

PETITORIO

AS: 91.727

Industria y Comercio
SUPERINTENDENCIA



03 085449 00

El presente formulario es el único para la solicitud de patente de invención, modelo de utilidad, o capítulo I o II, en el marco del Tratado de Madrid sobre el Derecho de la Patente, suscrito en Madrid el 14 de junio de 1979, y en el marco del Tratado de la Patente de Invención, suscrito en París el 19 de junio de 1977, y en el marco del Tratado de la Patente de Modelo de Utilidad, suscrito en París el 19 de junio de 1977.

FORMULARIO ÚNICO DE SOLICITUD DE PATENTE PCT ENTRADA EN FASE NACIONAL

1 SOLICITUD DE:			
☒ Patente de Invención.		☐ Patente de Modelo de Utilidad.	
☐ Capítulo I.		☒ Capítulo II.	
SOLICITANTE (71)	Nombre: BRISTOL - MYERS SQUIBB COMPANY		IDENTIFICACION C.C. ☐ NIT ☐ C.E. ☐ Otro ☐ Cual _____ Número _____
	Dirección: P.O. Box 4000, Princeton, NJ 08543-4000, Estados Unidos de América Nacionalidad o Domicilio: Estados Unidos Lugar de Constitución: Estados Unidos Teléfono: _____ Fax: _____ E-mail: _____		
3 REPRESENTANTE O APODERADO	Nombre: RAMIRO CASTRO DUQUE		IDENTIFICACION C.C. ☒ NIT ☐ C.E. ☐ Otro ☐ Cual _____ Número <u>170.322 TP 1003</u>
	Dirección: Cra. 7 No. 16-56 Piso 9 Teléfono: 380-2200 Fax: 380-2700 E-mail: _____		
INVENTOR (ES) (72)	Nombre: Spencer David Kimball, Louis J. Lombardo, David B. Rawlins, Hai-Yun Xiao, Robert Joseph Schmidt, David Kent Williams		
	Dirección: 13 Charred Oak Lane, East Windsor, NJ 08520, US; 49 West Street, Belle Mead, NJ 08502, US; 219 Vernon Road, Morrisville, PA 19067, US; 173 Jonathan Dayton Court, Princeton, NJ 08540, US; 3 South Deer Place, Hainesport, NJ 08036, US; 211 Paddock Way, Delran, NJ 08075, Estados Unidos de América (Respectivamente) Nacionalidad o Domicilio: Estados Unidos de América		
5 PCT (86) Solicitud Internacional No. <u>PCT/US02/09497</u> Fecha <u>26-03-2002</u> Publicación Internacional No. <u>WO 02/079149 A3</u> Fecha <u>10-10-2002</u>			
Título (54): COMPUESTOS NOVEDOSOS DE DIHIDROPIRIMIDINA CIANO-SUSTITUIDA Y SU USO PARA TRATAR ENFERMEDADES			
7 Clasificación Internacional (51) <u>A61K31/505</u>			
8 Prioridad SI ☒ NO ☐	(33) País de Origen <u>US</u>	(32) Fecha <u>29-03-2001</u>	(31) Número de Solicitud <u>60/279,956</u>

de pago No. 03-54.873

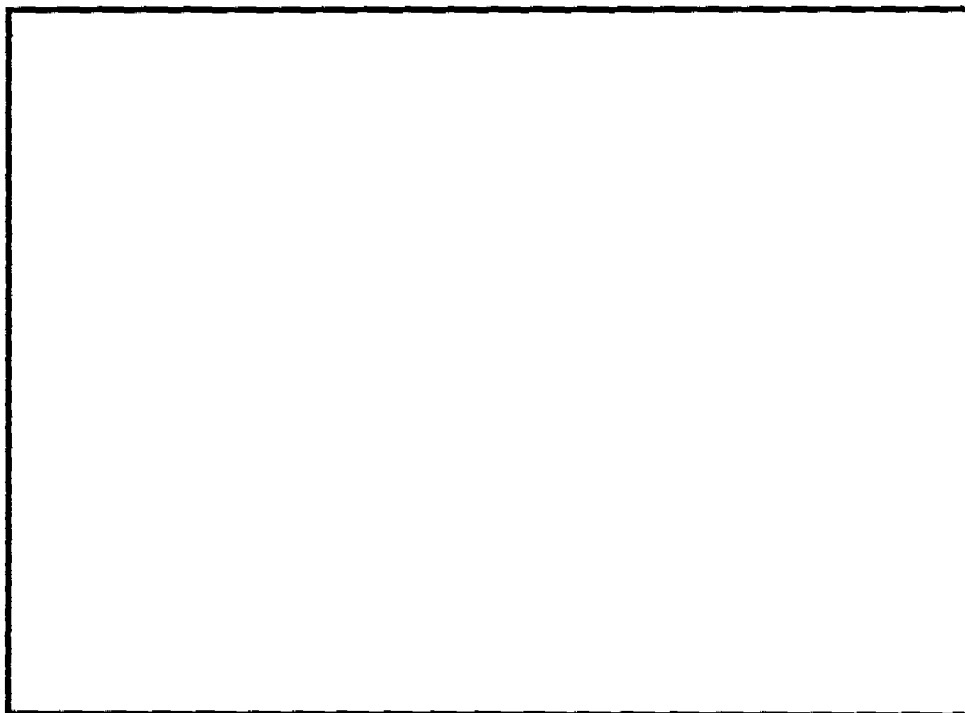
Fecha 24-09-2003

10

ANEXOS

- ☒ Comprobante de pago de la tasa de presentación de la solicitud. \$400.000
- ☐ Documento que acredita la existencia y representación legal cuando el solicitante sea persona jurídica.
- ☒ Poderes, si fuere el caso. Protocolo No. 19358
- ☒ Documento de cesión del inventor al solicitante o a su causante.
- ☐ Declaraciones
- ☒ Copia de la solicitud internacional. (Resumen, descripción, reivindicaciones, dibujos)
- ☒ Traducción de la solicitud internacional al castellano. (Resumen, descripción, reivindicaciones, dibujos)
- ☒ Copia del examen preliminar efectuado por la IPEA.
- ☒ Traducción del examen preliminar efectuado por la IPEA.
- ☐ De ser el caso, copia del contrato de acceso.
- ☐ De ser el caso, documento que acredite la licencia o autorización de uso de conocimientos tradicionales de las comunidades indígenas.
- ☐ De ser el caso, certificado de depósito del material biológico.
- ☒ Arte final 12x12.
- ☐ De ser el caso, información sobre otras solicitudes de patente o títulos obtenidos en el extranjero por el mismo titular o su causante, relacionadas parcial o totalmente con la invención de esta solicitud.
- ☒ Otros - Tarjeta de Propietarios

11 FIGURA CARACTERÍSTICA:



12 Solicito la concesión de la patente.

NOMBRE: RAMIRO CASTRO DUQUE

FIRMA: 

C.C. 170.322 de Bogotá T.P. 1003 del C.S.J.

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 03 - 54,873
FECHA : AGOSTO 5 DE 2003

32
NOMBRE: ...
NACIONALIDAD: ...
FECHA: ...
DIRECCION: ...
DIRECCION: ...

***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	Nº. PAGO	FECHA PGO	Vr. PAGO
BRIGARD & CASTRO LTDA	CONSIGNACION	BANCO POPULAR	050-00110-6	12651604	05/08/2003	19,360,000.00

***** CONCEPTO *****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-01 SOLICITUDES	1 TRAMITES DE SOL. DE PATENTE DE IN	400,000.00
		TOTAL :	400,000.00

SON: CUATROCIENTOS MIL PESOS

RESPONSABLE : 

RECIBO DE CAJA APLICADO AL EXPEDIENTE Nº. _____

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
10 October 2002 (10.10.2002)

PCT

(10) International Publication Number
WO 02/079149 A3

(51) International Patent Classification⁷: **C07D 239/42**,
409/04, 401/04, 403/12, A61K 31/505, 31/506, A61P 9/14

(74) Agents: **GIBBONS, Maureen** et al.; Bristol-Myers
Squibb Company, P.O. Box 4000, Rt. 206 & Province Line
Road, Princeton, NJ 08543-4000 (US).

(21) International Application Number: PCT/US02/09497

(22) International Filing Date: 26 March 2002 (26.03.2002)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/279,956 29 March 2001 (29.03.2001) US

(71) Applicant (for all designated States except US): **BRIS-
TOL-MYERS SQUIBB COMPANY** [US/US]; P.O. Box
4000, Rt. 206 & Province Line Road, Princeton, NJ 08543-
4000 (US).

(81) Designated States (national): AE, AG, AI, AM, AT, AU,
AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU,
CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH,
GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC,
LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW,
MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG,
SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ,
VN, YU, ZA, ZM, ZW.

(84) Designated States (regional): ARIPO patent (GH, GM,
KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW),
Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM),
European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR,
GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent
(BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR,
NE, SN, TD, TG).

(72) Inventors; and

(75) Inventors/Applicants (for US only): **KIMBALL,**
Spencer, David [US/US]; 13 Charred Oak Lane, East
Windsor, NJ 08520 (US). **LOMBARDO, Louis, J.**
[US/US]; 49 West Street, Belle Mead, NJ 08502 (US).
RAWLINS, David, B [US/US]; 219 Vernon Road,
Morrisville, PA 19067 (US). **XIAO, Hai-Yun** [CN/US];
173 Jonathan Dayton Court, Princeton, NJ 08540 (US).
SCHMIDT, Robert, Joseph [US/US]; 3 South Deer
Place, Hainesport, NJ 08036 (US). **WILLIAMS, David,**
Kent [US/US]; 211 Paddock Way, Delran, NJ 08075 (US).

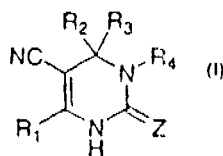
Published:

with international search report

(88) Date of publication of the international search report:
27 February 2003

For two-letter codes and other abbreviations, refer to the "Guid-
ance Notes on Codes and Abbreviations" appearing at the begin-
ning of each regular issue of the PCT Gazette.

(54) Title: NOVEL CYANO-SUBSTITUTED DIHYDROPYRIMIDINE COMPOUNDS AND THEIR USE TO TREAT DISEASES



(57) Abstract: The present invention provides compounds of formula (I) and pharmaceutically acceptable salts thereof. The formula I compounds induce mitotic arrest thereby making them useful as anti-cancer agents. The formula I compounds are also useful for the treatment of other diseases which can be treated by inducing mitotic arrest.

WO 02/079149 A3

**NOVEL CYANO-SUBSTITUTED DIHYDROPYRIMIDINE COMPOUNDS
AND THEIR USE TO TREAT DISEASES**

RELATED APPLICATIONS

5

This application claims the benefit under 35 U.S.C. Section 119(e) of U.S. Provisional Patent Application No. 60/279,956 filed March 29, 2001.

FIELD OF INVENTION

10

This invention relates to novel compounds that interrupt mitosis thereby making the compounds useful for the treatment of proliferative diseases, such as cancer.

15

BACKGROUND

Cell proliferation and programmed cell death play important roles in the growth and development of an organism. In proliferative diseases such as cancer, the processes of cell proliferation and/or programmed cell death are often perturbed. For example, a cancer cell may have unregulated cell division through either the overexpression of a positive regulator of the cell cycle or the loss of a negative regulator of the cell cycle, perhaps by mutation. Alternatively, a cancer cell may have lost the ability to undergo programmed cell death through the overexpression of a negative regulator of apoptosis. Hence, there is a need to develop new
20 chemotherapeutic drugs that will restore the processes of checkpoint control and
25 programmed cell death to cancerous cells.

One approach to the treatment of human cancers is to target a protein that is essential for cell cycle progression. In order for the cell cycle to proceed from one phase to the next, certain prerequisite events must be completed. There are
30 checkpoints within the cell cycle that enforce the proper order of events and phases. One such checkpoint is the spindle checkpoint that occurs during the metaphase stage of mitosis. Small molecules that target proteins with essential functions in mitosis may initiate the spindle checkpoint to arrest cells in mitosis. Of the small molecules



6
A

that arrest cells in mitosis, those which display anti-tumor activity in the clinic also induce apoptosis, the morphological changes associated with programmed cell death. An effective chemotherapeutic for the treatment of cancer may be one that induces checkpoint control and subsequent programmed cell death.

5 Most compounds known to cause mitotic arrest and apoptosis act as tubulin binding agents. These compounds alter the dynamic instability of microtubules and indirectly alter the function/structure of the mitotic spindle thereby causing mitotic arrest. Because most of these compounds target the tubulin protein, a component of all microtubules, they may also affect normal cellular processes in which
10 microtubules have a role. Hence, a need exists for small molecules that specifically target proteins associated with proliferating cells, such as Eg5.

Eg5 is one of several kinesin-like motor proteins that are localized to the mitotic spindle and known to be required for formation and/or function of the bipolar mitotic spindle. Recently, there was a report of a small molecule that disturbs
15 bipolarity of the mitotic spindle (Mayer, T.U. et. al. 1999. Science 286(5441) 971-4). More specifically, the small molecule induced the formation of an aberrant mitotic spindle wherein a monoastral array of microtubules emanated from a central pair of centrosomes, with chromosomes attached to the distal ends of the microtubules. The small molecule was dubbed "monastrol" after the monoastral array. This monoastral
20 array phenotype had been previously observed in mitotic cells that were immunodepleted of the Eg5 motor protein.

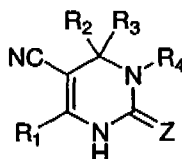
The distinctive monoastral array phenotype facilitated identification of monastrol as a potential inhibitor of Eg5. Indeed, monastrol was further shown to inhibit the Eg5 motor-driven motility of microtubules in an *in vitro* assay.
25 Furthermore, monastrol had no apparent effect upon the related kinesin motor or upon the motor(s) responsible for golgi apparatus movement within the cell. Cells that display the monoastral array phenotype, either through immunodepletion of Eg5 or monastrol inhibition of Eg5, arrest in M-phase of the cell cycle. Unfortunately, however, the mitotic arrest induced by either of these mechanisms is transient.
30 (Kapoor, 2000. *J. Cell. Biol.* 150(5) 975-80). Both the monoastral array phenotype and the monastrol induced cell cycle arrest in mitosis are reversible. Cells recover to form a normal bipolar mitotic spindle, to complete mitosis, and to proceed through the



cell cycle and normal cell proliferation. This suggests that a small molecule inhibitor of Eg5 that induced a transient mitotic arrest may not be effective for the treatment of cancer cell proliferation. Nonetheless, the discovery that monastrol causes mitotic arrest is intriguing and hence there is a need to further study and identify compounds that can be used to modulate the Eg5 motor protein in a manner that would be effective in the treatment of human cancers. There is also a need to explore the use of these compounds in combination with other antineoplastic agents.

SUMMARY

The compounds of the invention cause the interruption of mitosis, and as such, can be used to treat proliferative diseases. For example, the compounds of the instant invention can be used as antiproliferatives and anticancer agents. More specifically, the invention comprises a compound of formula I



I,

its enantiomers, diastereomers, pharmaceutically acceptable salts, prodrugs and solvates thereof, wherein

R₁ is selected from the group consisting of hydrogen, alkyl and cycloalkyl;

R₂ and R₃ are each independently selected from the group consisting of H, alkyl, aryl, heteroaryl, arylalkyl, cycloalkyl, heterocycloalkyl, cycloalkylalkyl, heterocycloalkylalkyl and heteroarylalkyl; or

R₂ and R₃ may also be taken together to form a carbocyclic or heterocyclic ring;

R₄ is selected from the group consisting of alkyl, arylalkyl, cycloalkylalkyl, heteroarylalkyl, heterocycloalkyl, aminoalkyl, heterocycloalkylalkyl, CN, C(O)R₅, CO₂R₅, C(O)SR₅ and CONR₅R₆;

R₅ and R₆ are each independently selected from the group consisting of H, alkyl, cycloalkyl, hydroxyalkyl, alkenyl, alkoxy, thioalkoxy, alkoxyalkyl, haloalkyl,



aryl, heteroaryl, arylalkyl, cycloalkylalkyl, heteroarylalkyl and heterocycloalkylalkyl or N-R₅R₆ together form a heterocycloalkyl

Z is selected from the group consisting of O, S and NR₈;

R₈ is selected from the group consisting of H, CN, sulfonamido, OR₇, alkyl, cycloalkyl, aryl, arylalkyl, heterocyclyl, heteroaryl and heteroarylalkyl; and

R₇ is selected from the group consisting of H, alkyl, arylalkyl, cycloalkylalkyl, heterocycloalkylalkyl and heteroarylalkyl.

In a preferred embodiment, R₂ is a heteroaryl, such as an optionally substituted thiophene, oxazole, isoxazole, or furan. Preferred substituents include methyl, ethyl, halo, haloalkyl, or aryl groups.

According to one embodiment, R₃ is H and R₂ is an optionally substituted phenyl wherein the substituents are selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, cyano, halo, haloalkyl, nitro, amino CO₂R₅, CONR₅R₆, alkenyloxy, aryloxy, wherein R₅ and R₆ are, independently, H or alkyl. Preferred substituents include methyl, methoxy, F, Cl, CF₃, dimethylamino, and ethoxymethyl, for example.

According to one embodiment of the present invention, R₁ is alkyl; R₂ is selected from the group consisting of aryl and heteroaryl; R₃ is H; R₄ is selected from the group consisting of alkyl, arylalkyl, CO₂R₅, and CONR₅R₆; R₅ and R₆ are independently selected from the group consisting of H, alkyl, aminoalkyl, hydroxyalkyl, phenylamino and arylalkyl; Z is selected from the group consisting of O, S, and NR₈; R₈ is selected from the group consisting of H and CN.

In a preferred embodiment, R₄ is selected from the group consisting of alkyl, arylalkyl, C(O)R₅, CO₂R₅, C(O)SR₅ and CONR₅R₆.

According to one embodiment, R₄ is CO₂R₅; Z is O; and R₅ is ethyl.

In another embodiment, R₄ is CONR₅R₆; Z is O; R₅ is H and R₆ is methyl, ethyl, propyl, phenyl, cyclopropyl, hydroxyethyl, thiophene, or 2-propylene.

In one embodiment of the present invention, R₄ is selected from the group consisting of alkyl and arylalkyl, and Z is O. In another embodiment R₁ is CH₃; R₂ is aryl; R₄ is CO₂R₅; R₅ is alkyl; and Z is O. In still another embodiment R₁ is CH₃; R₂ is aryl; R₄ is CONR₅R₆; R₅ is alkyl; R₆ is H and Z is O. In yet another embodiment, R₁ is CH₃; R₂ is heteroaryl; R₄ is CO₂R₅ or CONR₅R₆; R₆ is H and R₅ is ethyl.

110

The present invention also provides methods for preparing intermediates and compounds having Formula I.

The present invention also provides methods for treating a proliferative disease, such as cancer, via modulation of the Eg5 motor protein comprising
5 administering to a mammalian species in need of such treatment an effective amount of at least one compound of formula I, as defined above.

DESCRIPTION

The present invention provides for compounds of formula I, as defined above,
10 pharmaceutical compositions employing such compounds and methods of using such compounds.

Listed below are definitions of various terms used to describe the compounds of the instant invention. These definitions apply to the terms as they are used throughout the specification (unless they are otherwise limited in specific instances)
15 either individually or as part of a larger group.

The term "alkyl" herein alone or as part of another group refers to a monovalent alkane (hydrocarbon) derived radical containing from 1 to 12 carbon atoms unless otherwise defined. An alkyl group is an optionally substituted straight, branched or cyclic saturated hydrocarbon group. When substituted, alkyl groups may
20 be substituted with up to four substituent groups, R as defined, at any available point of attachment. When the alkyl group is said to be substituted with an alkyl group, this is used interchangeably with "branched alkyl group". Exemplary unsubstituted such groups include methyl, ethyl, propyl, isopropyl, n-butyl, t-butyl, isobutyl, pentyl, hexyl, isohexyl, heptyl, 4,4-dimethylpentyl, octyl, 2,2,4-trimethylpentyl, nonyl, decyl,
25 undecyl, dodecyl, and the like. Exemplary substituents may include but are not limited to one or more of the following groups: aryl, halo (such as F, Cl, Br, I), haloalkyl (such as CCl₃ or CF₃), alkoxy, alkylthio, hydroxy, carboxy (-COOH), alkyloxycarbonyl (-C(O)R), alkylcarbonyloxy (-OCOR), amino (-NH₂), carbamoyl (-NHCOOR- or -OCONHR-), urea (-NHCONHR-) or thiol (-SH). Alkyl groups as
30 defined may also comprise one or more carbon to carbon double bonds or one or more carbon to carbon triple bonds.



The term "alkenyl" herein alone or as part of another group refers to a hydrocarbon radical straight, branched or cyclic containing from 2 to 12 carbon atoms and at least one carbon to carbon double bond.

The term "alkynyl" herein alone or as part of another group refers to a hydrocarbon radical straight, branched or cyclic containing from 2 to 12 carbon atoms and at least one carbon to carbon triple bond.

