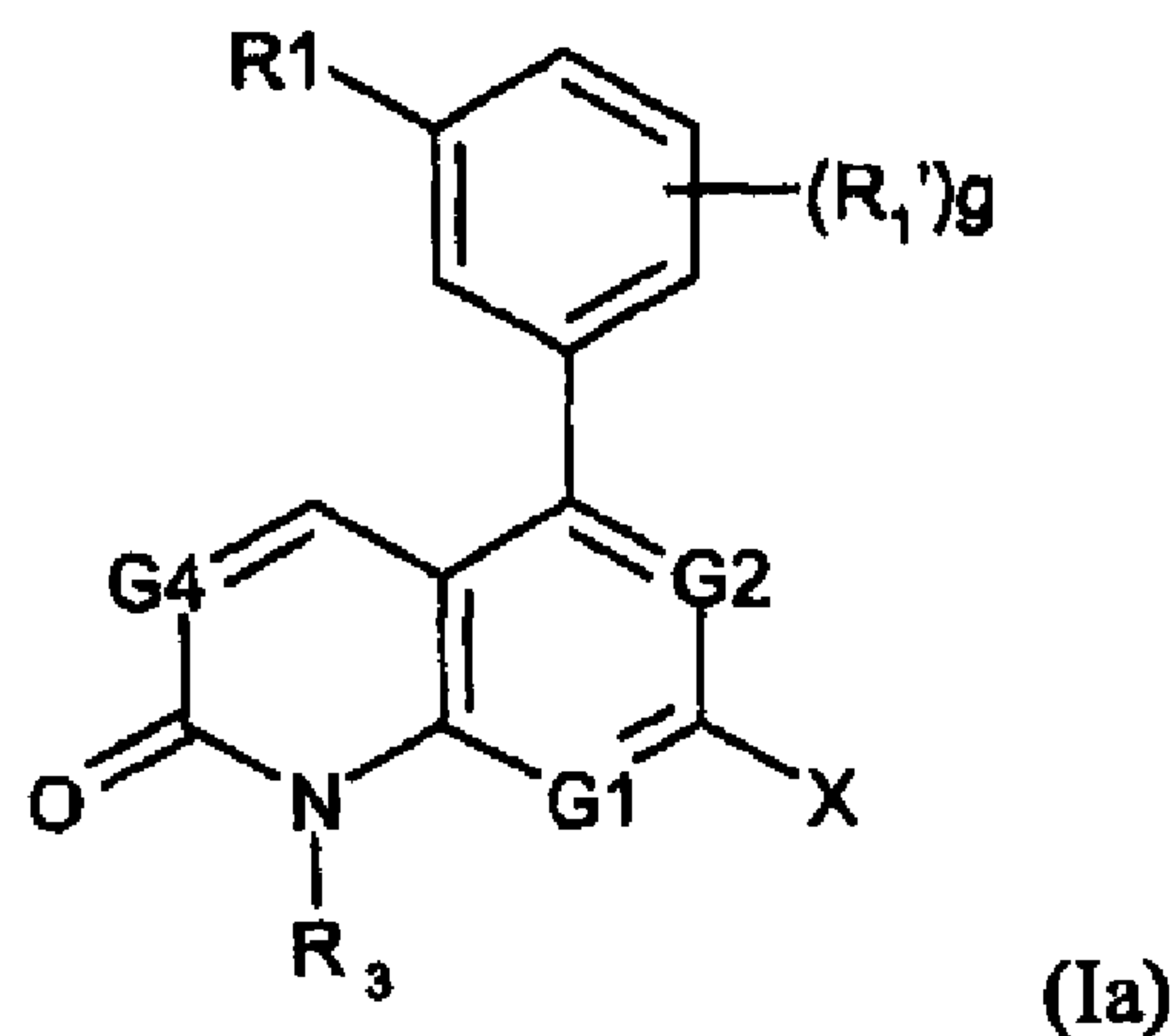
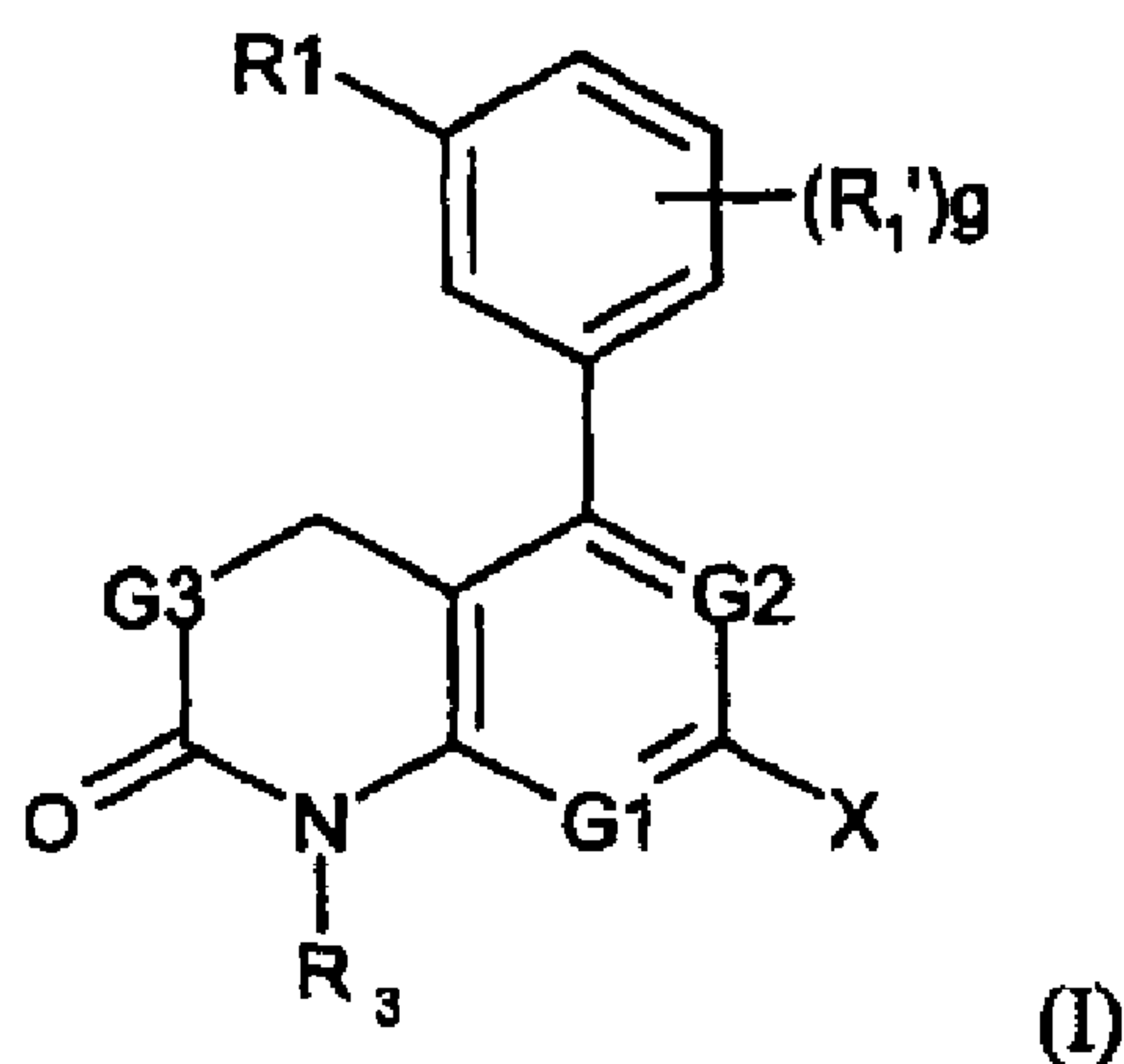




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(54) Titre : DERIVES DE 8H-PYRIDO[2,3-D]PYRIMIDIN-7-ONE 2,4,8-TRISUBSTITUE, SES COMPOSITIONS ET SES UTILISATIONS  
(54) Title: 2,4,8-TRISUBSTITUTED 8H-PYRIDO[2,3-D]PYRIMIDIN-7-ONE DERIVATIVES, COMPOSITIONS THEREOF, AND USES THEREOF



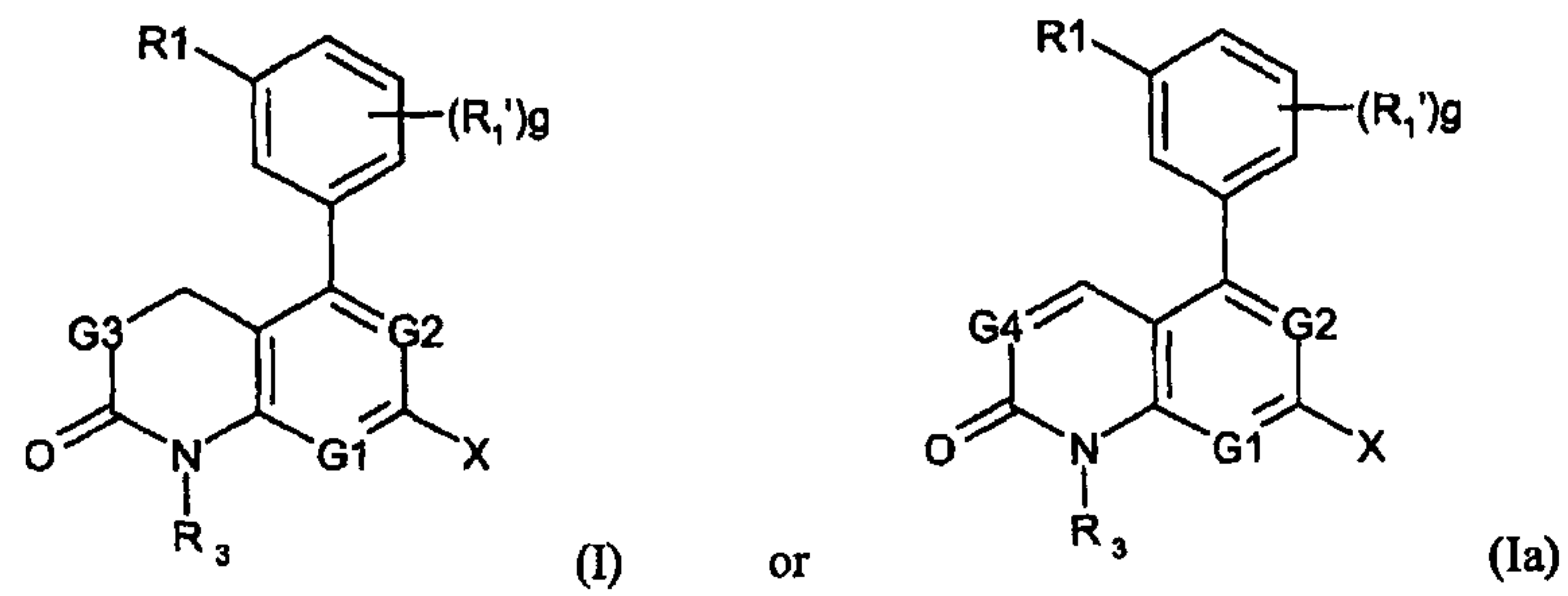
(57) Abrégé/Abstract:

Novel substituted 2,4,8-trisubstituted 8H-pyrido[2,3-d]pyrimidin-7-one containing compounds of Formula (I) and (Ia) are disclosed (see formula I) or (see formula Ia). These compounds and compositions thereof are used in therapy as CSBP/RK/p38 kinase inhibitors.



**ABSTRACT:**

Novel substituted 2,4,8-trisubstituted 8H-pyrido[2,3-d]pyrimidin-7-one containing compounds of Formula (I) and (Ia) are disclosed



These compounds and compositions thereof are used in therapy as CSBP/RK/p38 kinase inhibitors.

# **DEMANDES OU BREVETS VOLUMINEUX**

**LA PRÉSENTE PARTIE DE CETTE DEMANDE OU CE BREVETS  
COMPREND PLUS D'UN TOME.**

**CECI EST LE TOME \_\_1\_\_ DE \_\_2\_\_**

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# **JUMBO APPLICATIONS / PATENTS**

**THIS SECTION OF THE APPLICATION / PATENT CONTAINS MORE  
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**THIS IS VOLUME \_\_1\_\_ OF \_\_2\_\_**

NOTE: For additional volumes please contact the Canadian Patent Office.

WO 2006/104915

PCT/US2006/010855

**2,4,8-trisubstituted 8H-pyrido[2,3-d]pyrimidin-7-one  
derivatives, compositions thereof, and uses thereof**

**5 Summary of the Invention**

This invention relates to novel compounds and their use as pharmaceuticals, particularly as p38 kinase inhibitors, for the treatment of certain diseases and conditions.

**10 Background of the Invention**

Intracellular signal transduction is the means by which cells respond to extracellular stimuli. Regardless of the nature of the cell surface receptor (e. g. protein tyrosine kinase or seven-transmembrane G-protein coupled), protein kinases and phosphatases along with phospholipases are the essential machinery by which the signal is further transmitted within the cell [Marshall, J. C. Cell, **80**, 179-278 (1995)]. Protein kinases can be categorized into five classes with the two major classes being tyrosine kinases and serine / threonine kinases, depending upon whether the enzyme phosphorylates its substrate(s) on specific tyrosine(s) or serine / threonine(s) residues [Hunter, T., Methods in Enzymology (Protein Kinase Classification) p. 3, Hunter, T.; Sefton, B. M.; eds. vol. 200, Academic Press; San Diego, 1991].

Three major related intracellular pathways, the mitogen-activated kinases, or MAPKs, are now understood to transduce signals from many extracellular stimuli such as environmental stress, infectious agents, cytokines and growth factors. The MAPKs modulate the activity of numerous cell functions such as translocation and activation of transcription factors that control transcription of effector molecules such as cytokines, COX-2, iNOS; the activity of downstream kinases that effect translation of mRNAs; and cell cycle pathways through transcription or modification of enzymes. One of these three major pathways is the p38 MAPK pathway, which refers in most cell types to the isoform p38 $\alpha$  which is ubiquitously expressed. The role of p38 in a multitude of functions, particularly related to inflammatory response has been elucidated using selective p38 inhibitors in numerous in vitro and in vivo studies. These functions have been extensively reviewed and a summary can be found in Nature Reviews [Kumar, S. Nature Rev. Drug Discovery, **2**:717 (2003)]

Extracellular stimuli such as those described above are generated in a number of chronic diseases which are now understood to have a common underlying pathophysiology termed inflammation. An environmental insult or local cell damage activates cellular response pathways, including but not limited to p38; local cells then

generate cytokines and chemokines, in turn recruiting lymphocytes such as neutrophils and other granulocytes. In a secondary response, the consequences include recruitment of additional lymphocytes such as additional phagocytic cells or cytotoxic T cells, and ultimately the adaptive immune response is initiated through activation of T cells. It is not currently fully understood how this acute inflammatory response becomes a chronic response leading to diseases such as rheumatoid arthritis (RA), atherosclerosis, chronic obstructive pulmonary disease (COPD), inflammatory bowel disease (IBD), etc. Nevertheless, the features of inflammation are recognized to contribute to a large number of chronic diseases and pathways such as the p38 pathway are accepted to contribute to the initiation of inflammatory diseases.

For example, atherosclerosis is regarded as a chronic inflammatory disease, which develops in response to injury of the vessel wall and is characterized by the complex development of an occlusive and prothrombotic atheroma. The pathogenesis of this lesion generally involves endothelial dysfunction (reduced bioavailable NO), adhesion molecule expression, adhesion and infiltration of leukocytes, cytokine and growth factor generation, accumulation of foam cells, expansion of extracellular lipid and matrix, activation of matrix metalloproteases (MMPs) and proliferation of vascular smooth muscle cells.

The discovery of p38 (initially termed CSBP, now p38; the isoforms p38 $\alpha$  and p38 $\beta$  are the targets of the compounds described) provided a mechanism of action of a class of anti-inflammatory compounds for which SK&F 86002 was the prototypic example. These compounds inhibited IL-1 and TNF synthesis in human monocytes at concentrations in the low  $\mu$ M range [Lee, *et al.*; Int. J. Immunopharmac. 10(7), 835(1988)] and exhibited activity in animal models which are refractory to cyclooxygenase inhibitors [Lee; *et al.*, Annals N. Y. Acad. Sci., 696, 149(1993)].

The mechanism by which stress signals (including bacterial and viral infection, pro-inflammatory cytokines, oxidants, UV light and osmotic stress) activate p38 is through activation of kinases upstream from p38 which in turn phosphorylate p38 at threonine 180 and tyrosine 182 resulting in p38 activation. MAPKAP kinase-2 and MAPKAP kinase-3 have been identified as downstream substrates of CSBP/p38 which in turn phosphorylate heat shock protein Hsp27 and other substrates. Additional downstream substrates known to be phosphorylated by p38 include kinases (Mnk1/2, MSK1/2 and PRAK) and transcription factors (CHOP, MEF2, ATF2 and CREB). While many of the signaling pathways required for transduction of stress stimuli remain unknown it appears clear that many of the substrates for p38 listed above are involved. [Cohen, P. Trends Cell Biol., 353-361(1997) and Lee, J. C. *et al.*, Pharmacol. Ther. vol. 82, nos. 2-3, pp. 389-397, 1999]. There is also emerging evidence that p38 is involved

in modulation of the activity of the NF-kB signaling pathway through a role in histone phosphorylation or acetylation, or through reduction of transcription competence of the NF-kB complex [Saccini, S. Nature Immunol., 3: 69-75, (2002); Carter, AB et al J Biol Chem 274: 30858-63 (1999)]. Finally, a role for p38 in generation of response to IFNs through activation by the Type I IFN receptor has been described [Platanias, Pharmacol. Therap. 98:129-142 (2003)]. Activation of p38 is involved in the transcriptional regulation of IFN sensitive genes through modification of specific transcription factors binding to promotor elements in these genes. Direct phosphorylation of STATs by p38 has not been conclusively demonstrated.

In addition to inhibiting IL-1 and TNF upregulation in response to inflammatory stimuli, p38 kinase inhibitors (e.g., SK&F 86002 and SB-203580) are effective in a number of different cell types in decreasing the synthesis of a wide variety of pro-inflammatory proteins including, IL-6, IL-8, GM-CSF, RANTES and COX-2. Inhibitors of p38 kinase have also been shown to suppress the TNF-induced expression of VCAM-1 on endothelial cells, the TNF-induced phosphorylation and activation of cytosolic PLA2 and the IL-1-stimulated synthesis of collagenase and stromelysin. These and additional data demonstrate that p38 is involved not only cytokine synthesis in response to stress, but also in propagating the consequent cytokine signaling [CSBP/P38 kinase reviewed in Cohen, P. Trends Cell Biol., 353-361(1997)].

Interleukin-1 (IL-1) and Tumor Necrosis Factor (TNF) are important inflammatory cytokines produced by a variety of cells, such as monocytes, macrophages, and smooth muscle cells. IL-1 has been demonstrated to mediate a variety of biological activities thought to be important in immunoregulation and other physiological conditions such as inflammation [See, e.g., Dinarello et al., Rev. Infect. Disease, 6, 51 (1984)]. The myriad of known biological activities of IL-1 include the activation of T helper cells, induction of fever, stimulation of prostaglandin or collagenase production, neutrophil chemotaxis, induction of acute phase proteins and the suppression of plasma iron levels.

There are many disease states in which excessive or unregulated IL-1 production is implicated in exacerbating and/or causing the disease. These include rheumatoid arthritis, osteoarthritis, endotoxemia and/or toxic shock syndrome, other acute or chronic inflammatory disease states such as the inflammatory reaction induced by endotoxin or inflammatory bowel disease; tuberculosis, atherosclerosis, muscle degeneration, cachexia, psoriatic arthritis, Reiter's syndrome, rheumatoid arthritis, gout, traumatic arthritis, rubella arthritis, and acute synovitis. Evidence also links IL-1 activity to diabetes and pancreatic  $\beta$  cells [review of the biological activities which have been attributed to IL-1 Dinarello, J. Clinical Immunology, 5 (5), 287-297 (1985)].

Excessive or unregulated TNF production has been implicated in mediating or exacerbating a number of diseases including rheumatoid arthritis, rheumatoid spondylitis, osteoarthritis, gouty arthritis and other arthritic conditions; sepsis, septic shock, endotoxic shock, gram negative sepsis, toxic shock syndrome, adult respiratory distress syndrome, cerebral malaria, chronic obstructive pulmonary disease, silicosis, pulmonary sarcoisosis, bone resorption diseases, reperfusion injury, graft vs. host reaction, allograft rejections, fever and myalgias due to infection, such as influenza, cachexia secondary to infection or malignancy, cachexia, secondary to acquired immune deficiency syndrome (AIDS), AIDS, ARC (AIDS related complex), keloid formation, scar tissue formation, Crohn's disease, ulcerative colitis, or pyresis.

Inflammatory diseases are also marked by increases in IL-6 and C-reactive protein (CRP), both of which are sensitive to inhibition by p38 inhibitors. IL-6 stimulation of CRP production is directly inhibited by p38 inhibitors in human vascular endothelial cells, and CRP is produced by hepatocytes in response to IL-6. CRP is considered a major risk factor for cardiovascular disease [Circulation 2003.107: 363-369] and may be a significant independent risk factor for chronic obstructive pulmonary disease [Circulation 2003. 107:1514-1519]. IL-6 is also upregulated in endometriosis [Bedaiwy et al., 2002, Human Reproduction 17:426-431; Witz, 2000, Fertility and Sterility 73: 212-214].

Interleukin-8 (IL-8) and RANTES are chemotactic factors produced by several cell types including mononuclear cells, fibroblasts, endothelial cells, epithelial cells, neutrophils and T cells. Chemokine production is induced by pro-inflammatory stimuli such as IL-1, TNF, or lipopolysachharide (LPS), or viral infection. IL-8 stimulates a number of functions in vitro. It has been shown to have chemoattractant properties for neutrophils, T-lymphocytes, and basophils. In addition it induces histamine release from basophils from both normal and atopic individuals as well as lysozomal enzyme release and respiratory burst from neutrophils. IL-8 has also been shown to increase the surface expression of Mac-1 (CD11b/CD18) on neutrophils without de novo protein synthesis, which may contribute to increased adhesion of the neutrophils to vascular endothelial cells. Many diseases are characterized by massive neutrophil infiltration. Conditions such as chronic obstructive pulmonary disease associated with an increase in IL-8 production would benefit by compounds which are suppressive of IL-8 production. RANTES is produced by cells such as epithelial cells and airway smooth muscle in response to infection or cytokine stimulation. Its main chemoattraction is for T cell subtypes and blood-borne monocytes.

IL-1, TNF and other cytokines affect a wide variety of cells and tissues and these cytokines as well as other leukocyte derived cytokines are important as critical

inflammatory mediators of a wide variety of disease states and conditions. The inhibition of these cytokines is of benefit in controlling, reducing and alleviating many of these disease states.

In addition to the involvement of p38 signaling in the production of IL-1, TNF, IL-8, IL-6, GM-CSF, COX-2, collagenase and stromelysin, signal transduction via CSBP/p38 is required for the effector functions of several of these same pro-inflammatory proteins plus many others. For example, growth factors such as VEGF, PDGF, NGF signal through surface receptors which in turn activate cellular signaling pathways including p38 MAPK [Ono, K. and Han, J., Cellular Signalling, **12** 1-13 (2000); Kyriakis, JM and Avruch, J. Physiol Rev **81**: 807-869 (2001)]. TGF $\alpha$ , a key molecule in the control of inflammatory response, also activates p38 as a consequence of engagement of the TGF $\beta$  receptor. The involvement of CSBP/p38 in multiple stress-induced signal transduction pathways provides additional rationale for the potential utility of CSBP/p38 in the treatment of diseases resulting from the excessive and destructive activation of the immune system, or chronic inflammation. This expectation is supported by the potent and diverse activities described for CSBP/p38 kinase inhibitors [Badger, *et al.*, J. Pharm. Exp. Thera **279** (3): 1453-1461, (1996); Griswold, *et al.*, Pharmacol. Comm. **7**, 323-229 (1996); Jackson, *et al.*, J. Pharmacol. Exp. Ther. **284**, 687- 692 (1998); Underwood, *et al.*, J. Pharmacol. Exp. Ther. **293**, 281- 288 (2000); Badger, *et al.*, Arthritis Rheum. **43**, 175 -183 (2000)].

Chronic inflammation is also characterized by ongoing remodeling and repair of affected tissue, leading in some cases to excess fibrotic tissue. A role for p38 MAPK in fibrosis is supported by findings that this enzyme mediates signaling of transforming growth factor beta (TGF- $\beta$ ) on markers and proteins of fibrosis. For example, it has been shown that TGF- $\beta$  increases the kinase activity of p38 MAPK through the TGF- $\beta$  activated kinase TAK-1 (Hanafusa *et al.*, 1999, J. Biol. Chem. **274**:27161-27167). Furthermore, the p38 inhibitor SB-242235 inhibited the TGF- $\beta$ -induced increases in fibronectin and thrombospondin (Laping *et al.*, 2002, Molec. Pharmacol. **62**:58-64). These results show that p38 MAPK is a key signaling intermediate for the effect of the pro-fibrotic cytokine TGF- $\beta$  on components of the extracellular matrix and markers of fibrosis.

P38 also plays a role in directing survival and apoptosis of cells in response to various stimuli. Both survival and apoptosis can be p38 regulated depending on the stimulus and the cell type [Morin and Huot, Cancer Research. **64**:1893-1898 (2004)]. For example, TGF-beta can stimulate apoptosis in murine hepatocytes through activation of gadd45b, a protein involved in cell-cycle control, in a p38 mediated process [Yoo *et al.*, J. Biol. Chem. **278**:43001-43007, (2003)]. In a different response

pathway, UV-stress can activate p38 and trigger apoptosis of a damaged cell. P38 has also been shown to promote survival of lymphocytes in response to stress, including neutrophils and CD8+ T cells.

There remains a need for treatment, in this field, for compounds which are cytokine suppressive anti-inflammatory drugs, i.e. compounds which are capable of inhibiting the CSBP/p38/RK kinase. The present invention is directed to such novel compounds which are inhibitors of p38 kinase.

#### SUMMARY OF THE INVENTION

This invention relates to the novel compounds of Formula (I) and (Ia), (II) and (IIa), (III) and (IIIa), (IV) and (IVa), (V) and (Va), (VI), (VIa-VIi), (VIII), (VIIIa), (IX), (IXa), (A), (A1), (B), and (B1), and pharmaceutically acceptable salts, solvates or physiologically functional derivatives thereof; and pharmaceutical compositions comprising a compound of (I) and (Ia), (II) and (IIa), (III) and (IIIa), (IV) and (IVa), (V) and (Va), (VI), (VIa-VIi), (VIII), (VIIIa), (IX), (IXa), (A), (A1), (B), and (B1), and pharmaceutically acceptable salts, solvates or physiologically functional derivatives thereof, and a pharmaceutically acceptable diluent or carrier.

This invention relates to a method of treating a CSBP/RK/p38 kinase mediated disease in a mammal in need thereof, which comprises administering to said mammal an effective amount of a compound of Formula (I) and (Ia), (II) and (IIa), (III) and (IIIa), (IV) and (IVa), (V) and (Va), (VI), (VIa-VIi), (VIII), (VIIIa), (IX), (IXa), (A), (A1), (B), and (B1).

This invention also relates to a method of inhibiting cytokines and the treatment of a cytokine mediated disease, in a mammal in need thereof, which comprises administering to said mammal an effective amount of a compound of Formula (I) and (Ia), (II) and (IIa), (III) and (IIIa), (IV) and (IVa), (V) and (Va), (VIa-VIi), (VIII), (VIIIa), (IX), (IXa), (A), (A1), (B), and (B1).

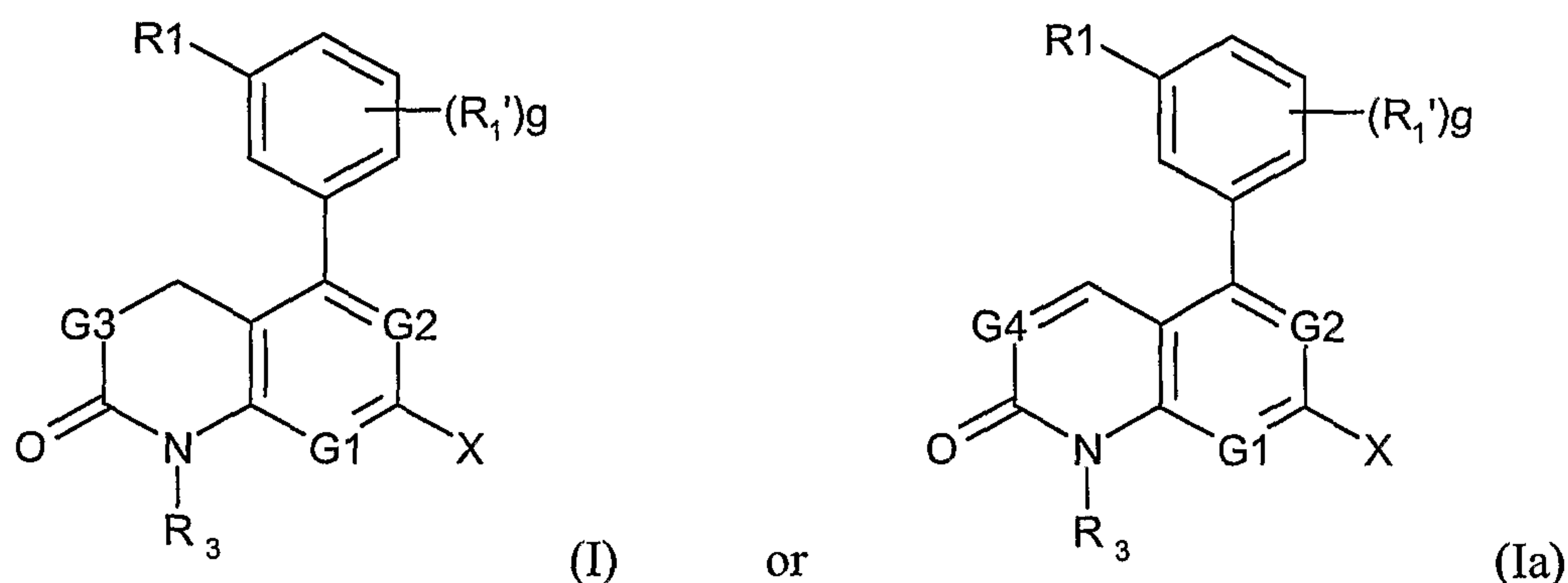
This invention also relates to a method of inhibiting the production of IL-1 in a mammal in need thereof which comprises administering to said mammal an effective amount of a compound of Formula (I) and (Ia), (II) and (IIa), (III) and (IIIa), (IV) and (IVa), (V) and (Va), (VIa-VIi), (VIII), (VIIIa), (IX), (IXa), (A), (A1), (B), and (B1).

This invention also relates to a method of inhibiting the production of IL-6 in a mammal in need thereof which comprises administering to said mammal an effective amount of a compound of Formula (I) and (Ia), (II) and (IIa), (III) and (IIIa), (IV) and (IVa), (V) and (Va), (VIa-VIi), (VIII), (VIIIa), (IX), (IXa), (A), (A1), (B), and (B1).

This invention also relates to a method of inhibiting the production of IL-8 in a mammal in need thereof which comprises administering to said mammal an effective amount of a compound of Formula (I) and (Ia), (II) and (IIa), (III) and (IIIa), (IV) and (IVa), (V) and (Va), (VIa-VIi), (VIII), (VIIIa), (IX), (IXa), (A), (A1), (B), and (B1).

This invention also relates to a method of inhibiting the production of TNF in a mammal in need thereof which comprises administering to said mammal an effective amount of a compound of Formula (I) and (Ia), (II) and (IIa), (III) and (IIIa), (IV) and (IVa), (V) and (Va), (VIa-VIi), (VIII), (VIIIa), (IX), (IXa), (A), (A1), (B), and (B1).

Accordingly, the present invention provides for a compound of Formula (I) and (Ia) having the structure:



wherein

G<sub>1</sub>, and G<sub>2</sub> are independently nitrogen;

G<sub>3</sub> is CH<sub>2</sub>;

G<sub>4</sub> is CH;

R<sub>1</sub> is C(Z)N(R<sub>10</sub>') (CR<sub>10</sub>R<sub>20</sub>)<sub>v</sub>R<sub>b</sub>, C(Z)O(CR<sub>10</sub>R<sub>20</sub>)<sub>v</sub>R<sub>b</sub>, N(R<sub>10</sub>')C(Z)(CR<sub>10</sub>R<sub>20</sub>)<sub>v</sub>R<sub>b</sub>, N(R<sub>10</sub>')C(Z)N(R<sub>10</sub>') (CR<sub>10</sub>R<sub>20</sub>)<sub>v</sub>R<sub>b</sub>, or N(R<sub>10</sub>')OC(Z)(CR<sub>10</sub>R<sub>20</sub>)<sub>v</sub>R<sub>b</sub>;

R<sub>1</sub>' is independently selected at each occurrence from halogen, C<sub>1-4</sub> alkyl, halo-substituted-C<sub>1-4</sub> alkyl, cyano, nitro, (CR<sub>10</sub>R<sub>20</sub>)<sub>v</sub>'NR<sub>d</sub>R<sub>d</sub>',

(CR<sub>10</sub>R<sub>20</sub>)<sub>v</sub>'C(O)R<sub>12</sub>, SR<sub>5</sub>, S(O)R<sub>5</sub>, S(O)<sub>2</sub>R<sub>5</sub>, or (CR<sub>10</sub>R<sub>20</sub>)<sub>v</sub>'OR<sub>13</sub>;

R<sub>b</sub> is hydrogen, C<sub>1-10</sub> alkyl, C<sub>3-7</sub> cycloalkyl, C<sub>3-7</sub> cycloalkyl C<sub>1-10</sub> alkyl, aryl, arylC<sub>1-10</sub>alkyl, heteroaryl, heteroarylC<sub>1-10</sub> alkyl, heterocyclic, or heterocyclylC<sub>1-10</sub> alkyl moiety, which moieties, excluding hydrogen, may all be optionally substituted;

X is  $R_2$ ,  $OR_2$ ,  $S(O)_mR_2$ ,  $(CH_2)_nN(R_{10})S(O)_mR_2$ ,  $(CH_2)_nN(R_{10})C(O)R_2$ ,  
 $(CH_2)_nNR_4R_{14}$ ,  $(CH_2)_nN(R_2)(R_2')$ , or  $N(R_{10})R_hNH-C(=N-CN)NR_qR_q'$ ;

$X_1$  is  $N(R_{11})$ , O,  $S(O)_m$ , or  $CR_{10}R_{20}$ ;

$R_h$  is selected from an optionally substituted  $C_{1-10}$  alkyl,  $-CH_2-C(O)-CH_2-$ ,

5  $-CH_2-CH_2-O-CH_2-CH_2-$ ,  $-CH_2-C(O)N(R_{10})CH_2-CH_2-$ ,  $-CH_2-$   
 $N(R_{10})C(O)CH_2-$ ,  $-CH_2-CH(OR_{10})-CH_2-$ ,  $-CH_2-C(O)O-CH_2-CH_2-$ , or  
 $-CH_2-CH_2-O-C(O)-CH_2-$ ;

$R_q$  and  $R_q'$  are independently selected at each occurrence from hydrogen,  $C_{1-10}$   
 10 alkyl,  $C_{3-7}$ cycloalkyl,  $C_{3-7}$ cycloalkyl $C_{1-10}$ alkyl,  $C_{5-7}$  cycloalkenyl,  $C_{5-7}$   
 cycloalkenyl- $C_{1-10}$ alkyl, aryl, aryl $C_{1-10}$  alkyl, heteroaryl, heteroaryl $C_{1-10}$   
 alkyl, heterocyclic, or a heterocyclyl $C_{1-10}$  alkyl moiety, wherein all of the  
 moieties except for hydrogen, are optionally substituted, or  $R_q$  and  $R_q'$  together  
 with the nitrogen to which they are attached form an optionally substituted  
 heterocyclic ring of 5 to 7 members, which ring may contain an additional  
 15 heteroatom selected from oxygen, nitrogen or sulfur;

$R_2$  is hydrogen,  $C_{1-10}$  alkyl,  $C_{3-7}$  cycloalkyl,  $C_{3-7}$  cycloalkylalkyl, aryl, aryl $C_{1-10}$   
 alkyl, heteroaryl, heteroaryl $C_{1-10}$  alkyl, heterocyclic, or a heterocyclyl $C_{1-10}$   
 alkyl moiety, and wherein each of these moieties, excluding hydrogen, may be  
 optionally substituted; or

20  $R_2$  is the moiety  $(CR_{10}R_{20})_qX_1(CR_{10}R_{20})_qC(A_1)(A_2)(A_3)$ , or  
 $(CR_{10}R_{20})_qC(A_1)(A_2)(A_3)$ ;

$R_2'$  is hydrogen,  $C_{1-10}$  alkyl,  $C_{3-7}$  cycloalkyl,  $C_{3-7}$  cycloalkylalkyl, aryl, aryl $C_{1-10}$   
 alkyl, heteroaryl, heteroaryl $C_{1-10}$  alkyl, heterocyclic, or a heterocyclyl $C_{1-10}$  alkyl  
 moiety, and wherein each of these moieties, excluding hydrogen, may be optionally  
 25 substituted;

$R_2''$  is hydrogen,  $C_{1-10}$  alkyl,  $C_{3-7}$  cycloalkyl,  $C_{3-7}$  cycloalkylalkyl, aryl, aryl $C_{1-10}$   
 alkyl, heteroaryl, heteroaryl $C_{1-10}$  alkyl, heterocyclic, or a heterocyclyl $C_{1-10}$  alkyl  
 moiety, and wherein these moieties, excluding hydrogen, may be optionally; or  
 wherein  $R_2''$  is the moiety  $(CR_{10}R_{20})_tX_1(CR_{10}R_{20})_qC(A_1)(A_2)(A_3)$ ;

30  $A_1$  is an optionally substituted  $C_{1-10}$  alkyl, heterocyclic, heterocyclic  $C_{1-10}$  alkyl,  
 heteroaryl, heteroaryl  $C_{1-10}$  alkyl, aryl, or aryl  $C_{1-10}$  alkyl;

$A_2$  is an optionally substituted  $C_{1-10}$  alkyl, heterocyclic, heterocyclic  $C_{1-10}$  alkyl,  
 heteroaryl, heteroaryl  $C_{1-10}$  alkyl, aryl, or aryl  $C_{1-10}$  alkyl;

$A_3$  is hydrogen or is an optionally substituted  $C_{1-10}$  alkyl;

35  $R_3$  is a  $C_{1-10}$  alkyl,  $C_{3-7}$  cycloalkyl,  $C_{3-7}$  cycloalkyl  $C_{1-10}$  alkyl, aryl, aryl $C_{1-10}$   
 alkyl, heteroaryl, heteroaryl $C_{1-10}$  alkyl, heterocyclic or a heterocyclyl $C_{1-10}$  alkyl  
 moiety, and wherein each of these moieties may be optionally substituted;

R<sub>4</sub> and R<sub>14</sub> are each independently selected at each occurrence from hydrogen, C<sub>1-4</sub> alkyl, C<sub>3-7</sub> cycloalkyl, C<sub>3-7</sub> cycloalkylC<sub>1-4</sub>alkyl, aryl, aryl-C<sub>1-4</sub> alkyl, heterocyclic, heterocyclic C<sub>1-4</sub> alkyl, heteroaryl or a heteroaryl C<sub>1-4</sub> alkyl moiety, and wherein each of these moieties, excluding hydrogen, may be optionally substituted; or the R<sub>4</sub> and R<sub>14</sub> together with the nitrogen which they are attached form an optionally substituted heterocyclic ring of 4 to 7 members, which ring optionally contains an additional heteroatom selected from oxygen, sulfur or nitrogen;

R<sub>4'</sub> and R<sub>14'</sub> are each independently selected at each occurrence from hydrogen or C<sub>1-4</sub> alkyl, or R<sub>4'</sub> and R<sub>14'</sub> together with the nitrogen to which they are attached form a heterocyclic ring of 5 to 7 members, which ring optionally contains an additional heteroatom selected from NR<sub>9'</sub>;

R<sub>5</sub> is independently selected at each occurrence from hydrogen, C<sub>1-4</sub> alkyl, C<sub>2-4</sub> alkenyl, C<sub>2-4</sub> alkynyl or NR<sub>4'</sub>R<sub>14'</sub>, excluding the moieties SR<sub>5</sub> being SNR<sub>4'</sub>R<sub>14'</sub>, S(O)<sub>2</sub>R<sub>5</sub> being SO<sub>2</sub>H and S(O)R<sub>5</sub> being SOH;

R<sub>9'</sub> is independently selected at each occurrence from hydrogen, or C<sub>1-4</sub> alkyl;

R<sub>10</sub> and R<sub>20</sub> are independently selected at each occurrence from hydrogen or C<sub>1-4</sub>alkyl;

R<sub>10'</sub> is independently selected at each occurrence from hydrogen or C<sub>1-4</sub>alkyl;

R<sub>11</sub> is independently selected at each occurrence from hydrogen or C<sub>1-4</sub>alkyl;

R<sub>12</sub> is independently selected at each occurrence from hydrogen, C<sub>1-4</sub> alkyl, halo-substituted C<sub>1-4</sub> alkyl, C<sub>2-4</sub> alkenyl, C<sub>2-4</sub> alkynyl, C<sub>3-7</sub> cycloalkyl, C<sub>3-7</sub>cycloalkylC<sub>1-4</sub> alkyl, C<sub>5-7</sub> cycloalkenyl, C<sub>5-7</sub>cycloalkenyl C<sub>1-4</sub> alkyl, aryl, arylC<sub>1-4</sub> alkyl, heteroaryl, heteroarylC<sub>1-4</sub> alkyl, heterocyclyl, or a heterocyclylC<sub>1-4</sub> alkyl moiety, and wherein each of these moieties, excluding hydrogen, may be optionally substituted;

R<sub>13</sub> is independently selected at each occurrence from hydrogen, C<sub>1-4</sub> alkyl, halo-substituted C<sub>1-4</sub> alkyl, C<sub>2-4</sub> alkenyl, C<sub>2-4</sub> alkynyl, C<sub>3-7</sub> cycloalkyl, C<sub>3-7</sub>cycloalkylC<sub>1-4</sub> alkyl, C<sub>5-7</sub> cycloalkenyl, C<sub>5-7</sub>cycloalkenyl C<sub>1-4</sub> alkyl, aryl, arylC<sub>1-4</sub> alkyl, heteroaryl, heteroarylC<sub>1-4</sub> alkyl, heterocyclyl, or a heterocyclylC<sub>1-4</sub> alkyl moiety, and wherein each of these moieties, excluding hydrogen, may be optionally substituted;

R<sub>d</sub> and R<sub>d'</sub> are each independently selected from hydrogen, C<sub>1-4</sub> alkyl, C<sub>3-6</sub> cycloalkyl, C<sub>3-6</sub> cycloalkylC<sub>1-4</sub>alkyl moiety, and wherein each of these moieties, excluding hydrogen, may be optionally substituted; or R<sub>d</sub> and R<sub>d'</sub> together with the nitrogen which they are attached form an optionally substituted heterocyclic

ring of 5 to 6 members, which ring optionally contains an additional heteroatom selected from oxygen, sulfur or NR<sub>9</sub>';

g is 0 or an integer having a value of 1, 2, 3, or 4;

n' is independently selected at each occurrence from 0 or an integer having a value of 1 to 10;

m is independently selected at each occurrence from 0 or an integer having a value of 1 or 2;

q is 0 or an integer having a value of 1 to 10;

q' is 0, or an integer having a value of 1 to 6;

10 t is an integer having a value of 2 to 6;

v is 0 or an integer having a value of 1 or 2;

v' is independently selected at each occurrence from 0 or an integer having a value of 1 or 2;

Z is independently selected at each occurrence from oxygen or sulfur; and

15 a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof.

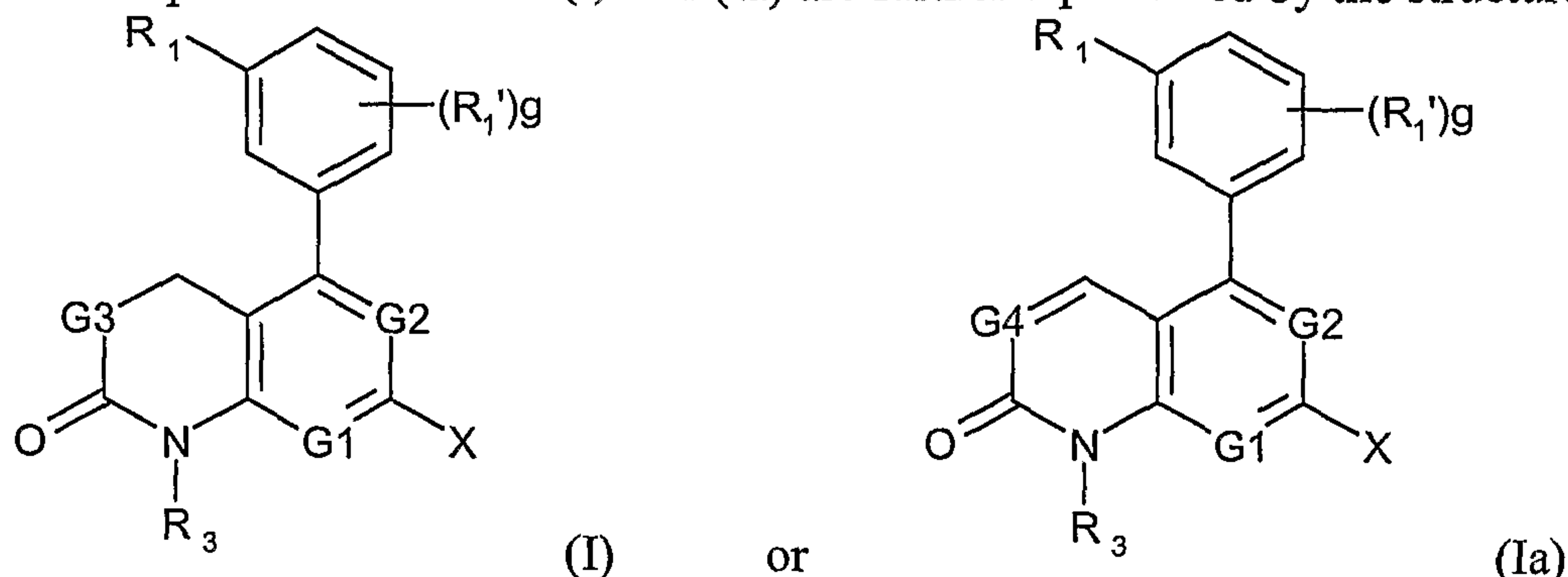
#### DETAILED DESCRIPTION OF THE INVENTION

The present invention is directed to novel compounds of (I) and (Ia), (II) and (IIa), (III) and (IIIa), (IV) and (IVa), (V) and (Va), (VI), (VIa-VIi), (VIII), (VIIIa), (IX), (IXa), (A), (A1), (B), and (B1) and a pharmaceutically acceptable salt solvate or physiologically functional derivative thereof. As will be readily recognized, the difference between compounds of Formula (I) and (Ia) lies in the unsaturation of the ring system. The difference between compound of Formula (I) and (Ia) and compounds of Formula (II) and (IIa), (III) and (IIIa), (IV) and (IVa), (V) and (Va), (VI) and (VIa-VIi), etc., lies in ring substitution on the aryl or heteroaryl moiety of the R<sub>1</sub> substituent, and the ring position of the nitrogen(s) for the pyridyl or pyrimidine moiety where applicable.

The respective R<sub>1</sub>, R<sub>2</sub>, R<sub>x</sub>, X and R<sub>3</sub>, etc., terms are the same for both groups within the formulas themselves, for instance, in Formula (I) and (Ia), and except for the additional G5/G6/G7/G8 terms, applicable across all formulas herein. For purposes herein, everything applicable to Formula (I) is also applicable to Formula (Ia) unless otherwise indicated, and for the remaining compounds of Formula (II) and (IIa), etc. unless specified otherwise.

35 It is recognized that for compounds of Formula (I) and (Ia) wherein G<sub>3</sub> and G<sub>4</sub> are both carbon, and G<sub>1</sub> and G<sub>2</sub> are both nitrogen, the core ring system is considered a 2,4,8-trisubstituted-8H-pyrido[2,3-d]pyrimidin-7-one.

Compounds of Formula (I) and (Ia) are further represented by the structure:



wherein

G<sub>1</sub>, and G<sub>2</sub> are independently nitrogen;

5 G<sub>3</sub> is CH<sub>2</sub>;

G<sub>4</sub> is CH;

R<sub>1</sub> is C(Z)N(R<sub>10</sub>') (CR<sub>10</sub>R<sub>20</sub>)<sub>v</sub>R<sub>b</sub>, C(Z)O(CR<sub>10</sub>R<sub>20</sub>)<sub>v</sub>R<sub>b</sub>,  
N(R<sub>10</sub>')C(Z)(CR<sub>10</sub>R<sub>20</sub>)<sub>v</sub>R<sub>b</sub>, N(R<sub>10</sub>')C(Z)N(R<sub>10</sub>') (CR<sub>10</sub>R<sub>20</sub>)<sub>v</sub>R<sub>b</sub>, or  
N(R<sub>10</sub>')OC(Z)(CR<sub>10</sub>R<sub>20</sub>)<sub>v</sub>R<sub>b</sub>;

10 R<sub>1</sub>' is independently selected at each occurrence from halogen, C<sub>1-4</sub> alkyl, halo-substituted-C<sub>1-4</sub> alkyl, cyano, nitro, (CR<sub>10</sub>R<sub>20</sub>)<sub>v</sub>'NR<sub>d</sub>R<sub>d</sub>',

(CR<sub>10</sub>R<sub>20</sub>)<sub>v</sub>'C(O)R<sub>12</sub>, SR<sub>5</sub>, S(O)R<sub>5</sub>, S(O)<sub>2</sub>R<sub>5</sub>, or (CR<sub>10</sub>R<sub>20</sub>)<sub>v</sub>'OR<sub>13</sub>;

X is R<sub>2</sub>, OR<sub>2</sub>', S(O)<sub>m</sub>R<sub>2</sub>', (CH<sub>2</sub>)<sub>n</sub>'N(R<sub>10</sub>')S(O)<sub>m</sub>R<sub>2</sub>', (CH<sub>2</sub>)<sub>n</sub>'N(R<sub>10</sub>')C(O)R<sub>2</sub>',  
(CH<sub>2</sub>)<sub>n</sub>'NR<sub>4</sub>R<sub>14</sub>, (CH<sub>2</sub>)<sub>n</sub>'N(R<sub>2</sub>') (R<sub>2</sub>''), or N(R<sub>10</sub>')R<sub>h</sub> NH-C(=N-CN)NR<sub>q</sub>R<sub>q</sub>';

15 X<sub>1</sub> is N(R<sub>11</sub>), O, S(O)<sub>m</sub>, or CR<sub>10</sub>R<sub>20</sub>;

R<sub>h</sub> is selected from an optionally substituted C<sub>1-10</sub> alkyl, -CH<sub>2</sub>-C(O)-CH<sub>2</sub>-,  
-CH<sub>2</sub>-CH<sub>2</sub>-O-CH<sub>2</sub>-CH<sub>2</sub>-, -CH<sub>2</sub>-C(O)N(R<sub>10</sub>')CH<sub>2</sub>-CH<sub>2</sub>-, -CH<sub>2</sub>-N(R<sub>10</sub>')C(O)CH<sub>2</sub>-,  
-CH<sub>2</sub>-CH(OR<sub>10</sub>')-CH<sub>2</sub>-, -CH<sub>2</sub>-C(O)O-CH<sub>2</sub>-CH<sub>2</sub>-, or -CH<sub>2</sub>-CH<sub>2</sub>-O-C(O)CH<sub>2</sub>-;

R<sub>q</sub> and R<sub>q</sub>' are independently selected at each occurrence from hydrogen, C<sub>1-10</sub>  
20 alkyl, C<sub>3-7</sub>cycloalkyl, C<sub>3-7</sub>cycloalkylC<sub>1-10</sub>alkyl, C<sub>5-7</sub> cycloalkenyl, C<sub>5-7</sub>  
cycloalkenyl-C<sub>1-10</sub>alkyl, aryl, arylC<sub>1-10</sub> alkyl, heteroaryl, heteroarylC<sub>1-10</sub>  
alkyl, heterocyclic, or a heterocyclylC<sub>1-10</sub> alkyl moiety, and wherein all of the  
moieties, excluding hydrogen, are optionally substituted, or R<sub>q</sub> and R<sub>q</sub>' together  
with the nitrogen to which they are attached form an optionally substituted  
25 heterocyclic ring of 5 to 7 members, which ring may contain an additional  
heteroatom selected from oxygen, nitrogen or sulfur;

A<sub>1</sub> is an optionally substituted C<sub>1-10</sub> alkyl, heterocyclic, heterocyclic C<sub>1-10</sub> alkyl,  
heteroaryl, heteroaryl C<sub>1-10</sub> alkyl, aryl, or aryl C<sub>1-10</sub> alkyl;

A<sub>2</sub> is an optionally substituted C<sub>1-10</sub> alkyl, heterocyclic, heterocyclic C<sub>1-10</sub> alkyl,  
30 heteroaryl, heteroaryl C<sub>1-10</sub> alkyl, aryl, or aryl C<sub>1-10</sub> alkyl;

A<sub>3</sub> is hydrogen or is an optionally C<sub>1-10</sub> alkyl;

R<sub>2</sub> is hydrogen, C<sub>1-10</sub> alkyl, C<sub>3-7</sub> cycloalkyl, C<sub>3-7</sub> cycloalkylalkyl, aryl, arylC<sub>1-10</sub> alkyl, heteroaryl, heteroarylC<sub>1-10</sub> alkyl, heterocyclic, or a heterocyclylC<sub>1-10</sub> alkyl moiety, and

5 wherein these moieties, excluding hydrogen, may be optionally substituted 1 to 4 times, independently, at each occurrence by C<sub>1-10</sub> alkyl, halo-substituted C<sub>1-10</sub> alkyl, C<sub>2-10</sub> alkenyl, C<sub>2-10</sub> alkynyl, C<sub>3-7</sub> cycloalkyl, C<sub>3-7</sub>cycloalkylC<sub>1-10</sub>alkyl, C<sub>5-7</sub>cycloalkenyl, C<sub>5-7</sub> cycloalkenyl C<sub>1-10</sub> alkyl, halogen, -C(O), cyano, nitro, aryl, aryl C<sub>1-10</sub> alkyl, heteroaryl, heteroarylC<sub>1-10</sub> alkyl, heterocyclic, heterocyclylC<sub>1-10</sub> alkyl, (CR<sub>10</sub>R<sub>20</sub>)<sub>n</sub>OR<sub>6</sub>, (CR<sub>10</sub>R<sub>20</sub>)<sub>n</sub>SH, (CR<sub>10</sub>R<sub>20</sub>)<sub>n</sub>S(O)<sub>m</sub>R<sub>7</sub>, (CR<sub>10</sub>R<sub>20</sub>)<sub>n</sub>N(R<sub>10'</sub>)S(O)<sub>2</sub>R<sub>7</sub>, (CR<sub>10</sub>R<sub>20</sub>)<sub>n</sub>NR<sub>e</sub>R<sub>e'</sub>, (CR<sub>10</sub>R<sub>20</sub>)<sub>n</sub>NR<sub>e</sub>R<sub>e'</sub>C<sub>1-4</sub>alkylNR<sub>e</sub>R<sub>e'</sub>, (CR<sub>10</sub>R<sub>20</sub>)<sub>n</sub>CN, (CR<sub>10</sub>R<sub>20</sub>)<sub>n</sub>S(O)<sub>2</sub>NR<sub>e</sub>R<sub>e'</sub>, (CR<sub>10</sub>R<sub>20</sub>)<sub>n</sub>C(Z)R<sub>6</sub>, (CR<sub>10</sub>R<sub>20</sub>)<sub>n</sub>OC(Z)R<sub>6</sub>, (CR<sub>10</sub>R<sub>20</sub>)<sub>n</sub>C(Z)OR<sub>6</sub>, (CR<sub>10</sub>R<sub>20</sub>)<sub>n</sub>C(Z)NR<sub>e</sub>R<sub>e'</sub>, (CR<sub>10</sub>R<sub>20</sub>)<sub>n</sub>N(R<sub>10'</sub>)C(Z)R<sub>6</sub>, (CR<sub>10</sub>R<sub>20</sub>)<sub>n</sub>N(R<sub>10'</sub>)C(=N(R<sub>10'</sub>)) NR<sub>e</sub>R<sub>e'</sub>, (CR<sub>10</sub>R<sub>20</sub>)<sub>n</sub>C(=NOR<sub>6</sub>)NR<sub>e</sub>R<sub>e'</sub>, (CR<sub>10</sub>R<sub>20</sub>)<sub>n</sub>OC(Z)NR<sub>e</sub>R<sub>e'</sub>, (CR<sub>10</sub>R<sub>20</sub>)<sub>n</sub>N(R<sub>10'</sub>)C(Z)NR<sub>e</sub>R<sub>e'</sub>, or (CR<sub>10</sub>R<sub>20</sub>)<sub>n</sub> N(R<sub>10'</sub>)C(Z)OR<sub>7</sub>; or

10 wherein R<sub>2</sub> is the moiety (CR<sub>10</sub>R<sub>20</sub>)<sub>q</sub>'X<sub>1</sub>(CR<sub>10</sub>R<sub>20</sub>)<sub>q</sub>C(A<sub>1</sub>)(A<sub>2</sub>)(A<sub>3</sub>), or (CR<sub>10</sub>R<sub>20</sub>)<sub>q</sub>'C(A<sub>1</sub>)(A<sub>2</sub>)(A<sub>3</sub>);

R<sub>2'</sub> is hydrogen, C<sub>1-10</sub> alkyl, C<sub>3-7</sub> cycloalkyl, C<sub>3-7</sub> cycloalkylalkyl, aryl, arylC<sub>1-10</sub> alkyl, heteroaryl, heteroarylC<sub>1-10</sub> alkyl, heterocyclic, or a heterocyclylC<sub>1-10</sub> alkyl moiety, and

25 wherein each of these moieties, excluding hydrogen, may be optionally substituted 1 to 4 times, independently, by C<sub>1-10</sub> alkyl, halo-substituted C<sub>1-10</sub> alkyl, C<sub>2-10</sub> alkenyl, C<sub>2-10</sub> alkynyl, C<sub>3-7</sub> cycloalkyl, C<sub>3-7</sub>cycloalkylC<sub>1-10</sub>alkyl, C<sub>5-7</sub>cycloalkenyl, C<sub>5-7</sub> cycloalkenyl C<sub>1-10</sub> alkyl, halogen, -C(O), cyano, nitro, aryl, aryl C<sub>1-10</sub> alkyl, heterocyclic, heterocyclic C<sub>1-10</sub> alkyl, heteroaryl, heteroaryl C<sub>1-10</sub> alkyl, (CR<sub>10</sub>R<sub>20</sub>)<sub>n</sub>OR<sub>6</sub>, (CR<sub>10</sub>R<sub>20</sub>)<sub>n</sub>SH, (CR<sub>10</sub>R<sub>20</sub>)<sub>n</sub>S(O)<sub>m</sub>R<sub>7</sub>, (CR<sub>10</sub>R<sub>20</sub>)<sub>n</sub>N(R<sub>10'</sub>)S(O)<sub>2</sub>R<sub>7</sub>, (CR<sub>10</sub>R<sub>20</sub>)<sub>n</sub>NR<sub>e</sub>R<sub>e'</sub>, (CR<sub>10</sub>R<sub>20</sub>)<sub>n</sub>NR<sub>e</sub>R<sub>e'</sub>C<sub>1-4</sub>alkylNR<sub>e</sub>R<sub>e'</sub>, (CR<sub>10</sub>R<sub>20</sub>)<sub>n</sub>CN, (CR<sub>10</sub>R<sub>20</sub>)<sub>n</sub>S(O)<sub>2</sub>NR<sub>e</sub>R<sub>e'</sub>, (CR<sub>10</sub>R<sub>20</sub>)<sub>n</sub>C(Z)R<sub>6</sub>, (CR<sub>10</sub>R<sub>20</sub>)<sub>n</sub>OC(Z)R<sub>6</sub>, (CR<sub>10</sub>R<sub>20</sub>)<sub>n</sub>C(Z)OR<sub>6</sub>, (CR<sub>10</sub>R<sub>20</sub>)<sub>n</sub>C(Z)NR<sub>e</sub>R<sub>e'</sub>, (CR<sub>10</sub>R<sub>20</sub>)<sub>n</sub>N(R<sub>10'</sub>)C(Z)R<sub>6</sub>, (CR<sub>10</sub>R<sub>20</sub>)<sub>n</sub> N(R<sub>10'</sub>)C(=N(R<sub>10'</sub>))NR<sub>e</sub>R<sub>e'</sub>, (CR<sub>10</sub>R<sub>20</sub>)<sub>n</sub>C(=NOR<sub>6</sub>)NR<sub>e</sub>R<sub>e'</sub>, (CR<sub>10</sub>R<sub>20</sub>)<sub>n</sub>OC(Z)NR<sub>e</sub>R<sub>e'</sub>, (CR<sub>10</sub>R<sub>20</sub>)<sub>n</sub>N(R<sub>10'</sub>)C(Z)NR<sub>e</sub>R<sub>e'</sub>, or (CR<sub>10</sub>R<sub>20</sub>)<sub>n</sub>N(R<sub>10'</sub>)C(Z)OR<sub>7</sub>;

R<sub>2</sub>' is hydrogen, C<sub>1-10</sub> alkyl, C<sub>3-7</sub> cycloalkyl, C<sub>3-7</sub> cycloalkylalkyl, aryl, arylC<sub>1-10</sub> alkyl, heteroaryl, heteroarylC<sub>1-10</sub> alkyl, heterocyclic, or a heterocyclylC<sub>1-10</sub> alkyl moiety, and

wherein these moieties, excluding hydrogen, may be optionally substituted 1 to 4 times, independently at each occurrence by C<sub>1-10</sub> alkyl, halo-substituted C<sub>1-10</sub> alkyl, C<sub>2-10</sub> alkenyl, C<sub>2-10</sub> alkynyl, C<sub>3-7</sub> cycloalkyl, C<sub>3-7</sub>cycloalkylC<sub>1-10</sub>alkyl, C<sub>5-7</sub>cycloalkenyl, C<sub>5-7</sub> cycloalkenyl C<sub>1-10</sub> alkyl, halogen, -C(O), cyano, nitro, aryl, aryl C<sub>1-10</sub> alkyl, heterocyclic, heterocyclic C<sub>1-10</sub> alkyl, heteroaryl, heteroaryl C<sub>1-10</sub> alkyl, (CR<sub>10</sub>R<sub>20</sub>)<sub>n</sub>OR<sub>6</sub>, (CR<sub>10</sub>R<sub>20</sub>)<sub>n</sub>SH, (CR<sub>10</sub>R<sub>20</sub>)<sub>n</sub>S(O)<sub>m</sub>R<sub>7</sub>, (CR<sub>10</sub>R<sub>20</sub>)<sub>n</sub> N(R<sub>10'</sub>)S(O)<sub>2</sub>R<sub>7</sub>, (CR<sub>10</sub>R<sub>20</sub>)<sub>n</sub>NR<sub>e</sub>R<sub>e'</sub>, (CR<sub>10</sub>R<sub>20</sub>)<sub>n</sub>NR<sub>e</sub>R<sub>e'</sub>C<sub>1-4</sub>alkylNR<sub>e</sub>R<sub>e'</sub>, (CR<sub>10</sub>R<sub>20</sub>)<sub>n</sub>CN, (CR<sub>10</sub>R<sub>20</sub>)<sub>n</sub>S(O)<sub>2</sub>NR<sub>e</sub>R<sub>e'</sub>, (CR<sub>10</sub>R<sub>20</sub>)<sub>n</sub>C(Z)R<sub>6</sub>, (CR<sub>10</sub>R<sub>20</sub>)<sub>n</sub>OC(Z)R<sub>6</sub>, (CR<sub>10</sub>R<sub>20</sub>)<sub>n</sub>C(Z)OR<sub>6</sub>, (CR<sub>10</sub>R<sub>20</sub>)<sub>n</sub>C(Z)NR<sub>e</sub>R<sub>e'</sub>, (CR<sub>10</sub>R<sub>20</sub>)<sub>n</sub> N(R<sub>10'</sub>)C(Z)R<sub>6</sub>, (CR<sub>10</sub>R<sub>20</sub>)<sub>n</sub>N(R<sub>10'</sub>)C(=N(R<sub>10'</sub>))NR<sub>e</sub>R<sub>e'</sub>, (CR<sub>10</sub>R<sub>20</sub>)<sub>n</sub>C(=NOR<sub>6</sub>)NR<sub>e</sub>R<sub>e'</sub>, (CR<sub>10</sub>R<sub>20</sub>)<sub>n</sub>OC(Z)NR<sub>e</sub>R<sub>e'</sub>, (CR<sub>10</sub>R<sub>20</sub>)<sub>n</sub>N(R<sub>10'</sub>)C(Z)NR<sub>e</sub>R<sub>e'</sub>, or (CR<sub>10</sub>R<sub>20</sub>)<sub>n</sub>N(R<sub>10'</sub>)C(Z)OR<sub>7</sub>; or

wherein R<sub>2</sub>' is the moiety (CR<sub>10</sub>R<sub>20</sub>)<sub>t</sub>X<sub>1</sub>(CR<sub>10</sub>R<sub>20</sub>)<sub>q</sub>C(A<sub>1</sub>)(A<sub>2</sub>)(A<sub>3</sub>);

R<sub>3</sub> is a C<sub>1-10</sub> alkyl, C<sub>3-7</sub> cycloalkyl, C<sub>3-7</sub> cycloalkyl C<sub>1-10</sub> alkyl, aryl, arylC<sub>1-10</sub> alkyl, heteroaryl, heteroarylC<sub>1-10</sub> alkyl, heterocyclic, or heterocyclylC<sub>1-10</sub> alkyl moiety, and

wherein these moieties are all optionally substituted one or more times, independently at each occurrence, by hydrogen, halogen, nitro, C<sub>1-10</sub> alkyl, halo-substituted C<sub>1-10</sub> alkyl, C<sub>2-10</sub> alkenyl, C<sub>2-10</sub>alkynyl, C<sub>3-7</sub>cycloalkyl, C<sub>3-7</sub>cycloalkylC<sub>1-10</sub> alkyl, C<sub>5-7</sub>cycloalkenyl, C<sub>5-7</sub>cycloalkenylC<sub>1-10</sub> alkyl, (CR<sub>10</sub>R<sub>20</sub>)<sub>n</sub>OR<sub>6</sub>, (CR<sub>10</sub>R<sub>20</sub>)<sub>n</sub>SH, (CR<sub>10</sub>R<sub>20</sub>)<sub>n</sub>S(O)<sub>m</sub>R<sub>7</sub>, (CR<sub>10</sub>R<sub>20</sub>)<sub>n</sub>N(R<sub>10'</sub>)S(O)<sub>2</sub>R<sub>7</sub>, (CR<sub>10</sub>R<sub>20</sub>)<sub>n</sub>NR<sub>16</sub>R<sub>26</sub>, (CR<sub>10</sub>R<sub>20</sub>)<sub>n</sub>CN, (CR<sub>10</sub>R<sub>20</sub>)<sub>n</sub>S(O)<sub>2</sub>NR<sub>16</sub>R<sub>26</sub>, (CR<sub>10</sub>R<sub>20</sub>)<sub>n</sub>C(Z)R<sub>6</sub>, (CR<sub>10</sub>R<sub>20</sub>)<sub>n</sub>OC(Z)R<sub>6</sub>, (CR<sub>10</sub>R<sub>20</sub>)<sub>n</sub>C(Z)OR<sub>6</sub>, (CR<sub>10</sub>R<sub>20</sub>)<sub>n</sub>C(Z)NR<sub>16</sub>R<sub>26</sub>, (CR<sub>10</sub>R<sub>20</sub>)<sub>n</sub>N(R<sub>10'</sub>)C(Z)R<sub>6</sub>, (CR<sub>10</sub>R<sub>20</sub>)<sub>n</sub> N(R<sub>10'</sub>)C(=N(R<sub>10'</sub>))NR<sub>16</sub>R<sub>26</sub>, (CR<sub>10</sub>R<sub>20</sub>)<sub>n</sub>OC(Z)NR<sub>16</sub>R<sub>26</sub>, (CR<sub>10</sub>R<sub>20</sub>)<sub>n</sub> N(R<sub>10'</sub>)C(Z)NR<sub>16</sub>R<sub>26</sub>, or (CR<sub>10</sub>R<sub>20</sub>)<sub>n</sub> N(R<sub>10'</sub>)C(Z)OR<sub>7</sub>;

R<sub>4</sub> and R<sub>14</sub> are each independently selected at each occurrence from hydrogen, C<sub>1-10</sub> alkyl, C<sub>3-7</sub> cycloalkyl, C<sub>3-7</sub> cycloalkylC<sub>1-4</sub>alkyl, aryl, aryl-C<sub>1-4</sub> alkyl, heterocyclic, heterocyclic C<sub>1-4</sub> alkyl, heteroaryl or heteroaryl C<sub>1-4</sub> alkyl; or the R<sub>4</sub> and R<sub>14</sub> together with the nitrogen which they are attached form an unsubstituted or substituted heterocyclic ring of 4 to 7 members which ring

optionally contains an additional heteroatom selected from oxygen, sulfur or nitrogen; and

wherein the C<sub>1-4</sub> alkyl, C<sub>3-7</sub>cycloalkyl, C<sub>3-7</sub>cycloalkylC<sub>1-4</sub> alkyl, aryl, aryl-C<sub>1-4</sub> alkyl, heteroaryl and heteroaryl C<sub>1-4</sub> alkyl moieties, and the R<sub>4</sub> and R<sub>14</sub> cyclized ring are optionally substituted, 1 to 4 times, independently at each occurrence, by halogen; hydroxy; hydroxy substituted C<sub>1-10</sub>alkyl; C<sub>1-10</sub>alkoxy; halosubstituted C<sub>1-10</sub> alkoxy; C<sub>1-10</sub> alkyl; halosubstituted C<sub>1-10</sub> alkyl; SR<sub>5</sub>; S(O)R<sub>5</sub>; S(O)<sub>2</sub>R<sub>5</sub>; C(O)R<sub>j</sub>; C(O)OR<sub>j</sub>; C(O)NR<sub>4'</sub>R<sub>14'</sub>;

(CR<sub>10</sub>R<sub>20</sub>)<sub>n</sub> N(R<sub>10'</sub>)C(Z)OR<sub>7</sub>; (CR<sub>10</sub>R<sub>20</sub>)<sub>n</sub> N(R<sub>10'</sub>)C(Z)NR<sub>d</sub>R<sub>d'</sub>;

NR<sub>4'</sub>C(O)C<sub>1-10</sub>alkyl; NR<sub>4'</sub>C(O)aryl; NR<sub>4'</sub>R<sub>14'</sub>; cyano; nitro;

C<sub>3-7</sub>cycloalkyl; C<sub>3-7</sub>cycloalkyl C<sub>1-10</sub> alkyl; an unsubstituted or substituted aryl, or arylC<sub>1-4</sub> alkyl; an unsubstituted or substituted heterocyclic, or heterocyclic C<sub>1-4</sub> alkyl; an unsubstituted or substituted heteroaryl, or heteroC<sub>1-4</sub> alkyl, and wherein these aryl, heterocyclic, and heteroaryl

containing moieties are substituted one to two times independently at each occurrence by halogen; C<sub>1-4</sub> alkyl, hydroxy; hydroxy substituted C<sub>1-4</sub> alkyl; C<sub>1-4</sub> alkoxy; S(O)<sub>m</sub>alkyl; amino, mono & di-substituted C<sub>1-4</sub> alkyl amino, or CF<sub>3</sub>;

R<sub>4'</sub> and R<sub>14'</sub> are each independently selected at each occurrence from hydrogen or C<sub>1-4</sub> alkyl, or R<sub>4'</sub> and R<sub>14'</sub> can cyclize together with the nitrogen to which they are attached to form a 5 to 7 membered ring which optionally contains an additional heteroatom selected from oxygen, sulfur or NR<sub>9'</sub>;

R<sub>4''</sub> and R<sub>14''</sub> are each independently selected at each occurrence from hydrogen or C<sub>1-4</sub> alkyl, or R<sub>4''</sub> and R<sub>14''</sub> together with the nitrogen to which they are attached, cyclize to form a heterocyclic 5 to 7 membered ring which optionally contains an additional heteroatom selected from oxygen, sulfur or NR<sub>9'</sub>;

R<sub>5</sub> is independently selected at each occurrence from hydrogen, C<sub>1-4</sub> alkyl, C<sub>2-4</sub> alkenyl, C<sub>2-4</sub> alkynyl or NR<sub>4'</sub>R<sub>14'</sub>, excluding the moieties SR<sub>5</sub> being SNR<sub>4'</sub>R<sub>14'</sub>, S(O)<sub>2</sub>R<sub>5</sub> being SO<sub>2</sub>H and S(O)R<sub>5</sub> being SOH;

R<sub>6</sub> is independently selected at each occurrence from hydrogen, C<sub>1-10</sub> alkyl, C<sub>3-7</sub> cycloalkyl, heterocyclyl, heterocyclyl C<sub>1-10</sub>alkyl, aryl, arylC<sub>1-10</sub> alkyl, heteroaryl or heteroarylC<sub>1-10</sub> alkyl, wherein each of these moieties, excluding hydrogen are optionally substituted;

R<sub>7</sub> is independently selected at each occurrence from C<sub>1-6</sub>alkyl, aryl, arylC<sub>1-6</sub>alkyl, heterocyclic, heterocyclylC<sub>1-6</sub> alkyl, heteroaryl, or heteroarylC<sub>1-6</sub>alkyl moiety, and wherein each of these moieties may be optionally substituted;

- R<sub>8</sub> is independently selected at each occurrence from hydrogen, C<sub>1-4</sub> alkyl, halo-substituted C<sub>1-4</sub> alkyl, C<sub>2-4</sub> alkenyl, C<sub>2-4</sub> alkynyl, C<sub>3-7</sub> cycloalkyl, C<sub>3-7</sub> cycloalkyl C<sub>1-4</sub> alkyl, C<sub>5-7</sub> cycloalkenyl, C<sub>5-7</sub>cycloalkenyl C<sub>1-4</sub> alkyl, aryl, arylC<sub>1-4</sub> alkyl, heteroaryl, heteroarylC<sub>1-4</sub> alkyl, heterocyclyl, or a  
 5 heterocyclylC<sub>1-4</sub> alkyl moiety, and wherein these moieties, excluding hydrogen, may be optionally substituted;
- R<sub>9</sub> is independently selected at each occurrence from hydrogen, C(Z)R<sub>6</sub>, optionally substituted C<sub>1-10</sub> alkyl, optionally substituted aryl, optionally substituted aryl-C<sub>1-4</sub> alkyl;
- 10 R<sub>9</sub>' is independently selected at each occurrence from hydrogen, or C<sub>1-4</sub> alkyl;  
 R<sub>10</sub> and R<sub>20</sub> are independently selected at each occurrence from hydrogen or C<sub>1-4</sub>alkyl;
- R<sub>10</sub>' is independently selected at each occurrence from hydrogen or C<sub>1-4</sub>alkyl;  
 R<sub>11</sub> is independently selected at each occurrence from hydrogen or C<sub>1-4</sub>alkyl;
- 15 R<sub>12</sub> is independently selected at each occurrence from hydrogen, C<sub>1-4</sub> alkyl, halo-substituted C<sub>1-4</sub> alkyl, C<sub>2-4</sub> alkenyl, C<sub>2-4</sub> alkynyl, C<sub>3-7</sub> cycloalkyl, C<sub>3-7</sub> cycloalkyl C<sub>1-4</sub> alkyl, C<sub>5-7</sub> cycloalkenyl, C<sub>5-7</sub>cycloalkenyl C<sub>1-4</sub> alkyl, aryl, arylC<sub>1-4</sub> alkyl, heteroaryl, heteroarylC<sub>1-4</sub> alkyl, heterocyclyl, or heterocyclylC<sub>1-4</sub> alkyl, and wherein these moieties, excluding hydrogen, may be  
 20 optionally substituted;
- R<sub>13</sub> is independently selected at each occurrence from hydrogen, C<sub>1-4</sub> alkyl, halo-substituted C<sub>1-4</sub> alkyl, C<sub>2-4</sub> alkenyl, C<sub>2-4</sub> alkynyl, C<sub>3-7</sub> cycloalkyl, C<sub>3-7</sub>cycloalkylC<sub>1-4</sub> alkyl, C<sub>5-7</sub> cycloalkenyl, C<sub>5-7</sub>cycloalkenyl C<sub>1-4</sub> alkyl, aryl, arylC<sub>1-4</sub> alkyl, heteroaryl, heteroarylC<sub>1-4</sub> alkyl, heterocyclyl, or a  
 25 heterocyclylC<sub>1-4</sub> alkyl moiety, and wherein each of these moieties, excluding hydrogen, may be optionally substituted;
- R<sub>15</sub> and R<sub>25</sub> are each independently selected at each occurrence from hydrogen, C<sub>1-4</sub> alkyl, C<sub>3-7</sub> cycloalkyl, C<sub>3-7</sub> cycloalkylC<sub>1-4</sub>alkyl, aryl, or aryl-C<sub>1-4</sub> alkyl, heterocyclic, heterocyclic C<sub>1-4</sub> alkyl heteroaryl or heteroaryl C<sub>1-4</sub> alkyl moiety,  
 30 and wherein these moieties, excluding hydrogen may be optionally substituted; or  
 R<sub>5</sub> and R<sub>25</sub> together with the nitrogen which they are attached form an optionally substituted heterocyclic ring of 4 to 7 members, which ring optionally contains an additional heteroatom selected from oxygen, sulfur or NR<sub>9</sub>; and
- wherein these moieties, excluding hydrogen, are optionally substituted 1 to 4  
 35 times, independently at each occurrence by halogen; hydroxy; hydroxy substituted C<sub>1-10</sub>alkyl; C<sub>1-10</sub> alkoxy; halosubstituted C<sub>1-10</sub> alkoxy; C<sub>1-4</sub>

- alkyl; halosubstituted C<sub>1-4</sub> alkyl; SR<sub>5</sub>, S(O)R<sub>5</sub>, S(O)<sub>2</sub>R<sub>5</sub>; C(O)R<sub>j</sub>; C(O)OR<sub>j</sub>; C(O)NR<sub>4</sub>'R<sub>14</sub>'; NR<sub>4</sub>'C(O)C<sub>1-10</sub>alkyl; NR<sub>4</sub>'C(O)aryl; NR<sub>4</sub>'R<sub>14</sub>'; cyano; nitro; C<sub>1-10</sub> alkyl; C<sub>3-7</sub>cycloalkyl; C<sub>3-7</sub>cycloalkyl C<sub>1-10</sub> alkyl; halosubstituted C<sub>1-10</sub> alkyl; aryl, aryl C<sub>1-4</sub> alkyl, heterocyclic, heterocyclic C<sub>1-4</sub> alkyl, heteroaryl, or hetero C<sub>1-4</sub> alkyl, and wherein these aryl, heterocyclic, and heteroaryl containing moieties may also be substituted one to two times independently at each occurrence by halogen, C<sub>1-4</sub> alkyl, hydroxy, hydroxy substituted C<sub>1-4</sub> alkyl, C<sub>1-10</sub> alkoxy, S(O)<sub>m</sub> C<sub>1-4</sub> alkyl, amino, mono & di-substituted C<sub>1-4</sub> alkylamino, C<sub>1-4</sub> alkyl, or CF<sub>3</sub>;
- 10 R<sub>16</sub> and R<sub>26</sub> are each independently selected at each occurrence from hydrogen, or C<sub>1-4</sub> alkyl; or the R<sub>16</sub> and R<sub>26</sub> together with the nitrogen which they are attached form an unsubstituted or substituted heterocyclic ring of 4 to 7 members, which ring optionally contains an additional heteroatom selected from oxygen, sulfur or NR<sub>9</sub>';
- 15 R<sub>21</sub>' and R<sub>31</sub>' are each independently selected at each occurrence from hydrogen or C<sub>1-4</sub> alkyl, or R<sub>21</sub>' and R<sub>31</sub>' together with the nitrogen to which they are attached cyclize to form a 5 to 7 membered ring which optionally contains an additional heteroatom selected from oxygen, sulfur or NR<sub>9</sub>';
- 20 R<sub>b</sub> is hydrogen, C<sub>1-10</sub> alkyl, C<sub>3-7</sub> cycloalkyl, C<sub>3-7</sub> cycloalkylC<sub>1-10</sub> alkyl, aryl, arylC<sub>1-10</sub>alkyl, heteroaryl, heteroarylC<sub>1-10</sub> alkyl, heterocyclic, or a heterocyclylC<sub>1-10</sub> alkyl moiety;
- which moieties may all be optionally substituted 1 to 4 times independently at each occurrence by halogen; hydroxy; hydroxy substituted C<sub>1-10</sub>alkyl; C<sub>1-10</sub> alkyl; C<sub>1-10</sub> alkoxy; halosubstituted C<sub>1-10</sub> alkoxy; OR<sub>8</sub>, SR<sub>5</sub>, S(O)R<sub>5</sub>, S(O)<sub>2</sub>R<sub>5</sub>; C(O)R<sub>j</sub>; C(O)OR<sub>j</sub>; C(O)NR<sub>15</sub>R<sub>25</sub>; cyano; nitro; NR<sub>15</sub>R<sub>25</sub>; -Z'-(CR<sub>10</sub>R<sub>20</sub>)s-Z'-, C<sub>3-7</sub>cycloalkyl; C<sub>3-7</sub>cycloalkyl C<sub>1-10</sub> alkyl; halosubstituted C<sub>1-10</sub> alkyl; an optionally substituted aryl or arylalkyl, an optionally substituted heteroaryl and heteroarylC<sub>1-10</sub> alkyl, and an optionally substituted heterocyclic and heterocyclicC<sub>1-10</sub> alkyl, and wherein these aryl, heteroaryl and heterocyclic containing moieties may also be substituted one to two times independently at each occurrence by halogen, hydroxy, hydroxy substituted alkyl, C<sub>1-10</sub> alkoxy, S(O)<sub>m</sub>C<sub>1-4</sub> alkyl, amino, mono & di-substituted C<sub>1-4</sub> alkyl amino, C<sub>1-4</sub> alkyl, or CF<sub>3</sub>;
- 30 R<sub>d</sub> and R<sub>d</sub>' are each independently selected at each occurrence from hydrogen, C<sub>1-4</sub> alkyl, C<sub>3-6</sub>cycloalkyl, C<sub>3-6</sub> cycloalkylC<sub>1-4</sub>alkyl, or the R<sub>d</sub> and R<sub>d</sub>' together with the nitrogen which they are attached form an optionally substituted heterocyclic
- 35

ring of 5 to 6 members, which ring optionally contains an additional heteroatom selected from oxygen, sulfur or NR<sub>9</sub>'; and

wherein the R<sub>d</sub> and R<sub>d</sub>' moieties which are C<sub>1-4</sub> alkyl, C<sub>3-6</sub>cycloalkyl, C<sub>3-6</sub>cycloalkylC<sub>1-4</sub> alkyl, and the R<sub>d</sub> and R<sub>d</sub>' cyclized ring are substituted, 1 to 4 times, independently at each occurrence by halogen, halosubstituted C<sub>1-4</sub> alkyl, hydroxy, hydroxy substituted C<sub>1-4</sub>alkyl, C<sub>1-4</sub> alkoxy, halosubstituted C<sub>1-4</sub> alkoxy, S(O)<sub>m</sub>R<sub>f</sub>, C(O)R<sub>j</sub>, C(O)OR<sub>j</sub>, C(O)NR<sub>4</sub>'R<sub>14</sub>', NR<sub>4</sub>'C(O)C<sub>1-4</sub>alkyl, S(O)<sub>2</sub>NR<sub>4</sub>'R<sub>14</sub>'C<sub>1-4</sub> alkyl, NR<sub>4</sub>'R<sub>14</sub>'S(O)<sub>2</sub>C<sub>1-4</sub> alkyl, or NR<sub>4</sub>'R<sub>14</sub>';

10 R<sub>e</sub> are R<sub>e</sub>' are each independently selected at each occurrence from hydrogen, C<sub>1-4</sub> alkyl, C<sub>3-7</sub> cycloalkyl, C<sub>3-7</sub> cycloalkylC<sub>1-4</sub>alkyl, aryl, aryl-C<sub>1-4</sub> alkyl, heteroaryl or a heteroaryl C<sub>1-4</sub> alkyl moiety; or R<sub>e</sub> and R<sub>e</sub>' together with the nitrogen which they are attached form an optionally substituted heterocyclic ring of 4 to 7 members, which ring optionally contains an additional heteroatom selected from oxygen, sulfur  
15 or nitrogen; and

wherein each of these moieties, excluding hydrogen, may be substituted 1 to 4 times, independently at each occurrence by halogen; hydroxy; hydroxy substituted C<sub>1-10</sub>alkyl; C<sub>1-10</sub> alkoxy; halosubstituted C<sub>1-10</sub> alkoxy; amino, mono & di-substituted C<sub>1-4</sub> alkyl amino, S(O)<sub>m</sub>R<sub>f</sub>; C(O)R<sub>j</sub>; C(O)OR<sub>j</sub>;  
20 (CR<sub>10</sub>R<sub>20</sub>)<sub>n</sub>N(R<sub>10</sub>')C(Z)OR<sub>7</sub>; (CR<sub>10</sub>R<sub>20</sub>)<sub>n</sub>N(R<sub>10</sub>')C(Z)NR<sub>d</sub>R<sub>d</sub>'; C(O)NR<sub>4</sub>'R<sub>14</sub>'; NR<sub>4</sub>'C(O)C<sub>1-10</sub>alkyl; NR<sub>4</sub>'C(O)aryl; cyano; nitro; C<sub>1-10</sub> alkyl; C<sub>3-7</sub>cycloalkyl; C<sub>3-7</sub>cycloalkyl C<sub>1-10</sub> alkyl; halosubstituted C<sub>1-10</sub> alkyl; aryl, aryl C<sub>1-4</sub> alkyl, heterocyclic, heterocyclicC<sub>1-4</sub> alkyl, heteroaryl, or heteroC<sub>1-4</sub>alkyl, and wherein these aryl, heterocyclic, and heteroaryl containing  
25 moieties may be optionally substituted one to two times independently at each occurrence by halogen, C<sub>1-4</sub> alkyl, hydroxy, hydroxy substituted C<sub>1-4</sub> alkyl, C<sub>1-10</sub> alkoxy, S(O)<sub>m</sub>alkyl, amino, mono & di-substituted C<sub>1-4</sub> alkyl amino, C<sub>1-4</sub> alkyl, or CF<sub>3</sub>;

R<sub>f</sub> is independently selected at each occurrence from C<sub>1-10</sub>alkyl, aryl, aryl

30 C<sub>1-10</sub>alkyl, heteroaryl, heteroaryl C<sub>1-10</sub>alkyl, heterocyclic, or a heterocyclic C<sub>1-10</sub>alkyl moiety, and wherein these moieties may be optionally substituted;

R<sub>j</sub> is independently selected at each occurrence from hydrogen, C<sub>1-4</sub>alkyl, aryl, aryl C<sub>1-4</sub>alkyl, heteroaryl, heteroaryl C<sub>1-4</sub>alkyl, heterocyclic, or a heterocyclic C<sub>1-4</sub>alkyl moiety, and wherein these moieties, excluding hydrogen, may be

35 optionally substituted;

g is 0, or integer having a value of 1, 2, 3, or 4;

n is independently selected at each occurrence from 0 or an integer having a value of 1 to 10;

n' is independently selected at each occurrence from 0 or an integer having a value of 1 to 10;

5 m is independently selected at each occurrence from 0 or an integer having a value of 1 or 2;

q is 0 or an integer having a value of 1 to 10;

q' is 0, or an integer having a value of 1 to 6;

v is 0 or an integer having a value of 1 or 2;

10 v' is independently selected at each occurrence from 0 or an integer having a value of 1 or 2;

s is independently selected at each occurrence from an integer having a value of 1, 2, or 3;

t is an integer having a value of 2 to 6;

15 Z is independently selected at each occurrence from oxygen or sulfur;

Z' is independently selected at each occurrence from oxygen, nitrogen, or sulfur; and a pharmaceutically acceptable salt thereof, solvate or physiologically functional derivative thereof.

20 Suitably, for compounds of Formula (I), and (Ia), and the remaining formulas described herein R<sub>1</sub> is C(Z)N(R<sub>10</sub>') (CR<sub>10</sub>R<sub>20</sub>)<sub>v</sub>R<sub>b</sub>, C(Z)O(CR<sub>10</sub>R<sub>20</sub>)<sub>v</sub>R<sub>b</sub>, N(R<sub>10</sub>')C(Z)(CR<sub>10</sub>R<sub>20</sub>)<sub>v</sub>R<sub>b</sub>, N(R<sub>10</sub>')C(Z)N(R<sub>10</sub>') (CR<sub>10</sub>R<sub>20</sub>)<sub>v</sub>R<sub>b</sub>, or N(R<sub>10</sub>')OC(Z)(CR<sub>10</sub>R<sub>20</sub>)<sub>v</sub>R<sub>b</sub>.

In one embodiment of the invention, R<sub>1</sub> is C(Z)N(R<sub>10</sub>') (CR<sub>10</sub>R<sub>20</sub>)<sub>v</sub>R<sub>b</sub>, or  
25 N(R<sub>10</sub>')C(Z)(CR<sub>10</sub>R<sub>20</sub>)<sub>v</sub>R<sub>b</sub>. In another embodiment of the invention, R<sub>1</sub> is C(Z)N(R<sub>10</sub>') (CR<sub>10</sub>R<sub>20</sub>)<sub>v</sub>R<sub>b</sub>.

Suitably, R<sub>1</sub>' is independently selected at each occurrence from halogen, C<sub>1-4</sub> alkyl, halo-substituted-C<sub>1-4</sub> alkyl, cyano, nitro, (CR<sub>10</sub>R<sub>20</sub>)<sub>v</sub>'NR<sub>d</sub>R<sub>d</sub>', (CR<sub>10</sub>R<sub>20</sub>)<sub>v</sub>'C(O)R<sub>12</sub>, SR<sub>5</sub>, S(O)R<sub>5</sub>, S(O)<sub>2</sub>R<sub>5</sub>, or (CR<sub>10</sub>R<sub>20</sub>)<sub>v</sub>'OR<sub>13</sub>.

30 In one embodiment, R<sub>1</sub>' is independently selected at each occurrence from halogen, C<sub>1-4</sub> alkyl, or halo-substituted-C<sub>1-4</sub> alkyl. In another embodiment, R<sub>1</sub>' is independently selected at each occurrence from fluorine, chlorine, methyl, or CF<sub>3</sub>.

Suitably, g is 0 or an integer having a value of 1, 2, 3, or 4. In one embodiment of the invention, g is 0, 1 or 2.

35 For compounds of Formula (I) and (Ia), when R<sub>1</sub>' is substituted on a phenyl ring in the ortho position, and a second R<sub>1</sub>' moiety is also substituted on the ring, then preferably the second substitution is not in the other ortho position. Suitably,

the phenyl ring is substituted in the 2-position and if a second substituent is present, in the 3-position with the R<sub>1</sub> moiety in the 5-position. Alternatively, the R<sub>1</sub>' moiety may be in the other ortho 2-position and the R<sub>1</sub> moiety in the 3-position, which will change the ring position numbering.

- 5 Suitably, R<sub>d</sub> and R<sub>d</sub>' are each independently selected at each occurrence from hydrogen, C<sub>1-4</sub> alkyl, C<sub>3-5</sub> cycloalkyl, C<sub>3-5</sub> cycloalkylC<sub>1-4</sub>alkyl, or the R<sub>d</sub> and R<sub>d</sub>' together with the nitrogen which they are attached form an optionally substituted heterocyclic ring of 5 to 6 members, which ring optionally contains an additional heteroatom selected from oxygen, sulfur or NR<sub>9</sub>', and wherein the R<sub>d</sub> and R<sub>d</sub>'
- 10 moieties which are C<sub>1-4</sub> alkyl, C<sub>3-6</sub>cycloalkyl, C<sub>3-6</sub>cycloalkylC<sub>1-4</sub> alkyl, and the R<sub>d</sub> and R<sub>d</sub>' cyclized ring are optionally substituted, 1 to 4 times, independently at each occurrence by halogen; halosubstituted C<sub>1-4</sub> alkyl; hydroxy; hydroxy substituted C<sub>1-4</sub>alkyl; C<sub>1-4</sub> alkoxy; C<sub>1-4</sub>alkyl; halosubstituted C<sub>1-4</sub> alkoxy; S(O)mR<sub>f</sub>; C(O)R<sub>j</sub>; C(O)OR<sub>j</sub>; C(O)NR<sub>4</sub>'R<sub>14</sub>', NR<sub>4</sub>'C(O)C<sub>1-4</sub>alkyl; S(O)<sub>2</sub>NR<sub>4</sub>'R<sub>14</sub>'C<sub>1-4</sub> alkyl;
- 15 NR<sub>4</sub>'R<sub>14</sub>'S(O)<sub>2</sub>C<sub>1-4</sub> alkyl; or NR<sub>4</sub>'R<sub>14</sub>'.

Suitably R<sub>9</sub>' is independently selected at each occurrence from hydrogen, or C<sub>1-4</sub> alkyl.

Suitably, Z is independently selected at each occurrence from oxygen or sulfur.

- 20 Suitably, v is 0 or an integer having a value of 1 to 2.

Suitably, v' is 0 or an integer having a value of 1 or 2.

Suitably, R<sub>10</sub> and R<sub>20</sub> are independently selected at each occurrence from hydrogen or C<sub>1-4</sub> alkyl.

- Suitably, R<sub>10</sub>' is independently selected at each occurrence from hydrogen or
- 25 C<sub>1-4</sub> alkyl.

- Suitably, R<sub>12</sub> is independently selected at each occurrence from hydrogen, C<sub>1-4</sub> alkyl, halo-substituted C<sub>1-4</sub> alkyl, C<sub>2-4</sub> alkenyl, C<sub>2-4</sub> alkynyl, C<sub>3-7</sub> cycloalkyl, C<sub>3-7</sub> cycloalkyl C<sub>1-4</sub> alkyl, C<sub>5-7</sub> cycloalkenyl, C<sub>5-7</sub>cycloalkenyl C<sub>1-4</sub> alkyl, aryl, arylC<sub>1-4</sub> alkyl, heteroaryl, heteroarylC<sub>1-4</sub> alkyl, heterocyclyl, or heterocyclylC<sub>1-4</sub>
- 30 alkyl, and wherein these moieties, excluding hydrogen, may be optionally substituted.

- Suitably, R<sub>13</sub> is independently selected at each occurrence from hydrogen, C<sub>1-4</sub> alkyl, halo-substituted C<sub>1-4</sub> alkyl, C<sub>2-4</sub> alkenyl, C<sub>2-4</sub> alkynyl, C<sub>3-7</sub> cycloalkyl, C<sub>3-7</sub>cycloalkylC<sub>1-4</sub> alkyl, C<sub>5-7</sub> cycloalkenyl, C<sub>5-7</sub>cycloalkenyl C<sub>1-4</sub> alkyl, aryl, arylC<sub>1-4</sub> alkyl, heteroaryl, heteroarylC<sub>1-4</sub> alkyl, heterocyclyl, or a heterocyclylC<sub>1-4</sub>
- 35 alkyl moiety, and wherein each of these moieties, excluding hydrogen, may be optionally substituted 1 to 4 times independently at each occurrence by halogen;

halosubstituted C<sub>1-4</sub> alkyl; C<sub>1-4</sub> alkyl; hydroxy; hydroxy substituted C<sub>1-4</sub>alkyl; C<sub>1-4</sub>alkoxy; halosubstituted C<sub>1-4</sub> alkoxy; S(O)<sub>m</sub>C<sub>1-4</sub> alkyl; -C(O), C(O)C<sub>1-4</sub> alkyl; or NR<sub>21'</sub>R<sub>31'</sub>.

Suitably, R<sub>21'</sub> and R<sub>31'</sub> are each independently selected at each occurrence from hydrogen or C<sub>1-4</sub> alkyl, or R<sub>21'</sub> and R<sub>31'</sub> together with the nitrogen to which they are attached cyclize to form an optionally substituted heterocyclic 5 to 7 membered ring, which ring optionally contains an additional heteroatom selected from O/N/S.

Suitably R<sub>b</sub> is hydrogen, C<sub>1-10</sub> alkyl, C<sub>3-7</sub> cycloalkyl, C<sub>3-7</sub> cycloalkylC<sub>1-10</sub> alkyl, aryl, arylC<sub>1-10</sub>alkyl, heteroaryl, heteroarylC<sub>1-10</sub> alkyl, heterocyclic, or a heterocyclylC<sub>1-10</sub> alkyl moiety, which moieties, excluding hydrogen are all optionally substituted.

The R<sub>b</sub> moieties, excluding hydrogen, may be optionally substituted, one or more times, preferably 1 to 4 times independently at each occurrence by halogen, such as fluorine, chlorine, bromine or iodine; hydroxy; hydroxy substituted C<sub>1-10</sub>alkyl; C<sub>1-10</sub> alkoxy, such as methoxy or ethoxy; halosubstituted C<sub>1-10</sub> alkoxy; OR<sub>8</sub>, such as methoxy, ethoxy or phenoxy; SR<sub>5</sub>, S(O)R<sub>5</sub>, S(O)<sub>2</sub>R<sub>5</sub>, such as methylthio, methylsulfinyl or methyl sulfonyl; C(O)R<sub>j</sub>; C(O)OR<sub>j</sub>; C(O)NR<sub>4'</sub>R<sub>14'</sub>; cyano; nitro; NR<sub>15</sub>R<sub>25</sub>; -Z'-(CR<sub>10</sub>R<sub>20</sub>)<sub>s</sub>-Z'-; C<sub>1-10</sub>alkyl; C<sub>3-7</sub>cycloalkyl or a C<sub>3-7</sub>cycloalkylC<sub>1-10</sub> alkyl group, such as cyclopropyl, or cyclopropyl methyl, or cyclopropylethyl, etc.; halosubstituted C<sub>1-10</sub> alkyl, such CF<sub>2</sub>CF<sub>2</sub>H, CH<sub>2</sub>CF<sub>3</sub>, or CF<sub>3</sub>; an optionally substituted aryl, such as phenyl, or an optionally substituted arylC<sub>1-10</sub>alkyl, such as benzyl or phenethyl; an optionally substituted heterocyclic or heterocyclicC<sub>1-10</sub>alkyl, or an optionally substituted heteroaryl or heteroarylC<sub>1-10</sub>alkyl, and wherein these aryl, heteroaryl, and heterocyclic containing moieties may also be substituted one to two times independently at each occurrence by halogen, hydroxy, hydroxy substituted alkyl, C<sub>1-10</sub> alkoxy, S(O)<sub>m</sub>alkyl, amino, mono & di-substituted C<sub>1-4</sub> alkyl amino, C<sub>1-4</sub> alkyl, or CF<sub>3</sub>.

The moiety -Z'-(CR<sub>10</sub>R<sub>20</sub>)<sub>s</sub>-Z' forms a cyclic ring, such as a dioxalane ring.

Suitably Z' is independently at each occurrence selected from oxygen or sulfur.

Suitably, s is independently selected at each occurrence from an integer having a value of 1, 2, or 3.

Suitably, R<sub>5</sub> is independently selected at each occurrence from hydrogen, C<sub>1-4</sub> alkyl, C<sub>2-4</sub> alkenyl, C<sub>2-4</sub> alkynyl or NR<sub>4'</sub>R<sub>14'</sub>, excluding the moieties SR<sub>5</sub> being SNR<sub>4'</sub>R<sub>14'</sub>, S(O)<sub>2</sub>R<sub>5</sub> being SO<sub>2</sub>H and S(O)R<sub>5</sub> being SOH.

Suitably, R<sub>4'</sub> and R<sub>14'</sub> are each independently selected at each occurrence from hydrogen or C<sub>1-4</sub> alkyl, or R<sub>4'</sub> and R<sub>14'</sub> can cyclize together with the nitrogen to which they are attached to form an optionally substituted 5 to 7 membered ring which optionally contains an additional heteroatom from oxygen, sulfur or NR<sub>9'</sub>.

5 Suitably, when R<sub>4'</sub> and R<sub>14'</sub> cyclize to form an optionally substituted ring, such rings include, but are not limited to pyrrolidine, piperidine, piperazine, morpholine, and thiomorpholine (including oxidizing the sulfur).

Suitably, R<sub>4''</sub> and R<sub>14''</sub> are each independently selected at each occurrence from hydrogen or C<sub>1-10</sub> alkyl, or R<sub>4''</sub> and R<sub>14''</sub> can cyclize together with the  
10 nitrogen to which they are attached to form an optionally substituted 5 to 7 membered ring which optionally contains an additional heteroatom selected from oxygen, sulfur or NR<sub>9'</sub>. Suitably, when R<sub>4''</sub> and R<sub>14''</sub> cyclize to form an optionally substituted ring, such rings include, but are not limited to pyrrolidine, piperidine, piperazine, morpholine, and thiomorpholine (including oxidizing the sulfur).

15 Suitably, R<sub>f</sub> is independently selected at each occurrence from hydrogen, C<sub>1-10</sub>alkyl, aryl, aryl C<sub>1-10</sub>alkyl, heteroaryl, heteroaryl C<sub>1-10</sub>alkyl, heterocyclic, or a heterocyclic C<sub>1-10</sub>alkyl moiety, and wherein these moieties, excluding hydrogen, may be optionally substituted.

Suitably, R<sub>j</sub> is independently selected at each occurrence from a C<sub>1-10</sub>alkyl, aryl, aryl C<sub>1-10</sub>alkyl, heteroaryl, heteroaryl C<sub>1-10</sub>alkyl, heterocyclic, or a  
20 heterocyclic C<sub>1-10</sub>alkyl moiety, and wherein each of these moieties may be optionally substituted.

Suitably, when R<sub>b</sub> is an optionally substituted C<sub>1-10</sub>alkyl, the moiety includes but is not limited to a methyl, ethyl, n-propyl, isopropyl, t-butyl, n-butyl, isobutyl, 1,2-dimethylpropyl, 2,2-dimethylpropyl, heptyl, 2-methylpropyl; a  
25 halosubstituted alkyl, such as 2,2,2-trifluoroethyl, trifluoromethyl, 2-fluoroethyl; a cyano substituted alkyl, such as cyanomethyl, cyanoethyl; an alkoxy, thio or hydroxy substituted alkyl, such as 2-methoxy-ethyl, 2-hydroxy propyl or serinol, or an ethylthioethyl.

30 In an alternative embodiment, when R<sub>b</sub> is an optionally substituted C<sub>1-10</sub>alkyl the moiety is a methyl, ethyl, n-propyl, isopropyl, t-butyl, n-butyl, or 2,2-dimethylpropyl or 2-hydroxy propyl group.

Suitably, when R<sub>b</sub> is an optionally substituted heteroaryl, or heteroarylalkyl, the heteroaryl containing moiety includes but is not limited to, furyl, pyranlyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, isoxazolyl, isothiazolyl, imidazolyl, pyrazolyl, oxadiazolyl, oxathiadiazolyl, triazolyl, tetrazolyl, thiadiazolyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, triazinyl, and uracil, indolyl, isoindolyl, indazolyl,  
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indolizinyl, azaindolyl, benzoxazolyl, benzimidazolyl, benzothiazolyl, benzofuranyl, benzothiophenyl, quinolyl, isoquinolyl, quinazolinyl, quinoxalinyl, naphthyridinyl, cinnolinyl, purinyl, and phthalazinyl.

In one embodiment, when  $R_b$  is an optionally substituted heteroaryl it is a 1,3-thiazol-2-yl or 5-methyl-1,3-thiazol-2-yl, isoquinolinyl, thiophene, e.g. a 3-thiophene, indol-5-yl, pyridinyl, e.g. a pyridin-3-yl, or pyridine-4-yl, indazolyl, benzothiazolyl, 2-methyl-1,3-benzothiazol-5-yl, 1*H*-imidazol-4-yl or 1*H*-imidazol-4-ylethyl. Further to this, the heteroaryl ring is an optionally substituted thiazolyl, pyridyl, or thiophene ring. Preferably,  $R_b$  is an optionally substituted 1,3-thiazol-2-yl.

Suitably, when  $R_b$  is an optionally substituted heterocyclic, or heterocyclicalkyl, the heterocyclic containing moiety includes but is not limited to tetrahydropyrrole, tetrahydropyran, tetrahydrofuran, tetrahydrothiophene (including oxidized versions of the sulfur moiety), azepine, diazepine, aziridinyl, pyrrolinyl, pyrrolidinyl, 2-oxo-1-pyrrolidinyl, 3-oxo-1-pyrrolidinyl, 1,3-benzdioxol-5-yl, imidazolinyl, imidazolidinyl, indolinyl, pyrazolinyl, pyrazolidinyl, piperidinyl, piperazinyl, morpholino and thiomorpholino (including oxidized versions of the sulfur moiety). In one embodiment, the heterocyclic, heterocyclic alkyl group is pyrazol-3-yl, 4-morpholino, unsubstituted and substituted 2-furanyl, 2-furanylmethyl, 2-thienyl, 2-thienylmethyl, tetrahydro-2*H*-pyran-4yl, tetrahydro-2*H*-pyran-4yl methyl, tetrahydro-2-furanyl, or tetrahydro-2-furanylmethyl.

Suitably, when  $R_b$  is an optionally substituted aryl or arylalkyl moiety, the aryl containing moiety is unsubstituted or substituted independently at each occurrence one or more times by halogen, alkyl, cyano,  $OR_8$ ,  $SR_5$ ,  $S(O)_2R_5$ ,  $C(O)R_j$ ,  $C(O)OR_j$ ,  $-Z'-(CR_{10}R_{20})_s-Z'$ , halosubstituted  $C_{1-10}$  alkyl, or an optionally substituted aryl.

In one embodiment,  $R_b$  is a phenyl, or naphthylene, 2-fluorophenyl, 3-fluorophenyl, 4-fluorophenyl, 2,3-difluorophenyl, 2,4-difluorophenyl, 3,4-difluorophenyl, 3,5-difluorophenyl, 3-chlorophenyl, 4-chlorophenyl, 3-chloro-4-fluorophenyl, 2-methyl phenyl, 3-methylphenyl, 4-methylphenyl, 6-methyl phenyl, 2-methyl phenyl, 3-amino phenyl, 3,4-dimethyl phenyl, 4-methyl-3-fluorophenyl, 4-trifluorophenyl, 4-ethoxyphenyl, 4-methoxyphenyl, 3-cyanophenyl, 4-cyanophenyl, 4-thiomethylphenyl, 4-acetylphenyl, 4-dimethylaminophenyl, benzyl, phenethyl, phenylpropyl, 2,3-difluoro-benzyl, 3,5-difluoro-benzyl, biphenyl, 4'-fluorobiphenyl, 4-sulfonamido-2-methylphenyl, or 3-phenyloxyphenyl, 4-phenyloxyphenyl, 4-(1-piperidinylsulfonyl)-phenyl, or 3-(aminocarbonyl)phenyl.

In another embodiment, R<sub>b</sub> is a phenyl, 2-fluorophenyl, 3-fluorophenyl, 4-fluorophenyl, 2,4-difluorophenyl, 3,4-difluorophenyl, 3,5-difluorophenyl, 3-chlorophenyl, 4-chlorophenyl, 3-chloro-4-fluorophenyl, 4-methyl-3-fluorophenyl, 4-trifluorophenyl, 2-methylphenyl, 3-methylphenyl, 4-ethoxyphenyl, 4-methoxyphenyl, 3-cyanophenyl, 4-cyanophenyl, 4-thiomethylphenyl, 4-acetylphenyl, 4-dimethylaminophenyl, biphenyl, 4'-fluorobiphenyl, 4-sulfonamido-2-methylphenyl, 3-phenyloxyphenyl, benzyl, or phenethyl. Further to this R<sub>b</sub> is a 4-fluorophenyl.

Suitably, when R<sub>b</sub> is an optionally substituted cycloalkyl or cycloalkyl alkyl moiety, the moiety is a cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cyclopropylmethyl, or a cyclopentylmethyl. In another embodiment, R<sub>b</sub> is a cyclopropyl or cyclopropylmethyl group.

In another embodiment, R<sub>b</sub> is C<sub>1-10</sub> alkyl, heteroaryl, or aryl, all optionally substituted.

In another embodiment, R<sub>b</sub> is hydrogen, or an optionally substituted alkyl.

In one embodiment of the invention R<sub>b</sub> is an alkyl, such as propyl or isopropyl; heteroaryl, such as a thiazolyl; an aryl, such phenyl, or 4-F phenyl; an arylalkyl, or a cycloalkylalkyl moiety, all optionally substituted. In another embodiment, R<sub>b</sub> is alkyl, heteroaryl, or aryl, all optionally substituted.

In another embodiment, R<sub>b</sub> is C<sub>1-10</sub> alkyl, heteroaryl, or aryl, all optionally substituted.

Suitably, m is independently selected at each occurrence from 0 or an integer having a value of 1 or 2.

For each of the integer variables where appropriate, e.g. n, n', m, q', s, t, or v', etc. they are independently chosen at each occurrence.

Suitably, R<sub>g</sub> is independently selected at each occurrence from hydrogen, C<sub>1-4</sub> alkyl, halo-substituted C<sub>1-4</sub> alkyl, C<sub>2-4</sub> alkenyl, C<sub>2-4</sub> alkynyl, C<sub>3-7</sub> cycloalkyl, C<sub>3-7</sub> cycloalkyl C<sub>1-4</sub> alkyl, C<sub>5-7</sub> cycloalkenyl, C<sub>5-7</sub>cycloalkenyl C<sub>1-4</sub> alkyl, aryl, arylC<sub>1-4</sub> alkyl, heteroaryl, heteroarylC<sub>1-4</sub> alkyl, heterocyclyl, or a heterocyclylC<sub>1-4</sub> alkyl moiety, and wherein these moieties, excluding hydrogen, may be optionally substituted 1 to 4 times by halogen; halosubstituted C<sub>1-4</sub> alkyl; C<sub>1-4</sub> alkyl; C<sub>3-5</sub>cycloalkyl; C<sub>3-5</sub>cycloalkyl C<sub>1-4</sub>alkyl; halosubstituted C<sub>1-4</sub> alkyl; hydroxy; hydroxy substituted C<sub>1-4</sub>alkyl; C<sub>1-4</sub>alkoxy; halosubstituted C<sub>1-4</sub> alkoxy; S(O)<sub>m</sub>C<sub>1-4</sub> alkyl; -C(O), C(O)C<sub>1-4</sub> alkyl; NR<sub>21</sub>R<sub>31</sub>'; or an aryl or arylalkyl, and wherein these aryl containing moieties may also be substituted independently at each occurrence, one to two times by halogen, hydroxy, hydroxy substituted alkyl, C<sub>1-4</sub> alkoxy,

S(O)<sub>m</sub>C<sub>1-4</sub>alkyl, amino, mono & di-substituted C<sub>1-4</sub> alkylamino, C<sub>1-4</sub> alkyl, or CF<sub>3</sub>.

Suitably, R<sub>15</sub> and R<sub>25</sub> are each independently selected at each occurrence from hydrogen, C<sub>1-4</sub> alkyl, C<sub>3-7</sub> cycloalkyl, C<sub>3-7</sub> cycloalkylC<sub>1-4</sub>alkyl, aryl, or aryl-C<sub>1-4</sub> alkyl, heteroaryl or heteroaryl C<sub>1-4</sub> alkyl moiety, and wherein these moieties, excluding hydrogen may be optionally substituted; or R<sub>15</sub> and R<sub>25</sub> together with the nitrogen which they are attached form an optionally substituted heterocyclic ring of 4 to 7 members, which ring optionally contains an additional heteroatom selected from oxygen, sulfur or NR<sub>9</sub>; and wherein these moieties are optionally substituted 1 to 4 times, independently at each occurrence by halogen; hydroxy; hydroxy substituted C<sub>1-10</sub>alkyl; C<sub>1-10</sub> alkoxy; halosubstituted C<sub>1-10</sub> alkoxy; C<sub>1-4</sub> alkyl; SR<sub>5</sub>, S(O)R<sub>5</sub>, S(O)<sub>2</sub>R<sub>5</sub>; C(O)R<sub>j</sub>; C(O)OR<sub>j</sub>; C(O)NR<sub>4</sub>R<sub>14</sub>; NR<sub>4</sub>C(O)C<sub>1-10</sub>alkyl; NR<sub>4</sub>C(O)aryl; NR<sub>4</sub>R<sub>14</sub>; cyano; nitro; C<sub>1-10</sub> alkyl; C<sub>3-7</sub>cycloalkyl; C<sub>3-7</sub>cycloalkylC<sub>1-10</sub> alkyl; halosubstitutedC<sub>1-10</sub> alkyl; aryl, arylC<sub>1-4</sub> alkyl, heterocyclic and heterocyclicC<sub>1-4</sub> alkyl, heteroaryl, or heteroC<sub>1-4</sub> alkyl, and wherein these aryl, heterocyclic and heteroaryl containing moieties may also be substituted one to two times independently at each occurrence by halogen, C<sub>1-4</sub> alkyl, hydroxy, hydroxy substituted C<sub>1-4</sub> alkyl, C<sub>1-10</sub> alkoxy, S(O)<sub>m</sub>alkyl, amino, mono & di-substituted C<sub>1-4</sub> alkyl amino, C<sub>1-4</sub> alkyl, or CF<sub>3</sub>.

Suitably, R<sub>4</sub> and R<sub>14</sub> are each independently selected at each occurrence from hydrogen, optionally substituted C<sub>1-10</sub> alkyl, optionally substituted C<sub>3-7</sub>cycloalkyl, optionally substituted C<sub>3-7</sub>cycloalkylC<sub>1-4</sub> alkyl, optionally substituted aryl or optionally substituted aryl-C<sub>1-4</sub> alkyl, optionally substituted heteroaryl, optionally substituted heteroaryl C<sub>1-4</sub> alkyl, optionally substituted heterocyclic, or optionally substituted heterocyclic C<sub>1-4</sub> alkyl, or R<sub>4</sub> and R<sub>14</sub> together with the nitrogen to which they are attached may form an optionally substituted heterocyclic ring of 4 to 7 members which ring optionally contains an additional heteroatom selected from oxygen, sulfur or nitrogen.

The R<sub>4</sub> and R<sub>14</sub> moieties, excluding hydrogen, of C<sub>1-10</sub>alkyl, C<sub>3-7</sub>cycloalkyl, C<sub>3-7</sub>cycloalkylC<sub>1-4</sub> alkyl, aryl, aryl-C<sub>1-4</sub> alkyl, heteroaryl, heteroaryl C<sub>1-4</sub> alkyl, heterocyclic, or heterocyclic C<sub>1-4</sub> alkyl moieties, and the R<sub>4</sub> and R<sub>14</sub> cyclized ring, are all be optionally substituted, one or more times, preferably 1 to 4 times, independently at each occurrence, by halogen, such as fluorine, chlorine, bromine or iodine; hydroxy; hydroxy substituted C<sub>1-10</sub>alkyl; C<sub>1-10</sub> alkoxy, such as methoxy or ethoxy; C<sub>1-10</sub>alkyl, halosubstituted C<sub>1-10</sub> alkoxy; SR<sub>5</sub>; S(O)R<sub>5</sub>; S(O)<sub>2</sub>R<sub>5</sub>, such as methyl thio, methylsulfinyl or methyl sulfonyl; C(O)R<sub>j</sub>; C(O)OR<sub>j</sub>;

C(O)NR<sub>4</sub>'R<sub>14</sub>'; (CR<sub>10</sub>R<sub>20</sub>)<sub>n</sub>N(R<sub>10</sub>')C(Z)OR<sub>7</sub>; (CR<sub>10</sub>R<sub>20</sub>)<sub>n</sub> N(R<sub>10</sub>')C(Z)NR<sub>d</sub>R<sub>d</sub>'; NR<sub>4</sub>'C(O)C<sub>1-10</sub>alkyl; NR<sub>4</sub>'C(O)aryl; NR<sub>4</sub>'R<sub>14</sub>'; cyano; nitro; C<sub>1-10</sub> alkyl, such as methyl, ethyl, n-propyl, t-butyl, etc.; C<sub>3-7</sub>cycloalkyl and C<sub>3-7</sub>cycloalkyl C<sub>1-10</sub> alkyl, such as cyclopropyl, cyclopropyl methyl, or cyclopropyl ethyl, etc.; halosubstituted C<sub>1-10</sub> alkyl, such CF<sub>2</sub>CF<sub>2</sub>H, CH<sub>2</sub>CF<sub>3</sub>, or CF<sub>3</sub>; C<sub>1-10</sub> alkyl substituted one or more times by an optionally substituted aryl; optionally substituted aryl, such as phenyl, or an optionally substituted arylC<sub>1-4</sub> alkyl, such as benzyl or phenethyl; an unsubstituted or substituted heteroaryl, or heteroC<sub>1-4</sub> alkyl, an unsubstituted or substituted heterocyclic, or heterocyclicC<sub>1-4</sub> alkyl, and wherein these aryl, heteroaryl and heterocyclic containing moieties may also be substituted independently at each occurrence, one to two times, by halogen, C<sub>1-4</sub> alkyl, hydroxy, hydroxy substituted C<sub>1-4</sub> alkyl, C<sub>1-4</sub> alkoxy, S(O)<sub>m</sub>alkyl, amino, mono & di-substituted C<sub>1-4</sub> alkyl amino, or CF<sub>3</sub>.

Suitably, when R<sub>4</sub> and R<sub>14</sub> together with the nitrogen cyclize to form an optionally substituted ring, such as described above, such rings include, but are not limited to pyrrolidine, piperidine, piperazine, morpholine, and thiomorpholine (including oxidizing the sulfur).

Suitably, R<sub>6</sub> is independently selected at each occurrence from hydrogen, C<sub>1-10</sub> alkyl, C<sub>3-7</sub> cycloalkyl, heterocyclyl, heterocyclyl C<sub>1-10</sub>alkyl, aryl, arylC<sub>1-10</sub> alkyl, heteroaryl or a heteroarylC<sub>1-10</sub> alkyl moiety, and wherein these moieties, excluding hydrogen may be optionally substituted independently at each occurrence, one or more times, suitably 1 to 2 times, by halogen; hydroxy; hydroxy substituted C<sub>1-10</sub>alkyl; C<sub>1-10</sub> alkoxy; halosubstituted C<sub>1-10</sub> alkoxy; S(O)<sub>m</sub> alkyl; C(O); NR<sub>4</sub>'R<sub>14</sub>'; C<sub>1-10</sub> alkyl; C<sub>3-7</sub>cycloalkyl; C<sub>3-7</sub>cycloalkyl C<sub>1-10</sub> alkyl; halosubstituted C<sub>1-10</sub> alkyl; an unsubstituted aryl or aryl C<sub>1-4</sub> alkyl, an unsubstituted or substituted heteroaryl or heteroaryl C<sub>1-4</sub> alkyl, or a unsubstituted or substituted heterocyclic or heterocyclic C<sub>1-4</sub> alkyl; and wherein these aryl, heterocyclic, or heteroaryl containing moieties may be substituted independently at each occurrence, one or two times by halogen, hydroxy, hydroxy substituted alkyl, C<sub>1-10</sub> alkoxy, S(O)<sub>m</sub>alkyl, amino, mono & di-substituted C<sub>1-4</sub> alkyl amino, C<sub>1-4</sub> alkyl, or CF<sub>3</sub>.

Suitably, R<sub>9</sub> is independently selected at each occurrence from hydrogen, C(Z)R<sub>6</sub>, optionally substituted C<sub>1-10</sub> alkyl, optionally substituted aryl or optionally substituted aryl-C<sub>1-4</sub> alkyl. These alkyl, aryl and arylalkyl moieties may be optionally substituted 1 or 2 times, independently at each occurrence by halogen; hydroxy; hydroxy substituted C<sub>1-10</sub>alkyl; C<sub>1-10</sub> alkoxy; halosubstituted C<sub>1-10</sub> alkoxy; S(O)<sub>m</sub> alkyl; -C(O); NR<sub>4</sub>'R<sub>14</sub>'; C<sub>1-10</sub> alkyl, C<sub>3-7</sub>cycloalkyl; C<sub>3-7</sub>cycloalkyl C<sub>1-10</sub> alkyl; halosubstituted C<sub>1-10</sub> alkyl; an aryl or aryl C<sub>1-4</sub> alkyl, and wherein these aryl

containing moieties may also be substituted one or two times independently at each occurrence by halogen, hydroxy, hydroxy substituted alkyl, C<sub>1-10</sub> alkoxy, S(O)<sub>m</sub>C<sub>1-4</sub> alkyl, amino, mono & di-substituted C<sub>1-4</sub> alkyl amino, C<sub>1-4</sub> alkyl, or CF<sub>3</sub>.

Suitably, R<sub>3</sub> is a C<sub>1-10</sub> alkyl, C<sub>3-7</sub> cycloalkyl, C<sub>3-7</sub> cycloalkyl C<sub>1-10</sub> alkyl, aryl, arylC<sub>1-10</sub> alkyl, heteroaryl, heteroarylC<sub>1-10</sub> alkyl, heterocyclic, or heterocyclylC<sub>1-10</sub> alkyl moiety, which moieties may be optionally substituted one or more times, suitably 1 to 4 times, independently at each occurrence by hydrogen, halogen, nitro, C<sub>1-10</sub> alkyl, halo-substituted C<sub>1-10</sub> alkyl, C<sub>2-10</sub> alkenyl, C<sub>2-10</sub> alkynyl, C<sub>3-7</sub> cycloalkyl, C<sub>3-7</sub> cycloalkylC<sub>1-10</sub> alkyl, C<sub>5-7</sub> cycloalkenyl, C<sub>5-7</sub> cycloalkenyl-C<sub>1-10</sub> alkyl, (CR<sub>10</sub>R<sub>20</sub>)<sub>n</sub>OR<sub>6</sub>, (CR<sub>10</sub>R<sub>20</sub>)<sub>n</sub>SH, (CR<sub>10</sub>R<sub>20</sub>)<sub>n</sub>S(O)<sub>m</sub>R<sub>7</sub>, (CR<sub>10</sub>R<sub>20</sub>)<sub>n</sub>N(R<sub>10'</sub>)S(O)<sub>2</sub>R<sub>7</sub>, (CR<sub>10</sub>R<sub>20</sub>)<sub>n</sub>NR<sub>16</sub>R<sub>26</sub>, (CR<sub>10</sub>R<sub>20</sub>)<sub>n</sub>CN, (CR<sub>10</sub>R<sub>20</sub>)<sub>n</sub>S(O)<sub>2</sub>NR<sub>16</sub>R<sub>26</sub>, (CR<sub>10</sub>R<sub>20</sub>)<sub>n</sub>C(Z)R<sub>6</sub>, (CR<sub>10</sub>R<sub>20</sub>)<sub>n</sub>OC(Z)R<sub>6</sub>, (CR<sub>10</sub>R<sub>20</sub>)<sub>n</sub>C(Z)OR<sub>6</sub>, (CR<sub>10</sub>R<sub>20</sub>)<sub>n</sub>C(Z)NR<sub>16</sub>R<sub>26</sub>, (CR<sub>10</sub>R<sub>20</sub>)<sub>n</sub>N(R<sub>10'</sub>)C(Z)R<sub>6</sub>, (CR<sub>10</sub>R<sub>20</sub>)<sub>n</sub>N(R<sub>10'</sub>)C(=N(R<sub>10'</sub>))NR<sub>16</sub>R<sub>26</sub>, (CR<sub>10</sub>R<sub>20</sub>)<sub>n</sub>OC(Z)NR<sub>16</sub>R<sub>26</sub>, (CR<sub>10</sub>R<sub>20</sub>)<sub>n</sub>N(R<sub>10'</sub>)C(Z)NR<sub>16</sub>R<sub>26</sub>, or (CR<sub>10</sub>R<sub>20</sub>)<sub>n</sub>N(R<sub>10'</sub>)C(Z)OR<sub>7</sub>.

In one embodiment, the R<sub>3</sub> moieties are optionally substituted 1 to 4 times, independently at each occurrence by halogen, nitro, C<sub>1-4</sub> alkyl, halo-substituted C<sub>1-4</sub> alkyl, C<sub>2-4</sub> alkenyl, C<sub>2-4</sub> alkynyl, C<sub>3-6</sub> cycloalkyl, C<sub>3-6</sub> cycloalkylC<sub>1-4</sub> alkyl, C<sub>5-6</sub> cycloalkenyl, C<sub>5-6</sub> cycloalkenylC<sub>1-4</sub> alkyl, (CR<sub>10</sub>R<sub>20</sub>)<sub>n</sub>OR<sub>6</sub>, (CR<sub>10</sub>R<sub>20</sub>)<sub>n</sub>SH, (CR<sub>10</sub>R<sub>20</sub>)<sub>n</sub>S(O)<sub>m</sub>R<sub>7</sub>, (CR<sub>10</sub>R<sub>20</sub>)<sub>n</sub>NHS(O)<sub>2</sub>R<sub>7</sub>, (CR<sub>10</sub>R<sub>20</sub>)<sub>n</sub>S(O)<sub>2</sub>NR<sub>16</sub>R<sub>26</sub>, (CR<sub>10</sub>R<sub>20</sub>)<sub>n</sub>NR<sub>16</sub>R<sub>26</sub>, (CR<sub>10</sub>R<sub>20</sub>)<sub>n</sub>CN, (CR<sub>10</sub>R<sub>20</sub>)<sub>n</sub>C(Z)R<sub>6</sub>, (CR<sub>10</sub>R<sub>20</sub>)<sub>n</sub>OC(Z)R<sub>6</sub>, (CR<sub>10</sub>R<sub>20</sub>)<sub>n</sub>C(Z)OR<sub>6</sub>, (CR<sub>10</sub>R<sub>20</sub>)<sub>n</sub>N(R<sub>10'</sub>)C(Z)R<sub>6</sub>, or (CR<sub>10</sub>R<sub>20</sub>)<sub>n</sub>C(Z)NR<sub>16</sub>R<sub>26</sub>.

In one embodiment the R<sub>3</sub> moieties are optionally substituted independently, one or more times, suitably 1 to 4 times, independently at each occurrence by the R<sub>3</sub> optional substituent is independently selected from halogen, C<sub>1-10</sub> alkyl, (CR<sub>10</sub>R<sub>20</sub>)<sub>n</sub>OR<sub>6</sub>, (CR<sub>10</sub>R<sub>20</sub>)<sub>n</sub>NR<sub>16</sub>R<sub>26</sub>, or halo-substituted C<sub>1-10</sub> alkyl.

In another embodiment the optional substituents are independently selected at each occurrence from halogen, C<sub>1-10</sub> alkyl, hydroxy, C<sub>1-10</sub> alkoxy, cyano, nitro, amino, or halosubstituted C<sub>1-10</sub> alkyl. In another embodiment, the R<sub>3</sub> substituents are selected independently from halogen, such as fluorine, chlorine, bromine or iodine, or C<sub>1-10</sub> alkyl, such as methyl.

In one embodiment the R<sub>3</sub> moieties are selected from an optionally substituted C<sub>1-10</sub> alkyl, optionally substituted C<sub>3-7</sub> cycloalkyl, optionally substituted C<sub>3-7</sub> cycloalkylalkyl, or an optionally substituted aryl. In another embodiment, the R<sub>3</sub> moiety is selected from an optionally substituted C<sub>1-10</sub> alkyl,

or an optionally substituted aryl. In another embodiment, R<sub>3</sub> is an optionally substituted phenyl. Further to this embodiment, R<sub>3</sub> is a phenyl ring substituted one or more times by independently at each occurrence by fluorine, chlorine, hydroxy, methoxy, amino, methyl, or trifluoromethyl. Preferably, R<sub>3</sub> is a 2,6-difluorophenyl.

Suitably, in one embodiment when R<sub>3</sub> is an aryl moiety, it is a phenyl ring.

The phenyl ring is optionally substituted, independently at each occurrence, one or more times, suitably 1 to 4 times by halogen, C<sub>1-4</sub> alkyl, or halo-substituted-C<sub>1-4</sub> alkyl. The phenyl ring may suitably be substituted in the 2, 4, or 6-position, or di-substituted in the 2,4- position, or 2,6-position, such as 2-fluoro, 4-fluoro, 2,4-difluoro, 2,6-difluoro, or 2-methyl-4-fluoro; or tri-substituted in the 2,4,6-position, such as 2,4,6-trifluoro.

Suitably, R<sub>7</sub> is independently selected at each occurrence from C<sub>1-6</sub>alkyl, aryl, arylC<sub>1-6</sub>alkyl, heterocyclic, heterocyclC<sub>1-6</sub> alkyl, heteroaryl, or heteroarylC<sub>1-6</sub>alkyl; and wherein each of these moieties may be optionally substituted one or two times independently at each occurrence, by halogen; hydroxy; hydroxy substituted C<sub>1-10</sub>alkyl; C<sub>1-10</sub> alkoxy; halosubstituted C<sub>1-10</sub> alkoxy; S(O)<sub>m</sub>alkyl; C(O); NR<sub>4</sub>R<sub>14</sub>'; C<sub>1-10</sub> alkyl; C<sub>3-7</sub>cycloalkyl; C<sub>3-7</sub>cycloalkylC<sub>1-10</sub> alkyl; halosubstituted C<sub>1-10</sub> alkyl; an aryl or aryl C<sub>1-4</sub> alkyl moiety, and wherein these aryl containing moieties may also be substituted one to two times by halogen, hydroxy, hydroxy substituted alkyl, C<sub>1-10</sub> alkoxy, S(O)<sub>m</sub>alkyl, amino, mono & di-substituted C<sub>1-4</sub> alkyl amino, C<sub>1-4</sub> alkyl, or CF<sub>3</sub>.

Suitably, R<sub>16</sub> and R<sub>26</sub> are each independently selected at each occurrence from hydrogen, or C<sub>1-4</sub> alkyl; or the R<sub>16</sub> and R<sub>26</sub> together with the nitrogen which they are attached form an unsubstituted or substituted heterocyclic ring of 4 to 7 members, which ring optionally contains an additional heteroatom selected from oxygen, sulfur or NR<sub>9</sub>'.

Suitably, n is 0, or an integer having a value of 1 to 10.

Suitably, X is R<sub>2</sub>, OR<sub>2</sub>', S(O)<sub>m</sub>R<sub>2</sub>', (CH<sub>2</sub>)<sub>n</sub>'N(R<sub>10</sub>')S(O)<sub>m</sub>R<sub>2</sub>', (CH<sub>2</sub>)<sub>n</sub>'N(R<sub>10</sub>')C(O)R<sub>2</sub>', (CH<sub>2</sub>)<sub>n</sub>'NR<sub>4</sub>R<sub>14</sub>, (CH<sub>2</sub>)<sub>n</sub>'N(R<sub>2</sub>')R<sub>2</sub>'', or N(R<sub>10</sub>')R<sub>h</sub>NH-C(=N-CN)NR<sub>q</sub>R<sub>q</sub>'.

In one embodiment of the invention X is N(R<sub>10</sub>')R<sub>h</sub>NH-C(=N-CN)NR<sub>q</sub>R<sub>q</sub>'.

Suitably, X<sub>1</sub> is N(R<sub>11</sub>), O, S(O)<sub>m</sub>, or CR<sub>10</sub>R<sub>20</sub>. In one embodiment of the invention, X<sub>1</sub> is N(R<sub>11</sub>), or O.

Suitably, R<sub>h</sub> is selected from an optionally substituted C<sub>1-10</sub> alkyl, -CH<sub>2</sub>-C(O)-CH<sub>2</sub>-, -CH<sub>2</sub>-CH<sub>2</sub>-O-CH<sub>2</sub>-CH<sub>2</sub>-, -CH<sub>2</sub>-C(O)N(R<sub>10</sub>')CH<sub>2</sub>-CH<sub>2</sub>-, -CH<sub>2</sub>-N(R<sub>10</sub>')C(O)CH<sub>2</sub>-, -CH<sub>2</sub>-CH(OR<sub>10</sub>')-CH<sub>2</sub>-, -CH<sub>2</sub>-C(O)O-CH<sub>2</sub>-CH<sub>2</sub>-, or -CH<sub>2</sub>-CH<sub>2</sub>-O-C(O)CH<sub>2</sub>-.

Suitably,  $R_q$  and  $R_{q'}$  are independently selected at each occurrence from hydrogen,  $C_{1-10}$  alkyl,  $C_{3-7}$  cycloalkyl,  $C_{3-7}$  cycloalkyl $C_{1-10}$  alkyl,  $C_{5-7}$  cycloalkenyl,  $C_{5-7}$  cycloalkenyl- $C_{1-10}$  alkyl, aryl, aryl $C_{1-10}$  alkyl, heteroaryl, heteroaryl $C_{1-10}$  alkyl, heterocyclic, or a heterocyclyl $C_{1-10}$  alkyl moiety, and  
 5 wherein all of the moieties, excluding hydrogen, are optionally substituted, or  $R_q$  and  $R_{q'}$  together with the nitrogen to which they are attached form an optionally substituted heterocyclic ring of 5 to 7 members, which ring may contain an additional heteroatom selected from oxygen, nitrogen or sulphur.

Suitably,  $R_{11}$  is independently selected at each occurrence from hydrogen, or  
 10  $C_{1-4}$  alkyl.

Suitably,  $R_2$  is independently selected from hydrogen, optionally substituted  $C_{1-10}$  alkyl, optionally substituted  $C_{3-7}$  cycloalkyl, optionally substituted  $C_{3-7}$  cycloalkylalkyl, optionally substituted aryl, optionally substituted aryl $C_{1-10}$  alkyl, optionally substituted heteroaryl, optionally substituted heteroaryl $C_{1-10}$  alkyl, optionally substituted heterocyclic, optionally substituted heterocyclyl $C_{1-10}$  alkyl moiety; or  $R_2$  is the moiety  
 15  $(CR_{10}R_{20})_q X_1 (CR_{10}R_{20})_q C(A_1)(A_2)(A_3)$ , or  $(CR_{10}R_{20})_q C(A_1)(A_2)(A_3)$ .

Suitably  $q'$  is 0, or an integer having a value of 1 to 6.

The  $R_2$  moieties, excluding hydrogen, may be optionally substituted one or  
 20 more times, preferably 1 to 4 times, independently at each occurrence by  $C_{1-10}$  alkyl, halo-substituted  $C_{1-10}$  alkyl,  $C_{2-10}$  alkenyl,  $C_{2-10}$  alkynyl,  $C_{3-7}$  cycloalkyl,  $C_{3-7}$  cycloalkyl $C_{1-10}$  alkyl,  $C_{5-7}$  cycloalkenyl,  $C_{5-7}$  cycloalkenyl  $C_{1-10}$  alkyl, halogen, -C(O), cyano, nitro,  $(CR_{10}R_{20})_n OR_6$ ,  $(CR_{10}R_{20})_n SH$ ,  $(CR_{10}R_{20})_n S(O)_m R_7$ ,  $(CR_{10}R_{20})_n N(R_{10'}) S(O)_2 R_7$ ,  $(CR_{10}R_{20})_n NR_e R_{e'}$ ,  
 25  $(CR_{10}R_{20})_n NR_e R_{e'} C_{1-4} alkyl NR_e R_{e'}$ ,  $(CR_{10}R_{20})_n CN$ ,  $(CR_{10}R_{20})_n S(O)_2 NR_e R_{e'}$ ,  $(CR_{10}R_{20})_n C(Z) R_6$ ,  $(CR_{10}R_{20})_n OC(Z) R_6$ ,  $(CR_{10}R_{20})_n C(Z) OR_6$ ,  $(CR_{10}R_{20})_n C(Z) NR_e R_{e'}$ ,  $(CR_{10}R_{20})_n N(R_{10'}) C(Z) R_6$ ,  $(CR_{10}R_{20})_n N(R_{10'}) C(=N(R_{10'})) NR_e R_{e'}$ ,  $(CR_{10}R_{20})_n C(=NOR_6) NR_e R_{e'}$ ,  $(CR_{10}R_{20})_n OC(Z) NR_e R_{e'}$ ,  $(CR_{10}R_{20})_n N(R_{10'}) C(Z) NR_e R_{e'}$ , or  
 30  $(CR_{10}R_{20})_n N(R_{10'}) C(Z) OR_7$ .

Suitably,  $R_e$  and  $R_{e'}$  are each independently selected at each occurrence from hydrogen,  $C_{1-4}$  alkyl,  $C_{3-7}$  cycloalkyl,  $C_{3-7}$  cycloalkyl $C_{1-4}$  alkyl, aryl, aryl- $C_{1-4}$  alkyl, heteroaryl or a heteroaryl  $C_{1-4}$  alkyl moiety, which moieties may be optionally substituted; or  $R_e$  and  $R_{e'}$  together with the nitrogen which they are attached form an  
 35 optionally substituted heterocyclic ring of 4 to 7 members, which ring optionally contains an additional heteroatom selected from oxygen, sulfur or  $NR_9$ ; and wherein each of these moieties, including the cyclized ring, and excluding hydrogen, may be

substituted 1 to 4 times, independently at each occurrence by halogen; hydroxy; hydroxy substituted C<sub>1-10</sub>alkyl; C<sub>1-10</sub> alkoxy; halosubstituted C<sub>1-10</sub> alkoxy; C<sub>1-10</sub>alkyl; halosubstituted C<sub>1-4</sub> alkyl; S(O)<sub>m</sub>R<sub>F</sub>; C(O)R<sub>j</sub>; C(O)OR<sub>j</sub>; (CR<sub>10</sub>R<sub>20</sub>)<sub>n</sub>N(R<sub>10'</sub>)C(Z)OR<sub>7</sub>; (CR<sub>10</sub>R<sub>20</sub>)<sub>n</sub> N(R<sub>10'</sub>)C(Z)NR<sub>d</sub>R<sub>d'</sub>; C(O)NR<sub>4</sub>R<sub>14'</sub>; NR<sub>4</sub>C(O)C<sub>1-10</sub>alkyl; NR<sub>4</sub>C(O)aryl; cyano; nitro; NR<sub>4</sub>R<sub>14'</sub>; C<sub>1-10</sub> alkyl; C<sub>3-7</sub>cycloalkyl; C<sub>3-7</sub>cycloalkyl C<sub>1-10</sub> alkyl; halosubstituted C<sub>1-10</sub> alkyl; aryl, arylC<sub>1-4</sub>alkyl, heterocyclic, heterocyclic C<sub>1-4</sub> alkyl, heteroaryl, or hetero C<sub>1-4</sub> alkyl, and wherein these aryl, heterocyclic or heteroaryl containing moieties may be optionally substituted one to two times independently at each occurrence by halogen, C<sub>1-4</sub> alkyl, hydroxy, hydroxy substituted C<sub>1-4</sub> alkyl, C<sub>1-10</sub> alkoxy, S(O)<sub>m</sub>alkyl, amino, mono & di-substituted C<sub>1-4</sub> alkyl amino, C<sub>1-4</sub> alkyl, or CF<sub>3</sub>.

Suitably, R<sub>F</sub> is independently selected at each occurrence from hydrogen, C<sub>1-10</sub>alkyl, aryl, aryl C<sub>1-10</sub>alkyl, heteroaryl, heteroaryl C<sub>1-10</sub>alkyl, heterocyclic, or a heterocyclic C<sub>1-10</sub>alkyl moiety, and wherein these moieties, excluding hydrogen, may be optionally substituted.

When X is R<sub>2</sub> and R<sub>2</sub> is an optionally substituted heterocyclic or heterocyclic alkyl, the heterocyclic containing moiety is suitably selected from tetrahydropyrrole, tetrahydropyran, tetrahydrofuran, tetrahydrothiophene (including oxidized versions of the sulfur moiety), aziridinyl, pyrrolinyl, pyrrolidinyl, 2-oxo-1-pyrrolidinyl, 3-oxo-1-pyrrolidinyl, 1,3-benzdioxol-5-yl, imidazolinyl, imidazolidinyl, indolinyl, pyrazolinyl, pyrazolidinyl, piperidinyl, piperazinyl, morpholino and thiomorpholino (including oxidized versions of the sulfur moiety).

In one embodiment, R<sub>2</sub> is an optionally substituted piperidinyl or piperazinyl ring.

In another embodiment, when R<sub>2</sub> is an optionally substituted heterocyclic or heterocyclic alkyl ring the ring is substituted one or more times independently by an optionally substituted heterocyclic, heterocyclic alkyl, aryl, arylalkyl, alkyl, (CR<sub>10</sub>R<sub>20</sub>)<sub>n</sub>NR<sub>e</sub>R<sub>e'</sub>, or (CR<sub>10</sub>R<sub>20</sub>)<sub>n</sub> N(R<sub>10'</sub>)C(Z)OR<sub>7</sub>. The second heterocyclic ring is suitably selected from an optionally substituted tetrahydropyrrole, tetrahydropyran, tetrahydrofuran, tetrahydrothiophene (including oxidized versions of the sulfur moiety), aziridinyl, pyrrolinyl, pyrrolidinyl, 2-oxo-1-pyrrolidinyl, 3-oxo-1-pyrrolidinyl, 1,3-benzdioxol-5-yl, imidazolinyl, imidazolidinyl, indolinyl, pyrazolinyl, pyrazolidinyl, piperidinyl, piperazinyl, diazepine, morpholino or thiomorpholino (including oxidized versions of the sulfur moiety). Suitably, the second heterocyclic ring is selected from morpholino, piperidine, or pyrrolidinyl.

In one embodiment, R<sub>2</sub> is a 4-amino-1-piperidinyl, 1,1-dimethylethyl)oxy]-carbonyl} amino)-1-piperidinyl, 4-methyl-1-piperazinyl, 4-ethyl-1-piperazinyl, 4-

propyl-1-piperazinyl, 4-butyl-1-piperazinyl, 4-(methylamino)-1-piperidinyl, 1,1-dimethylethyl-4-piperidinyl}methylcarbamate, 4-phenyl-1-piperazinyl, 1,4'-bipiperidin-1'-yl, 4-(1-pyrrolidinyl)-1-piperidinyl, 4-methyl-1,4'-bipiperidin-1'-yl, 4-(4-morpholinyl)-1-piperidinyl, 4-(diphenylmethyl)-1-piperazinyl, or 4-methylhexahydro-1H-1,4-diazepin-1-yl.

Suitably,  $R_2'$  is independently selected at each occurrence from hydrogen,  $C_{1-10}$  alkyl,  $C_{3-7}$  cycloalkyl,  $C_{3-7}$  cycloalkylalkyl, aryl, aryl $C_{1-10}$  alkyl, heteroaryl, heteroaryl $C_{1-10}$  alkyl, heterocyclic, or a heterocyclyl $C_{1-10}$  alkyl moiety, and wherein each of these moieties, excluding hydrogen, may be optionally substituted 1 to 4 times, independently, at each occurrence, by  $C_{1-10}$  alkyl, halo-substituted  $C_{1-10}$  alkyl,  $C_{2-10}$  alkenyl,  $C_{2-10}$  alkynyl,  $C_{3-7}$  cycloalkyl,  $C_{3-7}$ cycloalkyl $C_{1-10}$ alkyl,  $C_{5-7}$ cycloalkenyl,  $C_{5-7}$  cycloalkenyl  $C_{1-10}$  alkyl, halogen, -C(O), cyano, nitro, aryl, aryl  $C_{1-10}$  alkyl, heteroaryl, heteroaryl $C_{1-10}$  alkyl, heterocyclic, heterocyclyl $C_{1-10}$  alkyl,  $(CR_{10}R_{20})_nOR_6$ ,  $(CR_{10}R_{20})_nSH$ ,  $(CR_{10}R_{20})_nS(O)_mR_7$ ,  $(CR_{10}R_{20})_nN(R_{10}')S(O)_2R_7$ ,  $(CR_{10}R_{20})_nNR_eR_{e'}$ ,  $(CR_{10}R_{20})_nNR_eR_{e'}C_{1-4}alkylNR_eR_{e'}$ ,  $(CR_{10}R_{20})_nCN$ ,  $(CR_{10}R_{20})_nS(O)_2NR_eR_{e'}$ ,  $(CR_{10}R_{20})_nC(Z)R_6$ ,  $(CR_{10}R_{20})_nOC(Z)R_6$ ,  $(CR_{10}R_{20})_nC(Z)OR_6$ ,  $(CR_{10}R_{20})_nC(Z)NR_eR_{e'}$ ,  $(CR_{10}R_{20})_nN(R_{10}')C(Z)R_6$ ,  $(CR_{10}R_{20})_nN(R_{10}')C(=N(R_{10}'))NR_eR_{e'}$ ,  $(CR_{10}R_{20})_nC(=NOR_6)NR_eR_{e'}$ ,  $(CR_{10}R_{20})_nOC(Z)NR_eR_{e'}$ ,  $(CR_{10}R_{20})_nN(R_{10}')C(Z)NR_eR_{e'}$ , or  $(CR_{10}R_{20})_nN(R_{10}')C(Z)OR_7$ .

In one embodiment, when X is  $(CH_2)_nN(R_2')(R_2'')$ , one of  $R_2'$ , or  $R_2''$  is hydrogen, or methyl.

In one embodiment, when  $R_2'$  is an optionally substituted heterocyclic or heterocyclyl $C_{1-10}$  alkyl the heterocyclic containing moiety is substituted one or more time independently by  $C_{1-10}$  alkyl, aryl, heterocyclic,  $(CR_{10}R_{20})_nNR_eR_{e'}$ ,  $(CR_{10}R_{20})_nN(R_{10}')C(Z)OR_7$ , or  $(CR_{10}R_{20})_nC(Z)OR_6$ . More specifically, methyl, ethyl,  $NHC(O)O-CCH_3$ ,  $N(CH_3)C(O)O-CCH_3$ , amino, methylamino, dimethylamino, phenyl, piperidine, pyrrolidine, 1-ethylpropyl, 4-methyl-1,4'-bipiperidin-1'-yl, 1,4'-bipiperidin-1'-yl, morpholino,

In one embodiment, when X is  $(CH_2)_nN(R_2')(R_2'')$ ,  $R_2'$  is an optionally substituted  $C_{1-10}$  alkyl, cycloalkyl, heterocyclic, heterocyclyl  $C_{1-10}$  alkyl, heteroarylalkyl. Suitably, when  $R_2'$  is an optionally substituted cycloalkyl it is a cyclohexyl ring. In one embodiment the cyclohexyl ring is optionally substituted one or more times by  $(CR_{10}R_{20})_nNR_eR_{e'}$ .

Suitably, when  $R_2'$  is an optionally substituted heterocyclic, or a heterocyclyl $C_{1-10}$  alkyl, the ring is selected from tetrahydropyrrole, tetrahydropyran, tetrahydrofuran, tetrahydrothiophene (including oxidized versions of the sulfur moiety), aziridinyl, pyrrolinyl, pyrrolidinyl, 2-oxo-1-pyrrolidinyl, 3-oxo-1-pyrrolidinyl, 1,3-benzodioxol-5-yl, imidazolinyl, imidazolidinyl, indolinyl, pyrazolinyl, pyrazolidinyl, piperidinyl, piperazinyl, diazepine, hexahydro-1-H-azepine, morpholino or thiomorpholino (including oxidized versions of the sulfur moiety). Preferably, the ring is a piperidine, piperazine, pyrrolidinyl, 2-oxo-1-pyrrolidinyl, morpholino, hexahydro-1-H-azepine ring. In one embodiment, the rings are substituted one or more times, suitably 1 to 4 times, independently by  $C_{1-10}$  alkyl, aryl, arylalkyl,  $(CR_{10}R_{20})_nNR_eR_{e'}$ , or  $(CR_{10}R_{20})_nN(R_{10}')C(Z)OR_7$ .

In one embodiment,  $(CH_2)_nN(R_2')(R_2'')$  is 1-(phenylmethyl)-4-piperidinamine, 2-[4-(phenylmethyl)-1-piperazinyl]ethylamine, 2-(1-piperidinyl)ethylamine, 2-(1-methyl-2-pyrrolidinyl)ethylamine, 1-[(phenylmethyl)-3-pyrrolidinyl]amine, 3-[(1-pyrrolidinyl)propyl]amine, 3-[(hexahydro-1H-azepin-1-yl)propyl]amine, (1-methyl-4-piperidinyl)amine, 3-[(4-morpholinyl)propyl]amine, 3-[(2-oxo-1-pyrrolidinyl)propyl]amine, 2-[(4-morpholinyl)ethyl]amine, 2-[(1-pyrrolidinyl)ethyl]-amine, or [(1-ethyl-2-pyrrolidinyl)methyl]amino.

In one embodiment when X is  $(CH_2)_nN(R_2')(R_2'')$ , and  $R_2'$  is an optionally substituted  $C_{1-10}$  alkyl, the alkyl is substituted one or more times independently by  $(CR_{10}R_{20})_nNR_eR_{e'}$  or  $(CR_{10}R_{20})_nNR_eR_{e'}C_{1-4}alkylNR_eR_{e'}$ . In one embodiment  $R_e$  and  $R_{e'}$  are independently an optionally substituted  $C_{1-4}$  alkyl, such as methyl, ethyl, isopropyl, n-butyl, or t-butyl. Preferably,  $(CH_2)_nN(R_2')(R_2'')$  is 3-(dimethylamino)propyl(methyl)amine, 3-(diethylamino)propylamine, propylamine, (2,2-dimethylpropyl)amine, (2-hydroxypropyl)amino, 2-(dimethylamino)ethylamine, 2-(dimethylamino)ethyl(methyl)amine, 3-(dimethylamino)propylamine, 2-(dimethylamino)ethyl(methyl)amine, 3-(diethylamino)propylamine, 2-(methylamino)ethylamine, [(1-methylethyl)amino]ethylamine, 3-(diethylamino)propylamine, 3-(dibutylamino)propylamine, 3-[(1-methylethyl)amino]propylamine, 3-(1,1-dimethylethyl)aminopropylamine, 3-(dimethylamino)-2,2-dimethylpropylamine, 4-(diethylamino)-1-methylbutylamine, or 3-[[3-(dimethylamino)propyl]-(methyl)amino]propyl(methyl)amine.

Suitably,  $R_2''$  is selected from hydrogen,  $C_{1-10}$  alkyl,  $C_{3-7}$  cycloalkyl,  $C_{3-7}$ cycloalkylalkyl, aryl, aryl $C_{1-10}$  alkyl, heteroaryl, heteroaryl $C_{1-10}$  alkyl, heterocyclic, or a heterocyclyl $C_{1-10}$  alkyl moiety, and wherein the moieties, excluding hydrogen, may be optionally substituted 1 to 4 times, independently, at

each occurrence by C<sub>1-10</sub> alkyl, halo-substituted C<sub>1-10</sub> alkyl, C<sub>2-10</sub> alkenyl, C<sub>2-10</sub> alkynyl, C<sub>3-7</sub> cycloalkyl, C<sub>3-7</sub>cycloalkylC<sub>1-10</sub>alkyl, C<sub>5-7</sub>cycloalkenyl, C<sub>5-7</sub> cycloalkenyl C<sub>1-10</sub> alkyl, halogen, -C(O), cyano, nitro, aryl, aryl C<sub>1-10</sub> alkyl, heteroaryl, heteroarylC<sub>1-10</sub> alkyl, heterocyclic, heterocyclylC<sub>1-10</sub> alkyl,

- 5 (CR<sub>10</sub>R<sub>20</sub>)<sub>n</sub>OR<sub>6</sub>, (CR<sub>10</sub>R<sub>20</sub>)<sub>n</sub>SH, (CR<sub>10</sub>R<sub>20</sub>)<sub>n</sub>S(O)<sub>m</sub>R<sub>7</sub>,  
 (CR<sub>10</sub>R<sub>20</sub>)<sub>n</sub>N(R<sub>10'</sub>)S(O)<sub>2</sub>R<sub>7</sub>, (CR<sub>10</sub>R<sub>20</sub>)<sub>n</sub>NR<sub>e</sub>R<sub>e'</sub>,  
 (CR<sub>10</sub>R<sub>20</sub>)<sub>n</sub>NR<sub>e</sub>R<sub>e'</sub>C<sub>1-4</sub>alkylNR<sub>e</sub>R<sub>e'</sub>, (CR<sub>10</sub>R<sub>20</sub>)<sub>n</sub>CN, (CR<sub>10</sub>R<sub>20</sub>)<sub>n</sub>S(O)<sub>2</sub>NR<sub>e</sub>R<sub>e'</sub>,  
 (CR<sub>10</sub>R<sub>20</sub>)<sub>n</sub>C(Z)R<sub>6</sub>, (CR<sub>10</sub>R<sub>20</sub>)<sub>n</sub>OC(Z)R<sub>6</sub>, (CR<sub>10</sub>R<sub>20</sub>)<sub>n</sub>C(Z)OR<sub>6</sub>,  
 (CR<sub>10</sub>R<sub>20</sub>)<sub>n</sub>C(Z)NR<sub>e</sub>R<sub>e'</sub>, (CR<sub>10</sub>R<sub>20</sub>)<sub>n</sub>N(R<sub>10'</sub>)C(Z)R<sub>6</sub>,  
 10 (CR<sub>10</sub>R<sub>20</sub>)<sub>n</sub>N(R<sub>10'</sub>)C(=N(R<sub>10'</sub>))NR<sub>e</sub>R<sub>e'</sub>, (CR<sub>10</sub>R<sub>20</sub>)<sub>n</sub>C(=NOR<sub>6</sub>)NR<sub>e</sub>R<sub>e'</sub>,  
 (CR<sub>10</sub>R<sub>20</sub>)<sub>n</sub>OC(Z)NR<sub>e</sub>R<sub>e'</sub>, (CR<sub>10</sub>R<sub>20</sub>)<sub>n</sub>N(R<sub>10'</sub>)C(Z)NR<sub>e</sub>R<sub>e'</sub>, or  
 (CR<sub>10</sub>R<sub>20</sub>)<sub>n</sub>N(R<sub>10'</sub>)C(Z)OR<sub>7</sub>; or wherein R<sub>2</sub>' is the moiety  
 (CR<sub>10</sub>R<sub>20</sub>)<sub>t</sub>X<sub>1</sub>(CR<sub>10</sub>R<sub>20</sub>)<sub>q</sub>C(A<sub>1</sub>)(A<sub>2</sub>)(A<sub>3</sub>).

Suitably, t is an integer having a value of 2 to 6.

- 15 Suitably, q is 0 or an integer having a value of 1 to 10.

Suitably, A<sub>1</sub> is an optionally substituted C<sub>1-10</sub> alkyl, heterocyclic, heterocyclic C<sub>1-10</sub> alkyl, heteroaryl, heteroaryl C<sub>1-10</sub> alkyl, aryl, or aryl C<sub>1-10</sub> alkyl.

Suitably, A<sub>2</sub> is an optionally substituted C<sub>1-10</sub> alkyl, heterocyclic, heterocyclic C<sub>1-10</sub> alkyl, heteroaryl, heteroaryl C<sub>1-10</sub> alkyl, aryl, or aryl C<sub>1-10</sub> alkyl.

- 20 Suitably, A<sub>3</sub> is hydrogen or is an optionally substituted C<sub>1-10</sub> alkyl.

The A<sub>1</sub>, A<sub>2</sub>, and A<sub>3</sub> C<sub>1-10</sub> alkyl moieties may optionally substituted one or more times, independently, at each occurrence preferably from 1 to 4 times, with halogen, such as chlorine, fluorine, bromine, or iodine; halo-substituted C<sub>1-10</sub>alkyl, such as CF<sub>3</sub>, or CHF<sub>2</sub>CF<sub>3</sub>; C<sub>2-10</sub> alkenyl, C<sub>2-10</sub> alkynyl, C<sub>3-7</sub> cycloalkyl,

- 25 C<sub>3-7</sub>cycloalkylC<sub>1-10</sub>alkyl, C<sub>5-7</sub>cycloalkenyl, C<sub>5-7</sub> cycloalkenylC<sub>1-10</sub>alkyl,  
 (CR<sub>10</sub>R<sub>20</sub>)<sub>n</sub>OR<sub>6</sub>, (CR<sub>10</sub>R<sub>20</sub>)<sub>n</sub>SH, (CR<sub>10</sub>R<sub>20</sub>)<sub>n</sub>S(O)<sub>m</sub>R<sub>7</sub>,  
 (CR<sub>10</sub>R<sub>20</sub>)<sub>n</sub>N(R<sub>10'</sub>)S(O)<sub>2</sub>R<sub>7</sub>, (CR<sub>10</sub>R<sub>20</sub>)<sub>n</sub>NR<sub>4</sub>R<sub>14</sub>, (CR<sub>10</sub>R<sub>20</sub>)<sub>n</sub>CN,  
 (CR<sub>10</sub>R<sub>20</sub>)<sub>n</sub>S(O)<sub>2</sub>NR<sub>4</sub>R<sub>14</sub>, (CR<sub>10</sub>R<sub>20</sub>)<sub>n</sub>C(Z)R<sub>6</sub>, (CR<sub>10</sub>R<sub>20</sub>)<sub>n</sub>OC(Z)R<sub>6</sub>,  
 (CR<sub>10</sub>R<sub>20</sub>)<sub>n</sub>C(Z)OR<sub>6</sub>, (CR<sub>10</sub>R<sub>20</sub>)<sub>n</sub>C(Z)NR<sub>4</sub>R<sub>14</sub>, (CR<sub>10</sub>R<sub>20</sub>)<sub>n</sub>N(R<sub>10'</sub>)C(Z)R<sub>6</sub>,  
 30 (CR<sub>10</sub>R<sub>20</sub>)<sub>n</sub>N(R<sub>10'</sub>)C(=N(R<sub>10'</sub>))NR<sub>4</sub>R<sub>14</sub>, (CR<sub>10</sub>R<sub>20</sub>)<sub>n</sub>OC(Z)NR<sub>4</sub>R<sub>14</sub>,  
 (CR<sub>10</sub>R<sub>20</sub>)<sub>n</sub>N(R<sub>10'</sub>)C(Z)NR<sub>4</sub>R<sub>14</sub>, or (CR<sub>10</sub>R<sub>20</sub>)<sub>n</sub>N(R<sub>10'</sub>)C(Z)OR<sub>7</sub>.

In another embodiment of the present invention, X is R<sub>2</sub>, and R<sub>2</sub> is (CR<sub>10</sub>R<sub>20</sub>)<sub>q'</sub>X<sub>1</sub>(CR<sub>10</sub>R<sub>20</sub>)<sub>q</sub>C(A<sub>1</sub>)(A<sub>2</sub>)(A<sub>3</sub>), or (CR<sub>10</sub>R<sub>20</sub>)<sub>q'</sub>C(A<sub>1</sub>)(A<sub>2</sub>)(A<sub>3</sub>). In a further embodiment, q' is 0.

- 35 In another embodiment when R<sub>2</sub> is the moiety

(CR<sub>10</sub>R<sub>20</sub>)<sub>q'</sub>X<sub>1</sub>(CR<sub>10</sub>R<sub>20</sub>)<sub>q</sub>C(A<sub>1</sub>)(A<sub>2</sub>)(A<sub>3</sub>), q' is 0, X<sub>1</sub> is nitrogen, q is 0 or 1, A<sub>1</sub> is an optionally substituted heterocyclic or heterocyclic alkyl, and A<sub>2</sub> is an optionally

substituted aryl. More specifically,  $R_2$  is 2-phenyl-2-(1-pyrrolidinyl)ethyl]amino, or 1-phenyl-2-(1-pyrrolidinyl)ethyl]amino.

In one embodiment of the invention, one or more of the  $A_1$ ,  $A_2$  and  $A_3$  moieties are substituted with  $(CR_{10}R_{20})_nOR_6$ . In another embodiment of the invention, the  $R_6$  substituent in  $(CR_{10}R_{20})_nOR_6$  is hydrogen.

In yet another embodiment of the present invention,  $X$  is  $R_2$  and  $R_2$  is  $(CR_{10}R_{20})_{q'}C(A_1)(A_2)(A_3)$ , such as  $CH(CH_2OH)_2$ , or  $C(CH_3)(CH_2OH)_2$ ; or wherein  $R_2$  is  $(CR_{10}R_{20})_{q'}X_1(CR_{10}R_{20})_qC(A_1)(A_2)(A_3)$  and  $q'$  is 0, and the moiety is  $X_1(CR_{10}R_{20})_qCH(CH_2OH)_2$ , or  $X_1(CR_{10}R_{20})_qC(CH_3)(CH_2OH)_2$ ; in another embodiment  $X_1$  is oxygen or nitrogen.

In one embodiment of the present invention  $X$  is  $R_2$ ,  $OR_2$ ,  $(CH_2)_nNR_4R_{14}$ , or  $(CH_2)_nN(R_2')(R_2'')$ .

In another embodiment  $X$  is  $S(O)_mR_2$ ,  $(CH_2)_nNR_4R_{14}$ , or  $(CH_2)_nN(R_2')(R_2'')$ .

In yet another embodiment,  $X$  is  $(CH_2)_nNR_4R_{14}$ , or  $(CH_2)_nN(R_2')(R_2'')$ .

In yet another embodiment,  $X$  is  $(CH_2)_nNR_4R_{14}$ .

In yet another embodiment,  $X$  is  $(CH_2)_nN(R_2')(R_2'')$ .

In one embodiment of the present invention  $X$  is  $R_2$ ,  $OR_2$ ,  $(CH_2)_nNR_4R_{14}$ , or  $(CH_2)_nN(R_2')(R_2'')$ .

Suitably, when  $X$  is  $(CH_2)_nNR_4R_{14}$ , then  $R_4$  and  $R_{14}$  are  $C_{1-10}$  alkyl, aryl, aryl- $C_{1-4}$  alkyl, heterocyclic, heterocyclic  $C_{1-4}$  alkyl, heteroaryl or heteroaryl  $C_{1-4}$  alkyl. Suitably, the  $C_{1-4}$  alkyl may be substituted one or more times, independently at each occurrence with  $NR_4'R_{14}'$ ; halogen, hydroxy, alkoxy,  $C(O)NR_4'R_{14}'$ ; or  $NR_4'C(O)C_{1-10}$ alkyl. Preferably, the  $C_{1-4}$  alkyl is substituted with  $NR_4'R_{14}'$ .

In one embodiment at least one of  $R_4$  and  $R_{14}$  may be hydrogen when  $R_4$  and  $R_{14}$  are not cyclized. In another embodiment neither  $R_4$  and  $R_{14}$  is hydrogen.

In one embodiment when  $X$  is  $(CH_2)_nNR_4R_{14}$ , one of  $R_4$  and  $R_{14}$  are hydrogen, and the other is an optionally substituted heteroaryl  $C_{1-4}$  alkyl. Suitably, the optionally substituted heteroaryl alkyl is an imidazolyl alkyl, such as a 1*H*-imidazol-2-yl-methyl group.

In another embodiment when  $X$  is  $(CH_2)_nNR_4R_{14}$  and one of  $R_4$  and  $R_{14}$  is a heteroaryl  $C_{1-4}$  alkyl moiety, the heteroaryl ring is selected from an optionally substituted thienyl, pyrrolyl, oxazolyl, thiazolyl, isoxazolyl, isothiazolyl, imidazolyl, pyrazolyl, triazolyl, pyridazinyl, pyrimidinyl, pyrazinyl, benzoxazolyl, benzimidazolyl, and benzothiazolyl. Suitably, the heteroaryl  $C_{1-4}$  alkyl is selected from an optionally substituted pyrrolyl, oxazolyl, thiazolyl, isoxazolyl, imidazolyl, benzoxazolyl, benzimidazolyl, and benzothiazolyl.

In another embodiment when X is  $(\text{CH}_2)_n\text{NR}_4\text{R}_{14}$  and one of  $\text{R}_4$  and  $\text{R}_{14}$  is a heterocyclic  $\text{C}_{1-4}$  alkyl moiety, then the optionally substituted heterocyclic ring is selected from an optionally substituted tetrahydropyrrole, tetrahydropyran, tetrahydrofuran, pyrrolinyl, pyrrolidinyl, imidazolynyl, imidazolidinyl, indolynyl, pyrazolynyl, pyrazolidinyl, piperidinyl, piperazinyl, and morpholino. Suitably, the heterocyclic  $\text{C}_{1-4}$  alkyl moiety is selected from optionally substituted pyrrolinyl, pyrrolidinyl, piperidinyl, piperazinyl, and morpholino.

In another embodiment when X is  $(\text{CH}_2)_n\text{NR}_4\text{R}_{14}$  and  $\text{R}_4$  and  $\text{R}_{14}$  together with the nitrogen cyclize to form an optionally substituted ring, such as described above, such rings include, but are not limited to pyrrolidine, piperidine, piperazine, diazepine, and morpholine.

In one embodiment when X is  $(\text{CH}_2)_n\text{NR}_4\text{R}_{14}$ , the  $\text{R}_4$  and  $\text{R}_{14}$  substituents cyclize to form a heterocyclic 5 or 6 membered ring, which ring is optionally substituted as defined herein. When the  $\text{R}_4$  and  $\text{R}_{14}$  substituents cyclize to form a 4 to 7 membered ring, the optional substituents are suitably selected from an optionally substituted alkyl, an optionally substituted aryl, an optionally substituted heteroaryl, optionally substituted heterocyclic,  $(\text{CR}_{10}\text{R}_{20})_n\text{N}(\text{R}_{10}')\text{C}(\text{Z})\text{OR}_7$ ,  $\text{NR}_4'\text{R}_{14}'$ , or a  $\text{C}_{1-10}$  alkyl substituted one or more times by an optionally substituted aryl. Such substituents more specifically include phenyl, pyrrolidinyl, morpholino, piperazinyl, 4-methyl-1-piperazinyl, piperidinyl, 2-oxo-2,3-dihydro-1*H*-benzimidazol-1-yl, 5-chloro-2-oxo-2,3-dihydro-1*H*-benzimidazol-1-yl, diphenylmethyl, methyl, ethyl, propyl, butyl, amino, methylamino, and dimethylamino.

In one embodiment the X substituent is a 1,4'-bipiperin-1-yl ring which may be optionally substituted such as in 4-methyl-1,4'-bipiperin-1-yl; 4-piperidinylamino, 4-amino-1-piperidinyl, 2,2,6,6-tetramethyl-4-piperidinyl)amino, 4-methyl-1-piperazinyl, (4-morpholinyl)-1-piperidinyl, (4-methyl-1-piperazinyl)-1-piperidinyl, 4-ethyl-1-piperazinyl, (2-oxo-2,3-dihydro-1*H*-benzimidazol-1-yl)-1-piperidinyl, 5-chloro-(2-oxo-2,3-dihydro-1*H*-benzimidazol-1-yl)-1-piperidinyl, 4-(1-pyrrolidinyl)-1-piperidinyl, 4-(diphenylmethyl)-1-piperazinyl, 4-methylhexahydro-1*H*-1,4-diazepin-1-yl, 4-propyl-1-piperazinyl, or 4-butyl-1-piperazinyl. In a further embodiment, the X substituent is an optionally substituted 1,4'-bipiperin-1'-yl ring, a 4-amino-1-piperidinyl, or a 2,2,6,6-tetramethyl-4-piperidinyl)amino.

In another embodiment, when X is  $(\text{CH}_2)_n\text{N}(\text{R}_{2'}) (\text{R}_{2''})$ , and  $\text{R}_{2'}$  is an optionally substituted  $\text{C}_{1-10}$  alkyl moiety, and the alkyl is substituted by  $(\text{CR}_{10}\text{R}_{20})_n\text{NR}_e\text{R}_{e'}$ , and  $\text{R}_e$  and  $\text{R}_{e'}$  are hydrogen, or an optionally substituted  $\text{C}_{1-10}$  alkyl. Suitably, the X moiety is 3-(diethylamino)propylamino, 3-

(dimethylamino)propyl(methyl)amino, 3-(dimethylamino)propyl(methyl)amino, 2-(dimethylamino)ethylamino, 1-(methylethyl)amino-propylamino, (1,1-dimethylethyl)aminopropylamino, (1-methylethyl)aminoethylamino, 2-(methylamino)ethylamino, 2-aminoethyl(methyl)amino, or a 2-(dimethylamino)ethyl(methyl)amino.

In another embodiment when X is  $(CH_2)_nN(R_{2'}) (R_{2''})$ , and  $R_{2'}$  moiety is an optionally substituted heteroaryl  $C_{1-10}$  alkyl, the heteroaryl moiety is suitably an optionally substituted imidazole.

In one embodiment of the invention at least one of  $R_4$  and  $R_{14}$  may be hydrogen when  $R_4$  and  $R_{14}$  are not cyclized.

In one embodiment  $R_3$  is a 2,6-difluoro phenyl,  $R_{1'}$  is independently selected at each occurrence from hydrogen, fluorine, or methyl; g is 1 or 2; and  $R_1$  is selected from  $C(Z)N(R_{10'}) (CR_{10}R_{20})_vR_b$ , or  $C(Z)O(CR_{10}R_{20})_vR_b$ , or  $N(R_{10'})C(Z)(CR_{10}R_{20})_vR_b$ . Preferably,  $R_1$  is selected from  $C(Z)N(R_{10'}) (CR_{10}R_{20})_vR_b$ . In another embodiment, the  $R_b$  moiety is selected from thiazolyl,  $C_{1-10}$  alkyl or an optionally substituted aryl. In another embodiment the  $R_b$  moiety is propyl or 4-fluorophenyl. In another embodiment, the  $R_b$  moiety is thiazolyl.

In another embodiment, X is suitably selected from (1*H*-imidazol-2-ylmethyl)amino or 4-methyl-1,4'-bipiperidin-1'-yl, 2,2,6,6-tetramethyl-4-piperidiny)amino, 4-amino-1-piperidiny, 3-(diethylamino)propylamino, 3-(dimethylamino)propyl(methyl)amino, 3-(dimethylamino)propyl(methyl)amino, 2-(dimethylamino)ethylamino, 1-methylethyl)amino-propylamino, (1,1-dimethylethyl)aminopropylamino, (1-methylethyl)aminoethylamino, 2-(methylamino)ethylamino, 2-aminoethyl(methyl)amino, or 2-(dimethylamino)ethyl(methyl)amino.

In one embodiment,  $R_3$  is a 2,6-difluoro phenyl,  $R_{1'}$  is independently selected at each occurrence from hydrogen, fluorine, or methyl; g is 1 or 2; and  $R_1$  is selected from  $C(Z)N(R_{10'}) (CR_{10}R_{20})_vR_b$ ,  $R_b$  moiety is  $C_{1-10}$  alkyl or an optionally substituted aryl, preferably propyl or 4-fluorophenyl, or optionally substituted heteroaryl, preferably thiazolyl; X is  $(CH_2)_nN(R_{2'}) (R_{2''})$ , and n is 0. In another embodiment, X is  $(CH_2)_nN(R_{2'}) (R_{2''})$ ,  $R_{2''}$  is hydrogen, n is 0, and  $R_{2'}$  is an alkyl substituted by  $(CR_{10}R_{20})_nNR_eR_e'$ . In a further embodiment,  $R_e$  and  $R_e'$  are independently selected from an optionally substituted  $C_{1-4}$  alkyl, such as methyl, ethyl, isopropyl, n-butyl, or t-butyl, preferably ethyl.

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Another embodiment of the invention is the genus of compounds of formula (Ic), a subgenus of compounds of Formula (I) and (Ia) wherein  $R_1$  is  $C(Z)N(R_{10}')(CR_{10}R_{20})_vR_b$ , and  $R_b$  is an optionally substituted heteroaryl, an optionally substituted heteroaryl  $C_{1-10}$  alkyl, optionally substituted heterocyclic and optionally substituted heterocyclic  $C_{1-10}$  alkyl. The remaining groups are the same as enumerated above for Formula (I) and (Ia).

In another embodiment for compounds of Formula (Ic),  $R_1$  is  $C(Z)N(R_{10}')(CR_{10}R_{20})_vR_b$ , and  $R_b$  is an optionally substituted heteroaryl, or an optionally substituted heteroaryl  $C_{1-10}$  alkyl.

Suitably, the heteroaryl, heteroarylalkyl, heterocyclic and heterocyclicalkyl moieties are as defined above for Formula (I) and (Ia). A preferred heteroaryl ring is an optionally substituted thiazolyl ring, pyridyl, or thiophene ring.

In one embodiment of this invention, for compounds of Formula (I), (Ia), and (Ic), as well as the remaining formulas herein,  $R_1'$  is independently selected hydrogen, halogen,  $C_{1-4}$  alkyl, or halo-substituted- $C_{1-4}$  alkyl. In another embodiment,  $R_1'$  is independently selected from hydrogen, fluorine, chlorine, methyl, or  $CF_3$ . In one embodiment when  $R_1'$  is substituted on the phenyl ring in the ortho position, and a second  $R_1'$  moiety is also substituted on the ring, then preferably the second substitution is not in the other ortho position.

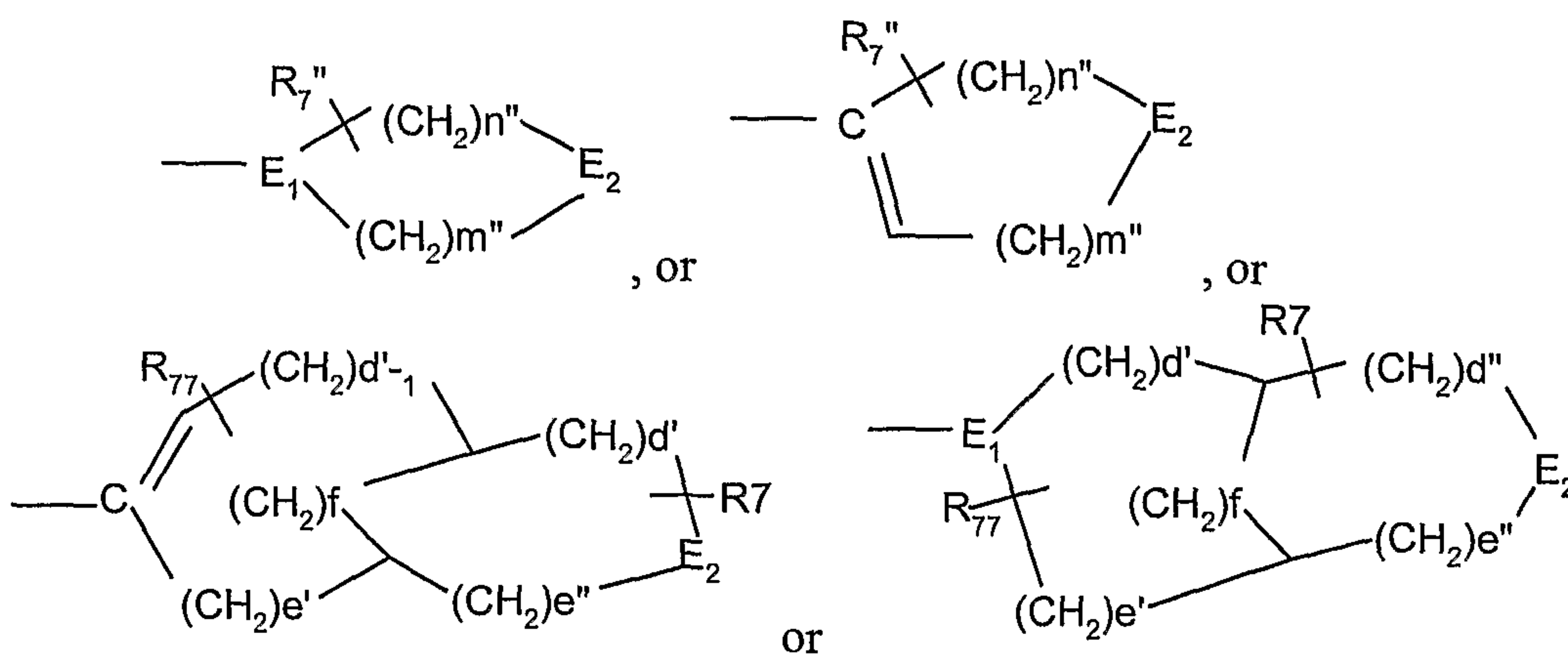
In one embodiment of the invention,  $g$  is 1 or 2.

Suitably, in one embodiment when  $R_3$  is an aryl moiety, it is a phenyl ring, and the phenyl ring is optionally substituted, independently at each occurrence, one or more times, suitably 1 to 4 times by halogen,  $C_{1-4}$  alkyl, or halo-substituted- $C_{1-4}$  alkyl. The phenyl ring may suitably be substituted in the 2, 4, or 6-position, or disubstituted in the 2,4- position, such as 2-fluoro, 4-fluoro, 2,4-difluoro, 2,6-difluoro, 6-difluoro, or 2-methyl-4-fluoro; or tri-substituted in the 2,4,6-position, such as 2,4,6-trifluoro. Preferably,  $R_3$  is a 2,6-difluoro phenyl.

In one embodiment,  $R_3$  is a 2,6-difluoro phenyl,  $R_1'$  is independently selected at each occurrence from hydrogen, fluorine, or methyl;  $g$  is 1 or 2.

In another embodiment of the present invention the compounds of Formula(s) (I) and (Ia), (II) and (IIa), (III) and (IIIa), (IV) and (IVa), (V) and (Va), (VI), (VIa-VIi), (VIII), (VIIIa), (IX), (IXa), (A), (A1), (B), and (B1), may also include for the X term the B-Non-Ar-cyc moiety as disclosed in US 6,809,199.

As represented by the disclosure in US 6,809,199, Non-Ar-Cyc is suitably selected from;



wherein

d is an integer having a value of 1, 2, 3, or 4;

5 d' is 0, or an integer having a value of 1, 2, or 3;

d'' is 0, or an integer having a value of 1, 2, or 3;

e is 0, or is an integer having a value of 1, 2, 3, or 4;

e' is 0, or an integer having a value of 1, 2, or 3;

e'' is 0, or an integer having a value of 1, 2, or 3;

10 f is 0, or is an integer having a value of 1, 2, or 3;

d + e is 2, 3, 4, 5, or 6;

d' + e'' = d

e' + e'' = m

Suitably, R<sub>7</sub>', R<sub>77</sub> and R<sub>77</sub>' are each independently selected from hydrogen, C<sub>1</sub>-

15 <sub>6</sub> alkyl-group, C<sub>2-6</sub> alkenyl-group, C<sub>4-6</sub> cycloalkyl-C<sub>0-6</sub> alkyl-group, N(C<sub>0-4</sub> alkyl)(C<sub>0-4</sub> alkyl)-C<sub>1-4</sub> alkyl-N(C<sub>0-4</sub> alkyl)-group, -N(C<sub>0-4</sub> alkyl)(C<sub>0-4</sub> alkyl) group, C<sub>1-3</sub> alkyl-CO—C<sub>0-4</sub> alkyl-group, C<sub>0-6</sub> alkyl-O—C(O)—C<sub>0-4</sub> alkyl-group, C<sub>0-6</sub> alkyl-C(O)-O—C<sub>0-4</sub>alkyl-group, N(C<sub>0-4</sub> alkyl)(C<sub>0-4</sub> alkyl)-(C<sub>0-4</sub> alkyl)C(O)(C<sub>0-4</sub> alkyl)-group, phenyl-C<sub>0-4</sub> alkyl-group, pyridyl-C<sub>0-4</sub> alkyl-group, pyrimidinyl-C<sub>0-4</sub> alkyl-group, pyrazinyl-C<sub>0-4</sub> alkyl-group, thiophenyl-C<sub>0-4</sub> alkyl-group, pyrazolyl-C<sub>0-4</sub> alkyl-group, imidazolyl-C<sub>0-4</sub> alkyl-group, triazolyl-C<sub>0-4</sub> alkyl-group, azetidyl-C<sub>0-4</sub> alkyl-group, pyrrolidinyl-C<sub>0-4</sub> alkyl-group, isoquinolinyl-C<sub>0-4</sub>alkyl-group, indanyl-C<sub>0-4</sub> alkyl-group, benzothiazolyl-C<sub>0-4</sub> alkyl-group, any of the groups optionally substituted with 1-6 substituents, each substituent independently being -OH, -N(C<sub>0-4</sub> alkyl)(C<sub>0-4</sub> alkyl), C<sub>1-4</sub>alkyl, C<sub>1-6</sub> alkoxyl, C<sub>1-6</sub> alkyl-CO—C<sub>0-4</sub> alkyl-, pyrrolidinyl-C<sub>0-4</sub> alkyl-, or halogen; or R<sub>7</sub>' together with a bond from an absent ring hydrogen is =O.

25 Suitably, B is -C<sub>1-6</sub>alkyl-, -C<sub>0-3</sub> alkyl-O-C<sub>0-3</sub>alkyl-, -C<sub>0-3</sub> alkyl-NH-C<sub>0-3</sub>alkyl-, -C<sub>0-3</sub>alkyl-NH-C<sub>3-7</sub>cycloalkyl-, -C<sub>0-3</sub>alkyl-N(C<sub>0-3</sub>alkyl)-C(O)-C<sub>0-3</sub> alkyl-, -C<sub>0-3</sub> alkyl-NH--SO<sub>2</sub>-C<sub>0-3</sub> alkyl-, -C<sub>0-3</sub> alkyl-, -C<sub>0-3</sub>alkyl-S-C<sub>0-3</sub> alkyl-, -C<sub>0-3</sub> alkyl-SO<sub>2</sub> -C<sub>0-3</sub>alkyl-,  
30 -C<sub>0-3</sub>alkyl-PH-C<sub>0-3</sub> alkyl-, C<sub>0-3</sub> alkyl -C(O)-C<sub>0-3</sub> alkyl, or a direct bond.

WO 2006/104915

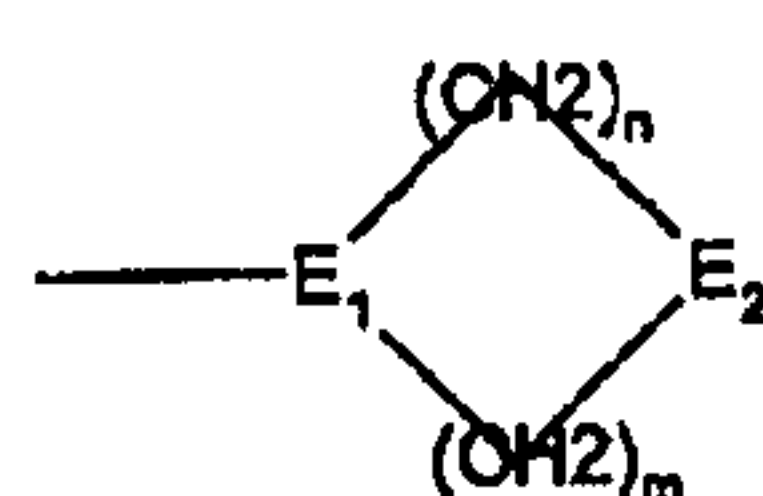
PCT/US2006/010855

Suitably,  $E_1$  is CH, N, or  $CR_{66}$ ; or B and  $E_1$  together form a double bond, i.e.,  $-CH=C$ .

Suitably,  $E_2$  is  $CH_2$ ,  $CHR_{77}$ ,  $C(OH)R_{77}$ ,  $NH$ ,  $NR_{77}$ , O, S,  $-S(O)-$ , or  $-S(O)_2-$ .

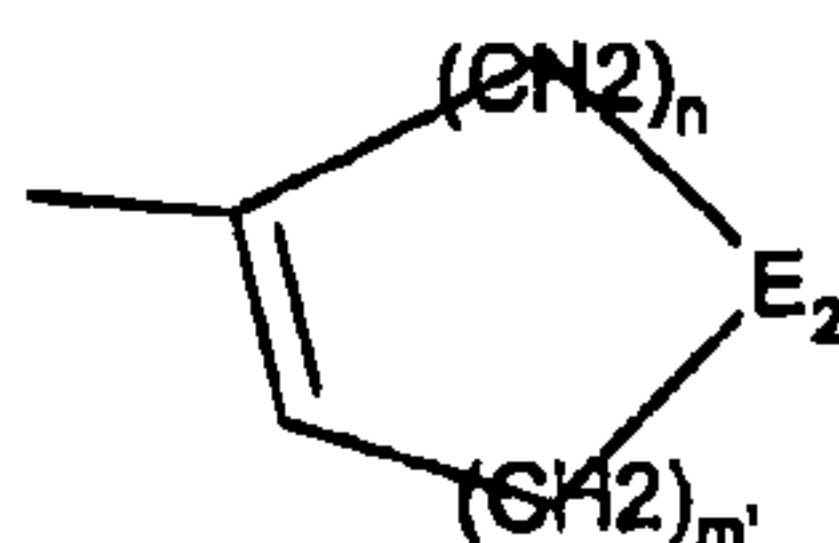
Suitably,  $R_{66}$  is independently selected from at each occurrence from  
 5 halogen,  $C_{0-4}$  alkyl,  $-C(O)-O$  ( $C_{0-4}$  alkyl), or  $-C(O)-N(C_{0-4}$  alkyl)-( $C_{0-4}$  alkyl).

In an alternative embodiment of this invention, Non-Ary Cyc is:



$n = 1$  to  $4$   
 $m = 0$  to  $4$   
 $n+m = 2$  to  $8$

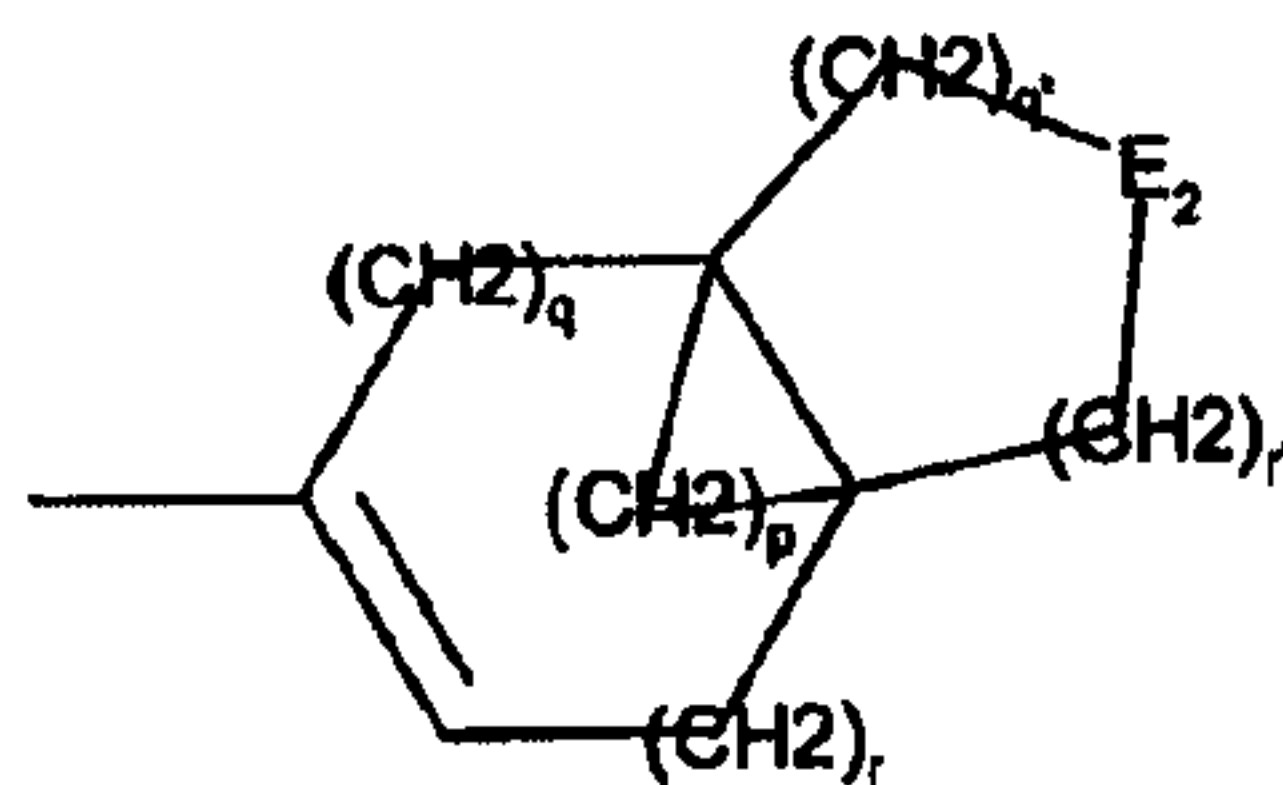
$E_1 = CH$ ,  $CR_6$ , N or B- $E_1$  can equal double bond ( $C=C$ ); or



$n = 1$  to  $4$   
 $m' = 0$  to  $3$   
 $n+m' = 1$  to  $5$

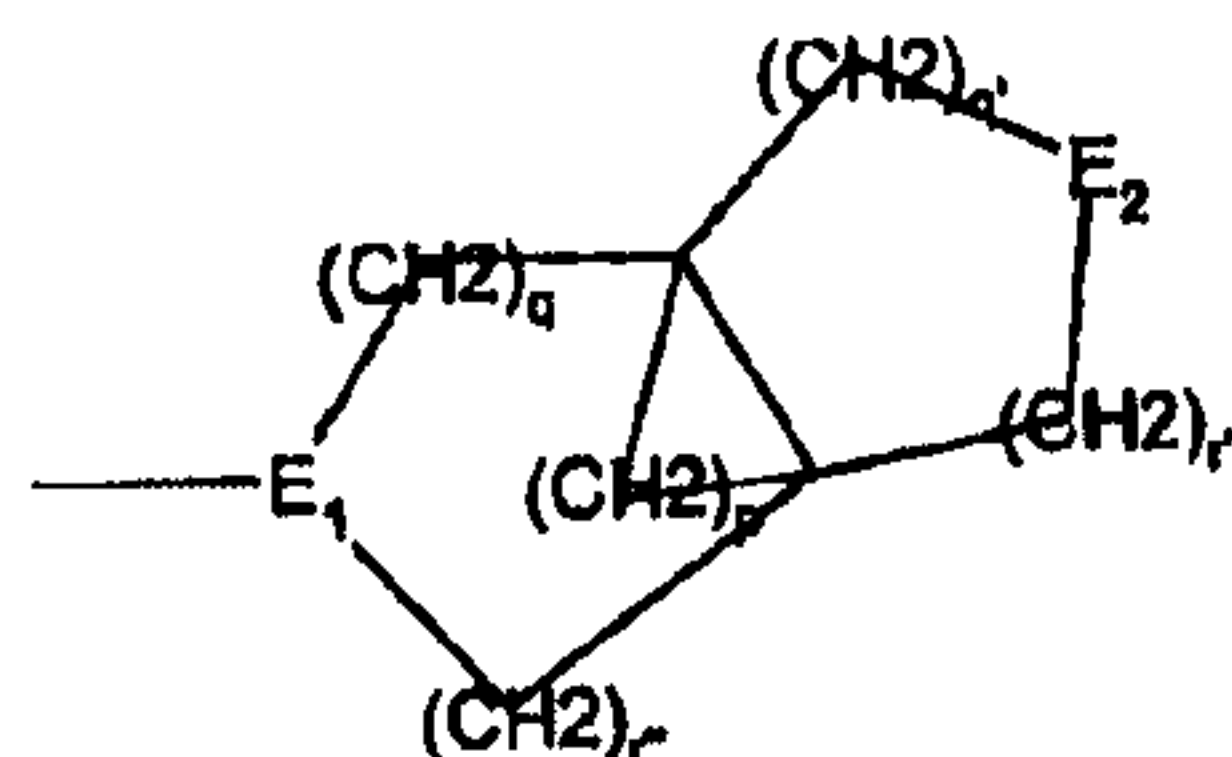
10

; or



$p = 0$  to  $3$   
 $q = 0$  to  $4$   
 $q' = 0$  to  $4$   
 $r = 0$  to  $4$   
 $r' = 0$  to  $4$   
 $q+q'+r+r' = 2$  to  $6$

; or



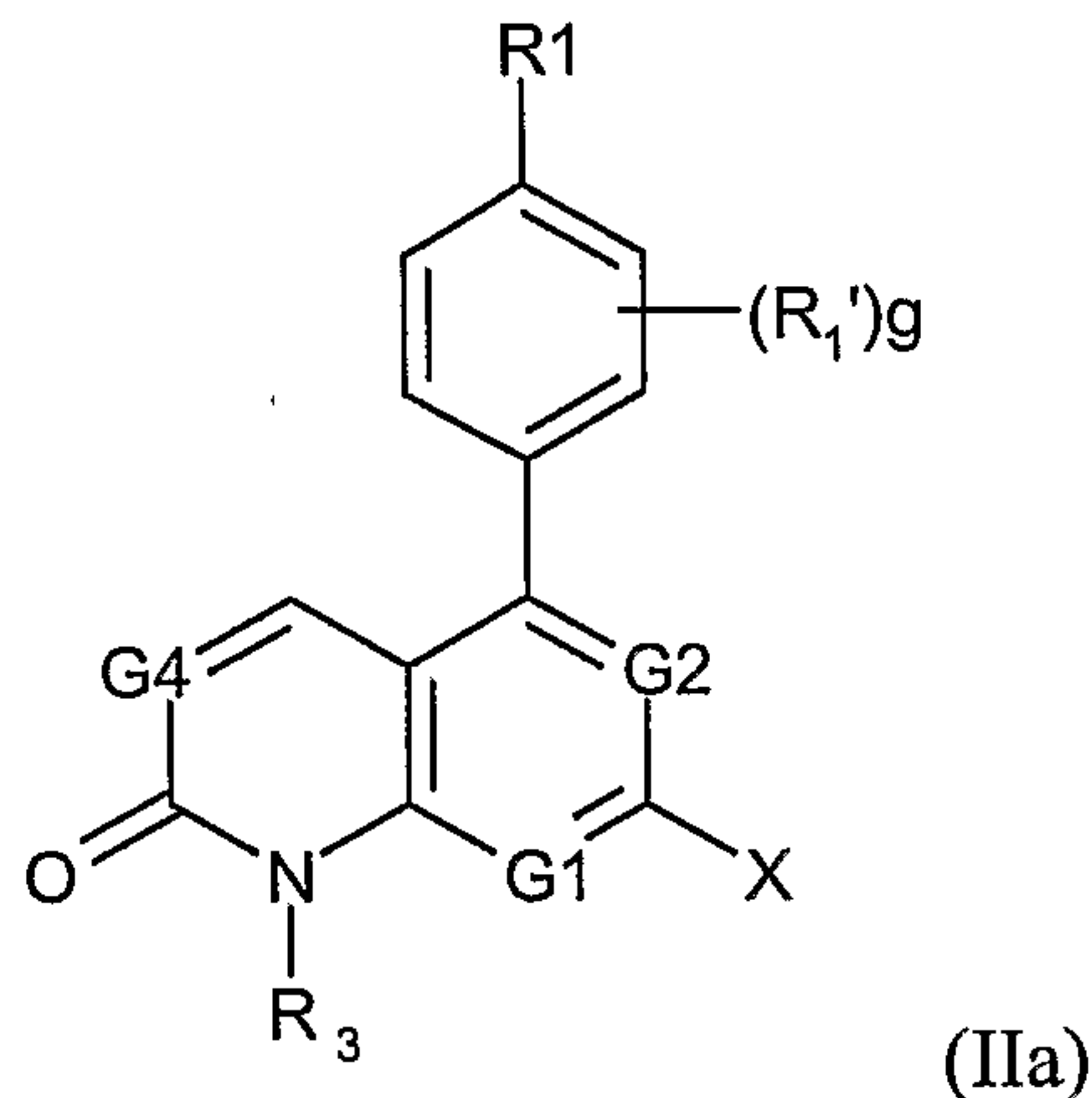
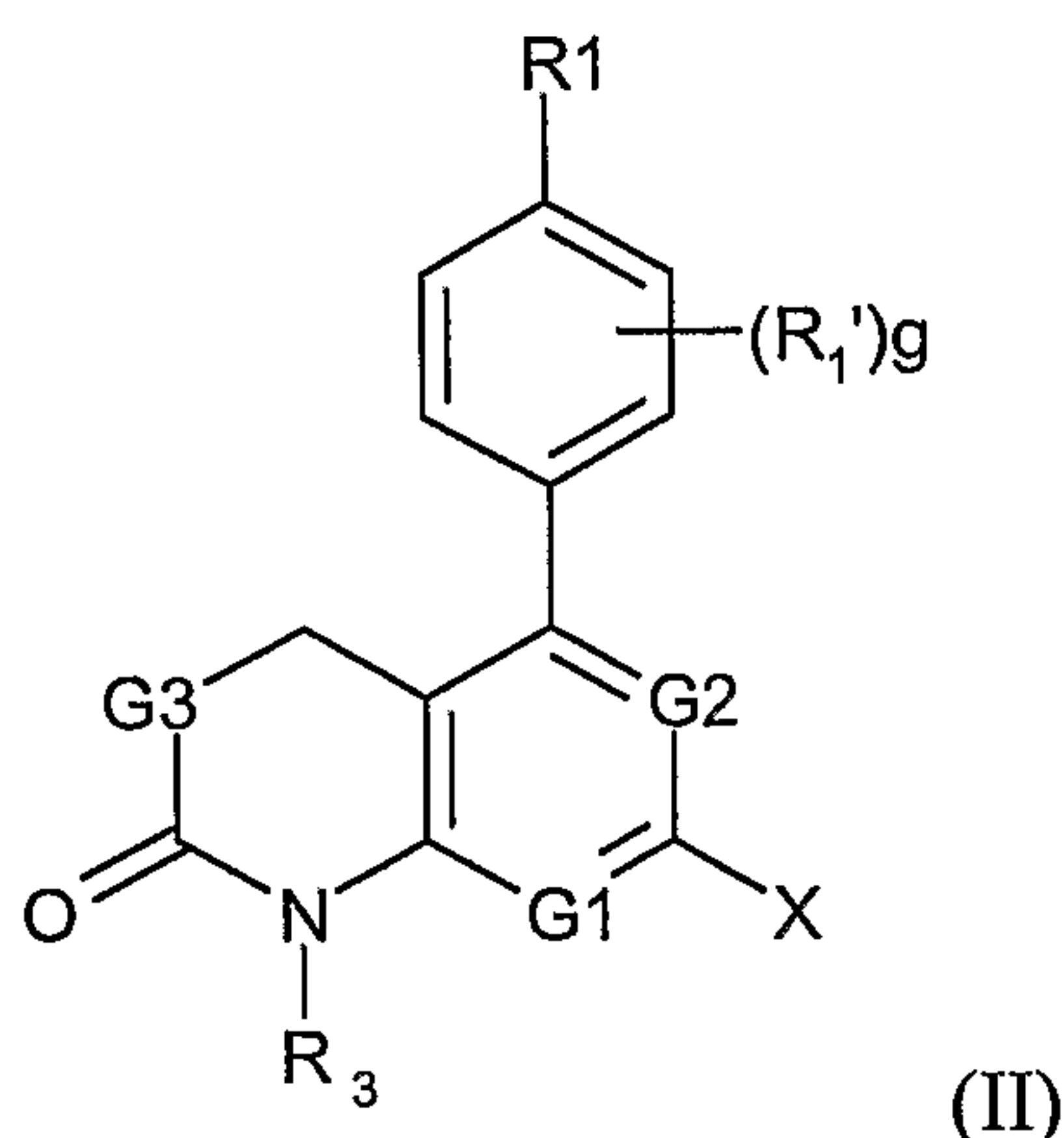
$p = 0$  to  $3$   
 $q = 0$  to  $4$   
 $q' = 0$  to  $4$   
 $r = 0$  to  $4$   
 $r' = 0$  to  $4$   
 $q+q'+r+r' = 2$  to  $7$

15

In another embodiment of the present invention, the compounds of Formula(s) (I) and (Ia), (II) and (IIa), (III) and (IIIa), (IV) and (IVa), (V) and (Va), (VI), (VIa-VIi), (VIII), (VIIIa), (IX), (IXa), (A), (A1), (B), and (B1), may also include for the X term, the X moieties as disclosed in WO 2004/073628, published September 2004, Boehm et al.

20

In another embodiment of the present invention, compounds of Formula (II) and (IIa) are represented by the structure:



5

wherein

G<sub>1</sub> and G<sub>2</sub> are nitrogen;

G<sub>3</sub> is CH<sub>2</sub>;

G<sub>4</sub> is CH;

10 R<sub>1</sub> is C(Z)N(R<sub>10</sub>') (CR<sub>10</sub>R<sub>20</sub>)<sub>v</sub>R<sub>b</sub>, C(Z)O(CR<sub>10</sub>R<sub>20</sub>)<sub>v</sub>R<sub>b</sub>,  
N(R<sub>10</sub>')C(Z)(CR<sub>10</sub>R<sub>20</sub>)<sub>v</sub>R<sub>b</sub>, N(R<sub>10</sub>')C(Z)N(R<sub>10</sub>') (CR<sub>10</sub>R<sub>20</sub>)<sub>v</sub>R<sub>b</sub>, or  
N(R<sub>10</sub>')OC(Z)(CR<sub>10</sub>R<sub>20</sub>)<sub>v</sub>R<sub>b</sub>;

R<sub>1</sub>' is independently selected at each occurrence from halogen, C<sub>1-4</sub> alkyl, halo-  
substituted-C<sub>1-4</sub> alkyl, cyano, nitro, (CR<sub>10</sub>R<sub>20</sub>)<sub>v</sub>NR<sub>d</sub>R<sub>d</sub>,

15 (CR<sub>10</sub>R<sub>20</sub>)<sub>v</sub>C(O)R<sub>12</sub>, SR<sub>5</sub>, S(O)R<sub>5</sub>, S(O)<sub>2</sub>R<sub>5</sub>, or (CR<sub>10</sub>R<sub>20</sub>)<sub>v</sub>OR<sub>13</sub>;

R<sub>b</sub> is hydrogen, C<sub>1-10</sub> alkyl, C<sub>3-7</sub> cycloalkyl, C<sub>3-7</sub> cycloalkyl C<sub>1-10</sub> alkyl, aryl,  
arylC<sub>1-10</sub>alkyl, heteroaryl, heteroarylC<sub>1-10</sub> alkyl, heterocyclic, or  
heterocyclylC<sub>1-10</sub> alkyl moiety, which moieties, excluding hydrogen, may all be  
optionally substituted;

20 X is R<sub>2</sub>, OR<sub>2</sub>', S(O)<sub>m</sub>R<sub>2</sub>', (CH<sub>2</sub>)<sub>n</sub>N(R<sub>10</sub>')S(O)<sub>m</sub>R<sub>2</sub>', (CH<sub>2</sub>)<sub>n</sub>N(R<sub>10</sub>')C(O)R<sub>2</sub>',  
(CH<sub>2</sub>)<sub>n</sub>NR<sub>4</sub>R<sub>14</sub>, (CH<sub>2</sub>)<sub>n</sub>N(R<sub>2</sub>') (R<sub>2</sub>',), or N(R<sub>10</sub>')R<sub>h</sub>NH-C(=N-CN)NR<sub>q</sub>R<sub>q</sub>';

X<sub>1</sub> is N(R<sub>11</sub>), O, S(O)<sub>m</sub>, or CR<sub>10</sub>R<sub>20</sub>;

R<sub>h</sub> is selected from an optionally substituted C<sub>1-10</sub> alkyl, -CH<sub>2</sub>-C(O)-CH<sub>2</sub>-,  
-CH<sub>2</sub>-CH<sub>2</sub>-O-CH<sub>2</sub>-CH<sub>2</sub>-, -CH<sub>2</sub>-C(O)N(R<sub>10</sub>')CH<sub>2</sub>-CH<sub>2</sub>-, -CH<sub>2</sub>-N(R<sub>10</sub>')C(O)CH<sub>2</sub>-,  
25 -CH<sub>2</sub>-CH(OR<sub>10</sub>')-CH<sub>2</sub>-, -CH<sub>2</sub>-C(O)O-CH<sub>2</sub>-CH<sub>2</sub>-, or -CH<sub>2</sub>-CH<sub>2</sub>-O-C(O)CH<sub>2</sub>-;

R<sub>q</sub> and R<sub>q</sub>' are independently selected at each occurrence from hydrogen, C<sub>1-10</sub>  
alkyl, C<sub>3-7</sub>cycloalkyl, C<sub>3-7</sub>cycloalkylC<sub>1-10</sub>alkyl, C<sub>5-7</sub> cycloalkenyl, C<sub>5-7</sub>  
cycloalkenyl-C<sub>1-10</sub>alkyl, aryl, arylC<sub>1-10</sub> alkyl, heteroaryl, heteroarylC<sub>1-10</sub>  
alkyl, heterocyclic, or a heterocyclylC<sub>1-10</sub> alkyl moiety, wherein all of the

moieties except for hydrogen, are optionally substituted, or  $R_q$  and  $R_{q'}$  together with the nitrogen to which they are attached form an optionally substituted heterocyclic ring of 5 to 7 members, which ring may contain an additional heteroatom selected from oxygen, nitrogen or sulfur;

- 5  $R_2$  is hydrogen,  $C_{1-10}$  alkyl,  $C_{3-7}$  cycloalkyl,  $C_{3-7}$  cycloalkylalkyl, aryl, aryl $C_{1-10}$  alkyl, heteroaryl, heteroaryl $C_{1-10}$  alkyl, heterocyclic, or a heterocyclyl $C_{1-10}$  alkyl moiety, and wherein each of these moieties, excluding hydrogen, may be optionally substituted; or
- $R_2$  is the moiety  $(CR_{10}R_{20})_qX_1(CR_{10}R_{20})_qC(A_1)(A_2)(A_3)$ , or
- 10  $(CR_{10}R_{20})_qC(A_1)(A_2)(A_3)$ ;
- $R_2'$  is hydrogen,  $C_{1-10}$  alkyl,  $C_{3-7}$  cycloalkyl,  $C_{3-7}$  cycloalkylalkyl, aryl, aryl $C_{1-10}$  alkyl, heteroaryl, heteroaryl $C_{1-10}$  alkyl, heterocyclic, or a heterocyclyl $C_{1-10}$  alkyl moiety, and wherein each of these moieties, excluding hydrogen, may be optionally substituted;
- 15  $R_2''$  is hydrogen,  $C_{1-10}$  alkyl,  $C_{3-7}$  cycloalkyl,  $C_{3-7}$  cycloalkylalkyl, aryl, aryl $C_{1-10}$  alkyl, heteroaryl, heteroaryl $C_{1-10}$  alkyl, heterocyclic, or a heterocyclyl $C_{1-10}$  alkyl moiety, and wherein these moieties, excluding hydrogen, may be optionally; or wherein  $R_2''$  is the moiety  $(CR_{10}R_{20})_tX_1(CR_{10}R_{20})_qC(A_1)(A_2)(A_3)$ ;
- $A_1$  is an optionally substituted  $C_{1-10}$  alkyl, heterocyclic, heterocyclic  $C_{1-10}$  alkyl, heteroaryl, heteroaryl  $C_{1-10}$  alkyl, aryl, or aryl  $C_{1-10}$  alkyl;
- 20  $A_2$  is an optionally substituted  $C_{1-10}$  alkyl, heterocyclic, heterocyclic  $C_{1-10}$  alkyl, heteroaryl, heteroaryl  $C_{1-10}$  alkyl, aryl, or aryl  $C_{1-10}$  alkyl;
- $A_3$  is hydrogen or is an optionally substituted  $C_{1-10}$  alkyl;
- $R_3$  is a  $C_{1-10}$  alkyl,  $C_{3-7}$  cycloalkyl,  $C_{3-7}$  cycloalkyl  $C_{1-10}$  alkyl, aryl, aryl $C_{1-10}$  alkyl, heteroaryl, heteroaryl $C_{1-10}$  alkyl, heterocyclic or a heterocyclyl $C_{1-10}$  alkyl
- 25 moiety, and wherein each of these moieties may be optionally substituted;
- $R_4$  and  $R_{14}$  are each independently selected at each occurrence from hydrogen,  $C_{1-4}$  alkyl,  $C_{3-7}$  cycloalkyl,  $C_{3-7}$  cycloalkyl $C_{1-4}$ alkyl, aryl, aryl- $C_{1-4}$  alkyl, heterocyclic, heterocyclic  $C_{1-4}$  alkyl, heteroaryl or a heteroaryl  $C_{1-4}$  alkyl
- 30 moiety, and wherein each of these moieties, excluding hydrogen, may be optionally substituted; or the  $R_4$  and  $R_{14}$  together with the nitrogen which they are attached form an optionally substituted heterocyclic ring of 4 to 7 members, which ring optionally contains an additional heteroatom selected from oxygen, sulfur or nitrogen;
- 35  $R_4'$  and  $R_{14}'$  are each independently selected at each occurrence from hydrogen or  $C_{1-4}$  alkyl, or  $R_4'$  and  $R_{14}'$  together with the nitrogen to which they are attached

form a heterocyclic ring of 5 to 7 members, which ring optionally contains an additional heteroatom selected from NR<sub>9</sub>';

R<sub>5</sub> is independently selected at each occurrence from hydrogen, C<sub>1-4</sub> alkyl, C<sub>2-4</sub> alkenyl, C<sub>2-4</sub> alkynyl or NR<sub>4</sub>'R<sub>14</sub>', excluding the moieties SR<sub>5</sub> being  
 5 SNR<sub>4</sub>'R<sub>14</sub>', S(O)<sub>2</sub>R<sub>5</sub> being SO<sub>2</sub>H and S(O)R<sub>5</sub> being SOH;

R<sub>9</sub>' is independently selected at each occurrence from hydrogen, or C<sub>1-4</sub> alkyl;

R<sub>10</sub> and R<sub>20</sub> are independently selected at each occurrence from hydrogen or C<sub>1-4</sub>alkyl;

R<sub>10</sub>' is independently selected at each occurrence from hydrogen or C<sub>1-4</sub>alkyl;

10 R<sub>11</sub> is independently selected at each occurrence from hydrogen or C<sub>1-4</sub>alkyl;

R<sub>12</sub> is independently selected at each occurrence from hydrogen, C<sub>1-4</sub> alkyl, halo-substituted C<sub>1-4</sub> alkyl, C<sub>2-4</sub> alkenyl, C<sub>2-4</sub> alkynyl, C<sub>3-7</sub> cycloalkyl, C<sub>3-7</sub>cycloalkylC<sub>1-4</sub> alkyl, C<sub>5-7</sub> cycloalkenyl, C<sub>5-7</sub>cycloalkenyl C<sub>1-4</sub> alkyl, aryl, arylC<sub>1-4</sub> alkyl, heteroaryl, heteroarylC<sub>1-4</sub> alkyl, heterocyclyl, or a  
 15 heterocyclylC<sub>1-4</sub> alkyl moiety, and wherein each of these moieties, excluding hydrogen, may be optionally substituted;

R<sub>13</sub> is independently selected at each occurrence from hydrogen, C<sub>1-4</sub> alkyl, halo-substituted C<sub>1-4</sub> alkyl, C<sub>2-4</sub> alkenyl, C<sub>2-4</sub> alkynyl, C<sub>3-7</sub> cycloalkyl, C<sub>3-7</sub>cycloalkylC<sub>1-4</sub> alkyl, C<sub>5-7</sub> cycloalkenyl, C<sub>5-7</sub>cycloalkenyl C<sub>1-4</sub> alkyl, aryl, arylC<sub>1-4</sub> alkyl, heteroaryl, heteroarylC<sub>1-4</sub> alkyl, heterocyclyl, or a  
 20 heterocyclylC<sub>1-4</sub> alkyl moiety, and wherein each of these moieties, excluding hydrogen, may be optionally substituted;

R<sub>d</sub> and R<sub>d</sub>' are each independently selected from hydrogen, C<sub>1-4</sub> alkyl, C<sub>3-6</sub> cycloalkyl, C<sub>3-6</sub> cycloalkylC<sub>1-4</sub>alkyl moiety, and wherein each of these moieties, excluding hydrogen, may be optionally substituted; or R<sub>d</sub> and R<sub>d</sub>' together with the nitrogen which they are attached form an optionally substituted heterocyclic ring of 5 to 6 members, which ring optionally contains an additional heteroatom selected from oxygen, sulfur or NR<sub>9</sub>';

g is 0 or an integer having a value of 1, 2, 3, or 4;

30 n' is independently selected at each occurrence from 0 or an integer having a value of 1 to 10;

m is independently selected at each occurrence from 0 or an integer having a value of 1 or 2;

q is 0 or an integer having a value of 1 to 10;

35 q' is 0, or an integer having a value of 1 to 6;

t is an integer having a value of 2 to 6;

v is 0 or an integer having a value of 1 or 2;

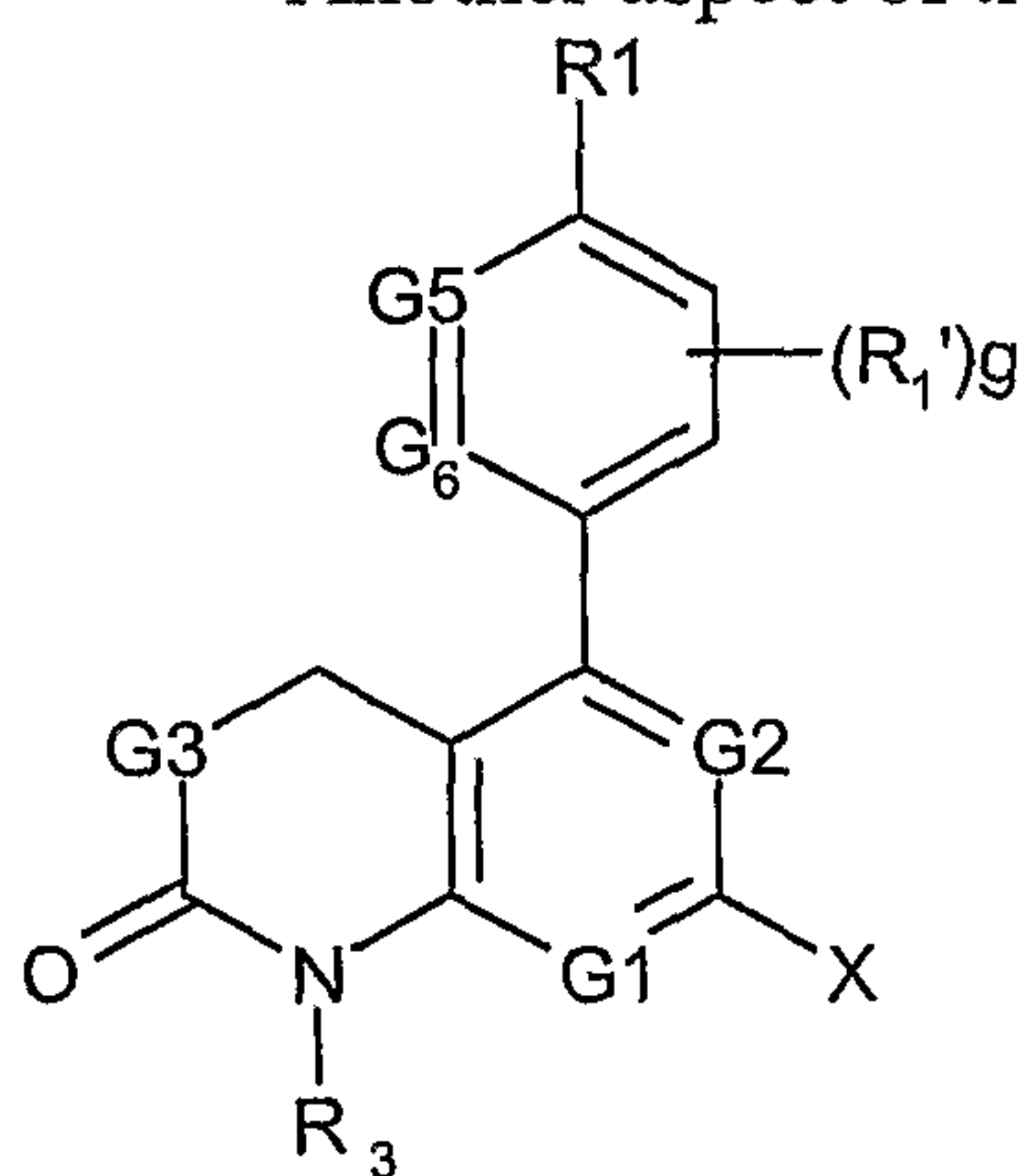
$v'$  is independently selected at each occurrence from 0 or an integer having a value of 1 or 2;

Z is independently selected at each occurrence from oxygen or sulfur; and

a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof.

