H, m), 1.45 - 1.54 (2H, m), 1.67 - 1.78 (5H, m), 3.59 - 3.67 (5H, m), 3.78 - 3.81 (4H, m), 8.72 (1H, s), 12.60 (1H, s)

m/z (ESI⁺) (M+H)⁺ = 292; HPLC t_R = 2.30 min.

Example 39

4-Cyclopentyl-N-[(2r,5s)-5-hydroxyadamantan-2-yl]-2-methylpyrimidine-5-carboxamide



20

Prepared from Intermediate 65 by the same process used for Example 31

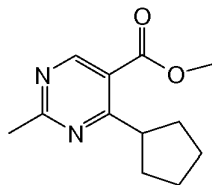
¹H NMR (400.132 MHz, CDCl₃) δ 1.56 - 1.72 (9H, m), 1.78 - 2.01 (10H, m), 2.18 (1H, s), 2.26 (2H, s), 2.70 (3H, s), 3.41 - 3.46 (1H, m), 4.20 - 4.25 (1H, m), 5.94 (1H, d), 8.52 (1H, s)

m/z (ESI⁺) (M+H)⁺ = 356; HPLC t_R = 1.70 min.

25

Intermediate 64

Methyl 4-cyclopentyl-2-methylpyrimidine-5-carboxylate

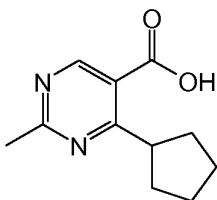


Prepared from Intermediate 53 by the same process used for Intermediate 54

- 5 $^1\text{H NMR}$ (400.132 MHz, CDCl_3) δ 1.64 - 1.73 (2H, m), 1.83 - 1.92 (4H, m), 1.97 - 2.04 (2H, m), 2.72 (3H, s), 3.93 (3H, s), 3.91 - 3.97 (1H, m), 8.94 (1H, s)
 m/z (ESI⁺) (M+H)⁺ = 221; HPLC t_R = 2.31 min.

Intermediate 65

- 10 4-Cyclopentyl-2-methylpyrimidine-5-carboxylic acid

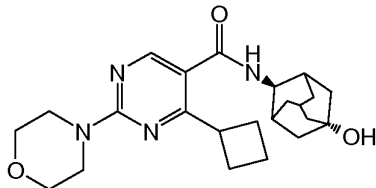


Prepared from Intermediate 64 by the same process used for Intermediate 2.

- $^1\text{H NMR}$ (400.132 MHz, CDCl_3) δ 1.67 - 1.76 (2H, m), 1.84 - 1.96 (4H, m), 2.01 - 2.08 (2H, m), 2.79 (3H, s), 4.05 - 4.16 (1H, m), 8.35 (1H, bs), 9.16 (1H, s)
 15 m/z (ESI⁺) (M+H)⁺ = 207; HPLC t_R = 1.63 min.

Example 40

4-Cyclobutyl-N-[(2r,5s)-5-hydroxyadamantan-2-yl]-2-morpholin-4-ylpyrimidine-5-carboxamide



20

Prepared from Intermediate 68 by the same process used for Example 38

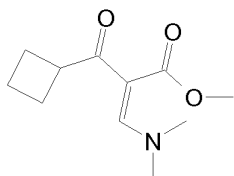
- $^1\text{H NMR}$ (400.132 MHz, CDCl_3) δ 1.43 (1H, s), 1.54 - 1.56 (2H, m), 1.69 (2H, d), 1.76 - 1.82 (4H, m), 1.86 - 2.07 (4H, m), 2.13 - 2.18 (1H, m), 2.21 - 2.28 (4H, m), 2.35 - 2.46

(2H, m), 3.77 (4H, t), 3.91 (4H, t), 3.94 - 4.03 (1H, m), 4.14 - 4.19 (1H, m), 5.81 (1H, d), 8.33 (1H, s)

m/z (ESI+) (M+H)⁺ = 413; HPLC t_R = 1.83 min.

5 **Intermediate 66**

Methyl 2-(cyclobutanecarbonyl)-3-(dimethylamino)acrylate

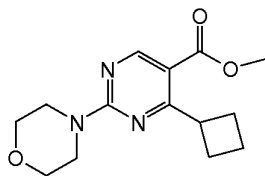


N,N-Dimethylformamide dimethyl acetal (5.62 mL, 42.26 mmol) was added in one portion to methyl 3-cyclobutyl-3-oxopropanoate (5.5 g, 35.22 mmol) in dioxane (50 mL) at room temperature under nitrogen. The resulting solution was stirred at 100 °C for 4 hours. The reaction mixture was evaporated, to afford crude product. The crude product was purified by flash silica (120g) chromatography, elution gradient 50 to 80% EtOAc in isohexane. Pure fractions were evaporated to dryness to afford (Z)-methyl 2-(cyclobutanecarbonyl)-3-(dimethylamino)acrylate (4.60 g, 61.8 %) as a yellow oil.

15 ¹H NMR (400.132 MHz, CDCl₃) δ 1.72 - 1.82 (1H, m), 1.85 - 1.97 (1H, m), 2.06 - 2.13 (2H, m), 2.18 - 2.29 (2H, m), 3.02 (6H, s), 3.68 - 3.75 (1H, m), 3.73 (3H, s), 7.62 (1H, s) m/z (ESI+) (M+Na)⁺ = 234; HPLC t_R = 1.42 min.

Intermediate 67

20 Methyl 4-cyclobutyl-2-morpholinopyrimidine-5-carboxylate



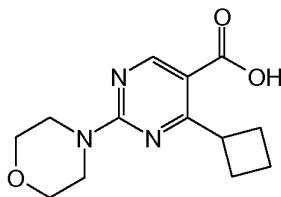
Prepared from Intermediate 66 by the same process used for Intermediate 2

¹H NMR (400.132 MHz, CDCl₃) δ 1.79 - 1.90 (1H, m), 1.97 - 2.08 (1H, m), 2.23 - 2.32 (2H, m), 2.34 - 2.42 (2H, m), 3.76 - 3.79 (4H, m), 3.83 (3H, s), 3.94 - 3.99 (4H, m), 4.31 (1H, quintet), 8.78 (1H, s)

m/z (ESI+) (M+H)⁺ = 278; HPLC t_R = 2.57 min.

Intermediate 68

4-Cyclobutyl-2-morpholinopyrimidine-5-carboxylic acid

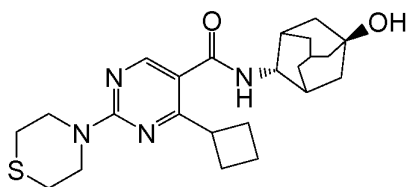


- 5 Prepared from Intermediate 67 by the same process used for Intermediate 3.
¹H NMR (400.132 MHz, DMSO) δ 1.73 - 1.81 (1H, m), 1.91 - 2.01 (1H, m), 2.14 - 2.22 (2H, m), 2.25 - 2.36 (2H, m), 3.67 (4H, t), 3.82 - 3.88 (4H, m), 4.30 (1H, quintet), 8.70 (1H, s), 12.38 (1H, s)
 m/z (ESI⁺) (M+H)⁺ = 264; HPLC t_R = 0.91 min.

10

Example 41

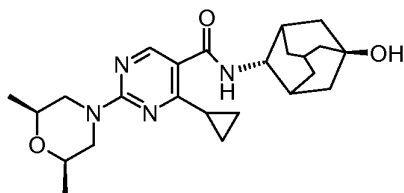
4-Cyclobutyl-N-[(2r,5s)-5-hydroxyadamantan-2-yl]-2-thiomorpholin-4-ylpyrimidine-5-carboxamide



- 15 Prepared from Intermediate 72 by the same process used for Example 33. ¹H NMR (400.132 MHz, CDCl₃) δ 1.37 (1H, s), 1.54 - 1.59 (2H, m), 1.67 - 1.73 (2H, m), 1.77 - 1.82 (4H, m), 1.87 - 2.09 (4H, m), 2.16 - 2.19 (1H, m), 2.22 - 2.28 (4H, m), 2.34 - 2.44 (2H, m), 2.64 - 2.70 (4H, m), 3.98 (1H, quintet), 4.14 - 4.19 (1H, m), 4.23 - 4.26 (4H, m), 5.81 (1H, d), 8.33 (1H, s)
 20 m/z (ESI⁺) (M+H)⁺ = 429; HPLC t_R = 2.27 min.

Example 42

4-Cyclopropyl-2-(2,6-dimethylmorpholin-4-yl)-N-[(2r,5s)-5-hydroxyadamantan-2-yl]pyrimidine-5-carboxamide (as approximately 90% 2S,6R diastereoisomer)



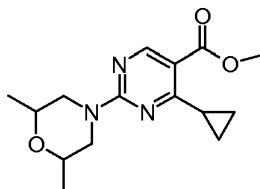
Prepared from Intermediate 74 by the same process used for Example 1.

¹H NMR (400.132 MHz, CDCl₃) δ 0.92 - 0.97 (2H, m), 1.11 - 1.16 (2H, m), 1.18 (6H, s), 1.32 (1H, s), 1.50 (2H, d), 1.59 - 1.77 (6H, m), 1.87 (2H, d), 2.11 (1H, s), 2.17 (2H, s), 2.40
 5 - 2.46 (1H, m), 2.49 (2H, d), 3.47 - 3.56 (2H, m), 4.14 (1H, d), 4.47 (2H, d), 5.96 (1H, d), 8.29 (1H, s)

m/z (ESI⁺) (M+H)⁺ = 427; HPLC t_R = 1.97 min.

Intermediate 73

10 Methyl 4-cyclopropyl-2-(2,6-dimethylmorpholino)pyrimidine-5-carboxylate (as approximately 90% 2S,6R diastereoisomer)



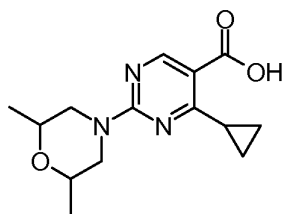
Prepared from methyl 2-(cyclopropanecarbonyl)-3-(dimethylamino)acrylate by the same process used for Intermediate 4.

15 ¹H NMR (400.132 MHz, CDCl₃) δ 1.00 - 1.05 (2H, m), 1.14 - 1.19 (2H, m), 1.24 (6H, d), 2.58 (2H, dd), 3.22 (1H, septet), 3.54 - 3.63 (2H, m), 3.87 (3H, s), 4.61 (2H, s), 8.75 (1H, s)

m/z (ESI⁺) (M+H)⁺ = 292; HPLC t_R = 2.72 min

20 **Intermediate 74**

4-cyclopropyl-2-(2,6-dimethylmorpholino)pyrimidine-5-carboxylic acid (as approximately 90% 2S,6R diastereoisomer)



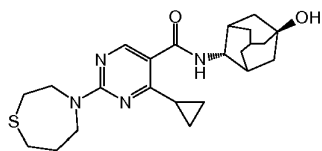
Prepared from Intermediate 73 by the same process used for Intermediate 3

^1H NMR (400.132 MHz, CDCl_3) δ 1.02 - 1.08 (2H, m), 1.17 - 1.22 (2H, m), 1.25 (6H, d), 2.61 (2H, dd), 3.23 - 3.31 (1H, m), 3.55 - 3.65 (2H, m), 4.62 (2H, d), 8.87 (1H, s)

5 m/z (ESI+) (M+H) $^+$ = 278; HPLC t_R = 2.13 min.

Example 43

4-Cyclopropyl-N-[(2r,5s)-5-hydroxyadamantan-2-yl]-2-(1,4-thiazepan-4-yl)pyrimidine-5-carboxamide



10

Prepared from Intermediate 80 by the same process used for Example 36

^1H NMR (400.132 MHz, CDCl_3) δ 0.97 - 1.03 (2H, m), 1.15 - 1.22 (2H, m), 1.41 (1H, s), 1.57 (2H, d), 1.67 - 1.84 (6H, m), 1.94 (2H, d), 2.03 - 2.15 (2H, m), 2.17 (1H, s), 2.24 (2H, s), 2.49 - 2.58 (3H, m), 2.72 - 2.80 (2H, m), 3.84 - 3.92 (2H, m), 3.97 - 4.07 (2H, m), 4.21

15

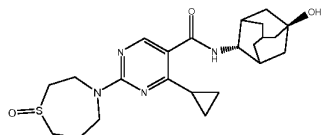
(1H, d), 6.03 (1H, d), 8.36 (1H, s)

m/z (ESI+) (M+H) $^+$ = 429; HPLC t_R = 2.09 min.

Example 44

4-Cyclopropyl-N-[(2r,5s)-5-hydroxyadamantan-2-yl]-2-(1-oxo-1,4-thiazepan-4-yl)pyrimidine-5-carboxamide

20



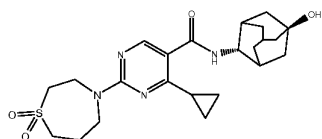
Prepared from Example 43 by the same process used for Example 36

^1H NMR (400.132 MHz, CDCl_3) δ 1.01 - 1.07 (2H, m), 1.15 - 1.21 (2H, m), 1.42 (1H, s), 1.58 (2H, d), 1.67 - 1.84 (6H, m), 1.94 (2H, d), 2.05 - 2.15 (1H, m), 2.18 (1H, s), 2.24 (2H,

s), 2.43 - 2.63 (3H, m), 2.85 (1H, t), 3.01 - 3.13 (1H, m), 3.15 (1H, q), 3.50 (1H, dt), 3.89 (1H, t), 4.18 - 4.44 (2H, m), 4.22 (1H, d), 6.04 (1H, d), 8.37 (1H, s)
 m/z (ESI+) (M+H)⁺ = 445; HPLC t_R = 1.37 min.

5 **Example 45**

4-Cyclopropyl-2-(1,1-dioxo-1,4-thiazepan-4-yl)-N-[(2r,5s)-5-hydroxyadamantan-2-yl]pyrimidine-5-carboxamide

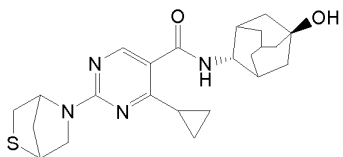


Prepared from Example 43 by the same process used for Example 37

10 ^1H NMR (400.132 MHz, CDCl₃) δ 1.02 - 1.09 (2H, m), 1.13 - 1.19 (2H, m), 1.41 (1H, s), 1.58 (2H, d), 1.68 - 1.85 (6H, m), 1.95 (2H, d), 2.16 - 2.28 (5H, m), 2.51 (1H, septet), 2.97 (2H, t), 3.31 (2H, s), 3.94 - 4.09 (4H, m), 4.22 (1H, d), 6.05 (1H, d), 8.37 (1H, s)
 m/z (ESI+) (M+H)⁺ = 461; HPLC t_R = 1.59 min.

15 **Example 46**

4-Cyclopropyl-N-[(2r,5s)-5-hydroxyadamantan-2-yl]-2-(3-thia-6-azabicyclo[2.2.1]heptan-6-yl)pyrimidine-5-carboxamide



4-cyclopropyl-N-[(2r,5s)-5-hydroxyadamantan-2-yl]-2-methylsulfinylpyrimidine-5-
 20 carboxamide (Intermediate 80, 826.3 mg, 2.20 mmol) and 2-thia-5-
 azabicyclo[2.2.1]heptane (301.2 mg, 2.61 mmol) were dissolved in THF (4 mL) and sealed
 into a microwave tube. The reaction was heated to 150 °C for 60 minutes in the microwave
 reactor and cooled to room temperature. The reaction mixture was evaporated to dryness
 and redissolved in EtOAc (150 mL), and washed sequentially with saturated brine (2x 75
 25 mL). The organic layer was dried over MgSO₄, filtered and evaporated to afford crude
 product. The crude product was purified by preparative HPLC (Phenomenex Gemini C18
 110A (axia) column, 5 μ silica, 30 mm diameter, 100 mm length), using decreasingly polar

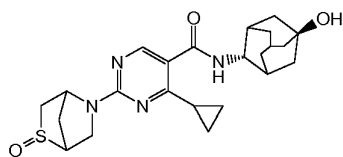
mixtures of water (containing 0.1% NH₃) and MeCN as eluents. Fractions containing the desired compound were evaporated to dryness to afford 4-cyclopropyl-N-[(2r,5s)-5-hydroxyadamantan-2-yl]-2-(3-thia-6-azabicyclo[2.2.1]heptan-6-yl)pyrimidine-5-carboxamide as a white solid.

- 5 ¹H NMR (400.13 MHz, DMSO-d₆) δ 0.89 - 0.95 (2H, m), 0.98 - 1.01 (2H, m), 1.32 (2H, d), 1.60 (3H, s), 1.63 (1H, s), 1.71 (2H, d), 1.85 (1H, d), 1.93 (1H, d), 1.99 (1H, s), 2.05 (2H, s), 2.23 (1H, d), 2.43 (1H, s), 2.94 (1H, d), 3.04 - 3.07 (1H, m), 3.27 (2H, s), 3.57 (1H, s), 3.67 (1H, s), 3.78 (1H, d), 3.89 - 3.93 (1H, m), 4.94 (1H, s), 8.03 (1H, d), 8.19 (1H, s) m/z (ESI⁺) (M+H)⁺ = 427; HPLC t_R = 2.03 min.

10

Example 47

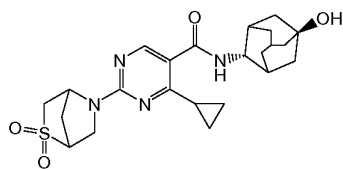
4-Cyclopropyl-N-[(2r,5s)-5-hydroxyadamantan-2-yl]-2-(3-oxo-3,4-thia-6-azabicyclo[2.2.1]heptan-6-yl)pyrimidine-5-carboxamide



- 15 Prepared from Example 46 by the same process used for Example 36
¹H NMR (400.13 MHz, CDCl₃) δ 0.95 - 0.98 (2H, m), 1.08 - 1.16 (2H, m), 1.49 (2H, d), 1.65 (2H, d), 1.70 - 1.73 (5H, m), 1.85 (2H, d), 2.09 (1H, d), 2.15 (2H, s), 2.28 - 2.32 (1H, m), 2.38 - 2.45 (1H, m), 2.66 (1H, d), 3.03 (1H, d), 3.40 (1H, d), 3.60 - 3.69 (1H, dd), 3.79 (1H, d), 4.09 - 4.14 (1H, m), 5.05 (1H, bs), 6.12 (1H, d), 8.24 (1H, s)
 20 m/z (ESI⁺) (M+H)⁺ = 443; HPLC t_R = 1.37 min.

Example 48

4-Cyclopropyl-2-(3,3-dioxo-3,4-thia-6-azabicyclo[2.2.1]heptan-6-yl)-N-[(2r,5s)-5-hydroxyadamantan-2-yl]pyrimidine-5-carboxamide



25

Prepared from Example 46 by the same process used for Example 37

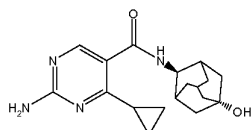
¹H NMR (400.13 MHz, CDCl₃) δ 0.96 - 0.99 (2H, m), 1.15 - 1.19 (2H, m), 1.50 (2H, d),

1.66 (2H, d), 1.71 (3H, s), 1.75 (1H, s), 1.86 (2H, d), 2.10 (1H, s), 2.17 (2H, s), 2.42 (2H, d), 2.62 (1H, d), 3.07 - 3.11 (1H, m), 3.15 - 3.20 (1H, m), 3.64 (1H, s), 3.67 (1H, s), 4.11 - 4.19 (1H, m), 5.01 (1H, bs), 6.07 (1H, d), 8.28 (2H, s)
 m/z (ESI+) (M+H)⁺ = 459; HPLC t_R = 1.58 min.

5

Example 49

2-Amino-4-cyclopropyl-N-[(2r,5s)-5-hydroxyadamantan-2-yl]pyrimidine-5-carboxamide



880 ammonia (10 ml, 168.19 mmol) was added to 4-cyclopropyl-N-[(2r,5s)-5-hydroxyadamantan-2-yl]-2-methylsulfonylpyrimidine-5-carboxamide (Intermediate 80, 1.2 g, 3.07 mmol) in dioxane (40 mL) at 20 °C. The resulting solution was stirred at 20 °C for 3 days.

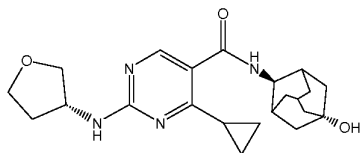
The reaction mixture was evaporated to dryness. Purified by preparative HPLC (Phenomenex Gemini C18 110A (axia) column, 5 μ silica, 30 mm diameter, 100 mm length), using decreasingly polar mixtures of water (containing 0.5% NH₃) and MeCN as eluents. Fractions containing the desired compound were evaporated to dryness to afford the product, which was triturated with ethyl acetate to give 2-amino-4-cyclopropyl-N-[(2r,5s)-5-hydroxyadamantan-2-yl]pyrimidine-5-carboxamide (0.420 g, 41.7 %) as a white solid.

¹H NMR (400.132 MHz, DMSO) δ 0.86 - 0.92 (2H, m), 0.97 - 1.00 (2H, m), 1.29 - 1.37 (2H, m), 1.60 - 1.65 (4H, m), 1.68 - 1.74 (2H, m), 1.91 - 2.02 (3H, m), 2.03 - 2.07 (2H, m), 2.38 - 2.45 (1H, m), 3.89 - 3.93 (1H, m), 4.43 (1H, s), 6.70 (2H, s), 8.07 (1H, d), 8.11 (1H, s)
 m/z (ES+) (M+H)⁺ = 329; HPLC t_R = 1.18 min.

25

Example 50

4-Cyclopropyl-N-[(2r,5s)-5-hydroxyadamantan-2-yl]-2-[(3R)-oxolan-3-ylamino]pyrimidine-5-carboxamide



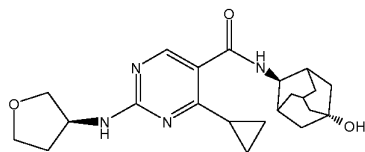
4-cyclopropyl-N-[(2r,5s)-5-hydroxyadamantan-2-yl]-2-methylsulfonylpyrimidine-5-carboxamide (Intermediate 80, 0.3 g, 0.77 mmol), (R)-tetrahydrofuran-3-amine 4-methylbenzenesulfonate (0.298 g, 1.15 mmol) and DIPEA (0.294 mL, 1.69 mmol) were dissolved in THF (5 mL) and sealed into a microwave tube. The reaction was heated to 150 °C for 1 hour in the microwave reactor and cooled to room temperature. The reaction mixture was diluted with DCM (20ml) and washed with saturated NaHCO₃, then separated through a phase sep tube and the DCM layer evaporated. Purified by preparative HPLC (Phenomenex Gemini C18 110A (axia) column, 5μ silica, 30 mm diameter, 100 mm length), using decreasingly polar mixtures of water (containing 0.5% NH₃) and MeCN as eluents. Fractions containing the desired compound were evaporated to dryness to afford the product, 4-cyclopropyl-N-[(2r,5s)-5-hydroxyadamantan-2-yl]-2-[(3R)-oxolan-3-ylamino]pyrimidine-5-carboxamide (0.104 g, 34 %). Chiral analysis was carried out using 5μm Chiralcel OJ-H (250mm x 4.6mm) - No DG022, eluting with iso-Hexane/EtOH 80/20. The compound appears to have a chiral purity >99%.

¹H NMR (400.13 MHz, DMSO-d₆) δ 0.90 - 0.93 (2H, m), 0.97 - 1.02 (2H, m), 1.31 (2H, d), 1.59 (3H, s), 1.62 (1H, s), 1.70 (2H, d), 1.82 - 1.87 (1H, m), 1.91 - 2.00 (3H, m), 2.03 (2H, s), 2.07 - 2.12 (1H, m), 2.39 - 2.44 (1H, m), 3.39 - 3.48 (1H, m), 3.65 - 3.71 (1H, m), 3.78 - 3.85 (2H, m), 3.88 - 3.92 (1H, m), 4.27 (1H, bs), 4.43 (1H, s), 7.52 (1H, bs), 8.07 (1H, d), 8.15 (1H, s)

m/z (ES⁺) (M+H)⁺ = 399; HPLC t_R = 1.50 min.

Example 51

N-[(2r,5s)-5-hydroxyadamantan-2-yl] 4-cyclopropyl-2-[(3S)-oxolan-3-yl]amino]pyrimidine-5-carboxamide



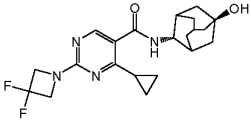
4-cyclopropyl-N-[(2r,5s)-5-hydroxyadamantan-2-yl]-2-methylsulfonylpyrimidine-5-

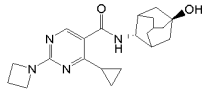
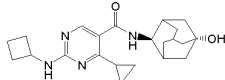
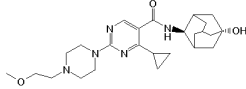
carboxamide (Intermediate 80, 0.3 g, 0.77 mmol), (S)-tetrahydrofuran-3-amine hydrochloride (0.189 g, 1.53 mmol) and DIPEA (0.294 mL, 1.69 mmol) were dissolved in THF (5 mL) and sealed into a microwave tube. The reaction was heated to 150 °C for 1 hour in the microwave reactor and cooled to room temperature. The reaction mixture was diluted with DCM (20ml) and washed with saturated NaHCO₃, then separated through a phase sep tube and the DCM layer evaporated. Purified by preparative HPLC (Phenomenex Gemini C18 110A (axia) column, 5μ silica, 30 mm diameter, 100 mm length), using decreasingly polar mixtures of water (containing 0.5% NH₃) and MeCN as eluents. Fractions containing the desired compound were evaporated to dryness to afford the product, 4-cyclopropyl-N-[(2r,5s)-5-hydroxyadamantan-2-yl]-2-[[[(3S)-oxolan-3-yl]amino]pyrimidine-5-carboxamide (0.106 g, 35 %). Chiral analysis was carried out using 5μm Chiralcel OJ-H (250mm x 4.6mm) - No DG022, eluting with iso-Hexane/EtOH 80/20. The compound appears to have a chiral purity >98%.

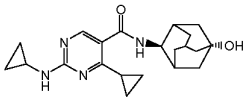
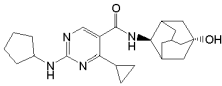
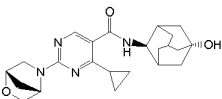
¹H NMR (400.132 MHz, CDCl₃) δ 1.00 - 1.03 (2H, m), 1.17 - 1.23 (2H, m), 1.55 (2H, d), 1.69 - 1.87 (8H, m), 1.94 (2H, d), 2.17 (1H, s), 2.24 - 2.34 (3H, m), 2.45 - 2.52 (1H, m), 3.67 (1H, dd), 3.81 - 3.87 (1H, m), 3.92 - 3.99 (2H, m), 4.18 - 4.23 (1H, m), 4.52 (1H, s), 5.32 (1H, d), 6.03 (1H, d), 8.32 (1H, s)

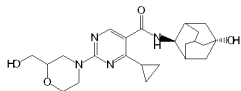
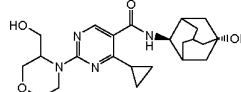
m/z (ES⁺) (M+H)⁺ = 399; HPLC t_R = 1.50 min.

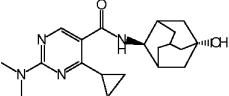
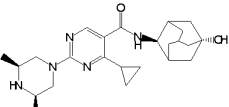
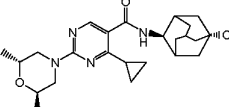
The following Examples were prepared in a similar manner to Example 46, using Intermediate 80 and an appropriate amine starting material:

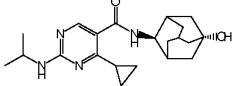
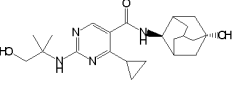
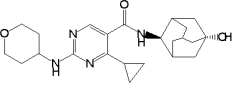
Structure	Ex	Name	¹ H NMR δ	MS m/e MH ⁺
	52	4-cyclopropyl-2-(3,3-difluoroazetidin-1-yl)-N-[(2r,5s)-5-hydroxyadamantan-2-yl]pyrimidine-	¹ H NMR (400.13 MHz, CDCl ₃) δ 0.96 - 0.99 (2H, m), 1.13 - 1.16 (2H, m), 1.50 (2H, d), 1.63 (1H, s), 1.66 (1H, s), 1.71 (3H, s), 1.74 (1H, s), 1.84 (1H, s), 1.87 (1H, s), 2.09 (1H, s), 2.17 (2H, s), 2.36 - 2.42 (1H, m),	m/z (ES ⁺) (M+H) ⁺ = 405; HPLC t _R = 1.99 min

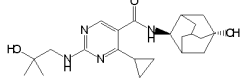
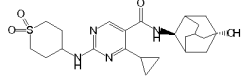
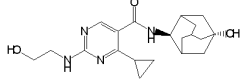
		5-carboxamide	4.11 - 4.16 (1H, m), 4.33 (4H, t), 6.08 (1H, d), 8.28 (1H, s)	
	53	2-(azetidin-1-yl)-4-cyclopropyl-N-[(2r,5s)-5-hydroxyadamantan-2-yl]pyrimidine-5-carboxamide	¹ H NMR (400.13 MHz, CDCl ₃) δ 0.89 - 0.93 (2H, m), 1.12 - 1.15 (2H, m), 1.48 (2H, d), 1.65 (2H, d), 1.69 (3H, s), 1.73 (1H, s), 1.84 - 1.86 (2H, m), 2.08 (1H, s), 2.15 (2H, s), 2.24 - 2.31 (2H, m), 2.35 - 2.42 (1H, m), 4.04 (4H, t), 4.08 - 4.13 (1H, m), 6.11 (1H, d), 8.24 (1H, s)	m/z (ES ⁺) (M+H) ⁺ = 369; HPLC t _R = 1.83min.
	54	2-(cyclobutylamino)-4-cyclopropyl-N-[(2r,5s)-5-hydroxyadamantan-2-yl]pyrimidine-5-carboxamide	¹ H NMR (400.13 MHz, DMSO-d ₆) δ 0.88 - 0.92 (2H, m), 1.00 (2H, s), 1.31 (2H, d), 1.60 - 1.72 (8H, m), 1.88 - 2.03 (7H, m), 2.14 - 2.22 (2H, m), 2.38 - 2.45 (1H, m), 3.16 (1H, d), 3.90 (1H, t), 4.40 (1H, s), 7.44 (1H, s), 8.00 (1H, d), 8.12 (1H, s)	m/z (ES ⁺) (M+H) ⁺ = 383; HPLC t _R = 2.00 min.
	55	4-cyclopropyl-N-[(2r,5s)-5-hydroxyadamantan-2-yl]-2-[4-(2-methoxyethyl)piperazin-1-yl]pyrimidine-5-carboxamide	¹ H NMR (400.13 MHz, DMSO-d ₆) δ 0.90 - 0.96 (2H, m), 0.99 - 1.01 (2H, m), 1.32 (2H, d), 1.62 (4H, d), 1.70 (2H, s), 1.93 (2H, d), 1.99 (1H, s), 2.04 (2H, s), 2.40 - 2.44 (5H, m), 2.45 - 2.55 (2H, t), 3.23 (3H, s), 3.41 - 3.46 (2H, t), 3.68 (4H, t), 3.91 (1H, m), 4.38 (1H, s), 8.03	m/z (ES ⁺) (M+H) ⁺ = 456; HPLC t _R = 1.71 min.

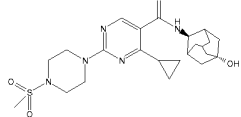
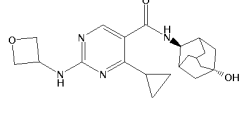
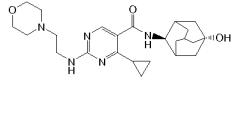
			(1H, d), 8.20 (1H, s)	
	56	4-cyclopropyl-2-(cyclopropylamino)-N-[(2r,5s)-5-hydroxyadamantan-2-yl]pyrimidine-5-carboxamide	1H NMR (400.13 MHz, DMSO-d ₆) δ 0.40 - 0.44 (2H, m), 0.60 - 0.65 (2H, m), 0.89 - 0.92 (2H, m), 1.01 (2H, d), 1.32 (2H, d), 1.60 - 1.63 (4H, m), 1.69 - 1.72 (2H, m), 1.93 - 1.96 (2H, m), 1.99 (1H, s), 2.04 (2H, s), 2.40 - 2.46 (1H, m), 2.63 - 2.70 (1H, m), 3.91 (1H, m), 4.37 (1H, s), 7.35 (1H, s), 8.02 (1H, d), 8.16 (1H, s)	m/z (ES+) (M+H) ⁺ = 369; HPLC t _R = 1.72 min.
	57	2-(cyclopentylamino)-4-cyclopropyl-N-[(2r,5s)-5-hydroxyadamantan-2-yl]pyrimidine-5-carboxamide	1H NMR (400.13 MHz, DMSO-d ₆) δ 0.88 - 0.91 (2H, m), 1.01 (2H, s), 1.32 (2H, d), 1.40 - 1.54 (4H, m), 1.60 - 1.66 (6H, m), 1.70 (2H, d), 1.81 - 1.87 (2H, m), 1.94 (2H, d), 1.99 (1H, s), 2.04 (2H, s), 2.40 - 2.46 (1H, m), 3.90 (1H, m), 4.04 - 4.08 (1H, m), 4.37 (1H, s), 7.17 (1H, s), 7.99 (1H, d), 8.13 (1H, s)	m/z (ES+) (M+H) ⁺ = 397; HPLC t _R = 2.12 min.
	58	4-cyclopropyl-N-[(2r,5s)-5-hydroxyadamantan-2-yl]-2-[(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-2-yl]pyrimidine-5-carboxamide	1H NMR (400.13 MHz, DMSO-d ₆) δ 0.91 - 0.94 (2H, m), 0.98 - 1.09 (2H, m), 1.32 (2H, d), 1.62 (4H, d), 1.71 (2H, d), 1.82 - 1.89 (2H, m), 1.94 (2H, d), 1.99 (1H, s), 2.04 (2H, s), 2.40 - 2.46 (1H, m)	m/z (ES+) (M+H) ⁺ = 411; HPLC t _R = 1.62 min.

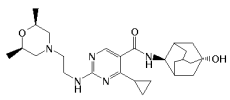
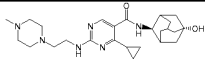
		1]hept-5-yl]pyrimidine-5-carboxamide	m), 3.32 - 3.44 (2H, m), 3.58 (1H, d), 3.76 - 3.78 (1H, m), 3.91 (1H, m), 4.38 (1H, s), 4.63 (1H, s), 4.88 (1H, s), 8.04 (1H, d), 8.19 (1H, s)	
	59	4-cyclopropyl-N-[(2r,5s)-5-hydroxyadamantan-2-yl]-2-[2-(hydroxymethyl)morpholin-4-yl]pyrimidine-5-carboxamide	¹ H NMR (400.13 MHz, DMSO-d ₆) δ 0.92 - 0.95 (2H, m), 1.01 - 1.03 (2H, m), 1.32 (2H, d), 1.62 (4H, d), 1.74 (2H, q), 1.93 (2H, d), 1.99 (1H, s), 2.04 (2H, s), 2.41 - 2.47 (1H, m), 2.65 - 2.71 (1H, m), 2.93 (1H, m), 3.32 - 3.51 (4H, m), 3.87 - 3.93 (2H, m), 4.37 (2H, d), 4.55 (1H, t), 4.76 (1H, t), 8.06 (1H, d), 8.22 (1H, m)	m/z (ES+) (M+H) ⁺ = 429; HPLC t _R = 1.47 min.
	60	4-cyclopropyl-N-[(2r,5s)-5-hydroxyadamantan-2-yl]-2-[3-(hydroxymethyl)morpholin-4-yl]pyrimidine-5-carboxamide	¹ H NMR (400.13 MHz, DMSO-d ₆) δ 0.92 - 0.98 (2H, m), 0.99 - 1.07 (2H, m), 1.32 (2H, d), 1.61 (3H, d), 1.71 (2H, d), 1.94 (3H, d), 1.99 (1H, s), 2.04 (2H, s), 2.38 - 2.44 (1H, m), 3.03 (1H, m), 3.31 - 3.45 (3H, m), 3.66 - 3.72 (1H, m), 3.85 - 3.88 (1H, m), 3.92 (1H, d), 4.05 (1H, d), 4.25 (1H, m), 4.38 - 4.42 (2H, m), 4.81 (1H, t), 8.05 (1H, d), 8.22 (1H, s)	m/z (ES+) (M+H) ⁺ = 429; HPLC t _R = 1.52 min
	61	4-cyclopropyl-	¹ H NMR (400.13 MHz,	m/z

		2-(dimethylamino)-N-[(2r,5s)-5-hydroxyadamantan-2-yl]pyrimidine-5-carboxamide	DMSO-d ₆) δ 0.90 - 0.94 (2H, m), 1.02 - 1.05 (2H, m), 1.30 - 1.34 (2H, m), 1.60 - 1.63 (4H, m), 1.69 - 1.72 (2H, m), 1.92 - 1.96 (2H, m), 1.99 (1H, s), 2.04 (2H, s), 2.47 (1H, m), 3.08 (6H, s), 3.91 (1H, m), 4.37 (1H, s), 7.99 (1H, d), 8.21 (1H, s)	(ES+) (M+H) ⁺ = 357; HPLC t _R = 1.85 min.
	62	4-cyclopropyl-2-[(3R,5S)-3,5-dimethylpiperazin-1-yl]-N-[(2r,5s)-5-hydroxyadamantan-2-yl]pyrimidine-5-carboxamide	¹ H NMR (400.13 MHz, DMSO-d ₆) δ 0.90 - 0.96 (2H, m), 0.99 (6H, d), (0.99 (2H, m), 1.32 (2H, d), 1.62 (4H, d), 1.70 (2H, d), 1.93 (2H, d), 1.99 (1H, s), 2.04 (2H, s), 2.22 (1H, s), 2.26 - 2.32 (2H, m), 2.42 - 2.46 (1H, m), 2.58 - 2.66 (2H, m), 3.91 (1H, m), 4.37 (1H, s), 4.46 - 4.49 (2H, m), 8.01 (1H, d), 8.19 (1H, s)	m/z (ES+) (M+H) ⁺ = 426; HPLC t _R = 1.66 min.
	63	4-cyclopropyl-2-[(2R,6R)-2,6-dimethylmorpholin-4-yl]-N-[(2r,5s)-5-hydroxyadamantan-2-yl]pyrimidine-5-carboxamide	¹ H NMR (400.13 MHz, DMSO-d ₆) δ 0.92 - 0.95 (2H, m), 0.98 - 1.13 (2H, m), 1.08 (6H, d), 1.32 (2H, d), 1.62 (4H, d), 1.71 (2H, d), 1.94 (2H, d), 1.99 (1H, s), 2.04 (2H, s), 2.42 - 2.46 (1H, m), 3.41 - 3.46 (2H, m), 3.80 (2H, d), 3.92 - 3.96 (3H, m), 4.37 (1H, s), 8.05 (1H, d), 8.21 (1H, s)	m/z (ES+) (M+H) ⁺ = 427; HPLC t _R = 1.94 min.

	64	4-cyclopropyl-N-[(2r,5s)-5-hydroxyadamantan-2-yl]-2-(isopropylamino)pyrimidine-5-carboxamide	¹ H NMR (400.13 MHz, DMSO-d ₆) δ 0.88 - 0.91 (2H, m), 1.00 (2H, s), 1.11 (6H, d), 1.32 (2H, d), 1.62 (4H, d), 1.70 (2H, d), 1.94 (2H, d), 1.99 (1H, s), 2.04 (2H, s), 2.40 - 2.47 (1H, m), 3.89 - 3.98 (2H, m), 4.38 (1H, s), 7.01 (1H, s), 7.98 (1H, d), 8.13 (1H, s)	m/z (ES+) (M+H) ⁺ = 371; HPLC t _R = 1.90 min.
	65	4-cyclopropyl-N-[(2r,5s)-5-hydroxyadamantan-2-yl]-2-[(2-hydroxy-1,1-dimethylethyl)amino]pyrimidine-5-carboxamide	¹ H NMR (400.13 MHz, DMSO-d ₆) δ 0.93 (2H, d), 0.96 - 1.01 (2H, m), 1.27 (6H, s), 1.32 (2H, d), 1.62 (4H, d), 1.70 (2H, d), 1.94 (2H, d), 1.99 (1H, s), 2.05 (2H, d), 2.39 - 2.45 (1H, m), 3.44 (2H, d), 3.91 (1H, m), 4.37 (1H, s), 4.85 (1H, m), 6.40 (1H, s), 8.02 (1H, d), 8.12 (1H, s)	m/z (ES+) (M+H) ⁺ = 401; HPLC t _R = 1.66 min.
	66	4-cyclopropyl-N-[(2r,5s)-5-hydroxyadamantan-2-yl]-2-(tetrahydro-2H-pyran-4-ylamino)pyrimidine-5-carboxamide	¹ H NMR (400.13 MHz, DMSO-d ₆) δ 0.89 - 0.96 (2H, m), 1.00 (2H, s), 1.32 (2H, d), 1.43 - 1.53 (2H, m), 1.62 (4H, d), 1.70 (2H, d), 1.77 (2H, d), 1.94 (2H, d), 1.99 (1H, s), 2.04 (2H, s), 2.42 (1H, s), 3.32 - 3.38 (2H, m), 3.84 (3H, d), 3.91 (1H, m), 4.37 (1H, s), 7.18 (1H, s), 8.00 (1H, d), 8.14 (1H, s)	m/z (ES+) (M+H) ⁺ = 413; HPLC t _R = 1.60 min.

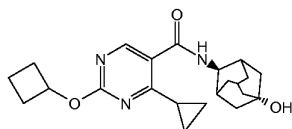
	67	4-cyclopropyl-N-[(2r,5s)-5-hydroxyadamantan-2-yl]-2-[(2-hydroxy-2-methylpropyl)amino]pyrimidine-5-carboxamide	¹ H NMR (400.13 MHz, DMSO-d ₆) δ 0.90 (2H, m), 1.01 (2H, m), 1.06 (6H, s), 1.32 (2H, d), 1.62 (4H, d), 1.70 (2H, d), 1.94 (2H, d), 1.99 (1H, s), 2.04 (2H, s), 2.43 (1H, m), 3.25 (2H, d), 3.90 (1H, m), 4.37 (1H, s), 4.49 (1H, s), 6.93 (1H, s), 8.02 (1H, d), 8.13 (1H, s)	m/z (ES+) (M+H) ⁺ = 401; HPLC t _R = 1.53 min.
	68	4-cyclopropyl-2-[(1,1-dioxido-2H-thiopyran-4-yl)amino]-N-[(2r,5s)-5-hydroxyadamantan-2-yl]pyrimidine-5-carboxamide	¹ H NMR (400.13 MHz, DMSO-d ₆) δ 0.90 - 0.94 (2H, m), 1.03 (2H, s), 1.32 (2H, d), 1.62 (4H, d), 1.69 - 1.76 (2H, m), 1.92 - 2.04 (7H, m), 2.10 - 2.15 (2H, m), 2.38 - 2.43 (1H, m), 3.11 (2H, d), 3.21 (2H, d), 3.91 (1H, m), 4.04 (1H, s), 4.38 (1H, s), 7.39 (1H, s), 8.03 (1H, d), 8.15 (1H, s)	m/z (ES+) (M+H) ⁺ = 461; HPLC t _R = 1.48 min.
	69	4-cyclopropyl-N-[(2r,5s)-5-hydroxyadamantan-2-yl]-2-[(2-hydroxyethyl)amino]pyrimidine-5-carboxamide	¹ H NMR (400.13 MHz, DMSO-d ₆) δ 0.89 - 0.96 (2H, m), 1.00 (2H, s), 1.32 (2H, d), 1.62 (4H, d), 1.72 (2H, m), 1.94 (2H, d), 1.99 (1H, s), 2.04 (2H, s), 2.40 - 2.46 (1H, m), 3.32 (2H, m), 3.46 (2H, q), 3.90 (1H, m), 4.37 (1H, s), 4.59 (1H, t), 7.04 (1H, s), 8.00 (1H, d), 8.13 (1H, s)	m/z (ES+) (M+H) ⁺ = 373; HPLC t _R = 1.31 min.

	70	4-cyclopropyl-N-[(2r,5s)-5-hydroxyadamantan-2-yl]-2-(4-methylsulfonylpiperazin-1-yl)pyrimidine-5-carboxamide	NMR: ¹ H NMR (400.132 MHz, CDCl ₃) δ 1.02 - 1.08 (2H, m), 1.16 - 1.21 (2H, m), 1.40 (1H, s), 1.56 - 1.63 (2H, m), 1.69 - 1.73 (2H, m), 1.77 - 1.82 (4H, m), 1.91 - 1.95 (2H, m), 2.18 (1H, s), 2.24 (2H, s), 2.47 - 2.54 (1H, m), 2.78 (3H, s), 3.25 (4H, t), 3.95 (4H, t), 4.19 - 4.24 (1H, m), 6.03 (1H, d), 8.36 (1H, s)	m/z (ES ⁺) (M+H) ⁺ = 476; HPLC t _R = 1.73min.
	71	4-cyclopropyl-N-[(2r,5s)-5-hydroxyadamantan-2-yl]-2-(oxetan-3-ylamino)pyrimidine-5-carboxamide	¹ H NMR (400.13 MHz, DMSO-d ₆) δ 0.83 - 0.95 (2H, m), 0.97 - 1.03 (2H, m), 1.31 (2H, d), 1.61 (4H, d), 1.70 (2H, d), 1.93 (2H, d), 1.98 (1H, s), 2.04 (2H, s), 2.37 - 2.44 (1H, m), 3.91 (1H, m), 4.37 (1H, s), 4.47 (2H, t), 4.69 - 4.72 (2H, t), 4.80 (1H, s), 7.93 (1H, s), 8.05 (1H, d), 8.15 (1H, s)	m/z (ES ⁺) (M+H) ⁺ = 385; HPLC t _R = 1.41 min.
	72	4-cyclopropyl-N-[(2r,5s)-5-hydroxyadamantan-2-yl]-2-[(2-morpholin-4-ylethyl)amino]pyrimidine-5-carboxamide	¹ H NMR (400 MHz, DMSO) δ 0.88 - 0.81 (2H, m), 0.95 (2H, s), 1.26 (2H, d), 1.56 (4H, d), 1.65 (2H, d), 1.95 - 1.83 (3H, m), 1.99 (2H, s), 2.39 - 2.28 (7H, m), 3.35 - 3.26 (2H, m), 3.56 - 3.45 (4H, m), 3.90 - 3.80 (1H, m), 4.32 (1H, s), 7.18 - 6.81 (1H, m),	m/z (ES ⁺) (M+H) ⁺ = 442; HPLC t _R = 1.46 min.