The numbers in the subscript after the symbol "C" define the number of carbon atoms a particular group can contain. For example "C₁₋₆ alkyl" means a straight or branched saturated carbon chain having from one to six carbon atoms; examples include methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, isobutyl, t-butyl, n-pentyl, sec-pentyl, isopentyl, and n-hexyl. Depending on the context, "C₁₋₆ alkyl" can also refer to C₁₋₆ alkylene which bridges two groups; examples include propane-1,3-diyl, butane-1,4-diyl, 2-methyl-butane-1,4-diyl, etc. "C₂₋₆ alkenyl" means a straight or branched carbon chain having at least one carbon-carbon double bond, and having from two to six carbon atoms; examples include ethenyl, propenyl, isopropenyl, butenyl, isobutenyl, pentenyl, and hexenyl. Depending on the context, "C₂₋₆ alkenyl" can also refer to C₂₋₆ alkenediyl which bridges two groups; examples include ethylene-1,2-diyl (vinylene), 2-methyl-2-butene-1,4-diyl, 2-hexene-1,6-diyl, etc. "C₂₋₆ alkynyl" means a straight or branched carbon chain having at least one carbon-carbon triple bond, and from two to six carbon atoms; examples include ethynyl, propynyl, butynyl, and hexynyl.

The term "cycloalkyl" herein alone or as part of another group is a specie of alkyl containing from 3 to 15 carbon atoms, without alternating or resonating double bonds between carbon atoms. It may contain from 1 to 4 rings. Exemplary unsubstituted such groups include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, adamantyl, etc. Exemplary substituents include one or more of the following groups: halogen, alkyl, alkoxy, alkyl hydroxy, amino, nitro, cyano, thiol and/or alkylthio.

The terms "alkoxy" or "alkylthio" herein alone or as part of another group denote an alkyl group as described above bonded through an oxygen linkage (-O-) or a sulfur linkage (-S-), respectively.



The term "alkyloxycarbonyl" herein alone or as part of another group denotes an alkoxy group bonded through a carbonyl group. An alkoxy carbonyl radical is represented by the formula: $-C(O)OR$, where the R group is a straight or branched C_{1-6} alkyl group.

5 The term "alkylcarbonyl" herein alone or as part of another group refers to an alkyl group bonded through a carbonyl group.

The term "alkylcarbonyloxy" herein alone or as part of another group denotes an alkylcarbonyl group which is bonded through an oxygen linkage.

10 The term "arylalkyl" herein alone or as part of another group denotes an aromatic ring bonded to an alkyl group as described above.

The term "aryl" herein alone or as part of another group refers to monocyclic or bicyclic aromatic rings, e.g. phenyl, substituted phenyl and the like, as well as groups which are fused, e.g., naphthyl, phenanthrenyl and the like. An aryl group thus contains at least one ring having at least 6 atoms, with up to five such rings being
15 present, containing up to 22 atoms therein, with alternating (resonating) double bonds between adjacent carbon atoms or suitable heteroatoms. Aryl groups may optionally be substituted with one or more groups including, but not limited to halogen, alkyl, alkoxy, hydroxy, carboxy, carbamoyl, alkyloxycarbonyl, nitro, alkenyloxy, trifluoromethyl, amino, cycloalkyl, cyano, alkyl $S(O)_m$ ($m=O, 1, 2$), or thiol.

20 The term "amino" herein alone or as part of another group refers to $-NH_2$. An "amino" may optionally be substituted with one or two substituents, which may be the same or different, such as alkyl, aryl, arylalkyl, alkenyl, alkynyl, heteroaryl, heteroarylalkyl, cycloheteroalkyl, cycloheteroalkylalkyl, cycloalkyl, cycloalkylalkyl, haloalkyl, hydroxyalkyl, alkoxyalkyl, thioalkyl, carbonyl or carboxyl. These
25 substituents may be further substituted with a carboxylic acid, any of the alkyl or aryl substituents set out herein. In some embodiments, the amino groups are substituted with carboxyl or carbonyl to form N-acyl or N-carbamoyl derivatives

The term "carbocyclic ring" herein alone or as part of another group refers to stable, saturated or partially unsaturated monocyclic ring hydrocarbyls of 3 to 7
30 carbon atoms such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl. The carbocyclic ring may be optionally substituted meaning that the carbocyclic ring may be substituted at one or more substitutable ring positions by one



or more groups independently selected from alkyl (preferably lower alkyl), alkoxy (preferably lower alkoxy), nitro, monoalkylamino (preferably a lower alkylamino), dialkylamino (preferably a di[lower]alkylamino), cyano, halo, haloalkyl (preferably trifluoromethyl), alkanoyl, aminocarbonyl, monoalkylaminocarbonyl,

5 dialkylaminocarbonyl, alkyl amido (preferably lower alkyl amido), alkoxyalkyl (preferably a lower alkoxy[lower]alkyl), alkoxycarbonyl (preferably a lower alkoxycarbonyl), alkylcarbonyloxy (preferably a lower alkylcarbonyloxy) and aryl (preferably phenyl), said aryl being optionally substituted by halo, lower alkyl and lower alkoxy groups.

10 The term "cycloalkyl" herein alone or as part of another group refers to fully saturated and partially unsaturated hydrocarbon rings of 3 to 9, preferably 3 to 7 carbon atoms. Further, a cycloalkyl may be substituted. A substituted cycloalkyl refers to such rings having one, two, or three substituents, preferably one, selected from the group consisting of halo, alkyl, substituted alkyl, alkenyl, alkynyl, nitro, 15 cyano, oxo (=O), hydroxy, alkoxy, thioalkyl, -CO₂H, -C(=O)H, CO₂-alkyl, -C(=O)alkyl, keto, =N-OH, =N-O-alkyl, aryl, heteroaryl, heterocyclo, a five or six membered ketal (*i.e.* 1,3-dioxolane or 1,3-dioxane), -NR'R'', -C(=O)NR'R'', -CO₂NR'R'', -C(=O)NR'R'', -NR'CO₂'R'', -NR'C(=O)R'', -SO₂NR'R'', and -NR'SO₂'R'', wherein each of R' and R'' is independently selected from hydrogen, 20 alkyl, substituted alkyl, and cycloalkyl, or R' and R'' together form a heterocyclo or heteroaryl ring.

The term "heteroaryl" herein alone or as part of another group refers to substituted and unsubstituted aromatic 5 or 6 membered monocyclic groups, 9 or 10 membered bicyclic groups, and 11 to 14 membered tricyclic groups which have at 25 least one heteroatom (O, S or N) in at least one of the rings. Each ring of the heteroaryl group containing a heteroatom can contain one or two oxygen or sulfur atoms and/or from one to four nitrogen atoms provided that the total number of heteroatoms in each ring is four or less and each ring has at least one carbon atom. The fused rings completing the bicyclic and tricyclic groups may contain only carbon 30 atoms and may be saturated, partially saturated, or unsaturated. The nitrogen and sulfur atoms may optionally be oxidized and the nitrogen atoms may optionally be quaternized. Heteroaryl groups which are bicyclic or tricyclic must include at least



one fully aromatic ring but the other fused ring or rings may be aromatic or non-aromatic. The heteroaryl group may be attached at any available nitrogen or carbon atom of any ring. The heteroaryl ring system may contain zero, one, two or three substituents selected from the group consisting of halo, alkyl, substituted alkyl, 5 alkenyl, alkynyl, aryl, nitro, cyano, hydroxy, alkoxy, thioalkyl, $-\text{CO}_2\text{H}$, $-\text{C}(=\text{O})\text{H}$, $-\text{CO}_2\text{-alkyl}$, $-\text{C}(=\text{O})\text{alkyl}$, phenyl, benzyl, phenylethyl, phenyloxy, phenylthio, cycloalkyl, substituted cycloalkyl, heterocyclo, heteroaryl, $-\text{NR}'\text{R}''$, $-\text{C}(=\text{O})\text{NR}'\text{R}''$, $-\text{CO}_2\text{NR}'\text{R}''$, $-\text{C}(=\text{O})\text{NR}'\text{R}''$, $-\text{NR}'\text{CO}_2\text{R}''$, $-\text{NR}'\text{C}(=\text{O})\text{R}''$, $-\text{SO}_2\text{NR}'\text{R}''$, and $-\text{NR}'\text{SO}_2\text{R}''$, wherein each of R' and R'' is independently selected from hydrogen, 10 alkyl, substituted alkyl, and cycloalkyl, or R' and R'' together form a heterocyclo or heteroaryl ring.

Exemplary monocyclic heteroaryl groups include pyrrolyl, pyrazolyl, pyrazolinyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl, thiadiazolyl, isothiazolyl, furanyl, thienyl, oxadiazolyl, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, triazinyl 15 and the like.

Exemplary bicyclic heteroaryl groups include indolyl, benzothiazolyl, benzodioxolyl, benzoxazolyl, benzothienyl, quinolinyl, tetrahydroisoquinolinyl, isoquinolinyl, benzimidazolyl, benzopyranyl, indolizinyl, benzofuranyl, chromonyl, coumarinyl, benzopyranyl, cinnolinyl, quinoxalinyl, indazolyl, pyrrolopyridyl, 20 furopyridinyl, dihydroisoindolyl, tetrahydroquinolinyl and the like.

Exemplary tricyclic heteroaryl groups include carbazolyl, benzidolyl, phenanthrollinyl, acridinyl, phenanthridinyl, xanthenyl and the like.

The term "heterocycloalkyl" herein alone or as part of another group refers to a cycloalkyl group (nonaromatic) in which one of the carbon atoms in the ring is 25 replaced by a heteroatom selected from O, S or N, and in which up to three additional carbon atoms may be replaced by said heteroatoms.

The term "heterocyclic ring" herein alone or as part of another group refers to a stable, saturated, or partially unsaturated monocyclic ring system containing 5 to 7 ring members of carbon atoms and other atoms selected from nitrogen, sulfur and/or oxygen. Preferably, a heterocyclyl is a 5 or 6-membered monocyclic ring and 30 contains one, two, or three heteroatoms selected from nitrogen, oxygen and/or sulfur. The heterocyclic ring may be optionally substituted which means that the heterocyclic



ring may be substituted at one or more substitutable ring positions by one or more groups independently selected from alkyl (preferably lower alkyl), alkoxy (preferably lower alkoxy), nitro, monoalkylamino (preferably a lower alkylamino), dialkylamino (preferably a di[lower]alkylamino), cyano, halo, haloalkyl (preferably trifluoromethyl), alkanoyl, aminocarbonyl, monoalkylaminocarbonyl, dialkylaminocarbonyl, alkyl amido (preferably lower alkyl amido), alkoxyalkyl (preferably a lower alkoxy[lower]alkyl), alkoxycarbonyl (preferably a lower alkoxycarbonyl), alkylcarbonyloxy (preferably a lower alkylcarbonyloxy) and aryl (preferably phenyl), said aryl being optionally substituted by halo, lower alkyl and lower alkoxy groups. Examples of such heterocyclic rings are isoxazolyl, imidazolyl, thiazolyl, imidazolidinyl, pyrrolyl, pyrrolinyl, pyranyl, pyrazinyl, piperidyl, morpholinyl and triazolyl. The heterocyclic ring may be attached to the parent structure through a carbon atom or through any heteroatom of the heterocyclyl that results in a stable structure.

The term "heterocyclyl" herein alone or as part of another group as used herein refers to a stable, saturated, or partially unsaturated, monocyclic, bridged monocyclic, bicyclic, and spiro ring system containing carbon atoms and other atoms selected from nitrogen, sulfur and/or oxygen. Preferably, a heterocyclyl is a 5 or 6-membered monocyclic ring or an 8-11 membered bicyclic ring which consists of carbon atoms and contains one, two, or three heteroatoms selected from nitrogen, oxygen and/or sulfur. The term "optionally substituted" as it refers to "heterocyclyl" herein indicates that the heterocyclyl group may be substituted at one or more substitutable ring positions by one or more groups independently selected from alkyl (preferably lower alkyl), alkoxy (preferably lower alkoxy), nitro, monoalkylamino (preferably a lower alkylamino), dialkylamino (preferably a di[lower]alkylamino), cyano, halo, haloalkyl (preferably trifluoromethyl), alkanoyl, aminocarbonyl, monoalkylaminocarbonyl, dialkylaminocarbonyl, alkyl amido (preferably lower alkyl amido), alkoxyalkyl (preferably a lower alkoxy[lower]alkyl), alkoxycarbonyl (preferably a lower alkoxycarbonyl), alkylcarbonyloxy (preferably a lower alkylcarbonyloxy) and aryl (preferably phenyl), said aryl being optionally substituted by halo, lower alkyl and lower alkoxy groups. Examples of such heterocyclyl groups are isoxazolyl, imidazolyl, thiazolyl, imidazolidinyl, pyrrolyl, pyrrolinyl, pyranyl, pyrazinyl,



15
10

piperidyl, morpholinyl and triazolyl. The heterocyclyl group may be attached to the parent structure through a carbon atom or through any heteroatom of the heterocyclyl that results in a stable structure.

The term "heteroatom" means O, S or N, selected on an independent basis. It should be noted that any heteroatom with unsatisfied valences is assumed to have the hydrogen atom to satisfy the valences.

The term "halogen" or "halo" refers to chlorine, bromine, fluorine or iodine selected on an independent basis.

When a functional group is termed "protected", this means that the group is in modified form to preclude undesired side reactions at the protected site. Suitable protecting groups for the compounds of the present invention will be recognized from the present application taking into account the level of skill in the art, and with reference to standard textbooks, such as Greene, T. W. et al., *Protective Groups in Organic Synthesis*, Wiley, N.Y. (1991).

As used herein, the term "patient" encompasses all mammalian species.

Suitable examples of salts of the compounds according to the invention with inorganic or organic acids are hydrochloride, hydrobromide, sulfate, methanesulfonate, maleate, fumarate, and phosphate. Salts which are unsuitable for pharmaceutical uses but which can be employed, for example, for the isolation or purification of free compounds I or their pharmaceutically acceptable salts, are also included.

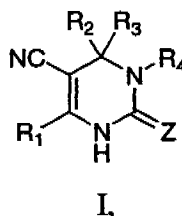
All stereoisomers of the compounds of the instant invention are contemplated, either in admixture or in pure or substantially pure form. The definition of the compounds according to the invention embraces all possible stereoisomers and their mixtures. It very particularly embraces the racemic forms and the isolated optical isomers having the specified activity. The racemic forms can be resolved by physical methods, such as, for example, fractional crystallization, separation or crystallization of diastereomeric derivatives or separation by chiral column chromatography. The individual optical isomers can be obtained from the racemates by conventional methods, such as, for example, salt formation with an optically active acid followed by crystallization.



It should be understood that the present invention includes prodrug forms of the compounds of formula I. Various forms of prodrugs are well known in the art. For examples of such prodrug derivatives, see:

- (a) Design of Prodrugs, edited by H. Bundgaard (Elsevier, 1985); and Methods in Enzymology, Vol. 42, pp. 309-396, edited by K. Widder et al., (Academic Press, 1985);
- (b) A Textbook of Drug Design and Development, edited by Krosgaard-Larsen and H. Bundgaard, Chapter 5, "Design and Application of Prodrugs," by H. Bundgaard, pp. 113-191 (1991);
- (c) H. Bundgaard, Advanced Drug Deliver Reviews, 8, pp. 1-38 (1992);
- (d) H. Bundgaard et al., Journal of Pharmaceutical Sciences, 77, 285 (1988); and
- (e) N. Kayeka et al., Chem. Phar. Bull., 32, 692 (1984).

In general, the instant invention comprises a compound of formula I



- its enantiomers, diastereomers, pharmaceutically acceptable salts, prodrugs and solvates thereof. R₁ is hydrogen, alkyl or cycloalkyl. R₂ and R₃ are each independently H, alkyl, aryl, heteroaryl, arylalkyl, cycloalkylalkyl, heterocycloalkylalkyl or heteroarylalkyl. Alternatively, R₂ and R₃ may be taken together to form either a carbocyclic or heterocyclic ring. R₄ is alkyl, arylalkyl, cycloalkylalkyl, heteroarylalkyl, heterocycloalkylalkyl, CN, COR₅, CO₂R₅ or CONR₅R₆. R₅ and R₆ are each independently H, alkyl, arylalkyl, cycloalkylalkyl, heteroarylalkyl or heterocycloalkylalkyl. Z is O, S or NR₈; R₈ is H, CN, sulfonamido, OR₇, alkyl, cycloalkyl, aryl, arylalkyl, heterocyclyl, heteroaryl or heteroarylalkyl. R₇ is H, alkyl, arylalkyl, cycloalkylalkyl, heterocycloalkylalkyl, or heteroarylalkyl.

- One preferred embodiment of the instant invention are compounds of formula I, as defined above, wherein R₁ is alkyl; R₂ is selected from the group consisting of



aryl and heteroaryl; R_3 is H; R_4 is selected from the group consisting of alkyl, arylalkyl, CO_2R_5 and CONR_5R_6 ; R_5 and R_6 are independently selected from the group consisting of H, alkyl and arylalkyl; Z is selected from the group consisting of O, S and NR_8 ; and R_8 is selected from the group consisting of H and CN.

5 In another preferred embodiment, the invention comprises compounds of formula I, as defined above, wherein R_4 is selected from the group consisting of alkyl, arylalkyl, CO_2R_5 and CONR_5R_6 .

In yet another preferred embodiment, the instant invention comprises the compounds of formula I, as defined above, wherein R_4 is CO_2R_5 or CONR_5R_6 and Z
10 is O.

In yet a further preferred embodiment, the instant invention comprises the compounds of formula I, as defined above, wherein R_4 is selected from the group consisting of alkyl and arylalkyl, and Z is O.

In still yet another preferred embodiment, the instant invention comprises the
15 compounds of formula I, as defined above, wherein R_1 is CH_3 ; R_2 is aryl; R_4 is CO_2R_5 ; R_5 is alkyl; and Z is O.

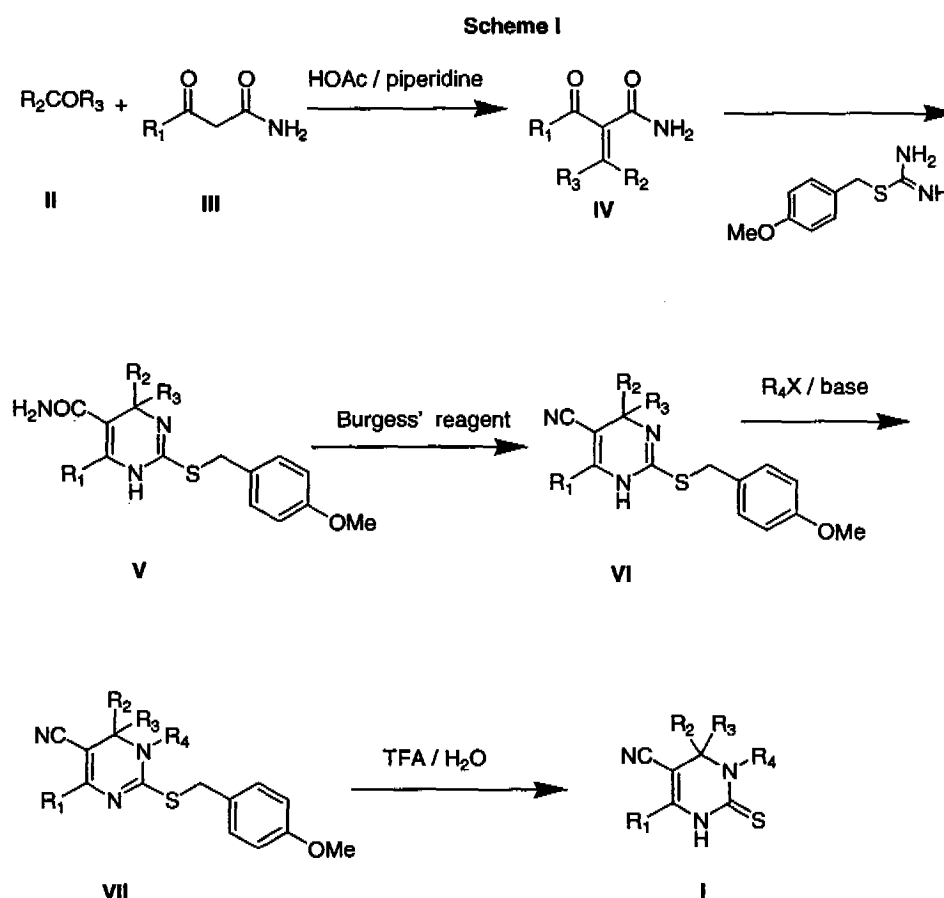
In still yet another preferred embodiment, the instant invention comprises the compounds of formula I, as defined above, wherein R_1 is CH_3 ; R_2 is aryl; R_4 is
20 CONR_5R_6 ; R_5 is alkyl, R_6 is H; and Z is O.

The invention further provides a pharmaceutical composition comprising a
25 compound of formula I, as defined above, and a pharmaceutically acceptable carrier. Optionally the pharmaceutical composition may further comprise at least one other anti-cancer agent formulated as a fixed dose.

