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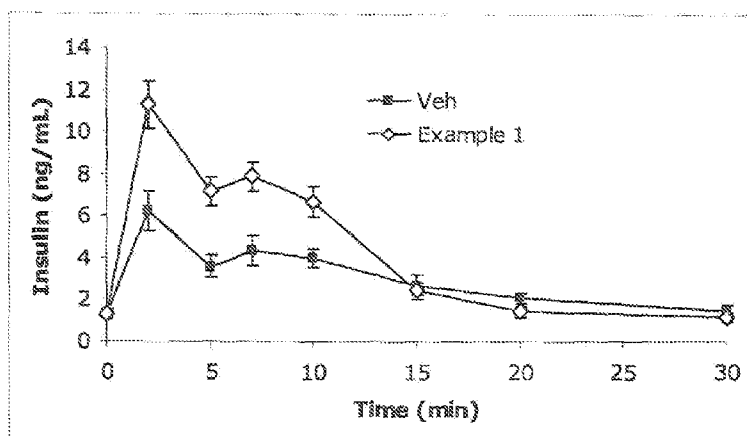
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(54) Title: GPR119 AGONISTS FOR THE TREATMENT OF DIABETES AND RELATED DISORDERS



(57) Abstract: The present invention relates to novel compounds that are useful in the treatment of metabolic disorders, particularly Type II diabetes mellitus and related disorders, and also to the methods for the making and use of such compounds.

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## CHEMICAL COMPOUNDS

### Field of the Invention

The present invention relates to novel compounds that are useful in the treatment  
5 and prevention of metabolic disorders, including diabetes mellitus (Type I and Type II),  
obesity, and related disorders, and also includes methods for making, pharmaceutical  
compositions containing, and therapeutic uses for such compounds.

### Background of the Invention

Diabetes mellitus is an ever-increasing threat to human health. For example, in  
10 the United States current estimates maintain that about 16 million people suffer from  
diabetes mellitus.

Type I diabetes, also known as insulin-dependent diabetes mellitus (IDDM), is  
caused by the autoimmune destruction of the insulin producing pancreatic  $\beta$ -cells, and  
necessitates regular administration of exogenous insulin. Without insulin, cells cannot  
15 absorb sugar (glucose), which they need to produce energy. Symptoms of Type I  
diabetes usually start in childhood or young adulthood. People often seek medical help  
because they are seriously ill from sudden symptoms of high blood sugar  
(hyperglycemia).

Type II diabetes, also known as non-insulin-dependent diabetes mellitus  
20 (NIDDM), manifests with an inability to adequately regulate blood-glucose levels. Type II  
diabetes may be characterized by a defect in insulin secretion or by insulin resistance,  
namely those that suffer from Type II diabetes have too little insulin or cannot use insulin  
effectively. Insulin resistance refers to the inability of body tissues to respond properly  
to endogenous insulin. Insulin resistance develops because of multiple factors, including  
25 genetics, obesity, increasing age, and having high blood sugar over long periods of time.  
Type II diabetes, sometimes called mature or adult onset diabetes, can develop at any  
age, but most commonly becomes apparent during adulthood. The incidence of Type II  
diabetes in children, however, is rising.

In diabetics, glucose levels build up in the blood and urine causing excessive  
30 urination, thirst, hunger, and problems with fat and protein metabolism. If left untreated,  
diabetes mellitus may cause life-threatening complications, including blindness, kidney  
failure, and heart disease.

Type II diabetes accounts for approximately 90-95% of diabetes cases, killing about 193,000 U.S. residents each year. Type II diabetes is the seventh leading cause of all deaths. In Western societies, Type II diabetes currently affects 6% of the adult population with world-wide frequency expected to grow by 6% per annum. Although  
5 there are certain inheritable traits that may predispose particular individuals to developing Type II diabetes, the driving force behind the current increase in incidence of the disease is the increased sedentary life-style, diet, and obesity now prevalent in developed countries. About 80% of diabetics with Type II diabetes are significantly overweight. As noted above, an increasing number of young people are developing the  
10 disease. Type II diabetes is now internationally recognized as one of the major threats to human health in the 21<sup>st</sup> century.

Type II diabetes currently is treated at several levels. A first level of therapy is through the use of diet and/or exercise, either alone or in combination with therapeutic agents. Such agents may include insulin or pharmaceuticals that lower blood glucose  
15 levels. About 49% of individuals with Type II diabetes require oral medication(s), about 40% of individuals require insulin injections or a combination of insulin injections and oral medication(s), and about 10% of individuals may use diet and exercise alone.

Current therapies for diabetes mellitus include: insulin; insulin secretagogues, such as sulphonylureas, which increase insulin secretion from pancreatic  $\beta$ -cells;  
20 glucose-lowering effectors, such as metformin which reduce glucose production from the liver; activators of the peroxisome proliferator-activated receptor- $\gamma$  (PPAR- $\gamma$ ), such as the thiazolidinediones, which enhances insulin action; and  $\alpha$ -glucosidase inhibitors which interfere with gut glucose production. There are, however, deficiencies associated with currently available treatments, including hypoglycemic episodes, weight gain, loss in  
25 responsiveness to therapy over time, gastrointestinal problems, and edema.

There are several areas at which research is being targeted in order to bring new, more effective, therapies to the marketplace. For example, on-going research includes exploring a reduction in excessive hepatic glucose production, enhancing the pathway by which insulin transmits its signal to the cells such that they take up glucose,  
30 enhancing glucose-stimulated insulin secretion from the pancreatic  $\beta$ -cells, and targeting obesity and associated problems with fat metabolism and accumulation.

GIP and GLP-1 are peptides, known as incretins, secreted from enteroendocrine K and L cells respectively in response to ingestion of nutrients, and have a wide variety of physiological effects that have been described in numerous publications over the past two decades. See, for example, Bojanowska, E. *et al.*, *Med. Sci. Monit.*, 2005, Aug 5 11(8): RA271-8; Perry, T. *et al.*, *Curr. Alzheimer Res.*, 2005, July 2(3): 377-85; and Meier, J.J. *et al.*, *Diabetes Metab. Res. Rev.*, 2005, Mar-Apr; 21(2): 91-117 (each herein incorporated by reference with regard to a background understanding of incretins). Moreover, although the mechanisms regulating GLP-1 secretion remain unclear, the initial rapid rise in GLP-1 following a meal may be a result of hormonal stimulation of neuronal afferents involving GIP. See, for example, J.N. Roberge and P.L. Brubaker, *Endocrinology* **133** (1993), pp. 233–240 (herein incorporated by reference with regard to such teaching). Furthermore, later increases in GLP-1 may involve direct activation of L-cells by nutrients in the distal small-intestine and the colon. GIP and GLP-1 are potent stimulators of the body's ability to produce insulin in response to elevated levels of blood 15 sugar.

In Type II diabetes the action of GLP-1 on the  $\beta$ -cell is maintained, although GLP-1 secretion, itself, is reduced. More recently, therefore, much research has been focused on GLP-1. Studies show glucose-lowering effects in addition to GLP-1's ability to stimulate glucose-dependent insulin secretion including, but not limited to, an 20 inhibition of the release of the hormone glucagon following meals, a reduction in the rate at which nutrients are absorbed into the bloodstream, and a reduction of food intake. Studies demonstrate that treatments to increase GLP-1, therefore, may be used for a variety of conditions and disorders including but not limited to metabolic disorders, gastrointestinal disorders, inflammatory diseases, psychosomatic, depressive, and 25 neuropsychiatric disease including but not limited to diabetes mellitus (Type 1 and Type 2), metabolic syndrome, obesity, appetite control and satiety, weight loss, stress, inflammation, myocardial ischemia/reperfusion injury, Alzheimer's Disease, and other diseases of the central nervous system. In Type II diabetes, patients display a decreased responsiveness to GIP but not GLP-1, with respect to its ability to stimulate 30 insulin secretion. The mechanism behind the decreased responsiveness to GIP remains unclear since Type II diabetics retain sensitivity to a bolus administration of GIP but not to a continuous infusion (Meier et al. 2004 *Diabetes* 53 S220-S224). Moreover recent studies with a long-acting fatty-acid derivative of GIP showed beneficial effects on



glucose homeostasis in ob/ob mice following 14 days of treatment (Irwin N. et al. (2006) J. Med. Chem. 49, 1047-1054).

The use of exogenous GLP-1 in clinical treatment is severely limited, however, due to its rapid degradation by the protease DPP-IV. There are multiple GLP-1 mimetics  
5 in development for type 2 diabetes that are reported in the literature, all are modified peptides, which display longer half-lives than endogenous GLP-1. For example, the product sold under the tradename BYETTA® is the first FDA-approved agent of this new class of medications. These mimetics, however, require injection. An oral medication that is able to elevate GLP-1 secretion is desirable. Orally available inhibitors of DPP-IV,  
10 which result in elevation in intact GLP-1, are now available, such as sitagliptin, marketed under the brand name JANUVIA®. Nevertheless, a molecule which may stimulate GLP-1 secretion would provide a therapeutic benefit. A molecule which could stimulate both GLP-1 secretion and insulin secretion through effects on the L-cell and direct effects on the  $\beta$ -cell would hold much promise for Type II diabetes therapy.

15 One particular target is GPR119. GPR119 is a member of the rhodopsin family of G-protein-coupled receptors. In addition to the "GPR119" identifier, several other identifiers exist, including but not limited to RUP 3, Snorf 25, 19 AJ, GPR116 (believed to be erroneous), AXOR 20, and PS1. GPR119 is expressed in human gastrointestinal regions and in human islets. Activation of GPR119 has been demonstrated to stimulate  
20 intracellular cAMP and lead to glucose-dependent GLP-1 and insulin secretion. See, T. Soga et al., *Biochemical and Biophysical Research Communications* 326 (2005) 744-751, herein incorporated by reference with regard to a background understanding of GPR119.

Agonists to GPR119 may be of therapeutic value for diabetes and associated  
25 conditions, particularly Type II diabetes, obesity, glucose intolerance, insulin resistance, metabolic syndrome X, hyperlipidemia, hypercholesterolemia, and atherosclerosis.

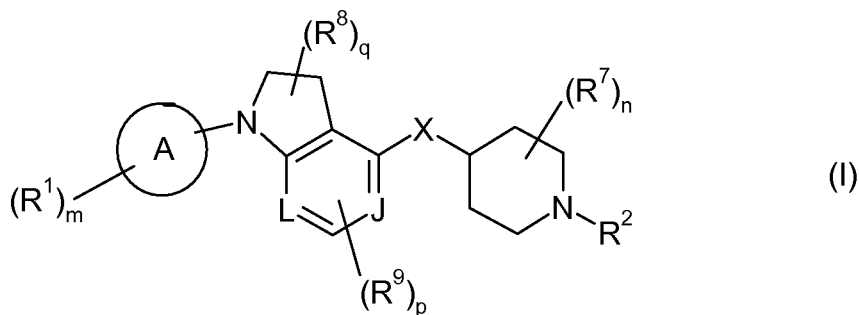
#### Summary of the Present Invention

The present invention includes a method for increasing GLP-1 secretion through the administration of a GPR119 agonist. Preferably the GPR119 agonist is a compound of  
30 formula (I) as herein defined.

The present invention includes a method for increasing GLP-1 secretion in a glucose independent and dependent manner through the administration of a GPR119 agonist. Preferably the GPR119 agonist is a compound of formula (I) as herein defined.

The present invention includes a method for increasing whole body insulin sensitivity through the administration of a GPR119 agonist. Preferably the GPR119 agonist is a compound of formula (I) as herein defined.

The present invention includes a compound of Formula (I):



5

or a salt, solvate, or prodrug thereof, wherein ring A is an aryl or heteroaryl;

m is 1, 2, or 3;

each R<sup>1</sup> independently is acyl; acylsulfonamide; acyloxy; C<sub>2</sub>-C<sub>6</sub> alkenyl; C<sub>1</sub>-C<sub>6</sub> alkoxy; C<sub>1</sub>-C<sub>6</sub> alkoxy carbonyl; C<sub>1</sub>-C<sub>6</sub> alkyl; C<sub>1</sub>-C<sub>6</sub> alkylamino; C<sub>1</sub>-C<sub>6</sub> alkylcarboxamide; C<sub>1</sub>-C<sub>6</sub> alkylthiocarboxamide; C<sub>2</sub>-C<sub>6</sub> alkynyl; C<sub>1</sub>-C<sub>6</sub> alkyloxyphosphoryl; C<sub>1</sub>-C<sub>6</sub> alkylsulfonamide; C<sub>1</sub>-C<sub>6</sub> alkylsulfinyl; C<sub>1</sub>-C<sub>6</sub> alkylsulfonyl; C<sub>1</sub>-C<sub>6</sub> alkylthio; C<sub>1</sub>-C<sub>6</sub> alkylthiourey; C<sub>1</sub>-C<sub>6</sub> alkylureyl; amino; aryl; aryl substituted with one or more C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkoxy, cyano, halogen, or C<sub>1</sub>-C<sub>6</sub> haloalkyl; carbamimidoyl; carboxamide; carboxy; cyano; C<sub>3</sub>-C<sub>7</sub> cycloalkyl; C<sub>3</sub>-C<sub>7</sub> cycloalkyl substituted with one or more C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkoxy, cyano, halogen, or C<sub>1</sub>-C<sub>6</sub> haloalkyl; C<sub>1</sub>-C<sub>6</sub> dialkylamino; C<sub>1</sub>-C<sub>6</sub> dialkylcarboxamide; C<sub>1</sub>-C<sub>6</sub> dialkyloxyphosphoryl; C<sub>1</sub>-C<sub>6</sub> dialkylsulfonamide; C<sub>1</sub>-C<sub>6</sub> dialkylthiocarboxamide; C<sub>1</sub>-C<sub>6</sub> haloalkoxy; C<sub>1</sub>-C<sub>6</sub> haloalkyl; C<sub>1</sub>-C<sub>6</sub> haloalkylsulfinyl; C<sub>1</sub>-C<sub>6</sub> haloalkylsulfonyl; C<sub>1</sub>-C<sub>6</sub> haloalkylthio; halogen; heterocyclyl; heterocyclyl substituted with one or more C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkoxy, cyano, halogen, or C<sub>1</sub>-C<sub>6</sub> haloalkyl; heteroaryl; heteroaryl substituted with one or more C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkoxy, cyano, halogen, or C<sub>1</sub>-C<sub>6</sub> haloalkyl; hydroxyl; nitro; sulfonamide; or thiol;

L and J each independently is CH or N;

n is 0, 1, 2, 3, or 4;

each R<sup>7</sup> independently is C<sub>1</sub>-C<sub>6</sub> alkyl;

q is 0, 1, or 2;

25

each R<sup>8</sup> independently is C<sub>1</sub>-C<sub>6</sub> alkyl, amino, C<sub>1</sub>-C<sub>6</sub> alkylamino, C<sub>1</sub>-C<sub>6</sub> dialkylamino, halogen, or C<sub>1</sub>-C<sub>6</sub> haloalkyl;

p is 0, 1, or 2;

when p is 1 or 2, then R<sup>9</sup> is substituted from a carbon atom on the depicted ring;

5 each R<sup>9</sup> independently is C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkoxy, amino, C<sub>1</sub>-C<sub>6</sub> alkylamino, C<sub>1</sub>-C<sub>6</sub> dialkylamino, halogen, C<sub>1</sub>-C<sub>6</sub> haloalkyl, or cyano;

X is -NR<sup>4</sup>-, -O-, -S-, -S(O)-, or -S(O)<sub>2</sub>-;

wherein R<sup>4</sup> is H or C<sub>1</sub>-C<sub>6</sub> alkyl;

R<sup>2</sup> is -Y<sub>t</sub>-R<sup>5</sup>;

10 wherein Y is -C(O)-, -C(O)O-, -C(S)-, -C(S)S-, -C(S)O-, or -C(O)S-;

t is 0 or 1; and

R<sup>5</sup> is hydrogen; acylalkylene; acylalkylene substituted with one or more C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkoxy, aryl, aralkyl, cyano, halogen, C<sub>1</sub>-C<sub>6</sub> haloalkyl, heteroaryl, or heteroaralkyl; C<sub>2</sub>-C<sub>6</sub> alkenyl; C<sub>1</sub>-C<sub>6</sub> alkoxyalkylene; C<sub>1</sub>-C<sub>6</sub> alkyl; C<sub>1</sub>-C<sub>6</sub> alkylamino; C<sub>2</sub>-C<sub>6</sub> alkynyl; C<sub>1</sub>-C<sub>6</sub>

15 alkylcarboxamidealkylene; C<sub>1</sub>-C<sub>6</sub> alkylsulfinyl; C<sub>1</sub>-C<sub>6</sub> alkylsulfonyl; C<sub>1</sub>-C<sub>6</sub>

alkylsulfonamide; C<sub>1</sub>-C<sub>6</sub> alkylsulfoximine; C<sub>1</sub>-C<sub>6</sub> alkylthio; amino; aryl; aryl substituted with one or more of C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkoxy, aryl, aralkyl, cyano, halogen, C<sub>1</sub>-C<sub>6</sub>

haloalkyl, heteroaryl, or heteroaralkyl; aralkyl; aralkyl substituted with one or more of C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkoxy, aryl, aralkyl, cyano, halogen, C<sub>1</sub>-C<sub>6</sub> haloalkyl, heteroaryl, or

20 heteroaralkyl; aralkylcarboxamidealkylene; aralkylcarboxamidealkylene substituted with one or more of C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkoxy, aryl, aralkyl, cyano, halogen, C<sub>1</sub>-C<sub>6</sub> haloalkyl, heteroaryl, or heteroaralkyl; arylamino; arylamino substituted with one or more of C<sub>1</sub>-C<sub>6</sub>

alkyl, C<sub>1</sub>-C<sub>6</sub> alkoxy, aryl, aralkyl, cyano, halogen, C<sub>1</sub>-C<sub>6</sub> haloalkyl, heteroaryl, or

25 heteroaralkyl; carbamimodoyl; cyano; C<sub>3</sub>-C<sub>7</sub> cycloalkyl; C<sub>3</sub>-C<sub>7</sub> cycloalkyl substituted with one or more of C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkoxy, aryl, aralkyl, cyano, halogen, C<sub>1</sub>-C<sub>6</sub> haloalkyl, heteroaryl, or heteroaralkyl; C<sub>1</sub>-C<sub>6</sub> cycloalkylalkylene; C<sub>1</sub>-C<sub>6</sub> cycloalkylalkylene

substituted with one or more of C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkoxy, aryl, aralkyl, cyano, halogen,

C<sub>1</sub>-C<sub>6</sub> haloalkyl, heteroaryl, or heteroaralkyl; C<sub>1</sub>-C<sub>6</sub> dialkylamino; diarylamino; C<sub>1</sub>-C<sub>6</sub>

dialkylcarboxamidealkylene; C<sub>1</sub>-C<sub>6</sub> dialkylsulfonamide C<sub>1</sub>-C<sub>6</sub> haloalkoxy; C<sub>1</sub>-C<sub>6</sub> haloalkyl;

30 C<sub>1</sub>-C<sub>6</sub> haloalkylsulfinyl; C<sub>1</sub>-C<sub>6</sub> haloalkylsulfonyl; C<sub>1</sub>-C<sub>6</sub> haloalkylthio; halogen;

heterocyclyl; heterocyclyl substituted with one or more of C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkoxy, aryl, aralkyl, cyano, halogen, C<sub>1</sub>-C<sub>6</sub> haloalkyl, heteroaryl, or heteroaralkyl; heteroaryl;

heteroaryl substituted with one or more of C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkoxy, aryl, aryl substituted

with one or more of C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkoxy, aryl, aralkyl, cyano, halogen, C<sub>1</sub>-C<sub>6</sub> haloalkyl, heteroaryl, or heteroaralkyl, aralkyl, cyano, halogen, C<sub>1</sub>-C<sub>6</sub> haloalkyl, heteroaryl, or heteroaralkyl; heteroaralkyl; heteroaralkyl substituted with one or more of C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkoxy, aryl, aralkyl, cyano, halogen, C<sub>1</sub>-C<sub>6</sub> haloalkyl, heteroaryl, or heteroaralkyl; heteroarylamino; hydroxyl; or nitro.

Preferably when A is aryl, then A is phenyl; and when A is heteroaryl, then A is pyridyl or pyrimidinyl.

Preferably m is 1 or 2. Preferably, R<sup>1</sup> is C<sub>1</sub>-C<sub>6</sub> alkylsulfonyl, cyano, halogen, or heteroaryl. In an embodiment m is 1 and R<sup>1</sup> is C<sub>1</sub>-C<sub>3</sub> alkylsulfonyl. In an embodiment m is 2 and one R<sup>1</sup> is C<sub>1</sub>-C<sub>3</sub> alkylsulfonyl and the other R<sup>1</sup> is halogen. Preferably one R<sup>1</sup> is methylsulfonyl and one R<sup>1</sup> is fluorine. Preferably the methylsulfonyl is located *para* to the depicted N atom and the fluorine is located *ortho* to the depicted N atom. In an embodiment m is 2 and one R<sup>1</sup> is cyano and the other R<sup>1</sup> is halogen.

In an embodiment L and J are the same. Preferably, both L and J are N.

In an embodiment p is 0 or 1.

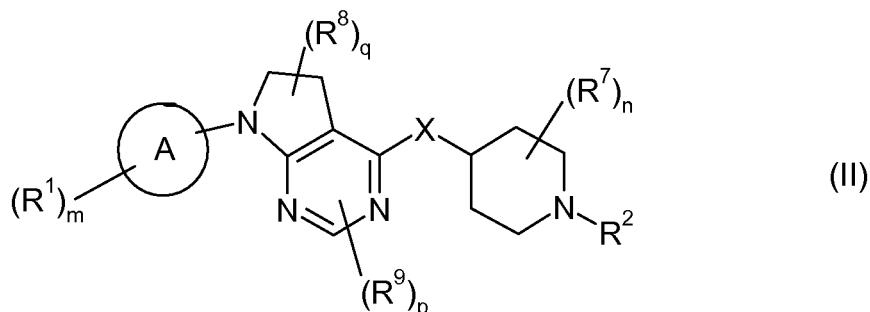
In an embodiment q is 0.

In an embodiment X is -O-.

In an embodiment t is 0. Preferably R<sup>5</sup> is heteroaryl or heteroaryl substituted with one or more of C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkoxy, aryl, C<sub>1</sub>-C<sub>6</sub> aralkyl, cyano, halogen, or C<sub>1</sub>-C<sub>6</sub> haloalkyl. Preferably the heteroaryl is pyrimidinyl or oxadiazolyl.

In an embodiment t is 1. Preferably Y is C(O)O. Preferably R<sup>5</sup> is C<sub>1</sub>-C<sub>6</sub> alkyl; aryl; aryl substituted with one or more of C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkoxy, aryl, C<sub>1</sub>-C<sub>6</sub> aralkyl, cyano, halogen, or C<sub>1</sub>-C<sub>6</sub> haloalkyl; C<sub>3</sub>-C<sub>7</sub> cycloalkyl. Preferably R<sup>5</sup> is C<sub>1</sub>-C<sub>6</sub> alkyl.

One embodiment of the present invention includes a compound of Formula (II):



25

or a salt, solvate, or prodrug thereof, wherein ring A is an aryl or heteroaryl;

m is 1, 2, or 3;

each R<sup>1</sup> independently is acyl; acylsulfonamide; acyloxy; C<sub>2</sub>-C<sub>6</sub> alkenyl; C<sub>1</sub>-C<sub>6</sub> alkoxy; C<sub>1</sub>-C<sub>6</sub> alkoxy carbonyl; C<sub>1</sub>-C<sub>6</sub> alkyl; C<sub>1</sub>-C<sub>6</sub> alkylamino; C<sub>1</sub>-C<sub>6</sub> alkylcarboxamide; C<sub>1</sub>-C<sub>6</sub> alkylthiocarboxamide; C<sub>2</sub>-C<sub>6</sub> alkynyl; C<sub>1</sub>-C<sub>6</sub> alkyloxyphosphoryl; C<sub>1</sub>-C<sub>6</sub> alkylsulfonamide;

5 C<sub>1</sub>-C<sub>6</sub> alkylsulfinyl; C<sub>1</sub>-C<sub>6</sub> alkylsulfonyl; C<sub>1</sub>-C<sub>6</sub> alkylthio; C<sub>1</sub>-C<sub>6</sub> alkylthiourey; C<sub>1</sub>-C<sub>6</sub> alkylureyl; amino; aryl; aryl substituted with one or more C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkoxy, cyano, halogen, or C<sub>1</sub>-C<sub>6</sub> haloalkyl; carbamimidoyl; carboxamide; carboxy; cyano; C<sub>3</sub>-C<sub>7</sub> cycloalkyl; C<sub>3</sub>-C<sub>7</sub> cycloalkyl substituted with one or more C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkoxy, cyano, halogen, or C<sub>1</sub>-C<sub>6</sub> haloalkyl; C<sub>1</sub>-C<sub>6</sub> dialkylamino; C<sub>1</sub>-C<sub>6</sub> dialkylcarboxamide; C<sub>1</sub>-C<sub>6</sub> dialkylalkoxyphosphoryl; C<sub>1</sub>-C<sub>6</sub> dialkylsulfonamide; C<sub>1</sub>-C<sub>6</sub> dialkylthiocarboxamide; C<sub>1</sub>-C<sub>6</sub> haloalkoxy; C<sub>1</sub>-C<sub>6</sub> haloalkyl; C<sub>1</sub>-C<sub>6</sub> haloalkylsulfinyl; C<sub>1</sub>-C<sub>6</sub> haloalkylsulfonyl; C<sub>1</sub>-C<sub>6</sub> haloalkylthio; halogen; heterocyclyl; heterocyclyl substituted with one or more C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkoxy, cyano, halogen, or C<sub>1</sub>-C<sub>6</sub> haloalkyl; heteroaryl; heteroaryl substituted with one or more C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkoxy, cyano, halogen, or C<sub>1</sub>-C<sub>6</sub> haloalkyl; hydroxyl; nitro; sulfonamide; or thiol;

n is 0, 1, 2, 3, or 4;

each R<sup>7</sup> independently is C<sub>1</sub>-C<sub>6</sub> alkyl;

q is 0, 1, or 2;

each R<sup>8</sup> independently is C<sub>1</sub>-C<sub>6</sub> alkyl, amino, C<sub>1</sub>-C<sub>6</sub> alkylamino, C<sub>1</sub>-C<sub>6</sub> dialkylamino,

20 halogen, or C<sub>1</sub>-C<sub>6</sub> haloalkyl;

p is 0, 1, or 2;

when p is 1 or 2, then R<sup>9</sup> is substituted from a carbon atom on the depicted ring;

each R<sup>9</sup> independently is C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkoxy, amino, C<sub>1</sub>-C<sub>6</sub> alkylamino, C<sub>1</sub>-C<sub>6</sub> dialkylamino, halogen, C<sub>1</sub>-C<sub>6</sub> haloalkyl, or cyano;

25 X is -NR<sup>4</sup>-, -O-, -S-, -S(O)-, or -S(O)<sub>2</sub>-;

wherein R<sup>4</sup> is H or C<sub>1</sub>-C<sub>6</sub> alkyl;

R<sup>2</sup> is -Y<sub>t</sub>-R<sup>5</sup>;

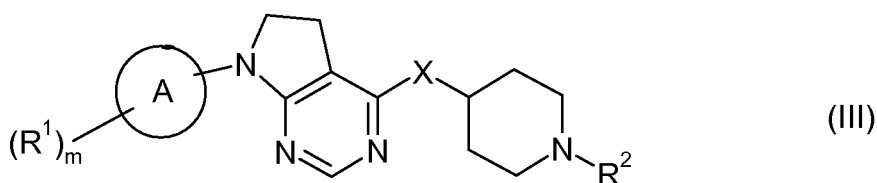
wherein Y is -C(O)-, -C(O)O-, -C(S)-, -C(S)S-, -C(S)O-, or -C(O)S-;

t is 0 or 1; and

30 R<sup>5</sup> is hydrogen; acylalkylene; acylalkylene substituted with one or more C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkoxy, aryl, aralkyl, cyano, halogen, C<sub>1</sub>-C<sub>6</sub> haloalkyl, heteroaryl, or heteroaralkyl; C<sub>2</sub>-C<sub>6</sub> alkenyl; C<sub>1</sub>-C<sub>6</sub> alkoxyalkylene; C<sub>1</sub>-C<sub>6</sub> alkyl; C<sub>1</sub>-C<sub>6</sub> alkylamino; C<sub>2</sub>-C<sub>6</sub> alkynyl; C<sub>1</sub>-C<sub>6</sub> alkylcarboxamidealkylene; C<sub>1</sub>-C<sub>6</sub> alkylsulfinyl; C<sub>1</sub>-C<sub>6</sub> alkylsulfonyl; C<sub>1</sub>-C<sub>6</sub>

alkylsulfonamide; C<sub>1</sub>-C<sub>6</sub> alkylsulfoximine; C<sub>1</sub>-C<sub>6</sub> alkylthio; amino; aryl; aryl substituted with one or more of C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkoxy, aryl, aralkyl, cyano, halogen, C<sub>1</sub>-C<sub>6</sub> haloalkyl, heteroaryl, or heteroaralkyl; aralkyl; aralkyl substituted with one or more of C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkoxy, aryl, aralkyl, cyano, halogen, C<sub>1</sub>-C<sub>6</sub> haloalkyl, heteroaryl, or heteroaralkyl; aralkylcarboxamidealkylene; aralkylcarboxamidealkylene substituted with one or more of C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkoxy, aryl, aralkyl, cyano, halogen, C<sub>1</sub>-C<sub>6</sub> haloalkyl, heteroaryl, or heteroaralkyl; arylamino; arylamino substituted with one or more of C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkoxy, aryl, aralkyl, cyano, halogen, C<sub>1</sub>-C<sub>6</sub> haloalkyl, heteroaryl, or heteroaralkyl; carbamimodoyl; cyano; C<sub>3</sub>-C<sub>7</sub> cycloalkyl; C<sub>3</sub>-C<sub>7</sub> cycloalkyl substituted with one or more of C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkoxy, aryl, aralkyl, cyano, halogen, C<sub>1</sub>-C<sub>6</sub> haloalkyl, heteroaryl, or heteroaralkyl; C<sub>1</sub>-C<sub>6</sub> cycloalkylalkylene; C<sub>1</sub>-C<sub>6</sub> cycloalkylalkylene substituted with one or more of C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkoxy, aryl, aralkyl, cyano, halogen, C<sub>1</sub>-C<sub>6</sub> haloalkyl, heteroaryl, or heteroaralkyl; C<sub>1</sub>-C<sub>6</sub> dialkylamino; diarylamino; C<sub>1</sub>-C<sub>6</sub> dialkylcarboxamidealkylene; C<sub>1</sub>-C<sub>6</sub> dialkylsulfonamide C<sub>1</sub>-C<sub>6</sub> haloalkoxy; C<sub>1</sub>-C<sub>6</sub> haloalkyl; C<sub>1</sub>-C<sub>6</sub> haloalkylsulfanyl; C<sub>1</sub>-C<sub>6</sub> haloalkylsulfonyl; C<sub>1</sub>-C<sub>6</sub> haloalkylthio; halogen; heterocyclyl; heterocyclyl substituted with one or more of C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkoxy, aryl, aralkyl, cyano, halogen, C<sub>1</sub>-C<sub>6</sub> haloalkyl, heteroaryl, or heteroaralkyl; heteroaryl; heteroaryl substituted with one or more of C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkoxy, aryl, aryl substituted with one or more of C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkoxy, aryl, aralkyl, cyano, halogen, C<sub>1</sub>-C<sub>6</sub> haloalkyl, heteroaryl, or heteroaralkyl, aralkyl, cyano, halogen, C<sub>1</sub>-C<sub>6</sub> haloalkyl, heteroaryl, or heteroaralkyl; heteroaralkyl; heteroaralkyl substituted with one or more of C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkoxy, aryl, aralkyl, cyano, halogen, C<sub>1</sub>-C<sub>6</sub> haloalkyl, heteroaryl, or heteroaralkyl; heteroarylamino; hydroxyl; or nitro.

One embodiment of the present invention includes a compound of Formula (III):



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or a salt, solvate, or prodrug thereof, wherein  
 ring A is an aryl or heteroaryl;  
 m is 1, 2, or 3;

- each R<sup>1</sup> independently is acyl; acylsulfonamide; acyloxy; C<sub>2</sub>-C<sub>6</sub> alkenyl; C<sub>1</sub>-C<sub>6</sub> alkoxy; C<sub>1</sub>-C<sub>6</sub> alkoxy carbonyl; C<sub>1</sub>-C<sub>6</sub> alkyl; C<sub>1</sub>-C<sub>6</sub> alkylamino; C<sub>1</sub>-C<sub>6</sub> alkylcarboxamide; C<sub>1</sub>-C<sub>6</sub> alkylthiocarboxamide; C<sub>2</sub>-C<sub>6</sub> alkynyl; C<sub>1</sub>-C<sub>6</sub> alkyloxyphosphoryl; C<sub>1</sub>-C<sub>6</sub> alkylsulfonamide; C<sub>1</sub>-C<sub>6</sub> alkylsulfinyl; C<sub>1</sub>-C<sub>6</sub> alkylsulfonyl; C<sub>1</sub>-C<sub>6</sub> alkylthio; C<sub>1</sub>-C<sub>6</sub> alkylthioureyll; C<sub>1</sub>-C<sub>6</sub> alkylureyl; amino; aryl; aryl substituted with one or more C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkoxy, cyano, halogen, or C<sub>1</sub>-C<sub>6</sub> haloalkyl; carbamimidoyl; carboxamide; carboxy; cyano; C<sub>3</sub>-C<sub>7</sub> cycloalkyl; C<sub>3</sub>-C<sub>7</sub> cycloalkyl substituted with one or more C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkoxy, cyano, halogen, or C<sub>1</sub>-C<sub>6</sub> haloalkyl; C<sub>1</sub>-C<sub>6</sub> dialkylamino; C<sub>1</sub>-C<sub>6</sub> dialkylcarboxamide; C<sub>1</sub>-C<sub>6</sub> dialkyloxyphosphoryl; C<sub>1</sub>-C<sub>6</sub> dialkylsulfonamide; C<sub>1</sub>-C<sub>6</sub> dialkylthiocarboxamide; C<sub>1</sub>-C<sub>6</sub> haloalkoxy; C<sub>1</sub>-C<sub>6</sub> haloalkyl; C<sub>1</sub>-C<sub>6</sub> haloalkylsulfinyl; C<sub>1</sub>-C<sub>6</sub> haloalkylsulfonyl; C<sub>1</sub>-C<sub>6</sub> haloalkylthio; halogen; heterocyclyl; heterocyclyl substituted with one or more C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkoxy, cyano, halogen, or C<sub>1</sub>-C<sub>6</sub> haloalkyl; heteroaryl; heteroaryl substituted with one or more C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkoxy, cyano, halogen, or C<sub>1</sub>-C<sub>6</sub> haloalkyl; hydroxyl; nitro; sulfonamide; or thiol;
- 5 X is -NR<sup>4</sup>-, -O-, -S-, -S(O)-, or -S(O)<sub>2</sub>-; wherein R<sup>4</sup> is H or C<sub>1</sub>-C<sub>6</sub> alkyl; R<sup>2</sup> is -Y<sub>t</sub>-R<sup>5</sup>; wherein Y is -C(O)-, -C(O)O-, -C(S)-, -C(S)S-, -C(S)O-, or -C(O)S-; t is 0 or 1; and
- 10 R<sup>5</sup> is hydrogen; acylalkylene; acylalkylene substituted with one or more C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkoxy, aryl, aralkyl, cyano, halogen, C<sub>1</sub>-C<sub>6</sub> haloalkyl, heteroaryl, or heteroaralkyl; C<sub>2</sub>-C<sub>6</sub> alkenyl; C<sub>1</sub>-C<sub>6</sub> alkoxyalkylene; C<sub>1</sub>-C<sub>6</sub> alkyl; C<sub>1</sub>-C<sub>6</sub> alkylamino; C<sub>2</sub>-C<sub>6</sub> alkynyl; C<sub>1</sub>-C<sub>6</sub> alkylcarboxamidealkylene; C<sub>1</sub>-C<sub>6</sub> alkylsulfinyl; C<sub>1</sub>-C<sub>6</sub> alkylsulfonyl; C<sub>1</sub>-C<sub>6</sub> alkylsulfonamide; C<sub>1</sub>-C<sub>6</sub> alkylsulfoximine; C<sub>1</sub>-C<sub>6</sub> alkylthio; amino; aryl; aryl substituted with one or more of C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkoxy, aryl, aralkyl, cyano, halogen, C<sub>1</sub>-C<sub>6</sub> haloalkyl, heteroaryl, or heteroaralkyl; aralkyl; aralkyl substituted with one or more of C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkoxy, aryl, aralkyl, cyano, halogen, C<sub>1</sub>-C<sub>6</sub> haloalkyl, heteroaryl, or heteroaralkyl; aralkylcarboxamidealkylene; aralkylcarboxamidealkylene substituted with one or more of C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkoxy, aryl, aralkyl, cyano, halogen, C<sub>1</sub>-C<sub>6</sub> haloalkyl, heteroaryl, or heteroaralkyl; arylamino; arylamino substituted with one or more of C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkoxy, aryl, aralkyl, cyano, halogen, C<sub>1</sub>-C<sub>6</sub> haloalkyl, heteroaryl, or heteroaralkyl; carbamimidoyl; cyano; C<sub>3</sub>-C<sub>7</sub> cycloalkyl; C<sub>3</sub>-C<sub>7</sub> cycloalkyl substituted with one or more of C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkoxy, aryl, aralkyl, cyano, halogen, C<sub>1</sub>-C<sub>6</sub> haloalkyl,
- 15 20 25 30

heteroaryl, or heteroaralkyl; C<sub>1</sub>-C<sub>6</sub> cycloalkylalkylene; C<sub>1</sub>-C<sub>6</sub> cycloalkylalkylene substituted with one or more of C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkoxy, aryl, aralkyl, cyano, halogen, C<sub>1</sub>-C<sub>6</sub> haloalkyl, heteroaryl, or heteroaralkyl; C<sub>1</sub>-C<sub>6</sub> dialkylamino; diarylamino; C<sub>1</sub>-C<sub>6</sub> dialkylcarboxamidealkylene; C<sub>1</sub>-C<sub>6</sub> dialkylsulfonamide C<sub>1</sub>-C<sub>6</sub> haloalkoxy; C<sub>1</sub>-C<sub>6</sub> haloalkyl; C<sub>1</sub>-C<sub>6</sub> haloalkylsulfanyl; C<sub>1</sub>-C<sub>6</sub> haloalkylsulfonyl; C<sub>1</sub>-C<sub>6</sub> haloalkylthio; halogen; heterocyclyl; heterocyclyl substituted with one or more of C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkoxy, aryl, aralkyl, cyano, halogen, C<sub>1</sub>-C<sub>6</sub> haloalkyl, heteroaryl, or heteroaralkyl; heteroaryl; heteroaryl substituted with one or more of C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkoxy, aryl, aryl substituted with one or more of C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkoxy, aryl, aralkyl, cyano, halogen, C<sub>1</sub>-C<sub>6</sub> haloalkyl, heteroaryl, or heteroaralkyl, aralkyl, cyano, halogen, C<sub>1</sub>-C<sub>6</sub> haloalkyl, heteroaryl, or heteroaralkyl; heteroaryl substituted with one or more of C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkoxy, aryl, aralkyl, cyano, halogen, C<sub>1</sub>-C<sub>6</sub> haloalkyl, heteroaryl, or heteroaralkyl; heteroaryl amino; hydroxyl; or nitro.

One embodiment of the present invention includes a compound selected from:

- 15 1-Methylethyl 4-({7-[2-fluoro-4-(methylsulfonyl)phenyl]-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-4-yl}oxy)-1-piperidinecarboxylate;  
 1,1-Dimethylethyl 4-({7-[2-fluoro-4-(methylsulfonyl)phenyl]-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-4-yl}oxy)-1-piperidinecarboxylate;  
 2-Methylpropyl 4-({7-[2-fluoro-4-(methylsulfonyl)phenyl]-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-4-yl}oxy)-1-piperidinecarboxylate;  
 20 2,2-Dimethylpropyl 4-({7-[2-fluoro-4-(methylsulfonyl)phenyl]-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-4-yl}oxy)-1-piperidinecarboxylate;  
 4-{{1-(5-Bromo-2-pyrimidinyl)-4-piperidinyl}oxy}-7-[2-fluoro-4-(methylsulfonyl)phenyl]-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidine;  
 25 7-[2-Fluoro-4-(methylsulfonyl)phenyl]-4-{{1-[5-(2-methylpropyl)-2-pyrimidinyl]-4-piperidinyl}oxy}-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidine;  
 7-[2-Fluoro-4-(methylsulfonyl)phenyl]-4-{{1-(2-pyrimidinyl)-4-piperidinyl}oxy}-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidine;  
 4-{{1-(5-Ethyl-2-pyrimidinyl)-4-piperidinyl}oxy}-7-[2-fluoro-4-(methylsulfonyl)phenyl]-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidine;  
 30 7-[2-Fluoro-4-(methylsulfonyl)phenyl]-4-{{1-(5-fluoro-2-pyrimidinyl)-4-piperidinyl}oxy}-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidine;



- 1-Methylethyl 4-[[7-(4-cyano-2-fluorophenyl)-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl]oxy]-1-piperidinecarboxylate;
- 1-Methylethyl 4-([7-[2-fluoro-4-(1,3-thiazol-2-yl)phenyl]-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl]oxy)-1-piperidinecarboxylate;
- 5 1-Methylethyl 4-([7-[4-(methylsulfonyl)phenyl]-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl]thio)-1-piperidinecarboxylate;
- 1-Methylethyl 4-([7-[2-fluoro-4-(methylsulfonyl)phenyl]-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl]sulfonyl)-1-piperidinecarboxylate;
- 1,1-Dimethylethyl 4-([7-[2-fluoro-4-(methylsulfonyl)phenyl]-2-methyl-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl]oxy)-1-piperidinecarboxylate;
- 10 1-Methylethyl 4-([7-[2-fluoro-4-(methylsulfonyl)phenyl]-2-methyl-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl]oxy)-1-piperidinecarboxylate;
- 7-[2-Fluoro-4-(methylsulfonyl)phenyl]-2-methyl-4-([1-[3-(1-methylethyl)-1,2,4-oxadiazol-5-yl]-4-piperidinyl]oxy)-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidine;
- 15 2,5-Difluoro-4-[4-([1-[3-(1-methylethyl)-1,2,4-oxadiazol-5-yl]-4-piperidinyl]oxy)-5,6-dihydro-7*H*-pyrrolo[2,3-*d*]pyrimidin-7-yl]benzotrile;
- 7-[2-Fluoro-4-(methylsulfonyl)phenyl]-4-([1-[3-(1-methylethyl)-1,2,4-oxadiazol-5-yl]-4-piperidinyl]oxy)-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidine;
- 7-(4-Bromo-2,5-difluorophenyl)-4-([1-[3-(1-methylethyl)-1,2,4-oxadiazol-5-yl]-4-piperidinyl]oxy)-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidine;
- 20 1,1-Dimethylethyl 4-[[7-(4-bromo-2,5-difluorophenyl)-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl]oxy]-1-piperidinecarboxylate;
- 1,1-Dimethylethyl 4-([1-[4-(methylsulfonyl)phenyl]-2,3-dihydro-1*H*-indol-4-yl]oxy)-1-piperidinecarboxylate;
- 25 1-Methylethyl 4-([1-[4-(methylsulfonyl)phenyl]-2,3-dihydro-1*H*-indol-4-yl]oxy)-1-piperidinecarboxylate;
- 1-Methylethyl 4-[[1-(4-cyanophenyl)-2,3-dihydro-1*H*-indol-4-yl]oxy]-1-piperidinecarboxylate;
- 1-Methylethyl 4-([1-[4-(1,3-thiazol-2-yl)phenyl]-2,3-dihydro-1*H*-indol-4-yl]oxy)-1-piperidinecarboxylate;
- 30 1,1-Dimethylethyl 4-([1-[5-(methylsulfonyl)-2-pyrimidinyl]-2,3-dihydro-1*H*-indol-4-yl]oxy)-1-piperidinecarboxylate;

- 1-Methylethyl 4-({1-[5-(methylsulfonyl)-2-pyrimidinyl]-2,3-dihydro-1*H*-indol-4-yl}oxy)-1-piperidinecarboxylate;
- 1-Methylethyl 4-({1-[4-[bis(butyloxy)phosphoryl]phenyl]-2,3-dihydro-1*H*-indol-4-yl}oxy)-1-piperidinecarboxylate;
- 5 4-Fluorophenyl 4-({1-[4-(methylsulfonyl)phenyl]-2,3-dihydro-1*H*-indol-4-yl}oxy)-1-piperidinecarboxylate;
- 1,1-Dimethylethyl 4-({1-[2-fluoro-4-(methylsulfonyl)phenyl]-2,3-dihydro-1*H*-indol-4-yl}oxy)-1-piperidinecarboxylate;
- 1-Methylethyl 4-({1-[2-fluoro-4-(methylsulfonyl)phenyl]-2,3-dihydro-1*H*-indol-4-yl}oxy)-1-piperidinecarboxylate;
- 10 (±)-1,1-Dimethylethyl 4-({1-[4-(methylsulfinyl)phenyl]-2,3-dihydro-1*H*-indol-4-yl}oxy)-1-piperidinecarboxylate;
- (+)-1,1-Dimethylethyl 4-({1-[4-(methylsulfinyl)phenyl]-2,3-dihydro-1*H*-indol-4-yl}oxy)-1-piperidinecarboxylate;
- 15 (-)-1,1-Dimethylethyl 4-({1-[4-(methylsulfinyl)phenyl]-2,3-dihydro-1*H*-indol-4-yl}oxy)-1-piperidinecarboxylate;
- 1,1-Dimethylethyl 4-({1-[4-[(ethyloxy)carbonyl]phenyl]-2,3-dihydro-1*H*-indol-4-yl}oxy)-1-piperidinecarboxylate;
- 4-{{4-[(1-{{(1,1-Dimethylethyl)oxy}carbonyl)-4-piperidinyl]oxy}-2,3-dihydro-1*H*-indol-1-yl]}benzoic acid;
- 20 1,1-Dimethylethyl 4-({1-[4-{{2-(methyloxy)ethyl}amino}carbonyl]phenyl]-2,3-dihydro-1*H*-indol-4-yl}oxy)-1-piperidinecarboxylate;
- 1,1-Dimethylethyl 4-({1-[4-{{(methylamino)carbonyl]phenyl]-2,3-dihydro-1*H*-indol-4-yl}oxy)-1-piperidinecarboxylate;
- 25 1,1-Dimethylethyl 4-{{1-[4-{{(3-hydroxypropyl)amino}carbonyl]phenyl]-2,3-dihydro-1*H*-indol-4-yl}oxy}-1-piperidinecarboxylate;
- 1,1-Dimethylethyl 4-{{1-[4-cyanophenyl]-2,3-dihydro-1*H*-indol-4-yl}oxy}-1-piperidinecarboxylate;
- 1,1-Dimethylethyl 4-{{1-[4-formylphenyl]-2,3-dihydro-1*H*-indol-4-yl}oxy}-1-piperidinecarboxylate;
- 30 1-[2-Fluoro-4-(methylsulfonyl)phenyl]-4-{{1-[2-pyrimidinyl]-4-piperidinyl}oxy}-2,3-dihydro-1*H*-indole;

- 4-{{1-(5-Fluoro-2-pyrimidinyl)-4-piperidinyl}oxy}-1-[4-(methylsulfonyl)phenyl]-2,3-dihydro-1*H*-indole;
- 1-[4-(Methylsulfonyl)phenyl]-4-{{1-(5-propyl-2-pyrimidinyl)-4-piperidinyl}oxy}-2,3-dihydro-1*H*-indole;
- 5 1-[4-(Methylsulfonyl)phenyl]-4-{{1-[5-(phenylmethyl)-2-pyrimidinyl]-4-piperidinyl}oxy}-2,3-dihydro-1*H*-indole;
- 1-[4-(Methylsulfonyl)phenyl]-4-{{1-(5-phenyl-2-pyrimidinyl)-4-piperidinyl}oxy}-2,3-dihydro-1*H*-indole;
- 4-{{1-(5-Bromo-2-pyrimidinyl)-4-piperidinyl}oxy}-1-[4-(methylsulfonyl)phenyl]-2,3-dihydro-1*H*-indole;
- 10 2-[4-{{1-[4-(Methylsulfonyl)phenyl]-2,3-dihydro-1*H*-indol-4-yl}oxy)-1-piperidinyl]-5-pyrimidinecarbonitrile;
- 4-{{1-(Cyclopentylacetyl)-4-piperidinyl}oxy}-1-[4-(methylsulfonyl)phenyl]-2,3-dihydro-1*H*-indole;
- 15 4-{{1-[3-(1-Methylethyl)-1,2,4-oxadiazol-5-yl]-4-piperidinyl}oxy}-1-[4-(methylsulfonyl)phenyl]-2,3-dihydro-1*H*-indole;
- 1-Methylethyl 4-{{1-[4-(3,5-dimethyl-4-isoxazolyl)phenyl]-2,3-dihydro-1*H*-indol-4-yl}oxy)-1-piperidinecarboxylate;
- 1-Methylethyl 4-{{1-[4-(3-furanyl)phenyl]-2,3-dihydro-1*H*-indol-4-yl}oxy)-1-piperidinecarboxylate;
- 20 1-Methylethyl 4-{{1-[4-(1-methyl-1*H*-pyrazol-4-yl)phenyl]-2,3-dihydro-1*H*-indol-4-yl}oxy)-1-piperidinecarboxylate;
- (1*R*,2*S*,5*R*)-5-Methyl-2-(1-methylethyl)cyclohexyl 4-{{7-[2-fluoro-4-(methylsulfonyl)phenyl]-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl}oxy)-1-piperidinecarboxylate;
- 25 1-Methylethyl 4-{{7-[4-(methylsulfonyl)phenyl]-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl}oxy)-1-piperidinecarboxylate;
- 1-Methylethyl 4-{{7-(4-cyanophenyl)-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl}oxy)-1-piperidinecarboxylate;
- 30 1-Methylethyl 4-{{7-[2-fluoro-4-(1-methyl-1*H*-pyrrol-2-yl)phenyl]-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl}oxy)-1-piperidinecarboxylate;
- (±)-1-Methylethyl 4-{{7-[2-fluoro-4-(methylsulfonyl)phenyl]-6-methyl-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl}oxy)-1-piperidinecarboxylate;

- (+)-1-Methylethyl 4-({7-[2-fluoro-4-(methylsulfonyl)phenyl]-6-methyl-6,7-dihydro-5H-pyrrolo[2,3-*d*]pyrimidin-4-yl}oxy)-1-piperidinecarboxylate;
- (-)-1-Methylethyl 4-({7-[2-fluoro-4-(methylsulfonyl)phenyl]-6-methyl-6,7-dihydro-5H-pyrrolo[2,3-*d*]pyrimidin-4-yl}oxy)-1-piperidinecarboxylate;
- 5 Methyl 4-({7-[2-fluoro-4-(methylsulfonyl)phenyl]-6,7-dihydro-5H-pyrrolo[2,3-*d*]pyrimidin-4-yl}oxy)-1-piperidinecarboxylate;
- Ethyl 4-({7-[2-fluoro-4-(methylsulfonyl)phenyl]-6,7-dihydro-5H-pyrrolo[2,3-*d*]pyrimidin-4-yl}oxy)-1-piperidinecarboxylate;
- Propyl 4-({7-[2-fluoro-4-(methylsulfonyl)phenyl]-6,7-dihydro-5H-pyrrolo[2,3-*d*]pyrimidin-4-yl}oxy)-1-piperidinecarboxylate;
- 10 n-Butyl 4-({7-[2-fluoro-4-(methylsulfonyl)phenyl]-6,7-dihydro-5H-pyrrolo[2,3-*d*]pyrimidin-4-yl}oxy)-1-piperidinecarboxylate;
- 2-Fluoroethyl 4-({7-[2-fluoro-4-(methylsulfonyl)phenyl]-6,7-dihydro-5H-pyrrolo[2,3-*d*]pyrimidin-4-yl}oxy)-1-piperidinecarboxylate;
- 15 3-Chloropropyl 4-({7-[2-fluoro-4-(methylsulfonyl)phenyl]-6,7-dihydro-5H-pyrrolo[2,3-*d*]pyrimidin-4-yl}oxy)-1-piperidinecarboxylate;
- 2-(Methyloxy)ethyl 4-({7-[2-fluoro-4-(methylsulfonyl)phenyl]-6,7-dihydro-5H-pyrrolo[2,3-*d*]pyrimidin-4-yl}oxy)-1-piperidinecarboxylate;
- 2-Propen-1-yl 4-({7-[2-fluoro-4-(methylsulfonyl)phenyl]-6,7-dihydro-5H-pyrrolo[2,3-*d*]pyrimidin-4-yl}oxy)-1-piperidinecarboxylate;
- 20 3-Buten-1-yl 4-({7-[2-fluoro-4-(methylsulfonyl)phenyl]-6,7-dihydro-5H-pyrrolo[2,3-*d*]pyrimidin-4-yl}oxy)-1-piperidinecarboxylate;
- 2-Butyn-1-yl 4-({7-[2-fluoro-4-(methylsulfonyl)phenyl]-6,7-dihydro-5H-pyrrolo[2,3-*d*]pyrimidin-4-yl}oxy)-1-piperidinecarboxylate;
- 25 Pentyl 4-({7-[2-fluoro-4-(methylsulfonyl)phenyl]-6,7-dihydro-5H-pyrrolo[2,3-*d*]pyrimidin-4-yl}oxy)-1-piperidinecarboxylate;
- Hexyl 4-({7-[2-fluoro-4-(methylsulfonyl)phenyl]-6,7-dihydro-5H-pyrrolo[2,3-*d*]pyrimidin-4-yl}oxy)-1-piperidinecarboxylate;
- 1-Methylethyl 4-([7-(2-methyl-3-pyridinyl)-6,7-dihydro-5H-pyrrolo[2,3-*d*]pyrimidin-4-yl]oxy)-1-piperidinecarboxylate;
- 30 1-Methylethyl 4-([7-(4-cyano-3-fluorophenyl)-6,7-dihydro-5H-pyrrolo[2,3-*d*]pyrimidin-4-yl]oxy)-1-piperidinecarboxylate;

- S-Ethyl 4-({7-[2-fluoro-4-(methylsulfonyl)phenyl]-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl}oxy)-1-piperidinecarbothioate;
- S-Methyl 4-({7-[2-fluoro-4-(methylsulfonyl)phenyl]-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl}oxy)-1-piperidinecarbothioate;
- 5 S-(1-Methylethyl) 4-({7-[2-fluoro-4-(methylsulfonyl)phenyl]-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl}oxy)-1-piperidinecarbothioate;
- S-(2-Methylpropyl) 4-({7-[2-fluoro-4-(methylsulfonyl)phenyl]-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl}oxy)-1-piperidinecarbothioate;
- (±)-S-(1,2-Dimethylpropyl) 4-({7-[2-fluoro-4-(methylsulfonyl)phenyl]-6,7-dihydro-5*H*-  
10 pyrrolo[2,3-*d*]pyrimidin-4-yl}oxy)-1-piperidinecarbothioate;
- (±)-S-(1-Methylpropyl) 4-({7-[2-fluoro-4-(methylsulfonyl)phenyl]-6,7-dihydro-5*H*-  
pyrrolo[2,3-*d*]pyrimidin-4-yl}oxy)-1-piperidinecarbothioate;
- S-(1,1-Dimethylpropyl) 4-({7-[2-fluoro-4-(methylsulfonyl)phenyl]-6,7-dihydro-5*H*-  
pyrrolo[2,3-*d*]pyrimidin-4-yl}oxy)-1-piperidinecarbothioate;
- 15 (±)-S-(2-Methylbutyl) 4-({7-[2-fluoro-4-(methylsulfonyl)phenyl]-6,7-dihydro-5*H*-  
pyrrolo[2,3-*d*]pyrimidin-4-yl}oxy)-1-piperidinecarbothioate;
- S-2-Propen-1-yl 4-({7-[2-fluoro-4-(methylsulfonyl)phenyl]-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl}oxy)-1-piperidinecarbothioate;
- S-(3-Chloropropyl) 4-({7-[2-fluoro-4-(methylsulfonyl)phenyl]-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl}oxy)-1-piperidinecarbothioate;
- 20 S-Cyclopentyl 4-({7-[2-fluoro-4-(methylsulfonyl)phenyl]-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl}oxy)-1-piperidinecarbothioate;
- S-Cyclohexyl 4-({7-[2-fluoro-4-(methylsulfonyl)phenyl]-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl}oxy)-1-piperidinecarbothioate;
- 25 S-(2,4-Difluorophenyl) 4-({7-[2-fluoro-4-(methylsulfonyl)phenyl]-6,7-dihydro-5*H*-  
pyrrolo[2,3-*d*]pyrimidin-4-yl}oxy)-1-piperidinecarbothioate;
- 1-Methylethyl 4-({7-[2-fluoro-4-(methylsulfonyl)phenyl]-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl}oxy)-1-piperidinecarbodithioate;
- 2-Methylpropyl 4-({7-[2-fluoro-4-(methylsulfonyl)phenyl]-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl}oxy)-1-piperidinecarbodithioate;
- 30 Phenyl 4-({7-[2-fluoro-4-(methylsulfonyl)phenyl]-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl}oxy)-1-piperidinecarbodithioate;

- 7-[2-Fluoro-4-(methylsulfonyl)phenyl]-4-{{1-(2-pyridinylmethyl)-4-piperidinyl}oxy}-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidine trifluoroacetate;
- N*-(1,1-Dimethylethyl)-2-[4-({7-[2-fluoro-4-(methylsulfonyl)phenyl]-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl}oxy)-1-piperidinyl]acetamide trifluoroacetate;
- 5 2-[4-({7-[2-Fluoro-4-(methylsulfonyl)phenyl]-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl}oxy)-1-piperidinyl]-1-[5-(2-pyridinyl)-2-thienyl]ethanone trifluoroacetate;
- 4-{{1-(Ethylsulfonyl)-4-piperidinyl}oxy}-7-[2-fluoro-4-(methylsulfonyl)phenyl]-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidine;
- 7-[2-Fluoro-4-(methylsulfonyl)phenyl]-4-{{1-[(1-methylethyl)sulfonyl]-4-piperidinyl}oxy)-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidine;
- 10 6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidine;
- 4-({7-[2-Fluoro-4-(methylsulfonyl)phenyl]-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl}oxy)-*N,N*-dimethyl-1-piperidinesulfonamide;
- N,N*-Diethyl-2-[4-({7-[2-fluoro-4-(methylsulfonyl)phenyl]-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl}oxy)-1-piperidinyl]acetamide trifluoroacetate;
- 15 2-[4-({7-[2-Fluoro-4-(methylsulfonyl)phenyl]-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl}oxy)-1-piperidinyl]-*N*-(phenylmethyl)acetamide;
- 2-[4-({7-[2-Fluoro-4-(methylsulfonyl)phenyl]-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl}oxy)-1-piperidinyl]-1-(5-methyl-2-thienyl)ethanone;
- 1-(5-Ethyl-2-thienyl)-2-[4-({7-[2-fluoro-4-(methylsulfonyl)phenyl]-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl}oxy)-1-piperidinyl]ethanone trifluoroacetate;
- 20 1-(5-Chloro-2-thienyl)-2-[4-({7-[2-fluoro-4-(methylsulfonyl)phenyl]-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl}oxy)-1-piperidinyl]ethanone trifluoroacetate;
- 7-[2-Fluoro-4-(methylsulfonyl)phenyl]-4-{{1-{{5-[4-(methoxy)phenyl]-1,2,4-oxadiazol-3-yl}methyl)-4-piperidinyl}oxy}-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidine;
- 25 2-[4-({7-[2-Fluoro-4-(methylsulfonyl)phenyl]-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl}oxy)-1-piperidinyl]-1-(1-methyl-1*H*-pyrrol-2-yl)ethanone;
- 2-[4-({7-[2-Fluoro-4-(methylsulfonyl)phenyl]-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl}oxy)-1-piperidinyl]-1-(5-phenyl-2-thienyl)ethanone;
- 7-[2-Fluoro-4-(methylsulfonyl)phenyl]-4-{{1-[5-(1-methylethyl)-1,2,4-oxadiazol-3-yl]-4-piperidinyl}oxy}-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidine;
- 30 7-[2-Fluoro-4-(methylsulfonyl)phenyl]-4-{{1-(1,4,5,6-tetrahydro-2-pyrimidinyl)-4-piperidinyl}oxy}-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidine;

- 1-Methylethyl 4-[(7-{4-[(dimethylamino)sulfonyl]phenyl}-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl)oxy]-1-piperidinecarboxylate;
- 1-Methylethyl 4-[[7-(5-cyano-2-pyridinyl)-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl]oxy]-1-piperidinecarboxylate;
- 5 1-Methylethyl 4-[[7-(5-fluoro-2-pyridinyl)-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl]oxy]-1-piperidinecarboxylate;
- 1,1-Dimethylethyl 4-({7-[2-fluoro-4-(methylsulfonyl)phenyl]-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl}amino)-1-piperidinecarboxylate trifluoroacetate;
- 1-Methylethyl 4-({7-[2-fluoro-4-(methylsulfonyl)phenyl]-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl}amino)-1-piperidinecarboxylate trifluoroacetate;
- 10 1-Methylethyl 4-[[7-[2-fluoro-4-(methylsulfonyl)phenyl]-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl](methylamino)-1-piperidinecarboxylate trifluoroacetate;
- 7-[2-Fluoro-4-(methylsulfonyl)phenyl]-*N*-[1-(2-fluoro-5-pyrimidinyl)-4-piperidinyl]-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine trifluoroacetate;
- 15 7-[2-Fluoro-4-(methylsulfonyl)phenyl]-4-[[1-(methylsulfonyl)-4-piperidinyl]oxy]-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidine trifluoroacetate;
- (±)-1-Methylethyl 4-({7-[5-(methylsulfinyl)-2-pyridinyl]-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl}oxy)-1-piperidinecarboxylate hydrochloride;
- 1-Methylethyl 4-({7-[5-(methylsulfonyl)-2-pyridinyl]-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl}oxy)-1-piperidinecarboxylate hydrochloride;
- 20 1-Methylethyl 4-({7-[6-(methylthio)-3-pyridinyl]-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl}oxy)-1-piperidinecarboxylate;
- (±)-1-Methylethyl 4-({7-[6-(methylsulfinyl)-3-pyridinyl]-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl}oxy)-1-piperidinecarboxylate hydrochloride;
- 25 1-Methylethyl 4-({7-[6-(methylsulfonyl)-3-pyridinyl]-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl}oxy)-1-piperidinecarboxylate hydrochloride;
- 1-Methylethyl 4-({7-[2-fluoro-4-(methylthio)phenyl]-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl}oxy)-1-piperidinecarboxylate;
- (±)-1-Methylethyl 4-({7-[2-fluoro-4-(methylsulfinyl)phenyl]-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl}oxy)-1-piperidinecarboxylate;
- 30 1-Methylethyl 4-({7-[2-fluoro-4-(methylsulfinyl)phenyl]-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl}oxy)-1-piperidinecarboxylate;

- (S)-1-Methylethyl 4-({7-[2-fluoro-4-(methylsulfinyl)phenyl]-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-4-yl}oxy)-1-piperidinecarboxylate;
- 7-[2-Fluoro-4-(methylthio)phenyl]-4-{{1-(5-fluoro-2-pyrimidinyl)-4-piperidinyl}oxy}-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidine;
- 5 (±)-7-[2-Fluoro-4-(methylsulfinyl)phenyl]-4-{{1-(5-fluoro-2-pyrimidinyl)-4-piperidinyl}oxy}-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidine;
- (R)-7-[2-fluoro-4-(methylsulfinyl)phenyl]-4-{{1-(5-fluoro-2-pyrimidinyl)-4-piperidinyl}oxy}-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidine;
- (S)-7-[2-Fluoro-4-(methylsulfinyl)phenyl]-4-{{1-(5-fluoro-2-pyrimidinyl)-4-piperidinyl}oxy}-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidine;
- 10 7-[2-Fluoro-4-(methylthio)phenyl]-4-({1-[3-(1-methylethyl)-1,2,4-oxadiazol-5-yl]-4-piperidinyl}oxy)-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidine;
- (±)-7-[2-Fluoro-4-(methylsulfinyl)phenyl]-4-({1-[3-(1-methylethyl)-1,2,4-oxadiazol-5-yl]-4-piperidinyl}oxy)-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidine;
- 15 (R)-7-[2-Fluoro-4-(methylsulfinyl)phenyl]-4-({1-[3-(1-methylethyl)-1,2,4-oxadiazol-5-yl]-4-piperidinyl}oxy)-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidine;
- (S)-7-[2-Fluoro-4-(methylsulfinyl)phenyl]-4-({1-[3-(1-methylethyl)-1,2,4-oxadiazol-5-yl]-4-piperidinyl}oxy)-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidine;
- 1-Methylethyl 4-({7-[4-(methylthio)phenyl]-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-4-yl}oxy)-1-piperidinecarboxylate;
- 20 (±)-1-Methylethyl 4-({7-[4-(methylsulfinyl)phenyl]-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-4-yl}oxy)-1-piperidinecarboxylate;
- (+)-1-Methylethyl 4-({7-[4-(methylsulfinyl)phenyl]-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-4-yl}oxy)-1-piperidinecarboxylate;
- 25 (-)-1-Methylethyl 4-({7-[4-(methylsulfinyl)phenyl]-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-4-yl}oxy)-1-piperidinecarboxylate;
- 1-Methylethyl 4-({2-amino-7-[2-fluoro-4-(methylsulfonyl)phenyl]-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-4-yl}oxy)-1-piperidinecarboxylate;
- 1-Methylethyl 4-{{7-[2-fluoro-4-(methylsulfonyl)phenyl]-2-(methylamino)-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-4-yl}oxy}-1-piperidinecarboxylate;
- 30 7-(4-Bromo-2-fluorophenyl)-4-{{1-(5-fluoro-2-pyrimidinyl)-4-piperidinyl}oxy}-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidine;



- 3-Fluoro-4-(4-([1-(5-fluoro-2-pyrimidinyl)-4-piperidinyl]oxy)-5,6-dihydro-7*H*-pyrrolo[2,3-*d*]pyrimidin-7-yl)benzotrile;
- 3-Fluoro-4-[4-({1-[3-(1-methylethyl)-1,2,4-oxadiazol-5-yl]-4-piperidinyl}oxy)-5,6-dihydro-7*H*-pyrrolo[2,3-*d*]pyrimidin-7-yl]benzotrile;
- 5 4-[4-({1-[3-(1-Methylethyl)-1,2,4-oxadiazol-5-yl]-4-piperidinyl}oxy)-5,6-dihydro-7*H*-pyrrolo[2,3-*d*]pyrimidin-7-yl]benzotrile;
- 4-(4-([1-(5-Fluoro-2-pyrimidinyl)-4-piperidinyl]oxy)-5,6-dihydro-7*H*-pyrrolo[2,3-*d*]pyrimidin-7-yl)benzotrile;
- 4-([1-(5-Fluoro-2-pyrimidinyl)-4-piperidinyl]oxy)-7-[4-(methylsulfonyl)phenyl]-6,7-dihydro-10 5*H*-pyrrolo[2,3-*d*]pyrimidine;
- 4-({1-[3-(1-Methylethyl)-1,2,4-oxadiazol-5-yl]-4-piperidinyl}oxy)-7-[4-(methylsulfonyl)phenyl]-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidine;
- 4-({1-[3-(1-Methylethyl)-1,2,4-oxadiazol-5-yl]-4-piperidinyl}oxy)-7-[4-(methylsulfinyl)phenyl]-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidine;
- 15 (*R*)- 4-({1-[3-(1-methylethyl)-1,2,4-oxadiazol-5-yl]-4-piperidinyl}oxy)-7-[4-(methylsulfinyl)phenyl]-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidine;
- (*S*)- 4-({1-[3-(1-Methylethyl)-1,2,4-oxadiazol-5-yl]-4-piperidinyl}oxy)-7-[4-(methylsulfinyl)phenyl]-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidine;
- 4-([1-(5-fluoro-2-pyrimidinyl)-4-piperidinyl]oxy)-7-[4-(methylsulfinyl)phenyl]-6,7-dihydro-20 5*H*-pyrrolo[2,3-*d*]pyrimidine;
- (*R*)- 4-([1-(5-Fluoro-2-pyrimidinyl)-4-piperidinyl]oxy)-7-[4-(methylsulfinyl)phenyl]-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidine;
- (*S*)- 4-([1-(5-Fluoro-2-pyrimidinyl)-4-piperidinyl]oxy)-7-[4-(methylsulfinyl)phenyl]-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidine;
- 25 *S*-Ethyl 4-({7-[2-fluoro-4-(methylsulfinyl)phenyl]-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl}oxy)-1-piperidinecarbothioate;
- (*R*)- *S*-Ethyl 4-({7-[2-fluoro-4-(methylsulfinyl)phenyl]-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl}oxy)-1-piperidinecarbothioate;
- (*S*)- *S*-Ethyl 4-({7-[2-fluoro-4-(methylsulfinyl)phenyl]-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl}oxy)-1-piperidinecarbothioate;
- 30 1-Methylethyl 4-({7-[2-fluoro-4-(*S*-methylsulfonimidoyl)phenyl]-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl}oxy)-1-piperidinecarboxylate;

(*R*)- 1-Methylethyl 4-({7-[2-fluoro-4-(*S*-methylsulfonimidoyl)phenyl]-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl}oxy)-1-piperidinecarboxylate;

(*S*)- 1-Methylethyl 4-({7-[2-fluoro-4-(*S*-methylsulfonimidoyl)phenyl]-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl}oxy)-1-piperidinecarboxylate;

5 1-Methylethyl 4-({7-[4-(*S*-methylsulfonimidoyl)phenyl]-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl}oxy)-1-piperidinecarboxylate;

(*R*)- 1-Methylethyl 4-({7-[4-(*S*-methylsulfonimidoyl)phenyl]-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl}oxy)-1-piperidinecarboxylate;

10 (*S*)- 1-Methylethyl 4-({7-[4-(*S*-methylsulfonimidoyl)phenyl]-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl}oxy)-1-piperidinecarboxylate;

(*R*)-1-Methylethyl 4-({7-[2,5-difluoro-4-(methylsulfinyl)phenyl]-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl}oxy)-1-piperidinecarboxylate;

(*S*)-1-Methylethyl 4-({7-[2,5-difluoro-4-(methylsulfinyl)phenyl]-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl}oxy)-1-piperidinecarboxylate;

15 or a salt, solvate, or prodrug thereof.

One embodiment of the present invention includes a pharmaceutical composition comprising a compound of the present invention as herein described. One embodiment of the present invention includes a compound of the present invention as herein described for use as an active therapeutic substance.

20 One embodiment of the present invention includes a compound of the present invention as herein described for use in the treatment or prophylaxis of diseases and conditions mediated through GPR119.

25 One embodiment of the present invention includes a compound of the present invention as herein described for use in the treatment or prophylaxis of metabolic disorders or conditions. Preferably the condition or disease is diabetes or obesity.

One embodiment of the present invention includes using a compound of the present invention in the manufacture of a medicament for use in the treatment or prophylaxis of metabolic disorders or conditions. Preferably the disorder or condition is diabetes or obesity.

30 One embodiment of the present invention includes a method for the treatment or prophylaxis of metabolic disorders or conditions comprising the administration of a compound of the present invention as herein described. Preferably the condition or disorder is diabetes or obesity.

The present invention covers all combinations of embodiments, particular recitations, and preferred groups herein described.

Detailed Description of the Preferred Embodiments

5 The present invention is described in terms known and appreciated by those skilled in the art. For ease of reference certain terms hereinafter are defined. The fact that certain terms are defined, however, should not be considered as indicative that defined terms are used in a manner inconsistent with the ordinary meaning or, alternatively, that any term that is undefined is indefinite or not used within the ordinary and accepted meaning. Rather, all terms used herein are believed to describe the  
10 invention such that one of ordinary skill can appreciate the scope of the present invention. The following definitions are meant to clarify, but not limit, the terms defined.

As used herein the term "alkyl" refers to a straight or branched chain hydrocarbon, preferably having from one to twelve carbon atoms. Examples of "alkyl" as used herein include, but are not limited to, methyl, ethyl, propyl, isopropyl, isobutyl, n-  
15 butyl, tert-butyl, isopentyl, n-pentyl, and the like.

As used throughout this specification, the preferred number of atoms, such as carbon atoms, will be represented by, for example, the phrase "C<sub>x</sub>-C<sub>y</sub> alkyl," which refers to an alkyl group, as herein defined, containing the specified number of carbon atoms. Similar terminology will apply for other preferred terms and ranges as well.

20 As used herein the term "alkenyl" refers to a straight or branched chain aliphatic hydrocarbon containing one or more carbon-to-carbon double bonds. Examples include, but are not limited to, vinyl, allyl, and the like

As used herein the term "alkynyl" refers to a straight or branched chain aliphatic hydrocarbon containing one or more carbon-to-carbon triple bonds. Examples include,  
25 but are not limited to, ethynyl and the like.

As used herein, the term "alkylene" refers to a straight or branched chain divalent hydrocarbon radical, preferably having from one to ten carbon atoms. Examples of "alkylene" as used herein include, but are not limited to, methylene, ethylene, n-propylene, n-butylene, and the like. As used herein, when the term "alkylene" appears  
30 as a suffix on a named substituent group, the intention is to describe a divalent hydrocarbon linker. As a non-limiting example, "alkylcarboxamidealkylene" refers to an alkylcarboxamide group, or -C(O)NHR, attached through an alkylene linker, namely -(CH<sub>2</sub>)<sub>n</sub>C(O)NHR. When used herein the terminology C<sub>1</sub>-C<sub>6</sub> refers to the substituent

group rather than the linker. Thus, C<sub>1</sub>-C<sub>6</sub> alkylcarboxamidealkylene refers to -(CH<sub>2</sub>)<sub>n</sub>C(O)NHR, where R is C<sub>1</sub>-C<sub>6</sub> alkyl. As noted hereinabove, n preferably is an integer from 1 to 10.

As used herein, the term "cycloalkyl" refers to a non-aromatic cyclic hydrocarbon ring. Exemplary "cycloalkyl" groups include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and cycloheptyl. As used herein, the term "cycloalkyl" includes a fused ring system where, for example, a cycloalkyl ring, such as a cyclopentyl ring, is fused with an aromatic ring, herein an "aryl" ring, such as a benzene ring, to form, for example, groups such as indane.

As used herein, the term "heterocycle" or "heterocyclyl" refers to a mono- or polycyclic non-aromatic ring system that may contain one or more degrees of unsaturation and also contains one or more heteroatoms. Preferred heteroatoms include N, O, and/or S, including N-oxides, sulfur oxides, and dioxides. Preferably the ring is three to twelve-membered and is either fully saturated or has one or more degrees of unsaturation. Such rings may be optionally fused to one or more of another "heterocyclic" ring(s) or cycloalkyl ring(s). Also, the terms include fused ring systems where, for example, a saturated heterocyclic ring (such as a pyrrolidine ring) is fused with an aromatic ring, herein an "aryl" ring, such as a benzene ring to form, for example, groups such as indoline. Further examples of "heterocyclic" groups include, but are not limited to, tetrahydrofuran, pyran, 1,4-dioxane, 1,3-dioxane, piperidine, pyrrolidine, morpholine, tetrahydrothiopyran, and tetrahydrothiophene.

As used herein, the term "aryl" refers to a benzene ring or to a fused benzene ring system, for example anthracene, phenanthrene, or naphthalene ring systems. Examples of "aryl" groups include, but are not limited to, phenyl, 2-naphthyl, 1-naphthyl, and the like.

As used herein, the term "heteroaryl" refers to a monocyclic five to seven membered aromatic ring or to a fused bicyclic aromatic ring system comprising two of such aromatic rings that contain one or more nitrogen, sulfur, and/or oxygen atoms, where N-oxides, sulfur oxides, and dioxides are permissible heteroatom substitutions. Examples of "heteroaryl" groups as used herein include, but should not be limited to, furan, thiophene, pyrrole, imidazole, pyrazole, triazole, tetrazole, thiazole, oxazole, isoxazole, oxadiazole, thiadiazole, isothiazole, pyridine, pyridazine, pyrazine, pyrimidine,

quinoline, isoquinoline, benzofuran, benzothiophene, indole, indazole, benzimidazolyl, imidazopyridinyl, pyrazolopyridinyl, pyrazolopyrimidinyl, and the like.

As used herein the term "acyl" refers to a group  $-C(O)R^a$ , where  $R^a$  is hydrogen, alkyl, cycloalkyl, aryl, heteroaryl, or heterocyclyl, as each is herein defined. For example, the term "acyl" encompasses a heteroarylcarbonyl group, such as  $-C(O)-Het$ , where "Het" refers to a heteroaryl group as defined herein. As used herein, the phrase "substituted acyl" refers to a group as herein defined wherein  $R^a$  is capable of being substituted, namely alkyl, cycloalkyl, aryl, heteroaryl, or heterocyclyl, and excludes where  $R^a$  is hydrogen. For example, the phrase "acyl substituted with one or more heteroaryl," encompasses a substituted heteroarylcarbonyl group, namely  $-C(O)Het-Het$ , where each "Het" refers to a heteroaryl group as defined herein.

As used herein the term "acylsulfonamide" refers to a group  $-S(O)_2NHC(O)R^a$ , where  $R^a$  is alkyl, cycloalkyl, aryl, heteroaryl, or heterocyclyl, as each is herein defined.

As used herein the term "acyloxy" refers to a group  $-OC(O)R^a$ , where  $R^a$  is alkyl, cycloalkyl, aryl, heteroaryl, or heterocyclyl, as each is herein defined.

As used herein the term "alkoxy" refers to a group  $-OR^a$ , where  $R^a$  is alkyl, as herein defined.

As used herein the term "alkylamino" refers to a group  $-NHR^a$ , where  $R^a$  is alkyl or substituted alkyl, where the alkyl group is substituted with an alkoxy group or a hydroxyl group as herein defined.

As used herein the term "alkylcarboxamide" refers to a group  $-C(O)NHR^a$  or, alternatively,  $-NHC(O)R^a$ , where each  $R^a$  independently is alkyl or substituted alkyl, where the alkyl group is substituted with an alkoxy group or a hydroxyl group as herein defined. The term, thus, includes groups such as alkoxyalkylcarboxamides ( $-C(O)-NH-(CH_2)_x-O-R^a$ ) and hydroxyalkylcarboxamides ( $-C(O)-NH-(CH_2)_x-OH$ ).

As used herein "alkoxycarbonyl" refers to a group  $-C(O)OR^a$  where  $R^a$  is alkyl, as herein defined.

As used herein the term "alkyloxyphosphoryl" refers to a group  $-P(O)(OR^a)(OR^a)$ , where each  $R^a$  independently is hydrogen, alkyl, or substituted alkyl, where the alkyl group is substituted with an alkoxy group or a hydroxyl group as herein defined.

As used herein the term "alkylthiocarboxamide" refers to a group  $-C(S)NHR^a$  or alternatively  $-NHC(S)R^a$ , where each  $R^a$  independently is alkyl or substituted alkyl, where the alkyl group is substituted with an alkoxy group or a hydroxyl group as herein defined.

As used herein the term "alkylsulfonamide" refers to a group  $-S(O)_2NHR^a$ , or alternatively  $-NR^aS(O)_2$ , where each  $R^a$  independently is alkyl or substituted alkyl, and where the alkyl group is substituted with an alkoxy group or a hydroxyl group as herein defined.

5 As used herein the term "alkylsulfinyl" refers to a group  $-S(O)R^a$  where  $R^a$  is alkyl, as herein defined.

As used herein the term "alkylsulfonyl" refers to a group  $-S(O)_2R^a$  where  $R^a$  is alkyl, as herein defined.

10 As used herein the term "alkylsulfoximine" refers to a group  $-S(NH)(O)R^a$ , where  $R^a$  is an alkyl group as herein defined.

As used herein the term "alkylthio" refers to a group  $-SR^a$  where  $R^a$  is alkyl, as herein defined.

As used herein the term "alkylthioureyll" refers to a group  $-N(R^a)C(S)N(R^a)(R^a)$ , where each  $R^a$  independently is hydrogen or alkyl, as herein defined.

15 As used herein the term "alkylureyl" refers to a group  $-N(R^a)C(O)N(R^a)(R^a)$ , where each  $R^a$  independently is hydrogen or alkyl, as herein defined.

As used herein the term "amino" refers to a group  $-NH_2$ .

20 As used herein the term "aralkyl" refers to a group  $-R^bR^a$ , where  $R^b$  is an alkylene and  $R^a$  is aryl, as each herein is defined. Preferably the alkylene group has one to ten carbon atoms, preferably one to six carbon atoms, and preferably is a methylene group,  $-CH_2-$ .

As used herein the term "carbamimidoyl" refers to a group  $-C(=N)N(R^a)(R^a)$ , where each  $R^a$  independently is hydrogen or alkyl, as herein defined.

As used herein "carboxy" refers to a group  $-C(O)OH$ .

25 As used herein the term "carboxamide" refers to a group  $-C(O)NH_2$ .

As used herein the term "cyano" refers to a group  $-CN$ .

As used herein the term "cycloalkylalkylene" refers to a group  $-R^bR^a$ , where  $R^b$  is an alkylene and  $R^a$  is cycloalkyl, as each herein is defined. As used herein "C<sub>1</sub>-C<sub>6</sub> cycloalkylalkylene" refers to a cycloalkyl group linked through a C<sub>1</sub>-C<sub>6</sub> alkylene group.

30 As used herein the term "dialkylamino" refers to a group  $-N(R^a)(R^a)$ , where each  $R^a$  independently is alkyl or substituted alkyl, where the alkyl group is substituted with an alkoxy group or a hydroxyl group as herein defined. The reference of C<sub>1</sub>-C<sub>6</sub> refers to

each alkyl group independently. Thus, C<sub>1</sub>-C<sub>6</sub> dialkylamino refers to a group -N(R<sup>a</sup>)(R<sup>a</sup>), where each R<sup>a</sup> independently is C<sub>1</sub>-C<sub>6</sub> alkyl as herein defined.

As used herein the term "dialkylcarboxamide" refers to a group -C(O)N(R<sup>a</sup>)(R<sup>a</sup>), where each R<sup>a</sup> independently is alkyl or substituted alkyl, where the alkyl group is substituted with an alkoxy group or a hydroxyl group as herein defined.