			7.95 (1H, d), 8.08 (1H, s).	
	73	4-cyclopropyl-2-({2-[(2R,6S)-2,6-dimethylmorpholin-4-yl]ethyl}amino)-N-[(2r,5s)-5-hydroxyadamantan-2-yl]pyrimidine-5-carboxamide	1H NMR (400 MHz, DMSO) d 1.02 - 0.93 (2H, m), 1.14 - 1.04 (7H, m), 1.39 (2H, d), 1.74 - 1.64 (6H, m), 1.77 (2H, d), 2.08 - 1.97 (3H, m), 2.11 (2H, s), 2.53 - 2.42 (3H, m), 2.81 (2H, d), 3.33 (1H, s), 3.45 - 3.37 (2H, m), 3.65 - 3.55 (2H, m), 3.98 (1H, s), 4.44 (1H, s), 8.07 (1H, d), 8.20 (1H, s).	m/z (ES+) (M+H)+ = 470; HPLC t_R = 1.69 min.
	74	4-cyclopropyl-N-[(2r,5s)-5-hydroxyadamantan-2-yl]-2-{[2-(4-methylpiperazin-1-yl)ethyl]amino}pyrimidine-5-carboxamide	1H NMR (400 MHz, DMSO) d 0.90 (2H, d), 1.00 (2H, s), 1.32 (2H, d), 1.61 (4H, d), 1.70 (2H, d), 2.00 - 1.89 (3H, m), 2.04 (2H, s), 2.13 (3H, s), 2.45 - 2.22 (11H, m), 3.41 - 3.11 (2H, m), 3.97 - 3.84 (1H, m), 4.37 (1H, s), 7.25 - 6.82 (1H, m), 8.00 (1H, d), 8.13 (1H, s).	m/z (ES+) (M+H)+ = 455; HPLC t_R = 1.41 min.

Example 75

2-(Cyclobutyloxy)-4-cyclopropyl-N-[(2r,5s)-5-hydroxyadamantan-2-yl]pyrimidine-5-carboxamide



5

Sodium hydride (30.6 mg, 0.77 mmol) was added to cyclobutanol (0.300 mL, 3.83 mmol) in THF (3 mL) at 20°C under nitrogen. The resulting solution was stirred at 20 °C for 30 minutes. Then 4-cyclopropyl-N-[(2r,5s)-5-hydroxyadamantan-2-yl]-2-

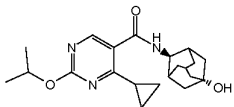
(methylsulfonyl)pyrimidine-5-carboxamide (300 mg, 0.77 mmol) in THF (4 mL) was added dropwise and the solution stirred for a further 2 hrs.

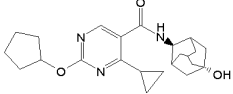
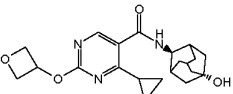
The reaction mixture was diluted with DCM (10 mL), and stirred with water (10 mL) before passing through a phase separation cartridge. The organic layer was evaporated to afford crude product. The crude product was purified by preparative HPLC (Waters XBridge Prep C18 OBD column, 5 μ silica, 50 mm diameter, 150 mm length), using decreasingly polar mixtures of water (containing 0.1% NH₃) and MeCN as eluents. Fractions containing the desired compound were evaporated to dryness to afford 2-(cyclobutyloxy)-4-cyclopropyl-N-[(2r,5s)-5-hydroxyadamantan-2-yl]pyrimidine-5-carboxamide (146 mg, 49.7 %) as a white solid.

¹H NMR (400.13 MHz, DMSO-d₆) δ 1.02 - 1.06 (4H, m), 1.33 (2H, d), 1.61 - 1.81 (8H, m), 1.91 - 2.09 (7H, m), 2.33 - 2.39 (3H, m), 3.95 (1H, m), 4.39 (1H, s), 5.00 - 5.08 (1H, m), 8.31 (1H, d), 8.35 (1H, s)

m/z (ES+) (M+H)⁺ = 384; HPLC t_R = 2.00 min

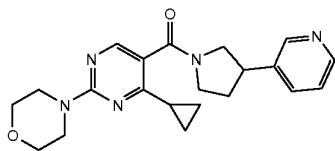
The following Examples were prepared in a similar manner to Example 75, using Intermediate 80 and an appropriate starting material:

Structure	Ex	Name	¹ H NMR δ	MS m/e MH ⁺
	76	4-cyclopropyl-N-[(2r,5s)-5-hydroxyadamantan-2-yl]-2-isopropoxy-pyrimidine-5-carboxamide	¹ H NMR (400.13 MHz, DMSO-d ₆) δ 1.00 - 1.08 (4H, m), 1.28 (6H, d), 1.33 (2H, d), 1.62 (4H, d), 1.72 (2H, d), 1.93 (2H, d), 1.99 (1H, s), 2.06 (2H, s), 2.33 - 2.39 (1H, m), 3.95 (1H, m), 4.39 (1H, s), 5.10 - 5.16 (1H, m), 8.29 (1H, d), 8.35 (1H, s)	m/z (ES+) (M+H) ⁺ = 372; HPLC t _R = 1.87 min.

	77	2-(cyclopentyloxy)-4-cyclopropyl-N-[(2r,5s)-5-hydroxyadamantan-2-yl]pyrimidine-5-carboxamide	1H NMR (400.13 MHz, DMSO-d ₆) δ 1.00 - 1.09 (4H, m), 1.33 (2H, d), 1.57 - 1.73 (12H, m), 1.89 - 1.99 (5H, m), 2.06 (2H, s), 2.33 - 2.39 (1H, m), 3.95 (1H, m), 4.39 (1H, s), 5.25 - 5.29 (1H, m), 8.29 (1H, d), 8.35 (1H, s)	m/z (ES+) (M+H) ⁺ = 398; HPLC t _R = 2.13 min.
	78	4-cyclopropyl-N-[(2r,5s)-5-hydroxyadamantan-2-yl]-2-(oxetan-3-yloxy)pyrimidine-5-carboxamide	1H NMR (400.13 MHz, DMSO-d ₆) δ 1.04 - 1.08 (3H, m), 1.18 - 1.23 (1H, m), 1.31 - 1.38 (2H, m), 1.62 (4H, d), 1.71 (2H, d), 1.92 (2H, d), 1.99 (1H, s), 2.06 (2H, s), 2.31 - 2.37 (1H, m), 3.95 (1H, m), 4.39 (1H, s), 4.52 - 4.55 (2H, m), 4.84 (2H, t), 5.46 - 5.52 (1H, m), 8.34 (1H, d), 8.38 (1H, s)	m/z (ES+) (M+H) ⁺ = 386; HPLC t _R = 1.39 min.

Example 79

(4-Cyclopropyl-2-morpholinopyrimidin-5-yl)(3-(pyridin-3-yl)pyrrolidin-1-yl)methanone



- 5 Morpholine (1.985 mL, 22.55 mmol) was added in one portion to (4-cyclopropyl-2-(methylsulfonyl)pyrimidin-5-yl)(3-(pyridin-3-yl)pyrrolidin-1-yl)methanone (Intermediate 82 0.240 g, 0.64 mmol) in THF (2 mL) at 18°C. The resulting solution was stirred at 150 °C for 12 hours. The reaction mixture was diluted with DCM (50 mL), and washed with

dil. aq. K₂CO₃ (20 mL). The organic layer was dried over MgSO₄, filtered and evaporated to afford crude product. The crude product was purified by preparative HPLC (Waters XBridge Prep C18 OBD column, 5 μ silica, 21 mm diameter, 150 mm length), using decreasingly polar mixtures of water (containing 1% NH₃) and MeCN as eluents.

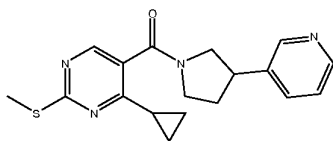
- 5 Fractions containing the desired compounds were evaporated to dryness to afford (4-cyclopropyl-2-morpholinopyrimidin-5-yl)(3-(pyridin-3-yl)pyrrolidin-1-yl)methanone (0.135 g, 55.2 %) and 3-(1-(4-cyclopropyl-2-morpholinopyrimidine-5-carbonyl)pyrrolidin-3-yl)pyridine 1-oxide (0.045 g, 17.66 %) as white solids.

¹H NMR (400.13 MHz, DMSO-*d*₆) δ 0.92 - 1.10 (4H, m), 1.99 - 2.12 (2H, m), 2.24 - 2.36 (1H, m), 3.36 - 4.06 (13H, m), 7.31 - 7.37 (1H, m), 7.68 - 7.78 (1H, m), 8.22 (1H, d), 8.42 - 8.56 (2H, m)

m/z (ESI+) (M+H)⁺ = 380.22; HPLC *t_R* = 1.73 min.

Intermediate 81

- 15 (4-cyclopropyl-2-(methylthio)pyrimidin-5-yl)(3-(pyridin-3-yl)pyrrolidin-1-yl)methanone



- N-Ethyl-diisopropylamine (0.741 mL, 4.28 mmol) was added in one portion to 4-cyclopropyl-2-(methylthio)pyrimidine-5-carboxylic acid (Intermediate 24, 1.8 g, 8.56 mmol), 3-(pyrrolidin-3-yl)pyridine (1.269 g, 8.56 mmol) and O-(7-Azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (3.91 g, 10.27 mmol) in DMF (50 mL) at 18°C under nitrogen. The resulting mixture was stirred at 18 °C for 18 hours. The reaction mixture was diluted with EtOAc (200 mL), and washed sequentially with water (2x50 mL), and saturated brine (50 mL). The organic layer was dried over MgSO₄, filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 0 to 100% (MeOH:7M NH₃ in MeOH:DCM (1:1:18) in DCM. Pure fractions were evaporated to dryness and dried under high vacuum to afford (4-cyclopropyl-2-(methylthio)pyrimidin-5-yl)(3-(pyridin-3-yl)pyrrolidin-1-yl)methanone (1.920 g, 65.9 %) as a tan solid foam.

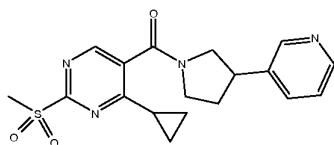
¹H NMR (400.13 MHz, DMSO-*d*₆) δ 1.03 - 1.26 (6H, m), 2.02 - 2.14 (2H, m), 2.25 - 2.40 (1H, m), 2.44 - 2.47 (3H, m), 3.34 - 3.82 (4H, m), 7.31 - 7.38 (1H, m), 7.68 - 7.79 (1H, m),

8.42 - 8.57 (2H, m)

m/z (ESI+) (M+H)+ = 341; HPLC t_R = 1.85 min.

Intermediate 82

5 (4-cyclopropyl-2-(methylsulfonyl)pyrimidin-5-yl)(3-(pyridin-3-yl)pyrrolidin-1-yl)methanone



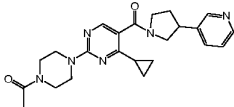
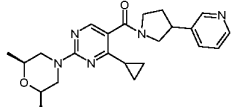
3-Chloroperoxybenzoic acid (70%) (3.16 g, 12.82 mmol) was added in one portion to (4-cyclopropyl-2-(methylthio)pyrimidin-5-yl)(3-(pyridin-3-yl)pyrrolidin-1-yl)methanone
 10 (Intermediate 81, 2.91 g, 8.55 mmol) in DCM (100 mL) at 0°C. The resulting solution was stirred at 20 °C for 24 hours. The reaction mixture was washed sequentially with saturated NaHCO₃ (50 mL), 2M NaOH (50 mL), and saturated brine (50 mL). The organic layer was dried over MgSO₄, filtered and evaporated to afford crude product. EN01579-03-1, 433mg). This material was 3 spots by tlc and at least 3 peaks by Lcms. Lcms suggests
 15 incorporation of 1, 2 and 3 oxygens which suggests the components are probably the sulphoxide / pyridine, the sulphone / pyridine and the sulphone / pyridine N-oxide. Further extraction of the aqueous gave after drying and evaporation a white solid. Both materials were used without further purification or characterisation.

m/z (ESI+) (M+H)+ = 373; HPLC t_R = 1.43 min.

20

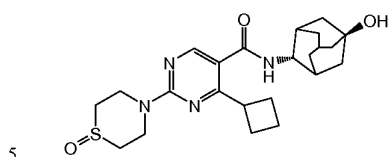
The following Examples were prepared in a similar manner to Example 79, using Intermediate 82 and an appropriate amine starting material:

25

Structure	Ex	Name	¹ H NMR δ	MS m/e MH ⁺
	80	1-(4-(4-cyclopropyl-5-(3-(pyridin-3-yl)pyrrolidine-1-carbonyl)pyrimidin-2-yl)piperazin-1-yl)ethanone	¹ H NMR (400.13 MHz, DMSO-d ₆) δ 0.93 - 1.10 (4H, m), 2.02 - 2.13 (5H, m), 2.25 - 2.36 (1H, m), 3.37 - 3.58 (7H, m), 3.60 - 3.73 (5.5H, m), 3.98 - 4.04 (0.5H, m), 7.31 - 7.38 (1H, m), 7.68 - 7.78 (1H, m), 8.23 (1H, d), 8.42 - 8.46 (1H, m), 8.49 - 8.56 (1H, m)	m/z (ESI ⁺) (M+H) ⁺ = 421; HPLC t _R = 1.6 min.
	81	(4-cyclopropyl-2-((2S,6R)-2,6-dimethylmorpholino)pyrimidin-5-yl)(3-(pyridin-3-yl)pyrrolidine-1-yl)methanone	¹ H NMR (400.13 MHz, DMSO-d ₆) δ 0.92 - 1.23 (10H, m), 2.03 - 2.12 (2H, m), 2.25 - 2.33 (1H, m), 2.43 - 2.54 (1H, m), 3.31 - 3.60 (6.5H, m), 3.71 - 3.76 (1H, m), 3.98 - 4.02 (0.5H, m), 4.40 - 4.46 (2H, m), 7.31 - 7.37 (1H, m), 7.68 - 7.78 (1H, m), 8.21 (1H, d), 8.42 - 8.46 (1H, m), 8.49 - 8.55 (1H, m)	m/z (ESI ⁺) (M+H) ⁺ = 408; HPLC t _R = 1.97 min.

Example 82

4-Cyclobutyl-N-[(2r,5s)-5-hydroxyadamantan-2-yl]-2-(1-oxo-1,4-thiazinan-4-yl)pyrimidine-5-carboxamide



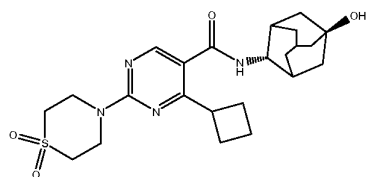
Prepared from Example 41 by the same process used for Example 36.

¹H NMR (400.132 MHz, CDCl₃) δ 1.44 (1H, s), 1.55 - 1.58 (2H, m), 1.67 - 1.73 (2H, m), 1.78 - 1.83 (4H, m), 1.87 - 1.95 (3H, m), 2.00 - 2.10 (1H, m), 2.15 - 2.29 (5H, m), 2.34 - 2.44 (2H, m), 2.71 - 2.90 (4H, m), 3.98 (1H, quintet), 4.14 - 4.29 (3H, m), 4.63 - 4.70 (2H, m), 5.87 (1H, d), 8.35 (1H, s)

5 m/z (ESI⁺) (M+H)⁺ = 445; HPLC t_R = 1.45 min

Example 83

4-Cyclobutyl-2-(1,1-dioxo-1,4-thiazinan-4-yl)-N-[(2r,5s)-5-hydroxyadamantan-2-yl]pyrimidine-5-carboxamide



10

Prepared from Example 41 by the same process used for Example 37.

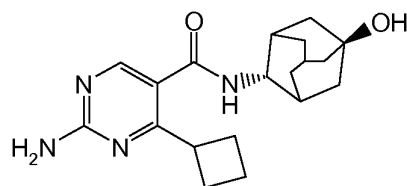
¹H NMR (400.132 MHz, CDCl₃) δ 1.38 (1H, s), 1.56 - 1.61 (2H, m), 1.66 - 1.74 (2H, m), 1.78 - 1.83 (4H, m), 1.87 - 1.96 (3H, m), 2.01 - 2.10 (1H, m), 2.16 - 2.29 (5H, m), 2.32 - 2.41 (2H, m), 3.03 - 3.09 (4H, m), 3.98 (1H, quintet), 4.16 - 4.21 (1H, m), 4.42 - 4.49 (4H, m), 5.83 (1H, d), 8.36 (1H, s)

15

m/z (ESI⁺) (M+H)⁺ = 461; HPLC t_R = 1.72 min

Example 84

2-Amino-4-cyclobutyl-N-[(2r,5s)-5-hydroxyadamantan-2-yl]pyrimidine-5-carboxamide



20

Prepared from Intermediate 72 by the same process used for Example 49

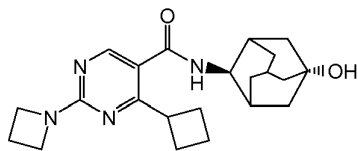
¹H NMR (400.13 MHz, DMSO-d₆) δ 1.31 (2H, d), 1.58 - 1.64 (4H, m), 1.67 - 1.77 (3H, m), 1.84 - 1.94 (3H, m), 1.95 - 1.99 (1H, m), 2.00 - 2.12 (4H, m), 2.22 - 2.32 (2H, m), 3.80 - 3.89 (2H, m), 4.38 (1H, s), 6.77 (2H, s), 7.94 (1H, d), 8.09 (1H, s)

25

m/z (ESI⁺) (M+H)⁺ = 343; HPLC t_R = 1.42 min.

Example 85

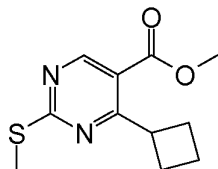
2-Azetidin-1-yl-4-cyclobutyl-N-[(2r,5s)-5-hydroxyadamantan-2-yl]pyrimidine-5-carboxamide



- 5 4-cyclobutyl-N-[(2r,5s)-5-hydroxyadamantan-2-yl]-2-(methylsulfonyl)pyrimidine-5-carboxamide (Intermediate 72, 270 mg, 0.67 mmol) and azetidine (125 mg, 1.33 mmol) were dissolved in THF (4 mL) and sealed into a microwave tube. The reaction was heated to 150 °C for 1 hour in the microwave reactor and cooled to room temperature. The reaction mixture was diluted with DCM (10 mL), and stirred with saturated NaHCO₃ (10 mL) before passing through a phase separation cartridge. The organic layer was evaporated to afford crude product. The crude product was purified by preparative HPLC (Waters XBridge Prep C18 OBD column, 5 μ silica, 50 mm diameter, 150 mm length), using decreasingly polar mixtures of water (containing 0.1% NH₃) and MeCN as eluents. Fractions containing the desired compound were evaporated to dryness to afford 2-azetidin-1-yl-4-cyclobutyl-N-[(2r,5s)-5-hydroxyadamantan-2-yl]pyrimidine-5-carboxamide (103 mg, 40.4 %) as a white solid.
- 1H NMR (400.13 MHz, DMSO-d₆) δ 1.31 (2H, d), 1.61 (4H, m), 1.70 (2H, d), 1.76 (1H, m), 1.87 - 2.01 (6H, m), 2.06 - 2.13 (2H, m), 2.22 - 2.35 (4H, m), 3.80 - 3.89 (2H, m), 4.07 (4H, t), 4.37 (1H, s), 7.96 (1H, d), 8.17 (1H, s)
- 20 m/z (ES⁺) (M+H)⁺ = 383; HPLC t_R = 1.85 min.

Intermediate 69

Methyl 4-cyclobutyl-2-(methylthio)pyrimidine-5-carboxylate

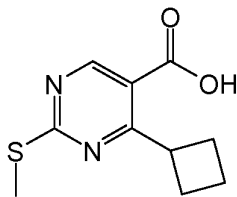


- 25 2-Methyl-2-Thiopseudourea Sulfate (1.932 g, 13.88 mmol) was added to (Z)-methyl 2-(cyclobutanecarbonyl)-3-(dimethylamino)acrylate (Intermediate 66, 2.6 g, 12.31 mmol) and sodium acetate (4.24 g, 51.69 mmol) in DMF (10 mL) at 20°C. The resulting solution

was stirred at 80 °C for 2 hours. Water was added to the cooled solution. The reaction mixture was diluted with EtOAc (200 mL), and washed sequentially with water (2x100 mL). The organic layer was dried over MgSO₄, filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 5 to 30% EtOAc in isohexane. Pure fractions were evaporated to dryness to afford methyl 4-cyclobutyl-2-(methylthio)pyrimidine-5-carboxylate (1.300 g, 44.3 %) as a white solid. ¹H NMR (400.132 MHz, CDCl₃) δ 1.86 - 1.94 (1H, m), 2.00 - 2.10 (1H, m), 2.26 - 2.35 (2H, m), 2.41 - 2.51 (2H, m), 2.65 (3H, s), 3.90 (3H, s), 4.35 (1H, quintet), 8.86 (1H, s) m/z (ESI+) (M+H)⁺ = 239; HPLC t_R = 2.75 min.

Intermediate 70

4-Cyclobutyl-2-(methylthio)pyrimidine-5-carboxylic acid

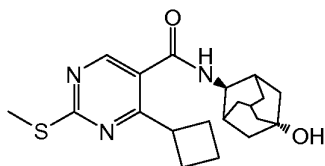


A solution of lithium hydroxide monohydrate (0.458 g, 10.91 mmol) in water (8 mL) was added to a stirred solution of methyl 4-cyclobutyl-2-(methylthio)pyrimidine-5-carboxylate (Intermediate 69, 1.3 g, 5.46 mmol) in THF (16 mL) at 20°C. The resulting mixture was stirred at 20 °C for 24 hours. The THF was evaporated and the aqueous washed with ethyl acetate (100ml) to remove any impurities. The aqueous was acidified with 1M citric acid and extracted into ethyl acetate (100ml). The organic layer was washed with brine (50ml), dried over MgSO₄, filtered and evaporated to give 4-cyclobutyl-2-(methylthio)pyrimidine-5-carboxylic acid (1.100 g, 90 %) as a white solid.

¹H NMR (400.132 MHz, CDCl₃) δ 1.87 - 1.96 (1H, m), 2.02 - 2.13 (1H, m), 2.31 - 2.39 (2H, m), 2.44 - 2.54 (2H, m), 2.67 (3H, s), 4.42 (1H, quintet), 9.00 (1H, s) m/z (ESI+) (M+H)⁺ = 225; HPLC t_R = 0.82 min.

Intermediate 71

4-cyclobutyl-N-[(2r,5s)-5-hydroxyadamantan-2-yl]-2-methylsulfanylpyrimidine-5-carboxamide

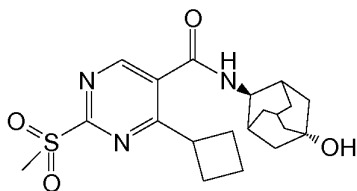


N-Ethyldiisopropylamine (3.39 mL, 19.62 mmol) was added to 4-cyclobutyl-2-(methylthio)pyrimidine-5-carboxylic acid (Intermediate 70, 1.1 g, 4.90 mmol), 4-aminoadamantan-1-ol hydrochloride (1.099 g, 5.40 mmol) and O-(7-Azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (2.238 g, 5.89 mmol) in DMF (20 mL) at 20°C under nitrogen. The resulting solution was stirred at 20 °C for 24 hours. The reaction mixture was evaporated to dryness and redissolved in EtOAc (75 mL), and washed sequentially with water (75 mL) and saturated brine (75 mL). The organic layer was dried over MgSO₄, filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 0 to 6% MeOH in DCM. Pure fractions were evaporated to dryness to afford 4-cyclobutyl-N-[(2r,5s)-5-hydroxyadamantan-2-yl]-2-methylsulfanylpuridine-5-carboxamide (1.500 g, 82 %) as a white solid.

¹H NMR (400.132 MHz, CDCl₃) δ 1.55 - 1.62 (2H, m), 1.66 - 1.71 (2H, m), 1.78 - 1.85 (5H, m), 1.91 - 1.97 (3H, m), 2.00 - 2.08 (1H, m), 2.15 - 2.19 (1H, m), 2.23 - 2.32 (4H, m), 2.43 - 2.52 (2H, m), 2.62 (3H, s), 3.92 - 4.00 (1H, m), 4.17 - 4.22 (1H, m), 5.90 (1H, d), 8.41 (1H, s)
m/z (ESI+) (M+H)⁺ = 374; HPLC t_R = 2.00 min.

Intermediate 72

4-Cyclobutyl-N-[(2r,5s)-5-hydroxyadamantan-2-yl]-2-methylsulfonylpuridine-5-carboxamide



3-Chloroperoxybenzoic acid (70%) (0.937 g, 3.80 mmol) was added in one portion to 4-cyclobutyl-N-[(2r,5s)-5-hydroxyadamantan-2-yl]-2-methylsulfanylpuridine-5-carboxamide (Intermediate 71, 0.71 g, 1.90 mmol) in DCM (35 mL) at 0°C. The resulting

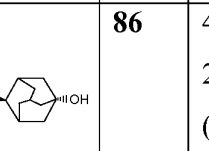
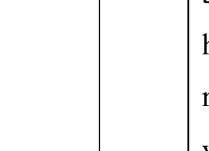
solution was stirred at 20 °C for 24 hours. The reaction mixture was diluted with DCM (50 mL), and washed sequentially with saturated NaHCO₃ (75 mL), 2M NaOH (75 mL), and saturated brine (75 mL). The organic layer was dried over MgSO₄, filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 0 to 6% MeOH in DCM. Pure fractions were evaporated to dryness to afford 4-cyclobutyl-N-[(2*r*,5*s*)-5-hydroxyadamantan-2-yl]-2-methylsulfonylpyrimidine-5-carboxamide (0.560 g, 72.6 %) as a white solid.

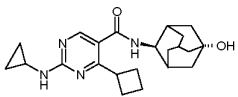
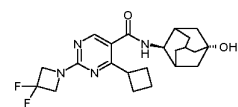
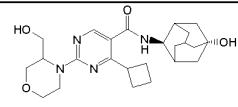
¹H NMR (400.132 MHz, CDCl₃) δ 1.44 (1H, s), 1.58 - 1.65 (2H, m), 1.74 - 1.87 (6H, m), 1.93 - 1.98 (3H, m), 2.05 - 2.15 (1H, m), 2.18 - 2.30 (3H, m), 2.32 - 2.39 (2H, m), 2.43 - 2.55 (2H, m), 3.34 (3H, s), 4.00 - 4.09 (1H, m), 4.21 - 4.28 (1H, m), 6.42 (1H, d), 8.71 (1H, s)

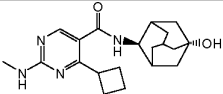
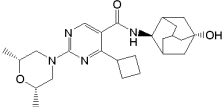
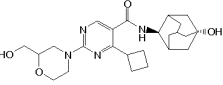
m/z (ESI+) (M+H)⁺ = 406; HPLC t_R = 1.59 min.

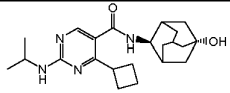
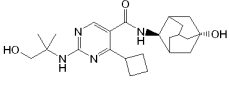
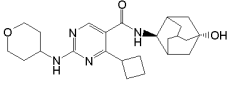
The following Examples were prepared in a similar manner to Example 46, using

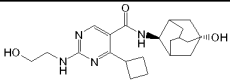
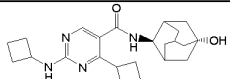
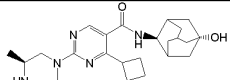
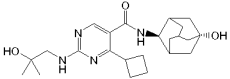
Intermediate 72 and an appropriate amine starting material:

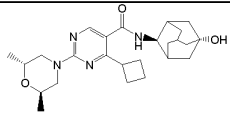
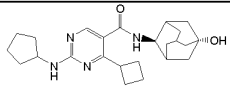
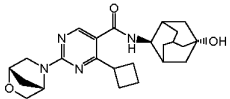
Structure	Ex	Name	¹ H NMR δ	MS m/e MH ⁺
	86	4-cyclobutyl-2-(dimethylamino)-N-[(2r,5s)-5-hydroxyadamantan-2-yl]pyrimidine-5-carboxamide	¹ H NMR (400.13 MHz, DMSO-d ₆) δ 1.31 (2H, d), 1.61 (4H, d), 1.70 (2H, d), 1.74 - 1.82 (1H, m), 1.88 - 2.02 (6H, m), 2.08 - 2.16 (2H, m), 2.24 - 2.34 (2H, m), 3.17 (6H, s), 3.84 - 3.92 (2H, m), 4.37 (1H, s), 7.92 (1H, d), 8.20 (1H, s)	m/z (ES+) (M+H) ⁺ = 371; HPLC t _R = 1.97 min.
	87	4-cyclobutyl-N-[(2r,5s)-5-hydroxyadamantan-2-yl]-2-(2-methoxyethoxy)ethylpyrimidine-5-carboxamide	¹ H NMR (400.13 MHz, DMSO-d ₆) δ 1.31 (2H, d), 1.61 (4H, d), 1.70 (2H, d), 1.75 - 1.79 (1H, m), 1.88 - 2.01 (6H, m), 2.08 - 2.16 (2H, m), 2.24 - 2.34 (2H, m), 3.17 (6H, s), 3.84 - 3.92 (2H, m), 4.37 (1H, s), 7.92 (1H, d), 8.20 (1H, s)	m/z (ES+) (M+H) ⁺ = 470; HPLC t _R = 1.97 min.

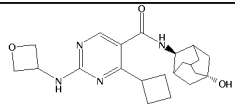
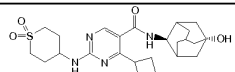
		[4-(2-methoxyethyl)piperazin-1-yl]pyrimidine-5-carboxamide	m), 2.07 - 2.15 (2H, m), 2.22 - 2.31 (2H, m), 2.45 - 2.52 (6H, m), 3.24 (3H, s), 3.46 (2H, t), 3.79 (4H, t), 3.88 (2H, m), 4.37 (1H, s), 7.95 (1H, d), 8.20 (1H, s)	HPLC t_R = 1.81 min.
	88	4-cyclobutyl-2-(cyclopropylamino)-N-[(2r,5s)-5-hydroxyadamantan-2-yl]pyrimidine-5-carboxamide	¹ H NMR (400.13 MHz, DMSO- d_6) δ 0.46 - 0.50 (2H, m), 0.64 - 0.69 (2H, m), 1.31 (2H, d), 1.61 (4H, d), 1.69 - 1.79 (3H, m), 1.85 - 2.02 (6H, m), 2.06 - 2.13 (2H, m), 2.25 - 2.34 (2H, m), 2.77 (1H, m), 3.81 - 3.88 (2H, m), 4.37 (1H, s), 7.49 (1H, d), 7.95 (1H, d), 8.16 (1H, s)	m/z (ES+) (M+H) ⁺ = 383; HPLC t_R = 1.77 min.
	89	4-cyclobutyl-2-(3,3-difluoroazetidin-1-yl)-N-[(2r,5s)-5-hydroxyadamantan-2-yl]pyrimidine-5-carboxamide	¹ H NMR (400.13 MHz, DMSO- d_6) δ 1.32 (2H, d), 1.62 (4H, d), 1.71 (2H, d), 1.78 (1H, m), 1.89 - 2.03 (6H, m), 2.08 - 2.16 (2H, m), 2.25 - 2.35 (2H, m), 3.81 - 3.91 (2H, m), 4.38 (1H, s), 4.51 (4H, t), 8.09 (1H, d), 8.27 (1H, s)	m/z (ES+) (M+H) ⁺ = 419; HPLC t_R = 2.04 min.
	90	4-cyclobutyl-N-[(2r,5s)-5-hydroxyadamantan-2-yl]-2-[3-(hydroxymethyl)-3-oxo-1,3-dihydro-2H-pyridin-2-yl]-2-oxo-1,3-dihydro-2H-pyridin-2-ylpyrimidine-5-carboxamide	¹ H NMR (400.13 MHz, DMSO- d_6) δ 1.31 (2H, d), 1.61 (4H, d), 1.70 (2H, d), 1.78 (1H, m), 1.90 - 2.02 (6H, m), 2.08 - 2.15 (2H, m), 2.19 - 2.31 (2H, m), 3.08 - 3.17 (1H, m), 3.38 -	m/z (ES+) (M+H) ⁺ = 443; HPLC t_R = 1.61

		l)morpholin-4-yl]pyrimidine-5-carboxamide	3.42 (2H, m), 3.44 - 3.53 (1H, m), 3.71 - 3.78 (1H, m), 3.82 - 3.95 (3H, m), 4.09 (1H, d), 4.37 (1H, s), 4.44 (1H, m), 4.55 (1H, m), 4.84 (1H, t), 7.97 (1H, d), 8.22 (1H, s)	min.
	91	4-cyclobutyl-N-[(2r,5s)-5-hydroxyadamantan-2-yl]-2-(methylamino)pyrimidine-5-carboxamide	¹ H NMR (400.13 MHz, DMSO-d ₆) δ 1.31 (2H, d), 1.61 (4H, d), 1.69 - 1.76 (3H, m), 1.87 - 2.13 (8H, m), 2.29 (2H, m), 2.84 (3H, d), 3.84 - 3.91 (2H, m), 4.37 (1H, s), 7.22 (1H, d), 7.92 (1H, d), 8.14 (1H, s)	m/z (ES+) (M+H) ⁺ = 357; HPLC t _R = 1.58 min.
	92	4-cyclobutyl-2-[(2R,6S)-2,6-dimethylmorpholin-4-yl]-N-[(2r,5s)-5-hydroxyadamantan-2-yl]pyrimidine-5-carboxamide	¹ H NMR (400.13 MHz, DMSO-d ₆) δ 1.16 (6H, d), 1.31 (2H, d), 1.61 (4H, d), 1.70 (2H, d), 1.76 - 1.81 (1H, m), 1.89 - 2.01 (6H, m), 2.08 - 2.16 (2H, m), 2.22 - 2.32 (2H, m), 2.53 - 2.59 (2H, m), 3.51 - 3.58 (2H, m), 3.82 - 3.90 (2H, m), 4.38 (1H, s), 4.60 (2H, d), 7.97 (1H, d), 8.21 (1H, s)	m/z (ES+) (M+H) ⁺ = 441; HPLC t _R = 2.11 min.
	93	4-cyclobutyl-N-[(2r,5s)-5-hydroxyadamantan-2-yl]-2-[2-(hydroxymethyl)morpholin-4-yl]pyrimidine-5-carboxamide	¹ H NMR (400.13 MHz, DMSO-d ₆) δ 1.31 (2H, d), 1.61 (4H, d), 1.70 (2H, d), 1.78 (1H, t), 1.89 - 1.98 (4H, m), 2.02 (2H, s), 2.08 - 2.16 (2H, m), 2.23 - 2.33 (2H, m), 2.72 - 2.78 (1H, m), 2.97 - 3.04 (1H, m), 3.37 - 3.45 (2H, m), 3.48 - 3.55	m/z (ES+) (M+H) ⁺ = 443; HPLC t _R = 1.55 min.

		5-carboxamide	(2H, m), 3.86 (2H, q), 3.92 - 3.96 (1H, m), 4.38 (1H, s), 4.53 (1H, d), 4.68 (1H, d), 4.79 (1H, t), 7.97 (1H, d), 8.23 (1H, s)	
	94	4-cyclobutyl-N-[(2r,5s)-5-hydroxyadamantan-2-yl]-2-(isopropylamino)pyrimidine-5-carboxamide	¹ H NMR (400.13 MHz, DMSO-d ₆) δ 1.16 (6H, d), 1.31 (2H, d), 1.60 - 1.63 (4H, m), 1.68 - 1.77 (3H, m), 1.85 - 2.01 (6H, m), 2.06 - 2.13 (2H, m), 2.23 - 2.33 (2H, m), 3.81 - 3.89 (2H, m), 4.11 (1H, q), 4.37 (1H, s), 7.15 (1H, d), 7.91 (1H, d), 8.13 (1H, s)	m/z (ES+) (M+H) ⁺ = 385; HPLC t _R = 2.11 min.
	95	4-cyclobutyl-N-[(2r,5s)-5-hydroxyadamantan-2-yl]-2-[(2-hydroxy-1,1-dimethylethyl)amino]pyrimidine-5-carboxamide	¹ H NMR (400.13 MHz, DMSO-d ₆) δ 1.31 (2H, d), 1.36 (6H, s), 1.61 (4H, m), 1.70 (2H, d), 1.79 (1H, m), 1.88 - 2.01 (6H, m), 2.08 - 2.15 (2H, m), 2.22 - 2.32 (2H, m), 3.52 (2H, d), 3.80 - 3.88 (2H, m), 4.37 (1H, s), 4.92 (1H, t), 6.53 (1H, s), 7.95 (1H, d), 8.12 (1H, s)	m/z (ES+) (M+H) ⁺ = 415; HPLC t _R = 1.68 min.
	96	4-cyclobutyl-N-[(2r,5s)-5-hydroxyadamantan-2-yl]-2-(tetrahydro-2H-pyran-4-ylamino)pyrimidine-5-	¹ H NMR (400.13 MHz, DMSO-d ₆) δ 1.31 (2H, d), 1.48 - 1.58 (2H, m), 1.61 (4H, m), 1.68 - 2.01 (11H, m), 2.10 (2H, q), 2.23 - 2.32 (2H, m), 3.35 - 3.41 (2H, m), 3.86 (4H, m), 3.98 (1H, m), 4.37 (1H, s), 7.31 (1H, d), 7.92 (1H, d), 8.13 (1H,	m/z (ES+) (M+H) ⁺ = 427; HPLC t _R = 1.67 min.

		carboxamide	s)	
	97	4-cyclobutyl-N-[(2r,5s)-5-hydroxyadamantan-2-yl]-2-[(2-hydroxyethyl)amino]pyrimidine-5-carboxamide	¹ H NMR (400.13 MHz, DMSO-d ₆) δ 1.31 (2H, d), 1.60 - 1.63 (4H, m), 1.69 - 1.77 (3H, m), 1.85 - 2.01 (6H, m), 2.06 - 2.13 (2H, m), 2.23 - 2.32 (2H, m), 3.39 (2H, m), 3.53 (2H, m), 3.81 - 3.87 (2H, m), 4.37 (1H, s), 4.63 (1H, t), 7.18 (1H, t), 7.93 (1H, d), 8.13 (1H, s)	m/z (ES+) (M+H) ⁺ = 387; HPLC t _R = 1.38 min.
	98*	N-[(2r,5s)-5-hydroxyadamantan-2-yl] 4-cyclobutyl-2-(cyclobutylamino)pyrimidine-5-carboxamide	¹ H NMR (400.13 MHz, DMSO-d ₆) δ 1.31 (2H, d), 1.39 (1H, s), 1.60 - 1.77 (8H, m), 1.87 - 2.01 (8H, m), 2.09 (2H, m), 2.23 - 2.33 (4H, m), 3.80 - 3.89 (2H, m), 4.37 - 4.42 (2H, m), 7.59 (1H, d), 7.92 (1H, d), 8.12 (1H, s)	m/z (ES+) (M+H) ⁺ = 397; HPLC t _R = 2.05 min.
	99	4-cyclobutyl-2-[(3R,5S)-3,5-dimethylpiperazin-1-yl]-N-[(2r,5s)-5-hydroxyadamantan-2-yl]pyrimidine-5-carboxamide	¹ H NMR (400.13 MHz, DMSO-d ₆) δ 1.02 (6H, d), 1.31 (2H, d), 1.61 (4H, d), 1.70 (2H, d), 1.75 - 1.81 (1H, m), 1.88 - 2.01 (6H, m), 2.07 - 2.15 (2H, m), 2.21 - 2.31 (3H, m), 2.33 - 2.39 (2H, m), 2.62 - 2.70 (2H, m), 3.82 - 3.90 (2H, m), 4.38 (1H, s), 4.63 (2H, d), 7.93 (1H, d), 8.18 (1H, s)	m/z (ES+) (M+H) ⁺ = 440; HPLC t _R = 1.77 min.
	100	4-cyclobutyl-N-[(2r,5s)-5-hydroxyadamantan-2-yl]pyrimidine-5-carboxamide	¹ H NMR (400.13 MHz, DMSO-d ₆) δ 1.11 (6H, s), 1.31 (2H, d), 1.61 (4H, d), 1.68 -	m/z (ES+) (M+H) ⁺

		ntan-2-yl]-2- [(2-hydroxy-2- methylpropyl)a mino]pyrimidi ne-5- carboxamide	1.77 (3H, m), 1.87 - 1.98 (4H, m), 2.02 (2H, s), 2.05 - 2.13 (2H, m), 2.23 - 2.33 (2H, m), 3.36 (2H, s), 3.83 - 3.87 (2H, m), 4.37 (1H, s), 4.58 (1H, s), 7.00 (1H, s), 7.95 (1H, d), 8.12 (1H, s)	= 415; HPLC t_R = 1.55 min.
	101	4-cyclobutyl- 2-[(2R,6R)- 2,6- dimethylmorph olin-4-yl]-N- [(2r,5s)-5- hydroxyadama ntan-2- yl]pyrimidine- 5-carboxamide	1H NMR (400.13 MHz, DMSO-d ₆) d 1.12 (6H, d), 1.31 (2H, d), 1.61 (4H, d), 1.70 (2H, d), 1.74 - 1.82 (1H, m), 1.88 - 1.97 (4H, m), 2.01 (2H, s), 2.08 - 2.16 (2H, m), 2.20 - 2.33 (2H, m), 3.54 (2H, m), 3.82 - 3.92 (4H, m), 3.96 - 4.03 (2H, m), 4.38 (1H, s), 7.98 (1H, d), 8.21 (1H, s)	m/z (ES+) (M+H)+ = 441; HPLC t_R = 2.07 min.
	102	4-cyclobutyl- 2- (cyclopentyla mino)-N- [(2r,5s)-5- hydroxyadama ntan-2- yl]pyrimidine- 5-carboxamide	1H NMR (400.13 MHz, DMSO-d ₆) d 1.31 (2H, m), 1.48 - 1.55 (4H, m), 1.61 (4H, d), 1.68 - 1.76 (5H, m), 1.85 - 1.97 (6H, m), 2.01 (2H, s), 2.09 (2H, m), 2.24 - 2.33 (2H, m), 3.81 - 3.87 (2H, m), 4.21 (1H, m), 4.37 (1H, s), 7.30 (1H, d), 7.91 (1H, d), 8.12 (1H, s)	m/z (ES+) (M+H)+ = 441; HPLC t_R = 2.07 min.
	103	4-cyclobutyl- N-[(2r,5s)-5- hydroxyadama ntan-2-yl]-2- [(1S,4S)-2-	1H NMR (400.13 MHz, DMSO-d ₆) d 1.31 (2H, d), 1.61 (4H, d), 1.70 (2H, d), 1.76 - 1.81 (1H, m), 1.86 - 1.98 (6H, m), 2.02 (2H, s), 2.11 (2H, m),	m/z (ES+) (M+H)+ = 425; HPLC t_R

		oxa-5-azabicyclo[2.2.1]hept-5-yl]pyrimidine-5-carboxamide	2.23 - 2.34 (2H, m), 3.45 - 3.51 (2H, m), 3.64 (1H, d), 3.81 - 3.88 (3H, m), 4.38 (1H, s), 4.67 (1H, s), 5.00 (1H, s), 7.96 (1H, d), 8.19 (1H, s)	= 1.73 min.
	104	4-cyclobutyl-N-[(2r,5s)-5-hydroxyadamantan-2-yl]-2-(oxetan-3-ylamino)pyrimidine-5-carboxamide	¹ H NMR (400.13 MHz, DMSO-d ₆) δ 1.31 (2H, d), 1.61 (4H, d), 1.68 - 1.80 (3H, m), 1.89 - 1.97 (4H, m), 2.01 (2H, s), 2.07 - 2.14 (2H, m), 2.21 - 2.31 (2H, m), 3.80 - 3.88 (2H, m), 4.37 (1H, s), 4.53 (2H, t), 4.77 (2H, t), 4.89 - 4.95 (1H, m), 7.97 (1H, d), 8.07 (1H, d), 8.15 (1H, s)	m/z (ES+) (M+H) ⁺ = 399; HPLC t _R = 1.48 min.
	105	4-cyclobutyl-2-[(1,1-dioxidotetrahydro-2H-thiopyran-4-yl)amino]-N-[(2r,5s)-5-hydroxyadamantan-2-yl]pyrimidine-5-carboxamide	¹ H NMR (400.13 MHz, DMSO-d ₆) δ 1.31 (2H, d), 1.61 (4H, d), 1.68 - 1.77 (3H, m), 1.89 - 2.01 (6H, m), 2.11 (6H, m), 2.24 - 2.34 (3H, m), 3.12 - 3.23 (3H, m), 3.80 - 3.87 (2H, m), 4.14 - 4.17 (1H, m), 4.37 (1H, s), 7.53 (1H, d), 7.95 (1H, d), 8.15 (1H, s)	m/z (ES-) (M-H) ⁻ = 473; HPLC t _R = 1.53 min.

Footnotes

* Example 98 may be prepared as follows:

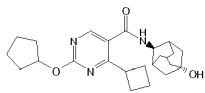
Cyclobutylamine (4.00 mL, 46.85 mmol) was added to 4-cyclobutyl-N-[(2r,5s)-5-hydroxyadamantan-2-yl]-2-methylsulfonylpyrimidine-5-carboxamide (Intermediate 72,
 5 3.8 g, 9.37 mmol) in THF (60 mL). The resulting solution was stirred at 20 °C for 70

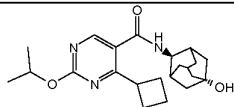
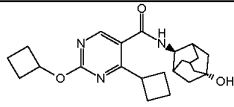
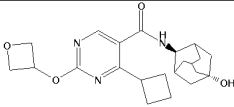
hours. The reaction mixture was evaporated to dryness and redissolved in EtOAc (150 mL), and washed sequentially with water (150 mL) and saturated brine (150 mL). The organic layer was dried over MgSO₄, filtered and evaporated to afford crude product. The crude gum was triturated with DCM to give a solid which was collected by filtration. The filtrate was purified by flash silica chromatography, elution gradient 0 to 5% MeOH in DCM. Pure fractions were evaporated to dryness to afford 4-cyclobutyl-2-(cyclobutylamino)-N-[(2r,5s)-5-hydroxyadamantan-2-yl]pyrimidine-5-carboxamide as a white foam. The solid from the trituration and the foam were combined and triturated with ethyl acetate to give 4-cyclobutyl-2-(cyclobutylamino)-N-[(2r,5s)-5-hydroxyadamantan-2-yl]pyrimidine-5-carboxamide (2.125 g, 57.2 %) as a white solid.

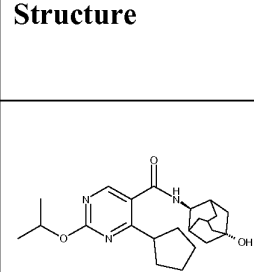
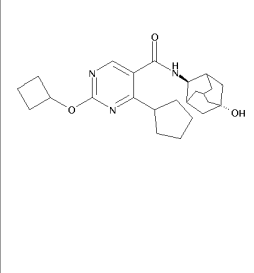
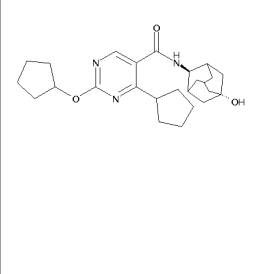
¹H NMR (400.132 MHz, CDCl₃) δ 1.42 (1H, s), 1.52 - 1.57 (2H, m), 1.66 - 1.71 (2H, m), 1.76 - 1.82 (6H, m), 1.88 - 2.04 (6H, m), 2.15 - 2.26 (5H, m), 2.36 - 2.48 (4H, m), 3.95 (1H, quintet), 4.14 - 4.21 (1H, m), 4.42 - 4.59 (1H, m), 5.47 (1H, s), 5.81 (1H, d), 8.28 (1H, s)

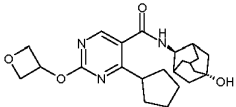
m/z (ES+) (M+H)⁺ = 397; HPLC t_R = 2.05 min.