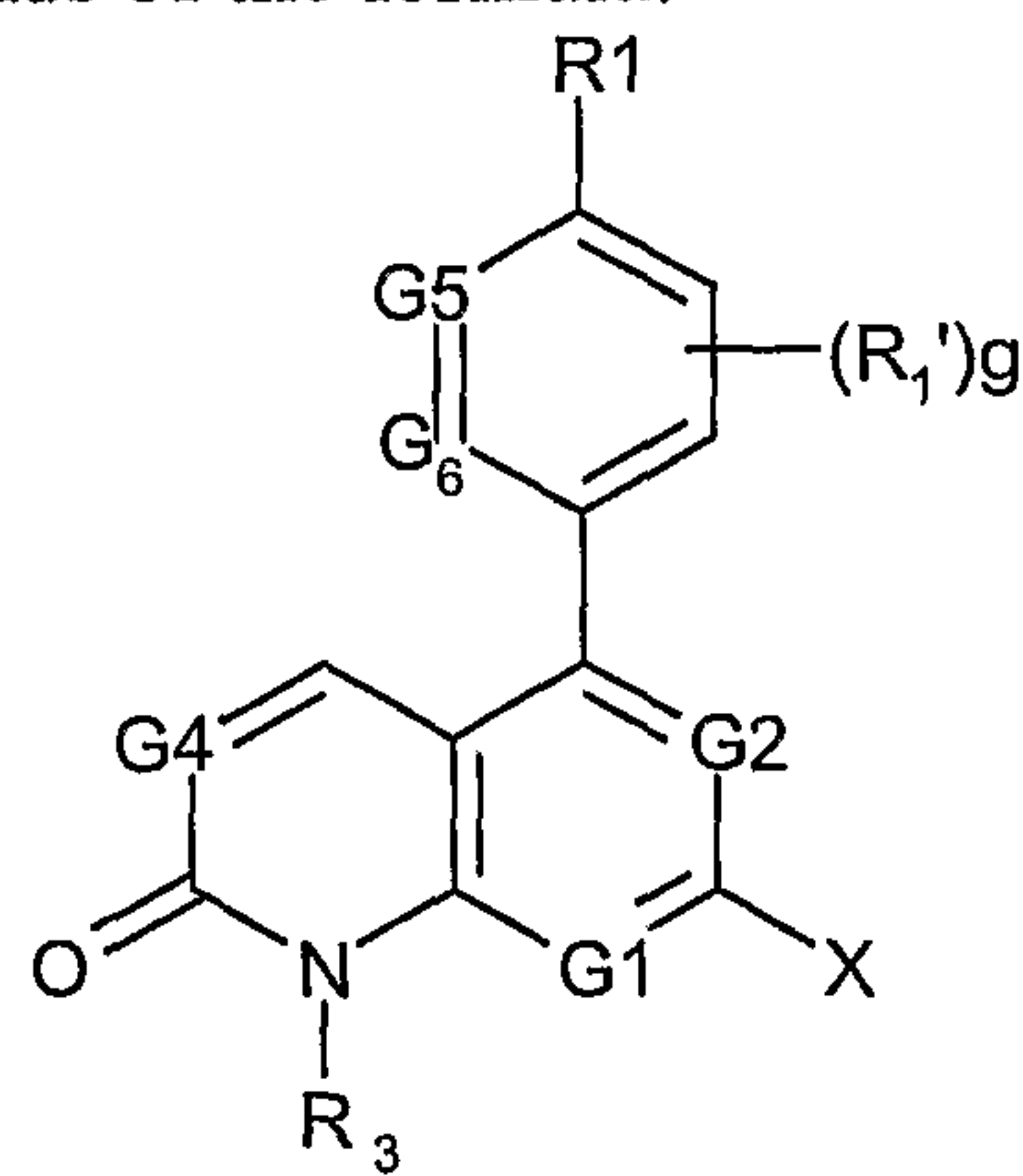
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Another aspect of the invention are compounds of the formula:



(III)

or



(IIIa)

10 wherein

$G_1$  and  $G_2$  are nitrogen;

$G_3$  is  $\text{CH}_2$ ;

$G_4$  is  $\text{CH}$ ;

$G_5$  and  $G_6$  are independently selected from nitrogen or  $\text{CH}$ ;

15  $R_1$  is  $\text{C}(\text{Z})\text{N}(\text{R}_{10}')(\text{CR}_{10}\text{R}_{20})_{v'}\text{R}_b$ ,  $\text{C}(\text{Z})\text{O}(\text{CR}_{10}\text{R}_{20})_{v'}\text{R}_b$ ,  
 $\text{N}(\text{R}_{10}')\text{C}(\text{Z})(\text{CR}_{10}\text{R}_{20})_{v'}\text{R}_b$ ,  $\text{N}(\text{R}_{10}')\text{C}(\text{Z})\text{N}(\text{R}_{10}')(\text{CR}_{10}\text{R}_{20})_{v'}\text{R}_b$ , or  
 $\text{N}(\text{R}_{10}')\text{OC}(\text{Z})(\text{CR}_{10}\text{R}_{20})_{v'}\text{R}_b$ ;

$R_1'$  is independently selected at each occurrence from halogen,  $\text{C}_1$ -4 alkyl, halo-substituted- $\text{C}_1$ -4 alkyl, cyano, nitro,  $(\text{CR}_{10}\text{R}_{20})_{v'}\text{NR}_d\text{R}_d'$ ,

20  $(\text{CR}_{10}\text{R}_{20})_{v'}\text{C}(\text{O})\text{R}_{12}$ ,  $\text{SR}_5$ ,  $\text{S}(\text{O})\text{R}_5$ ,  $\text{S}(\text{O})_2\text{R}_5$ , or  $(\text{CR}_{10}\text{R}_{20})_{v'}\text{OR}_{13}$ ;

$R_b$  is hydrogen,  $\text{C}_1$ -10 alkyl,  $\text{C}_3$ -7 cycloalkyl,  $\text{C}_3$ -7 cycloalkyl  $\text{C}_1$ -10 alkyl, aryl, aryl $\text{C}_1$ -10alkyl, heteroaryl, heteroaryl $\text{C}_1$ -10 alkyl, heterocyclic, or heterocyclyl $\text{C}_1$ -10 alkyl moiety, which moieties, excluding hydrogen, may all be optionally substituted;

25 X is  $\text{R}_2$ ,  $\text{OR}_2'$ ,  $\text{S}(\text{O})_m\text{R}_2'$ ,  $(\text{CH}_2)_n\text{N}(\text{R}_{10}')\text{S}(\text{O})_m\text{R}_2'$ ,  $(\text{CH}_2)_n\text{N}(\text{R}_{10}')\text{C}(\text{O})\text{R}_2'$ ,  
 $(\text{CH}_2)_n\text{NR}_4\text{R}_{14}$ ,  $(\text{CH}_2)_n\text{N}(\text{R}_2')(\text{R}_2'')$ , or  $\text{N}(\text{R}_{10}')\text{R}_h\text{NH}-\text{C}(=\text{N}-\text{CN})\text{NR}_q\text{R}_q'$ ;

$X_1$  is  $\text{N}(\text{R}_{11})$ , O,  $\text{S}(\text{O})_m$ , or  $\text{CR}_{10}\text{R}_{20}$ ;

$R_h$  is selected from an optionally substituted  $C_{1-10}$  alkyl,  $-CH_2-C(O)-CH_2-$ ,  
 $-CH_2-CH_2-O-CH_2-CH_2-$ ,  $-CH_2-C(O)N(R_{10'})CH_2-CH_2-$ ,  $-CH_2-N(R_{10'})C(O)CH_2-$ ,  
 $-CH_2-CH(OR_{10'})-CH_2-$ ,  $-CH_2-C(O)O-CH_2-CH_2-$ , or  $-CH_2-CH_2-O-C(O)CH_2-$ ;

$R_q$  and  $R_{q'}$  are independently selected at each occurrence from hydrogen,  $C_{1-10}$   
 5 alkyl,  $C_{3-7}$ cycloalkyl,  $C_{3-7}$ cycloalkyl $C_{1-10}$ alkyl,  $C_{5-7}$  cycloalkenyl,  $C_{5-7}$   
 cycloalkenyl- $C_{1-10}$ alkyl, aryl, aryl $C_{1-10}$  alkyl, heteroaryl, heteroaryl $C_{1-10}$   
 alkyl, heterocyclic, or a heterocyclyl $C_{1-10}$  alkyl moiety, wherein all of the  
 moieties except for hydrogen, are optionally substituted, or  $R_q$  and  $R_{q'}$  together  
 with the nitrogen to which they are attached form an optionally substituted  
 10 heterocyclic ring of 5 to 7 members, which ring may contain an additional  
 heteroatom selected from oxygen, nitrogen or sulfur;

$R_2$  is hydrogen,  $C_{1-10}$  alkyl,  $C_{3-7}$  cycloalkyl,  $C_{3-7}$  cycloalkylalkyl, aryl, aryl $C_{1-10}$   
 alkyl, heteroaryl, heteroaryl $C_{1-10}$  alkyl, heterocyclic, or a heterocyclyl $C_{1-10}$   
 alkyl moiety, and wherein each of these moieties, excluding hydrogen, may be  
 15 optionally substituted; or

$R_2$  is the moiety  $(CR_{10}R_{20})_qX_1(CR_{10}R_{20})_qC(A_1)(A_2)(A_3)$ , or  
 $(CR_{10}R_{20})_qC(A_1)(A_2)(A_3)$ ;

$R_{2'}$  is hydrogen,  $C_{1-10}$  alkyl,  $C_{3-7}$  cycloalkyl,  $C_{3-7}$  cycloalkylalkyl, aryl, aryl $C_{1-10}$   
 alkyl, heteroaryl, heteroaryl $C_{1-10}$  alkyl, heterocyclic, or a heterocyclyl $C_{1-10}$  alkyl  
 20 moiety, and wherein each of these moieties, excluding hydrogen, may be optionally  
 substituted;

$R_{2''}$  is hydrogen,  $C_{1-10}$  alkyl,  $C_{3-7}$  cycloalkyl,  $C_{3-7}$  cycloalkylalkyl, aryl, aryl $C_{1-10}$   
 alkyl, heteroaryl, heteroaryl $C_{1-10}$  alkyl, heterocyclic, or a heterocyclyl $C_{1-10}$  alkyl  
 moiety, and wherein these moieties, excluding hydrogen, may be optionally; or  
 25 wherein  $R_{2''}$  is the moiety  $(CR_{10}R_{20})_tX_1(CR_{10}R_{20})_qC(A_1)(A_2)(A_3)$ ;

$A_1$  is an optionally substituted  $C_{1-10}$  alkyl, heterocyclic, heterocyclic  $C_{1-10}$  alkyl,  
 heteroaryl, heteroaryl  $C_{1-10}$  alkyl, aryl, or aryl  $C_{1-10}$  alkyl;

$A_2$  is an optionally substituted  $C_{1-10}$  alkyl, heterocyclic, heterocyclic  $C_{1-10}$  alkyl,  
 heteroaryl, heteroaryl  $C_{1-10}$  alkyl, aryl, or aryl  $C_{1-10}$  alkyl;

30  $A_3$  is hydrogen or is an optionally substituted  $C_{1-10}$  alkyl;

$R_3$  is a  $C_{1-10}$  alkyl,  $C_{3-7}$  cycloalkyl,  $C_{3-7}$  cycloalkyl  $C_{1-10}$  alkyl, aryl, aryl $C_{1-10}$   
 alkyl, heteroaryl, heteroaryl $C_{1-10}$  alkyl, heterocyclic or a heterocyclyl $C_{1-10}$  alkyl  
 moiety, and wherein each of these moieties may be optionally substituted;

$R_4$  and  $R_{14}$  are each independently selected at each occurrence from hydrogen,  $C_{1-4}$   
 35 alkyl,  $C_{3-7}$  cycloalkyl,  $C_{3-7}$  cycloalkyl $C_{1-4}$ alkyl, aryl, aryl- $C_{1-4}$  alkyl,  
 heterocyclic, heterocyclic  $C_{1-4}$  alkyl, heteroaryl or a heteroaryl  $C_{1-4}$  alkyl  
 moiety, and wherein each of these moieties, excluding hydrogen, may be

optionally substituted; or the R<sub>4</sub> and R<sub>14</sub> together with the nitrogen which they are attached form an optionally substituted heterocyclic ring of 4 to 7 members, which ring optionally contains an additional heteroatom selected from oxygen, sulfur or nitrogen;

- 5 R<sub>4</sub>' and R<sub>14</sub>' are each independently selected at each occurrence from hydrogen or C<sub>1-4</sub> alkyl, or R<sub>4</sub>' and R<sub>14</sub>' together with the nitrogen to which they are attached form a heterocyclic ring of 5 to 7 members, which ring optionally contains an additional heteroatom selected from NR<sub>9</sub>';

- R<sub>5</sub> is independently selected at each occurrence from hydrogen, C<sub>1-4</sub> alkyl, C<sub>2-4</sub> alkenyl, C<sub>2-4</sub> alkynyl or NR<sub>4</sub>'R<sub>14</sub>', excluding the moieties SR<sub>5</sub> being  
10 SNR<sub>4</sub>'R<sub>14</sub>', S(O)<sub>2</sub>R<sub>5</sub> being SO<sub>2</sub>H and S(O)R<sub>5</sub> being SOH;

R<sub>9</sub>' is independently selected at each occurrence from hydrogen, or C<sub>1-4</sub> alkyl;

R<sub>10</sub> and R<sub>20</sub> are independently selected at each occurrence from hydrogen or C<sub>1-4</sub>alkyl;

- 15 R<sub>10</sub>' is independently selected at each occurrence from hydrogen or C<sub>1-4</sub>alkyl;

R<sub>11</sub> is independently selected at each occurrence from hydrogen or C<sub>1-4</sub>alkyl;

- R<sub>12</sub> is independently selected at each occurrence from hydrogen, C<sub>1-4</sub> alkyl, halo-substituted C<sub>1-4</sub> alkyl, C<sub>2-4</sub> alkenyl, C<sub>2-4</sub> alkynyl, C<sub>3-7</sub> cycloalkyl, C<sub>3-7</sub>cycloalkylC<sub>1-4</sub> alkyl, C<sub>5-7</sub> cycloalkenyl, C<sub>5-7</sub>cycloalkenyl C<sub>1-4</sub> alkyl, aryl, arylC<sub>1-4</sub> alkyl, heteroaryl, heteroarylC<sub>1-4</sub> alkyl, heterocyclyl, or a  
20 heterocyclylC<sub>1-4</sub> alkyl moiety, and wherein each of these moieties, excluding hydrogen, may be optionally substituted;

R<sub>13</sub> is independently selected at each occurrence from hydrogen, C<sub>1-4</sub> alkyl, halo-substituted C<sub>1-4</sub> alkyl, C<sub>2-4</sub> alkenyl, C<sub>2-4</sub> alkynyl, C<sub>3-7</sub> cycloalkyl,

- 25 C<sub>3-7</sub>cycloalkylC<sub>1-4</sub> alkyl, C<sub>5-7</sub> cycloalkenyl, C<sub>5-7</sub>cycloalkenyl C<sub>1-4</sub> alkyl, aryl, arylC<sub>1-4</sub> alkyl, heteroaryl, heteroarylC<sub>1-4</sub> alkyl, heterocyclyl, or a heterocyclylC<sub>1-4</sub> alkyl moiety, and wherein each of these moieties, excluding hydrogen, may be optionally substituted;

- R<sub>d</sub> and R<sub>d</sub>' are each independently selected from hydrogen, C<sub>1-4</sub> alkyl, C<sub>3-6</sub> cycloalkyl, C<sub>3-6</sub> cycloalkylC<sub>1-4</sub>alkyl moiety, and wherein each of these moieties, excluding hydrogen, may be optionally substituted; or R<sub>d</sub> and R<sub>d</sub>' together with the nitrogen which they are attached form an optionally substituted heterocyclic ring of 5 to 6 members, which ring optionally contains an additional heteroatom selected from oxygen, sulfur or NR<sub>9</sub>';

- 35 g is 0 or an integer having a value of 1, 2, 3, or 4;

n' is independently selected at each occurrence from 0 or an integer having a value of 1 to 10;

m is independently selected at each occurrence from 0 or an integer having a value of 1 or 2;

q is 0 or an integer having a value of 1 to 10;

q' is 0, or an integer having a value of 1 to 6;

5 t is an integer having a value of 2 to 6;

v is 0 or an integer having a value of 1 or 2;

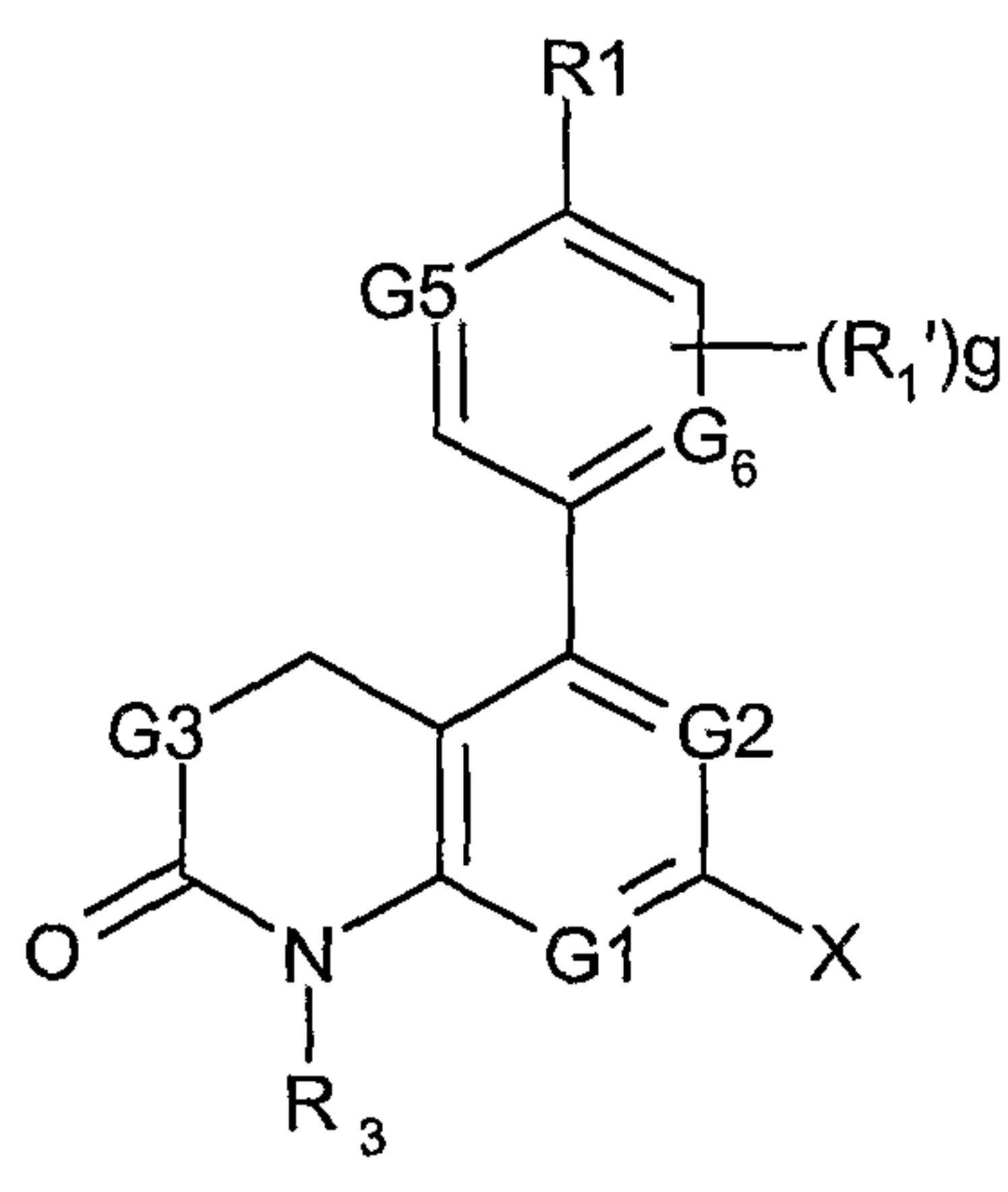
v' is independently selected at each occurrence from 0 or an integer having a value of 1 or 2;

Z is independently selected at each occurrence from oxygen or sulfur; and

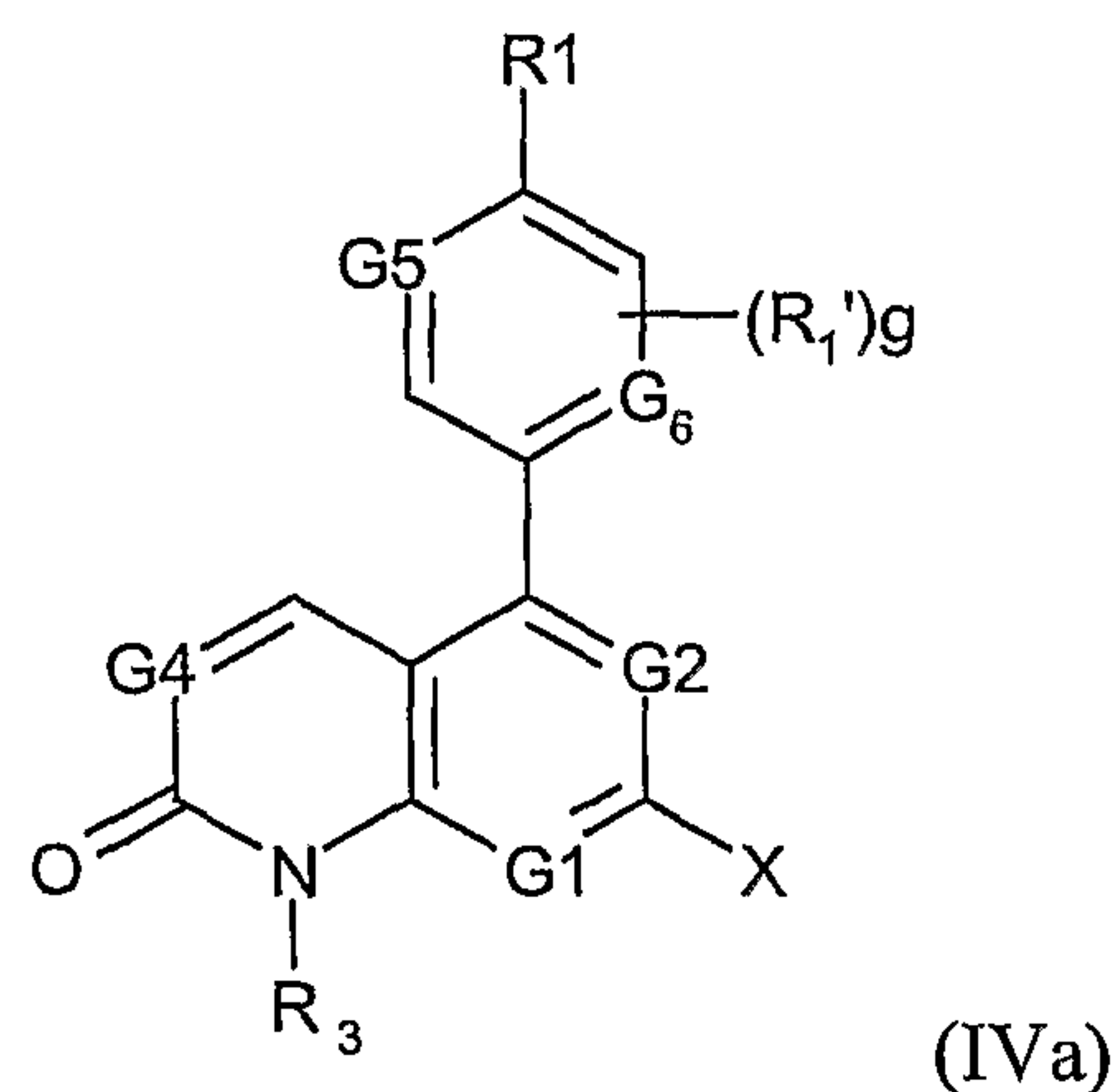
10 a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof.

It should be recognized that the difference between compounds of Formula (I) and (Ia), and Formula (II) and (IIa) and those of Formulas (III) and (IIIa) through  
 15 Formula (V) and (Va) lie not only in the in the ring substitution of the R<sub>1</sub> group, but the ring positions of the nitrogen in the pyridyl ring, e.g. the G5 and G6 variables. All of the remaining variables have the same meaning for Formulas (III) and (IIIa) through Formula (V) and (Va) as those described herein for Formula (I) and (Ia), etc.

20 Another aspect of the invention are compounds of the formula:



or



G<sub>1</sub> and G<sub>2</sub> are nitrogen:

G<sub>3</sub> is CH<sub>2</sub>;

25 G<sub>4</sub> is CH;

G<sub>5</sub> and G<sub>6</sub> are independently selected from nitrogen or CH;

R<sub>1</sub> is C(Z)N(R<sub>10</sub>') (CR<sub>10</sub>R<sub>20</sub>)<sub>v</sub>R<sub>b</sub>, C(Z)O(CR<sub>10</sub>R<sub>20</sub>)<sub>v</sub>R<sub>b</sub>,  
 N(R<sub>10</sub>')C(Z)(CR<sub>10</sub>R<sub>20</sub>)<sub>v</sub>R<sub>b</sub>, N(R<sub>10</sub>')C(Z)N(R<sub>10</sub>') (CR<sub>10</sub>R<sub>20</sub>)<sub>v</sub>R<sub>b</sub>, or  
 N(R<sub>10</sub>')OC(Z)(CR<sub>10</sub>R<sub>20</sub>)<sub>v</sub>R<sub>b</sub>;

R<sub>1</sub>' is independently selected at each occurrence from halogen, C<sub>1-4</sub> alkyl, halo-  
 5 substituted-C<sub>1-4</sub> alkyl, cyano, nitro, (CR<sub>10</sub>R<sub>20</sub>)<sub>v</sub>'NR<sub>d</sub>R<sub>d</sub>',  
 (CR<sub>10</sub>R<sub>20</sub>)<sub>v</sub>'C(O)R<sub>12</sub>, SR<sub>5</sub>, S(O)R<sub>5</sub>, S(O)<sub>2</sub>R<sub>5</sub>, or (CR<sub>10</sub>R<sub>20</sub>)<sub>v</sub>'OR<sub>13</sub>;

R<sub>b</sub> is hydrogen, C<sub>1-10</sub> alkyl, C<sub>3-7</sub> cycloalkyl, C<sub>3-7</sub> cycloalkyl C<sub>1-10</sub> alkyl, aryl,  
 arylC<sub>1-10</sub>alkyl, heteroaryl, heteroarylC<sub>1-10</sub> alkyl, heterocyclic, or  
 heterocyclylC<sub>1-10</sub> alkyl moiety, which moieties, excluding hydrogen, may all be  
 10 optionally substituted;

X is R<sub>2</sub>, OR<sub>2</sub>', S(O)<sub>m</sub>R<sub>2</sub>', (CH<sub>2</sub>)<sub>n</sub>'N(R<sub>10</sub>')S(O)<sub>m</sub>R<sub>2</sub>', (CH<sub>2</sub>)<sub>n</sub>'N(R<sub>10</sub>')C(O)R<sub>2</sub>',  
 (CH<sub>2</sub>)<sub>n</sub>'NR<sub>4</sub>R<sub>14</sub>, (CH<sub>2</sub>)<sub>n</sub>'N(R<sub>2</sub>') (R<sub>2</sub>''), or N(R<sub>10</sub>')R<sub>h</sub>NH-C(=N-CN)NR<sub>q</sub>R<sub>q</sub>';

X<sub>1</sub> is N(R<sub>11</sub>), O, S(O)<sub>m</sub>, or CR<sub>10</sub>R<sub>20</sub>;

R<sub>h</sub> is selected from an optionally substituted C<sub>1-10</sub> alkyl, -CH<sub>2</sub>-C(O)-CH<sub>2</sub>-,  
 15 -CH<sub>2</sub>-CH<sub>2</sub>-O-CH<sub>2</sub>-CH<sub>2</sub>-, -CH<sub>2</sub>-C(O)N(R<sub>10</sub>')CH<sub>2</sub>-CH<sub>2</sub>-,  
 -CH<sub>2</sub>-N(R<sub>10</sub>')C(O)CH<sub>2</sub>-, -CH<sub>2</sub>-CH(OR<sub>10</sub>')-CH<sub>2</sub>-, -CH<sub>2</sub>-C(O)O-CH<sub>2</sub>-CH<sub>2</sub>-, or  
 -CH<sub>2</sub>-CH<sub>2</sub>-O-C(O)CH<sub>2</sub>-;

R<sub>q</sub> and R<sub>q</sub>' are independently selected at each occurrence from hydrogen, C<sub>1-10</sub>  
 alkyl, C<sub>3-7</sub>cycloalkyl, C<sub>3-7</sub>cycloalkylC<sub>1-10</sub>alkyl, C<sub>5-7</sub> cycloalkenyl, C<sub>5-7</sub>  
 20 cycloalkenyl-C<sub>1-10</sub>alkyl, aryl, arylC<sub>1-10</sub> alkyl, heteroaryl, heteroarylC<sub>1-10</sub>  
 alkyl, heterocyclic, or a heterocyclylC<sub>1-10</sub> alkyl moiety, wherein all of the  
 moieties except for hydrogen, are optionally substituted, or R<sub>q</sub> and R<sub>q</sub>' together  
 with the nitrogen to which they are attached form an optionally substituted  
 heterocyclic ring of 5 to 7 members, which ring may contain an additional  
 25 heteroatom selected from oxygen, nitrogen or sulfur;

R<sub>2</sub> is hydrogen, C<sub>1-10</sub> alkyl, C<sub>3-7</sub> cycloalkyl, C<sub>3-7</sub> cycloalkylalkyl, aryl, arylC<sub>1-10</sub>  
 alkyl, heteroaryl, heteroarylC<sub>1-10</sub> alkyl, heterocyclic, or a heterocyclylC<sub>1-10</sub>  
 alkyl moiety, and wherein each of these moieties, excluding hydrogen, may be  
 optionally substituted; or

30 R<sub>2</sub> is the moiety (CR<sub>10</sub>R<sub>20</sub>)<sub>q</sub>'X<sub>1</sub>(CR<sub>10</sub>R<sub>20</sub>)<sub>q</sub>C(A<sub>1</sub>)(A<sub>2</sub>)(A<sub>3</sub>), or  
 (CR<sub>10</sub>R<sub>20</sub>)<sub>q</sub>'C(A<sub>1</sub>)(A<sub>2</sub>)(A<sub>3</sub>);

R<sub>2</sub>' is hydrogen, C<sub>1-10</sub> alkyl, C<sub>3-7</sub> cycloalkyl, C<sub>3-7</sub> cycloalkylalkyl, aryl, arylC<sub>1-10</sub>  
 alkyl, heteroaryl, heteroarylC<sub>1-10</sub> alkyl, heterocyclic, or a heterocyclylC<sub>1-10</sub> alkyl  
 moiety, and wherein each of these moieties, excluding hydrogen, may be optionally  
 35 substituted;

- R<sub>2</sub>' is hydrogen, C<sub>1-10</sub> alkyl, C<sub>3-7</sub> cycloalkyl, C<sub>3-7</sub> cycloalkylalkyl, aryl, arylC<sub>1-10</sub> alkyl, heteroaryl, heteroarylC<sub>1-10</sub> alkyl, heterocyclic, or a heterocyclylC<sub>1-10</sub> alkyl moiety, and wherein these moieties, excluding hydrogen, may be optionally; or wherein R<sub>2</sub>' is the moiety (CR<sub>10</sub>R<sub>20</sub>)<sub>t</sub>X<sub>1</sub>(CR<sub>10</sub>R<sub>20</sub>)<sub>q</sub>C(A<sub>1</sub>)(A<sub>2</sub>)(A<sub>3</sub>);
- 5 A<sub>1</sub> is an optionally substituted C<sub>1-10</sub> alkyl, heterocyclic, heterocyclic C<sub>1-10</sub> alkyl, heteroaryl, heteroaryl C<sub>1-10</sub> alkyl, aryl, or aryl C<sub>1-10</sub> alkyl;
- A<sub>2</sub> is an optionally substituted C<sub>1-10</sub> alkyl, heterocyclic, heterocyclic C<sub>1-10</sub> alkyl, heteroaryl, heteroaryl C<sub>1-10</sub> alkyl, aryl, or aryl C<sub>1-10</sub> alkyl;
- A<sub>3</sub> is hydrogen or is an optionally substituted C<sub>1-10</sub> alkyl;
- 10 R<sub>3</sub> is a C<sub>1-10</sub> alkyl, C<sub>3-7</sub> cycloalkyl, C<sub>3-7</sub> cycloalkyl C<sub>1-10</sub> alkyl, aryl, arylC<sub>1-10</sub> alkyl, heteroaryl, heteroarylC<sub>1-10</sub> alkyl, heterocyclic or a heterocyclylC<sub>1-10</sub> alkyl moiety, and wherein each of these moieties may be optionally substituted;
- R<sub>4</sub> and R<sub>14</sub> are each independently selected at each occurrence from hydrogen, C<sub>1-4</sub> alkyl, C<sub>3-7</sub> cycloalkyl, C<sub>3-7</sub> cycloalkylC<sub>1-4</sub>alkyl, aryl, aryl-C<sub>1-4</sub> alkyl,
- 15 heterocyclic, heterocyclic C<sub>1-4</sub> alkyl, heteroaryl or a heteroaryl C<sub>1-4</sub> alkyl moiety, and wherein each of these moieties, excluding hydrogen, may be optionally substituted; or the R<sub>4</sub> and R<sub>14</sub> together with the nitrogen which they are attached form an optionally substituted heterocyclic ring of 4 to 7 members, which ring optionally contains an additional heteroatom selected from oxygen,
- 20 sulfur or nitrogen;
- R<sub>4</sub>' and R<sub>14</sub>' are each independently selected at each occurrence from hydrogen or C<sub>1-4</sub> alkyl, or R<sub>4</sub>' and R<sub>14</sub>' together with the nitrogen to which they are attached form a heterocyclic ring of 5 to 7 members, which ring optionally contains an additional heteroatom selected from NR<sub>9</sub>';
- 25 R<sub>5</sub> is independently selected at each occurrence from hydrogen, C<sub>1-4</sub> alkyl, C<sub>2-4</sub> alkenyl, C<sub>2-4</sub> alkynyl or NR<sub>4</sub>'R<sub>14</sub>', excluding the moieties SR<sub>5</sub> being SNR<sub>4</sub>'R<sub>14</sub>', S(O)<sub>2</sub>R<sub>5</sub> being SO<sub>2</sub>H and S(O)R<sub>5</sub> being SOH;
- R<sub>9</sub>' is independently selected at each occurrence from hydrogen, or C<sub>1-4</sub> alkyl;
- R<sub>10</sub> and R<sub>20</sub> are independently selected at each occurrence from hydrogen or
- 30 C<sub>1-4</sub>alkyl;
- R<sub>10</sub>' is independently selected at each occurrence from hydrogen or C<sub>1-4</sub>alkyl;
- R<sub>11</sub> is independently selected at each occurrence from hydrogen or C<sub>1-4</sub>alkyl;
- R<sub>12</sub> is independently selected at each occurrence from hydrogen, C<sub>1-4</sub> alkyl, halo-substituted C<sub>1-4</sub> alkyl, C<sub>2-4</sub> alkenyl, C<sub>2-4</sub> alkynyl, C<sub>3-7</sub> cycloalkyl,
- 35 C<sub>3-7</sub>cycloalkylC<sub>1-4</sub> alkyl, C<sub>5-7</sub> cycloalkenyl, C<sub>5-7</sub>cycloalkenyl C<sub>1-4</sub> alkyl, aryl, arylC<sub>1-4</sub> alkyl, heteroaryl, heteroarylC<sub>1-4</sub> alkyl, heterocyclyl, or a

heterocyclylC<sub>1-4</sub> alkyl moiety, and wherein each of these moieties, excluding hydrogen, may be optionally substituted;

R<sub>13</sub> is independently selected at each occurrence from hydrogen, C<sub>1-4</sub> alkyl, halo-substituted C<sub>1-4</sub> alkyl, C<sub>2-4</sub> alkenyl, C<sub>2-4</sub> alkynyl, C<sub>3-7</sub> cycloalkyl,

5 C<sub>3-7</sub>cycloalkylC<sub>1-4</sub> alkyl, C<sub>5-7</sub> cycloalkenyl, C<sub>5-7</sub>cycloalkenyl C<sub>1-4</sub> alkyl, aryl, arylC<sub>1-4</sub> alkyl, heteroaryl, heteroarylC<sub>1-4</sub> alkyl, heterocyclyl, or a heterocyclylC<sub>1-4</sub> alkyl moiety, and wherein each of these moieties, excluding hydrogen, may be optionally substituted;

10 R<sub>d</sub> and R<sub>d</sub>' are each independently selected from hydrogen, C<sub>1-4</sub> alkyl, C<sub>3-6</sub> cycloalkyl, C<sub>3-6</sub> cycloalkylC<sub>1-4</sub>alkyl moiety, and wherein each of these moieties, excluding hydrogen, may be optionally substituted; or R<sub>d</sub> and R<sub>d</sub>' together with the nitrogen which they are attached form an optionally substituted heterocyclic ring of 5 to 6 members, which ring optionally contains an additional heteroatom selected from oxygen, sulfur or NR<sub>9</sub>';

15 g is 0 or an integer having a value of 1, 2, 3, or 4;

n' is independently selected at each occurrence from 0 or an integer having a value of 1 to 10;

m is independently selected at each occurrence from 0 or an integer having a value of 1 or 2;

20 q is 0 or an integer having a value of 1 to 10;

q' is 0, or an integer having a value of 1 to 6;

t is an integer having a value of 2 to 6;

v is 0 or an integer having a value of 1 or 2;

25 v' is independently selected at each occurrence from 0 or an integer having a value of 1 or 2;

Z is independently selected at each occurrence from oxygen or sulfur; and

a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof.

30 Representative examples of Formula (IV) and (IVa) are:

4-[2-{[3-(diethylamino)propyl]amino}-8-(2,6-difluorophenyl)-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl]benzoic acid

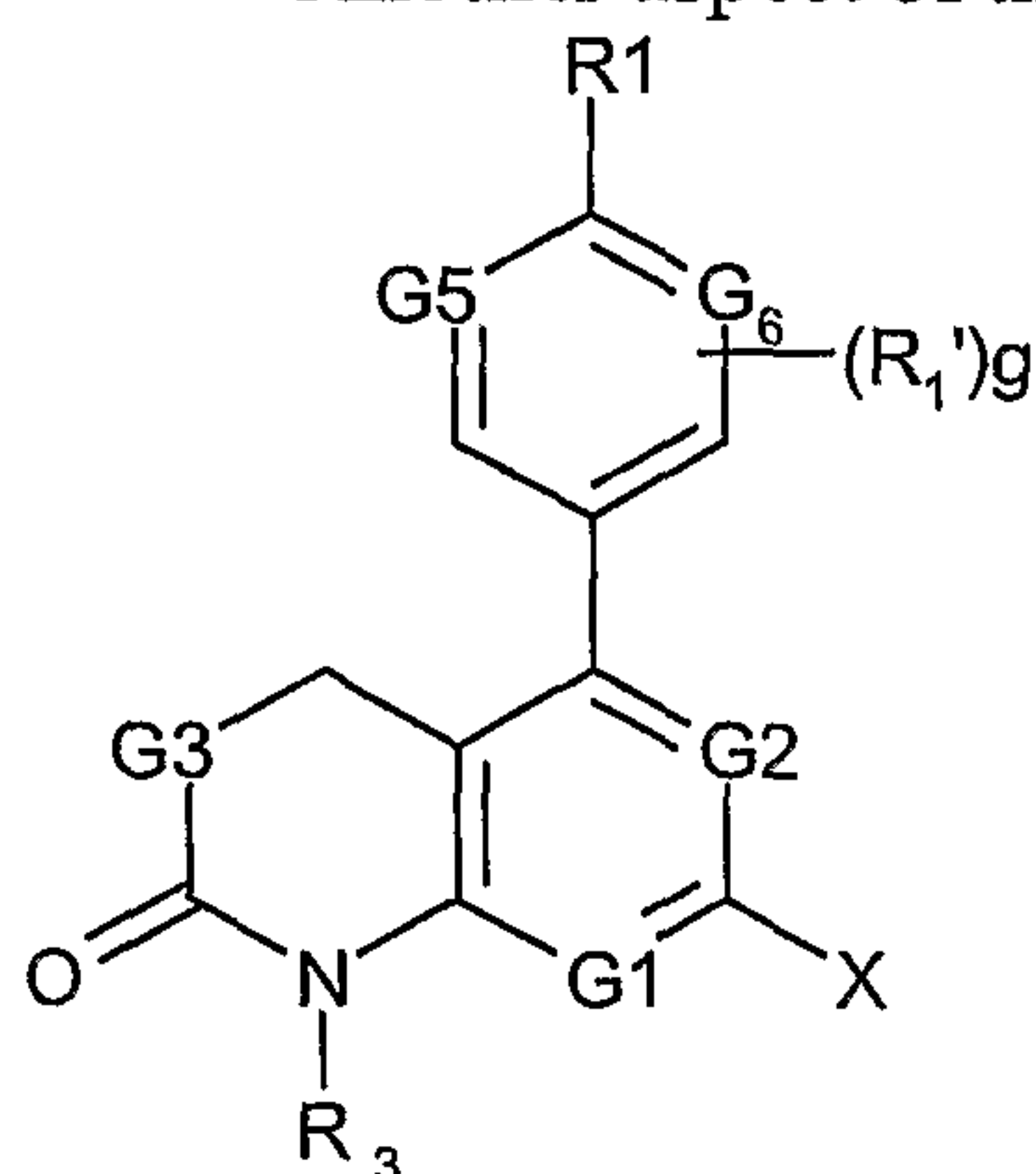
4-[2-{[3-(diethylamino)propyl]amino}-8-(2,6-difluorophenyl)-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl]-*N*-propylbenzamide

35 4-[2-{[3-(diethylamino)propyl]amino}-8-(2,6-difluorophenyl)-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl]-*N*-(1-methylethyl)benzamide

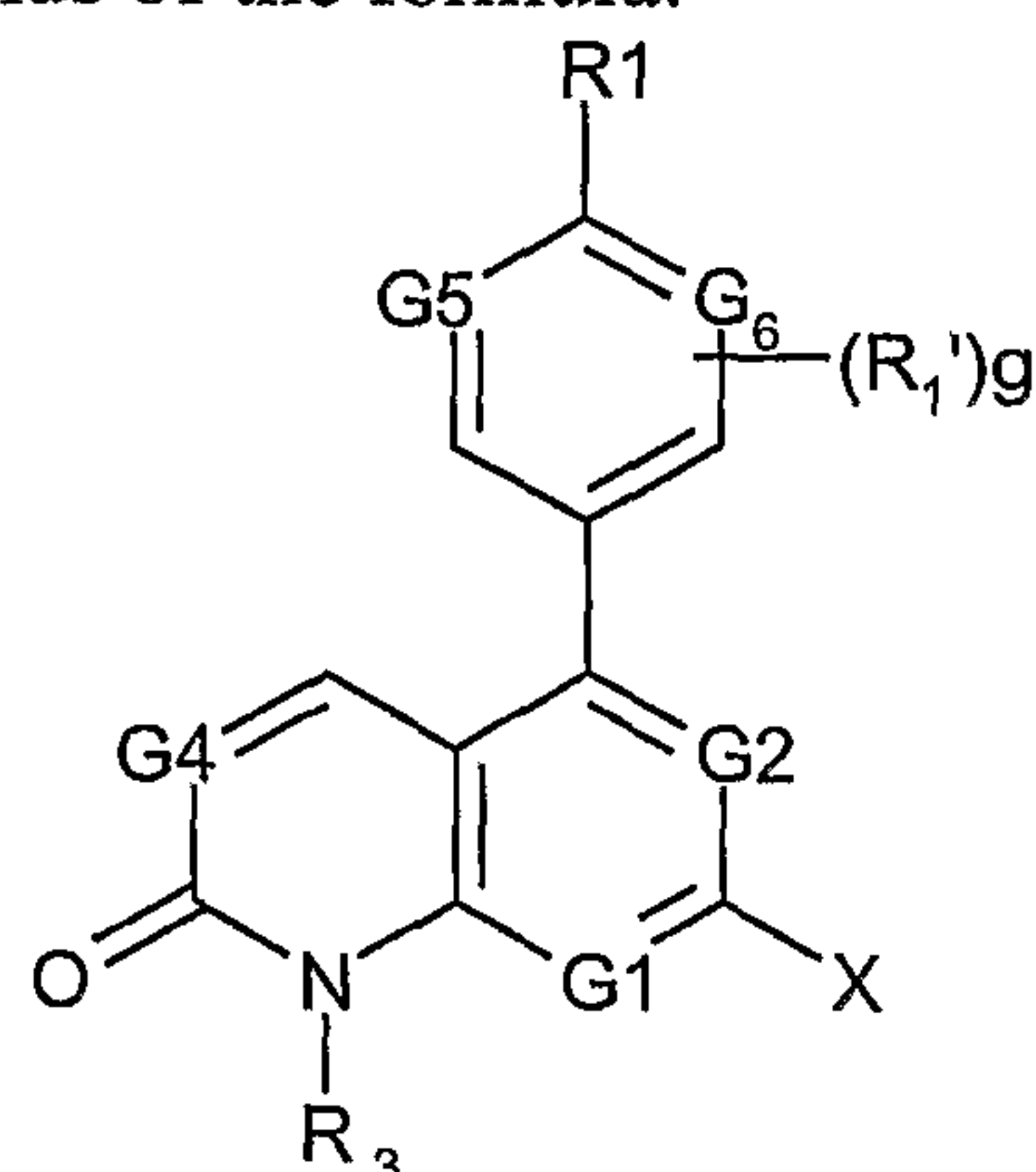
*N*-cyclopropyl-4-[2-{[3-(diethylamino)propyl]amino}-8-(2,6-difluorophenyl)-7-oxo-

- 7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl]benzamide  
 4-[2-{[3-(diethylamino)propyl]amino}-8-(2,6-difluorophenyl)-7-oxo-7,8-  
 dihydropyrido[2,3-*d*]pyrimidin-4-yl]-*N*-(4-fluorophenyl)benzamide  
 4-[2-{[3-(diethylamino)propyl]amino}-8-(2,6-difluorophenyl)-7-oxo-7,8-  
 5 dihydropyrido[2,3-*d*]pyrimidin-4-yl]-*N*-1,3-thiazol-2-ylbenzamide

Another aspect of the invention are compounds of the formula:



(V) or



(Va)

- 10 wherein  
 G<sub>1</sub> and G<sub>2</sub> are independently selected from nitrogen or carbon:  
 G<sub>3</sub> is CH<sub>2</sub>;  
 G<sub>4</sub> is CH;  
 G<sub>5</sub> and G<sub>6</sub> are nitrogen and CH, provided that only one of G<sub>5</sub> or G<sub>6</sub> is nitrogen and  
 15 the other is CH;  
 R<sub>1</sub> is C(Z)N(R<sub>10'</sub>)(CR<sub>10</sub>R<sub>20</sub>)<sub>v</sub>R<sub>b</sub>, C(Z)O(CR<sub>10</sub>R<sub>20</sub>)<sub>v</sub>R<sub>b</sub>,  
 N(R<sub>10'</sub>)C(Z)(CR<sub>10</sub>R<sub>20</sub>)<sub>v</sub>R<sub>b</sub>, N(R<sub>10'</sub>)C(Z)N(R<sub>10'</sub>)(CR<sub>10</sub>R<sub>20</sub>)<sub>v</sub>R<sub>b</sub>, or  
 N(R<sub>10'</sub>)OC(Z)(CR<sub>10</sub>R<sub>20</sub>)<sub>v</sub>R<sub>b</sub>;  
 R<sub>1'</sub> is independently selected at each occurrence from halogen, C<sub>1-4</sub> alkyl, halo-  
 20 substituted-C<sub>1-4</sub> alkyl, cyano, nitro, (CR<sub>10</sub>R<sub>20</sub>)<sub>v</sub>NR<sub>d</sub>R<sub>d'</sub>,  
 (CR<sub>10</sub>R<sub>20</sub>)<sub>v</sub>C(O)R<sub>12</sub>, SR<sub>5</sub>, S(O)R<sub>5</sub>, S(O)<sub>2</sub>R<sub>5</sub>, or (CR<sub>10</sub>R<sub>20</sub>)<sub>v</sub>OR<sub>13</sub>;  
 R<sub>b</sub> is hydrogen, C<sub>1-10</sub> alkyl, C<sub>3-7</sub> cycloalkyl, C<sub>3-7</sub> cycloalkyl C<sub>1-10</sub> alkyl, aryl,  
 arylC<sub>1-10</sub>alkyl, heteroaryl, heteroarylC<sub>1-10</sub> alkyl, heterocyclic, or  
 heterocyclylC<sub>1-10</sub> alkyl moiety, which moieties, excluding hydrogen, may all be  
 25 optionally substituted;  
 X is R<sub>2</sub>, OR<sub>2'</sub>, S(O)<sub>m</sub>R<sub>2'</sub>, (CH<sub>2</sub>)<sub>n</sub>N(R<sub>10'</sub>)S(O)<sub>m</sub>R<sub>2'</sub>, (CH<sub>2</sub>)<sub>n</sub>N(R<sub>10'</sub>)C(O)R<sub>2'</sub>,  
 (CH<sub>2</sub>)<sub>n</sub>NR<sub>4</sub>R<sub>14</sub>, (CH<sub>2</sub>)<sub>n</sub>N(R<sub>2'</sub>)(R<sub>2''</sub>), or N(R<sub>10'</sub>)R<sub>h</sub>NH-C(=N-CN)NR<sub>q</sub>R<sub>q'</sub>;  
 X<sub>1</sub> is N(R<sub>11</sub>), O, S(O)<sub>m</sub>, or CR<sub>10</sub>R<sub>20</sub>;

$R_h$  is selected from an optionally substituted  $C_{1-10}$  alkyl,  $-CH_2-C(O)-CH_2-$ ,  
 $-CH_2-CH_2-O-CH_2-CH_2-$ ,  $-CH_2-C(O)N(R_{10'})CH_2-CH_2-$ ,  $-CH_2-N(R_{10'})C(O)CH_2-$ ,  
 $-CH_2-CH(OR_{10'})-CH_2-$ ,  $-CH_2-C(O)O-CH_2-CH_2-$ , or  $-CH_2-CH_2-O-C(O)CH_2-$ ;

$R_q$  and  $R_{q'}$  are independently selected at each occurrence from hydrogen,  $C_{1-10}$

5 alkyl,  $C_{3-7}$ cycloalkyl,  $C_{3-7}$ cycloalkyl $C_{1-10}$ alkyl,  $C_{5-7}$  cycloalkenyl,  $C_{5-7}$   
 cycloalkenyl- $C_{1-10}$ alkyl, aryl, aryl $C_{1-10}$  alkyl, heteroaryl, heteroaryl $C_{1-10}$   
 alkyl, heterocyclic, or a heterocyclyl $C_{1-10}$  alkyl moiety, wherein all of the  
 moieties except for hydrogen, are optionally substituted, or  $R_q$  and  $R_{q'}$  together  
 with the nitrogen to which they are attached form an optionally substituted  
 10 heterocyclic ring of 5 to 7 members, which ring may contain an additional  
 heteroatom selected from oxygen, nitrogen or sulfur;

$R_2$  is hydrogen,  $C_{1-10}$  alkyl,  $C_{3-7}$  cycloalkyl,  $C_{3-7}$  cycloalkylalkyl, aryl, aryl $C_{1-10}$   
 alkyl, heteroaryl, heteroaryl $C_{1-10}$  alkyl, heterocyclic, or a heterocyclyl $C_{1-10}$   
 alkyl moiety, and wherein each of these moieties, excluding hydrogen, may be  
 15 optionally substituted; or

$R_2$  is the moiety  $(CR_{10}R_{20})_qX_1(CR_{10}R_{20})_qC(A_1)(A_2)(A_3)$ , or  
 $(CR_{10}R_{20})_qC(A_1)(A_2)(A_3)$ ;

$R_{2'}$  is hydrogen,  $C_{1-10}$  alkyl,  $C_{3-7}$  cycloalkyl,  $C_{3-7}$  cycloalkylalkyl, aryl, aryl $C_{1-10}$   
 alkyl, heteroaryl, heteroaryl $C_{1-10}$  alkyl, heterocyclic, or a heterocyclyl $C_{1-10}$  alkyl  
 20 moiety, and wherein each of these moieties, excluding hydrogen, may be optionally  
 substituted;

$R_{2''}$  is hydrogen,  $C_{1-10}$  alkyl,  $C_{3-7}$  cycloalkyl,  $C_{3-7}$  cycloalkylalkyl, aryl, aryl $C_{1-10}$   
 alkyl, heteroaryl, heteroaryl $C_{1-10}$  alkyl, heterocyclic, or a heterocyclyl $C_{1-10}$  alkyl  
 moiety, and wherein these moieties, excluding hydrogen, may be optionally; or  
 25 wherein  $R_{2''}$  is the moiety  $(CR_{10}R_{20})_tX_1(CR_{10}R_{20})_qC(A_1)(A_2)(A_3)$ ;

$A_1$  is an optionally substituted  $C_{1-10}$  alkyl, heterocyclic, heterocyclic  $C_{1-10}$  alkyl,  
 heteroaryl, heteroaryl  $C_{1-10}$  alkyl, aryl, or aryl  $C_{1-10}$  alkyl;

$A_2$  is an optionally substituted  $C_{1-10}$  alkyl, heterocyclic, heterocyclic  $C_{1-10}$  alkyl,  
 heteroaryl, heteroaryl  $C_{1-10}$  alkyl, aryl, or aryl  $C_{1-10}$  alkyl;

30  $A_3$  is hydrogen or is an optionally substituted  $C_{1-10}$  alkyl;

$R_3$  is a  $C_{1-10}$  alkyl,  $C_{3-7}$  cycloalkyl,  $C_{3-7}$  cycloalkyl  $C_{1-10}$  alkyl, aryl, aryl $C_{1-10}$   
 alkyl, heteroaryl, heteroaryl $C_{1-10}$  alkyl, heterocyclic or a heterocyclyl $C_{1-10}$  alkyl  
 moiety, and wherein each of these moieties may be optionally substituted;

$R_4$  and  $R_{14}$  are each independently selected at each occurrence from hydrogen,  $C_{1-4}$   
 35 alkyl,  $C_{3-7}$  cycloalkyl,  $C_{3-7}$  cycloalkyl $C_{1-4}$ alkyl, aryl, aryl- $C_{1-4}$  alkyl,  
 heterocyclic, heterocyclic  $C_{1-4}$  alkyl, heteroaryl or a heteroaryl  $C_{1-4}$  alkyl  
 moiety, and wherein each of these moieties, excluding hydrogen, may be

optionally substituted; or the R<sub>4</sub> and R<sub>14</sub> together with the nitrogen which they are attached form an optionally substituted heterocyclic ring of 4 to 7 members, which ring optionally contains an additional heteroatom selected from oxygen, sulfur or nitrogen;

- 5 R<sub>4</sub>' and R<sub>14</sub>' are each independently selected at each occurrence from hydrogen or C<sub>1-4</sub> alkyl, or R<sub>4</sub>' and R<sub>14</sub>' together with the nitrogen to which they are attached form a heterocyclic ring of 5 to 7 members, which ring optionally contains an additional heteroatom selected from NR<sub>9</sub>';

- 10 R<sub>5</sub> is independently selected at each occurrence from hydrogen, C<sub>1-4</sub> alkyl, C<sub>2-4</sub> alkenyl, C<sub>2-4</sub> alkynyl or NR<sub>4</sub>'R<sub>14</sub>', excluding the moieties SR<sub>5</sub> being SNR<sub>4</sub>'R<sub>14</sub>', S(O)<sub>2</sub>R<sub>5</sub> being SO<sub>2</sub>H and S(O)R<sub>5</sub> being SOH;

R<sub>9</sub>' is independently selected at each occurrence from hydrogen, or C<sub>1-4</sub> alkyl;

R<sub>10</sub> and R<sub>20</sub> are independently selected at each occurrence from hydrogen or C<sub>1-4</sub>alkyl;

- 15 R<sub>10</sub>' is independently selected at each occurrence from hydrogen or C<sub>1-4</sub>alkyl;

R<sub>11</sub> is independently selected at each occurrence from hydrogen or C<sub>1-4</sub>alkyl;

R<sub>12</sub> is independently selected at each occurrence from hydrogen, C<sub>1-4</sub> alkyl, halo-substituted C<sub>1-4</sub> alkyl, C<sub>2-4</sub> alkenyl, C<sub>2-4</sub> alkynyl, C<sub>3-7</sub> cycloalkyl,

- 20 C<sub>3-7</sub>cycloalkylC<sub>1-4</sub> alkyl, C<sub>5-7</sub> cycloalkenyl, C<sub>5-7</sub>cycloalkenyl C<sub>1-4</sub> alkyl, aryl, arylC<sub>1-4</sub> alkyl, heteroaryl, heteroarylC<sub>1-4</sub> alkyl, heterocyclyl, or a heterocyclylC<sub>1-4</sub> alkyl moiety, and wherein each of these moieties, excluding hydrogen, may be optionally substituted;

R<sub>13</sub> is independently selected at each occurrence from hydrogen, C<sub>1-4</sub> alkyl, halo-substituted C<sub>1-4</sub> alkyl, C<sub>2-4</sub> alkenyl, C<sub>2-4</sub> alkynyl, C<sub>3-7</sub> cycloalkyl,

- 25 C<sub>3-7</sub>cycloalkylC<sub>1-4</sub> alkyl, C<sub>5-7</sub> cycloalkenyl, C<sub>5-7</sub>cycloalkenyl C<sub>1-4</sub> alkyl, aryl, arylC<sub>1-4</sub> alkyl, heteroaryl, heteroarylC<sub>1-4</sub> alkyl, heterocyclyl, or a heterocyclylC<sub>1-4</sub> alkyl moiety, and wherein each of these moieties, excluding hydrogen, may be optionally substituted;

R<sub>d</sub> and R<sub>d</sub>' are each independently selected from hydrogen, C<sub>1-4</sub> alkyl, C<sub>3-6</sub>

- 30 cycloalkyl, C<sub>3-6</sub> cycloalkylC<sub>1-4</sub>alkyl moiety, and wherein each of these moieties, excluding hydrogen, may be optionally substituted; or R<sub>d</sub> and R<sub>d</sub>' together with the nitrogen which they are attached form an optionally substituted heterocyclic ring of 5 to 6 members, which ring optionally contains an additional heteroatom selected from oxygen, sulfur or NR<sub>9</sub>';

- 35 g is 0 or an integer having a value of 1, 2, 3, or 4;

n' is independently selected at each occurrence from 0 or an integer having a value of 1 to 10;

m is independently selected at each occurrence from 0 or an integer having a value of 1 or 2;

q is 0 or an integer having a value of 1 to 10;

q' is 0, or an integer having a value of 1 to 6;

5 t is an integer having a value of 2 to 6;

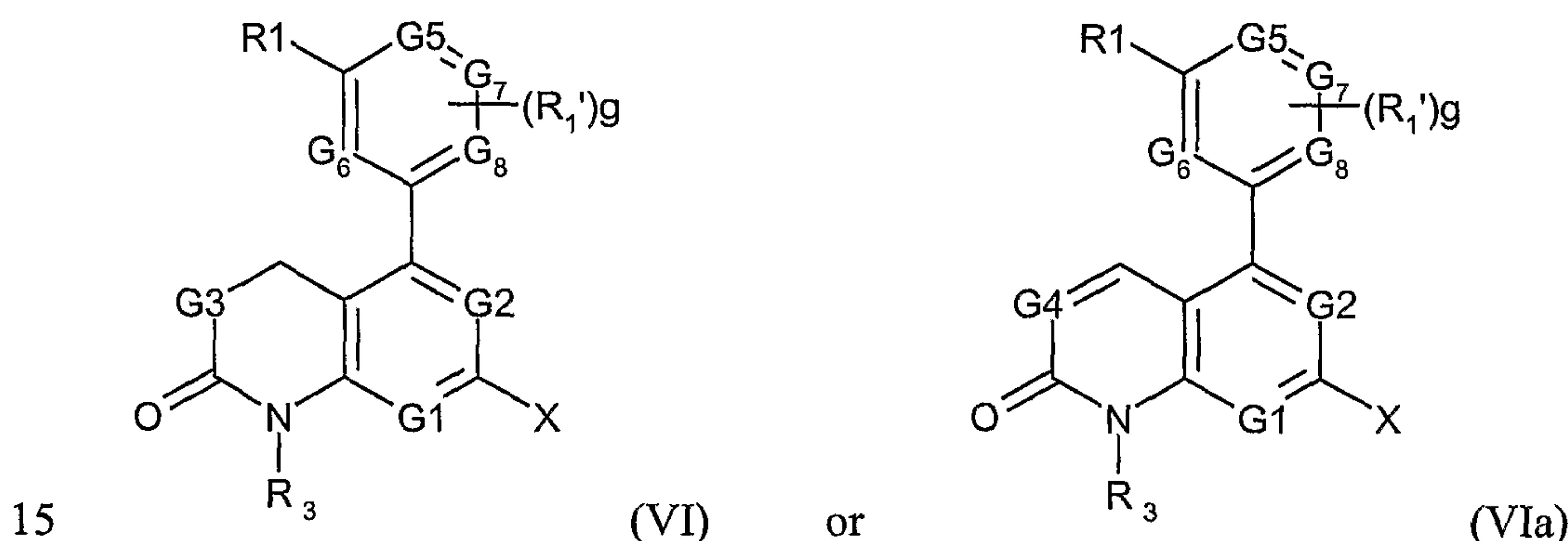
v is 0 or an integer having a value of 1 or 2;

v' is independently selected at each occurrence from 0 or an integer having a value of 1 or 2;

Z is independently selected at each occurrence from oxygen or sulfur; and

10 a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof.

Another aspect of the invention are compounds of the formula:



wherein

G<sub>1</sub> and G<sub>2</sub> are independently selected from nitrogen or CH:

G<sub>3</sub> is CH<sub>2</sub>;

20 G<sub>4</sub> is CH;

one of G<sub>5</sub>, G<sub>6</sub>, G<sub>7</sub> and G<sub>8</sub> is nitrogen and the others are CH;

R<sub>1</sub> is C(Z)N(R<sub>10</sub>') (CR<sub>10</sub>R<sub>20</sub>)<sub>v</sub>R<sub>b</sub>, C(Z)O(CR<sub>10</sub>R<sub>20</sub>)<sub>v</sub>R<sub>b</sub>,  
N(R<sub>10</sub>')C(Z)(CR<sub>10</sub>R<sub>20</sub>)<sub>v</sub>R<sub>b</sub>, N(R<sub>10</sub>')C(Z)N(R<sub>10</sub>') (CR<sub>10</sub>R<sub>20</sub>)<sub>v</sub>R<sub>b</sub>, or  
N(R<sub>10</sub>')OC(Z)(CR<sub>10</sub>R<sub>20</sub>)<sub>v</sub>R<sub>b</sub>;

25 R<sub>1</sub>' is independently selected at each occurrence from halogen, C<sub>1-4</sub> alkyl, halo-substituted-C<sub>1-4</sub> alkyl, cyano, nitro, (CR<sub>10</sub>R<sub>20</sub>)<sub>v</sub>'NR<sub>d</sub>R<sub>d</sub>',  
(CR<sub>10</sub>R<sub>20</sub>)<sub>v</sub>'C(O)R<sub>12</sub>, SR<sub>5</sub>, S(O)R<sub>5</sub>, S(O)<sub>2</sub>R<sub>5</sub>, or (CR<sub>10</sub>R<sub>20</sub>)<sub>v</sub>'OR<sub>13</sub>;  
R<sub>b</sub> is hydrogen, C<sub>1-10</sub> alkyl, C<sub>3-7</sub> cycloalkyl, C<sub>3-7</sub> cycloalkyl C<sub>1-10</sub> alkyl, aryl,  
arylC<sub>1-10</sub>alkyl, heteroaryl, heteroarylC<sub>1-10</sub> alkyl, heterocyclic, or

heterocyclylC<sub>1-10</sub> alkyl moiety, which moieties, excluding hydrogen, may all be optionally substituted;

X is R<sub>2</sub>, OR<sub>2</sub>', S(O)<sub>m</sub>R<sub>2</sub>', (CH<sub>2</sub>)<sub>n</sub>N(R<sub>10</sub>')S(O)<sub>m</sub>R<sub>2</sub>', (CH<sub>2</sub>)<sub>n</sub>N(R<sub>10</sub>')C(O)R<sub>2</sub>', (CH<sub>2</sub>)<sub>n</sub>NR<sub>4</sub>R<sub>14</sub>, (CH<sub>2</sub>)<sub>n</sub>N(R<sub>2</sub>')R<sub>2</sub>'', or N(R<sub>10</sub>')R<sub>h</sub>NH-C(=N-CN)NR<sub>q</sub>R<sub>q</sub>';

5 X<sub>1</sub> is N(R<sub>11</sub>), O, S(O)<sub>m</sub>, or CR<sub>10</sub>R<sub>20</sub>;

R<sub>h</sub> is selected from an optionally substituted C<sub>1-10</sub> alkyl, -CH<sub>2</sub>-C(O)-CH<sub>2</sub>-, -CH<sub>2</sub>-CH<sub>2</sub>-O-CH<sub>2</sub>-CH<sub>2</sub>-, -CH<sub>2</sub>-C(O)N(R<sub>10</sub>')CH<sub>2</sub>-CH<sub>2</sub>-, -CH<sub>2</sub>-N(R<sub>10</sub>')C(O)CH<sub>2</sub>-, -CH<sub>2</sub>-CH(OR<sub>10</sub>')-CH<sub>2</sub>-, -CH<sub>2</sub>-C(O)O-CH<sub>2</sub>-CH<sub>2</sub>-, or -CH<sub>2</sub>-CH<sub>2</sub>-O-C(O)CH<sub>2</sub>-;

10 R<sub>q</sub> and R<sub>q</sub>' are independently selected at each occurrence from hydrogen, C<sub>1-10</sub> alkyl, C<sub>3-7</sub>cycloalkyl, C<sub>3-7</sub>cycloalkylC<sub>1-10</sub>alkyl, C<sub>5-7</sub> cycloalkenyl, C<sub>5-7</sub> cycloalkenyl-C<sub>1-10</sub>alkyl, aryl, arylC<sub>1-10</sub> alkyl, heteroaryl, heteroarylC<sub>1-10</sub> alkyl, heterocyclic, or a heterocyclylC<sub>1-10</sub> alkyl moiety, wherein all of the moieties except for hydrogen, are optionally substituted, or R<sub>q</sub> and R<sub>q</sub>' together  
15 with the nitrogen to which they are attached form an optionally substituted heterocyclic ring of 5 to 7 members, which ring may contain an additional heteroatom selected from oxygen, nitrogen or sulfur;

R<sub>2</sub> is hydrogen, C<sub>1-10</sub> alkyl, C<sub>3-7</sub> cycloalkyl, C<sub>3-7</sub> cycloalkylalkyl, aryl, arylC<sub>1-10</sub> alkyl, heteroaryl, heteroarylC<sub>1-10</sub> alkyl, heterocyclic, or a heterocyclylC<sub>1-10</sub> alkyl moiety, and wherein each of these moieties, excluding hydrogen, may be optionally substituted; or

R<sub>2</sub> is the moiety (CR<sub>10</sub>R<sub>20</sub>)<sub>q</sub>X<sub>1</sub>(CR<sub>10</sub>R<sub>20</sub>)<sub>q</sub>C(A<sub>1</sub>)(A<sub>2</sub>)(A<sub>3</sub>), or (CR<sub>10</sub>R<sub>20</sub>)<sub>q</sub>C(A<sub>1</sub>)(A<sub>2</sub>)(A<sub>3</sub>);

R<sub>2</sub>' is hydrogen, C<sub>1-10</sub> alkyl, C<sub>3-7</sub> cycloalkyl, C<sub>3-7</sub> cycloalkylalkyl, aryl, arylC<sub>1-10</sub> alkyl, heteroaryl, heteroarylC<sub>1-10</sub> alkyl, heterocyclic, or a heterocyclylC<sub>1-10</sub> alkyl moiety, and wherein each of these moieties, excluding hydrogen, may be optionally substituted;

R<sub>2</sub>'' is hydrogen, C<sub>1-10</sub> alkyl, C<sub>3-7</sub> cycloalkyl, C<sub>3-7</sub> cycloalkylalkyl, aryl, arylC<sub>1-10</sub> alkyl, heteroaryl, heteroarylC<sub>1-10</sub> alkyl, heterocyclic, or a heterocyclylC<sub>1-10</sub> alkyl moiety, and wherein these moieties, excluding hydrogen, may be optionally; or  
30 wherein R<sub>2</sub>'' is the moiety (CR<sub>10</sub>R<sub>20</sub>)<sub>t</sub>X<sub>1</sub>(CR<sub>10</sub>R<sub>20</sub>)<sub>q</sub>C(A<sub>1</sub>)(A<sub>2</sub>)(A<sub>3</sub>);

A<sub>1</sub> is an optionally substituted C<sub>1-10</sub> alkyl, heterocyclic, heterocyclic C<sub>1-10</sub> alkyl, heteroaryl, heteroaryl C<sub>1-10</sub> alkyl, aryl, or aryl C<sub>1-10</sub> alkyl;

A<sub>2</sub> is an optionally substituted C<sub>1-10</sub> alkyl, heterocyclic, heterocyclic C<sub>1-10</sub> alkyl, heteroaryl, heteroaryl C<sub>1-10</sub> alkyl, aryl, or aryl C<sub>1-10</sub> alkyl;

35 A<sub>3</sub> is hydrogen or is an optionally substituted C<sub>1-10</sub> alkyl;

- R<sub>3</sub> is a C<sub>1-10</sub> alkyl, C<sub>3-7</sub> cycloalkyl, C<sub>3-7</sub> cycloalkyl C<sub>1-10</sub> alkyl, aryl, arylC<sub>1-10</sub> alkyl, heteroaryl, heteroarylC<sub>1-10</sub> alkyl, heterocyclic or a heterocyclylC<sub>1-10</sub> alkyl moiety, and wherein each of these moieties may be optionally substituted;
- R<sub>4</sub> and R<sub>14</sub> are each independently selected at each occurrence from hydrogen, C<sub>1-4</sub> alkyl, C<sub>3-7</sub> cycloalkyl, C<sub>3-7</sub> cycloalkylC<sub>1-4</sub>alkyl, aryl, aryl-C<sub>1-4</sub> alkyl, heterocyclic, heterocyclic C<sub>1-4</sub> alkyl, heteroaryl or a heteroaryl C<sub>1-4</sub> alkyl moiety, and wherein each of these moieties, excluding hydrogen, may be optionally substituted; or the R<sub>4</sub> and R<sub>14</sub> together with the nitrogen which they are attached form an optionally substituted heterocyclic ring of 4 to 7 members, which ring optionally contains an additional heteroatom selected from oxygen, sulfur or nitrogen;
- R<sub>4'</sub> and R<sub>14'</sub> are each independently selected at each occurrence from hydrogen or C<sub>1-4</sub> alkyl, or R<sub>4'</sub> and R<sub>14'</sub> together with the nitrogen to which they are attached form a heterocyclic ring of 5 to 7 members, which ring optionally contains an additional heteroatom selected from NR<sub>9'</sub>;
- R<sub>5</sub> is independently selected at each occurrence from hydrogen, C<sub>1-4</sub> alkyl, C<sub>2-4</sub> alkenyl, C<sub>2-4</sub> alkynyl or NR<sub>4'</sub>R<sub>14'</sub>, excluding the moieties SR<sub>5</sub> being SNR<sub>4'</sub>R<sub>14'</sub>, S(O)<sub>2</sub>R<sub>5</sub> being SO<sub>2</sub>H and S(O)R<sub>5</sub> being SOH;
- R<sub>9'</sub> is independently selected at each occurrence from hydrogen, or C<sub>1-4</sub> alkyl;
- R<sub>10</sub> and R<sub>20</sub> are independently selected at each occurrence from hydrogen or C<sub>1-4</sub>alkyl;
- R<sub>10'</sub> is independently selected at each occurrence from hydrogen or C<sub>1-4</sub>alkyl;
- R<sub>11</sub> is independently selected at each occurrence from hydrogen or C<sub>1-4</sub>alkyl;
- R<sub>12</sub> is independently selected at each occurrence from hydrogen, C<sub>1-4</sub> alkyl, halo-substituted C<sub>1-4</sub> alkyl, C<sub>2-4</sub> alkenyl, C<sub>2-4</sub> alkynyl, C<sub>3-7</sub> cycloalkyl, C<sub>3-7</sub>cycloalkylC<sub>1-4</sub> alkyl, C<sub>5-7</sub> cycloalkenyl, C<sub>5-7</sub>cycloalkenyl C<sub>1-4</sub> alkyl, aryl, arylC<sub>1-4</sub> alkyl, heteroaryl, heteroarylC<sub>1-4</sub> alkyl, heterocyclyl, or a heterocyclylC<sub>1-4</sub> alkyl moiety, and wherein each of these moieties, excluding hydrogen, may be optionally substituted;
- R<sub>13</sub> is independently selected at each occurrence from hydrogen, C<sub>1-4</sub> alkyl, halo-substituted C<sub>1-4</sub> alkyl, C<sub>2-4</sub> alkenyl, C<sub>2-4</sub> alkynyl, C<sub>3-7</sub> cycloalkyl, C<sub>3-7</sub>cycloalkylC<sub>1-4</sub> alkyl, C<sub>5-7</sub> cycloalkenyl, C<sub>5-7</sub>cycloalkenyl C<sub>1-4</sub> alkyl, aryl, arylC<sub>1-4</sub> alkyl, heteroaryl, heteroarylC<sub>1-4</sub> alkyl, heterocyclyl, or a heterocyclylC<sub>1-4</sub> alkyl moiety, and wherein each of these moieties, excluding hydrogen, may be optionally substituted;
- R<sub>d</sub> and R<sub>d'</sub> are each independently selected from hydrogen, C<sub>1-4</sub> alkyl, C<sub>3-6</sub> cycloalkyl, C<sub>3-6</sub> cycloalkylC<sub>1-4</sub>alkyl moiety, and wherein each of these moieties,

excluding hydrogen, may be optionally substituted; or R<sub>d</sub> and R<sub>d</sub>' together with the nitrogen which they are attached form an optionally substituted heterocyclic ring of 5 to 6 members, which ring optionally contains an additional heteroatom selected from oxygen, sulfur or NR<sub>9</sub>';

5 g is 0 or an integer having a value of 1, 2, 3, or 4;

n' is independently selected at each occurrence from 0 or an integer having a value of 1 to 10;

m is independently selected at each occurrence from 0 or an integer having a value of 1 or 2;

10 q is 0 or an integer having a value of 1 to 10;

q' is 0, or an integer having a value of 1 to 6;

t is an integer having a value of 2 to 6;

v is 0 or an integer having a value of 1 or 2;

v' is independently selected at each occurrence from 0 or an integer having a value of 15 1 or 2;

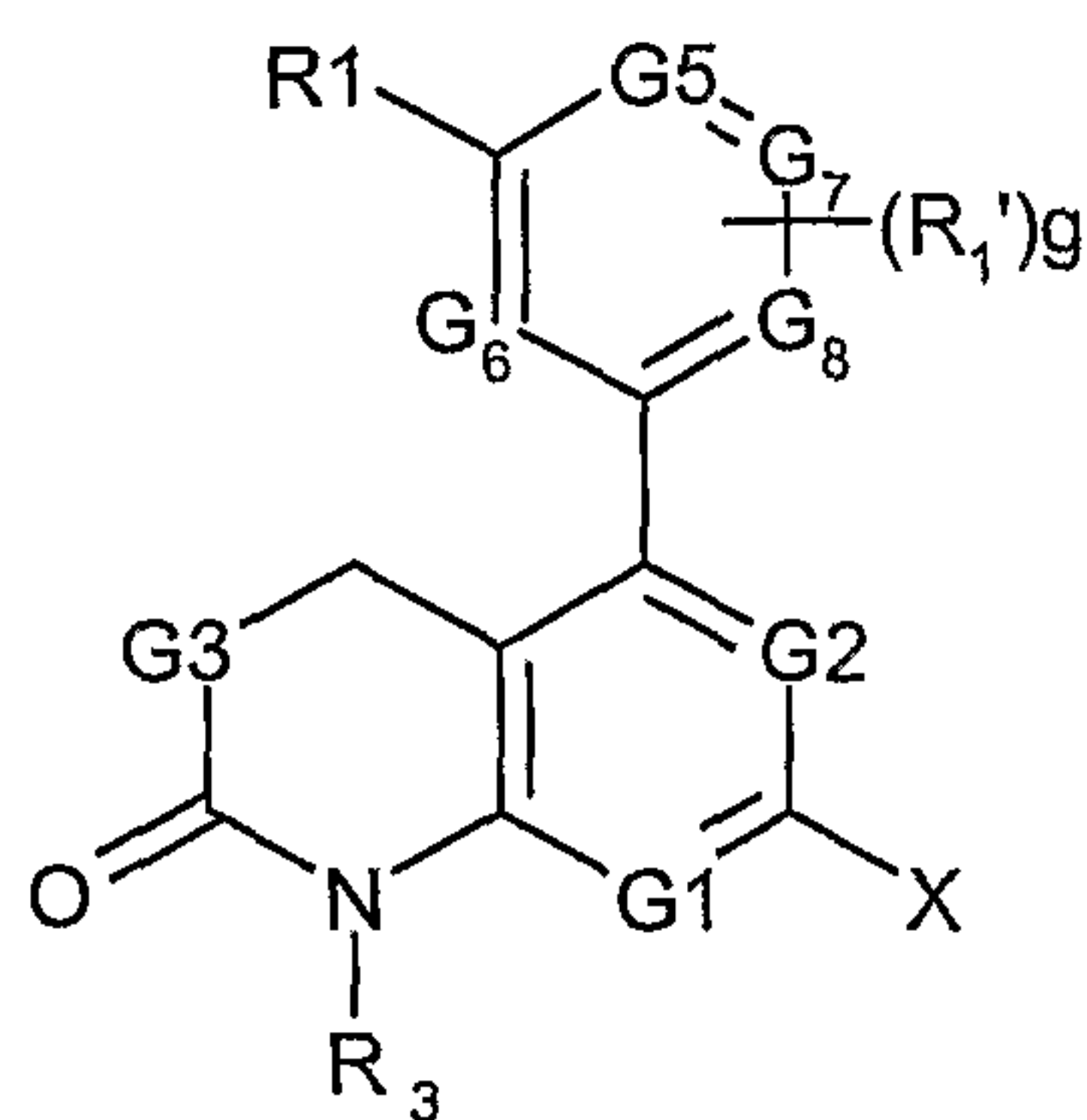
Z is independently selected at each occurrence from oxygen or sulfur; and

a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof.

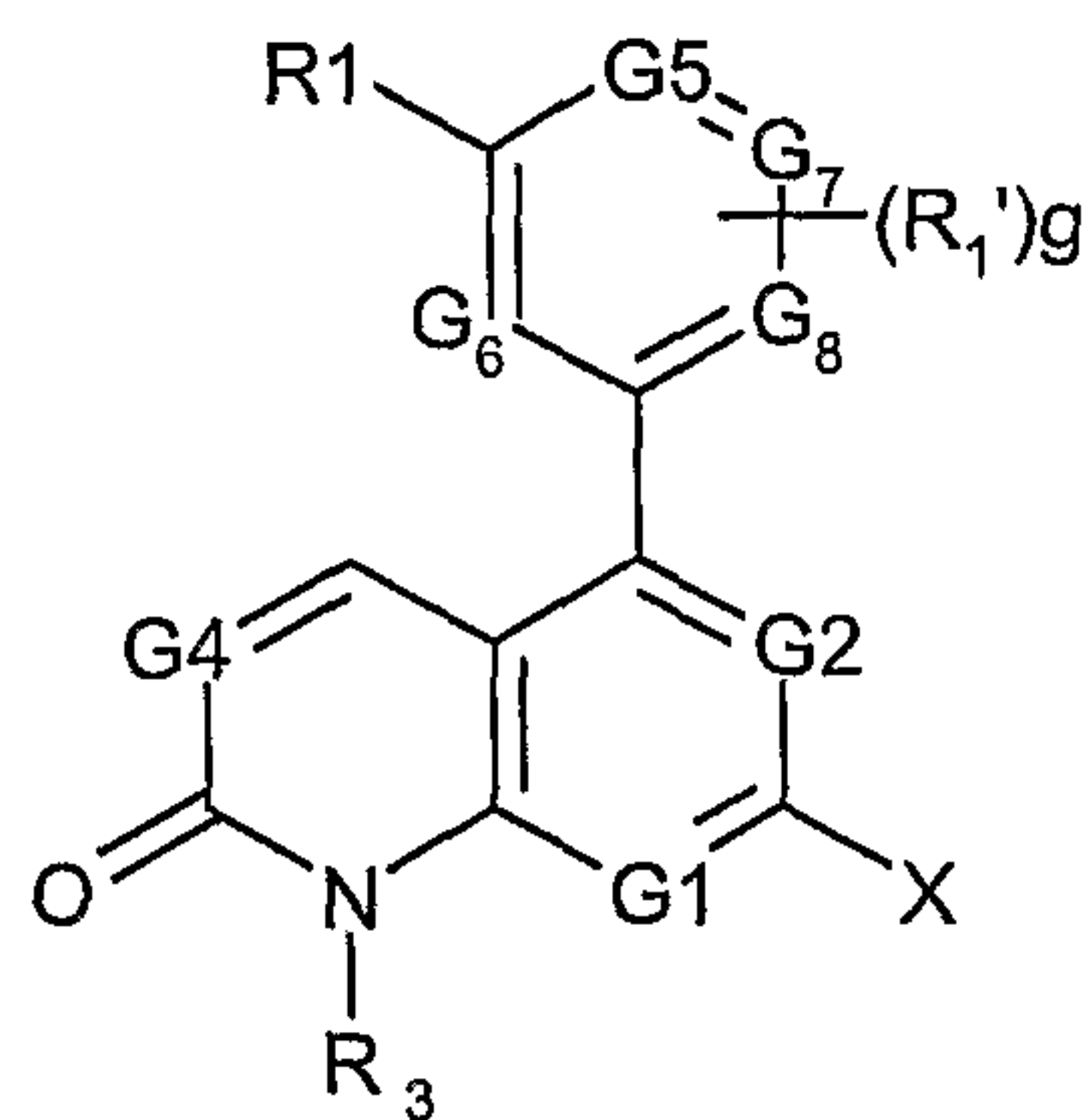
It should be recognized that the difference between compounds of Formula (I) and (Ia), and Formula (II) and (IIa) and those of Formulas (VII) through Formula (VIIi) lie not only in the in the ring substitution of the R<sub>1</sub> group, but that the ring position of the two nitrogen's in the pyrimidine ring. All of the remaining variables have the same meaning for Formulas (VI) through Formula (VIIi) as those described herein for Formula (I) and (Ia), etc.

25

Another aspect of the invention are compounds of the formula:



(VIb) or



(VIc)

30 wherein

G<sub>1</sub> and G<sub>2</sub> are nitrogen;

G<sub>3</sub> is CH<sub>2</sub>;

G<sub>4</sub> is CH;

G<sub>5</sub> and G<sub>6</sub> are nitrogen; and

5 G<sub>7</sub> and G<sub>8</sub> are CH;

R<sub>1</sub> is C(Z)N(R<sub>10'</sub>)(CR<sub>10</sub>R<sub>20</sub>)<sub>v</sub>R<sub>b</sub>, C(Z)O(CR<sub>10</sub>R<sub>20</sub>)<sub>v</sub>R<sub>b</sub>,  
N(R<sub>10'</sub>)C(Z)(CR<sub>10</sub>R<sub>20</sub>)<sub>v</sub>R<sub>b</sub>, N(R<sub>10'</sub>)C(Z)N(R<sub>10'</sub>)(CR<sub>10</sub>R<sub>20</sub>)<sub>v</sub>R<sub>b</sub>, or  
N(R<sub>10'</sub>)OC(Z)(CR<sub>10</sub>R<sub>20</sub>)<sub>v</sub>R<sub>b</sub>;

10 R<sub>1'</sub> is independently selected at each occurrence from halogen, C<sub>1-4</sub> alkyl, halo-substituted-C<sub>1-4</sub> alkyl, cyano, nitro, (CR<sub>10</sub>R<sub>20</sub>)<sub>v</sub>NR<sub>d</sub>R<sub>d'</sub>,

(CR<sub>10</sub>R<sub>20</sub>)<sub>v</sub>C(O)R<sub>12</sub>, SR<sub>5</sub>, S(O)R<sub>5</sub>, S(O)<sub>2</sub>R<sub>5</sub>, or (CR<sub>10</sub>R<sub>20</sub>)<sub>v</sub>OR<sub>13</sub>;

R<sub>b</sub> is hydrogen, C<sub>1-10</sub> alkyl, C<sub>3-7</sub> cycloalkyl, C<sub>3-7</sub> cycloalkyl C<sub>1-10</sub> alkyl, aryl, arylC<sub>1-10</sub>alkyl, heteroaryl, heteroarylC<sub>1-10</sub> alkyl, heterocyclic, or heterocyclylC<sub>1-10</sub> alkyl moiety, which moieties, excluding hydrogen, may all be

15 optionally substituted;

X is R<sub>2</sub>, OR<sub>2'</sub>, S(O)<sub>m</sub>R<sub>2'</sub>, (CH<sub>2</sub>)<sub>n</sub>N(R<sub>10'</sub>)S(O)<sub>m</sub>R<sub>2'</sub>, (CH<sub>2</sub>)<sub>n</sub>N(R<sub>10'</sub>)C(O)R<sub>2'</sub>,  
(CH<sub>2</sub>)<sub>n</sub>NR<sub>4</sub>R<sub>14</sub>, (CH<sub>2</sub>)<sub>n</sub>N(R<sub>2'</sub>)(R<sub>2''</sub>), or N(R<sub>10'</sub>)R<sub>h</sub>NH-C(=N-CN)NR<sub>q</sub>R<sub>q'</sub>;

X<sub>1</sub> is N(R<sub>11</sub>), O, S(O)<sub>m</sub>, or CR<sub>10</sub>R<sub>20</sub>;

20 R<sub>h</sub> is selected from an optionally substituted C<sub>1-10</sub> alkyl, -CH<sub>2</sub>-C(O)-CH<sub>2</sub>-,  
-CH<sub>2</sub>-CH<sub>2</sub>-O-CH<sub>2</sub>-CH<sub>2</sub>-, -CH<sub>2</sub>-C(O)N(R<sub>10'</sub>)CH<sub>2</sub>-CH<sub>2</sub>-,  
-CH<sub>2</sub>-N(R<sub>10'</sub>)C(O)CH<sub>2</sub>-, -CH<sub>2</sub>-CH(OR<sub>10'</sub>)-CH<sub>2</sub>-, -CH<sub>2</sub>-C(O)O-CH<sub>2</sub>-CH<sub>2</sub>-, or  
-CH<sub>2</sub>-CH<sub>2</sub>-O-C(O)CH<sub>2</sub>-;

25 R<sub>q</sub> and R<sub>q'</sub> are independently selected at each occurrence from hydrogen, C<sub>1-10</sub> alkyl, C<sub>3-7</sub>cycloalkyl, C<sub>3-7</sub>cycloalkylC<sub>1-10</sub>alkyl, C<sub>5-7</sub> cycloalkenyl, C<sub>5-7</sub> cycloalkenyl-C<sub>1-10</sub>alkyl, aryl, arylC<sub>1-10</sub> alkyl, heteroaryl, heteroarylC<sub>1-10</sub> alkyl, heterocyclic, or a heterocyclylC<sub>1-10</sub> alkyl moiety, wherein all of the moieties except for hydrogen, are optionally substituted, or R<sub>q</sub> and R<sub>q'</sub> together with the nitrogen to which they are attached form an optionally substituted heterocyclic ring of 5 to 7 members, which ring may contain an additional  
30 heteroatom selected from oxygen, nitrogen or sulfur;

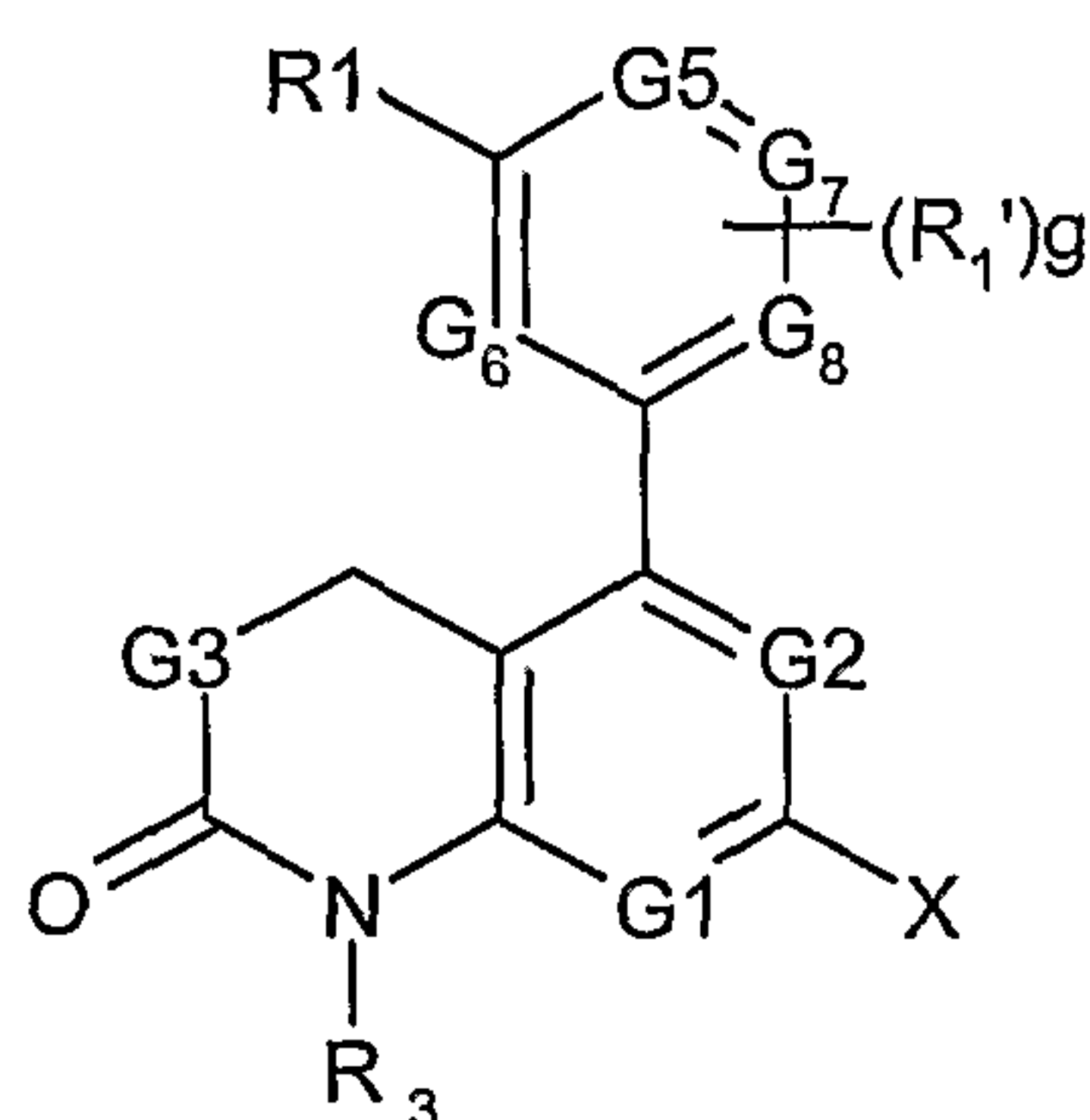
R<sub>2</sub> is hydrogen, C<sub>1-10</sub> alkyl, C<sub>3-7</sub> cycloalkyl, C<sub>3-7</sub> cycloalkylalkyl, aryl, arylC<sub>1-10</sub> alkyl, heteroaryl, heteroarylC<sub>1-10</sub> alkyl, heterocyclic, or a heterocyclylC<sub>1-10</sub> alkyl moiety, and wherein each of these moieties, excluding hydrogen, may be optionally substituted; or

35 R<sub>2</sub> is the moiety (CR<sub>10</sub>R<sub>20</sub>)<sub>q</sub>X<sub>1</sub>(CR<sub>10</sub>R<sub>20</sub>)<sub>q</sub>C(A<sub>1</sub>)(A<sub>2</sub>)(A<sub>3</sub>), or  
(CR<sub>10</sub>R<sub>20</sub>)<sub>q</sub>C(A<sub>1</sub>)(A<sub>2</sub>)(A<sub>3</sub>);

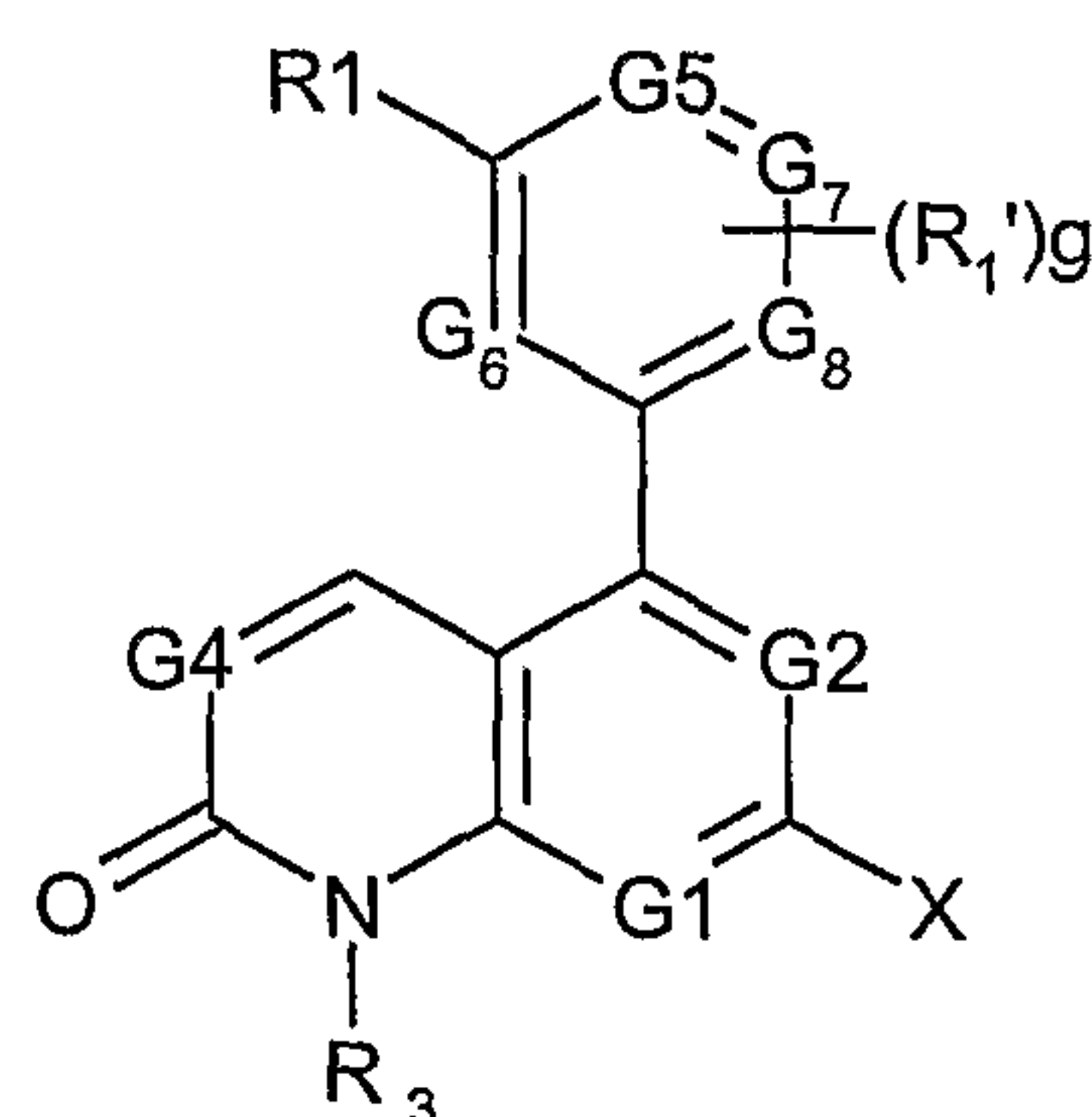
- R<sub>2</sub>' is hydrogen, C<sub>1-10</sub> alkyl, C<sub>3-7</sub> cycloalkyl, C<sub>3-7</sub> cycloalkylalkyl, aryl, arylC<sub>1-10</sub> alkyl, heteroaryl, heteroarylC<sub>1-10</sub> alkyl, heterocyclic, or a heterocyclylC<sub>1-10</sub> alkyl moiety, and wherein each of these moieties, excluding hydrogen, may be optionally substituted;
- 5 R<sub>2</sub>'' is hydrogen, C<sub>1-10</sub> alkyl, C<sub>3-7</sub> cycloalkyl, C<sub>3-7</sub> cycloalkylalkyl, aryl, arylC<sub>1-10</sub> alkyl, heteroaryl, heteroarylC<sub>1-10</sub> alkyl, heterocyclic, or a heterocyclylC<sub>1-10</sub> alkyl moiety, and wherein these moieties, excluding hydrogen, may be optionally; or wherein R<sub>2</sub>'' is the moiety (CR<sub>10</sub>R<sub>20</sub>)<sub>t</sub>X<sub>1</sub>(CR<sub>10</sub>R<sub>20</sub>)<sub>q</sub>C(A<sub>1</sub>)(A<sub>2</sub>)(A<sub>3</sub>);
- A<sub>1</sub> is an optionally substituted C<sub>1-10</sub> alkyl, heterocyclic, heterocyclic C<sub>1-10</sub> alkyl, heteroaryl, heteroaryl C<sub>1-10</sub> alkyl, aryl, or aryl C<sub>1-10</sub> alkyl;
- 10 A<sub>2</sub> is an optionally substituted C<sub>1-10</sub> alkyl, heterocyclic, heterocyclic C<sub>1-10</sub> alkyl, heteroaryl, heteroaryl C<sub>1-10</sub> alkyl, aryl, or aryl C<sub>1-10</sub> alkyl;
- A<sub>3</sub> is hydrogen or is an optionally substituted C<sub>1-10</sub> alkyl;
- R<sub>3</sub> is a C<sub>1-10</sub> alkyl, C<sub>3-7</sub> cycloalkyl, C<sub>3-7</sub> cycloalkyl C<sub>1-10</sub> alkyl, aryl, arylC<sub>1-10</sub> alkyl, heteroaryl, heteroarylC<sub>1-10</sub> alkyl, heterocyclic or a heterocyclylC<sub>1-10</sub> alkyl moiety, and wherein each of these moieties may be optionally substituted;
- 15 R<sub>4</sub> and R<sub>14</sub> are each independently selected at each occurrence from hydrogen, C<sub>1-4</sub> alkyl, C<sub>3-7</sub> cycloalkyl, C<sub>3-7</sub> cycloalkylC<sub>1-4</sub>alkyl, aryl, aryl-C<sub>1-4</sub> alkyl, heterocyclic, heterocyclic C<sub>1-4</sub> alkyl, heteroaryl or a heteroaryl C<sub>1-4</sub> alkyl moiety, and wherein each of these moieties, excluding hydrogen, may be optionally substituted; or the R<sub>4</sub> and R<sub>14</sub> together with the nitrogen which they are attached form an optionally substituted heterocyclic ring of 4 to 7 members, which ring optionally contains an additional heteroatom selected from oxygen, sulfur or nitrogen;
- 20 R<sub>4</sub>' and R<sub>14</sub>' are each independently selected at each occurrence from hydrogen or C<sub>1-4</sub> alkyl, or R<sub>4</sub>' and R<sub>14</sub>' together with the nitrogen to which they are attached form a heterocyclic ring of 5 to 7 members, which ring optionally contains an additional heteroatom selected from NR<sub>9</sub>';
- R<sub>5</sub> is independently selected at each occurrence from hydrogen, C<sub>1-4</sub> alkyl, C<sub>2-4</sub> alkenyl, C<sub>2-4</sub> alkynyl or NR<sub>4</sub>'R<sub>14</sub>', excluding the moieties SR<sub>5</sub> being SNR<sub>4</sub>'R<sub>14</sub>', S(O)<sub>2</sub>R<sub>5</sub> being SO<sub>2</sub>H and S(O)R<sub>5</sub> being SOH;
- 30 R<sub>9</sub>' is independently selected at each occurrence from hydrogen, or C<sub>1-4</sub> alkyl;
- R<sub>10</sub> and R<sub>20</sub> are independently selected at each occurrence from hydrogen or C<sub>1-4</sub>alkyl;
- 35 R<sub>10</sub>' is independently selected at each occurrence from hydrogen or C<sub>1-4</sub>alkyl;
- R<sub>11</sub> is independently selected at each occurrence from hydrogen or C<sub>1-4</sub>alkyl;

- R<sub>12</sub> is independently selected at each occurrence from hydrogen, C<sub>1-4</sub> alkyl, halo-substituted C<sub>1-4</sub> alkyl, C<sub>2-4</sub> alkenyl, C<sub>2-4</sub> alkynyl, C<sub>3-7</sub> cycloalkyl, C<sub>3-7</sub>cycloalkylC<sub>1-4</sub> alkyl, C<sub>5-7</sub> cycloalkenyl, C<sub>5-7</sub>cycloalkenyl C<sub>1-4</sub> alkyl, aryl, arylC<sub>1-4</sub> alkyl, heteroaryl, heteroarylC<sub>1-4</sub> alkyl, heterocyclyl, or a  
5 heterocyclylC<sub>1-4</sub> alkyl moiety, and wherein each of these moieties, excluding hydrogen, may be optionally substituted;
- R<sub>13</sub> is independently selected at each occurrence from hydrogen, C<sub>1-4</sub> alkyl, halo-substituted C<sub>1-4</sub> alkyl, C<sub>2-4</sub> alkenyl, C<sub>2-4</sub> alkynyl, C<sub>3-7</sub> cycloalkyl, C<sub>3-7</sub>cycloalkylC<sub>1-4</sub> alkyl, C<sub>5-7</sub> cycloalkenyl, C<sub>5-7</sub>cycloalkenyl C<sub>1-4</sub> alkyl, aryl, arylC<sub>1-4</sub> alkyl, heteroaryl, heteroarylC<sub>1-4</sub> alkyl, heterocyclyl, or a  
10 heterocyclylC<sub>1-4</sub> alkyl moiety, and wherein each of these moieties, excluding hydrogen, may be optionally substituted;
- R<sub>d</sub> and R<sub>d'</sub> are each independently selected from hydrogen, C<sub>1-4</sub> alkyl, C<sub>3-6</sub> cycloalkyl, C<sub>3-6</sub> cycloalkylC<sub>1-4</sub>alkyl moiety, and wherein each of these moieties, excluding hydrogen, may be optionally substituted; or R<sub>d</sub> and R<sub>d'</sub> together with the nitrogen which they are attached form an optionally substituted heterocyclic ring of 5 to 6 members, which ring optionally contains an additional heteroatom selected from oxygen, sulfur or NR<sub>9'</sub>;
- g is 0 or an integer having a value of 1, 2, 3, or 4;
- 20 n' is independently selected at each occurrence from 0 or an integer having a value of 1 to 10;
- m is independently selected at each occurrence from 0 or an integer having a value of 1 or 2;
- q is 0 or an integer having a value of 1 to 10;
- 25 q' is 0, or an integer having a value of 1 to 6;
- t is an integer having a value of 2 to 6;
- v is 0 or an integer having a value of 1 or 2;
- v' is independently selected at each occurrence from 0 or an integer having a value of 1 or 2;
- 30 Z is independently selected at each occurrence from oxygen or sulfur; and a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof.

Another aspect of the invention are compounds of the formula:



(VIId) or



(VIe)

5 wherein

G<sub>1</sub> and G<sub>2</sub> are independently selected from nitrogen or CH:

G<sub>3</sub> is CH<sub>2</sub>;

G<sub>4</sub> is CH;

G<sub>6</sub> and G<sub>8</sub> are nitrogen; and G<sub>5</sub> and G<sub>7</sub> are CH;

10 R<sub>1</sub> is C(Z)N(R<sub>10'</sub>)(CR<sub>10</sub>R<sub>20</sub>)<sub>v</sub>R<sub>b</sub>, C(Z)O(CR<sub>10</sub>R<sub>20</sub>)<sub>v</sub>R<sub>b</sub>,  
N(R<sub>10'</sub>)C(Z)(CR<sub>10</sub>R<sub>20</sub>)<sub>v</sub>R<sub>b</sub>, N(R<sub>10'</sub>)C(Z)N(R<sub>10'</sub>)(CR<sub>10</sub>R<sub>20</sub>)<sub>v</sub>R<sub>b</sub>, or  
N(R<sub>10'</sub>)OC(Z)(CR<sub>10</sub>R<sub>20</sub>)<sub>v</sub>R<sub>b</sub>;

R<sub>1'</sub> is independently selected at each occurrence from halogen, C<sub>1-4</sub> alkyl, halo-  
substituted-C<sub>1-4</sub> alkyl, cyano, nitro, (CR<sub>10</sub>R<sub>20</sub>)<sub>v</sub>'NR<sub>d</sub>R<sub>d</sub>';

15 (CR<sub>10</sub>R<sub>20</sub>)<sub>v</sub>'C(O)R<sub>12</sub>, SR<sub>5</sub>, S(O)R<sub>5</sub>, S(O)<sub>2</sub>R<sub>5</sub>, or (CR<sub>10</sub>R<sub>20</sub>)<sub>v</sub>'OR<sub>13</sub>;

R<sub>b</sub> is hydrogen, C<sub>1-10</sub> alkyl, C<sub>3-7</sub> cycloalkyl, C<sub>3-7</sub> cycloalkyl C<sub>1-10</sub> alkyl, aryl,  
arylC<sub>1-10</sub>alkyl, heteroaryl, heteroarylC<sub>1-10</sub> alkyl, heterocyclic, or  
heterocyclylC<sub>1-10</sub> alkyl moiety, which moieties, excluding hydrogen, may all be  
optionally substituted;

20 X is R<sub>2</sub>, OR<sub>2</sub>', S(O)<sub>m</sub>R<sub>2</sub>', (CH<sub>2</sub>)<sub>n</sub>'N(R<sub>10'</sub>)S(O)<sub>m</sub>R<sub>2</sub>', (CH<sub>2</sub>)<sub>n</sub>'N(R<sub>10'</sub>)C(O)R<sub>2</sub>',  
(CH<sub>2</sub>)<sub>n</sub>'NR<sub>4</sub>R<sub>14</sub>, (CH<sub>2</sub>)<sub>n</sub>'N(R<sub>2</sub>')R<sub>2</sub>'', or N(R<sub>10'</sub>)R<sub>h</sub>NH-C(=N-CN)NR<sub>q</sub>R<sub>q</sub>';

X<sub>1</sub> is N(R<sub>11</sub>), O, S(O)<sub>m</sub>, or CR<sub>10</sub>R<sub>20</sub>;

R<sub>h</sub> is selected from an optionally substituted C<sub>1-10</sub> alkyl, -CH<sub>2</sub>-C(O)-CH<sub>2</sub>-,  
-CH<sub>2</sub>-CH<sub>2</sub>-O-CH<sub>2</sub>-CH<sub>2</sub>-, -CH<sub>2</sub>-C(O)N(R<sub>10'</sub>)CH<sub>2</sub>-CH<sub>2</sub>-,

25 -CH<sub>2</sub>-N(R<sub>10'</sub>)C(O)CH<sub>2</sub>-, -CH<sub>2</sub>-CH(OR<sub>10'</sub>)-CH<sub>2</sub>-, -CH<sub>2</sub>-C(O)O-CH<sub>2</sub>-CH<sub>2</sub>-, or  
-CH<sub>2</sub>-CH<sub>2</sub>-O-C(O)CH<sub>2</sub>-;

R<sub>q</sub> and R<sub>q</sub>' are independently selected at each occurrence from hydrogen, C<sub>1-10</sub>  
alkyl, C<sub>3-7</sub>cycloalkyl, C<sub>3-7</sub>cycloalkylC<sub>1-10</sub>alkyl, C<sub>5-7</sub> cycloalkenyl, C<sub>5-7</sub>  
cycloalkenyl-C<sub>1-10</sub>alkyl, aryl, arylC<sub>1-10</sub> alkyl, heteroaryl, heteroarylC<sub>1-10</sub>  
30 alkyl, heterocyclic, or a heterocyclylC<sub>1-10</sub> alkyl moiety, wherein all of the

moieties except for hydrogen, are optionally substituted, or  $R_q$  and  $R_{q'}$  together with the nitrogen to which they are attached form an optionally substituted heterocyclic ring of 5 to 7 members, which ring may contain an additional heteroatom selected from oxygen, nitrogen or sulfur;

5  $R_2$  is hydrogen,  $C_{1-10}$  alkyl,  $C_{3-7}$  cycloalkyl,  $C_{3-7}$  cycloalkylalkyl, aryl, aryl $C_{1-10}$  alkyl, heteroaryl, heteroaryl $C_{1-10}$  alkyl, heterocyclic, or a heterocyclyl $C_{1-10}$  alkyl moiety, and wherein each of these moieties, excluding hydrogen, may be optionally substituted; or

10  $R_2$  is the moiety  $(CR_{10}R_{20})_qX_1(CR_{10}R_{20})_qC(A_1)(A_2)(A_3)$ , or  $(CR_{10}R_{20})_qC(A_1)(A_2)(A_3)$ ;

$R_2'$  is hydrogen,  $C_{1-10}$  alkyl,  $C_{3-7}$  cycloalkyl,  $C_{3-7}$  cycloalkylalkyl, aryl, aryl $C_{1-10}$  alkyl, heteroaryl, heteroaryl $C_{1-10}$  alkyl, heterocyclic, or a heterocyclyl $C_{1-10}$  alkyl moiety, and wherein each of these moieties, excluding hydrogen, may be optionally substituted;

15  $R_2''$  is hydrogen,  $C_{1-10}$  alkyl,  $C_{3-7}$  cycloalkyl,  $C_{3-7}$  cycloalkylalkyl, aryl, aryl $C_{1-10}$  alkyl, heteroaryl, heteroaryl $C_{1-10}$  alkyl, heterocyclic, or a heterocyclyl $C_{1-10}$  alkyl moiety, and wherein these moieties, excluding hydrogen, may be optionally; or wherein  $R_2''$  is the moiety  $(CR_{10}R_{20})_tX_1(CR_{10}R_{20})_qC(A_1)(A_2)(A_3)$ ;

20  $A_1$  is an optionally substituted  $C_{1-10}$  alkyl, heterocyclic, heterocyclic  $C_{1-10}$  alkyl, heteroaryl, heteroaryl  $C_{1-10}$  alkyl, aryl, or aryl  $C_{1-10}$  alkyl;

$A_2$  is an optionally substituted  $C_{1-10}$  alkyl, heterocyclic, heterocyclic  $C_{1-10}$  alkyl, heteroaryl, heteroaryl  $C_{1-10}$  alkyl, aryl, or aryl  $C_{1-10}$  alkyl;

$A_3$  is hydrogen or is an optionally substituted  $C_{1-10}$  alkyl;

25  $R_3$  is a  $C_{1-10}$  alkyl,  $C_{3-7}$  cycloalkyl,  $C_{3-7}$  cycloalkyl  $C_{1-10}$  alkyl, aryl, aryl $C_{1-10}$  alkyl, heteroaryl, heteroaryl $C_{1-10}$  alkyl, heterocyclic or a heterocyclyl $C_{1-10}$  alkyl moiety, and wherein each of these moieties may be optionally substituted;

30  $R_4$  and  $R_{14}$  are each independently selected at each occurrence from hydrogen,  $C_{1-4}$  alkyl,  $C_{3-7}$  cycloalkyl,  $C_{3-7}$  cycloalkyl $C_{1-4}$ alkyl, aryl, aryl- $C_{1-4}$  alkyl, heterocyclic, heterocyclic  $C_{1-4}$  alkyl, heteroaryl or a heteroaryl  $C_{1-4}$  alkyl moiety, and wherein each of these moieties, excluding hydrogen, may be optionally substituted; or the  $R_4$  and  $R_{14}$  together with the nitrogen which they are attached form an optionally substituted heterocyclic ring of 4 to 7 members, which ring optionally contains an additional heteroatom selected from oxygen, sulfur or nitrogen;

35  $R_4'$  and  $R_{14}'$  are each independently selected at each occurrence from hydrogen or  $C_{1-4}$  alkyl, or  $R_4'$  and  $R_{14}'$  together with the nitrogen to which they are attached

form a heterocyclic ring of 5 to 7 members, which ring optionally contains an additional heteroatom selected from NR<sub>9</sub>';

R<sub>5</sub> is independently selected at each occurrence from hydrogen, C<sub>1-4</sub> alkyl, C<sub>2-4</sub> alkenyl, C<sub>2-4</sub> alkynyl or NR<sub>4</sub>'R<sub>14</sub>', excluding the moieties SR<sub>5</sub> being

5 SNR<sub>4</sub>'R<sub>14</sub>', S(O)<sub>2</sub>R<sub>5</sub> being SO<sub>2</sub>H and S(O)R<sub>5</sub> being SOH;

R<sub>9</sub>' is independently selected at each occurrence from hydrogen, or C<sub>1-4</sub> alkyl;

R<sub>10</sub> and R<sub>20</sub> are independently selected at each occurrence from hydrogen or C<sub>1-4</sub>alkyl;

R<sub>10</sub>' is independently selected at each occurrence from hydrogen or C<sub>1-4</sub>alkyl;

10 R<sub>11</sub> is independently selected at each occurrence from hydrogen or C<sub>1-4</sub>alkyl;

R<sub>12</sub> is independently selected at each occurrence from hydrogen, C<sub>1-4</sub> alkyl, halo-substituted C<sub>1-4</sub> alkyl, C<sub>2-4</sub> alkenyl, C<sub>2-4</sub> alkynyl, C<sub>3-7</sub> cycloalkyl, C<sub>3-7</sub>cycloalkylC<sub>1-4</sub> alkyl, C<sub>5-7</sub> cycloalkenyl, C<sub>5-7</sub>cycloalkenyl C<sub>1-4</sub> alkyl, aryl, arylC<sub>1-4</sub> alkyl, heteroaryl, heteroarylC<sub>1-4</sub> alkyl, heterocyclyl, or a

15 heterocyclylC<sub>1-4</sub> alkyl moiety, and wherein each of these moieties, excluding hydrogen, may be optionally substituted;

R<sub>13</sub> is independently selected at each occurrence from hydrogen, C<sub>1-4</sub> alkyl, halo-substituted C<sub>1-4</sub> alkyl, C<sub>2-4</sub> alkenyl, C<sub>2-4</sub> alkynyl, C<sub>3-7</sub> cycloalkyl, C<sub>3-7</sub>cycloalkylC<sub>1-4</sub> alkyl, C<sub>5-7</sub> cycloalkenyl, C<sub>5-7</sub>cycloalkenyl C<sub>1-4</sub> alkyl, aryl, arylC<sub>1-4</sub> alkyl, heteroaryl, heteroarylC<sub>1-4</sub> alkyl, heterocyclyl, or a

20 heterocyclylC<sub>1-4</sub> alkyl moiety, and wherein each of these moieties, excluding hydrogen, may be optionally substituted;

R<sub>d</sub> and R<sub>d</sub>' are each independently selected from hydrogen, C<sub>1-4</sub> alkyl, C<sub>3-6</sub> cycloalkyl, C<sub>3-6</sub> cycloalkylC<sub>1-4</sub>alkyl moiety, and wherein each of these moieties, excluding hydrogen, may be optionally substituted; or R<sub>d</sub> and R<sub>d</sub>' together with the nitrogen which they are attached form an optionally substituted heterocyclic ring of 5 to 6 members, which ring optionally contains an additional heteroatom selected from oxygen, sulfur or NR<sub>9</sub>';

25

g is 0 or an integer having a value of 1, 2, 3, or 4;

30 n' is independently selected at each occurrence from 0 or an integer having a value of 1 to 10;

m is independently selected at each occurrence from 0 or an integer having a value of 1 or 2;

q is 0 or an integer having a value of 1 to 10;

35 q' is 0, or an integer having a value of 1 to 6;

t is an integer having a value of 2 to 6;

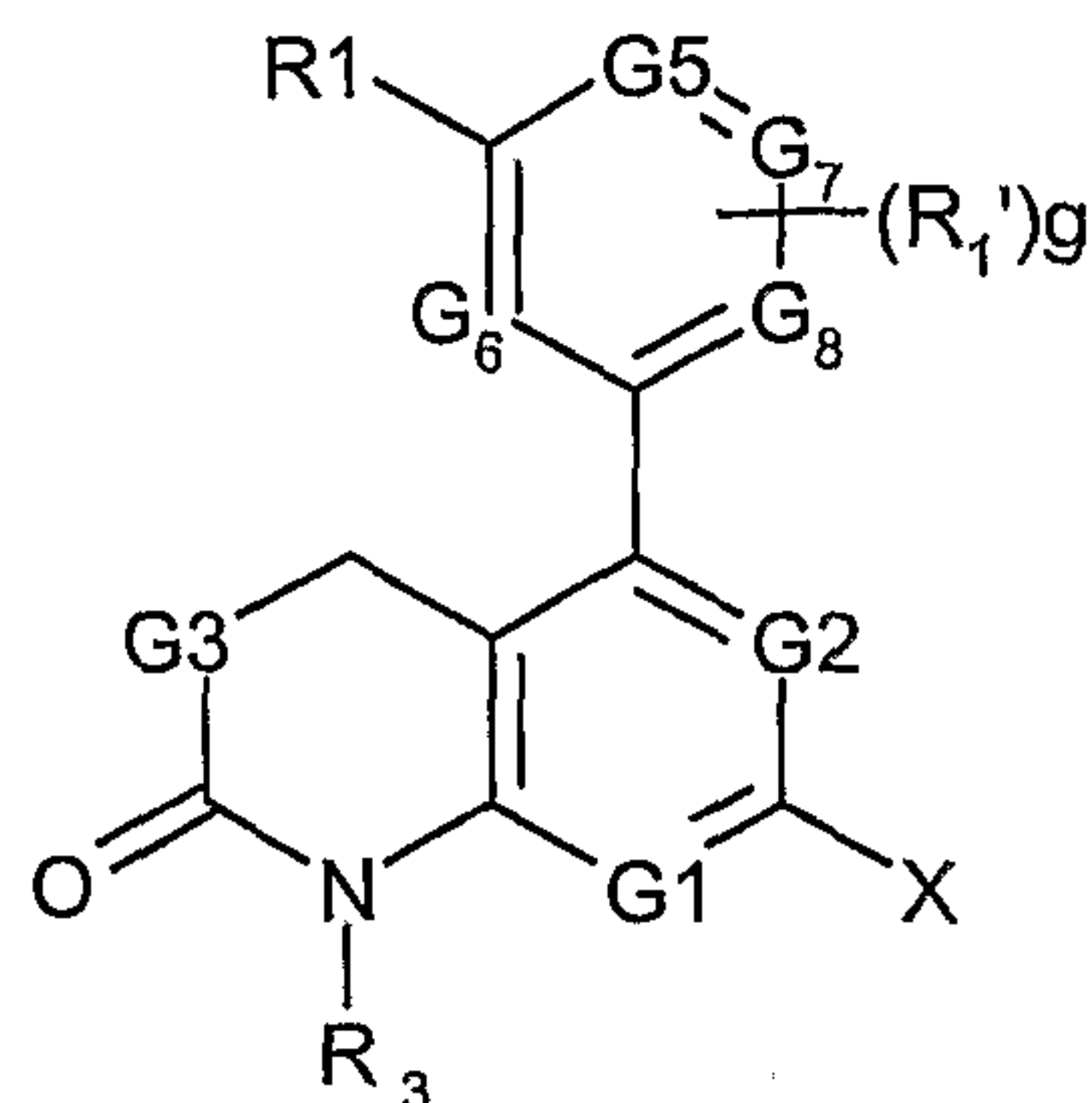
v is 0 or an integer having a value of 1 or 2;

$v'$  is independently selected at each occurrence from 0 or an integer having a value of 1 or 2;

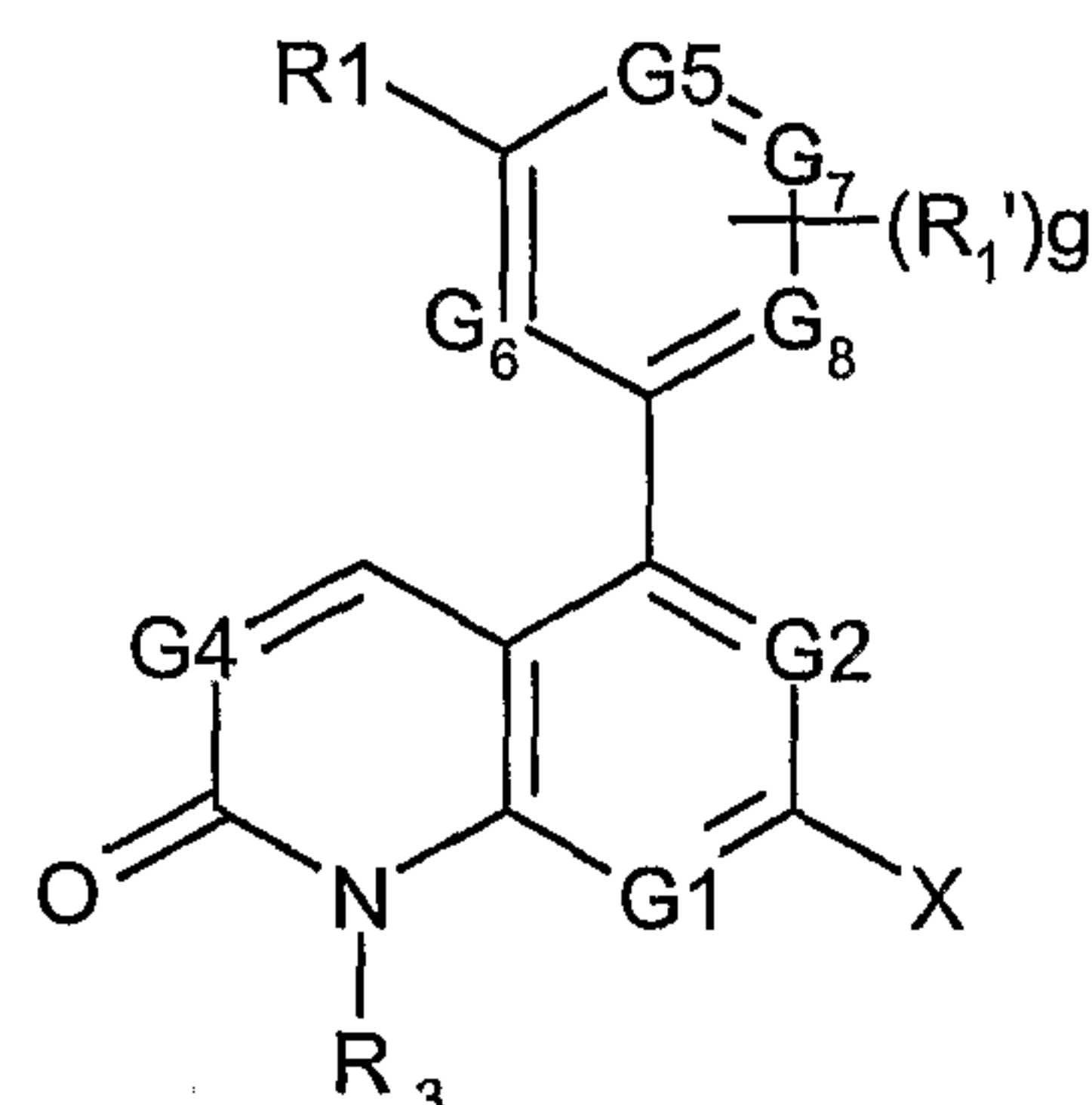
Z is independently selected at each occurrence from oxygen or sulfur; and

a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof.

Another aspect of the invention are compounds of the formula:



(VI f) or



(VI g)

wherein

G<sub>1</sub> and G<sub>2</sub> are nitrogen;

G<sub>3</sub> is CH<sub>2</sub>;

G<sub>4</sub> is CH;

G<sub>5</sub> and G<sub>8</sub> are nitrogen;

G<sub>6</sub> and G<sub>7</sub> are CH;

R<sub>1</sub> is C(Z)N(R<sub>10'</sub>)(CR<sub>10</sub>R<sub>20</sub>)<sub>v</sub>R<sub>b</sub>, C(Z)O(CR<sub>10</sub>R<sub>20</sub>)<sub>v</sub>R<sub>b</sub>,  
N(R<sub>10'</sub>)C(Z)(CR<sub>10</sub>R<sub>20</sub>)<sub>v</sub>R<sub>b</sub>, N(R<sub>10'</sub>)C(Z)N(R<sub>10'</sub>)(CR<sub>10</sub>R<sub>20</sub>)<sub>v</sub>R<sub>b</sub>, or  
N(R<sub>10'</sub>)OC(Z)(CR<sub>10</sub>R<sub>20</sub>)<sub>v</sub>R<sub>b</sub>;

R<sub>1'</sub> is independently selected at each occurrence from halogen, C<sub>1-4</sub> alkyl, halo-substituted-C<sub>1-4</sub> alkyl, cyano, nitro, (CR<sub>10</sub>R<sub>20</sub>)<sub>v</sub>NR<sub>d</sub>R<sub>d'</sub>,  
(CR<sub>10</sub>R<sub>20</sub>)<sub>v</sub>C(O)R<sub>12</sub>, SR<sub>5</sub>, S(O)R<sub>5</sub>, S(O)<sub>2</sub>R<sub>5</sub>, or (CR<sub>10</sub>R<sub>20</sub>)<sub>v</sub>OR<sub>13</sub>;

R<sub>b</sub> is hydrogen, C<sub>1-10</sub> alkyl, C<sub>3-7</sub> cycloalkyl, C<sub>3-7</sub> cycloalkyl C<sub>1-10</sub> alkyl, aryl, arylC<sub>1-10</sub>alkyl, heteroaryl, heteroarylC<sub>1-10</sub> alkyl, heterocyclic, or

heterocyclylC<sub>1-10</sub> alkyl moiety, which moieties, excluding hydrogen, may all be optionally substituted;

X is R<sub>2</sub>, OR<sub>2'</sub>, S(O)<sub>m</sub>R<sub>2'</sub>, (CH<sub>2</sub>)<sub>n</sub>N(R<sub>10'</sub>)S(O)<sub>m</sub>R<sub>2'</sub>, (CH<sub>2</sub>)<sub>n</sub>N(R<sub>10'</sub>)C(O)R<sub>2'</sub>,  
(CH<sub>2</sub>)<sub>n</sub>NR<sub>4</sub>R<sub>14</sub>, (CH<sub>2</sub>)<sub>n</sub>N(R<sub>2'</sub>)(R<sub>2''</sub>), or N(R<sub>10'</sub>)R<sub>h</sub>NH-C(=N-CN)NR<sub>q</sub>R<sub>q'</sub>;

X<sub>1</sub> is N(R<sub>11</sub>), O, S(O)<sub>m</sub>, or CR<sub>10</sub>R<sub>20</sub>;

$R_h$  is selected from an optionally substituted  $C_{1-10}$  alkyl,  $-CH_2-C(O)-CH_2-$ ,  $-CH_2-CH_2-O-CH_2-CH_2-$ ,  $-CH_2-C(O)N(R_{10'})CH_2-CH_2-$ ,  $-CH_2-N(R_{10'})C(O)CH_2-$ ,  $-CH_2-CH(OR_{10'})-CH_2-$ ,  $-CH_2-C(O)O-CH_2-CH_2-$ , or  $-CH_2-CH_2-O-C(O)CH_2-$ ;

5  $R_q$  and  $R_{q'}$  are independently selected at each occurrence from hydrogen,  $C_{1-10}$  alkyl,  $C_{3-7}$  cycloalkyl,  $C_{3-7}$  cycloalkyl $C_{1-10}$  alkyl,  $C_{5-7}$  cycloalkenyl,  $C_{5-7}$  cycloalkenyl- $C_{1-10}$  alkyl, aryl, aryl $C_{1-10}$  alkyl, heteroaryl, heteroaryl $C_{1-10}$  alkyl, heterocyclic, or a heterocyclyl $C_{1-10}$  alkyl moiety, wherein all of the moieties except for hydrogen, are optionally substituted, or  $R_q$  and  $R_{q'}$  together  
10 with the nitrogen to which they are attached form an optionally substituted heterocyclic ring of 5 to 7 members, which ring may contain an additional heteroatom selected from oxygen, nitrogen or sulfur;

$R_2$  is hydrogen,  $C_{1-10}$  alkyl,  $C_{3-7}$  cycloalkyl,  $C_{3-7}$  cycloalkylalkyl, aryl, aryl $C_{1-10}$  alkyl, heteroaryl, heteroaryl $C_{1-10}$  alkyl, heterocyclic, or a heterocyclyl $C_{1-10}$  alkyl moiety, and wherein each of these moieties, excluding hydrogen, may be  
15 optionally substituted; or

$R_2$  is the moiety  $(CR_{10}R_{20})_qX_1(CR_{10}R_{20})_qC(A_1)(A_2)(A_3)$ , or  $(CR_{10}R_{20})_qC(A_1)(A_2)(A_3)$ ;

$R_{2'}$  is hydrogen,  $C_{1-10}$  alkyl,  $C_{3-7}$  cycloalkyl,  $C_{3-7}$  cycloalkylalkyl, aryl, aryl $C_{1-10}$  alkyl, heteroaryl, heteroaryl $C_{1-10}$  alkyl, heterocyclic, or a heterocyclyl $C_{1-10}$  alkyl  
20 moiety, and wherein each of these moieties, excluding hydrogen, may be optionally substituted;

$R_{2''}$  is hydrogen,  $C_{1-10}$  alkyl,  $C_{3-7}$  cycloalkyl,  $C_{3-7}$  cycloalkylalkyl, aryl, aryl $C_{1-10}$  alkyl, heteroaryl, heteroaryl $C_{1-10}$  alkyl, heterocyclic, or a heterocyclyl $C_{1-10}$  alkyl  
25 moiety, and wherein these moieties, excluding hydrogen, may be optionally; or wherein  $R_{2''}$  is the moiety  $(CR_{10}R_{20})_tX_1(CR_{10}R_{20})_qC(A_1)(A_2)(A_3)$ ;

$A_1$  is an optionally substituted  $C_{1-10}$  alkyl, heterocyclic, heterocyclic  $C_{1-10}$  alkyl, heteroaryl, heteroaryl  $C_{1-10}$  alkyl, aryl, or aryl  $C_{1-10}$  alkyl;

$A_2$  is an optionally substituted  $C_{1-10}$  alkyl, heterocyclic, heterocyclic  $C_{1-10}$  alkyl, heteroaryl, heteroaryl  $C_{1-10}$  alkyl, aryl, or aryl  $C_{1-10}$  alkyl;  
30

$A_3$  is hydrogen or is an optionally substituted  $C_{1-10}$  alkyl;

$R_3$  is a  $C_{1-10}$  alkyl,  $C_{3-7}$  cycloalkyl,  $C_{3-7}$  cycloalkyl  $C_{1-10}$  alkyl, aryl, aryl $C_{1-10}$  alkyl, heteroaryl, heteroaryl $C_{1-10}$  alkyl, heterocyclic or a heterocyclyl $C_{1-10}$  alkyl  
moiety, and wherein each of these moieties may be optionally substituted;

35  $R_4$  and  $R_{14}$  are each independently selected at each occurrence from hydrogen,  $C_{1-4}$  alkyl,  $C_{3-7}$  cycloalkyl,  $C_{3-7}$  cycloalkyl $C_{1-4}$  alkyl, aryl, aryl- $C_{1-4}$  alkyl, heterocyclic, heterocyclic  $C_{1-4}$  alkyl, heteroaryl or a heteroaryl  $C_{1-4}$  alkyl

moiety, and wherein each of these moieties, excluding hydrogen, may be optionally substituted; or the R<sub>4</sub> and R<sub>14</sub> together with the nitrogen which they are attached form an optionally substituted heterocyclic ring of 4 to 7 members, which ring optionally contains an additional heteroatom selected from oxygen,  
 5 sulfur or nitrogen;

R<sub>4</sub>' and R<sub>14</sub>' are each independently selected at each occurrence from hydrogen or C<sub>1-4</sub> alkyl, or R<sub>4</sub>' and R<sub>14</sub>' together with the nitrogen to which they are attached form a heterocyclic ring of 5 to 7 members, which ring optionally contains an additional heteroatom selected from NR<sub>9</sub>';

10 R<sub>5</sub> is independently selected at each occurrence from hydrogen, C<sub>1-4</sub> alkyl, C<sub>2-4</sub> alkenyl, C<sub>2-4</sub> alkynyl or NR<sub>4</sub>'R<sub>14</sub>', excluding the moieties SR<sub>5</sub> being SNR<sub>4</sub>'R<sub>14</sub>', S(O)<sub>2</sub>R<sub>5</sub> being SO<sub>2</sub>H and S(O)R<sub>5</sub> being SOH;

R<sub>9</sub>' is independently selected at each occurrence from hydrogen, or C<sub>1-4</sub> alkyl;

R<sub>10</sub> and R<sub>20</sub> are independently selected at each occurrence from hydrogen or

15 C<sub>1-4</sub>alkyl;

R<sub>10</sub>' is independently selected at each occurrence from hydrogen or C<sub>1-4</sub>alkyl;

R<sub>11</sub> is independently selected at each occurrence from hydrogen or C<sub>1-4</sub>alkyl;

R<sub>12</sub> is independently selected at each occurrence from hydrogen, C<sub>1-4</sub> alkyl, halo-substituted C<sub>1-4</sub> alkyl, C<sub>2-4</sub> alkenyl, C<sub>2-4</sub> alkynyl, C<sub>3-7</sub> cycloalkyl,

20 C<sub>3-7</sub>cycloalkylC<sub>1-4</sub> alkyl, C<sub>5-7</sub> cycloalkenyl, C<sub>5-7</sub>cycloalkenyl C<sub>1-4</sub> alkyl, aryl, arylC<sub>1-4</sub> alkyl, heteroaryl, heteroarylC<sub>1-4</sub> alkyl, heterocyclyl, or a heterocyclylC<sub>1-4</sub> alkyl moiety, and wherein each of these moieties, excluding hydrogen, may be optionally substituted;

R<sub>13</sub> is independently selected at each occurrence from hydrogen, C<sub>1-4</sub> alkyl, halo-

25 substituted C<sub>1-4</sub> alkyl, C<sub>2-4</sub> alkenyl, C<sub>2-4</sub> alkynyl, C<sub>3-7</sub> cycloalkyl, C<sub>3-7</sub>cycloalkylC<sub>1-4</sub> alkyl, C<sub>5-7</sub> cycloalkenyl, C<sub>5-7</sub>cycloalkenyl C<sub>1-4</sub> alkyl, aryl, arylC<sub>1-4</sub> alkyl, heteroaryl, heteroarylC<sub>1-4</sub> alkyl, heterocyclyl, or a heterocyclylC<sub>1-4</sub> alkyl moiety, and wherein each of these moieties, excluding hydrogen, may be optionally substituted;

30 R<sub>d</sub> and R<sub>d</sub>' are each independently selected from hydrogen, C<sub>1-4</sub> alkyl, C<sub>3-6</sub> cycloalkyl, C<sub>3-6</sub> cycloalkylC<sub>1-4</sub>alkyl moiety, and wherein each of these moieties, excluding hydrogen, may be optionally substituted; or R<sub>d</sub> and R<sub>d</sub>' together with the nitrogen which they are attached form an optionally substituted heterocyclic ring of 5 to 6 members, which ring optionally contains an additional heteroatom  
 35 selected from oxygen, sulfur or NR<sub>9</sub>';

g is 0 or an integer having a value of 1, 2, 3, or 4;

$n'$  is independently selected at each occurrence from 0 or an integer having a value of 1 to 10;

$m$  is independently selected at each occurrence from 0 or an integer having a value of 1 or 2;

5  $q$  is 0 or an integer having a value of 1 to 10;

$q'$  is 0, or an integer having a value of 1 to 6;

$t$  is an integer having a value of 2 to 6;

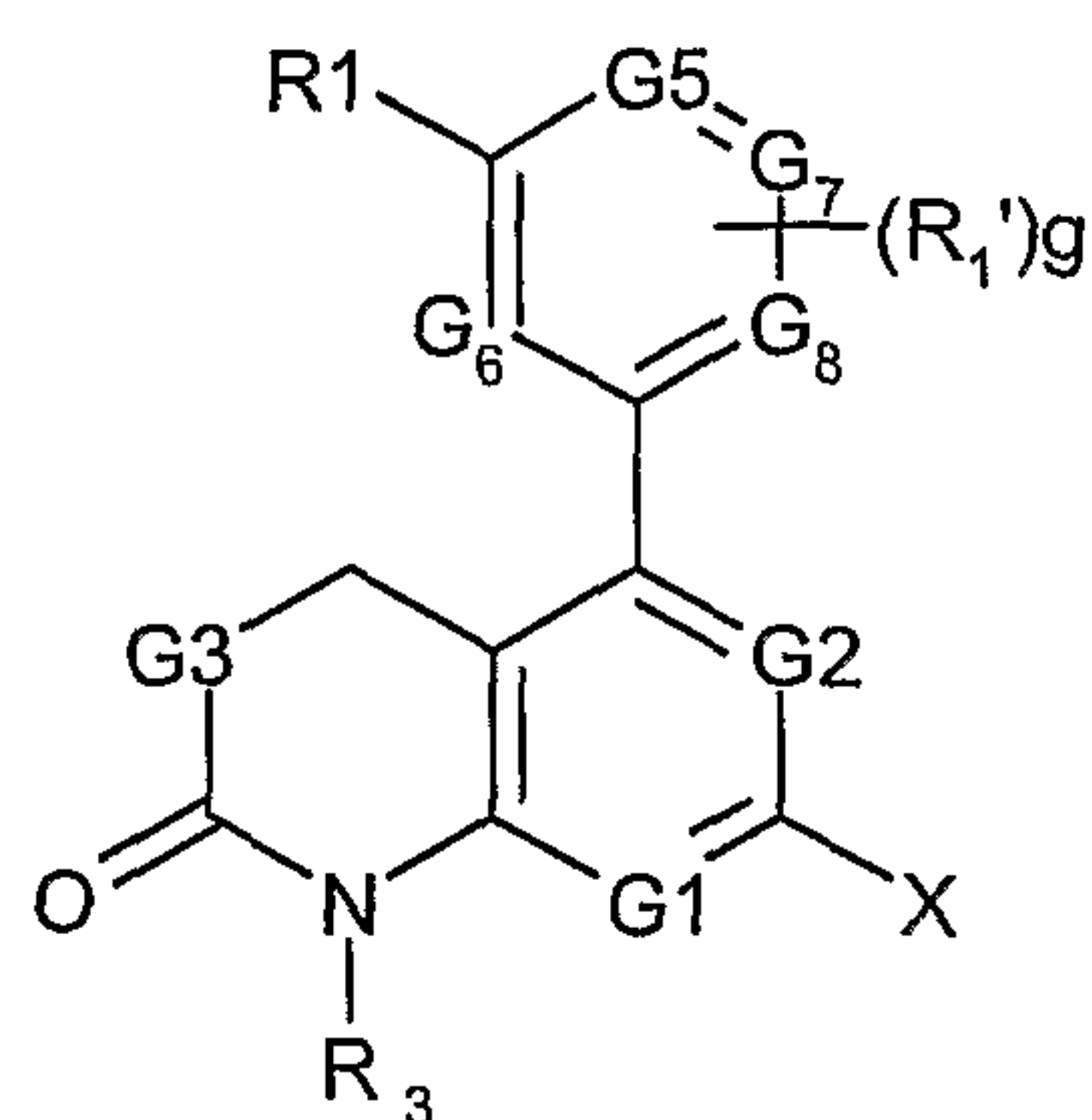
$v$  is 0 or an integer having a value of 1 or 2;

10  $v'$  is independently selected at each occurrence from 0 or an integer having a value of 1 or 2;

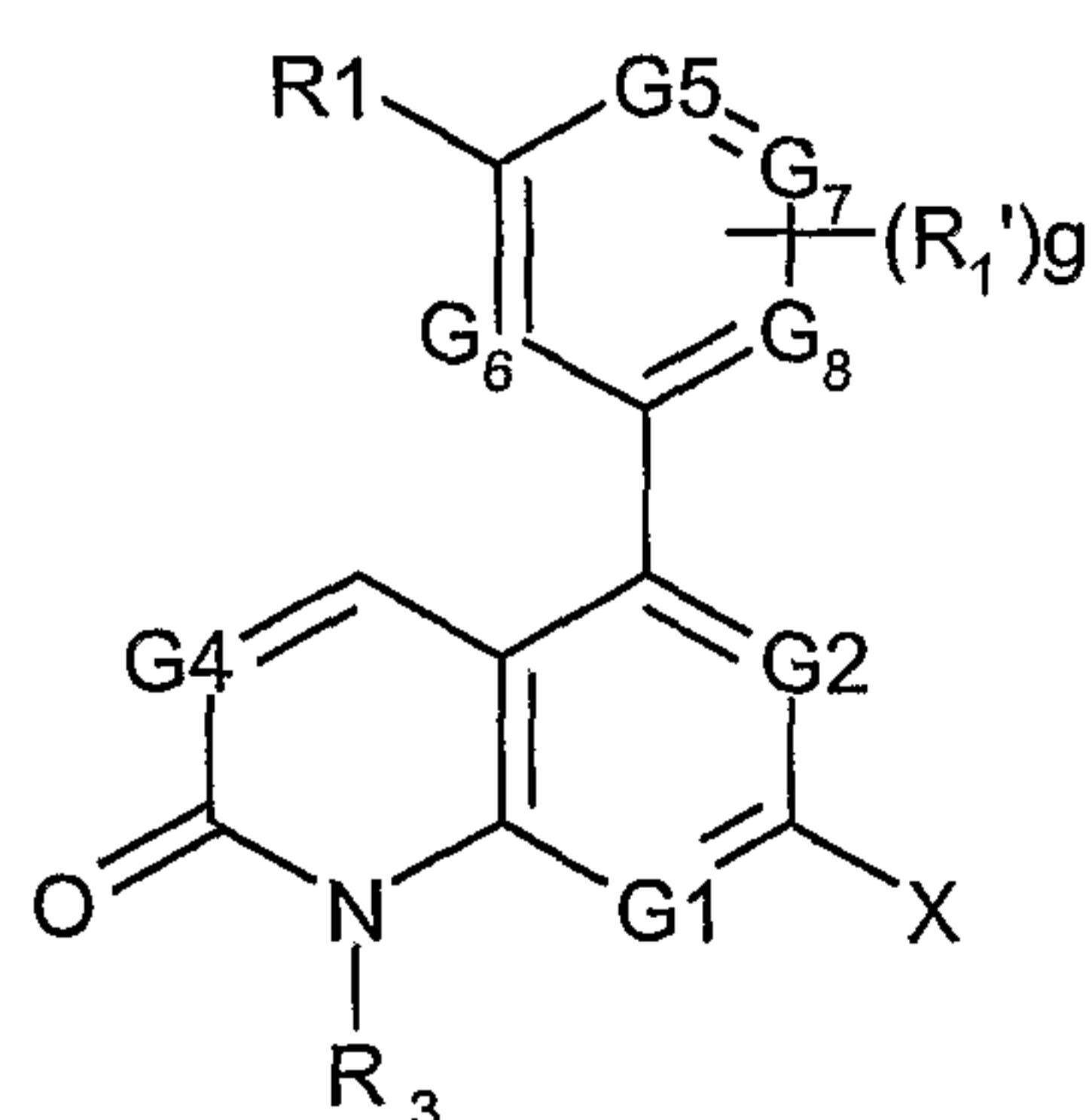
$Z$  is independently selected at each occurrence from oxygen or sulfur; and

a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof.

15 Another aspect of the invention are compounds of the formula:



(VIh) or



(VIi)

wherein

20  $G_1$  and  $G_2$  are nitrogen;

$G_3$  is  $\text{CH}_2$ ;

$G_4$  is  $\text{CH}$ ;

$G_6$  and  $G_7$  are nitrogen;

$G_5$  and  $G_8$  are  $\text{CH}$ ;

25  $R_1$  is  $\text{C}(\text{Z})\text{N}(\text{R}_{10}')(\text{CR}_{10}\text{R}_{20})_v\text{R}_b$ ,  $\text{C}(\text{Z})\text{O}(\text{CR}_{10}\text{R}_{20})_v\text{R}_b$ ,  
 $\text{N}(\text{R}_{10}')\text{C}(\text{Z})(\text{CR}_{10}\text{R}_{20})_v\text{R}_b$ ,  $\text{N}(\text{R}_{10}')\text{C}(\text{Z})\text{N}(\text{R}_{10}')(\text{CR}_{10}\text{R}_{20})_v\text{R}_b$ , or  
 $\text{N}(\text{R}_{10}')\text{OC}(\text{Z})(\text{CR}_{10}\text{R}_{20})_v\text{R}_b$ ;

$R_{10}'$  is independently selected at each occurrence from halogen,  $\text{C}_1$ -4 alkyl, halo-substituted- $\text{C}_1$ -4 alkyl, cyano, nitro,  $(\text{CR}_{10}\text{R}_{20})_{v'}\text{NR}_d\text{R}_d'$ ,

30  $(\text{CR}_{10}\text{R}_{20})_{v'}\text{C}(\text{O})\text{R}_{12}$ ,  $\text{SR}_5$ ,  $\text{S}(\text{O})\text{R}_5$ ,  $\text{S}(\text{O})_2\text{R}_5$ , or  $(\text{CR}_{10}\text{R}_{20})_{v'}\text{OR}_{13}$ ;

R<sub>b</sub> is hydrogen, C<sub>1-10</sub> alkyl, C<sub>3-7</sub> cycloalkyl, C<sub>3-7</sub> cycloalkyl C<sub>1-10</sub> alkyl, aryl, arylC<sub>1-10</sub>alkyl, heteroaryl, heteroarylC<sub>1-10</sub> alkyl, heterocyclic, or heterocyclylC<sub>1-10</sub> alkyl moiety, which moieties, excluding hydrogen, may all be optionally substituted;

5 X is R<sub>2</sub>, OR<sub>2</sub>', S(O)<sub>m</sub>R<sub>2</sub>', (CH<sub>2</sub>)<sub>n</sub>'N(R<sub>10</sub>')S(O)<sub>m</sub>R<sub>2</sub>', (CH<sub>2</sub>)<sub>n</sub>'N(R<sub>10</sub>')C(O)R<sub>2</sub>', (CH<sub>2</sub>)<sub>n</sub>'NR<sub>4</sub>R<sub>14</sub>, (CH<sub>2</sub>)<sub>n</sub>'N(R<sub>2</sub>')R<sub>2</sub>'', or N(R<sub>10</sub>')R<sub>h</sub>NH-C(=N-CN)NR<sub>q</sub>R<sub>q</sub>';

X<sub>1</sub> is N(R<sub>11</sub>), O, S(O)<sub>m</sub>, or CR<sub>10</sub>R<sub>20</sub>;

R<sub>h</sub> is selected from an optionally substituted C<sub>1-10</sub> alkyl, -CH<sub>2</sub>-C(O)-CH<sub>2</sub>-,

-CH<sub>2</sub>-CH<sub>2</sub>-O-CH<sub>2</sub>-CH<sub>2</sub>-, -CH<sub>2</sub>-C(O)N(R<sub>10</sub>')CH<sub>2</sub>-CH<sub>2</sub>-,

10 -CH<sub>2</sub>-N(R<sub>10</sub>')C(O)CH<sub>2</sub>-, -CH<sub>2</sub>-CH(OR<sub>10</sub>')-CH<sub>2</sub>-, -CH<sub>2</sub>-C(O)O-CH<sub>2</sub>-CH<sub>2</sub>-, or -CH<sub>2</sub>-CH<sub>2</sub>-O-C(O)CH<sub>2</sub>-;

R<sub>q</sub> and R<sub>q</sub>' are independently selected at each occurrence from hydrogen, C<sub>1-10</sub>

alkyl, C<sub>3-7</sub>cycloalkyl, C<sub>3-7</sub>cycloalkylC<sub>1-10</sub>alkyl, C<sub>5-7</sub> cycloalkenyl, C<sub>5-7</sub>

cycloalkenyl-C<sub>1-10</sub>alkyl, aryl, arylC<sub>1-10</sub> alkyl, heteroaryl, heteroarylC<sub>1-10</sub>

15 alkyl, heterocyclic, or a heterocyclylC<sub>1-10</sub> alkyl moiety, wherein all of the moieties except for hydrogen, are optionally substituted, or R<sub>q</sub> and R<sub>q</sub>' together with the nitrogen to which they are attached form an optionally substituted heterocyclic ring of 5 to 7 members, which ring may contain an additional heteroatom selected from oxygen, nitrogen or sulfur;

20 R<sub>2</sub> is hydrogen, C<sub>1-10</sub> alkyl, C<sub>3-7</sub> cycloalkyl, C<sub>3-7</sub> cycloalkylalkyl, aryl, arylC<sub>1-10</sub> alkyl, heteroaryl, heteroarylC<sub>1-10</sub> alkyl, heterocyclic, or a heterocyclylC<sub>1-10</sub> alkyl moiety, and wherein each of these moieties, excluding hydrogen, may be optionally substituted; or

R<sub>2</sub> is the moiety (CR<sub>10</sub>R<sub>20</sub>)<sub>q</sub>'X<sub>1</sub>(CR<sub>10</sub>R<sub>20</sub>)<sub>q</sub>C(A<sub>1</sub>)(A<sub>2</sub>)(A<sub>3</sub>), or

25 (CR<sub>10</sub>R<sub>20</sub>)<sub>q</sub>'C(A<sub>1</sub>)(A<sub>2</sub>)(A<sub>3</sub>);

R<sub>2</sub>' is hydrogen, C<sub>1-10</sub> alkyl, C<sub>3-7</sub> cycloalkyl, C<sub>3-7</sub> cycloalkylalkyl, aryl, arylC<sub>1-10</sub> alkyl, heteroaryl, heteroarylC<sub>1-10</sub> alkyl, heterocyclic, or a heterocyclylC<sub>1-10</sub> alkyl moiety, and wherein each of these moieties, excluding hydrogen, may be optionally substituted;

30 R<sub>2</sub>'' is hydrogen, C<sub>1-10</sub> alkyl, C<sub>3-7</sub> cycloalkyl, C<sub>3-7</sub> cycloalkylalkyl, aryl, arylC<sub>1-10</sub> alkyl, heteroaryl, heteroarylC<sub>1-10</sub> alkyl, heterocyclic, or a heterocyclylC<sub>1-10</sub> alkyl moiety, and wherein these moieties, excluding hydrogen, may be optionally; or wherein R<sub>2</sub>'' is the moiety (CR<sub>10</sub>R<sub>20</sub>)<sub>t</sub>X<sub>1</sub>(CR<sub>10</sub>R<sub>20</sub>)<sub>q</sub>C(A<sub>1</sub>)(A<sub>2</sub>)(A<sub>3</sub>);

A<sub>1</sub> is an optionally substituted C<sub>1-10</sub> alkyl, heterocyclic, heterocyclic C<sub>1-10</sub> alkyl, heteroaryl, heteroaryl C<sub>1-10</sub> alkyl, aryl, or aryl C<sub>1-10</sub> alkyl;

35 A<sub>2</sub> is an optionally substituted C<sub>1-10</sub> alkyl, heterocyclic, heterocyclic C<sub>1-10</sub> alkyl, heteroaryl, heteroaryl C<sub>1-10</sub> alkyl, aryl, or aryl C<sub>1-10</sub> alkyl;

- A<sub>3</sub> is hydrogen or is an optionally substituted C<sub>1-10</sub> alkyl;
- R<sub>3</sub> is a C<sub>1-10</sub> alkyl, C<sub>3-7</sub> cycloalkyl, C<sub>3-7</sub> cycloalkyl C<sub>1-10</sub> alkyl, aryl, arylC<sub>1-10</sub> alkyl, heteroaryl, heteroarylC<sub>1-10</sub> alkyl, heterocyclic or a heterocyclylC<sub>1-10</sub> alkyl moiety, and wherein each of these moieties may be optionally substituted;
- 5 R<sub>4</sub> and R<sub>14</sub> are each independently selected at each occurrence from hydrogen, C<sub>1-4</sub> alkyl, C<sub>3-7</sub> cycloalkyl, C<sub>3-7</sub> cycloalkylC<sub>1-4</sub>alkyl, aryl, aryl-C<sub>1-4</sub> alkyl, heterocyclic, heterocyclic C<sub>1-4</sub> alkyl, heteroaryl or a heteroaryl C<sub>1-4</sub> alkyl moiety, and wherein each of these moieties, excluding hydrogen, may be optionally substituted; or the R<sub>4</sub> and R<sub>14</sub> together with the nitrogen which they
- 10 are attached form an optionally substituted heterocyclic ring of 4 to 7 members, which ring optionally contains an additional heteroatom selected from oxygen, sulfur or nitrogen;
- R<sub>4'</sub> and R<sub>14'</sub> are each independently selected at each occurrence from hydrogen or C<sub>1-4</sub> alkyl, or R<sub>4'</sub> and R<sub>14'</sub> together with the nitrogen to which they are attached
- 15 form a heterocyclic ring of 5 to 7 members, which ring optionally contains an additional heteroatom selected from NR<sub>9'</sub>;
- R<sub>5</sub> is independently selected at each occurrence from hydrogen, C<sub>1-4</sub> alkyl, C<sub>2-4</sub> alkenyl, C<sub>2-4</sub> alkynyl or NR<sub>4'</sub>R<sub>14'</sub>, excluding the moieties SR<sub>5</sub> being SNR<sub>4'</sub>R<sub>14'</sub>, S(O)<sub>2</sub>R<sub>5</sub> being SO<sub>2</sub>H and S(O)R<sub>5</sub> being SOH;
- 20 R<sub>9'</sub> is independently selected at each occurrence from hydrogen, or C<sub>1-4</sub> alkyl;
- R<sub>10</sub> and R<sub>20</sub> are independently selected at each occurrence from hydrogen or C<sub>1-4</sub>alkyl;
- R<sub>10'</sub> is independently selected at each occurrence from hydrogen or C<sub>1-4</sub>alkyl;
- R<sub>11</sub> is independently selected at each occurrence from hydrogen or C<sub>1-4</sub>alkyl;
- 25 R<sub>12</sub> is independently selected at each occurrence from hydrogen, C<sub>1-4</sub> alkyl, halo-substituted C<sub>1-4</sub> alkyl, C<sub>2-4</sub> alkenyl, C<sub>2-4</sub> alkynyl, C<sub>3-7</sub> cycloalkyl, C<sub>3-7</sub>cycloalkylC<sub>1-4</sub> alkyl, C<sub>5-7</sub> cycloalkenyl, C<sub>5-7</sub>cycloalkenyl C<sub>1-4</sub> alkyl, aryl, arylC<sub>1-4</sub> alkyl, heteroaryl, heteroarylC<sub>1-4</sub> alkyl, heterocyclyl, or a heterocyclylC<sub>1-4</sub> alkyl moiety, and wherein each of these moieties, excluding
- 30 hydrogen, may be optionally substituted;
- R<sub>13</sub> is independently selected at each occurrence from hydrogen, C<sub>1-4</sub> alkyl, halo-substituted C<sub>1-4</sub> alkyl, C<sub>2-4</sub> alkenyl, C<sub>2-4</sub> alkynyl, C<sub>3-7</sub> cycloalkyl, C<sub>3-7</sub>cycloalkylC<sub>1-4</sub> alkyl, C<sub>5-7</sub> cycloalkenyl, C<sub>5-7</sub>cycloalkenyl C<sub>1-4</sub> alkyl, aryl, arylC<sub>1-4</sub> alkyl, heteroaryl, heteroarylC<sub>1-4</sub> alkyl, heterocyclyl, or a
- 35 heterocyclylC<sub>1-4</sub> alkyl moiety, and wherein each of these moieties, excluding hydrogen, may be optionally substituted;

$R_d$  and  $R_{d'}$  are each independently selected from hydrogen,  $C_{1-4}$  alkyl,  $C_{3-6}$  cycloalkyl,  $C_{3-6}$  cycloalkyl $C_{1-4}$ alkyl moiety, and wherein each of these moieties, excluding hydrogen, may be optionally substituted; or  $R_d$  and  $R_{d'}$  together with the nitrogen which they are attached form an optionally substituted heterocyclic ring of 5 to 6 members, which ring optionally contains an additional heteroatom selected from oxygen, sulfur or  $NR_9$ ;

$g$  is 0 or an integer having a value of 1, 2, 3, or 4;

$n'$  is independently selected at each occurrence from 0 or an integer having a value of 1 to 10;

$m$  is independently selected at each occurrence from 0 or an integer having a value of 1 or 2;

$q$  is 0 or an integer having a value of 1 to 10;

$q'$  is 0, or an integer having a value of 1 to 6;

$t$  is an integer having a value of 2 to 6;

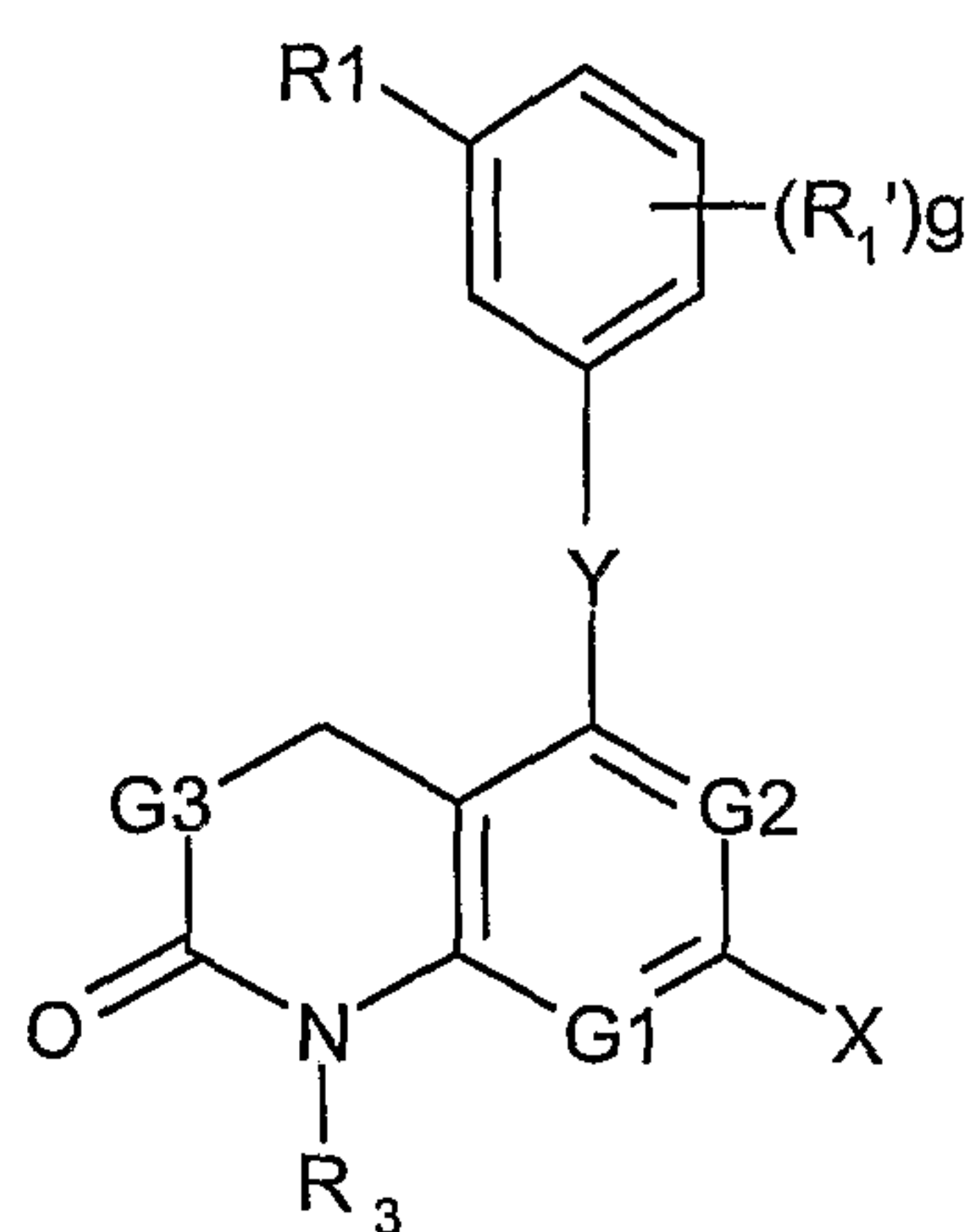
$v$  is 0 or an integer having a value of 1 or 2;

$v'$  is independently selected at each occurrence from 0 or an integer having a value of 1 or 2;

$Z$  is independently selected at each occurrence from oxygen or sulfur; and

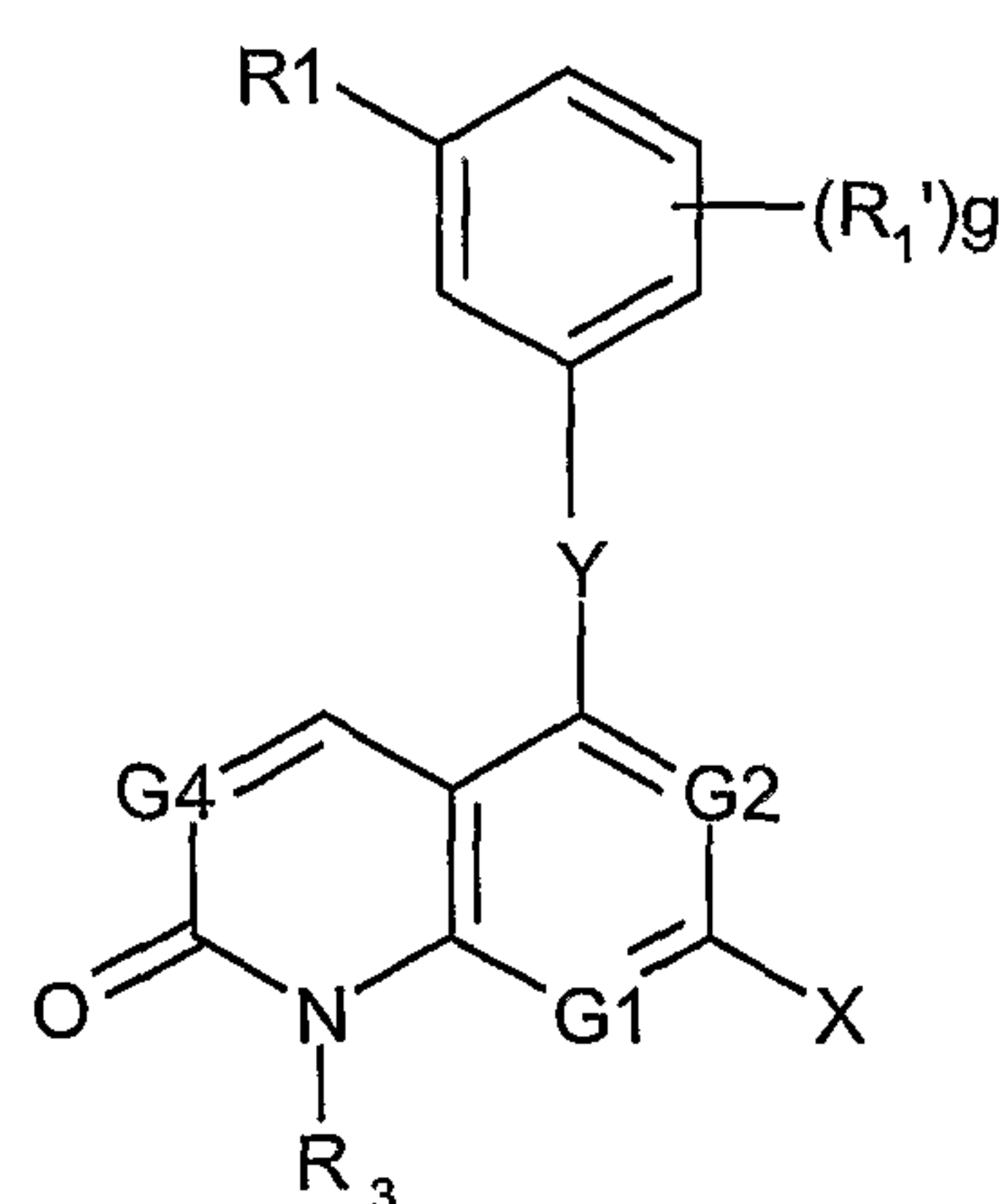
a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof.

Another aspect of the invention are compounds of Formula (A) and (A1):



(A)

or



(A1)

wherein

$G_1$ , and  $G_2$  are independently nitrogen;

$G_3$  is  $CH_2$ ;

- G<sub>4</sub> is CH;
- Y is C(R<sub>X</sub>)(R<sub>Z</sub>), C(O), N(R<sub>Z</sub>), N(R<sub>W</sub>)C(R<sub>Y</sub>)(R<sub>Z</sub>), oxygen, OC(R<sub>Y</sub>)(R<sub>Z</sub>), S(O)<sub>m</sub>, or S(O)<sub>m</sub>C(R<sub>Y</sub>)(R<sub>Z</sub>);
- R<sub>X</sub> is hydrogen, C<sub>1-2</sub> alkyl, N(R<sub>V</sub>)<sub>2</sub>, hydroxy, thio, C<sub>1-2</sub> alkoxy, or S(O)<sub>m</sub>C<sub>1-2</sub>alkyl;
- 5 R<sub>Y</sub> is hydrogen or C<sub>1-2</sub> alkyl;
- R<sub>Z</sub>' is hydrogen or C<sub>1-2</sub> alkyl;
- R<sub>W</sub> is hydrogen or C<sub>1-2</sub> alkyl;
- R<sub>V</sub> is independently selected from hydrogen or C<sub>1-2</sub> alkyl;
- R<sub>1</sub> is C(Z)N(R<sub>10</sub>') (CR<sub>10</sub>R<sub>20</sub>)<sub>v</sub>R<sub>b</sub>, C(Z)O(CR<sub>10</sub>R<sub>20</sub>)<sub>v</sub>R<sub>b</sub>,  
 10 N(R<sub>10</sub>')C(Z)(CR<sub>10</sub>R<sub>20</sub>)<sub>v</sub>R<sub>b</sub>, N(R<sub>10</sub>')C(Z)N(R<sub>10</sub>') (CR<sub>10</sub>R<sub>20</sub>)<sub>v</sub>R<sub>b</sub>, or  
 N(R<sub>10</sub>')OC(Z)(CR<sub>10</sub>R<sub>20</sub>)<sub>v</sub>R<sub>b</sub>;
- R<sub>1</sub>' is independently selected at each occurrence from halogen, C<sub>1-4</sub> alkyl, halo-substituted-C<sub>1-4</sub> alkyl, cyano, nitro, (CR<sub>10</sub>R<sub>20</sub>)<sub>v</sub>'NR<sub>d</sub>R<sub>d</sub>',  
 (CR<sub>10</sub>R<sub>20</sub>)<sub>v</sub>'C(O)R<sub>12</sub>, SR<sub>5</sub>, S(O)R<sub>5</sub>, S(O)<sub>2</sub>R<sub>5</sub>, or (CR<sub>10</sub>R<sub>20</sub>)<sub>v</sub>'OR<sub>13</sub>;
- 15 R<sub>b</sub> is hydrogen, C<sub>1-10</sub> alkyl, C<sub>3-7</sub> cycloalkyl, C<sub>3-7</sub> cycloalkyl C<sub>1-10</sub> alkyl, aryl, arylC<sub>1-10</sub>alkyl, heteroaryl, heteroarylC<sub>1-10</sub> alkyl, heterocyclic, or heterocyclylC<sub>1-10</sub> alkyl moiety, which moieties, excluding hydrogen, may all be optionally substituted;
- X is R<sub>2</sub>, OR<sub>2</sub>', S(O)<sub>m</sub>R<sub>2</sub>', (CH<sub>2</sub>)<sub>n</sub>'N(R<sub>10</sub>')S(O)<sub>m</sub>R<sub>2</sub>', (CH<sub>2</sub>)<sub>n</sub>'N(R<sub>10</sub>')C(O)R<sub>2</sub>',  
 20 (CH<sub>2</sub>)<sub>n</sub>'NR<sub>4</sub>R<sub>14</sub>, (CH<sub>2</sub>)<sub>n</sub>'N(R<sub>2</sub>') (R<sub>2</sub>''), or N(R<sub>10</sub>')R<sub>h</sub>NH-C(=N-CN)NR<sub>q</sub>R<sub>q</sub>';
- X<sub>1</sub> is N(R<sub>11</sub>), O, S(O)<sub>m</sub>, or CR<sub>10</sub>R<sub>20</sub>;
- R<sub>h</sub> is selected from an optionally substituted C<sub>1-10</sub> alkyl, -CH<sub>2</sub>-C(O)-CH<sub>2</sub>-,  
 -CH<sub>2</sub>-CH<sub>2</sub>-O-CH<sub>2</sub>-CH<sub>2</sub>-, -CH<sub>2</sub>-C(O)N(R<sub>10</sub>')CH<sub>2</sub>-CH<sub>2</sub>-,  
 -CH<sub>2</sub>-N(R<sub>10</sub>')C(O)CH<sub>2</sub>-, -CH<sub>2</sub>-CH(OR<sub>10</sub>')-CH<sub>2</sub>-, -CH<sub>2</sub>-C(O)O-CH<sub>2</sub>-CH<sub>2</sub>-, or  
 25 -CH<sub>2</sub>-CH<sub>2</sub>-O-C(O)CH<sub>2</sub>-;
- R<sub>q</sub> and R<sub>q</sub>' are independently selected at each occurrence from hydrogen, C<sub>1-10</sub> alkyl, C<sub>3-7</sub>cycloalkyl, C<sub>3-7</sub>cycloalkylC<sub>1-10</sub>alkyl, C<sub>5-7</sub> cycloalkenyl, C<sub>5-7</sub> cycloalkenyl-C<sub>1-10</sub>alkyl, aryl, arylC<sub>1-10</sub> alkyl, heteroaryl, heteroarylC<sub>1-10</sub> alkyl, heterocyclic, or a heterocyclylC<sub>1-10</sub> alkyl moiety, wherein all of the  
 30 moieties except for hydrogen, are optionally substituted, or R<sub>q</sub> and R<sub>q</sub>' together with the nitrogen to which they are attached form an optionally substituted heterocyclic ring of 5 to 7 members, which ring may contain an additional heteroatom selected from oxygen, nitrogen or sulfur;
- R<sub>2</sub> is hydrogen, C<sub>1-10</sub> alkyl, C<sub>3-7</sub> cycloalkyl, C<sub>3-7</sub> cycloalkylalkyl, aryl, arylC<sub>1-10</sub> alkyl, heteroaryl, heteroarylC<sub>1-10</sub> alkyl, heterocyclic, or a heterocyclylC<sub>1-10</sub> alkyl moiety, and wherein each of these moieties, excluding hydrogen, may be  
 35 optionally substituted; or

$R_2$  is the moiety  $(CR_{10}R_{20})_qX_1(CR_{10}R_{20})_qC(A_1)(A_2)(A_3)$ , or  $(CR_{10}R_{20})_qC(A_1)(A_2)(A_3)$ ;

$R_{2'}$  is hydrogen,  $C_{1-10}$  alkyl,  $C_{3-7}$  cycloalkyl,  $C_{3-7}$  cycloalkylalkyl, aryl, aryl $C_{1-10}$  alkyl, heteroaryl, heteroaryl $C_{1-10}$  alkyl, heterocyclic, or a heterocyclyl $C_{1-10}$  alkyl moiety, and wherein each of these moieties, excluding hydrogen, may be optionally substituted;

$R_{2''}$  is hydrogen,  $C_{1-10}$  alkyl,  $C_{3-7}$  cycloalkyl,  $C_{3-7}$  cycloalkylalkyl, aryl, aryl $C_{1-10}$  alkyl, heteroaryl, heteroaryl $C_{1-10}$  alkyl, heterocyclic, or a heterocyclyl $C_{1-10}$  alkyl moiety, and wherein these moieties, excluding hydrogen, may be optionally; or wherein  $R_{2''}$  is the moiety  $(CR_{10}R_{20})_tX_1(CR_{10}R_{20})_qC(A_1)(A_2)(A_3)$ ;

$A_1$  is an optionally substituted  $C_{1-10}$  alkyl, heterocyclic, heterocyclic  $C_{1-10}$  alkyl, heteroaryl, heteroaryl  $C_{1-10}$  alkyl, aryl, or aryl  $C_{1-10}$  alkyl;

$A_2$  is an optionally substituted  $C_{1-10}$  alkyl, heterocyclic, heterocyclic  $C_{1-10}$  alkyl, heteroaryl, heteroaryl  $C_{1-10}$  alkyl, aryl, or aryl  $C_{1-10}$  alkyl;

$A_3$  is hydrogen or is an optionally substituted  $C_{1-10}$  alkyl;

$R_3$  is a  $C_{1-10}$  alkyl,  $C_{3-7}$  cycloalkyl,  $C_{3-7}$  cycloalkyl  $C_{1-10}$  alkyl, aryl, aryl $C_{1-10}$  alkyl, heteroaryl, heteroaryl $C_{1-10}$  alkyl, heterocyclic or a heterocyclyl $C_{1-10}$  alkyl moiety, and wherein each of these moieties may be optionally substituted;

$R_4$  and  $R_{14}$  are each independently selected at each occurrence from hydrogen,  $C_{1-4}$  alkyl,  $C_{3-7}$  cycloalkyl,  $C_{3-7}$  cycloalkyl $C_{1-4}$ alkyl, aryl, aryl- $C_{1-4}$  alkyl, heterocyclic, heterocyclic  $C_{1-4}$  alkyl, heteroaryl or a heteroaryl  $C_{1-4}$  alkyl moiety, and wherein each of these moieties, excluding hydrogen, may be optionally substituted; or the  $R_4$  and  $R_{14}$  together with the nitrogen which they are attached form an optionally substituted heterocyclic ring of 4 to 7 members, which ring optionally contains an additional heteroatom selected from oxygen, sulfur or nitrogen;

$R_{4'}$  and  $R_{14'}$  are each independently selected at each occurrence from hydrogen or  $C_{1-4}$  alkyl, or  $R_{4'}$  and  $R_{14'}$  together with the nitrogen to which they are attached form a heterocyclic ring of 5 to 7 members, which ring optionally contains an additional heteroatom selected from  $NR_9$ ;

$R_5$  is independently selected at each occurrence from hydrogen,  $C_{1-4}$  alkyl,  $C_{2-4}$  alkenyl,  $C_{2-4}$  alkynyl or  $NR_4R_{14'}$ , excluding the moieties  $SR_5$  being  $SNR_4R_{14'}$ ,  $S(O)_2R_5$  being  $SO_2H$  and  $S(O)R_5$  being  $SOH$ ;

$R_{9'}$  is independently selected at each occurrence from hydrogen, or  $C_{1-4}$  alkyl;

$R_{10}$  and  $R_{20}$  are independently selected at each occurrence from hydrogen or  $C_{1-4}$ alkyl;

$R_{10'}$  is independently selected at each occurrence from hydrogen or  $C_{1-4}$ alkyl;

R<sub>11</sub> is independently selected at each occurrence from hydrogen or C<sub>1-4</sub>alkyl;

R<sub>12</sub> is independently selected at each occurrence from hydrogen, C<sub>1-4</sub> alkyl, halo-substituted C<sub>1-4</sub> alkyl, C<sub>2-4</sub> alkenyl, C<sub>2-4</sub> alkynyl, C<sub>3-7</sub> cycloalkyl, C<sub>3-7</sub>cycloalkylC<sub>1-4</sub> alkyl, C<sub>5-7</sub> cycloalkenyl, C<sub>5-7</sub>cycloalkenyl C<sub>1-4</sub> alkyl, aryl, arylC<sub>1-4</sub> alkyl, heteroaryl, heteroarylC<sub>1-4</sub> alkyl, heterocyclyl, or a heterocyclylC<sub>1-4</sub> alkyl moiety, and wherein each of these moieties, excluding hydrogen, may be optionally substituted;

R<sub>13</sub> is independently selected at each occurrence from hydrogen, C<sub>1-4</sub> alkyl, halo-substituted C<sub>1-4</sub> alkyl, C<sub>2-4</sub> alkenyl, C<sub>2-4</sub> alkynyl, C<sub>3-7</sub> cycloalkyl, C<sub>3-7</sub>cycloalkylC<sub>1-4</sub> alkyl, C<sub>5-7</sub> cycloalkenyl, C<sub>5-7</sub>cycloalkenyl C<sub>1-4</sub> alkyl, aryl, arylC<sub>1-4</sub> alkyl, heteroaryl, heteroarylC<sub>1-4</sub> alkyl, heterocyclyl, or a heterocyclylC<sub>1-4</sub> alkyl moiety, and wherein each of these moieties, excluding hydrogen, may be optionally substituted;

R<sub>d</sub> and R<sub>d'</sub> are each independently selected from hydrogen, C<sub>1-4</sub> alkyl, C<sub>3-6</sub> cycloalkyl, C<sub>3-6</sub> cycloalkylC<sub>1-4</sub>alkyl moiety, and wherein each of these moieties, excluding hydrogen, may be optionally substituted; or R<sub>d</sub> and R<sub>d'</sub> together with the nitrogen which they are attached form an optionally substituted heterocyclic ring of 5 to 6 members, which ring optionally contains an additional heteroatom selected from oxygen, sulfur or NR<sub>9'</sub>;

g is 0 or an integer having a value of 1, 2, 3, or 4;

n' is independently selected at each occurrence from 0 or an integer having a value of 1 to 10;

m is independently selected at each occurrence from 0 or an integer having a value of 1 or 2;

q is 0 or an integer having a value of 1 to 10;

q' is 0, or an integer having a value of 1 to 6;

t is an integer having a value of 2 to 6;

v is 0 or an integer having a value of 1 or 2;

v' is independently selected at each occurrence from 0 or an integer having a value of 1 or 2;

Z is independently selected at each occurrence from oxygen or sulfur; and

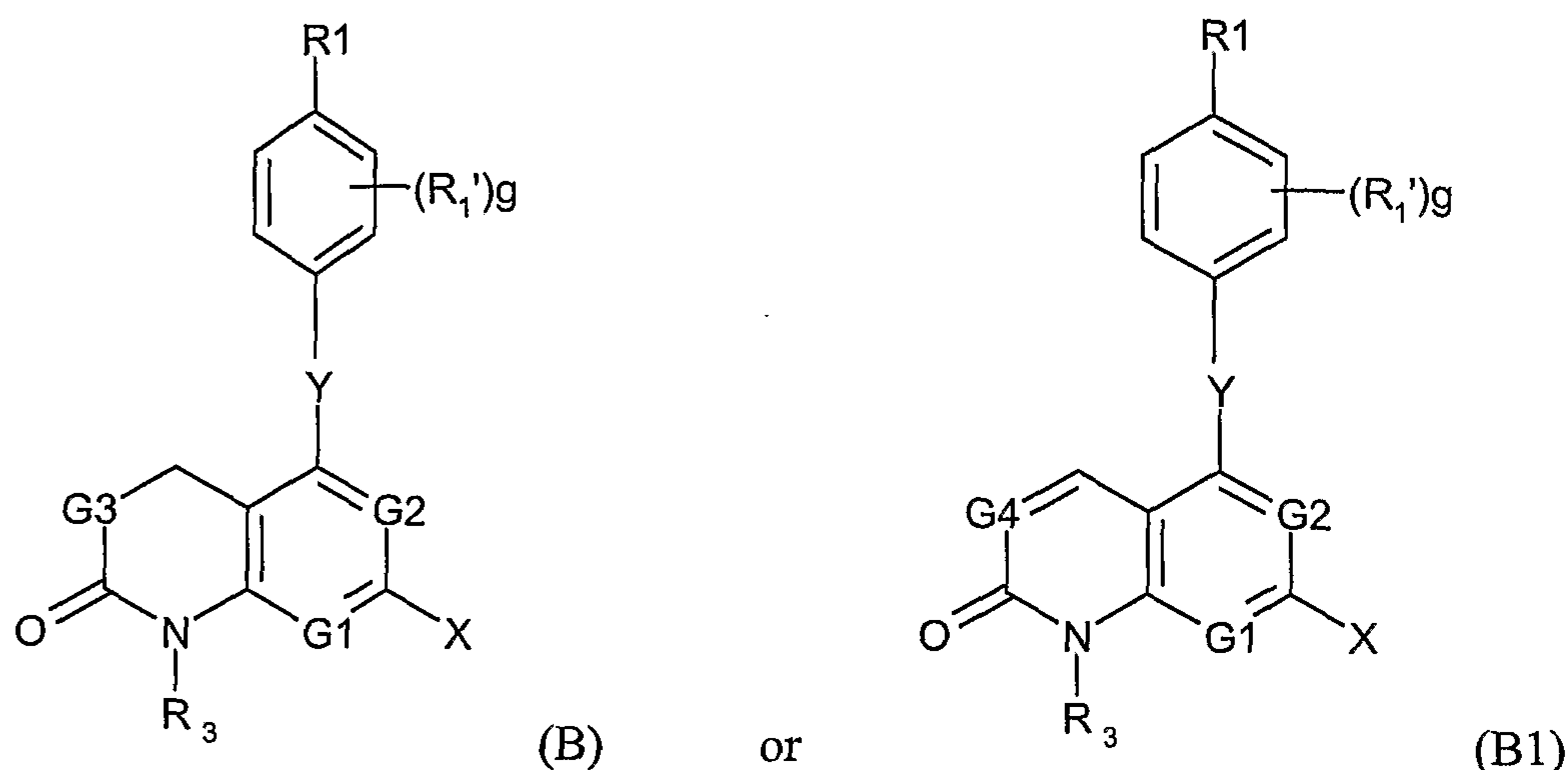
a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof.

The present invention is directed to novel compounds of Formula (A) and Formula (A1), or a pharmaceutically acceptable derivative thereof. As will be readily recognized, the difference between compounds of Formula (A) and Formula (A1),

and that of Formula (I) and (Ia) lies in the linker Y. The respective  $R_1$ ,  $R_2$ , and  $R_3$ , etc. terms are the same for both groups. For purposes herein, everything applicable to Formula (I) is also applicable to Formula (A) unless otherwise indicated.

Another aspect of the invention are compounds of Formula (B) and (B1):

5



wherein

$G_1$ , and  $G_2$  are independently nitrogen;

10  $G_3$  is  $CH_2$ ;

$G_4$  is  $CH$ ;

Y is  $C(R_X)(R_Z)$ ,  $C(O)$ ,  $N(R_Z)$ ,  $N(R_W)C(R_Y)(R_Z)$ , oxygen,  $OC(R_Y)(R_Z)$ ,  $S(O)_m$ , or  $S(O)_mC(R_Y)(R_Z)$ ;

$R_X$  is hydrogen,  $C_{1-2}$  alkyl,  $N(R_V)_2$ , hydroxy, thio,  $C_{1-2}$  alkoxy, or  $S(O)_mC_{1-2}$  alkyl;

15  $R_Y$  is hydrogen or  $C_{1-2}$  alkyl;

$R_{Z'}$  is hydrogen or  $C_{1-2}$  alkyl;

$R_W$  is hydrogen or  $C_{1-2}$  alkyl;

$R_V$  is independently selected from hydrogen or  $C_{1-2}$  alkyl;

20  $R_1$  is  $C(Z)N(R_{10'}) (CR_{10}R_{20})_v R_b$ ,  $C(Z)O(CR_{10}R_{20})_v R_b$ ,  $N(R_{10'})C(Z)(CR_{10}R_{20})_v R_b$ ,  $N(R_{10'})C(Z)N(R_{10'}) (CR_{10}R_{20})_v R_b$ , or  $N(R_{10'})OC(Z)(CR_{10}R_{20})_v R_b$ ;

$R_{1'}$  is independently selected at each occurrence from halogen,  $C_{1-4}$  alkyl, halo-substituted- $C_{1-4}$  alkyl, cyano, nitro,  $(CR_{10}R_{20})_v NR_d R_d'$ ,

25  $(CR_{10}R_{20})_v C(O)R_{12}$ ,  $SR_5$ ,  $S(O)R_5$ ,  $S(O)_2R_5$ , or  $(CR_{10}R_{20})_v OR_{13}$ ;

$R_b$  is hydrogen,  $C_{1-10}$  alkyl,  $C_{3-7}$  cycloalkyl,  $C_{3-7}$  cycloalkyl  $C_{1-10}$  alkyl, aryl, aryl $C_{1-10}$ alkyl, heteroaryl, heteroaryl $C_{1-10}$  alkyl, heterocyclic, or

heterocyclylC<sub>1-10</sub> alkyl moiety, which moieties, excluding hydrogen, may all be optionally substituted;

X is R<sub>2</sub>, OR<sub>2</sub>', S(O)<sub>m</sub>R<sub>2</sub>', (CH<sub>2</sub>)<sub>n</sub>'N(R<sub>10</sub>')S(O)<sub>m</sub>R<sub>2</sub>', (CH<sub>2</sub>)<sub>n</sub>'N(R<sub>10</sub>')C(O)R<sub>2</sub>', (CH<sub>2</sub>)<sub>n</sub>'NR<sub>4</sub>R<sub>14</sub>, (CH<sub>2</sub>)<sub>n</sub>'N(R<sub>2</sub>') (R<sub>2</sub>''), or N(R<sub>10</sub>')R<sub>h</sub>NH-C(=N-CN)NR<sub>q</sub>R<sub>q</sub>';

5 X<sub>1</sub> is N(R<sub>11</sub>), O, S(O)<sub>m</sub>, or CR<sub>10</sub>R<sub>20</sub>;

R<sub>h</sub> is selected from an optionally substituted C<sub>1-10</sub> alkyl, -CH<sub>2</sub>-C(O)-CH<sub>2</sub>-, --CH<sub>2</sub>-CH<sub>2</sub>-O-CH<sub>2</sub>-CH<sub>2</sub>-, -CH<sub>2</sub>-C(O)N(R<sub>10</sub>')CH<sub>2</sub>-CH<sub>2</sub>-, -CH<sub>2</sub>-N(R<sub>10</sub>')C(O)CH<sub>2</sub>-, -CH<sub>2</sub>-CH(OR<sub>10</sub>')-CH<sub>2</sub>-, -CH<sub>2</sub>-C(O)O-CH<sub>2</sub>-CH<sub>2</sub>-, or -CH<sub>2</sub>-CH<sub>2</sub>-O-C(O)CH<sub>2</sub>-;

10 R<sub>q</sub> and R<sub>q</sub>' are independently selected at each occurrence from hydrogen, C<sub>1-10</sub> alkyl, C<sub>3-7</sub>cycloalkyl, C<sub>3-7</sub>cycloalkylC<sub>1-10</sub>alkyl, C<sub>5-7</sub> cycloalkenyl, C<sub>5-7</sub> cycloalkenyl-C<sub>1-10</sub>alkyl, aryl, arylC<sub>1-10</sub> alkyl, heteroaryl, heteroarylC<sub>1-10</sub> alkyl, heterocyclic, or a heterocyclylC<sub>1-10</sub> alkyl moiety, wherein all of the moieties except for hydrogen, are optionally substituted, or R<sub>q</sub> and R<sub>q</sub>' together  
15 with the nitrogen to which they are attached form an optionally substituted heterocyclic ring of 5 to 7 members, which ring may contain an additional heteroatom selected from oxygen, nitrogen or sulfur;

R<sub>2</sub> is hydrogen, C<sub>1-10</sub> alkyl, C<sub>3-7</sub> cycloalkyl, C<sub>3-7</sub> cycloalkylalkyl, aryl, arylC<sub>1-10</sub> alkyl, heteroaryl, heteroarylC<sub>1-10</sub> alkyl, heterocyclic, or a heterocyclylC<sub>1-10</sub>  
20 alkyl moiety, and wherein each of these moieties, excluding hydrogen, may be optionally substituted; or

R<sub>2</sub> is the moiety (CR<sub>10</sub>R<sub>20</sub>)<sub>q</sub>'X<sub>1</sub>(CR<sub>10</sub>R<sub>20</sub>)<sub>q</sub>C(A<sub>1</sub>)(A<sub>2</sub>)(A<sub>3</sub>), or (CR<sub>10</sub>R<sub>20</sub>)<sub>q</sub>'C(A<sub>1</sub>)(A<sub>2</sub>)(A<sub>3</sub>);

R<sub>2</sub>' is hydrogen, C<sub>1-10</sub> alkyl, C<sub>3-7</sub> cycloalkyl, C<sub>3-7</sub> cycloalkylalkyl, aryl, arylC<sub>1-10</sub>  
25 alkyl, heteroaryl, heteroarylC<sub>1-10</sub> alkyl, heterocyclic, or a heterocyclylC<sub>1-10</sub> alkyl moiety, and wherein each of these moieties, excluding hydrogen, may be optionally substituted;

R<sub>2</sub>'' is hydrogen, C<sub>1-10</sub> alkyl, C<sub>3-7</sub> cycloalkyl, C<sub>3-7</sub> cycloalkylalkyl, aryl, arylC<sub>1-10</sub>  
30 alkyl, heteroaryl, heteroarylC<sub>1-10</sub> alkyl, heterocyclic, or a heterocyclylC<sub>1-10</sub> alkyl moiety, and wherein these moieties, excluding hydrogen, may be optionally; or wherein R<sub>2</sub>'' is the moiety (CR<sub>10</sub>R<sub>20</sub>)<sub>t</sub>X<sub>1</sub>(CR<sub>10</sub>R<sub>20</sub>)<sub>q</sub>C(A<sub>1</sub>)(A<sub>2</sub>)(A<sub>3</sub>);

A<sub>1</sub> is an optionally substituted C<sub>1-10</sub> alkyl, heterocyclic, heterocyclic C<sub>1-10</sub> alkyl, heteroaryl, heteroaryl C<sub>1-10</sub> alkyl, aryl, or aryl C<sub>1-10</sub> alkyl;

A<sub>2</sub> is an optionally substituted C<sub>1-10</sub> alkyl, heterocyclic, heterocyclic C<sub>1-10</sub> alkyl,  
35 heteroaryl, heteroaryl C<sub>1-10</sub> alkyl, aryl, or aryl C<sub>1-10</sub> alkyl;

A<sub>3</sub> is hydrogen or is an optionally substituted C<sub>1-10</sub> alkyl;

- R<sub>3</sub> is a C<sub>1-10</sub> alkyl, C<sub>3-7</sub> cycloalkyl, C<sub>3-7</sub> cycloalkyl C<sub>1-10</sub> alkyl, aryl, arylC<sub>1-10</sub> alkyl, heteroaryl, heteroarylC<sub>1-10</sub> alkyl, heterocyclic or a heterocyclylC<sub>1-10</sub> alkyl moiety, and wherein each of these moieties may be optionally substituted;
- R<sub>4</sub> and R<sub>14</sub> are each independently selected at each occurrence from hydrogen, C<sub>1-4</sub> alkyl, C<sub>3-7</sub> cycloalkyl, C<sub>3-7</sub> cycloalkylC<sub>1-4</sub>alkyl, aryl, aryl-C<sub>1-4</sub> alkyl, heterocyclic, heterocyclic C<sub>1-4</sub> alkyl, heteroaryl or a heteroaryl C<sub>1-4</sub> alkyl moiety, and wherein each of these moieties, excluding hydrogen, may be optionally substituted; or the R<sub>4</sub> and R<sub>14</sub> together with the nitrogen which they are attached form an optionally substituted heterocyclic ring of 4 to 7 members, which ring optionally contains an additional heteroatom selected from oxygen, sulfur or nitrogen;
- R<sub>4'</sub> and R<sub>14'</sub> are each independently selected at each occurrence from hydrogen or C<sub>1-4</sub> alkyl, or R<sub>4'</sub> and R<sub>14'</sub> together with the nitrogen to which they are attached form a heterocyclic ring of 5 to 7 members, which ring optionally contains an additional heteroatom selected from NR<sub>9'</sub>;
- R<sub>5</sub> is independently selected at each occurrence from hydrogen, C<sub>1-4</sub> alkyl, C<sub>2-4</sub> alkenyl, C<sub>2-4</sub> alkynyl or NR<sub>4'</sub>R<sub>14'</sub>, excluding the moieties SR<sub>5</sub> being SNR<sub>4'</sub>R<sub>14'</sub>, S(O)<sub>2</sub>R<sub>5</sub> being SO<sub>2</sub>H and S(O)R<sub>5</sub> being SOH;
- R<sub>9'</sub> is independently selected at each occurrence from hydrogen, or C<sub>1-4</sub> alkyl;
- R<sub>10</sub> and R<sub>20</sub> are independently selected at each occurrence from hydrogen or C<sub>1-4</sub>alkyl;
- R<sub>10'</sub> is independently selected at each occurrence from hydrogen or C<sub>1-4</sub>alkyl;
- R<sub>11</sub> is independently selected at each occurrence from hydrogen or C<sub>1-4</sub>alkyl;
- R<sub>12</sub> is independently selected at each occurrence from hydrogen, C<sub>1-4</sub> alkyl, halo-substituted C<sub>1-4</sub> alkyl, C<sub>2-4</sub> alkenyl, C<sub>2-4</sub> alkynyl, C<sub>3-7</sub> cycloalkyl, C<sub>3-7</sub>cycloalkylC<sub>1-4</sub> alkyl, C<sub>5-7</sub> cycloalkenyl, C<sub>5-7</sub>cycloalkenyl C<sub>1-4</sub> alkyl, aryl, arylC<sub>1-4</sub> alkyl, heteroaryl, heteroarylC<sub>1-4</sub> alkyl, heterocyclyl, or a heterocyclylC<sub>1-4</sub> alkyl moiety, and wherein each of these moieties, excluding hydrogen, may be optionally substituted;
- R<sub>13</sub> is independently selected at each occurrence from hydrogen, C<sub>1-4</sub> alkyl, halo-substituted C<sub>1-4</sub> alkyl, C<sub>2-4</sub> alkenyl, C<sub>2-4</sub> alkynyl, C<sub>3-7</sub> cycloalkyl, C<sub>3-7</sub>cycloalkylC<sub>1-4</sub> alkyl, C<sub>5-7</sub> cycloalkenyl, C<sub>5-7</sub>cycloalkenyl C<sub>1-4</sub> alkyl, aryl, arylC<sub>1-4</sub> alkyl, heteroaryl, heteroarylC<sub>1-4</sub> alkyl, heterocyclyl, or a heterocyclylC<sub>1-4</sub> alkyl moiety, and wherein each of these moieties, excluding hydrogen, may be optionally substituted;
- R<sub>d</sub> and R<sub>d'</sub> are each independently selected from hydrogen, C<sub>1-4</sub> alkyl, C<sub>3-6</sub> cycloalkyl, C<sub>3-6</sub> cycloalkylC<sub>1-4</sub>alkyl moiety, and wherein each of these moieties,

excluding hydrogen, may be optionally substituted; or R<sub>d</sub> and R<sub>d</sub>' together with the nitrogen which they are attached form an optionally substituted heterocyclic ring of 5 to 6 members, which ring optionally contains an additional heteroatom selected from oxygen, sulfur or NR<sub>g</sub>';

5 g is 0 or an integer having a value of 1, 2, 3, or 4;

n' is independently selected at each occurrence from 0 or an integer having a value of 1 to 10;

m is independently selected at each occurrence from 0 or an integer having a value of 1 or 2;

10 q is 0 or an integer having a value of 1 to 10;

q' is 0, or an integer having a value of 1 to 6;

t is an integer having a value of 2 to 6;

v is 0 or an integer having a value of 1 or 2;

v' is independently selected at each occurrence from 0 or an integer having a value of 1 or 2;

15 Z is independently selected at each occurrence from oxygen or sulfur; and

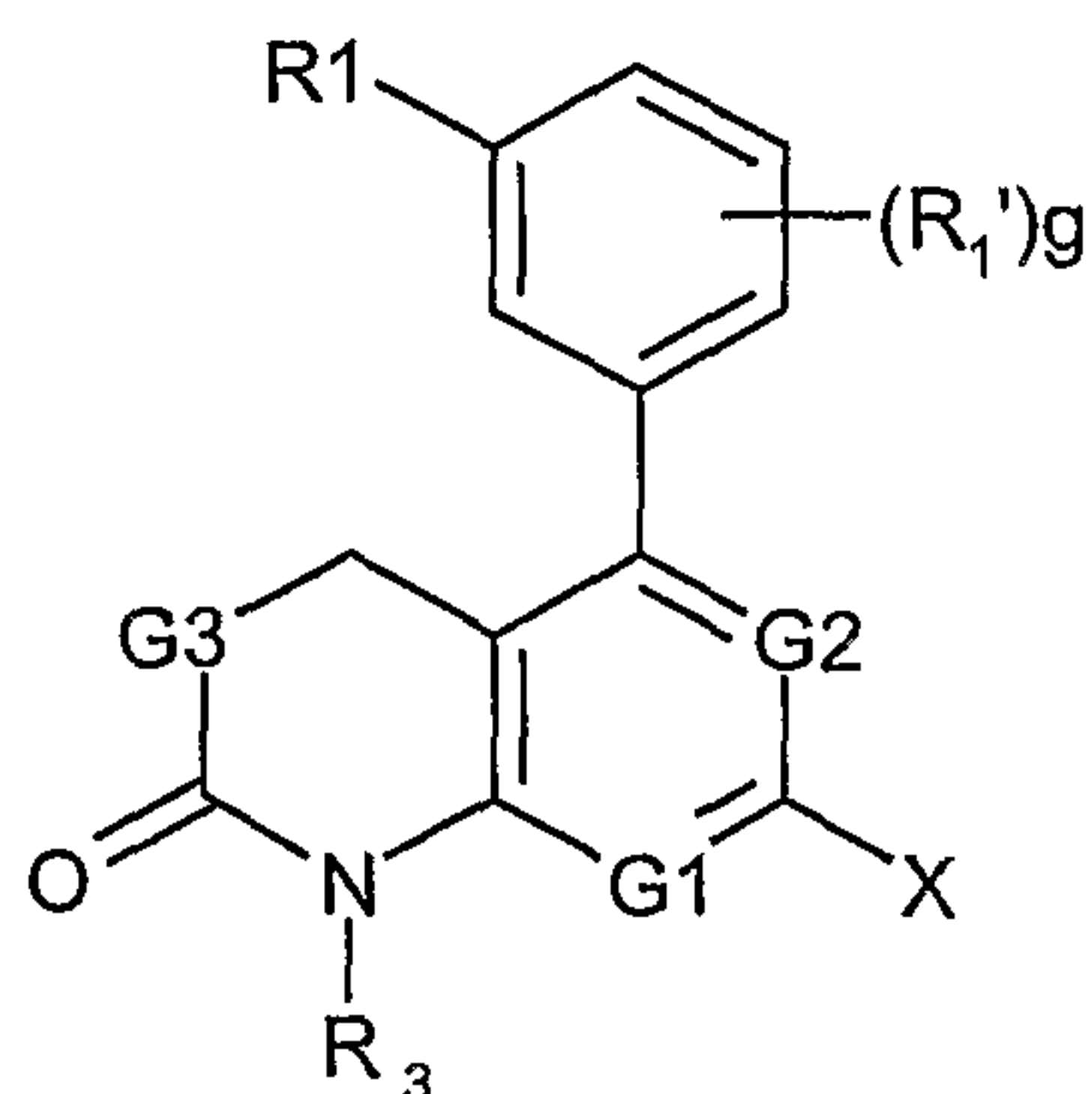
a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof.

As will be readily recognized, the differences between compounds of Formula (B) and Formula (B1), and that of Formula (II) and (IIa) lie in the linker Y. The respective R<sub>1</sub>, R<sub>2</sub>, and R<sub>3</sub>, etc. terms are the same for both groups. For purposes herein, everything applicable to Formula (II) is also applicable to Formula (B) unless otherwise indicated.