As used herein the term "dialkyloxyphosphoryl" refers to a group -P(O)(OR<sup>a</sup>)(OR<sup>a</sup>), where each R<sup>a</sup> independently is alkyl or substituted alkyl, where the alkyl group is substituted with an alkoxy group or a hydroxyl group as herein defined.

As used herein the term "dialkylsulfonamide" refers to a group -S(O)<sub>2</sub>N(R<sup>a</sup>)(R<sup>a</sup>), where each R<sup>a</sup> independently is alkyl or substituted alkyl, where the alkyl group is substituted with an alkoxy group or a hydroxyl group as herein defined.

As used herein the term "dialkylthiocarboxamide" refers to a group -C(S)N(R<sup>a</sup>)(R<sup>a</sup>), where each R<sup>a</sup> independently is alkyl or substituted alkyl, where the alkyl group is substituted with an alkoxy group or a hydroxyl group as herein defined.

As used herein "haloalkoxy" refers to a group -OR<sup>a</sup>, where R<sup>a</sup> is haloalkyl as herein defined.

As used herein the term "halogen" refers to fluorine, chlorine, bromine, or iodine.

As used herein the term "haloalkyl" refers to an alkyl group, as defined herein, which is substituted with at least one halogen. Examples of branched or straight chained "haloalkyl" groups useful in the present invention include, but are not limited to, methyl, ethyl, propyl, isopropyl, n-butyl, and t-butyl substituted independently with one or more halogens, e.g., fluoro, chloro, bromo, and iodo. The term "haloalkyl" should be interpreted to include such substituents such as perfluoroalkyl groups and the like.

As used herein the term "haloalkylsulfonyl" refers to a group -S(O)<sub>2</sub>R<sup>a</sup>, where R<sup>a</sup> is haloalkyl as herein defined.

As used herein the term "haloalkylthio" refers to a group -SR<sup>a</sup>, where R<sup>a</sup> is haloalkyl as herein defined.

As used herein the term "heteroaralkyl" refers to a group -R<sup>b</sup>R<sup>a</sup>, where R<sup>b</sup> is an alkylene and R<sup>a</sup> is heteroaryl, as each herein is defined. Preferably the alkylene group has one to ten carbon atoms, preferably one to six carbon atoms, and preferably is a methylene group, -CH<sub>2</sub>-.

As used herein the term "hydroxyl" refers to a group -OH.

As used herein the term "nitro" refers to a group -NO<sub>2</sub>.

As used herein the term "sulfonamide" refers to a group  $-S(O)_2NH_2$ , or alternatively  $-NHS(O)_2$ .

As used herein the term "thiol" refers to a group  $-SH$ .

The compounds of formula (I) may crystallize in more than one form, a  
5 characteristic known as polymorphism, and such polymorphic forms ("polymorphs") are within the scope of formula (I). Polymorphism generally can occur as a response to changes in temperature, pressure, or both. Polymorphism can also result from variations in the crystallization process. Polymorphs can be distinguished by various physical characteristics known in the art such as x-ray diffraction patterns, solubility, and  
10 melting point.

Certain of the compounds described herein may be capable of existing as stereoisomers. The scope of the present invention includes mixtures of stereoisomers as well as purified or enriched mixtures. Also included within the scope of the invention are the individual isomers of the compounds represented by formula (I), as well as any  
15 wholly or partially equilibrated mixtures thereof. Certain compounds of formula (I) contain a chiral center. Therefore, in particular, the scope of the present invention should be interpreted to include racemates, purified enantiomers, and enantiomerically enriched mixtures of the compounds of formula (I). As one example, the compounds of the present invention include racemic and chiral sulfones and sulfoxides.

20 Typically, but not absolutely, the salts of the present invention are pharmaceutically acceptable salts. Salts encompassed within the term "pharmaceutically acceptable salts" refer to non-toxic salts of the compounds of this invention. Salts of the compounds of the present invention may comprise acid addition salts. Representative salts include acetate, benzenesulfonate, benzoate, bicarbonate,  
25 bisulfate, bitartrate, borate, calcium edetate, camsylate, carbonate, clavulanate, citrate, dihydrochloride, edisylate, estolate, esylate, fumarate, gluceptate, gluconate, glutamate, glycollylarsanilate, hexylresorcinate, hydrabamine, hydrobromide, hydrochloride, hydroxynaphthoate, iodide, isethionate, lactate, lactobionate, laurate, malate, maleate, mandelate, mesylate, methylsulfate, monopotassium maleate, mucate, napsylate,  
30 nitrate, N-methylglucamine, oxalate, pamoate (embonate), palmitate, pantothenate, phosphate/diphosphate, polygalacturonate, potassium, salicylate, sodium, stearate, subacetate, succinate, sulfate, tannate, tartrate, teoclate, tosylate, triethiodide, trimethylammonium, and valerate salts. Other salts, which are not pharmaceutically



acceptable, may be useful in the preparation of compounds of this invention and these should be considered to form a further aspect of the invention.

As used herein, the term "solvate" refers to a complex of variable stoichiometry formed by a solute (in this invention, a compound of Formula I, or a salt or  
5 physiologically functional derivative thereof) and a solvent. Such solvents, for the purpose of the invention, should not interfere with the biological activity of the solute. Non-limiting examples of suitable solvents include, but are not limited to water, methanol, ethanol, and acetic acid. Preferably the solvent used is a pharmaceutically acceptable solvent. Non-limiting examples of suitable pharmaceutically acceptable  
10 solvents include water, ethanol, and acetic acid. Most preferably the solvent used is water.

As used herein, the term "prodrug" refers to any pharmaceutically acceptable derivative of a compound of the present invention that, upon administration to a mammal, is capable of providing (directly or indirectly) a compound of the present  
15 invention or an active metabolite thereof. Such derivatives, for example, esters and amides, will be clear to those skilled in the art, without undue experimentation. Reference may be made to the teaching of *Burger's Medicinal Chemistry And Drug Discovery*, 5<sup>th</sup> Edition, Vol 1: Principles and Practice, which is incorporated herein by reference to the extent that it teaches prodrugs.

As used herein, the term "effective amount" means that amount of a drug or pharmaceutical agent that will elicit the biological or medical response of a tissue,  
20 system, animal, or human that is being sought, for instance, by a researcher or clinician. The term "therapeutically effective amount" means any amount which, as compared to a corresponding subject who has not received such amount, results in improved treatment, healing, prevention, or amelioration of a disease, disorder, or side effect, or a decrease  
25 in the rate of advancement of a disease or disorder. The term also includes within its scope amounts effective to enhance normal physiological function. For use in therapy, therapeutically effective amounts of a compound of formula (I), as well as salts, solvates, and physiological functional derivatives thereof, may be administered as the raw  
30 chemical. Additionally, the active ingredient may be presented as a pharmaceutical composition.

Accordingly, the invention further provides pharmaceutical compositions that include effective amounts of compounds of the formula (I) and salts, solvates, and

physiological functional derivatives thereof, and one or more pharmaceutically acceptable carriers, diluents, or excipients. The compounds of formula (I) and salts, solvates, and physiologically functional derivatives thereof, are as herein described. The carrier(s), diluent(s) or excipient(s) must be acceptable, in the sense of being compatible  
5 with the other ingredients of the formulation and not deleterious to the recipient of the pharmaceutical composition.

In accordance with another aspect of the invention there is also provided a process for the preparation of a pharmaceutical formulation including admixing a compound of the formula (I) or salts, solvates, and physiological functional derivatives  
10 thereof, with one or more pharmaceutically acceptable carriers, diluents or excipients.

A therapeutically effective amount of a compound of the present invention will depend upon a number of factors. For example, the species, age, and weight of the recipient, the precise condition requiring treatment and its severity, the nature of the formulation, and the route of administration are all factors to be considered. The  
15 therapeutically effective amount ultimately should be at the discretion of the attendant physician or veterinarian. Regardless, an effective amount of a compound of formula (I) for the treatment of humans suffering from metabolic disorders such as diabetes and obesity, generally, should be in the range of 0.1 to 100 mg/kg body weight of recipient (mammal) per day. More usually the effective amount should be in the range of 0.1 to  
20 10 mg/kg body weight per day. Thus, for a 70 kg adult mammal the actual amount per day would usually be from 7 to 700 mg. This amount may be given in a single dose per day or in a number (such as two, three, four, five, or more) of sub-doses per day such that the total daily dose is the same. An effective amount of a salt, solvate, or physiologically functional derivative thereof, may be determined as a proportion of the  
25 effective amount of the compound of formula (I) *per se*. Similar dosages should be appropriate for treatment of the other conditions referred to herein.

Pharmaceutical formulations may be presented in unit dose forms containing a predetermined amount of active ingredient per unit dose. Such a unit may contain, as a non-limiting example, 0.5 mg to 1g of a compound of the formula (I), depending on the  
30 condition being treated, the route of administration, and the age, weight, and condition of the patient. Preferred unit dosage formulations are those containing a daily dose or sub-dose, as herein above recited, or an appropriate fraction thereof, of an active ingredient.

Such pharmaceutical formulations may be prepared by any of the methods well known in the pharmacy art.

Pharmaceutical formulations may be adapted for administration by any appropriate route, for example by an oral (including buccal or sublingual), rectal, nasal, 5 topical (including buccal, sublingual or transdermal), vaginal, or parenteral (including subcutaneous, intramuscular, intravenous or intradermal) route. Such formulations may be prepared by any method known in the art of pharmacy, for example by bringing into association the active ingredient with the carrier(s) or excipient(s). By way of example, and not meant to limit the invention, with regard to certain conditions and disorders for 10 which the compounds of the present invention are believed useful certain routes will be preferable to others.

Pharmaceutical formulations adapted for oral administration may be presented as discrete units such as capsules or tablets; powders or granules; solutions or 15 suspensions, each with aqueous or non-aqueous liquids; edible foams or whips; or oil-in-water liquid emulsions or water-in-oil liquid emulsions. For instance, for oral administration in the form of a tablet or capsule, the active drug component can be combined with an oral, non-toxic pharmaceutically acceptable inert carrier such as ethanol, glycerol, water, and the like. Generally, powders are prepared by comminuting the compound to a suitable fine size and mixing with an appropriate pharmaceutical 20 carrier such as an edible carbohydrate, as, for example, starch or mannitol. Flavorings, preservatives, dispersing agents, and coloring agents can also be present.

Capsules are made by preparing a powder, liquid, or suspension mixture and encapsulating with gelatin or some other appropriate shell material. Glidants and 25 lubricants such as colloidal silica, talc, magnesium stearate, calcium stearate, or solid polyethylene glycol can be added to the mixture before the encapsulation. A disintegrating or solubilizing agent such as agar-agar, calcium carbonate or sodium carbonate can also be added to improve the availability of the medicament when the capsule is ingested. Moreover, when desired or necessary, suitable binders, lubricants, disintegrating agents, and coloring agents can also be incorporated into the mixture. 30 Examples of suitable binders include starch, gelatin, natural sugars such as glucose or beta-lactose, corn sweeteners, natural and synthetic gums such as acacia, tragacanth, or sodium alginate, carboxymethylcellulose, polyethylene glycol, waxes, and the like. Lubricants useful in these dosage forms include, for example, sodium oleate, sodium

stearate, magnesium stearate, sodium benzoate, sodium acetate, sodium chloride, and the like. Disintegrators include, without limitation, starch, methyl cellulose, agar, bentonite, xanthan gum, and the like.

Tablets are formulated, for example, by preparing a powder mixture, granulating  
5 or slugging, adding a lubricant and disintegrant, and pressing into tablets. A powder mixture may be prepared by mixing the compound, suitably comminuted, with a diluent or base as described above. Optional ingredients include binders such as carboxymethylcellulose, alginates, gelatins, or polyvinyl pyrrolidone, solution retardants such as paraffin, resorption accelerators such as a quaternary salt, and/or absorption  
10 agents such as bentonite, kaolin, or dicalcium phosphate. The powder mixture can be wet-granulated with a binder such as syrup, starch paste, acadia mucilage, or solutions of cellulosic or polymeric materials, and forcing through a screen. As an alternative to granulating, the powder mixture can be run through the tablet machine and the result is imperfectly formed slugs broken into granules. The granules can be lubricated to  
15 prevent sticking to the tablet-forming dies by means of the addition of stearic acid, a stearate salt, talc or mineral oil. The lubricated mixture is then compressed into tablets. The compounds of the present invention can also be combined with a free flowing inert carrier and compressed into tablets directly without going through the granulating or slugging steps. A clear or opaque protective coating consisting of a sealing coat of  
20 shellac, a coating of sugar or polymeric material, and a polish coating of wax can be provided. Dyestuffs can be added to these coatings to distinguish different unit dosages.

Oral fluids such as solutions, syrups, and elixirs can be prepared in dosage unit form so that a given quantity contains a predetermined amount of the compound. Syrups can be prepared, for example, by dissolving the compound in a suitably flavored  
25 aqueous solution, while elixirs are prepared through the use of a non-toxic alcoholic vehicle. Suspensions can be formulated generally by dispersing the compound in a non-toxic vehicle. Solubilizers and emulsifiers such as ethoxylated isostearyl alcohols and polyoxy ethylene sorbitol ethers, preservatives; flavor additives such as peppermint oil, or natural sweeteners, saccharin, or other artificial sweeteners; and the like can also be  
30 added.

Where appropriate, dosage unit formulations for oral administration can be microencapsulated. The formulation can also be prepared to prolong or sustain the

release as for example by coating or embedding particulate material in polymers, wax, or the like.

The compounds of formula (I) and salts, solvates, and physiological functional derivatives thereof, can also be administered in the form of liposome delivery systems, such as small unilamellar vesicles, large unilamellar vesicles, and multilamellar vesicles. Liposomes can be formed from a variety of phospholipids, such as cholesterol, stearylamine, or phosphatidylcholines.

The compounds of formula (I) and salts, solvates, and physiologically functional derivatives thereof may also be delivered by the use of monoclonal antibodies as individual carriers to which the compound molecules are coupled.

The compounds may also be coupled with soluble polymers as targetable drug carriers. Such polymers can include polyvinylpyrrolidone (PVP), pyran copolymer, polyhydroxypropylmethacrylamide-phenol, polyhydroxyethyl-aspartamidephenol, or polyethyleneoxidepolylysine substituted with palmitoyl residues. Furthermore, the compounds may be coupled to a class of biodegradable polymers useful in achieving controlled release of a drug; for example, polylactic acid, polyepsilon caprolactone, polyhydroxy butyric acid, polyorthoesters, polyacetals, polydihydropyrans, polycyanoacrylates, and cross-linked or amphipathic block copolymers of hydrogels.

Pharmaceutical formulations adapted for transdermal administration may be presented as discrete patches intended to remain in intimate contact with the epidermis of the recipient for a prolonged period of time. For example, the active ingredient may be delivered from the patch by iontophoresis as generally described in *Pharmaceutical Research*, 3(6), 318 (1986), incorporated herein by reference as related to such delivery systems.

Pharmaceutical formulations adapted for topical administration may be formulated as ointments, creams, suspensions, lotions, powders, solutions, pastes, gels, sprays, aerosols, or oils.

For treatments of the eye or other external tissues, for example mouth and skin, the formulations may be applied as a topical ointment or cream. When formulated in an ointment, the active ingredient may be employed with either a paraffinic or a water-miscible ointment base. Alternatively, the active ingredient may be formulated in a cream with an oil-in-water cream base or a water-in-oil base.

Pharmaceutical formulations adapted for topical administrations to the eye include eye drops wherein the active ingredient is dissolved or suspended in a suitable carrier, especially an aqueous solvent.

5 Pharmaceutical formulations adapted for topical administration in the mouth include lozenges, pastilles, and mouthwashes.

10 Pharmaceutical formulations adapted for nasal administration, where the carrier is a solid, include a coarse powder having a particle size for example in the range 20 to 500 microns. The powder is administered in the manner in which snuff is taken, i.e., by rapid inhalation through the nasal passage from a container of the powder held close up to the nose. Suitable formulations wherein the carrier is a liquid, for administration as a nasal spray or as nasal drops, include aqueous or oil solutions of the active ingredient.

Pharmaceutical formulations adapted for administration by inhalation include fine particle dusts or mists, which may be generated by means of various types of metered dose pressurized aerosols, nebulizers, or insufflators.

15 Pharmaceutical formulations adapted for rectal administration may be presented as suppositories or as enemas.

Pharmaceutical formulations adapted for vaginal administration may be presented as pessaries, tampons, creams, gels, pastes, foams, or spray formulations.

20 Pharmaceutical formulations adapted for parenteral administration include aqueous and non-aqueous sterile injection solutions which may contain anti-oxidants, buffers, bacteriostats, and solutes that render the formulation isotonic with the blood of the intended recipient; and aqueous and non-aqueous sterile suspensions which may include suspending agents and thickening agents. The formulations may be presented in unit-dose or multi-dose containers, for example sealed ampules and vials, and may be stored in a freeze-dried (lyophilized) condition requiring only the addition of the sterile liquid carrier, for example water for injections, immediately prior to use.

25 Extemporaneous injection solutions and suspensions may be prepared from sterile powders, granules, and tablets.

30 In addition to the ingredients particularly mentioned above, the formulations may include other agents conventional in the art having regard to the type of formulation in question. For example, formulations suitable for oral administration may include flavoring or coloring agents.

The compounds of the present invention and their salts, solvates, and physiologically functional derivatives thereof, may be employed alone or in combination with other therapeutic agents. The compound(s) of formula (I) and the other pharmaceutically active agent(s) may be administered together or separately and, when administered separately, administration may occur simultaneously or sequentially, in any order. The amounts of the compound(s) of formula (I) and the other pharmaceutically active agent(s) and the relative timings of administration will be selected in order to achieve the desired combined therapeutic effect. The administration in combination of a compound of formula (I) salts, solvates, or physiologically functional derivatives thereof with other treatment agents may be in combination by administration concomitantly in: (1) a unitary pharmaceutical composition including both compounds; or (2) separate pharmaceutical compositions each including one of the compounds. Alternatively, the combination may be administered separately in a sequential manner wherein one treatment agent is administered first and the other second or vice versa. Such sequential administration may be close in time or remote in time.

The compounds of the present invention may be used in the treatment of a variety of disorders and conditions. As such, the compounds of the present invention may be used in combination with a variety of other therapeutic agents useful in the treatment or prophylaxis of those disorders or conditions. The compounds of the present invention may be used in combination with diet, exercise, insulin, an insulin sensitivity enhancer, a glucose absorption inhibitor, a biguanide, an insulin secretion enhancer, a SGLT2 inhibitor, an insulin or insulin analogue, a glucagon receptor antagonist, an insulin receptor kinase stimulant, a tripeptidyl peptidase II inhibitor, a dipeptidyl peptidase IV inhibitor, a protein tyrosine phosphatase-1B inhibitor, a glycogen phosphorylase inhibitor, an AXOR 109 agonist, a glucose-6-phosphatase inhibitor, a fructose-bisphosphatase inhibitor, a pyruvate dehydrogenase inhibitor, a hepatic gluconeogenesis inhibitor, D-chiroinsitol, a glycogen synthase kinase-3 inhibitor, glucagon-like peptide-1, a glucagon-like peptide-1 analogue, a glucagon-like peptide-1 agonist, amylin, an amylin analogue, an amylin agonist, an aldose reductase inhibitor, an advanced glycation endproducts formation inhibitor, a protein kinase C inhibitor, a  $\gamma$ -aminobutyric acid receptor antagonist, a sodium channel antagonist, a transcript factor NF- $\kappa$ B inhibitor, a lipid peroxidase inhibitor, an *N*-acetylated- $\alpha$ -linked-acid-dipeptidase inhibitor, insulin-like growth factor-I, platelet-derived growth factor, a platelet-derived

growth factor analogue, epidermal growth factor, nerve growth factor, a carnitine derivative, uridine, 5-hydroxy-1-methylhidantoin, EGB-761, bimoclolmol, sulodexide, Y-128, antidiarrhoics, cathartics, a hydroxymethylglutaryl coenzyme A reductase inhibitor, a fibric acid derivative, a  $\beta_3$ -adrenoceptor agonist, an acyl-coenzyme A cholesterol  
5 acyltransferase inhibitor, probcol, a thyroid hormone receptor agonist, a cholesterol absorption inhibitor, a lipase inhibitor, a microsomal triglyceride transfer protein inhibitor, a lipoxxygenase inhibitor, a carnitine palmitoyl-transferase inhibitor, a squalene synthase inhibitor, a low-density lipoprotein receptor enhancer, a nicotinic acid derivative, a bile  
10 acid sequestrant, a sodium/bile acid cotransporter inhibitor, a cholesterol ester transfer protein inhibitor, an appetite suppressant, an angiotensin-converting enzyme inhibitor, a neutral endopeptidase inhibitor, an angiotensin II receptor antagonist, an endothelin-converting enzyme inhibitor, an endothelin receptor antagonist, a diuretic agent, a calcium antagonist, a vasodilating antihypertensive agent, a sympathetic blocking agent, a centrally acting antihypertensive agent, an  $\alpha_2$ -adrenoceptor agonist, an antiplatelets  
15 agent, a uric acid synthesis inhibitor, a uricosuric agent, and a urinary alkalinizer.

Exemplary compounds are hereinafter described, however, a combination within the scope of the present invention should not be limited by this specific description. Rather, any combination within the perview of those skilled in the art is contemplated. In addition, this listing of exemplary compounds includes the free compounds, as well as  
20 salts, solvates, and physiologically functional derivatives.

As insulin sensitivity enhancers, peroxisome proliferator-activated receptor- $\gamma$  agonists such as troglitazone, pioglitazone, rosiglitazone, darglitazone, GI-262570, isaglitazone, LG-100641, NC-2100, T-174, DRF-2189, CLX-0921, CS-011, GW-1929, ciglitazone, englitazone, and NIP-221, peroxisome proliferator-activated receptor-  
25  $\alpha$  agonists such as GW-9578 and BM-170744, peroxisome proliferator-activated receptor- $\alpha/\gamma$  agonists such as GW-409544, KRP-297, NN-622, CLX-0940, LR-90, SB-219994, DRF-4158, and DRF-MDX8, retinoid X receptor agonists such as ALRT-268, AGN-4204, MX-6054, AGN-194204, LG-100754 and bexarotene, and other insulin sensitivity enhancers such as reglixane, ONO-5816, MBX-102, CRE-1625, FK-614,  
30 CLX-0901, CRE-1633, NN-2344, BM-13125, BM-501050, HQL-975, CLX-0900, MBX-668, MBX-675, S-15261, GW-544, AZ-242, LY-510929, AR-H049020 and GW-501516 are illustrated. Insulin sensitivity enhancers may be used for diabetes, impaired glucose



tolerance, diabetic complications, obesity, hyperinsulinemia, hyperlipidemia, hypercholesterolemia, hypertriglyceridemia, lipid metabolism disorder or atherosclerosis, and more preferably for diabetes, impaired glucose tolerance or hyperinsulinemia. Such compounds are believed to improve the disturbance of insulin signal transduction in  
5 peripheral tissues and enhancing glucose uptake into the tissues from the blood, leading to lowering of blood glucose level.

As glucose absorption inhibitors, for example,  $\alpha$ -glucosidase inhibitors such as acarbose, voglibose, miglitol, CKD-711, emiglitate, MDL-25,637, camiglibose and MDL-73,945, and  $\alpha$ -amylase inhibitors such as AZM-127 are illustrated. Glucose absorption  
10 inhibitors may be used for diabetes, impaired glucose tolerance, diabetic complications, obesity or hyperinsulinemia, and more preferably for impaired glucose tolerance. Such compounds are believed to inhibit the gastrointestinal enzymatic digestion of carbohydrates contained in foods, and inhibit and/or delay the absorption of glucose into the body.

As biguanides, phenformin, buformin, metformin, or the like are illustrated. Biguanides may be used for diabetes, impaired glucose tolerance, diabetic  
15 complications or hyperinsulinemia, and more preferably for diabetes, impaired glucose tolerance or hyperinsulinemia. Such compounds are believed to lower blood glucose level by inhibitory effects on hepatic gluconeogenesis, accelerating effects on anaerobic glycolysis in tissues or improving effects on insulin resistance in peripheral tissues.  
20

As insulin secretion enhancers, tolbutamide, chlorpropamide, tolazamide, acetohexamide, glyclopyramide, glyburide (glibenclamide), gliclazide, 1-butyl-3-metanilylurea, carbutamide, glibornuride, glipizide, gliquidone, glisoxapide, glybuthiazol, glybuzole, glyhexamide, sodium glymidine, glypinamide, phenbutamide, tolcyclamide,  
25 glimepiride, nateglinide, mitiglinide calcium hydrate, repaglinide or the like are illustrated. In addition, the insulin secretion enhancers include glucokinase activators such as RO-28-1675. Insulin secretion enhancers may be used for diabetes, impaired glucose tolerance or diabetic complications, and more preferably for diabetes or impaired glucose tolerance. Such compounds are believed to lower blood glucose level by acting  
30 on pancreatic  $\beta$ -cells and enhancing the insulin secretion.

As SGLT2 inhibitors, compounds described in Japanese patent publications Nos. Hei 10-237089 and 2001-288178, and International Publications Nos.

WO01/16147, WO01/27128, WO01/68660, WO01/74834, WO01/74835, WO02/28872, WO02/36602, WO02/44192, WO02/53573, and WO 03/99836 are illustrated. In addition, inhibitors identified as dapagliflozin, GW869682, and/or GSK189075 are illustrated as well. SGLT2 inhibitors may be used for diabetes, impaired glucose  
5 tolerance, diabetic complications, obesity or hyperinsulinemia, and more preferably for diabetes, impaired glucose tolerance, obesity or hyperinsulinemia. Such compounds are believed to lower blood glucose level by inhibiting the reabsorption of glucose at the kidney's proximal tubule.

As insulin or insulin analogues, human insulin, animal-derived insulin, human or  
10 animal-derived insulin analogues or the like are illustrated. These preparations may be used for diabetes, impaired glucose tolerance or diabetic complications, and more preferably for diabetes or impaired glucose tolerance.

AXOR 109, also known as TGR5, BG37, M-BAR, or hGPCR19, is a bile acid G-  
protein coupled receptor primarily expressed in monocytes/macrophages, lung, spleen,  
15 and the intestinal tract. AXOR109 agonists may be used for diabetes mellitus, stress, obesity, appetite control and satiety, Alzheimers, inflammation, and diseases of the central nervous system. AXOR109 agonists are believed to moderate blood glucose level by stimulating the release of GLP-1 from enteroendocrine cells.

As glucagon receptor antagonists, BAY-27-9955, NNC-92-1687 or the like are  
20 illustrated; as insulin receptor kinase stimulants, TER-17411, L-783281, KRX-613 or the like are illustrated; as tripeptidyl peptidase II inhibitors, UCL-1397 or the like are illustrated; as dipeptidyl peptidase IV inhibitors, vildagliptin, sitigliptin, denagliptin, saxagliptin, TSL-225, P-32/98 or the like are illustrated; as protein tyrosine phosphatase 1B inhibitors, PTP-112, OC-86839, PNU-177496 or the like are illustrated; as glycogen  
25 phosphorylase inhibitors, NN-4201, CP-368296 or the like are illustrated; as fructose-bisphosphatase inhibitors, R-132917 or the like are illustrated; as pyruvate dehydrogenase inhibitors, AZD-7545 or the like are illustrated; as hepatic gluconeogenesis inhibitors, FR-225659 or the like are illustrated; as glucagon-like peptide-1 analogues, exendin-4, CJC-1131 or the like are illustrated; as glucagon-like  
30 peptide 1 agonists; AZM-134, LY-315902 or the like are illustrated; and as amylin, amylin analogues or amylin agonists, pramlintide acetate or the like are illustrated. These drugs, glucose-6-phosphatase inhibitors, D-chiroinsitol, glycogen synthase kinase-3 inhibitors and glucagon-like peptide-1 may be used for diabetes, impaired

glucose tolerance, diabetic complications or hyperinsulinemia, and more preferably for diabetes or impaired glucose tolerance.

As aldose reductase inhibitors, ascorbyl gamolenate, tolrestat, epalrestat, ADN-138, BAL-ARI8, ZD-5522, ADN-311, GP-1447, IDD-598, fidarestat, sorbinil, ponalrestat, 5 risarestat, zenarestat, minalrestat, methosorbinil, AL-1567, imirestat, M-16209, TAT, AD-5467, zopolrestat, AS-3201, NZ-314, SG-210, JTT-811, lindolrestat or the like are illustrated. Aldose reductase inhibitors may be used for diabetic complications. Such compounds are believed to inhibit aldose reductase and lowering excessive intracellular accumulation of sorbitol in accelerated polyol pathway which are in continuous 10 hyperglycemic condition in the tissues in diabetic complications.

As advanced glycation endproducts formation inhibitors, pyridoxamine, OPB-9195, ALT-946, ALT-711, pimagedine hydrochloride or the like are illustrated. Advanced glycation endproducts formation inhibitors may be used for diabetic complications. Such compounds are believed to inhibit formation of advanced glycation endproducts which 15 are accelerated in continuous hyperglycemic condition in diabetes and declining of cellular damage.

As protein kinase C inhibitors, LY-333531, midostaurin or the like are illustrated. Protein kinase C inhibitors may be used for diabetic complications. Such compounds are believed to inhibit protein kinase C activity, which is accelerated in continuous 20 hyperglycemic condition in diabetic patients.

As  $\gamma$ -aminobutyric acid receptor antagonists, topiramate or the like are illustrated; as sodium channel antagonists, mexiletine hydrochloride, oxcarbazepine or the like are illustrated; as transcrit factor NF- $\kappa$ B inhibitors, dexlipotam or the like are illustrated; as lipid peroxidase inhibitors, tirilazad mesylate or the like are illustrated; as 25 *N*-acetylated- $\alpha$ -linked-acid-dipeptidase inhibitors, GPI-5693 or the like are illustrated; and as carnitine derivatives, carnitine, levacecarnine hydrochloride, levocarnitine chloride, levocarnitine, ST-261 or the like are illustrated. These drugs, insulin-like growth factor-I, platelet-derived growth factor, platelet derived growth factor analogues, epidermal growth factor, nerve growth factor, uridine, 5-hydroxy-1-methylhidantoin, 30 EGB-761, bimoclomol, sulodexide and Y-128 may be used for diabetic complications.

As antidiarrhoics or cathartics, polycarbophil calcium, albumin tannate, bismuth subnitrate or the like are illustrated. These drugs may be used for diarrhea, constipation or similar conditions that may accompany diabetes or other metabolic disorders.

As hydroxymethylglutaryl coenzyme A reductase inhibitors, sodium cerivastatin, sodium pravastatin, lovastatin, simvastatin, sodium fluvastatin, atorvastatin calcium hydrate, SC-45355, SQ-33600, CP-83101, BB-476, L-669262, S-2468, DMP-565, U-20685, BAY-x-2678, BAY-10-2987, calcium pitavastatin, calcium rosuvastatin, 5 colestolone, dalvastatin, acitemate, mevastatin, crilvastatin, BMS-180431, BMY-21950, glenvastatin, carvastatin, BMY-22089, bervastatin or the like are illustrated.

Hydroxymethylglutaryl coenzyme A reductase inhibitors may be used for hyperlipidemia, hypercholesterolemia, hypertriglyceridemia, lipid metabolism disorder or atherosclerosis, and more preferably for hyperlipidemia, hypercholesterolemia, or atherosclerosis. Such 10 compounds are believed to lower blood cholesterol level by inhibiting hydroxymethylglutaryl coenzyme A reductase.

As fibric acid derivatives, bezafibrate, beclobrate, binifibrate, ciprofibrate, clinofibrate, clofibrate, aluminum clofibrate, clofibric acid, etofibrate, fenofibrate, gemfibrozil, nicofibrate, pirifibrate, ronifibrate, simfibrate, theofibrate, AHL-157 or the like 15 are illustrated. Fibric acid derivatives may be used for hyperinsulinemia, hyperlipidemia, hypercholesterolemia, hypertriglyceridemia, lipid metabolism disorder or atherosclerosis, and more preferably for hyperlipidemia, hypertriglyceridemia, or atherosclerosis. Such compounds are believed to activate hepatic lipoprotein lipase and enhancing fatty acid oxidation, leading to a lowering of blood triglyceride levels.

As  $\beta_3$ -adrenoceptor agonists, BRL-28410, SR-58611A, ICI-198157, ZD-2079, BMS-194449, BRL-37344, CP-331679, CP-114271, L-750355, BMS-187413, SR-59062A, BMS-210285, LY-377604, SWR-0342SA, AZ-40140, SB-226552, D-7114, BRL-35135, FR-149175, BRL-26830A, CL-316243, AJ-9677, GW-427353 (solabegron), N-5984, GW-2696, YM178 or the like are illustrated.  $\beta_3$ -Adrenoceptor agonists may be 20 used for diabetes, obesity, hyperinsulinemia, hyperlipidemia, hypercholesterolemia, hypertriglyceridemia, lipid metabolism disorder, urinary incontinence, and IBS.

As acyl-coenzyme A cholesterol acyltransferase inhibitors, NTE-122, MCC-147, PD-132301-2, DUP-129, U-73482, U-76807, RP-70676, P-06139, CP-113818, RP-73163, FR-129169, FY-038, EAB-309, KY-455, LS-3115, FR-145237, T-2591, J-104127, 30 R-755, FCE-28654, YIC-C8-434, avasimibe, CI-976, RP-64477, F-1394, eldacimibe, CS-505, CL-283546, YM-17E, lecimibide, 447C88, YM-750, E-5324, KW-3033, HL-004, eflucimibe or the like are illustrated. Acyl-coenzyme A cholesterol acyltransferase inhibitors may be used for hyperlipidemia, hypercholesterolemia, hypertriglyceridemia or

lipid metabolism disorder, and more preferably for hyperlipidemia or hypercholesterolemia. Such compounds are believed to lower blood cholesterol levels by inhibiting acyl-coenzyme A cholesterol acyltransferase.

As thyroid hormone receptor agonists, sodium liothyronine, sodium  
5 levothyroxine, KB-2611 or the like are illustrated; as cholesterol absorption inhibitors, ezetimibe, SCH-48461 or the like are illustrated; as lipase inhibitors, orlistat, ATL-962, AZM-131, RED-103004 or the like are illustrated; as carnitine palmitoyltransferase inhibitors, etomoxir or the like are illustrated; as squalene synthase inhibitors, SDZ-268-198, BMS-188494, A-87049, RPR-101821, ZD-9720, RPR-107393, ER-27856 or the like  
10 are illustrated; as nicotinic acid derivatives, nicotinic acid, nicotinamide, nicomol, niceritrol, acipimox, nicorandil or the like are illustrated; as bile acid sequestrants, colestyramine, colestilan, colesevelam hydrochloride, GT-102-279 or the like are illustrated; as sodium/bile acid cotransporter inhibitors, 264W94, S-8921, SD-5613 or the like are illustrated; and as cholesterol ester transfer protein inhibitors, PNU-107368E,  
15 SC-795, JTT-705, CP-529414 or the like are illustrated. Probccl, microsomal triglyceride transfer protein inhibitors, lipoxygenase inhibitors, and low-density lipoprotein receptor enhancers may be used for hyperlipidemia, hypercholesterolemia, hypertriglyceridemia, or lipid metabolism disorder.

As appetite suppressants, monoamine reuptake inhibitors, serotonin reuptake  
20 inhibitors, serotonin releasing stimulants, serotonin agonists (especially 5HT<sub>2C</sub>-agonists), noradrenaline reuptake inhibitors, noradrenaline releasing stimulants,  $\alpha_1$ -adrenoceptor agonists,  $\beta_2$ -adrenoceptor agonists, dopamine agonists, cannabinoid receptor antagonists,  $\gamma$ -aminobutyric acid receptor antagonists, H<sub>3</sub>-histamine antagonists, L-histidine, leptin, leptin analogues, leptin receptor agonists, melanocortin receptor  
25 agonists (especially, MC3-R agonists, MC4-R agonists),  $\alpha$ -melanocyte stimulating hormone, cocaine-and amphetamine-regulated transcript, mahogany protein, enterostatin agonists, calcitonin, calcitonin-gene-related peptide, bombesin, cholecystokinin agonists (especially CCK-A agonists), corticotropin-releasing hormone, corticotrophin-releasing hormone analogues, corticotropin-releasing hormone agonists,  
30 urocortin, somatostatin, somatostatin analogues, somatostatin receptor agonists, pituitary adenylate cyclase-activating peptide, brain-derived neurotrophic factor, ciliary neurotrophic factor, thyrotropin-releasing hormone, neurotensin, sauvagine, neuropeptide Y antagonists, opioid peptide antagonists, galanin antagonists, melanin-

concentrating hormone antagonists, agouti-related protein inhibitors and orexin receptor antagonists are illustrated. As monoamine reuptake inhibitors, mazindol or the like are illustrated; as serotonin reuptake inhibitors, dexfenfluramine hydrochloride, fenfluramine, sibutramine hydrochloride, fluvoxamine maleate, sertraline hydrochloride or the like are illustrated; as serotonin agonists, inotripan, (+)-norfenfluramine or the like are illustrated; as noradrenaline reuptake inhibitors, bupropion, GW-320659 or the like are illustrated; as noradrenaline releasing stimulants, rolipram, YM-992 or the like are illustrated; as  $\beta_2$ -adrenoceptor agonists, amphetamine, dextroamphetamine, phentermine, benzphetamine, methamphetamine, phendimetrazine, phenmetrazine, diethylpropion, phenylpropanolamine, clobenzorex or the like are illustrated; as dopamine agonists, ER-230, doprexin, bromocriptine mesylate or the like are illustrated; as cannabinoid receptor antagonists, rimonabant or the like are illustrated; as  $\gamma$ -aminobutyric acid receptor antagonists, topiramate or the like are illustrated; as  $H_3$ -histamine antagonists, GT-2394 or the like are illustrated; as leptin, leptin analogues or leptin receptor agonists, LY-355101 or the like are illustrated; as cholecystokinin agonists (especially CCK-A agonists), SR-146131, SSR-125180, BP-3.200, A-71623, FPL-15849, GI-248573, GW-7178, GI-181771, GW-7854, A-71378 or the like are illustrated; and as neuropeptide Y antagonists, SR-120819-A, PD-160170, NGD-95-1, BIBP-3226, 1229-U-91, CGP-71683, BIBO-3304, CP-671906-01, J-115814 or the like are illustrated.

As angiotensin-converting enzyme inhibitors, captopril, enalapril maleate, alacepril, delapril hydrochloride, ramipril, lisinopril, imidapril hydrochloride, benazepril hydrochloride, ceronapril monohydrate, cilazapril, sodium fosinopril, perindopril erbumine, calcium moveltipril, quinapril hydrochloride, spirapril hydrochloride, temocapril hydrochloride, trandolapril, calcium zofenopril, moexipril hydrochloride, rentiapril or the like are illustrated. Angiotensin-converting enzyme inhibitors may be used for diabetic complications or hypertension.

As neutral endopeptidase inhibitors, omapatrilat, MDL-100240, fasidotril, sampatrilat, GW-660511X, mixanpril, SA-7060, E-4030, SLV-306, ecadotril or the like are illustrated. Neutral endopeptidase inhibitors may be used for diabetic complications or hypertension.

As angiotensin II receptor antagonists, candesartan cilexetil, candesartan cilexetil/hydrochlorothiazide, potassium losartan, eprosartan mesylate, valsartan, telmisartan, irbesartan, EXP-3174, L-158809, EXP-3312, olmesartan, tasosartan, KT-3-

671, GA-0113, RU-64276, EMD-90423, BR-9701 or the like are illustrated. Angiotensin II receptor antagonists may be used for diabetic complications or hypertension.

As endothelin-converting enzyme inhibitors, CGS-31447, CGS-35066, SM-19712 or the like are illustrated; as endothelin receptor antagonists, L-749805, TBC-3214, BMS-182874, BQ-610, TA-0201, SB-215355, PD-180988, sodium sitaxsentan, BMS-193884, darusentan, TBC-3711, bosentan, sodium tezosentan, J-104132, YM-598, S-0139, SB-234551, RPR-118031A, ATZ-1993, RO-61-1790, ABT-546, enlasentan, BMS-207940 or the like are illustrated. Such drugs may be used for diabetic complications or hypertension, and more preferably for hypertension.

As diuretic agents, chlorthalidone, metolazone, cyclopenthiiazide, trichloromethiazide, hydrochlorothiazide, hydroflumethiazide, benzylhydrochlorothiazide, penflutizide, methyclothiazide, indapamide, tripamide, mefruside, azosemide, etacrynic acid, torasemide, piretanide, furosemide, bumetanide, meticrane, potassium canrenoate, spironolactone, triamterene, aminophylline, cicletanine hydrochloride, LLU- $\gamma$ , PNU-80873A, isosorbide, D-mannitol, D-sorbitol, fructose, glycerin, acetazolamide, methazolamide, FR-179544, OPC-31260, lixivaptan, conivaptan hydrochloride or the like are illustrated. Diuretic drugs may be used for diabetic complications, hypertension, congestive heart failure or edema, and more preferably for hypertension, congestive heart failure or edema. Such compounds are believed to reduce blood pressure or improve edema by increasing urinary excretion.

As calcium antagonists, aranidipine, efonidipine hydrochloride, nicardipine hydrochloride, barnidipine hydrochloride, benidipine hydrochloride, manidipine hydrochloride, cilnidipine, nisoldipine, nitrendipine, nifedipine, nilvadipine, felodipine, amlodipine besilate, pranidipine, lercanidipine hydrochloride, isradipine, elgodipine, azelnidipine, lacidipine, vatanidipine hydrochloride, lemildipine, diltiazem hydrochloride, clentiazem maleate, verapamil hydrochloride, S-verapamil, fasudil hydrochloride, bepridil hydrochloride, gallopamil hydrochloride or the like are illustrated; as vasodilating antihypertensive agents, indapamide, todralazine hydrochloride, hydralazine hydrochloride, cadralazine, budralazine or the like are illustrated; as sympathetic blocking agents, amosulalol hydrochloride, terazosin hydrochloride, bunazosin hydrochloride, prazosin hydrochloride, doxazosin mesylate, propranolol hydrochloride, atenolol, metoprolol tartrate, carvedilol, nipradilol, celiprolol hydrochloride, nebivolol, betaxolol hydrochloride, pindolol, tertatolol hydrochloride, bevantolol hydrochloride,

timolol maleate, carteolol hydrochloride, bisoprolol hemifumarate, bopindolol malonate, nipradilol, penbutolol sulfate, acebutolol hydrochloride, tilisolol hydrochloride, nadolol, urapidil, indoramin or the like are illustrated; as centrally acting antihypertensive agents, reserpine or the like are illustrated; and as  $\alpha_2$ -adrenoceptor agonists, clonidine  
5 hydrochloride, methyldopa, CHF-1035, guanabenz acetate, guanfacine hydrochloride, moxonidine, lofexidine, talipexole hydrochloride or the like are illustrated. These drugs may be used for hypertension.

As antiplatelets agents, ticlopidine hydrochloride, dipyridamole, cilostazol, ethyl  
icosapentate, sarpogrelate hydrochloride, dilazep dihydrochloride, trapidil, beraprost  
10 sodium, aspirin or the like are illustrated. Antiplatelets agents may be used for atherosclerosis or congestive heart failure.

As uric acid synthesis inhibitors, allopurinol, oxypurinol or the like are illustrated; as uricosuric agents, benzbromarone, probenecid or the like are illustrated; and as urinary alkalinizers, sodium hydrogen carbonate, potassium citrate, sodium citrate or the  
15 like are illustrated. These drugs may be used for hyperuricemia or gout.

As noted, the compounds of the present invention may be used alone or may be combined with other medical therapies to treat and/or prevent a variety of disorders and conditions. More particularly, the diseases and conditions metabolic disorders, such as diabetes, including but not limited to diabetes types I and II, obesity, glucose intolerance,  
20 insulin resistance, metabolic syndrome X, hyperlipidemia, hypercholesterolemia, artherosclerosis, neurodegenerative diseases, and other indications such as stroke.

The compounds of this invention may be made by a variety of methods. Illustrative general synthetic methods are set out below followed by a description of exemplary synthesis of specific compounds of the invention as illustrated in the  
25 examples.

In the examples described below, protecting groups for sensitive or reactive groups are employed where necessary in accordance with general principles of synthetic chemistry. Protecting groups are manipulated according to standard methods of organic synthesis (T. W. Green and P. G. M. Wuts (1991) *Protective Groups in Organic  
30 Synthesis*, John Wiley & Sons, incorporated by reference with regard to protecting groups). These groups are removed at a convenient stage of the compound synthesis using methods that are readily apparent to those skilled in the art. The selection of



processes as well as the reaction conditions and order of their execution shall be consistent with the preparation of compounds of formula (I).

Those skilled in the art will recognize if a stereocenter exists in compounds of formula (I). Accordingly, the present invention includes all possible stereoisomers and includes not only racemic compounds but the individual enantiomers as well. When a compound is desired as a single enantiomer, such may be obtained by stereospecific synthesis, by resolution of the final product or any convenient intermediate, or by chiral chromatographic methods as are known in the art. Resolution of the final product, an intermediate, or a starting material may be affected by any suitable method known in the art. See, for example, *Stereochemistry of Organic Compounds* by E. L. Eliel, S. H. Wilen, and L. N. Mander (Wiley-Interscience, 1994), incorporated by reference with regard to stereochemistry.

The compounds of this invention may be made by a variety of methods, including well-known standard synthetic methods. The novel compounds of the present invention should not be limited by any specific process herein described.

#### Experimental Section

The symbols and conventions used in the following descriptions of processes, schemes, and examples are consistent with those used in the contemporary scientific literature, for example, the Journal of the American Chemical Society or the Journal of Biological Chemistry.

Unless otherwise indicated, all temperatures are expressed in °C (degrees Centigrade). All reactions were conducted at room temperature unless otherwise noted.

<sup>1</sup>H-NMR spectra were recorded on a Varian VXR-300, a Varian Unity-300, a Varian Unity-400 instrument, or a General Electric QE-300. Chemical shifts are expressed in parts per million (ppm, δ units). Coupling constants are in units of hertz (Hz). Splitting patterns describe apparent multiplicities and are designated as s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), or br (broad).

Mass spectra were obtained on Micromass Platform or ZMD mass spectrometers from Micromass Ltd., Altricham, UK, using either Atmospheric Chemical Ionization (APCI) or Electrospray Ionization (ESI).

Ozone was generated from oxygen using a standard ozonolysis unit as is known in the art (Ozonology, Inc.).

The microwave reactions were conducted using Emrys™ Optimizer / SmithSynthesizer from Biotage using standard protocols that are known in the art.

The absolute stereochemistry of chiral enantiopure sulfoxides was determined using *ab initio* Vibrational Circular Dichroism (VCD) Spectroscopy. The experimental

5 details are as follows:

- Spectrometer: BioTools ChiralIR™ VCD spectrometer equipped with a dual photoelastic modulator (PEM) and operated at 4 cm<sup>-1</sup> resolution.
- Frequency Range: 2000-800 cm<sup>-1</sup>
- PEM Calibration: dual PEM calibrated at 1400 cm<sup>-1</sup>
- PEM Retardation Settings: PEM1 = 0.250 λ; PEM2 = 0.275 λ
- Scan Method: single 5 min. DC scan + single 75 min. AC scan per enantiomer.
- Solvent: CDCl<sub>3</sub>
- Concentration: ~4mg/100 μl

10

15 Absolute configurations were assigned by comparing the sign (+/-) of an intense VCD band at 954 cm<sup>-1</sup> in experimental VCD spectra to the corresponding band in reference spectra. The sign (+/-) of a VCD marker band was identified as highly diagnostic for the absolute configuration of the aromatic methyl sulfinyl group. For related work see: (1) Stephens, P.J. *et al J. Org. Chem.*, **2001**, 66, 3671; (2) F.J. Devlin and Stephens P.J. *et al Chirality*, **2002**, 14, 400.

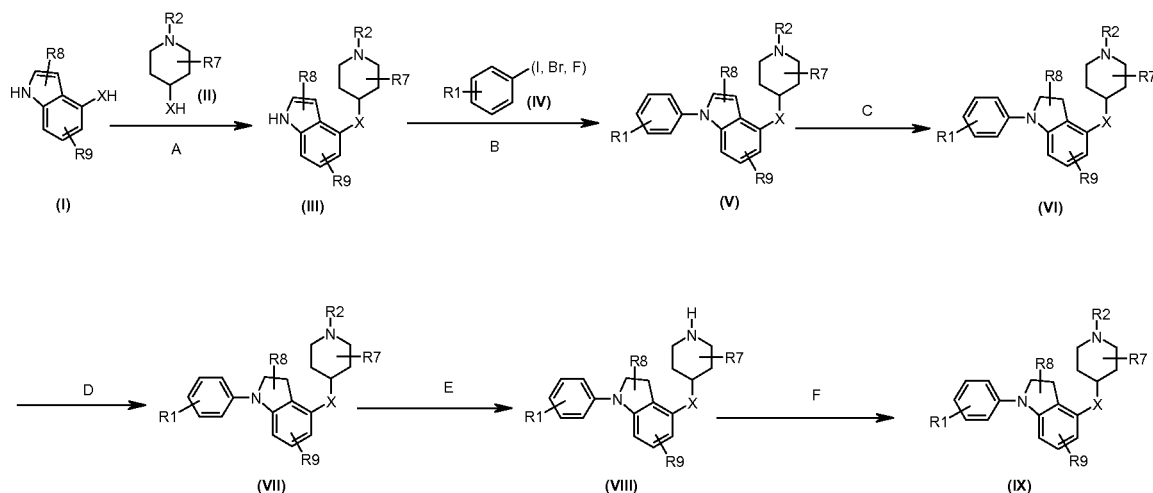
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### Synthetic Schemes

#### **Scheme 1**

#### **General Synthesis of Indoline-Based Ligands**

25



**Reagents and conditions:** **A)**  $\text{Ph}_3\text{P}$ , DIAD, THF, RT; **B)**  $\text{CuI}$ ,  $\text{K}_3\text{PO}_4$ , toluene, reflux, or 37%  $\text{KF} - \text{Al}_2\text{O}_3$ , 18-crown-6, DMSO, reflux; **C)**  $\text{NaCNBH}_3$ ,  $\text{AcOH}$ , RT; **D)** (a)  $\text{CuI}$ , L-proline,  $\text{NaOH}$ ,  $\text{CH}_3\text{SO}_2\text{Na}$ , DMSO,  $110^\circ\text{C}$ , or (b)  $\text{CuCN}$ , NMP,  $150^\circ\text{C}$ , or (c)  $\text{HP(O)(OR)}_2$ ,  $\text{CuI}$ ,  $\text{Cs}_2\text{CO}_3$ , toluene, reflux, or (d)  $\text{PdCl}_2(\text{PPh}_3)_2$  or  $\text{Pd}(\text{Ph}_3\text{P})_4$ , boronic acid, 2 N  $\text{Na}_2\text{CO}_3$ , THF, reflux, or (e)  $\text{Sn}(\text{Bu})_3\text{R}$ , Pd catalyst, THF, reflux; **E)** (a) TFA,  $\text{CH}_2\text{Cl}_2$ , RT, or (b) Conc.  $\text{HCl}$ ; **F)** (a)  $\text{R}_2\text{OCOCI}$ ,  $\text{Et}_3\text{N}$ ,  $\text{CH}_2\text{Cl}_2$ , RT, or (b) Substituted pyrimidine, DIPEA, ACN, reflux, or (c)  $\text{R}_2\text{COCl}$ ,  $\text{Et}_3\text{N}$ ,  $\text{CH}_2\text{Cl}_2$ , RT, or (d) i.  $\text{NaHCO}_3$ ,  $\text{H}_2\text{O}$ , ii.  $\text{CNBr}$ ,  $\text{Na}_2\text{CO}_3$ , iii.  $\text{RC}(\text{NH}_2)\text{NOH}$ , 1N  $\text{ZnCl}_2$  in  $\text{Et}_2\text{O}$ , iv.  $\text{EtOAc}$ ,  $\text{H}_3\text{O}^+$ ,  $\text{EtOH}$ , reflux.

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Indoline-based ligands can be prepared by following the general synthetic **Scheme 1**. A Mitsunobu reaction between substituted indole **I** and 4-OH piperidine derivative **II** can provide the compound of the formula **III**. For Mitsunobu reaction conditions, see Mitsunobu, *Synthesis*, **1981**, 1, and for a Mitsunobu reaction review see D.L. Hughes *Organic Reactions* **42**, 335, each herein incorporated by reference with regard to such synthetic teaching. The compound **III** upon N-arylation with variously substituted aryl halides using the standard reaction conditions can give the compound **V**. For N-arylation procedures, see S.L. Buchwald *et al J. Org. Chem.*, **2004**, *69*, 5578 and W.J. Smith *et al Tetrahedron Lett.*, **1996**, *37*, 299, each herein incorporated by reference with regard to such synthesis. Reduction of compound **V** with  $\text{NaCNBH}_3$  in  $\text{AcOH}$  or  $\text{CF}_3\text{CO}_2\text{H}$  can give the indoline of formula **VI**. For reaction conditions, G.W. Gribble *et al Synthesis* **1977**, 859 and also see G.W. Gribble *Chem. Soc. Rev.*, **1998**, *27*, 395, each

20

herein incorporated by reference with regard to such synthesis. The intermediate **VI** (where  $R^2$  preferably is BOC) can serve as a starting material for making a variety of analogues. Exploration of different functional groups at  $R^2$  of formula **VI** can be accessed by a sequence involving deprotection of a suitable protecting group, such as a BOC  
5 group, with acid, like TFA or 4 N HCl in dioxane to yield a compound such as **VIII**. Reaction of compound **VIII** with a variety of electrophiles would yield compounds of **IX**, wherein  $R^2$  represents part of a carbamate, urea, or pyrimidine moiety. For reaction conditions see Fyfe, M., *et al* WO 2006/067531A1 and WO2006/067532A1, each herein incorporated by reference with regard to such synthesis. Examples of electrophiles  
10 include chloroformates, isocyanates, and halopyrimidines that give carbamates, ureas, and piperidinopyrimidines, respectively. Reactions with electrophiles can be performed in a suitable solvent like dichloromethane, tetrahydrofuran, or acetonitrile under conditions known to those skilled in the art.

If  $R^1$  is Br or I, sulfonylation of **VI** can provide the indoline **VII** ( $R^1$  is  $SO_2R$ , where  
15 R is alkyl or aryl). For the conversion of aryl halides to the corresponding sulphones, see D. Ma., *et al*, *J.Org.Chem.* **2005**, *70*, 2696, herein incorporated by reference with regard to such synthesis. Metal catalyzed carbon-carbon bond forming reactions such as a Suzuki reaction with boronic acids or boronates or a Stille reaction with trialkyltin reagents can provide the corresponding indoline derivatives of **VII**. For reaction  
20 conditions of the Suzuki coupling reaction, see, N, Miyaura, A. Suzuki, *Chem. Rev.* **1995**, *95*, 2457–2483; A. Suzuki, A, *J. Organometallic Chem.* **1999**, *576*, 147–168; and A. Suzuki, in *Metal-catalyzed Cross-coupling Reactions*, F. Diederich., and P. J. Stang., Eds.; Wiley-VCH: New York, **1998**, 49–97, each herein incorporated by reference with regard to such teaching. The compound **VI** (where  $R^1$  is Br or I) under Rosunmund-von  
25 Braun conditions can give the corresponding nitrile compound **VII** ( $R^1$  is CN). For related reaction conditions see, C. Liangzhen *et al.*, *Synthetic Commun.* **2004**, *34*, 1215, herein incorporated by reference with regard to such synthesis. After transformation of  $R^1$ , the compound **VII** can also be treated with acid, like TFA or concentrated HCl to afford the compound of the formula **VIII**.

30 The nitrile of the compound **VII** can afford the carboxylic acid using standard reaction conditions appreciated in the art. The carboxylic acid can serve as a precursor for making several acyl amides. The carboxylic acid or sulfoxides can also be obtained

by following a different synthetic strategy where the N-arylation of **II** with an appropriate aryl halide can give an indole **V** (where R<sup>1</sup> is -CO<sub>2</sub>R, -SR). The compound **VII** (where R<sup>1</sup> is CN) can further be modified to give 1,3-thiazole derivatives to afford active ligands.

For reaction conditions, see R. Olsson *et al J. Med. Chem.* **2005**, *48*, 7517, herein

5 incorporated by reference with regard to such synthesis. The compound **VII** (where R<sup>1</sup> is -(O)P(OR)<sub>2</sub>) can be prepared from compound **VI** (where R<sup>1</sup> is I) using literature protocol that is well-known to those skilled in the art. The compound **VII** (where R<sup>1</sup> is Br or I) can, in turn, be converted to the compound **VII** (where R<sup>1</sup> = HOP(O)(OR)). For reaction conditions, S.L. Buchwald *et al Org. Lett.*, **2003**, *5*, 2315 and S. Gul *et al Biochem. J.*  
10 **2003**, *376*, 813, each herein incorporated by references with regard to such synthesis. For example if R<sup>1</sup> is a halogen in the compound **VI**, then alkyl or arylthiolation can afford the compound **VII** (where R<sup>1</sup> is SR), which in turn can be oxidized to give the sulfoxides **VII** (where R<sup>1</sup> is SOR). For the conversion of aryl or alkylhalides to the corresponding sulfides see, N. Taniguchi *et al J. Org. Chem.*, **2004**, *69*, 6904, herein incorporated by  
15 reference with regard to such synthesis. The compound **VI** can be treated with oxidant such as 30% aqueous H<sub>2</sub>O<sub>2</sub> in hexafluoroisopropanol to give the racemic sulfoxides of **VII** (where R<sup>1</sup> is SOR). For reaction conditions, see K.S. Ravikumar *et al Eur. J. Chem.* **1998**, *2937*, herein incorporated by reference with regard to such synthesis. The racemic sulfoxides can be separated using chiral HPLC analysis to give the pure or enriched (*R*  
20 and *S*) enantiomers. The compound **IX** can be derivatized further to give active compounds (herein also referred to as physiologically functional derivatives) by following the standard reaction conditions as are appreciated in the art.

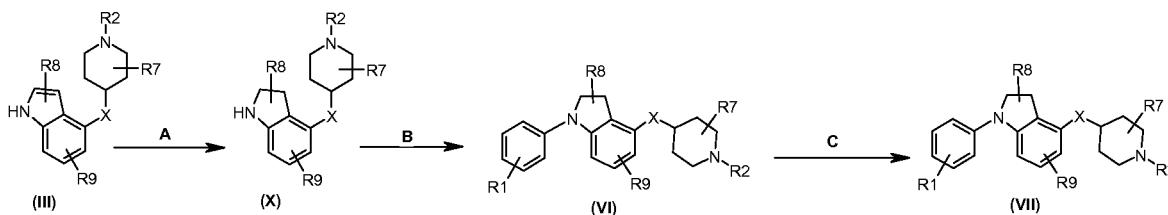
For example, the compound **VIII** can further be derivatized by varying the substitution on the N atom of the depicted piperidine. The compound **VIII** (where R<sup>2</sup> is H), obtained upon treating the compound **VII** (where R<sup>2</sup> is BOC) with CF<sub>3</sub>CO<sub>2</sub>H, may be  
25 used to make a variety of analogues. For example compound **VIII** can be converted, under basic conditions, to pyrimidine derivatives *via* a reaction with a variety of 2-chloro 5-substituted pyrimidines using the protocols appreciated in art. For related reaction conditions see, Fyfe, M., *et al* WO2006/067532A1, herein incorporated by reference  
30 with regard to such teaching. Compound **VIII** can also be used for the synthesis of N-acyl or N-alkyl derivatives using basic conditions that are well-appreciated in the art.

Compound **VIII** can also be used to make a variety of carbamates. The compound **VIII** can serve as a precursor for making many heterocycles, including

oxadiazoles. For reaction conditions, see R.M.Jones *et al*/ WO 2005/121121A2, herein incorporated by reference with regard to such synthesis. The compound **VIII** can be reacted with cyanogen bromide to give N-CN derivative which in turn can be converted to a heterocycle, including but not limited to an oxadiazole, of **IX**.

- 5 Alternatively, the indoline based-ligands can also be prepared by following the synthetic **Scheme 2**. Compound **III** can be converted to indoline **X** using a NaCNBH<sub>3</sub> / AcOH reduction protocol. The indoline **X** can be transformed to the compound **VI** via an N-arylation protocol, as is known in the art. The compound **VI** may serve as an intermediate for making several derivatives, as described above, of the indoline-based
- 10 ligands.

**Scheme 2**  
**Synthesis of Indoline-based Ligands**

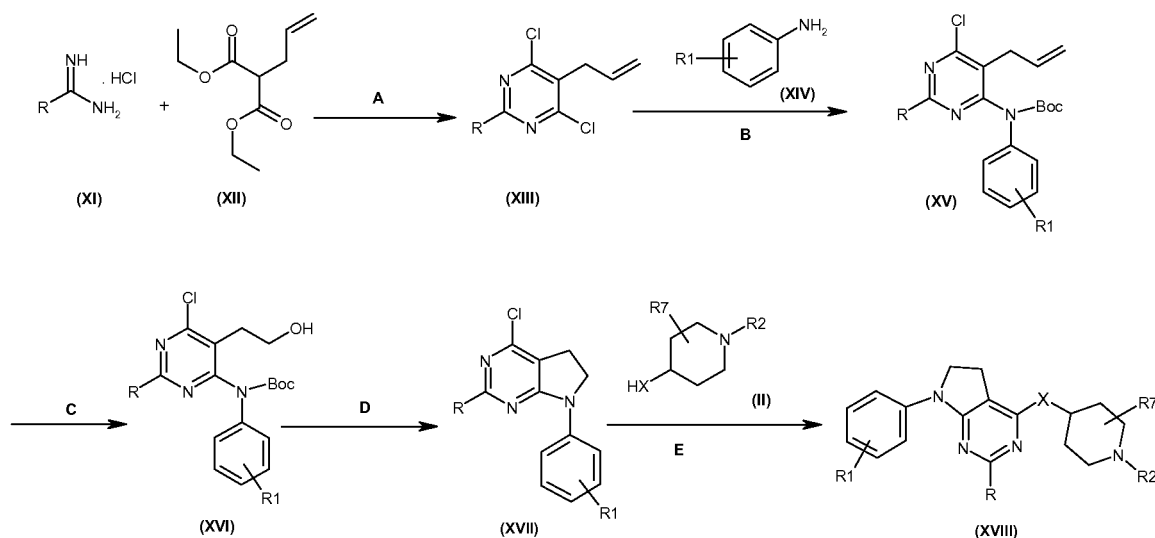


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*Reagents and conditions: A) NaCNBH<sub>3</sub>, AcOH, RT; B) ArX (where X is I, Br), CuI, K<sub>3</sub>PO<sub>4</sub>, toluene or DMF, reflux; C) CuI, L-proline, NaOH, CH<sub>3</sub>SO<sub>2</sub>Na, DMSO, 110 °C.*

20

**Scheme 3**  
**Synthesis of Dihydropyrrrolopyrimidines-based Ligands**



*Reagents and conditions:* **A**) (a) NaOMe, MeOH, RT, (b) POCl<sub>3</sub>, reflux; **B**) (a) NaH, THF, reflux, (b) (BOC)<sub>2</sub>O, DMAP (cat.), CH<sub>2</sub>Cl<sub>2</sub>, RT; **C**) (a) O<sub>3</sub>, -78 °C, CH<sub>2</sub>Cl<sub>2</sub>/ MeOH, (b) NaBH<sub>4</sub>, -78 °C to RT; **D**) (a) CH<sub>3</sub>SO<sub>2</sub>Cl or (CH<sub>3</sub>SO<sub>2</sub>)<sub>2</sub>O, Et<sub>3</sub>N, CH<sub>2</sub>Cl<sub>2</sub>, 5 °C to RT, (b) CF<sub>3</sub>CO<sub>2</sub>H, CH<sub>2</sub>Cl<sub>2</sub>, RT, (c) Et<sub>3</sub>N, CH<sub>2</sub>Cl<sub>2</sub>, RT; **E**) (a) NaH, THF, reflux or K<sub>2</sub>CO<sub>3</sub>, solvent, (b) CuI, L-proline, NaOH, CH<sub>3</sub>SO<sub>2</sub>Na, DMSO, 110 °C, heat; or (c) CuCN, NMP; 150 °C; or (d) HP(O)(OR)<sub>2</sub>, CuI, Cs<sub>2</sub>CO<sub>3</sub>, toluene, reflux, or (e) PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub> or Pd(PPh<sub>3</sub>)<sub>4</sub>, boronic acid or boronates, 2 N Na<sub>2</sub>CO<sub>3</sub>, THF, reflux; or (f) Sn(Bu)<sub>3</sub>R, Pd catalyst, THF, reflux.

The dihydropyrrolopyrimidine-based ligands of **XVIII** can be prepared following the general **Scheme 3**. Substituted pyrimidine **XIII** can be obtained from a reaction between **XI** and **XII**. Compound **XI** can be reacted with **XII** to afford a 4, 6-dihydroxy pyrimidine derivative. The intermediate 4,6-dihydroxypyrimidine derivative can be treated with POCl<sub>3</sub> to afford the compound **XIII** after work-up. Nucleophilic displacement reaction between the compound **XIII** and variously substituted anilines **XIV** can provide intermediate **XV**, which upon treating with (BOC)<sub>2</sub>O in presence of catalytic amount of DMAP in dichloromethane can afford the compound **XV**. The oxidation of the compound **XV** by ozonolysis followed by reduction with NaBH<sub>4</sub> can give the alcohol **XVI**. The compound **XVI** upon mesylation can provide mesylate derivative of **XVI**. The mesylate derivative of **XVI** can afford, *via* two step sequence *viz*: removal of BOC with TFA

followed by base treatment such as Et<sub>3</sub>N or NaH, the bicyclic compound of formula **XVII**. For reaction conditions for these kinds of transformations, see, D. F. Romano *et al* WO 2002 / 100863A1 incorporated by reference with regard to such synthesis.

The compound **XVII** can be used as an intermediate for making a variety of analogues. The compound **XVII** can react with the compound **II** to give the compound **XVIII** in presence of a base and solvent. The compound **XVIII** can be derivatized further using the standard organic reaction conditions. For example, if R<sup>1</sup> is Br or I, sulfonation can give the compound **XVIII** (where R<sup>1</sup> is SO<sub>2</sub>R). Reaction with alkyl or aryl disulfides can give the compound **XVIII** (where R<sup>1</sup> is SR), and the sulfide can, in turn, be oxidized using H<sub>2</sub>O<sub>2</sub> or Oxone to afford the corresponding sulfoxides. For reaction conditions, see **Scheme 1** as herein described. Racemic sulfoxides of **XIX** (where R<sup>1</sup> is SOR) may be resolved using chiral HPLC analysis and the individual enantiomers or enantiomerically enriched mixtures can be isolated, as is appreciated in the art. The compound **XVIII** can be reacted with alkyl phosphonate to afford the compound where R is P(O)(OR)<sub>2</sub>, and this compound, in turn, will provide the compound where R is HOP(O)(OR) *via* known synthetic transformations as are appreciated in the art. For reaction conditions, see S.L. Buchwald *et al Org. Lett.*, **2003**, 5, 2315 and S. Gul *et al Biochem. J.* **2003**, 376, 813, each herein incorporated by references with regard to such synthesis. The compound **XVIII** can serve as a substrate for making a variety of active analogues *via* known synthetic organic transformations as are appreciated in art. For example, the compound **XVIII** where R is CN can further be modified to give 1,3-thiazole derivatives to afford active ligands. For a related reaction conditions, see R. Olsson *et al J. Med. Chem* **2005**, 48, 7517, herein incorporated by references with regard to such teaching.

The "R" group in the compound **XVIII** can serve as a "handle" to make a variety of substitutions at that position. For example, when R is halogen (preferably Cl, Br, or I) or SO<sub>2</sub>R, a Suzuki reaction with alkyl, aryl, or heteroaryl boronic acids can give a variety of substitutions in that position. Likewise, if R is NH<sub>2</sub>, the N-alkylation of the primary amine can give additional analogues of **XVIII**. If R is alkyl such as CH<sub>3</sub>, oxidation can give the carboxylic acid that in turn can be used to make additional active analogues of the compound **XVIII**. For related reaction conditions see, Culshaw, A.J. *et al J. Med. Chem.* **2006**, 49, 471, herein incorporated by references with regard to such teaching.

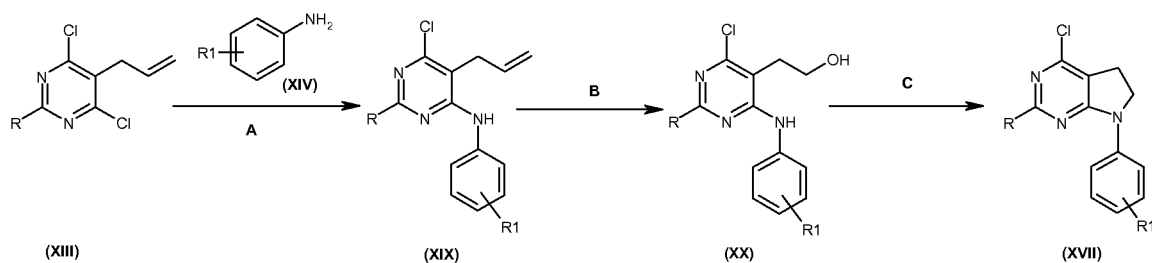
Alternatively, the bicyclic compound **XVII** can be prepared using the synthetic approach delineated in **Scheme 4**. The compound **XIX** can be subjected to ozonolysis



conditions and the resultant product(s) reduced with  $\text{NaBH}_4$  to afford the compound **XX**. For ozonolysis conditions see, Montgomery, J. A. *et al J. Med. Chem.* **1967**, *10*, 665; herein incorporated by reference with regard to such teachings. This compound **XX**, via an intermediate mesylate, can cyclize intramolecularly in basic conditions to afford the bicyclic compound **XVII**. For reaction conditions refer to the previous description regarding **Scheme 3**.

**Scheme 4**  
**Synthesis of Bicyclic Dihydropyrrolopyrimidine**

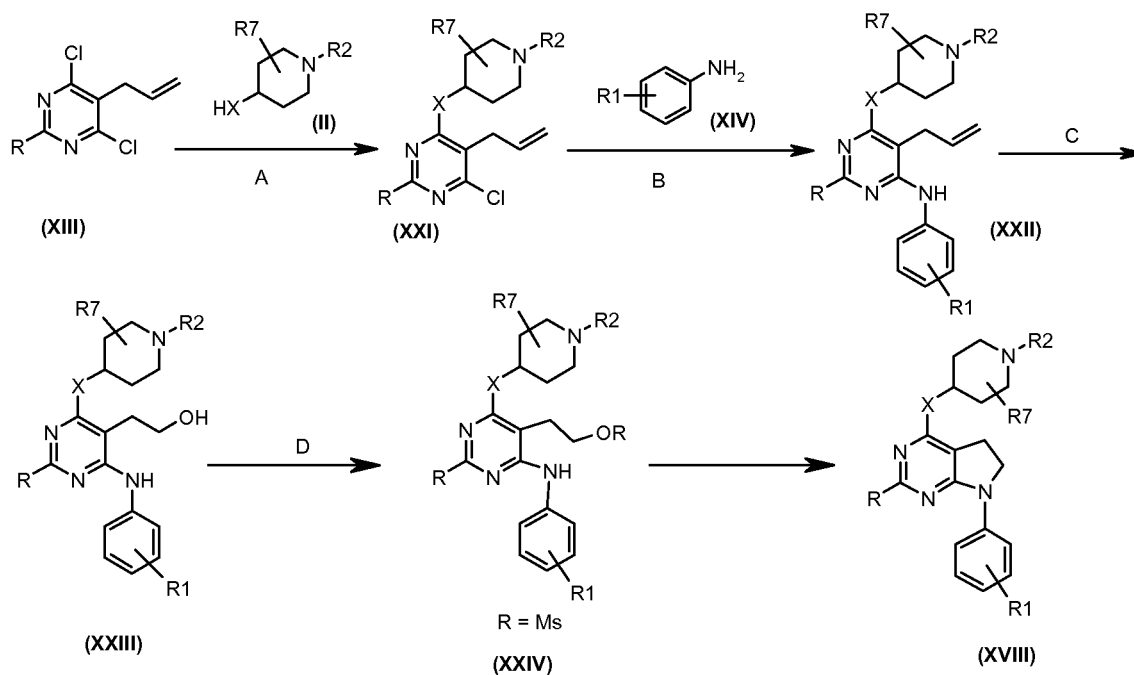
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*Reagents and conditions:* **A**) NaH, THF, RT to reflux; **B**) (a)  $\text{O}_3$ ,  $-78^\circ\text{C}$ ,  $\text{CH}_2\text{Cl}_2$  / MeOH, (b)  $\text{NaBH}_4$ ,  $-78^\circ\text{C}$  to RT, **C**) (a)  $\text{CH}_3\text{SO}_2\text{Cl}$  or  $(\text{CH}_3\text{SO}_2)_2\text{O}$ ,  $\text{Et}_3\text{N}$ ,  $\text{CH}_2\text{Cl}_2$ ,  $5^\circ\text{C}$  to RT.

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**Scheme 5**  
**Synthesis of Dihydropyrrolopyrimidine-based Ligands**

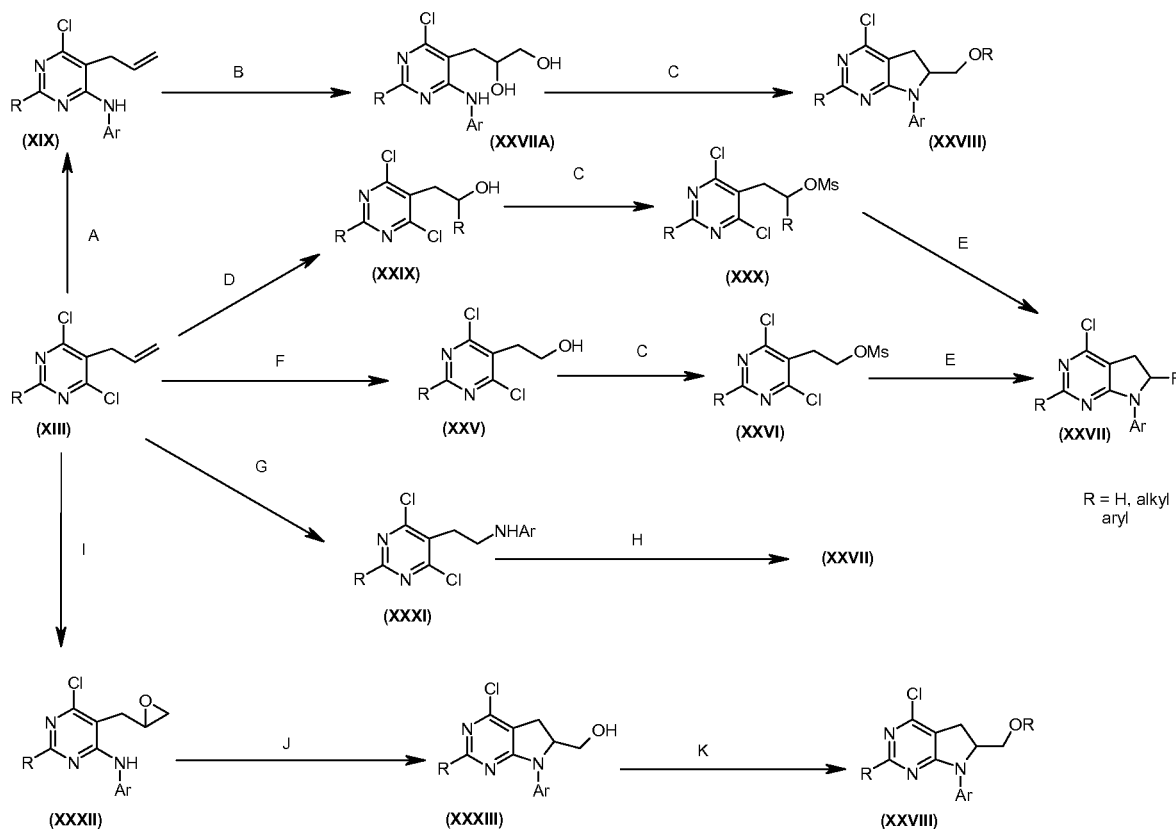


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*Reagents and conditions:* **A)** NaH, THF, RT to reflux; **B)** NaH, THF, reflux; **C)** (a) O<sub>3</sub>, CH<sub>2</sub>Cl<sub>2</sub>, -70 °C, (b) NaBH<sub>4</sub>, MeOH, -70 °C to RT, iv) Et<sub>3</sub>N, (CH<sub>3</sub>SO<sub>2</sub>)<sub>2</sub>O, CH<sub>2</sub>Cl<sub>2</sub>, RT; **D)** CH<sub>3</sub>SO<sub>2</sub>Cl or (CH<sub>3</sub>SO<sub>2</sub>)<sub>2</sub>O, Et<sub>3</sub>N, CH<sub>2</sub>Cl<sub>2</sub>, 5 °C to RT.

- 10 In another approach, compound **XIII** can be converted to **XXI** using substituted piperidine derivative **II** under basic / acidic conditions to give the compound **XXI**. For related reaction conditions Jones, R.M. *et al*/ WO2005/5007647A1 and WO2005/121121A2, herein incorporated by reference with regard to such synthesis. Compound **XXI** can be reacted, under the conditions described for **Scheme 3**, with
- 15 variously substituted anilines **XIV** to afford the compound **XXII**. The ozonolysis of **XXII** followed by reduction with NaBH<sub>4</sub> can give the alcohol **XXIII**. The compound of formula **XXIII** can cyclize intramolecularly *via* mesylate **XXIV** (where R is Ms) as an intermediate to afford the compound of formula **XVIII**. For reactions conditions and related literature references, see hereinabove **Scheme 3**.

**Scheme 6**  
**Synthetic Schemes for Intermediate**



5

**Reagents and conditions:** **A)** NaH, THF, ArNH<sub>2</sub>, THF, reflux; **B)** OsO<sub>4</sub>, Solvent, RT; **C)** Et<sub>3</sub>N, (CH<sub>3</sub>SO<sub>2</sub>)<sub>2</sub>O, CH<sub>2</sub>Cl<sub>2</sub>, 5 °C to RT; **D)** (a) O<sub>3</sub>, -78 °C, CH<sub>2</sub>Cl<sub>2</sub>; (b) RMgX, THF, RT; NaBH<sub>4</sub>, -78 °C to RT; **E)** ArNH<sub>2</sub>, NaH, DMF, 0 °C to RT; **F)** (a) O<sub>3</sub>, -78 °C, CH<sub>2</sub>Cl<sub>2</sub> / MeOH, (b) NaBH<sub>4</sub>, -78 °C to RT; **G)** (a) O<sub>3</sub>, -78 °C, CH<sub>2</sub>Cl<sub>2</sub>/MeOH, Me<sub>2</sub>S (b) ArNH<sub>2</sub>, NaCNBH<sub>3</sub>, AcOH, RT; **H)** CF<sub>3</sub>CO<sub>2</sub>H, RT; **I)** **A**, m-CPBA, CH<sub>2</sub>Cl<sub>2</sub>, 5 °C to RT; **J)** BF<sub>3</sub>·Et<sub>2</sub>O, CH<sub>2</sub>Cl<sub>2</sub>, 5 °C to RT; **K)** RX, base, solvent.

The intermediates **XXVII** and **XXVIII** can be prepared using any one of the sequences delineated in **Scheme 6**. The compound **XIII** can be transformed to **XIX** via nucleophilic displacement reaction with substituted anilines using NaH in an aprotic solvent like THF or DMF. The compound **XIX** may give dihydroxy compound **XXVII** via

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dihydroxylation reaction. For reaction conditions Sharpless, K. B. *et al J. Org. Chem.*, **1992**, 57, 2768., herein incorporated by reference with regard to such synthesis. The compound **XXVIIA** may cyclize to afford the compound of **XXVIII**.

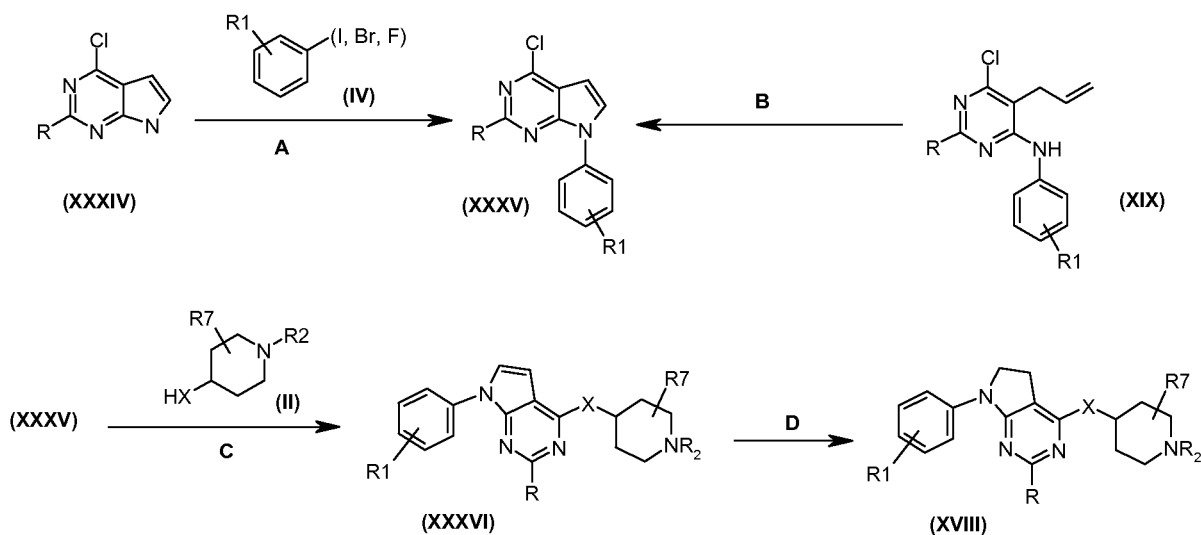
The compound **XIII** upon ozonolysis followed by reduction with NaBH<sub>4</sub> can give  
5 the compound **XXV**. The compound **XXV** can be transformed using the same mesylation conditions described herein above to afford the bicyclic compound **XXVII**.