The following Examples were prepared in a similar manner to Example 75, using Intermediate 72 and an appropriate starting material:

Structure	Ex	Name	¹ H NMR δ	MS m/e MH ⁺
	106	4-cyclobutyl-2-(cyclopentylxy)-N-[(2r,5s)-5-hydroxyadamantan-2-yl]pyrimidine-5-	¹ H NMR (400.13 MHz, DMSO-d ₆) δ 1.33 (2H, d), 1.57 - 1.66 (6H, m), 1.70 - 1.84 (7H, m), 1.88 - 2.03 (8H, m), 2.11 - 2.19 (2H, m), 2.25 - 2.35 (2H, m), 3.84 (1H, m), 3.92 (1H, m), 4.39 (1H, s), 5.38 - 5.42 (1H, m), 8.20 (1H, d), 8.37 (1H, s)	m/z (ES+) (M+H) ⁺ = 412; HPLC t _R = 2.24 min.

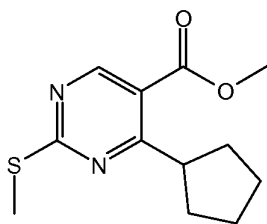
		carboxamide		
	107	4-cyclobutyl-N-[(2r,5s)-5-hydroxyadamantan-2-yl]-2-isopropoxy-pyrimidine-5-carboxamide	¹ H NMR (400.13 MHz, DMSO-d ₆) δ 1.31 (2H, s), 1.34 (6H, d), 1.62 (4H, d), 1.71 (2H, d), 1.76 - 1.84 (1H, m), 1.88 - 1.98 (4H, m), 2.02 (2H, s), 2.11 - 2.19 (2H, m), 2.25 - 2.34 (2H, m), 3.84 (1H, m), 3.92 (1H, m), 4.39 (1H, s), 5.23 - 5.30 (1H, m), 8.19 (1H, d), 8.37 (1H, s)	m/z (ES+) (M+H) ⁺ = 386; HPLC t _R = 2.02 min.
	108	4-cyclobutyl-2-(cyclobutyloxy)-N-[(2r,5s)-5-hydroxyadamantan-2-yl]pyrimidine-5-carboxamide	¹ H NMR (400.13 MHz, DMSO-d ₆) δ 1.32 (2H, d), 1.61 - 1.73 (7H, m), 1.77 - 1.85 (2H, m), 1.88 - 1.99 (4H, m), 2.01 - 2.06 (2H, m), 2.08 - 2.19 (4H, m), 2.24 - 2.34 (2H, m), 2.40 - 2.47 (2H, m), 3.80 - 3.89 (1H, m), 3.92 (1H, m), 4.39 (1H, s), 5.13 - 5.20 (1H, m), 8.21 (1H, d), 8.37 (1H, s)	m/z (ES+) (M+H) ⁺ = 398; HPLC t _R = 2.11 min.
	109	4-cyclobutyl-N-[(2r,5s)-5-hydroxyadamantan-2-yl]-2-(oxetan-3-yloxy)pyrimidine-5-carboxamide	¹ H NMR (400.13 MHz, DMSO-d ₆) δ 1.33 (2H, d), 1.62 (4H, d), 1.71 (2H, d), 1.75 - 1.85 (1H, m), 1.88 - 2.03 (6H, m), 2.08 - 2.19 (2H, m), 2.22 - 2.30 (2H, m), 3.80 - 3.89 (1H, m), 3.92 (1H, m), 4.39 (1H, s), 4.59 - 4.62 (2H, m), 4.91 (2H, t), 5.58 - 5.63 (1H, m), 8.24 (1H, d), 8.40 (1H, s)	m/z (ES+) (M+H) ⁺ = 400; HPLC t _R = 1.57 min.

Structure	Ex	Name	¹ H NMR δ	MS m/e MH ⁺
	110	4-cyclopentyl-N-[(2 <i>r</i> ,5 <i>s</i>)-5-hydroxyadamantan-2-yl]-2-propan-2-yloxy pyrimidine-5-carboxamide	¹ H NMR (400.132 MHz, CDCl ₃) δ 1.40 (7H, d), 1.57 - 1.62 (2H, m), 1.66 - 1.72 (4H, m), 1.78 - 2.05 (12H, m), 2.15 - 2.28 (3H, m), 3.51 - 3.56 (1H, m), 4.20 - 4.24 (1H, m), 5.26 - 5.35 (1H, m), 5.92 (1H, d), 8.44 (1H, s)	m/z (ESI ⁺) (M+H) ⁺ = 400; HPLC t _R = 2.15 min.
	111	2-cyclobutyloxy-4-cyclopentyl-N-[(2 <i>r</i> ,5 <i>s</i>)-5-hydroxyadamantan-2-yl]pyrimidine-5-carboxamide	¹ H NMR (400.132 MHz, CDCl ₃) δ 1.41 (1H, s), 1.59 (2H, d), 1.63 - 2.05 (18H, m), 2.15 - 2.30 (5H, m), 2.42 - 2.51 (2H, m), 3.51 (1H, quintet), 4.20 (1H, d), 5.19 (1H, quintet), 5.93 (1H, d), 8.43 (1H, s)	m/z (ESI ⁺) (M+H) ⁺ = 412; HPLC t _R = 2.29 min.
	112	4-cyclopentyl-2-cyclopentyl-N-[(2 <i>r</i> ,5 <i>s</i>)-5-hydroxyadamantan-2-	¹ H NMR (400.132 MHz, CDCl ₃) δ 1.41 (1H, s), 1.52 - 2.07 (26H, m), 2.19 (1H, s), 2.26 (2H, s), 3.52 (1H, t), 4.20 (1H, d), 5.41 (1H, septet), 5.93 (1H, d), 8.44 (1H, s)	m/z (ESI ⁺) (M+H) ⁺ = 426; HPLC t _R = 2.44 min.

		yl]pyrimidine -5- carboxamide		
	113	4-cyclopentyl-N-[(2r,5s)-5-hydroxyadamantan-2-yl]-2-(oxetan-3-yloxy)pyrimidine-5-carboxamide	¹ H NMR (400.132 MHz, CDCl ₃) δ 1.46 (1H, s), 1.59 (2H, d), 1.65 - 1.74 (4H, m), 1.77 - 1.90 (8H, m), 1.90 - 2.05 (5H, m), 2.19 (1H, s), 2.26 (2H, s), 3.51 (1H, quintet), 4.21 (1H, d), 4.80 (2H, t), 4.97 (2H, t), 5.61 (1H, quintet), 5.96 (1H, d), 8.44 (1H, s)	m/z (ESI+) (M+H) ⁺ = 414; HPLC t _R = 1.69 min.

Intermediate 83

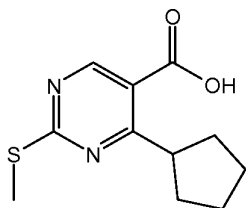
methyl 4-cyclopentyl-2-(methylthio)pyrimidine-5-carboxylate



- 5 Prepared from Intermediate 53 by the same process used for Intermediate 28
¹H NMR (400.132 MHz, CDCl₃) δ 1.67 - 1.72 (2H, m), 1.79 - 1.92 (4H, m), 1.99 - 2.05 (2H, m), 2.58 (3H, s), 3.91 (3H, s), 3.99 - 4.09 (1H, m), 8.85 (1H, s)
m/z (ESI+) (M+H)⁺ = 253; HPLC t_R = 3.04 min.

10 **Intermediate 84**

4-cyclopentyl-2-(methylthio)pyrimidine-5-carboxylic acid

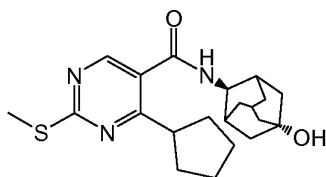


Prepared from Intermediate 83 by the same process used for Intermediate 21

¹H NMR (400.132 MHz, CDCl₃) δ 1.68 - 1.75 (2H, m), 1.81 - 1.96 (4H, m), 2.00 - 2.10 (2H, m), 2.61 (3H, s), 4.13 (1H, quintet), 9.00 (1H, s), 11.21 (1H, bs)
m/z (ESI⁺) (M+H)⁺ = 239; HPLC t_R = 1.19 min.

5 **Intermediate 85**

4-cyclopentyl-N-[(2r,5s)-5-hydroxyadamantan-2-yl]-2-methylsulfanylpurimidine-5-carboxamide

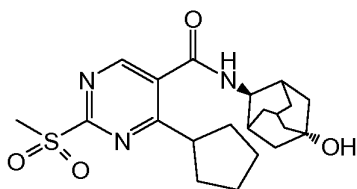


Prepared from Intermediate 84 by the same process used for Example 4

10 ¹H NMR (400.132 MHz, CDCl₃) δ 1.35 - 1.42 (1H, m), 1.58 - 1.62 (2H, m), 1.65 - 1.72 (4H, m), 1.79 - 2.01 (12H, m), 2.16 - 2.21 (1H, m), 2.24 - 2.27 (2H, m), 2.56 (3H, s), 3.51 (1H, quintet), 4.18 - 4.23 (1H, m), 5.92 (1H, d), 8.42 (1H, s)
m/z (ESI⁺) (M+H)⁺ = 388; HPLC t_R = 2.20 min.

15 **Intermediate 86**

4-cyclopentyl-N-[(2r,5s)-5-hydroxyadamantan-2-yl]-2-methylsulfonylpurimidine-5-carboxamide



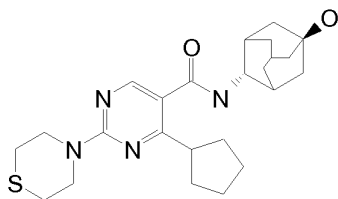
Prepared from Intermediate 85 by the same process used for Example 37

20 ¹H NMR (400.132 MHz, CDCl₃) δ 1.57 - 1.63 (2H, m), 1.69 - 1.99 (15H, m), 2.04 - 2.09 (2H, m), 2.17 - 2.23 (1H, m), 2.27 - 2.33 (2H, m), 3.30 (3H, s), 3.57 (1H, quintet), 4.23 - 4.27 (1H, m), 6.43 (1H, d), 8.72 (1H, s)
m/z (ESI⁺) (M+H)⁺ = 420; HPLC t_R = 1.75 min.

25 **Example 114**

4-Cyclopentyl-N-[(2s,5r)-5-hydroxyadamantan-2-yl]-2-thiomorpholin-4-ylpyrimidine-5-

carboxamide

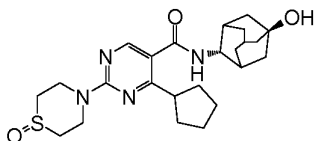


Prepared from Intermediate 86 by the same process used for Example 36

¹H NMR (400.13 MHz, DMSO-d₆) δ 1.32 (2H, d), 1.56 (1H, d), 1.61 (5H, d), 1.69 - 1.75 (2H, m), 1.72 - 1.76 (3H, m), 1.77 - 1.79 (1H, m), 1.85 (2H, d), 1.89 (1H, d), 1.93 (1H, s), 1.98 (1H, s), 2.02 (2H, s), 2.57 - 2.60 (4H, m), 3.41 - 3.49 (1H, m), 3.90 (1H, t), 4.07 - 4.10 (4H, m), 4.37 (1H, s), 8.07 (1H, d), 8.22 (1H, s)
m/z (ESI+) (M+H)⁺ = 443; HPLC t_R = 2.41 min.

10 Example 115

4-Cyclopentyl-N-[(2r,5s)-5-hydroxyadamantan-2-yl]-2-(1-oxo-1,4-thiazinan-4-yl)pyrimidine-5-carboxamide

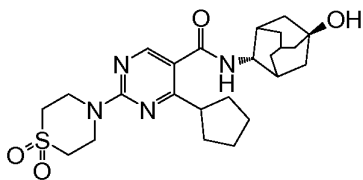


Prepared from Example 114 by the same process used for Example 36

¹H NMR (400.132 MHz, CDCl₃) δ 1.47 (1H, s), 1.58 (2H, d), 1.64 - 1.75 (4H, m), 1.75 - 1.90 (8H, m), 1.91 - 2.02 (4H, m), 2.18 (1H, s), 2.24 (2H, s), 2.69 - 2.78 (2H, m), 2.83 (2H, d), 3.56 (1H, quintet), 4.15 - 4.25 (3H, m), 4.58 (2H, d), 5.92 (1H, d), 8.34 (1H, s)
m/z (ESI+) (M+H)⁺ = 459; HPLC t_R = 1.59 min.

20 Example 116

4-Cyclopentyl-2-(1,1-dioxo-1,4-thiazinan-4-yl)-N-[(2r,5s)-5-hydroxyadamantan-2-yl]pyrimidine-5-carboxamide

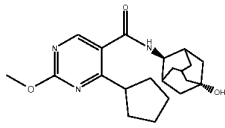
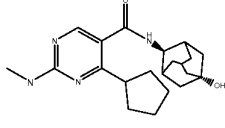
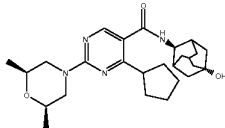


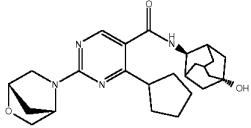
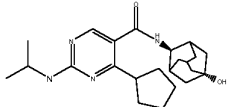
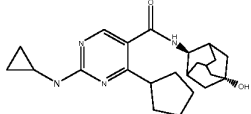
Prepared from Example 114 by the same process used for Example 37

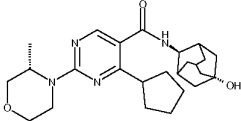
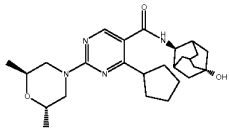
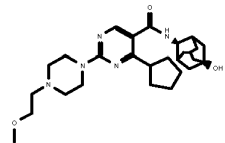
¹H NMR (400.132 MHz, CDCl₃) δ 1.40 (1H, s), 1.59 (2H, d), 1.64 - 1.74 (4H, m), 1.76 - 1.87 (8H, m), 1.90 - 2.03 (4H, m), 2.19 (1H, s), 2.25 (2H, s), 3.03 (4H, t), 3.55 (1H, quintet), 4.20 (1H, d), 4.37 - 4.42 (4H, m), 5.89 (1H, d), 8.35 (1H, s)
m/z (ESI+) (M+H)⁺ = 475; HPLC t_R = 1.87 min.

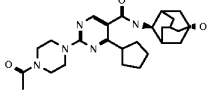
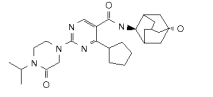
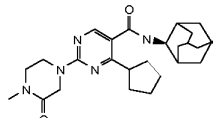
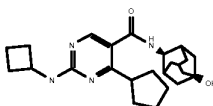
5

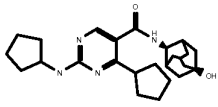
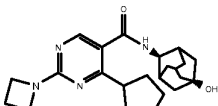
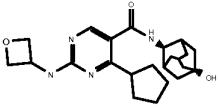
The following Examples were prepared in a similar manner to Example 46, using Intermediate 86 and an appropriate starting material:

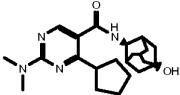
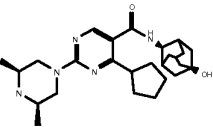
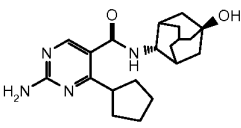
Structure	Ex	Name	¹ H NMR δ	MS m/e MH ⁺
	117	4-cyclopentyl-N-[(2r,5s)-5-hydroxyadamantan-2-yl]-2-methoxypyrimidine-5-carboxamide	¹ H NMR (400.132 MHz, CDCl ₃) δ 1.37 (1H, s), 1.57 - 1.62 (2H, m), 1.66 - 1.74 (4H, m), 1.78 - 2.04 (12H, m), 2.16 - 2.29 (3H, m), 3.51 - 3.58 (1H, m), 4.02 (3H, s), 4.18 - 4.24 (1H, m), 5.91 (1H, d), 8.48 (1H, s)	m/z (ESI+) (M+H) ⁺ = 372; HPLC t _R = 1.78 min
	118	4-cyclopentyl-N-[(2r,5s)-5-hydroxyadamantan-2-yl]-2-methylaminopyrimidine-5-carboxamide	¹ H NMR (400.132 MHz, CDCl ₃) δ 1.37 (1H, s), 1.56 - 1.60 (2H, m), 1.63 - 1.73 (4H, m), 1.77 - 1.97 (12H, m), 2.16 - 2.27 (3H, m), 3.02 (3H, d), 3.50 - 3.57 (1H, m), 4.15 - 4.20 (1H, m), 5.17 (1H, d), 5.86 (1H, d), 8.29 (1H, s)	m/z (ESI+) (M+H) ⁺ = 371; HPLC t _R = 1.74 min
	119	4-cyclopentyl-2-[(2S,6R)-2,6-dimethylmorpholin-4-yl]-N-[(2r,5s)-5-hydroxyadamantan-2-yl]-2-methylaminopyrimidine-5-carboxamide	¹ H NMR (400.132 MHz, CDCl ₃) δ 1.26 (6H, d), 1.37 (1H, s), 1.55 - 1.60 (2H, m), 1.64 - 1.71 (4H, m), 1.78 - 1.98 (12H, m), 2.15 - 2.26 (3H, m), 2.56 - 2.63 (2H, m), 3.50 - 3.57 (1H, m), 4.15 - 4.20 (1H, m), 5.17 (1H, d), 5.86 (1H, d), 8.29 (1H, s)	m/z (ESI+) (M+H) ⁺ = 455; HPLC t _R = 2.28 min

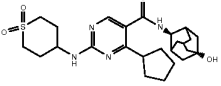
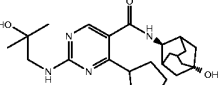
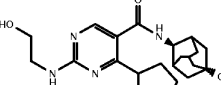
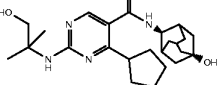
		hydroxyadaman-2-yl]pyrimidine-5-carboxamide	3.53 - 3.65 (3H, m), 4.14 - 4.19 (1H, m), 4.62 (2H, d), 5.87 (1H, d), 8.30 (1H, s)	min
	120	4-cyclopentyl-N-[(2r,5s)-5-hydroxyadaman-2-yl]-2-[(1s,4s)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl]pyrimidine-5-carboxamide	¹ H NMR (400.132 MHz, CDCl ₃) δ 1.37 (1H, s), 1.55 - 1.61 (2H, m), 1.63 - 1.72 (4H, m), 1.76 - 1.99 (14H, m), 2.14 - 2.26 (3H, m), 3.53 - 3.63 (3H, m), 3.83 - 3.91 (2H, m), 4.15 - 4.21 (1H, m), 4.71 (1H, s), 5.09 (1H, s), 5.85 (1H, d), 8.31 (1H, s)	m/z (ESI+) (M+H) ⁺ = 439; HPLC t _R = 1.85 min
	121	4-cyclopentyl-N-[(2r,5s)-5-hydroxyadaman-2-yl]-2-(propan-2-ylamino)pyrimidine-5-carboxamide	¹ H NMR (400.132 MHz, CDCl ₃) δ 1.25 (6H, d), 1.37 (1H, s), 1.56 - 1.61 (2H, m), 1.64 - 1.73 (4H, m), 1.77 - 1.97 (12H, m), 2.13 - 2.27 (3H, m), 3.50 - 3.57 (1H, m), 4.10 - 4.22 (2H, m), 5.06 (1H, d), 5.86 (1H, d), 8.27 (1H, s)	m/z (ESI+) (M+H) ⁺ = 399; HPLC t _R = 2.14 min
	122	4-cyclopentyl-2-(cyclopropylamino)-N-[(2r,5s)-5-hydroxyadaman-2-yl]pyrimidine-5-carboxamide	¹ H NMR (400.132 MHz, CDCl ₃) δ 0.54 - 0.58 (2H, m), 0.79 - 0.89 (2H, m), 1.37 (1H, s), 1.55 - 1.60 (2H, m), 1.62 - 1.72 (4H, m), 1.77 - 1.98 (12H, m), 2.14 - 2.25 (3H, m), 2.76 - 2.82 (1H, m), 3.52 - 3.56 (1H, m), 4.16 - 4.21 (1H, s)	m/z (ESI+) (M+H) ⁺ = 397; HPLC t _R = 1.93 min

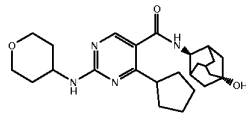
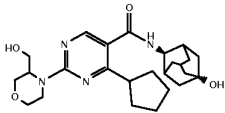
		5-carboxamide	m), 5.39 (1H, s), 5.87 (1H, d), 8.35 (1H, s)	
	123	4-cyclopentyl-N-[(2r,5s)-5-hydroxyadamantan-2-yl]-2-[(3S)-3-methylmorpholin-4-yl]pyrimidine-5-carboxamide	¹ H NMR (400.132 MHz, CDCl ₃) δ 1.29 (3H, d), 1.35 (1H, s), 1.56 - 1.60 (2H, m), 1.62 - 1.73 (4H, m), 1.76 - 1.99 (12H, m), 2.14 - 2.25 (3H, m), 3.21 - 3.31 (1H, m), 3.51 - 3.63 (2H, m), 3.68 - 3.80 (2H, m), 3.96 - 4.00 (1H, m), 4.15 - 4.20 (1H, m), 4.40 (1H, d), 4.73 (1H, d), 5.85 (1H, d), 8.33 (1H, s)	m/z (ESI+) (M+H) ⁺ = 441; HPLC t _R = 2.12 min
	124	4-cyclopentyl-2-[(2S,6S)-2,6-dimethylmorpholin-4-yl]-N-[(2r,5s)-5-hydroxyadamantan-2-yl]pyrimidine-5-carboxamide	¹ H NMR (400.132 MHz, CDCl ₃) δ 1.22 (6H, d), 1.36 (1H, s), 1.55 - 1.60 (2H, m), 1.62 - 1.72 (4H, m), 1.78 - 1.97 (12H, m), 2.14 - 2.25 (3H, m), 3.53 - 3.66 (3H, m), 3.94 (2H, d), 4.03 - 4.09 (2H, m), 4.15 - 4.20 (1H, m), 5.87 (1H, d), 8.33 (1H, s)	m/z (ESI+) (M+H) ⁺ = 455; HPLC t _R = 2.20 min
	125	4-cyclopentyl-N-[(2r,5s)-5-hydroxyadamantan-2-yl]-2-[4-(2-methoxyethyl)piperazin-1-yl]pyrimidine-5-carboxamide	¹ H NMR (400.132 MHz, CDCl ₃) δ 1.31 (1H, s), 1.45 - 1.53 (2H, m), 1.54 - 1.67 (4H, m), 1.68 - 1.93 (12H, m), 2.09 (1H, s), 2.16 (2H, s), 2.47 (4H, t), 2.55 (2H, t), 3.30 (3H, s), 3.45 - 3.53 (3H, m), 3.83 (4H, t), 4.10 (1H, d), 5.78 (1H, d), 8.24 (1H, s)	m/z (ESI+) (M+H) ⁺ = 484; HPLC t _R = 1.13 min.

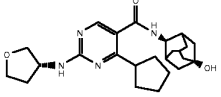
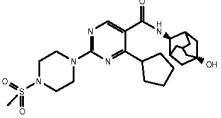
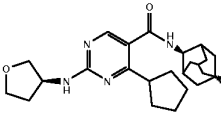
	126	2-(4-acetylpiperazin-1-yl)-4-cyclopentyl-N-[(2r,5s)-5-hydroxyadamantan-2-yl]pyrimidine-5-carboxamide	1H NMR (400.13 MHz, DMSO-d6) δ 1.30 - 1.33 (2H, m), 1.53 - 1.63 (7H, m), 1.69 - 1.93 (11H, m), 2.04 (5H, s), 3.49 - 3.52 (4H, m), 3.72 - 3.74 (2H, m), 3.80 (2H, t), 3.90 (1H, t), 4.38 (1H, s), 8.06 (1H, d), 8.23 (1H, s)	m/z (ESI+) (M+H) ⁺ = 468; HPLC t_R = 1.78 min.
	127	4-cyclopentyl-N-[(2r,5s)-5-hydroxyadamantan-2-yl]-2-(3-oxo-4-propan-2-ylpiperazin-1-yl)pyrimidine-5-carboxamide	1H NMR (400.13 MHz, DMSO-d6) δ 1.07 (6H, d), 1.30 - 1.33 (2H, m), 1.59 (6H, t), 1.69 - 2.03 (13H, m), 3.33 (2H, q), 3.42 - 3.50 (1H, m), 3.89 - 3.94 (3H, m), 4.24 (2H, s), 4.38 (1H, s), 4.63 - 4.69 (1H, m), 8.08 (1H, d), 8.25 (1H, s)	m/z (ESI+) (M+H) ⁺ = 482; HPLC t_R = 2.01 min.
	128	4-cyclopentyl-N-[(2r,5s)-5-hydroxyadamantan-2-yl]-2-(4-methyl-3-oxopiperazin-1-yl)pyrimidine-5-carboxamide	1H NMR (400.13 MHz, DMSO-d6) δ 1.30 - 1.33 (2H, m), 1.52 - 1.64 (6H, m), 1.69 - 1.93 (10H, m), 1.98 - 2.03 (3H, m), 2.88 (3H, s), 3.39 (2H, t), 3.44 - 3.50 (1H, m), 3.90 (1H, t), 3.99 - 4.06 (2H, m), 4.26 (2H, s), 4.38 (1H, s), 8.09 (1H, d), 8.25 (1H, s)	m/z (ESI+) (M+H) ⁺ = 454; HPLC t_R = 1.74 min.
	129	4-cyclopentyl-2-(cyclobutylamino)-N-[(2r,5s)-5-hydroxyadamantan-2-yl]pyrimidine-5-carboxamide	1H NMR (400.132 MHz, CDCl3) δ 1.41 (1H, s), 1.57 (2H, d), 1.61 - 2.00 (18H, m), 2.17 (1H, s), 2.23 (2H, s), 2.37	m/z (ESI+) (M+H) ⁺ = 411;

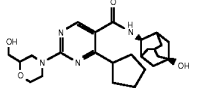
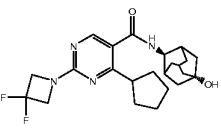
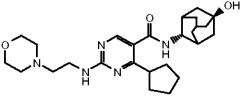
		5-hydroxyadaman-2-yl]pyrimidine-5-carboxamide	- 2.46 (2H, m), 3.52 (1H, t), 4.17 (1H, d), 4.44 (1H, q), 5.37 (1H, d), 5.86 (1H, d), 8.26 (1H, s)	HPLC t_R = 2.13 min.
	130	4-cyclopentyl-2-((cyclopentylamino)-N-[(2r,5s)-5-hydroxyadaman-2-yl]pyrimidine-5-carboxamide	¹ H NMR (400.132 MHz, CDCl ₃) δ 1.26 (1H, s), 1.38 - 1.53 (3H, m), 1.57 (2H, d), 1.61 - 2.00 (19H, m), 2.06 (2H, sextet), 2.17 (1H, s), 2.23 (2H, s), 3.53 (1H, t), 4.17 (1H, d), 4.27 (1H, q), 5.22 (1H, d), 5.87 (1H, d), 8.28 (1H, s)	m/z (ESI+) (M+H) ⁺ = 425; HPLC t_R = 2.26 min.
	131	2-(azetidin-1-yl)-4-cyclopentyl-N-[(2r,5s)-5-hydroxyadaman-2-yl]pyrimidine-5-carboxamide	¹ H NMR (400.132 MHz, CDCl ₃) δ 1.40 (1H, s), 1.56 (2H, d), 1.60 - 1.73 (4H, m), 1.74 - 1.98 (12H, m), 2.17 (1H, s), 2.23 (2H, s), 2.37 (2H, quintet), 3.53 (1H, quintet), 4.16 (5H, m), 5.85 (1H, d), 8.29 (1H, s)	m/z (ESI+) (M+H) ⁺ = 397; HPLC t_R = 2.06 min.
	132	4-cyclopentyl-N-[(2r,5s)-5-hydroxyadaman-2-yl]-2-(oxetan-3-ylamino)pyrimidine-5-carboxamide	¹ H NMR (400.132 MHz, CDCl ₃) δ 1.25 (1H, s), 1.57 (2H, d), 1.62 - 2.01 (16H, m), 2.16 (1H, s), 2.24 (2H, s), 3.52 (1H, quintet), 4.17 (1H, d), 4.59 (2H, t), 4.97 (2H, t), 5.10 (1H, q), 5.64 (1H, d), 5.86 (1H, d), 8.27 (1H, s)	m/z (ESI+) (M+H) ⁺ = 413; HPLC t_R = 1.68 min.

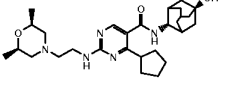
	133	4-cyclopentyl-2-dimethylamino-N-[(2r,5s)-5-hydroxyadamantan-2-yl]pyrimidine-5-carboxamide	1H NMR (400.132 MHz, CDCl ₃) δ 1.39 (1H, s), 1.52 - 1.60 (2H, m), 1.62 - 2.02 (16H, m), 2.16 (1H, s), 2.23 (2H, s), 3.20 (6H, s), 3.59 (1H, quintet), 4.17 (1H, d), 5.86 (1H, d), 8.32 (1H, s)	m/z (ESI+) (M+H) ⁺ = 385; HPLC t _R = 1.75 min
	134	4-cyclopentyl-2-[(3S,5R)-3,5-dimethylpiperazin-1-yl]-N-[(2r,5s)-5-hydroxyadamantan-2-yl]pyrimidine-5-carboxamide	1H NMR (400.132 MHz, CDCl ₃) δ 1.15 (6H, d), 1.48 - 2.02 (20H, m), 2.16 (1H, s), 2.23 (2H, s), 2.46 (2H, d), 2.80 - 2.90 (2H, m), 3.57 (1H, quintet), 4.17 (1H, d), 4.70 (2H, d), 5.86 (1H, d), 8.30 (1H, s)	m/z (ESI+) (M+H) ⁺ = 454; HPLC t _R = 1.95 min.
	135	2-amino-4-cyclopentyl-N-[(2r,5s)-5-hydroxyadamantan-2-yl]pyrimidine-5-carboxamide	1H NMR (400.13 MHz, DMSO-d ₆) δ 1.31 (2H, d), 1.51 - 1.57 (1H, m), 1.52 - 1.55 (1H, m), 1.59 (3H, s), 1.63 (1H, s), 1.68 (1H, s), 1.70 - 1.86 (7H), 1.92 (2H, d), 1.97 (1H, s), 2.02 (2H, s), 3.40 (1H, q), 3.86 - 3.90 (1H, m), 4.38 (1H, s), 6.68 (2H, s), 8.02 (1H, d), 8.08 (1H, d)	m/z (ESI+) (M+H) ⁺ = 357; HPLC t _R = 1.59 min.
	136	4-cyclopentyl-2-[(1,1-dioxothian-4-	1H NMR (400.132 MHz, CDCl ₃) δ 1.38 (1H, s), 1.57 - 1.61 (2H, m), 1.65 - 1.72 (4H,	m/z (ES+) (M+H) ⁺

		yl)amino]-N-[(2r,5s)-5-hydroxyadaman-2-yl]pyrimidine-5-carboxamide	m), 1.78 - 1.83 (8H, m), 1.90 - 2.01 (4H, m), 2.16 - 2.27 (5H, m), 2.39 - 2.47 (2H, m), 3.09 - 3.16 (4H, m), 3.47 - 3.55 (1H, m), 4.08 - 4.22 (2H, m), 5.17 (1H, d), 5.87 (1H, d), 8.28 (1H, s)	= 489; HPLC t_R = 1.71 min.
	137	4-cyclopentyl-N-[(2r,5s)-5-hydroxyadaman-2-yl]-2-[(2-hydroxy-2-methylpropyl)amino]pyrimidine-5-carboxamide	^1H NMR (400.132 MHz, $CDCl_3$) δ 1.26 (6H, s), 1.39 (1H, s), 1.58 - 1.62 (2H, m), 1.64 - 1.72 (4H, m), 1.76 - 1.87 (8H, m), 1.90 - 1.99 (4H, m), 2.18 (1H, s), 2.23 (2H, s), 3.48 (2H, d), 3.50 - 3.58 (2H, m), 4.14 - 4.21 (1H, m), 5.63 (1H, t), 5.86 (1H, d), 8.25 (1H, s)	m/z (ES+) (M+H)+ = 429; HPLC t_R = 1.72 min.
	138	4-cyclopentyl-N-[(2r,5s)-5-hydroxyadaman-2-yl]-2-(2-hydroxyethylamino)pyrimidine-5-carboxamide	^1H NMR (400.132 MHz, $CDCl_3$) δ 1.42 (1H, s), 1.54 - 1.57 (2H, m), 1.63 - 1.74 (4H, m), 1.77 - 1.85 (8H, m), 1.91 - 2.01 (4H, m), 2.17 (1H, s), 2.24 (2H, s), 3.43 (1H, s), 3.47 - 3.55 (1H, m), 3.59 - 3.64 (2H, m), 3.81 - 3.86 (2H, m), 4.14 - 4.20 (1H, m), 5.64 (1H, t), 5.91 (1H, d), 8.25 (1H, s)	m/z (ES+) (M+H)+ = 401; HPLC t_R = 1.53 min.
	139	4-cyclopentyl-N-[(2r,5s)-5-hydroxyadaman-2-yl]-2-	^1H NMR (400.132 MHz, $CDCl_3$) δ 1.39 (6H, s), 1.41 (1H, s), 1.58 - 1.60 (2H, m), 1.63 - 1.73 (4H, m), 1.77 -	m/z (ES+) (M+H)+ = 429;

		[(1-hydroxy-2-methylpropan-2-yl)amino]pyrimidine-5-carboxamide	1.86 (8H, m), 1.91 - 2.01 (4H, m), 2.18 (1H, s), 2.24 (2H, s), 3.50 (1H, quintet), 3.70 (2H, s), 4.14 - 4.20 (1H, m), 5.38 (1H, s), 5.55 (1H, s), 5.89 (1H, d), 8.22 (1H, s)	HPLC t_R = 1.80 min.
	140	4-cyclopentyl-N-[(2r,5s)-5-hydroxyadamantan-2-yl]-2-(oxan-4-ylamino)pyrimidine-5-carboxamide	¹ H NMR (400.132 MHz, CDCl ₃) δ 1.01 (1H, s), 1.45 (1H, s), 1.53 - 1.57 (3H, m), 1.65 - 1.74 (4H, m), 1.77 - 1.88 (8H, m), 1.91 - 1.97 (4H, m), 1.99 - 2.08 (2H, m), 2.18 (1H, s), 2.24 (2H, s), 3.51 - 3.57 (3H, m), 3.96 - 4.10 (3H, m), 4.15 - 4.20 (1H, m), 5.16 (1H, d), 5.87 (1H, d), 8.27 (1H, s)	m/z (ES+) (M+H) ⁺ = 441; HPLC t_R = 1.84 min.
	141	4-cyclopentyl-N-[(2r,5s)-5-hydroxyadamantan-2-yl]-2-[3-(hydroxymethyl)morpholin-4-yl]pyrimidine-5-carboxamide	¹ H NMR (400.132 MHz, CDCl ₃) δ 1.26 (1H, s), 1.57 - 1.60 (2H, m), 1.63 - 1.73 (4H, m), 1.77 - 1.86 (9H, m), 1.91 - 2.02 (4H, m), 2.17 (1H, s), 2.24 (2H, s), 3.30 - 3.37 (1H, m), 3.54 - 3.61 (2H, m), 3.64 - 3.69 (1H, m), 3.90 - 4.08 (4H, m), 4.16 - 4.20 (1H, m), 4.54 (1H, d), 4.71 - 4.78 (1H, m), 5.87 (1H, d), 8.32 (1H, s)	m/z (ES+) (M+H) ⁺ = 457; HPLC t_R = 1.73 min.
	142	4-cyclopentyl-N-[(2r,5s)-5-	¹ H NMR (400.132 MHz, CDCl ₃) δ 1.55 - 1.61 (4H, m),	m/z (ES+)

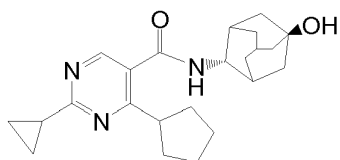
		hydroxyadamantan-2-yl]-2-[[[(3R)-oxolan-3-yl]amino]pyrimidine-5-carboxamide	1.64 - 1.73 (4H, m), 1.76 - 1.97 (12H, m), 2.17 (1H, s), 2.24 (2H, s), 2.28 - 2.37 (1H, m), 3.53 (1H, quintet), 3.71 (1H, dd), 3.83 - 3.89 (1H, m), 3.94 - 4.02 (2H, m), 4.16 - 4.20 (1H, m), 4.54 - 4.62 (1H, m), 5.36 (1H, d), 5.87 (1H, d), 8.28 (1H, s)	(M+H) ⁺ = 427; HPLC t _R = 1.76 min.
	143	4-cyclopentyl-N-[(2r,5s)-5-hydroxyadamantan-2-yl]-2-(4-methylsulfonylpiperazin-1-yl)pyrimidine-5-carboxamide	¹ H NMR (400.132 MHz, CDCl ₃) δ 1.38 (1H, s), 1.56 - 1.60 (2H, m), 1.65 - 1.72 (4H, m), 1.77 - 1.86 (8H, m), 1.91 - 1.99 (4H, m), 2.17 (1H, s), 2.24 (2H, s), 2.79 (3H, s), 3.28 (4H, t), 3.56 (1H, quintet), 4.01 (4H, t), 4.15 - 4.20 (1H, m), 5.87 (1H, d), 8.33 (1H, s)	m/z (ES ⁺) (M+H) ⁺ = 504; HPLC t _R = 2.00 min.
	144	4-cyclopentyl-N-[(2r,5s)-5-hydroxyadamantan-2-yl]-2-[[[(3S)-oxolan-3-yl]amino]pyrimidine-5-carboxamide	¹ H NMR (400.132 MHz, CDCl ₃) δ 1.55 - 1.60 (4H, m), 1.63 - 1.73 (4H, m), 1.77 - 1.97 (12H, m), 2.17 (1H, s), 2.24 (2H, s), 2.28 - 2.37 (1H, m), 3.53 (1H, quintet), 3.71 (1H, dd), 3.83 - 3.89 (1H, m), 3.94 - 4.02 (2H, m), 4.15 - 4.20 (1H, m), 4.54 - 4.63 (1H, m), 5.37 (1H, d), 5.87 (1H, d), 8.28 (1H, s)	m/z (ES ⁺) (M+H) ⁺ = 427; HPLC t _R = 1.79 min.
	145	4-cyclopentyl-N-[(2r,5s)-5-	¹ H NMR (400.132 MHz, CDCl ₃) δ 1.55 - 1.60 (2H, m),	m/z (ES ⁺)

		hydroxyadaman- tan-2-yl]-2- [2- (hydroxymethy- l)morpholin-4- yl]pyrimidine- 5-carboxamide	1.63 - 1.73 (5H, m), 1.77 - 1.87 (8H, m), 1.91 - 1.97 (4H, m), 2.16 (1H, s), 2.23 (2H, s), 2.89 - 2.97 (2H, m), 3.06 - 3.15 (1H, m), 3.52 - 3.79 (5H, m), 4.00 - 4.06 (1H, m), 4.17 - 4.19 (1H, m), 4.58 (2H, d), 5.90 (1H, d), 8.32 (1H, s)	(M+H)+ = 457; HPLC t _R = 1.73 min.
	146	4-cyclopentyl- 2-(3,3- difluoroazetidi- n-1-yl)-N- [(2r,5s)-5- hydroxyadama- ntan-2- yl]pyrimidine- 5-carboxamide	¹ H NMR (400.132 MHz, CDCl ₃) δ 1.53 - 1.60 (2H, m), 1.62 - 1.74 (5H, m), 1.77 - 1.88 (8H, m), 1.91 - 1.97 (4H, m), 2.17 (1H, s), 2.24 (2H, s), 3.53 (1H, quintet), 4.15 - 4.20 (1H, m), 4.46 (4H, t), 5.92 (1H, d), 8.33 (1H, s)	m/z (ES+) (M+H)+ = 433; HPLC t _R = 2.21 min.
	147	4-cyclopentyl- N-[(2r,5s)-5- hydroxytricycl- o[3.3.1.1.1,3,7]de- c-2-yl]-2-[(2- morpholin-4- ylethyl)amino] pyrimidine-5- carboxamide	¹ H NMR (400.13 MHz, DMSO-d ₆) δ 1.30 - 1.37 (2H, m), 1.54 - 1.57 (2H, m), 1.60 - 1.63 (3H, m), 1.68 - 1.73 (3H, m), 1.82 (2H, d), 1.92 (2H, d), 1.98 (1H, s), 2.02 (2H, s), 2.39 (4H, t), 2.45 (2H, t), 3.16 (4H, d), 3.40 (2H, q), 3.56 (4H, t), 3.88 (1H, m), 4.06 (1H, q), 4.38 (1H, s), 7.09 (1H, s), 8.01 (1H, d), 8.12 (1H, s)	m/z (ES+) (M+H)+ = 470; HPLC t _R = 1.68 min.
	148	4-cyclopentyl- 2-(2- [(2R,6S)-2,6-	¹ H NMR (400.13 MHz, DMSO-d ₆) δ 1.03 (6H, d), 1.31 (2H, d), 1.55 - 1.57 (2H,	m/z (ES+) (M+2H)

	dimethylmorpholin-4-yl]ethyl} amino)-N-[(2r,5s)-5-hydroxytricyclo[3.3.1.1 ^{3,7}]dec-2-yl]pyrimidine-5-carboxamide	m), 1.63 (6H, m), 1.70 – 1.73 (4H, m), 1.75 - 1.84 (4H, m), 1.92 (2H, d), 2.00 (3H, d), 2.42 (2H, t), 2.75 (2H, d), 3.37 - 3.45 (3H, m), 3.50 - 3.57 (2H, m), 3.88 (1H, t), 4.37 (1H, s), 7.10 (1H, s), 8.01 (1H, d), 8.12 (1H, s)	+ = 499; HPLC t_R = 1.91 min.
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Example 149

4-Cyclopentyl-2-cyclopropyl-N-[(2r,5s)-5-hydroxyadamantan-2-yl]pyrimidine-5-carboxamide



5

Prepared from Intermediate 88 by the same process used for Example 4

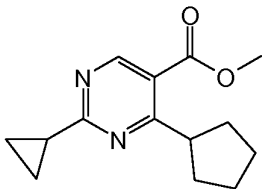
¹H NMR (400.132 MHz, CDCl₃) δ 0.81 - 0.91 (1H, m), 1.02 - 1.09 (2H, m), 1.11 - 1.19 (2H, m), 1.53 - 1.62 (4H, m), 1.62 - 1.73 (4H, m), 1.77 - 2.01 (11H, m), 2.12 - 2.19 (1H, m), 2.22 - 2.29 (2H, m), 3.41 - 3.54 (1H, m), 4.16 - 4.26 (1H, m), 5.85 - 5.98 (1H, m), 8.45 (1H, s)

10

m/z (ESI⁺) (M+H)⁺ = 382.42; HPLC t_R = 2.17 min.

Intermediate 87

methyl 4-cyclopentyl-2-cyclopropylpyrimidine-5-carboxylate



15

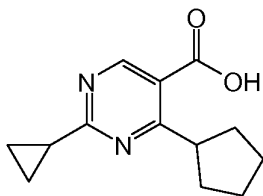
Prepared by the same process used for Intermediate 2 from Methyl 2-(cyclopentanecarbonyl)-3-(dimethylamino)acrylate

¹H NMR (400.132 MHz, CDCl₃) δ 1.06 - 1.12 (2H, m), 1.16 - 1.22 (2H, m), 1.64 - 1.74 (2H, m), 1.76 - 1.90 (4H, m), 1.91 - 2.02 (2H, m), 2.21 - 2.29 (1H, m), 3.91 (3H, s), 3.92 - 4.02 (1H, m), 8.89 (1H, s)
m/z (ESI⁺) (M+H)⁺ = 247.34; HPLC t_R = 2.97 min.

5

Intermediate 88

4-cyclopentyl-2-cyclopropylpyrimidine-5-carboxylic acid

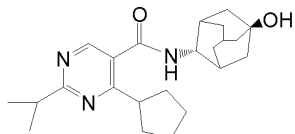


Prepared from Intermediate 87 by the same process used for Intermediate 29

10 ¹H NMR (400.132 MHz, CDCl₃) δ 1.08 - 1.17 (2H, m), 1.18 - 1.29 (2H, m), 1.61 - 1.76 (2H, m), 1.76 - 1.93 (4H, m), 1.94 - 2.06 (2H, m), 2.23 - 2.34 (1H, m), 4.02 - 4.14 (1H, m), 9.03 (1H, s)
m/z (ESI⁺) (M+H)⁺ = 233.33; HPLC t_R = 1.07 min.

15 **Example 150**

4-Cyclopentyl-N-[(2r,5s)-5-hydroxyadamantan-2-yl]-2-propan-2-ylpyrimidine-5-carboxamide

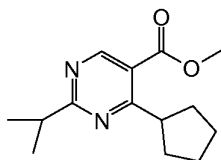


Prepared from Intermediate 90 by the same process used for Example 4

20 ¹H NMR (400.132 MHz, CDCl₃) δ 1.33 (6H, d), 1.53 - 1.63 (4H, m), 1.64 - 1.74 (4H, m), 1.77 - 2.05 (11H, m), 2.14 - 2.22 (1H, m), 2.23 - 2.30 (2H, m), 3.12 - 3.25 (1H, m), 3.44 - 3.55 (1H, m), 4.18 - 4.28 (1H, m), 5.87 - 6.02 (1H, m), 8.55 (1H, s)
m/z (ESI⁺) (M+H)⁺ = 384.44; HPLC t_R = 2.24 min.

25 **Intermediate 89**

methyl 4-cyclopentyl-2-isopropylpyrimidine-5-carboxylate

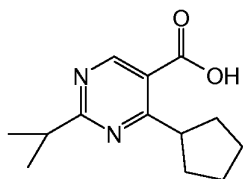


Prepared by the same process used for Intermediate 2 from Methyl 2-(cyclopentanecarbonyl)-3-(dimethylamino)acrylate

¹H NMR (400.132 MHz, CDCl₃) δ 1.34 (6H, d), 1.64 - 1.76 (2H, m), 1.79 - 2.03 (6H, m),
 3.14 - 3.27 (1H, m), 3.92 (3H, s), 3.94 - 4.02 (1H, m), 8.97 (1H, s)
 m/z (ESI⁺) (M+H)⁺ = 249.33; HPLC t_R = 3.10 min.

Intermediate 90

4-cyclopentyl-2-isopropylpyrimidine-5-carboxylic acid

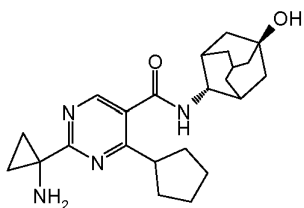


Prepared from Intermediate 89 by the same process used for Intermediate 29

¹H NMR (400.132 MHz, CDCl₃) δ 1.36 (6H, d), 1.64 - 1.77 (2H, m), 1.80 - 2.09 (6H, m),
 3.19 - 3.30 (1H, m), 4.05 - 4.17 (1H, m), 9.14 (1H, s)
 m/z (ESI⁺) (M+H)⁺ = 235.30; HPLC t_R = 1.05 min.

