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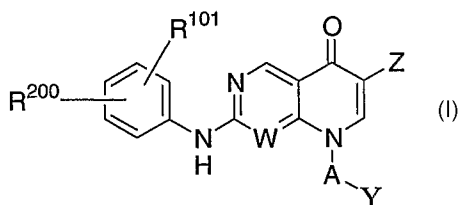
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(54) Title: 5-OXO-5,8-DIHYDRO-PYRIDO-PYRIMIDINES AS INHIBITORS OF C-FMS KINASE



(57) Abstract: The invention addresses the current need for selective and potent protein tyrosine kinase inhibitors by providing potent inhibitors of c-fms kinase. The invention is directed to the novel compounds of Formula (I) or a solvate, hydrate, tautomer or pharmaceutically acceptable salt thereof, wherein: W, A, Y, Z, R¹⁰¹ and R²⁰⁰ are described in the specification.



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5-OXO-5,8-DIHYDRO-PYRIDO-PYRIMIDINES AS INHIBITORS OF C-FMS KINASE

CROSS REFERENCE TO RELATED APPLICATIONS

This present application claims benefit of U.S. Provisional Patent Application Serial No. 60/714,527, filed September 14, 2005, which is incorporated herein by reference in its entirety and for all purposes.

BACKGROUND OF THE INVENTION

The invention relates to novel compounds that function as protein tyrosine kinase inhibitors. The family of 5-oxo-5,8-dihydro-pyrido-pyrimidines has exhibited promising pharmaceutical properties in the past; United States Patent 4,556,709, JP 09221424 and DE 19532235 are indicative of recent investigations. More particularly, the invention relates to novel compounds that function as inhibitors of c-fms kinase.

c-Fms is a type III receptor tyrosine kinase selectively expressed on macrophages and their progenitors. The extracellular Ig domain of c-fms binds macrophage colony stimulating factor (M-CSF), also known as colony stimulating factor-1 (CSF-1). Binding of CSF-1 induces receptor dimerization and trans-phosphorylation of the intracellular c-fms kinase domain on Y723 and other tyrosine residues. Once phosphorylated, c-fms efficiently phosphorylates several cytoplasmic signaling molecules that lead to *de novo* gene expression and proliferation. Small molecule inhibitors of the kinase catalytic site of c-fms are expected to prevent CSF-1 induced cellular responses.

Macrophages are a predominant source of tumor necrosis factor (TNF) and interleukin-1 (IL-1) in the destructive pannus of rheumatoid arthritis. TNF and IL-1 activate stromal expression of hematopoietic factors including CSF-1. In turn, CSF-1 recruits monocytes and promotes macrophage survival, functional activation, and in some settings, proliferation. Thus, TNF and CSF-1 interact in a perpetuating cycle that leads to inflammation and joint destruction. The exclusive receptor for CSF-1 is c-fms, and the disclosed invention is a c-fms inhibitor designed to interrupt this cycle.

Macrophages are abundant at sites of chronic inflammation where they are often the most important source of TNF, IL-1, and other cytokines. Moreover, macrophages can be an important source of factors that function in tissue remodeling such

as plasminogen activators, matrix metalloproteases, vascular endothelial growth factor, and transforming growth factor – β . The numbers of macrophages present within target tissues have strongly correlated with disease severity in rheumatoid arthritis (*Ann Rheum Dis* 53 (1994) pp 39-44), immune nephritis (*Kidney Int* 54 (1998) pp 143-151), and graft rejection (*Transpl Int* 7 Suppl 1 (1994) pp 577-579). Macrophage numbers are also elevated in atherosclerotic plaque (*Arch Pathol Lab Med* 109 (1985) pp 445-449), adipose tissue in obesity (*J Clin Invest* 112 (2003) pp 1796-1898), diabetic nephropathy (*Kidney Int* 65 (2004) pp 116-128), cardiac hypertrophy (*Hypertension* 25 (1999) pp 132-138), and in many solid tumors (*Trends in Immunology* 23 (2002) pp 549-555), particularly breast cancer (*J. Experimental Medicine* 193 (2001) pp 727-739), where they are thought to contribute to disease progression. Modulation of macrophage function through inhibition of c-fms thus is expected to be useful in treating inflammatory mediated diseases and conditions.

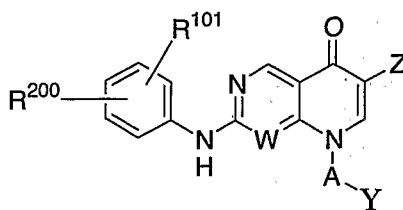
Another example of the invention is the use of any of the compounds described herein in the preparation of a medicament for treating: rheumatoid arthritis, graft rejection, atherosclerosis, obesity, diabetic nephropathy, cardiac hypertrophy and solid tumor diseases, especially breast cancer, in a subject in need of such treatment.

Preclinical data suggest CSF-1/FMS is a particularly viable therapeutic target for rheumatoid arthritis. Recent work has shown that neutralizing antibodies to CSF-1 reduce substantially the severity of collagen-induced arthritis in mice (*J Leukoc Biol* 68 (2000) pp 144-150). The authors additionally demonstrated that recombinant CSF-1 exacerbated the disease progress in this model. Therefore, a preferred use for the invention is the treatment of rheumatoid arthritis.

SUMMARY OF THE INVENTION

The invention addresses the current need for selective and potent protein tyrosine kinase inhibitors by providing potent inhibitors of c-fms kinase.

The invention is directed to the novel compounds of Formula I:



I

or a solvate, hydrate, tautomer or pharmaceutically acceptable salt thereof, wherein W, A, Y, Z, R¹⁰¹ and R²⁰⁰ are as defined herein.

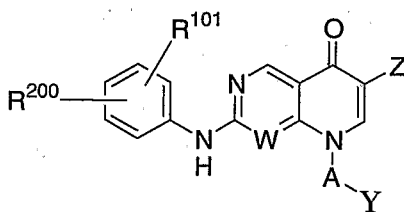
The invention is also directed to a method of using a compound of Formula I for inhibiting protein tyrosine kinase activity comprising administering an effective amount of at least one compound of Formula I.

The invention is directed to a method of inhibiting c-fms kinase activity in a subject in need thereof comprising administering to the subject an effective amount of at least one compound of Formula I.

The invention is also directed to a method of treating or ameliorating a c-fms kinase mediated disorder in a subject in need thereof comprising administering to the subject an effective amount of at least one compound of Formula I.

DETAILED DESCRIPTION OF THE INVENTION

This invention is directed to a compound of Formula I:



I

or a form thereof, wherein:

W is N or CH;

A is absent or alkyl;

Y is a ring selected from cycloalkyl, bicycloalkyl, aryl, alkylaryl, cycloalkylaryl, arylcycloalkyl, or heteroaryl provided that Y is not thiazole;

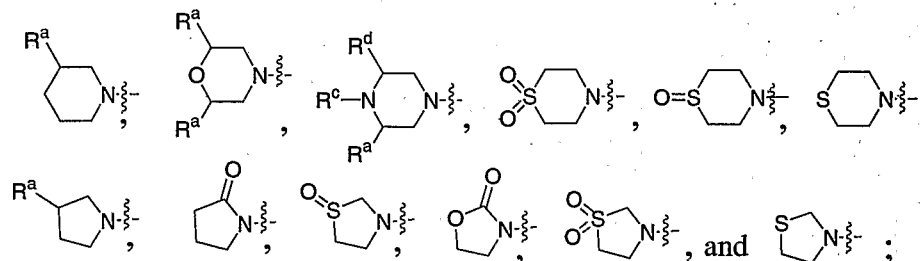
R^{101} is hydrogen, hydroxyl, methyl, halogen, $-CF_3$, or methoxy;

R^{200} is halogen, alkoxy optionally substituted with $-CH(OH)-CH_2-NR^{203}R^{204}$, alkyl optionally substituted with R^{201} , heterocyclyl optionally substituted with one alkyl and optionally substituted with one R^{202} , amino, alkylamino, dialkylamino, $-C(O)(CH_2)_nNR^{203}R^{204}$, heteroaryl, or $-R^{300}-R^{400}$; wherein n is 0, 1, 2, 3, or 4;

R^{201} is hydroxyl, methyl, halogen, $-CF_3$, amino, alkylamino, dialkylamino or methoxy;

R^{202} is alkyl, $-C(O)-CH_3$, $-CH_2-C(O)-CH_3$, $-C(O)(CH_2)_nNR^{203}R^{204}$, or $-CON-alkyl-NR^{203}R^{204}$; wherein n is 0, 1, 2, 3, or 4;

R^{203} and R^{204} are independently hydrogen, alkyl, or R^{203} and R^{204} may be taken together to form a ring selected from the following:



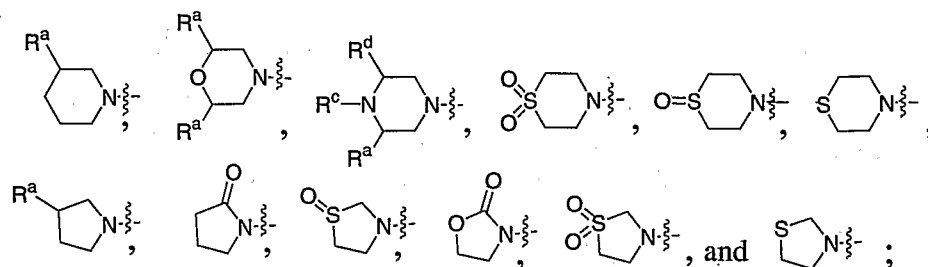
wherein R^a , R^c and R^d are independently hydrogen or alkyl;

R^{300} is alkyl;

R^{400} is $-NR^{403}R^{404}$, $-SO_2NR^{405}R^{406}$, oxazolidinonyl wherein said oxazolidinonyl is optionally substituted with one or two R^{401} , piperazinyl wherein said piperazinyl is optionally substituted with R^{202} or pyrrolidinonyl wherein said pyrrolidinonyl is optionally substituted with one or two R^{401} ;

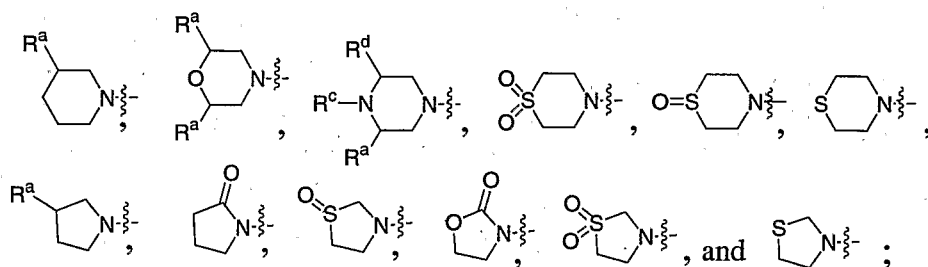
wherein R^{401} is methyl, $-C(O)-CH_3$, or $-CH_2-C(O)-CH_3$;

wherein R^{403} and R^{404} are independently hydrogen, alkyl, or R^{403} and R^{404} may be taken together to form a ring selected from the following:



wherein R^a , R^c and R^d are independently hydrogen or alkyl;

R^{405} and R^{406} are independently hydrogen, alkyl, or R^{405} and R^{406} may be taken together to form a ring selected from the following:



wherein R^a , R^c and R^d are independently hydrogen or alkyl; and

Z is CO_2H , CO_2alkyl , or CONR^1R^2 ; wherein R^1 is hydrogen or alkyl; and R^2 is hydrogen, alkyl, cycloalkyl, or alkoxy.

An example of the present invention is a compound of Formula I or a form thereof, wherein:

W is N or CH;

A is absent or alkyl;

Y is a ring selected from cycloalkyl, bicycloalkyl, aryl, alkylaryl, cycloalkylaryl, arylcycloalkyl, or heteroaryl provided that Y is not thiazole;

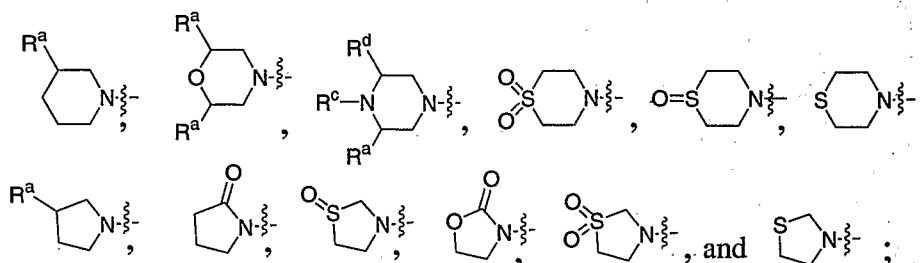
R^{101} is hydrogen, hydroxyl, methyl, halogen, $-\text{CF}_3$, or methoxy;

R^{200} is halogen, alkoxy optionally substituted with $-\text{CH}(\text{OH})-\text{CH}_2-\text{NR}^{203}\text{R}^{204}$, alkyl optionally substituted with R^{201} , heterocyclyl optionally substituted with one alkyl and optionally substituted with one R^{202} , dialkylamino, $-\text{C}(\text{O})(\text{CH}_2)_n\text{NR}^{203}\text{R}^{204}$, heteroaryl, or $-\text{R}^{300}-\text{R}^{400}$; wherein n is 0, 1, 2, 3, or 4;

R^{201} is hydroxyl, methyl, halogen, $-\text{CF}_3$, dialkylamino or methoxy;

R^{202} is alkyl, $-C(O)-CH_3$, $-CH_2-C(O)-CH_3$, $-C(O)(CH_2)_nNR^{203}R^{204}$, or $-CON-alkyl-NR^{203}R^{204}$; wherein n is 0, 1, 2, 3, or 4;

R^{203} and R^{204} are independently hydrogen, alkyl, or R^{203} and R^{204} may be taken together to form a ring selected from the following:



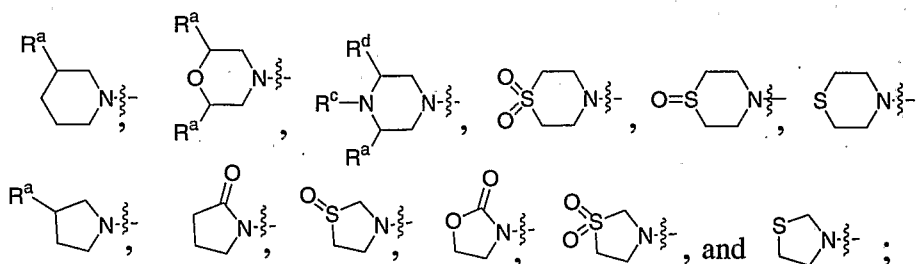
wherein R^a , R^c and R^d are independently hydrogen or alkyl;

R^{300} is alkyl;

R^{400} is $-NR^{403}R^{404}$, $-SO_2NR^{405}R^{406}$, oxazolidinonyl wherein said oxazolidinonyl is optionally substituted with one or two R^{401} , piperazinyl wherein said piperazinyl is optionally substituted with R^{202} or pyrrolidinonyl wherein said pyrrolidinonyl is optionally substituted with one or two R^{401} ;

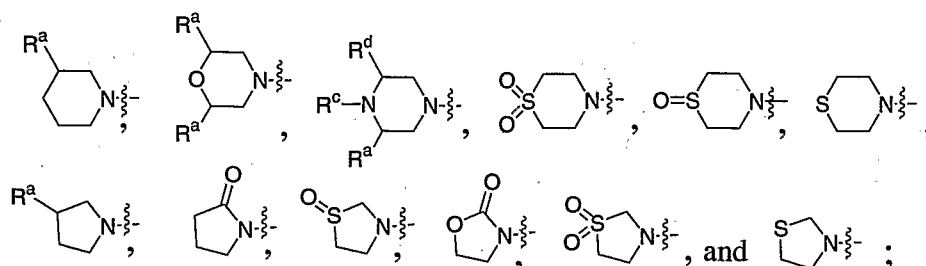
wherein R^{401} is methyl, $-C(O)-CH_3$, or $-CH_2-C(O)-CH_3$;

wherein R^{403} and R^{404} are independently hydrogen, alkyl, or R^{403} and R^{404} may be taken together to form a ring selected from the following:



wherein R^a , R^c and R^d are independently hydrogen or alkyl;

R^{405} and R^{406} are independently hydrogen, alkyl, or R^{405} and R^{406} may be taken together to form a ring selected from the following:



wherein R^a , R^c and R^d are independently hydrogen or alkyl; and

Z is CO_2H , CO_2alkyl , or CONR^1R^2 ; wherein R^1 is hydrogen or alkyl; and R^2 is hydrogen, alkyl, cycloalkyl, or alkoxy.

Examples of the present invention include those compounds of Formula I or a form thereof wherein one or more of the following limitations are present:

W is N or CH;

A is absent;

Y is a ring selected from cycloalkyl, bicycloalkyl, phenyl, alkylaryl, cycloalkylaryl, arylcycloalkyl, or heteroaryl provided that Y is not thiazole;

R^{101} is hydrogen, hydroxyl, methyl, halogen, $-\text{CF}_3$, or methoxy;

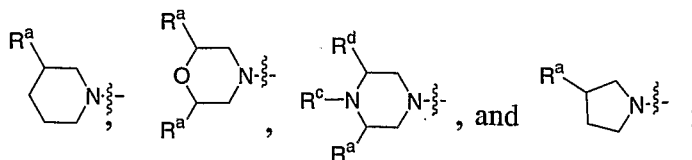
R^{200} is halogen, $\text{C}_{(1-4)}$ alkoxy optionally substituted with $-\text{CH}(\text{OH})-\text{CH}_2-\text{NR}^{203}\text{R}^{204}$,

$\text{C}_{(1-4)}$ alkyl optionally substituted with R^{201} , heterocyclyl optionally substituted with one $\text{C}_{(1-4)}$ alkyl and optionally substituted with one R^{202} , dialkylamino, $-\text{C}(\text{O})(\text{CH}_2)_n\text{NR}^{203}\text{R}^{204}$, heteroaryl, or $-\text{R}^{300}-\text{R}^{400}$; wherein n is 0, 1, 2, 3, or 4;

R^{201} is hydroxyl, methyl, halogen, $-\text{CF}_3$, dialkylamino or methoxy;

R^{202} is alkyl, $-\text{C}(\text{O})-\text{CH}_3$, $-\text{CH}_2-\text{C}(\text{O})-\text{CH}_3$, $-\text{C}(\text{O})(\text{CH}_2)_n\text{NR}^{203}\text{R}^{204}$, $-\text{C}(\text{O})\text{N}(\text{CH}_2)_n\text{NR}^{203}\text{R}^{204}$; wherein n is 0, 1, 2, 3, or 4;

R^{203} and R^{204} are independently hydrogen, $\text{C}_{(1-4)}$ alkyl, or R^{203} and R^{204} may be taken together to form a ring selected from the following:



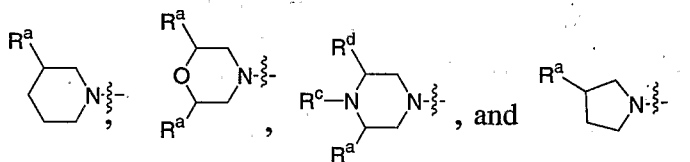
wherein R^a , R^c and R^d are independently hydrogen or alkyl;

R^{300} is $C_{(1-4)}$ alkyl; and

R^{400} is $-NR^{403}R^{404}$, $-SO_2NR^{405}R^{406}$, oxazolidinonyl wherein said oxazolidinonyl is optionally substituted with one or two R^{401} , piperazinyl wherein said piperazinyl is optionally substituted with R^{202} or pyrrolidinonyl wherein said pyrrolidinonyl is optionally substituted with one or two R^{401} ;

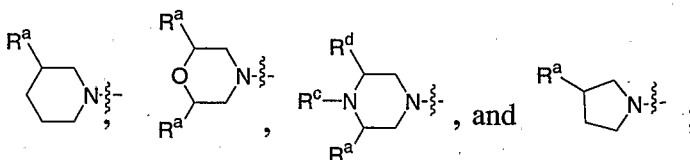
wherein R^{401} is methyl, $-C(O)-CH_3$, or $-CH_2-C(O)-CH_3$;

wherein R^{403} and R^{404} are independently hydrogen, $C_{(1-4)}$ alkyl, or R^{403} and R^{404} may be taken together to form a ring selected from the following:



wherein R^a , R^c and R^d are independently hydrogen or alkyl;

R^{405} and R^{406} are independently hydrogen, $C_{(1-4)}$ alkyl, or R^{405} and R^{406} may be taken together to form a ring selected from the following:



wherein R^a , R^c and R^d are independently hydrogen or alkyl; and

Z is CO_2 alkyl, or $CONR^1R^2$; wherein R^1 is hydrogen or $C_{(1-4)}$ alkyl; and R^2 is hydrogen, $C_{(1-4)}$ alkyl, cycloalkyl, or $C_{(1-4)}$ alkoxy.

In another embodiment of the invention one or more of the following limitations are present:

W is N;

A is absent;

Y is a ring selected from cycloalkyl or arylcycloalkyl;

R^{101} is hydrogen;

R^{200} is $-R^{300}-R^{400}$; and

Z is CO_2 alkyl, or $CONR^1R^2$; wherein R^1 and R^2 are independently hydrogen, or $C_{(1-4)}$ alkyl.

Examples of the present invention include those compounds of Formula I or a form thereof wherein one or more of the following limitations are present:

W is N;

A is absent;

Y is a ring selected from cycloalkyl or arylcycloalkyl;

R^{101} is hydroxyl, methyl, halogen, $-CF_3$, or methoxy;

R^{200} is piperazine optionally substituted with one or two methyl substituents, piperidine optionally substituted with one or two methyl substituents, morpholine or $-R^{300}-R^{400}$ wherein R^{300} is methyl or ethyl and R^{400} is piperazine optionally substituted with one or two methyl substituents; and

Z is CO_2 alkyl, or $CONR^1R^2$; wherein R^1 is hydrogen or $C_{(1-4)}$ alkyl; and R^2 is hydrogen, $C_{(1-4)}$ alkyl, or cycloalkyl.

Examples of the present invention include those compounds of Formula I or a form thereof wherein one or more of the following limitations are present:

W is N;

A is absent;

Y is a ring selected from cyclohexyl, cyclopentyl, bicyclo[2.2.1]heptyl, indanyl, phenyl or 1,2,3,4-tetrahydronaphthalenyl;

R^{101} is hydrogen, hydroxyl, methyl, halogen, $-CF_3$, or methoxy;

R^{200} is heterocyclyl (preferably tetrahydrofuranyl, pyrrolidinyl, piperidinyl, 4-methyl piperazin-1-yl, piperazinyl, morpholinyl, or thiomorpholino), dialkylamino, $-R^{300}-R^{400}$, or $C_{(1-4)}$ alkyl wherein said $C_{(1-4)}$ alkyl is optionally substituted with one or both substituents selected from hydroxyl and dialkylamino;

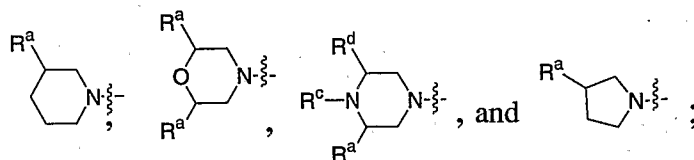
R^{300} is $C_{(1-4)}$ alkyl;

R^{400} is $-NR^{403}R^{404}$, $-SO_2NR^{405}R^{406}$, oxazolidinonyl wherein said oxazolidinonyl is optionally substituted with one or two R^{401} , piperazinyl wherein said piperazinyl is

optionally substituted with R^{202} or pyrrolidinonyl wherein said pyrrolidinonyl is optionally substituted with one or two R^{401} ;

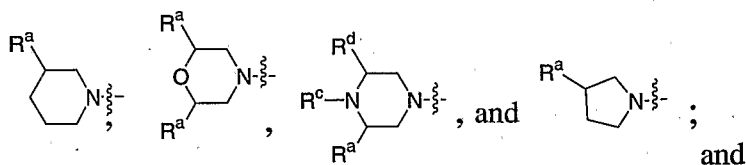
wherein R^{401} is methyl, $-C(O)-CH_3$, or $-CH_2-C(O)-CH_3$;

wherein R^{403} and R^{404} are independently hydrogen, $C_{(1-4)}$ alkyl, or R^{403} and R^{404} may be taken together to form a ring selected from the following:



wherein R^a , R^c and R^d are independently hydrogen or alkyl;

R^{405} and R^{406} are independently hydrogen, $C_{(1-4)}$ alkyl, or R^{405} and R^{406} may be taken together to form a ring selected from the following:



wherein R^a , R^c and R^d are independently hydrogen or alkyl;

Z is CO_2 alkyl, or $CONR^1R^2$; wherein R^1 is hydrogen or $C_{(1-4)}$ alkyl; and R^2 is hydrogen, $C_{(1-4)}$ alkyl, cycloalkyl, or $C_{(1-4)}$ alkoxy.

Examples of the present invention include those compounds of Formula I or a form thereof wherein one or more of the following limitations are present:

W is N or CH;

A is absent or alkyl;

Y is a ring selected from indan-5-yl, phenyl, cyclohexyl, cyclopentyl, bicyclo[2.2.1]heptyl or adamantan-2-yl;

R^{101} is hydrogen or hydroxyl;

R^{200} is fluorine, alkoxy substituted with $-CH(OH)-CH_2-N(CH_3)_2$, alkyl optionally substituted with R^{201} , morpholinyl, piperazinyl optionally substituted with R^{202} , 3,5-dimethyl piperazinyl, piperidinyl, piperidinyl substituted with

-C(O)-alkyl-N(CH₃)₂, -C(O)-alkyl-piperazinyl (optionally substituted on piperazinyl with alkyl), dimethylamino, -C(O)N(CH₃)₂, heteroaryl, or -R³⁰⁰-R⁴⁰⁰;

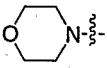
R²⁰¹ is hydroxyl or dimethylamino;

R²⁰² is -CH₃;

R³⁰⁰ is alkyl; and

R⁴⁰⁰ is -N(CH₃)₂, morpholinyl, -SO₂NR⁴⁰⁵R⁴⁰⁶, piperazinyl optionally substituted with R²⁰² or oxazolidinonyl;

R⁴⁰⁵ and R⁴⁰⁶ are independently hydrogen, alkyl, or R⁴⁰⁵ and R⁴⁰⁶ may be taken together to

form the following ring: ; and

Z is CO₂alkyl, or CONR¹R²; wherein R¹ is hydrogen or alkyl; and R² is hydrogen, alkyl, cycloalkyl, or alkoxy.

An example of the present invention includes compounds of Formula I or a form thereof wherein:

W is N or CH;

A is absent;

Y is a ring selected from cycloalkyl, bicycloalkyl, phenyl, alkylaryl, cycloalkylaryl, arylcycloalkyl, or heteroaryl provided that Y is not thiazole;

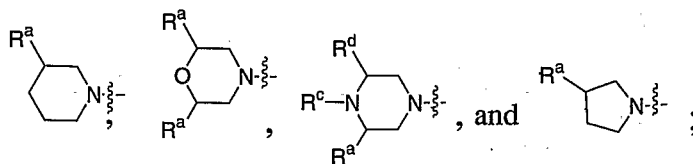
R¹⁰¹ is hydrogen, hydroxyl, methyl, halogen, -CF₃, or methoxy;

R²⁰⁰ is halogen, C₍₁₋₄₎alkoxy optionally substituted with -CH(OH)-CH₂-NR²⁰³R²⁰⁴, C₍₁₋₄₎alkyl optionally substituted with R²⁰¹, heterocyclyl optionally substituted with one C₍₁₋₄₎alkyl and optionally substituted with one R²⁰², dialkylamino, -C(O)(CH₂)_nNR²⁰³R²⁰⁴, heteroaryl, or -R³⁰⁰-R⁴⁰⁰; wherein n is 0, 1, 2, 3, or 4;

R²⁰¹ is hydroxyl, methyl, halogen, -CF₃, dialkylamino or methoxy;

R²⁰² is alkyl, -C(O)-CH₃, -CH₂-C(O)-CH₃, -C(O)(CH₂)_nNR²⁰³R²⁰⁴, -C(O)N(CH₂)_nNR²⁰³R²⁰⁴; wherein n is 0, 1, 2, 3, or 4;

R²⁰³ and R²⁰⁴ are independently hydrogen, C₍₁₋₄₎alkyl, or R²⁰³ and R²⁰⁴ may be taken together to form a ring selected from the following:



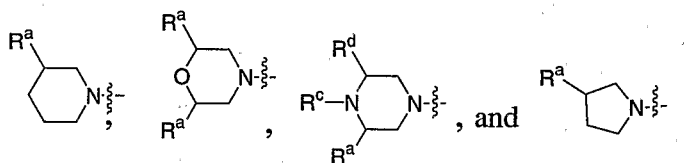
wherein R^a , R^c and R^d are independently hydrogen or alkyl;

R^{300} is $C_{(1-4)}$ alkyl; and

R^{400} is $-NR^{403}R^{404}$, $-SO_2NR^{405}R^{406}$, oxazolidinonyl wherein said oxazolidinonyl is optionally substituted with one or two R^{401} , piperazinyl wherein said piperazinyl is optionally substituted with R^{202} or pyrrolidinonyl wherein said pyrrolidinonyl is optionally substituted with one or two R^{401} ;

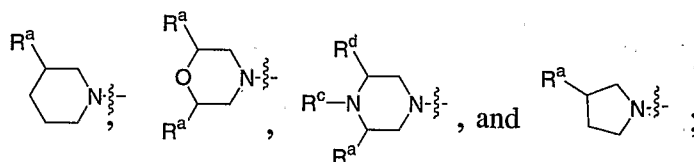
wherein R^{401} is methyl, $-C(O)-CH_3$, or $-CH_2-C(O)-CH_3$;

wherein R^{403} and R^{404} are independently hydrogen, $C_{(1-4)}$ alkyl, or R^{403} and R^{404} may be taken together to form a ring selected from the following:



wherein R^a , R^c and R^d are independently hydrogen or alkyl;

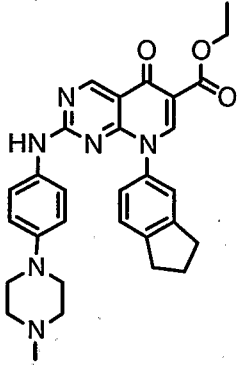
R^{405} and R^{406} are independently hydrogen, $C_{(1-4)}$ alkyl, or R^{405} and R^{406} may be taken together to form a ring selected from the following:



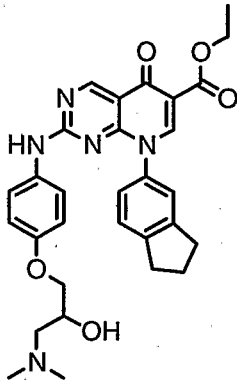
wherein R^a , R^c and R^d are independently hydrogen or alkyl; and

Z is CO_2H .

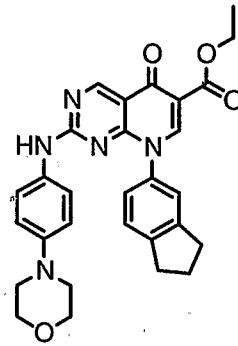
An example of the present invention is a compound of Formula I selected from the group consisting of:



