

**DESCRIPTION****Title of Invention**

CARBOXYLIC ACID COMPOUNDS

5

**Technical Field**

[0001]

The present disclosure relates to novel carboxylic acid compounds and, more particularly, to certain carboxylic acid compounds that may act as TLR7 agonists and at the same time may exhibit advantageous selectivity over TLR8 and hERG. This disclosure also relates to methods for the preparation of such compounds and intermediates useful in the preparation thereof, to pharmaceutical compositions containing such compounds, to the use of such compounds in the preparation of medicaments, and to the use of such compounds in the treatment of conditions mediated by TLR7, such as allergic diseases, autoimmune diseases, viral diseases and, in particular, cancer.

20 **Background Art**

[0002]

Toll-like receptors (TLRs) are expressed on a variety of immune cells, including macrophages and dendritic cells (DCs). TLRs recognise molecular motifs on pathogens called pathogen-associated molecular patterns (PAMPs). To date, 13

TLRs have been identified in man, these include TLRs 1, 2, 4, 5 and 6, which are confined to the cell surface, and TLRs 3, 7, 8 and 9, which are expressed in endosomes. Different TLRs recognise different pathogen-derived ligands, for example:

5 TLR2 (bacterial lipoproteins), TLR3 (double-stranded RNA/poly (I:C)), TLR4 (lipopolysaccharides), TLR5 (flagellin), TLR7 (single-stranded RNA), and TLR9 (CpG-containing DNA). Ligation of TLRs on antigen-presenting cells, such as DCs, leads to production of proinflammatory cytokines, DC maturation, and

10 priming of the adaptive immune system. TLR7 and TLR9 are expressed by plasmacytoid dendritic cells (pDCs) and ligand recognition leads to the secretion of interferon- $\alpha$  (INF- $\alpha$ ). Preclinical studies investigating the effects of activation of TLRs, using bacterial or viral components, dosed as monotherapy

15 and/or combined with anti-tumor agents, have shown tumour growth inhibition in a variety of murine tumour models.

[0003]

Several small molecule TLR7 agonists have been described, including the imidazoquinoline, imiquimod, which has been used

20 to treat a number of dermatological conditions, e.g., genital warts, molluscum contagiosum, and melanoma. In the case of melanoma, topically applied imiquimod (ALDARA<sup>TM</sup>, Graceway Pharmaceuticals, Bristol, TN) demonstrated therapeutic responses in cutaneous metastatic melanoma and lentigo maligna

25 and has been approved for the treatment of superficial basal

cell carcinoma (BCC). Preclinical and clinical studies indicate that imiquimod is likely to function through the induction of type 1 IFN and IFN-inducible genes, which in turn can have direct effects on tumour cell growth and/or harness components of the adaptive immune system. 852A is another imidazoquinoline, which, unlike imiquimod, is suitable for systemic administration. Currently, 852A is in phase II clinical trials in a number of cancer indications, including melanoma.

## 10 **Summary of Invention**

### **Technical Problem**

[0004]

Nevertheless, there remains a need for developing further TLR7 agonists which are expected to be more effective in the treatment of disease, for example cancer, by reason of their superior potency and/or advantageous physical properties (for example, higher solubility, and/or lower plasma protein binding) and/or favourable toxicity profiles and/or favourable metabolic profiles in comparison with other known TLR7 agonists, for example 852A.

### **Solution to Problem**

[0005]

As demonstrated herein, the carboxylic acid compounds of the present disclosure may be capable of activating TLR7 in vitro.

As a consequence of this activity, the compounds of the present disclosure may have value in the prevention and/or treatment of human disease, such as, for example cancer, either as a monotherapy or in combination with other chemotherapeutic agents or radiotherapy regimens.

#### **Advantageous Effects of Invention**

[0006]

In addition, compounds of the present disclosure may have surprisingly advantageous selectivity for TLR7 over TLR8. TLR7 and TLR8 differ in their cellular expression and as a result stimulation with selective agonists induces different cytokine profiles. TLR8 stimulation (either as a TLR8 selective agonist or a TLR7/8 dual agonist) results in enhanced levels of pro-inflammatory cytokines including TNF $\alpha$ , IL-1 $\beta$  and IL-6 (Gorden et al (2005) J. Immunol. 174, 1259-1268). Conversely, TLR8 stimulation may result in lower levels of IFN $\alpha$ . Therefore, a TLR7 selective agonist may favor induction of IFN $\alpha$ , which is important in suppression of Th2 cytokines (Huber et al (2010) J. Immunol. 185; 813-817) that are elevated in allergic disease. In addition, by making compounds selective for TLR7 compared to TLR8 the induction of proinflammatory cytokines may be reduced thus avoiding inflammatory responses in man.

[0007]

Furthermore, compounds of the present disclosure may have a

surprisingly advantageous hERG profile. Compounds that have significant activity against the hERG ion channel are disfavored because such activity is implicated in the development of Torsades de Pointes and cardiac death.

5

#### **Brief Description of Drawings**

[0008]

[Fig. 1]

Figure 1 is a differential scanning calorimetry (DSC) trace for  
10 Compound of Example 18 (Form B). The x-axis shows temperature  
(°C) and the y-axis heat flow (watts/g).

[Fig. 2]

Figure 2 is a differential scanning calorimetry (DSC) trace for  
Compound of Example 19 (Form A). The x-axis shows temperature  
15 (°C) and the y-axis heat flow (watts/g).

[Fig. 3]

Figure 3 is a differential scanning calorimetry (DSC) trace for  
Compound of Example 20 (Form E). The x-axis shows temperature  
(°C) and the y-axis heat flow (watts/g).

20 [Fig. 4]

Figure 4 is a differential scanning calorimetry (DSC) trace for  
Compound of Example 21 (Form A). The x-axis shows temperature  
(°C) and the y-axis heat flow (watts/g).

[Fig. 5]

25 Figure 5 is an X-ray powder diffraction pattern of Compound of

Example 18 (Form B)

x-axis shows the 2-theta value and the y-axis the intensity.

[Fig. 6]

Figure 6 is an X-ray powder diffraction pattern of Compound of

5 Example 19 (Form A) x-axis shows the 2-theta value and the y-axis the intensity.

[Fig. 7]

Figure 7 is an X-ray powder diffraction pattern of Compound of

Example 20 (Form E) x-axis shows the 2-theta value and the y-axis

10 the intensity.

[Fig. 8]

Figure 8 is an X-ray powder diffraction pattern of Compound of

Example 21 (Form A) x-axis shows the 2-theta value and the y-axis the intensity.

15 [Fig. 9]

Figure 9 shows the result of tumour growth inhibition activity to murine syngeneic renal carcinoma: Renca for the compound of Example 3 (mean and SD). X-axis: days post inoculation, Y-axis: Tumour volume, open diamond: 0.5% methylcellulose treated group, closed circle: compound of Example 3 treated group, \*:  $p < 0.05$  vs. vehicle.

20

[Fig. 10]

Figure 10 shows the result of tumour growth inhibition activity to murine syngeneic renal carcinoma: Renca for the compound of

25 Example 4 (mean and SD). X-axis: days post inoculation, Y-axis:

Tumour volume, open diamond: 0.5% methylcellulose treated group, closed circle: compound of Example 4 treated group, \*:  $p < 0.05$  vs. vehicle.

[Fig. 11]

5 Figure 11 shows the result of metastasis studies in LM8 tumour growth inhibition activity (mean and SD). X-axis: NT means no treatment and RT means radiation (2Gy x 5 consecutive days), Y-axis: lung weight at day36, \*:  $p < 0.05$  vs. vehicle, #:  $p < 0.05$  vs. RT

10 [Fig. 12]

Figure 12 shows the result of survival studies in CT26. NT means no treatment and RT means radiation (2Gy x 5 consecutive days). Closed circle: NT, closed square: RT, closed triangle: combination of RT and compound of Example 3.

15 [Fig. 13]

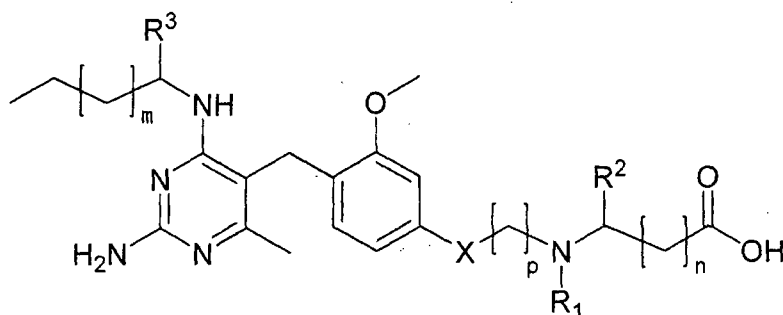
Figure 13 shows the result of survival studies in CT26. NT means no treatment and RT means radiation (2Gy x 5 consecutive days). Closed circle: NT, closed square: RT, closed triangle: combination of RT and compound of Example 4.

20

#### **Description of Embodiments**

[0009]

According to a first aspect of the present disclosure, there is therefore provided at least one such entity chosen from  
25 compounds of Formula (I):



(I)

wherein:

n is 0, 1, or 2;

5 m is 1 or 2;

p is 1, 2 or 3, provided that when X is oxygen, p is 2 or 3,  
and when X is a single bond, p is 1;

X is oxygen or a single bond;

10 R<sup>1</sup> is chosen from hydrogen, C<sub>1-4</sub> alkyl groups, C<sub>1-3</sub> alkyl-(CH<sub>2</sub>)-  
groups wherein the C<sub>1-3</sub> alkyl moiety is substituted by 1, 2, or  
3 fluorine atoms, C<sub>1-4</sub> alkyl groups substituted by cyano, C<sub>1-3</sub>  
alkoxy-C<sub>2-4</sub> alkyl groups, C<sub>3-6</sub> cycloalkyl groups, C<sub>1-4</sub>  
alkylcarbonyl groups, and formyl;

R<sup>2</sup> is chosen from hydrogen and C<sub>1-4</sub> alkyl groups;

15 or R<sup>1</sup> and R<sup>2</sup> together with the nitrogen and carbon atoms to which  
they are attached form a ring chosen from saturated and  
unsaturated 4- to 6-membered heterocyclyl rings that optionally  
contain a further heteroatom chosen from N, O, and S, wherein  
said N heteroatom may be optionally substituted by C<sub>1-3</sub> alkyl;

20 R<sup>3</sup> is chosen from hydrogen, hydroxymethyl, and 2-hydroxyethyl;  
and pharmaceutically acceptable salts thereof.

[0010]

It is to be understood that certain of the compounds of Formula (I) defined above and/or their pharmaceutically acceptable salts may exist in optically active or racemic forms by virtue of one or more asymmetric carbon atoms, the present disclosure includes in its scope any such optically active or racemic form. The synthesis of optically active forms may be carried out by standard techniques of organic chemistry well known in the art, for example, by synthesis from optically active starting materials or by resolution of a racemic form. The above-mentioned activity may be evaluated using the standard laboratory techniques referred to hereinafter.

[0011]

It is to be understood that certain compounds of Formula (I) above and/or their pharmaceutically acceptable salts may exist in unsolvated forms as well as solvated forms, such as, for example, hydrated forms. It is to be understood that the present disclosure encompasses all such solvated forms.

[0012]

It is also to be understood that certain compounds of the Formula (I) and/or their pharmaceutically acceptable salts may exist in crystalline form and exhibit polymorphism. The present disclosure encompasses all such forms.

[0013]

The term "C<sub>1-4</sub> alkyl" is intended to mean a saturated carbon chain

of 1 to 4 carbon atoms in length which may be straight chained or branched. However, references to individual alkyl groups such as, for example, "propyl" are specific for the straight chain version only and references to individual branched chain alkyl groups such as, for example, tert butyl are specific for the branched chain version only. Non-limiting examples of "C<sub>1-4</sub> alkyl" include methyl, ethyl, propyl, isopropyl, butyl, n-butyl, isobutyl, and tert-butyl. The terms "C<sub>2-4</sub> alkyl" and "C<sub>1-3</sub> alkyl" are to be construed accordingly.

10 [0014]

The term "C<sub>1-3</sub> alkoxy" is intended to mean an alkoxy group with saturated carbon chain of 1 to 3 carbon atoms in length which may be straight chained or branched. However references to individual alkoxy groups such as "propoxy" are specific for the straight chain version only and references to individual branched chain alkoxy groups such as isopropoxy are specific for the branched chain version only. Non-limiting examples of "C<sub>1-3</sub> alkoxy" include methoxy, ethoxy, propoxy, and isopropoxy.

[0015]

20 The term "C<sub>1-3</sub> alkoxy-C<sub>2-4</sub> alkyl" is intended to mean a C<sub>2-4</sub> alkyl substituted by C<sub>1-3</sub> alkoxy.

[0016]

The term "C<sub>1-3</sub> alkyl-(CH<sub>2</sub>)- wherein the C<sub>1-3</sub> alkyl moiety is substituted by 1, 2, or 3 fluorine atoms" is intended to mean a methylene group bound to a C<sub>1-3</sub> alkyl moiety in which 1, 2,

or 3 hydrogen atoms are replaced by fluorine atoms. Non-limiting examples of "C<sub>1-3</sub> alkyl-(CH<sub>2</sub>)- wherein the C<sub>1-3</sub> alkyl moiety is substituted by 1, 2, or 3 fluorine atoms" include 2-monofluoroethyl, 2,2-difluoroethyl, and  
5 2,2,2-trifluoroethyl.

[0017]

The term "C<sub>1-4</sub> alkyl substituted by cyano" is intended to mean a C<sub>1-4</sub> alkyl substituted by cyano.

[0018]

10 The term "C<sub>3-6</sub> cycloalkyl" is intended to mean a 3- to 6-membered saturated cycloalkyl. Non-limiting examples of "C<sub>3-6</sub> cycloalkyl" include cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl.

[0019]

15 The term "C<sub>1-4</sub> alkylcarbonyl" is intended to mean a carbonyl group substituted by C<sub>1-4</sub> alkyl. Non-limiting examples of "C<sub>1-4</sub> alkylcarbonyl" include acetyl, ethanoyl, propanoyl, butanoyl, pentanoyl, 2-methylpropanoyl, and 3-methylbutanoyl.

[0020]

20 The term "saturated 4- to 6-membered heterocyclyl ring" which is formed by R<sup>1</sup> and R<sup>2</sup> together with the nitrogen and carbon atoms to which they are attached is intended to mean a saturated 4-, 5-, or 6-membered heterocyclyl ring. That ring may optionally containing a further heteroatom chosen from N, O,  
25 and S, wherein said N atom may be optionally substituted by C<sub>1-3</sub>

alkyl. Non-limiting examples of such saturated 4- to 6-membered heterocyclyl rings include pyrrolidinyl, piperidinyl, morpholino, and piperazinyl.

[0021]

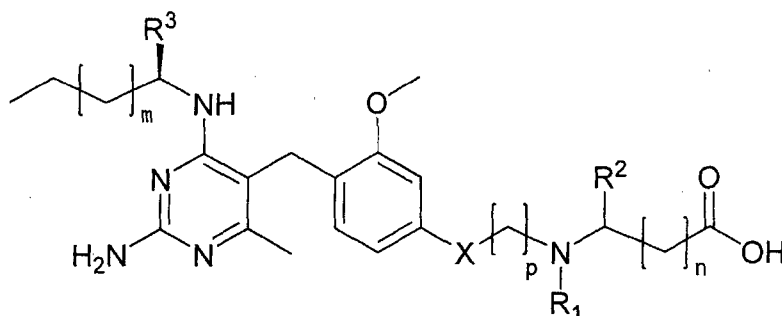
5 In the case where a "saturated or unsaturated 4- to 6-membered heterocyclyl ring" is substituted by C<sub>1-3</sub> alkyl on N atom, any hydrogen atom on an available N atom can be replaced by C<sub>1-3</sub> alkyl. A non-limiting example of an "available" nitrogen atom which may be optionally substituted by C<sub>1-3</sub> alkyl is the nitrogen at  
10 the 4 position of a piperazin-1-yl group.

[0022]

The term "unsaturated 4- to 6-membered heterocyclyl ring" which is formed by R<sup>1</sup> and R<sup>2</sup> together with the nitrogen and carbon atoms to which they are attached is intended to mean an  
15 unsaturated 4-, 5-, or 6-membered heterocyclyl ring. That ring may optionally containing a further heteroatom chosen from N, O, and S, wherein said N atom may be optionally substituted by C<sub>1-3</sub> alkyl. Non-limiting examples of the "unsaturated 4- to 6-membered heterocyclyl ring" include unsaturated 5- and  
20 6-membered heterocyclyl rings. Additional non-limiting examples of unsaturated 4- to 6-membered heterocyclyl rings include imidazolyl, pyrazolyl, and thiazolyl.

[0023]

In an embodiment, the at least one entity is chosen from  
25 compounds of Formula (IA):



(IA)

and pharmaceutically acceptable salts thereof, wherein the values of X, R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, m, n, and p may take any of the values  
5 defined in Formula (I), above.

[0024]

Non-limiting examples of the values that X, R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, m, n, and p in Formula (I) and/or Formula (IA) may take are indicated below. Such values may be used together with any of the  
10 definitions, claims, aspects, and/or embodiments defined herein to provide further embodiments or claims of the present disclosure, and unless the context does not permit, any number of said variable group definitions may be used in any combination with each other to form further embodiments,  
15 aspects, and/or claims.

- (i) m is 1;
- (ii) m is 2;
- (iii) n is 0 or 1;
- (iv) n is 0;
- 20 (v) n is 1;

- (vi) n is 2;
- (vii) X is a single bond and p is 1;
- (viii) X is an oxygen atom and p is 2;
- (ix) X is an oxygen atom and p is 3;
- 5 (x)  $R^1$  is chosen from  $C_{1-4}$  alkyl groups,  $C_{1-3}$  alkyl-(CH<sub>2</sub>)-groups wherein the  $C_{1-3}$  alkyl moiety is substituted by 1, 2, or 3 fluorine atoms,  $C_{1-4}$  alkyl groups substituted by cyano,  $C_{1-3}$  alkoxy- $C_{2-4}$  alkyl groups,  $C_{3-6}$  cycloalkyl groups,  $C_{1-4}$  alkylcarbonyl groups, and formyl;
- 10 (xi)  $R^1$  is chosen from ethyl, 2-monofluoroethyl, 2,2-difluoroethyl, 2,2,2-trifluoroethyl, and acetyl;
- (xii)  $R^1$  is chosen from ethyl, 2,2-difluoroethyl, 2,2,2-trifluoroethyl, and acetyl;
- (xiii)  $R^1$  is chosen from  $C_{1-4}$  alkyl groups;
- 15 (xiv)  $R^1$  is chosen from  $C_{1-3}$  alkyl groups;
- (xv)  $R^1$  is chosen from methyl, ethyl, and propyl;
- (xvi)  $R^1$  is ethyl optionally substituted by 1, 2, or 3 fluorine atom(s);
- (xvii)  $R^1$  is ethyl;
- 20 (xviii)  $R^1$  is 2,2-difluoroethyl or 2,2,2-trifluoroethyl;
- (xix)  $R^1$  is 2,2-difluoroethyl;
- (xx)  $R^1$  is 2,2,2-trifluoroethyl;
- (xxi)  $R^1$  is chosen from  $C_{1-4}$  alkylcarbonyl groups;
- (xxii)  $R^1$  is acetyl;
- 25 (xxiii)  $R^2$  is chosen from hydrogen and  $C_{1-4}$  alkyl groups;

(xxiv)  $R^2$  is chosen from hydrogen and  $C_{1-2}$  alkyl groups;

(xxv)  $R^2$  is hydrogen or methyl;

(xxvi)  $R^2$  is hydrogen;

(xxvii)  $R^1$  and  $R^2$  together with the nitrogen atom and carbon  
5 atoms to which they are attached form a saturated or unsaturated  
4- to 6-membered heterocyclyl ring optionally containing a  
further heteroatom chosen from N, O, and S, wherein said N  
heteroatom may be optionally substituted by  $C_{1-3}$  alkyl;

(xxviii)  $R^1$  and  $R^2$  together with the nitrogen and carbon atoms  
10 to which they are attached form a saturated 4- to 6-membered  
heterocyclyl ring optionally containing a further heteroatom  
chosen from N, O, and S, wherein said N heteroatom may be  
optionally substituted by  $C_{1-3}$  alkyl;

(xxix)  $R^1$  and  $R^2$  together with the nitrogen and carbon atoms  
15 to which they are attached form a pyrrolidinyl, piperidinyl,  
morpholino, or piperazinyl ring wherein the nitrogen atom at  
the 4 position is optionally substituted by  $C_{1-3}$  alkyl;

(xxx)  $R^1$  and  $R^2$  together with the nitrogen and carbon atoms  
to which they are attached form a pyrrolidinyl, piperidinyl,  
20 or morpholino ring wherein the nitrogen atom at the 4 position  
is optionally substituted by  $C_{1-3}$  alkyl;

(xxxi)  $R^1$  and  $R^2$  together with the nitrogen and carbon atoms  
to which they are attached form a pyrrolidinyl ring;

(xxxii)  $R^1$  and  $R^2$  together with the nitrogen and carbon atoms  
25 to which they are attached form an unsaturated 5- to 6-membered

heterocyclyl ring optionally containing a further heteroatom chosen from N, O, and S, wherein said N heteroatom may be optionally substituted by C<sub>1-3</sub> alkyl;

(xxxiii) R<sup>1</sup> and R<sup>2</sup> together with the nitrogen and carbon atoms

5 to which they are attached form an imidazolyl ring;

(xxxiv) R<sup>3</sup> is hydrogen, hydroxymethyl, or 2-hydroxyethyl;

(xxxv) R<sup>3</sup> is hydrogen or 2-hydroxyethyl; and

(xxxvi) R<sup>3</sup> is 2-hydroxyethyl.

[0025]

10 In one embodiment of the present disclosure, there is provided a compound of Formula (I) or Formula (IA), wherein X is a single bond, p is 1, and n is 0 or 1.

[0026]

In one embodiment of the present disclosure, there is provided  
15 a compound of Formula (I) or Formula (IA), wherein X is a single bond, p is 1, n is 0 or 1, and R<sup>2</sup> is hydrogen.

[0027]

In one embodiment of the present disclosure, there is provided  
a compound of Formula (I) or Formula (IA), wherein X is a single  
20 bond, p is 1, n is 0 or 1, and R<sup>1</sup> and R<sup>2</sup> together with the nitrogen and carbon atoms to which they are attached form a saturated or unsaturated 4- to 6-membered heterocyclyl ring optionally containing a further heteroatom chosen from N, O, and S, wherein said N heteroatom may be optionally substituted by C<sub>1-3</sub> alkyl.

25 [0028]

In one embodiment of the present disclosure, there is provided a compound of Formula (I) or Formula (IA), wherein X is a single bond, p is 1, and n is 0.

[0029]

- 5 In one embodiment of the present disclosure, there is provided a compound of Formula (I) or Formula (IA), wherein X is a single bond, p is 1, n is 0, and R<sup>2</sup> is hydrogen.

[0030]

- 10 In one embodiment of the present disclosure, there is provided a compound of Formula (I) or Formula (IA), wherein X is oxygen, p is 3, and n is 0.

[0031]

- 15 In one embodiment of the present disclosure, there is provided a compound of Formula (I) or Formula (IA), wherein X is oxygen, p is 3, n is 0, and R<sup>1</sup> and R<sup>2</sup> together with the nitrogen and carbon atoms to which they are attached form a saturated or unsaturated 4 to 6-membered heterocyclyl ring optionally containing a further heteroatom chosen from N, O, and S, wherein said N heteroatom may be optionally substituted by C<sub>1-3</sub> alkyl.

- 20 [0032]

In one embodiment of the present disclosure, there is provided a compound of Formula (I) or Formula (IA), wherein X is oxygen, p is 3, n is 0, and R<sup>1</sup> and R<sup>2</sup> combine together with adjacent nitrogen atom and carbon atom form pyrrolidinyl or imidazolyl.

- 25 [0033]

In one embodiment of the present disclosure, there is provided a compound of Formula (I) or Formula (IA), wherein  $m$  is 1 and  $R^3$  is 2-hydroxyethyl.

[0034]

5 In one embodiment of the present disclosure there is provided at least one entity chosen from compounds of Formula (I) and/or compounds of Formula (IA), wherein:

$n$  is 0 or 1;

$m$  is 1;

10  $p$  is 1 or 3, provided that when  $X$  is oxygen,  $p$  is 3 and when  $X$  is a single bond,  $p$  is 1;

$X$  is oxygen or a single bond;

$R^1$  is chosen from  $C_{1-4}$  alkyl groups,  $C_{1-3}$  alkyl- $(CH_2)$ - groups wherein the  $C_{1-3}$  alkyl moiety is substituted by 1, 2, or 3 fluorine  
15 atoms,  $C_{1-4}$  alkyl groups substituted by cyano, and  $C_{1-4}$  alkylcarbonyl groups;

$R^2$  is hydrogen;

or  $R^1$  and  $R^2$  together with the nitrogen and carbon atoms to which they are attached form a pyrrolidinyl, imidazolyl, or  
20 morpholino ring;

$R^3$  is hydrogen or 2-hydroxyethyl;

and pharmaceutically acceptable salts thereof.

[0035]

In one embodiment of the present disclosure there is provided  
25 at least one entity chosen from compounds of Formula (I) and/or

compounds of Formula (IA), wherein:

n is 0;

m is 1;

p is 1;

5 X is a single bond;

R<sup>1</sup> is chosen from C<sub>1-4</sub> alkyl groups, C<sub>1-3</sub> alkyl-(CH<sub>2</sub>)- groups wherein the C<sub>1-3</sub> alkyl moiety is substituted by 1, 2, or 3 fluorine atoms, C<sub>1-4</sub> alkyl groups substituted by cyano, and C<sub>1-4</sub> alkylcarbonyl groups;

10 R<sup>2</sup> is hydrogen;

or R<sup>1</sup> and R<sup>2</sup> together with the nitrogen and carbon atoms to which they are attached form a pyrrolidinyl, imidazolyl, or morpholino ring;

R<sup>3</sup> is hydrogen or 2-hydroxyethyl;

15 and pharmaceutically acceptable salts thereof.

[0036]

In one embodiment of the present disclosure there is provided at least one entity chosen from compounds of Formula (I) and/or compounds of Formula (IA), wherein:

20 n is 0;

m is 1;

p is 1;

X is a single bond;

R<sup>1</sup> is C<sub>1-4</sub> alkyl groups, C<sub>1-3</sub> alkyl-(CH<sub>2</sub>)- groups wherein  
25 the C<sub>1-3</sub> alkyl moiety is substituted by 1, 2, or 3 fluorine atoms;

R<sup>2</sup> is hydrogen; and

R<sup>3</sup> is hydrogen or 2-hydroxyethyl;

and pharmaceutically acceptable salts thereof.

[0037]

5 In one embodiment of the present disclosure, there is provided at least one entity chosen from:

2-((4-((2-amino-4-(1-hydroxyhexan-3-ylamino)-6-methylpyrimidin-5-yl)methyl)-3-methoxybenzyl)(ethyl)amino)acetic acid;

2-((4-((2-amino-4-(butylamino)-6-methylpyrimidin-5-yl)methyl)-3-methoxybenzyl)(ethyl) amino)acetic acid;

2-((4-((2-amino-4-(1-hydroxyhexan-3-ylamino)-6-methylpyrimidin-5-yl)methyl)-3-methoxybenzyl)(2,2-difluoroethyl)amino)acetic acid;

2-((4-((2-amino-4-(1-hydroxyhexan-3-ylamino)-6-methylpyrimidin-5-yl)methyl)-3-methoxybenzyl)(2,2,2-trifluoroethyl)amino)acetic acid;

3-((4-((2-amino-4-(1-hydroxyhexan-3-ylamino)-6-methylpyrimidin-5-yl)methyl)-3-methoxybenzyl)(ethyl)amino)propanoic acid;

20 3-((4-((2-amino-4-(1-hydroxyhexan-3-ylamino)-6-methylpyrimidin-5-yl)methyl)-3-methoxybenzyl)(2,2-difluoroethyl)amino)propanoic acid;

2-((N-(4-((2-amino-4-(1-hydroxyhexan-3-ylamino)-6-methylpyrimidin-5-yl)methyl)-3-methoxybenzyl)acetamido)acetic acid;

25 1-(3-(4-((2-amino-4-(1-hydroxyhexan-3-ylamino)-6-methylpyri

midin-5-yl)methyl)-3-methoxyphenoxy)propyl)pyrrolidine-2-carboxylic acid;

3-((3-(4-((2-amino-4-(1-hydroxyhexan-3-ylamino)-6-methylpyrimidin-5-yl)methyl)-3-methoxyphenoxy)propyl)(ethylamino)propanoic acid;

5

2-((3-(4-((2-amino-4-(1-hydroxyhexan-3-ylamino)-6-methylpyrimidin-5-yl)methyl)-3-methoxyphenoxy)propyl)(ethylamino)acetic acid;

10

2-((3-(4-((2-amino-4-(1-hydroxyhexan-3-ylamino)-6-methylpyrimidin-5-yl)methyl)-3-methoxyphenoxy)propyl)(2,2-difluoroethylamino)acetic acid;

1-(4-((2-amino-4-(1-hydroxyhexan-3-ylamino)-6-methylpyrimidin-5-yl)methyl)-3-methoxybenzyl)pyrrolidine-2-carboxylic acid;

15

1-(4-((2-amino-4-(1-hydroxyhexan-3-ylamino)-6-methylpyrimidin-5-yl)methyl)-3-methoxybenzyl)-1H-imidazole-5-carboxylic acid;

and pharmaceutically acceptable salts thereof.

[0038]

20

In one embodiment of the present disclosure, there is provided at least one entity chosen from

(S)-2-((4-((2-amino-4-(1-hydroxyhexan-3-ylamino)-6-methylpyrimidin-5-yl)methyl)-3-methoxybenzyl)(ethylamino)acetic acid and pharmaceutically acceptable salts thereof.

25

[0039]

In one embodiment of the present disclosure, there is provided (S)-2-((4-((2-amino-4-(1-hydroxyhexan-3-ylamino)-6-methylpyrimidin-5-yl)methyl)-3-methoxybenzyl)(ethyl)amino)acetic acid.

5 [0040]

In one embodiment of the present disclosure, there is provided at least one entity chosen from pharmaceutically acceptable salts of

(S)-2-((4-((2-amino-4-(1-hydroxyhexan-3-ylamino)-6-methylpyrimidin-5-yl)methyl)-3-methoxybenzyl)(ethyl)amino)acetic acid.

[0041]

In one embodiment of the present disclosure, there is provided at least one entity chosen from

15 (S)-2-((4-((2-amino-4-(1-hydroxyhexan-3-ylamino)-6-methylpyrimidin-5-yl)methyl)-3-methoxybenzyl)(2,2-difluoroethyl)amino)acetic acid and pharmaceutically acceptable salts thereof.

[0042]

In one embodiment of the present disclosure, there is provided

20 (S)-2-((4-((2-amino-4-(1-hydroxyhexan-3-ylamino)-6-methylpyrimidin-5-yl)methyl)-3-methoxybenzyl)(2,2-difluoroethyl)amino)acetic acid.

[0043]

In one embodiment of the present disclosure, there is provided

25 at least one entity chosen from pharmaceutically acceptable

salts of  
(S)-2-((4-((2-amino-4-(1-hydroxyhexan-3-ylamino)-6-methylpyrimidin-5-yl)methyl)-3-methoxybenzyl)(2,2-difluoroethyl)amino)acetic acid.

5 [0044]

In one embodiment of the present disclosure, there is provided at least one entity chosen from

(S)-2-((4-((2-amino-4-(1-hydroxyhexan-3-ylamino)-6-methylpyrimidin-5-yl)methyl)-3-methoxybenzyl)(2,2,2-trifluoroethyl)amino)acetic acid and pharmaceutically acceptable salts thereof.

[0045]

In one embodiment of the present disclosure, there is provided

(S)-2-((4-((2-amino-4-(1-hydroxyhexan-3-ylamino)-6-methylpyrimidin-5-yl)methyl)-3-methoxybenzyl)(2,2,2-trifluoroethyl)amino)acetic acid.

[0046]

In one embodiment of the present disclosure, there is provided at least one entity chosen from pharmaceutically acceptable

20 salts of  
(S)-2-((4-((2-amino-4-(1-hydroxyhexan-3-ylamino)-6-methylpyrimidin-5-yl)methyl)-3-methoxybenzyl)(2,2,2-trifluoroethyl)amino)acetic acid.

[0047]

25 A further aspect of the invention is any of the embodiments

defined herein with the proviso that one or more specific Examples, such as Example 1, Example 2, Example 3, Example 4, Example 5, Example 6 etc. are individually disclaimed.

[0048]

5 As previously mentioned, some compounds of formula (I) may exhibit polymorphism. It is generally known that crystalline materials may be analysed using conventional techniques such as X-Ray Powder Diffraction (hereinafter XRPD) analysis, Differential Scanning Calorimetry (hereinafter DSC), Thermal  
10 Gravimetric Analysis (hereinafter TGA), Diffuse Reflectance Infrared Fourier Transform (DRIFT) spectroscopy, Near Infrared (NIR) spectroscopy, solution and/or solid state nuclear magnetic resonance spectroscopy. The water content of such crystalline materials may be determined by Karl Fischer  
15 analysis.

[0049]

As an example, the compound of Example 3 exhibits polymorphism and three crystalline forms are identified herein.

[0050]

20 Accordingly, a further aspect of the invention is Form B of (S)-2-((4-((2-amino-4-(1-hydroxyhexan-3-ylamino)-6-methylpyrimidin-5-yl)methyl)-3-methoxybenzyl)(2,2-difluoroethyl)amino)acetic acid.

[0051]

25 According to a further aspect of the present invention, there

is provided a crystalline form, Form B of  
(S)-2-((4-((2-amino-4-(1-hydroxyhexan-3-ylamino)-6-methylpy  
rimidin-5-yl)methyl)-3-methoxybenzyl)(2,2-difluoroethyl)ami  
no)acetic acid, which has an X-ray powder diffraction pattern  
5 with at least one specific peak at about 2-theta = 6.5°.