Example 151

2-(1-Aminocyclopropyl)-4-cyclopentyl-N-[(2r,5s)-5-hydroxyadamantan-2-yl]pyrimidine-5-carboxamide



benzyl N-[1-[4-cyclopentyl-5-[(5-hydroxy-2-adamantyl)carbamoyl]pyrimidin-2-yl]cyclopropyl]carbamate (Intermediate 93, 174.4 mg, 0.33 mmol) and palladium, 10% wt on carbon (35.9 mg, 0.03 mmol) in ethanol (25 mL) was stirred under an atmosphere of hydrogen at room temperature and normal pressure over night. The reaction mixture was

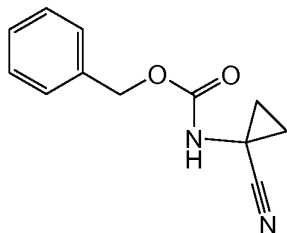
filtered through celite and the solvent volume reduced. The crude product was purified by preparative HPLC (Phenomenex Luna C18 100A column, 5 μ silica, 30 mm diameter, 100 mm length), using decreasingly polar mixtures of water (containing 0.1% NH₃) and MeCN as eluents. Fractions containing the desired compound were evaporated to dryness to afford
5 2-(1-aminocyclopropyl)-4-cyclopentyl-N-[(2*r*,5*s*)-5-hydroxyadamantan-2-yl]pyrimidine-5-carboxamide (60.3 mg, 46.3 %) as a white solid.

¹H NMR (400.13 MHz, DMSO-*d*₆) δ 1.05 (2H, q), 1.27 (2H, q), 1.33 (2H, d), 1.56 - 1.62 (4H, m), 1.64 (1H, s), 1.69 - 1.71 (1H, m), 1.72 - 1.89 (10H, m), 1.91 (1H, s), 1.98 (1H, s), 2.04 (2H, s), 2.44 (1H, s), 3.34 - 3.42 (1H, m), 3.93 - 3.97 (1H, m), 4.40 (1H, s), 8.35 (1H,
10 d), 8.45 (1H, s)

m/z (ESI+) (M+H)⁺ = 397; HPLC *t_R* = 1.67 min.

Intermediate 177

benzyl 1-cyanocyclopropylcarbamate



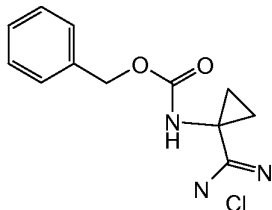
Benzyl chloroformate (4.76 mL, 33.49 mmol) was added dropwise to 1-aminocyclopropanecarbonitrile (2.5 g, 30.45 mmol) and triethylamine (8.48 mL, 60.90 mmol) in DCM (40 mL) at 0°C over a period of 10 minutes under nitrogen. The resulting solution was stirred at room temperature over night. The reaction mixture was diluted with
20 DCM (100 mL), and washed sequentially with saturated brine (2x75 mL). The organic layer was dried over MgSO₄, filtered and evaporated to afford crude. The crude product was purified by flash silica chromatography, elution gradient 0 to 40% EtOAc in isohexane. Pure fractions were evaporated to dryness to afford benzyl 1-cyanocyclopropylcarbamate (1.570 g, 23.84 %) as a white solid.

¹H NMR (400.13 MHz, CDCl₃) δ 1.27 - 1.31 (2H, m), 1.51 - 1.56 (2H, m), 5.17 (2H, s), 5.38 (1H, s), 7.32 - 7.39 (5H, m)

m/z (ESI-) (M-H)⁻ = 215; HPLC *t_R* = 1.88 min.

Intermediate 178

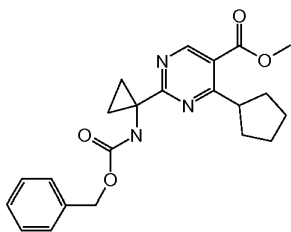
benzyl 1-carbamimidoylcyclopropylcarbamate hydrochloride



benzyl 1-cyanocyclopropylcarbamate (Intermediate 177, 0.84 g, 3.88 mmol) in dioxane (5
 5 mL) was added to a 4M HCl solution of dioxane (2 mL). The reaction was stirred at room
 temperature over night. The intermediate was not UV active but the mass peak could be
 seen in LC/MS. TLC indicated the reaction had gone to completion. The solvent volume
 was evaporated to dryness. The residue was re dissolved in methanol (3 mL) and 7M NH₃
 saturated in MeOH (2 mL) was added. The reaction was stirred at room temperature for 2
 10 hours. The solvent volume was evaporated to dryness and used in the next reaction step
 without further purification or characterisation.

¹H NMR (400.13 MHz, DMSO-d₆) δ 0.85 - 0.88 (2H, m), 1.20 - 1.23 (2H, m), 5.02 (2H,
 s), 7.03 (1H, s), 7.16 (1H, s), 7.27 - 7.37 (5H, m), 7.78 (1H, s)

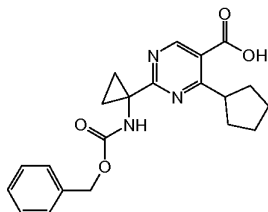
m/z (ESI+) (M+H)⁺ = 234; HPLC t_R = 1.61 min

Intermediate 91methyl 2-(1-(benzyloxycarbonylamino)cyclopropyl)-4-cyclopentylpyrimidine-5-
 carboxylate

Prepared by the same process used for Intermediate 2 from Methyl 2-
 (cyclopentanecarbonyl)-3-(dimethylamino)acrylate and benzyl 1-
 carbamimidoylcyclopropylcarbamate hydrochloride (Intermediate 178)
 m/z (ESI+) (M+H)⁺ = 396; HPLC t_R = 2.93 min.

Intermediate 92

2-(1-(benzyloxycarbonylamino)cyclopropyl)-4-cyclopentylpyrimidine-5-carboxylic acid

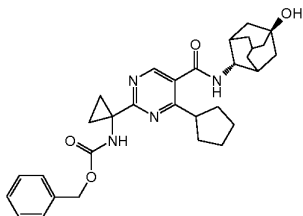


Prepared from Intermediate 91 by the same process used for Intermediate 29

- 5 ¹H NMR (400.13 MHz, CDCl₃) δ 1.19 - 1.31 (2H, m), 1.39 - 1.44 (1H, m), 1.53 - 1.59 (1H, m), 1.68 - 1.74 (3H, m), 1.72 (3H, s), 1.85 - 1.91 (2H, m), 3.97 - 4.05 (1H, m), 5.05 (2H, s), 6.04 - 6.09 (1H, m), 7.06 (1H, s), 7.16 - 7.29 (3H, d), 8.93 (1H, s)
m/z (ESI+) (M+H)⁺ = 382; HPLC t_R = 1.87 min.

10 **Intermediate 93**

benzyl N-[1-[4-cyclopentyl-5-[(5-hydroxy-2-adamantyl)carbamoyl]pyrimidin-2-yl]cyclopropyl]carbamate



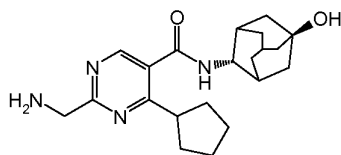
Prepared from Intermediate 92 by the same process used for Example 4

- 15 ¹H NMR (400.13 MHz, CDCl₃) δ 1.31 - 1.39 (2H, m), 1.46 (1H, m), 1.50 (2H, m), 1.53 - 1.59 (1H, m), 1.61 - 1.64 (4H, m), 1.69 - 1.76 (9H, t), 1.82 - 1.85 (4H, m), 2.08 (1H, s), 2.14 (2H, s), 4.07 - 4.12 (1H, m), 5.04 (2H, s), 5.79 (1H, s), 6.04 (1H, d), 7.21 - 7.33 (5H, m), 8.37 (1H, s)
m/z (ESI+) (M+H)⁺ = 531; HPLC t_R = 2.44 min.

20

Example 152

2-(Aminomethyl)-4-cyclopentyl-N-[(2r,5s)-5-hydroxyadamantan-2-yl]pyrimidine-5-carboxamide

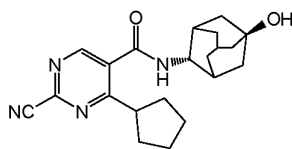


Prepared by the same process used for Example 151 from Intermediate 94

¹H NMR (400.13 MHz, CDCl₃) δ 1.58 (2H, d), 1.65 - 1.76 (3H, m), 1.79 (3H, s), 1.83 (1H, s), 1.84 - 1.89 (4H, m), 1.90 - 2.04 (5H, d), 2.17 (1H, s), 2.25 (2H, s), 3.47 - 3.54 (1H, q),
 4.06 (2H, s), 4.19 - 4.24 (1H, m), 6.15 (1H, d), 8.56 (1H, s)
 m/z (ESI+) (M+H)⁺ = 371; HPLC t_R = 1.46 min.

Intermediate 94

cyano; [4-cyclopentyl-5-[(5-hydroxy-2-adamantyl)carbamoyl]pyrimidin-2-yl]

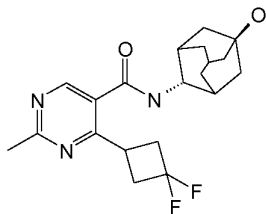


Sodium cyanide (0.148 g, 3.02 mmol) was added in one portion to 4-cyclopentyl-N-
 [(2r,5s)-5-hydroxyadamantan-2-yl]-2-methylsulfinylpyrimidine-5-carboxamide
 (Intermediate 86, 1.017 g, 2.52 mmol) in DMA (15 mL) at 0°C under nitrogen. The
 resulting solution was stirred at 0°C for 2 hours. The reaction mixture was quenched with
 saturated NaHCO₃ (50 mL), extracted with DCM (2 x 100 mL), the organic layer was
 dried over MgSO₄, filtered and evaporated to afford yellow solid. The crude product was
 purified by flash silica chromatography, elution gradient 0 to 100% EtOAc in isohexane.
 Pure fractions were evaporated to dryness to afford cyano; [4-cyclopentyl-5-[(5-hydroxy-
 2-adamantyl)carbamoyl]pyrimidin-2-yl] (0.758 g, 82 %) as a yellow oil.

¹H NMR (400.13 MHz, CDCl₃) δ 1.57 (2H, d), 1.68 - 1.77 (5H, m), 1.80 (3H, s), 1.84 (2H, s), 1.87 - 1.98 (6H, m), 2.18 (1H, s), 2.26 (2H, s), 3.48 (1H, q), 4.19 - 4.24 (1H, m), 6.59 (1H, d), 8.65 (1H, s)
 m/z (ESI-) (M-H)⁻ = 365; HPLC t_R = 2.10 min.

Example 153

4-(3,3-difluorocyclobutyl)-N-[(2s,5r)-5-hydroxyadamantan-2-yl]-2-methylpyrimidine-5-carboxamide



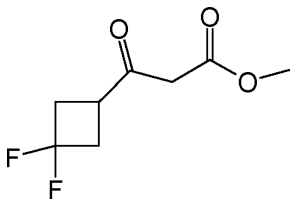
Prepared from Intermediate 102 by the same process used for Example 4

¹H NMR (400.13 MHz, DMSO-d₆) δ 1.35 (2H, d), 1.63 (4H, d), 1.72 (2H, d), 1.89 (2H, d),
1.99 (1H, s), 2.06 (2H, s), 2.66 (3H, s), 2.78 - 3.00 (4H, m), 3.66 - 3.71 (1H, m), 3.96 (1H,
5 t), 4.41 (1H, s), 8.38 (1H, d), 8.58 (1H, s)

m/z (ESI⁺) (M+H)⁺ = 378; HPLC t_R = 1.64 min m/z (ESI⁺) (M+H)⁺ = 378; HPLC t_R =
1.64 min.

Intermediate 95

10 methyl 3-(3,3-difluorocyclobutyl)-3-oxopropanoate

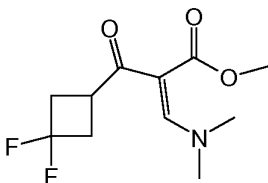


Prepared from 5-(3,3-difluorocyclobutanecarbonyl)-2,2-dimethyl-1,3-dioxane-4,6-dione by
the same process used for Intermediate 122

¹H NMR (400.13 MHz, CDCl₃) δ 2.69 - 2.90 (4H, m), 3.21 - 3.26 (1H, m), 3.49 (2H, s),
15 3.75 (3H, d)

Intermediate 96

(Z)-methyl 2-(3,3-difluorocyclobutanecarbonyl)-3-(dimethylamino)acrylate

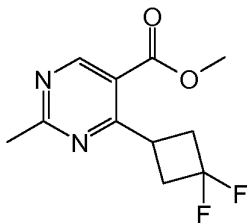


20 Prepared from methyl 3-(3,3-difluorocyclobutyl)-3-oxopropanoate by the same process
used for Intermediate 1

m/z (ESI⁺) (M+H)⁺ = 248; HPLC t_R = 1.63 min. 5 min Base

Intermediate 97

methyl 4-(3,3-difluorocyclobutyl)-2-methylpyrimidine-5-carboxylate

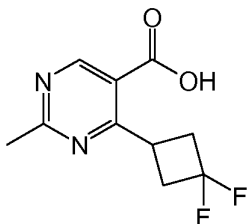


(Z)-methyl 2-(3,3-difluorocyclobutanecarbonyl)-3-(dimethylamino)acrylate (Intermediate 96, 500 mg, 2.02 mmol) was added dropwise to Acetamidine hydrochloride (191 mg, 2.02 mmol), Sodium methoxide (4045 μ L, 2.02 mmol) in methanol (20 mL) under nitrogen. The resulting solution was stirred at 60 °C for 4 hours then roomtemperature for a further 16 hours. The reaction mixture was evaporated to dryness and redissolved in EtOAc (50 mL), and washed sequentially with 2M HCl (25 mL), saturated brine (25 mL). The organic layer was dried over MgSO₄, filtered and evaporated to afford crude product. The crude product was purified by flash silica (40g) chromatography, elution gradient 20 to 50% EtOAc in isohexane. Pure fractions were evaporated to dryness to afford methyl 4-(3,3-difluorocyclobutyl)-2-methylpyrimidine-5-carboxylate (388 mg, 79 %) as a colourless oil which solidified on standing.

¹H NMR (400.13 MHz, CDCl₃) δ 2.79 (3H, s), 2.85 - 2.96 (2H, m), 2.99 - 3.12 (2H, m), 3.94 (3H, s), 4.16 - 4.21 (1H, m), 9.05 (1H, s)
m/z (ESI+) (M+H)⁺ = 243; HPLC t_R = 2.1 min.

Intermediate 98

4-(3,3-difluorocyclobutyl)-2-methylpyrimidine-5-carboxylic acid



Sodium hydroxide (2.002 mL, 4.00 mmol) was added in one portion to methyl 4-(3,3-difluorocyclobutyl)-2-methylpyrimidine-5-carboxylate (Intermediate 97, 388 mg, 1.60 mmol), in methanol (10 mL) under air. The resulting solution was stirred at 60 °C for 3

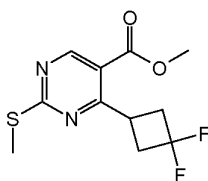
hours. The reaction mixture was evaporated to dryness and redissolved in water (10 mL),
The solution was acidified with concentrated HCl. The precipitate was collected by
filtration, washed with water (10 mL) and dried under vacuum to afford 4-(3,3-
difluorocyclobutyl)-2-methylpyrimidine-5-carboxylic acid (330 mg, 90 %) as a white
solid, which was used without further purification.

¹H NMR (400.13 MHz, DMSO-d₆) δ 2.69 (3H, s), 2.82 - 2.90 (2H, m), 2.94 - 3.06 (2H,
m), 4.16 - 4.21 (1H, m), 9.00 (1H, s)

m/z (ESI+) (M+H)⁺ = 229 HPLC t_R = 1.63min.

10 Intermediate 99

methyl 4-(3,3-difluorocyclobutyl)-2-(methylthio)pyrimidine-5-carboxylate



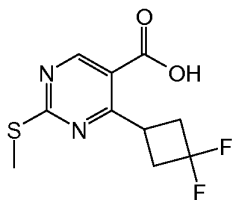
Prepared by the same process used for Intermediate 28 from (Z)-methyl 2-(3,3-
difluorocyclobutanecarbonyl)-3-(dimethylamino)acrylate (Intermediate 96)

¹H NMR (400.13 MHz, CDCl₃) δ 2.63 (3H, s), 2.88 - 2.98 (2H, m), 3.00 - 3.09 (2H, m),
3.92 (3H, s), 4.20 - 4.25 (1H, m), 8.94 (1H, s)

m/z (ESI+) (M+H)⁺ = 275; HPLC t_R = 2.61 min.

Intermediate 100

4-(3,3-difluorocyclobutyl)-2-methylsulfanylpurimidine-5-carboxylic acid



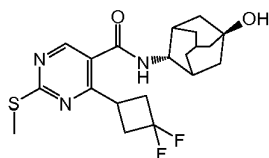
Prepared from Intermediate 99 by the same process used for Intermediate 29

¹H NMR (400.13 MHz, DMSO-d₆) δ 2.59 (3H, s), 2.83 - 2.94 (2H, m), 2.94 - 3.04 (2H,
m), 3.35 (1H,bs), 4.18 - 4.23 (1H, m), 8.92 (1H, s)

m/z (ESI+) (M+H)⁺ = 261; HPLC t_R = 2.13 min.

Intermediate 101

4-(3,3-difluorocyclobutyl)-N-[(2r,5s)-5-hydroxyadamantan-2-yl]-2-methylsulfanylpurimidine-5-carboxamide

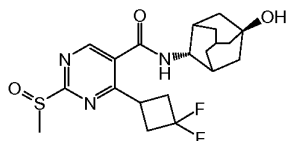


- 5 Prepared from Intermediate 100 by the same process used for Example 4
m/z (ESI+) (M+H)+ = 410; HPLC t_R = 2.03 min.

Intermediate 102

4-(3,3-difluorocyclobutyl)-N-[(2r,5s)-5-hydroxyadamantan-2-yl]-2-methylsulfinylpyrimidine-5-carboxamide

- 10

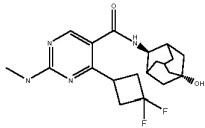
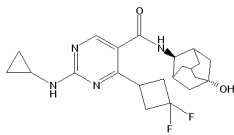


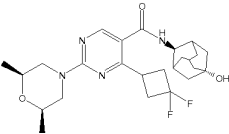
Prepared from Intermediate 101 by the same process used for Intermediate 60
m/z (ESI+) (M+H)+ = 426; HPLC t_R = 1.41 min

- 15 The following Examples were prepared in a similar manner to Example 46, using
Intermediate 102 and an appropriate amine starting material:

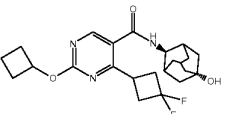
20

25

Structure	Ex	Name	¹ H NMR δ	MS m/e MH ⁺
	154	4-(3,3-difluorocyclobutyl)-N-[(2r,5s)-5-hydroxyadamantan-2-yl]-2-methylaminopyrimidine-5-carboxamide	¹ H NMR (400.132 MHz, CDCl ₃) δ 1.40 (1H, s), 1.58 (2H, d), 1.65 - 1.74 (2H, m), 1.75 - 1.85 (4H, m), 1.93 (2H, d), 2.14 - 2.26 (3H, m), 2.76 - 2.90 (2H, m), 2.90 - 3.10 (2H, m), 3.06 (3H, d), 3.86 (1H, t), 4.14 (1H, s), 5.34 (1H, s), 5.87 (1H, s), 8.34 (1H, s)	m/z (ES ⁺) (M+H) ⁺ = 393; HPLC t _R = 1.75 min.
	155	2-(cyclopropylamino)-4-(3,3-difluorocyclobutyl)-N-[(2r,5s)-5-hydroxyadamantan-2-yl]pyrimidine-5-carboxamide	¹ H NMR (400.132 MHz, CDCl ₃) δ 0.55 - 0.61 (2H, m), 0.79 - 0.91 (2H, m), 1.26 (1H, s), 1.58 (2H, d), 1.64 - 1.85 (6H, m), 1.93 (2H, d), 2.14 - 2.27 (3H, m), 2.76 - 2.90 (3H, m), 2.91 - 3.09 (2H, m), 3.86 (1H, quintet), 4.15 (1H, s), 5.56 (1H, s), 5.88 (1H, s), 8.39 (1H, s)	m/z (ES ⁺) (M+H) ⁺ = 419; HPLC t _R = 1.91 min.

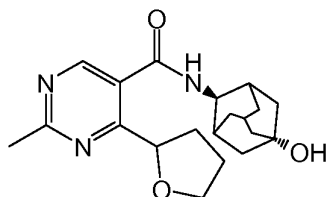
	156	4-(3,3-difluorocyclobutyl)-2,6-dimethylmorpholin-4-yl]-N-[(2r,5s)-5-hydroxyadamantan-2-yl]pyrimidine-5-carboxamide	¹ H NMR (400.132 MHz, CDCl ₃) δ 1.27 (6H, d), 1.42 - 1.72 (5H, m), 1.76 - 1.85 (4H, m), 1.93 (2H, d), 2.14 - 2.25 (3H, m), 2.65 (2H, dd), 2.80 - 3.03 (4H, m), 3.58 - 3.68 (2H, m), 3.89 (1H, quintet), 4.15 (1H, d), 4.65 (2H, d), 5.86 (1H, d), 8.36 (1H, s)	m/z (ES ⁺) (M+H) ⁺ = 477; HPLC t _R = 2.15 min.
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The following Examples were prepared in a similar manner to Example 75 , using Intermediate 102 and an appropriate amine starting material:

Structure	Ex	Name	¹ H NMR δ	MS m/e MH ⁺
	157	2-cyclobutyloxy-4-(3,3-difluorocyclobutyl)-N-[(2r,5s)-5-hydroxyadamantan-2-yl]pyrimidine-5-carboxamide	¹ H NMR (400.132 MHz, CDCl ₃) δ 1.41 (1H, s), 1.60 (2H, d), 1.65 - 1.91 (8H, m), 1.94 (2H, d), 2.15 - 2.31 (5H, m), 2.44 - 2.56 (2H, m), 2.80 - 3.09 (4H, m), 3.87 (1H, quintet), 4.18 (1H, d), 5.23 (1H, quintet), 5.95 (1H, d), 8.50 (1H, s)	m/z (ES ⁺) (M+H) ⁺ = 434; HPLC t _R = 2.16 min.

5 Example 158

N-[(2r,5s)-5-hydroxyadamantan-2-yl]-2-methyl-4-(oxolan-2-yl)pyrimidine-5-carboxamide

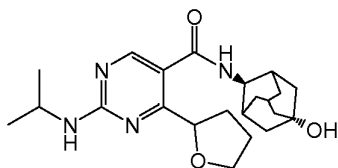


Prepared from Intermediate 110 by the same process used for Example 4

¹H NMR (400.132 MHz, CDCl₃) δ 1.36 (1H, s), 1.54 - 1.59 (2H, m), 1.75 - 1.84 (6H, m),
1.92 - 1.97 (2H, m), 2.04 - 2.30 (6H, m), 2.75 (3H, s), 2.79 - 2.85 (1H, m), 3.88 - 3.93 (1H,
5 m), 3.97 - 4.03 (1H, m), 4.21 - 4.26 (1H, m), 5.12 (1H, t), 7.73 (1H, d), 8.93 (1H, s)
m/z (ESI+) (M+H)⁺ = 358; HPLC t_R = 1.22 min.

Example 159

N-[(2r,5s)-5-hydroxyadamantan-2-yl]-4-(oxolan-2-yl)-2-(propan-2-ylamino)pyrimidine-5-
10 carboxamide



Isopropylamine (0.303 mL, 3.56 mmol) was added to N-[(2r,5s)-5-hydroxyadamantan-2-yl]-2-methylsulfonyl-4-(oxolan-2-yl)pyrimidine-5-carboxamide (Intermediate 110, 300
mg, 0.71 mmol) in THF (5 mL) at 20°C. The resulting solution was stirred at 20 °C for 2
15 hours.

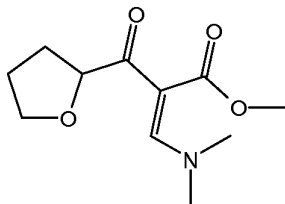
The reaction mixture was evaporated to dryness. Purified by preparative HPLC
(Phenomenex Gemini C18 110A (axia) column, 5μ silica, 30 mm diameter, 100 mm
length), using decreasingly polar mixtures of water (containing 0.5% NH₃) and MeCN as
eluent. Fractions containing the desired compound were evaporated to dryness to afford
20 the product, N-[(2r,5s)-5-hydroxyadamantan-2-yl]-4-(oxolan-2-yl)-2-(propan-2-ylamino)pyrimidine-5-carboxamide (143 mg, 50.2 %)

¹H NMR (400.132 MHz, CDCl₃) δ 1.25 (6H, d), 1.42 (1H, s), 1.48 - 1.57 (2H, m), 1.75 -
1.84 (6H, m), 1.90 - 1.97 (2H, m), 2.02 - 2.08 (2H, m), 2.14 - 2.25 (4H, m), 2.76 (1H, bs),
3.86 - 3.93 (1H, m), 3.98 - 4.03 (1H, m), 4.13 - 4.24 (2H, m), 5.08 (1H, t), 5.21 (1H, d),
25 7.79 (1H, s), 8.69 (1H, bs)

m/z (ES+) (M+H)⁺ = 401; HPLC t_R = 1.78 min.

Intermediate 104

(Z)-methyl 3-(dimethylamino)-2-(tetrahydrofuran-2-carbonyl)acrylate



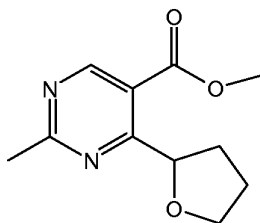
Prepared from methyl 3-oxo-3-(tetrahydrofuran-2-yl)propanoate by the same process used
5 for Intermediate 1;

¹H NMR (400.132 MHz, CDCl₃) δ 1.87 (2H, quintet), 2.00 - 2.09 (1H, m), 2.12 - 2.22
(1H, m), 3.05 (6H, s), 3.73 (3H, s), 3.83 - 3.89 (1H, m), 3.90 - 3.96 (1H, m), 4.97 (1H, t),
7.67 (1H, s)

m/z (ESI⁺) (M+H)⁺ = 228; HPLC t_R = 1.01 min.

Intermediate 105

methyl 2-methyl-4-(tetrahydrofuran-2-yl)pyrimidine-5-carboxylate



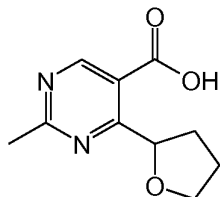
A solution of (Z)-methyl 3-(dimethylamino)-2-(tetrahydrofuran-2-carbonyl)acrylate
15 (Intermediate 104, 1.4 g, 6.16 mmol) in methanol (5 mL) was added dropwise to a stirred
suspension of Acetamidine hydrochloride (0.582 g, 6.16 mmol), and Sodium methoxide
(0.5M in MeOH) (12.32 mL, 6.16 mmol) in methanol (25 mL) at 20°C. The resulting
solution was stirred at 80 °C for 24 hours. The reaction mixture was evaporated to dryness
and redissolved in EtOAc (100 mL), and washed sequentially with water (75 mL) and
20 saturated brine (75 mL). The organic layer was dried over MgSO₄, filtered and evaporated
to afford crude product. The crude product was purified by flash silica chromatography,
elution gradient 40 to 70% EtOAc in isohexane. Pure fractions were evaporated to dryness
to afford methyl 2-methyl-4-(tetrahydrofuran-2-yl)pyrimidine-5-carboxylate (0.600 g, 43.8
%) as a colourless oil.

25 ¹H NMR (400.132 MHz, CDCl₃) δ 1.95 - 2.09 (3H, m), 2.40 - 2.51 (1H, m), 2.79 (3H, s),

3.94 (3H, s), 3.97 - 4.03 (1H, m), 4.13 - 4.20 (1H, m), 5.58 - 5.62 (1H, m), 8.96 (1H, s)
m/z (ESI+) (M+H)+ = 223; HPLC t_R = 1.27 min.

Intermediate 106

2-methyl-4-(tetrahydrofuran-2-yl)pyrimidine-5-carboxylic acid



5

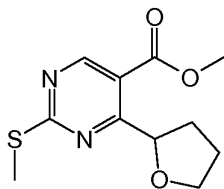
Prepared from Intermediate 105 by the same process used for Intermediate 29

^1H NMR (400.132 MHz, CDCl_3) δ 2.00 - 2.15 (3H, m), 2.40 - 2.54 (1H, m), 2.82 (3H, s),
4.04 - 4.09 (1H, m), 4.18 - 4.25 (1H, m), 5.63 - 5.67 (1H, m), 6.48 (1H, bs), 9.15 (1H, s)
m/z (ESI+) (M+H)+ = 209; HPLC t_R = 0.93 min.

10

Intermediate 107

methyl 2-(methylthio)-4-(tetrahydrofuran-2-yl)pyrimidine-5-carboxylate

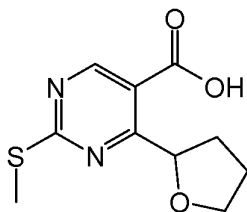


Prepared from Intermediate 104 by the same process used for Intermediate 28;

15 ^1H NMR (400.132 MHz, CDCl_3) δ 1.94 - 2.11 (3H, m), 2.38 - 2.47 (1H, m), 2.60 (3H, s),
3.91 (3H, s), 4.00 - 4.06 (1H, m), 4.11 - 4.19 (1H, m), 5.69 - 5.74 (1H, m), 8.88 (1H, s)
m/z (ESI+) (M+H)+ = 255; HPLC t_R = 1.88 min.

Intermediate 108

20 2-methylsulfanyl-4-(oxolan-2-yl)pyrimidine-5-carboxylic acid

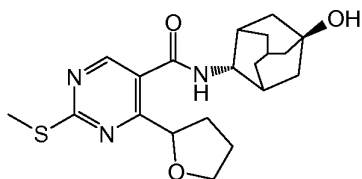


Prepared from Intermediate 107 by the same process used for Intermediate 21;

¹H NMR (400.132 MHz, CDCl₃) δ 2.00 - 2.19 (3H, m), 2.39 - 2.49 (1H, m), 2.62 (3H, s), 4.05 - 4.10 (1H, m), 4.17 - 4.23 (1H, m), 5.70 - 5.74 (1H, m), 6.13 (1H, bs), 9.03 (1H, s)
m/z (ESI⁺) (M+H)⁺ = 241; HPLC t_R = 0.69 min.

5 **Intermediate 109**

N-[(2r,5s)-5-hydroxyadamantan-2-yl]-2-methylsulfanyl-4-(oxolan-2-yl)pyrimidine-5-carboxamide

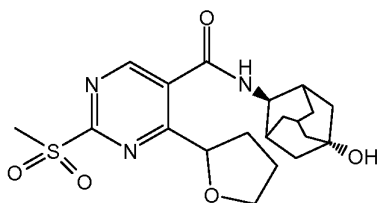


Prepared from Intermediate 108 by the same process used for Example ;4

10 ¹H NMR (400.132 MHz, CDCl₃) δ 1.50 - 1.59 (3H, m), 1.75 - 1.83 (6H, m), 1.90 - 1.97 (2H, m), 2.03 - 2.27 (6H, m), 2.59 (3H, s), 2.80 - 2.91 (1H, m), 3.89 - 3.93 (1H, m), 3.97 - 4.02 (1H, m), 4.20 - 4.26 (1H, m), 5.14 (1H, t), 7.91 (1H, d), 8.86 (1H, s)
m/z (ESI⁺) (M+H)⁺ = 390; HPLC t_R = 1.73 min.

15 **Intermediate 110**

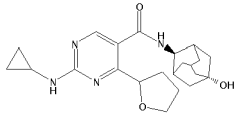
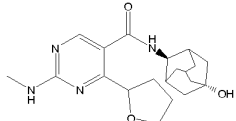
N-[(2r,5s)-5-hydroxyadamantan-2-yl]-2-methylsulfonyl-4-(oxolan-2-yl)pyrimidine-5-carboxamide

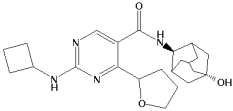
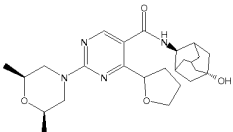


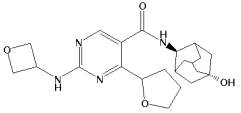
Prepared from Intermediate 109 by the same process used for Example 37;

20 ¹H NMR (400.132 MHz, CDCl₃) δ 1.50 - 1.60 (3H, m), 1.74 - 1.85 (6H, m), 1.90 - 1.98 (2H, m), 2.08 - 2.31 (6H, m), 2.79 - 2.90 (1H, m), 3.36 (3H, s), 3.90 - 4.04 (2H, m), 4.23 - 4.30 (1H, m), 5.24 (1H, t), 7.88 (1H, d), 9.17 (1H, s)
m/z (ESI⁺) (M+H)⁺ = 422; HPLC t_R = 1.22 min.

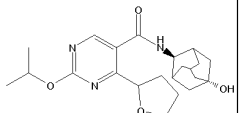
25 The following Examples were prepared in a similar manner to Example 159, using Intermediate 110 and an appropriate amine starting material:

Structure	Ex	Name	¹ H NMR δ	MS m/e MH ⁺
	160	2-(cyclopropylamino)-N-[(2r,5s)-5-hydroxyadaman-2-yl]-4-(oxolan-2-yl)pyrimidine-5-carboxamide	¹ H NMR (400.132 MHz, CDCl ₃) δ 0.52 - 0.60 (2H, m), 0.77 - 0.87 (2H, m), 1.50 - 1.56 (2H, m), 1.75 - 1.83 (6H, m), 1.90 - 1.96 (2H, m), 2.00 - 2.24 (7H, m), 2.73 - 2.83 (2H, m), 3.86 - 3.92 (1H, m), 3.99 - 4.03 (1H, m), 4.18 - 4.23 (1H, m), 5.10 (1H, t), 5.80 (1H, s), 7.83 (1H, s), 8.71 (1H, s)	m/z (ES ⁺) (M+H) ⁺ = 399; HPLC t _R = 1.60 min.
	161	N-[(2r,5s)-5-hydroxyadaman-2-yl]-2-methylamino-4-(oxolan-2-yl)pyrimidine-5-carboxamide	¹ H NMR (400.132 MHz, CDCl ₃) δ 1.47 - 1.57 (2H, m), 1.77 - 1.83 (6H, m), 1.89 - 1.97 (2H, m), 2.01 - 2.09 (2H, m), 2.13 - 2.24 (5H, m), 2.78 (1H, s), 3.03 (3H, d), 3.90 (1H, q), 3.98 - 4.03 (1H, m), 4.18 - 4.22 (1H, m), 5.09 (1H, t), 5.61 (1H, s), 7.86 (1H, s), 8.68 (1H, s)	m/z (ES ⁺) (M+H) ⁺ = 373; HPLC t _R = 1.37 min.

	162	2-(cyclobutylamino)-N-[(2r,5s)-5-hydroxyadamantan-2-yl]-4-(oxolan-2-yl)pyrimidine-5-carboxamide	1H NMR (400.132 MHz, CDCl ₃) δ 1.47 - 1.53 (3H, m), 1.73 - 1.84 (8H, m), 1.89 - 1.96 (4H, m), 2.02 - 2.07 (2H, m), 2.14 - 2.25 (4H, m), 2.37 - 2.46 (2H, m), 2.76 (1H, s), 3.85 - 3.92 (1H, m), 3.97 - 4.02 (1H, m), 4.18 - 4.24 (1H, m), 4.47 (1H, sextet), 5.07 (1H, t), 5.49 (1H, d), 7.77 (1H, s), 8.66 (1H, s)	m/z (ES+) (M+H) ⁺ = 413; HPLC t _R = 1.87 min.
	163	2-[(2S,6R)-2,6-dimethylmorpholin-4-yl]-N-[(2r,5s)-5-hydroxyadamantan-2-yl]-4-(oxolan-2-yl)pyrimidine-5-carboxamide	1H NMR (400.132 MHz, CDCl ₃) δ 1.26 (6H, d), 1.38 (1H, s), 1.48 - 1.53 (2H, m), 1.75 - 1.83 (6H, m), 1.91 - 1.97 (2H, m), 2.02 - 2.11 (2H, m), 2.14 - 2.25 (4H, m), 2.60 - 2.66 (2H, m), 2.74 - 2.84 (1H, m), 3.58 - 3.66 (2H, m), 3.91 (1H, q), 3.99 - 4.05 (1H, m), 4.20 - 4.24 (1H, m), 4.63 (2H, d), 5.08 (1H, t), 7.89 (1H, d), 8.75 (1H, s)	m/z (ES+) (M+H) ⁺ = 457; HPLC t _R = 1.96 min.

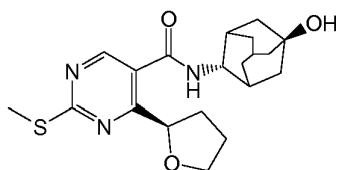
	164	N-[(2r,5s)-5-hydroxyadamantan-2-yl]-2-(oxetan-3-ylamino)-4-(oxolan-2-yl)pyrimidine-5-carboxamide	¹ H NMR (400.132 MHz, CDCl ₃) δ 1.48 - 1.56 (3H, m), 1.76 - 1.83 (6H, m), 1.88 - 1.96 (2H, m), 2.03 - 2.11 (2H, m), 2.15 - 2.23 (4H, m), 2.67 - 2.75 (1H, m), 3.87 - 3.93 (1H, m), 3.97 - 4.02 (1H, m), 4.18 - 4.24 (1H, m), 4.60 (2H, t), 4.95 - 5.00 (2H, m), 5.07 (1H, t), 5.14 (1H, sextet), 5.79 (1H, d), 7.77 (1H, s), 8.71 (1H, s)	m/z (ES ⁺) (M+H) ⁺ = 415; HPLC t _R = 1.31 min.
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The following Examples were prepared in a similar manner to Example 75, using Intermediate 110 and an appropriate amine starting material:

Structure	Ex	Name	¹ H NMR δ	MS m/e MH ⁺
	165	N-[(2r,5s)-5-hydroxyadamantan-2-yl]-4-(oxolan-2-yl)-2-propan-2-yloxy pyrimidine-5-carboxamide	¹ H NMR (400.132 MHz, CDCl ₃) δ 1.42 (6H, d), 1.48 - 1.59 (2H, m), 1.66 (1H, s), 1.76 - 1.82 (6H, m), 1.90 - 1.97 (2H, m), 2.02 - 2.28 (6H, m), 2.75 - 2.86 (1H, m), 3.86 - 3.94 (1H, m), 3.97 - 4.03 (1H, m), 4.19 - 4.26 (1H, m), 5.12 (1H, t), 5.33 (1H, septet), 7.84 (1H, d), 8.85 (1H, s)	m/z (ES ⁺) (M+H) ⁺ = 402; HPLC t _R = 1.78 min.

Example 166

N-[(2r,5s)-5-hydroxyadamantan-2-yl]-2-methylsulfanyl-4-[(2R)-oxolan-2-yl]pyrimidine-5-carboxamide



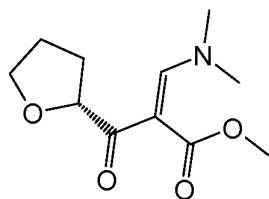
5 N-Ethyldiisopropylamine (3.57 mL, 20.48 mmol) was added to (R)-2-(methylthio)-4-(tetrahydrofuran-2-yl)pyrimidine-5-carboxylic acid (Intermediate 114, 1.23 g, 5.12 mmol), 4-aminoadamantan-1-ol hydrochloride (1.043 g, 5.12 mmol) and O-(7-Azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (2.336 g, 6.14 mmol) in DMF (15 mL) at ambient temperature under nitrogen. The resulting solution was stirred at ambient
10 temperature for 16 hours. The reaction mixture was evaporated to dryness and redissolved in EtOAc (50 mL) and washed sequentially with water (10 mL) and saturated brine (10mL). The organic layer was dried over MgSO₄, filtered and evaporated to afford crude product.

The crude product was purified by flash silica chromatography, elution gradient 1 to 6%
15 DCM in MeOH. Pure fractions were evaporated to dryness to afford N-[(2r,5s)-5-hydroxyadamantan-2-yl]-2-methylsulfanyl-4-[(2R)-oxolan-2-yl]pyrimidine-5-carboxamide (1.180 g, 59.2 %) as an off-white solid;

¹H NMR (400.132 MHz, CDCl₃) δ 1.50 - 1.59 (3H, m), 1.75 - 1.83 (6H, m), 1.90 - 1.97 (2H, m), 2.03 - 2.27 (6H, m), 2.59 (3H, s), 2.80 - 2.91 (1H, m), 3.89 - 3.93 (1H, m), 3.97 -
20 4.02 (1H, m), 4.20 - 4.26 (1H, m), 5.14 (1H, t), 7.91 (1H, d), 8.86 (1H, s)
m/z (ES⁺) (M+H)⁺ = 390; HPLC t_R = 1.69 min.

Intermediate 112

(R,Z)-methyl 3-(dimethylamino)-2-(tetrahydrofuran-2-carbonyl)acrylate



25 N,N-Dimethylformamide dimethyl acetal (1.668 mL, 12.55 mmol) was added in one

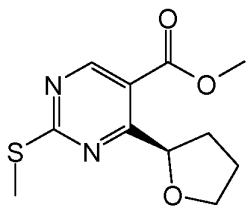
portion to (R)-methyl 3-oxo-3-(tetrahydrofuran-2-yl)propanoate (1.8 g, 10.45 mmol) in dioxane (25 mL) at room temperature under nitrogen. The resulting solution was stirred at 100 °C for 2 hours. The reaction mixture was evaporated, to afford crude product. The crude product was purified by flash silica (120g) chromatography, elution gradient 50 to 100% EtOAc in isohexane. Pure fractions were evaporated to dryness to afford (R,Z)-methyl 3-(dimethylamino)-2-(tetrahydrofuran-2-carbonyl)acrylate (1.800 g, 76 %) as a yellow oil.

¹H NMR (400.132 MHz, CDCl₃) δ 1.83 - 1.92 (2H, m), 2.00 - 2.08 (1H, m), 2.12 - 2.21 (1H, m), 3.04 (6H, s), 3.73 (3H, s), 3.83 - 3.96 (2H, m), 4.97 (1H, t), 7.67 (1H, s)

m/z (ES⁺) (M-H)⁻ = 226; HPLC t_R = 1.25 min.

Intermediate 113

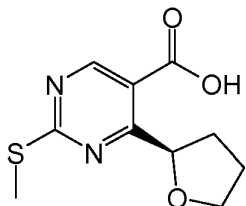
(R)-methyl 2-(methylthio)-4-(tetrahydrofuran-2-yl)pyrimidine-5-carboxylate



2-Methyl-2-Thiopseudourea Sulfate (1.543 g, 11.09 mmol) was added to (R,Z)-methyl 3-(dimethylamino)-2-(tetrahydrofuran-2-carbonyl)acrylate (Intermediate 112, 1.8 g, 7.92 mmol) and sodium acetate (2.73 g, 33.27 mmol) in DMF (30 mL) at 20°C. The resulting solution was stirred at 80 °C for 3 hours. Water was added to the cooled solution. The reaction mixture was diluted with EtOAc (200 mL), and washed sequentially with water (2x100 mL). The organic layer was dried over MgSO₄, filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 5 to 30% EtOAc in isohexane. Pure fractions were evaporated to dryness to afford (R)-methyl 2-(methylthio)-4-(tetrahydrofuran-2-yl)pyrimidine-5-carboxylate (1.460 g, 72.5 %) as a colourless oil.

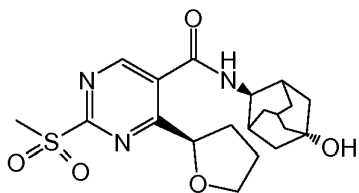
¹H NMR (400.132 MHz, CDCl₃) δ 1.96 - 2.10 (3H, m), 2.38 - 2.49 (1H, m), 2.60 (3H, s), 3.91 (3H, s), 4.00 - 4.05 (1H, m), 4.13 - 4.19 (1H, m), 5.69 - 5.74 (1H, m), 8.88 (1H, s)

m/z (ES⁺) (M+H)⁺ = 255; HPLC t_R = 1.88 min.

Intermediate 114**(R)-2-(methylthio)-4-(tetrahydrofuran-2-yl)pyrimidine-5-carboxylic acid**

A solution of Lithium hydroxide monohydrate (0.482 g, 11.48 mmol) in water (10 mL) was added to a stirred solution of (R)-methyl 2-(methylthio)-4-(tetrahydrofuran-2-yl)pyrimidine-5-carboxylate (Intermediate 113, 1.46 g, 5.74 mmol) in THF (20 mL) at 20°C. The resulting mixture was stirred at 20 °C for 70 hours. The THF was evaporated and the aqueous washed with ethyl acetate (100ml) to remove any impurities. The aqueous was acidified with 1M citric acid and extracted into ethyl acetate (100ml). The organic layer was washed with brine (50ml), dried over MgSO₄, filtered and evaporated to give (R)-2-(methylthio)-4-(tetrahydrofuran-2-yl)pyrimidine-5-carboxylic acid (1.230 g, 89 %) as a white solid;

¹H NMR (400.132 MHz, CDCl₃) δ 1.99 - 2.20 (3H, m), 2.39 - 2.49 (1H, m), 2.62 (3H, s), 4.03 - 4.11 (1H, m), 4.16 - 4.22 (1H, m), 5.66 - 5.70 (1H, m), 9.02 (1H, s)
m/z (ES⁺) (M+H)⁺ = 241; HPLC t_R = 0.59 min.

Intermediate 115**N-[(2r,5s)-5-hydroxyadamantan-2-yl]-2-methylsulfonyl-4-[(2R)-oxolan-2-yl]pyrimidine-5-carboxamide**

3-Chloroperoxybenzoic acid (70%) (1.392 g, 5.65 mmol) was added in one portion to N-[(2r,5s)-5-hydroxyadamantan-2-yl]-2-methylsulfonyl-4-[(2R)-oxolan-2-yl]pyrimidine-5-carboxamide (Example 166, 1.1 g, 2.82 mmol) in DCM (45 mL) at 0°C. The resulting solution was stirred at 20 °C for 24 hours. The reaction mixture was diluted with DCM (50 mL), and washed sequentially with saturated NaHCO₃ (4x75 mL) and saturated brine (75

mL). The organic layer was dried over MgSO₄, filtered and evaporated to afford N-[(2r,5s)-5-hydroxyadamantan-2-yl]-2-methylsulfonyl-4-[(2R)-oxolan-2-yl]pyrimidine-5-carboxamide (1.180 g, 99 %) as a white solid;

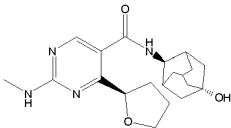
¹H NMR (400.132 MHz, CDCl₃) δ 1.50 - 1.60 (3H, m), 1.74 - 1.85 (6H, m), 1.90 - 1.98

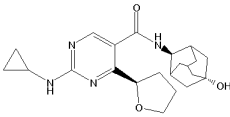
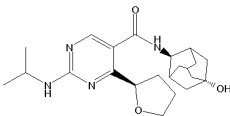
(2H, m), 2.08 - 2.31 (6H, m), 2.79 - 2.90 (1H, m), 3.36 (3H, s), 3.90 - 4.04 (2H, m), 4.23 - 4.30 (1H, m), 5.24 (1H, t), 7.88 (1H, d), 9.17 (1H, s)

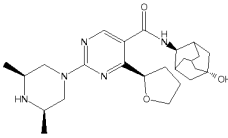
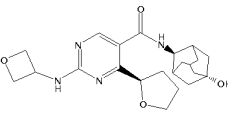
m/z (ES⁺) (M+H)⁺ = 422; HPLC t_R = 1.31 min.