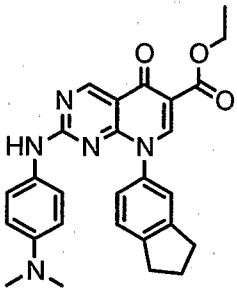
Cpd 1



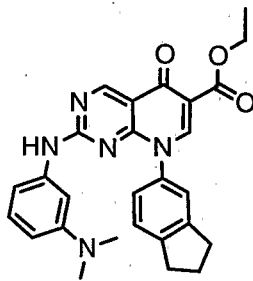
Cpd 2



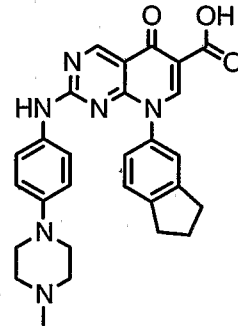
Cpd 3



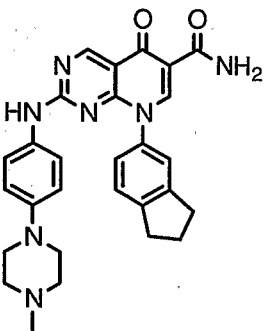
Cpd 4



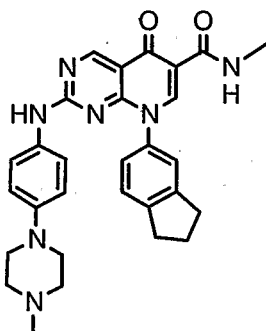
Cpd 5



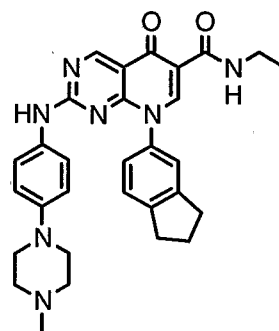
Cpd 6



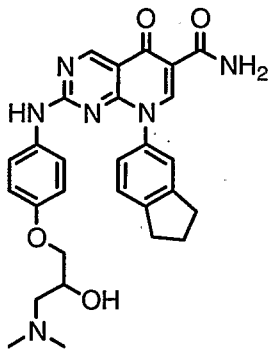
Cpd 7



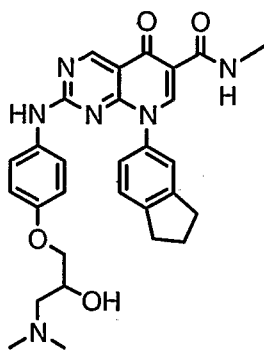
Cpd 8



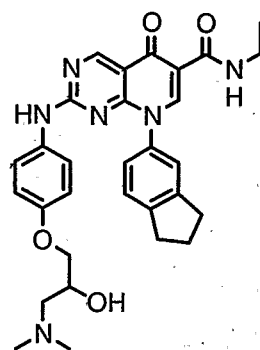
Cpd 9



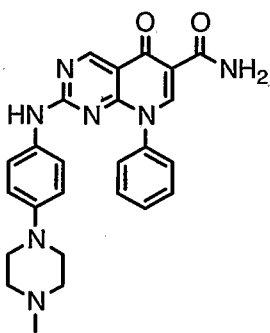
Cpd 10



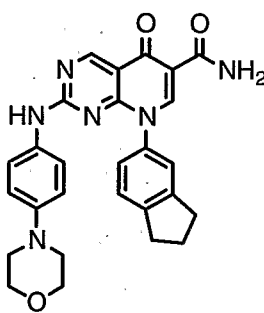
Cpd 11



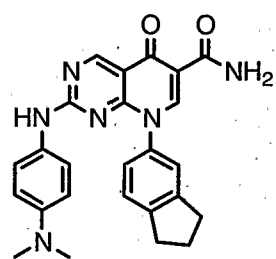
Cpd 12



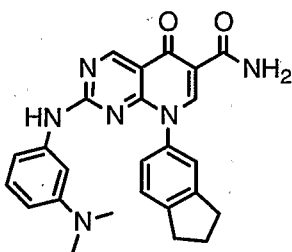
Cpd 13



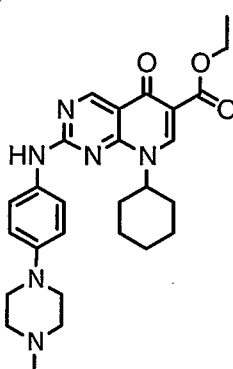
Cpd 14



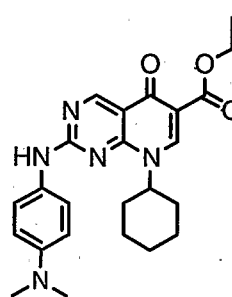
Cpd 15



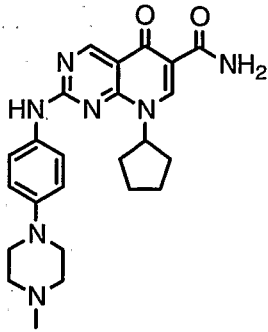
Cpd 16



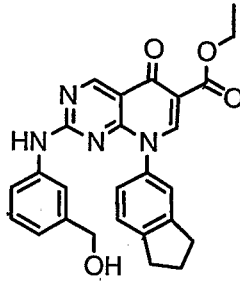
Cpd 17



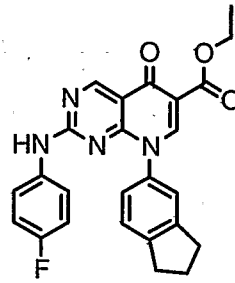
Cpd 18



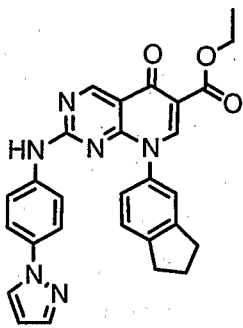
Cpd 19



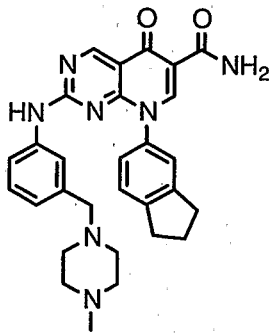
Cpd 20



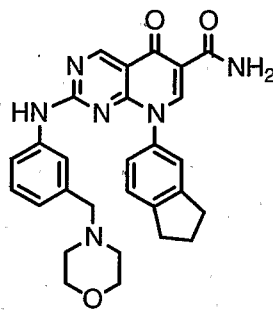
Cpd 21



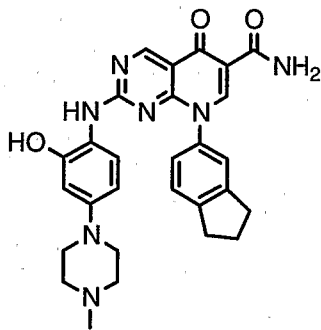
Cpd 22



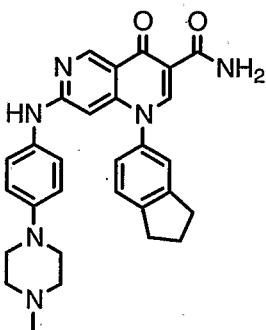
Cpd 23



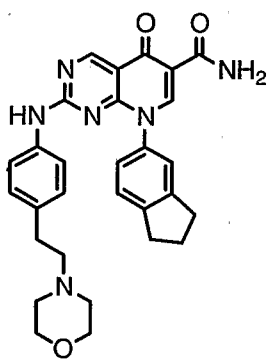
Cpd 24



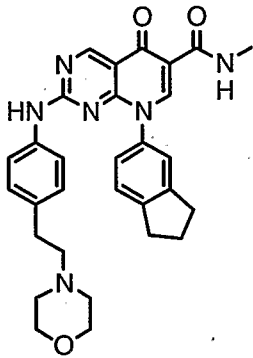
Cpd 25



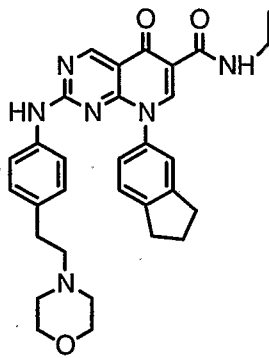
Cpd 26



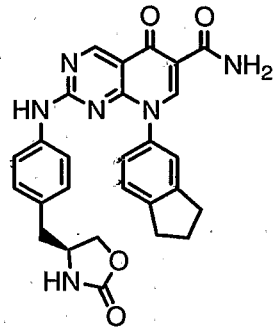
Cpd 27



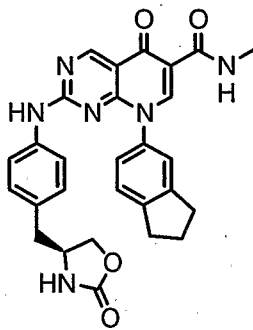
Cpd 28



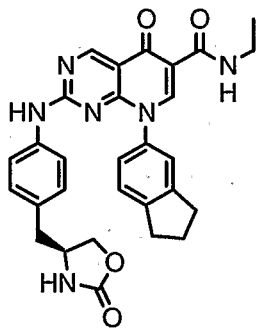
Cpd 29



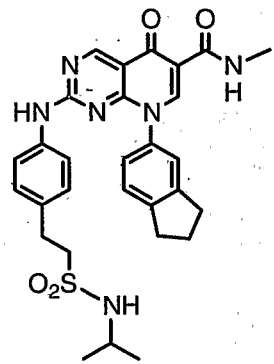
Cpd 30



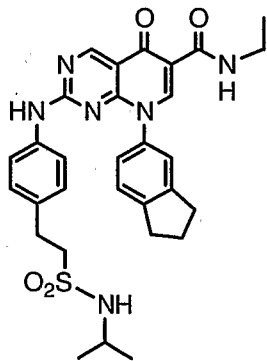
Cpd 31



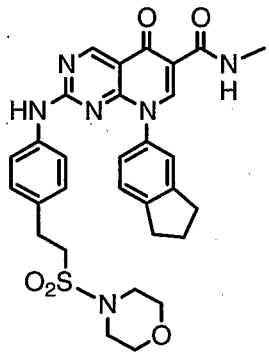
Cpd 32



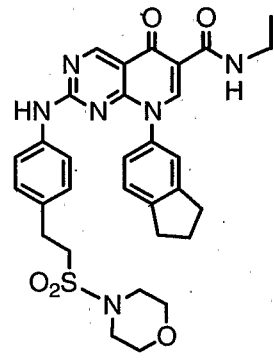
Cpd 33



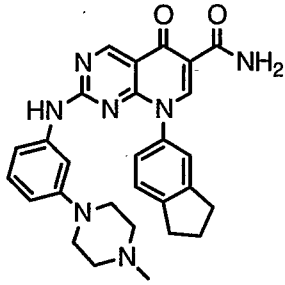
Cpd 34



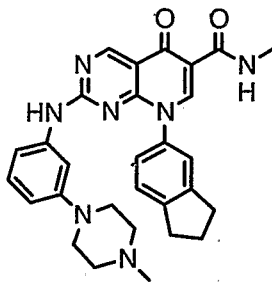
Cpd 35



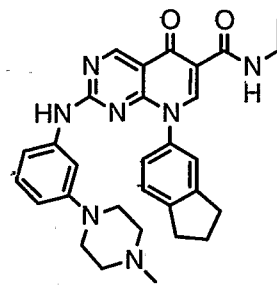
Cpd 36



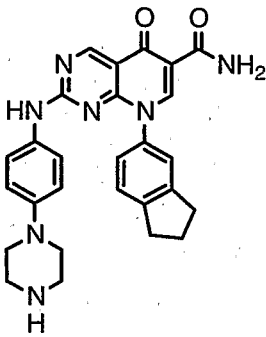
Cpd 37



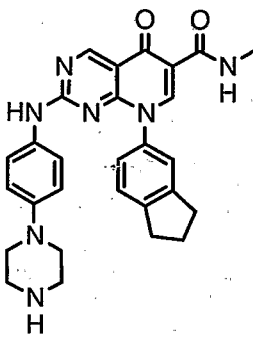
Cpd 38



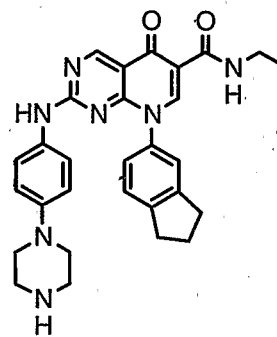
Cpd 39



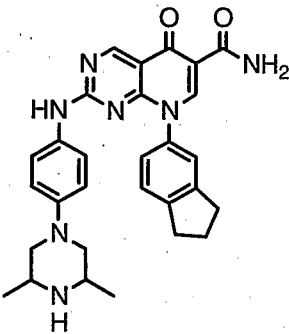
Cpd 40



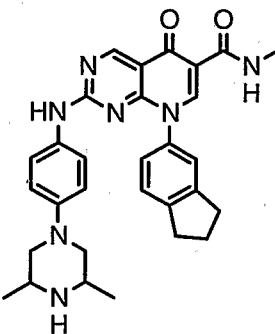
Cpd 41



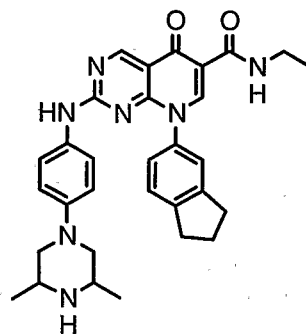
Cpd 42



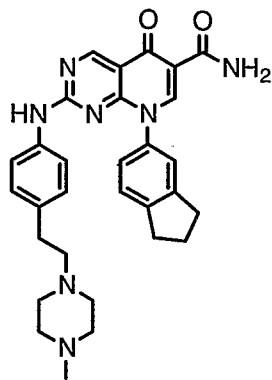
Cpd 43



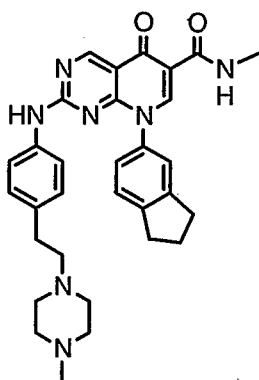
Cpd 44



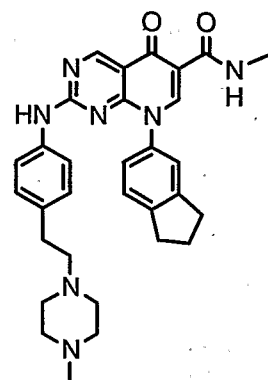
Cpd 45



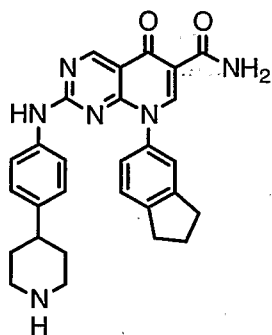
Cpd 46



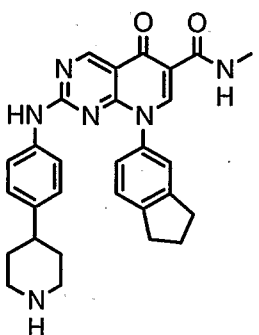
Cpd 47



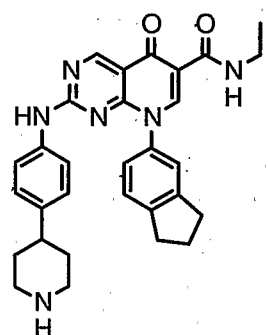
Cpd 48



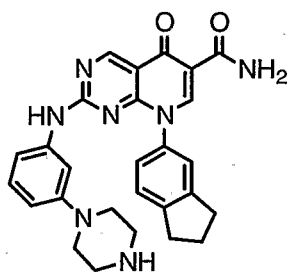
Cpd 49



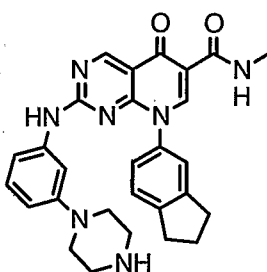
Cpd 50



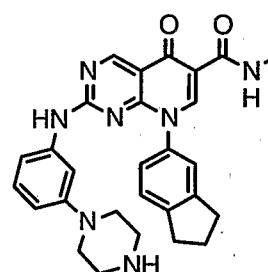
Cpd 51



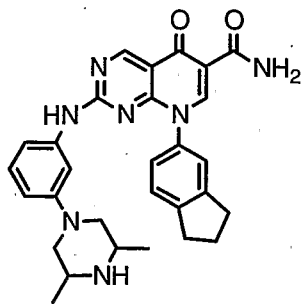
Cpd 52



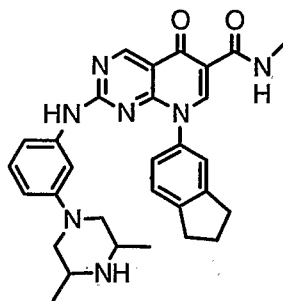
Cpd 534



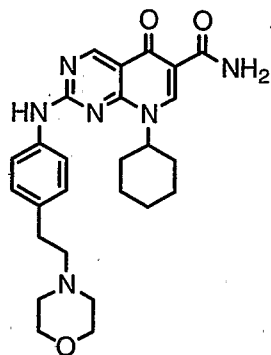
Cpd 54



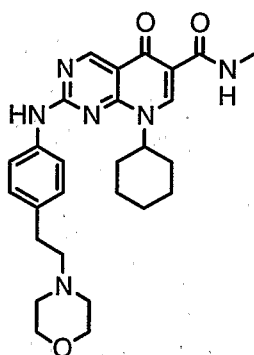
Cpd 55



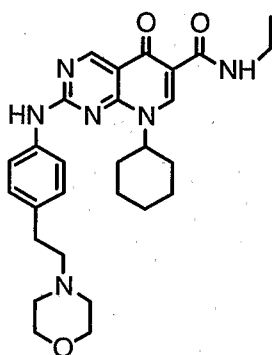
Cpd 56



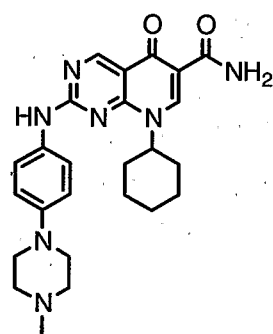
Cpd 57



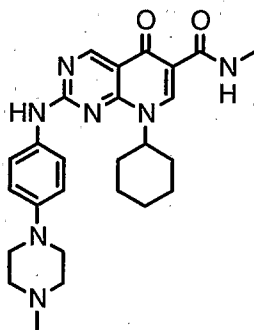
Cpd 58



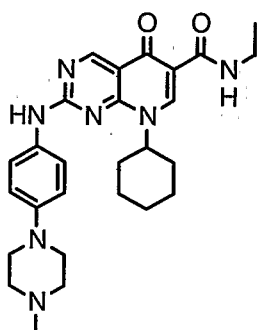
Cpd 59



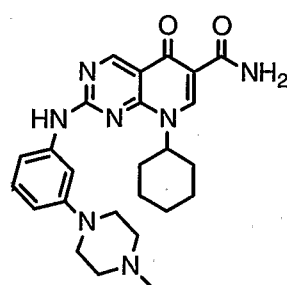
Cpd 60



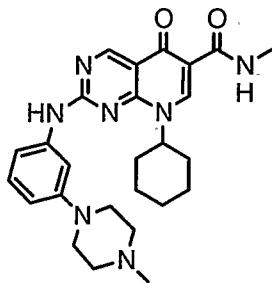
Cpd 61



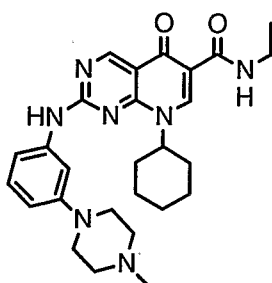
Cpd 62



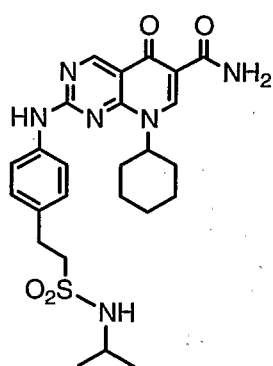
Cpd 63



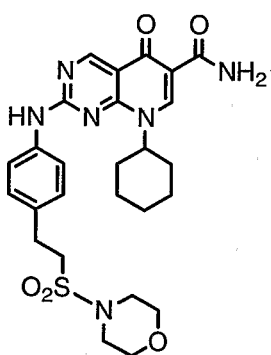
Cpd 64



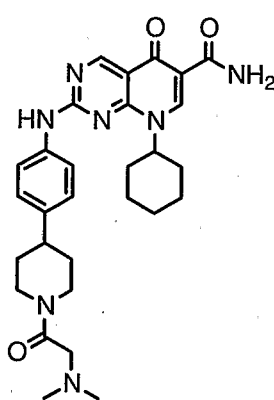
Cpd 65



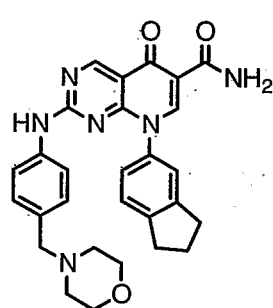
Cpd 66



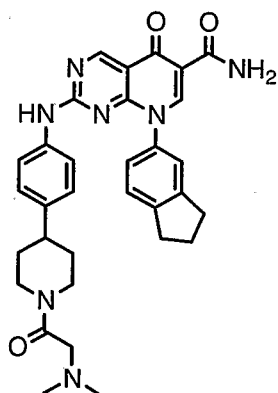
Cpd 67



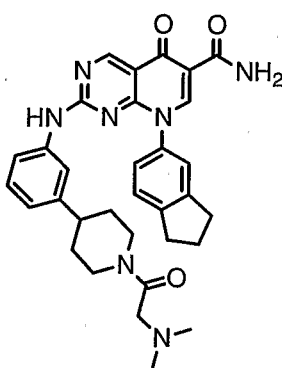
Cpd 68



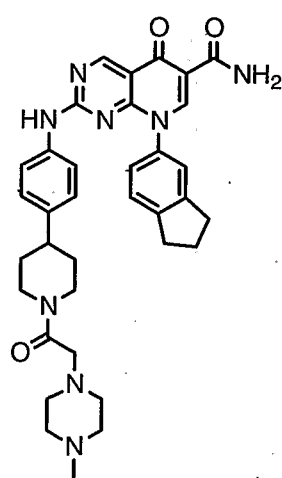
Cpd 69



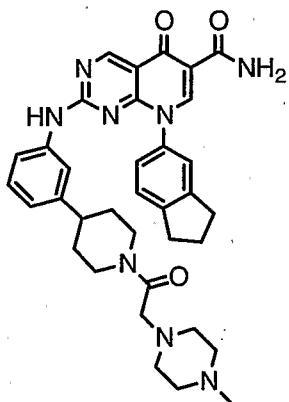
Cpd 70



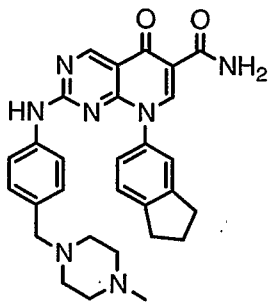
Cpd 71



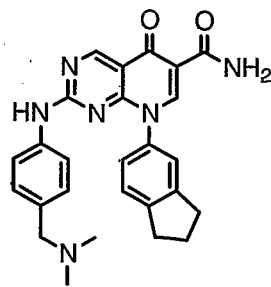
Cpd 72



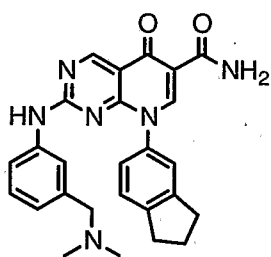
Cpd 73



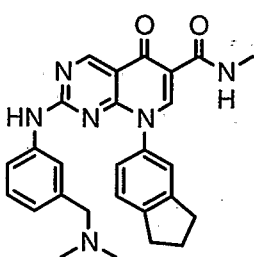
Cpd 74



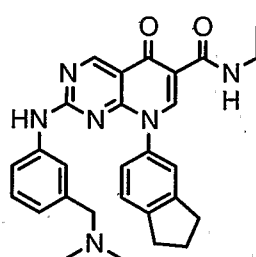
Cpd 75



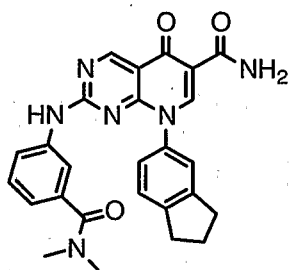
Cpd 76



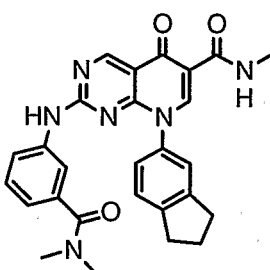
Cpd 77



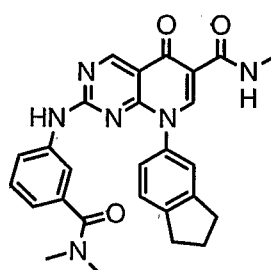
Cpd 78



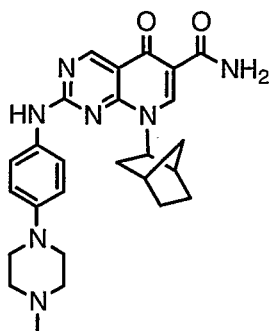
Cpd 79



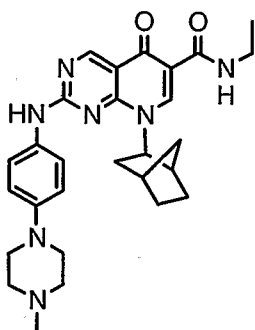
Cpd 80



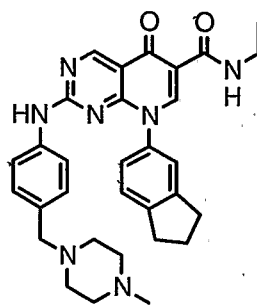
Cpd 81



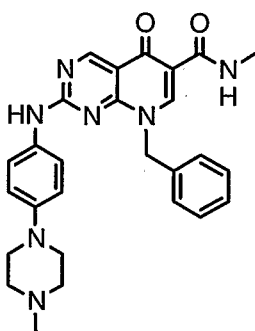
Cpd 82



Cpd 83



Cpd 84



Cpd 85

Examples of the present invention include those compounds of Formula I or a form thereof selected from, but not limited to, the following:

- 1 8-indan-5-yl-2-[4-(4-methyl-piperazin-1-yl)-phenylamino]-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid ethyl ester,
- 2 2-[4-(3-dimethylamino-2-hydroxy-propoxy)-phenylamino]-8-indan-5-yl-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid ethyl ester,
- 3 8-indan-5-yl-2-(4-morpholin-4-yl-phenylamino)-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid ethyl ester,
- 4 2-(4-dimethylamino-phenylamino)-8-indan-5-yl-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid ethyl ester,
- 5 2-(3-dimethylamino-phenylamino)-8-indan-5-yl-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid ethyl ester,
- 6 8-indan-5-yl-2-[4-(4-methyl-piperazin-1-yl)-phenylamino]-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid,
- 7 8-indan-5-yl-2-[4-(4-methyl-piperazin-1-yl)-phenylamino]-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid amide,
- 8 8-indan-5-yl-2-[4-(4-methyl-piperazin-1-yl)-phenylamino]-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid methylamide,

- 9 8-indan-5-yl-2-[4-(4-methyl-piperazin-1-yl)-phenylamino]-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid ethylamide,
- 10 2-[4-(3-dimethylamino-2-hydroxy-propoxy)-phenylamino]-8-indan-5-yl-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid amide,
- 11 2-[4-(3-dimethylamino-2-hydroxy-propoxy)-phenylamino]-8-indan-5-yl-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid methylamide
- 12 2-[4-(3-dimethylamino-2-hydroxy-propoxy)-phenylamino]-8-indan-5-yl-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid ethylamide,
- 13 2-[4-(4-Methyl-piperazin-1-yl)-phenylamino]-5-oxo-8-phenyl-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid amide,
- 14 8-indan-5-yl-2-(4-morpholin-4-yl-phenylamino)-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid amide,
- 15 2-(4-dimethylamino-phenylamino)-8-indan-5-yl-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid amide,
- 16 2-(3-dimethylamino-phenylamino)-8-indan-5-yl-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid amide,
- 17 8-cyclohexyl-2-[4-(4-methyl-piperazin-1-yl)-phenylamino]-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid ethyl ester,
- 18 8-cyclohexyl-2-(4-dimethylamino-phenylamino)-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid ethyl ester,
- 19 8-cyclopentyl-2-[4-(4-methyl-piperazin-1-yl)-phenylamino]-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid amide,
- 20 2-(3-hydroxymethyl-phenylamino)-8-indan-5-yl-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid amide,
- 21 2-(4-fluoro-phenylamino)-8-indan-5-yl-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid ethyl ester,
- 22 8-indan-5-yl-5-oxo-2-(4-pyrazol-1-yl-phenylamino)-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid amide,
- 23 8-indan-5-yl-2-[3-(4-methyl-piperazin-1-ylmethyl)-phenylamino]-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid amide,
- 24 8-indan-5-yl-2-(3-morpholin-4-ylmethyl-phenylamino)-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid amide,
- 25 2-[2-hydroxy-4-(4-methyl-piperazin-1-yl)-phenylamino]-8-indan-5-yl-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid amide,
- 26 1-indan-5-yl-7-[4-(4-methyl-piperazin-1-yl)-phenylamino]-4-oxo-1,4-dihydro-[1,6]naphthyridine-3-carboxylic acid amide,
- 27 8-Indan-5-yl-2-[4-(2-morpholin-4-yl-ethyl)-phenylamino]-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid amide,
- 28 8-Indan-5-yl-2-[4-(2-morpholin-4-yl-ethyl)-phenylamino]-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid methyl amide,

- 29 8-Indan-5-yl-2-[4-(2-morpholin-4-yl-ethyl)-phenylamino]-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid ethyl amide,
- 30 (4*S*)-8-Indan-5-yl-5-oxo-2-[4-(2-oxo-oxazolidin-4-ylmethyl)-phenylamino]-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid amide,
- 31 (4*S*)-8-Indan-5-yl-5-oxo-2-[4-(2-oxo-oxazolidin-4-ylmethyl)-phenylamino]-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid methyl amide,
- 32 (4*S*)-8-Indan-5-yl-5-oxo-2-[4-(2-oxo-oxazolidin-4-ylmethyl)-phenylamino]-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid ethyl amide,
- 33 8-Indan-5-yl-2-[4-(2-isopropylsulfamoyl-ethyl)-phenylamino]-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid methyl amide,
- 34 8-Indan-5-yl-2-[4-(2-isopropylsulfamoyl-ethyl)-phenylamino]-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid ethyl amide,
- 35 8-Indan-5-yl-2-[4-[2-(morpholine-4-sulfonyl)-ethyl]-phenylamino]-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid methyl amide,
- 36 8-Indan-5-yl-2-[4-[2-(morpholine-4-sulfonyl)-ethyl]-phenylamino]-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid ethyl amide,
- 37 8-Indan-5-yl-2-[3-(4-methyl-piperazin-1-yl)-phenylamino]-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid amide,
- 38 8-Indan-5-yl-2-[3-(4-methyl-piperazin-1-yl)-phenylamino]-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid methyl amide,
- 39 8-Indan-5-yl-2-[3-(4-methyl-piperazin-1-yl)-phenylamino]-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid ethyl amide,
- 40 8-Indan-5-yl-5-oxo-2-(4-piperazin-1-yl-phenylamino)-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid amide,
- 41 8-Indan-5-yl-5-oxo-2-(4-piperazin-1-yl-phenylamino)-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid methyl amide,
- 42 8-Indan-5-yl-5-oxo-2-(4-piperazin-1-yl-phenylamino)-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid ethyl amide,
- 43 2-[4-(3,5-Dimethyl-piperazin-1-yl)-phenylamino]-8-indan-5-yl-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid amide,
- 44 2-[4-(3,5-Dimethyl-piperazin-1-yl)-phenylamino]-8-indan-5-yl-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid methyl amide,
- 45 2-[4-(3,5-Dimethyl-piperazin-1-yl)-phenylamino]-8-indan-5-yl-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid ethyl amide,
- 46 8-Indan-5-yl-2-[4-[2-(4-methyl-piperazin-1-yl)-ethyl]-phenylamino]-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid amide,
- 47 8-Indan-5-yl-2-[4-[2-(4-methyl-piperazin-1-yl)-ethyl]-phenylamino]-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid methyl amide,
- 48 8-Indan-5-yl-2-[4-[2-(4-methyl-piperazin-1-yl)-ethyl]-phenylamino]-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid ethyl amide,

- 49 8-Indan-5-yl-5-oxo-2-(4-piperidin-4-yl-phenylamino)-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid amide,
- 50 8-Indan-5-yl-5-oxo-2-(4-piperidin-4-yl-phenylamino)-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid methyl amide,
- 51 8-Indan-5-yl-5-oxo-2-(4-piperidin-4-yl-phenylamino)-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid ethyl amide,
- 52 8-Indan-5-yl-5-oxo-2-(3-piperazin-1-yl-phenylamino)-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid amide,
- 53 8-Indan-5-yl-5-oxo-2-(3-piperazin-1-yl-phenylamino)-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid methyl amide,
- 54 8-Indan-5-yl-5-oxo-2-(3-piperazin-1-yl-phenylamino)-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid ethyl amide,
- 55 2-[3-(3,5-Dimethyl-piperazin-1-yl)-phenylamino]-8-indan-5-yl-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid amide,
- 56 2-[3-(3,5-Dimethyl-piperazin-1-yl)-phenylamino]-8-indan-5-yl-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid methyl amide,
- 57 8-Cyclohexyl-2-[4-(2-morpholin-4-yl-ethyl)-phenylamino]-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid amide,
- 58 8-Cyclohexyl-2-[4-(2-morpholin-4-yl-ethyl)-phenylamino]-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid methyl amide,
- 59 8-Cyclohexyl-2-[4-(2-morpholin-4-yl-ethyl)-phenylamino]-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid ethyl amide,
- 60 8-Cyclohexyl-2-[4-(4-methyl-piperazin-1-yl)-phenylamino]-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid amide,
- 61 8-Cyclohexyl-2-[4-(4-methyl-piperazin-1-yl)-phenylamino]-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid methyl amide,
- 62 8-Cyclohexyl-2-[4-(4-methyl-piperazin-1-yl)-phenylamino]-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid ethyl amide,
- 63 8-Cyclohexyl-2-[3-(4-methyl-piperazin-1-yl)-phenylamino]-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid amide,
- 64 8-Cyclohexyl-2-[3-(4-methyl-piperazin-1-yl)-phenylamino]-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid methyl amide,
- 65 8-Cyclohexyl-2-[3-(4-methyl-piperazin-1-yl)-phenylamino]-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid ethyl amide,
- 66 8-Cyclohexyl-2-[4-(2-isopropylsulfamoyl-ethyl)-phenylamino]-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid amide,
- 67 8-Cyclohexyl-2-[4-[2-(morpholine-4-sulfonyl)-ethyl]-phenylamino]-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid amide,
- 68 8-Cyclohexyl-2-[4-[1-(2-dimethylamino-acetyl)-piperidin-4-yl]-phenylamino]-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid amide,

- 69 8-Indan-5-yl-2-(4-morpholin-4-ylmethyl-phenylamino)-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid amide,
- 70 2-{4-[1-(2-Dimethylamino-acetyl)-piperidin-4-yl]-phenylamino}-8-indan-5-yl-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid amide,
- 71 2-{3-[1-(2-Dimethylamino-acetyl)-piperidin-4-yl]-phenylamino}-8-indan-5-yl-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid amide,
- 72 8-Indan-5-yl-2-(4-{1-[2-(4-methyl-piperazin-1-yl)-acetyl]-piperidin-4-yl}-phenylamino)-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid amide,
- 73 8-Indan-5-yl-2-(3-{1-[2-(4-methyl-piperazin-1-yl)-acetyl]-piperidin-4-yl}-phenylamino)-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid amide,
- 74 8-Indan-5-yl-2-[4-(4-methyl-piperazin-1-ylmethyl)-phenylamino]-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid amide,
- 75 2-(4-Dimethylaminomethyl-phenylamino)-8-indan-5-yl-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid amide,
- 76 2-(3-Dimethylaminomethyl-phenylamino)-8-indan-5-yl-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid amide,
- 77 2-(3-Dimethylaminomethyl-phenylamino)-8-indan-5-yl-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid methylamide,
- 78 2-(3-Dimethylaminomethyl-phenylamino)-8-indan-5-yl-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid ethylamide,
- 79 2-(3-Dimethylcarbamoyl-phenylamino)-8-indan-5-yl-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid amide,
- 80 2-(3-Dimethylcarbamoyl-phenylamino)-8-indan-5-yl-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid methylamide,
- 81 2-(3-Dimethylcarbamoyl-phenylamino)-8-indan-5-yl-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid ethylamide,
- 82 8-Bicyclo[2.2.1]hept-2-yl-2-[4-(4-methyl-piperazin-1-yl)-phenylamino]-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid amide,
- 83 8-Bicyclo[2.2.1]hept-2-yl-2-[4-(4-methyl-piperazin-1-yl)-phenylamino]-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid ethylamide,
- 84 8-Indan-5-yl-2-[4-(4-methyl-piperazin-1-ylmethyl)-phenylamino]-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid ethylamide, and
- 85 8-Benzyl-2-[4-(4-methyl-piperazin-1-yl)-phenylamino]-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid methylamide.

The most preferred compounds are those having a c-fms $IC_{50} < 25$ nm.

The invention also relates to methods of inhibiting protein tyrosine kinase activity in a mammal by administration of a therapeutically effective amount of at least one compound of Formula I. A preferred tyrosine kinase is c-fms.

The compounds of the present invention are further useful as markers for the c-fms receptor. Compounds of formula (I) when used as markers are for example radio-labeled by for example, substituting at least one hydrogen atom with a tritium atom. Other labeling techniques known in the arts can also be used.

An aspect of the use for a compound of Formula (I) includes use of an instant compound as a marker, wherein the compound is labeled with a ligand such as a radioligand (selected from deuterium, tritium and the like).

Compound Forms

The term "form" means, in reference to compounds of the present invention, such may exist as, without limitation, a salt, stereoisomer, tautomer, crystalline, polymorph, amorphous, solvate, hydrate, ester, prodrug or metabolite form. The present invention encompasses all such compound forms and mixtures thereof.

The term "isolated form" means, in reference to compounds of the present invention, such may exist in an essentially pure state such as, without limitation, an enantiomer, a racemic mixture, a geometric isomer (such as a *cis* or *trans* stereoisomer), a mixture of geometric isomers, and the like. The present invention encompasses all such compound forms and mixtures thereof.

Certain compounds of Formula (I) may exist in various stereoisomeric or tautomeric forms and mixtures thereof. The invention encompasses all such compounds, including active compounds in the form of essentially pure enantiomers, racemic mixtures and tautomers.

The compounds of the present invention may be present in the form of pharmaceutically acceptable salts. For use in medicines, the "pharmaceutically acceptable salts" of the compounds of this invention refer to non-toxic acidic/anionic or basic/cationic salt forms.

Suitable pharmaceutically acceptable salts of the compounds of this invention include acid addition salts which may, for example, be formed by mixing a solution of the compound according to the invention with a solution of a pharmaceutically acceptable acid such as hydrochloric acid, sulphuric acid, fumaric acid, maleic acid, succinic acid, acetic acid, benzoic acid, citric acid, tartaric acid, carbonic acid or phosphoric acid.

Furthermore when the compounds of the present invention carry an acidic moiety, suitable pharmaceutically acceptable salts thereof may include alkali metal salts, e.g. sodium or potassium salts; alkaline earth metal salts, e.g. calcium or magnesium salts; and salts formed with suitable organic ligands, e.g. quaternary ammonium salts. Thus, representative pharmaceutically acceptable salts include the following: acetate, benzenesulfonate, benzoate, bicarbonate, bisulfate, bitartrate, borate, bromide, calcium, camsylate (or camphosulphonate), carbonate, chloride, clavulanate, citrate, dihydrochloride, edetate, fumarate, gluconate, glutamate, hydrabamine, hydrobromine, hydrochloride, iodide, isothionate, lactate, malate, maleate, mandelate, mesylate, nitrate, oleate, pamoate, palmitate, phosphate/diphosphate, salicylate, stearate, sulfate, succinate, tartrate, tosylate.

The invention includes compounds of various isomers and mixtures thereof. The term "isomer" refers to compounds that have the same composition and molecular weight but differ in physical and/or chemical properties. Such substances have the same number and kind of atoms but differ in structure. The structural difference may be in constitution (geometric isomers) or in an ability to rotate the plane of polarized light (stereoisomers).

The term "optical isomer" means isomers of identical constitution that differ only in the spatial arrangement of their groups. Optical isomers rotate the plane of polarized light in different directions. The term "optical activity" means the degree to which an optical isomer rotates the plane of polarized light.

The term "racemate" or "racemic mixture" means an equimolar mixture of two enantiomeric species, wherein each of the isolated species rotates the plane of polarized light in the opposite direction such that the mixture is devoid of optical activity.

The term "enantiomer" means an isomer having a nonsuperimposable mirror image. The term "diastereomer" means stereoisomers that are not enantiomers.

The term "chiral" means a molecule which, in a given configuration, cannot be superimposed on its mirror image. This is in contrast to achiral molecules which can be superimposed on their mirror images.

The invention is considered to include the tautomeric forms of all compounds of Formula I. In addition, for chiral embodiments of the invention, the invention is considered to include pure enantiomers, racemic mixtures, as well as mixtures of enantiomers having 0.001% to 99.99% enantiomeric excess. In addition, some of the compounds represented by Formula I may be prodrugs, *i.e.*, derivatives of a drug that possess superior delivery capabilities and therapeutic value as compared to the active drug. Prodrugs are transformed into active drugs by *in vivo* enzymatic or chemical processes.

The two distinct mirror image versions of the chiral molecule are also known as levo (left-handed), abbreviated L, or dextro (right handed), abbreviated D, depending on which way they rotate polarized light. The symbols "R" and "S" represent the configuration of groups around a stereogenic carbon atom(s).

An example of an enantiomerically enriched form isolated from a racemic mixture includes a dextrorotatory enantiomer, wherein the mixture is substantially free of the levorotatory isomer. In this context, substantially free means the levorotatory isomer may, in a range, comprise less than 25% of the mixture, less than 10 %, less than 5 %, less than 2 % or less than 1 % of the mixture according to the formula:

$$\% \text{levorotatory} = \frac{(\text{mass levorotatory})}{(\text{mass dextrorotatory}) + (\text{mass levorotatory})} \times 100$$

Similarly, an example of an enantiomerically enriched form isolated from a racemic mixture includes a levorotatory enantiomer, wherein the mixture is substantially free of the dextrorotatory isomer. In this context, substantially free means the dextrorotatory isomer may, in a range, comprise less than 25% of the mixture, less than 10 %, less than 5 %, less than 2 % or less than 1 % of the mixture according to the formula:

$$\% \text{dextrorotatory} = \frac{(\text{mass dextrorotatory})}{(\text{mass dextrorotatory}) + (\text{mass levorotatory})} \times 100$$

“Geometric isomer” means isomers that differ in the orientation of substituent atoms in relationship to a carbon-carbon double bond, to a cycloalkyl ring, or to a bridged bicyclic system. Substituent atoms (other than hydrogen) on each side of a carbon-carbon double bond may be in an E or Z configuration. In the “E” configuration, the substituents are on opposite sides in relationship to the carbon-carbon double bond. In the “Z” configuration, the substituents are oriented on the same side in relationship to the carbon-carbon double bond.

Substituent atoms (other than hydrogen) attached to a ring system may be in a cis or trans configuration. In the “cis” configuration, the substituents are on the same side in relationship to the plane of the ring; in the “trans” configuration, the substituents are on opposite sides in relationship to the plane of the ring. Compounds having a mixture of “cis” and “trans” species are designated “cis/trans”.

The isomeric descriptors (“R,” “S,” “E,” and “Z”) indicate atom configurations relative to a core molecule and are intended to be used as defined in the literature.

Furthermore, compounds of the present invention may have at least one crystalline, polymorph or amorphous form. The plurality of such forms are included in the scope of the invention. In addition, some of the compounds may form solvates with water (i.e., hydrates) or common organic solvents (e.g., organic esters such as ethanolate and the like). The plurality of such solvates are also intended to be encompassed within the scope of this invention.

Chemical Nomenclature and Definitions

Bond lines drawn into a ring system from a substituent variable indicate that the substituent may be attached to any of the substitutable ring atoms.

As used herein, the following terms are intended to have the following meanings (additional definitions are provided where needed throughout the Specification). The definitions herein may specify that a chemical term has an indicated formula. The particular formula provided is not intended to limit the scope of the invention, but is provided as an illustration of the term. The scope of the *per se* definition of the term is intended to include the plurality of variations expected to be included by one of ordinary skill in the art.

Definitions

The term "alkyl" refers to both linear and branched chain radicals of up to 8 carbon atoms, unless otherwise indicated, and includes, but is not limited to, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, isopentyl, hexyl, and isoheptyl. The term " $C_{(x-y)}$ alkyl" refers to an alkyl chain of length not less than x carbons and not more than y carbons. For example, the term $C_{(1-4)}$ alkyl refers to both linear and branched chain radicals of up to 4 carbon atoms. Alkyl radicals or linking groups may be attached to a core molecule via a terminal carbon atom or *via* a carbon atom within the chain. Similarly, substituent variables may be attached to an alkyl linking group when allowed by available valences.

The term "amino" means an amine group of the formula: $-NH_2$.

The term "alkylamino or dialkylamino" refers to an amino with one or two alkyl substituents, respectively, wherein the amino group is the point of attachment to the rest of the molecule.

The term "aryl" refers to monocyclic or bicyclic aromatic ring systems containing from 6 to 12 carbons in the ring. Alkyl substituents may optionally be present on the ring. Examples include benzene, biphenyl, naphthalene (also referred to as naphthalenyl), azulenyl, anthracenyl and the like. Aryl radicals may be attached to a core molecule and further substituted on any atom when allowed by available valences.

The term "aromatic" refers to a cycloalkylic hydrocarbon ring system having an unsaturated, conjugated π electron system.

The term "aralkyl" refers to a C_{1-6} alkyl group containing an aryl substituent, in which the point of attachment is the alkyl group. Examples include benzyl, phenylethyl or 2-naphthylmethyl. It is possible that both the alkyl and aryl portion may be substituted, and in that case, it is intended that the alkyl group is closer to the core ring structure.

The term "alkylaryl" refers to a C_{1-6} alkyl group containing an aryl substituent, in which the point of attachment is the aryl group. It is possible that both the alkyl and aryl portion may be substituted, and in that case, it is intended that the aryl group is closer to the core ring structure.

The term "alkoxy" refers to a saturated branched or straight chain monovalent hydrocarbon alcohol radical derived by the removal of the hydrogen atom from the hydroxide oxygen substituent on a parent alkane, as in the formula: $-O-C_{1-8}$ alkyl. Examples include methoxy, ethoxy, propoxy, isopropoxy and butoxy. The term " $C_{(x-y)}$ alkoxy" refers to an alkoxy chain of length not less than x carbons and not more than y carbons. For example, the term $C_{(1-4)}$ alkoxy refers to both linear and branched alkoxy chain radicals of up to 4 carbon atoms. An alkoxy radical may be attached to a core molecule and further substituted when allowed by available valences.

The term "arylcycloalkyl" refers to a C_{8-10} fused bicyclic ring system comprising an aryl group and a cycloalkyl group in which the point of attachment is the aryl group, as in a benzofused C_{3-14} cycloalkyl ring system defined below. Examples include, but are not limited to 1*H*-indenyl, indanyl, and 1,2,3,4-tetrahydronaphthalenyl and the like.

The term "cycloalkyl" refers to a saturated or partially unsaturated ring composed of from 3 to 14 carbon atoms. Up to four alkyl substituents may optionally be present on the ring. The term also includes a C_{3-8} cycloalkyl, C_{3-10} cycloalkyl, C_{5-6} cycloalkyl, C_{5-8} cycloalkyl, C_{5-12} cycloalkyl, C_{8-10} cycloalkyl, C_{9-13} cycloalkyl, C_{3-14} cycloalkyl or benzofused C_{3-14} cycloalkyl ring system. Examples include 1,1-dimethyl cyclobutyl, 1,2,3-trimethylcyclopentyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cyclohexyl, cyclohexenyl, cycloheptyl, cyclooctyl, 1*H*-indenyl, indanyl, 9*H*-fluorenyl, 1,2,3,4-tetrahydro-naphthalenyl, acenaphthenyl, bicyclo[2.2.1]heptenyl and the like. C_{3-14} cycloalkyl radicals may be attached to a core molecule and further substituted on any atom when allowed by available valences.

The term "cycloalkylaryl" refers to a C_{8-10} fused bicyclic ring system comprising an aryl group and a cycloalkyl group in which the point of attachment is the cycloalkyl group, as in a benzofused C_{3-14} cycloalkyl ring system defined above, such as 1*H*-indenyl, indanyl, 1,2,3,4-tetrahydro-naphthalenyl and the like.

The term "bicycloalkyl" refers to a saturated or partially unsaturated fused ring pair composed of from 8 to 10 carbon atoms. Up to four alkyl substituents may optionally be present on the ring. Examples include adamantyl, bicyclo[2.2.1]heptenyl, decahydronaphthalenyl and 1,2,3,4 tetrahydropentalenyl and the like.

The term "hetero" used as a prefix for a ring system refers to the replacement of at least one ring carbon atom with one or more heteroatoms independently selected from N, S, or O. Examples include rings wherein 1, 2, 3 or 4 ring members are a nitrogen atom; or, 0, 1, 2 or 3 ring members are nitrogen atoms and 1 member is an oxygen or sulfur atom. When allowed by available valences, up to two adjacent ring members may be heteroatoms; wherein one heteroatom is nitrogen and the other is one heteroatom selected from N, S or O.

The term "heterocyclyl" refers to a nonaromatic (*i.e.* saturated or partially unsaturated) ring composed of from 3 to 7 carbon atoms and at least one heteroatom selected from N, O or S. Alkyl substituents and/or carbonyl substituents may optionally be present on the ring. Examples include tetrahydrofuranyl, dihydropyranyl, piperidinyl, 2,5-dimethylpiperidinyl, morpholinyl, piperazinyl, thiomorpholinyl, 2H-pyrrole, pyrrolidinyl, pyrrolinyl, pyrazolidinyl, pyrazolinyl, oxazolidinyl, imidazolidinyl, imidazoliny (also referred to as 4,5-dihydro-1H-imidazolyl), 1,3-dioxolanyl, tetrazolinyl, tetrazolidinyl, 1,4-dioxanyl, 1,4-dithianyl, azetidiny, azepanyl, hexahydro-1,4-diazepinyl, hexahydro-1,4-oxazepanyl, tetrahydro-thienyl, tetrahydro-pyranyl, tetrahydro-pyridazinyl, 1,3-benzodioxolyl (also referred to as benzo[1,3]dioxolyl), 2,3-dihydro-1,4-benzodioxinyl (also referred to as 2,3-dihydro-benzo[1,4]dioxinyl) and the like. Heterocyclyl radicals may be attached to a core molecule and further substituted on any atom when allowed by available valences.

The term "heteroaryl" refers to 5- to 7-membered mono- or 8- to 10-membered bicyclic aromatic ring systems, any ring of which may consist of from one to four heteroatoms selected from N, O, S, S(O) or SO₂ where the nitrogen and sulfur atoms can exist in any allowed oxidation state. Examples include benzoimidazolyl, benzothiazolyl, benzothieryl, benzoxazolyl, furanyl, imidazolyl, isothiazolyl, isoxazolyl, oxazolyl, pyrazinyl, pyrazolyl, pyridinyl, pyrimidinyl, pyrrolyl, quinolinyl, thiazolyl, thienyl, oxadiazolyl, triazolyl, thiadiazolyl, pyridazinyl, indoliziny, indolyl, azaindolyl, isoindolyl, benzofuranyl, indazolyl, azaindazolyl, benzoisoxazolyl, benzothiadiazolyl, benzotriazolyl, purinyl, 4H-quinoliziny, quinolinyl, isoquinolinyl, cinnolinyl, phthalziny, quinazoliny, quinoxaliny, 1,8-naphthyridiny, pteridinyl and the like. Heteroaryl radicals may be

attached to a core molecule and further substituted on any atom when allowed by available valences..

The term "heteroatom" refers to a nitrogen atom, an oxygen atom or a sulfur atom wherein the nitrogen and sulfur atoms can exist in any allowed oxidation states.

The term "sulfonyl" refers to the group $-S(O)_2R_z$, where R_z is hydrogen, alkyl, cycloalkyl, haloalkyl, aryl, aralkyl, heteroaryl and heterocyclyl.

The term "halogen" or "halo" means the group fluoro, chloro, bromo or iodo.

The term "substituted," refers to a core molecule on which one or more hydrogen atoms have been replaced with one or more functional radical moieties. The number that is allowed by available valences limits the amount of substituents. Substitution is not limited to the core molecule, but may also occur on a substituent radical, whereby the substituent radical becomes a linking group.

Therapeutic Uses

The compounds of Formula I represent novel potent inhibitors of protein tyrosine kinases, such as c-fms, and may be useful in the prevention and treatment of disorders resulting from actions of these kinases.

The invention also provides methods of inhibiting a protein tyrosine kinase comprising contacting the protein tyrosine kinase with an effective inhibitory amount of at least one of the compounds of Formula I. A preferred tyrosine kinase is c-fms. In one embodiment of inhibiting a protein tyrosine kinase, at least one of the compounds of Formula I is combined with a known tyrosine kinase inhibitor.

In various embodiments of the invention, the protein tyrosine kinases inhibited by the compounds of Formula I are located in cells, in a mammal or *in vitro*. In the case of mammals, which includes humans, a therapeutically effective amount of a pharmaceutically acceptable form of at least one of the compounds of Formula I is administered.

The invention further provides methods of treating cancer in mammals, including humans, by administration of a therapeutically effective amount of a pharmaceutically acceptable composition of least one compound of Formula I. Exemplary cancers include,

but are not limited to, ovarian cancer, uterine cancer, breast cancer, colon cancer, stomach cancer, hairy cell leukemia and non-small lung carcinoma. In one embodiment of the invention, an effective amount of at least one compound of Formula I is administered in combination with an effective amount of a chemotherapeutic agent.

The invention also provides methods of treating cardiovascular and inflammatory diseases in mammals, including humans, by administration of a therapeutically effective amount of a pharmaceutically acceptable form of at least one of the compounds of Formula I. Examples of diseases that may be effectively treated include atherosclerosis, cardiac hypertrophy, glomerulonephritis, rheumatoid arthritis, psoriasis, diabetes, tumor related angiogenesis, restenosis, schizophrenia and Alzheimer's dementia.

When employed as protein tyrosine kinase inhibitors, the compounds of the invention may be administered in an effective amount within the dosage range of about 0.5 mg to about 10 g, preferably between about 0.5 mg to about 5 g, in single or divided daily doses. A preferred dosage is 5 mg/kg, delivered orally. The dosage administered will be affected by factors such as the route of administration, the health, weight and age of the recipient, the frequency of the treatment and the presence of concurrent and unrelated treatments.

The compounds of Formula I may be formulated into pharmaceutical compositions comprising any known pharmaceutically acceptable carriers. Exemplary carriers include, but are not limited to, any suitable solvents, dispersion media, coatings, antibacterial and antifungal agents and isotonic agents. Exemplary excipients that may also be components of the formulation include fillers, binders, disintegrating agents and lubricants.

The pharmaceutically-acceptable salts of the compounds of Formula I include the conventional non-toxic salts or the quaternary ammonium salts which are formed from inorganic or organic acids or bases. Examples of such acid addition salts include acetate, adipate, benzoate, benzenesulfonate, citrate, camphorate, dodecylsulfate, hydrochloride, hydrobromide, lactate, maleate, methanesulfonate, nitrate, oxalate, pivalate, propionate, succinate, sulfate and tartrate. Base salts include ammonium salts, alkali metal salts such as sodium and potassium salts, alkaline earth metal salts such as calcium and magnesium salts, salts with organic bases such as dicyclohexylamine salts and salts with amino acids

such as arginine. Also, the basic nitrogen-containing groups may be quaternized with, for example, alkyl halides.

The pharmaceutical compositions of the invention may be administered by any means that accomplish their intended purpose. Examples include administration by parenteral, subcutaneous, intravenous, intramuscular, intraperitoneal, transdermal, buccal or ocular routes. Alternatively or concurrently, administration may be by the oral route. Suitable formulations for parenteral administration include aqueous solutions of the active compounds in water-soluble form, for example, water-soluble salts, acidic solutions, alkaline solutions, dextrose-water solutions, isotonic carbohydrate solutions and cyclodextrin inclusion complexes.

A representative compound of Formula (I) or a form thereof for use in the therapeutic methods and pharmaceutical compositions, medicines or medicaments described herein includes a compound selected from the group consisting of:

- 7 8-indan-5-yl-2-[4-(4-methyl-piperazin-1-yl)-phenylamino]-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid amide,
- 8 8-indan-5-yl-2-[4-(4-methyl-piperazin-1-yl)-phenylamino]-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid methylamide,
- 9 8-indan-5-yl-2-[4-(4-methyl-piperazin-1-yl)-phenylamino]-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid ethylamide,
- 10 2-[4-(3-dimethylamino-2-hydroxy-propoxy)-phenylamino]-8-indan-5-yl-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid amide,
- 11 2-[4-(3-dimethylamino-2-hydroxy-propoxy)-phenylamino]-8-indan-5-yl-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid methylamide
- 12 2-[4-(3-dimethylamino-2-hydroxy-propoxy)-phenylamino]-8-indan-5-yl-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid ethylamide,
- 14 8-indan-5-yl-2-(4-morpholin-4-yl-phenylamino)-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid amide,
- 15 2-(4-dimethylamino-phenylamino)-8-indan-5-yl-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid amide,
- 16 2-(3-dimethylamino-phenylamino)-8-indan-5-yl-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid amide,
- 19 8-cyclopentyl-2-[4-(4-methyl-piperazin-1-yl)-phenylamino]-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid amide,
- 23 8-indan-5-yl-2-[3-(4-methyl-piperazin-1-ylmethyl)-phenylamino]-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid amide,

- 24 8-indan-5-yl-2-(3-morpholin-4-ylmethyl-phenylamino)-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid amide,
- 25 2-[2-hydroxy-4-(4-methyl-piperazin-1-yl)-phenylamino]-8-indan-5-yl-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid amide,
- 26 1-indan-5-yl-7-[4-(4-methyl-piperazin-1-yl)-phenylamino]-4-oxo-1,4-dihydro-[1,6]naphthyridine-3-carboxylic acid amide,
- 27 8-Indan-5-yl-2-[4-(2-morpholin-4-yl-ethyl)-phenylamino]-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid amide,
- 28 8-Indan-5-yl-2-[4-(2-morpholin-4-yl-ethyl)-phenylamino]-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid methyl amide,
- 29 8-Indan-5-yl-2-[4-(2-morpholin-4-yl-ethyl)-phenylamino]-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid ethyl amide,
- 30 (4*S*)-8-Indan-5-yl-5-oxo-2-[4-(2-oxo-oxazolidin-4-ylmethyl)-phenylamino]-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid amide,
- 31 (4*S*)-8-Indan-5-yl-5-oxo-2-[4-(2-oxo-oxazolidin-4-ylmethyl)-phenylamino]-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid methyl amide,
- 32 (4*S*)-8-Indan-5-yl-5-oxo-2-[4-(2-oxo-oxazolidin-4-ylmethyl)-phenylamino]-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid ethyl amide,
- 33 8-Indan-5-yl-2-[4-(2-isopropylsulfamoyl-ethyl)-phenylamino]-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid methyl amide,
- 35 8-Indan-5-yl-2-[4-[2-(morpholine-4-sulfonyl)-ethyl]-phenylamino]-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid methyl amide,
- 37 8-Indan-5-yl-2-[3-(4-methyl-piperazin-1-yl)-phenylamino]-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid amide,
- 38 8-Indan-5-yl-2-[3-(4-methyl-piperazin-1-yl)-phenylamino]-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid methyl amide,
- 39 8-Indan-5-yl-2-[3-(4-methyl-piperazin-1-yl)-phenylamino]-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid ethyl amide,
- 40 8-Indan-5-yl-5-oxo-2-(4-piperazin-1-yl-phenylamino)-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid amide,
- 41 8-Indan-5-yl-5-oxo-2-(4-piperazin-1-yl-phenylamino)-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid methyl amide,
- 42 8-Indan-5-yl-5-oxo-2-(4-piperazin-1-yl-phenylamino)-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid ethyl amide,
- 43 2-[4-(3,5-Dimethyl-piperazin-1-yl)-phenylamino]-8-indan-5-yl-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid amide,
- 44 2-[4-(3,5-Dimethyl-piperazin-1-yl)-phenylamino]-8-indan-5-yl-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid methyl amide,
- 45 2-[4-(3,5-Dimethyl-piperazin-1-yl)-phenylamino]-8-indan-5-yl-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid ethyl amide,

- 46 8-Indan-5-yl-2-{4-[2-(4-methyl-piperazin-1-yl)-ethyl]-phenylamino}-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid amide,
- 47 8-Indan-5-yl-2-{4-[2-(4-methyl-piperazin-1-yl)-ethyl]-phenylamino}-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid methyl amide,
- 48 8-Indan-5-yl-2-{4-[2-(4-methyl-piperazin-1-yl)-ethyl]-phenylamino}-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid ethyl amide,
- 49 8-Indan-5-yl-5-oxo-2-(4-piperidin-4-yl-phenylamino)-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid amide,
- 50 8-Indan-5-yl-5-oxo-2-(4-piperidin-4-yl-phenylamino)-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid methyl amide,
- 51 8-Indan-5-yl-5-oxo-2-(4-piperidin-4-yl-phenylamino)-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid ethyl amide,
- 52 8-Indan-5-yl-5-oxo-2-(3-piperazin-1-yl-phenylamino)-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid amide,
- 53 8-Indan-5-yl-5-oxo-2-(3-piperazin-1-yl-phenylamino)-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid methyl amide,
- 54 8-Indan-5-yl-5-oxo-2-(3-piperazin-1-yl-phenylamino)-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid ethyl amide,
- 55 2-[3-(3,5-Dimethyl-piperazin-1-yl)-phenylamino]-8-indan-5-yl-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid amide,
- 56 2-[3-(3,5-Dimethyl-piperazin-1-yl)-phenylamino]-8-indan-5-yl-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid methyl amide,
- 57 8-Cyclohexyl-2-[4-(2-morpholin-4-yl-ethyl)-phenylamino]-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid amide,
- 60 8-Cyclohexyl-2-[4-(4-methyl-piperazin-1-yl)-phenylamino]-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid amide,
- 63 8-Cyclohexyl-2-[3-(4-methyl-piperazin-1-yl)-phenylamino]-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid amide,
- 64 8-Cyclohexyl-2-[3-(4-methyl-piperazin-1-yl)-phenylamino]-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid methyl amide,
- 69 8-Indan-5-yl-2-(4-morpholin-4-ylmethyl-phenylamino)-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid amide,
- 74 8-Indan-5-yl-2-[4-(4-methyl-piperazin-1-ylmethyl)-phenylamino]-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid amide,
- 75 2-(4-Dimethylaminomethyl-phenylamino)-8-indan-5-yl-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid amide,
- 76 2-(3-Dimethylaminomethyl-phenylamino)-8-indan-5-yl-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid amide,
- 79 2-(3-Dimethylcarbamoyl-phenylamino)-8-indan-5-yl-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid amide,

- 80 2-(3-Dimethylcarbamoyl-phenylamino)-8-indan-5-yl-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid methylamide,
- 82 8-Bicyclo[2.2.1]hept-2-yl-2-[4-(4-methyl-piperazin-1-yl)-phenylamino]-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid amide, and
- 84 8-Indan-5-yl-2-[4-(4-methyl-piperazin-1-ylmethyl)-phenylamino]-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid ethylamide.

General Synthetic Methods

The compounds of Formula I can be prepared by methods known to those who are skilled in the art. The following reaction schemes are only meant to represent examples of the invention and are in no way meant to limit the invention.

The following general reaction schemes display various methods of reaching the compounds of Formula I. It is recognized by those skilled in the art that some compounds of Formula I may be further derivatized to provide additional embodiments of the invention. Representative further derivitizations appear in schemes I, II, and V.

A typical preparation of compounds of the present invention is shown in Scheme I, wherein Ph is phenyl, which may be optionally further substituted with R¹⁰¹.

An amine was reacted with ethyl 3-chloropropionate at elevated temperature at the presence of an inorganic base and a catalytic amount of tetrabutylammonium bromide to afford the aminopropionate ester 1-1.

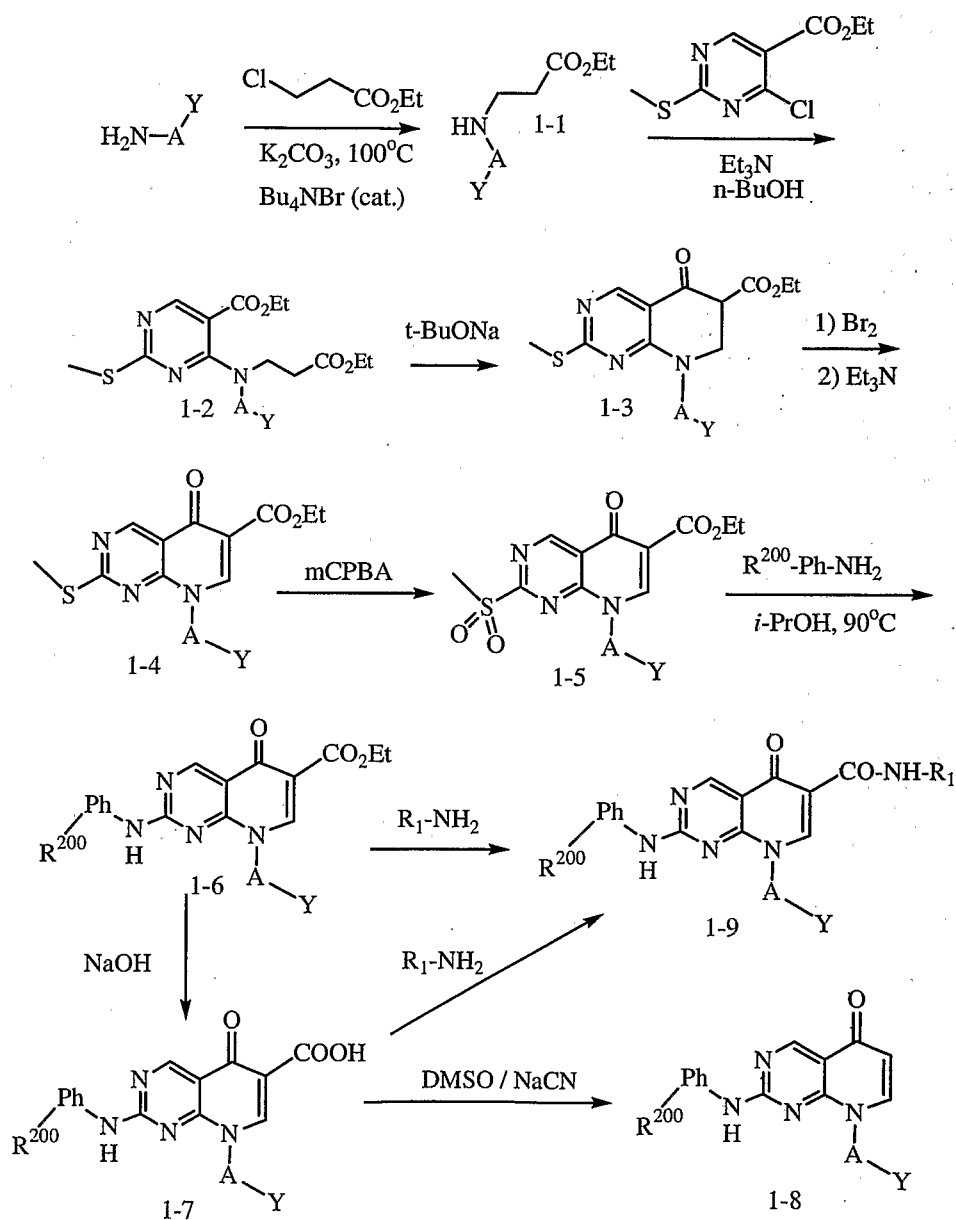
The amine was reacted with ethyl 4-chloro-2-methylthio-5-pyrimidinecarboxylate to produce the corresponding 4-substituted aminopyrimidine 1-2. Cyclization of this diester under Dieckmann conditions afforded the bicyclic compound 1-3.