[0052]

According to a further aspect of the present invention, there  
is provided a crystalline form, Form B of  
(S)-2-((4-((2-amino-4-(1-hydroxyhexan-3-ylamino)-6-methylpy  
10 rimidin-5-yl)methyl)-3-methoxybenzyl)(2,2-difluoroethyl)ami  
no)acetic acid, which has an X-ray powder diffraction pattern  
with at least one specific peak at about 2-theta = 9.5°.

[0053]

According to a further aspect of the present invention, there  
15 is provided a crystalline form, Form B of  
(S)-2-((4-((2-amino-4-(1-hydroxyhexan-3-ylamino)-6-methylpy  
rimidin-5-yl)methyl)-3-methoxybenzyl)(2,2-difluoroethyl)ami  
no)acetic acid, which has an X-ray powder diffraction pattern  
with at least two specific peaks at about 2-theta = 6.5° and  
20 9.5°.

[0054]

According to a further aspect of the present invention, there  
is provided a crystalline form, Form B of  
(S)-2-((4-((2-amino-4-(1-hydroxyhexan-3-ylamino)-6-methylpy  
25 rimidin-5-yl)methyl)-3-methoxybenzyl)(2,2-difluoroethyl)ami

no)acetic acid, which has an X-ray powder diffraction pattern with specific peaks at about 2-theta = 6.5, 9.5, 10.1, 10.9, 13.9, 15.2, 16.5 and 16.8°.

[0055]

5 According to a further aspect of the present invention, there is provided a crystalline form, Form B of (S)-2-((4-((2-amino-4-(1-hydroxyhexan-3-ylamino)-6-methylpyrimidin-5-yl)methyl)-3-methoxybenzyl)(2,2-difluoroethyl)amino)acetic acid, which has an X-ray powder diffraction pattern  
10 substantially the same as the X-ray powder diffraction pattern shown in Figure 5.

[0056]

A further aspect of the invention is Form A of (S)-2-((4-((2-amino-4-(1-hydroxyhexan-3-ylamino)-6-methylpyrimidin-5-yl)methyl)-3-methoxybenzyl)(2,2-difluoroethyl)amino)acetic acid.  
15

[0057]

According to a further aspect of the present invention, there is provided a crystalline form, Form A of  
20 (S)-2-((4-((2-amino-4-(1-hydroxyhexan-3-ylamino)-6-methylpyrimidin-5-yl)methyl)-3-methoxybenzyl)(2,2-difluoroethyl)amino)acetic acid, which has an X-ray powder diffraction pattern with at least one specific peak at about 2-theta = 7.9°.

[0058]

25 According to a further aspect of the present invention, there

is provided a crystalline form, Form A of  
(S)-2-((4-((2-amino-4-(1-hydroxyhexan-3-ylamino)-6-methylpy  
rimidin-5-yl)methyl)-3-methoxybenzyl)(2,2-difluoroethyl)ami  
no)acetic acid, which has an X-ray powder diffraction pattern  
5 with at least one specific peak at about 2-theta = 12.4°.

[0059]

According to a further aspect of the present invention, there  
is provided a crystalline form, Form A of  
(S)-2-((4-((2-amino-4-(1-hydroxyhexan-3-ylamino)-6-methylpy  
10 rimidin-5-yl)methyl)-3-methoxybenzyl)(2,2-difluoroethyl)ami  
no)acetic acid, which has an X-ray powder diffraction pattern  
with at least two specific peaks at about 2-theta = 7.9° and  
12.4°.

[0060]

15 According to a further aspect of the present invention, there  
is provided a crystalline form, Form A of  
(S)-2-((4-((2-amino-4-(1-hydroxyhexan-3-ylamino)-6-methylpy  
rimidin-5-yl)methyl)-3-methoxybenzyl)(2,2-difluoroethyl)ami  
no)acetic acid, which has an X-ray powder diffraction pattern  
20 with specific peaks at about 2-theta = 7.9, 10.9, 12.4, 13.1,  
14.7, 15.7, 16.3 and 17.0°.

[0061]

According to a further aspect of the present invention, there  
is provided a crystalline form, Form A of  
25 (S)-2-((4-((2-amino-4-(1-hydroxyhexan-3-ylamino)-6-methylpy

rimidin-5-yl)methyl)-3-methoxybenzyl)(2,2-difluoroethyl)amino)acetic acid, which has an X-ray powder diffraction pattern substantially the same as the X-ray powder diffraction pattern shown in Figure 6.

5 [0062]

A further aspect of the invention is Form E of (S)-2-((4-((2-amino-4-(1-hydroxyhexan-3-ylamino)-6-methylpyrimidin-5-yl)methyl)-3-methoxybenzyl)(2,2-difluoroethyl)amino)acetic acid.

10 [0063]

According to a further aspect of the present invention, there is provided a crystalline form, Form E of (S)-2-((4-((2-amino-4-(1-hydroxyhexan-3-ylamino)-6-methylpyrimidin-5-yl)methyl)-3-methoxybenzyl)(2,2-difluoroethyl)amino)acetic acid, which has an X-ray powder diffraction pattern with at least one specific peak at about 2-theta = 8.2°.

[0064]

According to a further aspect of the present invention, there is provided a crystalline form, Form E of (S)-2-((4-((2-amino-4-(1-hydroxyhexan-3-ylamino)-6-methylpyrimidin-5-yl)methyl)-3-methoxybenzyl)(2,2-difluoroethyl)amino)acetic acid, which has an X-ray powder diffraction pattern with at least one specific peak at about 2-theta = 11.6°.

[0065]

25 According to a further aspect of the present invention, there

is provided a crystalline form, Form E of  
(S)-2-((4-((2-amino-4-(1-hydroxyhexan-3-ylamino)-6-methylpy  
rimidin-5-yl)methyl)-3-methoxybenzyl)(2,2-difluoroethyl)ami  
no)acetic acid, which has an X-ray powder diffraction pattern  
5 with at least two specific peaks at about 2-theta = 8.2° and  
11.6°.

[0066]

According to a further aspect of the present invention, there  
is provided a crystalline form, Form E of  
10 (S)-2-((4-((2-amino-4-(1-hydroxyhexan-3-ylamino)-6-methylpy  
rimidin-5-yl)methyl)-3-methoxybenzyl)(2,2-difluoroethyl)ami  
no)acetic acid, which has an X-ray powder diffraction pattern  
with specific peaks at about 2-theta = 8.2, 11.6, 11.9, 12.9,  
14.7, 15.6, 16.3 and 18.3°.

15 [0067]

According to a further aspect of the present invention, there  
is provided a crystalline form, Form E of  
(S)-2-((4-((2-amino-4-(1-hydroxyhexan-3-ylamino)-6-methylpy  
rimidin-5-yl)methyl)-3-methoxybenzyl)(2,2-difluoroethyl)ami  
20 no)acetic acid, which has an X-ray powder diffraction pattern  
substantially the same as the X-ray powder diffraction pattern  
shown in Figure 7.

[0068]

It has been found that the compound of Example 4 also exhibits  
25 polymorphism, and one crystalline form is identified herein.

[0069]

Accordingly, a further aspect of the invention is Form A of  
(S)-2-((4-((2-amino-4-(1-hydroxyhexan-3-ylamino)-6-methylpy  
rimidin-5-yl)methyl)-3-methoxybenzyl)(2,2,2-trifluoroethyl)  
5 amino)acetic acid.

[0070]

According to a further aspect of the present invention, there  
is provided a crystalline form, Form A of  
(S)-2-((4-((2-amino-4-(1-hydroxyhexan-3-ylamino)-6-methylpy  
10 rimidin-5-yl)methyl)-3-methoxybenzyl)(2,2,2-trifluoroethyl)  
amino)acetic acid, which has an X-ray powder diffraction  
pattern with at least one specific peak at about 2-theta = 10.9°.

[0071]

According to a further aspect of the present invention, there  
15 is provided a crystalline form, Form A of  
(S)-2-((4-((2-amino-4-(1-hydroxyhexan-3-ylamino)-6-methylpy  
rimidin-5-yl)methyl)-3-methoxybenzyl)(2,2,2-trifluoroethyl)  
amino)acetic acid, which has an X-ray powder diffraction  
pattern with at least one specific peak at about 2-theta = 12.3°.

20 [0072]

According to a further aspect of the present invention, there  
is provided a crystalline form, Form A of  
(S)-2-((4-((2-amino-4-(1-hydroxyhexan-3-ylamino)-6-methylpy  
rimidin-5-yl)methyl)-3-methoxybenzyl)(2,2,2-trifluoroethyl)  
25 amino)acetic acid, which has an X-ray powder diffraction

pattern with at least two specific peaks at about 2-theta = 10.9° and 12.3°.

[0073]

According to a further aspect of the present invention, there  
5 is provided a crystalline form, Form A of  
(S)-2-((4-((2-amino-4-(1-hydroxyhexan-3-ylamino)-6-methylpyrimidin-5-yl)methyl)-3-methoxybenzyl)(2,2,2-trifluoroethyl  
amino)acetic acid, which has an X-ray powder diffraction  
pattern with specific peaks at about 2-theta = 7.9, 10.9, 12.3,  
10 13.0, 15.7, 16.3, 16.9 and 17.8°.

[0074]

According to a further aspect of the present invention, there  
is provided a crystalline form, Form A of  
(S)-2-((4-((2-amino-4-(1-hydroxyhexan-3-ylamino)-6-methylpyrimidin-5-yl)methyl)-3-methoxybenzyl)(2,2,2-trifluoroethyl  
15 amino)acetic acid, which has an X-ray powder diffraction  
pattern substantially the same as the X-ray powder diffraction  
pattern shown in Figure 8.

[0075]

20 It will be understood that 2-theta values of X-ray powder  
diffraction patterns may vary slightly from one machine to  
another or from one sample to another, and so the values quoted  
herein are not to be construed as absolute (see Jenkins, R &  
Snyder, R.L. 'Introduction to X-Ray Powder Diffractometry' John  
25 Wiley & Sons 1996; Bunn, C.W. (1948), Chemical Crystallography,

Clarendon Press, London; Klug, H. P. & Alexander, L. E. (1974), X-Ray Diffraction Procedures). Generally, a measurement error of a diffraction angle in an X-ray powder diffractogram is for example approximately plus or minus  $0.1^\circ$  2-theta, and such  
5 degree of a measurement error should be taken into account when considering the X-ray powder diffraction data. Furthermore, it should be understood that intensities might fluctuate depending on experimental conditions and sample preparation (preferred orientation).

10 [0076]

In a further aspect of the invention, there is provided a crystalline form characterised by the XRD 2-theta values recited herein, wherein said 2-theta values are plus or minus  $0.1$  2-theta.

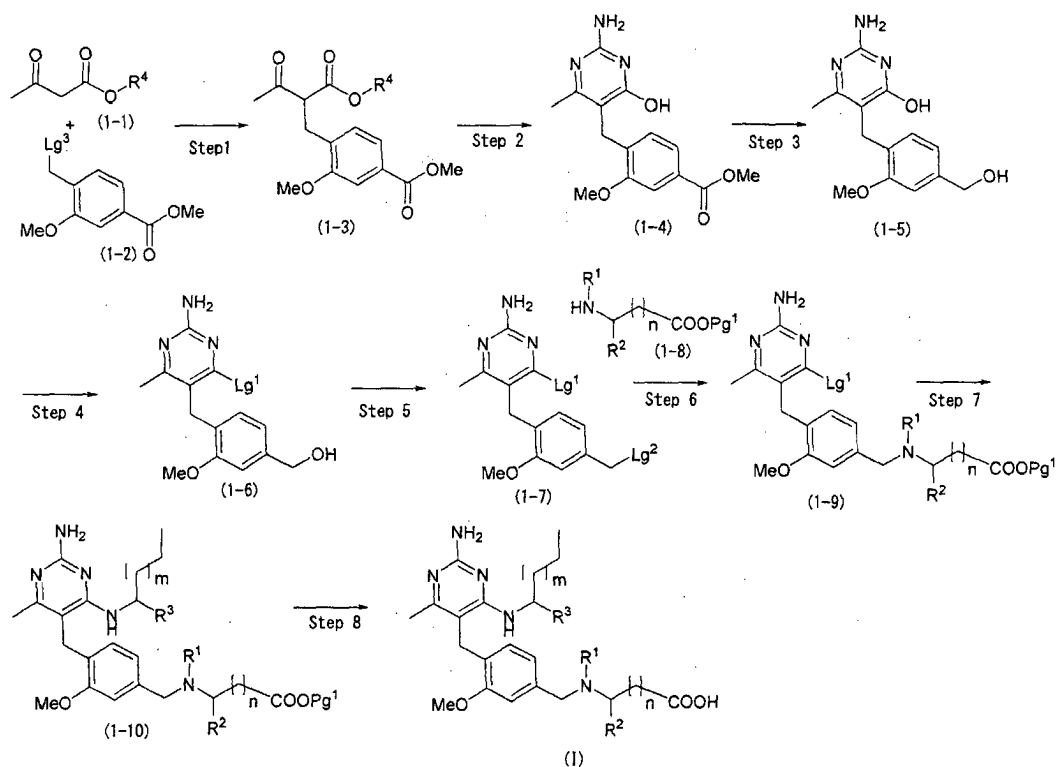
15 [0077]

It is also known that an X-ray powder diffraction pattern may be obtained which has one or more measurement errors depending on measurement conditions (such as the equipment or machine used). For example, the relative intensity of peaks can be  
20 affected by grains above 30 microns in size and non-unitary aspect ratios. The skilled person will also realize that the position of reflections can be affected by the precise height at which the sample sits in the diffractometer and the zero calibration of the diffractometer. The surface planarity of the  
25 sample may also have a small effect. Therefore it should be

understood that the crystalline Forms of the present invention described above, unless otherwise stated, are not limited to the crystals that provide X-ray powder diffraction patterns identical to the X-ray powder diffraction pattern shown in  
5 Figures 5, 6, 7 and 8 and any crystals providing X-ray powder diffraction patterns substantially the same as those shown in these Figures fall within the scope of the present invention. A person skilled in the art of X-ray powder diffraction is able to judge the substantial identity of X-ray powder diffraction  
10 patterns.

[0078]

In the case where X is a single bond and p is 0 in Formula (I), a compound of Formula (I) may be prepared by the sequence shown in Scheme 1:



Scheme 1

wherein  $m$ ,  $n$ ,  $R^1$ ,  $R^2$ , and  $R^3$  are as defined in Formula (I),  $R^4$  is chosen from  $C_{1-4}$  alkyl groups, and the  $Lg^1$ ,  $Lg^2$ , and  $Lg^3$  groups may be independently chosen from conventional leaving groups which are well-known to the skilled person in the art, for example, substituted and unsubstituted hydrocarbylsulfonyloxy leaving groups, for example, p-toluenesulfonyloxy groups, mesitylenesulfonyloxy, 2,4,6-triisopropylbenzenesulfonyloxy, and methanesulfonyloxy groups, and halo leaving groups such as, for example, iodo, bromo, or chloro leaving groups. The  $Pg^1$  group is chosen from protective groups for a carboxylic acid group, for example, an ester such as, for example, a methyl ester, ethyl ester or tert-butyl ester.

[0079]

(Step 1)

The compounds of Formula (1-3) may be prepared by a standard alkylation reaction using compounds of Formula (1-1) and  
5 Formula (1-2). For example, reaction of a compound of Formula (1-1) with a base, such as, for example, NaH, KOtBu, or sodium hexamethyldisilazide, in a suitable solvent, such as, for example, THF or DMF, at a suitable temperature, for example, at a temperature ranging from 0 °C to 20 °C, followed by addition  
10 of a compound of Formula (1-2). The reaction mixture may be heated, for example, at a temperature ranging from 50 °C to 100 °C, optionally in the presence of a catalytic amount of an iodide salt, such as, for example, potassium iodide.

[0080]

15 (Step 2)

The compounds of Formula (1-4) may be prepared by reacting a compound of Formula (1-3) with a guanidine or guanidine carbonate in a suitable solvent such as methanol or ethanol, at elevated temperature, for example, at a temperature ranging  
20 from 50 °C to 150 °C. The compounds of Formula (1-4) may be isolated as a salt.

[0081]

In one aspect of the present disclosure there is provided at least one entity chosen from compounds of Formula (1-4) as  
25 defined in Scheme 1 and salts thereof.

[0082]

(Step 3)

The compounds of Formula (1-5) may be prepared by reacting a compound of Formula (1-4) with a reducing agent, such as, for example, lithium triethylborohydride or lithium aluminium hydride, in a suitable solvent, such as, for example, THF, at a temperature ranging from 0 °C to 50°C.

[0083]

In one aspect of the present disclosure, there is provided at least one entity chosen from compounds of Formula (1-5) as defined in Scheme 1 and salts thereof.

[0084]

(Step 4)

In the case where Lg<sup>1</sup> is a hydrocarbylsulfonyloxy leaving group, such as, for example, methanesulfonyloxy, p-toluenesulfonyloxy, mesitylenesulfonyloxy, or 2,4,6-triisopropylbenzenesulfonyloxy, the compounds of Formula (1-6) may be prepared by reacting a compound of Formula (1-5) with a hydrocarbylsulfonyl halide such as, for example, 2-mesitylenesulfonyl chloride or 2,4,6-triisopropylbenzenesulfonyloxy chloride in the presence of a base such as, for example, a trialkylamine, such as, for example, diisopropylethylamine, triethylamine, or 1,4-diazabicyclo[2.2.2]octane, in a suitable solvent such as, for example, THF at a temperature ranging from 0 °C to 50 °C.

[0085]

In one aspect of the present disclosure, there is provided at least one entity chosen from compounds of Formula (1-6) as defined in Scheme 1 and salts thereof.

5 [0086]

(Step 5)

In the case where  $Lg^2$  is a halogen atom, such as, for example, chloro or bromo, the compounds of Formula (1-7) may be prepared by reacting a compound of Formula (1-6) with a hydrocarbylsulfonyl bromide or chloride in the presence of  
10 lithium bromide or lithium chloride, for example, methanesulfonyl chloride with lithium chloride, in a suitable solvent such as, for example, THF at a suitable temperature, for example, at a temperature ranging from 10 °C to 40 °C, followed by treatment with an acid such as, for example, HCl  
15 in dioxane, in a suitable solvent such as, for example, dichloromethane or THF, at ambient temperature, for example, at a temperature ranging from 10 °C to 40 °C.

[0087]

20 Alternatively, in the case where  $Lg^2$  is a hydrocarbylsulfonyloxy leaving group, such as, for example, methanesulfonyloxy, p-toluenesulfonyloxy, or mesitylenesulfonyloxy, the compounds of Formula (1-7) may be prepared by reacting a compound of Formula (1-6) with a hydrocarbylsulfonyl halide, such as, for  
25 example, 2-mesitylenesulfonyl chloride, in the presence of a

base, such as, for example, trialkylamine, for example, diisopropylethylamine or triethylamine, in a suitable solvent, such as, for example, THF, at a temperature ranging from 0 °C to 50 °C.

5 [0088]

In one aspect of the present disclosure, there is provided at least one entity chosen from the compounds of Formula (1-7) as defined in Scheme 1 and salts thereof.

[0089]

10 (Step 6)

The compounds of Formula (1-9) may be prepared by reacting a compound of Formula (1-7) with a compound of Formula (1-8) in the presence of a base, such as, for example, potassium bicarbonate or sodium bicarbonate, optionally with potassium  
15 iodide or sodium iodide, in a suitable solvent such as, for example, acetonitrile, at a temperature ranging from 0 °C to 100°C. The Step 5 may be followed by the Step 6 successively without isolating the compounds of Formula (1-7).

[0090]

20 In one aspect of the present disclosure, there is provided at least one entity chosen from compounds of Formula (1-9) as defined in Scheme 1 and salts thereof.

[0091]

(Step 7)

25 The compounds of Formula (1-10) may be prepared reacting a

compound of Formula (1-9) with an excess of the appropriate amine or amino alcohol, wherein the amino alcohol may optionally have its alcohol group protected, in a suitable solvent, such as, for example, propionitrile, butanol, anisole, chlorobenzene, or 1,4-dioxane, in the presence of trifluoroacetic acid at elevated temperature, for example, at a temperature ranging from 50 °C to 200 °C, using conventional or microwave heating.

[0092]

10 In one embodiment, there is provided at least one entity chosen from the compounds of Formula (1-10), as defined herein, and salts thereof.

[0093]

(Step 8)

15 The compounds of Formula (I) may be prepared by removing a protective group of carboxylic acid moiety. In the case where  $PG^1$  is  $C_{1-4}$  alkyl,  $PG^1$  may be removed by hydrolysis reaction in the presence of a base such as, for example, aqueous sodium hydroxide, at a temperature ranging from 0 °C to 40 °C. In the case where  $PG^1$  is tert-butyl,  $PG^1$  may be removed by hydrolysis  
20 in the presence of an acid such as 0.1 N to 10 N hydrochloric acid or trifluoroacetic acid, at a temperature ranging from 0 °C to 100 °C.

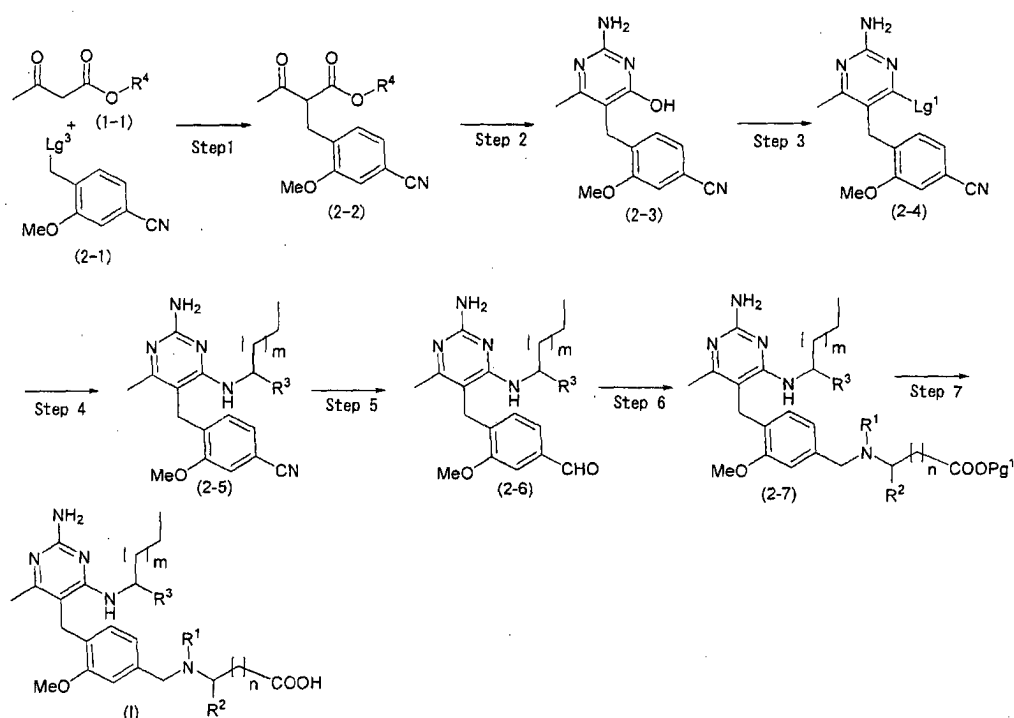
[0094]

25 In the case where  $R^3$  is hydroxymethyl or hydroxyethyl and the

hydroxy group is protected by a protective group, the protective group may also be removed according to a method which is well-known by a skilled person in the art.

[0095]

- 5 Alternatively, a compound of Formula (I) may be prepared by the sequence shown in Scheme 2:



Scheme 2

- wherein  $m$ ,  $n$ ,  $R^1$ ,  $R^2$ , and  $R^3$  are as defined in Formula (I),  $R^4$  is chosen from  $C_{1-4}$  alkyl groups, and the  $Lg^1$  and  $Lg^3$  groups may be independently chosen from conventional leaving groups which are well-known to the skilled person in the art, for example, substituted and unsubstituted hydrocarbylsulfonyloxy leaving groups, such as, for example, p-toluenesulfonyloxy groups, mesitylenesulfonyloxy groups,

2,4,6-triisopropylbenzenesulfonyloxy groups, and methanesulfonyloxy groups, and halo leaving groups, such as, for example, iodo, bromo, and chloro leaving groups. The Pg<sup>1</sup> group is chosen from protective groups for a carboxylic acid group, for example, an ester such as a methyl ester, ethyl ester or tert-butyl ester.

[0096]

(Step 1)

The compounds of Formula (2-2) may be prepared by a similar method to Step 1 of Scheme 1.

[0097]

(Step 2)

The compounds of Formula (2-3) may be prepared by a similar method to Step 2 of Scheme 1.

[0098]

(Step 3)

The compounds of Formula (2-4) may be prepared by a similar method to Step 4 of Scheme 1.

[0099]

(Step 4)

The compounds of Formula (2-5) may be prepared by a similar method to step 7 of Scheme 1.

[0100]

(Step 5)

The compounds of Formula (2-6) may be prepared by reacting a

compound of Formula (2-5) with a reducing agent such as Raney nickel in a suitable solvent mixture such as, for example, pyridine, acetic acid, and water, at a suitable temperature, for example, at a temperature ranging from 20 °C to 50 °C.

5 [0101]

(Step 6)

The compounds of Formula (2-7) or (1-10) may be prepared by the reaction of a compound of Formula (2-6) with an appropriate amine compound of Formula (1-8) under reductive amination conditions, which are well known to the skilled person. For example, the reductive amination may be carried out using a suitable reducing agent such as, for example, sodium triacetoxyborohydride, in a suitable solvent such as, for example, dichloromethane and an acid such as, for example, acetic acid in the presence of activated molecular sieves, or by using NaBH<sub>4</sub> in a suitable solvent such as, for example, methanol.

10  
15

[0102]

(Step 7)

20 The compounds of Formula (I) may be prepared by a similar method to Step 8 of Scheme 1.

[0103]

In one embodiment, there is provided at least one entity chosen from compounds of Formula (2-3) and salts thereof. In one embodiment, there is provided at least one entity chosen from

25

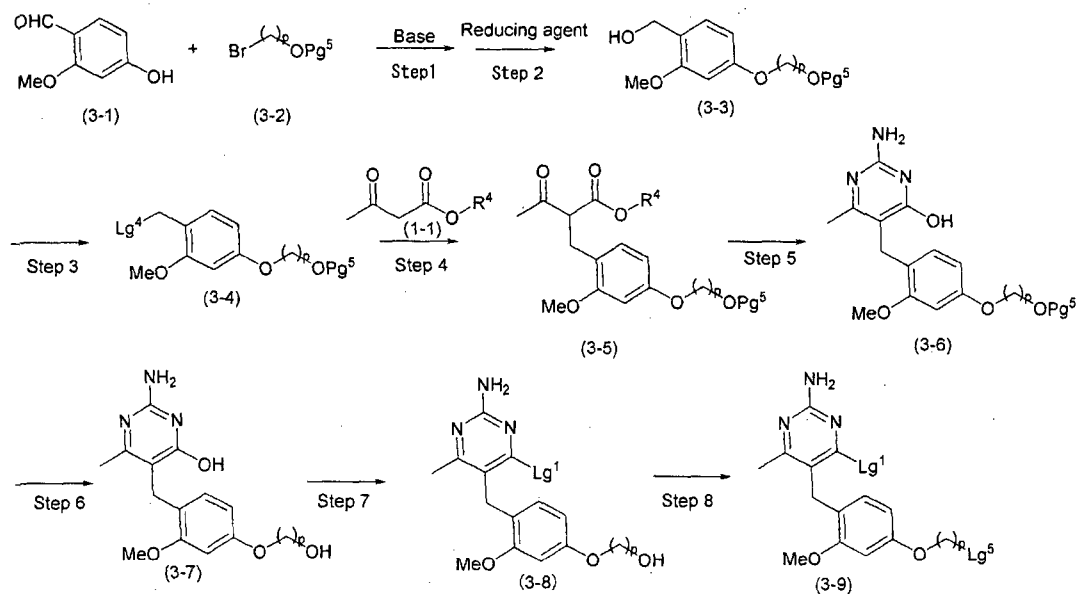
compounds of Formula (2-4) and salts thereof. In one embodiment, there is provided at least one entity chosen from compounds of Formula (2-5) and salts thereof. In one embodiment, there is provided at least one entity chosen from compounds of Formula (2-6) and salts thereof.

[0104]

The optional protecting group incorporated into the compounds of Formula (2-7) or Formula (1-10) may be removed at any convenient point in the synthesis using standard deprotection conditions that are well known to the skilled person. The compounds of Formula (2-7) and the compounds of Formula (1-10) may be isolated as a salt.

[0105]

In the case where X is oxygen and p is 2 or 3 in Formula (I), a compound of Formula (I) may be prepared by the sequence shown in Scheme 3-1 and 3-2, as follows:



## Scheme 3-1

wherein  $m$ ,  $n$ ,  $R^1$ , and  $R^2$  are as defined in Formula (I),  $p$  is 2 or 3,  $R^4$  is chosen from  $C_{1-4}$  alkyl groups, and the  $Lg^1$ ,  $Lg^4$ , and  $Lg^5$  groups may be independently chosen from conventional leaving groups which are well-known to the skilled person in the art, for example, substituted and unsubstituted hydrocarbylsulfonyloxy leaving groups, such as, for example, p-toluenesulfonyloxy groups, mesitylenesulfonyloxy groups, 2,4,6-triisopropylbenzenesulfonyloxy groups, and methanesulfonyloxy groups, and or halo leaving group, such as, for example, iodo, bromo, and chloro leaving groups. The  $Pg^5$  group is chosen from protective groups for a hydroxy group, for example, a trialkylsilyl group, such as, for example, a t-butyldimethylsilyl group.

[0106]

(Step 1 and 2)

The compounds of Formula (3-3) may be prepared by a conventional method known to the skilled person in the art. For example, a benzaldehyde compound of Formula (3-1) may be reacted with a compound of Formula (3-2) in the presence of base, such as, for example, potassium bicarbonate, in a suitable solvent such as, for example, DMF, at ambient temperature, followed by reduction of the product with a reducing agent, such as, for example, sodium borohydride, in a suitable solvent, for example, alcohol, such as, for example, methanol or ethanol, or ether, such as,

for example, THF, at a temperature ranging from 0 °C to 40 °C, to give the compounds of Formula (3-3).

[0107]

(Step 3)

5 The hydroxy group in the compounds of Formula (3-3) may be converted into a conventional leaving group which is well-known to the skilled person in the art, for example, a substituted or unsubstituted hydrocarbylsulfonyloxy leaving groups, for example, p-toluenesulfonyloxy, methanesulfonyloxy, and  
10 mesitylenesulfonyloxy, or halo leaving groups such as, for example, iodo, bromo, and chloro leaving groups, to give the compounds of Formula (3-4).

[0108]

(Step 4)

15 The compounds of Formula (3-5) may be prepared by a standard alkylation reaction using compounds of Formula (3-4) and Formula (1-1) as shown in the Step 1 of Scheme 1. For example, reaction of a compound of Formula (1-1) with a base, such as, for example, NaH, in a suitable solvent, such as, for example,  
20 THF or DMF, at a suitable temperature, for example, at a temperature ranging from 0 °C to 20 °C, followed by addition of a compound of Formula (3-4). The reaction mixture may be heated, for example, at a temperature ranging from 50 °C to 100 °C, optionally in the presence of a catalytic amount of an iodide  
25 salt, such as, for example, KI.

[0109]

(Step 5)

The compounds of Formula (3-6) may be prepared by reacting a compound of Formula (3-5) with a guanidine or guanidine carbonate in a suitable solvent, such as, for example, methanol or ethanol, at elevated temperature, for example, at a temperature ranging from 50 °C to 150 °C. The compounds of Formula (3-6) may be isolated as a salt.

[0110]

10 In one aspect of the present disclosure, there is provided at least one entity chosen from compounds of Formula (3-6) as defined in Scheme 3-1 and salts thereof.

[0111]

(Step 6)

15 The protective group Pg<sup>5</sup> of the compounds of Formula (3-6) may be removed with an appropriate de-protecting agent. In the case where Pg<sup>5</sup> is a trialkylsilyl group, the compounds of Formula (3-6) may be reacted with acid, such as, for example, hydrogen chloride, in methanol at a temperature ranging from 0 °C to 40 °C  
20 to give the compounds of Formula (3-7).

[0112]

(Step 7)

In the case where Lg<sup>1</sup> is a hydrocarbylsulfonyloxy leaving group, the compounds of Formula (3-8) may be prepared by reacting a  
25 compound of Formula (3-7) with hydrocarbylsulfonyl halide, such

as, for example, 2-mesytylenesulfonyl chloride, in the presence of a base, such as, for example, trialkylamine, for example, diisopropylethylamine or triethylamine, in a suitable solvent such as, for example, THF, at a temperature ranging from 0 °C to 50 °C.

[0113]

In one aspect of the present disclosure there is provided at least one entity chosen from the compounds of Formula (3-8) as defined in Scheme 3-1 and salts thereof.

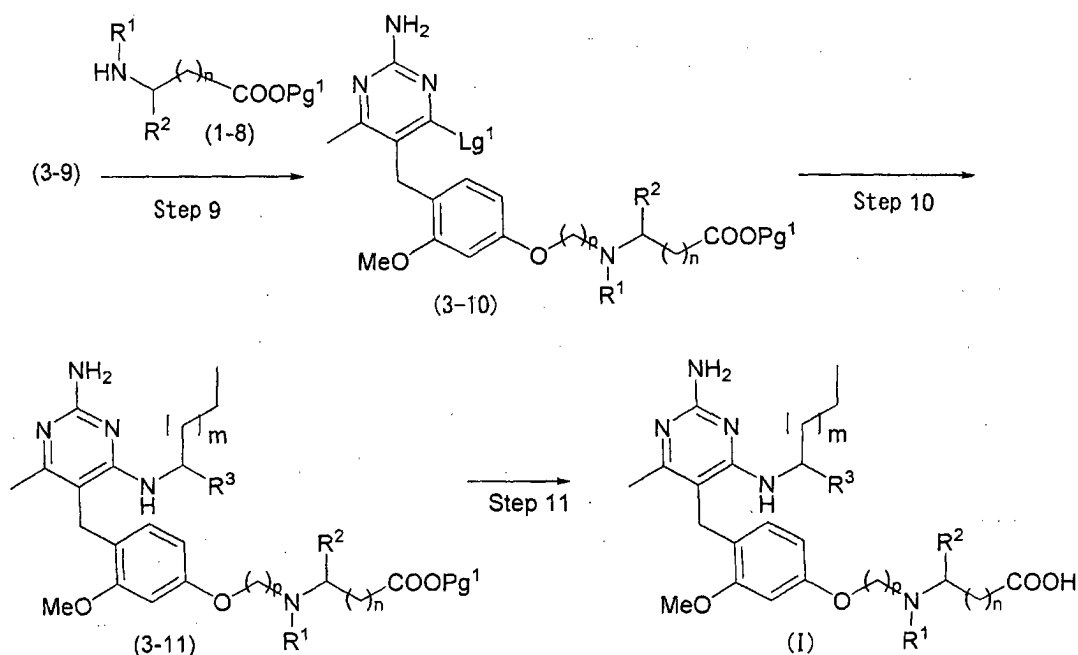
[0114]

(Step 8)

In the case where Lg<sup>5</sup> is a hydrocarbylsulfonyloxy leaving group, the compounds of Formula (3-9) may be prepared by reacting a compound of Formula (3-8) with hydrocarbylsulfonyl halide, such as, for example, methanesulfonyl chloride, in a suitable solvent, such as, for example, THF, at ambient temperature, for example, at a temperature ranging from 10 °C to 40°C. The compounds of Formula (3-9) may also be prepared by reacting a compound of Formula (3-8) with a halogenating agent, such as, for example, lithium bromide or lithium chloride, in the presence of hydrocarbylsulfonyl bromide or chloride, in a suitable solvent such as, for example, THF, at ambient temperature, for example at a temperature ranging from 10 °C to 40 °C.