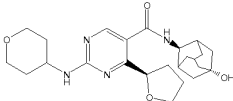
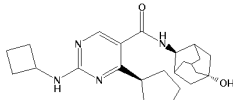
The following Examples were prepared in a similar manner to Example 159, using

Intermediate 115 and an appropriate amine starting material:

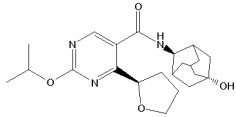
Structure	Ex	Name	¹ H NMR δ	MS m/e MH ⁺
	167	N-[(2r,5s)-5-hydroxyadamantan-2-yl]-2-methylamino-4-[(2R)-oxolan-2-yl]pyrimidine-5-carboxamide	¹ H NMR (400.132 MHz, CDCl ₃) δ 1.42 (1H, s), 1.52 (2H, t), 1.76 - 1.86 (6H, m), 1.90 - 1.97 (2H, m), 2.02 - 2.09 (2H, m), 2.14 - 2.26 (4H, m), 2.81 (1H, s), 3.04 (3H, d), 3.90 (1H, q), 4.01 (1H, q), 4.18 - 4.24 (1H, m), 5.09 (1H, t), 5.33 (1H, d), 7.83 (1H, s), 8.72 (1H, s)	m/z (ES ⁺) (M+H) ⁺ = 373; HPLC t _R = 1.37 min.

	170	2-(cyclopropylamino)-N-[(2r,5s)-5-hydroxyadamantan-2-yl]-4-[(2R)-oxolan-2-yl]pyrimidine-5-carboxamide	1H NMR (400.132 MHz, CDCl ₃) δ 0.54 - 0.58 (2H, m), 0.80 - 0.86 (2H, m), 1.37 (1H, s), 1.49 - 1.53 (2H, m), 1.76 - 1.85 (6H, m), 1.90 - 1.97 (2H, m), 2.02 - 2.09 (2H, m), 2.15 - 2.26 (4H, m), 2.72 - 2.85 (2H, m), 3.90 (1H, q), 4.01 (1H, q), 4.18 - 4.24 (1H, m), 5.10 (1H, t), 5.51 (1H, s), 7.77 (1H, s), 8.73 (1H, s)	m/z (ES+) (M+H) ⁺ = 399; HPLC t_R = 1.56 min.
	171	N-[(2r,5s)-5-hydroxyadamantan-2-yl]-4-[(2R)-oxolan-2-yl]-2-(propan-2-ylamino)pyrimidine-5-carboxamide	1H NMR (400.132 MHz, CDCl ₃) δ 1.25 (6H, s), 1.48 - 1.58 (3H, m), 1.72 - 1.86 (6H, m), 1.90 - 1.97 (2H, m), 2.02 - 2.09 (2H, m), 2.13 - 2.25 (4H, m), 2.76 (1H, s), 3.89 (1H, q), 4.01 (1H, q), 4.11 - 4.25 (2H, m), 5.08 (1H, t), 5.23 - 5.27 (1H, m), 7.80 (1H, s), 8.68 (1H, s)	m/z (ES+) (M+H) ⁺ = 401; HPLC t_R = 1.79 min.

	172	2-[(3S,5R)-3,5-dimethylpiperazin-1-yl]-N-[(2r,5s)-5-hydroxyadamantan-2-yl]-4-[(2R)-oxolan-2-yl]pyrimidine-5-carboxamide	¹ H NMR (400.132 MHz, CDCl ₃) δ 1.14 (6H, dd), 1.45 - 1.57 (4H, m), 1.75 - 1.83 (6H, m), 1.90 - 1.96 (2H, m), 2.00 - 2.09 (2H, m), 2.14 - 2.26 (4H, m), 2.45 - 2.52 (2H, m), 2.74 - 2.90 (3H, m), 3.90 (1H, q), 3.98 - 4.04 (1H, m), 4.19 - 4.24 (1H, m), 4.69 - 4.74 (2H, m), 5.08 (1H, t), 7.90 (1H, d), 8.74 (1H, s)	m/z (ES+) (M+H) ⁺ = 456; HPLC t _R = 1.59 min.
	173	N-[(2r,5s)-5-hydroxyadamantan-2-yl]-2-(oxetan-3-ylamino)-4-[(2R)-oxolan-2-yl]pyrimidine-5-carboxamide	¹ H NMR (400.132 MHz, CDCl ₃) δ 1.41 - 1.58 (3H, m), 1.75 - 1.85 (6H, m), 1.90 - 1.97 (2H, m), 2.03 - 2.11 (2H, m), 2.14 - 2.24 (4H, m), 2.66 - 2.78 (1H, m), 3.90 (1H, q), 3.97 - 4.03 (1H, m), 4.19 - 4.24 (1H, m), 4.60 (2H, t), 4.95 - 5.00 (2H, m), 5.07 (1H, t), 5.14 (1H, sextet), 5.83 (1H, d), 7.78 (1H, s), 8.71 (1H, s)	m/z (ES+) (M+H) ⁺ = 415; HPLC t _R = 1.31 min.

	174	N-[(2r,5s)-5-hydroxyadamantan-2-yl]-2-(oxan-4-ylamino)-4-[(2R)-oxolan-2-yl]pyrimidine-5-carboxamide	¹ H NMR (400.13 MHz, CDCl ₃) δ 1.48 - 1.62 (6H, m), 1.73 - 1.84 (6H, m), 1.89 - 1.97 (2H, m), 1.99 - 2.11 (4H, m), 2.14 - 2.25 (4H, d), 2.71 (1H, bs), 3.54 (2H, td), 3.87 - 3.93 (1H, m), 3.96 - 4.02 (2H, m), 4.04 - 4.12 (1H,m), 4.19 - 4.23 (1H, m), 5.08 (1H, t), 5.34 (1H, s), 7.76 (1H,bs), 8.69 (1H, s)	m/z (ESI+) (M+H) ⁺ = 443; HPLC t _R = 1.56 min.
	175	2-(cyclobutylamino)-N-[(2r,5s)-5-hydroxyadamantan-2-yl]-4-[(2R)-oxolan-2-yl]pyrimidine-5-carboxamide	¹ H NMR (400.13 MHz, DMSO-d ₆) δ 1.33 (2H,d), 1.59 (3H, s), 1.61 - 1.73 (6H,m), 1.83 - 1.92 (4H,m), 1.92 - 2.05 (5H,m), 2.09 (1H,s), 2.17 - 2.25 (2H,m), 3.73 - 3.80 (1H,m), 3.86 - 3.95 (2H,m), 4.30 - 4.38 (1H,m), 4.43 (1H,s), 5.04 (1H,bs), 7.69 (1H,d), 8.03 (1H,d), 8.25 (1H, s)	m/z (ESI+) (M+H) ⁺ = 413; HPLC t _R = 1.91 min.

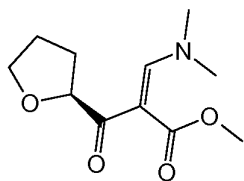
The following Examples were prepared in a similar manner to Example 75, using Intermediate 115 and an appropriate starting material:

Structure	Ex	Name	¹ H NMR δ	MS m/e MH ⁺
	176	N-[(2r,5s)-5-hydroxyadamantan-2-yl]-4-[(2R)-oxolan-2-yl]-2-propan-2-ylloxypyrimidine-5-carboxamide	1H NMR (400.132 MHz, CDCl ₃) δ 1.39 (1H, s), 1.41 (6H, d), 1.50 - 1.55 (2H, m), 1.75 - 1.85 (6H, m), 1.91 - 2.00 (2H, m), 2.05 - 2.26 (6H, m), 2.76 - 2.86 (1H, m), 3.91 (1H, q), 4.01 (1H, q), 4.20 - 4.25 (1H, m), 5.12 (1H, t), 5.33 (1H, septet), 7.84 (1H, d), 8.86 (1H, s)	m/z (ES ⁺) (M+H) ⁺ = 402; HPLC t _R = 1.77 min.

The following intermediates were used and were prepared as described below.

Intermediate 117

- 5 (S,Z)-methyl 3-(dimethylamino)-2-(tetrahydrofuran-2-carbonyl)acrylate

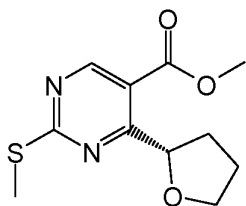


Prepared from (S)-methyl 3-oxo-3-(tetrahydrofuran-2-yl)propanoate by the same process used for Intermediate 1;

- 10 ¹H NMR (400.132 MHz, CDCl₃) δ 1.83 - 1.92 (2H, m), 2.01 - 2.08 (1H, m), 2.13 - 2.22 (1H, m), 3.05 (6H, s), 3.74 (3H, s), 3.83 - 3.96 (2H, m), 4.97 (1H, t), 7.67 (1H, s)
m/z (ES⁺) (M+H)⁺ = 228; HPLC t_R = 1.27 min.

Intermediate 118

(S)-methyl 2-(methylthio)-4-(tetrahydrofuran-2-yl)pyrimidine-5-carboxylate



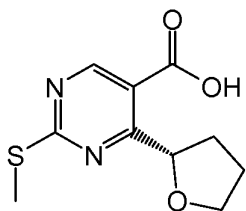
Prepared from Intermediate 117 by the same process used for Intermediate 28

¹H NMR (400.132 MHz, CDCl₃) δ 1.94 - 2.10 (3H, m), 2.37 - 2.46 (1H, m), 2.61 (3H, s), 3.91 (3H, s), 4.00 - 4.05 (1H, m), 4.12 - 4.19 (1H, m), 5.68 - 5.74 (1H, m), 8.88 (1H, s)

5 m/z (ES⁺) (M+H)⁺ = 255; HPLC t_R = 1.88 min.

Intermediate 119

(S)-2-(methylthio)-4-(tetrahydrofuran-2-yl)pyrimidine-5-carboxylic acid



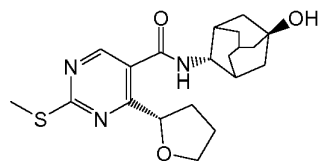
10 Prepared from Intermediate 118 by the same process used for Intermediate 29;

¹H NMR (400.132 MHz, CDCl₃) δ 2.00 - 2.17 (3H, m), 2.39 - 2.50 (1H, m), 2.62 (3H, s), 4.04 - 4.13 (1H, m), 4.17 - 4.24 (1H, m), 5.71 - 5.77 (1H, m), 7.03 (1H, bs), 9.03 (1H, s)

m/z (ES⁺) (M+H)⁺ = 241; HPLC t_R = 0.54 min.

15 Example 177

N-[(2r,5s)-5-hydroxyadamantan-2-yl]-2-methylsulfanyl-4-[(2S)-oxolan-2-yl]pyrimidine-5-carboxamide



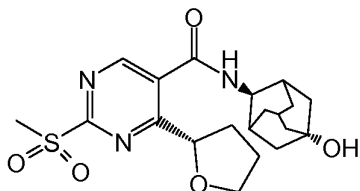
20 N-Ethyldiisopropylamine (11.89 mL, 68.25 mmol) was added to (S)-2-(methylthio)-4-(tetrahydrofuran-2-yl)pyrimidine-5-carboxylic acid (Intermediate 119, 4.1 g, 17.06 mmol), 4-aminoadamantan-1-ol hydrochloride (3.48 g, 17.06 mmol) and O-(7-Azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (7.79 g, 20.48 mmol) in DMF (40 mL) at ambient temperature under nitrogen. The resulting solution was stirred at ambient

temperature for 16 hours. The reaction mixture was evaporated to dryness and redissolved in EtOAc (50 mL) and washed sequentially with water (100 mL) and saturated brine (100mL). The organic layer was dried over MgSO₄, filtered and evaporated to afford crude product.

- 5 The crude product was purified by flash silica chromatography, elution gradient 1 to 6% DCM in MeOH. Pure fractions were evaporated to dryness to afford N-[(2r,5s)-5-hydroxyadamantan-2-yl]-2-methylsulfanyl-4-[(2S)-oxolan-2-yl]pyrimidine-5-carboxamide (3.48 g, 52.4 %) as an off-white solid;
- 1H NMR (400.132 MHz, CDCl₃) δ 1.50 - 1.59 (3H, m), 1.75 - 1.83 (6H, m), 1.90 - 1.97 (2H, m), 2.03 - 2.27 (6H, m), 2.59 (3H, s), 2.80 - 2.91 (1H, m), 3.89 - 3.93 (1H, m), 3.97 - 4.02 (1H, m), 4.20 - 4.26 (1H, m), 5.14 (1H, t), 7.91 (1H, d), 8.86 (1H, s)
- 10 m/z (ES+) (M+H)⁺ = 390; HPLC t_R = 1.69 min.

Intermediate 121

- 15 N-[(2r,5s)-5-hydroxyadamantan-2-yl]-2-methylsulfonyl-4-[(2S)-oxolan-2-yl]pyrimidine-5-carboxamide

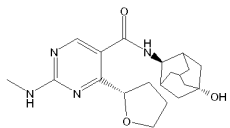
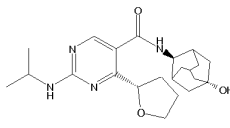


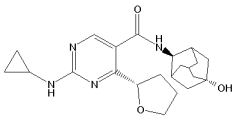
Prepared from Example 177 by the same process used for Example 4;

- 1H NMR (400.132 MHz, CDCl₃) δ 1.50 - 1.60 (3H, m), 1.74 - 1.85 (6H, m), 1.90 - 1.98 (2H, m), 2.08 - 2.31 (6H, m), 2.79 - 2.90 (1H, m), 3.36 (3H, s), 3.90 - 4.04 (2H, m), 4.23 - 4.30 (1H, m), 5.24 (1H, t), 7.88 (1H, d), 9.17 (1H, s)
- 20 m/z (ES+) (M+H)⁺ = 422; HPLC t_R = 1.30 min.

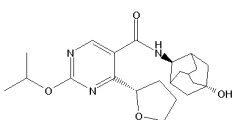
The following Examples were prepared in a similar manner to Example 159, using

- 25 Intermediate 121 and an appropriate amine starting material:

Structure	Ex	Name	¹ H NMR δ	MS m/e MH ⁺
	178	N-[(2r,5s)-5-hydroxyadamantan-2-yl]-2-methylamino-4-[(2S)-oxolan-2-yl]pyrimidine-5-carboxamide	1H NMR (400.132 MHz, CDCl ₃) δ 1.40 (1H, s), 1.52 (2H, t), 1.76 - 1.85 (6H, m), 1.90 - 1.96 (2H, m), 2.01 - 2.10 (2H, m), 2.14 - 2.25 (4H, m), 2.78 (1H, s), 3.04 (3H, d), 3.90 (1H, q), 4.01 (1H, q), 4.19 - 4.24 (1H, m), 5.09 (1H, t), 5.31 (1H, d), 7.80 (1H, s), 8.71 (1H, s)	m/z (ES ⁺) (M+H) ⁺ = 373; HPLC t _R = 1.36 min.
	179	N-[(2r,5s)-5-hydroxyadamantan-2-yl]-4-[(2S)-oxolan-2-yl]-2-(propan-2-ylamino)pyrimidine-5-carboxamide	1H NMR (400.132 MHz, CDCl ₃) δ 1.25 (6H, dd), 1.40 (1H, s), 1.52 (2H, t), 1.75 - 1.83 (6H, m), 1.91 - 1.96 (2H, m), 2.02 - 2.09 (2H, m), 2.13 - 2.26 (4H, m), 2.76 (1H, s), 3.89 (1H, q), 4.01 (1H, q), 4.12 - 4.23 (2H, m), 5.08 (1H, t), 5.20 (1H, d), 7.82 (1H, s), 8.69 (1H, s)	m/z (ES ⁺) (M+H) ⁺ = 401; HPLC t _R = 1.78 min.

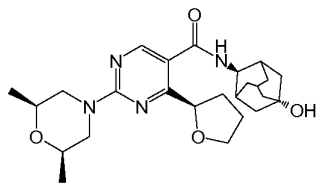
	180	2-(cyclopropylamino)-N-[(2r,5s)-5-hydroxyadamantan-2-yl]-4-[(2S)-oxolan-2-yl]pyrimidine-5-carboxamide	1H NMR (400.132 MHz, CDCl ₃) δ 0.54 - 0.58 (2H, m), 0.81 - 0.85 (2H, m), 1.42 (1H, s), 1.53 (2H, t), 1.77 - 1.86 (6H, m), 1.90 - 1.97 (2H, m), 2.02 - 2.09 (2H, m), 2.15 - 2.25 (4H, m), 2.71 - 2.85 (2H, m), 3.89 (1H, q), 4.01 (1H, q), 4.18 - 4.24 (1H, m), 5.10 (1H, t), 5.53 (1H, s), 7.78 (1H, s), 8.74 (1H, s)	m/z (ES ⁺) (M+H) ⁺ = 399; HPLC t _R = 1.56 min.
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The following Examples were prepared in a similar manner to Example 75, using Intermediate 121 and an appropriate starting material:

Structure	Ex	Name	¹ H NMR δ	MS m/e MH ⁺
	181	N-[(2r,5s)-5-hydroxyadamantan-2-yl]-4-[(2S)-oxolan-2-yl]-2-propan-2-yloxy pyrimidine-5-carboxamide	1H NMR (400.132 MHz, CDCl ₃) δ 1.39 (1H, s), 1.41 (6H, d), 1.49 - 1.57 (2H, m), 1.76 - 1.85 (6H, m), 1.91 - 1.96 (2H, m), 2.04 - 2.26 (6H, m), 2.76 - 2.85 (1H, m), 3.91 (1H, q), 4.00 (1H, q), 4.21 - 4.25 (1H, m), 5.12 (1H, t), 5.33 (1H, septet), 7.82 (1H, d), 8.86 (1H, s)	m/z (ES ⁺) (M+H) ⁺ = 402; HPLC t _R = 1.75 min.

5 Example 182

N-[(2r,5s)-5-Hydroxyadamantan-2-yl] 2-[(2S,6R)-2,6-dimethylmorpholin-4-yl]-4-[(2R)-oxolan-2-yl]pyrimidine-5-carboxamide



N-[(2R,5S)-5-hydroxyadamantan-2-yl]-2-methylsulfonyl-4-[(2R)-oxolan-2-yl]pyrimidine-5-carboxamide (Intermediate 115, 12.3 g, 29.18 mmol) and (2R,6S)-2,6-dimethylmorpholine (15 mL, 121.12 mmol) were dissolved in THF (150 mL) under N₂.

5 The resulting solution was stirred at 20 °C for 24 hours. The reaction mixture was evaporated to dryness and the crude product was purified by flash silica chromatography, elution gradient 1 to 5% MeOH in EtOAc. Pure fractions were evaporated to dryness and triturated with ether to afford N-[(2R,5S)-5-hydroxyadamantan-2-yl] 2-[(2S,6R)-2,6-dimethylmorpholin-4-yl]-4-[(2R)-oxolan-2-yl]pyrimidine-5-carboxamide (7.80 g, 58.5
10 %)

The compound was further purified by chiral chromatography (Merck 100mm 20µm Chiralpak AS column, Flow: 150 ml/min) eluting with iso-Hexane/EtOH 70/30. Pure fractions were evaporated to dryness to afford N-[(2R,5S)-5-hydroxyadamantan-2-yl] 2-[(2S,6R)-2,6-dimethylmorpholin-4-yl]-4-[(2R)-oxolan-2-yl]pyrimidine-5-carboxamide

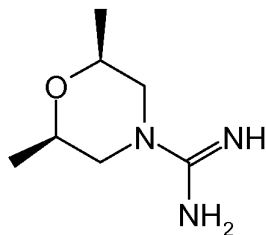
15 100% enantiomerically pure;

¹H NMR (400.132 MHz, CDCl₃) δ 1.26 (6H, d), 1.41 (1H, s), 1.48 - 1.58 (2H, m), 1.75 - 1.85 (6H, m), 1.89 - 1.96 (2H, m), 2.01 - 2.09 (2H, m), 2.14 - 2.23 (4H, m), 2.62 (2H, t), 2.74 - 2.82 (1H, m), 3.57 - 3.66 (2H, m), 3.91 (1H, q), 3.98 - 4.03 (1H, m), 4.19 - 4.26 (1H, m), 4.63 (2H, d), 5.08 (1H, t), 7.90 (1H, d), 8.75 (1H, s)

20 m/z (ES⁺) (M+H)⁺ = 457; HPLC t_R = 1.96 min.

Intermediate 173

(2R,6S)-2,6-dimethylmorpholine-4-carboximidamide



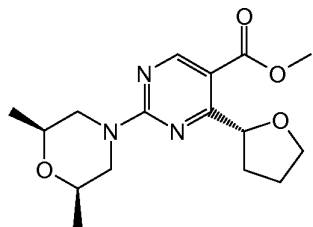
25 Methyl carbamimidothioate hemisulfate (148 g, 520.95 mmol) was added in one portion to

(2S,6R)-2,6-dimethylmorpholine (103 g, 868.26 mmol), in water (5 vol) (500 mL) warmed to 100°C. The resulting slurry was stirred at 100 °C for 1 hour. To the colourless solution was added dropwise Barium chloride dihydrate (127 g, 520.95 mmol) in water (400ml, 4 vol) and the reaction mixture left heating for another hour and the reaction was cooled to ambient and the white precipitate filtered off through Dicalite and the aqueous filtrates
5 evaporated to dryness then azetroped with toluene. To the residue was added ethanol (400ml, 4 vol) and the the white solid filtered washed with diethyl ether (200ml, 2 vol) air dried to give (2R,6S)-2,6-dimethylmorpholine-4-carboximidamide (92 g, 55%) and the mother liquors evaporated and more ethanol (200ml, 2 vol) charged the white solid filtered
10 off washed with ethanol (200ml, 2 vol) to give (2R,6S)-2,6-dimethylmorpholine-4-carboximidamide (3.2 g, 2%).

¹H NMR (400 MHz, DMSO) δ 1.09 (6H, d), 2.63 (2H, dd), 3.63 - 3.48 (2H, m), 3.83 (2H, d), 7.68 (4H, s).

15 Intermediate 169

methyl 2-((2S,6R)-2,6-dimethylmorpholino)-4-((R)-tetrahydrofuran-2-yl)pyrimidine-5-carboxylate



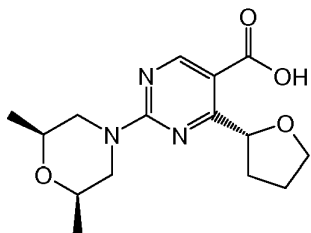
(2R,6S)-2,6-dimethylmorpholine-4-carboximidamide (Intermediate 173, 190 mg, 0.98 mmol) was added in one portion to (R,Z)-methyl 3-(dimethylamino)-2-(tetrahydrofuran-2-carbonyl)acrylate (Intermediate 112, 223 mg, 0.98 mmol), and Sodium acetate (338 mg, 4.12 mmol) in DMF (10 mL) at 20°C under nitrogen. The resulting suspension was stirred at 80 °C for 4 hours. LC-MS (EN01493-77-C2) shows 7% starting material so additional (2R,6S)-2,6-dimethylmorpholine-4-carboximidamide (20 mg, 0.1eq) was charged and left
25 stirring for an additional 2 hours LC-MS (EN01493-77-C4) shows 1.6% starting material the reaction was allowed to cool to ambient drowned out with water (100ml), extracted with ethyl acetate (2 x 50ml). The combined organic layers were washed with water (2 x 50ml) and the organic layer put down a phase separating cartridge to remove the water.

The crude product was purified by flash silica chromatography, elution gradient 30% EtOAc in isohexane. Pure fractions were evaporated to dryness to afford methyl 2-((2S,6R)-2,6-dimethylmorpholino)-4-((R)-tetrahydrofuran-2-yl)pyrimidine-5-carboxylate (213 mg, 67.5 %) as a pale yellow oil which solidified on standing;

- 5 ¹H NMR (400 MHz, CDCl₃) δ 1.19 (6H, d), 2.05 - 1.78 (3H, m), 2.45 - 2.26 (1H, m), 2.75 - 2.48 (2H, m), 3.69 - 3.46 (2H, m), 3.78 (3H, s), 4.02 - 3.93 (1H, m), 4.17 - 4.03 (1H, m), 4.79 - 4.49 (2H, m), 5.71 (1H, dd), 8.74 (1H, s).
m/z (ES⁺) (M+H)⁺ = 321; HPLC t_R = 2.27 min.

10 **Intermediate 170**

2-((2S,6R)-2,6-dimethylmorpholino)-4-((R)-tetrahydrofuran-2-yl)pyrimidine-5-carboxylic acid

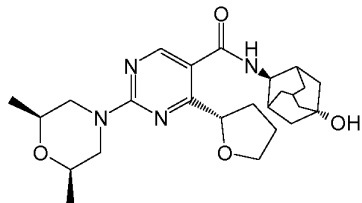


- Sodium hydroxide (0.327 mL, 0.65 mmol) was added dropwise to methyl 2-((2S,6R)-2,6-dimethylmorpholino)-4-((R)-tetrahydrofuran-2-yl)pyrimidine-5-carboxylate (Intermediate 169, 105 mg, 0.33 mmol) in methanol (10 mL) under nitrogen. The resulting solution was stirred at 20 °C for 3 hours. LC-MS (EN01493-86-C1) shows 1% product so additional Sodium hydroxide (0.327 mL, 0.65 mmol) was charged after a further 2 hours LC-MS (EN01493-86-C2) shows 2% product so 5N NaOH (0.327ml, 5eq) was charged and the reaction stirred overnight. LC-MS (EN01493-86-C3) shows 72% product and 28% SM so the reaction was warmed to 40°C after 5 hours LC-MS (EN01493-86-C7) shows no starting material. The reaction mixture was evaporated taken up with water (50ml) and the solution was adjusted to pH3 with 2M HCl. The aqueous layer was extracted with ethyl acetate (2 x 50ml) dried and evaporated to provide 2-((2S,6R)-2,6-dimethylmorpholino)-4-((R)-tetrahydrofuran-2-yl)pyrimidine-5-carboxylic acid (99 mg, 99 %) as a white solid;
- 25 ¹H NMR (400 MHz, CDCl₃) δ 1.20 (6H, d), 2.05 - 1.82 (3H, m), 2.47 - 2.25 (1H, m), 2.78 - 2.48 (2H, m), 3.70 - 3.47 (2H, m), 4.04 - 3.96 (1H, m), 4.18 - 4.04 (1H, m), 4.66 (2H, d), 8.85 (1H, s), 5.78 - 5.58 (1H, m)

m/z (ESI+) (M+H)⁺ = 308; HPLC t_R = 0.89 min.

Example 183

2-[(2S,6R)-2,6-Dimethylmorpholin-4-yl]-N-[(2r,5s)-5-hydroxyadamantan-2-yl]-4-[(2S)-oxolan-2-yl]pyrimidine-5-carboxamide



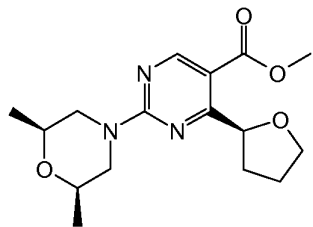
Prepared from Intermediate 172 by the same process used for Example 182

¹H NMR (400.13 MHz, CDCl₃) δ 1.26 (6H, d), 1.45 - 1.60 (3H, m), 1.75 - 1.84 (6H, m), 1.90 - 1.98 (2H, m), 2.01 - 2.11 (2H, m), 2.16 - 2.20 (2H, m), 2.18 - 2.23 (2H, m), 2.63 (2H, dd), 2.76 - 2.81 (1H, m), 3.59 - 3.66 (2H, m), 3.92 (1H, q), 3.98 - 4.03 (1H, m), 4.19 - 4.24 (1H, m), 4.63 (2H, d), 5.08 (1H, t), 7.90 (1H, d), 8.75 (1H, s)

m/z (ESI+) (M+H)⁺ = 457; HPLC t_R = 1.93 min.

Intermediate 171

methyl 2-((2S,6R)-2,6-dimethylmorpholino)-4-((S)-tetrahydrofuran-2-yl)pyrimidine-5-carboxylate



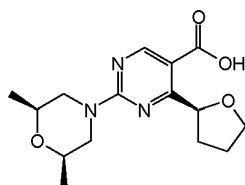
Prepared from Intermediate 117 by the same process used for Intermediate 169;

¹H NMR (400.13 MHz, CDCl₃) δ 1.24 - 1.28 (6H, m), 1.93 - 2.02 (3H, m), 2.37 - 2.45 (1H, m), 2.61 - 2.73 (2H, m), 3.58 - 3.67 (2H, m), 3.85 (3H, s), 4.04 - 4.19 (2H, m), 4.69 - 4.77 (2H, m), 5.75 - 5.79 (1H, m), 8.80 (1H, s)

m/z (ESI+) (M+H)⁺ = 322; HPLC t_R = 2.14 min.

Intermediate 172

2-((2S,6R)-2,6-dimethylmorpholino)-4-((S)-tetrahydrofuran-2-yl)pyrimidine-5-carboxylic acid

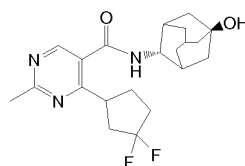


- 5 Prepared from Intermediate 171 by the same process used for Intermediate 170
 ^1H NMR (400.13 MHz, DMSO- d_6) δ 1.15 (6H, d), 1.82 - 1.96 (3H, m), 1.82 - 1.98 (1H, m), 2.21 - 2.26 (1H, m), 2.55 - 2.64 (2H, m), 3.52 - 3.57 (2H, m), 3.86 - 3.90 (1H, m), 3.99 - 4.05 (1H, m), 4.58 (2H, d), 5.66 - 5.70 (1H, m), 8.72 (1H, s)
 m/z (ESI+) (M+H) $^+$ = 308; HPLC t_R = 0.93 min.

10

Example 184

4-(3,3-Difluorocyclopentyl)-N-[(2r,5s)-5-hydroxyadamantan-2-yl]-2-methylpyrimidine-5-carboxamide

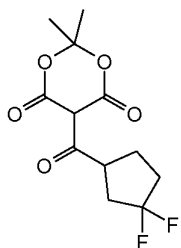


- 15 Prepared from Intermediate 125 by the same process used for Example 4;
 ^1H NMR (400.132 MHz, CDCl $_3$) δ 1.55 - 1.99 (11H, m), 2.02 - 2.23 (4H, m), 2.24 - 2.29 (2H, m), 2.30 - 2.47 (2H, m), 2.56 - 2.72 (1H, m), 2.73 (3H, s), 3.76 - 3.89 (1H, m), 4.18 - 4.26 (1H, m), 5.91 - 6.03 (1H, m), 8.57 (1H, s)
 m/z (ESI+) (M+H) $^+$ = 392; HPLC t_R = 1.77 min.

20

Intermediate 175

5-(3,3-difluorocyclopentanecarbonyl)-2,2-dimethyl-1,3-dioxane-4,6-dione

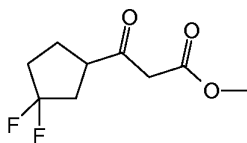


A solution of 3,3-difluorocyclopentanecarbonyl chloride (2.4 g, 14.24 mmol) in dichloromethane (5 mL) was added dropwise to a stirred solution of Isopropylidene malonate (2.257 g, 15.66 mmol) and Pyridine (2.301 mL, 28.47 mmol) in dichloromethane (50 mL) at 0°C, over a period of 10 minutes under nitrogen. The resulting suspension was stirred at 0 °C for 45 minutes then 4 hours at room temperature. The reaction mixture was diluted with DCM and washed sequentially with 1M citric acid, water and saturated brine. The organic layer was dried over MgSO₄, filtered and evaporated to afford 5-(3,3-difluorocyclopentanecarbonyl)-2,2-dimethyl-1,3-dioxane-4,6-dione (3.20 g, 81 %) as a brown oil which was used in the next stage without further purification.

m/z (ESI-) (M-H)- = 275; HPLC t_R = 2.34 min.

Intermediate 122

methyl 3-(3,3-difluorocyclopentyl)-3-oxopropanoate



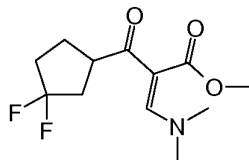
Methanol (50mL) was added in one portion to a stirred solution of 5-(3,3-difluorocyclopentanecarbonyl)-2,2-dimethyl-1,3-dioxane-4,6-dione (Intermediate 175, 3.2 g, 11.58 mmol) in toluene (100mL). The reaction was heated to 125 °C and maintained at this for 4 hours. The cooled reaction was evaporated to dryness to afford crude product. The crude product was purified by flash silica (120g) chromatography, elution gradient 0 to 20% EtOAc in isohexane. Pure fractions were evaporated to dryness to afford methyl 3-(3,3-difluorocyclopentyl)-3-oxopropanoate (1.040 g, 43.5 %) as a colourless oil;

¹H NMR (400.132 MHz, CDCl₃) δ 1.89 - 2.50 (6H, m), 3.20 - 3.31 (1H, m), 3.51 (2H, s), 3.75 (3H, s)

m/z no obvious mass ion - no major ion peak in + or -ve = ; HPLC t_R = 2.33 min

Intermediate 123

(Z)-methyl 2-(3,3-difluorocyclopentanecarbonyl)-3-(dimethylamino)acrylate



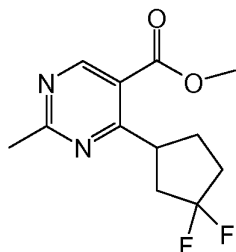
Prepared from methyl methyl 3-(3,3-difluorocyclopentyl)-3-oxopropanoate by the same process used for Intermediate 1;

¹H NMR (400.132 MHz, CDCl₃) δ 1.85 - 2.49 (6H, m), 2.60 - 3.43 (7H, m), 3.75 (3H, s), 7.71 (1H, s)

m/z (ESI⁺) (M+H)⁺ = 262; HPLC t_R = 1.70 min.

Intermediate 124

methyl 4-(3,3-difluorocyclopentyl)-2-methylpyrimidine-5-carboxylate



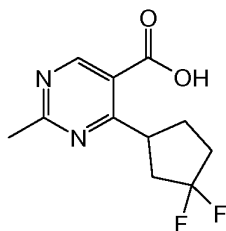
Prepared by the same process used for Intermediate 2 from (Z)-methyl 2-(3,3-difluorocyclopentanecarbonyl)-3-(dimethylamino)acrylate;

¹H NMR (400.132 MHz, CDCl₃) δ 1.97 - 2.27 (3H, m), 2.28 - 2.48 (2H, m), 2.58 - 2.73 (1H, m), 2.75 (3H, s), 3.94 (3H, s), 4.25 - 4.36 (1H, m), 9.03 (1H, s)

m/z (ESI⁺) (M+H)⁺ = 257; HPLC t_R = 2.19 min

Intermediate 125

4-(3,3-difluorocyclopentyl)-2-methylpyrimidine-5-carboxylic acid



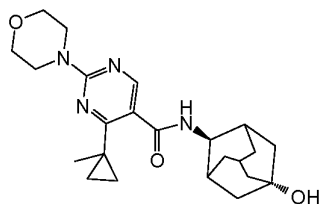
Prepared from Intermediate 124 by the same process used for Intermediate 29;

¹H NMR (400.132 MHz, CDCl₃) δ 2.00 - 2.14 (1H, m), 2.15 - 2.32 (2H, m), 2.33 - 2.54 (2H, m), 2.60 - 2.79 (1H, m), 2.81 (3H, s), 4.38 - 4.49 (1H, m), 7.52 - 9.12 (1H, m), 9.22 (1H, s)

5 m/z (ESI⁺) (M+H)⁺ = 243; HPLC t_R = 1.69 min.

Example 185

N-[(2r,5s)-5-hydroxyadamantan-2-yl]-4-(1-methylcyclopropyl)-2-morpholin-4-ylpyrimidine-5-carboxamide



10

4-(1-methylcyclopropyl)-2-morpholin-4-yl-N-(5-phenylmethoxy-2-adamantyl)pyrimidine-5-carboxamide (Intermediate 128, 0.45g, 0.90 mmol) and 10% Palladium on carbon (45 mg, 0.04 mmol) in ethanol (10 mL) and THF (10.00 mL) were stirred under an atmosphere of hydrogen at 1 atm and 20 °C for 20 hours. The reaction mixture was filtered through
 15 celite and evaporated to give a colourless oil. The crude product was purified by flash silica chromatography, elution gradient 0 to 6% MeOH in DCM. Pure fractions were evaporated to dryness to afford cis N-[(2r,5s)-5-hydroxyadamantan-2-yl]-4-(1-methylcyclopropyl)-2-morpholin-4-ylpyrimidine-5-carboxamide (0.087 g, 23.56 %) as a white solid and trans N-[(2r,5s)-5-hydroxyadamantan-2-yl]-4-(1-methylcyclopropyl)-2-morpholin-4-ylpyrimidine-5-carboxamide (0.042 g, 11.37 %) as a white solid.

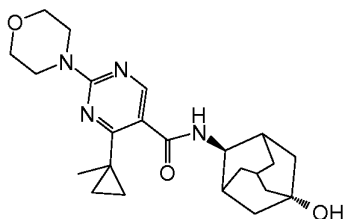
20

¹H NMR (400.132 MHz, CDCl₃) δ 0.76 - 0.79 (2H, m), 1.20 - 1.26 (2H, m), 1.46 (3H, s), 1.54 - 1.57 (1H, m), 1.69 - 1.84 (8H, m), 1.93 - 1.99 (2H, m), 2.15 - 2.20 (1H, m), 2.23 - 2.28 (2H, m), 3.75 (4H, t), 3.85 (4H, t), 4.22 - 4.27 (1H, m), 6.45 (1H, d), 8.55 (1H, s)
 m/z (ESI⁺) (M+H)⁺ = 413; HPLC t_R = 1.71 min

25

Example 186

N-[(2r,5s)-5-hydroxyadamantan-2-yl]-4-(1-methylcyclopropyl)-2-morpholin-4-ylpyrimidine-5-carboxamide

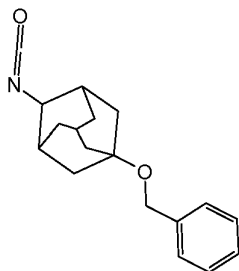


This compound was a byproduct from the synthesis of Example 185;

¹H NMR (400.132 MHz, CDCl₃) δ 0.75 - 0.81 (2H, m), 1.21 - 1.25 (2H, m), 1.46 (3H, s),
 1.49 - 1.51 (1H, m), 1.62 - 1.84 (10H, m), 2.16 - 2.19 (1H, m), 2.29 - 2.33 (2H, m), 3.75
 5 (4H, t), 3.85 (4H, t), 4.14 - 4.18 (1H, m), 6.48 (1H, d), 8.08 (1H, s)
 m/z (ESI⁺) (M+H)⁺ = 413; HPLC t_R = 1.71 min.

Intermediate 176

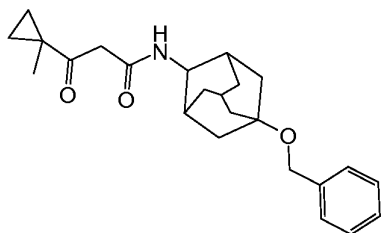
4-isocyanato-1-phenylmethoxyadamantane



10 A solution of 20% phosgene in toluene (16.57 ml, 31.5 mmol) was added to 5-
 phenylmethoxyadamantan-2-amine hydrochloride (4.63 g, 15.76 mmol) and the resulting
 suspension was stirred at 100 °C for 6 hours with a dry ice condenser to avoid loss of
 phosgene from the reaction mixture. All of the solid dissolves during the course of the
 15 heating. Cooled, filtered and evaporated to give the crude product, 4-isocyanato-1-
 phenylmethoxyadamantane (4.02 g, 90 %) as a red oil. Intermediate 176 was used in the
 next synthetic step without characterisation.

Intermediate 126

20 3-(1-methylcyclopropyl)-3-oxo-N-(5-phenylmethoxy-2-adamantyl)propanamide



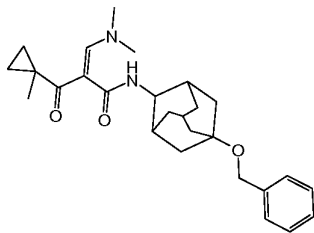
A solution of Lithium bis(trimethylsilyl)amide (15.61 mL, 15.61 mmol) was added to THF (15mL) and cooled under nitrogen to -78°C . A solution of 1-(1-methylcyclopropyl)ethanone (1.532 g, 15.61 mmol) in THF (5mL) was added dropwise over a period of 5 minutes under nitrogen. The resulting solution was stirred at -78°C for 15 minutes. A solution of 4-isocyanato-1-phenylmethoxyadamantane (Intermediate 176, 4.02 g, 14.19 mmol) in THF (10mL) was added over a period of 5 minutes under nitrogen. The resulting solution was stirred at -78°C for 1 hour and then allowed to warm to 20°C over 1h. The reaction mixture was poured into saturated NH_4Cl (250mL) and extracted with EtOAc (2 x 150mL), the organic layer was washed with water (50mL) and brine (50mL) dried over MgSO_4 , filtered and evaporated to afford a yellow oil. The crude product was purified by flash silica chromatography, elution gradient 20 to 60% EtOAc in isohexane. Pure fractions were evaporated to dryness to afford 3-(1-methylcyclopropyl)-3-oxo-N-(5-phenylmethoxy-2-adamantyl)propanamide (2.76 g, 51.0 %) as a colourless oil.

^1H NMR (400.132 MHz, CDCl_3) δ 0.83 - 0.89 (2H, m), 1.33 - 1.38 (5H, m), 1.71 - 2.02 (10H, m), 2.13 - 2.24 (3H, m), 3.33 (2H, 2xs), 3.93 - 4.07 (1H, m), 4.51 (2H, 2xs), 7.22 - 7.39 (5H, m), 7.75 - 7.86 (1H, m)

m/z (ESI+) $(\text{M}+\text{H})^+ = 382$; HPLC $t_R = 2.59$ min.

20 Intermediate 127

(Z)-3-dimethylamino-2-(1-methylcyclopropanecarbonyl)-N-(5-phenylmethoxy-2-adamantyl)prop-2-enamide



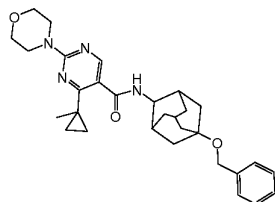
Prepared from Intermediate 126 by the same process used for Intermediate 1;

¹H NMR (400.132 MHz, CDCl₃) δ 0.62 - 0.71 (2H, m), 1.01 - 1.18 (2H, m), 1.36 (3H, s), 1.48 - 1.53 (1H, m), 1.67 - 1.79 (3H, m), 1.83 - 1.90 (4H, m), 1.98 - 2.06 (2H, m), 2.12 - 2.18 (2H, m), 2.21 - 2.26 (1H, m), 3.11 (6H, 2xs), 3.95 - 4.10 (1H, m), 4.52 (2H, 2xs), 7.21 - 7.25 (1H, m), 7.29 - 7.37 (5H, m), 7.90 (1H, d)

5 m/z (ESI+) (M+H)⁺ = 437; HPLC t_R = 2.23 min.

Intermediate 128

4-(1-methylcyclopropyl)-2-morpholin-4-yl-N-(5-phenylmethoxy-2-adamantyl)pyrimidine-5-carboxamide



10

A solution of (Z)-3-dimethylamino-2-(1-methylcyclopropanecarbonyl)-N-(5-phenylmethoxy-2-adamantyl)prop-2-enamide (Intermediate 127, 0.6 g, 1.37 mmol) in methanol (3 mL) was added dropwise to a stirred suspension of Morpholinoformamidinium hydrobromide (0.289 g, 1.37 mmol), and Sodium methoxide (0.5M in MeOH) (2.75 mL, 1.37 mmol) in methanol (8 mL) at 20°C. The resulting solution was stirred at 80 °C for 4 hours.

15

The reaction mixture was evaporated to dryness and redissolved in EtOAc (100 mL), and washed sequentially with water (75 mL) and saturated brine (75 mL). The organic layer was dried over MgSO₄, filtered and evaporated to afford crude product.

20

The crude product was purified by flash silica chromatography, elution gradient 40 to 70% EtOAc in isohexane. Pure fractions were evaporated to dryness to afford 4-(1-methylcyclopropyl)-2-morpholin-4-yl-N-(5-phenylmethoxy-2-adamantyl)pyrimidine-5-carboxamide (0.450 g, 65.1 %) as a colourless oil.

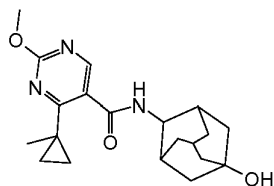
25

¹H NMR (400.132 MHz, CDCl₃) δ 0.76 - 0.81 (2H, m), 1.21 - 1.29 (2H, m), 1.46 (3H, 2xs), 1.58 - 1.64 (1H, m), 1.73 - 1.97 (7H, m), 2.06 - 2.11 (1H, m), 2.19 - 2.23 (1H, m), 2.28 - 2.37 (2H, m), 3.75 (4H, t), 3.85 (4H, t), 4.17 - 4.29 (1H, m), 4.51 (2H, 2xs), 6.44 - 6.56 (1H, m), 7.21 - 7.26 (1H, m), 7.30 - 7.35 (5H, m), 8.56 (1H, 2xs)

m/z (ESI+) (M+H)⁺ = 503; HPLC t_R = 2.98 min.

Example 187

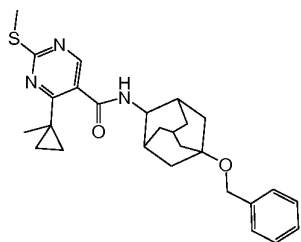
N-[(2r,5s)-5-hydroxyadamantan-2-yl]-2-methoxy-4-(1-methylcyclopropyl)pyrimidine-5-carboxamide



- 5 2-methoxy-4-(1-methylcyclopropyl)-N-(5-phenylmethoxy-2-adamantyl)pyrimidine-5-carboxamide (Intermediate 130, 0.17 g, 0.38 mmol) and 10% Palladium on carbon (17 mg, 0.02 mmol) in ethanol (5 mL) and THF (5.00 mL) were stirred under an atmosphere of hydrogen at 1 atm and 20 °C for 20 hours. The reaction mixture was filtered through celite and evaporated and the reaction repeated for a further 24 hrs.
- 10 The reaction mixture was filtered through celite and evaporated to give a colourless oil. The crude product was purified by flash silica chromatography, elution gradient 2 to 7% MeOH in DCM. Pure fractions were evaporated to dryness to afford N-[(2r,5s)-5-hydroxyadamantan-2-yl]-2-methoxy-4-(1-methylcyclopropyl)pyrimidine-5-carboxamide (0.080 g, 58.9 %) as a white solid;
- 15 ¹H NMR (400.132 MHz, CDCl₃) δ 0.83 - 0.87 (2H, m), 1.25 - 1.29 (2H, m), 1.43 - 1.48 (1H, m), 1.49 (3H, s), 1.56 - 1.59 (1H, m), 1.66 - 1.87 (8H, m), 1.91 - 1.98 (1H, m), 2.17 - 2.36 (3H, m), 4.02 (3H, 2xs), 4.15 - 4.30 (1H, m), 5.90 - 6.41 (1H, m), 8.54 (1H, 2xs) m/z (ESI+) (M+H)⁺ = 358; HPLC t_R = 1.50 min

Intermediate 129

4-(1-methylcyclopropyl)-2-methylsulfanyl-N-(5-phenylmethoxy-2-adamantyl)pyrimidine-5-carboxamide



Prepared from Intermediate 127 by the same process used for Intermediate 128;

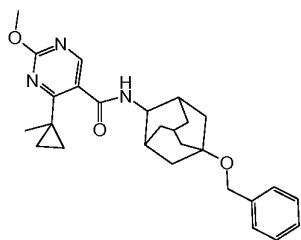
- 25 ¹H NMR (400.132 MHz, CDCl₃) δ 0.83 - 0.86 (2H, m), 1.26 - 1.30 (2H, m), 1.49 (3H,

2xs), 1.59 - 1.66 (1H, m), 1.71 - 1.97 (8H, m), 2.06 - 2.11 (1H, m), 2.19 - 2.24 (1H, m), 2.29 - 2.38 (2H, m), 2.56 (3H, 2xs), 4.18 - 4.31 (1H, m), 4.51 (2H, d), 6.30 - 6.38 (1H, m), 7.22 - 7.26 (1H, m), 7.30 - 7.38 (4H, m), 8.59 (1H, 2xs)
 m/z (ESI+) (M+H)+ = 464; HPLC t_R = 2.83 min.