Alternatively, the compound **XXVII** can also be obtained *via* reductive amination as illustrated in **Scheme 6**. The aldehyde generated by oxidation of the compound **XIII** by ozonolysis can be coupled with a substituted aniline / substituted pyridinamine to form  
10 an imine that, in turn, can be reduced with NaCNBH<sub>3</sub> to give the amine compound **XXXI**. The amine, under acidic conditions and treated with TFA, can form the the bicyclic compound **XXVII**. For related reaction conditions see, R.O. Hutchins *et al In Comprehensive Organic Synthesis*; B.M.Trost *et al* Eds.; Pergamon: Oxford, **1991**; Vol. 8, p 25; and Hudlicky, M. *Reductions in Organic Chemistry*, 2<sup>nd</sup> ed.; ACS Monograph  
15 188, **1996**; p 187, each herein incorporated by reference with regard to such synthesis. The aldehyde from an olefin **X111** can also be generated using K<sub>2</sub>OsO<sub>4</sub>•2H<sub>2</sub>O / NaIO<sub>4</sub> in aqueous acetone. The aldehyde thus obtained was treated with substituted aniline or substituted pyridinamine in TFA or acetic acid in the presence of Na(OAc)<sub>3</sub>BH to afford the bicyclic compound **XXVII** *via* an intermediacy of **XXXI**. For related reaction  
20 conditions see, Kempson, J. *et al Bioorg.Med.Chem.* **2005**, 15, 1829, herein incorporated by reference with regard to such transformation.

The compound **XIII** can also be used to make 6-substituted compound **XXVIII** *via* the sequence delineated in **Scheme 6**. The compound **XIII**, upon treatment with m-CPBA, can give an epoxide **XXXII**. The epoxide **XXXII** may be opened intramolecularly  
25 under Lewis-acid catalyzed conditions to give the compound **XXXIII**. The depicted primary alcohol of compound **XXXIII** can be converted to a variety of functional groups by making use of reactions that are well appreciated in the art.

Another approach can be employed for the synthesis of dihydropyrrolopyrimidine ligands as shown in **Scheme 7**.

**Scheme 7**  
**Synthesis of Dihydropyrrolopyrimidine-based Ligands**



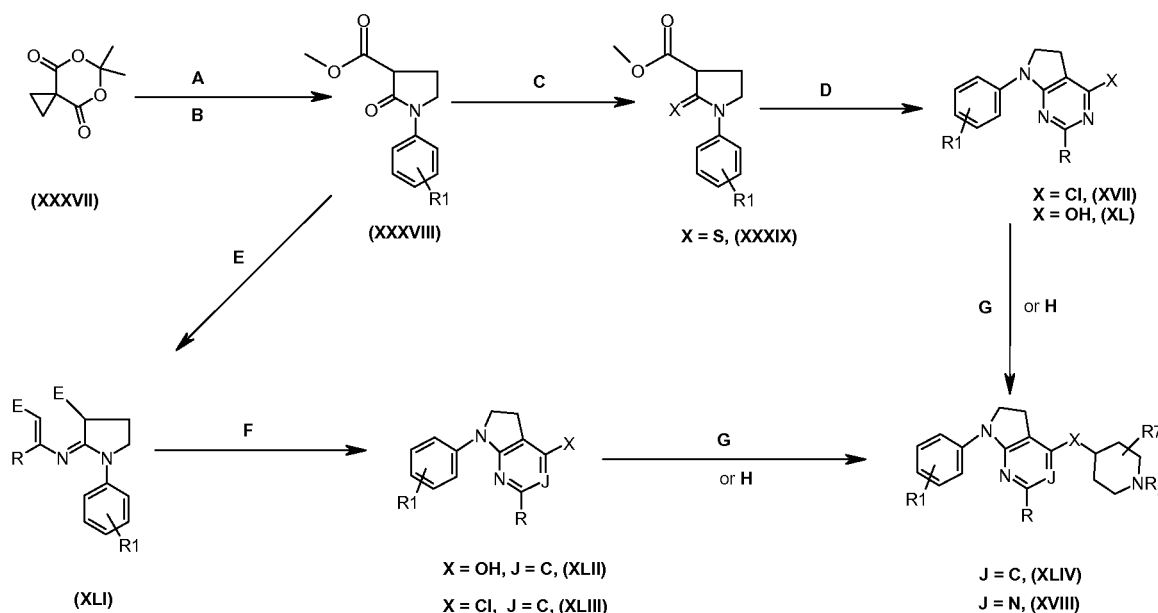
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*Reagents and conditions: A) CuI, K<sub>3</sub>PO<sub>4</sub>, toluene, Reflux; B) (a) O<sub>3</sub>, -78 °C, CH<sub>2</sub>Cl<sub>2</sub>; (b) Me<sub>2</sub>S, H<sup>+</sup>; C) NaH, THF, reflux; D) Pd/C, H<sub>2</sub>, ROH or EtOAc, autoclave.*

- 10 The compound **XXXV** can be synthesized either by an N-arylation procedure using the compound **XXXIV** or the oxidation of the compound **XIX** by ozonolysis followed by intramolecular cyclization involving an amination as an intermediate. For reaction conditions, refer herein above to **Scheme 4**. The compound **XXXV** can give the intermediate **XXXVI** using the reaction conditions described hereinabove for **Scheme 3**.
- 15 The hydrogenation, under autoclave conditions, of the compound **XXXVI** can afford the compound **XVIII**. For reaction conditions see, S, Senda., Jpn. Kokai Tokkyo Koho (1972), 2 pp., JP 47025192 19721019; JP 71-14817 19710317, herein incorporated by reference with regard to such synthesis.

20 A variety of dihydropyrrolopyrimidines can be prepared by using the compound **XVIII** by following reaction conditions that are well appreciated in the art.

**Scheme 8**  
**Preparation of Dihydropyrrolopyrimidine-based Ligands**



5

*Reagents and conditions:* **A**)  $\text{ArNH}_2$ , RT; **B**). MeOH,  $\text{H}_2\text{SO}_4$  (cat.), reflux; **C**)  $\text{P}_2\text{S}_5$  or Lawesson Reagent, THF, reflux; **D**) (a)  $\text{R}-\text{C}(\text{NH}_2)=\text{NH}$ , base, solvent, reflux; (b)  $\text{POCl}_3$ , reflux; **E**)  $\text{RC}(\text{NH}_2)=\text{CH}-\text{CO}_2\text{R}$ ,  $\text{POCl}_3$ , reflux; **F**) NaOMe, MeOH, Reflux,  $\text{H}^+$ ; **G**) **II**, NaH, THF, reflux; **H**) **II**, Mitsunobu conditions, hereinabove **Scheme 1, A**.

10

An alternative synthetic approach for making ligands of formulae **XVIII** and **XLIV** is delineated in **Scheme 8**. The cyclopropyl compound **XXXVII** can be treated with variously substituted anilines to afford 2-oxo-1-aryl-3-pyrrolidinecarboxylic acid, which upon esterification using Fisher esterification protocol, can afford the compound **XXXVIII**. For reaction conditions see, Organic Syntheses, Coll, Vol, 7, p. 411 (**1990**); Vol. 60, p. 66 (1981) and for Fischer-Speier esterification protocol Vogel's Textbook of Practical Organic Chemistry 5<sup>th</sup> Ed, 1989, p. 700, each herein incorporated by references with regard to such teaching. Thionation of **XXXVIII** using  $\text{P}_2\text{S}_5$  or Lawesson reagent can give the compound **XXXIX**. For related reaction conditions and references, see J.B. Charles *et al* US 1994 / 5302722, herein incorporated by reference with regard to such synthesis

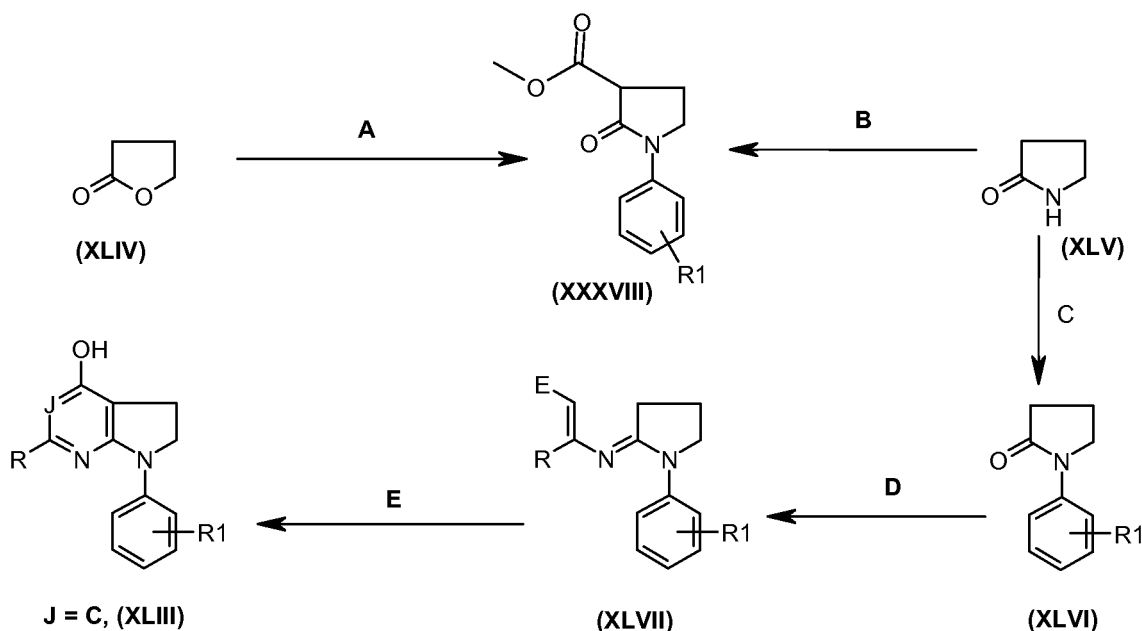
20

The compound **XVII** or **XL** can give the compound **XVIII** or **XLIV** respectively by following the reaction conditions illustrated in **Scheme 8**.

Alternatively, the compound **XXXVIII** can be converted to the compound of formula **XLI** using the reagents and conditions described in **Scheme 8**. The compound **XLI** can give the compound **XLII** via intramolecular cyclization under basic conditions. For the related reaction sequence and reaction conditions, see A. Daniele *et al* WO 2004 / 094420A1, herein incorporated by reference with regard to such synthesis. The hydroxyl compounds **XXXX** and **XLII** can be converted to the corresponding chloroderivatives **XVII** and **XLIII**, respectively, using POCl<sub>3</sub>. The bicyclic compounds **XVII** or **XL** can be transformed to the desired product **XVIII** using either basic or Mitsunobu reaction conditions. Similarly **XLII** or **XLIII** can also be converted to the desired compounds **XLIV**.

The intermediate **XXXVIII** can also be synthesized using the methods shown in **Scheme 9**. In one approach,  $\gamma$ -butyrolactone **XLIV** can be reacted with variously substituted anilines followed by carbomethoxylation procedure, using dimethylcarbonate, to afford the keto ester **XXXVIII**. For reaction conditions and literature references, see Lizuka Hajime EP 95 / 0668275A1, herein incorporated by reference with regard to such synthesis. Alternatively, the compound **XXXVIII** can also be obtained from 2-pyrrolidinone **XLV** by following N-arylation with substituted anilines and carbomethoxylation under basic conditions. For reaction conditions see, Deng, W., *et al Tetrahedron Lett.*, 2004, 45, 2311, herein incorporated by reference with regard to such synthesis.

**Scheme 9**  
**Synthesis of a Bicyclic Compound**



5

*Reagents and Conditions:* **A**) (a) ArNH<sub>2</sub>, heat, (b) NaH, CO(OMe)<sub>2</sub>, THF; **B**) (a) CuI, K<sub>3</sub>PO<sub>4</sub>, ArX, toluene, (b) NaH, CO(OMe)<sub>2</sub>, THF; **C**) Step (a) in **B**; **D**) RC(NH<sub>2</sub>)=NH, POCl<sub>3</sub>, reflux; **E**) *t*-BuOK, *t*-BuOH or NaOMe, MeOH, reflux, H<sup>+</sup>.

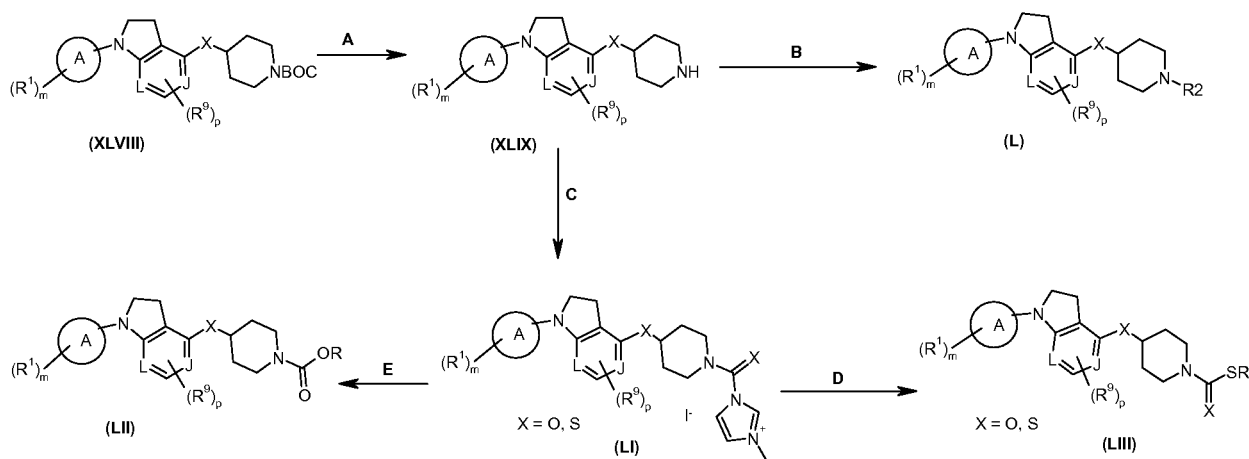
10 Ligands **XLIII** can also be prepared using the synthetic strategy as illustrated in **Scheme 9**. Intermediate **XLVI** can be prepared from 2-pyrrolidinone using an appropriate aryl halide as will be appreciated by those skilled in the art. For reaction conditions, see hereinabove **Scheme 7**. The compound **XLVI** can be transformed to the compound **XLVII** with a dehydrating agent such as POCl<sub>3</sub>. The compound **XLVII** may be  
15 converted to the intermediate **XLVIII** using basic conditions. For reaction conditions as well as a literature reference, refer hereinabove to **Scheme 8**.

20



## Scheme 10

## General Scheme for Various Substituted R2 Analogue Synthesis

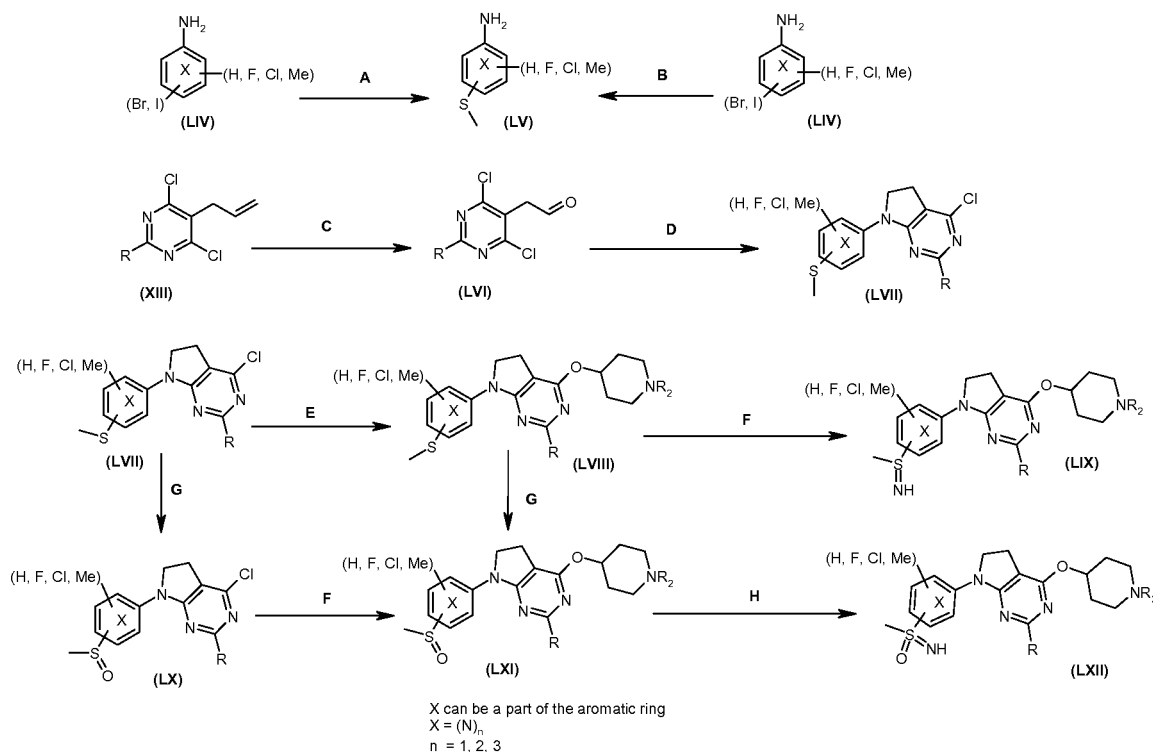


- 5 **Reagents and conditions: A)** CF<sub>3</sub>CO<sub>2</sub>H, CH<sub>2</sub>Cl<sub>2</sub>, RT, **B)** Et<sub>3</sub>N, ClCO<sub>2</sub>R or alkyl or aryl halides, CH<sub>2</sub>Cl<sub>2</sub>, RT, **C)** i. Im<sub>2</sub>CO or Im<sub>2</sub>CS, CH<sub>2</sub>Cl<sub>2</sub>, RT, ii. MeI, CH<sub>2</sub>Cl<sub>2</sub>/ CH<sub>3</sub>CN, RT, **D)** ArSH or RSH, Et<sub>3</sub>N, CH<sub>2</sub>Cl<sub>2</sub>, RT, **E)** ArOH or ROH, Et<sub>3</sub>N, CH<sub>2</sub>Cl<sub>2</sub>, RT

The R<sub>2</sub> substitution in the general formula can be changed by treating **XLVIII** with TFA in CH<sub>2</sub>Cl<sub>2</sub> followed by reaction with an intermediate **XLIX** with appropriate acylating or alkylating or arylating reagents in the presence of a base and solvent to afford compound of the formula **L** (**Scheme 10**). The synthesis of carbamates **LII** and thiocarbamates **LIII** can be accomplished using carbamoyl imidazolium salts of the formula **LI** and the appropriate nucleophiles. For reaction conditions see Batey, R.A., *Tetrahedron Lett.*, **1999**, *40*, 2669, herein incorporated by reference with regard to such teachings.

## Scheme 11

## General Synthesis of Sulfides, Sulfoxides, Sulfoximines, and Sulfilimines



- 5 **Reagents and Conditions:** **A**)  $\text{NiBr}_2$ , Zn, bpy,  $(\text{MeS})_2$ , DMF,  $110^\circ\text{C}$ , **B**) MeSNa, Cu, MeOH, heat, **C**)  $\text{K}_2\text{OsO}_4 \cdot 2\text{H}_2\text{O}$  or  $\text{OsO}_4$  / NMO,  $\text{NaIO}_4$ , aqueous acetone, RT, **D**) LV  $\text{Na}(\text{OAc})_3\text{BH}$ , TFA, or  $\text{CH}_3\text{CO}_2\text{H}$ ,  $-15^\circ\text{C}$  to RT, **E**) II, NaH, THF, reflux, **F**) MSH,  $\text{CH}_2\text{Cl}_2$ , RT, **G**) i.  $\text{H}_2\text{O}_2$ , HFIP, RT or ii Asymmetric sulfoxidation,  $\text{Ti}(\text{O}^i\text{Pr})_4$ , D or L-diethyl tartrate,  $t\text{BuOOH}$ , toluene or any known procedures in the art, **H**) MSH,  $\text{CH}_2\text{Cl}_2$ , RT or racemic
- 10 **LXI**, (S)-(+)- or (R)-(-)-camphorsulfonic acid, acetone.

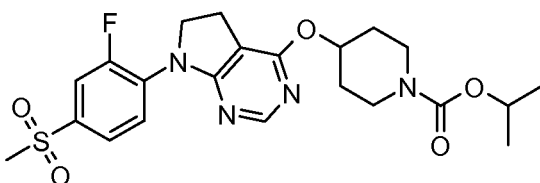
Compounds represented by **LIV** may include up to three heteroatoms, preferably N. The synthesis of sulfide of the formula **LVIII**, sulfoxide of the formula **LXI**, sulfilimine of the formula **LIX**, and sulfoximines of the formula **LXII** can be synthesized by following the synthetic routes delineated in scheme 11. The required substituted sulfide **LV** can be prepared by following the procedures known in the art, for related reaction conditions see Taniguchi, N. *J. Org. Chem.* **2004**, 69, 6904 (route **A**), Wade, P.C. *et al* US 4221796A (route **B**), herein incorporated by a reference with regard to such teachings. The aldehyde **LVI** can be prepared either by ozonolysis or by reaction with

$K_2OsO_4 \cdot 2H_2O$  and  $NaIO_4$ . The reductive amination between the aniline **LV** and an aldehyde **LVI** using the acidic conditions in the presence of  $Na(OAc)_3BH$  can give the bicyclic core **LVII**. For related reaction conditions see Kempson, J, *et al Bioorg. Chem. Lett.* **2005**, 15, 1829, herein incorporated by reference with regard to such teachings.

5 The compound **LVII** upon reaction with compound **II** in the presence of base and solvent afforded the sulfide of the formula **LVIII**. The sulfide **LVIII** would serve as a starting substrate for the preparation of a variety of analogues, for example sulfilimines **LX** can be prepared using the conditions that were reported in the art. For reaction conditions see, Tamura, Y. *et al Tetrahedron Lett.* **1972**, 4137 and Bolm, C. *et al Org. Lett.* **2006**, 8, 10 2349, herein incorporated by a references with regard to such teaching. The sulfides of the formulae **LVII** and **LVIII** can be oxidized using asymmetric sulfoxidation procedure to give enantiopure sulfoxides. In general enantiopure chiral sulfoxides can be prepared using any one of the known procedures: a) resolution of racemic mixtures, b) the asymmetric synthesis. For the details on the enantiopure sulfoxides synthesis and 15 related references see, a review by Bolm, C. *et al Adv. Synth. Catal.* **2005**, 347, 19-31. The enantiopure sulfoxides of the formulae **LX** and **LXI** can be prepared *via* a selective oxidation of prochiral sulfoxides **LVII** and **LVIII** using  $H_2O_2$  and hexafluoroisopropanol (HFIP) followed by chiral HPLC analysis to afford entiopure or enriched *R* and *S* sulfoxides. The absolute stereochemistry of the enantiopure sulfoxides can be 20 determined by VCD spectroscopy. For related analysis see, Stephens, P. J. *et al J. Org. Chem.* **2001**, 66, 3671, herein incorporated by a reference for such analysis. The sulfoxide **LX** can be transformed to an advanced sulfoxide **LXI** using the the compound **II** and base and solvent. The enantiopure sulfoximines can be prepared using the enatiopure sulfoxide of the formula **LXI** by following the procedure reported in the art 25 using *o*-mesitylsulfonylhydroxylamine (MSH) or by resolution of racemic sulfoximines. For reaction conditions see Johnson, C.R. *et al J. Org. Chem.* **1974**, 39, 2458, and Gaillard, S. *et al Tetrahedron* **2005**, 61, 8138 and Brandt, J. *et al Tetrahedron: Asymmetry* **1997**, 8, 909, Gaillard, S. *et al Tetrahedron* **2005**, 61, 8138, herein incorporated by a references with regard to such teachings.

**Examples**

The following specific examples are included as illustrations and are not to be construed as limiting the scope of the present invention.

**Example 1 (10)**

5

**Step 1: 6-Hydroxy-5-(2-propen-1-yl)-4(1H)-pyrimidinone (1)**

To a solution of sodium methoxide (0.5 M in MeOH, 1.89 L, 0.95 mol) was added formamidine hydrochloride (39.0 g, 0.48 mol) at ambient temperature under N<sub>2</sub>. The mixture was stirred at RT for 1 h. Diethyl allylmalonate (91.5 mL, 0.46 mol) was added to the above mixture and the resulting reaction mixture was stirred at RT for 36 h. The reaction mixture was filtered and the filtrate was concentrated under reduced pressure to afford the crude solid material. The crude material was dissolved in H<sub>2</sub>O (1000 mL) and acidified with concentrated HCl. The solid was filtered and dried to afford 62.8 g (90%) of the title compound **1** as a white solid. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>): δ 11.65 (br s, 2 H), 7.90 (s, 1 H), 5.79 – 5.71 (m, 1 H), 4.94 – 4.90 (app. dd, *J*<sub>1</sub> = 17.2 Hz, *J*<sub>2</sub> = 2.0 Hz, 2 H), 2.96 (d, *J* = 6.0 Hz, 2 H); LCMS (ESI): *m/z* 153 (M + H)<sup>+</sup>.

10

15

**Step 2: 4,6-Dichloro-5-(2-propen-1-yl)pyrimidine (2)**

A round-bottomed flask was charged, under N<sub>2</sub>, with 6-hydroxy-5-(2-propen-1-yl)-4(1H)-pyrimidinone (**1**) (19.0 g, 125.0 mmol) and phosphorous oxychloride (200 mL). The mixture was refluxed for 4 h and then cooled to RT. The reaction mixture was poured very slowly into ice cold (5 °C) water (2000 mL) with vigorous stirring. The product was extracted with CH<sub>2</sub>Cl<sub>2</sub> (4 x 250 mL). The combined organic layer was washed with sat. NaHCO<sub>3</sub> (1 x 100 mL), brine (1 x 50 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and the filtrate concentrated under reduced pressure to afford 22.70 g (96%) of the title compound **2** as a light yellow oil. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>): δ 8.08 (s, 1 H), 5.90 – 5.80 (m, 1 H), 5.17 – 5.09 (app. m, 2 H), 3.65 (app. d, *J* = 6.4 Hz, 2 H); LCMS (ESI): *m/z* 190 (M + H)<sup>+</sup>.

20

25

**Step 3: 2-Fluoro-4-(methylsulfonyl)aniline (3)**

As previously described hereinabove, the following example is a representative procedure for the conversion of an aryl halide to a corresponding sulphone derivative.

A mixture of 4-bromo-2-fluoroaniline (9.5 g, 50.0 mmol), sodium methanesulfinate (6.13 g, 60.0 mmol), copper iodide (0.95 g, 5.0 mmol), L-proline (1.15 g, 10.0 mmol), NaOH (0.40 g, 10.0 mmol), and DMSO (60 mL) in a sealed tube (pressure tube) was stirred at 95 °C for 60 h. The reaction was cooled to room temperature and then partitioned between EtOAc and water (1:1, 1000 mL). The layers were separated and the aqueous phase was further extracted with EtOAc (2 x 300 mL). The combined organic layer was washed with brine (1 x 100 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and the filtrate was concentrated under reduced pressure to afford the crude product. The product was purified by SiO<sub>2</sub> flash column chromatography to afford 7.41 g (78%) of the title product **3** as an off-white solid. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>): δ 7.47 and 7.44 (dd, *J*<sub>1</sub> = 11.2 Hz, *J*<sub>2</sub> = 2.0 Hz, 1 H), 7.40 and 7.37 (dd, *J*<sub>1</sub> = 8.8 Hz, *J*<sub>2</sub> = 2.0 Hz, 1 H), 6.84 (app. t, *J* = 6.8 Hz, 1 H), 6.17 (s, 2 H), 3.07 (s, 3 H); LCMS (ESI): *m/z* 190 (M + H)<sup>+</sup>.

**Step 4: 6-Chloro-*N*-[2-fluoro-4-(methylsulfonyl)phenyl]-5-(2-propen-1-yl)-4-pyrimidinamine (4)**

To a mixture of NaH (7.94 g, 60% dispersion in mineral oil, washed with anhydrous toluene) and anhydrous THF (50 mL) was added, at RT under N<sub>2</sub>, 2-fluoro-4-(methylsulfonyl)aniline (**3**) (12.51 g, 66.12 mmol) in THF (150 mL). The mixture was stirred at RT for 1 h and then compound **2** (12.50 g, 66.12 mmol) in THF (50 mL) was added. The resulting reaction mixture was refluxed for 3 h. The mixture was allowed to cool to room temperature and then poured slowly into H<sub>2</sub>O (600 mL) and the mixture was extracted with EtOAc (4 x 300 mL). The combined organic layer was washed with brine (1 x 50 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and the filtrate concentrated under reduced pressure. The crude product was crystallized from EtOAc to give 10.3 g of solid material. The mother liquor was concentrated and purified by SiO<sub>2</sub> flash column chromatography to give an additional 9.35 g of product. A total yield of 19.65 g (87%) of the title compound **4** was obtained as an off-white solid. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>): δ 9.10 (s, 1 H), 8.29 (s, 1 H), 7.84 – 7.82 (dd, *J*<sub>1</sub> = 9.2 Hz, *J*<sub>2</sub> = 1.6 Hz, 1 H), 7.78 – 7.72 (m, 2 H), 5.96 – 5.86 (m, 1 H), 5.11 and 5.09 (dd, *J*<sub>1</sub> = 10.4 Hz, *J*<sub>2</sub> = 1.2 Hz, 1 H), 5.07

and 5.03 (dd,  $J_1 = 16.0$  Hz,  $J_2 = 1.6$  Hz, 1 H), 3.58 (d,  $J = 5.6$  Hz, 2 H), 3.27 (s, 3 H); LCMS (ESI):  $m/z$  342 (M + H)<sup>+</sup>.

**Step 5: 1,1-Dimethylethyl [6-chloro-5-(2-propen-1-yl)-4-pyrimidinyl][2-fluoro-4-(methylsulfonyl)phenyl]carbamate (5)**

5 To a solution of compound **4** (9.0 g, 26.3 mmol) and CH<sub>2</sub>Cl<sub>2</sub> (200 mL) was added catalytic amount of DMAP (0.32 g, 2.63 mmol). Bis(1,1-dimethylethyl) dicarbonate (8.61 g, 39.5 mmol) was introduced to the above mixture slowly and the resulting mixture was stirred at RT for 15 h. The mixture was diluted with CH<sub>2</sub>Cl<sub>2</sub> (250 mL), washed with H<sub>2</sub>O (2 x 40 mL), brine (1 x 30 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, and filtered. The filtrate was  
10 concentrated under reduced pressure to afford the crude product, which was purified by SiO<sub>2</sub> flash column chromatography to give 10.46 g (90%) of the title product **5** as an off-white solid. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>): δ 8.84 (s, 1 H), 7.96 and 7.94 (dd,  $J_1 = 10.0$  Hz,  $J_2 = 2.0$  Hz, 1 H), 7.74 and 7.72 (dd,  $J_1 = 8.4$  Hz,  $J_2 = 2.0$  Hz, 1 H), 7.48 (app. t,  $J = 8.0$  Hz, 1 H), 5.84 – 5.74 (m, 1 H), 5.07 (app. d,  $J = 11.2$  Hz, 1 H), 4.97 (app. d,  $J = 17.2$   
15 Hz, 1 H), 3.47 (app. d,  $J = 5.6$  Hz, 2 H), 3.29 (s, 3 H), 1.39 (s, 9 H); LCMS (ESI):  $m/z$  442 (M + H)<sup>+</sup>.

**Step 6: 1,1-Dimethylethyl [6-chloro-5-(2-hydroxyethyl)-4-pyrimidinyl][2-fluoro-4-(methylsulfonyl)phenyl]carbamate (6)**

A solution of **5** (10.35 g, 23.42 mmol) and CH<sub>2</sub>Cl<sub>2</sub> (300 mL) was cooled to –70 °C and  
20 treated with a stream of ozone that was generated by an ozone generator for 2.5 h. The reaction mixture became light blue upon completion. Methanol (30 mL) and NaBH<sub>4</sub> (3.54 g, 93.68 mmol) were introduced to the cold reaction mixture. The mixture was stirred at –70 °C for 1 h and at RT for 2 h. The reaction mixture was poured into H<sub>2</sub>O (1000 mL) and then layers were separated. The aqueous phase was further extracted  
25 with CH<sub>2</sub>Cl<sub>2</sub> (4 x 250 mL). The combined organic layer was washed with brine (1 x 50 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, and then concentrated under reduced pressure to afford the crude material, which was purified by flash SiO<sub>2</sub> flash column chromatography to give 3.32 g (32%) of the title compound **6** as a white solid. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>): δ 8.75 (s, 1 H), 7.97 and 7.95 (dd,  $J_1 = 9.6$  Hz,  $J_2 = 2.0$  Hz, 1 H), 7.75 and 7.73 (dd,  $J_1 = 8.0$  Hz,  $J_2 = 1.6$  Hz, 1 H), 7.67 and 7.65 (app. t,  $J = 7.6$  Hz, 1 H), 4.99 (t,  $J = 5.6$  Hz, 1 H),  
30 3.68 (q,  $J = 6.0$  Hz, 2 H), 3.31 (s, 3 H), 2.89 (t,  $J = 6.4$  Hz, 2 H), 1.38 (s, 9 H); LCMS (ESI):  $m/z$  446 (M + H)<sup>+</sup>.

**Step 7: 2-(4-Chloro-6-(((1,1-dimethylethyl)oxy)carbonyl)[2-fluoro-4-(methylsulfonyl)phenyl]amino)-5-pyrimidinyl)ethyl methanesulfonate (**7**)**

To a solution of **6** (3.22 g, 7.22 mmol) and CH<sub>2</sub>Cl<sub>2</sub> (50 mL) were added Et<sub>3</sub>N (3.0 mL, 21.66 mmol), and DMAP (88 mg, 0.72 mmol). The solution was cooled to 5 °C and then  
5 methanesulfonic anhydride (1.89 g, 10.83 mmol) was introduced in portions. The reaction mixture was stirred at RT for 15 h under N<sub>2</sub>. The mixture was diluted with CH<sub>2</sub>Cl<sub>2</sub> (150 mL) and then washed with water (2 x 30 mL), brine (1 x 30 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, and filtered. The filtrate was concentrated under reduced pressure to afford the  
10 crude product that was purified by SiO<sub>2</sub> flash column chromatography to give 3.56 g (97%) of the title product **7** as a white solid. This material was used without further characterization in the next step.

**Step 8: 4-Chloro-7-[2-fluoro-4-(methylsulfonyl)phenyl]-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidine (**8**)**

To a solution of **7** (3.55 g, 7.02 mmol) and CH<sub>2</sub>Cl<sub>2</sub> (38 mL) was added, at RT under N<sub>2</sub>,  
15 CF<sub>3</sub>COOH (12 mL). The reaction mixture was stirred at RT for 3 h and then concentrated under reduced pressure to afford the crude reaction mixture. The mixture was redissolved in CH<sub>2</sub>Cl<sub>2</sub> (50 mL) and then treated with Et<sub>3</sub>N (5 mL) at RT for 2 h. The reaction mixture was concentrated under reduced pressure and then subjected to SiO<sub>2</sub> column chromatography to give 2.05 g (89%) of the title product **8** as a light yellow solid.  
20 <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>): δ 8.29 (s, 1 H), 7.94 (app. t, *J* = 7.6 Hz, 1 H), 7.91 and 7.88 (dd, *J*<sub>1</sub> = 15.6 Hz, *J*<sub>2</sub> = 1.6 Hz, 1 H), 7.80 – 7.78, (dd, *J*<sub>1</sub> = 8.4 Hz, *J*<sub>2</sub> = 2.0 Hz, 1 H), 4.20 (t, *J* = 8.4 Hz, 2 H), 3.27 (s, 3 H), 3.23 (t, *J* = 8.8 Hz, 2 H); LCMS (ESI): *m/z* 328 (M + H)<sup>+</sup>.

The bicyclic compound **8** was also synthesized, in good yield, by following the synthetic  
25 process as described hereinabove in **Scheme 4**.

**Step 9: 1-Methylethyl 4-hydroxy-1-piperidinecarboxylate (**9**)**

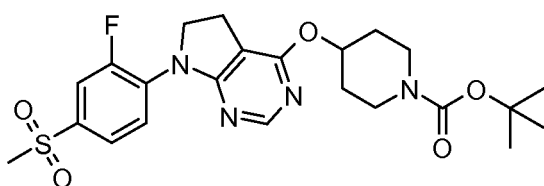
To a cold (5 °C) solution of 4-hydroxypiperidine (40.46 g, 0.40 mol) and CH<sub>2</sub>Cl<sub>2</sub> (500 mL) was added diisopropylethylamine (140 mL, 0.80 mol) under N<sub>2</sub>. A 1 M solution of isopropyl chloroformate (500 mL, 0.50 mol) in toluene was added dropwise over a period  
30 of 4 h. The resulting reaction mixture was stirred at RT for 48 h. The reaction mixture was washed with water (2 x 100 mL) and brine (1 x 100 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated under reduced pressure. The crude product was purified by flash

column chromatography to afford 64.60 g (86%) of the title product **9** as colorless oil. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>): δ 4.72 (m, 1 H), 3.68 – 3.62 (m, 2 H), 3.60 (septuplet, *J* = 4.4 Hz, 1 H), 2.96 (br m, 2 H), 1.68 – 1.62 (m, 2 H), 1.26 – 1.18 (m, 2 H), 1.14 (d, *J* = 6.4 Hz, 6 H).

**5 Step 10: 1-Methylethyl 4-({7-[2-fluoro-4-(methylsulfonyl)phenyl]-6,7-dihydro-5H-pyrrolo[2,3-*d*]pyrimidin-4-yl}oxy)-1-piperidinecarboxylate (**10**)**

To a stirred solution of NaH (0.73 g, 60% dispersion in mineral oil, washed with anhydrous toluene) and anhydrous THF (15 mL) was added **9** (1.09 g, 5.80 mmol) in THF (15 mL). The mixture was refluxed for 0.5 h and then cooled to RT. Compound **8**  
 10 (2.0 g, mmol) in THF (30 mL) was added and the reaction refluxed for 1.5 h. The reaction mixture was cooled to RT, poured into H<sub>2</sub>O (150 mL) and then extracted with CH<sub>2</sub>Cl<sub>2</sub> (4 x 60 mL). The combined organic layer was dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and then concentrated under reduced pressure. The crude product was purified by flash SiO<sub>2</sub> column chromatography using CHCl<sub>3</sub>: MeOH (100:0 to 98:02) as eluent to afford  
 15 1.96 g (71%) of the title product **10** as a white solid. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>): δ 8.22 (s, 1 H), 7.96 (app. t, *J* = 8.4 Hz, 1 H), 7.85 and 7.82 (dd, *J*<sub>1</sub> = 11.2 Hz, *J*<sub>2</sub> = 2.0 Hz, 1 H), 7.75 – 7.73 (dd, *J*<sub>1</sub> = 8.4 Hz, *J*<sub>2</sub> = 2.0 Hz, 1 H), 5.30 – 5.24 (m, 1 H), 4.76 (septuplet, *J* = 6.0 Hz, 1 H), 4.14 (t, *J* = 8.4 Hz, 2 H), 3.70 – 3.64 (m, 2 H), 3.25 (s, 3 H), 3.40 – 3.21 (m, 2 H), 3.05 (t, *J* = 8.8 Hz, 2 H), 1.95 – 1.90 (m, 2 H), 1.67 – 1.51 (m, 2 H),  
 20 1.17 (d, *J* = 6.0 Hz, 6 H); LCMS (ESI): *m/z* 479 (M + H)<sup>+</sup>.

**Example 2 (**11**)**



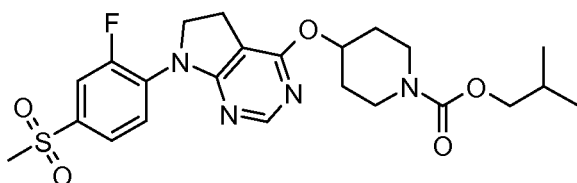
**25 1,1-Dimethylethyl 4-({7-[2-fluoro-4-(methylsulfonyl)phenyl]-6,7-dihydro-5H-pyrrolo[2,3-*d*]pyrimidin-4-yl}oxy)-1-piperidinecarboxylate (**11**)**

The procedure described for **10** was employed using 1,1-dimethylethyl 4-hydroxy-1-piperidinecarboxylate (0.816 g, 4.1 mmol), NaH (0.51 g, 60% dispersion in mineral oil, 12.8 mmol), and compound **8** (1.40 g, 4.27 mmol). Aqueous work-up followed by purification gave 1.45 g (73%) of the title product **11** as a light yellow solid. <sup>1</sup>H NMR



(400 MHz, DMSO-*d*<sub>6</sub>):  $\delta$  8.22 (s, 1 H), 7.96 (app. t,  $J$  = 7.6 Hz, 1 H), 7.85 and 7.82 (dd,  $J_1$  = 11.2 Hz,  $J_2$  = 2.0 Hz, 1 H), 7.75 and 7.73 (dd,  $J_1$  = 8.4 Hz,  $J_2$  = 2.0 Hz, 1 H), 5.26 (m, 1 H), 4.14 (t,  $J$  = 8.0 Hz, 2 H), 3.68 – 3.62 (m, 2 H), 3.25 (s, 3 H), 3.18 – 3.16 (m, 2 H), 3.05 (t,  $J$  = 9.2 Hz, 2 H), 1.94 – 1.89 (m, 2 H), 1.59 – 1.53 (m, 2 H), 1.39 (s, 9 H); LCMS (ESI):  $m/z$  493 (M + H)<sup>+</sup>.

### Example 3 (13)

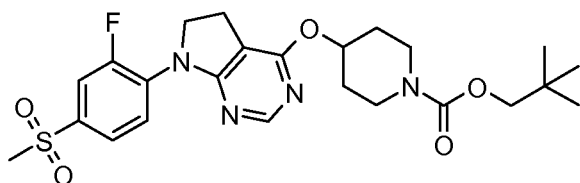


#### Step 1: 2-Methylpropyl 4-hydroxy-1-piperidinecarboxylate (12)

The procedure described for **9** was employed using 4-hydroxypiperidine (10.2 g, 100 mmol), diisopropylethylamine (35 mL, 200 mmol), and isobutyl chloroformate (17.1 g, 125 mmol). Standard aqueous work-up followed by purification gave 18.45 g (92%) of title product **12** as colorless oil. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>):  $\delta$  4.70 (d,  $J$  = 4.0 Hz, 1 H), 3.74 (d,  $J$  = 6.4 Hz, 2 H), 3.69 – 3.65 (m, 2 H), 3.61 (m, 1 H), 3.00 (br s, 2 H), 1.83 (app. septuplet,  $J$  = 6.8 Hz, 1 H), 1.69 – 1.65 (m, 2 H), 1.26 – 1.21 (m, 2 H), 0.85 (d,  $J$  = 6.4 Hz, 6 H).

#### Step 2: 2-Methylpropyl 4-((7-[2-fluoro-4-(methylsulfonyl)phenyl]-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-4-yl)oxy)-1-piperidinecarboxylate (13)

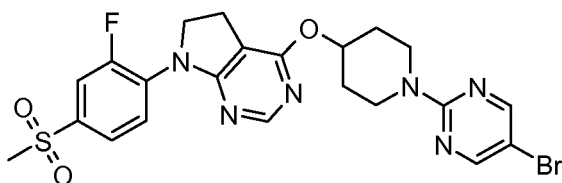
The procedure described for **10** was employed using the compound **8** (100 mg, 0.31 mmol), NaH (35 mg, 60% dispersion in mineral oil, 0.87 mmol), compound **12** (59 mg, 0.29 mmol) and THF (10 mL). Standard aqueous work-up followed by purification gave 118 mg (83%) of the title product **13** as a white solid. The product was lyophilized from acetonitrile to afford a white material. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>):  $\delta$  8.22 (s, 1 H), 7.96 (app. t,  $J$  = 8.0 Hz, 1 H), 7.85 and 7.82 (dd,  $J_1$  = 10.8 Hz,  $J_2$  = 1.6 Hz, 1 H), 7.75 and 7.73 (dd,  $J_1$  = 8.8 Hz,  $J_2$  = 2.0 Hz, 1 H), 5.28 (m, 1 H), 4.14 (t,  $J$  = 8.0 Hz, 2 H), 3.78 (d,  $J$  = 6.8 Hz, 2 H), 3.71 – 3.68 (m, 2 H), 3.25 (s, 3 H), 3.30 – 3.27 (m, 2 H), 3.05 (t,  $J$  = 8.8 Hz, 2 H), 1.97 – 1.91 (m, 2 H), 1.88 – 1.80 (m, 1 H), 1.63 – 1.54 (m, 2 H), 0.87 (d,  $J$  = 6.8 Hz, 6 H); LCMS (ESI):  $m/z$  493 (M + H)<sup>+</sup>.

**Example 4 (15)****Step 1: 2,2-Dimethylpropyl 4-hydroxy-1-piperidinecarboxylate (14)**

The procedure described for **9** was utilized using 4-hydroxypiperidine (3.32 g, 32.8 mmol), diisopropylethylamine (13.6 g, 98.5 mmol), and neopentyl chloroformate (5 mL, 32.84 mmol). The work-up followed by purification gave 5.85 g (83%) of the title product **14** as a white solid. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>): δ 4.71 (app. d, *J* = 4.4 Hz, 1 H), 3.65 (s, 2 H), 3.70 – 3.57 (m, 3 H), 3.0 (br s, 2 H), 1.69 – 1.65 (m, 2 H), 1.28 – 1.20 (m, 2 H), 0.87 (s, 9 H).

**Step 2: 2,2-Dimethylpropyl 4-({7-[2-fluoro-4-(methylsulfonyl)phenyl]-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-4-yl}oxy)-1-piperidinecarboxylate (15)**

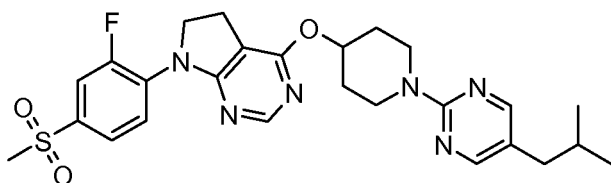
The procedure described for **10** was employed using compound **14** (33 mg, 0.145 mmol), NaH (19 mg, 0.46 mmol), and **8** (50 mg, 0.153 mmol). The aqueous work-up followed by flash SiO<sub>2</sub> column chromatography gave 53 mg (72%) of the title product **15** as a white solid. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>): δ 8.23 (s, 1 H), 7.96 (app. t, *J* = 8.0 Hz, 1 H), 7.85 and 7.82 (dd, *J*<sub>1</sub> = 10.8 Hz, *J*<sub>2</sub> = 1.6 Hz, 1 H), 7.75 and 7.73 (dd, *J*<sub>1</sub> = 8.8 Hz, *J*<sub>2</sub> = 2.0 Hz, 1 H), 5.29 (m, 1 H), 4.14 (t, *J* = 8.4 Hz, 2 H), 3.70 (s, 2 H), 3.73 – 3.64 (m, 2 H), 3.25 (s, 3 H), 3.30 – 3.27 (m, 2 H), 3.06 (t, *J* = 8.8 Hz, 2 H), 1.97 – 1.90 (m, 2 H), 1.62 – 1.52 (m, 2 H), 0.89 (s, 9 H); LCMS (ESI): *m/z* 507 (M + H)<sup>+</sup>.

**Example 5 (17)****Step 1: 1-(5-Bromo-2-pyrimidinyl)-4-piperidinol (16)**

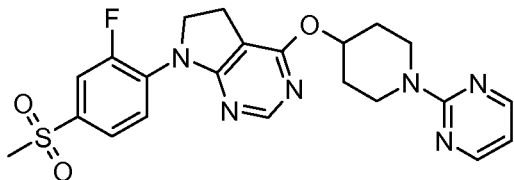
A round-bottomed flask was charged, under N<sub>2</sub>, with 4-hydroxypiperidine (1.93 g, 10 mmol), diisopropylethylamine (5.22 mL, 30 mmol), 5-bromo-2-chloropyrimidine (1.01 g, 10 mmol), and acetonitrile (50 mL). The mixture was refluxed for 15 h and then concentrated under reduced pressure. The crude product was redissolved in CH<sub>2</sub>Cl<sub>2</sub> (150 ml), washed with H<sub>2</sub>O (2 x 20 mL), brine (1 x 20 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, and filtered. The filtrate was concentrated under reduced pressure and the crude material was purified by flash SiO<sub>2</sub> column chromatography to afford 2.55 g (99%) of the title compound **16** as a white solid. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>): δ 8.34 (s, 2 H), 4.73 (d, *J* = 4.0 Hz, 1 H), 4.17 – 4.12 (m, 2 H), 3.74 – 3.68 (m, 1 H), 3.28 – 3.22 (m, 2 H), 1.76 – 1.70 (m, 2 H), 1.33 – 1.25 (m, 2 H); LCMS (ESI): *m/z* 260 (M + H)<sup>+</sup>.

**Step 2: 4-[[1-(5-Bromo-2-pyrimidinyl)-4-piperidinyl]oxy]-7-[2-fluoro-4-(methylsulfonyl)phenyl]-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidine (17)**

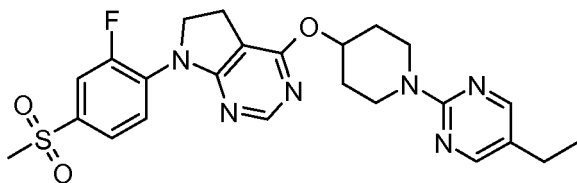
The procedure described for **10** was utilized. 1-(5-Bromo-2-pyrimidinyl)-4-piperidinol **16** (0.968 g, 3.75 mmol) was allowed to react, under N<sub>2</sub>, with **8** (0.98 g, 3 mmol) in the presence of NaH (360 mg, 9.0 mmol) and THF (40 mL). An aqueous work-up followed by purification gave 0.724 g (44%) of the title product **17** as a white solid. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>): δ 8.45 (s, 2 H), 8.24 (s, 1 H), 7.96 (app. t, *J* = 7.2 Hz, 1 H), 7.85 and 7.82 (dd, *J*<sub>1</sub> = 10.8 Hz, *J*<sub>2</sub> = 2.0 Hz, 1 H), 7.75 and 7.73 (dd, *J*<sub>1</sub> = 8.4 Hz, *J*<sub>2</sub> = 2.0 Hz, 1 H), 5.37 (m, 1 H), 4.16 – 4.09 (m, 4 H), 3.25 (s, 3 H), 3.06 (t, *J* = 8.8 Hz, 2 H), 2.03 – 1.97 (m, 2 H), 1.65 (m, 2 H); LCMS (ESI): *m/z* 550 (M + H)<sup>+</sup>.

**Example 6 (18)****7-[2-Fluoro-4-(methylsulfonyl)phenyl]-4-({1-[5-(2-methylpropyl)-2-pyrimidinyl]-4-piperidinyl}oxy)-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidine (18)**

- 5 A round-bottomed flask was charged with **17** (60 mg, 0.11 mmol), PdCl<sub>2</sub>(dppf)•CH<sub>2</sub>Cl<sub>2</sub> (8.8 mg, 0.01 mmol), K<sub>2</sub>CO<sub>3</sub> (75 mg, 0.55 mmol), (2-methylpropyl)boronic acid (34 mg, 0.33 mmol), THF (4 mL), and H<sub>2</sub>O (1 mL) and the mixture was refluxed for 15 h. The reaction mixture was cooled to RT, diluted with H<sub>2</sub>O (15 mL), and then extracted with EtOAc (4 x 20 mL). The combined organic layer was washed with brine (1 x 10 mL),
- 10 dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and the filtrate was concentrated under reduced pressure to afford the crude product, which was subjected to SiO<sub>2</sub> flash column chromatography to isolate two products in near-equal proportion. The less polar compound **18** (5 mg) was identified as the desired product **18**. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>): δ 8.24 (s, 2 H), 8.18 (s, 2 H), 7.96 (app. t, *J* = 8.0 Hz, 1 H), 7.85 and 7.82 (dd, *J*<sub>1</sub> = 10.8 Hz, *J*<sub>2</sub> = 2.8 Hz, 1 H),
- 15 7.75 and 7.73 (dd, *J*<sub>1</sub> = 8.4 Hz, *J*<sub>2</sub> = 1.6 Hz, 1 H), 5.35 (m, 1 H), 4.20 – 4.16 (m, 4 H), 4.14 (app. t, *J* = 8.4 Hz, 2 H), 3.49 (m, 2 H), 3.25 (s, 3 H), 3.05 (t, *J* = 8.4 Hz, 2 H), 2.26 (d, *J* = 7.2 Hz, 2 H), 1.72 (m, 1 H), 1.63 (m, 2 H), 0.83 (d, *J* = 6.4 Hz, 6 H); LCMS (ESI): *m/z* 527 (M + H)<sup>+</sup>.

**Example 7 (19)****7-[2-Fluoro-4-(methylsulfonyl)phenyl]-4-[[1-(2-pyrimidinyl)-4-piperidinyl]oxy]-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidine (19)**

- 5 The more polar compound **19** (5 mg) obtained as hereinabove described (Example 6) was identified as the compound resulting from debromination of the starting material. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>): δ 8.35 (d, *J* = 4.8 Hz, 2 H), 8.24 (s, 1 H), 7.96 (app. t, *J* = 8.0 Hz, 1 H), 7.85 and 7.82 (dd, *J*<sub>1</sub> = 10.8 Hz, *J*<sub>2</sub> = 2.0 Hz, 1 H), 7.75 and 7.73 (dd, *J*<sub>1</sub> = 8.4 Hz, *J*<sub>2</sub> = 2.0 Hz, 1 H), 6.61 (t, *J* = 4.8 Hz, 1 H), 5.37 (m, 1 H), 4.23 – 4.18 (m, 1 H), 4.14
- 10 (t, *J* = 8.4 Hz, 2 H), 3.56 – 3.49 (m, 2 H), 3.31 – 3.28 (m, 2 H), 3.25 (s, 3 H), 3.06 (t, *J* = 8.4 Hz, 2 H), 2.03 – 1.98 (m, 2 H); LCMS (ESI): *m/z* 471 (M + H)<sup>+</sup>.

**Example 8 (22)****Step 1: 1-(5-Ethyl-2-pyrimidinyl)-4-piperidinol (21)**

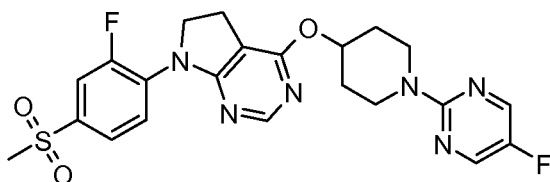
- The procedure described for **16** was employed using 4-hydroxypiperidine (5.0 g, 35.1 mmol), diisopropylethylamine (19 mL, 105.2 mmol), 5-ethyl-2-chloropyrimidine (3.56 g, 35.1 mmol), and acetonitrile (100 mL) under N<sub>2</sub>. The reaction mixture was refluxed for 36 h and concentrated under reduced pressure. The product was purified by SiO<sub>2</sub> flash
- 20 column chromatography to afford 7.05 g (97%) of the title compound **21** product as oil. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>): δ 8.19 (s, 1 H), 4.67 (br s, 1 H), 4.24 – 4.18 (m, 2 H), 3.68 (m, 2 H), 3.19 – 3.12 (m, 2 H), 2.38 (q, *J* = 7.6 Hz, 2 H), 1.75 – 1.69 (m, 2 H), 1.31 – 1.22 (m, 2 H), 1.09 (t, *J* = 7.2 Hz, 3 H); LCMS (ESI): *m/z* 207 (M + H)<sup>+</sup>.

**Step 2: 4-[[1-(5-Ethyl-2-pyrimidinyl)-4-piperidinyl]oxy]-7-[2-fluoro-4-(methylsulfonyl)phenyl]-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidine (22)**

25

The procedure described for **10** was employed using **8** (0.190 g, 0.58 mmol), NaH (70 mg, 1.74 mmol), **21** (114 mg, 0.55 mmol), and THF (10 mL). The aqueous work-up followed by purification gave 0.136 g (50%) of the title product **22** as a white solid. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>): δ 8.24 (s, 3 H), 7.96 (app. t, *J* = 8.4 Hz, 1 H), 7.85 and 7.82 (dd, *J*<sub>1</sub> = 10.8 Hz, *J*<sub>2</sub> = 2.0 Hz, 1 H), 7.75 and 7.73 (dd, *J*<sub>1</sub> = 8.4 Hz, *J*<sub>2</sub> = 2.0 Hz, 1 H), 5.36 (m, 1 H), 4.20 – 4.18 (m, 2 H), 4.14 (t, *J* = 8.4 Hz, 2 H), 3.51 – 3.45 (m, 2 H), 3.25 (s, 3 H), 3.05 (t, *J* = 8.8 Hz, 2 H), 2.41 (q, *J* = 7.6 Hz, 2 H), 2.01 – 1.97 (m, 2 H), 1.65 – 1.48 (m, 2 H), 1.11 (t, *J* = 7.6 Hz, 3 H); LCMS (ESI): *m/z* 499 (M + H)<sup>+</sup>.

### 10 Example 9 (**24**)



#### Step 1: 1-(5-Fluoro-2-pyrimidinyl)-4-piperidinol (**23**)

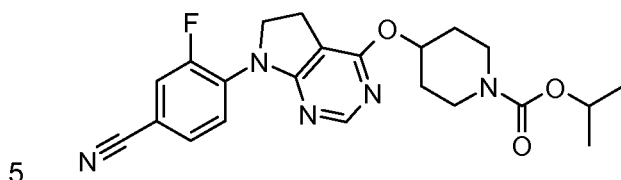
The procedure described for **16** was employed using 4-hydroxypiperidine (1.53 g, 15.1 mmol), diisopropylethylamine (7.9 mL, 45.3 mmol), 5-fluoro-2-chloropyrimidine (2.0 g, 15.1 mmol), and acetonitrile (50 mL) under N<sub>2</sub>. The reaction mixture was refluxed for 10 h and then concentrated under reduced pressure. The crude product was purified by SiO<sub>2</sub> flash column chromatography to afford 2.46 g (83%) of the title **23** product as a white solid. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>): δ 8.18 (s, 2 H), 4.37- 4.31 (m, 2 H), 3.97 – 3.91 (m, 1 H), 3.32 – 3.25 (m, 2 H), 1.98 – 1.92 (m, 2 H), 1.77 (br s, 1 H), 1.57 – 1.48 (m, 2 H); LCMS (ESI): *m/z* 198 (M + H)<sup>+</sup>.

#### Step 2: 7-[2-Fluoro-4-(methylsulfonyl)phenyl]-4-[[1-(5-fluoro-2-pyrimidinyl)-4-piperidinyl]oxy]-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidine (**24**)

The procedure described for **10** was employed using **8** (358 mg, 1.09 mmol), NaH (131 mg, 3.28 mmol), and **23** (215 mg, 1.09 mmol). The work-up followed by purification gave 210 mg (39%) of the title product **24** as a white solid. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>): δ 8.44 (s, 2 H), 8.24 (s, 1 H), 7.96 (app. t, *J* = 7.6 Hz, 1 H), 7.85 and 7.82 (dd, *J*<sub>1</sub> = 10.8 Hz, *J*<sub>2</sub> = 2.0 Hz, 1 H), 7.75 and 7.73 (dd, *J*<sub>1</sub> = 8.4 Hz, *J*<sub>2</sub> = 1.6 Hz, 1 H), 5.36 (m, 1 H), 4.16 – 4.10 (m, 2 H), 4.14 (t, *J* = 8.4 Hz, 2 H), 3.55 – 3.44 (m, 2 H), 3.25 (s, 3 H),

3.05 (t,  $J = 8.8$  Hz, 2 H), 2.03 – 1.98 (m, 2 H), 1.66 – 1.60 (m, 2 H); LCMS (ESI):  $m/z$  489 (M + H)<sup>+</sup>.

**Example 10 (31)**



**Step 1: *N*-(4-Bromo-2-fluorophenyl)-6-chloro-5-(2-propen-1-yl)-4-pyrimidinamine (25)**

The procedure described for **10 (Example 1, Step 4)** was employed. Compound **2** (4.7 g, 24.9 mmol) was allowed to react with 4-bromo-2-fluoroaniline (4.49 g, 23.6 mmol) in the presence of NaH (2.98 g, 74.6 mmol) in THF to give 6.21 g (73%) of the title compound **25** as a white solid. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 8.40 (s, 1 H), 8.31 (app. t,  $J = 8.4$  Hz, 1 H), 7.31 – 7.26 (m, 2 H), 7.02 (br s, 1 H), 5.94 – 5.84 (m, 1 H), 5.34 – 5.29 (m, 2 H), 3.60 (app. d,  $J = 6.4$  Hz, 2 H); LCMS (ESI):  $m/z$  343 (M + H)<sup>+</sup>.

10

**Step 2: 1,1-Dimethylethyl (4-bromo-2-fluorophenyl)[6-chloro-5-(2-propen-1-yl)-4-pyrimidinyl]carbamate (26)**

15

Following the procedure described for compound **10 (Example 1, Step 5)**, compound **25** (6.0 g, 17.5 mmol) was treated with (BOC)<sub>2</sub>O (9.56 g, 43.8 mmol) in the presence of catalytic amount of DMAP (214 mg, 1.75 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (100 mL) at RT to give 6.56 g (85%) of the title compound **26** as a white solid. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>): δ 8.81 (s, 1 H), 7.73 and 7.71 (dd,  $J_1 = 10.0$  Hz,  $J_2 = 2.0$  Hz, 1 H), 7.40 and 7.38 (dd,  $J_1 = 8.8$  Hz,  $J_2 = 2.0$  Hz, 1 H), 7.16 (app. t,  $J = 8.4$  Hz, 1 H), 5.82 – 5.75 (m, 1 H), 5.09 – 5.06 (app. dd,  $J_1 = 10.0$  Hz,  $J_2 = 1.6$  Hz, 1 H), 4.98 and 4.94 (app. dd,  $J_1 = 17.2$  Hz,  $J_2 = 1.2$  Hz, 1 H), 3.47 (app. d,  $J = 6.0$  Hz, 2 H), 1.36 (s, 9 H); LCMS (ESI):  $m/z$  443 (M + H)<sup>+</sup>.

20

**Step 3: 1,1-Dimethylethyl (4-bromo-2-fluorophenyl)[6-chloro-5-(2-hydroxyethyl)-4-pyrimidinyl]carbamate (27)**

25

Following the procedure described for **10 (Example 1, Step 6)**, compound **26** (3.15 g, 7.12 mmol) was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (100 mL). To the cold (–70 °C) mixture ozone was bubbled for 2 h. The resulting mixture was treated with NaBH<sub>4</sub> (1.08 g, 28.5 mmol) and

MeOH (10 mL) was added to the reaction mixture. Aqueous work-up followed by purification gave 1.40 g (44%) of the title product **27** as a white solid. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>): δ 8.81 (s, 1 H), 7.74 and 7.71 (dd, *J*<sub>1</sub> = 9.6 Hz, *J*<sub>2</sub> = 2.4 Hz, 1 H), 7.42 and 7.33 (m, 2 H), 4.97 (app. t, *J* = 5.2 Hz, 1 H), 3.66 (q, *J* = 4.8 Hz, 2 H), 2.88 (app. t, *J* = 6.4 Hz, 2 H), 1.37 (s, 9 H); LCMS (ESI): *m/z* 469 (M + Na)<sup>+</sup>.

**Step 4: 2-[4-((4-Bromo-2-fluorophenyl){[(1,1-dimethylethyl)oxy]carbonyl}amino)-6-chloro-5-pyrimidinyl]ethyl methanesulfonate (**28**)**

Following the procedure described for compound **10** (Example 1, Step 7), compound **27** (1.35g, 3.02 mmol) was treated with methanesulfonic anhydride (0.79 g, 4.53 mmol) in the presence of Et<sub>3</sub>N (1.25 mL, 9.07 mmol) and a catalytic amount of DMAP (37 mg, 0.302 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (30 mL) to give 1.46 g (92%) of the title compound **28** as a white solid. LCMS (ESI): *m/z* 521 (M + H)<sup>+</sup>.

**Step 5: 7-(4-Bromo-2-fluorophenyl)-4-chloro-6,7-dihydro-5H-pyrrolo[2,3-*d*]pyrimidine (**29**)**

The procedure described for compound **10** (Example 1, Step 8) was employed. A solution of **27** (1.45 g, 2.76 mmol) and CH<sub>2</sub>Cl<sub>2</sub> (19 mL) was added CF<sub>3</sub>COOH (6 mL) at RT. The mixture was stirred and concentrated under reduced pressure to give the crude product. The crude was redissolved in CH<sub>2</sub>Cl<sub>2</sub> (40 mL) and then treated with Et<sub>3</sub>N (10 mL) for 2 h. The mixture was worked-up to give 0.75 g (80%) of the title product **29** as an off-white solid. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>): δ 8.20 (s, 1 H), 7.70 – 7.68 (dd, *J*<sub>1</sub> = 10.4 Hz, *J*<sub>2</sub> = 2.4 Hz, 1 H), 7.57 (app. t, *J* = 8.4 Hz, 1 H), 7.48 and 7.46 (dd, *J*<sub>1</sub> = 8.4 Hz, *J*<sub>2</sub> = 2.0 Hz, 1 H), 4.09 (t, *J* = 8.4 Hz, 2 H), 3.19 (t, *J* = 8.4 Hz, 2 H); LCMS (ESI): *m/z* 329 (M + H)<sup>+</sup>.

**Step 6: 1-Methylethyl 4-[[7-(4-bromo-2-fluorophenyl)-6,7-dihydro-5H-pyrrolo[2,3-*d*]pyrimidin-4-yl]oxy]-1-piperidinecarboxylate (**30**)**

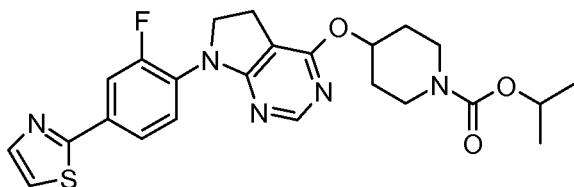
The procedure described for **10** (Example 1, Step 10) was utilized. Compound **29** (300 mg, 0.913 mmol) was reacted with compound **9** (162 mg, 0.87 mmol) in the presence of NaH (110 mg, 2.74 mmol) in THF (10 mL). The aqueous work-up followed by purification gave 410 g (94%) of the title product **30** as an off-white solid. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>): δ 8.13 (s, 1 H), 7.64 – 7.61 (dd, *J*<sub>1</sub> = 10.8 Hz, *J*<sub>2</sub> = 2.0 Hz, 1 H), 7.56 (app. t, *J* = 8.4 Hz, 1 H), 7.43 and 7.40 (dd, *J*<sub>1</sub> = 8.8 Hz, *J*<sub>2</sub> = 2.0 Hz, 1 H), 5.25 (m, 1 H),



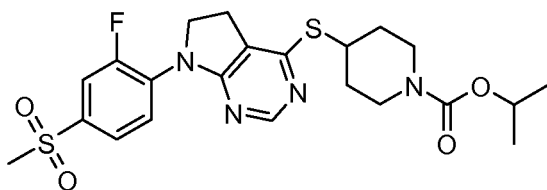
4.75 (septuplet,  $J = 6.4$  Hz, 1 H), 4.00 (t,  $J = 9.2$  Hz, 2 H), 3.72 – 3.68 (m, 2 H), 3.22 (m, 2 H), 3.02 (t,  $J = 8.8$  Hz, 2 H), 1.94 – 1.89 (m, 2 H), 1.60 – 1.55 (m, 2 H), 1.17 (d,  $J = 6.4$  Hz, 6 H); LCMS (ESI):  $m/z$  481 (M + H)<sup>+</sup>.

**Step 7: 1-Methylethyl 4-[[7-(4-cyano-2-fluorophenyl)-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-4-yl]oxy]-1-piperidinecarboxylate (**31**)**

5 A round-bottomed flask was charged with compound **30** (100 mg, 0.209 mmol), CuCN (42 mg, 0.47 mmol), and NMP (2 mL) under N<sub>2</sub>. The resulting mixture was heated to 150 °C for 15 h. The mixture was cooled to RT, poured into H<sub>2</sub>O (25 mL) and the mixture was extracted with EtOAc (4 x 25 mL). The combined organic layer was washed  
10 with brine (1 x 10 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and the filtrate was concentrated under reduced pressure. The crude product was purified by flash SiO<sub>2</sub> column chromatography to afford 76 mg (85%) of the title compound **31** as a white solid. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>):  $\delta$  8.23 (s, 2 H), 7.95 – 7.89 (m, 2 H), 7.69 and 7.67 (dd,  $J_1 = 8.0$  Hz,  $J_2 = 2.0$  Hz, 1 H), 5.27 (m,  $J = 4.0$  Hz, 1 H), 4.76 (septuplet,  $J = 6.4$  Hz, 1 H),  
15 4.14 (t,  $J = 8.0$  Hz, 2 H), 3.70 – 3.64 (m, 2 H), 3.25 – 3.21 (m, 2 H), 3.04 (t,  $J = 8.4$  Hz, 2 H), 1.95 – 1.90 (m, 2 H), 1.61 – 1.53 (m, 2 H), 1.17 (d,  $J = 6.0$  Hz, 6 H); LCMS (ESI):  $m/z$  426 (M + H)<sup>+</sup>.

**Example 11 (32)****1-Methylethyl 4-({7-[2-fluoro-4-(1,3-thiazol-2-yl)phenyl]-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-4-yl}oxy)-1-piperidinecarboxylate (32)**

- 5 A round-bottomed flask was charged with compound **30** (108 mg, 0.23 mmol), PdCl<sub>2</sub>(Ph<sub>3</sub>P)<sub>2</sub> (16 mg, 0.023 mmol), 2-(tributylstannanyl)-1,3-thiazole (85 mg, 0.23 mmol), and THF (4 mL) under N<sub>2</sub>. The reaction mixture was refluxed for 12 h. Aqueous work-up followed by purification gave 66 mg (61%) of the title product **32** as an off-white solid. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>): δ 8.18 (s, 1 H), 7.92 (d, *J* = 3.2 Hz, 1 H), 7.84 – 7.79 (m, 2 H), 7.78 – 7.74 (m, 2 H), 5.26 (m, 1 H), 4.76 (septuplet, *J* = 6.0 Hz, 1 H), 4.10 (t, *J* = 8.8 Hz, 1 H), 3.71 – 3.65 (m, 2 H), 3.25 – 3.21 (m, 2 H), 3.05 (t, *J* = 8.8 Hz, 2 H), 1.95 – 1.91 (m, 2 H), 1.61 – 1.53 (m, 2 H), 1.17 (d, *J* = 6.4 Hz, 6 H); LCMS (ESI): *m/z* 484 (M + H)<sup>+</sup>.
- 10

**15 Example 12 (36)****Step 1: 1-Methylethyl 4-bromo-1-piperidinecarboxylate (33)**

- A solution of 4-bromopiperidine hydrochloride (5.0 g, 20.4 mmol) in dichloromethane (100 mL) under N<sub>2</sub> at 0 °C was treated with diisopropylethylamine (7.8 mL, 44.9 mmol) followed by the dropwise addition of a solution of isopropyl chloroformate in toluene (20.4 mL of a 1.0 M solution). The mixture was stirred and allowed to warm to 25 °C over a 3 h period. The reaction was quenched by the addition of 1 N HCl and diluted with ethyl acetate. The aqueous layer was extracted with ethyl acetate (3 times) and the combined organic extracts were washed with saturated aqueous NaHCO<sub>3</sub> and brine,
- 20

dried ( $\text{MgSO}_4$ ) and concentrated to give a colorless oil **33** that was used without further purification.  $^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  4.91 (septuplet,  $J = 6.2$  Hz, 1 H), 4.35 (m,  $J = 3.8$  Hz, 1 H), 3.71 (m, 2 H), 3.36 (m, 2 H), 2.09 (m, 2 H), 1.93 (m, 2 H), 1.24 (d,  $J = 6.2$  Hz, 6 H).

5 **Step 2: 1-Methylethyl 4-(acetylthio)-1-piperidinecarboxylate (34)**

A solution of 1-methylethyl 4-bromo-1-piperidinecarboxylate (4.0 g, 16 mmol) in DMF (40 mL) under  $\text{N}_2$  at 25 °C was treated with potassium thioacetate (3.4 g, 29.8 mmol) and the mixture was stirred and heated at 100 °C for 3.5 h. The reaction mixture was allowed to cool to 25 °C and was quenched by the addition of water and diluted with ethyl acetate. The aqueous layer was extracted with ethyl acetate (3 times) and the combined organic extracts were washed with water, saturated aqueous  $\text{NaHCO}_3$  and brine, dried ( $\text{Na}_2\text{SO}_4$ ) and concentrated to dark brown oil. Purification by flash chromatography (80 g silica column, 10  $\rightarrow$  20% EtOAc / hexane) afforded 1-methylethyl 4-(acetylthio)-1-piperidinecarboxylate (**34**) (2.3 g, 59%) as a brown oil.  $^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  4.91 (septuplet,  $J = 6.2$  Hz, 1 H), 4.35 (m,  $J = 3.8$  Hz, 1 H), 3.71 (m, 2 H), 3.36 (m, 2 H), 2.09 (m, 2 H), 1.93 (m, 2 H), 1.24 (d,  $J = 6.2$  Hz, 6 H).

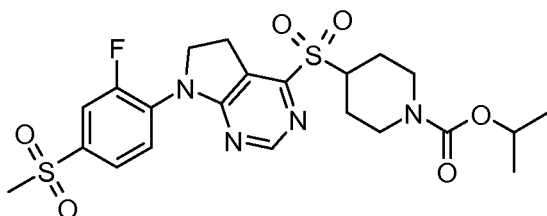
10 **Step 3: 1-Methylethyl 4-mercapto-1-piperidinecarboxylate (35)**

A solution of 1-methylethyl 4-(acetylthio)-1-piperidinecarboxylate (2.3 g, 9.4 mmol) in THF: water (1:1, 50 mL) under  $\text{N}_2$  at 0 °C was treated with 1 N NaOH (11.2 mL, 11.2 mmol) and the mixture was stirred at 0 °C for 2 h. The reaction mixture was quenched by the addition of aqueous citric acid and the aqueous layer was extracted with ethyl acetate (4 times). The combined organic extracts were washed with saturated aqueous  $\text{NaHCO}_3$  and brine; and were dried ( $\text{MgSO}_4$ ) and concentrated to give a brown oil. Purification by flash chromatography (40 g silica column, 10  $\rightarrow$  25% EtOAc / hexane) afforded the title product **35** (1.6 g, 89%) as an amber oil.  $^1\text{H NMR}$  (400 MHz,  $\text{DMSO-}d_6$ ):  $\delta$  4.72 (septuplet,  $J = 6.4$  Hz, 1 H), 3.80 (overlapping br. s, 2 H), 2.96 – 2.79 (br m, 3 H), 2.64 (d,  $J = 7.1$  Hz, 1 H), 1.90 – 1.82 (m, 2 H), 1.38 – 1.27 (m, 2 H), 1.15 (d,  $J = 6.4$  Hz, 6 H).

**Step 4: 1-Methylethyl 4-({7-[4-(methylsulfonyl)phenyl]-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-4-yl}thio)-1-piperidinecarboxylate (36)**

A solution of 1-methylethyl 4-mercapto-1-piperidinecarboxylate (**35**) (82 mg, 0.43 mmol) in acetone (2 mL) was treated with compound **8** (refer hereinabove to **Example 1, Step 8**, 140 mg, 0.43 mmol) under N<sub>2</sub> at 25 °C followed by K<sub>2</sub>CO<sub>3</sub> (89 mg, 0.64 mmol) and the mixture was stirred and heated in a sealed vial at 60 °C for 62 h. The reaction mixture was allowed to cool to 25 °C and was concentrated to ~1/3 volume and purified by flash chromatography (12 g silica column, 10 → 60% EtOAc / hexane, 35 min gradient) to afford the title product **36** (150 mg, 71%) as a white solid. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>): δ 8.35 (s, 1 H), 7.96 (t, *J* = 8.1 Hz, 1 H), 7.85 (d, *J* = 11.2 Hz, 1 H), 7.75 (d, *J* = 8.5 Hz, 1 H), 4.74 (septuplet, *J* = 6.2 Hz, 1 H), 4.15 (app. t, *J* = 8.5 Hz, 2 H), 4.11 (obscured m, 1 H), 3.82 (br d, *J* = 12.7 Hz, 2 H), 3.25 (s, 3 H), 3.07 (br m, 2 H), 2.99 (app. t, *J* = 8.5 Hz, 2 H), 2.01 (br d, *J* = 12.7 Hz, 2 H), 1.52 (m, 2 H), 1.16 (d, *J* = 6.2 Hz, 6 H); LCMS (ESI): *m/z* 495 (M + H)<sup>+</sup>.

15

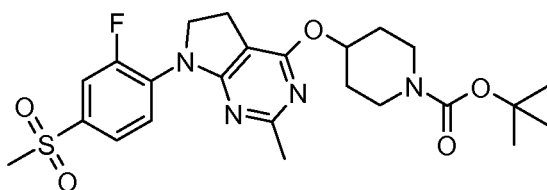
**Example 13 (37)****1-Methylethyl 4-({7-[2-fluoro-4-(methylsulfonyl)phenyl]-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-4-yl}thio)-1-piperidinecarboxylate (37)**

A solution of 1-methylethyl 4-({7-[4-(methylsulfonyl)phenyl]-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-4-yl}thio)-1-piperidinecarboxylate (**36**) (145 mg, 0.29 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (5 mL) was treated with *m*-CPBA (77% maximum by weight, 105 mg, 0.47 mmol) under N<sub>2</sub> at 0 °C and the mixture was stirred at 0 °C for 1.5 h. The reaction mixture was quenched by the addition of methanol, concentrated to ~1/3 volume, and purified by reverse phase HPLC (10 → 100% CH<sub>3</sub>CN / H<sub>2</sub>O + 0.5% trifluoroacetic acid, 10 min gradient, C18 column) to give the title product **37** (28 mg, 18%) as a white solid after lyophilization. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>): δ 8.57 (s, 1 H), 8.02 – 7.97 (overlapping m, 2 H), 7.88 (d, *J*

25

= 8.2 Hz, 1 H), 4.79 (septuplet,  $J = 6.0$  Hz, 1 H), 4.26 (app. t,  $J = 8.0$  Hz, 2 H), 4.08 (br m, 2 H), 3.84 (br m, 2 H), 3.55 (app. t,  $J = 8.0$  Hz, 2 H), 3.34 (s, 3 H), 2.89 (br m, 2 H), 1.95 (br d,  $J = 11.4$  Hz, 2 H), 1.54 (m, 2 H), 1.20 (d,  $J = 6.0$  Hz, 6 H); LCMS (ESI):  $m/z$  527 ( $M + H$ )<sup>+</sup>.

5

**Example 14 (45)****Step 1: 6-Hydroxy-2-methyl-5-(2-propen-1-yl)-4(1H)-pyrimidinone (38)**

Ethanimidamide hydrochloride (25.0 g, 0.27 mol) was dissolved in 0.5 M sodium methoxide in methanol (1.1 L, 0.52 mol) and stirred for 1 h at ambient temperature. Diethyl 2-propen-1-yl propanedioate (50.0 g, 0.253 mol) was then added dropwise to the above solution and the resulting mixture stirred at room temperature for 15 h. The reaction mixture was then concentrated under reduced pressure and the crude residue dissolved in 500 mL cold water. The solution was acidified with 4 N aqueous HCl and a white precipitate formed. The precipitate was removed *via* filtration and air-dried on the filter plate for 48 hours to give 32.6 g (78%) of the title compound **38** as a white solid. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>):  $\delta$  11.60 (s, 2 H), 5.61 – 5.86 (m, 1 H), 4.73 – 4.97 (m, 2 H), 2.92 (d,  $J = 6.1$  Hz, 2 H), 2.20 (s, 3 H).

**Step 2: 4,6-Dichloro-2-methyl-5-(2-propen-1-yl)pyrimidine (39)**

Compound **38** (6.0 g, 36.1 mmol) was combined with 60 mL phosphorus oxychloride and the mixture was heated to reflux for 4 h. The reaction was then cooled to room temperature and poured very slowly into 500 mL of ice water. The reaction was then extracted three times with ethyl acetate (250 mL each). The combined organics were washed with 300 mL of saturated aqueous NaHCO<sub>3</sub>, followed by 300 mL brine. The organics were dried over anhydrous magnesium sulfate, filtered and the solvent was removed under reduced pressure to give 6.1 g (85%) of the title compound **39** as a brown oil that was used without additional purification. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  5.72 – 5.90 (m, 1 H), 4.89 – 5.22 (m, 2 H), 3.54 (d,  $J = 6.1$  Hz, 2 H), 2.63 (s, 3 H).

**Step 3: 6-Chloro-N-[2-fluoro-4-(methylsulfonyl)phenyl]-2-methyl-5-(2-propen-1-yl)-4-pyrimidinamine (40)**

NaH (60% oil dispersion, 936 mg, 23.4 mmol) was added to a 100 mL round bottom flask along with 5 mL anhydrous toluene. The suspension was stirred for 10 minutes and the toluene was decanted off. 2-Fluoro-4-(methylsulfonyl)aniline (2.2 g, 11.7 mmol) in 20 mL anhydrous THF was then added to the dry NaH dropwise over several minutes. The resulting mixture was stirred at ambient temperature for 15 minutes and then compound **39** (2.5 g, 12.3 mmol) in 30 mL anhydrous THF was added slowly over several minutes. The mixture was then heated to reflux for 2 h, cooled to room temperature and diluted with 100 mL water. The reaction was extracted three times with ethyl acetate (100 mL each) and the organics dried over anhydrous magnesium sulfate. The solids were removed *via* filtration and the solvent removed under reduced pressure to give 4.4 g (97%) of the title compound **40** which was used without additional purification. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 2.60 (s, 3 H), 3.09 (s, 3 H), 3.61 (d, *J* = 6.1 Hz, 2 H), 5.22 – 5.42 (m, 2 H), 5.79 – 5.98 (m, 1 H), 7.31 – 7.41 (m, 1 H), 7.64 – 7.73 (m, 1 H), 7.74 – 7.81 (m, 1 H), 7.64 – 7.73 (m, 1 H), 8.83 (t, *J* = 7.6 Hz, 1 H).