Subsequent halogenation with bromine followed by dehydrohalogenation gave the unsaturated 1-4 (Eur J Med Chem 9 (2000) pp 585-590). The methylthio group was oxidized to the sulfone 1-5, which was subsequently replaced with an amine by nucleophilic substitution.

The resulting carboxylic ester 1-6 was converted to the carboxylic acid 1-7 via basic hydrolysis. Decarboxylation to give 1-8 occurred when the carboxylic acid was heated in DMSO in the presence of sodium cyanide (Tet Lett 35 (1994) pp 8303-8306).

The carboxylic acid 1-7 was reacted with an amine under normal coupling conditions to form the corresponding amide 1-9. The amide 1-9 could also be prepared directly from the ester 1-6 when the amine R_1-NH_2 was ammonia, or an alkylamine.

Scheme 1

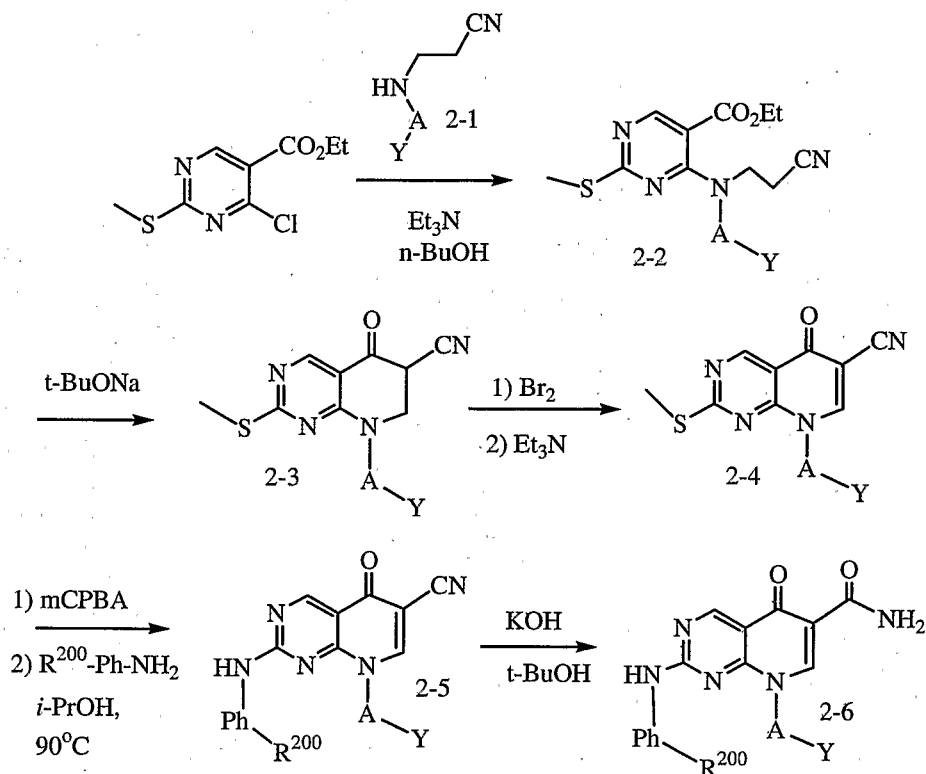


The synthesis was further extended to include the preparation of 5,8-dihydropyrido[2,3-d]pyrimidines with a carbonitrile functional group at the C_6 position. The method of preparation was identical with that used for preparing the esters (Scheme I)

except that suitably 3-substituted aminopropionitriles 2-1 were used in the first step (Scheme II).

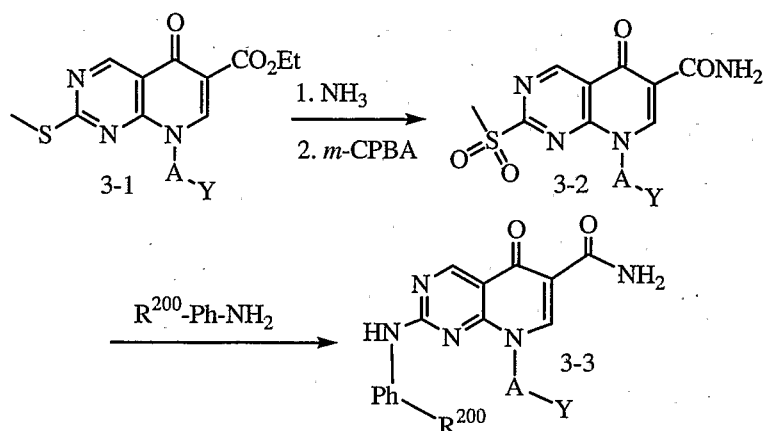
Hydrolysis of 2-5 under basic conditions provided the corresponding primary amide 2-6, wherein Ph is phenyl, which may be optionally further substituted with R¹⁰¹.

Scheme II



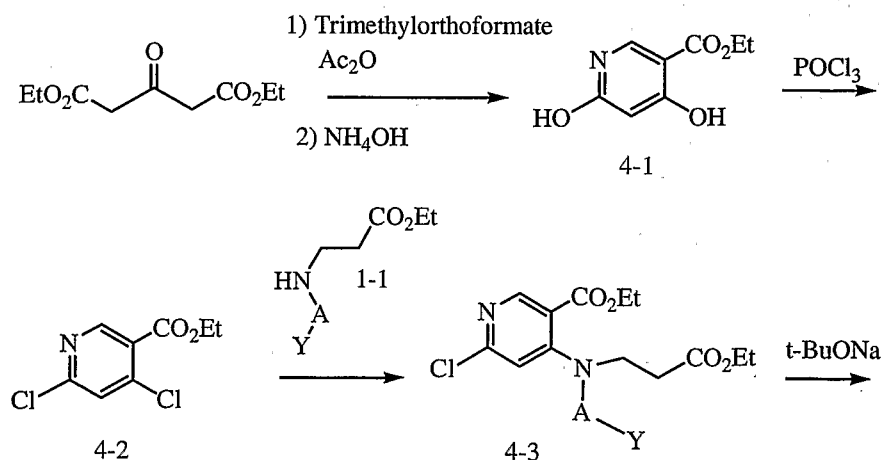
When 6-amide was the desired product, the intermediate 3-1 was converted to the primary amide 3-2 using liquid ammonia in a pressure bottle (Scheme III). Subsequent oxidation to methyl sulfone and nuclear substitution by an amine provided the desired 6-amide analogs 3-3, wherein Ph is phenyl, which may be optionally further substituted with R¹⁰¹.

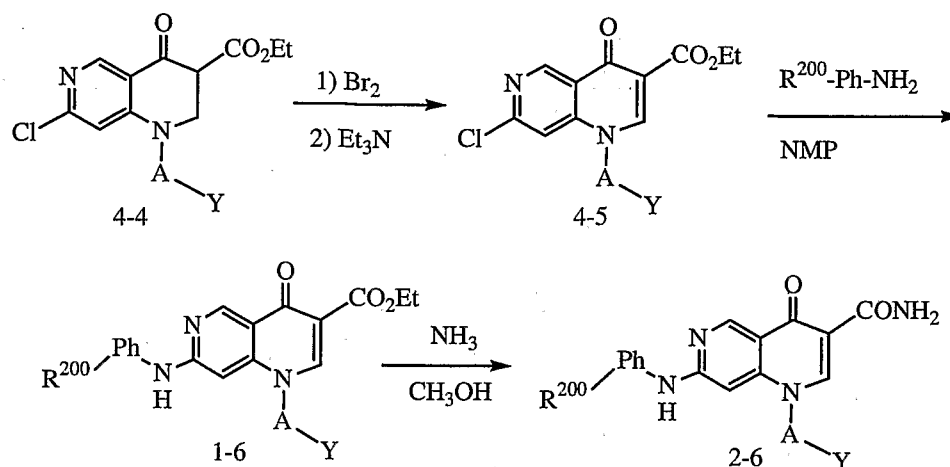
Scheme III



Compounds of formula (I) wherein W is CH were prepared by methods shown in Scheme IV, wherein Ph is phenyl, which may be optionally further substituted with R^{101} . 4,6-Dihydroxy-nicotinic acid ethyl ester 4-1 was obtained via two steps from diethyl 1,3-acetonedicarboxylate. Treatment of 4-1 with POCl_3 gave 4,6-dichloro-nicotinic acid ethyl ester 4-2. The following nucleophilic substitution and Dieckmann cyclization reactions were similar to the methods outlined in Scheme I. The intermediate 4-5 was treated with an amine in *N*-methyl pyrrolidinone (NMP) under microwave conditions to afford the ester 4-6, which was subsequently converted to the amide 4-7.

Scheme IV





Where R^{200} is heterocyclyl, alkoxy or dialkylamino, anilines of the form R^{200} -phenyl-NH₂ were prepared using S_NAr reactions as shown in Scheme V (A) followed by hydrogenation converting the nitro group to the amino group. The phenyl portion of the compounds depicted in Scheme V may be optionally substituted with R^{101} .

Where R^{300} is alkyl, anilines of the form R^{400} -alkyl-phenyl-NH₂ were prepared using S_N2 reactions as shown in Scheme V (B) followed by hydrogenation converting the nitro group to the amino group.

Where R^{200} is $-C(O)(CH_2)_nNR^{203}R^{204}$, preparation of the aniline R^{200} -phenyl-NH₂ may be accomplished using S_N2 reactions as shown in Scheme V (C) followed by hydrogenation converting the nitro group to the amino group. It is recognized by those skilled in the art that where $n=0$, the desired product may be obtained from nitrobenzoic acid, nitrobenzoyl chloride and other starting materials.

Alternatively, anilines where R^{200} is piperidinyl substituted with $-C(O)$ -alkyl-NR²⁰³R²⁰⁴, may be obtained according to Scheme V (D and E).

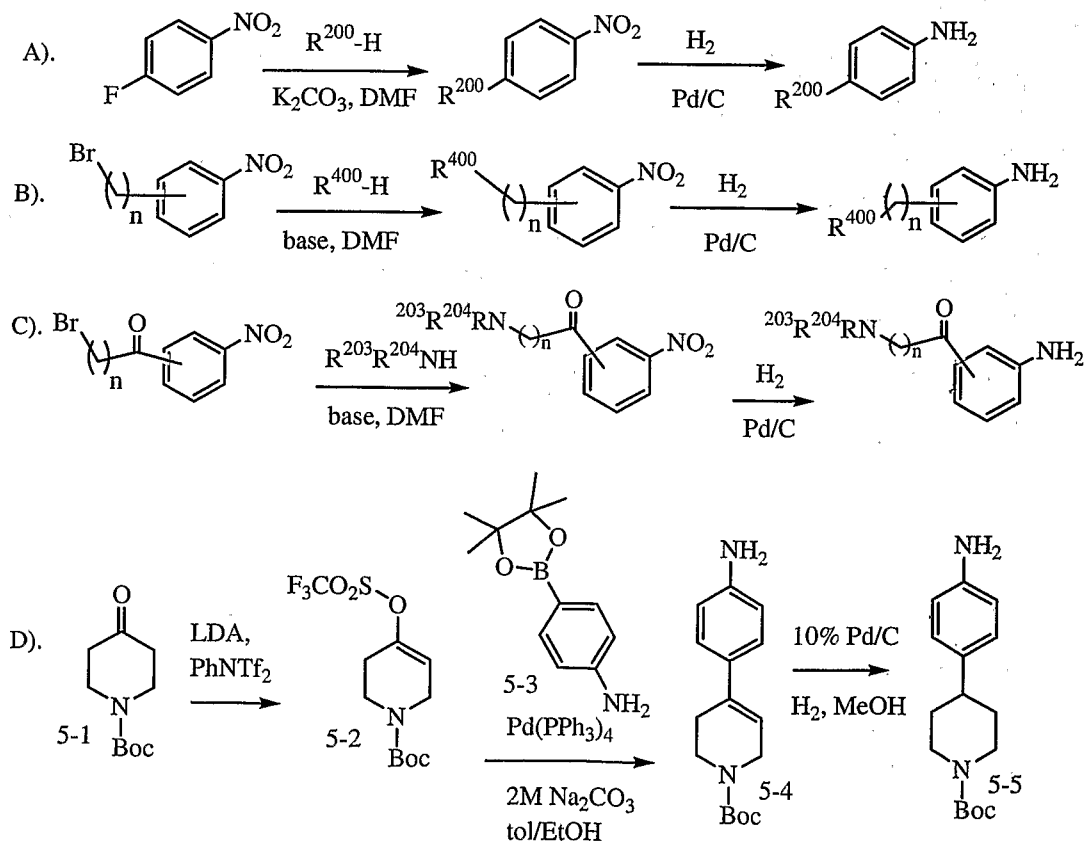
Ketones of formula 5-1 can be converted to a vinyl triflate of formula 5-2 by treatment with a non-nucleophilic base such as LDA and then trapping of the resulting enolate with a triflating reagent such as trifluoromethanesulfonic anhydride or preferably N-phenyltrifluoromethanesulfonimide.

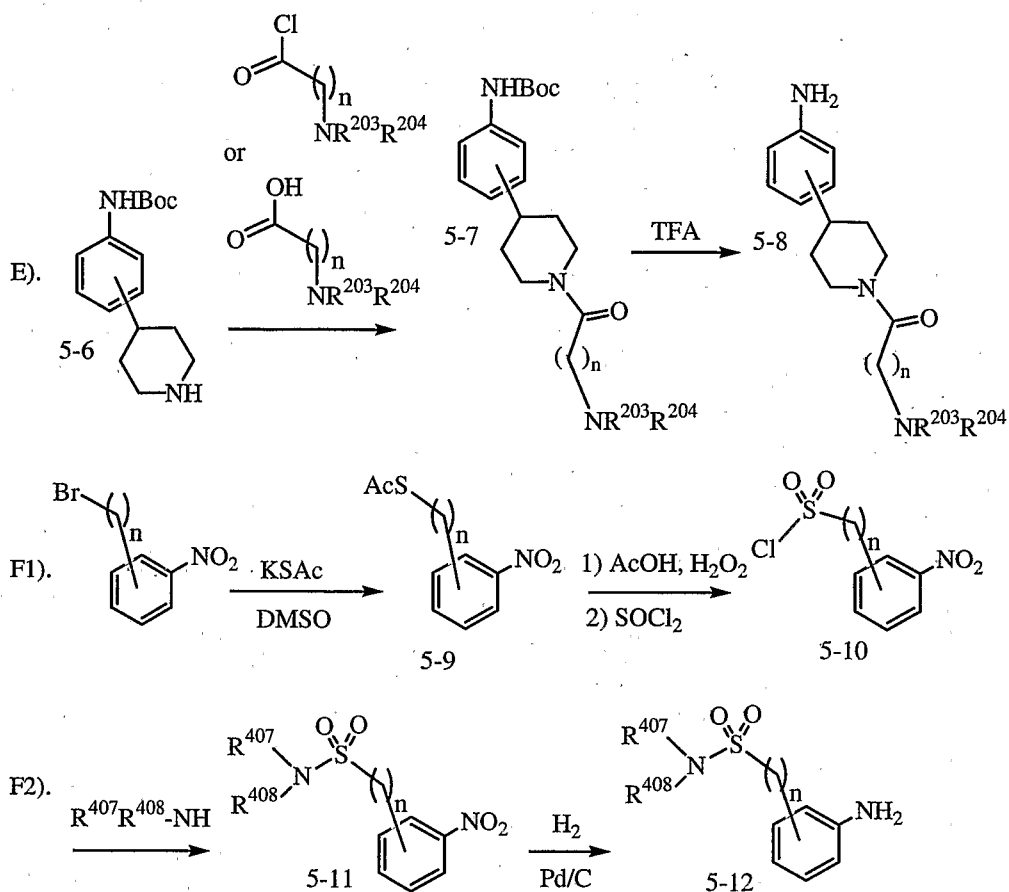
Suzuki coupling of boronic acids or boronate esters of formula 5-3 (prepared by palladium catalyzed borylation, see for example *J. Org. Chem.*, 60: 7508 (1995)) to vinyl

triflates of formula 5-2 provided compounds of formula 5-4 (see, for example, *Synthesis*, 993 (1991)). Reduction of the olefin with hydrogen over palladium on carbon gave the aniline 5-5. *N*-Boc protected anilines of formula 5-6 can be converted to amides of formula 5-7 through normal amide formation reactions (Scheme V, E). Anilines of formula 5-8 were obtained upon acidic deprotection of the Boc group. It is recognized by those skilled in the art that the same procedure described for Scheme V (E) can also be used to generate ureas wherein the R²⁰⁰ piperidine is substituted with -C(O)N-alkyl-NR²⁰³R²⁰⁴.

When R³⁰⁰ is alkyl, anilines of the form R⁴⁰⁷R⁴⁰⁸NSO₂-alkyl-phenyl-NH₂ were prepared as described in Scheme V (F). Thioacetate of formula 5-9 was obtained from nucleophilic replacement of bromide with potassium thioacetate. Hydrolysis followed by treatment with thionyl chloride afforded sulfonyl chloride of formula 5-10, which was subsequently converted to sulfonamides of formula 5-11 when treated with various amines. The final nitro reduction provided the anilines of formula 5-12.

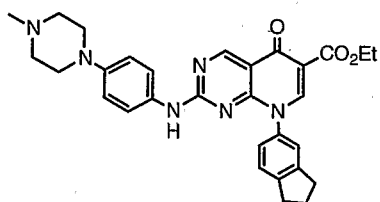
Scheme V





Example 1

8-Indan-5-yl-2-[4-(4-methyl-piperazin-1-yl)-phenylamino]-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid ethyl ester (Cpd 1)



A. 3-(Indan-5-ylamino)-propionic acid ethyl ester

Tetrabutylammonium bromide (200 mg) was added to a mixture of 5-aminoindan (5 g, 37.6 mmol), ethyl 3-chloropropionate (4.7 mL, 37.6 mmol) and potassium carbonate (5.2 g, 37.6 mmol). The mixture was stirred at 100 °C for 16 hours. After cooling to room temperature (rt), the mixture was extracted into ethyl acetate (EtOAc), washed with water, brine and then dried with sodium sulfate (Na_2SO_4). Removal of the solvent and

chromatography on silica, eluting with EtOAc/hexanes (1:20-1:10, v/v), gave 6.2 g (71%) of the title compound. ^1H NMR (300MHz, CDCl_3) δ (ppm): 7.03 (d, $J = 7.6\text{Hz}$, 1H), 6.55 (s, 1H), 6.43 (d, $J = 7.6\text{Hz}$, 1H), 4.15 (q, 2H), 3.86 (br, 1H), 3.43 (t, 2H), 2.82 (m, 4H), 2.60 (t, 2H), 2.06 (m, 2H), 1.27 (t, 3H).

B. 4-[(2-Ethoxycarbonyl-ethyl)-indan-5-yl-amino]-2-methylsulfanyl-pyrimidine-5-carboxylic acid ethyl ester

To a solution of 3-(indan-5-ylamino)-propionic acid ethyl ester (5 g, 21.4 mmol) and ethyl 4-chloro-2-methylthio-5-pyrimidinecarboxylate (5 g, 21.4 mmol) in 40 mL of *n*-butanol was added triethylamine (3 mL, 21.4 mmol). The solution was stirred at rt for 2 days. The solvent was removed under vacuum. The residue was extracted into EtOAc, washed with water, brine and then dried with Na_2SO_4 . Removal of the solvent and chromatography on silica, eluting with EtOAc/hexanes (1:10-1:6, v/v), gave 8.2 g (90%) of the titled compound as a white solid. ^1H NMR (300MHz, CDCl_3) δ (ppm): 8.22 (s, 1H), 7.16 (d, $J = 7.6\text{Hz}$, 1H), 6.95 (s, 1H), 6.87 (d, $J = 7.6\text{Hz}$, 1H), 4.35 (t, 2H), 4.06 (q, 2H), 3.55 (q, 2H), 2.82 (m, 4H), 2.69 (t, 2H), 2.58 (s, 3H), 2.06(m, 2H), 1.20 (t, 3H), 1.02 (t, 3H).

C. 8-Indan-5-yl-2-methylsulfanyl-5-oxo-5,6,7,8-tetrahydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid ethyl ester

To sodium (25 wt% dispersion in paraffin wax, 1.6 g, 16.9 mmol) was added *t*-butanol (30 mL) under stirring and N_2 . After 10 minutes, a solution of 4-[(2-ethoxycarbonyl-ethyl)-indan-5-yl-amino]-2-methylsulfanyl-pyrimidine-5-carboxylic acid ethyl ester (6.6 g, 15.4 mmol) in 40 mL of toluene was added to the sodium *t*-butoxide solution. The mixture was then heated at 90°C for 30 minutes. The solution was cooled and poured into crushed ice. The solution was adjusted to pH 7 using HCl solution. The precipitates were extracted into EtOAc twice. The solvent was evaporated under vacuum and the product (bright yellow solid, 4 g, 62%) was recrystallized from isopropanol. ^1H NMR (300MHz, CDCl_3) indicated that the presence of both enol and keto forms in a 4:1 ratio.

D. 8-Indan-5-yl-2-methylsulfanyl-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid ethyl ester

To a solution of 8-indan-5-yl-2-methylsulfanyl-5-oxo-5,6,7,8-tetrahydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid ethyl ester (0.32 g, 0.84 mmol) in 5 mL of methylene chloride (CH_2Cl_2) was added bromine (43 μL , 0.84 mmol) slowly under N_2 . The solution was stirred at room temperature for 2 hours (or to completion). The solvent was removed under vacuum without heating. The residue was redissolved in 2 mL of CH_2Cl_2 , and was added triethylamine (234 μL , 1.68 mmol) in 1 mL of CH_2Cl_2 . The solution was stirred at rt for 4 hours. The progress of the reaction was monitored by LC-MS. The solvent was evaporated and the residue was applied onto a silica gel column. The product was eluted with EtOAc/hexanes (1:5-1:2.5, v/v) and obtained as a white solid (0.30 g, 94%). ^1H NMR (300MHz, CDCl_3) δ (ppm): 9.42 (s, 1H), 8.59 (s, 1H), 7.37 (d, $J = 7.8\text{Hz}$, 1H), 7.24 (s, 1H), 7.16 (d, $J = 7.8\text{Hz}$, 1H), 4.40 (q, 2H), 3.00 (m, 4H), 2.35 (s, 3H), 2.10(m, 2H), 1.40 (t, 3H).

E. 8-Indan-5-yl-2-methanesulfonyl-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid ethyl ester

To a solution of 8-indan-5-yl-2-methylsulfanyl-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid ethyl ester (0.3 g, 0.79 mmol) in 5 mL of CH_2Cl_2 , was added 3-chloroperoxybenzoic acid (*m*-CPBA, 69.5%, 431 mg, 1.73 mmol) portionwise. The solution was stirred at room temperature for 3 hours. An aqueous solution of 10% sodium thiosulfate was added to quench the reaction. After 30 minutes saturated sodium bicarbonate solution was added, and the aqueous solution was extracted by CH_2Cl_2 . The combined CH_2Cl_2 solution was washed with brine and dried over Na_2SO_4 . Removal of the solvent and chromatography on silica, eluting with EtOAc/hexanes (1:3-1:1.6, v/v) gave 0.22 g (67%) of the title compound as an off-white solid. ^1H NMR (300MHz, CDCl_3) δ (ppm): 9.75 (s, 1H), 8.70 (s, 1H), 7.39 (d, $J = 7.8\text{Hz}$, 1H), 7.24 (s, 1H), 7.16 (d, $J = 7.8\text{Hz}$, 1H), 4.38 (q, 2H), 3.19 (s, 3H), 3.00 (m, 4H), 2.10(m, 2H), 1.40 (t, 3H).

F. 4-(4-Methyl-piperazin-1-yl)-phenylamine

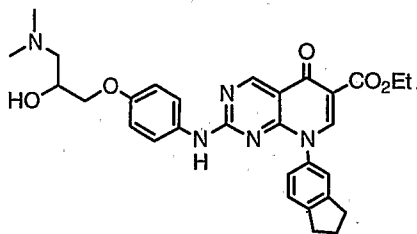
Potassium carbonate (1.9 g, 14.2 mmol) was added to a mixture of 1-fluoro-4-nitrobenzene (1 g, 7.1 mmol) and 1-methyl-piperazine (0.94 mL, 8.5 mmol) in methyl sulfoxide (DMSO, 5 mL). The mixture was stirred at 80 °C for 3 hours. After cooling down, the residue was extracted into EtOAc. The organic layer was washed with water, brine and then dried with Na₂SO₄. Removal of the solvent in vacuo yielded an orange solid. The solid was dissolved in 25 mL of methanol and palladium on carbon (10% Pd/C, 50 mg) was added slowly. The system was sealed and blanketed with hydrogen. The mixture was stirred at rt for 16 hours under hydrogen. The catalyst was filtered through a celite pad and the solvent was evaporated to leave a dark purple solid (1.3 g, 80%). ¹H NMR (300MHz, CD₃OD) δ (ppm): 6.90 (m, 2H), 6.81 (m, 2H), 3.38 (m, 4H), 3.26 (m, 4H), 2.93 (s, 3H).

G. 8-Indan-5-yl-2-[4-(4-methyl-piperazin-1-yl)-phenylamino]-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid ethyl ester (Cpd 1)

The mixture of 8-Indan-5-yl-2-methanesulfonyl-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid ethyl ester (11.2 mg, 0.027 mmol) and 4-(4-methyl-piperazin-1-yl)-phenylamine (5.2 mg, 0.027 mmol) in 1 mL of isopropanol was heated to 90 °C for 1 hour. The solvent was evaporated and the residue was re-dissolved in a mixture of methanol and CH₂Cl₂ (1:1, v/v) and applied onto a prep-TLC plate (2000 micro). The plate was developed in NH₄OH/MeOH/CH₂Cl₂ (1:9:90, v/v). 8-Indan-5-yl-2-[4-(4-methyl-piperazin-1-yl)-phenylamino]-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid ethyl ester (Cpd 1) was obtained as a yellow solid (8.6 mg, 61%). ¹H NMR (300MHz, CDCl₃) δ (ppm): 9.38 (s, 1H), 8.52 (s, 1H), 7.44 (m, 2H), 7.28 (s, 1H), 7.19 (m, 3H), 6.66 (m, 2H), 4.40 (q, 2H), 3.00-3.18 (m, 8H), 2.60 (m, 4H), 2.35 (s, 3H), 2.22 (m, 2H), 1.40 (t, 3H). Mass Spectrum (LCMS, ESI pos.) Calcd. For C₃₀H₃₂N₆O₃: 525.25 (M + H), Found: 525.4.

Example 2

2-[4-(3-Dimethylamino-2-hydroxy-propoxy)-phenylamino]-8-indan-5-yl-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid ethyl ester (Cpd 2)



A. 2-(4-Nitro-phenoxy)methyl)-oxirane

Potassium carbonate (1.3 g, 9.6 mmol) was added to a mixture of 4-nitrophenol (1.11 g, 8 mmol) and epibromohydrin (1.37 mL, 16 mmol). The mixture was stirred at 100 °C for 18 hours. After cooling down, the residue was extracted into EtOAc. The organic layer was washed with water, brine and then dried with Na₂SO₄. Removal of the solvent in vacuo gave an orange residue, which was purified chromatographically on silica eluting with EtOAc/ hexanes (1:10, v/v). The product was obtained as a yellow solid (0.8 g, 51%).
¹H NMR (300MHz, CDCl₃) δ (ppm): 8.21 (m, 2H), 6.98 (m, 2H), 4.37 (dd, *J* = 2.8Hz, 11.1Hz, 1H), 4.00 (dd, *J* = 5.9Hz, 11.1Hz, 1H), 3.90 (m, 1H), 2.93 (t, *J* = 4.8Hz, 1H), 2.77 (dd, *J* = 2.8Hz, 4.8Hz, 1H).

B. 1-(4-Amino-phenoxy)-3-dimethylamino-propan-2-ol

To a solution of 2-(4-nitro-phenoxy)methyl)-oxirane (0.2 g, 1 mmol) in 2 mL of ethanol was added a solution of dimethylamine (2 M in methanol, 2.5 mL). The solution was stirred at 80 °C for 2 hours in a capped vial. The solvent was removed in vacuo. Hydrogenation of the residue using the procedure described in Example 1 (f) gave the title compound as a brown solid. ¹H NMR (300MHz, CD₃OD) δ (ppm): 6.76 (m, 2H), 6.71 (m, 2H), 4.20 (m, 1H), 3.88 (d, 2H), 3.04 (m, 2H), 2.71 (s, 6H).

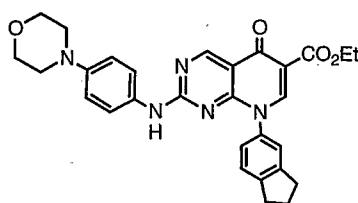
C. 2-[4-(3-dimethylamino-2-hydroxy-propoxy)-phenylamino]-8-indan-5-yl-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid ethyl ester

Using the procedure outlined in Example 1(g) the title compound was prepared from 1-(4-amino-phenoxy)-3-dimethylamino-propan-2-ol (18 mg, 0.083 mmol) and 8-

indan-5-yl-2-methanesulfonyl-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid ethyl ester (from Example 1(e) above, 34 mg, 0.083 mmol). 3.1 mg of 2-[4-(3-dimethylamino-2-hydroxy-propoxy)-phenylamino]-8-indan-5-yl-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid ethyl ester was obtained as a yellow solid. ^1H NMR (300MHz, CDCl_3) δ (ppm): 9.38 (s, 1H), 8.52 (s, 1H), 7.50 (br, 1H), 7.40 (d, 2H), 7.28 (m, 3H), 7.19 (d, 1H), 6.66 (br, 2H), 4.40 (q, 2H), 4.05 (m, 1H), 3.90 (d, 2H), 3.10 (m, 4H), 2.52 (dd, 1H), 2.33 (m, 7H), 2.22 (m, 2H), 1.40 (t, 3H). Mass Spectrum (LCMS, ESI pos.) Calcd. For $\text{C}_{30}\text{H}_{33}\text{N}_5\text{O}_5$: 544.25 (M + H), Found: 544.4.

Example 3

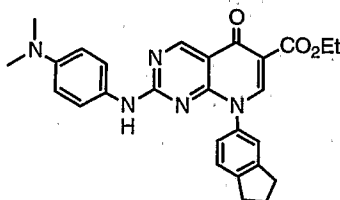
8-Indan-5-yl-2-(4-morpholin-4-yl-phenylamino)-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid ethyl ester (Cpd 3)



Using the procedure outlined in Example 1(g) the title compound was prepared from 4-morpholin-4-yl-phenylamine (6.5 mg, 0.036 mmol) and 8-indan-5-yl-2-methanesulfonyl-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid ethyl ester (from Example 1(e) above, 15 mg, 0.036 mmol). 11.9 mg of 8-indan-5-yl-2-(4-morpholin-4-yl-phenylamino)-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid ethyl ester was obtained as a yellow solid. ^1H NMR (400MHz, CDCl_3) δ (ppm): 9.38 (br, 1H), 8.53 (s, 1H), 7.69 (br, 1H), 7.43 (d, 1H), 7.23 (m, 4H), 6.64 (br, 2H), 4.36 (q, 2H), 3.87 (m, 4H), 3.04 (m, 8H), 2.22 (m, 2H), 1.39 (t, 3H). Mass Spectrum (LCMS, ESI pos.) Calcd. For $\text{C}_{29}\text{H}_{29}\text{N}_5\text{O}_4$: 512.24 (M + H), Found: 512.4.

Example 4

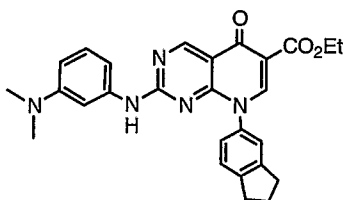
2-(4-Dimethylamino-phenylamino)-8-indan-5-yl-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid ethyl ester (Cpd 4)



Using the procedure outlined in Example 1(g) the title compound was prepared from 4-dimethylaminoaniline (5 μ L, 0.036 mmol) and 8-indan-5-yl-2-methanesulfonyl-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid ethyl ester (from Example 1(e) above, 15 mg, 0.036 mmol). 7.9 mg of 2-(4-dimethylamino-phenylamino)-8-indan-5-yl-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid ethyl ester was obtained as a yellow solid. ^1H NMR (400MHz, CDCl_3) δ (ppm): 9.31 (br, 1H), 8.53 (s, 1H), 7.82 (d, 1H), 7.61 (br, 1H), 7.41 (d, 1H), 7.29 (s, 1H), 7.17 (d, 1H), 6.76 (d, 1H), 6.46 (br, 2H), 4.39 (q, 2H), 3.03 (m, 4H), 2.89 (s, 6H), 2.22 (m, 2H), 1.37 (t, 3H). Mass Spectrum (LCMS, ESI pos.) Calcd. For $\text{C}_{27}\text{H}_{27}\text{N}_5\text{O}_3$: 470.21 (M + H), Found: 470.4.

Example 5

2-(3-Dimethylamino-phenylamino)-8-indan-5-yl-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid ethyl ester (Cpd 5)

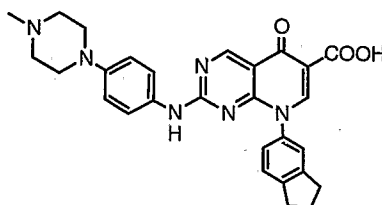


Using the procedure outlined in Example 1(g) the title compound was prepared from 3-dimethylaminoaniline dihydrochloride (7.6 mg, 0.036 mmol) and 8-indan-5-yl-2-methanesulfonyl-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid ethyl ester (from Example 1(e) above, 15 mg, 0.036 mmol) at the presence of triethylamine (11 μ L, 0.072 mmol). 6.6 mg of 2-(3-dimethylamino-phenylamino)-8-indan-5-yl-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid ethyl ester was obtained as a yellow

solid. ^1H NMR (300MHz, CDCl_3) δ (ppm): 9.41 (br, 1H), 8.53 (s, 1H), 7.47 (br, 1H), 7.40 (d, 1H), 7.29 (s, 1H), 7.18 (d, 1H), 6.90 (m, 2H), 6.50 (m, 2H), 4.39 (q, 2H), 3.00 (m, 4H), 2.80 (s, 6H), 2.21 (m, 2H), 1.37 (t, 3H). Mass Spectrum (LCMS, ESI pos.) Calcd. For $\text{C}_{27}\text{H}_{27}\text{N}_5\text{O}_3$: 470.21 (M + H), Found: 470.4.

Example 6

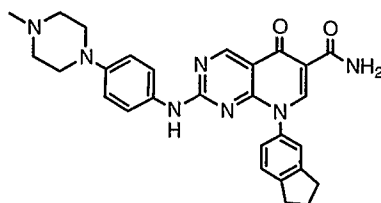
8-Indan-5-yl-2-[4-(4-methyl-piperazin-1-yl)-phenylamino]-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid (Cpd 6)



Hydrolysis of 8-indan-5-yl-2-[4-(4-methyl-piperazin-1-yl)-phenylamino]-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid ethyl ester Cpd 1 (Example 1(g), 50 mg) in a mixture of tetrahydrofuran (THF) and 1 N sodium hydroxide solution at an elevated temperature gave 8-indan-5-yl-2-[4-(4-methyl-piperazin-1-yl)-phenylamino]-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid Cpd 6, which was purified using preparative HPLC, resulting in a formic acid salt form (28 mg, yellow solid). ^1H NMR (300MHz, CDCl_3) δ (ppm): 9.38 (s, 1H), 8.80 (s, 1H), 8.35 (br, 1H), 7.83 (br, 1H), 7.42 (m, 2H), 7.20 (m, 4H), 6.65 (br, 2H), 3.20 (m, 4H), 3.03 (m, 4H), 2.88(m, 4H), 2.60(m, 4H), 2.50 (s, 3H), 2.20 (m, 2H). Mass Spectrum (LCMS, ESI pos.) Calcd. For $\text{C}_{28}\text{H}_{28}\text{N}_6\text{O}_3$: 497.22 (M + H), Found: 497.5.

Example 7

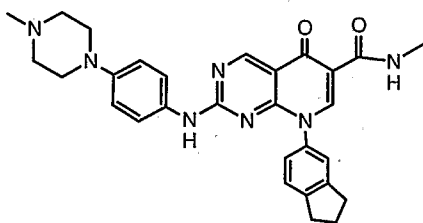
8-Indan-5-yl-2-[4-(4-methyl-piperazin-1-yl)-phenylamino]-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid amide (Cpd 7)



To a solution of 8-indan-5-yl-2-[4-(4-methyl-piperazin-1-yl)-phenylamino]-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid ethyl ester Cpd 1 (Example 1(g), 10 mg) in 1 mL of methanol was bubbled ammonia at -78°C for 5 minutes in a pressure bottle (10 mL). The bottle was capped and warmed up to room temperature and stirred for 16 hours. The solvent was evaporated to leave 8-Indan-5-yl-2-[4-(4-methyl-piperazin-1-yl)-phenylamino]-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid amide Cpd 7 as a yellow solid (8.1 mg). $^1\text{H NMR}$ (400MHz, $\text{DMSO-}d_6$) δ (ppm): 10.24 (s, 1H), 9.17 (s, 1H), 9.03 (s, 1H), 8.52 (s, 1H), 7.62 (d, 1H), 7.44 (m, 2H), 7.33 (d, 1H), 7.27 (m, 2H), 6.57 (m, 2H), 3.00 (m, 4H), 2.93 (m, 4H), 2.42 (m, 4H), 2.20 (s, 3H), 2.13 (m, 2H). Mass Spectrum (LCMS, ESI pos.) Calcd. For $\text{C}_{28}\text{H}_{29}\text{N}_7\text{O}_2$: 496.24 (M + H), Found: 496.4.

Example 8

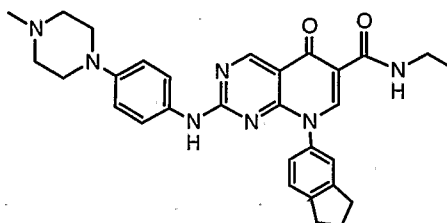
8-Indan-5-yl-2-[4-(4-methyl-piperazin-1-yl)-phenylamino]-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid methylamide (Cpd 8)



To a solution of 8-indan-5-yl-2-[4-(4-methyl-piperazin-1-yl)-phenylamino]-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid ethyl ester Cpd 1 (Example 1(g), 5 mg) in 1 mL of methanol was added 1 mL of methylamine (40 wt.% in water). The solution was stirred at 70°C for 30 minutes. The solvent was evaporated and the product was purified by preparative HPLC. 1.7 mg of 8-indan-5-yl-2-[4-(4-methyl-piperazin-1-yl)-phenylamino]-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid methylamide Cpd 8 was obtained as yellow solid. $^1\text{H NMR}$ (400MHz, CDCl_3) δ (ppm): 9.65 (s, 1H), 9.36 (s, 1H), 8.84 (s, 1H), 7.42 (d, 1H), 7.23 (m, 3H), 7.17 (d, 1H), 6.67 (br, 2H), 3.14 (m, 4H), 3.02 (m, 7H), 2.59 (m, 4H), 2.37 (s, 3H), 2.22 (m, 2H). Mass Spectrum (LCMS, ESI pos.) Calcd. For $\text{C}_{29}\text{H}_{31}\text{N}_7\text{O}_2$: 510.25 (M + H), Found: 510.2.

Example 9

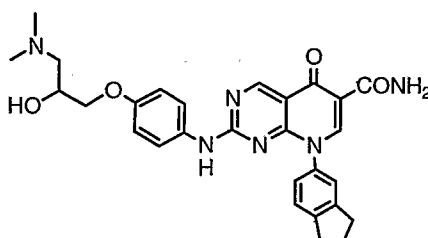
8-Indan-5-yl-2-[4-(4-methyl-piperazin-1-yl)-phenylamino]-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid ethylamide (Cpd 9)



To a solution of 8-indan-5-yl-2-[4-(4-methyl-piperazin-1-yl)-phenylamino]-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid ethyl ester Cpd 1 (Example 1(g), 5 mg) in 1 mL of methanol was added 1 mL of ethylamine (2 M in methanol). The solution was stirred at 70 °C for 30 minutes. The solvent was evaporated and the product was purified by preparative HPLC as the formic acid salt (1 mg, yellow solid). ¹H NMR (400MHz, CDCl₃) δ (ppm): 9.71 (m, 1H), 9.35 (s, 1H), 8.83 (s, 1H), 8.24 (br, 1H), 7.69 (br, 1H), 7.42 (d, 1H), 7.27 (m, 3H), 7.17 (d, 1H), 6.67 (br, 2H), 3.50 (m, 2H), 3.25 (m, 4H), 3.03 (m, 4H), 2.92 (m, 4H), 2.55 (s, 3H), 2.22 (m, 2H), 1.27 (t, 3H). Mass Spectrum (LCMS, ESI pos.) Calcd. For C₃₀H₃₃N₇O₂: 524.27 (M + H), Found: 524.3.

Example 10

2-[4-(3-Dimethylamino-2-hydroxy-propoxy)-phenylamino]-8-indan-5-yl-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid amide (Cpd 10)

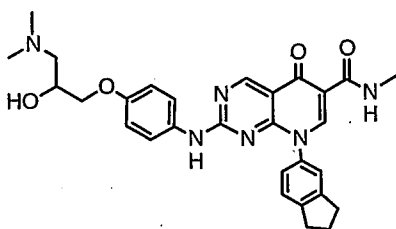


Using the procedure outlined in Example 7 the title compound was prepared from 2-[4-(3-dimethylamino-2-hydroxy-propoxy)-phenylamino]-8-indan-5-yl-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid ethyl ester (from Example 2(c), 5 mg). 4.3 mg of 2-[4-(3-dimethylamino-2-hydroxy-propoxy)-phenylamino]-8-indan-5-yl-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid amide was obtained as a yellow

solid. ^1H NMR (400MHz, $\text{DMSO-}d_6$) δ (ppm): 10.32 (br, 1H), 9.20 (s, 1H), 9.02 (br, 1H), 8.52 (s, 1H), 7.63 (d, 1H), 7.45 (m, 2H), 7.32 (m, 3H), 6.59 (br, 2H), 4.89 (br, 1H), 3.88 (m, 2H), 3.75 (m, 1H), 3.00 (m, 4H), 2.37 (m, 2H), 2.23 (s, 6H), 2.14 (m, 2H). Mass Spectrum (LCMS, ESI pos.) Calcd. For $\text{C}_{28}\text{H}_{30}\text{N}_6\text{O}_4$: 515.23 (M + H), Found: 515.3.

Example 11

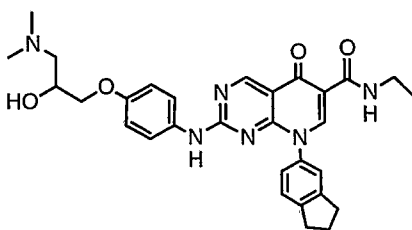
2-[4-(3-Dimethylamino-2-hydroxy-propoxy)-phenylamino]-8-indan-5-yl-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid methylamide (Cpd 11)



To a solution of 2-[4-(3-dimethylamino-2-hydroxy-propoxy)-phenylamino]-8-indan-5-yl-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid ethyl ester (from Example 2(c), 8 mg). in 1 mL of methanol was added 1 mL of methylamine (40 wt.% in water). The solution was stirred at 70 °C for 30 minutes. The solvent was evaporated to yield a yellow solid (6.6 mg). ^1H NMR (400MHz, CDCl_3) δ (ppm): 9.64 (m, 1H), 9.35 (s, 1H), 8.82 (s, 1H), 7.39 (m, 2H), 7.27 (m, 1H), 7.15 (m, 2H), 6.66 (br, 2H), 4.06 (m, 1H), 3.93 (m, 2H), 3.02 (m, 5H), 2.89 (m, 4H), 2.56 (dd, 1H), 2.35 (m, 7H), 2.22 (m, 2H). Mass Spectrum (LCMS, ESI pos.) Calcd. For $\text{C}_{29}\text{H}_{32}\text{N}_6\text{O}_4$: 529.25 (M + H), Found: 529.2.

Example 12

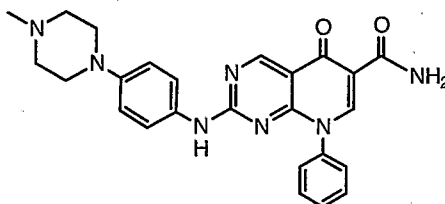
2-[4-(3-Dimethylamino-2-hydroxy-propoxy)-phenylamino]-8-indan-5-yl-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid ethylamide (Cpd 12)



To a solution of 2-[4-(3-dimethylamino-2-hydroxy-propoxy)-phenylamino]-8-indan-5-yl-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid ethyl ester (from Example 2(c), 8 mg). in 1 mL of methanol was added 1 mL of ethylamine (2M in methanol). The solution was stirred at 70 °C for 30 minutes. The solvent was evaporated and 2-[4-(3-dimethylamino-2-hydroxy-propoxy)-phenylamino]-8-indan-5-yl-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid ethylamide was purified by preparative HPLC as the trifluoroacetic acid salt (2.7 mg, brown solid). ¹H NMR (400MHz, CD₃OD) δ (ppm): 10.07 (br, 1H), 9.27 (s, 1H), 8.69 (s, 1H), 7.46 (m, 1H), 7.34 (m, 4H), 7.26 (m, 1H), 6.64 (br, 2H), 4.34 (m, 1H), 3.94 (m, 2H), 3.46 (m, 2H), 3.00 (m, 12H), 2.23 (m, 2H), 1.25 (t, 3H). Mass Spectrum (LCMS, ESI pos.) Calcd. For C₃₀H₃₄N₆O₄: 543.26 (M + H), Found: 543.2.

Example 13

2-[4-(4-Methyl-piperazin-1-yl)-phenylamino]-5-oxo-8-phenyl-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid amide (Cpd 13)



A. 4-[(2-Cyano-ethyl)-phenyl-amino]-2-methylsulfanyl-pyrimidine-5-carboxylic acid ethyl ester.

The title compound was prepared from ethyl 4-chloro-2-methylthio-5-pyrimidinecarboxylate (3.7 g, 15.8 mmol) and 3-phenylamino-propionitrile (2.3 g, 15.8 mmol) according to the procedure outlined in Example 1 (B). The product was purified chromatographically (silica, EtOAc/ hexanes 1:20-1:2, v/v). A white solid was obtained (3.5 g, 65%). ¹H NMR (300MHz, CDCl₃) δ (ppm): 8.32 (s, 1H), 7.34(m, 2H), 7.20 (m, 1H), 7.13 (m, 2H), 4.32 (t, J = 7.1Hz, 2H), 3.56 (q, J = 7.1Hz, 2H), 2.75 (t, J = 7.1Hz, 2H), 2.55 (s, 3H), 1.00 (t, J = 7.2Hz, 3H).

B. 2-Methylsulfanyl-5-oxo-8-phenyl-5,6,7,8-tetrahydro-pyrido[2,3-d]pyrimidine-6-carbonitrile.

The title compound was prepared from 4-[(2-cyano-ethyl)-phenyl-amino]-2-methylsulfanyl-pyrimidine-5-carboxylic acid ethyl ester (0.78 g, 2.27 mmol) according to the procedure outlined in Example 1 (C). The product was purified chromatographically (silica, EtOAc/ hexanes 1:1-1:0, v/v). A yellow solid was obtained (0.39 g, 58%). ¹H NMR (300MHz, CDCl₃) indicated that the presence of both enol and keto forms in a 1:1 ratio.

C. 2-Methylsulfanyl-5-oxo-8-phenyl-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carbonitrile

The title compound was prepared from 2-methylsulfanyl-5-oxo-8-phenyl-5,6,7,8-tetrahydro-pyrido[2,3-d]pyrimidine-6-carbonitrile (0.83 g, 2.8 mmol) according to the procedure outlined in Example 1 (D). The product was purified chromatographically (silica, EtOAc/ hexanes (1:5-1:2.5, v/v) and obtained as a white solid (0.73 g, 89%). ¹H NMR (300MHz, CDCl₃) δ (ppm): 9.42 (s, 1H), 8.59 (s, 1H), 7.37 (m, 2H), 7.24 (m, 1H), 7.14 (m, 2H), 2.37 (s, 3H).