The invention also provides a method for treating a proliferative disease via
25 modulation of the Eg5 motor protein, and/or, inducing apoptosis comprising administering to a mammalian species in need of such treatment an effective amount of at least one compound of formula I, as defined above. In another embodiment, the invention provides a method for treating a proliferative disease via modulation of the Eg5 motor protein comprising administering to a mammalian species in need of such
30 treatment an effective amount of at least one compound of formula I, as defined above, in combination (simultaneously or sequentially) with at least one other anti-cancer agent. In a preferred embodiment, the proliferative disease is cancer.



Certain compounds of formula I may generally be prepared according to the following schemes and the knowledge of one skilled in the art. Solvates (e.g., hydrates) of the compounds of formula I are also within the scope of the present invention. Methods of solvation are generally known in the art. Accordingly, the compounds of the instant invention may be in the free or hydrate form, and may be obtained by methods exemplified by the following schemes below.

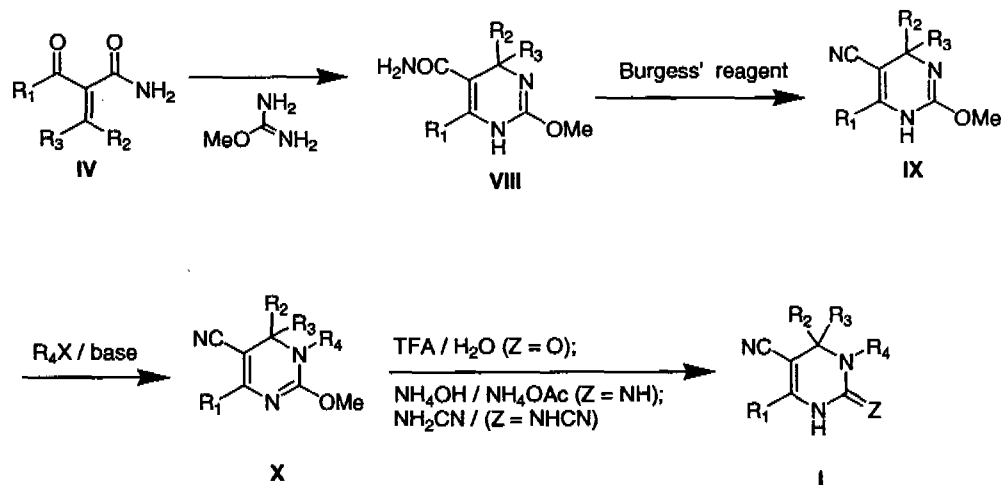


Compounds of formula I where Z is S may be made in accordance with Scheme I. A ketone or an aldehyde I (e.g., benzaldehyde, where R_2 is phenyl and R_3 is H), is condensed with an acetoacetamide III to give a Knoevenagel product IV as a mixture of isomers. Reaction with S-paramethoxybenzyl thiourea provides the protected dihydropyrimidine thione V. The primary amido group of V is dehydrated to the cyano substituent in VI using a dehydrating agent such as Burgess' reagent (methoxycarbonylsulfamoyl)triethylammonium hydroxide, inner salt. The N3 substituent is introduced by reaction with R_4X where R_4 is alkyl or acyl, and X is a



leaving group, or where R_4X is an isocyanate or haloformate. The protecting group is removed by treatment with acid in the presence of water to give compounds of formula I where Z is S.

Scheme II



5

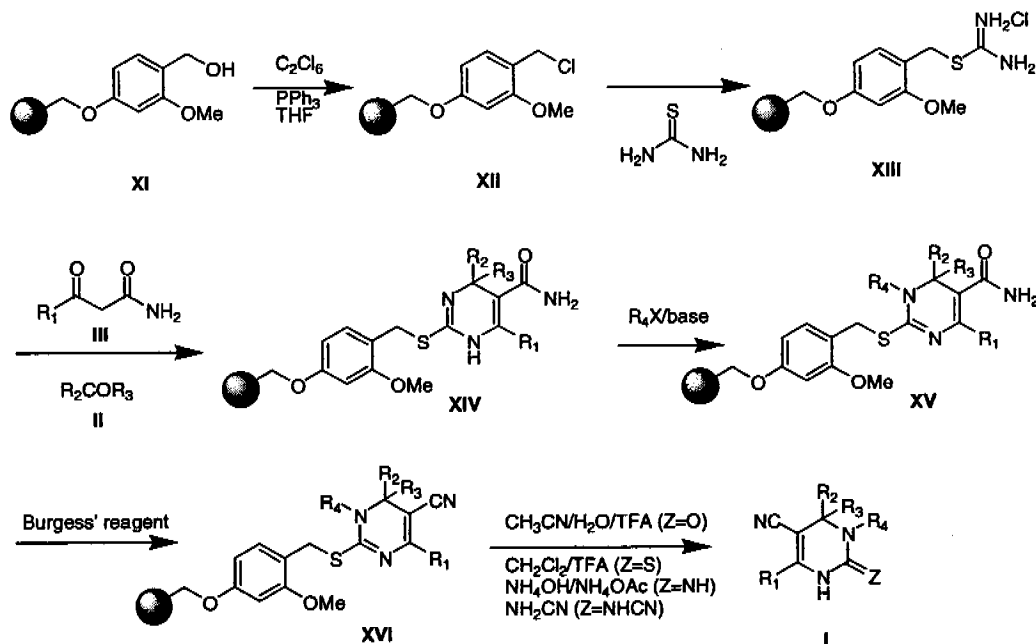
Compounds of formula I where Z is O, NH, or NR_8 are prepared from the reaction of Knoevenagel products IV with O-methyl isourea to provide the O-methyl dihydropyrimidines VIII. The primary amide is converted to a nitrile group using a dehydrating agent such as Burgess' reagent. The N3 substituent is introduced by reaction with R_4X where R_4 is alkyl or acyl, and X is a leaving group, or where R_4X is an isocyanate or haloformate. The methyl ether protecting group is removed by treatment with acid in the presence of water to give compounds of formula I where Z is O. Alternatively, treatment of compounds of formula X with ammonium hydroxide in the presence of ammonium acetate, or cyanamide in ethanol, provides compounds of formula I where Z is NH or NR_8 .

15

Compounds of formula I may also be prepared using the Bignelli reaction (D. J. Brown in *The Pyrimidines*, Wiley: New York, 1962, 440).



Scheme III
SOLID PHASE SYNTHESIS

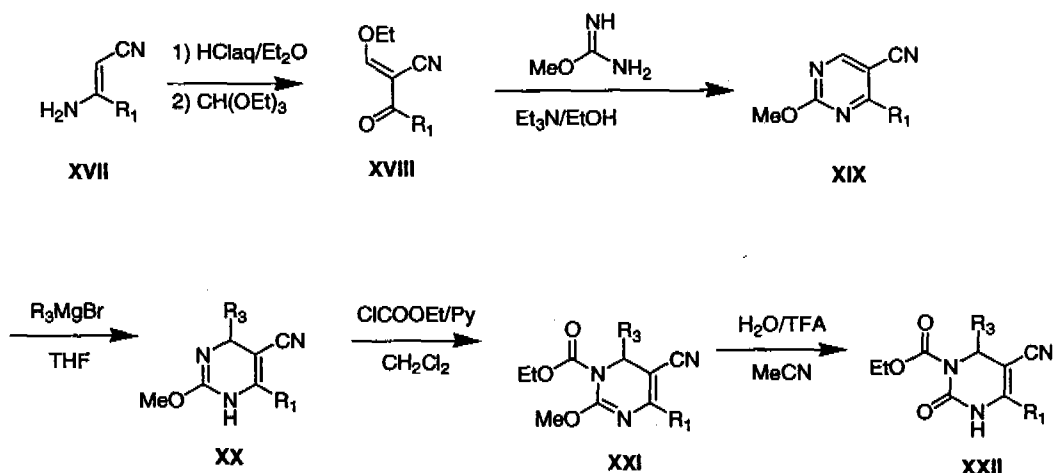


Compounds of formula I could be prepared on solid support as outlined in Scheme III. Starting compound XI denotes a resin-bound benzyl alcohol used for solid support synthesis which is prepared from a Merrifield resin denoted as ●, and 2-methoxy-4-hydroxybenzaldehyde, followed by reduction of the aldehyde with reducing agents such as NaBH₄. The benzyl alcohol is converted into the benzyl chloride using agents such as hexachloroethane and triphenylphosphine in THF to form resins of formula XII. The chloride is displaced with thiourea to form the isothiourea resin XIII. The resulting resin is treated with excess of ketoamides like acetoamide (III, R₁ is CH₃), in the presence of ketones of formula R₂COR₃ or aldehydes of formula R₂CHO to form the resin-bound pyrimidinethiones of formula XIV. The N3 substituent is introduced using R₄X, where X is a leaving group and R₄ is alkyl or acyl, or R₄X is an isocyanate, or haloformate, in the presence of base to form structures of formula XV. The primary amide can be dehydrated to the cyano group using reagents such as Burgess' reagent to form compounds of formula XVI. The products can be cleaved from the resin using a variety of conditions to form compounds of formula I, where Z is determined by the cleavage method employed. Cleavage in the presence of aqueous acid will form compounds of formula I with Z



being O, whereas cleavage under anhydrous acid conditions will form compounds of formula I with Z being S. Alternatively, treatment of resins with structure XVI with ammonium hydroxide in the presence of ammonium acetate will form compounds of formula I with Z being NH, while treatment with cyanamide, provides compounds of
5 formula I with Z being NHCN.

SCHEME IV



Compounds of formula XVIII may be prepared from a 3-amino-3-alkyl acrylonitrile XVII using the methods illustrated in Scheme IV. Reaction of a compound of formula XVII with aqueous acid, such as hydrochloric acid, followed by
10 treatment with triethyl orthoformate, provides a compound of formula XVIII. Reaction of a compound of formula XVIII with O-methyl isourea in the presence of a base such as triethylamine, provides a pyrimidine of formula XIX. Pyrimidines of formula XIX may be reacted with organometallic species such as a Grignard reagent, R_3MgBr , in a solvent such as ether or tetrahydrofuran, to give a pyrimidine of formula
15 XX, which is a compound of formula IX wherein R_2 is H. In analogy with Scheme II, a compound of formula XX may be converted into a compound of formula XXII, which is a compound of formula I in which R_4 is ethoxycarbonyl and R_2 is H.

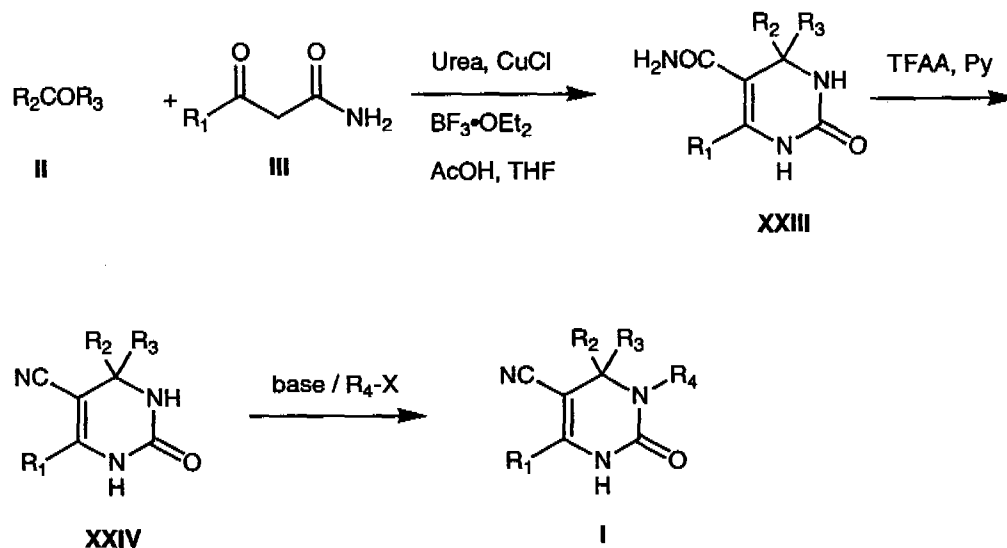
Alternatively, compounds of formula I, wherein $\text{Z} = \text{O}$, may be prepared in accordance with Scheme V. Following the procedure of E.H. Hu *et al* (J. Org. Chem,
20 1998, 63, 3454-3457), a carbonyl compound of formula II is condensed with an acylacetamide of formula III in the presence of urea, cuprous chloride and borontrifluoride etherate to give intermediate XXIII. Dehydration with trifluoroacetic anhydride in pyridine affords nitrile XXIV. The N3 substituent is introduced by



reaction with R_4X where R_4 is alkyl or acyl, and X is a leaving group, or where R_4X is an isocyanate or haloformate to give compounds of formula I. Deprotonation is effected with a base such as sodium hydride or LDA in aprotic solvents such as dimethylformamide or tetrahydrofuran.

5

Scheme V

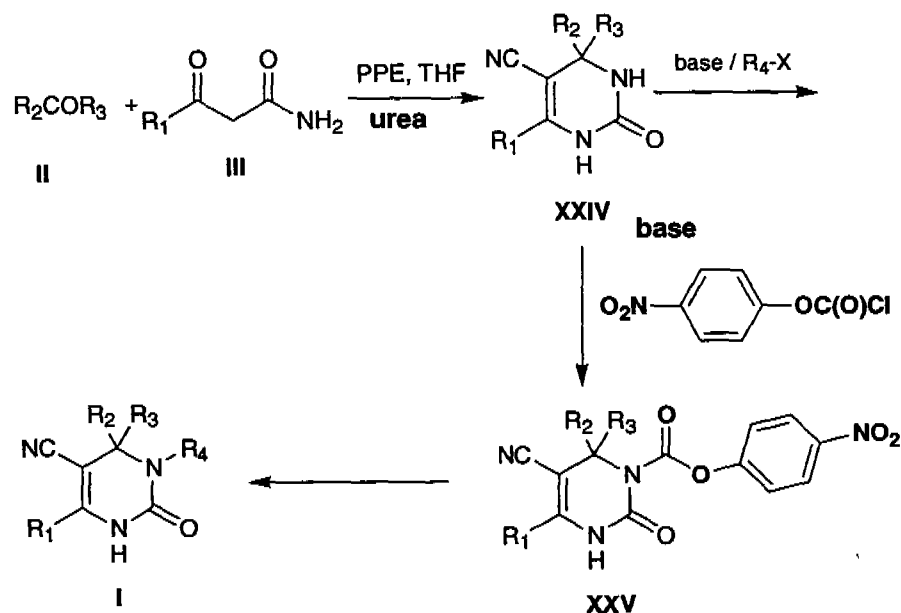


In yet another procedure, compounds of formula I, wherein $Z = \text{O}$, may be prepared in accordance with Scheme VI. A carbonyl compound of formula II is condensed with an acylacetamide of formula III in the presence of urea and polyphosphate ester to directly afford nitrile XXIV. Introduction of the N3 substituent follows the procedure as described in Scheme V. Compounds of formula I, where R_4 is aminocarbonyl, may also be obtained by first forming a reactive intermediate such as a nitrophenylcarbamate of formula XXV, which is subsequently reacted with an amine.

10



Scheme VI



In all of the above schema, a 2-acyl acetonitrile derivative, i.e., $\text{R}_1\text{COCH}_2\text{CN}$, may be substituted for a compound of formula III.

As discussed in the background section, Eg5 is a kinesin-like motor protein that facilitates spindle bipolarity during mitosis of the cell cycle. More specifically, the Eg5 protein acts to sort and bundle microtubules of the mitotic spindle during mitosis. Accordingly, Eg5 participates in cell cycle regulation through the spindle checkpoint during the M phase of the cycle. While not wishing to be bound by any theory, it is believed that the compounds of the instant invention act as Eg5 inhibitors.

This is theorized because the compounds of the instant invention induce a monopolar astral array of microtubules (the monoastral phenotype) and it has been shown that when Eg5 activity is absent, the monoastral phenotype forms. Regardless of the mechanism of action, the compounds of the instant invention have been shown to cause disruption of the bipolar spindle, spindle checkpoint initiation, mitotic arrest, programmed cell death and tumor cell proliferation inhibition. Furthermore, the compounds of the invention induce a cell cycle arrest in mitosis that is not transient but rather which progresses into programmed cell death. The compounds also exhibit high potency, inducing mitotic arrest and apoptosis in human cells *in vitro* at concentrations in the low or sub μM range. Additionally, in contrast to microtubule agents, the compounds do not disrupt the dynamic instability of microtubules. The instant invention may therefore more specifically target the mitotic spindle of



proliferating cells, which may provide for different toxicity profiles than those of existing anti-cancer drugs.

The compounds according to the invention have pharmacological properties; in particular, the compounds of formula I induce mitotic arrest and are believed to be
5 Eg5 inhibitors. The novel compounds of formula I are thus useful in the therapy of a variety of proliferative diseases (including but not limited to diseases associated with the Eg5 motor protein) such as cancer, autoimmune diseases, viral diseases, fungal diseases, neurodegenerative disorders and cardiovascular disease.

More specifically, the compounds of formula I are useful in the treatment of a
10 variety of cancers, including, but not limited to, the following:

- a) carcinoma, including that of the bladder, breast, colon, kidney, liver, lung, including small cell lung cancer, esophagus, gall bladder, ovary, pancreas, stomach, cervix, thyroid, prostate, and skin, including squamous cell carcinoma;
- 15 b) hematopoietic tumors of lymphoid lineage, including leukemia, acute lymphocytic leukemia, acute lymphoblastic leukemia, B-cell lymphoma, T-cell lymphoma, Hodgkins lymphoma, non-Hodgkins lymphoma, hairy cell lymphoma and Burkett's lymphoma;
- c) hematopoietic tumors of myeloid lineage, including acute and
20 chronic myelogenous leukemias, myelodysplastic syndrome and promyelocytic leukemia;
- d) tumors of mesenchymal origin, including fibrosarcoma and rhabdomyosarcoma;
- e) tumors of the central and peripheral nervous system, including
25 astrocytoma, neuroblastoma, glioma and schwannomas; and
- f) other tumors, including melanoma, seminoma, teratocarcinoma, osteosarcoma, xenoderoma pigmentosum, keratocanthoma, thyroid follicular cancer and Kaposi's sarcoma.

Due to the key role of motor proteins in the regulation of cellular proliferation
30 in general, inhibitors could act as reversible cytostatic agents which may be useful in the treatment of any disease process which features abnormal cellular proliferation, e.g., benign prostatic hyperplasia, familial adenomatosis polyposis, neuro-



fibromatosis, atherosclerosis, pulmonary fibrosis, arthritis, psoriasis, glomerulonephritis, restenosis following angioplasty or vascular surgery, hypertrophic scar formation, inflammatory bowel disease, transplantation rejection, endotoxic shock, and fungal infections.

5 Compounds of formula I induce apoptosis. The apoptotic response is aberrant in a variety of human diseases. Compounds of formula I, as modulators of apoptosis, will be useful in the treatment of cancer (including but not limited to those types mentioned herein above), viral infections (including but not limited to herpesvirus, poxvirus, Epstein-Barr virus, Sindbis virus and adenovirus), prevention of AIDS
10 development in HIV-infected individuals, autoimmune diseases (including but not limited to systemic lupus, erythematosus, autoimmune mediated glomerulonephritis, rheumatoid arthritis, psoriasis, inflammatory bowel disease, and autoimmune diabetes mellitus), neurodegenerative disorders (including but not limited to Alzheimer's disease, AIDS-related dementia, Parkinson's disease, amyotrophic lateral sclerosis, retinitis pigmentosa, spinal muscular atrophy and cerebellar degeneration),
15 myelodysplastic syndromes, aplastic anemia, ischemic injury associated with myocardial infarctions, stroke and reperfusion injury, arrhythmia, atherosclerosis, toxin-induced or alcohol related liver diseases, hematological diseases (including but not limited to chronic anemia and aplastic anemia), degenerative diseases of the
20 musculoskeletal system (including but not limited to osteoporosis and arthritis) aspirin-sensitive rhinosinusitis, cystic fibrosis, multiple sclerosis, kidney diseases and cancer pain.

 Compounds of formula I may modulate the level of cellular RNA and DNA synthesis. These agents would therefore be useful in the treatment of viral infections
25 (including but not limited to HIV, human papilloma virus, herpesvirus, poxvirus, Epstein-Barr virus, Sindbis virus and adenovirus).

 Compounds of formula I are useful in the chemoprevention of cancer. Chemoprevention is defined as inhibiting the development of invasive cancer by either blocking the initiating mutagenic event or by blocking the progression of pre-malignant cells that have already suffered an insult or inhibiting tumor relapse.
30

 Compounds of formula I may also be useful in inhibiting tumor angiogenesis and metastasis.



20
The instant invention may also inhibit other motor proteins, for example, including but not limited to: those human motor proteins that correspond to, Xklp2, MKLP1, CHO1, chromokinesins, Nod, Cenp-E, MCAK, members of the BimC family, and members of the Kar3 family. Additionally, compounds used in the
5 methods of the instant invention may also act as inhibitors of other kinesin or kinesin-like proteins and thus be effective in the treatment of diseases associated with other kinesin or kinesin-like proteins.