**Step 4: 1,1-Dimethylethyl [6-chloro-2-methyl-5-(2-propen-1-yl)-4-pyrimidinyl][2-fluoro-4-(methylsulfonyl)phenyl]carbamate (41)**

Compound **40** (4.4 g, 13.2 mmol) was dissolved in methylene chloride (40 mL) and treated with (BOC)<sub>2</sub>O (5.7 g, 26.5 mmol) and catalytic amount of DMAP (~50 mg). The resulting solution was stirred for 18 h at ambient temperature. The reaction was then diluted with 50 mL water and the phases were separated and the aqueous phase was extracted 3 times with ethyl acetate (100 mL each). The organics were then combined and dried over anhydrous magnesium sulfate. The solids were removed *via* filtration and the crude reaction was concentrated to dryness. The crude reaction was then purified *via* flash column chromatography (120 g of silica gel, 10 → 50% ethyl acetate/hexane) to give 3.0 g (50%) of the title compound **41** as a white solid. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 1.47 (s, 9 H), 2.61 (s, 3 H), 3.10 (s, 3 H), 3.43 (d, *J* = 6.1 Hz, 2 H), 4.89 – 5.10 (m, 2 H), 5.62 – 5.83 (m, 1 H), 7.36 – 7.49 (m, 1 H), 7.60 – 7.77 (m, 2 H).

**Step 5: 1,1-Dimethylethyl [6-chloro-5-(2-hydroxyethyl)-2-methyl-4-pyrimidinyl][2-fluoro-4-(methylsulfonyl)phenyl]carbamate (42)**

Compound **41** (3.0 g, 6.5 mmol) was dissolved in a mixture of methylene chloride (200 mL) and methanol (14 mL) and the resulting solution was cooled to  $-78^{\circ}\text{C}$ . Ozone was bubbled through the reaction until a blue color persisted. The reaction was then purged with oxygen followed by nitrogen until the blue color dissipated. The reaction was  
5 allowed to warm to  $-15^{\circ}\text{C}$  at which time solid sodium borohydride (962 mg, 26.0 mmol) was added. The reaction was allowed to stir for 5 h while warming to room temperature. The reaction was diluted with 50 mL water and the phases were separated. The aqueous phase was extracted with methylene chloride (2 x 50 mL) and the organics were combined and dried over anhydrous magnesium sulfate. The solids were removed  
10 *via* filtration and the crude reaction concentrated to dryness to give 2.4 g (82%) of the title compound **42** as a white solid.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  1.46 (s, 9 H), 2.58 (s, 3 H), 3.01 (t,  $J = 6.1$  Hz, 2 H), 3.10 (s, 3 H), 3.86 – 3.99 (m, 2 H), 7.54 – 7.83 (m, 3 H).

**Step 6: 2-(4-Chloro-6-{{[(1,1-dimethylethyl)oxy]carbonyl}[2-fluoro-4-(methylsulfonyl)phenyl]amino}-2-methyl-5-pyrimidinyl)ethyl methanesulfonate (**43**)**

15 Compound **42** (2.4 g, 5.22 mmol) was dissolved in methylene chloride (40 mL) and treated with DIPEA (2.7 mL, 15.6 mmol) followed by methanesulfonyl chloride (804  $\mu\text{L}$ , 10.45 mmol). The solution was stirred at ambient temperature for 4 h. The reaction was then diluted with 50 mL water and the phases were separated and the aqueous phase was extracted 3 times with methylene chloride (40 mL each). The organics were then  
20 combined and dried over anhydrous magnesium sulfate. The solids were removed *via* filtration and the crude reaction was concentrated to dryness to give 3.1 g of the title product **43** that was used without additional purification.  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO}-d_6$ ):  $\delta$  1.38 (s, 9 H), 2.50 (s, 3 H), 3.10 (t,  $J = 6.1$  Hz, 2 H), 3.16 (s, 3 H), 3.29 (s, 3 H), 3.42 (t,  $J = 6.1$  Hz, 2 H), 7.60 (t,  $J = 7.8$  Hz, 1 H), 7.67 – 7.78 (m, 1 H), 7.92 – 8.01 (m, 1 H).

25 **Step 7: 4-Chloro-7-[2-fluoro-4-(methylsulfonyl)phenyl]-2-methyl-6,7-dihydro-5H-pyrrolo[2,3-*d*]pyrimidine (**44**)**

Compound **43** (500 mg, 0.93 mmol) was treated with 25 mL of a solution of 20% TFA in methylene chloride (v/v). The solution was stirred at room temperature for 3 h then concentrated under reduced pressure. The residue was redissolved in 20 mL of  
30 methylene chloride and  $\text{Et}_3\text{N}$  (450  $\mu\text{L}$ , 2.53 mmol) added. The mixture was stirred at room temperature for 18 h, the solvent removed and the crude reaction purified *via* flash column chromatography (40 g of silica gel, 10  $\rightarrow$  50% ethyl acetate/hexane) to give 298

mg (94%) of the title compound **44** as a white solid.  $^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  2.48 (s, 3 H), 3.10 (s, 3 H), 3.24 (t,  $J = 7.3$  Hz, 2 H), 4.24 (t,  $J = 7.3$  Hz, 2 H), 7.57 – 7.84 (m, 2 H), 7.91 – 8.20 (m, 1 H); LCMS (ESI):  $m/z$  342 ( $M + H$ ) $^+$ .

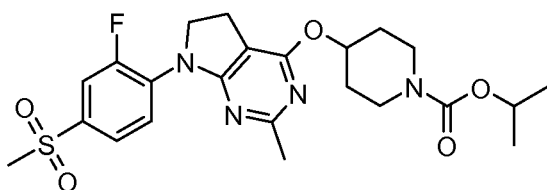
**Step 8: 1,1-Dimethylethyl 4-({7-[2-fluoro-4-(methylsulfonyl)phenyl]-2-methyl-6,7-**

**5 dihydro-5H-pyrrolo[2,3-d]pyrimidin-4-yl}oxy)-1-piperidinecarboxylate (**45**)**

1,1-Dimethylethyl 4-hydroxy-1-piperidinecarboxylate (122 mg, 0.609 mmol) was dissolved in 5 mL anhydrous THF. NaH (60% dispersion in oil, 70 mg, 1.74 mmol) was added to the solution and the mixture was stirred at room temperature for 0.5 h.

Compound **44** (198 mg, 0.581 mmol) was dissolved in 5 mL THF and added dropwise to the above solution. The mixture was then refluxed for 3 h. The heating bath was removed and the reaction stirred overnight at room temperature. The reaction was then treated with 5 mL of 1M aqueous HCl followed by 20 mL water. The crude reaction was then extracted 3 times with methylene chloride (20 mL each) and the organics were dried over anhydrous magnesium sulfate, filtered, and the crude reaction was concentrated to dryness. The reaction was purified *via* flash column chromatography using a gradient of (25 g of silica gel, 0  $\rightarrow$  50% ethyl acetate/hexane) to give 170 mg (60%) of the title compound **45** as a white solid.  $^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  1.46 (s, 9 H), 1.62 – 1.83 (m, 2 H), 1.86 – 2.11 (m, 2 H), 2.48 (s, 3 H), 2.86 – 3.18 (m, 5 H), 3.21 – 3.44 (m, 2 H), 3.57 – 3.87 (m, 2 H), 4.25 (t,  $J = 7.3$  Hz, 2 H), 5.30 – 5.47 (m, 1 H), 7.59 – 7.78 (m, 2 H), 7.06 – 8.22 (m, 1 H); LCMS (ESI):  $m/z$  507 ( $M + H$ ) $^+$ .

**Example 15 (**47**)**



**Step 1: 7-[2-Fluoro-4-(methylsulfonyl)phenyl]-2-methyl-4-(4-piperidinyloxy)-6,7-**

**25 dihydro-5H-pyrrolo[2,3-d]pyrimidine trifluoroacetate (**46**)**

Compound **45** (101 mg, 0.19 mmol) was treated with 10 mL of a solution of 20% TFA in methylene chloride (v/v). The solution was stirred at room temperature for 3 h. The solvent was then removed under reduced pressure and the crude residue was placed on



a high vacuum pump for 0.5 h to give 100 mg of the crude TFA salt **46** that was used without purification.

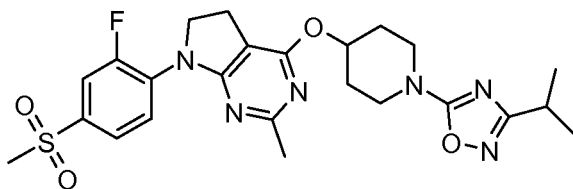
**Step 2: 1-Methylethyl 4-({7-[2-fluoro-4-(methylsulfonyl)phenyl]-2-methyl-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-4-yl}oxy)-1-piperidinecarboxylate (**47**)**

5 Compound **46** (50 mg, 0.10 mmol) was dissolved in methylene chloride (5 mL). A 1 M solution of isopropyl chloroformate in toluene (96  $\mu$ L, 0.10 mmol) was added to the above solution followed by diisopropylethylamine (61  $\mu$ L, 0.35 mmol) and the reaction mixture was stirred at room temperature for 18 h. The solvents were then removed under reduced pressure and the crude reaction purified *via* flash column

10 chromatography (15  $\rightarrow$  50% ethyl acetate/hexane) to give 48 mg (98%) of the title compound **47** as a white solid.  $^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  1.17 (d,  $J = 6.8$  Hz, 6 H), 1.60 – 1.82 (m, 2 H), 1.89 – 2.01 (m, 2 H), 2.47 (s, 3 H), 2.94 – 3.15 (m, 5 H), 3.25 – 3.46 (m, 2 H), 3.63 – 3.87 (m, 2 H), 4.19 (t,  $J = 7.3$  Hz, 2 H), 4.83 – 5.02 (m, 1 H), 5.30 – 5.47 (m, 1 H), 7.59 – 7.78 (m, 2 H), 7.06 – 8.22 (m, 1 H); LCMS (ESI):  $m/z$  493 (M + H) $^+$ .

15

**Example 16 (**50**)**



**Step 1: 4-Hydroxy-1-piperidinecarbonitrile (**48**)**

NaHCO<sub>3</sub> (41 g, 0.494 mol) was combined with 20 mL water and cooled to 0  $^{\circ}\text{C}$  on an ice

20 bath. 4-Hydroxypiperidine (25 g, 0.25 mol) in 75 mL of methylene chloride was added to the above solution with vigorous stirring. Cyanogen bromide (28 g, 0.27 mol) in 25 mL of methylene chloride was then added and the ice bath was removed. The mixture was then stirred at ambient temperature for 18 h. Na<sub>2</sub>CO<sub>3</sub> (75 g) was then added until pH  $\cong$  7 and MgSO<sub>4</sub> (25 g) was added to remove water. The solids were removed *via* filtration

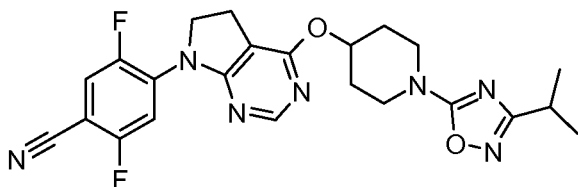
25 and the solids were washed several times with methylene chloride. The filtrate was then removed under reduced pressure and the title product **48** (24.8 g) was used without purification.

**Step 2: 1-[3-(1-Methylethyl)-1,2,4-oxadiazol-5-yl]-4-piperidinol (**49**)**

A solution of compound **48** (12.9 g, 0.102 mol) and compound **106** (see, **Example 48, Step 1**) (12.8 g, 0.125 mol) in a mixture of ethyl acetate (500 mL) and ether (100 mL) was treated with a 1 N solution of ZnCl<sub>2</sub> (120 mL, 0.120 mol) in ether. The mixture was stirred for 15 min and the supernatant was decanted off. The residue was washed 2  
5 times with 250 mL of ether, which was decanted off after each wash. The residue was then dissolved in a mixture of 4 N HCl (50 mL) and EtOH (100 mL). The resulting solution was refluxed for 1 h and the solvent was reduced under reduced pressure to about 25 mL and 25 g Na<sub>2</sub>CO<sub>3</sub> was added along with 100 mL methylene chloride. The solids were removed *via* filtration and phases were separated. The organic phase was  
10 dried over MgSO<sub>4</sub>, filtered, and concentrated to dryness to give 16 g of the desired compound **49** as a tan oil and the material was used without purification. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 1.13 – 1.38 (m, 6 H), 1.49 – 1.74 (m, 2 H), 1.80 – 2.05 (m, 2 H), 2.78 (m, 1 H), 3.20 – 3.44 (m, 2 H), 3.74 – 4.04 (m, 3 H).

**Step 3: 7-[2-Fluoro-4-(methylsulfonyl)phenyl]-2-methyl-4-({1-[3-(1-methylethyl)-1,2,4-oxadiazol-5-yl]-4-piperidinyloxy)-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidine**  
15 **(50)**

Compound **49** (100 mg, 0.292 mmol) was dissolved in 5 mL anhydrous THF. NaH (60% dispersion in oil, 35 mg, 0.876 mmol) was added to the solution and the mixture was stirred at room temperature for 0.5 h. Compound **44** (55 mg, 0.262 mmol) was dissolved  
20 in 5 mL THF and added dropwise to the above solution. The mixture was then refluxed for 3 hours. The crude reaction mixture was then concentrated *in vacuo* and the resulting residue was purified using the Gilson semi-preparative HPLC (Sunfire C18, 5 microns, 30/50 mm) using a gradient of 10-100% CH<sub>3</sub>CN / H<sub>2</sub>O / 0.1% TFA to give 76 mg (56%) of the title compound **50** as a white solid. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 1.27  
25 (d, *J* = 6.8 Hz, 6 H), 1.81 – 1.97 (m, 2 H), 2.01 – 2.13 (m, 2 H), 2.49 (s, 3 H), 2.80 – 2.95 (m, 1 H), 2.99 – 3.14 (m, 5 H), 3.54 – 3.66 (m, 2 H), 3.79 – 3.92 (m, 2 H), 4.19 (t, *J* = 7.3 Hz, 2 H), 5.39 – 5.54 (m, 1 H), 7.62 – 7.79 (m, 2 H), 7.92 – 8.13 (m, 1 H); LCMS (ESI): *m/z* 517 (M + H)<sup>+</sup>.

**Example 17 (56)****Step 1: 4-[[6-Chloro-5-(2-propen-1-yl)-4-pyrimidinyl]amino]-2,5-difluorobenzonitrile (51)**

5 NaH (60% dispersion in oil, 967 mg, 24.2 mmol) was added to a 100 mL round bottom flask along with 5 mL anhydrous toluene. The suspension was stirred for 10 min and the toluene was decanted off. 4-Amino-2,5-difluorobenzonitrile (1.9 g, 12.2 mmol) in 40 mL anhydrous THF was then added to the NaH slurry dropwise over several minutes. The resulting mixture was stirred at ambient temperature for 15 min at which time compound

10 **2** (2.4 g, 12.7 mmol) in 10 mL anhydrous THF was added slowly over several minutes. The mixture was then heated to reflux for 2 h. The reaction was then cooled to room temperature and diluted with 100 mL water and a white precipitate (1.62 g) formed which was removed *via* filtration and dried under reduced pressure. The filtrate was then transferred to a separatory funnel and was extracted with methylene chloride (3 x 100

15 mL). The combined organic extracts were then dried over anhydrous magnesium sulfate, filtered, and concentrated to dryness. The crude residue was then recrystallized from MeOH to give an additional 0.57 g of the desired product **51** as a white solid; 2.19 g total (51%). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 3.67 (d, *J* = 6.0 Hz, 2 H), 5.21 – 5.50 (m, 2 H), 5.77 – 6.02 (m, 1 H), 7.29 – 7.41 (m, 1 H), 7.41 – 7.53 (s, 1 H), 8.50 (s, 1 H), 8.67 – 8.85

20 (m, 1 H).

**Step 2: 1,1-Dimethylethyl [6-chloro-5-(2-propen-1-yl)-4-pyrimidinyl](4-cyano-2,5-difluorophenyl)carbamate (52).**

Compound **51** (2.2 g, 6.8 mmol) was dissolved in methylene chloride (40 mL) and treated with (BOC)<sub>2</sub>O (3.0 g, 13.6 mmol) and a catalytic amount of DMAP. The resulting

25 solution was stirred for 18 h at ambient temperature. The reaction was then diluted with 50 mL water and the aqueous phase was extracted 3 times with methylene chloride (50 mL each). The organics were then combined and dried over anhydrous magnesium sulfate. The solids were removed *via* filtration and the crude reaction was concentrated to dryness. The crude reaction was then purified *via* flash column chromatography (120

g of silica gel, 10 → 50% ethyl acetate/hexane) to give 2.4 g (83%) of the desired compound **52** as a white solid. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 1.44 (s, 9 H), 3.52 (d, *J* = 6.1 Hz, 2 H), 4.89 – 5.21 (m, 2 H), 5.63 – 5.98 (m, 1 H), 7.06 – 7.20 (m, 1 H), 7.32 – 7.52 (m, 1 H), 8.70 (s, 1 H).

5 **Step 3: 1,1-Dimethylethyl [6-chloro-5-(2-hydroxyethyl)-4-pyrimidinyl](4-cyano-2,5-difluorophenyl)carbamate (**53**)**

Compound **52** (2.4 g, 5.69 mmol) was dissolved in a mixture of methylene chloride (200 mL) and methanol (10 mL) and the resulting solution was cooled to –78 °C. Ozone was then bubbled through the solution until a blue color persisted. The reaction was then  
10 purged with oxygen followed by nitrogen until blue color dissipated. The reaction was then allowed to warm to –15 °C at which time solid sodium borohydride (841 mg, 22.74 mmol) was added. The reaction was allowed to stir for 5 h while warming to room temperature. The reaction was then diluted with 50 mL water and the aqueous phase was extracted 2 times with methylene chloride (50 mL each). The organics were then  
15 combined and dried over anhydrous magnesium sulfate. The solids were removed *via* filtration and the crude reaction was concentrated to dryness. The reaction was then purified *via* flash column chromatography (20 → 50% ethyl acetate / hexane) to give 810 mg (33%) of the desired compound **53**. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 1.49 (s, 9 H), 3.08 (t, *J* = 7.3 Hz, 2 H), 3.98 (t, *J* = 7.3 Hz, 2 H), 7.29 – 7.46 (m, 2 H), 8.50 (s, 1 H).

20 **Step 4: 2-[4-Chloro-6-((4-cyano-2,5-difluorophenyl){[(1,1-dimethylethyl)oxy]carbonyl}amino)-5-pyrimidinyl]ethyl methanesulfonate (**54**).**

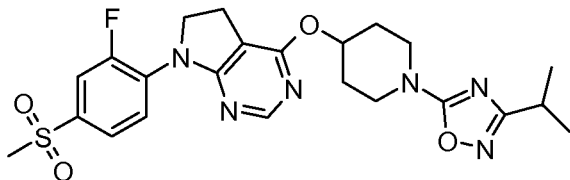
Compound **53** (810 mg, 1.90 mmol) was dissolved in methylene chloride (20 mL) and treated with DIPEA (1.0 mL, 5.7 mmol) followed by methanesulfonyl chloride (433 mg, 3.8 mmol). The solution was stirred at ambient temperature for 4 h. The reaction was  
25 then diluted with 50 mL water and the aqueous phase was extracted 3 times with methylene chloride (40 mL each). The organics were then combined and dried over anhydrous magnesium sulfate. The solids were removed *via* filtration and the crude reaction was concentrated to dryness to give 1.0 g of the crude title product **54** that was used without additional purification. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 1.40 (s, 9 H), 2.89 (s, 3 H), 3.25 (t, *J* = 7.3 Hz, 2 H), 4.50 (t, *J* = 7.3 Hz, 2 H), 7.29 – 7.46 (m, 2 H), 8.63 (s, 1  
30 H).

**Step 5: 4-(4-Chloro-5,6-dihydro-7H-pyrrolo[2,3-d]pyrimidin-7-yl)-2,5-difluorobenzonitrile (55)**

Compound **54** (1.0 g, 2.05 mmol) was treated with 10 mL of a solution of 20% TFA in methylene chloride (v/v). The solution was stirred at room temperature for 3 hours. The solvent was then removed *in vacuo* and the crude residue was placed on a high vacuum pump for 0.5 h. The residue was then redissolved in 10 mL of methylene chloride and TEA (3 mL, 16.8 mmol) was added to the solution. The mixture was stirred at room temperature for 18 h. Solvent was removed to give 594 mg (98%) of the title compound **55** that was used without additional purification. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 3.35 (t, *J* = 7.3 Hz, 2 H), 4.35 (t, *J* = 7.3 Hz, 2 H), 7.32 – 7.51 (m, 1 H), 7.89 – 8.13 (m, 1 H), 8.44 (s, 1 H).

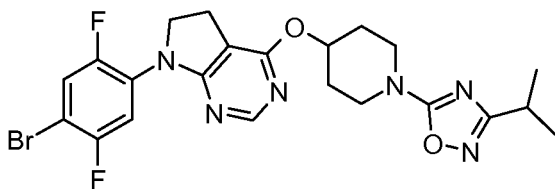
**Step 6: 2,5-Difluoro-4-[4-({1-[3-(1-methylethyl)-1,2,4-oxadiazol-5-yl]-4-piperidinyl}oxy)-5,6-dihydro-7H-pyrrolo[2,3-d]pyrimidin-7-yl]benzonitrile (56)**

Compound **49** (162 mg, 0.770 mmol) was dissolved in 5 mL anhydrous THF. NaH (60% dispersion in oil, 102 mg, 2.57 mmol) was added to the solution and the mixture was stirred at room temperature for 0.5 h. Compound **55** (250 mg, 0.856 mmol) was dissolved in 5 mL THF and added dropwise to the above solution. The mixture was then refluxed for 3 h. The crude reaction mixture was then concentrated *in vacuo* and the resulting residue was purified *via* flash column chromatography (10 → 50% ethyl acetate/hexane) to give 50 mg (13%) of the title compound **56** as a white solid. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 1.29 (d, *J* = 6.8 Hz, 6 H), 1.82 – 1.97 (m, 2 H), 2.06 – 2.17 (m, 2 H), 2.81 – 2.97 (m, 1 H), 3.09 (t, *J* = 7.3 Hz, 2 H), 3.47 – 3.62 (m, 2 H), 3.79 – 3.95 (m, 2 H), 4.25 (t, *J* = 7.3 Hz, 2 H), 5.33 – 5.52 (m, 1 H), 7.27 – 7.40 (m, 1 H), 8.00 – 8.19 (m, 1 H), 8.31 (s, 1 H); LC); LCMS (ESI): *m/z* 468 (M + H)<sup>+</sup>.

**Example 18 (57)**

**7-[2-Fluoro-4-(methylsulfonyl)phenyl]-4-({1-[3-(1-methylethyl)-1,2,4-oxadiazol-5-yl]-4-piperidinyl}oxy)-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidine (57)**

- 5 The protocol described for **10** (Example 1, Step 10) was followed. Compound **8** (540 mg, 1.65 mmol) was allowed to react with compound **49** (332 mg, 1.57 mmol) in presence of NaH (60% dispersion in oil, 200 mg, 4.94 mmol) and THF (20 mL) for 2.5 h. Work-up followed by purification gave 460 mg (55%) of the title product **57** as a white solid. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>): δ 8.27 (s, 1 H), 7.99 (app. t, *J* = 7.6 Hz, 1 H), 7.87 (app. br d, *J* = 10.8 Hz, 1H), 7.78 (app. br t, *J* = 8.4 Hz, 1H), 5.36 (br m, 1 H), 4.18 (t, *J* = 8.8 Hz, 2 H), 3.82 – 3.78 (m, 2 H), 3.56 – 3.50 (m, 2 H), 3.28 (s, 3 H), 3.10 (t, *J* = 8.4 Hz, 2 H), 2.83 (septuplet, *J* = 6.8 Hz, 1 H), 2.09 (m, 2 H), 1.78 (m, 2 H), 1.20 (d, *J* = 6.8 Hz, 6 H); LCMS (ESI): *m/z* 503 (M + H)<sup>+</sup>.

**Example 19 (62)**

**Step 1: (4-Bromo-N-[2-(4,6-dichloro-5-pyrimidinyl)ethyl]-2,5-difluoroaniline (58)**

- Compound **2** (1.71 g, 9.0 mmol) was dissolved in methylene chloride (200 mL) and methanol (10 mL) and the resulting solution was cooled to -78 °C. Ozone was then bubbled through the solution until a blue color persisted. The reaction was then purged with oxygen followed by nitrogen until blue color dissipated. The reaction was then treated with dimethylsulfide (589 mg, 9.5 mmol) and the mixture was stirred for 1.5 h while warming to room temperature. The reaction was then concentrated to dryness. 4-Bromo-2,5-difluoroaniline (1.79 g, 8.6 mmol) was then added to the crude residue and the mixture was dissolved in 50 mL methylene chloride. MeOH (10 mL) was then added to the above solution along with 1 mL of glacial acetic acid. The resulting solution was

then stirred for 1 h at which time solid sodium cyanoborohydride (1.6 g, 25.8 mmol) was added. The reaction was then left to stir at room temperature for 18 h. The reaction was then diluted with 50 mL water and the aqueous phase was extracted 3 times with methylene chloride (50 mL each). The organics were then combined and dried over anhydrous magnesium sulfate. The solids were removed *via* filtration and the crude reaction was concentrated to dryness. The reaction was then treated with MeOH and allowed to stand for 48 h. A yellow precipitate formed which was removed *via* filtration to give 510 mg (16%) of the title compound **58**. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 3.23 (t, *J* = 6.8 Hz, 2 H), 3.54 (t, *J* = 6.8 Hz, 2 H), 4.11 – 4.37 (br, 1 H), 6.39 – 6.68 (m, 1 H), 7.00 – 7.18 (m, 1 H), 8.64 (s, 1 H).

**Step 2: 7-(4-Bromo-2,5-difluorophenyl)-4-chloro-6,7-dihydro-5H-pyrrolo[2,3-*d*]pyrimidine (**59**)**

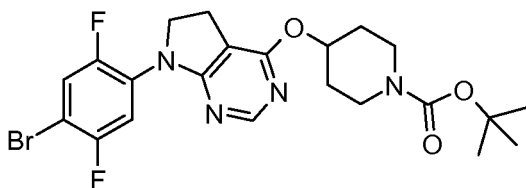
Compound **58** (367 mg) was dissolved in 10 mL methylene chloride and 1 mL TFA was added slowly. The resulting solution was allowed to stir at room temperature for 17 h. The reaction was then diluted with 10 mL of a saturated solution of NaHCO<sub>3</sub> and aqueous phase was extracted 2 times with methylene chloride. The organics were then combined and dried over anhydrous magnesium sulfate. The solids were removed *via* filtration and the crude reaction was concentrated to dryness to give 310 mg (94%) of the crude product **59** that was used without additional purification. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 3.26 (t, *J* = 6.8 Hz, 2 H), 4.21 (t, *J* = 6.8 Hz, 2 H), 7.30 – 7.44 (m, 1 H), 7.47 – 7.66 (m, 1 H), 8.36 (s, 1 H).

**Step 3: 7-(4-Bromo-2,5-difluorophenyl)-4-({1-[3-(1-methylethyl)-1,2,4-oxadiazol-5-yl]-4-piperidinyl}oxy)-6,7-dihydro-5H-pyrrolo[2,3-*d*]pyrimidine (**60**)**

Compound **49** (54 mg, 0.26 mmol) was dissolved in 5 mL anhydrous THF. NaH (60% dispersion in oil, 34 mg, 0.87 mmol) was added to the solution and the mixture was stirred at room temperature for 0.5 h. Compound **59** (100 mg, 0.29 mmol) was dissolved in 5 mL THF and added dropwise to the above solution. The mixture was then refluxed for 3 h. The crude reaction mixture was then diluted with 10 mL water and extracted 3 times with 10 mL methylene chloride. The combined organic extracts were dried over anhydrous magnesium sulfate, filtered, and concentrated to dryness. The resulting residue was purified *via* flash column chromatography (10 → 50% ethyl acetate/hexane) to give 100 mg (66%) of the title compound **60** as a white solid. <sup>1</sup>H NMR (400 MHz,

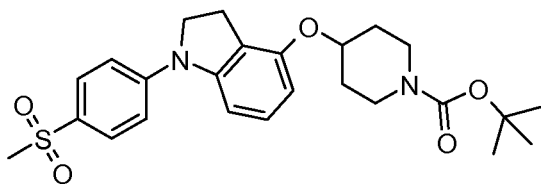
CDCl<sub>3</sub>): δ 1.21 – 1.38 (m, 6 H), 1.83 – 1.99 (m, 2 H), 2.02 – 2.19 (m, 2 H), 2.79 – 2.97 (m, 1 H), 3.10 (t, *J* = 9.0 Hz, 2 H), 3.51 – 3.73 (m, 2 H), 3.78 – 3.99 (m, 2 H), 4.09 (t, *J* = 9.0 Hz, 2 H), 5.25 – 5.52 (m, 1 H), 7.27 – 7.39 (m, 1 H), 7.44 – 7.66 (m, 1 H), 8.21 (s, 1 H); LCMS (ESI): *m/z* 522 (M + H)<sup>+</sup>.

5

**Example 20 (61)****1,1-Dimethylethyl 4-[[7-(4-bromo-2,5-difluorophenyl)-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-4-yl]oxy]-1-piperidinecarboxylate (62)**

10 1,1-Dimethylethyl 4-hydroxy-1-piperidinecarboxylate (109 mg, 0.546 mmol) was dissolved in 5 mL anhydrous THF. NaH (60% dispersion in oil, 72 mg, 1.8 mmol) was added to the solution and the mixture was stirred at room temperature for 0.5 h. Compound **59** (210 mg, 0.607 mmol) was dissolved in 5 mL THF and added dropwise to the above solution. The mixture was then refluxed for 3 h. The crude reaction mixture  
15 was then diluted with 10 mL water and extracted 3 times with 10 mL methylene chloride. The combined organic extracts were dried over anhydrous magnesium sulfate, filtered, and concentrated to dryness. The resulting residue was purified *via* flash column chromatography (10 → 50% ethyl acetate/ hexane) to give 176 mg (60%) of the title compound **62** as a white solid. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 1.46 (s, 9 H), 1.65 – 1.80 (m, 2 H), 1.90 – 2.03 (m, 2 H), 3.11 (t, *J* = 8.8 Hz, 2 H), 3.21 – 3.35 (m, 2 H), 3.68 – 3.82 (m, 2 H), 4.10 (t, *J* = 8.3 Hz, 2 H), 5.23 – 5.37 (m, 1 H), 7.28 – 7.37 (m, 1 H), 7.54 – 7.68 (m, 1 H), 8.19 (s, 1 H); LCMS (ESI): *m/z* 512 (M + H)<sup>+</sup>.

20

**Example 21 (66)**

25

**Step 1: 1,1-Dimethylethyl 4-(1H-indol-4-yloxy)-1-piperidinecarboxylate (63)**



To a solution of 4-hydroxyindole (9.98 g, 75 mmol), Ph<sub>3</sub>P (39.4 g, 150 mmol), 4-hydroxypiperidine (22.25 g, 113 mmol) and THF (600 mL) was added, dropwise at RT under N<sub>2</sub>, diisopropyl azodicarboxylate (26.0 mL, 135 mmol). The reaction mixture was stirred at RT for 15 h and concentrated to give the crude material. The crude product  
5 was purified by flash chromatography over SiO<sub>2</sub> (0 → 20% ethyl acetate / hexanes) to afford 17.6 g (74%) of the title compound **63** as a white solid. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>): δ 11.03 (br s, 1 H), 7.19 (t, *J* = 2.8 Hz, 1 H), 6.99 – 6.93 (m, 2 H), 6.54 and 6.53 (dd, *J*<sub>1</sub> = 7.2 Hz, *J*<sub>2</sub> = 1.2 Hz, 1 H), 6.41 (app. t, *J* = 2.4 Hz, 1 H), 4.63 (m, 1 H), 3.67 – 3.61 (m, 2 H), 3.26 – 3.21 (m, 2 H), 1.94 – 1.87 (m, 2 H), 1.64 – 1.52 (m, 2 H),  
10 1.40 (s, 9 H); LCMS (ESI): *m/z* 339 (M + Na)<sup>+</sup>.

**Step 2: 1,1-Dimethylethyl 4-[[1-(4-iodophenyl)-1*H*-indol-4-yl]oxy]-1-piperidinecarboxylate (**64**)**

A round-bottomed flask was charged, at RT under N<sub>2</sub>, with compound **63** (4.20 g, 13.3 mmol), CuI (253 mg, 1.3 mmol), K<sub>3</sub>PO<sub>4</sub> (5.92 g, 27.9 mmol), 1,4-diiodobenzene (5.47 g,  
15 16.6 mmol), trans- *N,N*-dimethyl-1,2-cyclohexanediamine (378 mg, 2.7 mmol), and anhydrous DMF (15 mL). The reaction mixture was stirred at 140 °C for 36 h. The reaction mixture was diluted with EtOAc (50 mL) and filtered through a pad of Celite (washed with EtOAc). The filtrate was concentrated under reduced pressure to afford the crude material. The product was purified by flash column chromatography (0 → 20%  
20 ethyl acetate/hexanes) to give 4.72 g (69%) of a title product **64** as an off-white solid. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>): δ 7.88 (t, *J* = 8.8 Hz, 2 H), 7.51 (d, *J* = 3.2 Hz, 1 H), 7.39 (d, *J* = 8.8 Hz, 2 H), 7.12 (t, *J* = 5.6 Hz, 1 H), 7.09 (t, *J* = 8.0 Hz, 1 H), 6.72 (d, *J* = 7.2 Hz, 1 H), 6.70 (d, *J* = 3.2 Hz, 1 H), 4.70 (m, 1 H), 3.66 – 3.60 (m, 2 H), 3.28 – 3.24 (m, 2 H), 1.94 – 1.89 (m, 2 H), 1.66 – 1.58 (m, 2 H), 1.39 (s, 9 H); LCMS (ESI): *m/z* 518 (M + H)<sup>+</sup>.

**Step 3: 1,1-Dimethylethyl 4-[[1-(4-iodophenyl)-2,3-dihydro-1*H*-indol-4-yl]oxy]-1-piperidinecarboxylate (**65**)**

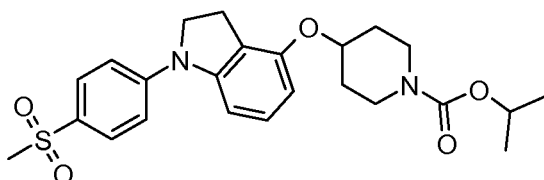
To a solution of **64** (330 mg, 0.64 mmol) in acetic acid (10 mL) at RT was added NaCNBH<sub>3</sub> (322 mg, 5.12 mmol). The mixture was stirred at RT for 15 h and then poured slowly into H<sub>2</sub>O (40 mL) and stirred for 10 min. The solid was filtered and dried to afford  
30 310 mg (93%) of the title product **65** as an off-white solid. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>): δ 7.59 (t, *J* = 8.4 Hz, 2 H), 7.02 (d, *J* = 8.8 Hz, 2 H), 6.99 (app. t, *J* = 8.0 Hz, 1 H), 6.71 (d, *J* = 8.0 Hz, 1 H), 6.49 (d, *J* = 8.4 Hz, 1 H), 4.54 (m, 1 H), 3.88 (t, *J* = 8.4 Hz, 2

H), 3.59 – 3.46 (m, 2 H), 3.24 – 3.19 (m, 2 H), 2.96 (t,  $J = 8.4$  Hz, 2 H), 1.87 – 1.82 (m, 2 H), 1.57 – 1.49 (m, 2 H), 1.38 (s, 9 H); LCMS (ESI):  $m/z$  521 ( $M + H$ )<sup>+</sup>.

**Step 4: 1,1-Dimethylethyl 4-({1-[4-(methylsulfonyl)phenyl]-2,3-dihydro-1H-indol-4-yl}oxy)-1-piperidinecarboxylate (**66**)**

5 A 10 mL glass tube was charged with **65** (260 mg, 0.50 mmol), MeSO<sub>2</sub>Na (102 mg, 1.0 mmol), L-proline (12 mg, 0.104 mmol), NaOH (5 mg, 0.104 mmol) and DMSO (3 mL). The tube was sealed and then stirred at 120 °C for 18 h. The reaction mixture was cooled, the tube was opened, and the contents of the tube were poured into H<sub>2</sub>O (40 mL). The mixture was stirred for 10 min, filtered the solid material, and the was purified  
10 by flash SiO<sub>2</sub> column chromatography gave dried to afford 222 mg (94%) of the title product **66** as an off-white solid. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>):  $\delta$  7.79 (t,  $J = 8.8$  Hz, 2 H), 7.35 (d,  $J = 8.8$  Hz, 2 H), 7.08 (app. t,  $J = 8.4$  Hz, 1 H), 6.93 (d,  $J = 8.0$  Hz, 1 H), 6.60 (d,  $J = 8.0$  Hz, 1 H), 4.60 – 4.52 (m, 1 H), 4.01 (t,  $J = 8.8$  Hz, 2 H), 3.61 – 3.55 (m, 2 H), 3.30 – 3.21 (m, 2 H), 3.13 (s, 3 H), 3.01 (t,  $J = 8.4$  Hz, 2 H), 1.89 – 1.84 (m, 2 H), 1.39 (s,  
15 9 H); LCMS (ESI):  $m/z$  495 ( $M + Na$ )<sup>+</sup>.

**Example 22 (**69**)**



**Step 1: 1-Methylethyl 4-([1-(4-iodophenyl)-1H-indol-4-yl]oxy)-1-piperidinecarboxylate (**67**)**

20 To a solution of **64** (3.150 g, 6.08 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (20 mL) at RT under N<sub>2</sub> was added CF<sub>3</sub>CO<sub>2</sub>H (5 mL). The reaction mixture was stirred at RT for 2.5 h and then concentrated under reduced pressure to afford the crude material. The crude material was redissolved in CH<sub>2</sub>Cl<sub>2</sub> (100 mL) and cooled to 5 °C. To the above mixture, DIPEA  
25 (3.2 mL, 18.2 mmol), DMAP (74 mg, 0.61 mmol), and a 1 M solution of isopropyl chloroformate in toluene (12.2 mL, 12.16 mmol) were added sequentially. The mixture was stirred at RT for 15 h. The reaction mixture was diluted with CH<sub>2</sub>Cl<sub>2</sub> (150 mL) and then washed with water (2 x 20 mL), brine (1 x 20 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and the filtrate was concentrated under reduced pressure to afford the crude material. The

product was purified by SiO<sub>2</sub> column chromatography (0 → 20% ethyl acetate/hexanes) to afford 2.56 g (83%) of the title product **67** as white solid. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>): δ 7.88 (d, *J* = 8.8 Hz, 2 H), 7.51 (d, *J* = 3.2 Hz, 1 H), 7.39 (d, *J* = 8.4 Hz, 2 H), 7.12 (app. t, *J* = 8.0 Hz, 1 H), 7.10 (app. t, *J* = 8.0 Hz, 1 H), 6.72 (d, *J* = 7.2 Hz, 1 H), 6.70 (d, *J* = 3.2 Hz, 1 H), 4.76 (septuplet, *J* = 6.4 Hz, 1 H), 4.72 (m, 1 H), 3.69 – 3.63 (m, 2 H), 3.33 – 3.29 (m, 2 H), 1.99 – 1.90 (m, 2 H), 1.68 – 1.60 (m, 2 H), 1.18 (d, *J* = 6.4 Hz, 6 H); LCMS (ESI): *m/z* 505 (M + Na)<sup>+</sup>.

**Step 2: 1-Methylethyl 4-([1-(4-iodophenyl)-2,3-dihydro-1*H*-indol-4-yl]oxy)-1-piperidinecarboxylate (**68**)**

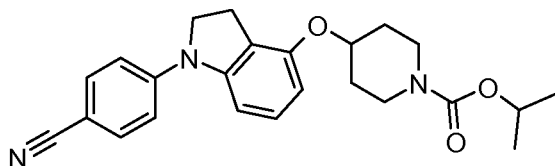
To a solution of **67** (2.41 g, 4.78 mmol) and acetic acid (40 mL) at RT was added NaCNBH<sub>3</sub> (3.00 mg, 47.8 mmol). The mixture was stirred at RT for 15 h and then H<sub>2</sub>O (150 mL) was added. The mixture was extracted with EtOAc (4 x 125 mL). The combined organic layer was washed with brine (1 x 50 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and the filtrate was concentrated under reduced pressure. The crude material was purified by flash SiO<sub>2</sub> column chromatography using (0 → 20% ethyl acetate/hexanes) to afford 2.31 mg (95%) of the title product **68** as a white solid. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>): δ 7.59 (t, *J* = 8.4 Hz, 2 H), 7.02 (d, *J* = 8.8 Hz, 2 H), 6.99 (app. t, *J* = 8.0 Hz, 1 H), 6.71 (d, *J* = 8.0 Hz, 1 H), 6.49 (d, *J* = 8.4 Hz, 1 H), 4.75 (septuplet, *J* = 5.6 Hz, 1 H), 4.56 (m, 1 H), 3.88 (t, *J* = 8.4 Hz, 2 H), 3.62 – 3.57 (m, 2 H), 3.31 – 3.20 (m, 2 H), 2.95 (t, *J* = 8.8 Hz, 2 H), 1.88 – 1.83 (m, 2 H), 1.58 – 1.50 (m, 2 H), 1.17 (d, *J* = 6.4 Hz, 6 H); LCMS (ESI): *m/z* 507 (M + H)<sup>+</sup>.

**Step 3: 1-Methylethyl 4-([1-[4-(methylsulfonyl)phenyl]-2,3-dihydro-1*H*-indol-4-yl]oxy)-1-piperidinecarboxylate (**69**)**

The procedure described for **3** was employed. A 10 mL glass tube was charged with **68** (720 mg, 1.42 mmol), MeSO<sub>2</sub>Na (290 mg, 2.84 mmol), L-proline (33 mg, 0.284 mmol), NaOH (12 mg, 0.284 mmol) and DMSO (5 mL). The tube was sealed and then heated to 120 °C and stirred for 24 h. The reaction mixture was cooled, opened, and then poured into H<sub>2</sub>O. The mixture was stirred for 10 min, the solid material filtered and purified by flash SiO<sub>2</sub> column chromatography to afford 632 mg (97%) of the title product **69** as an off-white solid. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>): δ 7.79 (t, *J* = 8.8 Hz, 2 H), 7.35 (d, *J* = 8.8 Hz, 2 H), 7.08 (app. t, *J* = 8.4 Hz, 1 H), 6.93 (d, *J* = 8.0 Hz, 1 H), 6.60 (d, *J* = 8.4 Hz, 1 H), 4.75 (septuplet, *J* = 6.0 Hz, 1 H), 4.60 (m, 1 H), 4.01 (t, *J* = 8.8 Hz, 2 H),

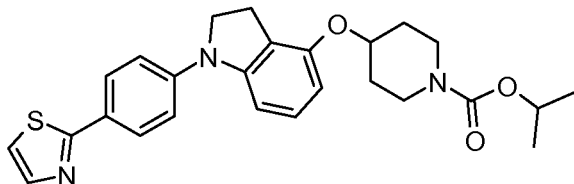
3.60 – 3.55 (m, 2 H), 3.28 – 3.26 (m, 2 H), 3.13 (s, 3 H), 3.01 (t,  $J = 8.4$  Hz, 2 H), 1.89 – 1.60 (m, 2 H), 1.59 - 1.52 (m, 2 H), 1.17 (d,  $J = 6.4$  Hz, 6 H); LCMS (ESI):  $m/z$  458 (M + H)<sup>+</sup>.

5 **Example 23 (70)**

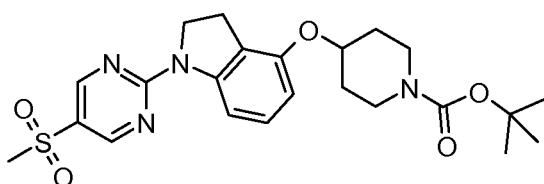


**1-Methylethyl 4-[[1-(4-cyanophenyl)-2,3-dihydro-1H-indol-4-yl]oxy]-1-piperidinecarboxylate (70)**

The procedure described for **31 (Example 10, Step 7)** was followed by using **68** (507 mg, 1 mmol) and CuCN (202 mg, 2.25 mmol) in NMP (10 mL) at 150 °C for 15 h. The mixture was purified by SiO<sub>2</sub> flash column chromatography to give 388 mg (96%) of the title product **70** as a white solid. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>): δ 7.70 (t,  $J = 8.8$  Hz, 2 H), 7.28 (d,  $J = 8.8$  Hz, 2 H), 7.08 (app. t,  $J = 8.4$  Hz, 1 H), 6.91 (d,  $J = 8.0$  Hz, 1 H), 6.61 (d,  $J = 8.4$  Hz, 1 H), 4.75 (septuplet,  $J = 6.4$  Hz, 1 H), 4.59 (m, 1 H), 3.99 (t,  $J = 8.4$  Hz, 2 H), 3.60 – 3.57 (m, 2 H), 3.30 – 3.26 (m, 2 H), 3.00 (t,  $J = 8.8$  Hz, 2 H), 1.89 – 1.84 (m, 2 H), 1.60 – 1.50 (m, 2 H), 1.38 (d,  $J = 6.4$  Hz, 6 H); LCMS (ESI):  $m/z$  406 (M + H)<sup>+</sup>.

**Example 24 (71)****1-Methylethyl 4-({1-[4-(1,3-thiazol-2-yl)phenyl]-2,3-dihydro-1H-indol-4-yl}oxy)-1-piperidinecarboxylate (71)**

- 5 The procedure described for **32 (Example 11)** was utilized. A round-bottomed flask at RT under N<sub>2</sub> was charged with **68** (100 mg, 0.20 mmol), PdCl<sub>2</sub>(Ph<sub>3</sub>P)<sub>2</sub> (7 mg, 0.001 mmol), 2-(tributylstannanyl)-1,3-thiazole (110 mg, 0.296 mmol), and THF (3 mL). The reaction mixture was refluxed for 15 h. The reaction mixture was cooled to RT and then chromatographed to afford 52 mg (57%) of the title product **71** as a white solid. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>): δ 7.88 (t, *J* = 8.8 Hz, 2 H), 7.83 (d, *J* = 3.2 Hz, 2 H), 7.65 (app. t, *J* = 3.2 Hz, 1 H), 7.28 (d, *J* = 8.8 Hz, 1 H), 7.05 (d, *J* = 8.0 Hz, 1 H), 6.86 (d, *J* = 8.4 Hz, 1 H), 7.05 (t, *J* = 8.4 Hz, 1 H), 6.86 (d, *J* = 8.4 Hz, 1 H), 6.54 (d, *J* = 8.4 Hz, 1 H), 4.76 (septuplet, *J* = 6.4 Hz, 1 H), 4.58 (m, 1 H), 3.99 (t, *J* = 8.8 Hz, 2 H), 3.64 – 3.58 (m, 2 H), 3.29 – 3.25 (m, 2 H), 3.00 (t, *J* = 8.8 Hz, 2 H), 1.89 – 1.85 (m, 2 H), 1.59 – 1.50 (m, 2 H), 1.17 (d, *J* = 6.4 Hz, 6 H); LCMS (ESI): *m/z* 464 (M + H)<sup>+</sup>.
- 10
- 15

**Example 25 (74)****Step 1: 1,1-Dimethylethyl 4-(2,3-dihydro-1H-indol-4-yloxy)-1-piperidinecarboxylate (72)**

- 20 The reduction procedure described for **65 (Example 21, Step 3)** was followed using compound **63** (1.30 g, 4.11 mmol), NaCNBH<sub>3</sub> (2.58 g, 41.0 mmol) and AcOH (40 mL) at ambient temperature. Aqueous work-up followed by purification gave 0.84 g (64%) of the title product **72** as an off-white solid. LCMS (ESI): *m/z* 319 (M + H)<sup>+</sup>.

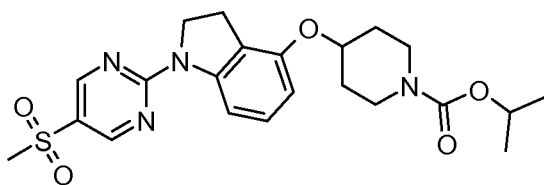
- 25 **Step 2: 1,1-Dimethylethyl 4-[[1-(5-bromo-2-pyrimidinyl)-2,3-dihydro-1H-indol-4-yl]oxy]-1-piperidinecarboxylate (73)**

To a solution of **72** (637 mg, 2 mmol) in acetonitrile (40 mL) were added, under N<sub>2</sub> at ambient temperature, DIPEA (1.1 mL) and 5-bromo-2-chloropyrimidine (483 mg, 2.5 mmol). The mixture was refluxed for 15 h and then concentrated under reduced pressure. The crude product was purified by SiO<sub>2</sub> flash column chromatography to afford 60 mg (6%) of the title product **73** as a white solid. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>): δ 8.67 (s, 2 H), 7.84 (d, *J* = 8.0 Hz, 1 H), 7.13 (t, *J* = 8.4 Hz, 1 H), 6.68 (d, *J* = 8.4 Hz, 1 H), 4.58 (m, 1 H), 4.13 (t, *J* = 8.8 Hz, 2 H), 3.60 – 3.54 (m, 2 H), 3.30 – 3.19 (m, 2 H), 3.04 (t, *J* = 8.8 Hz, 2 H), 1.89 – 1.80 (m, 2 H), 1.60 – 1.51 (m, 2 H), 1.38 (s, 9 H); LCMS (ESI): *m/z* 498 (M + Na)<sup>+</sup>.

10 **Step 3: 1,1-Dimethylethyl 4-({1-[5-(methylsulfonyl)-2-pyrimidinyl]-2,3-dihydro-1*H*-indol-4-yl}oxy)-1-piperidinecarboxylate (**74**)**

The procedure described for **3** (Example 1, Step 3) was employed using **73** (45 mg, 0.095 mmol), CuI (2 mg, 0.01 mmol), L-proline (3 mg, 0.02 mmol), NaOH (1 mg, 0.02 mmol), CH<sub>3</sub>SO<sub>2</sub>Na (20 mg, 0.19 mmol), and DMSO (2 mL). The mixture was heated to 110 °C for 24 h and then poured into H<sub>2</sub>O (20 mL). The solid was filtered and dried to afford 44 mg (98%) of the title product **74** as a light yellow solid. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>): δ 8.91 (s, 2 H), 7.97 (d, *J* = 8.4 Hz, 1 H), 7.19 (t, *J* = 8.4 Hz, 1 H), 6.78 (d, *J* = 8.0 Hz, 1 H), 4.62 (m, 1 H), 4.25 (t, *J* = 8.4 Hz, 2 H), 3.62 – 3.53 (m, 2 H), 3.28 (s, 3 H), 3.27 – 3.23 (m, 2 H), 3.08 (t, *J* = 8.8 Hz, 2 H), 3.89 – 3.82 (m, 2 H), 1.60 – 1.52 (m, 2 H), 1.39 (s, 9 H); LCMS (ESI): *m/z* 497 (M + Na)<sup>+</sup>.

**Example 26 (**75**)**

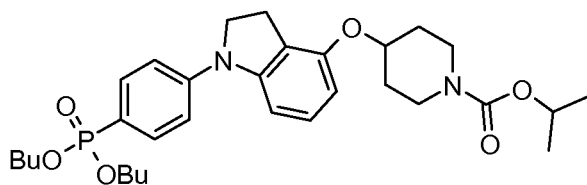


25 **1-Methylethyl 4-({1-[5-(methylsulfonyl)-2-pyrimidinyl]-2,3-dihydro-1*H*-indol-4-yl}oxy)-1-piperidinecarboxylate (**75**)**

To a mixture of **74** (30 mg, 0.063 mmol) and CH<sub>2</sub>Cl<sub>2</sub> (8 mL) was added CF<sub>3</sub>COOH (2 mL). The mixture was stirred at RT under N<sub>2</sub> for 2 h and then concentrated under reduced pressure. The crude material was redissolved in CH<sub>2</sub>Cl<sub>2</sub> (4 mL) and DIPEA (50 μL, 0.38 mmol), DMAP (8 mg, 0.006 mmol), and a 1 M solution of isopropyl

chloroformate (250  $\mu$ L, 0.252 mmol) in toluene were introduced sequentially. The mixture was stirred at RT for 15 h. Standard work-up followed by purification gave 28 mg (96%) of the title product **75** as a white solid.  $^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ ):  $\delta$  8.91 (s, 2 H), 7.97 (d,  $J$  = 8.4 Hz, 1 H), 7.20 (t,  $J$  = 8.0 Hz, 1 H), 6.78 (d,  $J$  = 8.4 Hz, 1 H), 4.76 (septuplet,  $J$  = 6.4 Hz, 1 H), 4.63 (m, 1 H), 4.25 (t,  $J$  = 8.8 Hz, 2 H), 3.65 – 3.56 (m, 2 H), 3.29 – 3.23 (m, 2 H), 3.28 (s, 3 H), 3.08 (t,  $J$  = 8.4 Hz, 2 H), 1.92 – 1.84 (m, 2 H), 1.60 – 1.52 (m, 2 H), 1.17 (d,  $J$  = 6.0 Hz, 6 H); LCMS (ESI):  $m/z$  461 (M + H) $^+$ .

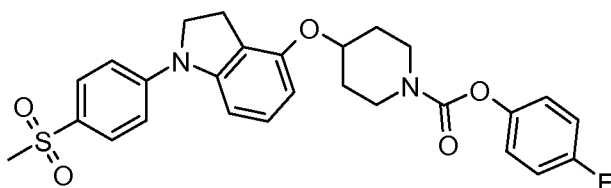
### Example 27 (**76**)



### 1-Methylethyl 4-[(1-{4-[bis(butyloxy)phosphoryl]phenyl}-2,3-dihydro-1H-indol-4-yl)oxy]-1-piperidinecarboxylate (**76**)

An oven dried 10 mL round-bottomed flask was evacuated and refilled with  $\text{N}_2$  and then charged with CuI (4 mg, 0.02 mmol) followed by anhydrous toluene (3 mL), dibutyl phosphonate (48 mg, 0.248 mmol), *N,N*-dimethylethylenediamine (4  $\mu$ L, 0.04 mmol), and compound **68** (100 mg, 0.197 mmol). The sealed tube was stirred at 110  $^\circ\text{C}$  for 24 h. The resulting suspension was cooled to RT, diluted with  $\text{H}_2\text{O}$ , and the mixture was extracted with EtOAc. The combined organic extracts were dried and then concentrated under reduced pressure. The product was purified by  $\text{SiO}_2$  flash column chromatography to afford 78 mg (69%) of the title product **76** as a white solid.  $^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ ):  $\delta$  7.61 (d,  $J$  = 8.4 Hz, 1 H), 7.58 (d,  $J$  = 8.8 Hz, 1 H), 7.30 (d,  $J$  = 3.2 Hz, 1 H), 7.27 (d,  $J$  = 3.2 Hz, 1H), 7.06 (app. t,  $J$  = 8.0 Hz, 1 H), 6.89 (d,  $J$  = 8.0 Hz, 1 H), 6.57 (d,  $J$  = 8.0 Hz, 1 H), 4.75 (m, 1 H), 4.58 (m, 1 H), 3.98 (t,  $J$  = 8.8 Hz, 2 H), 3.93 – 3.85 (m, 4 H), 3.62 – 3.57 (m, 2 H), 3.30 – 3.25 (m, 2 H), 2.99 (t,  $J$  = 8.4 Hz, 2 H), 1.89 – 1.84 (m, 2 H), 1.58 – 1.51 (m, 6 H), 1.31 (m,  $J$  = 7.6 Hz, 4 H), 1.17 (d,  $J$  = 6.0 Hz, 6 H), 0.84 (t,  $J$  = 7.6 Hz, 6 H); LCMS (ESI):  $m/z$  573 (M + H) $^+$ .

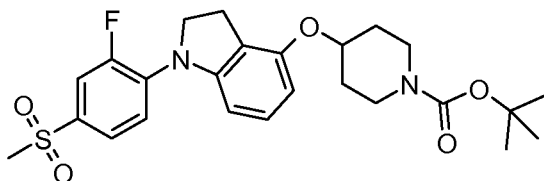
### Example 28 (**77**)



**4-Fluorophenyl 4-({1-[4-(methylsulfonyl)phenyl]-2,3-dihydro-1H-indol-4-yl}oxy)-1-piperidinecarboxylate (**77**)**

Compound **66** (42 mg, 0.089 mmol) was treated with concentrated HCl (5 mL) and was stirred at RT for 5 h. The mixture was poured into a 26% aqueous NH<sub>4</sub>OH solution (25 mL) and the mixture was extracted with EtOAc (4 x 20 mL). The combined organic layer was washed with brine (1 x 12 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and then the filtrate was concentrated under reduced pressure. The crude material was dissolved in CH<sub>2</sub>Cl<sub>2</sub> and then DIPEA (47 μL, 0.27 mmol) and 4-fluorophenyl chloroformate (88 mg, 0.45 mmol) were added sequentially. The mixture was stirred at RT for 15 h. Aqueous work-up followed by purification gave 29 mg (64%) of the title product **77** as a white solid. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>): δ 7.80 (d, *J* = 8.8 Hz, 2 H), 7.36 (d, *J* = 9.2 Hz, 2 H), 7.22 – 7.14 (m, 4 H), 7.10 (t, *J* = 8.0 Hz, 1 H), 6.94 (d, *J* = 8.0 Hz, 1 H), 6.64 (d, *J* = 8.4 Hz, 1 H), 4.68 (m, 1 H), 4.03 (t, *J* = 8.4 Hz, 2 H), 3.79 (app. br s, 1 H), 3.65 (app. br s, 1 H), 3.54 (app. br s, 1 H), 3.40 (app. br s, 1 H), 3.13 (s, 3 H), 3.05 (t, *J* = 8.4 Hz, 2 H), 1.96 (app. br s, 2 H), 1.71 (app. br s, 2 H); LCMS (ESI): *m/z* 511 (M + H)<sup>+</sup>.



**Example 29 (80)****Step 1: 1,1-Dimethylethyl 4-([1-(4-bromo-2-fluorophenyl)-1H-indol-4-yl]oxy)-1-piperidinecarboxylate (78)**

5 A round-bottomed flask was charged under N<sub>2</sub> with compound **63** (1.90 g, 6.0 mmol), CuI (171 mg, 0.9 mmol), K<sub>2</sub>CO<sub>3</sub> (1.66 g, 12 mmol), 4-bromo-2-fluoro-1-iodobenzene (3.61 g, 12 mmol) and anhydrous DMSO (20 mL). The reaction mixture was stirred at 110 °C for 60 h. The mixture was cooled to RT, diluted with EtOAc, filtered and the filtrate was concentrated under reduced pressure to afford the crude product, which was

10 purified by flash column chromatography to give 1.96 g (75%) of the title product **78** as a mixture of two products. This material was used directly in the next step without purification.

**Step 2: 1,1-Dimethylethyl 4-([1-[2-fluoro-4-(methylsulfonyl)phenyl]-1H-indol-4-yl]oxy)-1-piperidinecarboxylate (79)**

15 The procedure described for **3** (Example 1, Step 3) was employed using **78** (1.34 g, 3.08 mmol), CuI (58 mg, 0.30 mmol), L-proline (71 mg, 0.60 mmol), NaOH (24 mg, 0.60 mmol), CH<sub>3</sub>SO<sub>2</sub>Na (471 mg, 4.6 mmol), and DMSO (4 mL). Aqueous work-up followed by purification gave 630 mg (42%) of the title product **79** as a white solid. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>): δ 8.10 (app. d, *J* = 10.8 Hz, 1 H), 7.92 (m, 2 H), 7.51 (app. t, *J* = 2.0

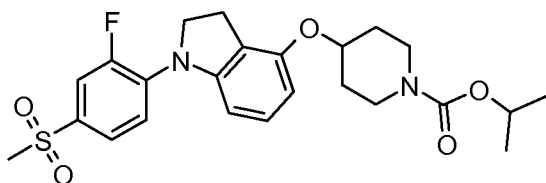
20 Hz, 1 H), 7.12 (app. t, *J* = 8.0 Hz, 1 H), 6.92 and 6.90 (dd, *J*<sub>1</sub> = 8.0 Hz, *J*<sub>2</sub> = 2.4 Hz, 1 H), 6.78 – 6.76 (m, 2 H), 4.72 (m, 1 H), 3.67 – 3.62 (m, 2 H), 3.45 (s, 3 H), 3.30 – 3.22 (m, 2 H), 1.97 – 1.91 (m, 2 H), 1.67 – 1.60 (m, 2 H), 1.40 (s, 9 H); LCMS (ESI): *m/z* 511 (M + Na)<sup>+</sup>.

**Step 3: 1,1-Dimethylethyl 4-([1-[2-fluoro-4-(methylsulfonyl)phenyl]-2,3-dihydro-1H-indol-4-yl]oxy)-1-piperidinecarboxylate (80)**

25 The procedure described for **65** (Example 21, Step 3) was followed using **79** (70 mg, 0.14 mmol), NaCNBH<sub>3</sub> (45 mg, 0.72 mmol), and acetic acid (2 mL). Aqueous work-up gave the crude mixture which was a 3:1 mixture (~ 50 mg) of product and starting material. An 18 mg portion of this mixture was again treated at RT with NaCNBH<sub>3</sub> (37

mg) in AcOH (3 mL) for 48 h. Aqueous work-up followed by purification by SiO<sub>2</sub> flash column chromatography gave 13 mg of the title product **80** as a white solid. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>): δ 7.81 and 7.78 (dd, *J*<sub>1</sub> = 11.6 Hz, *J*<sub>2</sub> = 2.4 Hz, 1 H), 7.69 and 7.67 (dd, *J*<sub>1</sub> = 8.4 Hz, *J*<sub>2</sub> = 2.0 Hz, 1 H), 7.59 (app. t, *J* = 8.4 Hz, 1 H), 7.03 (app. t, *J* = 8.4 Hz, 1 H), 6.56 (d, *J* = 8.4 Hz, 1 H), 6.37 and 6.35 (dd, *J*<sub>1</sub> = 7.6 Hz, *J*<sub>2</sub> = 4.4 Hz, 1 H), 4.60 – 4.52 (m, 1 H), 4.0 (t, *J* = 8.0 Hz, 2 H), 3.62 – 3.53 (m, 2 H), 3.22 (s, 3 H), 3.29 – 3.19 (m, 2 H), 3.02 (t, *J* = 8.4 Hz, 3 H), 1.89 – 1.84 (m, 2 H), 1.56 – 1.50 (m, 2 H), 1.51 (s, 9 H); LCMS (ESI): *m/z* 513 (M + Na)<sup>+</sup>.

10 **Example 30 (82)**



**Step 1: 1-Methylethyl 4-({1-[2-fluoro-4-(methylsulfonyl)phenyl]-1H-indol-4-yl}oxy)-1-piperidinecarboxylate (81)**

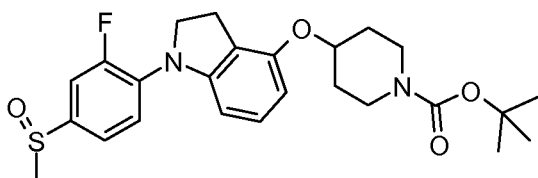
To a solution of **79** (200 mg, 0.409 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (20 mL) at RT under N<sub>2</sub> was added CF<sub>3</sub>COOH (5 mL) and resulting reaction mixture was stirred for 2 h. The mixture was concentrated under reduced pressure and dried. The crude material was redissolved in CH<sub>2</sub>Cl<sub>2</sub> and cooled to 5 °C. To the above mixture DIPEA (213 μL, 1.22 mmol) and a 1 M solution of isopropyl chloroformate (~1 mL) in toluene were added. The mixture was allowed to stir at RT for 1h. Standard work-up followed by purification gave 155 mg (80%) of the title product **81** as white solid. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>): δ 8.10 (app. d, *J* = 10.8 Hz, 1 H), 7.93 – 7.92 (m, 2 H), 7.51 (t, *J* = 2.0 Hz, 1 H), 7.12 (t, *J* = 8.0 Hz, 1 H), 6.93 and 6.91 (dd, *J*<sub>1</sub> = 8.4 Hz, *J*<sub>2</sub> = 2.4 Hz, 1 H), 6.78 – 6.76 (m, 2 H), 4.80 – 4.70 (m, 2 H), 3.70 – 3.65 (m, 2 H), 3.35 (s, 3 H), 3.32 – 3.29 (br m, 2 H), 1.97 – 1.92 (m, 2 H), 1.69 – 1.61 (m, 2 H), 1.18 (d, *J* = 6.0 Hz, 2 H); LCMS (ESI): *m/z* 475 (M + H)<sup>+</sup>.

25 **Step 2: 1-Methylethyl 4-({1-[2-fluoro-4-(methylsulfonyl)phenyl]-2,3-dihydro-1H-indol-4-yl}oxy)-1-piperidinecarboxylate (82)**

The procedure described for **65** (Example 21, Step 3) was followed using **81** (110 mg, 0.23 mmol), NaCNBH<sub>3</sub> (300 mg, 4.8 mmol), and AcOH (12 mL). The mixture was stirred for 60 h. Aqueous work gave a 3:1 mixture (~110 mg) of product and starting material

favoring the desired product. A 110 mg sample of the mixture obtained above, was treated again with NaCNBH<sub>3</sub> (291 mg, 4.6 mmol) in CF<sub>3</sub>CO<sub>2</sub>H (10 mL) at RT for 15 h. Aqueous work-up followed by purification gave 43 mg (39%) of the title product **82** as a white solid. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>): δ 7.81 and 7.78 (dd, *J*<sub>1</sub> = 11.6 Hz, *J*<sub>2</sub> = 2.0 Hz, 1 H), 7.69 and 7.67 (dd, *J*<sub>1</sub> = 8.4 Hz, *J*<sub>2</sub> = 2.0 Hz, 1 H), 7.59 (app. t, *J* = 8.4 Hz, 1 H), 7.03 (t, *J* = 8.0 Hz, 1 H), 6.56 (d, *J* = 8.4 Hz, 2 H), 6.37 – 6.35 (dd, *J*<sub>1</sub> = 7.6 Hz, *J*<sub>2</sub> = 4.4 Hz, 1 H), 4.76 (septuplet, *J* = 6.4 Hz, 1 H), 4.58 (m, 1 H), 4.0 (t, *J* = 8.4 Hz, 1 H), 3.68 – 3.57 (m, 2 H), 3.30 – 3.21 (m, 2 H), 3.22 (s, 3 H), 3.02 (t, *J* = 8.8 Hz, 2 H), 1.92 – 1.82 (m, 2 H), 1.61 – 1.52 (m, 2 H), 1.17 (d, *J* = 6.4 Hz, 6 H); LCMS (ESI): *m/z* 477 (M + H)<sup>+</sup>.

10

**Example 31 (85)****Step 1: 1,1-Dimethylethyl 4-({1-[4-(methylthio)phenyl]-1H-indol-4-yl}oxy)-1-piperidinecarboxylate (83)**

The N-arylation procedure described for **64** (Example 21, Step 2) was followed using compound **63** (3.40 g, 10.8 mmol), CuI (204 mg, 1.1 mmol), K<sub>3</sub>PO<sub>4</sub> (3.42 g, 16.1 mmol), 1-iodo-4-(methylthio)benzene (4.03 g, 16.1 mmol), trans- *N,N'*-dimethyl-1,2-cyclohexanediamine (323 μL, 2.7 mmol), and anhydrous 1,4-dioxane (25 mL). The reaction mixture was stirred at 110 °C for 48 h. Work-up followed by purification gave 2.56 g (54%) of a title product **83** as an off-white solid. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>): δ 7.50 – 7.47 (m, 3 H), 7.43 – 7.41 (m, 2 H), 7.09 – 7.07 (m, 2 H), 6.71 and 6.69 (dd, *J*<sub>1</sub> = 6.0 Hz, *J*<sub>2</sub> = 2.4 Hz, 1 H), 6.67 (d, *J* = 3.2 Hz, 1 H), 4.70 (m, 1 H), 3.67 – 3.61 (m, 2 H), 3.28 – 3.24 (m, 2 H), 2.52 (s, 3 H), 1.95 – 1.90 (m, 2 H), 1.66 – 1.58 (m, 2 H), 1.39 (s, 9 H); LCMS (ESI): *m/z* 439 (M + H)<sup>+</sup>.

**Step 2: 1,1-Dimethylethyl 4-({1-[4-(methylthio)phenyl]-2,3-dihydro-1H-indol-4-yl}oxy)-1-piperidinecarboxylate (84)**

The reduction procedure described for **65** (Example 21, Step 3) was employed using compound **83** (600 mg, 1.37 mmol), NaCNBH<sub>3</sub> (515 mg, 8.20 mmol), and acetic acid (10 mL). The aqueous work-up followed by purification by column chromatography afforded

25

528 mg (88%) of the title product **84** as a white solid. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>): δ 7.26 (t, *J* = 8.8 Hz, 2 H), 7.15 (d, *J* = 8.8 Hz, 2 H), 6.98 (app. t, *J* = 8.0 Hz, 1 H), 6.65 (d, *J* = 7.6 Hz, 1 H), 6.45 (d, *J* = 8.0 Hz, 1 H), 4.53 (septuplet, *J* = 3.2 Hz, 1 H), 3.88 (t, *J* = 8.4 Hz, 2 H), 3.60 – 3.54 (m, 2 H), 3.24 – 3.20 (m, 2 H), 2.95 (t, *J* = 8.8 Hz, 2 H), 2.42 (s, 3 H), 1.87 – 1.82 (m, 2 H), 1.57 – 1.49 (m, 2 H), 1.38 (s, 9 H); LCMS (ESI): *m/z* 441 (M + H)<sup>+</sup>.

**Step 3: (±)-1,1-Dimethylethyl 4-({1-[4-(methylsulfinyl)phenyl]-2,3-dihydro-1*H*-indol-4-yl}oxy)-1-piperidinecarboxylate (**85**)**

To a solution of **84** (200 mg, 0.454 mmol) and hexafluoroisopropanol (2.5 mL) was added 30% aqueous H<sub>2</sub>O<sub>2</sub> (100 μL). The mixture was stirred at RT for 0.5 h. A saturated sodium sulfide solution (8 mL) was introduced to the above mixture and stirred for 5 min. Layers were separated and the organic layer was subjected to column chromatography (0 → 20% ethyl acetate/hexanes) to afford 178 mg (86%) of the title product **85** as an off-white solid. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>): δ 7.61 (t, *J* = 8.8 Hz, 2 H), 7.34 (d, *J* = 8.8 Hz, 2 H), 7.04 (app. t, *J* = 8.0 Hz, 1 H), 6.83 (d, *J* = 8.0 Hz, 1 H), 6.54 (d, *J* = 8.4 Hz, 1 H), 4.56 (septuplet, *J* = 3.2 Hz, 1 H), 3.98 (t, *J* = 8.8 Hz, 2 H), 3.60 – 3.55 (m, 2 H), 3.25 – 3.22 (m, 2 H), 2.99 (t, *J* = 8.4 Hz, 2 H), 2.69 (s, 3 H), 1.88 – 1.83 (m, 2 H), 1.58 – 1.49 (m, 2 H), 1.39 (s, 9 H); LCMS (ESI): *m/z* 457 (M + H)<sup>+</sup>.

**Example 32**

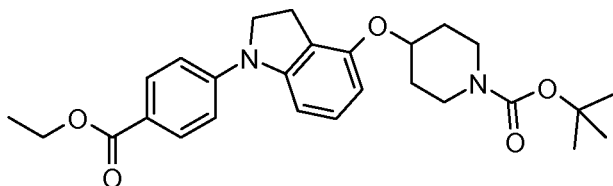
The racemic sulfoxide **85** (150 mg) was subjected to Chiral HPLC [column: Chiralpak AS (analytical), Chiralpak (prep.), mobile phase: 78% CO<sub>2</sub>: 22% MeOH (14 mL/min), pressure 140 bar, temperature 40 °C, 240 nm] analysis and then was separated into its two (*R* and *S*) enantiomers. The absolute stereochemistry was not assigned.

**Example 32A: (**86**)**

Tr (retention time) was 11.57 min, 33 mg (% ee >98%), and the spectral data are essentially the same to that of **Example 31 (**85**)**.

**Example 32B: (87)**

Tr was 14.04 min, 38 mg (% ee >97%), and the spectral data are essentially the same to that of Example 31 (85).

**5 Example 33 (89)****Step 1: 1,1-Dimethylethyl 4-[(1-{4-[(ethyloxy)carbonyl]phenyl}-1H-indol-4-yl)oxy]-1-piperidinecarboxylate (88)**

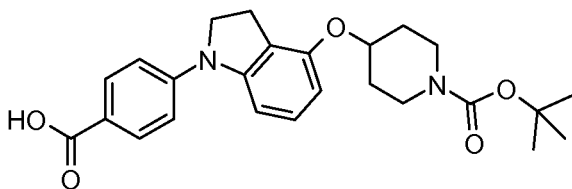
A mixture of 1,1-dimethylethyl 4-(1H-indol-4-yloxy)-1-piperidinecarboxylate (63) (1.00 g, 3.16 mmol), ethyl 4-fluorobenzoate (3.00 g, 17.84 mmol) 18-crown-6 (0.33 g, 1.23 mmol), KF/Al<sub>2</sub>O<sub>3</sub> (2.86 g, 19.69 mmol) and DMSO (30 mL) was heated at 130 °C for 7 h in a Biotage Initiator microwave apparatus. The reaction was diluted with 150 mL each water and EtOAc. The EtOAc fraction was washed with water (150 mL) and brine (150 mL), dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated to give an yellow oil. The crude product was purified by column chromatography on silica gel with 15% EtOAc/hexanes to afford 560 mg (38%) of compound 88 as white foam. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>): δ 1.33 (t, *J* = 7.1 Hz, 3 H), 1.39 (s, 9 H), 1.60 – 1.66 (m, 2 H), 1.91 – 1.95 (m, 2 H), 3.27 – 3.31 (m, 2 H), 3.62 - 3.66 (m, 2 H), 4.35 (q, *J* = 7.1 Hz, 2 H), 4.70 – 4.72 (m, 1 H), 6.75 (s, 1 H), 6.77 (d, *J* = 5.2 Hz, 1 H), 7.13 (t, *J* = 8.0 Hz, 1 H), 7.25 (d, *J* = 8.4 Hz, 1 H), 7.62 (d, *J* = 3.3 Hz, 1 H), 7.73 (d, *J* = 8.5 Hz, 2 H), 8.11 (d, *J* = 8.5 Hz, 2 H); LCMS (ESI): *m/z* 487 (M + Na)<sup>+</sup>.

**Step 2: 1,1-Dimethylethyl 4-[(1-{4-[(ethyloxy)carbonyl]phenyl}-2,3-dihydro-1H-indol-4-yl)oxy]-1-piperidinecarboxylate (89)**

To a stirring solution of compound 88 (0.11 g, 0.24 mmol) in glacial AcOH (3 mL) was added, in a single portion, NaCNBH<sub>3</sub> (0.15 g, 2.40 mmol). Gas evolution was observed over ~ 5 min and the reaction turned from light yellow to colorless. After 22 h the reaction was diluted with 50 mL each saturated aqueous NaHCO<sub>3</sub> and EtOAc. The EtOAc layer was rinsed with saturated aqueous NaHCO<sub>3</sub> (50 mL) and brine (50 mL) dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated to a pale yellow oil. The crude product was purified by

column chromatography on silica gel with 10% EtOAc/hexanes to afford the 84 mg (75%) of the title compound **89** as colorless oil. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>): δ 1.28 (t, *J* = 7.1 Hz, 3 H), 1.39 (s, 9 H), 1.51 – 1.57 (m, 2 H), 1.82 - 1.88 (m, 2 H), 3.00 (t, *J* = 8.5 Hz, 2 H), 3.21 – 3.26 (m, 2 H), 3.54 – 3.60 (m, 2 H), 3.99 (t, *J* = 8.5 Hz, 2 H), 4.25 (q, *J* = 7.1 Hz, 2 H), 4.55 – 4.59 (m, 1 H), 6.58 (d, *J* = 8.3 Hz, 1 H), 6.91 (d, *J* = 8.0 Hz, 1 H), 7.06 (t, *J* = 8.1 Hz, 1 H), 7.25 (d, *J* = 8.9 Hz, 2 H), 7.88 (d, *J* = 8.8 Hz, 2 H); LCMS (ESI): *m/z* 467 (M + H)<sup>+</sup>, *m/z* 489 (M + Na)<sup>+</sup>.

#### Example 34 (**90**)



10

#### 4-{4-[(1-[(1,1-Dimethylethyl)oxy]carbonyl]-4-piperidinyl)oxy]-2,3-dihydro-1H-indol-1-yl}benzoic acid (**90**)

To a stirring solution of compound **88** (84 mg, 0.18 mmol) in 10 mL 1:1 v/v THF / EtOH was added 2.8 mL 1 N aq. NaOH and the colorless solution was heated at reflux. After 4 h the reaction was poured onto 30 mL 1 N aqueous HCl (30 mL) followed by EtOAc (50 mL). The EtOAc layer was washed with brine (30 mL), dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated to a white solid. The solid was triturated with 25 mL hexanes (25 mL), filtered and air-dried to yield 73 mg (93%) of the title compound **90** as a white solid. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>): δ 1.39 (s, 9 H), 1.50 – 1.58 (m, 2 H), 1.83 – 1.88 (m, 2 H), 3.00 (t, *J* = 8.4 Hz, 2 H), 3.21 – 3.25 (m, 2 H), 3.55 – 3.60 (m, 2 H), 3.99 (t, *J* = 8.4 Hz, 2 H), 4.55 – 4.58 (m, 1 H), 6.56 (d, *J* = 8.2 Hz, 1 H), 6.90 (d, *J* = 8.0 Hz, 1 H), 7.06 (t, *J* = 8.2 Hz, 1 H), 7.23 (d, *J* = 8.9 Hz, 2 H), 7.87 (d, *J* = 8.8 Hz, 2 H), 12.46 (br s, 1 H); LCMS (APCI): *m/z* 439 (M + H)<sup>+</sup>, *m/z* 437 (M – H)<sup>-</sup>.

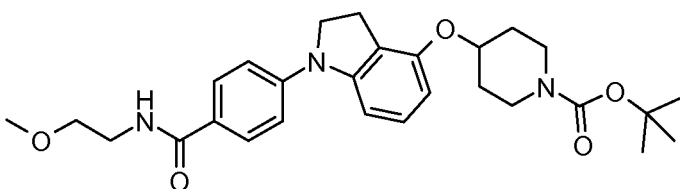
20

As illustrated herein, a general procedure for amide formation is applicable for compounds of the present invention. The following provides a synthetic description applicable to the examples that follow. The specific examples provide appropriate characterizing data.

25

To a solution of 4-{4-[(1-[(1,1-dimethylethyl)oxy]carbonyl]-4-piperidinyl)oxy]-2,3-dihydro-1*H*-indol-1-yl}benzoic acid (**90**, 75 mg, 0.17 mmol) and DIEA (78 mg, 0.60 mmol) in DMF (2 mL) was added a primary or secondary amine (0.60 mmol), the selection of which will be apparent to a person of ordinary skill in the art upon review of the examples, followed by a solution of HATU (91 mg, 0.24 mmol) in DMF (0.5 mL). The resulting solution was stirred at RT overnight. After 48 h the reaction was diluted with 30 mL each EtOAc and 1 N aqueous HCl. The EtOAc layer was washed with saturated aqueous NaHCO<sub>3</sub> (25 mL) and brine (25 mL), dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated to a crude product which was subsequently triturated with a few mL EtOAc.

10 **Example 35 (91)**

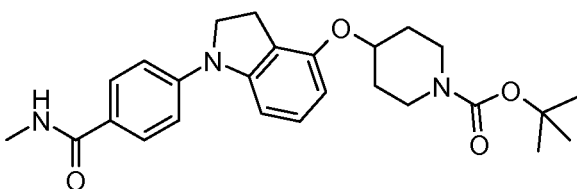


**1,1-Dimethylethyl 4-({1-[4-({[2-(methoxy)ethyl]amino}carbonyl)phenyl]-2,3-dihydro-1*H*-indol-4-yl}oxy)-1-piperidinecarboxylate (91)**

Trituration with EtOAc yielded a white solid that was further purified by column

15 chromatography on silica gel with 50% EtOAc / hexane. The title compound, **91**, was isolated as a white solid (15 mg, 25%). <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>): δ 1.38 (s, 9 H), 1.50 – 1.58 (m, 2 H), 1.64 (quintuplet, *J* = 6.7 Hz, 2 H), 1.83 – 1.88 (m, 2 H), 2.98 (t, *J* = 8.2 Hz, 2 H), 3.21 – 3.25 (m, 2 H), 3.24 (s, 3 H), 3.26 – 3.45 (m, 4 H), 3.55 – 3.58 (m, 2 H), 3.96 (t, *J* = 8.4 Hz, 2 H), 4.54 – 4.57 (m, 1 H), 6.53 (d, *J* = 8.4 Hz, 1 H), 6.84 (d, *J* = 8.1 Hz, 1 H), 7.03 (t, *J* = 8.1 Hz, 1 H), 7.20 (d, *J* = 8.8 Hz, 2 H), 7.83 (d, *J* = 8.8 Hz, 2 H), 8.33 (t, *J* = 4.8 Hz, 1 H); LCMS (ESI): *m/z* 496 (M + H)<sup>+</sup>, *m/z* 518 (M + Na)<sup>+</sup>.

**Example 36 (92)**

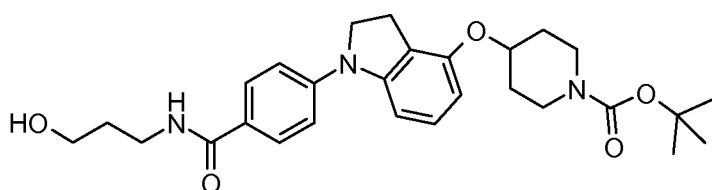


25 **1,1-Dimethylethyl 4-[(1-[4-[(methylamino)carbonyl]phenyl]-2,3-dihydro-1*H*-indol-4-yl}oxy)-1-piperidinecarboxylate (92)**

Trituration with EtOAc yielded 35 mg (46%) of the title compound, **92**, as a white solid.

<sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>): δ 1.39 (s, 9 H), 1.50 – 1.58 (m, 2 H), 1.83 – 1.88 (m, 2 H), 2.75 (d, *J* = 4.6 Hz, 3 H), 2.99 (t, *J* = 8.4 Hz, 2 H), 3.23 – 3.31 (m, 2 H), 3.56 – 3.60 (m, 2 H), 3.97 (t, *J* = 8.3 Hz, 2 H), 4.54 – 4.57 (m, 1 H), 6.53 (d, *J* = 8.2 Hz, 1 H), 6.84 (d, *J* = 8.1 Hz, 1 H), 7.04 (t, *J* = 8.2 Hz, 1 H), 7.21 (d, *J* = 8.8 Hz, 2 H), 7.80 (d, *J* = 8.7 Hz, 2 H), 8.24 (br q, *J* = 4.5 Hz, 1 H); LCMS (ESI): *m/z* 452 (M + H)<sup>+</sup>, *m/z* 474 (M + Na)<sup>+</sup>.