D. 2-Methanesulfonyl-5-oxo-8-phenyl-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carbonitrile

The title compound was prepared from 2-methylsulfanyl-5-oxo-8-phenyl-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carbonitrile (0.73 g, 2.5 mmol) according to the procedure outlined in Example 1 (E). The product was obtained as an off-white solid (0.77 g, 95%). ¹H NMR (300MHz, CDCl₃) δ (ppm): 9.51 (s, 1H), 8.62 (s, 1H), 7.38 (m, 2H), 7.24 (m, 1H), 7.14 (m, 2H), 3.20 (s, 3H).

E. 2-[4-(4-Methyl-piperazin-1-yl)-phenylamino]-5-oxo-8-phenyl-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carbonitrile

Using the procedure outlined in Example 1(G) the title compound was prepared from 4-(4-methyl-piperazin-1-yl)-phenylamine (32 mg, 0.16 mmol) and 2-methanesulfonyl-5-oxo-8-phenyl-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carbonitrile (Example 13 (D) above, 50 mg, 0.15 mmol). The product was obtained as a yellow solid (17.1 mg). ¹H NMR (300MHz, CDCl₃) δ (ppm): 9.34 (s, 1H), 8.55 (br, 1H), 7.61 (m, 3H),

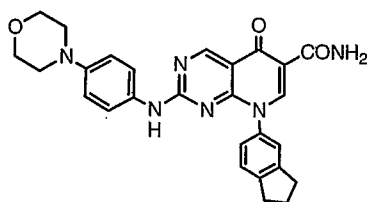
7.41 (d, 2H), 7.24 (m, 2H), 6.55 (d, 2H), 3.00 (m, 4H), 2.55 (m, 4H), 2.35 (s, 3H). Mass Spectrum (LCMS, ESI pos.) Calcd. For $C_{25}H_{23}N_7O$: 438.20 (M + H), Found: 438.5.

F. 2-[4-(4-Methyl-piperazin-1-yl)-phenylamino]-5-oxo-8-phenyl-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid amide

To a solution of 2-[4-(4-Methyl-piperazin-1-yl)-phenylamino]-5-oxo-8-phenyl-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carbonitrile (Example 13 F, 9 mg) in 1 mL of *t*-butanol was added potassium hydroxide (ground, 5 mg). The mixture was stirred at 85 °C for 1 hour. After cooling to rt, water was added and the precipitates were extracted into EtOAc. The organic layer was washed with brine and dried over Na_2SO_4 . The solvent was evaporated under vacuum to leave 2-[4-(4-methyl-piperazin-1-yl)-phenylamino]-5-oxo-8-phenyl-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid amide as a yellow solid (7.2 mg, 79%). 1H NMR (300MHz, $CDCl_3$) δ (ppm): 10.64 (br, 1H), 10.30 (s, 1H), 9.17 (s, 1H), 7.71 (m, 3H), 7.53 (br, 1H), 7.43 (m, 2H), 6.94 (br, 2H), 6.35 (br, 2H), 5.06 (br, 1H), 3.12 (m, 4H), 2.59 (m, 4H), 2.37 (s, 3H). Mass Spectrum (LCMS, ESI pos.) Calcd. For $C_{25}H_{25}N_7O_2$: 456.51 (M + H), Found: 456.6.

Example 14

8-Indan-5-yl-2-(4-morpholin-4-yl-phenylamino)-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid amide
(Cpd 14)

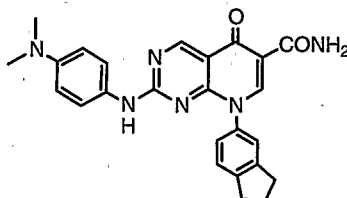


Using the procedure outlined in Example 7, the title compound was prepared from 8-indan-5-yl-2-(4-morpholin-4-yl-phenylamino)-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid ethyl ester (from Example 3 above, 9 mg, 0.017 mmol). 8-Indan-5-yl-2-(4-morpholin-4-yl-phenylamino)-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid amide was obtained as a yellow solid (8.6 mg, 100%). 1H NMR (400MHz, CD_2Cl_2/CD_3OD (20:1 v/v)) δ (ppm): 9.22 (br, 1H), 8.68 (br, 1H), 7.35

(br, 1H), 7.10-7.26 (m, 4H), 6.57 (br, 2H), 3.75 (m, 4H), 2.96 (m, 8H), 2.11 (m, 2H). Mass Spectrum (LCMS, ESI pos.) Calcd. For $C_{27}H_{26}N_6O_3$: 483.21 (M + H), Found: 483.2.

Example 15

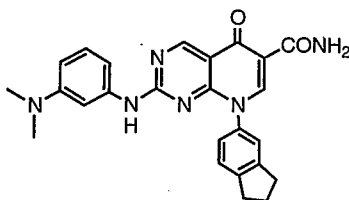
2-(4-Dimethylamino-phenylamino)-8-indan-5-yl-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid amide (Cpd 15)



Using the procedure outlined in Example 7, the title compound was prepared from 2-(4-dimethylamino-phenylamino)-8-indan-5-yl-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid ethyl ester (from Example 4 above, 4.9 mg, 0.010 mmol). 2-(4-Dimethylamino-phenylamino)-8-indan-5-yl-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid amide was obtained as a yellow solid (3.8 mg, 83%). 1H NMR (400MHz, CD_2Cl_2/CD_3OD (20:1 v/v)) δ (ppm): 9.19 (br, 1H), 8.68 (s, 1H), 7.66 (d, $J = 9.2$ Hz, 1H), 7.35 (d, $J = 7.9$ Hz, 1H), 7.22 (s, 1H), 7.11 (d, $J = 7.9$ Hz, 1H), 6.68 (d, $J = 9.2$ Hz, 1H), 6.38 (br, 1H), 2.94 (m, 4H), 2.79 (s, 6H), 1.96 (m, 2H). Mass Spectrum (LCMS, ESI pos.) Calcd. For $C_{25}H_{24}N_6O_2$: 444.1.20 (M + H), Found: 441.2.

Example 16

2-(3-Dimethylamino-phenylamino)-8-indan-5-yl-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid amide (Cpd 16)

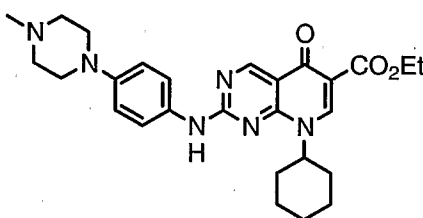


Using the procedure outlined in Example 7 the title compound was prepared from 2-(3-dimethylamino-phenylamino)-8-indan-5-yl-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid ethyl ester (from Example 5 above, 3.3 mg, 0.007 mmol). 2-(3-Dimethylamino-phenylamino)-8-indan-5-yl-5-oxo-5,8-dihydro-pyrido[2,3-

d]pyrimidine-6-carboxylic acid amide was obtained as a yellow solid (2.7 mg, 88%). ¹H NMR (400MHz, CD₂Cl₂/CD₃OD (20:1 v/v)) δ (ppm): 9.26 (s, 1H), 8.68 (s, 1H), 7.33 (d, *J* = 7.5 Hz, 1H), 7.22 (s, 1H), 7.18 (d, *J* = 7.5 Hz, 1H), 6.84 (br, 1H), 6.80 (d, *J* = 7.7 Hz, 1H), 6.54 (br, 1H), 6.36 (d, *J* = 7.7 Hz, 1H), 2.96 (m, 4H), 2.71 (s, 6H), 2.10 (m, 2H). Mass Spectrum (LCMS, ESI pos.) Calcd. For C₂₅H₂₄N₆O₂: 441.20 (M + H), Found: 441.2.

Example 17

8-Cyclohexyl-2-[4-(4-methyl-piperazin-1-yl)-phenylamino]-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid ethyl ester (Cpd 17)



A. 3-Cyclohexylamino-propionic acid ethyl ester

Cyclohexylamine (0.86 g, 8.7 mmol) and 3-chloro-propionic acid ethyl ester (1.18 g, 8.67 mmol) were combined neat and K₂CO₃ (1.2 g, 8.7 mmol) and a catalytic amount of tetrabutylammonium iodide (ca. 5 mg) was added. The mixture was heated at 80 °C overnight. The resulting mixture was then partitioned between water and DCM. The organic layer was dried (MgSO₄) and concentrated to afford 1.25 g (72%) of the title compound. ¹H-NMR (400 MHz, CDCl₃) δ ppm 4.14 (q, 2H, *J* = 7.2Hz), 2.90 (t, 2H, *J* = 6.6Hz), 2.50 (t, 2H, *J* = 6.6Hz), 1.86-1.89 (m, 2H), 1.70- 1.75 (m, 2H), 1.58-1.62 (m, 2H), 1.25 (t, 1H, *J* = 7.2Hz).

B. 4-[Cyclohexyl-(2-ethoxycarbonyl-ethyl)-amino]-2-methylsulfanyl-pyrimidine-5-carboxylic acid ethyl ester

3-Cyclohexylamino-propionic acid ethyl ester (1.0 g, 5.0 mmol) and 4-chloro-2-methylsulfanyl-pyrimidine-5-carboxylic acid ethyl ester (1.17 g, 5.02 mmol) were combined in DCM (15 mL) and diisopropylethylamine (0.81 g, 6.3 mmol) was added. After 16 h, the solution was partitioned between water and DCM and the organic layer was dried (MgSO₄) and concentrated. Chromatography (0-20 % EtOAc/ hexanes gradient) provided 1.63 g (84%) of the title compound. ¹H-NMR (400 MHz, CDCl₃) δ ppm 8.39 (s,

1H) 5.30 (s, 1H), 4.30 (q, 2H, J=7.1Hz), 4.14 (q, 1H, J=7.1Hz), 3.76-3.80 (m, 2H), 2.65-2.69 (m, 2H), 2.49 (s, 3H), 1.81-1.84 (m, 2H), 1.34-1.40 (m, 7H), 1.12-1.27 (m, 7H).

C. 8-Cyclohexyl-2-methylsulfanyl-5-oxo-5,6,7,8-tetrahydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid ethyl ester

Sodium (25 wt % dispersion in paraffin wax, 0.10g, 3.8 mmol) was added to *t*-butanol (1.8 mL) at rt. After 10 minutes, a solution of 4-[cyclohexyl-(2-ethoxycarbonyl-ethyl)-amino]-2-methylsulfanyl-pyrimidine-5-carboxylic acid ethyl ester (1.0 g, 2.5 mmol) in 10 mL of toluene was added to the sodium *t*-butoxide solution and the resulting mixture was heated at 90 °C for 30 minutes. The reaction mixture was then cooled and the solution was adjusted to pH 7 using a 1N HCl solution. The solution was then extracted with EtOAc (2 X 20 mL) and the organic layer was dried (MgSO₄) and concentrated to provide 0.55 g, (42%) of the title compound. ¹H NMR indicated the presence of both enol and keto forms in a 1:1.75 ratio. ¹H-NMR (400 MHz, CDCl₃) δ ppm 8.63 (s, 1H), 8.18 (s, 1H), 4.76-4.82 (m), 4.58-4.68 (m), 4.16-4.36 (m), 3.91-3.96 (m), 3.60-3.64 (m), 3.46-3.49 (m), 2.53 (s, 3H), 2.50 (s, 5.25H), 1.86-1.89 (m), 1.71-1.73 (m), 1.32-1.56 (m), 1.26 (t, J=7.2Hz), 1.10-1.21 (m).

D. 8-Cyclohexyl-2-methylsulfanyl-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid ethyl ester

Bromine (0.15 g, 0.94 mmol) was added to a solution of 8-cyclohexyl-2-methylsulfanyl-5-oxo-5,6,7,8-tetrahydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid ethyl ester (0.28 g, 0.79 mmol) in DCM (10 mL). After 5 min, the solution was concentrated and the crude residue was redissolved in DCM (10 mL) and diisopropylethylamine (0.42 mL, 2.4 mmol) was added. After 15 h, the reaction mixture was partitioned between water and DCM, the organic layer was separated, dried (MgSO₄) and concentrated to provide 0.28 g (87%) of the title compound.). Mass Spectrum (LCMS, ESI pos.) Calcd. For C₁₇H₂₁N₃O₃S: 347.13, found: (M + H) 348.3.

E. 8-Cyclohexyl-2-methanesulfonyl-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid ethyl ester

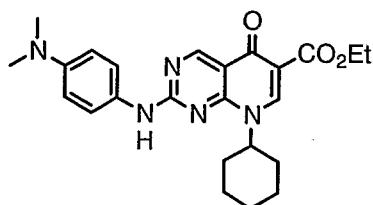
m-CPBA (0.33 g, 1.5 mmol of a 70% w/w mixture) was added to a solution of 8-cyclohexyl-2-methylsulfonyl-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid ethyl ester (0.206 g, 0.59 mmol) in DCM (15 mL). After 2 hours, a 10% solution of Na₂SO₃ (1 mL) was added and the mixture was partitioned between sat. NaHCO₃ and DCM. The organic layer was dried (MgSO₄) and concentrated to provide 0.22 g of the title compound. Mass Spectrum (LCMS, ESI pos.) Calcd. For C₁₇H₂₁N₃O₅S: 379.12, found: (M + H) 380.1.

F. 8-Cyclohexyl-2-[4-(4-methyl-piperazin-1-yl)-phenylamino]-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid ethyl ester

8-Cyclohexyl-2-methanesulfonyl-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid ethyl ester (20 mg, 0.051 mmol) and 4-(4-methyl-piperazin-1-yl)-phenylamine (10 mg, 0.051 mmol) were combined in *i*-PrOH (2 mL) and heated to 80 °C. After 14 h, the solution was concentrated and purified by preparative HPLC (30 mL/ min 0-100% H₂O/ MeCN gradient over 10 min) to provide 7.2 mg (29%) of 8-cyclohexyl-2-[4-(4-methyl-piperazin-1-yl)-phenylamino]-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid ethyl ester. ¹H-NMR (400 MHz, CDCl₃) δ ppm 9.32 (s, 1 H), 8.31 (s, 1 H), 7.57 (d, 2 H, J=9.0Hz), 6.96 (d, 1H, J=8.9Hz), 4.40 (q, 2 H, J=7.1Hz), 3.25-3.46 (m, 8 H), 2.82-2.84 (m, 3 H), 1.49-2.0 (m, 8 H), 1.41 (t, 3 H, J=7.1Hz). Mass Spectrum (LCMS, ESI pos.) Calcd. For C₂₇H₃₄N₆O₃: 490.27, found: (M + H) 491.3.

Example 18

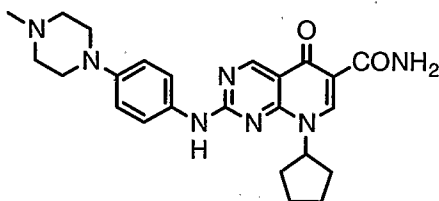
8-Cyclohexyl-2-(4-dimethylamino-phenylamino)-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid ethyl ester (Cpd 18)



8-Cyclohexyl-2-methanesulfonyl-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid ethyl ester (Example 17E) (20 mg, 0.051 mmol) and 4-*N,N*-dimethylaminoaniline (7.8 mg, 0.057 mmol) were combined in *i*-PrOH (1 mL) and heated to 80 °C. After 14 h, the solution was concentrated and purified by preparative HPLC (30 mL/ min 0-100% H₂O/ MeCN gradient over 10 min) to provide 3.4 mg of 8-cyclohexyl-2-(4-dimethylamino-phenylamino)-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid ethyl ester. ¹H-NMR (400 MHz, CDCl₃) δ ppm 9.34 (s, 1 H), 8.53 (s, 1 H), 7.73 (m, 1 H), 6.79-6.84 (m, 1 H), 6.62-6.64 (m, 1 H), 5.10-5.17 (m, 1 H), 4.40 (q, 2 H, J=7.0Hz), 3.01 (s, 6 H), 2.46-2.07 (m, 10 H), 1.41 (t, 1H, J=7.0Hz). Mass Spectrum (LCMS, ESI pos.) Calcd. For C₂₄H₂₉N₅O₃: 435.23, found: (M + H) 436.3.

Example 19

8-Cyclopentyl-2-[4-(4-methyl-piperazin-1-yl)-phenylamino]-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid amide (Cpd 19)



A. 3-Cyclopentylamino-propionic acid ethyl ester

Cyclopentylamine (1.72 g, 17.5 mmol) and 3-chloro-propionic acid ethyl ester (2.4 g, 18 mmol) were combined neat and K₂CO₃ (2.4 g, 18 mmol) and a catalytic amount of tetrabutylammonium iodide (ca. 5 mg) was added. The mixture was heated at 80 °C overnight. The resulting mixture was then partitioned between water and DCM. The organic layer was dried (MgSO₄) and concentrated to provide 2.68 g (83%) of the title compound. ¹H-NMR (400 MHz, CDCl₃) δ ppm 4.13 (p, 2H, J=7.0Hz), 3.07 (p, 1H, J=6.7Hz), 2.81-2.94 (m, 4 H), 2.51 (t, 1H, J=6.5Hz), 2.44 (t, 1H, J=7.4Hz), 1.29-1.88 (m, 6 H), 1.25 (t, 3H, J=7.1Hz)

B. 8-Cyclopentyl-2-methylsulfanyl-5-oxo-5,6,7,8-tetrahydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid ethyl ester

3-Cyclopentylamino-propionic acid ethyl ester (1.0 g, 5.4 mmol) and 4-chloro-2-methylsulfanyl-pyrimidine-5-carboxylic acid ethyl ester (1.25 g, 5.4 mmol) were combined in DCM (10 mL) and diisopropylethylamine (0.83 g, 6.5 mmol) was added. After 16 h, the solution was partitioned between water and DCM and the organic layer was dried (MgSO₄) and concentrated. Chromatography (0-20 % EtOAc/ hexanes gradient) provided the title compound that was directly carried on to the next step. Sodium (25 wt% dispersion in paraffin wax, 0.25 g, 6.0 mmol) was added to *t*-butanol (5.0 mL) at rt. After 10 minutes, a solution of 4-[cyclopentyl-(2-ethoxycarbonyl-ethyl)-amino]-2-methylsulfanyl-pyrimidine-5-carboxylic acid ethyl ester (2.0 g, 5.4 mmol) in 10 mL of toluene was added to the sodium *t*-butoxide solution and the resulting mixture was heated at 90 °C for 30 minutes. The reaction mixture was then cooled and the solution was adjusted to pH 7 using a 1N HCl solution. The solution was then extracted with EtOAc (2 X 20 mL) and the organic layer was dried (MgSO₄) and concentrated to provide 0.26 g (14%). ¹H-NMR (400 MHz, CDCl₃) δ ppm 12.0 (br s, 1 H), 8.20 (s, 1 H), 5.10-5.18 (m, 1 H), 4.26-4.31 (m, 3 H), 3.72 (q, 2H, J=7.0Hz), 2.50 (s, 3 H), 1.63-1.86 (m, 5 H), 1.20-1.35 (m, 5 H).

C. 8-Cyclopentyl-2-methylsulfanyl-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid ethyl ester

Bromine (0.13 g, 0.82 mmol) was added to a solution of 8-Cyclopentyl-2-methylsulfanyl-5-oxo-5,6,7,8-tetrahydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid ethyl ester (0.34 g, 0.82 mmol) in DCM (5 mL). After 15 min, the solution was concentrated and the crude residue was redissolved in DCM (5 mL) and triethylamine (0.16 mL, 0.24 mmol) was added. After 15 h, the reaction mixture was partitioned between water and DCM, the organic layer was separated, dried (MgSO₄) and concentrated to provide the title compound. Mass Spectrum (LCMS, ESI pos.) Calcd. For C₁₆H₁₉N₃O₃S: 333.11, found: (M + H) 334.1.

D. 8-Cyclopentyl-2-methanesulfonyl-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid ethyl ester

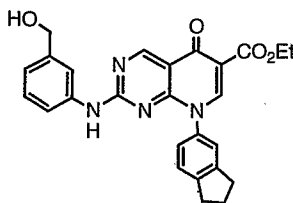
m-CPBA (0.45 g, 2.05 mmol of a 77% powder) was added to a solution of 8-cyclopentyl-2-methylsulfonyl-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid ethyl ester (0.27 g, 0.82 mmol) in DCM (5 mL). After 2 hours, a 10% solution of Na₂SO₃ (2 mL) was added and the mixture was partitioned between sat. NaHCO₃ and DCM. The organic layer was dried (MgSO₄) and concentrated to provide the title compound. Mass Spectrum (LCMS, ESI pos.) Calcd. For C₁₆H₁₉N₃O₅S: 365.10, found: (M + H) 366.1.

E. 8-Cyclopentyl-2-[4-(4-methyl-piperazin-1-yl)-phenylamino]-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid amide

8-Cyclopentyl-2-methanesulfonyl-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid ethyl ester (45 mg, 0.12 mmol) and 4-(4-methyl-piperazin-1-yl)-phenylamine (23 mg, 0.12 mmol) were combined in *i*-PrOH (1 mL) and heated to 80 °C. After 14 h, the solution was concentrated and purified by preparative HPLC (30 mL/min 0-100% H₂O/ MeCN gradient over 10 min) to provide 19.8 mg of 8-cyclopentyl-2-[4-(4-methyl-piperazin-1-yl)-phenylamino]-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid ethyl ester. The ester was dissolved in MeOH (2 mL) and cooled to -78 °C in a high pressure vessel. Ammonia was bubbled into the solution for 1 min and the vessel was sealed and allowed to warm to rt. After 14 h, the solution was cooled to -78 °C, the vessel was opened and the solution was allowed to warm to rt. The solution was concentrated to provide 5.4 mg of 8-cyclopentyl-2-[4-(4-methyl-piperazin-1-yl)-phenylamino]-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid amide. ¹H-NMR (400 MHz, CDCl₃) δ ppm 9.30 (s, 1 H), 8.51 (s, 1 H), 8.34 (s, 1 H), 7.53 (d, 2 H, J=8.9Hz), 6.94 (d, 2 H, J=9.0Hz), 5.23-5.52 (m, 4 H), 4.38 (q, 2 H, J=7.1Hz), 3.34-3.36 (m, 4 H), 3.00-3.01 (m, 4 H), 2.60 (s, 3 H), 2.21-2.28 (m, 2 H), 1.80-1.93 (m, 6 H), 1.40 (t, 3 H, J=7.1Hz). Mass Spectrum (LCMS, ESI pos.) Calcd. For C₂₆H₃₂N₆O₃: 476.25, found: (M + H) 477.3.

Example 20

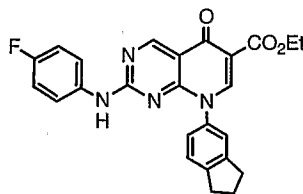
2-(3-Hydroxymethyl-phenylamino)-8-indan-5-yl-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid amide (Cpd 20)



Using the procedure outlined in Example 1(g) the title compound was prepared from (3-amino-phenyl)-methanol (3.2 mg, 0.026 mmol) and 8-indan-5-yl-2-methanesulfonyl-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid ethyl ester (from Example 1(e) above, 10 mg, 0.026 mmol). 2-(3-Hydroxymethyl-phenylamino)-8-indan-5-yl-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid amide was obtained as a white solid. ^1H NMR (400MHz, CDCl_3) δ (ppm): 9.37 (br s, 1 H), 8.50 (s, 1 H), 7.35-7.45 (m, 3H), 7.02-7.21 (m, 3H), 5.30 (s, 2H), 4.43 (br s, 1H), 4.39 (dd, 2H, $J=7.1\text{Hz}$, $J=14.3\text{Hz}$), 3.05 (td, 4H, $J=7.5\text{Hz}$, $J=28.2\text{Hz}$), 2.20-2.27 (m, 2H), 1.39 (t, 3H, $J=7.1\text{Hz}$). Mass Spectrum (LCMS, ESI pos.) Calcd. For $\text{C}_{24}\text{H}_{21}\text{N}_5\text{O}_3$: 427.16, found: (M + H) 428.1.

Example 21

2-(4-Fluoro-phenylamino)-8-indan-5-yl-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid ethyl ester (Cpd 21)

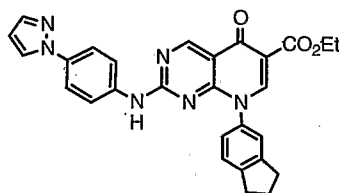


Using the procedure outlined in Example 1(g) 2-(4-fluoro-phenylamino)-8-indan-5-yl-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid ethyl ester was prepared from 4-fluoroaniline (6 mg, 0.05 mmol) and 8-indan-5-yl-2-methanesulfonyl-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid ethyl ester (from Example 1(e) above, 21 mg, 0.050 mmol). Purification by preparative HPLC (30 mL/ min 0-100% H_2O /

MeCN gradient over 10 min) provided 2-(4-fluoro-phenylamino)-8-indan-5-yl-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid ethyl ester (3.6 mg). $^1\text{H NMR}$ (400MHz, CDCl_3) δ (ppm): 9.21 (s, 1H), 8.44 (s, 1H), 7.84-7.94 (m, 1H), 7.10-7.48 (m, 6H), 4.23 (dd, 1H, $J=7.2\text{Hz}$, $J=14.5\text{Hz}$), 2.96 (td, 1H, $J=7.3\text{Hz}$, $J=25.1\text{Hz}$), 2.10-2.18 (m, 2H), 1.18-1.40 (m, 7H).). Mass Spectrum (LCMS, ESI pos.) Calcd. For $\text{C}_{25}\text{H}_{21}\text{FN}_4\text{O}_3$: 444.16.14, found: (M + H) 445.1.

Example 22

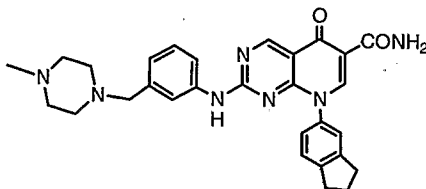
8-Indan-5-yl-5-oxo-2-(4-pyrazol-1-yl-phenylamino)-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid amide (Cpd 22)



Using the procedure outlined in Example 1(g) 8-indan-5-yl-5-oxo-2-(4-pyrazol-1-yl-phenylamino)-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid amide was prepared from 4-pyrazol-1-yl-phenylamine (8.0 mg, 0.053 mmol) and 8-indan-5-yl-2-methanesulfonyl-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid ethyl ester (from Example 1(e) above, 20 mg, 0.053 mmol). 8-Indan-5-yl-5-oxo-2-(4-pyrazol-1-yl-phenylamino)-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid amide was obtained as a white solid. $^1\text{H NMR}$ (400MHz, CDCl_3) δ (ppm): 9.30(br s, 1H), 8.48 (s, 1H), 7.75 (s, 1H), 7.64 (s, 1H), 7.13-7.23 (m, 5H), 6.39 (s, 1H), 4.31 (q, 1H, $J=7.1\text{Hz}$), 3.02 (t, 1H, $J=7.3\text{Hz}$), 2.94 (t, 1H, $J=7.3\text{Hz}$), 2.17 (p, 1H, $J=7.5\text{Hz}$), 1.32 (t, 1H, $J=7.1\text{Hz}$). Mass Spectrum (LCMS, ESI pos.) Calcd. For $\text{C}_{26}\text{H}_{21}\text{N}_7\text{O}_2$: 463.18, found: (M + H) 464.1.

Example 23

8-Indan-5-yl-2-[3-(4-methyl-piperazin-1-ylmethyl)-phenylamino]-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid amide (Cpd 23)



A. 3-(4-Methyl-piperazin-1-ylmethyl)-phenylamine

m-Nitrobenzyl bromide (500 mg, 2.31 mmol) was added to a mixture of 1-methylpiperazine (277 mg, 2.77 mmol) and potassium carbonate (414 g, 3.0 mmol) in 5 mL of DMF. The mixture was stirred at 90 °C for 16 hours. After cooling to room temperature, the mixture was extracted into ethyl acetate (EtOAc), washed with water, brine and then dried with sodium sulfate (Na₂SO₄). Removal of the solvent and chromatography on silica, eluting with EtOAc/CH₃OH/NH₄OH (10:1:0.1, v/v), gave 510 mg of 1-methyl-4-(3-nitro-benzyl)-piperazine, which was converted to the title compound under normal hydrogenation conditions. The titled compound was obtained as a yellow solid (450 mg, 95%). ¹H NMR (400MHz, CDCl₃) δ (ppm): 7.02 (t, *J* = 7.6Hz, 1H), 6.62 (s, 1H), 6.60 (d, *J* = 7.6Hz, 1H), 6.54 (d, *J* = 7.6Hz, 1H), 3.43 (s, 2H), 2.76 (br, 4H), 2.65 (br, 4H), 2.82 (m, 4H), 2.46 (s, 3H).

B. 8-Indan-5-yl-2-methanesulfonyl-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid amide

8-Indan-5-yl-2-methylsulfonyl-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid ethyl ester (from Example 1(d), 200 mg, 0.52 mmol) was dissolved in 2 mL of CH₃OH. To the solution was bubbled ammonia at -78 °C for 5 minutes in a pressure bottle (15 mL). The bottle was capped and warmed up to room temperature and stirred for 16 hours. The solvent was evaporated to leave an off-white solid. The solid was suspended in 50 mL of CH₂Cl₂. To the mixture was added *m*-CPBA (69.5%, 325 mg, 1.3 mmol). The mixture was stirred at r.t. for 4 hrs. An aqueous solution of 10% sodium thiosulfate was added to quench the reaction. After 30 minutes saturated sodium

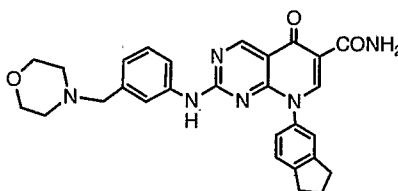
bicarbonate solution was added, and the aqueous solution was extracted by CH_2Cl_2 . The combined CH_2Cl_2 solution was washed with brine and dried over Na_2SO_4 . Removal of the solvent and chromatography on silica, eluting with EtOAc/hexanes (1:1-2:1, v/v) gave 0.18 g (90%) of the title compound as an off-white solid. ^1H NMR (400MHz, $\text{DMSO}-d_6$) δ (ppm): 9.75 (s, 1H), 8.75 (s, 1H), 8.69 (d, $J = 3.3$ Hz, 1H), 7.87 (d, $J = 3.3$ Hz, 1H), 7.49 (s, 1H), 7.46 (d, $J = 8.0$ Hz, 1H), 7.38 (d, $J = 8.0$ Hz, 1H), 3.19 (s, 3H), 2.93 (m, 4H), 2.10(m, 2H).

C. 8-Indan-5-yl-2-[3-(4-methyl-piperazin-1-ylmethyl)-phenylamino]-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid amide

To a suspension of 8-indan-5-yl-2-methanesulfonyl-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid amide (from Example 23 (b), 7 mg) in 1 mL of *i*-PrOH was added 3-(4-methyl-piperazin-1-ylmethyl)-phenylamine (5 mg). The mixture was stirred at 90 °C for 1 hr. After cooling down, the solvent was evaporated and the product was purified chromatographically ($\text{CH}_2\text{Cl}_2/\text{CH}_3\text{OH}/\text{NH}_4\text{OH}$ (10:1:0.1, v/v)). The title compound was obtained as white solid (2.7 mg, 29%). ^1H NMR (400MHz, CDCl_3) δ (ppm): 9.39 (br, 1H), 9.34 (s, 1H), 8.76 (s, 1H), 7.48 (br, 1H), 7.35 (d, $J = 8.0$ Hz, 1H), 7.29 (br, 1H), 7.17 (s, 1H), 7.12 (d, $J = 8.0$ Hz, 1H), 6.94 (br, 2H), 5.67 (br, 1H), 3.29 (br, 2H), 3.00 (t, $J = 7.3$ Hz, 2H), 2.92 (t, $J = 7.3$ Hz, 2H), 2.49 (br, 7H), 2.33 (br, 4H), 2.15 (m, 2H). Mass Spectrum (LCMS, ESI pos.) Calcd. For $\text{C}_{29}\text{H}_{31}\text{N}_7\text{O}_2$: 510.25 (M + H), Found: 510.1.

Example 24

8-Indan-5-yl-2-(3-morpholin-4-ylmethyl-phenylamino)-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid amide (Cpd 24)

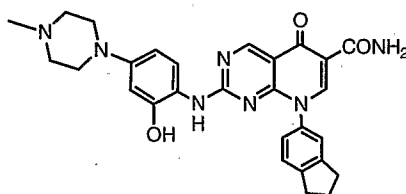


Using the procedure outlined in Example 23 (a and c), the title compound was prepared from 3-morpholin-4-ylmethyl-phenylamine (5 mg) and 8-indan-5-yl-2-

methanesulfonyl-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid amide (from Example 23 (b), 7 mg). Purification by preparative HPLC (32 mL/ min, 5-100% H₂O/ MeCN (0.01% TFA, v/v) gradient over 10 min) gave the title compound as a white solid (3.9 mg, 35%). ¹H NMR (400MHz, CDCl₃) δ (ppm): 9.55 (br, 1H), 9.42 (s, 1H), 8.83 (s, 1H), 7.60 (br, 1H), 7.50 (br, 1H), 7.43 (d, *J* = 8.0 Hz, 1H), 7.24 (s, 1H), 7.21 (d, *J* = 8.0 Hz, 1H), 7.13 (br, 2H), 6.23 (br, 1H), 4.00 (br, 4H), 3.32 (br, 2H), 3.08 (t, *J* = 7.3 Hz, 2H), 3.00 (t, *J* = 7.3 Hz, 2H), 2.72 (br, 2H), 2.23 (m, 2H). Mass Spectrum (LCMS, ESI pos.) Calcd. For C₂₈H₂₈N₆O₃: 497.22 (M + H), Found: 497.1.

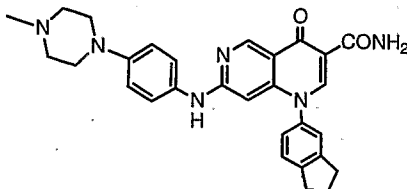
Example 25

2-[2-Hydroxy-4-(4-methyl-piperazin-1-yl)-phenylamino]-8-indan-5-yl-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid amide (Cpd 25)



Using the procedure outlined in Example 23 (c), the title compound was prepared from 2-amino-5-(4-methyl-piperazin-1-yl)-phenol (5 mg, prepared using the procedure outlined in Example 1 (F) from 1-fluoro-2-hydroxy-4-nitrobenzene and 1-methyl-piperazine) and 8-indan-5-yl-2-methanesulfonyl-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid amide (from Example 23 (b), 7 mg). Purification by preparative HPLC (32 mL/ min, 5-100% H₂O/ MeCN (0.01% TFA, v/v) gradient over 10 min) followed by a basic aqueous work-up gave the title compound as a yellow solid (3.7 mg, 40%). ¹H NMR (400MHz, CD₃OD) δ (ppm): 9.25 (br, 1H), 8.73 (s, 1H), 7.44 (d, *J* = 8.4 Hz, 2H), 7.36 (s, 1H), 7.25 (d, *J* = 7.1 Hz, 1H), 6.45 (s, 1H), 6.02 (br, 1H), 3.20 (br, 2H), 3.03 (m, 6H), 2.65 (s, 3H), 2.22 (m, 2H). Mass Spectrum (LCMS, ESI pos.) Calcd. For C₂₈H₂₉N₇O₃: 512.23 (M + H), Found: 512.1.

Example 26

1-Indan-5-yl-7-[4-(4-methyl-piperazin-1-yl)-phenylamino]-
4-oxo-1,4-dihydro-[1,6]naphthyridine-3-carboxylic acid
amide (Cpd 26)

A. 4,6-Dichloro-nicotinic acid ethyl ester

Diethyl 1,3-acetonedicarboxylate (10 mL, 49.5 mmol) was taken in 10 mL of acetic anhydride. To the solution was added trimethylorthoformate (8.2 mL, 49.5 mmol). The mixture was heated to 120 °C for 3 hours. The reaction was then cooled and 10 mL of NH₄OH (30%) was added. After stirring for additional 1 hour, the solution was triturated for 3 times in CH₂Cl₂ to afford 7.3 g of an off-white solid. The solid was suspended in 10 mL of POCl₃ and the mixture was heated at 100 °C for 6 hours. The reaction was cooled, quenched with water, and extracted 3 times with EtOAc. The organic layer was dried over Na₂SO₄ and concentrated in vacuo. Flash chromatography (EtOAc/Hexanes, 1:10 v/v) afforded the title compound as a white solid (6g, 68%). ¹H NMR (400MHz, CDCl₃) δ (ppm): 8.79 (s, 1H), 7.42 (s, 1H), 4.38 (q, *J* = 7.1 Hz, 2H), 1.37 (t, *J* = 7.1 Hz, 3H).

B. 6-Chloro-4-[(2-ethoxycarbonyl-ethyl)-indan-5-yl-amino]-nicotinic acid ethyl ester

To a solution of 4,6-dichloro-nicotinic acid ethyl ester (2 g, 9 mmol) and 3-(indan-5-ylamino)-propionic acid ethyl ester (from Example 1 (A), 2.3 g, 10 mmol) in 5 mL of DMF was added triethylamine (2 g, 20 mmol). The mixture was stirred at 100 °C for 48 hours. The reaction was cooled, quenched with water, and extracted 3 times with EtOAc. The organic layer was dried over Na₂SO₄ and concentrated in vacuo. Flash chromatography (EtOAc/Hexanes, 2:10 v/v) afforded the title compound as a white solid (1.6 g, 44%). ¹H NMR (400MHz, CDCl₃) δ (ppm): 8.22 (s, 1H), 7.15 (d, *J* = 8.0 Hz, 1H), 6.92 (s, 1H), 6.85 (m, 2H), 4.03-4.15 (m, 4H), 3.74 (q, *J* = 7.1Hz, 2H), 2.85 (t, *J* = 7.4Hz, 4H), 2.64 (m, 2H), 2.07 (m, 2H), 1.23 (t, *J* = 7.1Hz, 3H), 1.08 (t, *J* = 7.1Hz, 3H).

C. 7-Chloro-1-indan-5-yl-4-oxo-1,4-dihydro-[1,6]naphthyridine-3-carboxylic acid ethyl ester

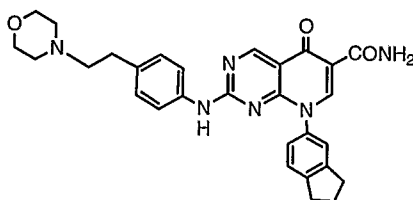
Using the procedures outlined in Example 1 (C and D), the title compound was prepared from 6-chloro-4-[(2-ethoxycarbonyl-ethyl)-indan-5-yl-amino]-nicotinic acid ethyl ester (1.6 g, 4 mmol). A white solid was obtained (500 mg, 34%). ¹H NMR (300MHz, CDCl₃) δ (ppm): 9.38 (s, 1H), 8.46 (s, 1H), 7.47 (d, *J* = 7.8 Hz, 1H), 7.23 (s, 1H), 7.14 (dd, *J* = 2.2 Hz, *J* = 7.8 Hz, 1H), 6.88 (s, 1H), 4.36 (q, *J* = 7.1Hz, 2H), 3.04 (m, 4H), 2.22 (m, 2H), 1.38 (t, *J* = 7.1Hz, 3H).

D. 1-Indan-5-yl-7-[4-(4-methyl-piperazin-1-yl)-phenylamino]-4-oxo-1,4-dihydro-[1,6]naphthyridine-3-carboxylic acid amide

To a solution of 7-chloro-1-indan-5-yl-4-oxo-1,4-dihydro-[1,6]naphthyridine-3-carboxylic acid ethyl ester (40 mg, 0.11 mmol) and 4-(4-Methyl-piperazin-1-yl)-phenylamine (45 mg, 0.23 mmol) in 1 mL of NMP was added triethylamine (24 mg, 0.24 mmol). The reaction was heated in a microwave reactor at 200 °C for 2 hours. The solvent was evaporated under vacuo and the product was purified by preparative HPLC (32 mL/min, 5-100% H₂O/ MeCN (0.01% TFA, v/v) gradient over 15 min). The title compound was obtained as a yellow solid (6.9 mg, 10%). ¹H NMR (400MHz, CD₃OD) δ (ppm): 9.11 (s, 1H), 8.57 (s, 1H), 7.45 (d, *J* = 7.9 Hz, 1H), 7.35 (m, 3H), 7.25 (dd, *J* = 1.9 Hz, *J* = 7.9 Hz, 1H), 6.96 (d, *J* = 8.8 Hz, 2H), 6.13 (s, 1H), 3.40-3.80 (br, 8H), 3.01 (m, 4H), 2.96 (s, 3H), 2.17 (m, 2H). Mass Spectrum (LCMS, ESI pos.) Calcd. For C₂₉H₃₀N₆O₂: 495.24 (M + H), Found: 495.1.

Example 27

8-Indan-5-yl-2-[4-(2-morpholin-4-yl-ethyl)-phenylamino]-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid amide (Cpd 27)



A. 4-(2-Morpholin-4-yl-ethyl)-phenylamine

1-(2-Bromo-ethyl)-4-nitro-benzene (1 g, 4.3 mmol) was added to a mixture of morpholine (435 μ L, 5 mmol) and potassium carbonate (690 mg, 5.0 mmol) in 5 mL of DMSO. The mixture was stirred at 100 °C for 1 hour. After cooling to room temperature, the mixture was extracted into ethyl acetate (EtOAc), washed with water, brine and then dried with sodium sulfate (Na_2SO_4). Removal of the solvent and chromatography on silica, eluting with EtOAc/ $\text{CH}_3\text{OH}/\text{NH}_4\text{OH}$ (10:1:0.1, v/v), gave 950 mg of 4-[2-(4-nitro-phenyl)-ethyl]-morpholine, which was converted to the title compound under normal hydrogenation conditions. The title compound was obtained as a yellow solid (880 mg, 99 %). ^1H NMR (400MHz, CDCl_3) δ (ppm): 6.98 (d, $J = 8.2$ Hz, 2H), 6.61 (d, $J = 8.2$ Hz, 2H), 3.73 (t, $J = 4.5$ Hz, 4H), 3.57 (br, 2H), 2.64-2.71 (m, 2H), 2.45-2.56 (m, 6H).

B. 8-Indan-5-yl-2-[4-(2-morpholin-4-yl-ethyl)-phenylamino]-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid ethyl ester

Using the procedure outlined in Example 1(g) the title compound was prepared from 4-(2-morpholin-4-yl-ethyl)-phenylamine (49 mg, 0.24 mmol) and 8-indan-5-yl-2-methanesulfonyl-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid ethyl ester (from Example 1(e) above, 100 mg, 0.24 mmol). The title compound was obtained as a yellow solid (60 mg, 46%). ^1H NMR (400MHz, CDCl_3) δ (ppm): 9.29 (s, 1H), 8.45 (s, 1H), 7.50 (br, 1H), 7.37 (d, $J = 7.9$ Hz, 1H), 7.21 (m, 3H), 7.13 (d, $J = 7.8$ Hz, 1H), 6.87 (br, 2H), 4.31 (q, $J = 7.0$ Hz, 2H), 3.69 (br, 4H), 2.96 (t, $J = 7.4$ Hz, 2H), 2.91 (t, $J = 7.4$ Hz, 2H), 2.67 (br, 2H), 2.46 (br, 6 H), 2.17 (m, 2H), 1.30 (t, $J = 7.1$ Hz, 3H).

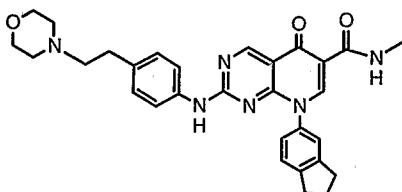
C. 8-Indan-5-yl-2-[4-(2-morpholin-4-yl-ethyl)-phenylamino]-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid amide

Using the procedure outlined in Example 7 the title compound was prepared from 8-indan-5-yl-2-[4-(2-morpholin-4-yl-ethyl)-phenylamino]-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid ethyl ester (20 mg, 0.037 mmol). A yellow solid was obtained (15.8 mg, 84%). ^1H NMR (400MHz, $\text{DMSO}-d_6$) δ (ppm): 10.37 (br, 1H), 9.22 (s, 1H), 9.01 (s, 1H), 8.54 (s, 1H), 7.64 (m, 1H), 7.47 (m, 2H), 7.32 (m, 2H), 6.87 (br, 2H), 3.55 (m, 4H), 3.01 (t, $J = 7.3$ Hz, 2H), 2.93 (t, $J = 7.4$ Hz, 2H), 2.61 (m, 2H), 2.37 (m, 6H),

2.14 (m, 2H). Mass Spectrum (LCMS, ESI pos.) Calcd. For $C_{29}H_{30}N_6O_3$: 511.24 (M + H), Found 511.0.

Example 28

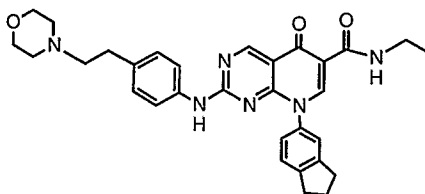
8-Indan-5-yl-2-[4-(2-morpholin-4-yl-ethyl)-phenylamino]-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid methyl amide (Cpd 28)



To a solution of 8-indan-5-yl-2-[4-(2-morpholin-4-yl-ethyl)-phenylamino]-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid ethyl ester (Example 27 (b), 20 mg, 0.037 mmol) in 1 mL methanol was added a solution of methylamine in THF (2N, 2mL). The mixture was stirred at 80 °C for 4 hours. The solvent was removed by vacuum to leave a yellow solid (17mg, 87%). 1H NMR (400MHz, $CDCl_3$) δ (ppm): 10.60 (br, 1H), 9.29 (s, 1H), 8.78 (s, 1H), 7.75 (s, 1H), 7.60 (br, 1H), 7.34 (d, $J = 7.6$ Hz, 1H), 7.20 (m, 2H), 7.12 (d, $J = 7.6$ Hz, 1H), 6.87 (br, 2H), 3.69 (br, 4H), 3.01 (t, $J = 7.3$ Hz, 2H), 2.94 (m, 5H), 2.65 (br, 2H), 2.49 (br, 6H), 2.17 (m, 2H). Mass Spectrum (LCMS, ESI pos.) Calcd. For $C_{30}H_{32}N_6O_3$: 525.25 (M + H), Found 525.0.

Example 29

8-Indan-5-yl-2-[4-(2-morpholin-4-yl-ethyl)-phenylamino]-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid ethyl amide (Cpd 29)

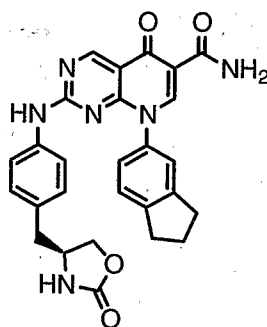


To a solution of 8-indan-5-yl-2-[4-(2-morpholin-4-yl-ethyl)-phenylamino]-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid ethyl ester (Example 27 (b), 20 mg, 0.037 mmol) in 1 mL methanol was added a solution of ethylamine in THF (2N, 2mL). The mixture was stirred at 80 °C for 16 hours. The solvent was removed by vacuum to

leave a yellow solid (12.7mg, 64%). ¹H NMR (400MHz, CDCl₃) δ (ppm): 10.60 (br, 1H), 9.29 (s, 1H), 8.78 (s, 1H), 7.75 (s, 1H), 7.60 (br, 1H), 7.34 (d, *J* = 7.6 Hz, 1H), 7.20 (m, 2H), 7.12 (d, *J* = 7.6 Hz, 1H), 6.87 (br, 2H), 3.69 (br, 4H), 3.42(q, *J* = 7.1 Hz, 2H), 3.01 (t, *J* = 7.3 Hz, 2H), 2.93 (t, *J* = 7.4 Hz, 2H), 2.65 (br, 2H), 2.49 (br, 6H), 2.17 (m, 2H). 1.08 (t, 7.1 Hz, 3H). Mass Spectrum (LCMS, ESI pos.) Calcd. For C₃₁H₃₄N₆O₃: 539.27 (M + H), Found 539.0.

Example 30

(4*S*)-8-Indan-5-yl-5-oxo-2-[4-(2-oxo-oxazolidin-4-ylmethyl)-phenylamino]-5,8-dihydro-pyrido[2,3-*d*]pyrimidine-6-carboxylic acid amide (Cpd 30)



A. (4*S*)-8-Indan-5-yl-5-oxo-2-[4-(2-oxo-oxazolidin-4-ylmethyl)-phenylamino]-5,8-dihydro-pyrido[2,3-*d*]pyrimidine-6-carboxylic acid ethyl ester

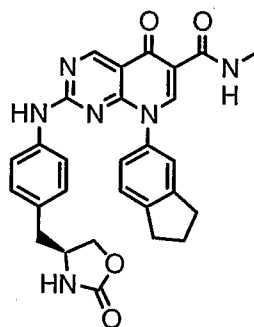
Using the procedure outlined in Example 1(g) the title compound was prepared from (4*S*)-4-(4-amino-benzyl)-1,3-oxazolidin-2-one (46 mg, 0.24 mmol) and 8-indan-5-yl-2-methanesulfonyl-5-oxo-5,8-dihydro-pyrido[2,3-*d*]pyrimidine-6-carboxylic acid ethyl ester (from Example 1(e) above, 100 mg, 0.24 mmol). The title compound was obtained as a white solid (56 mg, 44%). ¹H NMR (400MHz, CDCl₃) δ (ppm): 9.00 (br, 1H), 8.42 (s, 1H), 7.50 (br, 1H), 7.33 (d, *J* = 7.9 Hz, 1H), 7.28 (br, 2H), 7.18 (s, 1H), 7.08 (d, *J* = 7.8 Hz, 1H), 6.81 (br, 2H), 5.88 (s, 1H), 4.41 (t, *J* = 8.2 Hz, 1H), 4.31 (q, *J* = 7.0 Hz, 2H), 4.05 (m, 1H), 3.98 (m, 1H), 2.99 (t, *J* = 7.4 Hz, 2H), 2.92 (t, *J* = 7.4 Hz, 2H), 2.79-2.66 (m, 2H), 2.15 (m, 2H), 1.31 (t, *J* = 7.1 Hz, 3H).