The compounds of this invention may also be useful in combination (administered together or sequentially) with known anti-cancer treatments such as
10 radiation therapy or with cytostatic or cytotoxic agents, such as for example, but not limited to, DNA interactive agents, such as cisplatin or doxorubicin; topoisomerase II inhibitors, such as etoposide; topoisomerase I inhibitors such as CPT-11 or topotecan; tubulin interacting agents, such as paclitaxel, docetaxel or the epothilones; hormonal agents, such as tamoxifen; thymidilate synthase inhibitors, such as 5-fluorouracil; and
15 anti-metabolites, such as methotrexate.

If formulated as a fixed dose, such combination products employ the compounds of this invention within the dosage range described below and the other pharmaceutically active agent or treatment within its approved dosage range. Compounds of formula I may also be administered sequentially with known
20 anticancer or cytotoxic agents when a combination formulation is inappropriate. The invention is not limited in the sequence of administration; compounds of formula I may be administered either prior to or after administration of the known anticancer or cytotoxic agent(s).

25 ASSAYS

The pharmacological properties of the compounds of this invention may be confirmed by a number of pharmacological assays. The exemplified pharmacological assays which follow have been carried out with the compounds according to the invention and their salts. The compounds of formula I exhibited antiproliferative
30 activity. Preferred compounds exhibit IC₅₀ values less than or equal to about 10 μ M.



Cell Culture

Cell lines are maintained in RPMI-1640 plus 10% fetal bovine serum.

72-Hour Proliferation Assay

- 5 Cells are plated at a density of 3,000-6,000 cells/well, depending upon the cell line used, in a 96-well plate. The cultures are grown overnight. Cells were then treated in triplicate with a seven concentration dose-response curve. The maximum concentration of DMSO never exceeded 0.5%. Cells were exposed to compound for 72 hours. Proliferation was measured using XTT or MTS from Promega. The ovarian, breast, prostate, lung,
- 10 leukemia, and colorectal human cancer cell lines used in this assay included but were not limited to, for example, A2780S, SKBR3, MDA-MB-231, PC3, LX-1, K562, HT-29, WiDr, HCT-15 and HCT116. The compounds of formula I exhibited activity in the 72-hour cell proliferation assay, inhibiting cell proliferation in one or more of the cell lines listed above with at an IC_{50} less than or equal to about 10 μ M.

15

Clonogenic Growth Assay

- Colony growth inhibition was measured for A2780 ovarian carcinoma cells using a standard clonogenic assay. Briefly, 200 cells/well were seeded into 6-well tissue culture plates (Falcon, Franklin Lakes, NJ) and allowed to attach for 18 hours. Assay
- 20 medium consisted of RPMI-1640 plus 10% fetal bovine serum. Cells were then treated in duplicate with a six concentration dose-response curve. The maximum concentration of DMSO never exceeded 0.25%. Cells were exposed to compound for 4, 8 or 24 hours. Compound was then removed and the cells were washed with 2 volumes of PBS. The normal growth medium was then replaced. Colonies were fed
- 25 with fresh media every third day. Colony number was scored on day 10-14 using a Optimax imaging station. The compound concentration required to inhibit 50% or 90% of colony formation (IC_{50} or IC_{90} , respectively) was determined by non-linear regression analysis. The coefficient of variance ($SD/mean, n=3$) = 30%. When exposed to cells for 24 hours, the compounds of formula I exhibited activity in the
- 30 clonogenicity assay.



2723

Combination Studies - Clonogenic Growth Assays

Combination studies to examine the use of the Eg5 inhibitors of formula I in combination with other antineoplastic agents were conducted essentially the same as the standard colony growth assay with the exception of compound treatment. In the combination studies, the cells were treated with both a compound of formula I and another antineoplastic agent. The compounds were administered simultaneously or sequentially; both the order of sequence and length of treatment (1 to 24 hours) were varied. Data evaluation was based upon the isobologram analysis and the envelope of additivity, using the line of multiplicity which compares the survival fractions of combination treatments with those of single drug treatments.

Cell Cycle Analysis

The cell cycle profile of cells treated with compounds of formula I was monitored by flow cytometry. Briefly, A2780 ovarian carcinoma cells were seeded at a density of 2×10^5 per well in standard 6 well culture plates and permitted to grow for 17 hours. Cells were then exposed to compounds of formula I at varying concentrations for 2 to 24 hours. Following exposure, cell populations were harvested, stained with propidium iodide to determine DNA content and also stained with the appropriate immunological reagent for protein biomarkers of mitosis and apoptosis, including, for example, anti-phospho-ThreonineProline, anti-M Phase Phosphoprotein 2 (MMP2), and anti-p85 PARP. The compounds of formula I exhibited activity in the cell cycle profile analysis assay, producing significant increases in mitotic and apoptotic fractions of the cell population.

Immunocytochemistry Assays

A2780 ovarian carcinoma cells or PTK2 kangaroo rat kidney epithelial cells were plated at a density of 200 to 2000 cells per well in 4 chamber glass slides and allowed to attach overnight. Cells were then treated with compounds of formula I at concentrations of 100 nM to 50 μ M for 4 to 30 hours, fixed and permeabilized for subsequent staining. Stain reagents included, for example, propidium iodide, DAPI, rhodamine phalloidin, anti- α tubulin, anti- β tubulin, anti- γ tubulin, and the appropriate



fluorescent-tagged secondary antibodies. Cells were imaged by fluorescent and confocal fluorescent microscopy. The compounds of formula I inhibited bipolar spindle formation and induced a monoastral array of microtubules.

Further subject matter of the invention also includes pharmaceuticals for use as described above including controlling cancer, inflammation and arthritis, which contain at least one compound of the formula I as defined above or at least one of its pharmacologically acceptable acid addition salts, and the use of a compound of the formula I as defined above for the preparation of a pharmaceutical having activity against proliferative diseases as described previously including against cancer, inflammation and/or arthritis.

The following examples and preparations describe the manner and process of making and using the invention and are illustrative rather than limiting. It should be understood that there may be other embodiments which fall within the spirit and scope of the invention as defined by the claims appended hereto.

15

Example 1

5-Cyano-3,6-dihydro-4-methyl-6-(3-nitrophenyl)-2-thioxo-1-(2H)-pyrimidinecarboxylic acid, 1-ethyl ester

A. Step 1

A mixture of 6.42 g of acetoacetamide, 8.0 g of 3-nitrobenzaldehyde, 0.61 ml of acetic acid, and 0.21 ml of piperidine in 30 ml of toluene was heated to reflux. A Dean Stark trap was used to azeotrope the water produced. After refluxed for 2 h, the reaction mixture was cooled to room temperature, with a lot of solid appeared, it was treated with a solution of 300 ml of EtOAc and 25 ml MeOH, the solid was then filtered off, rinsed with 15 ml of EtOAc twice to give 3.1 g of desired product in 25% yield.

B. Step 2

A mixture of 200 mg of the compound of Example 1, Step 1, 198 mg of 2-(4-methoxybenzyl)-2-thiopseudourea HCl salt, 84 mg of sodium acetate in 3.6 ml DMF was heated at 85 °C for 15 h, then cooled to room temperature. The resulting reaction mixture was purified by preparative HPLC using a (YMC S5 ODS 20 X 100 mm)

column, the desired fraction was concentrated to dryness. Saturated NaHCO_3 (50 ml) was added and extracted with EtOAc (3 x 50 ml), combined EtOAc extracts were washed with 30 ml of brine, dried with MgSO_4 , filtered and concentrated under vacuum to give 126.1 mg desired product in 36% yield.

5

C. Step 3

A mixture of the compound of Example 1, Step 2 (86.5 mg) and Burgess reagent (150 mg) in 7.0 ml of anhydrous THF was stirred at room temperature for 1 h, concentrated under vacuum, then purified by preparative HPLC using a YMC S5 (10 ODS 20 X 100 mm) column to give 80.8 mg of desired product in 87% yield.

D. Step4

To a solution of the compound of Example 1, Step 3 (60 mg) and pyridine (0.1 ml) in 0.6 ml of CH_2Cl_2 , 17 μl of ethylchloroformate was added, after stirring for 2.5 h, 15 another 22 μl of ethylchloroformate was added, the reaction mixture was stirred for 2 h, then 0.3 ml of trifluoroacetic acid was added, the resulting mixture was stirred for another 1 h, and concentrated under vacuum, diluted with DMF, MeOH and a little CH_2Cl_2 , filtered, then purified by preparative HPLC using a (YMC S5 ODS 20 X 100 mm) column to give 22.5 mg of product in 42.7% yield. MS $(\text{M}-\text{H})^+ = 345$. HPLC RT 20 = 2.85 min (YMC S5 ODS column 4.6 x 50 mm, 10-90% aqueous methanol over 4 minutes containing 0.2% phosphoric acid, 4ml/min, monitoring at 220 nm)

Example 2

25 5-Cyano-3,6-dihydro-4-methyl-6-(3-nitrophenyl)-2-oxo-1-(2H)-pyrimidinecarboxylic acid, 1-ethyl ester

A. Step 1

10.92 g of NaHCO_3 was added portionwise to a solution of 7.83 g of the compound of Example 1, Step 1 and 7.48g of o-methylisourea hydrogen sulfate in DMF (100 ml), there was gas evolved. The reaction mixture was stirred for 2 h, then heated at 65°C 30 overnight, cooled to room temperature, diluted with 800 ml of EtOAc, washed with water (2 x 100 ml) and brine (1 x 100 ml). The organic layer was dried MgSO_4 ,



31
2
2

filtered and concentrated under vacuum. The resulting residue was triturated in EtOAc- CH₂Cl₂-hexane to give 5.48 g of desired product as solid (56%).

B. Step 2

- 5 A mixture of the compound of Example 2, Step 1 (209 mg) and Burgess reagent (274.5 mg) in CH₂Cl₂ (5 ml) and THF (10 ml) was stirred overnight. The reaction mixture was concentrated under vacuum, diluted with 150 ml of EtOAc, then washed with saturated NaHCO₃ (2 x 30 ml) and brine (1 x 30 ml), dried with MgSO₄, concentrated under vacuum. The resulting residue was purified silica gel
10 chromatography to give 136 mg (69.4%) of desired product.

C. Step 3

- 1.23 ml of pyridine was added to a solution of 2.075 g of the compound of Example 2, Step 2 in CH₂Cl₂ (30 ml) under argon at 0 °C, then 0.87 ml of ethyl chloroformate
15 was added slowly. The reaction mixture was warmed to room temperature and stirred for 3 h, diluted with a mixture of saturated of NaHCO₃ (50 ml) and brine (50 ml), extracted with EtOAc three times, the combined layers were washed with brine and dried with MgSO₄, filtered and concentrated under vacuum, purified by silica gel chromatography to give 2.57 g (98%) of desired product.

20

D. Step 4

- 2.5 ml of TFA was added to a solution of 1.44 g of the compound of Example 2, Step 3 in CH₃CN (25 ml) and H₂O (2.5 ml), the reaction mixture was stirred for 2 h, a lot of white solid appeared. The solid was filtered off, rinsed with CH₃CN (3 x 20 ml)
25 and hexane (2 x 20 ml), dried in air to give 860 mg (62.2%) desired product. The filtrate was concentrated under vacuum, the solid was recrystallized in CH₃CN to give another 320 mg (23.2%) of product. MS (M-H)⁺ = 329. HPLC RT = 2.53 min (YMC S5 ODS column 4.6 x 50 mm, 10-90% aqueous methanol over 4 minutes containing 0.2% phosphoric acid, 4ml/min, monitoring at 220 nm)

32
**Example 3****5-Cyano-3,6-dihydro-4-methyl-6-(3-nitrophenyl)-2-oxo-1-(2H)-pyrimidinecarboxylic acid, 1-ethyl amide.****A. Step 1**

- 5 To a solution of the compound of Example 2, Step 2 (100 mg; 0.37 mmol) and pyridine (0.74 mmol; 18 μ L) in dichloroethane (40 mL) was added 4-nitrophenyl chloroformate (81 mg; 0.40 mmol) and the resulting solution was stirred at room temperature for 1.5 hours. The reaction mixture was diluted with saturated NaHCO_3 (30 mL), extracted with ethyl acetate (3 x 50 mL), dried (MgSO_4) and concentrated in
10 vacuo to afford a white foam. Purification by chromatography (SiO_2 : 20% EtOAc/hexane) afforded the desired compound as a colorless foam (99 mg; 62%)

B. Step 2

- To a solution of the compound of Example 3, Step 1 (12 mg; 27 μ mol) in THF (0.1
15 mL) was added 2M ethylamine in THF solution (15 μ L; 30 mmol) in one portion at room temperature and the resulting yellow solution was stirred 30 minutes. Dilution of the reaction mixture with methanol (1.8 mL) afforded a yellow solid which was collected by suction filtration and purified by preparative HPLC to afford the title compound as a white solid (20 mg; 22%).

20

In contrast to the method of Example 2 above, in this case the 2-methoxy group hydrolyzed during isolation and purification to afford the dihydropyrimidinone ring without the need for treatment with TFA (Example 2, Step 4).

25

Example 4**5-Cyano-3,6-dihydro-4-methyl-6-(3-nitrophenyl)-2-oxo-1-(1-oxobutyl)-(2H)-pyrimidine****A. Step 1**

- 23.7 μ l of butyryl chloride was added to a solution of 52 mg of the compound of
30 Example 2, Step 2 and 0.15 ml of pyridine in 0.6 ml of anhydrous CH_2Cl_2 , the reaction mixture was stirred for 1h, then 24 μ l of butyryl chloride was added, the



reaction was stirred for 1.5 h, purified by preparative HPLC using a YMC S5 (ODS 20 x 100 mm) column to give 30 mg desired product.

B. Step 2

- 5 A solution of 30 mg of the compound of Example 4, Step 1, 0.2 ml of H₂O and 0.2 ml of TFA in 1.2 ml CH₃CN was stirred for 1.5 h, it was added another 0.1 ml of TFA and stirred for another 2.5 h. The reaction mixture was concentrated under vacuum, and purified by preparative HPLC using a YMC S5 (ODS 20 x 100 mm) column to give 11.8 mg desired product. MS (M-H)⁺ = 327. HPLC RT = 3.06 min (YMC S5
- 10 ODS column 4.6 x 50 mm, 10-90% aqueous methanol over 4 minutes containing 0.2% phosphoric acid, 4ml/min, monitoring at 220 nm)

Example 5

- enantio 5-Cyano-3,6-dihydro-4-methyl-6-(3-nitrophenyl)-2-oxo-1-(2H)-*
- 15 *pyrimidinecarboxylic acid, 1-ethyl ester (enantiomer A)*
- 53 mg of the compound of Example 2, Step 4 was dissolved in absolute EtOH, preparative chiral separation was carried out using a Chiralcel OD-H S5 (4.6 x 250 mm) column, 20 mg of enantiomer A and 27 mg of enantiomer B were obtained. MS (M-H)⁺ = 329. HPLC-Chiral RT = 10.44 min (Chiralcel OD-H, S5, column 4.6 x250
- 20 mm, 10% MeOH / 10% EtOH /Heptane, 1.0 ml /min, monitoring at 220 nm, 94.7% ee)

Example 6

- enantio 5-Cyano-3,6-dihydro-4-methyl-6-(3-nitrophenyl)-2-oxo-1-(2H)-*
- pyrimidinecarboxylic acid, 1-ethyl ester (enantiomer B)*
- 25 MS (M-H)⁺ = 329. HPLC-Chiral RT = 12.92 min (Chiralcel OD-H, S5, column 4.6 x250 mm, 10% MeOH / 10% EtOH /Heptane, 1.0 ml /min, monitoring at 220 nm, 99.64% ee)

Example 7

- 30 *5-Cyano-3,6-dihydro-4-methyl-6-(3-aminophenyl)-2-oxo-1-(2H)-*
- pyrimidinecarboxylic acid, 1-ethyl ester*



A solution of 12 mg of the compound of Example 1, Step 4 in ethanol was treated with 100 mg of tin (II) chloride and heated to reflux under argon for 90 min., the reaction was cooled down and quenched with saturated NaHCO₃ solution and extracted with EtOAc (3 x 50 ml). The combined organic layer was washed with H₂O, dried with Na₂SO₄ and concentrated under vacuum. It was triturated with hexane and ether to give 8 mg of crude product, which was further purified by preparative HPLC to afford 3 mg of desired product as TFA salt. MS (M+H)⁺ = 301. HPLC RT = 1.685 min (YMC S5 ODS column 4.6 x 50 mm, 10-90% aqueous methanol over 4 minutes containing 0.1% of TFA, 4ml/min, monitoring at 220 nm)

10

Example 8

5-Cyano-3,6-dihydro-4-methyl-6-(3-(N,N-dimethyl)aminophenyl)-2-oxo-1-(2H)-pyrimidinecarboxylic acid, 1-ethyl ester

A solution of 12 mg of the compound of Example 7 in CH₃CN (1 ml) was added paraformaldehyde (40 mg), sodium cyanoborohydride (30 mg) followed by 2 drops of acetic acid. The reaction mixture was stirred at room temperature for 2 h, then quenched with saturated NaHCO₃ solution and extracted with EtOAc three times. The combined organic layer was washed with brine, dried with Na₂SO₄ and concentrated under vacuum. The resulting residue was purified by preparative HPLC to yield 3.2 mg of desired product as TFA salt. MS (M+H)⁺ = 329. HPLC RT = 1.76 min (YMC S5 ODS column 4.6 x 50 mm, 10-90% aqueous methanol over 4 minutes containing 0.1% of TFA, 4ml/min, monitoring at 220 nm)

Examples 9 through 15 were prepared using the methods of Example 2 with the substitution of an appropriate benzaldehyde in Step 1.

25

Example 9

5-Cyano-3,6-dihydro-4-methyl-6-(3-trifluoromethylphenyl)-2-oxo-1-(2H)-pyrimidinecarboxylic acid, 1-ethyl ester

HPLC-HI 100% at 2.84 min (YMC S5 ODS column 4.6 x 50 mm, 10 - 90% aqueous methanol over 4 minutes containing 0.1% of TFA , 4 ml/min, monitoring at 220 nm). MS: [M+H]⁺ = 354.

30



Example 10

5-Cyano-3,6-dihydro-4-methyl-6-(2,3-dichlorophenyl)-2-oxo-1-(2H)-pyrimidinecarboxylic acid, 1-ethyl ester

HPLC-HI 100% at 3.2 min (YMC S5 ODS column 4.6 x 50 mm, 10 - 90% aqueous
5 methanol over 4 minutes containing 0.1% of TFA , 4 ml/min, monitoring at 220 nm).
MS: $[M-H]^- = 352$.

Example 11

5-Cyano-3,6-dihydro-4-methyl-6-(3-methoxyphenyl)-2-oxo-1-(2H)-pyrimidinecarboxylic acid, 1-ethyl ester

HPLC-HI 100% at 2.42 min (YMC S5 ODS column 4.6 x 50 mm, 10 - 90% aqueous
10 methanol over 4 minutes containing 0.1% of TFA , 4 ml/min, monitoring at 220 nm).
MS: $[M+H]^+ = 316$.

Example 12

5-Cyano-3,6-dihydro-4-methyl-6-(3,5-dichlorophenyl)-2-oxo-1-(2H)-pyrimidinecarboxylic acid, 1-ethyl ester

HPLC-HI 87% at 3.26 min (YMC S5 ODS column 4.6 x 50 mm, 10 - 90% aqueous
15 methanol over 4 minutes containing 0.1% of TFA , 4 ml/min, monitoring at 220 nm).
MS: $[M-H]^- = 352$.

20

Example 13

5-Cyano-3,6-dihydro-4-methyl-6-(3,4-dichlorophenyl)-2-oxo-1-(2H)-pyrimidinecarboxylic acid, 1-ethyl ester

HPLC-HI 100% at 3.197 min (YMC S5 ODS column 4.6 x 50 mm, 10 - 90% aqueous
25 methanol over 4 minutes containing 0.1% of TFA , 4 ml/min, monitoring at 220 nm).
MS: $[M-H]^- = 352$.

Example 14

5-Cyano-3,6-dihydro-4-methyl-6-(3-cyanophenyl)-2-oxo-1-(2H)-pyrimidinecarboxylic acid, 1-ethyl ester

30

HPLC-HI 93% at 2.32 min (YMC S5 ODS column 4.6 x 50 mm, 10 - 90% aqueous methanol over 4 minutes containing 0.1% of TFA, 4 ml/min, monitoring at 220 nm).
MS: $[M+H]^+ = 311$.

5

Example 15

5-Cyano-3,6-dihydro-4-methyl-6-(4-methoxyphenyl)-2-oxo-1-(2H)-pyrimidinecarboxylic acid, 1-ethyl ester

HPLC-HI 100% at 2.55 min (YMC S5 ODS column 4.6 x 50 mm, 10 - 90% aqueous methanol over 4 minutes containing 0.1% of TFA, 4 ml/min, monitoring at 220 nm).