5

Intermediate 130

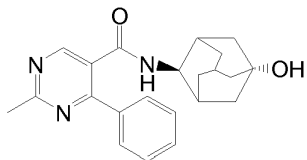
2-methoxy-4-(1-methylcyclopropyl)-N-(5-phenylmethoxy-2-adamantyl)pyrimidine-5-carboxamide



- 10 3-Chloroperoxybenzoic acid (70%) (1.276 g, 5.18 mmol) was added in one portion to 4-(1-methylcyclopropyl)-2-methylsulfanyl-N-(5-phenylmethoxy-2-adamantyl)pyrimidine-5-carboxamide (Intermediate 129, 1.2 g, 2.59 mmol) in DCM (50 mL) at 0°C. The resulting solution was stirred at 20 °C for 24 hours. The reaction mixture was diluted with DCM (50 mL), and washed sequentially with saturated NaHCO₃ (75 mL), 2M NaOH (75 mL), and
- 15 saturated brine (75 mL). The organic layer was dried over MgSO₄, filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 50 to 100% EtOAc in isohexane followed by 20% MeOH in DCM (to flush off the pyrimidone). Pure fractions were evaporated to dryness to afford 2-methoxy-4-(1-methylcyclopropyl)-N-(5-phenylmethoxy-2-adamantyl)pyrimidine-5-carboxamide
- 20 (0.170 g, 14.68 %) as a colourless oil and 2-hydroxy-4-(1-methylcyclopropyl)-N-(5-phenylmethoxy-2-adamantyl)pyrimidine-5-carboxamide (0.330 g, 29.4 %) as a white solid; ¹H NMR (400.132 MHz, CDCl₃) δ 0.81 - 0.88 (2H, m), 1.23 - 1.28 (2H, m), 1.49 (3H, 2xs), 1.58 - 1.61 (1H, m), 1.72 - 1.97 (8H, m), 2.06 - 2.11 (1H, m), 2.18 - 2.25 (1H, m), 2.30 - 2.38 (2H, m), 4.02 (3H, 2xs), 4.18 - 4.31 (1H, m), 4.51 (2H, 2xs), 6.37 - 6.42 (1H, m), 7.22 - 7.26 (1H, m), 7.30 - 7.35 (4H, m), 8.61 (1H, 2xs)
- 25 m/z (ESI+) M+H+ = 447; HPLC t_R = 2.78 min

Example 188

N-[(2r,5s)-5-hydroxyadamantan-2-yl]-2-methyl-4-phenylpyrimidine-5-carboxamide



O-(7-Azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (456 mg,
 5 1.2 mmol) was added in one portion to 2-methyl-4-phenylpyrimidine-5-carboxylic acid
 (214 mg, 1.00 mmol), 4-aminoadamantan-1-ol hydrochloride (203 mg, 1.00 mmol) and N-
 Ethyldiisopropylamine (0.522 mL, 3.00 mmol) in DMF (10 mL) at 25°C under nitrogen.
 The resulting solution was stirred at 25 °C for 3 hours.

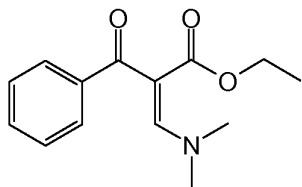
The reaction mixture was concentrated and diluted with EtOAc (100 mL), and washed
 10 sequentially with saturated NaHCO₃ (100 mL), saturated brine (100 mL), and water (100
 mL). The organic layer was dried over MgSO₄, filtered and evaporated to afford
 crude product. The crude product was purified by preparative HPLC (Waters XBridge Prep
 C18 OBD column, 5μ silica, 30 mm diameter, 100 mm length), using decreasingly polar
 mixtures of water (containing 0.1% NH₃) and MeCN as eluents. Fractions containing the
 15 desired compound were evaporated to dryness to afford N-[(2r,5s)-5-hydroxyadamantan-2-
 yl]-2-methyl-4-phenylpyrimidine-5-carboxamide (189 mg, 52.1 %) as a white solid;

¹H NMR (400.13 MHz, DMSO-d₆) δ 1.16 - 1.19 (2H, m), 1.47 - 1.67 (8H, m), 1.85 - 1.88
 (3H, m), 2.69 (3H, s), 3.88 (1H, t), 4.36 (1H, s), 7.39 - 7.51 (3H, m), 7.69 - 7.73 (2H, m),
 8.29 - 8.31 (1H, m), 8.64 (1H, s)

20 m/z (ESI⁺) (M+H)⁺ = 364; HPLC t_R = 1.42 min.

Intermediate 131

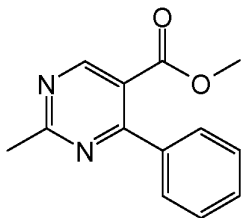
ethyl (Z)-2-benzoyl-3-dimethylaminoprop-2-enoate



25 Prepared from ethyl 3-oxo-3-phenylpropanoate by the same process used for Intermediate ;
 m/z (ESI⁺) (M+H)⁺ = 248; HPLC t_R = 1.79 min.

Intermediate 132

methyl 2-methyl-4-phenylpyrimidine-5-carboxylate



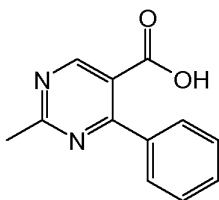
Prepared from Z)-methyl 2-benzoyl-3-(dimethylamino)acrylate by the same process used
5 for Intermediate 2;

¹H NMR (400.13 MHz, DMSO-d₆) δ 2.72 (3H, s), 3.71 (3H, s), 7.47 - 7.55 (3H, m), 7.57 -
7.60 (2H, m), 9.01 (1H, s)

m/z (ESI+) (M+H)⁺ = 229; HPLC t_R = 1.76 min.

Intermediate 133

2-methyl-4-phenylpyrimidine-5-carboxylic acid



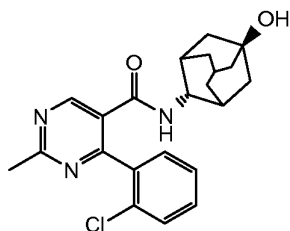
Prepared from Intermediate 132 by the same process used for Intermediate 29;

¹H NMR (400.13 MHz, DMSO-d₆) δ 2.71 (3H, s), 7.45 - 7.53 (3H, m), 7.58 - 7.63 (2H,
15 m), 8.98 (1H, s), 13.44 (1H, s)

m/z (ESI+) (M+H)⁺ = 215; HPLC t_R = 1.19 min.

Example 189

4-(2-Chlorophenyl)-N-[(2r,5s)-5-hydroxyadamantan-2-yl]-2-methylpyrimidine-5-
20 carboxamide



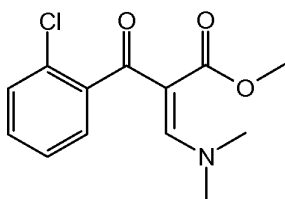
Prepared from Intermediate 136 by the same process used for Example 188;

¹H NMR (400.13 MHz, CDCl₃) δ 0.95 (2H, d), 1.22 (2H, d), 1.57 - 1.64 (1H, m), 1.73 (3H, d), 1.80 - 1.86 (3H, m), 1.83 (2H, d), 2.78 (3H, s), 3.94 - 3.99 (1H, m), 5.71 (1H, d), 7.38 - 7.41 (3H, m), 7.44 - 7.47 (1H, m), 9.10 (1H, s)

5 m/z (ESI+) (M+H)⁺ = 398; HPLC t_R = 1.53 min.

Intermediate 134

(Z)-methyl 2-(2-chlorobenzoyl)-3-(dimethylamino)acrylate



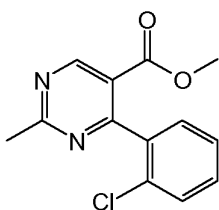
10 Prepared from methyl 3-(2-chlorophenyl)-3-oxopropanoate/84745/ by the same process used for Intermediate 1;

¹H NMR (400.13 MHz, CDCl₃) δ 2.91 (3H,bs), 3.25 (3H,bs), 3.38 (3H,s), 7.17 - 7.22 (2H, m), 7.26 - 7.29 (1H,m), 7.30 - 7.33 (1H,m), 7.71 (1H,s)

15 m/z (ESI+) (M+H)⁺ = 268; HPLC t_R = 1.50 min.

Intermediate 135

methyl 4-(2-chlorophenyl)-2-methylpyrimidine-5-carboxylate



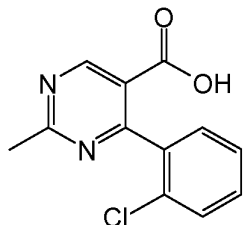
20 Prepared from (Z)-methyl 2-(2-chlorobenzoyl)-3-(dimethylamino)acrylate by the same process used for Intermediate 2;

¹H NMR (400.13 MHz, CDCl₃) δ 2.84 (3H, s), 3.73 (3H, s), 7.37 - 7.43 (4H, m), 9.19 (1H, s)

m/z (ESI+) (M+H)⁺ = 263; HPLC t_R = 1.90 min.

Intermediate 136

4-(2-chlorophenyl)-2-methylpyrimidine-5-carboxylic acid

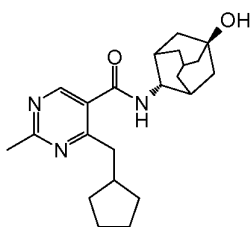


Prepared from Intermediate 135 by the same process used for Intermediate 29;

5 m/z (ESI+) $(M+H)^+ = 249$; HPLC $t_R = 1.41$ min.

Example 190

4-(Cyclopentylmethyl)-N-[(2r,5s)-5-hydroxyadamantan-2-yl]-2-methylpyrimidine-5-carboxamide



10

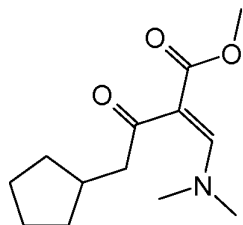
Prepared from Intermediate 140 by the same process used for Example 188;

^1H NMR (400.13 MHz, $CDCl_3$) δ 1.18 - 1.27 (2H, m), 1.47 - 1.56 (2H, m), 1.57 - 1.73 (9H, m), 1.81 (2H, s), 1.85 (1H, s), 1.96 (2H, d), 2.19 (1H, s), 2.27 (2H, s), 2.33 (1H, q), 2.74 (3H, s), 2.96 (2H, d), 4.21 - 4.25 (1H, m), 6.01 (1H, d), 8.57 (1H, s)

15 m/z (ESI+) $(M+H)^+ = 370$; HPLC $t_R = 1.68$ min.

Intermediate 138

(E)-methyl 4-cyclopentyl-2-((dimethylamino)methylene)-3-oxobutanoate

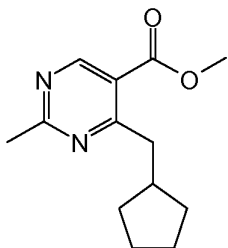


20 Prepared from methyl 4-cyclopentyl-3-oxobutanoate by the same process used for Intermediate 1;

¹H NMR (400.13 MHz, CDCl₃) δ 1.07 - 1.16 (2H, m), 1.46 - 1.60 (4H, m), 1.73 - 1.81 (2H, m), 2.20 - 2.28 (1H, m), 2.68 (2H, d), 3.01 (6H, bs), 3.73 (3H, s), 7.64 (1H, s)
m/z (ESI+) (M+H)⁺ = 240; HPLC t_R = 1.90 min.

5 **Intermediate 139**

methyl 4-(cyclopentylmethyl)-2-methylpyrimidine-5-carboxylate

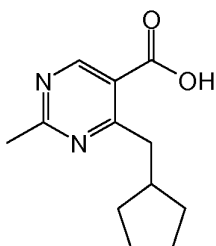


Prepared from Intermediate 138 by the same process used for Intermediate 2;

¹H NMR (400.13 MHz, CDCl₃) δ 1.13 - 1.22 (2H, m), 1.40 - 1.47 (2H, m), 1.55 - 1.64 (4H, m), 2.17 - 2.25 (1H, m), 2.67 (3H, s), 3.09 (2H, d), 3.86 (3H, s), 8.94 (1H, s)
10 m/z (ESI+) (M+H)⁺ = 235; HPLC t_R = 2.31 min.

Intermediate 140

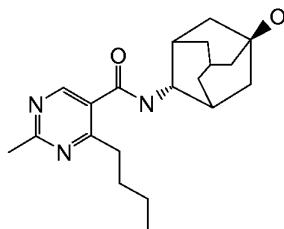
4-(cyclopentylmethyl)-2-methylpyrimidine-5-carboxylic acid



15 Prepared from Intermediate 139 by the same process used for Intermediate 29;
m/z (ESI+) (M+H)⁺ = 221; HPLC t_R = 0.68 min.

Example 191

20 4-Butyl-N-[(2r,5s)-5-hydroxyadamantan-2-yl]-2-methylpyrimidine-5-carboxamide

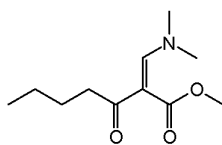


Prepared from Intermediate 144 by the same process used for Example 188;

¹H NMR (400.13 MHz, DMSO-d₆) δ 0.85 (3H, t), 1.23 - 1.35 (4H, m), 1.55 - 1.64 (6H, m), 1.71 - 1.74 (2H, m), 1.89 - 1.92 (2H, m), 1.97 - 2.00 (1H, m), 2.02 - 2.07 (2H, m), 2.59
 5 (3H, s), 2.75 (2H, t), 3.93 - 3.98 (1H, m), 4.40 (1H, s), 8.36 (1H, d), 8.48 (1H, s)
 m/z (ESI⁺) (M+H)⁺ = 344; HPLC t_R = 1.45 min.

Intermediate 142

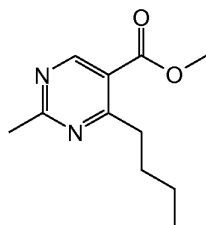
(Z)-methyl 2-((dimethylamino)methylene)-3-oxoheptanoate



Prepared from methyl 3-oxoheptanoate by the same process used for Intermediate 1 and
 used without characterisation to prepare Intermediate 143.

Intermediate 143

methyl 4-butyl-2-methylpyrimidine-5-carboxylate

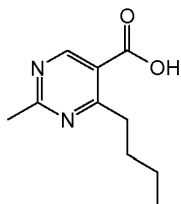


Prepared from (Z)-methyl 2-((dimethylamino)methylene)-3-oxoheptanoate by the same
 process used for Intermediate 2;

¹H NMR (400.13 MHz, DMSO-d₆) δ 0.89 (3H, t), 1.30 - 1.39 (2H, m), 1.57 - 1.65 (2H, m), 2.64 (3H, s), 3.00 (2H, t), 3.86 (3H, s), 8.96 (1H, s)
 20 m/z (ESI⁺) (M+H)⁺ = 209; HPLC t_R = 1.94 min.

Intermediate 144

4-butyl-2-methylpyrimidine-5-carboxylic acid

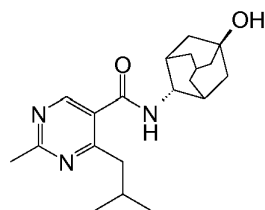


Prepared from Intermediate 143 by the same process used for Intermediate 29;

- 5 ^1H NMR (400.13 MHz, DMSO- d_6) δ 0.89 (3H, t), 1.28 - 1.38 (2H, m), 1.57 - 1.64 (2H, m), 2.62 (3H, s), 3.01 - 3.05 (2H, m), 8.94 (1H, s), 13.46 (1H, s)
 m/z (ESI+) (M+H) $^+$ = 195; HPLC t_R = 1.35 min.

Example 192

- 10 N-[(2s,5r)-5-Hydroxyadamantan-2-yl]-4-isobutyl-2-methylpyrimidine-5-carboxamide

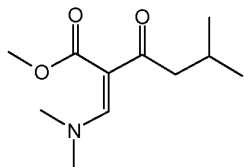


Prepared from Intermediate 148 by the same process used for Example 188;

- ^1H NMR (400.13 MHz, DMSO- d_6) δ 0.84 (6H, s), 1.33 (2H, d), 1.63 (4H, d), 1.71 - 1.74 (2H, m), 1.91 (2H, d), 1.98 (1H, s), 2.04 - 2.10 (3H, m), 2.60 (3H, s), 2.67 (2H, d), 3.96 (1H, t), 4.40 (1H, s), 8.36 (1H, d), 8.49 (1H, s)
 15 m/z (ESI+) (M+H) $^+$ = 344; HPLC t_R = 1.39 min.

Intermediate 146

(Z)-methyl 2-((dimethylamino)methylene)-5-methyl-3-oxohexanoate



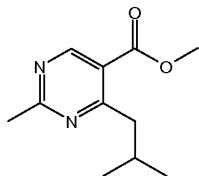
20

Prepared from methyl 5-methyl-3-oxohexanoate by the same process used for Intermediate 1;

m/z (ESI+) (M+H) $^+$ = 214; HPLC t_R = 1.48 min.

Intermediate 147

methyl 4-isobutyl-2-methylpyrimidine-5-carboxylate



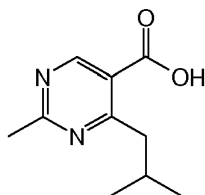
Prepared from (Z)-methyl 2-((dimethylamino)methylene)-5-methyl-3-oxohexanoate

5 by the same process used for Intermediate 2;

¹H NMR (400.13 MHz, DMSO-d₆) δ 0.87 (6H, d), 2.02 - 2.09 (1H, m), 2.63 (3H, s), 2.90 (2H, d), 3.86 (3H, s), 8.95 (1H, s)

m/z (ESI+) (M+H)⁺ = 209; HPLC t_R = 1.82 min.10 **Intermediate 148**

4-isobutyl-2-methylpyrimidine-5-carboxylic acid



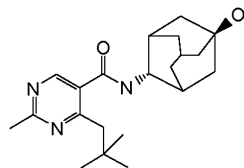
Prepared from Intermediate 147 by the same process used for Intermediate 29;

¹H NMR (400.13 MHz, DMSO-d₆) δ 0.86 (6H, d), 2.04 - 2.11 (1H, m), 2.63 (3H, s), 2.96 (2H, d), 8.94 (1H, s) COOH signal very diffuse and not seen.

15 m/z (ESI+) (M+H)⁺ = 195; HPLC t_R = 1.24min.**Example 193**

4-(2,2-Dimethylpropyl)-N-[(2r,5s)-5-hydroxyadamantan-2-yl]-2-methylpyrimidine-5-

20 carboxamide



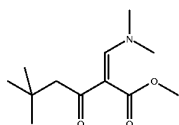
Prepared from Intermediate 152 by the same process used for Example 188;

¹H NMR (400.13 MHz, DMSO-d₆) δ 0.88 (9H, s), 1.29 - 1.36 (2H, m), 1.59 - 1.66 (4H,

m), 1.70 - 1.73 (2H, m), 1.90 - 2.02 (5H, m), 2.60 (3H, s), 2.81 (2H, s), 3.92 - 3.97 (1H, m), 4.39 (1H, s), 8.37 (1H, d), 8.52 (1H, s)
 m/z (ESI⁺) (M+H)⁺ = 358; HPLC t_R = 1.62 min

5 **Intermediate 150**

(Z)-methyl 2-((dimethylamino)methylene)-5,5-dimethyl-3-oxohexanoate

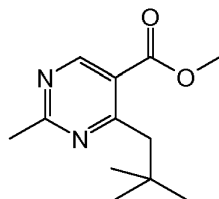


Prepared from methyl 5,5-dimethyl-3-oxohexanoate by the same process used for Intermediate 1 and used without characterisation to prepare Intermediate 151.

10

Intermediate 151

methyl 2-methyl-4-neopentylpyrimidine-5-carboxylate



15

Prepared from (Z)-methyl 2-((dimethylamino)methylene)-5,5-dimethyl-3-oxohexanoate by the same process used for Intermediate 2;

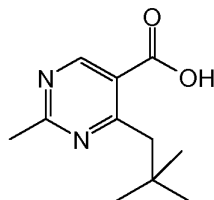
¹H NMR (400.13 MHz, DMSO-d₆) δ 0.88 (9H, s), 2.64 (3H, s), 3.04 (2H, s), 3.86 (3H, s), 8.94 (1H, s)

m/z (ESI⁺) (M+H)⁺ = 223; HPLC t_R = 2.08 min.

20

Intermediate 152

2-methyl-4-neopentylpyrimidine-5-carboxylic acid



Prepared from Intermediate 151 by the same process used for Intermediate 29;

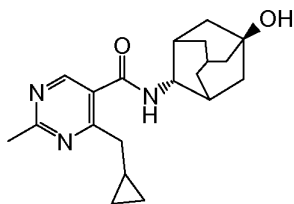
¹H NMR (400.13 MHz, DMSO-d₆) δ 0.90 (9H, s), 2.64 (3H, s), 3.10 (2H, s), 8.95 (1H, s),

13.56 (1H, s)

m/z (ESI+) (M+H)⁺ = 209; HPLC t_R = 0.56 min.

Example 194

- 5 4-(Cyclopropylmethyl)-N-[(2r,5s)-5-hydroxyadamantan-2-yl]-2-methylpyrimidine-5-carboxamide

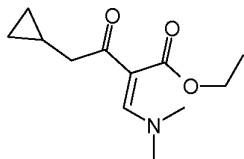


Prepared from Intermediate 156 by the same process used for Example 188;

- 1H NMR (400.132 MHz, CDCl₃) δ 0.27 (2H, q), 0.46 - 0.51 (2H, m), 1.11 - 1.19 (1H, m),
 10 1.37 (1H, s), 1.56 - 1.73 (4H, m), 1.78 - 1.84 (4H, m), 1.92 - 1.98 (2H, m), 2.16 - 2.27 (3H, m), 2.73 (3H, s), 2.84 (2H, d), 4.19 - 4.25 (1H, m), 5.98 (1H, d), 8.59 (1H, s)
 m/z (ESI+) (M+H)⁺ = 342; HPLC t_R = 1.32 min

Intermediate 154

- 15 (Z)-ethyl 4-cyclopropyl-2-((dimethylamino)methylene)-3-oxobutanoate

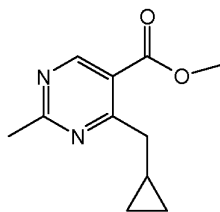


Prepared from ethyl 4-cyclopropyl-3-oxobutanoate by the same process used for Intermediate 1;

- 1H NMR (400.132 MHz, CDCl₃) δ 0.10 - 0.15 (2H, m), 0.45 - 0.51 (2H, m), 1.00 - 1.11
 20 (1H, m), 1.30 (3H, t), 2.60 (2H, d), 2.83 - 3.20 (6H, m), 4.21 (2H, q), 7.66 (1H, s)
 m/z (ESI+) (M+H)⁺ = 226; HPLC t_R = 1.53 min.

Intermediate 155

methyl 4-(cyclopropylmethyl)-2-methylpyrimidine-5-carboxylate



Prepared from (Z)-ethyl 4-cyclopropyl-2-((dimethylamino)methylene)-3-oxobutanoate by the same process used for Intermediate 2;

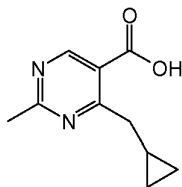
¹H NMR (400.132 MHz, CDCl₃) δ 0.19 - 0.25 (2H, m), 0.36 - 0.42 (2H, m), 1.06 - 1.15

5 (1H, m), 2.69 (3H, s), 2.97 (2H, d), 3.86 (3H, s), 8.97 (1H, s)

m/z (ESI⁺) (M+H)⁺ = 207; HPLC t_R = 1.70 min.

Intermediate 156

4-(cyclopropylmethyl)-2-methylpyrimidine-5-carboxylic acid



10

Prepared from Intermediate 155 by the same process used for Intermediate 29

¹H NMR (400.132 MHz, CDCl₃) δ 0.30 - 0.35 (2H, m), 0.46 - 0.51 (2H, m), 1.22 - 1.28

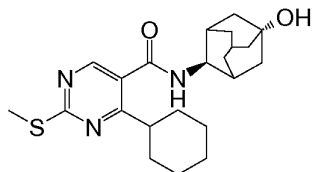
(1H, m), 2.82 (3H, s), 3.13 (2H, d), 9.21 (1H, s)

m/z (ESI⁺) (M+H)⁺ = 193; HPLC t_R = 1.13 min.

15

Example 195

4-Cyclohexyl-N-[(2r,5s)-5-hydroxyadamantan-2-yl]-2-(methylthio)pyrimidine-5-carboxamide



20 Prepared from Intermediate 158 by the same process used for Example 46;

¹H NMR (400.13 MHz, DMSO-d₆) δ 1.18 - 1.28 (3H, m), 1.31 - 1.37 (2H, m), 1.49 - 1.78

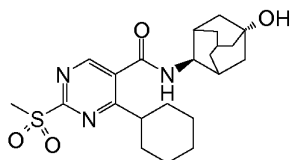
(13H, m), 1.86 - 1.93 (2H, m), 1.96 - 2.00 (1H, m), 2.02 - 2.07 (2H, m), 2.52 (3H, s), 2.88 -

2.97 (1H, m), 3.94 - 3.98 (1H, m), 4.40 (1H, s), 8.36 (1H, d), 8.41 (1H, s)

m/z (ESI+) (M+H)⁺ = 402; HPLC t_R = 2.29 min.

Intermediate 174

4-cyclohexyl-N-[(2r,5s)-5-hydroxyadamantan-2-yl]-2-(methylsulfonyl)pyrimidine-5-
 5 carboxamide



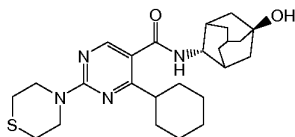
Prepared from Example 195 by the same process used for Example 37;

¹H NMR (400.13 MHz, DMSO-d₆) δ 1.20 - 1.31 (3H, m), 1.35 - 1.39 (2H, m), 1.54 - 1.88 (15H, m), 1.97 - 2.02 (1H, m), 2.04 - 2.10 (2H, m), 2.95 - 3.01 (1H, m), 3.42 (3H, s), 3.99 -
 10 4.04 (1H, m), 4.43 (1H, s), 8.61 (1H, d), 8.87 (1H, s)

m/z (ESI+) (M+H)⁺ = 434; HPLC t_R = 1.87 min.

Example 196

4-Cyclohexyl-N-[(2r,5s)-5-hydroxyadamantan-2-yl]-2-thiomorpholin-4-ylpyrimidine-5-
 15 carboxamide



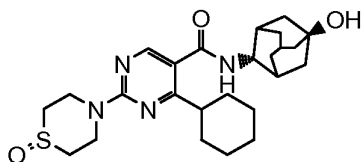
Prepared from Intermediate 174 by the same process used for Example 46;

¹H NMR (400.13 MHz, DMSO-d₆) δ 1.16 - 1.34 (5H, m), 1.44 - 1.53 (2H, m), 1.60 - 1.76 (11H, m), 1.91 - 2.03 (5H, m), 2.58 - 2.60 (4H, m), 2.97 - 3.02 (1H, m), 3.90 (1H, t), 4.07 -
 20 4.10 (4H, m), 4.38 (1H, s), 8.08 (1H, d), 8.22 (1H, s)

m/z (ESI+) (M+H)⁺ = 457; HPLC t_R = 2.56 min.

Example 197

4-Cyclohexyl-N-[(2r,5s)-5-hydroxyadamantan-2-yl]-2-(1-oxidithiomorpholin-4-
 25 yl)pyrimidine-5-carboxamide

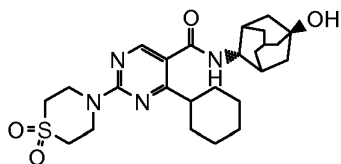


Prepared from Example 196 by the same process used for Example 36;

¹H NMR (400.13 MHz, DMSO-d₆) δ 1.17 - 1.34 (5H, m), 1.47 - 1.55 (2H, m), 1.60 - 1.77 (11H, m), 1.91 - 2.06 (5H, m), 2.70 - 2.77 (2H, m), 2.80 - 2.87 (2H, m), 2.97 - 3.05 (1H, m), 3.90 - 3.98 (3H, m), 4.38 (1H, s), 4.45 - 4.51 (2H, m), 8.11 (1H, d), 8.26 (1H, s)
 m/z (ESI+) (M+H)⁺ = 473; HPLC t_R = 1.69 min.

Example 198

4-Cyclohexyl-2-(1,1-dioxidothiomorpholin-4-yl)-N-[(2r,5s)-5-hydroxyadamantan-2-yl]pyrimidine-5-carboxamide

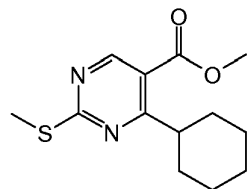


Prepared from Example 196 by the same process used for Example 37;

¹H NMR (400.13 MHz, DMSO-d₆) δ 1.16 - 1.34 (5H, m), 1.46 - 1.54 (2H, m), 1.61 - 1.77 (11H, m), 1.90 - 2.04 (5H, m), 2.95 - 3.05 (1H, m), 3.09 - 3.17 (4H, m), 3.89 - 3.94 (1H, m), 4.20 - 4.27 (4H, m), 4.39 (1H, s), 8.14 (1H, d), 8.28 (1H, s)
 m/z (ESI+) (M+H)⁺ = 489; HPLC t_R = 1.98 min.

Intermediate 157

methyl 4-cyclohexyl-2-(methylthio)pyrimidine-5-carboxylate

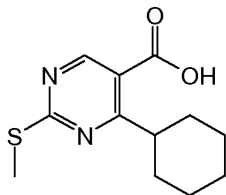


Prepared from Intermediate 61 by the same process used for Intermediate 2;

m/z (ESI+) (M+H)⁺ = 267; HPLC t_R = 3.11 min.

Intermediate 158

4-cyclohexyl-2-(methylthio)pyrimidine-5-carboxylic acid

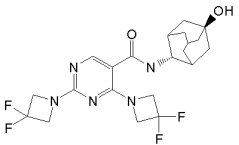
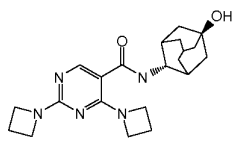


Prepared from Intermediate 157 by the same process used for Intermediate 29;

5 m/z (ESI⁺) (M+H)⁺ = 253; HPLC t_R = 2.51 min.

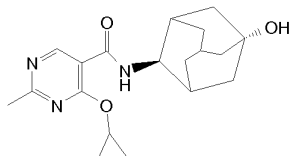
The following Examples were prepared in a similar manner to Example 21, using Intermediate 42 and an appropriate starting material:

Structure	Ex	Name	¹ H NMR δ	MS m/e MH⁺
	199	2,4-bis(dimethylamino)-N-[(2r,5s)-5-hydroxyadamantan-2-yl]pyrimidine-5-carboxamide	¹ H NMR (400.132 MHz, CDCl ₃) δ 1.36 (1H, s), 1.55 - 1.60 (2H, m), 1.65 - 1.80 (6H, m), 1.90 - 1.95 (2H, m), 2.12 - 2.22 (3H, m), 2.99 (6H, s), 3.17 (6H, s), 4.12 - 4.20 (1H, m), 6.40 (1H, d), 8.30 (1H, s)	m/z (ESI ⁺) (M+H) ⁺ = 360; HPLC t_R = 1.52 min

	200	2,4-bis(3,3-difluoroazetidin-1-yl)-N-[(2r,5s)-5-hydroxyadamantan-2-yl]pyrimidine-5-carboxamide	1H NMR (400.132 MHz, CDCl ₃) δ 1.36 (1H, s), 1.55 - 1.61 (2H, m), 1.67 - 1.83 (6H, m), 1.90 - 1.96 (2H, m), 2.16 - 2.22 (3H, m), 4.10 - 4.15 (1H, m), 4.42 (8H, t), 5.96 (1H, d), 8.18 (1H, s)	m/z (ESI+) (M+H) ⁺ = 456; HPLC t _R = 1.87 min
	201	2,4-bis(azetidin-1-yl)-N-[(2r,5s)-5-hydroxyadamantan-2-yl]pyrimidine-5-carboxamide	1H NMR (499.803 MHz, CDCl ₃) δ 1.38 - 1.58 (3H, m), 1.67 - 1.71 (2H, m), 1.75 - 1.79 (4H, m), 1.89 - 1.94 (2H, m), 2.13 - 2.20 (3H, m), 2.25 - 2.36 (4H, m), 4.06 - 4.14 (9H, m), 5.95 (1H, d), 8.12 (1H, s)	m/z (ESI+) (M+H) ⁺ = 384; HPLC t _R = 1.49 min

Example 202

N-[(2r,5s)-5-hydroxyadamantan-2-yl]-2-methyl-4-propan-2-yloxy pyrimidine-5-carboxamide



5

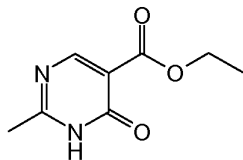
Prepared from Intermediate 161 by the same process used for Example 4;

1H NMR (400.132 MHz, CDCl₃) δ 1.41 (1H, s), 1.46 (6H, d), 1.59 (2H, d), 1.75 - 1.84 (6H, m), 1.94 (2H, d), 2.21 (3H, s), 2.65 (3H, s), 4.26 (1H, d), 5.73 (1H, quintet), 7.96 (1H, d), 9.17 (1H, s)

10 m/z (ESI+) (M+H)⁺ = 346; HPLC t_R = 1.74 min.

Intermediate 174

ethyl 2-methyl-6-oxo-1,6-dihydropyrimidine-5-carboxylate



diethyl 2-(ethoxymethylene)malonate (9.35 mL, 46.25 mmol) was added dropwise to
5 acetimidamide hydrochloride (4.37 g, 46.25 mmol), and sodium ethoxide (17.27 mL,
46.25 mmol) in ethanol (50 mL) at roomtemperature over a period of 5 minutes under
nitrogen. The resulting solution was stirred at 60 °C for 6 hours. The reaction mixture was
evaporated to dryness and redissolved in EtOAc (50 mL).The precipitate was collected by
filtration, washed with EtOH (10 mL) and dried under vacuum to afford ethyl 2-methyl-6-
10 oxo-1,6-dihydropyrimidine-5-carboxylate (4.17 g, 49.5 %) as a cream solid, which was
used without further purification.

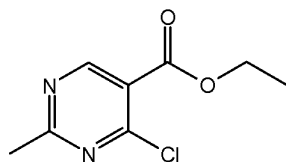
¹H NMR (400.13 MHz, DMSO-d₆) δ 1.15 - 1.23 (3H, t), 2.21 (3H, s), 4.09 - 4.17 (2H, q),
8.31 (1H, s)

m/z (ESI+) (M+H)⁺ = 183; HPLC t_R = 0.78 min.

15

Intermediate 159

ethyl 4-chloro-2-methylpyrimidine-5-carboxylate



Phosphorus oxychloride (50 mL, 23.33 mmol) was added to ethyl 2-methyl-6-oxo-1,6-
20 dihydropyrimidine-5-carboxylate (Intermediate 174, 4.25 g, 23.33 mmol). The insoluble
mixture was refluxed for 30 minutes. The product was soluble in POCl₃ where as the
starting material was not. The excess POCl₃ was removed under vacuum. The mixture was
evaporated to dryness and redissolved in EtOAc (100 mL), and washed sequentially with
water (75 mL) and saturated brine (75 mL). The organic layer was dried over MgSO₄,
25 filtered and evaporated to afford crude product.The crude product was purified by flash
silica chromatography, elution gradient 10 to 30% EtOAc in isohexane. Pure fractions
were evaporated to dryness to afford ethyl 4-chloro-2-methylpyrimidine-5-carboxylate

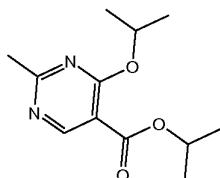
(2.70 g, 57.7 %) as a colourless oil.

^1H NMR (400.132 MHz, CDCl_3) δ 1.42 (3H, t), 2.78 (3H, s), 4.44 (2H, q), 9.05 (1H, s)

m/z (ESI+) (M+H) $^+$ = 201; HPLC t_R = 2.17 min.

5 Intermediate 160

isopropyl 4-isopropoxy-2-methylpyrimidine-5-carboxylate



ethyl 4-chloro-2-methylpyrimidine-5-carboxylate (Intermediate 159, 186 mg, 0.93 mmol),

Isopropyl alcohol (3549 μl , 46.36 mmol) and Sodium bis(trimethylsilyl)amide (927 μl ,

10 0.93 mmol) were mixed under nitrogen and the reaction was stirred at 20 °C for 2 hours.

The reaction mixture was diluted with EtOAc (40 mL), and washed sequentially with water

(10 mL), and saturated brine (10 mL). The organic layer was dried over MgSO_4 , filtered

and evaporated to afford crude product, which was used without further purification.

Because it was a mixture and had a weak chromophore it was used straight away in the

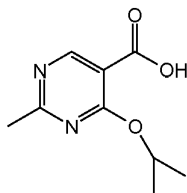
15 next step;

m/z (ESI+) (M+H) $^+$ = 225; HPLC t_R = 1.98 min 33% (ethyl ester with isopropyl ether plus

isopropyl ester with ethyl ether), (M+H) $^+$ = 239 ; HPLC t_R = 2.24 min 67% (isopropyl ester)

20 Intermediate 161

4-isopropoxy-2-methylpyrimidine-5-carboxylic acid



Prepared from Intermediate 160 by the same process used for Intermediate 2

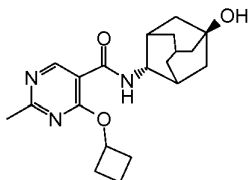
^1H NMR (400.132 MHz, CDCl_3) δ 1.49 (6H, d), 2.69 (3H, s), 5.73 (1H, quintet), 9.13

25 (1H, s)

m/z (ESI+) (M-H) $^-$ = 195; HPLC t_R = 0.93 min

Example 203

4-Cyclobutyloxy-N-[(2r,5s)-5-hydroxyadamantan-2-yl]-2-methylpyrimidine-5-carboxamide

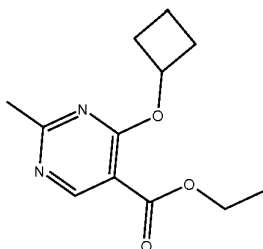


- 5 Prepared from Intermediate 163 by the same process used for Example 4;
¹H NMR (400.132 MHz, CDCl₃) δ 1.42 (1H, s), 1.60 (2H, d), 1.70 - 1.85 (7H, m), 1.90 - 1.99 (3H, m), 2.13 - 2.25 (5H, m), 2.53 - 2.61 (2H, m), 2.63 (3H, s), 4.27 (1H, d), 5.46 (1H, quintet), 7.95 (1H, d), 9.16 (1H, s)
 m/z (ESI⁺) (M+H)⁺ = 358; HPLC t_R = 1.94 min.

10

Intermediate 162

ethyl 4-cyclobutoxy-2-methylpyrimidine-5-carboxylate

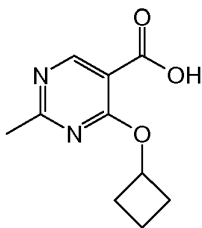


Prepared from Intermediate 159 by the same process used for Intermediate 160;

- 15 m/z (ESI⁺) (M+H)⁺ = 237; HPLC t_R = 2.18 min.

Intermediate 163

4-cyclobutoxy-2-methylpyrimidine-5-carboxylic acid



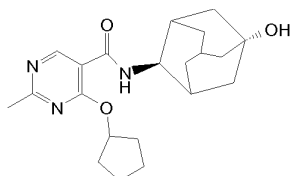
- 20 Prepared from Intermediate 162 by the same process used for Intermediate 2;
¹H NMR (400.132 MHz, CDCl₃) δ 1.70 - 1.81 (1H, m), 1.88 - 1.99 (1H, m), 2.21 - 2.32

(2H, m), 2.51 - 2.59 (2H, m), 2.68 (3H, s), 5.47 (1H, quintet), 9.09 (1H, s)

m/z (ESI+) (M+H)⁺ = 209; HPLC t_R = 1.18 min.

Example 204

- 5 4-Cyclopentyloxy-N-[(2r,5s)-5-hydroxyadamantan-2-yl]-2-methylpyrimidine-5-carboxamide



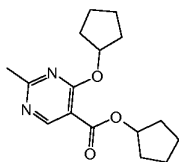
Prepared from Intermediate 165 by the same process used for Example 4;

- 1H NMR (400.132 MHz, CDCl₃) δ 1.42 (1H, s), 1.59 (2H, d), 1.66 - 1.91 (12H, m), 1.94
 10 (2H, d), 2.06 - 2.16 (2H, m), 2.17 - 2.26 (3H, m), 2.64 (3H, s), 4.25 (1H, d), 5.79 (1H, septet), 7.84 (1H, d), 9.15 (1H, s)

m/z (ESI+) (M+H)⁺ = 372; HPLC t_R = 2.04 min.

Intermediate 164

- 15 cyclopentyl 4-(cyclopentyloxy)-2-methylpyrimidine-5-carboxylate

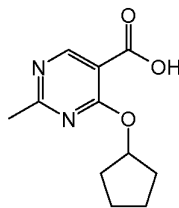


Prepared from Intermediate 159 by the same process used for Intermediate 160

m/z (ESI+) (M+H)⁺ = 291; HPLC t_R = 2.94 min

- 20 **Intermediate 165**

4-(cyclopentyloxy)-2-methylpyrimidine-5-carboxylic acid

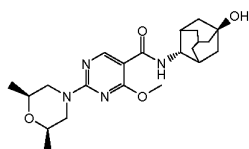


Prepared from Intermediate 164 by the same process used for Intermediate 2;

¹H NMR (400.132 MHz, CDCl₃) δ 1.67 - 1.96 (6H, m), 2.02 - 2.13 (2H, m), 2.69 (3H, s), 5.81 (1H, septet), 9.10 (1H, s)
 m/z (ESI⁺) (M-H)⁻ = 221; HPLC t_R = 1.33 min

5 **Example 205**

2-[(2R,6S)-2,6-Dimethylmorpholin-4-yl]-N-[(2r,5s)-5-hydroxytricyclo[3.3.1.1^{3,7}]dec-2-yl]-4-methoxypyrimidine-5-carboxamide

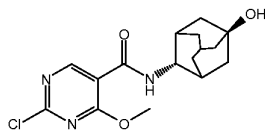


2-chloro-N-[(2r,5s)-5-hydroxytricyclo[3.3.1.1^{3,7}]dec-2-yl]-4-methoxypyrimidine-5-
 10 carboxamide (Intermediate 166, 0.215 g, 0.64 mmol), and cis-2,6-Dimethylmorpholine (0.157 mL, 1.27 mmol) were suspended in THF (4 mL) and sealed into a microwave tube. The reaction was heated to 50 °C for 30 minutes in the microwave reactor and cooled to RT. The reaction mixture was diluted with EtOAc (20 mL), and washed sequentially with saturated NH₄Cl (10 mL) and saturated brine (10 mL). The organic layer was dried over
 15 MgSO₄, filtered and evaporated to afford crude product. The crude product was purified by preparative HPLC (Waters XBridge Prep C18 OBD column, 5 μ silica, 50 mm diameter, 150 mm length), using decreasingly polar mixtures of water (containing 0.5% NH₃) and MeCN as eluents. Fractions containing the desired compounds were evaporated to dryness to afford 2-[(2R,6S)-2,6-dimethylmorpholin-4-yl]-N-[(2r,5s)-5-
 20 hydroxytricyclo[3.3.1.1^{3,7}]dec-2-yl]-4-methoxypyrimidine-5-carboxamide (0.047 g, 17.73 %) as a white solid.

¹H NMR (400.13 MHz, DMSO-d₆) δ 1.15 (6H, d), 1.43 (2H, d), 1.63 - 1.65 (4H, m), 1.69 - 1.72 (4H, m), 2.00 (2H, s), 2.05 (1H, s), 2.56 - 2.62 (2H, m), 3.50 - 3.58 (2H, m), 3.94 (1H, t), 4.02 (3H, s), 4.42 (1H, s), 4.55 (2H, d), 7.63 - 7.65 (1H, m), 8.61 (1H, s)
 25 m/z (ES⁺) (M+H)⁺ = 417; HPLC t_R = 1.90 min.

Intermediate 166

2-chloro-N-[(2r,5s)-5-hydroxytricyclo[3.3.1.1^{3,7}]dec-2-yl]-4-methoxypyrimidine-5-
 30 carboxamide



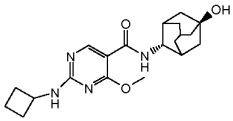
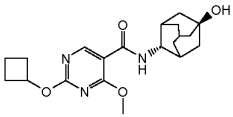
Sodium methoxide (0.050 g, 0.92 mmol) was added in one portion to a solution of 2,4-dichloro-N-[(2s,5r)-5-hydroxyadamantan-2-yl]pyrimidine-5-carboxamide (Intermediate 42, 0.3 g, 0.88 mmol) in THF (30 mL) at 0°C under nitrogen. The resulting suspension was stirred for 6 hours. The reaction mixture was diluted with EtOAc (75 mL), and washed sequentially with 0.1M HCl (25 mL), water (25 mL), and saturated brine (25 mL). The organic layer was dried over MgSO₄, filtered and evaporated to afford crude 2-chloro-N-[(2r,5s)-5-hydroxytricyclo[3.3.1.1^{3,7}]dec-2-yl]-4-methoxypyrimidine-5-carboxamide (0.250 g, 84 %) product as a yellow solid. Used directly in the next step without further purification.

¹H NMR (400.13 MHz, DMSO-d₆) δ 1.38 (2H, d), 1.62 - 1.65 (5H, m), 1.70 - 1.76 (2H, m), 1.76 (1H, m), 1.80 - 1.83 (2H, m), 1.98 (1H, s), 3.91 - 3.96 (1H, m), 4.02 (3H, s), 4.40 (1H, s), 8.03 (1H, d), 8.64 (1H, d)

m/z (ES⁺) (M+H)⁺ = 338; HPLC t_R = 1.62 min.