[0115]

In one aspect of the present disclosure, there is provided at least one entity chosen from compounds of Formula (3-9) as defined in Scheme 3-1 and salts thereof.



Scheme 3-2

wherein  $m$ ,  $n$ ,  $R^1$ ,  $R^2$ , and  $R^3$  are as defined in Formula (I),  $p$  is 2 or 3, and the  $Lg^1$  group may be independently chosen from conventional leaving groups which are well-known to the skilled person in the art, for example, substituted and unsubstituted hydrocarbylsulfonyloxy leaving groups, such as, for example, p-toluenesulfonyloxy, mesitylenesulfonyloxy, 2,4,6-triisopropylbenzenesulfonyloxy and methanesulfonyloxy groups, and halo leaving groups, such as, for example, iodo, bromo, and chloro leaving groups. The  $Pg^1$  group is chosen from protective groups for a carboxylic acid group, for example, an ester such as, for example, a methyl ester, ethyl ester or

tert-butyl ester..

[0116]

(Step 9)

The compounds of Formula (3-10) may be prepared by reacting a  
5 compound of Formula (3-9) with a compound of Formula (1-8) in  
the presence of a base such as, for example, potassium  
bicarbonate or sodium bicarbonate, optionally with potassium  
iodide or sodium iodide, in a suitable solvent, such as, for  
example, acetonitrile, at a temperature ranging from 0 °C to  
10 100°C.

[0117]

In one aspect of the present disclosure there is provided at  
least one entity chosen from the compounds of Formula (3-10)  
as defined in Scheme 1 and salts thereof.

15 [0118]

(Step 10)

The compounds of Formula (3-11) may be prepared reacting a  
compound of Formula (3-10) with an excess of the appropriate  
amine or amino alcohol, wherein the amino alcohol may optionally  
20 have its alcohol group protected, in a suitable solvent, such  
as, for example, propionitrile, butanol, or 1,4-dioxane, in the  
presence of trifluoroacetic acid at elevated temperature, for  
example, at a temperature ranging from 50 °C to 200°C, using  
conventional or microwave heating.

25 [0119]

In one aspect there is provided a compound of Formula (3-11), as defined herein, and salts thereof.

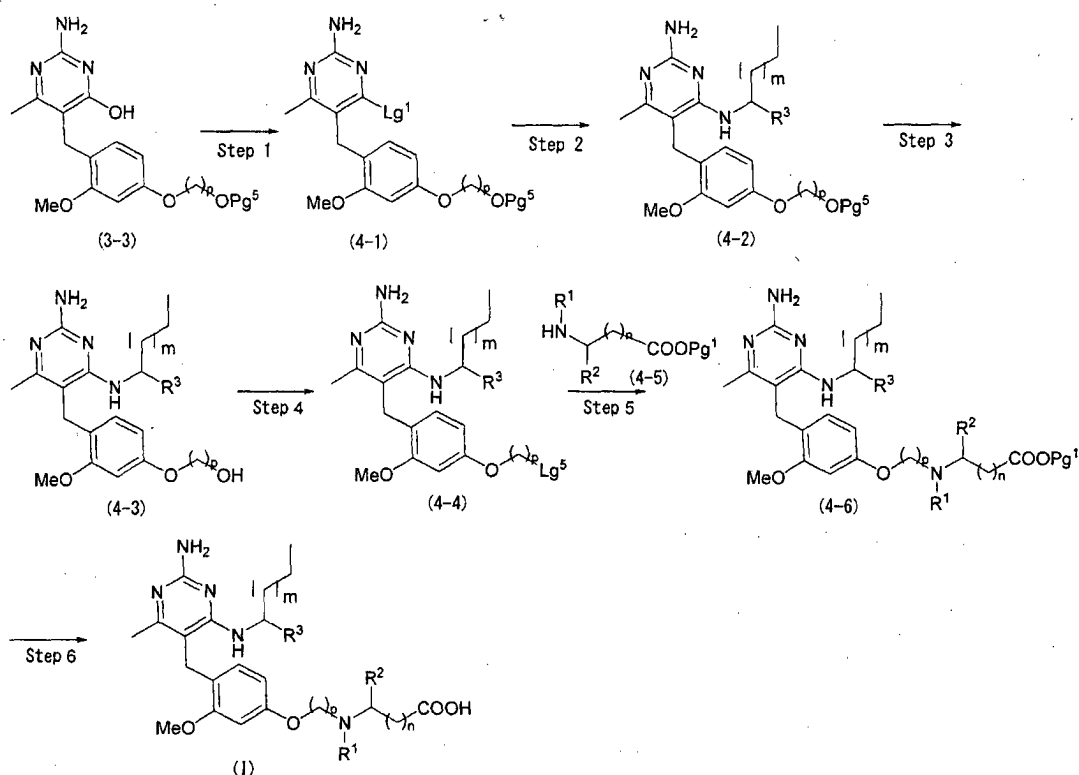
[0120]

(Step 11)

5 The compounds of Formula (I) may be prepared by removing a protective group of carboxylic acid moiety, in the presence of a base such as, for example, aqueous sodium hydroxide, at a temperature ranging from 0 °C to 40°C. In the case where R<sup>3</sup> is hydroxymethyl or hydroxyethyl and the hydroxy group is  
10 protected by a protective group, it may also be removed according to a method which is well-known by a skilled person in the art.

[0121]

Alternatively, a compound of Formula (I) may be prepared by the  
15 sequence shown in Scheme 4:



Scheme 4

wherein  $m$ ,  $n$ ,  $\text{R}^1$ ,  $\text{R}^2$ , and  $\text{R}^3$  are as defined in Formula (I),  $p$  is 2 or 3, and the  $\text{Lg}^1$  and  $\text{Lg}^5$  groups may be independently chosen from conventional leaving groups which are well-known to the skilled person in the art, for example, substituted and unsubstituted hydrocarbylsulfonyloxy leaving groups, such as, for example, *p*-toluenesulfonyloxy, mesitylenesulfonyloxy, 2,4,6-triisopropylbenzenesulfonyloxy and methanesulfonyloxy groups, and halo leaving groups such as, for example, iodo, bromo, and chloro leaving groups. The  $\text{Pg}^1$  group is chosen from protective groups for a carboxylic acid group, for example, an ester such as a methyl ester, ethyl ester or *tert*-butyl ester. The  $\text{Pg}^5$  group is chosen from protective groups for a hydroxy

group, for example, a trialkylsilyl group, such as, for example, t-butyl dimethylsilyl.

[0122]

(Step 1)

5 The compounds of Formula (4-1) may be prepared by the similar method as Step 7 of the Scheme 3-1.

[0123]

In one aspect of the present disclosure, there is provided at least one entity chosen from compounds of Formula (4-1) as  
10 defined in Scheme 1 and salts thereof.

[0124]

(Step 2)

The compounds of Formula (4-2) may be prepared by the similar method as Step 10 of the Scheme 3-2.

15 [0125]

In one aspect of the present disclosure, there is provided at least one entity chosen from compounds of Formula (4-2) as defined in Scheme 1 and salts thereof.

[0126]

20 (Step 3)

In the case where  $R^3$  is hydroxymethyl or hydroxyethyl and the hydroxy group is not protected, the hydroxy group may be protected by reacting a compound of Formula (4-2) with an acetic anhydride or acetyl chloride in the presence of a base, such  
25 as, for example, trialkylamine, for example,

diisopropylethylamine or triethylamine, and a catalytic amount of N,N-dimethyl-4-aminopyridine in a suitable solvent, such as, for example, THF, at a suitable temperature, for example, at a temperature ranging from 10 °C to 40 °C, followed by  
5 deprotection of the protective group Pg<sup>5</sup> with an appropriate de-protecting agent. In the case where Pg<sup>5</sup> is a trialkylsilyl group, the intermediate may be reacted with tetrabutylammonium fluoride in THF at a temperature ranging from 0 °C to 40°C to give the compounds of Formula (4-3).

10 [0127]

Alternatively, in the case that R<sup>3</sup> does not contain a free hydroxy group, the compounds of Formula (4-3) may be prepared by a similar method to Step 6 of Scheme 3-1.

[0128]

15 In one aspect of the present disclosure, there is provided at least one entity chosen from the compounds of Formula (4-3) as defined in Scheme 1 and salts thereof.

[0129]

(Step 4)

20 The compounds of Formula (4-4) may be prepared by a similar method to Step 8 of Scheme 3-1.

[0130]

In one aspect of the present disclosure, there is provided at least one entity chosen from the compounds of Formula (4-4) as  
25 defined in Scheme 1 and salts thereof.

[0131]

(Step 5)

The compounds of Formula (4-6) may be prepared by a similar method to Step 9 of Scheme 3-2.

5 [0132]

In one aspect of the present disclosure, there is provided at least one entity chosen from the compounds of Formula (4-6) as defined in Scheme 1 and salts thereof.

[0133]

10 (Step 6)

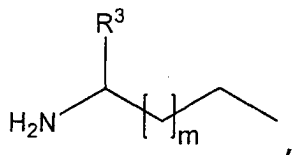
The compounds of Formula (I) may be prepared by removing a protective group of carboxylic acid moiety, in the presence of a base such as, for example, aqueous sodium hydroxide, at a temperature ranging from 0 °C to 40 °C. In the case where R<sup>3</sup> is hydroxymethyl or hydroxyethyl and the hydroxy group is protected by a protective group, it may also be removed according to a method which is well-known by a skilled person in the art.

[0134]

20 In the case where the hydroxyl group in R<sup>3</sup> is protected, such protective group can be, for example, an alkyl ester group, silicon-based protecting group, or a benzyl-based protecting group.

In one embodiment, such hydroxy group in R<sup>3</sup> in Formula (1-10),  
25 Formula (2-5), Formula (2-6), Formula (2-7), Formula (3-11) or

a compound of the formula:



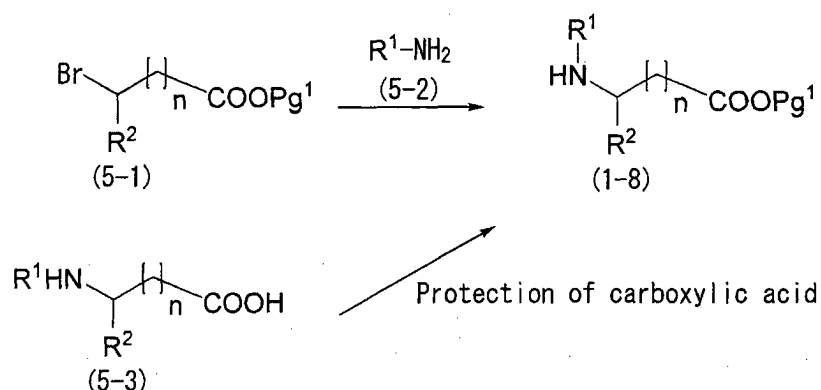
which is a starting material for these compounds may be protected by a silicon-based protective group or a benzyl-based protective group. The silicon-based protecting group may be a tri(C<sub>1-4</sub> alkyl)silyl group, for example, a trimethylsilyl group or a tert-butyldimethylsilyl group. In one embodiment, R<sup>3</sup> is tert-butyldimethylsilyl.

[0135]

In one embodiment, such hydroxy group in R<sup>3</sup> may be protected by acetyl group which can be removed under the basic condition in the last step in each Scheme.

[0136]

The compounds of Formula (1-8) may be commercially available or may be prepared by conventional methods known to a person skilled in the art. For example, when R<sup>2</sup> is hydrogen or C<sub>1-4</sub> alkyl, compounds of Formula (1-8) may be prepared according to Scheme 5-1:



Scheme 5-1

wherein  $n$ ,  $R^1$  and  $R^2$  are as defined in Formula (I), and the  $Pg^1$  group is chosen from protective groups for a carboxylic acid group, for example, an ester, such as a methyl ester, ethyl ester or tert-butyl ester.

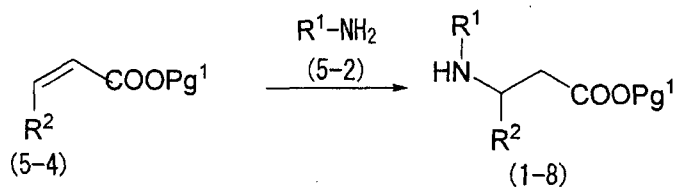
[0137]

The compounds of Formula (1-8) may be prepared by a reaction of a compound of Formula (5-1) with a compound of Formula (5-2) in the presence of a base, such as, for example, a trialkylamine, for example, triethylamine or diisopropylethylamine, in a suitable solvent, such as, for example, THF, acetonitrile, or dichloromethane, and at a suitable temperature, for example, at a temperature ranging from 10 °C to 40 °C.

[0138]

Alternatively, the compounds of Formula (1-8) may be prepared by protecting a carboxylic acid of Formula (5-3), which is commercially available or may be prepared by a conventional method known to the person skilled in the art. When  $n$  is 1, the compounds of Formula (1-8) may be prepared by an alkylation

reaction as in the Scheme 5-2 below.



Scheme 5-2

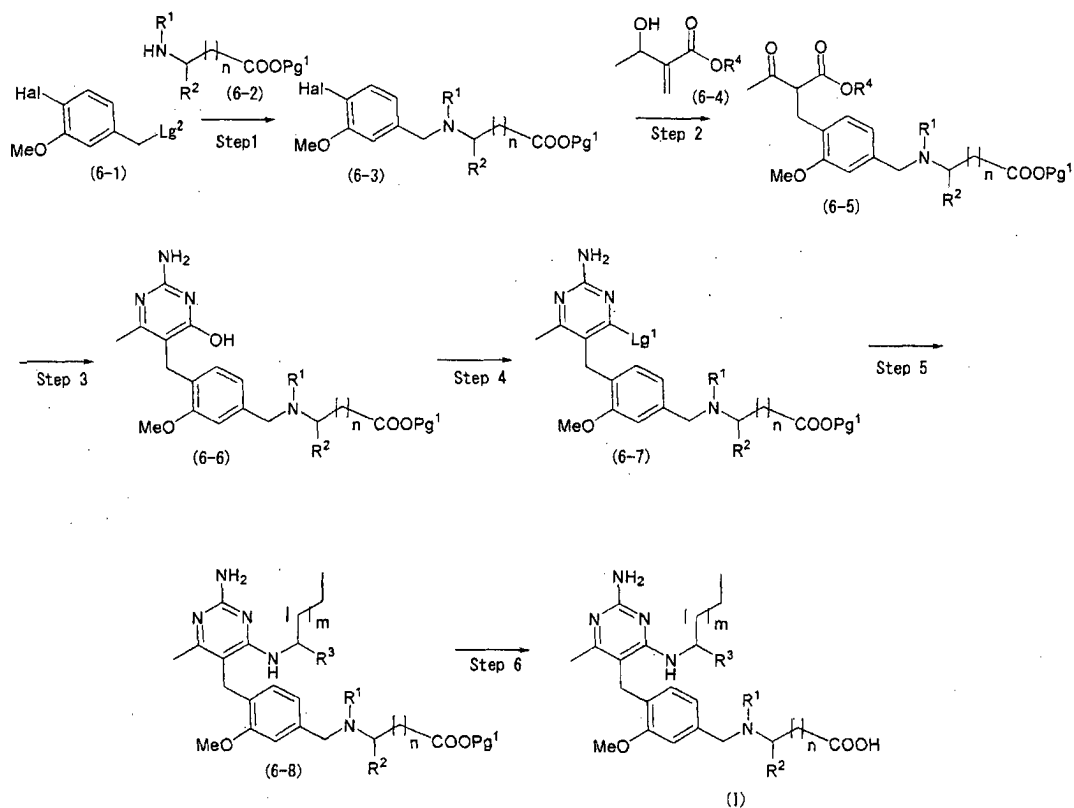
wherein  $\text{R}^1$  and  $\text{R}^2$  are as defined in Formula (I), and the  $\text{Pg}^1$  group  
 5 is chosen from protective groups for a carboxylic acid group,  
 for example, esters such as methyl ester, ethyl ester or  
 tert-butyl ester.

[0139]

A compound of Formula (5-4) may be reacted with a compound of  
 10 Formula (5-2) in a suitable solvent such as alcohol, for example,  
 ethanol, to give a compound of Formula (1-8).

[0140]

Alternatively, a compound of Formula (I) may be prepared by the  
 sequence shown in Scheme 6:



Scheme 6

wherein  $m$ ,  $n$ ,  $R^1$ ,  $R^2$  and  $R^3$  are as defined in Formula (I),  $R^4$  is chosen from  $C_{1-4}$ alkyl groups, the  $Lg^1$  and  $Lg^2$  groups may be independently chosen from conventional leaving groups which are well-known to the skilled person in the art, for example, substituted and unsubstituted hydrocarbylsulfonyloxy leaving groups such as *p*-toluenesulfonyloxy, mesitylenesulfonyloxy, 2,4,6-triisopropylbenzenesulfonyloxy and methanesulfonyloxy groups, and halogen atoms such as iodo, bromo or chloro. The  $Pg^1$  group is chosen from protective groups for a carboxylic acid group, for example, an ester such as a methyl ester, ethyl ester or tert-butyl ester. The Hal is bromine or iodine.

[0141]

(Step 1)

The compound of Formula (6-3) may be prepared by standard N-alkylation reaction using a compound of Formula (6-1) with  
5 a compound of Formula (6-2) in the presence of a base such as potassium bicarbonate, sodium bicarbonate, sodium carbonate, potassium carbonate, triethylamine or N,N-diisopropylethylamine optionally with potassium iodide or sodium iodide, in a suitable solvent such as acetonitrile,  
10 dimethylformamide and dimethylacetamide at a temperature, for example, ranging from 0 °C to 100°C.

[0142]

In one embodiment of the present disclosure, there is provided at least one entity chosen from compound of Formula (6-3) as  
15 defined in Scheme 6 and salts thereof.

[0143]

(Step 2)

The compound of Formula (6-5) may be prepared by a Heck reaction between a compound of Formula (6-3) and a compound of Formula  
20 (6-4). The reaction may be carried out using a palladium catalyst, such as Pd(OAc)<sub>2</sub> or 1,1'-bis(di-tert-butylphosphino)ferrocene palladium dichloride, a base such as potassium bicarbonate, sodium bicarbonate, sodium carbonate, potassium carbonate or  
25 dicyclohexylmethylamine, and an ammonium salt such as

tetrabutylammonium chloride or tetrabutylammonium bromide. The reaction may be performed in a suitable solvent such as tetrahydrofuran or dimethylacetamide at a temperature, for example, ranging from 50°C to 150°C.

5 [0144]

In one aspect of the present disclosure, there is provided at least one entity chosen from compounds of Formula (6-3) as defined in Scheme 6 and salts thereof.

[0145]

10 (Step 3)

The Compound of Formula (6-6) may be prepared by a similar method to Step 2 of Scheme 1.

[0146]

(Step 4)

15 The Compound of Formula (6-7) may be prepared by a similar method to Step 4 of Scheme 1.

[0147]

(Step 5)

The Compound of Formula (6-8) may be prepared by a similar method to Step 7 of Scheme 1.

20

[0148]

(Step 6)

The Compound of Formula (I) may be prepared by a similar method to Step 8 of scheme 1. In the case that R<sup>3</sup> is hydroxymethyl or hydroxyethyl and the hydroxy group is protected by a protective

25

group, it may also be removed according to a method which is well-known by a skilled person in the art.

[0149]

It will be appreciated that, in some of the reactions mentioned herein, it may be necessary or 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 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, 3<sup>rd</sup> edition, John Wiley and Sons, 1999). 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.

[0150]

The compounds described herein may be useful intermediates for the preparation of compounds of Formula (I) and may be isolated as a free base/acid or as a salt. Therefore, in certain aspects and embodiments of the present disclosure, there is provided an intermediate described herein, or a salt thereof, wherein any of the variable groups described for said intermediate may take any of the values described herein in connection with that group.

[0151]

Non-limiting examples of suitable pharmaceutically acceptable

salts of a compound of the Formula (I) include acid-addition salts of a compound of the Formula (I), for example, acid-addition salts with an inorganic or organic acid such as, for example, hydrochloric acid, hydrobromic acid, sulphuric acid, trifluoroacetic acid, citric acid, maleic acid, asparagine, or glutamine. Non-limiting examples of suitable pharmaceutically acceptable salts of a compound of the Formula (I) also include base-addition salts of a compound of the Formula (I), for example, base-addition salts with an inorganic or organic base such as, for example, a sodium salt, potassium salt, methylamine, or 2-aminoethanol.

[0152]

The at least one entity chosen from compounds of the Formula (I) and pharmaceutically acceptable salts thereof of the present disclosure may be administered in the form of a Pro-drug, i.e. a compound that is broken down in the human or animal body to release a compound or salt of the present disclosure. A Pro-drug may be used to alter the physical properties and/or the pharmacokinetic properties of at least one entity of the present disclosure. A Pro-drug can be formed when the at least one entity of the present disclosure contains at least one suitable group and/or substituent to which at least one property-modifying group can be attached. Non-limiting examples of Pro-drugs include in-vivo-cleavable amide derivatives which may, for example, be formed at at least one

amino group in the at least one entity chosen from compounds of the Formula (I) and pharmaceutically acceptable salts thereof.

[0153]

5 Accordingly, the present disclosure includes those compounds of the Formula (I) as defined hereinbefore and pharmaceutically acceptable salts thereof when made available by organic synthesis and when made available within the human or animal body by way of cleavage of a Pro-drug thereof. Accordingly, the  
10 present invention includes those compounds of the Formula (I) that are produced by organic synthetic means and also such compounds that are produced in the human or animal body by way of metabolism of a precursor compound, that is a compound of the Formula (I) may be a synthetically-produced compound or a  
15 metabolically-produced compound.

[0154]

A non-limiting example of a suitable pharmaceutically acceptable Pro-drug of a compound of the Formula (I) is one that is based on reasonable medical judgement as being suitable for  
20 administration to the human or animal body without undesirable pharmacological activities and without undue toxicity.

[0155]

Various forms of Pro-drug have been described, for example, in the following documents:

25 a) Methods in Enzymology, Vol. 42, p. 309-396, edited by K.

- Widder, et al. (Academic Press, 1985);
- b) Design of Pro-drugs, edited by H. Bundgaard, (Elsevier, 1985);
- c) A Textbook of Drug Design and Development, edited by  
5 Krogsgaard-Larsen and  
H. Bundgaard, Chapter 5 "Design and Application of Pro-drugs",  
by H. Bundgaard p. 113-191 (1991);
- d) H. Bundgaard, Advanced Drug Delivery Reviews, 8, 1-38  
(1992);
- 10 e) H. Bundgaard, et al., Journal of Pharmaceutical Sciences,  
77, 285 (1988);
- f) N. Kakeya, et al., Chem. Pharm. Bull., 32, 692 (1984);
- g) T. Higuchi and V. Stella, "Pro-Drugs as Novel Delivery  
Systems", A.C.S. Symposium Series, Volume 14; and
- 15 h) E. Roche (editor), "Bioreversible Carriers in Drug  
Design", Pergamon Press, 1987.

[0156]

A non-limiting example of a suitable pharmaceutically  
acceptable pro-drug of a compound of the Formula (I) that  
20 possesses an amino group is an in-vivo cleavable amide  
derivative thereof. Non-limiting examples of suitable  
pharmaceutically-acceptable amides from an amino group include  
an amide formed with a C<sub>1-10</sub> alkanoyl group, such as, for example,  
an acetyl group, a benzoyl group, a phenylacetyl group, a  
25 substituted benzoyl group, and a substituted phenylacetyl group.

Non-limiting examples of ring substituents on the phenylacetyl and benzoyl groups include aminomethyl, N alkylaminomethyl, N,N-dialkylaminomethyl, morpholinomethyl, piperazin-1-ylmethyl, and 4-(C<sub>1-4</sub> alkyl)piperazin-1-ylmethyl.

5 [0157]

The in-vivo effects of a compound of the Formula (I) may be exerted in part by one or more metabolites that are formed within the human or animal body after administration of a compound of the Formula (I). As stated hereinbefore, the in-vivo effects  
10 of a compound of the Formula (I) may also be exerted by way of metabolism of a precursor compound (a pro-drug).

[0158]

According to an embodiment of the present disclosure, there is provided a pharmaceutical composition which comprises at least  
15 one entity chosen from compounds of the Formula (I) and pharmaceutically acceptable salts thereof, as defined hereinbefore, in association with at least one pharmaceutically acceptable diluent or carrier. The pharmaceutical composition may be used in the treatment of cancer. The composition may be  
20 in a form suitable for oral administration, for example, as a tablet or capsule; for parenteral injection (including intravenous, subcutaneous, intramuscular, intravascular, or infusion) as a sterile solution, suspension, or emulsion; for topical administration, for example, as an ointment or cream;  
25 or for rectal administration, for example, as a suppository.

[0159]

The at least one entity chosen from compounds of Formula (I) and pharmaceutically acceptable salts thereof could also be administered as an air spray for inhalation. The air spray (e.g.,  
5 spray, aerosol, dry powder preparation, etc.) could be optionally formulated as an aqueous solution or suspension, or as an aerosol delivered from a pressurized pack such as a pressurized metered dose inhaler by using, for example, a liquefied propellant. A dry powder preparation may also be used.  
10 An aerosol appropriate for inhalation may be either a suspension or solution, and would typically contain the at least one entity chosen from compounds of Formula (I) and pharmaceutically acceptable salts thereof and any appropriate propellant(s) such as, for example a fluorocarbon- or hydrogen-containing  
15 chlorofluorocarbon or a mixture thereof. For instance, it may contain hydrofluoroalkane such as 1,1,1,2-tetrafluoroethane, heptafluoroalkane (HFA) such as 1,1,1,2,3,3,3-heptafluoro-n-propane, or a mixture thereof. An aerosol may optionally contain an additional preparation  
20 excipient well-known to those skilled in the art such as surfactant (e.g., oleic acid or lecithin) and cosolvent (e.g., ethanol), etc. For example, an aerosol preparation could be delivered using the inhaler known as "TURBUHALER™".

[0160]

25 For oral administration, the at least one entity chosen from

compounds of the Formula (I) and pharmaceutically acceptable salts thereof of the present disclosure may be admixed with at least one adjuvant and/or carrier, for example, chosen from lactose, saccharose, sorbitol, mannitol; starches, for example, potato starch, corn starch, or amylopectin; cellulose derivatives; binders, for example, gelatine or polyvinylpyrrolidone; and/or lubricants, for example, magnesium stearate, calcium stearate, polyethylene glycols, waxes, paraffins, and the like, and then compressed into tablets.

If coated tablets are desired, the cores, prepared as described above, may be coated with a concentrated sugar solution which may contain, for example, gum arabic, gelatine, talcum, and titanium dioxide. Alternatively, the tablet may be coated with a suitable polymer dissolved in a readily volatile organic solvent.

[0161]

For the preparation of soft gelatine capsules, the at least one entity chosen from compounds of the Formula (I) and pharmaceutically acceptable salts thereof of the present disclosure may be admixed with, for example, a vegetable oil or polyethylene glycol. Hard gelatine capsules may contain granules of the at least one entity using either the above-mentioned excipients for tablets. Also liquid or semisolid formulations of the at least one entity of the present disclosure may be filled into hard gelatine capsules. Liquid

preparations for oral application may be in the form of syrups or suspensions, for example, solutions containing the at least one entity of the present disclosure, the balance being sugar and a mixture of ethanol, water, glycerol, and propylene glycol.

5    Optionally such liquid preparations may contain colouring agents, flavouring agents, saccharine, carboxymethylcellulose as a thickening agent, and/or other excipients known to those skilled in art.

[0162]

10   The at least one entity chosen from compounds of the Formula (I) and pharmaceutically acceptable salts thereof may be administered to a subject such as a warm blooded animal at a unit dose ranging from 5 mg/m<sup>2</sup> to 5000 mg/m<sup>2</sup> body area of the animal, i.e. approximately ranging from 0.1 mg/m<sup>2</sup> to 100 mg/kg, 15   and this may provide a therapeutically effective dose. Doses are reported on the basis of the weight of the compound of Formula (I). A unit dose form such as a tablet or capsule will usually contain, for example, ranging from 1 mg to 250 mg of active ingredient, e.g., compound of Formula (I). For example, a daily 20   dose in the range of from 1 mg/kg to 50 mg/kg may be employed. However the daily dose will necessarily be varied depending upon the host treated, the particular route of administration, and the severity of the illness being treated. Accordingly the optimum dosage may be determined by the practitioner who is 25   treating any particular patient.

[0163]

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

[0164]

In the context of the present specification, the term "therapy" also includes "prophylaxis" unless there are specific indications to the contrary. The terms "therapeutic" and "therapeutically" should be construed accordingly.

[0165]

As used herein, the term "treatment" is intended to have its normal everyday meaning of dealing with a disease in order to entirely or partially relieve one, some or all of its symptoms, or to correct or compensate for the underlying pathology.

[0166]

As used herein, the term "prophylaxis" is intended to have its normal everyday meaning and includes primary prophylaxis to prevent the development of the disease and secondary prophylaxis whereby the disease has already developed and the patient is temporarily or permanently protected against exacerbation or worsening of the disease or the development of new symptoms associated with the disease.

[0167]

The at least one entity chosen from compounds of the Formula

(I) and pharmaceutically acceptable salts thereof of the present disclosure may be effective activators of TLR7 in vitro. Accordingly, the at least one entity of the present disclosure may be expected to be potentially useful agents in the treatment or prophylaxis of diseases or medical conditions mediated alone or in part by TLR7. For example, the following non-limiting diseases and conditions listed in paragraphs 1 to 8 below may be treatable with compounds of the present disclosure.

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

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

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

3. eyes: blepharitis; conjunctivitis, including perennial and vernal allergic conjunctivitis; iritis; anterior and posterior uveitis; choroiditis; autoimmune, degenerative or inflammatory disorders affecting the retina; ophthalmitis

including sympathetic ophthalmritis; sarcoidosis; infections including viral , fungal, and bacterial;

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

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

6. other auto-immune and allergic disorders including rheumatoid arthritis, irritable bowel syndrome, systemic lupus erythematosus, multiple sclerosis, Hashimoto's thyroiditis, Graves' disease, Addison's disease, diabetes mellitus, idiopathic thrombocytopaenic purpura, eosinophilic fasciitis, hyper-IgE syndrome, antiphospholipid syndrome and Sazary syndrome;

7. oncology: treatment of cancers including bladder, head and neck, prostate, breast, lung, ovarian, pancreatic, bowel and colon, colorectal, stomach, skin, kidney, renal, esophageal, liver, uterus, bone thyroid, cerebral, bile duct and brain tumors and malignancies affecting the bone marrow (including the leukaemias) and lymphoproliferative systems, such as

Hodgkin's and non-Hodgkin's lymphoma; including the prevention and treatment of metastatic disease and tumour recurrences, and paraneoplastic syndromes; and

8. infectious diseases: virus diseases such as genital  
5 warts, common warts, plantar warts, hepatitis B, hepatitis C, herpes simplex virus, molluscum contagiosum, variola, human immunodeficiency virus (HIV), human papilloma virus (HPV), cytomegalovirus (CMV), varicella zoster virus (VZV), rhinovirus, adenovirus, coronavirus, influenza,  
10 para-influenza; bacterial diseases such as tuberculosis and mycobacterium avium, leprosy; other infectious diseases, such as fungal diseases, chlamydia, candida, aspergillus, cryptococcal meningitis, pneumocystis carinii, cryptosporidiosis, histoplasmosis, toxoplasmosis,  
15 trypanosome infection, and leishmaniasis.

[0168]

It is envisaged that for the methods of treatment or prophylaxis mentioned herein, the at least one entity chosen from compounds of Formula (I) and pharmaceutically acceptable salts thereof  
20 will be administered to a mammal, such as a human being. Similarly, for the uses of at least one entity chosen from compounds of Formula (I) and pharmaceutically acceptable salts thereof for the treatment or prophylaxis of diseases or medical conditions mentioned herein, it is envisaged that the at least  
25 one entity will be administered to a mammal, such as a human

being.

[0169]

According to an another aspect of the present disclosure, there is therefore provided at least one entity chosen from compounds of Formula (I) and pharmaceutically acceptable salts thereof  
5 for use as a medicament.

[0170]

According to a further aspect of the present disclosure, there is provided at least one entity chosen from compounds of Formula (I) and pharmaceutically acceptable salts thereof for use in  
10 the treatment or prophylaxis of a disease mediated through TLR7.

In one embodiment of the present disclosure, said disease mediated through TLR7 is cancer. The compound of Formula (I), or a pharmaceutically acceptable salt thereof, is also expected  
15 to be of use in the treatment or prophylaxis of metastasis, tumour recurrence and paraneoplastic syndrome.