### Example 37 (**93**)

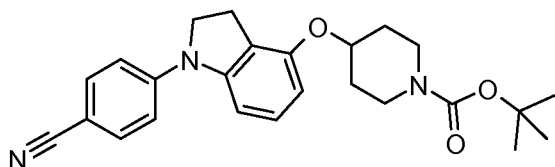


### 10 **1,1-Dimethylethyl 4-[[1-(4-[[[(3-hydroxypropyl)amino]carbonyl]phenyl)-2,3-dihydro-1H-indol-4-yl]oxy]-1-piperidinecarboxylate (**93**)**

Trituration with EtOAc yielded 32 mg (38%) of the title compound, **93**, as a pale yellow

solid. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>): δ 1.38 (s, 9 H), 1.52 – 1.58 (m, 2 H), 1.64 (quintuplet, *J* = 6.7 Hz, 2 H), 1.83 – 1.87 (m, 2 H), 2.98 (t, *J* = 8.4 Hz, 2 H), 2.99 (t, *J* = 8.4 Hz, 2 H), 3.23 – 3.30 (m, 2 H), 3.27 (m, 2 H), 3.43 (t, *J* = 6.2 Hz, 2 H), 3.55 – 3.58 (m, 2 H), 3.96 (t, *J* = 8.6 Hz, 2 H), 4.46 (t, *J* = 5.1 Hz, 2 H), 4.54 – 4.57 (m, 1 H), 6.52 (d, *J* = 8.5 Hz, 1 H), 6.83 (d, *J* = 7.9 Hz, 1 H), 7.03 (t, *J* = 8.2 Hz, 1 H), 7.20 (d, *J* = 8.8 Hz, 2 H), 7.80 (d, *J* = 8.7 Hz, 2 H), 8.25 (t, *J* = 4.5 Hz, 1 H); LCMS (ESI): *m/z* 496 (M + H)<sup>+</sup>, *m/z* 518 (M + Na)<sup>+</sup>.



**Example 38 (95)****Step 1: 1,1-Dimethylethyl 4-([1-(4-cyanophenyl)-1H-indol-4-yl]oxy)-1-piperidinecarboxylate (94)**

5 A mixture of 1,1-dimethylethyl 4-(1H-indol-4-yloxy)-1-piperidinecarboxylate (**63**, 1.00 g, 3.16 mmol), 4-fluorobenzonitrile (1.72 g, 14.14 mmol), 18-crown-6 (0.32 g, 1.34 mmol), KF/Al<sub>2</sub>O<sub>3</sub> (2.86 g, 19.70 mmol) and DMSO (25 mL) was heated at 130 °C in a Biotage Initiator microwave for 7 h. The reaction was diluted with 150 mL each of water and EtOAc. Brine (100 mL) was added to disperse an emulsion and the EtOAc fraction was

10 washed with water (1 x 150 mL) and brine (1 x 150 mL), dried (Na<sub>2</sub>SO<sub>4</sub>), and concentrated to pale yellow, viscous oil. The crude material was purified by column chromatography on silica gel with a gradient of 10 → 20% EtOAc/hexanes. The product was isolated as a white solid (1.14 g) contaminated with ~ 20% of the starting indole **63**. The white solid was recrystallized from 220 mL of EtOAc: hexanes (10:1 v/v) to yield 720

15 mg (55%) of the title compound **94** as a white crystalline solid. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>): δ 1.39 (s, 9 H), 1.61 – 1.67 (m, 2 H), 1.90 – 1.95 (m, 2 H), 3.24 – 3.29 (m, 2 H), 3.60 – 3.66 (m, 2 H), 4.69 – 4.74 (m, 1 H), 6.76 (s, 1 H), 6.77 (d, *J* = 4.9 Hz, 1 H), 7.14 (t, *J* = 8.1 Hz, 1 H), 7.25 (d, *J* = 8.3 Hz, 1 H), 7.65 (d, *J* = 3.4 Hz, 1 H), 7.80 (d, *J* = 8.5 Hz, 2 H), 8.01 (d, *J* = 8.7 Hz, 2 H); LCMS (ESI): *m/z* 440 (M + Na)<sup>+</sup>.

**Step 2: 1,1-Dimethylethyl 4-([1-(4-cyanophenyl)-2,3-dihydro-1H-indol-4-yl]oxy)-1-piperidinecarboxylate (95)**

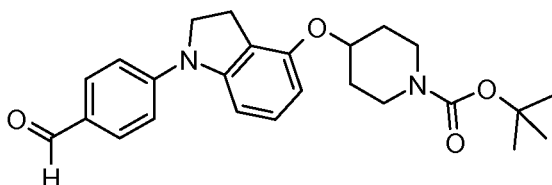
To a stirring solution of 1,1-dimethylethyl 4-([1-(4-cyanophenyl)-1H-indol-4-yl]oxy)-1-piperidinecarboxylate (**94**, 0.59 g, 1.41 mmol) and glacial AcOH (20 mL) was added, as a single portion, NaCNBH<sub>3</sub> (2.67 g, 42.45 mmol). Gas evolution was observed over 5

25 min and the reaction turned from colorless to light yellow. After 72 h the reaction was carefully poured onto 150 mL each saturated aqueous NaHCO<sub>3</sub> and EtOAc. The EtOAc layer was washed with brine (150 mL), dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated to reddish oil. The crude product was purified by column chromatography on silica gel with 15% EtOAc/hexane to yield 430 mg (73%) of compound **95** as a white solid. <sup>1</sup>H NMR (400

MHz, DMSO- $d_6$ ):  $\delta$  1.38 (s, 9 H), 1.50 – 1.58 (m, 2 H), 1.83 – 1.88 (m, 2 H), 3.00 (t,  $J$  = 8.4 Hz, 2 H), 3.21 – 3.25 (m, 2 H), 3.54 – 3.60 (m, 2 H), 3.99 (t,  $J$  = 8.4 Hz, 2 H), 4.56 – 4.60 (m, 1 H), 6.61 (d,  $J$  = 8.2 Hz, 1 H), 6.91 (d,  $J$  = 7.9 Hz, 1 H), 7.08 (t,  $J$  = 8.1 Hz, 1 H), 7.25 (d,  $J$  = 8.7 Hz, 2 H), 7.70 (d,  $J$  = 8.7 Hz, 2 H); LCMS (ESI):  $m/z$  442 (M + Na)<sup>+</sup>.

5

**Example 39 (96)**

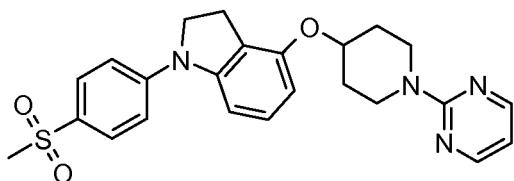


**1,1-Dimethylethyl 4-[[1-(4-formylphenyl)-2,3-dihydro-1H-indol-4-yl]oxy]-1-piperidinecarboxylate (96)**

10 A stirring solution of 1,1-dimethylethyl 4-[[1-(4-cyanophenyl)-2,3-dihydro-1H-indol-4-yl]oxy]-1-piperidinecarboxylate (**95**, 0.41 g, 0.98 mmol) in anhydrous toluene (15 mL) was chilled to  $-78$  °C, and DIBAL-H (1.5 M in toluene) added *via* syringe. The reaction was allowed to slowly warm to 0 °C. After 3 h the clear yellow reaction was quenched by

15 addition of MeOH (3 mL) followed by 1N HCl (10 mL) then stirred for 2 h while slowly warming from 0 °C to room temperature. The reaction was diluted with EtOAc (100 mL) and the organic fraction washed with brine (2 x 50 mL), dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated to viscous yellow oil. The crude product was chromatographed on silica gel with 15% EtOAc/hexane to yield 320 mg (78%) of the title compound **96** as a yellow solid. <sup>1</sup>H

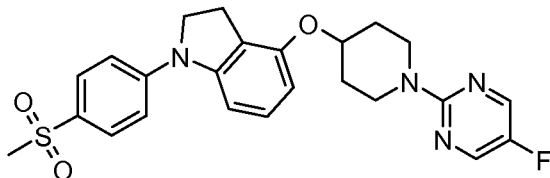
20 NMR (400 MHz, DMSO- $d_6$ ):  $\delta$  1.39 (s, 9 H), 1.51 – 1.59 (m, 2 H), 1.84 – 1.89 (m, 2 H), 3.02 (t,  $J$  = 8.4 Hz, 2 H), 3.21 – 3.28 (m, 2 H), 3.55 – 3.61 (m, 2 H), 4.04 (t,  $J$  = 8.4 Hz, 2 H), 4.56 – 4.63 (m, 1 H), 6.62 (d,  $J$  = 8.2 Hz, 1 H), 6.97 (d,  $J$  = 8.0 Hz, 1 H), 7.09 (t,  $J$  = 8.1 Hz, 1 H), 7.32 (d,  $J$  = 8.8 Hz, 2 H), 7.82 (d,  $J$  = 8.8 Hz, 2 H), 9.79 (s, 1 H); LCMS (ESI):  $m/z$  445 (M + Na)<sup>+</sup>.

**Example 40 (98)****Step 1: 1-[4-(Methylsulfonyl)phenyl]-4-(4-piperidinyloxy)-2,3-dihydro-1H-indole hydrochloride (97)**

5 Compound **66** (3.2 g, 6.7 mmol, prepared as a separate batch using the procedure hereinabove of **Steps 1-4** of **Example 21**) was dissolved in 25 mL of a 4 N solution of HCl in Dioxane. The resulting solution was then stirred at ambient temperature for 2 h. The solvent was then removed under reduced pressure and the material was dried on the high vacuum to give 2.6 g of the HCl salt **97** that was used without purification.

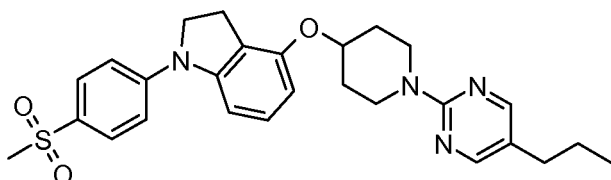
**Step 2: 1-[2-Fluoro-4-(methylsulfonyl)phenyl]-4-[[1-(2-pyrimidinyl)-4-piperidinyloxy]-2,3-dihydro-1H-indole (98)**

15 Compound **97** (50 mg, 0.12 mmol) was dissolved in 5 mL methylene chloride and treated with 2 mL of DIPEA followed by 2-chloropyrimidine (100 mg, 0.88 mmol). The reaction was then heated at 40 °C for 48 h while stirring. The reaction was cooled to room temperature and all the solvents were removed under reduced pressure. The crude reaction was then purified *via* reverse phase chromatography (C18, 10-100% CH<sub>3</sub>CN/H<sub>2</sub>O/0.05% TFA) to give 26 mg of the desired product **98** as a white solid (48%).  
 20 <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 1.78 – 1.94 (m, 2 H), 1.94 – 2.04 (m, 2 H), 3.02 (s, 3 H), 3.15 (t, *J* = 8.0 Hz, 2 H), 3.70 – 3.88 (m, 2 H), 3.95 – 4.19 (m, 4 H), 4.54 – 4.74 (m, 1 H), 6.42 – 6.59 (m, 2 H), 6.90 (d, *J* = 8.0 Hz, 1 H), 7.15 (t, *J* = 8.0 Hz, 1 H), 7.25 (d, *J* = 9.0 Hz, 2 H), 7.82 (d, *J* = 9.0 Hz, 2 H), 8.30 (d, *J* = 4.0 Hz, 2 H); LCMS (ESI): *m/z* 451 (M + H)<sup>+</sup>.

**Example 41 (99)****4-[[1-(5-Fluoro-2-pyrimidinyl)-4-piperidinyl]oxy]-1-[4-(methylsulfonyl)phenyl]-2,3-dihydro-1H-indole (99)**

5 Compound **97** (50 mg, 0.12 mmol) was dissolved in 5 mL methylene chloride and treated with 2 mL of DIPEA followed by 2-chloro-5-fluoropyrimidine (100 mg, 0.76 mmol). The reaction was then heated at 40 °C for 48 h while stirring. The reaction was cooled to room temperature and all the solvents were removed under reduced pressure. The crude reaction was then purified *via* reverse phase chromatography (C18, 10-100%  
 10 CH<sub>3</sub>CN/H<sub>2</sub>O/0.05% TFA) to give 35 mg (61%) of the title product **99** as a white solid. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 1.77 – 1.93 (m, 2 H), 1.94 – 2.07 (m, 2 H), 3.01 (s, 3 H), 3.15 (t, *J* = 8.0 Hz, 2 H), 3.65 – 3.83 (m, 2 H), 3.95 – 4.19 (m, 4 H), 4.54 – 4.74 (m, 1 H), 6.50 (d, *J* = 8.0 Hz, 2 H), 6.90 (d, *J* = 8.0 Hz, 1 H), 7.11 (t, *J* = 8.0 Hz, 1 H), 7.25 (d, *J* = 9.0 Hz, 2 H), 7.82 (d, *J* = 9.0 Hz, 2 H), 8.16 (s, 2 H); LCMS (ESI): *m/z* 469 (M + H)<sup>+</sup>.

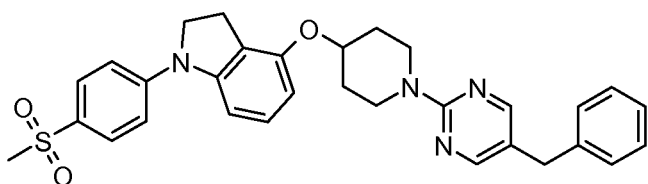
15

**Example 42 (100)****1-[4-(Methylsulfonyl)phenyl]-4-[[1-(5-propyl-2-pyrimidinyl)-4-piperidinyl]oxy]-2,3-dihydro-1H-indole (100)**

20 Compound **97** (50 mg, 0.12 mmol) was dissolved in 5 mL methylene chloride and treated with 5 mL of DIPEA followed by 2-chloro-5-propylpyrimidine (100 mg, 0.64 mmol). The reaction was then heated at 40 °C for 48 h while stirring. The reaction was cooled to room temperature and all the solvents were removed under reduced pressure. The crude reaction was then purified *via* reverse phase chromatography (C18, 10-100%  
 25 CH<sub>3</sub>CN/H<sub>2</sub>O/0.05% TFA) to give 9 mg (15%) of the title product **100** as a white solid. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 0.87 – 1.01 (t, *J* = 7.0 Hz, 3 H), 1.43 – 1.55 (m, 2 H), 1.86 –

1.94 (m, 2 H), 1.98 – 2.14 (m, 2 H), 2.38 – 2.51 (t,  $J = 7.0$  Hz, 2 H), 3.13 (s, 3 H), 3.18 (t,  $J = 8.0$  Hz, 2 H), 3.70 – 3.88 (m, 2 H), 3.98 – 4.10 (m, 4 H), 4.61 – 4.69 (m, 1 H), 6.50 (d,  $J = 8.0$  Hz, 1 H), 6.91 (d,  $J = 9.0$  Hz, 1 H), 7.10 (t,  $J = 8.0$  Hz, 1 H), 7.29 (d,  $J = 9.0$  Hz, 2 H), 7.82 (d,  $J = 9.0$  Hz, 2 H), 8.20 (s, 2 H); LCMS (ESI):  $m/z$  493 (M + H)<sup>+</sup>.

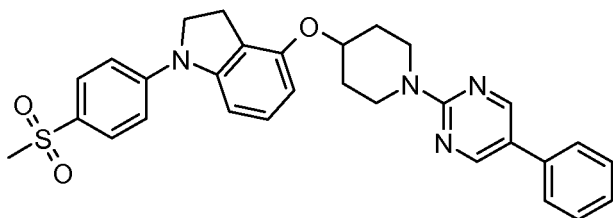
5

**Example 43 (101)****1-[4-(Methylsulfonyl)phenyl]-4-({1-[5-(phenylmethyl)-2-pyrimidinyl]-4-piperidinyl}oxy)-2,3-dihydro-1H-indole (101)**

10 Compound **97** (50 mg, 0.12 mmol) was dissolved in 2 mL methylene chloride and treated with 2 mL of DIPEA followed by 2-chloro-5-(phenylmethyl)pyrimidine (100 mg, 0.49 mmol). The reaction was then heated at 50 °C for 48 h while stirring. The reaction was cooled to room temperature and all the solvents were removed under reduced pressure. The crude reaction was then purified *via* column chromatography (5 → 50%

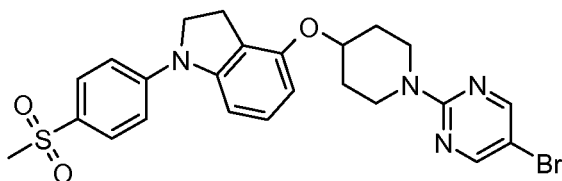
15 ethyl acetate/hexane) to give 10 mg (15%) of the title product **101** as a white solid (15%). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 1.88 – 1.93 (m, 2 H), 1.97 – 2.12 (m, 2 H), 3.07 (s, 3 H), 3.18 (t,  $J = 8.0$  Hz, 2 H), 3.67 – 3.83 (m, 4 H), 3.96 – 4.10 (m, 4 H), 4.50 – 4.69 (m, 1 H), 6.51 (d,  $J = 8.0$  Hz, 1 H), 6.91 (d,  $J = 8.0$  Hz, 1 H), 7.06 – 7.35 (m, 8 H), 7.83 (d,  $J = 9.0$  Hz, 2 H), 8.19 (s, 2 H); LCMS (ESI):  $m/z$  541 (M + H)<sup>+</sup>.

20

**Example 44 (102)****1-[4-(Methylsulfonyl)phenyl]-4-[[1-(5-phenyl-2-pyrimidinyl)-4-piperidinyl]oxy]-2,3-dihydro-1H-indole (102)**

Compound **97** (50 mg, 0.12 mmol) was dissolved in 2 mL methylene chloride and treated with 2 mL of DIPEA followed by 2-chloro-5-phenylpyrimidine (100 mg, 0.53 mmol). The reaction was then heated at 50 °C for 48 h while stirring. The reaction was cooled to room temperature and all the solvents were removed under reduced pressure.

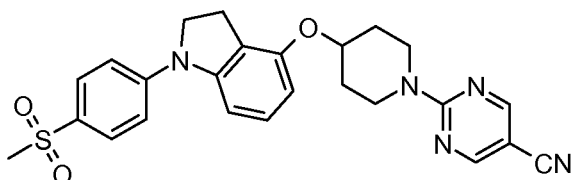
- 5 The crude reaction was then purified *via* column chromatography (5 → 50% ethyl acetate/hexane) to give 30 mg (45%) of the title product **102** as a white solid. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>): δ 1.79 – 1.92 (m, 2 H), 1.92 – 2.03 (m, 2 H), 3.05 (s, 3 H), 3.18 (t, *J* = 8.0 Hz, 2 H), 3.72 – 3.87 (m, 2 H), 3.96 – 4.10 (m, 4 H), 4.50 – 4.69 (m, 1 H), 6.51 (d, *J* = 8.0 Hz, 1 H), 6.91 (d, *J* = 8.0 Hz, 1 H), 7.06 – 7.35 (m, 8 H), 7.83 (d, *J* = 9.0 Hz, 2 H),  
10 8.19 (s, 2 H); LCMS (ESI): *m/z* 527 (M + H)<sup>+</sup>.

**Example 45 (103)****4-[[1-(5-Bromo-2-pyrimidinyl)-4-piperidinyloxy]-1-[4-(methylsulfonyl)phenyl]-2,3-dihydro-1H-indole (103)**

5 Compound **97** (500 mg, 1.23 mmol) was dissolved in 10 mL CH<sub>3</sub>CN and treated with DIPEA (655  $\mu$ L, 3.69 mmol) followed by 5-bromo-2-chloropyrimidine (260 mg, 1.35 mmol). The reaction was then heated at 80 °C for 48 h while stirring. The reaction was cooled to room temperature and treated with 2 mL MeOH. A white solid formed which was removed *via* filtration and dried on filter plate overnight to give 627 mg (96%) of the

10 title product **103** as a white solid. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>):  $\delta$  1.57 – 1.76 (m, 2 H), 1.83 – 2.03 (m, 2 H), 3.00 (t, *J* = 8.0 Hz, 2 H), 3.12 (s, 3 H), 3.58 – 3.82 (m, 2 H), 3.90 – 4.19 (m, 4 H), 4.60 – 4.81 (m, 1 H), 6.60 (d, *J* = 8.0 Hz, 1 H), 6.91 (d, *J* = 8.0 Hz, 1 H), 7.18 (t, *J* = 8.0 Hz, 1 H), 7.35 (d, *J* = 9.0 Hz, 2 H), 7.76 (d, *J* = 9.0 Hz, 2 H), 8.43 (s, 2 H); LCMS (ESI): *m/z* 530 (M + H)<sup>+</sup>.

15

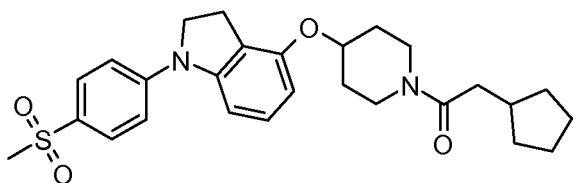
**Example 46 (104)****2-[4-{{1-[4-(Methylsulfonyl)phenyl]-2,3-dihydro-1H-indol-4-yl}oxy}-1-piperidiny]-5-pyrimidinecarbonitrile (104)**

20 Compound **103** (100 mg, 0.19 mmol) was dissolved in 5 mL DMF and treated with CuCN (100 mg, 1.12 mmol). The reaction was then heated at 150 °C for 18 h while stirring. The reaction was cooled to room temperature and treated with 2 mL water. A white solid formed which was removed *via* filtration and dried on filter plate. The solid was dissolved in chloroform and the solids were removed *via* filtration. The solvent was then

25 removed under reduced pressure to give 61 mg (68%) of the title product **104** as a white solid. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  1.79 – 1.93 (m, 2 H), 1.93 – 2.13 (m, 2 H), 3.05 (s, 3

H), 3.12 (t,  $J = 8.0$  Hz, 2 H), 3.73 – 3.88 (m, 2 H), 3.96 – 4.10 (m, 4 H), 4.56 – 4.70 (m, 1 H), 6.54 (d,  $J = 8.0$  Hz, 1 H), 6.91 (d,  $J = 8.0$  Hz, 1 H), 7.10 (t,  $J = 8.0$  Hz, 1 H), 7.28 (d,  $J = 9.0$  Hz, 2 H), 7.84 (d,  $J = 9.0$  Hz, 2 H), 8.29 (s, 2 H); LCMS (ESI):  $m/z$  476 (M + H)<sup>+</sup>.

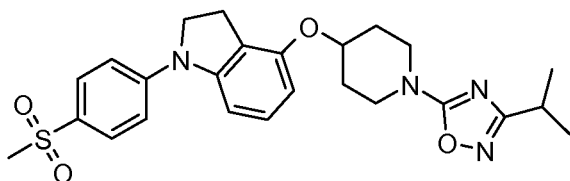
5 **Example 47 (105)**



**4-[[1-(Cyclopentylacetyl)-4-piperidinyl]oxy]-1-[4-(methylsulfonyl)phenyl]-2,3-dihydro-1H-indole (105)**

Compound **97** (50 mg, 0.12 mmol) was dissolved in 2 mL CH<sub>2</sub>Cl<sub>2</sub> and treated with 2 mL  
10 of DIPEA followed by cyclopentylacetyl chloride (100 mg, 0.68 mmol). The reaction was  
then stirred at room temperature for 18 h. All the solvents were removed under reduced  
pressure and the crude reaction was then purified *via* reverse phase chromatography  
(C18, 10-100% CH<sub>3</sub>CN/H<sub>2</sub>O/0.05% TFA) to give 12 mg (20%) of the title product **105** as  
a white solid. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  1.04 – 1.27 (m, 2 H), 1.42 – 1.69 (m, 4 H),  
15 1.72 – 2.04 (m, 6 H), 2.18 – 2.30 (m, 1 H), 2.41 (d,  $J = 7.0$  Hz, 2 H), 3.02 (s, 3 H), 3.14  
(t,  $J = 8.0$  Hz, 2 H), 3.38 – 3.52 (m, 1 H), 3.59 – 3.83 (m, 3 H), 4.01 (t,  $J = 8.0$  Hz, 2 H),  
4.53 – 4.66 (m, 1 H), 6.49 (d,  $J = 8.0$  Hz, 1 H), 6.94 (d,  $J = 8.0$  Hz, 1 H), 7.14 (t,  $J = 8.0$   
Hz, 1 H), 7.27 (d,  $J = 9.0$  Hz, 2 H), 7.80 (d,  $J = 9.0$  Hz, 2 H); LCMS (ESI):  $m/z$  483 (M +  
H)<sup>+</sup>.



**Example 48 (108)****Step 1: N-Hydroxy-2-methylpropanimidamide (106)**

5 2-Methylpropanenitrile (25 g, 0.362 mol) was combined with 100 mL hydroxylamine and the mixture was refluxed for 5 h. The solvent was then removed under reduced pressure and the residual solvent was removed azeotropically with toluene. The residue was then taken up in 50 mL methylene chloride and dried over anhydrous  $\text{MgSO}_4$ . The solvent was then removed *in vacuo* to afford 26 g of the title product **106** as clear oil  
 10 which was used without purification.  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO}-d_6$ ):  $\delta$  0.79 – 1.10 (m, 6 H), 2.02 – 2.35 (m, 1 H), 5.36 (s, 2 H), 8.82 (s, 1 H).

**Step 2: 4-({1-[4-(Methylsulfonyl)phenyl]-2,3-dihydro-1H-indol-4-yl}oxy)-1-piperidinecarbonitrile (107)**

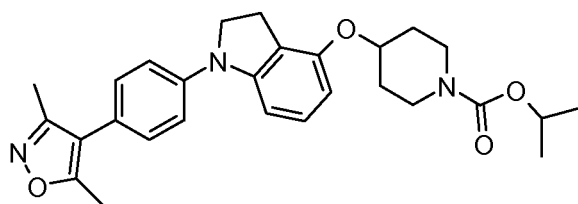
NaHCO<sub>3</sub> (309 mg, 3.68 mmol) was combined with 1 mL water and cooled to 0 °C in an  
 15 ice bath. Compound **97** (500 mg, 1.22 mmol) in 2.5 mL of methylene chloride was added to the above solution which was vigorously stirred. Cyanogen bromide (142 mg, 1.34 mmol) in 2.5 mL of methylene chloride was then added and the ice bath was removed. The mixture was stirred at ambient temperature for 18 h. Na<sub>2</sub>CO<sub>3</sub> (1.5 g) was then added until pH  $\cong$  7 and MgSO<sub>4</sub> (1 g) was added to remove water. The solids were  
 20 removed *via* filtration and the solids were washed several times with methylene chloride. The solvent was then removed under reduced pressure and the material **107** was used without purification.

**Step 3: 4-({1-[3-(1-Methylethyl)-1,2,4-oxadiazol-5-yl]-4-piperidinyl}oxy)-1-[4-(methylsulfonyl)phenyl]-2,3-dihydro-1H-indole (108)**

25 Compound **107** (500 mg, 1.26 mmol) was combined with compound **106** (500 mg, 4.90 mmol) in a mixture of ethyl acetate (9 mL) and ether (1 mL) and solid ZnCl<sub>2</sub> (800 mg, 5.88 mmol) was added to the solution. The mixture was stirred for 15 min and the supernatant was decanted off. The residue was washed 2 times with 10 mL of ethyl acetate, which was decanted off after each wash. The residue was then dissolved in a

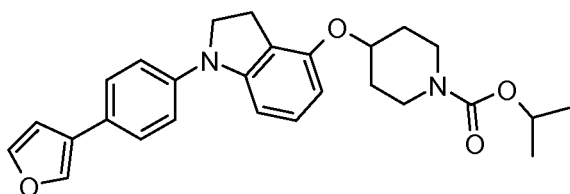
mixture of 4 N HCl (5 mL) and EtOH (15 mL). The resulting solution was then refluxed for 1 h. The solvent was reduced *in vacuo* and 500 mg Na<sub>2</sub>CO<sub>3</sub> was added along with 10 mL methylene chloride. The solids were removed *via* filtration and phases were separated. The organic phase was dried over MgSO<sub>4</sub>, filtered, and concentrated to dryness to give 31 mg of the title compound **108** as a white solid. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 1.10 – 1.43 (m, 6 H), 1.89 – 2.18 (m, 4 H), 2.80 – 2.98 (m, 1 H), 3.04 (s, 3 H), 3.12 (t, *J* = 8.0 Hz, 2 H), 3.57 – 3.85 (m, 4 H), 4.02 (t, *J* = 8.0 Hz, 2 H), 4.51 – 4.72 (m, 1 H), 6.45 (d, *J* = 8.0 Hz, 1 H), 6.91 (d, *J* = 8.0 Hz, 1 H), 7.10 (t, *J* = 8.0 Hz, 1 H), 7.28 (d, *J* = 9.0 Hz, 2 H), 7.86 (d, *J* = 9.0 Hz, 2 H); LCMS (ESI): *m/z* 483 (M + H)<sup>+</sup>.

10

**Example 49 (109)****1-Methylethyl 4-({1-[4-(3,5-dimethyl-4-isoxazolyl)phenyl]-2,3-dihydro-1H-indol-4-yl}oxy)-1-piperidinecarboxylate (109)**

15 A round-bottomed flask was charged with **68** (51 mg, 0.1 mmol), PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub> (7 mg, 0.01 mmol), (3,5-dimethyl-4-isoxazolyl)boronic acid (28 mg, 0.2 mmol), a 2 N aqueous solution of Na<sub>2</sub>CO<sub>3</sub> (250 μL, 0.5 mmol), and THF (3 mL). The resultant mixture was refluxed for 3 h under N<sub>2</sub>. Reaction mixture was cooled to RT, diluted with EtOAc (40 mL), and the mixture was washed with H<sub>2</sub>O (1 x 10 mL), brine (1 x 10 mL), dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure to afford the crude material. The product was purified by SiO<sub>2</sub> flash column chromatography to afford 30 mg (63%) of the title product **109** as an off-white solid. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>): δ 7.32 (d, *J* = 8.4 Hz, 2 H), 7.27 (d, *J* = 8.4 Hz, 2 H), 7.01 (app. t, *J* = 8.0 Hz, 1 H), 6.78 (d, *J* = 8.0 Hz, 1 H), 6.49 (d, *J* = 8.4 Hz, 1 H), 4.76 (septuplet, *J* = 7.0 Hz, 1 H), 3.96 (t, *J* = 8.4 Hz, 2 H), 20 3.61 (br m, 2 H), 3.30 (br m, 2 H), 2.99 (t, *J* = 8.4 Hz, 2 H), 2.38 (s, 3 H), 2.21 (s, 3 H), 25 1.86 (br m, 2 H), 1.56 (m, 2 H), 1.17 (d, *J* = 6.0 Hz, 6 H); LCMS (ESI): *m/z* 476 (M + H)<sup>+</sup>.

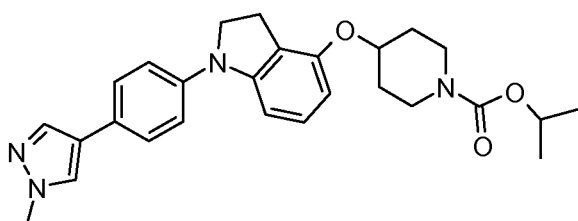
**Example 50 (110)**



**1-Methylethyl 4-({1-[4-(3-furanyl)phenyl]-2,3-dihydro-1H-indol-4-yl}oxy)-1-piperidinecarboxylate (**111**)**

The Suzuki procedure described for **109** was employed using **68** (66 mg, 0.13 mmol),  
 5 PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub> (9 mg, 0.013 mmol), 3-furanylboronic acid (29 mg, 0.26 mmol), a 2 N  
 aqueous solution of Na<sub>2</sub>CO<sub>3</sub> (325 μL, 0.65 mmol), and THF (3 mL). The work-up  
 followed by purification gave 22 mg (38%) of the title product **111** as a white solid. <sup>1</sup>H  
 NMR (400 MHz, DMSO-*d*<sub>6</sub>): δ 8.08 (s, 1 H), 7.69 (t, *J* = 1.6 Hz, 1 H), 7.55 (d, *J* = 8.4 Hz,  
 2 H), 7.20 (d, *J* = 8.8 Hz, 2 H), 6.99 (t, *J* = 8.0 Hz, 1 H), 6.90 (d, *J* = 1.2 Hz, 1 H), 6.72 (d,  
 10 *J* = 8.0 Hz, 1 H), 6.47 (d, *J* = 8.0 Hz, 1 H), 4.76 (septuplet, *J* = 6.4 Hz, 1 H), 4.56 (m, 1H),  
 3.93 (t, *J* = 8.8 Hz, 2 H), 3.64 – 3.58 (m, 2 H), 3.30 – 3.26 (m, 2 H), 2.98 (t, *J* = 8.4 Hz, 2  
 H), 1.90 – 1.84 (m, 2 H), 1.60 – 1.52 (m, 2 H), 1.17 (d, *J* = 6.0 Hz, 6 H); LCMS (ESI): *m/z*  
 447 (M + H)<sup>+</sup>.

15 **Example 51 (**112**)**

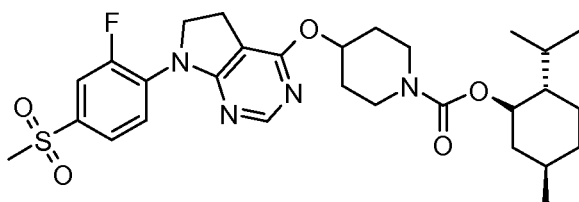


**1-Methylethyl 4-({1-[4-(1-methyl-1H-pyrazol-4-yl)phenyl]-2,3-dihydro-1H-indol-4-yl}oxy)-1-piperidinecarboxylate (**112**)**

Following the Suzuki coupling procedure described for **109**, a round-bottomed flask was  
 20 charged with compound **68** (51 mg, 0.1 mmol), PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub> (7 mg, 0.01 mmol), 1-  
 methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (42 mg, 0.20 mmol),  
 a 2 N aqueous solution of Na<sub>2</sub>CO<sub>3</sub> (250 μL, 0.5 mmol), and THF (3 mL). The mixture  
 was refluxed for 3 h. The work-up followed by purification gave 12 mg (25%) of the title  
 product **112** as a off-white solid. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>): δ 8.02 (s, 1 H), 7.77 (s,  
 25 1 H), 7.49 (d, *J* = 8.8 Hz, 1 H), 7.17 (d, *J* = 8.8 Hz, 1 H), 6.98 (app. t, *J* = 8.0 Hz, 1 H),

6.68 (d,  $J = 8.0$  Hz, 1 H), 6.45 (d,  $J = 8.4$  Hz, 1 H), 4.75 (septuplet,  $J = 6.4$  Hz, 1 H), 4.56 (m, 1 H), 3.92 (t,  $J = 8.4$  Hz, 2 H), 3.83 (s, 3 H), 3.62 – 3.56 (m, 2 H), 3.29 – 3.25 (m, 2 H), 2.97 (t,  $J = 8.4$  Hz, 2 H), 1.88 – 1.84 (m, 2 H), 1.59 – 1.52 (m, 2 H), 1.67 (d,  $J = 6.0$  Hz, 6 H); LCMS (ESI):  $m/z$  461 ( $M + H$ )<sup>+</sup>.

5

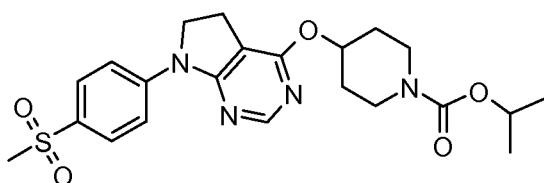
**Example 52 (113)**

**(1R,2S,5R)-5-Methyl-2-(1-methylethyl)cyclohexyl 4-({7-[2-fluoro-4-(methylsulfonyl)phenyl]-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-4-yl}oxy)-1-piperidinecarboxylate (113)**

10

The two step procedure described for **67** was used. The product **126** (*vide infra*), obtained from compound **11** upon treatment with TFA in  $\text{CH}_2\text{Cl}_2$  (125 mg, ~80% pure) was dissolved in  $\text{CH}_2\text{Cl}_2$  (25 mL) and treated with  $\text{Et}_3\text{N}$  (132  $\mu\text{L}$ , 1 mmol), DMAP (4 mg, 0.032 mmol), and (1R,2S,5R)-5-methyl-2-(1-methylethyl)cyclohexyl chloridocarbonate (136  $\mu\text{L}$ , 0.64 mmol). The mixture was stirred at RT for 15 h. The work-up followed by purification gave 44 mg (24%) of the title product **113** as an off-white solid.  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO}-d_6$ ):  $\delta$  8.22 (s, 1 H), 7.96 (t,  $J = 7.6$  Hz, 1 H), 7.85 and 7.82 (dd,  $J_1 = 10.8$  Hz,  $J_2 = 1.6$  Hz, 1 H), 7.75 and 7.73 (dd,  $J_1 = 8.4$  Hz,  $J_2 = 2.0$  Hz, 1 H), 5.28 (m, 1 H), 4.43 (m, 1 H), 4.14 (t,  $J = 8.4$  Hz, 2 H), 3.71 – 3.67 (m, 2 H), 3.25 (s, 3 H), 3.29 – 3.21 (m, 2 H), 3.05 (t,  $J = 8.8$  Hz, 2 H), 1.94 – 1.86 (br m, 3 H), 1.86 – 1.81 (m, 1 H), 1.63 – 1.51 (m, 4 H), 1.44 – 1.40 (m, 1 H), 1.41 – 1.30 (m, 1 H), 1.07 – 0.91 (m, 2 H), 0.86 (d,  $J = 6.4$  Hz, 6 H), 0.73 (s,  $J = 6.8$  Hz, 3 H); LCMS (ESI):  $m/z$  575 ( $M + H$ )<sup>+</sup>.

20

**Example 53 (118)**

25

**Step 1: *N*-(4-Bromophenyl)-6-chloro-5-(2-propen-1-yl)-4-pyrimidinamine (114)**

The procedure described for 4 was used. To a mixture of NaH (3.60 g, 60% dispersion in mineral oil, washed with anhydrous toluene) and anhydrous THF (50 mL) at RT under N<sub>2</sub> was added 4-bromoaniline (5.16 g, 30 mmol) in THF (100 mL). The mixture was stirred at RT for 1 h and then compound 2 (5.67 g, 30 mmol) in THF (50 mL) was added. The resulting reaction mixture was refluxed for 4 h. Aqueous work-up followed by purification by SiO<sub>2</sub> flash column chromatography afforded 6.81 g (~85% pure) of the product 114. This material was used in the next step without further purification. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>): δ 8.83 (s, 1 H), 8.29 (s, 1 H), 7.55 (d, *J* = 11.6 Hz, 2 H), 7.49 (d, *J* = 8.8 Hz, 2 H), 5.92 – 5.84 (m, 1 H), 5.07 – 5.00 (m, 2 H), 3.56 (d, *J* = 5.2 Hz, 2 H); LCMS (ESI): *m/z* 325 (M + H)<sup>+</sup>.

**Step 2: 2-{4-[(4-Bromophenyl)amino]-6-chloro-5-pyrimidinyl}ethanol (115)**

The ozonolysis procedure described for 6 was utilized using 114 (5.80 g, 17.87 mmol), CH<sub>2</sub>Cl<sub>2</sub> (300 mL), MeOH (50 mL), and NaBH<sub>4</sub> (2.70 g, 71.47 mmol) between –70 °C and RT. Aqueous work-up followed by purification afforded 3.120 (~90% pure) of the title product 115. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>): δ 9.10 (s, 1 H), 8.29 (s, 1 H), 7.56 – 7.48 (m, 4 H), 5.13 (t, *J* = 5.2 Hz, 1 H), 3.65 (q, *J* = 5.6 Hz, 2 H), 2.97 (t, *J* = 6.4 Hz, 2 H); LCMS (ESI): *m/z* 329 (M + H)<sup>+</sup>.

**Step 3: 7-(4-Bromophenyl)-4-chloro-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidine (116)**

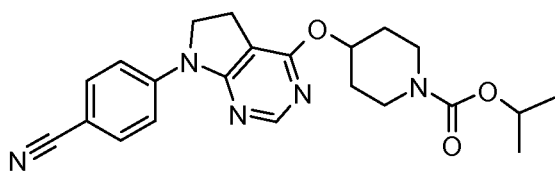
To a solution of 115 (2.72 g, 8.28 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (150 mL) were added, at 5 °C, Et<sub>3</sub>N (6.87 mL, 49.7 mmol) followed by methanesulfonic anhydride (2.16 g, 12.42 mmol). The resultant mixture was stirred at RT for 24 h. The reaction mixture was diluted with CH<sub>2</sub>Cl<sub>2</sub> (200 mL) and washed with H<sub>2</sub>O (2 x 50 mL), brine (1 x 25 mL), dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated to afford the crude material. The material was redissolved in CH<sub>2</sub>Cl<sub>2</sub> (50 mL) and then treated with Et<sub>3</sub>N (10 mL). The mixture was stirred at RT for 24 h and then kept at RT for overnight. The crystals were separated and dried to give 1.76 g as a white solid. The mother liquor was concentrated to afford the crude product which was purified by SiO<sub>2</sub> column chromatography to afford an additional 450 mg of the product. A total of 2.21 g of the title product 116 was obtained as a white solid. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>): δ 8.38 (s, 1 H), 7.65 (d, *J* = 9.2 Hz, 2 H), 7.49 (d, *J* = 8.8 Hz, 2 H), 4.12 (t, *J* = 8.8 Hz, 2 H), 3.20 (t, *J* = 8.4 Hz, 2 H); LCMS (ESI): *m/z* 311 (M + H)<sup>+</sup>.

**Step 4: 1-Methylethyl 4-{{7-(4-bromophenyl)-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-4-yl}oxy}-1-piperidinecarboxylate (117)**

Following the procedure described for **10** (Example 1, Step 10), compound **116** (932 g, 3 mmol) was allowed to react, at 65 °C, with compound **9** (562 mg, 3 mmol) in presence of NaH (60% dispersion in oil, 360 mg, 9 mmol) in THF (40 mL) for 2 h. Aqueous work-up followed by SiO<sub>2</sub> flash column chromatography afforded 966 mg (70%) of the title product **117** as a white solid. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>): δ 8.32 (s, 1 H), 7.63 (d, *J* = 9.2 Hz, 2 H), 7.47 (d, *J* = 8.8 Hz, 2 H), 5.36 (m, 1 H), 4.92 (septuplet, *J* = 6.0 Hz, 1 H), 4.07 (t, *J* = 9.2 Hz, 2 H), 3.79 (br s, 2 H), 3.36 – 3.30 (m, 2 H), 3.07 (t, *J* = 8.8 Hz, 2 H), 2.02 – 1.97 (m, 2 H), 1.77 – 1.68 (m, 2 H), 1.25 (d, *J* = 6.4 Hz, 6 H); LCMS (ESI): *m/z* 463 (M + H)<sup>+</sup>.

**Step 5: 1-Methylethyl 4-{{7-[4-(methylsulfonyl)phenyl]-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-4-yl}oxy}-1-piperidinecarboxylate (118)**

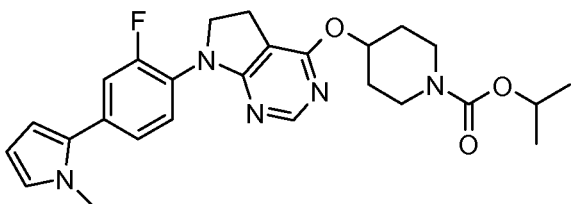
Following the representative procedure described for **3**, a 10 mL glass tube was charged with compound **117** (500 mg, 1.08 mmol), sodium methanesulfinate (221 mg, 2.17 mmol), copper iodide (21 mg, 0.11 mmol), L-proline (25 mg, 0.22 mmol), NaOH (9 mg, 0.22 mmol), and DMSO (4 mL). The sealed pressure tube was stirred at 120 °C for 15 h. Aqueous work-up followed by purification afforded 315 mg (63%) of the title product **118** as an off-white solid. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 8.39 (s, 1 H), 7.98 – 7.90 (m, 4 H), 5.38 (m, 1 H), 4.93 (septuplet, *J* = 6.4 Hz, 1 H), 4.15 (t, *J* = 8.8 Hz, 2 H), 3.83 (br m, 2 H), 3.37 – 3.30 (m, 2 H), 3.12 (t, *J* = 8.8 Hz, 2 H), 3.04 (s, 3 H), 2.12 – 1.96 (m, 2 H), 1.80 – 1.69 (m, 2 H), 1.25 (d, *J* = 6.4 Hz, 6 H); LCMS (ESI): *m/z* 461 (M + H)<sup>+</sup>.

**Example 54 (119)****1-Methylethyl 4-[[7-(4-cyanophenyl)-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-4-yl]oxy]-1-piperidinecarboxylate (119)**

Following the procedure described for **31** (Example 10, Step 7), a mixture of **117** (202 mg, 0.44 mmol), CuCN (99 mg, 1.1 mmol), and NMP (4 mL) was stirred at 150 °C for 36 h. Aqueous work-up followed by purification afforded 110 mg (61%) of the title product

**119** as a white solid.  $^1\text{H NMR}$  (400 MHz,  $\text{DMSO-}d_6$ ):  $\delta$  8.38 (s, 1 H), 8.0 (d,  $J = 8.8$  Hz, 2 H), 7.78 (d,  $J = 8.8$  Hz, 2 H), 5.28 (m, 2 H), 4.75 (septuplet,  $J = 6.4$  Hz, 1 H), 4.10 (t,  $J = 9.2$  Hz, 2 H), 3.69 – 3.64 (m, 2 H), 3.26 – 3.21 (br m, 2 H), 3.02 (t,  $J = 8.8$  Hz, 2H), 1.95 – 1.90 (m, 2 H), 1.62 – 1.52 (m, 2 H), 1.17 (d,  $J = 6.4$  Hz, 6 H); LCMS (ESI):  $m/z$  408 ( $\text{M} + \text{H}$ )<sup>+</sup>.

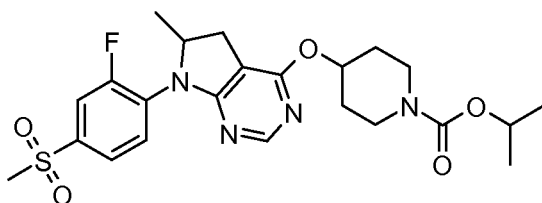
**Example 55 (120)**



10 **1-Methylethyl 4-({7-[2-fluoro-4-(1-methyl-1H-pyrrol-2-yl)phenyl]-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-4-yl}oxy)-1-piperidinecarboxylate (120)**

A 5 mL glass tube was charged with **30** (100 mg, 0.2 mmol),  $\text{PdCl}_2(\text{Ph}_3\text{P})_2$  (15 mg, 0.02 mmol), 1-methyl-2-(tributylstannanyl)-1H-pyrrole (70 mg, 0.20 mmol), and THF (3 mL) under  $\text{N}_2$ . The tube was sealed and then the mixture was subjected to microwave  
 15 conditions at 100 °C for 40 min. The reaction mixture was cooled to RT and then subjected to  $\text{SiO}_2$  flash column chromatography to afford 11 mg (12%) of the title product as a white solid.  $^1\text{H NMR}$  (400 MHz,  $\text{DMSO-}d_6$ ):  $\delta$  8.12 (s, 1 H), 7.58 (t,  $J = 8.4$  Hz, 1 H), 7.37 and 7.34 (dd,  $J_1 = 12.4$  Hz,  $J_2 = 2.0$  Hz, 1 H), 7.28 and 7.26 (dd,  $J_1 = 8.4$  Hz,  $J_2 = 1.6$  Hz, 1 H), 6.84 (t,  $J = 2.0$  Hz, 1 H), 6.23 and 6.22 (dd,  $J_1 = 3.6$  Hz,  $J_2 = 2.0$  Hz, 1 H), 6.04  
 20 (t,  $J = 3.2$  Hz, 1 H), 5.28 – 5.22 (m, 1 H), 4.76 (septuplet,  $J = 6.0$  Hz, 1 H), 4.04 (t,  $J = 9.2$  Hz, 2 H), 3.67 (s, 3 H), 3.71 – 3.65 (m, 2 H), 3.23 (app. br, t,  $J = 10$  Hz, 2 H), 3.04 (t,  $J = 9.2$  Hz, 2 H), 1.95 – 1.90 (m, 2 H), 1.61 – 1.52 (m, 2 H), 1.17 (d,  $J = 6.0$  Hz, 6 H); LCMS (ESI):  $m/z$  480 ( $\text{M} + \text{H}$ )<sup>+</sup>.

25 **Example 56 (125)**



**Step 1: 1,1-Dimethylethyl [6-chloro-5-(2-oxoethyl)-4-pyrimidinyl][2-fluoro-4-(methylsulfonyl)phenyl]carbamate (121)**

Following the procedure described for 209 was employed (see example 117, step 1). To a solution of compound 5 (3.42 g, 10 mmol) in 3:2 acetone-H<sub>2</sub>O (250 mL) was added K<sub>2</sub>OsO<sub>4</sub>·2H<sub>2</sub>O (147 mg, 0.4 mmol). Solid NaIO<sub>4</sub> (8.56 g, 40 mmol) was added portionwise and the reaction was stirred for 4 h. The workup gave 5.0 g (~100%) of the title 121 product as an off-white solid. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>): δ 9.63 (s, 1 H), 8.82 (s, 1 H), 7.96 – 7.94 (dd, *J*<sub>1</sub> = 9.6 Hz, *J*<sub>2</sub> = 2.0 Hz, 1 H), 7.78 – 7.76 (dd, *J*<sub>1</sub> = 8.4 Hz, *J*<sub>2</sub> = 1.6 Hz, 1 H), 7.59 (app. t, *J* = 7.6 Hz, 1 H), 3.93 (s, 2 H), 3.30 (s, 3 H), 1.38 (s, 9 H).

**Step 2: (±)-1,1-Dimethylethyl [6-chloro-5-(2-hydroxypropyl)-4-pyrimidinyl][2-fluoro-4-(methylsulfonyl)phenyl]carbamate (122)**

To a stirred solution of aldehyde 121 (2.0 g, 4.51 mmol) in anhydrous THF (50 mL) was added a 1.4 M solution of methylmagnesium in THF (6.5 mL, 9.01 mmol) at RT under N<sub>2</sub>. The resultant mixture was stirred at RT for 3 h. The reaction mixture was poured into 10% aqueous HCl (200 mL) and the mixture was extracted with EtOAc (4 x 75 mL). The combined organic layer was washed with brine (1 x 30 mL), dried over Na<sub>2</sub>SO<sub>4</sub> and then concentrated under reduced pressure to afford the crude product, which was subjected to column chromatography to give 0.815 g (39%) of the title carbinol 122 as a white solid. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>): δ 9.15 (s, 1 H), 8.28 (s, 1 H), 7.85 and 7.82 (dd, *J*<sub>1</sub> = 9.6 Hz, *J*<sub>2</sub> = 2.0 Hz, 1 H), 7.80 – 7.68 (m, 2 H), 5.06 – 4.99 (m, 1 H), 3.28 (s, 3H), 3.14 – 3.10 (m, 1 H), 3.05 – 3.02 (m, 1 H), 1.33 (d, *J* = 6.2 Hz, 3 H), 1.25 (s, 9 H); LCMS (ESI): *m/z* 460 (M + H)<sup>+</sup>.

**Step 3: (±)-1-(4-Chloro-6-[[2-fluoro-4-(methylsulfonyl)phenyl]amino]-5-pyrimidinyl)-2-propanol (123)**

To a solution of carbinol 122 (800 mg, 1.74 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (20 mL) was added TFA (5 mL) at RT under N<sub>2</sub>. The reaction mixture was stirred at RT for 3 h and then concentrated under reduced pressure to afford the title product 123, which was used without further purification in the next step. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>): δ 9.84 (s, 1



H), 8.42 (s, 1 H), 8.16 (app. t,  $J = 8.0$  Hz, 1 H), 7.83 and 7.80 (dd,  $J_1 = 10.4$  Hz,  $J_2 = 2.0$  Hz, 1 H), 7.74 and 7.72 (dd,  $J_1 = 8.8$  Hz,  $J_2 = 1.6$  Hz, 1 H), 5.87 (d,  $J = 2.8$  Hz, 1 H), 4.07 (app. br. s, 1 H), 3.24 (s, 3 H), 2.94 – 2.83 (m, 2 H), 1.20 (d,  $J = 6.4$  Hz, 3 H); LCMS (ESI):  $m/z$  360 ( $M + H$ )<sup>+</sup>.

5 **Step 4: (±)-4-Chloro-7-[2-fluoro-4-(methylsulfonyl)phenyl]-6-methyl-6,7-dihydro-5H-pyrrolo[2,3-*d*]pyrimidine (124)**

Following the procedure described for the compound **7** (example 1, step 7), to a solution of compound **123** in CH<sub>2</sub>Cl<sub>2</sub> (30 mL) was added Et<sub>3</sub>N (0.722 mL, 5.22 mmol) followed by methanesulfonic anhydride (0.606 g, 3.48 mmol) at RT for 24 h. The workup and  
10 chromatography gave 0.272 g (47%, for 2 steps) of the bicyclic compound **124** as an off-white solid. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>): δ 8.23 (s, 1 H), 7.94 and 7.92 (app. dd,  $J_1 = 10.8$  Hz,  $J_2 = 1.2$  Hz, 1 H), 7.87 – 7.81 (m, 2 H), 4.80 – 4.72 (m, 1 H), 3.47 – 3.42 (dd,  $J_1 = 17.2$  Hz,  $J_2 = 9.6$  Hz, 1 H), 3.30 (s, 3 H), 2.89 – 2.85 (dd,  $J_1 = 17.2$  Hz,  $J_2 = 7.2$  Hz, 1 H), 1.21 (d,  $J = 6.0$  Hz, 3 H); LCMS (ESI):  $m/z$  342 ( $M + H$ )<sup>+</sup>.

15 **Step 5: (±)-1-Methylethyl 4-({7-[2-fluoro-4-(methylsulfonyl)phenyl]-6-methyl-6,7-dihydro-5H-pyrrolo[2,3-*d*]pyrimidin-4-yl}oxy)-1-piperidinecarboxylate (125)**

Following the procedure described for **10**, compound **9** (128 mg, 0.68 mmol) in THF (2 mL) was added to a suspension of NaH (60%, 84 mg, 2.1 mmol) in THF (2 mL). The reaction mixture was refluxed for 15 min and the compound **124** (245 mg, 2.16 mmol) in  
20 THF (2 mL) was added and the resultant mixture was refluxed for 2 h. The work-up and chromatography gave 276 mg (82%) of the title compound **125** as a white solid. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>): δ 8.16 (s, 1 H), 7.87 (app. br. d,  $J = 10.4$  Hz, 1 H), 7.83 – 7.81 (app. br. d,  $J = 7.6$  Hz, 1 H), 7.78 – 7.76 (dd,  $J_1 = 8.4$  Hz,  $J_2 = 1.6$  Hz, 1 H), 5.30 – 5.22 (m, 1 H), 4.78 – 4.66 (m, 2 H), 3.68 – 3.64 (m, 2 H), 3.32 – 3.28 (m, 1 H), 3.28 (s, 3 H),  
25 3.28 – 3.22 (m, 2 H), 2.70 and 2.66 (app. dd,  $J_1 = 16.0$  Hz,  $J_2 = 7.2$  Hz, 1 H), 1.96 – 1.86 (m, 2 H), 1.62 – 1.50 (m, 2 H), 1.19 (app. d,  $J = 5.6$  Hz, 3 H), 1.17 (d,  $J = 6.0$  Hz, 6 H); LCMS (ESI):  $m/z$  493 ( $M + H$ )<sup>+</sup>.

**Examples 57**

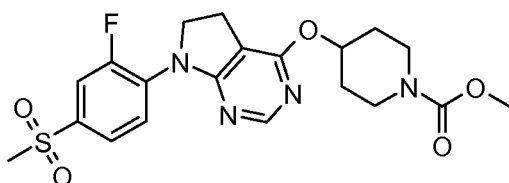
30 The racemic mixture **125** (200 mg) was subjected to Chiral HPLC [column: Chiralpak OJ (analytical), Chiralpak OJ (prep.), mobile phase: 95% CO<sub>2</sub>: 5% MeOH:CHCl<sub>3</sub> (90:1); 2

mL/min; pressure 140 bar, temperature 30 °C, 215 nm, and 280 nm) ] analysis and then separated two (*R* and *S*) enantiomers. The absolute stereochemistry was not assigned.

**Enantiomer I, 57A (125A):** Tr: 19.96 min, 46 mg (%ee > 98%); Spectral data are essentially the same to that of example 56 (125).

- 5 **Enantiomer II, 57B (125B):** Tr: 21.0 min, 66 mg (%ee > 98%); Spectral data are essentially the same to that of example 56 (125).

**Example 58 (127)**



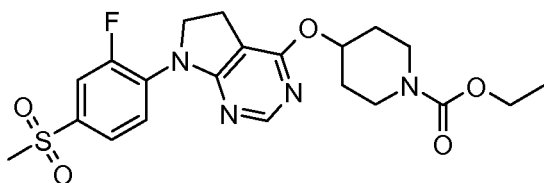
- 10 **Step 1: 7-[2-Fluoro-4-(methylsulfonyl)phenyl]-4-(4-piperidinyloxy)-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidine trifluoroacetate (126)**

To a solution of **11** (example 2, 1.0 g, 2.03 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (40 mL) was treated with TFA (10 mL) at RT for 2 h. The reaction mixture was stirred at RT for 2 h and then concentrated to afford to crude product **126**, which was dried and re-dissolved in 20 mL of CH<sub>2</sub>Cl<sub>2</sub> and Et<sub>3</sub>N (1.7 mL, ~6 equiv) to use in the next steps.

- 15 **Step 2: Methyl 4-({7-[2-fluoro-4-(methylsulfonyl)phenyl]-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-4-yl}oxy)-1-piperidinecarboxylate (127)**

A solution of **126** (2.2 mL from step 1) was treated with methyl chloridocarbonate (200 μL) at RT for 18 h. The reaction mixture was diluted with CH<sub>2</sub>Cl<sub>2</sub> (30 mL) and then washed with H<sub>2</sub>O (1 x 10 mL), brine (1 x 10 mL), dried over Na<sub>2</sub>SO<sub>4</sub> and then concentrated under reduced pressure to afford the crude product, which was subjected for column chromatography gave 76 mg of the title product **127** as a white solid. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>): δ 8.22 (s, 1 H), 7.96 (t, *J* = 8.0 Hz, 1 H), 7.85 and 7.82 (dd, *J*<sub>1</sub> = 11.2 Hz, *J*<sub>2</sub> = 2.0 Hz, 1 H), 7.74 and 7.72 (dd, *J*<sub>1</sub> = 8.4 Hz, *J*<sub>2</sub> = 2.4 Hz, 1 H), 5.30 – 5.22 (m, 1 H), 4.14 (t, *J* = 8.4 Hz, 2 H), 3.58 (s, 3 H), 3.70 – 3.64 (m, 2 H), 3.28 – 3.24 (app. br, m, 2 H), 3.25 (s, 3H), 3.05 (t, *J* = 8.8 Hz, 2 H), 1.96 – 1.91 (m, 2 H), 1.64 – 1.54 (m, 2 H); LCMS (ESI): *m/z* 451 (M + H)<sup>+</sup>.

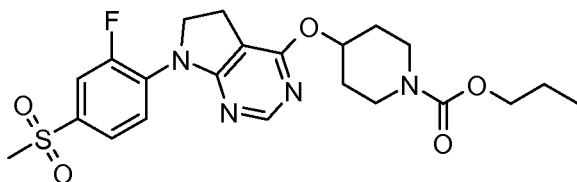
- 25 **Example 59 (128)**



**Ethyl 4-({7-[2-fluoro-4-(methylsulfonyl)phenyl]-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-4-yl}oxy)-1-piperidinecarboxylate (128)**

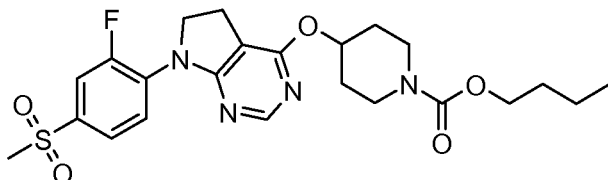
Following the general procedure described for the compound 127, a solution of 126 (2.2 mL) was treated with ethyl chloridocarbonate (100  $\mu$ L) at RT for 18 h. The work up and chromatography gave 85 mg of the title product 128 as a white solid.  $^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ ):  $\delta$  8.22 (s, 1 H), 7.96 (t,  $J$  = 7.6 Hz, 1 H), 7.84 and 7.82 (dd,  $J_1$  = 11.2 Hz,  $J_2$  = 2.0 Hz, 1 H), 7.75 and 7.72 (dd,  $J_1$  = 8.4 Hz,  $J_2$  = 2.0 Hz, 1H), 5.28 – 5.24 (m, 1 H), 4.14 (t,  $J$  = 8.4 Hz, 2 H), 4.02 (q,  $J$  = 7.2 Hz, 2 H), 3.71 – 3.65 (m, 2 H), 3.26 – 3.24 (br. s, 2 H), 3.25 (s, 3 H), 3.05 (t,  $J$  = 8.8 Hz, 2 H), 1.96 – 1.90 (br, m, 2 H), 1.62 – 1.54 (m, 2 H), 1.17 (t,  $J$  = 6.8 Hz, 3 H); LCMS (ESI):  $m/z$  465 (M + H) $^+$ .

**Example 60 (129)**



**Propyl 4-({7-[2-fluoro-4-(methylsulfonyl)phenyl]-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-4-yl}oxy)-1-piperidinecarboxylate (129)**

Following the general procedure described for the compound 127, to a solution of 126 (100 mg, 0.198 mmol, from a different batch) in  $\text{CH}_2\text{Cl}_2$  (4 mL) was added  $\text{Et}_3\text{N}$  (137  $\mu$ L, 1 mmol) followed by propyl chloridocarbonate (100  $\mu$ L) at RT and the mixture was stirred for 18 h. The work up and chromatography gave 72 mg (75%) of the title product 129 as a white solid.  $^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ ):  $\delta$  8.22 (s, 1 H), 7.96 (t,  $J$  = 8.0 Hz, 1 H), 7.85 and 7.82 (dd,  $J_1$  = 10.8 Hz,  $J_2$  = 2.0 Hz, 1 H), 7.75 and 7.72 (dd,  $J_1$  = 8.4 Hz,  $J_2$  = 2.4 Hz, 1 H), 5.30 – 5.24 (m, 1 H), 4.14 (t,  $J$  = 8.4 Hz, 2 H), 3.94 (t,  $J$  = 6.8 Hz, 2 H), 3.72 – 3.66 (m, 2 H), 3.30 – 3.24 (br, m, 2 H), 3.05 (t,  $J$  = 8.4 Hz, 2 H), 1.98 – 1.88 (m, 2 H), 1.62 – 1.52 (m, 4 H), 0.87 (t,  $J$  = 7.2 Hz, 2 H); LCMS (ESI):  $m/z$  479 (M + H) $^+$ .

**Example 61 (130)**

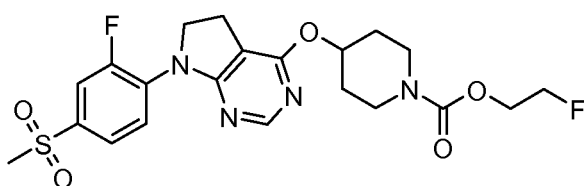
**n-Butyl 4-({7-[2-fluoro-4-(methylsulfonyl)phenyl]-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-4-yl}oxy)-1-piperidinecarboxylate (130)**

5

Following the general procedure described for the compound **127**, to a solution of **126** (100 mg, 0.198 mmol), from a different batch) in CH<sub>2</sub>Cl<sub>2</sub> (4 mL) was added Et<sub>3</sub>N (137 μL, 1 mmol) followed by butyl chloridocarbonate (100 μL) at RT and then stirred for 18 h.

The work up and chromatography gave 76 mg (77%) of the title product **130** as a white solid. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>): δ 8.22 (s, 1 H), 7.96 (t, *J* = 8.0 Hz, 1 H), 7.85 and 7.82 (dd, *J*<sub>1</sub> = 10.8 Hz, *J*<sub>2</sub> = 2.0 Hz, 1 H), 7.75 and 7.73 (dd, *J*<sub>1</sub> = 8.4 Hz, *J*<sub>2</sub> = 2.4 Hz, 1 H), 5.30 – 5.24 (m, 1 H), 4.14 (t, *J* = 8.0 Hz, 2 H), 3.98 (t, *J* = 6.4 Hz, 2 H), 3.71 – 3.66 (m, 2 H), 3.26 – 3.24 (br, s, 2 H), 3.25 (s, 3 H), 3.05 (t, *J* = 8.8 Hz, 2 H), 1.96 – 1.90 (m, 2 H), 1.62 – 1.49 (m, 4 H), 1.36 – 1.26 (m, 2 H), 0.88 (t, *J* = 7.6 Hz, 3 H); LCMS (ESI): *m/z* 493 (M + H)<sup>+</sup>.

15

**Example 62 (131)**

**2-Fluoroethyl 4-({7-[2-fluoro-4-(methylsulfonyl)phenyl]-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-4-yl}oxy)-1-piperidinecarboxylate (131)**

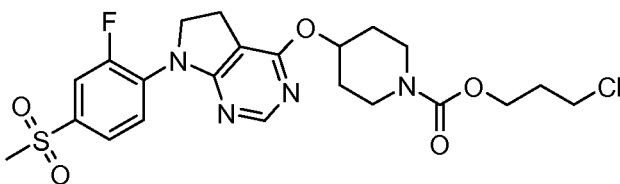
20

Following the general procedure described for the compound **127**, to a solution of **126** (100 mg, 0.198 mmol, from a different batch) in CH<sub>2</sub>Cl<sub>2</sub> (4 mL) was added Et<sub>3</sub>N (137 μL, 1 mmol) followed by 2-fluoroethyl chloridocarbonate (100 μL) at RT and then stirred for 18 h. The work up and chromatography gave 56 mg (58%) of the title product **131** as a white solid. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>): δ 8.23 (s, 1 H), 7.96 (t, *J* = 8.0 Hz, 1 H), 7.85 and 7.82 (dd, *J*<sub>1</sub> = 10.8 Hz, *J*<sub>2</sub> = 2.4 Hz, 1 H), 7.75 and 7.73 (dd, *J*<sub>1</sub> = 8.8 Hz, *J*<sub>2</sub> = 2.0 Hz,

25

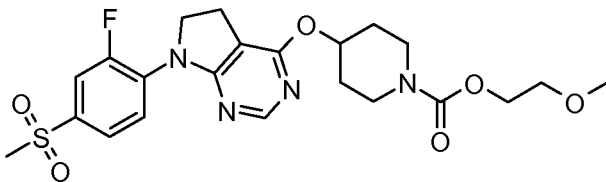
1H), 5.31 – 5.25 (m, 1 H), 4.65 (app. t,  $J = 4.0$  Hz, 1 H), 4.53 (app. t,  $J = 3.6$  Hz, 1 H), 4.27 (app. t,  $J = 4.0$  Hz, 1 H), 4.19 (app. t,  $J = 4.0$  Hz, 1 H), 4.14 (t,  $J = 8.0$  Hz, 2 H), 3.70 (app. m, 2 H), 3.28 – 3.25 (br, s, 2 H), 3.25 (s, 3 H), 3.06 (t,  $J = 8.8$  Hz, 2 H), 1.98 – 1.90 (m, 2 H), 1.65 – 1.56 (m, 2 H); LCMS (ESI):  $m/z$  483 ( $M + H$ )<sup>+</sup>.

5

**Example 63 (132)****3-Chloropropyl 4-({7-[2-fluoro-4-(methylsulfonyl)phenyl]-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-4-yl}oxy)-1-piperidinecarboxylate (132)**

10 Following the general procedure described for the compound **127**, a solution of 2.2 mL of **126** in CH<sub>2</sub>Cl<sub>2</sub> and Et<sub>3</sub>N was added 3-chloropropyl chloridocarbonate (200 μL) at RT and the reaction mixture was stirred for 18 h. The work up and chromatography gave 42 mg of the title product **132** as a white solid. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>): δ 8.22 (s, 1 H), 7.96 (t,  $J = 8.0$  Hz, 1 H), 7.86 and 7.82 (dd,  $J_1 = 10.8$  Hz,  $J_2 = 2.0$  Hz, 1 H), 7.76 and

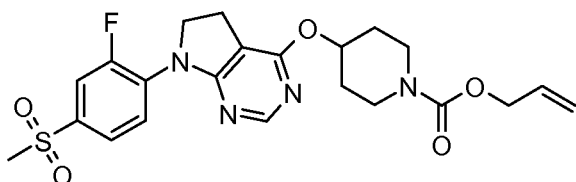
15 7.72 (dd,  $J_1 = 8.8$  Hz,  $J_2 = 2.0$  Hz, 1 H), 5.31 – 5.24 (m, 1 H), 4.14 (app. t,  $J = 8.4$  Hz, 2 H), 4.10 (t,  $J = 6.4$  Hz, 2 H), 3.70 (t,  $J = 6.4$  Hz, 2 H), 3.25 (s, 3 H), 3.30 - 3.24 (br. s, 2 H), 3.05 (t,  $J = 8.8$  Hz, 2 H), 2.02 (app. quintuplet,  $J = 12.4$  Hz, 2H), 1.96 – 1.82 (m, 2 H), 1.64 – 1.54 (m, 2 H); LCMS (ESI):  $m/z$  513 ( $M + H$ )<sup>+</sup>.

**Example 64 (133)****2-(Methoxy)ethyl 4-({7-[2-fluoro-4-(methylsulfonyl)phenyl]-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-4-yl}oxy)-1-piperidinecarboxylate (133)**

25 Following the general procedure described for the compound **127**, to a solution of **126** (100 mg, 0.198 mmol, from a different batch) in CH<sub>2</sub>Cl<sub>2</sub> (4 mL) was added Et<sub>3</sub>N (137 μL, 1 mmol) followed by 2-(methoxy)ethyl chloridocarbonate (100 μL) at RT and the

mixture was stirred for 18 h. The work up and chromatography gave 64 mg (65%) of the title product **129** as a white solid. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>): δ 8.22 (s, 1 H), 7.96 (t, *J* = 7.6 Hz, 1 H), 7.85 and 7.82 (dd, *J*<sub>1</sub> = 11.2 Hz, *J*<sub>2</sub> = 2.0 Hz, 1 H), 7.75 and 7.72 (dd, *J*<sub>1</sub> = 8.4 Hz, *J*<sub>2</sub> = 2.0 Hz, 1 H), 5.30 – 5.26 (m, 1 H), 4.16 – 4.09 (m, 2 H), 3.72 – 3.66 (m, 2 H), 3.50 (t, *J* = 4.4 Hz, 2 H), 3.24 (s, 3 H), 3.28 – 3.24 (br. s, 2 H), 3.05 (t, *J* = 8.8 Hz, 2 H), 5.30 – 5.26 (m, 1 H), 4.16 – 4.09 (m, 2 H), 3.72 – 3.66 (m, 2 H), 3.50 (t, *J* = 4.4 Hz, 2 H), 3.28 – 3.24 (br. s, 2 H), 3.24 (s, 6 H), 3.05 (t, *J* = 8.8 Hz, 2 H), 1.98 – 1.90 (m, 2 H), 1.63 – 1.54 (m, 2 H); LCMS (ESI): *m/z* 495 (M + H)<sup>+</sup>.

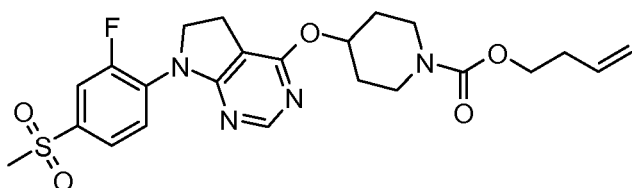
10 **Example 65 (134)**



**2-Propen-1-yl 4-({7-[2-fluoro-4-(methylsulfonyl)phenyl]-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-4-yl}oxy)-1-piperidinecarboxylate (134)**

Following the general procedure described for the compound **127**, to a solution of **126** (100 mg, 0.198 mmol, from a different batch) in CH<sub>2</sub>Cl<sub>2</sub> (4 mL) was added Et<sub>3</sub>N (137 μL, 1 mmol) followed by 2-propen-1-yl chloridocarbonate (100 μL) at RT and the mixture was stirred for 18 h. The work up and chromatography gave 56 mg (59%) of the title product **134** as a white solid. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>): δ 8.22 (s, 1 H), 7.96 (t, *J* = 7.6 Hz, 1H), 7.85 and 7.82 (dd, *J*<sub>1</sub> = 10.8 Hz, *J*<sub>2</sub> = 2.4 Hz, 1 H), 7.74 and 7.72 (dd, *J*<sub>1</sub> = 8.4 Hz, *J*<sub>2</sub> = 2.0 Hz, 1 H), 5.96 – 5.87 (m, 1 H), 5.30 – 5.24 (m, 2 H), 5.18 – 5.16 (dd, *J*<sub>1</sub> = 10.8 Hz, *J*<sub>2</sub> = 1.2 Hz, 1 H), 4.52 (d, *J* = 5.2 Hz, 2 H), 4.14 (t, *J* = 8.4 Hz, 2 H), 3.74 – 3.68 (m, 2 H), 3.30 – 3.24 (br. s, 2 H), 3.06 (t, *J* = 8.8 Hz, 2 H), 3.06 (t, *J* = 8.8 Hz, 2 H), 1.98 – 1.92 (m, 2 H), 1.64 – 1.54 (m, 2 H); LCMS (ESI): *m/z* 477 (M + H)<sup>+</sup>.

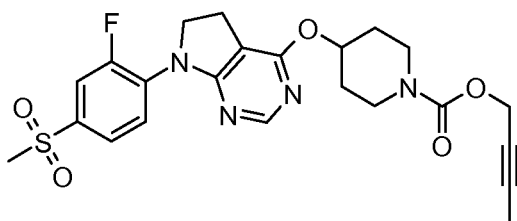
25 **Example 66 (135)**



**3-Buten-1-yl 4-({7-[2-fluoro-4-(methylsulfonyl)phenyl]-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-4-yl}oxy)-1-piperidinecarboxylate (**134**)**

Following the general procedure described for the compound **127**, a solution of **126** (2.2 mL, from step 1 of example **58**) in CH<sub>2</sub>Cl<sub>2</sub> was treated with Et<sub>3</sub>N (1.7 mL, 6 equiv) followed by 3-buten-1-yl chloridocarbonate (200 μL) at RT for 18 h. The work up and chromatography gave 66 mg of the title product **135** as a white solid. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>): δ 8.22 (s, 1 H), 7.96 (t, *J* = 8.0 Hz, 1 H), 7.86 and 7.82 (dd, *J*<sub>1</sub> = 10.8 Hz, *J*<sub>2</sub> = 2.0 Hz, 1 H), 7.76 and 7.74 (dd, *J*<sub>1</sub> = 8.4 Hz, *J*<sub>2</sub> = 2.0 Hz, 1 H), 5.84 – 5.74 (m, 1 H), 5.30 – 5.24 (m, 1 H), 5.11 – 5.08 (dd, *J*<sub>1</sub> = 17.2 Hz, *J*<sub>2</sub> = 2.0 Hz, 1 H), 5.06 and 5.02 (app. br. d, *J* = 10.4 Hz, 1 H), 4.14 (app. t, *J* = 8.4 Hz, 2 H), 4.04 (t, *J* = 6.8 Hz, 2 H), 3.72 – 3.64 (m, 2 H), 3.28 – 3.20 (br, s, 2 H), 3.25 (s, 3 H), 3.06 (t, *J* = 8.8 Hz, 2 H), 2.32 (app. q, *J* = 6.8 Hz, 2 H), 1.96 – 1.90 (m, 2 H), 1.62 – 1.54 (m, 2 H); LCMS (ESI): *m/z* 491 (M + H)<sup>+</sup>.

**Example 67 (136)**

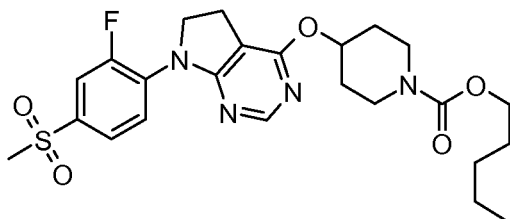


**2-Butyn-1-yl 4-({7-[2-fluoro-4-(methylsulfonyl)phenyl]-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-4-yl}oxy)-1-piperidinecarboxylate (**136**)**

Following the general procedure described for the compound **127**, a solution of **126** (2.2 mL, from step 1 of example **58**) in CH<sub>2</sub>Cl<sub>2</sub> was treated with Et<sub>3</sub>N (1.7 mL, 6 equiv) followed by 2-butyn-1-yl chloridocarbonate (200 μL) at RT for 18 h. The work up and chromatography gave 70 mg of the title product **136** as a white solid. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>): δ 8.22 (s, 1 H), 7.96 (t, *J* = 8.0 Hz, 1 H), 7.84 and 7.82 (dd, *J*<sub>1</sub> = 10.8 Hz, *J*<sub>2</sub> = 2.0 Hz, 1 H), 7.74 and 7.72 (dd, *J*<sub>1</sub> = 8.4 Hz, *J*<sub>2</sub> = 2.0 Hz, 1 H), 5.30 – 5.24 (m, 1H), 4.62

(app. d,  $J = 2.4$  Hz, 2 H), 4.14 (t,  $J = 8.4$  Hz, 2 H), 3.70-3.64 (m, 2 H), 3.28 – 3.24 (masked br. s, 2 H), 3.25 (s, 3 H), 3.06 (t,  $J = 8.8$  Hz, 2 H), 1.97 – 1.91 (m, 2 H), 1.81 (app. t,  $J = 2.4$  Hz, 3 H), 1.64 – 1.56 (m, 2 H); LCMS (ESI):  $m/z$  489 (M + H)<sup>+</sup>.

5 **Example 68 (137)**

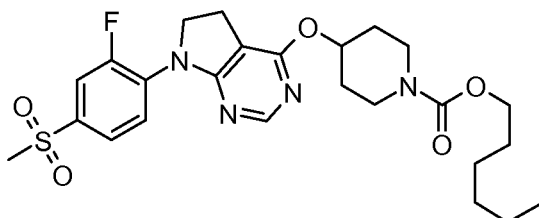


**Pentyl 4-({7-[2-fluoro-4-(methylsulfonyl)phenyl]-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-4-yl}oxy)-1-piperidinecarboxylate (137)**

10 Following the general procedure described for the compound **127**, to a solution of **126** (70 mg, 0.142 mmol, from different batch) in CH<sub>2</sub>Cl<sub>2</sub> (5 mL) was added Et<sub>3</sub>N (120 μL, 0.85 mmol) followed by pentyl chloridocarbonate (100 μL) at RT and the mixture was stirred for 18 h. The work up and chromatography gave 64 mg (89%) of the title product **137** as a white solid. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>): δ 8.22 (s, 1 H), 7.96 (t,  $J = 8.0$  Hz, 1 H), 7.84 and 7.82 (dd,  $J_1 = 11.2$  Hz,  $J_2 = 2.0$  Hz, 1 H), 7.74 and 7.72 (dd,  $J_1 = 8.4$  Hz,  $J_2 = 2.0$  Hz, 1 H), 5.30 – 5.24 (m, 1 H), 4.14 (t,  $J = 8.4$  Hz, 2 H), 3.98 (t,  $J = 6.8$  Hz, 2 H), 3.71 – 3.65 (m, 2 H), 3.28 – 3.22 (br, s, 2 H), 3.25 (s, 3 H), 3.05 (t,  $J = 8.8$  Hz, 2 H), 1.96 – 1.88 (m, 2 H), 1.62 – 1.50 (m, 4 H), 1.31 – 1.26 (m, 4 H), 0.86 (app. t,  $J = 7.2$  Hz, 3 H); LCMS (ESI):  $m/z$  507 (M + H)<sup>+</sup>.

20

**Example 69 (138)**

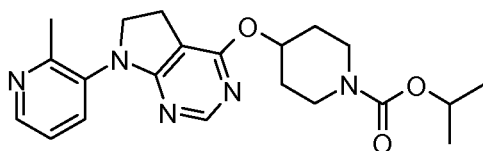


**Hexyl 4-({7-[2-fluoro-4-(methylsulfonyl)phenyl]-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-4-yl}oxy)-1-piperidinecarboxylate (138)**



Following the general procedure described for the compound **127**, to a solution of **126** (100 mg, 0.198 mmol, from a different batch) in CH<sub>2</sub>Cl<sub>2</sub> (4 mL) was added Et<sub>3</sub>N (137 μL, 1 mmol) followed by hexyl chloridocarbonate (100 μL) at RT and the mixture was stirred for 18 h. The work up and chromatography gave 72 mg (69%) of the title product **138** as a white solid. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>): δ 8.22 (s, 1 H), 7.96 (t, *J* = 8.0 Hz, 1 H), 7.84 and 7.82 (dd, *J*<sub>1</sub> = 10.8 Hz, *J*<sub>2</sub> = 2.0 Hz, 1 H), 7.75 and 7.72 (dd, *J*<sub>1</sub> = 8.4 Hz, *J*<sub>2</sub> = 2.0 Hz, 1 H), 5.32 – 5.24 (m, 1 H), 4.14 (t, *J* = 8.0 Hz, 2 H), 3.98 (t, *J* = 6.4 Hz, 2 H), 3.72 – 3.66 (m, 2 H), 3.28 – 3.20 (masked br, s, 2 H), 3.25 (s, 3 H), 3.05 (t, *J* = 6.8 Hz, 2 H), 1.96 – 1.91 (m, 2 H), 1.62 – 1.50 (m, 4 H), 1.31 – 1.21 (m, 6 H), 0.84 (app. t, *J* = 6.8 Hz, 3H); LCMS (ESI): *m/z* 521 (M + H)<sup>+</sup>.