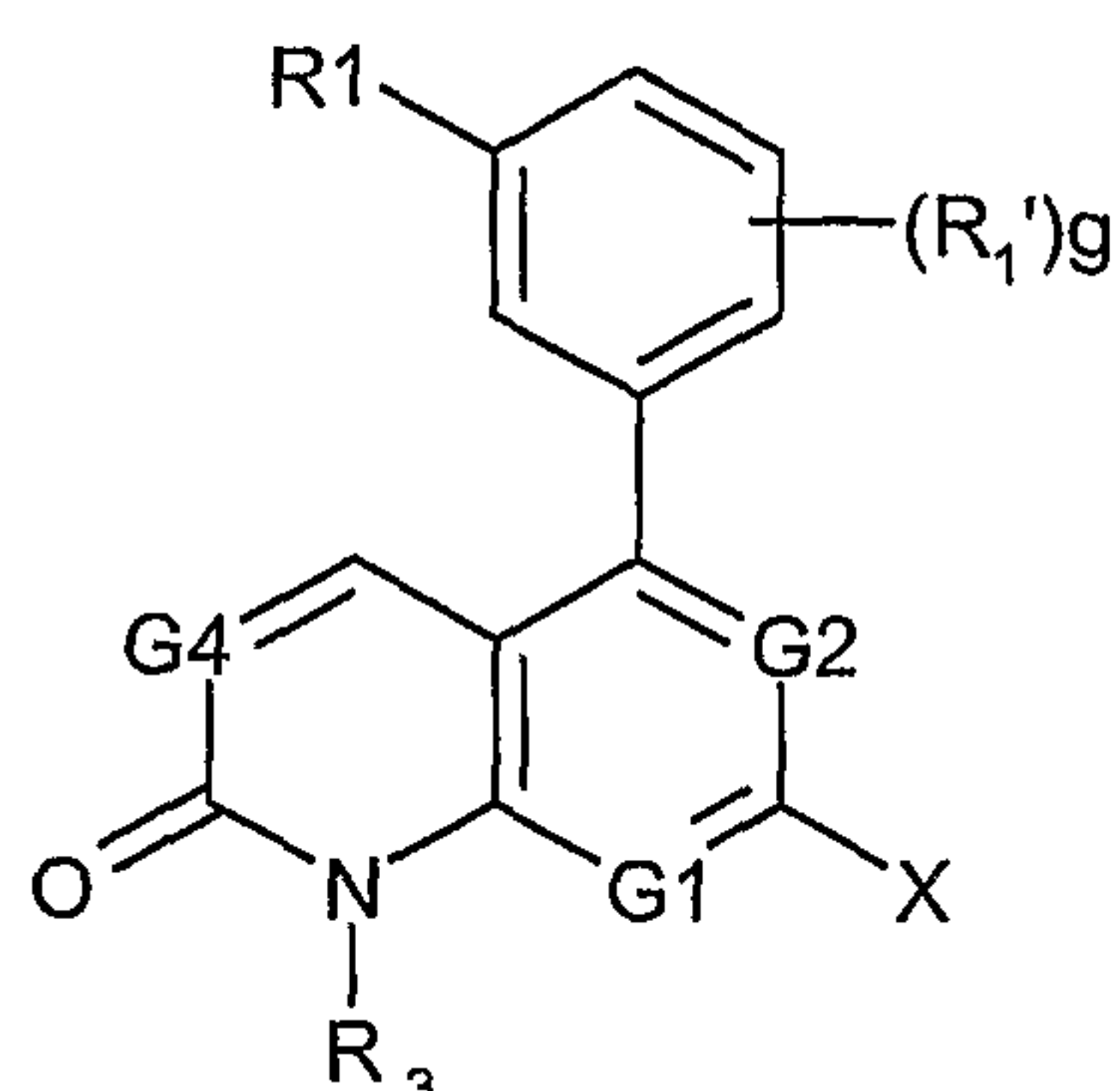
In another aspect of the invention, it is the linker Y may be present in a similar manner in the same position for all of the remaining formulas, Formula's (III) and (IIIa), (IV) and (IVa), (V) and (Va), (VI), (VIa-VIi), etc., herein. The respective R<sub>1</sub>, R<sub>2</sub>, and R<sub>3</sub>, etc. terms will be the same for all the groups.

Another aspect of the invention are compounds of Formula (VIII) and (VIIIa):

30



(VIII) or



(VIIIa)

wherein

$G_1$ ,  $G_2$  are independently nitrogen or CH, but  $G_1$  and  $G_2$  are not both nitrogen;

5  $G_3$  is  $CH_2$ ;

$G_4$  is CH;

$R_1$  is  $C(Z)N(R_{10'}) (CR_{10}R_{20})_v R_b$ ,  $C(Z)O(CR_{10}R_{20})_v R_b$ ,  
 $N(R_{10'})C(Z)(CR_{10}R_{20})_v R_b$ ,  $N(R_{10'})C(Z)N(R_{10'}) (CR_{10}R_{20})_v R_b$ , or  
 $N(R_{10'})OC(Z)(CR_{10}R_{20})_v R_b$ ;

10  $R_{10}'$  is independently selected at each occurrence from halogen,  $C_{1-4}$  alkyl, halo-substituted- $C_{1-4}$  alkyl, cyano, nitro,  $(CR_{10}R_{20})_v NR_d R_d'$ ,  
 $(CR_{10}R_{20})_v C(O)R_{12}$ ,  $SR_5$ ,  $S(O)R_5$ ,  $S(O)_2R_5$ , or  $(CR_{10}R_{20})_v OR_{13}$ ;

$R_b$  is hydrogen,  $C_{1-10}$  alkyl,  $C_{3-7}$  cycloalkyl,  $C_{3-7}$  cycloalkyl  $C_{1-10}$  alkyl, aryl, aryl  $C_{1-10}$  alkyl, heteroaryl, heteroaryl  $C_{1-10}$  alkyl, heterocyclic, or

15 heterocyclyl  $C_{1-10}$  alkyl moiety, which moieties, excluding hydrogen, may all be optionally substituted;

$X$  is  $R_2$ ,  $OR_2'$ ,  $S(O)_m R_2'$ ,  $(CH_2)_n N(R_{10'}) S(O)_m R_2'$ ,  $(CH_2)_n N(R_{10'}) C(O) R_2'$ ,  
 $(CH_2)_n NR_4 R_{14}$ ,  $(CH_2)_n N(R_2') (R_2'')$ , or  $N(R_{10'}) R_h NH-C(=N-CN) NR_q R_q'$ ;

$X_1$  is  $N(R_{11})$ , O,  $S(O)_m$ , or  $CR_{10}R_{20}$ ;

20  $R_h$  is selected from an optionally substituted  $C_{1-10}$  alkyl,  $-CH_2-C(O)-CH_2-$ ,  
 $-CH_2-CH_2-O-CH_2-CH_2-$ ,  $-CH_2-C(O)N(R_{10'})CH_2-CH_2-$ ,  
 $-CH_2-N(R_{10'})C(O)CH_2-$ ,  $-CH_2-CH(OR_{10'})-CH_2-$ ,  $-CH_2-C(O)O-CH_2-CH_2-$ , or  
 $-CH_2-CH_2-O-C(O)CH_2-$ ;

25  $R_q$  and  $R_q'$  are independently selected at each occurrence from hydrogen,  $C_{1-10}$  alkyl,  $C_{3-7}$  cycloalkyl,  $C_{3-7}$  cycloalkyl  $C_{1-10}$  alkyl,  $C_{5-7}$  cycloalkenyl,  $C_{5-7}$  cycloalkenyl- $C_{1-10}$  alkyl, aryl, aryl  $C_{1-10}$  alkyl, heteroaryl, heteroaryl  $C_{1-10}$  alkyl, heterocyclic, or a heterocyclyl  $C_{1-10}$  alkyl moiety, wherein all of the moieties except for hydrogen, are optionally substituted, or  $R_q$  and  $R_q'$  together with the nitrogen to which they are attached form an optionally substituted

heterocyclic ring of 5 to 7 members, which ring may contain an additional heteroatom selected from oxygen, nitrogen or sulfur;

R<sub>2</sub> is hydrogen, C<sub>1-10</sub> alkyl, C<sub>3-7</sub> cycloalkyl, C<sub>3-7</sub> cycloalkylalkyl, aryl, arylC<sub>1-10</sub> alkyl, heteroaryl, heteroarylC<sub>1-10</sub> alkyl, heterocyclic, or a heterocyclylC<sub>1-10</sub>

5 alkyl moiety, and wherein each of these moieties, excluding hydrogen, may be optionally substituted; or

R<sub>2</sub> is the moiety (CR<sub>10</sub>R<sub>20</sub>)<sub>q</sub>X<sub>1</sub>(CR<sub>10</sub>R<sub>20</sub>)<sub>q</sub>C(A<sub>1</sub>)(A<sub>2</sub>)(A<sub>3</sub>), or (CR<sub>10</sub>R<sub>20</sub>)<sub>q</sub>C(A<sub>1</sub>)(A<sub>2</sub>)(A<sub>3</sub>);

10 R<sub>2</sub>' is hydrogen, C<sub>1-10</sub> alkyl, C<sub>3-7</sub> cycloalkyl, C<sub>3-7</sub> cycloalkylalkyl, aryl, arylC<sub>1-10</sub> alkyl, heteroaryl, heteroarylC<sub>1-10</sub> alkyl, heterocyclic, or a heterocyclylC<sub>1-10</sub> alkyl moiety, and wherein each of these moieties, excluding hydrogen, may be optionally substituted;

R<sub>2</sub>'' is hydrogen, C<sub>1-10</sub> alkyl, C<sub>3-7</sub> cycloalkyl, C<sub>3-7</sub> cycloalkylalkyl, aryl, arylC<sub>1-10</sub> alkyl, heteroaryl, heteroarylC<sub>1-10</sub> alkyl, heterocyclic, or a heterocyclylC<sub>1-10</sub> alkyl

15 moiety, and wherein these moieties, excluding hydrogen, may be optionally; or wherein R<sub>2</sub>'' is the moiety (CR<sub>10</sub>R<sub>20</sub>)<sub>t</sub>X<sub>1</sub>(CR<sub>10</sub>R<sub>20</sub>)<sub>q</sub>C(A<sub>1</sub>)(A<sub>2</sub>)(A<sub>3</sub>);

A<sub>1</sub> is an optionally substituted C<sub>1-10</sub> alkyl, heterocyclic, heterocyclic C<sub>1-10</sub> alkyl, heteroaryl, heteroaryl C<sub>1-10</sub> alkyl, aryl, or aryl C<sub>1-10</sub> alkyl;

20 A<sub>2</sub> is an optionally substituted C<sub>1-10</sub> alkyl, heterocyclic, heterocyclic C<sub>1-10</sub> alkyl, heteroaryl, heteroaryl C<sub>1-10</sub> alkyl, aryl, or aryl C<sub>1-10</sub> alkyl;

A<sub>3</sub> is hydrogen or is an optionally substituted C<sub>1-10</sub> alkyl;

R<sub>3</sub> is a C<sub>1-10</sub> alkyl, C<sub>3-7</sub> cycloalkyl, C<sub>3-7</sub> cycloalkyl C<sub>1-10</sub> alkyl, aryl, arylC<sub>1-10</sub> alkyl, heteroaryl, heteroarylC<sub>1-10</sub> alkyl, heterocyclic or a heterocyclylC<sub>1-10</sub> alkyl

moiety, and wherein each of these moieties may be optionally substituted;

25 R<sub>4</sub> and R<sub>14</sub> are each independently selected at each occurrence from hydrogen, C<sub>1-4</sub> alkyl, C<sub>3-7</sub> cycloalkyl, C<sub>3-7</sub> cycloalkylC<sub>1-4</sub>alkyl, aryl, aryl-C<sub>1-4</sub> alkyl, heterocyclic, heterocyclic C<sub>1-4</sub> alkyl, heteroaryl or a heteroaryl C<sub>1-4</sub> alkyl

30 moiety, and wherein each of these moieties, excluding hydrogen, may be optionally substituted; or the R<sub>4</sub> and R<sub>14</sub> together with the nitrogen which they are attached form an optionally substituted heterocyclic ring of 4 to 7 members, which ring optionally contains an additional heteroatom selected from oxygen, sulfur or nitrogen;

35 R<sub>4</sub>' and R<sub>14</sub>' are each independently selected at each occurrence from hydrogen or C<sub>1-4</sub> alkyl, or R<sub>4</sub>' and R<sub>14</sub>' together with the nitrogen to which they are attached form a heterocyclic ring of 5 to 7 members, which ring optionally contains an additional heteroatom selected from NR<sub>9</sub>';

- R<sub>5</sub> is independently selected at each occurrence from hydrogen, C<sub>1-4</sub> alkyl, C<sub>2-4</sub> alkenyl, C<sub>2-4</sub> alkynyl or NR<sub>4'</sub>R<sub>14'</sub>, excluding the moieties SR<sub>5</sub> being SNR<sub>4'</sub>R<sub>14'</sub>, S(O)<sub>2</sub>R<sub>5</sub> being SO<sub>2</sub>H and S(O)R<sub>5</sub> being SOH;
- R<sub>9'</sub> is independently selected at each occurrence from hydrogen, or C<sub>1-4</sub> alkyl;
- 5 R<sub>10</sub> and R<sub>20</sub> are independently selected at each occurrence from hydrogen or C<sub>1-4</sub>alkyl;
- R<sub>10'</sub> is independently selected at each occurrence from hydrogen or C<sub>1-4</sub>alkyl;
- R<sub>11</sub> is independently selected at each occurrence from hydrogen or C<sub>1-4</sub>alkyl;
- R<sub>12</sub> is independently selected at each occurrence from hydrogen, C<sub>1-4</sub> alkyl, halo-
- 10 substituted C<sub>1-4</sub> alkyl, C<sub>2-4</sub> alkenyl, C<sub>2-4</sub> alkynyl, C<sub>3-7</sub> cycloalkyl, C<sub>3-7</sub>cycloalkylC<sub>1-4</sub> alkyl, C<sub>5-7</sub> cycloalkenyl, C<sub>5-7</sub>cycloalkenyl C<sub>1-4</sub> alkyl, aryl, arylC<sub>1-4</sub> alkyl, heteroaryl, heteroarylC<sub>1-4</sub> alkyl, heterocyclyl, or a heterocyclylC<sub>1-4</sub> alkyl moiety, and wherein each of these moieties, excluding hydrogen, may be optionally substituted;
- 15 R<sub>13</sub> is independently selected at each occurrence from hydrogen, C<sub>1-4</sub> alkyl, halo-substituted C<sub>1-4</sub> alkyl, C<sub>2-4</sub> alkenyl, C<sub>2-4</sub> alkynyl, C<sub>3-7</sub> cycloalkyl, C<sub>3-7</sub>cycloalkylC<sub>1-4</sub> alkyl, C<sub>5-7</sub> cycloalkenyl, C<sub>5-7</sub>cycloalkenyl C<sub>1-4</sub> alkyl, aryl, arylC<sub>1-4</sub> alkyl, heteroaryl, heteroarylC<sub>1-4</sub> alkyl, heterocyclyl, or a heterocyclylC<sub>1-4</sub> alkyl moiety, and wherein each of these moieties, excluding
- 20 hydrogen, may be optionally substituted;
- R<sub>d</sub> and R<sub>d'</sub> are each independently selected from hydrogen, C<sub>1-4</sub> alkyl, C<sub>3-6</sub> cycloalkyl, C<sub>3-6</sub> cycloalkylC<sub>1-4</sub>alkyl moiety, and wherein each of these moieties, excluding hydrogen, may be optionally substituted; or R<sub>d</sub> and R<sub>d'</sub> together with the nitrogen which they are attached form an optionally substituted heterocyclic
- 25 ring of 5 to 6 members, which ring optionally contains an additional heteroatom selected from oxygen, sulfur or NR<sub>9'</sub>;
- g is 0 or an integer having a value of 1, 2, 3, or 4;
- n' is independently selected at each occurrence from 0 or an integer having a value of 1 to 10;
- 30 m is independently selected at each occurrence from 0 or an integer having a value of 1 or 2;
- q is 0 or an integer having a value of 1 to 10;
- q' is 0, or an integer having a value of 1 to 6;
- t is an integer having a value of 2 to 6;
- 35 v is 0 or an integer having a value of 1 or 2;
- v' is independently selected at each occurrence from 0 or an integer having a value of 1 or 2;

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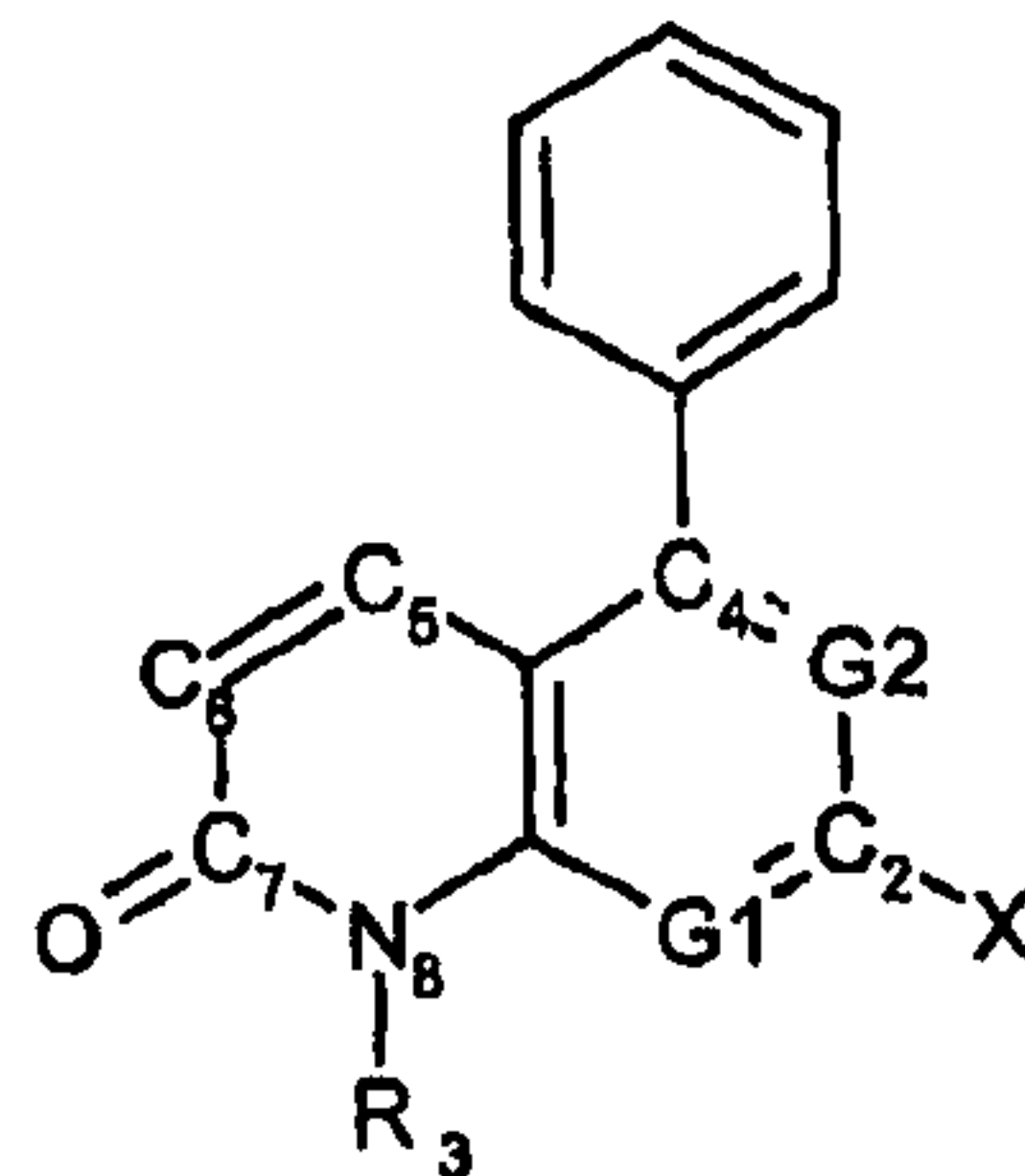
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Z is independently selected at each occurrence from oxygen or sulfur; and a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof.

In another embodiment of the present invention, for compounds of Formula (VIII) and (VIIIa) the X term may also be the B-Non-Ar-cyc moiety as disclosed above.

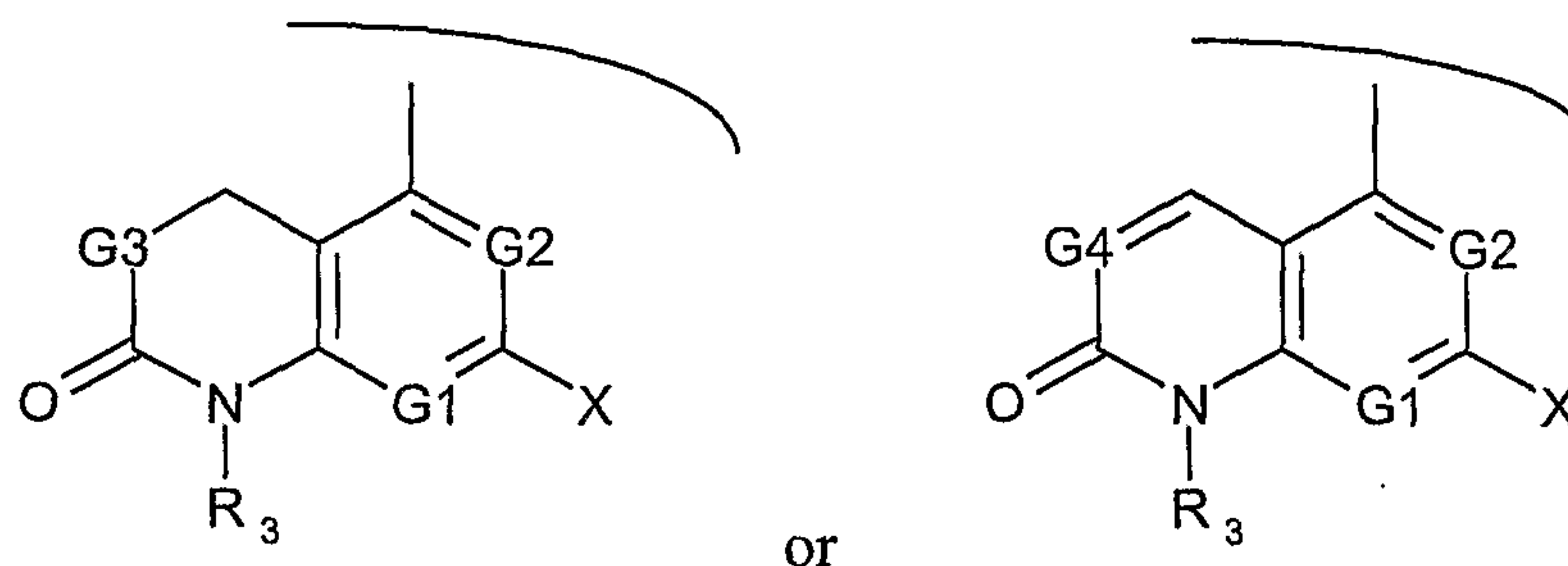
In another embodiment of the present invention, for compound of Formula (VIII) and (VIIIa), and the remaining formulas, the X term may also be the X moiety as disclosed in WO 2004/073628, published September 2004, Boehm et al.

For purposes herein the template containing the G<sub>1</sub> and G<sub>2</sub> moieties will have a numbering system that allows for different (R<sub>1</sub> and R<sub>1'</sub>) substituents on the phenyl, the pyridyl and pyrimidine ring at the C<sub>4</sub> position of the pharmacophore; the X term at the C<sub>2</sub> position and the R<sub>3</sub> substituent in the N<sub>8</sub> position.



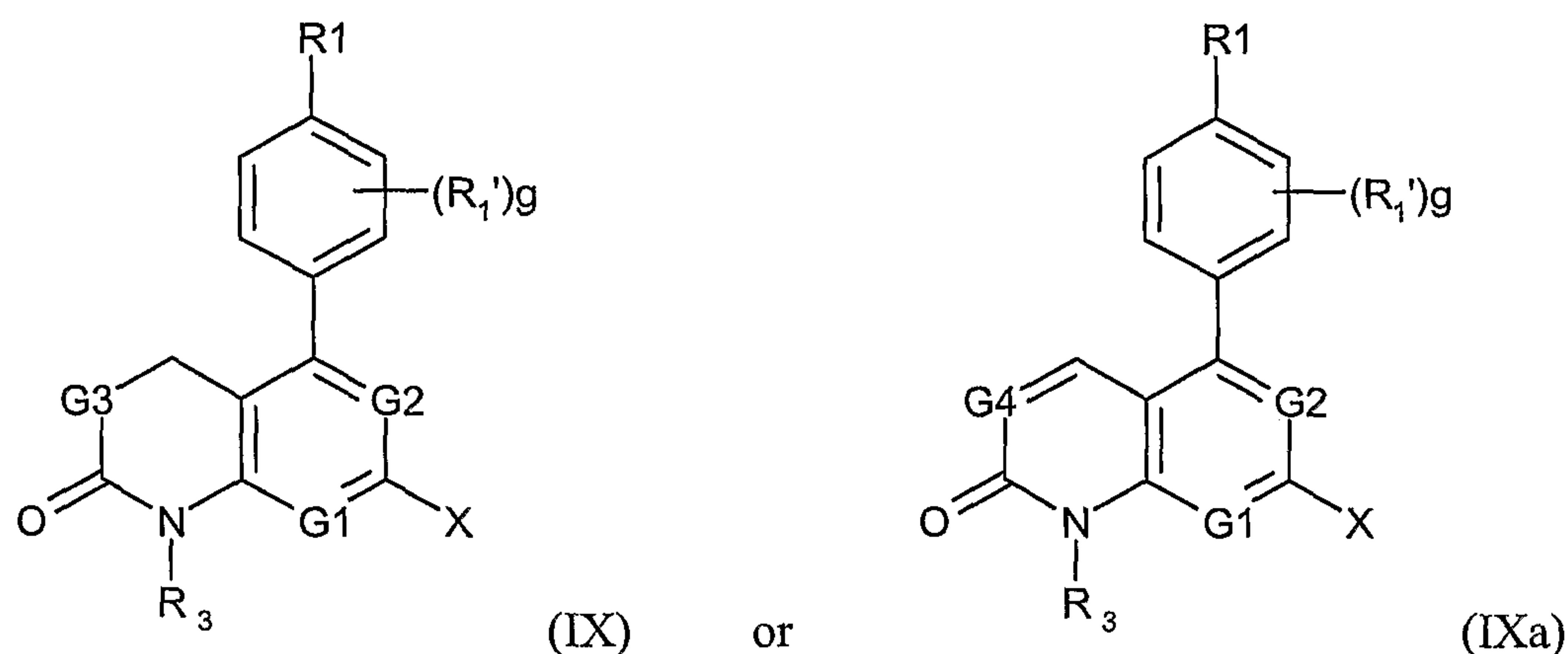
The respective R<sub>1</sub>, R<sub>2</sub>, R<sub>x</sub>, X and R<sub>3</sub>, etc., terms are the same for both groups within the formulas themselves, for instance, in Formula (VIII) and (VIIIa). For purposes herein, everything applicable to Formula (VIII) is also applicable to Formula (VIIIa) unless otherwise indicated.

It is recognized that for compounds of Formula (I) and (Ia), etc. and those of Formula (VIII) and (VIIIa) the difference is in the allowance of the G<sub>1</sub> and G<sub>2</sub> moieties to be carbon or nitrogen, independently. For purposes of brevity herein, the remaining compounds of Formulas (II) and (IIa), (III) and (IIIa), (IV) and (IVa), (V) and (Va), (VI) and (VIa-VIi), may also have the same pharmacophore template of:



Illustrative of this would be the C4 substitution from compounds of formula (II) and (IIa) on this pharmacophore template, represented by the structure:

5



wherein

G<sub>1</sub>, G<sub>2</sub> are independently nitrogen or CH, but G<sub>1</sub>, and G<sub>2</sub> are not both nitrogen;

10 G<sub>3</sub> is CH<sub>2</sub>;

G<sub>4</sub> is CH;

R<sub>1</sub> is C(Z)N(R<sub>10</sub>') (CR<sub>10</sub>R<sub>20</sub>)<sub>v</sub>R<sub>b</sub>, C(Z)O(CR<sub>10</sub>R<sub>20</sub>)<sub>v</sub>R<sub>b</sub>,

N(R<sub>10</sub>')C(Z)(CR<sub>10</sub>R<sub>20</sub>)<sub>v</sub>R<sub>b</sub>, N(R<sub>10</sub>')C(Z)N(R<sub>10</sub>') (CR<sub>10</sub>R<sub>20</sub>)<sub>v</sub>R<sub>b</sub>, or

N(R<sub>10</sub>')OC(Z)(CR<sub>10</sub>R<sub>20</sub>)<sub>v</sub>R<sub>b</sub>;

15 R<sub>1</sub>' is independently selected at each occurrence from halogen, C<sub>1-4</sub> alkyl, halo-substituted-C<sub>1-4</sub> alkyl, cyano, nitro, (CR<sub>10</sub>R<sub>20</sub>)<sub>v</sub>'NR<sub>d</sub>R<sub>d</sub>',

(CR<sub>10</sub>R<sub>20</sub>)<sub>v</sub>'C(O)R<sub>12</sub>, SR<sub>5</sub>, S(O)R<sub>5</sub>, S(O)<sub>2</sub>R<sub>5</sub>, or (CR<sub>10</sub>R<sub>20</sub>)<sub>v</sub>'OR<sub>13</sub>;

R<sub>b</sub> is hydrogen, C<sub>1-10</sub> alkyl, C<sub>3-7</sub> cycloalkyl, C<sub>3-7</sub> cycloalkyl C<sub>1-10</sub> alkyl, aryl, arylC<sub>1-10</sub>alkyl, heteroaryl, heteroarylC<sub>1-10</sub> alkyl, heterocyclic, or

20 heterocyclylC<sub>1-10</sub> alkyl moiety, which moieties, excluding hydrogen, may all be optionally substituted;

X is R<sub>2</sub>, OR<sub>2</sub>', S(O)<sub>m</sub>R<sub>2</sub>', (CH<sub>2</sub>)<sub>n</sub>'N(R<sub>10</sub>')S(O)<sub>m</sub>R<sub>2</sub>', (CH<sub>2</sub>)<sub>n</sub>'N(R<sub>10</sub>')C(O)R<sub>2</sub>',

(CH<sub>2</sub>)<sub>n</sub>'NR<sub>4</sub>R<sub>14</sub>, (CH<sub>2</sub>)<sub>n</sub>'N(R<sub>2</sub>') (R<sub>2</sub>''), or N(R<sub>10</sub>')R<sub>h</sub>NH-C(=N-CN)NR<sub>q</sub>R<sub>q</sub>';

X<sub>1</sub> is N(R<sub>11</sub>), O, S(O)<sub>m</sub>, or CR<sub>10</sub>R<sub>20</sub>;

$R_h$  is selected from an optionally substituted  $C_{1-10}$  alkyl,  $-CH_2-C(O)-CH_2-$ ,  $-CH_2-CH_2-O-CH_2-CH_2-$ ,  $-CH_2-C(O)N(R_{10'})CH_2-CH_2-$ ,  $-CH_2-N(R_{10'})C(O)CH_2-$ ,  $-CH_2-CH(OR_{10'})-CH_2-$ ,  $-CH_2-C(O)O-CH_2-CH_2-$ , or  $-CH_2-CH_2-O-C(O)CH_2-$ ;

5  $R_q$  and  $R_{q'}$  are independently selected at each occurrence from hydrogen,  $C_{1-10}$  alkyl,  $C_{3-7}$  cycloalkyl,  $C_{3-7}$  cycloalkyl $C_{1-10}$  alkyl,  $C_{5-7}$  cycloalkenyl,  $C_{5-7}$  cycloalkenyl- $C_{1-10}$  alkyl, aryl, aryl $C_{1-10}$  alkyl, heteroaryl, heteroaryl $C_{1-10}$  alkyl, heterocyclic, or a heterocyclyl $C_{1-10}$  alkyl moiety, wherein all of the moieties except for hydrogen, are optionally substituted, or  $R_q$  and  $R_{q'}$  together  
10 with the nitrogen to which they are attached form an optionally substituted heterocyclic ring of 5 to 7 members, which ring may contain an additional heteroatom selected from oxygen, nitrogen or sulfur;

$R_2$  is hydrogen,  $C_{1-10}$  alkyl,  $C_{3-7}$  cycloalkyl,  $C_{3-7}$  cycloalkylalkyl, aryl, aryl $C_{1-10}$  alkyl, heteroaryl, heteroaryl $C_{1-10}$  alkyl, heterocyclic, or a heterocyclyl $C_{1-10}$  alkyl moiety, and wherein each of these moieties, excluding hydrogen, may be  
15 optionally substituted; or

$R_2$  is the moiety  $(CR_{10}R_{20})_qX_1(CR_{10}R_{20})_qC(A_1)(A_2)(A_3)$ , or  $(CR_{10}R_{20})_qC(A_1)(A_2)(A_3)$ ;

$R_{2'}$  is hydrogen,  $C_{1-10}$  alkyl,  $C_{3-7}$  cycloalkyl,  $C_{3-7}$  cycloalkylalkyl, aryl, aryl $C_{1-10}$  alkyl, heteroaryl, heteroaryl $C_{1-10}$  alkyl, heterocyclic, or a heterocyclyl $C_{1-10}$  alkyl  
20 moiety, and wherein each of these moieties, excluding hydrogen, may be optionally substituted;

$R_{2''}$  is hydrogen,  $C_{1-10}$  alkyl,  $C_{3-7}$  cycloalkyl,  $C_{3-7}$  cycloalkylalkyl, aryl, aryl $C_{1-10}$  alkyl, heteroaryl, heteroaryl $C_{1-10}$  alkyl, heterocyclic, or a heterocyclyl $C_{1-10}$  alkyl  
25 moiety, and wherein these moieties, excluding hydrogen, may be optionally; or wherein  $R_{2''}$  is the moiety  $(CR_{10}R_{20})_tX_1(CR_{10}R_{20})_qC(A_1)(A_2)(A_3)$ ;

$A_1$  is an optionally substituted  $C_{1-10}$  alkyl, heterocyclic, heterocyclic  $C_{1-10}$  alkyl, heteroaryl, heteroaryl  $C_{1-10}$  alkyl, aryl, or aryl  $C_{1-10}$  alkyl;

$A_2$  is an optionally substituted  $C_{1-10}$  alkyl, heterocyclic, heterocyclic  $C_{1-10}$  alkyl, heteroaryl, heteroaryl  $C_{1-10}$  alkyl, aryl, or aryl  $C_{1-10}$  alkyl;  
30

$A_3$  is hydrogen or is an optionally substituted  $C_{1-10}$  alkyl;

$R_3$  is a  $C_{1-10}$  alkyl,  $C_{3-7}$  cycloalkyl,  $C_{3-7}$  cycloalkyl  $C_{1-10}$  alkyl, aryl, aryl $C_{1-10}$  alkyl, heteroaryl, heteroaryl $C_{1-10}$  alkyl, heterocyclic or a heterocyclyl $C_{1-10}$  alkyl  
moiety, and wherein each of these moieties may be optionally substituted;

35  $R_4$  and  $R_{14}$  are each independently selected at each occurrence from hydrogen,  $C_{1-4}$  alkyl,  $C_{3-7}$  cycloalkyl,  $C_{3-7}$  cycloalkyl $C_{1-4}$  alkyl, aryl, aryl- $C_{1-4}$  alkyl, heterocyclic, heterocyclic  $C_{1-4}$  alkyl, heteroaryl or a heteroaryl  $C_{1-4}$  alkyl

moiety, and wherein each of these moieties, excluding hydrogen, may be optionally substituted; or the R<sub>4</sub> and R<sub>14</sub> together with the nitrogen which they are attached form an optionally substituted heterocyclic ring of 4 to 7 members, which ring optionally contains an additional heteroatom selected from oxygen,  
 5 sulfur or nitrogen;

R<sub>4</sub>' and R<sub>14</sub>' are each independently selected at each occurrence from hydrogen or C<sub>1-4</sub> alkyl, or R<sub>4</sub>' and R<sub>14</sub>' together with the nitrogen to which they are attached form a heterocyclic ring of 5 to 7 members, which ring optionally contains an additional heteroatom selected from NR<sub>9</sub>';

10 R<sub>5</sub> is independently selected at each occurrence from hydrogen, C<sub>1-4</sub> alkyl, C<sub>2-4</sub> alkenyl, C<sub>2-4</sub> alkynyl or NR<sub>4</sub>'R<sub>14</sub>', excluding the moieties SR<sub>5</sub> being SNR<sub>4</sub>'R<sub>14</sub>', S(O)<sub>2</sub>R<sub>5</sub> being SO<sub>2</sub>H and S(O)R<sub>5</sub> being SOH;

R<sub>9</sub>' is independently selected at each occurrence from hydrogen, or C<sub>1-4</sub> alkyl;

R<sub>10</sub> and R<sub>20</sub> are independently selected at each occurrence from hydrogen or

15 C<sub>1-4</sub>alkyl;

R<sub>10</sub>' is independently selected at each occurrence from hydrogen or C<sub>1-4</sub>alkyl;

R<sub>11</sub> is independently selected at each occurrence from hydrogen or C<sub>1-4</sub>alkyl;

R<sub>12</sub> is independently selected at each occurrence from hydrogen, C<sub>1-4</sub> alkyl, halo-substituted C<sub>1-4</sub> alkyl, C<sub>2-4</sub> alkenyl, C<sub>2-4</sub> alkynyl, C<sub>3-7</sub> cycloalkyl,

20 C<sub>3-7</sub>cycloalkylC<sub>1-4</sub> alkyl, C<sub>5-7</sub> cycloalkenyl, C<sub>5-7</sub>cycloalkenyl C<sub>1-4</sub> alkyl, aryl, arylC<sub>1-4</sub> alkyl, heteroaryl, heteroarylC<sub>1-4</sub> alkyl, heterocyclyl, or a heterocyclylC<sub>1-4</sub> alkyl moiety, and wherein each of these moieties, excluding hydrogen, may be optionally substituted;

R<sub>13</sub> is independently selected at each occurrence from hydrogen, C<sub>1-4</sub> alkyl, halo-

25 substituted C<sub>1-4</sub> alkyl, C<sub>2-4</sub> alkenyl, C<sub>2-4</sub> alkynyl, C<sub>3-7</sub> cycloalkyl, C<sub>3-7</sub>cycloalkylC<sub>1-4</sub> alkyl, C<sub>5-7</sub> cycloalkenyl, C<sub>5-7</sub>cycloalkenyl C<sub>1-4</sub> alkyl, aryl, arylC<sub>1-4</sub> alkyl, heteroaryl, heteroarylC<sub>1-4</sub> alkyl, heterocyclyl, or a heterocyclylC<sub>1-4</sub> alkyl moiety, and wherein each of these moieties, excluding hydrogen, may be optionally substituted;

30 R<sub>d</sub> and R<sub>d</sub>' are each independently selected from hydrogen, C<sub>1-4</sub> alkyl, C<sub>3-6</sub> cycloalkyl, C<sub>3-6</sub> cycloalkylC<sub>1-4</sub>alkyl moiety, and wherein each of these moieties, excluding hydrogen, may be optionally substituted; or R<sub>d</sub> and R<sub>d</sub>' together with the nitrogen which they are attached form an optionally substituted heterocyclic ring of 5 to 6 members, which ring optionally contains an additional heteroatom  
 35 selected from oxygen, sulfur or NR<sub>9</sub>';

g is 0 or an integer having a value of 1, 2, 3, or 4;

n' is independently selected at each occurrence from 0 or an integer having a value of 1 to 10;

m is independently selected at each occurrence from 0 or an integer having a value of 1 or 2;

5 q is 0 or an integer having a value of 1 to 10;

q' is 0, or an integer having a value of 1 to 6;

t is an integer having a value of 2 to 6;

v is 0 or an integer having a value of 1 or 2;

10 v' is independently selected at each occurrence from 0 or an integer having a value of 1 or 2;

Z is independently selected at each occurrence from oxygen or sulfur; and a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof.

15 Therefore, compounds having the C4 position substitution from Formula (III) and (IIIa) with the G1/G2 pharmacophore template of carbon or nitrogen, would be considered compounds of Formula (X) and (Xa), etc.

20 It is to be understood that the present invention covers all combinations of particular and preferred groups described hereinabove. It is also to be understood that the present invention encompasses compounds of formula (I) in which a particular group or parameter, for example R<sub>5</sub>, R<sub>6</sub>, R<sub>9</sub>, R<sub>10</sub>, R<sub>11</sub>, R<sub>12</sub>, R<sub>13</sub>, p, n, or q, etc. may occur more than once. In such compounds it will be appreciated that each group or parameter is independently selected from the values listed. When any variable occurs more than one time in a Formula (as described herein), its definition on each occurrence  
25 is independent of its definition at every other occurrence.

Particular compounds according to the invention include those mentioned in the examples and their pharmaceutically derivatives.

30 As used herein, the term "pharmaceutically acceptable" means a compound which is suitable for pharmaceutical and veterinary usage. Salts and solvates of compounds of the invention which are suitable for use in medicine are those wherein the counterion or associated solvent is pharmaceutically acceptable. However, salts and solvates having non-pharmaceutically acceptable counterions or associated solvents are within the scope of the present invention, for example, for use as intermediates in the preparation of other compounds of the invention and their pharmaceutically acceptable  
35 salts and solvates.

As used herein, the term "pharmaceutically acceptable derivative", means any pharmaceutically acceptable salt, solvate or prodrug e.g. ester, of a compound of the

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invention, which upon administration to the recipient is capable of providing (directly or indirectly) a compound of the invention, or an active metabolite or residue thereof. Such derivatives are recognizable to those skilled in the art, without undue experimentation. Nevertheless, reference is made to the teaching of Burger's Medicinal Chemistry and Drug Discovery, 5<sup>th</sup> Edition, Vol. 1: Principles and Practice. In one embodiment pharmaceutically acceptable derivatives are salts, solvates, esters, carbamates and phosphate esters. In another embodiment pharmaceutically acceptable derivatives are salts, solvates and esters. In yet another embodiment of the invention pharmaceutically acceptable derivatives are salts and esters, in particular salts.

10

The compounds of the present invention may be in the form of and/or may be administered as a pharmaceutically acceptable salt. For a review on suitable salts see Berge *et al.*, J. Pharm. Sci., 1977, 66, 1-19.

Typically, a pharmaceutical acceptable salt may be readily prepared by using a desired acid or base as appropriate. The salt may precipitate from solution and be collected by filtration or may be recovered by evaporation of the solvent.

Salts of the compounds of the present invention may, for example, comprise acid addition salts resulting from reaction of an acid with a nitrogen atom present in a compound of formula (I). Salts encompassed within the term "pharmaceutically acceptable salts" refer to non-toxic salts of the compounds of this invention. Suitable addition salts are formed from acids which form non-toxic salts and examples are acetate, benzenesulfonate, benzoate, bicarbonate, bisulfate, bitartrate, borate, bromide, calcium edetate, camsylate, carbonate, chloride, clavulanate, citrate, dihydrochloride, edetate, edisylate, estolate, esylate, ethanesulphonate, formate, fumarate, gluceptate, gluconate, glutamate, glycolylarsanilate, hexylresorcinate, hydrabamine, hydrobromide, hydrochloride, hydrogen phosphate, hydroiodide, hydroxynaphthoate, iodide, isethionate, lactate, lactobionate, laurate, malate, maleate, mandelate, mesylate, methylbromide, methylnitrate, methylsulfate, monopotassium maleate, mucate, napsylate, nitrate, N-methylglucamine, oxalate, oxaloacetate, pamoate (embonate), palmitate, pantothenate, phosphate/diphosphate, piruvate, polygalacturonate, saccharate, salicylate, stearate, subacetate, succinate, sulphate, tannate, tartrate, teoclate, tosylate, triethiodide, trifluoroacetate and valerate.

Pharmaceutically acceptable base salts include ammonium salts such as a trimethylammonium salt, alkali metal salts such as those of sodium and potassium, alkaline earth metal salts such as those of calcium and magnesium and salts with organic bases, including salts of primary, secondary and tertiary amines, such as

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isopropylamine, diethylamine, ethanolamine, trimethylamine, dicyclohexyl amine and N-methyl-D-glucamine.

Those skilled in the art of organic chemistry will appreciate that many organic compounds can form complexes with solvents in which they are reacted or from which they are precipitated or crystallized. These complexes are known as "solvates". 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 thereof) and a solvent. Such solvents for the purpose of the invention may not interfere with the biological activity of the solute. Examples of suitable solvents include water, methanol, ethanol and acetic acid. Preferably the solvent used is a pharmaceutically acceptable solvent. Examples of suitable pharmaceutically acceptable solvents include water, ethanol and acetic acid. Most preferably the solvent used is water. A complex with water is known as a "hydrate". Solvates of the compound of the invention are within the scope of the invention.

As used herein, the term "prodrug" means a compound which is converted within the body, e.g. by hydrolysis in the blood, into its active form that has medical effects. Pharmaceutically acceptable prodrugs are described in T. Higuchi and V. Stella, Prodrugs as Novel Delivery Systems, Vol. 14 of the A.C.S. Symposium Series; Edward B. Roche, ed., Bioreversible Carriers in Drug Design, American Pharmaceutical Association and Pergamon Press, 1987; and in D. Fleisher, S. Ramon and H. Barbra "Improved oral drug delivery: solubility limitations overcome by the use of prodrugs", Advanced Drug Delivery Reviews (1996) 19(2) 115-130.

Prodrugs are any covalently bonded carriers that release a compound of formula (I) *in vivo* when such prodrug is administered to a patient. Prodrugs are generally prepared by modifying functional groups in a way such that the modification is cleaved, either by routine manipulation or *in vivo*, yielding the parent compound. Prodrugs include, for example, compounds of this invention wherein hydroxy or amine groups are bonded to any group that, when administered to a patient, cleaves to form the hydroxy or amine groups. Thus, representative examples of prodrugs include (but are not limited to) acetate, formate and benzoate derivatives of alcohol and amine functional groups of the compounds of formula (I). Further, in the case of a carboxylic acid (-COOH), esters may be employed, such as methyl esters, ethyl esters, and the like. Esters may be active in their own right and /or be hydrolysable under *in vivo* conditions in the human body. Suitable pharmaceutically acceptable *in vivo* hydrolysable ester groups include those which break down readily in the human body to leave the parent acid or its salt.

As used herein, "optionally substituted" unless specifically defined shall mean such groups as halogen, such as fluorine, chlorine, bromine or iodine; hydroxy; hydroxy substituted C<sub>1-10</sub>alkyl; C<sub>1-10</sub> alkoxy, such as methoxy or ethoxy; halosubstituted C<sub>1-10</sub> alkoxy; S(O)<sub>m</sub> alkyl, such as methyl thio, methylsulfinyl or methyl sulfonyl; a ketone (-C(O)), or an aldehyde (-C(O)R<sub>6'</sub>), such as C(O)C<sub>1-10</sub> alkyl or C(O)aryl, wherein R<sub>6'</sub> is hydrogen, C<sub>1-10</sub> alkyl, C<sub>3-7</sub> cycloalkyl, heterocyclyl, heterocyclyl C<sub>1-10</sub>alkyl, aryl, arylC<sub>1-10</sub> alkyl, heteroaryl or heteroarylC<sub>1-10</sub> alkyl, (and wherein the R<sub>6'</sub> moieties, excluding hydrogen, may themselves be optionally substituted 1 or 2 times, independently at each occurrence by halogen; hydroxy; hydroxy substituted alkyl; C<sub>1-4</sub> alkoxy; S(O)<sub>m</sub> C<sub>1-4</sub> alkyl; amino, mono & di-substituted C<sub>1-4</sub> alkyl amino; C<sub>1-4</sub> alkyl, or CF<sub>3</sub>); C(O)OR<sub>6'</sub>; NR<sub>4'</sub>R<sub>14'</sub>, wherein R<sub>4'</sub> and R<sub>14'</sub> are each independently hydrogen or C<sub>1-4</sub> alkyl, such as amino or mono or -disubstituted C<sub>1-4</sub> alkyl or wherein the R<sub>4'</sub>R<sub>14'</sub> can cyclize together with the nitrogen to which they are attached to form a 5 to 7 membered ring which optionally contains an additional heteroatom selected from O/N/S; C<sub>1-10</sub> alkyl, such as methyl, ethyl, propyl, isopropyl, t-butyl, etc.; C<sub>3-7</sub>cycloalkyl, or C<sub>3-7</sub>cycloalkyl C<sub>1-10</sub> alkyl group, such as cyclopropyl, cyclobutyl, or cyclopropyl methyl; halosubstituted C<sub>1-10</sub> alkyl, such CF<sub>2</sub>CF<sub>2</sub>H, or CF<sub>3</sub>; an optionally substituted aryl, such as phenyl, or an optionally substituted arylC<sub>1-4</sub> alkyl, such as benzyl or phenethyl, wherein these aryl containing moieties may also be substituted one to two times independently at each occurrence by halogen; hydroxy; hydroxy substituted alkyl; C<sub>1-4</sub> alkoxy; S(O)<sub>m</sub> C<sub>1-4</sub> alkyl; amino, mono & di-substituted C<sub>1-4</sub> alkyl amino; C<sub>1-4</sub> alkyl, or CF<sub>3</sub>.

Suitable pharmaceutically acceptable salts are well known to those skilled in the art and include salts formed with both organic and inorganic acids or bases. Pharmaceutically acceptable acid addition salts include those formed from hydrochloric, hydrobromic, sulphuric, citric, tartaric, phosphoric, lactic, pyruvic, acetic, trifluoroacetic, triphenylacetic, sulphamic, sulphanilic, succinic, oxalic, fumaric, maleic, malic, glutamic, aspartic, oxaloacetic, alkyl sulphonic acid derivatives, such as methanesulphonic, or ethanesulphonic, arylsulphonic acid derivatives, such as p-toluenesulphonic, m-toluenesulphonic, benzenesulphonic, camphor sulphonic, 4-chlorobenzenesulphonic, 4-bromobenzenesulphonic, 4-phenylbenzenesulphonic, naphthalenesulphonic or naphthalenedisulphonic), phenylacetic, mandelic, salicylic, glutaric, gluconic, tricarballic, cinnamic, substituted cinnamic (for example, phenyl, methyl, cyano, methoxy or halo substituted cinnamic, including 4-methyl and 4-methoxycinnamic acid), ascorbic, oleic, naphthoic, hydroxynaphthoic (for example 1- or 3-hydroxy-2-naphthoic),

naphthaleneacrylic (for example naphthalene-2-acrylic), benzoic, 4-methoxybenzoic, 2- or 4-hydroxybenzoic, 4-chlorobenzoic, 4-phenylbenzoic, benzeneacrylic (for example 1,4-benzenediacylic) and isethionic acids.

Pharmaceutically acceptable base salts include ammonium salts, alkali metal salts such as those of sodium and potassium, alkaline earth metal salts such as those of calcium and magnesium and salts with organic bases such as dicyclohexyl amine and N-methyl-D-glucamine.

In addition, pharmaceutically acceptable salts of compounds of Formula (I) may also be formed with a pharmaceutically acceptable cation, for instance, if a substituent group comprises a carboxy moiety. Suitable pharmaceutically acceptable cations are well known to those skilled in the art and include alkaline, alkaline earth, ammonium and quaternary ammonium cations.

The term "halo" or "halogens" is used herein to mean the halogens, chloro, fluoro, bromo and iodo.

As used herein, the term "C<sub>1-10</sub>alkyl" or "alkyl" or "alkyl<sub>1-10</sub>" is used herein to mean both straight and branched hydrocarbon chain containing the specified number of carbon atoms, e.g. C<sub>1-10</sub>alkyl means a straight or branched alkyl chain of at least 1, and at most 10, carbon atoms, unless the chain length is otherwise limited. Examples of "alkyl" as used herein include, but are not limited to, methyl, ethyl, n-propyl, n-butyl, n-pentyl, isobutyl, isopropyl, sec-butyl, *tert*-butyl or *t*-butyl and hexyl and the like.

As used herein, the term "alkenyl" refers to straight or branched hydrocarbon chains containing the specified number of carbon atoms and containing at least one double bond. For example, C<sub>2-6</sub>alkenyl means a straight or branched alkenyl containing at least 2, and at most 6, carbon atoms and containing at least one double bond. Examples of "alkenyl" as used herein include, but are not limited to ethenyl, 2-propenyl, 3-butenyl, 2-butenyl, 2-pentenyl, 3-pentenyl, 3-methyl-2-butenyl, 3-methylbut-2-enyl, 3-hexenyl, 1,1-dimethylbut-2-enyl and the like.

As used herein, the term "alkoxy" refers to straight or branched chain alkoxy groups containing the specified number of carbon atoms. For example, C<sub>1-6</sub>alkoxy means a straight or branched alkoxy containing at least 1, and at most 6, carbon atoms. Examples of "alkoxy" as used herein include, but are not limited to, methoxy, ethoxy, propoxy, prop-2-oxy, butoxy, but-2-oxy, 2-methylprop-1-oxy, 2-methylprop-2-oxy, pentoxy and hexyloxy.

As used herein, the term "cycloalkyl" refers to cyclic radicals, such as a non-aromatic hydrocarbon ring containing a specified number of carbon atoms. For example, C<sub>3-7</sub>cycloalkyl means a non-aromatic ring containing at least three, and at

most seven, ring carbon atoms. Representative examples of "cycloalkyl" as used herein include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl and the like.

5 The term "cycloalkenyl" is used herein to mean cyclic radicals, such as a non-aromatic hydrocarbon ring containing a specified number of carbon atoms preferably of 5 to 7 carbons, which have at least one bond including but not limited to cyclopentenyl, cyclohexenyl, and the like.

10 The term "alkenyl" is used herein at all occurrences to mean straight or branched chain radical of 2-10 carbon atoms, unless the chain length is limited thereto, including, but not limited to ethenyl, 1-propenyl, 2-propenyl, 2-methyl-1-propenyl, 1-butenyl, 2-butenyl and the like.

The term "aryl" is used herein to mean phenyl, naphthyl, and indene.

15 The terms "heteroaryl ring", "heteroaryl moiety", and "heteroaryl" are used herein to mean a monocyclic five- to seven- membered unsaturated hydrocarbon ring containing at least one heteroatom selected from oxygen, nitrogen and sulfur. Examples of heteroaryl rings include, but are not limited to, furyl, pyranyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, isoxazolyl, isothiazolyl, imidazolyl, pyrazolyl, oxadiazolyl, oxathiadiazolyl, triazolyl, tetrazolyl, thiadiazolyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, triazinyl, and uracil. The terms "heteroaryl ring", "heteroaryl moiety", and  
20 "heteroaryl" shall also used herein to refer to fused aromatic rings comprising at least one heteroatom selected from oxygen, nitrogen and sulfur. Each of the fused rings may contain five or six ring atoms. Examples of fused aromatic rings include, but are not limited to, indolyl, isoindolyl, indazolyl, indoliziny, azaindolyl, benzoxazolyl, benzimidazolyl, benzothiazolyl, benzofuranyl, benzothiophenyl, quinolyl, isoquinolyl, quinazolinyl, quinoxalinyl, naphthyridinyl, cinnolinyl, purinyl, and phthalazinyl.

25 The terms "heterocyclic rings", "heterocyclic moieties", and "heterocyclyl" is used herein to mean a monocyclic three- to seven-membered saturated or non-aromatic, unsaturated hydrocarbon ring containing at least one heteroatom selected from nitrogen, oxygen, sulphur or oxidized sulphur moieties, such as S(O)<sub>m</sub>, and m is 0 or an integer having a value of 1 or 2. The terms "heterocyclic rings", "heterocyclic moieties", and  
30 "heterocyclyl" shall also refer to fused rings, saturated or partially unsaturated, and wherein one of the rings may be aromatic, or heteroaromatic. Each of the fused rings may have from four to seven ring atoms. Examples of heterocyclyl groups include, but are not limited to, the saturated or partially saturated versions of the heteroaryl moieties  
35 as defined above, such as tetrahydropyrrole, tetrahydropyran, tetrahydrofuran, tetrahydrothiophene (including oxidized versions of the sulfur moiety), azepine, diazepine, aziridinyl, pyrrolinyl, pyrrolidinyl, 2-oxo-1-pyrrolidinyl, 3-oxo-1-

pyrrolidinyl, 1,3-benzdioxol-5-yl, imidazoliny, imidazolidinyl, indolinyl, pyrazolinyl, pyrazolidinyl, piperidinyl, piperazinyl, morpholino and thiomorpholino (including oxidized versions of the sulfur moiety).

5 The term "arylalkyl" or "heteroarylalkyl" or "heterocyclicalkyl" is used herein to mean a C<sub>1-4</sub> alkyl (as defined above) attached to an aryl, heteroaryl or heterocyclic moiety (as also defined above) unless otherwise indicated.

The term "sulfinyl" is used herein to mean the oxide S(O) of the corresponding sulfide, the term "thio" refers to the sulfide, and the term "sulfonyl" refers to the fully oxidized S (O)<sub>2</sub> moiety.

10 The term "aroyl" is used herein to mean C(O)Ar, wherein Ar is as phenyl, naphthyl, or aryl alkyl derivative such as defined above, such group include but are not limited to benzyl and phenethyl.

The term "alkanoyl" is used herein to mean C(O)C<sub>1-10</sub> alkyl wherein the alkyl is as defined above.

15 As used herein, the term "optionally" means that the subsequently described event(s) may or may not occur, and includes both event(s) which occur and events that do not occur.

As used herein, the term "substituted" refers to substitution with the named substituent or substituents, multiple degrees of substitution being allowed unless  
20 otherwise stated.

It is to be understood that the present invention covers all combinations of particular and preferred groups described hereinabove. It is also to be understood that the present invention encompasses compounds of formula (I) in which a particular group or parameter, for example R<sub>5</sub>, R<sub>6</sub>, R<sub>9</sub>, R<sub>10</sub>, R<sub>11</sub>, R<sub>12</sub>, R<sub>13</sub>, n, m, or t, etc. may  
25 occur more than once. In such compounds it will be appreciated that each group or parameter is independently selected from the values listed. When any variable occurs more than one time in a Formula (as described herein), its definition on each occurrence is independent of its definition at every other occurrence.

With regard to stereoisomers, the compounds of the Formulas herein may have  
30 one or more asymmetric carbon atom and may occur as racemates, racemic mixtures and as individual enantiomers or diastereomers. All such isomeric forms are included within the present invention, including mixtures thereof.

Cis (E) and trans (Z) isomerism may also occur. The present invention includes the individual stereoisomers of the compounds of the invention and where appropriate,  
35 the individual tautomeric forms thereof, together with mixtures thereof.

Separation of diastereoisomers or cis and trans isomers may be achieved by conventional techniques, e.g. by fractional crystallisation, chromatography or H.P.L.C.

A stereoisomeric mixture of the agent may also be prepared from a corresponding optically pure intermediate or by resolution, such as H.P.L.C. of the corresponding racemate using a suitable chiral support or by fractional crystallisation of the diastereoisomeric salts formed by reaction of the corresponding racemate with a  
5 suitable optically active acid or base, as appropriate.

Furthermore, some of the crystalline forms of the compounds of the Formulas herein may exist as polymorphs, which are included in the present invention.

Exemplified compounds of the compounds of this invention include the racemates, or optically active forms of the compounds of the working examples  
10 herein, and pharmaceutically acceptable salts thereof.

The compounds of this invention may be made by a variety of methods, including standard chemistry. Any previously defined variable will continue to have the previously defined meaning unless otherwise indicated. Illustrative general synthetic methods are set out below and then specific compounds of the invention are  
15 prepared in the working Examples.

#### METHODS OF MANUFACTURE

The compounds of Formula (I) and (Ia), (II) and (IIa), (III) and (IIIa), (IV) and (IVa), (V) and (Va), (VI), (VIa-VIi), (VIII), (VIIIa), (IX), (IXa), (A), (A1), (B),  
20 and (B1), may be obtained by applying the synthetic procedures described herein. The synthesis provided for is applicable to producing compounds of the Formulas herein having a variety of different R<sub>1</sub>, R<sub>2</sub>, X, and R<sub>3</sub> groups which are reacted, employing optional substituents which are suitably protected, to achieve compatibility with the reactions outlined herein. Subsequent deprotection, in those  
25 cases, then affords compounds of the nature generally disclosed. While a particular formula with particular substituent groups is shown herein, the synthesis is applicable to all formulas and all substituent groups herein.

Once the nucleus has been established, further compounds of Formula (I) and (Ia), (II) and (IIa), (III) and (IIIa), (IV) and (IVa), (V) and (Va), (VI), (VIa-VIi),  
30 (VIII), (VIIIa), (IX), (IXa), (A), (A1), (B), and (B1) may be prepared by applying standard techniques for functional group inter-conversion, well known in the art. For instance: C(O)NR<sub>4</sub>R<sub>14</sub> from CO<sub>2</sub>CH<sub>3</sub> by heating with HNR<sub>4</sub>R<sub>14</sub> in CH<sub>3</sub>OH with or without catalytic or stoichiometric metal cyanide or Aluminum trimethyl, e.g. NaCN; OC(O)R<sub>6</sub> from OH with e.g., ClC(O)R<sub>6</sub> in bases such as triethylamine and pyridine;  
35 NR<sub>10</sub>-C(S)NR<sub>4</sub>R<sub>14</sub> from NHR<sub>10</sub> with an alkylisothiocyanate, or thiocyanic acid and ClC(S)NR<sub>4</sub>R<sub>14</sub>; NR<sub>10</sub>C(O)OR<sub>6</sub> from NHR<sub>10</sub> with an alkyl or aryl chloroformate; NR<sub>10</sub>C(O)NR<sub>4</sub>H from NHR<sub>10</sub> by treatment with an isocyanate, e.g. R<sub>4</sub>N=C=O;

NR<sub>10</sub>-C(O)R<sub>6</sub> from NHR<sub>10</sub> by treatment with Cl-C(O)R<sub>6</sub> in pyridine;  
 C(=NR<sub>10</sub>)NR<sub>4</sub>R<sub>14</sub> from C(NR<sub>4</sub>R<sub>14</sub>)S with H<sub>3</sub>NR<sub>10</sub><sup>+</sup>OAc<sup>-</sup> by heating in alcohol;  
 C(NR<sub>4</sub>R<sub>14</sub>)SR<sub>6</sub> from C(S)NR<sub>4</sub>R<sub>14</sub> with R<sub>6</sub>-I in an inert solvent, e.g. acetone;  
 NR<sub>10</sub>SO<sub>2</sub>R<sub>7</sub> from NHR<sub>10</sub> by treatment with ClSO<sub>2</sub>R<sub>7</sub> by heating in bases such as  
 5 pyridine; NR<sub>10</sub>C(S)R<sub>6</sub> from NR<sub>10</sub>C(O)R<sub>6</sub> by treatment with Lawesson's reagent  
 [2,4-bis(4-methoxyphenyl)-1,3,2,4-dithiadiphosphetane-2,4-disulfide]; NR<sub>10</sub>SO<sub>2</sub>CF<sub>3</sub>  
 from NHR<sub>10</sub> with triflic anhydride and base wherein R<sub>6</sub>, R<sub>10</sub>, R<sub>4</sub> and R<sub>14</sub> are as  
 defined in Formula (I) herein.

Precursors of the groups R<sub>1</sub>, R<sub>2</sub> and R<sub>3</sub>, can be other R<sub>1</sub>, R<sub>2</sub> and R<sub>3</sub>, etc.  
 10 groups that may be interconverted by applying standard techniques for functional  
 group interconversion. For example, wherein a moiety is a halo substituted C<sub>1-10</sub>  
 alkyl can be converted to the corresponding C<sub>1-10</sub> alkylN<sub>3</sub> derivative by reacting  
 with a suitable azide salt, and thereafter if desired can be reduced to the  
 corresponding C<sub>1-10</sub>alkylNH<sub>2</sub> compound, which in turn can be reacted with  
 15 R<sub>7</sub>S(O)<sub>2</sub>X' wherein X' is halo (e.g., chloro) to yield the corresponding  
 C<sub>1-10</sub>alkylNHS(O)<sub>2</sub>R<sub>7</sub> compound.

Alternatively wherein the moiety is a halo-substituted C<sub>1-10</sub>-alkyl it can be  
 reacted with an amine R<sub>4</sub>R<sub>14</sub>NH to yield the corresponding C<sub>1-10</sub>-alkylNR<sub>4</sub>R<sub>14</sub>  
 compound, or can be reacted with an alkali metal salt of R<sub>7</sub>SH to yield the  
 20 corresponding C<sub>1-10</sub>alkylSR<sub>7</sub> compound.

As noted above, it may be desirable during the synthesis of the compounds of  
 this invention, to derivatize reactive functional groups in the molecule undergoing  
 reaction so as to avoid unwanted side reactions. Functional groups such as hydroxy,  
 amino, and acid groups are typically protected with suitable groups that can be readily  
 25 removed when desired. Suitable common protecting groups for use with hydroxyl  
 groups and nitrogen groups are well known in the art and described in many  
 references, for instance, Protecting Groups in Organic Synthesis, Greene et al., John  
 Wiley & Sons, New York, New York, (2nd edition, 1991 or the earlier 1981 version).  
 Suitable examples of hydroxyl protecting groups include ether forming groups such  
 30 as benzyl, and aryl groups such as *tert*-butoxycarbonyl (Boc), silyl ethers, such as *t*-  
 butyldimethyl or *t*-butyldiphenyl, and alkyl ethers, such as methyl connected by an  
 alkyl chain of variable link, (CR<sub>10</sub>R<sub>20</sub>)<sub>n</sub>. Amino protecting groups may include  
 benzyl, aryl such as acetyl and trialkylsilyl groups. Carboxylic acid groups are  
 typically protected by conversion to an ester that can easily be hydrolyzed, for  
 35 example, trichloethyl, *tert*-butyl, benzyl and the like.

Pharmaceutically acid addition salts of compounds of the various Formulas described herein may be obtained in known manner, for example by treatment thereof with an appropriate amount of acid in the presence of a suitable solvent.

5 An illustration of the preparation of compounds of the present invention is shown in the scheme below. For purposes herein, the compounds in Schemes I and II are shown with an S-methyl, or S(O)<sub>2</sub>-methyl group which is deemed representative of the S(O)<sub>m</sub>-R<sub>g</sub> group, as described in the formulas below.

Preparation of compounds with Formula (Ia) can be achieved through  
10 compound **2**, which in turn may be constructed from aldehyde **1** as shown in **Scheme 1**. Leaving groups (LG, described as Leaving group 1 (LG1) & LG2) in Scheme 1, and elsewhere can be independently selected from -Cl, -Br, -I, or -OTf and these groups can be installed through the transformation of another functional group (e.g. -OH) by following the methods well known in the art (e.g., treatment of the -OH  
15 compound with POCl<sub>3</sub>).

**Method A** is for conversion of **1** to **2**. Treatment of **1** with an amine R<sub>3</sub>NH<sub>2</sub> in the presence of an olefin forming agent, such as bis(2,2,2-trifluoroethyl)-(methoxycarbonylmethyl)-phosphonate or an acylating agent, such as acetic acid anhydride, Meldrum's acid or acetyl chloride affords compound **2**. While the olefin  
20 forming reagent bis(2,2,2-trifluoroethyl)(methoxycarbonylmethyl)phosphonate is used, alternative cyclization reagents, include, but are not limited to bis(2,2,2-trifluoroethyl)-(ethoxycarbonylmethyl)phosphonate, bis(2,2,2-trifluoroethyl)-(isopropoxycarbonyl-methyl)phosphonate, (diethoxy-phosphoryl)-acetic acid methyl ester, (diisopropoxy-phosphoryl)-acetic acid methyl ester, (diphenyloxy-phosphoryl)-  
25 acetic acid methyl ester, (diethoxy-phosphoryl)-acetic acid ethyl ester, (diisopropoxy-phosphoryl)-acetic acid ethyl ester, or (diphenyloxy-phosphoryl)-acetic acid ethyl ester. Elevated temperatures (reflux or microwave irradiations), longer reaction times (over night or 24 hours) and presence of triethyl amine or diisopropyl ethyl amine or NaH (or Na) may be necessary for reaction completion. The reaction solvents can be  
30 various organic solvents, such as chloroform, methylene chloride, acetonitrile, toluene, DMF, or n-methylpyrrolidine, DCM, THF, toluene, DMSO, or combinations thereof. While the reaction shows triethylamine as a base, suitable alternative bases can include, but are not limited to pyridine, diisopropyl ethyl amine, or pyrrolidone, or combinations thereof.

35 The reaction temperature of this particular step in the reaction scheme can be varied from room temperature to > 100 °C, i.e. reflux temperature of the solvent.

Alternatively, this reaction process step may be performed under suitable microwave conditions.

**Method B** is for the installation of group -X [e.g., 2 to 3, 6 to (Ia), or 5 to 4]. This may or may not require first conversion of sulfide (-SMe) to sulfoxide (-SOMe) or sulfone (-SO<sub>2</sub>Me). This conversion can be achieved using *meta*-chloroperoxybenzoic acid (mCPBA) in high yield and purity. Suitable oxidation methods for use herein include use of one or two equivalents of *meta*-chloroperoxybenzoic acid (mCPBA) or Oxone<sup>®</sup> to afford either the sulfoxides or sulfones or a mixture of both. Oxidation of the sulfides to sulfoxides or sulfones can also be effected by OsO<sub>4</sub> and catalytic tertiary amine N-oxide, hydrogen peroxide, hydrogen peroxide/NaWO<sub>4</sub>, and other peracids, oxygen, ozone, organic peroxides, potassium and zinc permanganate, potassium persulfate, and sodium hypochlorite. The subsequent displacement of sulfone group -SO<sub>2</sub>Me (likewise, all displacement reactions mentioned below may be achieved using the sulfide -SMe or sulfoxide -SOMe) requires a suitable nucleophile (e.g., amine, alcohol) containing the unit -X. Displacements with amines were usually done with an excess of amine in N-methylpyrrolidine (Barvian et al., *J. Med. Chem.* (2000), 4606-4616). A wide range of primary amines underwent this reaction with excellent yields. In some cases (e.g., in O-displacement) an anion of the nucleophile was prepared with base (usually sodium hydride) in DMF (or DMSO) and then added to the sulfone. Yields for these reactions were usually lower. The sulfone may be displaced by primary and secondary alkylamines without additional base catalysis, preferably in a polar aprotic solvent, such as but not limited to, N-methyl pyrrolidin-2-one (NMP), and at varying temperatures depending upon the nucleophilicity of the amine. For instance displacement of the sulfone with ethanolamine, in NMP, occurred in 30 min. at 65° C, while a more hindered amine such as tris(hydroxymethyl)-aminomethane may require elevated temperatures and extended reaction times (80° C over a 24 hour reaction time). The sulfone can also be displaced by a primary or secondary amine with an additional non-nucleophilic base (e.g. DIPEA) in aprotic solvents like DCM, CH<sub>3</sub>CN, NMP, and at varying temperatures depending upon the nucleophilicity of the amine.

The sulfone may also be displaced with a substituted arylamine, or heteroarylamine at elevated temperatures, sometimes requiring formation of the aryl or heteroarylamine anion with sodium hydride, or other suitable base, in DMSO. In addition, the sulfone may be readily displaced with aluminum salts of aryl or heteroaryl amines as previously described in the patent literature (WO 99/32121, Likewise, sulfone may be

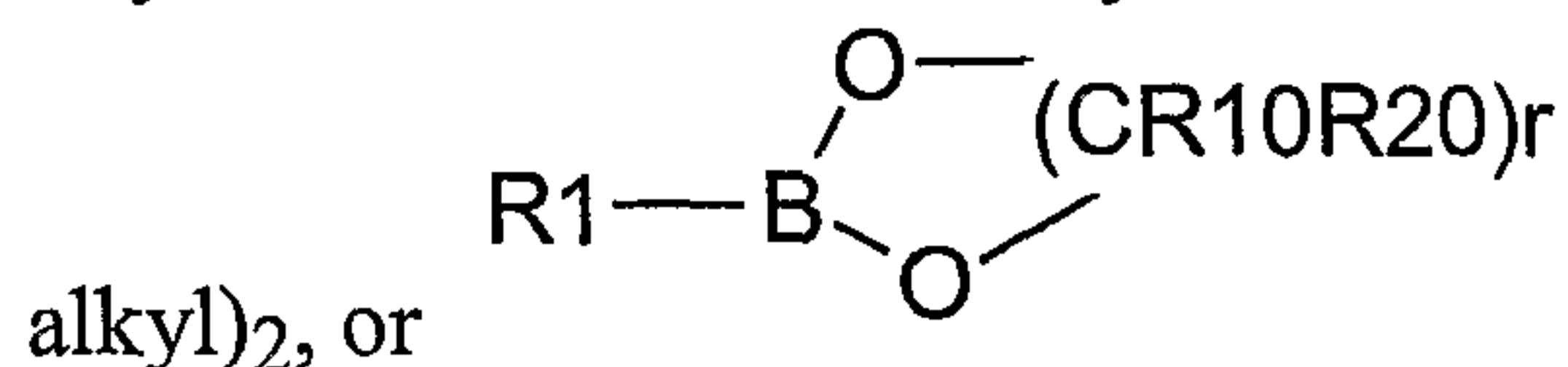
displaced with aryl or heteroaryl or alkyl thiols or alkyl or aryl or heteroaryl alcohols. Analogs containing sulfones as the X substituents may be displaced with sodium alkoxide in the alcohol, or alternatively reactive alkoxide or phenoxide nucleophiles that may be generated from the alcohol or phenol with a suitable base such as sodium, NaH or sodium bistrimethylsilyl amide in a polar aprotic solvent such as DMSO, or run as a neat reaction. Similarly the sulfone may be displaced with carbon nucleophiles. Suitable carbon nucleophiles include, but not limited to aryl Grignard reagents, alkyl Grignard reagents or related organometallics such as organo lithium, zinc, tin, copper or boron. These reactions may, in some cases, require transition metal catalysis such as with Pd or Ni catalysts.

**Method C** is for coupling with appropriate aryl groups to convert **3** to compounds with Formula (**Ia**) (or **2** to **6**). This transformation may be achieved using, but not limited to boronic acids (e.g., **C1A**) under Suzuki cross-coupling conditions, employing a palladium catalyst, such as tetrakis(triphenylphosphine) palladium(0).

Alternatively, the cross-coupling may be performed using aryl or heteroaryl organozinc, (e.g., aryl/heteroaryl-ZnBr, aryl/heteroaryl-ZnCl, aryl/heteroaryl-Zn-R1), organocopper, [e.g., (aryl/heteroaryl)<sub>2</sub>-CuLi], organotin [e.g., aryl/heteroaryl-Sn(CH<sub>3</sub>)<sub>3</sub>, aryl/heteroaryl -Sn(CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>)<sub>3</sub>], (e.g., **C1C**), or other organometallic reagents (e.g., **C1B**) known in the art [see for example Solberg, J.; Undheim, K. *Acta Chemica Scandinavia* **1989**, 62-68].

**Method D** is for coupling of **2** (or **3** or **7**) with an aryl group whose structure has a suitable precursor (e.g., acidic group -CO<sub>2</sub>H, ester group -CO<sub>2</sub>Me) to the final substituent R<sub>1</sub> in Formula (**Ia**). This transformation may be achieved using, but not limited to boronic acids (e.g., **D1A**) or protected acids (e.g., **D1C**, **D1E**) under Suzuki coupling conditions, (THF/H<sub>2</sub>O, and K<sub>2</sub>CO<sub>3</sub>) employing a palladium catalyst, such as tetrakis(triphenylphosphine) palladium(0). If desired, these Suzuki coupling reactions may be run under microwave conditions. The boronic acid (**D1A** or **D1E**) or ester can be synthesized either by the palladium catalyzed coupling of an aryl halide and 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi-1,3,2-dioxaborolane or the transmetalation of an aryl halide with a Grignard reagent, e.g., isopropylmagnesium bromide followed by a trialkylborate (e.g., triethylborate) in a suitable solvent like THF.

Suitably the arylboronic acids, or their corresponding boronic acid esters are Aryl -boronic acid or an Aryl -boronic acid ester; e.g. Aryl B(OH)<sub>2</sub>, Aryl -B(O-C<sub>1-4</sub>



wherein R<sub>1</sub>, R<sub>10</sub>, and R<sub>20</sub> is as defined for compounds of Formula (I) herein; and r is an integer having a value of 2 to 6.

The coupling conditions include the use of appropriate solvents. These solvents include, but are not limited to dioxane, THF, DMF, DMSO, NMP, acetone, water, or a combination or a mixture thereof. Preferably, the solvent is THF/H<sub>2</sub>O, or dioxane/H<sub>2</sub>O.

The coupling conditions also include the presence of catalytic amount of catalysts and these catalysts include, but not limited to tetrakis(triphenylphosphine)-palladium (0), PdCl<sub>2</sub>, Pd(OAc)<sub>2</sub>, (CH<sub>3</sub>CN)<sub>2</sub>PdCl<sub>2</sub>, Pd(dppf)<sub>2</sub>, or [1,1'-bis(diphenylphosphino)-ferrocene]-dichloropalladium(II).

The coupling reaction may or may not require the presence of a base. Suitable bases include, but are not limited to NaHCO<sub>3</sub>, KHCO<sub>3</sub>, Na<sub>2</sub>CO<sub>3</sub>, K<sub>2</sub>CO<sub>3</sub>, KOAc or combination or mixture thereof. Preferably, the base is K<sub>2</sub>CO<sub>3</sub> and KOAc.

The coupling reaction may or may not require heating. The heating can be carried out with a regular oil bath or microwave irradiations and the temperature can be varied from room temperature to >100 °C, i.e. reflux temperature of the solvent. The coupling reaction may or may not require a sealed reaction vessel and the internal pressure can be varied from one atmosphere to 100 atmospheres.

The aryl or heteroaryl boronic acid or ester intermediates containing the R<sub>1</sub> moiety, used in the Suzuki coupling reactions may or may not be commercially available and they can be prepared by utilizing proper methods in the literature known to those with appropriate training. Examples of these methods include, but not limited to palladium catalyzed coupling of an aryl halide and 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi-1,3,2-dioxaborolane or the transmetalation of an aryl halide with a Grignard reagent, e.g., isopropylmagnesium bromide followed by a trialkylborate (e.g., triethylborate) in a suitable solvent. These solvents include, but not limited to CH<sub>2</sub>Cl<sub>2</sub>, chloroform, CH<sub>3</sub>CN, benzene, THF, hexane, ethyl ether, *tert*-butyl methyl ether, DMSO, DMF, toluene, n-methyl-pyrrolidine, dioxane. The reaction temperature can be varied from -78 °C to >100 °C, i.e. reflux temperature of the solvent. Alternatively, this reaction process step may or may not be performed under suitable microwave irradiation conditions. This reaction may or may not require a sealed reaction vessel and the internal pressure can be varied from one atmosphere to 100 atmospheres.

Alternatively, the cross-coupling may be performed using aryl or heteroaryl organozinc, organocopper, organotin (e.g., **D1B**), or other organometallic reagents (e.g., **D1D**) known in the art [see for example Solberg, J.; Undheim, K. *Acta Chemica*

*Scandinavia* 1989, 62-68]. Suitable de-protection is followed if a protected precursor (e.g., **D1C**, **D1D**, **D1E**) is used.

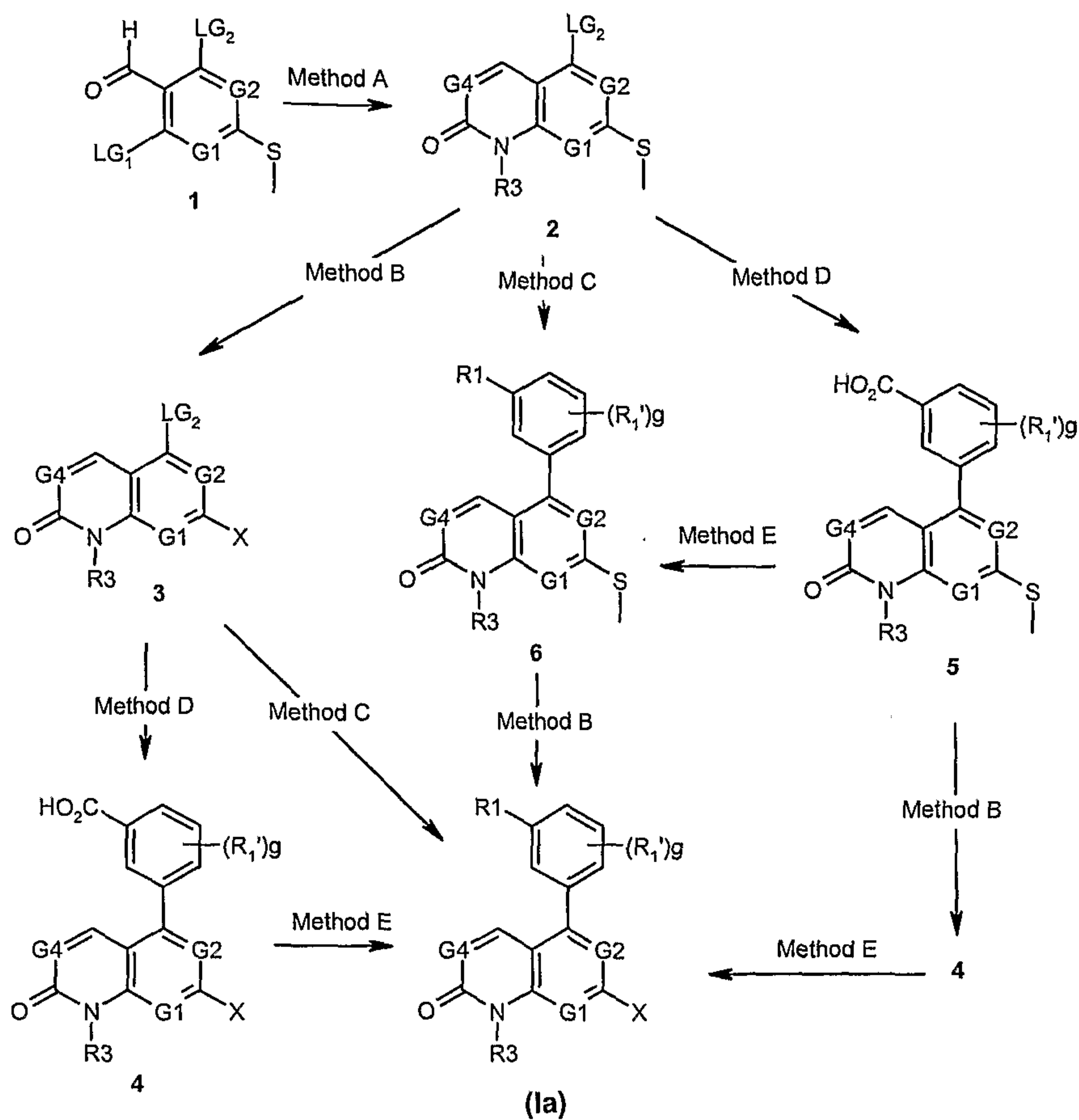
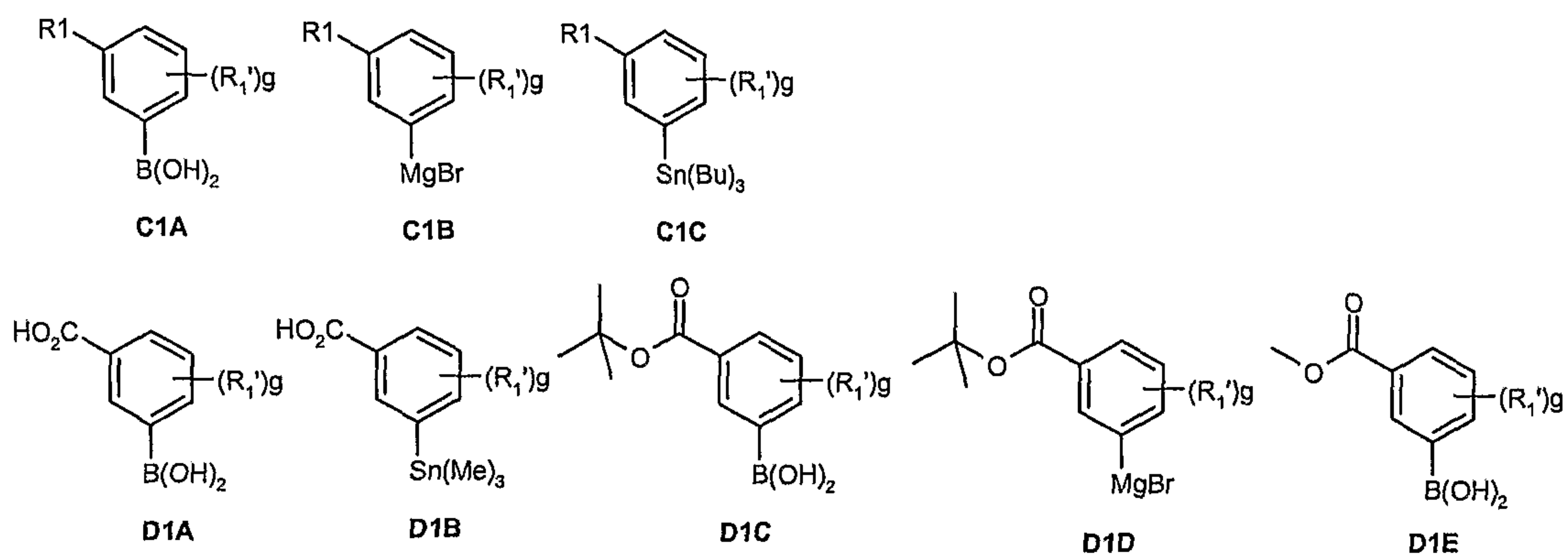
This coupling reaction may be performed utilizing aryl or heteroaryl organozinc (e.g., Aryl-ZnBr, R<sub>1</sub>-ZnCl, Aryl -Zn- Aryl), organocopper [e.g., (Aryl)<sub>2</sub>-CuLi], organotin (e.g., Aryl-Sn(CH<sub>3</sub>)<sub>3</sub>, Aryl -Sn(CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>)<sub>3</sub>], or other organometallic reagents to afford the cross-coupling product. If the desired aryl organozinc (e.g., Aryl-ZnBr, R<sub>1</sub>-ZnCl, Aryl -Zn- Aryl), organocopper [e.g., (Aryl)<sub>2</sub>-CuLi], organotin (e.g., Aryl -Sn(CH<sub>3</sub>)<sub>3</sub>, Aryl -Sn(CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>)<sub>3</sub>], or other organometallic reagent is not commercially available, they can readily be prepared by utilizing proper methods, known in the literature.

These types of coupling reactions require the use of appropriate solvents. Such solvents include, but are not limited to dioxane, THF, methylene chloride, chloroform, benzene, hexane, ethyl ether, *tert*-butyl methyl ether or a combination or a mixture thereof. The coupling reaction may, or may not, require the presence of catalytic amount of a catalyst. Such catalysts include, but are not limited to tetrakis(triphenylphosphine)palladium (0), PdCl<sub>2</sub>, Pd(OAc)<sub>2</sub>, (CH<sub>3</sub>CN)<sub>2</sub>PdCl<sub>2</sub>, Pd(dppf)<sub>2</sub>.

The reaction temperature can be varied from -78 °C to >100 °C, i.e. reflux temperature of the solvent. Alternatively, this reaction process step may be performed under suitable microwave irradiation conditions, if needed. This reaction may, or may not, require a sealed reaction vessel and the internal pressure can be varied from one atmosphere to 100 atmospheres.

**Method E** is for the transformation of the suitable precursor (e.g., acidic group -COOH in **4**, **5**, **9**, **11**, **15**, **16**, **17**, or **18**) to the final substituent R<sub>1</sub>. This type of transformations can be achieved by utilizing well-established strategies in the art. The transformation may be done in one step (such as coupling with amines HN(R<sub>10'</sub>)R<sub>b</sub> under standard coupling conditions e.g. EDC/HOBT/ET<sub>3</sub>N in CH<sub>3</sub>CN; coupling with alcohol, HOR<sub>b</sub> under standard coupling conditions, e.g. DCC, DMAP in DCM to form esters or reduction to alcohol) or in more than one step (e.g., Curtius rearrangement to form isocyanates followed by urea formation with amines or acid chloride formation followed by addition of an amine, HN(R<sub>10'</sub>)R<sub>b</sub> or an alcohol, HOR<sub>b</sub> plus a non-nucleophilic base, e.g. DIPEA in an aprotic solvent like DCM. This conversion may require a deprotection step to install the precursor at first (e.g., hydrolysis of -CO<sub>2</sub>Me with LiOH/THF/water to prepare -COOH).

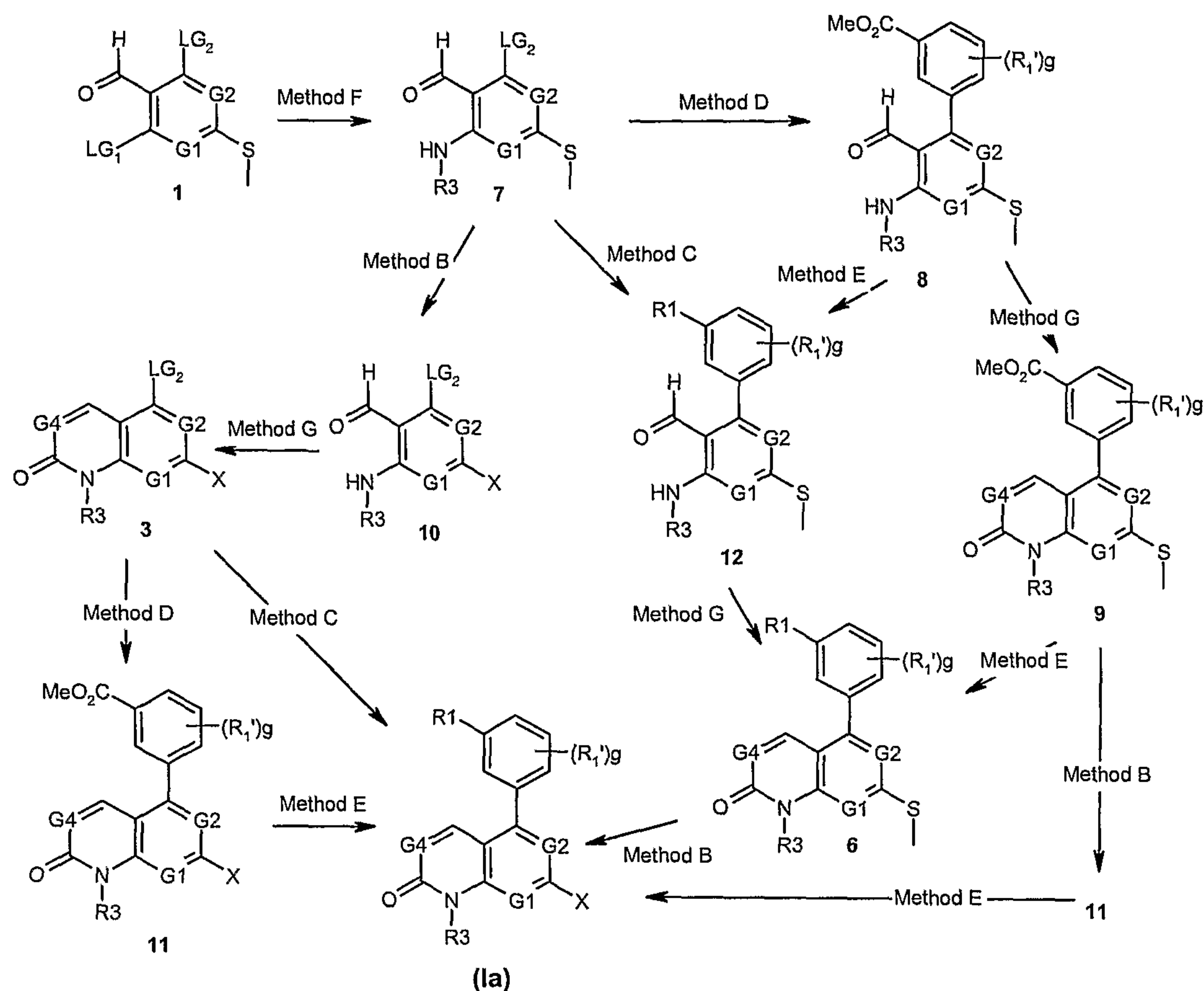
35

**Scheme 1****Examples of Reagents for methods C & D**

5 Preparation of compounds with Formula (Ia) can also be achieved through compound 7, which in turn may be constructed from aldehyde 1 as shown in **Scheme 2**. Suitable methods from **Methods A-E** can be utilized to furnish appropriate conversions in **Scheme 2**.

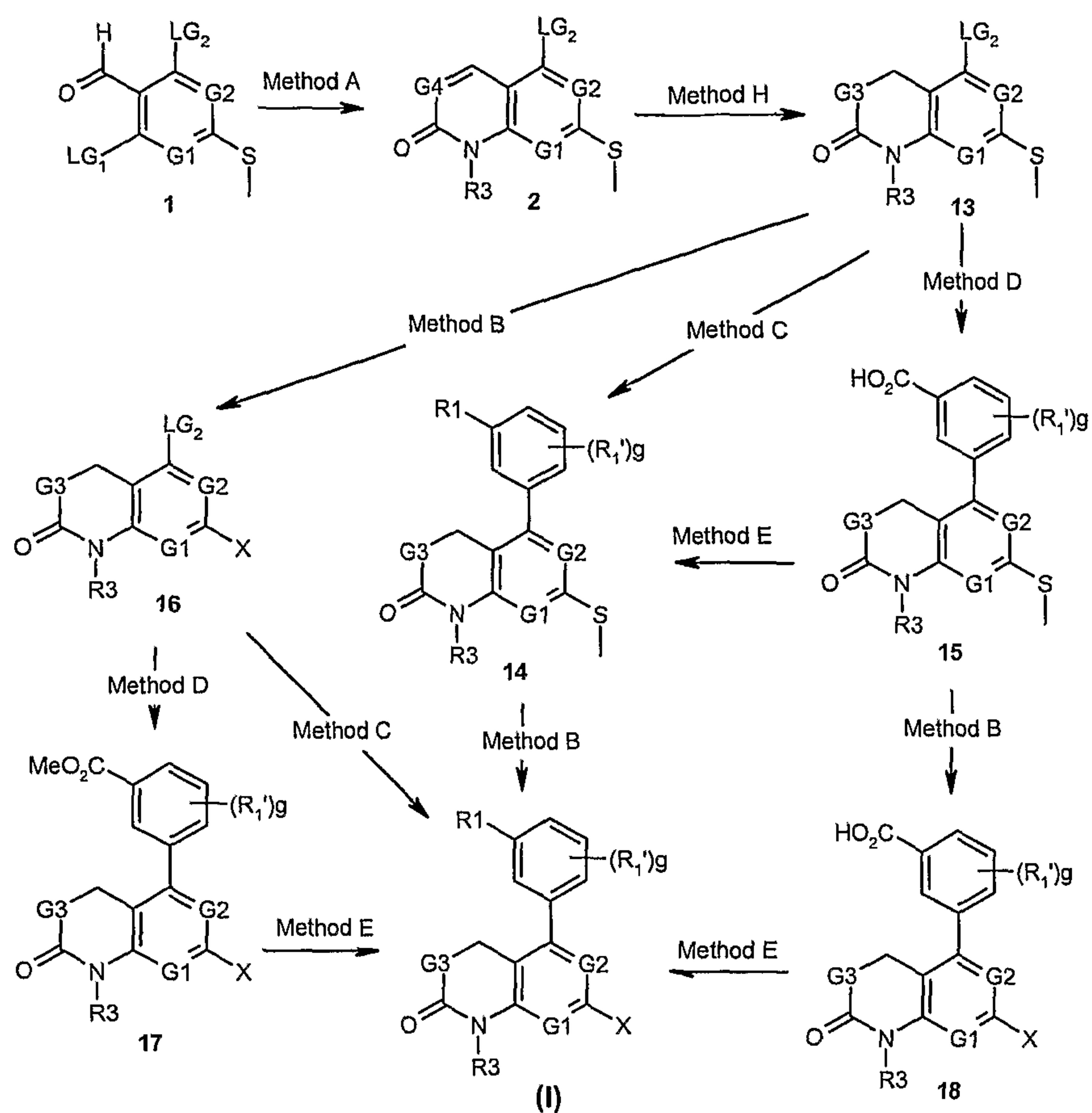
**Method F** is for selective displacement of suitable aldehyde **1** with an amine ( $R_3-NH_2$ ). This type of displacement may be achieved using triethylamine and the desired amine  $R_3NH_2$  in chloroform at room temperature for 10 minutes. The reaction was very effective for a range of alkyl amines (78-95% yield). For aryl or heteroaryl amines, elevated temperatures (reflux or microwave irradiations), longer reaction times (overnight or 24 hours) and presence of NaH (or Na) may be necessary for reaction completion. Use of the base could be omitted when 3 or more equivalent of desired amine were used. Other suitable bases include but are not limited to pyridine, diisopropyl ethylamine or pyrrolidine, which may also be used in an appropriate organic solvent, including but not limited to THF, diethyl ether, DCM, DMF, DMSO, toluene or dioxane.

**Method G** is for cyclization of **8** to **9**. It may be achieved by mixing compound **8** with an olefin forming agent (e.g., Wittig reagents) or amide forming agent (e.g., acid, acid chloride, ester) or an agent with both potential reactivities such as bis(2,2,2-trifluoroethyl)-(methoxycarbonylmethyl)-phosphonate, bis(2,2,2-trifluoroethyl)-(ethoxycarbonylmethyl)phosphonate, bis(2,2,2-trifluoroethyl)-(isopropoxycarbonylmethyl)phosphonate, (diethoxy-phosphoryl)-acetic acid methyl ester, (diisopropoxy-phosphoryl)-acetic acid methyl ester, (diphenyloxy-phosphoryl)-acetic acid methyl ester, (diethoxy-phosphoryl)-acetic acid ethyl ester, (diisopropoxy-phosphoryl)-acetic acid ethyl ester, (diphenyloxy-phosphoryl)-acetic acid ethyl ester, acetic acid, thioacetic acid, acetic acid anhydride, Meldrum's acid, or acetyl chloride. Elevated temperatures (reflux or microwave irradiations), longer reaction times (overnight or 24 hours) and presence of triethyl amine, diisopropyl ethyl amine, NaOAc, or NaH (or Na) may be necessary for reaction completion. Reaction solvent can be DCM, THF, toluene, DMSO or DMF. During the cyclization, the protected group ( $-CO_2Me$  in **8**) may or may not be hydrolyzed. Either output may be utilized to the advantage of expanding structure-activity-relationship (SAR) studies. If necessary, the hydrolysis can be achieved by mixing with LiOH in THF/water. A different protecting group at this position (e.g., tert-butyl) may require a different de-protection method (e.g., treatment with TFA).

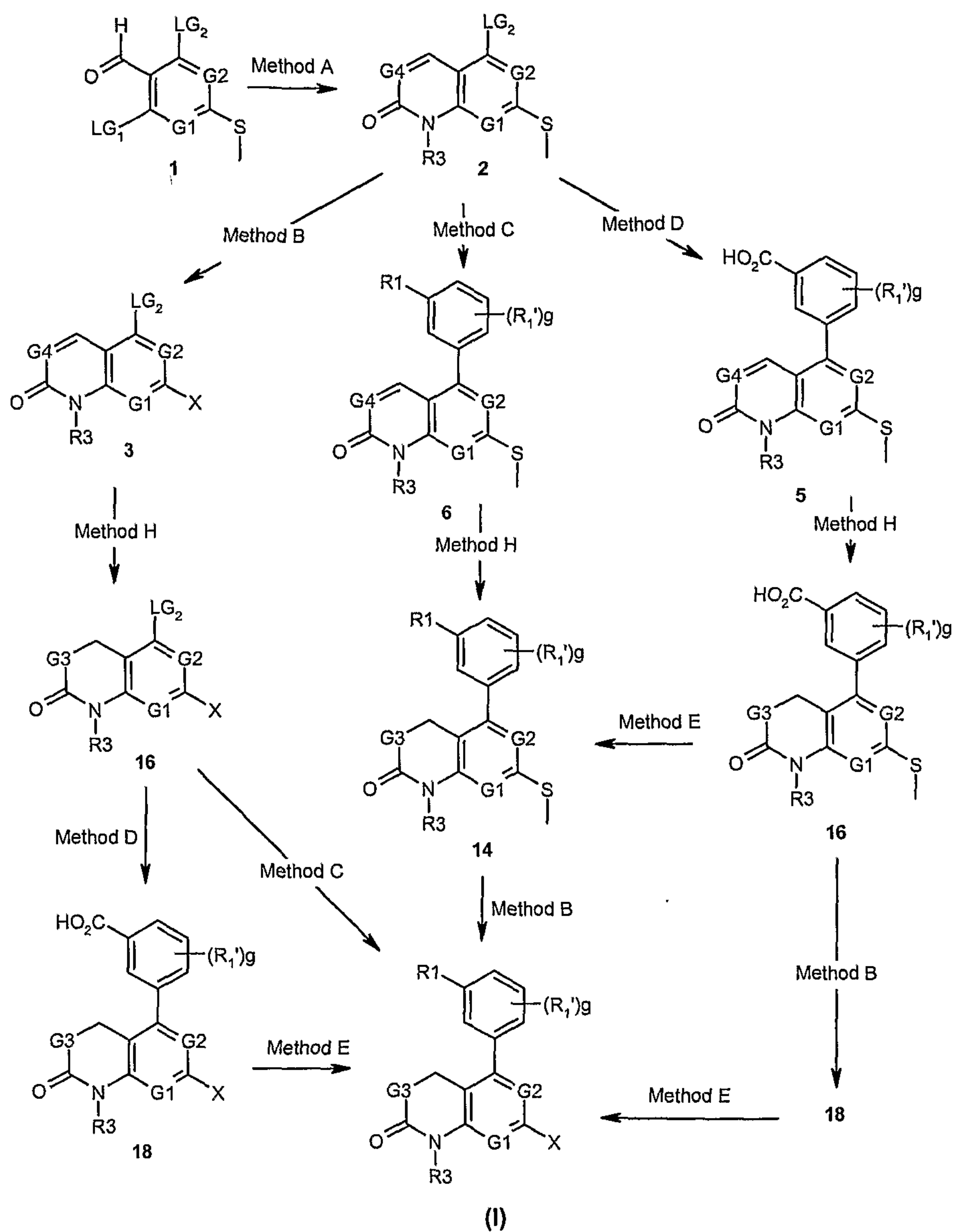
**Scheme 2**

Preparation of compounds with Formula (I) can be achieved through compound 14, which in turn may be constructed from aldehyde 1 as shown in Scheme 3. Suitable methods from Methods A-G can be utilized to furnish appropriate conversions in Scheme 3.

Method H is for the reduction of a double bond that is directly connected to a carbonyl group [-C(=O)-]. This type of conversion can be achieved by utilizing suitable methods well documented in the literature for the 1,4-reduction of an enone system [e.g., -CH=CH-C(=O)-]. These methods include, but not limited to, Li/NH<sub>3</sub>, H<sub>2</sub> (catalyst Rh-Al<sub>2</sub>O<sub>3</sub>), NaBH<sub>4</sub> / CoCl<sub>2</sub>·6H<sub>2</sub>O, NaBH<sub>3</sub>CN / ZnCl<sub>2</sub>, LiHCu(*n*-Bu), or Et<sub>3</sub>SiH.

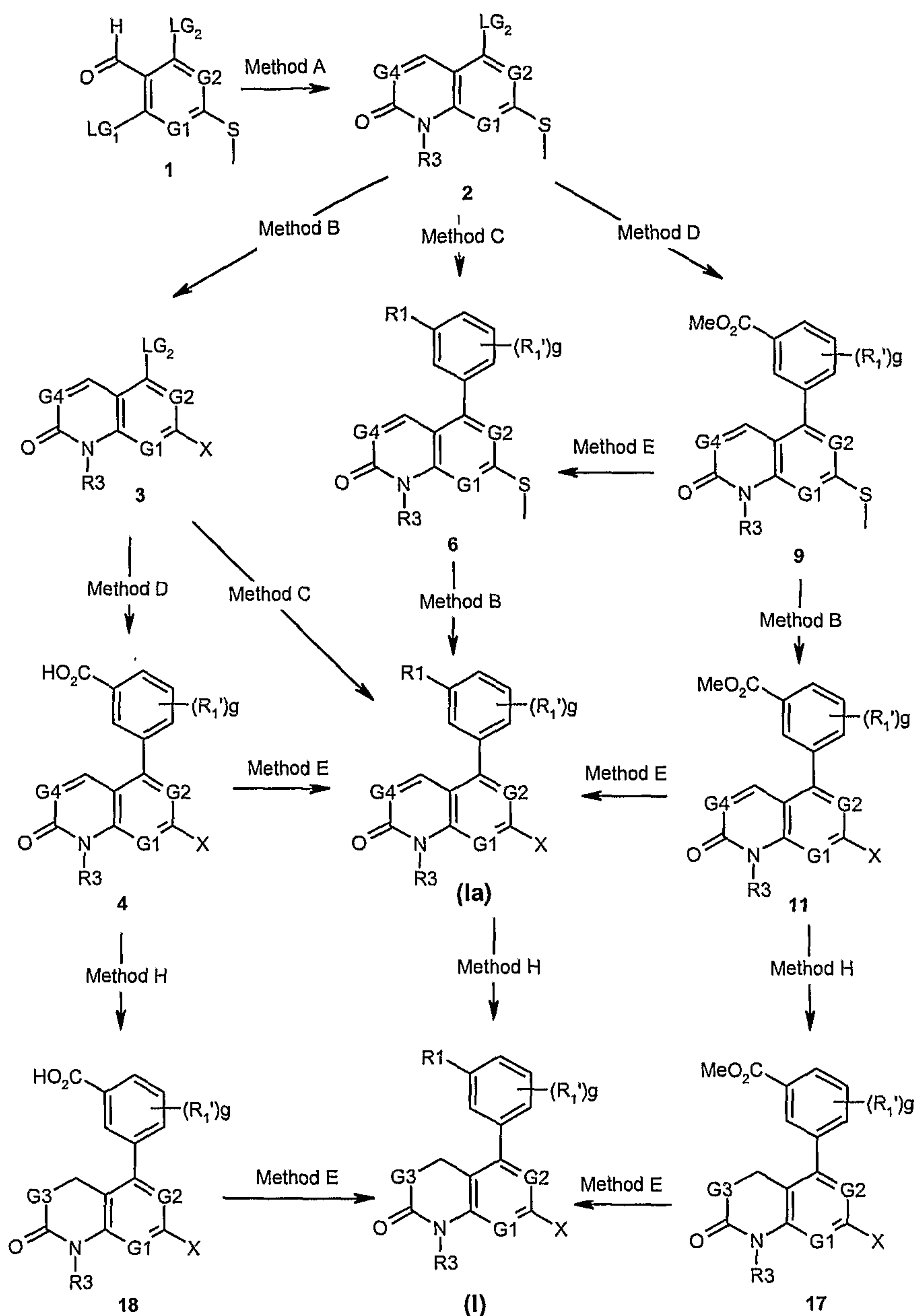
**Scheme 3**

Preparation of compounds with Formula (I) may also be achieved through compound 2, which in turn may be constructed from aldehyde 1 as shown in **Scheme 4**. Suitable methods from **Methods A-H** can be utilized to furnish appropriate conversions in **Scheme 4**.

**Scheme 4**

Preparation of compounds with Formula (I) may also be achieved through compound 2, which in turn may be constructed from aldehyde 1 as shown in **Scheme 5**. Suitable methods from **Methods A-H** can be utilized to furnish appropriate conversions in **Scheme 5**.

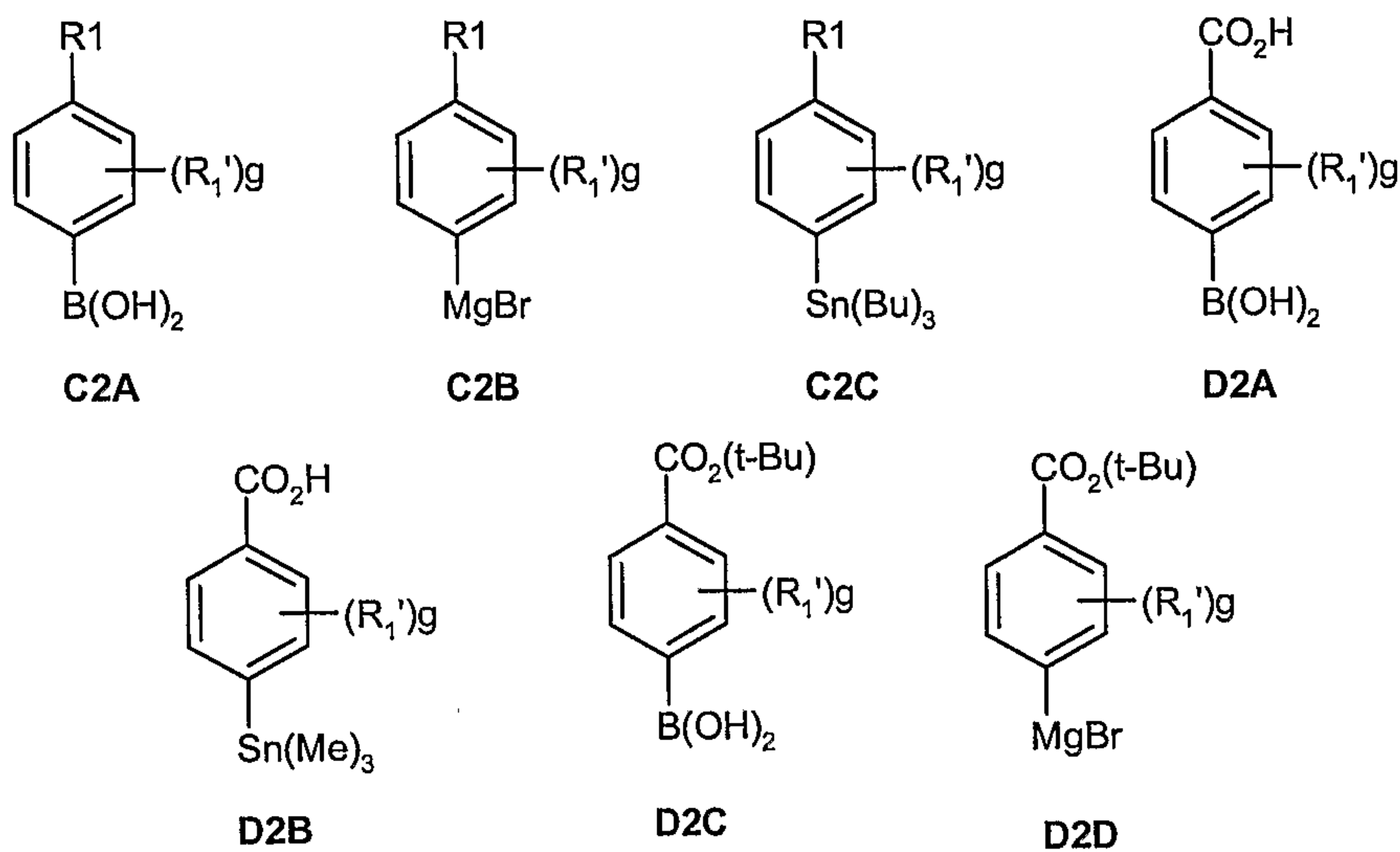
## Scheme 5



The compounds of Formula (II) and (IIa), (III) and (IIIa), (IV) and (IVa), (V) and (Va), (VI) and (VIa-VII) may be obtained by applying the synthetic procedures described above in **Schemes 1 to 5** except suitable reagents in **Method C & D** should be utilized. Examples of these reagents include, but not limited to those shown in **Scheme 6**. Suitable reagents in **Method C & D** for the preparation of compounds with Formula (VIb-VII) require the presence of G<sub>5</sub>-8 in appropriate position.

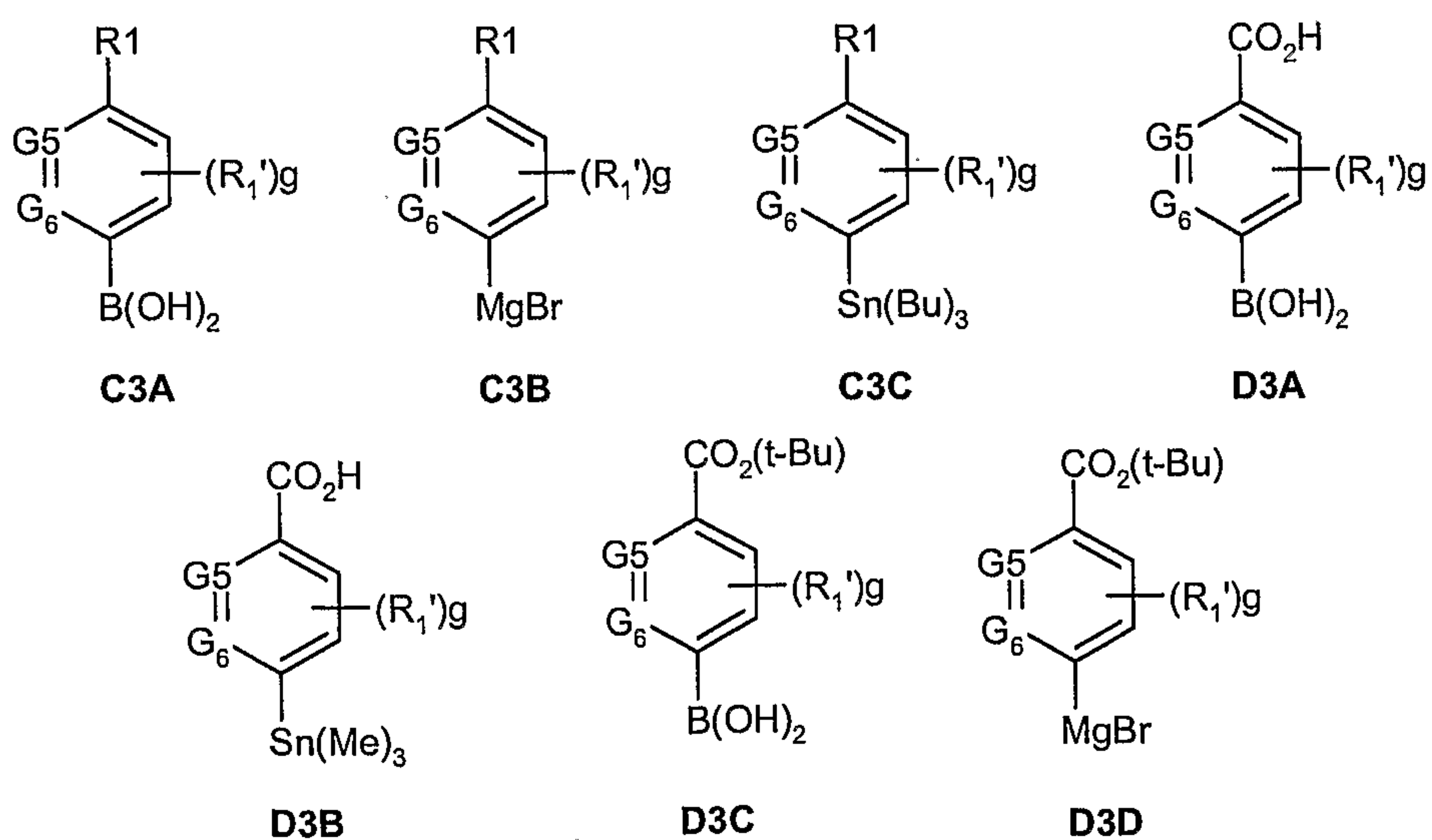
## Scheme 6

## Examples of Reagents in Method C &amp; D for the Preparation of Compounds with Formula (II) &amp; (IIa)



5

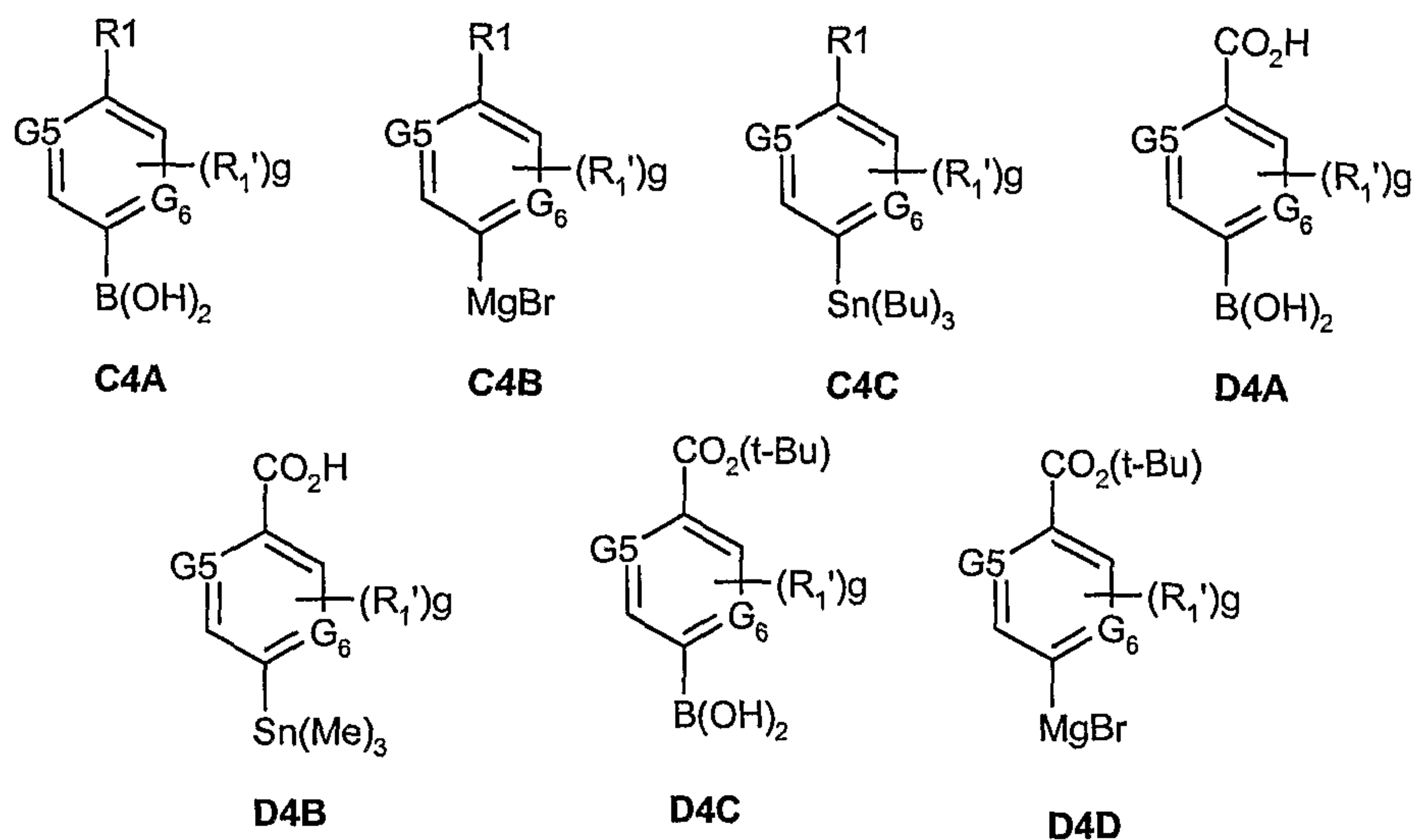
## Examples of Reagents in Method C &amp; D for the Preparation of Compounds with Formula (III) &amp; (IIIa)



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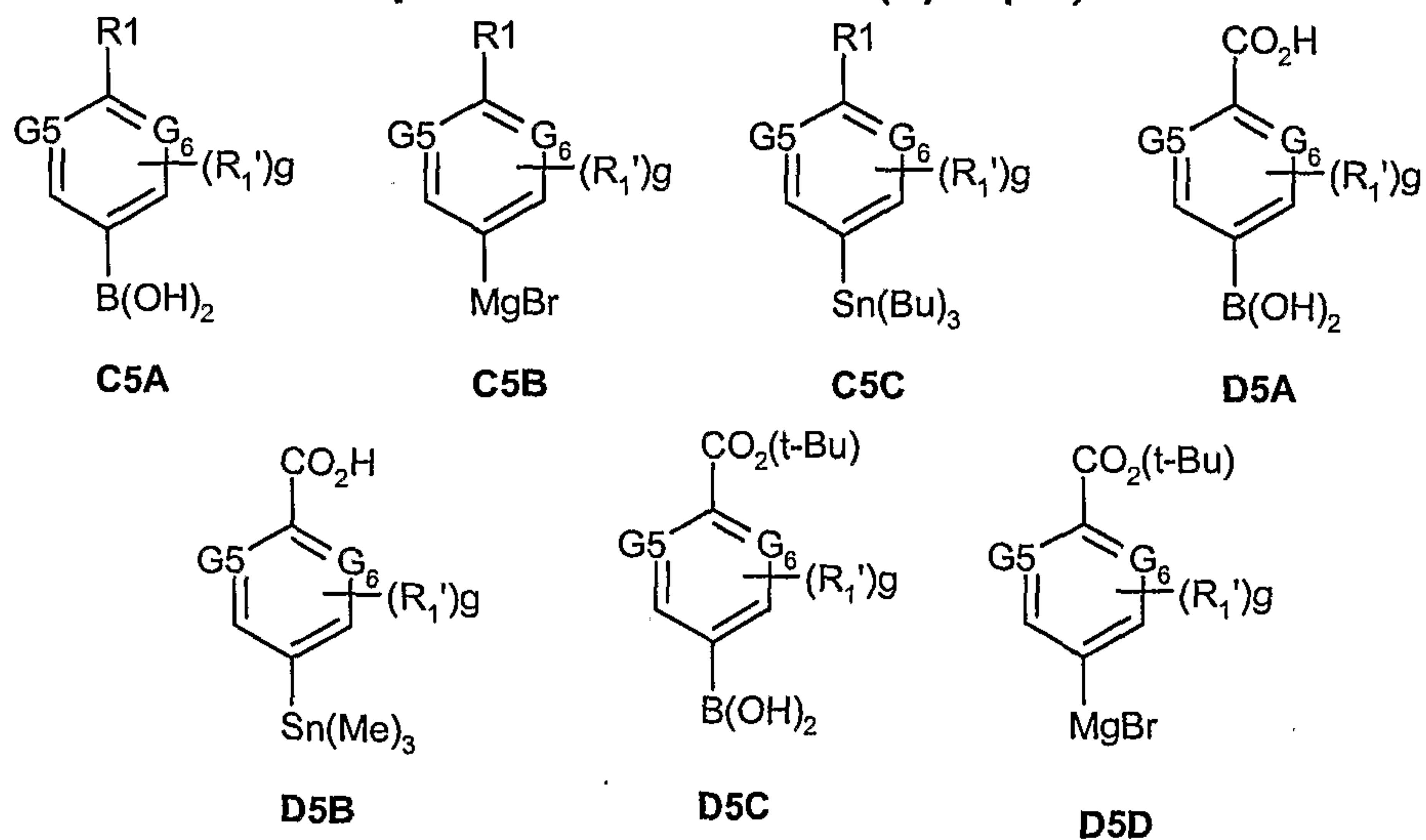
## Scheme 6 continued

## Examples of Reagents in Method C &amp; D for the Preparation of Compounds with Formula (IV) &amp; (IVa)



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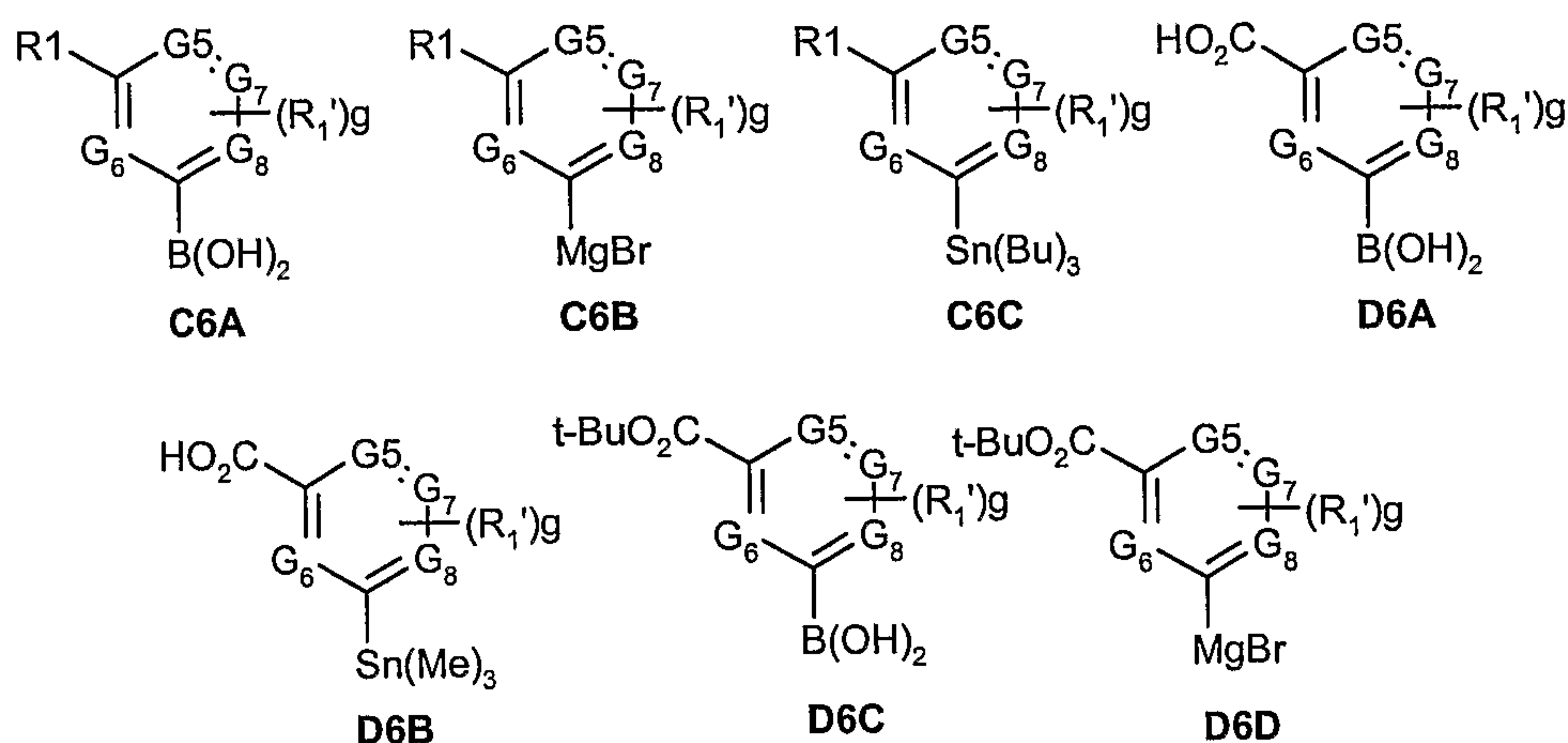
## Examples of Reagents in Method C &amp; D for the Preparation of Compounds with Formula (V) &amp; (Va)



10

## Scheme 6 continued

## Examples of Reagents in Method C &amp; D for the Preparation of Compounds with Formula (VI) &amp; (VIa)



5

The starting material **1-Scheme 7** may be obtained from the commercially available 4,6-dihydroxy-2-methylmercaptopyrimidine by known literature procedures, such as those noted in Santilli et al., *J. Heterocycl. Chem.* (1971), 445-53, wherein  $\text{POCl}_3$  and DMF are used.

The intermediate **2-Scheme 7** was produced by two different routes. In the first route, coupling of dichloro aldehyde **1-Scheme 7** with aryl amines in the presence of NaH in DMSO (Santilli et al., *J. Heterocycl. Chem.* (1971), 445-53) afforded the desired compound **2-Scheme 7** along with imine **13-Scheme 7**. The imine was converted to aldehyde **2-Scheme 7** by treatment with aqueous HCl in THF. Conversion of **1-Scheme 7** to **2-Scheme 7** may also be achieved using triethylamine and the desired amine in chloroform at room temperature for 10 minutes. The reaction was very effective for a range of alkyl amines (78-95 % yield). For aryl amines, elevated temperatures (reflux) and longer reaction time (24 hours) were necessary for reaction completion. Use of the base could be omitted when 3 or more equivalent of amine were used. Other suitable bases, include but are not limited to pyridine, diisopropyl ethylamine or pyrrolidine, which may also be used in an appropriate organic solvent, including but not limited to THF, diethyl ether or dioxane.

In the second route, the nitrile **9-Scheme 7** was prepared in three steps from the aldehyde **1-Scheme 7** (Santilli et al., *J. Heterocycl. Chem.* (1971), 445-53). Coupling of dichloro nitrile **9-Scheme 7** with aryl amines in the presence of NaH in

DMSO afforded the desired compound 10-Scheme 7. Other suitable bases such as pyridine, diisopropyl ethylamine, or sodium may also be used in an appropriate organic solvent such as THF, DMF or dioxane. Production and use of the nitrile 9-Scheme-I may also be found in PCT/US01/06688, filed March 2, 2001 .

5

The nitrile 10-Scheme 7 was easily reduced with DIBAL in dichloromethane at room temperature (Boschelliat et al., *J. Med. Chem.* (1998), 4365-4377) to afford desired 2-Scheme 7 along with the unsubstituted imine 13-Scheme 7 (R=H). The latter was hydrolyzed to 2-Scheme 7 *in situ* with HCl. Other reduction agents, such as lithium aluminum hydride, Raney Ni, or SnCl<sub>2</sub>, may be utilized in an appropriate organic solvent such as THF, diethyl ether or dioxane to perform the conversion of 10-Scheme 7 to 2-Scheme 7.

Aldehyde 2-Scheme 7 was coupled to arylboronic acids under Suzuki coupling conditions, using a palladium catalyst, such as tetrakis(triphenylphosphine) palladium(0), to afford good to excellent yields of 3-Scheme 7. Alternatively, the bi-aryl coupling reaction of 2-Scheme 7 may be performed using aryl or heteroaryl organozinc, organocopper, organotin, or other organometallic reagents known to afford bi-aryl cross-coupling products such as 3-Scheme 7 [see for example Solberg, J.; Undheim, K. *Acta Chemica Scandinavia* 1989, 62-68]. Displacement of the chlorine in 2-Scheme 7 may also be achieved with nitrogen nucleophiles [for related aminations see US patent 3,631,045 and 3,910,913], sulphur nucleophiles, [see Tumkevicius, S. *Liebigs Ann.* 1995, 1703-1705], oxygen nucleophiles, or alkyl nucleophiles.

3-Scheme 7 was then converted to pyridopyrimidinone 5-Scheme 7 by one of three procedures. The first procedure used the Wittig reaction, as modified by Horner-Emmons, converting 3-Scheme 7 to 4-Scheme 7. In this reaction, the aldehyde 3-Scheme 7 was treated with a suitable phosphorus ylide, such as triethyl phosphonoacetate or methyl diethylphosphonoacetate, to give the olefin intermediate 4-Scheme 7. The reaction was performed under reflux, in a suitable base, such as sodium hydride, sodium methoxide, or sodium hydroxide, and in a suitable organic solvent such as diethyl ether, dioxane or ethanol. The conversion of 3-Scheme 7 to 4-Scheme 7 may also be performed using the Peterson olefination reaction, or an aldol-based olefination reaction that utilizes acetic anhydride, malonic acid and its monoalkyl esters, or ethyl acetate.

Heating of 4-Scheme 7 in toluene at 220 °C in a sealed tube (Matyus et al. *Heterocycles* (1985), 2057-64), followed by solvent removal, afforded the desired product 5-Scheme 7. This reaction may be run in the presence of a suitable base, such

as DBU or diisopropylethyl amine, pyridine, lithium bi(trimethylsilyl)amide, or LDA and in an appropriate organic solvent such as an organic hydrocarbon, cresol, dioxane, DMF, pyridine, or xylene.

5 The second procedure used a Horner-Emmons reaction with Still modification (Still et al., *Tetrahedron Lett.* (1983), 4405-8; Jacobsen et al., *Tetrahedron* (1994), 4323-34) to produce a mixture of desired product **5-Scheme 7** and *trans* isomer **4-Scheme 7**. *Trans* isomer **4-Scheme 7** was isolated and converted to the desired product **5-Scheme 7** by heating to 220 °C in toluene in a sealed tube as described above.

10 The third procedure involved acetylation of **3-Scheme 7**, followed by the intramolecular aldol condensation, promoted by an acetylating agent (such as acetic anhydride, acetyl chloride, or a ketene) and a suitable base (such as pyridine, diisopropyl ethylamine, or pyrrolidine), to generate **5-Scheme 7** in a very good yield. The third procedure is optimal when R<sub>3</sub> is an optionally substituted aryl, or  
15 heteroaryl. When R<sub>3</sub> is an arylalkyl, or heteroarylalkyl substituent it is not clear that the reaction will form the key intermediate of Formula (VII), as shown below (**3a-Scheme 8**), which may optionally be isolated, as shown in Scheme 8 below. Compounds of Formula (VII) are preferably not isolated but further reacted with a base or with heat to cyclize into **5-Scheme-7**. The first and second procedures should  
20 be utilized for all other R<sub>3</sub> moieties.

Oxidation of the sulfide **5-Scheme 7** to the sulfone **6-Scheme 7** was performed using *meta*-chloroperoxybenzoic acid (mCPBA) in high yield and purity. Suitable oxidation methods for use herein include use of one or two equivalents of *meta*-chloroperoxybenzoic acid (mCPBA) or Oxone<sup>®</sup> to afford either the sulfoxides or  
25 sulfones. Oxidation of the sulfides to sulfoxides or sulfones can also be effected by OsO<sub>4</sub> and catalytic tertiary amine N-oxide, hydrogen peroxide, other peracids, oxygen, ozone, organic peroxides, potassium and zinc permanganate, potassium persulfate, and sodium hypochlorite.

Displacements of the sulfones **6-Scheme 7** to the final products **7-Scheme-7**  
30 were usually done with an excess of amine in N-methylpyrrolidine (Barvian et al., *J. Med. Chem.* (2000), 4606-4616). A wide range of primary amines underwent this reaction with excellent yields. In some cases (in O-displacement or sulfonamide formation) an anion of the nucleophile was prepared with base (usually sodium hydride) in dimethylformamide and then added to the sulfone. Yields for these  
35 reactions were usually lower. Similarly related sulfones and sulfoxides of the compounds herein wherein X is SO-alkyl or SO<sub>2</sub>-alkyl have been reported in the literature to be displaced by a wide variety of nucleophiles. Thus the analogs of the

compounds herein wherein X is an alkyl sulfone or sulfoxide may be displaced by primary and secondary alkylamines with or without additional base catalysis, preferably in a polar aprotic solvent, such as but not limited to, N-methyl pyrrolidin-2-one (NMP), and at varying temperatures depending upon the nucleophilicity of the amine. For instance displacement of the sulfone of analogs of Formula (I) compounds with ethanolamine, in NMP, occurred in 30 min. at 65° C, while a more hindered amine such as tris(hydroxymethyl)-aminomethane may require elevated temperatures and extended reaction times (80° C over a 24 hour reaction time). The sulfone can also be displaced by a primary or secondary amine with an additional non-nucleophilic base (e.g. DIPEA) in aprotic solvents like DCM, CH<sub>3</sub>CN, NMP, and at varying temperatures depending upon the nucleophilicity of the amine.

The sulfone may also be displaced with a substituted arylamine, or heteroarylamine at elevated temperatures, sometimes requiring formation of the aryl or heteroarylamine anion with sodium hydride, or other suitable base, in DMSO. In addition, the sulfoxide analogs of Formula (I) compounds may be readily displaced with aluminum salts of aryl or heteroaryl amines as previously described in the patent literature (WO 99/32121). Likewise, sulfone and sulfoxide analogs of Formula (I) and (Ia) may be displaced with aryl or heteroaryl or alkyl thiols or alkyl or aryl or heteroaryl alcohols. For instance analogs of (I) containing sulfones as the X substituents may be displaced with sodium alkoxide in the alcohol, or alternatively reactive alkoxide or phenoxide nucleophiles may be generated from the alcohol or phenol with a suitable base such as sodium, NaH or sodium bistrimethylsilyl amide in a polar aprotic solvent such as DMSO, or run as a neat reaction. Similarly sulfones related to Formula (I) and (Ia), for instance, may be displaced with carbon nucleophiles such as aryl or alkyl Grignard reagents or related organometallics such as organo lithium, zinc, tin or boron. These reactions may, in some cases, require transition metal catalysis such as with Pd or Ni catalysts. Displacement of related 2-pyrimidine sulfones with cyanide, malonate anions, unactivated enolates, or heterocyclic C nucleophiles such as 1-methylimidazole anion, by the generation of the anion with NaH or other suitable base in THF also has precedent (see for example, Chem Pharm Bull. **1987**, 4972-4976.). For example, analogs of Formula (I) and (Ia) compounds wherein X is an alkyl sulfone may be displaced with the anion of 1-methyl imidazole, generated by treatment of 1-methyl imidazole with n-butyl lithium in a solvent such as THF at temperatures of about -70°, to afford the C-alkylated product substituted on the imidazole C-2.

For the purposes herein, compounds of Formulas (I), (Ia), (II) and (IIa) wherein X is R<sub>2</sub> or NHS(O)mR<sub>2</sub> may be obtained from compounds of **6-Scheme 7** by

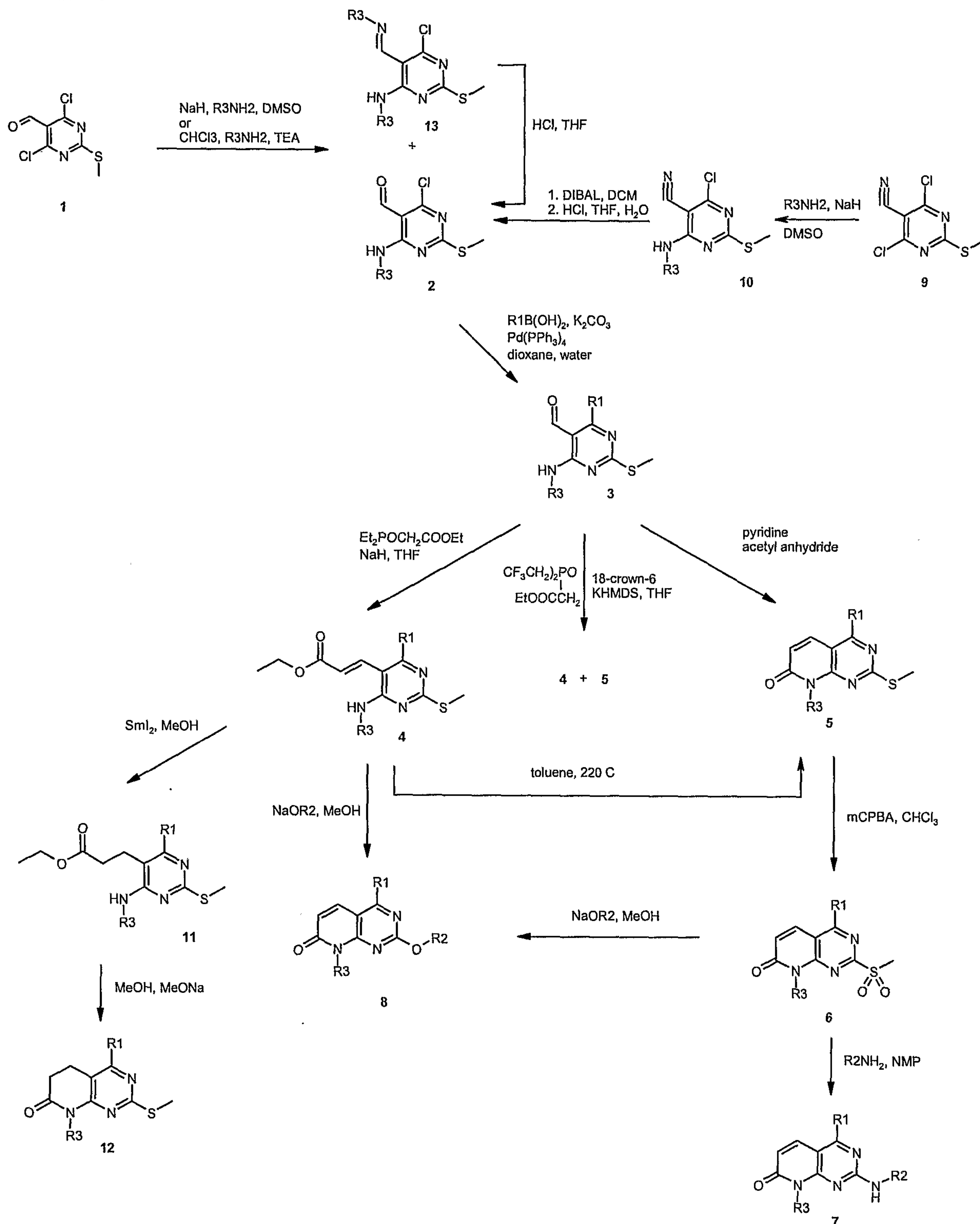
displacement of the sulfone using the appropriate "X" functionality as defined in Formula (I) and (Ia). To obtain compounds of Formulas (I), (Ia), (II) and (IIa) wherein X is  $S(O)_mR_2$  and  $R_2$  is other than methyl, displacement of the sulfone on the corresponding compound **6-Scheme 7** by thiol ( $R_2SH$ ) and then followed by oxidation, if desired, with an appropriate oxidating agent, such as MCPBA, or  $KMnO_4$ . Suitable oxidation methods for use herein include use of an oxidant such as one or two equivalents of *meta*-chloroperoxybenzoic acid or Oxone<sup>®</sup> to afford either the sulfoxides or sulfones. Oxidation of the sulfides to sulfones may also be effected by  $OsO_4$  and catalytic tertiary amine N-oxide. Other methods for sulfide oxidation include the use of hydrogen peroxide, other peracids, oxygen, ozone, organic peroxides, potassium and zinc permanganate, potassium persulfate, and sodium hypochlorite.

**8-Scheme 7** can be also prepared by heating the *trans* ester **4-Scheme 7** in alcohol in the presence of the corresponding sodium alkoxide. The yield of this reaction was very high for primary alcohols, but longer reaction times were required for secondary alcohols. Sodium alkoxides may be easily prepared from corresponding alcohol and base, such as sodium or sodium hydride.

Reduction of *trans* ester **4-Scheme 7** with  $SmI_2$  gives the reduced analogue **11-Scheme 7**. This reduction can be also done in the presence of other reducing agents such as hydrogen gas, lithium in liquid ammonia, magnesium or sodium borohydride in the appropriate organic solvent such as THF, ethanol or diethyl ether.

Cyclization of the ester **11-Scheme 7** can be done utilizing sodium methoxide in methanol to give reduced analogue **12-Scheme 7**. Other organic bases, such as sodium, sodium ethoxide or TEA can be used in an appropriate organic solvent such as methanol, ethanol or dioxane. The product **12-Scheme 7** can be also obtained by heating ester **11-Scheme 7** to 150 °C in an appropriate organic solvent, such as toluene, xylene or isopropanol.

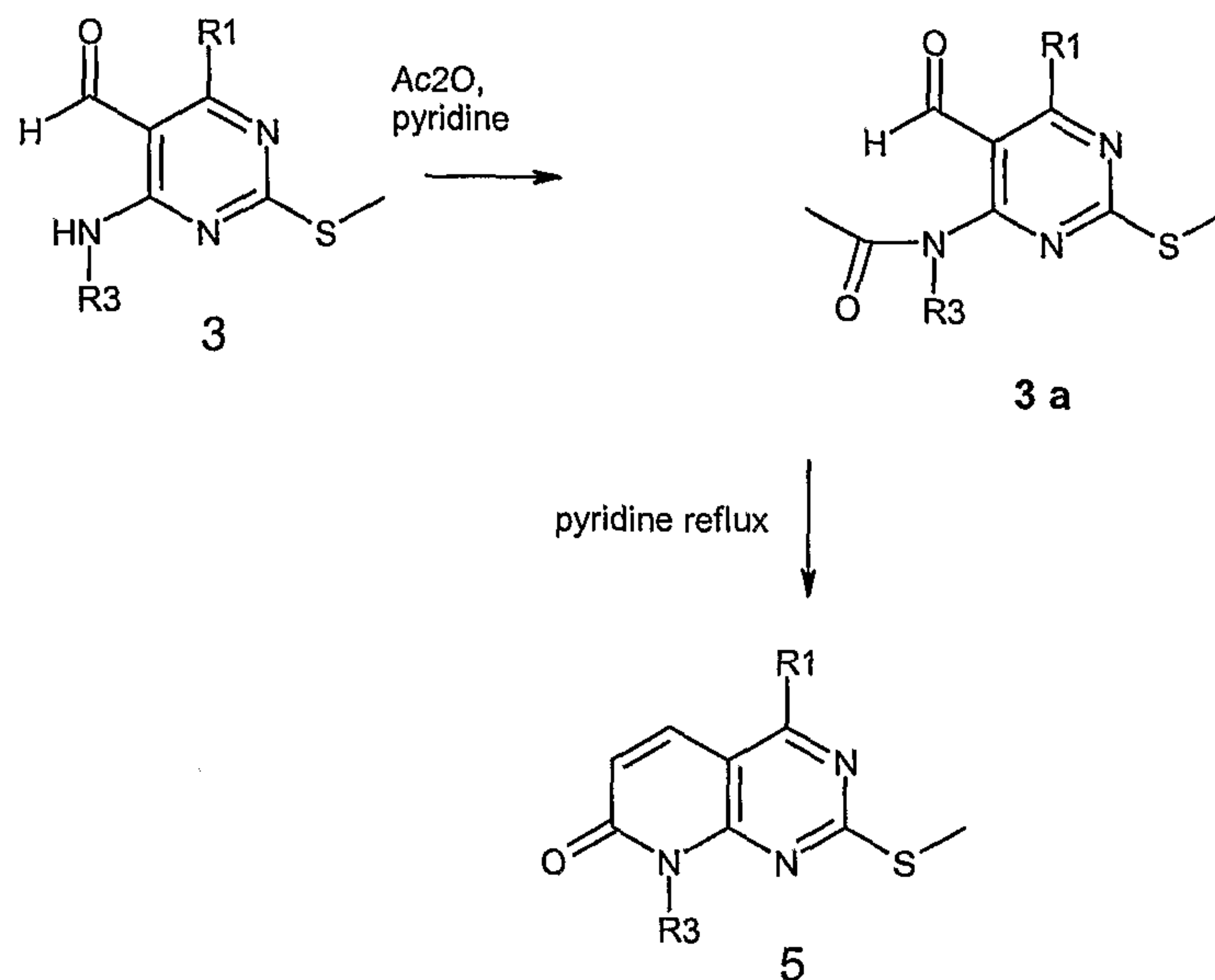
Scheme 7



Additional procedures for producing similar intermediates to those herein, which the skilled artisan may find may be found in WO 99/41253, now US Patent 6,200,977; US 6,153,619; US 6,268,310; US 5,468,751; US 5,474,996; and EP 1 040 831.

An illustration for an alternative preparation of compounds of Formula (VII) is shown in Scheme 8 below.

**Scheme 8**



5

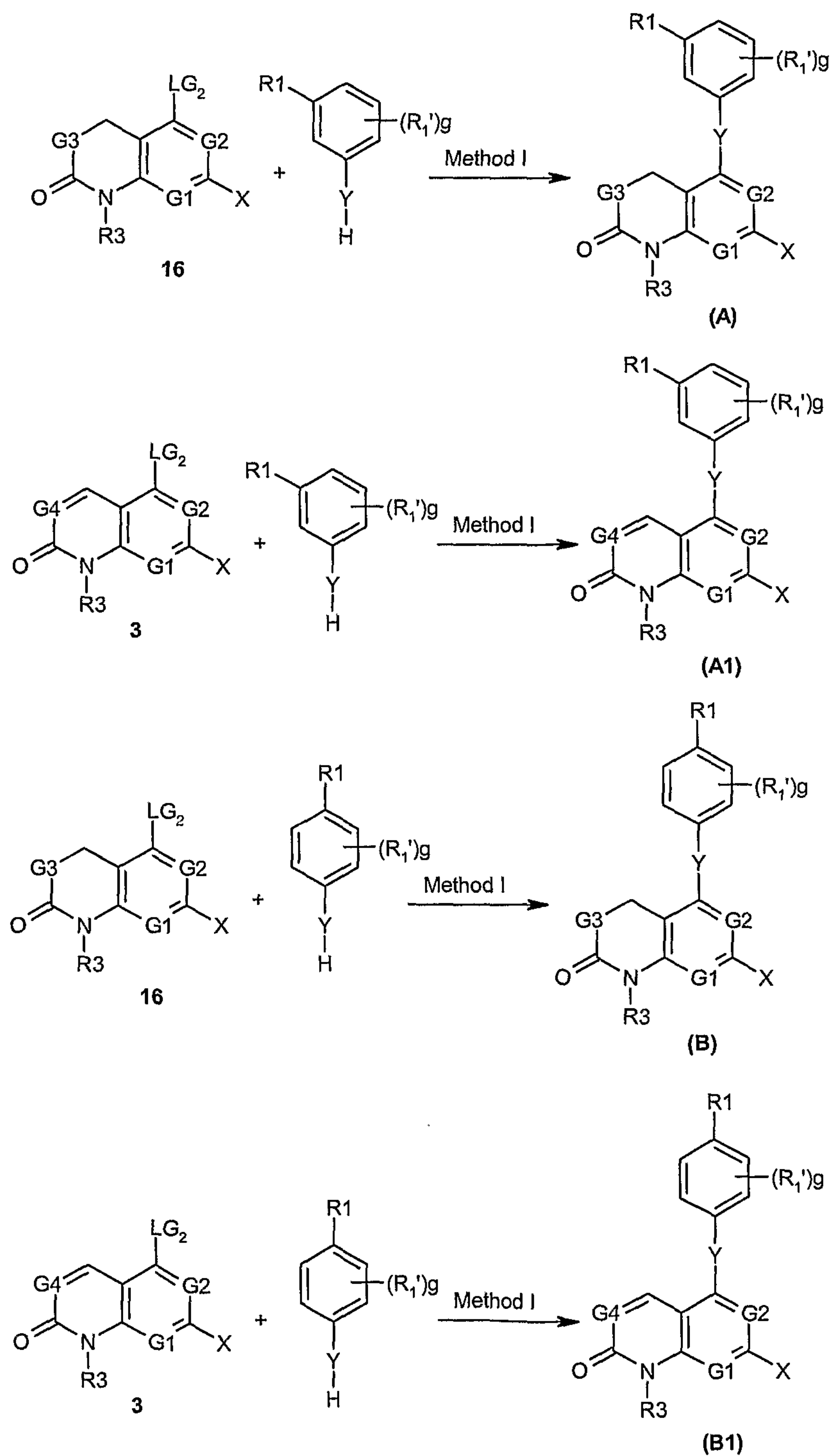
Preparation of compounds with Formula (A), (A1), (B) or (B1) can be achieved from appropriate intermediates in **Scheme 1** through **Scheme 5** using proper synthetic methods known to the scientists with appropriate training in the literature.

10 An example of these types of preparations is demonstrated, but not limited to, in **Scheme 9**. The preparation can be achieved by reacting compound **16** (for A or B) or **3** (for A1 or B1) with another reagent with appropriate structures as shown in **Scheme 9** employing Method I.

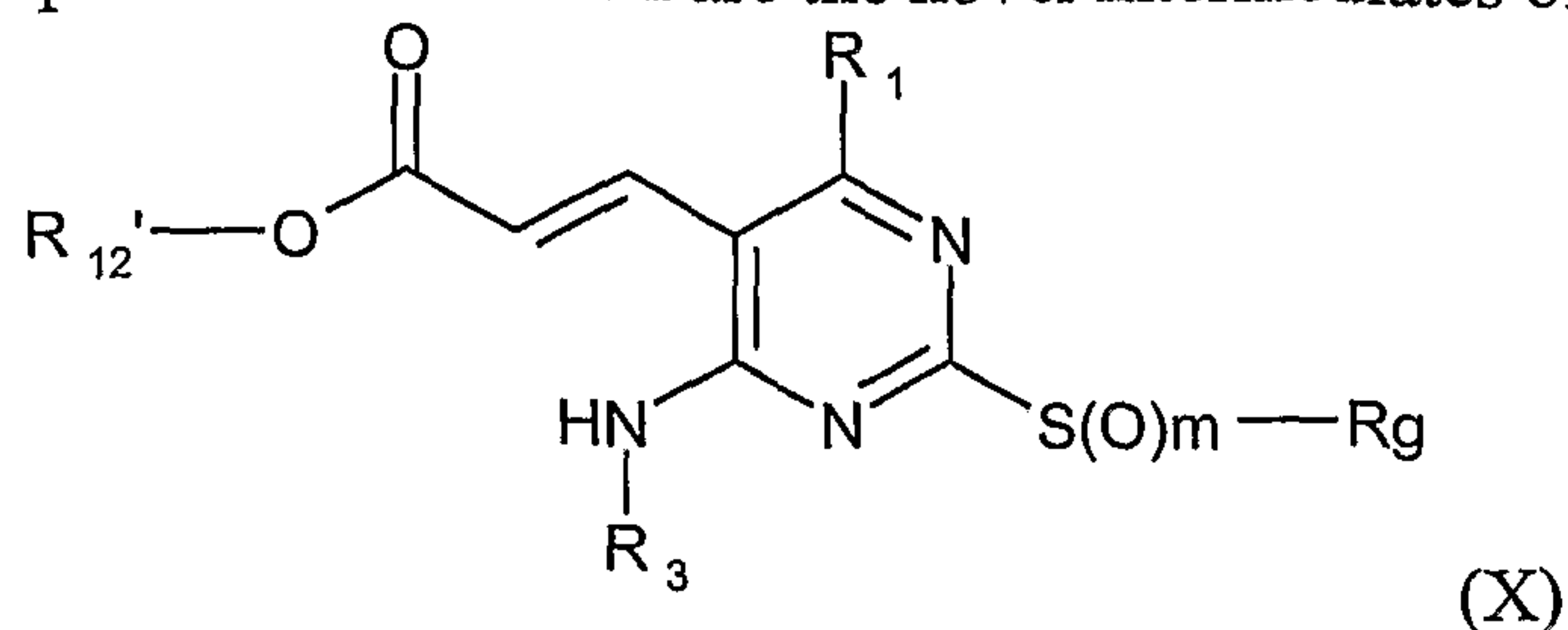
**Method I** is for the substitution of -LG<sub>2</sub> with appropriate compound  
 15 containing the structural unit of -Y-H. This can be achieved by heating the reaction mixtures in appropriate solvents. The heating method can be selected from either a regular oil bath or microwave irradiations. Solvents can be CH<sub>2</sub>Cl<sub>2</sub>, DMSO, DMF, toluene, benzene, CH<sub>3</sub>CN or NMP. The reaction may or may not require the presence of bases. An example of the base can be selected from, but not limited to triethyl  
 20 amine, diisopropyl ethyl amine, NaH, *n*-BuLi, *tert*-BuLi, *tert*-BuOK, Li<sub>2</sub>CO<sub>3</sub>, Cs<sub>2</sub>CO<sub>3</sub> and pyridine. This transformation may also require the presence of catalytic amount of catalysts containing transition metals (e.g., Pd, Cu, Ni, or W). These catalysts include, but not limited to Pd/C, Pd(PPh<sub>3</sub>)<sub>4</sub> and PdCl<sub>2</sub>. Compounds that have Y=S(O)<sub>m</sub> or S(O)<sub>m</sub>C(R<sub>y</sub>)(R<sub>z</sub>) may also be prepared by the oxidation of their  
 25 corresponding compounds with Y=S or SC(R<sub>y</sub>)(R<sub>z</sub>). Suitable oxidation methods for

use herein include, but not limited to mCPBA, Oxone, OsO<sub>4</sub>, H<sub>2</sub>O<sub>2</sub>, potassium and zinc permanganate.

### Scheme 9



Another aspect of the invention are the novel intermediates of the formula (X)



wherein

R<sub>1</sub> is an aryl ring substituted as defined in compounds of Formula (I) and (II)

5 inclusive;

R<sub>3</sub> is an C<sub>1-10</sub> alkyl, C<sub>3-7</sub> cycloalkyl, C<sub>3-7</sub> cycloalkylalkyl, aryl, arylC<sub>1-10</sub> alkyl, heteroaryl, heteroarylC<sub>1-10</sub> alkyl, heterocyclic, or a heterocyclylC<sub>1-10</sub> alkyl moiety, which moieties are optionally substituted;

R<sub>12'</sub> is a C<sub>1-10</sub> alkyl, aryl, heteroaryl, or arylalkyl;

10 m is 0 or an integer having a value of 1 or 2; and

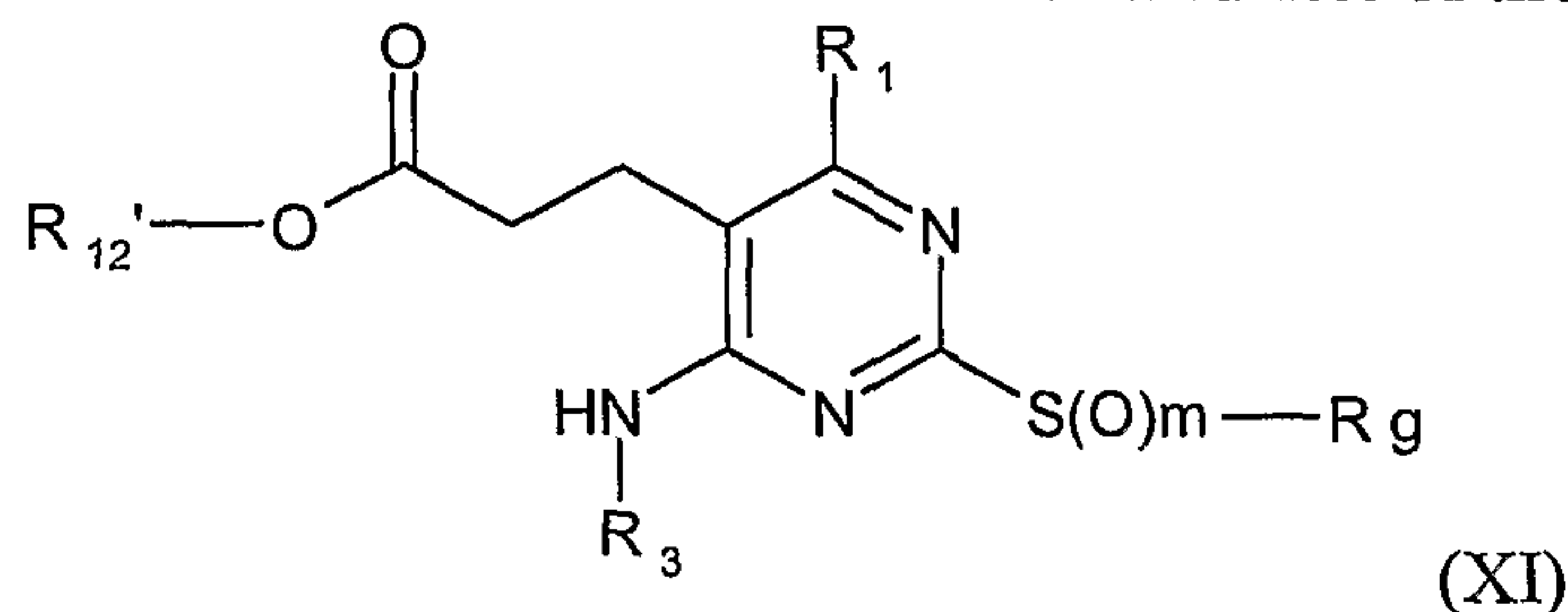
R<sub>g</sub> is a C<sub>1-4</sub> alkyl.

Preferably, R<sub>g</sub> is a C<sub>1-4</sub> alkyl, and more preferably methyl.

Preferably, m is 0 or an integer having a value of 1 or 2. More preferably m is 0 or 2.

15

Another aspect of the invention are the novel intermediates of the formula (XI)

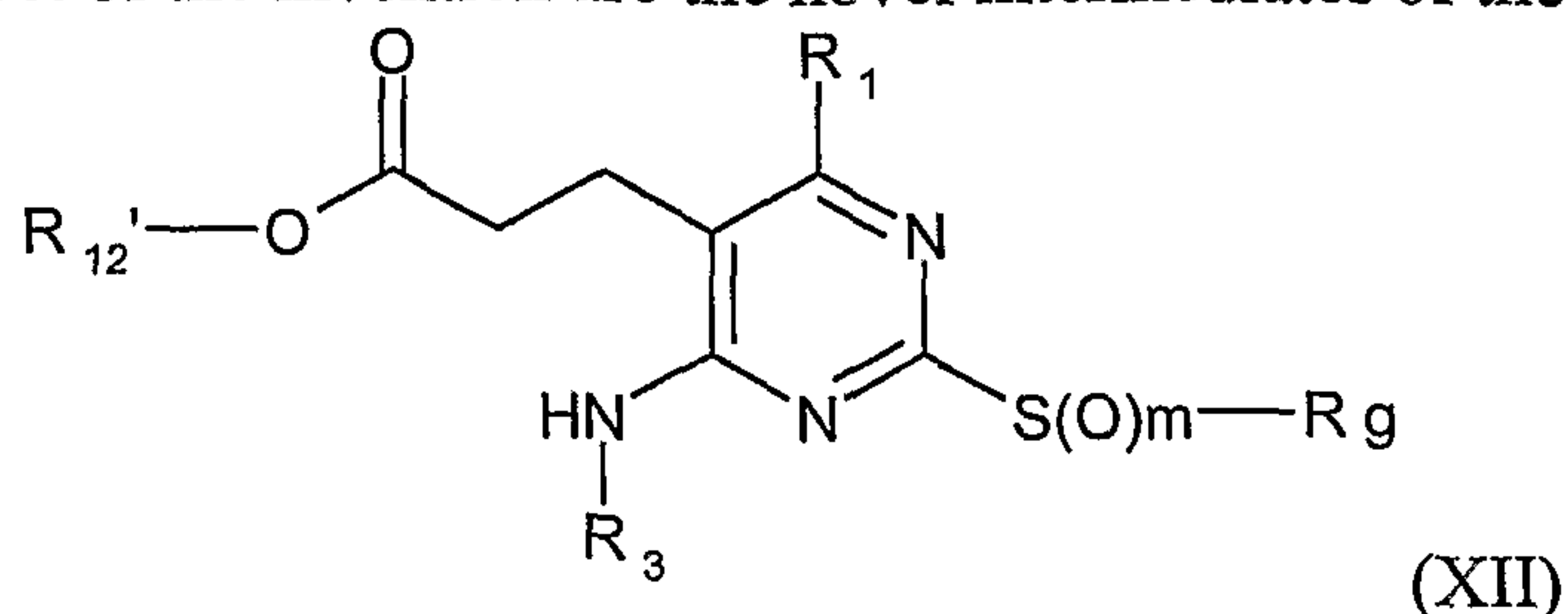


wherein

R<sub>3</sub>, R<sub>12'</sub>, m and R<sub>g</sub> are as defined for Formula (VII) above; and

20 R<sub>1</sub> is a ring substituted as defined in compounds of Formula (III).

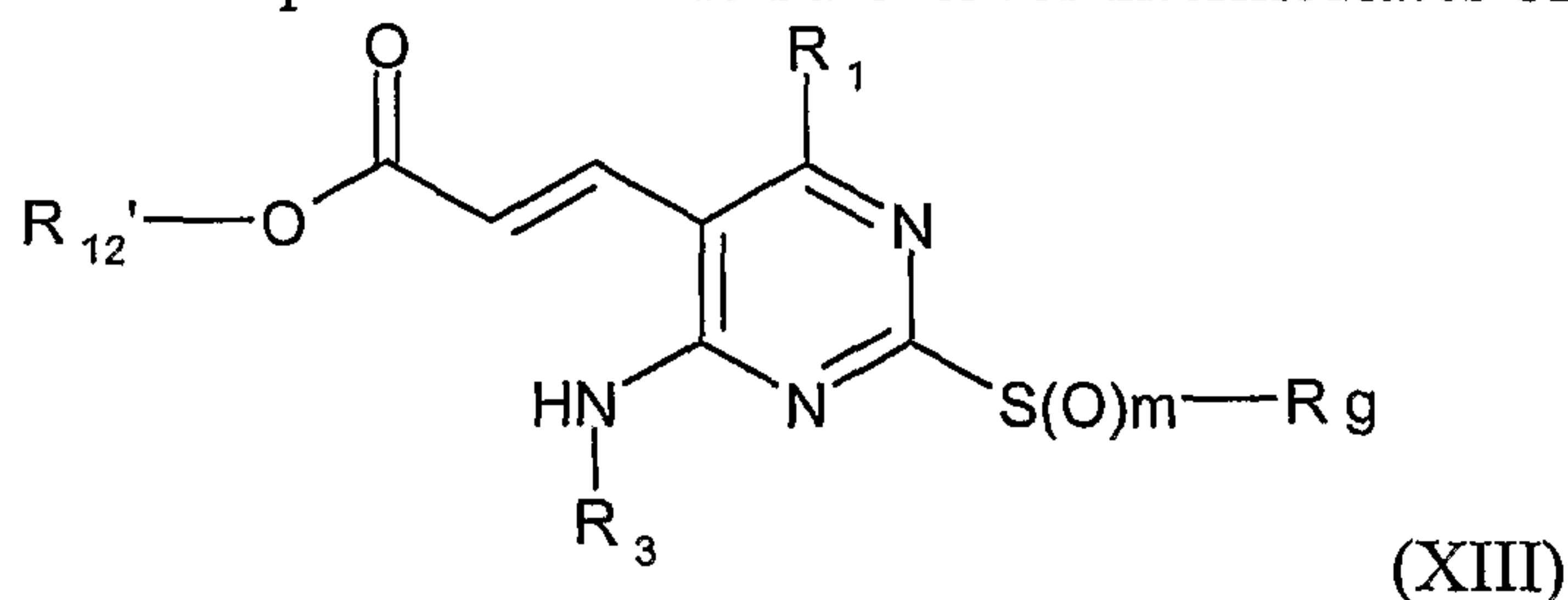
Another aspect of the invention are the novel intermediates of the formula (XII)



$R_3$ ,  $R_{12'}$ ,  $m$  and  $R_g$  are as defined for Formula (VII) above; and  $R_1$  is a ring substituted as defined in compounds of Formula (IV).

5

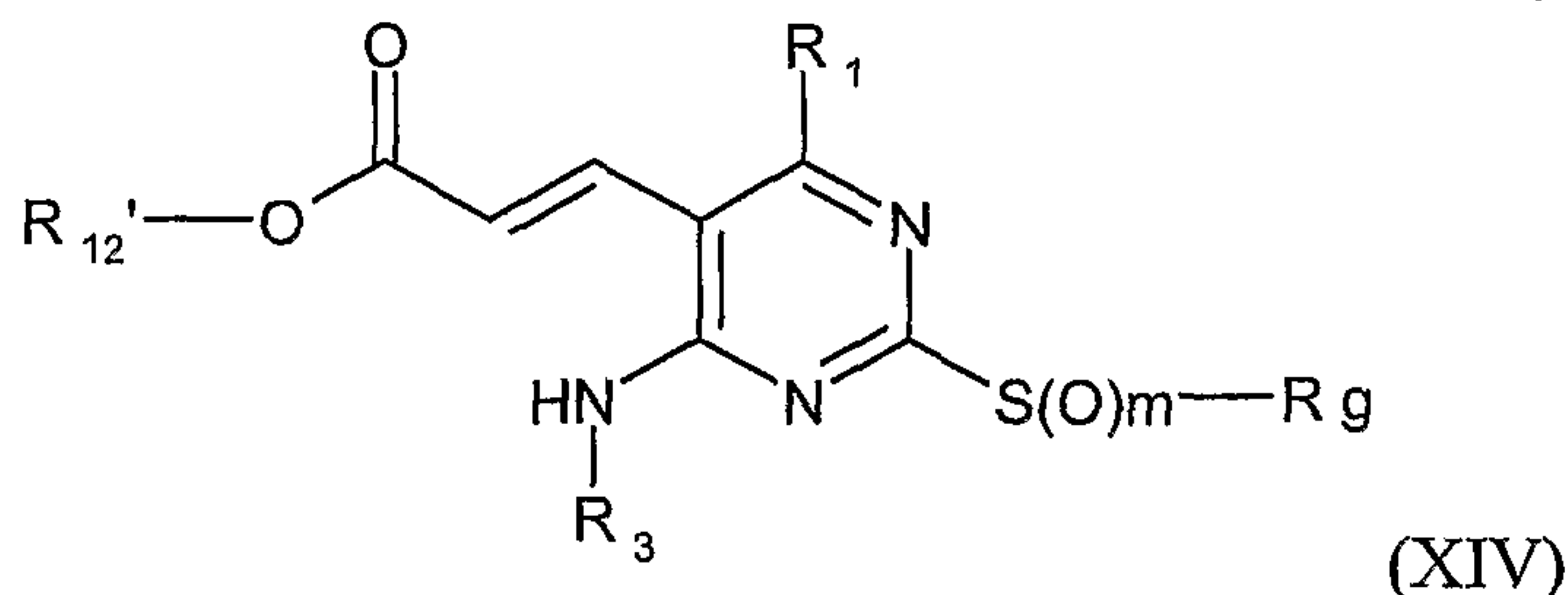
Another aspect of the present invention are novel intermediates of the formula (XIII)



wherein  $R_3$ ,  $R_{12'}$ ,  $m$  and  $R_g$  are as defined for Formula (VII) above; and  $R_1$  is a ring substituted as defined in compounds of Formula (V).

10

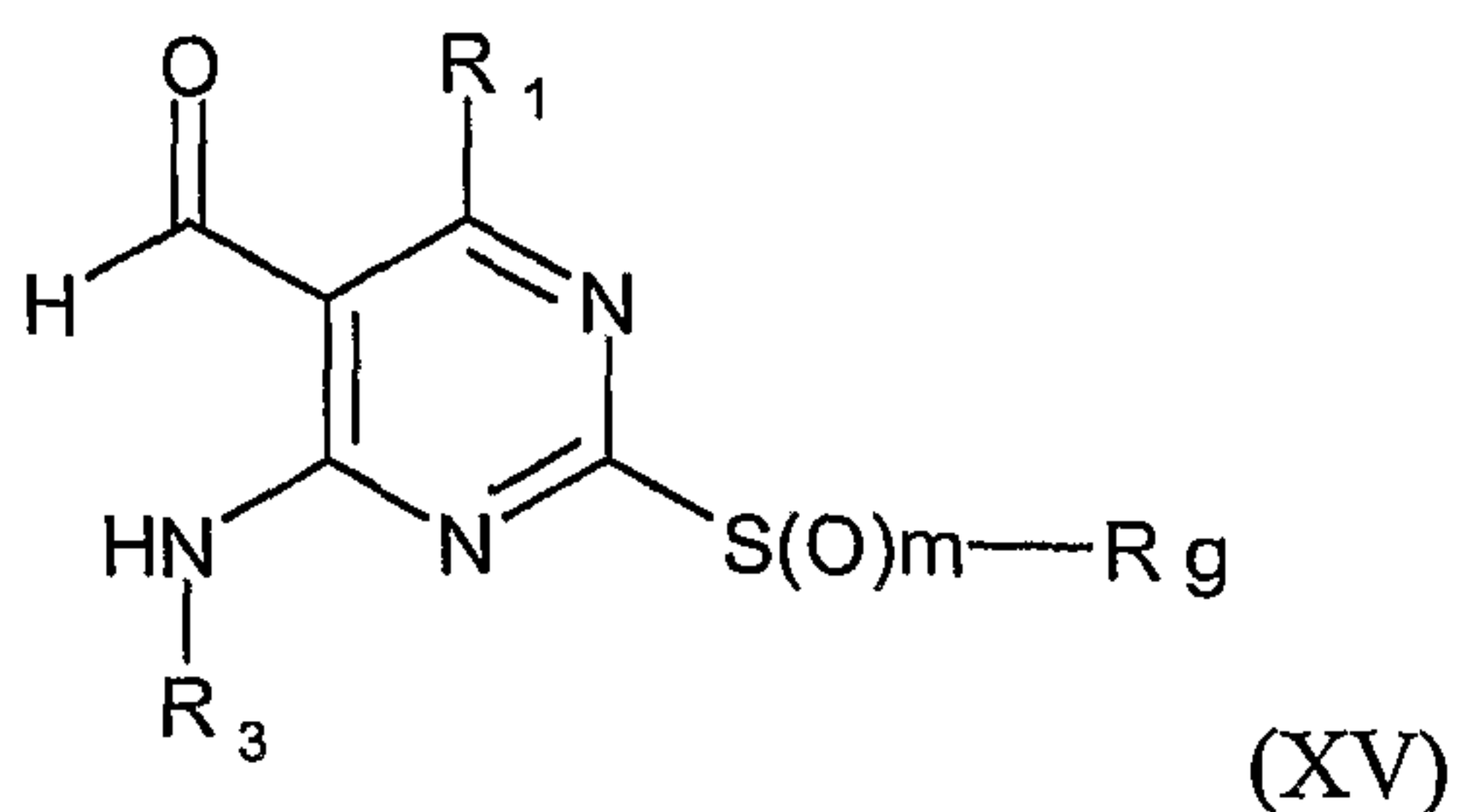
Another aspect of the invention are the novel intermediates of the formula (XIV)



wherein  $R_3$ ,  $R_{12'}$ ,  $m$  and  $R_g$  are as defined for Formula (VII) above; and  $R_1$  is a ring substituted as defined in compounds of Formula (VI).

15

Another aspect of the present invention are the novel intermediates of the formula



wherein

R<sub>1</sub> is a phenyl ring substituted as defined in Formula (I) or (II);

R<sub>3</sub> is hydrogen, C<sub>1-10</sub> alkyl, C<sub>3-7</sub> cycloalkyl, C<sub>3-7</sub> cycloalkylalkyl, aryl, arylC<sub>1-10</sub> alkyl, heteroaryl, heteroarylC<sub>1-10</sub> alkyl, heterocyclic, or a heterocyclC<sub>1-10</sub> alkyl moiety, which moieties are optionally substituted; provided that when R<sub>3</sub> is hydrogen, then R<sub>1</sub> is other than chlorine;

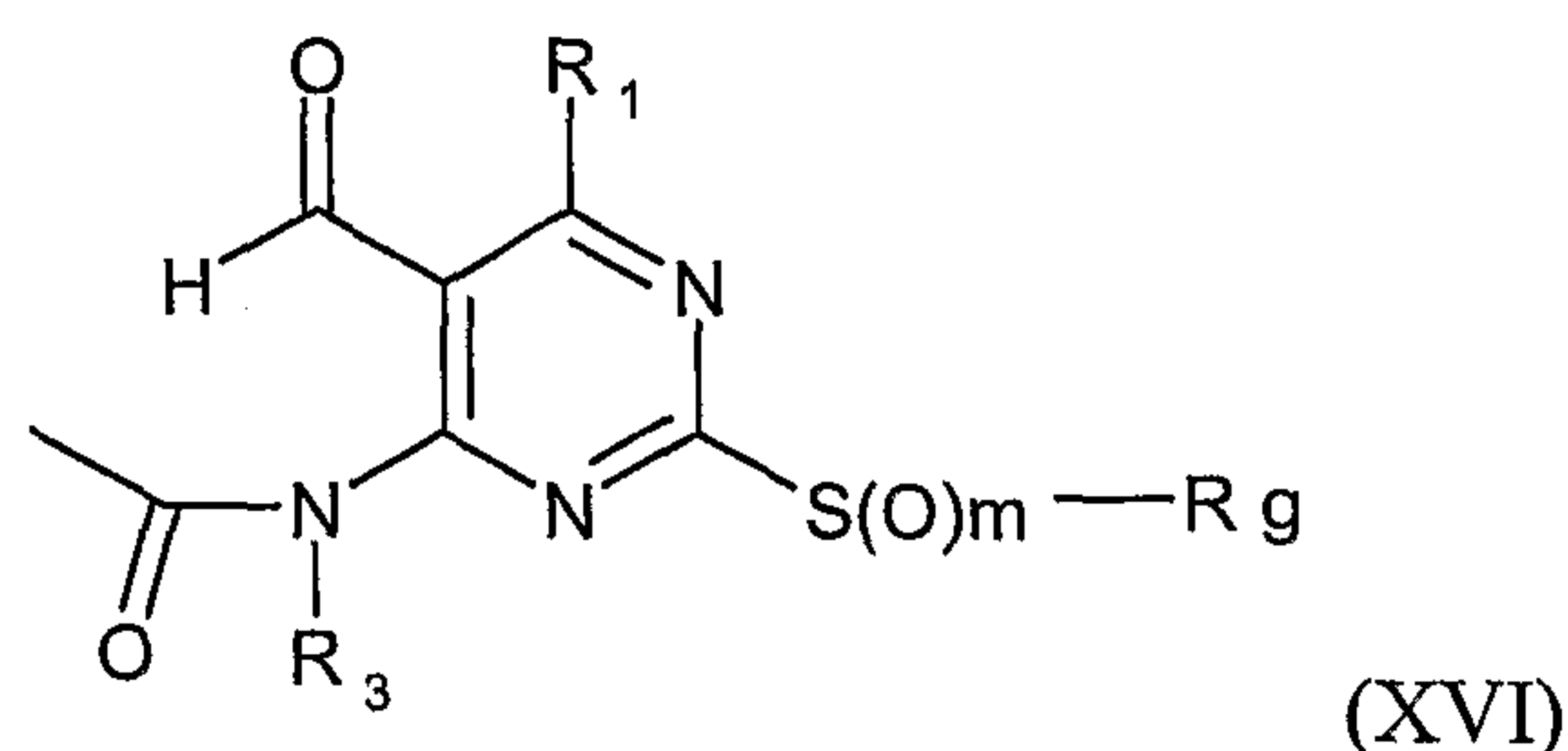
m is 0 or an integer having a value of 1 or 2; and

R<sub>g</sub> is a C<sub>1-4</sub> alkyl.

In one embodiment, R<sub>3</sub> is an optionally substituted C<sub>1-10</sub> alkyl, C<sub>3-7</sub> cycloalkyl, C<sub>3-7</sub> cycloalkylalkyl, or aryl.

In another embodiment the R<sub>3</sub> optional substituents are independently selected from halogen, alkyl, hydroxy, alkoxy, amino, or halosubstituted alkyl.

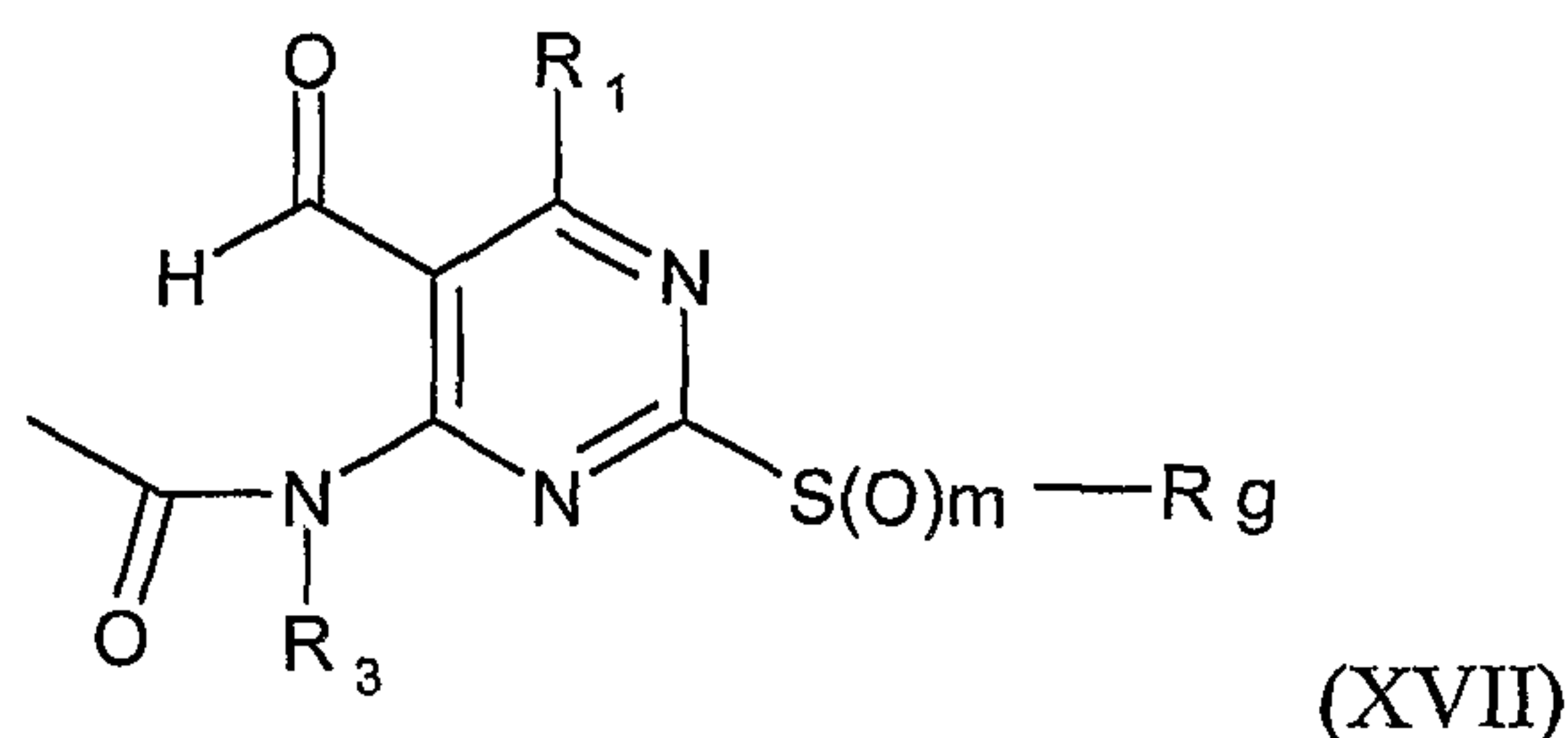
Another aspect of the invention are the novel intermediates of Formula (XVI)



wherein

R<sub>1</sub> is as defined above for Formula (I) and (II) compounds, and R<sub>3</sub>, R<sub>g</sub>, and m is an optionally substituted aryl or heteroaryl moiety, as defined for Formula (VII) compounds.

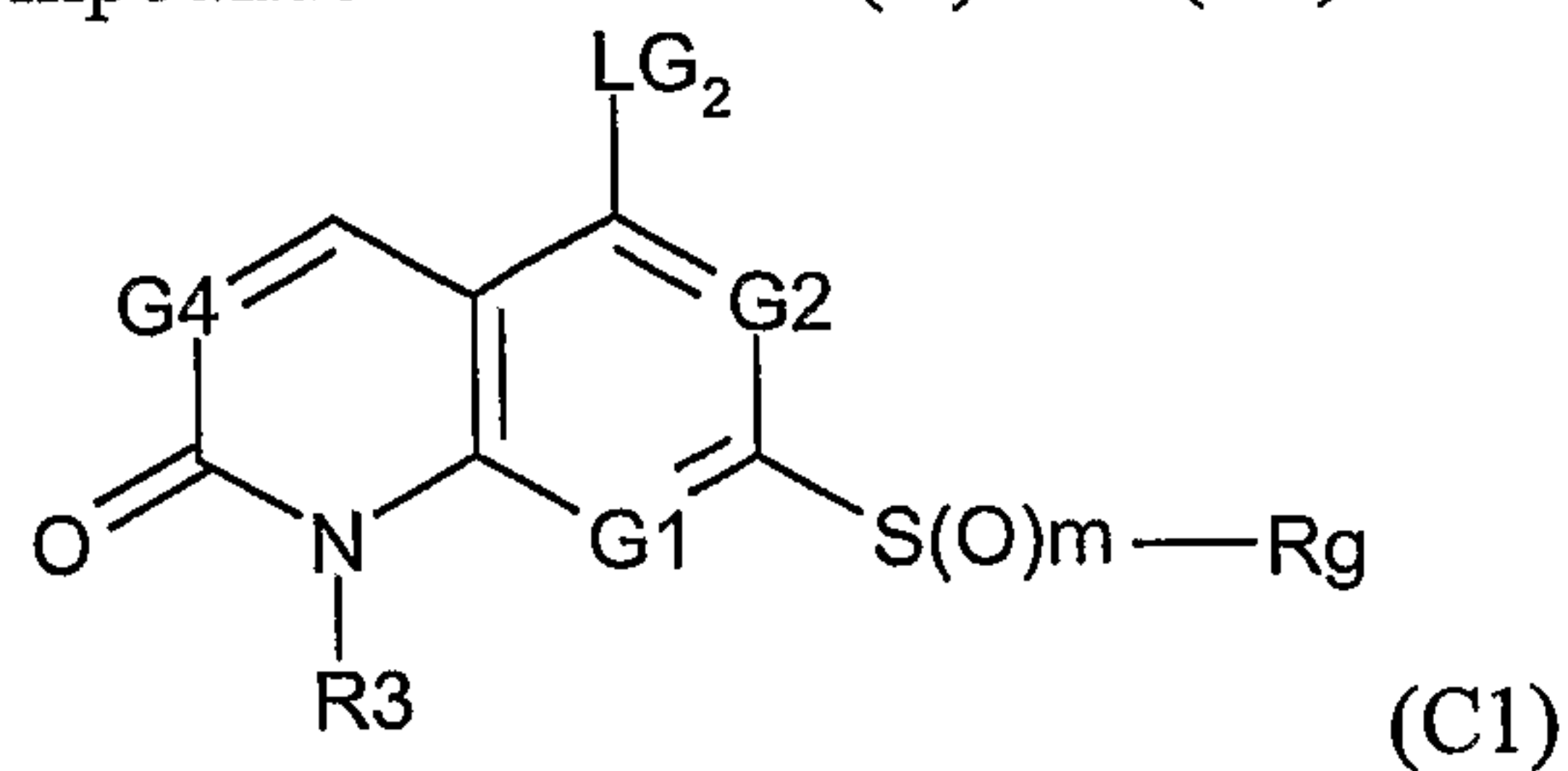
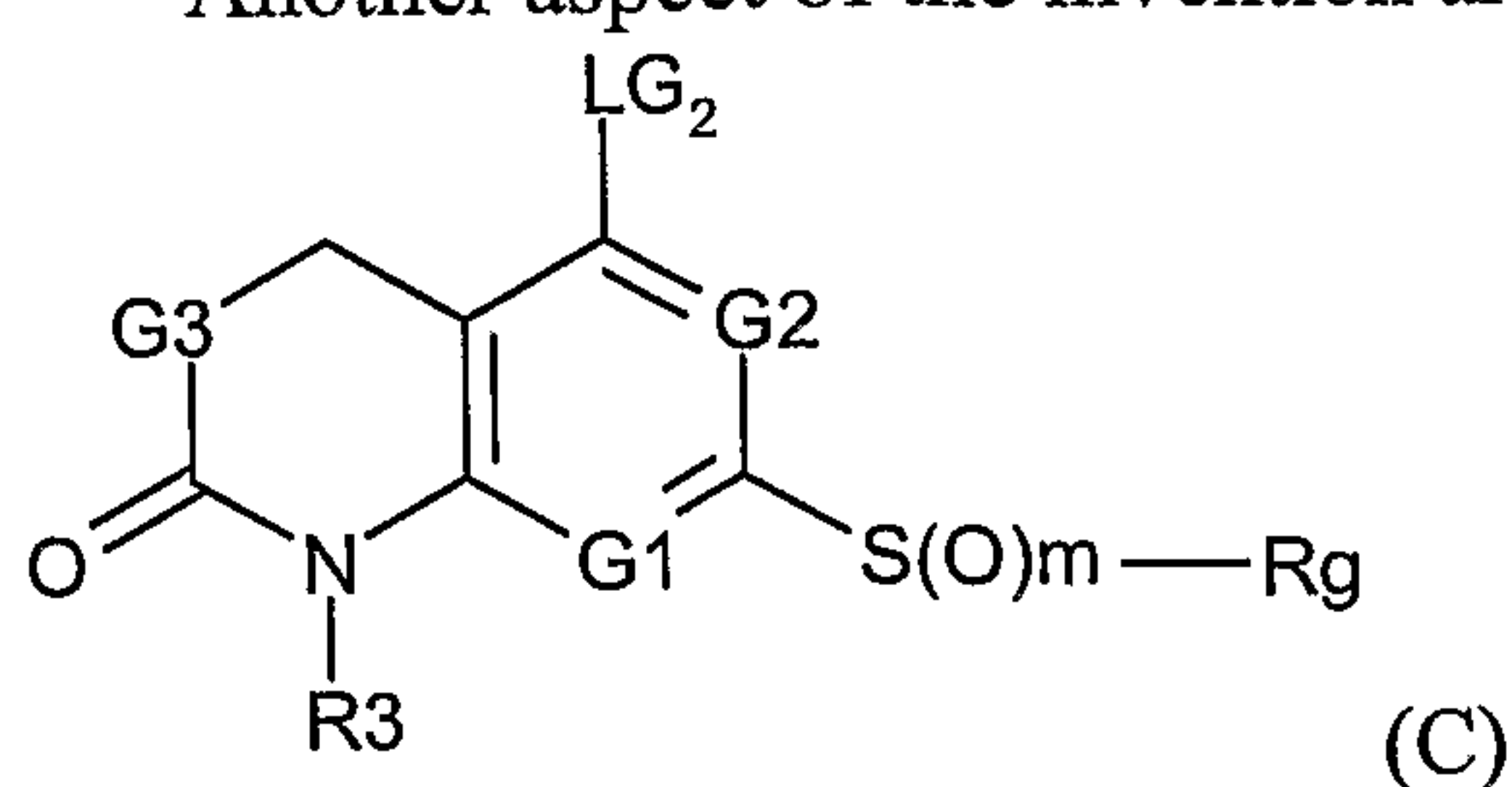
Another aspect of the invention are the novel intermediates of Formula (XVII)



wherein

$R_1$  is defined above for Formula (III) to (VI) compounds, and  $R_3$ ,  $R_g$ , and  $m$  is an optionally substituted aryl or heteroaryl moiety, as defined for Formula (VII) compounds.

5 Another aspect of the invention are compounds of Formula (C) and (C1):



wherein,

$G_1$ ,  $G_2$ ,  $G_3$ , and  $G_4$  are as described for Formula (I) and (Ia) herein;

$m$  is 0 or an integer having a value of 1 or 2;

10  $R_g$  is a  $C_{1-10}$ alkyl;

$LG_2$  is chlorine, bromine, iodine, or  $O-S(O)_2CF_3$ ;

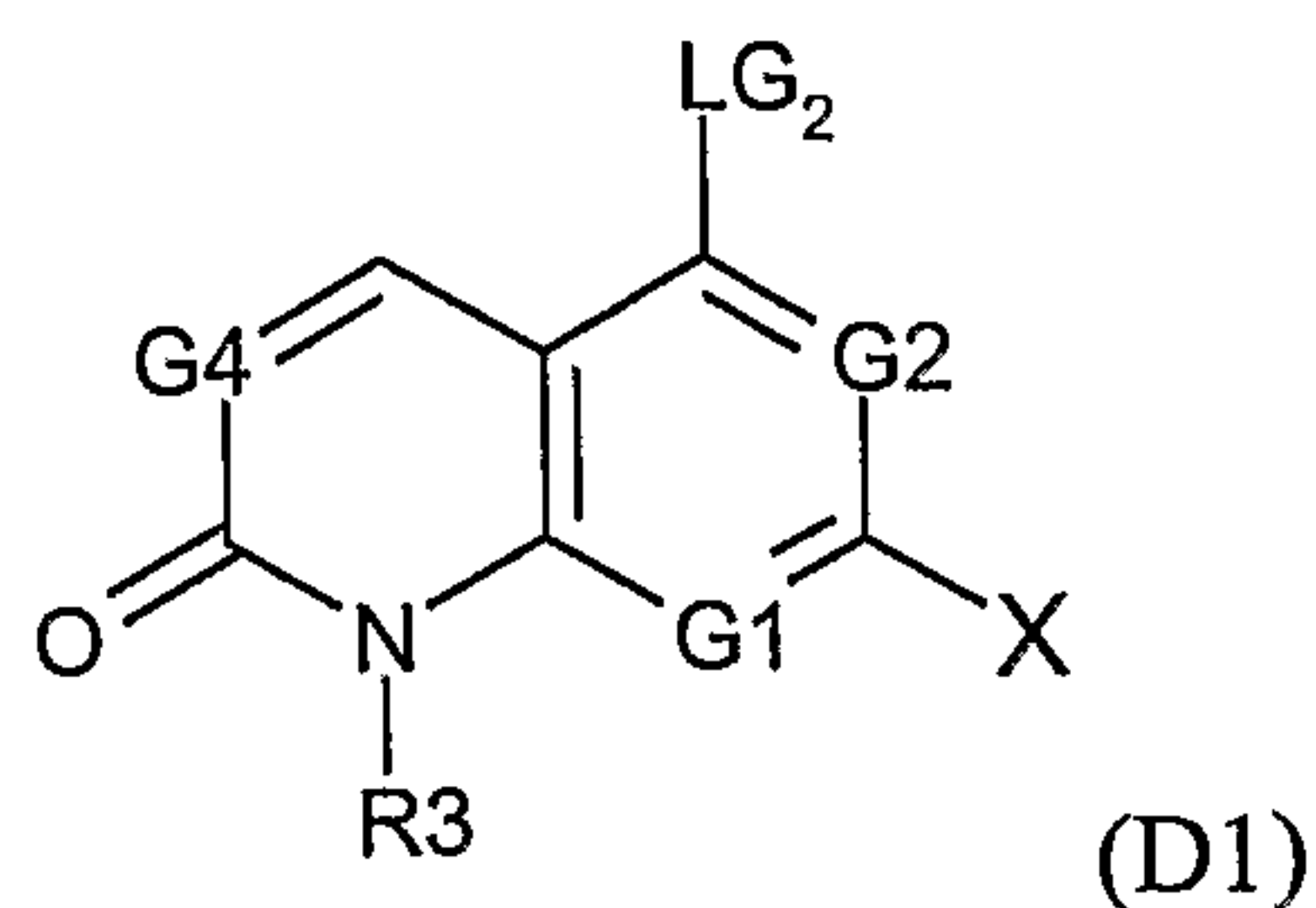
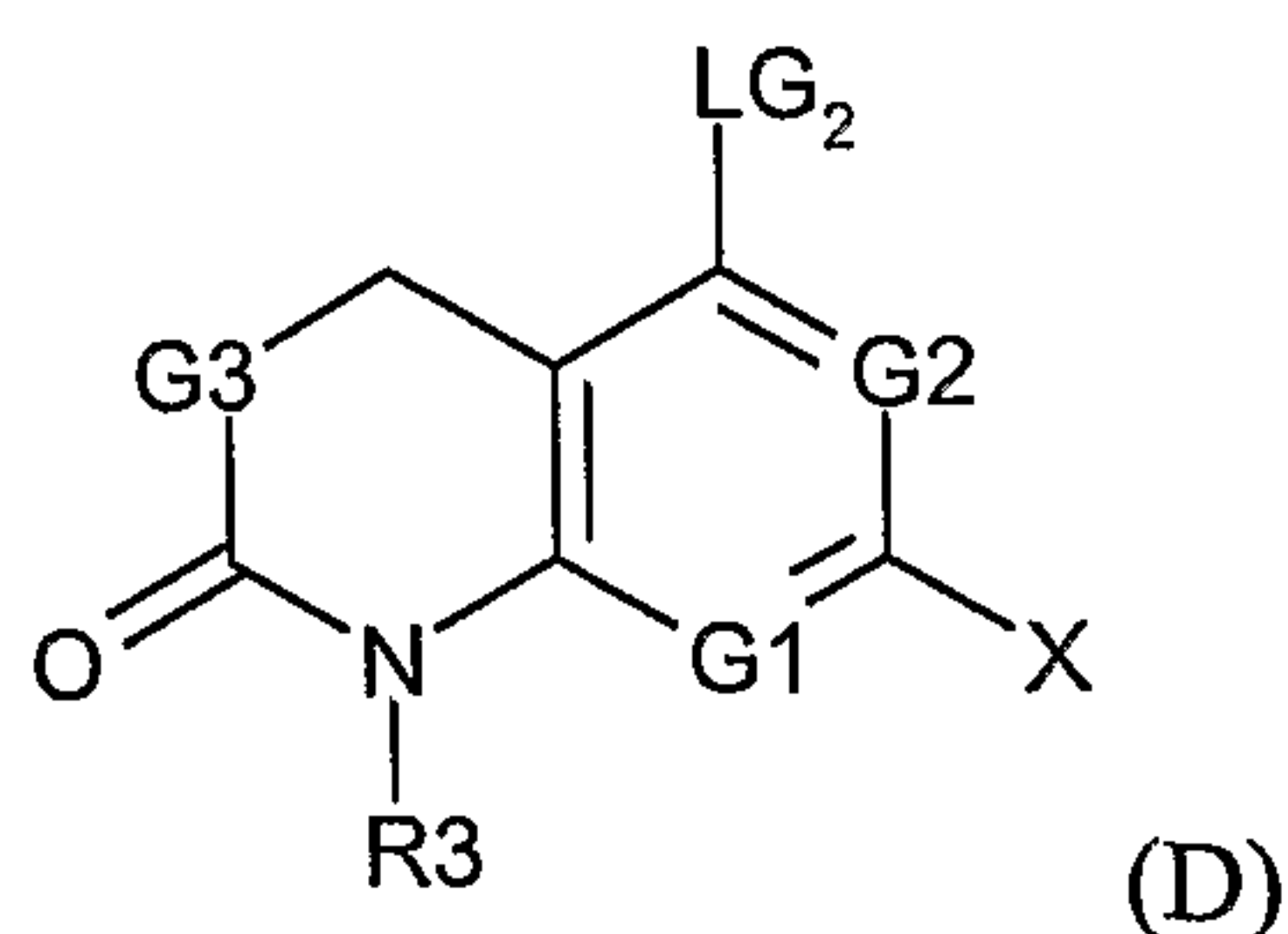
$R_3$  is a  $C_{1-10}$  alkyl,  $C_{3-7}$  cycloalkyl,  $C_{3-7}$  cycloalkyl  $C_{1-10}$  alkyl, aryl, aryl  $C_{1-10}$  alkyl, heteroaryl, heteroaryl  $C_{1-10}$  alkyl, heterocyclic or a heterocyclyl  $C_{1-10}$  alkyl moiety, and wherein each of these moieties may be optionally substituted, and is

15 as defined for compound of Formula (I) and (Ia) herein.

In one embodiment,  $R_g$  is methyl. In another embodiment,  $m$  is 0 or 1.

Another aspect of the invention are compounds of Formula (D) and (D1) represented by the structure:

20



wherein,

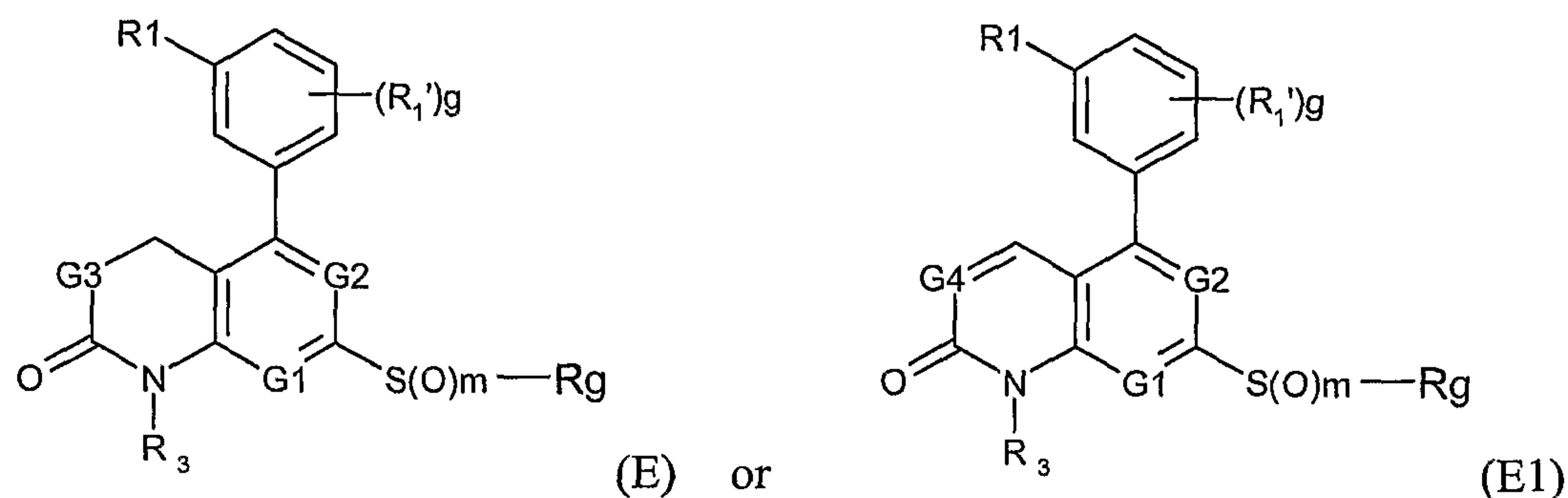
$G_1$ ,  $G_2$ ,  $G_3$ ,  $G_4$  and  $X$  are as described for compounds Formula (I) and (Ia) herein;

25  $LG_2$  is chlorine, bromine, iodine, or  $O-S(O)_2CF_3$ ;

$R_3$  is a  $C_{1-10}$  alkyl,  $C_{3-7}$  cycloalkyl,  $C_{3-7}$  cycloalkyl  $C_{1-10}$  alkyl, aryl, aryl  $C_{1-10}$  alkyl, heteroaryl, heteroaryl  $C_{1-10}$  alkyl, heterocyclic or a heterocyclyl  $C_{1-10}$  alkyl

moiety, and wherein each of these moieties may be optionally substituted (and are as defined for compounds of Formula (I) and (Ia) herein).

Another aspect of the invention compounds of Formula (E) and (E1)  
5 represented by the structure:



wherein,

10 G<sub>1</sub>, G<sub>2</sub>, G<sub>3</sub>, G<sub>4</sub>, R<sub>1</sub> and (R<sub>1</sub>)<sub>g</sub> are as described for compounds of Formula (I) and (Ia) herein;

m is 0 or an integer having a value of 1 or 2;

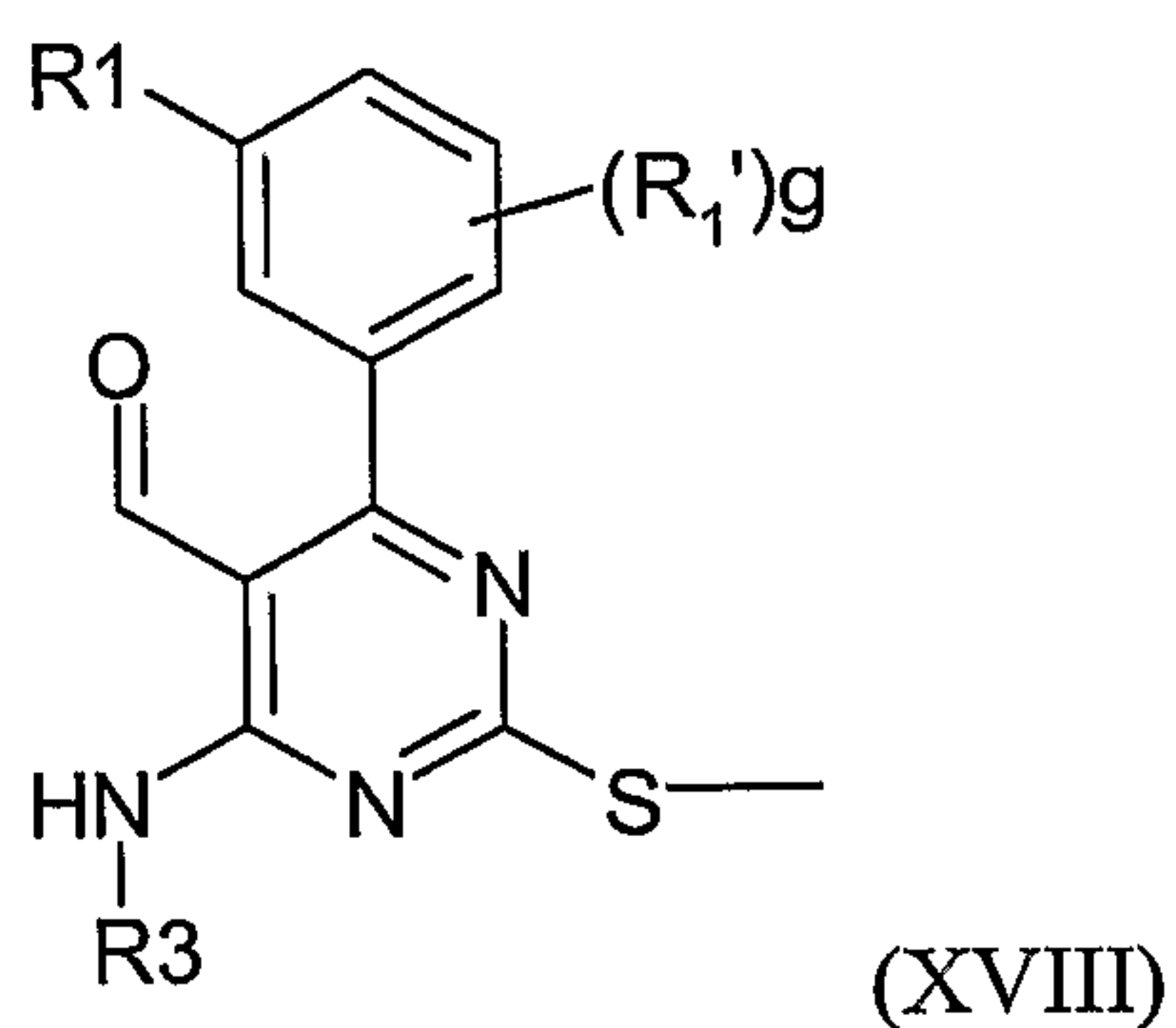
R<sub>g</sub> is a C<sub>1-10</sub>alkyl;

LG<sub>2</sub> is chlorine, bromine, iodine, or O-S(O)<sub>2</sub>CF<sub>3</sub>;

15 R<sub>3</sub> is a C<sub>1-10</sub> alkyl, C<sub>3-7</sub> cycloalkyl, C<sub>3-7</sub> cycloalkyl C<sub>1-10</sub> alkyl, aryl, aryl C<sub>1-10</sub> alkyl, heteroaryl, heteroarylC<sub>1-10</sub> alkyl, heterocyclic or a heterocyclC<sub>1-10</sub> alkyl moiety, and wherein each of these moieties may be optionally substituted (as defined for compounds of Formula (I) and (Ia) herein).

20 It is also recognized that a similar set of Formulas (F) and (F1) are contemplated when the R<sub>1</sub> moiety is substituted in the 3-position of the phenyl ring, as shown in compounds of Formula (II) and (IIa). Similar intermediates are also contemplated for the remaining Formulas herein wherein the C4 position of the pharmacophore is substituted with the various heteroaryl rings, e.g. G<sub>5</sub>/G<sub>6</sub>, etc. of the  
25 formulas described herein as Formula (III) and (IIIa), (IV) and (IVa), etc.