B. (4*S*)-8-Indan-5-yl-5-oxo-2-[4-(2-oxo-oxazolidin-4-ylmethyl)-phenylamino]-5,8-dihydro-pyrido[2,3-*d*]pyrimidine-6-carboxylic acid amide

Using the procedure outlined in Example 7 the title compound was prepared from (4*S*)-8-indan-5-yl-5-oxo-2-[4-(2-oxo-oxazolidin-4-ylmethyl)-phenylamino]-5,8-dihydro-pyrido[2,3-*d*]pyrimidine-6-carboxylic acid ethyl ester (15 mg, 0.028 mmol). A white solid was obtained (9.9 mg, 71%) after a preparative HPLC (32 mL/ min 5-100% MeCN/ H₂O gradient over 10 min) purification. ¹H NMR (400MHz, DMSO-*d*₆) δ (ppm): 10.41 (br, 1H), 9.24 (s, 1H), 9.01 (d, *J* = 3.6 Hz, 1H), 8.54 (s, 1H), 7.70 (s, 1H), 7.64 (d, *J* = 3.9 Hz, 1H), 7.45 (m, 2H), 7.36 (m, 3H), 6.89 (br, 2H), 5.72 (s, 1H), 4.21 (t, *J* = 7.8Hz, 1H), 3.92 (m, 2H), 3.02 (t, *J* = 7.4 Hz, 2H), 2.93 (t, *J* = 7.4 Hz, 2H), 2.73-2.60 (m, 2H), 2.14 (m, 2H). Mass Spectrum (LCMS, ESI pos.) Calcd. For C₂₇H₂₄N₆O₄: 497.10 (M + H), Found 497.0.

Example 31

(4*S*)-8-Indan-5-yl-5-oxo-2-[4-(2-oxo-oxazolidin-4-ylmethyl)-phenylamino]-5,8-dihydro-pyrido[2,3-*d*]pyrimidine-6-carboxylic acid methyl amide (Cpd 31)

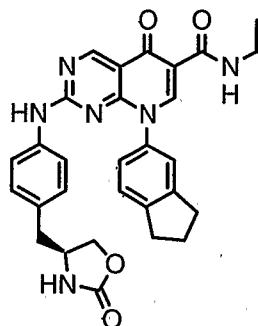


Using the procedure outlined in Example 28 the title compound was prepared from (4*S*)-8-indan-5-yl-5-oxo-2-[4-(2-oxo-oxazolidin-4-ylmethyl)-phenylamino]-5,8-dihydro-pyrido[2,3-*d*]pyrimidine-6-carboxylic acid ethyl ester (20 mg, 0.038 mmol). A white solid was obtained (17.3 mg, 89%) after a preparative HPLC (32 mL/ min 5-100% MeCN/ H₂O gradient over 10 min) purification. ¹H NMR (400MHz, CDCl₃) δ (ppm): 9.58 (t, *J* = 5.6 Hz, 1H), 9.20 (br, 1H), 8.76 (s, 1H), 7.95 (br, 1H), 7.75 (s, 1H), 7.34 (d, *J* = 7.9 Hz, 1H), 7.29 (br, 2H), 7.18 (s, 1H), 7.09 (d, *J* = 7.8 Hz, 1H), 6.85 (br, 2H), 5.22 (s, 1H), 4.42 (t, *J* = 8.2 Hz, 1H), 4.06 (m, 1H), 3.96 (m, 1H), 3.22 (s, 3H), 3.00 (t, *J* = 7.4 Hz, 2H), 2.93 (t, *J* =

7.4 Hz, 2H), 2.80-2.66 (m, 2H), 2.16 (m, 2H). Mass Spectrum (LCMS, ESI pos.) Calcd. For $C_{28}H_{26}N_6O_4$: 511.20 (M + H), Found 511.0.

Example 32

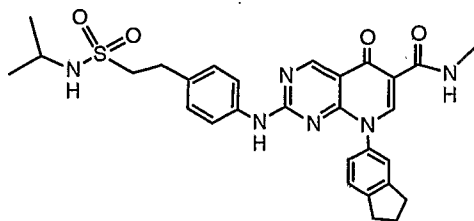
(4*S*)-8-Indan-5-yl-5-oxo-2-[4-(2-oxo-oxazolidin-4-ylmethyl)-phenylamino]-5,8-dihydro-pyrido[2,3-*d*]pyrimidine-6-carboxylic acid ethyl amide (Cpd 32)



Using the procedure outlined in Example 29 the title compound was prepared from (4*S*)-8-indan-5-yl-5-oxo-2-[4-(2-oxo-oxazolidin-4-ylmethyl)-phenylamino]-5,8-dihydro-pyrido[2,3-*d*]pyrimidine-6-carboxylic acid ethyl ester (20 mg, 0.038 mmol). A white solid was obtained (13.5 mg, 68 %) after a preparative HPLC (32 mL/min 5-100% MeCN/ H₂O gradient over 10 min) purification. ¹H NMR (400MHz, CDCl₃) δ (ppm): 9.58 (t, *J* = 5.6 Hz, 1H), 9.20 (br, 1H), 8.76 (s, 1H), 7.95 (br, 1H), 7.75 (s, 1H), 7.34 (d, *J* = 7.9 Hz, 1H), 7.29 (br, 2H), 7.18 (s, 1H), 7.09 (d, *J* = 7.8 Hz, 1H), 6.85 (br, 2H), 5.22 (s, 1H), 4.42 (t, *J* = 8.2 Hz, 1H), 4.06 (m, 1H), 3.96 (m, 1H), 3.44 (m, 2H), 3.00 (t, *J* = 7.4 Hz, 2H), 2.93 (t, *J* = 7.4 Hz, 2H), 2.80-2.66 (m, 2H), 2.16 (m, 2H), 1.21 (t, *J* = 7.3 Hz, 3H). Mass Spectrum (LCMS, ESI pos.) Calcd. For $C_{29}H_{28}N_6O_4$: 525.22 (M + H), Found 525.0.

Example 33

8-Indan-5-yl-2-[4-(2-isopropylsulfamoyl-ethyl)-phenylamino]-5-oxo-5,8-dihydro-pyrido[2,3-*d*]pyrimidine-6-carboxylic acid methyl amide (Cpd 33)



A. 2-(4-Nitro-phenyl)-ethanesulfonyl chloride

1-(2-Bromo-ethyl)-4-nitro-benzene (3 g, 13 mmol) and potassium thioacetate (3 g, 26 mmol) in DMSO (10 mL) were stirred at r.t. for 3 hours. EtOAc was used to dilute the reaction. The organic layer was washed with water twice (2X 100 mL), brine and dried over Na₂SO₄. The solvent was evaporated under vacuum to give a brown solid (~3 g), which was taken in 50 mL of acetic acid. To the stirring solution was added 20 mL of hydrogen peroxide (30% in water). The resulting yellow solution was stirred at r.t. overnight. Water (50 mL) was added and the solvent was evaporated in vacuum with minimal heating. The yellow residue was dried on high vacuum for two days. Then it was suspended in thionyl chloride (18 mL) and the mixture was heated to reflux (80 °C) for 6 hours. The volatiles were evaporated to leave a yellow solid, which was used for next step without purification.

B. 2-(4-Amino-phenyl)-ethanesulfonic acid isopropylamide

2-(4-Nitro-phenyl)-ethanesulfonyl chloride (300 mg) was suspended in 5 mL of THF. To the stirring solution was added isopropylamine (600 µL) dropwise at r.t. After 5 hours the solvent was evaporated. The nitro product was purified by flash chromatography (CH₂Cl₂/ CH₃OH 10:1 v/v) and was converted to the title compound under normal hydrogenation conditions. The title compound was obtained as a yellow solid (182 mg, 54 %). ¹H NMR (300MHz, CD₃OD) δ (ppm): 6.96 (d, *J* = 8.3 Hz, 2H), 6.69 (d, *J* = 8.3 Hz, 2H), 3.53 (m, 1H), 3.19 (m, 2H), 2.91 (m, 2H), 1.20 (s, 3H), 1.18 (s, 3H).

C. 8-Indan-5-yl-2-[4-(2-isopropylsulfamoyl-ethyl)-phenylamino]-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid ethyl ester

Using the procedure outlined in Example 1(g) the title compound was prepared from 2-(4-amino-phenyl)-ethanesulfonic acid isopropylamide (58 mg, 0.24 mmol) and 8-indan-5-yl-2-methanesulfonyl-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid ethyl ester (from Example 1(e) above, 100 mg, 0.24 mmol). The title compound was obtained as a white solid (50 mg, 36%). ¹H NMR (400MHz, CDCl₃) δ (ppm): 9.34 (s, 1H), 8.53 (s, 1H), 7.88 (br, 1H), 7.42 (d, *J* = 7.9 Hz, 1H), 7.27 (m, 3H), 7.18 (d, *J* = 7.9 Hz, 1H),

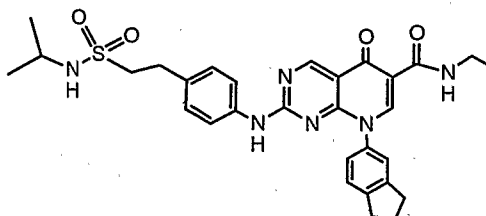
6.94 (br, 2H), 5.88 (s, 1H), 4.37 (q, $J = 7.1$ Hz, 2H), 3.61 (m, 1H), 3.22 (m, 2H), 3.10-2.96 (m, 6H), 2.23 (m, 2H), 1.38 (t, $J = 7.1$ Hz, 3H), 1.25 (s, 3H), 1.22 (s, 3H).

D. 8-Indan-5-yl-2-[4-(2-isopropylsulfamoyl-ethyl)-phenylamino]-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid methyl amide

Using the procedure outlined in Example 28 the title compound was prepared from 8-indan-5-yl-2-[4-(2-isopropylsulfamoyl-ethyl)-phenylamino]-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid ethyl ester (20 mg, 0.034 mmol). A yellow solid was obtained (13.9 mg, 70%). ^1H NMR (400MHz, CDCl_3) δ (ppm): 9.59 (br, 1H), 9.31 (s, 1H), 8.77 (s, 1H), 7.52 (br, 1H), 7.34 (d, $J = 7.9$ Hz, 1H), 7.24 (m, 3H), 7.09 (d, $J = 7.9$ Hz, 1H), 6.88 (br, 2H), 3.88 (d, $J = 7.7$ Hz, 1H), 3.60 (s, 3H), 3.55 (m, 1H), 3.14 (m, 2H), 3.03-2.90 (m, 6H), 2.16 (m, 2H), 1.15 (s, 3H), 1.13 (s, 3H). Mass Spectrum (LCMS, ESI pos.) Calcd. For $\text{C}_{29}\text{H}_{32}\text{N}_6\text{O}_4\text{S}$: 561.22 (M + H), Found 561.0.

Example 34

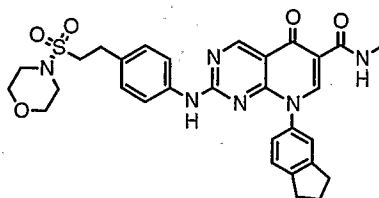
8-Indan-5-yl-2-[4-(2-isopropylsulfamoyl-ethyl)-phenylamino]-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid ethyl amide (Cpd 34)



Using the procedure outlined in Example 29 the title compound was prepared from 8-indan-5-yl-2-[4-(2-isopropylsulfamoyl-ethyl)-phenylamino]-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid ethyl ester (15 mg, 0.026 mmol). A yellow solid was obtained (7.5 mg, 50%). ^1H NMR (400MHz, CDCl_3) δ (ppm): 9.59 (br, 1H), 9.31 (s, 1H), 8.77 (s, 1H), 7.52 (br, 1H), 7.34 (d, $J = 7.9$ Hz, 1H), 7.24 (m, 3H), 7.09 (d, $J = 7.9$ Hz, 1H), 6.88 (br, 2H), 3.88 (d, $J = 7.7$ Hz, 1H), 3.55 (m, 1H), 3.43 (m, 2H), 3.14 (m, 2H), 3.03-2.90 (m, 6H), 2.16 (m, 2H), 1.20 (t, $J = 7.3$ Hz, 3H), 1.15 (s, 3H), 1.13 (s, 3H). Mass Spectrum (LCMS, ESI pos.) Calcd. For $\text{C}_{30}\text{H}_{34}\text{N}_6\text{O}_4\text{S}$: 575.24 (M + H), Found 575.0.

Example 35

8-Indan-5-yl-2-{4-[2-(morpholine-4-sulfonyl)-ethyl]-phenylamino}-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid methyl amide (Cpd 35)



A. 4-[2-(Morpholine-4-sulfonyl)-ethyl]-phenylamine

2-(4-Nitro-phenyl)-ethanesulfonyl chloride (from Example 33 (A), 300 mg) was suspended in 5 mL of THF. To the stirring solution was added morpholine (1 mL) dropwise at r.t. After 5 hours the solvent was evaporated. The nitro product was purified by flash chromatography (CH₂Cl₂/ CH₃OH 10:1 v/v) and was converted to the title compound under normal hydrogenation conditions. The title compound was obtained as a yellow solid (167 mg, 52 %). ¹H NMR (400MHz, CD₃OD) δ (ppm): 7.01 (d, *J* = 8.4 Hz, 2H), 6.65 (d, *J* = 8.4 Hz, 2H), 3.72 (t, *J* = 4.7 Hz, 4H), 3.23 (t, *J* = 4.7 Hz, 4H), 3.11 (m, 2H), 2.98 (m, 2H).

B. 8-Indan-5-yl-2-{4-[2-(morpholine-4-sulfonyl)-ethyl]-phenylamino}-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid ethyl ester

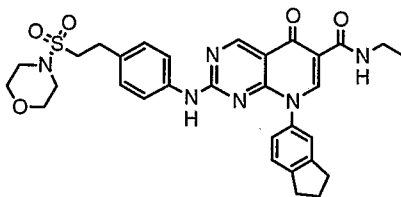
Using the procedure outlined in Example 1(g) the title compound was prepared from 4-[2-(morpholine-4-sulfonyl)-ethyl]-phenylamine (65 mg, 0.24 mmol) and 8-indan-5-yl-2-methanesulfonyl-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid ethyl ester (from Example 1(e) above, 100 mg, 0.24 mmol). The title compound was obtained as a white solid (42 mg, 29%). ¹H NMR (400MHz, CDCl₃) δ (ppm): 9.35 (s, 1H), 8.53 (s, 1H), 8.01 (br, 1H), 7.42 (d, *J* = 7.8 Hz, 1H), 7.30 (m, 3H), 7.19 (d, *J* = 7.8 Hz, 1H), 6.94 (br, 2H), 4.37 (q, *J* = 7.1 Hz, 2H), 3.72 (t, *J* = 4.5 Hz, 4H), 3.25 (t, *J* = 4.7 Hz, 4H), 3.08 (m, 6H), 3.01 (t, *J* = 7.4 Hz, 2H), 2.24 (m, 2H), 1.38 (t, *J* = 7.1 Hz, 3H).

C. 8-Indan-5-yl-2-{4-[2-(morpholine-4-sulfonyl)-ethyl]-phenylamino}-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid methyl amide

Using the procedure outlined in Example 28 the title compound was prepared from 8-indan-5-yl-2-{4-[2-(morpholine-4-sulfonyl)-ethyl]-phenylamino}-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid ethyl ester (12 mg, 0.020 mmol). A yellow solid was obtained (6.4 mg, 54%). ¹H NMR (400MHz, CDCl₃) δ (ppm): 9.59 (br, 1H), 9.31 (s, 1H), 8.77 (s, 1H), 8.25 (br, 1H), 7.36 (d, *J* = 7.9 Hz, 1H), 7.26 (br, 2H), 7.19 (s, 1H), 7.10 (d, *J* = 7.9 Hz, 1H), 6.89 (br, 2H), 3.67 (t, *J* = 4.7 Hz, 4H), 3.22 (s, 3H), 3.18 (t, *J* = 4.7 Hz, 4H), 3.01 (m, 6H), 2.94 (t, *J* = 7.4 Hz, 2H), 2.17 (m, 2H). Mass Spectrum (LCMS, ESI pos.) Calcd. For C₃₀H₃₂N₆O₅S: 589.22 (M + H), Found 589.0.

Example 36

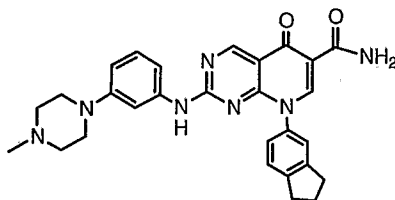
8-Indan-5-yl-2-{4-[2-(morpholine-4-sulfonyl)-ethyl]-phenylamino}-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid ethyl amide (Cpd 36)



Using the procedure outlined in Example 29 the title compound was prepared from 8-indan-5-yl-2-{4-[2-(morpholine-4-sulfonyl)-ethyl]-phenylamino}-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid ethyl ester (Example 35 (B), 12 mg, 0.020 mmol). A yellow solid was obtained (7.6 mg, 63%). ¹H NMR (400MHz, CDCl₃) δ (ppm): 9.59 (br, 1H), 9.31 (s, 1H), 8.77 (s, 1H), 8.25 (br, 1H), 7.36 (d, *J* = 7.9 Hz, 1H), 7.26 (br, 2H), 7.19 (s, 1H), 7.10 (d, *J* = 7.9 Hz, 1H), 6.89 (br, 2H), 3.67 (t, *J* = 4.7 Hz, 4H), 3.43 (m, 2H), 3.18 (t, *J* = 4.7 Hz, 4H), 3.01 (m, 6H), 2.94 (t, *J* = 7.4 Hz, 2H), 2.17 (m, 2H), 1.20 (t, *J* = 7.3 Hz, 3H). Mass Spectrum (LCMS, ESI pos.) Calcd. For C₃₁H₃₄N₆O₅S: 603.23 (M + H), Found 602.9

Example 37

8-Indan-5-yl-2-[3-(4-methyl-piperazin-1-yl)-phenylamino]-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid amide (Cpd 37)



A. 3-(4-Methyl-piperazin-1-yl)-phenylamine

To a suspension of 1-fluoro-3-nitrobenzene (3.77 mL, 35.4 mmol) and potassium carbonate (10g, 71 mmol) in DMSO (30 mL) was added 1-methyl piperazine (59 mL, 53.2 mmol). The mixture was stirred at 122 °C for 24 hours. After cooling down, the mixture was diluted with water (100 mL) and extracted with EtOAc (3x 100 mL). The combined organic layers were washed with brine, dried with sodium sulfate (Na₂SO₄), and concentrated *in vacuo* to afford an orange oil. Recrystallization from EtOAc/hexanes gave 4.2 g of 1-(4-methyl-piperazin-1-yl)-3-nitrobenzene, which was reduced via hydrogenation to give the title compound (beige solid, 3 g). ¹H NMR (400MHz, CDCl₃) δ (ppm): 7.04 (t, *J* = 8.0 Hz, 1H), 6.38 (dd, *J* = 2.3, 8.2 Hz, 1H), 6.26 (t, *J* = 2.2 Hz, 1H), 6.22 (dd, *J* = 2.3, 8.2 Hz, 1H), 3.60 (br, 2H), 3.18 (t, *J* = 4.9 Hz, 4H), 2.55 (t, *J* = 4.9 Hz, 4H), 2.34 (s, 3H).

B. 8-Indan-5-yl-2-[3-(4-methyl-piperazin-1-yl)-phenylamino]-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid ethyl ester

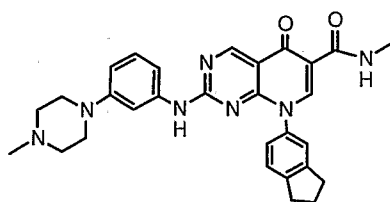
Using the procedure outlined in Example 1(g) the title compound was prepared from 3-(4-methyl-piperazin-1-yl)-phenylamine (50 mg, 0.27 mmol) and 8-indan-5-yl-2-methanesulfonyl-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid ethyl ester (from Example 1(e) above, 100 mg, 0.24 mmol). The title compound was obtained as a yellow solid (60 mg, 46%). ¹H NMR (400MHz, CDCl₃) δ (ppm): 9.29 (s, 1H), 8.44 (s, 1H), 7.49 (br, 1H), 7.31 (d, *J* = 7.9 Hz, 1H), 7.20 (m, 2H), 7.09 (d, *J* = 7.8 Hz, 1H), 6.94 (d, *J* = 7.9 Hz, 1H), 6.87 (br, 1H), 6.52 (d, *J* = 7.9 Hz, 1H), 4.32 (q, *J* = 7.1 Hz, 2H), 3.02-2.90 (m, 8H), 2.45 (m, 4H), 2.26 (s, 3H), 2.14 (m, 2H), 1.32 (t, *J* = 7.1 Hz, 3H).

C. 8-Indan-5-yl-2-[3-(4-methyl-piperazin-1-yl)-phenylamino]-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid amide

Using the procedure outlined in Example 7 the title compound was prepared from 8-indan-5-yl-2-[3-(4-methyl-piperazin-1-yl)-phenylamino]-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid ethyl ester (from B above, 20 mg, 0.038 mmol). A yellow solid was obtained (8.3 mg, 44%). ¹H NMR (400MHz, CD₂Cl₂) δ (ppm): 9.35 (br, 1H), 9.27 (s, 1H), 8.69 (s, 1H), 7.34 (d, *J* = 8.1 Hz, 1H), 7.21 (s, 1H), 7.12 (d, *J* = 8.1 Hz, 1H), 6.97 (d, *J* = 7.9 Hz, 1H), 6.86 (br, 1H), 6.65 (br, 1H), 6.53 (d, *J* = 7.9 Hz, 1H), 5.91 (br, 1H), 3.00-2.84 (m, 8H), 2.43 (br, 4H), 2.22 (s, 3H), 2.12 (m, 2H). Mass Spectrum (LCMS, ESI pos.) Calcd. For C₂₈H₂₉N₇O₂: 496.24 (M + H), Found 496.1.

Example 38

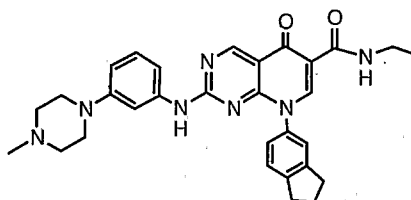
8-Indan-5-yl-2-[3-(4-methyl-piperazin-1-yl)-phenylamino]-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid methyl amide (Cpd 38)



Using the procedure outlined in Example 28 the title compound was prepared from 8-indan-5-yl-2-[3-(4-methyl-piperazin-1-yl)-phenylamino]-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid ethyl ester (from Example 37(B) above, 15 mg, 0.028 mmol). A yellow solid was obtained (8.8 mg, 62%) after a preparative HPLC (32 mL/ min 5-100% MeCN/ H₂O gradient over 10 min) purification. ¹H NMR (400MHz, CDCl₃) δ (ppm): 9.55 (br, 1H), 9.31 (s, 1H), 8.75 (s, 1H), 7.46 (br, 1H), 7.30 (d, *J* = 8.1 Hz, 1H), 7.19 (s, 1H), 7.10 (d, *J* = 8.1 Hz, 1H), 6.98 (d, *J* = 7.9 Hz, 1H), 6.88 (br, 1H), 6.60 (br, 1H), 6.54 (d, *J* = 7.9 Hz, 1H), 3.06-2.89 (m, 11H), 2.45 (m, 4H), 2.27 (s, 3H), 2.12 (m, 2H). Mass Spectrum (LCMS, ESI pos.) Calcd. For C₂₉H₃₁N₇O₂: 510.25 (M + H), Found 510.1.

Example 39

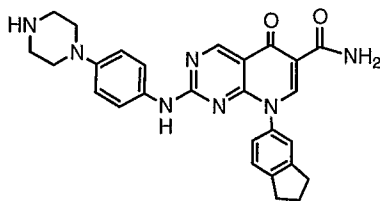
8-Indan-5-yl-2-[3-(4-methyl-piperazin-1-yl)-phenylamino]-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid ethyl amide (Cpd 39)



Using the procedure outlined in Example 29 the title compound was prepared from 8-indan-5-yl-2-[3-(4-methyl-piperazin-1-yl)-phenylamino]-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid ethyl ester (from Example 37(B) above, 15 mg, 0.028 mmol). A yellow solid was obtained (8.6 mg, 59%) after a preparative HPLC (32 mL/min 5-100% MeCN/ H₂O gradient over 10 min) purification. ¹H NMR (400MHz, CDCl₃) δ (ppm): 9.62 (br, 1H), 9.31 (s, 1H), 8.75 (s, 1H), 7.46 (br, 1H), 7.30 (d, *J* = 8.1 Hz, 1H), 7.19 (s, 1H), 7.10 (d, *J* = 8.1 Hz, 1H), 6.98 (d, *J* = 7.9 Hz, 1H), 6.88 (br, 1H), 6.64 (br, 1H), 6.56 (d, *J* = 7.9 Hz, 1H), 3.43 (m, 2H), 3.06-2.86 (m, 8H), 2.45 (m, 4H), 2.27 (s, 3H), 2.13 (m, 2H), 1.20 (t, *J* = 7.3 Hz, 1H). Mass Spectrum (LCMS, ESI pos.) Calcd. For C₃₀H₃₃N₇O₂: 524.27 (M + H), Found 524.1.

Example 40

8-Indan-5-yl-5-oxo-2-(4-piperazin-1-yl-phenylamino)-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid amide (Cpd 4)



A. 4-(4-Amino-phenyl)-piperazine-1-carboxylic acid tert-butyl ester

To a suspension of 1-fluoro-4-nitrobenzene (1.4 mL, 13 mmol) and potassium carbonate (2.5 g, 18 mmol) in DMSO (10 mL) was added 1-Boc-piperazine (2.75 g, 14.8 mmol). The mixture was stirred at 100 °C for 2 hours. After cooling down, the mixture was diluted with water (50 mL) and extracted with EtOAc (3x 50 mL). The combined organic

layers were washed with brine, dried with sodium sulfate (Na_2SO_4), and concentrated *in vacuo* to afford a yellow solid. Recrystallization from EtOAc/hexanes gave 4.0 g of 1-(4-Boc-piperazin-1-yl)-4-nitrobenzene, which was reduced via hydrogenation to give the title compound (purple solid, 3 g). ^1H NMR (400MHz, CDCl_3) δ (ppm): 6.68 (d, $J = 8.8$ Hz, 2H), 6.64 (d, $J = 8.8$ Hz, 2H), 3.56 (t, $J = 5.0$ Hz, 4H), 2.96 (t, $J = 5.0$ Hz, 4H), 1.46 (s, 9H).

B. 8-Indan-5-yl-5-oxo-2-(4-piperazin-1-yl-phenylamino)-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid ethyl ester

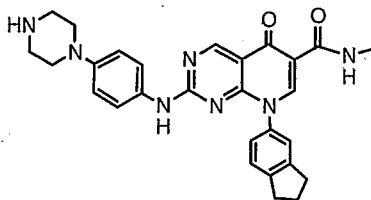
Using the procedure outlined in Example 1(g) the title compound was prepared from 4-(4-amino-phenyl)-piperazine-1-carboxylic acid tert-butyl ester (52 mg, 0.19 mmol) and 8-indan-5-yl-2-methanesulfonyl-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid ethyl ester (from Example 1(e) above, 70 mg, 0.17 mmol). A yellow solid was obtained (75 mg, 86 %) after a preparative HPLC (32 mL/min 5-100% MeCN/ H_2O gradient over 10 min) purification. The Boc group was removed by treatment with TFA in CH_2Cl_2 (1:1 v/v) to give the title compound. ^1H NMR (400MHz, CDCl_3) δ (ppm): 9.25 (s, 1H), 8.45 (s, 1H), 7.61 (br, 1H), 7.35 (d, $J = 7.9$ Hz, 1H), 7.21 (s, 1H), 7.14 (br, 2H), 7.10 (d, $J = 7.9$ Hz, 1H), 6.57 (br, 2H), 4.30 (q, $J = 7.1$ Hz, 2H), 3.02-2.90 (m, 12H), 2.15 (m, 2H), 1.30 (t, $J = 7.1$ Hz, 3H).

C. 8-Indan-5-yl-5-oxo-2-(4-piperazin-1-yl-phenylamino)-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid amide

Using the procedure outlined in Example 7 the title compound was prepared from 8-indan-5-yl-5-oxo-2-(4-piperazin-1-yl-phenylamino)-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid ethyl ester (from B above, 20 mg, 0.038 mmol). The title compound was obtained as a TFA salt after a preparative HPLC (32 mL/min 5-100% MeCN/ H_2O gradient over 10 min) purification (12.8 mg, 52%). ^1H NMR (400MHz, $\text{CD}_2\text{Cl}_2/\text{CD}_3\text{OD}$ 10:1 v/v) δ (ppm): 9.23 (s, 1H), 8.70 (s, 1H), 7.36 (d, $J = 7.9$ Hz, 1H), 7.27 (br, 2H), 7.23 (s, 1H), 7.14 (d, $J = 7.9$ Hz, 1H), 6.63 (br, 2H), 3.25 (m, 12H), 2.96 (m, 4H), 2.13 (m, 2H). Mass Spectrum (LCMS, ESI pos.) Calcd. For $\text{C}_{27}\text{H}_{27}\text{N}_7\text{O}_2$: 482.22 (M + H), Found 482.0.

Example 41

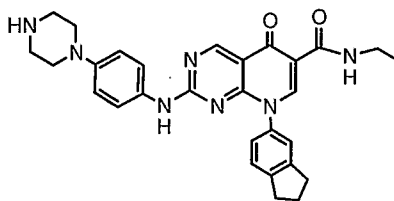
8-Indan-5-yl-5-oxo-2-(4-piperazin-1-yl-phenylamino)-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid methyl amide (Cpd 41)



Using the procedure outlined in Example 28 the title compound was prepared from 8-indan-5-yl-5-oxo-2-(4-piperazin-1-yl-phenylamino)-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid ethyl ester (from Example 40(B) above, 20 mg, 0.039 mmol). A yellow solid was obtained (TFA salt, 12.2 mg, 51%) after a preparative HPLC (32 mL/min 5-100% MeCN/ H₂O gradient over 10 min) purification. ¹H NMR (400MHz, CDCl₃/CD₃OD 10:1 v/v) δ (ppm): 9.67 (br, 1H), 9.26 (s, 1H), 8.71 (s, 1H), 7.37 (d, *J* = 7.9 Hz, 1H), 7.25 (br, 2H), 7.20 (s, 1H), 7.11 (d, *J* = 7.9 Hz, 1H), 6.58 (br, 2H), 3.24 (m, 8H), 2.97-2.93 (m, 7H), 2.15 (m, 2H). Mass Spectrum (LCMS, ESI pos.) Calcd. For C₂₈H₂₉N₇O₂: 496.24 (M + H), Found 496.0.

Example 42

8-Indan-5-yl-5-oxo-2-(4-piperazin-1-yl-phenylamino)-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid ethyl amide (Cpd 42)

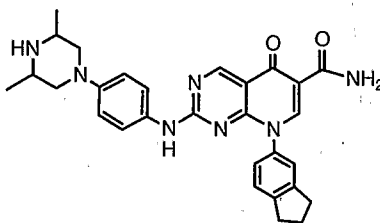


Using the procedure outlined in Example 29 the title compound was prepared from 8-indan-5-yl-5-oxo-2-(4-piperazin-1-yl-phenylamino)-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid ethyl ester (from Example 40(B) above, 20 mg, 0.039 mmol). A yellow solid was obtained (TFA salt, 4.4 mg, 22%) after a preparative HPLC (32 mL/min 5-100% MeCN/ H₂O gradient over 10 min) purification. ¹H NMR (400MHz, CDCl₃/CD₃OD 10:1 v/v) δ (ppm): 9.67 (br, 1H), 9.26 (s, 1H), 8.71 (s, 1H), 7.37 (d, *J* = 7.9

Hz, 1H), 7.25 (br, 2H), 7.20 (s, 1H), 7.11 (d, $J = 7.9$ Hz, 1H), 6.58 (br, 2H), 3.42 (m, 2H), 3.25 (m, 8H), 2.91-3.00 (m, 4H), 2.15 (m, 2H), 1.20 (t, $J = 7.3$ Hz, 3H). Mass Spectrum (LCMS, ESI pos.) Calcd. For $C_{29}H_{31}N_7O_2$: 510.25 (M + H), Found 510.0.

Example 43

2-[4-(3,5-Dimethyl-piperazin-1-yl)-phenylamino]-8-indan-5-yl-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid amide (Cpd 43)



A. 4-(3,5-Dimethyl-piperazin-1-yl)-phenylamine

To a suspension of 1-fluoro-4-nitrobenzene (2.12 mL, 20 mmol) and potassium carbonate (3.5 g, 25 mmol) in DMSO (10 mL) was added 3,5-dimethyl-piperazine (2.5 g, 22 mmol). The mixture was stirred at 100 °C for 2 hours. After cooling down, the mixture was diluted with water (50 mL) and extracted with EtOAc (3x 50 mL). The combined organic layers were washed with brine, dried with sodium sulfate (Na_2SO_4), and concentrated *in vacuo* to afford a yellow solid. Recrystallization from EtOAc/hexanes gave 3.9 g of 3,5-dimethyl-1-(4-nitro-phenyl)-piperazine, which was reduced via hydrogenation to give the title compound (purple solid, 3 g). 1H NMR (400MHz, $CDCl_3$) δ (ppm): 6.80 (d, $J = 8.8$ Hz, 2H), 6.64 (d, $J = 8.8$ Hz, 2H), 3.40 (br, 2H), 3.32 (d, $J = 9.5$ Hz, 2H), 3.05 (m, 2H), 2.19 (t, $J = 10.5$ Hz, 2H), 1.12 (s, 3H), 1.10 (s, 3H).

B. 2-[4-(3,5-Dimethyl-piperazin-1-yl)-phenylamino]-8-indan-5-yl-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid ethyl ester

Using the procedure outlined in Example 1(g) the title compound was prepared from 4-(3,5-dimethyl-piperazin-1-yl)-phenylamine (from the previous step, 27 mg, 0.13 mmol) and 8-indan-5-yl-2-methanesulfonyl-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid ethyl ester (from Example 1(e) above, 50 mg, 0.12 mmol). A yellow solid was obtained (40 mg, 62 %) after a preparative HPLC (32 mL/ min 5-100% MeCN/ H_2O

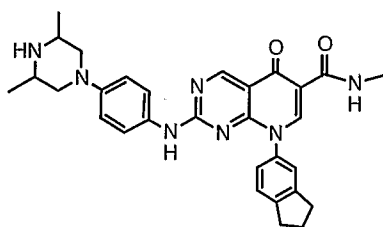
gradient over 10 min) purification. ^1H NMR (400MHz, CDCl_3) δ (ppm): 9.31 (s, 1H), 8.52 (s, 1H), 7.83 (br, 1H), 7.40 (d, $J = 7.9$ Hz, 1H), 7.27 (s, 1H), 7.20 (br, 2H), 7.17 (d, $J = 7.9$ Hz, 1H), 6.63 (br, 2H), 4.36 (q, $J = 7.1$ Hz, 2H), 3.38 (d, $J = 10.5$ Hz, 2H), 3.03 (m, 6H), 2.24 (m, 4H), 1.38 (t, $J = 7.1$ Hz, 3H), 1.14 (s, 3H), 1.13 (s, 3H).

C. 2-[4-(3,5-Dimethyl-piperazin-1-yl)-phenylamino]-8-indan-5-yl-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid amide

Using the procedure outlined in Example 7 the title compound was prepared from 2-[4-(3,5-dimethyl-piperazin-1-yl)-phenylamino]-8-indan-5-yl-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid ethyl ester (from B above, 15 mg, 0.028 mmol). The title compound was obtained as a TFA salt after a preparative HPLC (32 mL/ min 5-100% MeCN/ H_2O gradient over 10 min) purification (10.5 mg, 60%). ^1H NMR (400MHz, $\text{CD}_2\text{Cl}_2/\text{CD}_3\text{OD}$ 10:1 v/v) δ (ppm): 9.24 (s, 1H), 8.70 (s, 1H), 7.38 (d, $J = 7.9$ Hz, 1H), 7.27 (br, 2H), 7.23 (s, 1H), 7.14 (d, $J = 7.9$ Hz, 1H), 6.62 (br, 2H), 3.49 (d, $J = 10.5$ Hz, 2H), 3.37 (m, 2H), 2.96 (m, 4H), 2.65 (t, $J = 11.5$ Hz, 2H), 2.13 (m, 2H), 1.31 (s, 3H), 1.29 (s, 3H). Mass Spectrum (LCMS, ESI pos.) Calcd. For $\text{C}_{29}\text{H}_{31}\text{N}_7\text{O}_2$: 510.25 (M + H), Found 510.0.

Example 44

2-[4-(3,5-Dimethyl-piperazin-1-yl)-phenylamino]-8-indan-5-yl-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid methyl amide (Cpd 44)

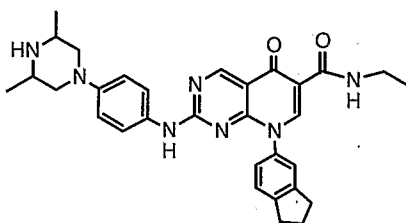


Using the procedure outlined in Example 28 the title compound was prepared from 2-[4-(3,5-dimethyl-piperazin-1-yl)-phenylamino]-8-indan-5-yl-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid ethyl ester (from Example 43(B) above, 15 mg, 0.028 mmol). A yellow solid was obtained (TFA salt, 9.6 mg, 54%) after a preparative HPLC (32 mL/ min 5-100% MeCN/ H_2O gradient over 10 min) purification. ^1H NMR (400MHz, CDCl_3) δ (ppm): 10.14 (br, 1H), 9.62 (m, 1H), 9.26 (s, 1H), 8.98 (br, 1H), 8.75

(s, 1H), 7.35 (d, $J = 7.9$ Hz, 1H), 7.22 (m, 3H), 7.09 (d, $J = 7.9$ Hz, 1H), 6.60 (br, 2H), 3.46-3.38 (m, 4H), 3.00-2.82 (m, 9H), 2.14 (m, 2H), 1.32 (s, 3H), 1.30 (s, 3H). Mass Spectrum (LCMS, ESI pos.) Calcd. For $C_{30}H_{33}N_7O_2$: 524.27 (M + H), Found 524.0.

Example 45

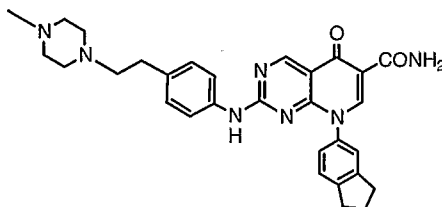
2-[4-(3,5-Dimethyl-piperazin-1-yl)-phenylamino]-8-indan-5-yl-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid ethyl amide (Cpd 45)



Using the procedure outlined in Example 29, the title compound was prepared from 2-[4-(3,5-dimethyl-piperazin-1-yl)-phenylamino]-8-indan-5-yl-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid ethyl ester (from Example 43(B) above, 10 mg, 0.018 mmol). A yellow solid was obtained (TFA salt, 5.2mg, 44%) after a preparative HPLC (32 mL/min 5-100% MeCN/ H₂O gradient over 10 min) purification. ¹H NMR (400MHz, CDCl₃) δ (ppm): 10.14 (br, 1H), 9.62 (m, 1H), 9.26 (s, 1H), 8.98 (br, 1H), 8.75 (s, 1H), 7.35 (d, $J = 7.9$ Hz, 1H), 7.22 (m, 3H), 7.09 (d, $J = 7.9$ Hz, 1H), 6.60 (br, 2H), 3.46-3.38 (m, 4H), 3.00-2.82 (m, 6H), 2.66 (br, 2H), 2.14 (m, 2H), 1.32 (s, 3H), 1.30 (s, 3H), 1.19 (t, $J = 7.3$ Hz, 3H). Mass Spectrum (LCMS, ESI pos.) Calcd. For $C_{31}H_{35}N_7O_2$: 538.27 (M + H), Found 538.1.

Example 46

8-Indan-5-yl-2-[4-[2-(4-methyl-piperazin-1-yl)-ethyl]-phenylamino]-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid amide (Cpd 46)



A. 4-[2-(4-Methyl-piperazin-1-yl)-ethyl]-phenylamine

1-(2-Bromo-ethyl)-4-nitro-benzene (0.9 g, 3.9 mmol) was added to a mixture of 1-methyl-piperazine (520 μ L, 4.7 mmol) and potassium carbonate (1 g, 4.7 mmol) in 5 mL of DMSO. The mixture was stirred at 100 °C for 2 hour. After cooling to room temperature, the mixture was extracted into ethyl acetate (EtOAc), washed with water, brine and then dried with sodium sulfate (Na_2SO_4). Removal of the solvent and chromatography on silica, eluting with EtOAc/ $\text{CH}_3\text{OH}/\text{NH}_4\text{OH}$ (10:1:0.1, v/v), gave 850 mg of 1-methyl-4-[2-(4-nitro-phenyl)-ethyl]-piperazine, which was converted to the title compound under normal hydrogenation conditions. The title compound was obtained as a yellow solid (780 mg, 91 %). ^1H NMR (400MHz, CDCl_3) δ (ppm): 6.98 (d, $J = 8.3$ Hz, 2H), 6.61 (d, $J = 8.3$ Hz, 2H), 3.57 (br, 2H), 2.71 (br, 12H), 2.43 (br, 3H).

B. 8-Indan-5-yl-2-{4-[2-(4-methyl-piperazin-1-yl)-ethyl]-phenylamino}-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid ethyl ester

Using the procedure outlined in Example 1(g) the title compound was prepared from 4-[2-(4-methyl-piperazin-1-yl)-ethyl]-phenylamine (53 mg, 0.24 mmol) and 8-indan-5-yl-2-methanesulfonyl-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid ethyl ester (from Example 1(e) above, 100 mg, 0.24 mmol). The title compound was obtained as a yellow solid (70 mg, 53%). ^1H NMR (400MHz, CDCl_3) δ (ppm): 9.28 (s, 1H), 8.46 (s, 1H), 7.60 (br, 1H), 7.34 (d, $J = 7.9$ Hz, 1H), 7.21 (s, 1H), 7.16 (br, 2H), 7.12 (d, $J = 7.9$ Hz, 1H), 6.86 (br, 2H), 4.30 (q, $J = 7.1$ Hz, 2H), 2.99 (t, $J = 7.4$ Hz, 2H), 2.93 (t, $J = 7.4$ Hz, 2H), 2.64 (m, 2H), 2.47 (m, 10H), 2.34 (s, 3H), 2.16 (m, 2H), 1.32 (t, $J = 7.1$ Hz, 3H).

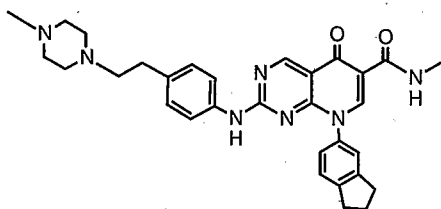
C. 8-Indan-5-yl-2-{4-[2-(4-methyl-piperazin-1-yl)-ethyl]-phenylamino}-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid amide

Using the procedure outlined in Example 7 the title compound was prepared from 8-indan-5-yl-2-{4-[2-(4-methyl-piperazin-1-yl)-ethyl]-phenylamino}-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid ethyl ester (20 mg, 0.036 mmol). A yellow solid was obtained (5.8 mg, 30%). ^1H NMR (400MHz, $\text{DMSO}-d_6$) δ (ppm): 10.48 (br, 1H), 9.31 (s, 1H), 9.10 (s, 1H), 8.62 (s, 1H), 7.75 (m, 1H), 7.54 (m, 2H), 7.41 (m, 2H), 6.97 (br,

2H), 3.55 (m, 4H), 3.09 (t, $J = 7.3$ Hz, 2H), 3.01 (t, $J = 7.4$ Hz, 2H), 2.71 (m, 2H), 2.57 (m, 13H), 2.22 (m, 2H). Mass Spectrum (LCMS, ESI pos.) Calcd. For $C_{30}H_{33}N_7O_2$: 524.27 (M + H), Found 524.1.

Example 47

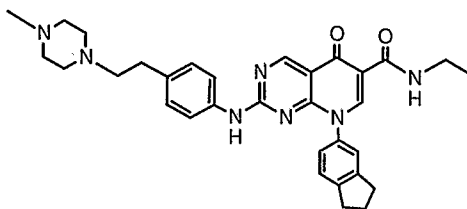
8-Indan-5-yl-2-{4-[2-(4-methyl-piperazin-1-yl)-ethyl]-phenylamino}-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid methyl amide (Cpd 47)



Using the procedure outlined in Example 28 the title compound was prepared from 8-indan-5-yl-2-{4-[2-(4-methyl-piperazin-1-yl)-ethyl]-phenylamino}-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid ethyl ester (from Example 46(B) above, 20 mg, 0.036 mmol). A yellow solid was obtained (5.1 mg, 26%) after a preparative HPLC (32 mL/min 5-100% MeCN/ H₂O gradient over 10 min) purification. ¹H NMR (400MHz, CDCl₃/CD₃OD 20:1 v/v) δ (ppm): 9.61 (m, 1H), 9.29 (s, 1H), 8.75 (s, 1H), 7.35 (d, $J = 7.9$ Hz, 1H), 7.19 (m, 3H), 7.09 (d, $J = 7.9$ Hz, 1H), 6.84 (br, 2H), 3.00-2.90 (m, 7H), 2.64 (m, 2H), 2.47 (m, 10H), 2.24 (s, 3H), 2.15 (m, 2H). Mass Spectrum (LCMS, ESI pos.) Calcd. For $C_{31}H_{35}N_7O_2$: 538.29 (M + H), Found 538.1.

Example 48

8-Indan-5-yl-2-{4-[2-(4-methyl-piperazin-1-yl)-ethyl]-phenylamino}-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid ethyl amide (Cpd 48)

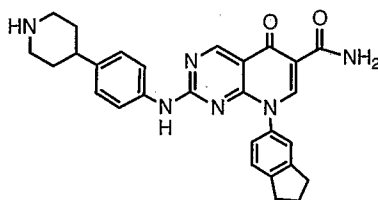


Using the procedure outlined in Example 29 the title compound was prepared from 8-indan-5-yl-2-{4-[2-(4-methyl-piperazin-1-yl)-ethyl]-phenylamino}-5-oxo-5,8-dihydro-

pyrido[2,3-d]pyrimidine-6-carboxylic acid ethyl ester (from Example 46(B) above, 20 mg, 0.036 mmol). A yellow solid was obtained (7.1 mg, 36%) after a preparative HPLC (32 mL/min 5-100% MeCN/ H₂O gradient over 10 min) purification. ¹H NMR (400MHz, CDCl₃/CD₃OD 20:1 v/v) δ (ppm): 9.61 (m, 1H), 9.29 (s, 1H), 8.75 (s, 1H), 7.35 (d, *J* = 7.9 Hz, 1H), 7.19 (m, 3H), 7.09 (d, *J* = 7.9 Hz, 1H), 6.84 (br, 2H), 3.50 (m, 2H), 3.06 (t, *J* = 7.4 Hz, 2H), 2.99 (t, *J* = 7.4 Hz, 2H), 2.73 (m, 2H), 2.53 (m, 10H), 2.31 (s, 3H), 2.22 (m, 2H), 1.26 (t, *J* = 7.3 Hz, 3H). Mass Spectrum (LCMS, ESI pos.) Calcd. For C₃₂H₃₇N₇O₂: 552.30 (M + H), Found 552.1.

Example 49

8-Indan-5-yl-5-oxo-2-(4-piperidin-4-yl-phenylamino)-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid amide
(Cpd 49)



A. 4-(4-Amino-phenyl)-3,6-dihydro-2H-pyridine-1-carboxylic acid *tert*-butyl ester

The title compound was prepared by Suzuki coupling of 4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenylamine with 4-trifluoromethanesulfonyloxy-3,6-dihydro-2H-pyridine-1-carboxylic acid *tert*-butyl ester (*Synthesis*, 993, (1991)). Mass spectrum (ESI, *m/z*): Calcd. for C₁₆H₂₂N₂O₂, 275.2 (M+H), found 275.1.

B. 4-(4-Amino-phenyl)-piperidine-1-carboxylic acid *tert*-butyl ester

A solution of 4-(4-amino-phenyl)-3,6-dihydro-2H-pyridine-1-carboxylic acid *tert*-butyl ester (0.35 g, 1.2 mmol) (as prepared in the previous step) in methanol was hydrogenated over 10 % Pd/C at 20 psi for 1 h. The solution was filtered and concentrated to give 0.35 g (100 %) of the title compound as a yellow solid. ¹H NMR (400MHz, DMSO-*d*₆) δ (ppm): 6.85 (d, *J* = 8.3 Hz, 2H), 6.50 (d, *J* = 8.3 Hz, 2H), 4.81 (s, 2H), 4.012 (m, 2H), 3.85 (br, 2H), 2.44 (m, 1H), 2.66 (m, 2H), 1.42 (m, 11H).