#### Example 70 (**140**)



#### Step 1: 4-Chloro-7-(2-methyl-3-pyridinyl)-6,7-dihydro-5H-pyrrolo[2,3-*d*]pyrimidine (**139**)

A round bottom flask was charged with 2-methyl-3-pyridinamine (5.20 g, 47 mmol) and then cooled to -15°C. Trifluoroacetic acid (100 mL) was added to the above cold pyridinamine while stirring the contents for 0.5 h. Na(OAc)<sub>3</sub>BH (32.5 g, 48 mmol) was added portion-wise to the above mixture and stirred for additional 0.5 h. The aldehyde **209** (see example 117, step 1, 7.4 g, 48 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (25 mL) was added to the above mixture. The resultant mixture was allowed to warm up to the ambient temperature and stirred for 18 h. The reaction mixture was concentrated under reduced pressure and the residue was poured into sat. NaHCO<sub>3</sub> solution (250 mL) and then the mixture was extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 x 250 mL). The combined organic layer was washed with brine (1 x 100 mL), dried over sat. Na<sub>2</sub>SO<sub>4</sub> and then concentrated under reduced pressure to afford ~11.5 g (~100%) the crude material. The required bicyclic product was not obtained, but the uncyclized *N*-[2-(4,6-dichloro-5-pyrimidinyl)ethyl]-2-methyl-3-pyridinamine was isolated as a major product. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>): δ 8.81 (s, 1 H), 7.95-7.94 (m, 1 H), 7.71-7.66 (m, 2 H), 6.63 (app. t, *J* = 5.6 Hz, 1 H), 3.59

(app. q,  $J = 6.0$  Hz, 2 H), 3.08 (t,  $J = 6.4$  Hz, 2 H), 2.40 (s, 3 H), LCMS (ESI):  $m/z$  285 ( $M + H$ )<sup>+</sup>.

The round bottom flask was charged with the product (~ 11.0 g) obtained above.

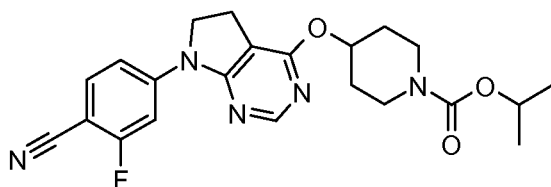
PdCl<sub>2</sub>(Ph<sub>3</sub>P)<sub>2</sub> (1.36 g, 2 mmol), potassium *tert*-butoxide (8.72 g, 77.7 mmol), K<sub>2</sub>CO<sub>3</sub> (10.74 g, 77.7 mmol), and toluene (200 mL) at RT under N<sub>2</sub>. The reaction mixture was refluxed for 18 h. The reaction mixture was cooled to RT and then filtered through a pad of celite. The filtrate was concentrated under reduced pressure to afford the crude product which was subjected for flash column chromatography to afford 0.850 g of the title product **139** (87% pure). <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>): δ 8.42 and 8.40 (dd,  $J_1 = 4.8$  Hz,  $J_2 = 1.2$  Hz, 1 H), 8.11 (s, 1H), 7.76 – 7.74 (dd,  $J_1 = 8.0$  Hz,  $J_2 = 1.6$  Hz, 1 H), 7.32 and 7.30 (dd,  $J_1 = 8.0$  Hz,  $J_2 = 4.8$  Hz, 1 H), 4.03 (t,  $J = 8.8$  Hz, 2 H), 3.20 (t,  $J = 8.4$  Hz, 2 H), 2.34 (s, 3 H), LCMS (ESI):  $m/z$  247 ( $M + H$ )<sup>+</sup>.

**Step 2: 1-Methylethyl 4-[[7-(2-methyl-3-pyridinyl)-6,7-dihydro-5H-pyrrolo[2,3-*d*]pyrimidin-4-yl]oxy]-1-piperidinecarboxylate (**140**)**

The procedure described for **10** (example 1, step 10) was employed using the compound **9** (266 mg, 1.42 mmol), NaH (170 mg, 60% dispersion in mineral oil, 4.26 mmol), compound **139** (350 mg, 1.42 mmol) in THF at reflux temperature for 2 h. Standard work-up followed by purification gave 310 mg (55%) of the title product **140** as a white solid. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>): δ 8.36 and 8.35 (dd,  $J_1 = 4.8$  Hz,  $J_2 = 1.2$  Hz, 1 H), 8.05 (s, 1 H), 7.70 – 7.68 (dd,  $J_1 = 8.0$  Hz,  $J_2 = 1.6$  Hz, 1 H), 7.27 and 7.25 (dd,  $J_1 = 8.0$  Hz,  $J_2 = 4.8$  Hz, 1 H), 5.27 – 5.20 (m, 1 H), 4.27 (septuplet,  $J = 6.4$  Hz, 1 H), 3.94 (t,  $J = 8.8$  Hz, 2 H), 3.71 – 3.66 (m, 2 H), 3.21 (app. br. t,  $J = 10.0$  Hz, 2 H), 3.04 (t,  $J = 9.2$  Hz, 2 H), 2.35 (s, 3 H), 1.95 – 1.89 (m, 2 H), 1.60 – 1.50 (m, 2 H), 1.17 (d,  $J = 6.0$  Hz, 6 H); LCMS (ESI):  $m/z$  398 ( $M + H$ )<sup>+</sup>.

25

**Example 71 (**143**)**



**Step 1: 7-(4-Bromo-3-fluorophenyl)-4-chloro-6,7-dihydro-5H-pyrrolo[2,3-*d*]pyrimidine (**141**)**

A round bottom flask was charged with 4-bromo-3-fluoroaniline (10.0 g, 52.5 mmol) and then cooled to  $-15^{\circ}\text{C}$ . Trifluoroacetic acid (50 mL) was added to the above cold aniline while stirring the contents for 0.5 h.  $\text{Na}(\text{OAc})_3\text{BH}$  (15.9 g, 50 mmol) was added portion wise to the above mixture and stirred for additional 0.5 h. The aldehyde **209** (see  
5 example 118, step 1, 7.85 g, 75 mmol) in  $\text{CH}_2\text{Cl}_2$  (15 mL) was added to the above mixture. The resultant mixture was allowed to warm up to the ambient temperature and stirred for 24 h. The reaction mixture was concentrated under reduced pressure and the residue was poured into sat.  $\text{NaHCO}_3$  solution (250 mL) and then the mixture was extracted with  $\text{CH}_2\text{Cl}_2$  (3 x 250 mL). The combined organic layer was washed with brine  
10 (1 x 100 mL), dried over sat.  $\text{Na}_2\text{SO}_4$  and then concentrated under reduced pressure to afford crude material, which was recrystallized from  $\text{CH}_2\text{Cl}_2$  and MeOH to afford 8.65 g (53%) of the title product **141** as an off-white solid.  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO}-d_6$ ):  $\delta$  8.42 (s, 1 H), 7.88 and 7.86 (dd,  $J_1 = 11.2$  Hz,  $J_2 = 2.8$  Hz, 2 H), 7.51 (t,  $J = 8.0$  Hz, 1 H), 7.36 and 7.34 (dd,  $J_1 = 9.2$  Hz,  $J_2 = 2.4$  Hz, 1 H), 4.11 (t,  $J = 8.8$  Hz, 2 H), 3.22 (t,  $J = 8.4$   
15 Hz, 2 H); LCMS (ESI):  $m/z$  329 ( $\text{M} + \text{H}$ ) $^+$ .

**Step 2: 1-Methylethyl 4-[[7-(4-bromo-3-fluorophenyl)-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-4-yl]oxy]-1-piperidinecarboxylate (142)**

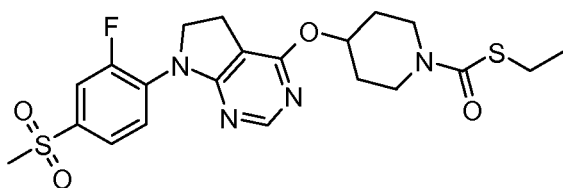
The procedure described for **10** (example 1, step 10) was employed using the compound **9** (1.79 g, 9.5 mmol), NaH (1.20 g, 60% dispersion in mineral oil, 30 mmol),  
20 compound **141** (3.30 mg, 10 mmol) in THF at reflux temperature for 2 h. Standard work-up followed by purification gave 3.46 mg (72%) of the title product **142** as a white solid.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  8.33 (s, 1H), 7.86 and 7.82 (dd,  $J_1 = 12.0$  Hz,  $J_2 = 2.4$  Hz, 1H s, 1 H), 7.47 (t,  $J = 8.0$  Hz, 1 H), 7.35 – 7.32 (dd,  $J_1 = 8.8$  Hz,  $J_2 = 2.8$  Hz, 1 H), 5.37 – 5.32 (m, 1 H), 4.93 (septuplet,  $J = 6.0$  Hz, 1H), 4.04 (t,  $J = 8.8$  Hz, 2 H), 3.82 – 3.76  
25 (br, m, 2 H), 3.36 – 3.30 (m, 2 H), 3.07 (t,  $J = 8.8$  Hz, 2 H), 2.02 – 1.95 (m, 2 H), 1.77 – 1.69 (m, 2 H), 1.25 (d,  $J = 6.4$  Hz, 6 H); LCMS (ESI):  $m/z$  481 ( $\text{M} + \text{H}$ ) $^+$ .

**Step 3: 1-Methylethyl 4-[[7-(4-cyano-3-fluorophenyl)-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-4-yl]oxy]-1-piperidinecarboxylate (143)**

The procedure described for **31** (example 10, step 7) was employed using the  
30 compound **142** (400 mg, 0.834 mmol), CuCN (150 mg, 1.67 mmol) in NMP at  $150^{\circ}\text{C}$  for 18 h. Standard work-up followed by purification gave 66 mg (19%) of the title product **143** as a white solid.  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO}-d_6$ ):  $\delta$  8.42 (s, 1 H), 8.13 – 8.09 (dd,  $J_1 =$

13.6 Hz,  $J_2 = 1.6$  Hz, 1 H), 7.84 (app. t,  $J = 8.0$  Hz, 1 H), 7.75 – 7.72 (dd,  $J_1 = 8.8$  Hz,  $J_2 = 2.0$  Hz, 1 H), 5.32 – 5.25 (m, 1 H), 4.75 (septuplet,  $J = 6.4$  Hz, 1 H), 4.10 (t,  $J = 8.8$  Hz, 2 H), 3.70 – 3.64 (m, 2 H), 3.24 (app.  $J = 9.6$  Hz, 2 H), 3.03 (t,  $J = 8.8$  Hz, 2 H), 1.96 – 1.89 (m, 2 H), 1.61 – 1.53 (m, 2 H), 1.16 (d,  $J = 6.0$  Hz, 6 H); LCMS (ESI):  $m/z$  426 (M + H)<sup>+</sup>.

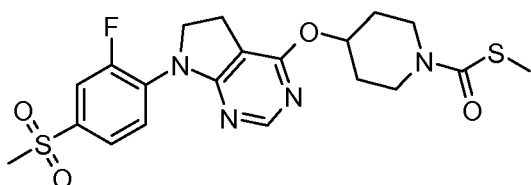
### Example 72 (144)



### S-Ethyl 4-({7-[2-fluoro-4-(methylsulfonyl)phenyl]-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-4-yl}oxy)-1-piperidinecarbothioate (144)

Following the procedure described for the compound **127**, compound **11** (example 2, 493 mg, 1 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (15 mL) was treated with TFA (2.5 mL) at RT for 1 h. The reaction mixture was concentrated under reduced pressure to afford the crude product **126** and the product was dried thoroughly and then re-dissolved in CH<sub>2</sub>Cl<sub>2</sub> (15 min). Et<sub>3</sub>N (1 mL, 7.22 mmol) followed by ethyl chlorothioformate (208 μL, 2 mmol) was introduced slowly to the above mixture at RT under N<sub>2</sub>. The reaction mixture was stirred at RT for 18 h. The reaction mixture was diluted with CH<sub>2</sub>Cl<sub>2</sub> (50 mL), washed with H<sub>2</sub>O (2 x 15 mL), brine (1 x 10 mL), dried over Na<sub>2</sub>SO<sub>4</sub> and then concentrated under reduced pressure to afford the crude product, which was subjected for flash column chromatography to afford 416 mg (87%) of the title product **144** as a white solid. <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>): δ 8.23 (s, 1 H), 7.96 (t,  $J = 8.0$  Hz, 1 H), 7.85 and 7.82 dd,  $J_1 = 11.2$  Hz,  $J_2 = 2.0$  Hz, 1 H), 7.75 and 7.73 (dd,  $J_1 = 8.4$  Hz,  $J_2 = 2.0$  Hz, 1 H), 5.36 – 5.29 (m, 1 H), 4.14 (t,  $J = 8.4$  Hz, 2 H), 3.76 (app. br. s, 2 H), 3.41-3.36 (m, 2 H), 3.25 (s, 3 H), 3.06 (t,  $J = 8.8$  Hz, 2 H), 2.81 (q,  $J = 7.2$  Hz, 2 H), 1.96 (br. s, 2 H), 1.62 (br. s, 2 H), 1.18 (t,  $J = 7.6$  Hz, 2 H); LCMS (ESI):  $m/z$  481 (M + H)<sup>+</sup>.

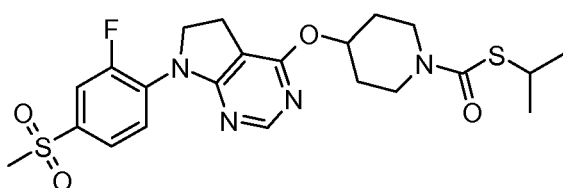
### Example 73 (145)



**S-Methyl 4-({7-[2-fluoro-4-(methylsulfonyl)phenyl]-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-4-yl}oxy)-1-piperidinecarbothioate (**145**)**

Following the procedure described for the compound **127**, compound **126** (70 mg, 0.142 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (2 mL) was treated with TFA (0.5 mL) at RT for 2 h. The reaction mixture was concentrated under reduced pressure to afford the crude product and the product was dried thoroughly and then re-dissolved in CH<sub>2</sub>Cl<sub>2</sub> (5 min). Et<sub>3</sub>N (120 μL, 0.852 mmol) followed by methyl chlorothioformate (37 μL, 0.43 mmol) was introduced slowly to the above mixture at RT under N<sub>2</sub>. The work-up and chromatography gave 56 mg (85%) of the title product **145** as a white solid. <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>): δ 8.22 (s, 1 H), 7.96 (app. t, *J* = 8.4 Hz, 1 H), 7.86 – 7.82 (dd, *J*<sub>1</sub> = 10.8 Hz, *J*<sub>2</sub> = 2.0 Hz, 1 H), 7.76 and 7.72 (dd, *J*<sub>1</sub> = 8.4 Hz, *J*<sub>2</sub> = 2.0 Hz, 1 H), 5.36 – 5.28 (m, 2 H), 4.14 (t, *J* = 8.0 Hz, 2 H), 3.74 (br. s, 2 H), 3.42-3.34 (m, 2 H), 3.25 (s, 3 H), 3.06 (t, *J* = 8.8 Hz, 2 H), 2.24 (s, 3 H), 1.96 (app. br. s, 2 H), 1.62 (app. br. m, 2 H); LCMS (ESI): *m/z* 467 (M + H)<sup>+</sup>.

**Example 74 (148)**



**Step 1: 7-[2-Fluoro-4-(methylsulfonyl)phenyl]-4-[[1-(1H-imidazol-1-yl)carbonyl]-4-piperidinyloxy]-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidine (**146**)**

Following the procedure described for **126** (example 58, step 1), the compound **11** (example 2, 20 g, 4.06 mmol) was treated with a 20% TFA in CH<sub>2</sub>Cl<sub>2</sub> (50 mL) at RT for 3 h. The reaction mixture was concentrated under reduced pressure to afford to crude material. To a solution of the product, thus obtained above, in CH<sub>2</sub>Cl<sub>2</sub> (150 mL) was added 1,1'-(oxomethanediyl)bis-1H-imidazole (725 mg, 4.47 mmol) at 5 °C. The reaction mixture was allowed to warm to ambient temperature and allowed to stir for 24 h. The

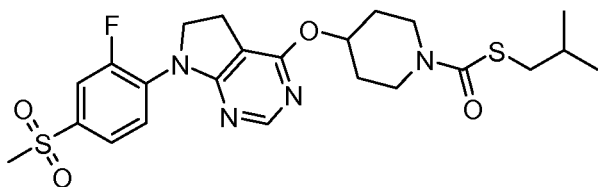
reaction mixture was diluted with CH<sub>2</sub>Cl<sub>2</sub> (200 mL) and the mixture was washed with H<sub>2</sub>O (2 x 40 mL). The organic layer was dried over Na<sub>2</sub>SO<sub>4</sub> and then concentrated under reduced pressure to afford crude product, which was recrystallized from CH<sub>2</sub>Cl<sub>2</sub> to give 1.91 g (97%) of the title product **146** as a white solid. <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>): δ 8.24 (s, 1 H), 8.02 (s, 1 H), 7.96 (app. t, *J* = 8.0 Hz, 1 H), 7.85 and 7.83 (dd, *J*<sub>1</sub> = 11.2 Hz, *J*<sub>2</sub> = 2.4 Hz, 1 H), 7.75 – 7.73 (dd, *J*<sub>1</sub> = 8.4 Hz, *J*<sub>2</sub> = 2.0 Hz, 1 H), 7.47 (s, 1 H), 7.02 (s, 1 H), 5.40 – 5.28 (m, 1 H), 4.15 (t, *J* = 8.4 Hz, 2 H), 3.71 (m, 2 H), 3.48 – 3.42 (m, 2 H), 3.25 (s, 3 H), 3.07 (t, *J* = 9.2 Hz, 2 H), 2.10 – 2.02 (m, 2 H), 1.83 – 1.75 (m, 2 H); LCMS (ESI): *m/z* 487 (M + H)<sup>+</sup>.

10 **Step 2: 1-[[4-({7-[2-Fluoro-4-(methylsulfonyl)phenyl]-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-4-yl}oxy)-1-piperidinyl]carbonyl]-3-methyl-1H-imidazol-3-ium iodide (147)**

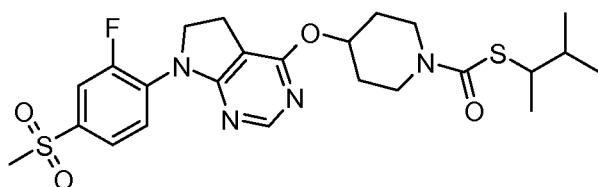
To a stirred solution of **146** (1.9 g, 3.90 mmol) in CH<sub>3</sub>CN (30 mL) and CH<sub>2</sub>Cl<sub>2</sub> (30 mL) was added methyl iodide (1.46 mL, 23.46 mmol) at RT under N<sub>2</sub>. The reaction mixture was stirred at RT for 24 h and then concentrated under reduced pressure to afford 2.46 g (100%) of the title product **147** as an off-white solid. <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>): δ 9.55 (s, 1 H), 8.24 (s, 1 H), 8.03 (app. t, *J* = 3.6 Hz, 1 H), 7.96 (t, *J* = 8.0 Hz, 1 H), 7.86 – 7.82 (m, 2H), 7.76 and 7.74 (dd, *J*<sub>1</sub> = 8.4 Hz, *J*<sub>2</sub> = 2.0 Hz, 1 H), (app. t, *J* = 8.0 Hz, 1 H), 5.42 (m, 1 H), 4.16 (t, *J* = 8.4 Hz, 2 H), 3.90 (s, 3 H), 3.71 (br, s, 2 H), 3.50 (br, s, 2 H), 3.25 (s, 3 H), 3.07 (t, *J* = 9.2 Hz, 2 H), 2.12 – 2.04 (br. m, 2 H), 1.88 – 1.80 (m, 2 H).

20 **Step 3: S-(1-Methylethyl) 4-({7-[2-fluoro-4-(methylsulfonyl)phenyl]-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-4-yl}oxy)-1-piperidinecarbothioate (148)**

To a suspension of compound **147** (315 mg, 0.5 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (3 mL) were added Et<sub>3</sub>N (70 μL, 0.5 mmol) and isopropylthiol (38 mg, 0.5 mmol) at RT under N<sub>2</sub>. The reaction mixture was stirred at RT for 18 h. The work-up and column chromatography gave 156 mg (63%) of the title product **148** as a white solid. <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>): δ 8.23 (s, 1H), 7.96 (app. t, *J* = 8.0 Hz, 1 H), 7.85 and 7.82 (app. br. d, *J* = 10.8 Hz, 1 H), 7.74 (app. br. d, *J* = 6.8 Hz, 1 H), 5.30 – 5.28 (m, 1 H), 4.14 (t, *J* = 8.4 Hz, 2 H), 3.46 (m, 1 H), 3.37 – 3.30 (app. br. m, 2 H), 3.25 (s, 3 H), 3.06 (t, *J* = 8.4 Hz, 2 H), 1.94 (app. br. s, 2 H), 1.61 (app. br. s, 2 H), 1.26 (d, *J* = 6.4 Hz, 6 H); LCMS (ESI): *m/z* 495 (M + H)<sup>+</sup>.

**Example 75 (149)****S-(2-Methylpropyl) 4-({7-[2-fluoro-4-(methylsulfonyl)phenyl]-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-4-yl}oxy)-1-piperidinecarbothioate (149)**

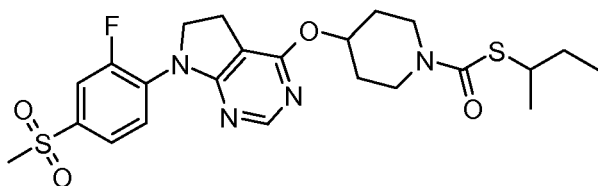
- 5 Following the procedure described for the compound **148**, to a solution of imidazole salt **147** (115 mg, 0.183 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (5 mL) were added Et<sub>3</sub>N (76 μL, 0.55 mmol) and isobutylthiol (100 μL). The reaction was stirred for 15 h. The workup and chromatography gave 52 mg (56%) of the title product **149** as a white solid. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>): δ 8.22 (s, 1 H), 7.96 (t, *J* = 7.2 Hz, 1 H), 7.84 (br, d, *J* = 11.2 Hz, 1 H), 7.73 (br, d, *J* = 8.4 Hz, 1 H), 5.32 (app. br, s, 1 H), 4.14 (t, *J* = 8.8 Hz, 2 H), 3.75 (br, s, 2 H), 3.42 – 3.37 (m, 2 H), 3.25 (s, 3 H), 3.06 (t, *J* = 8.8 Hz, 2 H), 2.75 (d, *J* = 6.8 Hz, 2 H), 1.96 (app. br. s, 2 H), 1.78 – 1.68 (m, 1 H), 1.62 (app. br. s, 2 H), 0.91 (d, *J* = 5.2 Hz, 6 H); LCMS (ESI): *m/z* 509 (M + H)<sup>+</sup>.
- 10

**Example 76 (150)****(±)-S-(1,2-Dimethylpropyl) 4-({7-[2-fluoro-4-(methylsulfonyl)phenyl]-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-4-yl}oxy)-1-piperidinecarbothioate (150)**

- 20 Following the procedure described for the compound **148**, to a solution of imidazole salt **147** (115 mg, 0.183 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (5 mL) were added Et<sub>3</sub>N (76 μL, 0.55 mmol) and 3-methyl-2-butanethiol (100 μL). The reaction was stirred for 15 h. The workup and chromatography gave 65 mg (68%) of the title product **150** as a white solid. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>): δ 8.22 (s, 1 H), 7.96 (t, *J* = 7.2 Hz, 1 H), 7.85-7.82 (dd, *J*<sub>1</sub> = 10.8 Hz, *J*<sub>2</sub> = 2.0 Hz, 1 H), 7.75 and 7.73 (dd, *J*<sub>1</sub> = 8.4 Hz, *J*<sub>2</sub> = 2.0 Hz, 1 H), 5.35 – 5.29 (m, 1 H), 4.14 (t, *J* = 7.6 Hz, 2 H), 3.73 (app. br, s, 2 H), 3.44 – 3.35 (m, 3 H), 3.25 (s, 3 H),
- 25

3.06 (t,  $J = 7.2$  Hz, 2 H), 1.98 – 1.96 (app. br, s, 2 H), 1.89 – 1.82 (m, 2 H), 1.64 – 1.58 (m, 2 H), 1.21 (d,  $J = 9.2$  Hz, 3 H), 0.90 (d,  $J = 6.8$  Hz, 6 H); LCMS (ESI):  $m/z$  523 (M + H)<sup>+</sup>.

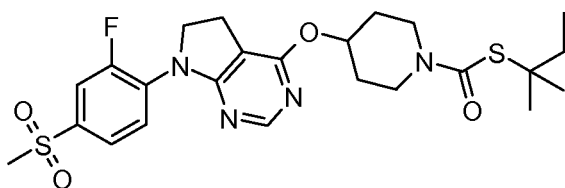
5 **Example 77 (151)**



**(±)-S-(1-Methylpropyl) 4-({7-[2-fluoro-4-(methylsulfonyl)phenyl]-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-4-yl}oxy)-1-piperidinecarbothioate (151)**

Following the procedure described for the compound **148**, to a solution of imidazole salt **147** (115 mg, 0.183 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (5 mL) were added Et<sub>3</sub>N (76 μL, 0.55 mmol) and 2-butanethiol (100 μL). The reaction was stirred for 15 h. The workup and chromatography gave 58 mg (62%) of the title product **151** as a white solid. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>): δ 8.22 (s, 1 H), 7.96 (t,  $J = 8.0$  Hz, 1 H), 7.85-7.82 (dd,  $J_1 = 10.8$  Hz,  $J_2 = 2.0$  Hz, 1 H), 7.75 and 7.72 (dd,  $J_1 = 8.4$  Hz,  $J_2 = 2.0$  Hz, 1 H), 5.34 – 5.28 (m, 1 H), 4.14 (t,  $J = 8.4$  Hz, 2 H), 3.40 – 3.30 (m, 3 H), 3.25 (s, 3 H), 3.06 (t,  $J = 8.8$  Hz, 2 H), 1.97 – 1.95 (app. br. m, 2 H), 1.65 – 1.52 (m, 4 H), 1.25 (d,  $J = 6.8$  Hz, 3 H), 0.90 (t,  $J = 7.2$  Hz, 3 H); LCMS (ESI):  $m/z$  509 (M + H)<sup>+</sup>.

**Example 78 (152)**



20

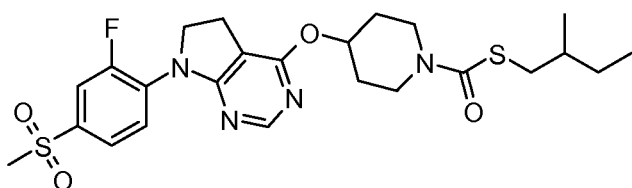
**S-(1,1-Dimethylpropyl) 4-({7-[2-fluoro-4-(methylsulfonyl)phenyl]-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-4-yl}oxy)-1-piperidinecarbothioate (152)**

Following the procedure described for the compound **148**, to a solution of imidazole salt **147** (115 mg, 0.183 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (5 mL) were added Et<sub>3</sub>N (76 μL, 0.55 mmol) and



2-methyl-2-butanethiol (100  $\mu$ L). The reaction was stirred for 15 h. The work up and chromatography gave 56 mg (58%) of the title product **152** as a white solid.  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO-}d_6$ ):  $\delta$  8.22 (s, 1 H), 7.96 (t,  $J = 8.0$  Hz, 1 H), 7.85-7.82 (dd,  $J_1 = 10.8$  Hz,  $J_2 = 2.0$  Hz, 1 H), 7.75 and 7.72 (dd,  $J_1 = 8.8$  Hz,  $J_2 = 2.0$  Hz, 1 H), 5.33 – 5.27 (m, 1 H), 4.14 (t,  $J = 8.4$  Hz, 2H), 3.71 (app. br. m, 2 H), 1.76 (q,  $J = 7.2$  Hz, 2 H), 1.63 – 1.56 (m, 2 H), 1.38 (s, 6 H), 0.87 (t,  $J = 7.2$  Hz, 3 H); LCMS (ESI):  $m/z$  523 ( $\text{M} + \text{H}$ ) $^+$ .

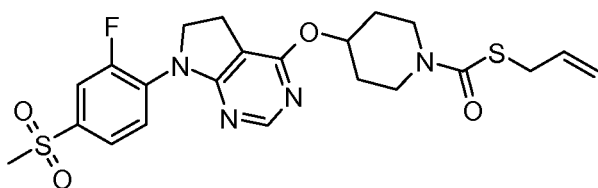
### Example 79 (**153**)



### 10 ( $\pm$ )-S-(2-Methylbutyl) 4-({7-[2-fluoro-4-(methylsulfonyl)phenyl]-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-4-yl}oxy)-1-piperidinecarbothioate (**153**)

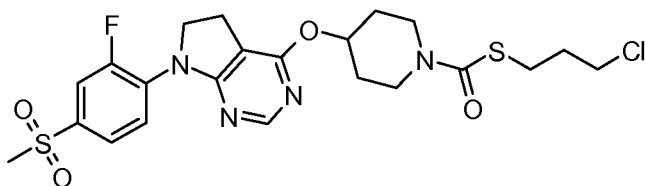
Following the procedure described for the compound **148**, to a solution of imidazole salt **147** (115 mg, 0.183 mmol) in  $\text{CH}_2\text{Cl}_2$  (5 mL) were added  $\text{Et}_3\text{N}$  (76  $\mu$ L, 0.55 mmol) and 2-methyl-1-butanethiol (100  $\mu$ L). The reaction was stirred for 15 h. The workup and chromatography gave 62 mg (65%) of the title product **153** as a white solid.  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO-}d_6$ ):  $\delta$  8.22 (s, 1 H), 7.96 (t,  $J = 8.0$  Hz, 1 H), 7.85-7.82 (dd,  $J_1 = 11.2$  Hz,  $J_2 = 2.0$  Hz, 1 H), 7.75 and 7.72 (dd,  $J_1 = 8.8$  Hz,  $J_2 = 2.0$  Hz, 1 H), 5.33 – 5.30 (m, 1 H), 4.14 (t,  $J = 8.4$  Hz, 2 H), 3.75 (app. br. s, 2 H), 3.43 – 3.36 (m, 2 H), 3.25 (s, 3 H), 3.06 (t,  $J = 8.8$  Hz, 2 H), 2.90 and 2.87 (dd,  $J_1 = 13.2$  Hz,  $J_2 = 5.6$  Hz, 1 H), 1.96 (app. br, s, 2 H), 1.62 (app. br. s, 2H), 1.56 – 1.48 (m, 1 H), 1.44 – 1.33 (m, 1 H), 1.21 – 1.10 (m, 1 H), 0.89 – 0.82 (m, 6 H); LCMS (ESI):  $m/z$  523 ( $\text{M} + \text{H}$ ) $^+$ .

### Example 80 (**154**)



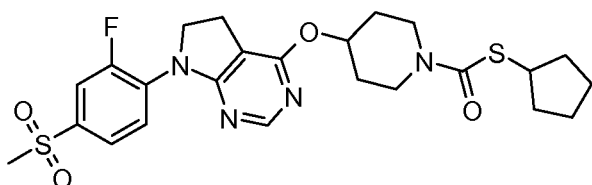
**S-2-Propen-1-yl 4-({7-[2-fluoro-4-(methylsulfonyl)phenyl]-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-4-yl}oxy)-1-piperidinecarbothioate (154)**

Following the procedure described for the compound **148**, to a solution of imidazole salt **147** (115 mg, 0.183 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (5 mL) were added Et<sub>3</sub>N (76 μL, 0.55 mmol) and 2-propene-1-thiol (100 μL). The reaction was stirred for 15h. The workup and chromatography gave 32 mg (36%) of the title product **154** as a white solid. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>): δ 8.22 (s, 1 H), 7.96 (t, *J* = 8.0 Hz, 1 H), 7.85 – 7.82 (dd, *J*<sub>1</sub> = 11.2 Hz, *J*<sub>2</sub> = 2.0 Hz, 1 H), 7.75 and 7.72 (dd, *J*<sub>1</sub> = 8.8 Hz, *J*<sub>2</sub> = 2.0 Hz, 1 H), 5.86 – 5.75 (m, 1 H), 5.35 – 5.30 (m, 1 H), 5.23 and 5.19 (dd, *J*<sub>1</sub> = 16.8 Hz, *J*<sub>2</sub> = 1.6 Hz, 1 H), 5.05 (app. br. d, *J* = 10.0 Hz, 1 H), 4.14 (t, *J* = 8.4 Hz, 2 H), 3.72 (app. br. s, 2 H), 3.52 (app. d, *J* = 6.8 Hz, 2 H), 3.42 – 3.36 (m, 2 H), 3.25 (s, 3 H), 3.06 (t, *J* = 8.8 Hz, 2 H), 2.02 – 1.92 (br. m, 2 H), 1.68 – 1.56 (br. m, 2 H); LCMS (ESI): *m/z* 493 (M + H)<sup>+</sup>.

**Example 81 (155)****S-(3-Chloropropyl) 4-({7-[2-fluoro-4-(methylsulfonyl)phenyl]-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-4-yl}oxy)-1-piperidinecarbothioate (155)**

Following the procedure described for the compound **148**, to a solution of imidazole salt **147** (115 mg, 0.183 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (5 mL) were added Et<sub>3</sub>N (76 μL, 0.55 mmol) and 3-chloro-1-propanethiol (100 μL). The reaction was stirred for 15 h. The workup and chromatography gave 71 mg (73%) of the title product **155** as a white solid. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>): δ 8.22 (s, 1 H), 7.96 (t, *J* = 8.0 Hz, 1 H), 7.85 – 7.82 (dd, *J*<sub>1</sub> = 11.2 Hz, *J*<sub>2</sub> = 2.0 Hz, 1 H), 7.75 and 7.72 (dd, *J*<sub>1</sub> = 8.8 Hz, *J*<sub>2</sub> = 2.0 Hz, 1H), 5.35 – 5.30 (m, 1 H), 4.14 (t, *J* = 8.4 Hz, 2 H), 3.65 (br. s, 2 H), 3.67 (t, *J* = 6.4 Hz, 2 H), 3.40 – 3.36 (m, 2 H), 3.25 (s, 3 H), 3.06 (t, *J* = 9.2 Hz, 2 H), 2.99 (t, *J* = 7.2 Hz, 2 H), 2.00 – 1.94 (m, 4 H), 1.68 – 1.58 (m, 2 H); LCMS (ESI): *m/z* 530 (M + H)<sup>+</sup>.

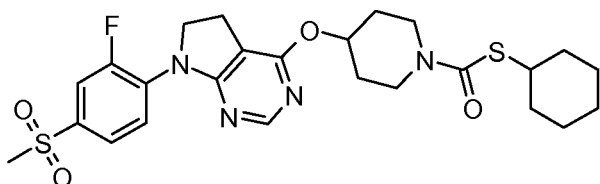
**Example 82 (156)**



**S-Cyclopentyl 4-({7-[2-fluoro-4-(methylsulfonyl)phenyl]-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-4-yl}oxy)-1-piperidinecarbothioate (156)**

Following the procedure described for the compound **148**, to a solution of imidazole salt **147** (115 mg, 0.183 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (5 mL) were added Et<sub>3</sub>N (76 μL, 0.55 mmol) and cyclopentanethiol (100 μL). The reaction was stirred for 15 h. The work up and chromatography gave 74 mg (78%) of the title product **156** as a white solid. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>): δ 8.22 (s, 1 H), 7.96 (t, *J* = 8.0 Hz, 1 H), 7.85 – 7.82 (dd, *J*<sub>1</sub> = 11.2 Hz, *J*<sub>2</sub> = 2.0 Hz, 1 H), 7.75 and 7.72 (dd, *J*<sub>1</sub> = 8.8 Hz, *J*<sub>2</sub> = 2.0 Hz, 1 H), 5.34 – 5.28 (m, 1 H), 4.14 (t, *J* = 8.4 Hz, 2 H), 3.70 (br. s, 2 H), 3.56 (m, 1 H), 3.38 – 3.31 (m, 3 H), 3.25 (s, 3 H), 3.06 (t, *J* = 8.4 Hz, 2 H), 2.06 – 1.90 (m, 4 H), 1.67 – 1.44 (m, 8 H); LCMS (ESI): *m/z* 521 (M + H)<sup>+</sup>.

**Example 83 (157)**

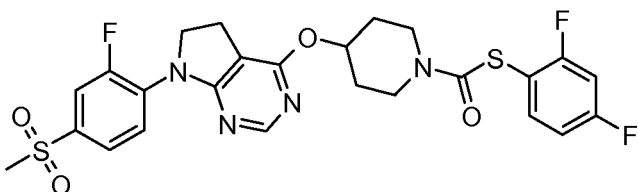


**S-Cyclohexyl 4-({7-[2-fluoro-4-(methylsulfonyl)phenyl]-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-4-yl}oxy)-1-piperidinecarbothioate (157)**

Following the procedure described for the compound **148**, to a solution of imidazole salt **147** (115 mg, 0.183 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (5 mL) were added Et<sub>3</sub>N (76 μL, 0.55 mmol) and cyclohexanethiol (100 μL). The reaction was stirred for 15 h. The workup and chromatography gave 69 mg (70%) of the title product **157** as a white solid. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>): δ 8.22 (s, 1 H), 7.95 (t, *J* = 8.0 Hz, 1 H), 7.85-7.82 (dd, *J*<sub>1</sub> = 11.2 Hz, *J*<sub>2</sub> = 2.0 Hz, 1 H), 7.75 and 7.72 (dd, *J*<sub>1</sub> = 8.8 Hz, *J*<sub>2</sub> = 2.0 Hz, 1 H), 5.35 – 5.28 (m, 1 H), 4.14 (t, *J* = 8.4 Hz, 2 H), 3.70 (br. s, 2 H), 3.39 – 3.31 (m, 4 H), 3.25 (s, 3 H), 3.06 (t,

$J = 8.8$  Hz, 2 H), 1.97 – 1.87 (m, 4 H), 1.64 – 1.58 (m, 4 H), 1.41 – 1.29 (m, 4 H), 1.26 – 1.21 (m, 1 H); LCMS (ESI):  $m/z$  535 (M + H)<sup>+</sup>.

#### Example 84 (158)



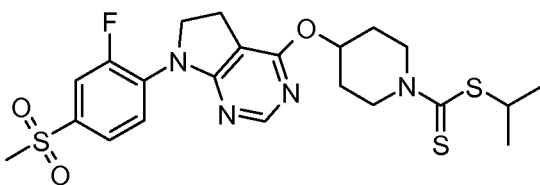
5

#### S-(2,4-Difluorophenyl) 4-({7-[2-fluoro-4-(methylsulfonyl)phenyl]-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-4-yl}oxy)-1-piperidinecarbothioate (158)

Following the procedure described for the compound **148**, to a solution of imidazole salt **147** (115 mg, 0.183 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (5 mL) were added Et<sub>3</sub>N (76 μL, 0.55 mmol) and 2,4-difluorobenzenethiol (100 μL). The reaction was stirred for 15 h. The workup and chromatography gave 76 mg (73%) of the title product **158** as a white solid. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>): δ 8.24 (s, 1 H), 7.96 (t,  $J = 8.0$  Hz, 1 H), 7.85 – 7.82 (dd,  $J_1 = 10.8$  Hz,  $J_2 = 2.0$  Hz, 1 H), 7.75 and 7.72 (dd,  $J_1 = 8.8$  Hz,  $J_2 = 2.0$  Hz, 1 H), 7.62 – 7.56 (m, 1 H), 7.44 – 7.38 (m, 1 H), 7.18 – 7.13 (m, 1 H), 5.39 – 5.33 (m, 1 H), 4.15 (t,  $J = 8.4$  Hz, 2 H), 3.78 – 3.74 (m, 2 H), 3.47 (br. s, 2 H), 3.25 (s, 3 H), 3.08 (t,  $J = 8.8$  Hz, 2 H), 2.02 (br. s, 2 H), 1.70 (br. s, 2 H); LCMS (ESI):  $m/z$  565 (M + H)<sup>+</sup>.

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#### Example 85 (161)



#### Step 1: 7-[2-Fluoro-4-(methylsulfonyl)phenyl]-4-[[1-(1H-imidazol-1-yl)carbonothioyl]-4-piperidinyloxy]-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidine (159)

Following the procedure described for **126** (example 58, step 1), the compound **11** (example 2, 1.14 g, 2.31 mmol) was treated with a 20% TFA in CH<sub>2</sub>Cl<sub>2</sub> (25 mL) at RT for 2 h. The reaction mixture was concentrated under reduced pressure to afford to crude material. To a solution of the product, thus obtained above, in CH<sub>2</sub>Cl<sub>2</sub> (100 mL) was added 1,1'-(thioxomethanediyl)bis-1H-imidazole (453 mg, 2.54 mmol) at 5 °C. The

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reaction mixture was allowed to warm to ambient temperature and allowed to stir for 24 h. The work up described for **146** was employed to isolate 1.12 g (95%) of the title product **159** (95%) as a white solid. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>): δ 8.24 (s, 1 H), 8.03 (s, 1 H), 7.96 (t, *J* = 8.0 Hz, 1 H), 7.86 and 7.83 (dd, *J*<sub>1</sub> = 10.8 Hz, *J*<sub>2</sub> = 2.0 Hz, 1 H), 7.76 and 7.73 (dd, *J*<sub>1</sub> = 8.4 Hz, *J*<sub>2</sub> = 2.4 Hz, 1 H), 7.51 (s, 1 H), 7.02 (s, 1 H), 5.47 – 5.41 (m, 1 H), 4.16 (t, *J* = 8.4 Hz, 2 H), 3.25 (s, 3 H), 3.07 (t, *J* = 8.8 Hz, 2 H), 2.12 (app. br. s, 2H), 1.89 (app. br. s, 2 H); LCMS (ESI): *m/z* 503 (M + H)<sup>+</sup>.

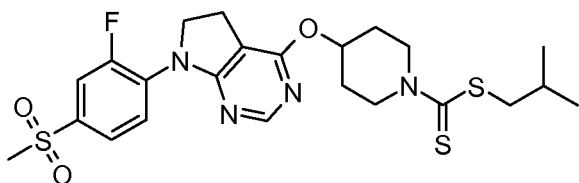
**Step 2: 1-([4-({7-[2-Fluoro-4-(methylsulfonyl)phenyl]-6,7-dihydro-5H-pyrrolo[2,3-*d*]pyrimidin-4-yl}oxy)-1-piperidinyl]carbonothioyl)-3-methyl-1H-imidazol-3-ium iodide (**160**)**

The procedure described for **147** was employed using compound **159** (1.0 g, 2 mmol), MeI (750 μL, 12 mmol), CH<sub>2</sub>Cl<sub>2</sub> (20 mL), and CH<sub>3</sub>CN (20 mL) at RT. The reaction mixture was concentrated under reduced pressure to afford 1.30 g (~100%) of the title salt **160** as a yellow solid. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>): δ 9.62 (s, 1 H), 8.24 (s, 1 H), 8.10 (m, 1 H), 7.96 (t, *J* = 7.6 Hz, 1 H), 7.86 and 7.84 (m, 2 H), 7.76 and 7.74 (dd, *J*<sub>1</sub> = 8.8 Hz, *J*<sub>2</sub> = 4.0 Hz, 1 H), 5.50 – 5.46 (m, 1 H), 4.32 (br. s, 1 H), 4.19 – 4.10 (br. s, 4 H), 3.89 (s, 3 H), 3.76 (br. s, 1 H), 3.64 (br. s, 1 H), 3.25 (s, 3 H), 3.08 (t, *J* = 8.4 Hz, 2 H), 2.22 and 2.10 (br. s, 2 H), 1.96 – 1.90 (br. s, 1 H), (app. br. s, 2 H), 1.89 (app. br. s, 2 H).

**Step 3: 1-Methylethyl 4-({7-[2-fluoro-4-(methylsulfonyl)phenyl]-6,7-dihydro-5H-pyrrolo[2,3-*d*]pyrimidin-4-yl}oxy)-1-piperidinecarbodithioate (**161**)**

The procedure described for **148** (example 74, step 3) was employed using compound **160** (323 g, 0.5 mmol), Et<sub>3</sub>N (70 μL, 0.5 mmol), 2-propanethiol (38 mg, 0.5 mmol), and CH<sub>2</sub>Cl<sub>2</sub> (3 mL). The work up followed by purification afforded 132 mg (52%) of the title product **161** as an off-white solid. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>): δ 8.24 (s, 1 H), 7.96 (t, *J* = 8.0 Hz, 1 H), 7.85 and 7.82 (dd, *J*<sub>1</sub> = 11.2 Hz, *J*<sub>2</sub> = 2.0 Hz, 1 H), 7.76 and 7.73 (dd, *J*<sub>1</sub> = 8.8 Hz, *J*<sub>2</sub> = 2.0 Hz, 1 H), 7.51 (s, 1 H), 7.02 (s, 1 H), 5.44 – 5.39 (m, 1 H), 4.47 (app. br. s, 1 H), 4.21 (app. br. s, 1 H), 4.15 (t, *J* = 8.8 Hz, 2 H), 4.14 – 4.06 (app. br. m, 2 H), 3.92 – 3.84 (m, 1 H), 3.25 (s, 3 H), 3.07 (t, *J* = 8.4 Hz, 2 H), 2.06 – 2.00 (m, 2 H), 1.74 – 1.68 (m, 2 H), 1.35 (d, *J* = 6.8 Hz, 6 H); LCMS (ESI): *m/z* 511(M + H)<sup>+</sup>.

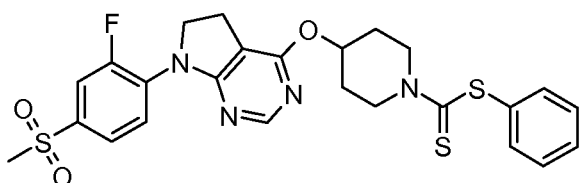
**Example 86 (**162**)**



**2-Methylpropyl 4-({7-[2-fluoro-4-(methylsulfonyl)phenyl]-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-4-yl}oxy)-1-piperidinecarbodithioate (**162**)**

The procedure described for **148** (example 74, step 3) was employed using compound  
 5 **160** (120 g, 0.19 mmol), Et<sub>3</sub>N (76 μL, 0.56 mmol), 2-methyl-1-propanethiol (34 mg, 0.37 mL), and CH<sub>2</sub>Cl<sub>2</sub> (5 mL). The work up followed by purification afforded 58 mg (60%) of the title product **162** as an off-white solid. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>): δ 8.24 (s, 1 H), 7.96 (t, *J* = 8.0 Hz, 1 H), 7.85 and 7.82 (dd, *J*<sub>1</sub> = 10.8 Hz, *J*<sub>2</sub> = 2.0 Hz, 1 H), 7.75 and 7.73 (dd, *J*<sub>1</sub> = 8.4 Hz, *J*<sub>2</sub> = 2.0 Hz, 1 H), 5.45 – 5.40 (m, 1 H), 4.49 (br. s, 1 H), 4.22 (br. s, 1 H), 4.14 (app. br. s, 1 H), 4.15 (t, *J* = 8.0 Hz, 2 H), 3.95 (br. s, 1 H), 3.25 (s, 3 H), 3.15  
 10 (d, *J* = 7.2 Hz, 2 H), 3.08 (t, *J* = 9.2 Hz, 2 H), 2.04 (br. s, 2 H), 1.98 – 1.84 (m, 1 H), 1.75 (m, 2 H), 0.95 (d, *J* = 6.8 Hz, 6 H); LCMS (ESI): *m/z* 525 (M + H)<sup>+</sup>.

**Example 87 (163)**



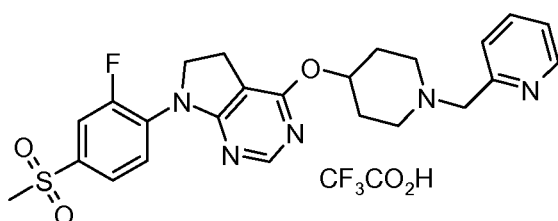
15

**Phenyl 4-({7-[2-fluoro-4-(methylsulfonyl)phenyl]-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-4-yl}oxy)-1-piperidinecarbodithioate (**163**)**

To a stirred solution of **11** (example 2, 175 mg, 0.355 mmol) was treated with 20% TFA in CH<sub>2</sub>Cl<sub>2</sub> (5 mL) at RT for 2 h. The reaction mixture concentrated under reduced  
 20 pressure to afford the crude product **126**, which was dried and then dissolved in CH<sub>2</sub>Cl<sub>2</sub>. Et<sub>3</sub>N (280 μL, 2.01 mmol) and phenyl chloridodithiocarbonate (167 mg, 0.89 mmol) were added sequentially and the reaction mixture was stirred at RT for 15 h. The work up followed by purification gave 106 mg (55%) of the title product **163** as a white solid. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>): δ 8.25 (s, 1 H), 7.96 (t, *J* = 8.0 Hz, 1 H), 7.86 and 7.84 (dd, *J*<sub>1</sub> = 11.2 Hz, *J*<sub>2</sub> = 2.0 Hz, 1 H), 7.76 and 7.74 (dd, *J*<sub>1</sub> = 8.4 Hz, *J*<sub>2</sub> = 1.6 Hz, 1 H), 7.48 – 7.40 (m, 5 H), 5.48 – 5.42 (m, 1 H), 4.46 (app. br. s, 1 H), 4.22 (br. s, 2 H), 4.16 (t, *J* =  
 25

8.4 Hz, 2 H), 4.06 (br. s, 2 H), 3.26 (s, 3 H), 3.09 (t,  $J = 8.8$  Hz, 2 H), 2.20 – 2.06 (br. s, 2H), 1.92 – 1.72 (br. s, 2H); LCMS (ESI):  $m/z$  525 ( $M + H$ )<sup>+</sup>.

**Example 88 (164)**



**Step 1: 7-[2-Fluoro-4-(methylsulfonyl)phenyl]-4-(4-piperidinyloxy)-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidine trifluoroacetate (126)**

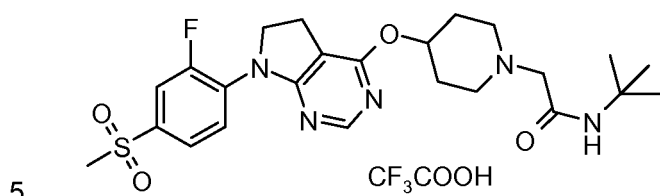
1,1-Dimethylethyl 4-({7-[2-fluoro-4-(methylsulfonyl)phenyl]-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-4-yl}oxy)-1-piperidinecarboxylate (**11**) (550 mg, 1.12 mmol) was dissolved in  
 10  $CH_2Cl_2$  (15 mL) and of trifluoroacetic acid (2 mL). The resulting solution was stirred at room temperature for 1 h. All solvents were then removed under reduced pressure to give 560 mg of the desired compound **126** as a clear oil that was used without additional purification. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>):  $\delta$  8.67 – 8.34 (m, 2 H), 8.21 (s, 1 H), 7.95 (app. t,  $J = 8.5$  Hz, 1 H), 7.85 (dd,  $J_1 = 10.9$ ,  $J_2 = 2.2$  Hz, 1 H), 7.79 (dd,  $J_1 = 8.5$ ,  $J_2 = 2.2$   
 15 Hz, 1 H), 5.41 – 5.30 (m, 1 H), 4.18 (t,  $J = 8.5$  Hz, 2 H), 3.38 – 3.33 (m, 5 H), 3.19 – 3.0 (m, 4 H), 2.19 – 2.06 (m, 2 H) 1.93 – 1.76 (m, 2 H); LCMS (ESI):  $m/z$  393 ( $M + H$ )<sup>+</sup>.

**Step 2: 7-[2-Fluoro-4-(methylsulfonyl)phenyl]-4-[[1-(2-pyridinylmethyl)-4-piperidinyl]oxy]-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidine trifluoroacetate (164)**

Compound **126** (50 mg, 0.100 mmol) was combined with triethylamine (50  $\mu$ L, 0.535 mmol) into 10 mL of methylene chloride. The mixture was stirred at room temperature for 15 minutes. 2-Pyridyl benzaldehyde (50 mg, 0.467 mmol) was then added to the solution followed by macroporous cyanoborohydride resin (100 mg, 47.6 mmol). The resulting mixture was stirred at room temperature for 18 h. The crude reaction was then filtered and concentrated to dryness, and purified *via* reverse phase chromatography  
 20 using a gradient of 5-95% acetonitrile in water (0.1% trifluoroacetic acid additive) to give 21 mg (36%) of the desired compound **164** as a trifluoroacetate salt. <sup>1</sup>H NMR (400 MHz,  $CDCl_3$ ):  $\delta$  8.71 – 8.53 (m, 1 H), 8.23 (s, 1 H), 8.10 (app. t,  $J = 8.5$  Hz, 1 H), 7.95 – 7.87 (m, 2 H), 7.57 (d,  $J = 8.5$  Hz, 2 H), 7.53 – 7.35 (m, 2 H), 5.52 – 5.36 (m, 1 H), 4.48 (s, 2

H), 4.22 (t,  $J = 8.5$  Hz 2 H), 3.56 – 3.30 (m, 4 H), 3.17 (t,  $J = 8.5$  Hz 2 H), 3.05 (s, 3 H), 2.41 – 2.29 (m, 2 H), 2.29 – 2.18 (m, 2 H); LCMS (ESI):  $m/z$  568 (M + H)<sup>+</sup>.

**Example 89 (165)**



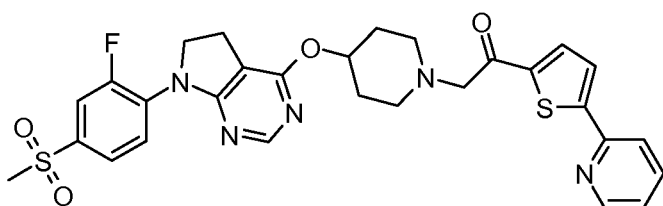
***N*-(1,1-Dimethylethyl)-2-[4-({7-[2-fluoro-4-(methylsulfonyl)phenyl]-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl}oxy)-1-piperidiny]acetamide trifluoroacetate (165)**

The title compound was prepared in a manner similar to that described for example 88 (step 2) using compound **126** (50 mg, 0.098 mmol), macroporous carbonate resin (100 mg, 36.2 mmol), a catalytic amount of sodium iodide, and 2-chloro-*N*-(1-*tert*-butyl)acetamide. (50 mg, 0.336 mmol) to give 5 mg (8%) of trifluoroacetate salt after purification. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  8.26 (s, 1 H), 7.96 (app. t,  $J = 8.5$  Hz, 1 H), 7.84 – 7.66 (m, 2 H), 5.61 – 5.37 (m, 1 H), 4.29 (t,  $J = 8.5$  Hz, 2 H), 3.74 (s, 2 H), 3.61 – 3.33 (m, 4 H), 3.19 (t,  $J = 8.5$  Hz, 2 H), 3.00 (s, 3 H), 2.55 – 2.12 (m, 4 H), 1.85 (s, 9 H); LCMS (ESI):  $m/z$  505 (M + H)<sup>+</sup>.

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**Example 90 (166)**



**2-[4-({7-[2-Fluoro-4-(methylsulfonyl)phenyl]-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl}oxy)-1-piperidiny]-1-[5-(2-pyridinyl)-2-thienyl]ethanone trifluoroacetate (166)**

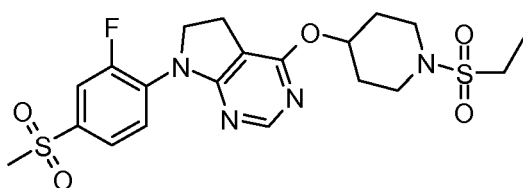
20

The title compound was prepared in a manner similar to that described for example 88 (step 2) using compound **126** (50 mg, 0.098 mmol), macroporous carbonate (100 mg, 36.2 mmol), a catalytic amount of sodium iodide, and 2-bromo-1-[5-(2-pyridinyl)-2-thienyl]ethanone (50 mg, 0.177 mmol) to give 9 mg (13%) of trifluoroacetate salt of the

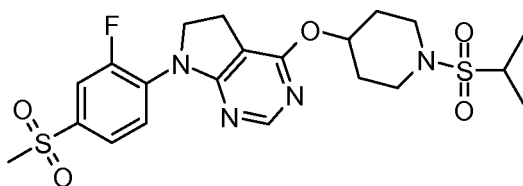
25



title product **166** after purification.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  8.68 – 8.58 (m, 2 H), 8.27 (s, 1 H), 8.05 (app. t,  $J = 8.5$  Hz, 1 H), 7.92 (d,  $J = 4.2$  Hz, 1 H), 7.82 – 7.65 (m, 3 H), 7.60 (d,  $J = 4.2$  Hz, 1 H), 5.35 – 5.11 (m, 1 H), 4.26 (t,  $J = 8.5$  Hz, 2 H), 3.73 (s, 2 H), 3.61 – 3.33 (m, 2 H), 3.19 (t,  $J = 8.5$  Hz, 2 H), 3.01 (s, 3 H), 2.96 – 2.81 (m, 2 H), 2.67 – 2.44 (m, 2 H), 2.19 – 2.06 (m, 2 H), 2.04 – 1.85 (m, 2 H); LCMS (ESI):  $m/z$  594 ( $\text{M} + \text{H}$ ) $^+$ .

**Example 91 (167)****10 4-[[1-(Ethylsulfonyl)-4-piperidinyl]oxy]-7-[2-fluoro-4-(methylsulfonyl)phenyl]-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidine (167)**

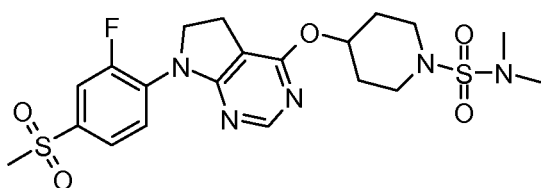
Compound **126** (70 mg, 0.138 mmol) was combined with diisopropylethylamine (1 mL, 7.72 mmol) into 5 mL of methylene chloride. The mixture was stirred at room temperature for 30 minutes. Ethanesulfonyl chloride (50 mg, 0.467 mmol) was then added to the solution. The resulting mixture was stirred at room temperature for 18 hours. The crude reaction was then concentrated to dryness, and purified via reverse phase chromatography using a gradient of 5-90% acetonitrile (contains 0.5% TFA) in water to give 46 mg (70%) of the desired compound **167** as a tan solid.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  8.27 (s, 1 H), 7.86 (app. t,  $J = 8.5$  Hz, 1 H), 7.78 – 7.68 (m, 2 H), 5.42 – 5.25 (m, 1 H), 4.26 (t,  $J = 8.5$  Hz 2 H), 3.69 – 3.52 (m, 2 H), 3.35 – 3.23 (m, 2 H), 3.19 (t,  $J = 8.5$  Hz, 2 H), 3.06 (s, 3 H), 2.99 (q,  $J = 7.8$  Hz, 2 H), 2.20 – 2.05 (m, 2 H), 1.98 – 1.81 (m, 2 H), 1.38 (t,  $J = 8.5$  Hz 3 H); LCMS (ESI):  $m/z$  485 ( $\text{M} + \text{H}$ ) $^+$ .

**Example 92 (168)**

**7-[2-Fluoro-4-(methylsulfonyl)phenyl]-4-{{1-[(1-methylethyl)sulfonyl]-4-piperidinyl}oxy}-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidine (168)**

The title compound was prepared in a manner similar to that described for example 91 using compound **126** (70 mg, 0.138 mmol), diisopropylethylamine (1 mL, 7.72 mmol), and 2-propanesulfonyl chloride (70 mg, 0.492 mmol) to give 37 mg (54%) of the title product **168** after purification. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 8.31 (s, 1 H), 7.91 (app. t, *J* = 8.5 Hz, 1 H), 7.87 – 7.60 (m, 2 H), 5.49 – 5.20 (m, 1 H), 4.31 (t, *J* = 8.5 Hz, 2 H), 3.80 – 3.52 (m, 2 H), 3.42 – 3.26 (m, 2 H), 3.24 – 3.12 (m, 4 H), 2.23 – 1.99 (m, 2 H), 1.98 – 1.81 (m, 2 H), 1.97 – 1.75 (m, 2 H), 1.32 (d, *J* = 6.8 Hz, 6 H); LCMS (ESI): *m/z* 499 (M + H)<sup>+</sup>.

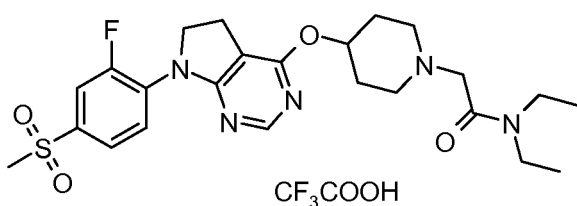
**Example 93 (169)**



**4-({7-[2-Fluoro-4-(methylsulfonyl)phenyl]-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-4-yl}oxy)-N,N-dimethyl-1-piperidinesulfonamide (169)**

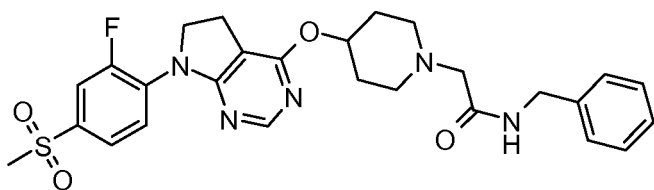
The title compound was prepared in a manner similar to that described for example 91 using compound **126** (70 mg, 0.138 mmol), diisopropylethylamine (1 mL, 7.72 mmol), and dimethylsulfamoyl chloride (70 mg, 0.489 mmol) to give 10 mg (14%) of the title product **169** after purification. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 8.28 (s, 1 H), 8.00 (app. t, *J* = 8.5 Hz, 1 H), 7.76 – 7.67 (m, 2 H), 5.38 – 5.29 (m, 1 H), 4.19 (t, *J* = 8.5 Hz, 2 H), 3.57 – 3.48 (m, 2 H), 3.29 – 3.20 (m, 2 H), 3.13 (t, *J* = 8.5 Hz, 2 H), 3.04 (s, 3 H), 2.84 (s, 6 H), 2.13 – 2.02 (m, 2 H), 1.96 – 1.85 (m, 2 H); LCMS (ESI): *m/z* 500 (M + H)<sup>+</sup>.

**Example 94 (170)**



***N,N*-Diethyl-2-[4-({7-[2-fluoro-4-(methylsulfonyl)phenyl]-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl}oxy)-1-piperidinyl]acetamide trifluoroacetate (**170**)**

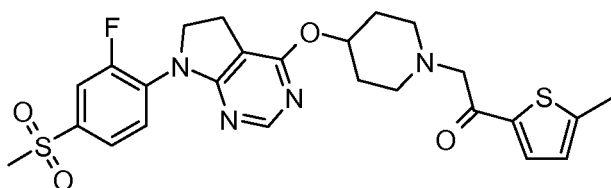
The title compound was prepared in a manner similar to that described for example 88 (step 2) using compound **126** (75 mg, 0.148 mmol), diisopropylethylamine (92  $\mu$ L, 0.518 mmol), a catalytic amount of sodium iodide, and 2-chloro-*N,N*-diethylacetamide (24 mg, 0.163 mmol) to give 23 mg (37%) of the product **170** as a trifluoroacetate salt after purification.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  8.28 (s, 1 H), 7.96 (app. t,  $J = 8.5$  Hz, 1 H), 7.76 – 7.73 (m, 2 H), 5.58 – 5.39 (m, 1 H), 4.22 (t,  $J = 8.5$  Hz, 2 H), 4.08 (s, 2 H), 3.74 – 3.58 (m, 2 H), 3.56 – 3.43 (m, 2 H), 3.41 – 3.16 (m, 6 H), 3.06 (s, 3 H), 2.43 – 2.30 (m, 2 H), 2.29 – 2.17 (m, 2 H), 1.18 – 1.12 (m, 6 H); LCMS (ESI):  $m/z$  506 ( $M + \text{H}$ ) $^+$ .

**Example 95 (**171**)****2-[4-({7-[2-Fluoro-4-(methylsulfonyl)phenyl]-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl}oxy)-1-piperidinyl]-*N*-(phenylmethyl)acetamide (**171**)**

The title compound was prepared in a manner similar to that described for example 88 (step 2) using compound **126** (75 mg, 0.148 mmol), diisopropylethylamine (92  $\mu$ L, 0.518 mmol), a catalytic amount of sodium iodide, and 2-chloro-*N*-(phenylmethyl)acetamide (27 mg, 0.148 mmol) to give 18 mg (28%) of the product **171** after purification.  $^1\text{H}$  NMR (400 MHz,  $\text{CD}_3\text{OD}$ ):  $\delta$  8.15 (s, 1 H), 7.97 (app. t,  $J = 8.5$  Hz, 1 H), 7.80 – 7.75 (m, 2 H), 7.33 – 7.22 (m, 5 H), 5.21 – 5.17 (m, 1 H), 4.42 (s, 2 H), 4.17 (t,  $J = 8.5$  Hz, 2 H), 3.30 (s, 2 H), 3.15 – 3.09 (m, 5 H), 2.80 – 2.74 (m, 2 H), 2.71 – 2.60 (m, 2 H), 2.10 – 2.02 (m, 2 H), 1.89 – 1.80 (m, 2 H); LCMS (ESI):  $m/z$  540 ( $M + \text{H}$ ) $^+$ .

25

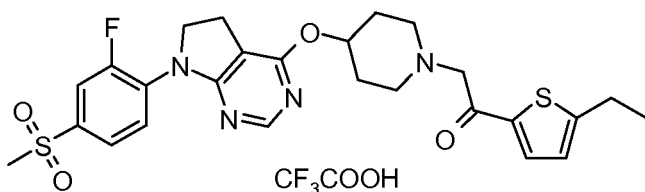
**Example 96 (**172**)**



**2-[4-({7-[2-Fluoro-4-(methylsulfonyl)phenyl]-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-4-yl}oxy)-1-piperidinyl]-1-(5-methyl-2-thienyl)ethanone (**172**)**

The title compound was prepared in a manner similar to that described for example 88  
 5 (step 2) using compound **126** (100 mg, 0.197 mmol), diisopropylethylamine (70  $\mu$ L, 0.395 mmol), and 2-chloro-1-(5-methyl-2-thienyl)ethanone (34 mg, 0.197 mmol) to give 21 mg (17%) of the product **172** after purification.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  8.26 (s, 1 H), 8.02 (app. t,  $J = 8.5$  Hz, 1 H), 7.76 – 7.68 (m, 3 H), 6.79 (d,  $J = 3.4$  Hz, 1 H), 5.22 – 5.10 (m, 1 H), 4.19 (t,  $J = 8.5$  Hz, 2 H), 3.63 (s, 2 H), 3.14 – 2.87 (m, 5 H), 2.86 – 2.80  
 10 (m, 2 H), 2.71 – 2.60 (m, 5 H), 2.16 – 2.01 (m, 2 H), 1.93 – 1.80 (m, 2 H); LCMS (ESI):  $m/z$  531 ( $\text{M} + \text{H}$ ) $^+$ .

**Example 97 (**173**)**



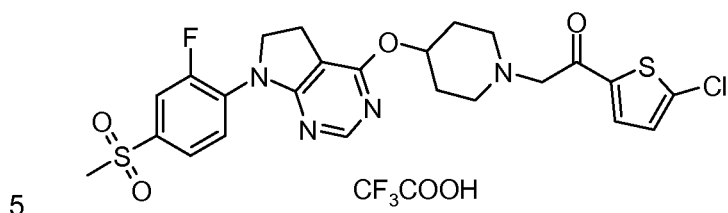
15

**1-(5-Ethyl-2-thienyl)-2-[4-({7-[2-fluoro-4-(methylsulfonyl)phenyl]-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-4-yl}oxy)-1-piperidinyl]ethanone trifluoroacetate (**173**)**

The title compound was prepared in a manner similar to that described in example 88  
 20 (step 2) using compound **126** (100 mg, 0.197 mmol), diisopropylethylamine (70  $\mu$ L, 0.395 mmol), and 2-chloro-1-(5-ethyl-2-thienyl)ethanone (37 mg, 0.197 mmol) in 5 mL acetonitrile to give 13 mg (10%) of the product **173** as a trifluoroacetate salt after purification.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  8.26 (s, 1 H), 7.99 (app. t,  $J = 8.5$  Hz, 1 H), 7.75 – 7.68 (m, 2 H), 7.63 (d,  $J = 3.6$  Hz, 1 H), 6.90 (d,  $J = 3.6$  Hz, 1 H), 5.51 – 5.45 (m, 1 H), 4.57 (s, 2 H), 4.26 (t,  $J = 8.5$  Hz, 2 H), 3.82 – 3.69 (m, 2 H), 3.58 – 3.42 (m, 2 H),

3.28 – 3.09 (m, 2 H), 3.06 (s, 3 H), 2.91 (q,  $J = 7.6$  Hz, 2 H), 2.46 – 2.38 (m, 2 H), 2.30 – 2.18 (m, 2 H), 1.34 (t,  $J = 7.3$  Hz, 3 H); LCMS (ESI):  $m/z$  545 ( $M + H$ )<sup>+</sup>.

**Example 98 (174)**



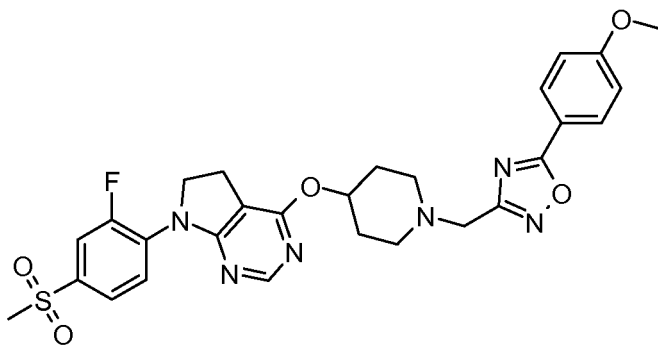
**1-(5-Chloro-2-thienyl)-2-[4-({7-[2-fluoro-4-(methylsulfonyl)phenyl]-6,7-dihydro-5H-pyrrolo[2,3-*d*]pyrimidin-4-yl}oxy)-1-piperidinyl]ethanone trifluoroacetate (175)**

The title compound was prepared in a manner similar to that described for example 88 (step 2) using compound **126** (100 mg, 0.197 mmol), diisopropylethylamine (70  $\mu$ L, 0.395 mmol), and 2-bromo-1-(5-chloro-2-thienyl)ethanone (47 mg, 0.197 mmol) in 5 mL acetonitrile to give 2 mg (1%) of the product **174** as a trifluoroacetate salt after purification. <sup>1</sup>H NMR (400 MHz,  $CDCl_3$ ):  $\delta$  8.27 (s, 1 H), 8.00 (app. t,  $J = 8.5$  Hz, 1 H), 7.98 – 7.71 (m, 2 H), 7.60 (d,  $J = 3.4$  Hz, 1 H), 6.79 (d,  $J = 3.4$  Hz, 1 H), 5.53 – 5.40 (m, 1 H), 4.59 (s, 2 H), 4.24 (t,  $J = 8.5$  Hz, 2 H), 3.89 – 3.71 (m, 2 H), 3.58 – 3.41 (m, 2 H), 3.28 – 3.19 (m, 2 H), 3.06 (s, 3 H), 2.43 – 2.21 (m, 4 H); LCMS (ESI):  $m/z$  552 ( $M + H$ )<sup>+</sup>.

10

15

**Example 99 (175)**

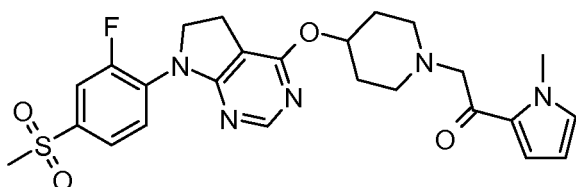


**7-[2-Fluoro-4-(methylsulfonyl)phenyl]-4-[[1-({5-[4-(methyloxy)phenyl]-1,2,4-oxadiazol-3-yl}methyl)-4-piperidinyl]oxy]-6,7-dihydro-5H-pyrrolo[2,3-*d*]pyrimidine (175)**

20

The title compound was prepared in a manner similar to that described for example 88 (step 2) using compound **126** (100 mg, 0.197 mmol), diisopropylethylamine (70  $\mu$ L, 0.395 mmol), and 3-(chloromethyl)-5-[4-(methoxy)phenyl]-1,2,4-oxadiazole (44 mg, 0.20 mmol) in 5 mL acetonitrile to give 38 mg (28%) of the title compound **175** after purification *via* flash column chromatography using 0-1.5% methanol in methylene chloride.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  8.26 (s, 1 H), 8.17 – 7.96 (m, 3 H), 7.78 – 7.60 (m, 2 H), 7.00 (d,  $J = 9.0$  Hz, 2 H), 5.27 – 5.02 (m, 1 H), 4.19 (t,  $J = 8.5$  Hz, 2 H), 3.87 (s, 3 H), 3.76 (s, 2 H), 3.16 – 2.98 (m, 5 H), 2.97 – 2.80 (m, 2 H), 2.63 – 2.46 (m, 2 H), 2.14 – 2.00 (m, 2 H), 1.97 – 1.82 (m, 2 H); LCMS (ESI):  $m/z$  580 ( $M + H$ ) $^+$ .

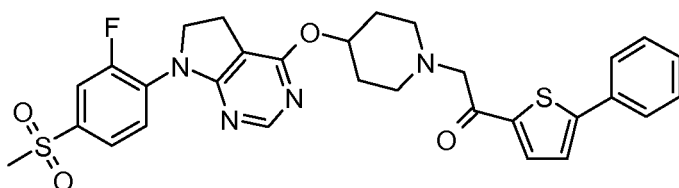
10

**Example 100 (176)****2-[4-({7-[2-Fluoro-4-(methylsulfonyl)phenyl]-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-4-yl}oxy)-1-piperidinyl]-1-(1-methyl-1H-pyrrol-2-yl)ethanone (176)**

15 The title compound was prepared in a manner similar to that described in example 88 (step 2) using compound **126** (100 mg, 0.197 mmol), diisopropylethylamine (87  $\mu$ L, 0.492 mmol), and 2-chloro-1-(1-methyl-1H-pyrrol-2-yl)ethanone (31 mg, 0.197 mmol) in 5 mL acetonitrile to give 62 mg (61%) of the title compound **176** after purification *via* flash column chromatography using 1% methanol in methylene chloride.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  8.26 (s, 1 H), 8.05 (app. t,  $J = 8.5$  Hz, 1 H), 7.77 – 7.62 (m, 2 H), 7.05 (dd,  $J = 1.3$  Hz;  $J = 4.0$  Hz, 1 H), 6.80 (m, 1 H), 6.11 (dd,  $J = 2.4$  Hz;  $J = 4.0$  Hz, 1 H), 5.27 – 5.12 (m, 1 H), 4.19 (t,  $J = 8.5$  Hz, 2 H), 3.94 (s, 3 H), 3.64 (s, 2 H), 3.16 – 2.98 (m, 5 H), 2.94 – 2.78 (m, 2 H), 2.56 – 2.41 (m, 2 H), 2.15 – 2.03 (m, 2 H), 2.01 – 1.79 (m, 2 H); LCMS (ESI):  $m/z$  514 ( $M + H$ ) $^+$ .

25

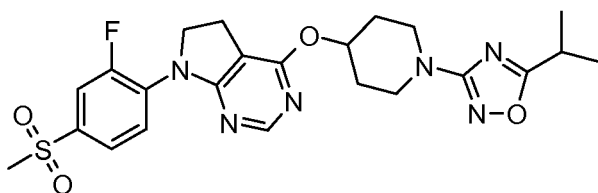
**Example 101 (177):**



**2-[4-({7-[2-Fluoro-4-(methylsulfonyl)phenyl]-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-4-yl}oxy)-1-piperidinyl]-1-(5-phenyl-2-thienyl)ethanone (177)**

The title compound was prepared in a manner similar to that described for example 88 using compound 126 (100 mg, 0.197 mmol), diisopropylethylamine (87  $\mu$ L, 0.492 mmol), and 2-chloro-1-(5-phenyl-2-thienyl)ethanone (55 mg, 0.197 mmol) in 5 mL acetonitrile to give 62 mg (61%) of the title compound 177 after purification *via* flash column chromatography using 0-1.5% methanol in methylene chloride.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  8.27 (s, 1 H), 8.06 (app. t,  $J = 8.5$  Hz, 1 H), 7.92 (d,  $J = 4.2$  Hz, 1 H), 7.74 – 7.62 (m, 3 H), 7.49 – 7.28 (m, 5 H), 5.30 – 5.15 (m, 1 H), 4.20 (t,  $J = 8.5$  Hz, 2 H), 3.70 (s, 2 H), 3.15 (t,  $J = 8.5$  Hz, 2 H), 3.04 (s, 3 H), 3.00 – 2.88 (m, 2 H), 2.67 – 2.51 (m, 2 H), 2.20 – 2.06 (m, 2 H), 2.02 – 1.90 (m, 2 H); LCMS (ESI):  $m/z$  593 ( $M + H$ ) $^+$ .

**Example 102 (178)**



**Step 1: 4-({7-[2-Fluoro-4-(methylsulfonyl)phenyl]-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-4-yl}oxy)-N-hydroxy-1-piperidinecarboximidamide (178)**

Compound 126 (obtained from a different batch, 500 mg, 0.99 mmol) was combined with cyanogen bromide (560  $\mu$ L, 1.68 mmol), and diisopropylethyl amine (526  $\mu$ L, 2.96 mmol) in 10 mL of dichloromethane at 0  $^\circ\text{C}$ . The reaction was allowed to warm to room temperature while stirring for 18 h. The crude reaction mixture was then purified *via* flash column chromatography with 1% methanol in dichloromethane to give 142 mg (34%) of 4-({7-[2-fluoro-4-(methylsulfonyl)phenyl]-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-4-yl}oxy)-1-piperidinecarbonitrile (**178A**) as a white solid.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  8.27 (s, 1 H), 8.03 (app. t,  $J = 8.5$  Hz, 1 H), 7.76 – 7.62 (m, 2 H), 5.39 – 5.25 (m, 1 H),

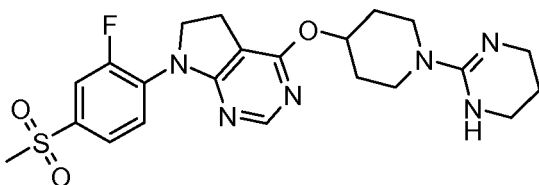
4.22 (t,  $J = 8.5$  Hz, 2 H), 3.57 – 3.43 (m, 2 H), 3.29 – 3.19 (m, 2 H), 3.13 (t,  $J = 8.4$  Hz, 2H), 3.05 (s, 3 H), 2.16 – 2.03 (m, 2 H), 1.98 – 1.83 (m, 2 H); LCMS (ESI):  $m/z$  418 ( $M + H$ )<sup>+</sup>. The compound **178A** (130 mg, 0.310 mmol) was combined with hydroxylamine hydrochloride (64 mg, 0.930 mmol), and sodium carbonate (131 mg, 1.24 mmol) in 20 mL of ethanol and heated to reflux for 2 h. The solids were removed *via* filtration and the material **178** was used without purification (143 mg); LCMS (ESI):  $m/z$  451 ( $M + H$ )<sup>+</sup>.

**Step 2: 7-[2-Fluoro-4-(methylsulfonyl)phenyl]-4-({1-[5-(1-methylethyl)-1,2,4-oxadiazol-3-yl]-4-piperidinyl}oxy)-6,7-dihydro-5H-pyrrolo[2,3-*d*]pyrimidine (**179**)**

2-Methylpropanoic acid (19  $\mu$ L, 0.310 mmol) was combined with HATU [O-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate, 129 mg, 0.340 mmol] and diisopropylethylamine (129 mg, 0.340 mmol) into N,N-dimethyl formamide (10 mL) and the solution was stirred at room temperature for 15 minutes. Compound **178** (140 mg, 0.310 mmol) was then added and the mixture was stirred at room temperature for 30 minutes. The reaction was then heated to 100 °C for 1 hour. The reaction was then diluted with water and extracted three times with diethylether. The combined organic extracts were washed three times with water and the organic layer was dried over anhydrous magnesium sulfate, filtered and concentrated to dryness under reduced pressure. The crude reaction was then purified on via reverse phase chromatography using a gradient of 50-100% acetonitrile in water (0.1% trifluoroacetic acid additive) to give 15 mg (9%) of the title compound **179** as a tan solid. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  8.28 (s, 1 H), 7.98 (app. t,  $J = 8.5$  Hz, 1 H), 7.82 – 7.67 (m, 2 H), 5.45 – 5.34 (m, 1 H), 4.21 (t,  $J = 8.5$  Hz, 2 H), 3.87 – 3.68 (m, 2 H), 3.46 – 3.27 (m, 2 H), 3.20 – 2.97 (m, 5 H), 2.15 – 2.02 (m, 2 H), 1.94 – 1.79 (m, 2 H) 1.2 (d,  $J = 7.1$  Hz, 6 H); LCMS (ESI):  $m/z$  503 ( $M + H$ )<sup>+</sup>.

25

**Example 103 (**182**)**



**Step 1: 1-(2-Pyrimidinyl)-4-piperidinol (**180**)**



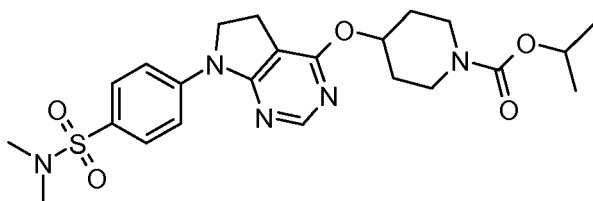
4-Hydroxypiperidine (1.5 g, 14.7 mmol) was combined with 2-chloropyrimidine (1.5 g, 13.4 mmol) and diisopropylethylamine (6 mL, 33.5 mmol) into 50 mL acetonitrile. The mixture was heated at 80 °C for 18 hours. The reaction mixture was then concentrated to dryness and the crude residue was then purified on via flash column chromatography using a gradient of 0-60% ethylacetate/hexane to give 2.1 g (81%) of the desired compound **180** as a white solid. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 8.28 (d, *J* = 4.6 Hz 2 H), 6.49 (t, *J* = 4.8 Hz, 1 H), 4.49 – 4.33 (m, 2 H), 4.01 – 3.88 (m, 1 H), 3.37 – 3.21 (m, 2 H), 2.02 – 1.90 (m, 2 H), 1.60 – 1.45 (m, 2 H); LCMS (ESI): *m/z* 180 (M + H)<sup>+</sup>.

**Step 2: 1-(1,4,5,6-Tetrahydro-2-pyrimidinyl)-4-piperidinol (**181**)**

Compound **180** (300 mg, 1.67 mmol) was combined with 10% palladium on carbon (Degussa type) (100 mg, cat.) and concentrated hydrochloric acid (500 μL) into 10 mL of acetic acid. The mixture was subjected to hydrogenation for 18 h at room temperature. The reaction mixture was then filtered and the solvent was removed under reduced pressure to give 304 mg (84%) of the desired compound **181**. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>): δ 8.25 (m, 2 H), 4.03 – 3.41 (m, 3 H), 2.95 – 2.86 (m, 4 H), 2.09 – 1.55 (m, 6 H), 1.55 – 1.18 (m, 2 H).