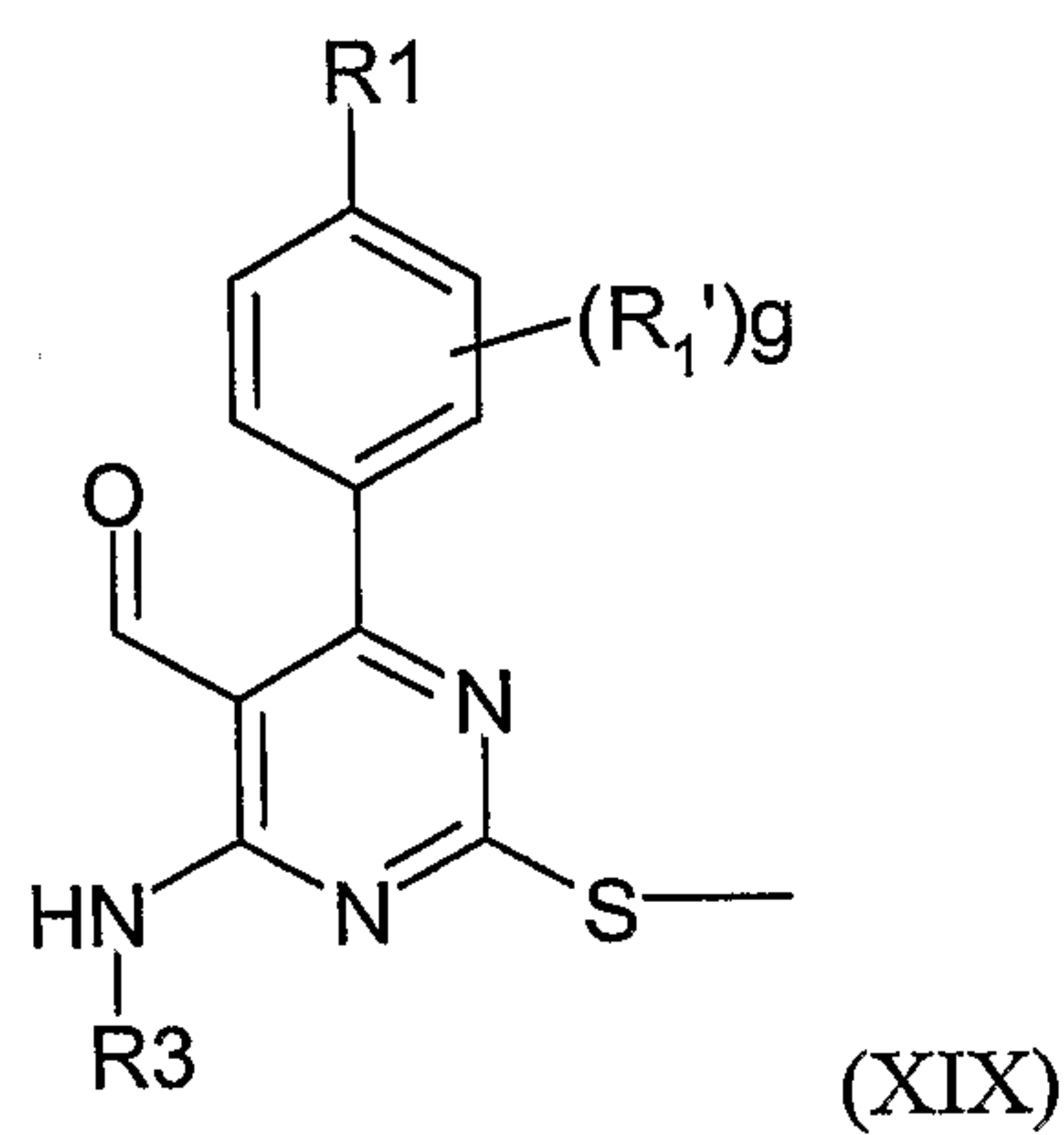
Another aspect of the invention are compounds of Formula (XVIII):



wherein

- 5      $R_1$ ,  $R_1'$ ,  $g$ , and  $R_3$  are as defined for Formula (I) herein.

Another aspect of the invention are compounds of Formula (XIX):



10     wherein

- $R_1$ ,  $R_1'$ ,  $g$ , and  $R_3$  are as defined for Formula (II) herein.

WO 2006/104915

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## SYNTHETIC EXAMPLES

The invention will now be described by reference to the following examples which are merely illustrative and are not to be construed as a limitation of the scope of the present invention. All temperatures are given in degrees centigrade, all solvents are highest available purity and all reactions run under anhydrous conditions in an Ar atmosphere where necessary.

## List of Abbreviations

|                                                                                                    |                                                                                             |
|----------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------|
| EDC: 1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride                                   | dppf: 1,1'-Bis(diphenylphosphino)ferrocene                                                  |
| DMAP: 4-(Dimethylamino)pyridine                                                                    | DMSO: Dimethylsulfoxide                                                                     |
| m-CPBA: 3-Chlorobenzene-carboxyperoxy acid                                                         | EtOAc: Ethyl acetate                                                                        |
| HPLC: High Pressure Liquid Chromatography                                                          | DIPEA or DIEA: <i>N,N</i> -Diisopropylethylamine                                            |
| DCM: Dichloromethane                                                                               | SPE: Solid phase extraction                                                                 |
| TFA: Trifluoroacetic anhydride                                                                     | MDAP: Mass directed auto preparation                                                        |
| HATU: <i>O</i> -(7-Azabenzotriazol-1-yl)- <i>N,N,N',N'</i> -tetramethyluronium hexafluorophosphate | HBTU: <i>O</i> -Benzotriazol-1-yl- <i>N,N,N',N'</i> -tetramethyluronium hexafluorophosphate |
| NIS: <i>N</i> -Iodosuccinimide                                                                     | HOBT: 1-Hydroxybenzotriazole hydrate                                                        |
| DMF: <i>N,N</i> -Dimethylformamide                                                                 | THF: Tetrahydrofuran                                                                        |
| IPA: isopropyl alcohol                                                                             | M: molar                                                                                    |
| DSC: differential scanning calorimetry                                                             | mmol: millimoles                                                                            |
| mL: milliliters                                                                                    | aq: aqueous                                                                                 |
| mg: milligrams                                                                                     | eq: equivalents                                                                             |
| rt: room temperature                                                                               | mp: melting point                                                                           |
| min: minutes                                                                                       | g: grams                                                                                    |
| L: liters                                                                                          | h: hours                                                                                    |
| mol: moles                                                                                         | satd: saturated                                                                             |
| NMP = 1-methyl-2-pyrrolidinone                                                                     | mEq: miliequivalents                                                                        |

Other abbreviations as used herein are described in the ACS Style Guide (American Chemical Society, Washington, DC, 1986).

**LC-MS Experimental Conditions:*****Liquid Chromatograph***

System: Shimadzu LC system with SCL-10A Controller and dual UV detector

Autosampler: Leap CTC with a Valco six port injector

5 Column: Aquasil/Aquasil (C18 40x1 mm)

Inj. Vol.(uL): 2.0

Solvent A: H<sub>2</sub>O, 0.02% TFA

Solvent B: MeCN, 0.018% TFA

Gradient: linear

10 Channel A: UV 214 nm

Channel B: ELS

| Step | Time (min) | Dura.(min) | Flow (μL/min) | Sol.A | Sol.B |
|------|------------|------------|---------------|-------|-------|
| 0    | 0.00       | 0.00       | 300.00        | 95.00 | 5.00  |
| 1    | 0.00       | 0.01       | 300.00        | 95.00 | 5.00  |
| 15 2 | 0.01       | 3.20       | 300.00        | 10.00 | 90.00 |
| 3    | 3.21       | 1.00       | 300.00        | 10.00 | 90.00 |
| 4    | 4.21       | 0.10       | 300.00        | 95.00 | 5.00  |
| 5    | 4.31       | 0.40       | 300.00        | 95.00 | 5.00  |

20 Mass Spectrometer: PE Sciex Single Quadrupole LC/MS API-150

Polarity: Positive

Acquisition mode: Profile

**General Procedures**

25 Nuclear magnetic resonance spectra were recorded at 400 MHz using on a Bruker AC 400 spectrometer. CDCl<sub>3</sub> is deuteriochloroform, DMSO-d<sub>6</sub> is hexadeuteriodimethylsulfoxide, and CD<sub>3</sub>OD (or MeOD) is tetradeuteriomethanol. Chemical shifts are reported in parts per million (δ) downfield from the internal standard tetramethylsilane (TMS) or the NMR solvent. Abbreviations for NMR data are as follows: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, dd = doublet of doublets, dt = doublet of triplets, app = apparent, br = broad. J indicates the NMR coupling constant measured in Hertz. Mass spectra were taken on a instruments, using electrospray (ES) ionization techniques. All temperatures are reported in degrees Celsius.

35 Analtech Silica Gel GF and E. Merck Silica Gel 60 F-254 thin layer plates were used for thin layer chromatography. Both flash and gravity chromatography were carried out on E. Merck Kieselgel 60 (230-400 mesh) silica gel. Preparative hplc

were performed using a Gilson Preparative System using a Luna 5u C18(2) 100A reverse phase column eluting with a 10-80 gradient (0.1%TFA in acetonitrile/0.1% aqueous TFA) or a 10-80 gradient (acetonitrile/water). The CombiFlash system used for purification in this application was purchased from Isco, Inc. CombiFlash  
5 purification was carried out using a prepacked SiO<sub>2</sub> column, a detector with UV wavelength at 254nm and mixed solvents.

Heating of reaction mixtures with microwave irradiations was carried out on a Smith Creator (purchased from Personal Chemistry, Forboro/MA, now owned by Biotage), a Emrys Optimizer (purchased from Personal Chemistry) or an Explorer  
10 (provided by CEM Discover, Matthews/NC) microwave.

### General Procedure for EDC Couplings

The acid is dissolved in CHCl<sub>3</sub> and EDC (1.1 equivalents (hereinafter "eq")) is added. The amine (2 eq.) is added dropwise followed by DMAP (cat.) and allowed to stir until the reaction is judged to be complete. The reaction mixture is  
15 washed with water. The aqueous portion is extracted with ethyl acetate. The ethyl acetate portion is washed with brine and combined with the other organic portion, dried (MgSO<sub>4</sub>) and concentrated.

### General Procedure for Sulfide Oxidations

The sulfide is dissolved in CHCl<sub>3</sub> and mCPBA (1.5eq.) is added. The  
20 mixture is allowed to stir for 30 minutes (hereinafter "min") then quenched with NaHCO<sub>3</sub>. The organic portion is washed with brine and dried (MgSO<sub>4</sub>).

### General Procedure for Sulfoxide/Sulfone Displacement

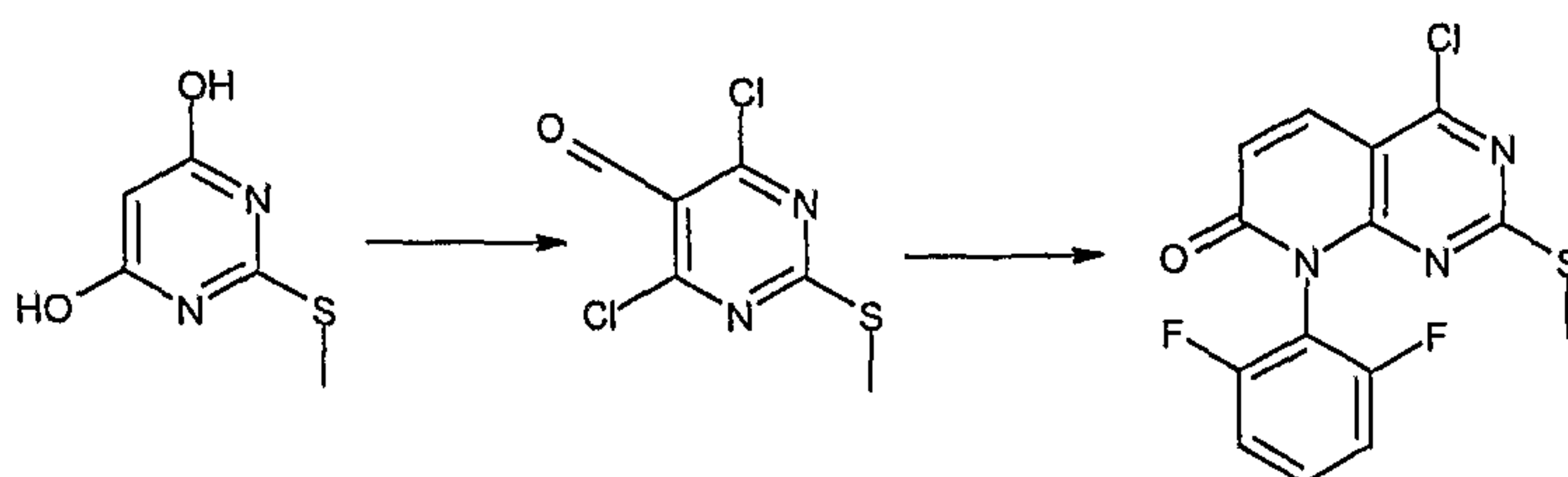
The sulfoxide/sulfone is dissolved in THF and the amine (5 eq.) is added and allowed to stir for 1h. The mixture is concentrated *in vacuo*.  
25

**Example 1**

N-(cyclopropylmethyl)-3-(8-(2,6-difluorophenyl)-2- $\{[2$ -hydroxy-1-(hydroxymethyl)ethyl]amino $\}$ -7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl)-4-methylbenzamide

5

1a) 4-chloro-8-(2,6-difluorophenyl)-2-(methylthio)pyrido[2,3-*d*]pyrimidin-7(8*H*)-one

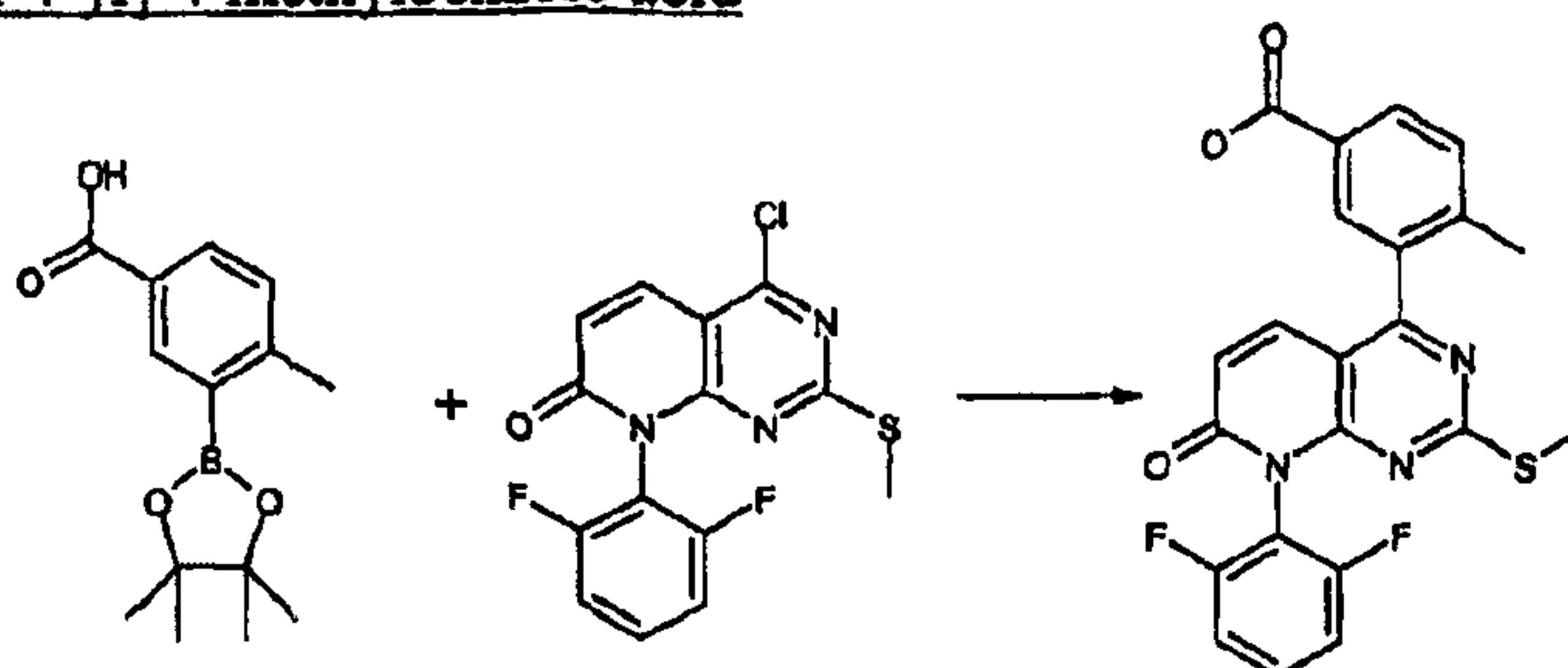


To the solution of phosphorus oxychloride (65 mL, 0.70 mol) in trichloroethylene (46.5 mL) was added DMF (25 mL, 0.32 mol) slowly to keep the temperature between 5 °C to 10 °C. The solution was then warmed up to room temperature before 6-hydroxy-2-(methylthio)-4(1*H*)-pyrimidinone (25 g, 0.16 mol) was added in portions. The resultant reaction mixture was heated at 80 °C overnight followed by concentration under vacuum. The resulting slurry like residue was poured into ice, stirred for 2 hours then filtered to afford the crude product. The crude product was further purified by recrystallization with hexane to afford 4,6-dichloro-2-(methylthio)-5-pyrimidinecarbaldehyde (21.3 g, 61%). <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ 2.66 (s, 3 H), 10.4 (s, 1 H).

To a solution of 4,6-dichloro-2-(methylthio)-5-pyrimidinecarbaldehyde (10.0 g, 44.8 mmol) in THF (250 mL) was added 2,6-difluoroaniline (5.35 mL, 49.3 mmol, 1.1 eq) followed by Et<sub>3</sub>N (12.6 mL, 89.6 mmol, 2 eq). The reaction mixture was heated to 55°C for about 22 h before concentrated. The slurry was re-dissolved in DCM (250 mL) and washed with H<sub>2</sub>O (2 x 100 mL), then concentrated and further washed with acetone (2 x 10 mL) to give 9.87 g (70 %) of pure 4-chloro-6-[(2,6-difluorophenyl)amino]-2-(methylthio)-5-pyrimidinecarbaldehyde. LC-MS *m/z* 316 (M+H)<sup>+</sup>.

A solution of 4-chloro-6-[(2,6-difluorophenyl)amino]-2-(methylthio)-5-pyrimidinecarbaldehyde (200 mg, 0.63 mmol) in DMF (4.0 mL) and acetic anhydride (2.0 mL) was heated with a microwave (160°C) for about 30 minutes. The resultant mixture was then concentrated. Flash chromatography (EtOAc / Hexane, 1 : 5) provided the title compound (109 mg, 51%): LC-MS *m/z* 340 (M+H)<sup>+</sup>.

1b) 3-[8-(2,6-difluorophenyl)-2-(methylthio)-7-oxo-7,8-dihydropyrido[2,3-  
d]pyrimidin-4-yl]-4-methylbenzoic acid

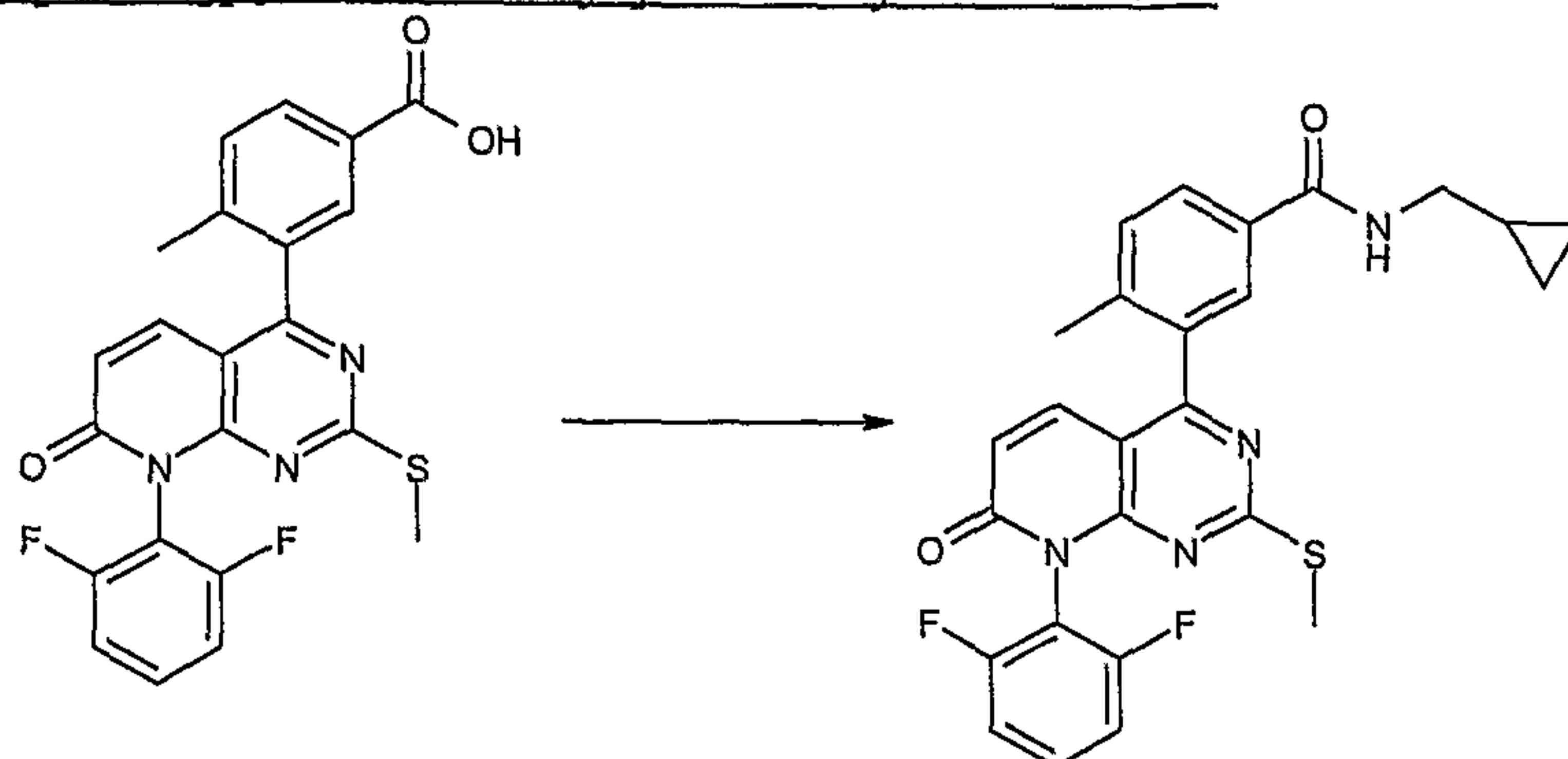


To a stirring solution of 3-iodo-4-methylbenzoic acid (60 g, 0.22 mol, 1 eq)  
 5 in degassed DMF (1400 mL, 23.3 vol.) was charged 4,4,4',4',5,5,5',5'-octamethyl-  
 2,2'-bi-1,3,2-dioxaborolane (81.4 g, 0.32 mol, 1.4 eq) followed by potassium acetate  
 (112 g, 1.14 mole, 5eq) and [1,1'-bis(diphenylphosphino)ferrocene]-  
 dichloropalladium(II) (18.7 g, 0.02 mole, 0.1eq). The resulting mixture was placed  
 under a nitrogen atmosphere and was heated to 80 °C with the exclusion of light  
 10 overnight. The mixture was then concentrated under high vacuum and the residue  
 partitioned between EtOAc and 2M HCl. The mixture was then filtered and the  
 layers separated. The aqueous phase was re-extracted with EtOAc. The combined  
 organics were then washed with brine, dried and evaporated to yield a brown solid  
 that was applied to a silica plug then eluted with 2:1 cyclohexane : ethyl acetate.  
 15 Fractions were then combined and evaporated to yield a brown foam that was  
 triturated with cyclohexane, collected by filtration then dried in *vacuo* to yield 4-  
 methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoic acid.  $\delta$  (CDCl<sub>3</sub>)  
 8.50-8.49 (1H, d), 8.04-8.02 (1H, dd), 7.27-7.25 (1H, d), 2.61 (3H, s), 1.36 (12H, s)

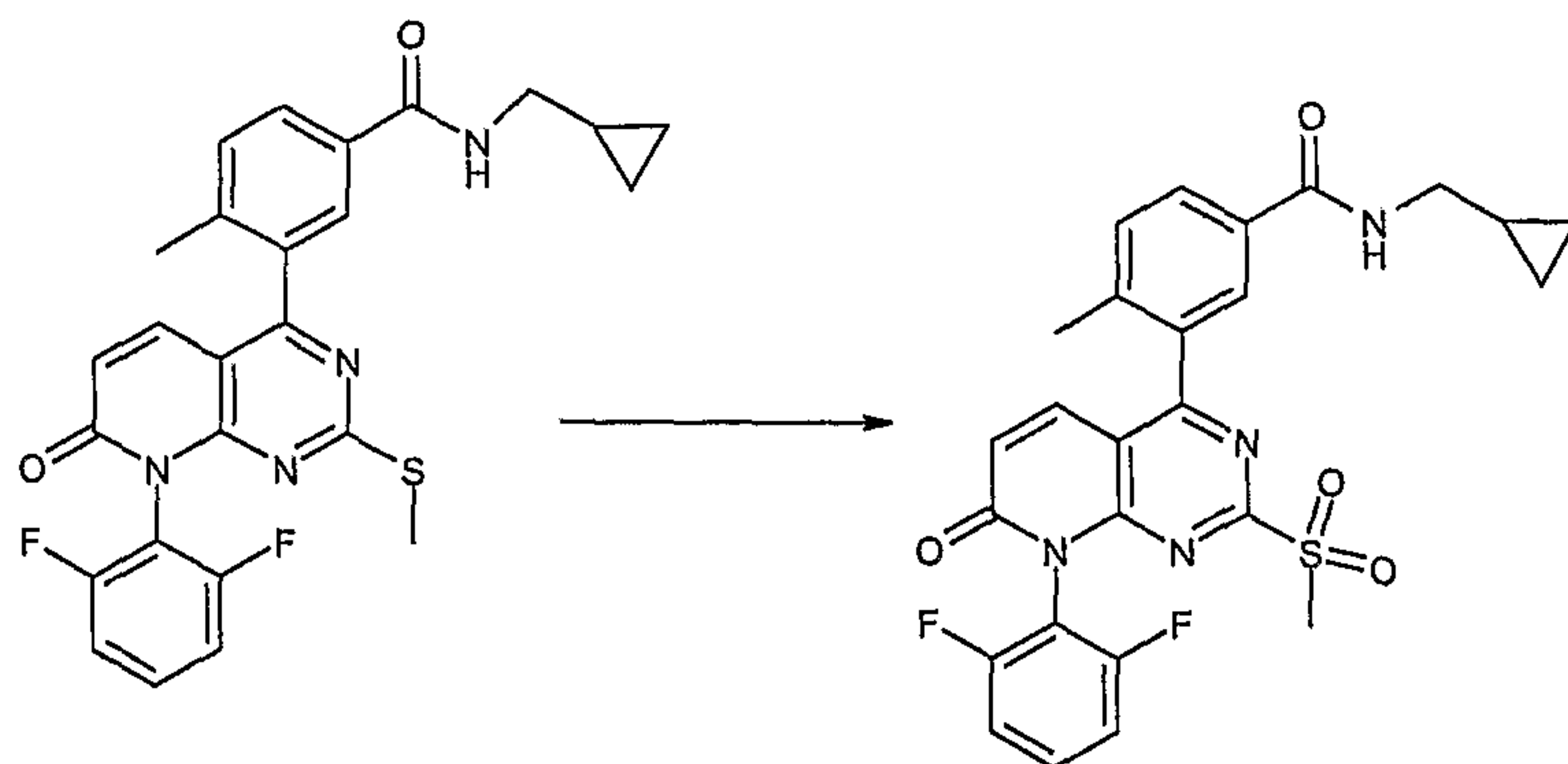
The solution of 4-chloro-8-(2,6-difluorophenyl)-2-(methylthio) pyrido[2,3-  
 20 d]pyrimidin-7(8H)-one (1.70 g, 5.00 mmol) in DME (150 mL) and H<sub>2</sub>O (50 mL), in  
 a pressure flask (500 mL, Chemglass), was added 4-methyl-3-(4,4,5,5-tetramethyl-  
 1,3,2-dioxaborolan-2-yl) benzoic acid (1.97 g, 7.50 mmol) and K<sub>2</sub>CO<sub>3</sub> (4.15 g, 30.0  
 mmol). The resulting mixture was degassed with Argon for 5 minutes, mixed with  
 Pd(PPh<sub>3</sub>)<sub>4</sub> (0.232 g, 0.20 mmol) and heated with a preheated oil bath (160 °C) under  
 25 vigorous stirring for 30 minutes. The reaction mixture was filtered through celite,\*  
 concentrated under vacuum to remove DME. It was then mixed with EtOAc (200  
 mL) and AcOH (2.5 mL), and shaken. The layers were separated. The organic layer  
 was collected, further washed with brine (70 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered,  
 concentrated and purified via a flash chromatography (load column with DCM,  
 30 mobile phase EtOAc/Hexane) to afford the title compound as a white solid 2.15g (98

LC-MS (ES)  $m/z$  440 ( $M + H$ )<sup>+</sup>; <sup>1</sup>H-NMR (MeOD)  $\delta$  2.27 (s, 3 H), 2.31 (s, 3 H), 6.71 (d,  $J = 9.6$  Hz, 1 H), 7.28 (t,  $J = 8.2$  Hz, 2 H), 7.57 (d,  $J = 8.4$  Hz, 1 H), 7.64 (m, 2 H), 8.00 (d,  $J = 1.6$  Hz, 1 H), 8.14 (dd,  $J_1 = 7.6$  Hz,  $J_2 = 1.6$  Hz, 1 H).

1c) *N*-(cyclopropylmethyl)-3-[8-(2,6-difluorophenyl)-2-(methylsulfonyl)-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl]-4-methylbenzamide

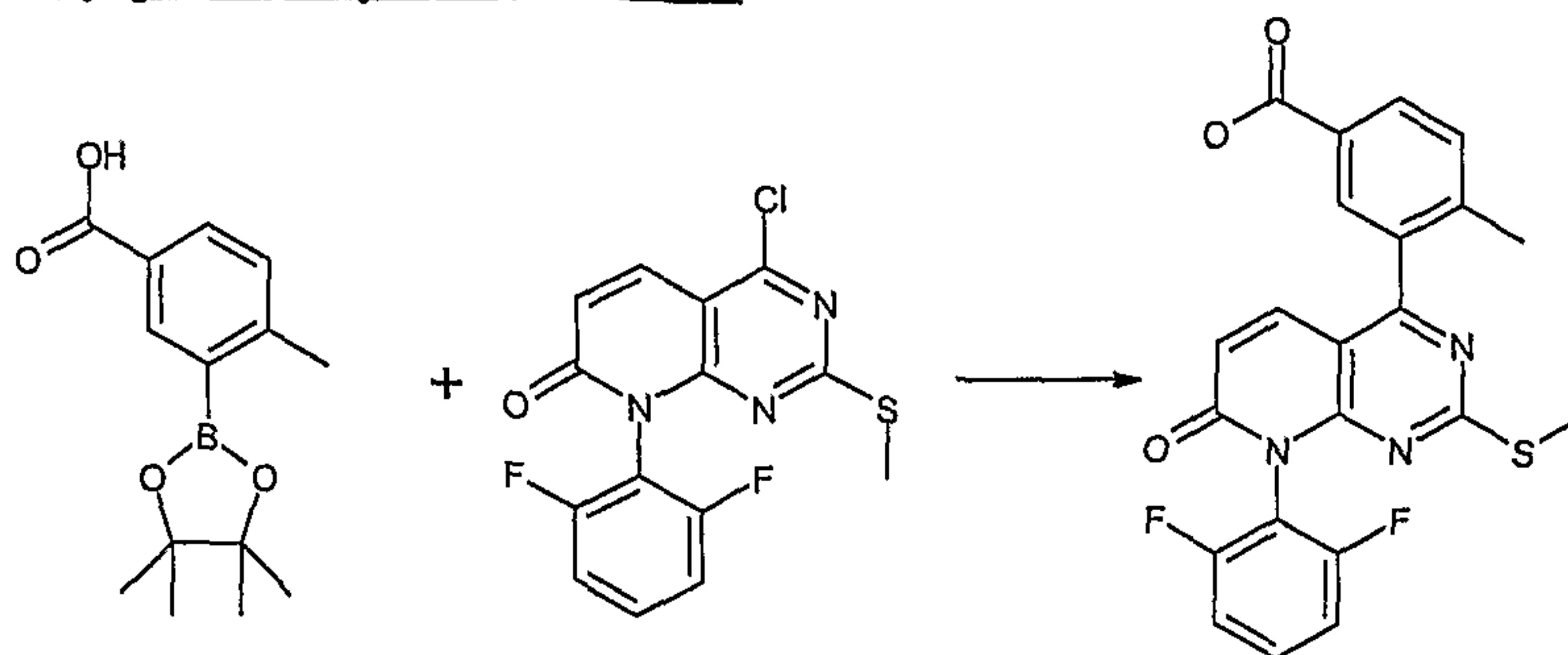


To a solution of 3-[8-(2,6-difluorophenyl)-2-(methylthio)-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl]-4-methylbenzoic acid (246.0 mg, 0.5 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (10.0 ml) was added DMAP (122.0 mg, 1.0 mmol), EDC (115.0 mg, 0.6 mmol), HOBT (81.0 mg, 0.6 mmol), and 1-cyclopropylmethanamine (71.0 mg, 1.0 mmol). The reaction mixture was stirred for about 14 h at room temperature and concentrated. It was then diluted with H<sub>2</sub>O (5.0 mL) and EtOAc (10.0 mL). The organic layer was separated and the aqueous layer was extracted with EtOAc (3x10 mL). The combined organic layers were washed with saturated aq. NaCl, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated. Purification via the CombiFlash system (hexane:ethylacetate=3:1) then afforded *N*-(cyclopropylmethyl)-3-[8-(2,6-difluorophenyl)-2-(methylthio)-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl]-4-methylbenzamide (210.0 mg, 85%): LC-MS  $m/z$  493 ( $M + H$ )<sup>+</sup>, 2.33 min (ret. time).



To a solution of *N*-(cyclopropylmethyl)-3-[8-(2,6-difluorophenyl)-2-(methylthio)-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl]-4-methylbenzamide (493.0 mg, 1.0 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (15.0 mL) was added *m*-CPBA (449.0 mg, 2.0

1b) 3-[8-(2,6-difluorophenyl)-2-(methylthio)-7-oxo-7,8-dihydropyrido[2,3-  
d]pyrimidin-4-yl]-4-methylbenzoic acid

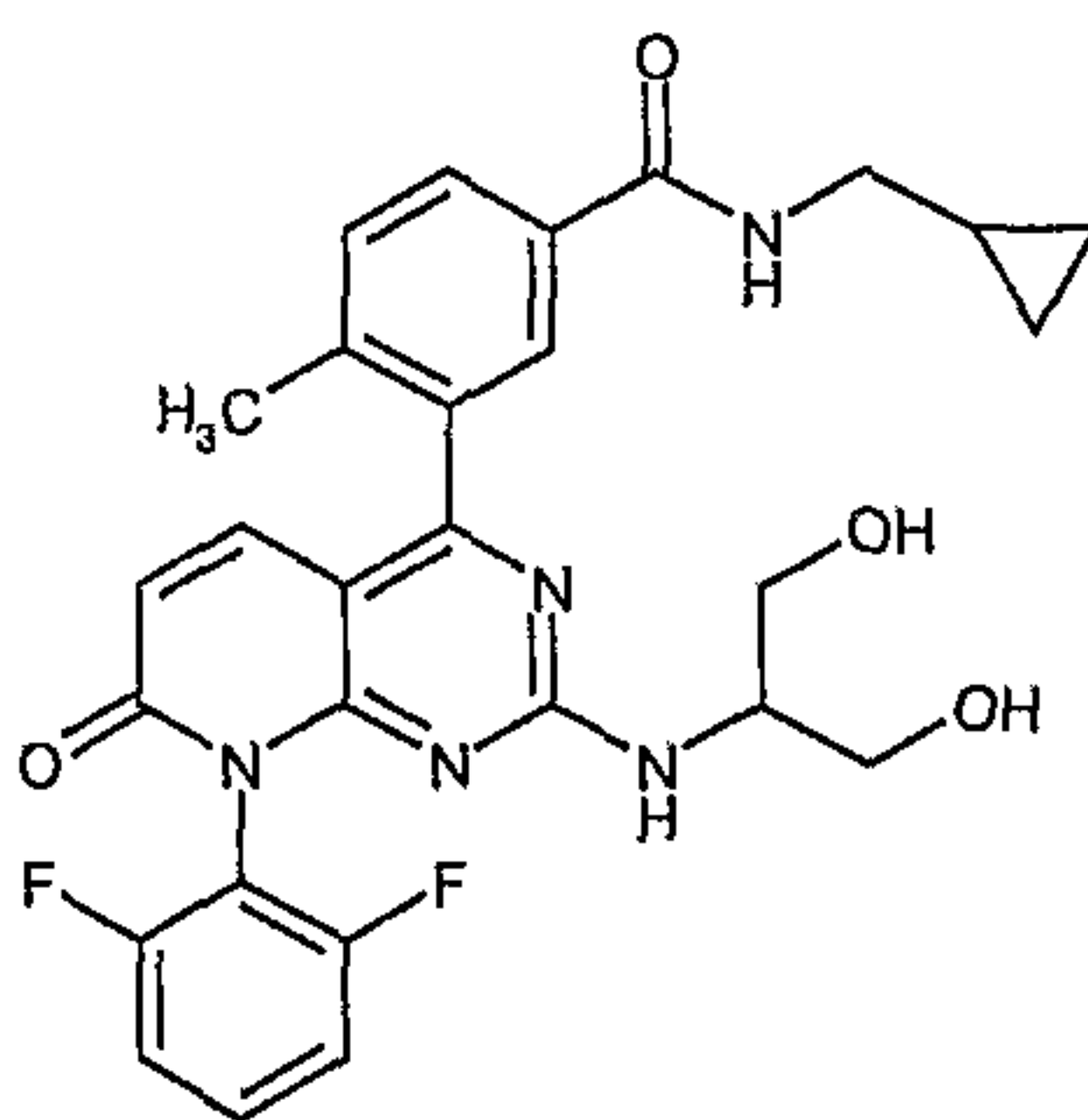


To a stirring solution of 3-iodo-4-methylbenzoic acid (60 g, 0.22 mol, 1 eq)  
 5 in degassed DMF (1400 mL, 23.3 vol.) was charged 4,4,4',4',5,5,5',5'-octamethyl-  
 2,2'-bi-1,3,2-dioxaborolane (81.4 g, 0.32 mol, 1.4 eq) followed by potassium acetate  
 (112 g, 1.14 mole, 5eq) and [1,1'-bis(diphenylphosphino)ferrocene]-  
 dichloropalladium(II) (18.7 g, 0.02 mole, 0.1eq). The resulting mixture was placed  
 under a nitrogen atmosphere and was heated to 80 °C with the exclusion of light  
 10 overnight. The mixture was then concentrated under high vacuum and the residue  
 partitioned between EtOAc and 2M HCl. The mixture was then filtered and the  
 layers separated. The aqueous phase was re-extracted with EtOAc. The combined  
 organics were then washed with brine, dried and evaporated to yield a brown solid  
 that was applied to a silica plug then eluted with 2:1 cyclohexane : ethyl acetate.  
 15 Fractions were then combined and evaporated to yield a brown foam that was  
 triturated with cyclohexane, collected by filtration then dried in *vacuo* to yield 4-  
 methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoic acid.  $\delta$  (CDCl<sub>3</sub>)  
 8.50-8.49 (1H, d), 8.04-8.02 (1H, dd), 7.27-7.25 (1H, d), 2.61 (3H, s), 1.36 (12H, s)

The solution of 4-chloro-8-(2,6-difluorophenyl)-2-(methylthio) pyrido[2,3-  
 20 d]pyrimidin-7(8H)-one (1.70 g, 5.00 mmol) in DME (150 mL) and H<sub>2</sub>O (50 mL), in  
 a pressure flask (500 mL, Chemglass), was added 4-methyl-3-(4,4,5,5-tetramethyl-  
 1,3,2-dioxaborolan-2-yl) benzoic acid (1.97 g, 7.50 mmol) and K<sub>2</sub>CO<sub>3</sub> (4.15 g, 30.0  
 mmol). The resulting mixture was degassed with Argon for 5 minutes, mixed with  
 Pd(PPh<sub>3</sub>)<sub>4</sub> (0.232 g, 0.20 mmol) and heated with a preheated oil bath (160 °C) under  
 25 vigorous stirring for 30 minutes. The reaction mixture was filtered through celite,  
 concentrated under vacuum to remove DME. It was then mixed with EtOAc (200  
 mL) and AcOH (2.5 mL), and shaken. The layers were separated. The organic layer  
 was collected, further washed with brine (70 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered,  
 concentrated and purified via a flash chromatography (load column with DCM,  
 30 mobile phase EtOAc/Hexane) to afford the title compound as a white solid 2.15g (98

mmol). The reaction mixture was stirred for about 12 h at room temperature and concentrated. It was diluted with H<sub>2</sub>O (5.0 mL) and EtOAc (20.0 mL). The organic layer was separated and the aqueous layer was extracted with EtOAc (3x20 mL). The combined organic layers were washed with saturated aq. NaCl, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated. Purification via the CombiFlash system (hexane:EtOAc = 4:1) afforded the title sulfone compound (490.0mg, 93%): LC-MS *m/z* 526 (M+H)<sup>+</sup>, 2.00 min (ret. time)

1d) N-(cyclopropylmethyl)-3-(8-(2,6-difluorophenyl)-2-{[2-hydroxy-1-(hydroxymethyl)ethyl]amino}-7-oxo-7,8-dihydropyrido[2,3-d]pyrimidin-4-yl)-4-methylbenzamide

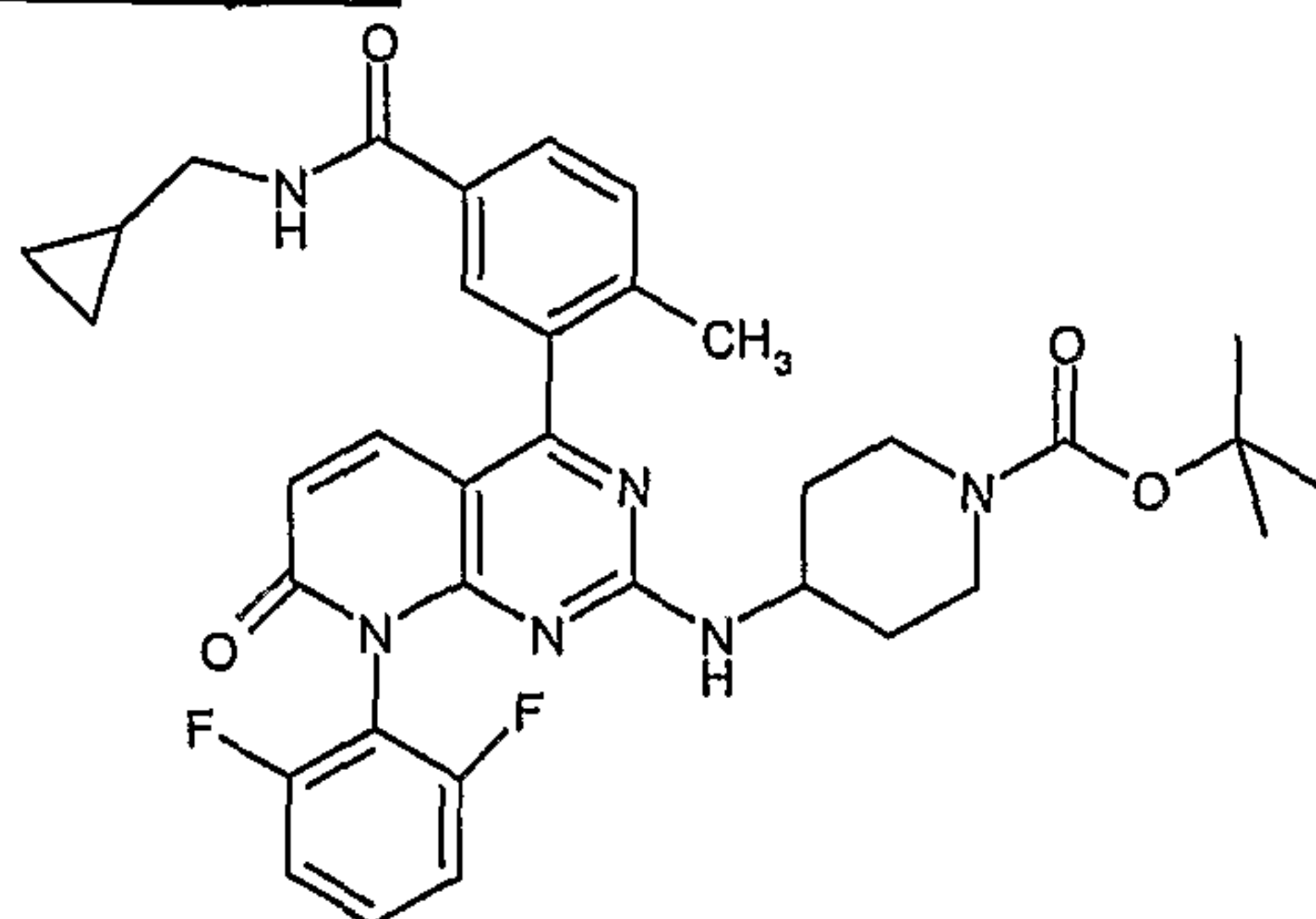


To a solution of N-(cyclopropylmethyl)-3-(8-(2,6-difluorophenyl)-2-methyl sulfone-7-oxo-7,8-dihydropyrido[2,3-d]pyrimidin-4-yl)-4-methylbenzamide (50.0 milligrams (hereinafter "mg"), 0.095 millimoles (hereinafter "mmol")) in THF (5.0 milliliters (hereinafter "mL")) was added 2-amino-3-propanediol (10.0 mg, 0.105 mmol, 1.1 eq). The reaction mixture was stirred for about 4 hours (hereinafter "h") at room temperature and concentrated. Purification via a CombiFlash system (DCM:MeOH = 1:10) then afforded the title compound: LC-MS *m/z* 536 (M+H)<sup>+</sup>, 1.70 min (ret time).

### Example 2

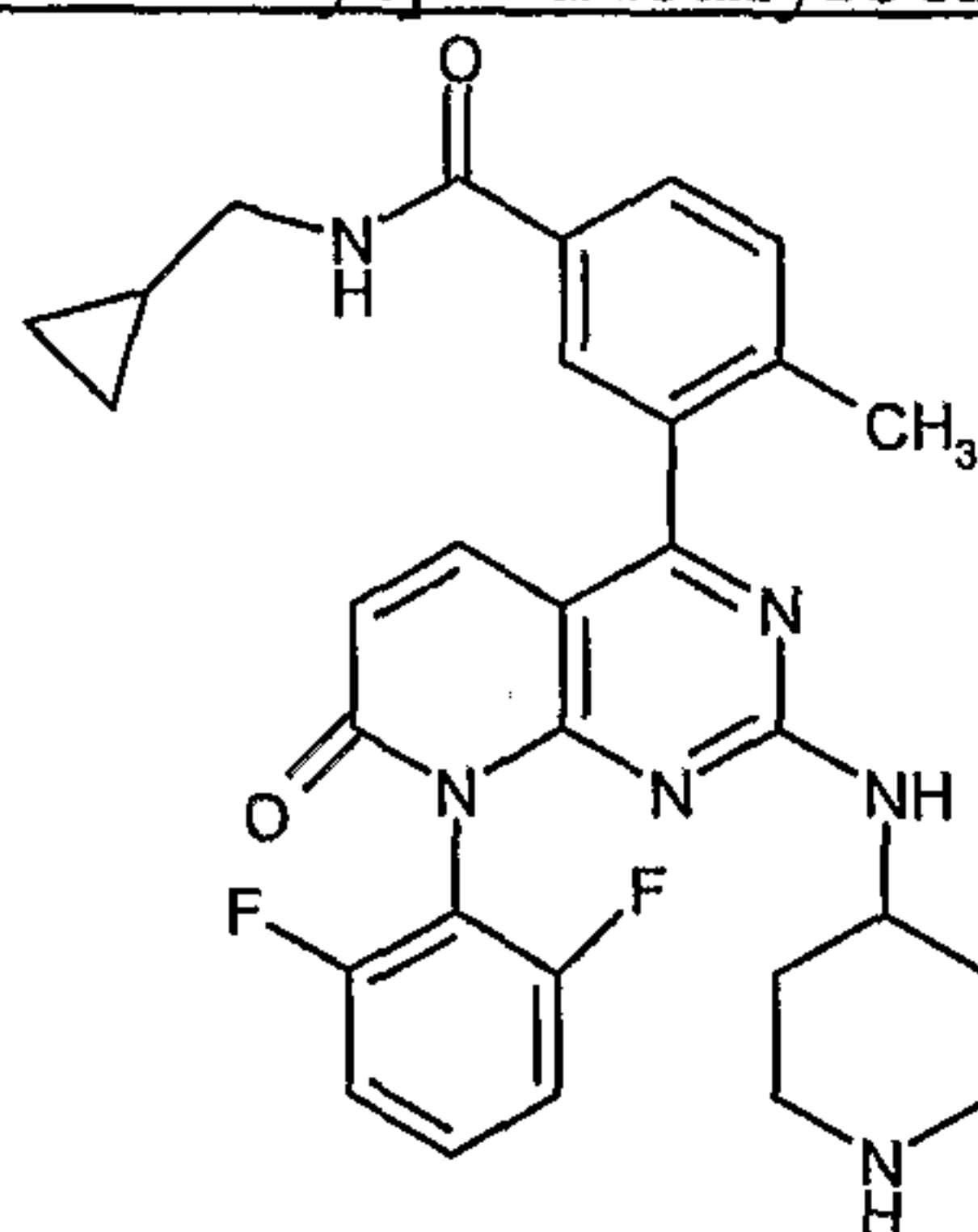
N-(cyclopropylmethyl)-3-[8-(2,6-difluorophenyl)-7-oxo-2-(4-piperidinylamino)-7,8-dihydropyrido[2,3-d]pyrimidin-4-yl]-4-methylbenzamide

2a) 1,1-dimethylethyl 4-{[4-(5-{[(cyclopropylmethyl)amino]carbonyl}-2-methylphenyl)-8-(2,6-difluorophenyl)-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-2-yl]amino}-1-piperidinecarboxylate



5 The title compound was prepared by following the procedure in Example 1d from N-(cyclopropylmethyl)-3-(8-(2,6-difluorophenyl)-2-methyl sulfone-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl)-4-methylbenzamide and 1,1-dimethylethyl 4-amino-1-piperidinecarboxylate.

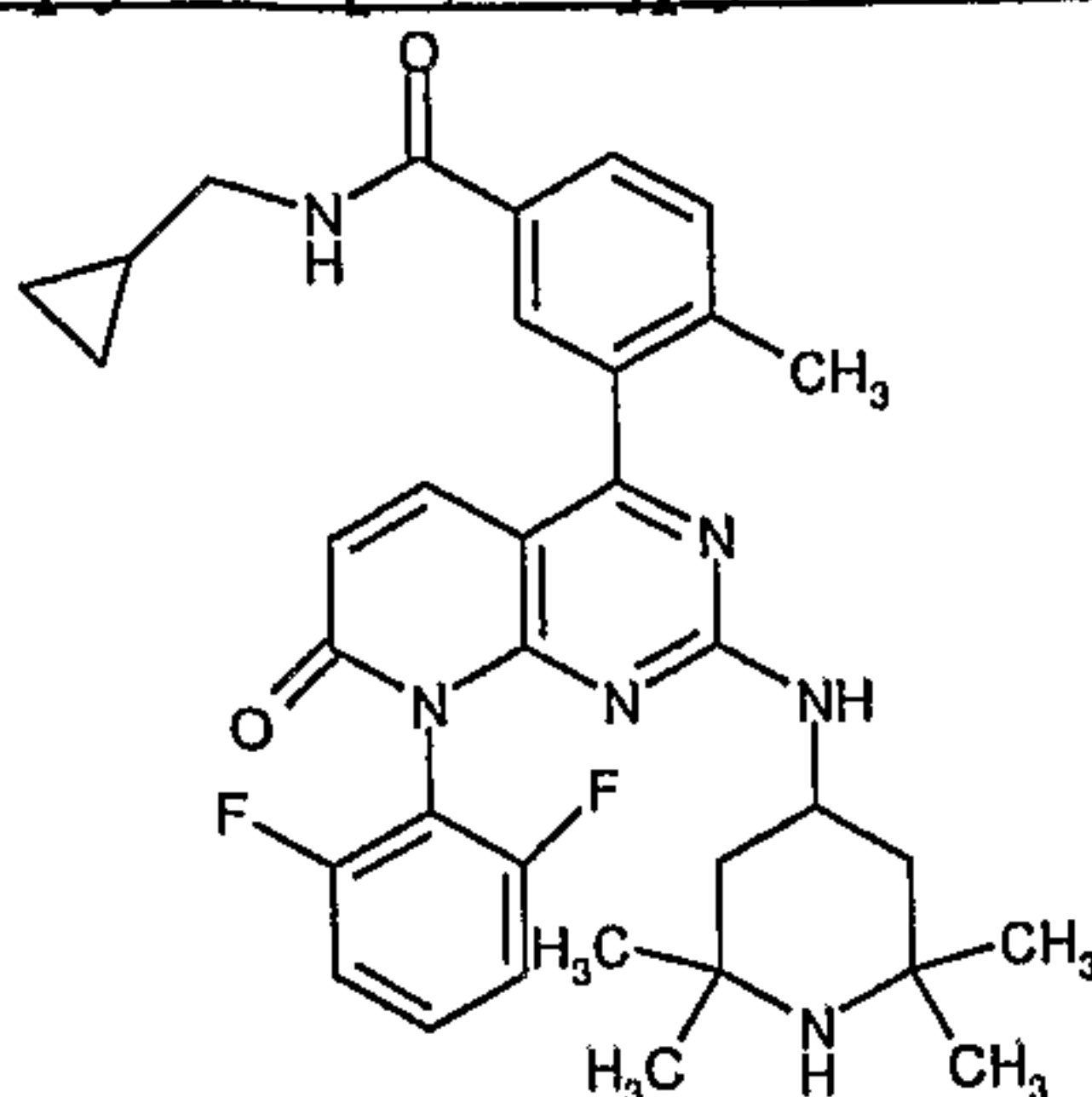
10 2b) N-(cyclopropylmethyl)-3-[8-(2,6-difluorophenyl)-7-oxo-2-(4-piperidinylamino)-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl]-4-methylbenzamide



To a solution of 1,1-dimethylethyl 4-{[4-(5-{[(cyclopropylmethyl)-  
amino]carbonyl}-2-methylphenyl)-8-(2,6-difluorophenyl)-7-oxo-7,8-  
15 dihydropyrido[2,3-*d*]pyrimidin-2-yl]amino}-1-piperidinecarboxylate in THF (2 mL) was added TFA (3.0 mL). The reaction mixture was stirred for about 12 h and concentrated. The residue was mixed with H<sub>2</sub>O (5.0 mL) and EtOAc (20.0 mL) and the resultant mixture was basified with 2.5 N NaOH aqueous (hereinafter "aq") solution. The organic layer was separated and the aqueous layer was extracted with  
20 EtOAc (3 x 15 mL). The combined organic phases were washed with saturated aq. NaCl, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated. Purification via a CombiFlash system (DCM:MeOH = 10:1) then afforded the title compound: LC-MS *m/z* 545 (M+H)<sup>+</sup>, 1.65 min (ret. time).

**Example 3**

N-(cyclopropylmethyl)-3-{8-(2,6-difluorophenyl)-7-oxo-2-[(2,2,6,6-tetramethyl-4-piperidinyl)amino]-7,8-dihydropyrido[2,3-d]pyrimidin-4-yl}-4-methylbenzamide

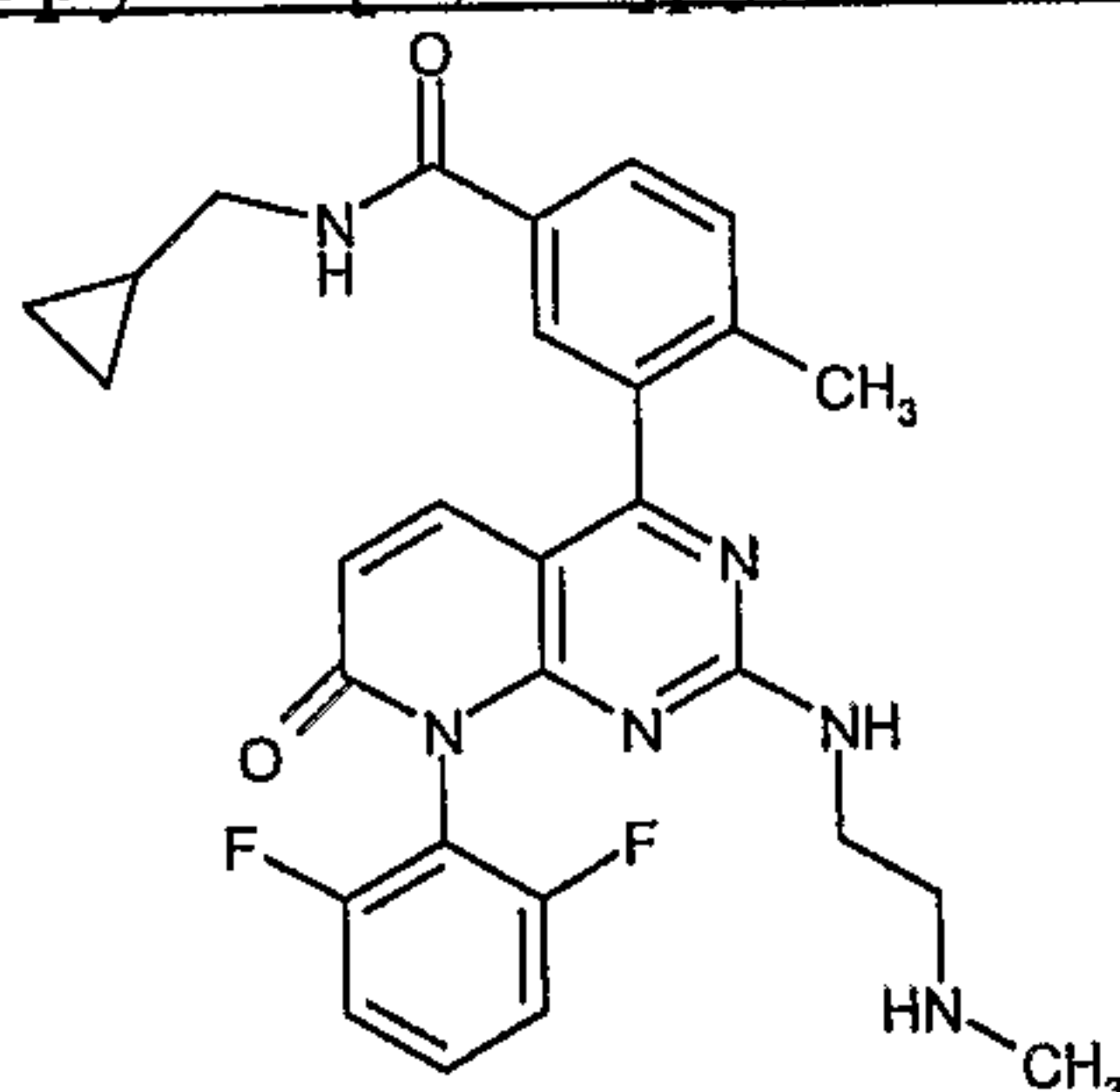


- 5 The title compound was prepared as described in Example 1d from N-(cyclopropylmethyl)-3-(8-(2,6-difluorophenyl)-2-methyl sulfone-7-oxo-7,8-dihydropyrido[2,3-d]pyrimidin-4-yl)-4-methylbenzamide and 2,2,6,6-tetramethyl-4-piperidinamine: LC-MS  $m/z$  601 ( $M+H$ )<sup>+</sup>, 1.75 min (ret. time)

10

**Example 4**

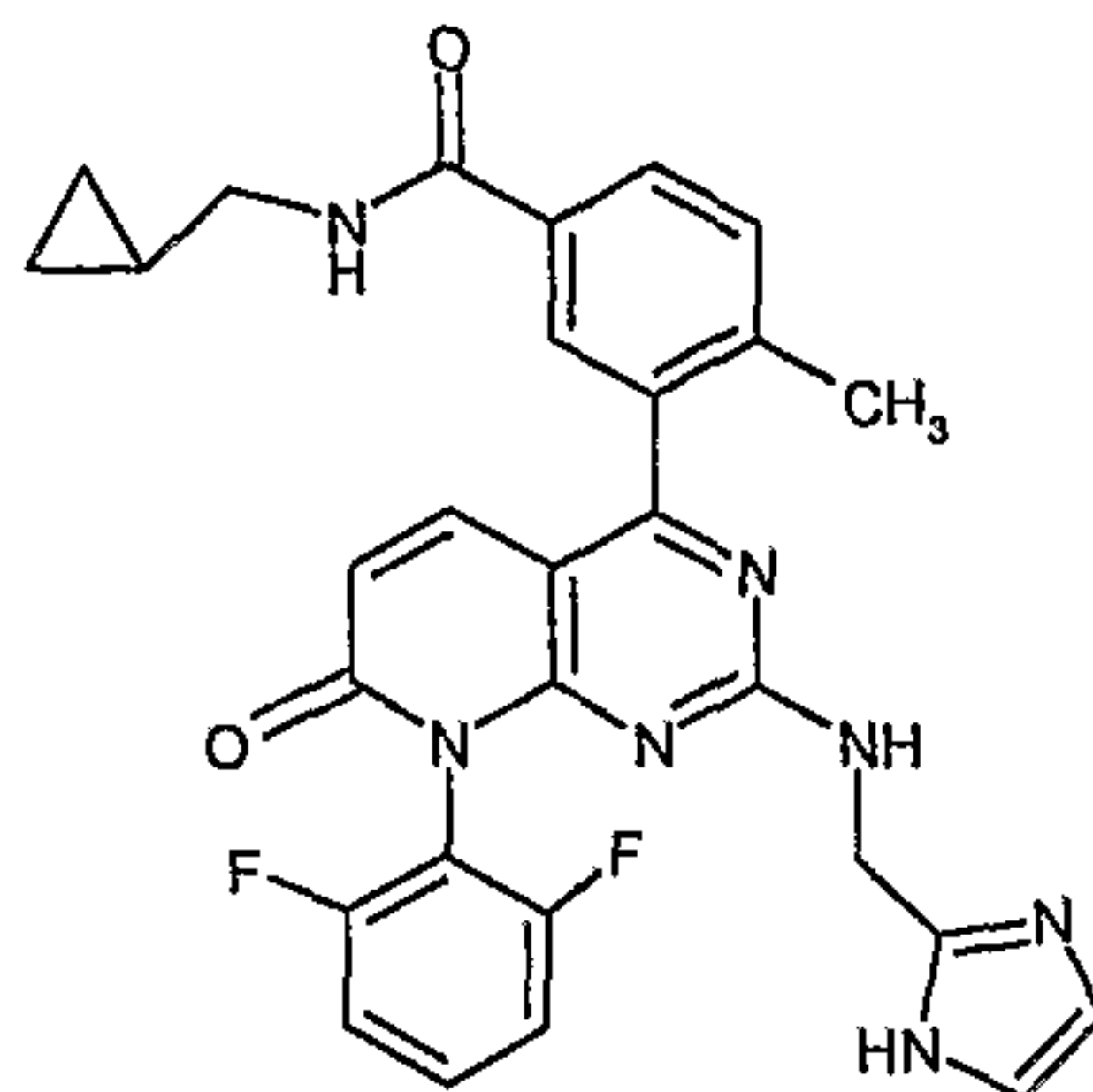
N-(cyclopropylmethyl)-3-{8-(2,6-difluorophenyl)-7-oxo-2-[(2,2,6,6-tetramethyl-4-piperidinyl)amino]-7,8-dihydropyrido[2,3-d]pyrimidin-4-yl}-4-methylbenzamide



- 15 The title compound was prepared as described in Example 1d from N-(cyclopropylmethyl)-3-(8-(2,6-difluorophenyl)-2-methyl sulfone-7-oxo-7,8-dihydropyrido[2,3-d]pyrimidin-4-yl)-4-methylbenzamide and N-methyl-1,2-ethanediamine: LC-MS  $m/z$  519 ( $M+H$ )<sup>+</sup>, 1.60 min (ret. time).

**Example 5**

N-(cyclopropylmethyl)-3-{8-(2,6-difluorophenyl)-2-[(1H-imidazol-2-ylmethyl)amino]-7-oxo-7,8-dihydropyrido[2,3-d]pyrimidin-4-yl}-4-methylbenzamide



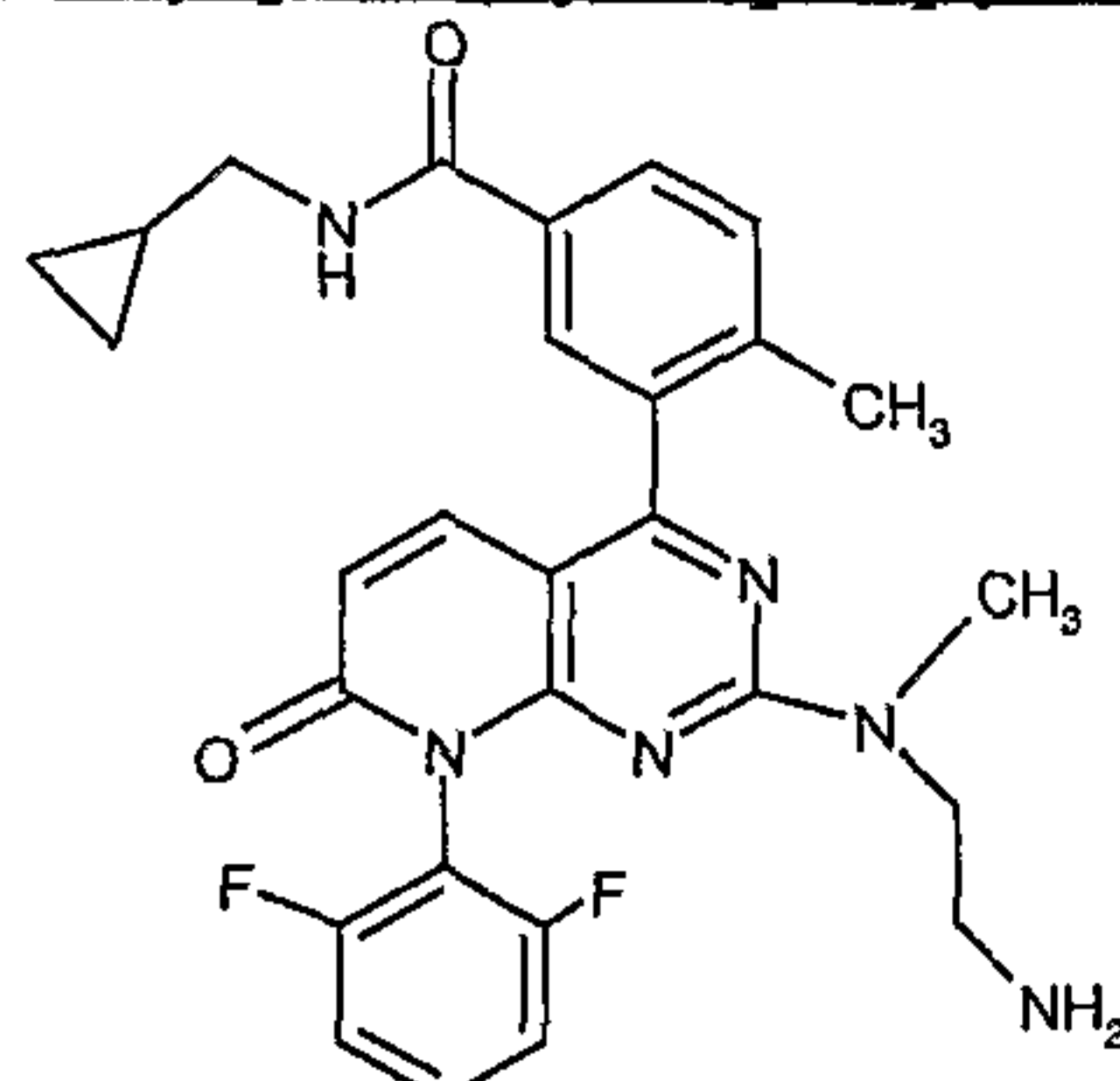
5

The title compound was prepared as described in Example 1d from N-(cyclopropylmethyl)-3-(8-(2,6-difluorophenyl)-2-methyl sulfone-7-oxo-7,8-dihydropyrido[2,3-d]pyrimidin-4-yl)-4-methylbenzamide and (1H-imidazol-2-ylmethyl)amine dihydrochloride: LC-MS  $m/z$  542 (M+H)<sup>+</sup>, 1.61 min (ret. time).

10

**Example 6**

3-[2-[(2-aminoethyl)(methyl)amino]-8-(2,6-difluorophenyl)-7-oxo-7,8-dihydropyrido[2,3-d]pyrimidin-4-yl]-N-(cyclopropylmethyl)-4-methylbenzamide



15

The title compound was prepared as described in Example 2 from N-(cyclopropylmethyl)-3-(8-(2,6-difluorophenyl)-2-methyl sulfone-7-oxo-7,8-dihydropyrido[2,3-d]pyrimidin-4-yl)-4-methylbenzamide and 1,1-dimethylethyl [2-(methylamino)ethyl]carbamate: LC-MS  $m/z$  519 (M+H)<sup>+</sup>, 1.62 min (ret. time).

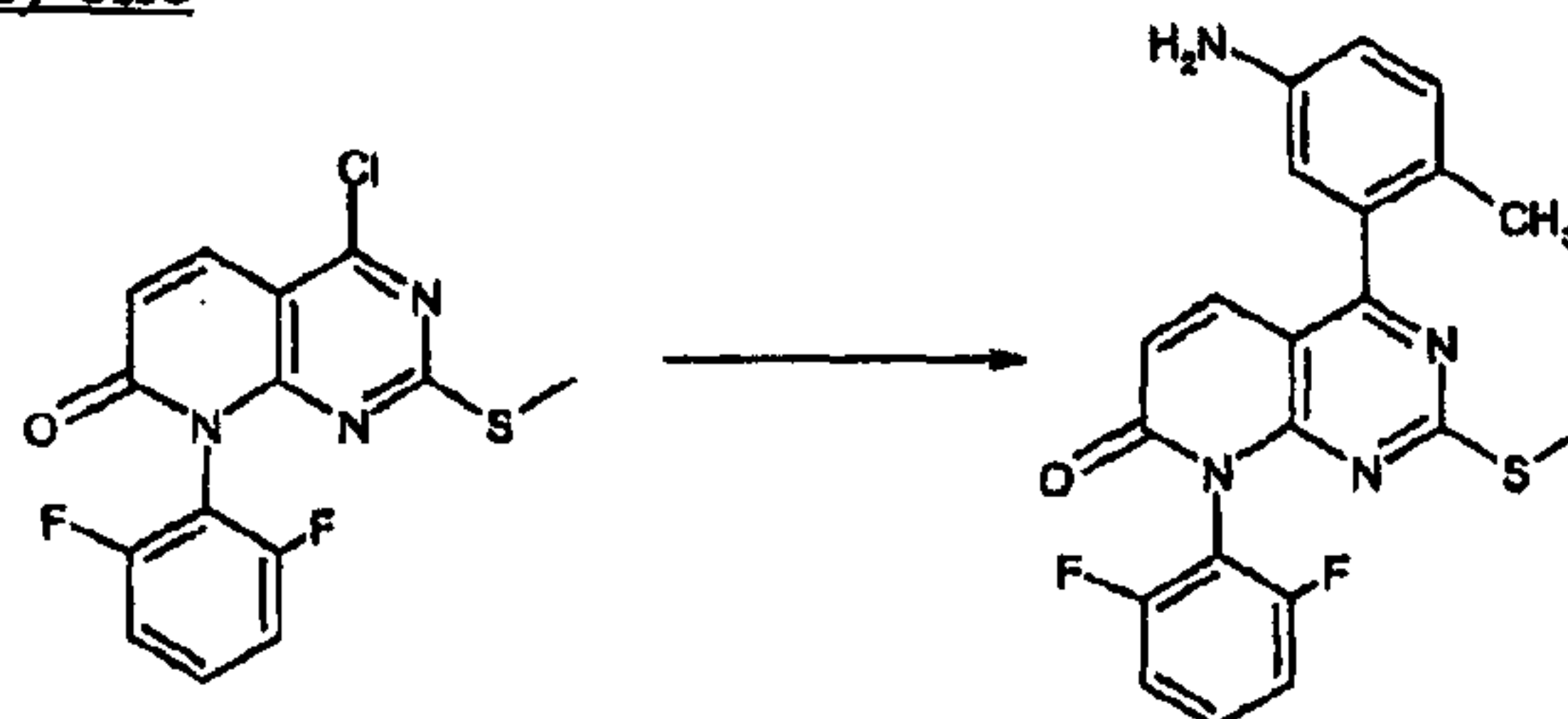
WO 2006/104915

PCT/US2006/010855

## Example 7

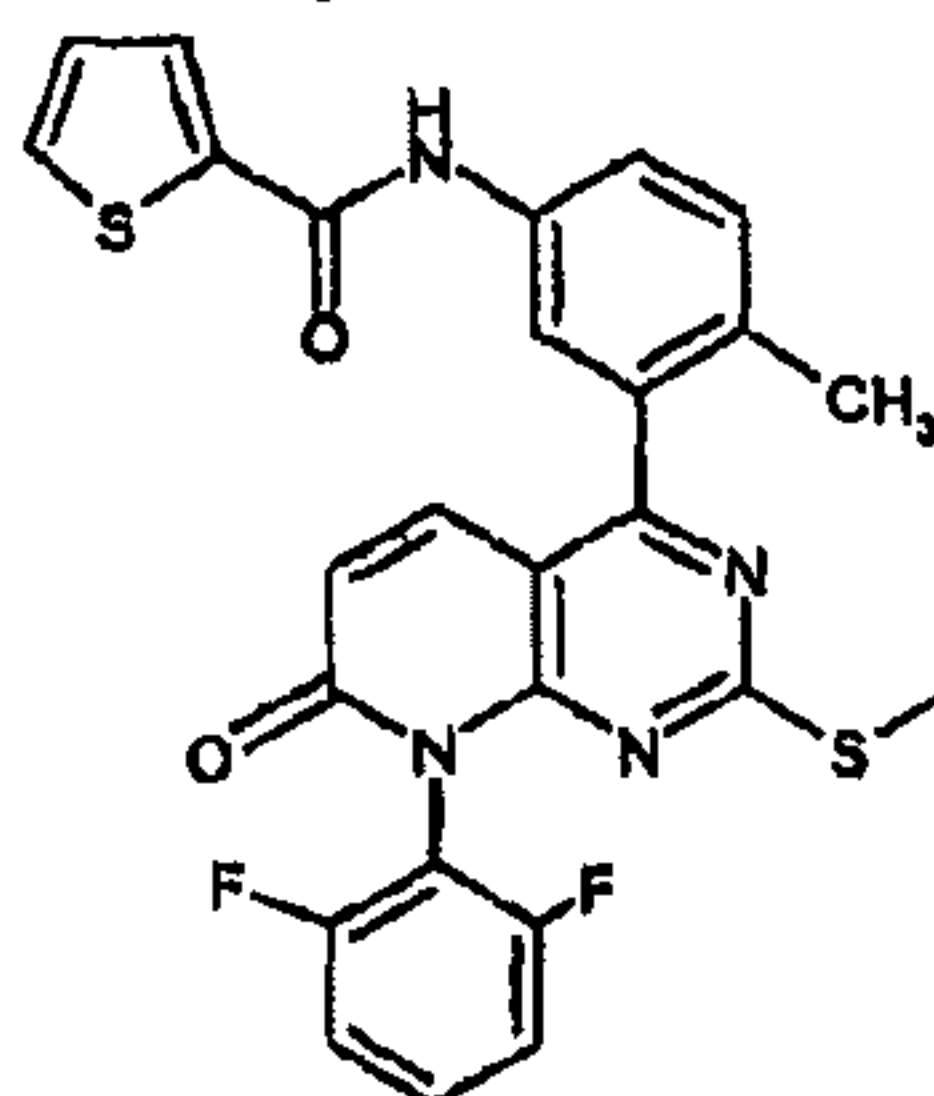
N-{3-[8-(2,6-difluorophenyl)-7-oxo-2-(4-piperidinylamino)-7,8-dihydropyrido[2,3-d]pyrimidin-4-yl]-4-methylphenyl}-2-thiophenecarboxamide

7a) 4-(5-amino-2-methylphenyl)-8-(2,6-difluorophenyl)-2-(methylthio)pyrido[2,3-d]pyrimidin-7(8H)-one



To a solution of 3-iodo-4-methylaniline (110.0 mg, 0.47 mmol) in dioxane (1.0 mL) was added (under argon) triethylamine (0.26 mL, 1.86 mmol), palladium diacetate (5.2 mg, 0.023 mmol), 2-(dicyclohexyl phosphino) biphenyl (33.0 mg, 0.093 mmol), and pinacolborane (0.20 mL, 1.40 mmol). The mixture was stirred at about 80 °C for about 1 hour, cooled to room temperature (rt), and added with water (0.2 mL), barium hydroxide octahydrate (440.0 mg, 1.40 mmol) and 4-chloro-8-(2,6-difluorophenyl)-2-(methylthio)pyrido[2,3-d]pyrimidin-7(8H)-one (180.0mg, 0.47mmol). The mixture was heated at about 100 °C under stirring for about 1 hour, cooled to room temperature, filtered through celite\*, and diluted with brine (5.0 mL). The mixture was then extracted with CH<sub>2</sub>Cl<sub>2</sub> (3x10 mL). The combined organic phases were dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated. Purification via the CombiFlash system then afforded the title compound (155.0mg, 75%): LC-MS m/z 411 (M+H)<sup>+</sup>, 2.60 min (ret. time).

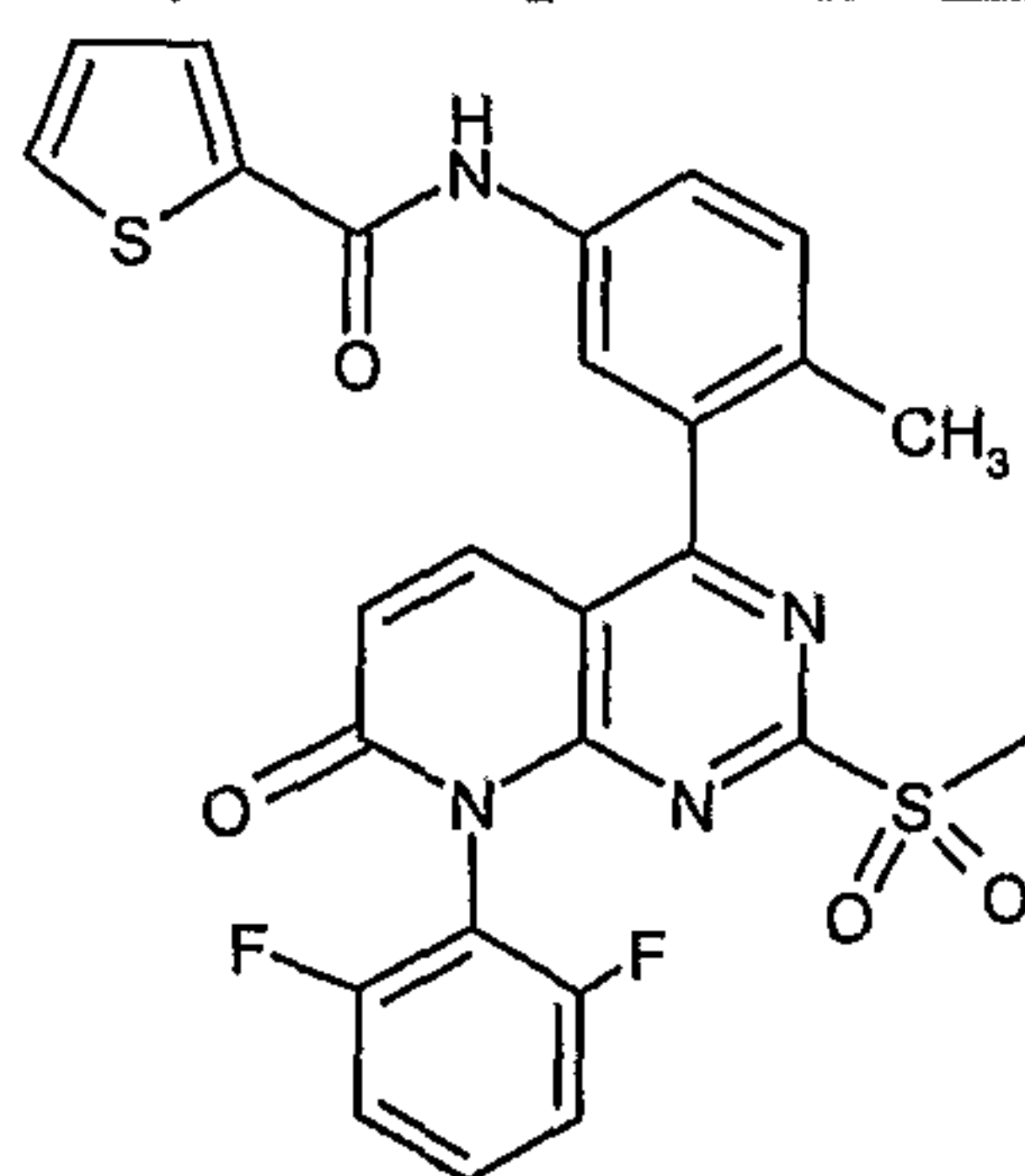
7b) N-{3-[8-(2,6-difluorophenyl)-2-(methylthio)-7-oxo-7,8-dihydropyrido[2,3-d]pyrimidin-4-yl]-4-methylphenyl}-2-thiophenecarboxamide



To a solution of 4-(5-amino-2-methylphenyl)-8-(2,6-difluorophenyl)-2-(methylthio)pyrido[2,3-d]pyrimidin-7(8H)-one (411.0 mg, 1.0 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (10 mL) at 0 °C was added Et<sub>3</sub>N (200.0 mg, 2.0 mmol, 2.0 eq), DMAP (5.0 mg, 0.2

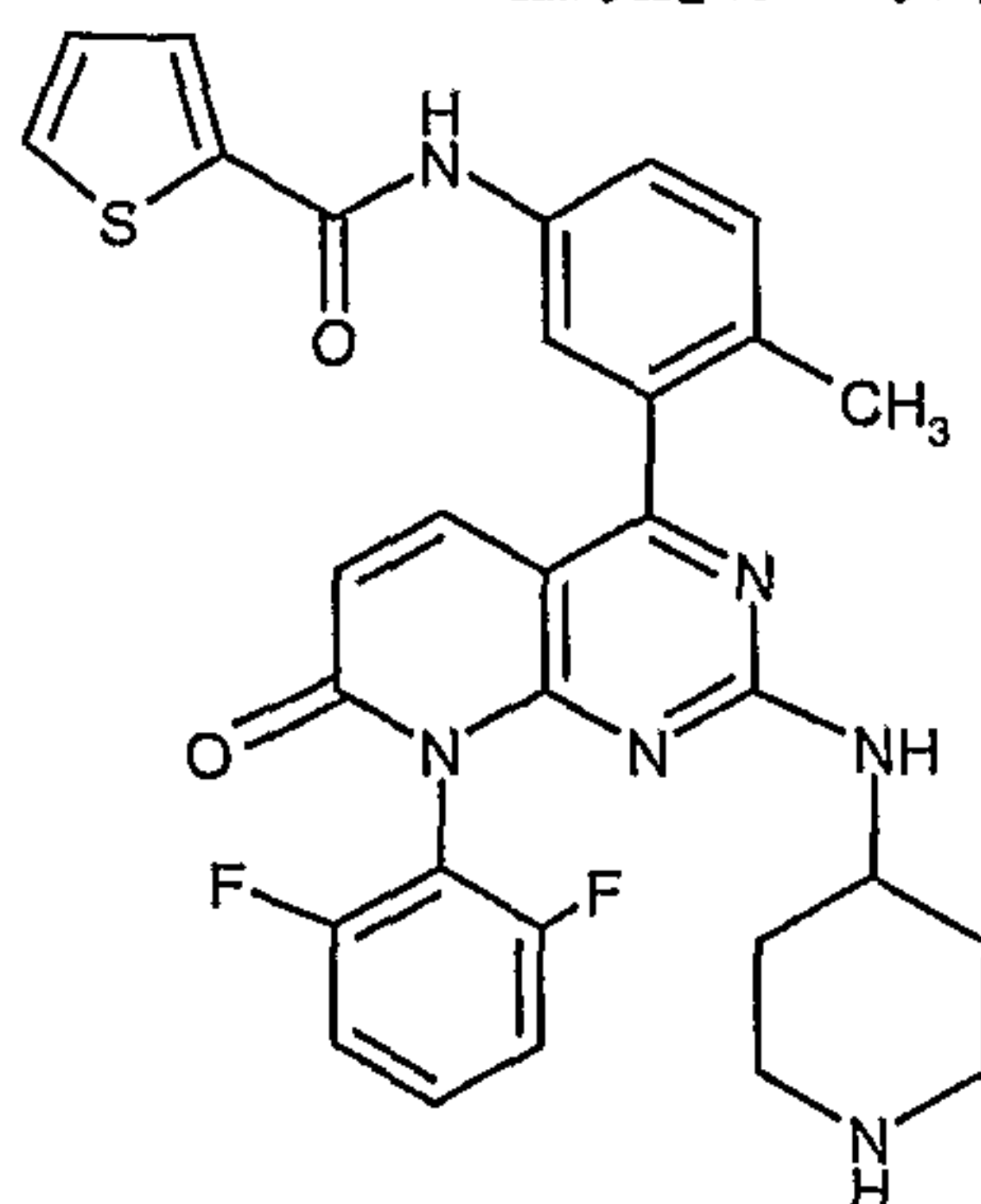
mmol, 0.2 eq) and 2-thiophenecarbonyl chloride (292.0 mg, 2.0 mmol, 2.0 eq). After addition the reaction mixture was stirred for about 14 h at ambient temperature. The mixture was concentrated and mixed with H<sub>2</sub>O (5.0 mL) and EtOAc (20.0 mL). The organic layer was separated and the aqueous layer was extracted with EtOAc (3 x 15 mL). The combined organic phases were washed with saturated aq. NaCl solution, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated. Purification via a CombiFlash system (hexane : EtOAc; 4:1) then afforded the title compound: LC-MS *m/z* 521 (M+H)<sup>+</sup>, 2.57 min (ret time).

10 7c) *N*-{3-[8-(2,6-difluorophenyl)-2-(methylsulfonyl)-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl]-4-methylphenyl}-2-thiophenecarboxamide



To a solution of *N*-{3-[8-(2,6-difluorophenyl)-2-(methylthio)-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl]-4-methylphenyl}-2-thiophenecarboxamide (521.0 mg, 1.0 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (15.0 mL) was added *m*-CPBA (449.0 mg, 2.0 mmol, 2.0 eq). The reaction mixture was stirred for about 14 h at room temperature, concentrated, and mixed with H<sub>2</sub>O (5.0 mL) and EtOAc (20.0 mL). The organic layer was separated and the aqueous layer was extracted with EtOAc (3 x 15 mL). The combined organic phases were washed with saturated aq. NaCl solution, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated. Purification via a CombiFlash system (hexane : EtOAc; 4:1) then afforded the title compound: LC-MS *m/z* 553 (M+H)<sup>+</sup>, 2.30 min (ret time).

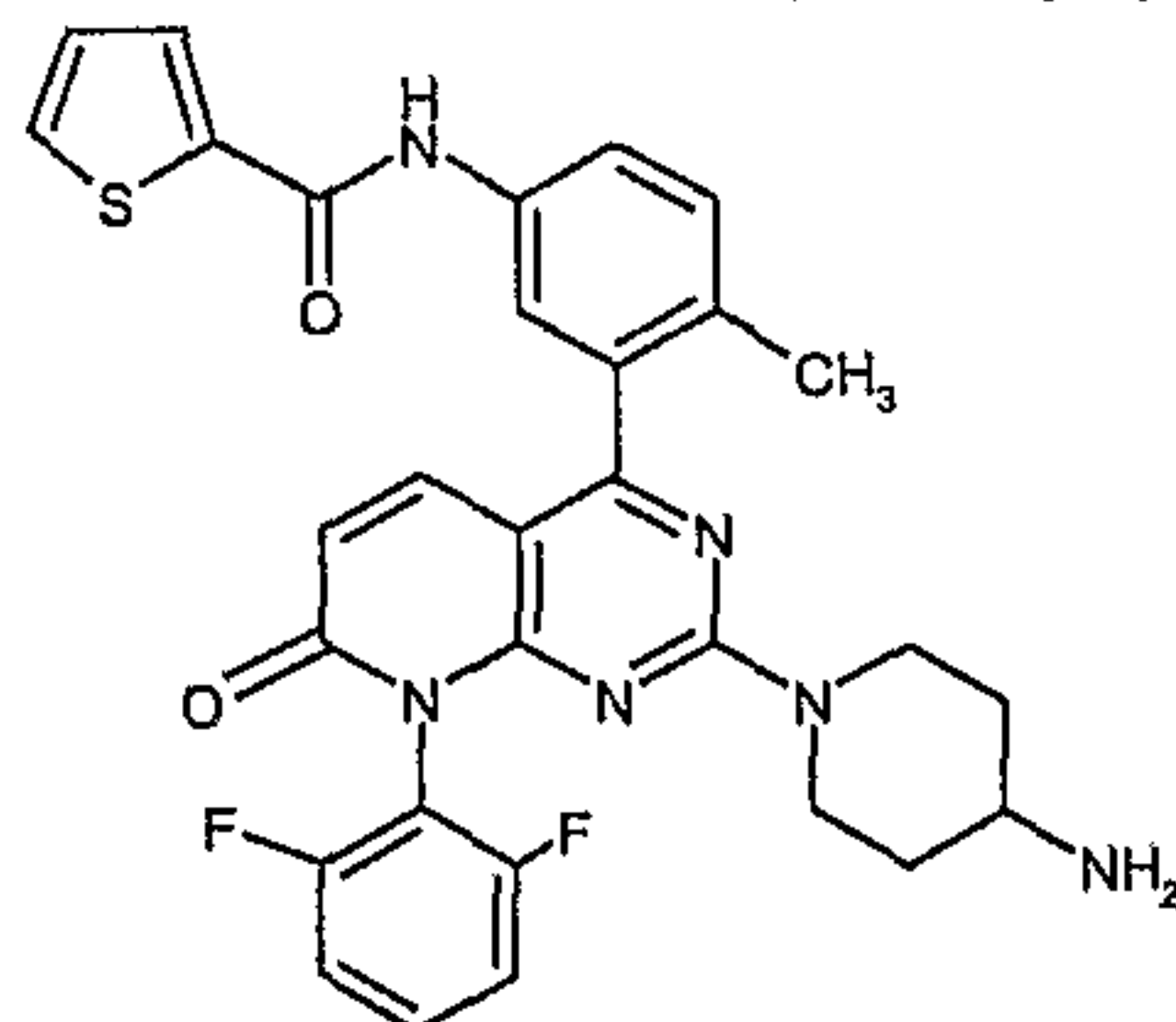
7d) N-{3-[8-(2,6-difluorophenyl)-7-oxo-2-(4-piperidinylamino)-7,8-dihydropyrido[2,3-d]pyrimidin-4-yl]-4-methylphenyl}-2-thiophenecarboxamide



The title compound was prepared as described in Example 2 from *N*-{3-[8-(2,6-difluorophenyl)-2-(methylsulfonyl)-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl]-4-methylphenyl}-2-thiophenecarboxamide and 1,1-dimethylethyl 4-amino-1-piperidinecarboxylate. LC-MS *m/z* 573 (*M*+*H*)<sup>+</sup>, 1.90 min (ret time).

### Example 8

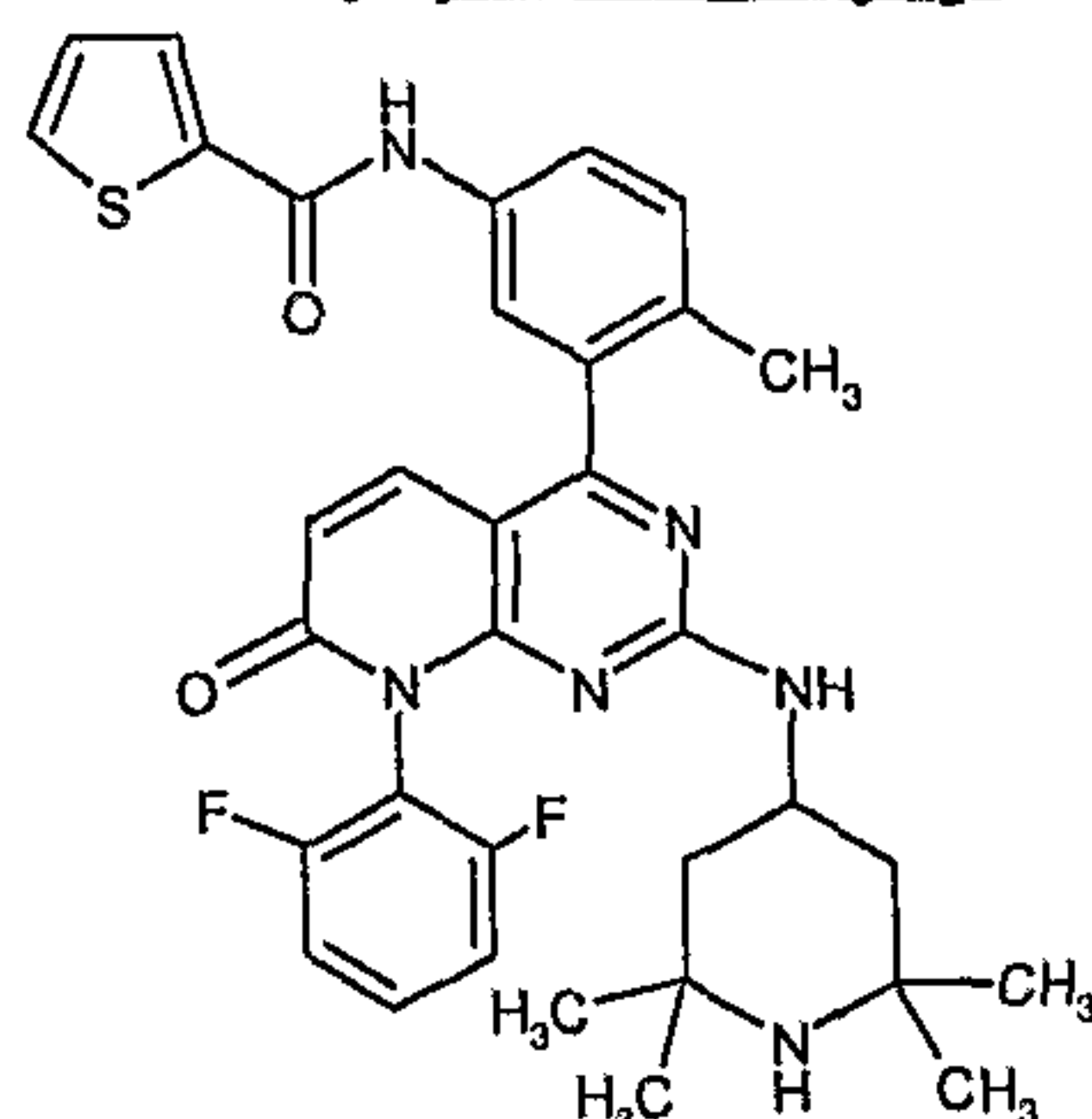
10 N-{3-[2-(4-amino-1-piperidinyl)-8-(2,6-difluorophenyl)-7-oxo-7,8-dihydropyrido[2,3-d]pyrimidin-4-yl]-4-methylphenyl}-2-thiophenecarboxamide



The title compound was prepared as described in Example 2 from *N*-{3-[8-(2,6-difluorophenyl)-2-(methylsulfonyl)-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl]-4-methylphenyl}-2-thiophenecarboxamide and 1,1-dimethylethyl 4-piperidinylcarbamate: LC-MS *m/z* 573 (*M*+*H*)<sup>+</sup>, 1.90 min (ret time).

**Example 9**

N-(3-{8-(2,6-difluorophenyl)-7-oxo-2-[(2,2,6,6-tetramethyl-4-piperidinyl)amino]-7,8-dihydropyrido[2,3-d]pyrimidin-4-yl}-4-methylphenyl)-2-thiophenecarboxamide

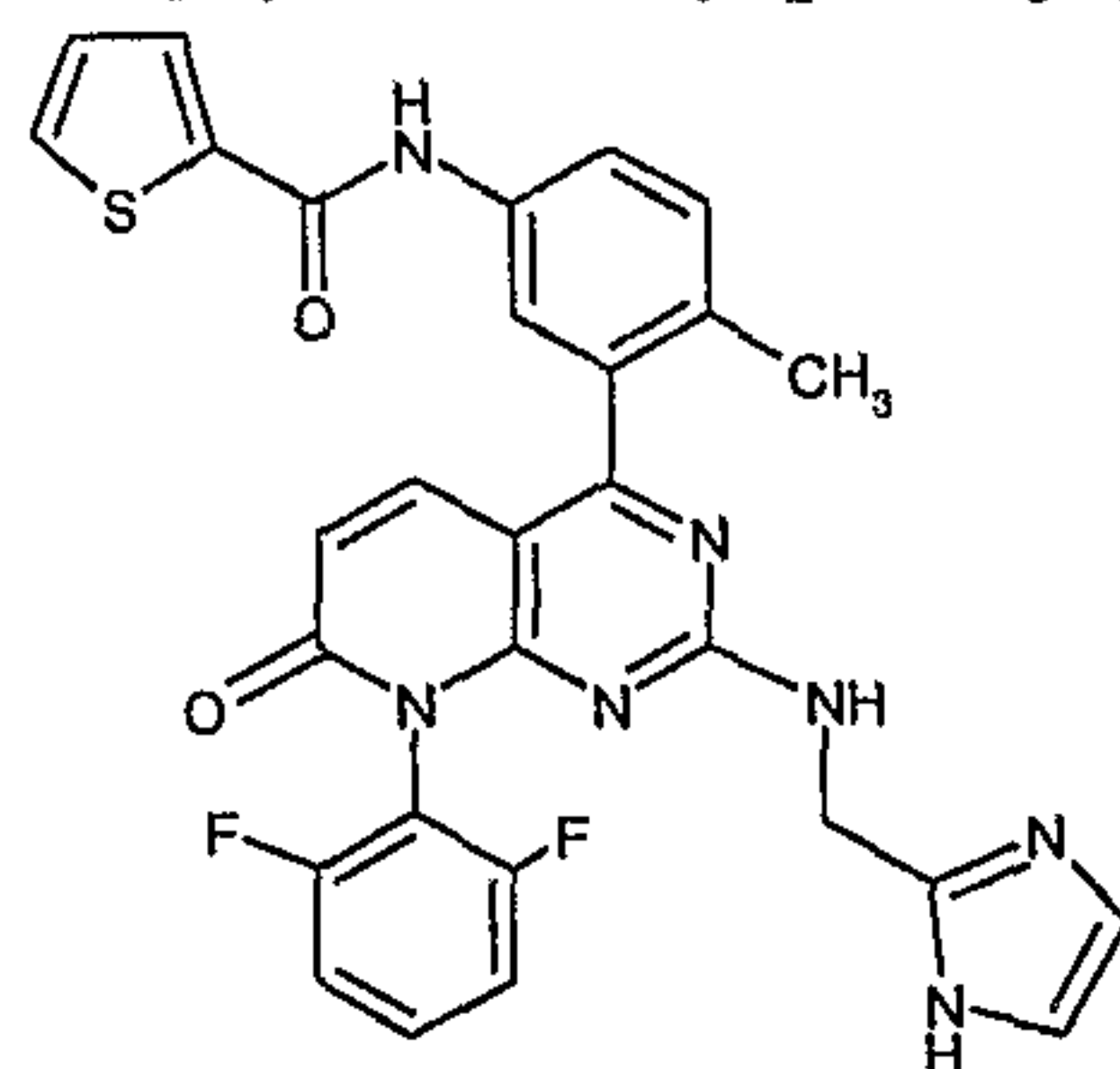


- 5 The title compound was prepared as described in Example 1d from *N*-{3-[8-(2,6-difluorophenyl)-2-(methylsulfonyl)-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl]-4-methylphenyl}-2-thiophenecarboxamide and 2,2,6,6-tetramethyl-4-piperidinamine: LC-MS *m/z* 629 ( $M+H$ )<sup>+</sup>, 2.0 min (ret time).

10

**Example 10**

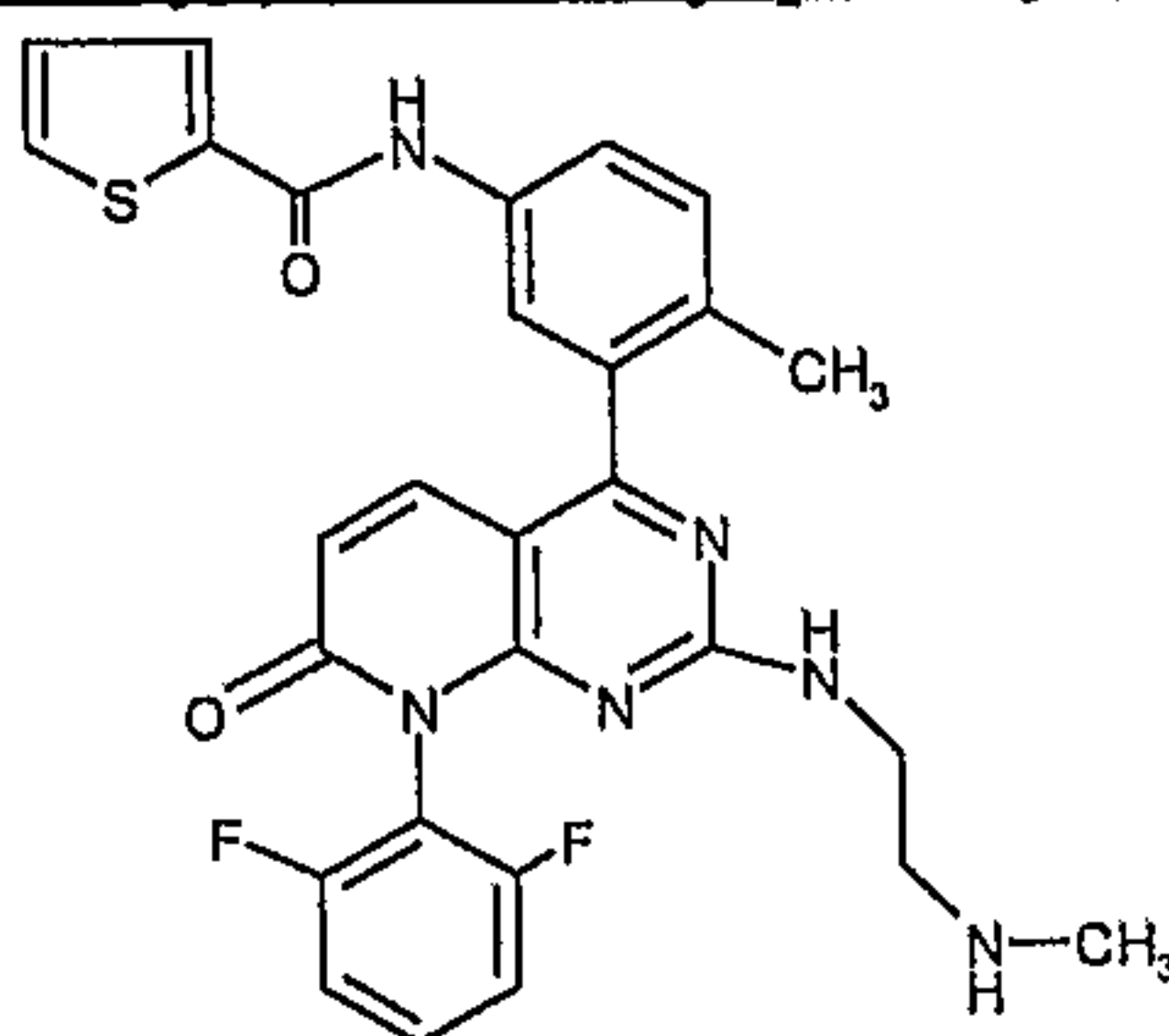
N-(3-{8-(2,6-difluorophenyl)-2-[(1*H*-imidazol-2-ylmethyl)amino]-7-oxo-7,8-dihydropyrido[2,3-d]pyrimidin-4-yl}-4-methylphenyl)-2-thiophenecarboxamide



- 15 The title compound was prepared as described in Example 1d from *N*-{3-[8-(2,6-difluorophenyl)-2-(methylsulfonyl)-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl]-4-methylphenyl}-2-thiophenecarboxamide and (1*H*-imidazol-2-ylmethyl)amine dihydrochloride: LC-MS *m/z* 570 ( $M+H$ )<sup>+</sup>, 1.70 min (ret time).

**Example 11**

N-[3-(8-(2,6-difluorophenyl)-2-{[2-(methylamino)ethyl]amino}-7-oxo-7,8-dihydropyrido[2,3-d]pyrimidin-4-yl)-4-methylphenyl]-2-thiophenecarboxamide

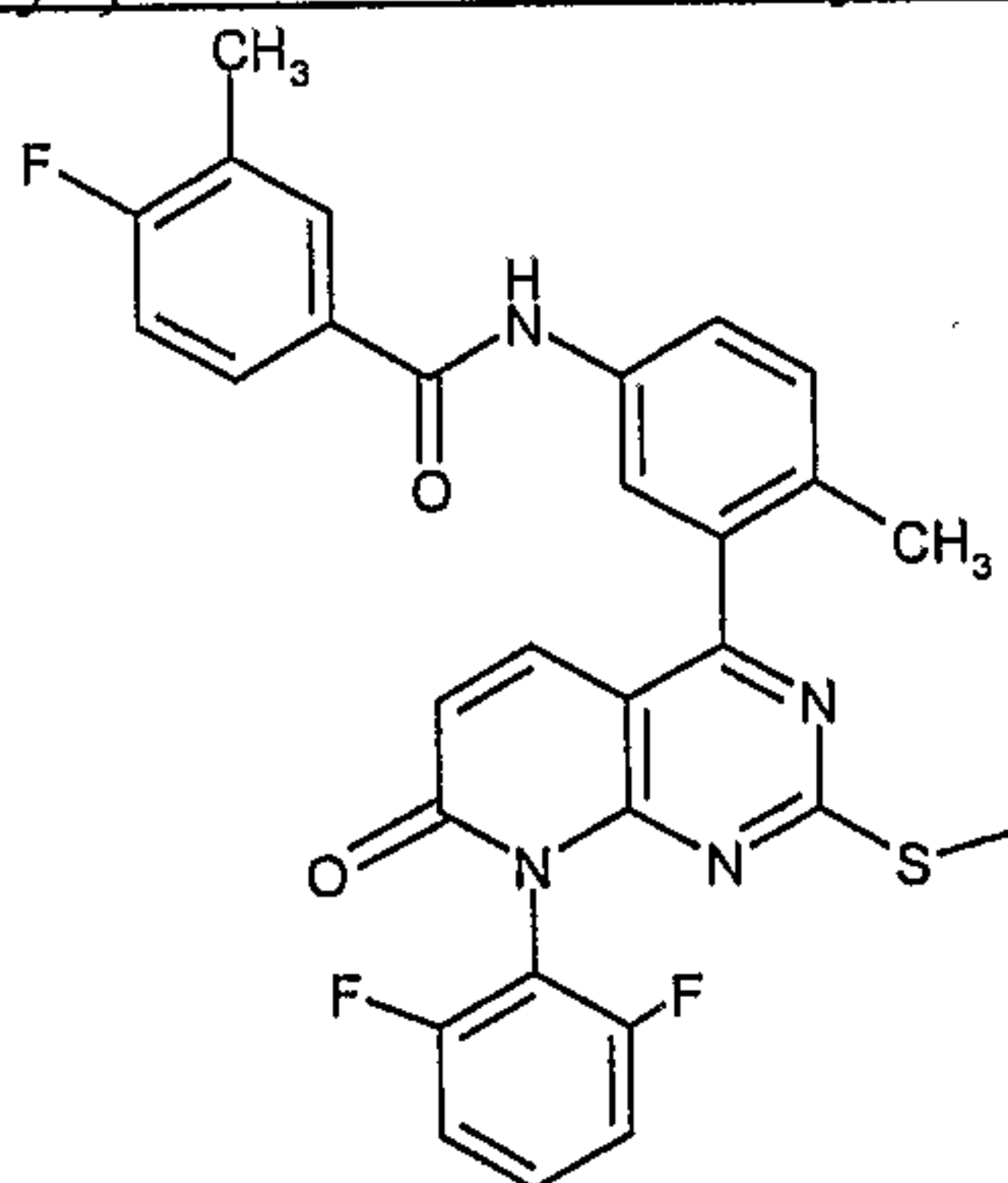


5 The title compound was prepared as described in Example 2 from *N*-{3-[8-(2,6-difluorophenyl)-2-(methylsulfonyl)-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl]-4-methylphenyl}-2-thiophenecarboxamide and 1,1-dimethylethyl (2-aminoethyl)methylcarbamate: LC-MS *m/z* 547 (M+H)<sup>+</sup>, 1.80 min (ret time).

**Example 12**

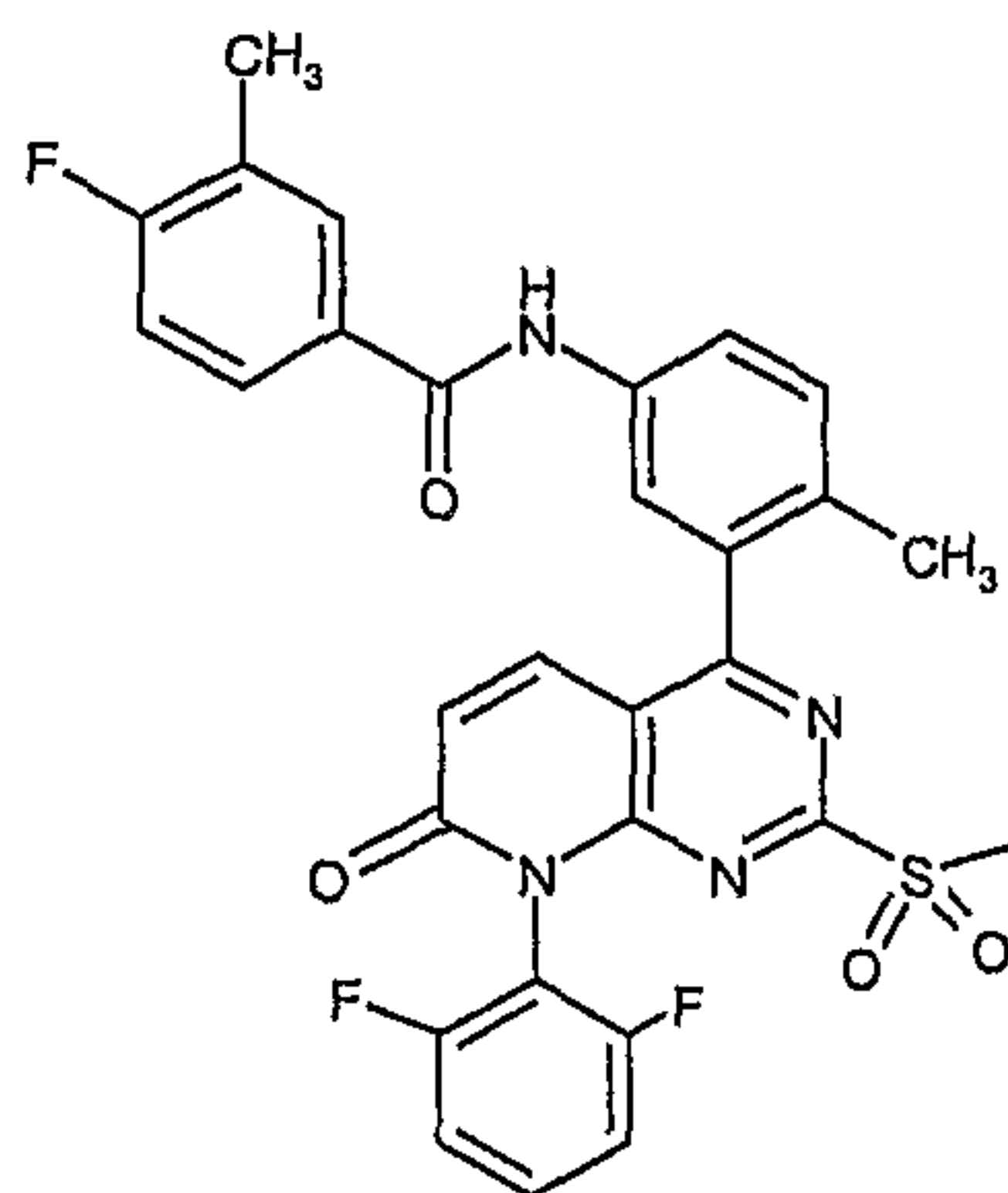
10 N-{3-[8-(2,6-difluorophenyl)-7-oxo-2-(4-piperidinylamino)-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl]-4-methylphenyl}-4-fluoro-3-methylbenzamide

12a) *N*-{3-[8-(2,6-difluorophenyl)-2-(methylthio)-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl]-4-methylphenyl}-4-fluoro-3-methylbenzamide



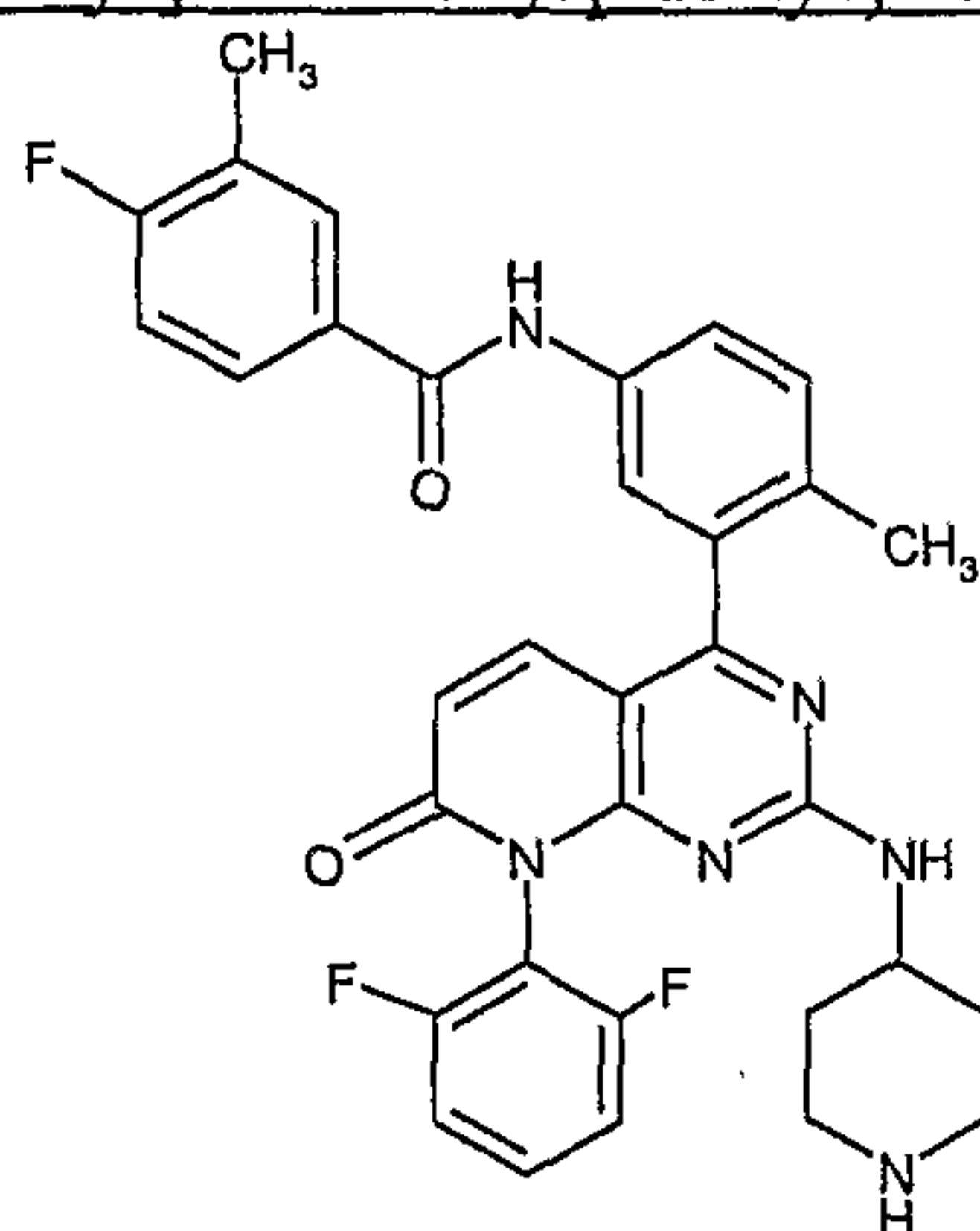
15 The title compound was prepared as described in Example 7b from 4-(5-amino-2-methylphenyl)-8-(2,6-difluorophenyl)-2-(methylthio)pyrido[2,3-*d*]pyrimidin-7(8*H*)-one and 4-fluoro-3-methylbenzoyl chloride: LC-MS *m/z* 547(M+H)<sup>+</sup>, 2.70 min (ret time).

12b) *N*-{3-[8-(2,6-difluorophenyl)-2-(methylsulfonyl)-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl]-4-methylphenyl}-4-fluoro-3-methylbenzamide



The title compound was prepared as described in Example 7c from *N*-{3-[8-(2,6-difluorophenyl)-2-(methylthio)-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl]-4-methylphenyl}-4-fluoro-3-methylbenzamide and *m*-CPBA: LC-MS *m/z* 580 (*M*+*H*)<sup>+</sup>,  
 5 2.40 min (ret time).

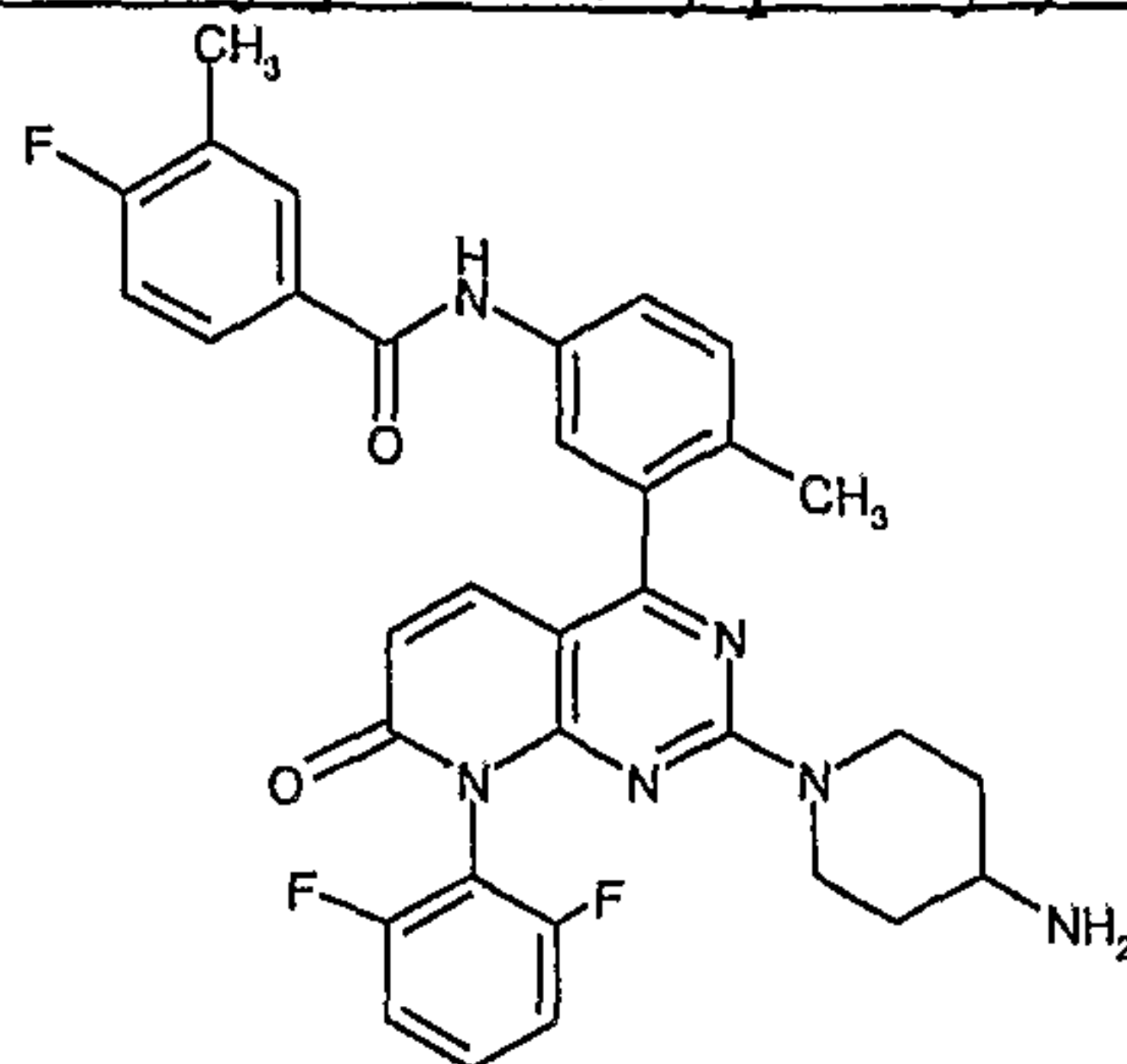
12c) *N*-{3-[8-(2,6-difluorophenyl)-7-oxo-2-(4-piperidinylamino)-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl]-4-methylphenyl}-4-fluoro-3-methylbenzamide



10 The title compound was prepared as described in Example 2 from *N*-{3-[8-(2,6-difluorophenyl)-2-(methylsulfonyl)-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl]-4-methylphenyl}-4-fluoro-3-methylbenzamide and 1,1-dimethylethyl 4-amino-1-piperidinecarboxylate: LC-MS *m/z* 599 (*M*+*H*)<sup>+</sup>, 1.98 min (ret time).

**Example 13**

N-{3-[2-(4-amino-1-piperidiny)-8-(2,6-difluorophenyl)-7-oxo-7,8-dihydropyrido[2,3-d]pyrimidin-4-yl]-4-methylphenyl}-4-fluoro-3-methylbenzamide

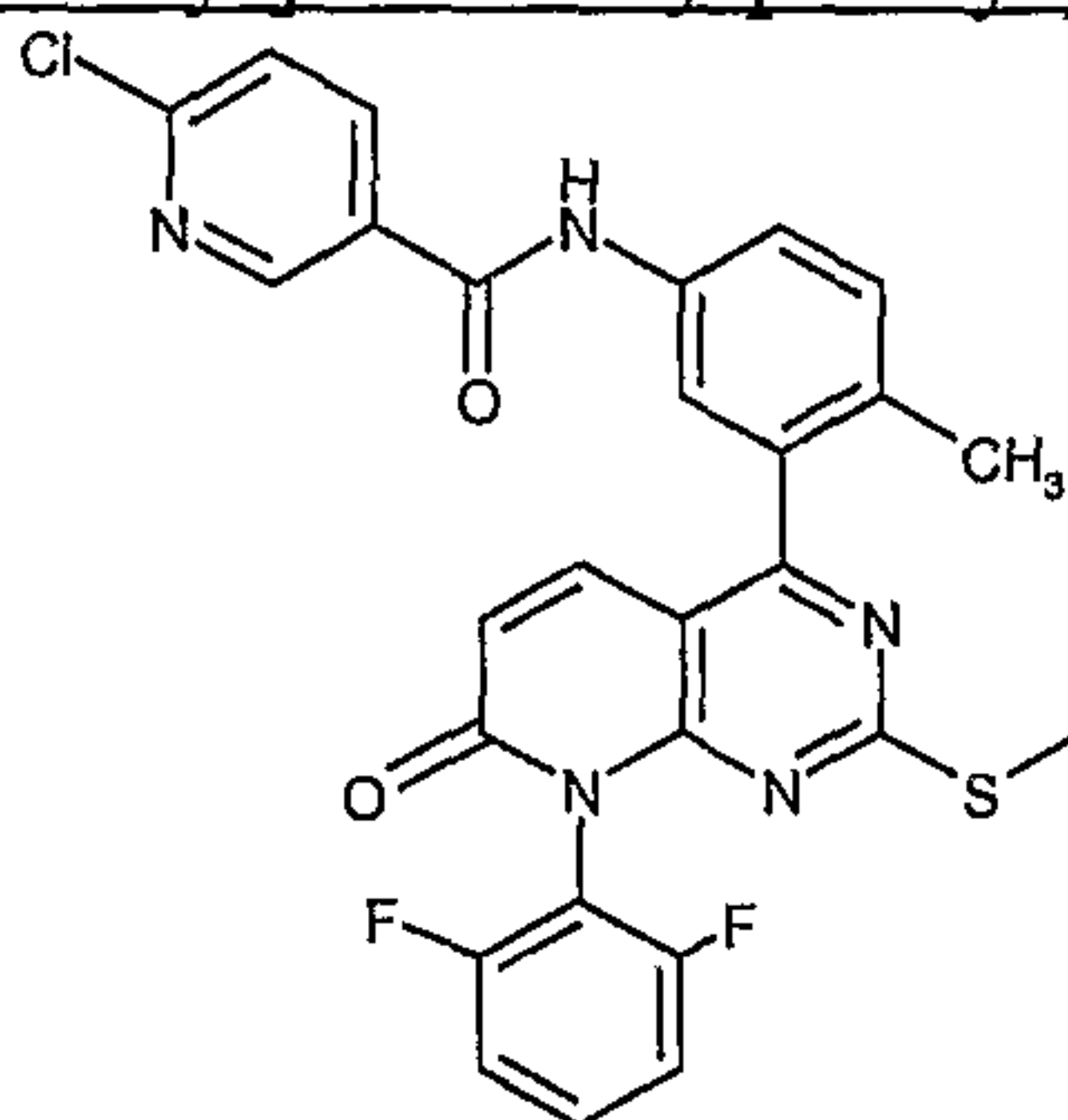


5 The title compound was prepared as described in Example 2 from *N*-{3-[8-(2,6-difluorophenyl)-2-(methylsulfonyl)-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl]-4-methylphenyl}-4-fluoro-3-methylbenzamide and 1,1-dimethylethyl 4-piperidinylcarbamate: LC-MS *m/z* 599 (*M*+*H*)<sup>+</sup>, 1.99 min (ret time).

10

**Example 14**

6-chloro-N-{3-[8-(2,6-difluorophenyl)-7-oxo-2-(4-piperidinylamino)-7,8-dihydropyrido[2,3-d]pyrimidin-4-yl]-4-methylphenyl}-3-pyridinecarboxamide  
 14a) 6-chloro-N-{3-[8-(2,6-difluorophenyl)-2-(methylthio)-7-oxo-7,8-dihydropyrido[2,3-d]pyrimidin-4-yl]-4-methylphenyl}-3-pyridinecarboxamide

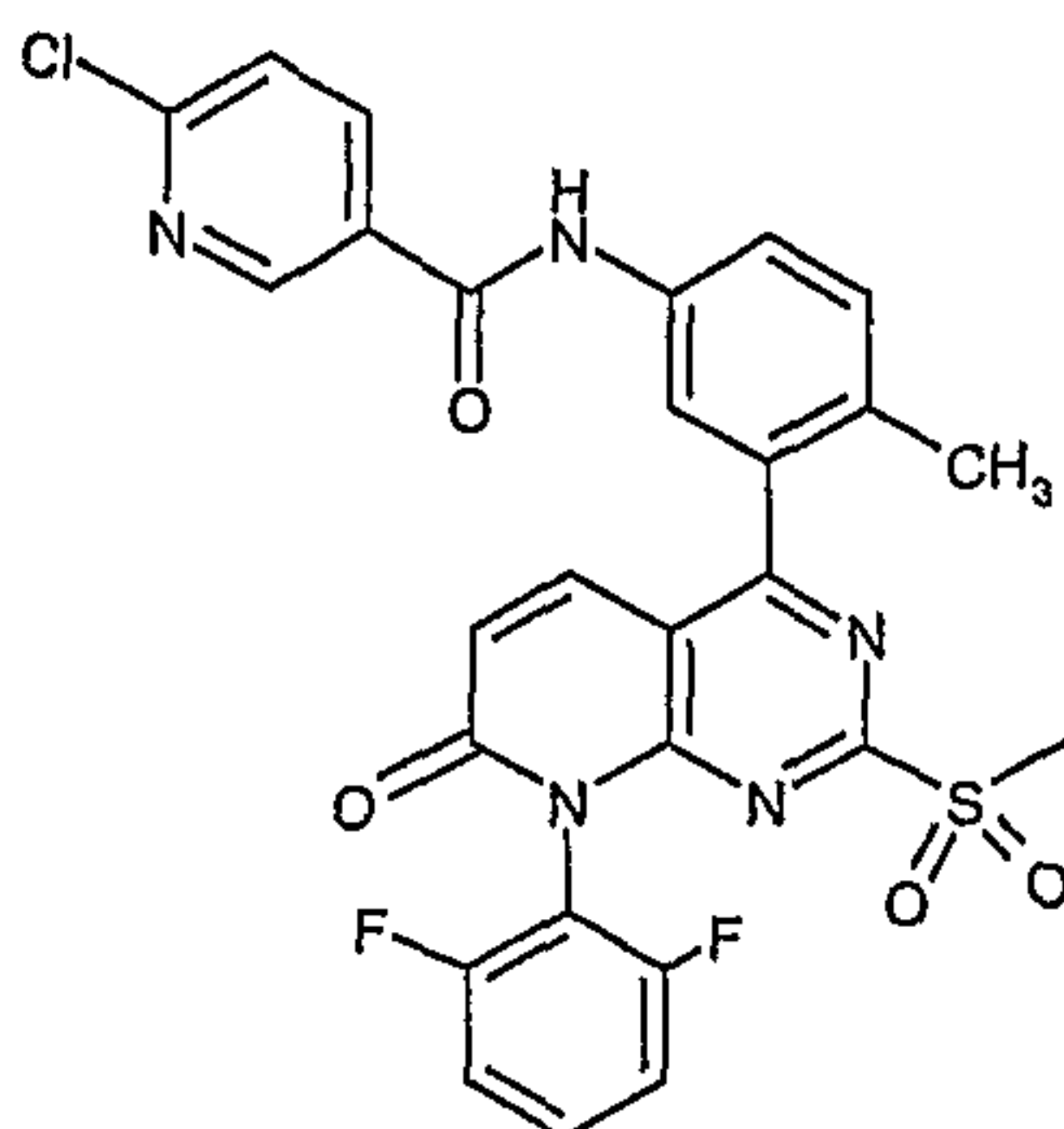


15

The title compound was prepared as described in Example 7b from 4-(5-amino-2-methylphenyl)-8-(2,6-difluorophenyl)-2-(methylthio)pyrido[2,3-*d*]pyrimidin-7(8*H*)-one and 6-chloro-3-pyridinecarbonyl chloride: LC-MS *m/z* 550 (*M*+*H*)<sup>+</sup>, 2.63 min (ret time).

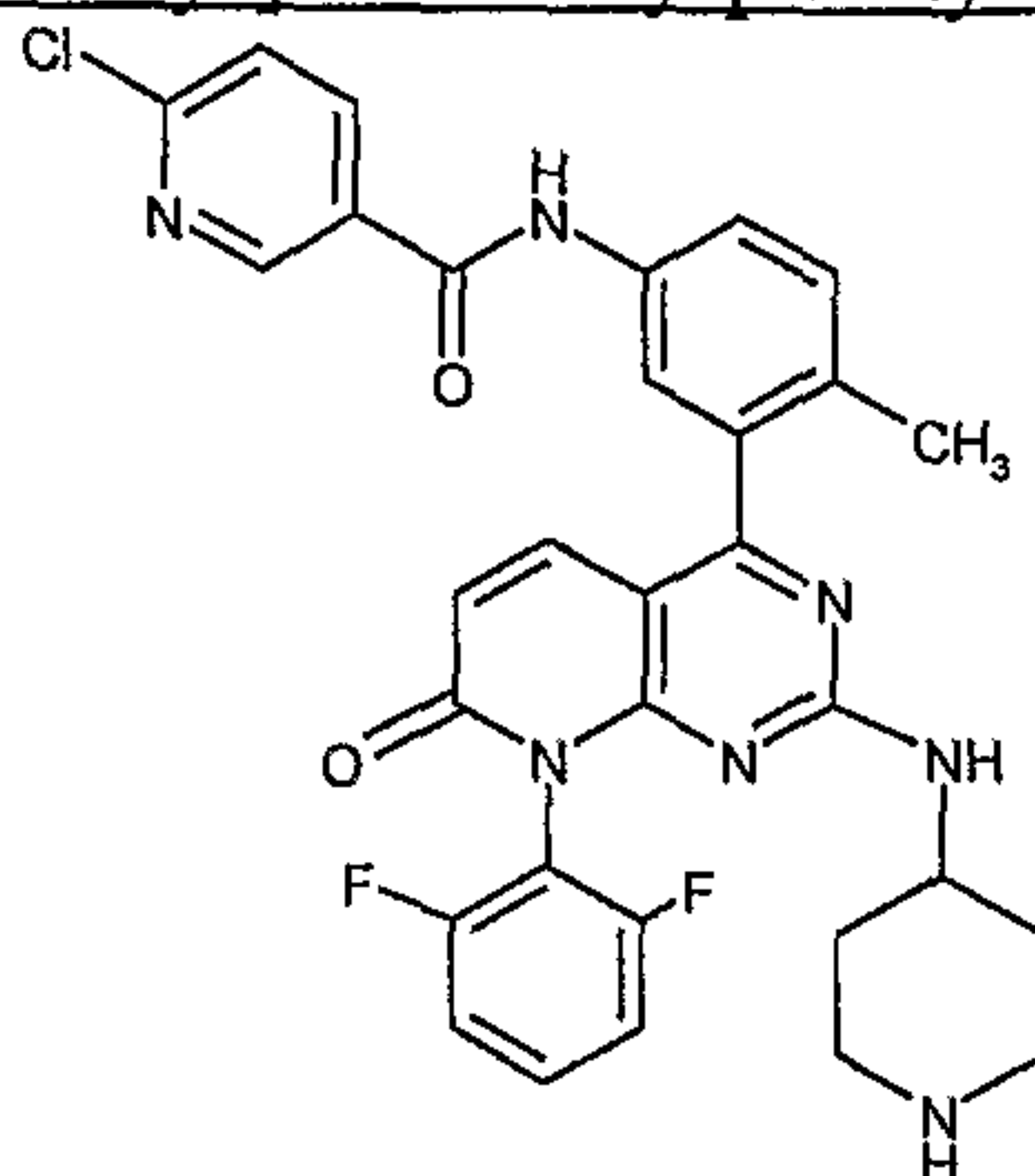
20

14b) 6-chloro-N-{3-[8-(2,6-difluorophenyl)-2-(methylsulfonyl)-7-oxo-7,8-dihydropyrido[2,3-d]pyrimidin-4-yl]-4-methylphenyl}-3-pyridinecarboxamide



The title compound was prepared as described in Example 7c from 6-chloro-*N*-{3-[8-(2,6-difluorophenyl)-2-(methylthio)-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl]-4-methylphenyl}-3-pyridinecarboxamide and *m*-CPBA: LC-MS  
 5 *m/z* 582 (M+H)<sup>+</sup>, 2.30 min (ret time).

14c) 6-chloro-*N*-{3-[8-(2,6-difluorophenyl)-7-oxo-2-(4-piperidinylamino)-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl]-4-methylphenyl}-3-pyridinecarboxamide

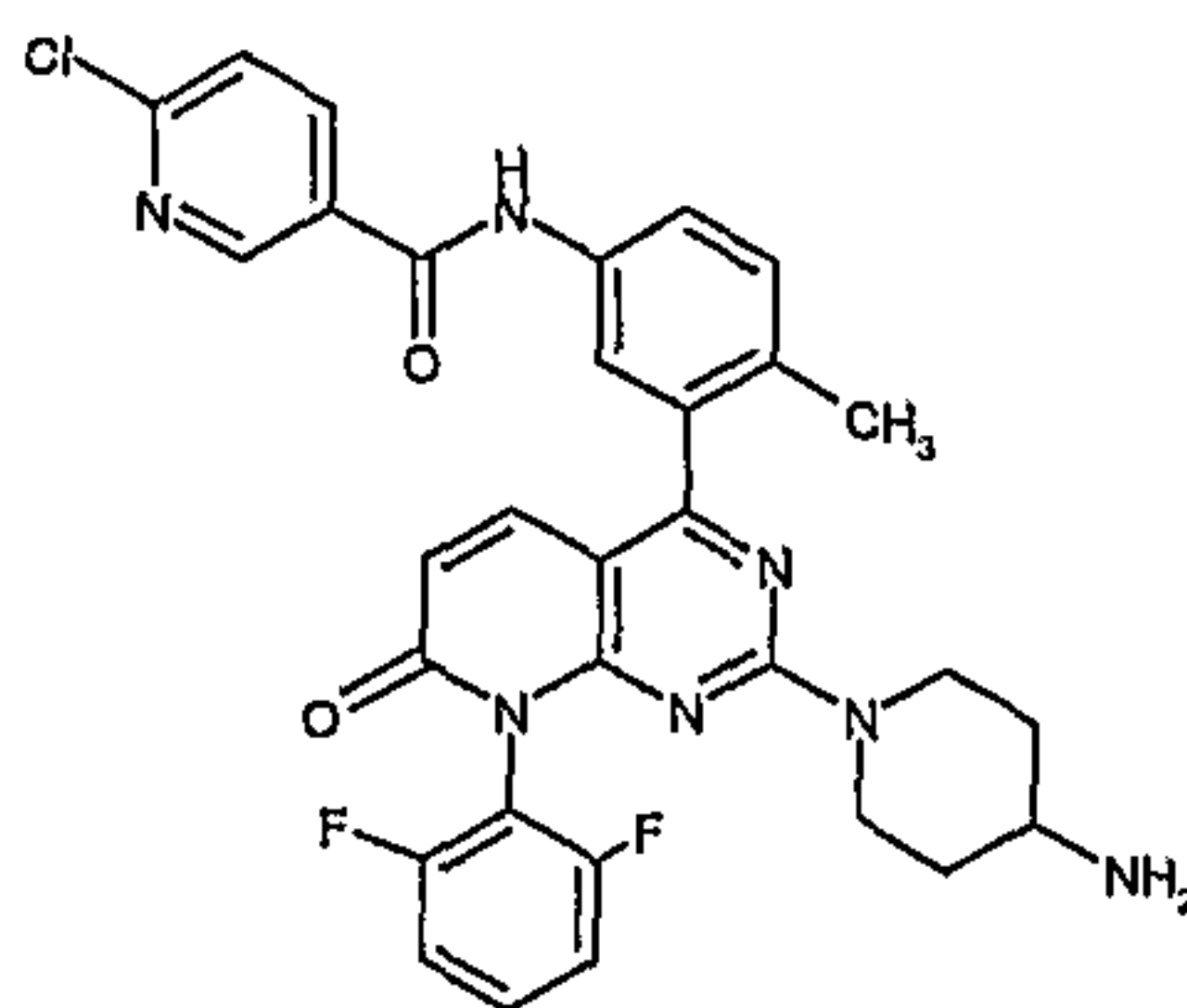


10 The title compound was prepared as described in Example 2 from 6-chloro-*N*-{3-[8-(2,6-difluorophenyl)-2-(methylsulfonyl)-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl]-4-methylphenyl}-3-pyridinecarboxamide and 1,1-dimethylethyl 4-amino-1-piperidinecarboxylate: LC-MS *m/z* 602 (M+H)<sup>+</sup>, 1.75 min (ret time).

15

### Example 15

*N*-{3-[2-(4-amino-1-piperidinyl)-8-(2,6-difluorophenyl)-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl]-4-methylphenyl}-6-chloro-3-pyridinecarboxamide

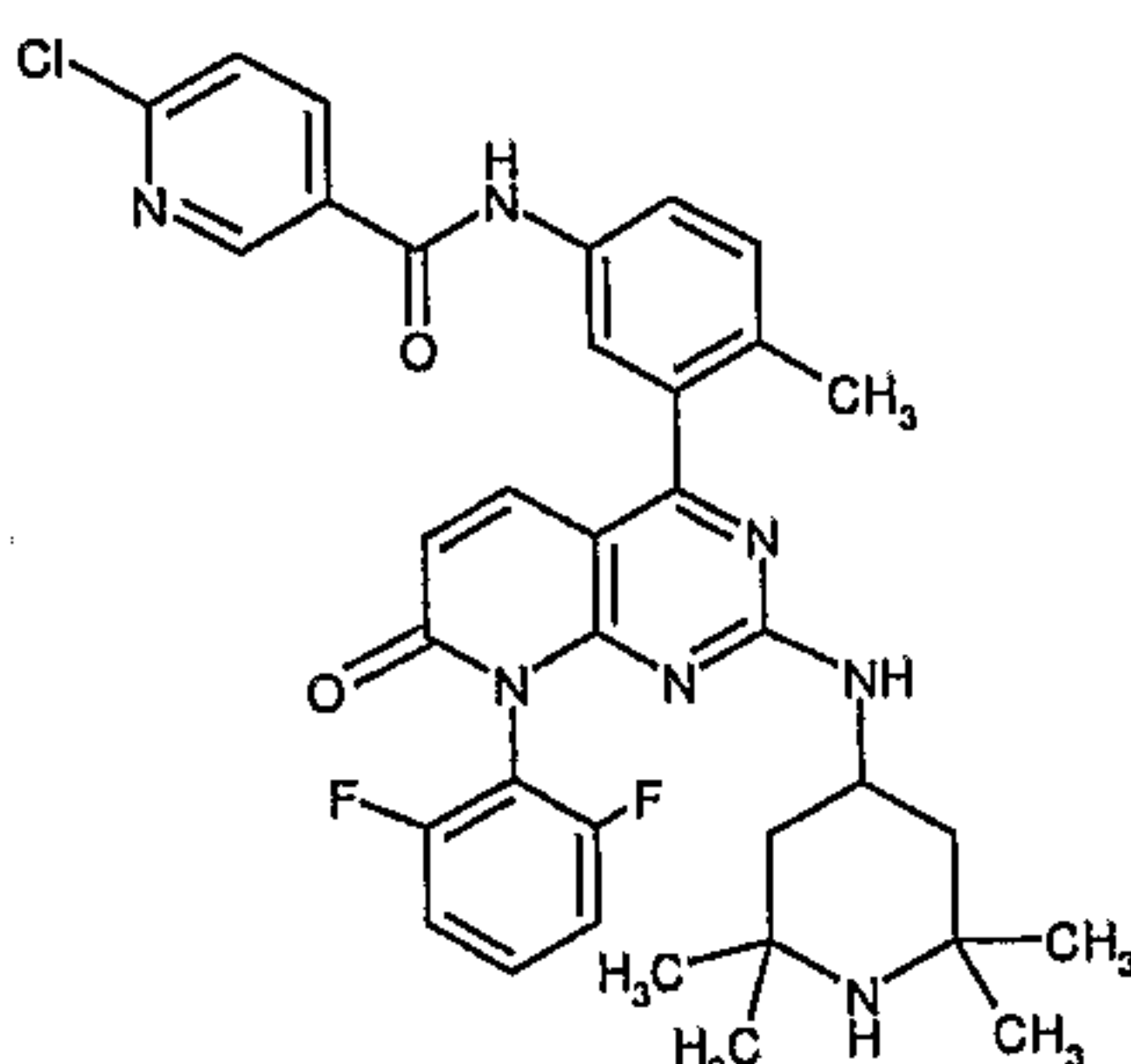


The title compound was prepared as described in Example 2 from 6-chloro-*N*-{3-[8-(2,6-difluorophenyl)-2-(methylsulfonyl)-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl]-4-methylphenyl}-3-pyridinecarboxamide and 1,1-dimethylethyl 4-piperidinylcarbamate: LC-MS *m/z* 602 (M+H)<sup>+</sup>, 1.75 min (ret time).

5

### Example 16

6-chloro-*N*-(3-{8-(2,6-difluorophenyl)-7-oxo-2-[(2,2,6,6-tetramethyl-4-piperidinyl)amino]-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl}-4-methylphenyl)-3-pyridinecarboxamide



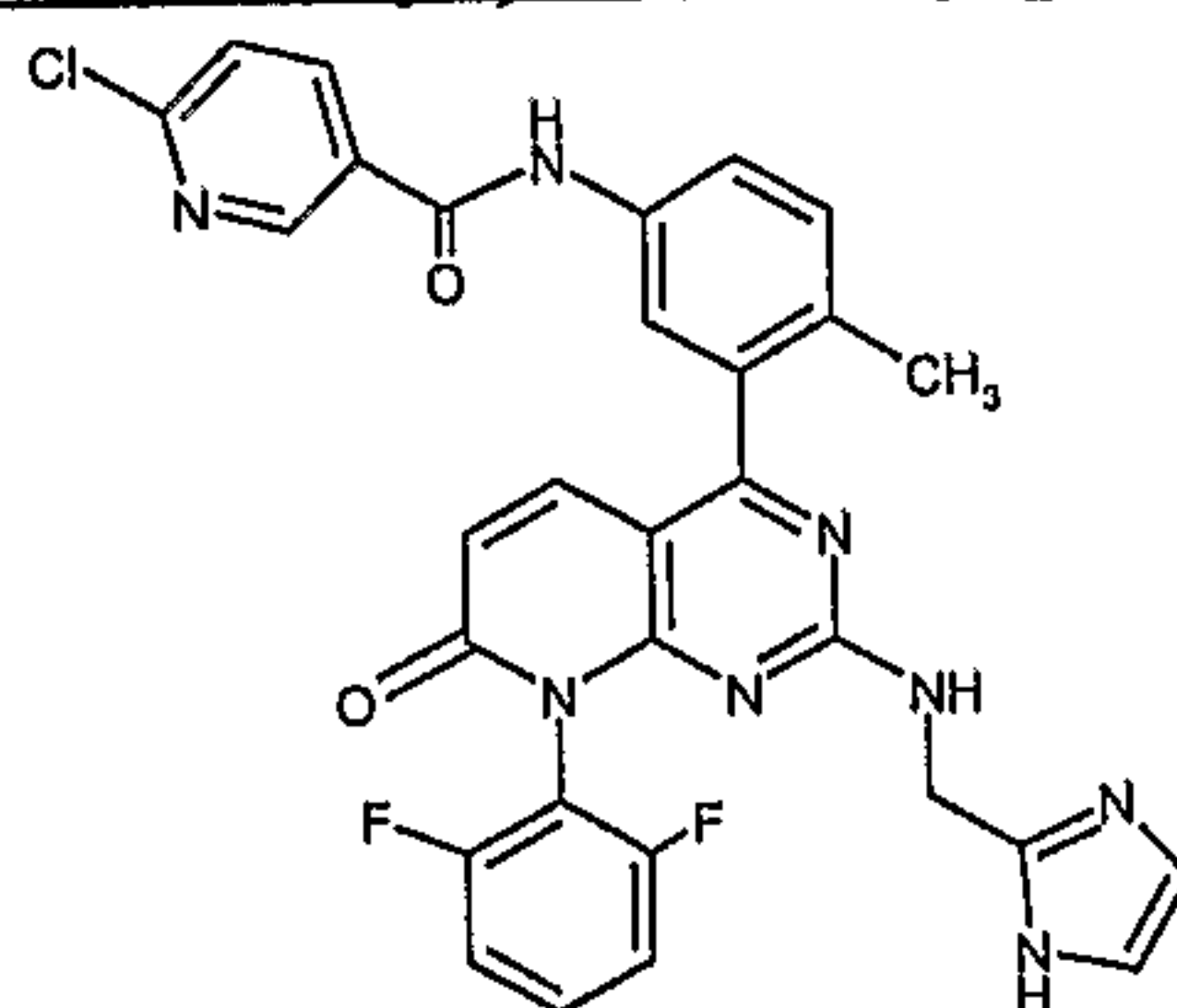
10

The title compound was prepared as described in Example 1d from 6-chloro-*N*-{3-[8-(2,6-difluorophenyl)-2-(methylsulfonyl)-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl]-4-methylphenyl}-3-pyridinecarboxamide and 2,2,6,6-tetramethyl-4-piperidinamine: LC-MS *m/z* 658 (M+H)<sup>+</sup>, 1.92 min (ret time).

15

### Example 17

6-chloro-*N*-(3-{8-(2,6-difluorophenyl)-2-[(1*H*-imidazol-2-ylmethyl)amino]-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl}-4-methylphenyl)-3-pyridinecarboxamide



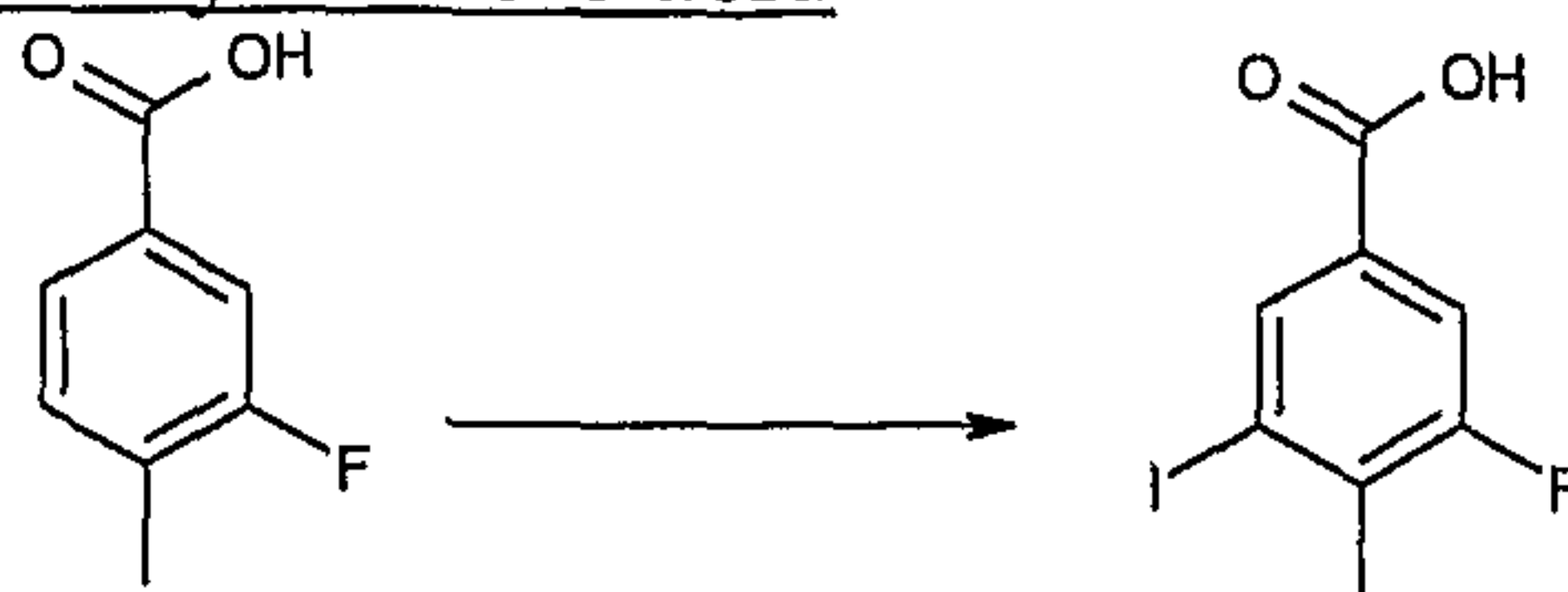
20

The title compound was prepared as described in Example 1d from 6-chloro-*N*-{3-[8-(2,6-difluorophenyl)-2-(methylsulfonyl)-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl]-4-methylphenyl}-3-pyridinecarboxamide and (1*H*-imidazol-2-ylmethyl)amine dihydrochloride: LC-MS *m/z* 599 (M+H)<sup>+</sup>, 1.92 min (ret time).

**Example 18**

*N*-cyclopropyl-3-(8-(2,6-difluorophenyl)-2-[[2-hydroxy-1-(hydroxymethyl)ethyl]amino]-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl)-5-fluoro-4-methylbenzamide

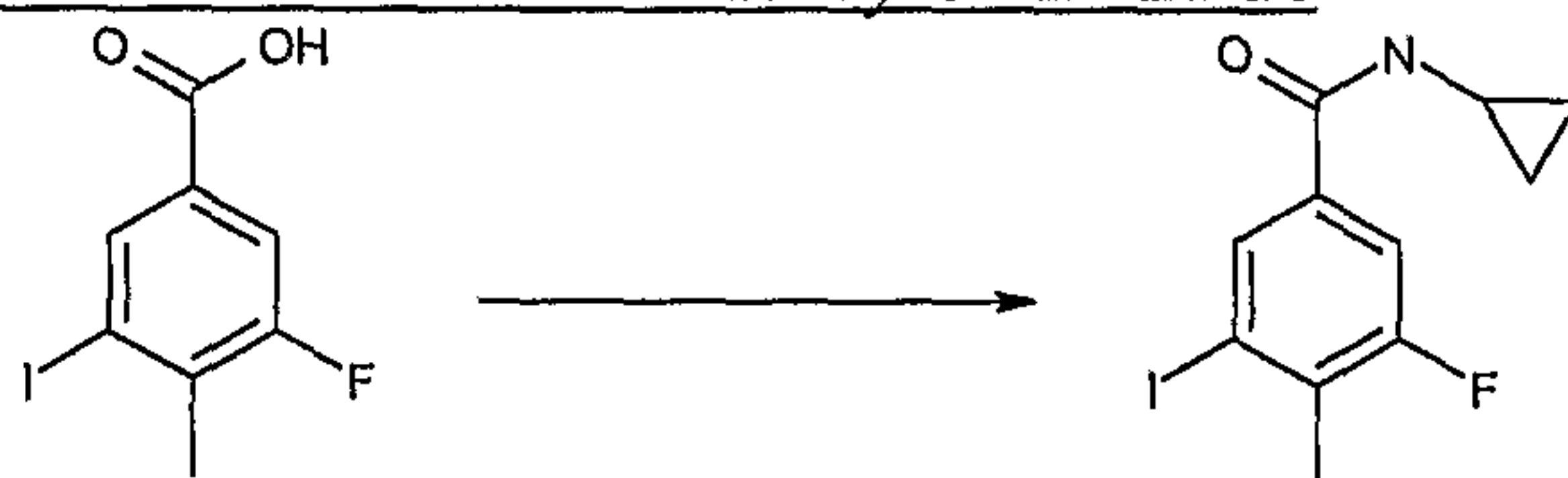
5    18a) 3-fluoro-5-iodo-4-methylbenzoic acid



The benzoic acid (1.54 g, 0.01 mol) is dissolved in trifluoromethanesulfonic acid (10 mL) and cooled to about 0 °C. NIS (2.25 g, 0.01 mol) is added in several portions over a 6 h period while maintaining the reaction temperature at about 0 °C.

10 The mixture is allowed to warm to rt. overnight. The reaction mixture is then poured over ice and extracted with ethyl acetate (3x). The organic layers are washed (Na<sub>2</sub>S<sub>2</sub>O<sub>5</sub>) and concentrated. The material is carried on crude.

15    18b) *N*-cyclopropyl-3-fluoro-5-iodo-4-methylbenzamide



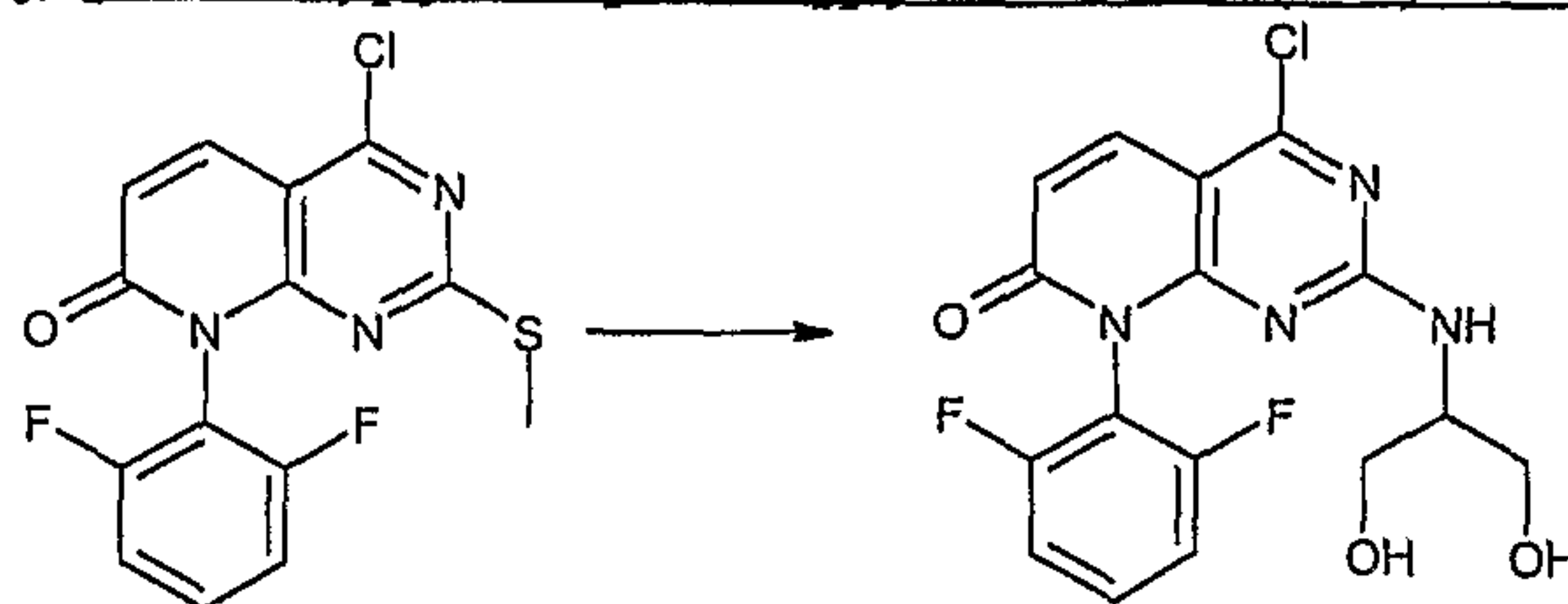
The crude acid from Example 18a (~1.5 g) is dissolved in thionyl chloride (75 mL) and heated to 80 °C for about 2 h. The mixture is then cooled to room temperature and stirred under N<sub>2</sub> overnight. The mixture is concentrated in vacuo and dissolved in 15 mL DCM. Na<sub>2</sub>CO<sub>3</sub> (3g) is added along with the cyclopropyl amine (0.69 mL, 0.01 moles (hereinafter "mol")). The mixture is allowed to stir overnight and purified via flash chromatography (5% MeOH / CH<sub>2</sub>Cl<sub>2</sub>) to afford 0.904g of the title compound.

25    18c) *N*-cyclopropyl-3-fluoro-4-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide



The iodo compound from Example 18b (0.904 g, 2.83 mmol) is dissolved in DMF (30 mL). Bis-pinicalato-diborane (1.44 g, 2.83 mmol) is added followed by PdCl<sub>2</sub>.dppf (55 mg) and potassium acetate (1.38 g, 14.15 mmol). The mixture are stirred for about 18 h, concentrated *in vacuo* and purified via flash chromatography to afford the title compound (60 mg).

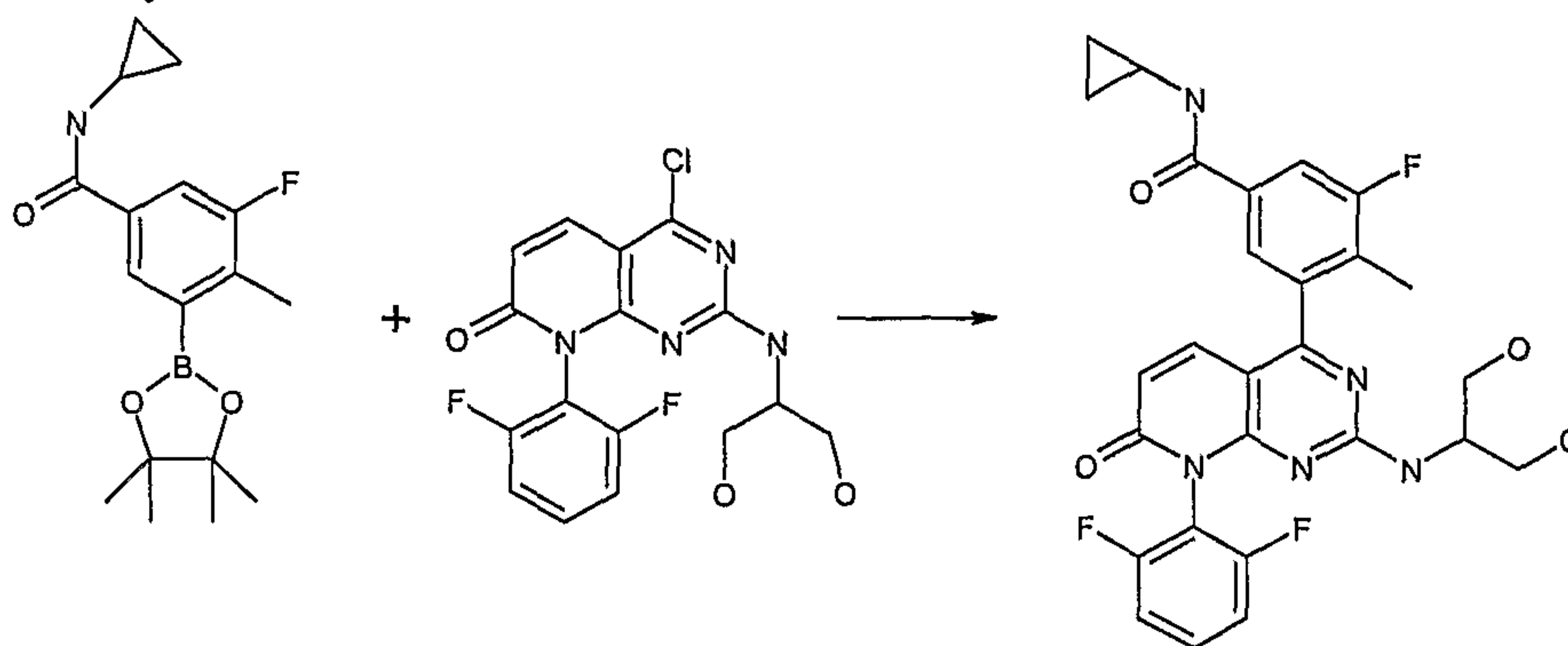
18d) 4-chloro-8-(2,6-difluorophenyl)-2-{[2-hydroxy-1-(hydroxymethyl)ethyl]amino}pyrido[2,3-*d*]pyrimidin-7(8*H*)-one



To a solution of 4-chloro-8-(2,6-difluorophenyl)-2-(methylthio)pyrido[2,3-*d*]pyrimidin-7(8*H*)-one (2.7 mmol) in dichloromethane (50 mL) was added *m*-CPBA (0.63 g, 4.0 mmol). The resultant mixture was stirred at room temperature for 10 minutes, then concentrated under *vacuo*. Flash chromatography (EtOAc / Hexane, 1 : 3) afforded 4-chloro-2-methylsulfinyl-8-(2,6-difluoro-phenyl)-8*H*-pyrido[2,3-*d*]pyrimidin-7-one (88%): LC-MS *m/z* 356 (due to solventlysis with methanol, M+H)<sup>+</sup>; <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ 2.85 (s, 3H), 7.03 (d, *J* = 9.6 Hz, 1H), 7.15 (m, 2H), 7.53 (m, 1H), 8.18 (d, *J* = 9.6 Hz, 1H).

A solution of 4-chloro-2-methylsulfinyl-8-(2,6-difluoro-phenyl)-8*H*-pyrido[2,3-*d*]pyrimidin-7-one (0.75 mmol) in dichloromethane (30 mL) was mixed with a solution of serinol (0.075 g, 0.82 mmol) and Et<sub>3</sub>N (0.21 mL, 1.5 mmol) in DMF (0.75mL). The resultant mixture was stirred at room temperature for about 1 hour, then concentrated under vacuum. Flash chromatography (EtOAc : Hexane, 3 : 1) provided the title compound 4-chloro-8-(2,6-difluorophenyl)-2-{[2-hydroxy-1-(hydroxy-methyl)ethyl]amino}pyrido[2,3-*d*]pyrimidin-7(8*H*)-one (42%): LC-MS *m/z* 383 (M+H)<sup>+</sup>; <sup>1</sup>H-NMR(CDCl<sub>3</sub>) δ 1.95 (s, br, 2H), 3.90 (m, br, 5H), 6.05 (m, br, 1H), 6.56 (d, *J* = 9.6 Hz, 1H), 7.10 (m, 2H), 7.48 (d, *J* = 8.1 Hz, 2H), 7.94 (d, *J* = 9.6 Hz, 1H).

18e) *N*-cyclopropyl-3-(8-(2,6-difluorophenyl)-2-{[2-hydroxy-1-(hydroxymethyl)ethyl]amino}-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl)-5-

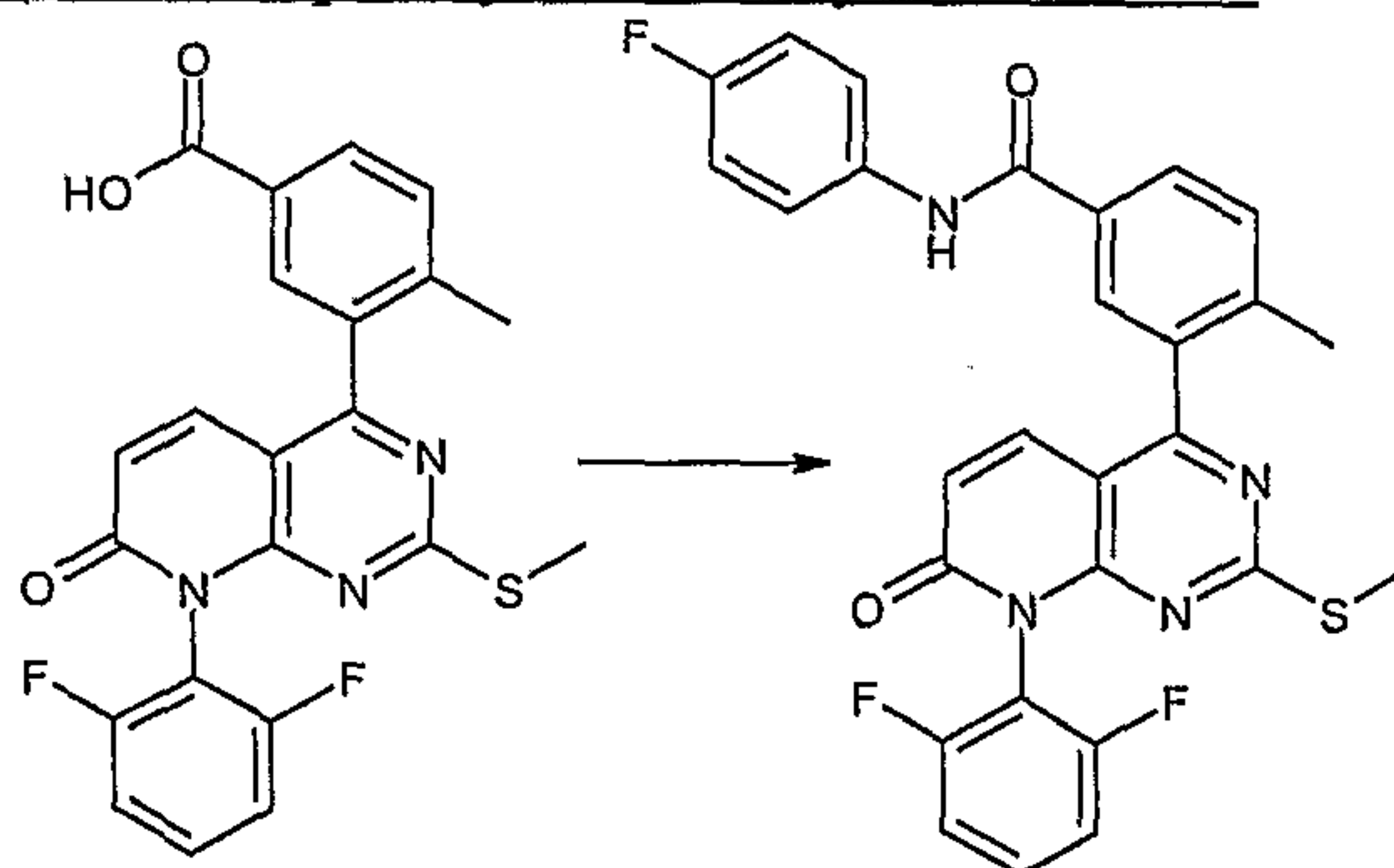
fluoro-4-methylbenzamide

The chloride (0.056 g, 0.17 mmol), borate ester (0.065 g, 0.17 mmol),  $K_2CO_3$  (0.07 g, 0.51 mmol) and tetrakis triphenyl phosphine palladium (10 mg, 0.05eq) are dissolved in dioxane / water (3:1, 10 mL) and heated to about 100 °C for about 3 h. The mixture is concentrated and purified via reverse phase HPLC to afford the title compound (9 mg, yellow powder, mp 214.2-217.5): LC-MS  $m/z$  540 ( $M+H$ )<sup>+</sup>, 1.69 min (ret time). HPLC indicates 96% pure.

**Example 19**

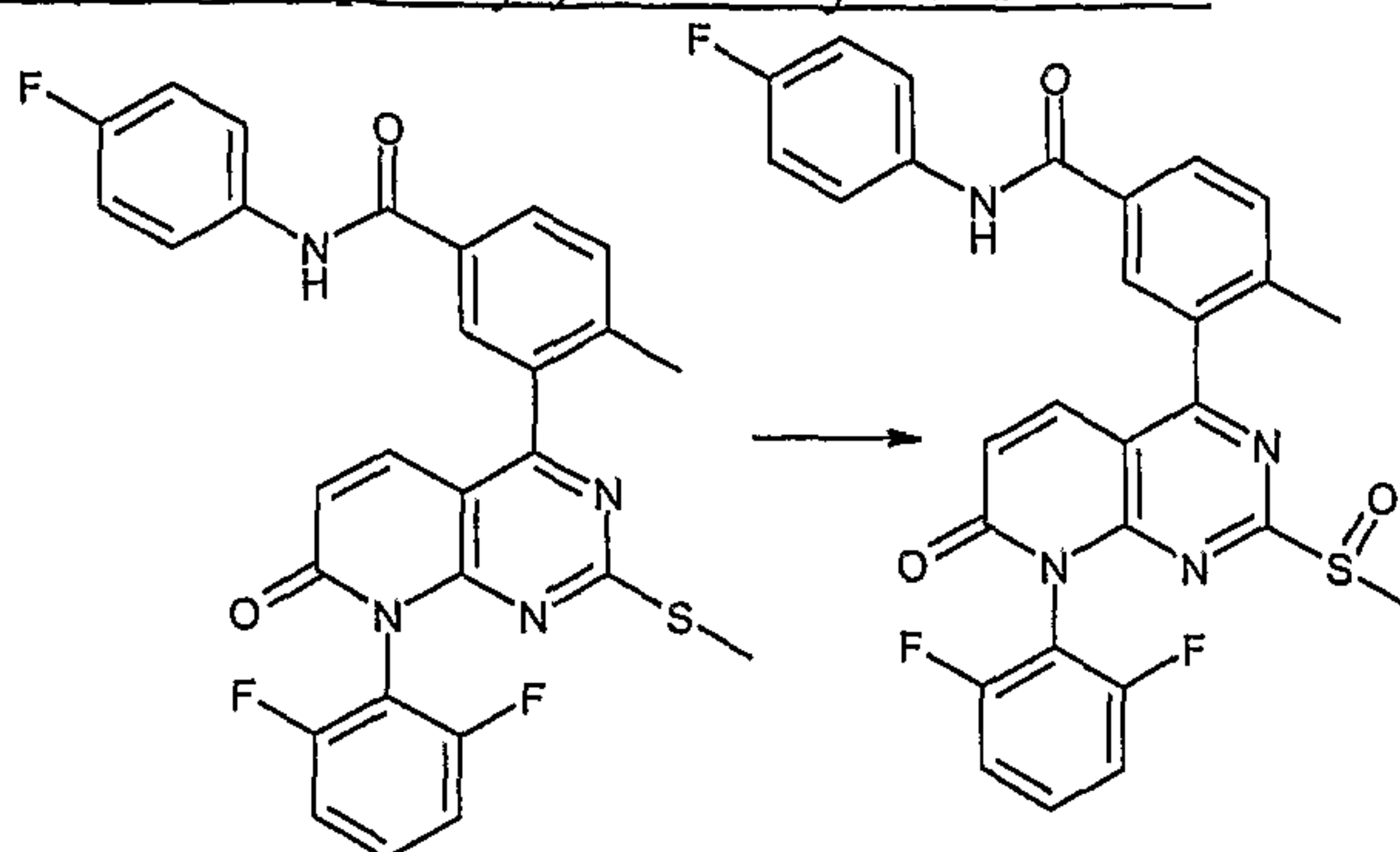
3-(8-(2,6-difluorophenyl)-2-{[2-hydroxy-1-(hydroxymethyl)ethyl]amino}-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl)-*N*-(4-fluorophenyl)-4-methylbenzamide

19a) 3-[8-(2,6-difluorophenyl)-2-(methylthio)-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl]-*N*-(4-fluorophenyl)-4-methylbenzamide



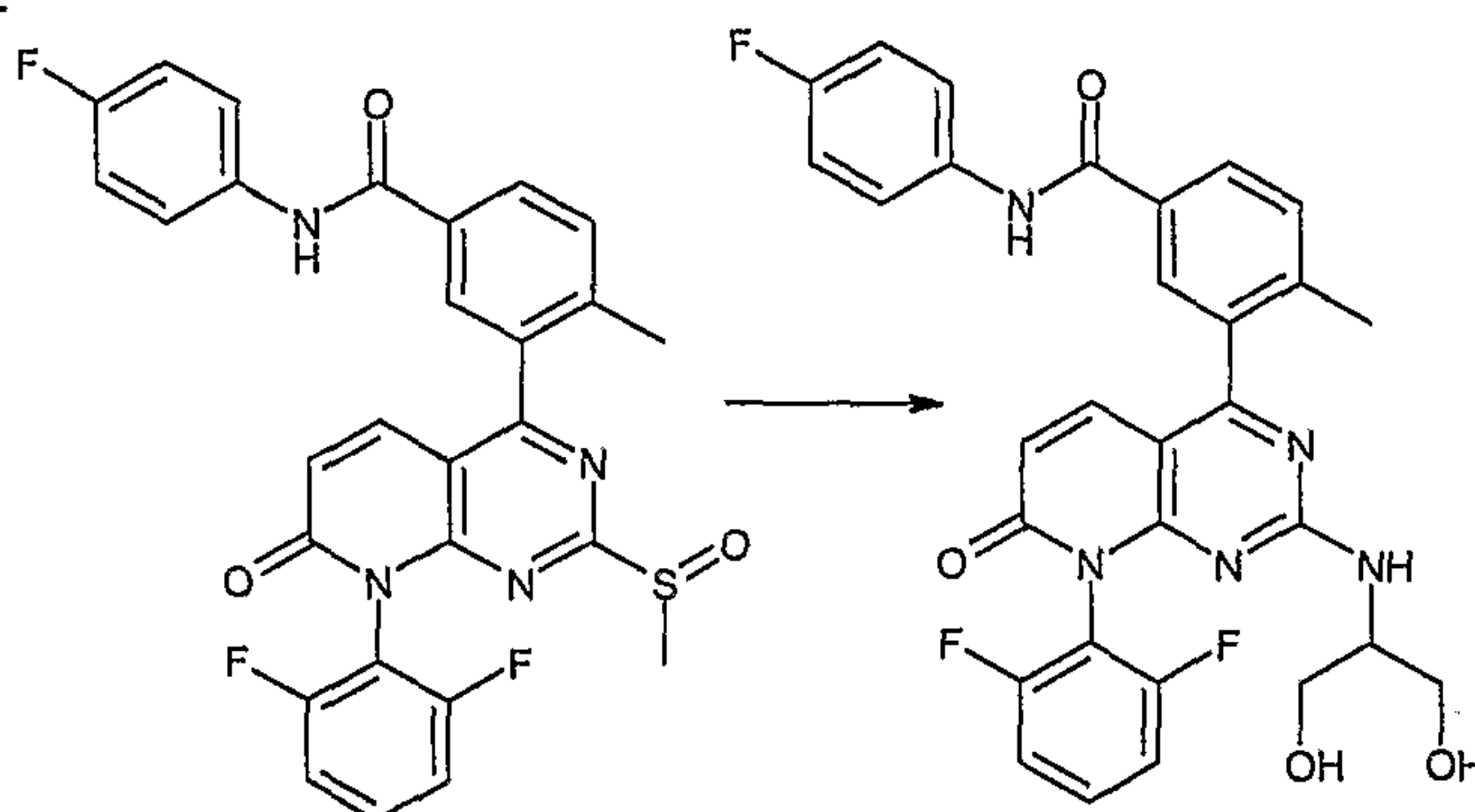
The title compound was prepared from 3-[8-(2,6-difluorophenyl)-2-(methylthio)-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl]-4-methylbenzoic acid and 4-fluoroaniline by following the General Procedure for EDC couplings as disclosed in the general experimental section above. Crude reaction mixture was purified via flash chromatography (EtOAc:Hexanes, 2:1) to afford the title compound (0.125 g, 34%).

19b) 3-[8-(2,6-difluorophenyl)-2-(methylsulfinyl)-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl]-*N*-(4-fluorophenyl)-4-methylbenzamide



The title compound (0.105 g, 79%) was prepared by following the General  
5 Procedure for sulfide oxidations, as disclosed above.

19c) 3-(8-(2,6-difluorophenyl)-2-{[2-hydroxy-1-(hydroxymethyl)ethyl]amino}-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl)-*N*-(4-fluorophenyl)-4-methylbenzamide

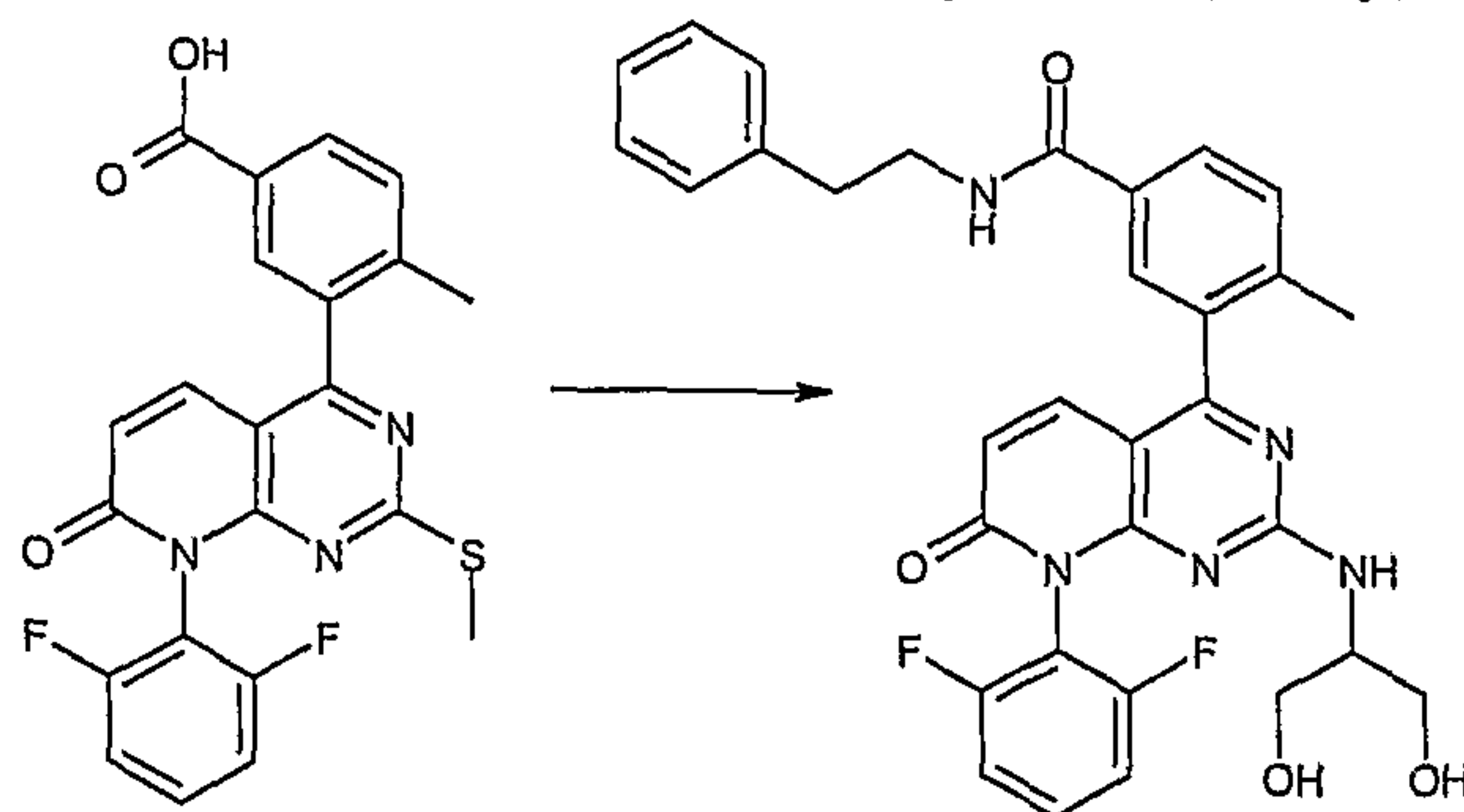


10

The title compound is prepared by following the General Procedure for  
Sulfoxide/Sulfone/sulfone displacement as disclosed above. Concentrated reaction  
mixture is purified via reversed-phase HPLC to give the desired compound as a  
white solid (43 mg, 39%): LC-MS  $m/z$  576 ( $M+H$ )<sup>+</sup>, 1.89 min (ret time). HPLC  
15 (254nm) indicates 90% pure.

**Example 20**

3-(8-(2,6-difluorophenyl)-2-{[2-hydroxy-1-(hydroxymethyl)ethyl]amino}-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl)-4-methyl-*N*-(2-phenylethyl)benzamide

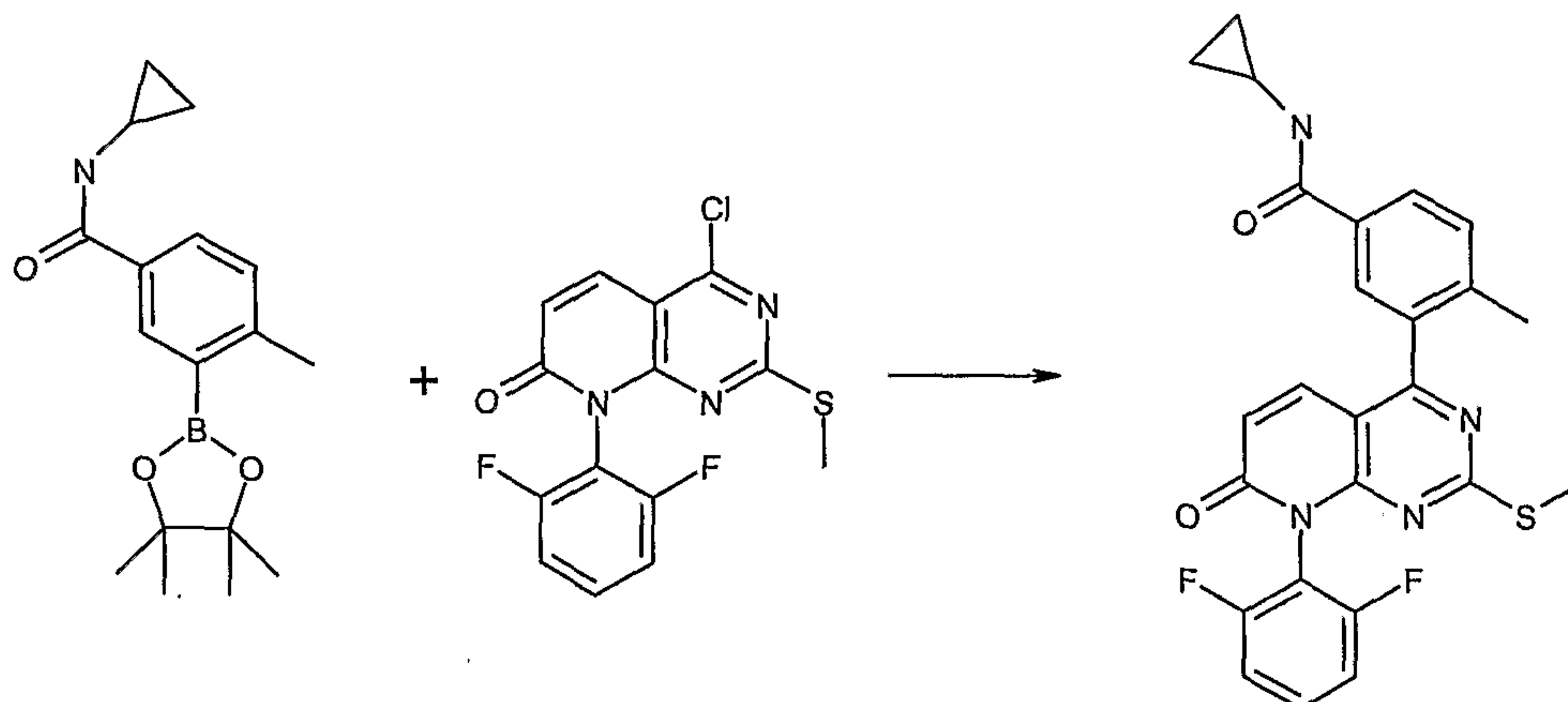


- 5 The title compound was prepared by following the procedures as described in Example 19 using 2-phenylethanamine for the amide formation: LC-MS  $m/z$  586 ( $M+H$ )<sup>+</sup>, 1.82 min (ret time).

**Example 21**

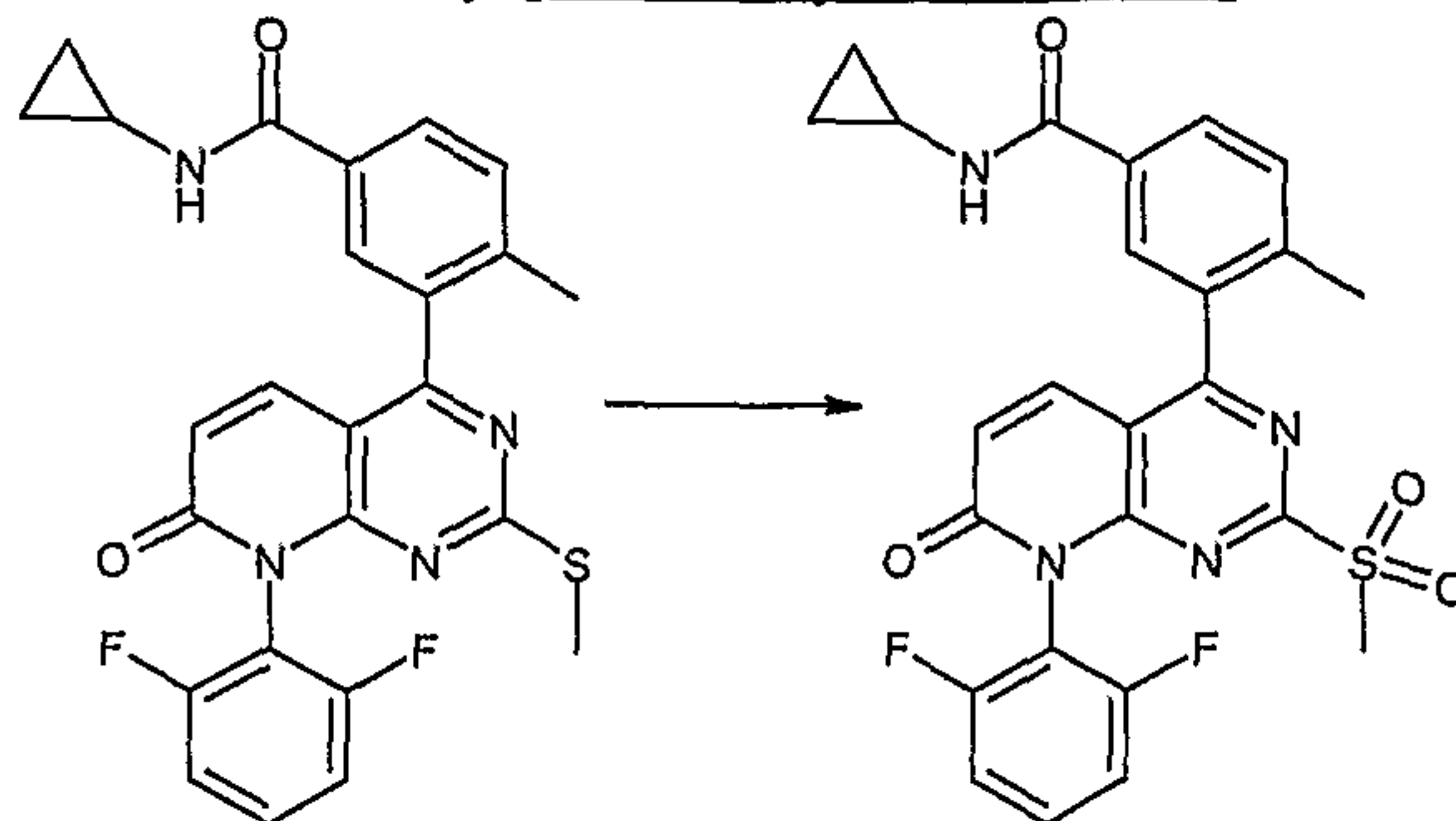
- 10 3-{8-(2,6-difluorophenyl)-7-oxo-2-[(2,2,6,6-tetramethyl-4-piperidiny]amino]-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl}-4-methyl-*N*-(1-methylpropyl)benzamide

21a) *N*-cyclopropyl-3-[8-(2,6-difluorophenyl)-2-(methylthio)-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl]-4-methylbenzamide



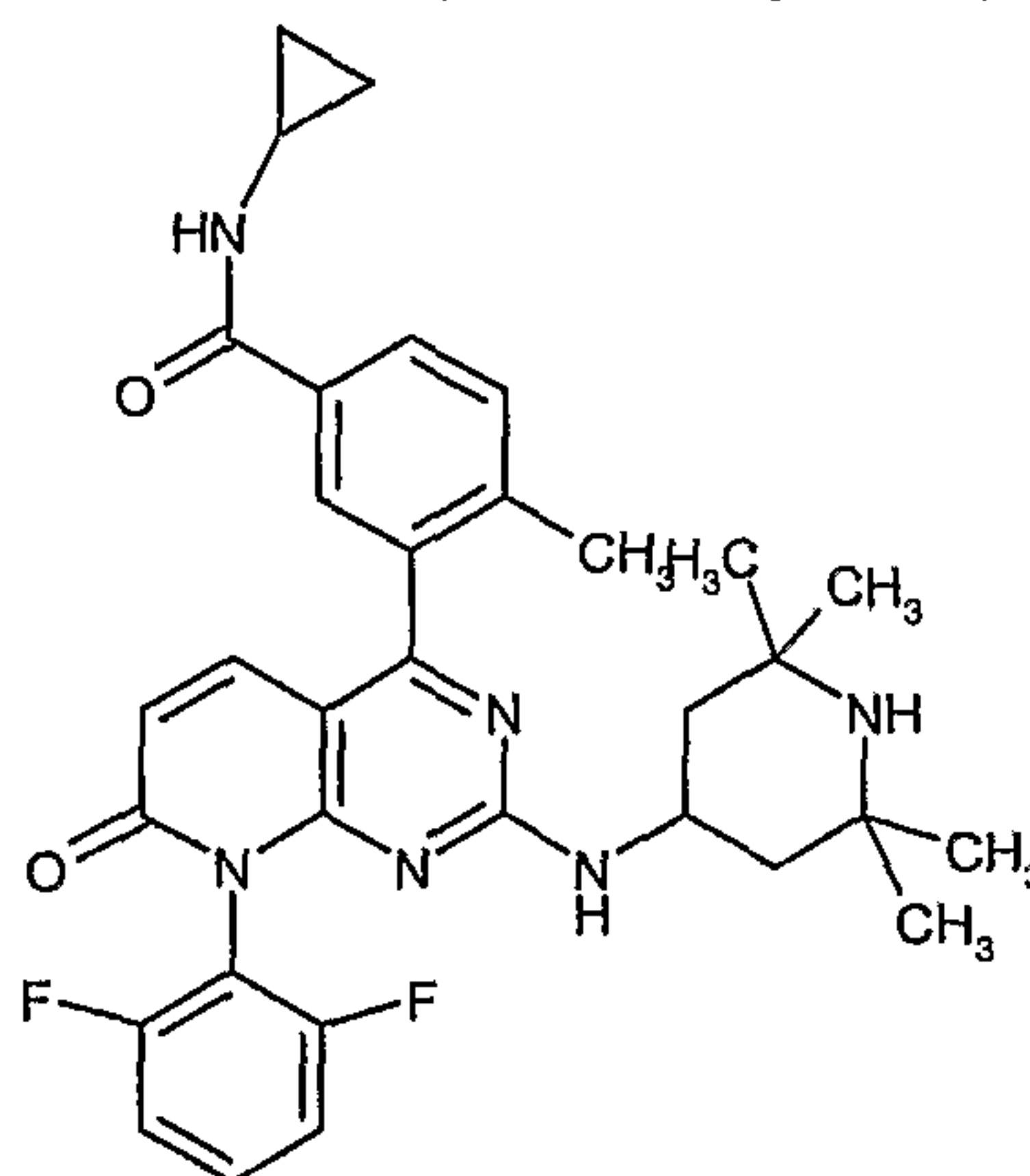
- 15 The borate ester (0.683 g, 2.27 mmol), chloride (0.768 g, 2.27 mmol), K<sub>2</sub>CO<sub>3</sub> (0.941 g, 6.81 mmol) and tetrakis(triphenylphosphine) palladium (131 mg, 0.11 mmol) are dissolved in dioxane / water (3:1) and heated at reflux for about 4 h. The reaction mixture is then taken up in ethyl acetate and washed with water, brine and dried with Na<sub>2</sub>SO<sub>4</sub>. The concentrated mixture was purified via flash  
20 chromatography to give the desired product (0.6 g, 55%).

21b) N-cyclopropyl-3-[8-(2,6-difluorophenyl)-2-(methylsulfonyl)-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl]-4-methylbenzamide



5 The title compound is prepared according to the General Procedure for sulfide oxidation, as disclosed above. It is concentrated to give the desired product as a yellow powder (0.3 g, 49%).

21c) 3-{8-(2,6-difluorophenyl)-7-oxo-2-[(2,2,6,6-tetramethyl-4-piperidiny)amino]-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl}-4-methyl-N-(1-methylpropyl)benzamide



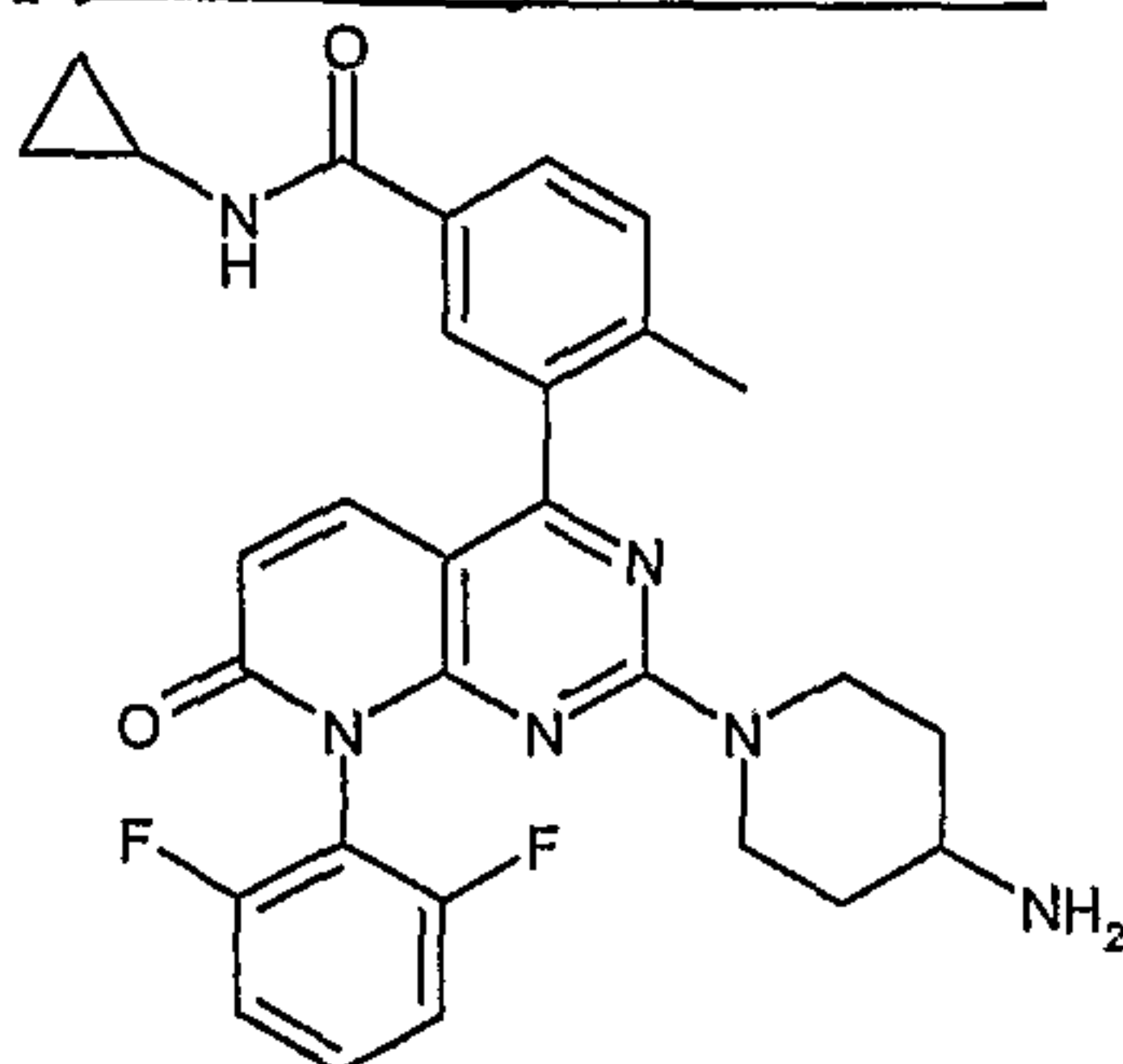
10

The title compound is prepared according to the General Procedure for Sulfoxide/Sulfone/Sulfone Displacement, as disclosed above. The concentrated reaction mixture is precipitated with DMSO / water, and filtered. The desired product is obtained as a white solid (m.p. 326.3-327.9) 95% pure by HPLC (55 mg, 45%); LC-MS  $m/z$  587 ( $M+H$ )<sup>+</sup>, 1.74 min (ret time).

15

**Example 22**

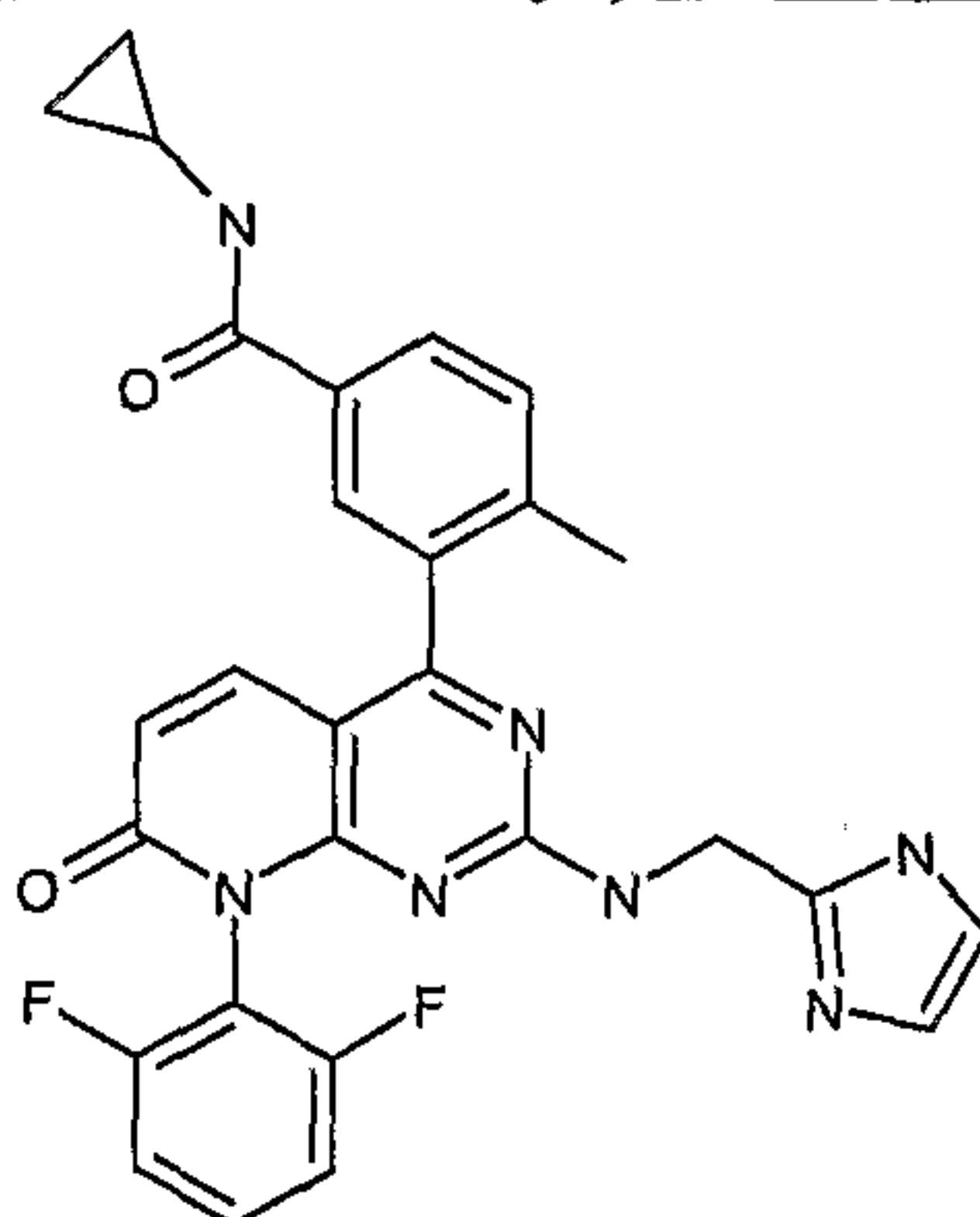
3-[2-(4-amino-1-piperidinyl)-8-(2,6-difluorophenyl)-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl]-*N*-cyclopropyl-4-methylbenzamide



5 The title compound is prepared from compound *N*-cyclopropyl-3-[8-(2,6-difluorophenyl)-2-(methylsulfonyl)-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl]-4-methylbenzamide and 4-piperidinamine by following the General Procedure for Sulfoxide/Sulfone/Sulfone Displacement, as disclosed above. The concentrated  
10 reaction mixture is precipitated with ethyl acetate/hexanes, and filtered. The desired product is obtained as a yellow solid (75 mg, 100%) 94% pure by HPLC: LC-MS  $m/z$  531 ( $M+H$ )<sup>+</sup>, 1.65 min (ret time).

**Example 23**

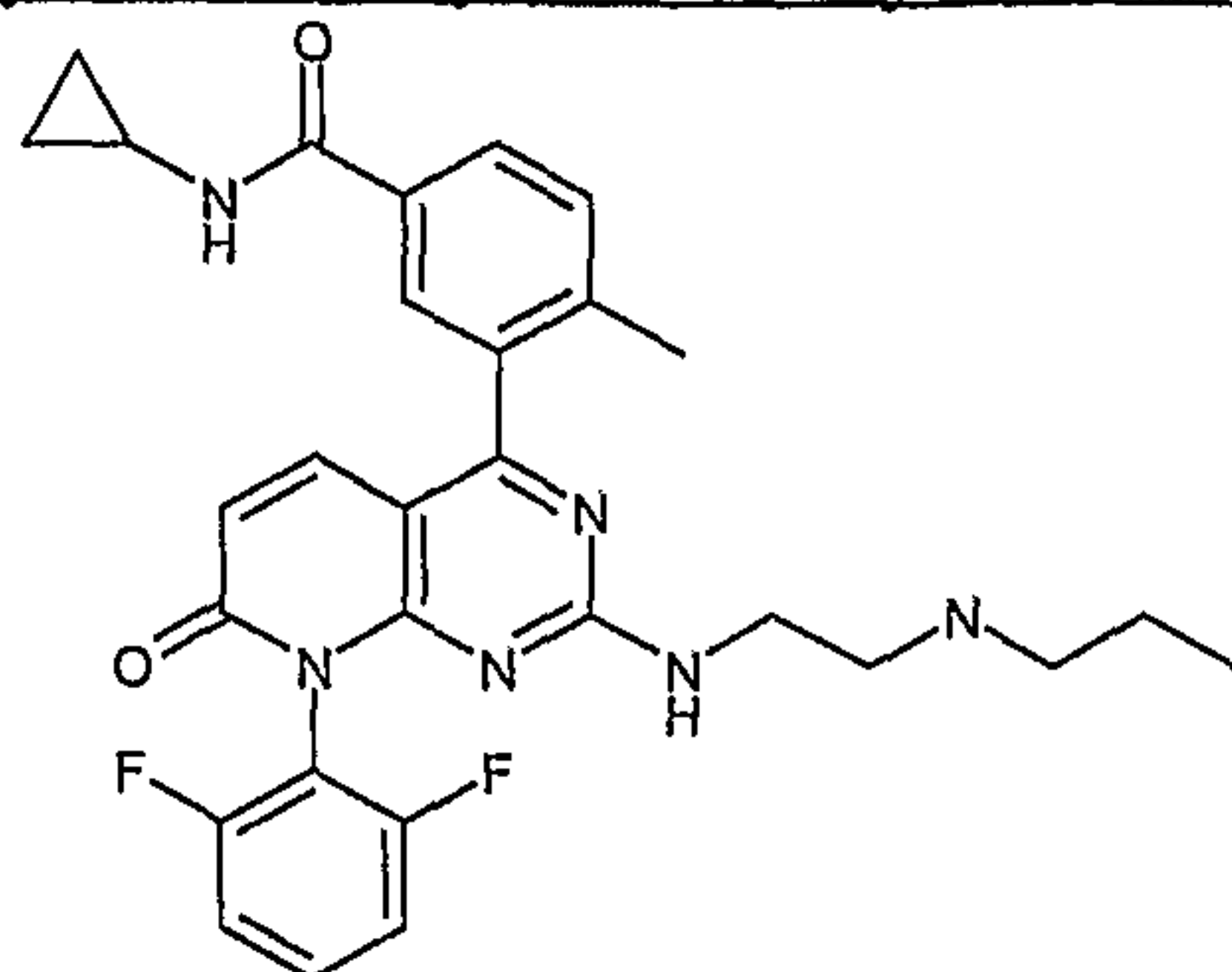
*N*-cyclopropyl-3-[8-(2,6-difluorophenyl)-2-[(1*H*-imidazol-2-ylmethyl)amino]-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl]-4-methylbenzamide



*N*-cyclopropyl-3-[8-(2,6-difluorophenyl)-2-(methylsulfonyl)-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl]-4-methylbenzamide (0.1 g, 0.2 mmol) is dissolved in DMF (10 mL) and (1*H*-imidazol-2-ylmethyl)amine dihydrochloride (0.053 g, 0.4 mmol) is added followed by triethylamine (0.167 mL, 1.2 mmol). The  
20 mixture is heated to about 60 °C for about 3 h. The reaction is judged to be complete by LCMS and the crude mixture is purified via reversed-phase HPLC. HPLC indicates 95% pure (254 nm) and the desired product is obtained as a white powder (54 mg, 50%): LC-MS  $m/z$  528 ( $M+H$ )<sup>+</sup>, 1.45 min (ret time).