C. 8-Indan-5-yl-5-oxo-2-(4-piperidin-4-yl-phenylamino)-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid ethyl ester

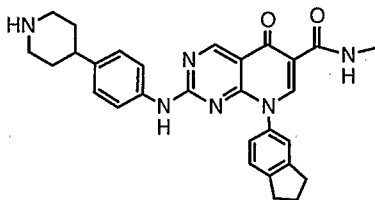
Using the procedure outlined in Example 1(g) the title compound was prepared from 4-(4-amino-phenyl)-piperidine-1-carboxylic acid *tert*-butyl ester (from the previous step, 66 mg, 0.24 mmol) and 8-indan-5-yl-2-methanesulfonyl-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid ethyl ester (from Example 1(e), 100 mg, 0.24 mmol). A yellow solid was obtained (75 mg, 51 %) after a preparative HPLC (32 mL/ min 5-100% MeCN/ H₂O gradient over 10 min) purification. The Boc group was removed by treatment with TFA in CH₂Cl₂ (1:1 v/v) to give the title compound. ¹H NMR (400MHz, CDCl₃) δ (ppm): 9.31 (s, 1H), 8.54 (s, 1H), 7.42 (d, *J* = 7.9 Hz, 1H), 7.29 (br, 2H), 7.27 (s, 1H), 7.18 (d, *J* = 7.9 Hz, 1H), 6.91 (br, 2H), 4.35 (q, *J* = 7.1 Hz, 2H), 3.52 (m, 2H), 3.16 (br, 2H), 2.97 (m, 4H), 2.68 (m, 1H), 2.22 (m, 2H), 1.95 (m, 2H), 1.35 (t, *J* = 7.1 Hz, 3H).

D. 8-Indan-5-yl-5-oxo-2-(4-piperidin-4-yl-phenylamino)-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid amide

Using the procedure outlined in Example 7 the title compound was prepared from 8-indan-5-yl-5-oxo-2-(4-piperidin-4-yl-phenylamino)-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid ethyl ester (27 mg, 0.053 mmol). A yellow solid was obtained as a TFA salt after a preparative HPLC (32 mL/ min 5-100% MeCN/ H₂O gradient over 10 min) purification (24 mg, 76 %). ¹H NMR (400MHz, DMSO-*d*₆) δ (ppm): 10.48 (br, 1H), 9.31 (s, 1H), 9.10 (s, 1H), 8.62 (s, 1H), 7.75 (m, 1H), 7.54 (m, 2H), 7.41 (m, 2H), 6.97 (br, 2H), 3.55 (m, 4H), 3.09 (t, *J* = 7.3 Hz, 2H), 3.01 (t, *J* = 7.4 Hz, 2H), 2.81 (m, 1H), 2.22 (m, 2H), 1.95 (m, 2H), 1.75 (m, 2H). Mass Spectrum (LCMS, ESI pos.) Calcd. For C₂₈H₂₈N₆O₂: 481.23 (M + H), Found 481.1.

Example 50

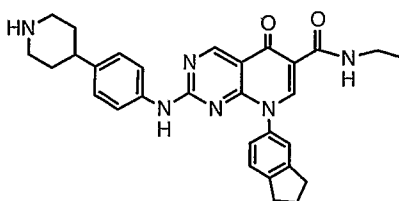
8-Indan-5-yl-5-oxo-2-(4-piperidin-4-yl-phenylamino)-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid methyl amide (Cpd 50)



Using the procedure outlined in Example 28 the title compound was prepared from 8-indan-5-yl-5-oxo-2-(4-piperidin-4-yl-phenylamino)-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid ethyl ester (from Example 48(C) above, 20 mg, 0.039 mmol). A yellow solid was obtained (TFA salt, 8.9 mg, 37%) after a preparative HPLC (32 mL/min 5-100% MeCN/ H₂O gradient over 10 min) purification. ¹H NMR (400MHz, CDCl₃/CD₃OD 20:1 v/v) δ (ppm): 9.30 (s, 1H), 8.75 (s, 1H), 7.35 (d, *J* = 7.9 Hz, 1H), 7.19 (m, 3H), 7.09 (d, *J* = 7.9 Hz, 1H), 6.84 (br, 2H), 3.48 (m, 2H), 2.97 (m, 11H), 2.62 (m, 1H), 2.16 (m, 2H), 1.88 (m, 2H). Mass Spectrum (LCMS, ESI pos.) Calcd. For C₂₉H₃₀N₆O₂: 495.24 (M + H), Found 495.1.

Example 51

8-Indan-5-yl-5-oxo-2-(4-piperidin-4-yl-phenylamino)-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid ethyl amide (Cpd 51)

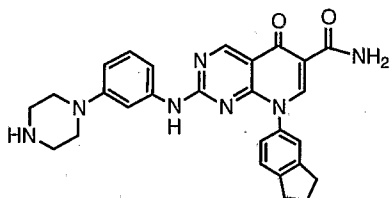


Using the procedure outlined in Example 29 the title compound was prepared from 8-indan-5-yl-5-oxo-2-(4-piperidin-4-yl-phenylamino)-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid ethyl ester (from Example 48(C) above, 20 mg, 0.039 mmol). A yellow solid was obtained (TFA salt, 7.3 mg, 30%) after a preparative HPLC (32 mL/min 5-100% MeCN/ H₂O gradient over 10 min) purification. ¹H NMR (400MHz, CDCl₃/CD₃OD 20:1 v/v) δ (ppm): 9.30 (s, 1H), 8.75 (s, 1H), 7.35 (d, *J* = 7.9 Hz, 1H), 7.19

(m, 3H), 7.09 (d, $J = 7.9$ Hz, 1H), 6.84 (br, 2H), 3.48 (m, 4H), 2.97 (m, 8H), 2.64 (m, 1H), 2.20 (m, 2H), 1.90 (m, 2H), 1.26 (t, $J = 7.3$ Hz, 3H). Mass Spectrum (LCMS, ESI pos.)
 Calcd. For $C_{30}H_{32}N_6O_2$: 509.26 (M + H), Found 509.1.

Example 52

8-Indan-5-yl-5-oxo-2-(3-piperazin-1-yl-phenylamino)-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid amide
 (Cpd 52)



A. 4-(3-Amino-phenyl)-piperazine-1-carboxylic acid *tert*-butyl ester

Using the procedure outlined in Example 37 (A), the title compound was prepared from 1-fluoro-3-nitrobenzene (1g, 7 mmol) and 1-Boc-piperazine (1.9 g, 10 mmol) 1H NMR (400MHz, $CDCl_3$) δ (ppm): 7.03 (t, $J = 8.0$ Hz, 1H), 6.34 (d, $J = 8.2$ Hz, 1H), 6.23 (m, 2H), 3.62 (br, 2H), 3.53 (m, 4H), 3.07 (m, 2H), 1.47 (s, 9H).

B. 8-Indan-5-yl-5-oxo-2-(3-piperazin-1-yl-phenylamino)-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid ethyl ester

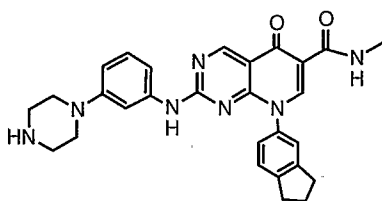
Using the procedure outlined in Example 1(g) the title compound was prepared from 4-(3-amino-phenyl)-piperazine-1-carboxylic acid *tert*-butyl ester (from the previous step, 54 mg, 0.19 mmol) and 8-indan-5-yl-2-methanesulfonyl-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid ethyl ester (from Example 1(e) above, 80 mg, 0.19 mmol). A yellow solid was obtained (60 mg, 62 %) after a preparative HPLC (32 mL/min 5-100% MeCN/ H_2O gradient over 10 min) purification. The Boc group was removed by treatment with TFA in CH_2Cl_2 (1:1 v/v) to give the title compound. 1H NMR (400MHz, $CDCl_3/CD_3OD$ 10:1 v/v) δ (ppm): 9.26 (br, 1H), 8.49 (s, 1H), 7.35 (d, $J = 7.9$ Hz, 1H), 7.20 (s, 1H), 7.11 (m, 2H), 6.78 (br, 2H), 6.54 (m, 1H), 4.24 (q, $J = 7.1$ Hz, 2H), 3.98 (m, 4H), 2.29 (m, 4H), 2.96 (m, 4H), 2.14 (m, 2H), 1.27 (t, $J = 7.1$ Hz, 3H).

C. 8-Indan-5-yl-5-oxo-2-(3-piperazin-1-yl-phenylamino)-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid amide

Using the procedure outlined in Example 7 the title compound was prepared from 8-indan-5-yl-5-oxo-2-(3-piperazin-1-yl-phenylamino)-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid ethyl ester (from the previous step, 20 mg, 0.038 mmol). The title compound was obtained as a TFA salt after a preparative HPLC (32 mL/min 5-100% MeCN/ H₂O gradient over 10 min) purification (6.9 mg, 30%). ¹H NMR (400MHz, DMSO-*d*₆) δ (ppm): 10.21 (br, 1H), 9.20 (s, 1H), 8.96 (s, 1H), 8.63 (s, 1H), 8.48 (s, 1H), 7.61 (d, *J* = 3.4 Hz, 1H), 7.41(m, 2H), 7.30 (d, *J* = 8.1 Hz, 1H), 7.10 (d, *J* = 7.7 Hz, 1H), 6.81 (br, 1H), 6.57 (d, *J* = 8.5 Hz, 1H), 3.14 (m, 4H), 2.90 (m, 4H), 2.05 (m, 2H). Mass Spectrum (LCMS, ESI pos.) Calcd. For C₂₇H₂₇N₇O₂: 482.22 (M + H), Found 482.1.

Example 53

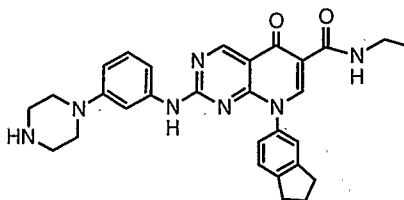
8-Indan-5-yl-5-oxo-2-(3-piperazin-1-yl-phenylamino)-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid methyl amide (Cpd 53)



Using the procedure outlined in Example 28 the title compound was prepared from 8-indan-5-yl-5-oxo-2-(3-piperazin-1-yl-phenylamino)-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid ethyl ester (from Example 52(B) above, 20 mg, 0.039 mmol). A yellow solid was obtained (TFA salt, 13.2 mg, 56%) after a preparative HPLC (32 mL/min 5-100% MeCN/ H₂O gradient over 10 min) purification. ¹H NMR (400MHz, CDCl₃/CD₃OD 10:1 v/v) δ (ppm): 9.67 (br, 1H), 9.35 (s, 1H), 8.77 (s, 1H), 7.36 (d, *J* = 7.9 Hz, 1H), 7.23 (s, 1H), 7.17 (br, 1H), 7.13 (d, *J* = 7.9 Hz, 1H), 6.87 (br, 1H), 6.67 (br, 1H), 6.57 (m, 1H), 3.27 (m, 4H), 2.97 (m, 7H), 2.44 (br, 4H), 2.16 (m, 2H). Mass Spectrum (LCMS, ESI pos.) Calcd. For C₂₈H₂₉N₇O₂: 496.24 (M + H), Found 496.0.

Example 54

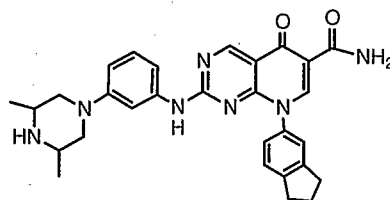
8-Indan-5-yl-5-oxo-2-(3-piperazin-1-yl-phenylamino)-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid ethyl amide (Cpd 54)



Using the procedure outlined in Example 29 the title compound was prepared from 8-indan-5-yl-5-oxo-2-(3-piperazin-1-yl-phenylamino)-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid ethyl ester (from Example 52(B) above, 20 mg, 0.039 mmol). A yellow solid was obtained (TFA salt, 8.5 mg, 35%) after a preparative HPLC (32 mL/min 5-100% MeCN/ H₂O gradient over 10 min) purification. ¹H NMR (400MHz, CDCl₃/CD₃OD 10:1 v/v) δ (ppm): 9.30 (s, 1H), 8.72 (s, 1H), 7.34 (d, *J* = 7.9 Hz, 1H), 7.19 (s, 1H), 7.15 (br, 1H), 7.10 (d, *J* = 7.9 Hz, 1H), 6.84 (br, 1H), 6.61 (br, 1H), 6.54 (m, 1H), 3.41 (m, 2H), 3.22 (m, 4H), 2.96 (m, 4H), 2.77 (br, 4H), 2.14 (m, 2H), 1.18 (t, *J* = 7.3 Hz, 3H). Mass Spectrum (LCMS, ESI pos.) Calcd. For C₂₉H₃₁N₇O₂: 510.25 (M + H), Found 510.1.

Example 55

2-[3-(3,5-Dimethyl-piperazin-1-yl)-phenylamino]-8-indan-5-yl-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid amide (Cpd 55)



A. 3-(3,5-Dimethyl-piperazin-1-yl)-phenylamine

Using the procedure outlined in Example 37 (A), the title compound was prepared from 1-fluoro-3-nitrobenzene (1g, 7 mmol) and 3,5-dimethyl-piperazine (1.14 g, 10 mmol). ¹H NMR (400MHz, CDCl₃) δ (ppm): 7.00 (t, *J* = 8.0 Hz, 1H), 6.33 (d, *J* = 8.2 Hz,

1H), 6.21 (m, 1H), 6.15 (d, $J = 8.2$ Hz, 1H), 3.60 (br, 2H), 3.45 (d, $J = 9.8$ Hz, 2H), 2.98 (m, 1H), 2.22 (t, $J = 11.3$ Hz, 2H), 1.10 (s, 3H), 1.08 (s, 3H).

B. 2-[3-(3,5-Dimethyl-piperazin-1-yl)-phenylamino]-8-indan-5-yl-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid ethyl ester

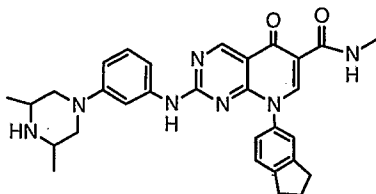
Using the procedure outlined in Example 1(g) the title compound was prepared from 3-(3,5-dimethyl-piperazin-1-yl)-phenylamine (from the previous step, 52 mg, 0.25 mmol) and 8-indan-5-yl-2-methanesulfonyl-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid ethyl ester (from Example 1(e) above, 100 mg, 0.24 mmol). A yellow solid was obtained (67 mg, 52 %) after a preparative HPLC (32 mL/min 5-100% MeCN/ H₂O gradient over 10 min) purification. ¹H NMR (400MHz, CDCl₃) δ (ppm): 9.29 (s, 1H), 8.44 (s, 1H), 7.49 (br, 1H), 7.31 (d, $J = 7.9$ Hz, 1H), 7.20 (m, 2H), 7.09 (d, $J = 7.8$ Hz, 1H), 6.94 (d, $J = 7.9$ Hz, 1H), 6.87 (br, 1H), 6.52 (d, $J = 7.9$ Hz, 1H), 4.32 (q, $J = 7.1$ Hz, 2H), 3.38 (d, $J = 10.5$ Hz, 2H), 3.03 (m, 6H), 2.25 (m, 2H), 2.12 (m, 2H), 1.32 (t, $J = 7.1$ Hz, 3H), 1.10 (s, 3H), 1.08 (s, 3H).

C. 2-[3-(3,5-Dimethyl-piperazin-1-yl)-phenylamino]-8-indan-5-yl-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid amide

Using the procedure outlined in Example 7 the title compound was prepared from 2-[3-(3,5-dimethyl-piperazin-1-yl)-phenylamino]-8-indan-5-yl-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid ethyl ester (from the previous step, 15 mg, 0.028 mmol). The title compound was obtained as a TFA salt after a preparative HPLC (32 mL/min 5-100% MeCN/ H₂O gradient over 10 min) purification (10.8 mg, 62%). ¹H NMR (400MHz, CDCl₃/CD₃OD 5:1 v/v) δ (ppm): 9.67 (br, 1H), 9.35 (s, 1H), 8.77 (s, 1H), 7.36 (d, $J = 7.9$ Hz, 1H), 7.23 (s, 1H), 7.17 (br, 1H), 7.13 (d, $J = 7.9$ Hz, 1H), 6.87 (br, 1H), 6.67 (br, 1H), 6.57 (m, 1H), 3.49 (d, $J = 10.5$ Hz, 2H), 3.37 (m, 2H), 2.96 (m, 4H), 2.65 (t, $J = 11.5$ Hz, 2H), 2.13 (m, 2H), 1.31 (s, 3H), 1.29 (s, 3H). Mass Spectrum (LCMS, ESI pos.) Calcd. For C₂₉H₃₁N₇O₂: 510.25 (M + H), Found 510.1.

Example 56

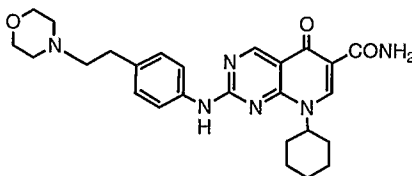
2-[3-(3,5-Dimethyl-piperazin-1-yl)-phenylamino]-8-indan-5-yl-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid methyl amide (Cpd 56)



Using the procedure outlined in Example 28 the title compound was prepared from 2-[3-(3,5-dimethyl-piperazin-1-yl)-phenylamino]-8-indan-5-yl-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid ethyl ester (from Example 55(B), 15 mg, 0.028 mmol). A yellow solid was obtained (TFA salt, 5.3 mg, 30%) after a preparative HPLC (32 mL/min 5-100% MeCN/ H₂O gradient over 10 min) purification. ¹H NMR (400MHz, CDCl₃) δ (ppm): 9.67 (br, 1H), 9.34 (s, 1H), 8.77 (s, 1H), 7.36 (d, *J* = 7.9 Hz, 1H), 7.22 (s, 1H), 7.17 (br, 1H), 7.13 (d, *J* = 7.9 Hz, 1H), 6.85 (br, 1H), 6.67 (br, 1H), 6.55 (m, 1H), 3.49 (d, *J* = 10.5 Hz, 2H), 3.37 (m, 2H), 2.97 (m, 7H), 2.74 (m, 4H), 2.13 (m, 2H), 1.33 (s, 3H), 1.31 (s, 3H). Mass Spectrum (LCMS, ESI pos.) Calcd. For C₃₀H₃₃N₇O₂: 524.27 (M + H), Found 524.1.

Example 57

8-Cyclohexyl-2-[4-(2-morpholin-4-yl-ethyl)-phenylamino]-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid amide (Cpd 57)



A. 8-Cyclohexyl-2-[4-(2-morpholin-4-yl-ethyl)-phenylamino]-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid ethyl ester

Using the procedure outlined in Example 1(g) the title compound was prepared from 4-(2-morpholin-4-yl-ethyl)-phenylamine (from Example 27(A), 54 mg, 0.26 mmol) and 8-cyclohexyl-2-methanesulfonyl-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-

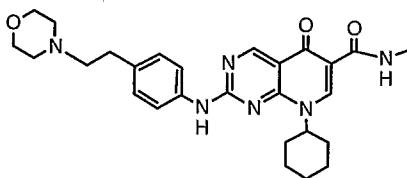
carboxylic acid ethyl ester (from Example 17(e) above, 100 mg, 0.26 mmol). The title compound was obtained as a white solid (77 mg, 59%). ¹H NMR (400MHz, CDCl₃) δ (ppm): 9.28 (s, 1H), 8.46 (s, 1H), 7.98 (br, 1H), 7.50 (d, *J* = 8.5 Hz, 2H), 7.17 (d, *J* = 8.5 Hz, 2H), 5.04 (m, 1H), 4.32 (q, *J* = 7.1 Hz, 2H), 3.67 (t, *J* = 4.6 Hz, 4H), 2.76 (m, 2H), 2.54 (m, 2H), 2.47 (m, 4H), 1.99 (m, 4H), 1.78 (m, 1H), 1.61 (m, 2H), 1.46 (m, 2H), 1.34 (t, *J* = 7.1 Hz, 3H), 1.23 (m, 1H).

B. 8-Cyclohexyl-2-[4-(2-morpholin-4-yl-ethyl)-phenylamino]-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid amide

Using the procedure outlined in Example 7 the title compound was prepared from 8-cyclohexyl-2-[4-(2-morpholin-4-yl-ethyl)-phenylamino]-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid ethyl ester (from the previous step, 20 mg, 0.039 mmol). The title compound was obtained as yellow solid after a preparative HPLC (32 mL/ min 5-100% MeCN/ H₂O gradient over 10 min) purification (10.7 mg, 56%). ¹H NMR (400MHz, CDCl₃) δ (ppm): 9.42 (br, 1H), 9.31 (s, 1H), 8.78 (s, 1H), 7.50 (d, *J* = 8.5 Hz, 2H), 7.17 (d, *J* = 8.5 Hz, 2H), 5.10 (m, 1H), 3.67 (t, *J* = 4.6 Hz, 4H), 2.76 (m, 2H), 2.54 (m, 2H), 2.46 (m, 4H), 1.99 (m, 4H), 1.78-1.19 (m, 10H). Mass Spectrum (LCMS, ESI pos.) Calcd. For C₂₆H₃₂N₆O₃: 477.25 (M + H), Found 477.1.

Example 58

8-Cyclohexyl-2-[4-(2-morpholin-4-yl-ethyl)-phenylamino]-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid methyl amide (Cpd 58)

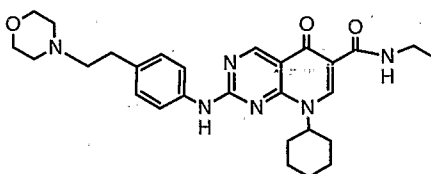


Using the procedure outlined in Example 28 the title compound was prepared from 8-cyclohexyl-2-[4-(2-morpholin-4-yl-ethyl)-phenylamino]-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid ethyl ester (from Example 57(A), 20 mg, 0.039 mmol). The title compound was obtained as yellow solid after a preparative HPLC (32 mL/ min 5-100% MeCN/ H₂O gradient over 10 min) purification (13.4 mg, 70%). ¹H NMR (400MHz,

CDCl₃) δ (ppm): 9.57 (m, 1H), 9.30 (s, 1H), 8.78 (s, 1H), 7.70 (br, 1H), 7.50 (d, $J = 8.5$ Hz, 2H), 7.16 (d, $J = 8.5$ Hz, 2H), 5.09 (m, 1H), 3.67 (t, $J = 4.6$ Hz, 4H), 2.94 (d, $J = 4.9$ Hz, 3H), 2.76 (m, 2H), 2.54 (m, 2H), 2.46 (m, 4H), 1.97 (m, 4H), 1.71 (m, 3H), 1.44 (m, 2H), 1.23 (m, 1H). Mass Spectrum (LCMS, ESI pos.) Calcd. For C₂₇H₃₄N₆O₃: 491.27 (M + H), Found 491.0.

Example 59

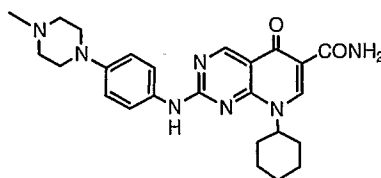
8-Cyclohexyl-2-[4-(2-morpholin-4-yl-ethyl)-phenylamino]-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid ethyl amide (Cpd **59**)



Using the procedure outlined in Example 29, the title compound was prepared from 8-cyclohexyl-2-[4-(2-morpholin-4-yl-ethyl)-phenylamino]-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid ethyl ester (from Example 57(A), 20 mg, 0.039 mmol). The title compound was obtained as yellow solid after a preparative HPLC (32 mL/ min 5-100% MeCN/ H₂O gradient over 10 min) purification (11.9 mg, 60%). ¹H NMR (400MHz, CDCl₃) δ (ppm): 9.64 (m, 1H), 9.30 (s, 1H), 8.78 (s, 1H), 7.70 (br, 1H), 7.50 (d, $J = 8.5$ Hz, 2H), 7.16 (d, $J = 8.5$ Hz, 2H), 5.07 (m, 1H), 3.67 (t, $J = 4.6$ Hz, 4H), 3.42 (m, 2H), 2.76 (m, 2H), 2.54 (m, 2H), 2.46 (m, 4H), 1.97 (m, 4H), 1.71 (m, 3H), 1.44 (m, 2H), 1.18 (m, 4H). Mass Spectrum (LCMS, ESI pos.) Calcd. For C₂₈H₃₆N₆O₃: 505.28 (M + H), Found 505.0.

Example 60

8-Cyclohexyl-2-[4-(4-methyl-piperazin-1-yl)-phenylamino]-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid amide (Cpd **60**)



A. 8-Cyclohexyl-2-[4-(4-methyl-piperazin-1-yl)-phenylamino]-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid ethyl ester

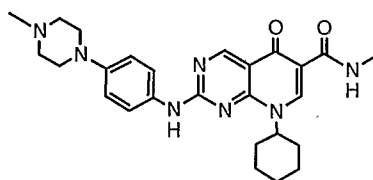
Using the procedure outlined in Example 1(g) the title compound was prepared from 4-(4-methyl-piperazin-1-yl)-phenylamine (50 mg, 0.26 mmol) and 8-cyclohexyl-2-methanesulfonyl-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid ethyl ester (from Example 17(e), 100 mg, 0.26 mmol). The title compound was obtained as a yellow solid (80 mg, 63%). ¹H NMR (400MHz, CDCl₃) δ (ppm): 9.25 (s, 1H), 8.44 (s, 1H), 7.56 (br, 1H), 7.43 (d, *J* = 8.9 Hz, 2H), 6.87 (d, *J* = 9.0 Hz, 2H), 5.00 (m, 1H), 4.32 (q, *J* = 7.1 Hz, 2H), 3.16 (t, *J* = 4.9 Hz, 4H), 2.55 (t, *J* = 4.9 Hz, 4H), 2.30 (s, 3H), 1.94 (m, 4H), 1.76 (m, 1H), 1.62 (m, 2H), 1.42 (m, 2H), 1.34 (t, *J* = 7.1 Hz, 3H), 1.21 (m, 1H).

B. 8-Cyclohexyl-2-[4-(4-methyl-piperazin-1-yl)-phenylamino]-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid amide

Using the procedure outlined in Example 7 the title compound was prepared from 8-cyclohexyl-2-[4-(4-methyl-piperazin-1-yl)-phenylamino]-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid ethyl ester (from the previous step, 20 mg, 0.040 mmol). The title compound was obtained as yellow solid after a preparative HPLC (32 mL/ min 5-100% MeCN/ H₂O gradient over 10 min) purification (9.9 mg, 54%). ¹H NMR (400MHz, DMSO-*d*₆) δ (ppm): 10.27 (br, 1H), 9.15 (s, 1H), 9.05 (m, 1H), 8.68 (s, 1H), 7.60 (m, 3H), 6.92 (d, *J* = 9.0 Hz, 2H), 4.99 (m, 1H), 3.09 (m, 4H), 2.44 (m, 4H), 2.20 (s, 3H), 1.92 (m, 4H), 1.71 (m, 3H), 1.42 (m, 2H), 1.30 (m, 1H). Mass Spectrum (LCMS, ESI pos.) Calcd. For C₂₅H₃₁N₇O₂: 462.25 (M + H), Found 462.0.

Example 61

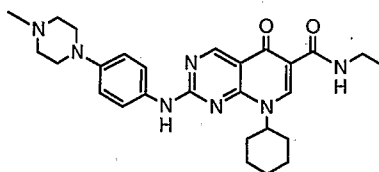
8-Cyclohexyl-2-[4-(4-methyl-piperazin-1-yl)-phenylamino]-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid methyl amide (Cpd 61)



Using the procedure outlined in Example 28 the title compound was prepared from 8-cyclohexyl-2-[4-(4-methyl-piperazin-1-yl)-phenylamino]-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid ethyl ester (from Example 60(A), 20 mg, 0.040 mmol). The title compound was obtained as yellow solid after a preparative HPLC (32 mL/ min 5-100% MeCN/ H₂O gradient over 10 min) purification (9.0 mg, 47%). ¹H NMR (400MHz, CDCl₃) δ (ppm): 9.60 (m, 1H), 9.27 (s, 1H), 8.76 (s, 1H), 7.50 (br, 1H), 7.44 (d, *J* = 8.6 Hz, 2H), 6.88 (d, *J* = 9.0 Hz, 2H), 5.05 (m, 1H), 3.14 (m, 4H), 2.92 (d, *J* = 4.9 Hz, 3H), 2.54 (m, 4H), 2.30 (s, 3H), 1.95 (m, 4H), 1.66 (m, 3H), 1.44 (m, 2H), 1.20 (m, 1H). Mass Spectrum (LCMS, ESI pos.) Calcd. For C₂₆H₃₃N₇O₂: 476.27 (M + H), Found 476.0.

Example 62

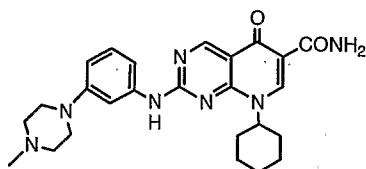
8-Cyclohexyl-2-[4-(4-methyl-piperazin-1-yl)-phenylamino]-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid ethyl amide (Cpd 62)



Using the procedure outlined in Example 29 the title compound was prepared from 8-cyclohexyl-2-[4-(4-methyl-piperazin-1-yl)-phenylamino]-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid ethyl ester (from Example 60(A), 20 mg, 0.040 mmol). The title compound was obtained as yellow solid after a preparative HPLC (32 mL/ min 5-100% MeCN/ H₂O gradient over 10 min) purification (8.3 mg, 42%). ¹H NMR (400MHz, CDCl₃) δ (ppm): 9.60 (m, 1H), 9.27 (s, 1H), 8.76 (s, 1H), 7.50 (br, 1H), 7.44 (d, *J* = 8.6 Hz, 2H), 6.88 (d, *J* = 9.0 Hz, 2H), 5.05 (m, 1H), 3.42 (m, 2H), 3.14 (m, 4H), 2.54 (m, 4H), 2.30 (s, 3H), 1.95 (m, 4H), 1.66 (m, 3H), 1.44 (m, 2H), 1.23 (m, 1H), 1.18 (t, *J* = 7.3 Hz, 3H). Mass Spectrum (LCMS, ESI pos.) Calcd. For C₂₇H₃₅N₇O₂: 490.29 (M + H), Found 490.0.

Example 63

8-Cyclohexyl-2-[3-(4-methyl-piperazin-1-yl)-phenylamino]-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid amide (Cpd 63)



A. 8-Cyclohexyl-2-[3-(4-methyl-piperazin-1-yl)-phenylamino]-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid ethyl ester

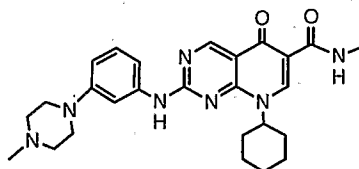
Using the procedure outlined in Example 1(g) the title compound was prepared from 3-(4-methyl-piperazin-1-yl)-phenylamine (from Example 37(A), 55 mg, 0.29 mmol) and 8-cyclohexyl-2-methanesulfonyl-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid ethyl ester (from Example 17(e), 100 mg, 0.26 mmol). The title compound was obtained as a yellow solid (72 mg, 56%). ¹H NMR (400MHz, CDCl₃) δ (ppm): 9.27 (s, 1H), 8.46 (s, 1H), 7.75 (br, 1H), 7.29 (m, 1H), 7.22 (d, *J* = 8.5 Hz, 1H), 6.86 (m, 1H), 6.66 (d, *J* = 8.5 Hz, 1H), 5.05 (m, 1H), 4.31 (q, *J* = 7.1 Hz, 2H), 3.17 (t, *J* = 4.9 Hz, 4H), 2.51 (t, *J* = 4.9 Hz, 4H), 2.28 (s, 3H), 1.94 (m, 4H), 1.76-1.19 (m, 6H), 1.34 (t, *J* = 7.1 Hz, 3H).

B. 8-Cyclohexyl-2-[3-(4-methyl-piperazin-1-yl)-phenylamino]-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid amide

Using the procedure outlined in Example 7 the title compound was prepared from 8-cyclohexyl-2-[3-(4-methyl-piperazin-1-yl)-phenylamino]-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid ethyl ester (from the previous step, 20 mg, 0.040 mmol). The title compound was obtained as yellow solid after a preparative HPLC (32 mL/ min 5-100% MeCN/ H₂O gradient over 10 min) purification (2.3 mg, 12%). ¹H NMR (400MHz, CDCl₃) δ (ppm): 9.44 (br, 1H), 9.32 (s, 1H), 8.77 (s, 1H), 7.50 (br, 1H), 7.29 (br, 1H), 7.22 (m, 1H), 6.86 (br, 1H), 6.70 (d, *J* = 8.5 Hz, 1H), 5.67 (br, 1H), 5.11 (m, 1H), 3.18 (m, 4H), 2.52 (m, 4H), 2.29 (s, 3H), 1.95 (m, 4H), 1.69 (m, 3H), 1.44 (m, 2H), 1.20 (m, 1H). Mass Spectrum (LCMS, ESI pos.) Calcd. For C₂₅H₃₁N₇O₂: 462.25 (M + H), Found 462.1.

Example 64

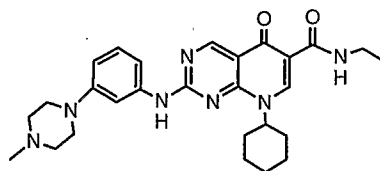
8-Cyclohexyl-2-[3-(4-methyl-piperazin-1-yl)-phenylamino]-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid methyl amide (Cpd 64)



Using the procedure outlined in Example 28 the title compound was prepared from 8-cyclohexyl-2-[3-(4-methyl-piperazin-1-yl)-phenylamino]-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid ethyl ester (from Example 63(A), 20 mg, 0.040 mmol). The title compound was obtained as yellow solid after a preparative HPLC (32 mL/ min 5-100% MeCN/ H₂O gradient over 10 min) purification (8.9 mg, 47%). ¹H NMR (400MHz, CDCl₃) δ (ppm): 9.59 (m, 1H), 9.31 (s, 1H), 8.78 (s, 1H), 7.50 (br, 1H), 7.29 (m, 1H), 7.22 (d, *J* = 8.5 Hz, 1H), 6.87 (m, 1H), 6.68 (d, *J* = 8.5 Hz, 1H), 5.09 (m, 1H), 3.14 (m, 4H), 2.92 (d, *J* = 4.9 Hz, 3H), 2.54 (m, 4H), 2.30 (s, 3H), 1.95 (m, 4H), 1.66 (m, 3H), 1.44 (m, 2H), 1.20 (m, 1H). Mass Spectrum (LCMS, ESI pos.) Calcd. For C₂₆H₃₃N₇O₂: 476.27 (M + H), Found 476.1.

Example 65

8-Cyclohexyl-2-[3-(4-methyl-piperazin-1-yl)-phenylamino]-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid ethyl amide (Cpd 65)

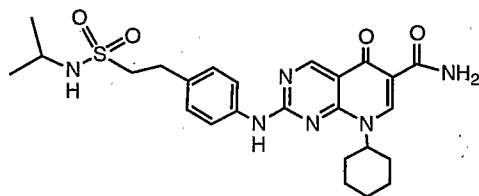


Using the procedure outlined in Example 29 the title compound was prepared from 8-cyclohexyl-2-[3-(4-methyl-piperazin-1-yl)-phenylamino]-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid ethyl ester (from Example 63(A), 20 mg, 0.040 mmol). The title compound was obtained as yellow solid after a preparative HPLC (32 mL/ min 5-100% MeCN/ H₂O gradient over 10 min) purification (7.5 mg, 38%). ¹H NMR (400MHz, CDCl₃) δ (ppm): 9.65 (m, 1H), 9.30 (s, 1H), 8.78 (s, 1H), 7.47 (br, 1H), 7.29 (m, 1H), 7.22

(d, $J = 8.5$ Hz, 1H), 6.87 (m, 1H), 6.68 (d, $J = 8.5$ Hz, 1H), 5.09 (m, 1H), 3.42 (m, 2H), 3.14 (m, 4H), 2.54 (m, 4H), 2.30 (s, 3H), 1.95 (m, 4H), 1.66 (m, 3H), 1.44 (m, 2H), 1.23 (m, 1H), 1.18 (t, $J = 7.3$ Hz, 3H). Mass Spectrum (LCMS, ESI pos.) Calcd. For $C_{27}H_{35}N_7O_2$: 490.29 (M + H), Found 490.1.

Example 66

8-Cyclohexyl-2-[4-(2-isopropylsulfamoyl-ethyl)-phenylamino]-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid amide (Cpd 66)



A. 8-Cyclohexyl-2-[4-(2-isopropylsulfamoyl-ethyl)-phenylamino]-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid ethyl ester

Using the procedure outlined in Example 1(g) the title compound was prepared from 2-(4-amino-phenyl)-ethanesulfonic acid isopropylamide (from Example 33(B), 68 mg, 0.28 mmol) and 8-cyclohexyl-2-methanesulfonyl-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid ethyl ester (from Example 17(e), 100 mg, 0.26 mmol). The title compound was obtained as a yellow solid (50 mg, 35%). 1H NMR (400MHz, $CDCl_3$) δ (ppm): 9.34 (s, 1H), 8.54 (s, 1H), 7.88 (br, 1H), 7.61 (d, $J = 8.3$ Hz, 2H), 7.25 (d, $J = 8.3$ Hz, 2H), 5.10 (m, 1H), 4.40 (q, $J = 7.1$ Hz, 2H), 4.17 (m, 1H), 3.66 (m, 1H), 3.29 (m, 2H), 3.14 (m, 2H), 2.06 (m, 4H), 1.86 (m, 1H), 1.68 (m, 2H), 1.51 (m, 2H), 1.41 (t, $J = 7.1$ Hz, 3H), 1.31(m, 1H), 1.24 (s, 3H), 1.23 (s, 3H).

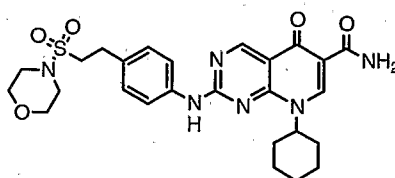
B. 8-Cyclohexyl-2-[4-(2-isopropylsulfamoyl-ethyl)-phenylamino]-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid amide

Using the procedure outlined in Example 7 the title compound was prepared from 8-cyclohexyl-2-[4-(2-isopropylsulfamoyl-ethyl)-phenylamino]-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid ethyl ester (from the previous step, 20 mg, 0.037 mmol). The title compound was obtained as yellow solid after a preparative HPLC (32 mL/ min 5-100% MeCN/ H_2O gradient over 10 min) purification (6.6 mg, 35%). 1H

NMR (400MHz, DMSO-*d*₆) δ (ppm): 10.45 (br, 1H), 9.20 (s, 1H), 9.03 (m, 1H), 8.71 (s, 1H), 7.72 (d, *J* = 7.6 Hz, 2H), 7.58 (m, 1H), 7.26 (d, *J* = 8.3 Hz, 1H), 7.04 (d, *J* = 7.5 Hz, 1H), 5.01 (br, 1H), 3.47 (m, 1H), 3.23 (m, 2H), 2.92 (m, 2H), 1.93 (m, 4H), 1.43 (m, 3H), 1.30 (m, 2H), 1.12 (m, 1H), 1.12 (s, 3H), 1.10 (s, 3H). Mass Spectrum (LCMS, ESI pos.)
 Calcd. For C₂₅H₃₂N₆O₄S: 513.22 (M + H), Found 513.0.

Example 67

8-Cyclohexyl-2-{4-[2-(morpholine-4-sulfonyl)-ethyl]-phenylamino}-5-oxo-5,8-dihydro-pyrido[2,3-*d*]pyrimidine-6-carboxylic acid amide (Cpd 67)



A. 8-Cyclohexyl-2-{4-[2-(morpholine-4-sulfonyl)-ethyl]-phenylamino}-5-oxo-5,8-dihydro-pyrido[2,3-*d*]pyrimidine-6-carboxylic acid ethyl ester

Using the procedure outlined in Example 1(g) the title compound was prepared from 4-[2-(morpholine-4-sulfonyl)-ethyl]-phenylamine (from Example 35(A), 75 mg, 0.28 mmol) and 8-cyclohexyl-2-methanesulfonyl-5-oxo-5,8-dihydro-pyrido[2,3-*d*]pyrimidine-6-carboxylic acid ethyl ester (from Example 17(e), 100 mg, 0.26 mmol). The title compound was obtained as a yellow solid (57 mg, 38%). ¹H NMR (400MHz, CDCl₃) δ (ppm): 9.26 (s, 1H), 8.46 (s, 1H), 7.65 (br, 1H), 7.55 (d, *J* = 8.4 Hz, 2H), 7.19 (d, *J* = 8.4 Hz, 2H), 5.04 (m, 1H), 4.32 (q, *J* = 7.1 Hz, 2H), 3.68 (m, 4H), 3.22 (m, 4H), 3.10 (m, 4H), 2.00 (m, 4H), 1.80 (m, 1H), 1.62 (m, 2H), 1.48 (m, 2H), 1.34 (t, *J* = 7.1 Hz, 3H), 1.31 (m, 1H).

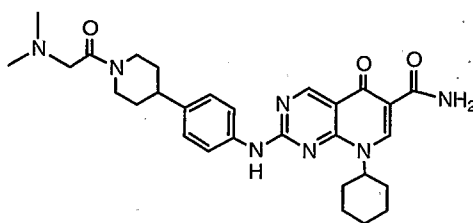
B. 8-Cyclohexyl-2-{4-[2-(morpholine-4-sulfonyl)-ethyl]-phenylamino}-5-oxo-5,8-dihydro-pyrido[2,3-*d*]pyrimidine-6-carboxylic acid amide

Using the procedure outlined in Example 7 the title compound was prepared from 8-cyclohexyl-2-{4-[2-(morpholine-4-sulfonyl)-ethyl]-phenylamino}-5-oxo-5,8-dihydro-pyrido[2,3-*d*]pyrimidine-6-carboxylic acid ethyl ester (from the previous step, 20 mg, 0.035 mmol). The title compound was obtained as yellow solid after a preparative HPLC

(32 mL/min 5-100% MeCN/ H₂O gradient over 10 min) purification (9.2 mg, 49%). ¹H NMR (400MHz, CD₂Cl₂) δ (ppm): 9.26 (br, 1H), 8.76 (s, 1H), 7.62 (d, *J* = 8.0 Hz, 2H), 7.20 (d, *J* = 8.0 Hz, 2H), 5.08 (br, 1H), 3.64 (m, 4H), 3.18 (m, 8H), 1.97 (m, 4H), 1.71 (m, 3H), 1.45 (m, 2H), 1.27 (m, 1H). Mass Spectrum (LCMS, ESI pos.) Calcd. For C₂₆H₃₂N₆O₅S: 541.22 (M + H), Found 541.0.

Example 68

8-Cyclohexyl-2-{4-[1-(2-dimethylamino-acetyl)-piperidin-4-yl]-phenylamino}-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid amide (Cpd **68**)



A. 8-Cyclohexyl-2-{4-[1-(2-dimethylamino-acetyl)-piperidin-4-yl]-phenylamino}-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid ethyl ester

Using the procedure outlined in Example 1(g) the title compound was prepared from 4-[1-(2-dimethylamino-acetyl)-piperidin-4-yl]-phenylamine (from Example 70(B)), 73 mg, 0.28 mmol) and 8-cyclohexyl-2-methanesulfonyl-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid ethyl ester (from Example 17(e), 100 mg, 0.26 mmol). The title compound was obtained as a white solid (40 mg, 25%). ¹H NMR (400MHz, CDCl₃) δ (ppm): 9.21 (s, 1H), 8.99 (s, 1H), 8.41 (s, 1H), 7.47 (d, *J* = 8.5 Hz, 2H), 7.13 (d, *J* = 8.5 Hz, 2H), 4.96 (m, 3H), 4.31 (q, *J* = 7.1 Hz, 2H), 3.00 (m, 4H), 2.77 (m, 1H), 2.30 (s, 6H), 1.93 (m, 6 H), 1.64 (m, 5H), 1.42 (m, 2H), 1.34 (t, *J* = 7.1 Hz, 3H), 1.18(m, 1H).

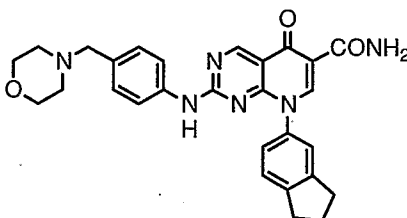
B. 8-Cyclohexyl-2-{4-[1-(2-dimethylamino-acetyl)-piperidin-4-yl]-phenylamino}-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid amide

Using the procedure outlined in Example 7 the title compound was prepared from 8-cyclohexyl-2-{4-[1-(2-dimethylamino-acetyl)-piperidin-4-yl]-phenylamino}-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid ethyl ester (from the previous step, 20 mg, 0.036 mmol). The title compound was obtained as yellow solid after a preparative HPLC (32 mL/min 5-100% MeCN/ H₂O gradient over 10 min) purification (16 mg, 84%).

^1H NMR (400MHz, CDCl_3) δ (ppm): 9.58 (m, 1H), 9.30 (s, 1H), 9.05 (s, 1H), 8.78 (s, 1H), 7.52 (d, $J = 8.5$ Hz, 2H), 7.20 (d, $J = 8.5$ Hz, 2H), 5.08 (m, 3H), 3.06 (m, 4H), 2.86 (m, 1H), 2.37 (s, 6H), 1.99 (m, 6 H), 1.72 (m, 5H), 1.41 (m, 3H), 1.18(m, 1H). Mass Spectrum (LCMS, ESI pos.) Calcd. For $\text{C}_{29}\text{H}_{37}\text{N}_7\text{O}_3$: 532.30 (M + H), Found 532.1.

Example 69

8-Indan-5-yl-2-(4-morpholin-4-ylmethyl-phenylamino)-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid amide (Cpd 69)



A. 8-Indan-5-yl-2-(4-morpholin-4-ylmethyl-phenylamino)-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid ethyl ester

8-Indan-5-yl-2-methanesulfonyl-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid ethyl ester (0.28 g, 0.068 mmol) and 4-morpholin-4-ylmethyl-phenylamine (0.013 g, 0.068 mmol) were combined in *i*-PrOH (1 mL) and heated to 90 °C. After 3 h, the reaction mixture was concentrated and purified by preparative HPLC (30 mL/min 5-100% MeCN/ H_2O gradient over 10 min) and lyophilized to provide 22 mg (62%) of 8-indan-5-yl-2-(4-morpholin-4-ylmethyl-phenylamino)-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid ethyl ester. ^1H NMR (300MHz, CDCl_3) δ (ppm): 9.38 (br s, 1H), 8.55 (s, 1H), 7.44 (d, 2H, $J=7.6\text{Hz}$), 7.05-7.30 (m, 5H), 4.40 (q, 2H, $J=7.1\text{Hz}$), 3.71 (br s, 4H), 3.43 (s, 2H), 3.09 (t, 2H, $J=7.5\text{Hz}$), 3.02 (t, 2H, $J=7.2\text{Hz}$), 2.42 (br s, 4H), 2.21-2.31 (m, 2H), 1.40 (t, 3H, $J=7.1\text{Hz}$).

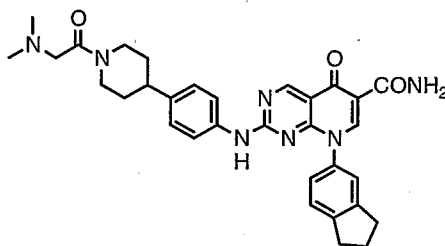
B. 8-Indan-5-yl-2-(4-morpholin-4-ylmethyl-phenylamino)-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid amide

8-Indan-5-yl-2-(4-morpholin-4-ylmethyl-phenylamino)-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid ethyl ester (18 mg, 0.034 mmol) was dissolved in MeOH (2 mL) and cooled to -78 °C in a high pressure vessel. Ammonia was bubbled into the solution for 1 min and the vessel was sealed and allowed to warm to rt. After 14 h,

the solution was cooled to $-78\text{ }^{\circ}\text{C}$, the vessel was opened and the solution was allowed to warm to rt. The solution was concentrated and water (2 mL) and MeCN (1 mL) was added, the solution frozen and lyophilized to provide 11.6 mg of 8-Indan-5-yl-2-(4-morpholin-4-ylmethyl-phenylamino)-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid amide. ^1H NMR (400MHz, CDCl_3) δ (ppm): 9.31 (s, 1H), 8.77 (s, 1H), 7.35 (d, 2H, $J=7.9\text{Hz}$), 7.10 (d, 2H, $J=7.3\text{Hz}$), 6.91-7.01 (m, 3H), 3.62-3.64 (m, 4H), 3.35 (s, 2H), 3.01 (t, 2H, $J=7.2\text{Hz}$), 2.92 (t, 2H, $J=7.3\text{Hz}$), 2.43 (br s, 4H), 2.15-2.19 (m, 2H). Mass Spectrum (LCMS, ESI pos.) Calcd. for $\text{C}_{31}\text{H}_{34}\text{N}_6\text{O}_3$: 538.27, Found: 539.2 (M + H).