[0171]

In a further embodiment of the present disclosure, said cancer is chosen from bladder cancer, head and neck cancer, prostate cancer, breast cancer, lung cancer, uterus cancer, pancreatic  
20 cancer, liver cancer, renal cancer, ovarian cancer, colon cancer, stomach cancer, skin cancer, bone cancer, thyroid cancer, bile duct cancer, cerebral tumor, malignant myeloma, and lymphoproliferative tumors. In one embodiment of the  
25 present disclosure, said disease mediated through TLR7 is

asthma, COPD, allergic rhinitis, allergic conjunctivitis, atopic dermatitis, hepatitis B, hepatitis C, HIV, HPV, bacterial infections, or dermatosis.

[0172]

5 According to a further aspect of the present disclosure, there is provided the use of at least one entity chosen from compounds of Formula (I) and pharmaceutically acceptable salts thereof for the preparation of a medicament for the treatment or prophylaxis of a disease mediated through TLR7. In one  
10 embodiment of the present disclosure, said disease mediated through TLR7 is cancer. In a further embodiment of the present disclosure, said cancer is chosen from bladder cancer, head and neck cancer, prostate cancer, breast cancer, lung cancer, uterus cancer, pancreatic cancer, liver cancer, renal cancer,  
15 ovarian cancer, colon cancer, stomach cancer, skin cancer, bone cancer, thyroid cancer, bile duct cancer, cerebral tumor, malignant myeloma, and lymphoproliferative tumors. In one embodiment of the present disclosure, said disease mediated through TLR7 is asthma, COPD, allergic rhinitis, allergic  
20 conjunctivitis, atopic dermatitis, hepatitis B, hepatitis C, HIV, HPV, bacterial infections, or dermatosis.

[0173]

According to a further aspect of the present disclosure, there is provided the use of at least one entity chosen from compounds  
25 of Formula (I) and pharmaceutically acceptable salts thereof

for the preparation of a medicament for the treatment or prophylaxis of cancer. In one embodiment of the present disclosure, said cancer is chosen from bladder cancer, head and neck cancer, prostate cancer, breast cancer, lung cancer, uterus cancer, pancreatic cancer, liver cancer, renal cancer, ovarian cancer, colon cancer, stomach cancer, skin cancer, cerebral tumor, malignant myeloma, and lymphoproliferative tumors.

[0174]

10 According to a further aspect of the present disclosure, there is provided the use of at least one entity chosen from compounds of Formula (I) and pharmaceutically acceptable salts thereof for the preparation of a medicament for the treatment or prophylaxis of asthma, COPD, allergic rhinitis, allergic  
15 conjunctivitis, atopic dermatitis, hepatitis B, hepatitis C, HIV, HPV, bacterial infections, or dermatosis.

[0175]

In one aspect of the present disclosure there is provided at least one entity chosen from compounds of Formula (I) and  
20 pharmaceutically acceptable salts thereof for use in the treatment of cancer.

[0176]

According to a further aspect of the present disclosure, there is provided a method of using at least one entity chosen from  
25 compounds of Formula (I) and pharmaceutically acceptable salts

thereof for the treatment or prophylaxis of cancer. Accordingly there is therefore provided a method of treating or prophylaxis cancer in a subject such as a warm-blooded animal, further such as a human, in need of such treatment or prophylaxis, which  
5 comprises administering to said subject a therapeutically effective amount of at least one entity chosen from compounds of Formula (I) and pharmaceutically acceptable salts thereof as defined herein. In one embodiment of the present disclosure, said cancer is chosen from bladder cancer, head and neck cancer,  
10 prostate cancer, breast cancer, lung cancer, uterus cancer, pancreatic cancer, liver cancer, renal cancer, ovarian cancer, colon cancer, stomach cancer, skin cancer, bone cancer, thyroid cancer, bile duct cancer, cerebral tumor, malignant myeloma, and lymphoproliferative tumors.

15 [0177]

According to a further aspect of the present disclosure, there is provided a method of using at least one entity chosen from compounds of Formula (I) and pharmaceutically acceptable salts thereof for the treatment or prophylaxis of asthma, COPD,  
20 allergic rhinitis, allergic conjunctivitis, atopic dermatitis, hepatitis B, hepatitis C, HIV, HPV, bacterial infections, or dermatosis.

[0178]

According to a further aspect of the present disclosure, there  
25 is provided a method of treating or prophylaxis a human

suffering from a disease in which activation of TLR7 is beneficial, comprising the steps of administering to a person in need thereof of a therapeutically effective amount of at least one entity chosen from compounds of Formula (I) and pharmaceutically acceptable salts thereof. In one embodiment of the present disclosure, the disease in which activation of TLR7 is beneficial is cancer. In a further embodiment of the present disclosure, said cancer is chosen from bladder cancer, head and neck cancer, prostate cancer, breast cancer, lung cancer, uterus cancer, pancreatic cancer, liver cancer, renal cancer, ovarian cancer, colon cancer, stomach cancer, skin cancer, bone cancer, thyroid cancer, bile duct cancer, cerebral tumor, malignant myeloma, and lymphoproliferative tumors. In one embodiment of the present disclosure, the disease in which activation of TLR7 is beneficial is asthma, COPD, allergic rhinitis, allergic conjunctivitis, atopic dermatitis, hepatitis B, hepatitis C, HIV, HPV, bacterial infections, or dermatosis.

[0179]

In any aspect or embodiment described herein, the cancer may be bladder cancer.

[0180]

In any aspect or embodiment described herein, the cancer may be head and neck cancer.

[0181]

In any aspect or embodiment described herein, the cancer may be prostate cancer.

[0182]

In any aspect or embodiment described herein, the cancer may  
5 be breast cancer.

[0183]

In any aspect or embodiment described herein, the cancer may be lung cancer.

[0184]

10 In any aspect or embodiment described herein, the cancer may be uterus cancer.

[0185]

In any aspect or embodiment described herein, the cancer may be pancreatic cancer.

15 [0186]

In any aspect or embodiment described herein, the cancer may be liver cancer.

[0187]

In any aspect or embodiment described herein, the cancer may  
20 be renal cancer.

[0188]

In any aspect or embodiment described herein, the cancer may be ovarian cancer.

[0189]

25 In any aspect or embodiment described herein, the cancer may

be colon cancer.

[0190]

In any aspect or embodiment described herein, the cancer may be stomach cancer.

5 [0191]

In any aspect or embodiment described herein, the cancer may be skin cancer.

[0192]

10 In any aspect or embodiment described herein, the cancer may be bone cancer.

[0193]

In any aspect or embodiment described herein, the cancer may be thyroid cancer.

[0194]

15 In any aspect or embodiment described herein, the cancer may be bile duct cancer.

[0195]

In any aspect or embodiment described herein, the cancer may be cerebral tumor.

20 [0196]

In any aspect or embodiment described herein, the cancer may be malignant myeloma cancer.

[0197]

25 In any aspect or embodiment described herein, the cancer may be lymphoproliferative tumors.

[0198]

The anticancer treatment or prophylaxis defined herein may be applied as a sole therapy or may involve, in addition to the compounds of the present disclosure, conventional surgery or  
5 radiotherapy or chemotherapy.

[0199]

Such conventional surgery could be applied before or after treatment with the compound of invention.

[0200]

10 Such radiotherapy could be administered concurrently, simultaneously, sequentially or separately to treatment with the compound of the invention and may include one or more of the external-beam radiation therapy, internal radiation therapy or systemic radiation therapy using a radioactive  
15 substance such as a radio-labelled monoclonal antibody.

[0201]

In a further aspect of the invention there is provided a combination comprising a compound of Formula (I), or a pharmaceutically acceptable salt thereof and radiotherapy,  
20 for use in the treatment of cancer.

[0202]

In a further aspect of the invention, there is provided a method of treating cancer in a warm blooded animal, such as man, in need of such treatment, which comprises administering to said  
25 animal an effective amount of a compound of Formula (I), or a

pharmaceutically acceptable salt thereof, in combination with an effective amount of radiotherapy.

[0203]

Such chemotherapy could be administered concurrently,  
5 simultaneously, sequentially or separately to treatment with the compound of the invention and may include one or more of the following non-limiting categories of anti-tumour agents:  
(i) other antiproliferative/antineoplastic drugs and combinations thereof, as used in medical oncology, such as  
10 alkylating agents (for example cis platin, oxaliplatin, carboplatin, miriplatin, cyclophosphamide, nitrogen mustard, melphalan, chlorambucil, busulphan, bendamustine temozolamide and nitrosoureas); antimetabolites (for example gemcitabine and antifolates such as fluoropyrimidines like 5 fluorouracil  
15 and tegafur, raltitrexed, methotrexate, cytosine arabinoside, hydroxyurea and purine analogues such as fludarabine); antitumour antibiotics (for example anthracyclines like adriamycin, bleomycin, doxorubicin, daunomycin, epirubicin, amrubicin, idarubicin, mitomycin-C, dactinomycin and  
20 mithramycin); antimitotic agents (for example vinca alkaloids like vincristine, vinblastine, vindesine and vinorelbine and taxoids like taxol and taxotere and polokinase inhibitors); and topoisomerase inhibitors (for example epipodophyllotoxins like etoposide and teniposide, amsacrine, topotecan and  
25 camptothecin);

(ii) cytostatic agents such as antioestrogens (for example tamoxifen, fulvestrant, toremifene, raloxifene, droloxifene and idoxifene), antiandrogens (for example bicalutamide, flutamide, nilutamide and cyproterone acetate), the androgen receptor antagonists MDV3100 or ARN-509 which prevent nuclear translocation of the androgen receptor and its binding to either DNA or coactivator proteins, inhibitors of CYP17A1 such as abiraterone (ZYTIGA™), and mixed inhibitors of androgen receptor function and CYP17A1 such as TOK-001 (galeterone), LHRH antagonists or LHRH agonists (for example goserelin, leuporelin and buserelin), progestogens (for example megestrol acetate), aromatase inhibitors (for example as anastrozole, letrozole, vorazole and exemestane), and inhibitors of 5 $\alpha$ -reductase such as finasteride;

(iii) anti-invasion agents [for example c-Src kinase family inhibitors like 4-(6-chloro-2,3-methylenedioxyanilino)-7-[2-(4-methylpiperazin-1-yl)ethoxy]-5-tetrahydropyran-4-yloxyquinazoline (AZD0530; International Patent Application WO 01/94341), N-(2-chloro-6-methylphenyl)-2-{6-[4-(2-hydroxyethyl)piperazin-1-yl]-2-methylpyrimidin-4-ylamino}thiazole-5-carboxamide (dasatinib, BMS-354825; J. Med. Chem., 2004, 47, 6658-6661) and bosutinib (SKI-606), and metalloproteinase inhibitors like marimastat, inhibitors of urokinase plasminogen activator receptor function, or antibodies to Heparanase;

(iv) inhibitors of growth factor function: for example such inhibitors include growth factor antibodies and growth factor receptor antibodies (for example the anti erbB2 antibody trastuzumab [Herceptin™], the anti-EGFR antibody panitumumab, the anti erbB1 antibody cetuximab [Erbix, C225] and any growth factor or growth factor receptor antibodies disclosed by Stern et al. Critical reviews in oncology/haematology, 2005, Vol. 54, pp11-29); such inhibitors also include tyrosine kinase inhibitors, for example, inhibitors of the epidermal growth factor family (for example EGFR family tyrosine kinase inhibitors such as

N-(3-chloro-4-fluorophenyl)-7-methoxy-6-(3-morpholinopropoxy)quinazolin-4-amine (gefitinib, ZD1839),  
N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)quinazolin-4-amine (erlotinib, OSI 774), and  
6-acrylamido-N-(3-chloro-4-fluorophenyl)-7-(3-morpholinopropoxy)-quinazolin-4-amine (CI 1033), erbB2 tyrosine kinase inhibitors such as lapatinib); inhibitors of the hepatocyte growth factor family; inhibitors of the insulin growth factor family; inhibitors of the platelet-derived growth factor family such as imatinib and/or nilotinib (AMN107); inhibitors of serine/threonine kinases (for example Ras/Raf signalling inhibitors such as farnesyl transferase inhibitors, for example sorafenib (BAY 43-9006), tipifarnib (R115777), BRAF inhibitor (Vemurafenib) and lonafarnib (SCH66336)), inhibitors of cell

signalling through MEK(e.g. Selumetinib) and/or AKT kinases, c-kit inhibitors, abl kinase inhibitors, PI3 kinase inhibitors, Plt3 kinase inhibitors, CSF-1R kinase inhibitors, IGF receptor (insulin-like growth factor) kinase inhibitors; aurora kinase inhibitors (for example AZD1152, PH739358, VX-680, MLN8054, R763, MP235, MP529, VX-528 AND AX39459), and cyclin dependent kinase inhibitors such as CDK2 and/or CDK4 inhibitors;

(v) antiangiogenic agents such as those which inhibit the effects of vascular endothelial growth factor, [for example the anti vascular endothelial cell growth factor antibody bevacizumab (AVASTIN™) and for example, a VEGF receptor tyrosine kinase inhibitor such as vandetanib (ZD6474), vatalanib (PTK787), sunitinib (SU11248), axitinib (AG-013736), pazopanib (GW 786034), and 4-(4-fluoro-2-methylindol-5-yloxy)-6-methoxy-7-(3-pyrrolidin-1-ylpropoxy)quinazoline (AZD2171; Example 240 within WO 00/47212), compounds such as those disclosed in International Patent Applications WO97/22596, WO 97/30035, WO 97/32856, and WO 98/13354 and compounds that work by other mechanisms (for example linomide, inhibitors of integrin  $\alpha v \beta 3$  function and angiostatin)];

(vi) vascular damaging agents such as Combretastatin A4 and compounds disclosed in International Patent Applications WO 99/02166, WO 00/40529, WO 00/41669, WO 01/92224, WO 02/04434, and WO 02/08213;

(vii) an endothelin receptor antagonist, for example zibotentan (ZD4054) or atrasentan;

(viii) antisense therapies, for example those which are directed to the targets listed above, such as ISIS 2503, an anti-ras antisense;

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

(x) immunotherapy approaches, including, for example, approaches to inhibit immune checkpoint such as anti-CTLA4 antibody ipilimumab (Yervoy™), anti-CTLA4 antibody (MEDI-1123), anti-PD1 antibody (BMS-936558, or MK3475), or anti-PDL1 antibody (BMS-936559), approaches to stimulate immune response such as anti-CD40 antibody (HCD-122), anti-OX-40 antibody, or anti-4-1BB antibody (BMS-663513 or PF-05082566), approaches to induce apoptosis such as anti-TRAIL antibody (AMG-951), anti-TRAIL-R1 antibody (HGS-ETR1), or anti-TRAIL-R2 antibody (AMG-655), ex vivo and in vivo approaches to increase the immunogenicity of patient tumour cells, such as transfection with cytokines such as interleukin 2, interleukin 4 or granulocyte macrophage colony stimulating

factor, approaches to decrease T cell anergy, approaches using transfected immune cells such as cytokine transfected dendritic cells, approaches using cytokine transfected tumour cell lines and approaches using anti idiotypic antibodies, approaches to  
5 decrease the function of immune suppressive cells such as regulatory T cells, myeloid-derived suppressor cells or IDO (indoleamine 2,3,-deoxygenase)-expressing dendritic cells, and approaches using cancer vaccines consisting of proteins or peptides derived from tumour-associated antigens such as  
10 NY-ESO-1, MAGE-3, WT1, or Her2/neu.

[0204]

According to another aspect of the present disclosure, there is provided a pharmaceutical product comprising at least one entity chosen from compounds of Formula (I) and  
15 pharmaceutically acceptable salts thereof as defined herein and at least one additional anti-tumour substance as defined herein for the conjoint treatment of cancer.

[0205]

According to this aspect of the present disclosure, there is  
20 provided a pharmaceutical product comprising at least one entity chosen from compounds of Formula (I) and pharmaceutically acceptable salts thereof as defined herein, and at least one additional anti-tumour substance as defined herein for the conjoint treatment of cancer.

25 [0206]

According to this aspect of the present disclosure, there is provided a pharmaceutical product comprising at least one entity chosen from compounds of Formula (I) and pharmaceutically acceptable salts thereof as defined herein, and at least one additional anti-tumour substance for the conjoint treatment of cancer.

[0207]

According to this aspect of the present disclosure, there is provided a combination suitable for use in the treatment of cancer comprising at least one entity chosen from compounds of Formula (I) and pharmaceutically acceptable salts thereof, and at least one anti-tumour agents chosen from the anti-tumour agents listed under (i)-(ix) above.

[0208]

According to this aspect of the invention there is provided a combination suitable for use in the treatment of cancer comprising a compound of Formula (I) as defined hereinbefore, or a pharmaceutically acceptable salt thereof, and any one of the anti-tumour agents listed under (i)-(x) above.

[0209]

Therefore in a further aspect of the present disclosure, there is provided at least one entity chosen from compounds of Formula (I) and pharmaceutically acceptable salts thereof in combination with at least one anti-tumour agent chosen from those listed under (i)-(ix) herein above.

[0210]

Therefore in a further aspect of the invention there is provided a compound of Formula (I), or a pharmaceutically acceptable salt thereof, in combination with an anti-tumour agent selected from  
5 one listed under (i)-(x) herein above.

[0211]

In one embodiment there is provided a combination comprising a compound of Formula (I), or a pharmaceutically acceptable salt thereof and gemcitabine, for use in the treatment of cancer.  
10 In one embodiment there is provided a combination comprising a compound of Formula (I), or a pharmaceutically acceptable salt thereof and an anti-CTLA4 antibody (such as Yervoy™ or MEDI-1123), for use in the treatment of cancer.

[0212]

15 In one embodiment there is provided a combination comprising a compound of Formula (I), or a pharmaceutically acceptable salt thereof and an anti-PDL1 antibody (such as BMS-936559), for use in the treatment of cancer.

[0213]

20 Herein, where the term "combination" is used, it is to be understood that this refers to simultaneous, separate, or sequential administration. In one embodiment, "combination" refers to simultaneous administration. In another embodiment, "combination" refers to separate administration.

25 [0214]

In a further embodiment, "combination" refers to sequential administration. Where the administration is sequential or separate, the delay in administering the second component should not be such as to lose the beneficial effect of the combination.

[0215]

According to a further aspect of the present disclosure, there is provided a pharmaceutical composition which comprises at least one entity chosen from compounds of Formula (I) and pharmaceutically acceptable salts thereof in combination with an anti-tumour agent chosen from those listed under (i)-(ix) herein above, in association with at least one pharmaceutically acceptable diluent or carrier.

[0216]

According to a further aspect of the invention there is provided a pharmaceutical composition which comprises a compound of Formula (I), or a pharmaceutically acceptable salt thereof, in combination with an anti-tumour agent selected from one listed under (i)-(x) herein above, in association with a pharmaceutically acceptable diluent or carrier.

[0217]

According to a further aspect of the present disclosure, there is provided a pharmaceutical composition which comprises at least one entity chosen from compounds of Formula (I) and pharmaceutically acceptable salts thereof in combination with

at least one anti-tumour agent chosen from those listed under (i)-(ix) herein above, in association with at least one pharmaceutically acceptable diluent or carrier for use in the treatment of cancer.

5 [0218]

According to a further aspect of the invention there is provided a pharmaceutical composition which comprises a compound of Formula (I), or a pharmaceutically acceptable salt thereof, in combination with an anti-tumour agent selected from one listed  
10 under (i)-(x) herein above, in association with a pharmaceutically acceptable diluent or carrier for use in the treatment of cancer.

[0219]

According to another feature of the present disclosure, there  
15 is provided the use of at least one entity chosen from compounds of Formula (I) and pharmaceutically acceptable salts thereof, in combination with at least one anti-tumour agent chosen from those listed under (i)-(ix) herein above, in the manufacture of a medicament for use in cancer in a warm blooded animal, such  
20 as human.

[0220]

According to a further aspect of the invention there is provided a pharmaceutical composition which comprises a compound of Formula (I), or a pharmaceutically acceptable salt thereof, in  
25 combination with an anti-tumour agent selected from one listed

under (i)-(x) herein above, in association with a pharmaceutically acceptable diluent or carrier for use in the treatment of cancer.

[0221]

5 According to another feature of the present disclosure, there is provided at least one entity chosen from compounds of Formula (I) and pharmaceutically acceptable salts thereof, in combination with at least one anti-tumour agent chosen from those listed under (i)-(ix) herein above for use in the  
10 treatment of cancer in a warm blooded animal, such as human.

[0222]

According to another feature of the invention there is provided a compound of the Formula (I), or a pharmaceutically acceptable salt thereof, in combination with an anti-tumour agent selected  
15 from one listed under (i)-(x) herein above for use in the treatment of cancer in a warm blooded animal, such as man.

[0223]

Therefore in an additional feature of the present disclosure, there is provided a method of treating cancer in a warm blooded  
20 animal, such as human, in need of such treatment which comprises administering to said animal a therapeutically effective amount of at least one entity chosen from compounds of Formula (I) and pharmaceutically acceptable salts thereof, in combination with at least one anti-tumour agent chosen from those listed under  
25 (i)-(ix) herein above.

[0224]

Therefore in an additional feature of the invention, there is provided a method of treating cancer in a warm blooded animal, such as man, in need of such treatment which comprises  
5 administering to said animal an effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, in combination with an anti-tumour agent selected from one listed under (i)-(x) herein above.

[0225]

10 According to a further aspect of the present disclosure, there is provided a kit comprising at least one entity chosen from compounds of Formula (I) and pharmaceutically acceptable salts thereof, in combination with at least one anti-tumour agent chosen from those listed under (i)-(ix) herein above.

15 [0226]

According to a further aspect of the present invention there is provided a kit comprising a compound of Formula (I), or a pharmaceutically acceptable salt thereof, in combination with an anti-tumour agent selected from one listed under (i)-(x)  
20 herein above.

[0227]

According to a further aspect of the present disclosure, there is provided a kit comprising:

a) at least one entity chosen from compounds of Formula (I) and  
25 pharmaceutically acceptable salts thereof, in a first unit

dosage form;

b) at least one anti-tumour agent chosen from the anti-tumour agents listed under (i)-(ix) herein above, in a second unit dosage form; and

5 c) container means for containing at least said first and second dosage forms.

According to a further aspect of the present disclosure, there is provided a kit comprising at least one entity chosen from compounds of Formula (I) and pharmaceutically acceptable salts thereof, in combination with at least one additional  
10 anti-tumour agent.

[0228]

According to a further aspect of the present invention there is provided a kit comprising:

15 a) a compound of Formula (I), or a pharmaceutically acceptable salt thereof, in a first unit dosage form;

b) an anti-tumour agent selected from one listed under (i)-(x) herein above; in a second unit dosage form; and

c) container means for containing said first and second dosage  
20 forms.

[0229]

According to a further aspect of the present invention there is provided a kit comprising a compound of Formula (I), or a pharmaceutically acceptable salt thereof, in combination with  
25 an additional anti-tumour agent.

[0230]

According to a further aspect of the present disclosure, there is provided a kit comprising:

- a) at least one entity chosen from compounds of Formula (I) and pharmaceutically acceptable salts thereof, in a first unit dosage form;
- b) at least one second anti-tumour agent in a second unit dosage form; and
- c) container means for containing said first and second dosage forms.

[0231]

In one aspect of the present disclosure, the at least one entity chosen from compounds of Formula (I) and pharmaceutically acceptable salts thereof may be useful as vaccine adjuvants.

[0232]

As a further aspect of the present disclosure, there is provided at least one entity chosen from compounds of Formula (I) and pharmaceutically acceptable salts thereof, as defined herein, for use as a vaccine adjuvant.

[0233]

As a further aspect of the present disclosure, there is provided the use of at least one entity chosen from compounds of Formula (I) and pharmaceutically acceptable salts thereof, as defined herein, as a vaccine adjuvant, in the manufacture of a vaccine for the treatment of a disease or condition.

[0234]

The present disclosure still further provides a method of treating, or reducing the risk of, a disease or condition, which method comprises administering to a patient in need thereof a  
5 therapeutically effective amount of a vaccine and at least one entity chosen from compounds of Formula (I) and pharmaceutically acceptable salts thereof, as defined herein.

[0235]

The present disclosure still further provides a method of  
10 increasing the response to a vaccine in a patient, which method comprises administering to a patient in need thereof a therapeutically effective amount of a vaccine and at least one entity chosen from compounds of Formula (I) and pharmaceutically acceptable salts thereof, as defined herein.

15 [0236]

Experimental Procedures (Chemical Syntheses and Biological Assays)

In the experimental procedures described below, the following abbreviations may be used:

20 "EtOAc" = ethyl acetate; "min(s)" = minute(s); "THF" = tetrahydrofuran; "DMF" = N,N-dimethylformamide; "NaH" = sodium hydride; "M" = mol/L; "h" = hour(s); "Amino silica gel" = flash column chromatography using silica that is surface-modified by aminopropyl (HiFlash Column Amino 40  $\mu$ M 60 A; Cat. No. W091,  
25 W092 or W093 packed with silica gel that is surface-modified

by aminopropyl, purchased from Yamazen Science, Inc); "DMSO" = dimethylsulfoxide; "Mes" = mesitylenyl; "Ms" = methanesulfonyl; "sat." = saturated aqueous solution; "RT" = room temperature; "LC-MS" = liquid chromatography with mass spectrometry; "m/z" = measured mass to charge ratio; "M" = molarity; "EtOH" = ethanol. Proton nuclear magnetic resonance data ( $^1\text{H}$  NMR) was generally obtained at 300-500 MHz and using deuterated DMSO unless otherwise stated. Abbreviations used for  $^1\text{H}$  NMR are: "s" = singlet, "d" = doublet; "t" = triplet; "q" = quartet; "m" = multiplet; "dd" = doublet of doublets; "br s" = broad singlet; "dt" = doublet of triplets, "td" = triplet of doublets, etc.

[0237]

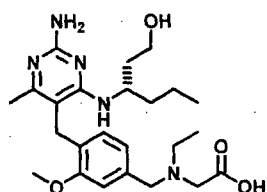
Preparative reverse phase HPLC ("RPHPLC") was carried out using a Phenomenex Gemini<sup>TM</sup> C18 5  $\mu\text{m}$  column, using  $\text{CH}_3\text{CN}$  in an aqueous 0.1%  $\text{NH}_3$  solution as eluent. Fractions were collected following detection by UV spectroscopy at a wavelength such as 220 or 254 nm.

**Examples**

[0238]

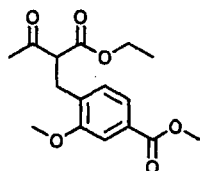
Example 1:

(S)-2-((4-((2-amino-4-(1-hydroxyhexan-3-ylamino)-6-methylpyrimidin-5-yl)methyl)-3-methoxybenzyl)(ethylamino)acetic acid



The title compound was prepared as described below:

(i) Methyl  
3-methoxy-4-(2-(methoxycarbonyl)-3-oxobutyl)benzoate

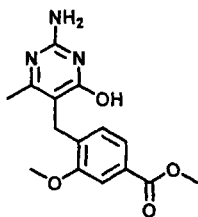


NaH (60% in mineral oil, 1.5 g) was added portion-wise over 10 mins to a solution of ethyl acetoacetate (4.4 mL) in THF (60 mL) at 0 °C. The mixture was then stirred for 10 mins. Then, a solution of methyl 4-(bromomethyl)-3-methoxybenzoate (7.5 g) in THF (40 mL) was added and the mixture was warmed to 70°C and stirred for 15 h. The mixture was then poured into ice/water (300 mL) and stirred for 30 mins. The resulting aqueous mixture was extracted with EtOAc. The organic extracts were combined, dried and concentrated in vacuo to provide crude product. The reaction was repeated on the same scale. The two batches of crude

product were combined and purified by flash column chromatography on silica gel to give the sub-title compound (15 g) as a colourless oil;  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  = 7.48 (1H, dd), 7.45 (1H, d), 7.24 (1H, d), 4.05 (2H, q), 3.95 (1H, dd), 3.86 (3H, s), 3.84 (3H, s), 3.10 (1H, dd), 3.00 (1H, dd), 2.17 (3H, s), 1.09 (3H, t).

[0239]

(ii) Methyl  
4-((2-amino-4-hydroxy-6-methylpyrimidin-5-yl)methyl)-3-methoxybenzoate  
10 oxybenzoate

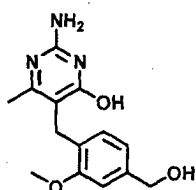


Guanidinium carbonate (7.2 g) was added to a solution of the product from step (i) (9.0 g) in EtOH (60 mL) and the mixture was then heated at 80 °C for 15 h. After cooling the resulting solid was collected by filtration. This solid was then suspended in water and collected by filtration. The solid was then washed with EtOAc and dried to give the sub-title compound (5.8 g) as a colourless solid, which was used without further purification;  $^1\text{H}$  NMR (300 MHz,  $d_6$ -DMSO)  $\delta$  = 10.78 (1H, s), 7.46 (1H, d), 7.45 (1H, s), 6.98 (1H, d), 6.42 (2H, s), 3.89 (3H, s), 3.83 (3H, s), 3.61 (2H, s), 1.93 (3H, s); LC-MS: m/z 304.

[0240]

(iii)

2-amino-5-(4-(hydroxymethyl)-2-methoxybenzyl)-6-methylpyrimidin-4-ol

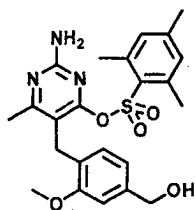


5 Lithium triethylborohydride (93 mL) was added to a solution of the product from step (ii) (5.0 g) in THF (25mL) over 5 min and the reaction mixture was stirred at RT for 3.5 h. Water (60 mL) and 2M-hydrogen chloride (40 mL) was added to the mixture. The organic solvent was removed by evaporation. 2M-hydrogen  
10 chloride (16 mL) was added and the mixture was stirred at RT for 4 h. The mixture was neutralized by saturated aqueous sodium hydrogen carbonate. The precipitate was collected by filtration, washed with water and dried in vacuo at 50 °C to afford the sub-title compound (4.7 g) as a white solid; <sup>1</sup>H NMR (300 MHz, d<sub>6</sub>-DMSO); 10.76 (1H, br s), 6.89 (1H, s), 6.77-6.70 (2H, m), 6.30 (2H, br s), 5.10 (1H, t), 4.42 (2H, d), 3.79 (3H, s), 3.51  
15 (2H, s), 1.91 (3H, s).

[0241]

(iv)

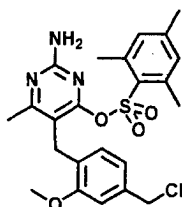
20 2-amino-5-(4-(hydroxymethyl)-2-methoxybenzyl)-6-methylpyrimidin-4-yl 2,4,6-trimethylbenzenesulfonate



2-Mesitylenesulfonyl chloride (7.2 g) was added to a suspension of diisopropylethylamine (5.5 mL) and the product from step (iii) (6.1 g) in THF (200 mL) and the mixture was stirred under reflux for 12 h. The resulting mixture was diluted with water and extracted with EtOAc. The combined organic layer was washed with brine, dried and concentrated under reduced pressure. The residue was purified by flash column chromatography on amino silica gel to afford the sub-title compound (8.6 g) as a white solid;  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ); 6.92 (2H, s), 6.86 (1H, s), 6.77 (2H, s), 4.67 (2H, br s), 4.64 (2H, d), 3.82 (3H, s), 3.81 (2H, s), 2.57 (6H, s), 2.29 (3H, s), 2.21 (3H, s), 1.81 (1H, t). [0242]

(v)

2-amino-5-(4-(chloromethyl)-2-methoxybenzyl)-6-methylpyrimidin-4-yl 2,4,6-trimethylbenzenesulfonate

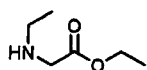


Methanesulfonyl chloride (1.4 mL) was added to a mixture of lithium chloride (0.74 g) and the product from step (iv) (4.0

g) in THF (45 mL). The mixture was stirred at RT for 1.5 h, diluted with water and extracted with EtOAc. The combined organic layer was washed with brine, dried and concentrated under reduced pressure to afford the crude product as a pale yellow oil, which was used for next reaction without further purification; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>); 6.91 (2H, s), 6.83 (1H, s), 6.81-6.74 (2H, m), 4.69 (2H, br s), 4.54 (2H, s), 3.82 (3H, s), 3.80 (2H, s), 2.54 (6H, s), 2.29 (3H, s), 2.24 (3H, s).

[0243]

10 (vi) ethyl 2-(ethylamino)acetate



Sulfuric acid (3 mL) was added to a solution of N-ethylglycine (2.0 g) in EtOH (15 mL) and the mixture was stirred under reflux for 9 h. The mixture was cooled to RT and neutralized with 5M-sodium hydroxide, and saturated aqueous sodium hydrogen carbonate. The solution was extracted with EtOAc, the combined organic layer was washed with brine, dried and concentrated under reduced pressure. The sub-title compound (1.4 g) was obtained as a pale yellow oil; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>); 4.17 (2H, q), 3.38 (2H, s), 2.63 (2H, q), 1.25 (3H, t), 1.10 (3H, t).

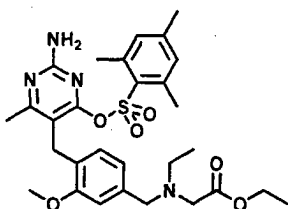
[0244]

(vii)

ethyl

2-((4-((2-amino-4-(mesitylsulfonyloxy)-6-methylpyrimidin-5-

yl)methyl)-3-methoxybenzyl)(ethyl)amino)acetate



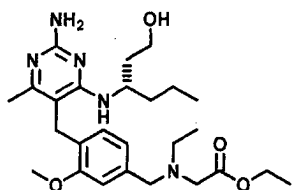
The product from step (vi) (390 mg) was added to the mixture of potassium dicarbonate (410 mg), potassium iodide (49 mg) and the crude product from step (v) in acetonitrile (5 mL). After the mixture was stirred at 70 °C for 4 h, the reaction mixture was cooled to RT, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography to afford the sub-title compound (490 mg) as a colourless amorphous solid; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>); 6.91 (2H, s), 6.87 (1H, s), 6.72 (2H, s), 4.65 (2H, br s), 4.14 (2H, q), 3.82-3.79 (5H, m), 3.70 (2H, s), 3.28 (2H, s), 2.67 (2H, q), 2.56 (6H, s), 2.28 (3H, s), 2.23 (3H, s), 1.25 (3H, t), 1.07 (3H, t).