**Example 24**

*N*-cyclopropyl-3-(8-(2,6-difluorophenyl)-7-oxo-2-{[2-(propylamino)ethyl]amino}-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl)-4-methylbenzamide



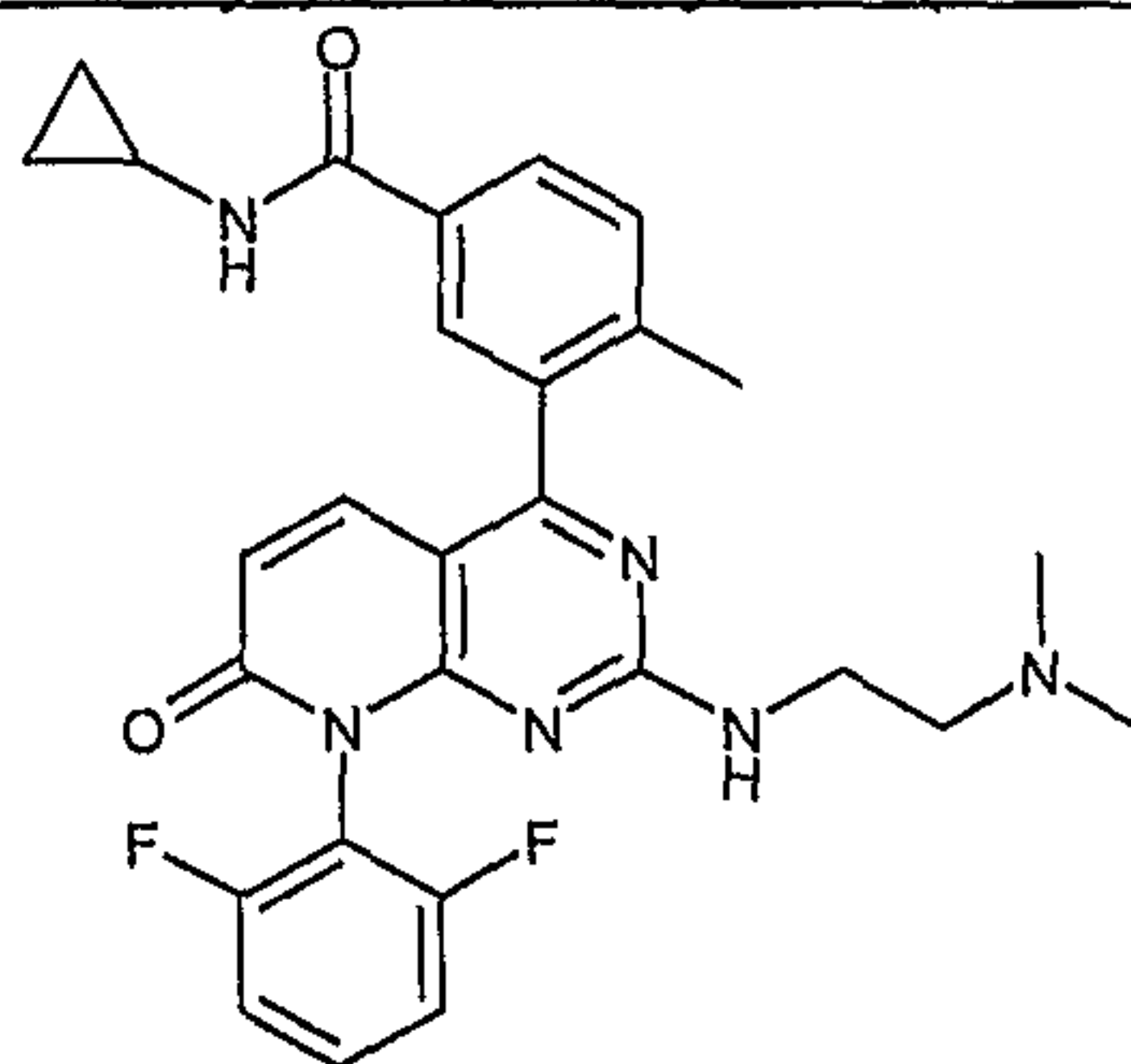
5

The title compound is prepared from *N*-cyclopropyl-3-[8-(2,6-difluorophenyl)-2-(methylsulfonyl)-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl]-4-methylbenzamide and *N*-propyl-1,2-ethanediamine following the General Procedure for Sulfoxide/Sulfone Displacement, disclosed above. The concentrated reaction mixture is purified via reversed-phase HPLC. The desired product is obtained as a yellow solid (m.p. 120-134) >95% pure by HPLC (65 mg, 61%): LC-MS *m/z* 533 (M+H)<sup>+</sup>, 1.84 min (ret time).

10

**Example 25**

3-(8-(2,6-difluorophenyl)-2-{[2-(dimethylamino)ethyl]amino}-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl)-4-methyl-*N*-(1-methylpropyl)benzamide



15

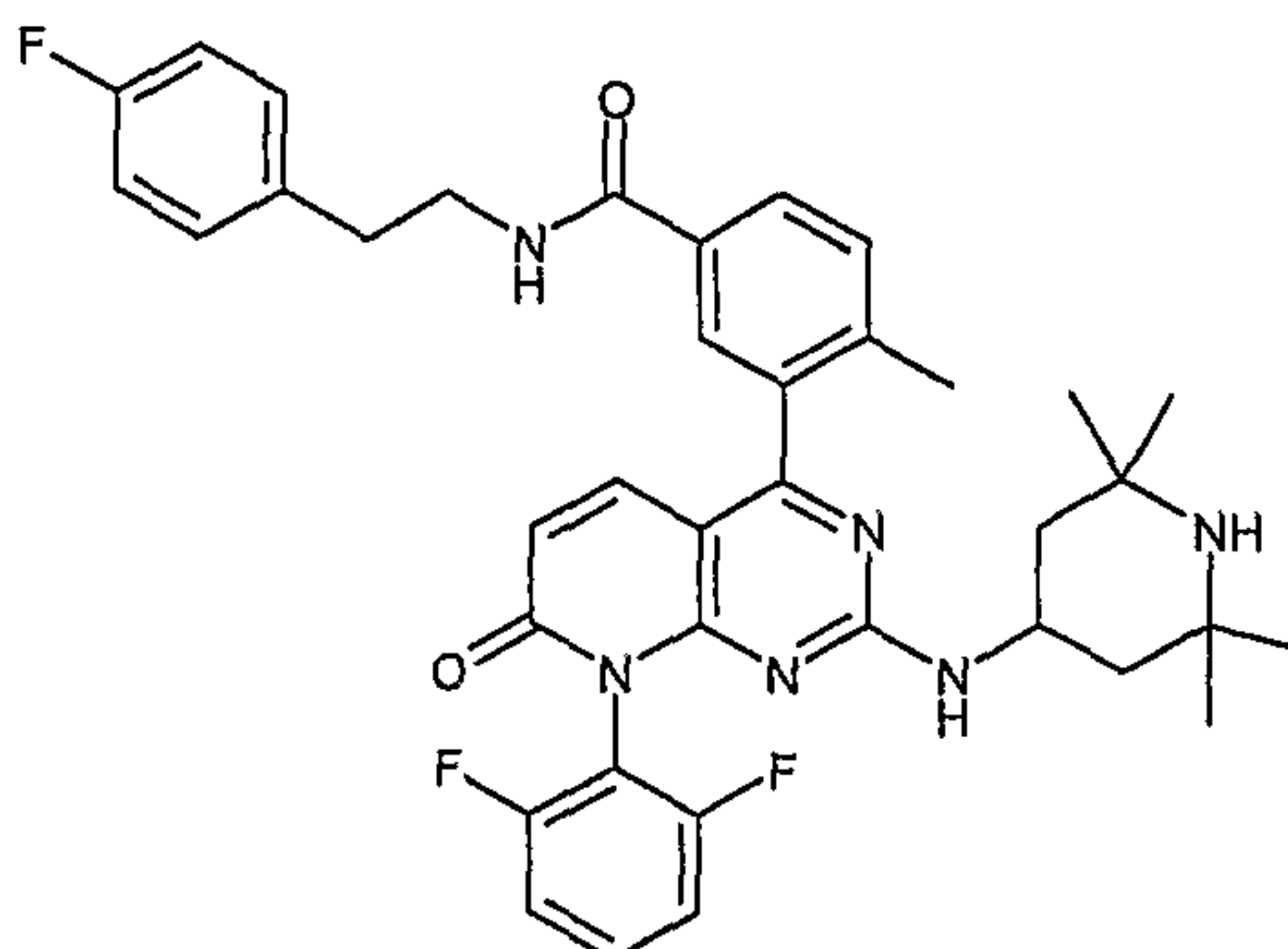
The title compound is prepared from the compound from *N*-cyclopropyl-3-[8-(2,6-difluorophenyl)-2-(methylsulfonyl)-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl]-4-methylbenzamide and *N,N'*-dimethyl-1,2-ethanediamine by following the General Procedure for Sulfoxide/Sulfone Displacement, disclosed above. The concentrated reaction mixture is purified via reversed-phase HPLC. The desired product is obtained as an off-white solid (m.p. 214.7-217.5 °C) >95% pure by HPLC (69 mg, 67%): LC-MS *m/z* 519 (M+H)<sup>+</sup>, 1.54 min (ret time).

20

25

**Example 26**

3-[8-(2,6-difluorophenyl)-7-oxo-2-[(2,2,6,6-tetramethyl-4-piperidiny]amino]-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl]-*N*-[2-(4-fluorophenyl)ethyl]-4-methylbenzamide



5

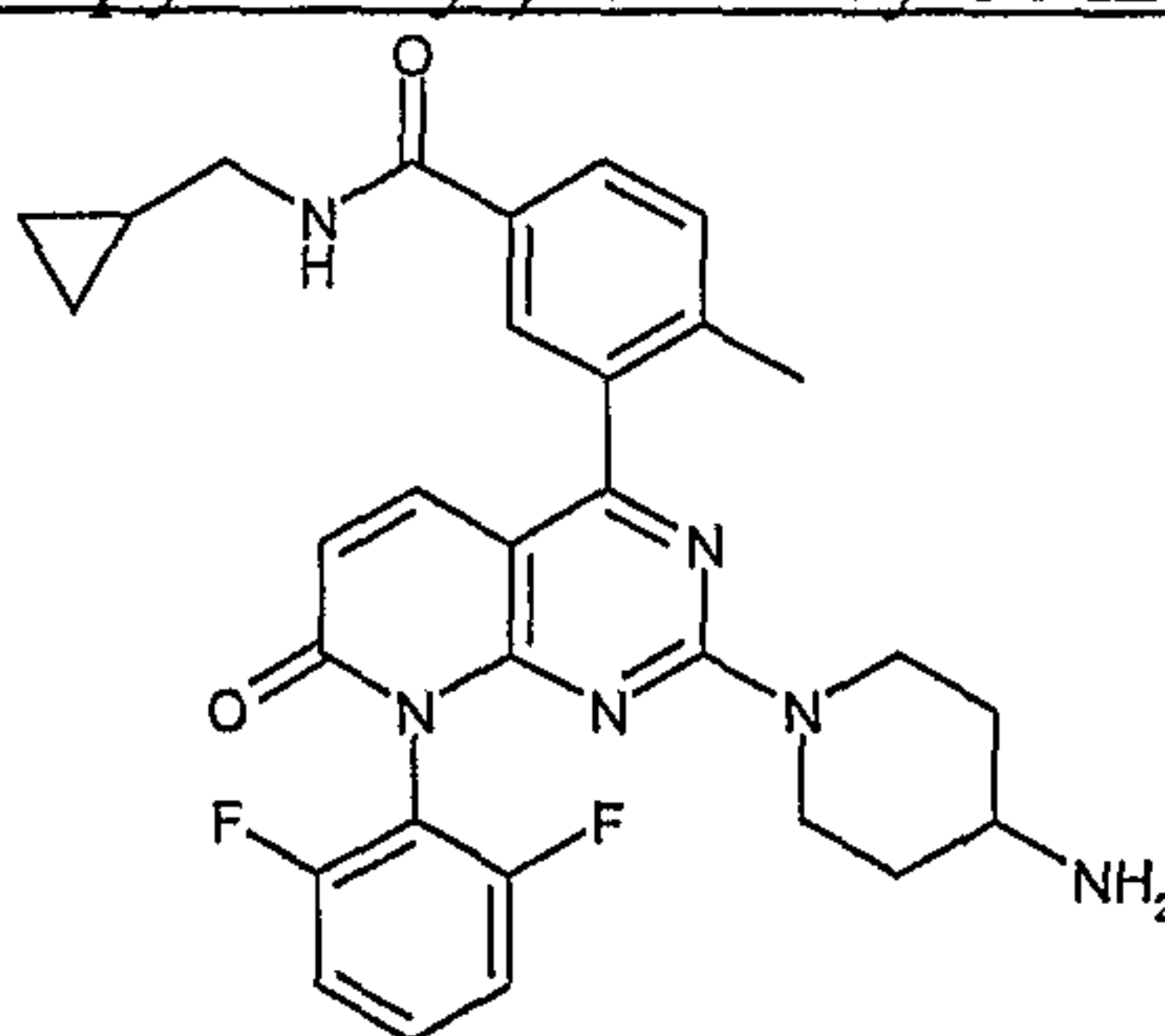
The title compound is prepared from the acid from 3-[8-(2,6-difluorophenyl)-2-(methylthio)-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl]-4-methylbenzoic acid by following the procedures in Example 19 using 2-(4-fluorophenyl)ethanamine for the amide formation and 2,2,6,6-tetramethyl-4-piperidinamine for the displacement reaction: LC-MS  $m/z$  669 ( $M+H$ )<sup>+</sup>, 2.03 min (ret time).

10

**Example 27**

3-[2-(4-amino-1-piperidiny]-8-(2,6-difluorophenyl)-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl]-*N*-(cyclopropylmethyl)-4-methylbenzamide

15

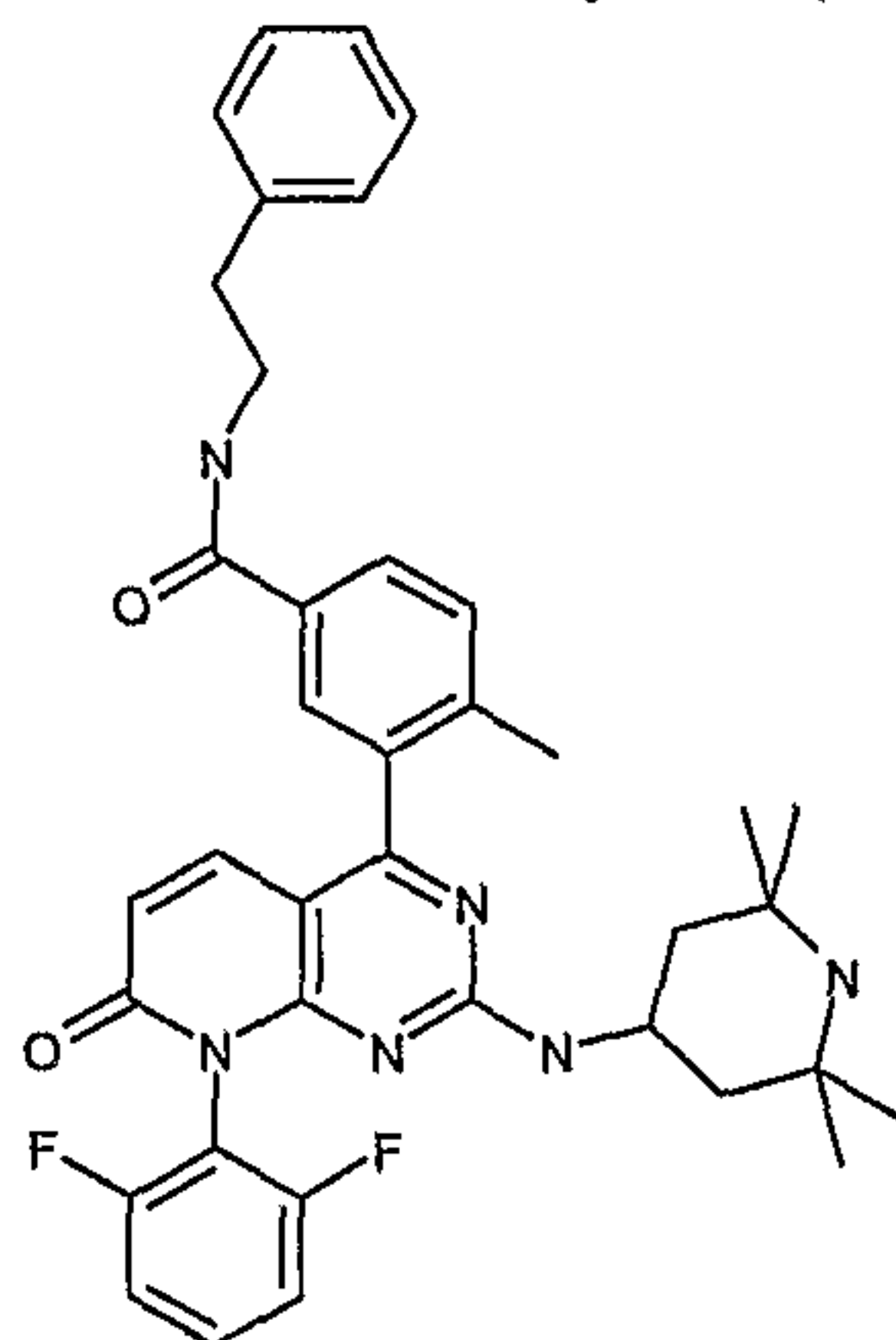


The title compound is prepared from 3-[8-(2,6-difluorophenyl)-2-(methylthio)-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl]-4-methylbenzoic acid by following the procedures in Example 19 using (cyclopropylmethyl)amine for the amide formation and 4-piperidinamine for the displacement reaction: LC-MS  $m/z$  545 ( $M+H$ )<sup>+</sup>, 1.63 min (ret time).

20

**Example 28**

3-{8-(2,6-difluorophenyl)-7-oxo-2-[(2,2,6,6-tetramethyl-4-piperidinyl)amino]-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl}-4-methyl-*N*-(2-phenylethyl)benzamide

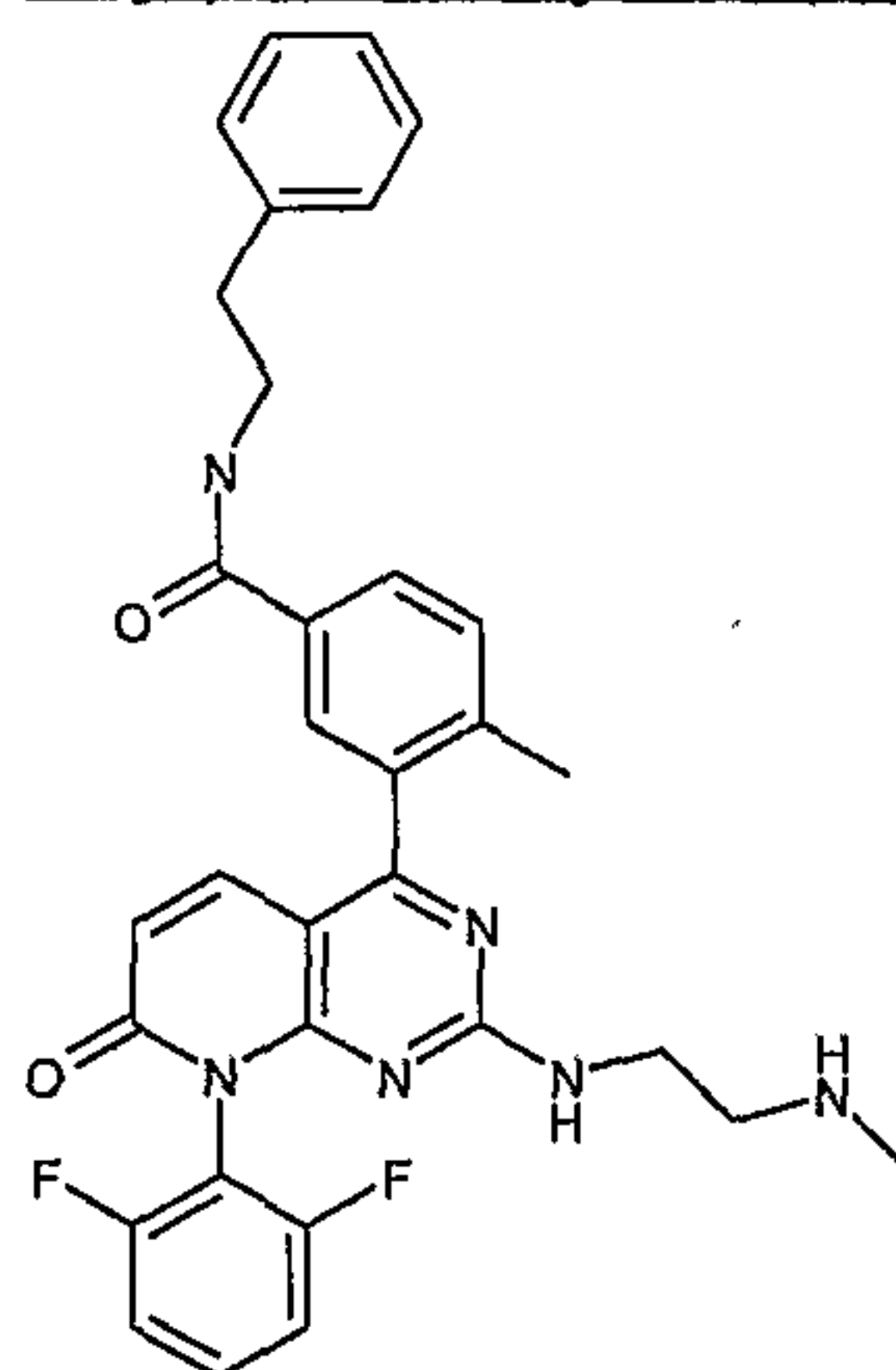


5 The title compound is prepared from 3-[8-(2,6-difluorophenyl)-2-(methylthio)-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl]-4-methylbenzoic acid by following the procedures in Example 19 using 2-phenylethanamine for the amide formation and 2,2,6,6-tetramethyl-4-piperidinamine for the displacement reaction: LC-MS *m/z* 651 (M+H)<sup>+</sup>, 1.87 min (ret time).

10

**Example 29**

3-(8-(2,6-difluorophenyl)-2-{[2-(methylamino)ethyl]amino}-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl)-4-methyl-*N*-(2-phenylethyl)benzamide

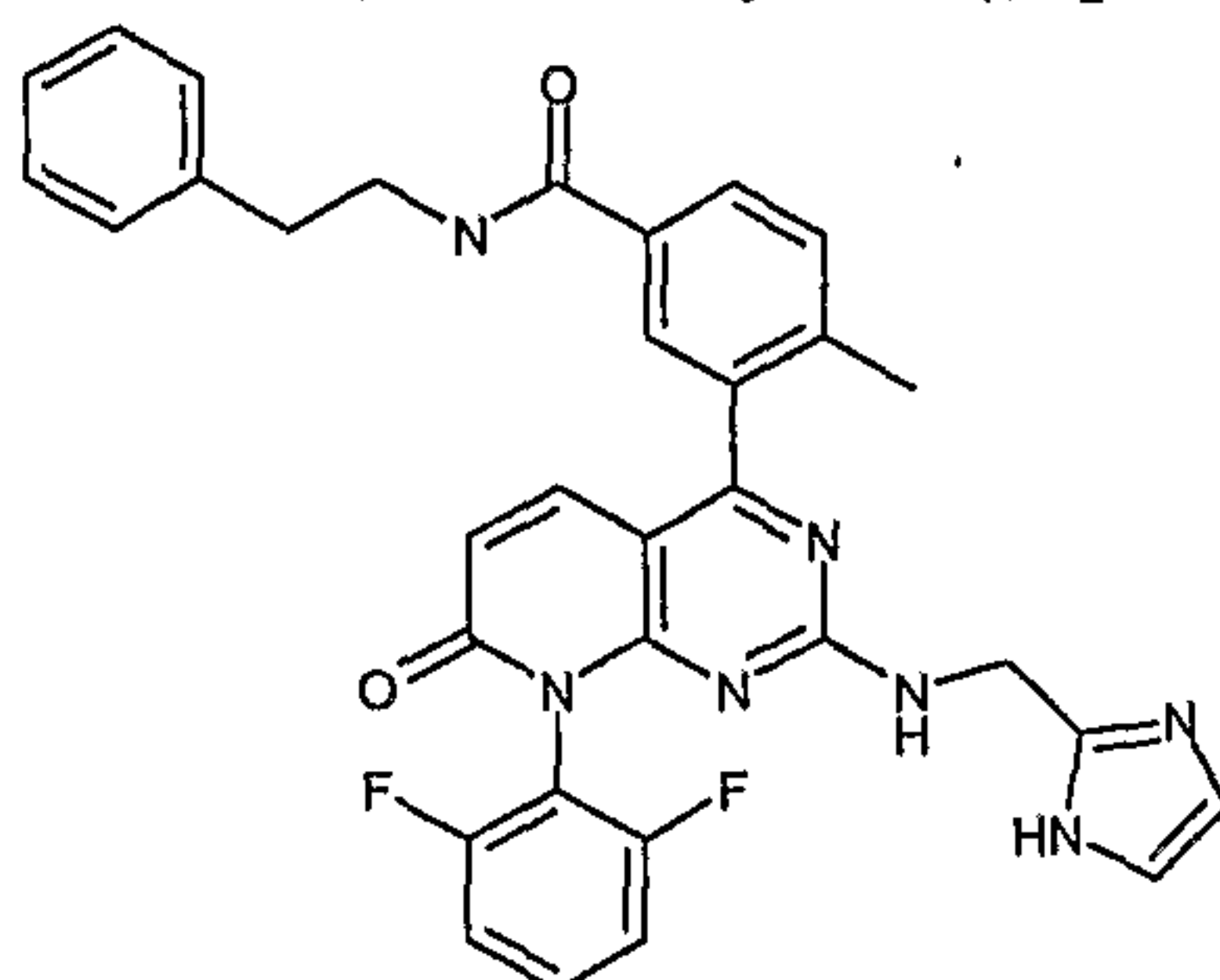


15 The title compound is prepared from 3-[8-(2,6-difluorophenyl)-2-(methylthio)-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl]-4-methylbenzoic acid by following the procedures in Example 19 using 2-phenylethanamine for the amide formation and (2-aminoethyl)methylamine for the displacement reaction: LC-MS *m/z* 569 (M+H)<sup>+</sup>, 1.69 min (ret time).

20

**Example 30**

3-{8-(2,6-difluorophenyl)-2-[(1*H*-imidazol-2-ylmethyl)amino]-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl}-4-methyl-*N*-(2-phenylethyl)benzamide

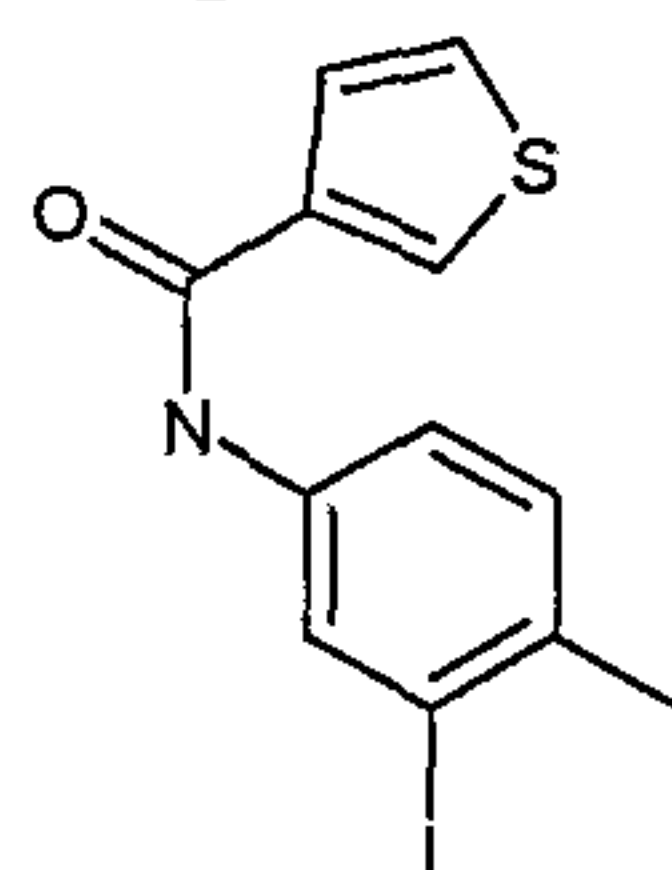


5 The title compound is prepared from 3-[8-(2,6-difluorophenyl)-2-(methylthio)-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl]-4-methylbenzoic acid by following the procedures in Example 19 using 2-phenylethanamine for the amide formation and (1*H*-imidazol-2-ylmethyl)amine dihydrochloride for the displacement reaction: LC-MS *m/z* 592 (*M*+*H*)<sup>+</sup>, 1.77 min (ret time).

10

**Example 31**

*N*-(3-{8-(2,6-difluorophenyl)-7-oxo-2-[(2,2,6,6-tetramethyl-4-piperidinyl)amino]-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl}-4-methylphenyl)-3-thiophenecarboxamide  
31a) *N*-(3-iodo-4-methylphenyl)-3-thiophenecarboxamide

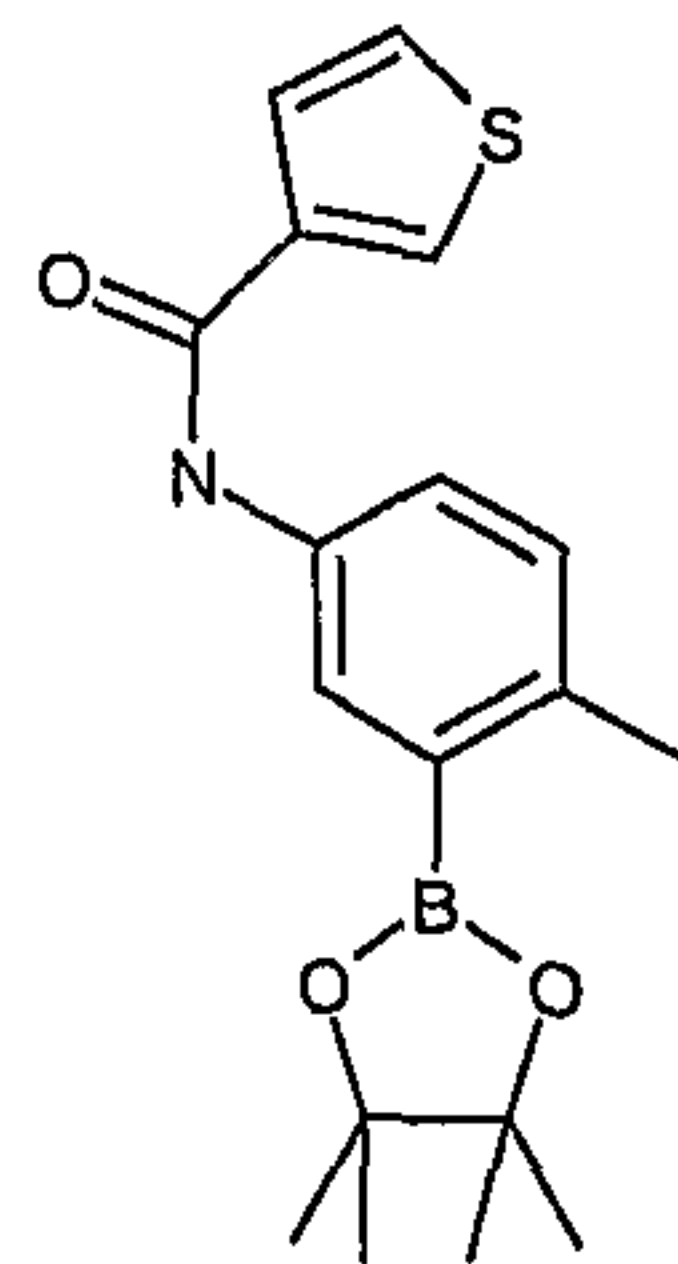


15

3-Thiophenecarboxylic acid (2.0 g, 15.6 mmol) was dissolved in methylene chloride (100 mL) and 2 drops of DMF were added. The mixture was cooled to about 0 °C and oxalyl chloride (1.5 mL, 17.1 mmol) was added slowly and allowed to warm to room temperature. Gas evolution was observed during warming. 3-Methyl-4-iodoaniline (5.45 g, 23.5 mmol), 4 drops of pyridine and K<sub>2</sub>CO<sub>3</sub> (2.58 g, 18.7 mmol) are dissolved in CH<sub>2</sub>Cl<sub>2</sub> (10 mL) and cooled to about 0 °C. After about 1h, the acid chloride mixture is slowly added to the cooled aniline mixture and allowed to warm to room temperature and stirred for about 18h. The resulting mixture is filtered, washed with ethyl acetate and the filtrate is concentrated to a brown oil. The crude material was purified via flash chromatography (10-30% ethyl acetate in hexanes) to afford the desired product (1.56 g, 29%) as an off-white solid.

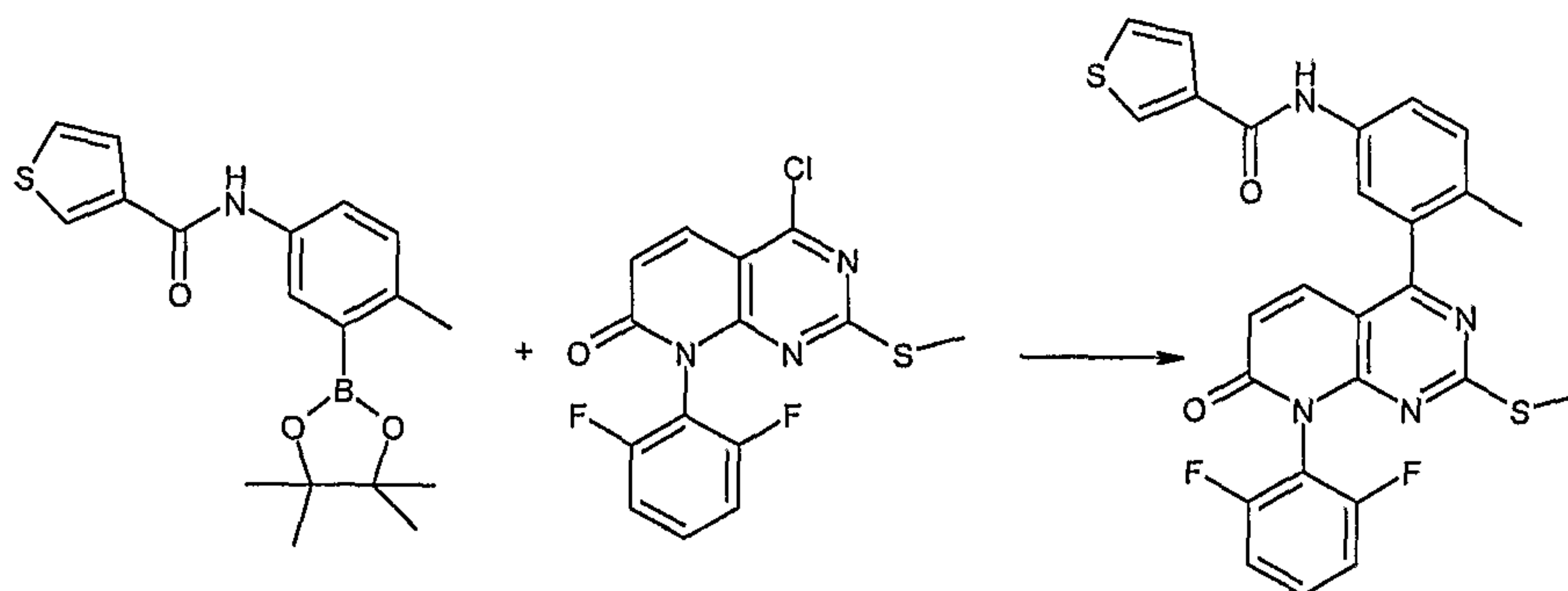
25

31b) *N*-[4-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-3-thiophenecarboxamide



The iodide from Example 31a (1.56 g, 4.5 mmol), bis(pinacolato)diboran  
 5 (2.3 g, 9.0 mmol), potassium acetate (2.21 g, 22.5 mmol) and PdCl<sub>2</sub>.dppf (0.15 g, 0.225 mmol) are dissolved in DMF (50 mL) and heated to about 85 °C for about 24 h. The mixture was then concentrated to an oil and ethyl acetate and water were added. The organic portion was washed with brine and dried (Na<sub>2</sub>SO<sub>4</sub>). The concentrated organic layer was purified via flash chromatography to give the desired  
 10 product (0.212 g, 13%).

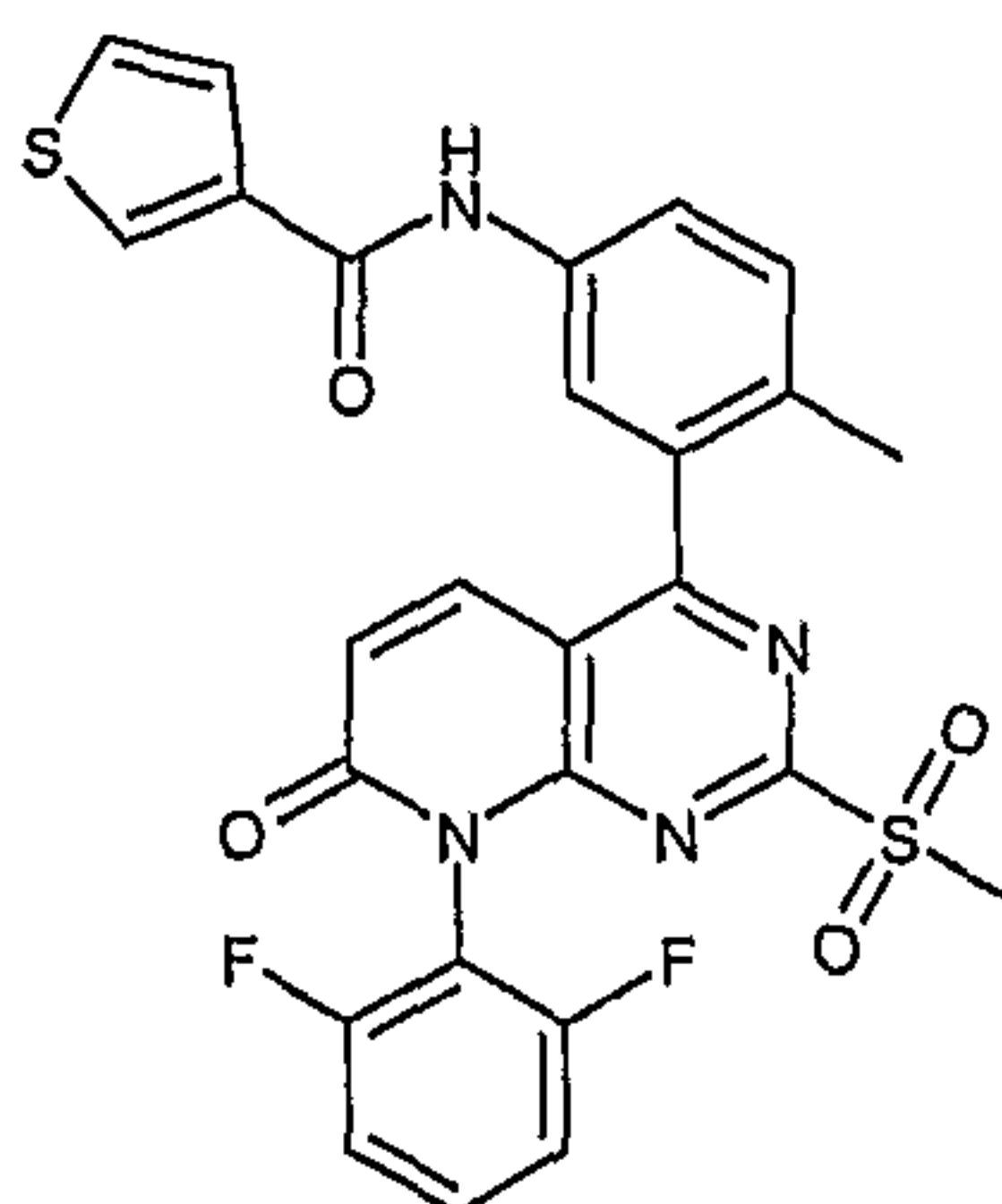
31c) *N*-{3-[8-(2,6-difluorophenyl)-2-(methylthio)-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl]-4-methylphenyl}-3-thiophenecarboxamide



15

The title compound was prepared from the compound from Example 31b according to the procedures in Example 1b. Flash chromatography followed by recrystallization (ethyl acetate) afforded the desired compound (0.292 g, 90%).

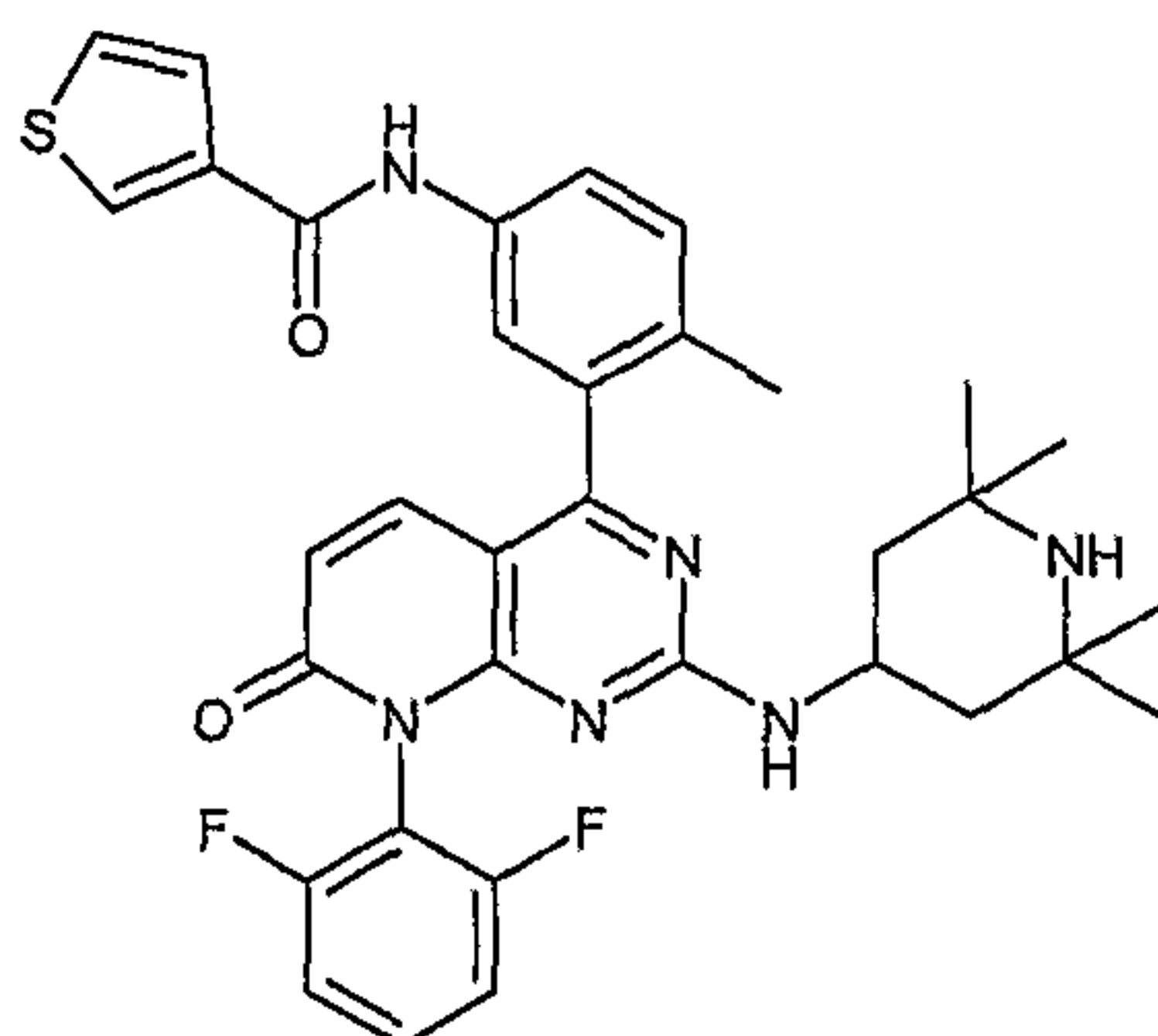
20 31d) *N*-{3-[8-(2,6-difluorophenyl)-2-(methylsulfonyl)-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl]-4-methylphenyl}-3-thiophenecarboxamide



The title compound was prepared from the compound from Example 31c according to General Procedure for Sulfide Oxidation. The desired compound was obtained without need for purification (0.08 g, 63%).

5

31e) N-(3-{8-(2,6-difluorophenyl)-7-oxo-2-[(2,2,6,6-tetramethyl-4-piperidinyl)amino]-7,8-dihydropyrido[2,3-d]pyrimidin-4-yl}-4-methylphenyl)-3-thiophenecarboxamide



10

The title compound was prepared from *N*-{3-[8-(2,6-difluorophenyl)-2-(methylsulfonyl)-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl]-4-methylphenyl}-3-thiophenecarboxamide and 2,2,6,6-tetramethyl-4-piperidinamine according to General Procedure for Sulfoxide/Sulfone Displacement, described above. The concentrated reaction mixture was slurried with acetonitrile and filtered. The solid was recrystallized from methanol/water to afford the desired product as a crystalline solid (0.2 g, 16%). HPLC indicated >99% pure: LC-MS *m/z* 629 (M+H)<sup>+</sup>, 1.86 min (ret time).

15

31f) N-(3-{8-(2,6-difluorophenyl)-7-oxo-2-[(2,2,6,6-tetramethyl-4-piperidinyl)amino]-7,8-dihydropyrido[2,3-d]pyrimidin-4-yl}-4-methylphenyl)-3-thiophenecarboxamide hydrochloride

20

Added IPA (5 mL) to *N*-(3-{8-(2,6-difluorophenyl)-7-oxo-2-[(2,2,6,6-tetramethyl-4-piperidinyl)amino]-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl}-4-methylphenyl)-3-thiophenecarboxamide (196.5 mg) and heated to about 60 °C.

25

Added hydrochloric acid (1.1eq; 1M in water), and solution mostly clarified. After a

few minutes at about 60 °C, crystallization had already begun, then cooled to RT. Stirred for about 3 hrs at rt, then filtered, washed with IPA, and dried to provide the title compound (160.9 mg).

5 31g) *N*-(3-{8-(2,6-difluorophenyl)-7-oxo-2-[(2,2,6,6-tetramethyl-4-piperidinyl)amino]-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl}-4-methylphenyl)-3-thiophenecarboxamide 4-methylbenzenesulfonate

Added IPA (5 mL) to *N*-(3-{8-(2,6-difluorophenyl)-7-oxo-2-[(2,2,6,6-tetramethyl-4-piperidinyl)amino]-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl}-4-methylphenyl)-3-thiophenecarboxamide (203.2 mg) and heated to 60 °C. Added *p*-toluenesulfonic acid (1.1 eq; 1M in water), and solution clarified. After a few minutes at about 60 °C, cooled to rt. Stirred for about 3 hrs at rt, then filtered, washed with IPA, and dried in vacuum oven at 50 °C to provide the title compound (123.9 mg). Melting point (tested with DSC) is 335 °C.

15 31h) *N*-(3-{8-(2,6-difluorophenyl)-7-oxo-2-[(2,2,6,6-tetramethyl-4-piperidinyl)amino]-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl}-4-methylphenyl)-3-thiophenecarboxamide methanesulfonate

Added 320 uL of CH<sub>3</sub>CN to *N*-(3-{8-(2,6-difluorophenyl)-7-oxo-2-[(2,2,6,6-tetramethyl-4-piperidinyl)amino]-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl}-4-methylphenyl)-3-thiophenecarboxamide (16.0 mg) and heated to about 60 °C. Added methanesulfonic acid (1.1 eq; 1M in IPA), and solution clarified except for tiny amount stuck to bottom. After a few minutes at about 60 °C, cooled to rt. Got lots of white precipitate. Stirred overnight at rt. Next day, filtered and dried to provide the title compound (3.5 mg). Melting point (tested with DSC) is 331 °C

25 31i) *N*-(3-{8-(2,6-difluorophenyl)-7-oxo-2-[(2,2,6,6-tetramethyl-4-piperidinyl)amino]-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl}-4-methylphenyl)-3-thiophenecarboxamide hydrobromide

30 Added 400 uL of acetone to *N*-(3-{8-(2,6-difluorophenyl)-7-oxo-2-[(2,2,6,6-tetramethyl-4-piperidinyl)amino]-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl}-4-methylphenyl)-3-thiophenecarboxamide (9.8 mg), mostly dissolved. Added hydrobromic acid (1.1 eq; 1M in water). After about 2.5 weeks, small amounts of crystals were seen. The cap was loosened and let to evaporate overnight. This  
35 resulted in more crystals the next day. To this was added back 50 uL of acetone, filtered and dried to provide the title compound.

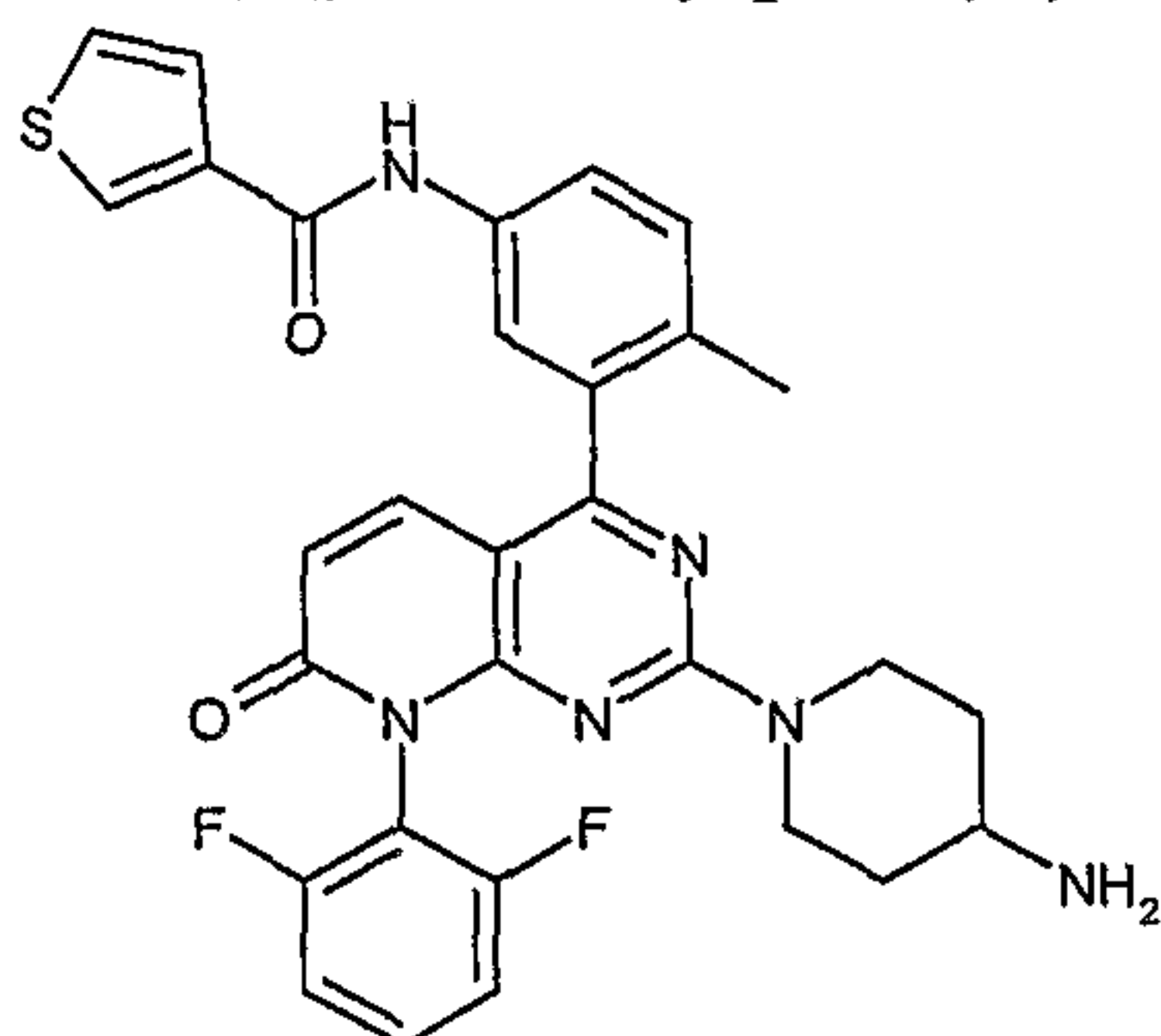
31j) *N*-(3-{8-(2,6-difluorophenyl)-7-oxo-2-[(2,2,6,6-tetramethyl-4-piperidinyl)amino]-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl}-4-methylphenyl)-3-thiophenecarboxamide sulfate

Added 400 uL of acetone to *N*-(3-{8-(2,6-difluorophenyl)-7-oxo-2-[(2,2,6,6-tetramethyl-4-piperidinyl)amino]-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl}-4-methylphenyl)-3-thiophenecarboxamide (9.1 mg), mostly dissolved. Added sulfuric acid (1.1 eq; 1M in water). After about 2.5 weeks, a lot of crystals were seen, and this was filtered and dried to provide the title compound.

10

**Example 32**

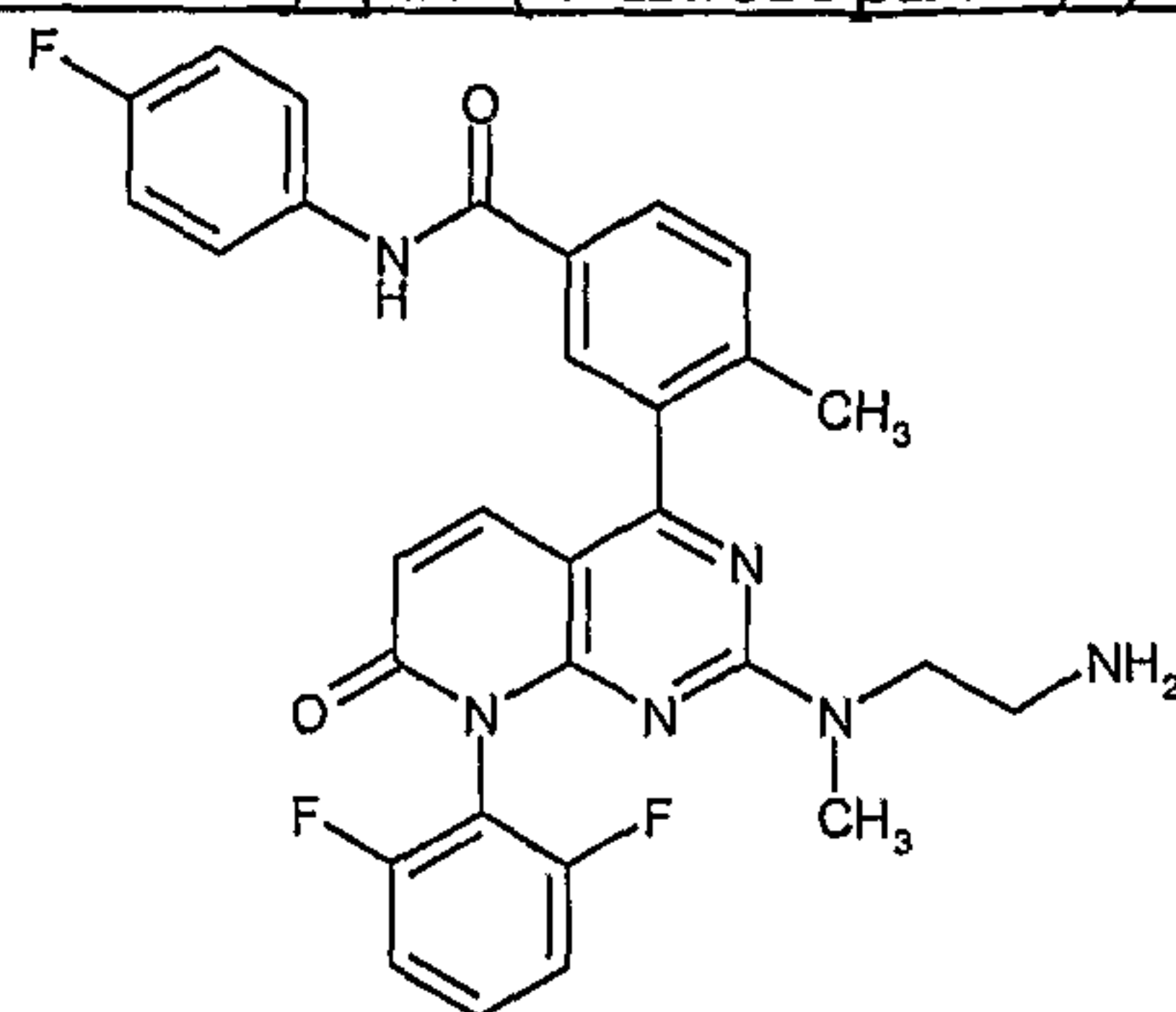
*N*-(3-[2-(4-amino-1-piperidinyl)-8-(2,6-difluorophenyl)-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl]-4-methylphenyl)-3-thiophenecarboxamide



The title compound was prepared from *N*-(3-[8-(2,6-difluorophenyl)-2-(methylsulfonyl)-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl]-4-methylphenyl)-3-thiophenecarboxamide and 4-piperidinamine according to General Procedure for Sulfoxide/Sulfone Displacement, described above. The concentrated reaction mixture was purified via reversed-phase HPLC to give the desired compound as a light tan powder (0.041 g, 32%). HPLC indicated the material to be >95% pure (m.p. 183.8-187.9): LC-MS *m/z* 573 (M+H)<sup>+</sup>, 1.79 min (ret time).

**Example 33**

3-[2-[(2-aminoethyl)(methyl)amino]-8-(2,6-difluorophenyl)-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl]-N-(4-fluorophenyl)-4-methylbenzamide

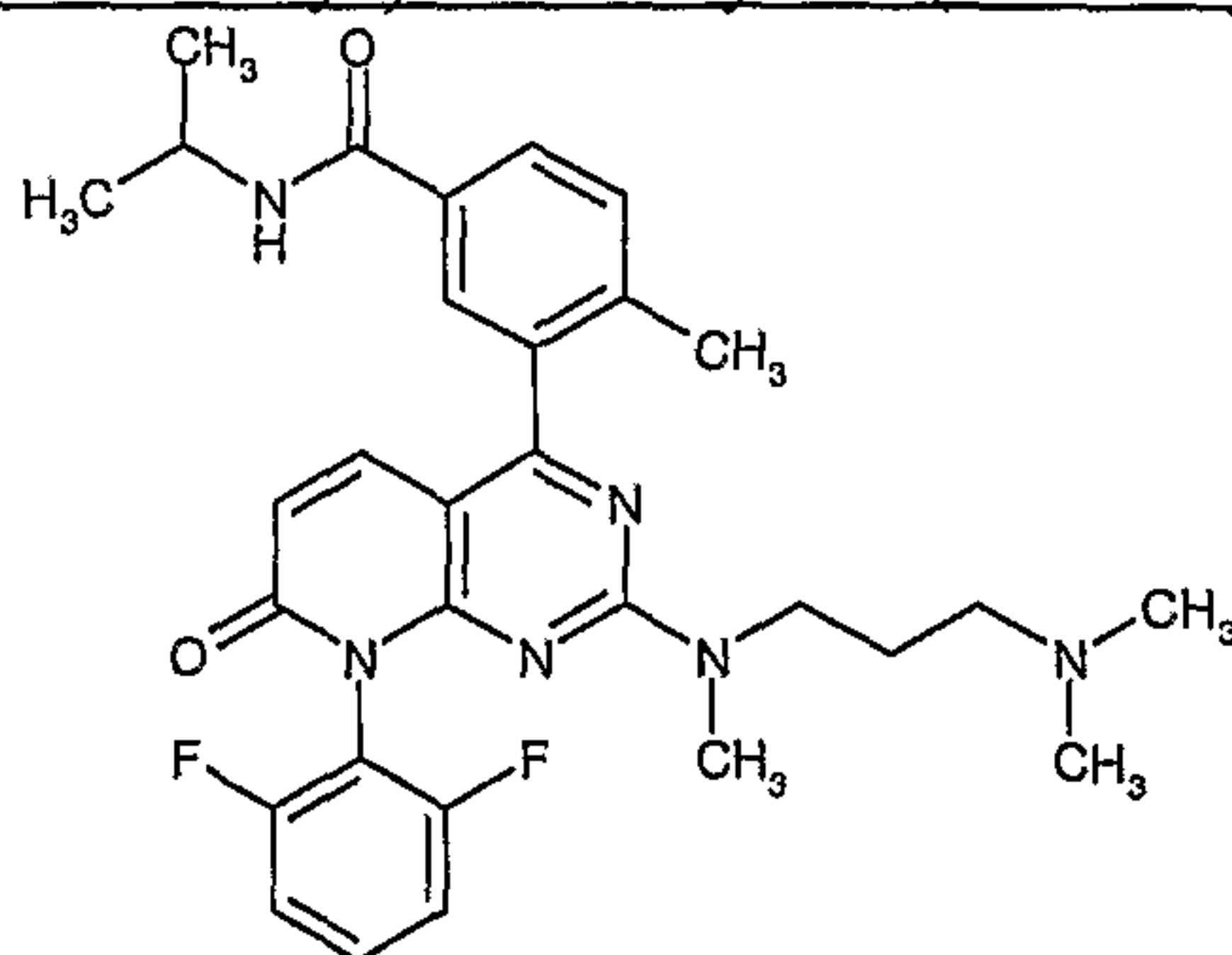


5 To a solution of 3-[8-(2,6-difluorophenyl)-2-(methylsulfinyl)-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl]-N-(4-fluorophenyl)-4-methylbenzamide (50 mg, 0.09 mmol) in THF (5 mL) was added N-methyl-1,2-ethanediamine (0.044 mL, 0.5 mmol). The resultant mixture was stirred at room temperature overnight. The mixture was concentrated under vacuo. Flash chromatography (90% CH<sub>2</sub>Cl<sub>2</sub> / 7% MeOH / 3% NH<sub>4</sub>OH) then provide the title compound (8.0 mg, 16%). LC-MS (ES) m/z 559 (M+H)<sup>+</sup>; <sup>1</sup>H-NMR(MeOD) δ 2.35 (s, 3H), 2.65 (m, 1H), 2.86 (m, 1H), 2.92 (m, 1H), 3.26 (m, 1H), 3.35 (m, 1H), 3.40 (m, 1H), 3.77 (m, 1H), 6.36 (d, 1H), 7.14 (m, 2H), 7.25 (m, 2H), 7.52 (d, 1H), 7.59 (d, 1H), 7.62 (m, 1H), 7.71 (m, 2H), 7.92 (s, 1H), 8.06 (d, 1H).

15

**Example 34**

3-{8-(2,6-difluorophenyl)-2-[[3-(dimethylamino)propyl](methyl)amino]-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl}-4-methyl-N-(1-methylethyl)benzamide



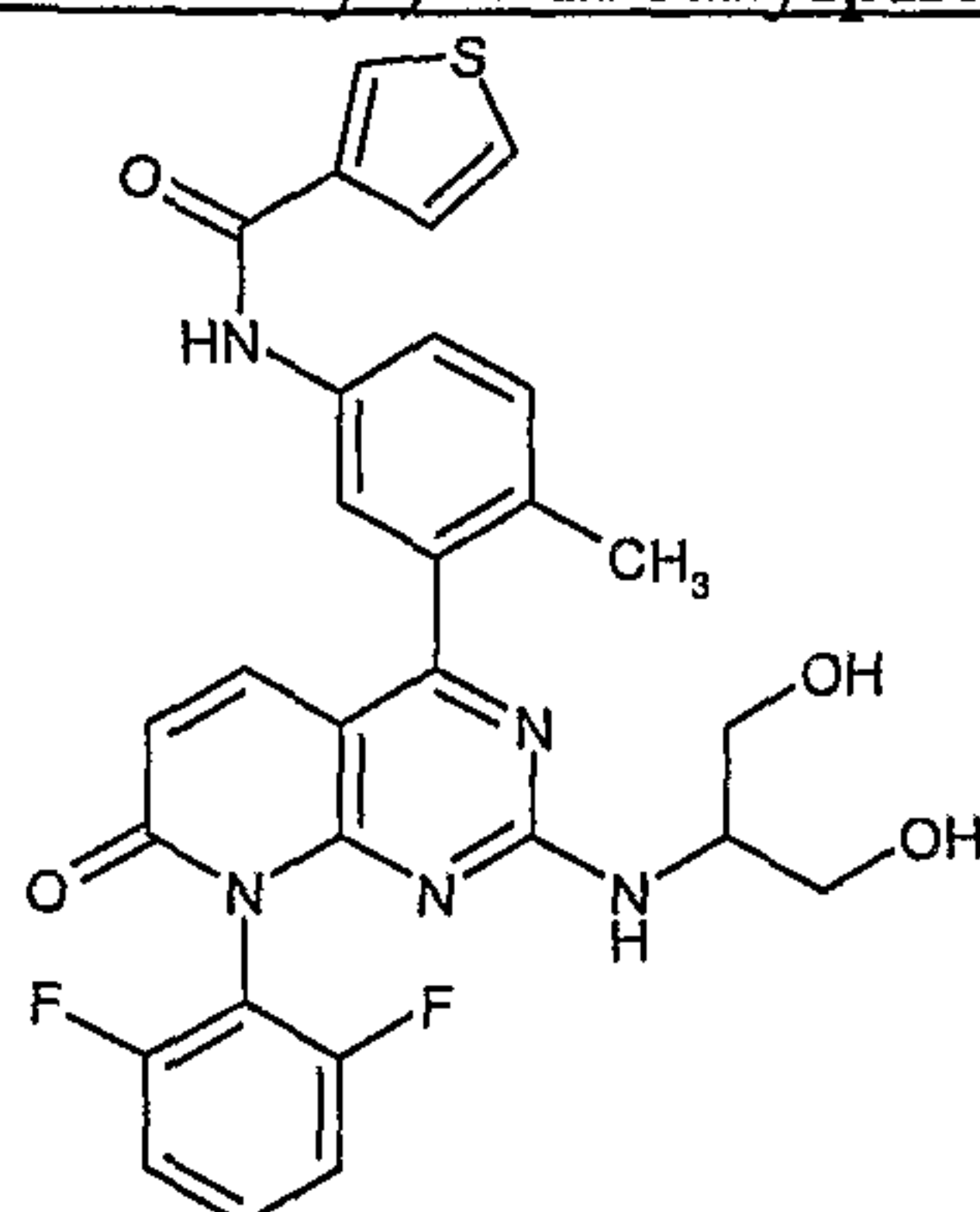
20 The title compound was prepared from 3-[8-(2,6-difluorophenyl)-2-(methylthio)-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl]-4-methylbenzoic acid by following the procedures in Example 19 using 2-propanamine for the amide formation and N,N,N'-trimethyl-1,3-propanediamine for the displacement reaction (88%). LC-MS (ES) m/z 549 (M+H)<sup>+</sup>; <sup>1</sup>H-NMR(MeOD) δ 1.27 (d, 6H), 1.60 (m,

1H), 1.80 (m, 1H), 2.06 (m, 1H), 2.22 (m, 6H), 2.33 (m, 4H), 2.86 (m, 1H), 3.19 (m, 2H), 3.40 (m, 1H), 3.70 (m, 1H), 4.30 (m, 1H), 6.00 (m, 1H), 6.33 (d, 1H), 7.10 (t, 2H), 7.30 (m, 2H), 7.42 (d, 1H), 7.48 (m, 1H), 7.66 (s, 1H), 7.85 (d, 1H).

5

**Example 35**

N-[3-(8-(2,6-difluorophenyl)-2-{[2-hydroxy-1-(hydroxymethyl)ethyl]amino}-7-oxo-7,8-dihydropyrido[2,3-d]pyrimidin-4-yl)-4-methylphenyl]-3-thiophenecarboxamide

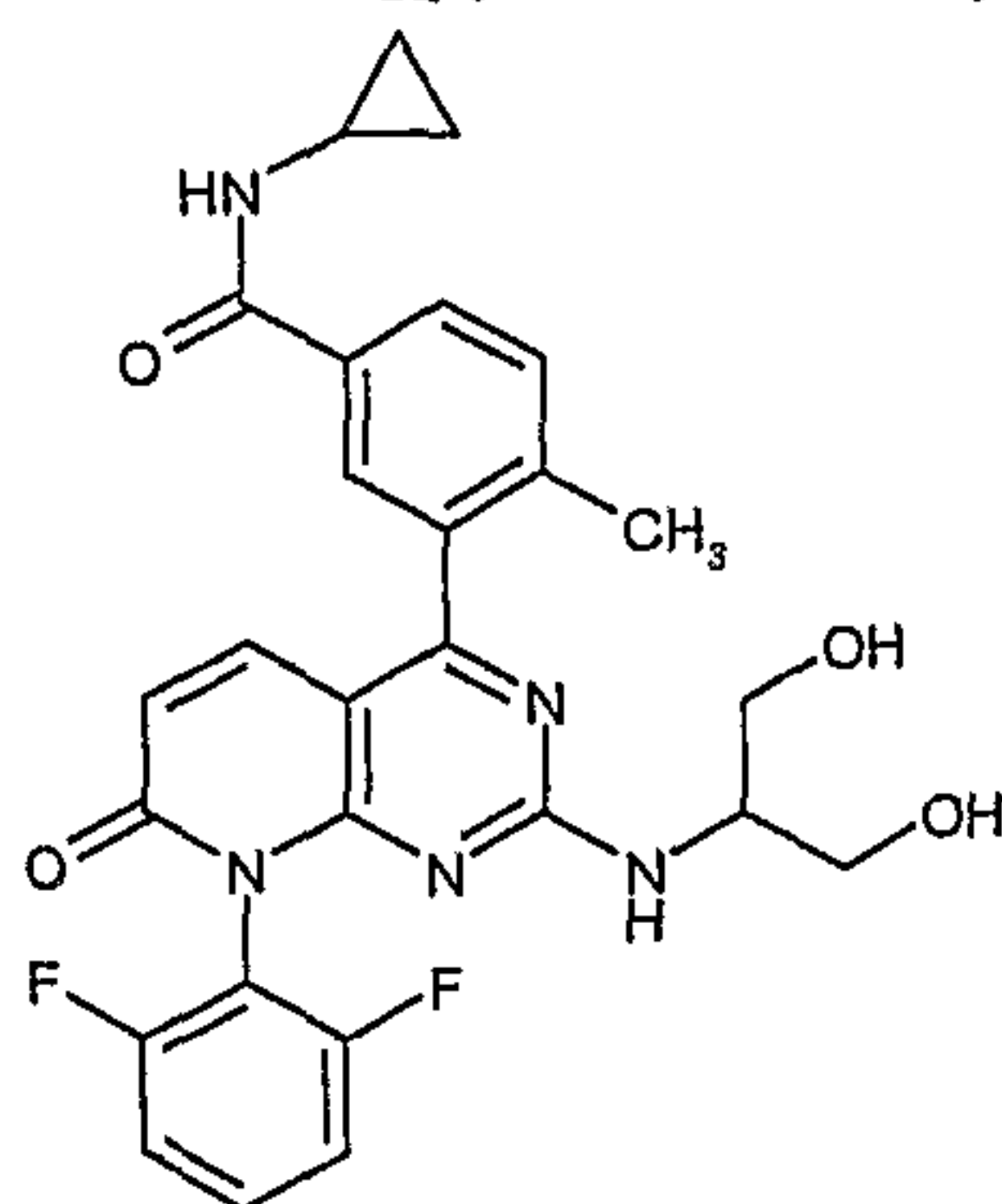


To a solution of 4-chloro-2-(2-hydroxy-1-hydroxymethyl-ethylamino)-8-(2,4-difluoro-phenyl)-8H-pyrido[2,3-d]pyrimidin-7-one (40.0 mg, 0.105 mmol) in dioxane/H<sub>2</sub>O (3:1, 4.8 mL) was added N-[4-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-3-thiophene carboxamide (53.9 mg, 0.157 mmol) and K<sub>2</sub>CO<sub>3</sub> (58.0 mg, 0.420 mmol). The resultant mixture was bubbled with argon for 5 minutes, then added by Pd(PPh<sub>3</sub>)<sub>4</sub> (2.4 mg, 0.0021 mmol). The reaction tube was sealed and heated in "Smith Creator" (microwave, 150 °C) for about 15 minutes. The mixture was concentrated under vacuo. Flash chromatography (EtOAc / Hexane, 3:1) then provided the title compound (50.0 mg, 85%): LC-MS (ES) *m/z* 564 (M+H)<sup>+</sup>, <sup>1</sup>H-NMR(MeOD) δ 2.24 (s, 3H), 3.63 (m, 5H), 6.38 (m, 1H), 7.22 (m, 2H), 7.39 (d, 1H), 7.65 (m, 6H), 8.24 (s, 1H).

20

**Example 36**

*N*-cyclopropyl-3-(8-(2,6-difluorophenyl)-2-{{2-hydroxy-1-(hydroxymethyl)ethyl}-amino}-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl)-4-methylbenzamide

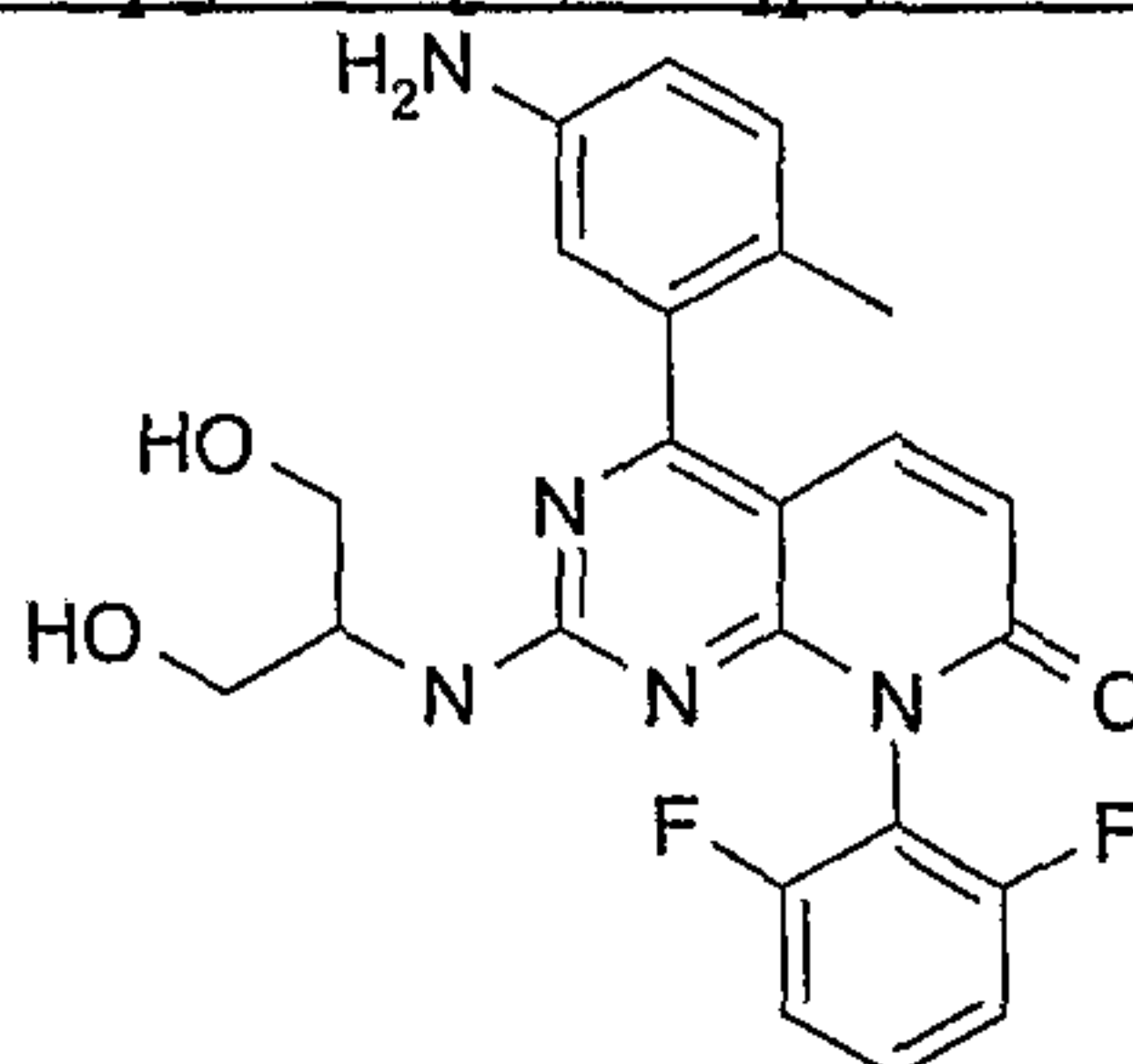


- 5 The title compound was prepared from 4-chloro-8-(2,6-difluorophenyl)-2-  
 {[2-hydroxy-1-(hydroxymethyl)ethyl]amino}pyrido[2,3-*d*]pyrimidin-7(8*H*)-one by  
 following the procedures of Example 35 using 3-*N*-cyclopropyl-4-methyl-3-(4,4,5,5-  
 tetramethyl-1,3,2-dioxaborolan-2-yl) benzamide for the Suzuki cross-coupling  
 reaction (29.6 mg, 55%): LC-MS (ES) *m/z* 522 (*M*+*H*)<sup>+</sup>, <sup>1</sup>H-NMR(MeOD) δ 0.65  
 10 (m, 2H), 0.81 (m, 2H), 2.31 (s, 3H), 2.87 (m, 1H), 3.64 (m, 5H), 6.39 (m, 1H), 7.25  
 (m, 2H), 7.45 (d, 1H), 7.51 (d, 1H), 7.59 (m, 1H), 7.78 (m, 1H), 7.91 (m, 1H).

**Example 37**

- N*-[3-(8-(2,6-difluorophenyl)-2-{{2-hydroxy-1-(hydroxymethyl)ethyl}amino}-7-oxo-  
 15 7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl)-4-methylphenyl]-3-  
 isoquinolinecarboxamide trifluoroacetate

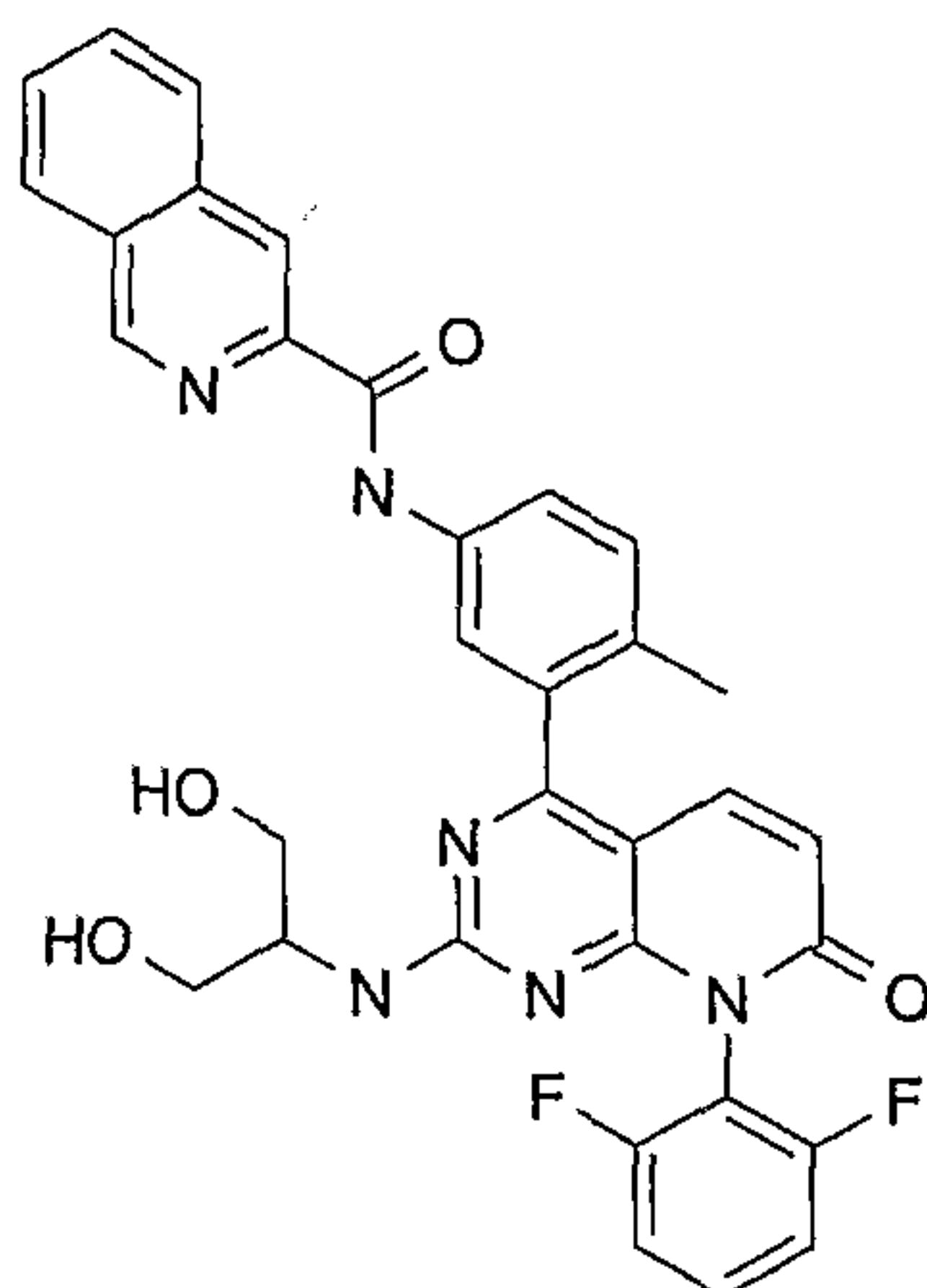
37a) 4-(5-amino-2-methyl-phenyl)-8-(2,6-difluoro-phenyl)-2-(2-hydroxy-1-  
 hydroxymethyl-ethylamino)-8*H*-pyrido[2,3-*d*]pyrimidin-7-one



20

The title compound was prepared from 4-methyl-3-(4,4,5,5-tetramethyl-  
 1,3,2-dioxaborolan-2-yl)aniline by following the procedures in Example 18e.

37b) *N*-[3-(8-(2,6-difluorophenyl)-2-{[2-hydroxy-1-(hydroxymethyl)ethyl]amino}-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl)-4-methylphenyl]-3-isoquinolinecarboxamide trifluoroacetate

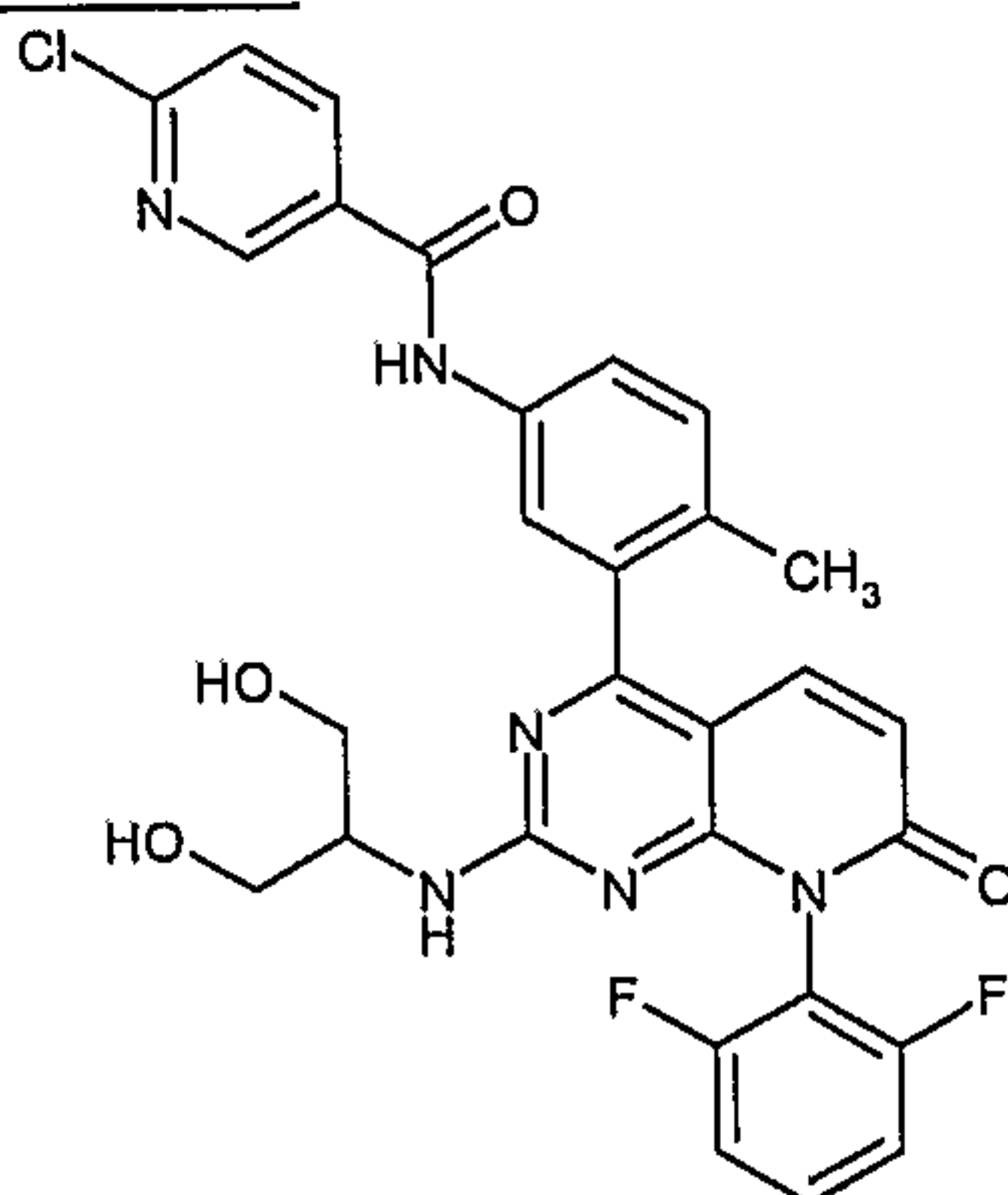


5

To isoquinoline-3-carboxylic acid (11.5 mg, 0.066 mmol, 1 eq) was added HATU (38.02 mg, 0.1 mmol, 1.5 eq) in DMF (250  $\mu$ L). DIPEA (34.84  $\mu$ L, 0.2 mmol, 3 eq) was then added. The resulting mixture was then allowed to stand for about 5 minutes before 4-(5-amino-2-methyl-phenyl)-8-(2,6-difluoro-phenyl)-2-(2-hydroxy-1-hydroxymethyl-ethylamino)-8H-pyrido[2,3-*d*]pyrimidin-7-one (30.23 mg, 0.066 mmol, 1 eq) was added. The resulting mixture was shaken to ensure efficient mixing of the reagents then was left to stand overnight. The solvent was then removed in vacuo. The residue was dissolved in methanol and was then placed down an aminopropyl SPE flushing the column with methanol. The elute from the SPE was then treated with NaOH (2 M, 200  $\mu$ L) and the mixture was allowed to stand for about 1 hr. This was followed by HCl (2M, 200  $\mu$ L) then the solvent was removed in vacuo. The residue was purified by MDAP. LC-MS  $m/z$  609 (M+H)<sup>+</sup>, 3.31 min (ret time).

**Example 38**

6-chloro-N-[3-(8-(2,6-difluorophenyl)-2-{[2-hydroxy-1-(hydroxymethyl)ethyl]-amino}-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl)-4-methylphenyl]-3-pyridinecarboxamide trifluoroacetate



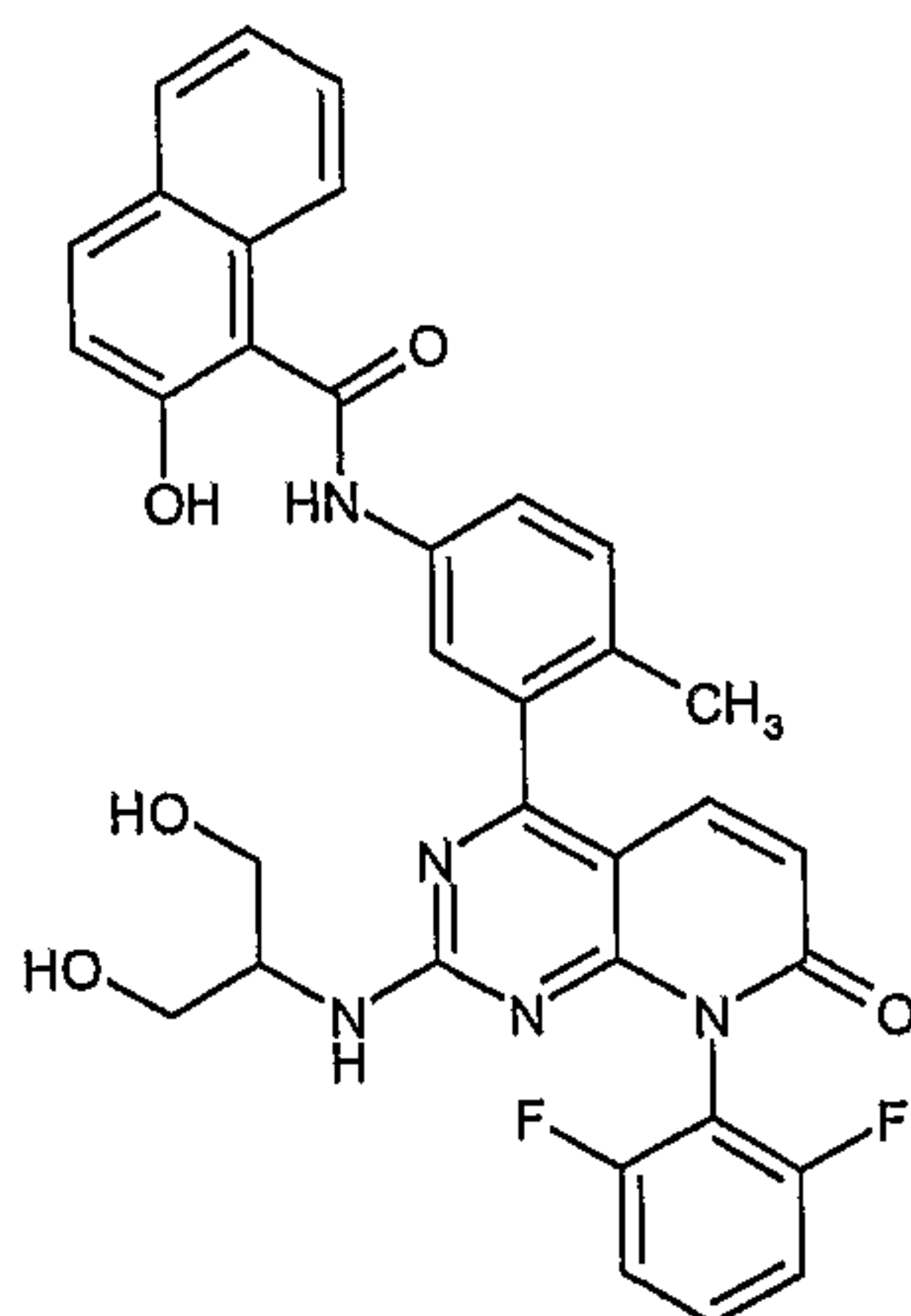
5

The title compound was prepared from 6-chloro-3-pyridinecarboxylic acid by following the procedures in Example 37b: LC-MS  $m/z$  593 ( $M+H$ )<sup>+</sup>, 2.99 min (ret time).

10

**Example 39**

N-[3-(8-(2,6-difluorophenyl)-2-{[2-hydroxy-1-(hydroxymethyl)ethyl]amino}-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl)-4-methylphenyl]-2-hydroxy-1-naphthalenecarboxamide trifluoroacetate

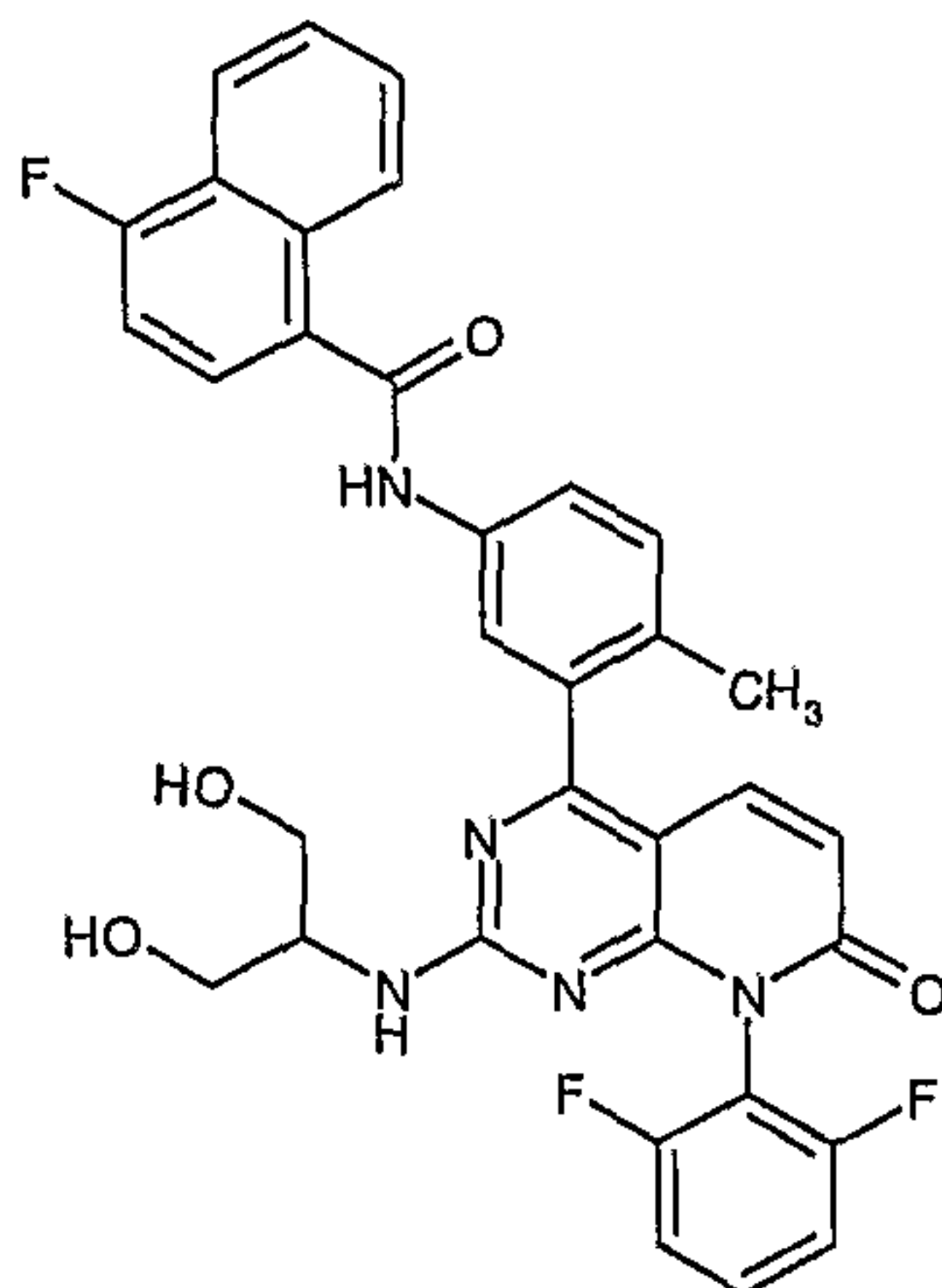


15

The title compound was prepared from 2-hydroxy-1-naphthalenecarboxylic acid by following the procedures in Example 37b: LC-MS  $m/z$  624 ( $M+H$ )<sup>+</sup>, 3.37 min (ret time).

**Example 40**

*N*-[3-(8-(2,6-difluorophenyl)-2-{[2-hydroxy-1-(hydroxymethyl)ethyl]amino}-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl)-4-methylphenyl]-4-fluoro-1-naphthalenecarboxamide trifluoroacetate



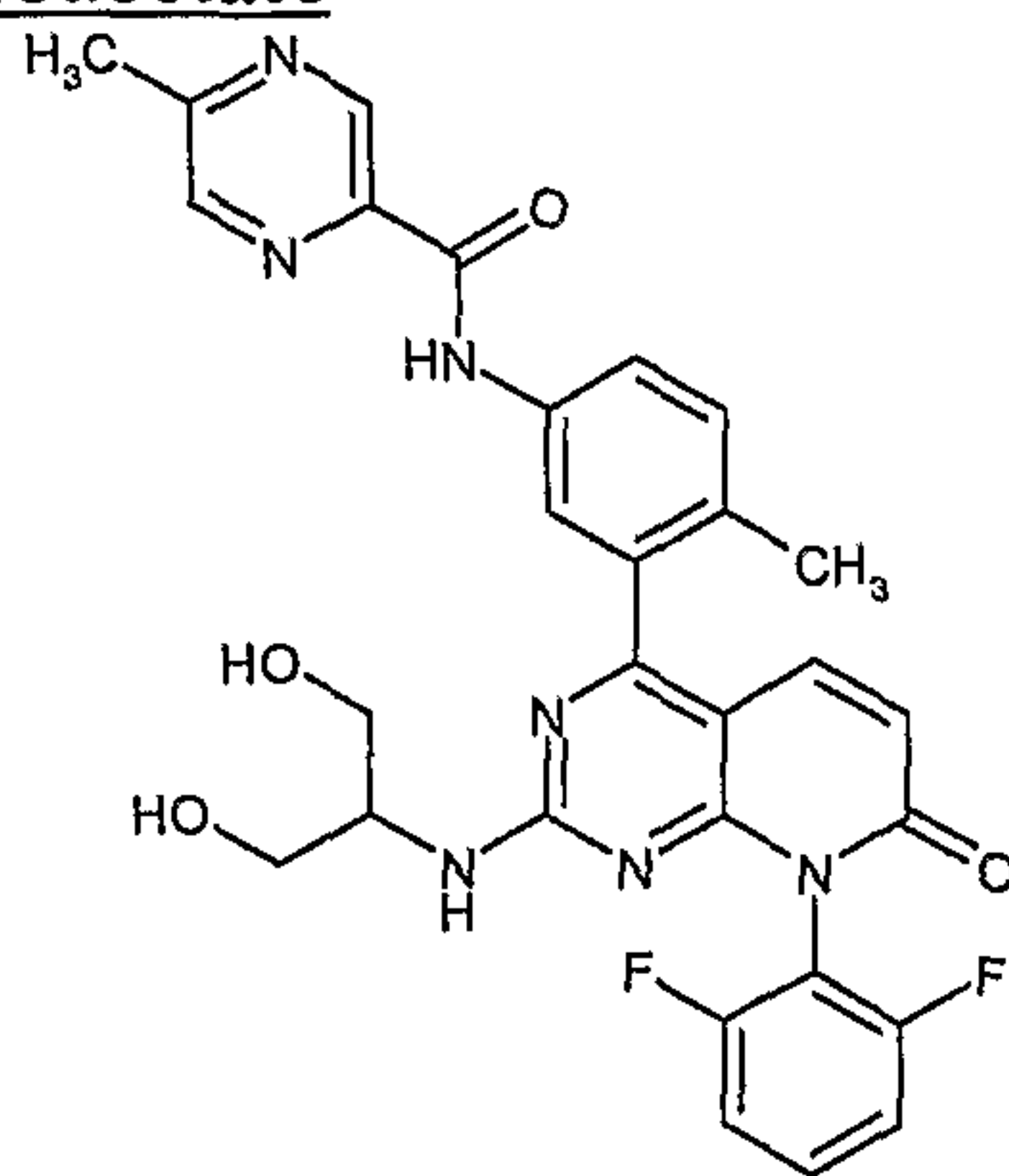
5

The title compound was prepared from 4-fluoro-1-naphthalenecarboxylic acid by following the procedures in Example 37b: LC-MS *m/z* 626 (M+H)<sup>+</sup>, 3.32 min (ret time).

10

**Example 41**

*N*-[3-(8-(2,6-difluorophenyl)-2-{[2-hydroxy-1-(hydroxymethyl)ethyl]amino}-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl)-4-methylphenyl]-5-methyl-2-pyrazinecarboxamide trifluoroacetate

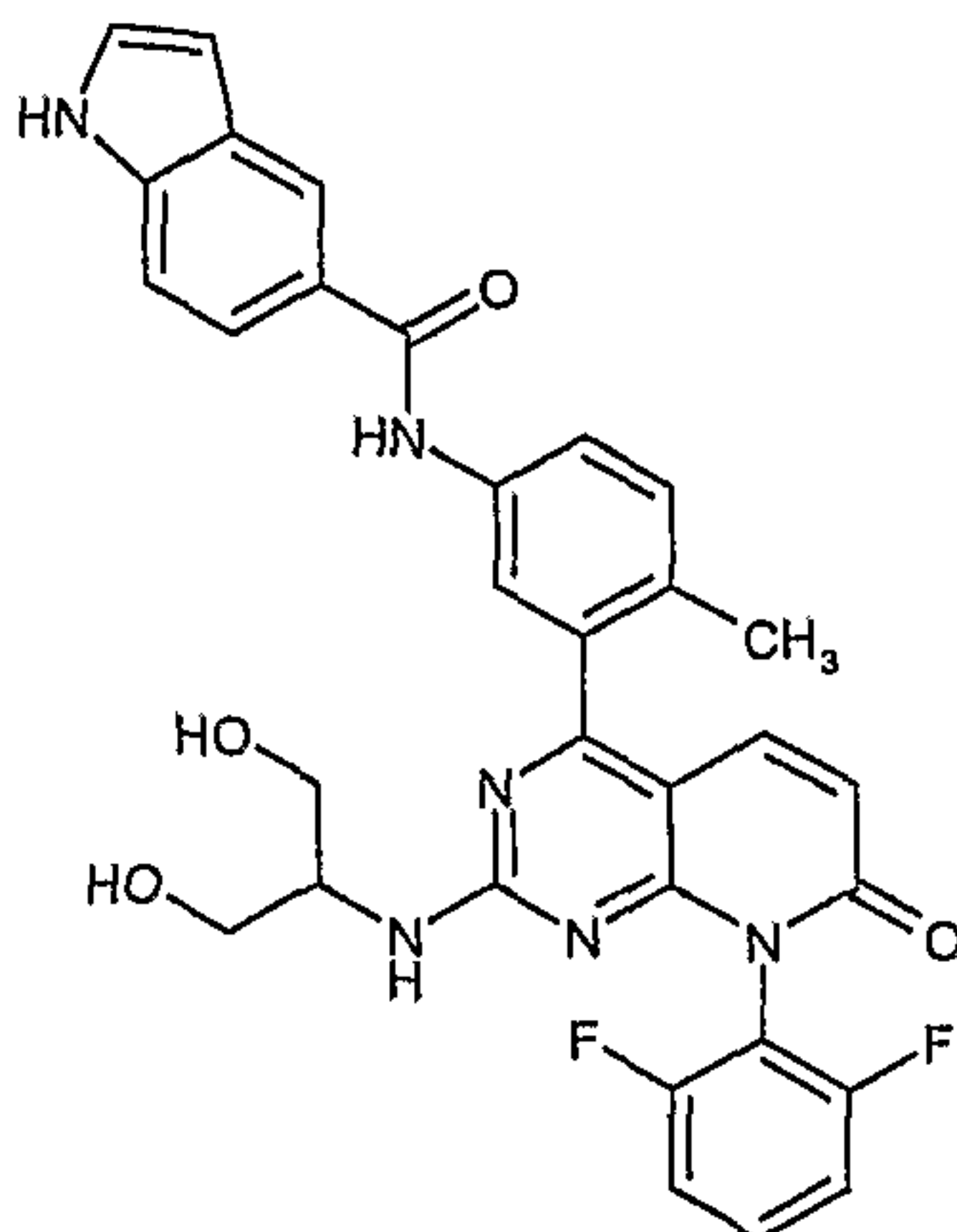


15

The title compound was prepared from 5-methyl-2-pyrazinecarboxylic acid by following the procedures in Example 37b: LC-MS *m/z* 574 (M+H)<sup>+</sup>, 2.86 min (ret time).

**Example 42**

*N*-[3-(8-(2,6-difluorophenyl)-2-{[2-hydroxy-1-(hydroxymethyl)ethyl]amino}-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl)-4-methylphenyl]-1*H*-indole-5-carboxamide trifluoroacetate



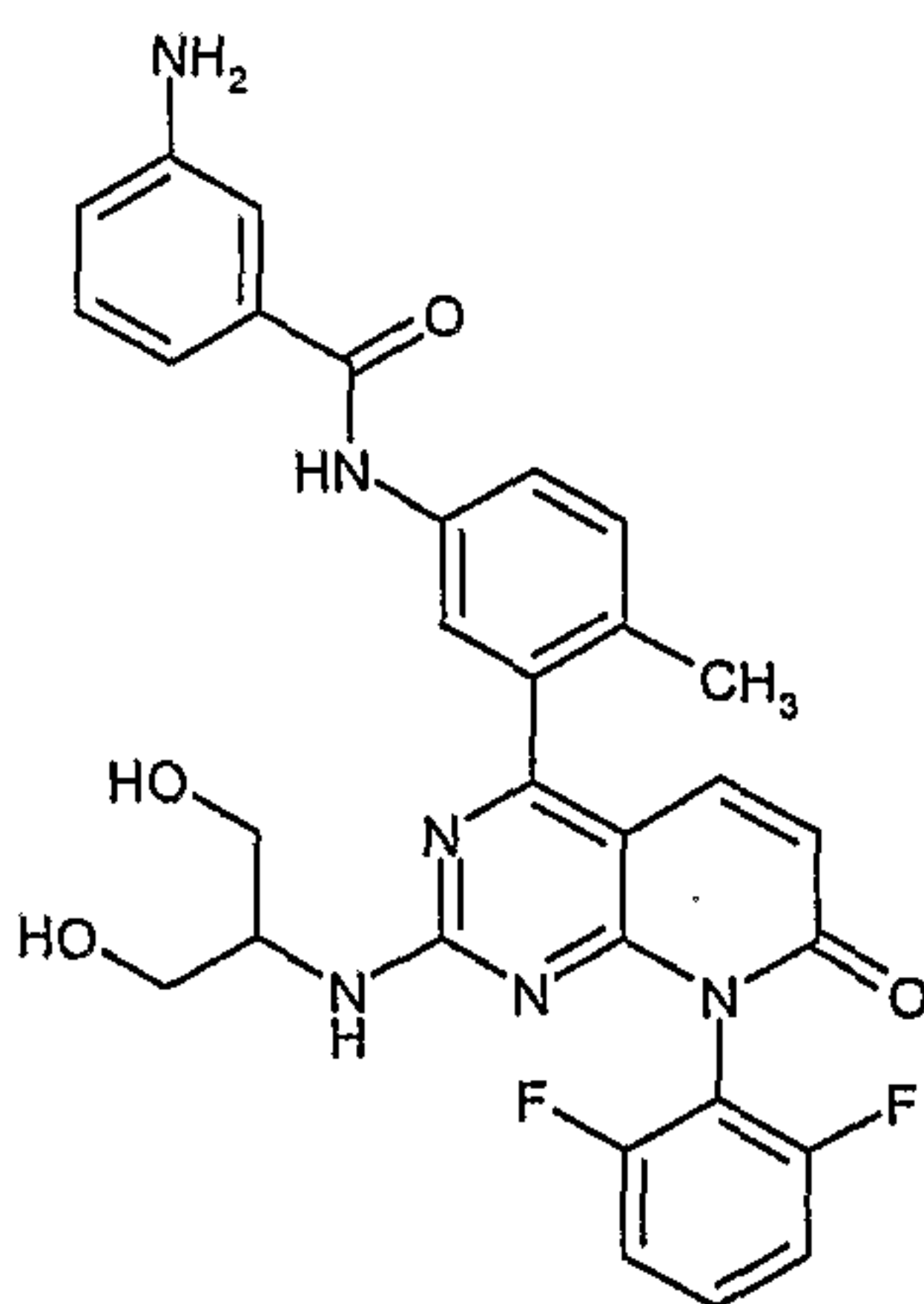
5

The title compound was prepared from 1*H*-indole-5-carboxylic acid by following the procedures in Example 37b: LC-MS *m/z* 597 (M+H)<sup>+</sup>, 3.06 min (ret time).

10

**Example 43**

3-amino-*N*-[3-(8-(2,6-difluorophenyl)-2-{[2-hydroxy-1-(hydroxymethyl)ethyl]-amino}-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl)-4-methylphenyl]benzamide trifluoroacetate



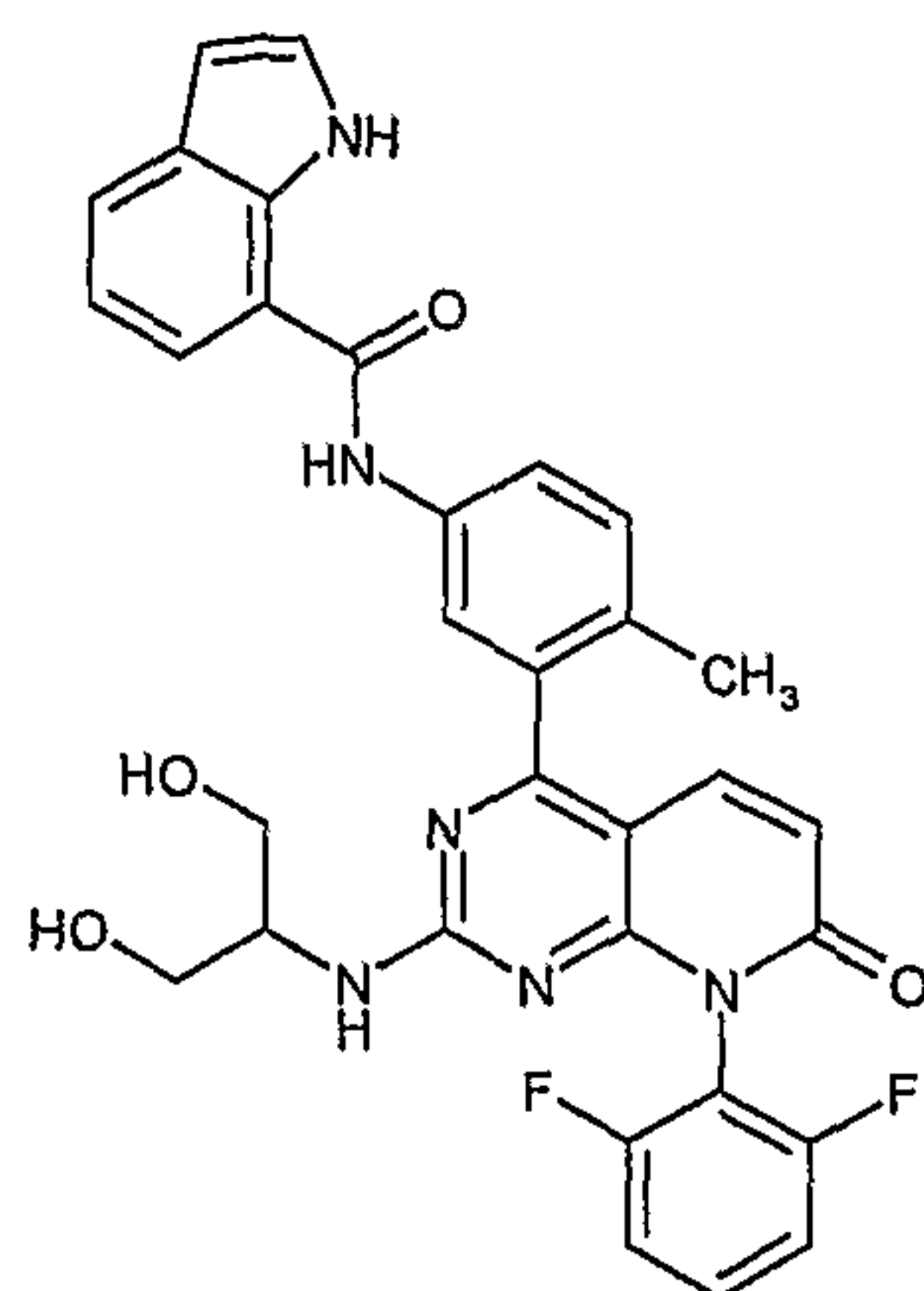
15

The title compound was prepared from 3-aminobenzoic acid by following the procedures in Example 37b: LC-MS *m/z* 573 (M+H)<sup>+</sup>, 2.77 min (ret time).

**Example 44**

*N*-[3-(8-(2,6-difluorophenyl)-2-{[2-hydroxy-1-(hydroxymethyl)ethyl]amino}-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl)-4-methylphenyl]-1*H*-indole-7-carboxamide trifluoroacetate

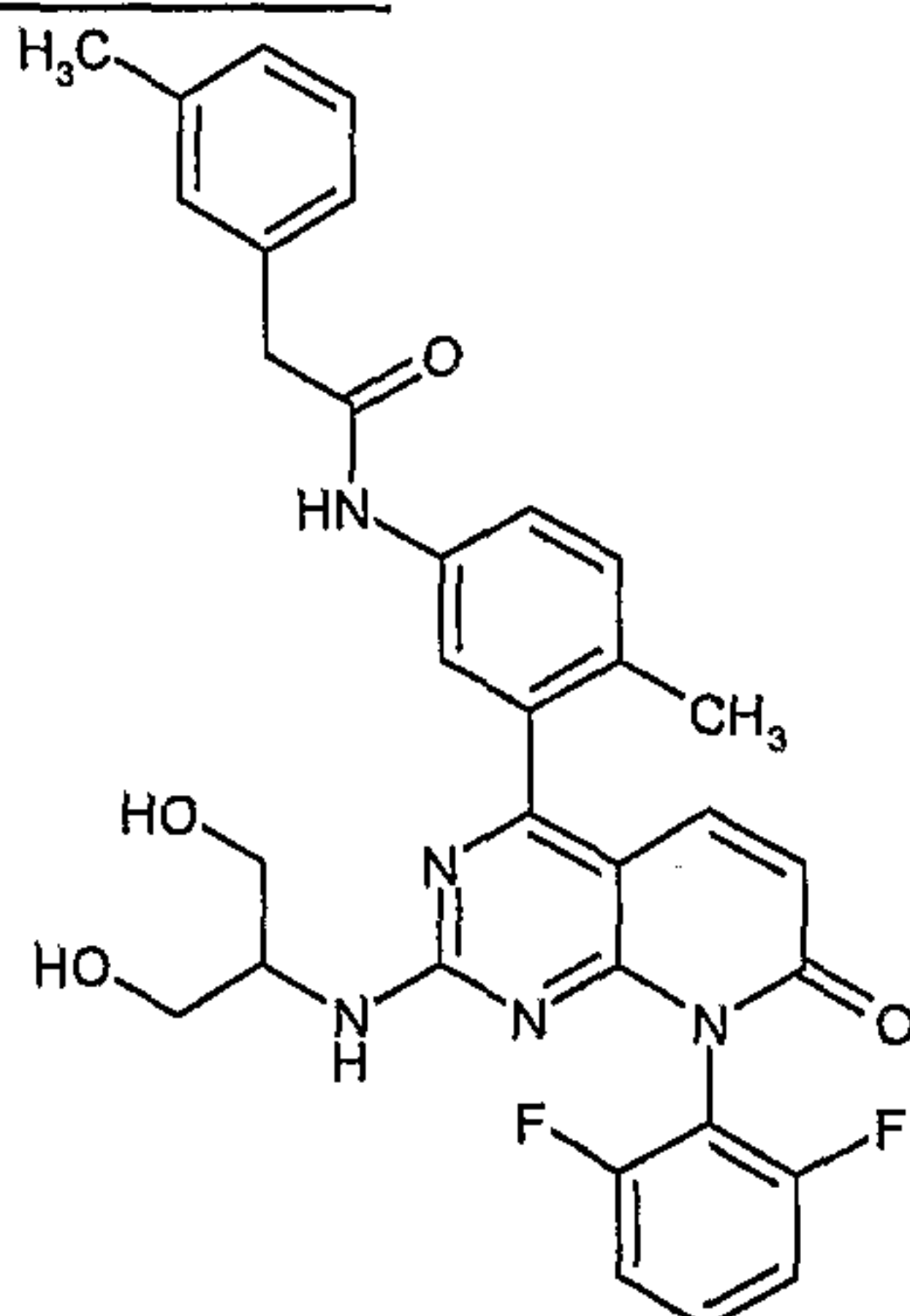
20



The title compound was prepared from 1*H*-indole-7-carboxylic acid by following the procedures in Example 37b: LC-MS  $m/z$  597 ( $M+H$ )<sup>+</sup>, 3.27 min (ret time).

#### Example 45

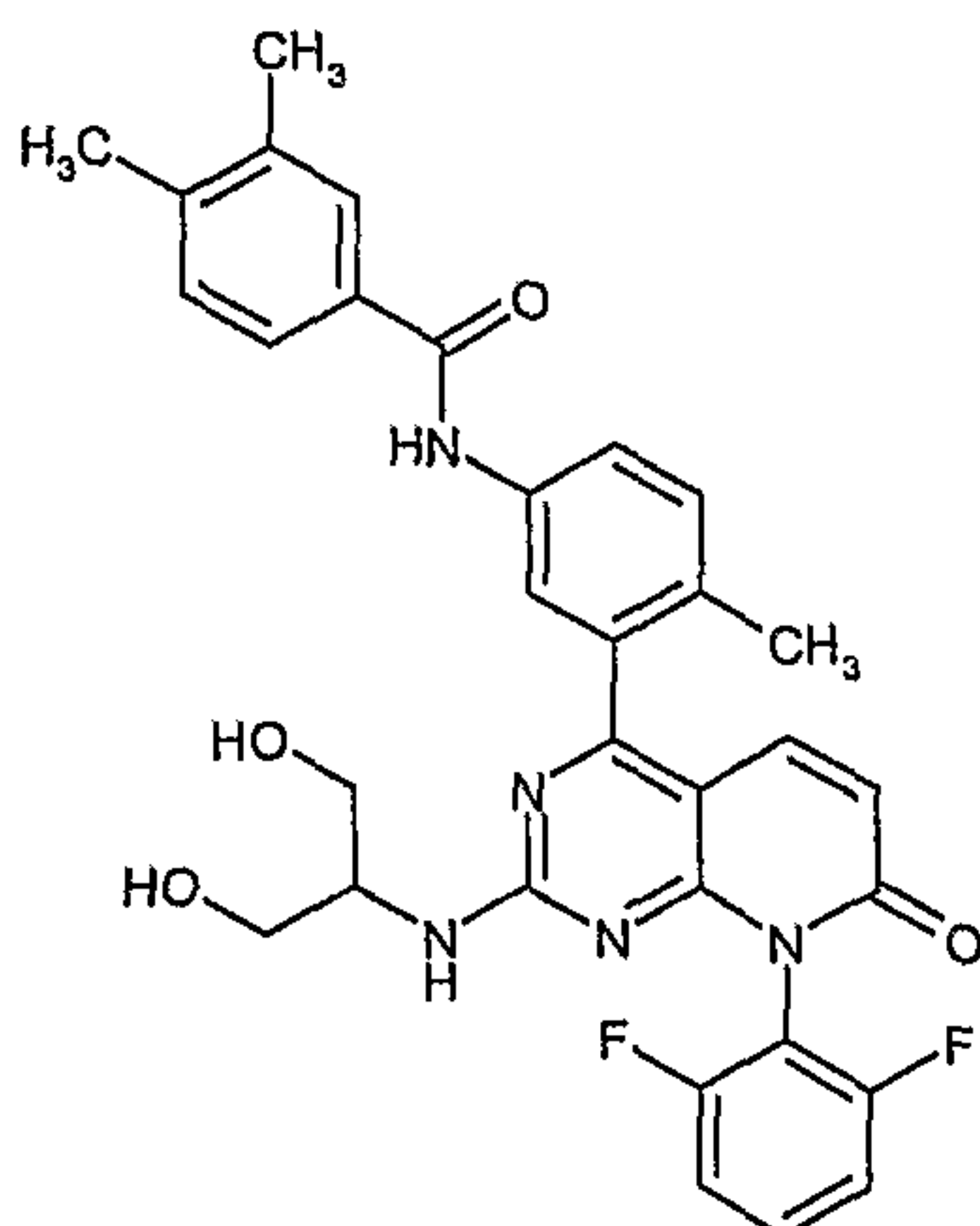
*N*-[3-(8-(2,6-difluorophenyl)-2-{[2-hydroxy-1-(hydroxymethyl)ethyl]amino}-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl)-4-methylphenyl]-2-(3-methylphenyl)acetamide trifluoroacetate



The title compound was prepared from (3-methylphenyl)acetic acid by following the procedures in Example 37b: LC-MS  $m/z$  586 ( $M+H$ )<sup>+</sup>, 3.15 min (ret time).

**Example 46**

*N*-[3-(8-(2,6-difluorophenyl)-2-{[2-hydroxy-1-(hydroxymethyl)ethyl]amino}-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl)-4-methylphenyl]-3,4-dimethylbenzamide trifluoroacetate



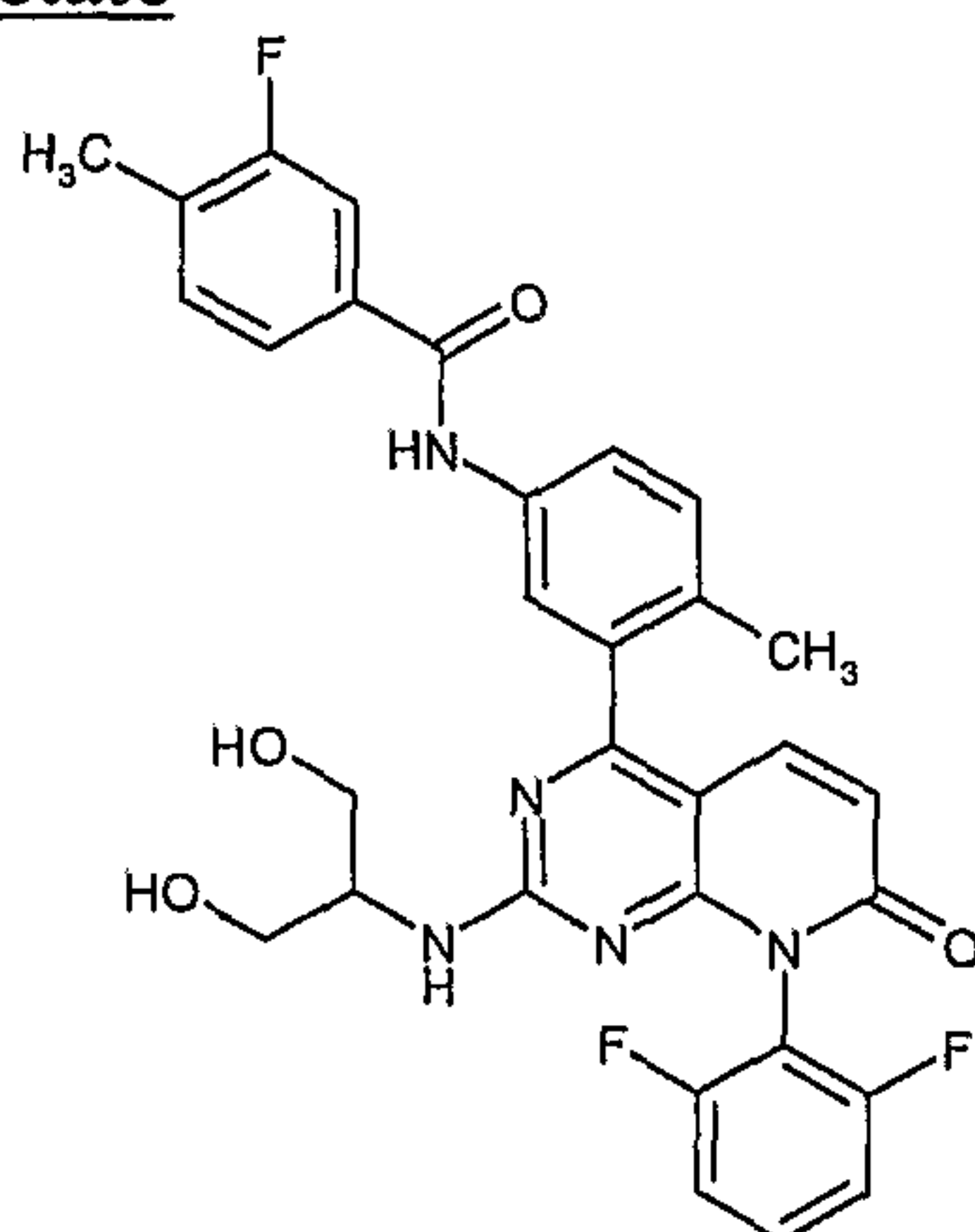
5

The title compound was prepared from 3,4-dimethylbenzoic acid by following the procedures in Example 37b: LC-MS  $m/z$  586 ( $M+H$ )<sup>+</sup>, 3.25 min (ret time).

10

**Example 47**

*N*-[3-(8-(2,6-difluorophenyl)-2-{[2-hydroxy-1-(hydroxymethyl)ethyl]amino}-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl)-4-methylphenyl]-3-fluoro-4-methylbenzamide trifluoroacetate

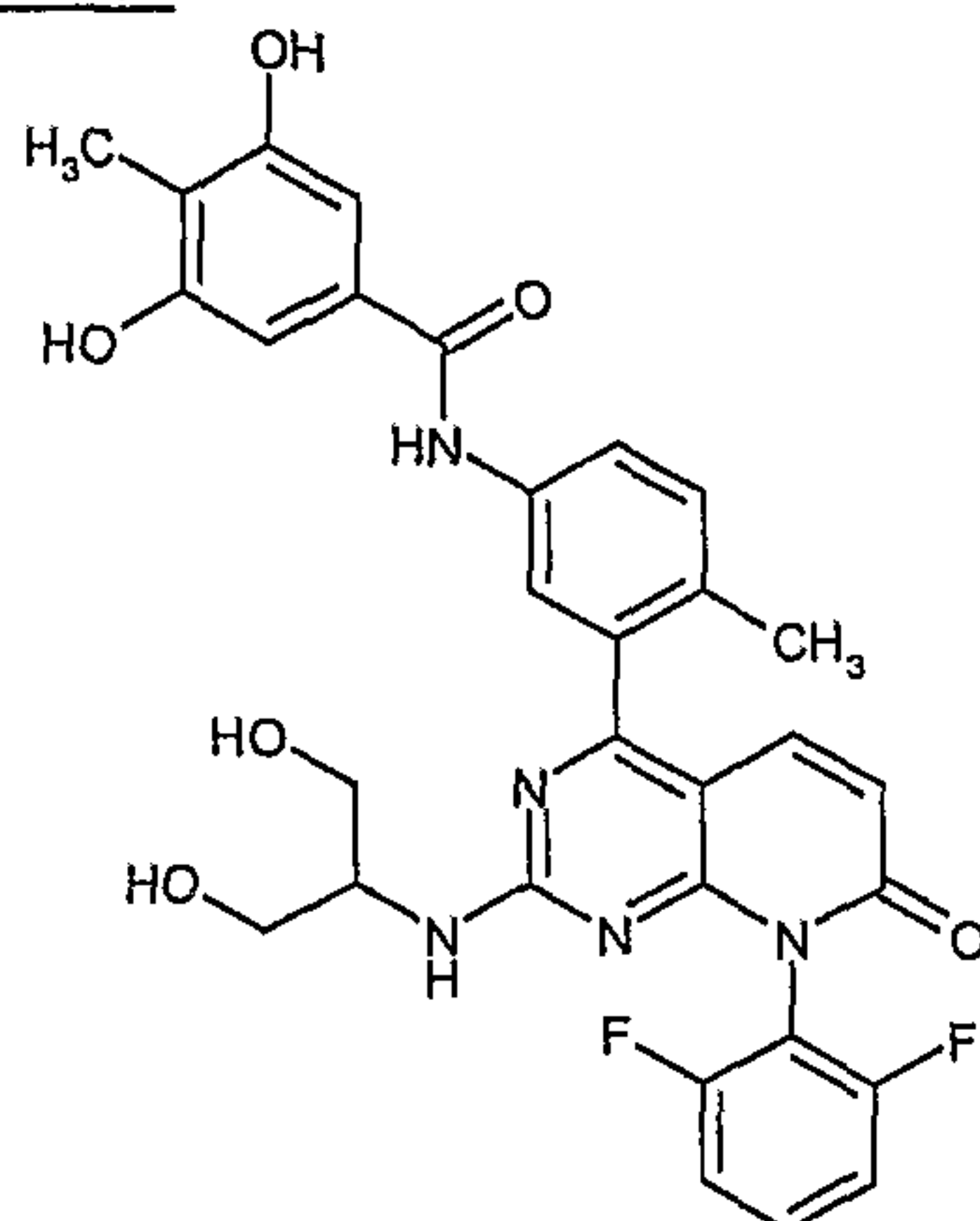


15

The title compound was prepared from 3-fluoro-4-methylbenzoic acid by following the procedures in Example 37b: LC-MS  $m/z$  590 ( $M+H$ )<sup>+</sup>, 3.23 min (ret time).

**Example 48**

*N*-[3-(8-(2,6-difluorophenyl)-2-{[2-hydroxy-1-(hydroxymethyl)ethyl]amino}-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl)-4-methylphenyl]-3,5-dihydroxy-4-methylbenzamide trifluoroacetate



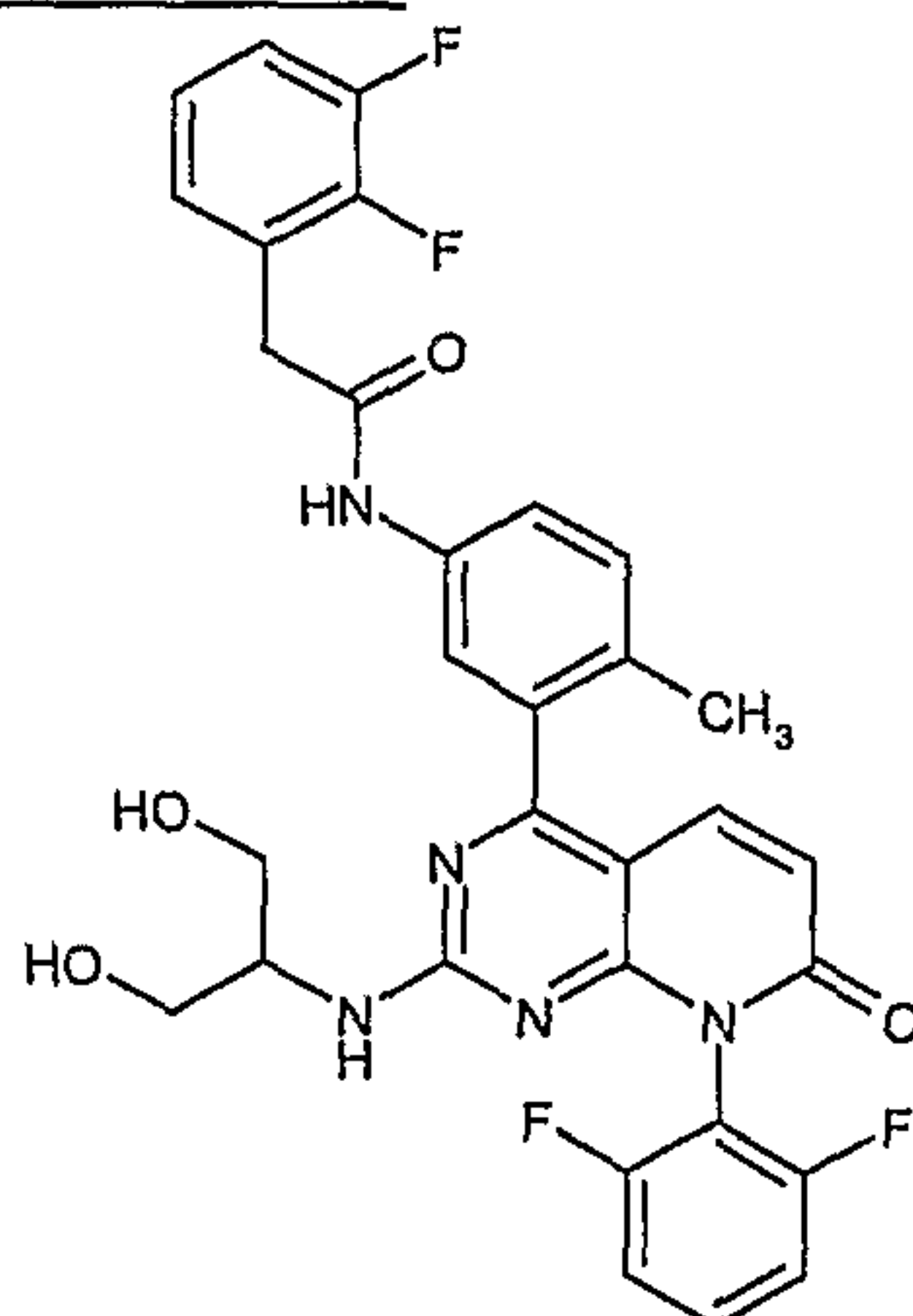
5

The title compound was prepared from 3,5-dihydroxy-4-methylbenzoic acid by following the procedures in Example 37b: LC-MS  $m/z$  604 ( $M+H$ )<sup>+</sup>, 2.88 min (ret time).

10

**Example 49**

2-(2,3-difluorophenyl)-*N*-[3-(8-(2,6-difluorophenyl)-2-{[2-hydroxy-1-(hydroxymethyl)ethyl]amino}-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl)-4-methylphenyl]acetamide trifluoroacetate

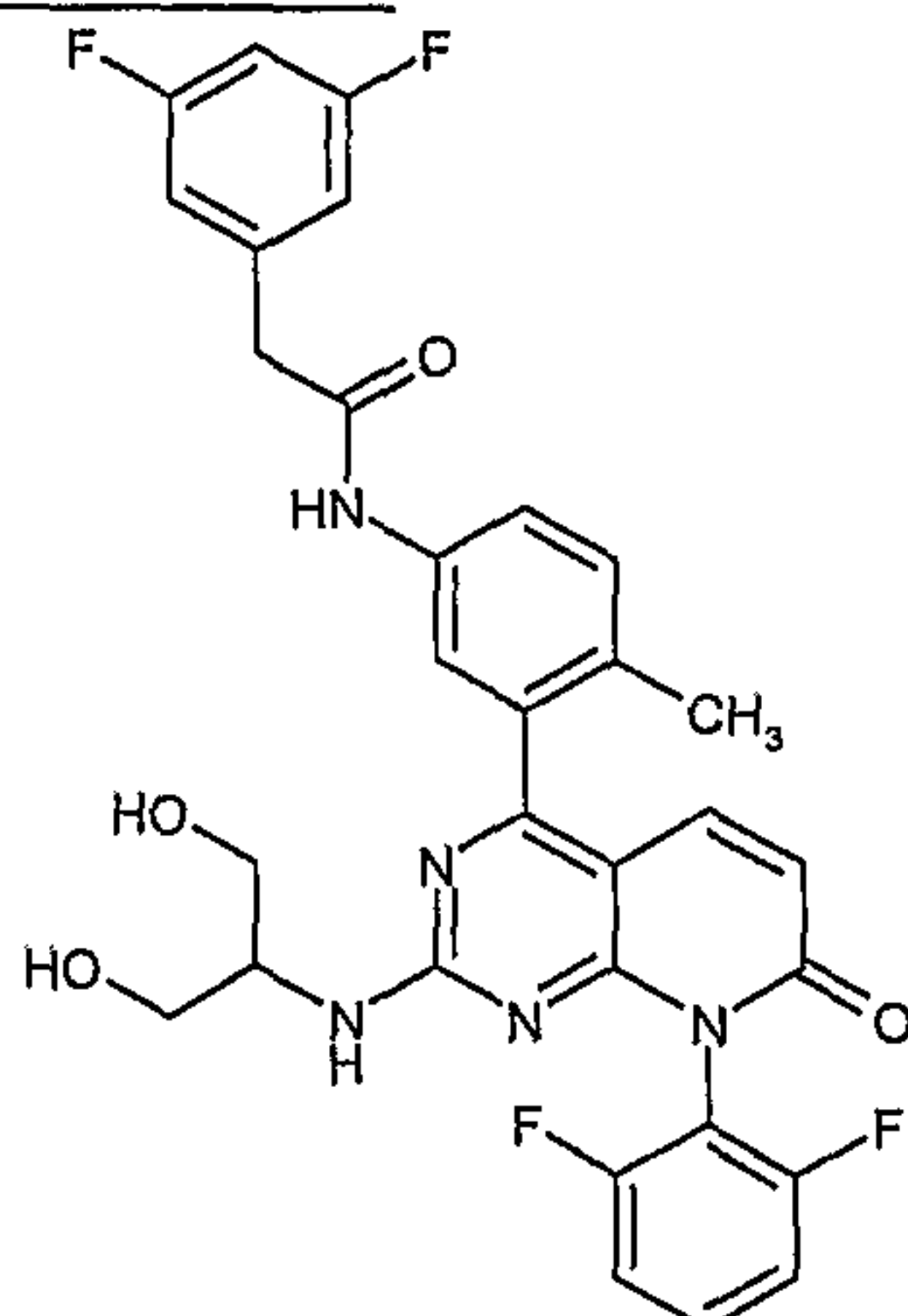


15

The title compound was prepared from (2,3-difluorophenyl)acetic acid by following the procedures in Example 37b: LC-MS  $m/z$  608 ( $M+H$ )<sup>+</sup>, 3.12 min (ret time).

**Example 50**

2-(3,5-difluorophenyl)-N-[3-(8-(2,6-difluorophenyl)-2-{[2-hydroxy-1-(hydroxymethyl)ethyl]amino}-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl)-4-methylphenyl]acetamide trifluoroacetate



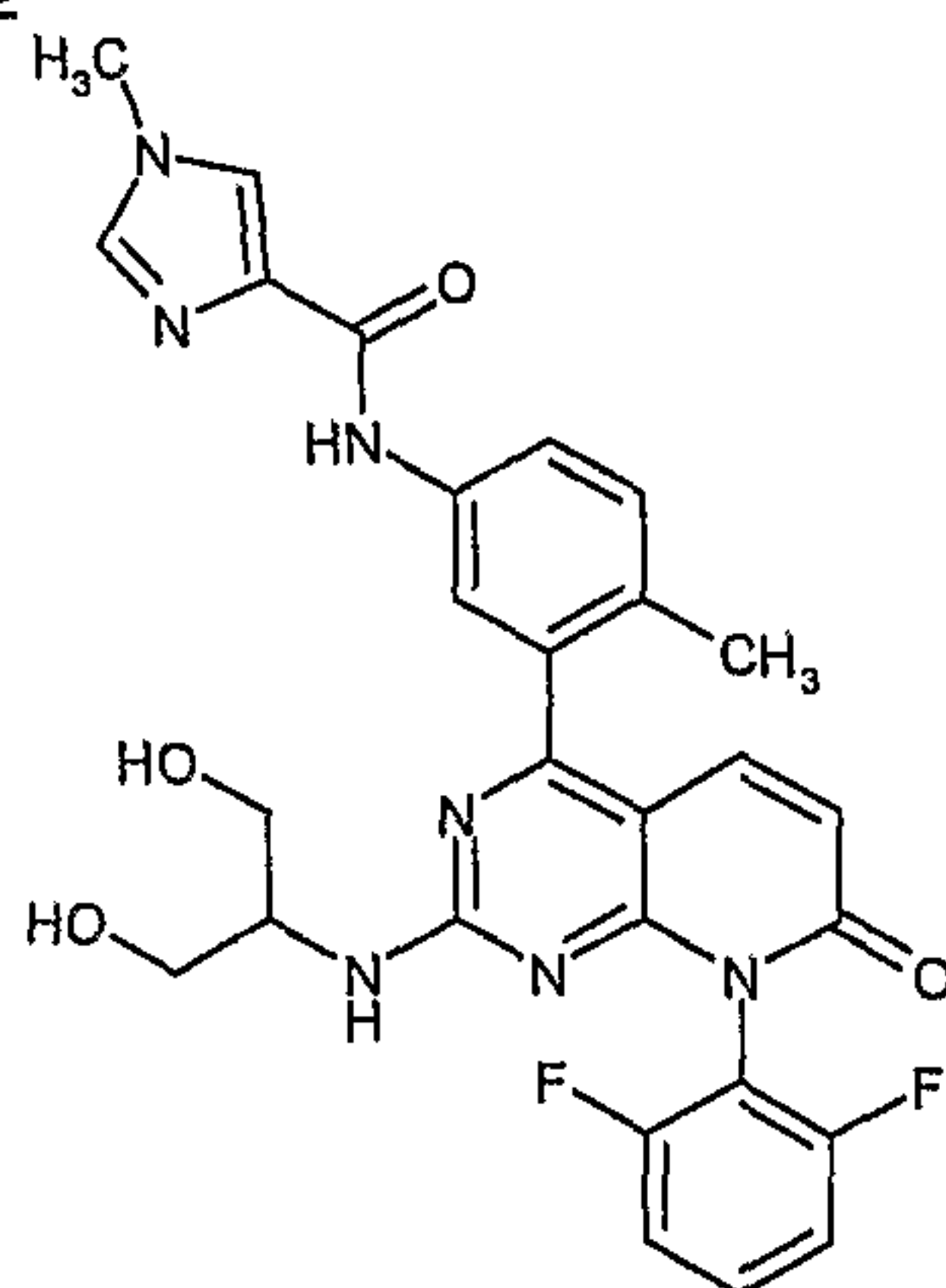
5

The title compound was prepared from (3,5-difluorophenyl)acetic acid by following the procedures in Example 37b: LC-MS  $m/z$  608 ( $M+H$ )<sup>+</sup>, 3.17 min (ret time).

10

**Example 51**

N-[3-(8-(2,6-difluorophenyl)-2-{[2-hydroxy-1-(hydroxymethyl)ethyl]amino}-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl)-4-methylphenyl]-1-methyl-1*H*-imidazole-4-carboxamide trifluoroacetate

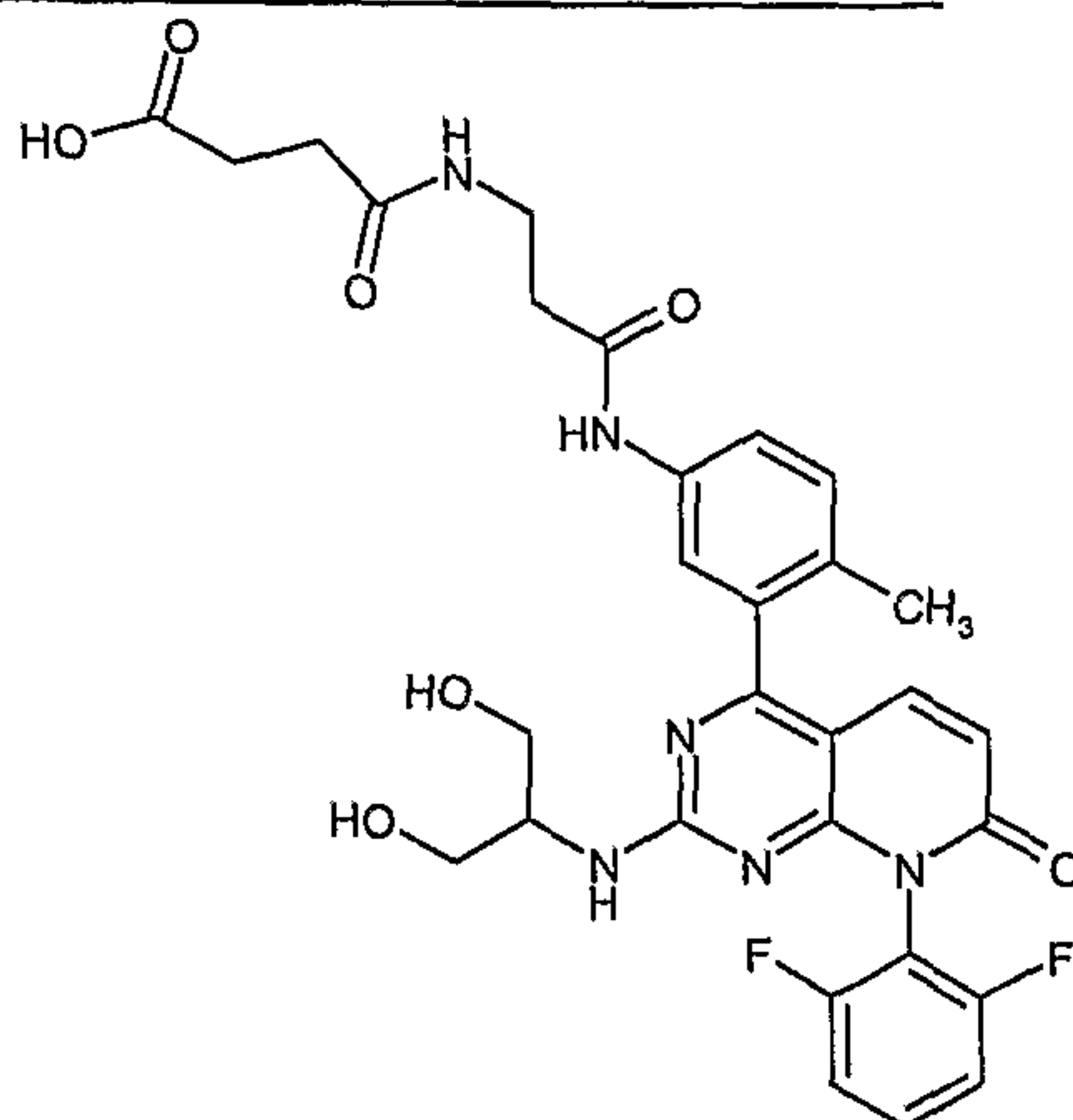


15

The title compound was prepared from 1-methyl-1*H*-imidazole-4-carboxylic acid by following the procedures in Example 37b: LC-MS  $m/z$  562 ( $M+H$ )<sup>+</sup>, 2.65 min (ret time).

**Example 52**

4-[(3-{[3-(8-(2,6-difluorophenyl)-2-{[2-hydroxy-1-(hydroxymethyl)ethyl]amino}-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl)-4-methylphenyl]amino}-3-oxopropyl)amino]-4-oxobutanoic acid trifluoroacetate



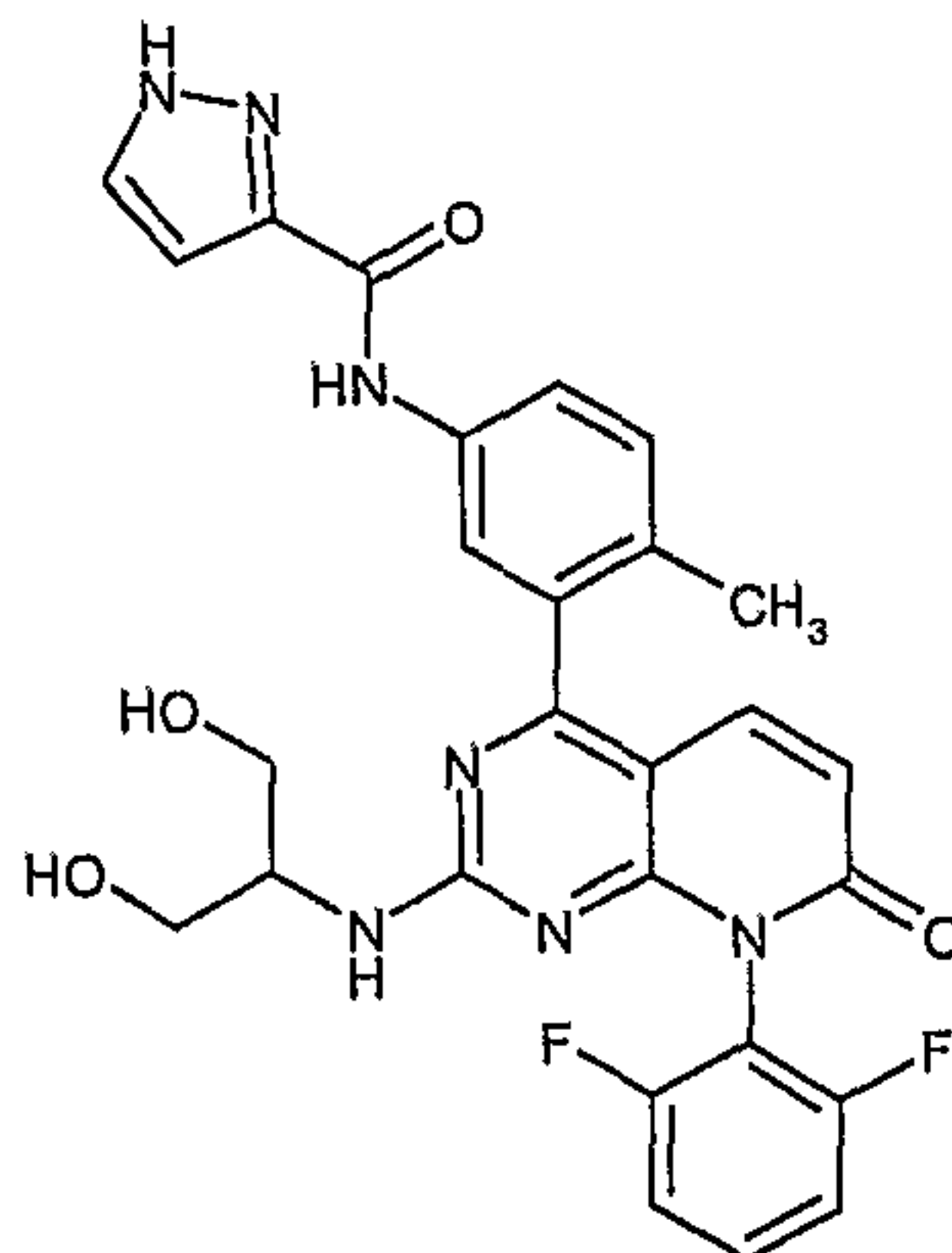
5

The title compound was prepared from 3-(2,5-dioxo-1-pyrrolidinyl)-propanoic acid by following the procedures in Example 37b: LC-MS  $m/z$  607 ( $M+H$ )<sup>+</sup>, 2.56 min (ret time).

10

**Example 53**

*N*-[3-(8-(2,6-difluorophenyl)-2-{[2-hydroxy-1-(hydroxymethyl)ethyl]amino}-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl)-4-methylphenyl]-1*H*-pyrazole-3-carboxamide trifluoroacetate



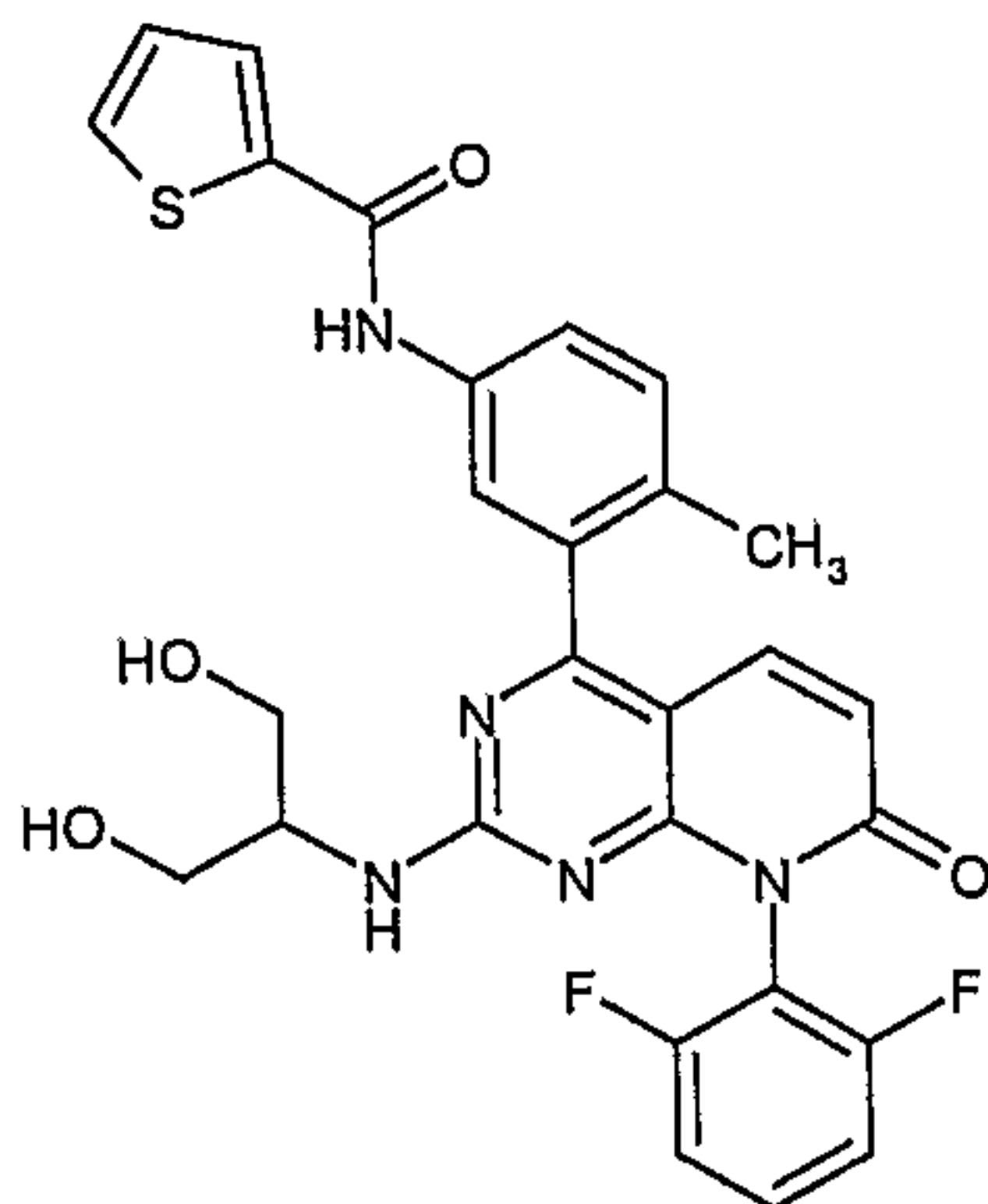
15

The title compound was prepared from 1*H*-pyrazole-3-carboxylic acid by following the procedures in Example 37b: LC-MS  $m/z$  548 ( $M+H$ )<sup>+</sup>, 2.74 min (ret time).

20

**Example 54**

*N*-[3-(8-(2,6-difluorophenyl)-2-{[2-hydroxy-1-(hydroxymethyl)ethyl]amino}-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl)-4-methylphenyl]-2-thiophenecarboxamide trifluoroacetate



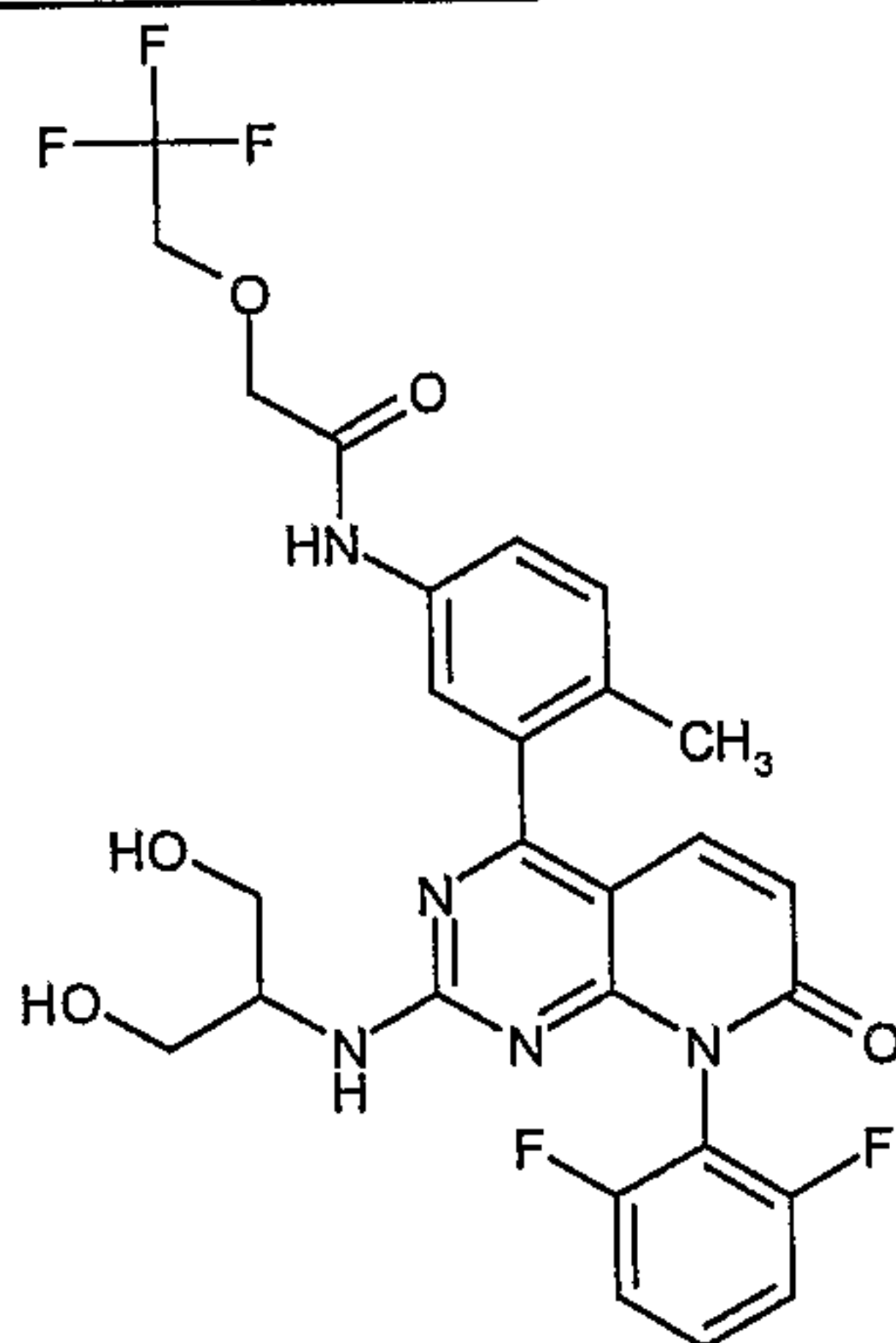
5

The title compound was prepared from 2-thiophenecarboxylic acid by following the procedures in Example 37b: LC-MS  $m/z$  564 ( $M+H$ )<sup>+</sup>, 3.03 min (ret time).

10

**Example 55**

*N*-[3-(8-(2,6-difluorophenyl)-2-{[2-hydroxy-1-(hydroxymethyl)ethyl]amino}-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl)-4-methylphenyl]-2-[(2,2,2-trifluoroethyl)oxy]acetamide trifluoroacetate



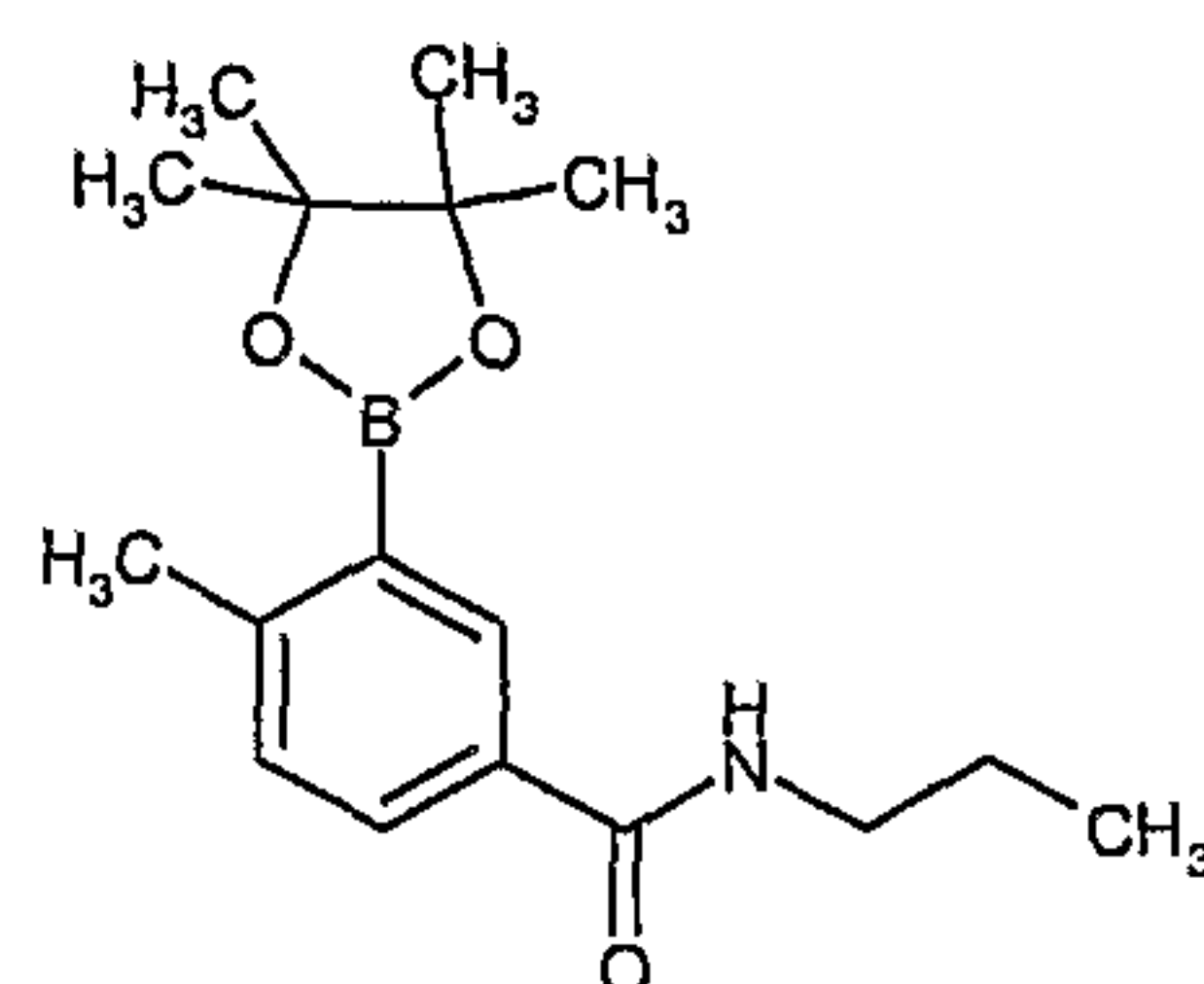
15

The title compound was prepared from [(2,2,2-trifluoroethyl)oxy]acetic acid by following the procedures in Example 37b: LC-MS  $m/z$  594 ( $M+H$ )<sup>+</sup>, 2.96 min (ret time).

**Example 56**

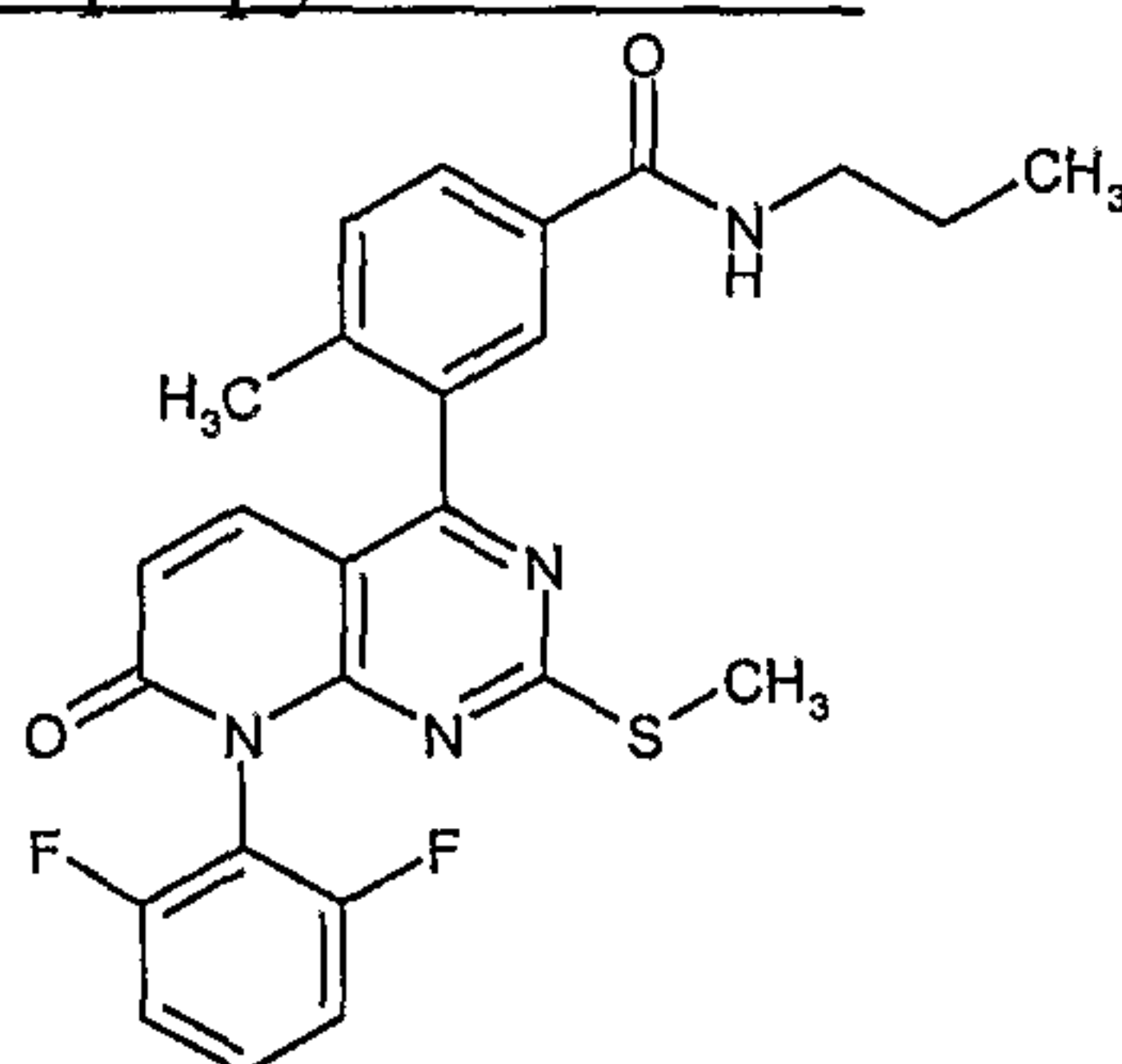
20 3-(8-(2,6-difluorophenyl)-2-{[2-(methylamino)ethyl]amino}-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl)-4-methyl-*N*-propylbenzamide

56a) 4-Methyl-N-propyl-3-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-benzamide



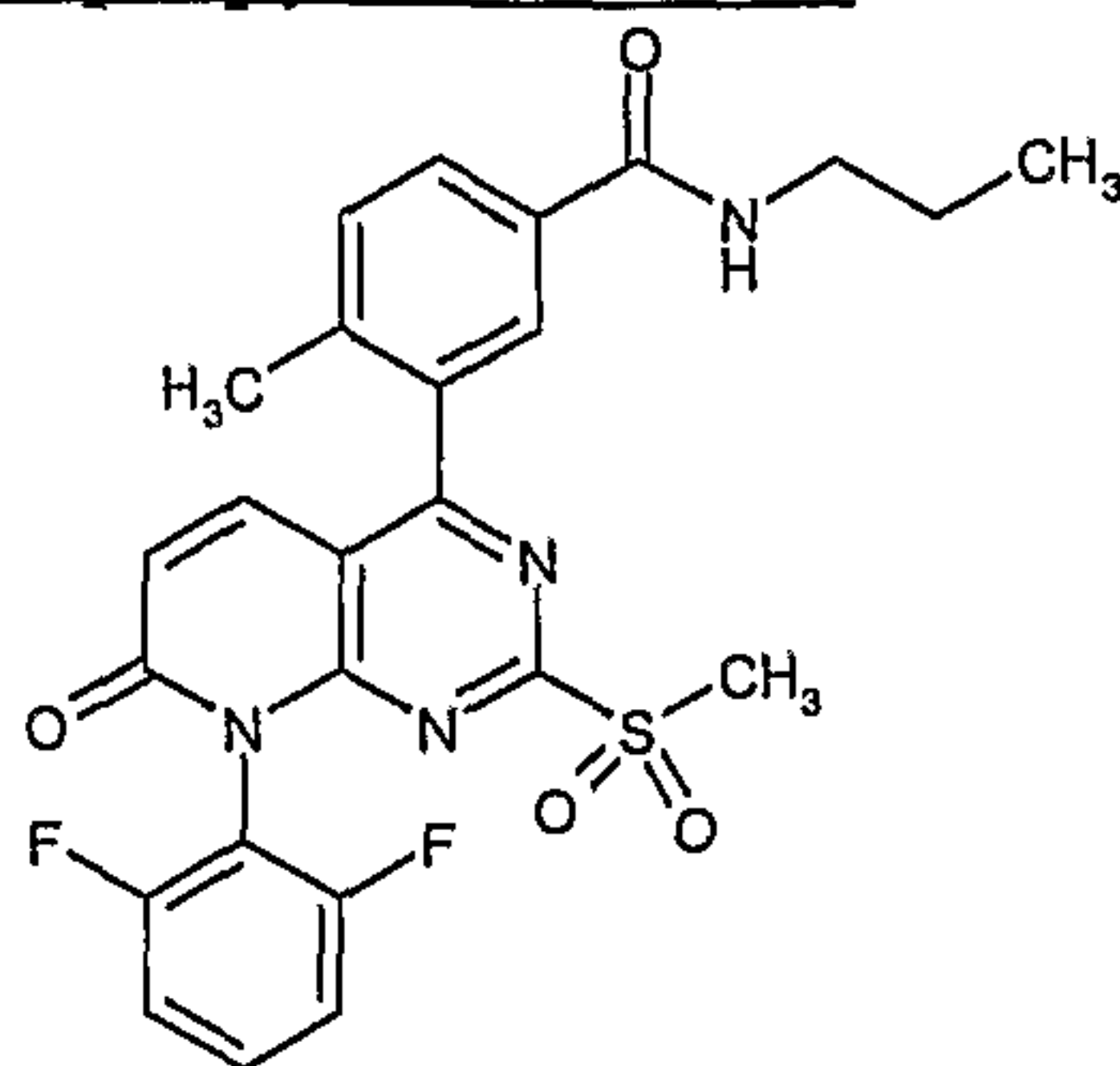
5 To 4-methyl-3-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-benzoic acid (524 mg, 2 mmol, 1 eq) was added HBTU (642 mg, 2 mmol, 1 eq) in DMF (5 mL). DIPEA (700 uL, 4 mmol, 2 eq) was then added in 100 uL portions. After 10 min propylamine (328 uL, 4 mmol, 2 eq) was then added and the mixture was stirred overnight at room temperature. The solvent was then removed in vacuo. The  
10 residue was then dissolved in chloroform and purified by aminopropyl SPE: LC-MS  $m/z$  304 (M+H)<sup>+</sup>, 3.37 min (ret time).

56b) 3-[8-(2,6-Difluoro-phenyl)-2-methylsulfanyl-7-oxo-7,8-dihydro-pyrido[2,3-d]pyrimidin-4-yl]-4-methyl-N-propyl-benzamide



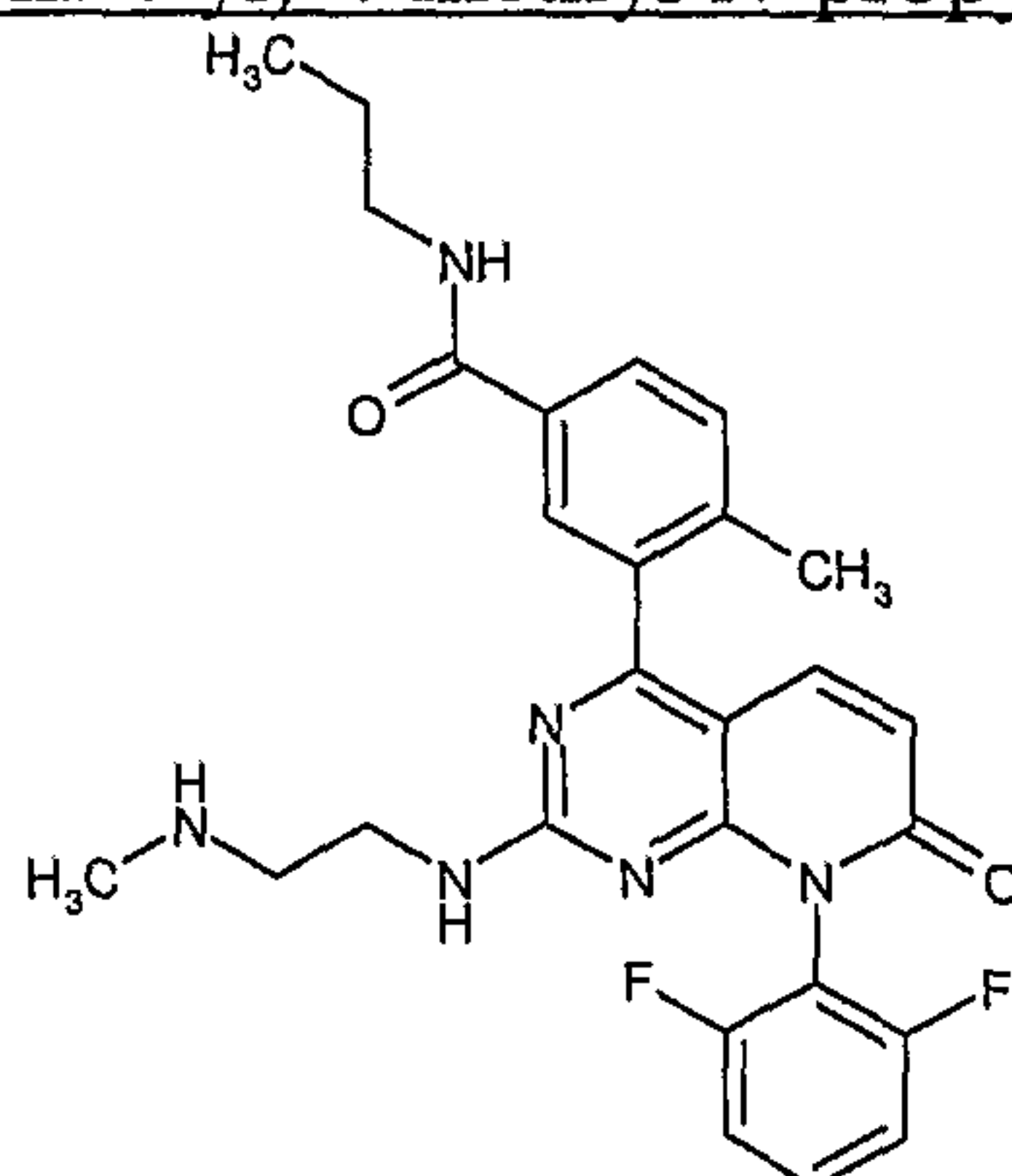
15 To 4-chloro-8-(2,6-difluoro-phenyl)-2-methylsulfanyl-8H-pyrido[2,3-d]pyrimidin-7 one (200 mg, 0.589 mmol, 1 eq) and 4-methyl-N-propyl-3-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-benzamide (268 mg, 0.883 mmol, 1.5 eq) in isopropanol (6 mL) was added sodium bicarbonate (148 mg, 1.76 mmol, 3 eq) in  
20 water (1.5 mL). The reaction mixture was then purged with nitrogen followed by addition of tetrakis(triphenylphosphine)-palladium(0) (34 mg, 0.029 mmol, 5 mol%). The mixture was then heated to about 80 °C overnight. The mixture was then allowed to cool to room temperature before the solvent was removed in vacuo. The residue was then purified on the Flashmaster 2™: LC-MS  $m/z$  481 (M+H)<sup>+</sup>,  
25 3.34 min (ret time).

56c) 3-[8-(2,6-Difluoro-phenyl)-2-methanesulfonyl-7-oxo-7,8-dihydro-pyrido[2,3-d]pyrimidin-4-yl]-4-methyl-N-propyl-benzamide



3-[8-(2,6-Difluoro-phenyl)-2-methylsulfonyl-7-oxo-7,8-dihydro-pyrido[2,3-d]pyrimidin-4-yl]-4-methyl-N-propyl-benzamide (204 mg, 0.426 mmol, 1 eq) was suspended in acetonitrile (6 mL). The suspension was added to a stirring suspension of Oxone® (786 mg, 1.28 mmol, 3 eq) in water (3 mL). The resulting mixture was stirred overnight at about 40 °C. The reaction mixture was then partitioned between dichloromethane and sodium metabisulfite (10% aq solution). The layers were separated then the organic was dried over magnesium sulfate, filtered then evaporated to furnish the title compound: LC-MS  $m/z$  513 ( $M+H$ )<sup>+</sup>, 2.9 min (ret time).

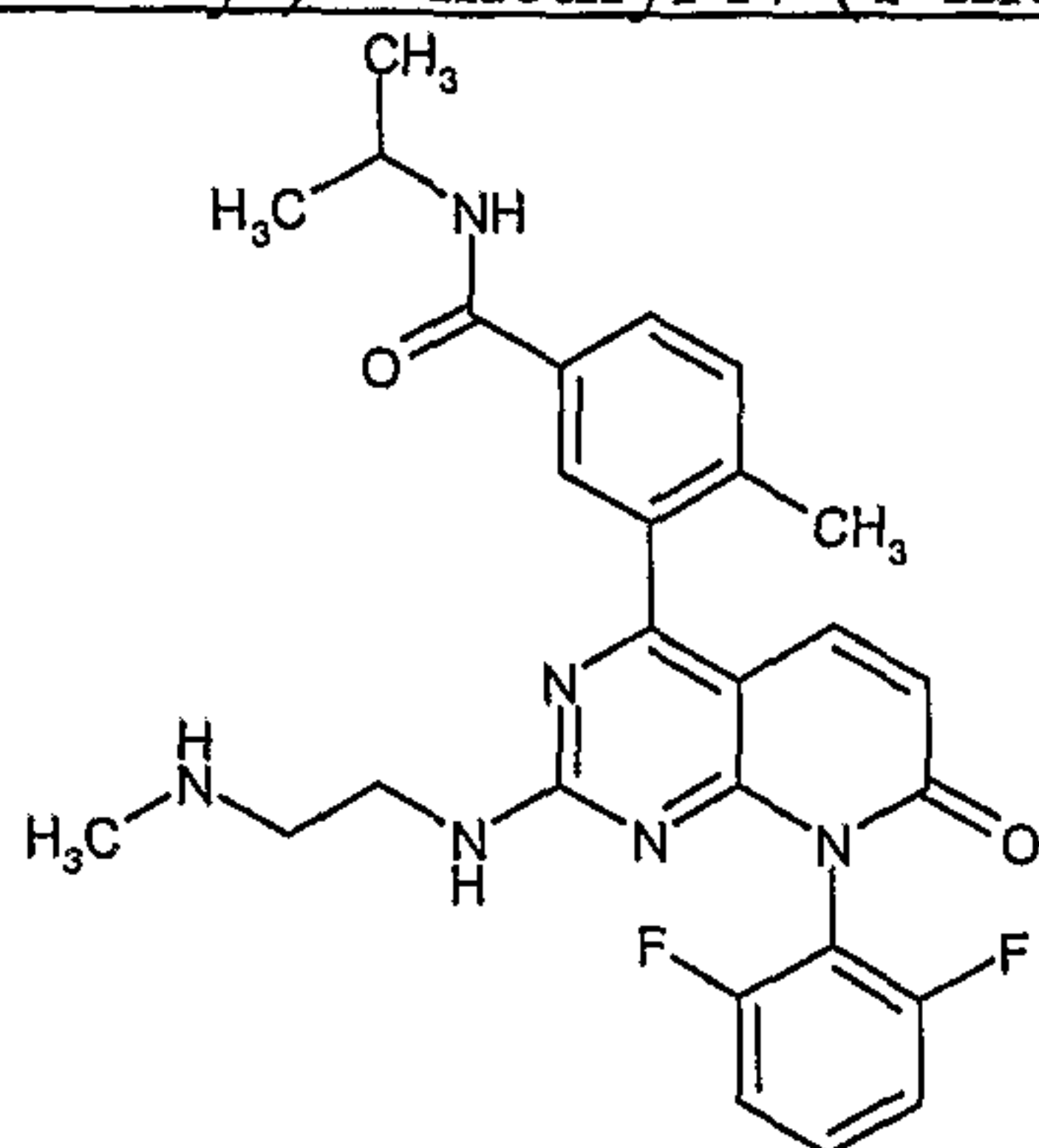
56d) 3-(8-(2,6-difluorophenyl)-2-{[2-(methylamino)ethyl]amino}-7-oxo-7,8-dihydropyrido[2,3-d]pyrimidin-4-yl)-4-methyl-N-propylbenzamide



The title compound was prepared from the compound from Example 56c and (2-aminoethyl)methylamine by following the procedures in Example 31e: LC-MS  $m/z$  507 ( $M+H$ )<sup>+</sup>, 2.31 min (ret time).

**Example 57**

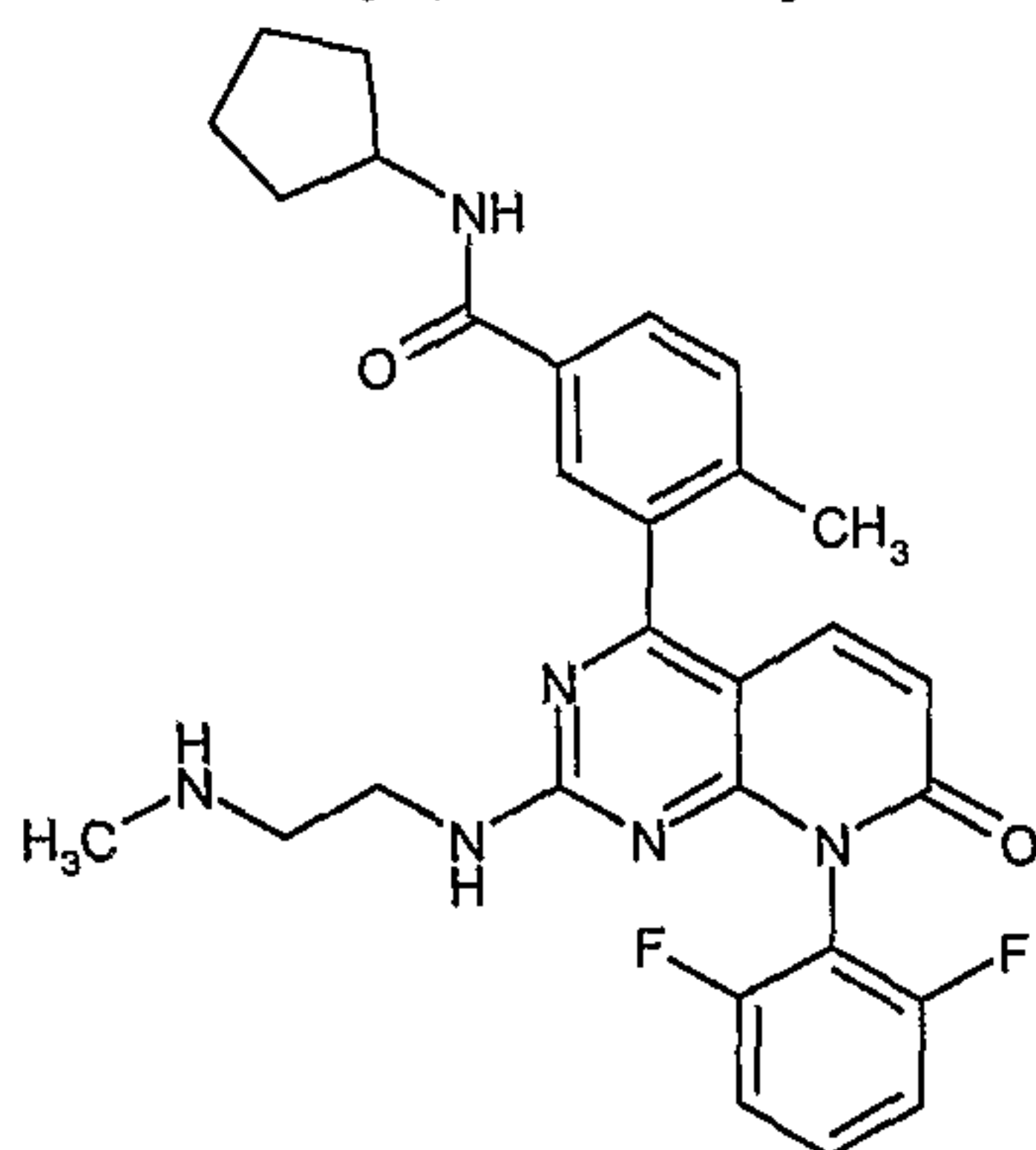
3-(8-(2,6-difluorophenyl)-2-{[2-(methylamino)ethyl]amino}-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl)-4-methyl-*N*-(1-methylethyl)benzamide



- 5 The title compound was prepared by following the procedures in Example 56 using 2-propanamine for amide formation and (2-aminoethyl)methylamine for the displacement: LC-MS  $m/z$  507 ( $M+H$ )<sup>+</sup>, 2.3 min (ret time).

**Example 58**

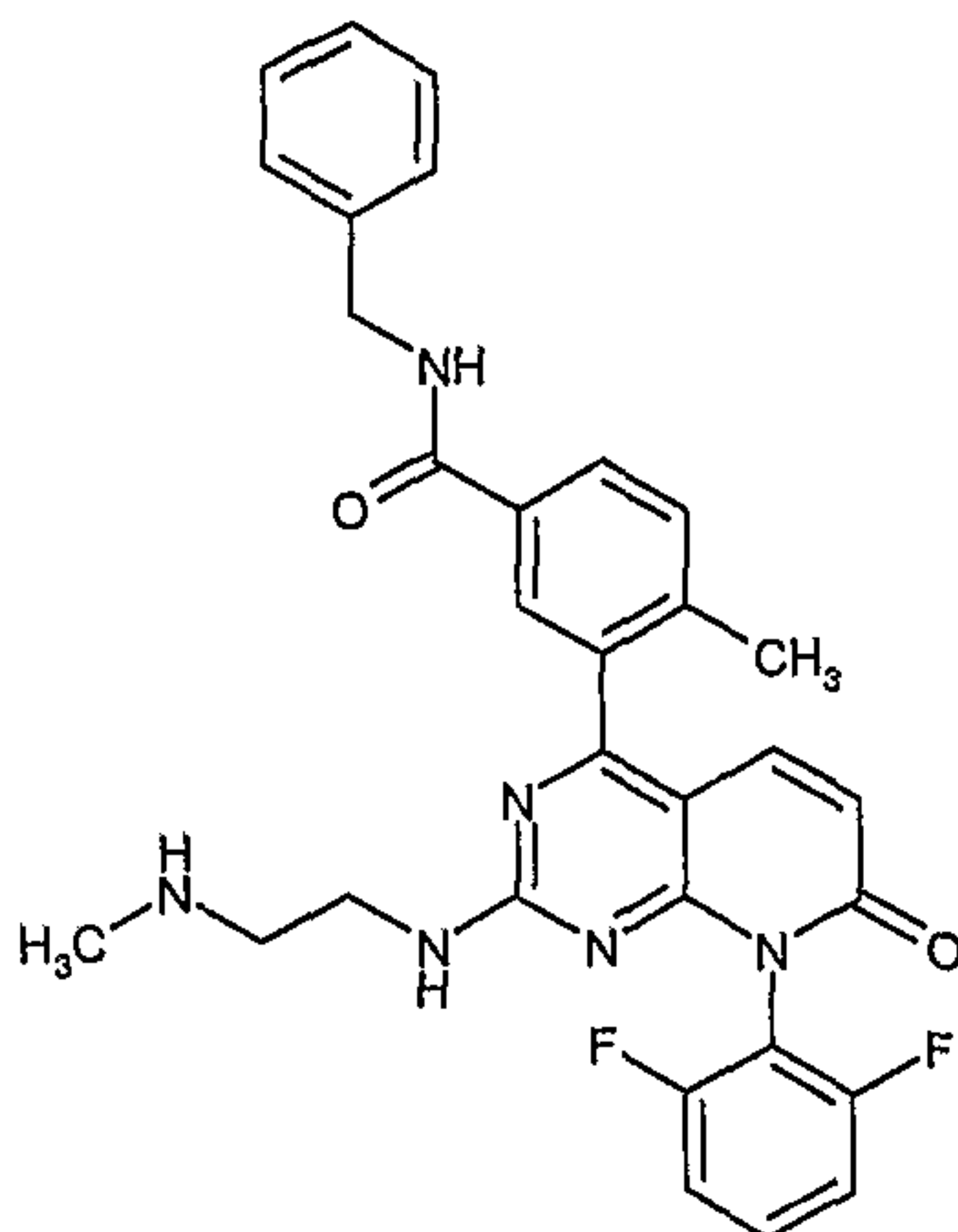
- 10 *N*-cyclopentyl-3-(8-(2,6-difluorophenyl)-2-{[2-(methylamino)ethyl]amino}-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl)-4-methylbenzamide



- 15 The title compound was prepared by following the procedures in Example 56 using cyclopentylamine for amide formation and (2-aminoethyl)methylamine for the displacement: LC-MS  $m/z$  533 ( $M+H$ )<sup>+</sup>, 2.43 min (ret time).

**Example 59**

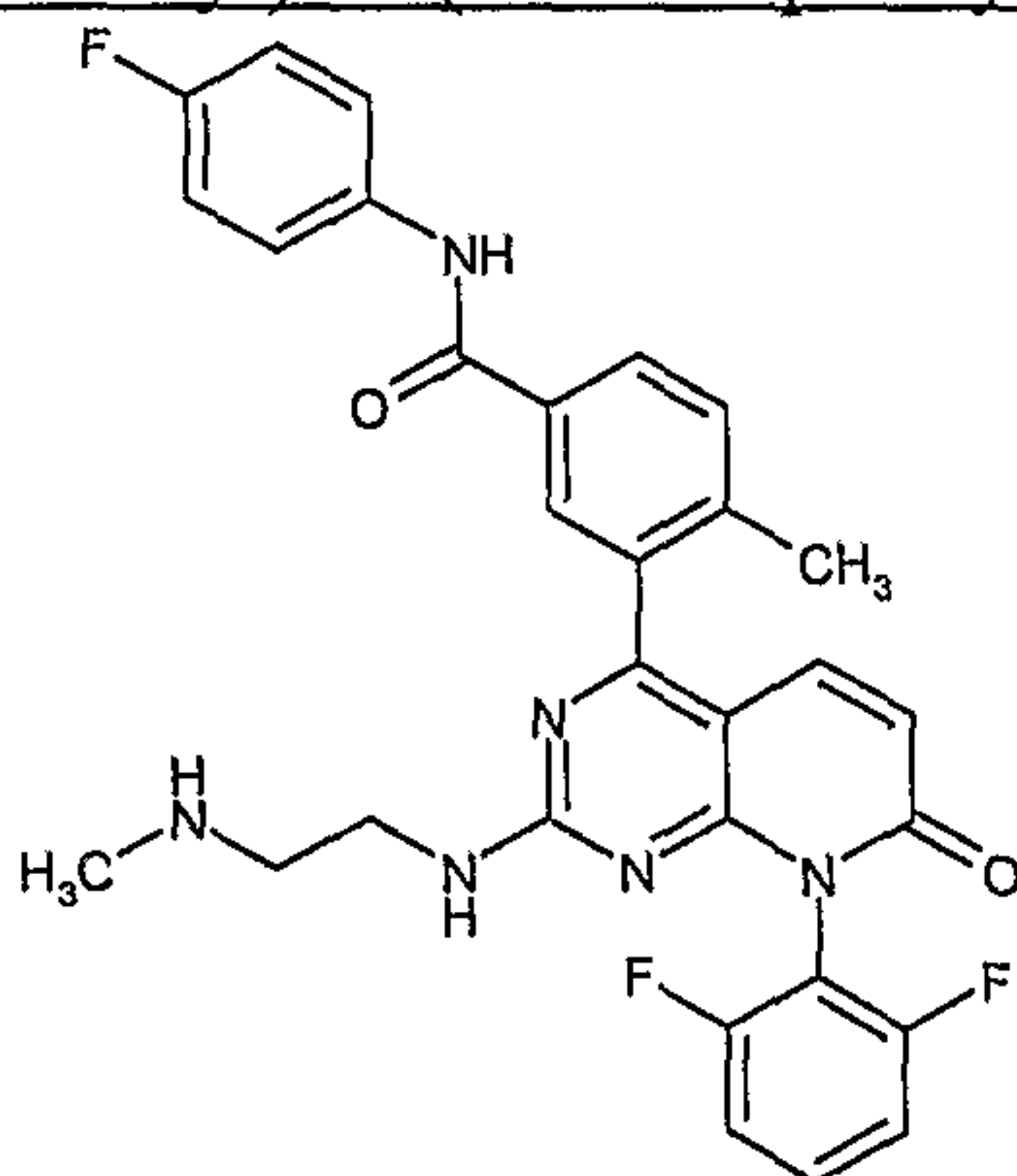
3-(8-(2,6-difluorophenyl)-2-{[2-(methylamino)ethyl]amino}-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl)-4-methyl-*N*-(phenylmethyl)benzamide



- 5 The title compound was prepared by following the procedures in Example 56 using benzylamine for the amide formation and (2-aminoethyl)methylamine for the displacement: LC-MS  $m/z$  555 ( $M+H$ )<sup>+</sup>, 2.48 min (ret time).

**Example 60**

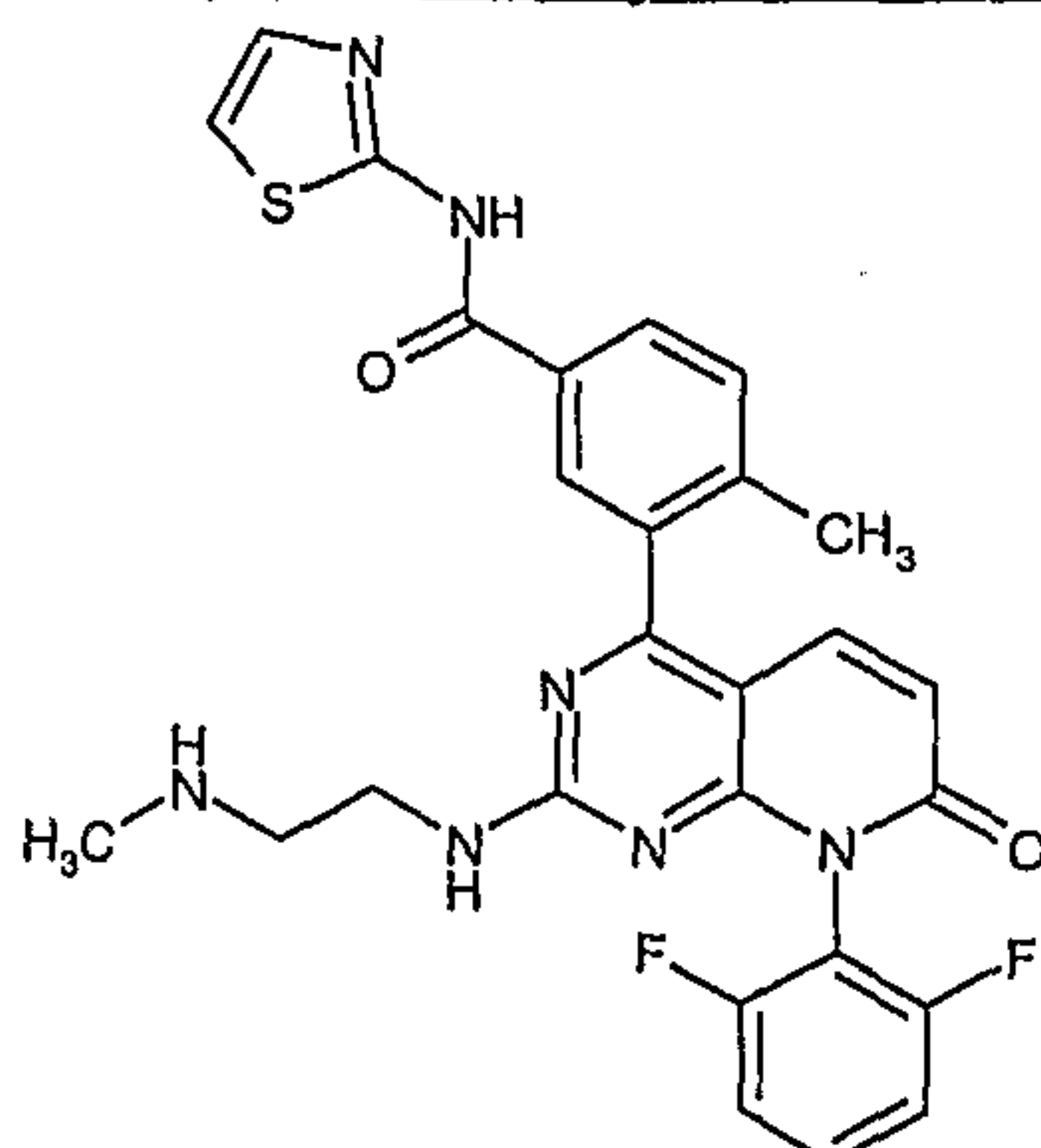
- 10 3-(8-(2,6-difluorophenyl)-2-{[2-(methylamino)ethyl]amino}-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl)-*N*-(4-fluorophenyl)-4-methylbenzamide



- 15 The title compound was prepared by following the procedures in example 56 using 4-fluoroaniline for the amide formation and (2-aminoethyl)methylamine for the displacement: LC-MS  $m/z$  559 ( $M+H$ )<sup>+</sup>, 2.55 min (ret time).

**Example 61**

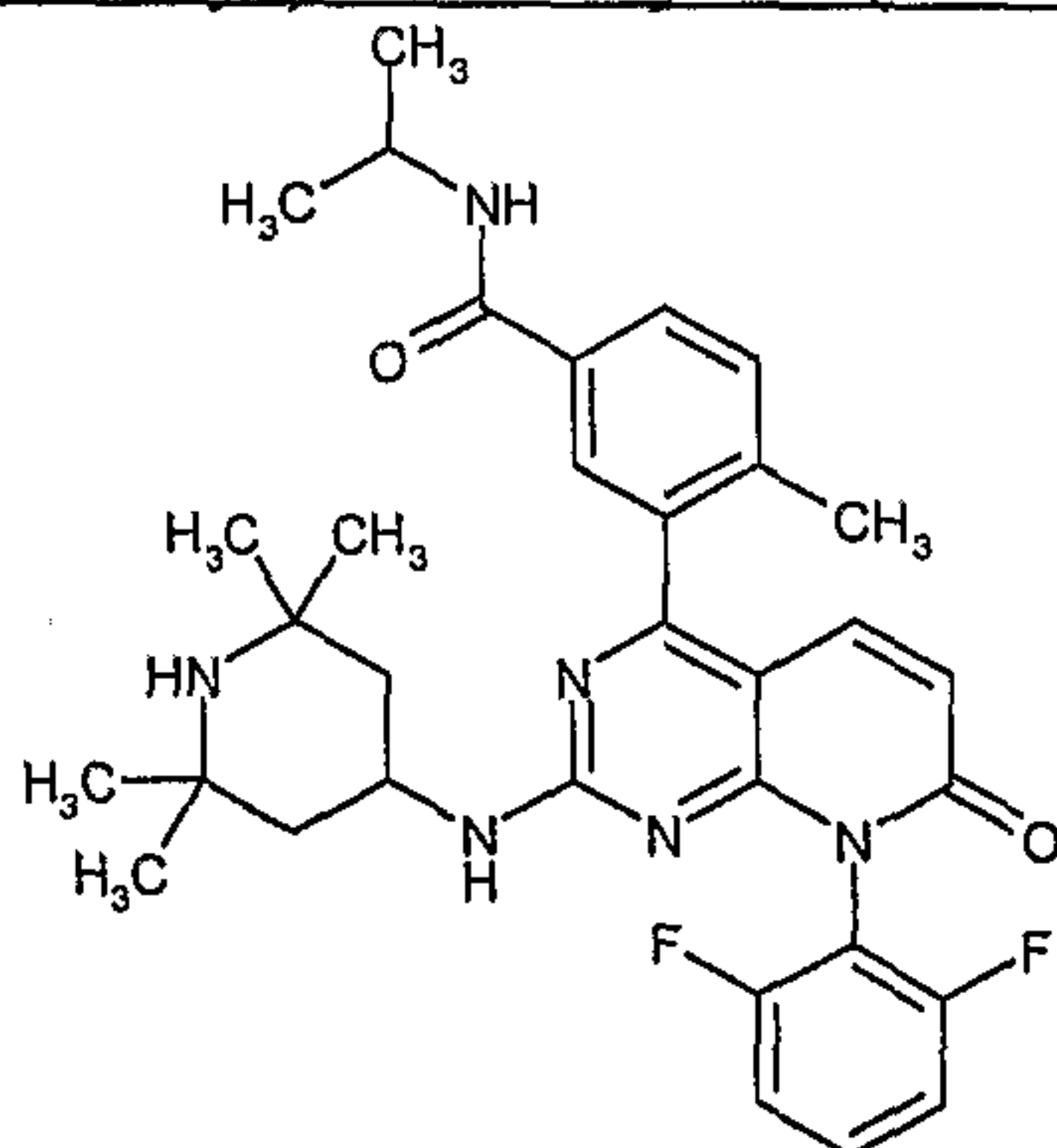
3-(8-(2,6-difluorophenyl)-2-{[2-(methylamino)ethyl]amino}-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl)-4-methyl-*N*-1,3-thiazol-2-ylbenzamide



- 5 The title compound was prepared by following the procedures in Example 56 using 1,3-thiazole-2-amine for the amide formation and (2-aminoethyl)methylamine for the displacement: LC-MS  $m/z$  548 ( $M+H$ )<sup>+</sup>, 2.41 min (ret time).

**Example 62**

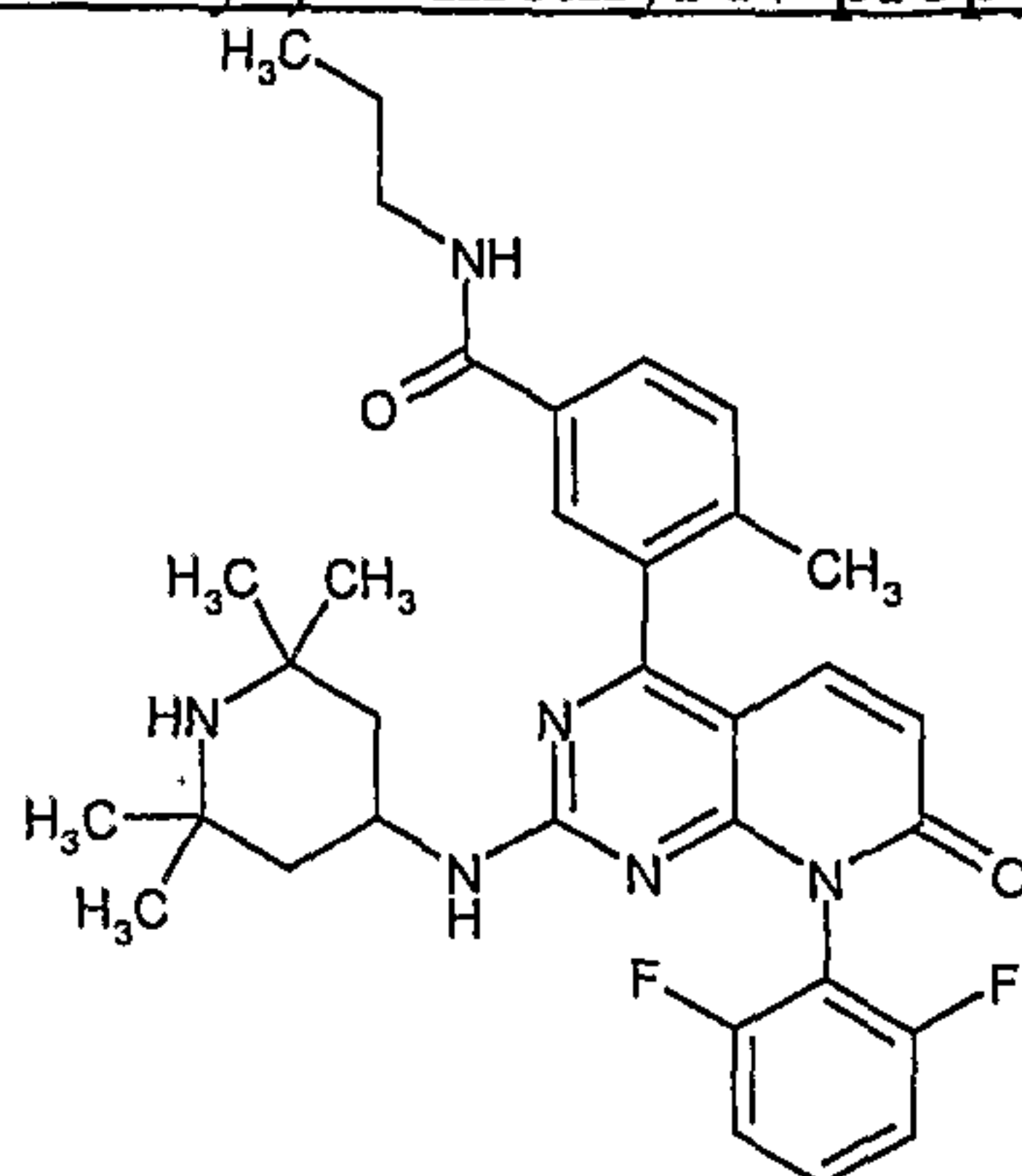
- 10 3-{8-(2,6-difluorophenyl)-7-oxo-2-[(2,2,6,6-tetramethyl-4-piperidinyl)amino]-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl}-4-methyl-*N*-(1-methylethyl)benzamide



- The title compound was prepared by following the procedures in Example 56 using 2-propanamine for the amide formation and 2,2,6,6-tetramethyl-4-piperidinamine for the displacement: LC-MS  $m/z$  589 ( $M+H$ )<sup>+</sup>, 2.46 min (ret time).
- 15

**Example 63**

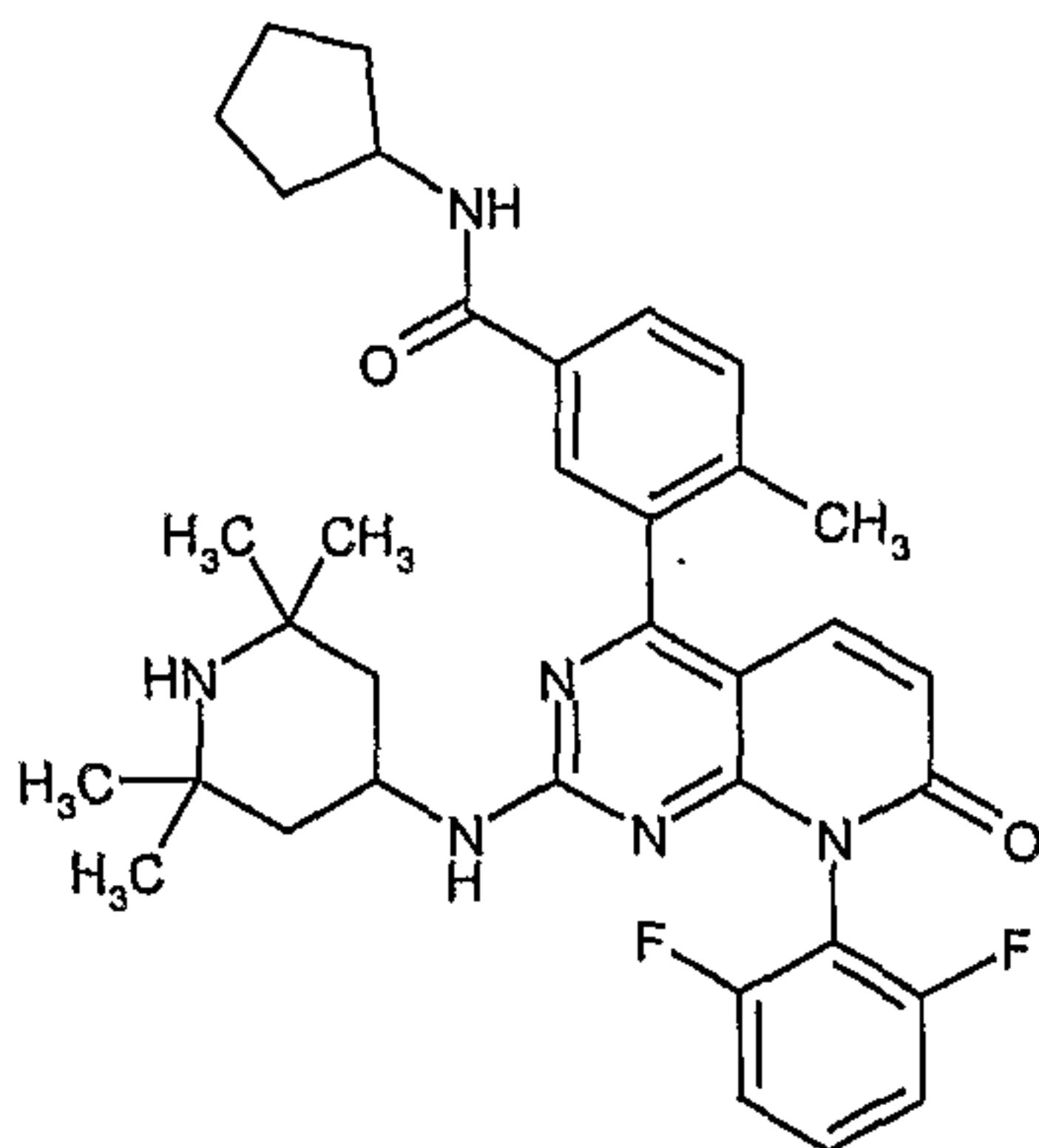
3-{8-(2,6-difluorophenyl)-7-oxo-2-[(2,2,6,6-tetramethyl-4-piperidiny)amino]-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl}-4-methyl-*N*-propylbenzamide



- 5 The title compound was prepared by following the procedures in Example 56 using propanamine for the amide formation and 2,2,6,6-tetramethyl-4-piperidinamine for the displacement: LC-MS  $m/z$  589 (M+H)<sup>+</sup>, 2.47 min (ret time).