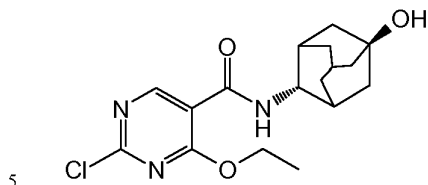
The following Examples were prepared in a similar manner to Example 205, using Intermediate 166 and an appropriate starting material:

Structure	Ex	Name	¹ H NMR δ	MS m/e MH ⁺
	206	2-(cyclopropylamino)-N-[(2r,5s)-5-hydroxytricyclo[3.3.1.1.3,7]dec-2-yl]-4-methoxypyrimidine-5-carboxamide	¹ H NMR (400.13 MHz, DMSO-d ₆) δ 0.48 - 0.56 (2H, m), 0.69 (2H, d), 1.44 (2H, d), 1.64 (4H, d), 1.71 (4H, d), 2.00 - 2.05 (3H, m), 2.76 - 2.82 (1H, m), 3.16 (2H, d), 3.95 (2H, d), 4.43 (1H, s), 7.64 (1H, d), 7.81 - 7.91 (1H, m), 8.55 (1H, s)	m/z (ES ⁺) (M+H) ⁺ = 359; HPLC t _R = 1.72 min.

	207	2-(cyclobutylamino)-N-[(2r,5s)-5-hydroxytricyclo[3.3.1.1.3,7]dec-2-yl]-4-methoxypyrimidine-5-carboxamide	1H NMR (400.13 MHz, DMSO-d ₆) δ 1.43 (2H, d), 1.62 - 1.69 (11H, m), 1.99 (4H, s), 2.04 (2H, s), 2.24 (2H, s), 3.96 (2H, d), 4.01 (2H, s), 4.42 (1H, s), 7.61 (1H, d), 8.53 (1H, s)	m/z (ES+) (M+H) ⁺ = 373; HPLC t _R = 1.92 min.
	208	2-(cyclobutylloxymethyl)-N-[(2r,5s)-5-hydroxytricyclo[3.3.1.1.3,7]dec-2-yl]-4-methoxypyrimidine-5-carboxamide	1H NMR (400.13 MHz, DMSO-d ₆) δ 1.41 (2H, d), 1.62 - 1.66 (5H, m), 1.67 - 1.80 (5H, m), 2.02 (3H, s), 2.05 - 2.14 (2H, m), 2.38 - 2.45 (2H, m), 3.94 (1H, t), 4.02 (3H, s), 4.44 (1H, s), 5.12 - 5.19 (1H, m), 7.80 (1H, d), 8.61 (1H, s)	m/z (ES+) (M+H) ⁺ = 374; HPLC t _R = 1.95 min.

Intermediate 167

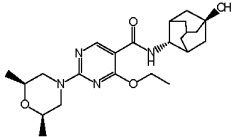
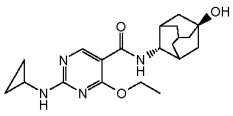
2-chloro-4-ethoxy-N-[(2r,5s)-5-hydroxytricyclo[3.3.1.1.3,7]dec-2-yl]pyrimidine-5-carboxamide

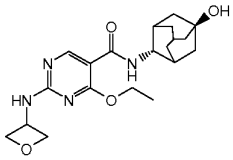
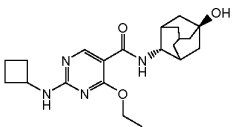
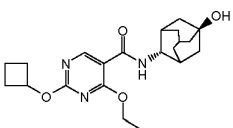


Prepared from Intermediate 42 by the same process used for Intermediate 2
m/z (ES-) M- = 350; HPLC t_R = 1.83 min.

The following Examples were prepared in a similar manner to Example 205, using

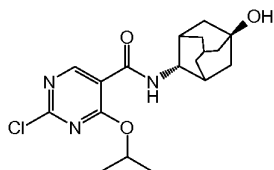
Intermediate 167 and an appropriate starting material:

Structure	Ex	Name	¹ H NMR δ	MS m/e MH ⁺
	209	2-[(2S,6R)-2,6-dimethylmorpholin-4-yl]-4-ethoxy-N-[(2r,5s)-5-hydroxyadamantan-2-yl]pyrimidine-5-carboxamide	¹ H NMR (400.13 MHz, CDCl ₃) δ 1.25 (3H, d), 1.26 (3H, s), 1.49 (3H, t), 1.56 (2H, d), 1.66 (1H, s), 1.75 - 1.82 (7H, s), 1.92 - 1.95 (2H, m), 2.18 (3H, s), 2.64 (2H, dd), 3.58 - 3.66 (2H, m), 4.22 - 4.26 (1H, m), 4.52 (2H, q), 7.75 (1H, d), 8.95 (1H, s)	m/z (ESI ⁺) (M+H) ⁺ = 431; HPLC t _R = 2.11 min.
	210	2-(cyclopropylamino)-4-ethoxy-N-[(2r,5s)-5-hydroxytricyclo[3.3.1.1.3,7]dec-2-yl]pyrimidine-5-carboxamide	¹ H NMR (400.13 MHz, DMSO-d ₆) δ 0.48 - 0.52 (2H, m), 0.66 - 0.69 (2H, m), 1.40 (3H, t), 1.35 - 1.47 (2H, m), 1.64 (4H, d), 1.72 (4H, d), 2.00 (2H, s), 2.04 (1H, s), 2.77 (1H, d), 3.98 (1H, t), 4.43 (1H, s), 4.52 (1H, s), 7.68 (1H, d), 7.78 - 7.90 (1H, m), 8.58 (1H, s)	m/z (ES ⁺) (M+H) ⁺ = 373; HPLC t _R = 1.51 min.

	211	4-ethoxy-N-[(2r,5s)-5-hydroxytricyclo[3.3.1.1.3,7]dec-2-yl]-2-(oxetan-3-ylamino)pyrimidine-5-carboxamide	1H NMR (400.13 MHz, DMSO-d ₆) δ 1.39 (3H, t), 1.44 (2H, d), 1.62 - 1.65 (4H, m), 1.70 - 1.73 (4H, m), 1.99 (2H, s), 2.04 (1H, s), 3.16 (1H, d), 3.97 (1H, t), 4.43 (1H, s), 4.45 (2H, q), 4.53 (2H, t), 4.75 (2H, t), 4.90 (1H, s), 7.66 (1H, d), 8.58 (1H, s)	m/z (ES+) (M+H) ⁺ = 389; HPLC t _R = 1.45 min.
	212	2-(cyclobutylamino)-4-ethoxy-N-[(2r,5s)-5-hydroxytricyclo[3.3.1.1.3,7]dec-2-yl]pyrimidine-5-carboxamide	1H NMR (400.13 MHz, DMSO-d ₆) δ 1.35 - 1.45 (5H, m), 1.55 - 1.65 (5H, m), 1.70 - 1.82 (5H, m), 1.99 (4H, s), 2.04 (1H, s), 2.23 (2H, s), 3.97 (1H, m), 4.43 (2H, s), 4.47 (2H, m), 7.65 (1H, d), 8.04 (1H, d), 8.55 (1H, s)	m/z (ES+) (M+H) ⁺ = 387; HPLC t _R = 2.13 min.
	213	2-(cyclobutylloxyl)-4-ethoxy-N-[(2r,5s)-5-hydroxytricyclo[3.3.1.1.3,7]dec-2-yl]pyrimidine-5-carboxamide	1H NMR (400.13 MHz, DMSO-d ₆) δ 1.37 - 1.41 (4H, m), 1.44 (1H, s), 1.64 (5H, d), 1.70 (2H, s), 1.75 - 1.78 (3H, m), 1.82 (1H, d), 2.02 (3H, s), 2.07 - 2.12 (2H, m), 2.38 - 2.44 (1H, m), 3.96 (1H, d), 4.43 (1H, s), 4.49 (2H, t), 5.10 - 5.17 (1H, m), 7.80 (1H, d), 8.67 (1H, s)	m/z (ES+) (M+H) ⁺ = 388; HPLC t _R = 2.12 min.

Intermediate 168

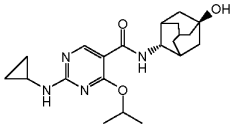
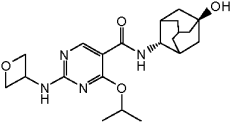
2-chloro-N-[(2r,5s)-5-hydroxytricyclo[3.3.1.1^{3,7}]dec-2-yl]-4-(1-methylethoxy)pyrimidine-5-carboxamide

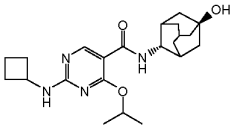
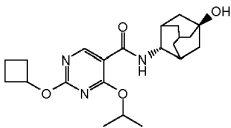


- 5 Prepared from Intermediate 42 by the same process used for Intermediate 2;
m/z (ES⁺) (M+H)⁺ = 366; HPLC t_R = 2.01 min.

The following Examples were prepared in a similar manner to Example 205, using Intermediate 168 and an appropriate starting material:

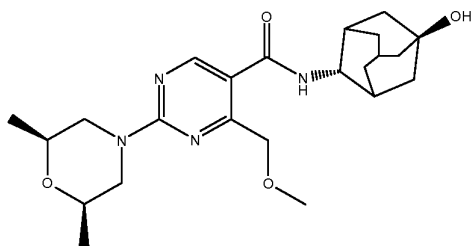
Structure	Ex	Name	¹ H NMR δ	MS m/e MH ⁺
	214	2-[(2R,6S)-2,6-dimethylmorpholin-4-yl]-N-[(2r,5s)-5-hydroxytricyclo[3.3.1.1 ^{3,7}]dec-2-yl]-4-(1-methylethoxy)pyrimidine-5-carboxamide	¹ H NMR (400.13 MHz, DMSO-d ₆) δ 1.14 (6H, d), 1.38 (3H, s), 1.39 (3H, s), 1.45 - 1.48 (2H, m), 1.64 (4H, m), 1.71 (4H, s), 2.00 (2H, s), 2.05 (1H, s), 2.57 - 2.63 (2H, m), 3.50 - 3.58 (2H, m), 3.98 (1H, m), 4.43 (1H, s), 4.50 (2H, s), 5.46 - 5.52 (1H, m), 7.66 (1H, d), 8.65 (1H, s)	m/z (ES ⁺) (M+H) ⁺ = 445; HPLC t _R = 2.17 min.

	215	2-(cyclopropylamino)-N-[(2R,5S)-5-hydroxy-2-cyclopropylmethylcarbamoyl]-4-(1-methylethoxy)pyrimidine-5-carboxamide	1H NMR (400.13 MHz, DMSO-d ₆) δ 0.44 - 0.56 (2H, m), 0.66 - 0.70 (2H, m), 1.39 (6H, s), 1.47 (2H, d), 1.64 (4H, d), 1.72 (4H, d), 1.99 (2H, s), 2.05 (1H, s), 2.75 (1H, s), 3.98 (1H, t), 4.43 (1H, s), 5.53 (1H, s), 7.66 - 7.68 (1H, m), 7.92 (1H, s), 8.60 (1H, d)	m/z (ES+) (M+H) ⁺ = 387; HPLC t _R = 1.96 min.
	216	N-[(2R,5S)-5-hydroxy-2-cyclopropylmethylcarbamoyl]-4-(1-methylethoxy)-2-(oxetan-3-ylamino)pyrimidine-5-carboxamide	1H NMR (400.13 MHz, DMSO-d ₆) δ 1.36 (3H, d), 1.38 (3H, s), 1.45 - 1.48 (2H, m), 1.63 - 1.65 (4H, m), 1.69 (4H, d), 1.99 (2H, s), 2.05 (1H, s), 3.97 (1H, t), 4.43 (1H, s), 4.54 (2H, s), 4.76 (2H, t), 4.88 (1H, s), 5.46 (1H, s), 7.65 (1H, d), 8.45 (1H, s), 8.60 (1H, s)	m/z (ES+) (M+H) ⁺ = 403; HPLC t _R = 1.63 min.

	217	2- (cyclobutylamino)-N- [(2r,5s)-5-hydroxytricyclo[3.3.1.13,7]dec-2-yl]-4-(1-methylethoxy)pyrimidine-5-carboxamide	1H NMR (400.13 MHz, DMSO-d ₆) δ 1.37 (4H, d), 1.39 (2H, s), 1.45 - 1.48 (2H, m), 1.63 - 1.63 (3H, m), 1.65 (2H, s), 1.68 (2H, d), 1.70 (3H, s), 1.99 (4H, s), 2.05 (1H, s), 2.23 (2H, s), 3.97 (1H, t), 4.27 (1H, d), 4.40 - 4.43 (1H, m), 5.46 - 5.52 (1H, m), 7.65 (1H, d), 8.04 (1H, d), 8.53 - 8.57 (1H, m)	m/z (ES+) (M+H) ⁺ = 401; HPLC t _R = 2.18 min.
	218	2- (cyclobutylloxy)-N-[(2r,5s)-5-hydroxytricyclo[3.3.1.13,7]dec-2-yl]-4-(1-methylethoxy)pyrimidine-5-carboxamide	1H NMR (400.13 MHz, DMSO-d ₆) δ 1.35 - 1.40 (6H, m), 1.45 (2H, d), 1.63 (3H, d), 1.66 (2H, s), 1.73 (4H, t), 2.02 (3H, s), 2.06 - 2.15 (2H, m), 2.37 - 2.45 (2H, m), 3.16 (1H, d), 3.97 (1H, t), 4.43 (1H, s), 5.09 - 5.16 (1H, m), 5.44 - 5.50 (1H, m), 7.76 (1H, d), 8.70 (1H, s)	m/z (ES+) (M+H) ⁺ = 402; HPLC t _R = 1.77 min.

Example 219

2-[(2S,6R)-2,6-Dimethylmorpholin-4-yl]-N-[(2r,5s)-5-hydroxyadamantan-2-yl]-4-(methoxymethyl)pyrimidine-5-carboxamide



2-((2S,6R)-2,6-Dimethylmorpholino)-4-(methoxymethyl)pyrimidine-5-carboxylic acid

(605.9 mg, 2.15 mmol), 2-(3H-[1,2,3]triazolo[4,5-b]pyridin-3-yl)-1,1,3,3-

tetramethylisouronium hexafluorophosphate(V) (Intermediate 170, 1.23 g, 3.23 mmol) and

5 N-ethyl-N-isopropylpropan-2-amine (0.737 mL, 4.31 mmol) were dissolved in DMF (50 mL). The resulting solution was stirred at room temperature for 15 minutes. 4-

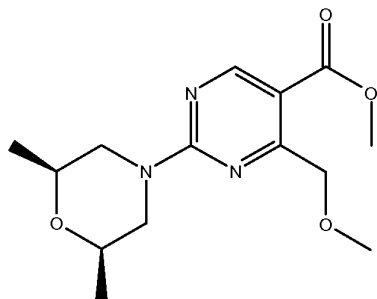
aminoadamantan-1-ol hydrochloride (565.1 mg, 2.77 mmol) was then added and continued to stir at room temperature over night. The reaction mixture was evaporated to dryness and redissolved in EtOAc (150 mL) and washed sequentially with water (2x100 mL) and

10 saturated brine (100mL). The organic layer was dried over MgSO₄, filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 0 to 10% MeOH in DCM. Pure fractions were evaporated to dryness to afford 2-[(2S,6R)-2,6-dimethylmorpholin-4-yl]-N-[(2R,5S)-5-hydroxyadamantan-2-yl]-4-(methoxymethyl)pyrimidine-5-carboxamide as a orange solid. The crude product was

15 purified by crystallisation from hot EtOAc to afford 2-[(2S,6R)-2,6-dimethylmorpholin-4-yl]-N-[(2R,5S)-5-hydroxyadamantan-2-yl]-4-(methoxymethyl)pyrimidine-5-carboxamide (723 mg, 78 %) as a white solid.

1H NMR (400.13 MHz, CDCl₃) δ 1.27 (6H, d), 1.43 - 1.53 (2H, m), 1.55 (1H, s), 1.78 (3H, s), 1.80 (2H, s), 1.92 - 1.95 (2H, m), 2.16 (1H, s), 2.21 (2H, s), 2.63 (2H, dd), 3.48 (3H, s), 3.58 - 3.66 (2H, m), 4.19 - 4.23 (1H, m), 4.51 (2H, s), 4.67 (2H, dd), 7.93 (1H, d), 8.84 (1H, s)

m/z (ESI⁺) (M+H)⁺ = 431; HPLC t_R = 2.88 min.

Intermediate 169**Methyl 2-((2S,6R)-2,6-dimethylmorpholino)-4-(methoxymethyl)pyrimidine-5-carboxylate**

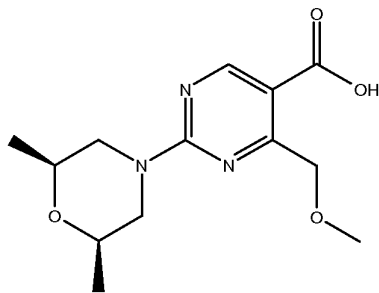
- 5 (2R,6S)-2,6-dimethylmorpholine-4-carboximidamide hydrochloride (1.95 g, 10.07 mmol) was added in one portion to (Z)-methyl 2-((dimethylamino)methylene)-4-methoxy-3-oxobutanoate (2.01 g, 9.99 mmol) and sodium acetate (2.04 g, 24.87 mmol) in DMF (15mL) at 20°C under nitrogen. The resulting suspension was stirred at 80 °C over night. The reaction mixture was evaporated to dryness and redissolved in EtOAc (100 mL), and
- 10 washed sequentially with water (2x75 mL) and saturated brine (75 mL). The organic layer was dried over MgSO₄, filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 0 to 50% EtOAc in isohexane. Pure fractions were evaporated to dryness to afford methyl 2-((2S,6R)-2,6-dimethylmorpholino)-4-(methoxymethyl)pyrimidine-5-carboxylate (1.598 g,
- 15 54 %) as a colourless oil which solidified on standing. White Solid.

¹H NMR (400.13 MHz, CDCl₃) δ 1.27 (6H, d), 2.67 (2H, dd), 3.52 (3H, s), 3.59 - 3.67 (2H, m), 3.85 (3H, s), 4.74 - 4.77 (2H, m), 4.81 (2H, s), 8.82 (1H, s)

- 20 m/z (ESI+) (M+H)⁺ = 296; HPLC t_R = 2.73 min.

Intermediate 170

2-((2S,6R)-2,6-Dimethylmorpholino)-4-(methoxymethyl)pyrimidine-5-carboxylic acid



sodium hydroxide (27.1 mL, 54.18 mmol) was added in one portion to methyl 2-((2S,6R)-2,6-dimethylmorpholino)-4-(methoxymethyl)pyrimidine-5-carboxylate (Intermediate 169, 1.60 g, 5.42 mmol) in methanol (70 mL) at 20°C. The resulting suspension was stirred at
 5 room temperature over night.

The reaction mixture was evaporated to dryness and redissolved in water (150 mL), which was acidified to pH 4 with 2N HCl. The aqueous layer was washed sequentially with EtOAc (3x 100 mL). The organic layer was dried over MgSO₄, filtered and evaporated to afford crude 2-((2S,6R)-2,6-dimethylmorpholino)-4-(methoxymethyl)pyrimidine-5-
 10 carboxylic acid (0.606 g, 40 %) as a white solid, which was used without further purification and characterisation.

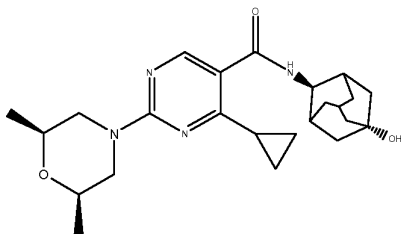
¹H NMR (400.13 MHz, DMSO-d₆) δ 1.15 (6H, d), 2.62 (2H, dd), 3.35 (3H, s), 3.51 - 3.59 (2H, m), 4.63 (2H, d), 4.69 (2H, s), 8.73 (1H, s)

15

m/z (ESI⁺) (M+H)⁺ = 282; HPLC t_R = 1.12 min.

Example 220

4-Cyclopropyl-2-[(2S,6R)-2,6-dimethylmorpholin-4-yl]-N-[(2r,5s)-5-hydroxyadamantan-2-yl]pyrimidine-5-carboxamide
 20



(2R,6S)-2,6-dimethylmorpholine (Intermediate 80, 4.71 g, 40.87 mmol) was added to 4-cyclopropyl-N-[(2r,5s)-5-hydroxyadamantan-2-yl]-2-methylsulfonylpyrimidine-5-

carboxamide (3.2 g, 8.17 mmol) in THF (60 mL) at 20°C under nitrogen. The resulting solution was stirred at 20 °C for 20 hours.

The reaction mixture was evaporated to dryness and redissolved in EtOAc (150 mL), and washed sequentially with water (150 mL) and saturated brine (150 mL). The organic layer
 5 was dried over MgSO₄, filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 1 to 5% MeOH in DCM.

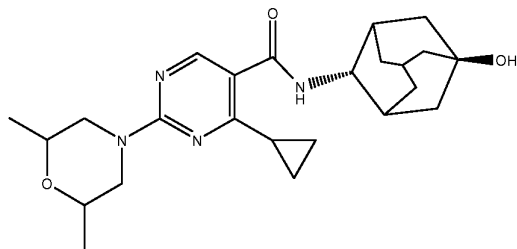
Pure fractions were evaporated to dryness to afford the product as a white foam which was triturated with ether to give 4-cyclopropyl-2-[(2S,6R)-2,6-dimethylmorpholin-4-yl]-N-
 [(2r,5s)-5-hydroxyadamantan-2-yl]pyrimidine-5-carboxamide (2.220 g, 64 %) as a white
 10 solid.

¹H NMR (400.132 MHz, CDCl₃) δ 0.99 - 1.05 (2H, m), 1.18 - 1.21 (2H, m), 1.24 (6H, d),
 1.41 (1H, s), 1.56 - 1.59 (2H, m), 1.69 - 1.73 (2H, m), 1.76 - 1.82 (4H, m), 1.90 - 1.96 (2H,
 m), 2.15 - 2.18 (1H, m), 2.23 - 2.26 (2H, m), 2.48 - 2.61 (3H, m), 3.53 - 3.62 (2H, m), 4.19
 15 - 4.24 (1H, m), 4.49 - 4.56 (2H, m), 6.03 (1H, d), 8.37 (1H, s)

m/z (ES⁺) (M+H)⁺ = 427; HPLC t_R = 1.98 min.

Example 221

20 4-Cyclopropyl-2-(2,6-dimethylmorpholin-4-yl)-N-[(2r,5s)-5-hydroxyadamantan-2-yl]pyrimidine-5-carboxamide



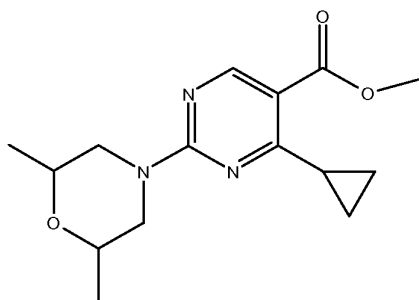
O-(7-Azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (811 mg, 2.13 mmol) was added to 4-cyclopropyl-2-(2,6-dimethylmorpholino)pyrimidine-5-
 25 carboxylic acid (Intermediate 74, 473 mg, 1.71 mmol), 4-aminoadamantan-1-ol hydrochloride (347 mg, 1.71 mmol) and N-Ethyl-diisopropylamine (0.654 mL, 3.75 mmol) in DMF (5 mL) at ambient temperature under nitrogen. The resulting solution was stirred at ambient temperature for 16 hours. The reaction mixture was evaporated to dryness and

redissolved in EtOAc (50 mL) and washed sequentially with water (10 mL), 1N citric acid (10 mL), saturated NaHCO₃ (5 mL) and saturated brine (10mL). The organic layer was dried over MgSO₄, filtered and evaporated to afford crude product. The crude product was purified by preparative HPLC Waters XBridge Prep C18 OBD column, 5 μ silica, 50 mm diameter, 150 mm length), using decreasingly polar mixtures of water (containing 0.5% NH₃) and MeCN as eluents. Fractions containing the desired compound were evaporated to dryness to afford 4-cyclopropyl-2-(2,6-dimethylmorpholin-4-yl)-N-[(2r,5s)-5-hydroxyadamantan-2-yl]pyrimidine-5-carboxamide (389 mg, 54 %) as a white solid.

¹H NMR (400.132 MHz, CDCl₃) δ 0.92 - 0.97 (2H, m), 1.11 - 1.16 (2H, m), 1.18 (6H, s), 1.32 (1H, s), 1.50 (2H, d), 1.59 - 1.77 (6H, m), 1.87 (2H, d), 2.11 (1H, s), 2.17 (2H, s), 2.40 - 2.46 (1H, m), 2.49 (2H, d), 3.47 - 3.56 (2H, m), 4.14 (1H, d), 4.47 (2H, d), 5.96 (1H, d), 8.29 (1H, s)

m/z (ESI⁺) (M+H)⁺ = 427; HPLC t_R = 1.97 min.

Intermediate 73 may be prepared as follows: methyl 4-cyclopropyl-2-(2,6-dimethylmorpholino)pyrimidine-5-carboxylate



A solution of (Z)-ethyl 2-(cyclopropanecarbonyl)-3-(dimethylamino)acrylate (0.528 g, 2.5 mmol) in methanol (10 mL) was added dropwise to a stirred suspension of 2,6-dimethylmorpholine-4-carboximidamide hydrobromide (0.595 g, 2.50 mmol) and Sodium methoxide 0.5M in methanol (5.00 mL, 2.50 mmol) in methanol (10 mL) at room temperature, over a period of 5 minutes under nitrogen. The resulting suspension was stirred at 70 °C for 4 hours. The reaction mixture was evaporated to dryness and redissolved in EtOAc (50 mL), and washed sequentially with water (10 mL) and saturated brine (10 mL). The organic layer was dried over MgSO₄, filtered and evaporated to afford

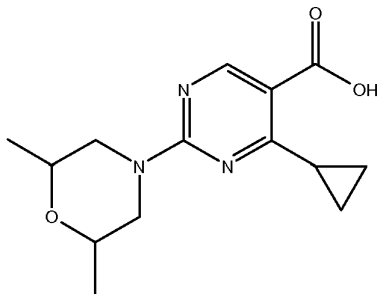
methyl 4-cyclopropyl-2-(2,6-dimethylmorpholino)pyrimidine-5-carboxylate as an oil, which crystallised and was used without purification in the next step.

¹H NMR (400.132 MHz, CDCl₃) δ 1.00 - 1.05 (2H, m), 1.14 - 1.19 (2H, m), 1.24 (6H, d),
5 2.58 (2H, dd), 3.22 (1H, septet), 3.54 - 3.63 (2H, m), 3.87 (3H, s), 4.61 (2H, s), 8.75 (1H, s)

m/z (ESI+) (M+H)⁺ = 292; HPLC t_R = 2.72 min methyl ester and (M+H)⁺ = 306; HPLC t_R = 2.98 min ethyl ester

10

Intermediate 74 may be prepared as follows: 4-cyclopropyl-2-(2,6-dimethylmorpholino)pyrimidine-5-carboxylic acid



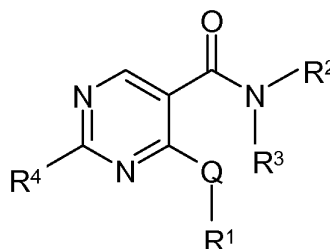
A solution of Lithium hydroxide 1M (4.64 mL, 4.64 mmol) was added dropwise to a stirred
15 solution of methyl 4-cyclopropyl-2-(2,6-dimethylmorpholino)pyrimidine-5-carboxylate (**Intermediate 73**, 676 mg, 2.32 mmol) in tetrahydrofuran (5 mL):methanol (1.7 mL) over a period of 5 minutes. The resulting solution was stirred at 20 °C for 16 hours. The reaction mixture was concentrated and diluted with water (15 mL), and washed sequentially with ethyl acetate (2x10 mL), the aqueous phase was acidified with 2M HCl. The precipitate
20 was collected by filtration, washed with water (10 mL) and dried under vacuum to afford 4-cyclopropyl-2-(2,6-dimethylmorpholino)pyrimidine-5-carboxylic acid (473 mg, 74 %) as a white solid, which was used without further purification.

¹H NMR (400.132 MHz, CDCl₃) δ 1.02 - 1.08 (2H, m), 1.17 - 1.22 (2H, m), 1.25 (6H, d),
25 2.61 (2H, dd), 3.23 - 3.31 (1H, m), 3.55 - 3.65 (2H, m), 4.62 (2H, d), 8.87 (1H, s)

m/z (ESI+) (M+H)⁺ = 278; HPLC t_R = 2.13 min.

CLAIMS

1. A compound of formula (1):

**(1)**

wherein:

Q is O, S, N(R⁸) or a single bond;

R⁸ is selected from hydrogen, C₁₋₄alkyl, C₃₋₅cycloalkyl and C₃₋₅cycloalkylmethyl (each of which is optionally substituted by 1, 2 or 3 fluoro atoms);

- 10 **R¹** is selected from C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₇cycloalkyl, heterocyclyl, heteroaryl, aryl, arylC₁₋₃alkyl, heteroarylC₁₋₃alkyl, C₃₋₇cycloalkylC₁₋₃alkyl, heterocyclylC₁₋₃alkyl, C₃₋₇cycloalkylC₂₋₃alkenyl and C₃₋₇cycloalkylC₂₋₃alkynyl, [each of which is optionally substituted, on available carbon atoms, by 1, 2 or 3 substituents independently selected from C₁₋₃alkyl, hydroxy, halo, oxo, cyano, trifluoromethyl,
- 15 C₁₋₃alkoxy, C₁₋₃alkylS(O)_n- (wherein n is 0, 1, 2 or 3), R^{5'}CON(R^{5'})-, (R^{5'})(R^{5''})N-, (R^{5'})(R^{5''})NC(O)-, R^{5'}C(O)O-, R^{5'}OC(O)-, (R^{5'})(R^{5''})NC(O)N(R^{5'''})-, R^{5'}SO₂N(R^{5''})-, (R^{5'})(R^{5''})NSO₂- and C₁₋₂alkyl optionally substituted by 1, 2 or 3 substituents independently selected from hydroxy, halo, carboxy and C₁₋₃alkoxy (wherein R⁵ is C₁₋₃alkyl optionally substituted by 1, 2 or 3 substituents independently selected from
- 20 hydroxyl, halo and cyano; and
- R^{5'}, R^{5''} and R^{5'''} are independently selected from hydrogen and C₁₋₃alkyl optionally substituted by 1, 2 or 3 substituents independently selected from hydroxyl, halo, C₁₋₃alkoxy, carboxy and cyano or R^{5'} and R^{5''} together with the nitrogen atom to which they are attached form a 4-7 membered saturated ring) and optionally substituted, on an
- 25 available nitrogen, by a substituent independently selected from C₁₋₄alkyl, C₂₋₄alkanoyl and C₁₋₄alkanesulphonyl each of which is optionally substituted by 1, 2 or 3 substituent independently selected from hydroxyl, halo, C₁₋₄alkoxy, carboxy and cyano]; or

R^1 and R^8 together with the nitrogen atom to which they are attached form a saturated mono, bicyclic or bridged ring system optionally containing 1 or 2 additional ring heteroatoms independently selected from nitrogen, oxygen and sulphur and optionally fused to a saturated, partially saturated or unsaturated monocyclic ring wherein the resulting ring system is optionally substituted, on available carbon atoms, by 1, 2, or 3 substituents independently selected from R^9 and optionally substituted, on an available nitrogen, by a substituent independently selected from C_{1-4} alkyl, C_{2-4} alkanoyl and C_{1-4} alkanesulphonyl each of which is optionally substituted by 1, 2 or 3 substituent independently selected from hydroxyl, halo, C_{1-4} alkoxy, carboxy and cyano;

R^2 is selected from adamantyl optionally substituted, on available carbon atoms, by 1 or substituents independently selected from R^6 ;

R^3 is hydrogen;

R^4 is selected from hydrogen, R^{10} , $-OR^{10}$, $-SR^{10}$ and $-NR^{11}R^{12}$;

R^{10} is selected from C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-7} cycloalkyl, heterocyclyl, aryl C_{1-3} alkyl, heteroaryl C_{1-3} alkyl, heterocyclyl C_{1-3} alkyl, C_{3-7} cycloalkyl C_{1-3} alkyl, C_{3-7} cycloalkyl C_{2-3} alkenyl and C_{3-7} cycloalkyl C_{2-3} alkynyl, [each of which is optionally substituted, on available carbon atoms, by 1, 2 or 3 substituents independently selected from C_{1-3} alkyl, hydroxy, halo, oxo, cyano, trifluoromethyl, C_{1-3} alkoxy, C_{1-3} alkylS(O)_p- (wherein p is 0, 1, 2 or 3), $R^{13}CON(R^{13'})$ -, $(R^{13'})(R^{13''})N$ -, $(R^{13'})(R^{13''})NC(O)$ -, $R^{13'}C(O)O$ -, $R^{13'}OC(O)$ -, $(R^{13'})(R^{13''})NC(O)N(R^{13'''})$ -, $R^{13}SO_2N(R^{13''})$ -, $(R^{13'})(R^{13''})NSO_2$ - and C_{1-2} alkyl optionally substituted by 1, 2 or 3 substituents independently selected from hydroxy, halo, carboxy and C_{1-3} alkoxy (wherein R^{13} is C_{1-3} alkyl optionally substituted by 1, 2 or 3 substituents selected from hydroxyl, halo and cyano; and

$R^{13'}$, $R^{13''}$ and $R^{13'''}$ are independently selected from hydrogen and C_{1-3} alkyl optionally substituted by 1, 2 or 3 substituents independently selected from hydroxyl, halo, C_{1-3} alkoxy, carboxy and cyano or $R^{13'}$ and $R^{13''}$ together with the nitrogen atom to which they are attached form a 4-7 membered saturated ring) and optionally substituted, on an available nitrogen, by a substituent independently selected from C_{1-4} alkyl, C_{2-4} alkanoyl and C_{1-4} alkanesulphonyl each of which is optionally substituted by 1, 2 or 3 substituent independently selected from hydroxyl, halo, C_{1-4} alkoxy, carboxy and cyano];

R^{11} is selected from hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-7} cycloalkyl, heterocyclyl, aryl C_{1-3} alkyl, heteroaryl C_{1-3} alkyl, heterocyclyl C_{1-3} alkyl, C_{3-}

γ -cycloalkylC₁₋₃alkyl, C₃₋₇cycloalkylC₂₋₃alkenyl and C₃₋₇cycloalkylC₂₋₃alkynyl, [each of which is optionally substituted, on available carbon atoms, by 1, 2 or 3 substituents independently selected from C₁₋₃alkyl, hydroxy, halo, oxo, cyano, trifluoromethyl, C₁₋₃alkoxy, C₁₋₃alkylS(O)_q- (wherein q is 0, 1, 2 or 3), R¹⁴CON(R^{14'})-, (R^{14'})(R^{14''})NC(O)-, R^{14'}C(O)O-, R^{14'}OC(O)-, (R^{14'})(R^{14''})NC(O)N(R^{14'''})-, R¹⁴SO₂N(R^{14''})-, (R^{14'})(R^{14''})NSO₂- and C₁₋₂alkyl optionally substituted by 1, 2 or 3 substituents independently selected from hydroxy, halo, carboxy and C₁₋₃alkoxy (wherein R¹⁴ is C₁₋₃alkyl optionally substituted by 1, 2 or 3 substituents independently selected from hydroxyl, halo and cyano; and R^{14'}, R^{14''} and R^{14'''} are independently selected from hydrogen and C₁₋₃alkyl optionally substituted by 1, 2 or 3 substituents independently selected from hydroxyl, halo, C₁₋₃alkoxy, carboxy and cyano or R^{14'} and R^{14''} together with the nitrogen atom to which they are attached form a 4-7 membered saturated ring) and optionally substituted, on an available nitrogen, by a substituent independently selected from C₁₋₄alkyl, C₂₋₄alkanoyl and C₁₋₄alkanesulphonyl each of which is optionally substituted by 1, 2 or 3 substituent independently selected from hydroxyl, halo, C₁₋₄alkoxy, carboxy and cyano]; and R¹² is selected from hydrogen, C₁₋₄alkyl, C₃₋₅cycloalkyl and C₃₋₅cycloalkylmethyl (each of which is optionally substituted by 1, 2 or 3 fluoro atoms); or R¹¹ and R¹² together with the nitrogen atom to which they are attached form a saturated mono, bicyclic or bridged ring system optionally containing 1 or 2 additional ring heteroatoms independently selected from nitrogen, oxygen and sulphur and optionally fused to a saturated, partially saturated or unsaturated monocyclic ring (optionally containing 1 or 2 additional ring heteroatoms independently selected from nitrogen, oxygen and sulphur) wherein the resulting ring system is optionally substituted, on available carbon atoms, by 1, 2, or 3 substituents independently selected from R¹⁵ and optionally substituted on an available nitrogen by a substituent independently selected from C₁₋₄alkyl, C₂₋₄alkanoyl and C₁₋₄alkanesulphonyl each of which is optionally substituted by 1, 2 or 3 substituent independently selected from hydroxyl, halo, C₁₋₄alkoxy, carboxy and cyano; R⁶, R⁷, R⁹ and R¹⁵ are independently selected from hydroxyl, halo, oxo, carboxy, cyano, trifluoromethyl, R¹⁶, R¹⁶O-, R¹⁶CO-, R¹⁶C(O)O-, R¹⁶CON(R^{16'})-, (R^{16'})(R^{16''})NC(O)-, (R^{16'})(R^{16''})N-, R¹⁶S(O)_a- wherein a is 0 to 2, R^{16'}OC(O)-, (R^{16'})(R^{16''})NSO₂-, R¹⁶SO₂N(R^{16''})-, (R^{16'})(R^{16''})NC(O)N(R^{16'''})-, phenyl and heteroaryl [wherein the phenyl

and heteroaryl groups are optionally fused to a phenyl, heteroaryl or a saturated or partially-saturated 5- or 6-membered ring optionally containing 1, 2 or 3 heteroatoms independently selected from nitrogen, oxygen and sulphur and the resulting ring system is optionally substituted, on available carbon atoms, by 1, 2 or 3 substituents independently selected from C₁₋₄alkyl, hydroxyl, cyano, trifluoromethyl, trifluoromethoxy, halo, C₁₋₄alkoxy, C₁₋₄alkoxyC₁₋₄alkyl, amino, N-C₁₋₄alkylamino, di-N,N-(C₁₋₄alkyl)amino, N-C₁₋₄alkylcarbonyl, di-N,N-(C₁₋₄alkyl)carbonyl, C₁₋₄alkylS(O)_r- and C₁₋₄alkylS(O)_rC₁₋₄alkyl (wherein r is independently selected 0, 1 and 2) and optionally substituted, on an available nitrogen, by a substituent independently selected from C₁₋₄alkyl, C₂₋₄alkanoyl and C₁₋₄alkanesulphonyl each of which is optionally substituted by 1, 2 or 3 substituent independently selected from hydroxyl, halo, C₁₋₄alkoxy, carboxy and cyano];

R¹⁶ is independently selected from, C₁₋₃alkyl optionally substituted by 1, 2 or 3 substituents independently selected from hydroxyl, halo, C₁₋₄alkoxy, carboxy and cyano;

R^{16'}, R^{16''} and R^{16'''} are independently selected from hydrogen and C₁₋₃alkyl optionally substituted by 1, 2, or 3 substituents independently selected from hydroxyl, halo, C₁₋₄alkoxy, carboxy and cyano);

or a pharmaceutically-acceptable salt thereof.

2. A compound of formula (I) as defined in claim 1 or a pharmaceutically-acceptable salt thereof wherein Q is a single bond.

3. A compound of the formula (I) as defined in either claim 1 or claim 2 or a pharmaceutically-acceptable salt thereof wherein R¹ is selected from C₃₋₇cycloalkyl and heterocyclyl [each of which is optionally substituted, on available carbon atoms, by 1, 2 or 3 substituents independently selected from C₁₋₃alkyl, halo, cyano, trifluoromethyl, C₁₋₃alkoxy and C₁₋₂alkyl optionally substituted by 1, 2 or 3 substituents independently selected from hydroxy, halo, carboxy and C₁₋₃alkoxy; and optionally substituted, on an available nitrogen, by a substituent independently selected from C₁₋₄alkyl and C₂₋₄alkanoyl].

4. A compound of the formula (I) as defined in any one of claims 1 to 3 or a pharmaceutically-acceptable salt thereof wherein R^4 is $-NR^{11}R^{12}$ and wherein R^{11} and R^{12} are as defined in claim 1.

5. A compound of the formula (I) as defined in claim 4 or a pharmaceutically-acceptable salt thereof wherein R^4 is $-NHR^{11}$ and R^{11} is selected from C_{1-6} alkyl, C_{3-7} cycloalkyl, heterocyclyl, aryl C_{1-3} alkyl, heteroaryl C_{1-3} alkyl, C_{3-7} cycloalkyl C_{1-3} alkyl and C_{3-7} cycloalkyl [each of which is optionally substituted, on available carbon atoms, by 1, 2 or 3 substituents independently selected from C_{1-3} alkyl, hydroxy, halo, oxo, cyano, trifluoromethyl, C_{1-3} alkoxy, C_{1-3} alkylS(O)_q- (wherein q is 0, 1, 2 or 3), R^{14} CON($R^{14'}$)- and ($R^{14'}$)($R^{14''}$)NC(O)-, (wherein R^{14} is C_{1-3} alkyl and $R^{14'}$, $R^{14''}$ and $R^{14'''}$ are independently selected from hydrogen and C_{1-3} alkyl optionally substituted by 1, 2 or 3 substituents independently selected from hydroxyl, halo, C_{1-3} alkoxy, carboxy and cyano or $R^{14'}$ and $R^{14''}$ together with the nitrogen atom to which they are attached form a 4-7 membered saturated ring) and optionally substituted, on an available nitrogen, by a substituent independently selected from C_{1-4} alkyl and C_{2-4} alkanoyl].