Example 70

2-{4-[1-(2-Dimethylamino-acetyl)-piperidin-4-yl]-phenylamino}-8-indan-5-yl-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid amide (Cpd 70)



A. {4-[1-(2-Dimethylamino-acetyl)-piperidin-4-yl]-phenyl}-carbamic acid tert-butyl ester

Dimethylamino-acetyl chloride (0.14 g, 0.86 mmol) and (4-piperidin-4-yl-phenyl)-carbamic acid tert-butyl ester (0.20 g, 0.72 mmol) were combined in CH_2Cl_2 (5 mL) and triethylamine (0.21 g, 2.2 mmol) was added. After 6 h, water (5 mL) was added. The reaction mixture was extracted with CH_2Cl_2 (3 x 5 mL) and the combined organic extracts were dried (MgSO_4) and concentrated. The compound was found to be unstable on silica and therefore carried on without further purification. ^1H NMR (400MHz, CDCl_3) δ (ppm): 9.04 (s, 1H), 7.52 (d, 2H, $J=8.5\text{Hz}$), 7.16 (d, 2H, $J=8.5\text{Hz}$), 3.06 (s, 2H), 2.76-2.82 (m, 2H), 2.59-2.65 (m, 1H), 2.37 (s, 6H), 1.78-1.81 (m, 2H), 1.54-1.64 (m, 2H), 1.48 (s, 9H), 1.30 (br s, 2H).

B. 1-[4-(4-Amino-phenyl)-piperidin-1-yl]-2-dimethylamino-ethanone

{4-[1-(2-Dimethylamino-acetyl)-piperidin-4-yl]-phenyl}-carbamic acid tert-butyl ester (0.72 mmol) was diluted in CH₂Cl₂ (3 mL) and TFA (3 mL) was added. After 1 h, the reaction mixture was concentrated. Water (2 mL) was added and the solution was frozen and lyophilized overnight to provide (0.11 g) (59%) of 1-[4-(4-amino-phenyl)-piperidin-1-yl]-2-dimethylamino-ethanone. ¹H NMR (TFA salt) (400MHz, CDCl₃) δ (ppm): 10.54 (s, 1H), 7.52 (d, 2H, J=8.5Hz), 7.20 (d, 2H, J=8.5Hz), 4.10 (s, 2H), 3.34-3.37 (m, 2H), 2.97-3.12 (m, 3H), 2.85 (s, 6H), 1.88-1.91 (m, 2H), 1.69-1.78 (m, 2H).

C. 2-{4-[1-(2-Dimethylamino-acetyl)-piperidin-4-yl]-phenylamino}-8-indan-5-yl-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid ethyl ester

8-Indan-5-yl-2-methanesulfonyl-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid ethyl ester (20.5 mg, 0.050 mmol) and 1-[4-(4-amino-phenyl)-piperidin-1-yl]-2-dimethylamino-ethanone di-TFA salt (24 mg g, 0.050 mmol) were combined in *i*-PrOH (1 mL) and TEA (10.6 mg, 0.11 mmol) was added and the mixture was heated to 90 °C. After 3 h, the reaction mixture was concentrated and purified by preparative HPLC (30 mL/ min 5-100% MeCN/ H₂O gradient over 10 min) and lyophilized to provide 24 mg (80%) of 2-{4-[1-(2-Dimethylamino-acetyl)-piperidin-4-yl]-phenylamino}-8-indan-5-yl-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid ethyl ester. ¹H NMR (300MHz, CDCl₃) δ (ppm): 9.31 (s, 1H), 9.10 (br s, 1H), 8.48 (s, 1H), 7.51 (d, 2H, J=8.1Hz), 7.22-7.34 (2H), 7.13-7.16 (m 3H), 4.38 (q, 2H, J=7.0Hz), 3.09 (br s, 2H), 2.95-3.02 (m, 6H), 2.71-2.80 (m, 2H), 2.39 (s, 6H), 2.11-2.22 (m, 2H), 1.55-1.93 (m, 4H), 1.39 (t, 3H, J=7.2Hz).

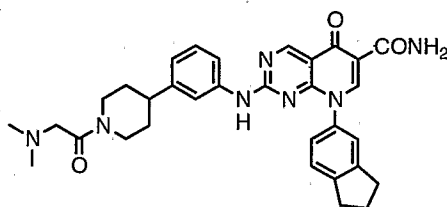
D. 2-{4-[1-(2-Dimethylamino-acetyl)-piperidin-4-yl]-phenylamino}-8-indan-5-yl-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid amide

2-{4-[1-(2-Dimethylamino-acetyl)-piperidin-4-yl]-phenylamino}-8-indan-5-yl-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid ethyl ester (20 mg, 0.034 mmol) was dissolved in MeOH (2 mL) and cooled to -78 °C in a high pressure vessel. Ammonia was bubbled into the solution for 1 min and the vessel was sealed and allowed to warm to rt. After 14 h, the solution was cooled to -78 °C, the vessel was opened and the

solution was allowed to warm to rt. The solution was concentrated and water (2 mL) and MeCN (1 mL) was added, the solution frozen and lyophilized to provide 15 mg of 2-{4-[1-(2-Dimethylamino-acetyl)-piperidin-4-yl]-phenylamino}-8-indan-5-yl-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid amide. ¹H NMR (400MHz, CDCl₃) δ (ppm): 9.24 (s, 1H), 8.68 (s, 1H), 7.43 (d, 2H, J=8.4Hz), 7.16-7.25 (m, 3H), 7.07 (d, 2H, J=8.5Hz), 3.01 (s, 2H), 2.87-2.93 (m, 4H), 2.30 (s, 6H), 2.04-2.12 (m, 2H), 1.73-1.85 (m, 2H), 1.61 (br s, 4H). Mass Spectrum (LCMS, ESI pos.) Calcd. for C₃₂H₃₅N₇O₃: 565.28, Found: 566.3 (M + H).

Example 71

2-{3-[1-(2-Dimethylamino-acetyl)-piperidin-4-yl]-phenylamino}-8-indan-5-yl-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid amide (Cpd 71)



A 1-[3-(4-Amino-phenyl)-piperidin-1-yl]-2-dimethylamino-ethanone

Dimethylamino-acetyl chloride (0.14 g, 0.86 mmol) and (3-piperidin-4-yl-phenyl)-carbamic acid tert-butyl ester (0.20 g, 0.72 mmol) were combined in CH₂Cl₂ (5 mL) and triethylamine (0.21 g, 2.2 mmol) was added. After 6 h, water (5 mL) was added. The reaction mixture was extracted with CH₂Cl₂ (3 x 5 mL) and the combined organic extracts were dried (MgSO₄) and concentrated. The compound was found to be unstable on silica and therefore carried on without further purification. (3-Piperidin-4-yl-phenyl)-carbamic acid tert-butyl ester (0.72 mmol) was diluted in CH₂Cl₂ (3 mL) and TFA (3 mL) was added. After 1 h, the reaction mixture was concentrated. Water (2 mL) was added and the solution was frozen and lyophilized overnight to provide (0.090 g) (48%) of 1-[4-(3-amino-phenyl)-piperidin-1-yl]-2-dimethylamino-ethanone.

B. 2-{3-[1-(2-Dimethylamino-acetyl)-piperidin-4-yl]-phenylamino}-8-indan-5-yl-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid ethyl ester

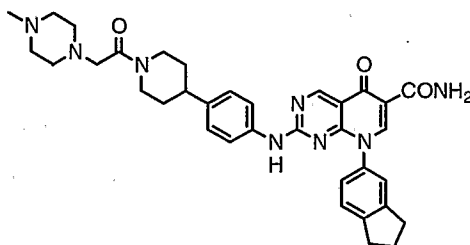
8-Indan-5-yl-2-methanesulfonyl-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid ethyl ester (32.5 mg, 0.079 mmol) and 1-[3-(4-amino-phenyl)-piperidin-1-yl]-2-dimethylamino-ethanone di-TFA salt (38.5 mg, 0.079 mmol) were combined in *i*-PrOH (1 mL) and TEA (17 mg, .16 mmol) was added and the mixture was heated to 90 °C. After 3 h, the reaction mixture was concentrated and purified by preparative HPLC (30 mL/min 5-100% MeCN/ H₂O gradient over 10 min) and lyophilized to provide 16.5 mg of 2-{3-[1-(2-dimethylamino-acetyl)-piperidin-4-yl]-phenylamino}-8-indan-5-yl-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid ethyl ester. ¹H NMR (400MHz, CDCl₃) δ (ppm): 9.23 (s, 1H), 9.08 (br s, 1H), 8.40 (s, 1H), 7.44 (s, 1H), 7.17-7.29 (m, 4H), 7.08 (dd, 1H, J=1.9Hz, J=7.9Hz), 6.85 (d, 1H, J=7.6Hz), 4.29 (q, 2H, J=7.1Hz), 3.02 (br s, 2H), 2.88-2.93 (m, 5H), 2.66-2.73 (m, 2H), 2.32 (s, 6H), 2.05-2.12 (m, 2H), 1.75-1.84 (m, 2H), 1.55 (br s, 2H), 1.31 (t, 3H, J=7.1Hz).

C. 2-{3-[1-(2-Dimethylamino-acetyl)-piperidin-4-yl]-phenylamino}-8-indan-5-yl-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid amide

2-{4-[1-(2-Dimethylamino-acetyl)-piperidin-4-yl]-phenylamino}-8-indan-5-yl-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid ethyl ester (16 mg, 0.027 mmol) was dissolved in MeOH (2 mL) and cooled to -78 °C in a high pressure vessel. Ammonia was bubbled into the solution for 1 min and the vessel was sealed and allowed to warm to rt. After 14 h, the solution was cooled to -78 °C, the vessel was opened and the solution was allowed to warm to rt. The solution was concentrated and water (2 mL) and MeCN (1 mL) was added, the solution frozen and lyophilized to provide 13.6 mg of 2-{3-[1-(2-Dimethylamino-acetyl)-piperidin-4-yl]-phenylamino}-8-indan-5-yl-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid amide. ¹H NMR (400MHz, CDCl₃) δ (ppm): 9.49 (br s, 1H), 9.25 (s, 1H), 9.04 (br s, 1H), 8.69 (s, 1H), 7.47 (s, 1H), 7.15-7.27 (m, 2H), 7.07 (d, 2H, J=7.8Hz), 6.85 (d, 1H, J=7.5Hz), 5.80 (br s, 1H), 3.00 (s, 2H), 2.87-2.92 (m, 4H), 2.30 (s, 6H), 2.04-2.12 (m, 2H), 1.76-1.87 (m, 2H), 1.57 (br s, 2H). Mass Spectrum (LCMS, ESI pos.) Calcd. for C₃₂H₃₅N₇O₃; 565.28, Found: 566.3 (M + H).

Example 72

8-Indan-5-yl-2-(4-{1-[2-(4-methyl-piperazin-1-yl)-acetyl]-piperidin-4-yl}-phenylamino)-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid amide (Cpd 72)



A. 8-Indan-5-yl-2-(4-{1-[2-(4-methyl-piperazin-1-yl)-acetyl]-piperidin-4-yl}-phenylamino)-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid ethyl ester
 (4-Piperidin-4-yl-phenyl)-carbamic acid tert-butyl ester (0.20 g, 0.72 mmol), (4-methyl-piperazin-1-yl)-acetic acid (0.11 g, 0.72 mmol), HOBt (0.10 g, 0.72 mmol), DCI (0.14 g, 0.72 mmol), and DIEA (0.10 g, 0.72 mmol) were all combined in DMF (5 mL). After 16 h, water (10 mL) and CH₂Cl₂ (10 mL) were added. The organic layer was washed with water (3 x 10 mL), dried (MgSO₄) and concentrated. Chromatography (0-15% EtOAc/ hexanes gradient) provided 0.24 g (83%) of (4-{1-[2-(4-methyl-piperazin-1-yl)-acetyl]-piperidin-4-yl}-phenyl)-carbamic acid tert-butyl ester. (4-{1-[2-(4-Methyl-piperazin-1-yl)-acetyl]-piperidin-4-yl}-phenyl)-carbamic acid tert-butyl ester (0.72 mmol) was diluted in CH₂Cl₂ (3 mL) and TFA (3 mL) was added. After 1 h, the reaction mixture was concentrated. Water (2 mL) was added and the solution was frozen and lyophilized overnight to provide (0.16 g) (72%) of 1-[4-(4-Amino-phenyl)-piperidin-1-yl]-2-(4-methyl-piperazin-1-yl)-ethanone. 8-Indan-5-yl-2-methanesulfonyl-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid ethyl ester (32.5 mg, 0.079 mmol) and 1-[4-(4-Amino-phenyl)-piperidin-1-yl]-2-(4-methyl-piperazin-1-yl)-ethanone tri-TFA salt (52 mg, 0.079 mmol) were combined in *i*-PrOH (1 mL) and TEA (25 mg, 0.25 mmol) was added and the mixture was heated to 90 °C. After 3 h, the reaction mixture was concentrated and purified by preparative HPLC (30 mL/ min 5-100% MeCN/ H₂O gradient over 10 min) and lyophilized to provide 8.6 mg of 8-indan-5-yl-2-(4-{1-[2-(4-methyl-piperazin-1-yl)-acetyl]-piperidin-4-yl}-phenylamino)-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid ethyl ester. ¹H NMR (400MHz, CDCl₃) δ (ppm): 9.23 (s,

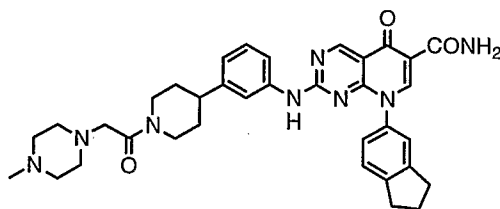
1H), 8.39 (s, 1H), 7.40-7.42 (m, 2H), 7.17-7.26 (m, 3H), 7.06-7.09 (m, 2H), 4.30 (q, 2H, J=7.1Hz), 3.07 (br s, 1H), 2.87-2.93 (m, 6H), 2.48-2.67 (m, 7H), 2.28 (br s, 3H), 2.05-2.12 (m, 2H), 1.72-1.82 (m, 2H), 1.49 (br s, 2H), 1.31 (t, 3H, J=7.1Hz).

B. 8-Indan-5-yl-2-(4-{1-[2-(4-methyl-piperazin-1-yl)-acetyl]-piperidin-4-yl}-phenylamino)-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid amide

8-Indan-5-yl-2-(4-{1-[2-(4-methyl-piperazin-1-yl)-acetyl]-piperidin-4-yl}-phenylamino)-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid ethyl ester (15 mg, 0.024 mmol) was dissolved in MeOH (2 mL) and cooled to -78 °C in a high pressure vessel. Ammonia was bubbled into the solution for 1 min and the vessel was sealed and allowed to warm to rt. After 14 h, the solution was cooled to -78 °C, the vessel was opened and the solution was allowed to warm to rt. The solution was concentrated and water (2 mL) and MeCN (1 mL) was added, the solution frozen and lyophilized to provide 11.6 mg of 8-Indan-5-yl-2-(4-{1-[2-(4-methyl-piperazin-1-yl)-acetyl]-piperidin-4-yl}-phenylamino)-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid amide. ¹H NMR (400MHz, CDCl₃) δ (ppm): 9.46 (br s, 1H), 9.25 (s, 1H), 8.80 (br s, 1H), 8.69 (s, 1H), 7.40 (d, 2H, J=8.3Hz), 7.15-7.24 (m, 3H), 7.07 (d, 2H, J=8.3Hz), 5.70 (br s, 1H), 3.10 (s, 2H), 2.86-2.92 (m, 6H), 2.68 (br s, 12H), 2.41 (br s, 2H), 2.04-2.12 (m, 2H), 1.74-1.86 (m, 2H), 1.50 (br s, 2H). Mass Spectrum (LCMS, ESI pos.) Calcd. for C₃₅H₄₀N₈O₃: 620.32, Found: 621.3 (M + H).

Example 73

8-Indan-5-yl-2-(3-{1-[2-(4-methyl-piperazin-1-yl)-acetyl]-piperidin-4-yl}-phenylamino)-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid amide (Cpd 73)



A. 2-{3-[1-(2-Dimethylamino-acetyl)-piperidin-4-yl]-phenylamino}-8-indan-5-yl-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid ethyl ester

(3-Piperidin-4-yl-phenyl)-carbamic acid tert-butyl ester (0.20 g, 0.72 mmol), (4-methyl-piperazin-1-yl)-acetic acid (0.11 g, 0.72 mmol), HOBt (0.10 g, 0.72 mmol), DCI (0.14 g, 0.72 mmol), and DIEA (0.10 g, 0.72 mmol) were all combined in DMF (5 mL). After 16 h, water (10 mL) and CH₂Cl₂ (10 mL) were added. The organic layer was washed with water (3 x 10 mL), dried (MgSO₄) and concentrated. Chromatography (0-15% EtOAc/ hexanes gradient) provided 0.22 g (73%) of 1-[4-(3-Amino-phenyl)-piperidin-1-yl]-2-(4-methyl-piperazin-1-yl)-ethanone. (3-{1-[2-(4-Methyl-piperazin-1-yl)-acetyl]-piperidin-4-yl}-phenyl)-carbamic acid tert-butyl ester (0.72 mmol) was diluted in CH₂Cl₂ (3 mL) and TFA (3 mL) was added. After 1 h, the reaction mixture was concentrated. Water (2 mL) was added and the solution was frozen and lyophilized overnight to provide (0.18 g) (81%) of 1-[4-(3-Amino-phenyl)-piperidin-1-yl]-2-(4-methyl-piperazin-1-yl)-ethanone. 8-Indan-5-yl-2-methanesulfonyl-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid ethyl ester (32.5 mg, 0.079 mmol) and 1-[3-(4-amino-phenyl)-piperidin-1-yl]-2-dimethylamino-ethanone di-TFA salt (38.5 mg g, 0.079 mmol) were combined in *i*-PrOH (1 mL) and TEA (17 mg, 0.16 mmol) was added and the mixture was heated to 90 °C. After 3 h, the reaction mixture was concentrated and purified by preparative HPLC (30 mL/ min 5-100% MeCN/ H₂O gradient over 10 min) and lyophilized to provide 16.5 mg of 2-{3-[1-(2-Dimethylamino-acetyl)-piperidin-4-yl]-phenylamino}-8-indan-5-yl-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid ethyl ester. ¹H NMR (400MHz, CDCl₃) δ (ppm): 9.23 (s, 1H), 9.08 (br s, 1H), 8.40 (s, 1H), 7.44 (s, 1H), 7.17-7.29 (m, 4H), 7.08 (dd, 1H, J=1.9Hz, J=7.9Hz), 6.85 (d, 1H, J=7.6Hz), 4.29 (q, 2H, J=7.1Hz), 3.02 (br s, 2H), 2.88-2.93 (m, 5H), 2.66-2.73 (m, 2H), 2.32 (s, 6H), 2.05-2.12 (m, 2H), 1.75-1.84 (m, 2H), 1.55 (br s, 2H), 1.31 (t, 3H, J=7.1Hz).

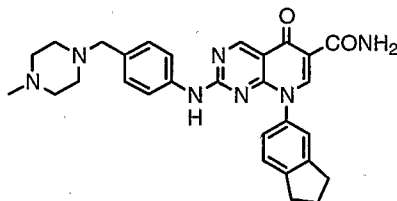
B. 2-{3-[1-(2-Dimethylamino-acetyl)-piperidin-4-yl]-phenylamino}-8-indan-5-yl-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid amide

2-{4-[1-(2-Dimethylamino-acetyl)-piperidin-4-yl]-phenylamino}-8-indan-5-yl-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid ethyl ester (16 mg, 0.027 mmol) was dissolved in MeOH (2 mL) and cooled to -78 °C in a high pressure vessel.

Ammonia was bubbled into the solution for 1 min and the vessel was sealed and allowed to warm to rt. After 14 h, the solution was cooled to -78 °C, the vessel was opened and the solution was allowed to warm to rt. The solution was concentrated and water (2 mL) and MeCN (1 mL) was added, the solution frozen and lyophilized to provide 13.6 mg of 8-indan-5-yl-2-(3-{1-[2-(4-methyl-piperazin-1-yl)-acetyl]-piperidin-4-yl}-phenylamino)-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid amide. ¹H NMR (400MHz, CDCl₃) δ (ppm): 9.49 (br s, 1H), 9.25 (s, 1H), 9.04 (br s, 1H), 8.69 (s, 1H), 7.47 (s, 1H), 7.15-7.27 (m, 2H), 7.07 (d, 2H, J=7.8Hz), 6.85 (d, 1H, J=7.5Hz), 5.80 (br s, 1H), 3.00 (s, 2H), 2.87-2.92 (m, 4H), 2.30 (s, 6H), 2.04-2.12 (m, 2H), 1.76-1.87 (m, 2H), 1.57 (br s, 2H). Mass Spectrum (LCMS, ESI pos.) Calcd. for C₃₅H₄₀N₈O₃: 620.32, Found: 621.3 (M+H).

Example 74

8-Indan-5-yl-2-[4-(4-methyl-piperazin-1-ylmethyl)-phenylamino]-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid amide (Cpd 74)



A. 8-Indan-5-yl-2-[4-(4-methyl-piperazin-1-ylmethyl)-phenylamino]-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid ethyl ester

8-Indan-5-yl-2-methanesulfonyl-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid ethyl ester (0.098 g, 0.24 mmol) and 4-(4-methyl-piperazin-1-ylmethyl)-phenylamine (0.049 g, 0.24 mmol) were combined in *i*-PrOH (2 mL) and heated to 90 °C. After 3 h, the reaction mixture was concentrated and purified by preparative HPLC (30 mL/min 5-100% MeCN/ H₂O gradient over 10 min) and lyophilized to provide 20 mg of 8-Indan-5-yl-2-[4-(4-methyl-piperazin-1-ylmethyl)-phenylamino]-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid ethyl ester. ¹H NMR (400MHz, CDCl₃) δ (ppm): 9.36 (s, 1H), 8.54 (s, 1H), 7.43 (d, 2H, J=7.9Hz), 7.29 (m, 2H), 7.18 (dd, 2H, J=2.0Hz, J=7.9Hz), 7.03-7.05 (m, 1H), 4.38 (q, 2H, J=7.1Hz), 3.44 (s, 2H), 3.08 (t, 2H,

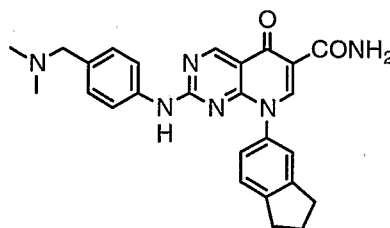
J=7.4Hz), 3.01 (t, 2H, J=7.5Hz), 2.52 (br s, 8H), 2.36 (s, 3H), 2.19-2.29 (m, 2H), 1.39 (t, 3H, J=7.1Hz).

B. 8-Indan-5-yl-2-[4-(4-methyl-piperazin-1-ylmethyl)-phenylamino]-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid amide

8-Indan-5-yl-2-[4-(4-methyl-piperazin-1-ylmethyl)-phenylamino]-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid ethyl ester (10 mg, 0.020 mmol) was dissolved in MeOH (2 mL) and cooled to -78 °C in a high pressure vessel. Ammonia was bubbled into the solution for 1 min and the vessel was sealed and allowed to warm to rt. After 14 h, the solution was cooled to -78 °C, the vessel was opened and the solution was allowed to warm to rt. The solution was concentrated and water (2 mL) and MeCN (1 mL) was added, the solution frozen and lyophilized to provide 6.3 mg of 8-indan-5-yl-2-[4-(4-methyl-piperazin-1-ylmethyl)-phenylamino]-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid amide. ¹H NMR (400MHz, CDCl₃) δ (ppm): 9.39 (s, 1H), 9.32 (s, 1H), 8.78 (s, 1H), 7.34 (d, 2H, J=7.8Hz), 7.10 (d, 2H, J=7.9Hz), 6.97-6.99 (m, 3H), 5.68 (br s, 1H), 3.37 (s, 2H), 3.00 (t, 2H, J=7.4Hz), 2.92 (t, 2H, J=7.5Hz), 2.81 (s, 3H), 2.44 (br s, 4H), 2.28 (br s, 4H), 2.13-2.15 (m, 2H). Mass Spectrum (LCMS, ESI pos.) Calcd. for C₂₉H₃₈N₆O₃: 518.30, Found: 519.2 (M + H).

Example 75

2-(4-Dimethylaminomethyl-phenylamino)-8-indan-5-yl-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid amide (Cpd 75)



A. 2-(4-Dimethylaminomethyl-phenylamino)-8-indan-5-yl-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid ethyl ester

8-Indan-5-yl-2-methanesulfonyl-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid ethyl ester (87 mg, 0.21 mmol) and 4-dimethylaminomethyl-phenylamine

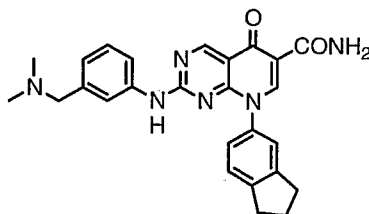
(32 mg, 0.21 mmol) were combined in *i*-PrOH (2 mL) and heated to 90 °C. After 3 h, the reaction mixture was concentrated and purified by preparative HPLC (30 mL/ min 5-100% MeCN/ H₂O gradient over 10 min) and lyophilized to provide 66 mg of 2-(4-Dimethylaminomethyl-phenylamino)-8-indan-5-yl-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid ethyl ester. ¹H NMR (400MHz, CDCl₃) δ (ppm): 9.38 (s, 1H), 8.54 (s, 1H), 7.09-7.43 (m, 7H), 4.35-4.42 (m, 2H), 3.57 (s, 2H), 2.90-3.08 (m, 4H), 2.35 (s, 6H), 2.16-2.26 (m, 2H), 1.39 (t, 3H, J=7.1Hz).

B. 2-(4-Dimethylaminomethyl-phenylamino)-8-indan-5-yl-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid amide

2-(4-Dimethylaminomethyl-phenylamino)-8-indan-5-yl-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid ethyl ester (30 mg, 0.062 mmol) was dissolved in MeOH (2 mL) and cooled to -78 °C in a high pressure vessel. Ammonia was bubbled into the solution for 1 min and the vessel was sealed and allowed to warm to rt. After 14 h, the solution was cooled to -78 °C, the vessel was opened and the solution was allowed to warm to rt. The solution was concentrated and water (2 mL) and MeCN (1 mL) was added, the solution frozen and lyophilized to provide 3.5 mg of 2-(4-dimethylaminomethyl-phenylamino)-8-indan-5-yl-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid amide. ¹H NMR (400MHz, CDCl₃) δ (ppm): 9.39 (br s, 1H), 9.35 (s, 1H), 8.79 (s, 1H), 7.03-7.45 (m, 7H), 3.01 (t, 2H, J=7.3Hz), 2.93 (t, 2H, J=7.8Hz), 2.37 (br s, 2H), 2.10-2.18 (m, 2H), 1.19 (s, 6H). Mass Spectrum (LCMS, ESI pos.) Calcd. for C₂₆H₂₆N₆O₂: 454.21, Found: 455.2 (M + H).

Example 76

2-(3-Dimethylaminomethyl-phenylamino)-8-indan-5-yl-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid amide (Cpd 76)



A. 2-(3-Dimethylaminomethyl-phenylamino)-8-indan-5-yl-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid ethyl ester

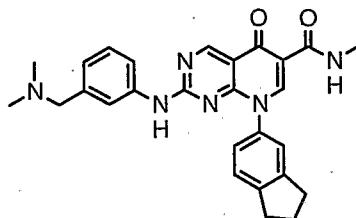
8-Indan-5-yl-2-methanesulfonyl-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid ethyl ester (105 mg, 0.25 mmol) and 3-dimethylaminomethyl-phenylamine (38 mg, 0.25 mmol) were combined in iPrOH (2 mL) and heated to 90 °C. After 3 h, the reaction mixture was concentrated and purified by preparative HPLC (30 mL/min 5-100% MeCN/H₂O gradient over 10 min) and lyophilized to provide 56 mg of 2-(3-Dimethylaminomethyl-phenylamino)-8-indan-5-yl-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid ethyl ester. ¹H NMR (400MHz, CDCl₃) δ (ppm): 9.31 (br s, 1H), 8.98 (br s, 1H), 8.51 (s, 1H), 8.39 (s, 1H), 7.00-7.53 (m, 7H), 4.28-4.40 (m, 2H), 3.64 (br s, 2H), 2.88-3.09 (m, 4H), 2.40 (s, 6H), 2.05-2.25 (m, 2H), 1.32-1.40 (m, 3H).

B. 2-(3-Dimethylaminomethyl-phenylamino)-8-indan-5-yl-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid amide

2-(3-Dimethylaminomethyl-phenylamino)-8-indan-5-yl-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid ethyl ester (20 mg, 0.041 mmol) was dissolved in MeOH (2 mL) and cooled to -78 °C in a high pressure vessel. Ammonia was bubbled into the solution for 1 min and the vessel was sealed and allowed to warm to rt. After 14 h, the solution was cooled to -78 °C, the vessel was opened and the solution was allowed to warm to rt. The solution was concentrated and water (2 mL) and MeCN (1 mL) was added, the solution frozen and lyophilized to provide 2.5 mg of 2-(3-dimethylaminomethyl-phenylamino)-8-indan-5-yl-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid amide. ¹H NMR (400MHz, CDCl₃) δ (ppm): 9.36 (s, 2H), 8.77 (s, 1H), 6.97-4.45 (m, 7H), 3.00 (t, 2H, J=7.6Hz), 2.93 (t, 2H, J=7.4Hz), 2.13-2.21 (m, 2H), 1.47 (br s, 2H), 1.19 (s, 6H). Mass Spectrum (LCMS, ESI pos.) Calcd. for C₂₆H₂₆N₆O₂: 454.21, Found: 455.2 (M + H).

Example 77

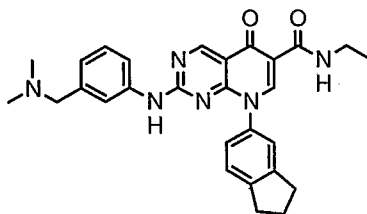
2-(3-Dimethylaminomethyl-phenylamino)-8-indan-5-yl-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid methylamide (Cpd 77)



2-(3-Dimethylaminomethyl-phenylamino)-8-indan-5-yl-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid ethyl ester (15 mg, 0.032 mmol) was dissolved in MeOH (1 mL) and methylamine (1 mL of 1.0 M solution in THF, 1.0 mmol) was added and the reaction mixture was heated at 80 °C. After 16 h, the solution was cooled to rt and purified by preparative HPLC (C-18 column, 32 mL/ min 5-100% MeCN/ H₂O gradient over 15 min) and lyophilized to provide 2.3 mg of 2-(3-dimethylaminomethyl-phenylamino)-8-indan-5-yl-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid methylamide. ¹H NMR (TFA salt) (400MHz, CDCl₃) δ (ppm): 9.51 (s, 1H), 9.35 (s, 1H), 8.75 (s, 1H), 7.01-7.50 (m, 7H), 3.90 (br s, 2H), 2.90-3.02 (m, 7H), 2.60 (s, 6H), 2.11-2.19 (m, 2H). Mass Spectrum (LCMS, ESI pos.) Calcd. for C₂₇H₂₈N₆O₂: 468.23, Found: 469.1 (M + H).

Example 78

2-(3-Dimethylaminomethyl-phenylamino)-8-indan-5-yl-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid ethylamide (Cpd 78)

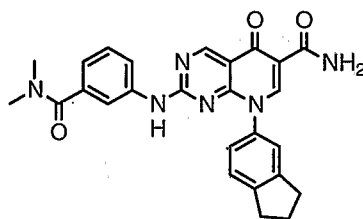


2-(3-Dimethylaminomethyl-phenylamino)-8-indan-5-yl-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid ethyl ester (15 mg, 0.032 mmol) was dissolved in MeOH (1 mL) and ethylamine (1 mL of 1.0 M solution in THF, 1.0 mmol) was added

and the reaction mixture was heated at 80 °C. After 16 h, the solution was cooled to rt and purified by preparative HPLC (C-18 column, 32 mL/ min 5-100% MeCN/ H₂O gradient over 15 min) and lyophilized to provide 2.1 mg of 2-(3-dimethylaminomethyl-phenylamino)-8-indan-5-yl-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid methylamide. ¹H NMR (TFA salt) (400MHz, CDCl₃) δ (ppm): 9.57 (s, 1H), 9.34 (s, 1H), 8.74 (s, 1H), 6.99-7.37 (m, 7H), 3.89 (br s, 2H), 3.39-3.46 (m, 2H), 2.89-3.02 (m, 4H), 2.60 (s, 6H), 2.13-2.17 (m, 2H), 1.19 (t, 1H, J=7.3Hz). Mass Spectrum (LCMS, ESI pos.) Calcd. for C₂₈H₃₀N₆O₂: 482.24, Found: 483.2 (M + H).

Example 79

2-(3-Dimethylcarbamoyl-phenylamino)-8-indan-5-yl-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid amide (Cpd 79)



A. 2-(3-Dimethylcarbamoyl-phenylamino)-8-indan-5-yl-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid ethyl ester

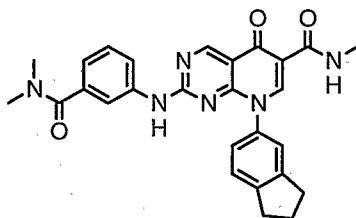
8-Indan-5-yl-2-methanesulfonyl-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid ethyl ester (20 mg, 0.048 mmol) and 3-amino-N,N-dimethyl-benzamide (8 mg, 0.05 mmol) were combined in *i*-PrOH (2 mL) and heated to 90 °C. After 15 h, the reaction mixture was concentrated and purified by preparative HPLC (C-18 column, 32 mL/ min 5-100% MeCN/ H₂O gradient over 15 min) and lyophilized to provide 15.6 mg of 2-(3-dimethylcarbamoyl-phenylamino)-8-indan-5-yl-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid ethyl ester. ¹H NMR (400MHz, CDCl₃) δ (ppm): 9.31 (s, 1H), 1.13 (s, 1H), 7.46 (br s, 1H), 7.33 (d, 1H, J=7.9Hz), 7.16-7.21 (m, 2H), 7.10 (d, 1H, J=7.6Hz), 6.96 (br s, 2H), 4.29 (q, 2H, J=7.1Hz), 2.97-3.04 (m, 5H), 2.85-2.93 (m, 5H), 2.14 (p, 2H, J=7.4Hz), 1.29 (t, 3H, J=7.1Hz)

B 2-(3-Dimethylcarbamoyl-phenylamino)-8-indan-5-yl-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid amide

2-(3-Dimethylcarbamoyl-phenylamino)-8-indan-5-yl-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid ethyl ester (5.2 mg, 0.010 mmol) was dissolved in MeOH (2 mL) and cooled to -78 °C in a high pressure vessel. Ammonia was bubbled into the solution for 1 min and the vessel was sealed and allowed to warm to rt. After 14 h, the solution was cooled to -78 °C, the vessel was opened and the solution was allowed to warm to rt. The solution was concentrated and water (2 mL) and MeCN (1 mL) was added, the solution frozen and lyophilized to provide 4.1 mg of 2-(3-dimethylcarbamoyl-phenylamino)-8-indan-5-yl-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid amide. ¹H NMR (400MHz, CDCl₃) δ (ppm): 9.42 (s, 1H), 9.29 (s, 1H), 8.88 (s, 1H), 7.49 (m, 4H), 6.88-6.90 (m, 3H), 3.29 (br s, 2H), 2.44-2.93 (m), 1.94-2.15 (m), 1.19-1.76 (m). Mass Spectrum (LCMS, ESI pos.) Calcd. for C₂₆H₂₄N₆O₃: 468.19, Found: 469.2 (M + H).

Example 80

2-(3-Dimethylcarbamoyl-phenylamino)-8-indan-5-yl-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid methylamide (Cpd 80)

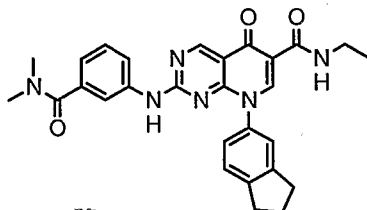


2-(3-Dimethylcarbamoyl-phenylamino)-8-indan-5-yl-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid ethyl ester (5.2 mg, 0.010 mmol) was dissolved in MeOH (1 mL) and methylamine (1 mL of 1.0 M solution in THF, 1.0 mmol) was added and the reaction mixture was heated at 80 °C. After 16 h, the solution was cooled to rt and purified by preparative HPLC (C-18 column, 32 mL/ min 5-100% MeCN/ H₂O gradient over 15 min) and lyophilized to provide 2.1 mg of 2-(3-dimethylcarbamoyl-phenylamino)-8-indan-5-yl-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid methylamide. ¹H NMR (TFA salt) (400MHz, CDCl₃) δ (ppm): 9.56 (br. S, 1H), 9.33 (s, 1H), 8.77 (s, 1H), 7.51 (dd, 1H, J=2.3Hz, J=9.3Hz), 7.34 (d, 1H, J=7.9Hz), 7.11 (dd, 1H, J=1.7Hz,

J=7.8Hz), 6.99 (br. S, 1H), 2.86-3.05 (m, 13H), 2.12-2.19 (m, 2H). Mass Spectrum (LCMS, ESI pos.) Calcd. for $C_{27}H_{26}N_6O_3$, 482.21, Found: 483.2 (M + H).

Example 81

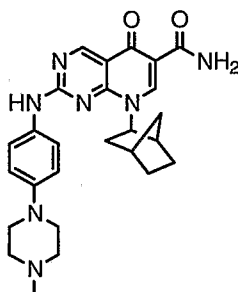
2-(3-Dimethylcarbamoyl-phenylamino)-8-indan-5-yl-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid ethylamide (Cpd **81**)



2-(3-Dimethylcarbamoyl-phenylamino)-8-indan-5-yl-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid ethyl ester (5.2 mg, 0.010 mmol) was dissolved in MeOH (1 mL) and ethylamine (1 mL of 1.0 M solution in THF, 1.0 mmol) was added and the reaction mixture was heated at 80 °C. After 16 h, the solution was cooled to rt and purified by preparative HPLC (C-18 column, 32 mL/ min 5-100% MeCN/ H₂O gradient over 15 min) and lyophilized to provide 2.1 mg of 2-(3-dimethylcarbamoyl-phenylamino)-8-indan-5-yl-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid ethylamide. ¹H NMR (TFA salt) (400MHz, CDCl₃) δ (ppm): 9.64 (s, 1H), 9.32 (s, 1H), 8.77 (s, 1H), 7.51 (dd, 1H, J=2.3Hz, J=9.3Hz), 7.34 (d, 1H, J=7.8Hz), 7.17-7.19 (m, 3H), 7.11 (dd, 1H, J=2.0Hz, J=8.0Hz), 6.99 (br. S, 1H), 3.44 (dq, 2H, J=5.8Hz, J=7.3Hz), 2.86-3.05 (m, 10H), 2.11-2.19 (m, 2H), 1.21 (t, 1H, J=7.3Hz). Mass Spectrum (LCMS, ESI pos.) Calcd. for $C_{28}H_{28}N_6O_3$, 496.22, Found: 497.2 (M + H).

Example 82

8-Bicyclo[2.2.1]hept-2-yl-2-[4-(4-methyl-piperazin-1-yl)-phenylamino]-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid amide (Cpd 82)



A. 3-(Bicyclo[2.2.1]hept-2-ylamino)-propionic acid ethyl ester

Bicyclo[2.2.1]hept-2-ylamine (2.0 g, 18.0 mmol) and 4-chloro-2-methylsulfanyl-pyrimidine-5-carboxylic acid ethyl ester (2.45 g, 18.0 mmol) were combined neat and K_2CO_3 (3.72 g, 27.0 mmol) and a catalytic amount of tetrabutylammonium iodide (ca. 2 mg) was added. The mixture was heated at 80 °C overnight. The resulting mixture was then partitioned between water and DCM. The organic layer was dried ($MgSO_4$) and concentrated to provide 1.5 g of 3-(bicyclo[2.2.1]hept-2-ylamino)-propionic acid ethyl ester. 1H NMR (400MHz, $CDCl_3$) δ (ppm): 5.29 (s, 1H), 4.13 (q, 2H, $J=7.1$ Hz), 2.77-2.92 (m, 2H), 2.57 (dd, 1H, $J=3.1$ Hz, $J=7.3$ Hz), 2.50 (t, 2H, $J=6.6$ Hz), 2.16-2.20 (m, 2H), 1.57 (ddd, 1H, $J=2.2$ Hz, $J=7.5$ Hz, $J=12.3$ Hz), 1.41-1.49 (m, 3H), 1.25 (t, 3H, $J=7.2$ Hz), 1.01-1.10 (m, 4H).

B. 8-Bicyclo[2.2.1]hept-2-yl-2-[4-(4-methyl-piperazin-1-yl)-phenylamino]-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid ethyl ester

3-(Bicyclo[2.2.1]hept-2-ylamino)-propionic acid ethyl ester (1.5 g, 7.1 mmol) and 4-chloro-2-methylsulfanyl-pyrimidine-5-carboxylic acid ethyl ester (1.6 g, 7.1 mmol) were combined in CH_2Cl_2 (20 mL) and triethylamine (1.0 g, 10 mmol) was added. After 16 h, water (10 mL) was added the organic layer was separated, dried ($MgSO_4$), and concentrated. Chromatography (10-50% EtOAc/ hexanes gradient) provided 1.8 g of 4-[bicyclo[2.2.1]hept-2-yl-(2-ethoxycarbonyl-ethyl)-amino]-2-methylsulfanyl-pyrimidine-5-carboxylic acid ethyl ester. Sodium (30 wt % dispersion in paraffin wax, 0.55 g, 7.2 mmol) was added to *t*-butanol (5.0 mL) at rt. After 30 minutes, a solution of 4-

[bicyclo[2.2.1]hept-2-yl-(2-ethoxycarbonyl-ethyl)-amino]-2-methylsulfanyl-pyrimidine-5-carboxylic acid ethyl ester (1.8 g, 4.4 mmol) in 20 mL of toluene was added to the sodium *t*-butoxide solution and the resulting mixture was heated at 90 °C for 30 minutes. The reaction mixture was then cooled and the solution was adjusted to pH 7 using a 1N HCl solution. The solution was then extracted with EtOAc (2 X 20 mL) and the organic layer was dried (MgSO₄), and concentrated. Recrystallization from *i*-PrOH provided 0.51 g of 8-bicyclo[2.2.1]hept-2-yl-2-methylsulfanyl-5-oxo-5,6,7,8-tetrahydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid ethyl ester. 8-Bicyclo[2.2.1]hept-2-yl-2-methanesulfonyl-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid ethyl ester (46 mg, 0.12 mmol) and 4-(4-methyl-piperazin-1-yl)-phenylamine (22 mg, 0.12 mmol) were combined in *i*-PrOH (2 mL) and heated to 90 °C. After 3 h, the reaction mixture was concentrated and purified by preparative HPLC (C-18 column, 32 mL/min 5-100% MeCN/ H₂O gradient over 15 min) and lyophilized to provide 11.4 mg of 8-bicyclo[2.2.1]hept-2-yl-2-[4-(4-methyl-piperazin-1-yl)-phenylamino]-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid ethyl ester. ¹H NMR (400MHz, CDCl₃) δ (ppm): 9.21 (s, 1H), 8.59 (s, 1H), 7.52 (d, 2H, J=8.9Hz), 6.87 (d, 2H, J=9.0Hz), 4.31 (q, 2H, J=7.1Hz), 3.52-3.62 (m, 4H), 3.28 (br s, 2H), 2.98 (br s, 2H), 2.82 (s, 3H), 2.14-2.53 (m, 5H), 1.58-1.75 (m, 4H), 1.22-1.42 (m, 5H).

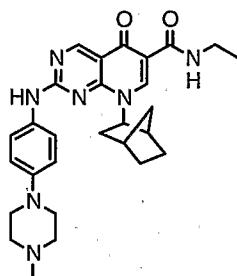
C. 8-Bicyclo[2.2.1]hept-2-yl-2-[4-(4-methyl-piperazin-1-yl)-phenylamino]-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid amide

8-Bicyclo[2.2.1]hept-2-yl-2-[4-(4-methyl-piperazin-1-yl)-phenylamino]-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid ethyl ester (5.7 mg, 0.11 mmol) was dissolved in MeOH (2 mL) and cooled to -78 °C in a high pressure vessel. Ammonia was bubbled into the solution for 1 min and the vessel was sealed and allowed to warm to rt. After 14 h, the solution was cooled to -78 °C, the vessel was opened and the solution was allowed to warm to rt. The solution was concentrated and water (2 mL) and MeCN (1 mL) was added, the solution frozen and lyophilized to provide 3.2 mg of 8-bicyclo[2.2.1]hept-2-yl-2-[4-(4-methyl-piperazin-1-yl)-phenylamino]-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid amide. ¹H NMR (TFA salt) (400MHz, CDCl₃) δ (ppm): 9.36-9.39 (m, 2H), 8.78 (s, 1H), 7.52 (d, 1H, J=7.2Hz), 7.33 (d, 1H, J=7.9Hz), 7.12 (d, 1H,

J=8.0Hz), 6.98 (br s, 1H), 5.69 (br s, 1H), 2.86-3.04 (m, 11H), 2.13-2.17 (m, 2H), 1.52 (br s, 6H). Mass Spectrum (LCMS, ESI pos.) Calcd. for $C_{26}H_{31}N_7O_2$: 473.25, Found: 474.3 (M + H).

Example 83

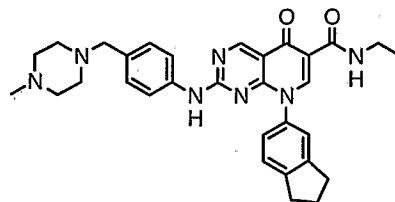
8-Bicyclo[2.2.1]hept-2-yl-2-[4-(4-methyl-piperazin-1-yl)-phenylamino]-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid ethylamide (Cpd 83)



8-Bicyclo[2.2.1]hept-2-yl-2-[4-(4-methyl-piperazin-1-yl)-phenylamino]-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid ethyl ester (5.7 mg, 0.11 mmol) was dissolved in MeOH (1 mL) and ethylamine (1 mL of 1.0 M solution in THF, 1.0 mmol) was added and the reaction mixture was heated at 80 °C. After 16 h, the solution was cooled to rt and purified by preparative HPLC (C-18 column, 32 mL/ min 5-100% MeCN/ H₂O gradient over 15 min) and lyophilized to provide 3.7 of 8-bicyclo[2.2.1]hept-2-yl-2-[4-(4-methyl-piperazin-1-yl)-phenylamino]-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid ethylamide. ¹H NMR (TFA salt) (400MHz, CDCl₃) δ (ppm): 9.62 (s, 1H), 9.26 (s, 1H), 8.90 (s, 1H), 7.54 (d, 2H, J=8.8Hz), 6.89 (d, 2H, J=8.9Hz), 4.85-4.88 (m, 1H), 3.26-3.64 (m, 9H), 2.91-2.94 (m, 2H), 2.82 (s, 3H), 2.55 (s, 1H), 2.44 (s, 1H), 2.03 (br s, 8H), 1.59-1.61 (m, 4H), 1.35-1.41 (m, 2H), 1.19 (t, 1H, J=7.3Hz). Mass Spectrum (LCMS, ESI pos.) Calcd. for $C_{28}H_{35}N_7O_2$: 501.29, Found: 502.3 (M + H).

Example 84

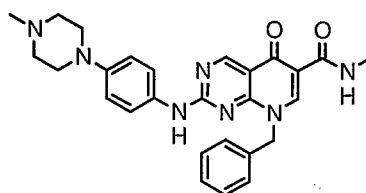
8-Indan-5-yl-2-[4-(4-methyl-piperazin-1-ylmethyl)-phenylamino]-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid ethylamide (Cpd 84)



8-Indan-5-yl-2-[4-(4-methyl-piperazin-1-ylmethyl)-phenylamino]-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid ethyl ester (9.2 mg, 0.017 mmol) was dissolved in MeOH (1 mL) and ethylamine (1 mL of 1.0 M solution in THF, 1.0 mmol) was added and the reaction mixture was heated at 80 °C. After 16 h, the solution was cooled to rt and purified by preparative HPLC (C-18 column, 32 mL/ min 5-100% MeCN/H₂O gradient over 15 min) and lyophilized to provide 5.2 mg of 8-indan-5-yl-2-[4-(4-methyl-piperazin-1-ylmethyl)-phenylamino]-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid ethylamide. ¹H NMR TFA salt (400MHz, CDCl₃) δ (ppm): 9.38 (br s, 1H), 9.37 (s, 1H), 8.84 (s, 1H), 7.58-7.60 (m, 1H), 7.40-7.47 (m, 2H), 7.16 (dd, 2H, J=2.0Hz, J=7.9Hz), 7.05 (br s, 2H), 3.43-3.55 (m, 4H), 3.07 (t, 2H, J=7.3Hz), 2.99 (t, 2H, J=7.4Hz), 2.53 (br s, 8H), 2.36 (s, 3H), 2.18-2.27 (m, 2H), 1.15-1.39 (m, 3H). Mass Spectrum (LCMS, ESI pos.) Calcd. for C₃₁H₃₅N₇O₂: 537.29, Found: 538.3 (M + H).