**Example 64**

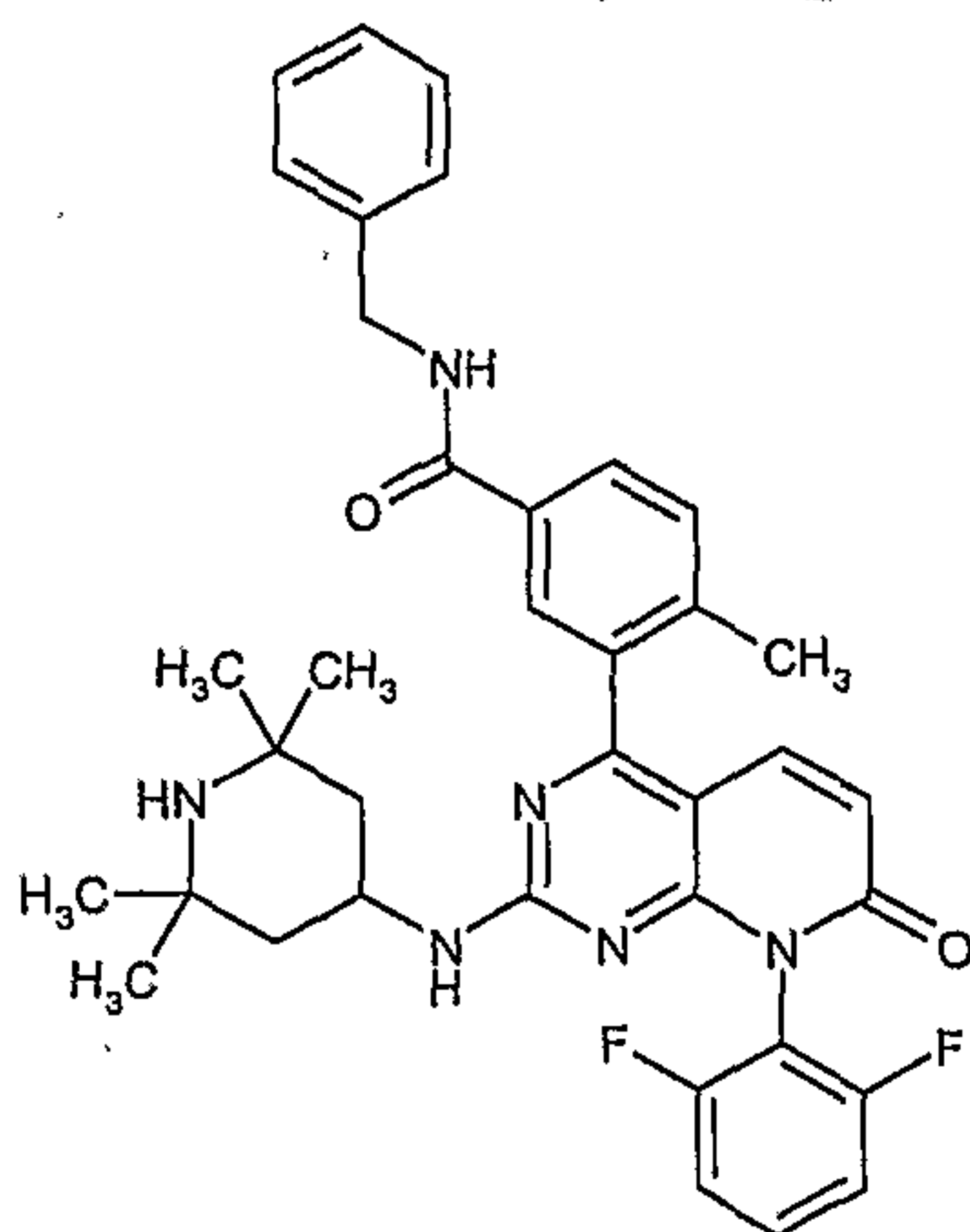
- 10 *N*-cyclopentyl-3-{8-(2,6-difluorophenyl)-7-oxo-2-[(2,2,6,6-tetramethyl-4-piperidiny)amino]-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl}-4-methylbenzamide



- 15 The title compound was prepared by following the procedures in Example 56 using cyclopentylamine for the amide formation and 2,2,6,6-tetramethyl-4-piperidinamine for the displacement: LC-MS  $m/z$  615 (M+H)<sup>+</sup>, 2.58 min (ret time).

**Example 65**

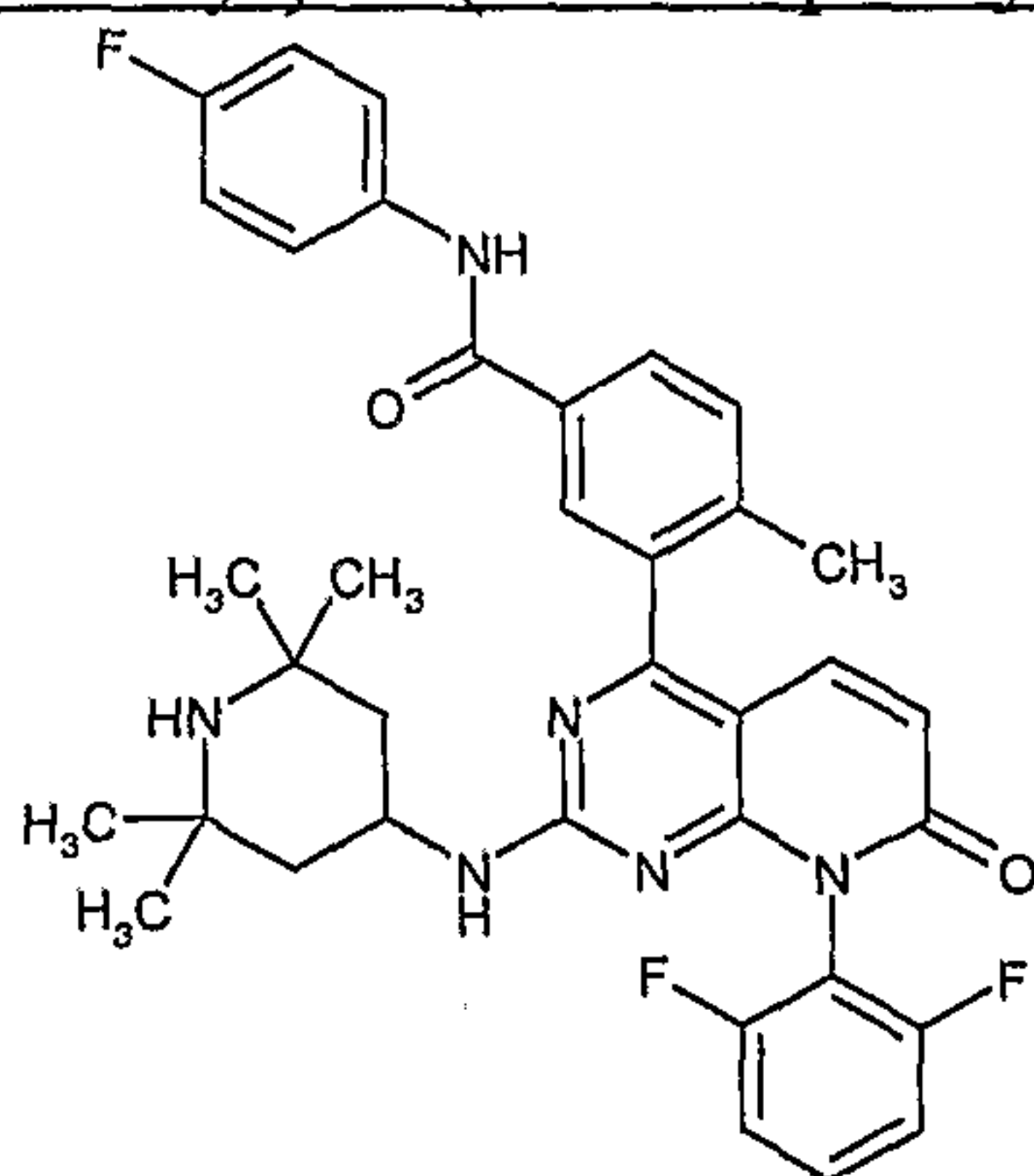
3-{8-(2,6-difluorophenyl)-7-oxo-2-[(2,2,6,6-tetramethyl-4-piperidinyl)amino]-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl}-4-methyl-*N*-(phenylmethyl)benzamide



- 5 The title compound was prepared by following the procedures in Example 56 using benzylamine for the amide formation and 2,2,6,6-tetramethyl-4-piperidinamine for the displacement: LC-MS  $m/z$  637 ( $M+H$ )<sup>+</sup>, 2.63 min (ret time).

**Example 66**

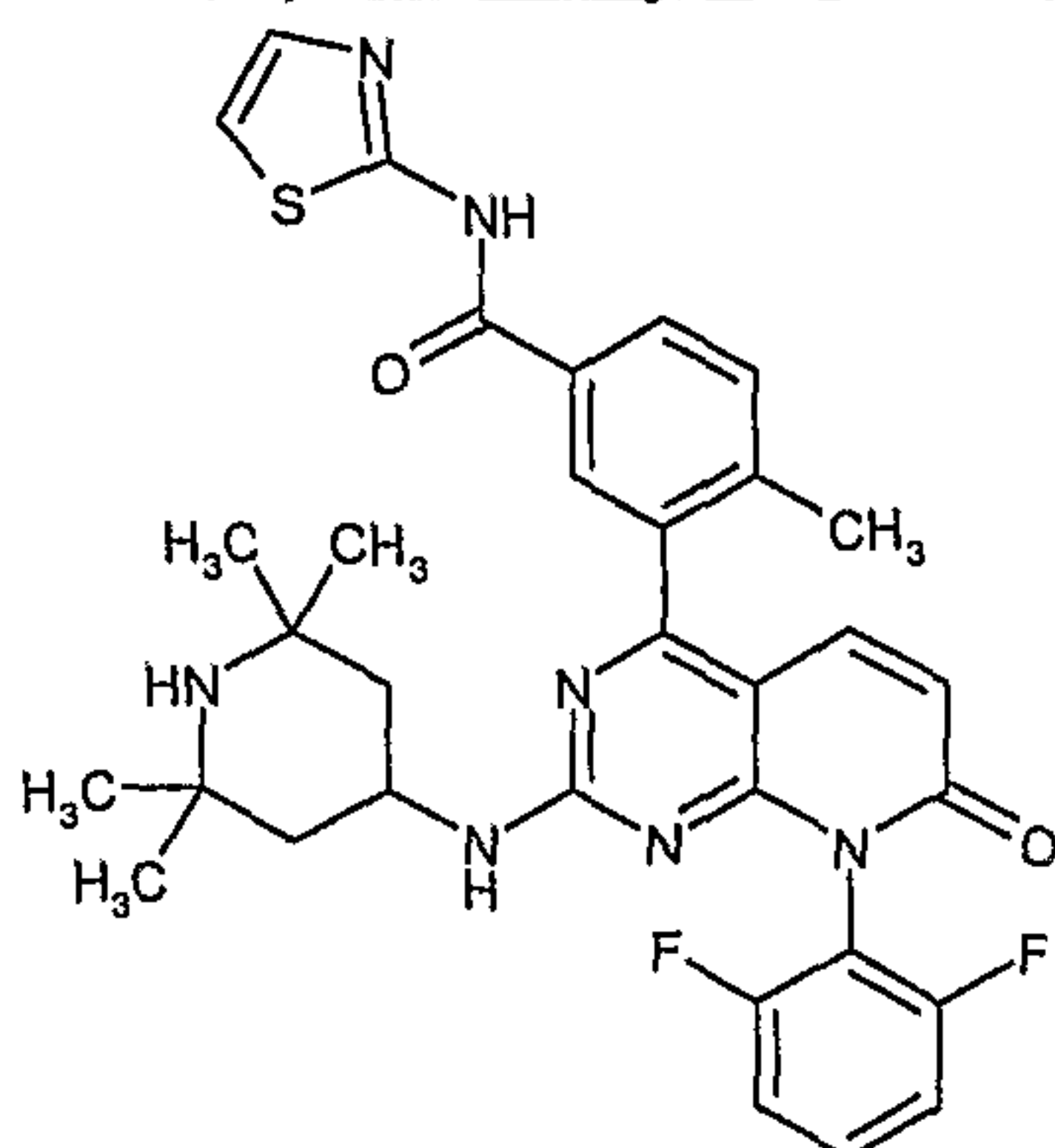
- 10 3-{8-(2,6-difluorophenyl)-7-oxo-2-[(2,2,6,6-tetramethyl-4-piperidinyl)amino]-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl}-*N*-(4-fluorophenyl)-4-methylbenzamide



- 15 The title compound was prepared by following the procedures in Example 56 using 4-fluoroaniline for the amide formation and 2,2,6,6-tetramethyl-4-piperidinamine for the displacement: LC-MS  $m/z$  641 ( $M+H$ )<sup>+</sup>, 2.71 min (ret time).

**Example 67**

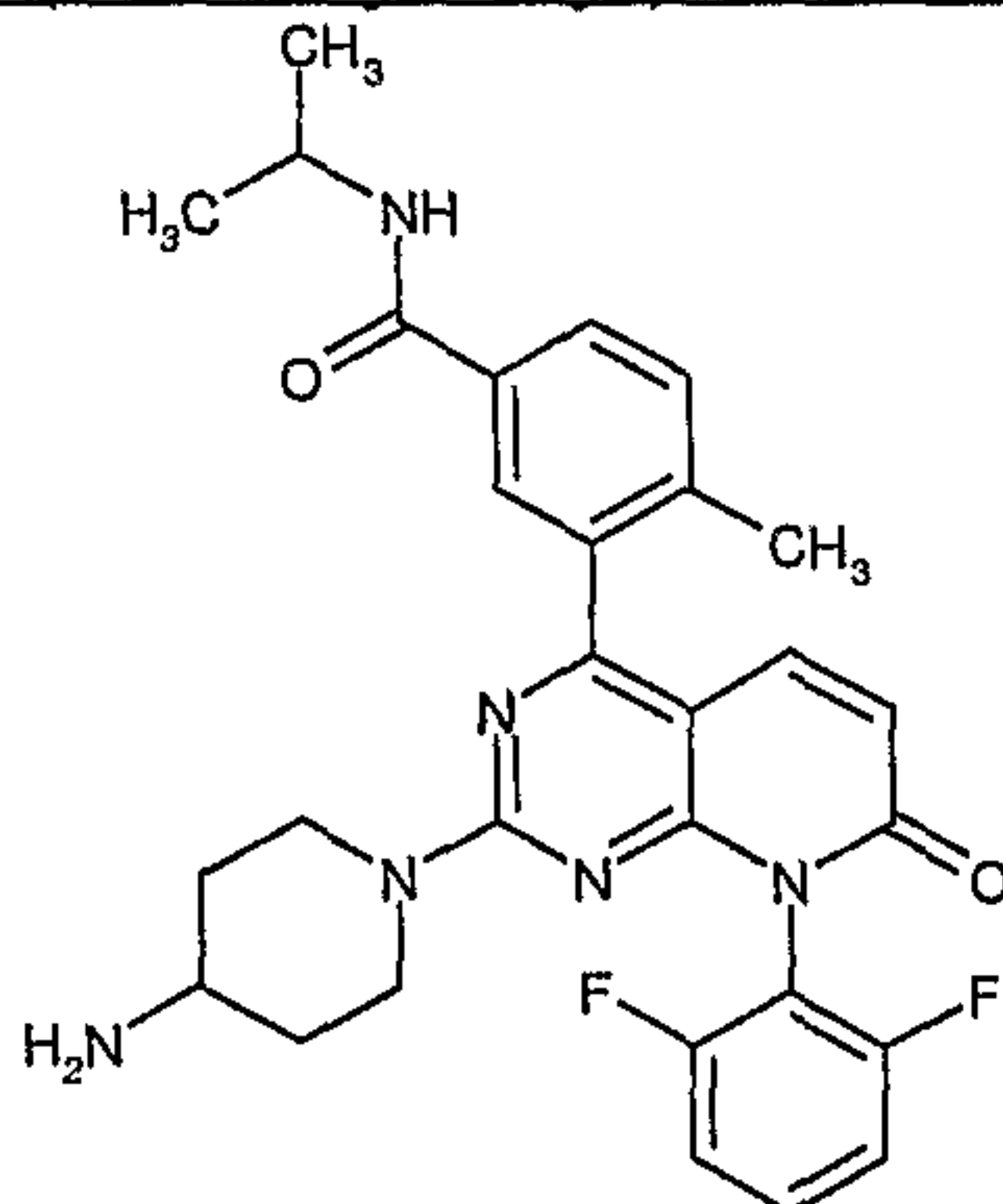
3-{8-(2,6-difluorophenyl)-7-oxo-2-[(2,2,6,6-tetramethyl-4-piperidiny)amino]-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl}-4-methyl-*N*-1,3-thiazol-2-ylbenzamide



- 5 The title compound was prepared by following the procedures in Example 56 using 1,3-thiazole-2-amine for the amide formation and 2,2,6,6-tetramethyl-4-piperidinamine for the displacement: LC-MS  $m/z$  630 ( $M+H$ )<sup>+</sup>, 2.57 min (ret time).

**Example 68**

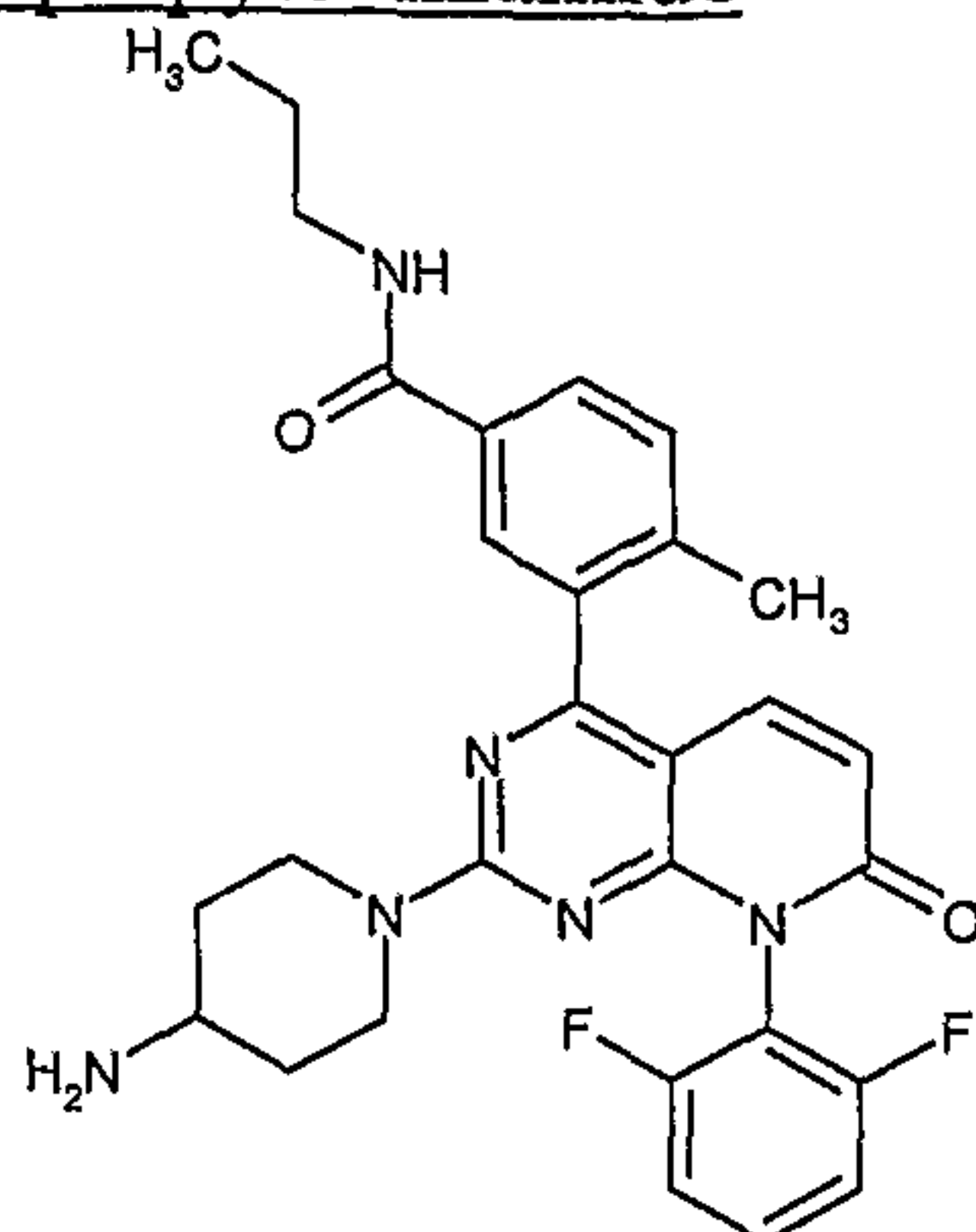
- 10 3-[2-(4-amino-1-piperidiny)-8-(2,6-difluorophenyl)-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl]-4-methyl-*N*-(1-methylethyl)benzamide



- 15 The title compound was prepared by following the procedures in Example 56 using 2-propanamine for the amide formation and 4-piperidinamine for the displacement: LC-MS  $m/z$  533 ( $M+H$ )<sup>+</sup>, 2.42 min (ret time).

**Example 69**

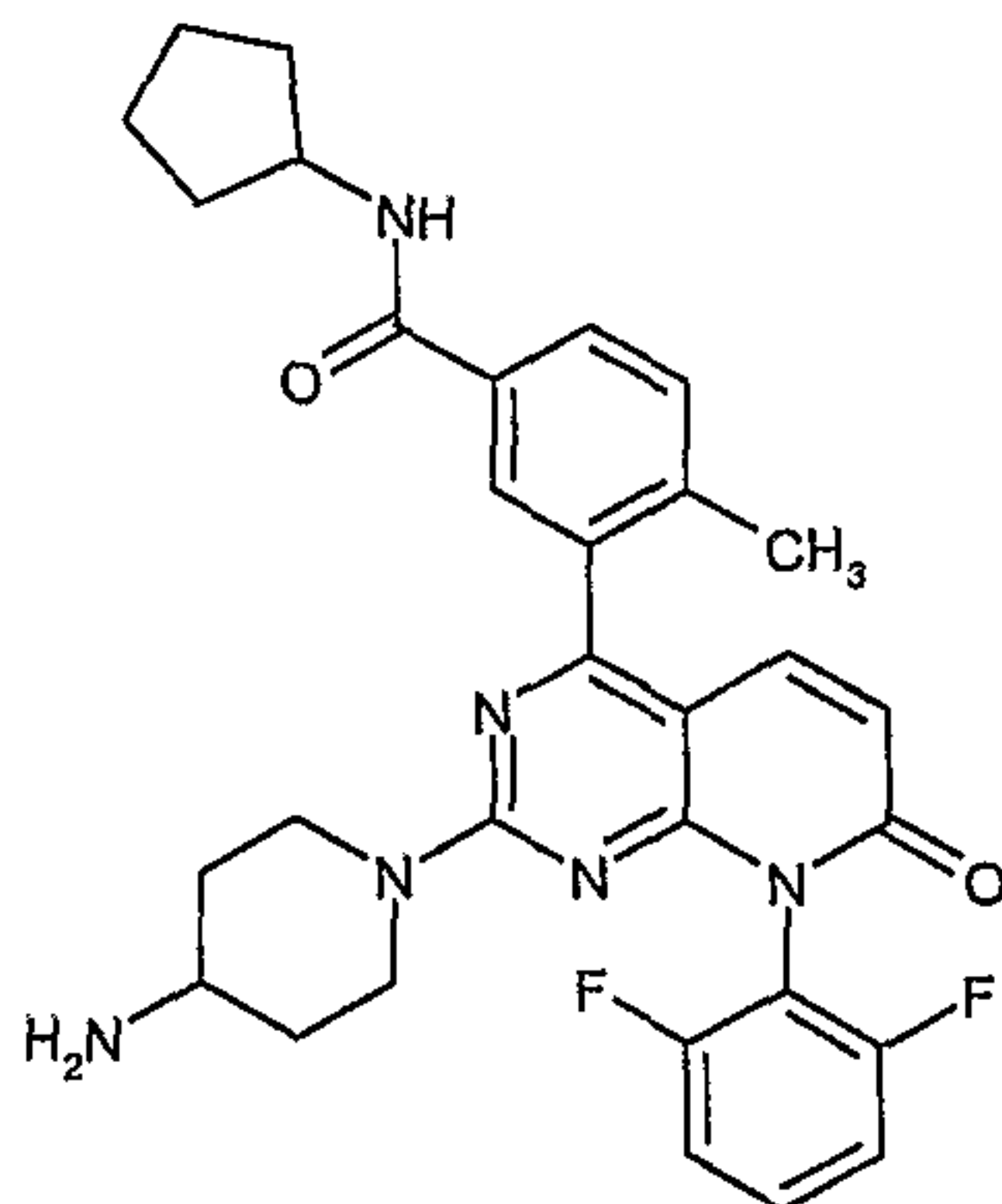
3-[2-(4-amino-1-piperidiny)-8-(2,6-difluorophenyl)-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl]-4-methyl-*N*-propylbenzamide



- 5           The title compound was prepared by following the procedures in Example 56 using propanamine for the amide formation and 4-piperidinamine for the displacement: LC-MS  $m/z$  533 ( $M+H$ )<sup>+</sup>, 2.43 min (ret time).

**Example 70**

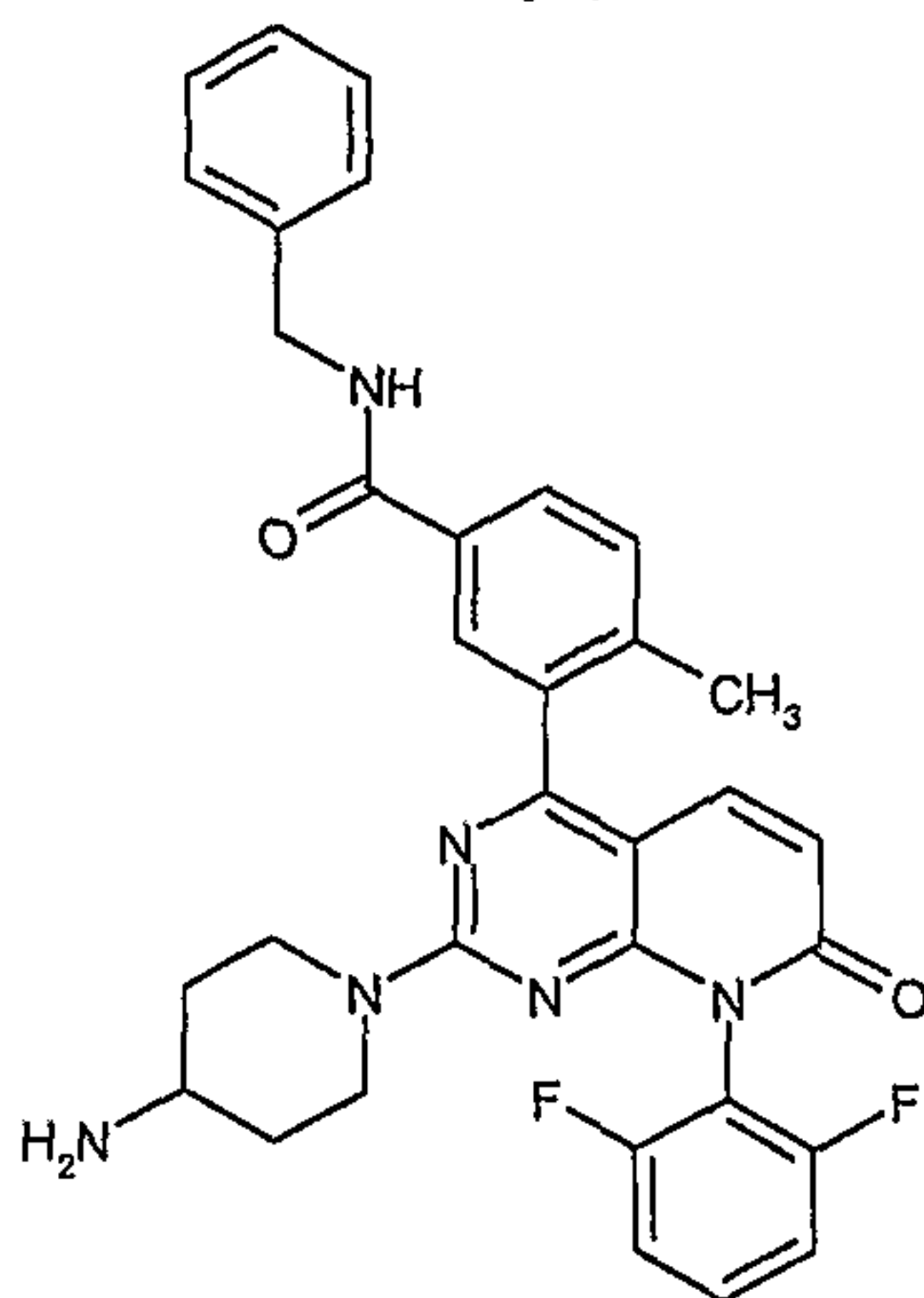
- 10       3-[2-(4-amino-1-piperidiny)-8-(2,6-difluorophenyl)-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl]-*N*-cyclopentyl-4-methylbenzamide



- 15           The title compound was prepared by following the procedures in Example 56 using cyclopentylamine for the amide formation and 4-piperidinamine for the displacement: LC-MS  $m/z$  559 ( $M+H$ )<sup>+</sup>, 2.53 min (ret time).

**Example 71**

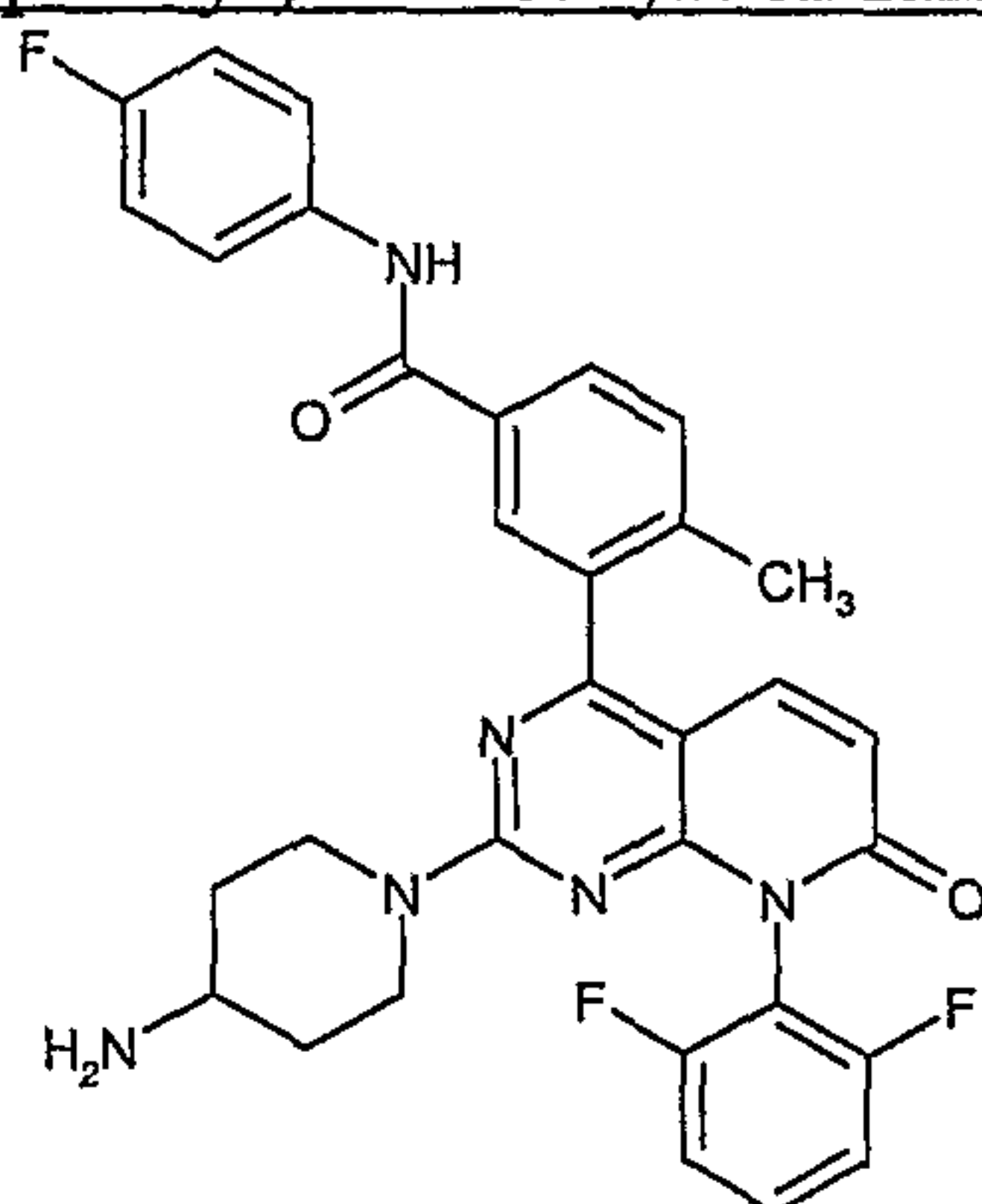
3-[2-(4-amino-1-piperidiny)-8-(2,6-difluorophenyl)-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl]-4-methyl-*N*-(phenylmethyl)benzamide



- 5        The title compound was prepared by following the procedures in Example 56 using benzylamine for the amide formation and 4-piperidinamine for the displacement: LC-MS  $m/z$  581 ( $M+H$ )<sup>+</sup>, 2.59 min (ret time).

**Example 72**

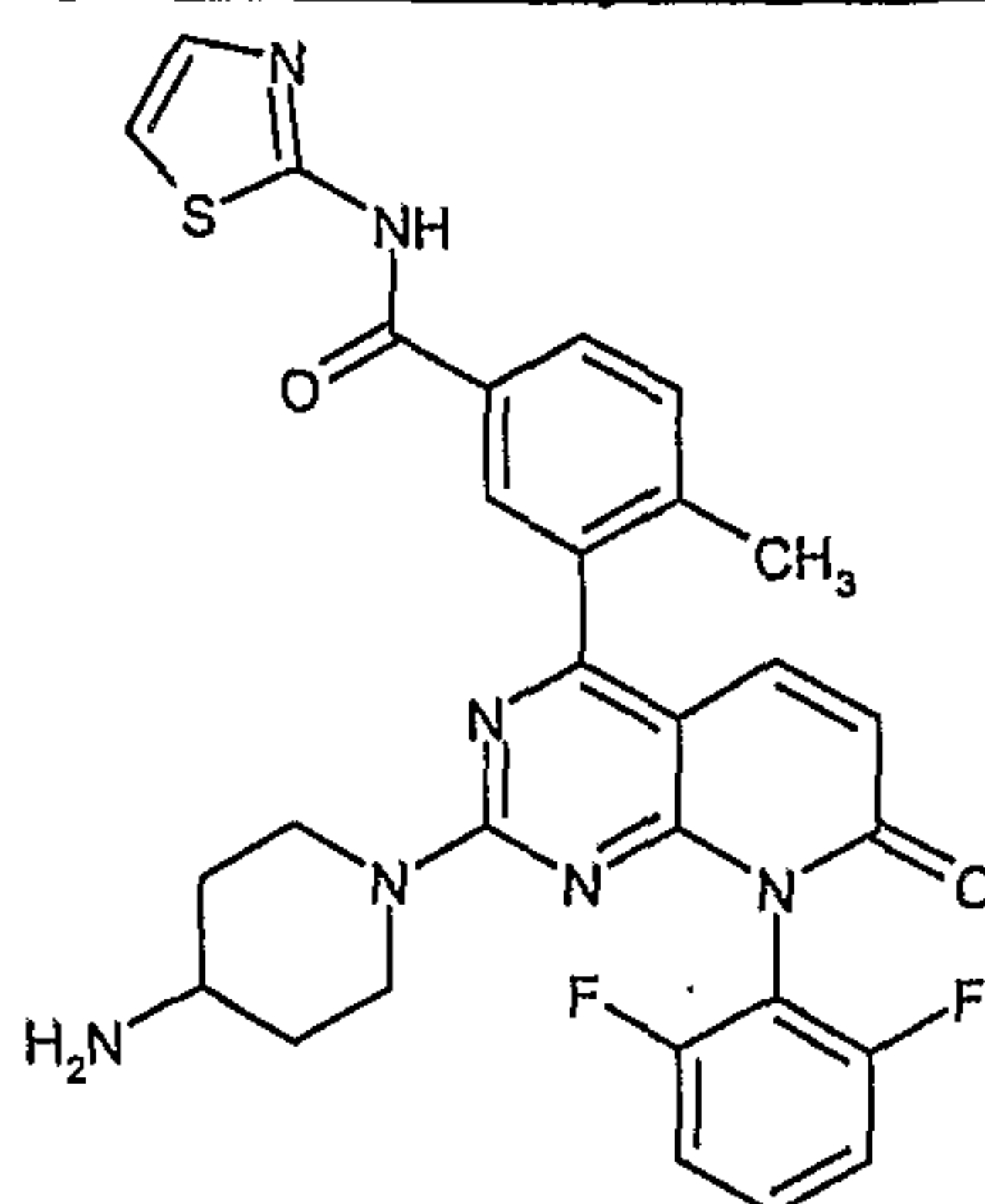
- 10    3-[2-(4-amino-1-piperidiny)-8-(2,6-difluorophenyl)-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl]-*N*-(4-fluorophenyl)-4-methylbenzamide



- 15    The title compound was prepared by following the procedures in Example 56 using 4-fluoroaniline for the amide formation and 4-piperidinamine for the displacement: LC-MS  $m/z$  585 ( $M+H$ )<sup>+</sup>, 2.67 min (ret time).

**Example 73**

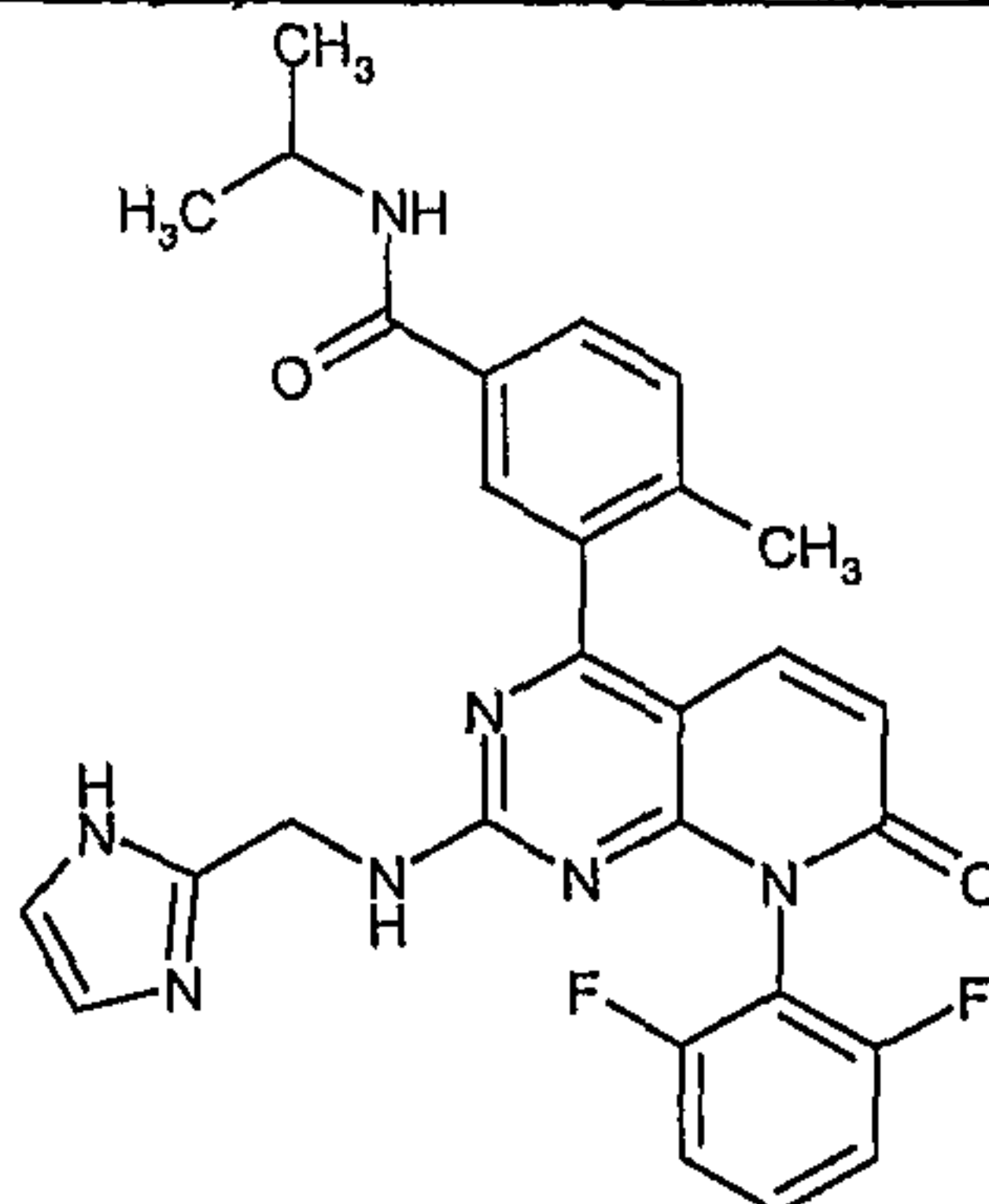
3-[2-(4-amino-1-piperidiny)-8-(2,6-difluorophenyl)-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl]-4-methyl-*N*-1,3-thiazol-2-ylbenzamide



- 5 The title compound was prepared by following the procedures in Example 56 using 1,3-thiazole-2-amine for the amide formation and 4-piperidinamine for the displacement: LC-MS  $m/z$  574 ( $M+H$ )<sup>+</sup>, 2.53 min (ret time).

**Example 74**

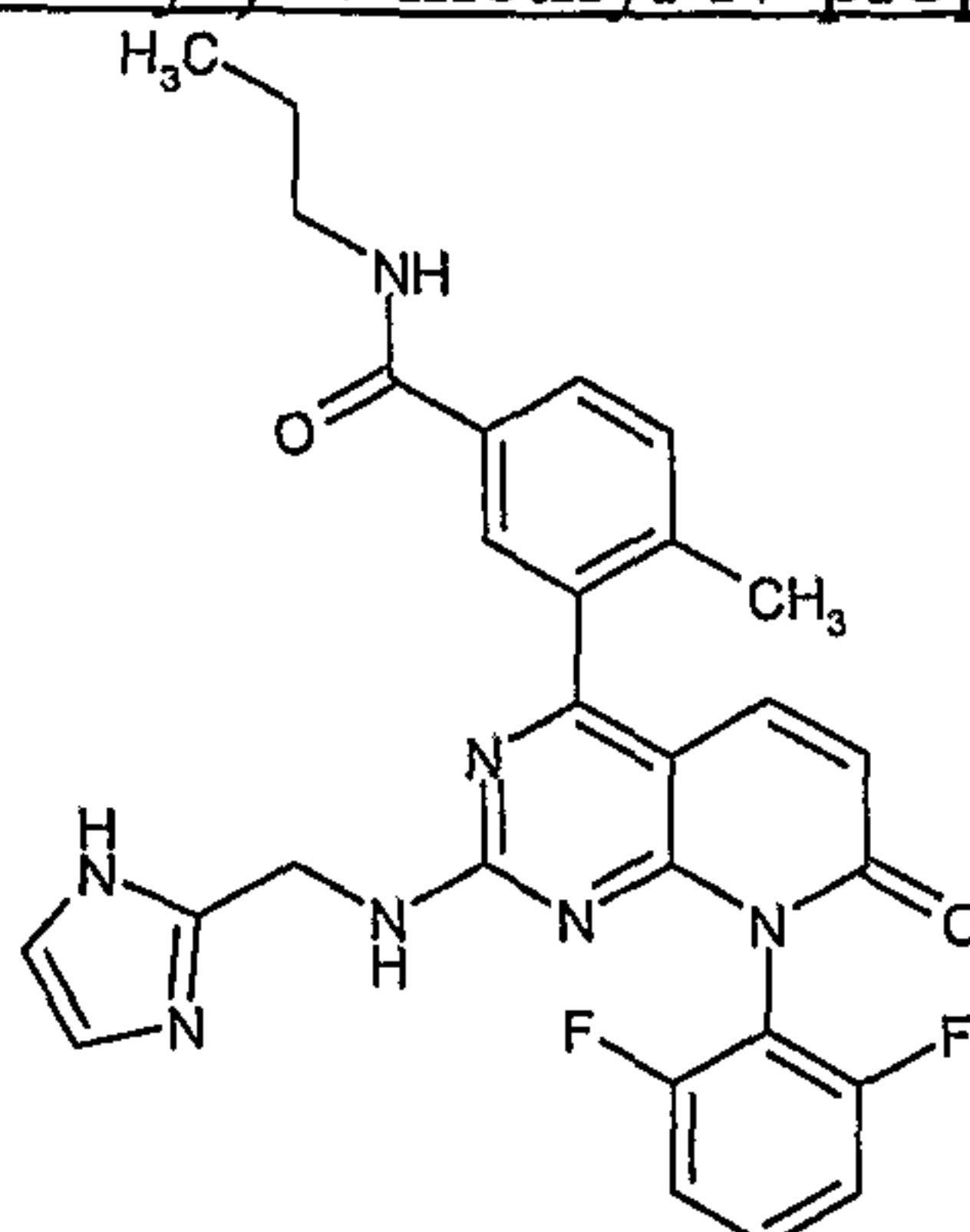
- 10 3-{8-(2,6-difluorophenyl)-2-[(1*H*-imidazol-2-ylmethyl)amino]-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl}-4-methyl-*N*-(1-methylethyl)benzamide



- 15 The title compound was prepared by following the procedures in Example 56 using 2-propanamine for the amide formation and (1*H*-imidazol-2-ylmethyl)amine hydrochloride for the displacement: LC-MS  $m/z$  530 ( $M+H$ )<sup>+</sup>, 2.25 min (ret time).

**Example 75**

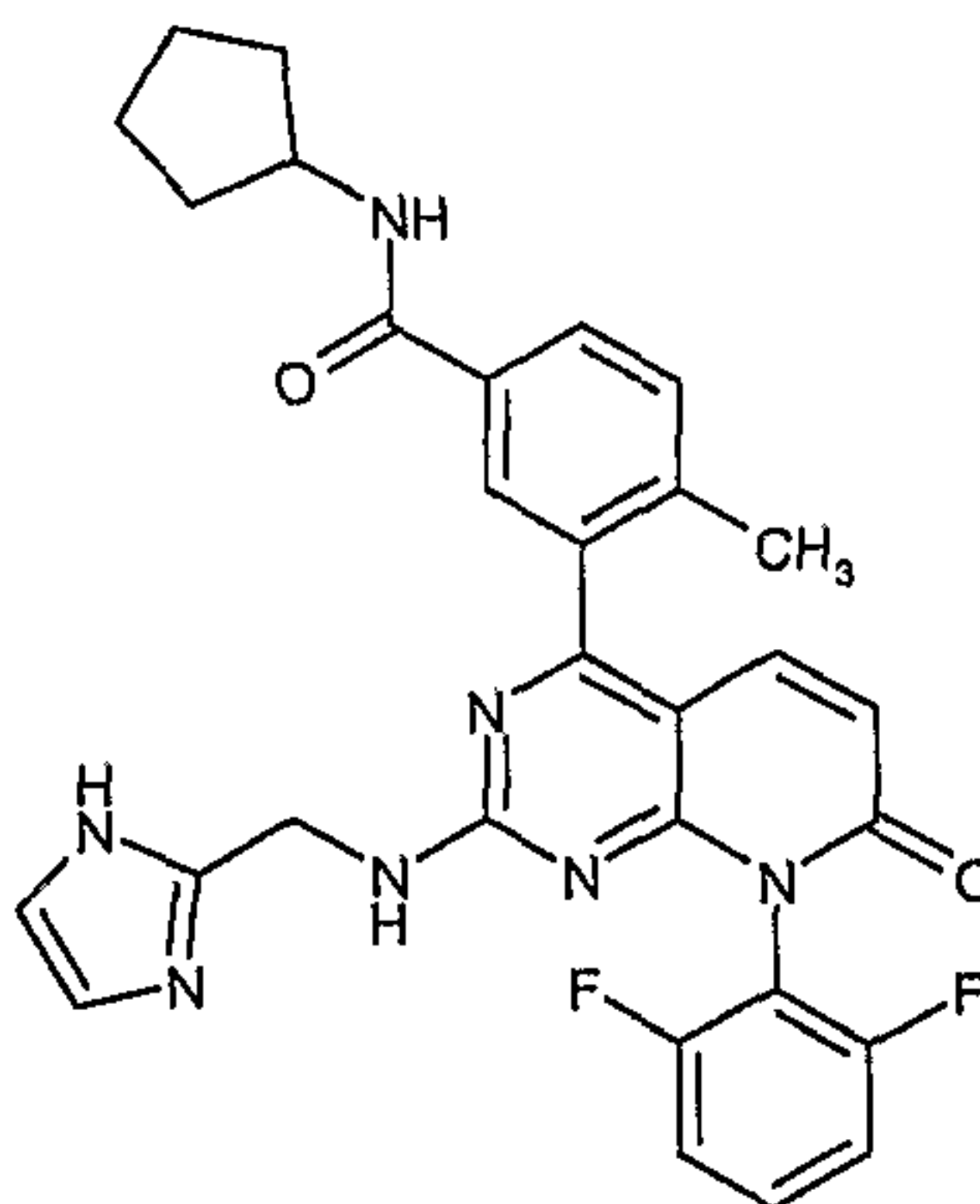
3-{8-(2,6-difluorophenyl)-2-[(1*H*-imidazol-2-ylmethyl)amino]-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl}-4-methyl-*N*-propylbenzamide



- 5           The title compound was prepared by following the procedures in Example 56 using propanamine for the amide formation and (1*H*-imidazol-2-ylmethyl)amine hydrochloride for the displacement : LC-MS *m/z* 530 (M+H)<sup>+</sup>, 2.26 min (ret time).

**Example 76**

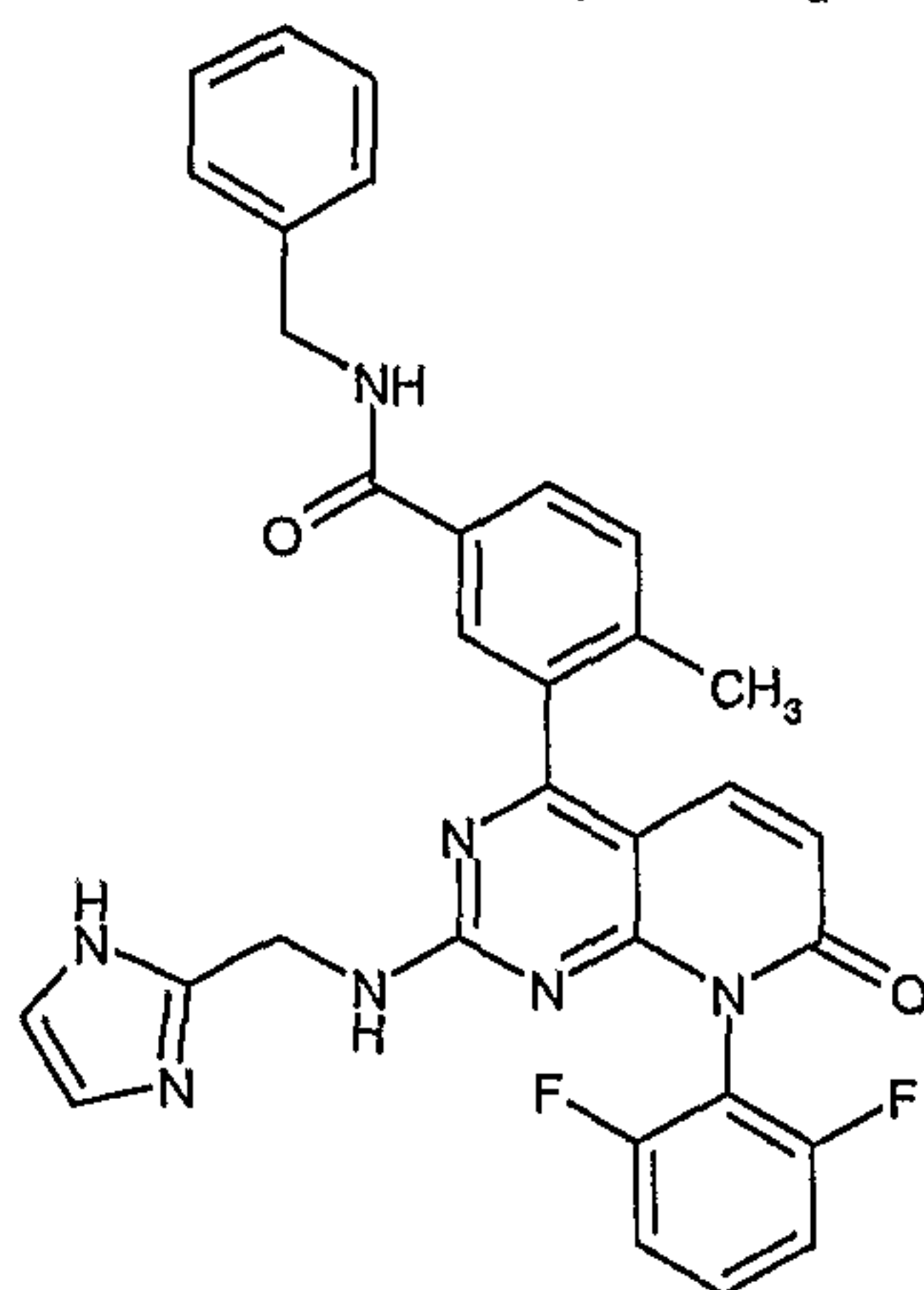
- 10   *N*-cyclopentyl-3-{8-(2,6-difluorophenyl)-2-[(1*H*-imidazol-2-ylmethyl)amino]-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl}-4-methylbenzamide



- 15           The title compound was prepared by following the procedures in Example 56 using cyclopentylamine for the amide formation and (1*H*-imidazol-2-ylmethyl)amine hydrochloride for the displacement: LC-MS *m/z* 556 (M+H)<sup>+</sup>, 2.38 min (ret time).

**Example 77**

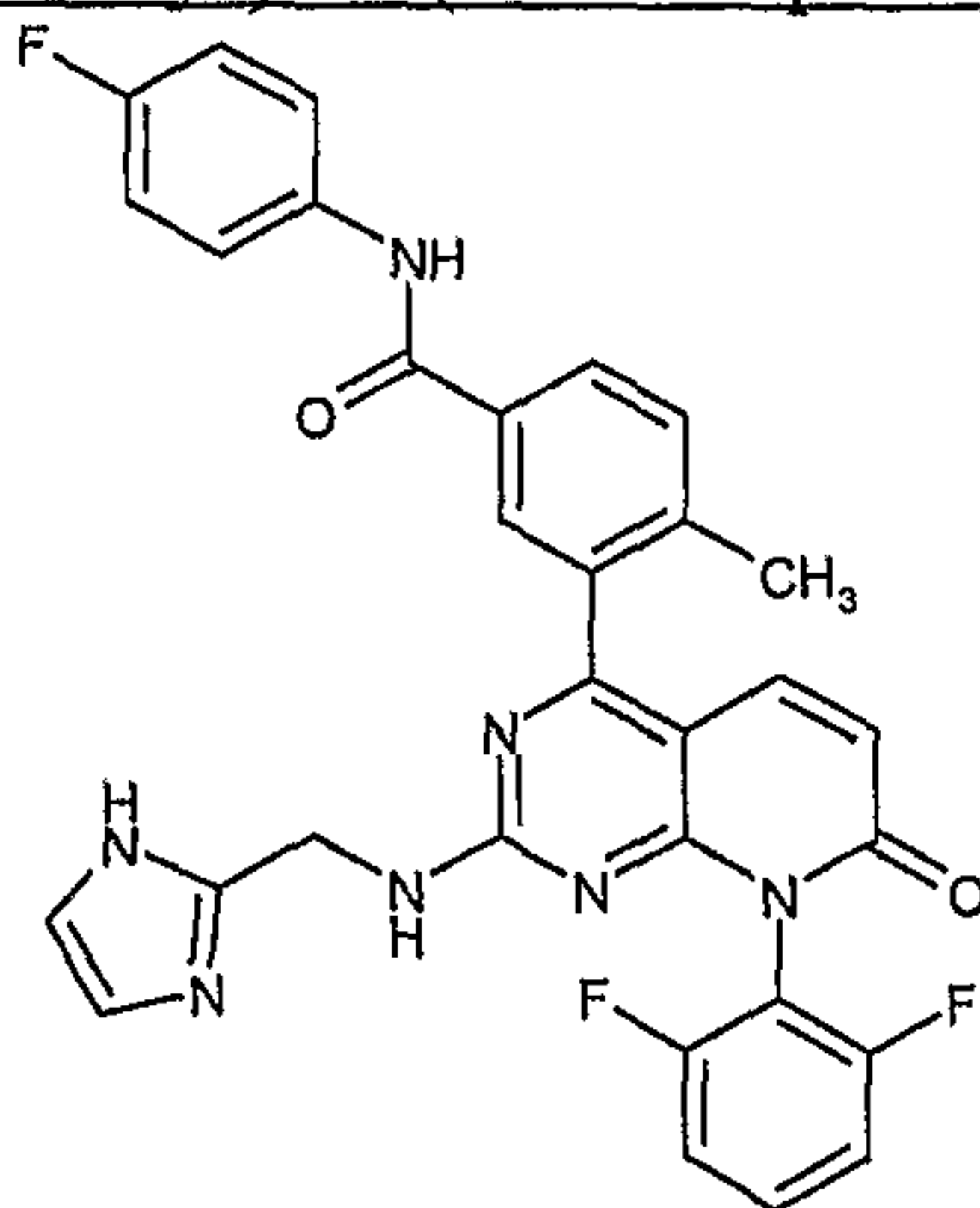
3-{8-(2,6-difluorophenyl)-2-[(1*H*-imidazol-2-ylmethyl)amino]-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl}-4-methyl-*N*-(phenylmethyl)benzamide



- 5 The title compound was prepared by following the procedures in Example 56 using benzylamine for the amide formation and (1*H*-imidazol-2-ylmethyl)amine hydrochloride for the displacement: LC-MS *m/z* 578 (M+H)<sup>+</sup>, 2.44 min (ret time).

**Example 78**

- 10 3-{8-(2,6-difluorophenyl)-2-[(1*H*-imidazol-2-ylmethyl)amino]-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl}-*N*-(4-fluorophenyl)-4-methylbenzamide

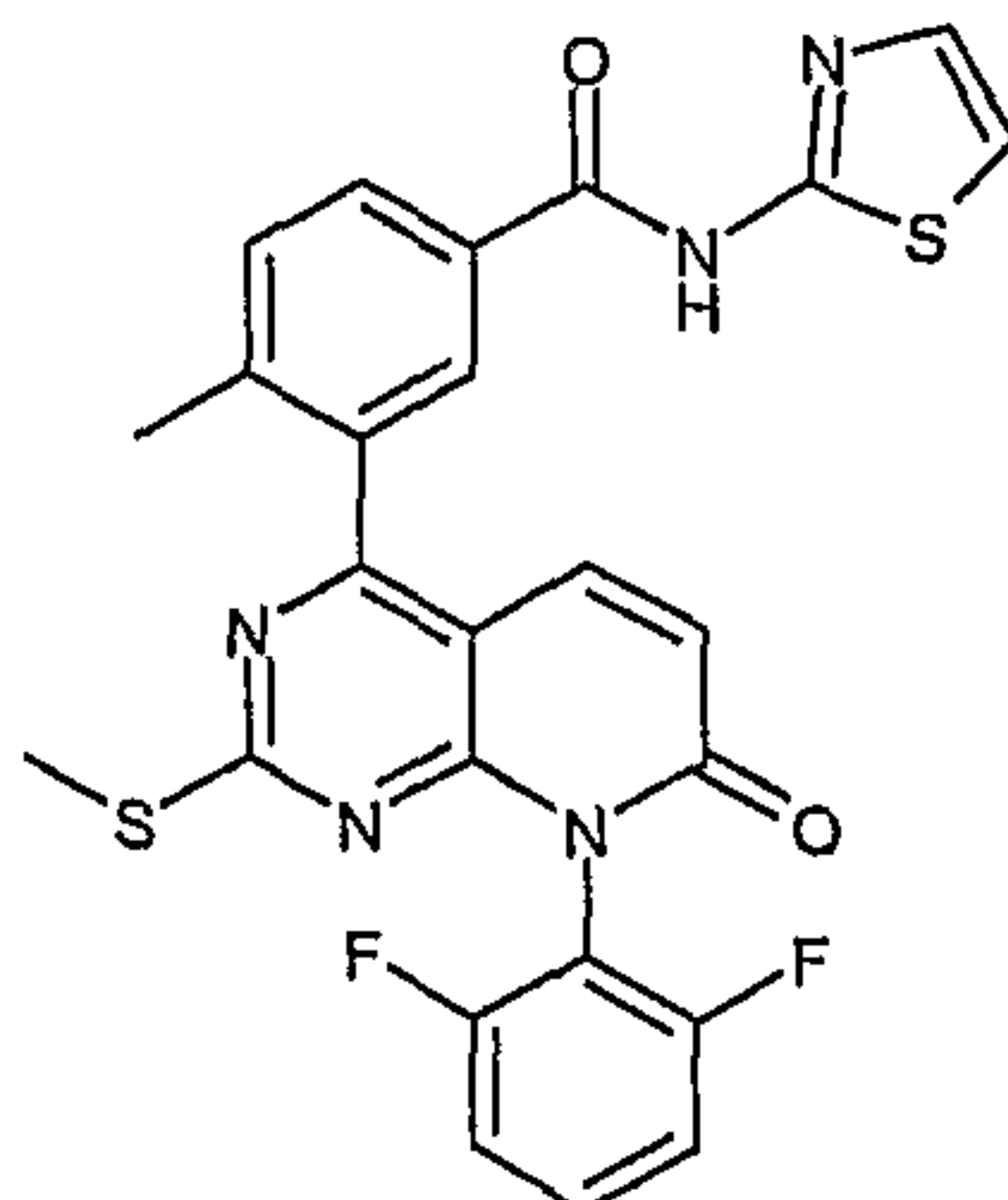


- 15 The title compound was prepared by following the procedures in Example 56 using 4-fluoroaniline for the amide formation and (1*H*-imidazol-2-ylmethyl)amine hydrochloride for the displacement: LC-MS *m/z* 582 (M+H)<sup>+</sup>, 2.52 min (ret time).

**Example 79**

3-{8-(2,6-difluorophenyl)-2-[(1*H*-imidazol-2-ylmethyl)amino]-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl}-4-methyl-*N*-1,3-thiazol-2-ylbenzamide

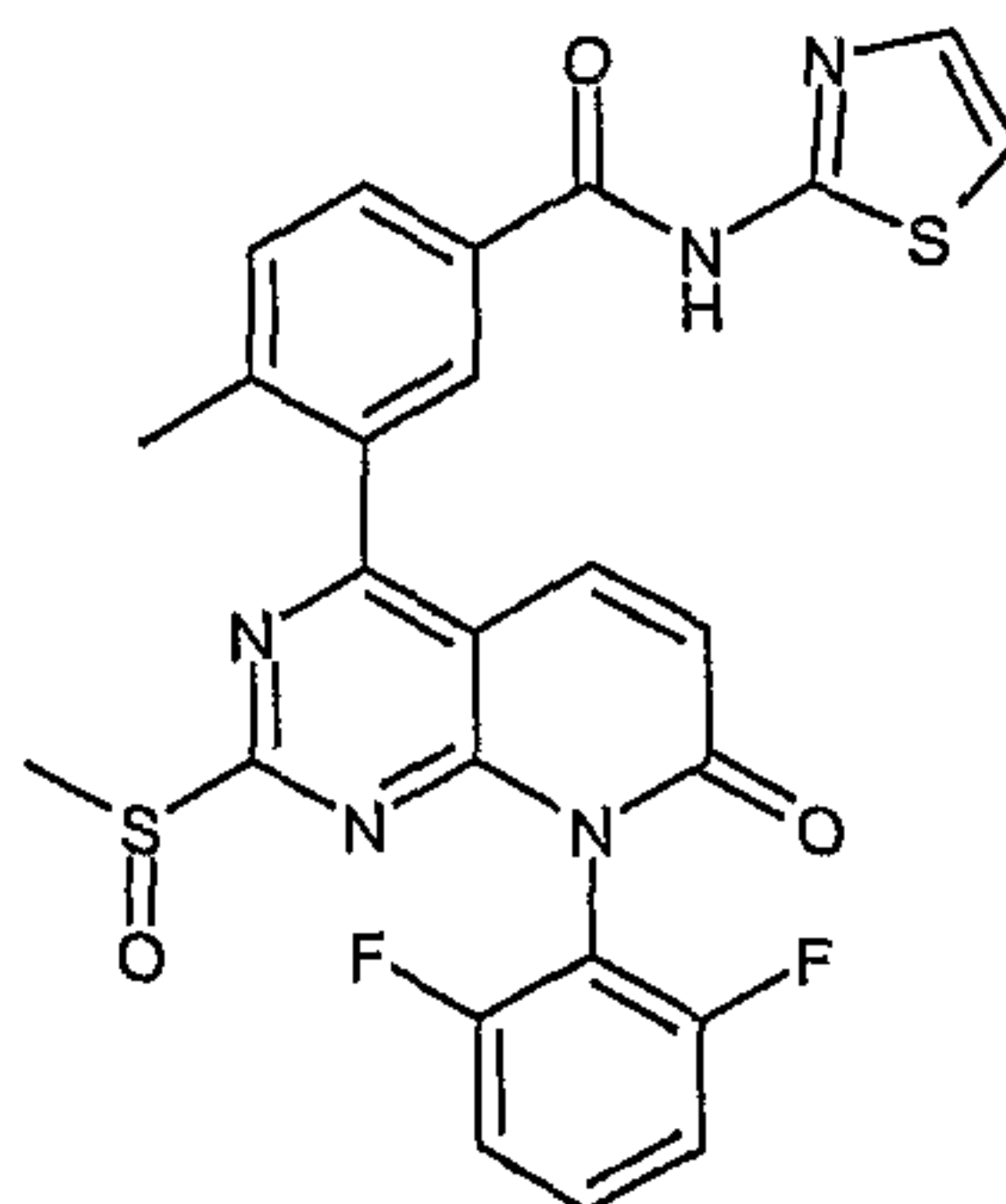
79a) 3-[8-(2,6-difluorophenyl)-2-(methylthio)-7-oxo-7,8-dihydropyrido[2,3-d]pyrimidin-4-yl]-4-methyl-N-1,3-thiazol-2-ylbenzamide



A solution of 3-[8-(2,6-difluorophenyl)-2-(methylthio)-7-oxo-7,8-dihydropyrido[2,3-d]pyrimidin-4-yl]-4-methylbenzoic acid (440 mg, 1.00 mmol) in DMF (15 mL) was mixed with DIEA (0.697 mL, 4.0 mmol), HATU (418 mg, 1.1 mmol) and 2-aminothiazole (150 mg, 1.5 mmol). The reaction mixture was stirred over night, diluted with H<sub>2</sub>O (0.5 mL), and concentrated under vacuum to remove DMF. Flash chromatography (load column with DCM, mobile phase EtOAc/Hexane) then provided the title compound as a white solid 425 mg (81 %).

**MS** (ES) *m/z* 522 (*M* + *H*)<sup>+</sup>; **<sup>1</sup>H-NMR** (MeOD) δ 2.25 (s, 3 H), 2.37 (s, 3 H), 6.65 (d, *J* = 6.0 Hz, 1 H), 6.95 (d, *J* = 3.6 Hz, 1 H), 7.15 (t, *J* = 8.4 Hz, 2 H), 7.20 (d, *J* = 3.6 Hz, 1 H), 7.46 (d, *J* = 9.6 Hz, 1 H), 7.54 (m, 2 H), 7.96 (d, *J* = 1.6 Hz, 1 H), 8.11 (dd, *J*<sub>1</sub> = 8.0 Hz, *J*<sub>2</sub> = 1.6 Hz, 1 H).

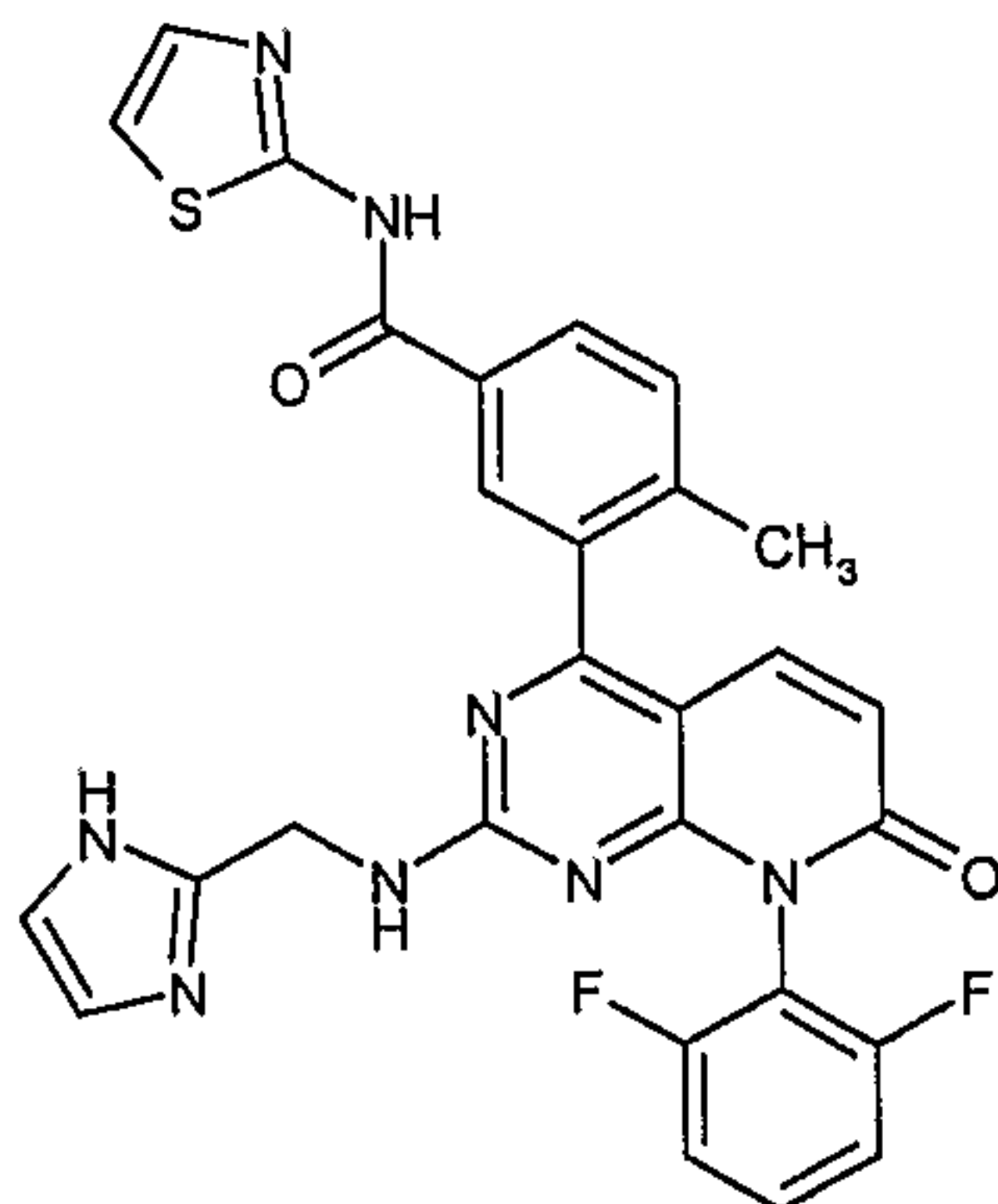
79b) 3-[8-(2,6-difluorophenyl)-2-(methylsulfinyl)-7-oxo-7,8-dihydropyrido[2,3-d]pyrimidin-4-yl]-4-methyl-N-1,3-thiazol-2-ylbenzamide



A solution of 3-[8-(2,6-difluorophenyl)-2-(methylthio)-7-oxo-7,8-dihydropyrido[2,3-d]pyrimidin-4-yl]-4-methyl-N-1,3-thiazol-2-ylbenzamide (1.65 g, 3.16 mmol) in DCM (53 mL) was mixed with *m*CPBA (0.736 g, 4.75 mmol). The mixture was stirred at room temperature for about 10 minutes before directly loaded onto a column. Flash chromatography (mobile phase EtOAc/Hexane) then provided the title compound as a white solid 1.38 g (81 %). **MS** (ES) *m/z* 538 (*M* + *H*)<sup>+</sup>; **<sup>1</sup>H-**

NMR (MeOD)  $\delta$  2.35 (s, 3 H), 2.81 (s, 3 H), 6.98 (d,  $J = 10.0$  Hz, 1 H), 7.30 (d,  $J = 3.6$  Hz, 1 H), 7.46 (t,  $J = 8.6$  Hz, 2 H), 7.57 (d,  $J = 3.6$  Hz, 1 H), 7.66 (d,  $J = 8.0$  Hz, 1 H), 7.72 (m, 1 H), 7.85 (d,  $J = 10.0$  Hz, 1 H), 8.25 (d,  $J = 8.0$  Hz, 2 H).

5 79c) 3-{8-(2,6-difluorophenyl)-2-[(1*H*-imidazol-2-ylmethyl)amino]-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl}-4-methyl-*N*-1,3-thiazol-2-ylbenzamide



To the solution of 3-[8-(2,6-difluorophenyl)-2-(methylsulfinyl)-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl]-4-methyl-*N*-1,3-thiazol-2-ylbenzamide (1.37 g, 2.54 mmol) in DCM (127 mL) were added Et<sub>3</sub>N (1.78 mL, 12.7 mmol) and (1*H*-imidazol-2-yl)-methylamine dihydrochloride (0.625 g, 3.81 mmol). The mixture was stirred at room temperature over night and concentrated under vacuum. Flash chromatography [mobile phase DCM/DCM (90)+MeOH(7)+NH<sub>4</sub>OH(3)] then provided the title compound as a white solid 1.23 g (85 %). MS (ES)  $m/z$  571 ( $M + H$ )<sup>+</sup>; <sup>1</sup>H-NMR (MeOD)  $\delta$  2.16 (s, 1.5 H), 2.32 (s, 1.5 H), 3.18 (d,  $J = 4.4$  Hz, 0.75 H), 4.11 (d,  $J = 5.2$  Hz, 0.25 H), 4.21 (d,  $J = 5.0$  Hz, 1 H), 4.50 (m, 1 H), 6.37 (d,  $J = 9.6$  Hz, 1 H), 6.85 (s, 2 H), 7.29 (s, 2 H), 7.43 (m, 2 H), 7.57 (m, 3 H), 8.18 (m, 3 H), 11.60 (s, br, 1 H), 12.64 (s, br, 2 H).

20 79d) 3-{8-(2,6-difluorophenyl)-2-[(1*H*-imidazol-2-ylmethyl)amino]-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl}-4-methyl-*N*-1,3-thiazol-2-ylbenzamide methanesulfonate

Using material as made above in Example 79c, a reaction vessel is charged with the amorphous free-base version of 3-{8-(2,6-difluorophenyl)-2-[(1*H*-imidazol-2-ylmethyl)amino]-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl}-4-methyl-*N*-1,3-thiazol-2-ylbenzamide (11.0 mg) and acetonitrile (250  $\mu$ L) at room temperature (RT). The mixture is warmed to about 50°C. To the warmed mixture is added 1 eq of methanesulfonic acid solution (1N in water). The temperature is maintained for a few minutes until the solution clarifies. Heating is discontinued and the mixture is

allowed to cool to room temperature while shaking. Shaking is continued at room temperature overnight. The product is filtered and washed with THF. Place cake in crystallization dish and dry for several hrs *in vacuo* (house vacuum, 50°C, N<sub>2</sub> bleed). The yield is 70.8% (9.1 mg) of 3-{8-(2,6-difluorophenyl)-2-[(1*H*-imidazol-2-ylmethyl)amino]-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl}-4-methyl-*N*-1,3-thiazol-2-ylbenzamide methanesulfonate salt with a melting onset at 320°C (determined by DSC).

Alternatively, using material as made above in Example 79c, a reaction vessel is charged with the free-base version of 3-{8-(2,6-difluorophenyl)-2-[(1*H*-imidazol-2-ylmethyl)amino]-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl}-4-methyl-*N*-1,3-thiazol-2-ylbenzamide (10.05 g) and acetone (201 mL) at room temperature (RT). The mixture is warmed to about 50°C and the temperature maintained for about 15 minutes. To the warm mixture is added 1 eq of methanesulfonic acid solution (1N in water). Maintain the temperature for about 5 min until the solution clarifies. To the warm mixture is added a small amount of seed material and the temperature is maintained at about 50°C for an additional 30 min. Heating is discontinued and the mixture is allowed to cool to room temperature while stirring. Continue stirring at room temperature for at least two hours.

Filter using a Büchner funnel, collect the solid on Whatman No. 1 filter. Wash cake with 3x1 vol of acetone and suction dry. Place cake in crystallization dish and dry at least 8hrs *in vacuo* (house vacuum, 50°C, N<sub>2</sub> bleed) to provide the title compound (11.14 g, 94.9%).

In the following examples, alternative embodiments of salts of the title compound were made: hydrochloric, hydrobromic, sulfuric (sulfonate), benzoic, *p*-toluenesulfonic (methylbenzenesulfonate), citrate, ethane sulphonic acid (ethanesulphonate), benzenesulphonic acid (benzenesulfonate), fumaric acid (fumarate). Additional salts include the camphor sulphonic acid, 1,2-dichlorobenzensulphonic acid and 1,2-naphthalenesulphonic acid. Single equivalents of the acid were introduced to ensure protonation of the most basic nitrogen and reduce the likelihood of protonating the other less basic nitrogens.

79e) 3-{8-(2,6-difluorophenyl)-2-[(1*H*-imidazol-2-ylmethyl)amino]-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl}-4-methyl-*N*-1,3-thiazol-2-ylbenzamide 4-methylbenzenesulfonate

THF (17.5 mL) was added to free-base version of 3-{8-(2,6-difluorophenyl)-2-[(1*H*-imidazol-2-ylmethyl)amino]-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl}-4-methyl-*N*-1,3-thiazol-2-ylbenzamide from Example 79c (762.2 mg) at room temperature resulting in a clear solution. *P*-toluenesulfonic acid was added (0.4 equivalent; 1N in water), and the mixture stirred for several hours. The product was filtered, washed with THF, and dried overnight in a vacuum oven at 50°C with a slow nitrogen bleed. The yield was 32.9% (327.0 mg) of the title compound with a melting onset at 259°C (determined by DSC).

79f) 3-{8-(2,6-difluorophenyl)-2-[(1*H*-imidazol-2-ylmethyl)amino]-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl}-4-methyl-*N*-1,3-thiazol-2-ylbenzamide hydrochloride Acetone (250 uL) was added to amorphous free-base version of 3-{8-(2,6-difluorophenyl)-2-[(1*H*-imidazol-2-ylmethyl)amino]-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl}-4-methyl-*N*-1,3-thiazol-2-ylbenzamide from Example 79c (12.3 mg), and the resulting mixture was heated to about 50°C. Hydrochloric acid was added (1.0 equivalent; 1N in 1,4 dioxane). The mixture was cooled to room temperature and shook for several hours. The product was filtered, washed with acetone, and dried for several hours in a vacuum oven at 50°C with a slow nitrogen bleed. The yield was 58.1% (7.6 mg) of title compound (melt begins at <50°C by DSC).

Alternatively, acetone (535 uL) was added to amorphous free-base version of 3-{8-(2,6-difluorophenyl)-2-[(1*H*-imidazol-2-ylmethyl)amino]-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl}-4-methyl-*N*-1,3-thiazol-2-ylbenzamide from Example 79c (26.6 mg), and the resulting mixture was heated to about 50°C. Hydrochloric acid was added (1.0 equivalent; 1N in water) resulting in a clear solution. Seed crystals were added, and the mixture was cooled to room temperature and stirred for several hours. The product was filtered, washed with acetone, and dried overnight in a vacuum oven at 50°C with a slow nitrogen bleed. The yield was 73.2% (20.7 mg).

79g) 3-{8-(2,6-difluorophenyl)-2-[(1*H*-imidazol-2-ylmethyl)amino]-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl}-4-methyl-*N*-1,3-thiazol-2-ylbenzamide sulfate

Acetonitrile (250 uL) was added to amorphous free-base version of 3-{8-(2,6-difluorophenyl)-2-[(1*H*-imidazol-2-ylmethyl)amino]-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl}-4-methyl-*N*-1,3-thiazol-2-ylbenzamide from Example 79c (11.2 mg), and the resulting mixture was heated to about 50°C. Sulfuric acid was added (1.0 equivalent; 1N in water). The mixture was cooled to

room temperature and shook for several hours. The product was filtered, washed with acetonitrile, and dried for several hours in a vacuum oven at about 50°C with a slow nitrogen bleed. The yield was 72.5% (9.5 mg) of title compound (melt begins around 50°C by DSC).

5

Alternatively, THF (550 uL) was added to amorphous free-base version of 3-{8-(2,6-difluorophenyl)-2-[(1*H*-imidazol-2-ylmethyl)amino]-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl}-4-methyl-*N*-1,3-thiazol-2-ylbenzamide from Example 79c (27.4 mg) at room temperature resulting in a clear solution. Sulfuric acid was added (1.0 equivalent; 1N in water). Seed crystals were added, and the mixture stirred for several hours. The product was filtered, washed with THF, and dried overnight in a vacuum oven at about 50°C with a slow nitrogen bleed. The yield was 88.9% (28.5 mg).

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79h) 3-{8-(2,6-difluorophenyl)-2-[(1*H*-imidazol-2-ylmethyl)amino]-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl}-4-methyl-*N*-1,3-thiazol-2-ylbenzamide hydrobromide

20

Acetonitrile (300 uL) was added to amorphous free-base version of 3-{8-(2,6-difluorophenyl)-2-[(1*H*-imidazol-2-ylmethyl)amino]-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl}-4-methyl-*N*-1,3-thiazol-2-ylbenzamide from Example 79c (16.0 mg) at room temperature resulting in a mixture. Hydrobromic acid was added (1.0 equivalent; 1N in water) resulting in a clear solution. The following day, a white precipitate was observed. The product was filtered, washed with acetonitrile, and dried overnight in a vacuum oven at about 50°C with a slow nitrogen bleed. The yield was 52.0% (9.5 mg) of title compound (melt begins at <50°C by DSC).

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79i) 3-{8-(2,6-difluorophenyl)-2-[(1*H*-imidazol-2-ylmethyl)amino]-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl}-4-methyl-*N*-1,3-thiazol-2-ylbenzamide citrate

30

Isopropanol (200 uL) was added to free-base version of 3-{8-(2,6-difluorophenyl)-2-[(1*H*-imidazol-2-ylmethyl)amino]-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl}-4-methyl-*N*-1,3-thiazol-2-ylbenzamide from (10.6 mg), and the resulting mixture was heated to 50°C. Citric acid was added (1.0 equivalent; 1N in THF). The mixture was cooled to room temperature and shook for several days. The product was filtered, washed with isopropanol, and dried for several hours in a vacuum oven at 50°C with a slow nitrogen bleed. The yield was 61.4% (8.7 mg) of title compound with a melting onset at 179°C (determined by DSC).

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Alternatively, Isopropanol (502 uL) was added to free-base version of 3-{8-(2,6-difluorophenyl)-2-[(1*H*-imidazol-2-ylmethyl)amino]-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl}-4-methyl-*N*-1,3-thiazol-2-ylbenzamide from (25.1 mg), and the resulting mixture was heated to 50°C. Citric acid was added (1.0 equivalent; 1N in THF) resulting in an immediate precipitate. Seed crystals were added, and the mixture stirred for several hours. The product was filtered, washed with isopropanol, and dried overnight in a vacuum oven at 50°C with a slow nitrogen bleed. The yield was 71.4% (24.0 mg).

79j) 3-{8-(2,6-difluorophenyl)-2-[(1*H*-imidazol-2-ylmethyl)amino]-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl}-4-methyl-*N*-1,3-thiazol-2-ylbenzamide ethanesulfonate Acetone (200 uL) was added to free-base version of 3-{8-(2,6-difluorophenyl)-2-[(1*H*-imidazol-2-ylmethyl)amino]-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl}-4-methyl-*N*-1,3-thiazol-2-ylbenzamide (25.1 mg), and the resulting mixture was heated to 50°C. Ethanesulfonic acid was added (1.0 equivalent; 1N in THF), and the mixture stirred for several days. The product was filtered, washed with acetone, and dried overnight in a vacuum oven at 50°C with a slow nitrogen bleed. The yield was 70.6 % (9.1 mg) of title compound with a melting onset at 296°C (determined by DSC).

Alternatively, acetone (501 uL) was added to free-base version of 3-{8-(2,6-difluorophenyl)-2-[(1*H*-imidazol-2-ylmethyl)amino]-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl}-4-methyl-*N*-1,3-thiazol-2-ylbenzamide (25.1 mg), and the resulting mixture was heated to 50°C. Ethanesulfonic acid was added (1.0 equivalent; 1N in THF). Seed crystals were added, and the mixture stirred for several days. The product was filtered, washed with acetone, and dried overnight in a vacuum oven at 50°C with a slow nitrogen bleed. The yield was 78.1 % (23.3 mg).

79k) 3-{8-(2,6-difluorophenyl)-2-[(1*H*-imidazol-2-ylmethyl)amino]-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl}-4-methyl-*N*-1,3-thiazol-2-ylbenzamide benzenesulfonate

Acetone (200 uL) was added to free-base version of 3-{8-(2,6-difluorophenyl)-2-[(1*H*-imidazol-2-ylmethyl)amino]-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl}-4-methyl-*N*-1,3-thiazol-2-ylbenzamide (10.4 mg), and the resulting mixture was heated to 50°C. Benzenesulfonic acid was added (1.0

equivalent; 1N in water) resulting in a clear solution. The mixture was cooled to room temperature and shook overnight. The product was filtered, washed with acetone, and dried for several hours in a vacuum oven at 50°C with a slow nitrogen bleed. The yield was 83.2% (5.8 mg) of title compound with a melting onset at  
5 317°C (determined by DSC).

Alternatively, acetone (494 uL) was added to free-base version of 3-{8-(2,6-difluorophenyl)-2-[(1*H*-imidazol-2-ylmethyl)amino]-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl}-4-methyl-*N*-1,3-thiazol-2-ylbenzamide from Example (24.7 mg)  
10 at room temperature resulting in a mixture. Benzenesulfonic acid was added (1.0 equivalent; 1N in water) resulting in a clear solution. Seed crystals were added, and the mixture stirred for several hours. The product was filtered, washed with acetone, and dried overnight in a vacuum oven at 50°C with a slow nitrogen bleed. The yield was 83.2% (26.3 mg).

15 791) 3-{8-(2,6-difluorophenyl)-2-[(1*H*-imidazol-2-ylmethyl)amino]-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl}-4-methyl-*N*-1,3-thiazol-2-ylbenzamide fumarate

Isopropanol (200 uL) was added to free-base version of 3-{8-(2,6-difluorophenyl)-2-[(1*H*-imidazol-2-ylmethyl)amino]-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl}-4-methyl-*N*-1,3-thiazol-2-ylbenzamide from Example 79c (10.5 mg), and the resulting mixture was heated to 50°C. Fumaric acid was added (1.0 equivalent; 0.2 N in ethanol). The mixture was cooled to room temperature and shook for several days. The product was filtered, washed with isopropanol, and  
20 dried overnight in a vacuum oven at 50°C with a slow nitrogen bleed. The yield was 61.4% (6.0 mg) of title compound with a melting onset at 251°C (determined by DSC).

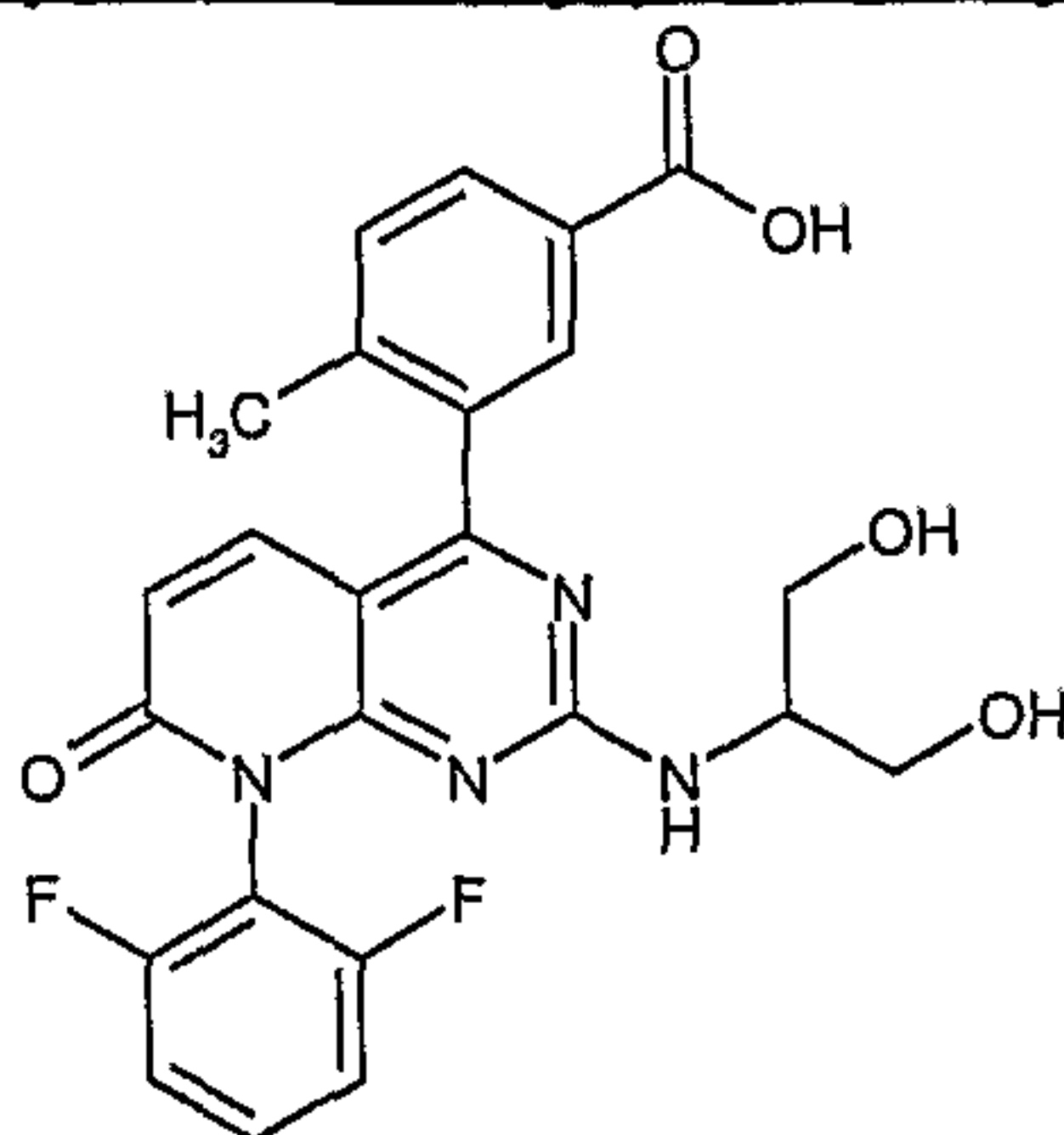
Alternatively, isopropanol (488 uL) was added to free-base version of 3-{8-(2,6-difluorophenyl)-2-[(1*H*-imidazol-2-ylmethyl)amino]-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl}-4-methyl-*N*-1,3-thiazol-2-ylbenzamide from Example 79c (24.4 mg), and the resulting mixture was heated to 50°C. Fumaric acid was added (1.0 equivalent; 0.2 N in ethanol) resulting in an immediate precipitate. Seed crystals were added, and the mixture stirred for several hours. The  
30 product was filtered, washed with isopropanol, and dried overnight in a vacuum oven at 50°C with a slow nitrogen bleed. The yield was 63.0% (18.5 mg).

**Example 80**

3-(8-(2,6-difluorophenyl)-2-{[2-hydroxy-1-(hydroxymethyl)ethyl]amino}-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl)-4-methyl-*N*-propylbenzamide trifluoroacetate

5

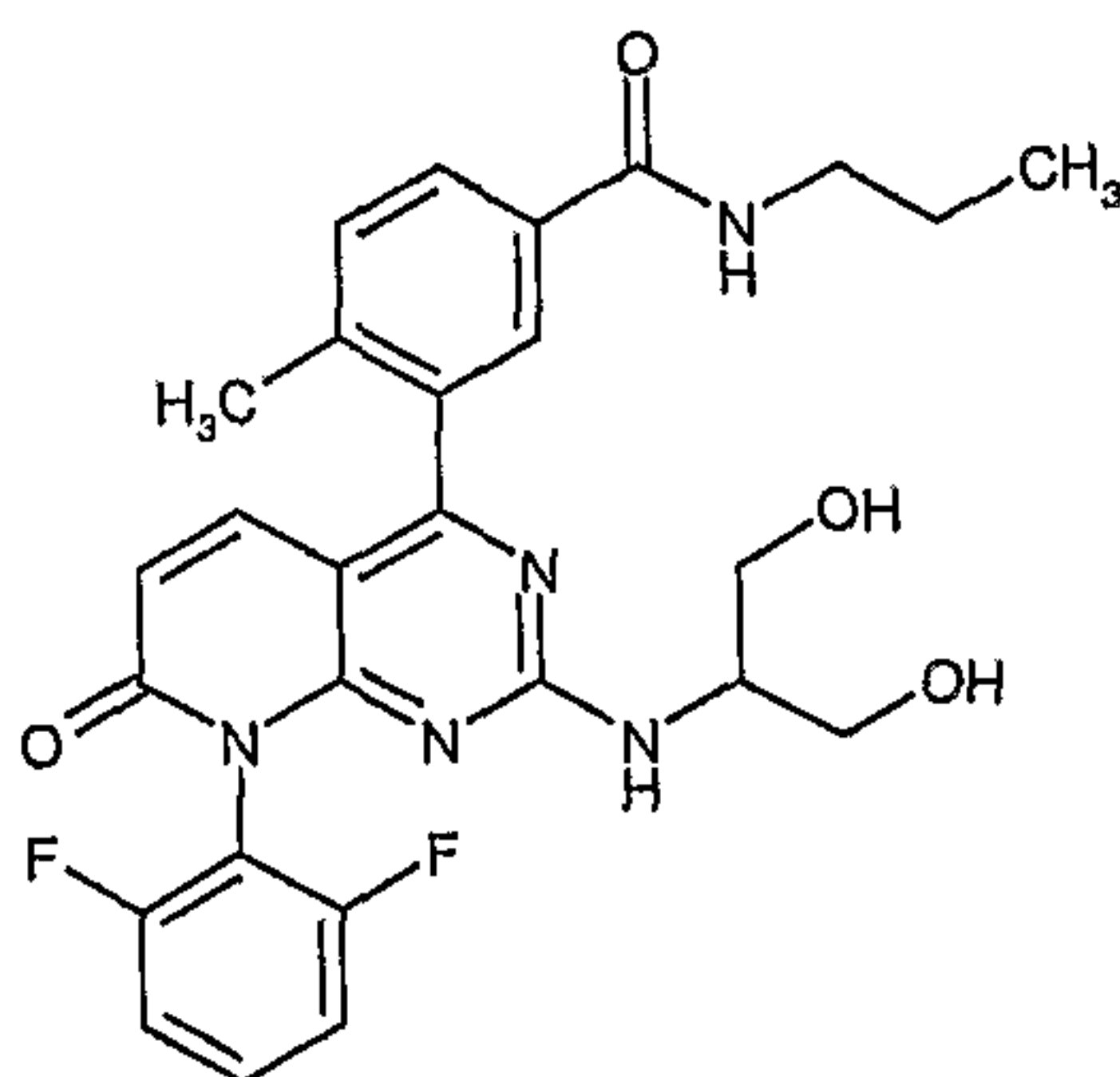
80a) 3-(8-(2,6-difluorophenyl)-2-{[2-hydroxy-1-(hydroxymethyl)-ethyl]amino}-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl)-4-methylbenzoic acid



The title compound was prepared by following the procedures in Example 1b using 4-chloro-8-(2,6-difluorophenyl)-2-{[2-hydroxy-1-(hydroxymethyl)ethyl]-amino}pyrido[2,3-*d*]pyrimidin-7(8*H*)-one for the Suzuki cross-coupling reaction.

80b) 3-(8-(2,6-difluorophenyl)-2-{[2-hydroxy-1-(hydroxymethyl)ethyl]amino}-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl)-4-methyl-*N*-propylbenzamide trifluoroacetate

15

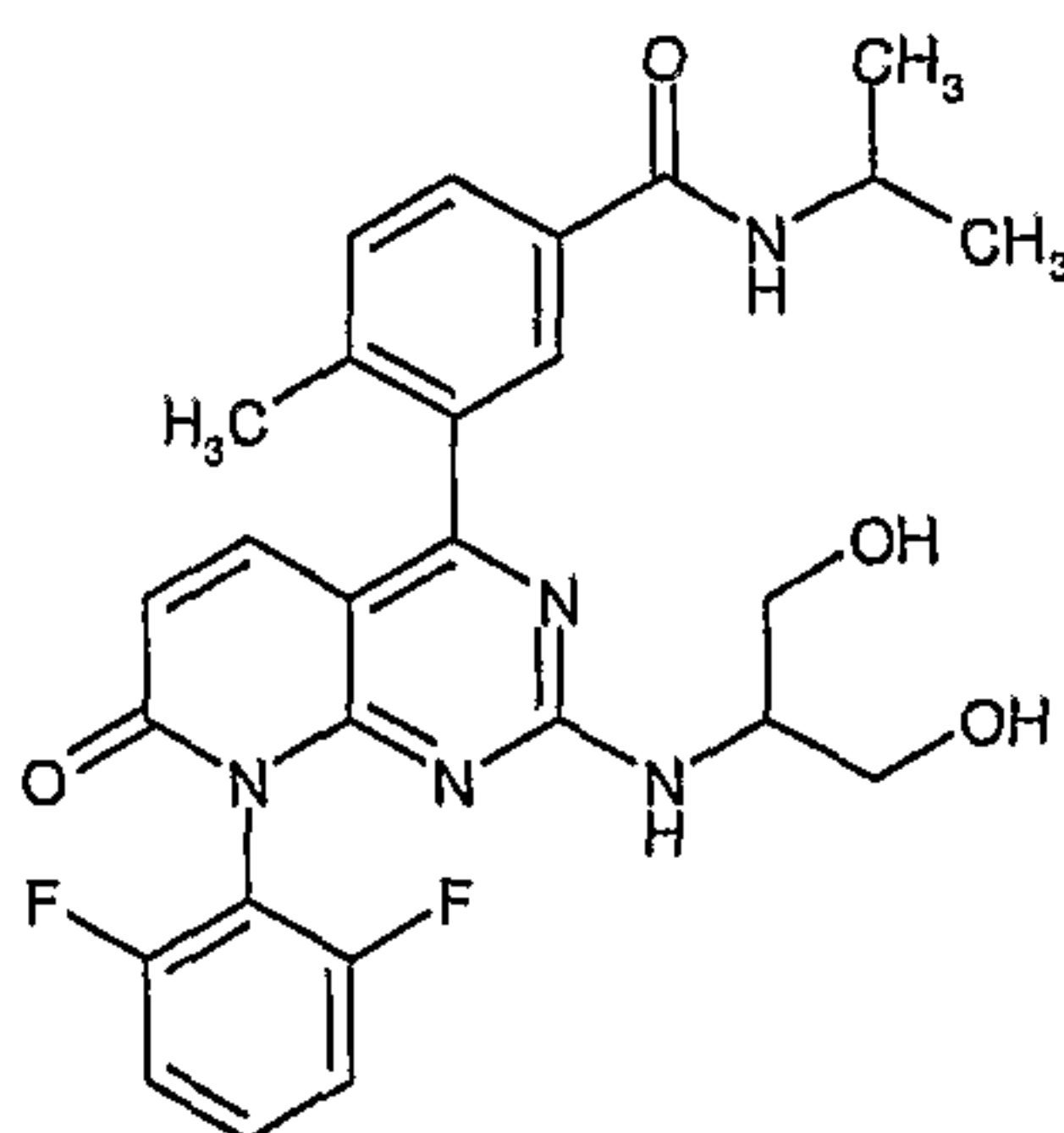


To the acid from Example 80a (32.3 mg, 0.066 mmol, 1 eq) was added HATU (28.5 mg, 0.075 mmol) in DMF (500  $\mu$ L). DIPEA (34  $\mu$ L, 0.2 mmol, 3 eq) was then added. The resulting mixture was then allowed to stand for about 5 minutes before adding to propylamine (6 mg, 0.1 mmol) in DMF (250  $\mu$ L). The resulting mixture was shaken to ensure efficient mixing of the reagents then was left to stand overnight. The solvent was then removed in vacuo. The residue dissolved in methanol and was then placed down an aminopropyl SPE flushing the column

with methanol. The residue was purified by MDAP to give the above named compound (7.4 mg): LC-MS  $m/z$  524 (M+H)<sup>+</sup>, 2.63 min (ret time).

### Example 81

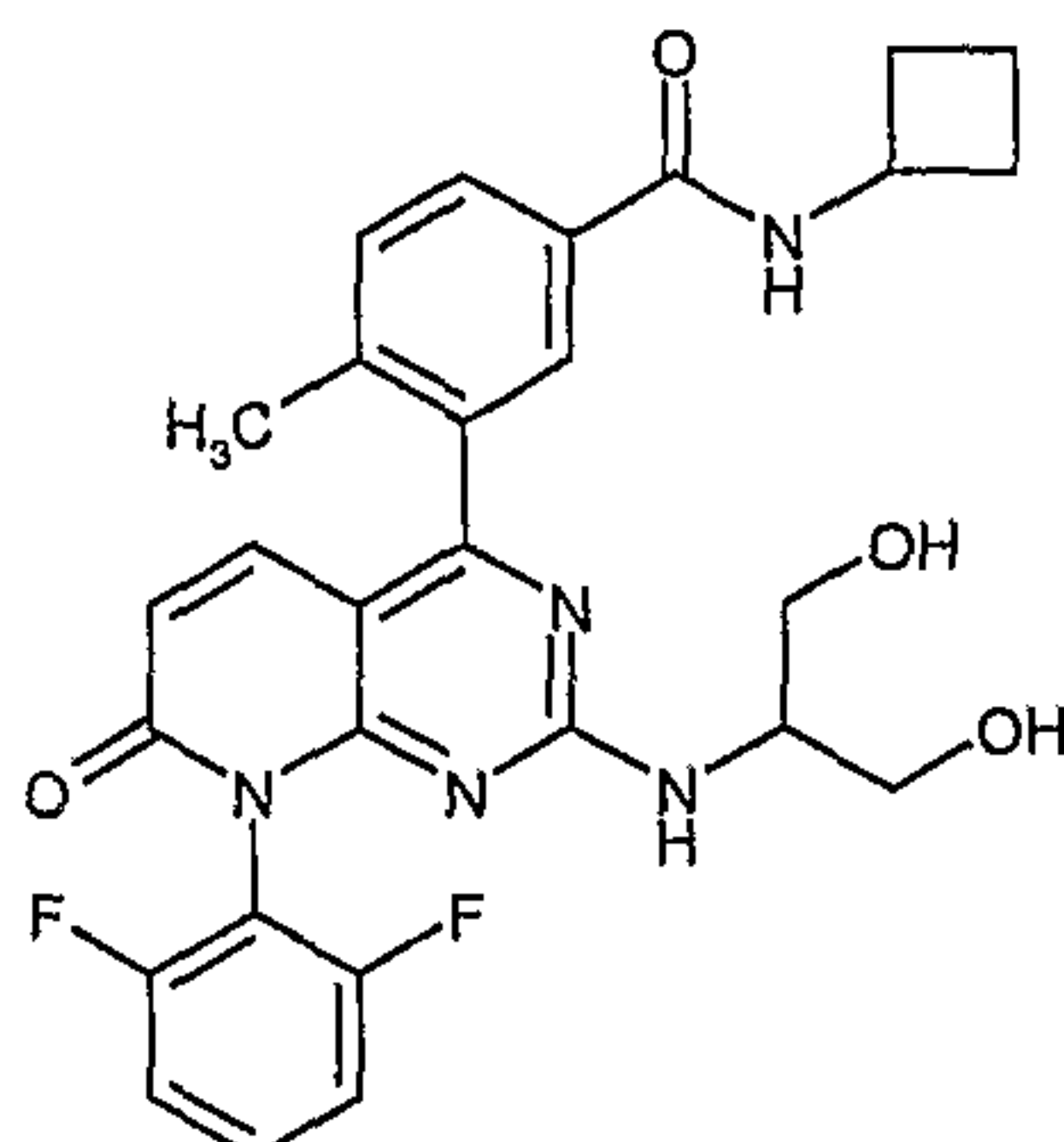
- 5 3-(8-(2,6-difluorophenyl)-2-{[2-hydroxy-1-(hydroxymethyl)ethyl]amino}-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl)-4-methyl-*N*-(1-methylethyl)benzamide trifluoroacetate



- 10 The title compound was prepared by following the procedures in Example 80b except using 1-methylethylamine: LC-MS  $m/z$  524 (M+H)<sup>+</sup>, 2.62 min (ret time).

### Example 82

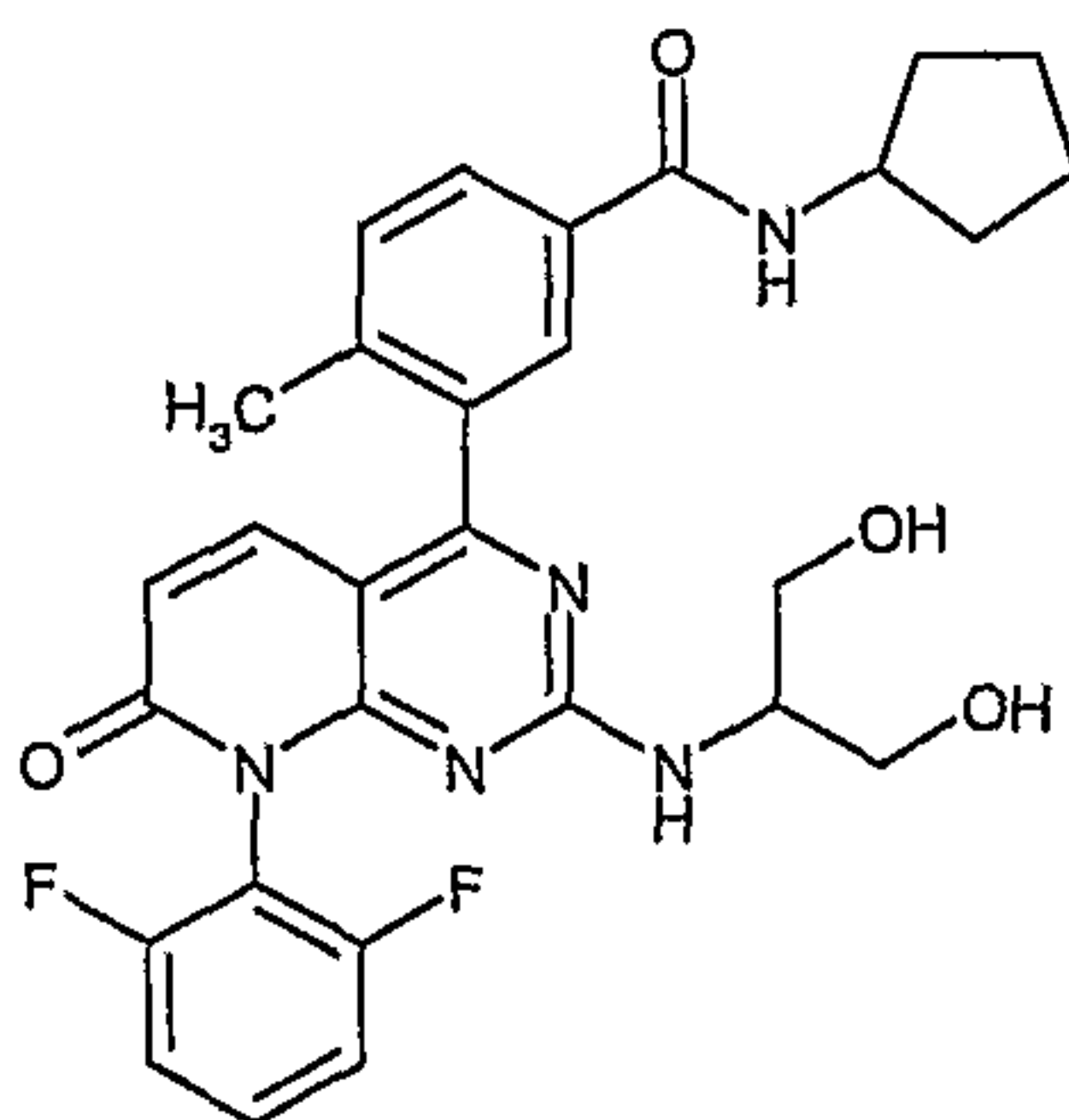
- 15 *N*-cyclobutyl-3-(8-(2,6-difluorophenyl)-2-{[2-hydroxy-1-(hydroxymethyl)ethyl]amino}-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl)-4-methylbenzamide trifluoroacetate



The title compound was prepared by following the procedures in Example 80b except using cyclobutanamine: LC-MS  $m/z$  536 (M+H)<sup>+</sup>, 2.7 min (ret time).

**Example 83**

*N*-cyclopentyl-3-(8-(2,6-difluorophenyl)-2-{[2-hydroxy-1-(hydroxymethyl)ethyl]-amino}-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl)-4-methylbenzamide trifluoroacetate

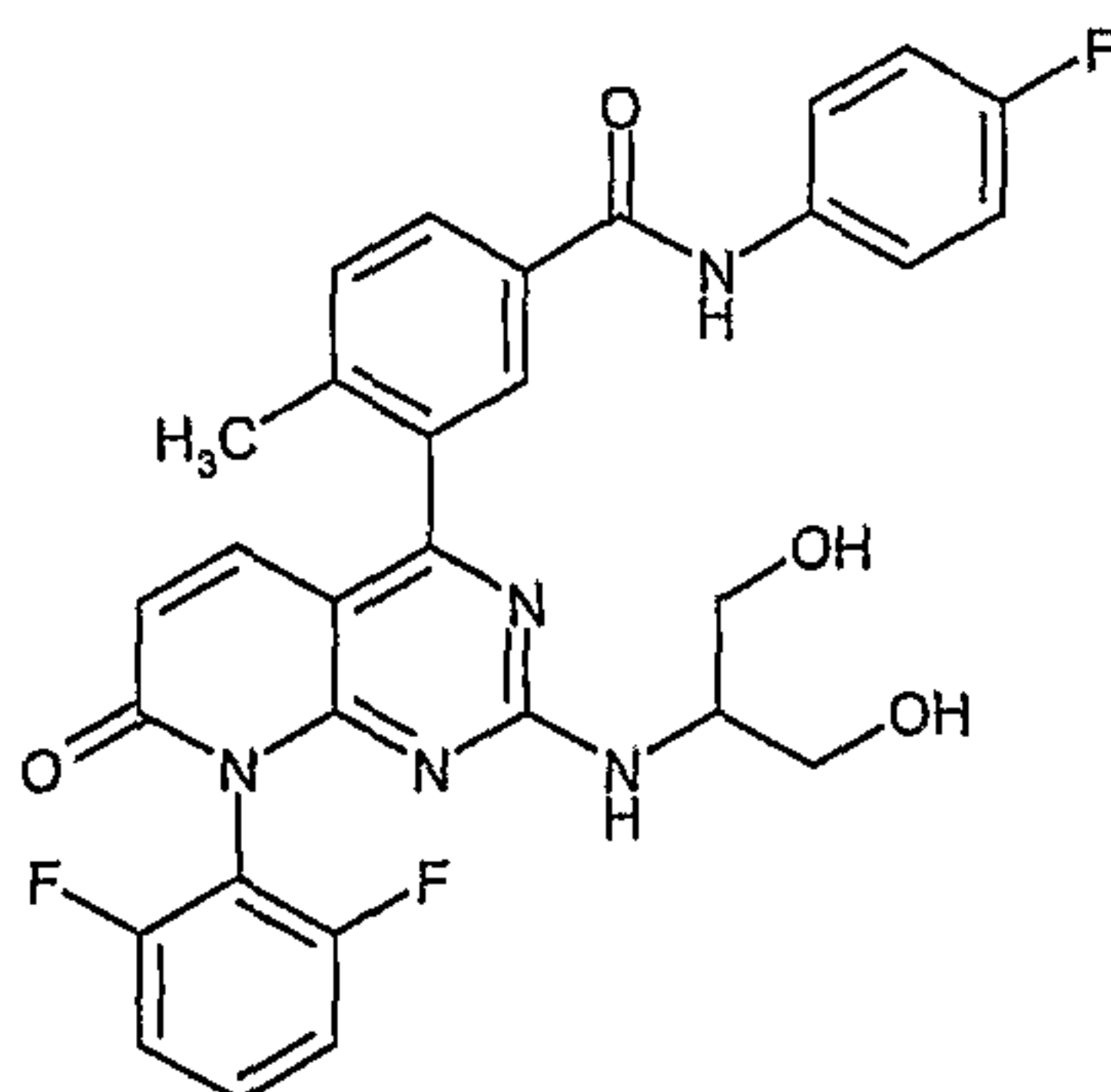


5

The title compound was prepared by following the procedures in Example 80b except using cyclopentylamine: LC-MS  $m/z$  550 ( $M+H$ )<sup>+</sup>, 2.78 min (ret time).

**Example 84**

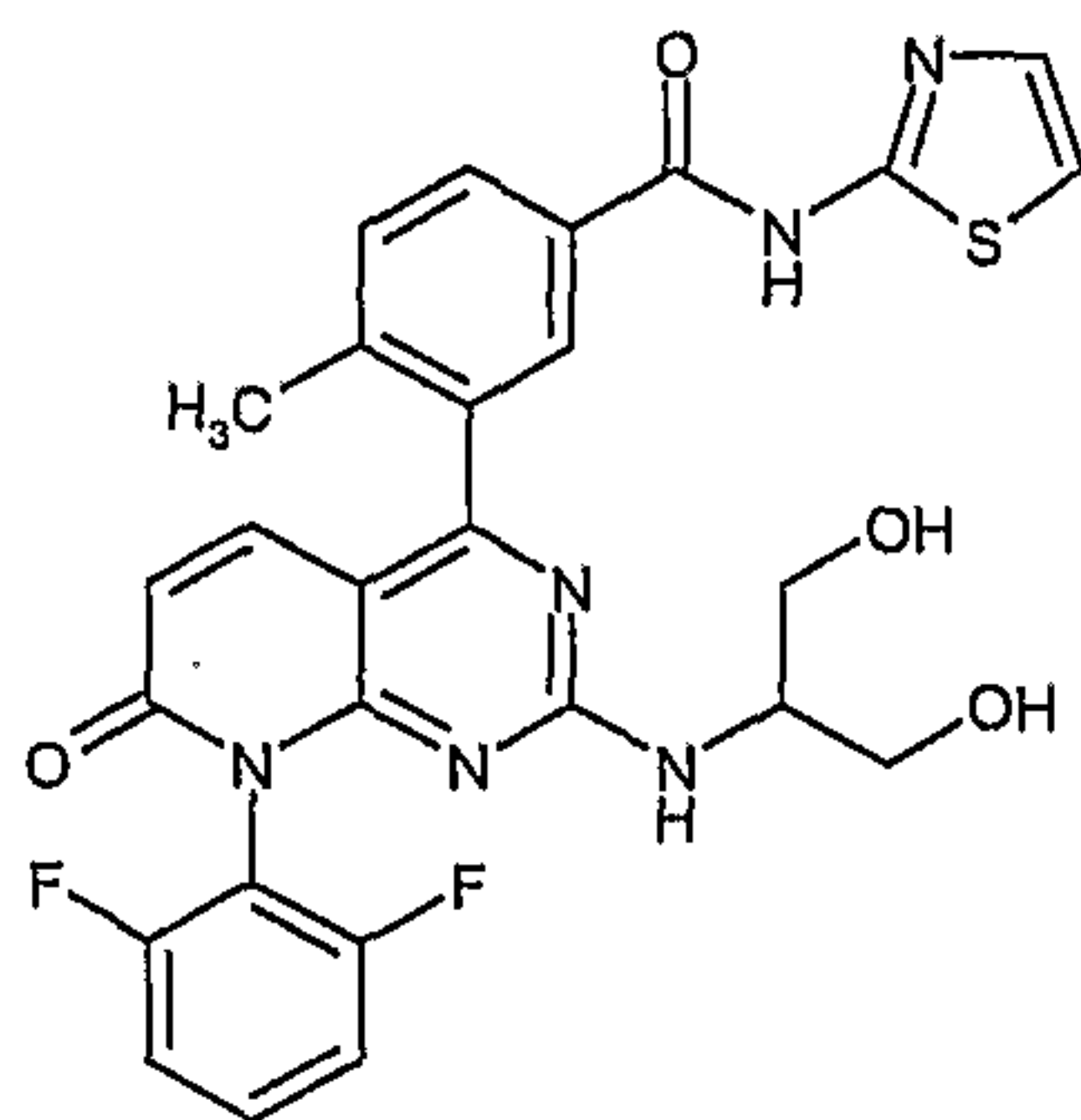
10 3-(8-(2,6-difluorophenyl)-2-{[2-hydroxy-1-(hydroxymethyl)ethyl]amino}-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl)-*N*-(4-fluorophenyl)-4-methylbenzamide trifluoroacetate



15 The title compound was prepared by following the procedures in Example 80b except using 4-fluoroaniline: LC-MS  $m/z$  576 ( $M+H$ )<sup>+</sup>, 2.95 min (ret time).

**Example 85**

3-(8-(2,6-difluorophenyl)-2-{[2-hydroxy-1-(hydroxymethyl)ethyl]amino}-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl)-4-methyl-*N*-1,3-thiazol-2-ylbenzamide trifluoroacetate

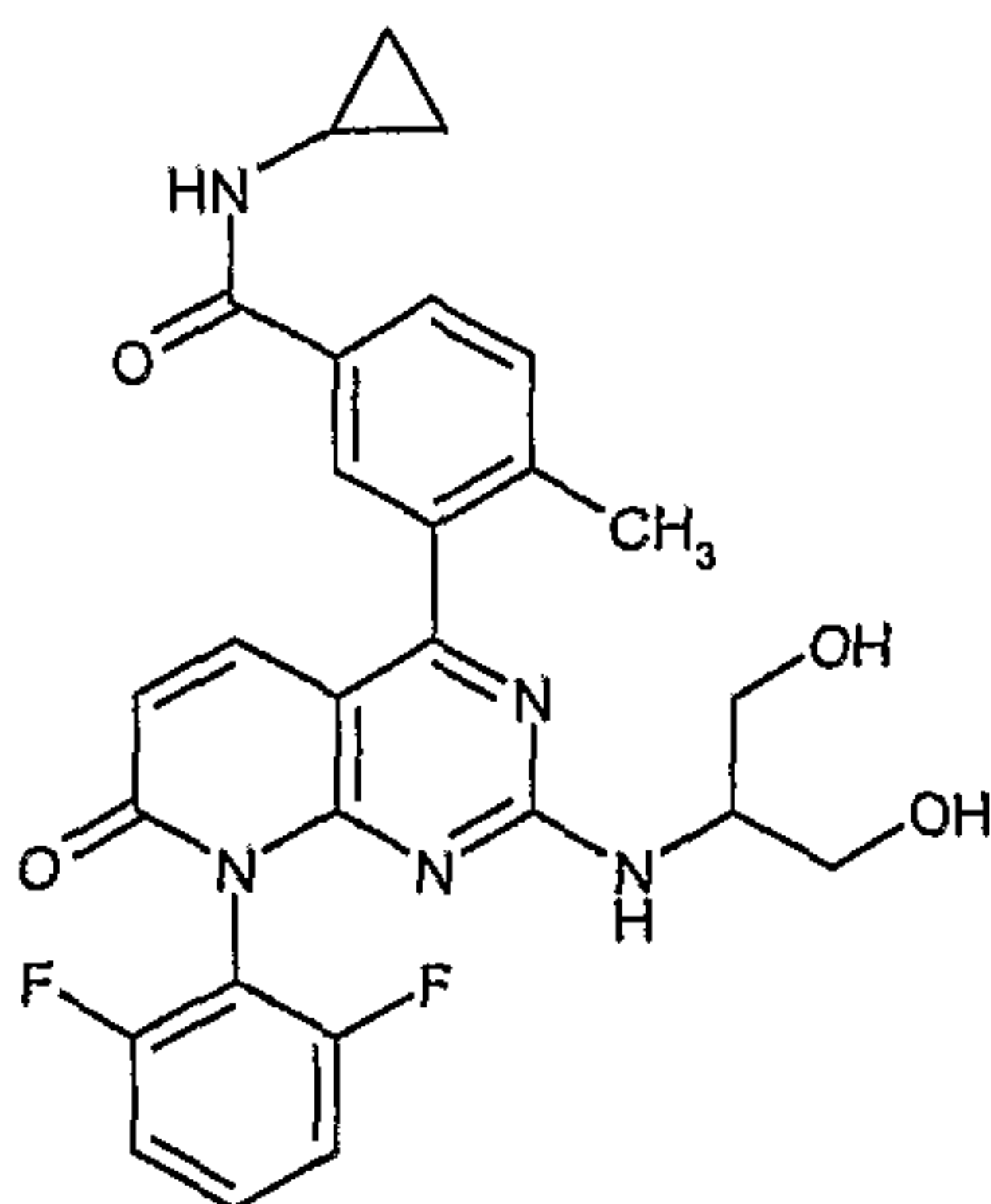


5

The title compound was prepared by following the procedures in Example 80b except using 1,3-thiazol-2-amine: LC-MS  $m/z$  565 (M+H)<sup>+</sup>, 2.75 min (ret time).

**Example 86**

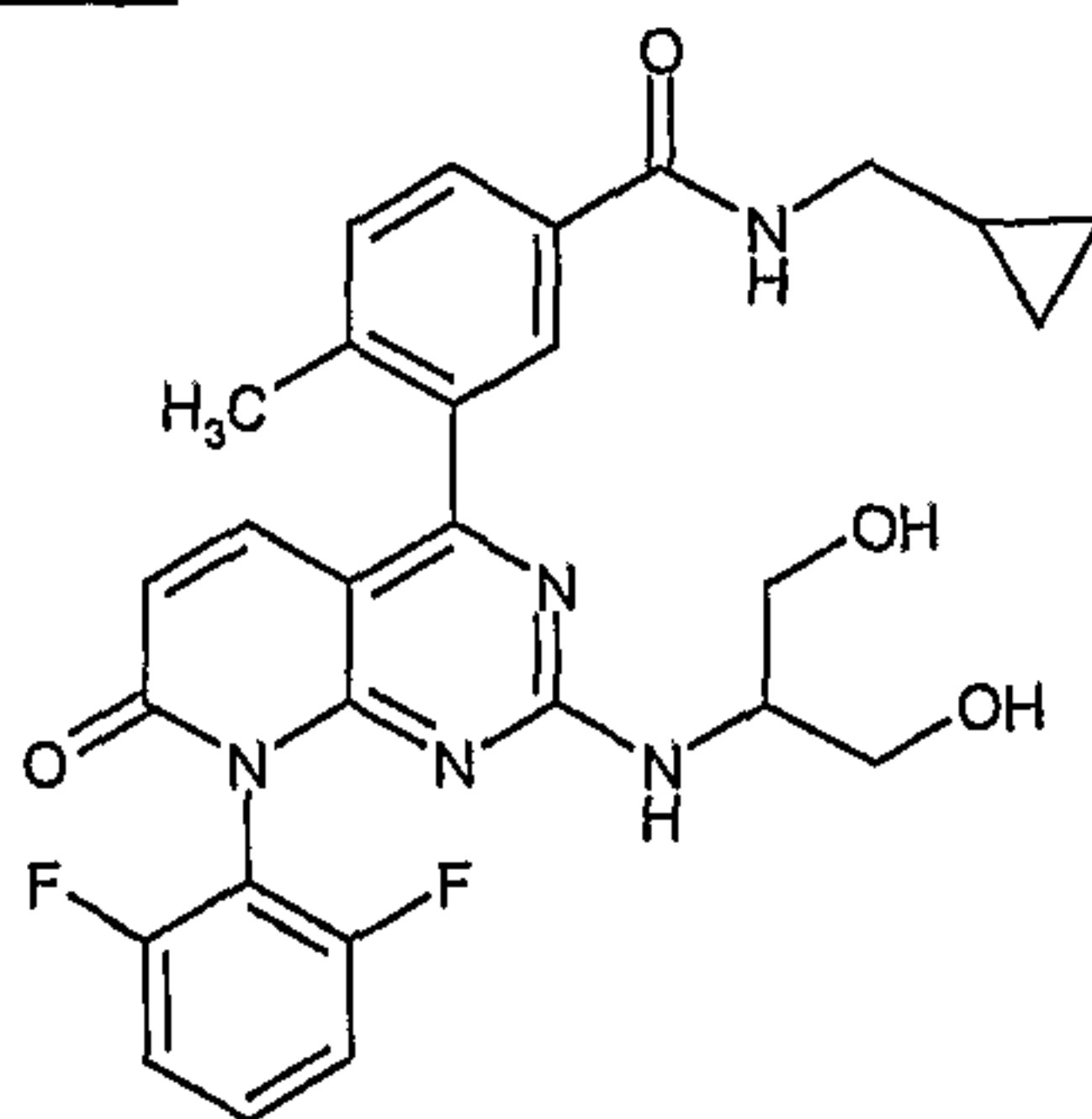
10 *N*-cyclopropyl-3-(8-(2,6-difluorophenyl)-2-{[2-hydroxy-1-(hydroxymethyl)ethyl]-amino}-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl)-4-methylbenzamide trifluoroacetate



15 The title compound was prepared by following the procedures in Example 80b except using cyclopropylamine: LC-MS  $m/z$  522 (M+H)<sup>+</sup>, 2.55 min (ret time).

**Example 87**

*N*-(cyclopropylmethyl)-3-(8-(2,6-difluorophenyl)-2-{[2-hydroxy-1-(hydroxymethyl)ethyl]amino}-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl)-4-methylbenzamide trifluoroacetate



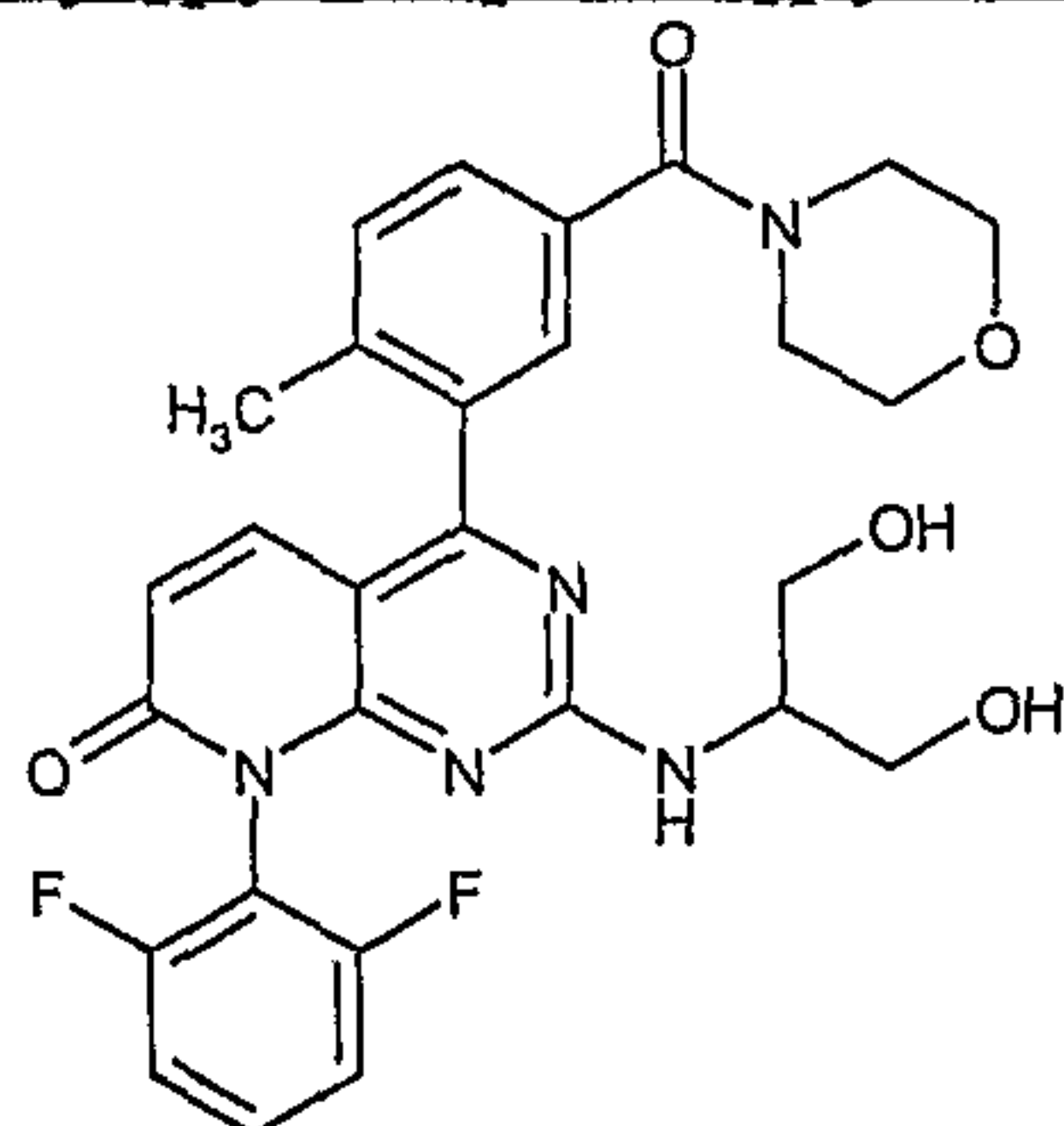
5

The title compound was prepared by following the procedures in Example 80b except using cyclopropylmethylamine: LC-MS  $m/z$  536 ( $M+H$ )<sup>+</sup>, 2.67 min (ret time).

10

**Example 88**

8-(2,6-difluorophenyl)-2-{[2-hydroxy-1-(hydroxymethyl)ethyl]amino}-4-[2-methyl-5-(4-morpholinylcarbonyl)phenyl]pyrido[2,3-*d*]pyrimidin-7(8*H*)-one trifluoroacetate



15

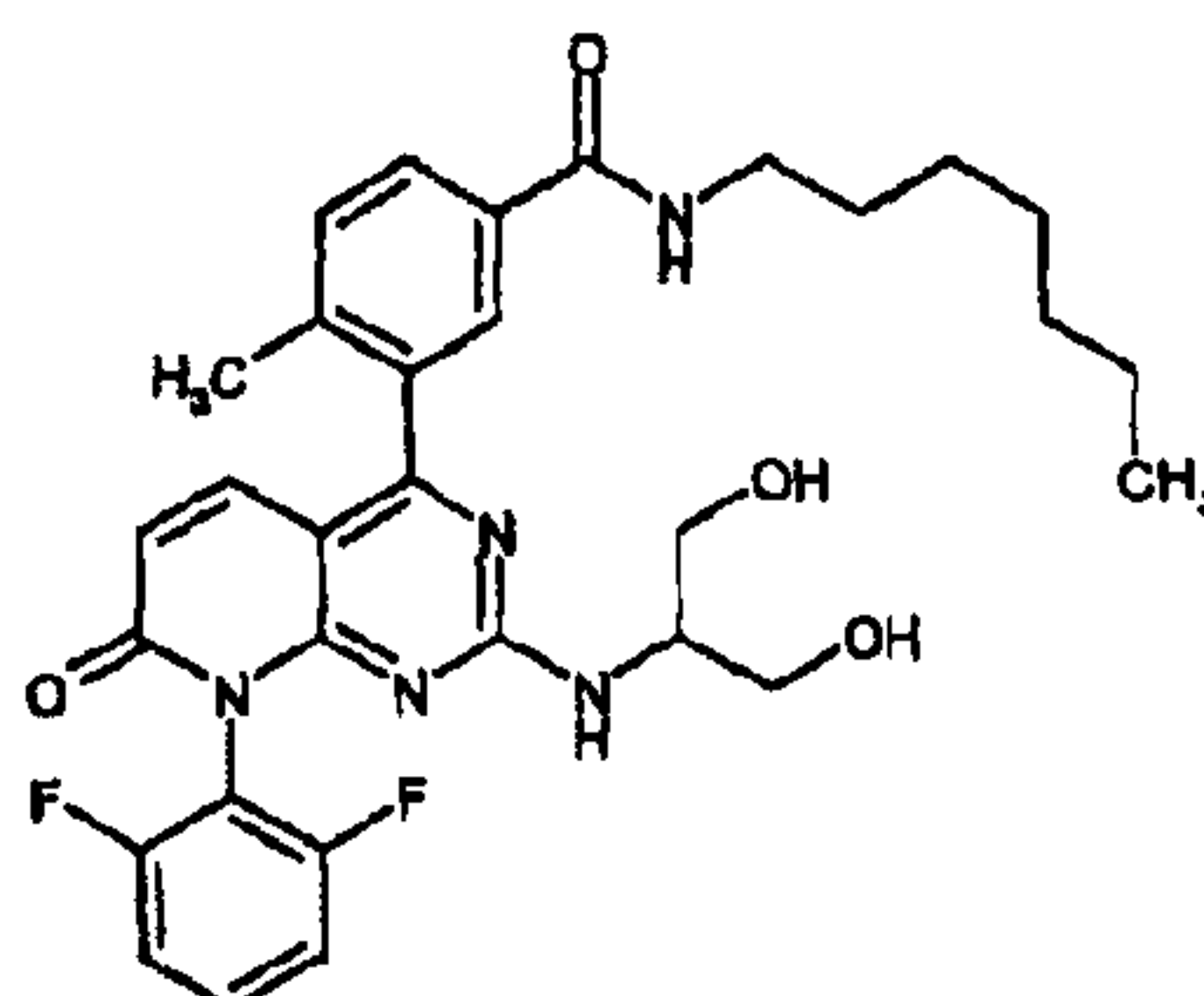
The title compound was prepared by following the procedures in Example 80b except using morpholine: LC-MS  $m/z$  552 ( $M+H$ )<sup>+</sup>, 2.44 min (ret time).

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**Example 89**

3-(8-(2,6-difluorophenyl)-2-[[2-hydroxy-1-(hydroxymethyl)ethyl]amino]-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl)-*N*-heptyl-4-methylbenzamide trifluoroacetate

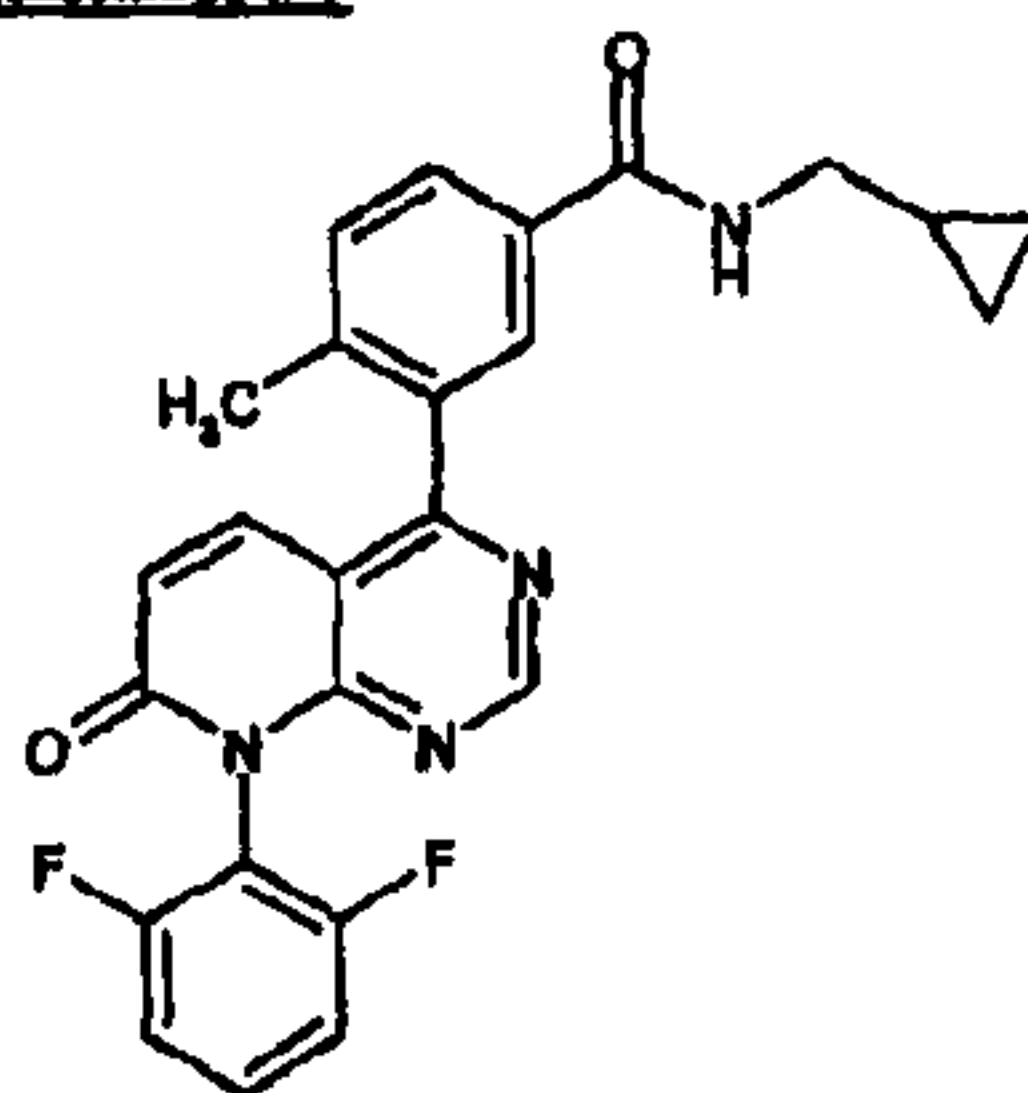


5

The title compound was prepared by following the procedures in Example 80b except using heptylamine: LC-MS  $m/z$  580 ( $M+H$ )<sup>+</sup>, 3.16 min (ret time).

**Example 90**

10 *N*-(cyclopropylmethyl)-3-[8-(2,6-difluorophenyl)-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl]-4-methylbenzamide



15 *N*-(cyclopropylmethyl)-3-[8-(2,6-difluorophenyl)-2-(methylthio)-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl]-4-methylbenzamide (13.5mg, 0.027mmol), was dissolved in anhydrous methanol (2 mL) and was added to a tube containing nickel chloride hexahydrate (2 mg). The tube was placed under an atmosphere of nitrogen and cooled using a dry-ice/acetone bath to about -15°C. Sodium borohydride (2 mg) was then added (nitrogen removed during addition and then replaced) and the solution turned black. The solution was stirred in the dry

20 ice/acetone bath for 1.5 h. 1 N HCl (4 mL) was added and the solution was allowed to warm to room temperature and stirred under an air atmosphere for about 2 hours. Dichloromethane (2 mL) was added to the solution and it was stirred vigorously for 10 min. The solution was filtered through a hydrophobic frit packed with celite\* and was washed with further dichloromethane (2 mL × 2). The filtrate was concentrated

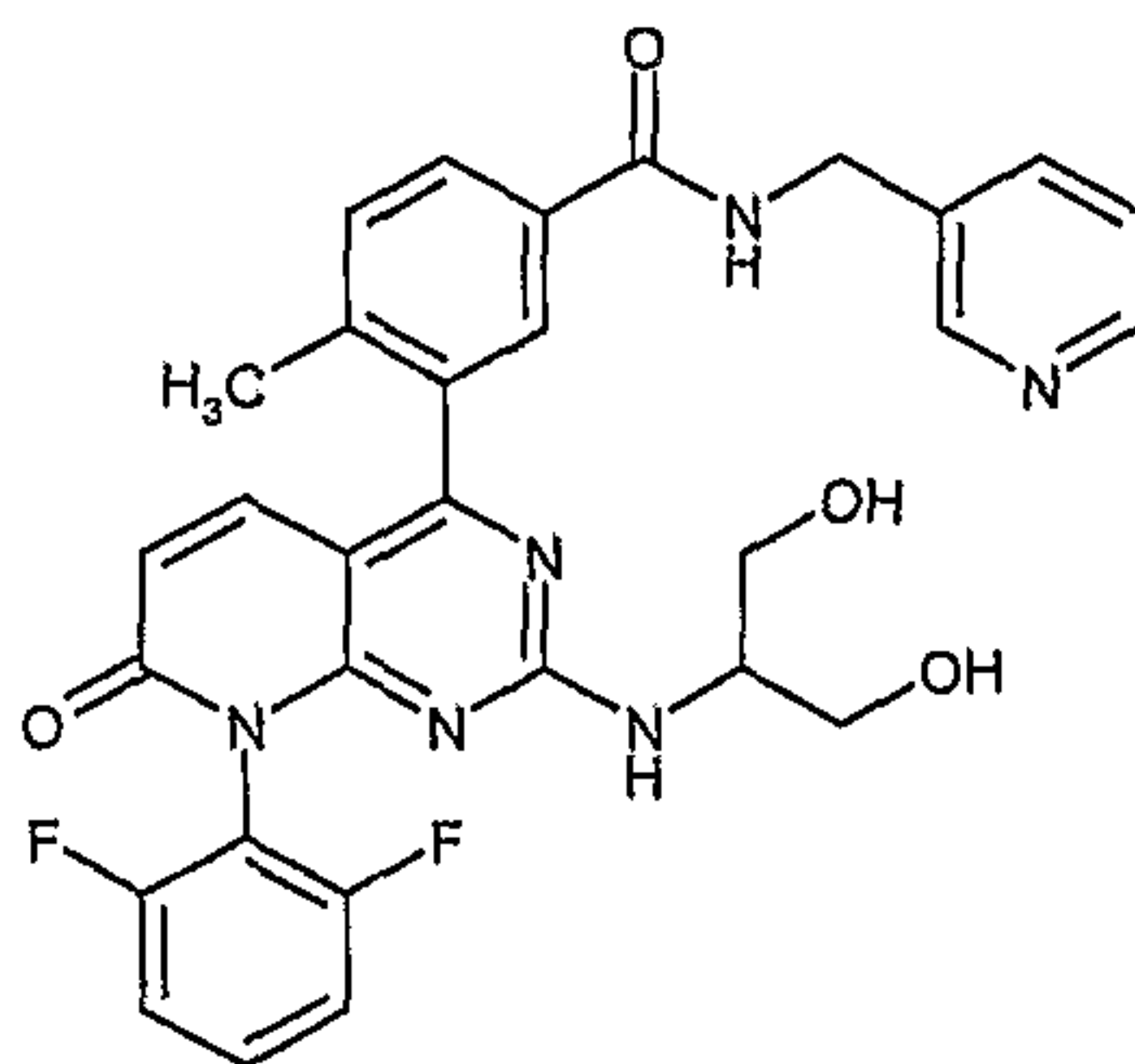
25 and purified by HPLC to give the title product (1 mg, 8.2%). LC-MS  $m/z$  447

(M+H)<sup>+</sup>, 2.98 min (ret time). <sup>1</sup>H-NMR (d<sub>6</sub>-DMSO) δ 0.22 (m, 2H), 0.42 (m, 2H), 1.01 (br s, 1H), 2.23 (s, 3H), 3.14 (br s, 2H), 6.87 (m, 1H), 7.43 (m, 2H), 7.65 (m, 2H), 7.95 (m, 2H), 8.60 (m, 1H), 9.07 (s, 1H).

5

**Example 91**

3-(8-(2,6-difluorophenyl)-2-{[2-hydroxy-1-(hydroxymethyl)ethyl]amino}-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl)-4-methyl-*N*-(3-pyridinylmethyl)benzamide trifluoroacetate



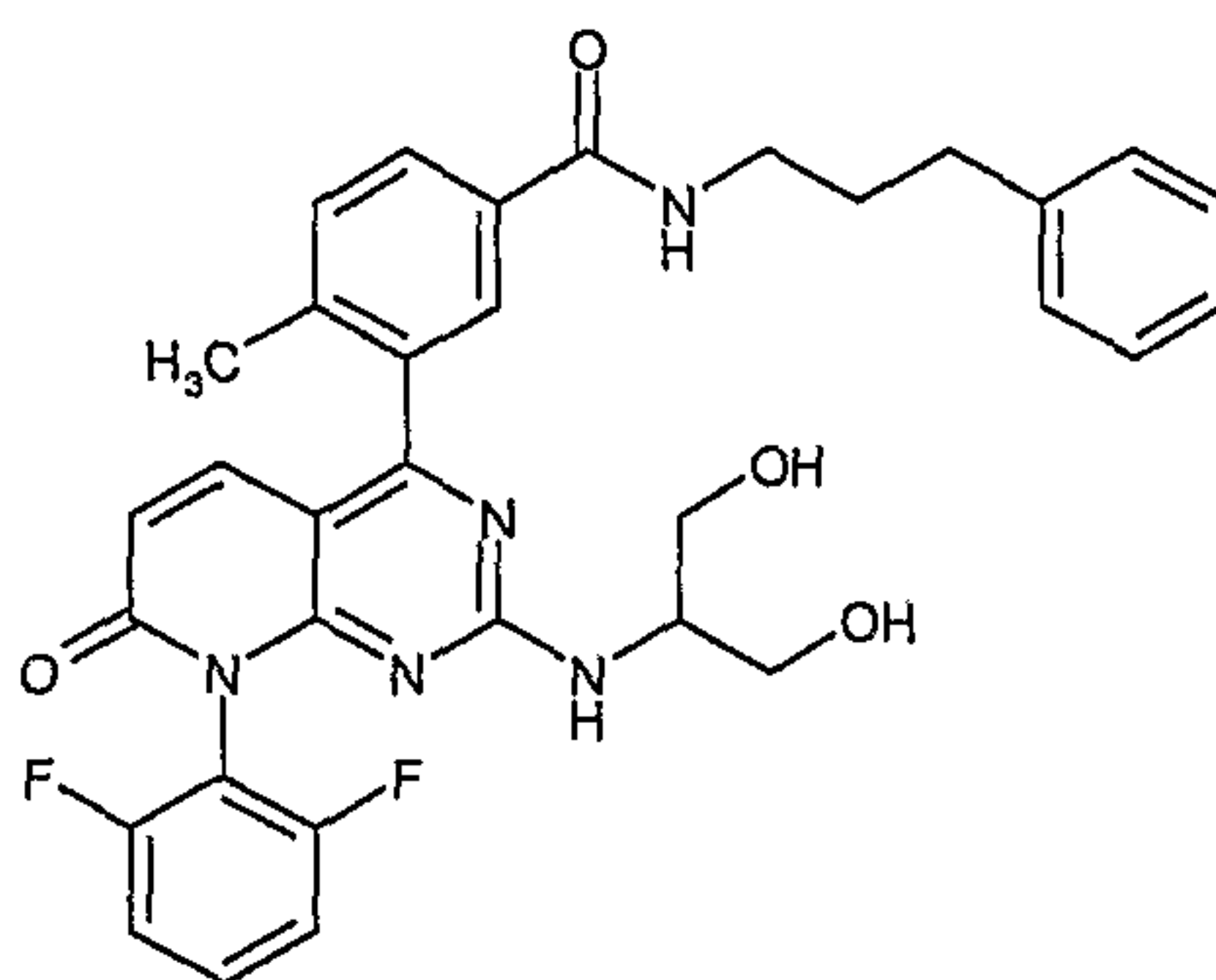
10

The title compound was prepared by following the procedures in Example 80b except using (3-pyridinylmethyl)amine: LC-MS *m/z* 573 (M+H)<sup>+</sup>, 2.03 min (ret time).

**Example 92**

15

3-(8-(2,6-difluorophenyl)-2-{[2-hydroxy-1-(hydroxymethyl)ethyl]amino}-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl)-4-methyl-*N*-(3-phenylpropyl)benzamide trifluoroacetate

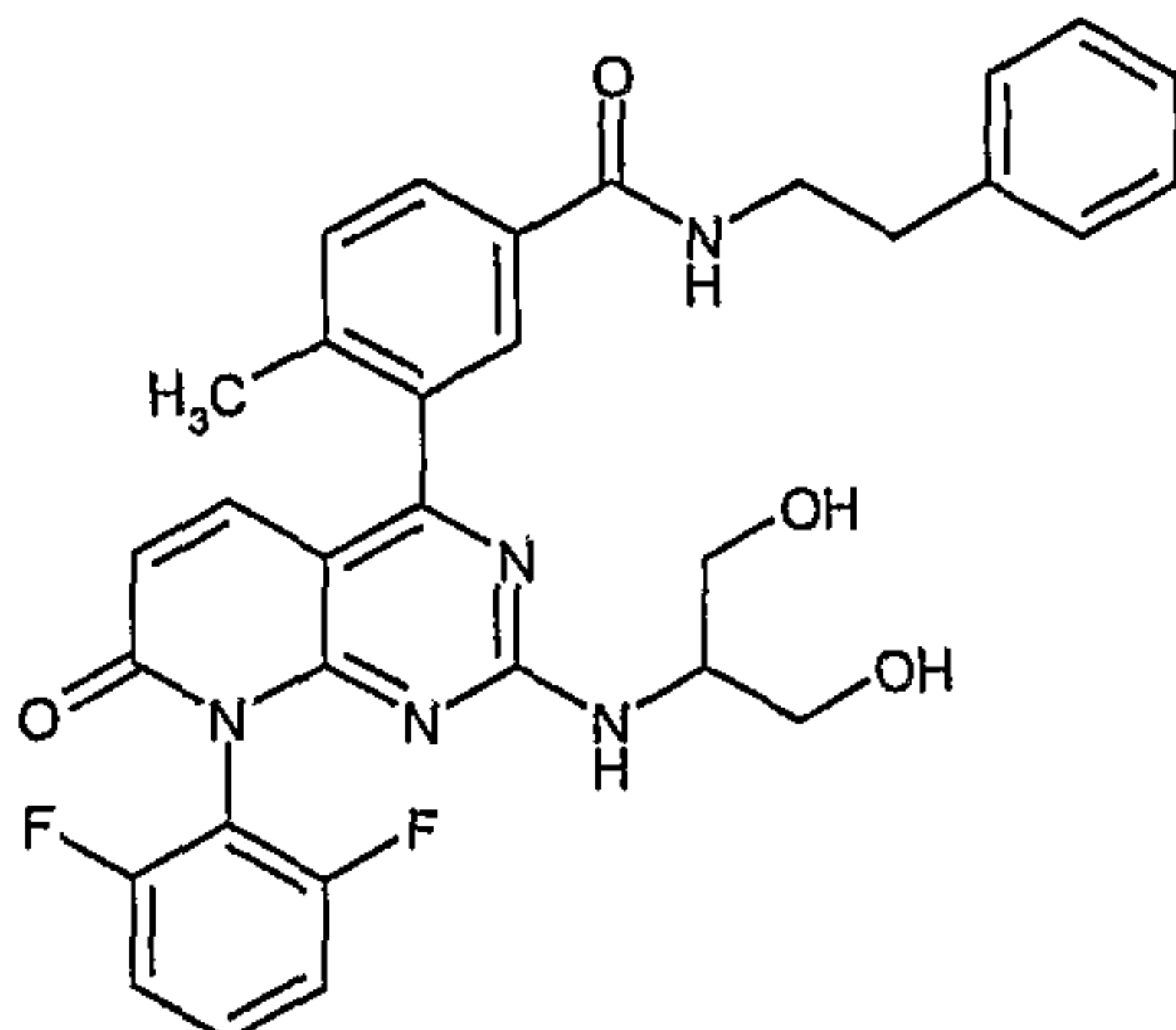


20

The title compound was prepared by following the procedures in Example 80b except using 3-phenyl-1-propanamine: LC-MS *m/z* 600 (M+H)<sup>+</sup>, 2.97 min (ret time).

**Example 93**

3-(8-(2,6-difluorophenyl)-2-{[2-hydroxy-1-(hydroxymethyl)ethyl]amino}-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl)-4-methyl-*N*-(2-phenylethyl)benzamide trifluoroacetate



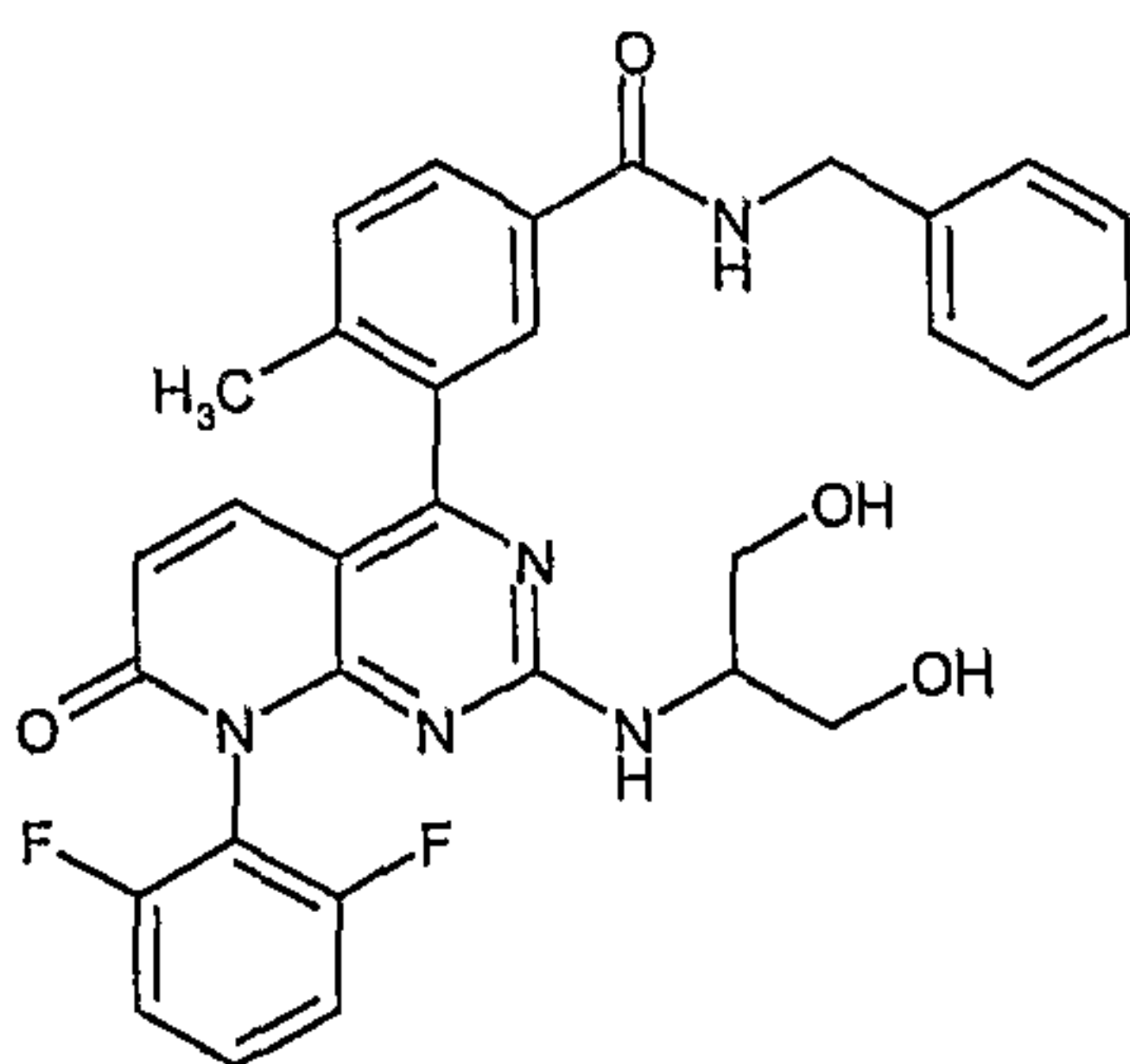
5

The title compound was prepared by following the procedures in Example 80b except using (2-phenylethyl)amine: LC-MS  $m/z$  586 (M+H)<sup>+</sup>, 2.88 min (ret time).

10

**Example 94**

3-(8-(2,6-difluorophenyl)-2-{[2-hydroxy-1-(hydroxymethyl)ethyl]amino}-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl)-4-methyl-*N*-(phenylmethyl)benzamide trifluoroacetate

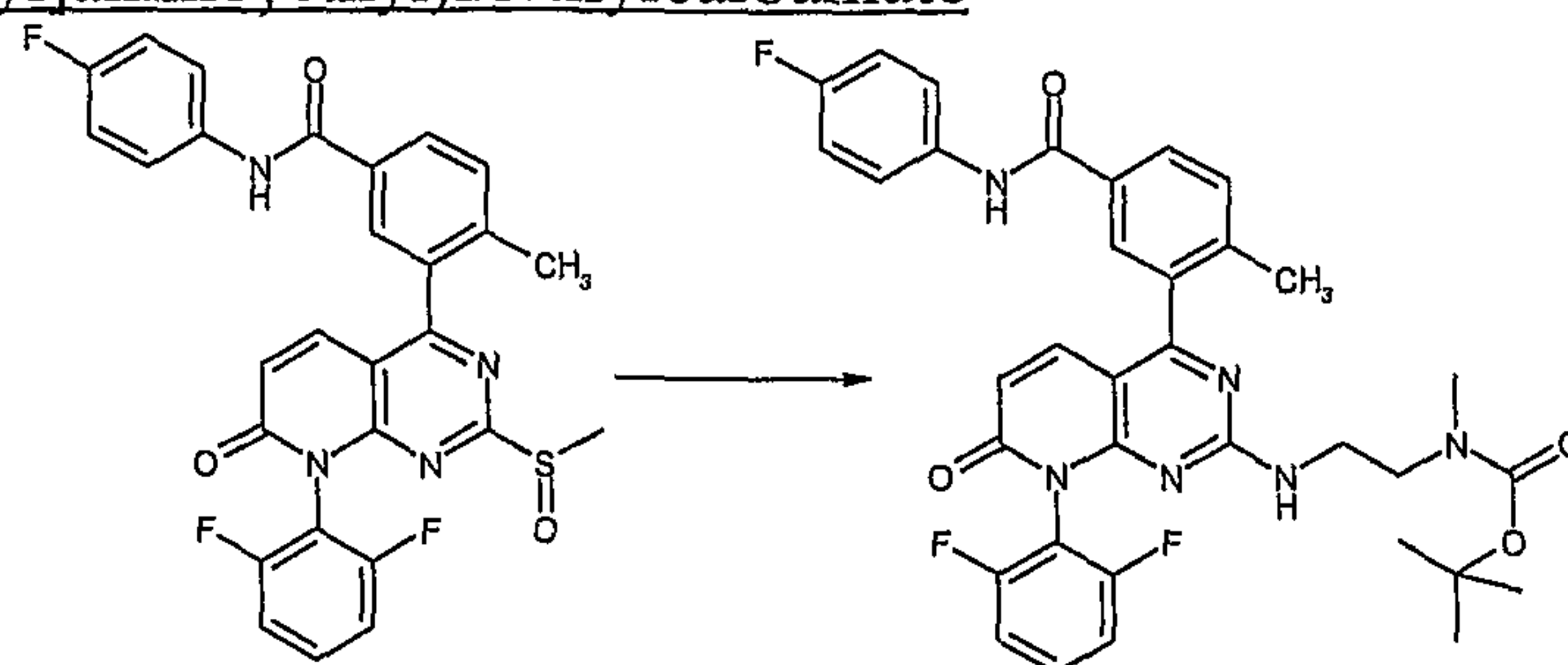


15

The title compound was prepared by following the procedures in Example 80b except using (phenylmethyl)amine: LC-MS  $m/z$  572 (M+H)<sup>+</sup>, 2.83 min (ret time).

**Example 95**

1,1-dimethylethyl (2-{[8-(2,6-difluorophenyl)-4-(5-{[(4-fluorophenyl)amino]carbonyl}-2-methylphenyl)-7-oxo-7,8-dihydropyrido[2,3-d]pyrimidin-2-yl]amino}ethyl)methylcarbamate



5

To a solution of 3-[8-(2,6-difluorophenyl)-2-(methylsulfinyl)-7-oxo-7,8-dihydropyrido[2,3-d]pyrimidin-4-yl]-N-(4-fluorophenyl)-4-methylbenzamide (50 mg, 0.09 mmol) in DCM (5 mL) was added 1,1-dimethylethyl (2-aminoethyl)-methylcarbamate (0.09 mL, 0.5 mmol). The resultant mixture was stirred at room temperature overnight. The mixture was concentrated under vacuo. Flash chromatography (90% CH<sub>2</sub>Cl<sub>2</sub> / 7% MeOH / 3% NH<sub>4</sub>OH) then provide the title compound (61 mg, 100%). LC-MS (ES) m/z 659 (M+H)<sup>+</sup>; <sup>1</sup>H-NMR(CDCl<sub>3</sub>) δ 1.39 (s, 9H), 1.70 (br, 1H), 2.32 (s, 3H), 2.65 (s, 2H), 2.82 (s, 2H), 3.22 (s, 3H), 3.60 (br, 1H), 6.34 (d, 1H), 7.03 (m, 4H), 7.34 (m, 1H), 7.48 (m, 2H), 7.64 (m, 1H), 7.84 (m, 2H), 8.14 (d, 1H).

10

15

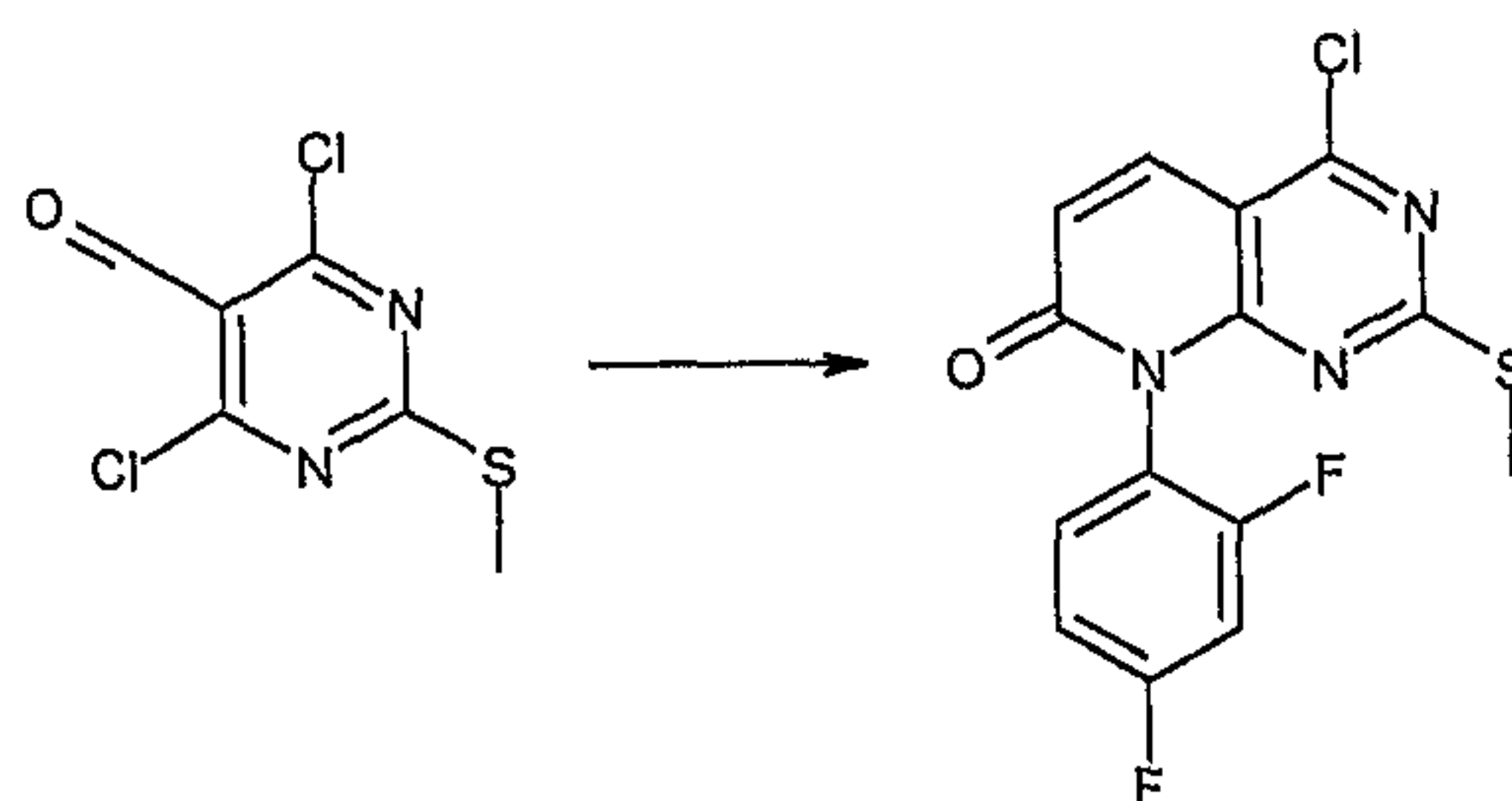
**Example 96**

3-(8-(2,4-difluorophenyl)-2-{[2-hydroxy-1-(hydroxymethyl)ethyl]amino}-7-oxo-7,8-dihydropyrido[2,3-d]pyrimidin-4-yl)benzoic acid

96a) 4-chloro-8-(2,4-difluorophenyl)-2-(methylthio)pyrido[2,3-d]pyrimidin-7(8H)-one

20

one

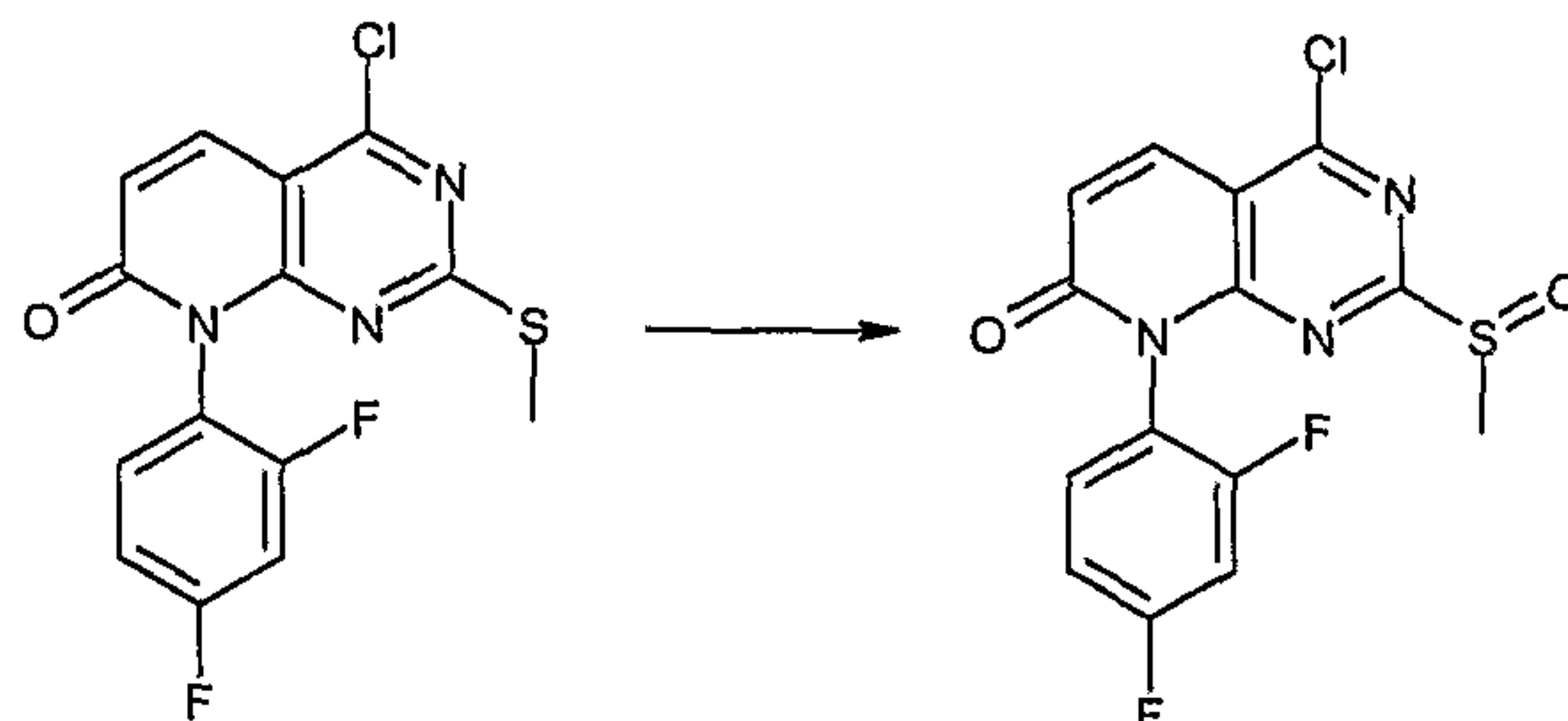


To a solution of 4,6-dichloro-2-methylsulfanyl-pyrimidine-5-carbaldehyde (4.2g, 18.95mmol) and triethylamine (5.3ml, 38mmol) in THF (100ml) was added 2,4-difluoroaniline (2.1ml, 20.58mmol). The mixture was stirred for 2h, and methyl {bis[(2,2,2-trifluoroethyl)oxy]phosphoryl}acetate (6.0g, 18.95mmol) was added. The mixture was stirred for 18h, diluted with DCM (200ml) and washed with water

25

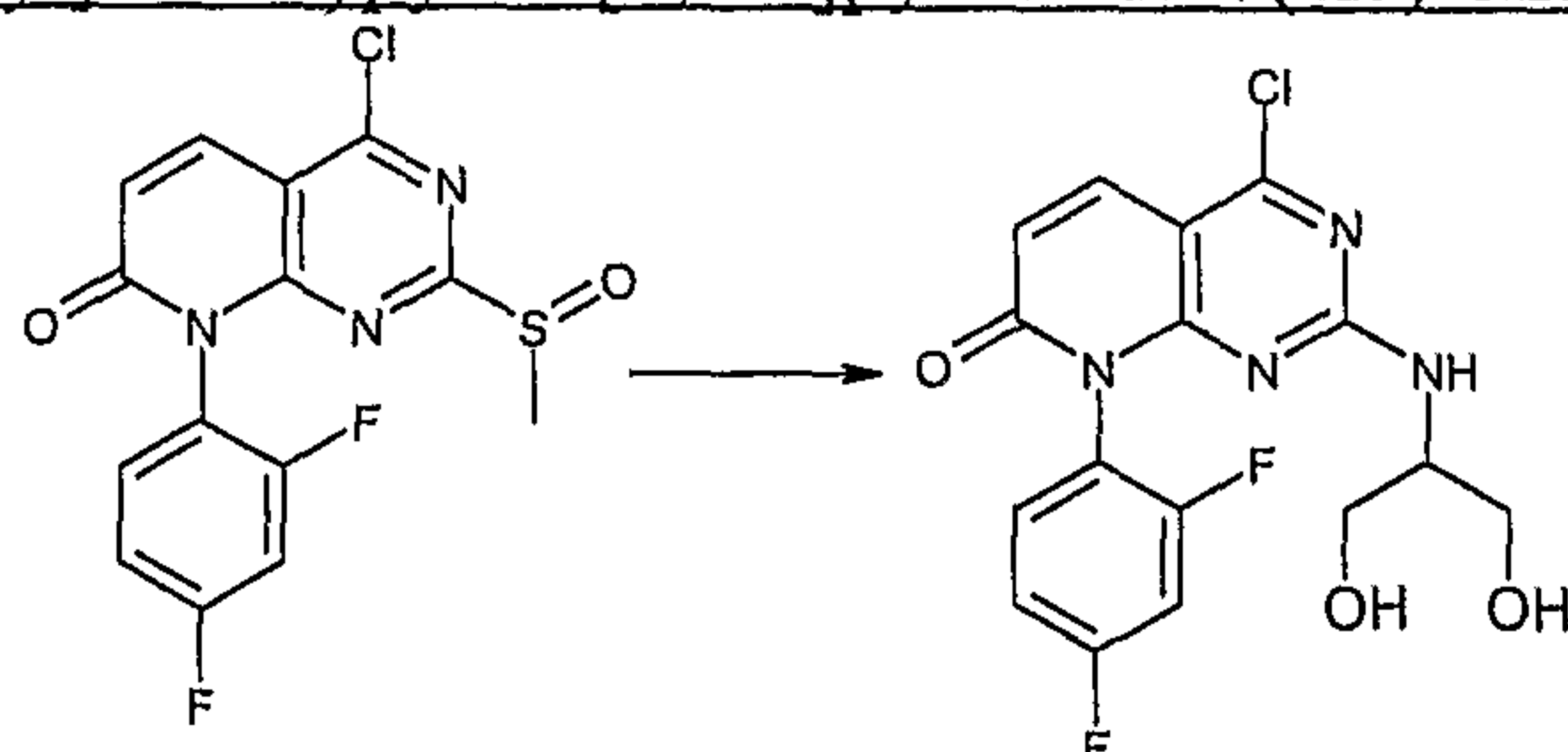
(2 x 100ml). The dried (Na<sub>2</sub>SO<sub>4</sub>) organic phase was filtered and evaporated. Flash chromatography (EtOAc/ Hexane, 1:5) provided the title compound as a cream solid (2.5g, 40%): LC-MS *m/z* 340 (M+H)<sup>+</sup> retention 3.24min.

5 96b) 4-chloro-8-(2,4-difluorophenyl)-2-(methylsulfinyl)pyrido[2,3-*d*]pyrimidin-7(8*H*)-one



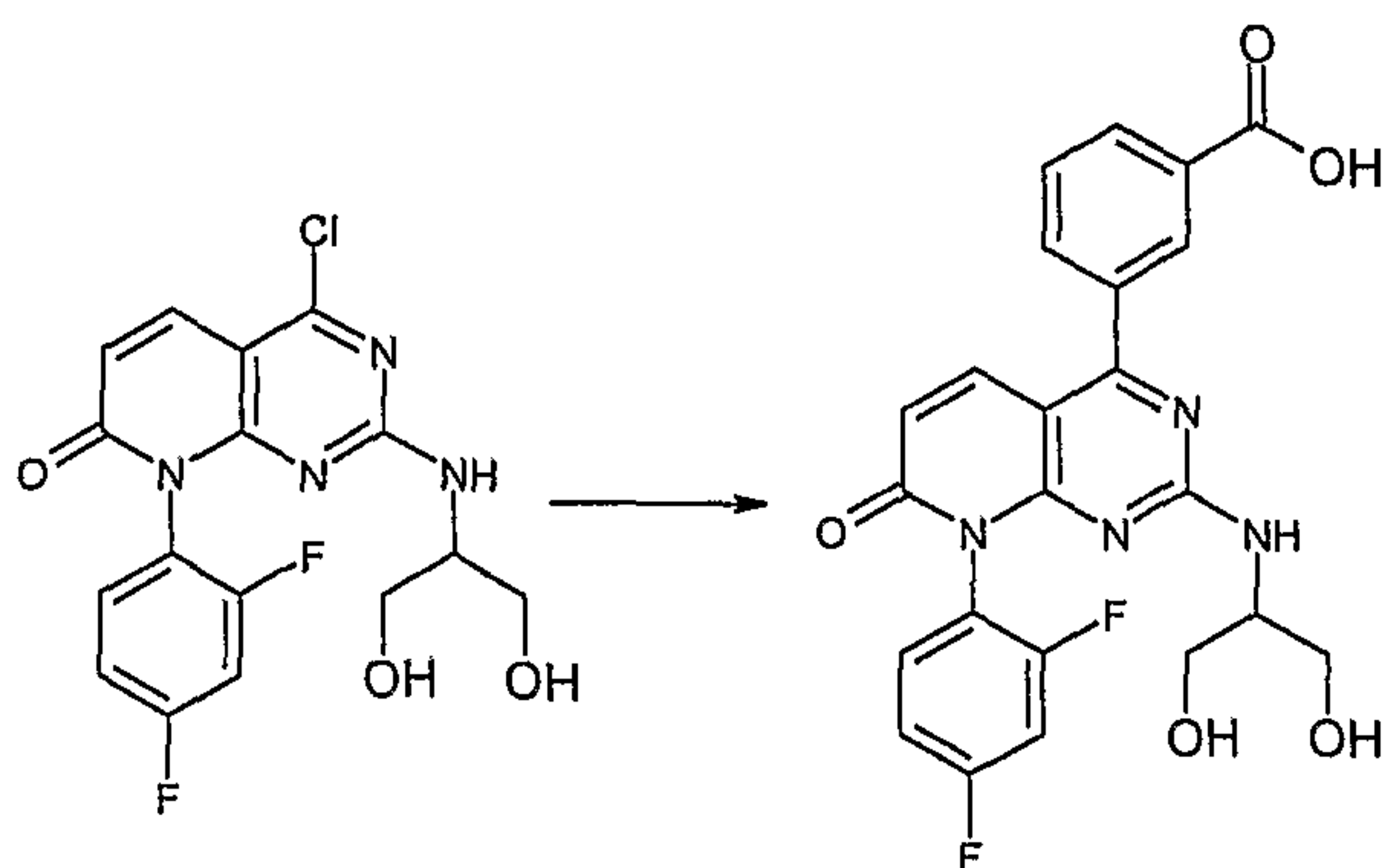
To a solution of 4-chloro-8-(2,4-difluorophenyl)-2-(methylthio)pyrido[2,3-*d*]pyrimidin-7(8*H*)-one (2.5g, 7.6mmol) in DCM (100ml) was added *m*-CPBA (2.2g, 10.2mmol). The mixture was stirred for 10 min and evaporated. Flash chromatography (EtOAc) provided the title compound as a yellow solid (2.1g, 80%): LC-MS *m/z* 356 (M+H)<sup>+</sup> retention 2.43min.

15 96c) 4-chloro-8-(2,4-difluorophenyl)-2-{[2-hydroxy-1-(hydroxymethyl)ethyl]amino}pyrido[2,3-*d*]pyrimidin-7(8*H*)-one



To a solution of 4-chloro-8-(2,4-difluorophenyl)-2-(methylsulfinyl)pyrido[2,3-*d*]pyrimidin-7(8*H*)-one (2.0g, 5.6mmol) in DCM (100ml) was added a solution of serinol (650mg, 7.1mmol) in DMF (5ml). The mixture was stirred for 2h, washed with water (2 x 50ml), dried (Na<sub>2</sub>SO<sub>4</sub>), and evaporated. Flash chromatography (EtOAc/ Hexane, 3:1) provided the title compound as a white solid (1.1g, 50%): LC-MS *m/z* 383 (M+H)<sup>+</sup> retention 2.45 min.

25 96d) 3-(8-(2,4-difluorophenyl)-2-{[2-hydroxy-1-(hydroxymethyl)ethyl]amino}-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl)benzoic acid

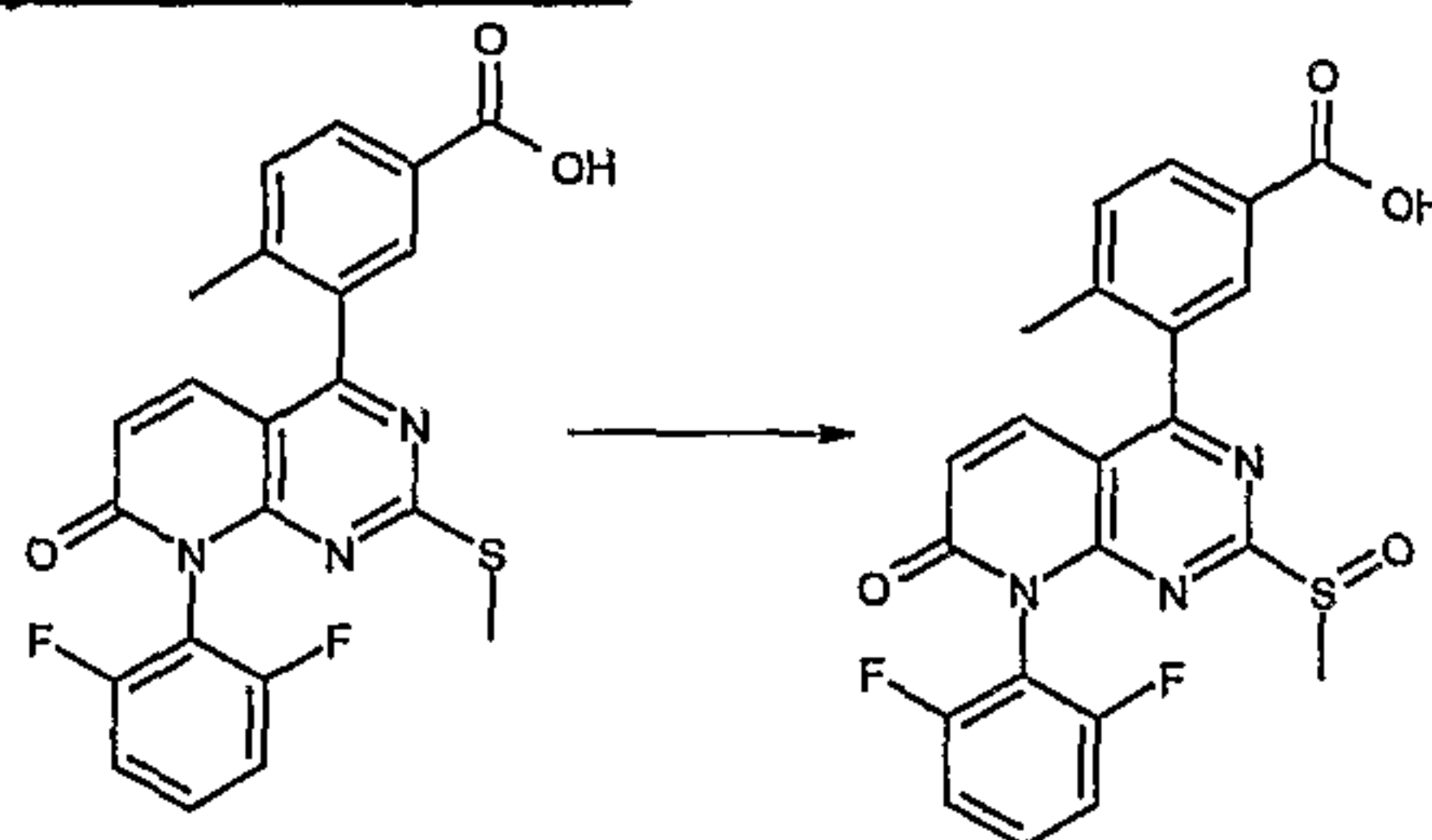


A mixture of 4-chloro-8-(2,4-difluorophenyl)-2-[[2-hydroxy-1-(hydroxymethyl)ethyl]amino]pyrido[2,3-*d*]pyrimidin-7(8*H*)-one (20mg, 0.047mmol), 3-(dihydroxyboranyl)benzoic acid (11.8mg, 0.07mmol), K<sub>2</sub>CO<sub>3</sub> (20mg, 0.14mmol), tetrakis(triphenylphosphine)palladium (2mg, 0.0017mmol), dioxane (1.2ml), and water (0.4ml) was heated in a sealed microwave vessel at 150 degrees for 10 min. The cooled solution was treated with DCM (3ml), passed through a hydrophobic frit directly onto a silica cartridge (2g). The cartridge was eluted with EtOAc followed by EtOAc/MeOH (9:1) to provide the title compound as a brown solid (20mg, 80%) LC-MS *m/z* 469 (M+H)<sup>+</sup> retention 2.73 min.

### Example 97

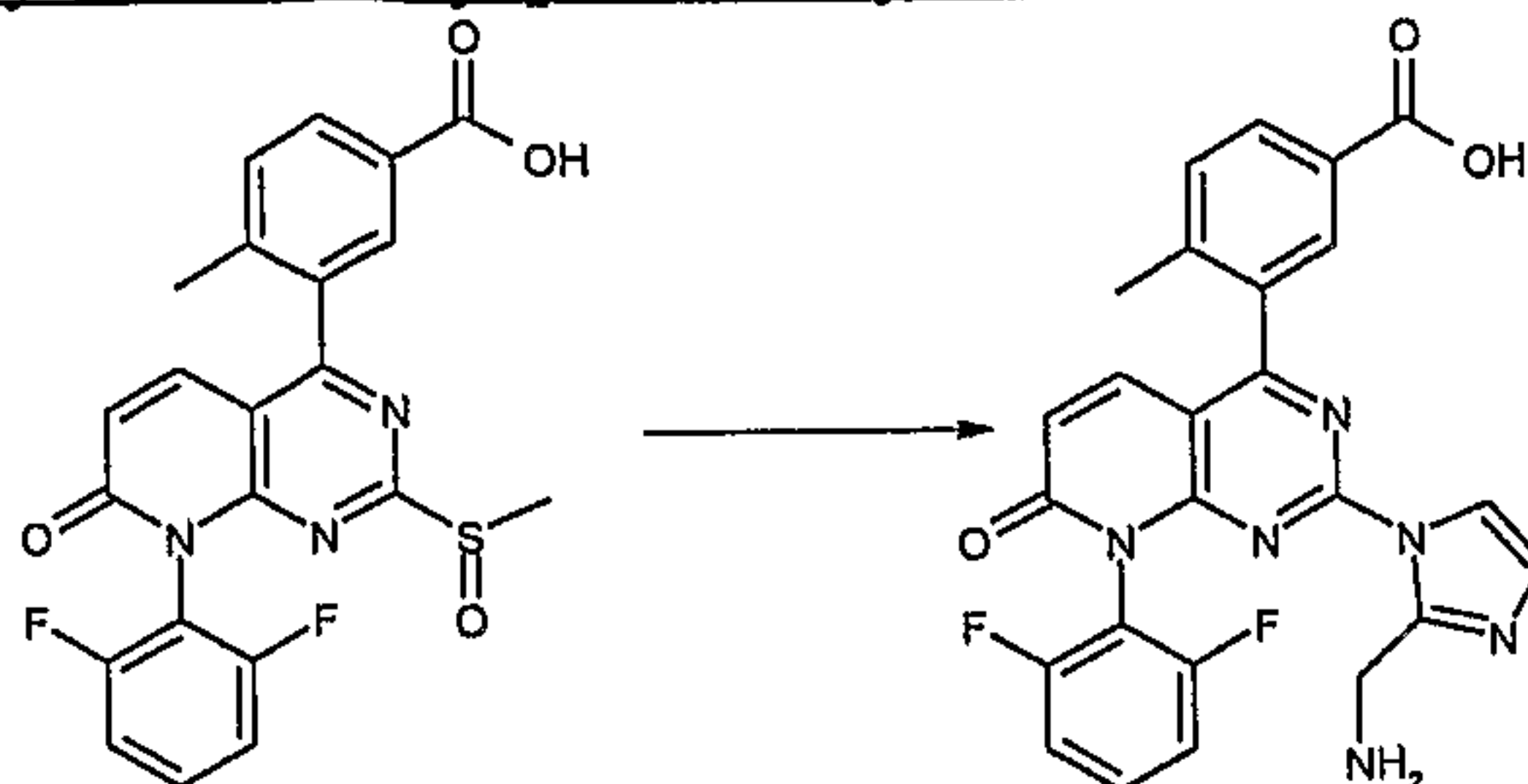
3-[2-[2-(aminomethyl)-1H-imidazol-1-yl]-8-(2,6-difluorophenyl)-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl]-4-methylbenzoic acid trifluoroacetate

97a) 3-[8-(2,6-difluorophenyl)-2-(methylsulfinyl)-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl]-4-methylbenzoic acid



To a solution of 3-[8-(2,6-difluorophenyl)-2-(methylthio)-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl]-4-methylbenzoic acid (30.0 mg, 0.068 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (5.0 ml) was added 3-chlorobenzenecarboxylic acid (23 mg, 0.103 mmol). The resultant mixture was stirred at room temperature 10 mins. Flash chromatography (EtOAc/Hex = 1:1) then provided the title compound (20 mg, 64%). LC-MS (ES) *m/z* 456 (M+H)<sup>+</sup>.

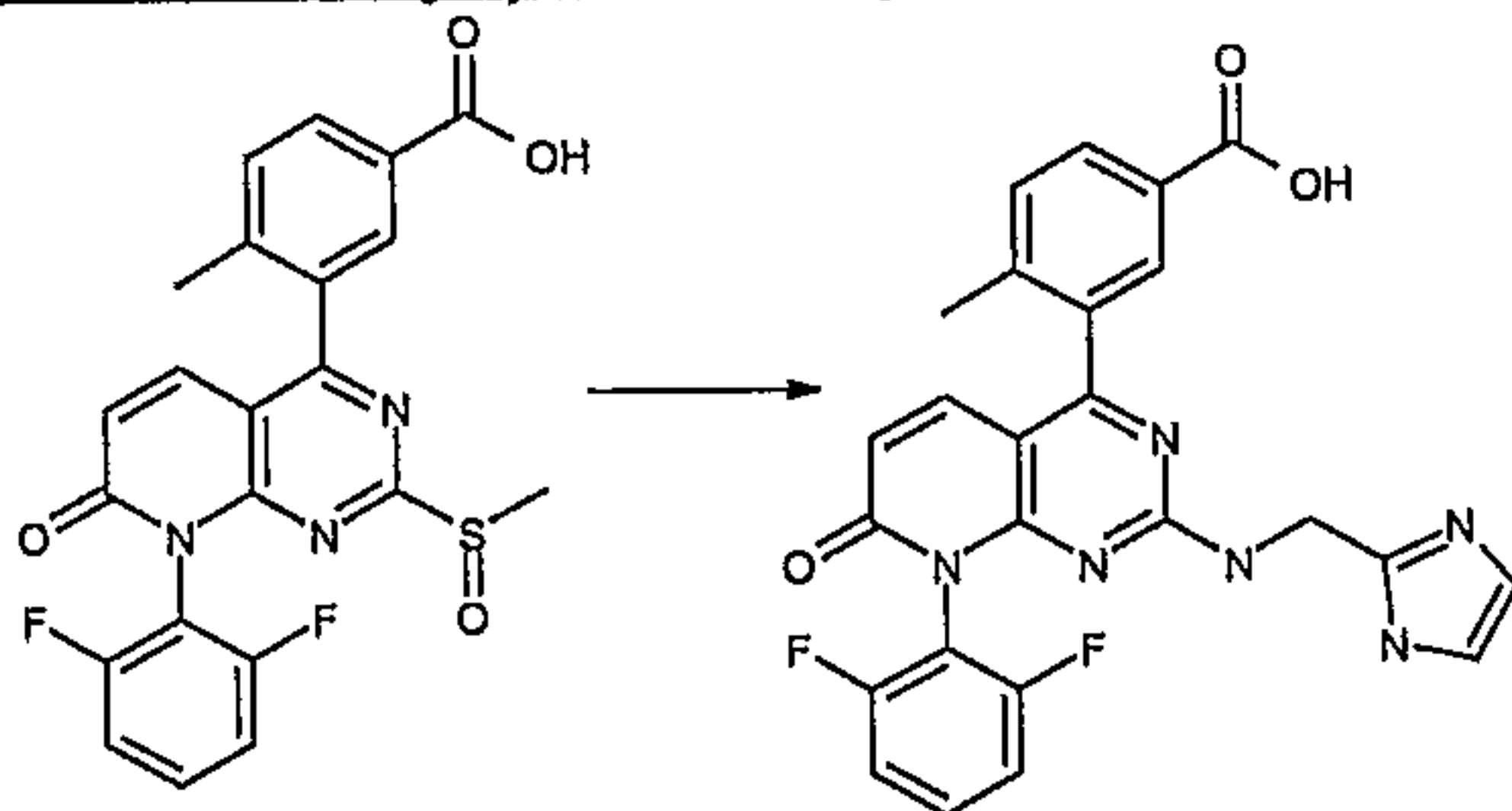
97b) 3-[2-[2-(aminomethyl)-1H-imidazol-1-yl]-8-(2,6-difluorophenyl)-7-oxo-7,8-dihydropyrido[2,3-d]pyrimidin-4-yl]-4-methylbenzoic acid trifluoroacetate



To a solution of 3-[8-(2,6-difluorophenyl)-2-(methylsulfinyl)-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl]-4-methylbenzoic acid (50 mg, 0.09 mmol) in DCM (5 mL) was added (1*H*-imidazol-2-ylmethyl)amine dihydrochloride (75 mg, 0.44 mmol), triethylamine (0.2 mL, 1.44 mmol). The resultant mixture was stirred at room temperature overnight. The mixture was concentrated and purified by HPLC to give the title product as the minor component (8 mg, 15%). LC-MS (ES)  $m/z$  489 ( $M+H$ )<sup>+</sup>; <sup>1</sup>H-NMR(MeOD)  $\delta$  2.39 (s, 3H), 4.26 (s, 2H), 6.86 (d, 1H), 7.08 (s, 1H), 7.38 (t, 2H), 7.64 (d, 1H), 7.77 (m, 2H), 7.82 (s, 1H), 8.11 (s, 1H), 8.20 (d, 1H).

**Example 98**

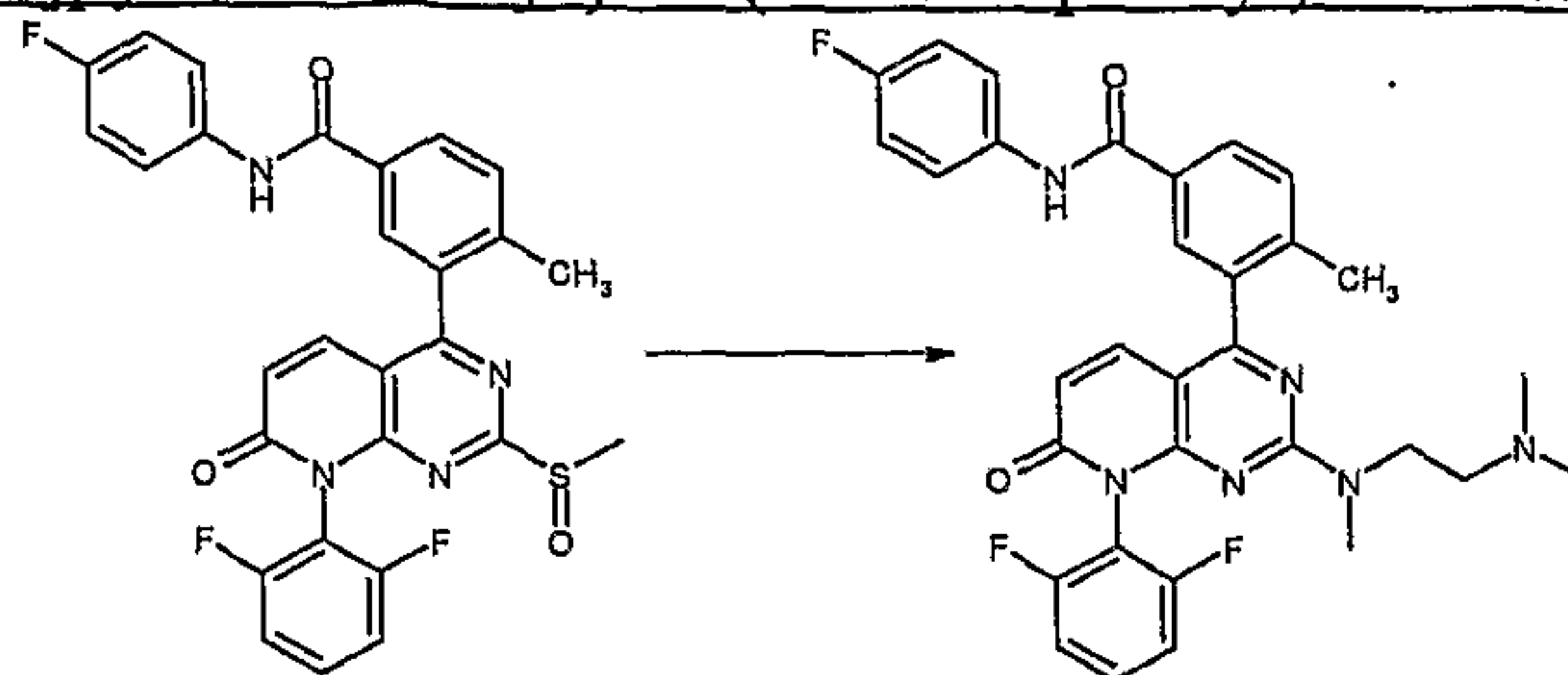
15 3-[8-(2,6-difluorophenyl)-2-[(1*H*-imidazol-2-ylmethyl)amino]-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl]-4-methylbenzoic acid trifluoroacetate



To a solution of 3-[8-(2,6-difluorophenyl)-2-(methylsulfinyl)-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl]-4-methylbenzoic acid (50 mg, 0.09 mmol) in DCM (5 mL) was added (1*H*-imidazol-2-ylmethyl)amine dihydrochloride (75 mg, 0.44 mmol), triethylamine (0.2 mL, 1.44 mmol). The resultant mixture was stirred at room temperature overnight. The mixture was concentrated and purified by HPLC to give the title product as the major component (20 mg, 37%). LC-MS (ES)  $m/z$  489 ( $M+H$ )<sup>+</sup>; <sup>1</sup>H-NMR(MeOD)  $\delta$  2.36 (s, 3H), 4.58 (s, 2H), 6.48 (d, 1H), 7.12 (m, 1H), 7.21 (m, 1H), 7.39 (s, 2H), 7.56 (m, 3H), 8.00 (s, 1H), 8.14 (d, 1H).

**Example 99**

3-{8-(2,6-difluorophenyl)-2-[[2-(dimethylamino)ethyl](methyl)amino]-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl}-*N*-(4-fluorophenyl)-4-methylbenzamide

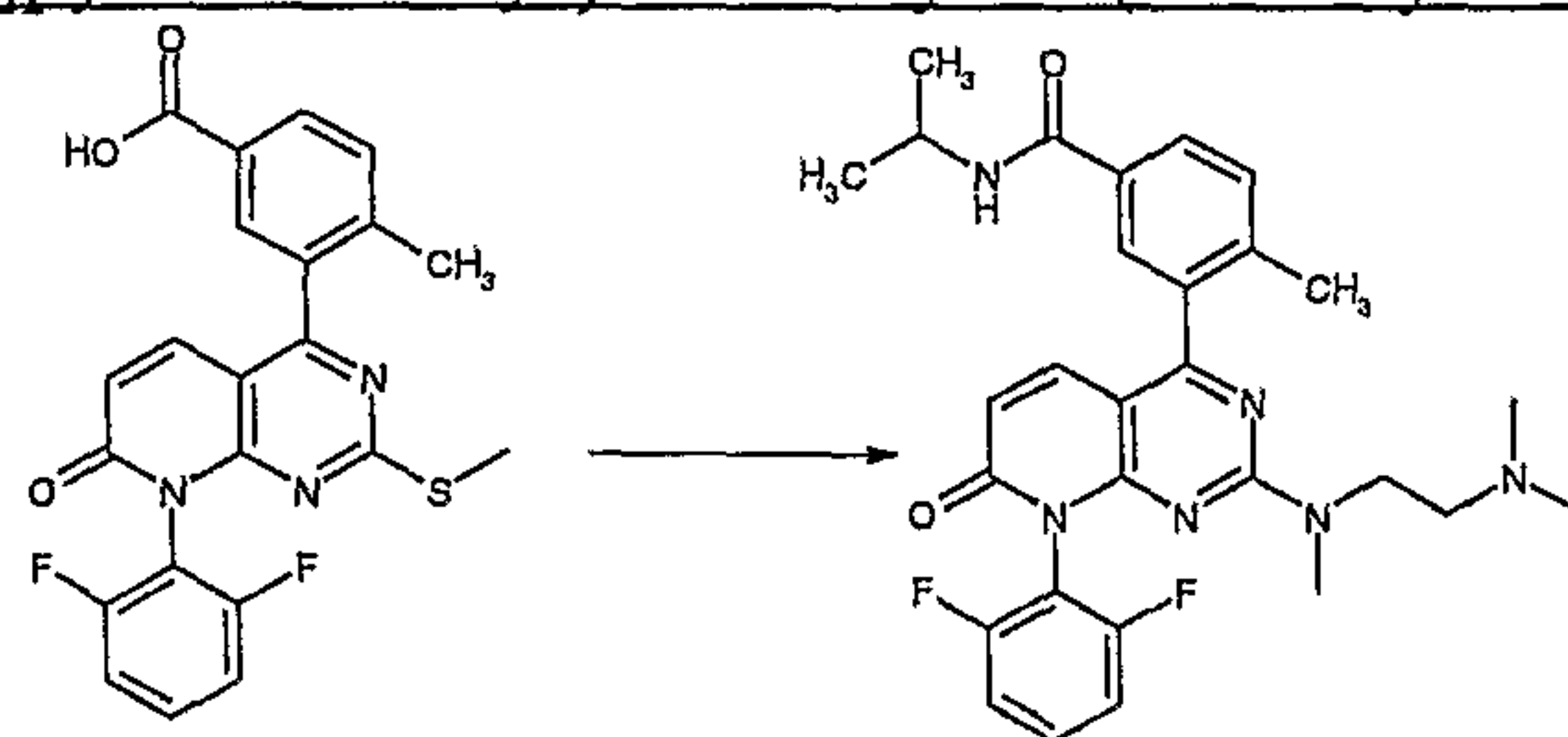


5 To a solution of 3-[8-(2,6-difluorophenyl)-2-(methylsulfinyl)-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl]-*N*-(4-fluorophenyl)-4-methylbenzamide (50 mg, 0.09 mmol) in DCM (10 mL) was added *N,N,N'*-trimethyl-1,2-ethanediamine (0.057 mL, 0.44 mmol). The resultant mixture was stirred at room temperature overnight. The mixture was concentrated under vacuo. Flash chromatography (90%  
10 CH<sub>2</sub>Cl<sub>2</sub> / 7% MeOH / 3% NH<sub>4</sub>OH) then provided the title compound (13 mg, 25%). LC-MS (ES) *m/z* 587 (*M*+*H*)<sup>+</sup>; <sup>1</sup>H-NMR(MeOD) δ 2.09 (s, 3H), 2.24 (s, 3H), 2.38 (s, 3H), 2.41 (m, 1H), 2.59 (m, 1H), 2.91 (s, 1H), 3.22 (s, 2H), 3.52 (m, 1H), 3.88 (m, 1H), 6.38 (d, 1H), 7.13 (m, 2H), 7.25 (m, 2H), 7.52 (d, 1H), 7.62 (m, 2H), 7.71 (m, 2H), 7.92 (s, 1H), 8.06 (d, 1H).

15

**Example 100**

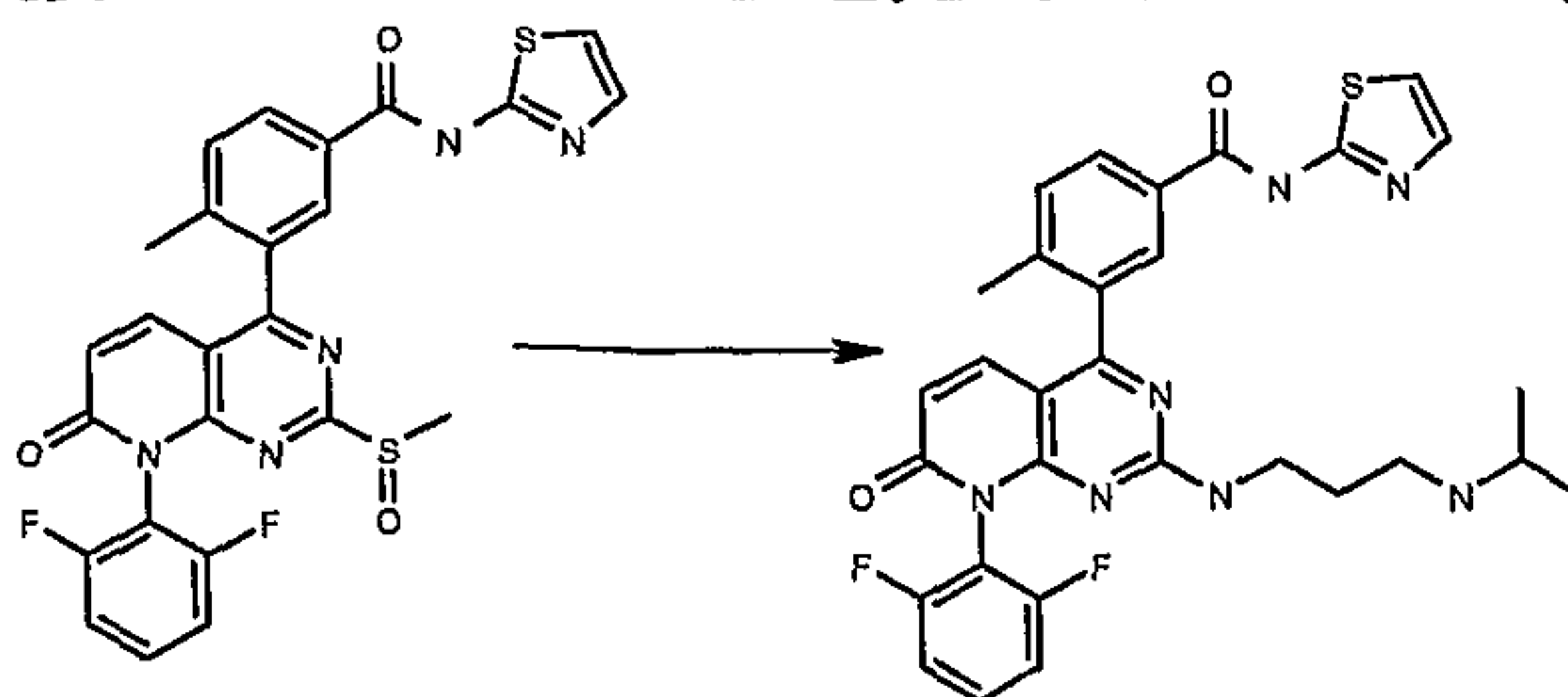
3-{8-(2,6-difluorophenyl)-2-[[2-(dimethylamino)ethyl](methyl)amino]-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl}-4-methyl-*N*-(1-methylethyl)benzamide



20 The title compound was prepared from 3-[8-(2,6-difluorophenyl)-2-(methylthio)-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl]-4-methylbenzoic acid by following the procedures in Example 19 using 2-propanamine for the amide formation and *N,N,N'*-trimethyl-1,2-ethanediamine for the displacement reaction. LC-MS (ES) *m/z* 534 (*M*+*H*)<sup>+</sup>; <sup>1</sup>H-NMR(MeOD) δ 1.27 (d, 6H), 2.08 (m, 3H), 2.23  
25 (m, 3H), 2.32 (s, 3H), 2.38 (m, 1H), 2.52 (m, 1H), 2.90 (s, 1H), 3.21 (s, 2H), 3.50 (m, 1H), 3.83 (m, 1H), 4.23 (m, 1H), 6.36 (d, 1H), 7.27 (t, 2H), 7.48 (d, 1H), 7.52 (d, 1H), 7.62 (m, 1H), 7.79 (s, 1H), 7.93 (d, 1H).