**Step 3: 7-[2-Fluoro-4-(methylsulfonyl)phenyl]-4-[[1-(1,4,5,6-tetrahydro-2-pyrimidinyl)-4-piperidinyl]oxy]-6,7-dihydro-5H-pyrrolo[2,3-*d*]pyrimidine (**182**)**

Compound **181** (300 mg, 1.38 mmol) was dissolved in 5 mL anhydrous DMF and treated with sodium hydride (294 mg, 7.3 mmol). The mixture was stirred at room temperature for 15 minutes. 4-Chloro-7-[2-fluoro-4-(methylsulfonyl)phenyl]-6,7-dihydro-5H-pyrrolo[2,3-*d*]pyrimidine **8** in 5 mL DMF was then added dropwise to the stirring solution. The mixture was then stirred at room temperature for 18 h. The reaction was then quenched with water. The crude reaction was then concentrated to dryness under reduced pressure and the crude residue was then purified *via* reverse phase chromatography using a gradient of 5 – 95% acetonitrile in water (0.5% trifluoroacetic acid additive) on C18 to give 56 mg (6%) of the title compound **182** as a white solid. <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD): δ 8.46 (s, 1 H), 8.17 (s, 1 H), 7.95 (app. t, *J* = 8.5 Hz, 1 H), 7.88 – 7.66 (m, 2 H), 5.54 – 5.37 (m, 1 H), 4.20 (t, *J* = 8.5 Hz, 2 H), 3.75 – 3.57 (m, 2 H), 3.49 – 3.33 (m, 6 H), 3.19 – 3.07 (m, 5 H), 2.21 – 2.06 (m, 2 H), 2.01 – 1.76 (m, 4 H); LCMS (ESI): *m/z* 475 (M + H)<sup>+</sup>.

**Example 104 (184)****Step 1: 4-(4-Chloro-5,6-dihydro-7H-pyrrolo[2,3-d]pyrimidin-7-yl)-N,N-dimethylbenzenesulfonamide (183)**

5 Following the procedure described for **141** (example 71, step 1), a round bottom flask was charged with N1,N1-dimethylsulfanilamide (0.19 g, 0.95 mmol) and cooled to -15°C. Trifluoroacetic acid (0.9 mL, 11.7 mmol) was added and the solution was stirred for 10 minutes at -15°C. Na(OAc)<sub>3</sub>BH (0.32 g, 1.51 mmol) was added to the reaction mixture and stirred for 10 minutes. A solution of aldehyde **209** (0.2 g, 1.05 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (1.2

10 mL) was added dropwise and the reaction mixture was stirred at -15°C for 30 minutes, then stirred at RT for 15 h. Mixture was concentrated under reduced pressure, diluted with 10% NaHCO<sub>3</sub>, extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 x 10 mL), dried over MgSO<sub>4</sub>, filtered, and concentrated under reduced pressure to afford the crude material, which was purified by SiO<sub>2</sub> flash column chromatography to give 0.17 g (47%) of the title compound **183** as a

15 white solid. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 8.51 (s, 1 H), 8.00 (d, J = 9.28 Hz, 2 H), 7.83 (d, J = 9.10 Hz, 2 H), 4.11 – 4.36 (m, 2 H), 3.19 – 3.37 (m, 2 H), 2.73 (s, 1 H); LCMS (APCI): m/z 339 (M + H)<sup>+</sup>.

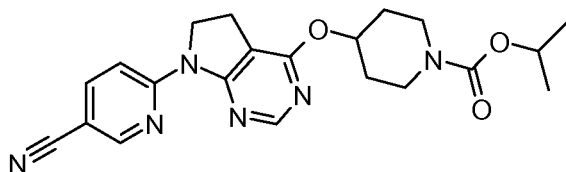
**Step 2: 1-Methylethyl 4-[(7-{4-[(dimethylamino)sulfonyl]phenyl}-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-4-yl)oxy]-1-piperidinecarboxylate (184)**

20 Following the general procedure described for example **1** (step 10), a solution of **9** (0.15 g, 0.8 mmol) and THF (1.5 mL) was added to a round bottom flask containing NaH (0.027 g, 95%, 1.12 mmol) and the resulting solution was heated to 50°C and stirred for 35 minutes. A solution of **183** (0.109 g, 0.32 mmol) and THF (1.5 mL) was added and resulting mixture was refluxed for 16 h. The reaction mixture was cooled to RT, poured

25 into H<sub>2</sub>O (10 mL) and then extracted with ethyl acetate. The combined organic layer was dried over MgSO<sub>4</sub>, filtered, and concentrated under reduced pressure. The crude product was purified by recrystallization from methanol to give 0.026 g (17%) of the title product **184** as a white solid. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 8.38 (s, 1 H), 7.96 (d, J = 9.0 Hz, 2 H), 7.77 (d, J = 8.8 Hz, 2 H), 5.30 – 5.42 (m, 1 H), 4.86 – 4.99 (m, 1 H), 4.14 (t, J =

8.8 Hz, 2 H), 3.75 – 3.91 (m, 2 H), 3.27 – 3.41 (m, 2 H), 3.12 (t,  $J = 8.8$  Hz, 2 H), 2.70 (s, 6 H), 1.92 – 2.09 (m, 2 H), 1.66 – 1.83 (m, 2 H), 1.26 (d,  $J = 6.24$  Hz, 6 H); LCMS (ESI):  $m/z$  491 (M + H)<sup>+</sup>.

### 5 Example 105 (186)



#### Step 1: 6-(4-Chloro-5,6-dihydro-7H-pyrrolo[2,3-d]pyrimidin-7-yl)-3-pyridinecarbonitrile (185)

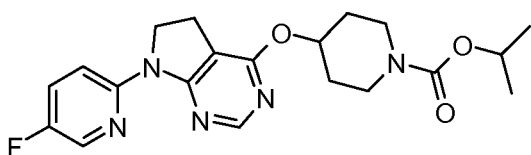
- 10 A round bottom flask was charged with 2-amino-5-cyanopyridine (0.26 g, 2.18 mmol) and cooled to  $-15^{\circ}\text{C}$ . Acetic acid (1.52 mL, 26.8 mmol) was added and the solution was stirred for 10 minutes at  $-15^{\circ}\text{C}$ .  $\text{Na}(\text{OAc})_3\text{BH}$  (0.742 g, 3.5 mmol) was added to the reaction mixture and stirred for 5 minutes. A solution of the aldehyde 209 (0.5 g, 2.62 mmol) in  $\text{CH}_2\text{Cl}_2$  (1.6 mL) was added dropwise and the reaction mixture was stirred at
- 15  $-15^{\circ}\text{C}$  for 30 minutes, then stirred at RT for 15 h. Mixture was diluted with  $\text{H}_2\text{O}$ , extracted with  $\text{CH}_2\text{Cl}_2$ , dried over  $\text{MgSO}_4$ , filtered, and concentrated under reduced pressure to afford the crude material, which was purified by  $\text{SiO}_2$  flash column chromatography to give 0.16 g of the title compound 185 and 6-[[2-(4,6-dichloro-5-pyrimidinyl)ethyl]amino]-3-pyridinecarbonitrile as an inseparable mixture.  $^1\text{H}$  NMR (400
- 20 MHz,  $\text{CD}_3\text{OD}$ ):  $\delta$  8.66 (s, 1 H), 8.19 – 8.27 (m, 1 H), 7.52 – 7.61 (m, 1 H), 6.42 – 6.52 (m, 1 H), 3.83 (t,  $J = 6.87$  Hz, 3 H), 3.19 (t,  $J = 6.87$  Hz, 3 H); LCMS (APCI):  $m/z$  258 (M + H)<sup>+</sup>.

#### Step 2: 1-Methylethyl 4-[[7-(5-cyano-2-pyridinyl)-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-4-yl]oxy]-1-piperidinecarboxylate (186)

- 25 To a stirred solution of 9 (0.252 g, 1.35 mmol) and THF (2 mL) was added NaH (0.045 g, 95%, 1.89 mmol) and heated to  $50^{\circ}\text{C}$  for 30 minutes. A solution of 185 (0.139 g, 0.54 mmol) in THF (3 mL) was added dropwise and the resulting mixture was refluxed for 16 h. The reaction mixture was cooled to RT, poured into  $\text{H}_2\text{O}$  and then extracted with ethyl acetate. The combined organic layer was dried over  $\text{MgSO}_4$ , filtered, and concentrated

under reduced pressure. The crude product was purified by recrystallization from methanol to give 0.012 g (5%) of the title product **186** as a white solid.  $^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  8.85 – 8.90 (m, 1H), 8.57 – 8.61 (m, 1 H), 8.42 (s, 1 H), 7.82 – 7.87 (m, 1 H), 5.33 – 5.42 (m, 1 H), 4.90 – 4.99 (m, 1 H), 4.35 (t,  $J = 8.61$  Hz, 2 H), 3.74 – 3.89 (m, 2 H), 3.29 – 3.42 (m, 2 H), 3.07 (t,  $J = 8.06$  Hz, 2 H), 1.94 – 2.08 (m, 2 H), 1.70 – 1.83 (m, 2 H), 1.27 (d,  $J = 6.23$  Hz, 6 H); LCMS (ESI):  $m/z$  409 ( $\text{M} + \text{H}$ ) $^+$ .

### Example 106 (**188**)



10

#### Step 1: *N*-[2-(4,6-Dichloro-5-pyrimidinyl)ethyl]-5-fluoro-2-pyridinamine (**187**)

A round bottom flask was charged with 2-amino-5-fluoropyridine (0.323 g, 2.88 mmol) and cooled to  $-15^\circ\text{C}$ . Trifluoroacetic acid (2.5 mL, 32.2 mmol) was added and the solution was stirred for 10 minutes at  $-15^\circ\text{C}$ .  $\text{Na}(\text{OAc})_3\text{BH}$  (0.89 g, 4.2 mmol) was added to the reaction mixture and stirred for 10 minutes. A solution of **209** (0.5 g, 2.62 mmol) in  $\text{CH}_2\text{Cl}_2$  (2.0 mL) was added dropwise and the reaction mixture was stirred at  $-15^\circ\text{C}$  for 30 minutes, then stirred at RT for 15 h. Mixture was concentrated under reduced pressure, diluted with 10%  $\text{NaHCO}_3$ , extracted with  $\text{CH}_2\text{Cl}_2$  (3 x 10 mL), dried over  $\text{MgSO}_4$ , filtered, and concentrated under reduced pressure to afford the crude material, which was purified by  $\text{SiO}_2$  flash column chromatography to give 0.17 g of the title compound **187** and 4-chloro-7-(5-fluoro-2-pyridinyl)-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidine as an inseparable mixture.  $^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  8.62 (s, 1 H), 7.92 (d,  $J = 2.68$  Hz, 1 H), 7.14 – 7.23 (m, 1 H), 6.37 (dd,  $J_1 = 9.10$  Hz,  $J_2 = 3.39$  Hz, 1 H), 4.60 (br. s, 1 H), 6.67 (q,  $J = 6.54$  Hz, 2 H), 3.24 (t,  $J = 6.87$  Hz, 2 H); LCMS (APCI):  $m/z$  287 ( $\text{M} + \text{H}$ ) $^+$ .

25

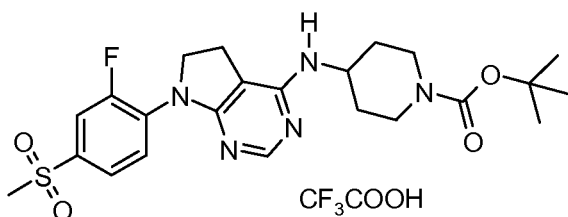
#### Step 2: 1-Methylethyl 4-[[7-(5-fluoro-2-pyridinyl)-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl]oxy]-1-piperidinecarboxylate (**188**)

The procedure described for **10** was employed using **9** (0.166 g, 0.88 mmol), NaH (0.037 g, 1.54 mmol), and compound **187** (0.11 g, 0.44 mmol). Aqueous work-up followed by recrystallization from methanol gave 0.027 g (15%) of the title compound

30

**188** as a white solid.  $^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  8.66 (dd,  $J_1 = 9.34$  Hz,  $J_2 = 4.03$  Hz, 1 H), 8.35 (s, 1 H), 8.17 (d,  $J = 3.11$  Hz, 1 H), 7.40 – 7.47 (m, 1 H), 5.30 – 5.41 (m, 1 H), 4.89 – 5.00 (m, 1 H), 4.30 (t,  $J = 8.61$  Hz, 2 H), 3.73 – 3.89 (m, 2 H), 3.30 – 3.42 (m, 2 H), 3.04 (t,  $J = 8.61$  Hz, 2 H), 1.93 – 2.07 (m, 2 H), 1.67 – 1.84 (m, 2 H), 1.26 (d,  $J = 6.23$  Hz, 6 H); LCMS (ESI):  $m/z$  402 ( $M + H$ ) $^+$ .

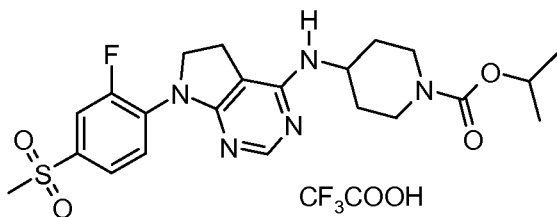
#### Example 107 (**189**)



**1,1-Dimethylethyl 4-({7-[2-fluoro-4-(methylsulfonyl)phenyl]-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-4-yl}amino)-1-piperidinecarboxylate trifluoroacetate (**189**)**

To a solution of **8** (50 mg, 0.153 mmol) in DMF (1.5 mL) was added 1,1-dimethylethyl 4-amino-1-piperidinecarboxylate (62 mg, 0.306 mmol) and  $\text{K}_2\text{CO}_3$  (42 mg, 0.306 mmol). The reaction mixture was sealed and heated in a microwave for 15 min at 150 °C. After an LCMS trace showed mostly **8**, the reaction mixture was heated in a microwave an additional 20 min at 200 °C. Another LCMS trace still showed the presence of **8**, so the reaction mixture was heated again in a microwave for 20 min at 175 °C. The reaction mixture was then diluted with water (2 mL) and extracted with EtOAc (3 x 5 mL). The combined organic layer was dried over  $\text{MgSO}_4$ , filtered, and concentrated under reduced pressure. The crude product was purified twice by preparative HPLC (water/acetonitrile eluent) to give 4 mg (4%) of the title product **189** as a light tan solid. LCMS (ESI):  $m/z$  492 ( $M + H$ ) $^+$ .

#### Example 108 (**191**)

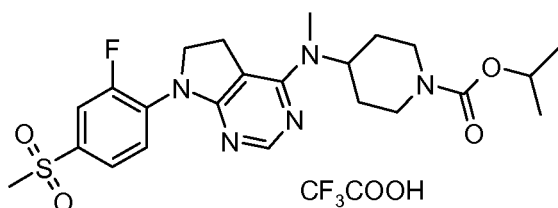


**Step 1: 1-Methylethyl 4-([(1,1-dimethylethyl)oxy]carbonyl)amino)-1-piperidinecarboxylate (**190**)**

To a stirred solution of 1,1-dimethylethyl 4-piperidinylcarbamate (512 mg, 2.56 mmol) and Et<sub>3</sub>N (0.714 mL, 5.12 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (25 mL) was added isopropylchloroformate (1.0 M in toluene, 2.8 mL, 2.81 mmol) dropwise via an addition funnel at RT. The reaction mixture was stirred at RT for 17 hours, then washed with water (1 x 15 mL), dried over MgSO<sub>4</sub>, filtered, and concentrated under reduced pressure to give 585 mg (80%) of the title product **190** as a colorless oil. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 4.85 (septuplet, *J* = 6.4 Hz, 1 H), 4.63 – 4.48 (m, 1 H), 4.13 – 3.89 (m, 2 H), 3.55 (br s, 1 H), 2.82 (t, *J* = 11.7 Hz, 2 H), 1.88 – 1.85 (m, 2 H), 1.39 (s, 9 H), 1.29 – 1.22 (m, 2 H), 1.19 (d, *J* = 6.1 Hz, 6 H).

**Step 2: 1-Methylethyl 4-({7-[2-fluoro-4-(methylsulfonyl)phenyl]-6,7-dihydro-5H-pyrrolo[2,3-*d*]pyrimidin-4-yl}amino)-1-piperidinecarboxylate trifluoroacetate (**191**)**

To a solution of **8** (50 mg, 0.153 mmol) in DMF (1.5 mL) was added **190** (87 mg, 0.305 mmol) and K<sub>2</sub>CO<sub>3</sub> (42 mg, 0.305 mmol). The reaction mixture was sealed and heated in a microwave for 20 min at 200 °C. After an LCMS trace showed mostly **8**, the reaction mixture was heated in a microwave an additional 60 min at 220 °C. The reaction mixture was then diluted with water (2 mL) and extracted with EtOAc (3 x 5 mL). The combined organic layer was dried over MgSO<sub>4</sub>, filtered, and concentrated under reduced pressure. The crude product was purified by preparative HPLC (water/acetonitrile eluent) to give 11 mg (12%) of the title product **191** as a yellow solid. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 8.09 (s, 1 H), 7.81 – 7.77 (m, 2 H), 7.72 – 7.69 (m, 1 H), 4.91 (septuplet, *J* = 6.4 Hz, 1 H), 4.29 (t, *J* = 9.0 Hz, 2 H), 4.23 – 4.12 (m, 2 H), 3.79 – 3.68 (m, 1 H), 3.43 – 3.38 (m, 2 H), 3.09 (s, 3 H), 2.96 – 2.86 (m, 2 H), 1.97 – 1.93 (m, 2 H), 1.77 – 1.67 (m, 2 H), 1.25 (d, *J* = 6.4 Hz, 6 H); LCMS (ESI): *m/z* 478 (M + H)<sup>+</sup>.

**Example 109 (**193**)**

**Step 1: 1-Methylethyl 4-[[[(1,1-dimethylethyl)oxy]carbonyl](methyl)amino]-1-piperidinecarboxylate (**192**)**

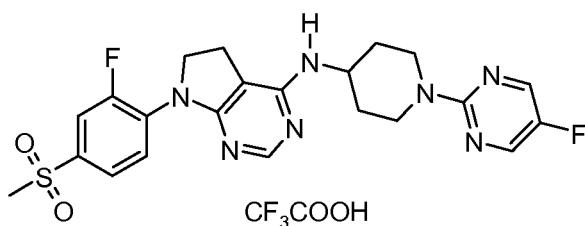
To a stirred solution of 1,1-dimethylethyl methyl(4-piperidinyl)carbamate (500 mg, 2.33 mmol) and Et<sub>3</sub>N (0.65 mL, 4.66 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (23 mL) was added

- 5 isopropylchloroformate (1.0 M in toluene, 2.6 mL, 2.57 mmol) dropwise *via* an addition funnel at RT. The reaction mixture was stirred at RT for 17 hours, then washed with water (1 x 15 mL), dried over MgSO<sub>4</sub>, filtered, and concentrated under reduced pressure to give 608 mg (87%) of the title product **192** as a colorless oil. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 4.88 (septuplet, *J* = 6.4 Hz, 1 H), 4.28 – 4.16 (m, 3 H), 2.77 – 2.71 (m, 2 H),  
 10 2.68 (s, 3 H), 1.62 – 1.57 (m, 2 H), 1.55 – 1.50 (m, 2 H), 1.44 (s, 9 H), 1.21 (d, *J* = 6.4 Hz, 6 H).

**Step 2: 1-Methylethyl 4-[[7-[2-fluoro-4-(methylsulfonyl)phenyl]-6,7-dihydro-5H-pyrrolo[2,3-*d*]pyrimidin-4-yl](methyl)amino]-1-piperidinecarboxylate trifluoroacetate (**193**)**

- 15 To a solution of **8** (50 mg, 0.153 mmol) in DMF (1.5 mL) was added **192** (92 mg, 0.305 mmol) and K<sub>2</sub>CO<sub>3</sub> (42 mg, 0.305 mmol). The reaction mixture was sealed and heated in a microwave for 1 h at 220 °C. The reaction mixture was then diluted with water (2 mL) and extracted with EtOAc (3 x 5 mL). The combined organic layer was dried over MgSO<sub>4</sub>, filtered, and concentrated under reduced pressure. The crude product was  
 20 purified by preparative HPLC (water/acetonitrile eluent) to give 8 mg (9%) of the title product **193** as a yellow solid. LCMS (ESI): *m/z* 492 (M + H)<sup>+</sup>.

**Example 110 (**195**)**



- 25 **Step 1: 1,1-Dimethylethyl [1-(2-fluoro-5-pyrimidinyl)-4-piperidinyl]carbamate (**194**)**

To a stirred solution of 1,1-dimethylethyl 4-piperidinylcarbamate (500 mg, 2.50 mmol) and diisopropylethylamine (0.871 mL, 5.0 mmol) in acetonitrile (25 mL) was added 2-chloro-5-fluoropyrimidine (0.34 mL, 2.75 mmol) via syringe at RT. The reaction mixture was heated to reflux for 19 hours, then cooled to RT and concentrated under reduced

pressure. The crude oil was purified by SiO<sub>2</sub> flash chromatography (20% to 50% EtOAc in hexanes) to give 495 mg (67%) of the title product **194** as a viscous oil. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 8.17 (s, 2 H), 4.56 – 4.52 (m, 2 H), 4.47 – 4.41 (m, 1 H), 3.70 (br s, 1 H), 3.07 – 3.00 (m, 2 H), 2.02 – 1.98 (m, 2 H), 1.44 (s, 9 H), 1.39 – 1.28 (m, 2 H).

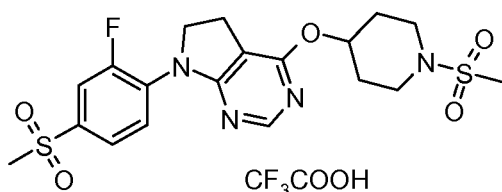
5 **Step 2: 7-[2-Fluoro-4-(methylsulfonyl)phenyl]-N-[1-(2-fluoro-5-pyrimidinyl)-4-piperidiny]-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-4-amine trifluoroacetate (**195**)**

To a solution of **8** (57 mg, 0.174 mmol) in DMF (1.7 mL) was added **194** (103 mg, 0.348 mmol) and K<sub>2</sub>CO<sub>3</sub> (48 mg, 0.348 mmol). The reaction mixture was sealed and heated in a microwave for 1 h at 220 °C. After an LCMS trace showed an appreciable amount of **8**, the reaction mixture was heated in a microwave an additional 60 min at 220 °C. The reaction mixture was then diluted with water (2 mL) and extracted with EtOAc (3 x 5 mL). The combined organic layer was dried over MgSO<sub>4</sub>, filtered, and concentrated under reduced pressure. The crude product was purified by preparative HPLC (water/acetonitrile eluent) to give 3 mg (3%) of the title product **195** as a yellow solid.

10 **8**, the reaction mixture was heated in a microwave an additional 60 min at 220 °C. The reaction mixture was then diluted with water (2 mL) and extracted with EtOAc (3 x 5 mL). The combined organic layer was dried over MgSO<sub>4</sub>, filtered, and concentrated under reduced pressure. The crude product was purified by preparative HPLC (water/acetonitrile eluent) to give 3 mg (3%) of the title product **195** as a yellow solid.

15 LCMS (ESI): m/z 488 (M + H)<sup>+</sup>.

**Example 111 (**198**)**



**Step 1: 1,1-Dimethylethyl 4-(acetyloxy)-1-piperidinecarboxylate (**196**)**

20 To a stirred solution of 1,1-dimethylethyl 4-hydroxy-1-piperidinecarboxylate (4.0 g, 19.9 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (50 mL) was added sequentially Et<sub>3</sub>N (8.3 mL, 59.6 mmol) and acetic anhydride (5.6 mL, 59.6 mmol) via syringes at RT. The reaction mixture was stirred at RT for 5 h. The reaction mixture was then washed with water (1 x 25 mL), dried over MgSO<sub>4</sub>, filtered, and concentrated under reduced pressure. The crude oil was dried

25 under high vacuum overnight to give 5.83 g (120%; some acetic anhydride is present in the sample) of the title product **196** as a light brown oil which was used without further purification. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 4.88 (septuplet, *J* = 3.9 Hz, 1 H), 3.74 – 3.67 (m, 2 H), 3.20 – 3.14 (m, 2 H), 2.04 (s, 3 H), 1.86 – 1.79 (m, 2 H), 1.61 – 1.52 (m, 2 H), 1.44 (s, 9 H).



**Step 2: 1-(Methylsulfonyl)-4-piperidinol (197)**

To a stirred solution of 196 (5.83 g from previous reaction) in CH<sub>2</sub>Cl<sub>2</sub> (100 mL) was added TFA (18.5 mL, 239.6 mmol) via syringe at RT. The reaction mixture was stirred at RT for 3 h at which point it was concentrated under reduced pressure and dried under

5 high vacuum to remove as much excess TFA as possible. The crude yellow oil was then dissolved in CH<sub>2</sub>Cl<sub>2</sub> (150 mL) with stirring. To this solution was added Et<sub>3</sub>N (54 mL, 389 mmol) via syringe at RT and then the reaction mixture was cooled to 0 °C.

Methanesulfonyl chloride (9.0 mL, 116.4 mmol) was added dropwise via addition funnel at 0 °C. The reaction mixture was then allowed to warm to RT and stirred 15 h. The

10 reaction mixture was washed with water (1 x 50 mL), dried over MgSO<sub>4</sub>, filtered, concentrated under reduced pressure, and dried under high vacuum for 1 h to remove excess Et<sub>3</sub>N. The crude oil was then dissolved in dioxane (100 mL) with stirring. To this solution was added NaOH (2.5 M in water, 100 mL) and the reaction mixture was stirred at RT for 5 h during which time it turned to a brownish color. The reaction mixture was

15 acidified with conc. HCl to pH~7 and then extracted with EtOAc (3 x 100 mL). The combined organic layer was dried over MgSO<sub>4</sub>, filtered, and concentrated under reduced pressure to give 1.99 g (56% from starting material in step 1) of the title product 197 as a light brown solid. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 3.93 (septuplet, *J* = 3.7 Hz, 1 H), 3.70 (s, 1H), 3.49 – 3.43 (m, 2 H), 3.15 – 3.09 (m, 2 H), 2.78 (s, 3 H), 1.99 – 1.93 (m, 2 H), 1.74

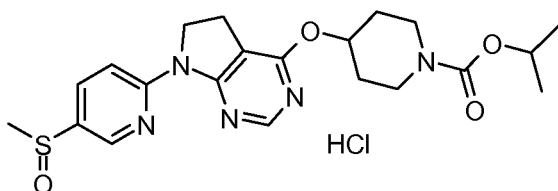
20 – 1.66 (m, 2 H).

**Step 3: 7-[2-Fluoro-4-(methylsulfonyl)phenyl]-4-[[1-(methylsulfonyl)-4-piperidinyl]oxy]-6,7-dihydro-5H-pyrrolo[2,3-*d*]pyrimidine trifluoroacetate (198)**

To a stirred solution of 8 (50 mg, 0.153 mmol) and 197 (41 mg, 0.229 mmol) in THF (2.0 mL) was added NaH (60% dispersion in mineral oil, 25 mg, 0.612 mmol) in one portion

25 at RT. The reaction mixture was heated to reflux for 18 h, cooled to RT, and quenched with water (2 mL). The mixture was extracted with EtOAc (3 x 5 mL), dried over MgSO<sub>4</sub>, filtered, and concentrated under reduced pressure. The crude oil was purified via preparative HPLC (water/acetonitrile eluent) to give 15 mg (17%) of the title product 198 as a white solid. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 8.32 (s, 1 H), 7.83 – 7.74 (m, 3 H), 5.35

30 (septuplet, *J* = 3.9 Hz, 1 H), 4.23 (t, *J* = 9.3 Hz, 2 H), 3.59 – 3.54 (m, 2 H), 3.24 – 3.18 (m, 4 H), 3.07 (s, 3 H), 2.83 (s, 3 H), 2.19 – 2.11 (m, 2 H), 2.00 – 1.91 (m, 2 H); LCMS (ESI): *m/z* 471 (M + H)<sup>+</sup>.

**Example 112 (202)****Step 1: 5-(Methylthio)-2-pyridinamine (199)**

5 To a stirred solution of 2-amino-5-iodopyridine (11.6 g, 52.6 mmol) in MeOH (250 mL) was added sodium thiomethoxide (5.16 g, 73.6 mmol) and copper powder (1.07 g, 16.8 mmol) at RT. The reaction mixture was heated in a sealed tube at 120 °C for 68 h. The reaction mixture was then cooled to RT and filtered through a pad of Celite. The Celite was rinsed with MeOH and the combined organics were concentrated under reduced  
10 pressure and redissolved in EtOAc. The organic layer was washed with water (1 x 50 mL) and the aqueous layer was extracted with EtOAc (2 x 100 mL). The combined organic layer was dried over MgSO<sub>4</sub>, filtered, and concentrated under reduced pressure to give 6.23 g (84%) of the title product **199** as an off-white solid. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 8.09 (s, 1 H), 7.51 – 7.48 (m, 1 H), 6.48 – 6.45 (m, 1 H), 4.35 (br s, 2 H), 2.38  
15 (s, 3 H).

**Step 2: 4-Chloro-7-[5-(methylthio)-2-pyridinyl]-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidine (200)**

To a stirred solution of (4,6-dichloro-5-pyrimidinyl)acetaldehyde **209** (see example **116**, step 1, 3.41 g, 17.8 mmol) in MeOH (180 mL) was added **199** (3.0 g, 21.4 mmol) at RT.  
20 The reaction mixture was cooled to -15 °C with an ice/methanol bath and glacial acetic acid (3.1 mL, 53.4 mmol) and NaBH<sub>3</sub>CN (3.35 g, 53.4 mmol) were added. The reaction mixture was stirred at -15 °C for 15 min then allowed to warm to RT and stir for 19 h. The reaction mixture was then diluted with water (50 mL) and extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 x 100 mL). The combined organic layer was dried over MgSO<sub>4</sub>, filtered, and concentrated  
25 under reduced pressure to a yellow oil. The crude oil was dissolved in THF (500 mL) with stirring and then *t*-BuOK (5.99 g, 53.4 mmol) was added in one portion at RT. The reaction mixture changed immediately to a brown color and was stirred at RT for 22 h. The reaction mixture was quenched with water (50 mL), concentrated under reduced pressure, and then redissolved in EtOAc (200 mL). The organic layer was washed with

water (1 x 50 mL) and the aqueous layer was extracted with EtOAc (2 x 100 mL). The combined organic layer was dried over MgSO<sub>4</sub>, filtered, and concentrated under reduced pressure to a brown oil. The crude oil was purified using SiO<sub>2</sub> flash chromatography (20% to 40% EtOAc in hexanes; monitored at 319 nm) to give 550 mg (11%) of the title product **200** as a colorless oil. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 8.57 (d, *J* = 9.0 Hz, 1 H), 8.43 (s, 1 H), 8.29 (d, *J* = 2.4 Hz, 1 H), 7.68 and 7.66 (dd, *J*<sub>1</sub> = 8.8 Hz, *J*<sub>2</sub> = 2.4 Hz, 1 H), 4.37 – 4.33 (m, 2 H), 3.16 (t, *J* = 8.8 Hz, 2 H), 2.47 (s, 3 H).

**Step 3: 1-Methylethyl 4-({7-[5-(methylthio)-2-pyridinyl]-6,7-dihydro-5H-pyrrolo[2,3-*d*]pyrimidin-4-yl}oxy)-1-piperidinecarboxylate (**201**)**

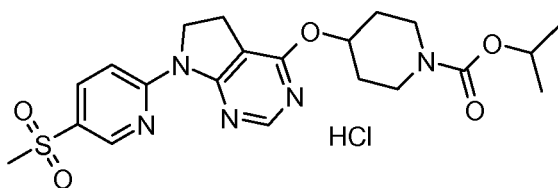
To a stirred solution of **200** (652 mg, 2.35 mmol) and 1-methylethyl 4-hydroxy-1-piperidinecarboxylate **9** (526 mg, 2.81 mmol) in THF (24 mL) was added NaH (60% dispersion in mineral oil, 282 mg, 7.05 mmol) in one portion at RT. The reaction mixture was heated to reflux for 18 h, cooled to RT, and quenched with water (20 mL). The mixture was extracted with EtOAc (3 x 50 mL), dried over MgSO<sub>4</sub>, filtered, and concentrated under reduced pressure. The crude oil was purified using SiO<sub>2</sub> flash chromatography (40% EtOAc in hexanes) to give 373 mg (37%) of the title product **201** as a colorless oil. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 8.73 – 8.66 (m, 1H), 8.42 – 8.39 (m, 1 H), 8.30 (d, *J* = 2.4 Hz, 1 H), 8.77 – 8.70 (m, 1 H), 5.39 – 5.32 (m, 1 H), 4.92 (septuplet, *J* = 6.1 Hz, 1 H), 4.46 – 4.36 (m, 2 H), 3.85 – 3.76 (m, 2 H), 3.36 – 3.30 (m, 2 H), 3.12 – 3.05 (m, 2 H), 2.48 (s, 3 H), 2.03 – 1.95 (m, 2 H), 1.79 – 1.70 (m, 2 H), 1.25 (d, *J* = 6.4 Hz, 6 H); LCMS (ESI): *m/z* 430 (M + H)<sup>+</sup>.

**Step 4: (±)-1-Methylethyl 4-({7-[5-(methylsulfinyl)-2-pyridinyl]-6,7-dihydro-5H-pyrrolo[2,3-*d*]pyrimidin-4-yl}oxy)-1-piperidinecarboxylate hydrochloride (**202**)**

To a stirred solution of **201** (180 mg, 0.419 mmol) in hexafluoroisopropanol (4.0 mL) at 0 °C was added H<sub>2</sub>O<sub>2</sub> (30% wt aqueous solution, 95 mg, 0.839 mmol) *via* syringe. The reaction mixture was allowed to warm to RT and stirred for 30 min. The reaction mixture was diluted with water (5 mL) and extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 x 20 mL). The combined organic layer was dried over MgSO<sub>4</sub>, filtered, and concentrated under reduced pressure. The resulting colorless oil was dissolved in a 1:1 mixture of acetone:Et<sub>2</sub>O (15 mL) using a heat gun with stirring. To this solution was added HCl (1.0 M in Et<sub>2</sub>O, 1.5 mL) and a white solid precipitated immediately. The solvent was removed under reduced pressure and the material was triturated with Et<sub>2</sub>O, filtered, and dried under high vacuum to give

169 mg (84%) of the title product **202** as a white solid.  $^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  8.67 - 8.63 (m, 1 H), 8.60 (s, 1 H), 8.52 (s, 1 H), 8.09 - 8.05 (m, 1 H), 5.42 - 5.36 (m, 1 H), 4.91 (septuplet,  $J = 6.1$  Hz, 1 H), 4.41 - 4.37 (m, 2 H), 3.86 - 3.77 (m, 2 H), 3.35 - 3.29 (m, 2 H), 3.13 - 3.09 (m, 2 H), 2.78 (s, 3 H), 2.04 - 1.96 (m, 2 H), 1.78 - 1.70 (m, 2 H), 1.24 (d,  $J = 6.1$  Hz, 6 H); LCMS (ESI):  $m/z$  446 ( $\text{M} + \text{H}$ ) $^+$ .

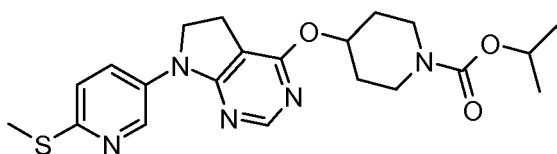
### Example 113 (**203**)



### 1-Methylethyl 4-({7-[5-(methylsulfonyl)-2-pyridinyl]-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-4-yl}oxy)-1-piperidinecarboxylate hydrochloride (**203**)

To a stirred solution of **201** (186 mg, 0.433 mmol) in MeOH (4 mL) and acetone (3 mL) was added a solution of Oxone (798 mg, 1.3 mmol) in water (4 mL) *via* pipet at RT. A white solid precipitated immediately and the reaction mixture was stirred at RT for 1 h. The reaction mixture was quenched with a sat. aqueous solution of  $\text{Na}_2\text{SO}_3$  and extracted with  $\text{CH}_2\text{Cl}_2$  (3 x 10 mL). The combined organic layer was dried over  $\text{MgSO}_4$ , filtered, and concentrated under reduced pressure. The resulting solid was dissolved in a mixture of  $\text{Et}_2\text{O}$  (8 mL) and acetone (3 mL) using a heat gun with stirring. To this solution was added HCl (1.0 M in  $\text{Et}_2\text{O}$ , 0.88 mL) and a white solid precipitated immediately. The material was filtered, washed with  $\text{Et}_2\text{O}$ , and dried under high vacuum to give 190 mg (81%) of the title product **203** as a white solid.  $^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  9.01 (d,  $J = 2.4$  Hz, 1 H), 8.83 (s, 1 H), 8.19 and 8.16 (dd,  $J_1 = 8.8$  Hz,  $J_2 = 2.2$  Hz, 1 H), 7.70 (d,  $J = 8.8$  Hz, 1 H), 5.56 (septuplet,  $J = 4.2$  Hz, 1 H), 4.93 (app. quintuplet,  $J = 6.4$  Hz, 1 H), 4.57 (t,  $J = 8.8$  Hz, 2 H), 3.89 - 3.83 (m, 2 H), 3.38 - 3.29 (m, 4 H), 3.05 (s, 3 H), 2.10 - 2.04 (m, 2 H), 1.84 - 1.76 (m, 2 H), 1.26 (d,  $J = 6.4$  Hz, 6 H); LCMS (ESI):  $m/z$  462 ( $\text{M} + \text{H}$ ) $^+$ .

### Example 114 (**206**)

**Step 1: 6-(Methylthio)-3-pyridinamine (204)**

To a stirred solution of 5-amino-2-bromopyridine (9.97 g, 57.63 mmol) in MeOH (250 mL) was added sodium thiomethoxide (5.65 g, 80.68 mmol) and copper powder (1.17 g, 18.44 mmol) at RT. The reaction mixture was heated in a sealed tube at 120 °C for 64 h. The reaction mixture was then cooled to RT and filtered through a pad of Celite. The Celite<sup>®</sup> was rinsed with MeOH and the combined organics were concentrated under reduced pressure and redissolved in EtOAc. The organic layer was washed with water (1 x 50 mL) and the aqueous layer was extracted with EtOAc (2 x 100 mL). The combined organic layer was dried over MgSO<sub>4</sub>, filtered, and concentrated under reduced pressure. The resulting crude oil was purified using SiO<sub>2</sub> flash chromatography (40% to 70% EtOAc in hexanes) to give 2.08 g (26%) of the title product **204** as a brown solid.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ, 8.00 (d, *J* = 2.9 Hz, 1 H), 7.06 – 7.00 (m, 1 H), 6.92 – 6.89 (m, 1 H), 3.50 (br s, 2 H), 2.51 (s, 3 H).

**Step 2: 4-Chloro-7-[6-(methylthio)-3-pyridinyl]-6,7-dihydro-5H-pyrrolo[2,3-*d*]pyrimidine (205)**

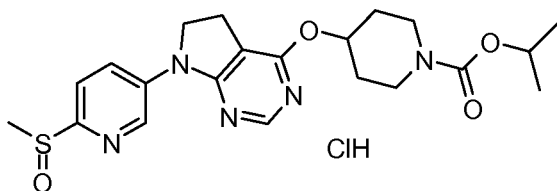
To a stirred solution of (4,6-dichloro-5-pyrimidinyl)acetaldehyde **209** (2.36 g, 12.36 mmol) in MeOH (120 mL) was added **204** (2.08 g, 14.8 mmol) at RT. The reaction mixture was cooled to -15 °C with an ice/methanol bath and glacial acetic acid (2.12 mL, 37.08 mmol) and NaBH<sub>3</sub>CN (2.33 g, 37.08 mmol) were added. The reaction mixture was stirred at -15 °C for 15 min then allowed to warm to RT and stir for 18 h. The reaction mixture was then diluted with water (50 mL) and extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 x 100 mL). The combined organic layer was dried over MgSO<sub>4</sub>, filtered, and concentrated under reduced pressure to a yellow oil. The crude oil was dissolved in THF (350 mL) with stirring and then *t*-BuOK (4.16 g, 37.08 mmol) was added in one portion at RT. The reaction mixture changed immediately to a brown color and was stirred at RT for 17 h. The reaction mixture was quenched with water (50 mL), concentrated under reduced pressure, and then redissolved in EtOAc (200 mL). The organic layer was washed with water (1 x 50

mL) and the aqueous layer was extracted with EtOAc (2 x 100 mL). The combined organic layer was dried over MgSO<sub>4</sub>, filtered, and concentrated under reduced pressure to a brown oil. The crude oil was purified using SiO<sub>2</sub> flash chromatography (20% to 40% EtOAc in hexanes; monitored at 319 nm) to give 1.31 g (38%) of the title product **205** as a colorless oil. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 8.63 and 8.62 (dd, *J*<sub>1</sub> = 2.9 Hz, *J*<sub>2</sub> = 0.7 Hz, 1 H), 8.36 – 8.35 (m, 1 H), 8.28 – 8.24 (m, 1 H), 7.21 – 7.19 (m, 1 H), 4.15 – 4.11 (m, 2 H), 3.25 – 3.20 (m, 2 H), 2.56 (s, 3 H).

**Step 3: 1-Methylethyl 4-({7-[6-(methylthio)-3-pyridinyl]-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-4-yl}oxy)-1-piperidinecarboxylate (**206**)**

To a stirred solution of **205** (1.31 g, 4.71 mmol) and 1-methylethyl 4-hydroxy-1-piperidinecarboxylate **9** (1.06 g, 5.65 mmol) in THF (47 mL) was added NaH (60% dispersion in mineral oil, 565 mg, 14.13 mmol) in one portion at RT. The reaction mixture was heated to reflux for 18 h, cooled to RT, and quenched with water (10 mL). The mixture was extracted with EtOAc (3 x 75 mL), dried over MgSO<sub>4</sub>, filtered, and concentrated under reduced pressure. The crude oil was purified using SiO<sub>2</sub> flash chromatography (40% EtOAc in hexanes) to give 500 mg (25%) of the title product **206** as a colorless oil. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 8.58 (d, *J* = 2.7 Hz, 1 H), 8.41 - 8.37 (m, 1 H), 8.27 (s, 1 H), 7.21 (d, *J* = 8.8 Hz, 1 H), 5.32 (septuplet, *J* = 3.9 Hz, 1 H), 4.91 (app. quintuplet, *J* = 6.1 Hz, 1 H), 4.05 (t, *J* = 8.8 Hz, 2 H), 3.82 – 3.75 (m, 2 H), 3.35 – 3.28 (m, 2 H), 3.08 (t, *J* = 8.8 Hz, 2 H), 2.59 (s, 3 H), 2.00 – 1.93 (m, 2 H), 1.75 – 1.67 (m, 2 H), 1.24 (d, *J* = 6.8 Hz, 6 H); LCMS (ESI): *m/z* 430 (M + H)<sup>+</sup>.

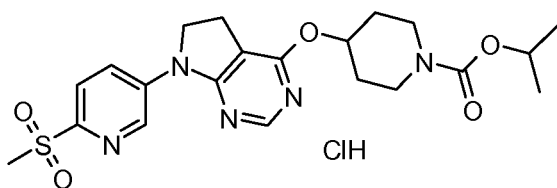
**Example 115 (**207**)**



**(±)-1-Methylethyl 4-({7-[6-(methylsulfinyl)-3-pyridinyl]-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-4-yl}oxy)-1-piperidinecarboxylate hydrochloride (**207**)**

To a stirred solution of **206** (198 mg, 0.460 mmol) in hexafluoroisopropanol (4.0 mL) at 0 °C was added H<sub>2</sub>O<sub>2</sub> (30% wt aqueous solution, 104 mg, 0.920 mmol) via syringe. The reaction mixture was allowed to warm to RT and stirred for 30 min. The reaction mixture

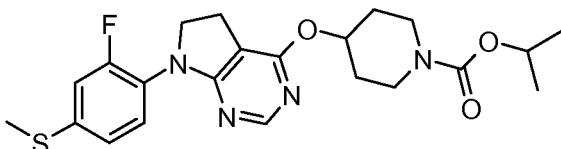
was diluted with water (5 mL) and extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 x 20 mL). The combined organic layer was dried over MgSO<sub>4</sub>, filtered, and concentrated under reduced pressure. The resulting colorless oil was dissolved in a 1:1 mixture of acetone:Et<sub>2</sub>O (15 mL) using a heat gun with stirring. To this solution was added HCl (1.0 M in Et<sub>2</sub>O, 1.7 mL) and a white solid precipitated immediately. The solvent was removed under reduced pressure and the material was triturated with Et<sub>2</sub>O, filtered, and dried under high vacuum to give 151 mg (68%) of the title product **207** as a light yellow solid solid. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 9.12 (d, *J* = 1.5 Hz, 1 H), 8.55 (s, 1 H), 8.46 and 8.43 (dd, *J*<sub>1</sub> = 9.0 Hz, *J*<sub>2</sub> = 2.2 Hz, 1 H), 8.15 (d, *J* = 8.6 Hz, 1 H), 5.64 (septuplet, *J* = 4.1 Hz, 1 H), 4.91 (app. quintuplet, *J* = 6.4 Hz, 1 H), 4.33 (t, *J* = 8.6 Hz, 2 H), 3.93 – 3.87 (m, 2 H), 3.36 – 3.24 (m, 4 H), 2.96 (s, 3 H), 2.14 – 2.08 (m, 2 H), 1.78 – 1.69 (m, 2 H), 1.23 (d, *J* = 6.1 Hz, 6 H); LCMS (ESI): *m/z* 446 (M + H)<sup>+</sup>.

**Example 116 (208)****1-Methylethyl 4-({7-[6-(methylsulfonyl)-3-pyridinyl]-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-4-yl}oxy)-1-piperidinecarboxylate hydrochloride (208)**

To a stirred solution of **206** (302 mg, 0.70 mmol) in MeOH (5 mL) and acetone (5 mL) was added a solution of Oxone (1.30 g, 2.11 mmol) in water (5 mL) via pipet at RT. A white solid precipitated immediately and the reaction mixture was stirred at RT for 1 h. The reaction mixture was quenched with a sat. aqueous solution of Na<sub>2</sub>SO<sub>3</sub> and extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 x 10 mL). The combined organic layer was dried over MgSO<sub>4</sub>, filtered, and concentrated under reduced pressure. The resulting solid was dissolved in a mixture of Et<sub>2</sub>O (10 mL) and acetone (5 mL) using a heat gun with stirring. To this solution was added HCl (1.0 M in Et<sub>2</sub>O, 1.2 mL) and a white solid precipitated immediately. The material was filtered, washed with Et<sub>2</sub>O, and dried under high vacuum to give 260 mg (75%) of the title product **208** as a white solid. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 9.02 (d, *J* = 2.4 Hz, 1 H), 8.58 and 8.56 (dd, *J*<sub>1</sub> = 8.8 Hz, *J*<sub>2</sub> = 2.7 Hz, 1 H), 8.37 (s, 1 H), 8.04 (d, *J* = 8.8 Hz, 1 H), 5.36 (septuplet, *J* = 3.9 Hz, 1 H), 4.91 (app. quintuplet,

$J = 6.4$  Hz, 1 H), 4.14 (t,  $J = 8.8$  Hz, 2 H), 3.84 – 3.76 (m, 2 H), 3.35 – 3.28 (m, 2 H), 3.18 (s, 3 H), 3.15 (t,  $J = 8.8$  Hz, 2 H), 2.02 – 1.95 (m, 2 H), 1.77 – 1.68 (m, 2 H), 1.24 (d,  $J = 6.4$  Hz, 6 H); LCMS (ESI):  $m/z$  462 (M + H)<sup>+</sup>.

### 5 Example 117 (112)



#### Step 1: (4,6-Dichloro-5-pyrimidinyl)acetaldehyde (209)

To a stirred solution of 4,6-dichloro-5-(2-propen-1-yl)pyrimidine (**2**, 274 g, 1.45 mol) in 1:1 acetone-H<sub>2</sub>O (7.6 L) was added K<sub>2</sub>OsO<sub>4</sub>•2H<sub>2</sub>O (18 g, 0.0493 mol). Solid NaIO<sub>4</sub> (1.24 kg, 5.8 mol) was added portionwise during 1h; the reaction temperature did not exceed 40 °C. The resulting suspension was stirred for 1h as the reaction cooled to RT. The mixture was filtered and the filtrate was concentrated to remove the acetone. The aqueous layer was extracted with CH<sub>2</sub>Cl<sub>2</sub> (5 x 1 L). The combined extracts were washed with 10% Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> solution (2 x 3.5 L), with brine, dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated to give 204 g (74%) of the product **209** as a shiny amber solid. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>): δ 9.72 (s, 1 H), 8.86 (s, 1H), 4.21 (s, 2 H).

#### Step 2: [2-Fluoro-4-(methylthio)phenyl]amine (210)

To a mixture of Nickel (II) bromide (9.12 g, 42 mmol), 2,2'-dipyridyl (6.56 g, 42 mmol), zinc dust (55 g, 844 mmol), and anhydrous DMF (300 mL) were added 2-fluoro-4-iodoaniline (100 g, 0.422g, mmol) and dimethyldisulfide (96 mL, 1.06 mol) under N<sub>2</sub>. The resultant mixture was stirred at 75 °C for 1.5 h. The reaction mixture was concentrated under reduced pressure to afford the crude residue, which was dissolved in Et<sub>2</sub>O (500 mL) and filtered through a pad of Celite (washings were done with Et<sub>2</sub>O). The filtrate was concentrated under reduced pressure to afford the crude material. The crude material was subjected to flash column chromatography to afford 48.70 g (73%) of the title product **210** as a brown liquid. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>): δ 7.02 and 6.98 (dd,  $J_1 = 11.2$  Hz,  $J_2 = 2.0$  Hz, 1 H), 6.94 and 6.92 (dd,  $J_1 = 8.4$  Hz,  $J_2 = 4.0$  Hz, 1 H), 6.70 (t,  $J = 8.8$  Hz, 1 H), 3.69 (br, s, 2 H), 2.40 (s, 3 H), 9.72 (s, 1 H), 8.86 (s, 1 H), 4.21 (s, 2 H); LCMS (ESI):  $m/z$  158 (M + H)<sup>+</sup>.



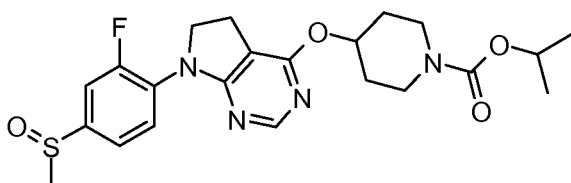
**Step 3: 4-Fluoro-7-[2-fluoro-4-(methylthio)phenyl]-6,7-dihydro-5H-pyrrolo[2,3-*d*]pyrimidine (211)**

A round bottom flask was charged with aniline **210** (7.86 g, 50 mmol) and then cooled to -15°C. Trifluoroacetic acid (50 mL) was added to the above cold aniline **210** while stirring the contents for 0.5 h. Na(OAc)<sub>3</sub>BH was added portion wise to the above mixture and stirred for additional 0.5 h. The aldehyde **209** (9.17 g 48 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (20 mL) was added to the above mixture. The resultant mixture was allowed to warm up to the ambient temperature and stirred for 15 h. The reaction mixture was concentrated under reduced pressure and the residue was poured into sat. NaHCO<sub>3</sub> solution (300 mL) and then the mixture was extracted with CH<sub>2</sub>Cl<sub>2</sub> (4 x 250 mL). The combined organic layer was washed with brine (1 x 100 mL), dried over sat. Na<sub>2</sub>SO<sub>4</sub> and then concentrated under reduced pressure to afford the crude material. The crude material was recrystallized from CH<sub>2</sub>Cl<sub>2</sub> and MeOH to afford 6.26 g (44%) of the title product **211** as an off-white solid. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>): δ 8.16 (s, 1 H), 7.48 (t, *J* = 8.0 Hz, 1 H), 7.26 and 7.22 (dd, *J*<sub>1</sub> = 11.6 Hz, *J*<sub>2</sub> = 2.0 Hz, 1 H), 7.14 and 7.11 (dd, *J*<sub>1</sub> = 8.0 Hz, *J*<sub>2</sub> = 2.4 Hz, 1 H), 4.05 (t, *J* = 8.8 Hz, 1 H), 3.18 (t, *J* = 8.4 Hz, 2 H), 2.49 (s, 3 H); LCMS (ESI): *m/z* 296 (M + H)<sup>+</sup>.

**Step 4: 1-Methylethyl 4-({7-[2-fluoro-4-(methylthio)phenyl]-6,7-dihydro-5H-pyrrolo[2,3-*d*]pyrimidin-4-yl}oxy)-1-piperidinecarboxylate (212)**

Following the procedure described for **10** (example 1, step 10), the reagent **9** (3.07g, 16.4 mmol), NaH (2.08 g, 52 mmol), and the compound **211** (5.11 g, 17.3 mmol) were refluxed for 2.5 h. The regular work-up and chromatography afforded 5.72 g (78%) of the title product **212** as an off-white solid. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>): δ 8.10 (s, 1 H), 7.46 (t, *J* = 8.4 Hz, 1 H), 7.22 and 7.19 (dd, *J*<sub>1</sub> = 12.0 Hz, *J*<sub>2</sub> = 2.0 Hz, 1 H), 7.10 and 7.08 (dd, *J*<sub>1</sub> = 8.0 Hz, *J*<sub>2</sub> = 2.0 Hz, 1 H), 5.26 – 5.20 (m, 1 H), 4.75 (septuplet, *J* = 6.4 Hz, 1 H), 3.96 (t, *J* = 8.8 Hz, 2 H), 3.70 – 3.64 (m, 2 H), 3.22 (app. t, *J* = 9.6 Hz, 2 H), 3.01 (t, *J* = 8.8 Hz, 2 H), 1.94 – 1.88 (m, 2 H), 1.59 – 1.50 (m, 2 H), 1.17 (d, *J* = 6.4 Hz, 6 H); LCMS (ESI): *m/z* 447 (M + H)<sup>+</sup>.

**Example 118 (213)**



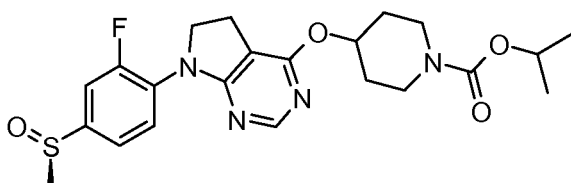
**(±)-1-Methylethyl 4-({7-[2-fluoro-4-(methylsulfinyl)phenyl]-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-4-yl}oxy)-1-piperidinecarboxylate (213)**

Following the oxidation procedure described for 85 (example 32, step 3), the sulfide 212 (1.8 g, 4.03 mmol) was treated with a 35% wt H<sub>2</sub>O<sub>2</sub> (800 μL, 8.06 mmol) in HFIP (20 mL) at RT to afford 1.85 g (~100%) of the desired sulfoxide 213 as a white solid after work up. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>): δ 8.16 (s, 1 H), 7.82 (app. t, *J* = 8.0 Hz, 1 H), 7.64 and 7.60 (dd, *J*<sub>1</sub> = 10.8 Hz, *J*<sub>2</sub> = 2.0 Hz, 1 H), 7.52 and 7.50 (dd, *J*<sub>1</sub> = 8.4 Hz, *J*<sub>2</sub> = 2.0 Hz, 1 H), 5.28 – 5.22 (m, 1 H), 4.76 (septuplet, *J* = 6.4 Hz, 1 H), 4.08 (t, *J* = 8.4 Hz, 2 H), 3.70-3.64 (m, 2 H), 3.22 (app. br. t, *J* = 9.6 Hz, 2 H), 3.04 (t, *J* = 8.8 Hz, 2 H), 2.77 (s, 3 H), 1.94 – 1.90 (m, 2 H), 1.60 – 1.52 (m, 2 H), 1.17 (d, *J* = 6.0 Hz, 6 H); LCMS (ESI): *m/z* 463 (M + H)<sup>+</sup>.

**Example 119**

The racemic sulfoxide 213 (2.60 g) was subjected for Chiral HPLC [column: Chiralpak AS-H, mobile phase: 80% CO<sub>2</sub>: 20% MeOH (2 mL/min), pressure 140 bar, temperature 40 °C, 240 nm] analysis and then separated two (*R* and *S*) enantiomers. The absolute stereochemistry was determined based on VCD spectroscopy.

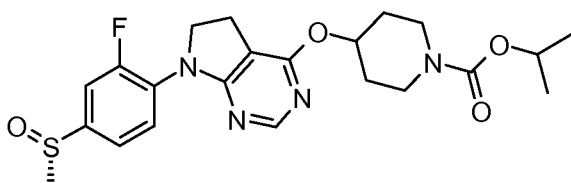
**Enantiomer I, 119A (213A)**



**(*R*)-1-Methylethyl 4-({7-[2-fluoro-4-(methylsulfinyl)phenyl]-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-4-yl}oxy)-1-piperidinecarboxylate (213A)**

Tr: 8.30 min, 1.150 g (% ee > 98%); Spectral data are essentially the same to that of example 118 (213).

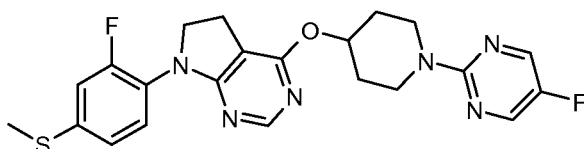
**Enantiomer II, 119B (213B)**



**(S)-1-Methylethyl 4-({7-[2-fluoro-4-(methylsulfinyl)phenyl]-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-4-yl}oxy)-1-piperidinecarboxylate (**213B**)**

Tr: 10.4 min, 1.0 g (% ee, > 98%), Spectral data are essentially the same to that of  
5 example 118 (**213**).

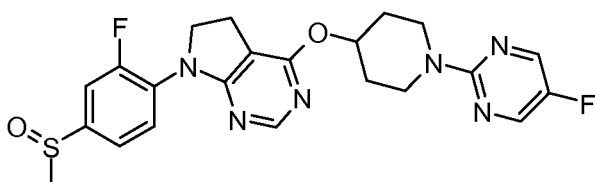
**Example 120 (**218**)**



10 **7-[2-Fluoro-4-(methylthio)phenyl]-4-{{1-(5-fluoro-2-pyrimidinyl)-4-piperidinyl}oxy}-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidine (**214**)**

Following the procedure described for **10** (example 1, step 10), the reagent **23** (0.641g, 3.25 mmol), NaH (0.39 g, 9.8 mmol), and the compound **211** (0.96 g, 3.25 mmol) were refluxed for 5 h. The regular work-up and chromatography afforded 1.145 g (77%) of the title product **214** as a white solid. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>): δ 8.43 (s, 2 H), 8.11 (s, 1 H), 7.47 (t, *J* = 8.4 Hz, 1 H), 7.22 and 7.20 (dd, *J*<sub>1</sub> = 12.0 Hz, *J*<sub>2</sub> = 2.0 Hz, 1 H), 7.10 and 7.08 (dd, *J*<sub>1</sub> = 8.4 Hz, *J*<sub>2</sub> = 2.0 Hz, 1 H), 5.36 – 5.20 (m, 1 H), 4.16 - 4.10 (m, 2 H), 3.96 (t, *J* = 8.8 Hz, 2 H), 3.53 - 3.47 (m, 2 H), 3.0 (t, *J* = 8.8 Hz, 2 H), 2.48 (s, 3 H), 2.01 - 1.96 (m, 2 H), 1.66 - 1.58 (m, 2 H); LCMS (ESI): *m/z* 457 (M + H)<sup>+</sup>.

20 **Example 121 (**215**)**



**(±)-7-[2-Fluoro-4-(methylsulfinyl)phenyl]-4-{{1-(5-fluoro-2-pyrimidinyl)-4-piperidinyl}oxy}-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidine (**215**)**

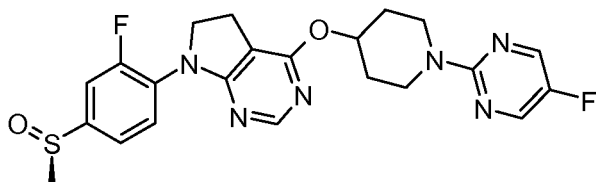
Following the oxidation procedure described for **85** (example 32, step 3), the sulfide **214** (1.07 g, 2.34 mmol) was treated with a 35% wt H<sub>2</sub>O<sub>2</sub> (460 μL, 4.7 mmol) in HFIP (15 mL) at RT to afford 1.10 g (99%) of the desired sulfoxide **215** as a white solid after recrystallization from EtOAc / n-hexanes. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>): δ 8.44 (s, 2 H), 8.18 (s, 1 H), 7.82 (t, *J* = 8.0 Hz, 1 H), 7.62 (app. br. d, *J* = 10.8 Hz, 1 H), 7.52 (app. br. d, *J* = 8.4 Hz, 1 H), 5.36 – 5.30 (m, 1 H), 4.16 4.10 (m, 2 H), 4.08 (t, *J* = 8.8 Hz, 2 H), 3.51 (app. t, *J* = 9.6 Hz, 2 H), 3.04 (t, *J* = 8.8 Hz, 2 H), 2.78 (s, 3 H), 2.04 – 1.96 (m, 2 H), 1.68 – 1.58 (m, 2 H); LCMS (ESI): *m/z* 473 (M + H)<sup>+</sup>.

### 10 Example 122

The racemic sulfoxide **215** (545 mg) was subjected for Chiral HPLC [column: Chiralpak AS-H (analytical), Chiralpak AS-H (prep.), mobile phase: 75% CO<sub>2</sub>: 25% MeOH (2 mL / min), pressure 140 bar, temperature 40 °C, 230 nm] analysis and then separated two (*R* and *S*) enantiomers. The absolute stereochemistry was determined based on VCD spectroscopy.

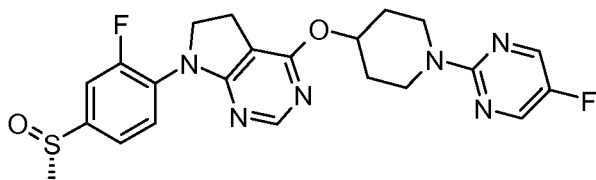
#### Enantiomer I, 122A (**215A**)

(*R*)-7-[2-fluoro-4-(methylsulfinyl)phenyl]-4-[[1-(5-fluoro-2-pyrimidinyl)-4-piperidinyl]oxy]-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidine (**215A**)



20 Tr: 12.4 min, 172 mg (%ee > 99%), Spectral data are essentially the same to that of example 121 (**125A**).

#### Enantiomer II, 122B (**215B**)

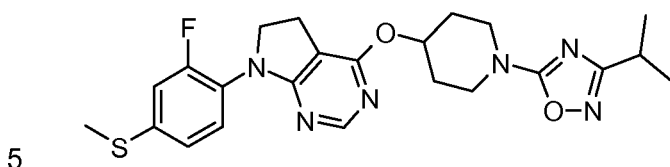


(*S*)-7-[2-Fluoro-4-(methylsulfinyl)phenyl]-4-[[1-(5-fluoro-2-pyrimidinyl)-4-piperidinyl]oxy]-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidine (**215B**)

25

Tr : 17.4 min, 181 mg (%ee >97%), Spectral data are essentially the same to that of example 121 (**215**).

### Example 123 (**216**)



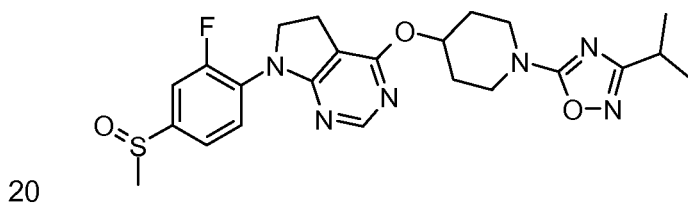
### 7-[2-Fluoro-4-(methylthio)phenyl]-4-({1-[3-(1-methylethyl)-1,2,4-oxadiazol-5-yl]-4-piperidinyl}oxy)-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidine (**216**)

Following the procedure described for **10** (example 1, step 10), the reagent **49** (0.678 g, 3.21 mmol), NaH (0.406 g, 3.21 mmol), and the compound **211** (1.0 g, 3.38 mmol) were refluxed for 2.5 h. The regular work-up and chromatography afforded 1.140 g (76%) of the title product **216** as a white solid. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>): δ 8.11 (s, 1 H), 7.47 (t, *J* = 8.4 Hz, 1 H), 7.22 and 7.20 (dd, *J*<sub>1</sub> = 12.0 Hz, *J*<sub>2</sub> = 2.0 Hz, 1 H), 7.10 and 7.08 (dd, *J*<sub>1</sub> = 8.4 Hz, *J*<sub>2</sub> = 2.0 Hz, 1 H), 5.32 – 5.28 (m, 1 H), 3.98 (t, *J* = 8.8 Hz, 2 H), 3.79 – 3.73 (m, 2 H), 3.52 – 3.45 (m, 2 H), 3.03 (t, *J* = 8.8 Hz, 2 H), 2.80 (septuplet, *J* = 6.8 Hz, 1 H), 2.48 (s, 3 H), 2.05 – 2.00 (m, 2 H), 1.76 – 1.68 (m, 2 H), 1.17 (d, *J* = 6.8 Hz, 6 H); LCMS (ESI): *m/z* 471 (M + H)<sup>+</sup>.

10

15

### Example 124 (**217**)



### (±)-7-[2-Fluoro-4-(methylsulfinyl)phenyl]-4-({1-[3-(1-methylethyl)-1,2,4-oxadiazol-5-yl]-4-piperidinyl}oxy)-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidine (**217**)

Following the oxidation procedure described for **85** (example 32, step 3), the sulfide **216** (600 mg, 1.28 mmol) was treated with a 35% wt H<sub>2</sub>O<sub>2</sub> (300 μL, 3.1 mmol) in HFIP (5 mL) at RT. The work-up and chromatography gave 0.620 g (~100%) of the desired sulfoxide **217** as a white solid after work up. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>): δ 8.18 (s, 1 H), 7.82 (t,

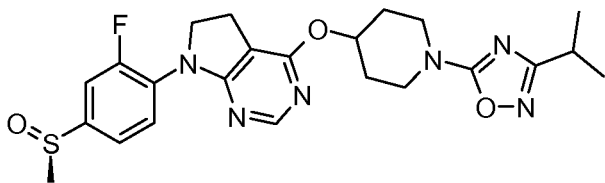
25

$J = 8.0$  Hz, 1 H), 7.64 and 7.61 (dd,  $J_1 = 10.8$  Hz,  $J_2 = 1.6$  Hz, 1 H), 7.54 and 7.51 (dd,  $J_1 = 8.4$  Hz,  $J_2 = 1.6$  Hz, 1 H), 5.34 – 5.28 (m, 1 H), 4.08 (t,  $J = 8.4$  Hz, 2 H), 3.80 – 3.74 (m, 2 H), 3.52 – 3.46 (m, 2 H), 3.06 (t,  $J = 8.8$  Hz, 2 H), 2.08 – 2.0 (m, 2 H), 1.78 – 1.70 (m, 2 H), 1.17 (d,  $J = 7.2$  Hz, 6 H); LCMS (ESI):  $m/z$  487 (M + H)<sup>+</sup>.

5

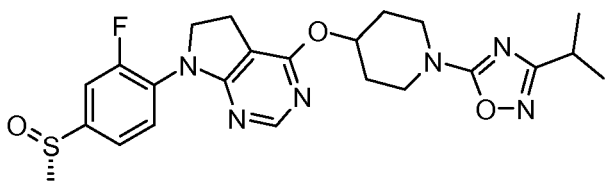
**Example 125**

The racemic sulfoxide **217** (560 mg) was subjected for Chiral HPLC [column: Chiralpak AS-H (analytical), Chiralpak AS-H (prep.), mobile phase: 78% CO<sub>2</sub>: 22% MeOH (2 mL/min), pressure 140 bar, temperature 40 °C, 240 nm) ] analysis and then separated  
10 two (*R* and *S*) enantiomers. The absolute stereochemistry was determined based on VCD spectroscopy.

**Enantiomer I, 125A (217A)**

**(*R*)-7-[2-Fluoro-4-(methylsulfinyl)phenyl]-4-({1-[3-(1-methylethyl)-1,2,4-oxadiazol-5-yl]-4-piperidinyl}oxy)-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidine (217A)**  
15

Tr: 8.6 min, 186 mg (% ee >98%); Spectral data are essentially the same to that of example 124 (**217**).

**Enantiomer II, 125B (217B)**

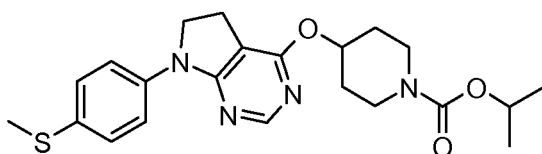
20

**(*S*)-7-[2-Fluoro-4-(methylsulfinyl)phenyl]-4-({1-[3-(1-methylethyl)-1,2,4-oxadiazol-5-yl]-4-piperidinyl}oxy)-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidine (217B)**

Tr: 10.92, 201 mg (%ee >98%); Spectral data are essentially the same to that of example 124 (**217**).

25

**Example 126 (218)**



**Step 1: 7-(4-Bromophenyl)-4-chloro-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidine (116)**

Following the general reductive amination procedure described for 211 (example 117, step 3), a round bottom flask was charged with 4-bromoaniline (9.03 g, 52.5 mmol) in TFA (50 mL), Na(OAc)<sub>3</sub>BH (15.03 g, mmol), aldehyde 209 (7.85 g, 50 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (20 mL) at -15 °C. The resultant mixture was stirred for 15 h at RT. The work-up and recrystallization from CH<sub>2</sub>Cl<sub>2</sub> and MeOH gave 7.86 g (51%) of the title product 116 as an off-white solid. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 8.38 (s, 1 H), 7.66 (app. dd, J<sub>1</sub> = 6.8 Hz, J<sub>2</sub> = 2.0 Hz, 2 H), 7.49 (app. dd, J<sub>1</sub> = 6.8 Hz, J<sub>2</sub> = 2.0 Hz, 2 H), 4.12 (t, J = 8.80 Hz, 2 H), 3.21 (t, J = 8.4 Hz, 2 H); LCMS (ESI): m/z 311 (M + H)<sup>+</sup>.

**Step 2: 1-Methylethyl 4-([7-(4-bromophenyl)-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-4-yl]oxy)-1-piperidinecarboxylate (117)**

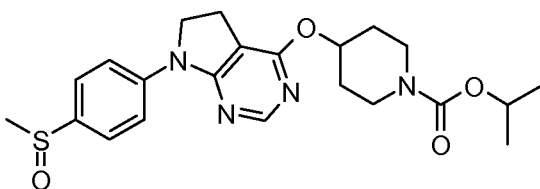
Following the procedure described for 10 (example 1, step 10), the reagent 9 (1.51 g, 8.05 mmol), NaH (0.966 g, 24.2 mmol), and the compound 116 (2.50 g, 8.05 mmol) were refluxed for 2 h. The regular work-up and chromatography afforded 3.15 g (85%) of the title product 117 as a white solid. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 8.30 (s, 1 H), 7.65 and 7.63 (app. dd, J<sub>1</sub> = 8.8 Hz, J<sub>2</sub> = 2.0 Hz, 2 H), 7.46 and 7.44 (app. dd, J<sub>1</sub> = 9.2 Hz, J<sub>2</sub> = 2.0 Hz, 2 H), 5.36-5.28 (m, 1 H), 4.92 (septuplet, J = 6.4 Hz, 1 H), 4.04 (t, J = 8.8 Hz, 2 H), 3.82 – 3.78 (br, m, 2 H), 3.36 – 3.30 (m, 2 H), 3.06 (t, J = 9.2 Hz, 2 H), 2.02 – 1.94 (m, 2 H), 1.76 – 1.68 (m, 2 H), 1.24 (d, J = 6.4 Hz, 6 H); LCMS (ESI): m/z 463 (M + H)<sup>+</sup>.

**Step 3: 1-Methylethyl 4-([7-[4-(methylthio)phenyl]-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-4-yl]oxy)-1-piperidinecarboxylate (218)**

Following the procedure described for 210 (example 117, step 2) to a mixture of nickel (II) bromide (76 mg, 0.35 mmol), 2,2'-dipyridyl (55 mg, 0.35 mmol), zinc dust (284 mg, 4.4 mmol), and anhydrous DMF (20 mL) were added compound 117 (1.6 g, 3.47 mmol) and dimethyldisulfide (1.6 mL, 26.1 mmol) under N<sub>2</sub>. The resultant mixture was stirred at 75 °C for 12 h. The reaction was not complete, but the product was seen (TLC). At that point of time additional nickel (II) bromide (152 mg), dipyridyl (110 mg), zn (568 mg), and dimethyldisulfide (1.6 mL) were introduced. The reaction mixture was stirred at

120 °C for 12 h. The work up and chromatography gave 280 mg of the titled sulfide **218** as a white solid. Around 800 mg of starting material was also recovered from this reaction. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 8.30 (s, 1 H), 7.65 and 7.63 (app, dd, *J*<sub>1</sub> = 7.6 Hz, *J*<sub>2</sub> = 1.6 Hz, 2 H), 7.42 and 7.30 (app. dd, *J*<sub>1</sub> = 8.0 Hz, *J*<sub>2</sub> = 2.0 Hz, 2 H), 5.34 – 5.30 (m, 1H), 5.0 – 4.88 (m, 1 H), 4.07 (t, *J* = 8.8 Hz, 2 H), 3.78 (app, br, s, 2 H), 3.36 – 3.30 (m, 2 H), 3.05 (t, *J* = 8.8 Hz, 2 H), 1.98 (app. br. s, 2 H), 1.78 – 1.66 (br, m, 2 H), 1.24 (d, *J* = 6.0 Hz, 6 H), LCMS (ESI): *m/z* 429 (M + H)<sup>+</sup>.

### Example 127 (**219**)



10

### (±)-1-Methylethyl 4-({7-[4-(methylsulfinyl)phenyl]-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-4-yl}oxy)-1-piperidinecarboxylate (**219**)

Following the oxidation procedure described for **85** (example 32, step 3), the sulfide **218** (260 mg, 0.61 mmol), was treated with a 35% wt H<sub>2</sub>O<sub>2</sub> (120 μL, 1.24 mmol), in HFIP (10 mL) at RT for 0.5 h. The work-up and chromatography followed by recrystallization gave 265 mg (98%) of the desired sulfoxide **219** as a white solid. <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>): δ 8.34 (s, 1 H), 8.0 (app, d, *J* = 8.8 Hz, 2 H), 7.65 (app. d, *J* = 8.8 Hz, 2 H), 5.30-5.24 (m, 1 H), 4.76 (septuplet, *J* = 6.4 Hz, 1 H), 4.10 (t, *J* = 9.2 Hz, 2 H), 3.70 (m, 2 H), 3.23 (app. br. t, *J* = 9.6 Hz, 2 H), 3.02 (t, *J* = 8.8 Hz, 2 H), 2.70 (s, 3 H), 1.96-1.90 (m, 2 H), 1.62-1.50 (m, 2 H), 1.17 (d, *J* = 6.4 Hz, 6 H); LCMS (ESI): *m/z* 445 (M + H)<sup>+</sup>.

20

### Example 128

The racemic sulfoxide **127** (150 mg) was subjected for Chiral HPLC [column: R, R Whelk O-1 column mobile phase: 70% CO<sub>2</sub>: 30% MeOH (2 mL/min), pressure 140 bar, temperature 40 °C, 240 nm] analysis and then separated two (*R* and *S*) enantiomers. The absolute stereochemistry was not assigned.

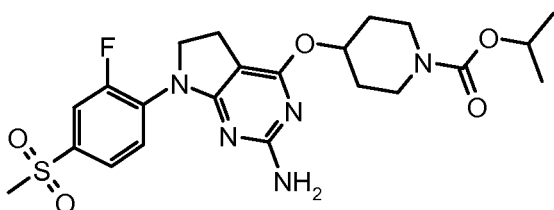
25

**Enantiomer I, 128A:** Tr: 22.9 min. Spectral data are essentially the same to that of example 127 (**219**).



**Enantiomer II, 128B:** Tr 33.4 min, Spectral data are essentially same to that of example 127 (**219**).

**Example 129 (**224**)**



5

**Step 1: Methyl 1-[2-fluoro-4-(methylsulfonyl)phenyl]-2-oxo-3-pyrrolidinecarboxylate (**220**)**

A mixture of 2-fluoro-4-(methylsulfonyl)aniline (3.3 g, 17.3 mmol), 6,6-dimethyl-5,6-dioxaspiro[2.5]octane (9.7 g, 57 mmol) and CH<sub>3</sub>CN (10 mL) was heated at 60°C for 3 h under N<sub>2</sub>. Solvent was evaporated and the residue was heated to 70°C for 5 h. Methanol (15 mL) and concentrated H<sub>2</sub>SO<sub>4</sub> (0.2 mL) were added and the mixture was heated to reflux for 2 h. The mixture was concentrated and the residue was purified by SiO<sub>2</sub> flash column chromatography to give 2.3 g (43%) of the title compound **220** as an off-white solid. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>): δ 7.89 (br d, *J* = 10.0 Hz, 1 H), 7.81-7.73 (m, 2 H), 3.85 (br t, *J* = 7.2 Hz, 2 H), 3.75 (t, *J* = 8.7 Hz, 1 H), 3.68 (s, 3 H), 3.30 – 3.25 (br s, 3 H), 2.45 – 2.35 (m, 2 H); LCMS (ESI): *m/z* 316 (M + H)<sup>+</sup>.

15

**Step 2: Methyl 1-[2-fluoro-4-(methylsulfonyl)phenyl]-2-thioxo-3-pyrrolidinecarboxylate (**221**)**

A mixture of methyl 1-[2-fluoro-4-(methylsulfonyl)phenyl]-2-oxo-3-pyrrolidinecarboxylate (**220**) (2.3 g, 7.2 mmol) and P<sub>4</sub>S<sub>10</sub> (3.9 g, 8.7 mmol) and THF (100 mL) was heated to 70°C for 12 h under N<sub>2</sub>. The mixture was filtered twice washing with EtOAc. The filtrate was concentrated and the residue was purified by Si<sub>2</sub>O flash column chromatography to afford 1.2 g (50%) of the title product **221** as a pale yellow solid. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>): δ 7.98 (br d, *J* = 9.3 Hz, 1 H), 7.89 (br d, *J* = 8.3 Hz, 1 H), 7.81 (dd, *J* = 7.5 Hz, 1 H), 4.12 – 4.08 (m, 3 H), 3.70 (s, 3 H), 3.30 (s, 3 H), 2.60 – 2.50 (m, 2 H); LCMS (ESI): *m/z* 332 (M+H)<sup>+</sup>.

20

**Step 3: 2-Amino-7-[2-fluoro-4-(methylsulfonyl)phenyl]-1,5,6,7-tetrahydro-4H-pyrrolo[2,3-*d*]pyrimidin-4-one (**222**)**

25

To a solution of guanidine hydrochloride (0.3 g, 3.2 mmol) in anhydrous MeOH (3 mL) was added freshly prepared 1M NaOMe/MeOH (3.2 mL, 3.2 mmol) and the mixture was stirred for 30 min at ambient temperature under N<sub>2</sub>. The mixture was filtered and the filtrate added to methyl 1-[2-fluoro-4-(methylsulfonyl)phenyl]-2-thioxo-3-

5 pyrrolidinecarboxylate (**222**) (0.22 g, 0.64 mmol). The yellow mixture was stirred for 5 min then concentrated and heated stepwise from 60 to 90°C with a slight vacuum for 1 h. The mixture was allowed to cool to ambient temperature and H<sub>2</sub>O was added. The pH was adjusted to 6 with 1M HCl/H<sub>2</sub>O and the mixture was stirred at ambient temperature for 18 h. The solid was filtered and dried in vacuum for 2 h to provide 0.12 g of crude **3**  
10 as an yellow solid. LCMS (ESI): m/z 325 (M+H)<sup>+</sup>.

**Step 4: 4-Chloro-7-[2-fluoro-4-(methylsulfonyl)phenyl]-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-2-amine (**223**)**

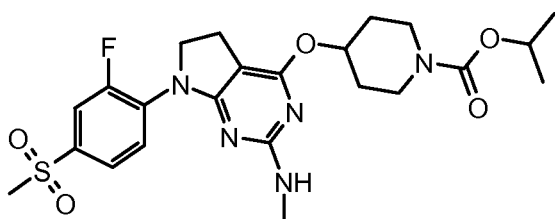
To a suspension of crude 2-amino-7-[2-fluoro-4-(methylsulfonyl)phenyl]-1,5,6,7-tetrahydro-4H-pyrrolo[2,3-d]pyrimidin-4-one (**222**) (0.12 g, 0.36 mmol) in POCl<sub>3</sub> (1.2 mL)  
15 was added carefully iPr<sub>2</sub>NEt (0.13 mL, 0.1 g, 0.72 mmol) and the mixture was slowly heated to 70°C. After 1 h, the mixture was concentrated and the residue was partitioned between EtOAc/CH<sub>2</sub>Cl<sub>2</sub> and saturated NaHCO<sub>3</sub>/H<sub>2</sub>O. The organic phase was filtered, dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated to give 51 mg of crude **223** as a dark green solid. LCMS (ESI): m/z 343 (M+H)<sup>+</sup>.

20 **Step 5: 1-Methylethyl 4-({2-amino-7-[2-fluoro-4-(methylsulfonyl)phenyl]-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-4-yl}oxy)-1-piperidinecarboxylate (**224**)**

To a suspension of 60% NaH/mineral oil (70 mg, 1.8 mmol) in THF (3 mL) was added 1-methylethyl 4-hydroxy-1-piperidinecarboxylate (0.16 g, 0.87 mmol) and the mixture was heated to 50°C for 30 min under N<sub>2</sub> then cooled to 0°C. This mixture was added to a  
25 solution of crude 4-chloro-7-[2-fluoro-4-(methylsulfonyl)phenyl]-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-2-amine (**223**) (51 mg, 0.15 mmol) in THF(1 mL). The mixture was heated to 60°C for 4 h then partitioned between saturated NH<sub>4</sub>Cl/H<sub>2</sub>O and EtOAc. The organic phase was dried over Na<sub>2</sub>SO<sub>4</sub>, concentrated, and purified by Si<sub>2</sub>O flash column chromatography using EtOAc:hexanes (0:100 to 70:30) as eluent to afford 5 mg  
30 (7%) of the title product **224** as an off-white solid. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 8.10 – 8.00 (br s, 1 H), 7.7 – 7.65 (m, 2 H), 5.30 (br s, 1 H), 4.90 (heptuplet, J = 6.0 Hz, 1 H), 4.85 – 4.60 (m, 2 H), 4.15 (br t, J = 7.7 Hz, 2 H), 3.85 – 3.70 (m, 2 H), 3.40 – 3.30 (m, 2

H), 3.05 (s, 3 H), 2.95 (t,  $J = 8.5$  Hz, 2 H), 2.00 – 1.95 (m, 2 H), 1.85 – 1.80 (m, 2 H), 1.24 (d,  $J = 6.0$  Hz, 6 H); LCMS (ESI):  $m/z$  494 (M+H)<sup>+</sup>.