10 MS: $[M+H]^+ = 316$.

Example 16

5-Cyano-3,6-dihydro-4-methyl-6-(4-methylphenyl)-2-oxo-1-(2H)-pyrimidinecarboxylic acid, 1-ethyl ester

15 A. Step 1

A cloudy solution of 3-aminocrotononitrile (41 g, 0.5 mol) in Et₂O (500 ml) was added dropwise to the 15% HCl solution (115 ml) at 0°C over 30 min with vigorous stirring, and the reaction mixture was stirred at 0°C for 15 min. The aqueous solution was then separated, extracted with Et₂O (2 x 125 ml), the combined organic phases
20 dried with Na₂SO₄. Triethyl orthoformate (83 ml) in a 500 ml three-neck flask equipped with addition funnel and distillation set was stirred in 60°C-65°C oil bath, the above ether solution was added dropwise such that the rate of addition was equal to the rate of distillation. An additional 83 ml of triethyl orthoformate was added to the reaction when the addition of the ether solution was half complete, the oil bath
25 temperature was slowly raised to 100°C, and the reaction mixture was then stirred for 5 h. Distillation gave 26.6 g (38%) of desired red solid product at 150-155°C/ 2mm Hg.

B. Step 2

30 To a mixture of O-methylisourea sulfate (9.9 g, 80 mmol), the compound of Example 16, Step 1 (7.4 g, 53 mmol) and ethanol (90 ml) was added Et₃N (11 ml, 80 mmol). The mixture was stirred at room temperature for 15 min, then stirred at 66°C for 3 h,

32
20

and concentrated to remove EtOH. EtOAc (80 ml) and H₂O (80 ml) were added, the aqueous layer were separated and extracted with EtOAc (2 x 80 ml), the combined organic layer were dried with Na₂SO₄, concentrated to give brown solid, which was dissolved in EtOAc, filtered through a silica gel pad, washed with EtOAc/heptane (1/1) to remove dark color, and the combined filtrate was concentrated. The solid thus obtained was recrystallized in heptane / EtOAc to give yellow crystal 5.18 g in 65% yield.

C. Step 3

10 A solution of p-tolylmagnesium bromide in ether (1M, 1 ml, 1 mmol) was added dropwise to a solution of the compound of Example 16, Step 2 (75 mg, 0.5 mmol) in THF (2 ml) at 0°C under argon. The reaction mixture was stirred at the temperature for 1.5 h, another 3 ml of Grignard reagent was added at -78°C, the reaction was slowly warmed to room temperature and stirred for 2 min. Saturated NH₄Cl (5 ml) and H₂O (5 ml) were added, the mixture was extracted with EtOAc (2 x 15 ml), the combined organic layer was dried, concentrated and chromatographed on silica gel to give 45.6 mg of desired product in 91% yield.

D. Step 4

20 To a solution of the compound of Example 16, Step 3 (109 mg, 0.45 mmol) was added pyridine (0.2 ml, 2.5 mmol) in dry CH₂Cl₂ (5 ml) followed by ethyl chloroformate (0.1 ml, 1.05 mmol), and the resulting reaction mixture was stirred at room temperature overnight. MeOH was added, the resulting mixture was stirred for 15 min, concentrated, and chromatographed on silica gel column to give 100 mg desired product as colorless oil (71%).

E. Step 5

30 A mixture of the compound of Example 15, Step 4 (100 mg, 0.32 mmol), H₂O (0.7 ml), CH₃CN (0.5 ml) and TFA (7 ml) was stirred at room temperature for 2 h. The solution was then concentrated to remove CH₃CN, saturated NaHCO₃ was added to make the mixture basic, the white solid precipitate was filtered, washed with H₂O, and dried to give the desired product (64 mg). The crude product was dried and recrystallized from EtOH / H₂O to give another 20 mg desired product as white solid.

MS (M+H)⁺ = 300. HPLC RT = 3.40 min (YMC S5 ODS column 4.6 x 50 mm, 10-90% aqueous methanol over 4 minutes containing 0.2% phosphoric acid, 4 ml/min, monitoring at 220 nm)

Example 17

5 **5-Cyano-3,6-dihydro-4-methyl-6-cyclohexyl-2-oxo-1-(2H)-pyrimidinecarboxylic acid, 1-ethyl ester**

To a solution of the compound of Example 16, Step 2 (30 mg, 0.2 mmol) in THF (1.2 ml) was added cyclohexylmagnesium chloride (2 M in ether, 1.0 ml, 2 mmol) at -44°C under argon, the reaction was slowly warmed to room temperature, and stirred
10 for 10 min. Saturated NH₄Cl was added, the resulting mixture was extracted several times with EtOAc, the combined organic layer dried, filtered through a silica gel pad, and concentrated to give yellow oil. The oil was dissolved in CH₂Cl₂ (2 ml), then pyridine (80 µl, 0.9 mmol) and ethyl chloroformate (50 µl, 0.5 mmol) were added, the mixture was stirred at room temperature for 30 min, stirred for another 10 min after
15 which H₂O (25 µl) and EtOAc were added, and the mixture dried over Na₂SO₄, filtered through a silica gel pad, and concentrated to give yellow oil. The oil was dissolved in CH₃CN (2 ml), H₂O (0.3 ml) and TFA (0.2 ml) were added, and the mixture stirred at room temperature for 2 h. Saturated NaHCO₃ solution and EtOAc were added, the aqueous layer was separated and extracted with EtOAc, and the
20 combined organic layer was dried over Na₂SO₄, concentrated and chromatographed on silica gel to give 35 mg of desired product as yellow foam (60%). MS (M+H)⁺ = 392. HPLC RT = 3.60 min (YMC S5 ODS column 4.6 x 50 mm, 10-90% aqueous methanol over 4 minutes containing 0.2% phosphoric acid, 4 ml/min, monitoring at 220 nm)

25

Example 18

5-Cyano-3,6-dihydro-4-methyl-6-phenyl-2-oxo-1-(2H)-pyrimidinecarboxylic acid, 1-ethyl ester

To a solution of the compound of Example 16, Step 2 (55 mg, 0.37 mmol) in dry THF
30 (2 ml) was added phenylmagnesium bromide (2 M in THF, 2 ml, 4 mmol) dropwise at -78°C under argon. After addition, the reaction was slowly warmed to room

temperature and stirred for about 10 min, until starting material disappeared. Saturated NH_4Cl solution and H_2O were added, the mixture was extracted with EtOAc for two times, and the combined organic layer was dried over Na_2SO_4 , concentrated and chromatographed on silica gel to give solid intermediate. The solid
5 was dissolved in CH_2Cl_2 (5 ml), pyridine (0.15 ml, 1.8 mmol) and ethyl chloroformate (0.1 ml, 1 mmol) were added, and the reaction mixture was stirred at room temperature for 0.5 h. The reaction was quenched with 50 μl of H_2O , diluted with 5 ml of EtOAc, the resulting mixture was dried over Na_2SO_4 , filtered through silica gel column to give the intermediate as an oil. The oil was dissolved in CH_3CN (5 ml),
10 H_2O (0.5 ml) and TFA (0.4 ml) were added, the reaction mixture stirred for 1.5 h, and concentrated in vacuo. Saturated NaHCO_3 solution was added to neutralize the mixture, and the precipitate was then filtered and air dried. Recrystallization in EtOAc / heptane to give 70 mg solid product in 66% yield. MS $(\text{M}+\text{H})^+ = 286$. HPLC RT = 1.28 min. (Phenom-Prime S5 C18 4.6 x 30 mm, 10-90 % aqueous methanol over 2
15 minutes containing 0.1 % TFA, 5 ml/min, monitoring at 220 nm)

Examples 19 through 24 were prepared using the method of Example 18 with the substitution of an appropriate arylmagnesiumhalide.

20

Example 19

5-Cyano-3,6-dihydro-4-methyl-6-(2-methylphenyl)-2-oxo-1-(2H)-pyrimidinecarboxylic acid, 1-ethyl ester

MS $(\text{M}+\text{H})^+ = 300$. HPLC RT = 1.41 min. (Phenom-Prime S5 C18 4.6 x 30 mm, 10-90 % aqueous methanol over 2 minutes containing 0.1 % TFA, 5 ml/min, monitoring
25 at 220 nm)

Example 20

5-Cyano-3,6-dihydro-4-methyl-6-(3-chlorophenyl)-2-oxo-1-(2H)-pyrimidinecarboxylic acid, 1-ethyl ester

30 MS $(\text{M}+\text{H})^+ = 320$. HPLC RT = 1.43 min. (Phenom-Prime S5 C18 4.6 x 30 mm, 10-90 % aqueous methanol over 2 minutes containing 0.1 % TFA, 5 ml/min, monitoring at 220 nm)



10
4**Example 21**

5-Cyano-3,6-dihydro-4-methyl-6-(3-fluorophenyl)-2-oxo-1-(2H)-pyrimidinecarboxylic acid, 1-ethyl ester

MS (M+H)⁺ = 304. HPLC RT = 1.29 min. (Phenom-Prime S5 C18 4.6 x 30 mm, 10-
5 90 % aqueous methanol over 2 minutes containing 0.1 % TFA, 5 ml/min, monitoring
at 220 nm)

Example 22

5-Cyano-3,6-dihydro-4-methyl-6-(4-chlorophenyl)-2-oxo-1-(2H)-pyrimidinecarboxylic acid, 1-ethyl ester

MS (M+H)⁺ = 320. HPLC RT = 1.44 min. (Phenom-Prime S5 C18 4.6 x 30 mm, 10-
10 90 % aqueous methanol over 2 minutes containing 0.1 % TFA, 5 ml/min, monitoring
at 220 nm)

15 **Example 23**

5-Cyano-3,6-dihydro-4-methyl-6-(4-fluorophenyl)-2-oxo-1-(2H)-pyrimidinecarboxylic acid, 1-ethyl ester

MS (M+H)⁺ = 304. HPLC RT = 3.21 min (YMC S5 ODS column 4.6 x 50 mm, 10-
20 90% aqueous methanol over 4 minutes containing 0.2% phosphoric acid, 4 ml/min,
monitoring at 220 nm)

Example 24

5-Cyano-3,6-dihydro-4-methyl-6-(2-fluorophenyl)-2-oxo-1-(2H)-pyrimidinecarboxylic acid, 1-ethyl ester

MS (M+H)⁺ = 304. HPLC RT = 3.05 min (YMC S5 ODS column 4.6 x 50 mm, 10-
25 90% aqueous methanol over 4 minutes containing 0.2% phosphoric acid, 4 ml/min,
monitoring at 220 nm)

Example 25

30 **6-(3,5-Bis-trifluoromethylphenyl)-5-cyano-4-methyl-2-oxo-3,6-dihydro-2H-pyrimidine-1-carboxylic acid ethyl ester**

2

A. Step 1

4-(3,5-Bis-trifluoromethylphenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid amide. A mixture of 3,5-bis(trifluoromethyl)benzaldehyde (2.42 g, 10.0 mmol), acetoacetamide (1.01 g, 10.0 mmol), urea (0.90 g, 15.0 mmol), copper chloride (0.1 g, 1.0 mmol), boron trifluoride etherate (0.09 mL), AcOH (0.04 mL), and THF (20 mL) was heated at 65 °C for 18 h and cooled to room temperature. The resulting precipitates were collected by vacuum filtration, washed with THF, and air dried to give the title compound as an off-white solid (1.33 g, 36%).

10 B. Step 2

4-(3,5-Bis-trifluoromethylphenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydro-pyrimidine-5-carbonitrile. To a mixture of compound from Step 1 (1.10 g, 3.0 mmol) and pyridine (12 mL) at 0 °C was added trifluoroacetic anhydride (1.3 mL, 9.0 mmol) slowly over 10 min. The reaction mixture became a clear brown solution and was stirred for 18 h, then poured into water. The resulting off-white precipitates were collected by vacuum filtration, washed with water, and air dried to give the title compound as a light brown solid (1.06 g, 100%).

C. Step 3

6-(3,5-Bis-trifluoromethylphenyl)-5-cyano-4-methyl-2-oxo-3,6-dihydro-2H-pyrimidine-1-carboxylic acid ethyl ester. To a solution of compound from Step 2 (60.0 mg, 0.17 mmol) in THF (2 mL) chilled to -78 °C was added LDA (0.15 mL, 0.30 mmol, 2.0 M in hexanes). The resulting mixture was stirred at -78 °C for 15 min, warmed to -25 °C for 15 min, recooled to -78 °C and ethyl chloroformate (20 µL, 0.20 mmol) was added via a syringe. The reaction mixture was stirred at -78 °C for 15 min, gradually warmed to room temperature and stirred for 1 h, quenched with MeOH and concentrated in vacuo. The residue was purified by preparative HPLC (methanol/water); product fractions were combined and concentrated in vacuo to afford the title compound as an off-white solid (28.4 mg, 40%).

¹H-NMR (DMSO-d₆, 400 MHz): δ 10.64 (s, 1 H), 8.19 (s, 1 H), 7.93 (s, 2 H), 6.15 (s, 1 H), 4.17 (m, 2 H), 2.10 (s, 3 H), 1.17 (t, 3 H, *J* = 7.0 Hz). LC/MS (ES+) 444 (M+Na)⁺.

42
2**Example 26****6-Butyl-5-cyano-4-methyl-2-oxo-3,6-dihydro-2H-pyrimidine-1-carboxylic acid ethyl ester**

5

A. Step 1**4-Hexyl-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carbonitrile.**

Polyphosphate ester (1.15 g, 3.89 mmol, 0.30 eq) was added to a sealed tube containing a solution of urea (1.17 g, 19.4 mmol), valeraldehyde (1.38 ml, 12.9 mmol) and acetoacetamide (1.31 g, 12.9 mmol) in THF (15 mL) under argon and heated at 75°C for three hours. The reaction mixture was cooled to room temperature, polyphosphate ester (8.80 g, 29.8 mmol) was added and the reaction mixture was heated at 85°C for four hours. The reaction mixture was cooled to room temperature and poured on ice. The aqueous solution was neutralized with 1N NaOH and extracted with chloroform (3X100 mL). The combined organic layers were dried (Na₂SO₄), filtered and concentrated under vacuum to give the title compound (0.940 g, 97%): HRMS 192.1143 (M-H)⁻. The product was used in the next step without further purification.

20 **B. Step 2****6-Butyl-5-cyano-4-methyl-2-oxo-3,6-dihydro-2H-pyrimidine-1-carboxylic acid ethyl ester.**

LDA (0.585 mL, 1.17 mmol, 2.0 M in hexane) was added dropwise to a solution of compound from Step 1 (0.150 g, 0.777 mmol) in THF (5mL) at -78°C. The reaction mixture was stirred at -78°C for twenty minutes and ethyl chloroformate (0.111 mL, 1.17 mmol) was added in one portion. The reaction mixture was allowed to warm to room temperature and was stirred for sixteen hours. The reaction mixture was quenched with saturated ammonium chloride (35 ml) and the solution was extracted with chloroform (3X100 ml). The combined organic layers were dried (Na₂SO₄), filtered and concentrated under vacuum. The residue was purified by flash chromatography (eluting 2/1 ethyl acetate/hexanes) to afford the title compound (0.110 g, 53%) as a solid.

43
A

¹H-NMR (DMSO-d₆, 400 MHz): δ 0.86 (t, 3 H, J = 6.79), 1.21-1.33 (m, 7H), 1.54-1.65 (m, 2H), 2.04 (s, 3H), 4.17-4.23 (m, 2H), 4.68 (t, 1H, J = 6.42), 10.33 (s, 1H). MS 264 (M-H)⁻. HRMS 266.1506 (M+H)⁺.

5

Example 27**5-Cyano-4-methyl-6-(3-nitrophenyl)-2-oxo-3,6-dihydro-2H-pyrimidine-1-carboxylic acid methylamide****A. Step 1**

10 **5-Cyano-4-methyl-6-(3-nitrophenyl)-2-oxo-3,6-dihydro-2H-pyrimidine-1-carboxylic acid 4-nitrophenyl ester.** To a suspension of 6-Methyl-4-(3-nitrophenyl)-2-oxo-1,2,3,4-tetrahydro-pyrimidine-5-carbonitrile (0.43 g, 1.7 mmol, prepared by the method described in Example 26, Step 1, in 77 % yield) in THF (15 mL) at -78 °C was added LDA (1.25 mL, 2.5 mmol, 2.0 M in hexanes). The resulting
15 mixture was stirred at -78 °C for 15 min, warmed to -25 °C for 15 min, recooled to -78 °C and 4-nitrophenyl chloroformate (0.50 g, 2.5 mmol) was added in one portion. The reaction mixture was stirred at -78 °C for 15 min, gradually warmed to room temperature, quenched with water and extracted with ethyl acetate. The organic extract was washed with brine, dried (MgSO₄) and concentrated in vacuo. The
20 residue was purified by flash column chromatography on silica gel using 50% to 70% ethyl acetate-hexane as eluant to give the title compound as a light yellow solid (0.38 g, 53%).

B. Step 2

25 **5-Cyano-4-methyl-6-(3-nitrophenyl)-2-oxo-3,6-dihydro-2H-pyrimidine-1-carboxylic acid methylamide.** To a solution of compound from Step 1 (12.5 mg, 0.03 mmol) in THF (1 mL) was added methylamine (4.1 uL, 0.033 mmol, 8 M in EtOH). The reaction mixture was stirred for 2 h and concentrated in vacuo. The residue was purified by preparative HPLC (methanol/water). Product fractions were
30 combined, concentrated in vacuo and lyophilized to give the title compound as a colorless solid (8.2 mg, 87%).

¹H-NMR (MeOH-d₄, 400 MHz): δ 8.22 (m, 1 H), 8.17 (t, 1 H, J = 1.8 Hz), 7.76 (m, 1 H), 7.65 (t, 1 H, J = 7.9 Hz), 6.30 (s, 1 H), 2.82 (s, 3 H), 2.18 (s, 3 H). LC/MS (ES+) 338 (M+Na)⁺.

5

Example 28

5-Cyano-4-methyl-2-oxo-6-phenyl-3,6-dihydro-2H-pyrimidine-1-carboxylic acid ethylamide. To a solution 6-Methyl-2-oxo-4-phenyl-1,2,3,4-tetrahydropyrimidine-5-carbonitrile (100 mg, 0.47 mmole, obtained in 65 % yield by the procedure described in Example 26, Step 1) in 4 mL of tetrahydrofuran under argon at room temperature was added oil free sodium hydride (17 mg, 0.70 mmole). After stirring for ten minutes, ethyl isocyanate (50 mg, 0.70 mmole) was added. The reaction mixture was diluted with ethyl acetate and washed with dilute citric acid, water and saturated brine. The dried (anhydrous magnesium sulfate) organic extract was concentrated *in vacuo* and the product purified by flash chromatography on silica gel, eluting with ethyl acetate/hexanes (3:2) to give 100 mg (75 %) of title compound as a white solid. ¹H-NMR (DMSO-d₆, 400 MHz) δ 10.51 (br s, 1 H); 8.79 (t, J = 5.4 Hz, 1 H); 7.22-7.48 (m, 5 H); 6.09 (s, 1 H); 3.10-3.25 (m, 2 H); 2.08 (s, 3 H); 1.03 (t, J = 7.2 Hz, 3 H). LC/MS (ES+) 285 (M+H)⁺.

20

Example 29

5-Cyano-6-(3,5-dichlorophenyl)-4-methyl-2-oxo-3,6-dihydro-2H-pyrimidine-1-carboxylic acid 2-methoxy-ethyl ester

Using 3,5-dichlorobenzaldehyde and following the procedure described in Example 2, the title compound was obtained in 3 % overall yield.

¹H-NMR (DMSO-d₆, 500 MHz): δ 10.59 (s, 1 H), 7.66 (t, 1 H, J = 1.6 Hz), 7.31 (d, 2 H, J = 1.6 Hz), 5.90 (s, 1 H), 4.26 (m, 2 H), 3.54 (m, 2 H), 3.25 (s, 3 H), 2.11 (s, 3 H). LC/MS (ES+) 384 (M+H)⁺.

25

45
H**Example 30****5-Cyano-4-methyl-2-oxo-6-(3-trifluoromethylphenyl)-3,6-dihydro-2H-pyrimidine-1-carboxylic acid ethylamide**

Using 3-trifluoromethylbenzaldehyde and following a modification of the procedure
5 described in Example 2, the title compound was obtained in 3 % overall yield.

¹H-NMR (CDCl₃, 400 MHz): δ 8.68 (s, 1 H), 7.60 (m, 2 H), 7.53 (m, 2 H), 6.37 (s, 1 H), 3.30 (m, 2 H), 2.08 (s, 3 H), 1.17 (t, 3 H, J = 7.0 Hz). LC/MS (ES+) 353 (M+H)⁺, 375 (M+Na)⁺.

10

Example 31**5-Cyano-6-(3,5-dichlorophenyl)-4-methyl-2-oxo-3,6-dihydro-2H-pyrimidine-1-carboxylic acid ethylamide**

Using 3,5-dichlorobenzaldehyde and following a modification of the procedure
described in Example 2, the title compound was obtained in 5 % overall yield.