**Example 101**

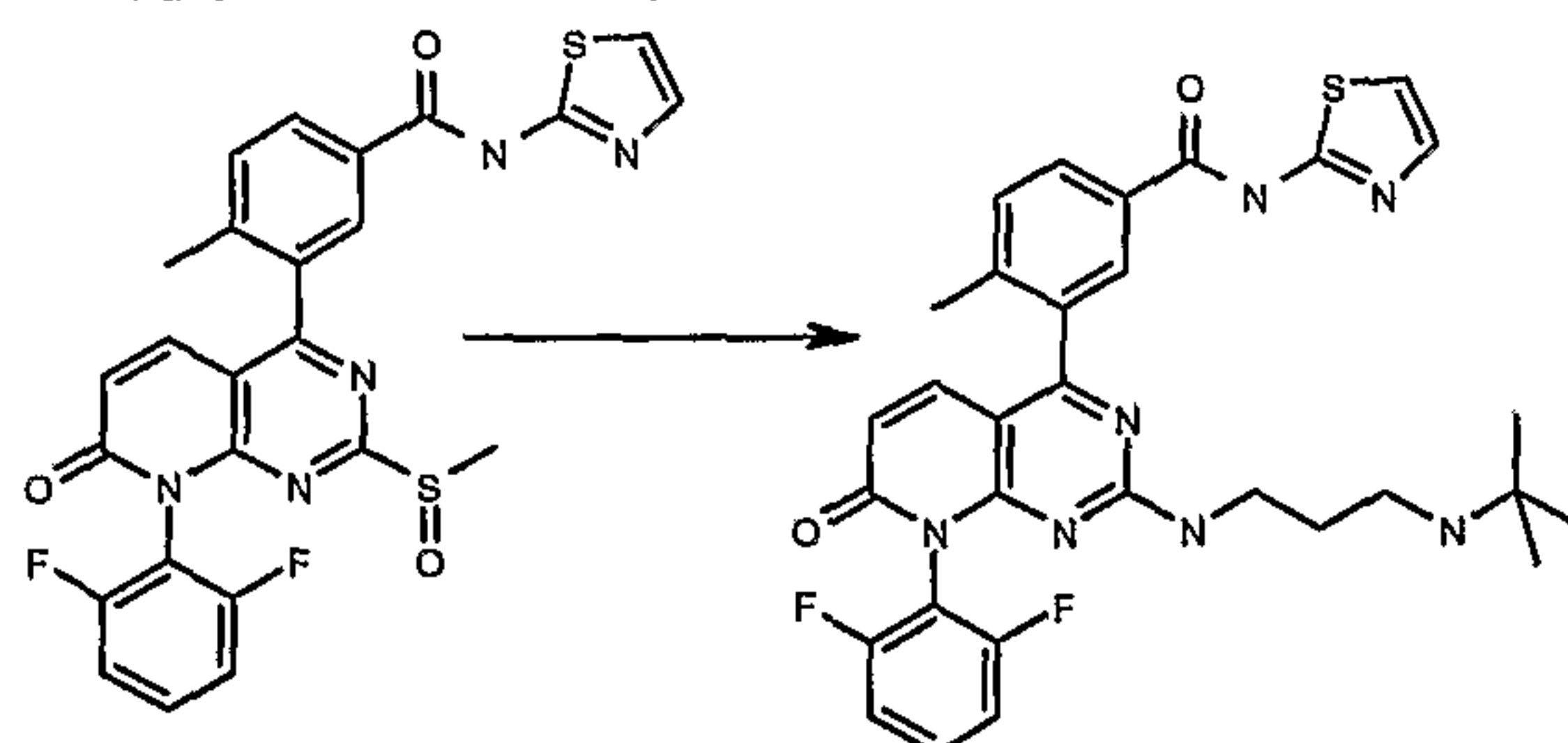
3-[8-(2,6-difluorophenyl)-2-({3-[(1-methylethyl)amino]propyl}amino)-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl]-4-methyl-*N*-1,3-thiazol-2-ylbenzamide



5 The title compound was prepared from 3-[8-(2,6-difluorophenyl)-2-(methylsulfinyl)-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl]-4-methyl-*N*-1,3-thiazol-2-ylbenzamide and *N*-(1-methylethyl)-1,3-propanediamine by following the procedures in Example 79c. LC-MS  $m/z$  590 ( $M + H$ )<sup>+</sup>; <sup>1</sup>H-NMR (MeOD) 1.02 (m, 6 H), 1.68 (m, 2 H), 2.32 (m, 3 H), 2.46 (m, 1 H), 2.66 (m, 1 H), 2.82 (m, 1 H), 3.11  
10 (m, 1 H), 3.46 (m, 1 H), 6.35 (d,  $J = 8.8$  Hz, 1 H), 7.11 (m, 1 H), 7.24 (m, 2 H), 7.46 (m, 2 H), 7.55 (m, 2 H), 8.02 (m, 1 H), 8.11 (d,  $J = 7.6$  Hz, 1 H).

**Example 102**

15 3-[8-(2,6-difluorophenyl)-2-({3-[(1,1-dimethylethyl)amino]propyl}amino)-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl]-4-methyl-*N*-1,3-thiazol-2-ylbenzamide

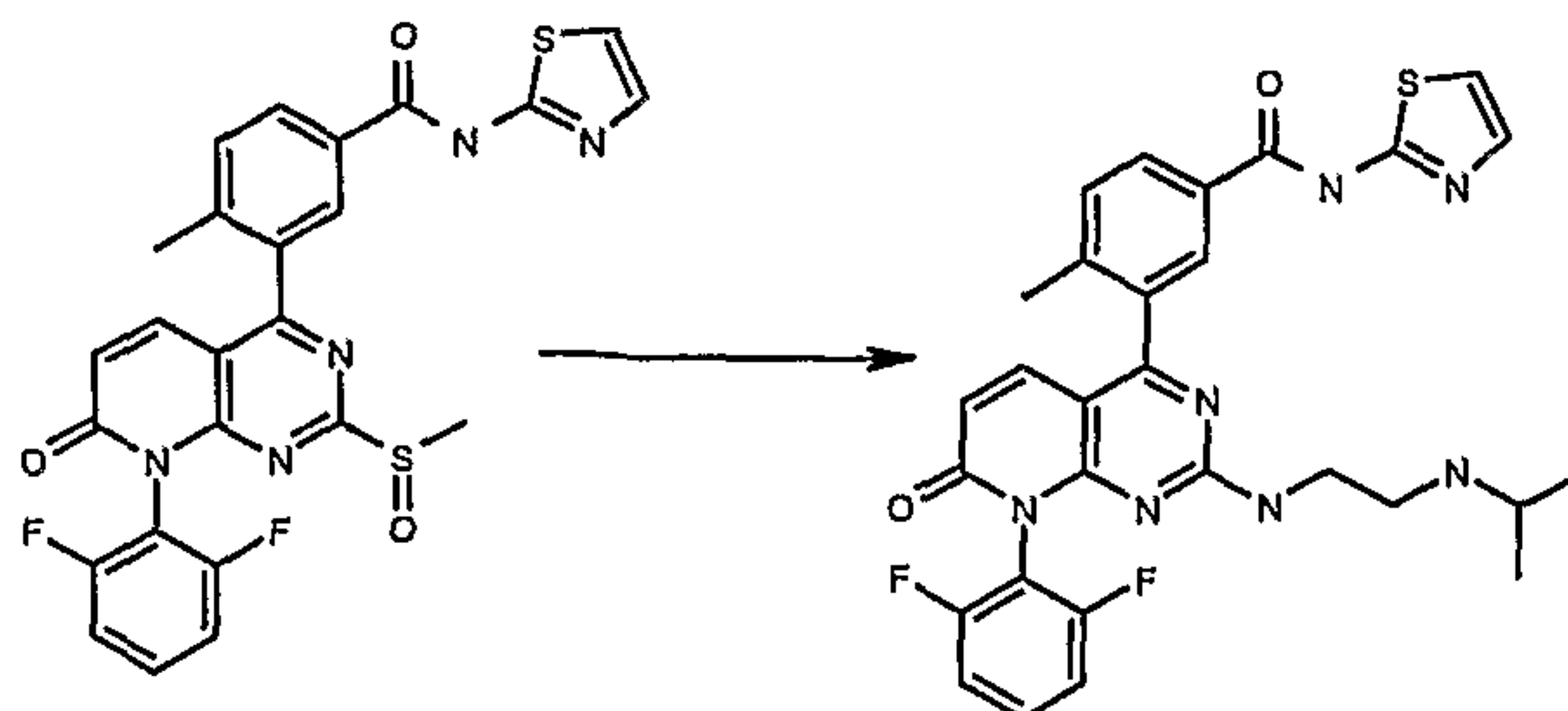


20 The title compound was prepared from 3-[8-(2,6-difluorophenyl)-2-(methylsulfinyl)-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl]-4-methyl-*N*-1,3-thiazol-2-ylbenzamide and *N*-(1,1-dimethylethyl)-1,3-propanediamine by following the procedures in Example 79c. LC-MS  $m/z$  604 ( $M + H$ )<sup>+</sup>; <sup>1</sup>H-NMR (MeOD) 1.09 (m, 9 H), 1.70 (m, 2 H), 2.33 (m, 3 H), 2.47 (m, 1 H), 2.66 (m, 1 H), 3.13 (m, 1 H), 3.47 (m, 1 H), 6.36 (d,  $J = 8.8$  Hz, 1 H), 7.10 (m, 1 H), 7.23 (m, 2 H), 7.47 (m, 2 H), 7.58 (m, 2 H), 8.04 (m, 1 H), 8.13 (d,  $J = 7.6$  Hz, 1 H).

25

**Example 103**

3-[8-(2,6-difluorophenyl)-2-({2-[(1-methylethyl)amino]ethyl}amino)-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl]-4-methyl-*N*-1,3-thiazol-2-ylbenzamide

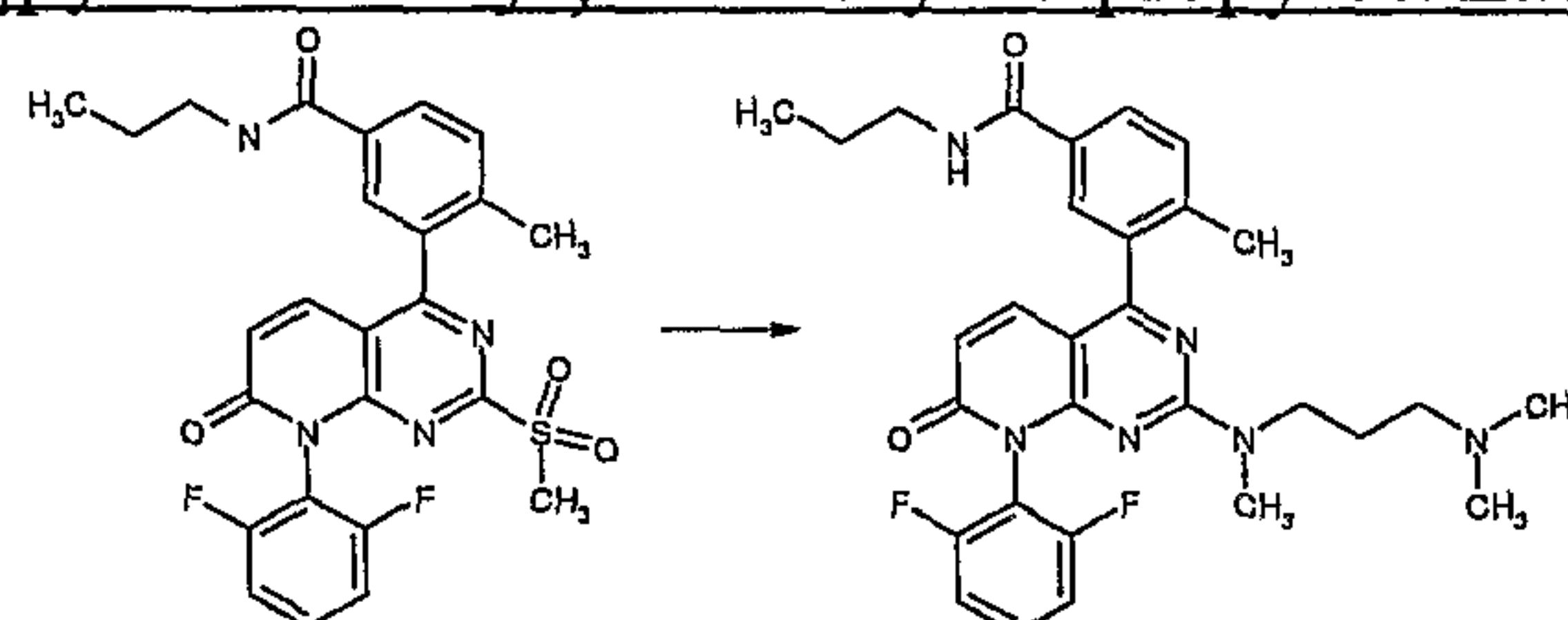


The title compound was prepared from 3-[8-(2,6-difluorophenyl)-2-(methylsulfinyl)-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl]-4-methyl-*N*-1,3-thiazol-2-ylbenzamide and *N*-(1-methylethyl)-1,2-ethanediamine by following the procedures in Example 79c. LC-MS  $m/z$  576 ( $M + H$ )<sup>+</sup>; <sup>1</sup>H-NMR (MeOD) 1.02 (d,  $J = 6.0$  Hz, 6 H), 2.31 (m, 3 H), 2.72 (m, 3 H), 3.23 (m, 1 H), 3.55 (m, 1 H), 6.36 (d,  $J = 8.8$  Hz, 1 H), 7.13 (m, 1 H), 7.24 (m, 2 H), 7.47 (m, 2 H), 7.56 (m, 2 H), 8.00 (s, 1 H), 8.10 (d,  $J = 7.6$  Hz, 1 H).

10

**Example 104**

3-{8-(2,6-difluorophenyl)-2-[[3-(dimethylamino)propyl](methyl)amino]-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl}-4-methyl-*N*-propylbenzamide



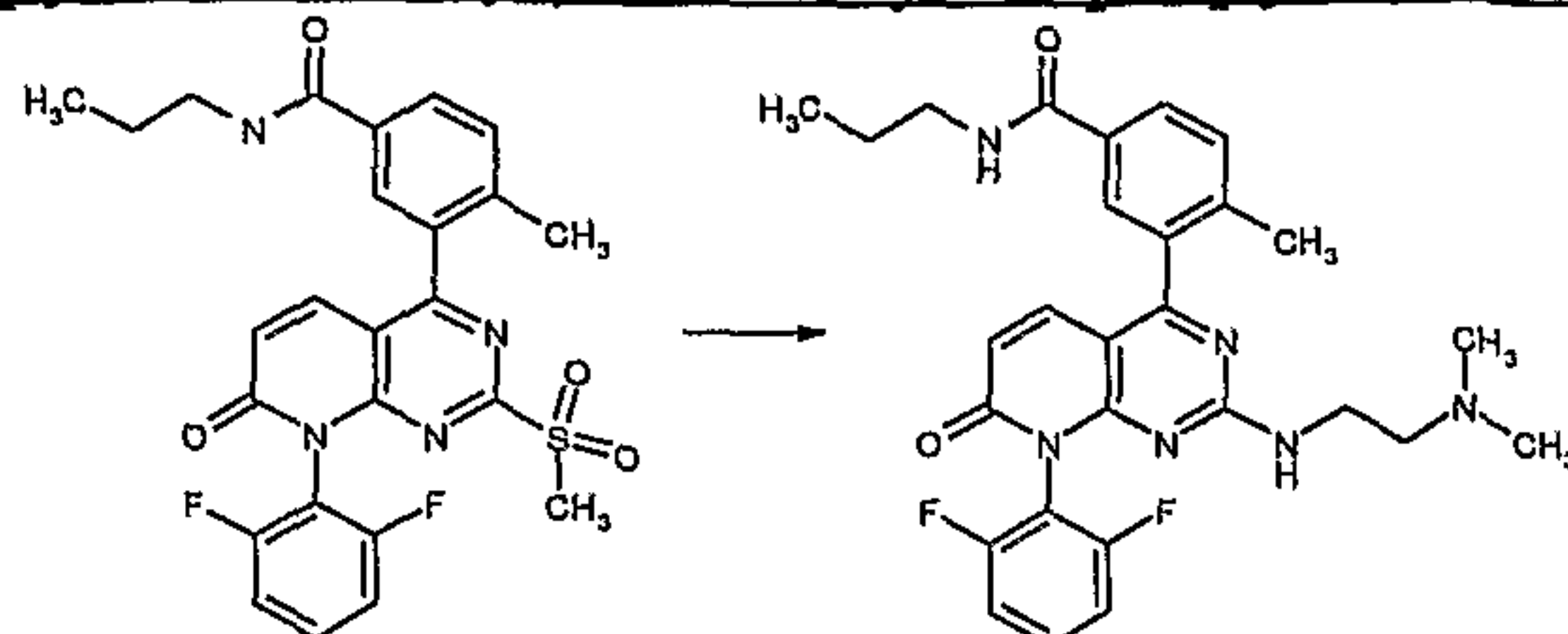
15

20

3-[8-(2,6-difluorophenyl)-2-(methylsulfonyl)-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl]-4-methyl-*N*-propylbenzamide (0.04 g, 0.078 mmol), *N,N,N'*-trimethyl-1,3-propanediamine (0.134 g, 0.115 mmol), and TEA (0.016 g, 0.156 mmol) were combined in CH<sub>2</sub>Cl<sub>2</sub> (5 mL) and stirred under argon at room temperature. The solvents were pumped off *in vacuo*. The residue was flash chromatographed on silica gel (10 g) eluted with CH<sub>2</sub>Cl<sub>2</sub> to 6 : 1 : 0.1, CH<sub>2</sub>Cl<sub>2</sub> : ethanol : NH<sub>4</sub>OH. The compound had an impurity which was removed by filtering through a silica gel plug with 3% MeOH/CH<sub>2</sub>Cl<sub>2</sub> to give the title compound as an off-white amorphous solid. mp 104-109°C. LC-MS  $m/z$  549 ( $M + H$ )<sup>+</sup>, 1.65 min (ret time).

**Example 105**

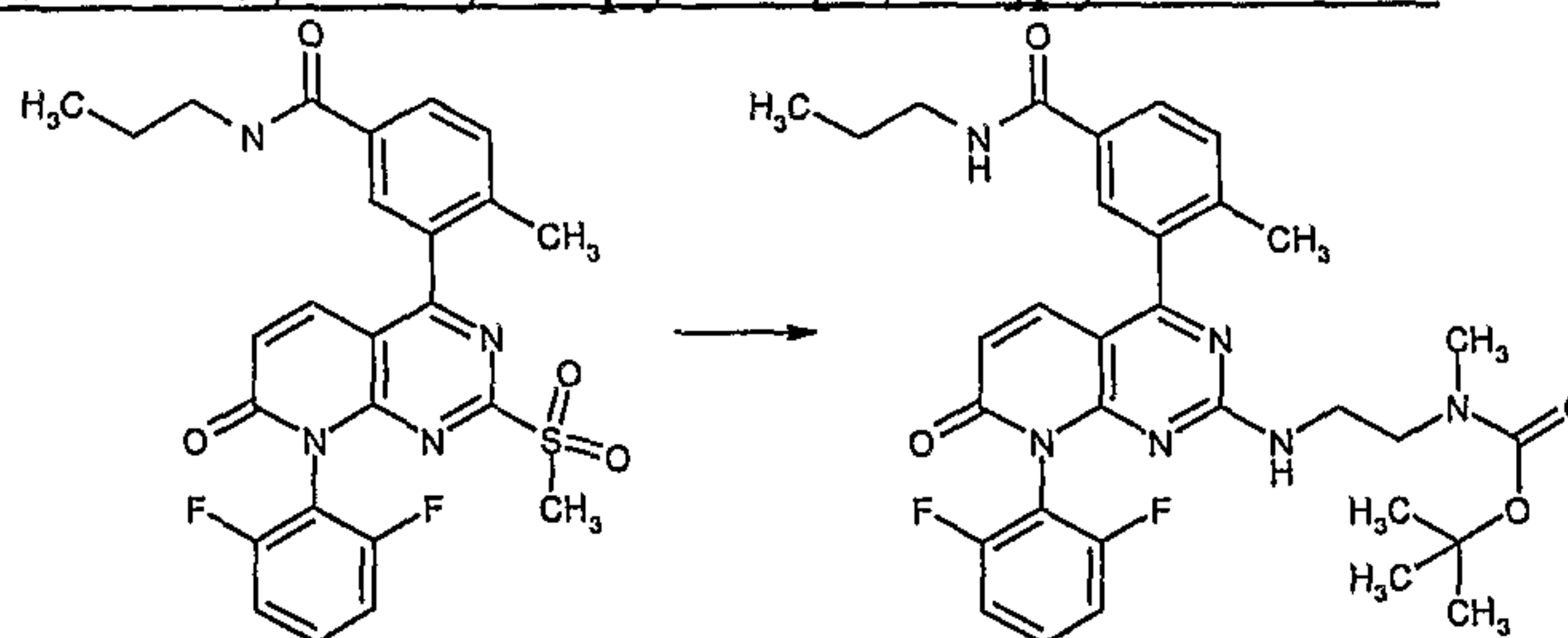
3-(8-(2,6-difluorophenyl)-2-{[2-(dimethylamino)ethyl]amino}-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl)-4-methyl-*N*-propylbenzamide



5            3-[8-(2,6-difluorophenyl)-2-(methylsulfonyl)-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl]-4-methyl-*N*-propylbenzamide (0.07 g, 0.13mmol), *N,N*-dimethylethylenediamine (0.0173 g, 0.15 mmol), and TEA (0.026g, 0.26 mmol) were combined in CH<sub>2</sub>Cl<sub>2</sub> (5 mL) and stirred under argon at room temperature for 1 h. The solvents were pumped off *in vacuo*. The residue was flash chromatographed on silica gel (10 g) eluted with CH<sub>2</sub>Cl<sub>2</sub> to 6 : 1 : 0.1, CH<sub>2</sub>Cl<sub>2</sub> : ethanol : NH<sub>4</sub>OH to  
10            give the title compound as a white amorphous solid. mp 139-142°C. LC-MS *m/z* 521 (M+H)<sup>+</sup>, 1.61 min (ret time).

**Example 106**

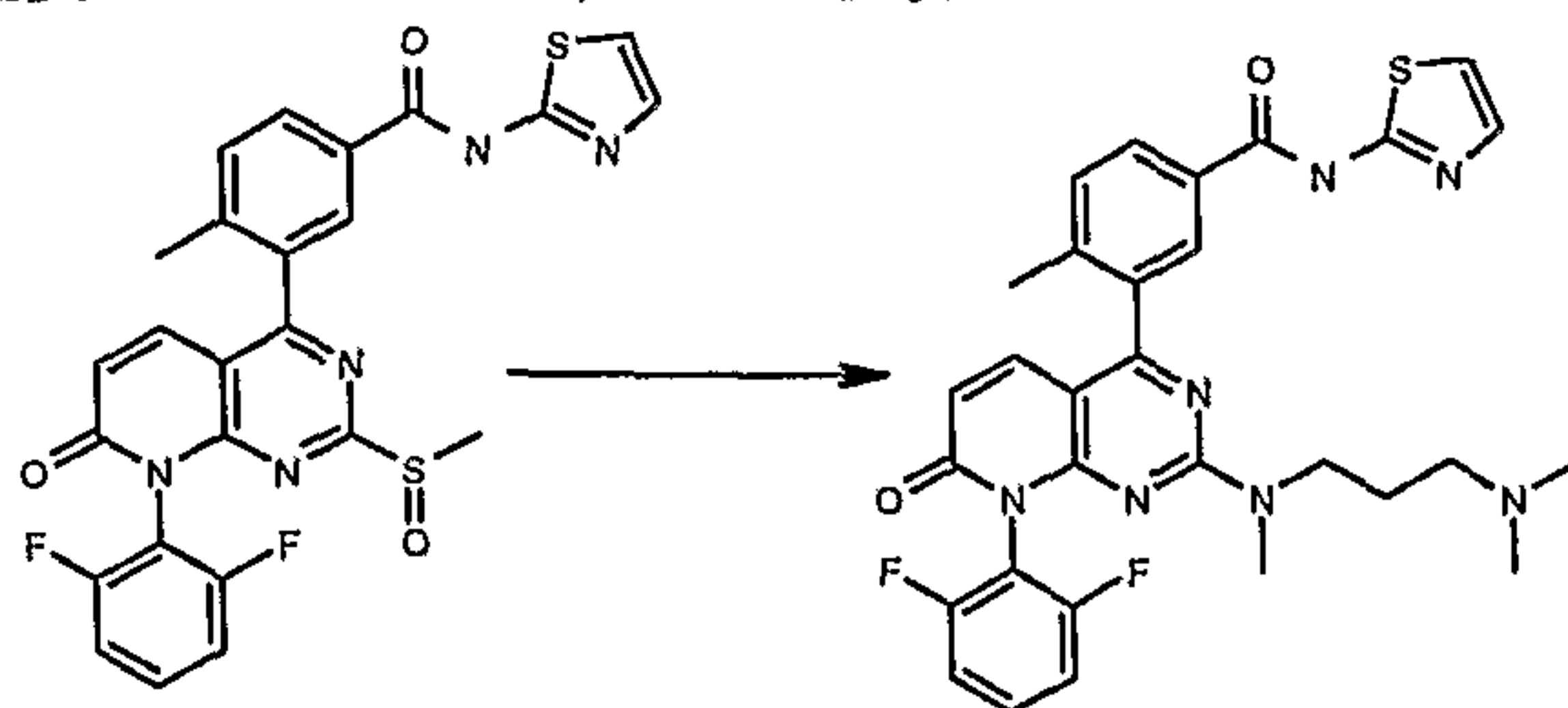
15            1,1-dimethylethyl {2-[(8-(2,6-difluorophenyl)-4-{2-methyl-5-[(propylamino)carbonyl]phenyl}-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-2-



yl)amino]ethyl} methylcarbamate  
              3-[8-(2,6-difluorophenyl)-2-(methylsulfonyl)-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl]-4-methyl-*N*-propylbenzamide (1.59 g, 3.1 mmol), was dissolved  
20            in CH<sub>2</sub>Cl<sub>2</sub> (140 mL) and stirred under argon at room temperature. 1,1-dimethylethyl (2-aminoethyl)methylcarbamate (0.806 g, 4.65 mmol), and TEA (0.87mL, 6.2 mmol) were combined in CH<sub>2</sub>Cl<sub>2</sub> (10 mL) and added to the solution of the sulfone. The resulting reaction mixture was stirred under argon overnight. The solvents were pumped off *in vacuo*. The residue was flash chromatographed on silica gel (150 g)  
25            eluted with 0-40% EtOAc/CH<sub>2</sub>Cl<sub>2</sub> to give the title compound as a white amorphous solid. mp 115-118°C. LC-MS *m/z* 607 (M+H)<sup>+</sup>, 2.27 min (ret time).

**Example 107**

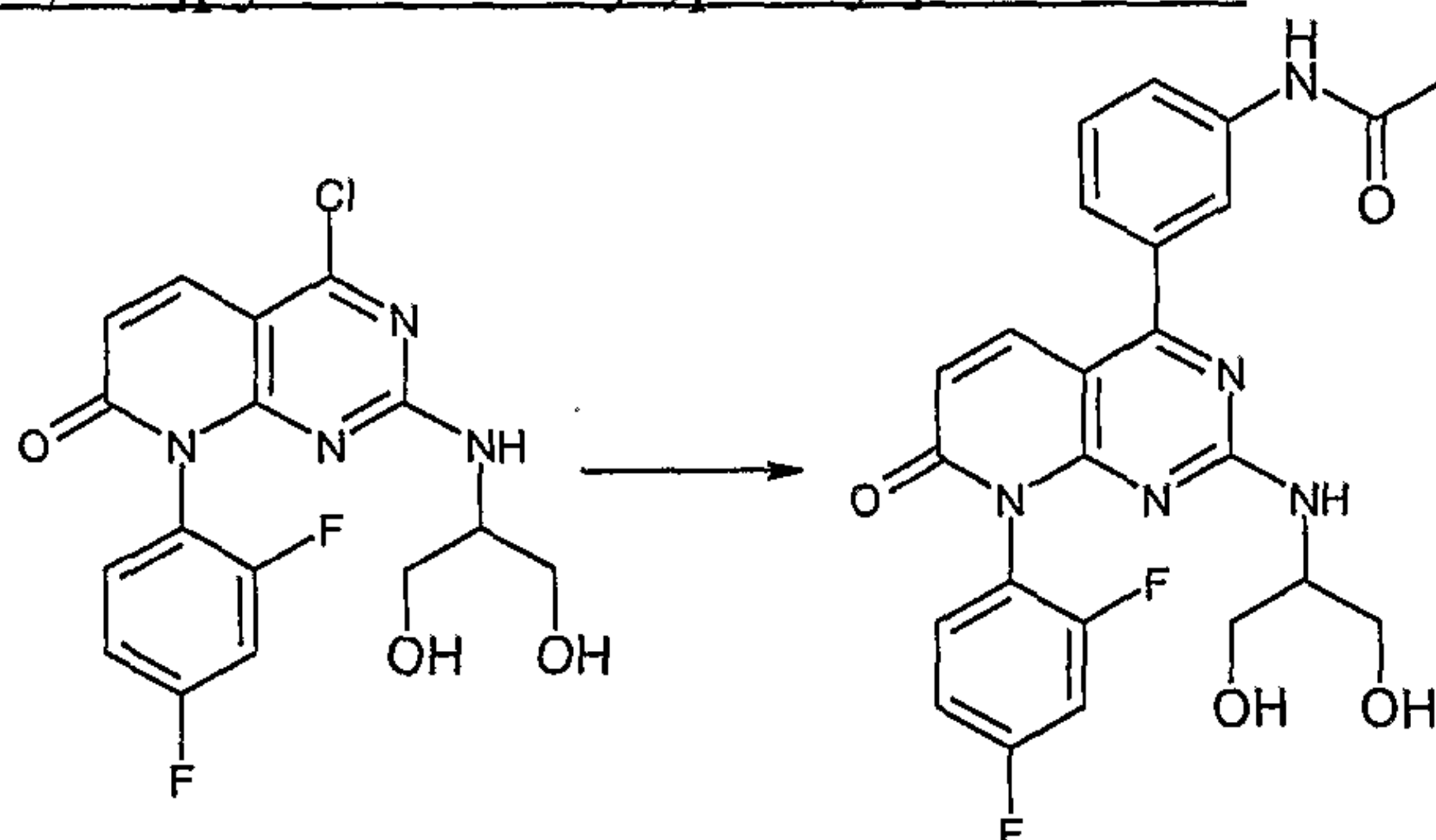
3-{8-(2,6-difluorophenyl)-2-[[3-(dimethylamino)propyl](methyl)amino]-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl}-4-methyl-*N*-1,3-thiazol-2-ylbenzamide



5 The title compound was prepared from 3-[8-(2,6-difluorophenyl)-2-(methylsulfinyl)-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl]-4-methyl-*N*-1,3-thiazol-2-ylbenzamide and *N,N,N'*-trimethyl-1,3-propanediamine by following the procedures in Example 79c. LC-MS  $m/z$  590 ( $M + H$ )<sup>+</sup>; <sup>1</sup>H-NMR (MeOD) 1.70 (m, 2 H), 2.04 (m, 2 H), 2.20 (s, 6 H), 2.36 (s, 3 H), 2.89-3.21 (m, 3 H), 3.36-3.70 (m, 2  
10 H), 6.36 (d,  $J = 8.4$  Hz, 1 H), 7.16 (m, 1 H), 7.27 (m, 2 H), 7.50 (m, 2 H), 7.59 (m, 2 H), 8.01 (s, 1 H), 8.13 (m, 1 H).

**Example 108**

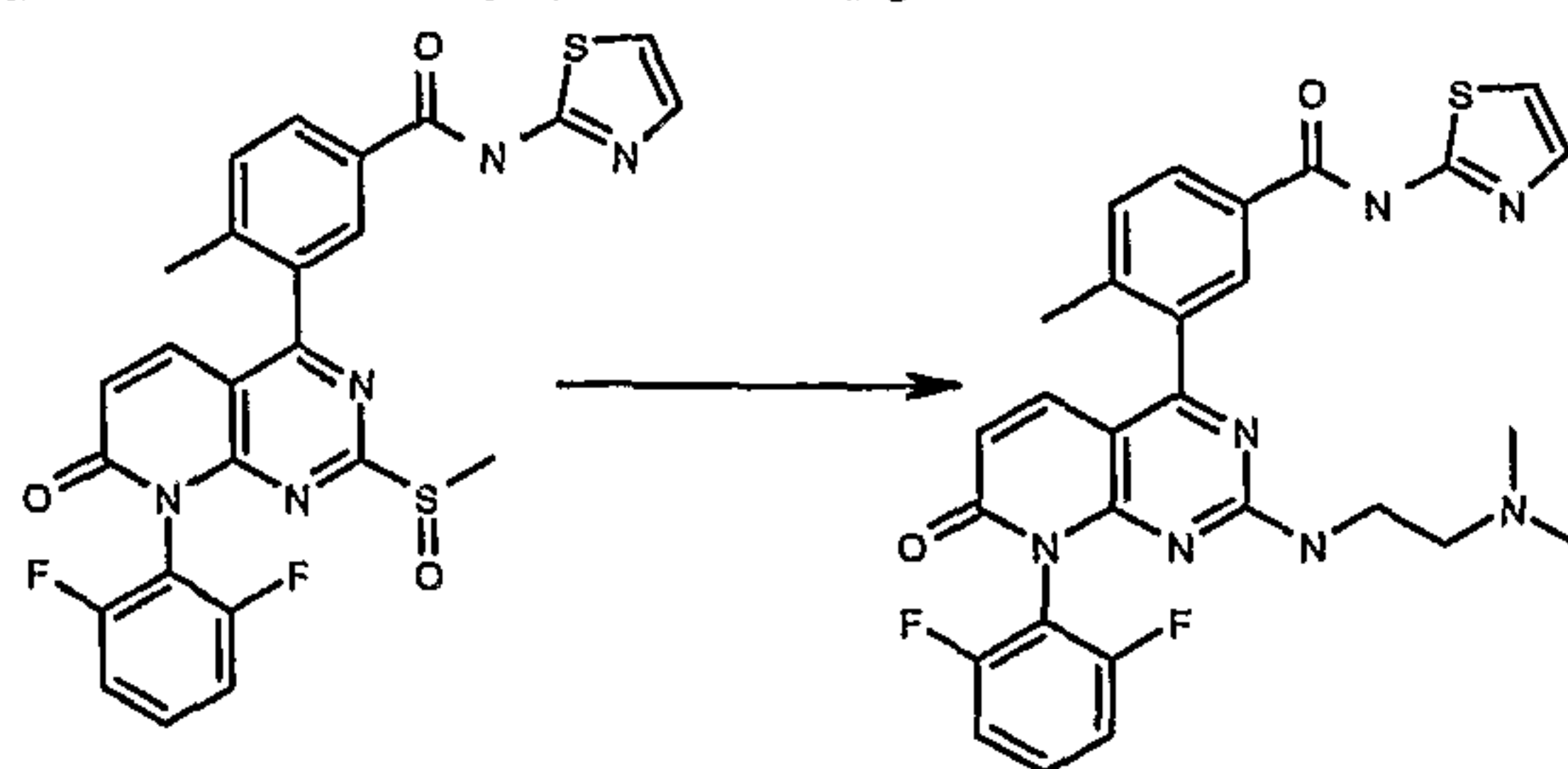
*N*-[3-(8-(2,4-difluorophenyl)-2-{[2-hydroxy-1-(hydroxymethyl)ethyl]amino}-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl)phenyl]acetamide



The title compound was prepared by following the procedure in example 96d from 4-chloro-8-(2,4-difluorophenyl)-2-{[2-hydroxy-1-(hydroxymethyl)ethyl]amino}pyrido[2,3-*d*]pyrimidin-7(8*H*)-one and [3-(acetylamino)phenyl]boronic acid: LC-MS  $m/z$  482 ( $M+H$ )<sup>+</sup>, retention 2.69 min.  
20

**Example 109**

3-(8-(2,6-difluorophenyl)-2-[[2-(dimethylamino)ethyl]amino]-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl)-4-methyl-*N*-1,3-thiazol-2-ylbenzamide

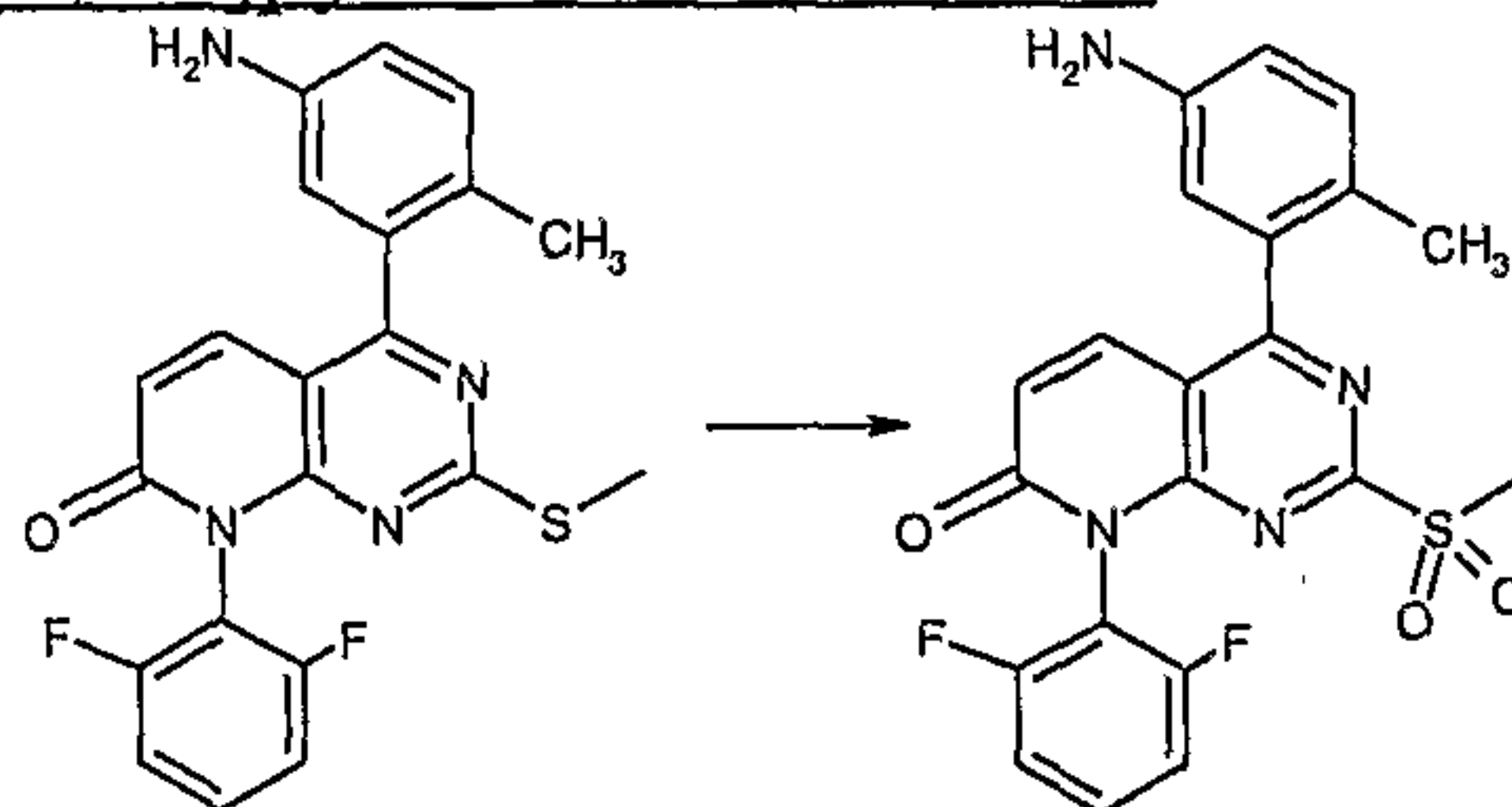


5 The title compound was prepared from 3-[8-(2,6-difluorophenyl)-2-(methylsulfinyl)-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl]-4-methyl-*N*-1,3-thiazol-2-ylbenzamide and *N,N*-dimethyl-1,2-ethanediamine by following the procedures in Example 79c. LC-MS  $m/z$  562 ( $M + H$ )<sup>+</sup>; <sup>1</sup>H-NMR (MeOD) 2.15 (m, 6 H), 2.36 (m, 4 H), 2.65 (m, 1 H), 3.27 (m, 2 H), 6.38 (d,  $J = 8.4$  Hz, 1 H), 7.17 (m, 10 1 H), 7.25 (m, 2 H), 7.49 (m, 2 H), 7.59 (m, 2 H), 8.00 (s, 1 H), 8.11 (d,  $J = 8.0$  Hz, 1 H).

**Example 110**

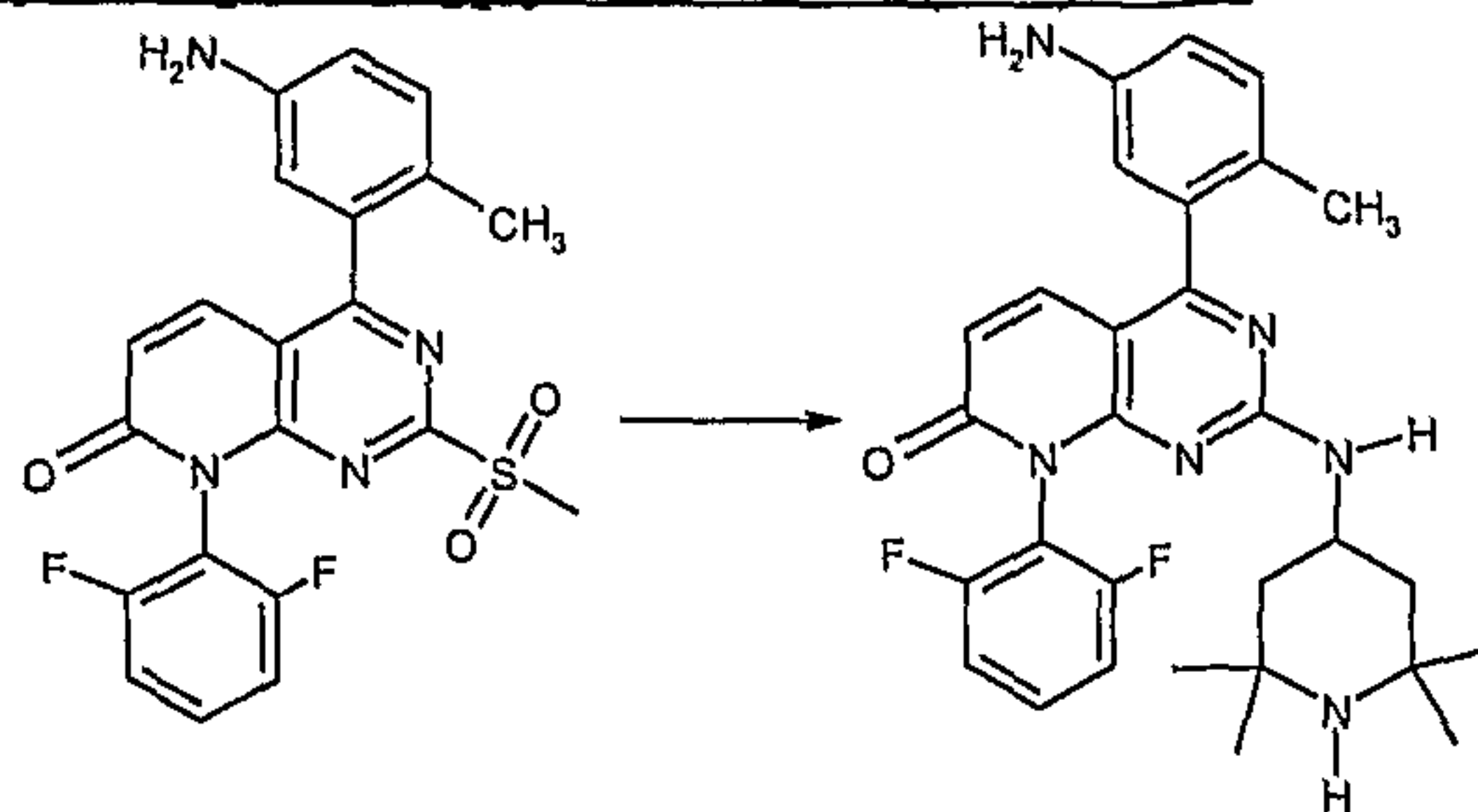
15 4-(5-amino-2-methylphenyl)-8-(2,6-difluorophenyl)-2-[(2,2,6,6-tetramethyl-4-piperidiny)amino]pyrido[2,3-*d*]pyrimidin-7(8*H*)-one

110a) 4-(5-amino-2-methylphenyl)-8-(2,6-difluorophenyl)-2-(methylsulfonyl)pyrido[2,3-*d*]pyrimidin-7(8*H*)-one



20 To a solution of 4-(5-amino-2-methylphenyl)-8-(2,6-difluorophenyl)-2-(methylthio)pyrido[2,3-*d*]pyrimidin-7(8*H*)-one (170.0 mg, 0.41 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (20.0 mL) was added *m*-CPBA (224.0 mg, 1.0 mmol). The reaction mixture was stirred for 12 h at room temperature and concentrated. It was diluted with H<sub>2</sub>O (5.0 mL) and EtOAc (25.0 mL). The organic layer was separated and the aqueous layer 25 was extracted with EtOAc (3x10 mL). The combined organic layers were washed with saturated aq. NaCl, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated. Purification via the CombiFlash system (hexane : EtOAc = 4:1) then afforded the title compound (190.0mg, 94%): LC-MS  $m/z$  443 ( $M+H$ )<sup>+</sup>, 2.12min (ret. time)

110b) 4-(5-amino-2-methylphenyl)-8-(2,6-difluorophenyl)-2-[(2,2,6,6-tetramethyl-4-piperidiny]amino]pyrido[2,3-d]pyrimidin-7(8H)-one

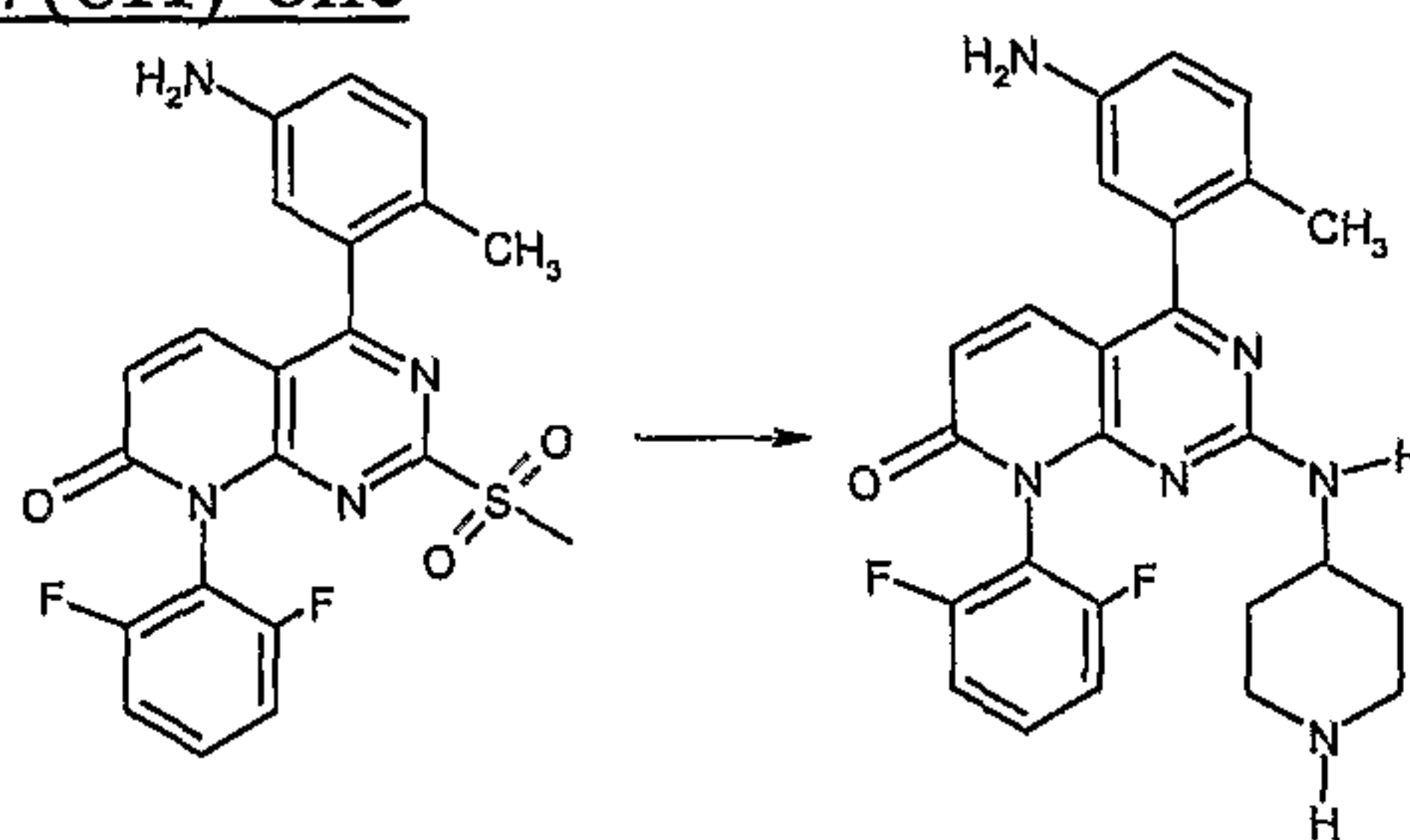


- 5 The title compound was prepared as described in Example 1d from 4-(5-amino-2-methylphenyl)-8-(2,6-difluorophenyl)-2-(methylsulfonyl)pyrido[2,3-d]pyrimidin-7(8H)-one and 2,2,6,6-tetramethyl-4-piperidinamine: LC-MS  $m/z$  519 ( $M+H$ )<sup>+</sup>, 1.8 min (ret time).

10

**Example 111**

4-(5-amino-methylphenyl)-8-(2,6-difluorophenyl)-2-(4-piperidinylamino)-pyrido[2,3-d]pyrimidin-7(8H)-one



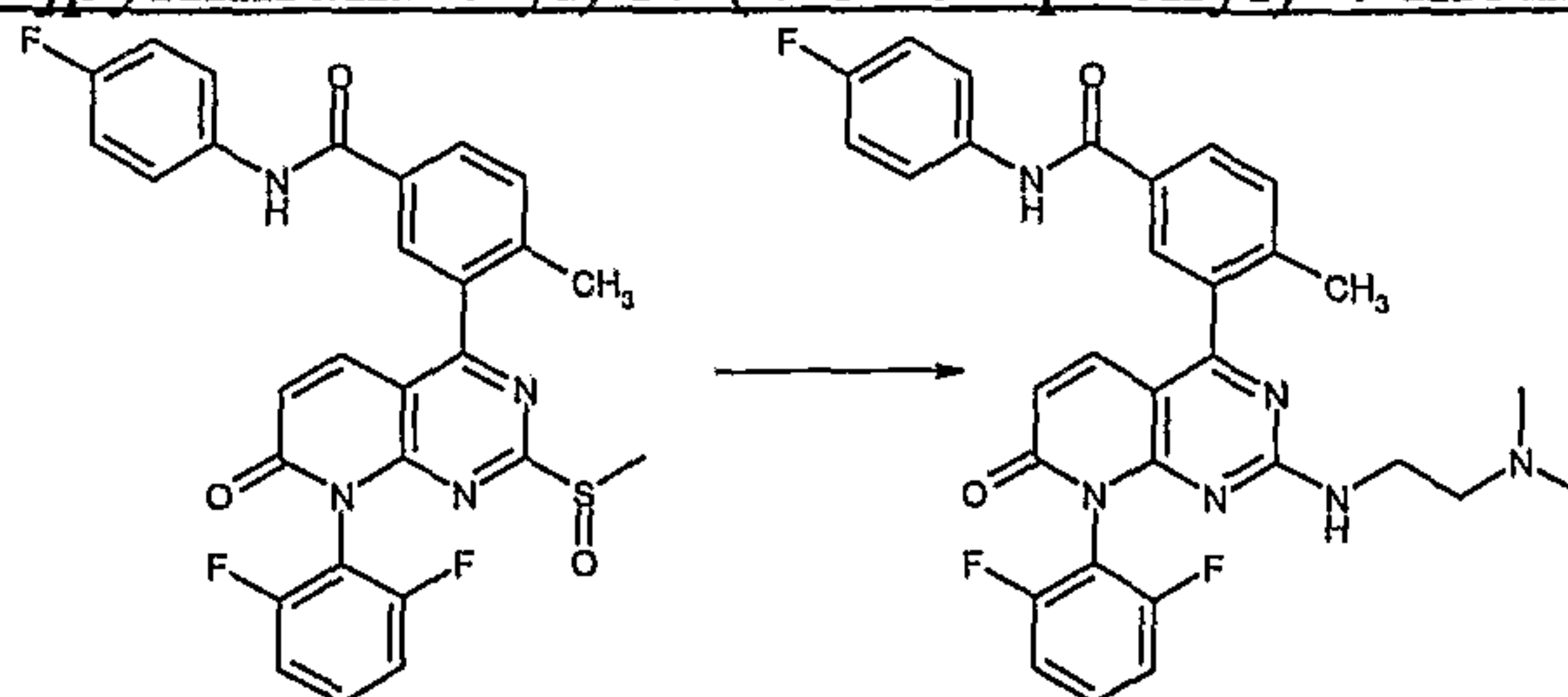
15

The title compound was prepared as described in Example 2 from 4-(5-amino-2-methylphenyl)-8-(2,6-difluorophenyl)-2-(methylsulfonyl)pyrido[2,3-d]pyrimidin-7(8H)-one and 1,1-dimethylethyl 4-amino-1-piperidinecarboxylate. LC-MS  $m/z$  463 ( $M+H$ )<sup>+</sup>, 1.73 min (ret time).

**Example 112**

20

3-(8-(2,6-difluorophenyl)-2-{[2-(dimethylamino)ethyl]amino}-7-oxo-7,8-dihydropyrido[2,3-d]pyrimidin-4-yl)-N-(4-fluorophenyl)-4-methylbenzamide

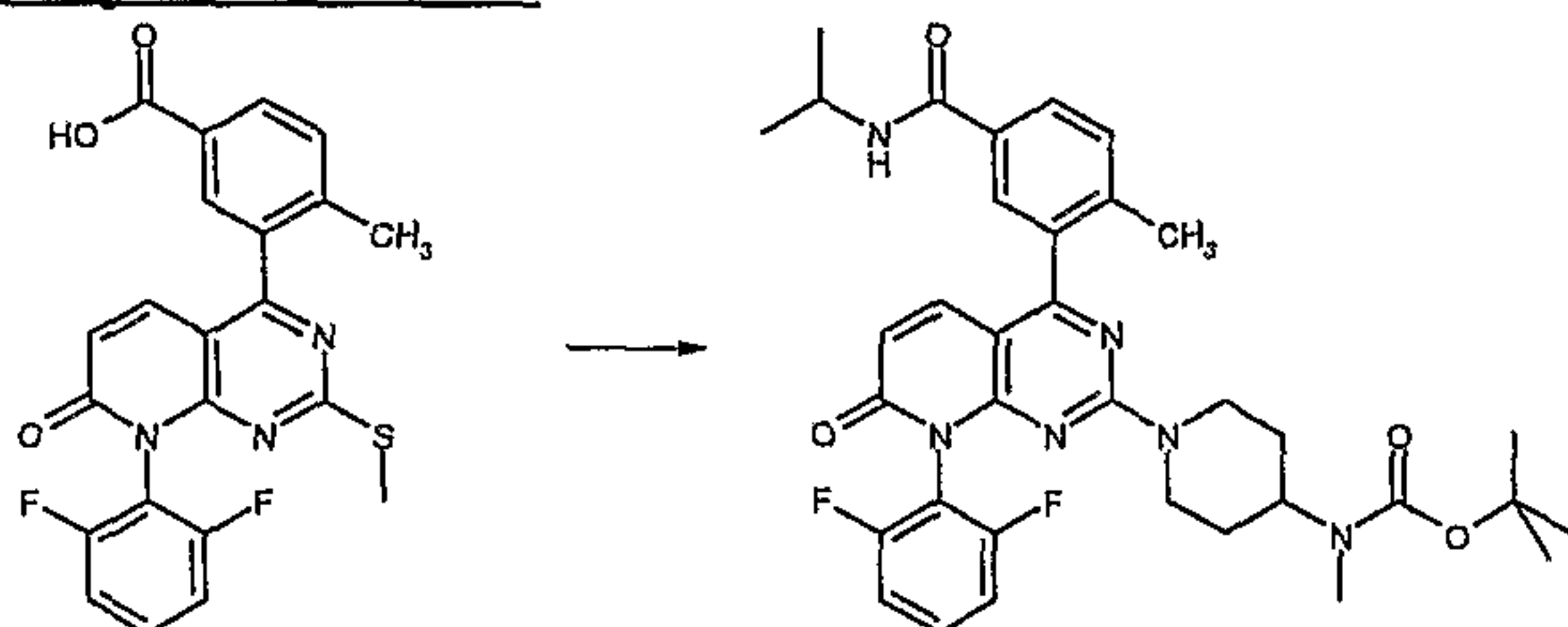


To a solution of 3-[8-(2,6-difluorophenyl)-2-(methylsulfinyl)-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl]-*N*-(4-fluorophenyl)-4-methylbenzamide (15 mg, 0.027 mmol) in DCM (5 mL) was added *N,N*-dimethyl-1,2-ethanediamine (0.009 mL, 0.083 mmol). The resultant mixture was stirred at room temperature overnight. The mixture was concentrated under vacuo. Flash chromatography (90% CH<sub>2</sub>Cl<sub>2</sub> / 7% MeOH / 3% NH<sub>4</sub>OH) then provide the title compound (11 mg, 72%). LC-MS (ES) *m/z* 573 (M+H)<sup>+</sup>; <sup>1</sup>H-NMR(CDCl<sub>3</sub>) δ 2.21 (s, 6H), 2.30 (s, 3H), 2.40 (br, 1H), 2.43 (m, 2H), 3.17 (m, 2H), 3.55 (br, 1H), 6.23 (d, 1H), 6.89 (m, 1H), 7.04 (m, 3H), 7.29 (m, 1H), 7.36 (m, 1H), 7.47 (d, 1H), 7.61 (m, 2H), 7.84 (s, 1H), 8.05 (d, 1H).

### Example 113

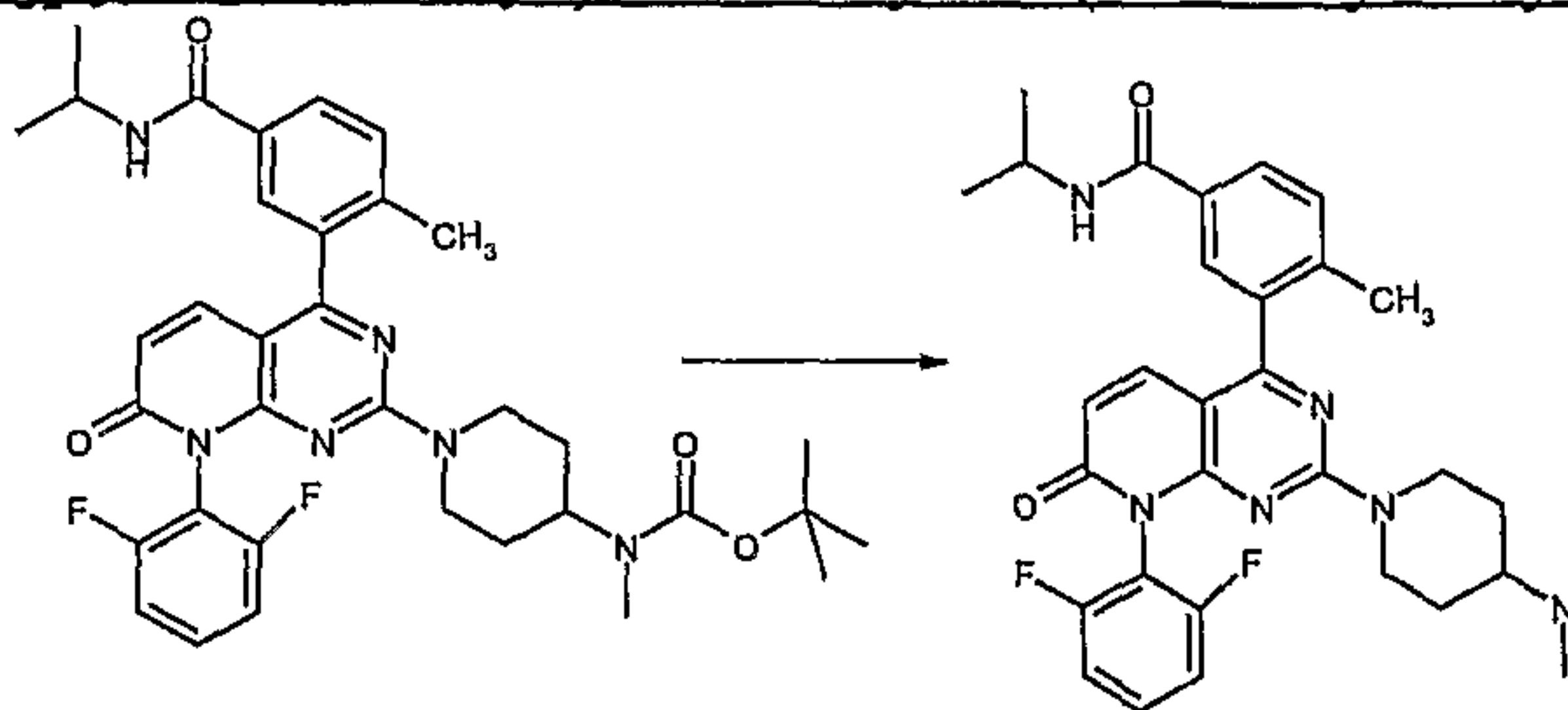
3-{8-(2,6-difluorophenyl)-2-[4-(methylamino)-1-piperidinyl]-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl}-4-methyl-*N*-(1-methylethyl)benzamide

113a) 1,1-dimethylethyl {1-[8-(2,6-difluorophenyl)-4-(2-methyl-5-[(1-methylethyl)amino]carbonyl}phenyl)-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-2-yl]-4-piperidinyl}methylcarbamate



The title compound was prepared from 3-[8-(2,6-difluorophenyl)-2-(methylthio)-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl]-4-methylbenzoic acid by following the procedures in Example 19 using 2-propanamine for the amide formation and 1,1-dimethylethyl methyl(4-piperidinyl)carbamate for the displacement reaction. LC-MS (ES) *m/z* 647 (M+H)<sup>+</sup>.

113b) 3-{8-(2,6-difluorophenyl)-2-[4-(methylamino)-1-piperidinyl]-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl}-4-methyl-*N*-(1-methylethyl)benzamide

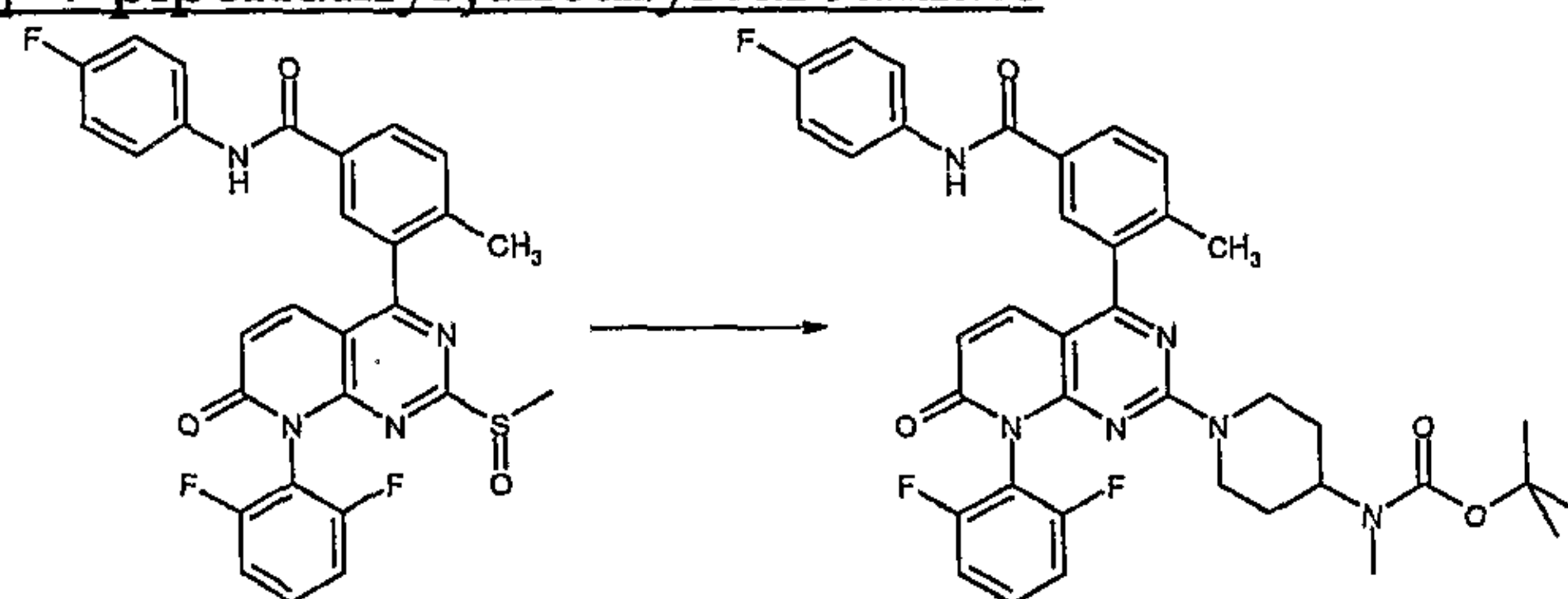


To a solution of 1,1-dimethylethyl {1-[8-(2,6-difluorophenyl)-4-(2-methyl-5-  
 5 {[(1-methylethyl)amino]carbonyl}phenyl)-7-oxo-7,8-dihydropyrido[2,3-  
*d*]pyrimidin-2-yl]-4-piperidinyl}methylcarbamate in DCM (2 mL) was added TFA  
 (0.03 mL). The reaction mixture was stirred at room temperature overnight,  
 quenched with triethylamine (0.5 mL) at -78°C. The residue was mixed with H<sub>2</sub>O  
 (5.0 mL). The organic layer was separated and the aqueous layer was extracted with  
 DCM (3 x 15 mL). The combined organic phases were washed with saturated aq.  
 NaCl, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated. Purification via a CombiFlash  
 system (90% CH<sub>2</sub>Cl<sub>2</sub> / 7% MeOH / 3% NH<sub>4</sub>OH) then afforded the title compound.  
 10 LC-MS (ES) *m/z* 547 (M+H)<sup>+</sup>; <sup>1</sup>H-NMR(MeOD) δ 1.20 (m, 2H), 1.26 (d, 6H), 1.90  
 (m, 2H), 2.31 (s, 3H), 2.38 (s, 3H), 2.65 (m, 1H), 2.95 (m, 2H), 3.23 (m, 1H), 4.23  
 (m, 2H), 6.35 (d, 1H), 7.25 (t, 2H), 7.50 (d, 1H), 7.52 (d, 1H), 7.62 (m, 1H), 7.78 (s,  
 1H), 7.93 (d, 1H).

#### Example 114

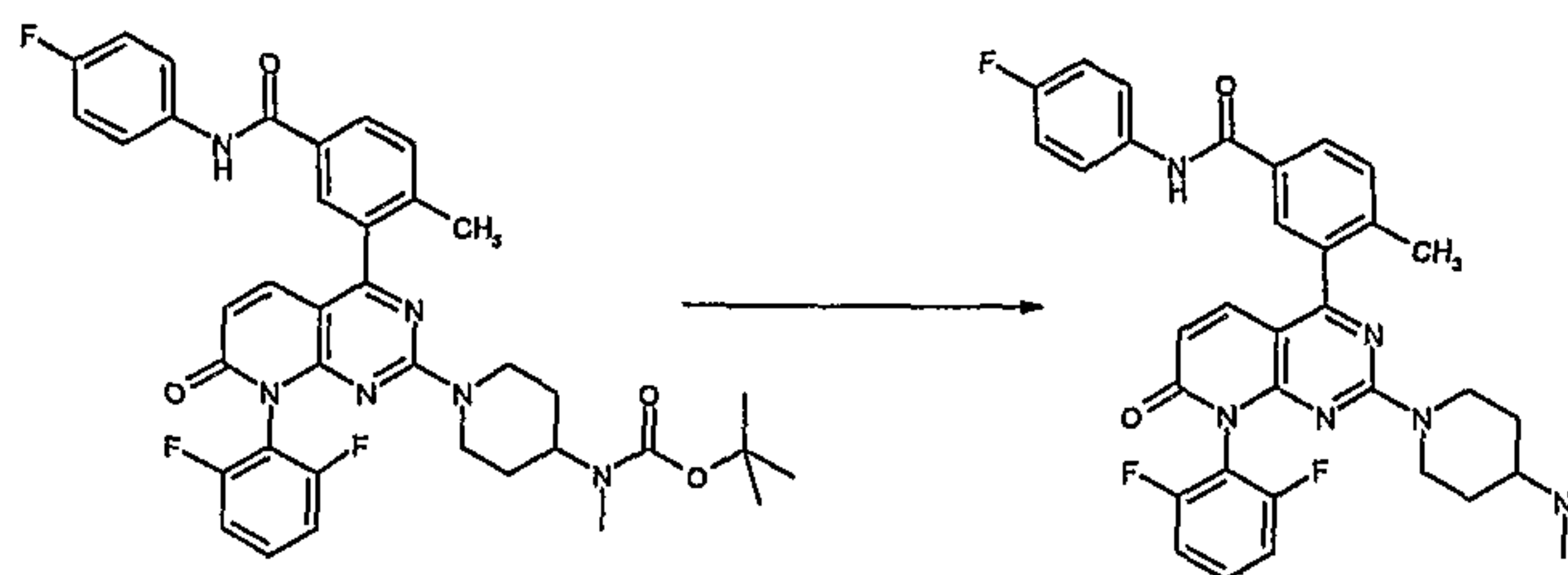
3-{8-(2,6-difluorophenyl)-2-[4-(methylamino)-1-piperidinyl]-7-oxo-7,8-  
dihydropyrido[2,3-*d*]pyrimidin-4-yl}-N-(4-fluorophenyl)-4-methylbenzamide

114a) 1,1-dimethylethyl {1-[8-(2,6-difluorophenyl)-4-(5-{[(4-  
 20 fluorophenyl)amino]carbonyl}-2-methylphenyl)-7-oxo-7,8-dihydropyrido[2,3-  
*d*]pyrimidin-2-yl]-4-piperidinyl}methylcarbamate



To a solution of 3-[8-(2,6-difluorophenyl)-2-(methylsulfinyl)-7-oxo-7,8-  
 dihydropyrido[2,3-*d*]pyrimidin-4-yl]-N-(4-fluorophenyl)-4-methylbenzamide  
 25 (Example 19b, 10 mg, 0.018 mmol) in DCM (5 mL) was added 1,1-dimethylethyl  
 methyl(4-piperidinyl)carbamate (19 mg, 0.089 mmol). The resultant mixture was  
 stirred at room temperature overnight. The mixture was concentrated under vacuo.  
 The titled compound was carried to the next step without purification. LC-MS (ES)  
*m/z* 699 (M+H)<sup>+</sup>.

114b) 3-{8-(2,6-difluorophenyl)-2-[4-(methylamino)-1-piperidinyl]-7-oxo-7,8-  
dihydropyrido[2,3-*d*]pyrimidin-4-yl}-N-(4-fluorophenyl)-4-methylbenzamide

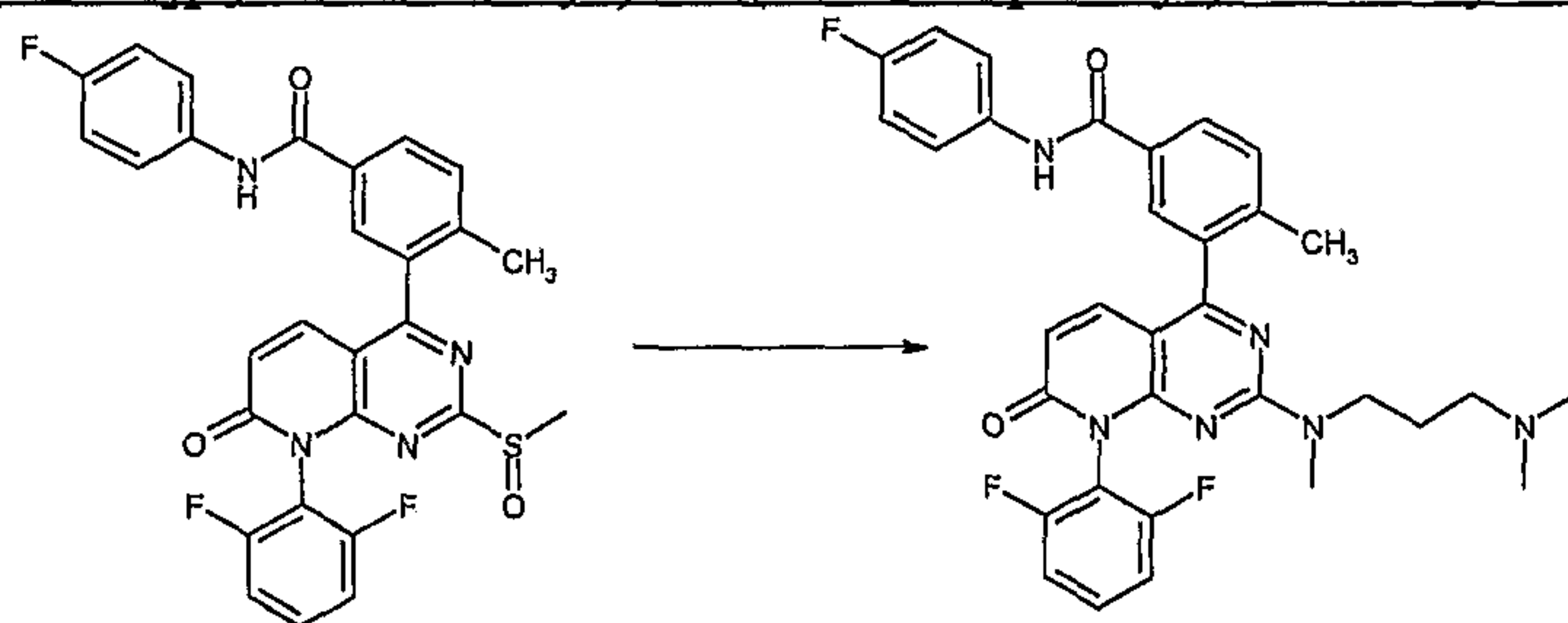


To a solution of 1,1-dimethylethyl {1-[8-(2,6-difluorophenyl)-4-(5-[(4-fluorophenyl)amino]carbonyl)-2-methylphenyl)-7-oxo-7,8-dihydropyrido[2,3-  
 5 *d*]pyrimidin-2-yl]-4-piperidinyl}methylcarbamate in DCM (2 mL) was added TFA (0.03 mL). The reaction mixture was stirred at room temperature overnight, quenched with triethylamine (0.5 mL) at  $-78^{\circ}\text{C}$ , . The residue was mixed with  $\text{H}_2\text{O}$  (5.0 mL). The organic layer was separated and the aqueous layer was extracted with DCM (3 x 15 mL). The combined organic phases were washed with saturated aq. NaCl, dried over  $\text{Na}_2\text{SO}_4$ , filtered, and concentrated. Purification via a CombiFlash  
 10 system (90%  $\text{CH}_2\text{Cl}_2$  / 7% MeOH / 3%  $\text{NH}_4\text{OH}$ ) then afforded the title compound (6 mg, 57%, 2 steps). LC-MS (ES)  $m/z$  599 ( $\text{M}+\text{H}^+$ );  $^1\text{H-NMR}$ (MeOD)  $\delta$  1.29 (m, 2H), 1.37 (m, 1H), 1.95 (m, 2H), 2.39 (s, 3H), 2.45 (s, 3H), 2.77 (m, 1H), 2.95 (m, 2H), 3.50 (m, 1H), 6.38 (d, 1H), 7.14 (m, 2H), 7.25 (m, 2H), 7.52 (d, 1H), 7.62 (m, 2H), 7.71 (m, 2H), 7.92 (s, 1H), 8.06 (d, 1H).

15

### Example 115

3-{8-(2,6-difluorophenyl)-2-[[3-(dimethylamino)propyl](methyl)amino]-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl]-*N*-(4-fluorophenyl)-4-methylbenzamide



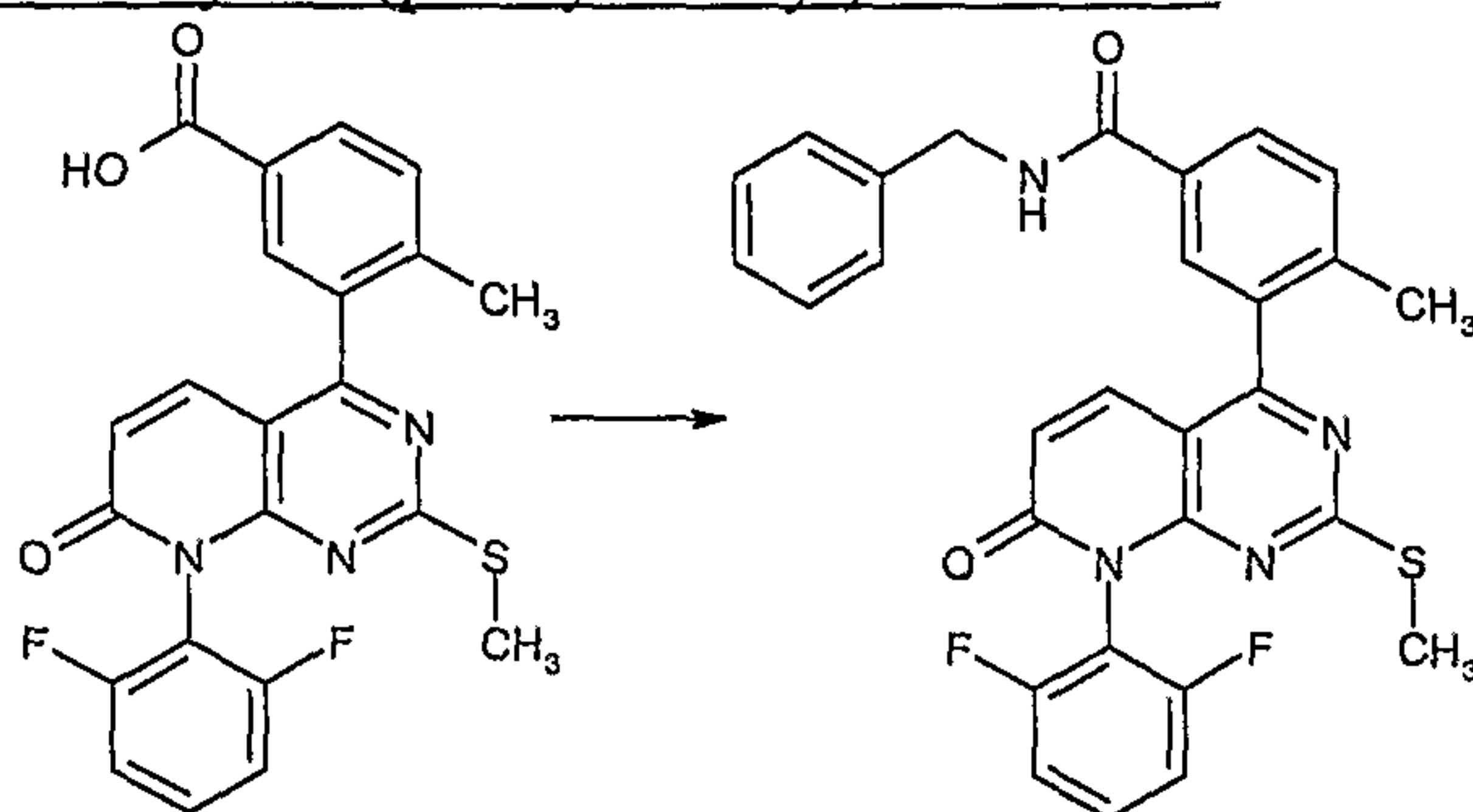
To a solution of 3-[8-(2,6-difluorophenyl)-2-(methylsulfinyl)-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl]-*N*-(4-fluorophenyl)-4-methylbenzamide (15 mg, 0.027 mmol) in DCM (5 mL) was added *N,N,N'*-trimethyl-1,3-propanediamine (0.021 mL, 0.14 mmol). The resultant mixture was stirred at room temperature overnight. The mixture was concentrated under vacuo. Flash chromatography (90%  
 20  $\text{CH}_2\text{Cl}_2$  / 7% MeOH / 3%  $\text{NH}_4\text{OH}$ ) then provide the title compound (10 mg, 63%). LC-MS (ES)  $m/z$  601 ( $\text{M}+\text{H}^+$ );  $^1\text{H-NMR}$ (MeOD)  $\delta$  1.62 (m, 1H), 1.80 (m, 1H), 2.05 (m, 2H), 2.20 (s, 6H), 2.32 (m, 4H), 2.89 (m, 2H), 3.32 (s, 2H), 6.36 (d, 1H), 7.14

(m, 2H), 7.28 (m, 2H), 7.52 (d, 1H), 7.59 (d, 1H), 7.65 (m, 1H), 7.71 (m, 2H), 7.92 (s, 1H), 8.06 (d, 1H).

### Example 116

5 3-[8-(2,6-difluorophenyl)-2-[(1*H*-imidazol-2-ylmethyl)amino]-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl]-4-methyl-*N*-(phenylmethyl)benzamide

116a) 3-[8-(2,6-difluorophenyl)-2-(methylthio)-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl]-4-methyl-*N*-(phenylmethyl)benzamide

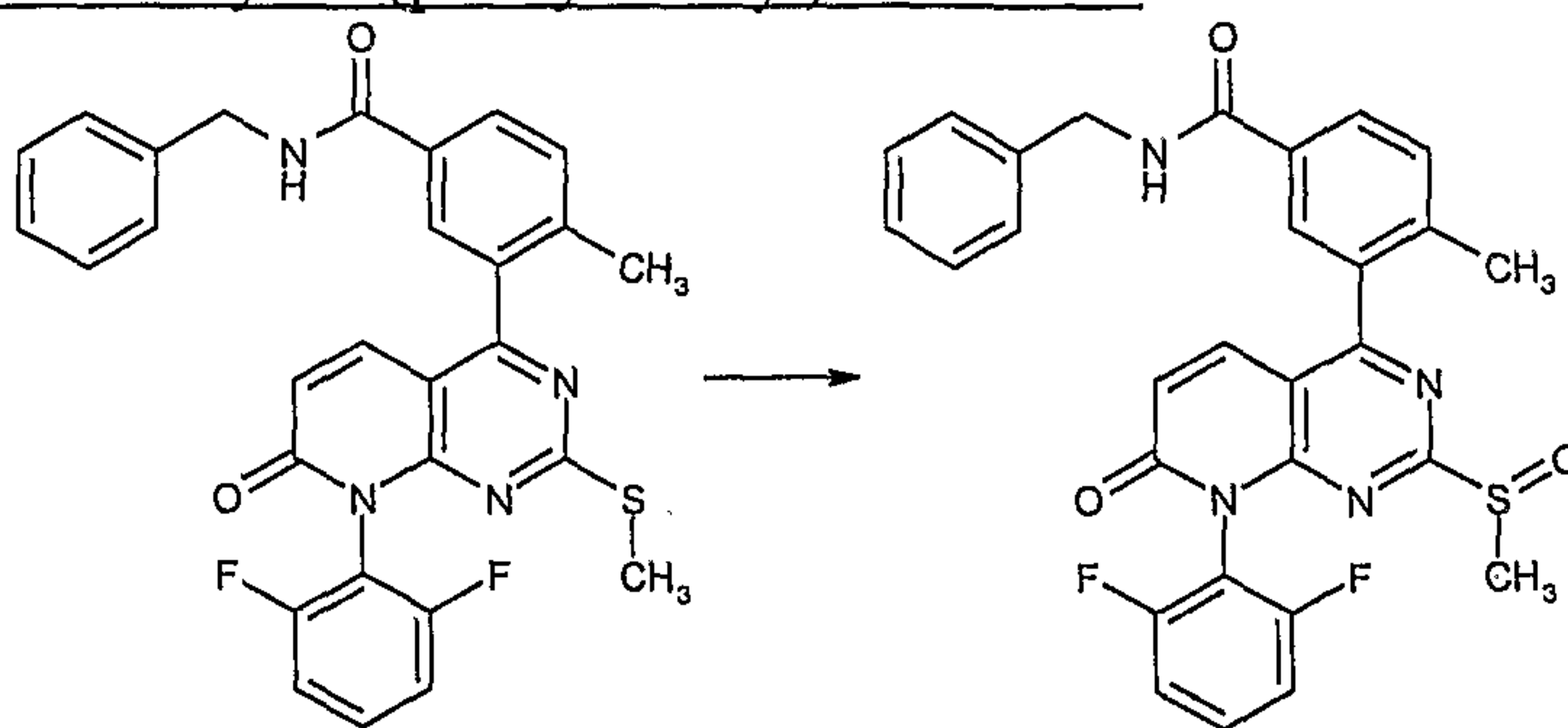


10

3-[8-(2,6-difluorophenyl)-2-(methylthio)-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl]-4-methylbenzoic acid (0.15 g, 0.342 mmol) was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (10 mL) and stirred under argon at room temperature. N-Benzylamine (0.11g, 1.03 mmol) was added followed by EDC (0.082 g, 0.41mmol) and HOBT (0.055 g, 0.41 mmol). The reaction was stirred overnight. The solvents were pumped off *in vacuo*, and the residue taken up in EtOAc and washed twice with H<sub>2</sub>O, once with brine, dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> filtered and evaporated. The residue was flash chromatographed on silica gel (20 g) eluted with 0-1.5% MeOH / CH<sub>2</sub>Cl<sub>2</sub> to give the title compound. mp (dec) 124-130°C. LC-MS *m/z* 529 (M+H)<sup>+</sup>, 2.36 min (ret time).

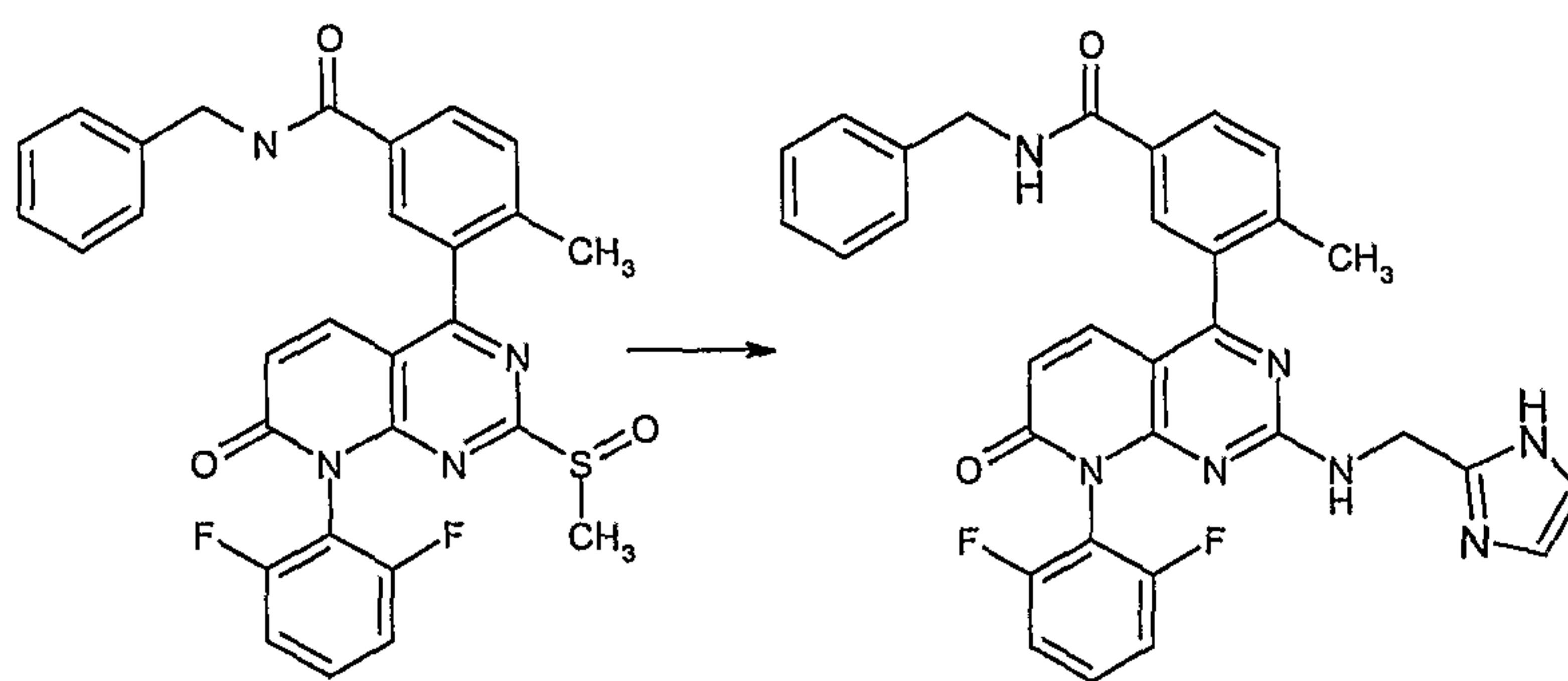
20

116b) 3-[8-(2,6-difluorophenyl)-2-(methylsulfinyl)-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl]-4-methyl-*N*-(phenylmethyl)benzamide



3-[8-(2,6-difluorophenyl)-2-(methylthio)-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl]-4-methyl-*N*-(phenylmethyl)benzamide (0.12g 0.227 mmol) was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (5 mL) and 50-60% 3-chloroperoxybenzoic acid (0.106 g, 0.34 mmol) was added and the mixture stirred for 10 min. The solvents were pumped off, and the residue taken up in EtOAc and washed with H<sub>2</sub>O, brine, dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> filtered and evaporated. The crude product which contained a small amount of sulfone, was flashed on silica gel (20 g) eluted with a hexane to EtOAc gradient to isolate the title compound. mp (dec) 268-270°C. LC-MS *m/z* 545 (M+H)<sup>+</sup>, 1.87 min (ret time).

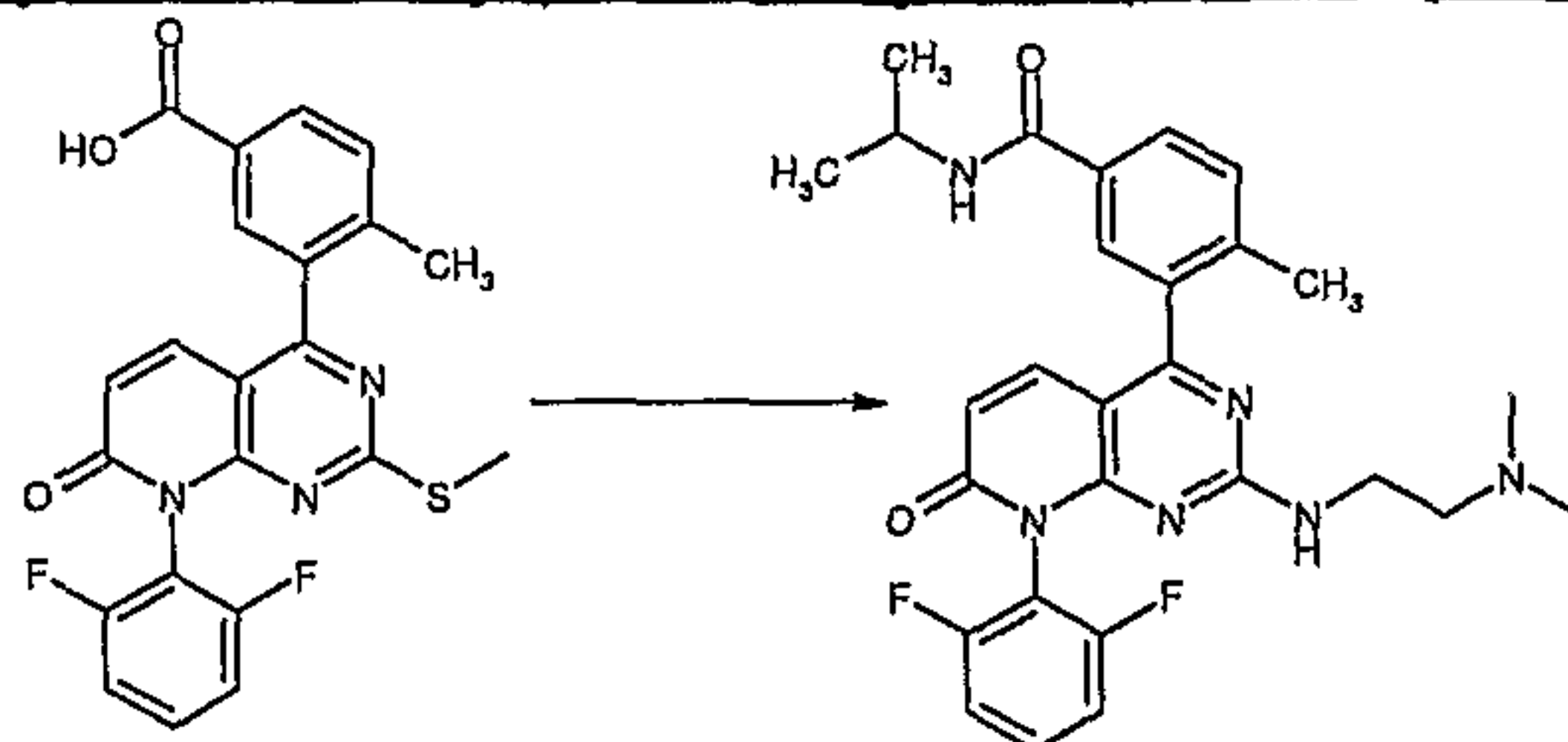
116c) 3-{8-(2,6-difluorophenyl)-2-[(1*H*-imidazol-2-ylmethyl)amino]-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl}-4-methyl-*N*-(phenylmethyl)benzamide



3-[8-(2,6-Difluorophenyl)-2-(methylsulfinyl)-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl]-4-methyl-*N*-(phenylmethyl)benzamide (0.084 g, 0.154 mmol) and (1*H*-imidazol-2-ylmethyl)amine dihydrochloride (0.039 g, 0.23 mmol) were dissolved in CH<sub>2</sub>Cl<sub>2</sub> (5 mL) and triethylamine (0.7 mL). The resulting mixture was stirred under argon at room temperature overnight. The solvents were pumped off *in vacuo*, and the residue taken up in EtOAc and 1 N NaOH. The organic phase was washed with brine, dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> filtered and evaporated. The residue was flash chromatographed on silica gel (20 g) eluted with 6:1:0.05 CH<sub>2</sub>Cl<sub>2</sub>:isopropanol:NH<sub>4</sub>OH. The material isolated was not pure, and was rechromatographed on silica gel (20 g) eluted with 0-5% MeOH/CH<sub>2</sub>Cl<sub>2</sub> to give the title compound as a white amorphous solid. mp (dec) 185-190°C. LC-MS *m/z* 578 (M+H)<sup>+</sup>, 1.76 min (ret time).

**Example 117**

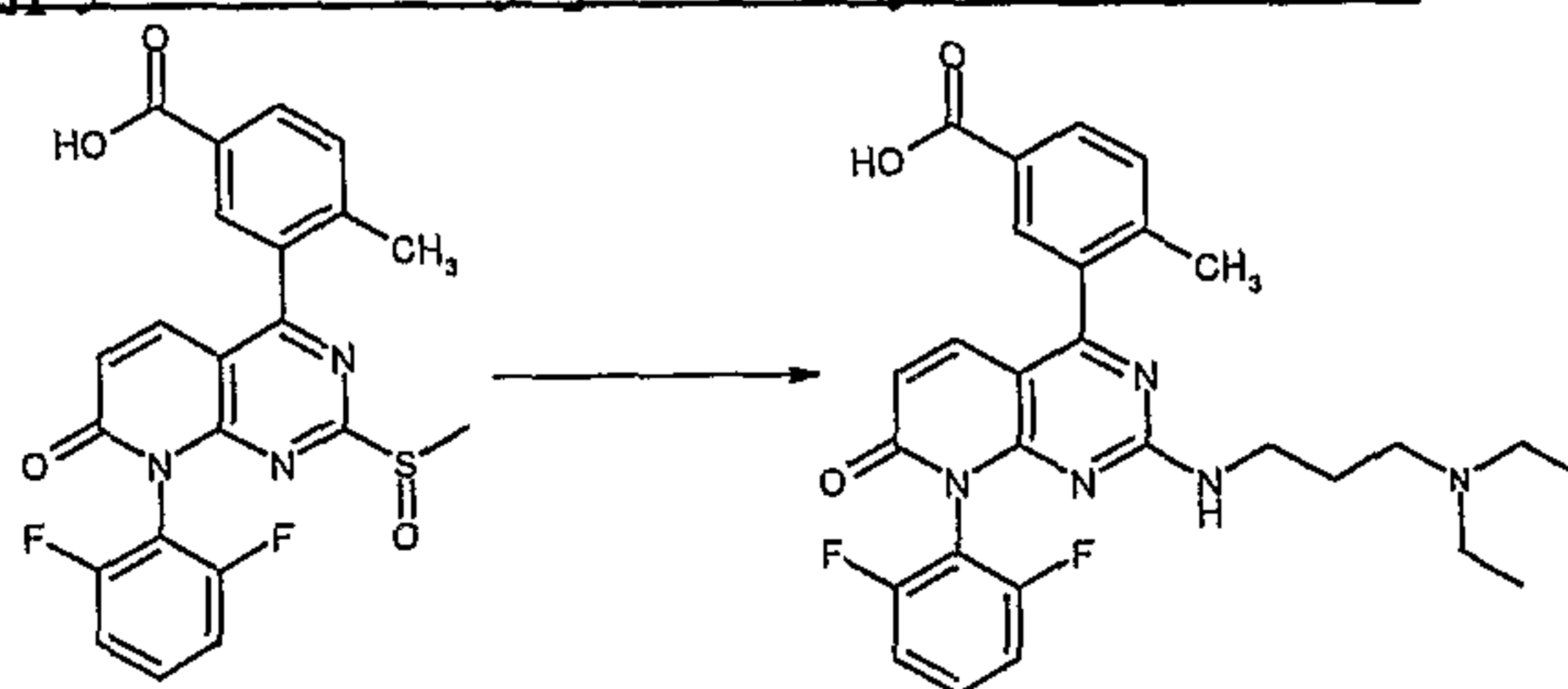
3-(8-(2,6-difluorophenyl)-2-{[2-(dimethylamino)ethyl]amino}-7-oxo-7,8-dihydropyrido[2,3-d]pyrimidin-4-yl)-4-methyl-N-(1-methylethyl)benzamide



5 The title compound was prepared from 3-[8-(2,6-difluorophenyl)-2-(methylthio)-7-oxo-7,8-dihydropyrido[2,3-d]pyrimidin-4-yl]-4-methylbenzoic acid by following the procedures in Example 19 using 2-propanamine for the amide formation and *N,N*-dimethyl-1,2-ethanediamine for the displacement reaction. LC-MS (ES)  $m/z$  521 ( $M+H$ )<sup>+</sup>; <sup>1</sup>H-NMR(MeOD)  $\delta$  1.26 (d, 6H), 2.12 (s, 6H), 2.30 (m, 2H), 2.36 (m, 5H), 3.27 (m, 2H), 4.23 (m, 1H), 6.38 (d, 1H), 7.25 (m, 2H), 7.44 (d, 1H), 7.49 (d, 1H), 7.59 (m, 1H), 7.79 (s, 1H), 7.93 (d, 1H).

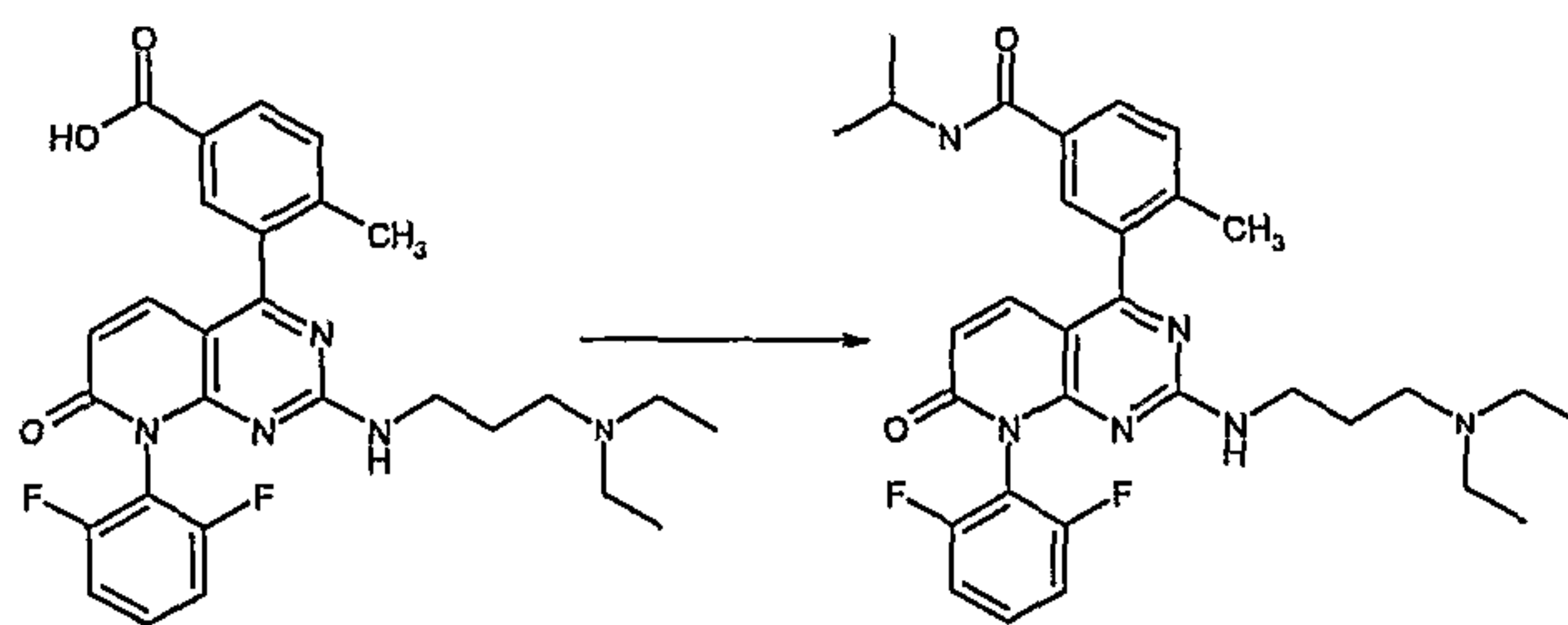
**Example 118**

15 3-[2-{[3-(diethylamino)propyl]amino}-8-(2,6-difluorophenyl)-7-oxo-7,8-dihydropyrido[2,3-d]pyrimidin-4-yl]-4-methyl-N-(1-methylethyl)benzamide 118a  
3-[2-{[3-(diethylamino)propyl]amino}-8-(2,6-difluorophenyl)-7-oxo-7,8-dihydropyrido[2,3-d]pyrimidin-4-yl]-4-methylbenzoic acid



20 To the compound 3-[8-(2,6-difluorophenyl)-2-(methylsulfinyl)-7-oxo-7,8-dihydropyrido[2,3-d]pyrimidin-4-yl]-4-methylbenzoic acid (600 mg, 1.32 mmol) in dichloromethane (30 mL) was added *N,N*-diethyl-1,3-propanediamine (0.624 mL, 4.0 mol). The mixture was stirred at room temperature overnight. Solvent was removed by rotovap. Separation by HPLC with TFA afforded the title compound (695 mg, 85%). LC-MS  $m/z$  522 ( $M+H$ )<sup>+</sup>.

25 118b 3-[2-{[3-(diethylamino)propyl]amino}-8-(2,6-difluorophenyl)-7-oxo-7,8-dihydropyrido[2,3-d]pyrimidin-4-yl]-4-methyl-N-(1-methylethyl)benzamide

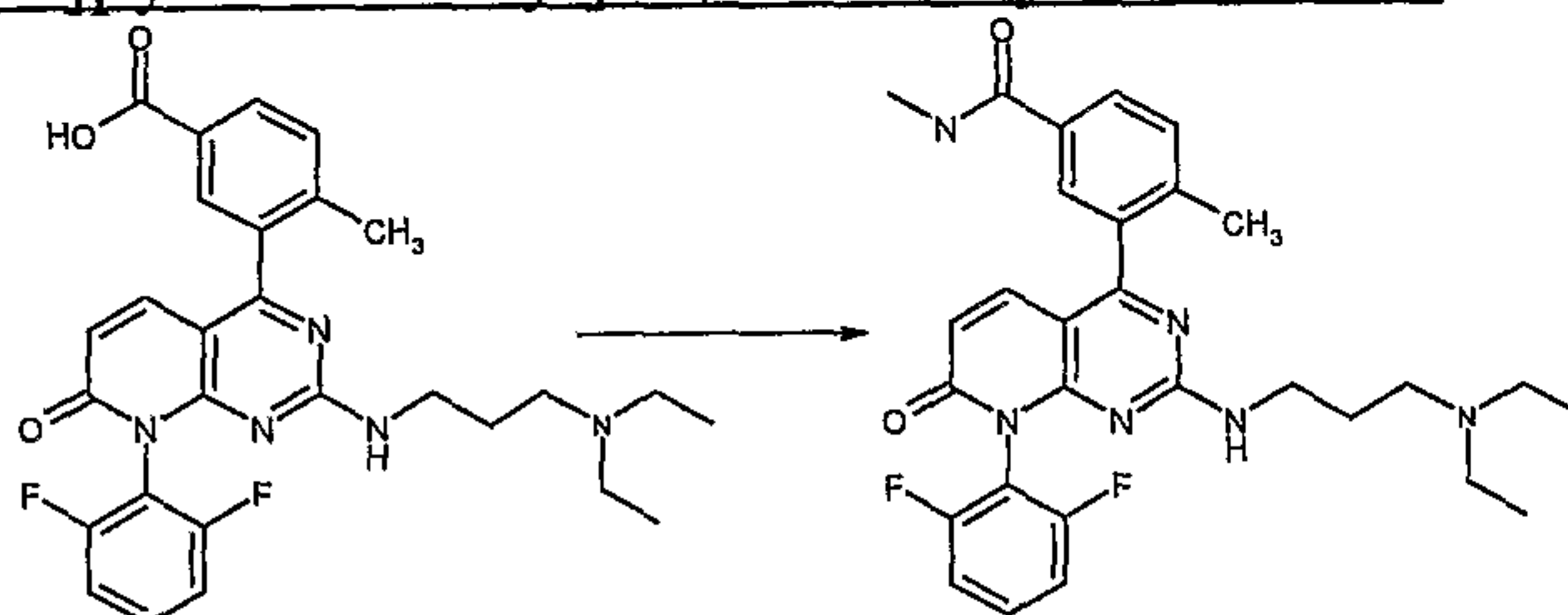


To the compound 3-[2-[[3-(diethylamino)propyl]amino]-8-(2,6-difluorophenyl)-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl]-4-methylbenzoic acid (40 mg, 0.074 mmol) in dichloromethane (2 mL) were added HBTU (30 mg, 0.079 mmol) and isopropylamine (0.032 mL, 0.37 mmol). The mixture was stirred at r.t. overnight. Solvent was removed by rotovap. Separation by chromatography (90% methylene chloride / 7% MeOH / 3% ammonia) afforded the title compound (22mg, 51%). LC-MS  $m/z$  563 ( $M+H$ )<sup>+</sup>.

10

**Example 119**

3-[2-[[3-(diethylamino)propyl]amino]-8-(2,6-difluorophenyl)-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl]-*N*,4-dimethylbenzamide



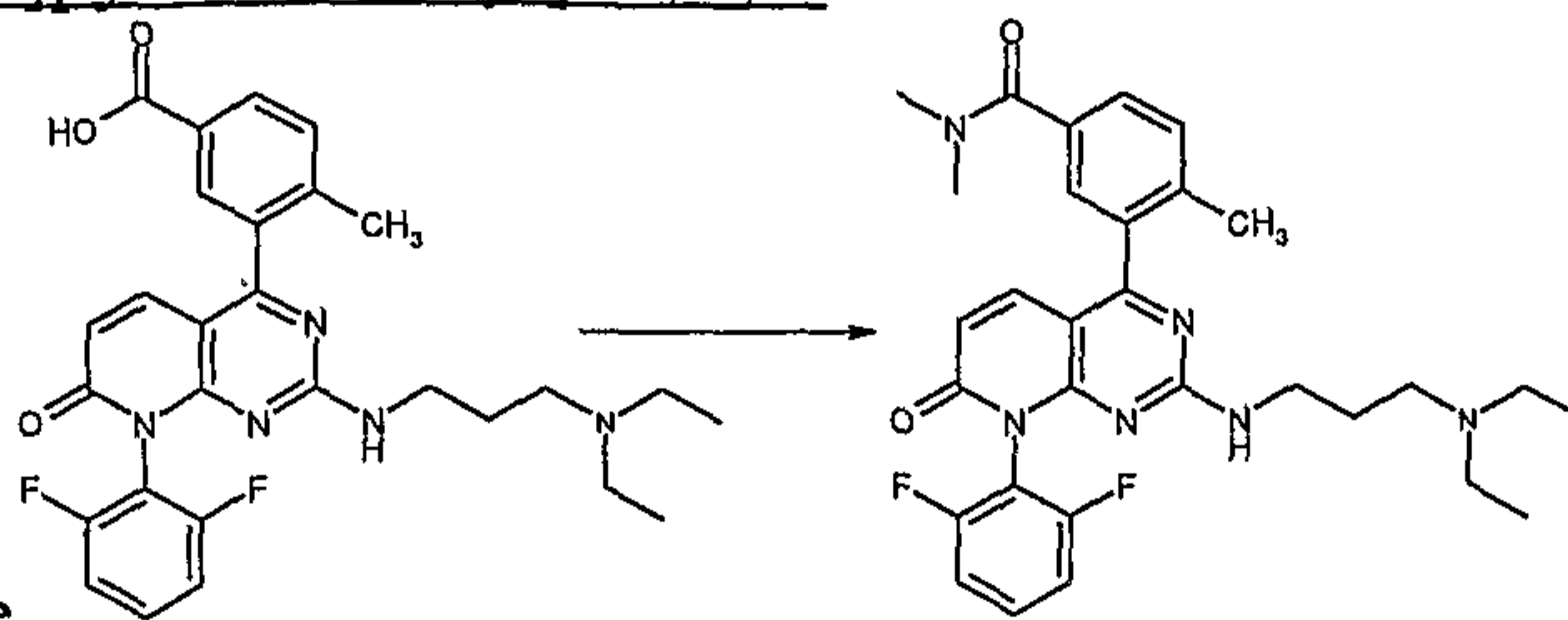
To the compound 3-[2-[[3-(diethylamino)propyl]amino]-8-(2,6-difluorophenyl)-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl]-4-methylbenzoic acid (40 mg, 0.074 mmol) in dichloromethane (2 mL) were added HBTU (30 mg, 0.079 mmol) and methylamine (0.185 mL, 0.37 mmol, 2.0M soln in THF). The mixture was stirred at rt overnight. Solvent was removed by rotovap. Separation by chromatography (90% methylene chloride / 7% MeOH / 3% ammonia) afforded the title compound (32 mg, 78%). LC-MS  $m/z$  535 ( $M+H$ )<sup>+</sup>.

20

**Example 120**

3-[2-{[3-(diethylamino)propyl]amino}-8-(2,6-difluorophenyl)-7-oxo-7,8-  
dihydropyrido[2,3-*d*]pyrimidin-4-yl]-*N,N*,4-

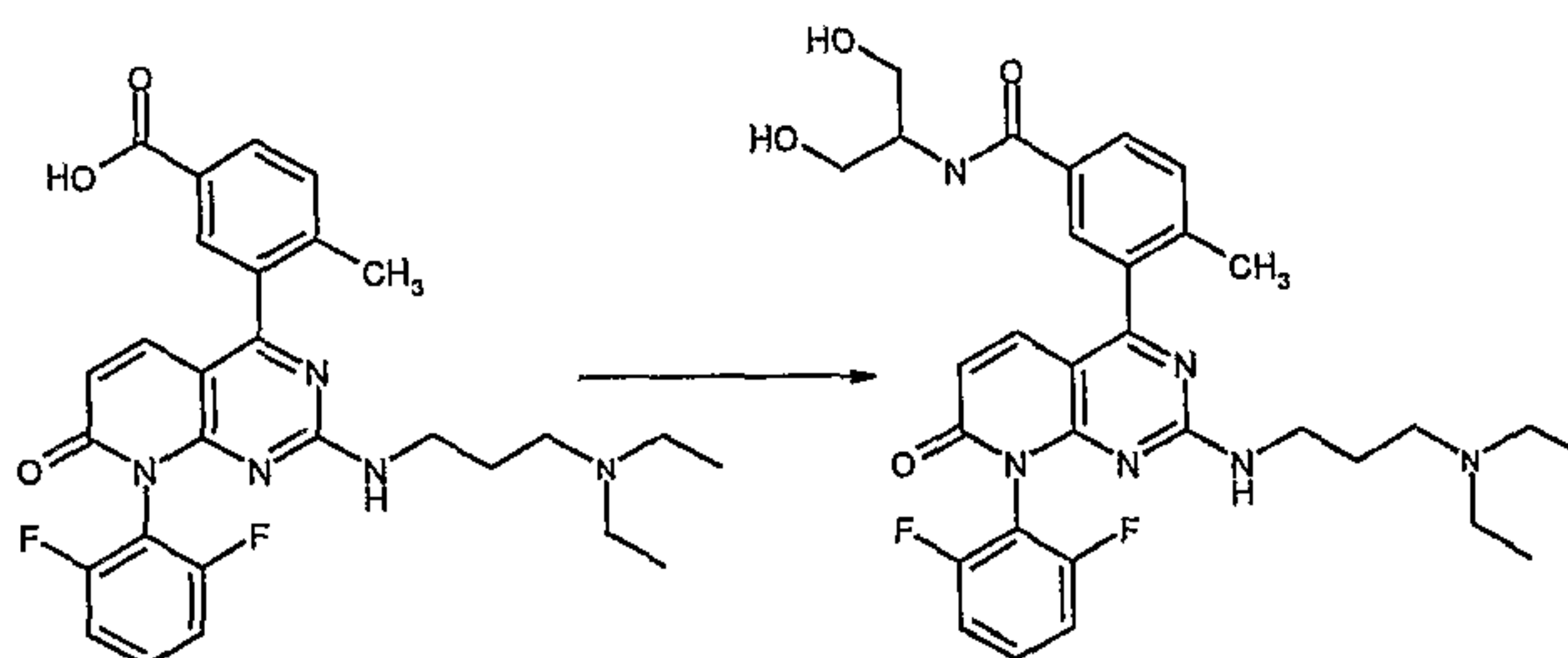
trimethylbenzamide



- 5 To the compound 3-[2-{[3-(diethylamino)propyl]amino}-8-(2,6-difluorophenyl)-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl]-4-methylbenzoic acid (40 mg, 0.074 mmol) in dichloromethane (2 mL) were added HBTU (30 mg, 0.079 mmol) and dimethylamine (0.185 mL, 0.37 mmol, 2.0M soln in THF). The mixture was stirred at rt overnight. Solvent was removed by rotovap. Separation by
- 10 chromatography (90% methylene chloride / 7% MeOH / 3% ammonia) afforded the title compound (42 mg, 99%). LC-MS  $m/z$  549 ( $M+H$ )<sup>+</sup>.

**Example 121**

- 15 3-[2-{[3-(diethylamino)propyl]amino}-8-(2,6-difluorophenyl)-7-oxo-7,8-  
dihydropyrido[2,3-*d*]pyrimidin-4-yl]-*N*-[2-hydroxy-1-(hydroxymethyl)ethyl]-4-  
methylbenzamide

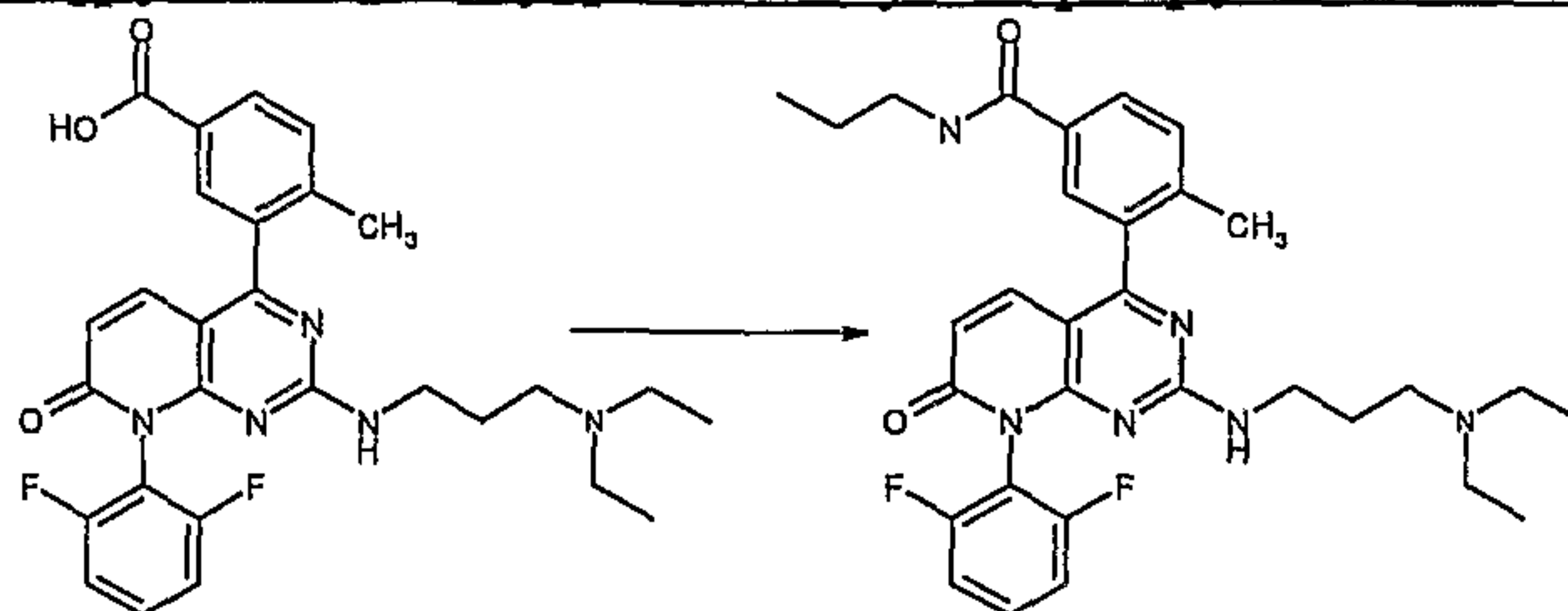


- 20 To the compound 3-[2-{[3-(diethylamino)propyl]amino}-8-(2,6-difluorophenyl)-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl]-4-methylbenzoic acid (40 mg, 0.074 mmol) in THF (2 mL) were added HBTU (30 mg, 0.079 mmol) and serinol (35 mg, 0.37 mmol). The mixture was stirred at rt overnight. Solvent was removed by rotovap. Separation by HPLC with TFA, followed by neutralization with SPE amine cartridge afforded the title compound (40 mg, 88%). LC-MS  $m/z$  595 ( $M+H$ )<sup>+</sup>.

25

**Example 122**

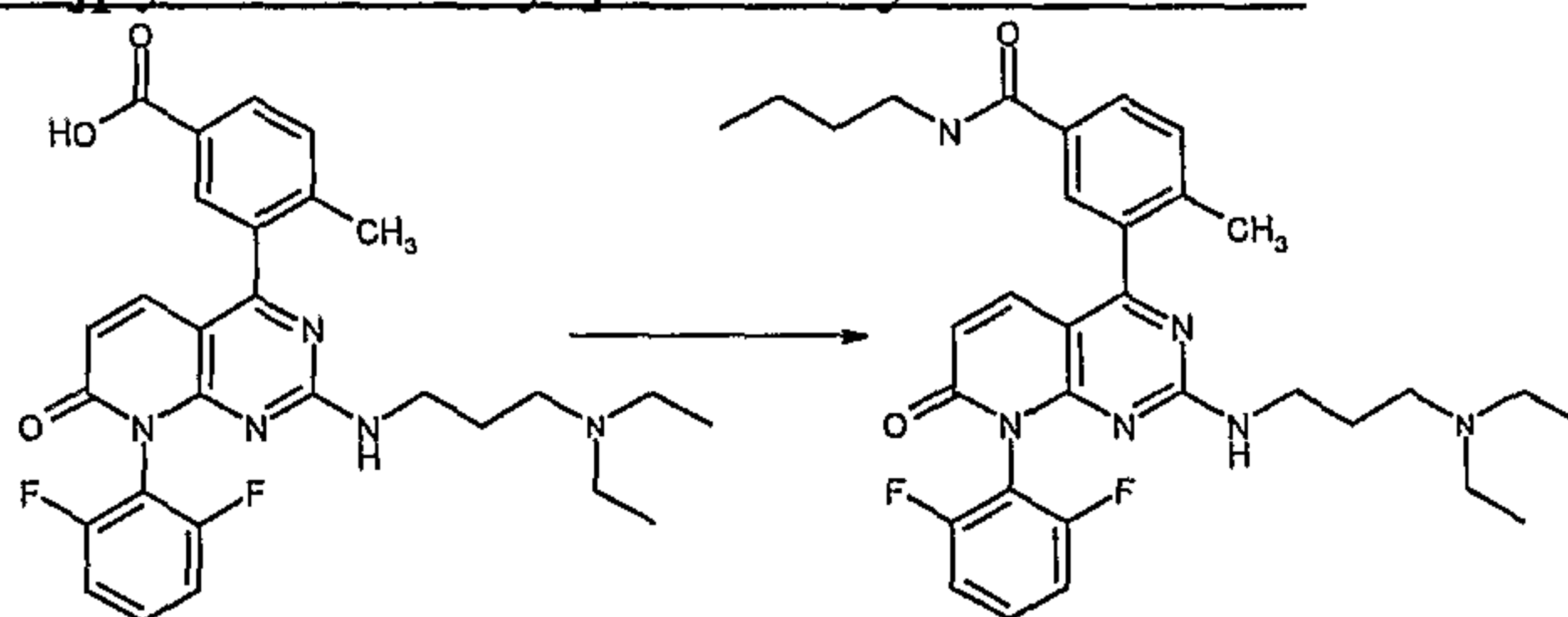
3-[2-{[3-(diethylamino)propyl]amino}-8-(2,6-difluorophenyl)-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl]-4-methyl-*N*-propylbenzamide



- 5 To the compound 3-[2-{[3-(diethylamino)propyl]amino}-8-(2,6-difluorophenyl)-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl]-4-methylbenzoic acid (40 mg, 0.074 mmol) in THF (2 mL) were added HBTU (30 mg, 0.079 mmol) and propylamine (0.031 mL, 0.37 mmol). The mixture was stirred at rt overnight. Solvent was removed by rotovap. Separation by HPLC with TFA, followed by  
10 neutralization with SPE amine cartridge afforded the title compound (16 mg, 37%). LC-MS  $m/z$  563 ( $M+H$ )<sup>+</sup>.

**Example 123**

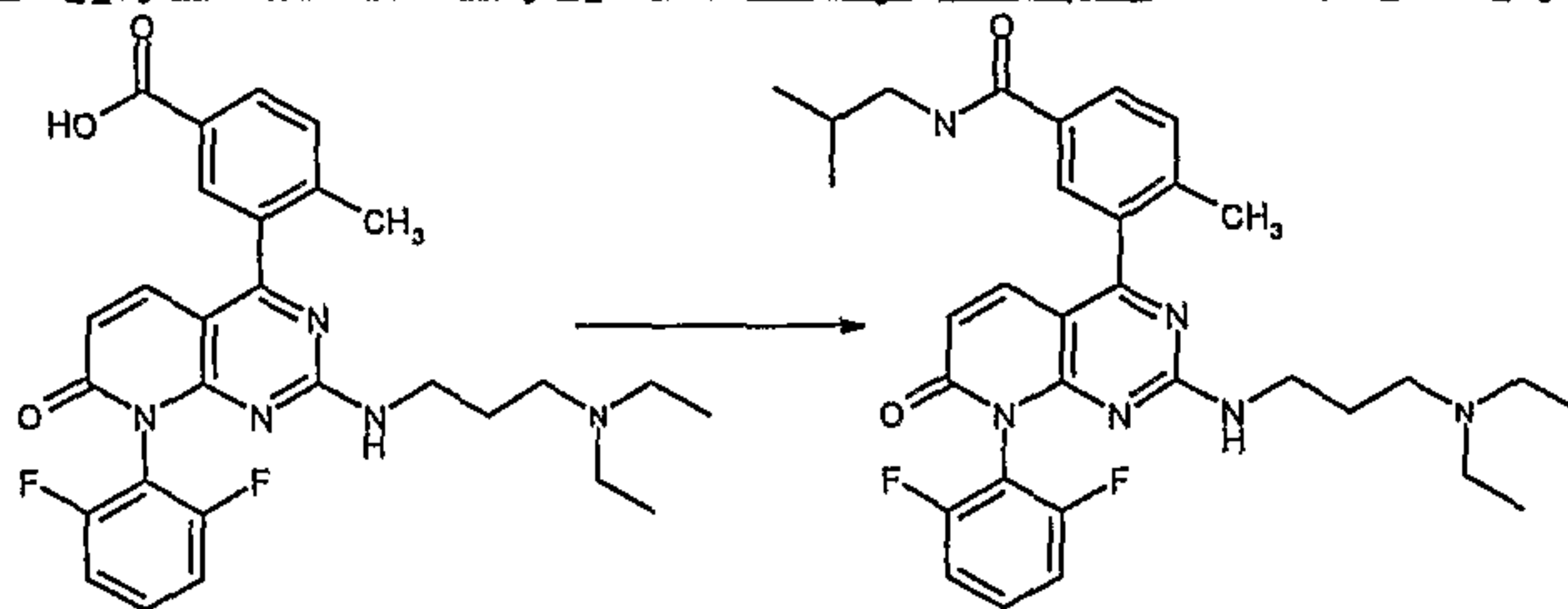
- 15 *N*-butyl-3-[2-{[3-(diethylamino)propyl]amino}-8-(2,6-difluorophenyl)-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl]-4-methylbenzamide



- To the compound 3-[2-{[3-(diethylamino)propyl]amino}-8-(2,6-difluorophenyl)-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl]-4-methylbenzoic acid (40 mg, 0.074 mmol) in methylene chloride (2 mL) were added HBTU (30 mg, 0.079 mmol) and butylamine (0.038 mL, 0.37 mmol). The mixture was stirred at rt overnight. Solvent was removed by rotovap. Separation by HPLC with TFA, followed by neutralization with SPE amine cartridge afforded the title compound (29  
20 mg, 66%). LC-MS  $m/z$  577 ( $M+H$ )<sup>+</sup>.

**Example 124**

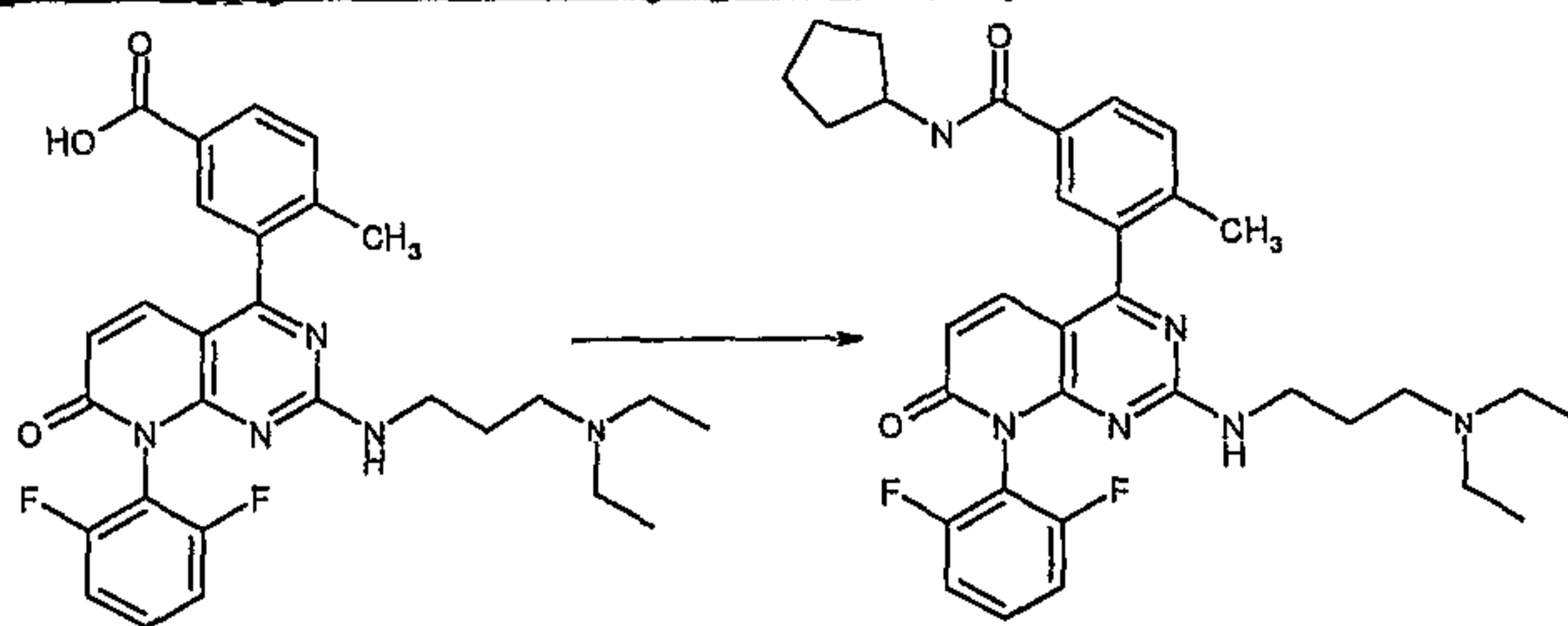
3-[2-{[3-(diethylamino)propyl]amino}-8-(2,6-difluorophenyl)-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl]-4-methyl-*N*-(2-methylpropyl)benzamide



- 5 To the compound 3-[2-{[3-(diethylamino)propyl]amino}-8-(2,6-difluorophenyl)-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl]-4-methylbenzoic acid (40 mg, 0.074 mmol) in methylene chloride (2 mL) were added HBTU (30 mg, 0.079 mmol) and isobutylamine (0.038 mL, 0.37 mmol). The mixture was stirred at rt overnight. Solvent was removed by rotovap. Separation by HPLC with TFA,  
10 followed by neutralization with SPE amine cartridge afforded the title compound (19 mg, 43%). LC-MS  $m/z$  577 ( $M+H$ )<sup>+</sup>.

**Example 125**

*N*-cyclopentyl-3-[2-{[3-(diethylamino)propyl]amino}-8-(2,6-difluorophenyl)-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl]-4-methylbenzamide

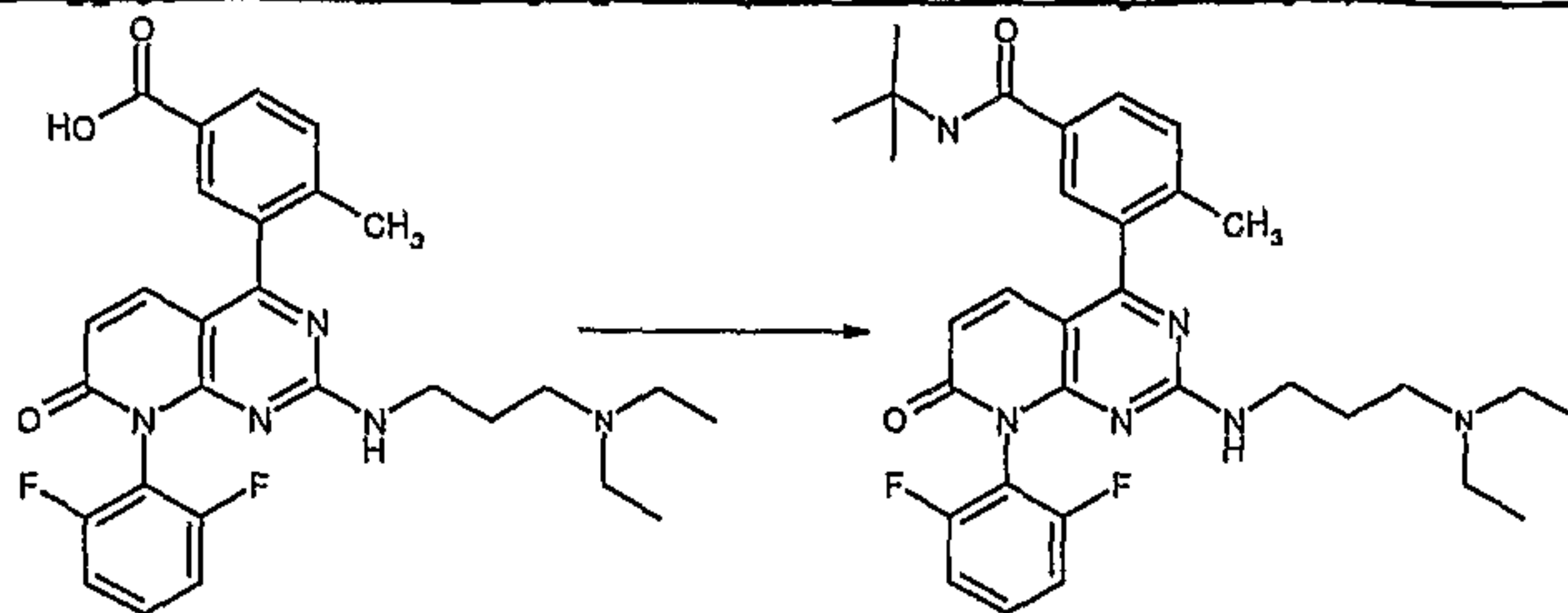


- To the compound 3-[2-{[3-(diethylamino)propyl]amino}-8-(2,6-difluorophenyl)-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl]-4-methylbenzoic acid (40 mg, 0.074 mmol) in methylene chloride (2 mL) was bubbled with nitrogen  
20 for 5 min, then it was added HBTU (30 mg, 0.079 mmol) and cyclopentylamine (0.038 mL, 0.37 mmol). The mixture was stirred at rt overnight. Solvent was removed by rotovap. Separation by HPLC with TFA, followed by neutralization with SPE amine cartridge afforded the title compound (21 mg, 47%). LC-MS  $m/z$  589 ( $M+H$ )<sup>+</sup>.

25

**Example 126**

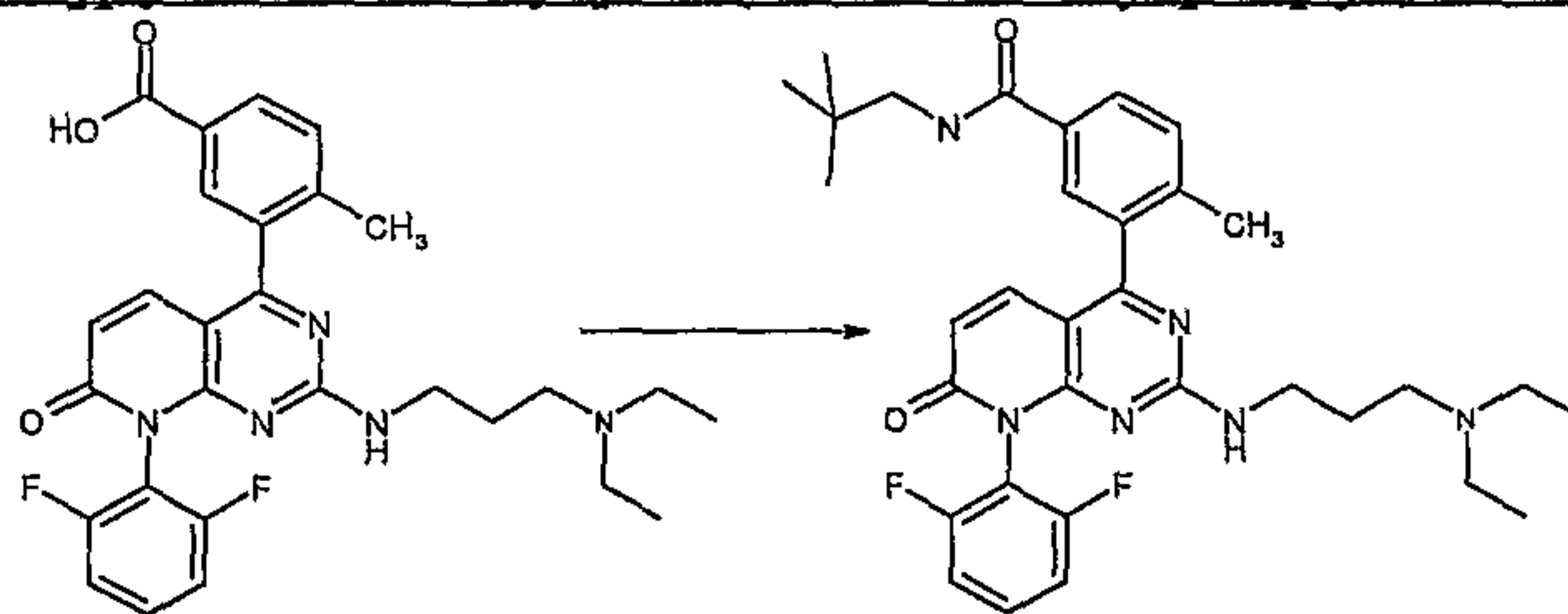
3-[2-{[3-(diethylamino)propyl]amino}-8-(2,6-difluorophenyl)-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl]-*N*-(1,1-dimethylethyl)-4-methylbenzamide



- 5 To the compound 3-[2-{[3-(diethylamino)propyl]amino}-8-(2,6-difluorophenyl)-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl]-4-methylbenzoic acid (40 mg, 0.074 mmol) in methylene chloride (2 mL) were added HBTU (30 mg, 0.079 mmol) and t-butylamine (0.040 mL, 0.37 mmol). The mixture was stirred at rt overnight. Solvent was removed by rotovap. Separation by HPLC with TFA,  
10 followed by neutralization with SPE amine cartridge afforded the title compound (39 mg, 88%). LC-MS  $m/z$  577 ( $M+H$ )<sup>+</sup>.

**Example 127**

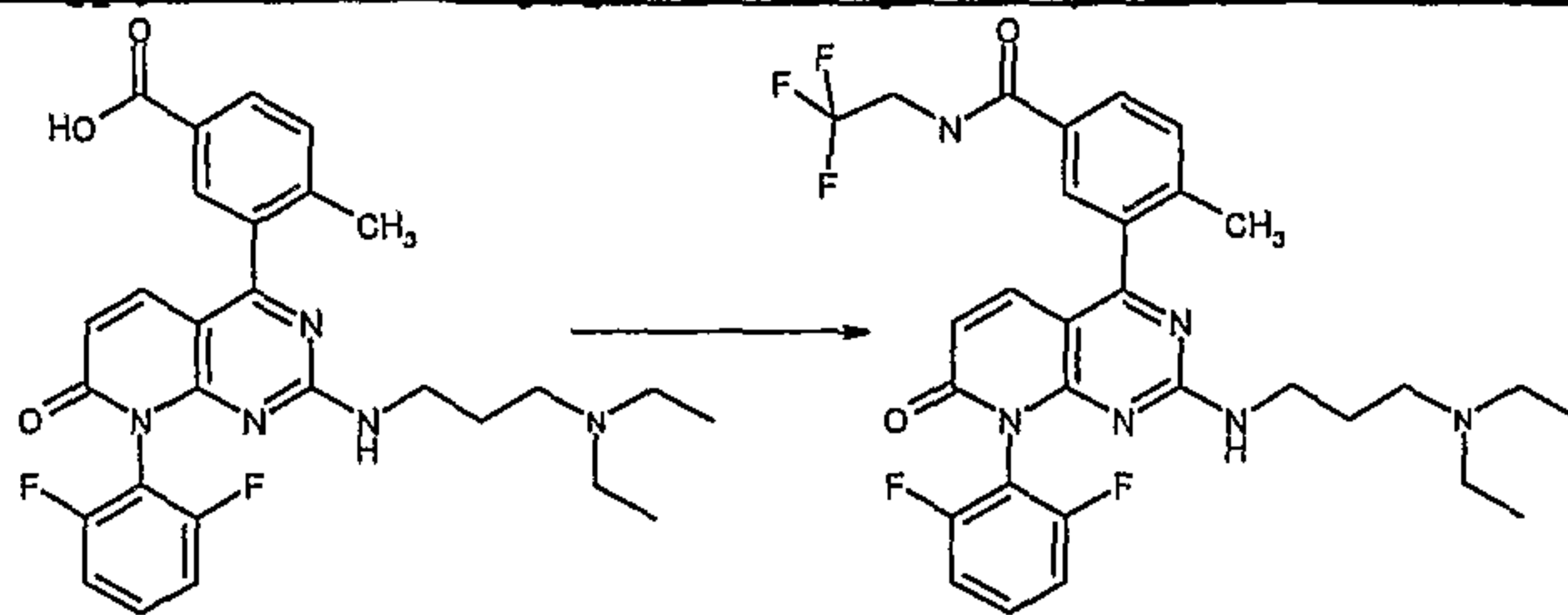
3-[2-{[3-(diethylamino)propyl]amino}-8-(2,6-difluorophenyl)-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl]-*N*-(2,2-dimethylpropyl)-4-methylbenzamide



- To the compound 3-[2-{[3-(diethylamino)propyl]amino}-8-(2,6-difluorophenyl)-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl]-4-methylbenzoic acid (40 mg, 0.074 mmol) in methylene chloride (2 mL) were added HBTU (30 mg, 0.079 mmol) and (2,2-dimethylpropyl)amine (0.045 mL, 0.37 mmol). The mixture  
20 was stirred at rt overnight. Solvent was removed by rotovap. Separation by HPLC with TFA, followed by neutralization with SPE amine cartridge afforded the title compound (39 mg, 86%). LC-MS  $m/z$  591 ( $M+H$ )<sup>+</sup>.

**Example 128**

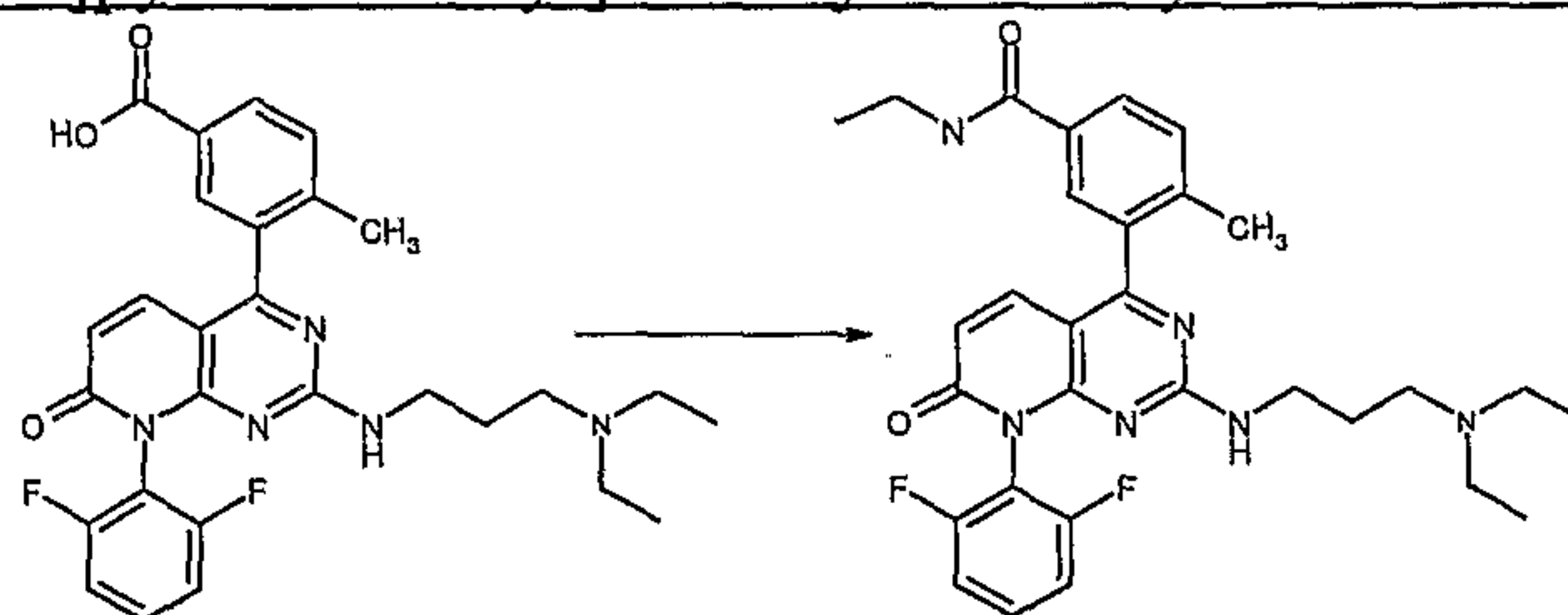
3-[2-{[3-(diethylamino)propyl]amino}-8-(2,6-difluorophenyl)-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl]-4-methyl-*N*-(2,2,2-trifluoroethyl)benzamide



5 To the compound 3-[2-{[3-(diethylamino)propyl]amino}-8-(2,6-difluorophenyl)-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl]-4-methylbenzoic acid (40 mg, 0.074 mmol) in methylene chloride (2 mL) were added HBTU (30 mg, 0.079 mmol) and (2,2,2-trifluoroethyl)amine (0.031 mL, 0.37 mmol). The mixture was stirred at rt overnight. Solvent was removed by rotovap. Separation by HPLC  
10 with TFA, followed by neutralization with SPE amine cartridge afforded the title compound (37 mg, 80%). LC-MS  $m/z$  603 ( $M+H$ )<sup>+</sup>.

**Example 129**

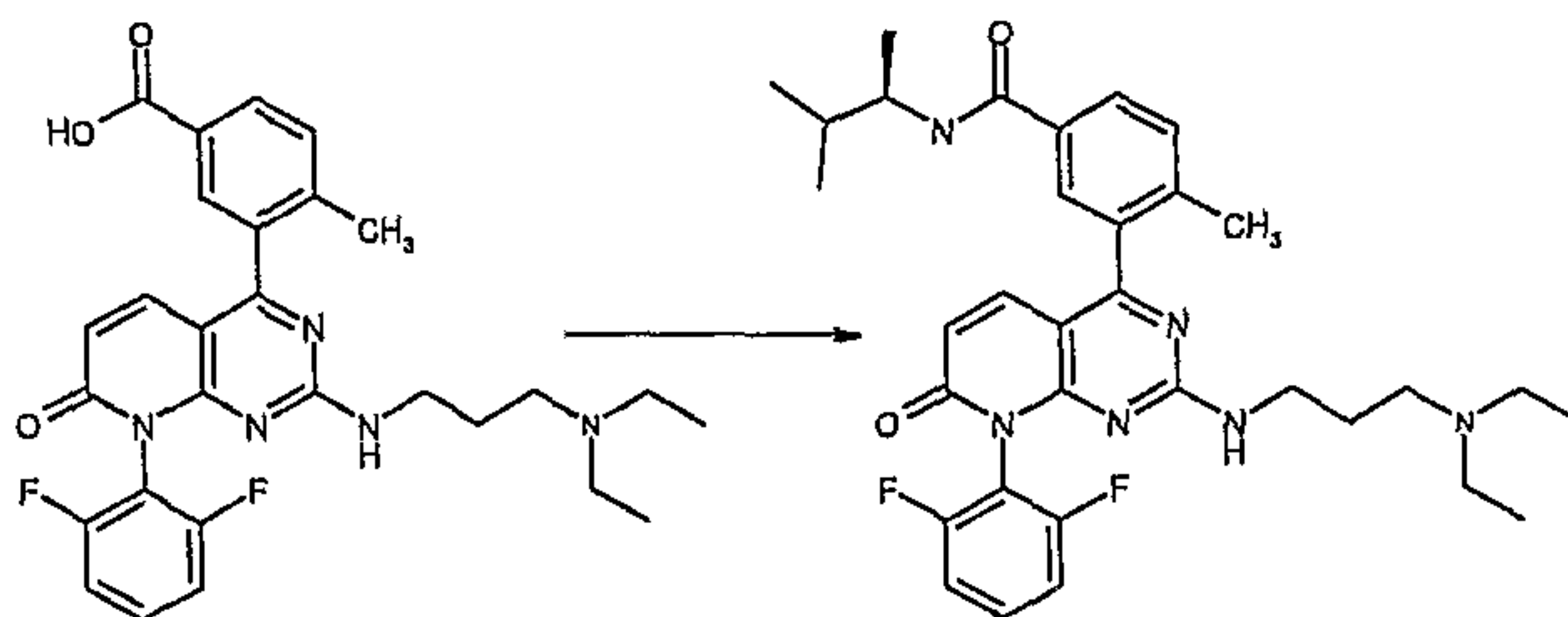
15 3-[2-{[3-(diethylamino)propyl]amino}-8-(2,6-difluorophenyl)-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl]-*N*-ethyl-4-methylbenzamide



To the compound 3-[2-{[3-(diethylamino)propyl]amino}-8-(2,6-difluorophenyl)-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl]-4-methylbenzoic acid (40 mg, 0.074 mmol) in methylene chloride (2 mL) were added HBTU (30 mg, 0.079 mmol) and ethylamine (0.19 mL, 0.37 mmol, 2.0M soln in THF). The  
20 mixture was stirred at rt overnight. Solvent was removed by rotovap. Separation by chromatography (90% methylene chloride / 7% MeOH / 3% ammonia) afforded the title compound (17 mg, 40%). LC-MS  $m/z$  549 ( $M+H$ )<sup>+</sup>.

**Example 130**

3-[2-{[3-(diethylamino)propyl]amino}-8-(2,6-difluorophenyl)-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl]-*N*-[(1*R*)-1,2-dimethylpropyl]-4-methylbenzamide



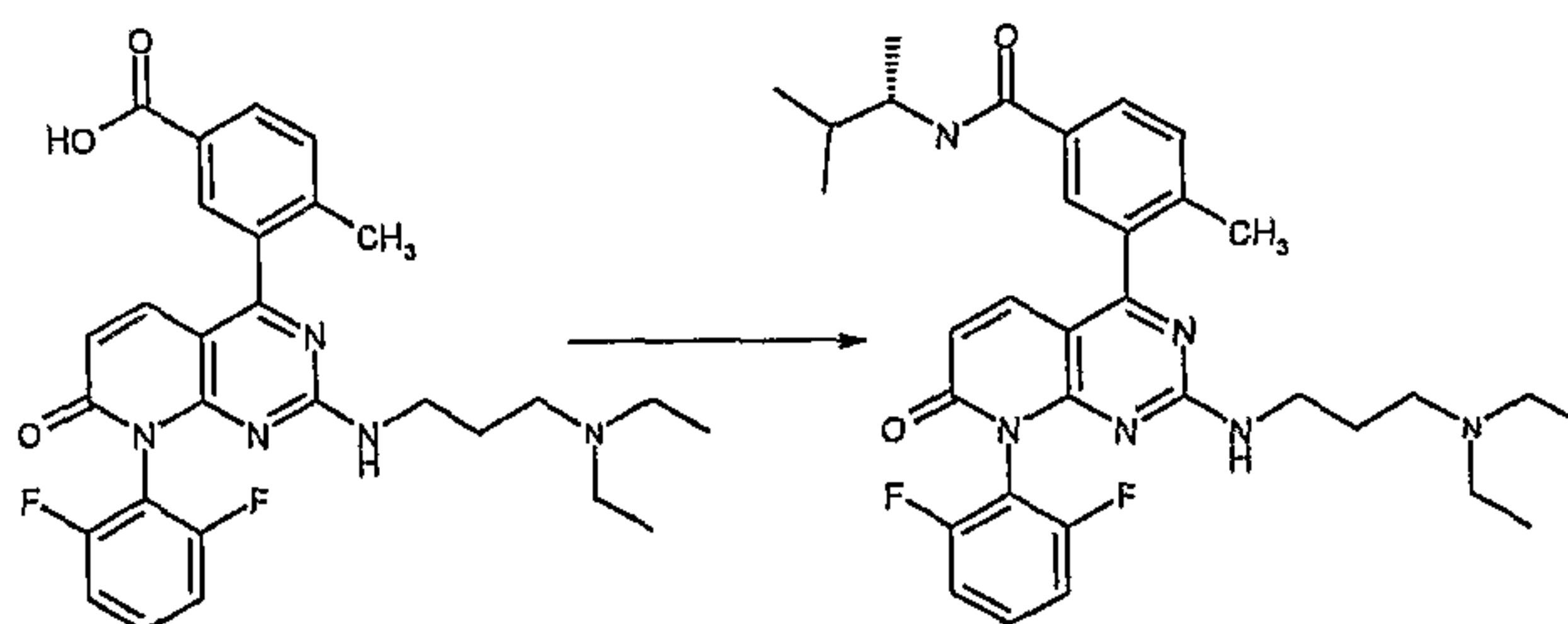
5

To the compound 3-[2-{[3-(diethylamino)propyl]amino}-8-(2,6-difluorophenyl)-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl]-4-methylbenzoic acid (31 mg, 0.06 mmol) in DMF (0.5 mL) were added HBTU (27 mg, 0.072 mmol), triethylamine (16.9 uL, 0.12 mmol) and (2*R*)-3-methyl-2-butanamine (10.5 uL, 0.09 mmol). The mixture was stirred at rt overnight. Separation by HPLC with TFA, followed by neutralization with SPE amine cartridge afforded the title compound (14 mg, 40%). LC-MS *m/z* 591 (*M*+*H*)<sup>+</sup>.

10

**Example 131**

15 3-[2-{[3-(diethylamino)propyl]amino}-8-(2,6-difluorophenyl)-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl]-*N*-[(1*S*)-1,2-dimethylpropyl]-4-methylbenzamide



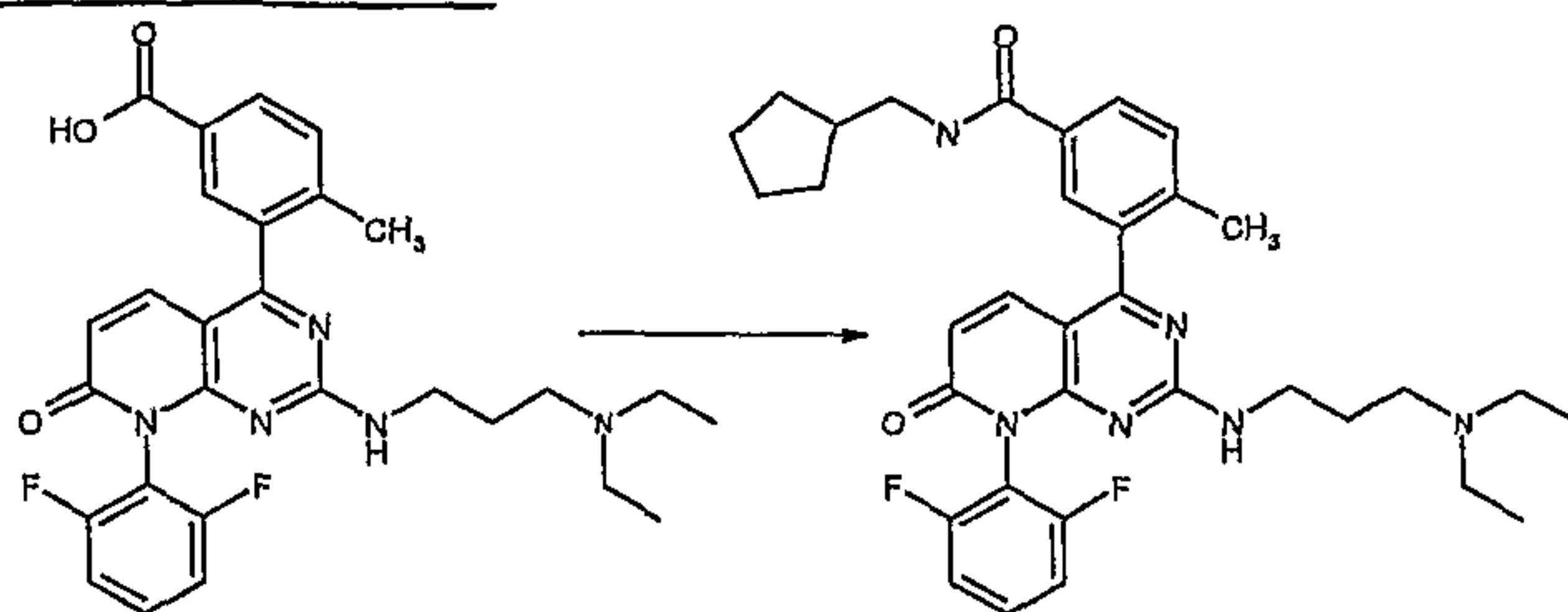
20

To the compound 3-[2-{[3-(diethylamino)propyl]amino}-8-(2,6-difluorophenyl)-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl]-4-methylbenzoic acid (31 mg, 0.06 mmol) in DMF (0.5 mL) were added HBTU (27 mg, 0.072 mmol), triethylamine (16.9 uL, 0.12 mmol) and (2*S*)-3-methyl-2-butanamine (10.5 uL, 0.09 mmol). The mixture was stirred at rt overnight. Separation by HPLC with TFA, followed by neutralization with SPE amine cartridge afforded the title compound (14 mg, 40%). LC-MS *m/z* 591 (*M*+*H*)<sup>+</sup>.

25

**Example 132**

*N*-(cyclopentylmethyl)-3-[2-{[3-(diethylamino)propyl]amino}-8-(2,6-difluorophenyl)-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl]-4-methylbenzamidetrifluoroacetate



5

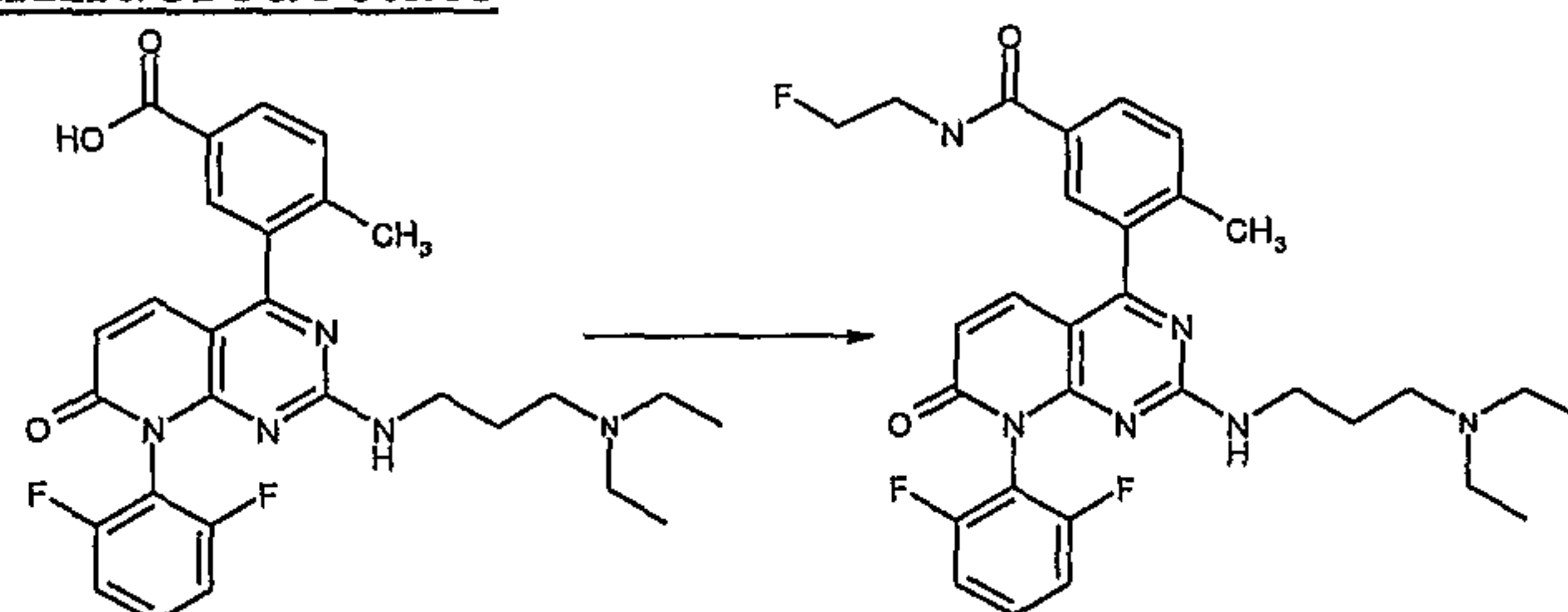
To the compound 3-[2-{[3-(diethylamino)propyl]amino}-8-(2,6-difluorophenyl)-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl]-4-methylbenzoic acid (26 mg, 0.05 mmol) in DMF (0.5 mL) were added HBTU (28 mg, 0.075 mmol), triethylamine (21.1  $\mu$ L, 0.15 mmol) and 1-cyclopentylmethanamine (9.9 mg, 0.1 mmol). The mixture was stirred at rt overnight. Separation by HPLC with TFA, afforded the title compound (10 mg, 33%). LC-MS  $m/z$  603 ( $M+H$ )<sup>+</sup>.

10

**Example 133**

3-[2-{[3-(diethylamino)propyl]amino}-8-(2,6-difluorophenyl)-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl]-*N*-(2-fluoroethyl)-4-methylbenzamidetrifluoroacetate

15

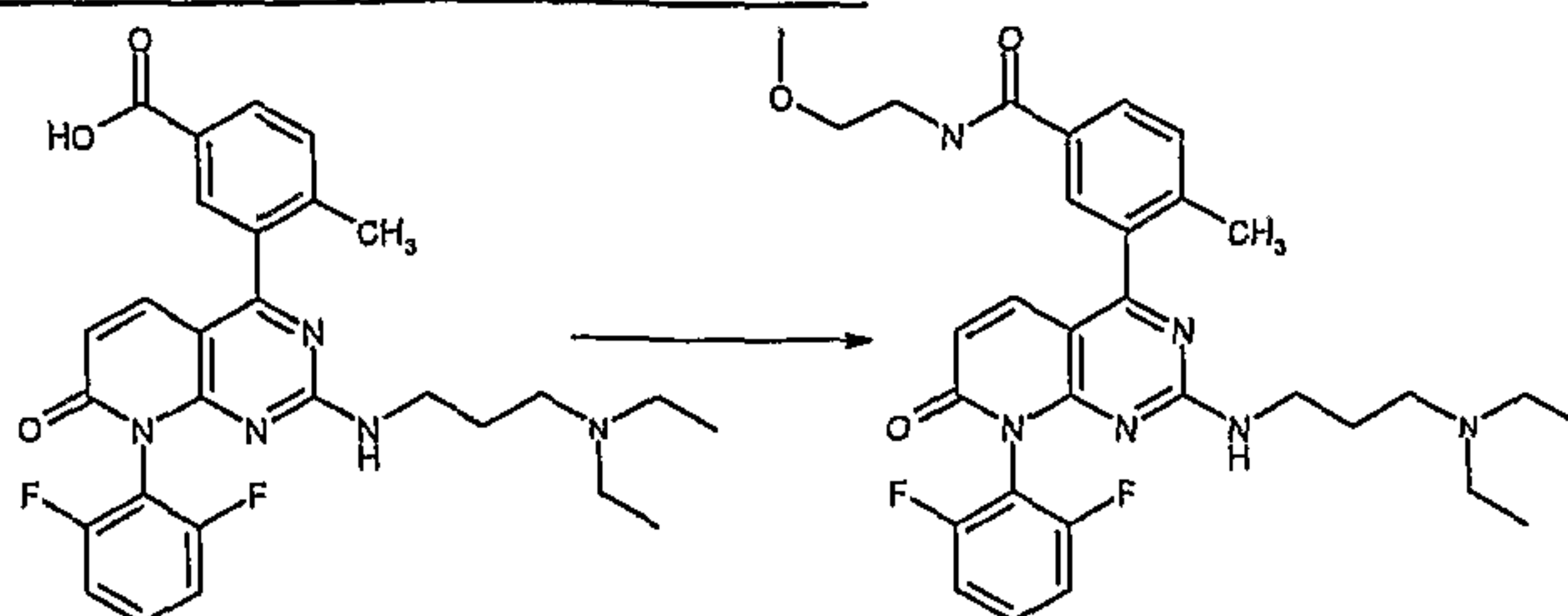


20

To the compound 3-[2-{[3-(diethylamino)propyl]amino}-8-(2,6-difluorophenyl)-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl]-4-methylbenzoic acid (26 mg, 0.05 mmol) in DMF (0.5 mL) were added HBTU (28 mg, 0.075 mmol), triethylamine (21.1  $\mu$ L, 0.15 mmol) and 2-fluoroethanamine hydrochloride (10 mg, 0.1 mmol). The mixture was stirred at rt overnight. Separation by HPLC with TFA, afforded the title compound (9 mg, 32%). LC-MS  $m/z$  567 ( $M+H$ )<sup>+</sup>.

**Example 134**

3-[2-{[3-(diethylamino)propyl]amino}-8-(2,6-difluorophenyl)-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl]-4-methyl-*N*-[2-(methyloxy)ethyl]benzamidetrifluoroacetate



5

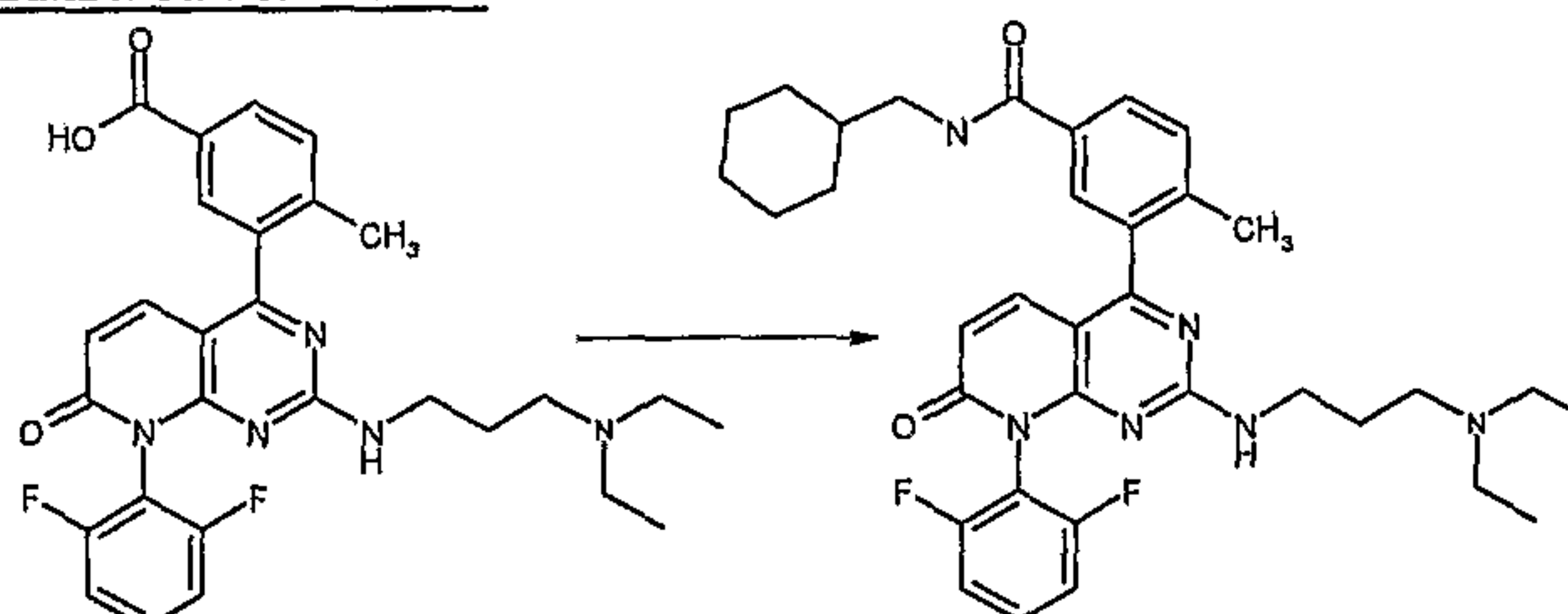
To the compound 3-[2-{[3-(diethylamino)propyl]amino}-8-(2,6-difluorophenyl)-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl]-4-methylbenzoic acid (26 mg, 0.05 mmol) in DMF (0.5 mL) were added HBTU (28 mg, 0.075 mmol), triethylamine (21.1 uL, 0.15 mmol) and 2-(methyloxy)ethanamine (8.6 uL, 0.1 mmol). The mixture was stirred at rt overnight. Separation by HPLC with TFA, afforded the title compound (11 mg, 38%). LC-MS  $m/z$  579 ( $M+H$ )<sup>+</sup>.

10

**Example 135**

*N*-(cyclohexylmethyl)-3-[2-{[3-(diethylamino)propyl]amino}-8-(2,6-difluorophenyl)-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl]-4-methylbenzamidetrifluoroacetate

15

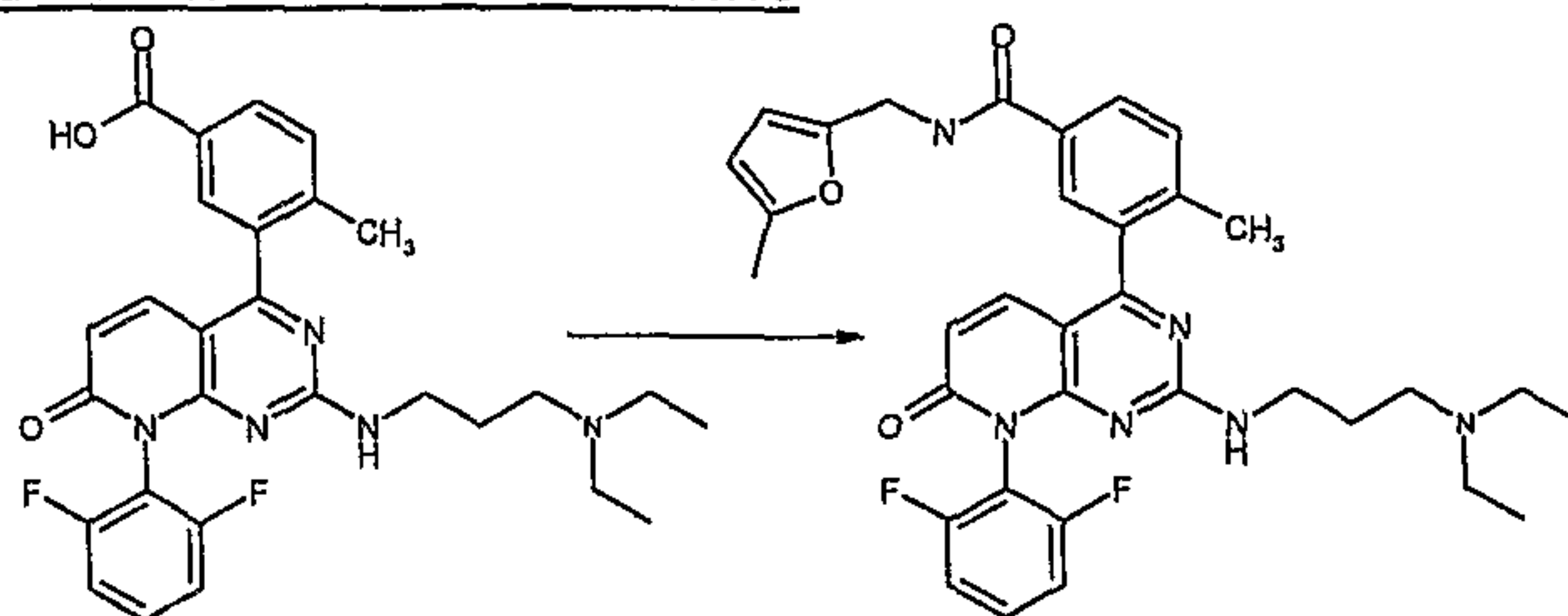


20

To the compound 3-[2-{[3-(diethylamino)propyl]amino}-8-(2,6-difluorophenyl)-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl]-4-methylbenzoic acid (26 mg, 0.05 mmol) in DMF (0.5 mL) were added HBTU (28 mg, 0.075 mmol), triethylamine (21.1 uL, 0.15 mmol) and (cyclohexylmethyl)amine (13.0 uL, 0.1 mmol). The mixture was stirred at rt overnight. Separation by HPLC with TFA, afforded the title compound (10 mg, 32%). LC-MS  $m/z$  617 ( $M+H$ )<sup>+</sup>.

**Example 136**

3-[2-{[3-(diethylamino)propyl]amino}-8-(2,6-difluorophenyl)-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl]-4-methyl-*N*-[(5-methyl-2-furanyl)methyl]benzamide trifluoroacetate



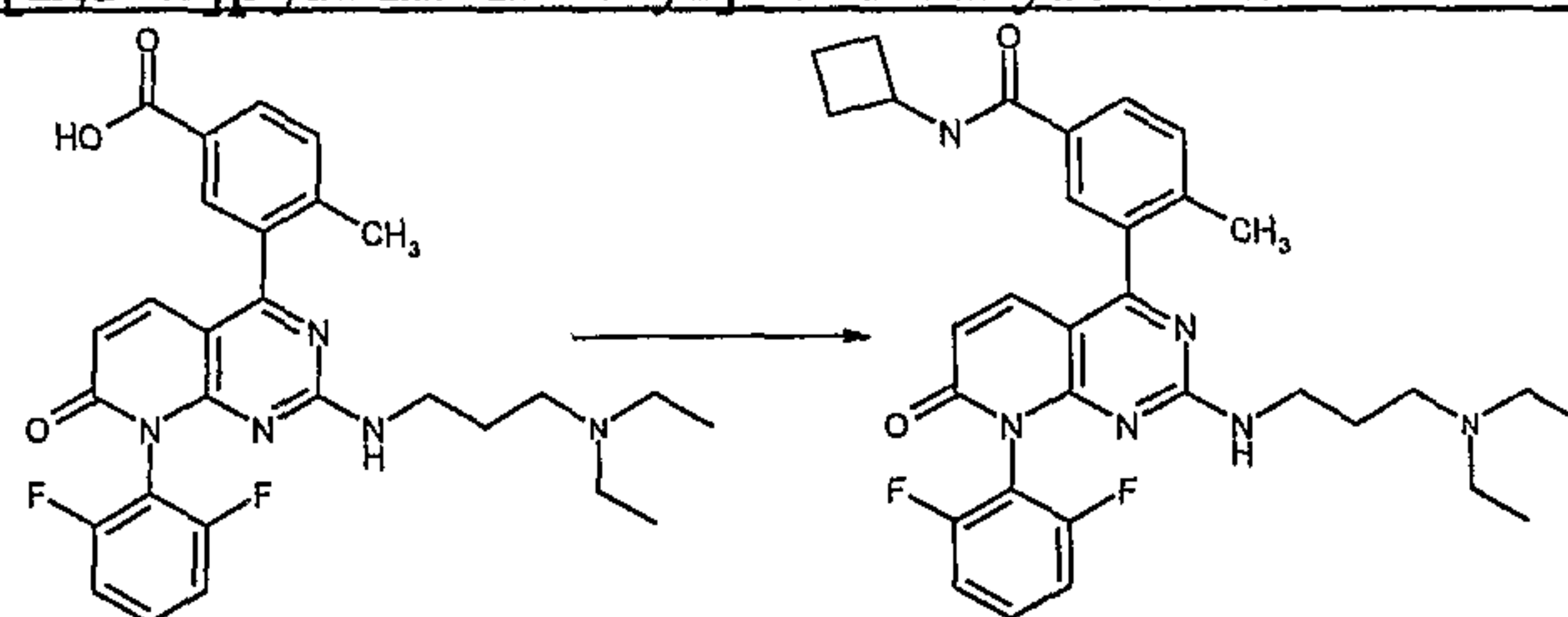
5

To the compound 3-[2-{[3-(diethylamino)propyl]amino}-8-(2,6-difluorophenyl)-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl]-4-methylbenzoic acid (26 mg, 0.05 mmol) in DMF (0.5 mL) was added HBTU (28 mg, 0.075 mmol), triethylamine (21.1 uL, 0.15 mmol) and [(5-methyl-2-furanyl)methyl]amine (11.2 uL, 0.1 mmol). The mixture was stirred at rt overnight. Separation by HPLC with TFA, afforded the title compound (13 mg, 42%). LC-MS  $m/z$  615 ( $M+H$ )<sup>+</sup>.

10

**Example 137**

*N*-cyclobutyl-3-[2-{[3-(diethylamino)propyl]amino}-8-(2,6-difluorophenyl)-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl]-4-methylbenzamide trifluoroacetate



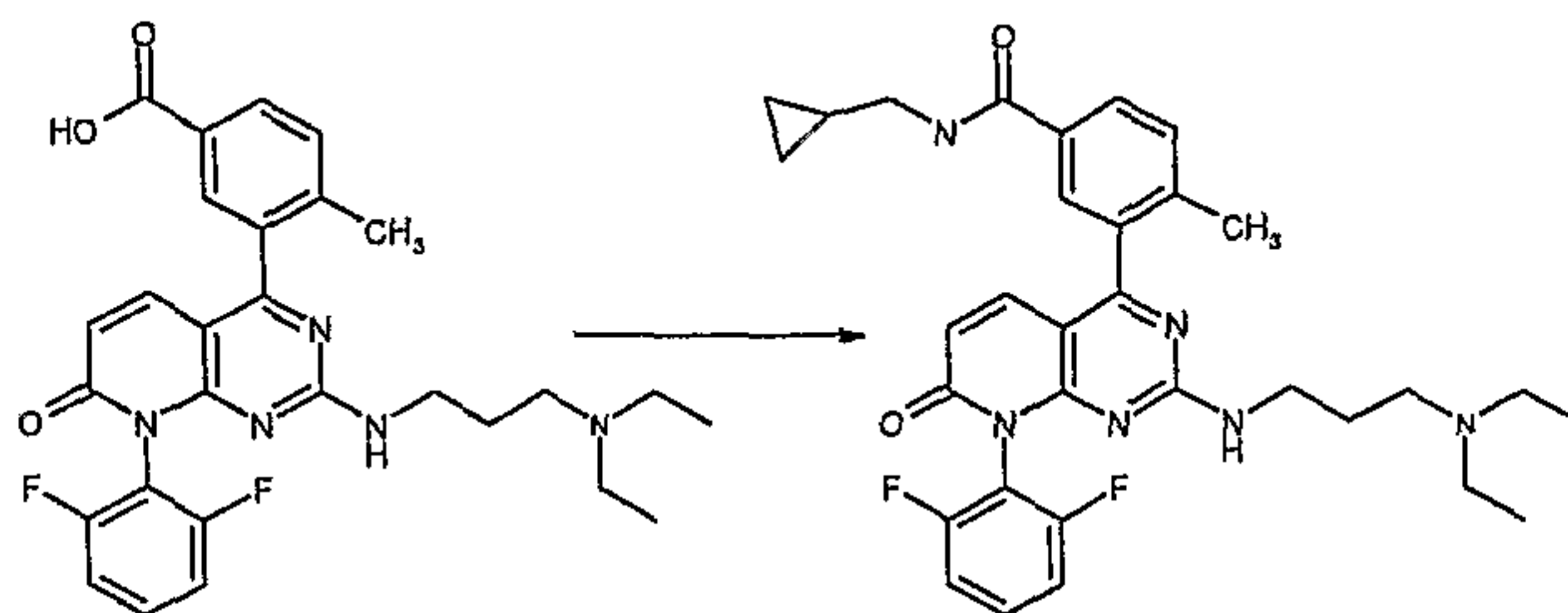
15

To the compound 3-[2-{[3-(diethylamino)propyl]amino}-8-(2,6-difluorophenyl)-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl]-4-methylbenzoic acid (26 mg, 0.05 mmol) in DMF (0.5 mL) were added HBTU (28 mg, 0.075 mmol), triethylamine (21.1 uL, 0.15 mmol) and cyclobutylamine (8.5 uL, 0.1 mmol). The mixture was stirred at rt overnight. Separation by HPLC with TFA, afforded the title compound (10 mg, 35%). LC-MS  $m/z$  575 ( $M+H$ )<sup>+</sup>.

20

**Example 138**

*N*-(cyclopropylmethyl)-3-[2-{[3-(diethylamino)propyl]amino}-8-(2,6-difluorophenyl)-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl]-4-methylbenzamide trifluoroacetate



5

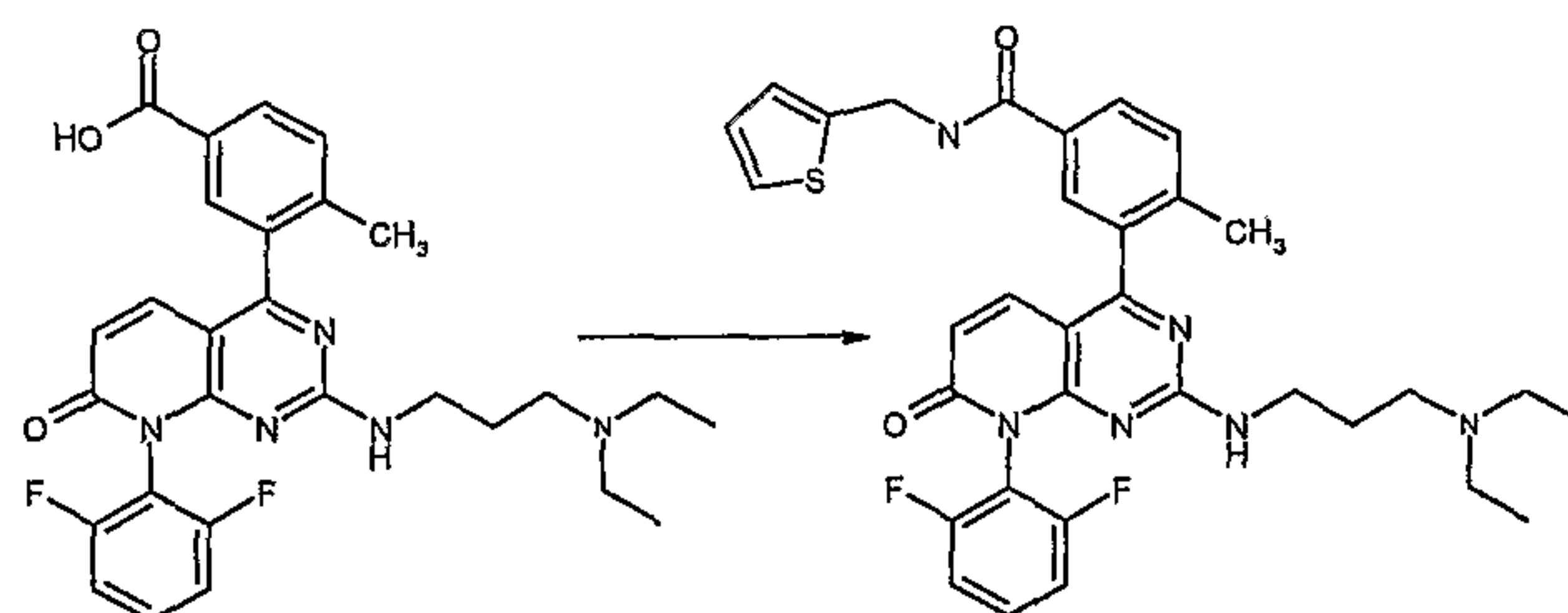
To the compound 3-[2-{[3-(diethylamino)propyl]amino}-8-(2,6-difluorophenyl)-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl]-4-methylbenzoic acid (26 mg, 0.05 mmol) in DMF (0.5 mL) were added HBTU (28 mg, 0.075 mmol), triethylamine (21.1 uL, 0.15 mmol) and (cyclopropylmethyl)amine (10.3 uL, 0.1 mmol). The mixture was stirred at rt overnight. Separation by HPLC with TFA, afforded the title compound (9 mg, 31%). LC-MS  $m/z$  575 ( $M+H$ )<sup>+</sup>.

10

**Example 139**

3-[2-{[3-(diethylamino)propyl]amino}-8-(2,6-difluorophenyl)-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl]-4-methyl-*N*-(2-thienylmethyl)benzamide trifluoroacetate

15

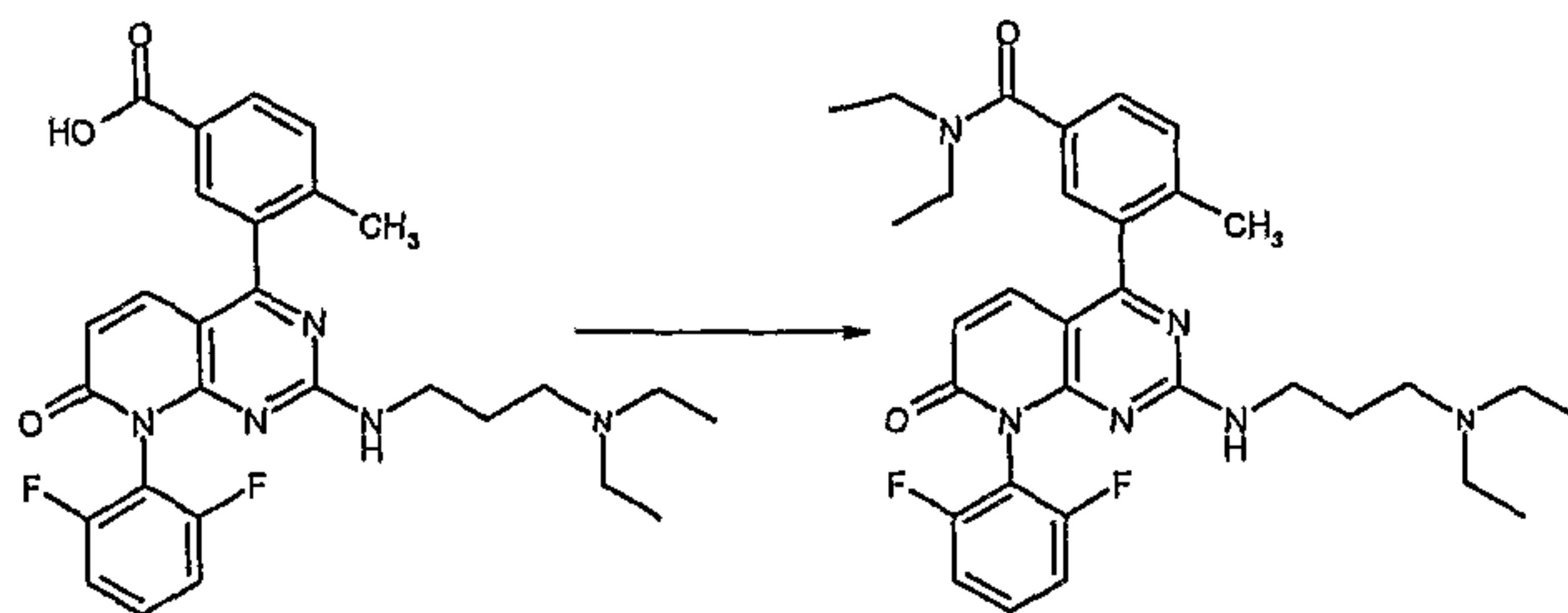


To the compound 3-[2-{[3-(diethylamino)propyl]amino}-8-(2,6-difluorophenyl)-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl]-4-methylbenzoic acid (26 mg, 0.05 mmol) in DMF (0.5 mL) were added HBTU (28 mg, 0.075 mmol), triethylamine (21.1 uL, 0.15 mmol) and (2-thienylmethyl)amine (15.1 uL, 0.1 mmol). The mixture was stirred at rt overnight. Separation by HPLC with TFA, afforded the title compound (11 mg, 36%). LC-MS  $m/z$  617 ( $M+H$ )<sup>+</sup>.

20

**Example 140**

3-[2-{[3-(diethylamino)propyl]amino}-8-(2,6-difluorophenyl)-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl]-*N,N*-diethyl-4-methylbenzamide trifluoroacetate



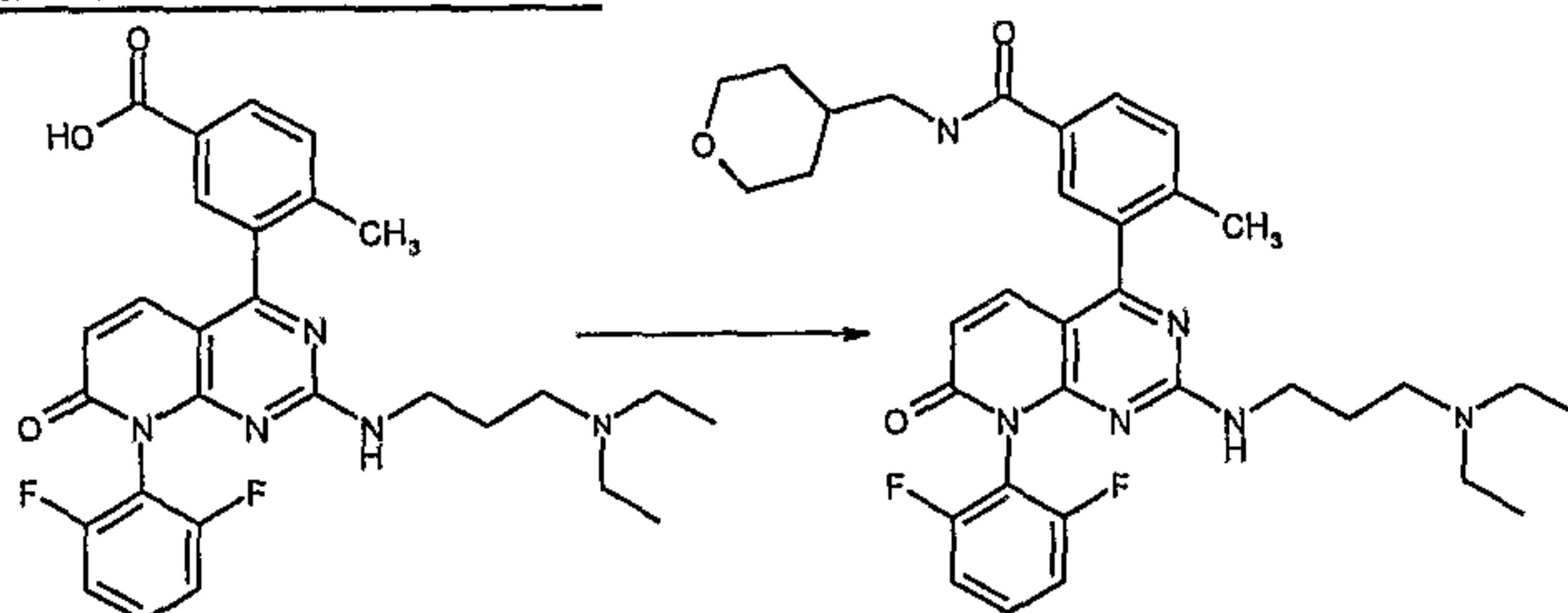
5

To the compound 3-[2-{[3-(diethylamino)propyl]amino}-8-(2,6-difluorophenyl)-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl]-4-methylbenzoic acid (26 mg, 0.05 mmol) in DMF (0.5 mL) were added HBTU (28 mg, 0.075 mmol), triethylamine (21.1  $\mu$ L, 0.15 mmol) and diethyl amine (7.4  $\mu$ L, 0.1 mmol). The mixture was stirred at rt overnight. Separation by HPLC with TFA, afforded the title compound (7 mg, 24%). LC-MS  $m/z$  577 ( $M+H$ )<sup>+</sup>.

10

**Example 141**

3-[2-{[3-(diethylamino)propyl]amino}-8-(2,6-difluorophenyl)-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl]-4-methyl-*N*-(tetrahydro-2*H*-pyran-4-ylmethyl)benzamide trifluoroacetate



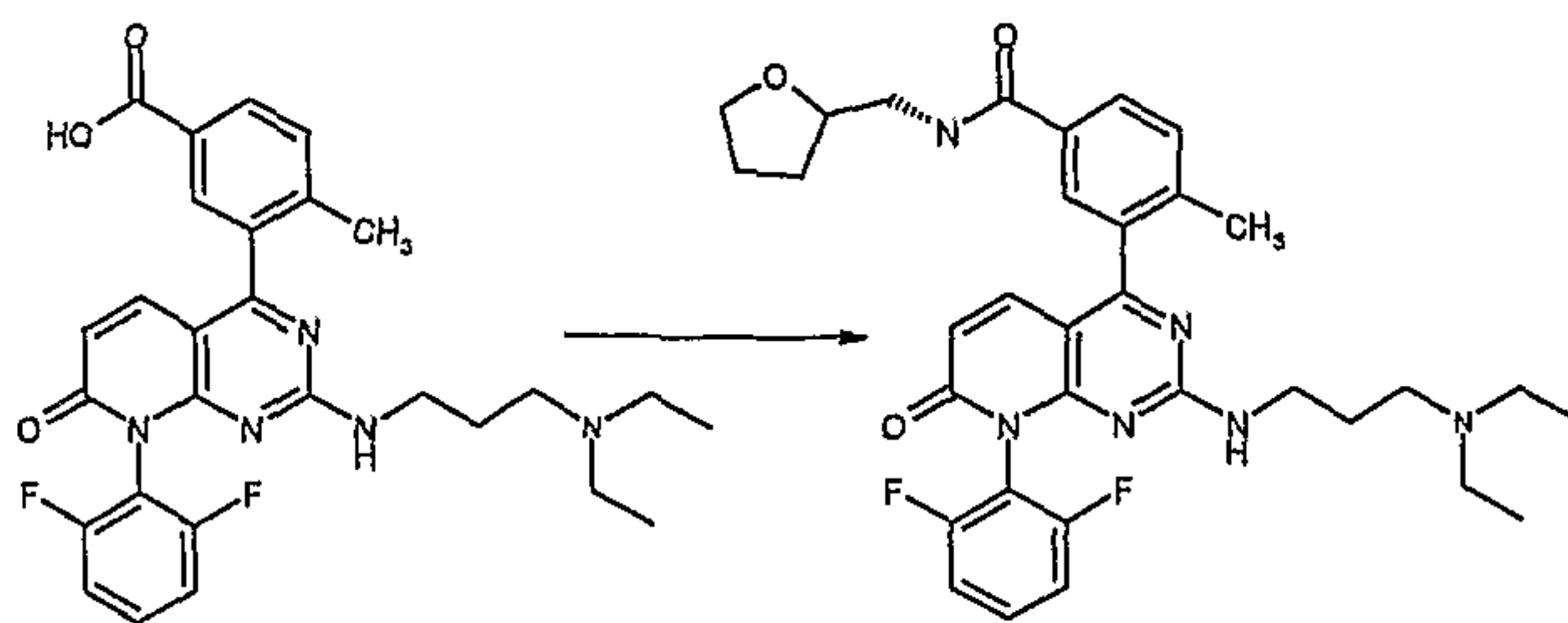
To the compound 3-[2-{[3-(diethylamino)propyl]amino}-8-(2,6-difluorophenyl)-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl]-4-methylbenzoic acid (26 mg, 0.05 mmol) in DMF (0.5 mL) were added HBTU (28 mg, 0.075 mmol), triethylamine (21.1  $\mu$ L, 0.15 mmol) and (tetrahydro-2*H*-pyran-4-ylmethyl)amine (15.4  $\mu$ L, 0.1 mmol). The mixture was stirred at rt overnight. Separation by HPLC with TFA, afforded the title compound (8 mg, 26%). LC-MS  $m/z$  617 ( $M+H$ )<sup>+</sup>.

20

25

**Example 142**

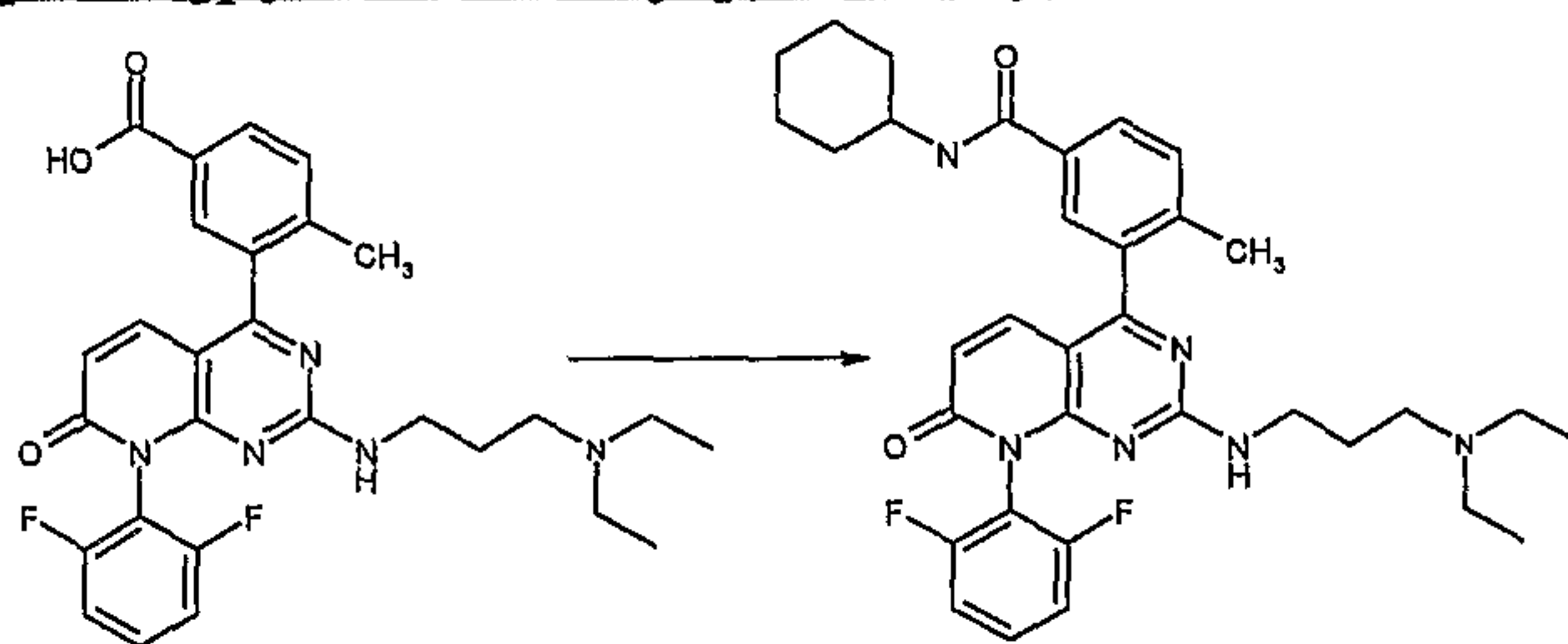
3-[2-{[3-(diethylamino)propyl]amino}-8-(2,6-difluorophenyl)-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl]-4-methyl-*N*-(tetrahydro-2-furanylmethyl)benzamide trifluoroacetate



To the compound 3-[2-[[3-(diethylamino)propyl]amino]-8-(2,6-difluorophenyl)-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl]-4-methylbenzoic acid (26 mg, 0.05 mmol) in DMF (0.5 mL) were added HBTU (28 mg, 0.075 mmol), triethylamine (21.1 uL, 0.15 mmol) and (tetrahydro-2-furanylmethyl)amine (10.3 uL, 0.1 mmol). The mixture was stirred at rt overnight. Separation by HPLC with TFA afforded the title compound (9 mg, 30%). LC-MS *m/z* 605 (*M*+*H*)<sup>+</sup>.

### Example 143

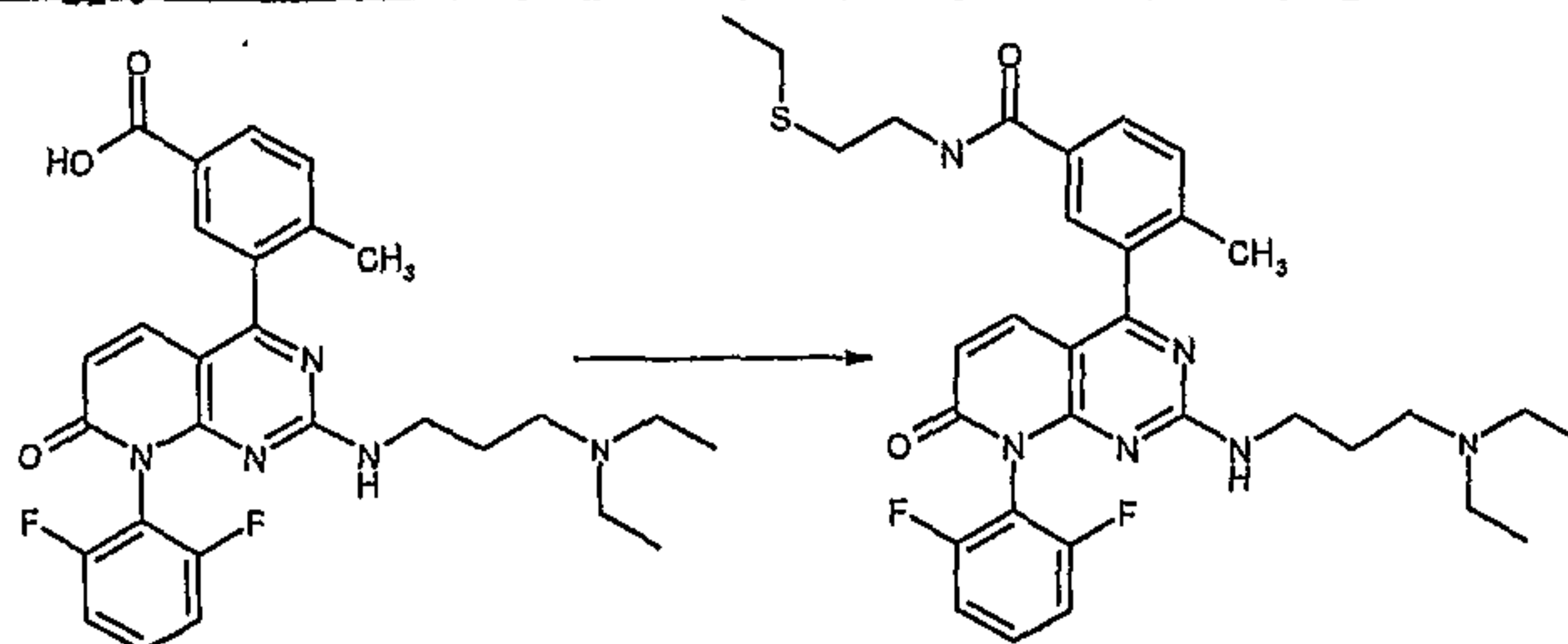
10 *N*-cyclohexyl-3-[2-[[3-(diethylamino)propyl]amino]-8-(2,6-difluorophenyl)-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl]-4-methylbenzamide



To the compound 3-[2-[[3-(diethylamino)propyl]amino]-8-(2,6-difluorophenyl)-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl]-4-methylbenzoic acid (26 mg, 0.05 mmol) in DMF (0.5 mL) were added HBTU (28 mg, 0.075 mmol), triethylamine (21.1 uL, 0.15 mmol) and cyclohexylamine (11.5 uL, 0.1 mmol). The mixture was stirred at rt overnight. Separation by HPLC with TFA, followed by neutralization with SPE amine cartridge afforded the title compound (9 mg, 30%). LC-MS *m/z* 603 (*M*+*H*)<sup>+</sup>.

### Example 144

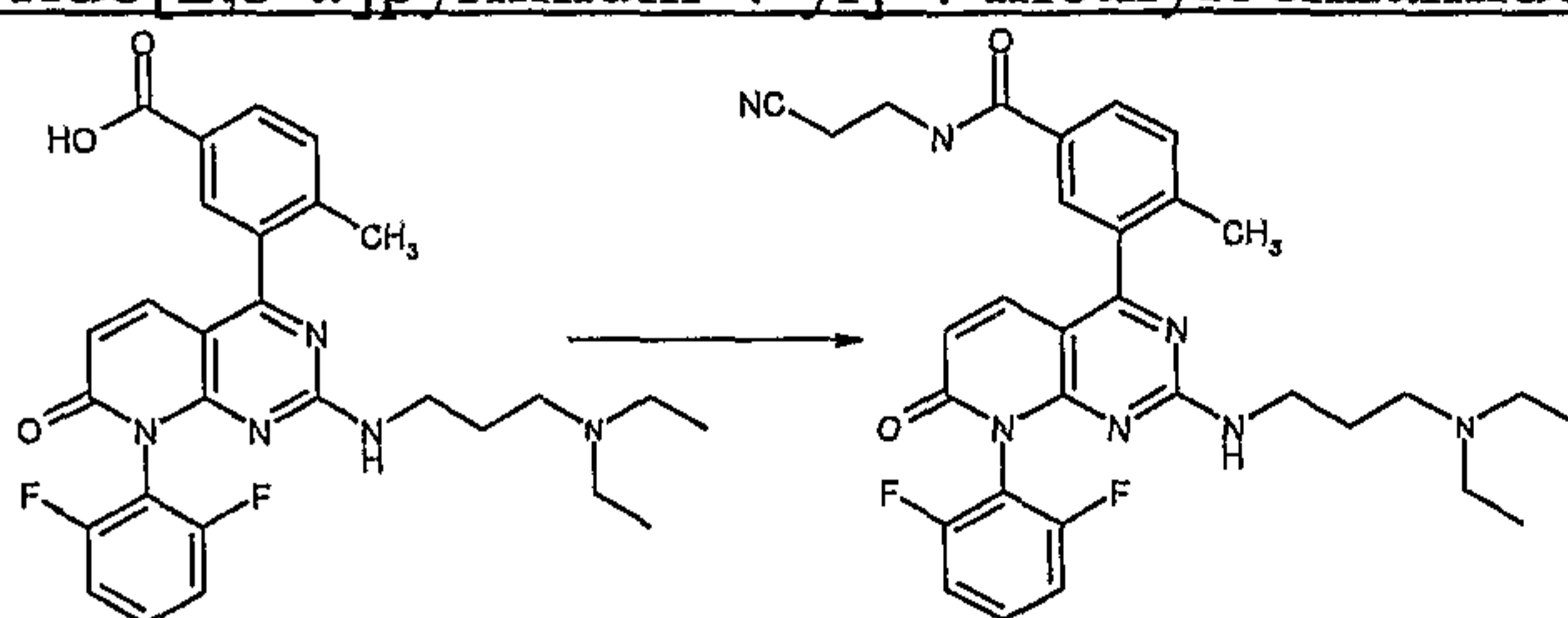
20 3-[2-[[3-(diethylamino)propyl]amino]-8-(2,6-difluorophenyl)-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl]-*N*-[2-(ethylthio)ethyl]-4-methylbenzamide



To the compound 3-[2-{[3-(diethylamino)propyl]amino}-8-(2,6-difluorophenyl)-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl]-4-methylbenzoic acid (26 mg, 0.05 mmol) in DMF (0.5 mL) were added HBTU (28 mg, 0.075 mmol), triethylamine (21.1  $\mu$ L, 0.15 mmol) and [2-(ethylthio)ethyl]amine hydrochloride (14.2 mg, 0.1 mmol). The mixture was stirred at rt overnight. Separation by HPLC with TFA, followed by neutralization with SPE amine cartridge afforded the title compound (7 mg, 23%). LC-MS  $m/z$  607 ( $M+H$ )<sup>+</sup>.