[0245]

(viii)

(S)-ethyl

2-((4-((2-amino-4-(1-hydroxyhexan-3-ylamino)-6-methylpyrimidin-5-yl)methyl)-3-methoxybenzyl)(ethyl)amino)acetate



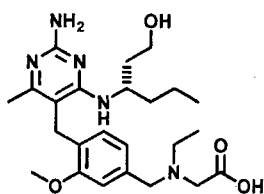
Trifluoroacetic acid (0.066 mL) was added to a mixture of

(S)-3-aminohexan-1-ol (300 mg) and the product from step (vii) (490 mg) in propionitrile (5 mL). The mixture was heated at 120 °C for 16 h and cooled to RT. The solvent was removed by evaporation. The residue was purified by flash column chromatography on amino silica gel to afford the sub-title compound (330 mg) as a colourless gum; <sup>1</sup>H NMR (CDCl<sub>3</sub>); 6.94 (1H, s), 6.88 (1H, d), 6.79 (1H, d), 4.66 (1H, d), 4.58 (2H, br s), 4.13 (2H, q), 4.11-4.06 (1H, m), 3.88 (3H, s), 3.70 (2H, s), 3.66 (2H, s), 3.42 (1H, ddd), 3.28-3.20 (3H, m), 2.65 (2H, q), 2.34 (3H, s), 1.82-1.74 (1H, m), 1.45-1.33 (1H, m), 1.26-1.21 (5H, m), 1.07-1.02 (5H, m), 0.73 (3H, t).

[0246]

(ix)

(S)-2-((4-((2-amino-4-(1-hydroxyhexan-3-ylamino)-6-methylpyrimidin-5-yl)methyl)-3-methoxybenzyl)(ethylamino)acetic acid



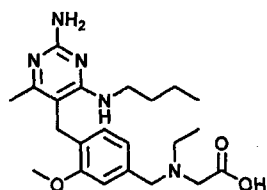
3M-sodium hydroxide (1 mL) was added to a solution of the product from step (viii) (310 mg) in methanol (3 mL). The solution was stirred at RT for 16 h. The reaction mixture was neutralized with 4M-hydrogen chloride (1mL) and extracted with chloroform/EtOH (3/1). The combined organic layer was dried and concentrated under reduced pressure to afford the sub-title

compound (300 mg) as a colourless amorphous solid;  $^1\text{H}$  NMR (DMSO);  
 7.00 (1H, s), 6.79 (1H, d), 6.72 (1H, d), 5.87 (2H, br s), 5.63  
 (1H, d), 4.20-4.14 (1H, m), 3.83 (3H, s), 3.76 (2H, s), 3.60  
 (2H, s), 3.27 (2H, q), 3.13 (2H, s), 2.66 (2H, q), 2.02 (3H,  
 5 s), 1.60-1.51 (1H, m), 1.45-1.31 (3H, m), 1.13-1.06 (2H, m),  
 1.00 (3H, t), 0.75 (3H, t).

[0247]

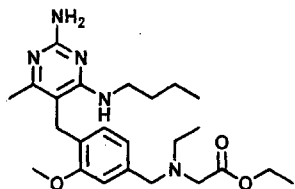
Example 2:

2-((4-((2-amino-4-(butylamino)-6-methylpyrimidin-5-yl)methy  
 10 1)-3-methoxybenzyl) (ethyl)amino)acetic acid



The title compound was prepared by the sequence of steps  
 described below:

(i) ethyl  
 15 2-((4-((2-amino-4-(butylamino)-6-methylpyrimidin-5-yl)methy  
 1)-3-methoxy- benzyl) (ethyl) amino)acetate



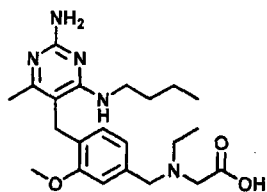
The sub-title compound was synthesized by the method of example  
 1 step (viii) from the product of example 1 step (vii) (150 mg)  
 20 and 1-butylamine (56 mg). The sub-title compound (77 mg) was  
 obtained as a yellow oil;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ); 6.94 (1H, s), 6.86

(1H, d), 6.77 (1H, d), 4.84 (1H, t), 4.55 (2H, br s), 4.13 (2H, q), 3.88 (3H, s), 3.70 (2H, s), 3.64 (2H, s), 3.30-3.23 (4H, m), 2.66 (2H, q), 2.30 (3H, s), 1.43-1.34 (2H, m), 1.24 (3H, t), 1.19-1.12 (2H, m), 1.06 (3H, t), 0.83 (3H, t).

5 [0248]

(ii)

2-((4-((2-amino-4-(butylamino)-6-methylpyrimidin-5-yl)methyl)-3-methoxybenzyl)(ethyl)amino)acetic acid



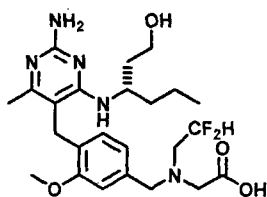
10 The sub-title compound was synthesized by the method of example 1 step (ix) from the product of step (i) (71 mg). The sub-title compound (74 mg) was obtained as a cream solid; <sup>1</sup>H NMR (DMSO); 7.00 (1H, s), 6.77 (1H, d), 6.65 (1H, d), 6.09 (1H, t), 5.85 (2H, br s), 3.83 (3H, s), 3.76 (2H, s), 3.58 (2H, s), 3.22 (2H, dt), 3.15 (2H, s), 2.66 (2H, q), 1.96 (3H, s), 1.44-1.34 (2H, m), 1.23-1.10 (2H, m), 1.00 (3H, t), 0.81 (3H, t).

[0249]

Example 3:

(S)-2-((4-((2-amino-4-(1-hydroxyhexan-3-ylamino)-6-methylpyrimidin-5-yl)methyl)-3-methoxybenzyl)(2,2-difluoroethyl)amino)acetic acid

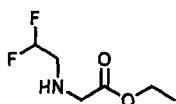
20



The title compound was prepared by the sequence of steps described below:

(i) ethyl 2-(2,2-difluoroethylamino)acetate

5



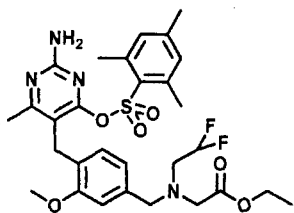
10

2,2-difluoroethylamine (4.0 g) was added to a suspension of ethyl bromoacetate (5.4 mL), potassium iodide (0.82 g), diisopropylethylamine (9.8 mL) in acetonitrile (100 mL) and the mixture was stirred at RT for 25 h. The mixture was concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel to afford the sub-title compound (7.0 g) as a colorless oil; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>); 5.82 (1H, tt), 4.18 (2H, q), 3.46 (2H, s), 3.00 (2H, dt), 1.26 (3H, t).

[0250]

15

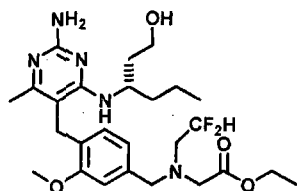
(ii) ethyl 2-((4-((2-amino-4-(mesitylsulfonyloxy)-6-methylpyrimidin-5-yl)methyl)-3-methoxybenzyl)(2,2-difluoroethyl)amino)acetate



The sub-title compound was synthesized by the method of example 1 step (vii) from the product of step (i) (490 mg) and example 1 step (v) (470 mg). The sub-title compound (520 mg) was obtained as a colourless amorphous solid;  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ); 6.91 (2H, s), 6.83 (1H, s), 6.76-6.72 (2H, m), 5.75 (1H, tt), 4.65 (2H, br s), 4.10 (2H, q), 3.85 (2H, s), 3.79 (5H, s), 3.11-3.01 (4H, m), 2.55 (6H, s), 2.29 (3H, s), 2.24 (3H, s), 1.25 (3H, t).

[0251]

(iii) (S)-ethyl 2-((4-((2-amino-4-(1-hydroxyhexan-3-ylamino)-6-methylpyrimidin-5-yl)methyl)-3-methoxybenzyl)(2,2-difluoroethyl)amino)acetate



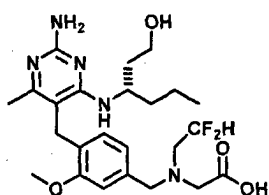
The sub-title compound was synthesized by the method of example 1 step (viii) from the product of step (ii) (520 mg) and (S)-3-aminohexan-1-ol (300 mg). The sub-title compound (340 mg) was obtained as a colourless gum;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ); 6.90-6.88 (2H, m), 6.78 (1H, d), 5.73 (1H, tt), 4.60 (1H, d), 4.55 (2H, br s), 4.15 (2H, q), 4.11-4.03 (1H, m), 3.88 (3H, s), 3.85 (2H, s), 3.66 (2H, s), 3.47-3.37 (3H, m), 3.25 (1H, ddd), 3.04 (2H, dt), 2.33 (3H, s), 1.83-1.73 (1H, m), 1.51-1.32 (3H, m), 1.25 (3H,

t), 1.06-0.99 (2H, m), 0.73 (3H, t).

[0252]

(iv)

(S)-2-((4-((2-amino-4-(1-hydroxyhexan-3-ylamino)-6-methylpyrimidin-5-yl)methyl)-3-methoxybenzyl)(2,2-difluoroethyl)amino)acetic acid

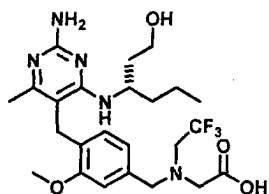


The sub-title compound was synthesized by the method of example 1 step (ix) from the product of step (iii) (330 mg). The sub-title compound (330 mg) was obtained as a colourless amorphous solid; <sup>1</sup>H NMR (DMSO); 6.94 (1H, s), 6.76-6.70 (2H, m), 6.40 (2H, br s), 6.02 (1H, tt), 5.93 (1H, d), 4.24-4.17 (1H, m), 3.82 (5H, s), 3.60 (2H, s), 3.31-3.25 (4H, m), 3.03 (2H, dt), 2.02 (3H, s), 1.60-1.54 (1H, m), 1.48-1.43 (1H, m), 1.38-1.32 (2H, m), 1.12-1.03 (2H, m), 0.75 (3H, t).

[0253]

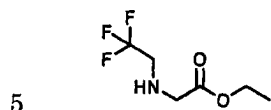
Example 4:

(S)-2-((4-((2-amino-4-(1-hydroxyhexan-3-ylamino)-6-methylpyrimidin-5-yl)methyl)-3-methoxybenzyl)(2,2,2-trifluoroethyl)amino)acetic acid



The title compound was prepared by the sequence of steps described below:

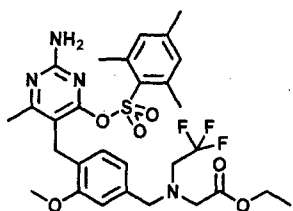
(i) ethyl 2-(2,2,2-trifluoroethylamino)acetate



2,2,2-trifluoroethylamine (2.0 g) was added to a suspension of ethyl bromoacetate (2.3 mL), potassium iodide (0.34 g) in diisopropylethylamine (3.3 mL) and the mixture was stirred at RT for 5.5 h. The mixture was diluted with diethyl ether (30 mL), stirred at RT for 30 mins. The suspension was filtered and concentrated under reduced pressure. The sub-title compound (2.6 g) was obtained as a yellow oil;  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ); 4.19 (2H, q), 3.50 (2H, s), 3.22 (2H, q), 1.26 (3H, t).

[0254]

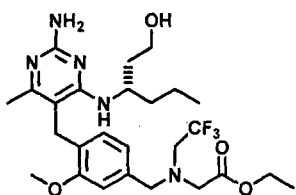
15 (ii) ethyl 2-((4-((2-amino-4-(mesitylsulfonyloxy)-6-methylpyrimidin-5-yl)methyl)-3-methoxybenzyl)(2,2,2-trifluoroethylamino)acetate



The sub-title compound was synthesized by the method of example 1 step (vii) from the product of step (i) (190 mg) and example 1 step (v) (500 mg). The sub-title compound (360 mg) was obtained as a yellow oil; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>); 6.91 (2H, s), 6.86 (1H, s), 6.76-6.68 (2H, m), 4.67 (2H, br s), 4.15 (2H, q), 3.95 (2H, s), 3.79 (5H, s), 3.45 (2H, s), 3.35 (2H, q), 2.53 (6H, s), 2.29 (3H, s), 2.24 (3H, s), 1.04 (3H, t).

[0255]

- 10 (iii) (S)-ethyl 2-((4-((2-amino-4-(1-hydroxyhexan-3-ylamino)-6-methylpyrimidin-5-yl)methyl)-3-methoxybenzyl)(2,2,2-trifluoroethyl)amino)acetate



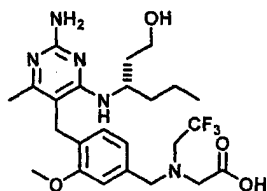
- 15 The sub-title compound was synthesized by the method of example 1 step (viii) from the product of step (ii) (61 mg) and (S)-3-amino-1-hexanol (34 mg). The sub-title compound (24 mg) was obtained as a pale yellow gum; <sup>1</sup>H NMR (CDCl<sub>3</sub>); 6.93 (1H, s), 6.89 (1H, d), 6.76 (1H, d), 4.62-4.59 (3H, m), 4.15 (2H, q),

4.10-4.04 (1H, m), 3.91 (2H, s), 3.87 (3H, s), 3.66 (2H, s),  
3.44 (2H, s), 3.37-3.20 (4H, m), 2.33 (3H, s), 1.82-1.69 (1H,  
m), 1.42-1.32 (3H, m), 1.24 (3H, t), 1.09-0.98 (2H, m), 0.73  
(3H, t).

5 [0256]

(iv)

(S)-2-((4-((2-amino-4-(1-hydroxyhexan-3-ylamino)-6-methylpyrimidin-5-yl)methyl)-3-methoxybenzyl)(2,2,2-trifluoroethylamino)acetic acid



10

The sub-title compound was synthesized by the method of example 1 step (ix) from the product of step (iii) (20 mg). The sub-title compound (20 mg) was obtained as a pale yellow solid; <sup>1</sup>H NMR (DMSO); 6.90 (1H, s), 6.71 (2H, s), 5.79 (2H, br s), 5.52 (1H, d), 4.17-4.10 (1H, m), 3.87 (2H, s), 3.81 (3H, s), 3.58 (2H, s), 3.54-3.44 (2H, m), 3.23- 3.17 (2H, m), 2.95 (2H, s), 2.03 (3H, s), 1.59-1.50 (1H, m), 1.45-1.23 (3H, m), 1.14-1.05 (2H, m), 0.76 (3H, t).

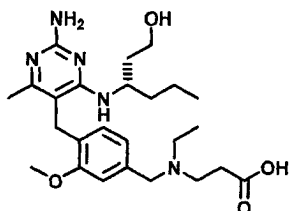
15

[0257]

20 Example 5:

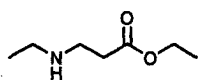
(S)-3-((4-((2-amino-4-(1-hydroxyhexan-3-ylamino)-6-methylpyrimidin-5-yl)methyl)-3-methoxybenzyl)(ethylamino)propanoic

acid



The title compound was prepared by the sequence of steps described below:

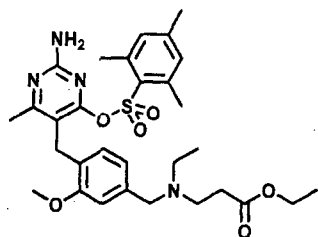
- 5 (i) ethyl 3-(ethylamino)propanoate



- A solution of ethylamine (70% in water, 5.8 mL) in EtOH (30 mL) was added to a suspension of ethyl acrylate (2.0 g) in EtOH (20 mL) at 0 °C and the mixture was stirred at RT for 30 mins. The mixture was concentrated under reduced pressure. The residue was purified by flash column chromatography on amino silica gel to afford the sub-title compound (2.4 g) as a pale yellow oil; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>); 4.13 (2H, q), 2.88 (2H, t), 2.66 (2H, q), 2.52 (2H, t), 1.24 (2H, t), 1.11 (3H, t).
- 10

- 15 [0258]

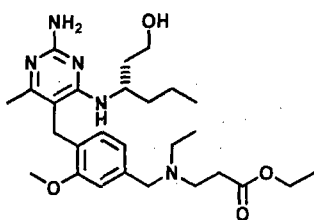
(ii) ethyl  
3-((4-((2-amino-4-(mesitylsulfonyloxy)-6-methylpyrimidin-5-yl)methyl)-3-methoxybenzyl)(ethylamino)propanoate



The sub-title compound was synthesized by the method of example 1 step (vii) from the product of step (i) and example 1 step (v) (3.1 g). The sub-title compound (2.7 g) was obtained as a yellow gum;  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ); 6.91 (2H, s), 6.82 (1H, s), 6.70 (2H, s), 4.65 (2H, br s), 4.10 (2H, q), 3.82-3.79 (5H, m), 3.51 (2H, s), 2.79 (2H, t), 2.56 (6H, s), 2.51-2.45 (4H, m), 2.28 (3H, s), 2.24 (3H, s), 1.21 (3H, t), 1.01 (3H, t).

[0259]

(iii) (S)-ethyl 3-((4-((2-amino-4-(1-hydroxyhexan-3-ylamino)-6-methylpyrimidin-5-yl)methyl)-3-methoxybenzyl)(ethylamino)propanoate



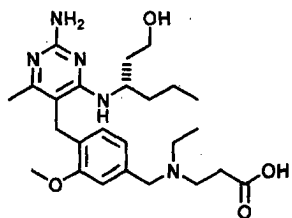
The sub-title compound was synthesized by the method of example 1 step (viii) from the product of step (ii) (2.7 g) (S)-3-amino-1-hexanol (1.6 g). The sub-title compound (670 mg) was obtained as a colourless gum;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ); 6.93 (1H, s), 6.86 (1H, d), 6.76 (1H, d), 4.80-4.65 (3H, m), 4.09 (2H, q), 3.88 (3H, s), 3.65 (2H, s), 3.50 (2H, s), 3.42-3.37 (1H, m),

3.24 (1H, ddd), 2.77 (2H, t), 2.46-2.41 (4H, m), 2.02 (3H, s),  
1.82-1.72 (1H, m), 1.42-1.29 (1H, m), 1.26-1.19 (5H, m),  
1.07-0.96 (5H, m), 0.74 (3H, t).

[0260]

5 (iv)

(S)-3-((4-((2-amino-4-(1-hydroxyhexan-3-ylamino)-6-methylpyrimidin-5-yl)methyl)-3-methoxybenzyl)(ethylamino)propanoic acid

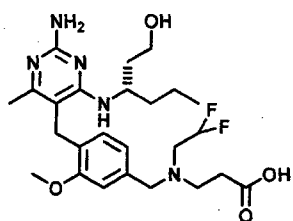


10 The sub-title compound was synthesized by the method of example  
1 step (ix) from the product of step (iii) (670 mg). The subtitle  
compound (640 mg) was obtained as a white solid; <sup>1</sup>H NMR (DMSO);  
6.97 (1H, s), 6.79-6.70 (4H, m), 6.56-6.51 (1H, m), 4.31-4.23  
(1H, m), 3.83 (3H, s), 3.64 (2H, s), 3.57 (2H, s), 3.33-3.26  
15 (4H, m), 2.70 (2H, t), 2.36 (2H, t), 2.07 (3H, s), 1.60-1.49  
(2H, m), 1.42-1.34 (2H, m), 1.13-1.04 (2H, m), 0.96 (3H, t),  
0.76 (3H, t).

[0261]

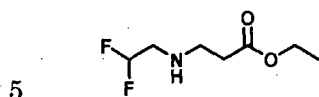
Example 6:

20 (S)-3-((4-((2-amino-4-(1-hydroxyhexan-3-ylamino)-6-methylpyrimidin-5-yl)methyl)-3-methoxybenzyl)(2,2-difluoroethylamino)propanoic acid



The title compound was prepared by the sequence of steps described below:

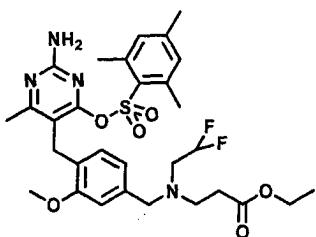
(i) ethyl 3-(2,2-difluoroethylamino)propanoate



2,2-difluoroethylamine (0.50 g) was added to a suspension of ethyl 3-bromopropanoate (1.1 g), potassium iodide (0.10 g) in diisopropylethylamine (1.2 mL) and the mixture was stirred at 100 °C for 3.5 h. The mixture was cooled to RT and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel to afford the sub-title compound (0.69 g) as a pale yellow oil; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>); 5.81 (1H, tt), 4.13 (2H, q), 2.95 (2H, dt), 2.93 (2H, t), 2.48 (2H, t), 1.24 (3H, t).

15 [0262]

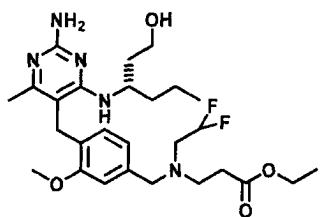
(ii) ethyl 3-((4-((2-amino-4-(mesitylsulfonyloxy)-6-methylpyrimidin-5-yl)methyl)-3-methoxybenzyl)(2,2-difluoroethyl)amino)propanoate



The sub-title compound was synthesized by the method of example 1 step (vii) from the product of step (i) and example 1 step (v) (260 mg). The sub-title compound (310 mg) was obtained as a pale yellow oil;  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ); 6.91 (2H, s), 6.80 (1H, s), 6.74 (1H, d), 6.68 (1H, d), 5.70 (1H, tt), 4.64 (2H, br s), 4.10 (2H, q), 3.79 (5H, s), 3.65 (2H, s), 2.80 (2H, dt), 2.55 (6H, s), 2.51-2.45 (4H, m), 2.29 (3H, s), 2.24 (3H, s), 1.24 (3H, t).

10 [0263]

(iii) (S)-ethyl 3-((4-((2-amino-4-(1-hydroxyhexan-3-ylamino)-6-methylpyrimidin-5-yl)methyl)-3-methoxybenzyl)(2,2-difluoroethyl)amino)propanoate



15

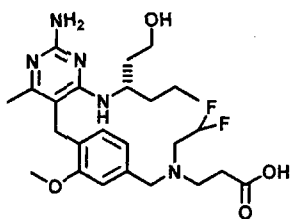
The sub-title compound was synthesized by the method of example 1 step (viii) from the product of step (ii) (190 mg) (S)-3-amino-1-hexanol (110 mg). The sub-title compound (130 mg) was obtained as a colourless gum;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ); 6.91 (1H, s),

6.87 (1H, d), 6.79 (1H, d), 5.72 (1H, tt), 5.69 (2H, br s),  
 4.19-4.15 (2H, m), 4.11 (2H, q), 3.89 (3H, s), 3.65-3.64 (4H,  
 m), 3.45-3.40 (1H, m), 3.21 (1H, ddd), 2.90 (2H, t), 2.78 (2H,  
 dt), 2.48-2.43 (5H, m), 1.85-1.74 (1H, m), 1.49-1.37 (1H, m),  
 5 1.32-1.17 (5H, t), 1.09-0.99 (2H, m), 0.77 (3H, t).

[0264]

(iv)

(S)-3-((4-((2-amino-4-(1-hydroxyhexan-3-ylamino)-6-methylpy  
 rimidin-5-yl)methyl)-3-methoxybenzyl)(2,2-difluoroethyl)ami  
 10 no)propanoic acid



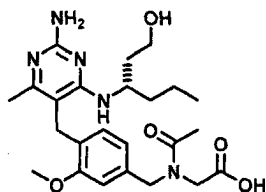
The sub-title compound was synthesized by the method of example  
 1 step (ix) from the product of step (iii) (120 mg). The sub-title  
 compound (86 mg) was obtained as a white solid; <sup>1</sup>H NMR (DMSO);  
 15 6.95 (1H, s), 6.75-6.68 (2H, m), 6.01 (1H, tt), 5.74 (2H, br  
 s), 5.59 (1H, d), 4.19-4.12 (1H, m), 3.83 (3H, s), 3.62 (2H,  
 s), 3.58 (2H, s), 3.49-3.21 (2H, m), 2.79 (2H, dt), 2.71 (2H,  
 t), 2.19 (2H, t), 2.00 (3H, s), 1.59-1.50 (1H, m), 1.43-1.27  
 (3H, m), 1.16-1.05 (2H, m), 0.76 (3H, t).

20 [0265]

Example 7:

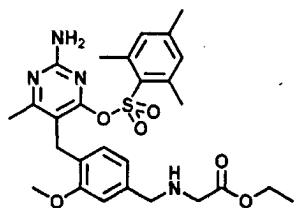
(S)-2-(N-(4-((2-amino-4-(1-hydroxyhexan-3-ylamino)-6-methyl

pyrimidin-5-yl)methyl)-3-methoxybenzyl)acetamido)acetic acid



The title compound was prepared by the sequence of steps described below:

(i) ethyl 2-(4-((2-amino-4-(mesitylsulfonyloxy)-6-methylpyrimidin-5-yl)methyl)-3-methoxybenzylamino)acetate

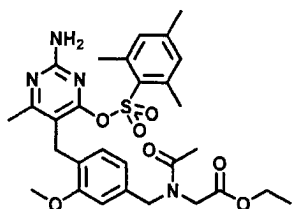


The sub-title compound was synthesized by the method of example 1 step (vii) from the product of example 1 step (v) (100 mg) and ethyl glycinate. The sub-title compound (23 mg) was obtained as a colourless amorphous solid;  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ); 6.92 (2H, s), 6.84 (1H, s), 6.76-6.70 (2H, m), 4.68 (2H, br s), 4.18 (2H, q), 3.81 (3H, s), 3.79 (2H, s), 3.77 (2H, s), 3.39 (2H, s), 2.56 (6H, s), 2.28 (3H, s), 2.22 (3H, s), 1.26 (3H, t); LC-MS:  $m/z = 543$ .

[0266]

(ii) ethyl 2-(N-(4-((2-amino-4-(mesitylsulfonyloxy)-6-methylpyrimidin-

5-yl)methyl)-3-methoxybenzyl)acetamido)acetate



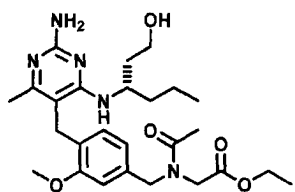
Acetic anhydride (6  $\mu$ L) was added to a solution of the product from step (i) (23 mg) and triethyl amine (9  $\mu$ L) in THF (1 mL), and the mixture was stirred at RT for 3 h. The mixture was quenched with water, extracted with EtOAc, combined organic layer was washed with brine, dried and concentrated under reduced pressure. The sub-title compound (25 mg) was obtained as a colourless gum, which was used for next reaction without further purification; LC-MS:  $m/z$  = 585.

[0267]

(iii)

(S)-ethyl

2-(N-(4-((2-amino-4-(1-hydroxyhexan-3-ylamino)-6-methylpyrimidin-5-yl)methyl)-3-methoxybenzyl)acetamido)acetate



15

The sub-title compound was synthesized by the method of example 1 step (viii) from the product of step (ii) (25 mg) and (S)-3-aminohexan-1-ol (15 mg). The sub-title compound (5.1 mg) was obtained as a colourless gum;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ); 6.93 (1H, d), 6.72-6.67 (2H, m), 4.82 (2H, br s), 4.65 (1H, d), 4.56 (2H, s),

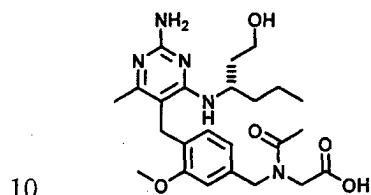
20

4.18-4.08 (3H, m), 3.99 (2H, s), 3.88 (3H, s), 3.65 (2H, s),  
 3.48-3.42 (1H, m), 3.32-3.26 (1H, m), 2.33 (3H, s), 2.17 (3H,  
 s), 1.84-1.74 (1H, m), 1.46-1.35 (1H, m), 1.23 (3H, t),  
 1.16-0.97 (4H, m), 0.73 (3H, t); LC-MS: m/z = 502.

5 [0268]

(iv)

(S)-2-(N-(4-((2-amino-4-(1-hydroxyhexan-3-ylamino)-6-methyl  
 pyrimidin-5-yl)methyl)-3-methoxybenzyl)acetamido)acetic  
 acid

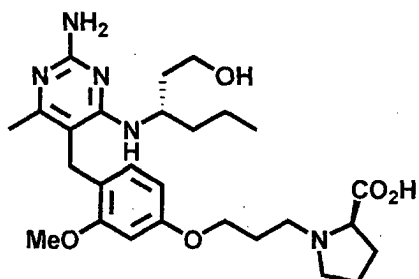


The sub-title compound was synthesized by the method of example  
 1 step (ix) from the product of step (iii) (330 mg). The sub-title  
 compound (330 mg) was obtained as a colourless amorphous  
 solid; <sup>1</sup>H NMR (DMSO); 6.96-6.92 (4H, m), 6.81 (1H, d), 5.83 (1H,  
 15 d), 4.73 (1H, d), 4.50 (1H, d), 4.21-4.10 (1H, m), 3.88 (3H,  
 s), 3.80 (2H, s), 3.60 (2H, s), 3.21-3.06 (2H, m), 2.38 (3H,  
 s), 2.14 (3H, s), 1.81-1.71 (1H, m), 1.43-1.37 (1H, m),  
 1.31-1.09 (4H, m), 0.82 (3H, t); LC-MS: m/z = 474.

[0269]

20 Example 8:

(R)-1-(3-(4-((2-amino-4-((S)-1-hydroxyhexan-3-ylamino)-6-me  
 thylpyrimidin-5-yl)methyl)-3-methoxyphenoxy)propyl)pyrrolid  
 ine-2-carboxylic acid

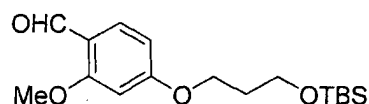


The title compound may be prepared by the steps described below:

(i)

4-[3-(tert-Butyldimethylsilyloxy)propoxy]-2-methoxybenzaldehyde

5



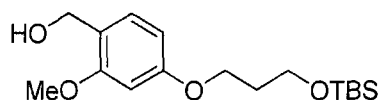
The mixture of 4-hydroxy-2-methoxybenzaldehyde (10.0 g), (3-bromopropoxy)-tert-butyldimethylsilane (25.0 g), and potassium dicarbonate (13.6 g) in DMF (100 mL) was stirred at RT for 5h. The mixture was diluted with water and extracted with EtOAc. And the combined organic solutions were washed with water and brine, dried and concentrated. The residue was purified by silica gel chromatography eluting with hexane/EtOAc to give 21.3 g of the subtitle compound as a yellow oil [as a mixture with (3-bromopropoxy)-tert-butyldimethylsilane].

15

[0270]

(ii)

{4-[3-(tert-Butyldimethylsilyloxy)propoxy]-2-methoxyphenyl} methanol

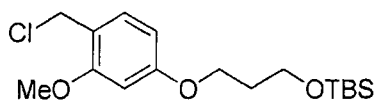


Sodium borohydride (1.24 g) was added to a solution of the product from step (i) (21.3 g) in THF (100 mL), methanol (15 mL) and stirred at RT for 2.5h. The mixture was diluted with water and brine, and extracted with EtOAc. And the combined organic solutions were dried and concentrated. The residue was purified by silica gel chromatography eluting with hexane/EtOAc to give the subtitle compound (18.5 g) as a colourless oil; <sup>1</sup>H NMR: 7.14 (1H, d), 6.42-6.48 (2H, m), 4.61 (2H, d), 4.06 (2H, t), 3.84 (3H, s), 3.80 (2H, t), 2.15 (1H, t), 1.94-2.02 (2H, m), 0.89 (9H, s), 0.04 (6H, s).

[0271]

(iii)

tert-Butyl{3-[4-(chloromethyl)-3-methoxyphenoxy]propoxy}dimethylsilane



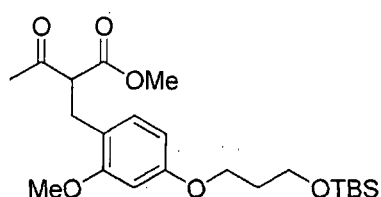
Methanesulfonyl chloride (4.02 mL) was added to the mixture of the product from step (ii) (8.47 g), diisopropylethylamine (13.4 mL) and lithium chloride (3.29 g) in THF (105 mL) at RT and stirred for 40 mins. The mixture was diluted with water and brine, and extracted with EtOAc. The combined organic solutions were washed with brine, dried and concentrated to give 10.0 g of the subtitle compound as a yellow oil; <sup>1</sup>H NMR: 7.23 (1H, dd),

6.44-6.49 (2H, m), 4.63 (2H, s), 4.06 (2H, t), 3.85 (3H, s),  
3.79 (2H, t), 1.94-2.02 (2H, m), 0.89 (9H, s), 0.04 (6H, s).  
[0272]

(iv)

Methyl

5 2-(4-[3-(tert-butyldimethylsilyloxy)propoxy]-2-methoxybenzy  
1)-3-oxobutanoate



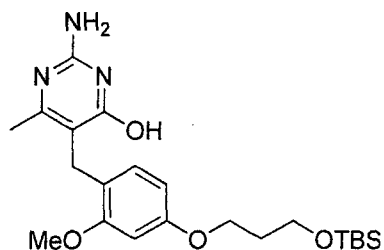
Methyl acetoacetate (4.18 mL) was added to a suspension of NaH  
(55% oil dispersion, 1.70 g) in DMF (60 mL) at 0°C and stirred  
10 at r.t. for 0.5h. The product from step (iii) (10.0 g) in DMF  
(60 mL) and potassium iodide (4.73 g) were added to the mixture  
and stirred at 80°C for 6h. The mixture was cooled to RT and  
diluted with water and extracted with EtOAc. And the combined  
organic solutions were washed with water and brine, dried and  
15 concentrated. The residue was purified by silica gel  
chromatography to give 9.98 g of the subtitle compound as a  
yellow oil; <sup>1</sup>H NMR: 6.99 (1H, d), 6.42 (1H, d), 6.37 (1H, dd),  
4.02 (2H, t), 3.89 (1H, t), 3.80 (3H, s), 3.79 (2H, t), 3.67  
(3H, s), 2.99-3.14 (2H, m), 2.17 (3H, s), 1.92-2.00 (2H, m),  
20 0.88 (9H, s), 0.04 (6H, s).