15 ¹H-NMR (DMSO-d₆, 400 MHz): δ 10.56 (s, 1 H), 8.76 (t, 1 H, J = 5.3 Hz), 7.63 (t, 1 H, J = 1.8 Hz), 7.27 (d, 2 H, J = 1.8 Hz), 6.10 (s, 1 H), 3.16 (m, 2 H), 2.09 (s, 3 H), 1.03 (t, 3 H, J = 7.0 Hz). LC/MS (ES+) 353 (M+H)⁺, 375 (M+Na)⁺.

Example 32**3-Butyryl-4-(3,5-dichlorophenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carbonitrile**

Using 3,5-dichlorobenzaldehyde and following the procedure described in Example 2,
the title compound was obtained in 7 % overall yield.

25 ¹H-NMR (DMSO-d₆, 500 MHz): δ 10.63 (s, 1 H), 7.63 (t, 1 H, J = 1.6 Hz), 7.26 (d, 2 H, J = 1.6 Hz), 6.04 (s, 1 H), 2.95 (m, 1 H), 2.74 (m, 1 H), 1.54 (m, 2 H), 2.11 (s, 3 H), 0.86 (t, 3 H, J = 7.1 Hz).

Example 33**5-Cyano-4-methyl-2-oxo-6-(3-trifluoromethylphenyl)-3,6-dihydro-2H-pyrimidine-1-carboxylic acid (2-dimethylamino-ethyl)-amide**

Using 3-trifluoromethylbenzaldehyde and following the procedure described in
Example 2, the title compound was obtained in 8 % overall yield.

¹H-NMR (MeOH-d₄, 400 MHz): δ 7.64 (m, 1 H), 7.59 (m, 3 H), 6.25 (s, 1 H), 3.43 (m, 1 H), 3.38 (m, 1 H), 2.56 (t, 1 H, J = 6.2 Hz), 2.32 (s, 6 H), 2.15 (d, 3 H, J = 0.9 Hz); LC/MS (ES+) 396 (M+H)⁺.

5

Example 34**5-Cyano-4-methyl-2-oxo-6-(3-trifluoromethylphenyl)-3,6-dihydro-2H-pyrimidine-1-carbothioic acid S-ethyl ester**

Using 3-trifluoromethylbenzaldehyde and following a modification of the procedure described in Example 2, the title compound was obtained in 3 % overall yield.

10 ¹H-NMR (CDCl₃, 400 MHz): δ 8.21 (s, 1 H), 7.61 (m, 1 H), 7.52 (m, 3 H), 6.24 (s, 1 H), 2.87 (m, 2 H), 2.26 (d, 3 H, J = 0.9 Hz), 1.26 (t, 3 H, J = 7.5 Hz). LC/MS (ES+) 392 (M+Na)⁺.

Example 35

15 **5-Cyano-4-methyl-2-oxo-6-(3-trifluoromethylphenyl)-3,6-dihydro-2H-pyrimidine-1-carboxylic acid (2-hydroxy-ethyl)-amide**

Using 3-trifluoromethylbenzaldehyde and following a modification of the procedure described in Example 2, the title compound was obtained in 15 % overall yield.

¹H-NMR (MeOH-d₄, 400 MHz): δ 7.63 (m, 1 H), 7.58 (m, 3 H), 6.25 (s, 1 H), 3.58 (m, 2 H), 3.35 (m, 2 H), 2.15 (s, 3 H). LC/MS (ES+) 369 (M+H)⁺.

Example 36**4-(3,5-Dichlorophenyl)-6-methyl-2-oxo-3-(thiophene-2-carbonyl)-1,2,3,4-tetrahydropyrimidine-5-carbonitrile**

25 Using 3,5-dichlorobenzaldehyde and following the procedure described in Example 2, the title compound was obtained in 5 % overall yield

¹H-NMR (DMSO-d₆, 400 MHz): δ 10.78 (s, 1 H), 7.96 (d, 1 H, J = 4.8 Hz), 7.72 (d, 1 H, J = 3.1 Hz), 7.64 (t, 1 H, J = 1.8 Hz), 7.36 (d, 2 H, J = 1.8 Hz), 7.17 (m, 1 H), 5.92 (s, 1 H), 2.82 (s, 3 H), 2.18 (s, 3 H). LC/MS (ES+) 415 (M+Na)⁺.

30

Example 37**5-Cyano-6-(3,5-difluorophenyl)-4-methyl-2-oxo-3,6-dihydro-2H-pyrimidine-1-carboxylic acid ethylamide**

Intermediate IX was obtained using 3,5-difluorobenzaldehyde and following the
5 procedure described in Example 2. The title compound was obtained in 28 % yield
following the procedure of Example 3.

¹H-NMR (CD₃Cl, 400 MHz): δ 6.77 (m, 2 H), 6.67 (m, 1 H), 6.21 (s, 1 H), 3.27 (m, 2
H), 2.15 (s, 3 H), 1.12 (t, 3H, J = 10.4 Hz). LC/MS (ES+) 321 (M+H)⁺.

10

Example 38**5-Cyano-6-(3,5-difluorophenyl)-4-methyl-2-oxo-3,6-dihydro-2H-pyrimidine-1-carboxylic acid ethyl ester**

Using 3,5-difluorobenzaldehyde and following the procedure described in Example 2,
the title compound was obtained in 36 % yield for the final two steps.

15 ¹H-NMR (CD₃Cl, 400 MHz): δ 8.26 (s, 1 H), 6.83 (m, 2 H), 6.73 (m, 1 H), 5.80 (s, 1
H), 4.27 (m, 2 H), 2.15 (s, 3 H), 1.26 (t, 3H, J = 10.4 Hz). LC/MS (ES+) 322 (M+H)⁺.

Example 39**4-(3,5-Difluorophenyl)-6-methyl-2-oxo-3-(piperidine-1-carbonyl)-1,2,3,4-tetrahydropyrimidine-5-carbonitrile**

20 Intermediate IX was obtained using 3,5-difluorobenzaldehyde and following the
procedure described in Example 2. The title compound was obtained in 30 % yield
following the procedure of Example 3.

¹H-NMR (CD₃OD, 400 MHz): δ 7.01 (m, 3 H), 5.62(s, 1 H), 5.48 (s, 1 H), 3.37 (m, 2 H), 3.24 (m, 2
25 H), 2.14 (s, 3 H), 1.84 (m, 4), 1.28 (m, 4H). LC/MS (ES+) 361 (M+H)⁺.

Example 40**4-(3,5-Difluorophenyl)-6-methyl-2-oxo-3-(pyrrolidine-1-carbonyl)-1,2,3,4-tetrahydropyrimidine-5-carbonitrile**

Intermediate IX was obtained using 3,5-difluorobenzaldehyde and following the
30 procedure described in Example 2. The title compound was obtained in 18 % yield
following the procedure of Example 3.

¹H-NMR (CD₃OD, 400 MHz): δ 8.25 (s, 1 H), 8.24(d, 1 H, J = 7.9 Hz), 7.82 (d, 1 H, J = 7.9 Hz), 7.67 (t, 2 H, J = 7.9 Hz), 5.77 (s, 1H), 2.29-3.30 (m, 4 H), 2.16 (s, 3 H), 1.77 (m, 4). LC/MS (ES+) 355 (M+H)⁺.

5

Example 41**5-Cyano-4-methyl-6-naphthalen-1-yl-2-oxo-3,6-dihydro-2H-pyrimidine-1-carboxylic acid ethyl ester**

Using naphthalene-1-carboxaldehyde and following the procedure of Example 25, intermediate XXIV was obtained in 44 % yield and the title compound was obtained in 22 % yield.

10

¹H-NMR (DMSO-d₆, 400 MHz): δ 10.57 (s, 1 H), 8.40 (d, 1 H, J = 8.4 Hz), 7.98 (d, 1 H, J = 7.9 Hz), 7.94 (d, 1 H, J = 8.4 Hz), 7.61 (m, 2 H), 7.55 (t, 1 H, J = 7.0 Hz), 7.39 (d, 1 H, J = 7.0 Hz), 6.73 (s, 1 H), 4.04 (m, 2 H), 2.05 (s, 3 H), 1.00 (t, 3 H, J = 7.0 Hz). LC/MS (ES+) 336 (M+H)⁺.

15

Example 42**5-Cyano-4-methyl-6-naphthalen-1-yl-2-oxo-3,6-dihydro-2H-pyrimidine-1-carboxylic acid ethylamide**

Using naphthalene-1-carboxaldehyde and following the procedure of Example 25, intermediate XXIV was obtained in 44 % yield. The title compound was obtained in 67 % yield following the procedure described in Example 28.

20

¹H-NMR (CDCl₃, 400 MHz): δ 8.83 (t, 1 H, J = 5.3 Hz), 8.43 (d, 1 H, J = 8.4 Hz), 7.96 (s, 1 H), 7.84 (m, 2 H), 7.61 (m, 1 H), 7.52 (t, 1 H, J = 7.0 Hz), 7.42 (t, 1 H, J = 7.9 Hz), 7.36 (d, 1 H, J = 6.2 Hz), 7.14 (s, 1 H), 3.30 (m, 1 H), 3.21 (m, 1 H), 1.92 (s, 3 H), 1.11 (t, 3 H, J = 7.5 Hz). LC/MS (ES+) 335 (M+H)⁺, 357 (M+Na)⁺.

25

Example 43**6-(3-Bromophenyl)-5-cyano-4-methyl-2-oxo-3,6-dihydro-2H-pyrimidine-1-carboxylic acid ethyl ester**

Using 3-bromobenzaldehyde and following the procedure of Example 25, intermediate XXIV was obtained in 25 % yield and the title compound was obtained in 80 % yield.

30

¹H-NMR (CDCl₃, 400 MHz): δ 7.48 (m, 2 H), 7.27 (m, 2 H), 5.87 (s, 1 H), 4.33 (m, 2 H), 2.22 (s, 3 H), 1.33 (t, 3 H, J = 7.0 Hz). LC/MS (ES+) 364 (M+H)⁺.

Example 44

5 **6-(3-Bromophenyl)-5-cyano-4-methyl-2-oxo-3,6-dihydro-2H-pyrimidine-1-carboxylic acid ethylamide**

Using 3-bromobenzaldehyde and following the procedure of Example 25, intermediate XXIV was obtained in 25 % yield. The title compound was obtained in 88 % yield following the procedure described in Example 28.

10 ¹H-NMR (CDCl₃, 400 MHz): δ 8.65 (t, 1 H, J = 5.3 Hz), 7.91 (s, 1 H), 7.84 (m, 1 H), 7.38 (m, 1 H), 7.19 (m, 2 H), 6.24 (s, 1 H), 3.24 (m, 2 H), 2.10 (s, 3 H), 1.10 (t, 3 H, J = 7.0 Hz). LC/MS (ES+) 363 (M+H)⁺.

Example 45

15 **5-Cyano-4-methyl-2-oxo-6-(2-trifluoromethylphenyl)-3,6-dihydro-2H-pyrimidine-1-carboxylic acid ethyl ester**

Using 2-trifluoromethylbenzaldehyde and following the procedure of Example 25, intermediate XXIV was obtained in 43 % yield and the title compound was obtained in 30 % yield.

20 ¹H-NMR (DMSO-d₆, 400 MHz) δ 10.58 (s, 1 H), 7.77 (m, 2 H), 7.58 (t, 1 H, J = 7.5 Hz), 7.51 (d, 1 H, J = 8.4 Hz), 6.06 (d, 1 H, J = 0.9 Hz), 4.06 (m, 2 H), 2.05 (d, 3 H, J = 0.9 Hz), 1.05 (t, 3 H, J = 7.0 Hz). LC/MS (ES+) 354 (M+H)⁺, 376 (M+Na)⁺.

Example 46

25 **5-Cyano-4-methyl-2-oxo-6-(2-trifluoromethylphenyl)-3,6-dihydro-2H-pyrimidine-1-carboxylic acid ethylamide**

Using 2-trifluoromethylbenzaldehyde and following the procedure of Example 25, intermediate XXIV was obtained in 43 % yield. The title compound was obtained in 26 % yield following the procedure described in Example 28.

30 ¹H-NMR (MeOH-d₄, 400 MHz): δ 9.07 (s, 1 H), 7.69 (d, 1 H, J = 7.9 Hz), 7.64 (d, 1 H, J = 7.9 Hz), 7.54 (d, 1 H, J = 7.9 Hz), 7.49 (t, 1 H, J = 7.9 Hz), 6.48 (s, 1 H), 3.17

(m, 2 H), 2.11 (s, 3 H), 1.06 (t, 3 H, $J = 7.0$ Hz). LC/MS (ES+) 353 (M+H)⁺, 375 (M+Na)⁺.

Example 47

5 **5-Cyano-6-(3-methoxycarbonylphenyl)-4-methyl-2-oxo-3,6-dihydro-2H-pyrimidine-1-carboxylic acid ethyl ester**

Using methyl 3-formylbenzoate and following the procedure of Example 25, intermediate XXIV was obtained in 30 % yield and the title compound was obtained in 50 % yield.

10 ¹H-NMR (MeOH-d₄, 400 MHz): δ 8.02 (m, 2 H), 7.60 (m, 1 H), 7.52 (m, 1 H), 5.93 (s, 1 H), 4.28 (m, 2 H), 3.92 (s, 3 H), 2.18 (s, 3 H), 1.29 (t, 3 H, $J = 7.0$ Hz). LC/MS (ES+) 344 (M+H)⁺, 366 (M+Na)⁺.

Example 48

15 **3-(5-Cyano-3-ethylcarbamoyl-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidin-4-yl)-benzoic acid methyl ester**

Using methyl 3-formylbenzoate and following the procedure of Example 25, intermediate XXIV was obtained in 30 % yield. The title compound was obtained in 40 % yield following the procedure described in Example 28.

20 ¹H-NMR (MeOH-d₄, 400 MHz): δ 8.94 (s, 1 H), 7.89 (m, 2 H), 7.48 (d, 1 H, $J = 7.9$ Hz), 7.40 (t, 1 H, $J = 7.9$ Hz), 6.15 (s, 1 H), 3.83 (s, 3 H), 3.17 (m, 2 H), 2.07 (s, 3 H), 1.05 (t, 3 H, $J = 7.0$ Hz). LC/MS (ES+) 343 (M+H)⁺, 365 (M+Na)⁺.

Example 49

25 **BMS-511181 6-Butyl-5-cyano-4-methyl-2-oxo-3,6-dihydro-2H-pyrimidine-1-carboxylic acid ethylamide**

Using 1-butanaldehyde and following the procedure of Example 26, intermediate XXIV was obtained in 97 % yield. The title compound was obtained in 55 % yield following the procedure described in Example 28.

30 ¹H-NMR (DMSO-d₆, 400 MHz): δ 0.85 (t, 3 H, $J = 6.7$), 1.07 (t, 3H, $J = 7.2$), 1.23-1.29 (m, 4H), 1.44-1.60 (m, 2H), 2.05 (s, 3H), 3.17-3.32 (m, 2H), 5.04 (t, 1H, $J = 6.0$), 8.70(t, 1H, $J = 5.5$), 10.30 (s, 1H). MS 263 (M-H)⁻.

Example 50**6-(3,5-Bis-trifluoromethylphenyl)-5-cyano-4-methyl-2-oxo-3,6-dihydro-2H-pyrimidine-1-carboxylic acid ethylamide**

- 5 Using 3,5-bis-trifluoromethylbenzaldehyde and following the procedure of Example 25, intermediate XXIV was obtained in 100 % yield. The title compound was obtained in 50 % yield following the procedure described in Example 28.

¹H-NMR (CDCl₃, 400 MHz): δ 8.68 (t, 1 H, J = 5.3 Hz), 7.86 (s, 1 H), 7.77 (s, 2 H), 7.48 (s, 1 H), 6.46 (s, 1 H), 3.31 (m, 2 H), 2.24 (s, 3 H), 1.17 (t, 3 H, J = 7.0 Hz).

- 10 LC/MS (ES+) 421 (M+H)⁺.

Example 51**6-(2,5-Bis-trifluoromethylphenyl)-5-cyano-4-methyl-2-oxo-3,6-dihydro-2H-pyrimidine-1-carboxylic acid ethylamide**

- 15 Using 2,5-bis-trifluoromethylbenzaldehyde and following the procedure of Example 25, intermediate XXIV was obtained in 25 % yield. The title compound was obtained in 38 % yield following the procedure described in Example 28.

¹H-NMR (MeOH-d₄, 400 MHz): δ 7.94 (d, 1 H, J = 8.4 Hz), 7.84 (d, 1 H, J = 8.4 Hz), 7.75 (s, 1 H), 6.50 (s, 1 H), 3.17 (m, 2 H), 2.12 (d, 3 H, J = 0.9 Hz), 1.05 (t, 3 H, J = 7.0 Hz). LC/MS (ES+) 421 (M+H)⁺, 443 (M+Na)⁺.

20

Example 52**6-(2,5-Bis-trifluoromethylphenyl)-5-cyano-4-methyl-2-oxo-3,6-dihydro-2H-pyrimidine-1-carboxylic acid ethyl ester**

- 25 Using 2,5-bis-trifluoromethylbenzaldehyde and following the procedure of Example 25, intermediate XXIV was obtained in 25 % yield and the title compound was obtained in 55 % yield

¹H-NMR (CDCl₃, 400 MHz): δ 8.43 (s, 1 H), 7.88 (m, 1 H), 7.76 (m, 2 H), 6.25 (s, 1 H), 4.23 (q, 2 H, J = 7.0 Hz), 2.22 (s, 3 H), 1.19 (t, 3 H, J = 7.0 Hz). LC/MS (ES+)

- 30 422 (M+H)⁺.

Example 53**5-Cyano-6-(3-ethylcarbamoylphenyl)-4-methyl-2-oxo-3,6-dihydro-2H-pyrimidine-1-carboxylic acid ethylamide**

Starting with the product of Example 48, the title compound was obtained in 57 %
5 yield by ester hydrolysis (lithium hydroxide in aqueous methanol) and coupling of the
resulting carboxylic acid with ethylamine (water soluble carbodiimide and
hydroxybenzotriazole in acetonitrile).

¹H-NMR (MeOH-d₄, 400 MHz): δ 8.97 (s, 1 H), 7.68 (d, 1 H, J = 1.8 Hz), 7.65 (m, 1
H), 7.38 (m, 2 H), 6.10 (s, 1 H), 3.30 (m, 2 H), 3.13 (m, 2 H), 2.05 (s, 3 H), 1.12 (t, 3
10 H, J = 7.0 Hz), 1.01 (t, 3 H, J = 7.0 Hz). LC/MS (ES+) 356 (M+H)⁺.

Example 54**5-Cyano-6-(3-cyano-4-fluorophenyl)-4-methyl-2-oxo-3,6-dihydro-2H-pyrimidine-1-carboxylic acid ethylamide**

15 Using 3-cyano-4-fluorobenzaldehyde and following the procedure of Example 25,
intermediate XXIV was obtained in 62 % yield. The title compound was obtained in
51 % yield following the procedure described in Example 28.

¹H-NMR (CDCl₃, 500 MHz) δ 8.66 (s, 1 H), 7.74 (s, 1 H), 7.65 (m, 1 H), 7.57 (m, 1
H), 7.22 (t, 1 H, J = 8.2 Hz), 6.32 (s, 1 H), 3.29 (m, 2 H), 2.22 (s, 3 H), 1.16 (t, 3 H, J
20 = 7.2 Hz). LC/MS (ES+) 328 (M+H)⁺, 350 (M+Na)⁺.

Example 55**5-Cyano-6-(3-cyano-4-fluorophenyl)-4-methyl-2-oxo-3,6-dihydro-2H-pyrimidine-1-carboxylic acid ethyl ester**

25 Using 3-cyano-4-fluorobenzaldehyde and following the procedure of Example 25,
intermediate XXIV was obtained in 62 % yield and the title compound was obtained
in 30 % yield.

¹H-NMR (MeOH-d₄, 400 MHz): δ 7.71 (m, 2 H), 7.38 (t, 1 H, J = 8.3 Hz), 5.93 (s, 1
H), 4.32 (m, 2 H), 2.20 (d, 3 H, J = 0.9 Hz), 1.32 (t, 3 H, J = 7.0 Hz). LC/MS (ES+)
30 329 (M+H)⁺.

Example 56**5-Cyano-6-(2,2-dimethylpropyl)-4-methyl-2-oxo-3,6-dihydro-2H-pyrimidine-1-carboxylic acid ethylamide**

Using 2,2-dimethylpropionaldehyde and following the procedure of Example 26,
5 intermediate XXIV was obtained in 57 % yield. The title compound was obtained in 54 % yield following the procedure described in Example 28.

¹H-NMR (DMSO-d₆, 400 MHz): δ 0.92 (s, 9H), 1.06 (t, 3H, J = 7.15Hz), 1.43-1.47 (m, 2H), 2.05 (s, 3H), 3.21 (m, 2H), 5.20 (m, 1H), 8.60 (m, 1H), 10.42 (s, 1H). MS 277 (M-H)⁻.