### Example 145

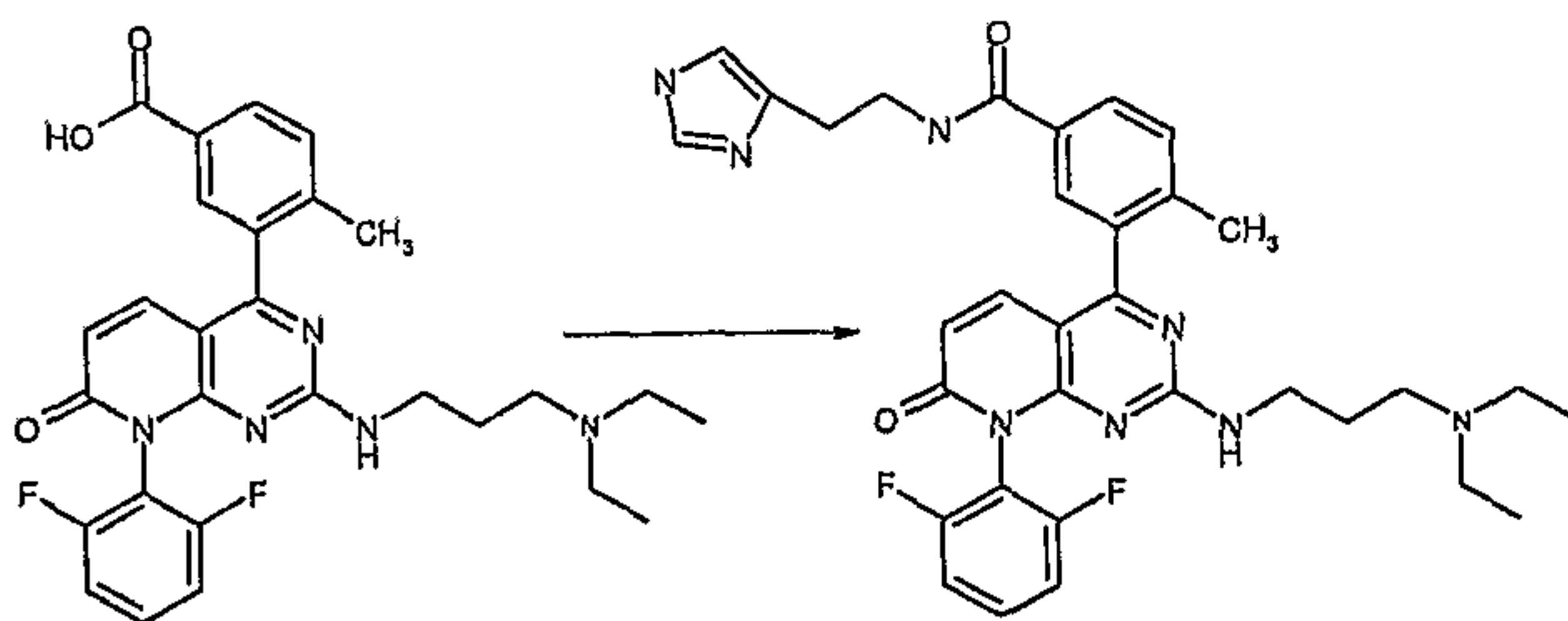
*N*-(2-cyanoethyl)-3-[2-{[3-(diethylamino)propyl]amino}-8-(2,6-difluorophenyl)-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl]-4-methylbenzamide



To the compound 3-[2-{[3-(diethylamino)propyl]amino}-8-(2,6-difluorophenyl)-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl]-4-methylbenzoic acid (26 mg, 0.05 mmol) in DMF (0.5 mL) were added HBTU (28 mg, 0.075 mmol), triethylamine (21.1  $\mu$ L, 0.15 mmol) and 3-aminopropanenitrile hydrochloride (9.3 mg, 0.1 mmol). The mixture was stirred at rt overnight. Separation by HPLC with TFA, followed by neutralization with SPE amine cartridge afforded the title compound (6 mg, 21%). LC-MS  $m/z$  560 ( $M+H$ )<sup>+</sup>.

### Example 146

3-[2-{[3-(diethylamino)propyl]amino}-8-(2,6-difluorophenyl)-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl]-*N*-[2-(1*H*-imidazol-4-yl)ethyl]-4-methylbenzamide



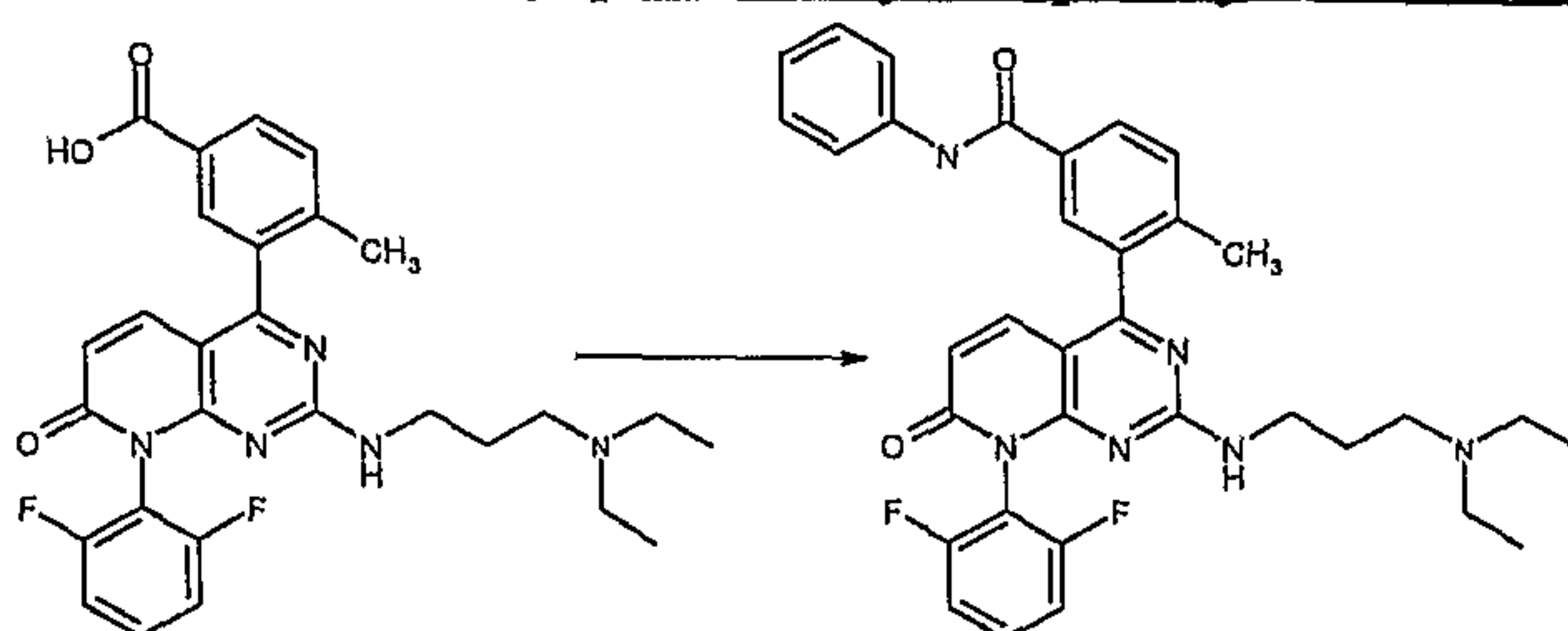
To the compound 3-[2-{[3-(diethylamino)propyl]amino}-8-(2,6-difluorophenyl)-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl]-4-methylbenzoic acid (26 mg, 0.05 mmol) in DMF (0.5 mL) were added HBTU (28 mg, 0.075 mmol), triethylamine (21.1  $\mu$ L, 0.15 mmol) and [2-(1*H*-imidazol-4-yl)ethyl]amine

(22.2 mg, 0.2 mmol). The mixture was stirred at rt overnight. Separation by HPLC with TFA, followed by neutralization with SPE amine cartridge afforded the title compound (26 mg, 85%). LC-MS  $m/z$  615 ( $M+H$ )<sup>+</sup>.

5

**Example 147**

3-[2-{[3-(diethylamino)propyl]amino}-8-(2,6-difluorophenyl)-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl]-4-methyl-*N*-phenylbenzamide



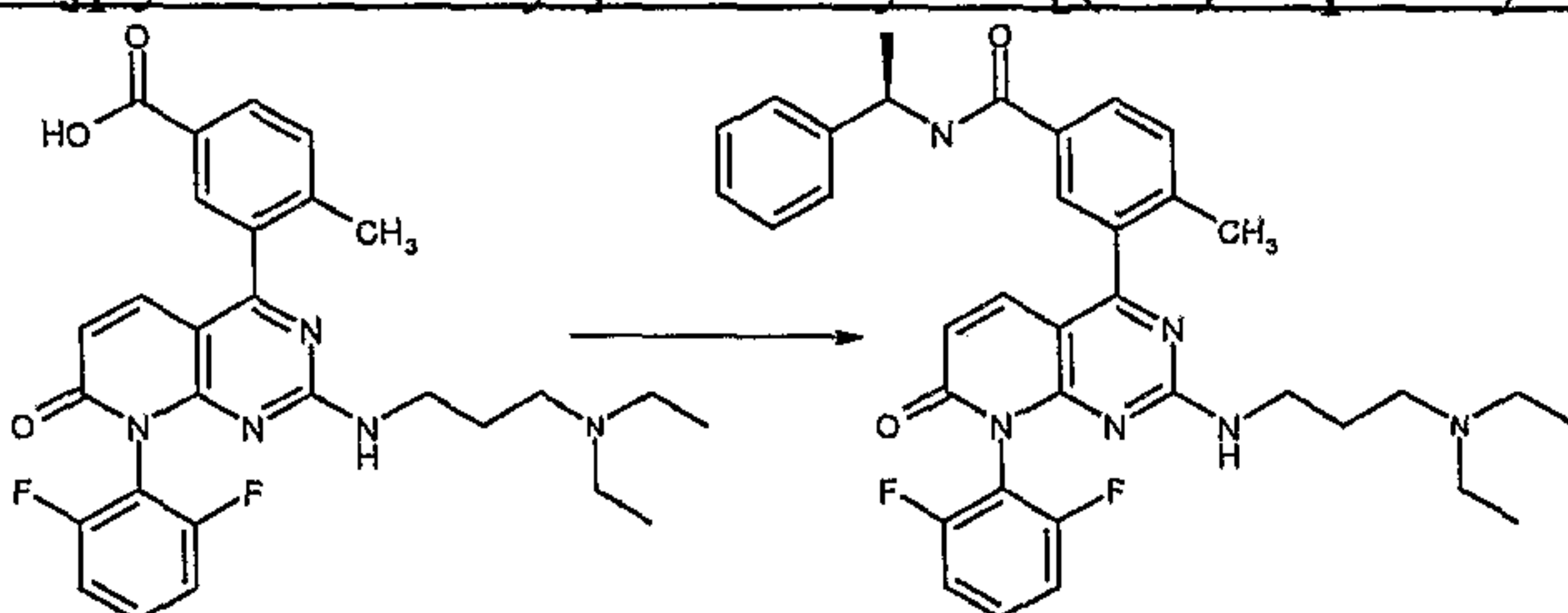
To the compound 3-[2-{[3-(diethylamino)propyl]amino}-8-(2,6-difluorophenyl)-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl]-4-methylbenzoic acid (26 mg, 0.05 mmol) in DMF (0.5 mL) were added HBTU (28 mg, 0.075 mmol), triethylamine (21.1  $\mu$ L, 0.15 mmol) and aniline (9.1  $\mu$ L, 0.1 mmol). The mixture was stirred at rt overnight. To the mixture was added 5 mL dichloromethane and 2 mL water, stirred for 3 min. The organic layer was loaded onto the silica gel column. Chromatography (90% methylene chloride / 7% MeOH / 3% ammonia) afforded the title compound (9 mg, 30%). LC-MS  $m/z$  597 ( $M+H$ )<sup>+</sup>.

15

**Example 148**

3-[2-{[3-(diethylamino)propyl]amino}-8-(2,6-difluorophenyl)-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl]-4-methyl-*N*-[(1*R*)-1-phenylethyl]benzamide

20

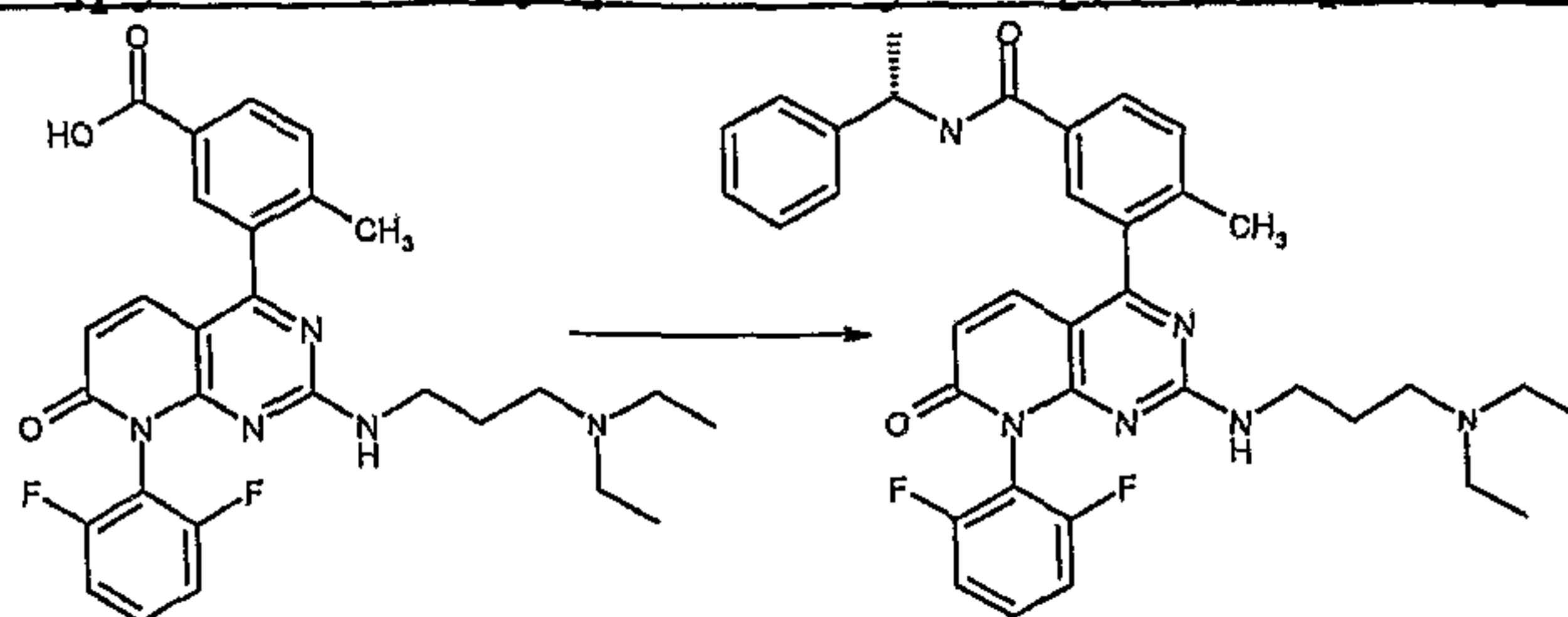


To the compound 3-[2-{[3-(diethylamino)propyl]amino}-8-(2,6-difluorophenyl)-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl]-4-methylbenzoic acid (26 mg, 0.05 mmol) in DMF (0.5 mL) were added HBTU (28 mg, 0.075 mmol), triethylamine (21.1  $\mu$ L, 0.15 mmol) and [(1*R*)-1-phenylethyl]amine (12.9  $\mu$ L, 0.1 mmol). The mixture was stirred at rt overnight. Separation by HPLC with TFA, followed by neutralization with SPE amine cartridge afforded the title compound (14 mg, 45%). LC-MS  $m/z$  625 ( $M+H$ )<sup>+</sup>.

25

**Example 149**

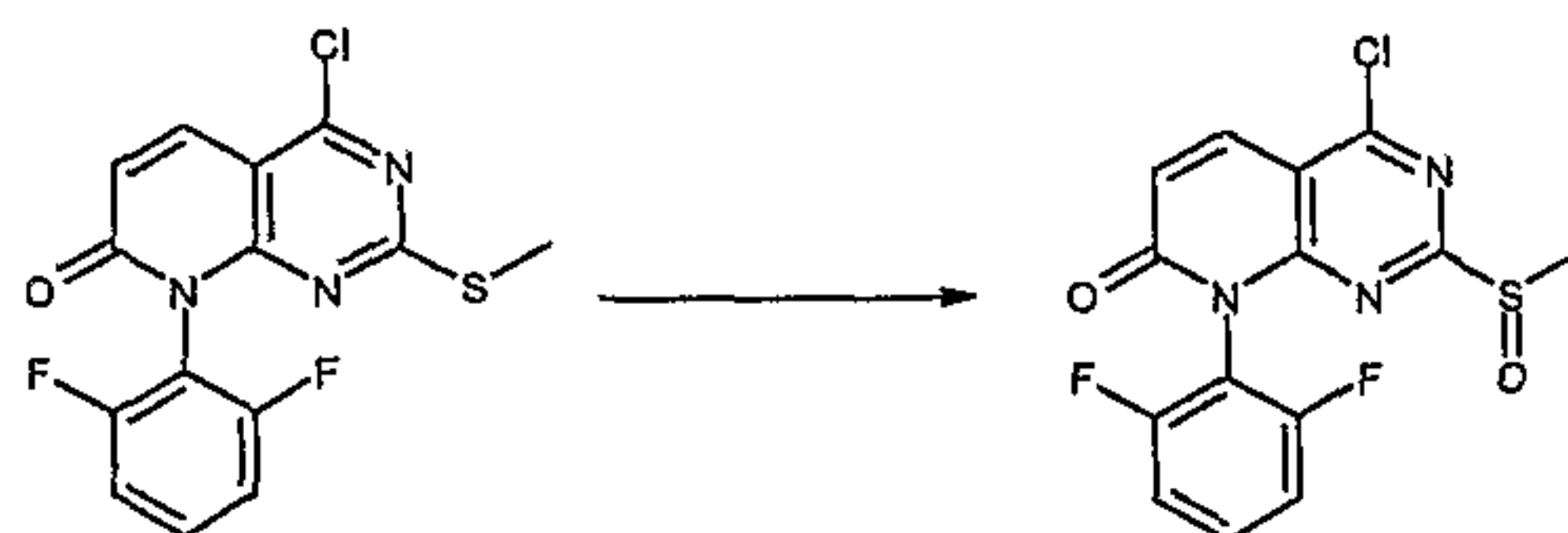
3-[2-{[3-(diethylamino)propyl]amino}-8-(2,6-difluorophenyl)-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl]-4-methyl-*N*-[(1*S*)-1-phenylethyl]benzamide



To the compound 3-[2-{[3-(diethylamino)propyl]amino}-8-(2,6-difluorophenyl)-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl]-4-methylbenzoic acid (26 mg, 0.05 mmol) in DMF (0.5 mL) were added HBTU (28 mg, 0.075 mmol), triethylamine (21.1  $\mu$ L, 0.15 mmol) and [(1*S*)-1-phenylethyl]amine (12.9  $\mu$ L, 0.1 mmol). The mixture was stirred at rt overnight. Separation by HPLC with TFA, followed by neutralization with SPE amine cartridge afforded the title compound (14 mg, 45%). LC-MS  $m/z$  625 ( $M+H$ )<sup>+</sup>.

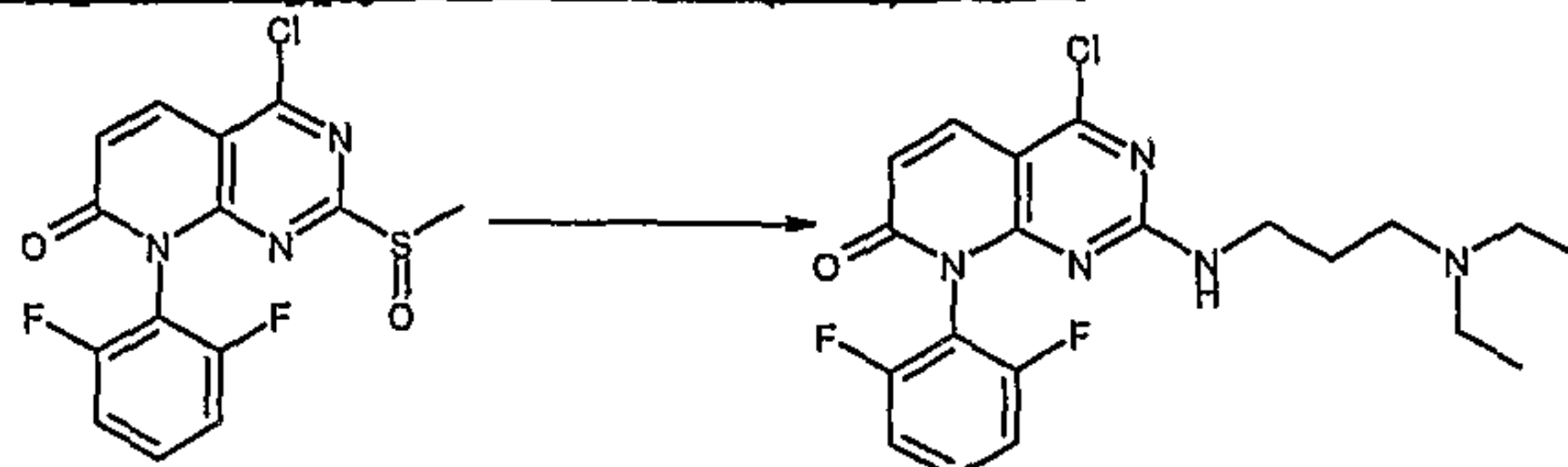
**Example 150**

3-[2-{[3-(diethylamino)propyl]amino}-8-(2,6-difluorophenyl)-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl]-2-methyl-*N*-1,3-thiazol-2-ylbenzamide  
150a)4-chloro-8-(2,6-difluorophenyl)-2-(methylsulfinyl)pyrido[2,3-*d*]pyrimidin-7(8*H*)-one



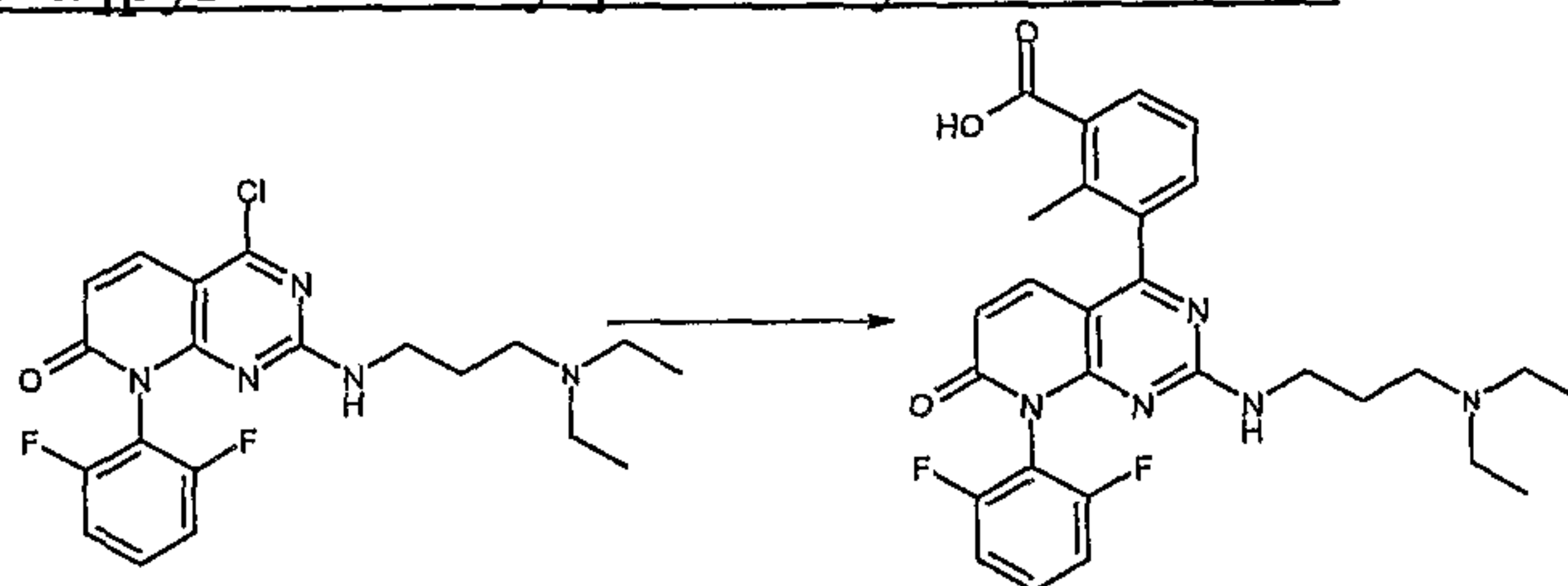
To the compound 4-chloro-8-(2,6-difluorophenyl)-2-(methylthio)pyrido[2,3-*d*]pyrimidin-7(8*H*)-one (1.70 g, 5.0 mmol) in dichloromethane (100 mL) was added mCPBA (1.16 g, 7.5 mmol). The mixture was stirred at rt for 10 min. Chromatography with hexane/ethyl acetate afforded the title compound (1.59 g, 89%). LC-MS  $m/z$  356 ( $M+H$ )<sup>+</sup>.

150b) 4-chloro-2-{[3-(diethylamino)propyl]amino}-8-(2,6-difluorophenyl)pyrido[2,3-*d*]pyrimidin-7(8*H*)-one



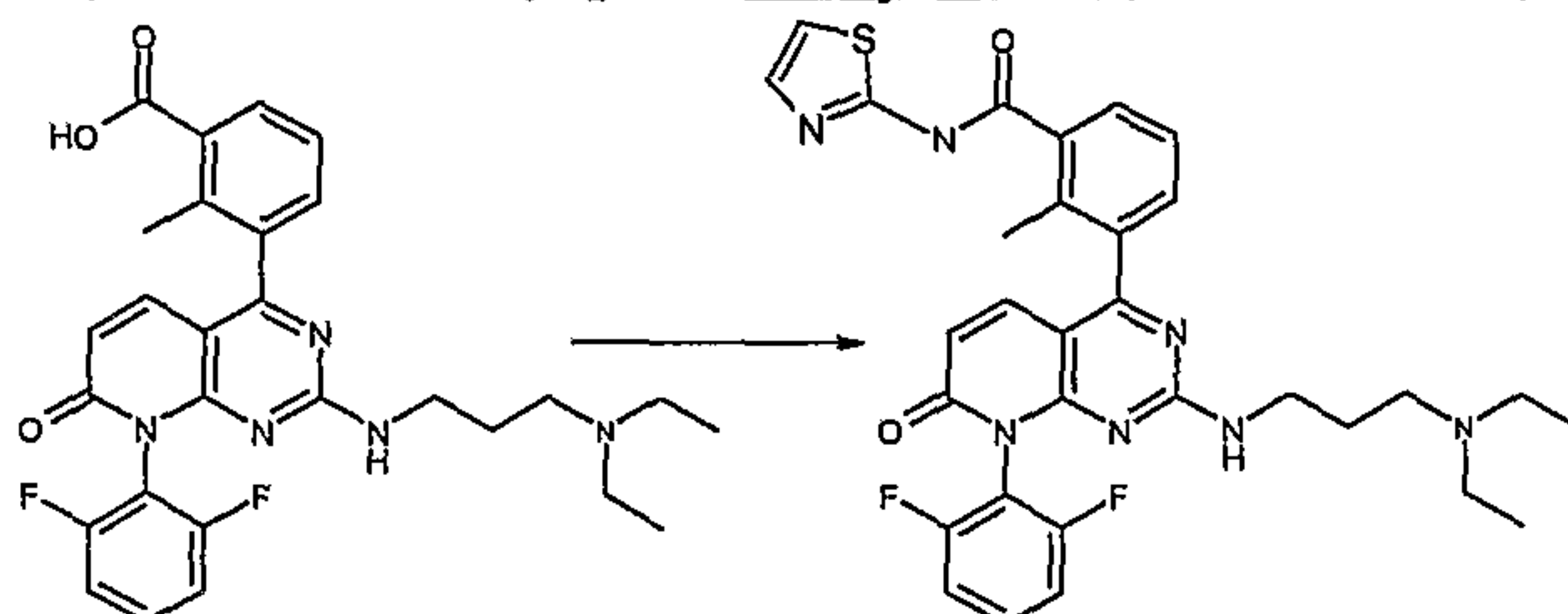
- To the compound 4-chloro-8-(2,6-difluorophenyl)-2-(methylsulfinyl)-pyrido[2,3-*d*]pyrimidin-7(8*H*)-one (1.59 g, 4.47 mmol) in dichloromethane (89.4 mL) were added *N,N*-diethyl-1,3-propanediamine (0.845 mL, 5.36 mol) and triethylamine (1.26 uL, 8.94 mmol). The mixture was stirred at rt overnight. Some white precipitate was formed during the reaction. Filtration followed by wash with ethyl acetate/dichloromethane/methanol afforded the title compound (1.028 g, 60%).
- LC-MS *m/z* 383 (*M*+*H*)<sup>+</sup>.

150c) 3-[2-{[3-(diethylamino)propyl]amino}-8-(2,6-difluorophenyl)-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl]-2-methylbenzoic acid



- To the compound 4-chloro-2-{[3-(diethylamino)propyl]amino}-8-(2,6-difluorophenyl)pyrido[2,3-*d*]pyrimidin-7(8*H*)-one (176 mg, 0.418 mmol) in dioxane (4.5 mL) and water (1.5 mL) was added 2-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoic acid (173 mg, 0.626 mol), potassium carbonate (289 mg, 2.09 mmol) and tetrakis(triphenylphosphine)palladium(0) (24.2 mg, 0.0259 mmol).
- The mixture was heated with microwave at 150 °C for 15 min. The mixture was filtered. Separation by HPLC with TFA afforded the title compound (238 mg, 99%). LC-MS *m/z* 522 (*M*+*H*)<sup>+</sup>.

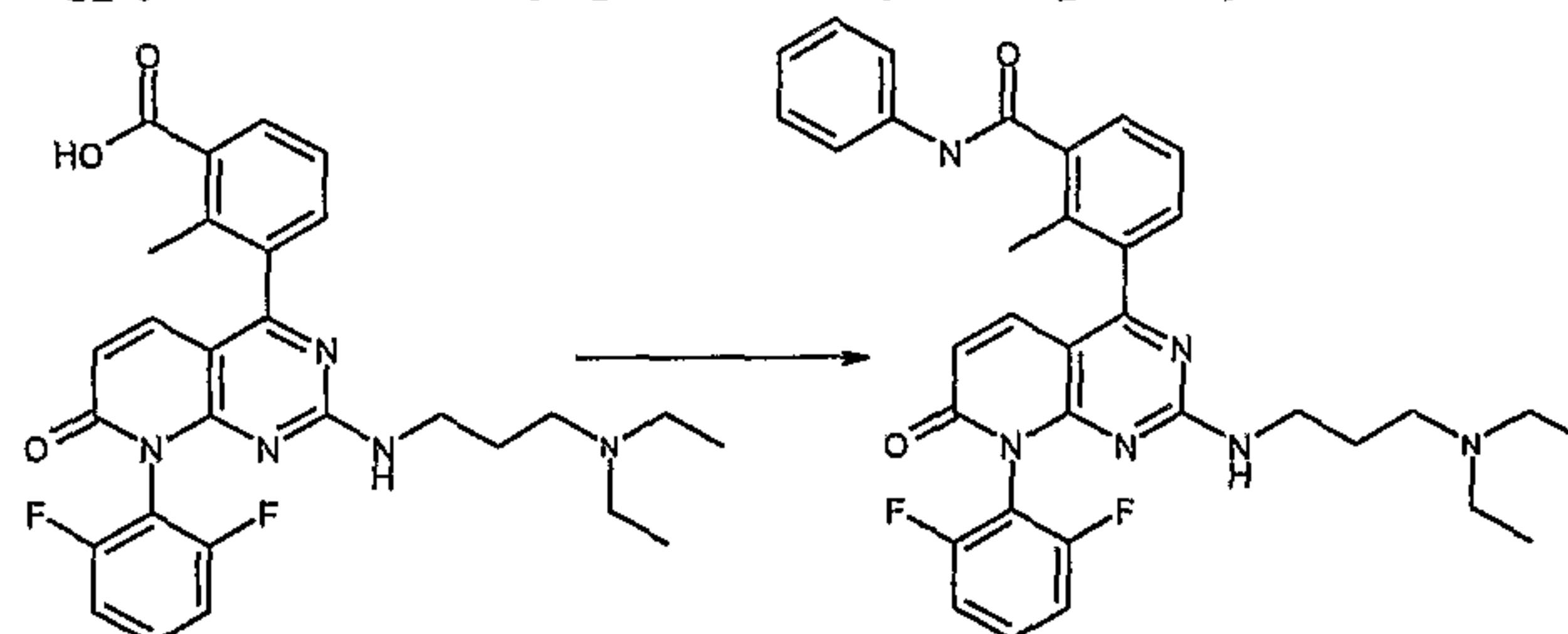
150d)3-[2-{[3-(diethylamino)propyl]amino}-8-(2,6-difluorophenyl)-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl]-2-methyl-*N*-1,3-thiazol-2-ylbenzamide



To the compound 3-[2-{[3-(diethylamino)propyl]amino}-8-(2,6-difluorophenyl)-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl]-2-methylbenzoic acid (26 mg, 0.05 mmol) in DMF (0.5 mL) were added HBTU (28 mg, 0.075 mmol), triethylamine (21.1  $\mu$ L, 0.15 mmol) and 1,3-thiazol-2-amine (10.0 mg, 0.1 mmol). The mixture was stirred at rt overnight. Separation by HPLC with TFA, followed by neutralization with SPE amine cartridge afforded the title compound (9 mg, 30%). LC-MS  $m/z$  604 ( $M+H$ )<sup>+</sup>.

**Example 151**

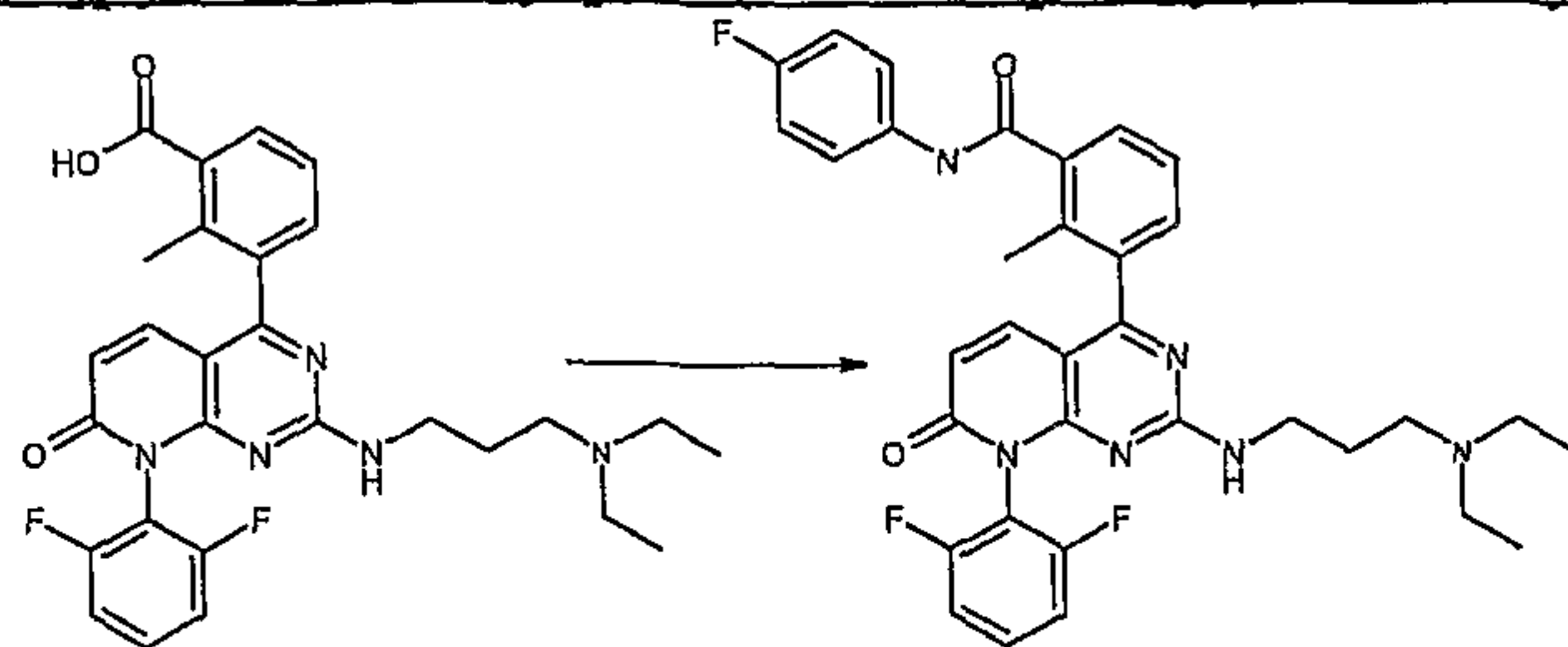
3-[2-{[3-(diethylamino)propyl]amino}-8-(2,6-difluorophenyl)-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl]-2-methyl-*N*-phenylbenzamide



To the compound 3-[2-{[3-(diethylamino)propyl]amino}-8-(2,6-difluorophenyl)-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl]-2-methylbenzoic acid (26 mg, 0.05 mmol) in DMF (0.5 mL) were added HBTU (28 mg, 0.075 mmol), triethylamine (21.1  $\mu$ L, 0.15 mmol) and aniline (9.1  $\mu$ L, 0.1 mmol). The mixture was stirred at rt overnight. Separation by HPLC with TFA, followed by neutralization with SPE amine cartridge afforded the title compound (18 mg, 60%). LC-MS  $m/z$  597 ( $M+H$ )<sup>+</sup>.

**Example 152**

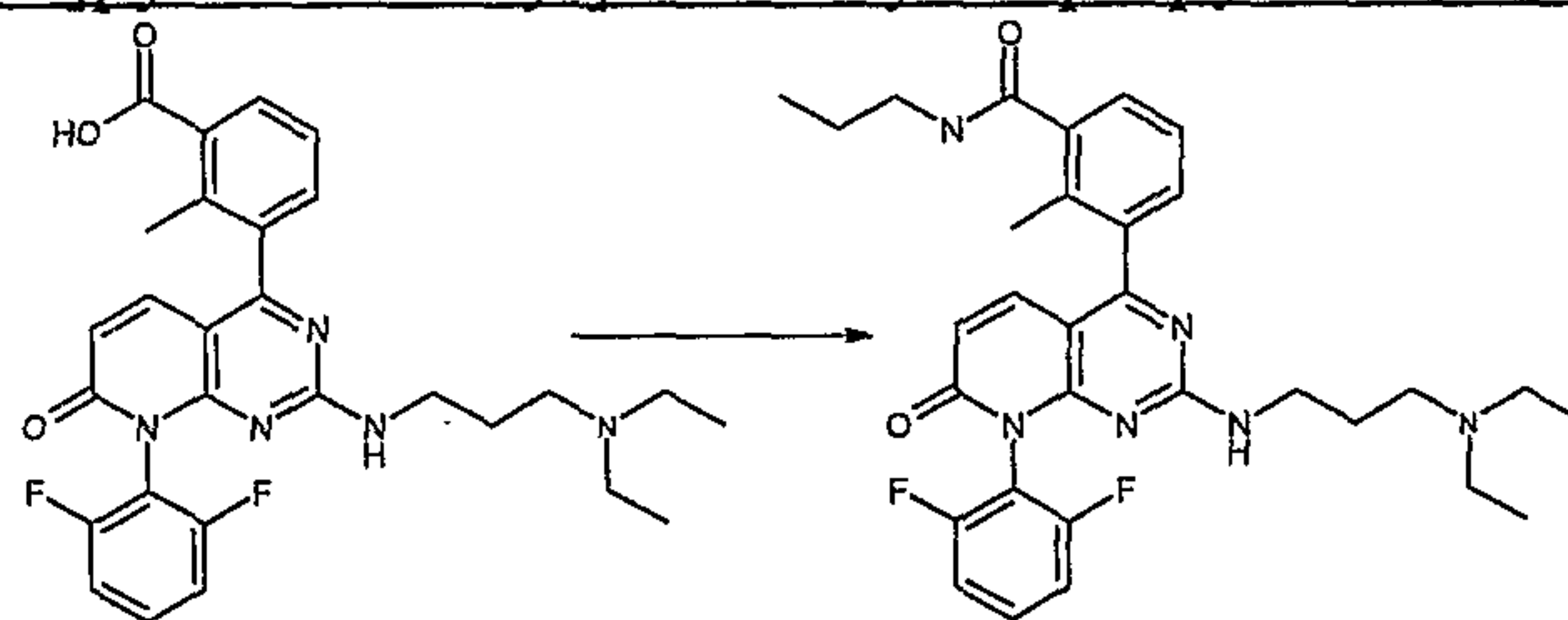
3-[2-{[3-(diethylamino)propyl]amino}-8-(2,6-difluorophenyl)-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl]-*N*-(4-fluorophenyl)-2-methylbenzamide



5 To the compound 3-[2-{[3-(diethylamino)propyl]amino}-8-(2,6-difluorophenyl)-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl]-2-methylbenzoic acid (26 mg, 0.05 mmol) in DMF (0.5 mL) were added HBTU (28 mg, 0.075 mmol), triethylamine (21.1 uL, 0.15 mmol) and 4-fluoroaniline (9.6 uL, 0.1 mmol). The mixture was stirred at rt overnight. Separation by HPLC with TFA, followed by  
10 neutralization with SPE amine cartridge afforded the title compound (14 mg, 46%). LC-MS  $m/z$  615 ( $M+H$ )<sup>+</sup>.

**Example 153**

15 3-[2-{[3-(diethylamino)propyl]amino}-8-(2,6-difluorophenyl)-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl]-2-methyl-*N*-propylbenzamide

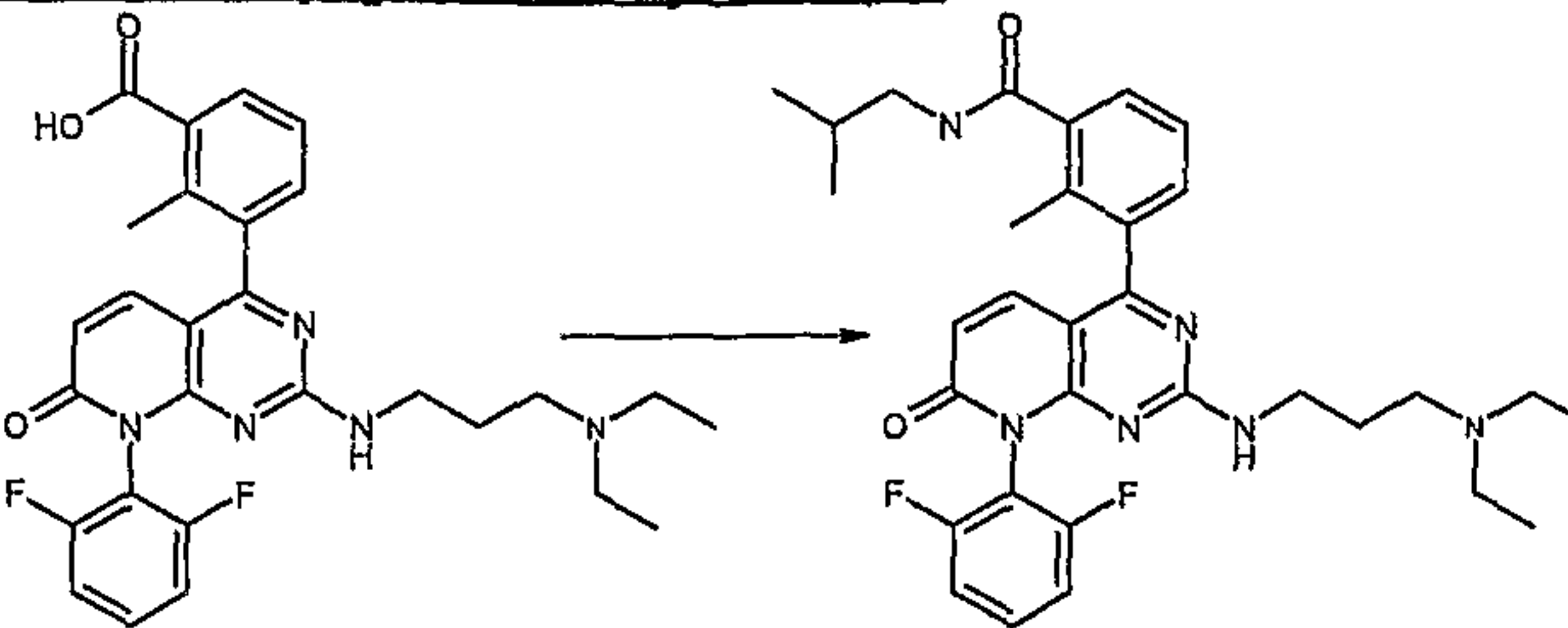


To the compound 3-[2-{[3-(diethylamino)propyl]amino}-8-(2,6-difluorophenyl)-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl]-2-methylbenzoic acid (26 mg, 0.05 mmol) in DMF (0.5 mL) were added HBTU (28 mg, 0.075  
20 mmol), triethylamine (21.1 uL, 0.15 mmol) and propylamine (8.2 uL, 0.1 mmol). The mixture was stirred at rt overnight. Separation by HPLC with TFA, followed by neutralization with SPE amine cartridge afforded the title compound (15 mg, 53%). LC-MS  $m/z$  563 ( $M+H$ )<sup>+</sup>.

**Example 154**

3-[2-{[3-(diethylamino)propyl]amino}-8-(2,6-difluorophenyl)-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl]-2-methyl-*N*-(2-

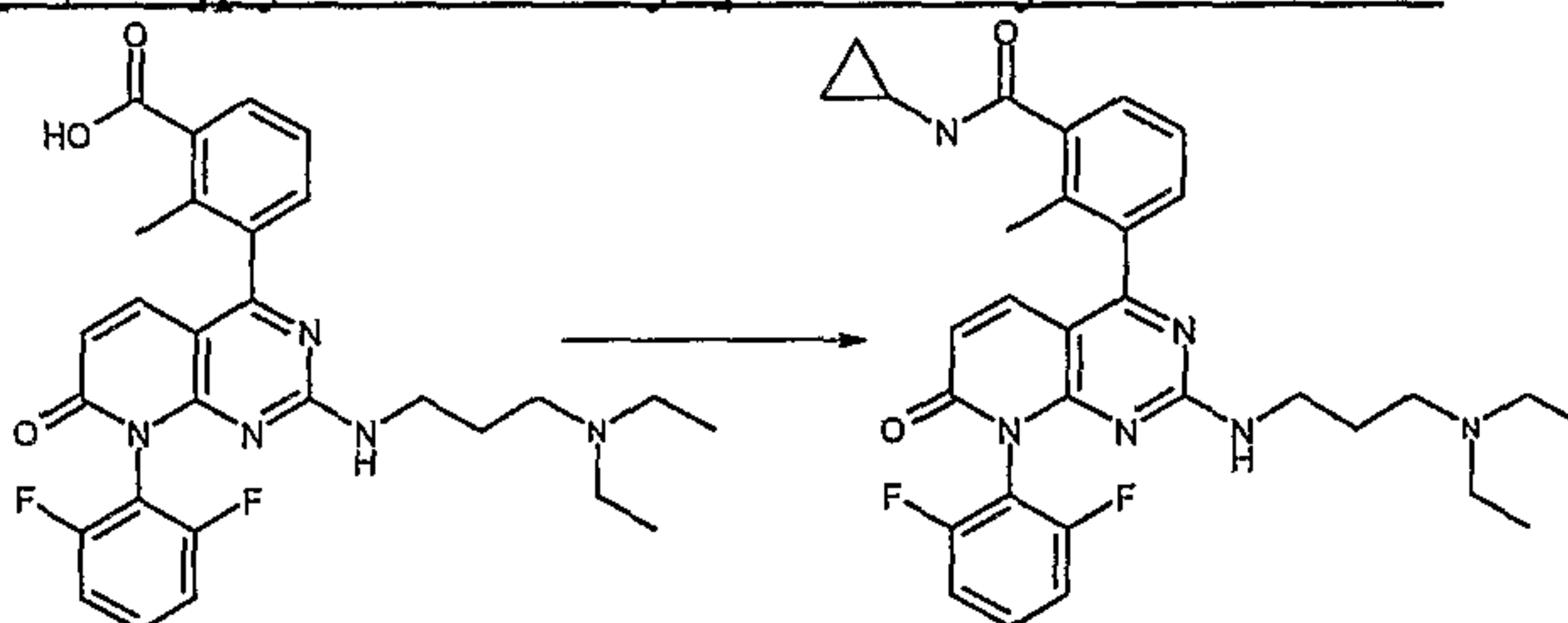
methylpropyl)benzamide



- 5 To the compound 3-[2-{[3-(diethylamino)propyl]amino}-8-(2,6-difluorophenyl)-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl]-2-methylbenzoic acid (26 mg, 0.05 mmol) in DMF (0.5 mL) were added HBTU (28 mg, 0.075 mmol), triethylamine (21.1 uL, 0.15 mmol) and isobutylamine (10.0 uL, 0.1 mmol). The mixture was stirred at rt overnight. Separation by HPLC with TFA, followed by  
10 neutralization with SPE amine cartridge afforded the title compound (12.6 mg, 44%). LC-MS *m/z* 577 (*M*+*H*)<sup>+</sup>.

**Example 155**

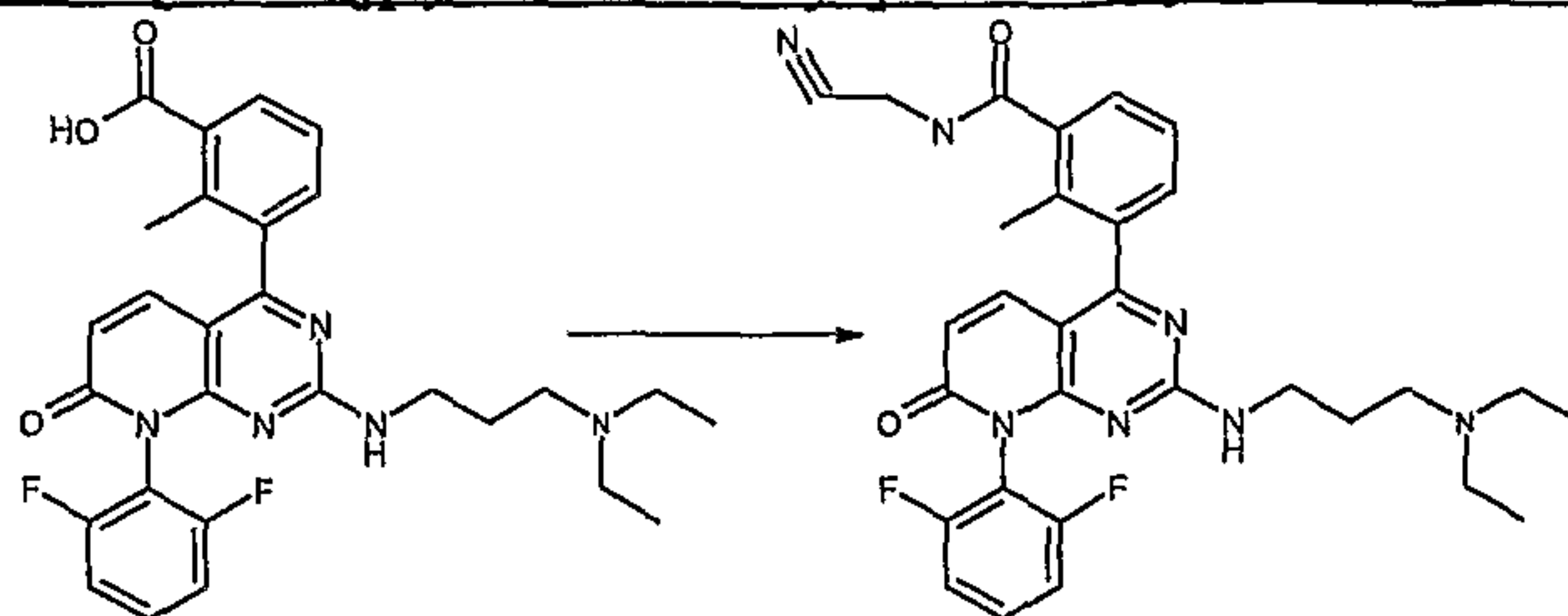
*N*-cyclopropyl-3-[2-{[3-(diethylamino)propyl]amino}-8-(2,6-difluorophenyl)-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl]-2-methylbenzamide



- To the compound 3-[2-{[3-(diethylamino)propyl]amino}-8-(2,6-difluorophenyl)-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl]-2-methylbenzoic acid (26 mg, 0.05 mmol) in DMF (0.5 mL) were added HBTU (28 mg, 0.075  
20 mmol), triethylamine (21.1 uL, 0.15 mmol) and cyclopropylamine (6.9 uL, 0.1 mmol). The mixture was stirred at rt overnight. Separation by HPLC with TFA, followed by neutralization with SPE amine cartridge afforded the title compound (13.5 mg, 48%). LC-MS *m/z* 561 (*M*+*H*)<sup>+</sup>.

**Example 156**

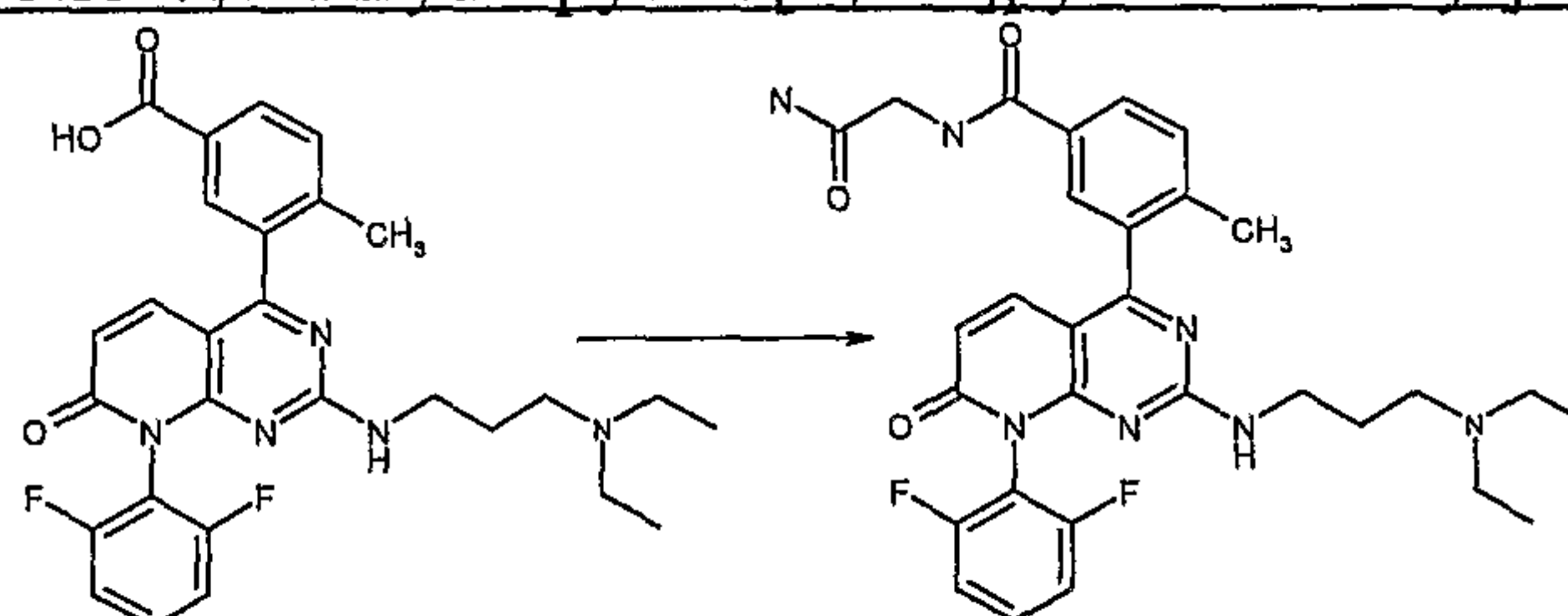
*N*-(cyanomethyl)-3-[2-{[3-(diethylamino)propyl]amino}-8-(2,6-difluorophenyl)-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl]-2-methylbenzamide



- 5 To the compound 3-[2-{[3-(diethylamino)propyl]amino}-8-(2,6-difluorophenyl)-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl]-2-methylbenzoic acid (26 mg, 0.05 mmol) in DMF (0.5 mL) were added HBTU (28 mg, 0.075 mmol), triethylamine (21.1  $\mu$ L, 0.15 mmol) and aminoacetonitrile (9.3 mg, 0.1 mmol). The mixture was stirred at rt overnight. Separation by HPLC with TFA, followed by neutralization with SPE amine cartridge afforded the title compound
- 10 (9.1 mg, 33%). LC-MS  $m/z$  560 ( $M+H$ )<sup>+</sup>.

**Example 157**

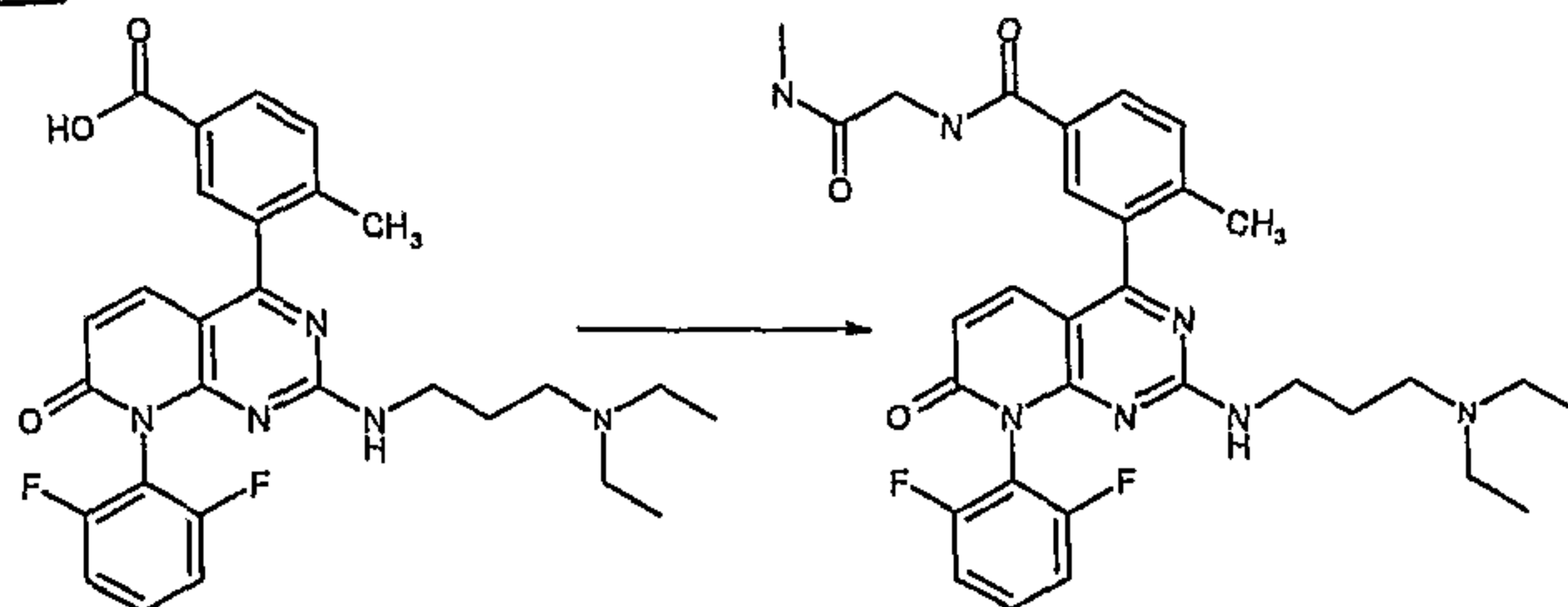
*N*-(2-amino-2-oxoethyl)-3-[2-{[3-(diethylamino)propyl]amino}-8-(2,6-difluorophenyl)-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl]-4-methylbenzamide



- To the compound 3-[2-{[3-(diethylamino)propyl]amino}-8-(2,6-difluorophenyl)-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl]-4-methylbenzoic acid (26 mg, 0.05 mmol) in DMF (0.5 mL) were added HBTU (28 mg, 0.075 mmol), triethylamine (21.1  $\mu$ L, 0.15 mmol) and glycylglycine (11.1 mg, 0.1 mmol). The mixture was stirred at rt overnight. Separation by HPLC with TFA, followed by neutralization with SPE amine cartridge afforded the title compound (9 mg, 31%). LC-MS  $m/z$  578 ( $M+H$ )<sup>+</sup>.
- 20

**Example 158**

3-[2-{[3-(diethylamino)propyl]amino}-8-(2,6-difluorophenyl)-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl]-4-methyl-*N*-[2-(methylamino)-2-oxoethyl]benzamide



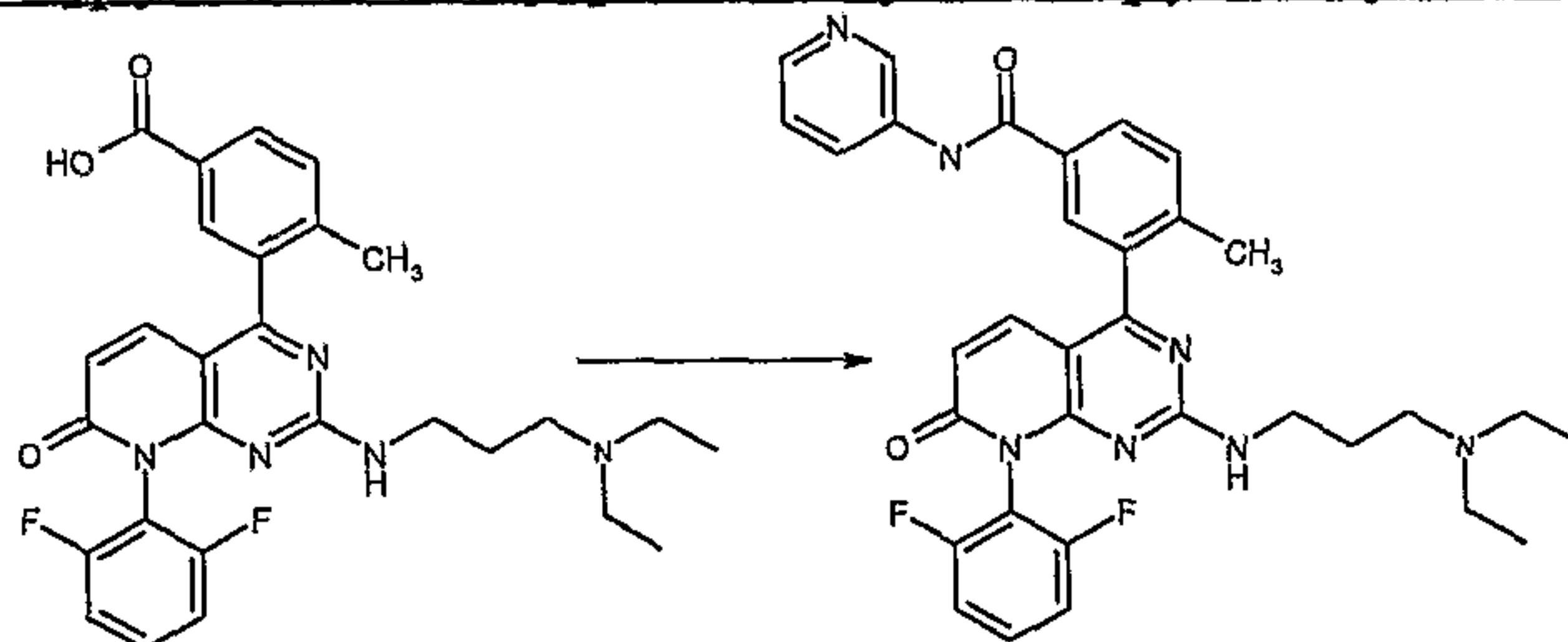
5

To the compound 3-[2-{[3-(diethylamino)propyl]amino}-8-(2,6-difluorophenyl)-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl]-4-methylbenzoic acid (26 mg, 0.05 mmol) in DMF (0.5 mL) were added HBTU (28 mg, 0.075 mmol), triethylamine (21.1  $\mu$ L, 0.15 mmol) and *N*<sup>1</sup>-methylglycinamide (12.5 mg, 0.1 mmol). The mixture was stirred at rt overnight. Separation by HPLC with TFA, followed by neutralization with SPE amine cartridge afforded the title compound (9 mg, 30%). LC-MS  $m/z$  592 ( $M+H$ )<sup>+</sup>.

10

**Example 159**

3-[2-{[3-(diethylamino)propyl]amino}-8-(2,6-difluorophenyl)-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl]-4-methyl-*N*-3-pyridinylbenzamide



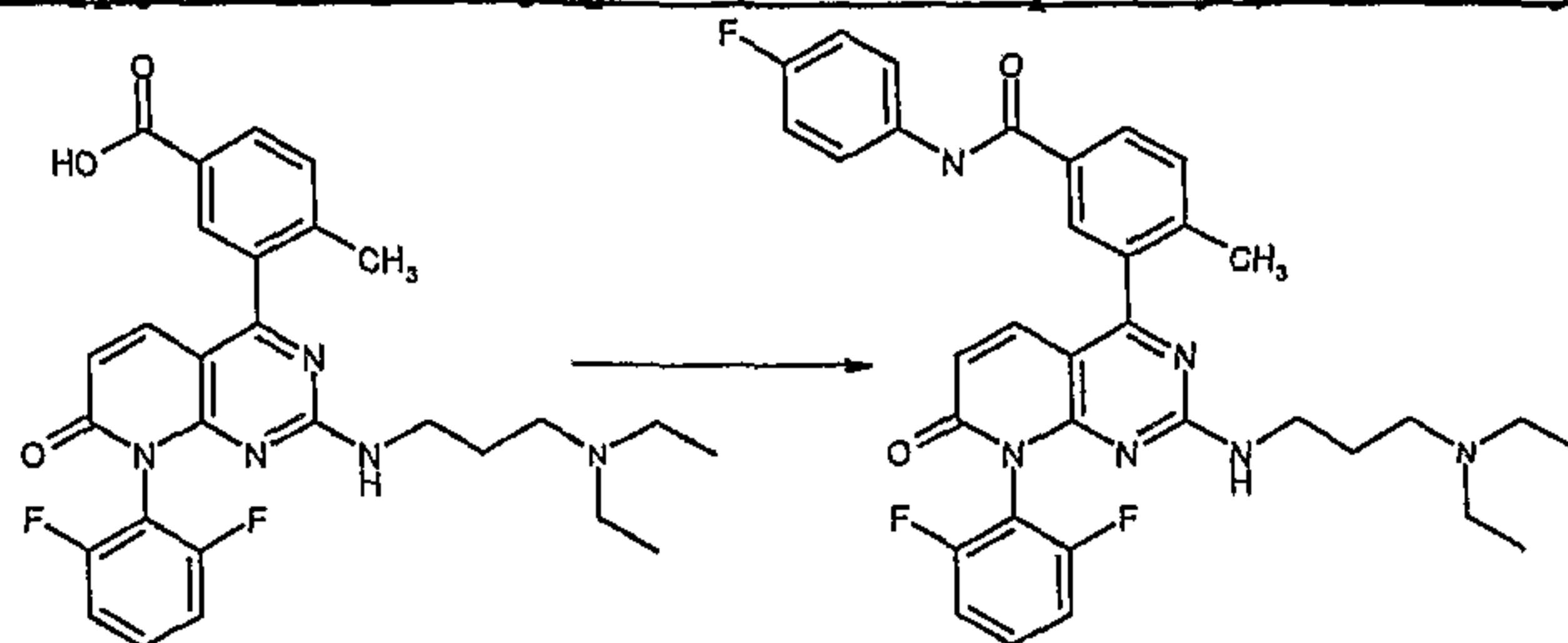
To the compound 3-[2-{[3-(diethylamino)propyl]amino}-8-(2,6-difluorophenyl)-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl]-4-methylbenzoic acid (31.3 mg, 0.06 mmol) in DMF (0.5 mL) were added HBTU (27.3 mg, 0.072 mmol), triethylamine (16.9  $\mu$ L, 0.12 mmol) and 3-aminopyridine (11.3 mg, 0.08 mmol). The mixture was stirred at rt overnight. Separation by HPLC with TFA, followed by neutralization with SPE amine cartridge afforded the title compound (3.3 mg, 9%). LC-MS  $m/z$  598 ( $M+H$ )<sup>+</sup>.

20

25

**Example 160**

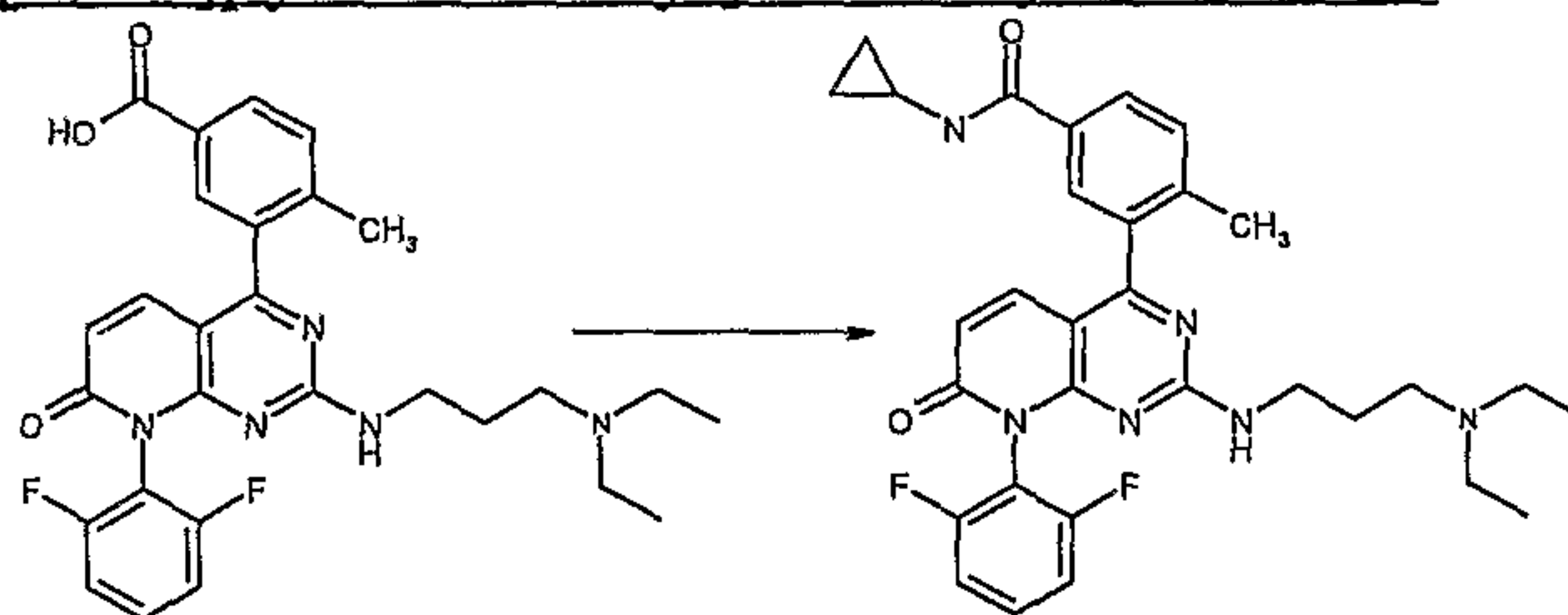
3-[2-{[3-(diethylamino)propyl]amino}-8-(2,6-difluorophenyl)-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl]-*N*-(4-fluorophenyl)-4-methylbenzamide



5 To the compound 3-[2-{[3-(diethylamino)propyl]amino}-8-(2,6-difluorophenyl)-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl]-4-methylbenzoic acid (31.3 mg, 0.06 mmol) in DMF (0.5 mL) were added HBTU (27.3 mg, 0.072 mmol), triethylamine (16.9  $\mu$ L, 0.12 mmol) and 4-fluoroaniline (8.64  $\mu$ L, 0.08 mmol). The mixture was stirred at rt overnight. Separation by HPLC with TFA,  
10 followed by neutralization with SPE amine cartridge afforded the title compound (10 mg, 27%). LC-MS  $m/z$  615 ( $M+H$ )<sup>+</sup>.

**Example 161**

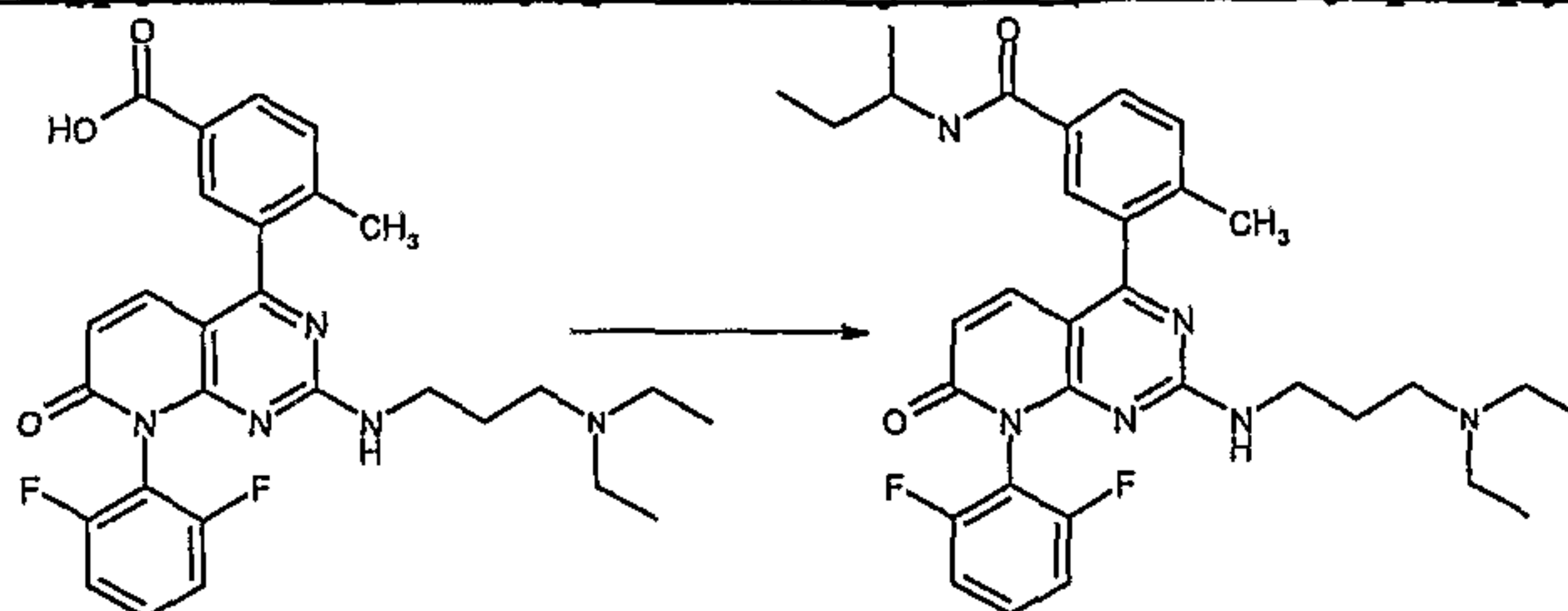
15 *N*-cyclopropyl-3-[2-{[3-(diethylamino)propyl]amino}-8-(2,6-difluorophenyl)-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl]-4-methylbenzamide



To the compound 3-[2-{[3-(diethylamino)propyl]amino}-8-(2,6-difluorophenyl)-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl]-4-methylbenzoic acid (31.3 mg, 0.06 mmol) in DMF (0.5 mL) were added HBTU (27.3 mg, 0.072 mmol), triethylamine (16.9  $\mu$ L, 0.12 mmol) and cyclopropylamine (6.24  $\mu$ L, 0.08 mmol). The mixture was stirred at rt overnight. Separation by HPLC with TFA,  
20 followed by neutralization with SPE amine cartridge afforded the title compound (10 mg, 30%). LC-MS  $m/z$  562 ( $M+H$ )<sup>+</sup>.

**Example 162**

3-[2-{[3-(diethylamino)propyl]amino}-8-(2,6-difluorophenyl)-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl]-4-methyl-*N*-(1-methylpropyl)benzamide

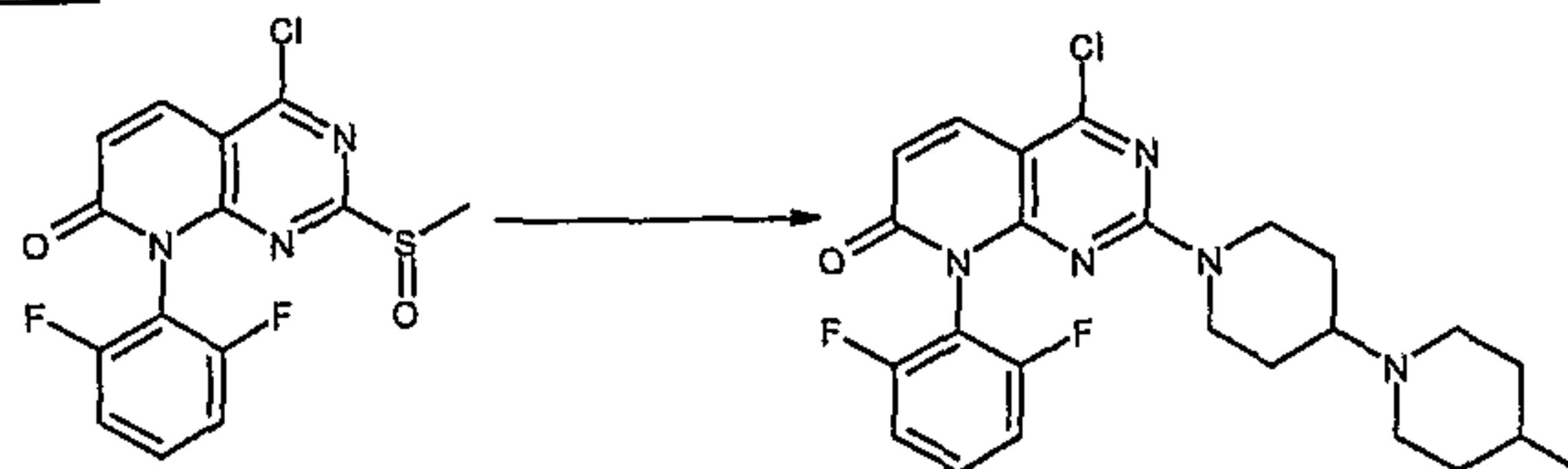


5 To the compound 3-[2-{[3-(diethylamino)propyl]amino}-8-(2,6-difluorophenyl)-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl]-4-methylbenzoic acid (31.3 mg, 0.06 mmol) in DMF (0.5 mL) were added HBTU (27.3 mg, 0.072 mmol), triethylamine (16.9  $\mu$ L, 0.12 mmol) and sec-butylamine (12.12  $\mu$ L, 0.08 mmol). The mixture was stirred at rt overnight. Separation by HPLC with TFA,  
10 followed by neutralization with SPE amine cartridge afforded the title compound (3.2 mg, 9%). LC-MS  $m/z$  577 ( $M+H$ )<sup>+</sup>.

**Example 163**

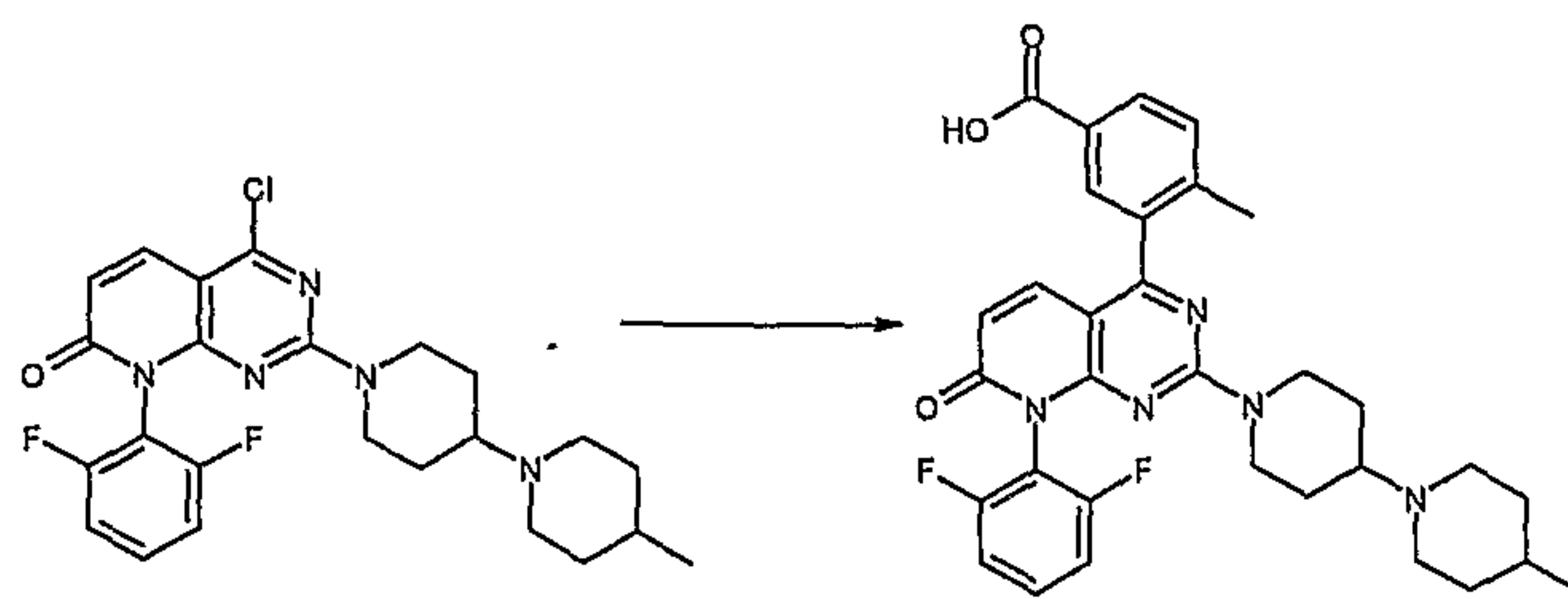
3-[8-(2,6-difluorophenyl)-2-(4-methyl-1,4'-bipiperidin-1'-yl)-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl]-4-methyl-*N*-(1-methylethyl)benzamide

163a) 4-chloro-8-(2,6-difluorophenyl)-2-(4-methyl-1,4'-bipiperidin-1'-yl)pyrido[2,3-*d*]pyrimidin-7(8*H*)-one



20 To the compound 4-chloro-8-(2,6-difluorophenyl)-2-(methylsulfinyl)pyrido[2,3-*d*]pyrimidin-7(8*H*)-one (1.39 g, 3.9 mmol) in dichloromethane (80 mL) were added 4-methyl-1,4'-bipiperidine (0.75 g, 5.85 mol) and triethylamine (1.03 mL, 11.7 mmol). The mixture was stirred at -20<sup>0</sup>C overnight. Filtration followed by concentration, the crude was purified with flash  
25 chromatography to afford the title compound (0.904 g, 51%). LC-MS  $m/z$  474 ( $M+H$ )<sup>+</sup>.

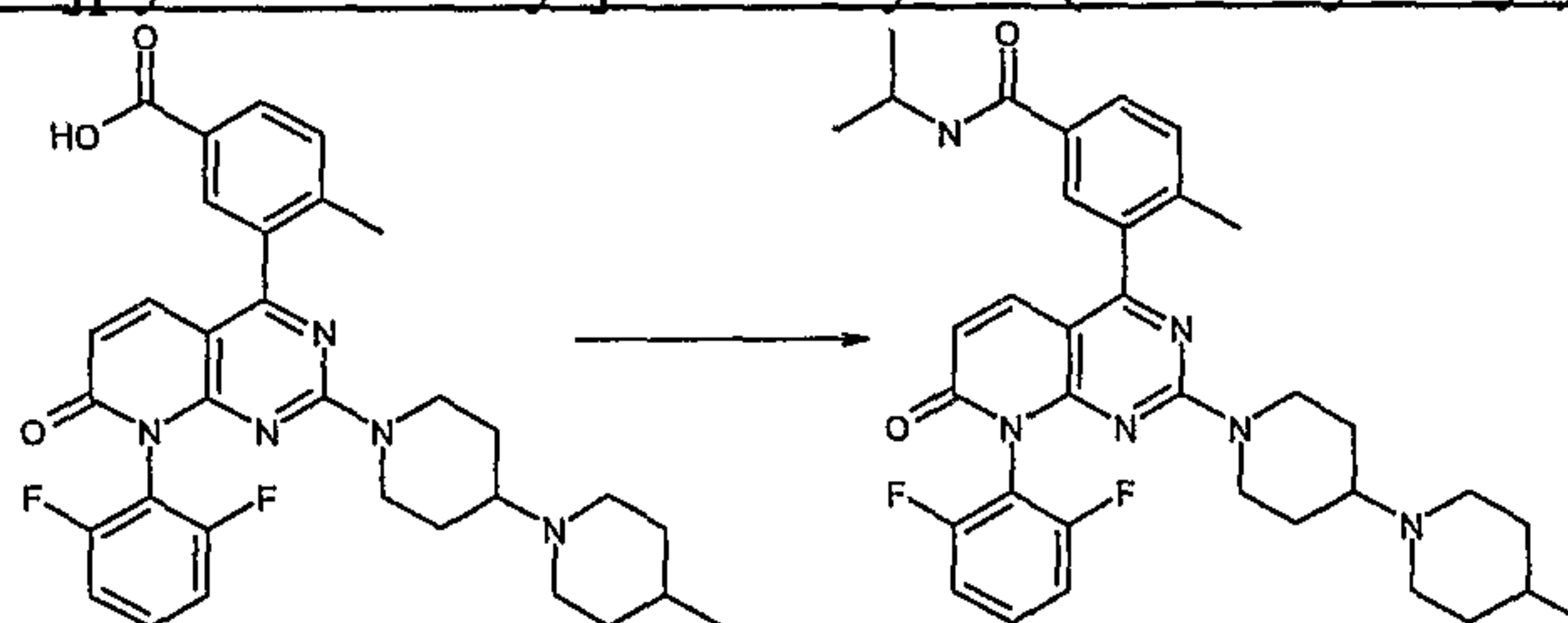
163b) 3-[8-(2,6-difluorophenyl)-2-(4-methyl-1,4'-bipiperidin-1'-yl)-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl]-4-methylbenzoic acid (GSK1080365A)



To the compound 4-chloro-8-(2,6-difluorophenyl)-2-(4-methyl-1,4'-bipiperidin-1'-yl)pyrido[2,3-*d*]pyrimidin-7(8*H*)-one (47.5 mg, 0.1 mmol) in dioxane (3 mL) and water (1 mL) were added 6-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoic acid (38.4 mg, 0.15 mol), potassium carbonate (83 mg, 0.6 mmol) and tetrakis(triphenylphosphine)palladium(0) (4.6 mL, 0.005 mmol). The mixture was heated with microwave at 150°C for 15 min. The mixture was concentrated, & then added was DMSO (0.75 mL) and water (0.25 mL). Separation by HPLC afforded the title compound (39 mg, 68%). LC-MS *m/z* 574 (M+H)<sup>+</sup>.

10

163c) 3-[8-(2,6-difluorophenyl)-2-(4-methyl-1,4'-bipiperidin-1'-yl)-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl]-4-methyl-*N*-(1-methylethyl)benzamide

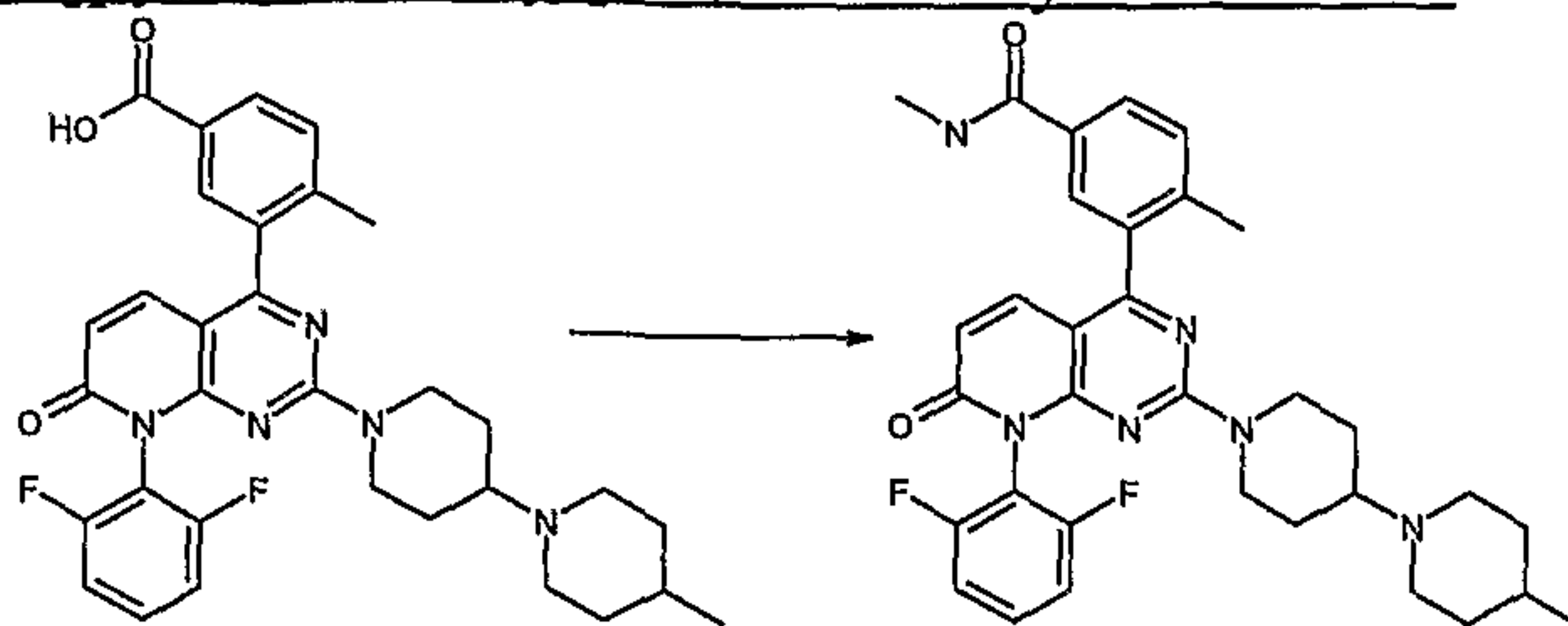


To the compound 3-[8-(2,6-difluorophenyl)-2-(4-methyl-1,4'-bipiperidin-1'-yl)-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl]-4-methylbenzoic acid (31.6 mg, 0.055 mmol) in DMF (0.5 mL) were added HBTU (25 mg, 0.066 mmol), triethylamine (15.5 uL, 0.11 mmol) and isopropylamine (7.03 uL, 0.0825 mmol). The mixture was stirred at rt overnight. Separation by HPLC with TFA, followed by neutralization with SPE amine cartridge afforded the title compound (16.4 mg, 48.5%). LC-MS *m/z* 615 (M+H)<sup>+</sup>.

20

**Example 164**

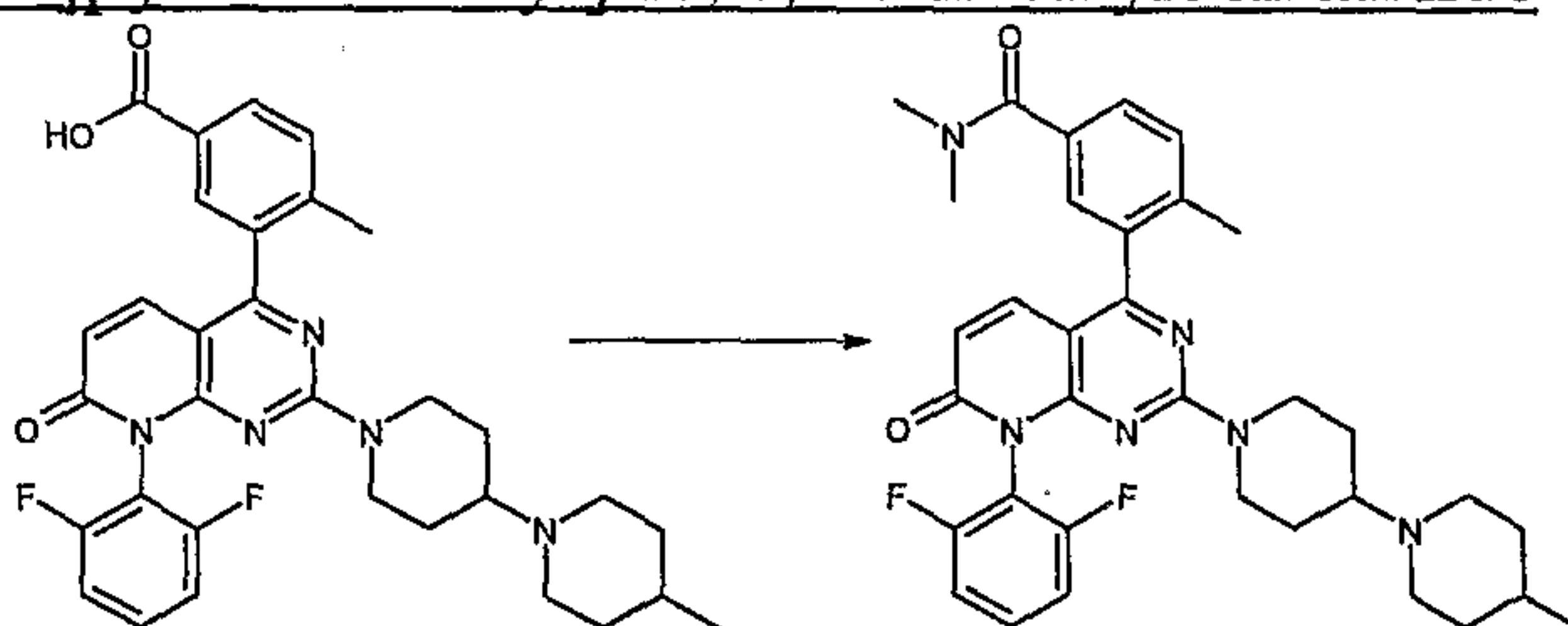
3-[8-(2,6-difluorophenyl)-2-(4-methyl-1,4'-bipiperidin-1'-yl)-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl]-*N*,4-dimethylbenzamide



- 5 To the compound 3-[8-(2,6-difluorophenyl)-2-(4-methyl-1,4'-bipiperidin-1'-yl)-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl]-4-methylbenzoic acid (31.6 mg, 0.055 mmol) in DMF (0.5 mL) were added HBTU (25 mg, 0.066 mmol), triethylamine (15.5 uL, 0.11 mmol) and methylamine (41.3 uL, 0.0825 mmol, 2M soln in THF). The mixture was stirred at rt overnight. Separation by HPLC with
- 10 TFA, followed by neutralization with SPE amine cartridge afforded the title compound (7.2 mg, 22%). LC-MS  $m/z$  587 ( $M+H$ )<sup>+</sup>.

**Example 165**

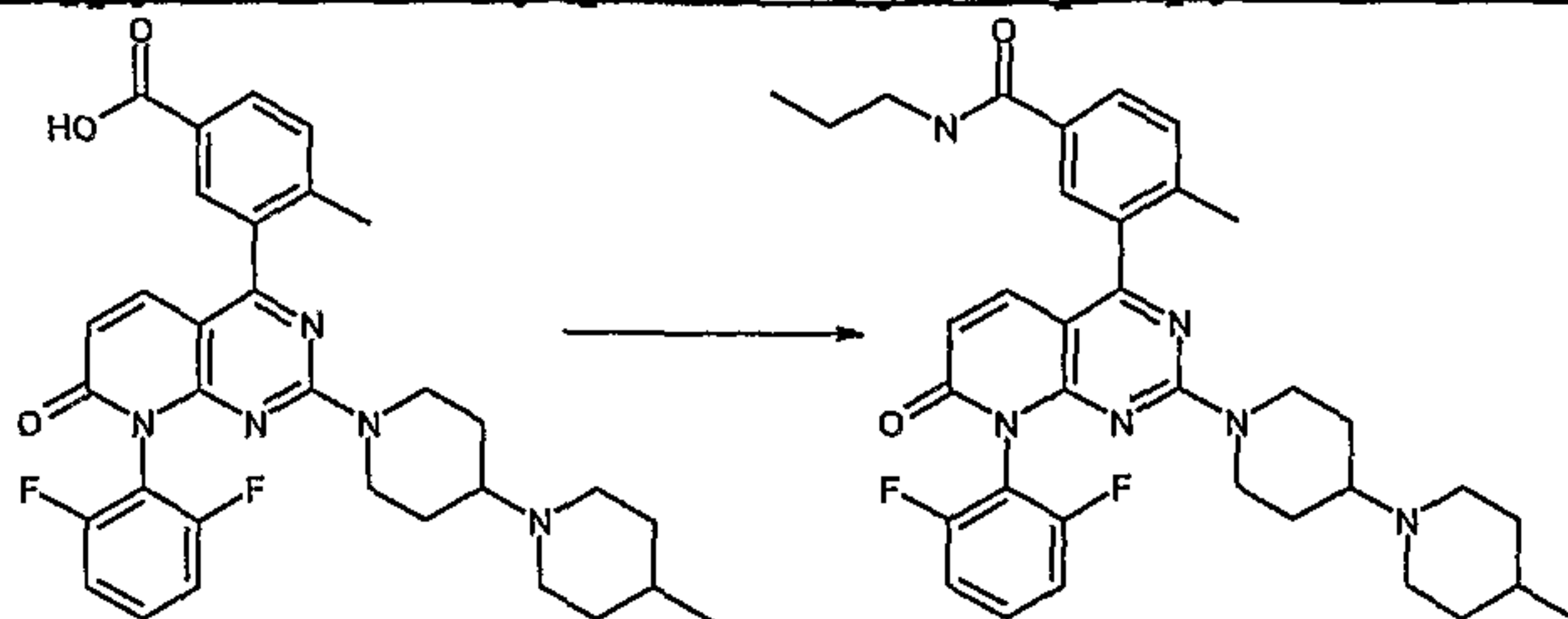
15 3-[8-(2,6-difluorophenyl)-2-(4-methyl-1,4'-bipiperidin-1'-yl)-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl]-*N,N*,4-trimethylbenzamide



- To the compound 3-[8-(2,6-difluorophenyl)-2-(4-methyl-1,4'-bipiperidin-1'-yl)-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl]-4-methylbenzoic acid (31.6 mg, 0.055 mmol) in DMF (0.5 mL) were added HBTU (25 mg, 0.066 mmol),
- 20 triethylamine (15.5 uL, 0.11 mmol) and dimethylamine (41.3 uL, 0.0825 mmol, 2M soln in THF). The mixture was stirred at rt overnight. Separation by HPLC with TFA, followed by neutralization with SPE amine cartridge afforded the title compound (11.5 mg, 35%). LC-MS  $m/z$  601 ( $M+H$ )<sup>+</sup>.

**Example 166**

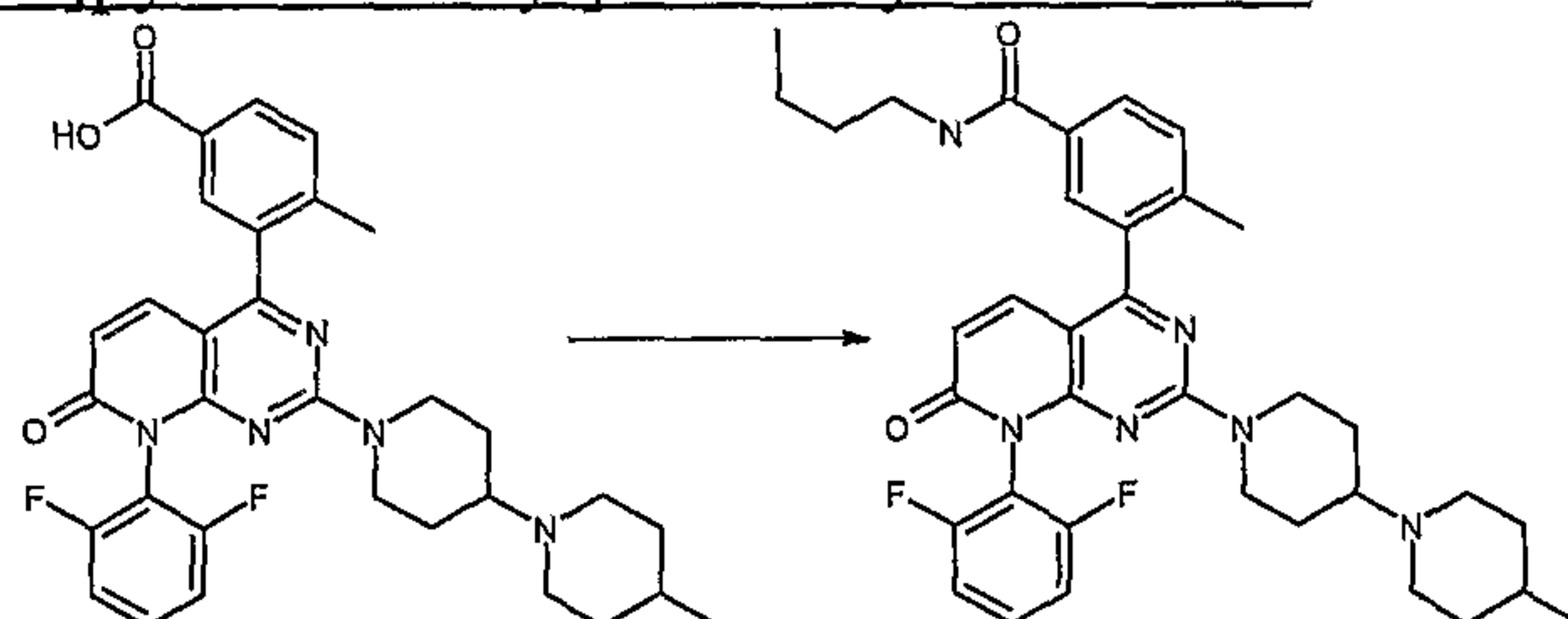
3-[8-(2,6-difluorophenyl)-2-(4-methyl-1,4'-bipiperidin-1'-yl)-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl]-4-methyl-*N*-propylbenzamide



5 To the compound 3-[8-(2,6-difluorophenyl)-2-(4-methyl-1,4'-bipiperidin-1'-yl)-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl]-4-methylbenzoic acid (31.6 mg, 0.055 mmol) in DMF (0.5 mL) were added HBTU (25 mg, 0.066 mmol), triethylamine (15.5 uL, 0.11 mmol) and propylamine (6.78 uL, 0.0825 mmol). The mixture was stirred at rt overnight. Separation by HPLC with TFA, followed by  
10 neutralization with SPE amine cartridge afforded the title compound (18.6 mg, 55%). LC-MS  $m/z$  615 ( $M+H$ )<sup>+</sup>.

**Example 167**

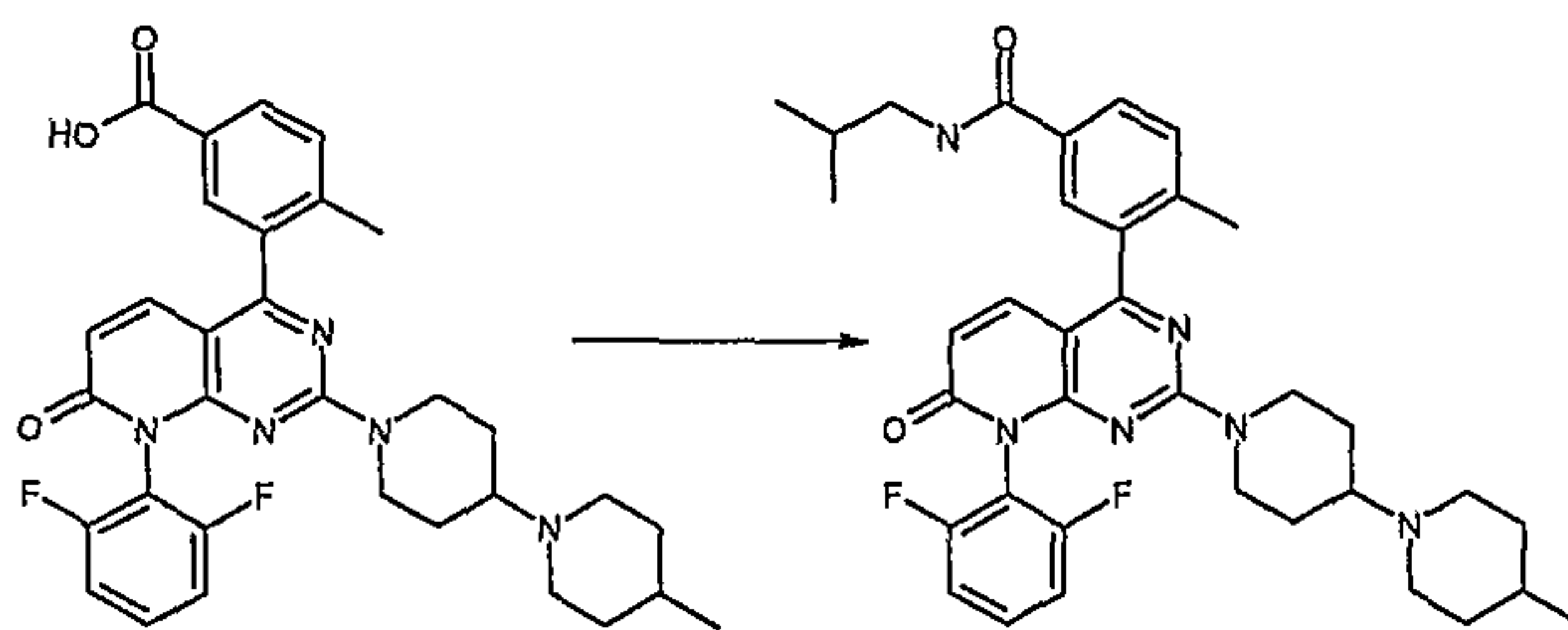
15 *N*-butyl-3-[8-(2,6-difluorophenyl)-2-(4-methyl-1,4'-bipiperidin-1'-yl)-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl]-4-methylbenzamide



To the compound 3-[8-(2,6-difluorophenyl)-2-(4-methyl-1,4'-bipiperidin-1'-yl)-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl]-4-methylbenzoic acid (31.6 mg, 0.055 mmol) in DMF (0.5 mL) were added HBTU (25 mg, 0.066 mmol),  
20 triethylamine (15.5 uL, 0.11 mmol) and butylamine (8.19 uL, 0.0825 mmol). The mixture was stirred at rt overnight. Separation by HPLC with TFA, followed by neutralization with SPE amine cartridge afforded the title compound (18.7 mg, 55%). LC-MS  $m/z$  629 ( $M+H$ )<sup>+</sup>.

**Example 168**

25 3-[8-(2,6-difluorophenyl)-2-(4-methyl-1,4'-bipiperidin-1'-yl)-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl]-4-methyl-*N*-(2-methylpropyl)benzamide

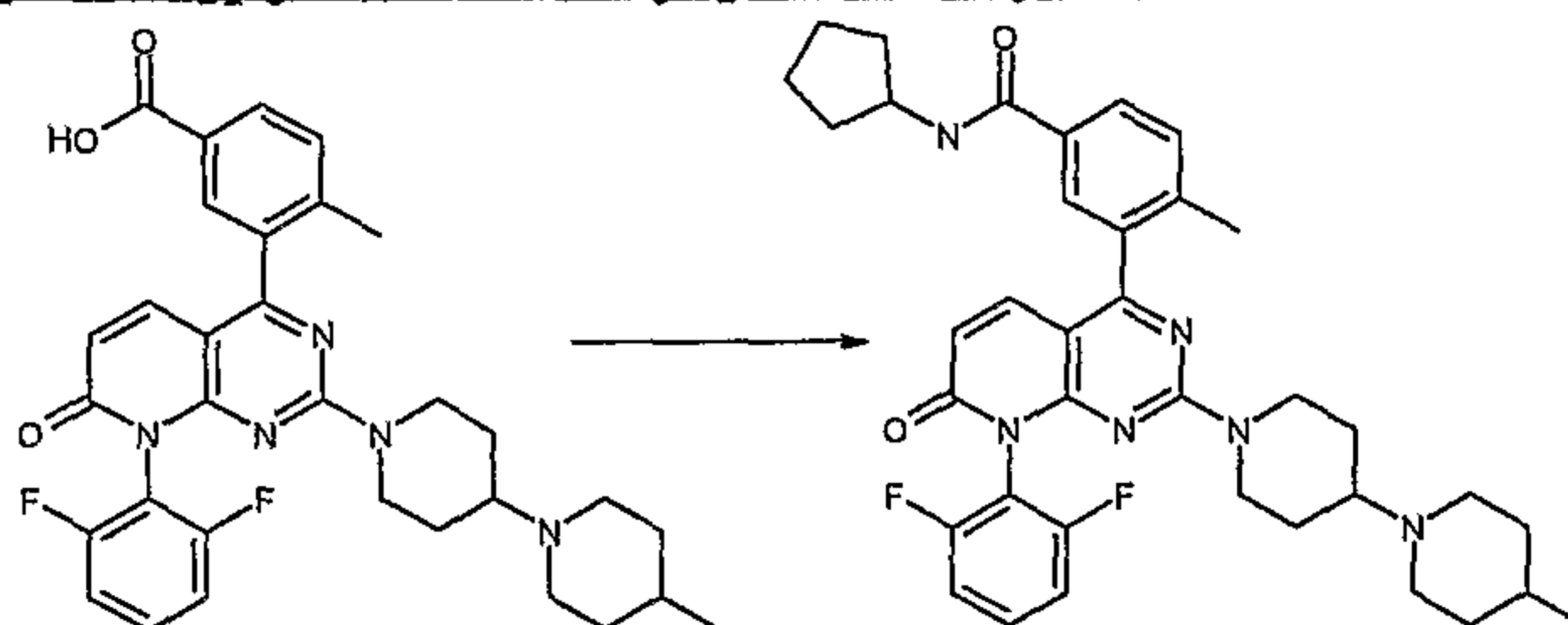


To the compound 3-[8-(2,6-difluorophenyl)-2-(4-methyl-1,4'-bipiperidin-1'-yl)-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl]-4-methylbenzoic acid (31.6 mg, 0.055 mmol) in DMF (0.5 mL) were added HBTU (25 mg, 0.066 mmol),  
 5 triethylamine (15.5 uL, 0.11 mmol) and isobutylamine (8.28 uL, 0.0825 mmol). The mixture was stirred at rt overnight. Separation by HPLC with TFA, followed by neutralization with SPE amine cartridge afforded the title compound (18.4 mg, 53%). LC-MS  $m/z$  629 ( $M+H$ )<sup>+</sup>.

10

**Example 169**

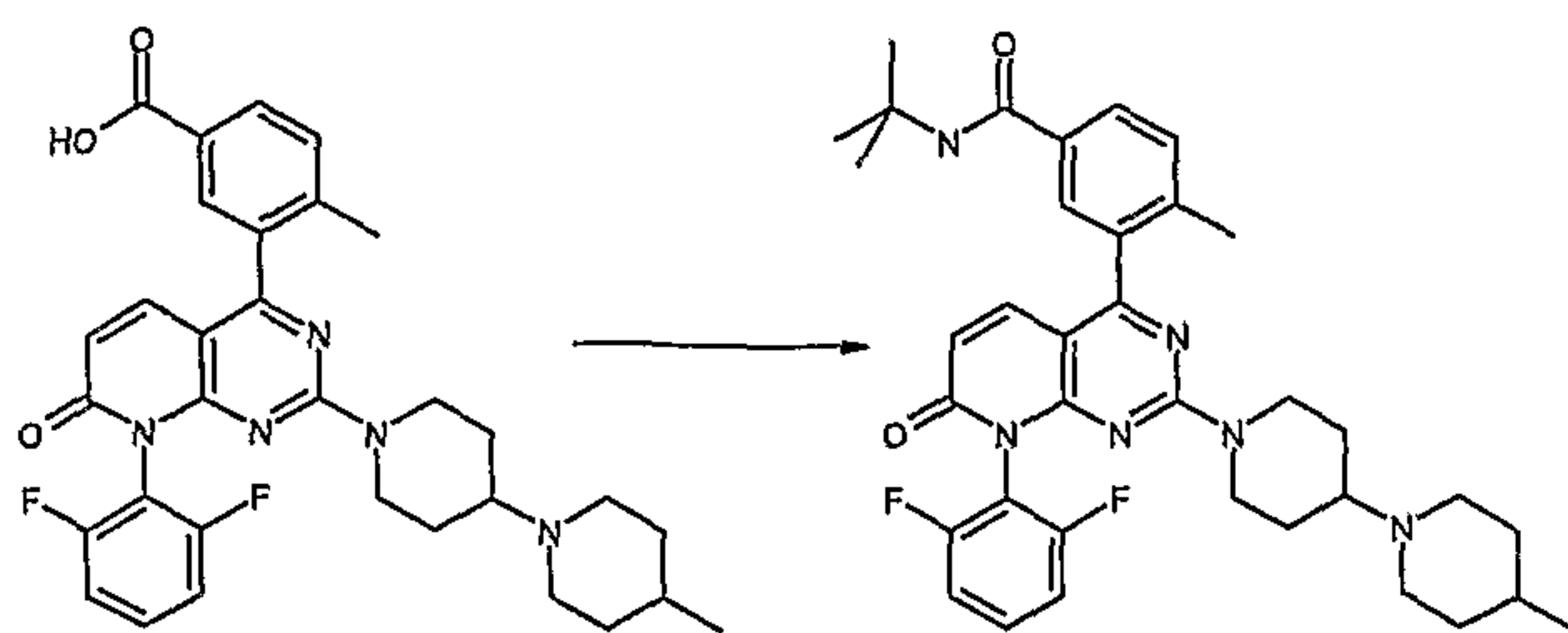
*N*-cyclopentyl-3-[8-(2,6-difluorophenyl)-2-(4-methyl-1,4'-bipiperidin-1'-yl)-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl]-4-methylbenzamide



To the compound 3-[8-(2,6-difluorophenyl)-2-(4-methyl-1,4'-bipiperidin-1'-yl)-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl]-4-methylbenzoic acid (31.6 mg, 0.055 mmol) in DMF (0.5 mL) were added HBTU (25 mg, 0.066 mmol),  
 15 triethylamine (15.5 uL, 0.11 mmol) and cyclopentanamine (8.15 uL, 0.0825 mmol). The mixture was stirred at rt overnight. Separation by HPLC with TFA, followed by neutralization with SPE amine cartridge afforded the title compound (16.9 mg,  
 20 48%). LC-MS  $m/z$  641 ( $M+H$ )<sup>+</sup>.

**Example 170**

3-[8-(2,6-difluorophenyl)-2-(4-methyl-1,4'-bipiperidin-1'-yl)-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl]-*N*-(1,1-dimethylethyl)-4-methylbenzamide

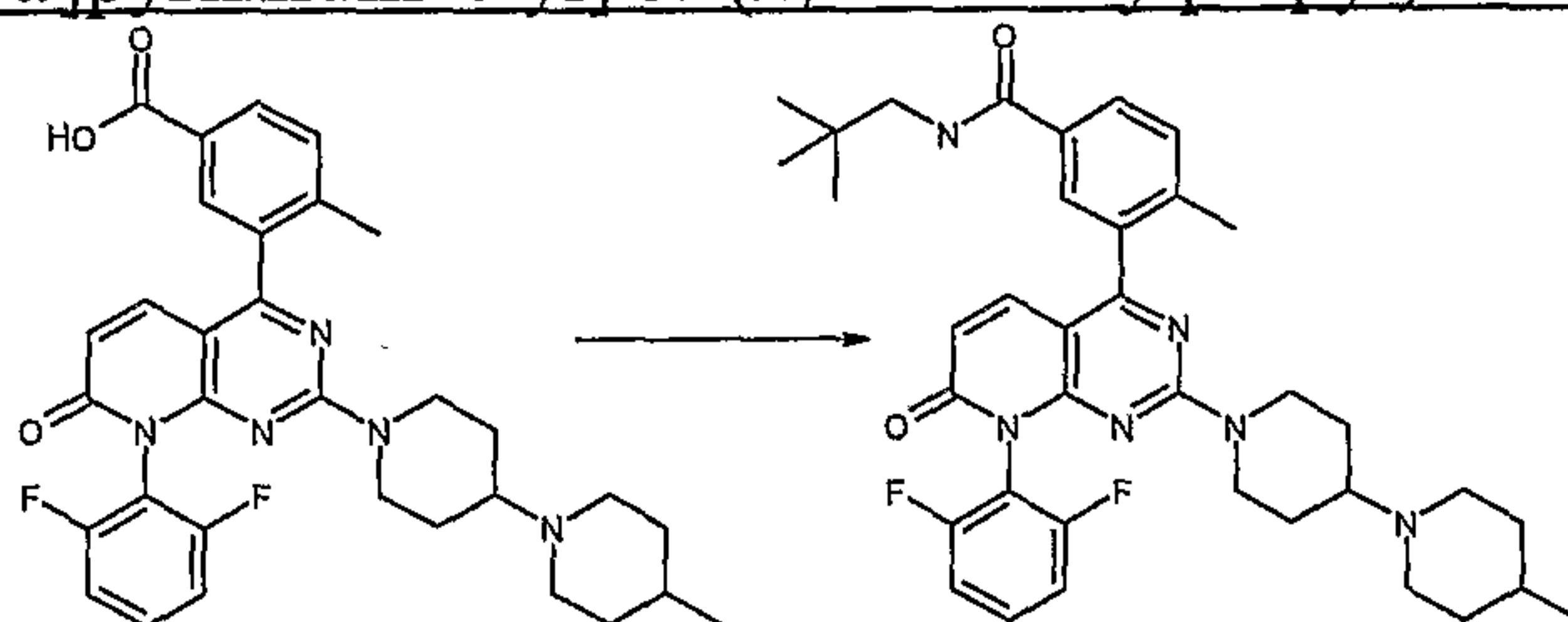


To the compound 3-[8-(2,6-difluorophenyl)-2-(4-methyl-1,4'-bipiperidin-1'-yl)-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl]-4-methylbenzoic acid (31.6 mg, 0.055 mmol) in DMF (0.5 mL) were added HBTU (25 mg, 0.066 mmol), triethylamine (15.5 uL, 0.11 mmol) and t-butylamine (8.71 uL, 0.0825 mmol). The mixture was stirred at rt overnight. Separation by HPLC with TFA, followed by neutralization with SPE amine cartridge afforded the title compound (17.6 mg, 51%). LC-MS *m/z* 629 (*M*+H)<sup>+</sup>.

10

**Example 171**

3-[8-(2,6-difluorophenyl)-2-(4-methyl-1,4'-bipiperidin-1'-yl)-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl]-N-(2,2-dimethylpropyl)-4-methylbenzamide



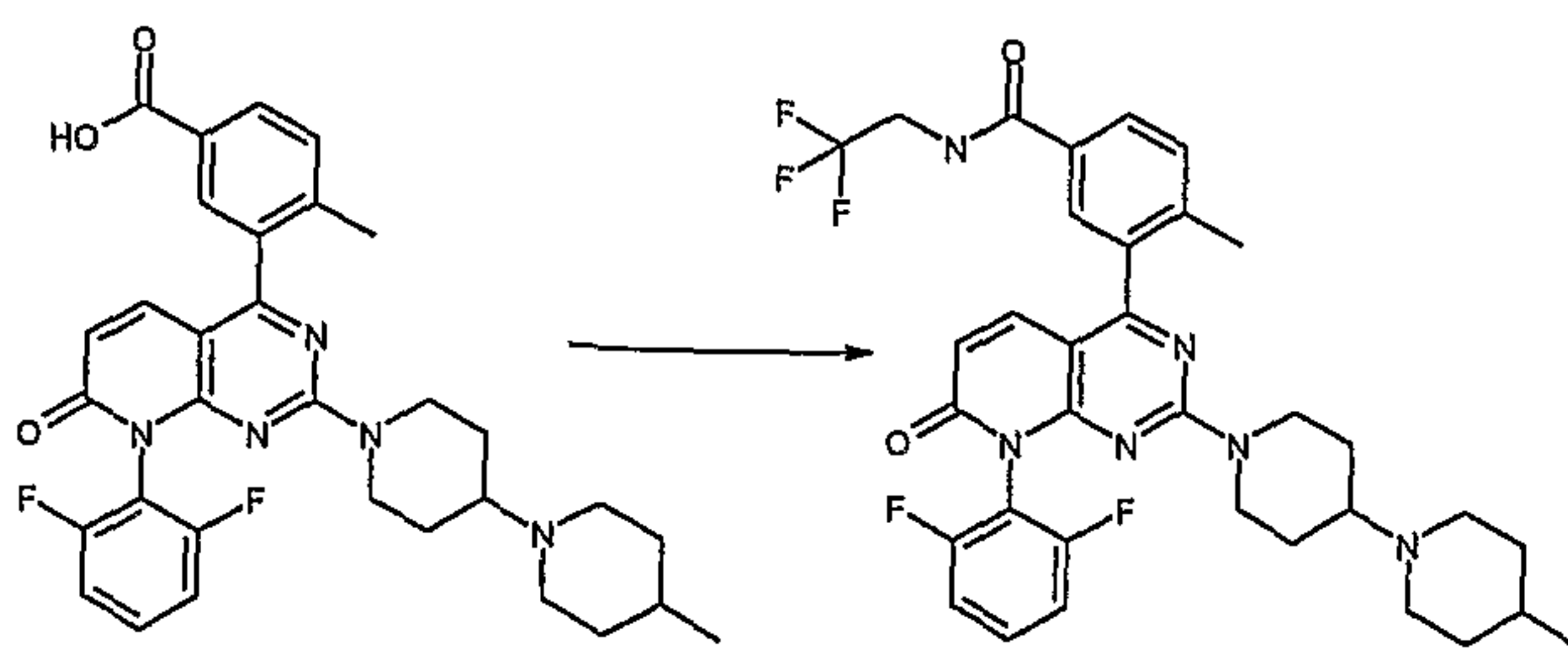
15

To the compound 3-[8-(2,6-difluorophenyl)-2-(4-methyl-1,4'-bipiperidin-1'-yl)-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl]-4-methylbenzoic acid (31.6 mg, 0.055 mmol) in DMF (0.5 mL) were added HBTU (25 mg, 0.066 mmol), triethylamine (15.5 uL, 0.11 mmol) and 2,2-dimethyl-1-propanamine (8.65 uL, 0.0825 mmol). The mixture was stirred at rt overnight. Separation by HPLC with TFA, followed by neutralization with SPE amine cartridge afforded the title compound (17.8 mg, 50%). LC-MS *m/z* 643 (*M*+H)<sup>+</sup>.

20

**Example 172**

3-[8-(2,6-difluorophenyl)-2-(4-methyl-1,4'-bipiperidin-1'-yl)-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl]-4-methyl-N-(2,2,2-trifluoroethyl)benzamide

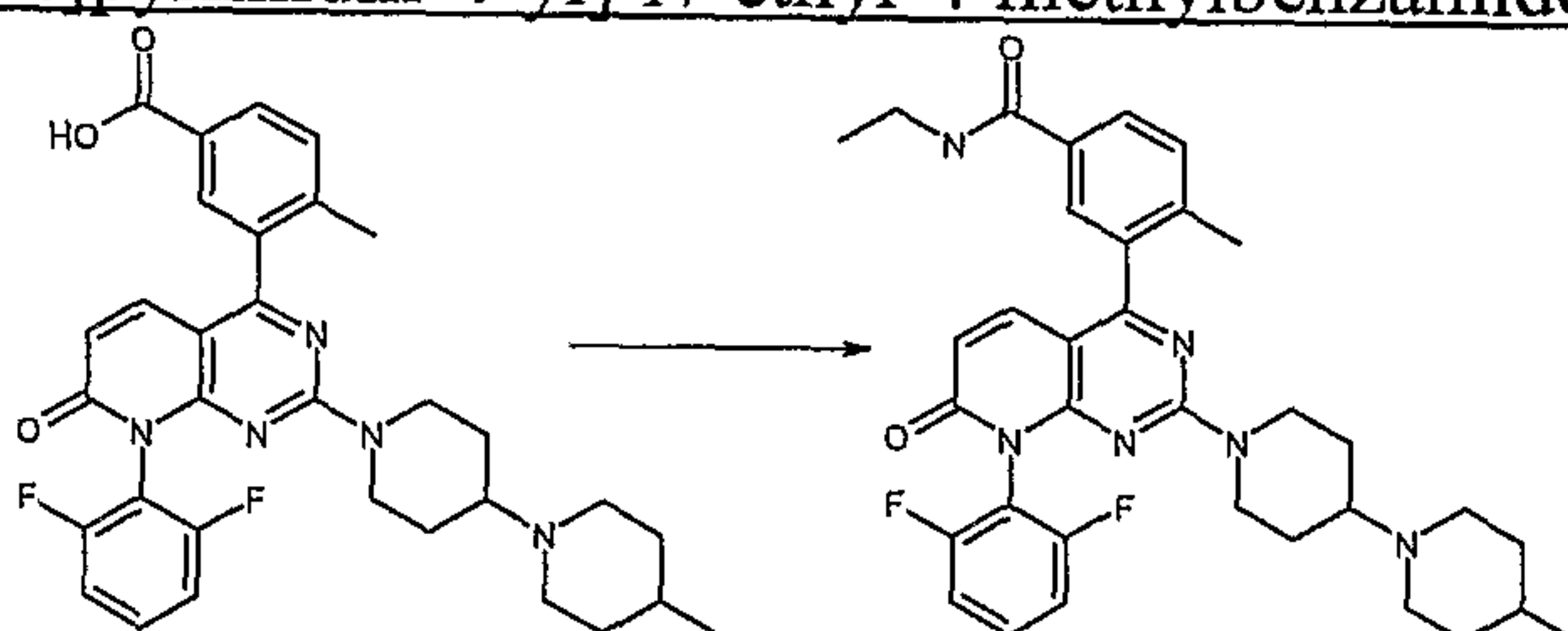


To the compound 3-[8-(2,6-difluorophenyl)-2-(4-methyl-1,4'-bipiperidin-1'-yl)-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl]-4-methylbenzoic acid (31.6 mg, 0.055 mmol) in DMF (0.5 mL) were added HBTU (25 mg, 0.066 mmol), triethylamine (15.5 uL, 0.11 mmol) and 2,2,2-trifluoroethanamine (6.56 uL, 0.0825 mmol). The mixture was stirred at rt overnight. Separation by HPLC with TFA, followed by neutralization with SPE amine cartridge afforded the title compound (24.6 mg, 68%). LC-MS  $m/z$  655 ( $M+H$ )<sup>+</sup>.

10

**Example 173**

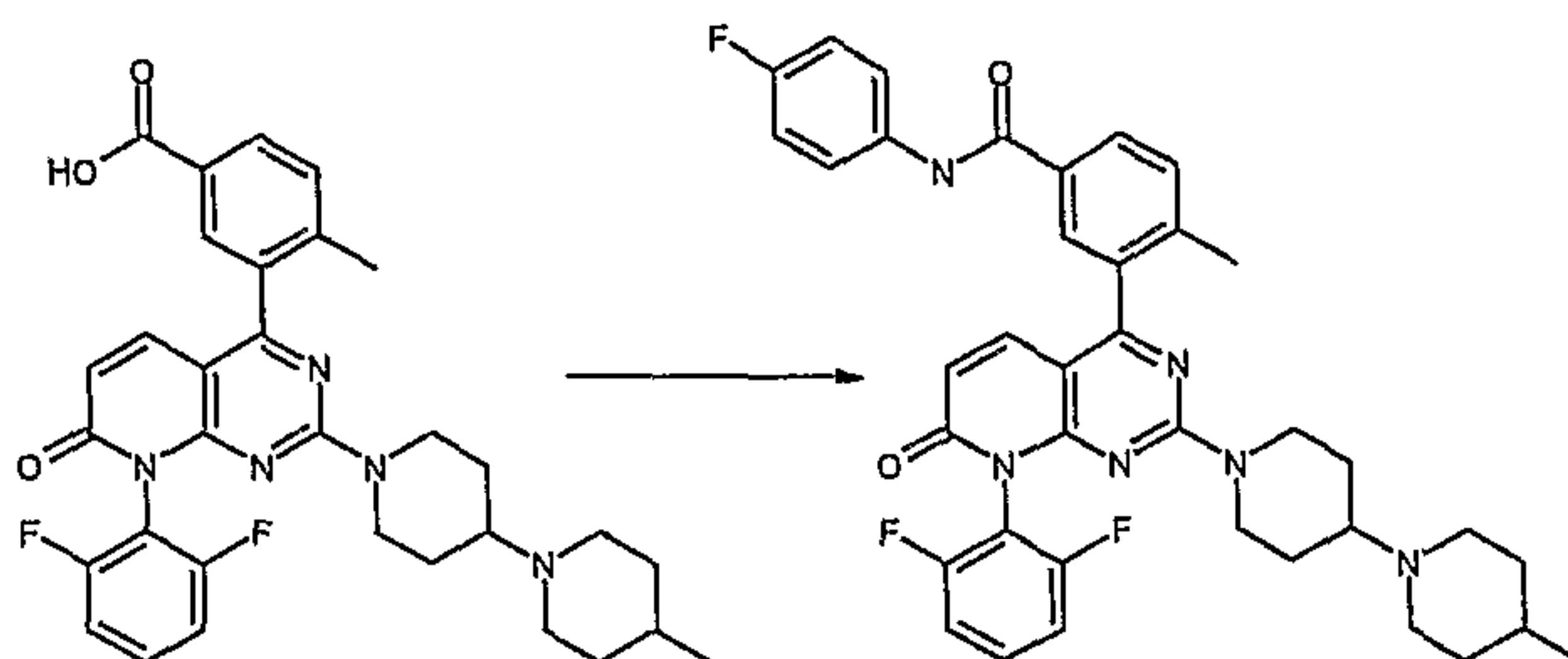
3-[8-(2,6-difluorophenyl)-2-(4-methyl-1,4'-bipiperidin-1'-yl)-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl]-*N*-ethyl-4-methylbenzamide



To the compound 3-[8-(2,6-difluorophenyl)-2-(4-methyl-1,4'-bipiperidin-1'-yl)-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl]-4-methylbenzoic acid (31.6 mg, 0.055 mmol) in DMF (0.5 mL) were added HBTU (25 mg, 0.066 mmol), triethylamine (15.5 uL, 0.11 mmol) and ethylamine (41.3 uL, 0.0825 mmol, 2M soln in THF). The mixture was stirred at rt overnight. Separation by HPLC with TFA, followed by neutralization with SPE amine cartridge afforded the title compound (26.2 mg, 78%). LC-MS  $m/z$  601 ( $M+H$ )<sup>+</sup>.

**Example 174**

3-[8-(2,6-difluorophenyl)-2-(4-methyl-1,4'-bipiperidin-1'-yl)-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl]-*N*-(4-fluorophenyl)-4-methylbenzamide

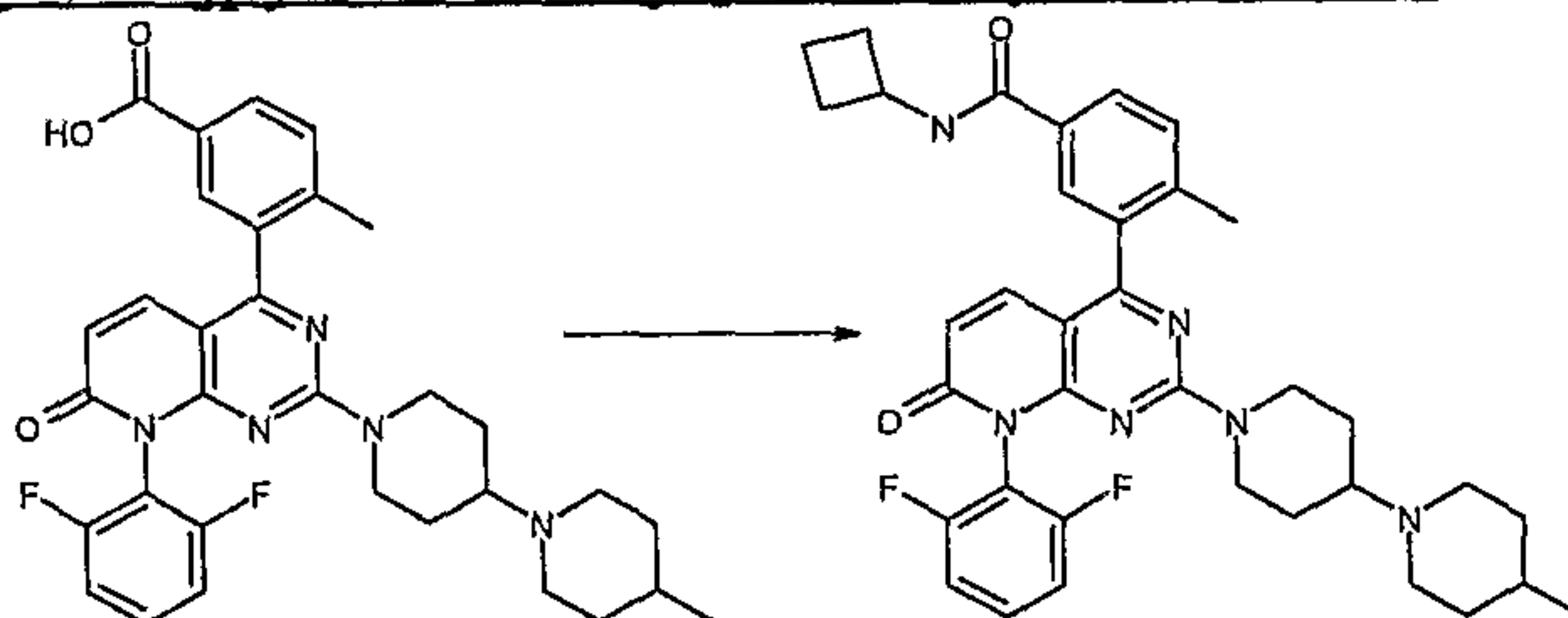


To the compound 3-[8-(2,6-difluorophenyl)-2-(4-methyl-1,4'-bipiperidin-1'-yl)-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl]-4-methylbenzoic acid (31.6 mg, 0.055 mmol) in DMF (0.5 mL) were added HBTU (25 mg, 0.066 mmol),  
 5 triethylamine (15.5 uL, 0.11 mmol) and 4-fluoroaniline (7.92 uL, 0.0825 mmol). The mixture was stirred at rt overnight. Separation by HPLC with TFA, followed by neutralization with SPE amine cartridge afforded the title compound (26.4 mg, 72%). LC-MS  $m/z$  667 ( $M+H$ )<sup>+</sup>.

10

**Example 175**

*N*-cyclobutyl-3-[8-(2,6-difluorophenyl)-2-(4-methyl-1,4'-bipiperidin-1'-yl)-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl]-4-methylbenzamide

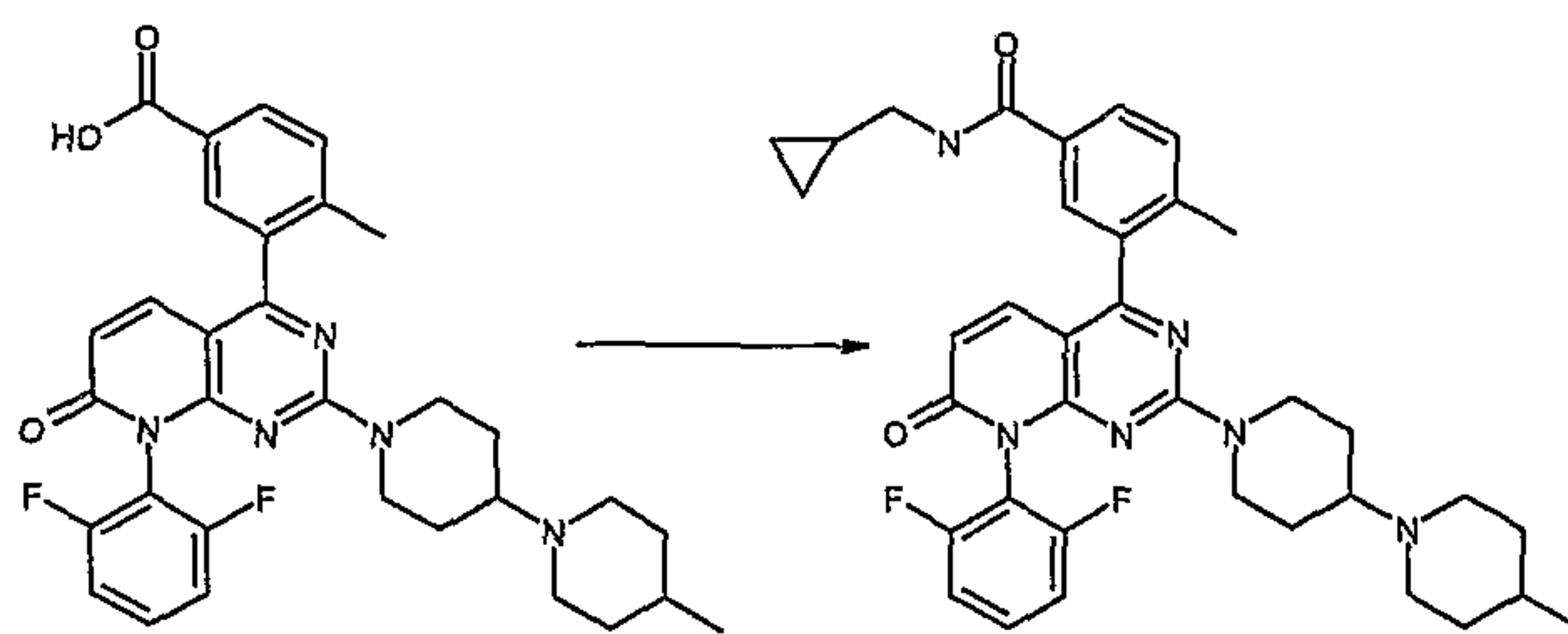


15

To the compound 3-[8-(2,6-difluorophenyl)-2-(4-methyl-1,4'-bipiperidin-1'-yl)-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl]-4-methylbenzoic acid (31.6 mg, 0.055 mmol) in DMF (0.5 mL) were added HBTU (25 mg, 0.066 mmol),  
 triethylamine (15.5 uL, 0.11 mmol) and cyclobutanamine (7.04 uL, 0.0825 mmol). The mixture was stirred at rt overnight. Separation by HPLC with TFA, followed by neutralization with SPE amine cartridge afforded the title compound (24.8 mg,  
 20 72%). LC-MS  $m/z$  627 ( $M+H$ )<sup>+</sup>.

**Example 176**

*N*-(cyclopropylmethyl)-3-[8-(2,6-difluorophenyl)-2-(4-methyl-1,4'-bipiperidin-1'-yl)-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl]-4-methylbenzamide

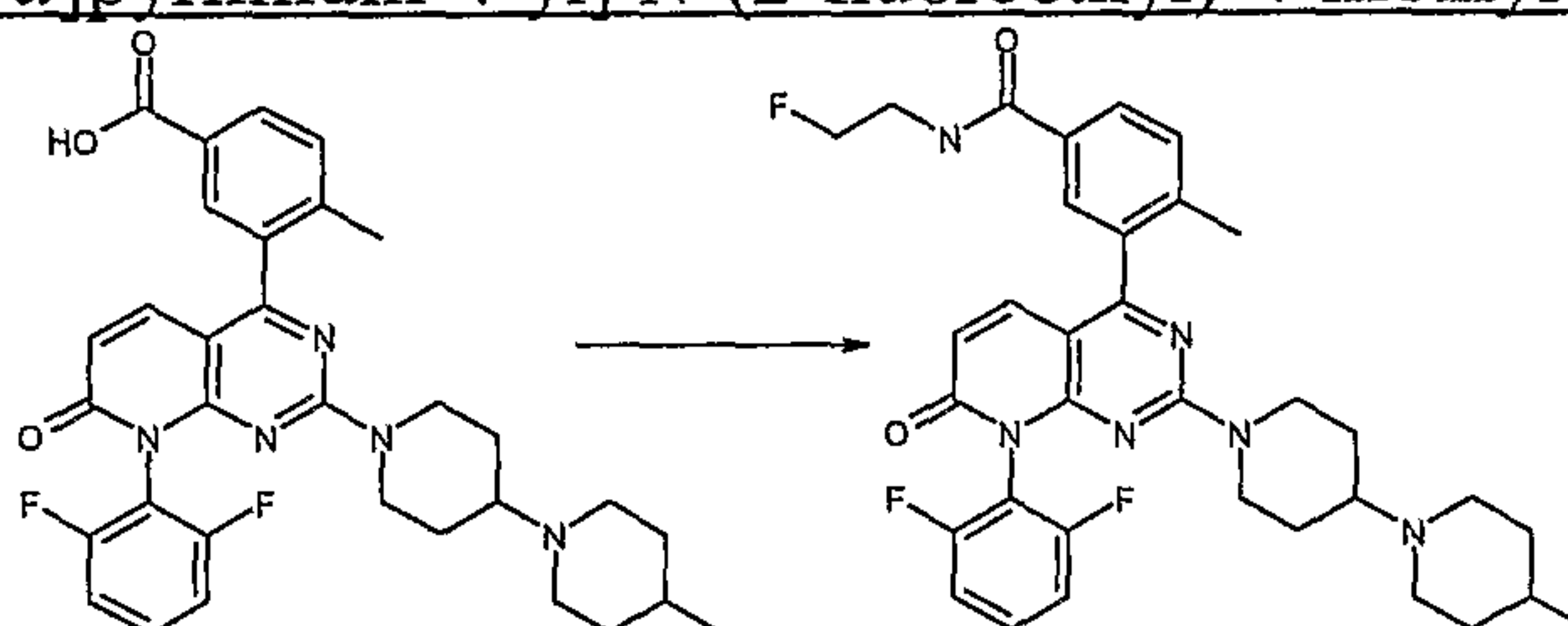


To the compound 3-[8-(2,6-difluorophenyl)-2-(4-methyl-1,4'-bipiperidin-1'-yl)-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl]-4-methylbenzoic acid (31.6 mg, 0.055 mmol) in DMF (0.5 mL) were added HBTU (25 mg, 0.066 mmol), triethylamine (15.5 uL, 0.11 mmol) and 1-cyclopropylmethanamine (7.15 uL, 0.0825 mmol). The mixture was stirred at rt overnight. Separation by HPLC with TFA, followed by neutralization with SPE amine cartridge afforded the title compound (6.2 mg, 18%). LC-MS  $m/z$  627 ( $M+H$ )<sup>+</sup>.

10

**Example 177**

3-[8-(2,6-difluorophenyl)-2-(4-methyl-1,4'-bipiperidin-1'-yl)-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl]-N-(2-fluoroethyl)-4-methylbenzamide



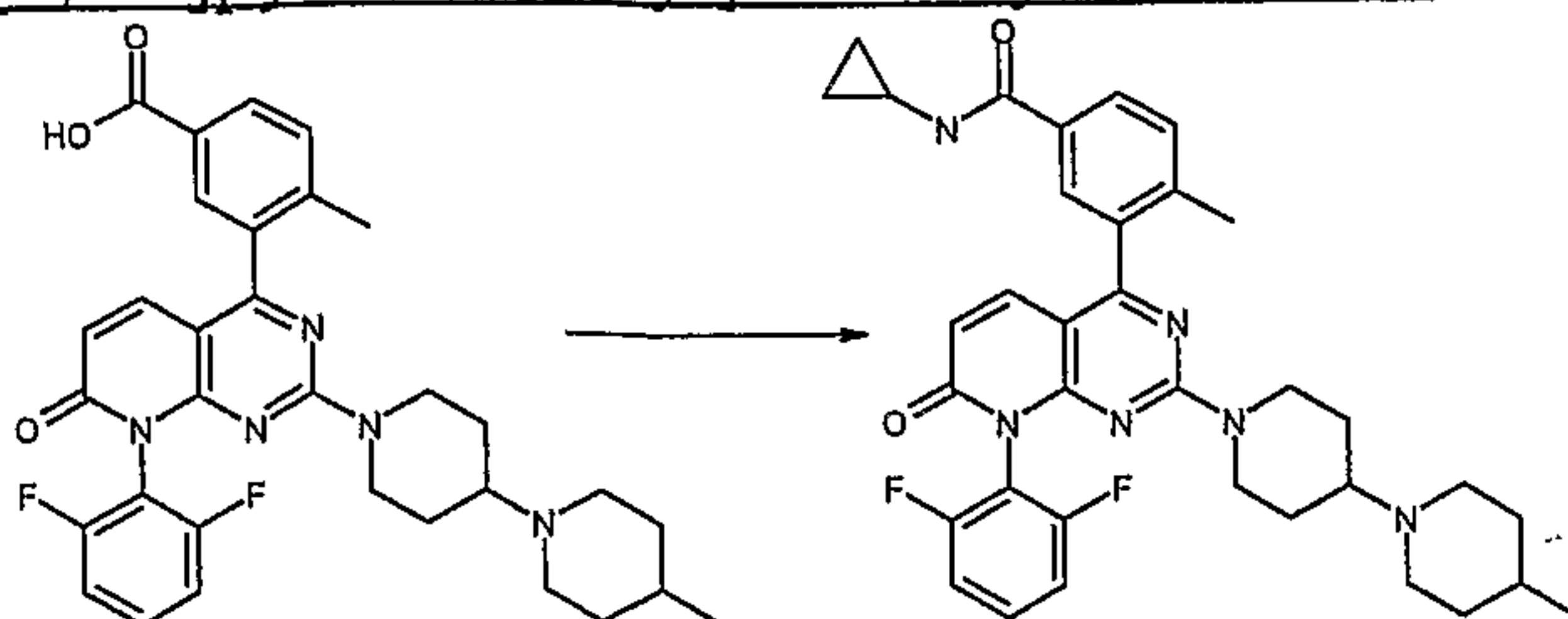
15

To the compound 3-[8-(2,6-difluorophenyl)-2-(4-methyl-1,4'-bipiperidin-1'-yl)-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl]-4-methylbenzoic acid (31.6 mg, 0.055 mmol) in DMF (0.5 mL) were added HBTU (25 mg, 0.066 mmol), triethylamine (15.5 uL, 0.11 mmol) and 2-fluoroethylamine hydrochloride (8.09 mg, 0.0825 mmol). The mixture was stirred at rt overnight. Separation by HPLC with TFA, followed by neutralization with SPE amine cartridge afforded the title compound (11.1 mg, 33%). LC-MS  $m/z$  619 ( $M+H$ )<sup>+</sup>.

20

**Example 178**

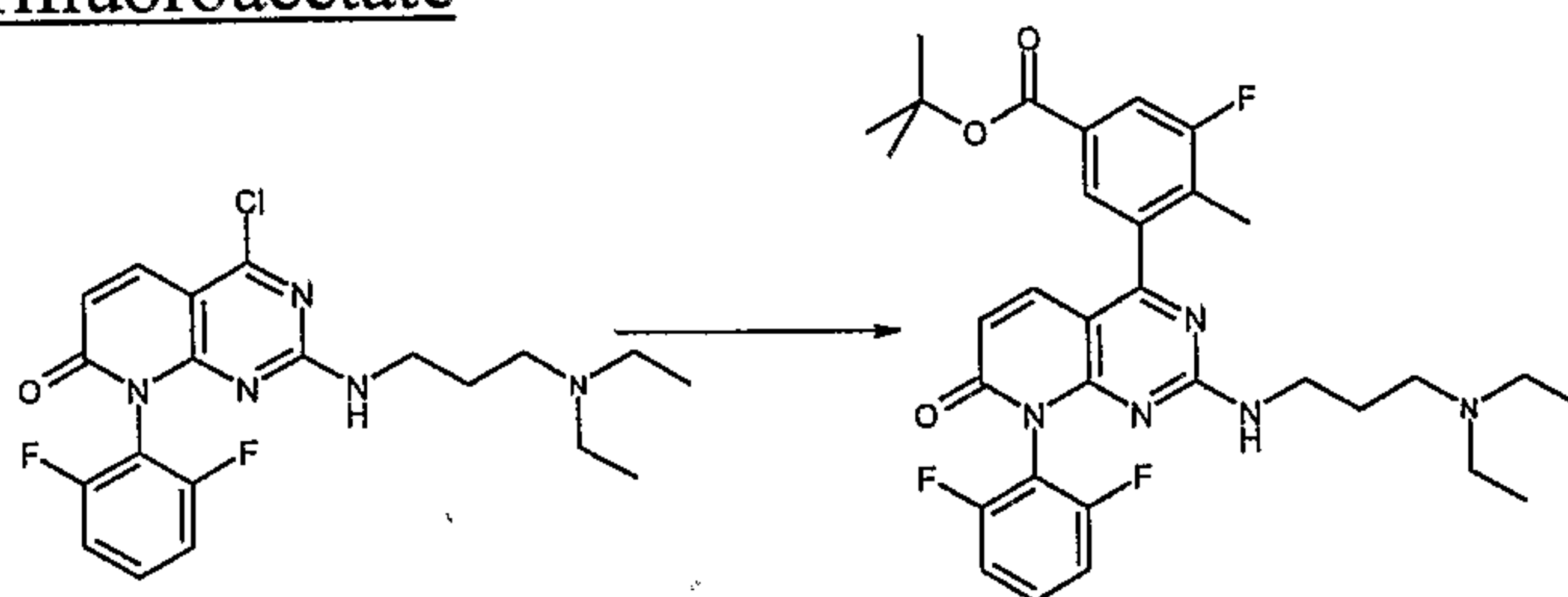
*N*-cyclopropyl-3-[8-(2,6-difluorophenyl)-2-(4-methyl-1,4'-bipiperidin-1'-yl)-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl]-4-methylbenzamide



- 5 To the compound 3-[8-(2,6-difluorophenyl)-2-(4-methyl-1,4'-bipiperidin-1'-yl)-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl]-4-methylbenzoic acid (31.6 mg, 0.055 mmol) in DMF (0.5 mL) were added HBTU (25 mg, 0.066 mmol), triethylamine (15.5  $\mu$ L, 0.11 mmol) and cyclopropylamine (5.71  $\mu$ L, 0.0825 mmol). The mixture was stirred at rt overnight. Separation by HPLC with TFA, followed by  
10 neutralization with SPE amine cartridge afforded the title compound (13.8 mg, 41%). LC-MS  $m/z$  613 ( $M+H$ )<sup>+</sup>.

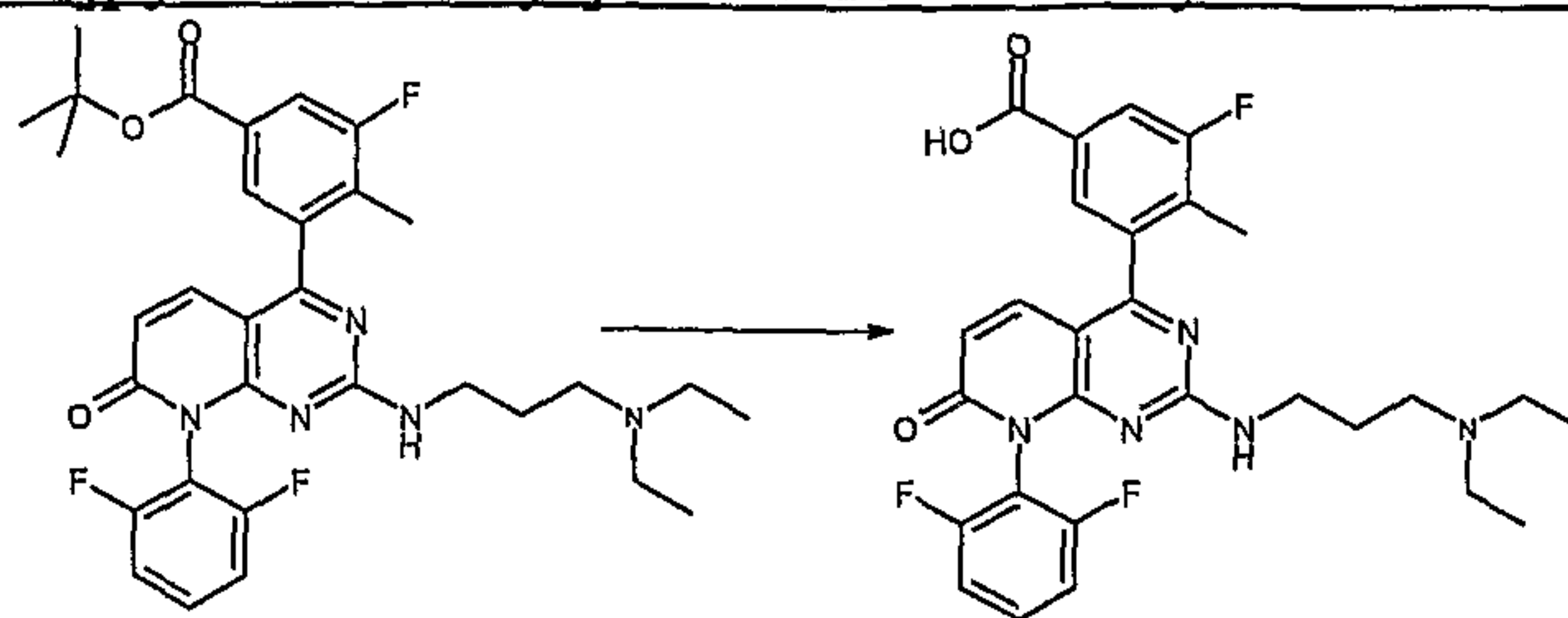
**Example 179**

15 3-[2-{[3-(diethylamino)propyl]amino}-8-(2,6-difluorophenyl)-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl]-5-fluoro-4-methyl-*N*-(1-methylethyl)benzamide  
179a) 1,1-dimethylethyl 3-[2-{[3-(diethylamino)propyl]amino}-8-(2,6-difluorophenyl)-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl]-5-fluoro-4-methylbenzoate trifluoroacetate



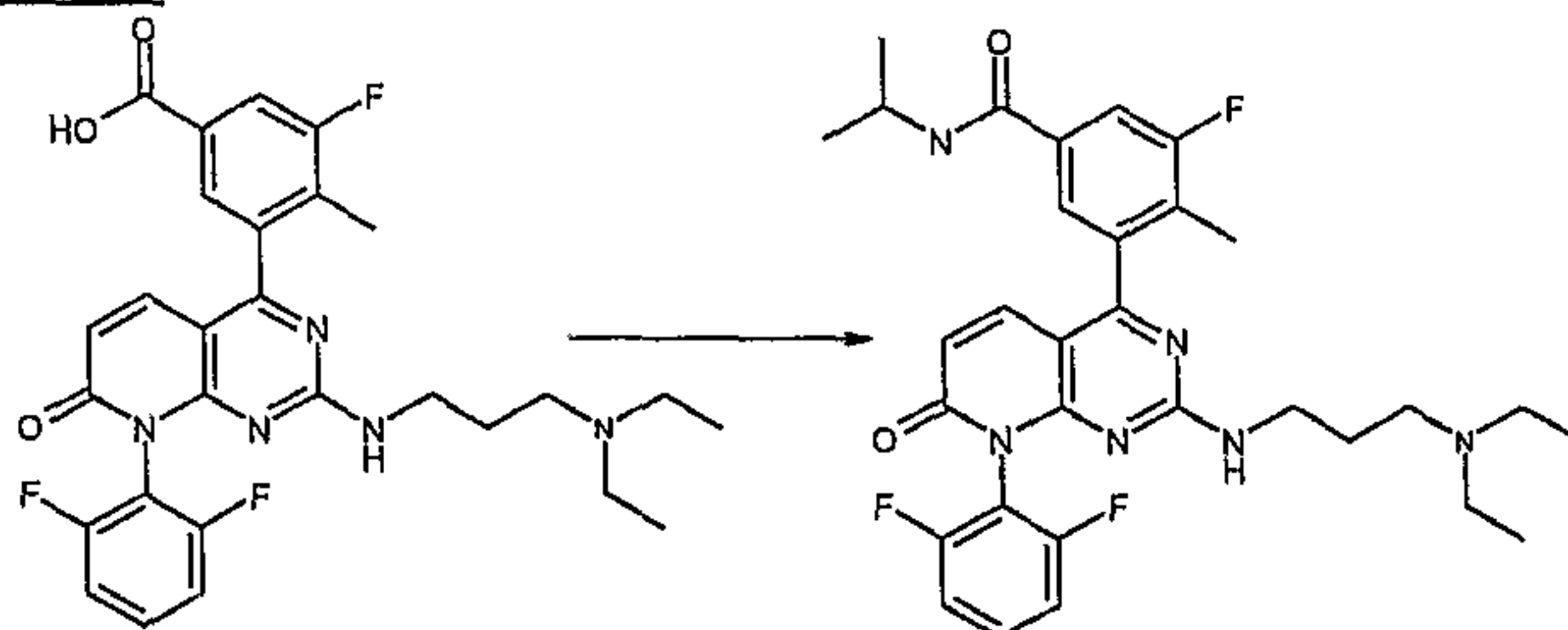
- 20 To the compound 4-chloro-2-{[3-(diethylamino)propyl]amino}-8-(2,6-difluorophenyl)pyrido[2,3-*d*]pyrimidin-7(8*H*)-one (600 mg, 1.422 mmol) in dioxane (15 mL) and water (5 mL) were added 1,1-dimethylethyl 3-fluoro-4-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoate (542 mg, 2.132 mol),  
25 potassium carbonate (590 mg, 4.26 mmol) and tetrakis(triphenylphosphine)-palladium(0) (82 mg, 0.071 mmol). The mixture was heated with microwave at 150  $^{\circ}$ C for 15 minutes. The mixture was filtered. Separation by HPLC with TFA afforded the crude title compound.

179b) 3-[2-{[3-(diethylamino)propyl]amino}-8-(2,6-difluorophenyl)-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl]-5-fluoro-4-methylbenzoic acid trifluoroacetate



5 To the crude compound 1,1-dimethylethyl 3-[2-{[3-(diethylamino)-propyl]amino}-8-(2,6-difluorophenyl)-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl]-5-fluoro-4-methylbenzoate trifluoroacetate in dichloromethane (1.5 mL, 23.3 mmol) were added TFA (0.703 mL, 9.5 mmol) and triethylsilane (0.281 mL, 1.82 mmol). The mixture was stirred at rt overnight. Separation by HPLC with TFA  
10 afforded the title compound (301 mg, 40%, 2 steps yield). LC-MS  $m/z$  540 ( $M+H$ )<sup>+</sup>.

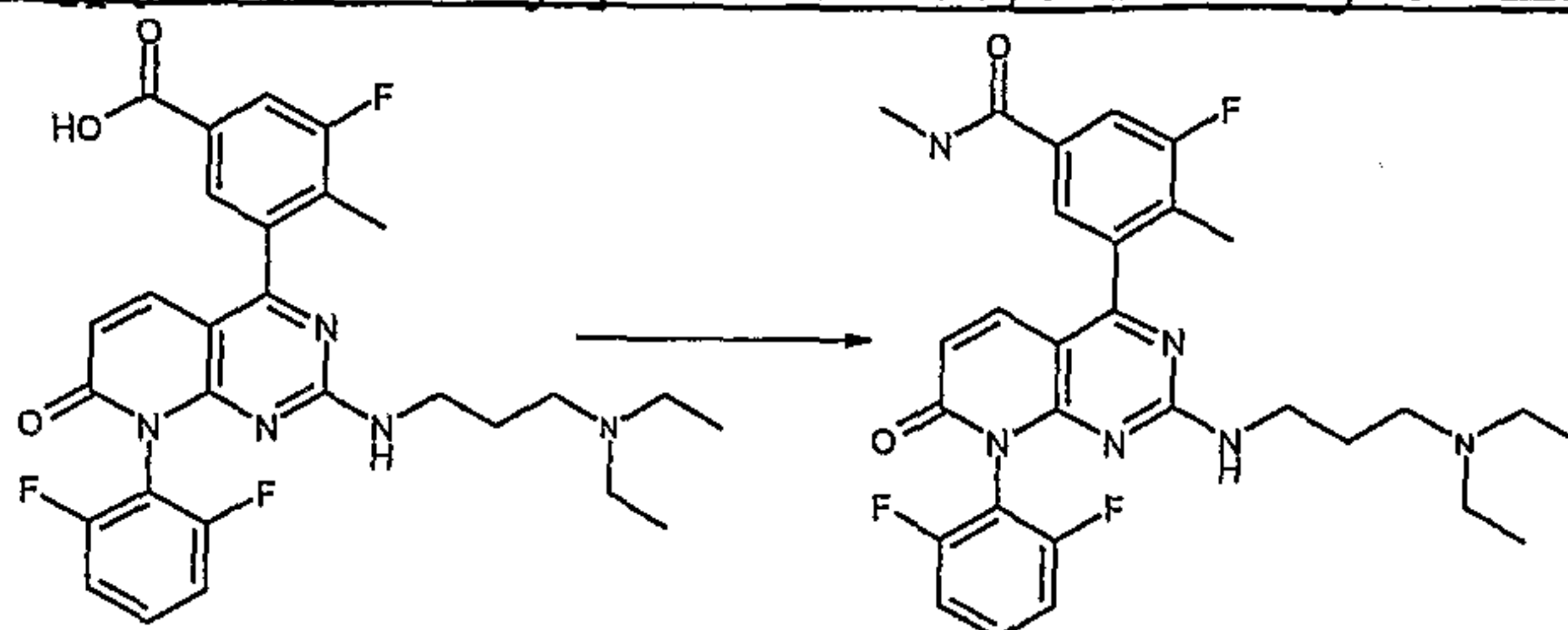
179c) 3-[2-{[3-(diethylamino)propyl]amino}-8-(2,6-difluorophenyl)-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl]-5-fluoro-4-methyl-*N*-(1-methylethyl)benzamide



15 To the compound 3-[2-{[3-(diethylamino)propyl]amino}-8-(2,6-difluorophenyl)-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl]-5-fluoro-4-methylbenzoic acid trifluoroacetate (30 mg, 0.055 mmol) in DMF (0.5 mL) were added HBTU (25 mg, 0.066 mmol), triethylamine (15.5 uL, 0.11 mmol) and  
20 isopropylamine (7.03 uL, 0.0825 mmol). The mixture was stirred at rt overnight. Separation by HPLC with TFA, followed by neutralization with SPE amine cartridge afforded the title compound (19.3 mg, 60%). LC-MS  $m/z$  581 ( $M+H$ )<sup>+</sup>.

**Example 180**

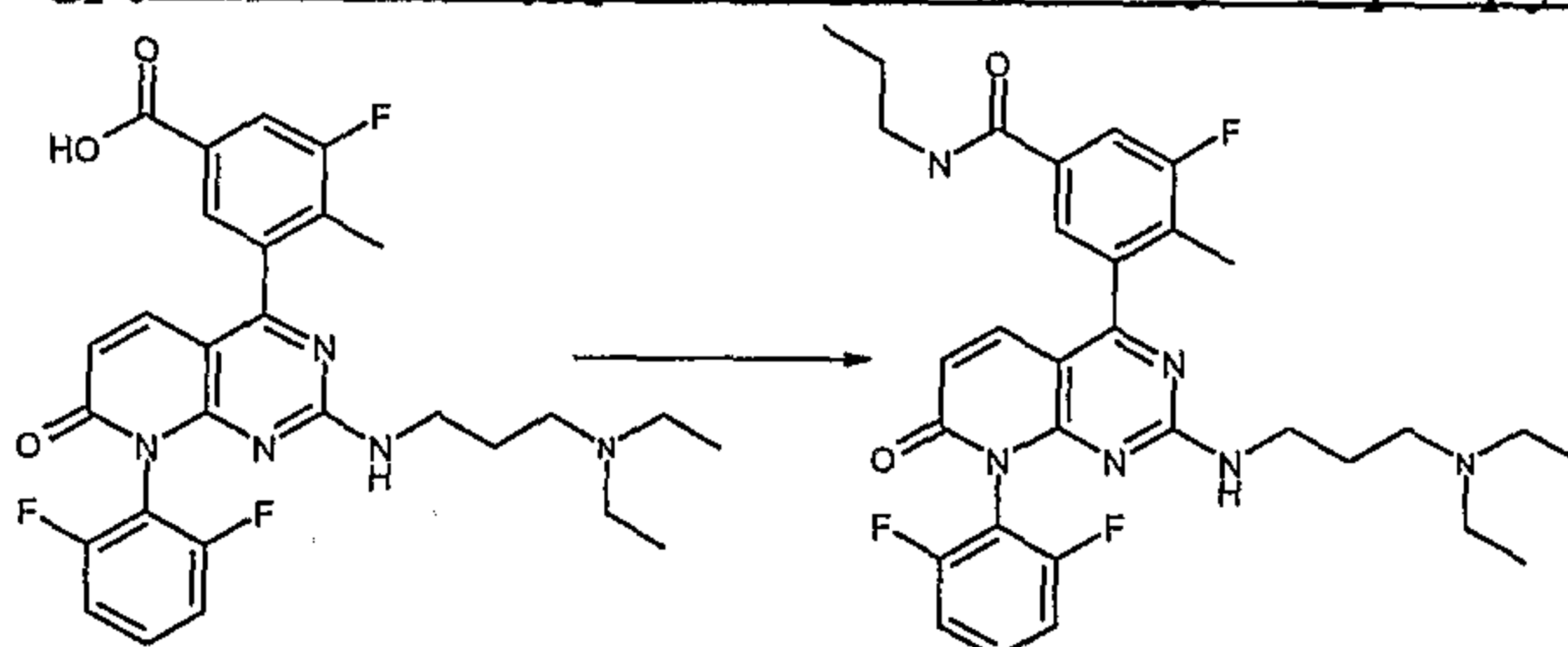
3-[2-{[3-(diethylamino)propyl]amino}-8-(2,6-difluorophenyl)-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl]-5-fluoro-*N*,4-dimethylbenzamide



5 To the compound 3-[2-{[3-(diethylamino)propyl]amino}-8-(2,6-difluorophenyl)-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl]-5-fluoro-4-methylbenzoic acid (30 mg, 0.055 mmol) in DMF (0.5 mL) were added HBTU (25 mg, 0.066 mmol), triethylamine (15.5 uL, 0.11 mmol) and methylamine (41.5 uL, 0.0825 mmol, 2M soln in THF). The mixture was stirred at rt overnight. Separation  
10 by HPLC with TFA, followed by neutralization with SPE amine cartridge afforded the title compound (9.6 mg, 31.5%). LC-MS *m/z* 553 (*M*+*H*)<sup>+</sup>.

**Example 181**

15 3-[2-{[3-(diethylamino)propyl]amino}-8-(2,6-difluorophenyl)-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl]-5-fluoro-4-methyl-*N*-propylbenzamide

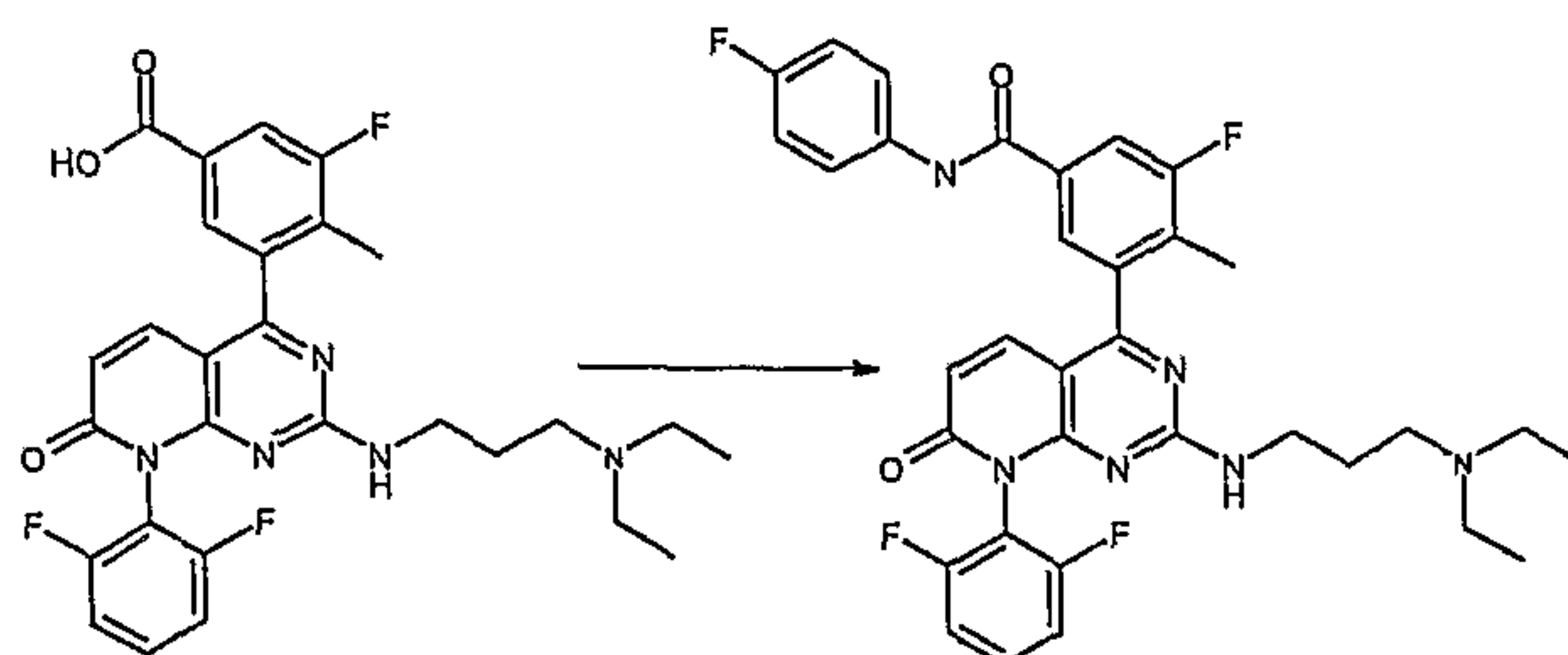


To the compound 3-[2-{[3-(diethylamino)propyl]amino}-8-(2,6-difluorophenyl)-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl]-5-fluoro-4-methylbenzoic acid (30 mg, 0.055 mmol) in DMF (0.5 mL) were added HBTU (25 mg, 0.066 mmol), triethylamine (15.5 uL, 0.11 mmol) and propylamine (6.78 uL, 0.0825 mmol). The mixture was stirred at rt overnight. Separation by HPLC with  
20 TFA, followed by neutralization with SPE amine cartridge afforded the title compound (18.7 mg, 58%). LC-MS *m/z* 581 (*M*+*H*)<sup>+</sup>.

25

**Example 182**

3-[2-{[3-(diethylamino)propyl]amino}-8-(2,6-difluorophenyl)-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl]-5-fluoro-*N*-(4-fluorophenyl)-4-methylbenzamide

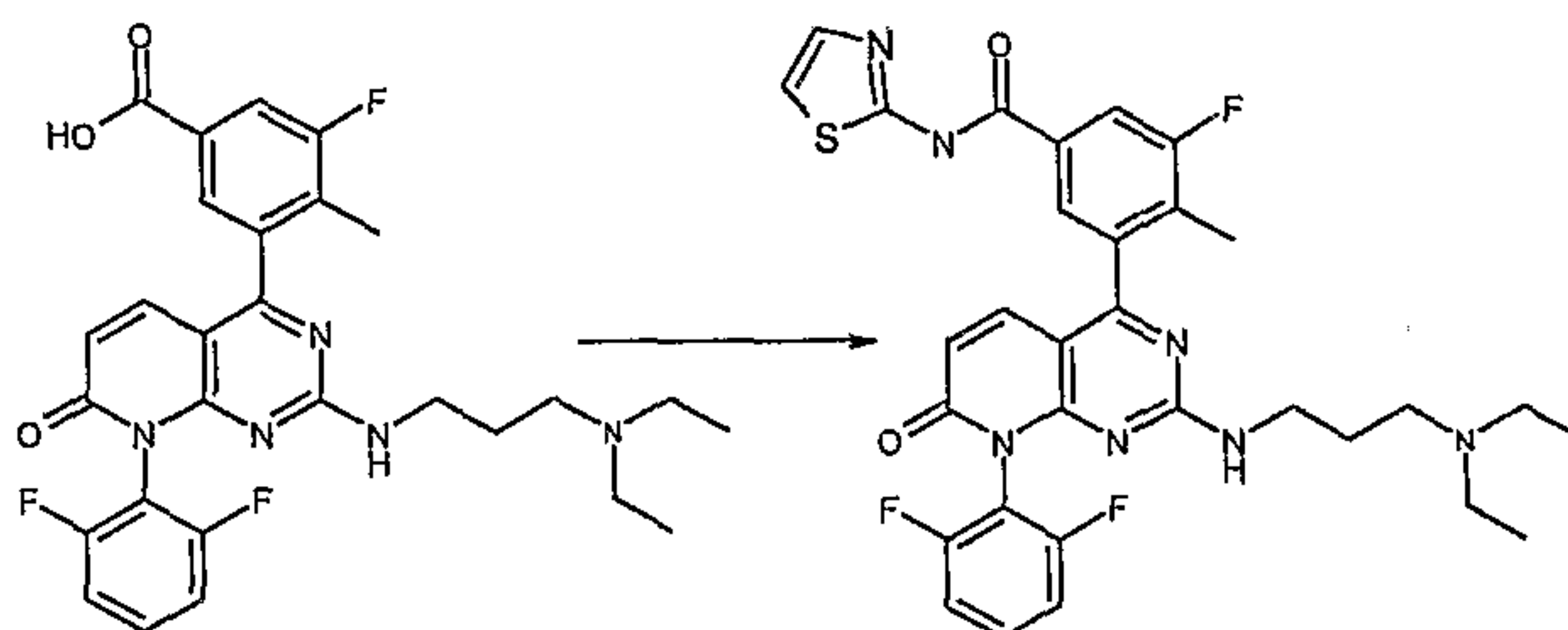


To the compound 3-[2-[[3-(diethylamino)propyl]amino]-8-(2,6-difluorophenyl)-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl]-5-fluoro-4-methylbenzoic acid (30 mg, 0.055 mmol) in DMF (0.5 mL) were added HBTU (25 mg, 0.066 mmol), triethylamine (15.5  $\mu$ L, 0.11 mmol) and 4-fluoroaniline (7.92  $\mu$ L, 0.0825 mmol). The mixture was stirred at rt overnight. Separation by HPLC with TFA, followed by neutralization with SPE amine cartridge afforded the title compound (20.1 mg, 58%). LC-MS  $m/z$  633 ( $M+H$ )<sup>+</sup>.

10

**Example 183**

3-[2-[[3-(diethylamino)propyl]amino]-8-(2,6-difluorophenyl)-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl]-5-fluoro-4-methyl-N-1,3-thiazol-2-ylbenzamide



15

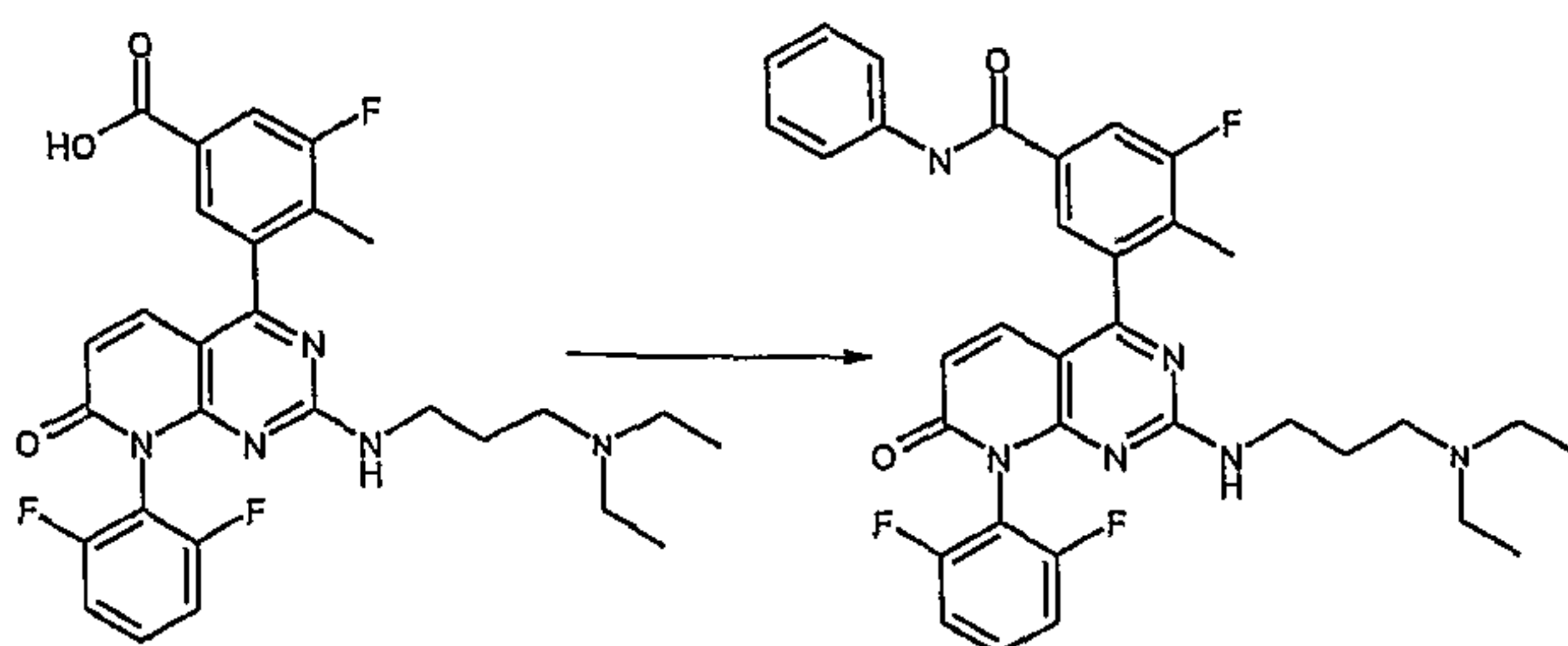
To the compound 3-[2-[[3-(diethylamino)propyl]amino]-8-(2,6-difluorophenyl)-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl]-5-fluoro-4-methylbenzoic acid (30 mg, 0.055 mmol) in DMF (0.5 mL) were added HBTU (25 mg, 0.066 mmol), triethylamine (15.5  $\mu$ L, 0.11 mmol) and 2-aminothiazole (8.26 mg, 0.0825 mmol). The mixture was stirred at rt overnight. Separation by HPLC with TFA, followed by neutralization with SPE amine cartridge afforded the title compound (15.6 mg, 46%). LC-MS  $m/z$  622 ( $M+H$ )<sup>+</sup>.

20

**Example 184**

3-[2-[[3-(diethylamino)propyl]amino]-8-(2,6-difluorophenyl)-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl]-5-fluoro-4-methyl-N-phenylbenzamide

25

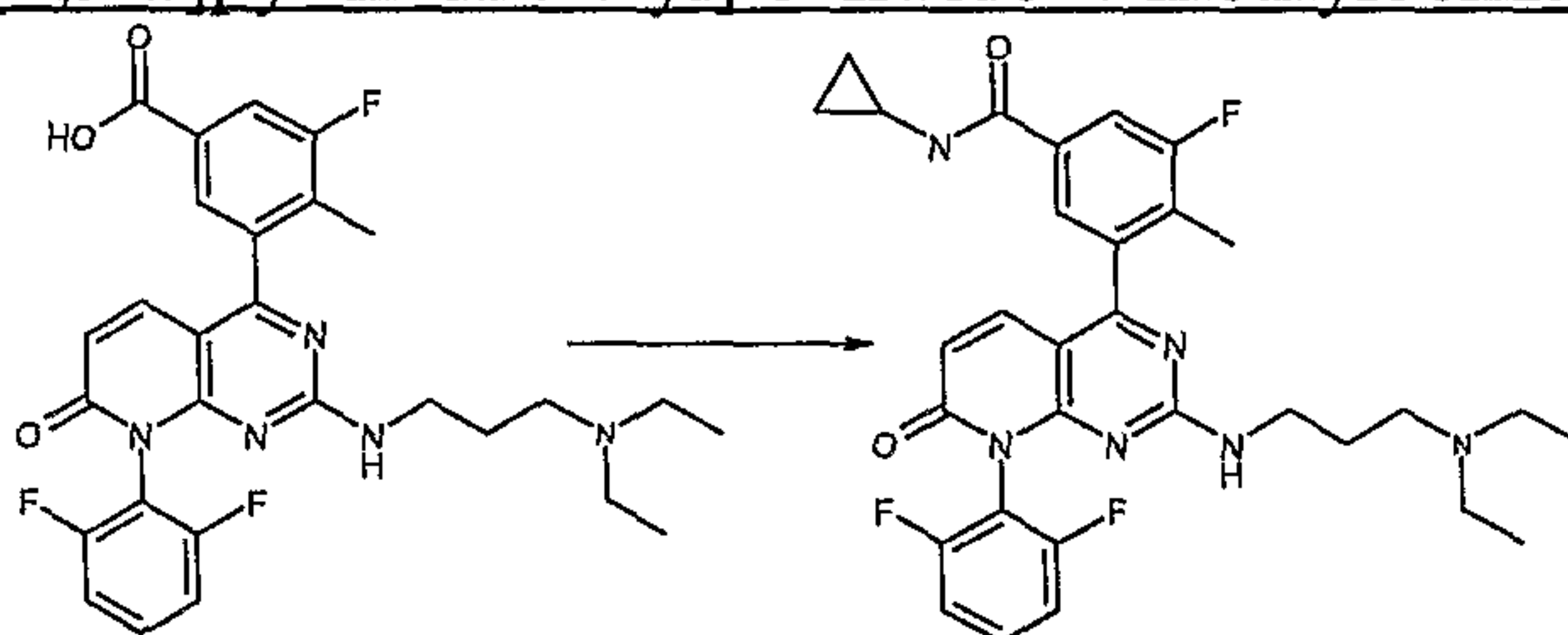


To the compound 3-[2-{[3-(diethylamino)propyl]amino}-8-(2,6-difluorophenyl)-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl]-5-fluoro-4-methylbenzoic acid (30 mg, 0.055 mmol) in DMF (0.5 mL) were added HBTU (25 mg, 0.066 mmol), triethylamine (15.5 uL, 0.11 mmol) and aniline (7.51 uL, 0.0825 mmol). The mixture was stirred at rt overnight. Separation by HPLC with TFA, followed by neutralization with SPE amine cartridge afforded the title compound (14.1 mg, 42%). LC-MS  $m/z$  615 ( $M+H$ )<sup>+</sup>.

10

**Example 185**

*N*-cyclopropyl-3-[2-{[3-(diethylamino)propyl]amino}-8-(2,6-difluorophenyl)-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl]-5-fluoro-4-methylbenzamide



To the compound 3-[2-{[3-(diethylamino)propyl]amino}-8-(2,6-difluorophenyl)-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl]-5-fluoro-4-methylbenzoic acid (30 mg, 0.055 mmol) in DMF (0.5 mL) were added HBTU (25 mg, 0.066 mmol), triethylamine (15.5 uL, 0.11 mmol) and cyclopropylamine (5.71 uL, 0.0825 mmol). The mixture was stirred at rt overnight. Separation by HPLC with TFA, followed by neutralization with SPE amine cartridge afforded the title compound (20 mg, 60%). LC-MS  $m/z$  579 ( $M+H$ )<sup>+</sup>.

20

**Example 186**

*N*-cyclopentyl-3-[2-{[3-(diethylamino)propyl]amino}-8-(2,6-difluorophenyl)-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl]-5-fluoro-4-methylbenzamide

# **DEMANDES OU BREVETS VOLUMINEUX**

**LA PRÉSENTE PARTIE DE CETTE DEMANDE OU CE BREVETS  
COMPREND PLUS D'UN TOME.**

**CECI EST LE TOME \_\_1\_\_ DE \_\_2\_\_**

NOTE: Pour les tomes additionels, veuillez contacter le Bureau Canadien des Brevets.

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# **JUMBO APPLICATIONS / PATENTS**

**THIS SECTION OF THE APPLICATION / PATENT CONTAINS MORE  
THAN ONE VOLUME.**

**THIS IS VOLUME \_\_1\_\_ OF \_\_2\_\_**

NOTE: For additional volumes please contact the Canadian Patent Office.

**CLAIMS:**

1. A compound which is:

3-[2-{[3-(diethylamino)propyl]amino}-8-(2,6-difluorophenyl)-7-oxo-7,8-  
 5 dihydropyrido[2,3-*d*]pyrimidin-4-yl]-5-fluoro-4-methyl-*N*-(1-methylethyl)benzamide;

*N*-cyclopropyl-3-[2-{[3-(diethylamino)propyl]amino}-8-(2,6-difluorophenyl)-7-oxo-  
 7,8 dihydropyrido[2,3-*d*]pyrimidin-4-yl]-5-fluoro-4-methylbenzamide;

3-{8-(2,6-difluorophenyl)-2-[(1*H*-imidazol-2-ylmethyl)amino]-7-oxo-7,8-  
 10 dihydropyrido[2,3-*d*]pyrimidin-4-yl}-4-methyl-*N*-1,3-thiazol-2-ylbenzamide,  
 or a salt thereof.

2. A pharmaceutical composition comprising a compound or pharmaceutically  
 acceptable salt according to Claim 1 in admixture with one or more pharmaceutically  
 15 acceptable carriers or excipients.

3. The pharmaceutical composition according to Claim 2 adapted for administration by  
 intravenous, intramuscular, subcutaneous, intranasal, oral inhalation, intrarectal, intravaginal  
 or intraperitoneal means.

4. The pharmaceutical composition according to Claim 2 adapted for oral or nasal  
 inhalation.

5. The pharmaceutical composition according to Claim 2 adapted for topical  
 25 administration.

6. Use of a compound according to Claim 1 in the manufacture of a medicament for the  
 treatment and prophylaxis of a CSBP/RK/p38 kinase mediated disease in a mammal in need  
 thereof, wherein the CSBP/RK/p38 kinase mediated disease is any one of psoriatic arthritis,  
 30 Reiter's syndrome, gout, rubella arthritis, acute synovitis, rheumatoid arthritis, rheumatoid  
 spondylitis, osteoarthritis, gouty arthritis, sepsis, septic shock, endotoxic shock, toxic shock

syndrome, cerebral malaria, meningitis, ischemic and hemorrhagic stroke, neurotrauma/closed head injury, asthma, adult respiratory distress syndrome, chronic pulmonary inflammatory disease, chronic obstructive pulmonary disease (COPD), silicosis, pulmonary sarcososis, bone resorption disease, osteoporosis, restenosis, cardiac and brain and renal reperfusion injury, congestive heart failure, coronary arterial bypass grafting (CABG) surgery, thrombosis, glomerulonephritis, chronic renal failure, diabetes, diabetic retinopathy, macular degeneration, graft vs. host reaction, allograft rejection, Crohn's disease, ulcerative colitis, neurodegenerative disease, muscle degeneration, atherosclerosis, diabetic retinopathy, macular degeneration, tumor growth and metastasis, angiogenic disease, influenza induced pneumonia, eczema, contact dermatitis, psoriasis, sunburn, or conjunctivitis.

7. Use of a compound according to Claim 1 for the treatment and prophylaxis of a CSBP/RK/p38 kinase mediated disease in a mammal in need thereof, wherein the CSBP/RK/p38 kinase mediated disease is any one of psoriatic arthritis, Reiter's syndrome, gout, rubella arthritis, acute synovitis, rheumatoid arthritis, rheumatoid spondylitis, osteoarthritis, gouty arthritis, sepsis, septic shock, endotoxic shock, toxic shock syndrome, cerebral malaria, meningitis, ischemic and hemorrhagic stroke, neurotrauma/closed head injury, asthma, adult respiratory distress syndrome, chronic pulmonary inflammatory disease, chronic obstructive pulmonary disease (COPD), silicosis, pulmonary sarcososis, bone resorption disease, osteoporosis, restenosis, cardiac and brain and renal reperfusion injury, congestive heart failure, coronary arterial bypass grafting (CABG) surgery, thrombosis, glomerulonephritis, chronic renal failure, diabetes, diabetic retinopathy, macular degeneration, graft vs. host reaction, allograft rejection, Crohn's disease, ulcerative colitis, neurodegenerative disease, muscle degeneration, atherosclerosis, diabetic retinopathy, macular degeneration, tumor growth and metastasis, angiogenic disease, influenza induced pneumonia, eczema, contact dermatitis, psoriasis, sunburn, or conjunctivitis.

8. The use according to claim 6 or 7, wherein the CSBP/RK/p38 kinase mediated disease is gram negative sepsis.

9. The use according to claim 6 or 7, wherein the CSBP/RK/p38 kinase mediated disease is inflammatory bowel disease.

10. The use according to claim 6 or 7, wherein the CSBP/RK/p38 kinase mediated disease is rubella arthritis, acute synovitis, rheumatoid arthritis, rheumatoid spondylitis, osteoarthritis, or gouty arthritis.

11. The compound of Claim 1 which is 3-[2-{[3-(diethylamino)propyl]amino}-8-(2,6-difluorophenyl)-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl]-5-fluoro-4-methyl-*N*-(1-methylethyl)benzamide or a salt thereof.

12. A pharmaceutical composition comprising a compound or a pharmaceutically acceptable salt according to Claim 11, in admixture with one or more pharmaceutically acceptable carriers or excipients.

13. The pharmaceutical composition according to Claim 11 adapted for administration by intravenous, intramuscular, subcutaneous, intranasal, oral inhalation, intrarectal, intravaginal or intraperitoneal means.

14. The pharmaceutical composition according to Claim 12 adapted for oral or nasal inhalation.

15. The pharmaceutical composition according to Claim 12 adapted for topical administration.

16. Use of a compound according to Claim 10 in the manufacture of a medicament for the treatment and prophylaxis of a CSBP/RK/p38 kinase mediated disease in a mammal in need thereof, wherein the CSBP/RK/p38 kinase mediated disease is any one of psoriatic arthritis, Reiter's syndrome, gout, rubella arthritis, acute synovitis, rheumatoid arthritis, rheumatoid spondylitis, osteoarthritis, gouty arthritis, sepsis, septic shock, endotoxic shock, toxic shock syndrome, cerebral malaria, meningitis, ischemic and hemorrhagic stroke,

neurotrauma/closed head injury, asthma, adult respiratory distress syndrome, chronic pulmonary inflammatory disease, chronic obstructive pulmonary disease (COPD), silicosis, pulmonary sarcososis, bone resorption disease, osteoporosis, restenosis, cardiac and brain and renal reperfusion injury, congestive heart failure, coronary arterial bypass grafting (CABG) surgery, thrombosis, glomerularnephritis, chronic renal failure, diabetes, diabetic retinopathy, macular degeneration, graft vs. host reaction, allograft rejection, Crohn's disease, ulcerative colitis, neurodegenerative disease, muscle degeneration, atherosclerosis, diabetic retinopathy, macular degeneration, tumor growth and metastasis, angiogenic disease, influenza induced pneumonia, eczema, contact dermatitis, psoriasis, sunburn, or conjunctivitis.

10

17. Use of a compound according to Claim 10 for the treatment and prophylaxis of a CSBP/RK/p38 kinase mediated disease in a mammal in need thereof, wherein the CSBP/RK/p38 kinase mediated disease is any one of psoriatic arthritis, Reiter's syndrome, gout, rubella arthritis, acute synovitis, rheumatoid arthritis, rheumatoid spondylitis,

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osteoarthritis, gouty arthritis, sepsis, septic shock, endotoxic shock, toxic shock syndrome, cerebral malaria, meningitis, ischemic and hemorrhagic stroke, neurotrauma/closed head injury, asthma, adult respiratory distress syndrome, chronic pulmonary inflammatory disease, chronic obstructive pulmonary disease (COPD), silicosis, pulmonary sarcososis, bone resorption disease, osteoporosis, restenosis, cardiac and brain and renal reperfusion injury,

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congestive heart failure, coronary arterial bypass grafting (CABG) surgery, thrombosis, glomerularnephritis, chronic renal failure, diabetes, diabetic retinopathy, macular degeneration, graft vs. host reaction, allograft rejection, Crohn's disease, ulcerative colitis, neurodegenerative disease, muscle degeneration, atherosclerosis, diabetic retinopathy, macular degeneration, tumor growth and metastasis, angiogenic disease, influenza induced pneumonia,

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eczema, contact dermatitis, psoriasis, sunburn, or conjunctivitis.

18. The use according to claim 16 or 17, wherein the CSBP/RK/p38 kinase mediated disease is gram negative sepsis.

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19. The use according to claim 16 or 17, wherein the CSBP/RK/p38 kinase mediated disease is inflammatory bowel disease.

20. The use according to claim 16 or 17, wherein the CSBP/RK/p38 kinase mediated disease is rubella arthritis, acute synovitis, rheumatoid arthritis, rheumatoid spondylitis, osteoarthritis, or gouty arthritis.

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21. A compound of Claim 1 which is *N*-cyclopropyl-3-[2-{[3-(diethylamino)propyl]amino}-8-(2,6-difluorophenyl)-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl]-5-fluoro-4-methylbenzamide or a salt thereof.

10 22. A pharmaceutical composition comprising a compound or pharmaceutically acceptable salt according to Claim 21, in admixture with one or more pharmaceutically acceptable carriers or excipients.

15 23. The pharmaceutical composition according to Claim 22 adapted for administration by intravenous, intramuscular, subcutaneous, intranasal, oral inhalation, intrarectal, intravaginal or intraperitoneal means.

24. The pharmaceutical composition according to Claim 22 adapted for oral or nasal inhalation.

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25. The pharmaceutical composition according to Claim 22 adapted for topical administration.

26. Use of a compound according to Claim 21 in the manufacture of a medicament for the  
 25 treatment and prophylaxis of a CSBP/RK/p38 kinase mediated disease in a mammal in need thereof, wherein the CSBP/RK/p38 kinase mediated disease is any one of psoriatic arthritis, Reiter's syndrome, gout, rubella arthritis, acute synovitis, rheumatoid arthritis, rheumatoid spondylitis, osteoarthritis, gouty arthritis, sepsis, septic shock, endotoxic shock, toxic shock syndrome, cerebral malaria, meningitis, ischemic and hemorrhagic stroke, neurotrauma/closed  
 30 head injury, asthma, adult respiratory distress syndrome, chronic pulmonary inflammatory disease, chronic obstructive pulmonary disease (COPD), silicosis, pulmonary sarcososis, bone

resorption disease, osteoporosis, restenosis, cardiac and brain and renal reperfusion injury, congestive heart failure, coronary arterial bypass grafting (CABG) surgery, thrombosis, glomerulonephritis, chronic renal failure, diabetes, diabetic retinopathy, macular degeneration, graft vs. host reaction, allograft rejection, Crohn's disease, ulcerative colitis, neurodegenerative disease, muscle degeneration, atherosclerosis, diabetic retinopathy, macular degeneration, tumor growth and metastasis, angiogenic disease, influenza induced pneumonia, eczema, contact dermatitis, psoriasis, sunburn, or conjunctivitis.

27. Use of a compound according to Claim 21 for the treatment and prophylaxis of a CSBP/RK/p38 kinase mediated disease in a mammal in need thereof, wherein the CSBP/RK/p38 kinase mediated disease is any one of psoriatic arthritis, Reiter's syndrome, gout, rubella arthritis, acute synovitis, rheumatoid arthritis, rheumatoid spondylitis, osteoarthritis, gouty arthritis, sepsis, septic shock, endotoxic shock, toxic shock syndrome, cerebral malaria, meningitis, ischemic and hemorrhagic stroke, neurotrauma/closed head injury, asthma, adult respiratory distress syndrome, chronic pulmonary inflammatory disease, chronic obstructive pulmonary disease (COPD), silicosis, pulmonary sarcososis, bone resorption disease, osteoporosis, restenosis, cardiac and brain and renal reperfusion injury, congestive heart failure, coronary arterial bypass grafting (CABG) surgery, thrombosis, glomerulonephritis, chronic renal failure, diabetes, diabetic retinopathy, macular degeneration, graft vs. host reaction, allograft rejection, Crohn's disease, ulcerative colitis, neurodegenerative disease, muscle degeneration, atherosclerosis, diabetic retinopathy, macular degeneration, tumor growth and metastasis, angiogenic disease, influenza induced pneumonia, eczema, contact dermatitis, psoriasis, sunburn, or conjunctivitis.

28. The use according to claim 26 or 27, wherein the CSBP/RK/p38 kinase mediated disease is gram negative sepsis.

29. The use according to claim 26 or 27, wherein the CSBP/RK/p38 kinase mediated disease is inflammatory bowel disease.

30. The use according to claim 26 or 27, wherein the CSBP/RK/p38 kinase mediated disease is rubella arthritis, acute synovitis, rheumatoid arthritis, rheumatoid spondylitis, osteoarthritis, or gouty arthritis.

5 31. A compound of claim 1 which is which is 3-{8-(2,6-difluorophenyl)-2-[(1*H*imidazol-2-ylmethyl)amino]-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl}-4-methyl-*N*-1,3-thiazol-2-ylbenzamide or a salt thereof.

32. A pharmaceutical composition comprising a compound or pharmaceutically acceptable salt according to Claim 31 in admixture with one or more pharmaceutically acceptable carriers or excipients.

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33. The pharmaceutical composition according to Claim 32 adapted for administration by intravenous, intramuscular, subcutaneous, intranasal, oral inhalation, intrarectal, intravaginal or intraperitoneal means.

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34. The pharmaceutical composition according to Claim 32 adapted for oral or nasal inhalation.

20 35. The pharmaceutical composition according to Claim 32 adapted for topical administration.

36. Use of a compound according to Claim 31 in the manufacture of a medicament for the treatment and prophylaxis of a CSBP/RK/p38 kinase mediated disease in a mammal in need thereof, wherein the CSBP/RK/p38 kinase mediated disease is any one of psoriatic arthritis, Reiter's syndrome, gout, rubella arthritis, acute synovitis, rheumatoid arthritis, rheumatoid spondylitis, osteoarthritis, gouty arthritis, sepsis, septic shock, endotoxic shock, toxic shock syndrome, cerebral malaria, meningitis, ischemic and hemorrhagic stroke, neurotrauma/closed head injury, asthma, adult respiratory distress syndrome, chronic pulmonary inflammatory disease, chronic obstructive pulmonary disease (COPD), silicosis, pulmonary sarcososis, bone resorption disease, osteoporosis, restenosis, cardiac and brain and renal reperfusion injury,

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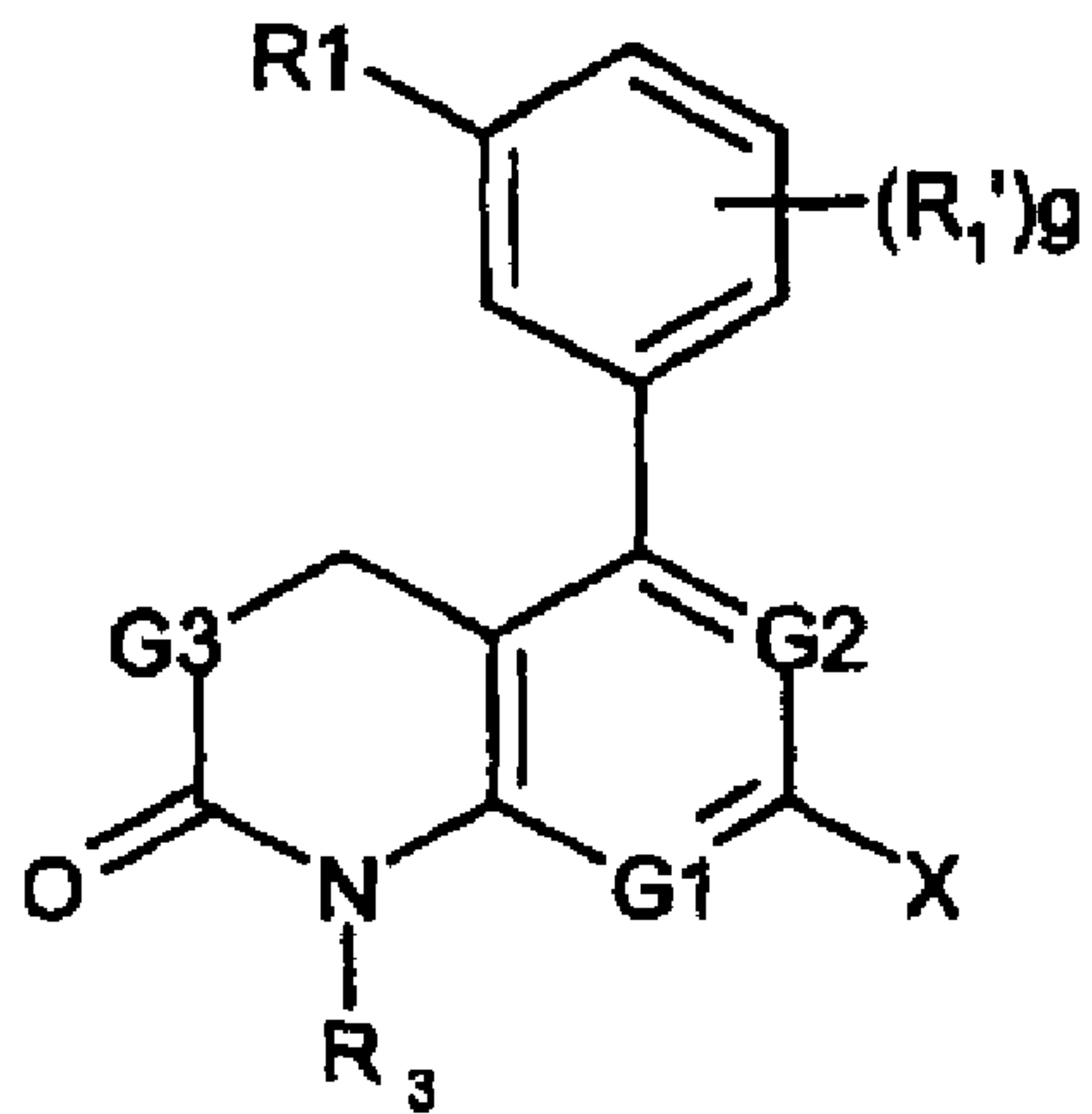
congestive heart failure, coronary arterial bypass grafting (CABG) surgery, thrombosis, glomerulonephritis, chronic renal failure, diabetes, diabetic retinopathy, macular degeneration, graft vs. host reaction, allograft rejection, Crohn's disease, ulcerative colitis, neurodegenerative disease, muscle degeneration, atherosclerosis, diabetic retinopathy, macular  
 5 degeneration, tumor growth and metastasis, angiogenic disease, influenza induced pneumonia, eczema, contact dermatitis, psoriasis, sunburn, or conjunctivitis.

37. Use of a compound according to Claim 31 for the treatment and prophylaxis of a CSBP/RK/p38 kinase mediated disease in a mammal in need thereof, wherein the  
 10 CSBP/RK/p38 kinase mediated disease is any one of psoriatic arthritis, Reiter's syndrome, gout, rubella arthritis, acute synovitis, rheumatoid arthritis, rheumatoid spondylitis, osteoarthritis, gouty arthritis, sepsis, septic shock, endotoxic shock, toxic shock syndrome, cerebral malaria, meningitis, ischemic and hemorrhagic stroke, neurotrauma/closed head injury, asthma, adult respiratory distress syndrome, chronic pulmonary inflammatory disease,  
 15 chronic obstructive pulmonary disease (COPD), silicosis, pulmonary sarcososis, bone resorption disease, osteoporosis, restenosis, cardiac and brain and renal reperfusion injury, congestive heart failure, coronary arterial bypass grafting (CABG) surgery, thrombosis, glomerulonephritis, chronic renal failure, diabetes, diabetic retinopathy, macular degeneration, graft vs. host reaction, allograft rejection, Crohn's disease, ulcerative colitis,  
 20 neurodegenerative disease, muscle degeneration, atherosclerosis, diabetic retinopathy, macular degeneration, tumor growth and metastasis, angiogenic disease, influenza induced pneumonia, eczema, contact dermatitis, psoriasis, sunburn, or conjunctivitis.

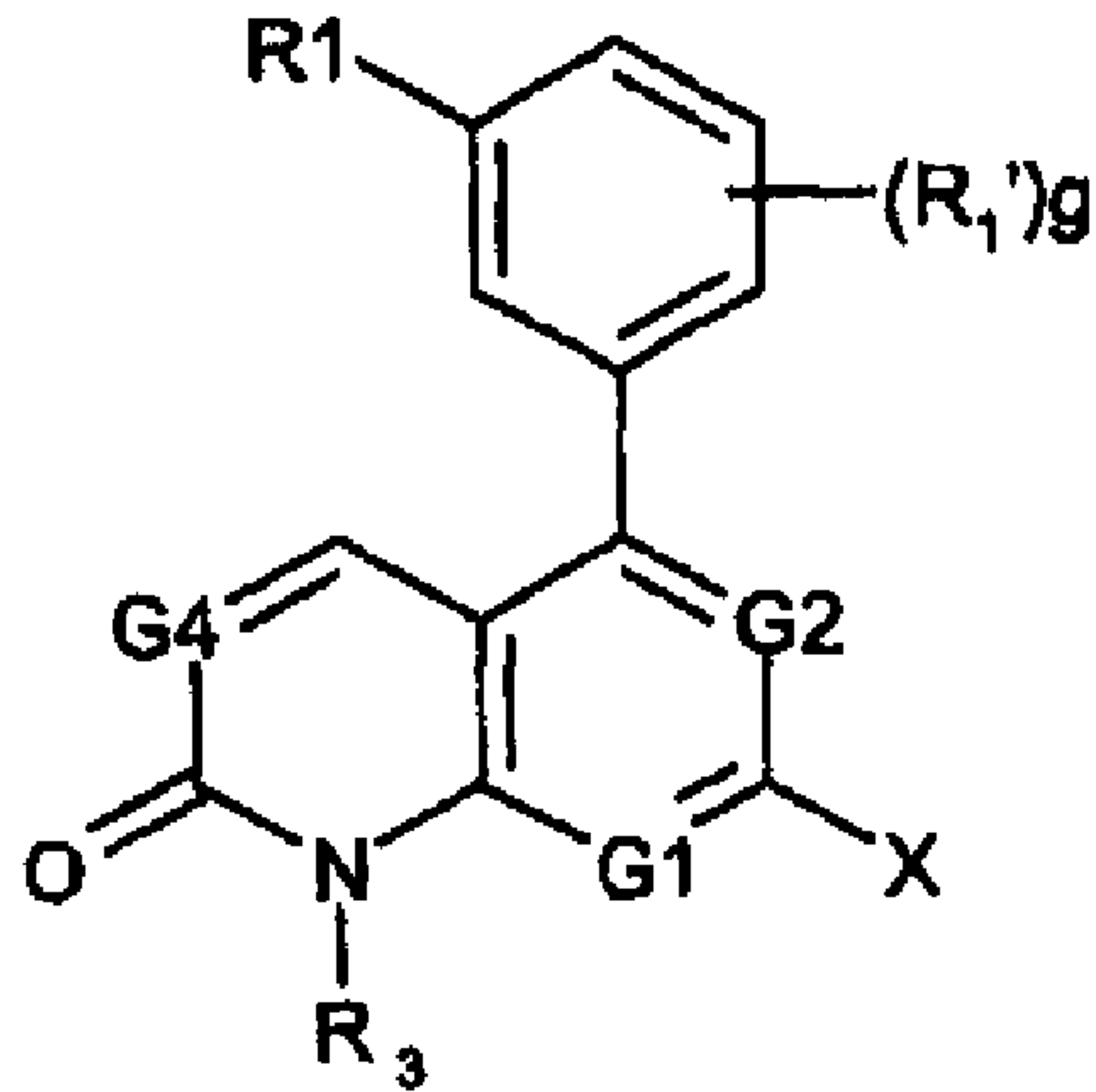
38. The use according to claim 36 or 37, wherein the CSBP/RK/p38 kinase mediated  
 25 disease is gram negative sepsis.

39. The use according to claim 36 or 37, wherein the CSBP/RK/p38 kinase mediated disease is inflammatory bowel disease.

40. The use according to claim 36 or 37, wherein the CSBP/RK/p38 kinase mediated disease is rubella arthritis, acute synovitis, rheumatoid arthritis, rheumatoid spondylitis, osteoarthritis, or gouty arthritis.



(I)



(Ia)