[0273]

(v)

2-Amino-5-(4-[3-(tert-butyldimethylsilyloxy)propoxy]-2-meth

oxybenzyl}-6-methylpyrimidin-4-ol

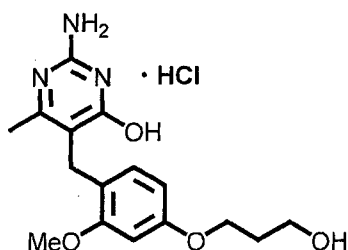


Guanidium carbonate (6.40 g) was added to a solution of the product from step (iv) (11.6 g) in methanol (116 mL) and heated at 75 °C for 8 h. The mixture was cooled to r.t. and concentrated. The residue was diluted with EtOAc (50 mL) and water (50 mL), and stirred for 5.5h. The precipitate was collected and washed with water and EtOAc to afford 7.49 g of the subtitle compound as a white solid; <sup>1</sup>H NMR: (d<sup>6</sup>-DMSO) 10.75 (1H, br s), 6.71 (1H, d), 6.48 (1H, d), 6.36 (1H, dd), 6.30 (2H, br s), 3.97 (2H, t), 3.77 (3H, s), 3.73 (2H, t), 3.45 (2H, s), 1.92 (3H, s), 1.82-1.90 (2H, m), 0.85 (9H, s), 0.02 (6H, s).

[0274]

(vi)

2-amino-5-(4-(3-hydroxypropoxy)-2-methoxybenzyl)-6-methylpyrimidin-4-ol hydrochloride



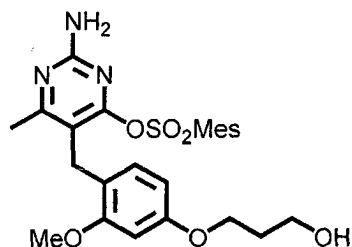
Concentrated hydrogen chloride (2.5 mL) was added dropwise to a solution of the product from step (v) (4.33 g) in methanol

(43 mL) at RT and stirred for 14 h. The mixture was concentrated and diluted with methanol. The precipitate was collected by filtration, washed with methanol and dried to give 2.87 g of the sub-title compound as a white solid, which was used without further purification;  $^1\text{H}$  NMR (300 MHz,  $d_6$ -DMSO)  $\delta$  = 12.59 (2H, brs), 8.05 (2H, s), 6.89 (1H, d), 6.51 (1H, d), 6.36 (1H, dd), 3.97 (2H, t), 3.52 (2H, t), 3.46 (2H, s), 2.13 (3H, s), 1.78-1.86 (2H, m); LC-MS: m/z 320.

[0275]

10 (vii)

2-amino-5-(4-(3-hydroxypropoxy)-2-methoxybenzyl)-6-methylpyrimidin-4-yl 2,4,6-trimethylbenzenesulfonate



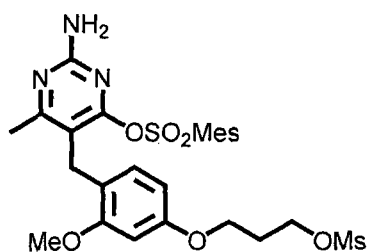
15 2-Mesitylenesulfonyl chloride (2.7 g) was added to a suspension of diisopropylethylamine (4.6 mL) and the product from step (vi) (2.9 g) in THF (200 mL) and the mixture was stirred under reflux for 18 h. The resulting mixture was diluted with water and extracted with EtOAc. The combined organic layer was washed with brine, dried and concentrated under reduced pressure. The residue was purified by flash column chromatography on amino silica gel to afford the sub-title compound (3.6 g) as a white solid;  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ); 6.92 (2H, s), 6.71 (1H, d), 6.40

(1H, d), 6.32 (1H, dd), 4.70 (2H, br s), 4.07 (2H, t), 3.88-3.82 (2H, m), 3.76 (3H, s), 3.73 (2H, s), 2.57 (6H, s), 2.29 (3H, s), 2.24 (3H, s), 2.06-1.98 (2H, m); LC-MS: m/z 502.

[0276]

5 (viii)

2-amino-5-(2-methoxy-4-(3-(methanesulfonyloxy)propoxy)benzyl)-6-methylpyrimidin-4-yl 2,4,6-trimethylbenzenesulfonate



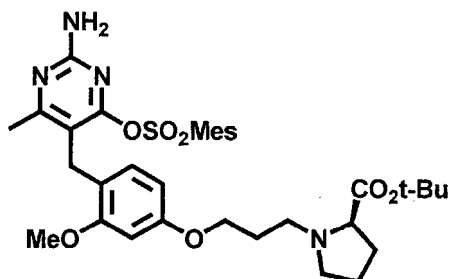
Methanesulfonyl chloride (0.293 mL) was added to a solution of diisopropylethylamine (0.988 mL) and the product from step (vii) (0.95 g) in THF (9.5 mL). The mixture was stirred at RT for 2 h, diluted with water and extracted with EtOAc. The combined organic layer was washed with brine, dried and concentrated under reduced pressure to afford the crude product as a pale yellow oil, which was used for next reaction without further purification; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>); 6.93 (2H, s), 6.73 (1H, d), 6.39 (1H, d), 6.31 (1H, dd), 4.76 (2H, br s), 4.43 (2H, t), 4.03 (2H, t), 3.77 (3H, s), 3.73 (2H, s), 2.98 (3H, s), 2.57 (6H, s), 2.29 (3H, s), 2.25 (3H, s), 2.24-2.16 (2H, m); LC-MS: m/z 580.

[0277]

(ix)

(R)-tert-butyl

1-(3-(4-((2-amino-4-(mesitylsulfonyloxy)-6-methylpyrimidin-5-yl)methyl)-3-methoxyphenoxy)propyl)pyrrolidine-2-carboxylate



5 (R)-tert-butyl pyrrolidine-2-carboxylate (485 mg) was added to the mixture of potassium carbonate (393 mg), potassium iodide (31 mg) and the crude product from step (viii) in CH<sub>3</sub>CN (20 mL). After the mixture was stirred at 70 °C for 16 h, the reaction mixture was cooled to RT, diluted with water and extracted with

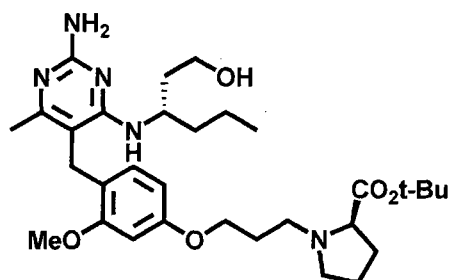
10 EtOAc. The combined organic layer was washed with water and brine, dried and concentrated under reduced pressure. The residue was purified by flash column chromatography on amino silica gel to afford the sub-title compound (975 mg) as a white amorphous solid; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>); 6.92 (2H, s), 6.67 (1H, d), 6.39 (1H, d), 6.30 (1H, dd), 4.64 (2H, br s), 4.03-3.90 (2H, m), 3.76 (3H, s), 3.73 (2H, s), 3.20-3.00 (2H, m), 2.96-2.80 (1H, m), 2.66-2.50 (1H, m), 2.57 (6H, s), 2.46-2.30 (1H, m), 2.28 (3H, s), 2.22 (3H, s), 2.21-1.74 (6H, m), 1.43 (9H, s); LC-MS: m/z 655.

20 [0278]

(x)

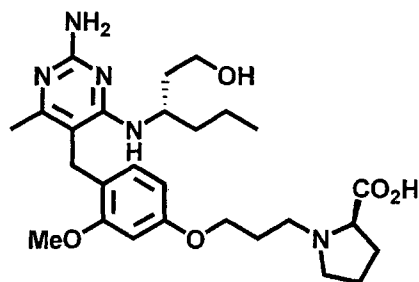
(R)-tert-butyl

1-(3-(4-((2-amino-4-((S)-1-hydroxyhexan-3-ylamino)-6-methylpyrimidin-5-yl)methyl)-3-methoxyphenoxy)propyl)pyrrolidine-2-carboxylate



5. Trifluoroacetic acid (0.091 mL) was added to the mixture of (S)-3-aminohexan-1-ol (416 mg) and the product from step (ix) (775 mg) in propionitrile (8 mL). After the mixture was heated at 120 °C for 16 h, the reaction mixture was cooled to RT, diluted with sat. sodium hydrogen dicarbonate and extracted with EtOAc.
- 10 The combined organic layer was dried and concentrated under reduced pressure. The residue was purified by flash column chromatography on amino silica gel to afford the sub-title compound (520 mg) as a white gum; <sup>1</sup>H NMR (CDCl<sub>3</sub>); 6.81 (1H, d), 6.44 (1H, d), 6.38 (1H, dd), 4.80 (2H, br s), 4.13-4.03 (1H, m), 4.03-3.90 (2H, m), 3.84 (3H, s), 3.59 (2H, s), 3.49-3.37 (1H, m), 3.34-3.22 (1H, m), 3.18-3.08 (1H, m), 3.08-3.00 (1H, m), 2.91-2.80 (1H, m), 2.62-2.49 (1H, m), 2.41-2.30 (1H, m), 2.35 (3H, s), 2.10-1.70 (8H, m), 1.44-1.34 (1H, m), 1.42 (9H, s), 1.28-0.89 (4H, m), 0.75 (3H, t); LC-MS: m/z 573.
- 20 [0279]
- (xi)

(R)-1-(3-(4-((2-amino-4-((S)-1-hydroxyhexan-3-ylamino)-6-methylpyrimidin-5-yl)methyl)-3-methoxyphenoxy)propyl)pyrrolidine-2-carboxylic acid



5 Trifluoroacetic acid (6 mL) was added to the product from step (x) (505 mg) and the mixture was stirred at RT for 14 h. After the reaction mixture was concentrated, 1M-sodium hydroxide (20 mL) and methanol (10 mL) was added to the residue and the mixture was stirred in methanol for 30 mins. The reaction mixture was

10 concentrated, diluted with water and washed with chloroform. The aqueous layer was neutralized with 6M-hydrogen chloride and sat. sodium hydrogen dicarbonate and extracted with chloroform/EtOH (3/1). The combined organic layer was dried and concentrated. The residue was diluted with chloroform, filtered,

15 concentrated and diluted with chloroform/EtOAc. The precipitate was collected by filtration, washed with EtOAc and dried to give 450 mg of the sub-title compound as a white solid; <sup>1</sup>H NMR (CDCl<sub>3</sub>); 6.78 (1H, d), 6.48 (1H, d), 6.38 (1H, dd), 5.35-5.20 (1H, m), 4.20-3.97 (3H, m), 3.86 (3H, s), 3.55 (2H, s), 3.63-3.47 (1H, m), 3.40-3.09 (4H, m), 2.91-2.75 (1H, m), 2.60-2.45 (1H, m), 2.35 (3H, s), 2.30-2.02 (4H, m), 2.02-1.70 (3H, m),

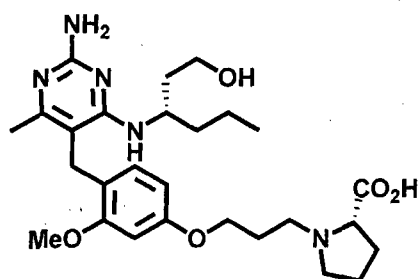
20

1.50-1.33 (1H, m), 1.33-0.95 (5H, m), 0.77 (3H, t); LC-MS: m/z 516.

[0280]

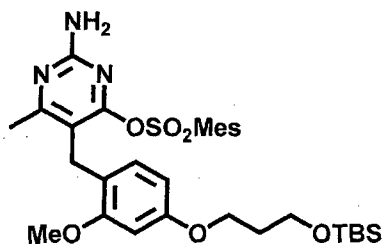
Example 9:

- 5 (S)-1-(3-(4-((2-amino-4-((S)-1-hydroxyhexan-3-ylamino)-6-methylpyrimidin-5-yl)methyl)-3-methoxyphenoxy)propyl)pyrrolidine-2-carboxylic acid



The title compound may be prepared by the steps described below:

- 10 (i)  
2-Amino-5-{4-[3-(tert-butyldimethylsilyloxy)propoxy]-2-methoxybenzyl}-6-methylpyrimidin-4-yl  
2,4,6-trimethylbenzenesulfonate



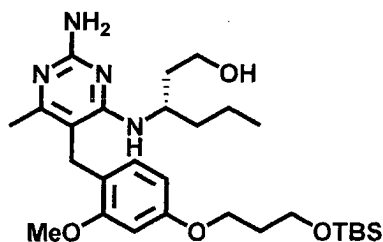
- 15 2-Mesitylenesulfonyl chloride (4.96 g, 22.7 mmol) was added to a solution of N,N,N',N'-tetramethyl-1,3-propanediamine (3.79 mL, 22.7 mmol) and the product of example 8 step step (v) (6.55 g, 15.1 mmol) in THF (66 mL) and the mixture was stirred at RT

for 3h. The resulting mixture was diluted with water and extracted with EtOAc. And the combined organic solutions were washed with brine, dried and concentrated. The residue was purified via chromatography on silica to give 8.87 g of the subtitle compound as a white solid;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ); 6.93 (2H, s), 6.71 (1H, d), 6.41 (1H, d), 6.33 (1H, dd), 4.66 (2H, br s), 4.02 (2H, t), 3.78 (3H, s), 3.77-3.82 (2H, m), 3.75 (2H, s), 2.59 (6H, s), 2.31 (3H, s), 2.25 (3H, s), 1.93-2.01 (2H, m), 0.89 (9H, s), 0.05 (6H, s); LC-MS: m/z 616.

10 [0281]

(ii)

(S)-3-(2-amino-5-(4-(3-(tert-butyldimethylsilyloxy)propoxy)-2-methoxybenzyl)-6-methylpyrimidin-4-ylamino)hexan-1-ol



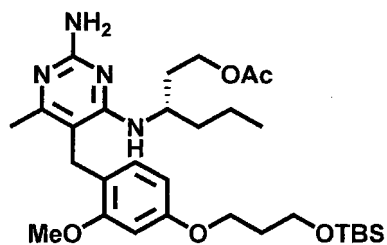
15 Trifluoroacetic acid (0.154 mL) was added to the mixture of (S)-3-aminohexan-1-ol (586 mg) and the product from step (i) (616 mg) in propionitrile (6 mL). After the mixture was heated at 120 °C for 23 h, the reaction mixture was cooled to RT, diluted with sat. sodium hydrogen carbonate and extracted with EtOAc.

20 The combined organic layer was dried and concentrated under reduced pressure. The residue was purified by flash column chromatography on amino silica gel to afford the sub-title

compound (430 mg) as a colorless oil;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ); 6.83 (1H, d), 6.44 (1H, d), 6.39 (1H, dd), 4.79 (2H, br s), 4.15-4.04 (1H, m), 4.00 (2H, t), 3.85 (3H, s), 3.77 (2H, t), 3.60 (2H, s), 3.50-3.40 (1H, m), 3.33-3.22 (1H, m), 2.36 (3H, s), 2.00-1.88 (2H, m), 1.86-1.71 (1H, m), 1.48-1.32 (1H, m), 1.30-0.95 (4H, m), 0.86 (9H, s), 0.75 (3H, t), 0.01 (6H, s); LC-MS:  $m/z$  534. [0282]

(iii)

(S)-3-(2-amino-5-(4-(3-(tert-butyldimethylsilyloxy)propoxy)-2-methoxybenzyl)-6-methylpyrimidin-4-ylamino)hexyl acetate



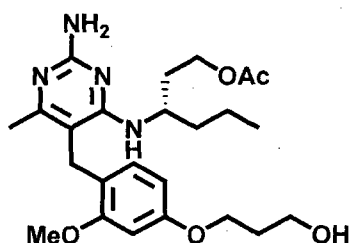
4-Dimethylaminopyridine (cat. amount) was added to the mixture of acetic anhydride (0.162 mL), diisopropylethylamine (0.697 mL) and the product from step (ii) (760 mg) in THF (10 mL). After the mixture was stirred at RT for 3.5h, the reaction mixture was diluted with water and sat. sodium hydrogen dicarbonate and extracted with EtOAc. The combined organic layer was washed with water and brine, dried and concentrated under reduced pressure to afford the crude product as pale yellow oil, which was used for next reaction without further purification;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ); 6.81 (1H, d), 6.44 (1H, d), 6.38 (1H, dd), 4.79 (2H, br s), 4.25-4.15 (1H, m), 3.99 (2H, t), 3.96-3.88 (2H, m), 3.85 (3H,

s), 3.76 (2H, t), 3.58 (2H, s), 2.33 (3H, s), 1.97 (3H, s), 2.00-1.88 (2H, m), 1.86-1.71 (1H, m), 1.64-1.50 (1H, m), 1.48-1.32 (1H, m), 1.30-0.95 (3H, m), 0.86 (9H, s), 0.76 (3H, t), 0.02 (6H, s); LC-MS: m/z 576.

5 [0283]

(iv)

(S)-3-(2-amino-5-(4-(3-hydroxypropoxy)-2-methoxybenzyl)-6-methylpyrimidin-4-yl-amino)hexyl acetate



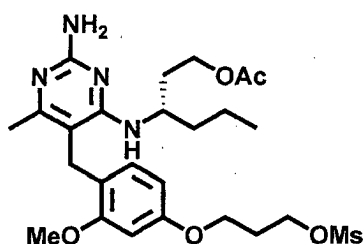
10 Tetra-n-butylammonium fluoride (561 mg) was added to the mixture of the product from step (iii) in THF (14 mL). After the mixture was stirred at RT for 1.5h, the reaction mixture was diluted with water and sat. sodium hydrogen carbonate and extracted with EtOAc. The combined organic layer was washed with  
15 brine, dried and concentrated under reduced pressure. The residue was purified by flash column chromatography on amino silica gel to afford the sub-title compound (660 mg) as a colourless oil; <sup>1</sup>H NMR (CDCl<sub>3</sub>); 6.82 (1H, d), 6.45 (1H, d), 6.39 (1H, dd), 4.71 (2H, br s), 4.23-4.13 (1H, m), 4.07 (2H, t), 3.85 (3H, s), 3.85-3.74 (4H, m), 3.58 (2H, s), 2.33 (3H, s), 2.15 (1H, br s), 2.04-1.97 (2H, m), 1.97 (3H, s), 1.88-1.75 (1H, m), 1.60-1.47 (1H, m), 1.45-1.32 (1H, m), 1.31-1.19 (1H, m),  
20

1.17-1.03 (2H, m), 0.79 (3H, t); LC-MS: m/z 461.

[0284]

(v)

(S)-3-(2-amino-5-(2-methoxy-4-(3-(methylsulfonyloxy)propoxy)  
5 )benzyl)-6-methylpyrimidin-4-ylamino)hexyl acetate



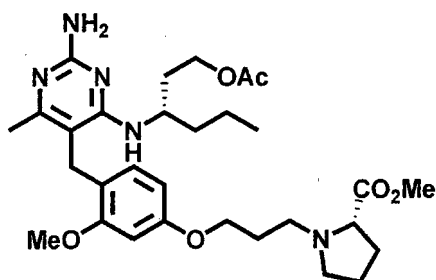
Methanesulfonyl chloride (0.083 mL) was added to a solution of diisopropylethylamine (0.279 mL) and the product from step (iv) (0.246 g) in THF (10 mL). The mixture was stirred at RT for 3  
10 h and additional diisopropylethylamine (0.14 mL) and methanesulfonyl chloride (0.042 mL) was added. The mixture was stirred at RT for 2 h, diluted with water and sat. sodium hydrogen dicarbonate and extracted with EtOAc. The combined organic layer was dried and concentrated under reduced pressure to  
15 afford the crude product (300 mg) as a pale yellow oil, which was used for the next reaction without further purification; LC-MS: m/z 539.

[0285]

(vi)

(S)-methyl

1-(3-(4-((4-((S)-1-acetoxyhexan-3-ylamino)-2-amino-6-methyl  
20 pyrimidin-5-yl)methyl)-3-methoxyphenoxy)propyl)pyrrolidine-2-carboxylate



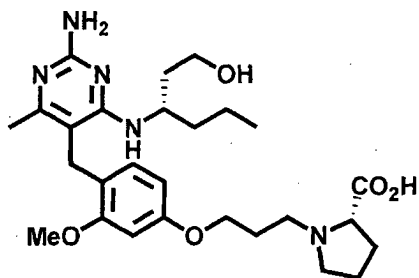
(S)-methyl pyrrolidine-2-carboxylate hydrochloride (44 mg) was added to the mixture of potassium carbonate (74 mg), potassium iodide (3 mg) and the crude product (75 mg) from step 5 (v) in acetonitrile (2 mL). After the mixture was stirred at 70 °C for 16 h, the reaction mixture was cooled to RT, diluted with water and sat. sodium hydrogen dicarbonate and extracted with EtOAc. The combined organic layer was dried and concentrated under reduced pressure. The residue was purified by flash column chromatography on amino silica gel to afford the sub-title compound (60 mg) as a colourless oil; <sup>1</sup>H NMR (CDCl<sub>3</sub>); 6.80 (1H, d), 6.44 (1H, d), 6.37 (1H, dd), 4.85 (2H, br s), 4.24-4.15 (1H, m), 4.00-3.87 (4H, m), 3.85 (3H, s), 3.67 (3H, s), 3.57 (2H, s), 3.22-3.14 (2H, m), 2.89-2.78 (1H, m), 2.61-2.50 (1H, m), 2.42-2.30 (1H, m), 2.34 (3H, s), 2.16-2.05 (1H, s), 1.97 (3H, s), 1.97-1.70 (6H, m), 1.63-1.49 (1H, m), 1.46-1.32 (1H, m), 1.29-1.15 (1H, m), 1.12-0.98 (2H, m), 0.77 (3H, t); LC-MS: m/z 572.

[0286]

20 (vii)

(S)-1-(3-(4-((2-amino-4-((S)-1-hydroxyhexan-3-ylamino)-6-me

thylpyrimidin-5-yl)methyl)-3-methoxyphenoxy)propyl)pyrrolidine-2-carboxylic acid



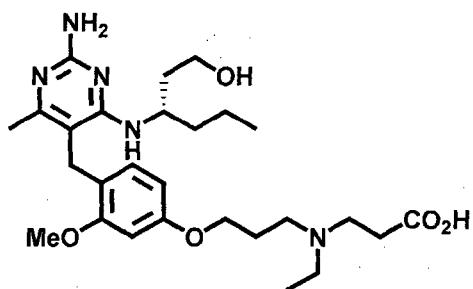
1M-sodium hydroxide (2 mL) was added to a solution of the product  
 5 (60 mg) from step (vi) in methanol (2 mL) and the mixture was  
 stirred at RT for 9 h. The reaction mixture was concentrated,  
 diluted with water and washed with chloroform. The aqueous layer  
 was neutralized with 2M-hydrogen chloride and extracted with  
 chloroform/EtOH (3/1). The combined organic layer was dried and  
 10 concentrated. The residue was diluted with chloroform, filtered,  
 concentrated under reduced pressure to afford the sub-title  
 compound (48 mg) as a white solid; <sup>1</sup>H NMR (CDCl<sub>3</sub>); 6.79 (1H,  
 d), 6.48 (1H, d), 6.38 (1H, dd), 6.17 (1H, br s), 5.24 (1H, br  
 s), 4.20-3.97 (3H, m), 3.85 (3H, s), 3.70-3.58 (1H, m), 3.55  
 15 (2H, s), 3.48-3.34 (2H, m), 3.32-3.15 (2H, m), 3.05-2.80 (1H,  
 m), 2.75-2.55 (1H, m), 2.35 (3H, s), 2.30-2.07 (4H, m),  
 2.05-1.85 (2H, m), 1.85-1.70 (1H, m), 1.48-1.34 (1H, m),  
 1.33-0.98 (4H, m), 0.77 (3H, t); LC-MS: m/z 516.

[0287]

20 Example 10:

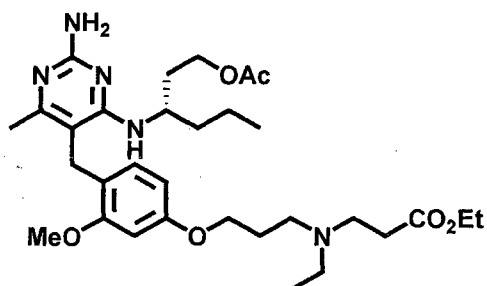
(S)-3-((3-((4-((2-amino-4-(1-hydroxyhexan-3-ylamino)-6-methy

lpyrimidin-5-yl)methyl)-3-methoxyphenoxy)propyl) (ethyl) amin  
o)propanoic acid



The title compound may be prepared by the steps described below:

- 5 (i) (S)-ethyl  
3-((3-(4-((4-(1-acetoxyhexan-3-ylamino)-2-amino-6-methylpyr  
imidin-5-yl)methyl)-3-methoxyphenoxy)propyl) (ethyl) amino)pr  
opanoate

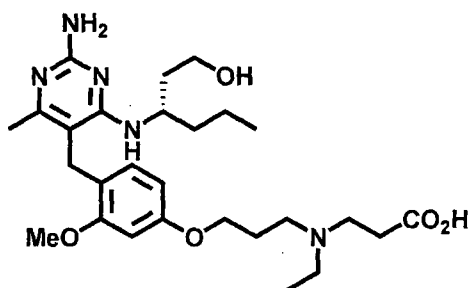


- 10 The sub-title compound was synthesized by the method of example  
9 step (vi) from the product of example 9 step (v) (75 mg) and  
the product of example 5 step (i). The sub-title compound (60  
mg) was obtained as a pale yellow oil; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>);  
6.81 (1H, d), 6.45 (1H, d), 6.37 (1H, dd), 4.95 (2H, br s),  
15 4.28-4.13 (1H, m), 4.09 (2H, q), 3.97-3.86 (4H, m), 3.86 (3H,  
s), 3.57 (2H, s), 2.77 (2H, t), 2.56 (2H, t), 2.50 (2H, q), 2.41  
(2H, t), 2.35 (3H, s), 1.97 (3H, s), 1.92-1.70 (3H, m), 1.63-1.50

(1H, m), 1.46-1.32 (1H, m), 1.30-1.15 (2H, m), 1.22 (3H, t),  
1.13-0.95 (2H, m), 0.99 (3H, t), 0.77 (3H, t); LC-MS: m/z 588.  
[0288]

(ii)

- 5 (S)-3-((3-(4-((2-amino-4-(1-hydroxyhexan-3-ylamino)-6-methylpyrimidin-5-yl)methyl)-3-methoxyphenoxy)propyl)(ethylamino)propanoic acid



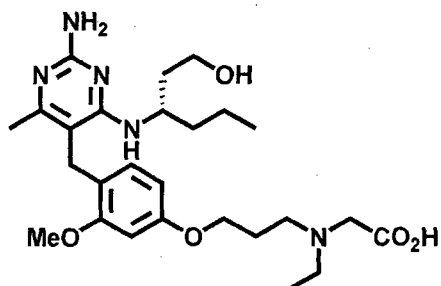
- The sub-title compound was synthesized by the method of example  
10 9 step (vii) from the product of step (i) (60 mg). The sub-title compound (47 mg) was obtained as a white amorphous solid; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>); 6.81 (1H, d), 6.44 (1H, d), 6.37 (1H, dd), 5.61 (1H, br s), 5.06-4.92 (1H, m), 4.18-4.04 (1H, m), 3.98 (2H, t), 3.86 (3H, s), 3.58 (2H, s), 3.46-3.36 (1H, m), 3.30-3.19 (1H, m), 2.94-2.66 (6H, m), 2.47 (2H, t), 2.35 (3H, s), 2.08-1.93 (2H, m), 1.85-1.70 (1H, m), 1.48-1.35 (1H, m), 1.34-1.00 (7H, m), 0.77 (3H, t); LC-MS: m/z 518.

[0289]

Example 11:

- 20 (S)-2-((3-(4-((2-amino-4-(1-hydroxyhexan-3-ylamino)-6-methylpyrimidin-5-yl)methyl)-3-methoxyphenoxy)propyl)(ethylamino)propanoic acid

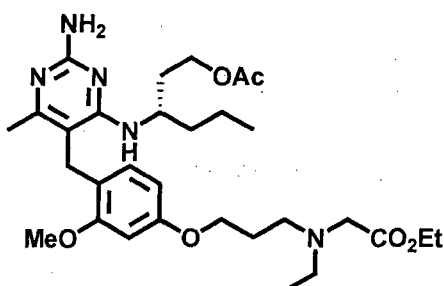
o)acetic acid



The title compound may be prepared by the steps described below:

(i) (S)-ethyl

5 2-((3-(4-((4-(1-acetoxyhexan-3-ylamino)-2-amino-6-methylpyrimidin-5-yl)methyl)-3-methoxyphenoxy)propyl)(ethyl)amino)acetate



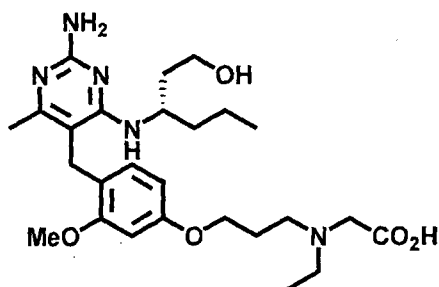
The sub-title compound was synthesized by the method of example  
 10 9 step (vi) from the product of example 9 step (v) (75 mg) and  
 the product of example 1 step (vi). The sub-title compound (60  
 mg) was obtained as a pale yellow oil; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>);  
 6.81 (1H, d), 6.44 (1H, d), 6.38 (1H, dd), 4.95 (2H, br s),  
 4.28-4.05 (3H, m), 4.00-3.85 (4H, m), 3.85 (3H, s), 3.57 (2H,  
 15 s), 3.32 (2H, s), 2.77-2.62 (4H, m), 2.36 (3H, s), 1.97 (3H,  
 s), 1.95-1.72 (3H, m), 1.63-1.50 (1H, m), 1.48-1.33 (1H, m),  
 1.30-1.15 (2H, m), 1.24 (3H, t), 1.11-0.98 (2H, m), 1.03 (3H,

t), 0.77 (3H, t); LC-MS: m/z 574.

[0290]

(ii)

(S)-2-((3-(4-((2-amino-4-(1-hydroxyhexan-3-ylamino)-6-methylpyrimidin-5-yl)methyl)-3-methoxyphenoxy)propyl)(ethylamino)acetic acid

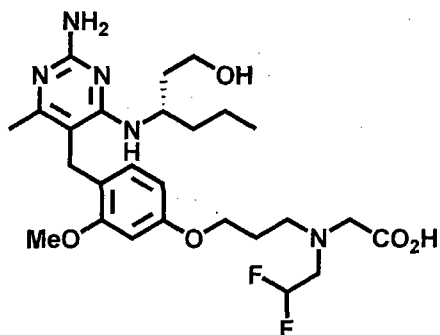


The sub-title compound was synthesized by the method of example 9 step (vii) from the product of step (i) (52 mg). The sub-title compound (44 mg) was obtained as a white amorphous solid;  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ); 6.90-6.60 (1H, m), 6.79 (1H, d), 6.47 (1H, d), 6.40 (1H, dd), 5.40 (1H, d), 4.20-4.07 (1H, m), 4.03 (2H, t), 3.85 (3H, s), 3.55 (2H, s), 3.40-3.30 (1H, m), 3.32 (2H, s), 3.24-3.14 (1H, m), 3.02-2.87 (4H, m), 2.37 (3H, s), 2.10-1.98 (2H, m), 1.85-1.70 (1H, m), 1.49-1.36 (1H, m), 1.34-0.98 (7H, m), 0.78 (3H, t); LC-MS: m/z 504.

[0291]

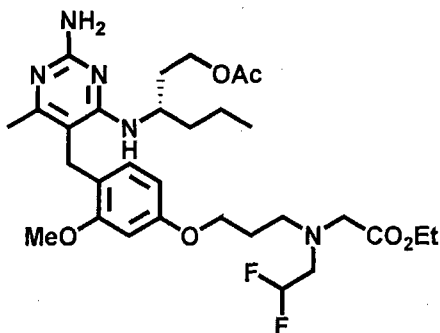
Example 12:

(S)-2-((3-(4-((2-amino-4-(1-hydroxyhexan-3-ylamino)-6-methylpyrimidin-5-yl)methyl)-3-methoxyphenoxy)propyl)(2,2-difluoroethylamino)acetic acid



The title compound may be prepared by the steps described below:

- (i) (S)-ethyl  
2-((3-(4-((4-(1-acetoxyhexan-3-ylamino)-2-amino-6-methylpyr  
imidin-5-yl)methyl)-3-methoxyphenoxy)propyl)(2,2-difluoroet  
hyl)amino)acetate

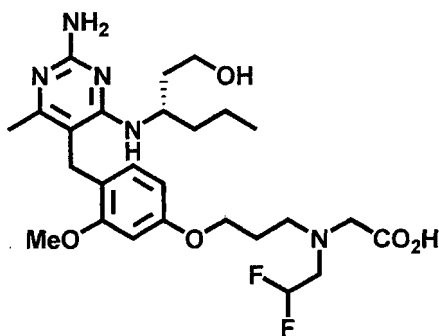


The sub-title compound was synthesized by the method of example 9 step (vi) from the product of example 9 step (v) (75 mg) and the product of example 3 step (i) (112 mg). The sub-title compound (44 mg) was obtained as a pale yellow oil;  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ); 6.81 (1H, d), 6.44 (1H, d), 6.37 (1H, dd), 5.77 (1H, tt), 4.97 (2H, br s), 4.28-4.09 (3H, m), 4.00-3.85 (4H, m), 3.86 (3H, s), 3.58 (2H, s), 3.45 (2H, s), 3.11-2.86 (4H, m), 2.36 (3H, s), 1.97 (3H, s), 1.95-1.74 (3H, m), 1.63-1.50 (1H, m), 1.46-1.33 (1H, m), 1.30-1.15 (5H, m), 1.12-0.98 (2H, m), 0.77 (3H, t); LC-MS: m/z 610.

[0292]

(ii)

(S)-2-((3-(4-((2-amino-4-(1-hydroxyhexan-3-ylamino)-6-methylpyrimidin-5-yl)methyl)-3-methoxyphenoxy)propyl)(2,2-difluoroethyl)amino)acetic acid

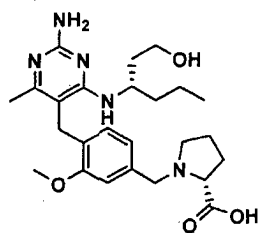


The sub-title compound was synthesized by the method of example 9 step (vii) from the product of step (i) (44 mg). The sub-title compound (38 mg) was obtained as a white amorphous solid;  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ); 6.80 (1H, d), 6.48-6.40 (2H, m), 5.89 (1H, tt), 5.89-5.73 (1H, m), 4.28-4.13 (1H, m), 4.07-3.97 (2H, m), 3.86 (3H, s), 3.63-3.56 (1H, m), 3.56 (2H, s), 3.40-3.30 (1H, m), 3.33 (2H, s), 3.17-2.85 (5H, m), 2.44 (3H, s), 1.96-1.85 (2H, m), 1.85-1.71 (1H, m), 1.52-1.39 (1H, m), 1.39-1.00 (4H, m), 0.81 (3H, t); LC-MS: m/z 540.