10

Example 57**5-Cyano-6-cyclopropyl-4-methyl-2-oxo-3,6-dihydro-2H-pyrimidine-1-carboxylic acid ethyl ester**

Using cyclopropanecarboxaldehyde and following the procedure of Example 26,
15 intermediate XXIV was obtained in 83 % yield and the title compound was obtained in 36 % yield.

¹H-NMR (DMSO-d₆, 400 MHz): δ 0.35-0.65 (m, 4H), 1.10-1.21 (m, 1H), 1.23 (t, 3H, J = 7.09 Hz), 2.05 (s, 3H), 4.18-4.21 (m, 2 H), 4.33 (d, 1H, J = 8.13 Hz), 10.36 (s, 1H). MS 248 (M-H)⁻.

20

Example 58**5-Cyano-6-cyclopropyl-4-methyl-2-oxo-3,6-dihydro-2H-pyrimidine-1-carboxylic acid ethylamide**

Using cyclopropanecarboxaldehyde and following the procedure of Example 26,
25 intermediate XXIV was obtained in 83 % yield. The title compound was obtained in 15 % yield following the procedure described in Example 28.

¹H-NMR (DMSO-d₆, 400 MHz): δ 0.36-0.51 (m, 4H), 1.05-1.09 (m, 4H), 2.06 (s, 3H), 3.20-3.23 (m, 2 H), 4.66 (d, 1H, J = 8.30 Hz), 8.74 (m, 1H), 10.36 (s, 1H). MS 247 (M-H)⁻. HRMS 247.1195 (M-H)⁻.

30

24 4

Example 59**5-Cyano-6-(2-fluoro-5-trifluoromethylphenyl)-4-methyl-2-oxo-3,6-dihydro-2H-pyrimidine-1-carboxylic acid ethylamide**

Using 2-fluoro-5-trifluoromethylbenzaldehyde and following the procedure of

- 5 Example 25, intermediate XXIV was obtained in 41 % yield. The title compound was obtained in 75 % yield following the procedure described in Example 28.

¹H-NMR (CDCl₃, 400 MHz): δ 8.68 (t, 1 H, J = 4.8 Hz), 7.60 (m, 2 H), 7.37 (s, 1 H), 7.22 (t, 1 H, J = 9.2 Hz), 6.41 (s, 1 H), 3.30 (m, 1 H), 3.24 (m, 1 H), 2.18 (d, 3 H, J = 0.9 Hz), 1.14 (t, 3 H, J = 7.0 Hz). LC/MS (ES+) 371 (M+H)⁺, 393 (M+Na)⁺.

10

Example 60**5-Cyano-6-(2-fluoro-5-trifluoromethylphenyl)-4-methyl-2-oxo-3,6-dihydro-2H-pyrimidine-1-carboxylic acid ethyl ester**

Using 2-fluoro-5-trifluoromethylbenzaldehyde and following the procedure of

- 15 Example 25, intermediate XXIV was obtained in 41 % yield and the title compound was obtained in 38 % yield.

¹H-NMR (CDCl₃, 400 MHz): δ 8.27 (s, 1 H), 7.65 (m, 1 H), 7.58 (m, 1 H), 7.25 (t, 1 H, J = 9.2 Hz), 6.03 (s, 1 H), 4.28 (m, 2 H), 2.20 (d, 3 H, J = 0.9 Hz), 1.29 (t, 3 H, J = 7.0 Hz). LC/MS (ES+) 372 (M+H)⁺, 394 (M+Na)⁺.

20

Example 61**5-Cyano-6-isopropyl-4-methyl-2-oxo-3,6-dihydro-2H-pyrimidine-1-carboxylic acid ethyl ester**

Using cyclopropanecarboxaldehyde and following the procedure of Example 26,

- 25 intermediate XXIV was obtained in 76 % yield and the title compound was obtained in 23 % yield.

¹H-NMR (DMSO-d₆, 400 MHz): δ 0.88-0.92 (m, 6H), 1.23 (t, 3H, J = 7.10 Hz), 1.90-1.95 (m, 1H), 2.07 (s, 3H), 4.16-4.22 (m, 2H), 4.51 (d, 1H, J = 6.82 Hz), 10.37 (s, 1H). MS: 250 (M-H)⁻.

30

Example 62**5-Cyano-4-methyl-6-naphthalen-2-yl-2-oxo-3,6-dihydro-2H-pyrimidine-1-carboxylic acid ethyl ester**

Using naphthalene-2-carboxaldehyde and following the procedure of Example 25, intermediate XXIV was obtained in 64 % yield and the title compound was obtained in 39 % yield.

¹H-NMR (DMSO-d₆, 400 MHz): δ 10.54 (s, 1 H), 7.96 (m, 3 H), 7.78 (s, 1 H), 7.56 (m, 2 H), 7.44 (d, 1 H, J = 8.3 Hz), 5.98 (s, 1 H), 4.18 (q, 2 H, J = 7.0 Hz), 2.12 (s, 3 H), 1.20 (t, 3 H, J = 7.0 Hz). LC/MS (ES+) 336 (M+H)⁺.

Example 63

5-Cyano-6-[3-(2-hydroxyethylcarbamoyl)-phenyl]-4-methyl-2-oxo-3,6-dihydro-2H-pyrimidine-1-carboxylic acid ethylamide

Starting with the product of Example 48, the title compound was obtained in 60 % yield by ester hydrolysis (lithium hydroxide in aqueous methanol) and coupling of the resulting carboxylic acid with 2-aminoethanol (water soluble carbodiimide and hydroxybenzotriazole in acetonitrile).

¹H-NMR (CDCl₃, 400 MHz): δ 8.73 (t, 1 H, J = 5.3 Hz), 8.03 (s, 1 H), 7.75 (t, 1 H, J = 1.8 Hz), 7.68 (m, 1 H), 7.51 (d, 1 H, J = 7.5 Hz), 7.39 (t, 1 H, J = 7.5 Hz), 7.00 (t, 1 H, J = 4.8 Hz), 6.29 (s, 1 H), 3.80 (t, 2 H, J = 4.8 Hz), 3.59 (q, 2 H, J = 4.8 Hz), 3.31 (m, 1 H), 3.22 (m, 1 H), 2.18 (s, 3 H), 1.13 (t, 3 H, J = 7.0 Hz). LC/MS (ES+) 372 (M+H)⁺, 394 (M+Na)⁺.

Example 64

5-Cyano-6-(2-methoxyphenyl)-4-methyl-2-oxo-3,6-dihydro-2H-pyrimidine-1-carboxylic acid ethyl ester

Using 2-methoxybenzaldehyde and following the procedure of Example 26, intermediate XXIV was obtained in 17 % yield and the title compound was obtained in 28 % yield.

¹H-NMR (400 MHz, CDCl₃): δ 1.27 (t, J = 7.0 Hz, 3H), 2.12 (d, J = 0.6Hz, 3H), 3.86 (s, 3H), 4.25 (m, 2H), 6.04 (s, 1H), 6.93 (m, 2H), 7.06 (s, 1H), 7.2 (m, 1H), 7.33 (m, 1H). MS 316 (M+H)⁺.

36
X**Example 65****5-Cyano-6-(2-methoxyphenyl)-4-methyl-2-oxo-3,6-dihydro-2H-pyrimidine-1-carboxylic acid ethylamide**

Using 2-methoxybenzaldehyde and following the procedure of Example 26,

5 intermediate XXIV was obtained in 17 % yield. Using the procedure of Example 27, the title compound was obtained in 8 % yield.

¹H-NMR (400 MHz, CDCl₃): δ 1.13 (t, J = 7.0 Hz, 3H), 2.1 (s, 3H), 3.25 (m, 1H), 3.33 (m, 1H), 3.86 (s, 3H), 6.47 (s, 1H), 6.62 (s, 1H), 6.9 (m, 2H), 7.2 (dd, J₁ = 1.5 Hz, J₂ = 7.6 Hz, 1H), 7.3 (dt, J₁ = 1.7 Hz, J₂ = 7.2 Hz, 1H), 8.7 (bs, 1H). MS 315 (M+H)⁺.

Example 66**6-(2-Allyloxyphenyl)-5-cyano-4-methyl-2-oxo-3,6-dihydro-2H-pyrimidine-1-carboxylic acid ethyl ester**

Using 2-allyloxybenzaldehyde and following the procedure of Example 26,

15 intermediate XXIV was obtained in 33 % yield and the title compound was obtained in 43 % yield.

¹H-NMR (400 MHz, CDCl₃): δ 1.26 (t, J = 7.0 Hz, 3H), 2.1 (s, 3H), 4.25 (m, 2H), 4.6 (m, 2H), 5.30(d, J = 10.4 Hz, 1H), 5.36 (d, J = 16.0 Hz), 6.0 (s, 1H), 6.1 (m, 1H), 6.9 (m, 3H), 7.25 (m, 2H). MS 342 (M+H)⁺.

20

Example 67**6-(2-Allyloxyphenyl)-5-cyano-4-methyl-2-oxo-3,6-dihydro-2H-pyrimidine-1-carboxylic acid ethylamide**

Using 2-allyloxybenzaldehyde and following the procedure of Example 26,

25 intermediate XXIV was obtained in 33 % yield. Using the procedure of Example 27, the title compound was obtained in 23 % yield.

¹H-NMR (400 MHz, CDCl₃): δ 1.12 (t, J = 7.0 Hz, 3H), 2.1 (s, 3H), 3.2 (m, 1H), 3.3 (m, 1H), 4.6 (m, 2H), 5.35 (m, 2H), 6.1 (m, 1H), 6.38 (s, 1H), 6.50 (s, 1H), 6.9 (m, 2H), 7.25 (m, 2H), 8.7 (bs, 1H). MS 341 (M+H)⁺.

30

54

Example 68**6-(2-Bromophenyl)-5-cyano-4-methyl-2-oxo-3,6-dihydro-2H-pyrimidine-1-carboxylic acid ethyl ester**

Using 2-bromobenzaldehyde and following the procedure of Example 25,

- 5 intermediate XXIV was obtained in 50 % yield and the title compound was obtained in 31 % yield.

$^1\text{H-NMR}$ (400 MHz, CDCl_3): δ 1.24 (t, $J = 7.2$ Hz, 3H), 2.16 (s, 3H), 4.24 (q, $J = 7.1$ Hz, 2H), 6.33 (s, 1H), 7.20 (m, 1H), 7.33 (m, 3H), 7.6 (d, $J = 8.0$ Hz, 1H). MS 364 ($\text{M}+\text{H}^+$).

10

Example 69**6-(2-Bromophenyl)-5-cyano-4-methyl-2-oxo-3,6-dihydro-2H-pyrimidine-1-carboxylic acid ethylamide**

Using 2-bromobenzaldehyde and following the procedure of Example 25,

- 15 intermediate XXIV was obtained in 50 % yield. The title compound was obtained in 46 % yield following the procedure described in Example 28.

$^1\text{H-NMR}$ (MeOH-d_4 , 500 MHz): δ 7.55 (m, 1 H), 7.30 (m, 2 H), 7.15 (m, 1 H), 6.46 (s, 1 H), 3.14 (m, 2 H), 2.04 (s, 3 H), 1.04 (t, 3 H, $J = 7.1$ Hz). LC/MS (ES^+) 364 ($\text{M}+\text{H}^+$).

20

Example 70**5-Cyano-6-(3-methoxyphenyl)-4-methyl-2-oxo-3,6-dihydro-2H-pyrimidine-1-carboxylic acid ethylamide**

Using 3-methoxybenzaldehyde and following the procedure of Example 25,

- 25 intermediate XXIV was obtained in 66 % yield. The title compound was obtained in 62 % yield following the procedure described in Example 28.

$^1\text{H-NMR}$ (DMSO-d_6 , 500 MHz): δ 10.49 (s, 1 H), 8.79 (t, 1 H, $J = 5.5$ Hz), 7.32 (t, 1 H, $J = 7.7$ Hz), 6.92 (m, 1 H), 6.81 (d, 1 H, $J = 7.7$ Hz), 6.75 (s, 1 H), 6.06 (s, 1 H), 3.74 (s, 3 H), 3.17 (m, 2 H), 2.07 (s, 3 H), 1.04 (t, 3 H, $J = 7.1$ Hz). LC/MS (ES^+) 315 ($\text{M}+\text{H}^+$).

30

58
57**Example 71****6-(2-Benzyloxyphenyl)-5-cyano-4-methyl-2-oxo-3,6-dihydro-2H-pyrimidine-1-carboxylic acid ethyl ester**

Using 2-benzyloxybenzaldehyde and following the procedure of Example 26,

- 5 intermediate XXIV was obtained in 47 % yield and the title compound was obtained in 54 % yield.

¹H-NMR (CDCl₃, 400 MHz): δ 1.25 (t, J = 7.0 Hz, 3H), 1.82 (d, J = 0.9 Hz, 3H), 4.21 (m, 2H), 5.04 (dd, J₁ = 10.5 Hz, J₂ = 31.2 Hz, 2H), 5.71 (s, 1H), 5.84 (s, 1H), 6.96 (m, 2H), 7.30 (m, 2H), 7.45 (m, 5H). MS 392 (M+H)⁺.

10

Example 72**6-Benzyloxymethyl-5-cyano-4-methyl-2-oxo-3,6-dihydro-2H-pyrimidine-1-carboxylic acid ethylamide**

Using 2-benzyloxyacetaldehyde and following the procedure of Example 26,

- 15 intermediate XXIV was obtained in 45 % yield. The title compound was obtained in 30 % yield following the procedure described in Example 28.

¹H-NMR (DMSO-d₆): δ 1.10 (t, 3H, J = 7.33 Hz), 2.07 (s, 3H), 3.22-3.26 (m, 2H), 3.49-3.52 (m, 2H), 4.51 (s, 2H), 5.29 (m, 1H), 7.27-7.34 (m, 5H), 7.90 (br m, 1H), 8.75 (br m, 1H). MS: 327 (M-H)⁻. HRMS 327.1450 (M-H)⁻.

20

Example 73**6-Benzyloxymethyl-5-cyano-4-methyl-2-oxo-3,6-dihydro-2H-pyrimidine-1-carboxylic acid ethyl ester**

Using 2-benzyloxyacetaldehyde and following the procedure of Example 26,

- 25 intermediate XXIV was obtained in 45 % yield and the title compound was obtained in 80 % yield.

¹H-NMR (DMSO-d₆): δ 1.28 (t, 3H, J = 7.13), 2.05 (s, 3H), 3.58-3.70 (m, 2H), 4.29-4.35 (m, 2H), 4.53 (s, 3H), 4.97-4.99 (m, 1H), 7.25-7.35 (m, 5H). MS: 328 (M-H)⁻. 328.1297 HRMS (M-H)⁻.

30

30

Example 74**6-(3-Bromo-4-fluorophenyl)-5-cyano-4-methyl-2-oxo-3,6-dihydro-2H-pyrimidine-1-carboxylic acid ethylamide**

Using 3-bromo-4-fluorobenzaldehyde and following the procedure of Example 26,
5 intermediate XXIV was obtained in 99 % yield. The title compound was obtained in 69 % yield following the procedure described in Example 28.

¹H-NMR (DMSO-d₆, 400 MHz): δ 10.55 (s, 1 H), 8.75 (t, 1 H, J = 5.3 Hz), 7.55 (m, 1 H), 7.42 (t, 1 H, J = 8.8 Hz), 7.33 (m, 1 H), 6.10 (s, 1 H), 3.16 (m, 2 H), 2.09 (s, 3 H), 1.03 (t, 3 H, J = 7.0 Hz). LC/MS (ES+) 381 (M+H⁺).

10

Example 75**6-(3-Bromo-4-fluorophenyl)-5-cyano-4-methyl-2-oxo-3,6-dihydro-2H-pyrimidine-1-carboxylic acid cyclopropylamide**

Using 3-bromo-4-fluorobenzaldehyde and following the procedure of Example 26,
15 intermediate XXIV was obtained in 99 % yield. The title compound was obtained in 54 % yield following the procedure described in Example 28.

¹H-NMR (MeOH-d₄, 500 MHz): δ 7.46 (m, 1 H), 7.25 (m, 1 H), 7.14 (t, 1 H, J = 8.8 Hz), 6.04 (s, 1 H), 2.54 (m, 1 H), 2.05 (s, 3 H), 0.63 (m, 2 H), 0.42 (m, 1 H), 0.37 (m, 1 H). LC/MS (ES+) 393 (M+H⁺).

20

Example 76**6-(5-Bromo-2-fluorophenyl)-5-cyano-4-methyl-2-oxo-3,6-dihydro-2H-pyrimidine-1-carboxylic acid ethylamide**

Using 5-bromo-2-fluorobenzaldehyde and following the procedure of Example 26,
25 intermediate XXIV was obtained in 71 % yield. The title compound was obtained in 70 % yield following the procedure described in Example 28.

¹H-NMR (MeOH-d₄, 500 MHz): δ 7.50 (m, 1 H), 7.43 (m, 1 H), 7.10 (m, 1 H), 6.22 (s, 1 H), 3.22 (m, 2 H), 2.11 (d, 3 H, J = 2.2 Hz), 1.11 (m, 3 H).

60 15

Example 77**6-(5-Bromo-2-fluorophenyl)-5-cyano-4-methyl-2-oxo-3,6-dihydro-2H-pyrimidine-1-carboxylic acid cyclopropylamide**

Using 5-bromo-2-fluorobenzaldehyde and following the procedure of Example 26,
5 intermediate XXIV was obtained in 71 % yield. The title compound was obtained in 70 % yield following the procedure described in Example 28.

¹H-NMR (MeOH-d₄, 500 MHz): δ 7.51 (m, 1 H), 7.44 (m, 1 H), 7.11 (m, 1 H), 6.21 (s, 1 H), 2.60 (m, 1 H), 2.10 (d, 3 H, J = 1.6 Hz), 0.70 (m, 2 H), 0.51 (m, 1 H), 0.44 (m, 1 H).

10

Example 78**5-Cyano-6-(3,5-dibromophenyl)-4-methyl-2-oxo-3,6-dihydro-2H-pyrimidine-1-carboxylic acid ethylamide**

Using 3,5-dibromobenzaldehyde and following the procedure of Example 26,
15 intermediate XXIV was obtained in 46 % yield. The title compound was obtained in 83 % yield following the procedure described in Example 28.

¹H-NMR (DMSO-d₆, 400 MHz) δ 10.60 (br s, 1 H); 8.77 (t, J = 5.4 Hz, 1 H); 7.85 (t, J = 1.6 Hz, 1 H); 7.42 (d, J = 1.7 Hz, 2 H); 6.08 (s, 1 H); 3.18-3.26 (m, 2 H); 2.08 (s, 3 H), 1.03 (t, J = 7.1 Hz, 3 H). LC/MS (ES+) 441 (M+H)⁺.

20

Example 79**5-Cyano-4-methyl-6-(3-nitrophenyl)-2-oxo-3,6-dihydro-2H-pyrimidine-1-carboxylic acid cyclopropylmethylamide**

Using 3-nitrobenzaldehyde and following the procedure of Example 26, intermediate
25 XXIV was obtained in 92 % yield. The title compound was obtained in 53 % yield following the procedure described in Example 28.

¹H-NMR (MeOH-d₄, 500 MHz): δ 9.15 (s, 1 H), 8.21 (m, 1 H), 8.17 (d, 1 H, J = 1.6 Hz), 7.76 (d, 1 H, J = 7.7 Hz), 7.66 (t, 1 H, J = 7.7 Hz), 6.29 (s, 1 H), 3.68 (d, 1 H, J = 7.1 Hz), 3.09 (m, 2 H), 2.17 (s, 3 H), 0.98 (m, 1 H), 0.48 (m, 2 H), 0.20 (m, 2 H).

30 LC/MS (ES+) 356 (M+H)⁺.

61
62**Example 80****5-Cyano-4-methyl-2-oxo-6-phenethyloxymethyl-3,6-dihydro-2H-pyrimidine-1-carboxylic acid ethyl ester**

Using 2-phenethyloxyacetaldehyde and following the procedure of Example 26,
5 intermediate XXIV was obtained in 38 % yield and the title compound was obtained in 18 % yield.

¹H-NMR (DMSO-d₆, 400MHz): 1.23 (t, 3H, J = 7.1 Hz), 2.00 (s, 3H), 2.75 (t, 2H, J = 6.7 Hz), 3.59-3.85 (m, 4H), 4.18-4.20 (m, 2H), 4.81 (br m, 1H), 7.19-7.27 (m, 5H), 10.26 (s, 1H). MS 342 (M-H)⁻. HRMS 342.1458 (M-H)⁻.

10

Example 81**5-Cyano-4-methyl-2-oxo-6-phenethyl-3,6-dihydro-2H-pyrimidine-1-carboxylic acid ethylamide**

Using 3-phenylpropionaldehyde and following the procedure of Example 26,
15 intermediate XXIV was obtained in 58 % yield. The title compound was obtained in 42 % yield following the procedure described in Example 28.