Example 85

8-Benzyl-2-[4-(4-methyl-piperazin-1-yl)-phenylamino]-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid methylamide (Cpd 85)



A. 4-[Benzyl-(2-ethoxycarbonyl-ethyl)-amino]-2-methylsulfanyl-pyrimidine-5-carboxylic acid ethyl ester

3-Benzylamino-propionic acid ethyl ester (2.0 g, 9.6 mmol) and 4-chloro-2-methylsulfanyl-pyrimidine-5-carboxylic acid ethyl ester (2.2 g, 9.6 mmol) were combined in DCM (50 mL) and triethylamine (1.5 g, 14.5 mmol) was added. After 14 h, water (25 mL) was added and the organic layer was separated, dried (MgSO₄), and concentrated. Chromatography on silica (0-30% EtOAc/ hexanes gradient) provided 2.91 g of 4-[benzyl-(2-ethoxycarbonyl-ethyl)-amino]-2-methylsulfanyl-pyrimidine-5-carboxylic acid ethyl ester. ¹H NMR (400MHz, CDCl₃) δ (ppm): 8.46 (s, 1H), 7.23-7.33 (m, 5H), 4.75 (s, 2H), 4.21 (q, 2H, J=7.2Hz), 4.06-4.15 (m, 2H), 3.77 (t, 2H, J=7.2Hz), 2.66-2.70 (app t, 2H), 2.45 (s, 3H), 1.19-1.29 (m, 6H).

B. 8-Benzyl-2-methylsulfanyl-5-oxo-5,6,7,8-tetrahydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid ethyl ester

Sodium (30 wt % dispersion in paraffin wax, 0.55 g, 7.2 mmol) was added to *t*-butanol (5.0 mL) at rt. After 30 minutes, a solution of 4-[benzyl-(2-ethoxycarbonyl-ethyl)-amino]-2-methylsulfanyl-pyrimidine-5-carboxylic acid ethyl ester (2.9 g, 7.2 mmol) in 20 mL of toluene was added to the sodium *t*-butoxide solution and the resulting mixture was heated at 90 °C for 30 minutes. The reaction mixture was then cooled and the solution was adjusted to pH 7 using a 1N HCl solution. The solution was then extracted with EtOAc (2 X 20 mL) and the organic layer was dried (MgSO₄), and concentrated. Recrystallization from *i*-PrOH provided 1.53 g of 8-benzyl-2-methylsulfanyl-5-oxo-5,6,7,8-tetrahydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid ethyl ester. ¹H NMR mixture of tautomers in a 2.3 : 1 ratio, (400MHz, CDCl₃) δ (ppm): 8.65 (s, 1H), 8.25 (s, 1H), 7.24-7.36 (m, 5H), 5.07 (d, 1H, J=14.9Hz), 4.83 (d, 1H, J=14.9Hz), 4.79 (s, 2H), 4.17-4.22 (m, 2H), 2.51 (s, 1.3H), 2.46 (s, 3H), 0.85-0.89 (m, 3H).

C. 8-Benzyl-2-methylsulfanyl-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid ethyl ester

Bromine (0.68 g, 4.3 mmol) was added to a solution of 8-benzyl-2-methylsulfanyl-5-oxo-5,6,7,8-tetrahydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid ethyl ester (1.53 g,

4.28 mmol) in DCM (20 mL). After 30 minutes, the reaction mixture was concentrated. The residue was redissolved in DCM (20 mL) and triethylamine (1.08 g, 10.7 mmol) was added. After 15 h, water (10 mL) was added, the organic layer separated, dried (MgSO₄), and concentrated. Chromatography on silica (0-50% EtOAc/ hexanes gradient) provided 0.39 g 8-benzyl-2-methylsulfanyl-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid ethyl ester. ¹H NMR (400MHz, CDCl₃) δ (ppm): 9.26 (s, 1H), 8.51 (s, 1H), 7.21-7.29 (m, 5H), 5.45 (s, 2H), 4.27 (q, 2H, J=7.1Hz), 2.48 (s, 3H), 1.30 (t, 3H, J=7.1Hz).

D. 8-Benzyl-2-methanesulfonyl-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid ethyl ester

8-Benzyl-2-methylsulfanyl-5-oxo-5,6,7,8-tetrahydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid ethyl ester (0.39 g, 1.1 mmol) and *m*-CPBA (0.61 g (77% w/w), 2.7 mmol) were combined in DCM (20 mL). After 2 hours, a 10% solution of Na₂SO₃ (5 mL) was added and the mixture was partitioned between sat. NaHCO₃ and DCM. The organic layer was dried (MgSO₄) and concentrated. Chromatography on silica (25-100% EtOAc/ hexanes gradient) provided 0.21 g of 8-benzyl-2-methanesulfonyl-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid ethyl ester. ¹H NMR (400MHz, CDCl₃) δ (ppm): 9.70 (s, 1H), 8.72 (s, 1H), 7.38-7.41 (m, 5H), 5.57 (s, 2H), 4.40 (q, 2H, J=7.1Hz), 3.38 (s, 3H), 1.40 (t, 3H, J=7.1Hz).

E. 8-Benzyl-2-[4-(4-methyl-piperazin-1-yl)-phenylamino]-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid methylamide

8-Benzyl-2-[4-(4-methyl-piperazin-1-yl)-phenylamino]-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid ethyl ester (7.6 mg, 0.015 mmol) was dissolved in MeOH (1 mL) and methylamine (1 mL of 1.0 M solution in THF, 1.0 mmol) was added and the reaction mixture was heated at 80 °C. After 16 h, the solution was cooled to rt and purified by preparative HPLC (C-18 column, 32 mL/ min 5-100% MeCN/ H₂O gradient over 15 min) and lyophilized to provide 1.3 mg of 8-benzyl-2-[4-(4-methyl-piperazin-1-yl)-phenylamino]-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid methylamide. ¹H NMR (TFA salt) (400MHz, CDCl₃) δ (ppm): 9.54 (br s, 1H), 9.25 (s, 1H), 8.70 (s, 1H), 7.23-7.30 (m, 5H), 7.13-7.15 (m, 2H), 6.83 (d, 2H, J=8.9Hz), 5.35 (s,

2H), 3.13 (br s, 4H), 2.91 (s, 3H), 2.53 (br s, 4H), 2.30 (br s, 3H). Mass Spectrum (LCMS, ESI pos.) Calcd. for $C_{27}H_{29}N_7O_2$: 483.24, Found: 484.3 (M + H).

Biological Examples

Example 1

Autophosphorylation, Fluorescence Polarization Competition Immunoassay

An autophosphorylation, fluorescence polarization competition immunoassay was used to determine the potency for c-fms inhibition exhibited by selected compounds of Formula I. The assay was performed in black 96-well microplates (LJL BioSystems). The assay buffer used was 100 mM 4-(2-hydroxyethyl)piperazine 1-ethanesulfonic acid (HEPES), pH 7.5, 1 mM 1,4-dithio-DL-threitol (DTT), 0.01 % (v/v) Tween-20. Compounds were diluted in assay buffer containing 4 % dimethylsulfoxide (DMSO) just prior to the assay. To each well, 5 μ L of compound were added followed by the addition of 3 μ L of a mix containing 33 nM c-fms and 16.7 mM $MgCl_2$ (Sigma) in assay buffer. The kinase reaction was initiated by adding 2 μ L of 5 mM ATP (Sigma) in assay buffer. The final concentrations in the assay were 10 nM c-fms, 1 mM ATP, 5 mM $MgCl_2$, 2 % DMSO. Control reactions were ran in each plate: in positive and negative control wells, assay buffer (made 4 % in DMSO) was substituted for the compound; in addition, positive control wells received 1.2 μ L of 50 mM ethylenediaminetetraacetic acid (EDTA).

The plates were incubated at room temperature for 45 min. At the end of the incubation, the reaction was quenched with 1.2 μ L of 50 mM EDTA (EDTA was *not* added to the positive control wells at this point; see above). Following a 5-min incubation, each well received 10 μ L of a 1:1:3 mixture of anti-phosphotyrosine antibody, 10X, PTK green tracer, 10X (vortexed), FP dilution buffer, respectively (all from PanVera, cat. # P2837). The plate was covered, incubated for 30 min at room temperature and the fluorescence polarization was read on the Analyst. The instrument settings were: 485 nm excitation filter; 530 nm emission filter; Z height: middle of well; G factor: 0.93. Under these conditions, the fluorescence polarization values for positive and negative controls were approximately 300 and 150, respectively, and were used to define the 100 % and 0 % inhibition of the c-fms reaction.

The IC₅₀ values shown in Table 1 are averages of three independent measurements.

Table 1
c-fms Autophosphorylation IC₅₀ Values

Cpd	IC₅₀ (μM)	Cpd	IC₅₀ (μM)	Cpd	IC₅₀ (μM)
1	0.28	30	0.012	58	0.12
2	0.44	31	0.02	59	0.19
3	2.9	32	0.033	60	0.035
4	>10	33	0.1	61	0.16
5	0.59	34	>1	62	0.19
6	1.1	35	0.08	63	0.021
7	0.013	36	1.0	64	0.05
8	0.031	37	0.008	65	0.11
9	0.068	38	0.009	66	0.12
10	0.013	39	0.013	67	0.12
11	0.046	40	0.005	68	0.13
12	0.077	41	0.011	69	0.018
13	0.73	42	0.016	70	1.1
14	0.019	43	0.007	71	7.4
15	0.07	44	0.008	72	4.1
16	0.012	45	0.012	73	> 1
17	1.7	46	0.008	74	0.032
18	10	47	0.015	75	0.021
19	0.056	48	0.032	76	0.018
20	1.4	49	0.008	77	0.15
21	10	50	0.015	78	0.14
22	>10	51	0.025	79	0.062
23	0.014	52	0.005	80	0.074
24	0.018	53	0.008	81	0.11
25	0.093	54	0.011	82	0.081
26	0.056	55	0.006	83	0.3
27	0.01	56	0.01	84	0.032
28	0.03	57	0.026	85	0.42
29	0.033				

Example 2

Peptide (Non-Phosphorylated) Assay

A fluorescence polarization competition immunoassay was used to measure compound inhibition of CSF-1R phosphorylation of tyrosine on a synthetic CSF-1R₅₅₅₋₅₆₈ peptide (SYEGNSYTFIDPTQ). The assay was performed in black 96-well microplates (Cat # 42-000-0117, Molecular Devices, Sunnyvale, CA). To each well, 5 μ L of compound (in 4% DMSO) were mixed with 2 μ L of 3.5 nM CSF-1R, 25 mM MgCl₂ in assay buffer (100 mM HEPES, pH 7.5, 1 mM DTT, 0.01% Tween-20), and 2 μ L of 1540 μ M peptide in assay buffer. The kinase reaction was initiated by adding 1 μ L of 10 mM ATP in assay buffer. The final concentrations in the 10 μ L reaction mixture were 100 mM HEPES, pH 7.5, 1 mM DTT, 0.01% Tween-20, 2% DMSO, 308 μ M SYEGNSYTFIDPTQ, 1 mM ATP, 5 mM MgCl₂, and 0.7 nM CSF-1R. Positive and negative control wells were included on each plate, where 4% DMSO in assay buffer was substituted for the compound; in addition, positive control wells received 1.2 μ L of 50 mM EDTA before the start of the reaction.

The plates were covered and incubated at room temperature for 80 min. Reactions were stopped by addition of 1.2 μ L of 50 mM EDTA. Each well then received 10 μ L of a 1:1:3 mixture of 10X anti-phosphotyrosine antibody, 10X PTK green tracer, and FP dilution buffer, respectively (Cat. # P2837, Invitrogen, Carlsbad, CA). The plates were covered, incubated for 30 min at room temperature, and the fluorescence polarization was read on an Analyst plate reader (Molecular Devices). Instrument settings were: 485 nm excitation, 530 nm emission, with a 505 nm cut-off filter; Z height: middle of well; G factor: 0.93. Under these conditions, the fluorescence polarization values for positive and negative controls were approximately 290 and 160, respectively, and were used to define 100% and 0% inhibition of the CSF-1R reaction.

The IC₅₀ values reported in Table 2 are the mean of at least three determinations.

Table 2
c-fms Peptide IC₅₀ Values

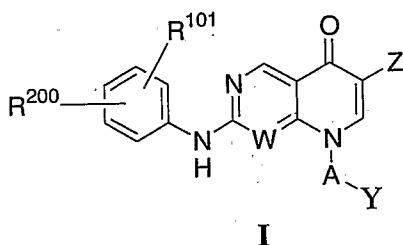
Cpd	IC₅₀ (μM)	Cpd	IC₅₀ (μM)	Cpd	IC₅₀ (μM)
7	0.0039	43	0.00058	53	0.00046
10	0.0027	44	0.00053	54	0.0011
11	0.0056	46	0.00074	55	0.00051
16	0.0043	47	0.0013	56	0.0011
23	0.0015	49	0.00049		
28	0.0016	50	0.00097		
40	0.00024	52	0.00042		

While the foregoing specification teaches the principles of the present invention, with examples provided for the purpose of illustration, it will be understood that the practice of the invention encompasses all of the usual variations, adaptations and/or modifications as come within the scope of the following claims and their equivalents.

All publications disclosed in the above specification are hereby incorporated by reference in full.

We claim:

1. A compound of Formula I:



or a form thereof, wherein:

W is N or CH;

A is absent or alkyl;

Y is a ring selected from cycloalkyl, bicycloalkyl, aryl, alkylaryl, cycloalkylaryl, arylcycloalkyl, or heteroaryl provided that Y is not thiazole;

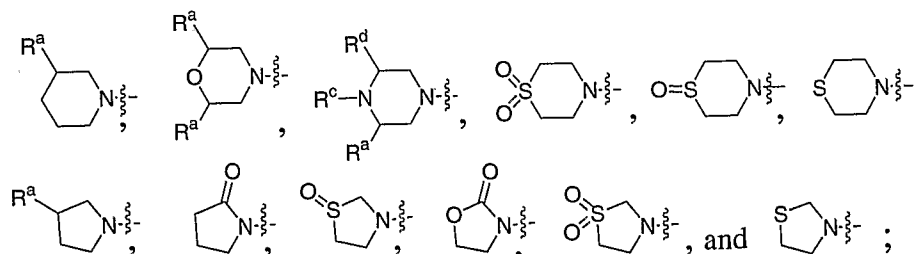
R¹⁰¹ is hydrogen, hydroxyl, methyl, halogen, -CF₃, or methoxy;

R²⁰⁰ is halogen, alkoxy optionally substituted with -CH(OH)-CH₂-NR²⁰³R²⁰⁴, alkyl optionally substituted with R²⁰¹, heterocyclyl optionally substituted with one alkyl and optionally substituted with one R²⁰², amino, alkylamino, dialkylamino, -C(O)(CH₂)_nNR²⁰³R²⁰⁴, heteroaryl, or -R³⁰⁰-R⁴⁰⁰; wherein n is 0, 1, 2, 3, or 4;

R²⁰¹ is hydroxyl, methyl, halogen, -CF₃, amino, alkylamino, dialkylamino or methoxy;

R²⁰² is alkyl, -C(O)-CH₃, -CH₂-C(O)-CH₃, -C(O)(CH₂)_nNR²⁰³R²⁰⁴, or -CON-alkyl-NR²⁰³R²⁰⁴; wherein n is 0, 1, 2, 3, or 4;

R²⁰³ and R²⁰⁴ are independently hydrogen, alkyl, or R²⁰³ and R²⁰⁴ may be taken together to form a ring selected from the following:



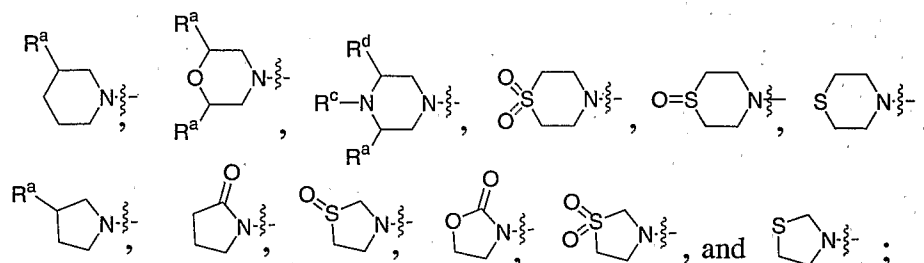
wherein R^a , R^c and R^d are independently hydrogen or alkyl;

R^{300} is alkyl;

R^{400} is $-NR^{403}R^{404}$, $-\text{SO}_2NR^{405}R^{406}$, oxazolidinonyl wherein said oxazolidinonyl is optionally substituted with one or two R^{401} , piperazinyl wherein said piperazinyl is optionally substituted with R^{202} or pyrrolidinonyl wherein said pyrrolidinonyl is optionally substituted with one or two R^{401} ;

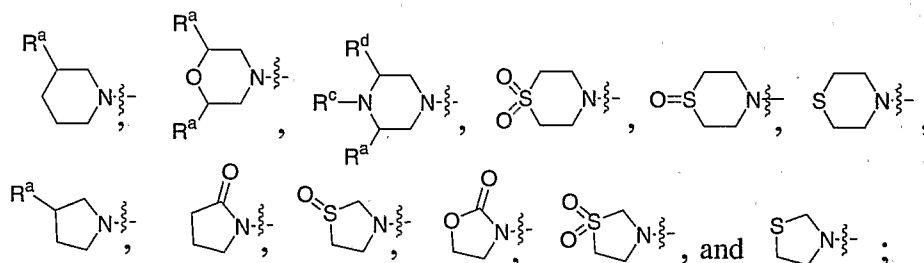
wherein R^{401} is methyl, $-\text{C}(\text{O})-\text{CH}_3$, or $-\text{CH}_2-\text{C}(\text{O})-\text{CH}_3$;

wherein R^{403} and R^{404} are independently hydrogen, alkyl, or R^{403} and R^{404} may be taken together to form a ring selected from the following:



wherein R^a , R^c and R^d are independently hydrogen or alkyl;

R^{405} and R^{406} are independently hydrogen, alkyl, or R^{405} and R^{406} may be taken together to form a ring selected from the following:



wherein R^a , R^c and R^d are independently hydrogen or alkyl; and

Z is CO_2H , CO_2alkyl , or CONR^1R^2 ; wherein R^1 is hydrogen or alkyl; and R^2 is hydrogen, alkyl, cycloalkyl, or alkoxy.

2. The compound of Claim 1 wherein:

A is absent;

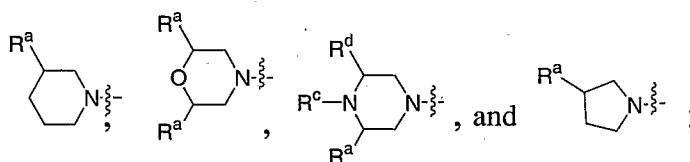
Y is a ring selected from cycloalkyl, bicycloalkyl, phenyl, alkylaryl, cycloalkylaryl, arylcycloalkyl, or heteroaryl provided that Y is not thiazole;

R^{200} is halogen, $C_{(1-4)}$ alkoxy optionally substituted with $-\text{CH}(\text{OH})-\text{CH}_2-\text{NR}^{203}\text{R}^{204}$, $C_{(1-4)}$ alkyl optionally substituted with R^{201} , heterocyclyl optionally substituted with one $C_{(1-4)}$ alkyl and optionally substituted with one R^{202} , dialkylamino, $-\text{C}(\text{O})(\text{CH}_2)_n\text{NR}^{203}\text{R}^{204}$, heteroaryl, or $-\text{R}^{300}-\text{R}^{400}$; wherein n is 0, 1, 2, 3, or 4;

R^{201} is hydroxyl, methyl, halogen, $-\text{CF}_3$, dialkylamino or methoxy;

R^{202} is alkyl, $-\text{C}(\text{O})-\text{CH}_3$, $-\text{CH}_2-\text{C}(\text{O})-\text{CH}_3$, $-\text{C}(\text{O})(\text{CH}_2)_n\text{NR}^{203}\text{R}^{204}$, $-\text{C}(\text{O})\text{N}(\text{CH}_2)_n\text{NR}^{203}\text{R}^{204}$; wherein n is 0, 1, 2, 3, or 4;

R^{203} and R^{204} are independently hydrogen, $C_{(1-4)}$ alkyl, or R^{203} and R^{204} may be taken together to form a ring selected from the following:



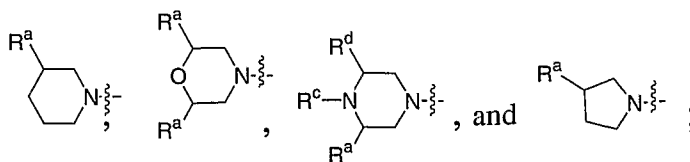
wherein R^a , R^c and R^d are independently hydrogen or alkyl;

R^{300} is $C_{(1-4)}$ alkyl; and

R^{400} is $-\text{NR}^{403}\text{R}^{404}$, $-\text{SO}_2\text{NR}^{405}\text{R}^{406}$, oxazolidinonyl wherein said oxazolidinonyl is optionally substituted with one or two R^{401} , piperazinyl wherein said piperazinyl is optionally substituted with R^{202} or pyrrolidinonyl wherein said pyrrolidinonyl is optionally substituted with one or two R^{401} ;

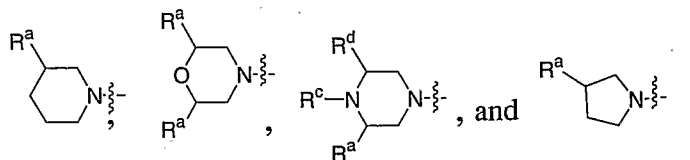
wherein R^{401} is methyl, $-\text{C}(\text{O})-\text{CH}_3$, or $-\text{CH}_2-\text{C}(\text{O})-\text{CH}_3$;

wherein R^{403} and R^{404} are independently hydrogen, $C_{(1-4)}$ alkyl, or R^{403} and R^{404} may be taken together to form a ring selected from the following:



wherein R^a , R^c and R^d are independently hydrogen or alkyl;

R^{405} and R^{406} are independently hydrogen, $C_{(1-4)}$ alkyl, or R^{405} and R^{406} may be taken together to form a ring selected from the following:



wherein R^a , R^c and R^d are independently hydrogen or alkyl; and

Z is CO_2 alkyl, or $CONR^1R^2$; wherein R^1 is hydrogen or $C_{(1-4)}$ alkyl; and R^2 is hydrogen, $C_{(1-4)}$ alkyl, cycloalkyl, or $C_{(1-4)}$ alkoxy.

3. The compound of Claim 1 wherein:

Y is a ring selected from indan-5-yl, phenyl, cyclohexyl, cyclopentyl, bicyclo[2.2.1]heptyl or adamantan-2-yl;

R^{101} is hydrogen or hydroxyl;

R^{200} is fluorine, alkoxy substituted with $-CH(OH)-CH_2-N(CH_3)_2$, alkyl optionally substituted with R^{201} , morpholinyl, piperazinyl optionally substituted with R^{202} , 3,5-dimethyl piperazinyl, piperidinyl, piperidinyl substituted with $-CO$ -alkyl- $N(CH_3)_2$, $-C(O)$ -alkyl-piperazinyl (optionally substituted on piperazinyl with alkyl), dimethylamino, $-C(O)N(CH_3)_2$, heteroaryl, or $-R^{300}-R^{400}$;

R^{201} is hydroxyl or dimethylamino;

R^{202} is $-CH_3$;

R^{300} is alkyl; and

R^{400} is $-N(CH_3)_2$, morpholinyl, $-SO_2NR^{405}R^{406}$, piperazinyl optionally substituted with R^{202} or oxazolidinonyl;

R^{405} and R^{406} are independently hydrogen, alkyl, or R^{405} and R^{406} may be taken together to

form the following ring: .

4. The compounds of Claim 1 wherein:

W is N;

A is absent;

Y is a ring selected from cycloalkyl or arylcycloalkyl;

R^{200} is piperazine optionally substituted with one or two methyl substituents, piperidine optionally substituted with one or two methyl substituents, morpholine or $-R^{300}-R^{400}$ wherein R^{300} is methyl or ethyl and R^{400} is piperazine optionally substituted with one or two methyl substituents.

Z is CO_2 alkyl, or $CONR^1R^2$; wherein R^1 is hydrogen or $C_{(1-4)}$ alkyl; and R^2 is hydrogen, $C_{(1-4)}$ alkyl, or cycloalkyl.

5. A compound of Formula I wherein:

W is N or CH;

A is absent;

Y is a ring selected from cycloalkyl, bicycloalkyl, phenyl, alkylaryl, cycloalkylaryl, arylcycloalkyl, or heteroaryl provided that Y is not thiazole;

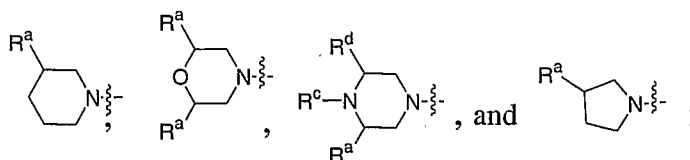
R^{101} is hydrogen, hydroxyl, methyl, halogen, $-CF_3$, or methoxy;

R^{200} is halogen, $C_{(1-4)}$ alkoxy optionally substituted with $-CH(OH)-CH_2-NR^{203}R^{204}$, $C_{(1-4)}$ alkyl optionally substituted with R^{201} , heterocyclyl optionally substituted with one $C_{(1-4)}$ alkyl and optionally substituted with one R^{202} , dialkylamino, $-C(O)(CH_2)_nNR^{203}R^{204}$, heteroaryl, or $-R^{300}-R^{400}$; wherein n is 0, 1, 2, 3, or 4;

R^{201} is hydroxyl, methyl, halogen, $-CF_3$, dialkylamino or methoxy;

R^{202} is alkyl, $-C(O)-CH_3$, $-CH_2-C(O)-CH_3$, $-C(O)(CH_2)_nNR^{203}R^{204}$, $-C(O)N(CH_2)_nNR^{203}R^{204}$; wherein n is 0, 1, 2, 3, or 4;

R^{203} and R^{204} are independently hydrogen, $C_{(1-4)}$ alkyl, or R^{203} and R^{204} may be taken together to form a ring selected from the following:



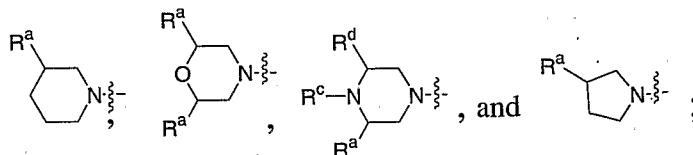
wherein R^a , R^c and R^d are independently hydrogen or alkyl;

R^{300} is $C_{(1-4)}$ alkyl; and

R^{400} is $-NR^{403}R^{404}$, $-SO_2NR^{405}R^{406}$, oxazolidinonyl wherein said oxazolidinonyl is optionally substituted with one or two R^{401} , piperazinyl wherein said piperazinyl is optionally substituted with R^{202} or pyrrolidinonyl wherein said pyrrolidinonyl is optionally substituted with one or two R^{401} ;

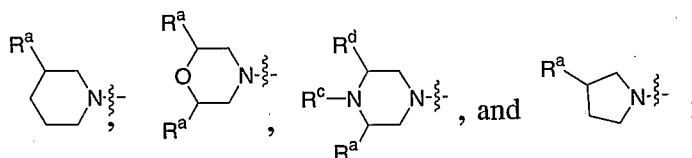
wherein R^{401} is methyl, $-C(O)-CH_3$, or $-CH_2-C(O)-CH_3$;

wherein R^{403} and R^{404} are independently hydrogen, $C_{(1-4)}$ alkyl, or R^{403} and R^{404} may be taken together to form a ring selected from the following:



wherein R^a , R^c and R^d are independently hydrogen or alkyl;

R^{405} and R^{406} are independently hydrogen, $C_{(1-4)}$ alkyl, or R^{405} and R^{406} may be taken together to form a ring selected from the following:



wherein R^a , R^c and R^d are independently hydrogen or alkyl; and

Z is CO_2H .

6. A compound selected from the group consisting of:

- 8-indan-5-yl-2-[4-(4-methyl-piperazin-1-yl)-phenylamino]-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid ethyl ester,
- 2-[4-(3-dimethylamino-2-hydroxy-propoxy)-phenylamino]-8-indan-5-yl-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid ethyl ester,
- 8-indan-5-yl-2-(4-morpholin-4-yl-phenylamino)-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid ethyl ester,
- 2-(4-dimethylamino-phenylamino)-8-indan-5-yl-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid ethyl ester,

2-(3-dimethylamino-phenylamino)-8-indan-5-yl-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid ethyl ester,
8-indan-5-yl-2-[4-(4-methyl-piperazin-1-yl)-phenylamino]-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid,
8-indan-5-yl-2-[4-(4-methyl-piperazin-1-yl)-phenylamino]-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid amide,
8-indan-5-yl-2-[4-(4-methyl-piperazin-1-yl)-phenylamino]-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid methylamide,
8-indan-5-yl-2-[4-(4-methyl-piperazin-1-yl)-phenylamino]-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid ethylamide,
2-[4-(3-dimethylamino-2-hydroxy-propoxy)-phenylamino]-8-indan-5-yl-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid amide,
2-[4-(3-dimethylamino-2-hydroxy-propoxy)-phenylamino]-8-indan-5-yl-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid methylamide
2-[4-(3-dimethylamino-2-hydroxy-propoxy)-phenylamino]-8-indan-5-yl-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid ethylamide,
2-[4-(4-Methyl-piperazin-1-yl)-phenylamino]-5-oxo-8-phenyl-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid amide,
8-indan-5-yl-2-(4-morpholin-4-yl-phenylamino)-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid amide,
2-(4-dimethylamino-phenylamino)-8-indan-5-yl-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid amide,
2-(3-dimethylamino-phenylamino)-8-indan-5-yl-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid amide,
8-cyclohexyl-2-[4-(4-methyl-piperazin-1-yl)-phenylamino]-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid ethyl ester,
8-cyclohexyl-2-(4-dimethylamino-phenylamino)-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid ethyl ester,
8-cyclopentyl-2-[4-(4-methyl-piperazin-1-yl)-phenylamino]-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid amide,
2-(3-hydroxymethyl-phenylamino)-8-indan-5-yl-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid amide,
2-(4-fluoro-phenylamino)-8-indan-5-yl-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid ethyl ester,
8-indan-5-yl-5-oxo-2-(4-pyrazol-1-yl-phenylamino)-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid amide,
8-indan-5-yl-2-[3-(4-methyl-piperazin-1-ylmethyl)-phenylamino]-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid amide,
8-indan-5-yl-2-(3-morpholin-4-ylmethyl-phenylamino)-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid amide,

2-[2-hydroxy-4-(4-methyl-piperazin-1-yl)-phenylamino]-8-indan-5-yl-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid amide,
1-indan-5-yl-7-[4-(4-methyl-piperazin-1-yl)-phenylamino]-4-oxo-1,4-dihydro-[1,6]naphthyridine-3-carboxylic acid amide,
8-Indan-5-yl-2-[4-(2-morpholin-4-yl-ethyl)-phenylamino]-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid amide,
8-Indan-5-yl-2-[4-(2-morpholin-4-yl-ethyl)-phenylamino]-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid methyl amide,
8-Indan-5-yl-2-[4-(2-morpholin-4-yl-ethyl)-phenylamino]-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid ethyl amide,
(4*S*)-8-Indan-5-yl-5-oxo-2-[4-(2-oxo-oxazolidin-4-ylmethyl)-phenylamino]-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid amide,
(4*S*)-8-Indan-5-yl-5-oxo-2-[4-(2-oxo-oxazolidin-4-ylmethyl)-phenylamino]-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid methyl amide,
(4*S*)-8-Indan-5-yl-5-oxo-2-[4-(2-oxo-oxazolidin-4-ylmethyl)-phenylamino]-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid ethyl amide,
8-Indan-5-yl-2-[4-(2-isopropylsulfamoyl-ethyl)-phenylamino]-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid methyl amide,
8-Indan-5-yl-2-[4-(2-isopropylsulfamoyl-ethyl)-phenylamino]-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid ethyl amide,
8-Indan-5-yl-2-[4-[2-(morpholine-4-sulfonyl)-ethyl]-phenylamino]-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid methyl amide,
8-Indan-5-yl-2-[4-[2-(morpholine-4-sulfonyl)-ethyl]-phenylamino]-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid ethyl amide,
8-Indan-5-yl-2-[3-(4-methyl-piperazin-1-yl)-phenylamino]-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid amide,
8-Indan-5-yl-2-[3-(4-methyl-piperazin-1-yl)-phenylamino]-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid methyl amide,
8-Indan-5-yl-2-[3-(4-methyl-piperazin-1-yl)-phenylamino]-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid ethyl amide,
8-Indan-5-yl-5-oxo-2-(4-piperazin-1-yl-phenylamino)-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid amide,
8-Indan-5-yl-5-oxo-2-(4-piperazin-1-yl-phenylamino)-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid methyl amide,
8-Indan-5-yl-5-oxo-2-(4-piperazin-1-yl-phenylamino)-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid ethyl amide,
2-[4-(3,5-Dimethyl-piperazin-1-yl)-phenylamino]-8-indan-5-yl-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid amide,
2-[4-(3,5-Dimethyl-piperazin-1-yl)-phenylamino]-8-indan-5-yl-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid methyl amide,

2-[4-(3,5-Dimethyl-piperazin-1-yl)-phenylamino]-8-indan-5-yl-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid ethyl amide,
8-Indan-5-yl-2-[4-[2-(4-methyl-piperazin-1-yl)-ethyl]-phenylamino]-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid amide,
8-Indan-5-yl-2-[4-[2-(4-methyl-piperazin-1-yl)-ethyl]-phenylamino]-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid methyl amide,
8-Indan-5-yl-2-[4-[2-(4-methyl-piperazin-1-yl)-ethyl]-phenylamino]-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid ethyl amide,
8-Indan-5-yl-5-oxo-2-(4-piperidin-4-yl-phenylamino)-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid amide,
8-Indan-5-yl-5-oxo-2-(4-piperidin-4-yl-phenylamino)-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid methyl amide,
8-Indan-5-yl-5-oxo-2-(4-piperidin-4-yl-phenylamino)-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid ethyl amide,
8-Indan-5-yl-5-oxo-2-(3-piperazin-1-yl-phenylamino)-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid amide,
8-Indan-5-yl-5-oxo-2-(3-piperazin-1-yl-phenylamino)-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid methyl amide,
8-Indan-5-yl-5-oxo-2-(3-piperazin-1-yl-phenylamino)-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid ethyl amide,
2-[3-(3,5-Dimethyl-piperazin-1-yl)-phenylamino]-8-indan-5-yl-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid amide,
2-[3-(3,5-Dimethyl-piperazin-1-yl)-phenylamino]-8-indan-5-yl-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid methyl amide,
8-Cyclohexyl-2-[4-(2-morpholin-4-yl-ethyl)-phenylamino]-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid amide,
8-Cyclohexyl-2-[4-(2-morpholin-4-yl-ethyl)-phenylamino]-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid methyl amide,
8-Cyclohexyl-2-[4-(2-morpholin-4-yl-ethyl)-phenylamino]-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid ethyl amide,
8-Cyclohexyl-2-[4-(4-methyl-piperazin-1-yl)-phenylamino]-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid amide,
8-Cyclohexyl-2-[4-(4-methyl-piperazin-1-yl)-phenylamino]-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid methyl amide,
8-Cyclohexyl-2-[4-(4-methyl-piperazin-1-yl)-phenylamino]-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid ethyl amide,
8-Cyclohexyl-2-[3-(4-methyl-piperazin-1-yl)-phenylamino]-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid amide,
8-Cyclohexyl-2-[3-(4-methyl-piperazin-1-yl)-phenylamino]-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid methyl amide,

8-Cyclohexyl-2-[3-(4-methyl-piperazin-1-yl)-phenylamino]-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid ethyl amide,
8-Cyclohexyl-2-[4-(2-isopropylsulfamoyl-ethyl)-phenylamino]-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid amide,
8-Cyclohexyl-2-{4-[2-(morpholine-4-sulfonyl)-ethyl]-phenylamino}-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid amide,
8-Cyclohexyl-2-{4-[1-(2-dimethylamino-acetyl)-piperidin-4-yl]-phenylamino}-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid amide,
8-Indan-5-yl-2-(4-morpholin-4-ylmethyl-phenylamino)-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid amide,
2-{4-[1-(2-Dimethylamino-acetyl)-piperidin-4-yl]-phenylamino}-8-indan-5-yl-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid amide,
2-{3-[1-(2-Dimethylamino-acetyl)-piperidin-4-yl]-phenylamino}-8-indan-5-yl-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid amide,
8-Indan-5-yl-2-(4-{1-[2-(4-methyl-piperazin-1-yl)-acetyl]-piperidin-4-yl}-phenylamino)-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid amide,
8-Indan-5-yl-2-(3-{1-[2-(4-methyl-piperazin-1-yl)-acetyl]-piperidin-4-yl}-phenylamino)-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid amide,
8-Indan-5-yl-2-[4-(4-methyl-piperazin-1-ylmethyl)-phenylamino]-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid amide,
2-(4-Dimethylaminomethyl-phenylamino)-8-indan-5-yl-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid amide,
2-(3-Dimethylaminomethyl-phenylamino)-8-indan-5-yl-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid amide,
2-(3-Dimethylaminomethyl-phenylamino)-8-indan-5-yl-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid methylamide,
2-(3-Dimethylaminomethyl-phenylamino)-8-indan-5-yl-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid ethylamide,
2-(3-Dimethylcarbamoyl-phenylamino)-8-indan-5-yl-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid amide,
2-(3-Dimethylcarbamoyl-phenylamino)-8-indan-5-yl-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid methylamide,
2-(3-Dimethylcarbamoyl-phenylamino)-8-indan-5-yl-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid ethylamide,
8-Bicyclo[2.2.1]hept-2-yl-2-[4-(4-methyl-piperazin-1-yl)-phenylamino]-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid amide,
8-Bicyclo[2.2.1]hept-2-yl-2-[4-(4-methyl-piperazin-1-yl)-phenylamino]-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid ethylamide,
8-Indan-5-yl-2-[4-(4-methyl-piperazin-1-ylmethyl)-phenylamino]-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid ethylamide, and

8-Benzyl-2-[4-(4-methyl-piperazin-1-yl)-phenylamino]-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid methylamide.

7. A compound selected from the group consisting of:

8-indan-5-yl-2-[4-(4-methyl-piperazin-1-yl)-phenylamino]-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid amide,

8-indan-5-yl-2-[4-(4-methyl-piperazin-1-yl)-phenylamino]-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid methylamide,

8-indan-5-yl-2-[4-(4-methyl-piperazin-1-yl)-phenylamino]-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid ethylamide,

2-[4-(3-dimethylamino-2-hydroxy-propoxy)-phenylamino]-8-indan-5-yl-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid amide,

2-[4-(3-dimethylamino-2-hydroxy-propoxy)-phenylamino]-8-indan-5-yl-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid methylamide

2-[4-(3-dimethylamino-2-hydroxy-propoxy)-phenylamino]-8-indan-5-yl-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid ethylamide,

8-indan-5-yl-2-(4-morpholin-4-yl-phenylamino)-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid amide,

2-(4-dimethylamino-phenylamino)-8-indan-5-yl-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid amide,

2-(3-dimethylamino-phenylamino)-8-indan-5-yl-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid amide,

8-cyclopentyl-2-[4-(4-methyl-piperazin-1-yl)-phenylamino]-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid amide,

8-indan-5-yl-2-[3-(4-methyl-piperazin-1-ylmethyl)-phenylamino]-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid amide,

8-indan-5-yl-2-(3-morpholin-4-ylmethyl-phenylamino)-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid amide,

2-[2-hydroxy-4-(4-methyl-piperazin-1-yl)-phenylamino]-8-indan-5-yl-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid amide,

1-indan-5-yl-7-[4-(4-methyl-piperazin-1-yl)-phenylamino]-4-oxo-1,4-dihydro-[1,6]naphthyridine-3-carboxylic acid amide,

8-Indan-5-yl-2-[4-(2-morpholin-4-yl-ethyl)-phenylamino]-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid amide,

8-Indan-5-yl-2-[4-(2-morpholin-4-yl-ethyl)-phenylamino]-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid methyl amide,

8-Indan-5-yl-2-[4-(2-morpholin-4-yl-ethyl)-phenylamino]-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid ethyl amide,

(4S)-8-Indan-5-yl-5-oxo-2-[4-(2-oxo-oxazolidin-4-ylmethyl)-phenylamino]-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid amide,

(4*S*)-8-Indan-5-yl-5-oxo-2-[4-(2-oxo-oxazolidin-4-ylmethyl)-phenylamino]-5,8-dihydro-pyrido[2,3-*d*]pyrimidine-6-carboxylic acid methyl amide,
(4*S*)-8-Indan-5-yl-5-oxo-2-[4-(2-oxo-oxazolidin-4-ylmethyl)-phenylamino]-5,8-dihydro-pyrido[2,3-*d*]pyrimidine-6-carboxylic acid ethyl amide,
8-Indan-5-yl-2-[4-(2-isopropylsulfamoyl-ethyl)-phenylamino]-5-oxo-5,8-dihydro-pyrido[2,3-*d*]pyrimidine-6-carboxylic acid methyl amide,
8-Indan-5-yl-2-[4-[2-(morpholine-4-sulfonyl)-ethyl]-phenylamino]-5-oxo-5,8-dihydro-pyrido[2,3-*d*]pyrimidine-6-carboxylic acid methyl amide,
8-Indan-5-yl-2-[3-(4-methyl-piperazin-1-yl)-phenylamino]-5-oxo-5,8-dihydro-pyrido[2,3-*d*]pyrimidine-6-carboxylic acid amide,
8-Indan-5-yl-2-[3-(4-methyl-piperazin-1-yl)-phenylamino]-5-oxo-5,8-dihydro-pyrido[2,3-*d*]pyrimidine-6-carboxylic acid methyl amide,
8-Indan-5-yl-2-[3-(4-methyl-piperazin-1-yl)-phenylamino]-5-oxo-5,8-dihydro-pyrido[2,3-*d*]pyrimidine-6-carboxylic acid ethyl amide,
8-Indan-5-yl-5-oxo-2-(4-piperazin-1-yl-phenylamino)-5,8-dihydro-pyrido[2,3-*d*]pyrimidine-6-carboxylic acid amide,
8-Indan-5-yl-5-oxo-2-(4-piperazin-1-yl-phenylamino)-5,8-dihydro-pyrido[2,3-*d*]pyrimidine-6-carboxylic acid methyl amide,
8-Indan-5-yl-5-oxo-2-(4-piperazin-1-yl-phenylamino)-5,8-dihydro-pyrido[2,3-*d*]pyrimidine-6-carboxylic acid ethyl amide,
2-[4-(3,5-Dimethyl-piperazin-1-yl)-phenylamino]-8-indan-5-yl-5-oxo-5,8-dihydro-pyrido[2,3-*d*]pyrimidine-6-carboxylic acid amide,
2-[4-(3,5-Dimethyl-piperazin-1-yl)-phenylamino]-8-indan-5-yl-5-oxo-5,8-dihydro-pyrido[2,3-*d*]pyrimidine-6-carboxylic acid methyl amide,
2-[4-(3,5-Dimethyl-piperazin-1-yl)-phenylamino]-8-indan-5-yl-5-oxo-5,8-dihydro-pyrido[2,3-*d*]pyrimidine-6-carboxylic acid ethyl amide,
8-Indan-5-yl-2-[4-[2-(4-methyl-piperazin-1-yl)-ethyl]-phenylamino]-5-oxo-5,8-dihydro-pyrido[2,3-*d*]pyrimidine-6-carboxylic acid amide,
8-Indan-5-yl-2-[4-[2-(4-methyl-piperazin-1-yl)-ethyl]-phenylamino]-5-oxo-5,8-dihydro-pyrido[2,3-*d*]pyrimidine-6-carboxylic acid methyl amide,
8-Indan-5-yl-2-[4-[2-(4-methyl-piperazin-1-yl)-ethyl]-phenylamino]-5-oxo-5,8-dihydro-pyrido[2,3-*d*]pyrimidine-6-carboxylic acid ethyl amide,
8-Indan-5-yl-5-oxo-2-(4-piperidin-4-yl-phenylamino)-5,8-dihydro-pyrido[2,3-*d*]pyrimidine-6-carboxylic acid amide,
8-Indan-5-yl-5-oxo-2-(4-piperidin-4-yl-phenylamino)-5,8-dihydro-pyrido[2,3-*d*]pyrimidine-6-carboxylic acid methyl amide,
8-Indan-5-yl-5-oxo-2-(4-piperidin-4-yl-phenylamino)-5,8-dihydro-pyrido[2,3-*d*]pyrimidine-6-carboxylic acid ethyl amide,
8-Indan-5-yl-5-oxo-2-(3-piperazin-1-yl-phenylamino)-5,8-dihydro-pyrido[2,3-*d*]pyrimidine-6-carboxylic acid amide,

8-Indan-5-yl-5-oxo-2-(3-piperazin-1-yl-phenylamino)-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid methyl amide,
8-Indan-5-yl-5-oxo-2-(3-piperazin-1-yl-phenylamino)-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid ethyl amide,
2-[3-(3,5-Dimethyl-piperazin-1-yl)-phenylamino]-8-indan-5-yl-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid amide,
2-[3-(3,5-Dimethyl-piperazin-1-yl)-phenylamino]-8-indan-5-yl-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid methyl amide,
8-Cyclohexyl-2-[4-(2-morpholin-4-yl-ethyl)-phenylamino]-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid amide,
8-Cyclohexyl-2-[4-(4-methyl-piperazin-1-yl)-phenylamino]-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid amide,
8-Cyclohexyl-2-[3-(4-methyl-piperazin-1-yl)-phenylamino]-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid amide,
8-Cyclohexyl-2-[3-(4-methyl-piperazin-1-yl)-phenylamino]-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid methyl amide,
8-Indan-5-yl-2-(4-morpholin-4-ylmethyl-phenylamino)-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid amide,
8-Indan-5-yl-2-[4-(4-methyl-piperazin-1-ylmethyl)-phenylamino]-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid amide,
2-(4-Dimethylaminomethyl-phenylamino)-8-indan-5-yl-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid amide,
2-(3-Dimethylaminomethyl-phenylamino)-8-indan-5-yl-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid amide,
2-(3-Dimethylcarbamoyl-phenylamino)-8-indan-5-yl-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid amide,
2-(3-Dimethylcarbamoyl-phenylamino)-8-indan-5-yl-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid methylamide,
8-Bicyclo[2.2.1]hept-2-yl-2-[4-(4-methyl-piperazin-1-yl)-phenylamino]-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid amide, and
8-Indan-5-yl-2-[4-(4-methyl-piperazin-1-ylmethyl)-phenylamino]-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid ethylamide.

8. A pharmaceutical composition, comprising a compound of Claim 1 and a pharmaceutically acceptable carrier.
9. A method for inhibiting protein tyrosine kinase activity, comprising contacting the kinase with an effective inhibitory amount of at least one compound of Claim 1.
10. A method according to claim 9, wherein the protein tyrosine kinase is c-fms.

11. A method of treating inflammation in a mammal, comprising administering to the mammal a therapeutically effective amount of at least one compound of Claim 1.
12. A method of treating cancer in a mammal, comprising administering to the mammal a therapeutically effective amount of at least one compound of Claim 1.
13. A method of treating cardiovascular disease in a mammal, comprising administering to the mammal a therapeutically effective amount of at least one compound of Claim 1.
14. A method of treating glomerulonephritis, rheumatoid arthritis, inflammatory bowel disease, prosthesis failure, sarcoidosis, congestive obstructive pulmonary disease, pancreatitis, HIV infection, psoriasis, diabetes, tumor related angiogenesis, restenosis, schizophrenia or Alzheimer's dementia in a mammal, comprising administering to the mammal a therapeutically effective amount of at least one compound of Claim 1.
15. A pharmaceutical dosage form comprising a pharmaceutically acceptable carrier and from about 0.5 mg to about 10 g of at least one compound of Claim 1.
16. A dosage form according to Claim 15 adapted for parenteral or oral administration.
17. The use of a compound as in Claim 1 for the preparation of a medicament for the treatment of: rheumatoid arthritis, graft rejection, atherosclerosis, obesity, diabetic nephropathy, cardiac hypertrophy and solid tumor diseases, especially breast cancer, in a subject in need of such treatment.

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2006/035619

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D471/04 A61K31/519 A61P9/00 A61P29/00 A61P35/00

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, BEILSTEIN Data, CHEM ABS Data, EMBASE, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0 787 726 A1 (DAINIPPON PHARMACEUTICAL CO [JP]) 6 August 1997 (1997-08-06) Claims 1-24; Formulae (I), (I-b); compound 14, example C-17; Tables 1-3	1-17
A	WO 96/34867 A (WARNER LAMBERT CO [US]) 7 November 1996 (1996-11-07) Claims 1-55; Formula (I); examples 54, 56, 63-64, 69, 71-78, 82-83, 87, 101-106, 108-124; Table I	1-17
A	WO 99/09030 A (WARNER LAMBERT CO [US]; BARVIAN MARK ROBERT [US]; DENNY WILLIAM ALEXAN) 25 February 1999 (1999-02-25) Claims 1-65; Formula (I); examples M, O, U, W-Z, AA-BB; Tables 1 and 4	1-17

Further documents are listed in the continuation of Box C.

See patent family annex.

* Special categories of cited documents :

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *&* document member of the same patent family

Date of the actual completion of the international search

2 February 2007

Date of mailing of the international search report

09/02/2007

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2006/035619

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 9-14 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- The additional search fees were accompanied by the applicant's protest.
- No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/US2006/035619

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