6. A compound as defined in claim 1 selected from the following:

4-cyclopropyl-N-[(2s,5r)-5-hydroxyadamantan-2-yl]-2-morpholin-4-ylpyrimidine-5-carboxamide;

4-cyclopropyl-N-[(2r,5s)-5-hydroxyadamantan-2-yl]-2-methylpyrimidine-5-carboxamide;

4-cyclopropyl-N-[(2r,5s)-5-hydroxyadamantan-2-yl]pyrimidine-5-carboxamide;

4-tert-butyl-N-[(2r,5s)-5-hydroxyadamantan-2-yl]-2-morpholin-4-ylpyrimidine-5-carboxamide;

N-[(2r,5s)-5-hydroxyadamantan-2-yl]-4-methyl-2-morpholin-4-ylpyrimidine-5-carboxamide;

4-tert-butyl-N-[(2r,5s)-5-hydroxyadamantan-2-yl]-2-methylpyrimidine-5-carboxamide;

4-tert-butyl-N-[(2r,5s)-5-hydroxyadamantan-2-yl]pyrimidine-5-carboxamide;

N-[(2r,5s)-5-hydroxyadamantan-2-yl]-2-morpholin-4-yl-4-propylsulfanylpyrimidine-5-carboxamide;

- N-[(2r,5s)-5-hydroxyadamantan-2-yl]-2-methyl-4-propylsulfanylpuridine-5-carboxamide;
- N-[(2r,5s)-5-hydroxyadamantan-2-yl]-4-propylsulfanylpuridine-5-carboxamide;
- 4-cyclopropyl-N-[(2r,5s)-5-hydroxyadamantan-2-yl]-2-methylsulfanylpuridine-5-carboxamide;
- 5 N-(2-adamantyl)-4-cyclopropyl-2-methyl-puridine-5-carboxamide;
- N-(2-adamantyl)-4-cyclopropyl-2-morpholino-puridine-5-carboxamide;
- N-(2-adamantyl)-4-tert-butyl-2-morpholin-4-ylpuridine-5-carboxamide;
- N-(2-adamantyl)-4-methyl-2-morpholin-4-ylpuridine-5-carboxamide;
- 10 N-[(2r,5s)-5-hydroxyadamantan-2-yl]-2,4-bis(propylsulfanylpuridine-5-carboxamide;
- 2-dimethylamino-N-[(2r,5s)-5-hydroxyadamantan-2-yl]-4-propylsulfanylpuridine-5-carboxamide;
- 4-dimethylamino-N-[(2r,5s)-5-hydroxyadamantan-2-yl]-2-propylsulfanylpuridine-5-carboxamide;
- 15 {(3S)-1-[5-(cyclohexylcarbamoyl)-4-(propylthio)puridin-2-yl]piperidin-3-yl}acetic acid;
- N-[(2r,5s)-5-hydroxyadamantan-2-yl]-2-methylamino-4-propylsulfanylpuridine-5-carboxamide;
- N-[(2r,5s)-5-hydroxyadamantan-2-yl]-4-methylamino-2-propylsulfanylpuridine-5-carboxamide;
- 20 2-[(2S,6R)-2,6-dimethylmorpholin-4-yl]-N-[(2r,5s)-5-hydroxyadamantan-2-yl]-4-propylsulfanylpuridine-5-carboxamide;
- 4-[(2S,6R)-2,6-dimethylmorpholin-4-yl]-N-[(2r,5s)-5-hydroxyadamantan-2-yl]-2-propylsulfanylpuridine-5-carboxamide;
- 4-(4-acetylpiperazin-1-yl)-N-[(2r,5s)-5-hydroxyadamantan-2-yl]-2-propylsulfanylpuridine-5-carboxamide;
- 25 2-(4-acetylpiperazin-1-yl)-N-[(2r,5s)-5-hydroxyadamantan-2-yl]-4-propylsulfanylpuridine-5-carboxamide;
- 2-(4-acetylpiperazin-1-yl)-N-(2-adamantyl)-4-propylsulfanylpuridine-5-carboxamide;
- N-(2-adamantyl)-2-(4-methylsulfonylpiperazin-1-yl)-4-propylsulfanylpuridine-5-carboxamide;
- 30 N-(2-adamantyl)-2-[4-(dimethylcarbamoyl)piperazin-1-yl]-4-propylsulfanylpuridine-5-carboxamide;

- 4-cyclopentyl-N-[(2s,5r)-5-hydroxyadamantan-2-yl]-2-morpholin-4-ylpyrimidine-5-carboxamide;
- N-[(2s,5r)-5-hydroxyadamantan-2-yl]-2-morpholin-4-yl-4-propoxypyrimidine-5-carboxamide;
- 5 4-cyclopropyl-N-[(2r,5s)-5-hydroxyadamantan-2-yl]-2-[(3R)-oxolan-3-ylamino]pyrimidine-5-carboxamide;
- N-[(2r,5s)-5-hydroxyadamantan-2-yl] 4-cyclopropyl-2-[(3S)-oxolan-3-yl]amino]pyrimidine-5-carboxamide;
- N-[(2s,5r)-5-hydroxyadamantan-2-yl]-2,4-dimorpholin-4-ylpyrimidine-5-carboxamide;
- 10 4-cyclopropyl-N-[(2r,5s)-5-hydroxyadamantan-2-yl]-2-methoxypyrimidine-5-carboxamide;
- 4-cyclopropyl-N-[(2r,5s)-5-hydroxyadamantan-2-yl]-2-methylaminopyrimidine-5-carboxamide;
- 4-cyclopropyl-N-[(2r,5s)-5-hydroxyadamantan-2-yl]-2-thiomorpholin-4-ylpyrimidine-5-
- 15 carboxamide
- 4-cyclopropyl-N-[(2r,5s)-5-hydroxyadamantan-2-yl]-2-(1-oxo-1,4-thiazinan-4-yl)pyrimidine-5-carboxamide;
- 4-cyclopropyl-2-(1,1-dioxo-1,4-thiazinan-4-yl)-N-[(2r,5s)-5-hydroxyadamantan-2-yl]pyrimidine-5-carboxamide;
- 20 4-cyclohexyl-N-[(2r,5s)-5-hydroxyadamantan-2-yl]-2-morpholin-4-ylpyrimidine-5-carboxamide;
- 4-cyclopentyl-N-[(2r,5s)-5-hydroxyadamantan-2-yl]-2-methylpyrimidine-5-carboxamide;
- 4-cyclobutyl-N-[(2r,5s)-5-hydroxyadamantan-2-yl]-2-morpholin-4-ylpyrimidine-5-carboxamide;
- 25 4-cyclobutyl-N-[(2r,5s)-5-hydroxyadamantan-2-yl]-2-thiomorpholin-4-ylpyrimidine-5-carboxamide
- 4-cyclopropyl-2-(2,6-dimethylmorpholin-4-yl)-N-[(2r,5s)-5-hydroxyadamantan-2-yl]pyrimidine-5-carboxamide;
- 4-cyclopropyl-2-(3,3-difluoroazetidin-1-yl)-N-[(2r,5s)-5-hydroxyadamantan-2-
- 30 yl]pyrimidine-5-carboxamide;
- 2-(azetidin-1-yl)-4-cyclopropyl-N-[(2r,5s)-5-hydroxyadamantan-2-yl]pyrimidine-5-carboxamide;

- 2-(cyclobutylamino)-4-cyclopropyl-N-[(2r,5s)-5-hydroxyadamantan-2-yl]pyrimidine-5-carboxamide;
- 4-cyclopropyl-N-[(2r,5s)-5-hydroxyadamantan-2-yl]-2-[4-(2-methoxyethyl)piperazin-1-yl]pyrimidine-5-carboxamide;
- 5 4-cyclopropyl-2-(cyclopropylamino)-N-[(2r,5s)-5-hydroxyadamantan-2-yl]pyrimidine-5-carboxamide;
- 2-(cyclopentylamino)-4-cyclopropyl-N-[(2r,5s)-5-hydroxyadamantan-2-yl]pyrimidine-5-carboxamide;
- 4-cyclopropyl-N-[(2r,5s)-5-hydroxyadamantan-2-yl]-2-[(1S,4S)-2-oxa-5-
- 10 azabicyclo[2.2.1]hept-5-yl]pyrimidine-5-carboxamide;
- 4-cyclopropyl-N-[(2r,5s)-5-hydroxyadamantan-2-yl]-2-[2-(hydroxymethyl)morpholin-4-yl]pyrimidine-5-carboxamide;
- 4-cyclopropyl-N-[(2r,5s)-5-hydroxyadamantan-2-yl]-2-[3-(hydroxymethyl)morpholin-4-yl]pyrimidine-5-carboxamide;
- 15 4-cyclopropyl-2-(dimethylamino)-N-[(2r,5s)-5-hydroxyadamantan-2-yl]pyrimidine-5-carboxamide;
- 4-cyclopropyl-2-[(3R,5S)-3,5-dimethylpiperazin-1-yl]-N-[(2r,5s)-5-hydroxyadamantan-2-yl]pyrimidine-5-carboxamide;
- 4-cyclopropyl-2-[(2R,6R)-2,6-dimethylmorpholin-4-yl]-N-[(2r,5s)-5-hydroxyadamantan-
- 20 2-yl]pyrimidine-5-carboxamide;
- 4-cyclopropyl-N-[(2r,5s)-5-hydroxyadamantan-2-yl]-2-(isopropylamino)pyrimidine-5-carboxamide;
- 4-cyclopropyl-N-[(2r,5s)-5-hydroxyadamantan-2-yl]-2-[(2-hydroxy-1,1-dimethylethyl)amino]pyrimidine-5-carboxamide;
- 25 4-cyclopropyl-N-[(2r,5s)-5-hydroxyadamantan-2-yl]-2-(tetrahydro-2H-pyran-4-ylamino)pyrimidine-5-carboxamide;
- 4-cyclopropyl-N-[(2r,5s)-5-hydroxyadamantan-2-yl]-2-[(2-hydroxy-2-methylpropyl)amino]pyrimidine-5-carboxamide;
- 4-cyclopropyl-2-[(1,1-dioxidotetrahydro-2H-thiopyran-4-yl)amino]-N-[(2r,5s)-5-
- 30 hydroxyadamantan-2-yl]pyrimidine-5-carboxamide;
- 4-cyclopropyl-N-[(2r,5s)-5-hydroxyadamantan-2-yl]-2-[(2-hydroxyethyl)amino]pyrimidine-5-carboxamide;

- 4-cyclopropyl-N-[(2r,5s)-5-hydroxyadamantan-2-yl]-2-(4-methylsulfonylpiperazin-1-yl)pyrimidine-5-carboxamide;
- 4-cyclopropyl-N-[(2r,5s)-5-hydroxyadamantan-2-yl]-2-(oxetan-3-ylamino)pyrimidine-5-carboxamide;
- 5 4-cyclopropyl-N-[(2r,5s)-5-hydroxyadamantan-2-yl]-2-[(2-morpholin-4-ylethyl)amino]pyrimidine-5-carboxamide;
- 4-cyclopropyl-2-({2-[(2R,6S)-2,6-dimethylmorpholin-4-yl]ethyl} amino)-N-[(2r,5s)-5-hydroxyadamantan-2-yl]pyrimidine-5-carboxamide;
- 4-cyclopropyl-N-[(2r,5s)-5-hydroxyadamantan-2-yl]-2-{[2-(4-methylpiperazin-1-yl)ethyl]amino} pyrimidine-5-carboxamide;
- 10 2-(cyclobutyloxy)-4-cyclopropyl-N-[(2r,5s)-5-hydroxyadamantan-2-yl]pyrimidine-5-carboxamide;
- 4-cyclopropyl-N-[(2r,5s)-5-hydroxyadamantan-2-yl]-2-isopropoxypyrimidine-5-carboxamide;
- 15 2-(cyclopentyloxy)-4-cyclopropyl-N-[(2r,5s)-5-hydroxyadamantan-2-yl]pyrimidine-5-carboxamide;
- 4-cyclopropyl-N-[(2r,5s)-5-hydroxyadamantan-2-yl]-2-(oxetan-3-yloxy)pyrimidine-5-carboxamide;
- (4-cyclopropyl-2-morpholinopyrimidin-5-yl)(3-(pyridin-3-yl)pyrrolidin-1-yl)methanone
- 20 1-(4-(4-cyclopropyl-5-(3-(pyridin-3-yl)pyrrolidine-1-carbonyl)pyrimidin-2-yl)piperazin-1-yl)ethanone;
- (4-cyclopropyl-2-((2S,6R)-2,6-dimethylmorpholino)pyrimidin-5-yl)(3-(pyridin-3-yl)pyrrolidin-1-yl)methanone;
- 4-cyclobutyl-N-[(2r,5s)-5-hydroxyadamantan-2-yl]-2-(1-oxo-1,4-thiazinan-4-yl)pyrimidine-5-carboxamide;
- 25 4-cyclobutyl-2-(1,1-dioxo-1,4-thiazinan-4-yl)-N-[(2r,5s)-5-hydroxyadamantan-2-yl]pyrimidine-5-carboxamide;
- 2-amino-4-cyclobutyl-N-[(2r,5s)-5-hydroxyadamantan-2-yl]pyrimidine-5-carboxamide;
- 2-azetidin-1-yl-4-cyclobutyl-N-[(2r,5s)-5-hydroxyadamantan-2-yl]pyrimidine-5-
- 30 carboxamide;
- 4-cyclobutyl-2-(dimethylamino)-N-[(2r,5s)-5-hydroxyadamantan-2-yl]pyrimidine-5-carboxamide;

- 4-cyclobutyl-N-[(2r,5s)-5-hydroxyadamantan-2-yl]-2-[4-(2-methoxyethyl)piperazin-1-yl]pyrimidine-5-carboxamide;
- 4-cyclobutyl-2-(cyclopropylamino)-N-[(2r,5s)-5-hydroxyadamantan-2-yl]pyrimidine-5-carboxamide;
- 5 4-cyclobutyl-2-(3,3-difluoroazetidin-1-yl)-N-[(2r,5s)-5-hydroxyadamantan-2-yl]pyrimidine-5-carboxamide;
- 4-cyclobutyl-N-[(2r,5s)-5-hydroxyadamantan-2-yl]-2-[3-(hydroxymethyl)morpholin-4-yl]pyrimidine-5-carboxamide;
- 4-cyclobutyl-N-[(2r,5s)-5-hydroxyadamantan-2-yl]-2-(methylamino)pyrimidine-5-
- 10 carboxamide;
- 4-cyclobutyl-2-[(2R,6S)-2,6-dimethylmorpholin-4-yl]-N-[(2r,5s)-5-hydroxyadamantan-2-yl]pyrimidine-5-carboxamide;
- 4-cyclobutyl-N-[(2r,5s)-5-hydroxyadamantan-2-yl]-2-[2-(hydroxymethyl)morpholin-4-yl]pyrimidine-5-carboxamide;
- 15 4-cyclobutyl-N-[(2r,5s)-5-hydroxyadamantan-2-yl]-2-(isopropylamino)pyrimidine-5-carboxamide;
- 4-cyclobutyl-N-[(2r,5s)-5-hydroxyadamantan-2-yl]-2-[(2-hydroxy-1,1-dimethylethyl)amino]pyrimidine-5-carboxamide;
- 4-cyclobutyl-N-[(2r,5s)-5-hydroxyadamantan-2-yl]-2-(tetrahydro-2H-pyran-4-
- 20 ylamino)pyrimidine-5-carboxamide;
- 4-cyclobutyl-N-[(2r,5s)-5-hydroxyadamantan-2-yl]-2-[(2-hydroxyethyl)amino]pyrimidine-5-carboxamide;
- N-[(2r,5s)-5-hydroxyadamantan-2-yl] 4-cyclobutyl-2-(cyclobutylamino) pyrimidine-5-carboxamide;
- 25 4-cyclobutyl-2-[(3R,5S)-3,5-dimethylpiperazin-1-yl]-N-[(2r,5s)-5-hydroxyadamantan-2-yl]pyrimidine-5-carboxamide;
- 4-cyclobutyl-N-[(2r,5s)-5-hydroxyadamantan-2-yl]-2-[(2-hydroxy-2-methylpropyl)amino]pyrimidine-5-carboxamide;
- 4-cyclobutyl-2-[(2R,6R)-2,6-dimethylmorpholin-4-yl]-N-[(2r,5s)-5-hydroxyadamantan-2-
- 30 yl]pyrimidine-5-carboxamide;
- 4-cyclobutyl-2-(cyclopentylamino)-N-[(2r,5s)-5-hydroxyadamantan-2-yl]pyrimidine-5-carboxamide;

- 4-cyclobutyl-N-[(2r,5s)-5-hydroxyadamantan-2-yl]-2-[(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl]pyrimidine-5-carboxamide;
- 4-cyclobutyl-N-[(2r,5s)-5-hydroxyadamantan-2-yl]-2-(oxetan-3-ylamino)pyrimidine-5-carboxamide;
- 5 4-cyclobutyl-2-[(1,1-dioxidotetrahydro-2H-thiopyran-4-yl)amino]-N-[(2r,5s)-5-hydroxyadamantan-2-yl]pyrimidine-5-carboxamide;
- 4-cyclobutyl-2-(cyclopentyloxy)-N-[(2r,5s)-5-hydroxyadamantan-2-yl]pyrimidine-5-carboxamide;
- 4-cyclobutyl-N-[(2r,5s)-5-hydroxyadamantan-2-yl]-2-isopropoxypyrimidine-5-
- 10 carboxamide;
- 4-cyclobutyl-2-(cyclobutyloxy)-N-[(2r,5s)-5-hydroxyadamantan-2-yl]pyrimidine-5-carboxamide;
- 4-cyclobutyl-N-[(2r,5s)-5-hydroxyadamantan-2-yl]-2-(oxetan-3-yloxy)pyrimidine-5-carboxamide;
- 15 4-cyclopentyl-N-[(2r,5s)-5-hydroxyadamantan-2-yl]-2-propan-2-yloxypyrimidine-5-carboxamide;
- 2-cyclobutyloxy-4-cyclopentyl-N-[(2r,5s)-5-hydroxyadamantan-2-yl]pyrimidine-5-carboxamide;
- 4-cyclopentyl-2-cyclopentyloxy-N-[(2r,5s)-5-hydroxyadamantan-2-yl]pyrimidine-5-
- 20 carboxamide;
- 4-cyclopentyl-N-[(2r,5s)-5-hydroxyadamantan-2-yl]-2-(oxetan-3-yloxy)pyrimidine-5-carboxamide;
- 4-cyclopentyl-N-[(2s,5r)-5-hydroxyadamantan-2-yl]-2-thiomorpholin-4-ylpyrimidine-5-carboxamide;
- 25 4-cyclopentyl-N-[(2r,5s)-5-hydroxyadamantan-2-yl]-2-(1-oxo-1,4-thiazinan-4-yl)pyrimidine-5-carboxamide;
- 4-cyclopentyl-2-(1,1-dioxo-1,4-thiazinan-4-yl)-N-[(2r,5s)-5-hydroxyadamantan-2-yl]pyrimidine-5-carboxamide;
- 4-cyclopentyl-N-[(2r,5s)-5-hydroxyadamantan-2-yl]-2-methoxypyrimidine-5-
- 30 carboxamide;
- 4-cyclopentyl-N-[(2r,5s)-5-hydroxyadamantan-2-yl]-2-methylaminopyrimidine-5-carboxamide;

- 4-cyclopentyl-2-[(2S,6R)-2,6-dimethylmorpholin-4-yl]-N-[(2r,5s)-5-hydroxyadamantan-2-yl]pyrimidine-5-carboxamide;
- 4-cyclopentyl-N-[(2r,5s)-5-hydroxyadamantan-2-yl]-2-[(1S,4S)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl]pyrimidine-5-carboxamide;
- 5 4-cyclopentyl-N-[(2r,5s)-5-hydroxyadamantan-2-yl]-2-(propan-2-ylamino)pyrimidine-5-carboxamide;
- 4-cyclopentyl-2-(cyclopropylamino)-N-[(2r,5s)-5-hydroxyadamantan-2-yl]pyrimidine-5-carboxamide;
- 4-cyclopentyl-N-[(2r,5s)-5-hydroxyadamantan-2-yl]-2-[(3S)-3-methylmorpholin-4-yl]pyrimidine-5-carboxamide;
- 10 4-cyclopentyl-2-[(2S,6S)-2,6-dimethylmorpholin-4-yl]-N-[(2r,5s)-5-hydroxyadamantan-2-yl]pyrimidine-5-carboxamide;
- 4-cyclopentyl-N-[(2r,5s)-5-hydroxyadamantan-2-yl]-2-[4-(2-methoxyethyl)piperazin-1-yl]pyrimidine-5-carboxamide;
- 15 2-(4-acetylpiperazin-1-yl)-4-cyclopentyl-N-[(2r,5s)-5-hydroxyadamantan-2-yl]pyrimidine-5-carboxamide;
- 4-cyclopentyl-N-[(2r,5s)-5-hydroxyadamantan-2-yl]-2-(3-oxo-4-propan-2-ylpiperazin-1-yl)pyrimidine-5-carboxamide;
- 4-cyclopentyl-N-[(2r,5s)-5-hydroxyadamantan-2-yl]-2-(4-methyl-3-oxopiperazin-1-yl)pyrimidine-5-carboxamide;
- 20 4-cyclopentyl-2-(cyclobutylamino)-N-[(2r,5s)-5-hydroxyadamantan-2-yl]pyrimidine-5-carboxamide;
- 4-cyclopentyl-2-(cyclopentylamino)-N-[(2r,5s)-5-hydroxyadamantan-2-yl]pyrimidine-5-carboxamide;
- 25 2-(azetidin-1-yl)-4-cyclopentyl-N-[(2r,5s)-5-hydroxyadamantan-2-yl]pyrimidine-5-carboxamide;
- 4-cyclopentyl-N-[(2r,5s)-5-hydroxyadamantan-2-yl]-2-(oxetan-3-ylamino)pyrimidine-5-carboxamide;
- 4-cyclopentyl-2-dimethylamino-N-[(2r,5s)-5-hydroxyadamantan-2-yl]pyrimidine-5-carboxamide;
- 30 4-cyclopentyl-2-[(3S,5R)-3,5-dimethylpiperazin-1-yl]-N-[(2r,5s)-5-hydroxyadamantan-2-yl]pyrimidine-5-carboxamide;

- 2-amino-4-cyclopentyl-N-[(2r,5s)-5-hydroxyadamantan-2-yl]pyrimidine-5-carboxamide;
4-cyclopentyl-2-[(1,1-dioxothian-4-yl)amino]-N-[(2r,5s)-5-hydroxyadamantan-2-yl]pyrimidine-5-carboxamide;
4-cyclopentyl-N-[(2r,5s)-5-hydroxyadamantan-2-yl]-2-[(2-hydroxy-2-methylpropyl)amino]pyrimidine-5-carboxamide;
5 4-cyclopentyl-N-[(2r,5s)-5-hydroxyadamantan-2-yl]-2-(2-hydroxyethylamino)pyrimidine-5-carboxamide;
4-cyclopentyl-N-[(2r,5s)-5-hydroxyadamantan-2-yl]-2-[(1-hydroxy-2-methylpropan-2-yl)amino]pyrimidine-5-carboxamide;
10 4-cyclopentyl-N-[(2r,5s)-5-hydroxyadamantan-2-yl]-2-(oxan-4-ylamino)pyrimidine-5-carboxamide;
4-cyclopentyl-N-[(2r,5s)-5-hydroxyadamantan-2-yl]-2-[3-(hydroxymethyl)morpholin-4-yl]pyrimidine-5-carboxamide;
4-cyclopentyl-N-[(2r,5s)-5-hydroxyadamantan-2-yl]-2-[(3R)-oxolan-3-yl]amino]pyrimidine-5-carboxamide;
15 4-cyclopentyl-N-[(2r,5s)-5-hydroxyadamantan-2-yl]-2-(4-methylsulfonylpiperazin-1-yl)pyrimidine-5-carboxamide;
4-cyclopentyl-N-[(2r,5s)-5-hydroxyadamantan-2-yl]-2-[(3S)-oxolan-3-yl]amino]pyrimidine-5-carboxamide;
20 4-cyclopentyl-N-[(2r,5s)-5-hydroxyadamantan-2-yl]-2-[2-(hydroxymethyl)morpholin-4-yl]pyrimidine-5-carboxamide;
4-cyclopentyl-2-(3,3-difluoroazetidin-1-yl)-N-[(2r,5s)-5-hydroxyadamantan-2-yl]pyrimidine-5-carboxamide;
4-cyclopentyl-N-[(2r,5s)-5-hydroxytricyclo[3.3.1.1^{3,7}]dec-2-yl]-2-[(2-morpholin-4-ylethyl)amino]pyrimidine-5-carboxamide;
25 4-cyclopentyl-2-({2-[(2R,6S)-2,6-dimethylmorpholin-4-yl]ethyl}amino)-N-[(2r,5s)-5-hydroxytricyclo[3.3.1.1^{3,7}]dec-2-yl]pyrimidine-5-carboxamide;
4-cyclopentyl-2-cyclopropyl-N-[(2r,5s)-5-hydroxyadamantan-2-yl]pyrimidine-5-carboxamide;
30 4-cyclopentyl-N-[(2r,5s)-5-hydroxyadamantan-2-yl]-2-propan-2-ylpyrimidine-5-carboxamide-2-(1-aminocyclopropyl)-4-cyclopentyl-N-[(2r,5s)-5-hydroxyadamantan-2-yl]pyrimidine-5-carboxamide;

- 2-(aminomethyl)-4-cyclopentyl-N-[(2r,5s)-5-hydroxyadamantan-2-yl]pyrimidine-5-carboxamide;
- 4-(3,3-difluorocyclobutyl)-N-[(2s,5r)-5-hydroxyadamantan-2-yl]-2-methylpyrimidine-5-carboxamide;
- 5 4-(3,3-difluorocyclobutyl)-N-[(2r,5s)-5-hydroxyadamantan-2-yl]-2-methylaminopyrimidine-5-carboxamide;
- 2-(cyclopropylamino)-4-(3,3-difluorocyclobutyl)-N-[(2r,5s)-5-hydroxyadamantan-2-yl]pyrimidine-5-carboxamide;
- 4-(3,3-difluorocyclobutyl)-2-[(2S,6R)-2,6-dimethylmorpholin-4-yl]-N-[(2r,5s)-5-hydroxyadamantan-2-yl]pyrimidine-5-carboxamide;
- 10 2-cyclobutyloxy-4-(3,3-difluorocyclobutyl)-N-[(2r,5s)-5-hydroxyadamantan-2-yl]pyrimidine-5-carboxamide;
- N-[(2r,5s)-5-hydroxyadamantan-2-yl]-2-methyl-4-(oxolan-2-yl)pyrimidine-5-carboxamide;
- N-[(2r,5s)-5-hydroxyadamantan-2-yl]-4-(oxolan-2-yl)-2-(propan-2-ylamino)pyrimidine-5-carboxamide;
- 15 2-(cyclopropylamino)-N-[(2r,5s)-5-hydroxyadamantan-2-yl]-4-(oxolan-2-yl)pyrimidine-5-carboxamide;
- N-[(2r,5s)-5-hydroxyadamantan-2-yl]-2-methylamino-4-(oxolan-2-yl)pyrimidine-5-carboxamide;
- 20 2-(cyclobutylamino)-N-[(2r,5s)-5-hydroxyadamantan-2-yl]-4-(oxolan-2-yl)pyrimidine-5-carboxamide;
- 2-[(2S,6R)-2,6-dimethylmorpholin-4-yl]-N-[(2r,5s)-5-hydroxyadamantan-2-yl]-4-(oxolan-2-yl)pyrimidine-5-carboxamide;
- N-[(2r,5s)-5-hydroxyadamantan-2-yl]-2-(oxetan-3-ylamino)-4-(oxolan-2-yl)pyrimidine-5-carboxamide;
- 25 N-[(2r,5s)-5-hydroxyadamantan-2-yl]-4-(oxolan-2-yl)-2-propan-2-yloxy pyrimidine-5-carboxamide;
- N-[(2r,5s)-5-hydroxyadamantan-2-yl]-2-methylsulfanyl-4-[(2R)-oxolan-2-yl]pyrimidine-5-carboxamide;
- 30 N-[(2r,5s)-5-hydroxyadamantan-2-yl]-2-methylamino-4-[(2R)-oxolan-2-yl]pyrimidine-5-carboxamide;
- 2-(cyclopropylamino)-N-[(2r,5s)-5-hydroxyadamantan-2-yl]-4-[(2R)-oxolan-2-

- yl]pyrimidine-5-carboxamide;
N-[(2r,5s)-5-hydroxyadamantan-2-yl]-4-[(2R)-oxolan-2-yl]-2-(propan-2-ylamino)pyrimidine-5-carboxamide;
2-[(3S,5R)-3,5-dimethylpiperazin-1-yl]-N-[(2r,5s)-5-hydroxyadamantan-2-yl]-4-[(2R)-oxolan-2-yl]pyrimidine-5-carboxamide;
5 N-[(2r,5s)-5-hydroxyadamantan-2-yl]-2-(oxetan-3-ylamino)-4-[(2R)-oxolan-2-yl]pyrimidine-5-carboxamide;
N-[(2r,5s)-5-hydroxyadamantan-2-yl]-2-(oxan-4-ylamino)-4-[(2R)-oxolan-2-yl]pyrimidine-5-carboxamide;
10 2-(cyclobutylamino)-N-[(2r,5s)-5-hydroxyadamantan-2-yl]-4-[(2R)-oxolan-2-yl]pyrimidine-5-carboxamide;
N-[(2r,5s)-5-hydroxyadamantan-2-yl]-4-[(2R)-oxolan-2-yl]-2-propan-2-yloxy pyrimidine-5-carboxamide;
N-[(2r,5s)-5-hydroxyadamantan-2-yl]-2-methylsulfanyl-4-[(2S)-oxolan-2-yl]pyrimidine-5-carboxamide;
15 N-[(2r,5s)-5-hydroxyadamantan-2-yl]-2-methylamino-4-[(2S)-oxolan-2-yl]pyrimidine-5-carboxamide;
N-[(2r,5s)-5-hydroxyadamantan-2-yl]-4-[(2S)-oxolan-2-yl]-2-(propan-2-ylamino)pyrimidine-5-carboxamide;
20 2-(cyclopropylamino)-N-[(2r,5s)-5-hydroxyadamantan-2-yl]-4-[(2S)-oxolan-2-yl]pyrimidine-5-carboxamide;
N-[(2r,5s)-5-hydroxyadamantan-2-yl]-4-[(2S)-oxolan-2-yl]-2-propan-2-yloxy pyrimidine-5-carboxamide;
2-[(2S,6R)-2,6-Dimethylmorpholin-4-yl]-N-[(2r,5s)-5-hydroxyadamantan-2-yl]-4-[(2R)-oxolan-2-yl]pyrimidine-5-carboxamide;
25 2-[(2S,6R)-2,6-Dimethylmorpholin-4-yl]-N-[(2r,5s)-5-hydroxyadamantan-2-yl]-4-[(2S)-oxolan-2-yl]pyrimidine-5-carboxamide;
4-(3,3-Difluorocyclopentyl)-N-[(2r,5s)-5-hydroxyadamantan-2-yl]-2-methylpyrimidine-5-carboxamide;
30 N-[(2r,5s)-5-hydroxyadamantan-2-yl]-4-(1-methylcyclopropyl)-2-morpholin-4-ylpyrimidine-5-carboxamide;

- N-[(2r,5s)-5-hydroxyadamantan-2-yl]-4-(1-methylcyclopropyl)-2-morpholin-4-ylpyrimidine-5-carboxamide;
- (Z)-3-dimethylamino-2-(1-methylcyclopropanecarbonyl)-N-(5-phenylmethoxy-2-adamantyl)prop-2-enamide;
- 5 N-[(2r,5s)-5-hydroxyadamantan-2-yl]-2-methyl-4-phenylpyrimidine-5-carboxamide;
- 4-(2-Chlorophenyl)-N-[(2r,5s)-5-hydroxyadamantan-2-yl]-2-methylpyrimidine-5-carboxamide;
- 4-(cyclopentylmethyl)-N-[(2r,5s)-5-hydroxyadamantan-2-yl]-2-methylpyrimidine-5-carboxamide;
- 10 4-butyl-N-[(2r,5s)-5-hydroxyadamantan-2-yl]-2-methylpyrimidine-5-carboxamide;
- N-[(2s,5r)-5-hydroxyadamantan-2-yl]-4-isobutyl-2-methylpyrimidine-5-carboxamide;
- 4-(2,2-dimethylpropyl)-N-[(2r,5s)-5-hydroxyadamantan-2-yl]-2-methylpyrimidine-5-carboxamide;
- 4-(cyclopropylmethyl)-N-[(2r,5s)-5-hydroxyadamantan-2-yl]-2-methylpyrimidine-5-
- 15 carboxamide
- 4-cyclohexyl-N-[(2r,5s)-5-hydroxyadamantan-2-yl]-2-(methylthio)pyrimidine-5-carboxamide;
- 4-cyclohexyl-N-[(2r,5s)-5-hydroxyadamantan-2-yl]-2-thiomorpholin-4-ylpyrimidine-5-carboxamide;
- 20 4-cyclohexyl-N-[(2r,5s)-5-hydroxyadamantan-2-yl]-2-(1-oxidothiomorpholin-4-yl)pyrimidine-5-carboxamide;
- 4-cyclohexyl-2-(1,1-dioxidothiomorpholin-4-yl)-N-[(2r,5s)-5-hydroxyadamantan-2-yl]pyrimidine-5-carboxamide;
- 2,4-bis(dimethylamino)-N-[(2r,5s)-5-hydroxyadamantan-2-yl]pyrimidine-5-carboxamide;
- 25 2,4-bis(3,3-difluoroazetidin-1-yl)-N-[(2r,5s)-5-hydroxyadamantan-2-yl]pyrimidine-5-carboxamide;
- 2,4-bis(azetidin-1-yl)-N-[(2r,5s)-5-hydroxyadamantan-2-yl]pyrimidine-5-carboxamide;
- N-[(2r,5s)-5-hydroxyadamantan-2-yl]-2-methyl-4-propan-2-yloxy-pyrimidine-5-carboxamide;
- 30 4-cyclobutyloxy-N-[(2r,5s)-5-hydroxyadamantan-2-yl]-2-methylpyrimidine-5-carboxamide;
- 4-cyclopentyloxy-N-[(2r,5s)-5-hydroxyadamantan-2-yl]-2-methylpyrimidine-5-

- carboxamide;
- 2-[(2R,6S)-2,6-Dimethylmorpholin-4-yl]-N-[(2r,5s)-5-hydroxytricyclo[3.3.1.1³,7]dec-2-yl]-4-methoxypyrimidine-5-carboxamide;
- 2-(cyclopropylamino)-N-[(2r,5s)-5-hydroxytricyclo[3.3.1.1³,7]dec-2-yl]-4-methoxypyrimidine-5-carboxamide;
- 5 2-(cyclobutylamino)-N-[(2r,5s)-5-hydroxytricyclo[3.3.1.1³,7]dec-2-yl]-4-methoxypyrimidine-5-carboxamide;
- 2-(cyclobutylloxy)-N-[(2r,5s)-5-hydroxytricyclo[3.3.1.1³,7]dec-2-yl]-4-methoxypyrimidine-5-carboxamide;
- 10 2-[(2S,6R)-2,6-dimethylmorpholin-4-yl]-4-ethoxy-N-[(2r,5s)-5-hydroxyadamantan-2-yl]pyrimidine-5-carboxamide;
- 2-(cyclopropylamino)-4-ethoxy-N-[(2r,5s)-5-hydroxytricyclo[3.3.1.1³,7]dec-2-yl]pyrimidine-5-carboxamide;
- 4-ethoxy-N-[(2r,5s)-5-hydroxytricyclo[3.3.1.1³,7]dec-2-yl]-2-(oxetan-3-ylamino)pyrimidine-5-carboxamide;
- 15 2-(cyclobutylamino)-4-ethoxy-N-[(2r,5s)-5-hydroxytricyclo[3.3.1.1³,7]dec-2-yl]pyrimidine-5-carboxamide;
- 2-(cyclobutylloxy)-4-ethoxy-N-[(2r,5s)-5-hydroxytricyclo[3.3.1.1³,7]dec-2-yl]pyrimidine-5-carboxamide;
- 20 2-[(2R,6S)-2,6-dimethylmorpholin-4-yl]-N-[(2r,5s)-5-hydroxytricyclo[3.3.1.1³,7]dec-2-yl]-4-(1-methylethoxy)pyrimidine-5-carboxamide;
- 2-(cyclopropylamino)-N-[(2r,5s)-5-hydroxytricyclo[3.3.1.1³,7]dec-2-yl]-4-(1-methylethoxy)pyrimidine-5-carboxamide;
- N-[(2r,5s)-5-hydroxytricyclo[3.3.1.1³,7]dec-2-yl]-4-(1-methylethoxy)-2-(oxetan-3-ylamino)pyrimidine-5-carboxamide;
- 25 2-(cyclobutylamino)-N-[(2r,5s)-5-hydroxytricyclo[3.3.1.1³,7]dec-2-yl]-4-(1-methylethoxy)pyrimidine-5-carboxamide;
- 2-(cyclobutylloxy)-N-[(2r,5s)-5-hydroxytricyclo[3.3.1.1³,7]dec-2-yl]-4-(1-methylethoxy)pyrimidine-5-carboxamide;
- 30 N-[(2r,5s)-5-hydroxyadamantan-2-yl] 2-[(2S,6R)-2,6-dimethylmorpholin-4-yl]-4-[(2R)-oxolan-2-yl]pyrimidine-5-carboxamide;

4-cyclopropyl-2-[(2S,6R)-2,6-dimethylmorpholin-4-yl]-N-[(2r,5s)-5-hydroxyadamantan-2-yl]pyrimidine-5-carboxamide; and

2-[(2S,6R)-2,6-dimethylmorpholin-4-yl]-N-[(2r,5s)-5-hydroxyadamantan-2-yl]-4-(methoxymethyl)pyrimidine-5-carboxamide;

5 or a pharmaceutically-acceptable salt thereof.

7. A pharmaceutical composition, which comprises a compound of formula (1), or a pharmaceutically acceptable salt thereof, as claimed in claim 1 in association with a pharmaceutically-acceptable diluent or carrier.

10

8. A compound of formula (1) wherein:

Q is O, S, N(R⁸) or a single bond;

R⁸ is selected from hydrogen, C₁₋₄alkyl, C₃₋₅cycloalkyl and C₃₋₅cycloalkylmethyl (each of which is optionally substituted by 1, 2 or 3 fluoro atoms);

15 **R¹** is selected from C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₇cycloalkyl, heterocyclyl, heteroaryl, aryl, arylC₁₋₃alkyl, heteroarylC₁₋₃alkyl, C₃₋₇cycloalkylC₁₋₃alkyl, heterocyclylC₁₋₃alkyl, C₃₋₇cycloalkylC₂₋₃alkenyl and C₃₋₇cycloalkylC₂₋₃alkynyl, [each of which is optionally substituted, on available carbon atoms, by 1, 2 or 3 substituents

independently selected from C₁₋₃alkyl, hydroxy, halo, oxo, cyano, trifluoromethyl, C₁₋₃alkoxy, C₁₋₃alkylS(O)_n- (wherein n is 0, 1, 2 or 3), R⁵CON(R^{5'})-, (R^{5'})(R^{5''})N-, (R^{5'})(R^{5''})NC(O)-, R^{5'}C(O)O-, R^{5'}OC(O)-, (R^{5'})(R^{5''})NC(O)N(R^{5'''})-, R⁵SO₂N(R^{5''})-, (R^{5'})(R^{5''})NSO₂- and C₁₋₂alkyl optionally substituted by 1, 2 or 3 substituents

20 independently selected from hydroxy, halo, carboxy and C₁₋₃alkoxy (wherein R⁵ is C₁₋₃alkyl optionally substituted by 1, 2 or 3 substituents independently selected from hydroxyl, halo and cyano; and

25 R^{5'}, R^{5''} and R^{5'''} are independently selected from hydrogen and C₁₋₃alkyl optionally substituted by 1, 2 or 3 substituents independently selected from hydroxyl, halo, C₁₋₃alkoxy, carboxy and cyano or R^{5'} and R^{5''} together with the nitrogen atom to which they are attached form a 4-7 membered saturated ring) and optionally substituted, on an available nitrogen, by a substituent independently selected from C₁₋₄alkyl, C₂₋₄alkanoyl and C₁₋₄alkanesulphonyl each of which is optionally substituted by 1, 2 or 3 substituent

30 independently selected from hydroxyl, halo, C₁₋₄alkoxy, carboxy and cyano]; or

R^1 and R^8 together with the nitrogen atom to which they are attached form a saturated mono, bicyclic or bridged ring system optionally containing 1 or 2 additional ring heteroatoms independently selected from nitrogen, oxygen and sulphur and optionally fused to a saturated, partially saturated or unsaturated monocyclic ring wherein the resulting ring system is optionally substituted, on available carbon atoms, by 1, 2, or 3 substituents independently selected from R^9 and optionally substituted, on an available nitrogen, by a substituent independently selected from C_{1-4} alkyl, C_{2-4} alkanoyl and C_{1-4} alkanesulphonyl each of which is optionally substituted by 1, 2 or 3 substituent independently selected from hydroxyl, halo, C_{1-4} alkoxy, carboxy and cyano;

R^2 is selected from C_{3-7} cycloalkyl $(CH_2)_m$ -, and C_{6-12} polycycloalkyl $(CH_2)_m$ - (wherein m is 0, 1 or 2 and the rings optionally contain 1 or 2 ring atoms independently selected from nitrogen, oxygen and sulphur are optionally substituted, on available carbon atoms, by 1, 2 or 3 substituents independently selected from R^6 and optionally substituted, on an available nitrogen, by a substituent independently selected from C_{1-4} alkyl, C_{2-4} alkanoyl and C_{1-4} alkanesulphonyl each of which is optionally substituted by 1, 2 or 3 substituent independently selected from hydroxyl, halo, C_{1-4} alkoxy, carboxy and cyano);

R^3 is selected from hydrogen, C_{1-4} alkyl, C_{3-5} cycloalkyl and C_{3-5} cycloalkylmethyl (each of which is optionally substituted by 1, 2 or 3 fluoro atoms);

R^2 and R^3 together with the nitrogen atom to which they are attached form a saturated mono, bicyclic or bridged ring system optionally containing 1 or 2 additional ring heteroatoms independently selected from nitrogen, oxygen and sulphur and optionally fused to a saturated, partially saturated or unsaturated monocyclic ring wherein the resulting ring system is optionally substituted, on available carbon atoms, by 1, 2, or 3 substituents independently selected from R^7 and optionally substituted, on an available nitrogen, by a substituent independently selected from C_{1-4} alkyl, C_{2-4} alkanoyl and C_{1-4} alkanesulphonyl each of which is optionally substituted by 1, 2 or 3 substituent independently selected from hydroxyl, halo, C_{1-4} alkoxy, carboxy and cyano;

R^4 is selected from hydrogen, R^{10} , $-OR^{10}$, $-SR^{10}$ and $-NR^{11}R^{12}$;

R^{10} is selected from C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-7} cycloalkyl, heterocyclyl, aryl C_{1-3} alkyl, heteroaryl C_{1-3} alkyl, heterocyclyl C_{1-3} alkyl, C_{3-7} cycloalkyl C_{1-3} alkyl, C_{3-7} cycloalkyl C_{2-3} alkenyl and C_{3-7} cycloalkyl C_{2-3} alkynyl, [each of which is optionally substituted, on available carbon atoms, by 1, 2 or 3 substituents independently selected

from C₁₋₃alkyl, hydroxy, halo, oxo, cyano, trifluoromethyl, C₁₋₃alkoxy, C₁₋₃alkylS(O)_p- (wherein p is 0, 1, 2 or 3), R¹³CON(R^{13'})-, (R^{13'})(R^{13''})N-, (R^{13'})(R^{13''})NC(O)-, R^{13'}C(O)O-, R^{13'}OC(O)-, (R^{13'})(R^{13''})NC(O)N(R^{13'''})-, R¹³SO₂N(R^{13''})-, (R^{13'})(R^{13''})NSO₂- and C₁₋₂alkyl optionally substituted by 1, 2 or 3 substituents independently selected from hydroxy, halo, carboxy and C₁₋₃alkoxy (wherein R¹³ is C₁₋₃alkyl optionally substituted by 1, 2 or 3 substituents selected from hydroxyl, halo and cyano; and R^{13'}, R^{13''} and R^{13'''} are independently selected from hydrogen and C₁₋₃alkyl optionally substituted by 1, 2 or 3 substituents independently selected from hydroxyl, halo, C₁₋₃alkoxy, carboxy and cyano or R^{13'} and R^{13''} together with the nitrogen atom to which they are attached form a 4-7 membered saturated ring) and optionally substituted, on an available nitrogen, by a substituent independently selected from C₁₋₄alkyl, C₂₋₄alkanoyl and C₁₋₄alkanesulphonyl each of which is optionally substituted by 1, 2 or 3 substituent independently selected from hydroxyl, halo, C₁₋₄alkoxy, carboxy and cyano]; R¹¹ is selected from hydrogen, C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₇cycloalkyl, heterocyclyl, arylC₁₋₃alkyl, heteroarylC₁₋₃alkyl, heterocyclylC₁₋₃alkyl, C₃₋₇cycloalkylC₁₋₃alkyl, C₃₋₇cycloalkylC₂₋₃alkenyl and C₃₋₇cycloalkylC₂₋₃alkynyl, [each of which is optionally substituted, on available carbon atoms, by 1, 2 or 3 substituents independently selected from C₁₋₃alkyl, hydroxy, halo, oxo, cyano, trifluoromethyl, C₁₋₃alkoxy, C₁₋₃alkylS(O)_q- (wherein q is 0, 1, 2 or 3), R¹⁴CON(R^{14'})-, (R^{14'})(R^{14''})NC(O)-, R^{14'}C(O)O-, R^{14'}OC(O)-, (R^{14'})(R^{14''})NC(O)N(R^{14'''})-, R¹⁴SO₂N(R^{14''})-, (R^{14'})(R^{14''})NSO₂- and C₁₋₂alkyl optionally substituted by 1, 2 or 3 substituents independently selected from hydroxy, halo, carboxy and C₁₋₃alkoxy (wherein R¹⁴ is C₁₋₃alkyl optionally substituted by 1, 2 or 3 substituents independently selected from hydroxyl, halo and cyano; and R^{14'}, R^{14''} and R^{14'''} are independently selected from hydrogen and C₁₋₃alkyl optionally substituted by 1, 2 or 3 substituents independently selected from hydroxyl, halo, C₁₋₃alkoxy, carboxy and cyano or R^{14'} and R^{14''} together with the nitrogen atom to which they are attached form a 4-7 membered saturated ring) and optionally substituted, on an available nitrogen, by a substituent independently selected from C₁₋₄alkyl, C₂₋₄alkanoyl and C₁₋₄alkanesulphonyl each of which is optionally substituted by 1, 2 or 3 substituent independently selected from hydroxyl, halo, C₁₋₄alkoxy, carboxy and cyano]; and R¹² is selected from hydrogen, C₁₋₄alkyl, C₃₋₅cycloalkyl and C₃₋₅cycloalkylmethyl (each of which is optionally substituted by 1, 2 or 3 fluoro atoms); or

R^{11} and R^{12} together with the nitrogen atom to which they are attached form a saturated mono, bicyclic or bridged ring system optionally containing 1 or 2 additional ring heteroatoms independently selected from nitrogen, oxygen and sulphur and optionally fused to a saturated, partially saturated or unsaturated monocyclic ring (optionally containing 1 or 2 additional ring heteroatoms independently selected from nitrogen, oxygen and sulphur) wherein the resulting ring system is optionally substituted, on available carbon atoms, by 1, 2, or 3 substituents independently selected from R^{15} and optionally substituted on an available nitrogen by a substituent independently selected from C_{1-4} alkyl, C_{2-4} alkanoyl and C_{1-4} alkanesulphonyl each of which is optionally substituted by 1, 2 or 3 substituent independently selected from hydroxyl, halo, C_{1-4} alkoxy, carboxy and cyano;

R^6 , R^7 , R^9 and R^{15} are independently selected from hydroxyl, halo, oxo, carboxy, cyano, trifluoromethyl, R^{16} , $R^{16}O-$, $R^{16}CO-$, $R^{16}C(O)O-$, $R^{16}CON(R^{16'})-$, $(R^{16'})(R^{16''})NC(O)-$, $(R^{16'})(R^{16''})N-$, $R^{16}S(O)_a-$ wherein a is 0 to 2, $R^{16'}OC(O)-$, $(R^{16'})(R^{16''})NSO_2-$, $R^{16}SO_2N(R^{16''})-$, $(R^{16'})(R^{16''})NC(O)N(R^{16''''})-$, phenyl and heteroaryl [wherein the phenyl and heteroaryl groups are optionally fused to a phenyl, heteroaryl or a saturated or partially-saturated 5- or 6-membered ring optionally containing 1, 2 or 3 heteroatoms independently selected from nitrogen, oxygen and sulphur and the resulting ring system is optionally substituted, on available carbon atoms, by 1, 2 or 3 substituents independently selected from C_{1-4} alkyl, hydroxyl, cyano, trifluoromethyl, trifluoromethoxy, halo, C_{1-4} alkoxy, C_{1-4} alkoxy C_{1-4} alkyl, amino, $N-C_{1-4}$ alkylamino, di- $N,N-(C_{1-4}$ alkyl)amino, $N-C_{1-4}$ alkylcarbamoyl, di- $N,N-(C_{1-4}$ alkyl)carbamoyl, C_{1-4} alkylS(O) $_r$ - and C_{1-4} alkylS(O) $_rC_{1-4}$ alkyl (wherein r is independently selected 0, 1 and 2) and optionally substituted, on an available nitrogen, by a substituent independently selected from C_{1-4} alkyl, C_{2-4} alkanoyl and C_{1-4} alkanesulphonyl each of which is optionally substituted by 1, 2 or 3 substituent independently selected from hydroxyl, halo, C_{1-4} alkoxy, carboxy and cyano];

R^{16} is independently selected from, C_{1-3} alkyl optionally substituted by 1, 2 or 3 substituents independently selected from hydroxyl, halo, C_{1-4} alkoxy, carboxy and cyano;

$R^{16'}$, $R^{16''}$ and $R^{16'''}$ are independently selected from hydrogen and C_{1-3} alkyl optionally substituted by 1, 2, or 3 substituents independently selected from hydroxyl, halo, C_{1-4} alkoxy, carboxy and cyano);

or a pharmaceutically-acceptable salt thereof;
as a medicament for producing a 11 β HSD1-inhibitory effect.

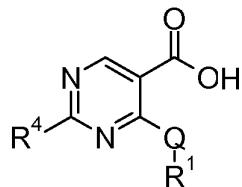
9. A compound of formula (1), or a pharmaceutically acceptable salt thereof, as
5 claimed in claim 1, for use in a method of prophylactic or therapeutic treatment of a
warm-blooded animal, such as man.

10. A compound of formula (1), or a pharmaceutically acceptable salt thereof, as
claimed in claim 1 for use as a medicament.

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11. A process for preparing a compound of formula (1) or a pharmaceutically
acceptable salt thereof which process (wherein variable groups are, unless otherwise
specified, as defined in claim 1) comprises:

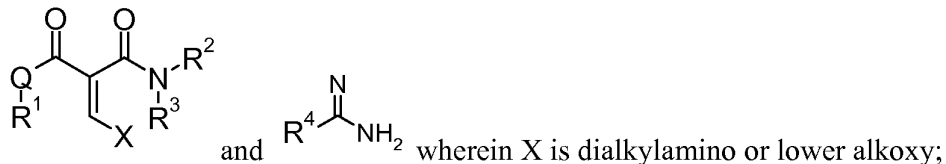
i) reacting a compound of formula:



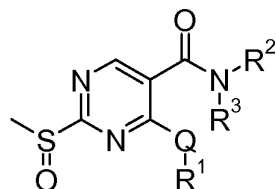
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or a reactive derivative thereof with an amine of formula HNR^2R^3 ;

ii) reacting together compounds of the formulae:



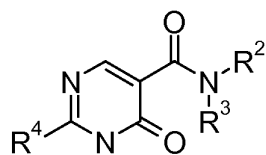
iii) when R^4 is $-\text{SR}^{10}$, reacting a compound of the formula:



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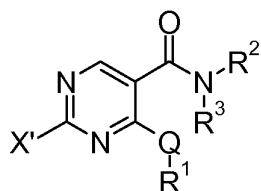
with the appropriate nucleophile to convert $-\text{SOMe}$ to $-\text{R}^4$;

iv) reacting an activated derivative of a compound of the formula:



with a nucleophile of the formula Q-R¹;

v) reacting a compound of the formula:



wherein X' is halo with a nucleophile R⁴;

and thereafter if necessary or desirable:

- 5 i) converting a compound of the formula (1) into another compound of the formula (1);
- ii) removing any protecting groups;
- iii) resolving enantiomers;
- iv) forming a pharmaceutically-acceptable salt thereof.