[0293]

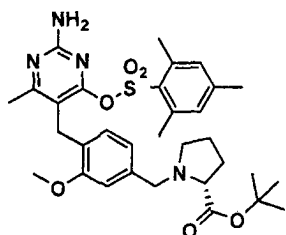
Example 13:

(R)-1-(4-((2-amino-4-((S)-1-hydroxyhexan-3-ylamino)-6-methylpyrimidin-5-yl)methyl)-3-methoxybenzyl)pyrrolidine-2-carboxylic acid



The title compound was prepared by the sequence of steps described below:

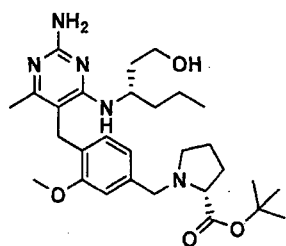
- (i) (R)-tert-butyl  
 5 1-(4-((2-amino-4-(mesitylsulfonyloxy)-6-methylpyrimidin-5-yl)methyl)-3-methoxybenzyl)pyrrolidine-2-carboxylate



The sub-title compound was synthesized by the method of example 1 step (vii) from the product of example 1 step (v) (200 mg) and (R)-tert-butyl pyrrolidine-2-carboxylate (108 mg). The  
 10 sub-title compound (234 mg) was obtained as a colourless amorphous solid; LC-MS: m/z 611.

[0294]

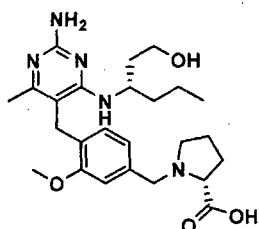
- (ii) (R)-tert-butyl  
 15 1-(4-((2-amino-4-((S)-1-hydroxyhexan-3-ylamino)-6-methylpyrimidin-5-yl)methyl)-3-methoxybenzyl)pyrrolidine-2-carboxylate



The sub-title compound was synthesized by the method of example 1 step (viii) from the product of step (i) (234 mg) and (S)-3-aminohexan-1-ol (X mg). The sub-title compound (70 mg) was obtained as a colourless amorphous solid; LC-MS: m/z 528. [0295]

(iii)

(R)-1-(4-((2-amino-4-((S)-1-hydroxyhexan-3-ylamino)-6-methylpyrimidin-5-yl)methyl)-3-methoxybenzyl)pyrrolidine-2-carboxylic acid



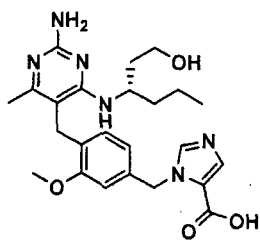
To a solution of the product of step (ii) (70 mg) in chloroform (1.5 mL) was added trifluoroacetic acid (1.5 mL) and the mixture was stirred at RT. After 12 h, methanol (10 mL) was stirred at room temperature. After 12 h, the mixture was concentrated under reduced pressure. 10% aqueous potassium dicarbonate was added and the resulting mixture was extracted with chloroform/EtOH (3/1). The combined organic layer was dried and concentrated under reduced pressure to afford the sub-title compound (50 mg)

as a white solid;  $^1\text{H}$  NMR (methanol- $d_4$ ); 7.23 (1H, d), 7.02-6.97 (2H, m), 4.47 (1H, m), 4.34 (2H, s), 3.97 (3H, s), 3.85-3.80 (3H, m), 3.64 (1H, m), 3.45-3.41 (2H, m), 2.44 (1H, m), 2.28 (3H, s), 2.11 (2H, m), 1.96 (1H, m), 1.74-1.20 (7H, m), 0.87 (3H, t); LC-MS:  $m/z$  472.

[0296]

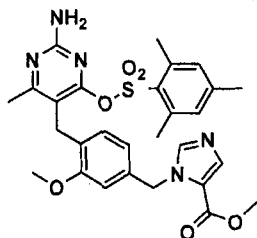
Example 14:

(S)-1-(4-((2-amino-4-(1-hydroxyhexan-3-ylamino)-6-methylpyrimidin-5-yl)methyl)-3-methoxybenzyl)-1H-imidazole-5-carboxylic acid



The title compound was prepared by the sequence of steps described below:

(i) methyl  
1-(4-((2-amino-4-(mesitylenesulfonyloxy)-6-methylpyrimidin-5-yl)methyl)-3-methoxybenzyl)-1H-imidazole-5-carboxylate



The sub-title compound was synthesized by the method of example 1 step (vii) from the product of example 1 step (v) (500 mg)

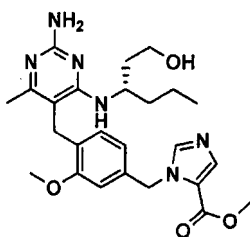
and Methyl 1H-imidazole-5-carboxylate (199 mg). The sub-title compound (90 mg) was obtained as a white solid; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>); 7.73 (1H, s), 7.61 (1H, s), 6.89 (2H, s), 6.83 (1H, d), 6.61 (1H, s), 6.55 (1H, d), 5.42 (2H, s), 3.78 (3H, s), 3.68 (5H, s), 2.46 (3H, s), 2.42 (6H, s), 2.26 (3H, s); LC-MS: m/z 566.

[0297]

(ii)

(S)-methyl

1-(4-((2-amino-4-(1-hydroxyhexan-3-ylamino)-6-methylpyrimidin-5-yl)methyl)-3-methoxybenzyl)-1H-imidazole-5-carboxylate

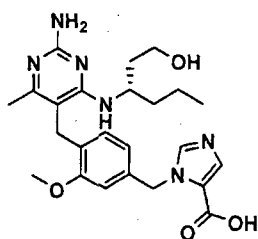


The sub-title compound was synthesized by the method of example 1 step (viii) from the product of step (i) (90 mg) and (S)-3-aminohexan-1-ol (56 mg). The sub-title compound (53 mg) was obtained as a colourless oil; LC-MS: m/z 483.

[0298]

(iii)

(S)-1-(4-((2-amino-4-(1-hydroxyhexan-3-ylamino)-6-methylpyrimidin-5-yl)methyl)-3-methoxybenzyl)-1H-imidazole-5-carboxylic acid



The sub-title compound was synthesized by the method of example 1 step (ix) from the product of step (ii) (53 mg). The sub-title compound (16 mg) was obtained as a colourless amorphous solid;

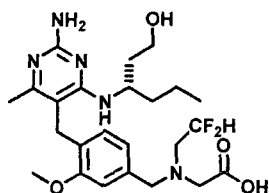
5 LC-MS: m/z 469.

[0299]

Example 15: Alternative procedure for

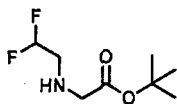
(S)-2-((4-((2-amino-4-(1-hydroxyhexan-3-ylamino)-6-methylpyrimidin-5-yl)methyl)-3-methoxybenzyl)(2,2-difluoroethyl)amino)acetic acid

10



The title compound was prepared by the sequence of steps described below:

(i) tert-butyl 2-(2,2-difluoroethylamino)acetate



15

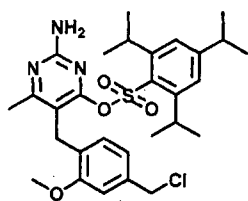
tert-Butyl bromoacetate (2.72 g) was added to a suspension of 2,2-difluoroethylamine (1.46 g) and potassium carbonate (2.48 g) in acetonitrile (5 mL) and the mixture was stirred at RT for

24 h. The mixture was diluted with EtOAc (10 mL) and hexane (10 mL). The suspension was washed with the mixture of aqueous NaHCO<sub>3</sub> (20 mL) and brine (10 mL). The organic extracts were dried and concentrated in vacuo to provide crude product. The crude product was purified by vacuum distillation (12hPa, 78-80°C) to afford sub-title compound (1.85 g) as a colourless oil; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>); 5.82 (1H, tt, J=4.4, 56 Hz), 3.45 (2H, s), 2.98 (2H, dt, J=4.4, 15.1 Hz), 1.45 (9H, s).

[0300]

10 (ii)

2-Amino-5-(4-chloromethyl-2-methoxybenzyl)-6-methylpyrimidin-4-yl 2,4,6-triisopropylbenzenesulfonate



To a solution of

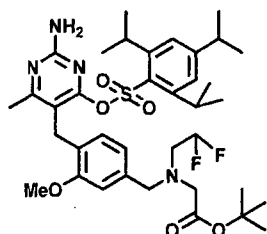
15 2-amino-5-(4-hydroxymethyl-2-methoxybenzyl)-6-methylpyrimidin-4-ol (5.0 g) and N,N-diisopropylethylamine (11.7 g) in tetrahydrofuran (50 g), 2,4,6-triisopropylbenzenesulfonyl chloride (8.3 g) was added and refluxed for 10 h. After cooling to RT, lithium chloride (2.3 g) was added to the reaction mixture and stirred for 0.5 h, methanesulfonyl chloride (4.2 g) was added over 0.25 h dropwise and the reaction mixture was stirred for 4 h at RT. To the reaction mixture, water (25 g) was added and extracted with ethyl acetate (25 g). The organic layer was

washed with water (25 mL) and concentrated in vacuo. To the residue, toluene (20 g) was added and concentrated on vacuo to obtain a light brown solid. The solid was precipitated with toluene (30 g) to obtain sub-title compound (6.8 g).

5  $^1\text{H-NMR}$ (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.17(2H, s), 6.90-6.82 (3H, m), 5.16 (2H, brs), 4.55 (2H, s), 4.10 (2H, septet,  $J=6.8\text{Hz}$ ), 3.82 (3H, s), 3.81 (2H, s), 2.91 (1H, septet,  $J=6.8\text{Hz}$ ), 2.32 (3H, s), 1.25 (6H, d,  $J=7.2\text{Hz}$ ), 1.19 (12H, d,  $J=6.8\text{Hz}$ )

[0301]

10 (iii) tert-butyl  
2-((4-((2-amino-4-methyl-6-(2,4,6-triisopropylphenylsulfonyloxy)pyrimidin-5-yl)methyl)-3-methoxybenzyl)(2,2-difluoroethyl)amino)acetate

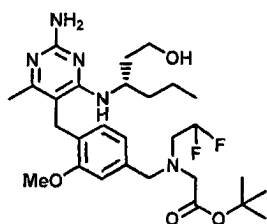


15 The mixture of the product of step (i) (209 mg), step (ii) (500 mg), sodium carbonate (283 mg) and potassium iodide (44 mg) in acetonitrile (4.0 g) was refluxed for 7 h. After cooling to RT, water (7.5 mL) was added to the mixture and extracted with mixture of EtOAc (10 mL) and n-heptane (4mL). The organic layer  
20 was dried with  $\text{Na}_2\text{SO}_4$  and concentrated in vacuo. The residue was precipitated with n-heptane (18 g) to afford sub-title compound (537 mg).

<sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>) δ 7.24 (2H, s), 6.83 (1H, s), 6.78 (1H, d, J=7.6Hz), 6.71 (1H, dd, J=7.6Hz, 1.2Hz), 5.74 (1H, tt, J=4.4, 56 Hz), 4.73 (2H, brs), 4.17-4.08 (2H, m), 3.85 (2H, s), 3.80-3.77 (5H, m), 3.33 (2H, s), 3.04 (2H, dt, J=4.4, 15 Hz), 2.93-2.85 (1H, m), 2.23 (3H, s), 1.45 (9H, s), 1.18 (6H, d, J=6.8Hz), 1.12 (12H, d, J=6.8Hz)

[0302]

(iv) (S)-tert-butyl 2-((4-((2-amino-4-(1-hydroxyhexan-3-ylamino)-6-methylpyrimidin-5-yl)methyl)-3-methoxybenzyl)(2,2-difluoroethyl)amino)acetate



The mixture of the product of step (iii) (300 mg), (S)-3-amino-1-hexanol (98 mg) and trifluoro acetic acid (24 mg) in mono-chlorobenzene (1.5 mL) was refluxed for 8 h. The mixture was cooled to RT and diluted with toluene (4 mL) and THF (1 mL). The mixture was washed with 0.5% aqueous LiOH (10 mL) for three times and brine (5 mL). The organic layer was dried, concentrated in vacuo and purified by flash column chromatography on silica gel to afford the sub-title compound (210 mg) as a colourless oil. <sup>1</sup>H NMR (300 MHz, CD<sub>3</sub>Cl<sub>3</sub>); 6.91-6.76 (2H, m), 6.78 (1H, d, J=7.6 Hz), 5.73 (1H, tt, J=4.4, 56 Hz),

4.87 (1H, brs), 4.69 (2H, brs), 4.15-4.05 (1H, m), 3.88 (3H, s), 3.85 (2H, s), 3.66 (1H, s), 3.48-3.42 (2H, m), 3.30-3.07 (3H, m), 3.03 (2H, dt, J=4.4, 15 Hz), 2.35 (3H, s), 1.83-1.75 (1H, m), 1.43-0.99 (15H, m), 0.74 (3H, t, J=7.6 Hz).

5 [0303]

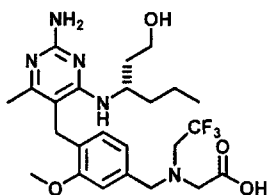
(v)

(S)-2-((4-((2-amino-4-(1-hydroxyhexan-3-ylamino)-6-methylpyrimidin-5-yl)methyl)-3-methoxybenzyl)(2,2-difluoroethyl)amino)acetic acid

10 The mixture of the product of step (iv) (13 mg) in 3N HCl (1 mL) was stirred at 50°C for 1.5 h. The mixture was cooled to RT and pH of the mixture was adjusted between pH 5 and pH 6 with 1N aqueous NaOH. The mixture was extracted with ethanol/chloroform (1/3) and the organic layer was dried and  
15 concentrated in vacuo to afford the sub-title compound (12 mg) as a colourless powder.

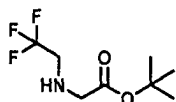
[0304]

Example 16: Alternative procedure of  
(S)-2-((4-((2-amino-4-(1-hydroxyhexan-3-ylamino)-6-methylpyrimidin-5-yl)methyl)-3-methoxybenzyl)(2,2,2-trifluoroethyl)amino)acetic acid  
20



The title compound was prepared by the sequence of steps described below:

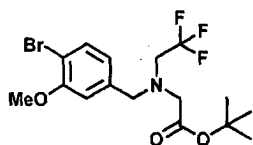
(i) tert-butyl 2-(2,2,2-trifluoroethylamino)acetate



5       The subtitled compound was synthesized by the method of example 15 step (i) from tert-butyl bromoacetate (13.6 g) and 2,2,2-trifluoroethylamine (8.9 g). The sub-title compound (11 g) was obtained as a colourless oil; <sup>1</sup>HNMR (300 MHz, CDCl<sub>3</sub>); 3.39 (2H, s), 3.20 (2H, q, J=9.4 Hz), 1.44 (9H, s).

10       [0305]

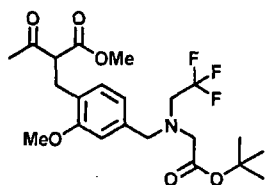
(ii) tert-butyl  
2-((4-bromo-3-methoxybenzyl)(2,2,2-trifluoroethyl)amino)acetate



15       The mixture of 1-bromo-4-(bromomethyl)-2-methoxybenzene (200 mg), the product of step (i) (228 mg), potassium carbonate (179 mg) and potassium iodide (35 mg) in N,N-dimethylacetamide (2 mL) was stirred at 75°C for 2 h. The mixture was diluted with EtOAc (10 mL) and the mixture was washed with water (10 mL) and  
20       brine (10 mL). The organic layer was dried, concentrated in vacuo and purified by flash column chromatography on silica gel to afford the sub-title compound (166 mg) as a colourless oil;

<sup>1</sup>H NMR (300 MHz, DMSO-d<sub>6</sub>); 7.51 (1H, d, J=8.0 Hz), 7.12 (1H, d, J=1.6 Hz), 6.82 (1H, dd, J=1.6, 8.0 Hz), 3.89 (2H, s), 3.81 (3H, s), 3.50 (2H, q, J=10 Hz), 3.35 (2H, s), 1.41 (9H, s).  
[0306]

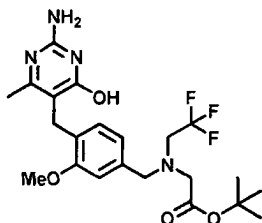
- 5 (iii) methyl  
2-(4-(((2-tert-butoxy-2-oxoethyl)(2,2,2-trifluoroethyl)amino)methyl)-2-methoxybenzyl)-3-oxobutanoate



The mixture of the product of step (ii) (110 mg), methyl  
10 3-hydroxy-2-methylenebutanoate (70 mg),  
N-methyldicyclohexylamine (105 mg), tetrabutylammonium  
chloride (8 mg) and 1,1'-bis(di-tert-butylphosphino)ferrocene  
palladium dichloride (19 mg) in N,N-dimethylacetamide (1 mL)  
was stirred at 100°C for 8 h. The mixture was diluted with EtOAc  
15 (10 mL) and washed with aqueous NaHCO<sub>3</sub> (10 mL). The organic layer  
was dried, concentrated in vacuo and purified by flash column  
chromatography on silica gel to afford the sub-title compound  
(81 mg) as a colourless oil; <sup>1</sup>H NMR (300 MHz, DMSO-d<sub>6</sub>); 7.01  
(1H, d, J=7.6 Hz), 6.86 (1H, s), 6.75 (1H, d, J=7.6 Hz), 3.91-3.84  
20 (3H, m), 3.75 (3H, s), 3.57 (3H, s), 3.48 (2H, q, J=10 Hz),  
3.04-2.89 (2H, m), 2.13 (3H, s), 1.42 (9H, s). MS:APCI 462 (M+1).  
[0307]

- (iv) tert-butyl

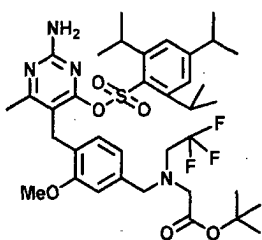
2-((4-((2-amino-4-hydroxy-6-methylpyrimidin-5-yl)methyl)-3-methoxybenzyl)(2,2,2-trifluoroethyl)amino)acetate



The mixture of the product of step (iii) (75 mg) and guanidine carbonate (50 mg) in MeOH (1 mL) was stirred at 65°C for 12 h. The mixture was cooled to RT and pH of the mixture was adjusted around pH8 with acetic acid and stirred for 0.5 h. The residue was filtered and the filtrate was purified by flash column chromatography on silica gel to afford the sub-title compound (35 mg) as a colourless powder; <sup>1</sup>H NMR (300 MHz, DMSO-d<sub>6</sub>); 10.71 (1H, s), 6.87-6.84 (1H, m), 6.79-6.77 (1H, m), 6.71-6.68 (1H, m), 6.28 (2H, s), 3.85 (2H, s), 3.78 (3H, s), 3.52-3.45 (4H, m), 1.92 (3H, s), 1.41 (9H, s).

[0308]

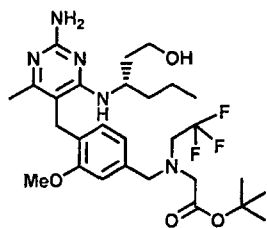
(v) tert-butyl 2-((4-((2-amino-4-methyl-6-(2,4,6-triisopropylphenylsulfonyloxy)pyrimidin-5-yl)methyl)-3-methoxybenzyl)(2,2,2-trifluoroethyl)amino)acetate



The mixture of the product of step (iv) (28 mg), 2,4,6-triisopropylbenzenesulfonylchloride (30 mg) and DABCO (5.5 mg) in THF (1 mL) was stirred at 40°C for 3 hours. The mixture was cooled to RT and diluted with EtOAc (10 mL). The mixture was washed with aqueous NaHCO<sub>3</sub> (10 mL). The organic layer was dried, concentrated in vacuo and purified by flash column chromatography on silica gel to afford the sub-title compound (28 mg) as a colourless oil; <sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>) δ 7.16 (2H, s), 6.88 (1H, d, J=1.2Hz), 6.79 (1H, d, J=7.6Hz), 6.71 (1H, dd, J=7.6Hz, 1.2Hz), 4.73 (2H, brs), 4.15 (2H, septet, J=6.8Hz), 3.92 (2H, s), 3.82 (2H, s), 3.80 (3H, s), 3.39-3.32 (4H, m), 2.91 (1H, septet, J=7.2Hz), 2.25 (3H, s), 1.47 (9H, s), 1.25 (6H, d, J=6.8Hz), 1.19 (12H, d, J=6.4Hz)

[0309]

(vi) (S)-tert-butyl 2-((4-((2-amino-4-(1-hydroxyhexan-3-ylamino)-6-methylpyrimidin-5-yl)methyl)-3-methoxybenzyl)(2,2,2-trifluoroethyl)amino)acetate



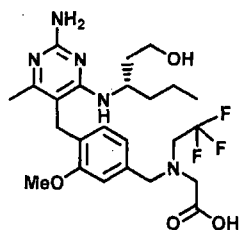
The sub-title compound was synthesized by the method of example 15 step (iv) from the product of Example 16 step (v) (25 mg). The sub-title compound (12 mg) was obtained as a colourless oil;

<sup>1</sup>H NMR (300 MHz, CD<sub>3</sub>OD); 7.01 (1H, s), 6.87-6.85 (1H, m),  
 6.81-6.78 (1H, m), 4.23-4.20 (1H, m), 3.92 (2H, s), 3.90 (3H,  
 s), 3.72 (2H, s), 3.44-3.30 (6H, m), 2.24 (3H, s), 1.85-1.70  
 (1H, m), 1.46-1.30 (13H, m), 1.23-1.08 (2H, m), 0.81-0.77 (3H,  
 m).

[0310]

(vii)

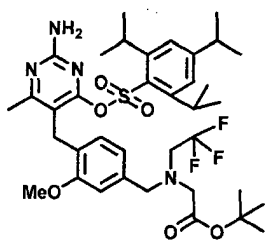
(S)-2-((4-((2-amino-4-(1-hydroxyhexan-3-ylamino)-6-methylpyrimidin-5-yl)methyl)-3-methoxybenzyl)(2,2,2-trifluoroethyl)amino)acetic acid



The sub-title compound was synthesized by the method of example 15 step (v) from the product of step (vi) (12 mg). The sub-title compound (11 mg) was obtained as a colourless powder.

[0311]

Example 17: Alternative procedure for tert-butyl 2-((4-((2-amino-4-methyl-6-(2,4,6-triisopropylphenylsulfonyloxy)pyrimidin-5-yl)methyl)-3-methoxybenzyl)(2,2,2-trifluoroethyl)amino)acetate



The mixture of 2-amino-5-(4-chloromethyl-2-methoxybenzyl)-6-methylpyrimidin-4-yl 2,4,6-triisopropylbenzenesulfonate (6.0 g), tert-butyl 2-(2,2,2-trifluoroethylamino)acetate (2.7 g), sodium carbonate (3.4 g) and potassium iodide (0.5 g) in acetonitrile (48 g) was refluxed for 8 h. After cooling to RT, water (30 g) was added to the mixture and extracted with toluene (48 g). The organic layer was washed with water (30 g) and concentrated in vacuo. The residue was precipitated with n-heptane (18 g) to afford the sub-title compound (12.2 g).

[0312]

Example 18: Preparation of the form B of the Compound of Example 3

To a solution of the product of example 3 step (iii) (1.38 g) in MeOH (12.5 mL), 3 M NaOH aq. (4.2 mL) was added. The mixture was stirred for 3 h at room temperature, and neutralized with 4 M HCl aq. (5.0 mL) and sat. NaHCO<sub>3</sub> aq. (5.0 mL). The resulting suspension was concentrated to about half in volume. Then, the precipitation crystals were filtered and washed with cooled water (15 mL). After vacuum drying, Form B of example 3 (1.0 g) was obtained as a white solid.

[0313]

Example 19: Preparation of the form A of the Compound of Example  
3

The compound of Example 18 (45 mg) was mixed with water (1 mL)  
5 and acetone (0.2 mL) and stirred at 60°C for 1 hr. Then water  
(0.5 mL) was added, and the mixture was cooled to ambient  
temperature. After 1h, the precipitation crystals were filtered.  
After vacuum drying Form A of example 3 (38 mg) was obtained  
as a white solid.

10 [0314]

Example 20: Preparation of the form E of the Compound of Example  
3

The compound of Example 19 (5mg) was dissolved by EtOH (50 ml)  
at 90 °C. The solution was cooled to ambient temperature. After  
15 1h, the precipitation crystals were filtered and put in 93 %RH  
condition for 3days. Form E of example 3 (2 mg) was obtained  
as a white solid.

[0315]

Example 21: Preparation of the form A of the Compound of Example

20 4

3N-NaOH (0.5 mL) was added to the solution of the product of  
example 4 step (iii) (170 mg) in MeOH (2 mL). The solution was  
stirred at room temperature for 1.5 h. The reaction mixture was  
acidified with 2N-HCl (1.4 mL), neutralized with saturated  
25 aqueous NaHCO<sub>3</sub> (0.3 mL) and extracted with CHCl<sub>3</sub>/EtOH (v/v =

3/1). The combined organic layer was dried over  $\text{Na}_2\text{SO}_4$ , filtered and concentrated under reduced pressure. EtOAc (20 mL) was added to the residue and sonicated. The mixture was stirred under reflux condition for 5 min then cooled to room temperature. The suspension was stirred at room temperature for 30 min. The precipitate was collected by filtration. Form A of compound example 4 (143 mg) was obtained as a white solid.

[0316]

Example 22: Differential Scanning Calorimetry (DSC) of the compound obtained in Example 18-21.

The calorimetric response of the test sample to increasing temperature was investigated using a TA Instruments Q1000 Differential Scanning Calorimeter (DSC). Measurements were performed from 10 to 250 °C with a ramp rate of 10 °C per minute. Approximately 0.5 to 5 mg of the test sample was placed in an aluminum pan with lid (crimped and pinholed) under a flow of nitrogen gas (50 mL/min).

The result is shown in Figure 1-4. An endothermic peak and an exothermic peak appeared from 260 °C.

[0317]

Example 23: X-Ray Powder Diffraction Analyses of the compound obtained in Example 18-21.

Panalytical X'pert Alpha 1 system with monochromatic  $\text{CuK}\alpha$  radiation (45 kV and 40 mA) was used for the analysis. The primary optics contained metal mask and an automatic divergence slit.

Flat samples were prepared on the zero background plates that were rotated during the measurements. The secondary optics contained soller slits, an automatic anti scatter slit and a monochromator. The diffracted signal was detected with a detector (X'Celerator). Diffraction patterns were collected at  $4^\circ \leq 2\theta$  (theta)  $\leq 30$ - $40^\circ$  in a continuous scan mode with 100-second exposure per  $0.017^\circ$ . Raw data were stored electronically. The results are shown in Figure 5-8 and Table 1-4

10 [Table 1]

Table 1 XRD data of Example 18(From B).

| Pos. [ $2\theta$ ] | d-spacing [ $\text{\AA}$ ] | relative<br>intensity [%] |
|--------------------|----------------------------|---------------------------|
| 6.5405             | 13.50317                   | 100                       |
| 9.5427             | 9.26071                    | 6.19                      |
| 10.1255            | 8.72892                    | 75.35                     |
| 10.9117            | 8.10168                    | 58.65                     |
| 13.0489            | 6.77919                    | 10.92                     |
| 13.9263            | 6.35398                    | 16.1                      |
| 15.2431            | 5.80793                    | 15.96                     |
| 16.4823            | 5.37392                    | 8                         |
| 16.777             | 5.28021                    | 24.4                      |
| 17.0169            | 5.2063                     | 17.93                     |
| 17.5125            | 5.06006                    | 11.74                     |

|         |         |       |
|---------|---------|-------|
| 17.9973 | 4.92482 | 15.27 |
| 18.3734 | 4.82485 | 13.12 |
| 18.6586 | 4.75175 | 10.63 |
| 19.2222 | 4.61369 | 43.79 |
| 19.5965 | 4.52639 | 11.33 |
| 20.0458 | 4.42594 | 9.6   |
| 20.4279 | 4.34401 | 10.49 |
| 20.8812 | 4.25072 | 32.04 |
| 22.1453 | 4.01086 | 14.91 |
| 22.8051 | 3.89628 | 7.87  |
| 23.637  | 3.761   | 55.76 |
| 24.2084 | 3.67352 | 12.39 |
| 25.1576 | 3.53702 | 13.37 |
| 25.6668 | 3.46799 | 15.53 |
| 25.9557 | 3.43004 | 27.97 |
| 26.5107 | 3.35948 | 14.07 |
| 27.4235 | 3.24969 | 17.76 |
| 30.814  | 2.89941 | 5.88  |

---

[Table 2]

Table 2 XRD data of Example 19 (Form A).

| Pos. [ $2\theta$ ] | d-spacing [ $\text{\AA}$ ] | relative      |
|--------------------|----------------------------|---------------|
|                    |                            | intensity [%] |
| 7.8835             | 11.20558                   | 38.83         |
| 10.9385            | 8.08194                    | 45.5          |
| 12.3678            | 7.15094                    | 68.29         |
| 13.1016            | 6.75202                    | 14.38         |
| 14.6608            | 6.03724                    | 17.09         |
| 15.7499            | 5.62214                    | 25.46         |
| 16.0343            | 5.52306                    | 10.08         |
| 16.3252            | 5.4253                     | 14.29         |
| 16.9925            | 5.21372                    | 49.92         |
| 17.763             | 4.98927                    | 43.88         |
| 18.3066            | 4.84233                    | 10.49         |
| 18.588             | 4.76965                    | 40.3          |
| 19.1668            | 4.62689                    | 32.82         |
| 19.6059            | 4.52424                    | 20.27         |
| 20.9633            | 4.23426                    | 100           |
| 21.5335            | 4.12342                    | 12.96         |
| 21.937             | 4.04846                    | 31.4          |
| 22.5622            | 3.93768                    | 20.21         |
| 23.3569            | 3.80547                    | 19.35         |

|         |         |       |
|---------|---------|-------|
| 23.8257 | 3.73164 | 44.83 |
| 24.4437 | 3.63867 | 57.1  |
| 25.787  | 3.45209 | 41.09 |
| 27.3243 | 3.26126 | 10.13 |
| 28.8489 | 3.09229 | 10.23 |
| 29.8528 | 2.99055 | 19.07 |
| 30.9551 | 2.88652 | 13.15 |
| 31.2064 | 2.86385 | 11.54 |
| 31.7293 | 2.81783 | 10.8  |
| 31.9519 | 2.79871 | 15.59 |
| 37.4073 | 2.40213 | 10.72 |

[Table 3]

Table 3 XRD data of Example 20 (Form E)

| Pos. [ $2\theta$ ] | d-spacing [Å] | relative<br>intensity [%] |
|--------------------|---------------|---------------------------|
| 8.1575             | 10.82981      | 100                       |
| 11.2091            | 7.88743       | 5.81                      |
| 11.5525            | 7.65373       | 6.57                      |
| 11.9207            | 7.41815       | 26.96                     |
| 12.8753            | 6.87017       | 48.08                     |
| 14.6921            | 6.02448       | 9.64                      |
| 15.0144            | 5.89585       | 5.33                      |

|         |         |       |
|---------|---------|-------|
| 15.5873 | 5.68043 | 8.02  |
| 15.8084 | 5.60147 | 8.22  |
| 16.3069 | 5.43135 | 12.71 |
| 17.4032 | 5.09159 | 7.27  |
| 18.2706 | 4.85179 | 16.74 |
| 19.2195 | 4.61433 | 5.18  |
| 19.853  | 4.4685  | 10.6  |
| 20.0704 | 4.42058 | 11.12 |
| 20.8876 | 4.24944 | 10.7  |
| 21.3279 | 4.16269 | 10.49 |
| 21.8003 | 4.07355 | 7.31  |
| 22.0481 | 4.02832 | 5.39  |
| 22.7843 | 3.89979 | 20.23 |
| 23.1742 | 3.83505 | 9.78  |
| 23.9179 | 3.71747 | 18.89 |
| 24.5882 | 3.61762 | 11.8  |
| 24.9957 | 3.55956 | 27.96 |
| 25.402  | 3.50353 | 13.89 |
| 25.9936 | 3.42513 | 6.99  |

---

[Table 4]

Table 4 XRD data of Example 21 (Form A)

| Pos. [ $2\theta$ ] | d-spacing [Å] | relative<br>intensity [%] |
|--------------------|---------------|---------------------------|
| 7.8637             | 11.23377      | 16.54                     |
| 10.9314            | 8.08713       | 71.64                     |
| 12.2995            | 7.1905        | 69.75                     |
| 13.0374            | 6.78512       | 15.64                     |
| 14.6241            | 6.05231       | 9.45                      |
| 15.7034            | 5.63871       | 44.31                     |
| 16.2899            | 5.43698       | 12.05                     |
| 16.8872            | 5.24598       | 49.59                     |
| 17.7791            | 4.98477       | 57.52                     |
| 18.2426            | 4.85916       | 20.16                     |
| 18.5466            | 4.7802        | 56.98                     |
| 19.0971            | 4.64362       | 28.99                     |
| 19.5228            | 4.54331       | 15.32                     |
| 20.9586            | 4.23519       | 100                       |
| 21.4725            | 4.13499       | 15.31                     |
| 21.9023            | 4.0548        | 51.87                     |
| 22.5885            | 3.93316       | 15.63                     |
| 23.2747            | 3.81872       | 35.35                     |
| 23.7843            | 3.73804       | 33.87                     |
| 24.2659            | 3.66493       | 19.29                     |

|         |         |       |
|---------|---------|-------|
| 24.5021 | 3.63014 | 52.36 |
| 25.7954 | 3.45099 | 37.51 |
| 27.2366 | 3.27157 | 14.86 |
| 28.8434 | 3.09287 | 9.74  |
| 29.8817 | 2.98772 | 16.53 |
| 31.6801 | 2.8221  | 12.73 |
| 31.9161 | 2.80177 | 9.19  |
| 36.6275 | 2.45146 | 9.52  |
| 37.0775 | 2.42274 | 10.56 |

---

[0318]

Example 24: Human TLR7 assay

Recombinant human TLR7 was stably expressed in a HEK293 cell  
5 line already stably expressing the pNiFty2-SEAP reporter  
plasmid; integration of the reporter gene was maintained by  
selection with the antibiotic zeocin. The most common variant  
sequence of human TLR7 (represented by the EMBL sequence  
AF240467) was cloned into the mammalian cell expression vector  
10 pUNO and transfected into this reporter cell-line.  
Transfectants with stable expression were selected using the  
antibiotic blasticidin. In this reporter cell-line, expression  
of secreted alkaline phosphatase (SEAP) is controlled by an  
NFkB/ELAM-1 composite promoter comprising five NFkB sites  
15 combined with the proximal ELAM-1 promoter. TLR signaling leads  
to the translocation of NFkB and activation of the promoter

results in expression of the SEAP gene. TLR7-specific activation was assessed by determining the level of SEAP produced following overnight incubation of the cells at 37°C with the standard compound in the presence of 0.1% (v/v) dimethylsulfoxide (DMSO). Concentration dependent induction of SEAP production by compounds was expressed as the concentration of compound which produced half of the maximal level of SEAP induction for that compound (EC<sub>50</sub>). TLR7 activity for compounds of the present disclosure was assessed using the human TLR7 assay and the results are shown in Table 5 below wherein the degree of TLR7 activation for each compound is expressed as a pEC<sub>50</sub> value.