**Example 130 (225)**



5

**Step 1: 7-[2-Fluoro-4-(methylsulfonyl)phenyl]-2-(methylamino)-1,5,6,7-tetrahydro-4H-pyrrolo[2,3-d]pyrimidin-4-one (225)**

To a solution of *N*-methylguanidine hydrochloride (0.35 g, 3.2 mmol) in anhydrous MeOH (3 mL) was added freshly prepared 1M NaOMe/MeOH (3.2 mL, 3.2 mmol) and the mixture was stirred for 30 min at ambient temperature under N<sub>2</sub>. The mixture was filtered and the filtrate added to methyl 1-[2-fluoro-4-(methylsulfonyl)phenyl]-2-thioxo-3-pyrrolidinecarboxylate (**221**) (0.22 g, 0.64 mmol). The yellow mixture was stirred for 5 min then concentrated and heated stepwise from 60 to 90°C with a slight vacuum for 1 h. The mixture was allowed to cool to ambient temperature and H<sub>2</sub>O was added. The pH was adjusted to 6 with 1M HCl/H<sub>2</sub>O and the mixture was stirred at ambient temperature for 18 h. The aqueous phase was decanted and the sticky solid was co-evaporated with CH<sub>3</sub>CN to provide 0.12 g of crude **225** as an orange solid. LCMS (ESI):  $m/z$  339 (M+H)<sup>+</sup>.

10

15

**Step 2: 4-Chloro-7-[2-fluoro-4-(methylsulfonyl)phenyl]-*N*-methyl-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-2-amine (226)**

To a suspension of crude 7-[2-fluoro-4-(methylsulfonyl)phenyl]-2-(methylamino)-1,5,6,7-tetrahydro-4H-pyrrolo[2,3-d]pyrimidin-4-one (**225**) (0.12 g, 0.36 mmol) in POCl<sub>3</sub> (1.2 mL) was added carefully iPr<sub>2</sub>NEt (0.13 mL, 0.1 g, 0.72 mmol) and the mixture was slowly heated to 70 °C. After 1 h, the mixture was concentrated and the residue was partitioned between EtOAc/CH<sub>2</sub>Cl<sub>2</sub> and saturated NaHCO<sub>3</sub>/H<sub>2</sub>O. The organic phase was filtered, dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated. The dark green residue was triturated with EtOAc and filtered. The filtrate was concentrated to give 16 mg of **226** as an off-white solid. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>): δ 8.00 – 7.90 (br m, 1 H), 7.84 (br d,  $J = 7.8$  Hz, 1 H), 7.74

20

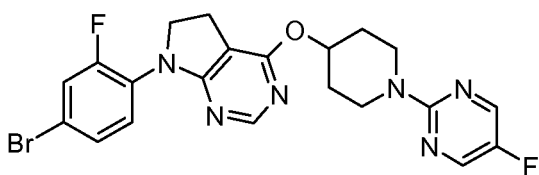
25

(dd,  $J_1 = 8.5$ ,  $J_2 = 1.7$  Hz, 1 H), 7.20 – 7.10 (br m, 1 H), 4.20 – 4.00 (br m, 2 H), 3.26 (s, 3 H), 3.00 (t,  $J = 8.3$  Hz, 2 H), 2.66 (d,  $J = 4.6$  Hz, 3 H); LCMS (ESI):  $m/z$  357 (M+H)<sup>+</sup>.

**Step 3: 1-Methylethyl 4-[[7-[2-fluoro-4-(methylsulfonyl)phenyl]-2-(methylamino)-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-4-yl]oxy]-1-piperidinecarboxylate (227)**

5 To a suspension of 60% NaH/mineral oil (8.4 mg, 0.21 mmol) in THF (1.5 mL) was added 1-methylethyl 4-hydroxy-1-piperidinecarboxylate (20 mg, 0.11 mmol) and the mixture was heated to 50 °C for 30 min under N<sub>2</sub> then cooled to 0°C. This mixture was added to a solution of 4-chloro-7-[2-fluoro-4-(methylsulfonyl)phenyl]-*N*-methyl-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-2-amine (226) (15 mg, 0.04 mmol) in THF (1 mL). The mixture was heated to 60°C for 4 h then partitioned between saturated NH<sub>4</sub>Cl/H<sub>2</sub>O and EtOAc. The organic phase was dried over Na<sub>2</sub>SO<sub>4</sub>, concentrated, and purified by preparative HPLC (C18 column, CH<sub>3</sub>CN:H<sub>2</sub>O gradient) followed by Si<sub>2</sub>O flash column chromatography using EtOAc:hexanes (0:100 to 70:30) as eluent to afford 5 mg (23%) of the title product 227 as an off-white solid foam. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 8.15 – 8.05 (br s, 1 H), 7.7 – 7.65 (m, 2 H), 5.30 (br s, 1 H), 4.90 (heptuplet,  $J = 6.0$  Hz, 1 H), 4.85 – 4.60 (m, 1 H), 4.15 (br t,  $J = 7.3$  Hz, 2 H), 3.85 – 3.70 (m, 2 H), 3.40 – 3.30 (m, 2 H), 3.05 (s, 3 H), 2.95 (t,  $J = 8.5$  Hz, 2 H), 2.92 (d,  $J = 4.9$  Hz, 3 H), 2.00 – 1.95 (m, 2 H), 1.85 – 1.80 (m, 2 H), 1.24 (d,  $J = 6.0$  Hz, 6 H); LCMS (ESI):  $m/z$  508 (M+H)<sup>+</sup>.

20 **Example 131 (228)**



**7-(4-Bromo-2-fluorophenyl)-4-[[1-(5-fluoro-2-pyrimidinyl)-4-piperidinyl]oxy]-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidine (228)**

25 Following the procedure described for 10 (example 1, step 10), the reagent 23 (1.25 g, 6.34 mmol), NaH (.950 g, 23.73 mmol), and the compound 29 (prepared *via* reductive amination using the aldehyde 209 and 4-bromo-2-fluoroaniline following the procedure described for 211, 2.60 g, 7.91 mmol) were refluxed for 4 h. The regular work-up and chromatography afforded 2.90 g (94%) of the title product 228 as a white solid. <sup>1</sup>H NMR

(400 MHz, DMSO-*d*<sub>6</sub>):  $\delta$  8.23 (s, 1 H), 8.20 (s, 2 H), 7.50 (t, *J* = 8.4 Hz, 1 H), 7.33 – 7.28 (m, 2 H), 5.44 – 5.36 (m, 1 H), 4.22 – 4.16 (m, 2 H), 4.05 (t, *J* = 8.8 Hz, 2 H), 3.63 – 3.56 (m, 2 H), 3.09 (t, *J* = 8.8 Hz, 2 H), 2.09 – 2.03 (m, 2 H), 1.83 – 1.74 (m, 2 H), LCMS (ESI): *m/z* 490 (M + H)<sup>+</sup>.

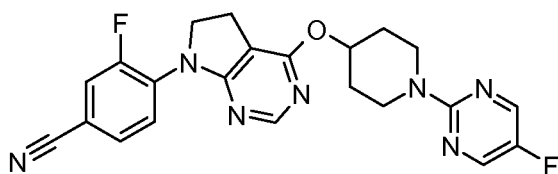
5

### Prophetic Examples

The following examples may be prepared by methods analogous to those herein described:

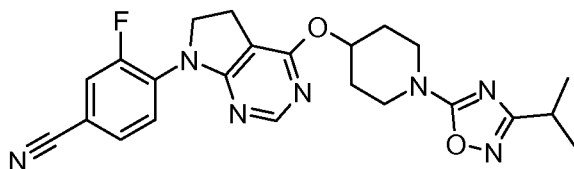
#### Example 132

10 **3-Fluoro-4-(4-{{1-(5-fluoro-2-pyrimidinyl)-4-piperidinyl}oxy}-5,6-dihydro-7*H*-pyrrolo[2,3-*d*]pyrimidin-7-yl)benzotrile**



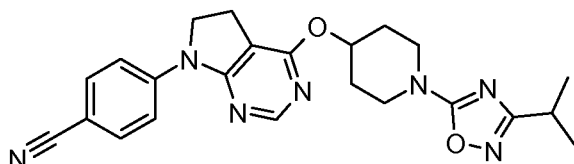
#### Example 133

15 **3-Fluoro-4-[4-{{1-[3-(1-methylethyl)-1,2,4-oxadiazol-5-yl]-4-piperidinyl}oxy}-5,6-dihydro-7*H*-pyrrolo[2,3-*d*]pyrimidin-7-yl]benzotrile**



#### Example 134

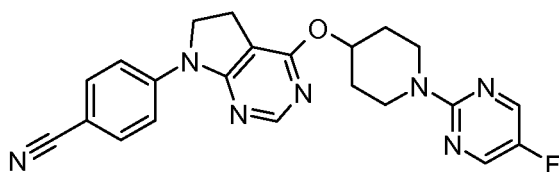
**4-[4-{{1-[3-(1-Methylethyl)-1,2,4-oxadiazol-5-yl]-4-piperidinyl}oxy}-5,6-dihydro-7*H*-pyrrolo[2,3-*d*]pyrimidin-7-yl]benzotrile**



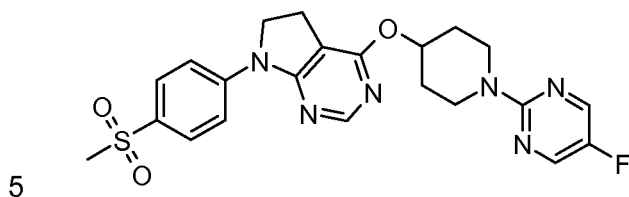
20

#### Example 135

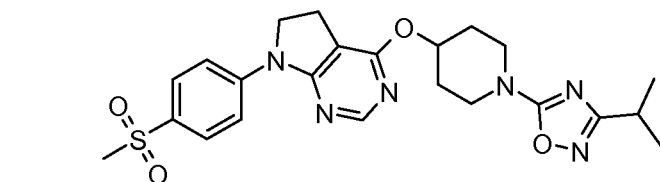
**4-(4-{{1-(5-Fluoro-2-pyrimidinyl)-4-piperidinyl}oxy}-5,6-dihydro-7*H*-pyrrolo[2,3-*d*]pyrimidin-7-yl)benzotrile**

**Example 136**

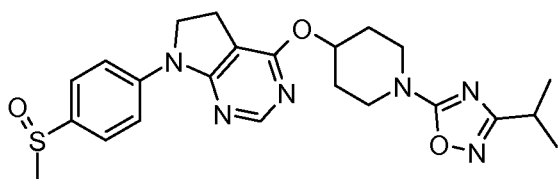
4-[[1-(5-Fluoro-2-pyrimidinyl)-4-piperidinyl]oxy]-7-[4-(methylsulfonyl)phenyl]-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidine

**Example 137**

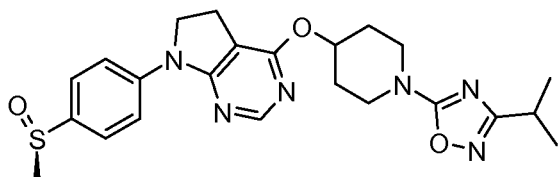
4-({1-[3-(1-Methylethyl)-1,2,4-oxadiazol-5-yl]-4-piperidinyl}oxy)-7-[4-(methylsulfonyl)phenyl]-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidine

**Example 138**

4-({1-[3-(1-Methylethyl)-1,2,4-oxadiazol-5-yl]-4-piperidinyl}oxy)-7-[4-(methylsulfinyl)phenyl]-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidine

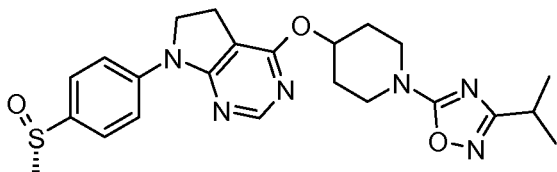
**Example 139**

15 **Example 139A:** (*R*)- 4-({1-[3-(1-methylethyl)-1,2,4-oxadiazol-5-yl]-4-piperidinyl}oxy)-7-[4-(methylsulfinyl)phenyl]-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidine

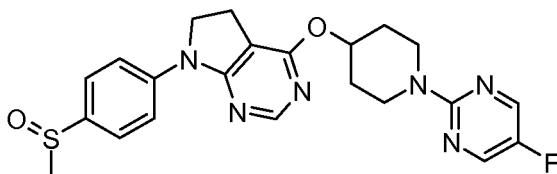


**Example 139B**

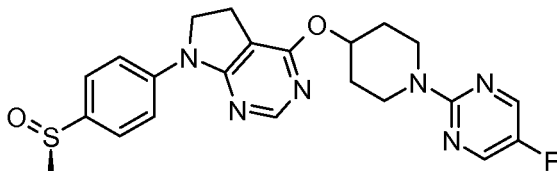
**(S)- 4-({1-[3-(1-Methylethyl)-1,2,4-oxadiazol-5-yl]-4-piperidinyl}oxy)-7-[4-(methylsulfinyl)phenyl]-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidine**

5 **Example 140**

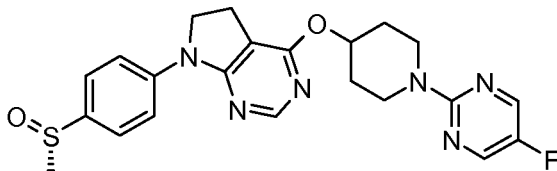
**4-{{1-[5-fluoro-2-pyrimidinyl]-4-piperidinyl}oxy}-7-[4-(methylsulfinyl)phenyl]-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidine**

**Example 141**

10 **Example 141A: (R)- 4-{{1-[5-Fluoro-2-pyrimidinyl]-4-piperidinyl}oxy}-7-[4-(methylsulfinyl)phenyl]-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidine**



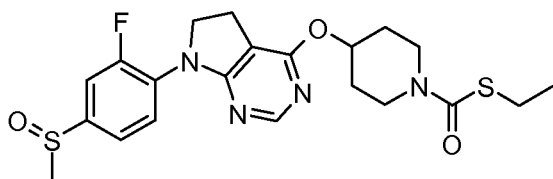
**Example 141B: (S)- 4-{{1-[5-Fluoro-2-pyrimidinyl]-4-piperidinyl}oxy}-7-[4-(methylsulfinyl)phenyl]-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidine**



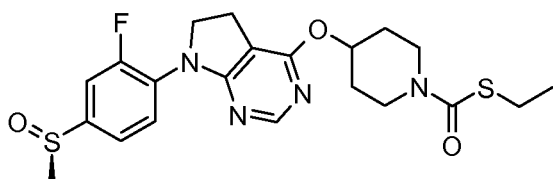
15

**Example 142**

**S-Ethyl 4-({7-[2-fluoro-4-(methylsulfinyl)phenyl]-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-4-yl}oxy)-1-piperidinecarbothioate**

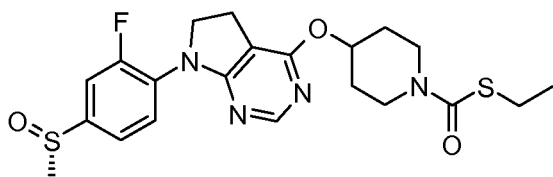
**Example 143**

**Example 143A: (R)- S-Ethyl 4-({7-[2-fluoro-4-(methylsulfinyl)phenyl]-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-4-yl}oxy)-1-piperidinecarbothioate**



5

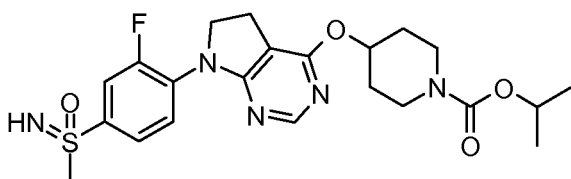
**Example 143B: (S)- S-Ethyl 4-({7-[2-fluoro-4-(methylsulfinyl)phenyl]-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-4-yl}oxy)-1-piperidinecarbothioate**



10

**Example 144**

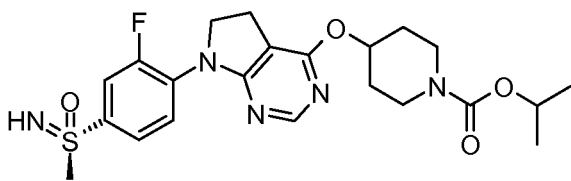
**1-Methylethyl 4-({7-[2-fluoro-4-(S-methylsulfonimidoyl)phenyl]-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-4-yl}oxy)-1-piperidinecarboxylate**

**Example 145**

15

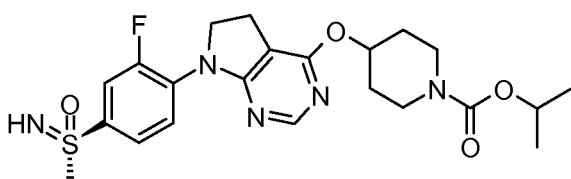
**(R)- 1-Methylethyl 4-({7-[2-fluoro-4-(S-methylsulfonimidoyl)phenyl]-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-4-yl}oxy)-1-piperidinecarboxylate**



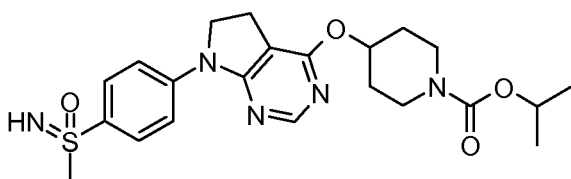
**Example 146**

**(S)- 1-Methylethyl 4-({7-[2-fluoro-4-(S-methylsulfonimidoyl)phenyl]-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-4-yl}oxy)-1-piperidinecarboxylate**

5

**Example 147**

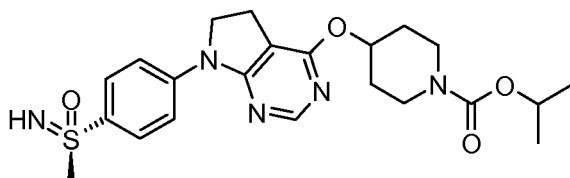
**1-Methylethyl 4-({7-[4-(S-methylsulfonimidoyl)phenyl]-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-4-yl}oxy)-1-piperidinecarboxylate**



10

**Example 148**

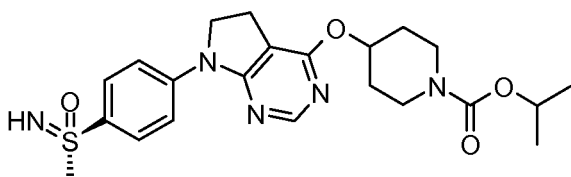
**(R)- 1-Methylethyl 4-({7-[4-(S-methylsulfonimidoyl)phenyl]-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-4-yl}oxy)-1-piperidinecarboxylate**



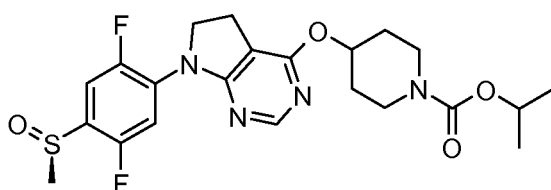
15

**Example 149**

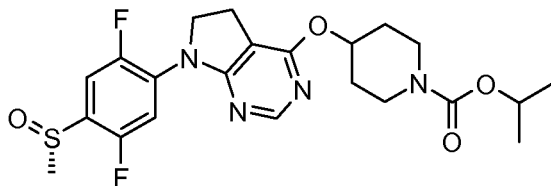
**(S)- 1-Methylethyl 4-({7-[4-(S-methylsulfonimidoyl)phenyl]-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-4-yl}oxy)-1-piperidinecarboxylate**

**Example 150**

5 **(R)-1-Methylethyl 4-({7-[2,5-difluoro-4-(methylsulfinyl)phenyl]-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-4-yl}oxy)-1-piperidinecarboxylate**

**Example 151**

10 **(S)-1-Methylethyl 4-({7-[2,5-difluoro-4-(methylsulfinyl)phenyl]-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-4-yl}oxy)-1-piperidinecarboxylate**

Biological Experimentals and DataGPR119 Agonist Activity

15 Compounds of the current invention are believed useful in the treatment and/or prophylaxis of conditions and diseases mediated through GPR119. Activity mediated through GPR119 was determined using cells transfected with the human GPR119 receptor.

Materials

20 Black, 384-well, tissue culture-treated plates (#781091) were obtained from Greiner, (Germany), Steady-Glo™ Luciferase Assay System Kit (# E2550) was from Promega (Madison, WI), plate seals (#097-05-00006) were from Beckman/Sagian (Fullerton, CA). DMEM/F12 medium (#11039-021), fetal bovine serum (# 16140-071), L-

glutamine (#25030-081), 0.05% trypsin (# 25300-054), G418 (#10131-035) and dPBS (#4190-144) were obtained from Gibco BRL (Gaithersburg, MD). Chinese hamster ovary cells stably expressing 6xCRE-luc<sup>+</sup> (CHO6CRE) were generated in-house.

#### Methods

5 CHO6CRE cells were transfected by electroporation with the human GPR119 receptor. A stable clone was selected using G418 for functional agonist assays. GPR119-CHO6CRE cells were propagated in complete medium (DMEM/F12, 5% FBS, 2 mM l-glutamine) in T225 flasks. Twenty-four hours prior to assay, cells were harvested with 5 ml of 0.05% trypsin, washed with complete medium and plated at a  
10 concentration of 15,000 cells/well in complete medium in black 384-well plates. The next day, the medium was removed from the cells and replaced with 20  $\mu$ l/well of serum-free DMEM/F12, 1% DMSO using Matrix Well-mate. Immediately following this addition, agonists (20  $\mu$ L, 1% DMSO) as 11-point concentration curves were pipetted into the medium using a Packard Minitrak and plates were incubated for five hours at 37°C in a  
15 cell culture incubator. Following the incubation, 15  $\mu$ l of a 1:1 mixture of Steady-Glo™ and dPBS/1 mM CaCl<sub>2</sub>/1 mM MgCl<sub>2</sub> was added to the plates using the Well-mate. Plates were sealed and luciferase activity was quantitated on a TopCount™ microplate scintillation counter (Packard) using 3 seconds/well count time. Agonist activity was quantified by non-linear regression analysis using a curve-fitting program based in  
20 Microsoft EXCEL.

The compounds of the present invention are believed to provide a pIC<sub>50</sub> of 5 or greater.

Although pIC<sub>50</sub> values were generated for certain of the present compounds, these values should be considered exemplary. Those skilled in the art will appreciate  
25 the variability in performing and recording data using the biological activity assays that are herein described. As used herein, the focus on pIC<sub>50</sub> values of 5 or greater is a subjective choice and is not indicative that compounds having less activity are inactive or inoperable.

#### 30 GPR119 agonists as GLP-1 and GIP secretagogues

The effect of a GPR119 agonist on circulating GLP-1 and GIP assessed *in vivo* in mice.

Ten weeks old C57BL/6 male mice (Taconic Farms, USA) were fasted overnight then randomly distributed into 6 treatment groups (n=10 mice per treatment group) receiving either vehicle (0.5% HPMC/ 0.1% Tween80), or a GPR119 agonist (Example 1) at five different doses (1, 3, 10, 30 or 60 mg/kg) by oral gavage. All animals were dosed with a volume of 10mL/kg of their designated treatment. Sixty minutes after the oral gavage the mice were anesthetized using isoflurane for collection of blood samples by cardiac puncture. All mice were euthanized by cervical dislocation immediately following the cardiac puncture. Blood samples were placed in chilled K<sub>2</sub>-EDTA coated capiject tubes (Cat.#T-MQK, Terumo Medical Corp, Elkton MD), supplemented with a DPP4 inhibitor and Aprotinin (Trasylol; Bayer Pharmaceuticals, West Haven, CT) yielding a final concentration of 30µL and 250KIU/mL respectively. The tubes were immediately centrifuged at 4°C, the plasma collected and stored at -80°C for subsequent hormone measurements. Total GLP-1 levels were determined using a MULTI-ARRAY<sup>®</sup> electrochemoluminescence assay from Meso Scale Discovery (Cat # K110-FAC-2; Gaithersburg, MD). Total GIP levels were determined using an ELISA assay (Cat # EZRMGIP-55K, Linco Diagnostic Services, St Charles, MO).

Data are represented as box plots summarizing the distribution of individual data point for each treatment group. The upper and lower end of the box corresponds to the 75<sup>th</sup> and 25<sup>th</sup> percentile respectively, with whiskers extending to points within the 1.5\*interquartile range. Horizontal lines represents mean data. Figure 1 and figure 2 show total GLP-1 and total GIP respectively measured in circulation following administration of vehicle or a GPR119 agonist (Example 1) at doses as indicated.

These results illustrate that administration of Example 1, a GPR119 agonist, produces a dose dependent increase in circulating total GLP-1 and total GIP levels in mice.

The effect of a GPR119 agonist on circulating GLP-1 and GIP evaluated *in vivo* in wild-type and GPR119 knock-out mice.

17 weeks old male transgenic wild-type (WT) and GPR119 knock-out (KO) mice (Charles River Laboratories, USA) were fasted overnight then randomly distributed into two treatment groups for each genotype with n=8 and n=10 animals per treatment group for KO and WT mice respectively. Animals received either vehicle (0.5% HPMC/ 0.1% Tween80) or a GPR119 agonist (Example 1) at a dose of 30 mg/kg (10mL/kg),

administered by oral gavage. Sixty minutes after the oral gavage the mice were anesthetized using isoflurane and a blood sample was collected by cardiac puncture, before sacrificing the animal by cervical dislocation. Blood samples were treated as described above for determination of incretin hormone levels. Plasma glucose levels were measured using an Olympus AU640 analyzer (Olympus America Inc, Melville, NY), and insulin levels an electrochemoluminescence assay (Bioveris, Gaithersburg MD).

Data are represented as box plots summarizing the distribution of data for each treatment group, as described above. Horizontal lines represent the mean data.

Figure 3 and Figure 4 show total GLP-1 and GIP levels measured in circulation following administration of vehicle or 30 mg/kg GPR119 agonist (Example 1) in WT and KO mice. Corresponding glucose and insulin levels are shown in figure 5 and figure 6.

These results illustrate that the increase in incretin hormone levels produced by Example 1, a GPR119 agonist, is dependent on the GPR119 receptor as the compound was without effect in GPR119 knock out mice. Furthermore, fasting glucose and insulin levels were not affected.

#### The effect of a GPR119 agonist on circulating GLP-1 and GIP evaluated *in vivo* in rats

Male Sprague-Dawley rats (Charles River Laboratories, USA) had a catheter surgically implanted into the jugular and allowed to recover for one week following the surgery. On the day before the experiment, food was removed in the afternoon and the following morning animals were randomly assigned to two treatment groups, vehicle (n=7) or a GPR119 agonist (Example 1; n=8). Blood samples were collected prior to, and 90 minutes following oral administration of either vehicle (0.5% HPMC/ 0.1% Tween80) or 10 mg/kg of Example 1. Blood samples were treated as described above and analyzed for incretin hormones, plasma glucose and insulin. The rats were sacrificed at the end of the study by an overdose of Nembutal® pentobarbital.

Data are represented as line graphs of the measurements prior to gavage (Pre) and 90 min following administration of vehicle or GPR119 agonist (Post) analyzed for total GLP-1 (figure 7), total GIP (figure 8), plasma glucose (figure 9) and insulin (figure 10) for individual animals.

These results demonstrates that the circulating levels of total GLP-1 and total GIP increases in rats treated with a GPR119 agonist whereas the hormone levels decrease with time in vehicle treated animal. As in mice, fasting glucose and insulin are

not significantly affected by the GPR119 agonist compared to vehicle, or the baseline measurements within the treatment group.

GPR119 agonists as modulator of glucose stimulated insulin secretion.

5 The effect of a GPR119 agonist on glucose stimulated insulin secretion *in vivo* in rats assessed by the hyperglycemic clamp.

Male Wistar rats (Taconic farms, USA), weighing 300-350gram, had catheters surgically implanted into the jugular and femoral veins and allowed to recover for one week following the surgery. On the day before the experiment, food was removed in the afternoon for an overnight fast. The following morning animals were randomly assigned to three treatment groups, vehicle (n=19) and either 1 mg/kg (n=8) or 10 mg/kg (n=8) of a GPR119 agonist (Example 1), and baseline blood samples were collected from the jugular vein. Animals were then administered either vehicle or Example 1 by oral gavage. A second blood sample was collected approximately 90 minutes after the oral gavage immediately prior to starting the hyperglycemic clamp. The clamp was initiated by infusing an empirically determined glucose bolus over 15-30 seconds into the femoral vein, followed by a variable rate glucose infusion adjusted to achieve a stable plasma glucose level of 190-210 mg/dl. After infusion of the glucose bolus, blood samples were collected every 5 minutes for glucose measurements. Samples for C-peptide level were collected a 2, 5, 10, 15, 20, 25, 30, 46, 60, 90 and 120 minutes during the hyperglycemic clamp. C-peptide was measured as a surrogate for insulin as it is co-secreted with insulin in equimolar amount with lower hepatic clearance, thus a better reflection of insulin secretion from the pancreatic  $\beta$ -cells. All blood samples were placed in individual tubes containing a gel clot activator (Cat # T-MG, Terumo Medial Corporation, Elkton, MD) and allowed to clot in room temperature for 20min before centrifugation and collection of serum. Glucose levels were measured using an Olympus AU640 analyzer (Olympus America Inc, Melville, NY), and C-peptide levels by an RIA (Linco Diagnostic services, St Charles, MO). The rats were sacrificed at the end of the study by an overdose of Nembutal.

30 Figure 11 shows the plasma glucose levels  $\pm$  SEM achieved during the hyperglycemic clamp. There was no difference in plasma glucose levels between treatment groups. The glucose infusion rates (GIR) required to sustain the hyperglycemic clamp is shown in Figure 12. Animals treated with 10 mg/kg Example 1

required more exogenous glucose to maintain the clamp compared to 1 mg/kg Example 1 or vehicle. The characteristic biphasic insulin secretion response (measured as an increase in C-peptide levels) elicited by the rapid increase in plasma glucose levels is shown in Figure 13, with the first phase occurring within the first 5 minutes and the  
5 second phase from 15 minutes and beyond. At 10 mg/kg, Example 1 significantly increased C-peptide levels compared to either vehicle or 1 mg/kg of Example 1 throughout the duration of the hyperglycemic clamp.

These data illustrate that GPR119 agonists, as demonstrated with Example 1  
10 augments both the first (0-5min) and the second phase (15-90min) glucose stimulated insulin secretory response during the hyperglycemic clamp in rat.

Effect of a GPR119 agonist on glucose stimulated insulin secretion and glucose disposal *in vivo* in rats assessed by the intravenous glucose tolerance test.

Male Sprague-Dawley rats (Charles River Laboratories, USA) had catheters  
15 surgically implanted into the jugular vein and allowed to recover for one week. On the day of the experiment, food was removed in the morning and animals were randomly assigned to two treatment groups, vehicle (n=8) or GPR119 agonist (Example 1; n=9). In the afternoon, baseline blood samples were collected prior to, and 90 minutes  
20 following oral administration of either vehicle (0.5% HPMC/ 0.1% Tween80) or 10 mg/kg Example 1. The intravenous glucose tolerance test was initiated immediately after the 90 minute blood sample by intravenous infusion of 0.5 g/kg dextrose over 15-30 seconds into the jugular vein, Blood samples were collected from the jugular vein at 2, 5, 10, 15,  
25 20 and 30min and treated as described for the hyperglycemic clamp. Serum was collected for analysis of glucose levels using an Olympus AU640 clinical chemistry analyzer (Olympus America Inc, Melville, NY) and insulin levels by an  
electrochemoluminescence assay (Bioveris, Gaithersburg MD). The rats were sacrificed at the end of the study by an overdose of Nembutal.

Figure 14 and figure 15 show circulating plasma glucose and insulin  
concentrations at each time point throughout the intravenous glucose tolerance test.  
30 The data are represented as the average glucose and insulin levels  $\pm$  SEM for all animals in for the two treatment groups. The area under the glucose curve (AUC) was significantly reduced, and the rate of glucose elimination was significantly increased in animals treated with Example 1 compared to vehicle treated animals. The peak (2

minute) insulin response and the area under the insulin curve were significantly increased in Example 1 treated animals compared to vehicle.

These results illustrates that GPR119 agonists, here represented by Example 1, augments glucose stimulated insulin secretion and enhance glucose disposal during the intravenous glucose tolerance test.

#### GPR119 agonists and glucose homeostasis

##### The effect of a GPR119 agonists on oral glucose tolerance in normal mice

Nine weeks old male C57BL/6 mice (Taconic farms, USA) were fasted overnight and randomly assigned to three different treatment groups (n=9-10 per treatment arm) to receive vehicle (0.5%HPMC/0.1%Tween80), a GPR119 agonist (Example 1, 30 mg/kg) or a positive control (10 mg/kg), specifically a DPPIV inhibitor known to improve glucose tolerance in vivo by preventing degradation of the GLP-1 and GIP. Vehicle or compounds were delivered by oral gavage at a volume of 10mL/kg, and the tip of tail was nicked using a scalpel to allow whole blood glucose measurements. One hour after administration of vehicle or test compounds, 2 g/kg of dextrose was administered by oral gavage. Whole blood glucose levels were determined from the abrasion at the tip of the tail at time points as indicated in figure 16 using a Glucometer (Freestyle, Therasense). At the end of the study the mice were sacrificed by cervical dislocation.

Figure 16 shows the average whole blood glucose concentration  $\pm$  SEM for the animals in each treatment group. These results illustrate that GPR119 agonists, as demonstrated with Example 1, and the DPPIV compound significantly enhanced glucose disposal during the course of the oral glucose tolerance test in mice.

##### The effect of a GPR119 agonist on oral glucose tolerance in wild type and GPR119 knockout mice

Male transgenic wild type (WT) and GPR119 knock-out (KO) mice (Charles River Laboratories, USA), at an age of 12 weeks, were fasted overnight (approximately 15 hrs) then randomly grouped (n=8-10) to receive vehicle (0.5%HPMC/0.1%Tween80), a GPR119 agonist (30mg/kg) or a positive control (10mg/kg), the DPPIV inhibitor as described above. Vehicle or compounds were delivered orally by oral gavage at a volume of 10 mL/kg, and the tip of tail was nicked using a scalpel to allow whole blood glucose measurements. One hour after administration of vehicle or test compounds,



dextrose was administered orally at 2g/kg. Whole blood glucose levels were measured prior to, and 10, 20, 30, 45, 60, 90 and 120min after the oral glucose load using a Glucometer (Freestyle, Therasense) from the tip of tail. At the end of the study the mice were sacrificed by cervical dislocation.

5           The glucose tolerance was calculated as the area under the glucose curve (AUC). Data are represented as box plots summarizing the distribution of data for each treatment group, as described above. Horizontal lines represent the mean data. Figure 17 shows the total glucose AUC for each treatment group in WT and KO mice. Example 1 at 30 mg/kg, and the positive control (DPPIV) improved glucose tolerance as it reduced the total glucose AUC by 28%, and 47% respectively. In GPR119 KO mice  
10       Example 1 had no effect on glucose tolerance whereas DPPIV significantly reduced total glucose AUC by 45%.

          These results demonstrate that GPR119 agonists, here illustrated by Example 1, improve glucose tolerance through interaction with the GPR119 receptor.

15

#### The effect of a GPR119 agonist on oral glucose tolerance in rats

          Eight weeks old male Sprague-Dawley rats had catheters surgically implanted into the jugular catheter vein and allowed to recover for one week. Food was removed in the afternoon the day before the experiment to fast animals overnight. The following  
20       morning animals were randomly assigned to treatment groups to receive vehicle (n=7) (0.5%HPMC/0.1%Tween80), a GPR119 agonist (Example 1, 10 mg/kg) or a positive control (10mg/kg), namely a DPPIV inhibitor as described above. Vehicle and compounds were delivered by oral gavage at a volume of 10mg/kg. Two and a half  
25       hours after administration of vehicle or GPR119 agonist and one hour administration of DPPIV inhibitor, 2 g/kg dextrose was administered orally. Blood samples were collected at timepoints as indicated in figure 18, and placed in chilled K<sub>2</sub>-EDTA containing tubes (Cat.#T-MQK, Terumo Medical Corp, Elkton MD), supplemented with a DPP4 inhibitor and Aprotinin (TrasyloI; Bayer Pharmaceuticals, West Haven, CT) yielding a final  
30       concentration of 30µL and 250KIU/mL respectively. The tubes were immediately centrifuged, plasma collected for subsequent measurement of glucose and hormone levels and stored at -80°C. Plasma glucose, insulin and total GLP-1 levels were measured as described above.

Figure 18 shows the glucose concentration, figure 19 the insulin concentrations and figure 20 the total GLP-1 concentrations throughout the glucose tolerance test for the different treatment groups as indicated. The data are represents as mean values  $\pm$  SEM from all animals within each treatment group.

5           These results show that GPR119 agonists, as illustrated with Example 1, as well as the DPPIV inhibitor, significantly decreased the glucose excursion during the 120 minutes time course of the oral glucose tolerance test compared to vehicle. The total glucose area under the curve (AUC) was reduced by 38 and 24% respectively. Insulin AUC was not significantly different between the treatment groups. Both baseline total  
10   GLP-1 and the total GLP-1 AUC were significantly increased for the treatment group receiving the GPR119 agonist compared to vehicle and DPPIV treated animals.

          These results illustrate that GPR119 agonists, as demonstrated with Example 1, improves glucose disposal during the course of an oral glucose tolerance test in rats. Furthermore, GPR119 agonists, here demonstrated with Example 1, increase the total  
15   GLP-1 levels independent of glucose prior to the oral glucose tolerance test, as well as augment the nutrient stimulated increase in total GLP-1 following the oral glucose load.

#### Insulin sensitizing effects of GPR119 agonists

Whole body insulin sensitivity assessed by the euglycemic hyperinsulinemic clamps *in*  
20 *vivo* in rats

          Male Sprague Dawley rats, weighing at 300-350gram, had catheters surgically implanted into the jugular and femoral veins and allowed to recover for one week following the surgery. On the day before the experiment, food was removed in the afternoon to fast the animals overnight. The following morning animals were randomly  
25   assigned to two treatment groups, vehicle (n=7) and or 10 mg/kg of a GPR119 agonist (Example 1, n=9). Blood samples were collected from the jugular vein for baseline glucose measurements prior to oral administration of the respective treatment. The euglycemic hyperinsulinemic clamp was initiated approximately 90 minutes following oral administration of the respective treatments, by starting the constant insulin infusion at a  
30   rate of 1 mU/kg/min human insulin (Humulin, Eli Lilly and Company, Indianapolis, ID) into the femoral vein of conscious animals. Whole blood glucose levels were measured every 10 minutes throughout the clamp. As the plasma glucose levels began to fall exogenous glucose infusion was started at a variable rate adjusted to achieve a stable

plasma glucose level of 90-100mg/dl. The glucose infusion rate required to maintain euglycemia was recorded throughout the experiment for each animal, and represents a measure of insulin sensitivity. Plasma glucose and human insulin levels were measured at the end of the clamp (at 180min) as described above. At the end of the study the rats were sacrificed by an overdose of Nembutal.

Figure 21 shows the average human insulin levels and plasma glucose levels as measured at the end of the clamp for each treatment group. Data are represented as box plots summarizing the distribution of data for each treatment group, as described above. Horizontal lines represent the mean data. There was no significant difference in steady state insulin exposure or euglycemia between treatment groups. Figure 22 shows the glucose infusion rates (GIR) required to maintain euglycemic in the two treatment groups throughout the clamp. The data are represented as mean GIR  $\pm$  SEM. At steady state, 180 minutes after starting the clamp, the glucose infusion rate required to maintain euglycemia in Example 1 treated animals were three times that of vehicle treated animals.

This data demonstrates that treatment with a GPR119 agonist, here illustrated with Example 1, enhances whole body insulin sensitivity in normal rats.

Test compounds were employed in free or salt form.

All research complied with the principles of laboratory animal care (NIH publication No. 85-23, revised 1985) and GlaxoSmithKline policy on animal use.

Although specific embodiments of the present invention are herein illustrated and described in detail, the invention is not limited thereto. The above detailed descriptions are provided as exemplary of the present invention and should not be construed as constituting any limitation of the invention. Modifications will be obvious to those skilled in the art, and all modifications that do not depart from the spirit of the invention are intended to be included with the scope of the appended claims.

What is claimed is:

1. A method for increasing GLP-1 secretion through the administration of a GPR119 agonist.
2. The method of claim 1 wherein the GPR119 agonist is a compound of formula (I).
3. A method for increasing GLP-1 secretion in a glucose independent and dependent manner through the administration of a GPR119 agonist.
4. The method of claim 3 wherein the GPR119 agonist is a compound of formula (I).
5. A method for increasing whole body insulin sensitivity through the administration of a GPR119 agonist.
6. The method of claim 5 wherein the GPR119 agonist is a compound of formula (I).

FIGURE 1

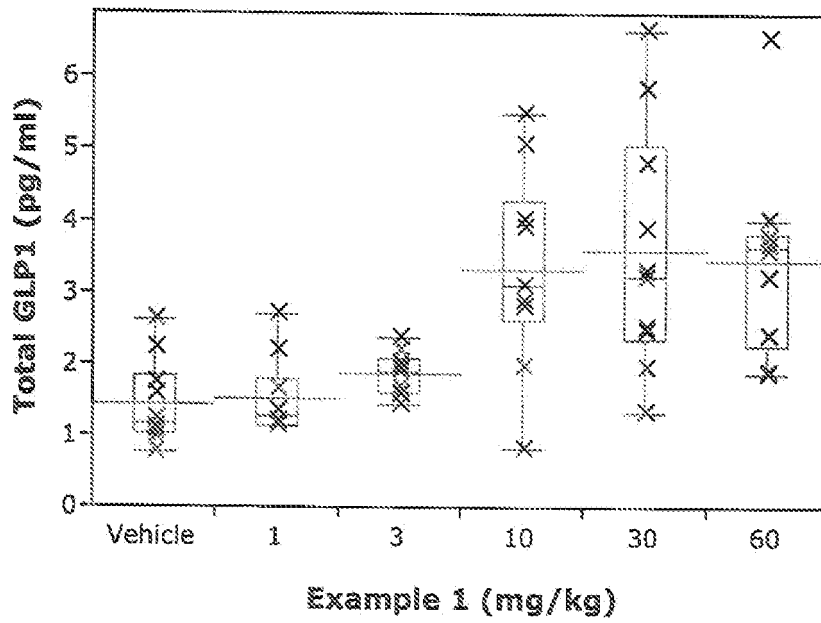


FIGURE 2

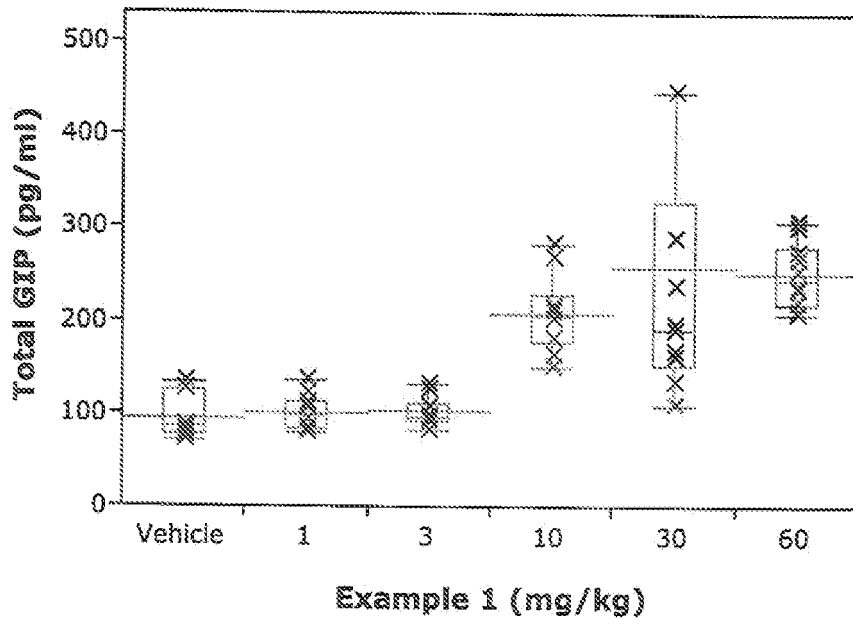


FIGURE 3

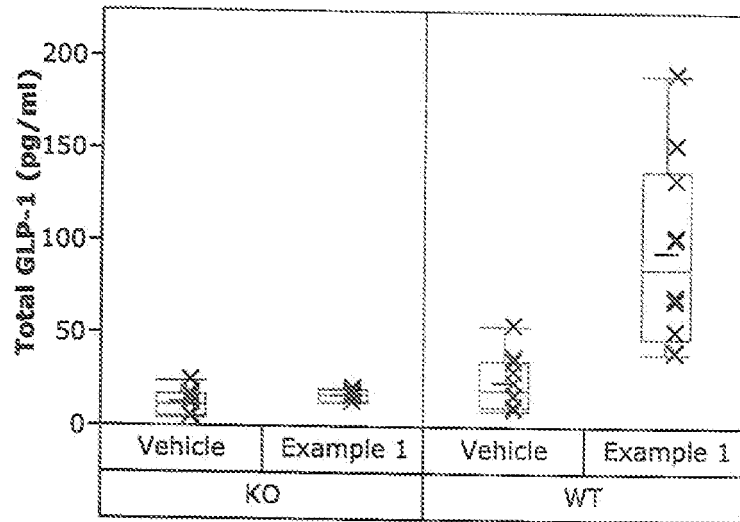


FIGURE 4

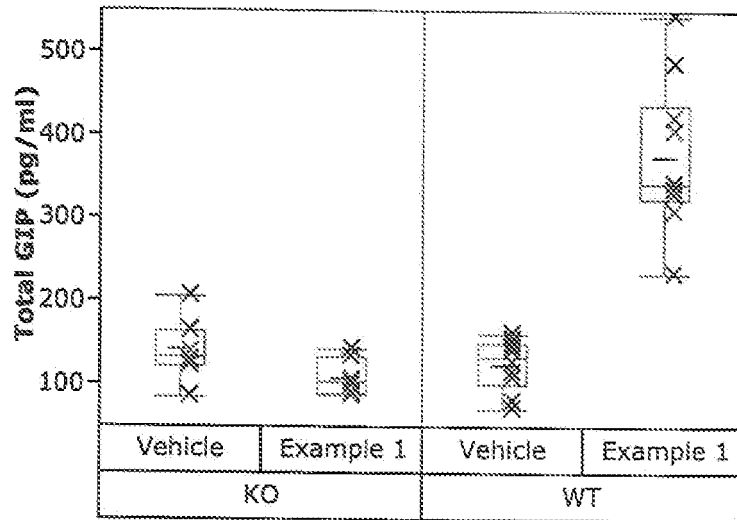




FIGURE 5

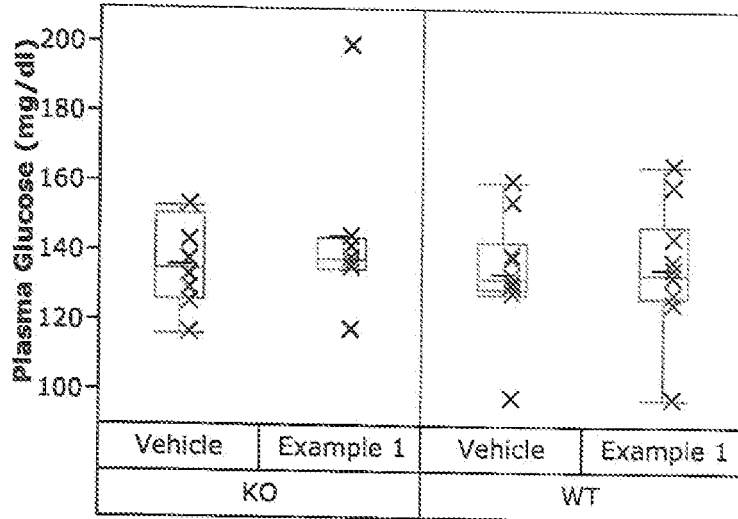


FIGURE 6

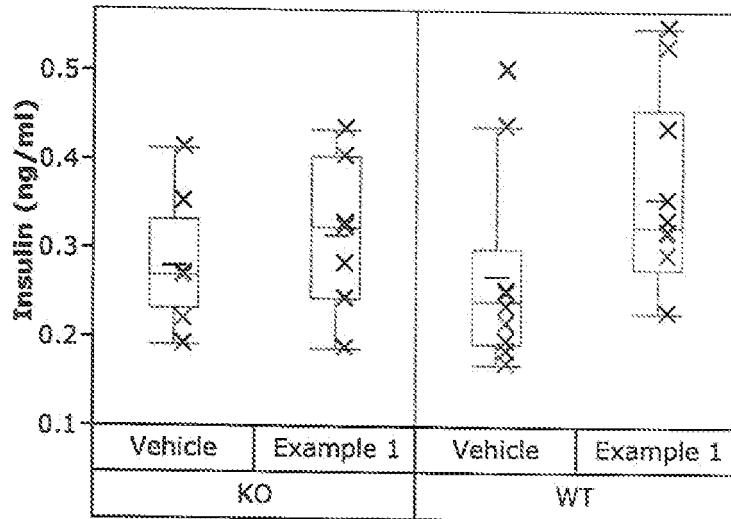


FIGURE 7

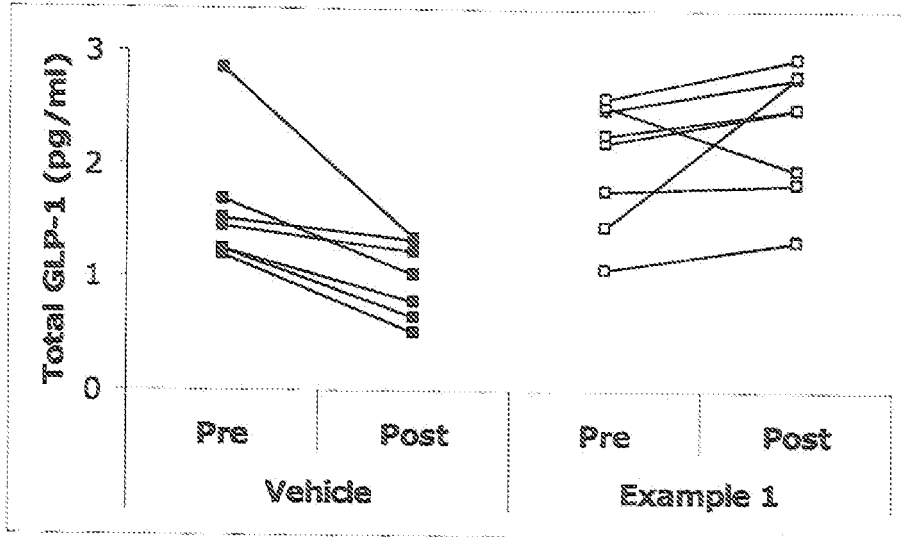


FIGURE 8

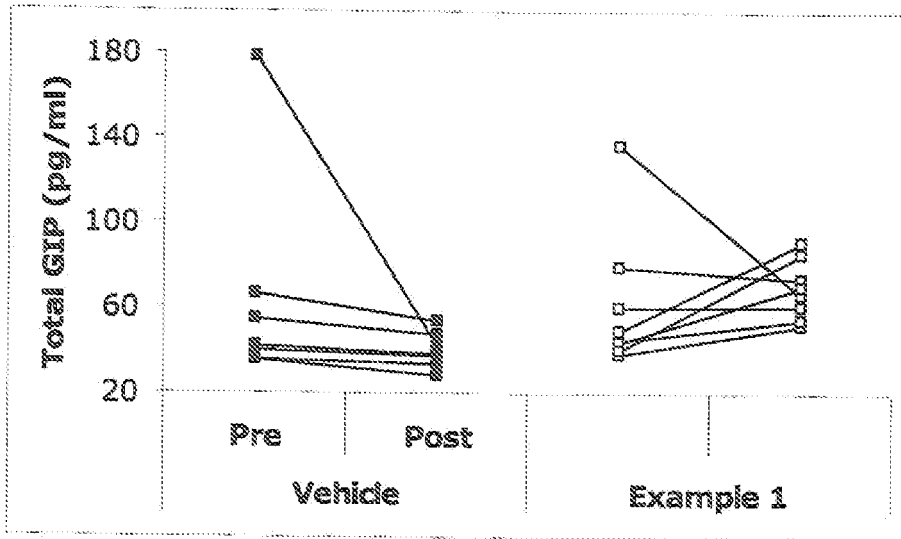


FIGURE 9

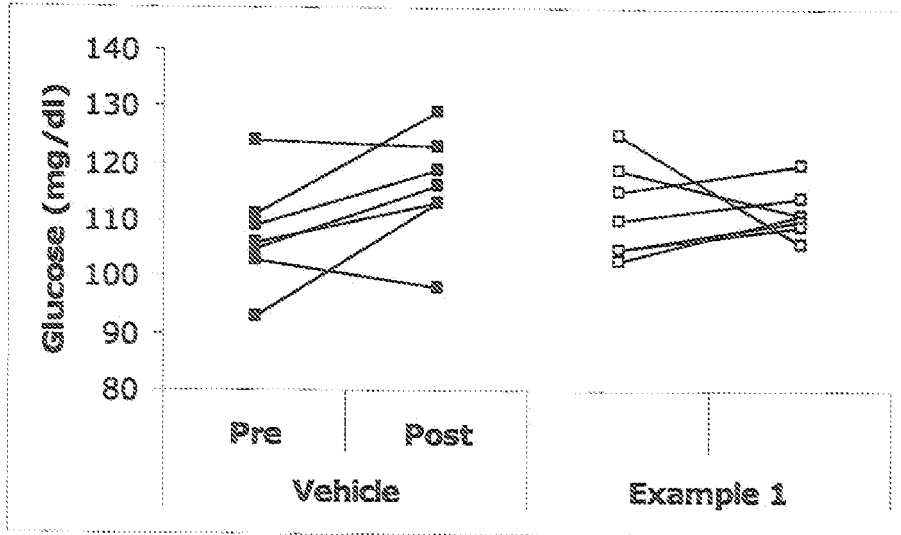


FIGURE 10

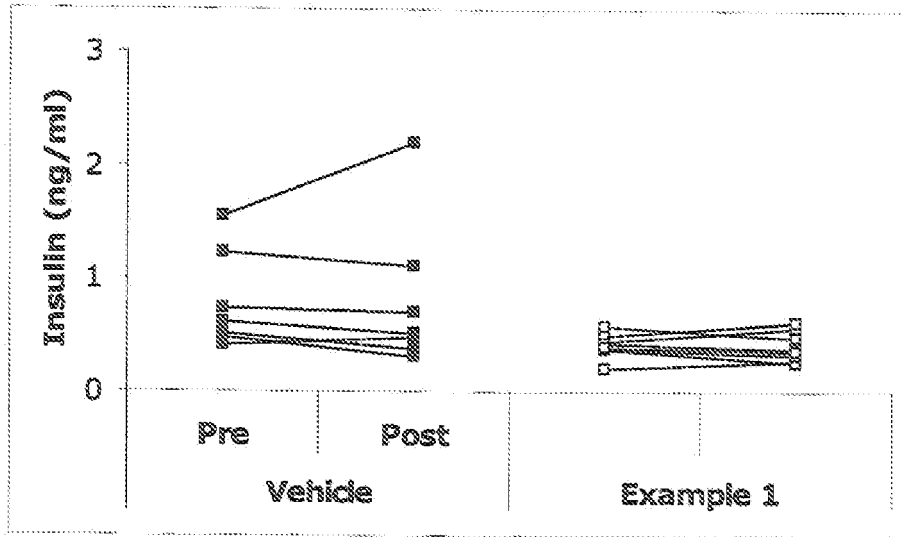


FIGURE 11

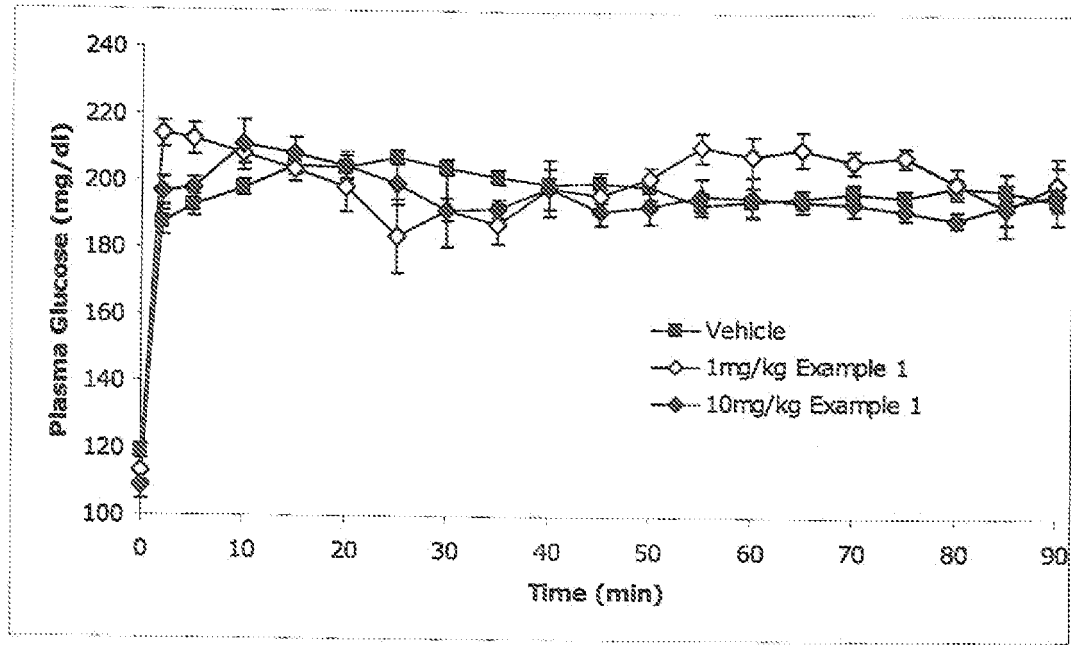


FIGURE 12

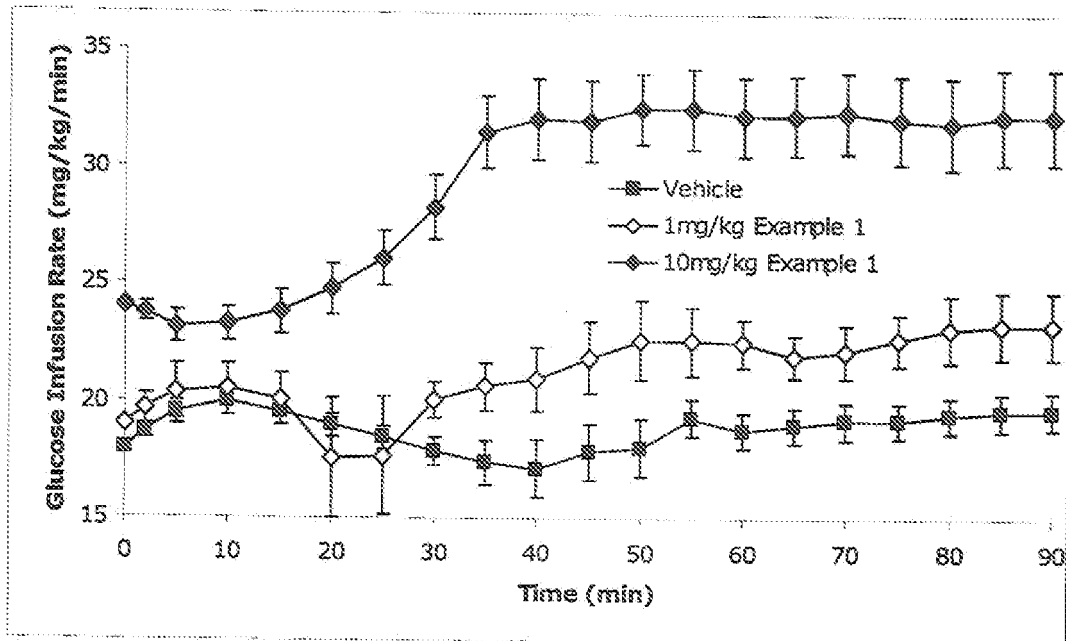




FIGURE 13

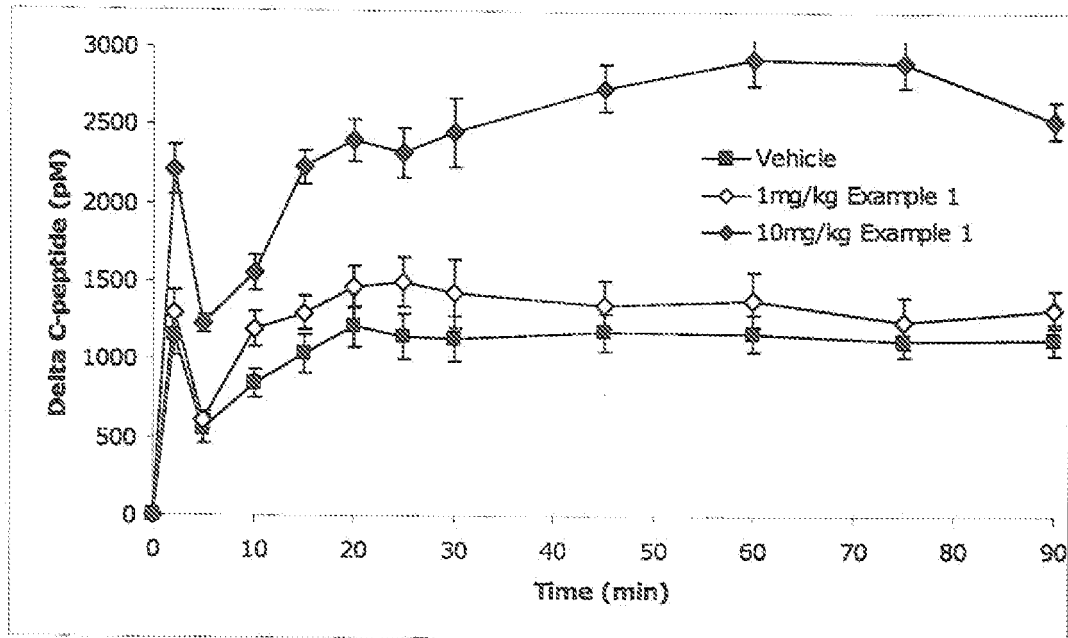


FIGURE 14

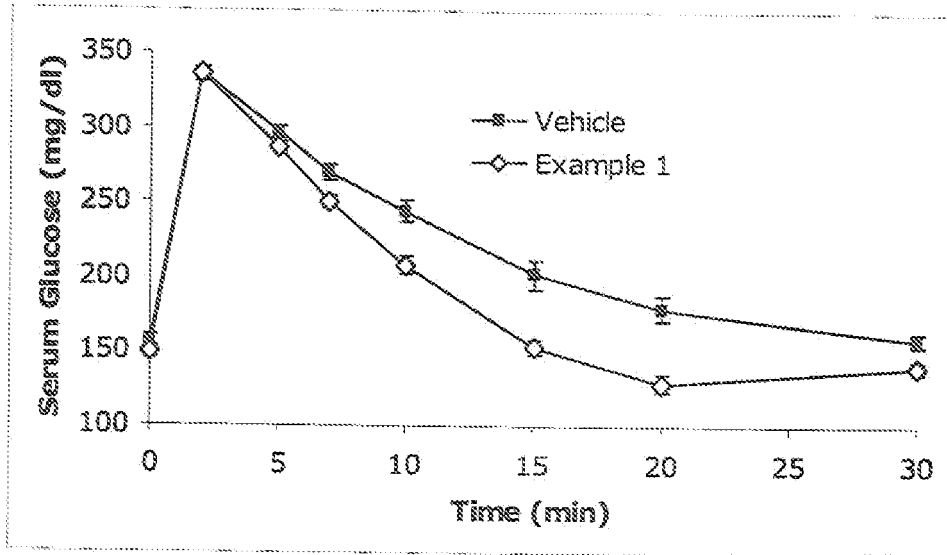


FIGURE 15

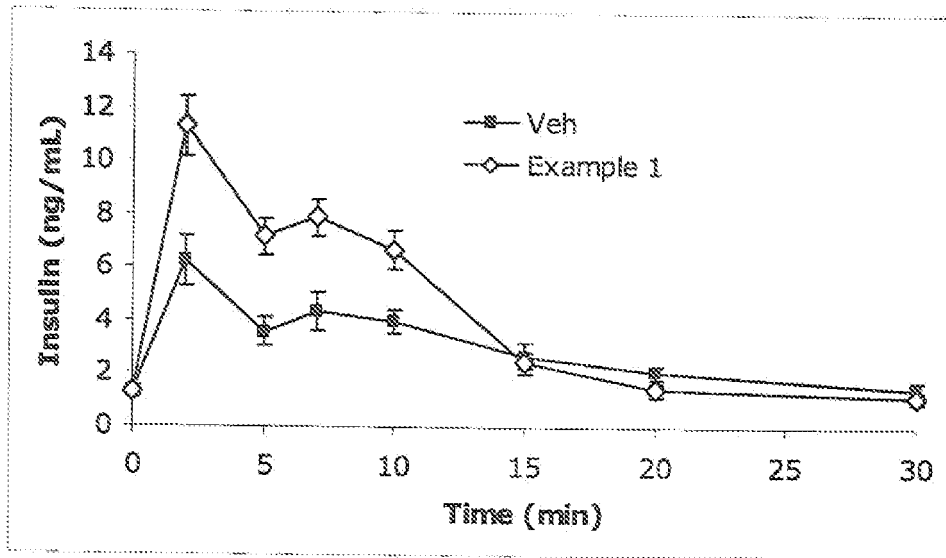


FIGURE 16

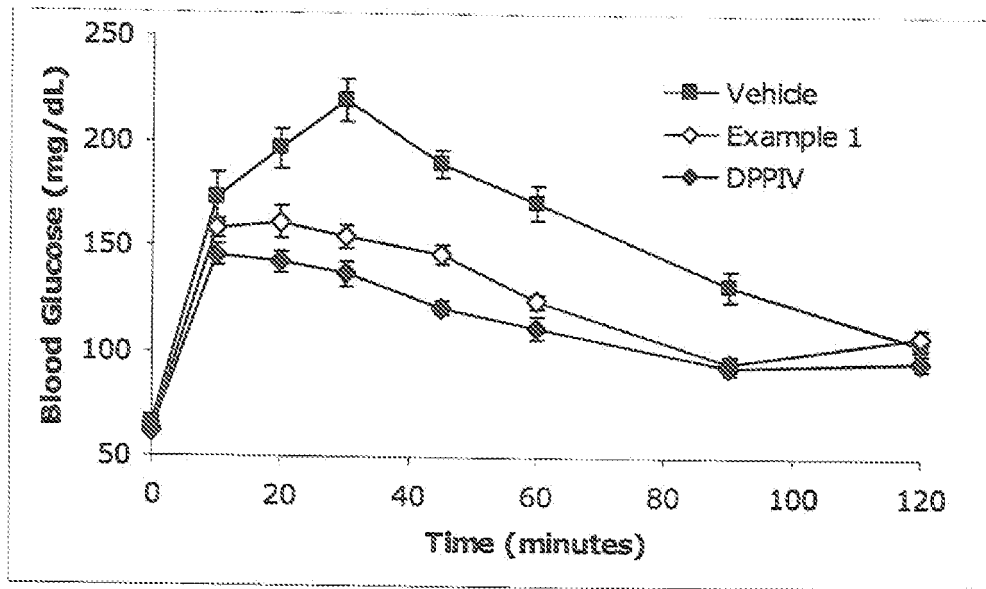


FIGURE 17

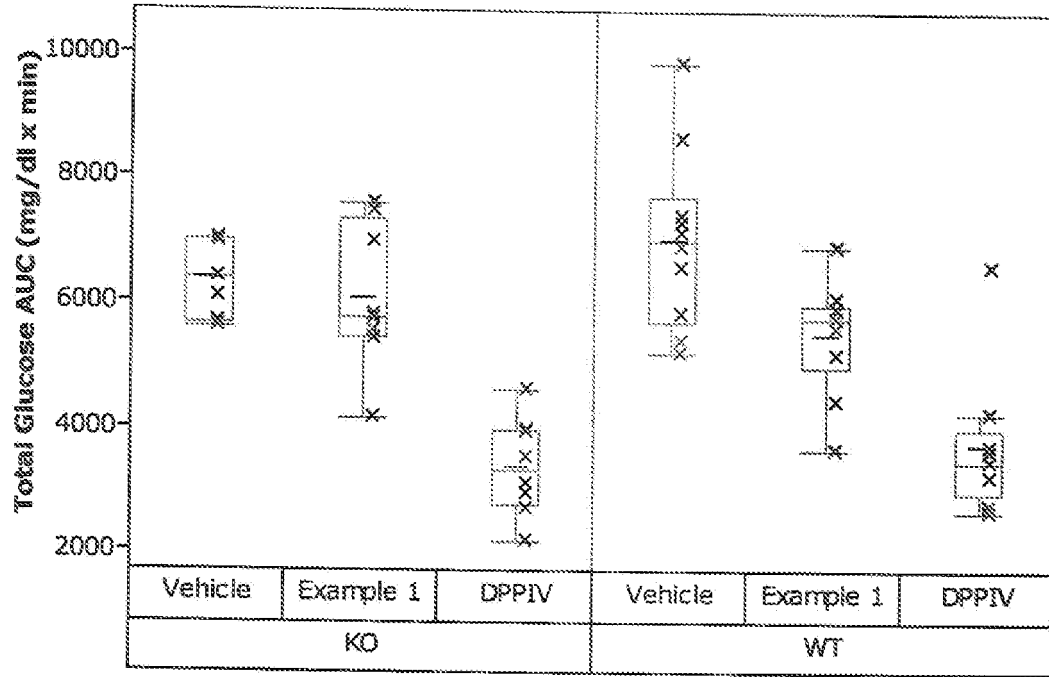


FIGURE 18

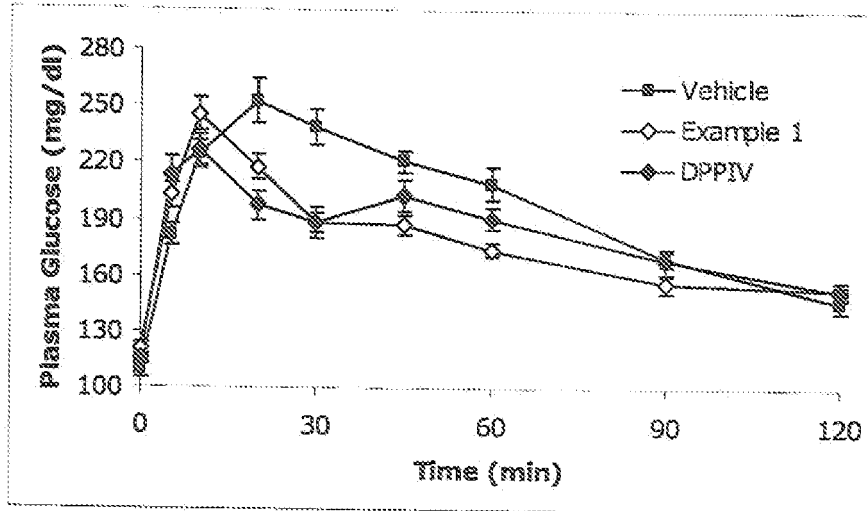


FIGURE 19

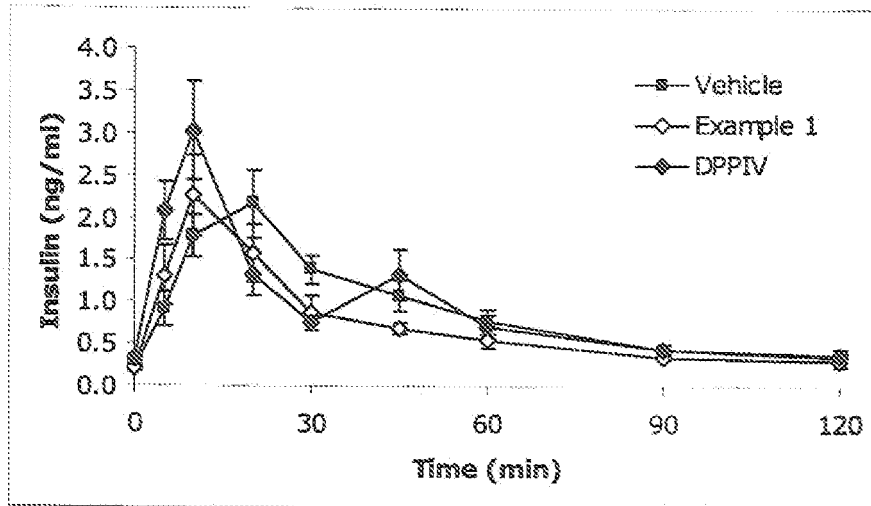


FIGURE 20

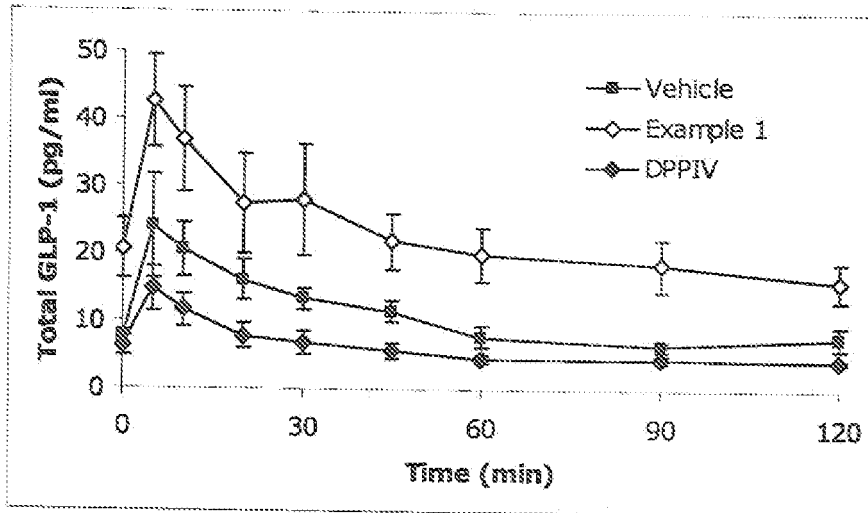




FIGURE 21

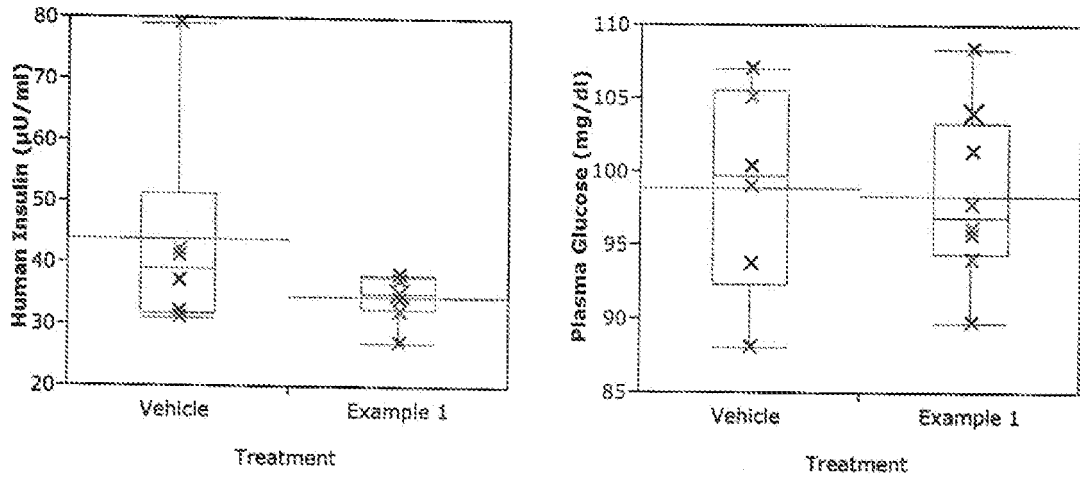
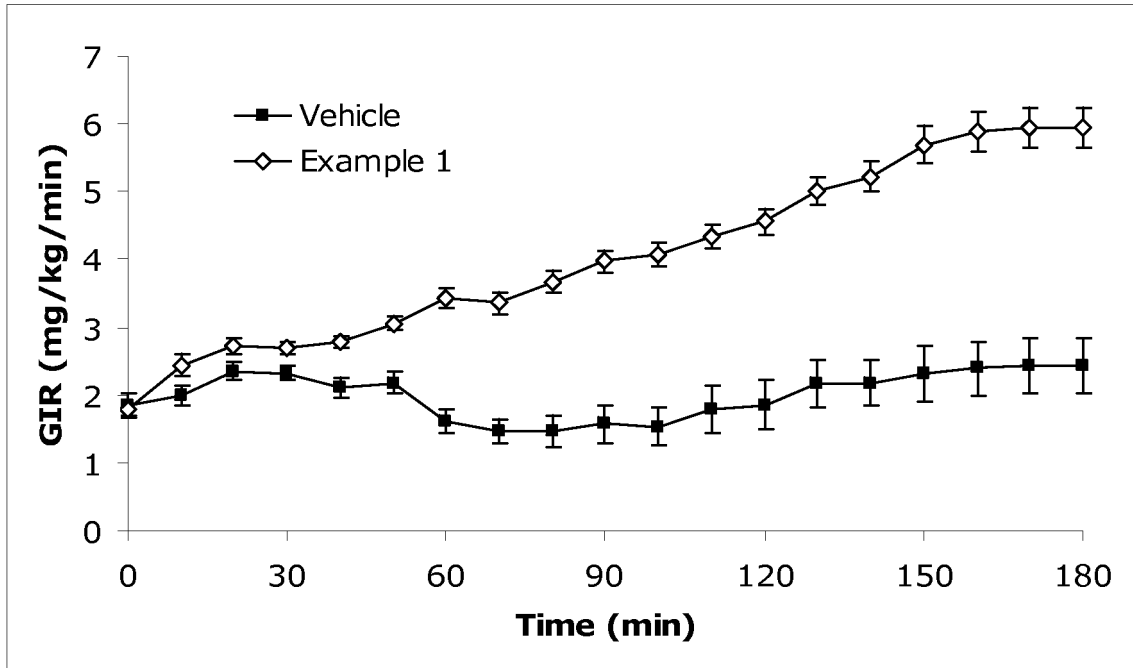


FIGURE 22



**INTERNATIONAL SEARCH REPORT**

International application No  
PCT/US2007/073364

**A. CLASSIFICATION OF SUBJECT MATTER**  
INV. A61K31/495 A61P3/10

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

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)  
A61K

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

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)  
EPO-Internal, WPI Data, EMBASE, BIOSIS, CHEM ABS Data

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>MAYET S ET AL: "GPR119 activation increases glucose-dependent insulin secretion in insulin-producing cells and isolated rat islets" DIABETOLOGIA, BERLIN, DE, vol. 48, no. Suppl 1, 2005, page A166, XP002449852 ISSN: 0012-186X paragraph [0449]</p> <p align="center">----- -/--</p>	1,3,5

Further documents are listed in the continuation of Box C.       See patent family annex.

- \* Special categories of cited documents :
- \*A\* document defining the general state of the art which is not considered to be of particular relevance
  - \*E\* earlier document but published on or after the international filing date
  - \*L\* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
  - \*O\* document referring to an oral disclosure, use, exhibition or other means
  - \*P\* document published prior to the international filing date but later than the priority date claimed
  - \*T\* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
  - \*X\* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
  - \*Y\* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
  - \*&\* document member of the same patent family

Date of the actual completion of the international search  22 November 2007	Date of mailing of the international search report  06/12/2007
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Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Authorized officer  Terenzi, Carla
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## INTERNATIONAL SEARCH REPORT

International application No

PCT/US2007/073364

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	FYFE MATTHEW ET AL: "Discovery of novel, orally active, synthetic GPR119 agonists as potential agents for treatment of obesity and associated metabolic disorders" DIABETES, NEW YORK, NY, US, vol. 55, no. suppl 1, June 2006 (2006-06), page A81, XP009089696 ISSN: 0012-1797 page A81, paragraph 346-OR -----	1,3,5
X	SOGA T ET AL: "Lysophosphatidylcholine enhances glucose-dependent insulin secretion via an orphan G-protein-coupled receptor" BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS, ACADEMIC PRESS INC. ORLANDO, FL, US, vol. 326, no. 4, 28 January 2005 (2005-01-28), pages 744-751, XP004682876 ISSN: 0006-291X abstract page 745, column 1, line 30 - line 33 -----	1,3,5
X	OVERTON HILARY A ET AL: "Deorphanization of a G protein-coupled receptor for oleylethanolamide and its use in the discovery of small-molecule hypophagic agents" CELL METABOLISM, CELL PRESS, CAMBRIDGE, MA, US, vol. 3, no. 3, March 2006 (2006-03), pages 167-175, XP002449851 ISSN: 1550-4131 abstract page 173, column 1, paragraph 2 page 173, column 2, paragraph 1 -----	1,3,5
X	WO 2004/076413 A (ARENA PHARM INC [US]; JONES ROBERT M [US]; SEMPLE GRAEME [US]; CHOI JI) 10 September 2004 (2004-09-10) page 63, line 7 - line 15 -----	1,3,5
P,A	US 2006/154866 A1 (CHU ZHI-LIANG [US] ET AL) 13 July 2006 (2006-07-13) page 1, paragraph 12 -----	1-6

# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/US2007/073364

## Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1.  Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:  

Although claims 1-6 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2.  Claims Nos.:  
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3.  Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1.  As all required additional search fees were timely paid by the applicant, this international search report covers allsearchable claims.
2.  As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.
3.  As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4.  No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

### Remark on Protest

- The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- No protest accompanied the payment of additional search fees.

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No PCT/US2007/073364
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