[Table 5]

Table 5

| Compound<br>of Ex. No. | TLR7 (pEC <sub>50</sub> ) | Compound<br>of Ex. No. | TLR7 (pEC <sub>50</sub> ) |
|------------------------|---------------------------|------------------------|---------------------------|
| 1                      | 6.8                       | 8                      | 6.9                       |
| 2                      | 6.1                       | 9                      | 6.7                       |
| 3                      | 7.1                       | 10                     | 6.6                       |
| 4                      | 7.0                       | 11                     | 6.7                       |
| 5                      | 7.3                       | 12                     | 7.0                       |
| 6                      | 6.6                       | 13                     | 6.7                       |
| 7                      | 6.6                       | 14                     | 5.7                       |

## Example 25: Human TLR8 assay

TLR8/NF- $\kappa$ B/SEAPorter™ HEK 293 Cell Line (Imgenex Corporation) is a stably co-transfected cell line which expresses full-length human TLR8 and the secreted alkaline phosphatase (SEAP) reporter gene under the transcriptional control of an NF- $\kappa$ B response element. TLR8 expression in this cell line has been tested by flow cytometry. Transfectants with stable expression were selected using the antibiotic blasticidin and geneticin. TLR signaling leads to the translocation of NF- $\kappa$ B and activation of the promoter results in expression of the SEAP gene. TLR8-specific activation was assessed by determining the level of SEAP produced following overnight incubation of the cells at 37°C with the standard compound in the presence of 0.1% (v/v) dimethylsulfoxide (DMSO). Concentration dependent induction of SEAP production by compounds was expressed as the concentration of compound which produced half of the maximal level of SEAP induction for that compound (EC<sub>50</sub>). TLR8 activity for compounds of the present disclosure was assessed using the human TLR8 assay and the results are shown in Table 6 below wherein the degree of TLR8 activation for each compound is expressed as a pEC<sub>50</sub> value.

[Table 6]

**Table 6**

| Compound of<br>Ex. No. | TLR8 pEC <sub>50</sub> | Compound of<br>Ex. No. | TLR8 pEC <sub>50</sub> |
|------------------------|------------------------|------------------------|------------------------|
| 1                      | <5                     | 8                      | <5                     |
| 2                      | <5                     | 9                      | <5                     |
| 3                      | <5                     | 10                     | <5                     |
| 4                      | <5                     | 11                     | <5                     |
| 5                      | <5                     | 12                     | <5                     |
| 6                      | <5                     | 13                     | <5                     |
| 7                      | <5                     | 14                     | <5                     |

[0320]

## 5 Example 26: hERG Analysis - Method 1

## Cell culture

The hERG-expressing Chinese hamster ovary K1 (CHO) cells described by (Persson, Carlsson, Duker, & Jacobson, 2005) were grown to semi-confluence at 37°C in a humidified environment (5% CO<sub>2</sub>) in F-12 Ham medium containing L-glutamine, 10% foetal calf serum (FCS) and 0.6mg/mL hygromycin (all available from Sigma-Aldrich). Prior to use, the monolayer was washed using a pre-warmed (37°C) 3mL aliquot of Versene 1:5,000 (Invitrogen). After aspiration of this solution the flask was incubated at 37°C in an incubator with a further 2mL of Versene 1:5,000 for

a period of 6 minutes. Cells were then detached from the bottom of the flask by gentle tapping and 10mL of Dulbecco's Phosphate-Buffered Saline containing calcium (0.9mM) and magnesium (0.5mM) (PBS; Invitrogen) was then added to the flask and aspirated into a 15mL centrifuge tube prior to centrifugation (50g, for 4 mins). The resulting supernatant was discarded and the pellet gently re-suspended in 3mL of PBS. A 0.5mL aliquot of cell suspension was removed and the number of viable cells (based on trypan blue exclusion) was determined in an automated reader (Cedex; Innovatis) so that the cell re-suspension volume can be adjusted with PBS to give the desired final cell concentration. It is the cell concentration at this point in the assay that is quoted when referring to this parameter. CHO-Kv1.5 cells, which were used to adjust the voltage offset on IONWORKS™ HT, were maintained and prepared for use in the same way.

[0321]

#### Electrophysiology

The principles and operation of this device have been described by (Schroeder, Neagle, Trezise, & Worley, 2003). Briefly, the technology is based on a 384-well plate (PATCHPLATE™) in which a recording was attempted in each well by using suction to position and hold a cell on a small hole separating two isolated fluid chambers. Once sealing had taken place, the solution on the underside of the PATCHPLATE™ was changed to one containing

amphotericin B. This permeabilises the patch of cell membrane covering the hole in each well and, in effect, allowed a perforated, whole-cell patch clamp recording to be made.

[0322]

5 A  $\beta$ -test IONWORKS™ HT from Essen Instrument was used. There is no capability to warm solutions in this device hence it is operated at ~r.t. (~21°C), as follows. The reservoir in the "Buffer" position was loaded with 4 mL of PBS and that in the "Cells" position with the CHO-hERG cell suspension described  
10 above. A 96-well plate (V-bottom, Greiner Bio-one) containing the compounds to be tested (at 3-fold above their final test concentration) was placed in the "Plate 1" position and a PATCHPLATE™ was clamped into the PATCHPLATE™ station. Each compound plate was laid-out in 12 columns to enable ten, 8-point  
15 concentration-effect curves to be constructed; the remaining two columns on the plate were taken up with vehicle (final concentration 0.33% DMSO), to define the assay baseline, and a supra-maximal blocking concentration of cisapride (final concentration 10  $\mu$ M) to define the 100% inhibition level. The  
20 fluidics-head (F-Head) of IONWORKS™ HT then added 3.5  $\mu$ L of PBS to each well of the PATCHPLATE™ and its underside was perfused with "internal" solution that had the following composition (in mM): K-Gluconate (100 parts), KCl (40 parts), MgCl<sub>2</sub> (3.2 parts), EGTA (3 parts) and HEPES (5 parts, pH 7.25-7.30 using 10M KOH).  
25 After priming and de-bubbling, the electronics-head (E-head)

then moved around the PATCHPLATE™ performing a hole test (i.e. applying a voltage pulse to determine whether the hole in each well is open). The F-head then dispensed 3.5µL of the cell suspension described above into each well of the PATCHPLATE™

5 and the cells were given 200 seconds to reach and seal to the hole in each well. Following this, the E-head moved around the PATCHPLATE™ to determine the seal resistance obtained in each well. Next, the solution on the underside of the PATCHPLATE™ was changed to "access" solution that has the following

10 composition (in mM): KCl (140 parts), EGTA (1 part), MgCl<sub>2</sub> (1 part), and HEPES (20 parts, pH 7.25-7.30 using 10M KOH) plus 100µg/mL of amphotericin B (Sigma-Aldrich). After allowing 9 minutes for patch perforation to take place, the E-head moved around the PATCHPLATE™ 48 wells at a time to obtain pre-compound

15 hERG current measurements. The F-head then added 3.5µL of solution from each well of the compound plate to 4 wells on the PATCHPLATE™ (the final DMSO concentration is 0.33% in every well). This was achieved by moving from the most dilute to the most concentrated well of the compound plate to minimise the

20 impact of any compound carry-over. After approximately 3.5 mins incubation, the E-head then moved around all 384-wells of the PATCHPLATE™ to obtain post-compound hERG current measurements. In this way, non-cumulative concentration-effect curves can be produced where, providing the acceptance criteria are achieved

25 in a sufficient percentage of wells (see below), the effect of

each concentration of test compound was based on recording from between 1 and 4 cells.

[0323]

The pre- and post-compound hERG current was evoked by a single  
5 voltage pulse consisting of a 20 second period holding at -70mV,  
a 160millisecond step to -60mV (to obtain an estimate of leak),  
a 100millisecond step back to -70mV, a 1 second step to + 40mV,  
a 2 second step to -30mV and finally a 500 millisecond step to  
-70mV. In between the pre- and post-compound voltage pulses  
10 there was no clamping of the membrane potential. Currents were  
leak-subtracted based on the estimate of current evoked during  
the +10mV step at the start of the voltage pulse protocol. Any  
voltage offsets in IONWORKS™ HT were adjusted in one of two ways.  
When determining compound potency, a depolarising voltage ramp  
15 was applied to CHO-Kv1.5 cells and the voltage noted at which  
there was an inflection point in the current trace (i.e. the  
point at which channel activation is seen with a ramp protocol).  
The voltage at which this occurred has previously been  
determined using the same voltage command in conventional  
20 electrophysiology and found to be -15mV (data not shown); thus  
an offset potential could be entered into the IONWORKS™ HT  
software using this value as a reference point. When determining  
the basic electrophysiological properties of hERG, any offset  
was adjusted by determining the hERG tail current reversal  
25 potential in IonWorks™ HT, comparing it with that found in

conventional electrophysiology (-82mV) and then making the necessary offset adjustment in the IONWORKS™ HT software. The current signal is sampled at 2.5kHz.

[0324]

5 Pre- and post-scan hERG current magnitude was measured automatically from the leak subtracted traces by the IonWorks™ HT software by taking a 40ms average of the current during the initial holding period at -70 mV (baseline current) and subtracting this from the peak of the tail current response.

10 The acceptance criteria for the currents evoked in each well are: pre-scan seal resistance >60MΩ, pre-scan hERG tail current amplitude >150pA; post-scan seal resistance >60MΩ. The degree of inhibition of the hERG current can be assessed by dividing the post-scan hERG current by the respective pre-scan hERG

15 current for each well. References: Persson, F. et al, J Cardiovasc. Electrophysiol., 16, 329-341 (2005), and Schroeder, K., et al, J Biomol Screen., 8, 50-64, (2003).

[0325]

Example 27: hERG analysis - Method 2

20 The hERG potassium current was measured in a hERG-stably-expressing Chinese hamster ovary K1 (CHO) cells. The experiments were performed using an automated planar patch-clamp system QPATCH HT (Sophion Bioscience A/S). The application of pressure for forming gigaseals and whole-cell

25 patch clamp configuration were established using the QPATCH

assay software. Patch-clamp experiments were performed in voltage-clamp mode and whole-cell currents were recorded from individual cells. The following stimulation protocol was applied to investigate the effects of compounds on hERG potassium channel. : The membrane potential was held at -80 mV and repetitively (every 15 s) depolarized to +20 mV for 5 s after the pulse to -50 mV for 20 ms served to define the baseline, followed by repolarizing step to -50 mV for 5 s to evaluate of the tail current amplitude. Experiments were conducted at room temperature (22±2°C).

[0326]

Effects of compounds were determined from cumulative applications of increasing 4 concentrations and calculated as percent of blocked current. The data points were fitted with Hill equation to calculate half-maximal inhibition concentrations. The test solution includes:

Extracellular solution (mM): 2mM of CaCl<sub>2</sub>, 1mM of MgCl<sub>2</sub>, 10mM of HEPES, 4mM of KCl, 145 mM of NaCl, and 10mM of Glucose; and Intracellular solution (mM): 5.4mM of CaCl<sub>2</sub>, 1.8mM of MgCl<sub>2</sub>, 10mM of HEPES, 31mM of KOH, 10mM of EGTA, 120mM of KCl, and 4mM of ATP.

The results of the hERG analysis are shown in Table 7:

[Table 7]

Table 7

| Ex. No. | hERG (Method 1) $\mu$ M | hERG (Method 2) $\mu$ M |
|---------|-------------------------|-------------------------|
| 1       | >33                     | >10                     |
| 2       |                         | >10                     |
| 3       | >33                     | >10                     |
| 4       |                         | >10                     |
| 5       | >33                     | >10                     |
| 6       | >33                     | >10                     |
| 7       |                         | >10                     |
| 8       |                         | >10                     |
| 9       |                         | >10                     |

[0327]

5 Example 28: Tumour growth studies in Renca, a murine syngeneic renal carcinoma tumour model

Experiments were conducted on female mice (Balb/C genotype, at least 5 weeks old). Renca mouse tumour cells (Cancer Chemother Pharmacol. 1995; 36 (1): 7-12) were kindly provided by Dr. T. Fujioka at Department of Urology, Iwate Medical University School of Medicine. Renca mouse tumour cells ( $5 \times 10^4$ ) were implanted subcutaneously in the flank of mice on day 0. Mice were treated with either drug vehicle (0.5% methylcellulose), the compound of Example 3 (0.3 mg/kg once a week) or the compound of Example 4 (3 mg/kg once a week) administered orally (p. o.)

10

15

on days 1, 8, and 15. Tumour volumes were assessed at least twice weekly by bilateral vernier caliper measurements.

Tumour growth inhibition from the start of treatment was assessed by comparison of the differences in tumour growth rate

5 between control and the compound of Example 3 treated groups, as shown in Figure 9.

Tumour growth inhibition from the start of treatment was assessed by comparison of the differences in tumour growth rate between control and the compound of the Example 4 treated groups,

10 as shown in Figure 10.

Figure 9 and Figure 10 show that compound of Example 3 and 4 inhibited tumour growth via oral administration.

[0328]

Example 29: Metastasis studies in LM8, a murine osteosarcoma  
15 tumour model

Experiments were conducted on female mice (C3H genotype, at least 5 weeks old). LM8 mouse tumour cells (RCB1450) were purchased from RIKEN. LM8 mouse tumour cells ( $3 \times 10^6$ ) were implanted subcutaneously in the flank of mice on day 0. Mice  
20 in radiotherapy alone (RT) group and combination group were anesthetized and received radiation therapy (2Gy) at days 11, 12, 13, 14, and 15. Mice in combination group were also treated with either drug: a compound of Example 3 (10 mg/kg once a week) or a compound of Example 4 (5 mg/kg once a week) administered  
25 intravenously (i.v.) on days 11, 18, 25, and 32. Mice were

euthanized at day 36, and lungs were isolated. Each lung were weighed, and observed metastasis.

Compared to control group, lung metastasis was significantly inhibited in RT treated group and combination group. Compared to RT group, lung metastasis was significantly inhibited in combination group, as shown in Figure 11.

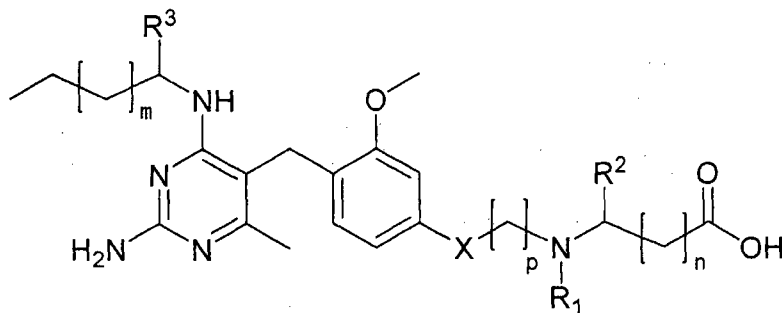
[0329]

Example 30: Survival studies in CT26, a murine syngeneic colon carcinoma tumour model

Experiments were conducted on female mice (Balb/C genotype, at least 5 weeks old). CT26 mouse tumour cells (CRL-2638) were purchased from ATCC. CT26 mouse tumour cells ( $1 \times 10^6$ ) were implanted subcutaneously in the flank of mice on day 0. Mice in radiotherapy alone (RT) group and combination group were anesthetized and received radiation therapy (2Gy) at days 7, 8, 9, 10, and 11. Mice in combination group were also treated with a compound of Example 3 (30 mg/kg once a week) administered orally (p.o.) or Example 4 (5 mg/kg once a week) administered intravenously (i. v.) on days 7, 14, 22, and 27. Tumour volumes were assessed at least twice weekly by bilateral vernier caliper measurements. Survival period was determined by the time taken for tumours to reach 4 times the volume at the time of treatment. Mice in combination treat group survived significantly longer than control or RT treatment group, Figure 12 and 13.

## CLAIMS

1. At least one entity chosen from compounds of Formula (I):



(I)

wherein:

$n$  is 0, 1, or 2;

$m$  is 1 or 2;

$p$  is 1, 2, or 3, provided that when  $X$  is oxygen,  $p$  is 2 or 3,

and when  $X$  is a single bond,  $p$  is 1;

$X$  is oxygen or a single bond;

$R^1$  is chosen from hydrogen,  $C_{1-4}$  alkyl groups,  $C_{1-3}$  alkyl- $(CH_2)$ -groups wherein  $C_{1-3}$  alkyl moiety is substituted by 1, 2, or 3 fluorine atoms,  $C_{1-4}$  alkyl groups substituted by cyano,  $C_{1-3}$  alkoxy- $C_{2-4}$  alkyl groups,  $C_{3-6}$  cycloalkyl groups,  $C_{1-4}$  alkylcarbonyl groups, and formyl;

$R^2$  is chosen from hydrogen and  $C_{1-4}$  alkyl groups;

or  $R^1$  and  $R^2$  together with the nitrogen and carbon atoms to which they are attached form a saturated or unsaturated 4- to 6-membered heterocyclyl ring optionally containing a further

heteroatom chosen from N, O, and S, wherein said N heteroatom may be optionally substituted by C<sub>1-3</sub> alkyl;

R<sup>3</sup> is chosen from hydrogen, hydroxymethyl, and 2-hydroxyethyl; and pharmaceutically acceptable salts thereof.

5     2.     The compound according to claim 1, wherein m is 1, or a pharmaceutically acceptable salt thereof.

3.     The compound according to claim 1 or 2, wherein R<sup>3</sup> is 2-hydroxyethyl, or a pharmaceutically acceptable salt thereof.

4.     The compound according to any one of claims 1 to 3, wherein  
10    R<sup>2</sup> is hydrogen or C<sub>1-4</sub> alkyl, or a pharmaceutically acceptable salt thereof.

5.     The compound according to claim 4, wherein R<sup>2</sup> is hydrogen, or a pharmaceutically acceptable salt thereof.

6.     The compound according to claim 4 or 5, wherein X is single  
15    bond and p is 1, or a pharmaceutically acceptable salt thereof.

7.     The compound according to any one of claims 4 or 5, wherein X is oxygen and p is 3, or a pharmaceutically acceptable salt thereof.

8.     The compound according to any one of claims 4 to 7, wherein  
20    n is 0 or 1, or a pharmaceutically acceptable salt thereof.

9.     The compound according to any one of claims 1 to 3, wherein R<sup>1</sup> and R<sup>2</sup> together with the nitrogen atom and carbon atoms to which they are attached form a saturated or unsaturated 4- to 6-membered heterocyclyl ring optionally containing a further  
25    heteroatom selected from N, O and S, wherein said N heteroatom

may be optionally substituted by C<sub>1-3</sub>alkyl; or a pharmaceutically acceptable salt thereof.

10. The compound according to claim 9, wherein R<sup>1</sup> and R<sup>2</sup> together with the nitrogen atom and carbon atoms to which they are attached form a saturated 4- to 6-membered heterocyclyl ring optionally containing a further heteroatom selected from N, O and S, wherein said N heteroatom may be optionally substituted by C<sub>1-3</sub>alkyl; or a pharmaceutically acceptable salt thereof.

11. The compound according to claim 10, wherein the saturated 4- to 6-membered heterocyclyl ring is pyrrolidine, piperidine, or morpholine; or a pharmaceutically acceptable salt thereof.

12. The compound according to claim 9, wherein R<sup>1</sup> and R<sup>2</sup> together with the nitrogen atom and carbon atoms to which they are attached form an unsaturated 5- or 6-membered heterocyclyl ring optionally containing a further heteroatom selected from N, O and S, wherein said N heteroatom may be optionally substituted by C<sub>1-3</sub>alkyl; or a pharmaceutically acceptable salt thereof.

13. The compound according to claim 12, wherein the unsaturated 5- or 6-membered heterocyclyl ring is imidazole; or a pharmaceutically acceptable salt thereof.

14. The compound according to any one of claims 9 to 13, wherein n is 0, or pharmaceutically acceptable salt thereof.

15. The compound according to any one of claims 9 to 14, wherein X is oxygen and p is 3, or a pharmaceutically acceptable

salt thereof.

16. The compound according to any one of claims 9 to 14, wherein X is single bond and p is 1.

17. The compound according to any one of claims 1 to 16,  
5 wherein R<sup>1</sup> is C<sub>1-4</sub>alkyl, C<sub>1-3</sub>alkyl-(CH<sub>2</sub>)- wherein C<sub>1-3</sub>alkyl is substituted by 1, 2 or 3 fluorine atoms, C<sub>1-4</sub>alkyl substituted by cyano, C<sub>1-3</sub>alkoxyC<sub>2-4</sub>alkyl, C<sub>3-6</sub>cycloalkyl, C<sub>1-4</sub>alkylcarbonyl or formyl, or a pharmaceutically acceptable salt thereof.

18. The compound according to claim 17, wherein R<sup>1</sup> is ethyl,  
10 2-monofluoroethyl, 2,2-difluoroethyl, 2,2,2-trifluoroethyl or acetyl, or a pharmaceutically acceptable salt thereof.

19. The compound according to claim 18, wherein R<sup>1</sup> is ethyl, 2,2-difluoroethyl, 2,2,2-trifluoroethyl or acetyl, or a pharmaceutically acceptable salt thereof.

15 20. The compound according to any one of claims 1 to 19, wherein m is 1, or a pharmaceutically acceptable salt thereof.

21. The at least one entity according to claim 1, wherein m is 1.

22. The at least one entity according to claim 1, wherein R<sup>3</sup>  
20 is 2-hydroxyethyl.

23. The at least one entity according to claim 1, wherein R<sup>2</sup> is chosen from C<sub>1-4</sub> alkyl groups.

24. The at least one entity according to claim 1, wherein R<sup>2</sup> is hydrogen.

25 25. The at least one entity according to claim 1, wherein X

is single bond and p is 1.

26. The at least one entity according to claim 1, wherein X is oxygen and p is 3.

27. The at least one entity according to claim 1, wherein n  
5 is 0 or 1.

28. The at least one entity according to claim 1, wherein R<sup>1</sup> and R<sup>2</sup> together with the nitrogen atom and carbon atoms to which they are attached form a saturated or unsaturated 4- to 6-membered heterocyclyl ring optionally containing a further  
10 heteroatom chosen from N, O, and S, wherein said N heteroatom may be optionally substituted by C<sub>1-3</sub> alkyl.

29. The at least one entity according to claim 28, wherein R<sup>1</sup> and R<sup>2</sup> together with the nitrogen atom and carbon atoms to which they are attached form a saturated 4- to 6-membered  
15 heterocyclyl ring optionally containing a further heteroatom chosen from N, O, and S, wherein said N heteroatom may be optionally substituted by C<sub>1-3</sub> alkyl.

30. The at least one entity according to claim 29, wherein the saturated 4- to 6-membered heterocyclyl ring is  
20 pyrrolidinyl, piperidinyl, morpholino, or piperazinyl.

31. The at least one entity according to claim 28, wherein R<sup>1</sup> and R<sup>2</sup> together with the nitrogen atom and carbon atoms to which they are attached form an unsaturated 5- or 6-membered heterocyclyl ring optionally containing a further heteroatom  
25 chosen from N, O, and S, wherein said N heteroatom may be

optionally substituted by C<sub>1-3</sub> alkyl.

32. The at least one entity according to claim 31, wherein the unsaturated 5- or 6-membered heterocyclyl ring is imidazolyl.

5 33. The at least one entity according to claim 1, wherein n is 0.

34. The at least one entity according to claim 1, wherein X is oxygen and p is 3.

35. The at least one entity according to claim 1, wherein X  
10 is single bond and p is 1.

36. The at least one entity according to claim 1, wherein R<sup>1</sup> is chosen from C<sub>1-4</sub> alkyl groups, C<sub>1-3</sub> alkyl-(CH<sub>2</sub>)- groups wherein C<sub>1-3</sub> alkyl moiety is substituted by 1, 2, or 3 fluorine atoms, C<sub>1-4</sub> alkyl groups substituted by cyano, C<sub>1-3</sub> alkoxy-C<sub>2-4</sub> alkyl  
15 groups, C<sub>3-6</sub> cycloalkyl groups, C<sub>1-4</sub> alkylcarbonyl groups, and formyl.

37. The at least one entity according to claim 36, wherein R<sup>1</sup> is chosen from ethyl, 2-monofluoroethyl, 2,2-difluoroethyl, 2,2,2-trifluoroethyl, and acetyl.

20 38. The at least one entity according to claim 37, wherein R<sup>1</sup> is chosen from ethyl, 2,2-difluoroethyl, 2,2,2-trifluoroethyl, and acetyl.

39. A pharmaceutical composition comprising  
at least one entity chosen from compounds according to any one  
25 of claims 1 to 38 and pharmaceutically acceptable salts thereof,

and

at least one pharmaceutically acceptable diluent or carrier.

40. A method of treating a disease or medical condition mediated alone or in part by TLR7 in a subject in need thereof comprising: administering to said subject a therapeutically effective amount of at least one entity chosen from compounds according to any one of claims 1 to 38 and pharmaceutically acceptable salts thereof.

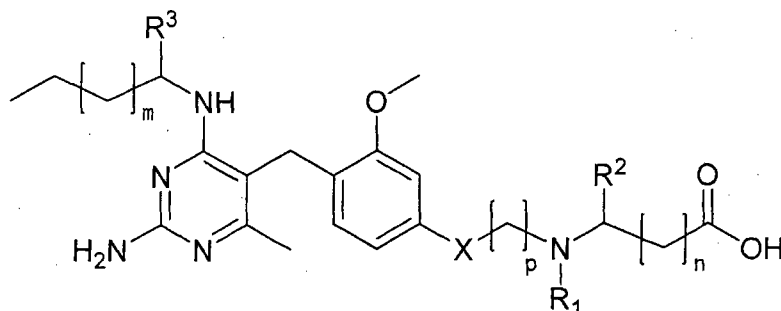
41. The method according to claim 40, wherein the disease or medical condition mediated alone or in part by TLR7 is cancer.

42. The method according to claim 41, wherein the cancer is chosen from bladder cancer, head and neck cancer, prostate cancer, breast cancer, lung cancer, uterus cancer, pancreatic cancer, liver cancer, renal cancer, ovarian cancer, colon cancer, stomach cancer, skin cancer, cerebral tumor, malignant myeloma, and lymphoproliferative tumors.

43. The method according to claim 40, wherein the disease or medical condition mediated alone or in part by TLR7 is asthma, COPD, allergic rhinitis, allergic conjunctivitis, atopic dermatitis, hepatitis B, hepatitis C, HIV, HPV, bacterial infections, or dermatosis.

44. A method of treating cancer in a subject in need thereof comprising:  
administering to said subject a therapeutically effective amount of at least one entity chosen from compounds of Formula

(I) and pharmaceutically acceptable salts thereof,



(I)

wherein:

- 5     n is 0, 1, or 2;
- m is 1 or 2;
- p is 1, 2, or 3, provided that when X is oxygen, p is 2 or 3,  
and when X is a single bond, p is 1;
- X is oxygen or a single bond;
- 10    R<sup>1</sup> is chosen from hydrogen, C<sub>1-4</sub> alkyl groups, C<sub>1-3</sub> alkyl-(CH<sub>2</sub>)-  
groups wherein C<sub>1-3</sub> alkyl moiety is substituted by 1, 2, or 3  
fluorine atoms, C<sub>1-4</sub> alkyl groups substituted by cyano, C<sub>1-3</sub>  
alkoxy-C<sub>2-4</sub> alkyl groups, C<sub>3-6</sub> cycloalkyl groups, C<sub>1-4</sub>  
alkylcarbonyl groups, and formyl;
- 15    R<sup>2</sup> is chosen from hydrogen and C<sub>1-4</sub> alkyl groups;  
or R<sup>1</sup> and R<sup>2</sup> together with the nitrogen and carbon atoms to which  
they are attached form a saturated or unsaturated 4- to  
6-membered heterocyclyl ring optionally containing a further  
heteroatom chosen from N, O, and S, wherein said N heteroatom  
20    may be optionally substituted by C<sub>1-3</sub> alkyl; and  
      R<sup>3</sup> is chosen from hydrogen, hydroxymethyl, and 2-hydroxyethyl.

45. A compound according to any one of claims 1 to 38, or a pharmaceutically acceptable salt thereof, for use as a medicament.

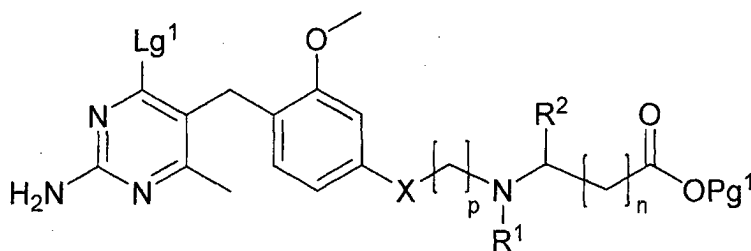
5 46. A compound according to any one of claims 1 to 38, or a pharmaceutically acceptable salt thereof, for use in the treatment of cancer.

47. Use of a compound according to any one of claims 1 to 38, or a pharmaceutically acceptable salt thereof, in the  
10 manufacture of a medicament for use in the treatment of cancer.

48. A method of treating cancer in a warm blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a compound of the Formula (I), or a pharmaceutically acceptable salt thereof, as defined  
15 in any one of claims 1 to 38.

49. A method of preparing a compound according to any one of claims 1 to 38 or a pharmaceutical salt thereof comprising a step of (1) and (2) :

(1) contacting a compound of Formula (II):



## (II)

wherein n is 0, 1 or 2;

p is 1, 2 or 3, provided that p is 2 or 3 when X is oxygen and p is 1 when X is a single bond;

5 X is oxygen or a single bond;

R<sup>1</sup> is hydrogen, C<sub>1-4</sub>alkyl, C<sub>1-3</sub>alkyl-(CH<sub>2</sub>)- wherein C<sub>1-3</sub>alkyl is substituted by 1, 2 or 3 fluorine atoms, C<sub>1-4</sub>alkyl substituted by cyano, C<sub>1-3</sub>alkoxyC<sub>2-4</sub>alkyl, C<sub>3-6</sub>cycloalkyl, C<sub>1-4</sub>alkylcarbonyl or formyl;

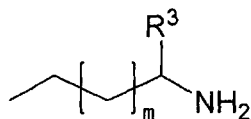
10 R<sup>2</sup> is hydrogen or C<sub>1-4</sub> alkyl;

or R<sup>1</sup> and R<sup>2</sup> together with the nitrogen and carbon atoms to which they are attached form a saturated or unsaturated 4 to 6-membered heterocyclyl ring optionally containing a further heteroatom selected from N, O and S, wherein said N heteroatom  
15 may be optionally substituted by C<sub>1-3</sub>alkyl;

LG<sup>1</sup> is a leaving group; and

PG<sup>1</sup> is a protective group of carboxylic acid;

with a compound of Formula (III):



20

## (III)

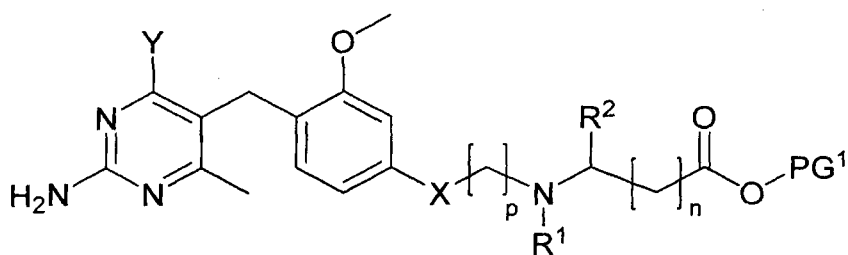
wherein m is 1 or 2; and R<sup>3</sup> is hydrogen, hydroxymethyl or 2-hydroxyethyl;

in the presence of base, and

(2) removing the protective group of the compound obtained in step (1), and

(3) Forming a pharmaceutically acceptable salt if necessary.

50. A compound of Formula (IV):



(IV)

wherein:

n is 0, 1 or 2;

p is 1, 2 or 3, provided that p is 2 or 3 when X is oxygen and

10 p is 1 when X is a single bond;

X is oxygen or a single bond;

R<sup>1</sup> is hydrogen, C<sub>1-4</sub>alkyl, C<sub>1-3</sub>alkyl-(CH<sub>2</sub>)- wherein C<sub>1-3</sub>alkyl is substituted by 1, 2 or 3 fluorine atoms, C<sub>1-4</sub>alkyl substituted by cyano, C<sub>1-3</sub>alkoxyC<sub>2-4</sub>alkyl, C<sub>3-6</sub>cycloalkyl, C<sub>1-4</sub>alkylcarbonyl

15 or formyl;

R<sup>2</sup> is hydrogen or C<sub>1-4</sub> alkyl;

or R<sup>1</sup> and R<sup>2</sup> together with the nitrogen and carbon atoms to which they are attached form a saturated or unsaturated 4 to 6-membered heterocyclyl ring optionally containing a further

20 heteroatom selected from N, O and S, wherein said N heteroatom may be optionally substituted by C<sub>1-3</sub>alkyl;

Y is hydroxy or a leaving group; and  
PG<sup>1</sup> is a protective group of carboxylic acid;  
or a salt thereof.