¹H-NMR (DMSO-d₆, 400 MHz): 1.07 (t, 3H, J = 7.1 Hz), 1.80-2.03 (m, 2H), 2.06 (s, 3H), 2.51-2.75 (m, 2H), 3.19-3.22 (m, 2H), 5.12 (br m, 1H), 7.18-7.30 (m, 5H), 8.70 (br m, 1H), 10.36 (s, 1H). MS 311 (M-H)⁻. HRMS 311.1493 (M-H)⁻.

20

Example 82**5-Cyano-4-methyl-2-oxo-6-thiophen-3-yl-3,6-dihydro-2H-pyrimidine-1-carboxylic acid ethyl ester**

Using thiophene-3-carboxaldehyde and following the procedure of Example 26,
25 intermediate XXIV was obtained in 50 % yield and the title compound was obtained in 30 % yield.

¹H-NMR (DMSO-d₆, 400 MHz): δ 1.23 (t, J = 7.1 Hz, 3H), 2.10 (s, 3H), 4.21 (m, 2H), 5.87 (s, 1H), 7.03 (m, 1H), 7.44 (s, 1H), 7.60 (m, 1H), 10.48 (s, 1H). MS 292 (ES⁺): 292 (M+H)⁺.

30

Example 83**5-Cyano-4-methyl-6-(5-methylisoxazol-3-yl)-2-oxo-3,6-dihydro-2H-pyrimidine-1-carboxylic acid ethyl ester**

Using 5-methylisoxazole-3-carboxaldehyde and following the procedure of Example 26, intermediate XXIV was obtained in 27 % yield and the title compound was obtained in 67 % yield.

¹H-NMR (DMSO-d₆, 400 MHz): δ 10.52 (s, 1H), 6.20 (s, 1H), 5.95 (s, 1H), 4.21 (q, 2H, J = 7.0 Hz), 2.40 (s, 3H), 2.05 (s, 3H), 1.22 (t, 3H, J = 7.0 Hz). ¹³C-NMR (DMSO-d₆, 400 MHz): δ 170.87, 161.63, 151.86, 150.57, 147.09, 116.44, 99.35, 81.29, 63.08, 49.55, 16.85, 13.68, 11.56. MS (ESI), 291 (M+H)⁺.

Example 84**5-Cyano-6-(3,5-dimethylisoxazol-4-yl)-4-methyl-2-oxo-3,6-dihydro-2H-pyrimidine-1-carboxylic acid ethyl ester**

Using 3,5-dimethylisoxazole-4-carboxaldehyde and following the procedure of Example 26, intermediate XXIV was obtained in 74 % yield and the title compound was obtained in 47 % yield.

¹H-NMR (DMSO-d₆, 400 MHz): δ 10.56 (s, 1H), 5.82 (s, 1H), 4.15 (q, 2H, J = 7.0 Hz), 2.38 (s, 3H), 2.14 (s, 1H), 2.07 (s, 3H), 1.17 (t, 3H, J = 7.0 Hz). ¹³C-NMR (DMSO-d₆, 400 MHz): δ 167.03, 157.45, 152.17, 147.60, 146.95, 116.44, 113.45, 81.58, 62.96, 48.58, 16.77, 13.64, 10.50, 9.57. MS (ESI), 305 (M+H)⁺.

Example 85**5-Cyano-4-methyl-2-oxo-6-thiophen-2-yl-3,6-dihydro-2H-pyrimidine-1-carboxylic acid ethyl ester**

Using thiophene-2-carboxaldehyde and following the procedure of Example 26, intermediate XXIV was obtained in 41 % yield and the title compound was obtained in 58 % yield.

¹H-NMR (DMSO-d₆, 400 MHz): δ 1.25 (t, J = 7.1 Hz, 3H), 2.12 (s, 3H), 4.24 (m, 2H), 6.08 (s, 1H), 7.02 (m, 1H), 7.07 (d, J = 3.4 Hz, 1H), 7.56 (m, 1H), 10.58 (s, 1H). MS (ESI) 290 (M-H)⁻.

HRMS (ESI) 290.0598 (M-H)⁻.

63
67

Example 86

5-methyl-6-(3-methylthiophen-2-yl)-2-oxo-3,6-dihydro-2H-pyrimidine-1-carboxylic acid ethylamide

Using 3-methylthiophene-2-carboxaldehyde and following the procedure of Example 26, intermediate XXIV was obtained in 33 % yield. The title compound was obtained in 17 % yield following the procedure described in Example 28.

¹H NMR (DMSO-d₆, 400 MHz): δ 1.03 (t, J = 7.2 Hz, 3H), 2.05 (s, 3H), 3.15 (m, 2H), 3.33 (s, 3H), 6.41 (s, 1H), 6.82 (d, J = 5.1 Hz, 1H), 7.35 (d, J = 5.1 Hz, 1H),
10 8.73 (t, J = 5.6 Hz, 1H), 10.62 (s, 1H).

MS (ESI) 303 (M-H)⁻. HRMS (ESI) 303.0927 (M-H)⁻.

Example 87

5-Cyano-4-methyl-6-(3-methylthiophen-2-yl)-2-oxo-3,6-dihydro-2H-pyrimidine-1-carboxylic acid ethyl ester

Using 3-methylthiophene-2-carboxaldehyde and following the procedure of Example 26, intermediate XXIV was obtained in 33 % yield and the title compound was obtained in 14 % yield.

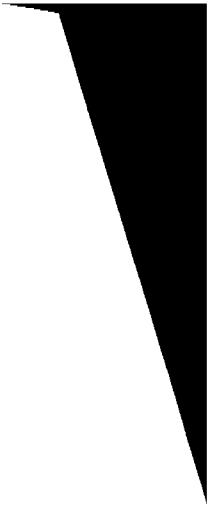
¹H-NMR (DMSO-d₆, 400 MHz): δ 1.20 (t, J = 7.1 Hz, 3H), 2.05 (s, 3H), 3.33 (s, 3H), 4.17 (q, J = 7.1 Hz, 2H), 6.14 (s, 1H), 6.84 (d, J = 5.1 Hz, 1H), 7.38 (d, J = 5.1 Hz, 1H), 10.61 (s, 1H). MS (ESI) 304 (M-H). HRMS (ESI) 304.0746 (M-H)⁻.

Example 88

5-Cyano-4-methyl-6-(2-methylthiazol-4-yl)-2-oxo-3,6-dihydro-2H-pyrimidine-1-carboxylic acid ethyl ester

Using 2-methylthiazole-4-carboxaldehyde and following the procedure of Example 26, intermediate XXIV was obtained in 26 % yield and the title compound was obtained in 16 % yield.

¹H-NMR (CDCl₃, 400 MHz): δ 7.96 (s, 1H), 7.11 (s, 1H), 5.93 (s, 1H), 4.31 (m, 2H),
30 2.67 (s, 3H), 2.16 (s, 3H), 1.32 (t, 3H, J = 6.9 Hz); ¹³C-NMR (CDCl₃, 400 MHz): δ 168.13, 152.34, 151.77, 149.06, 147.71, 116.31, 115.88, 85.39, 64.24, 35.87, 19.17, 17.81, 14.09. MS (ESI) 307 (M+H)⁺.



31
5**Example 89****6-(4-Bromothiophen-2-yl)-5-cyano-4-methyl-2-oxo-3,6-dihydro-2H-pyrimidine-1-carboxylic acid ethylamide**

- 5 Using 4-bromothiophene-2-carboxaldehyde and following the procedure of Example 26, intermediate XXIV was obtained in 68 % yield. The title compound was obtained in 49 % yield following the procedure described in Example 28. ¹H-NMR (DMSO-d₆, 400 MHz): δ 1.07 (t, J = 7.1 Hz, 3H), 2.15 (s, 3H), 3.22 (m, 2H), 6.36 (s, 1H), 7.06 (s, 1H), 7.67 (s, 1H), 8.68 (t, J = 5.6 Hz, 1H), 10.64 (s, 1H). MS (ES+) 369 (M+H)⁺.
10 HRMS (ESI): 366.9876 (M-H)⁻.

Example 90**6-(4-Bromothiophen-2-yl)-5-cyano-4-methyl-2-oxo-3,6-dihydro-2H-pyrimidine-1-carboxylic acid ethyl ester**

- 15 Using 4-bromothiazole-2-carboxaldehyde and following the procedure of Example 26, intermediate XXIV was obtained in 68 % yield and the title compound was obtained in 45 % yield. ¹H-NMR (DMSO-d₆, 400 MHz): δ 1.25 (t, J = 7.1 Hz, 3H), 2.14 (s, 3H), 4.24 (m, 2H), 6.09 (s, 1H), 7.10 (s, 1H), 7.71 (s, 1H), 10.63 (s, 1H). MS (ESI) 368 [M-H]⁻. HRMS (ESI) 367.9697 (M-H)⁻.
20

Example 91**5-Cyano-4-methyl-2-oxo-6-[2-(4-trifluoromethylphenyl)-thiazol-4-yl]-3,6-dihydro-2H-pyrimidine-1-carboxylic acid ethyl ester**

- Using 2-(4-trifluoromethylphenyl)thiazole-4-carboxaldehyde and following the
25 procedure of Example 26, intermediate XXIV was obtained in 17 % yield and the title compound was obtained in 31 % yield.
¹H-NMR (DMSO-d₆, 400 MHz): δ 10.53 (s, 1H), 8.08 (d, 2H, J = 8.2 Hz), 7.89 (d, 2H, J = 8.1 Hz), 7.78 (s, 1H), 5.96 (s, 1H), 4.20 (m, 2H), 2.07 (s, 3H), 1.22 (t, 3H, J = 7.1 Hz); ¹³C-NMR (DMSO-D₆, 400 MHz): δ 166.18, 154.51, 152.00, 149.60, 142.48, 135.79, 130.05, 129.78, 126.45, 125.96, 124.71, 122.30, 117.75, 116.84, 82.69, 62.83,
30 52.82, 16.87, 13.66. MS (ESI), 437 (M+H)⁺.

Example 92**6-[5-(4-Chlorophenyl)-oxazol-4-yl]-5-cyano-4-methyl-2-oxo-3,6-dihydro-2H-pyrimidine-1-carboxylic acid ethyl ester**

Using 5-(4-Chlorophenyl)oxazole-4-carboxaldehyde and following the procedure of
5 Example 26, intermediate XXIV was obtained in 22 % yield and the title compound was obtained in 16 % yield.

¹H-NMR (DMSO-d₆, 400 MHz): δ 10.48 (s, 1H), 8.47 (m, 1H), 7.79 (d, 2H, J= 8.6 Hz), 7.64 (d, 2H, J= 8.6 Hz), 6.14 (s, 1H), 4.01 (q, 2H, J= 7.1 Hz), 2.05 (s, 3H), 0.96 (t, 3H, J = 7.1 Hz); ¹³C-NMR (DMSO-D₆, 400 MHz): δ 152.07, 151.98, 149.50,
10 147.60, 143.20, 133.40, 133.20, 129.01, 127.58, 125.33, 116.82, 81.25, 62.71, 49.80, 16.80, 13.20. MS (ESI), 387 (M+H)⁺.

Example 93**6-(2-Bromothiazol-5-yl)-5-cyano-4-methyl-2-oxo-3,6-dihydro-2H-pyrimidine-1-carboxylic acid ethyl ester**

Using 2-Bromothiazole-5-carboxaldehyde and following the procedure of Example
26, intermediate XXIV was obtained in 44 % yield and the title compound was
obtained in 41 % yield

¹H-NMR (DMSO-d₆, 400 MHz): δ 10.67 (s, 1H), 7.72 (s, 1H), 6.15 (s, 1H), 4.26 (m,
20 2H), 2.15 (s, 3H), 1.27 (t, 3H, J = 7.1 Hz); ¹³C-NMR (DMSO-D₆, 400 MHz): δ 152.49, 151.78, 147.11, 141.99, 140.14, 137.93, 116.70, 82.49, 63.91, 50.06, 17.52, 14.18. MS (ESI), 371.0 (M+H)⁺.

Example 94**5-Cyano-4-methyl-2-oxo-6-(4-phenylthiophen-2-yl)-3,6-dihydro-2H-pyrimidine-1-carboxylic acid ethylamide**

Using 4-bromothiophene-2-carboxaldehyde and following the procedure of Example
26, intermediate XXIV was obtained in 68 % yield. The 4-bromothiophenyl intermediate
was converted to 4-phenylthienyl intermediate by the Suzuki reaction in 91 % yield
30 The title compound was obtained in 33 % yield following the procedure described in
Example 28.

¹H-NMR (DMSO-d₆, 400 MHz): δ 1.07 (t, J = 7.1 Hz, 3H), 2.17 (s, 3H), 3.23 (m, 2H), 6.42 (s, 1H), 7.30 (t, J = 5.1 Hz, 1H), 7.41-7.43 (m, 3H), 7.66-7.68 (m, 2H), 7.83 (s, 1H), 8.71 (t, J = 5.6 Hz, 1H), 10.61 (s, 1H). MS (ESI) 365 (M-H)⁻. HRMS (ESI) 365.1064(M-H)⁻.

5

Example 95

6-[5-(4-Chlorophenyl)-furan-2-yl]-5-cyano-4-methyl-2-oxo-3,6-dihydro-2H-pyrimidine-1-carboxylic acid ethylamide

Using 5-(4-Chlorophenyl)furan-2-carboxaldehyde and following the procedure of Example 26, intermediate XXIV was obtained in 16 % yield. The title compound was obtained in 43 % yield following the procedure described in Example 28.

¹H-NMR (DMSO-d₆, 400 MHz): δ 1.07 (t, J = 7.1 Hz, 3H), 2.12 (s, 3H), 3.22 (m, 2H), 6.27 (s, 1H), 6.46 (d, J = 3.4 Hz, 1H), 6.97 (d, J = 3.4 Hz, 1H), 7.51 (m, 2H), 7.63 (m, 2H), 8.70 (t, J = 5.5 Hz, 1H), 10.62 (s, 1H). MS (ESI) 383 (M-H)⁻. HRMS (ESI) 383.0913 (M-H)⁻.

15

Example 96

5-Cyano-4-methyl-2-oxo-6-(4-trifluoromethylthiazol-5-yl)-3,6-dihydro-2H-pyrimidine-1-carboxylic acid ethyl ester

Using 4-trifluoromethylthiazole-5-carboxaldehyde and following the procedure of Example 26, intermediate XXIV was obtained in 63 % yield and the title compound was obtained in 52 % yield.

¹H-NMR (DMSO-d₆, 400 MHz): δ 10.84 (s, 1H), 9.22 (s, 1H), 6.45 (s, 1H), 4.15 (q, 2H, J = 5.7 Hz), 2.06 (s, 3H), 1.16 (t, 3H, J = 5.7 Hz). ¹³C-NMR (DMSO-D₆, 400 MHz): δ 165.51, 151.90, 149.88, 146.79, 142.70, 138.70, 116.10, 83.68, 63.78, 50.42, 17.44, 13.94; MS (ESI) 361 (M+H)⁺.

25

Example 97

5-Cyano-4-methyl-2-oxo-6-(4-trifluoromethylthiazol-5-yl)-3,6-dihydro-2H-pyrimidine-1-carboxylic acid ethylamide

30

Using 4-trifluoromethylthiazole-5-carboxaldehyde and following the procedure of Example 26, intermediate XXIV was obtained in 63 % yield. The title compound was obtained in 59 % yield following the procedure described in Example 28.

¹H-NMR (DMSO-d₆, 400 MHz): δ 10.84 (s, 1H), 9.19 (s, 1H), 8.69 (m, 1H), 6.68 (s, 1H), 3.15 (m, 1H), 2.06 (s, 3H), 1.01 (t, 3H, J = 7.0 Hz); ¹³C-NMR (DMSO-d₆, 400 MHz): δ 155.54, 151.46, 150.25, 149.38, 143.23, 138.70, 115.63, 82.55, 47.93, 34.83, 16.87, 14.34. MS (ESI) 360 (M+H)⁺.

Example 98

10 5-Cyano-6-[5-(4-methanesulfonylphenyl)-oxazol-4-yl]-4-methyl-2-oxo-3,6-dihydro-2H-pyrimidine-1-carboxylic acid ethylamide

Using 5-(4-methanesulfonylphenyl)oxazole-4-carboxaldehyde and following the procedure of Example 26, intermediate XXIV was obtained in 22 % yield. The title compound was obtained in 63 % yield following the procedure described in Example 28.

¹H-NMR (DMF-d₇, 400 MHz): δ 10.60 (s, 1H), 8.96 (t, J = 4.8 Hz, 1H), 8.62 (s, 1H), 8.25 (d, J = 8.3 Hz, 2H), 8.18 (d, J = 8.3 Hz, 2H), 6.67 (s, 1H), 3.37 (s, 3H), 3.25 (m, 2H), 2.21 (s, 3H), 1.07 (t, J = 7.4 Hz, 3H). MS (ESI) 430 (M+H)⁺.

20 Example 99

6-[5-(4-Chlorophenyl)-oxazol-4-yl]-5-cyano-4-methyl-2-oxo-3,6-dihydro-2H-pyrimidine-1-carboxylic acid ethylamide

Using 5-(4-chlorophenyl)oxazole-4-carboxaldehyde and following the procedure of Example 26, intermediate XXIV was obtained in 40 % yield. The title compound was obtained in 58 % yield following the procedure described in Example 28.

¹H-NMR (DMSO-d₆, 400 MHz): δ 10.51 (s, 1H), 8.78 (m, 1H), 8.43 (s, 1H), 7.85 (d, 2H, J = 8.5 Hz), 7.62 (d, 2H, J = 8.5 Hz), 6.38 (s, 1H), 3.11 (m, 2H), 2.02 (s, 3H), 0.99 (t, 3H, J = 7.2 Hz). ¹³C-NMR (DMSO-D₆, 400 MHz): δ 152.99, 152.51, 152.11, 149.30, 143.70, 134.17, 129.52, 128.13, 126.40, 117.20, 81.80, 48.09, 35.17, 17.28, 14.95. MS (ESI), 386 (M+H)⁺.

Example 100**5-Cyano-4-methyl-2-oxo-6-[5-(4-trifluoromethylphenyl)-oxazol-4-yl]-3,6-dihydro-2H-pyrimidine-1-carboxylic acid ethylamide**

Using 5-(4-trifluoromethylphenyl)oxazole-4-carboxaldehyde and following the
5 procedure of Example 26, intermediate XXIV was obtained in 31 % yield. The title
compound was obtained in 52 % yield following the procedure described in Example
28.

¹H-NMR (DMSO-d₆, 400 MHz): δ 10.54 (s, 1H), 8.78 (m, 1H), 8.50 (s, 1H), 8.06 (d,
2H, J = 8.1 Hz), 7.91 (d, 2H, J = 8.1 Hz), 6.46 (s, 1H), 3.10 (m, 2H), 2.03 (s, 3H), 0.99
10 (t, 3H, J = 7.2 Hz); ¹³C-NMR (DMSO-d₆, 400 MHz): δ 152.53, 152.31, 151.52,
149.03, 142.70, 134.96, 130.69, 126.41, 125.88, 116.62, 81.03, 47.69, 34.65, 16.75,
14.41; MS (ESI), 420.13 (M+H)⁺.

Example 101**15 5-Cyano-4-methyl-2-oxo-6-(5-phenyloxazol-4-yl)-3,6-dihydro-2H-pyrimidine-1-carboxylic acid ethylamide**

Catalytic reduction (10 % Pd/C, ammonium formate in refluxing acetonitrile) of the
product of Example 99 gave the title compound in 45 % yield.

¹H-NMR (CDCl₃, 400 MHz): δ 8.69 (m, 1H), 7.87 (m, 3H), 7.50 (m, 2H), 7.41 (m,
20 1H), 7.00 (s, 1H), 6.63 (s, 1H), 3.30 (m, 2H), 2.18 (s, 3H), 1.13 (t, 3H, J = 7.2 Hz).
¹³CNMR (CDCl₃, 400 MHz): δ 152.40, 152.13, 150.25, 146.90, 132.60, 129.50,
129.12, 126.79, 116.57, 80.93, 48.25, 35.70, 17.87, 14.72; MS (ESI), 352.16 (M+H)⁺.

Example 102**25 5-Cyano-4-methyl-6-[5-(4-nitrophenyl)-oxazol-4-yl]-2-oxo-3,6-dihydro-2H-pyrimidine-1-carboxylic acid ethylamide**

Using 5-(4-nitrophenyl)oxazole-4-carboxaldehyde and following the procedure of
Example 26, intermediate XXIV was obtained in 36 % yield. The title compound was
obtained in 70 % yield following the procedure described in Example 28.

30 ¹H-NMR (DMSO-d₆, 400 MHz): δ 10.56 (s, 1H), 8.79 (m, 1H), 8.56 (s, 1H), 8.38 (m,
2H), 8.13 (m, 2H), 6.50 (s, 1H), 3.12 (m, 2H), 2.03 (s, 3H), 0.99 (t, 3H, J = 7.2 Hz).
¹³C-NMR (DMSO-d₆, 400 MHz): δ 153.04, 152.37, 151.51, 149.13, 146.97, 136.16,



132.85, 126.72, 124.19, 116.57, 80.93, 47.87, 34.70, 16.81, 14.45. MS (ESI) 397 (M+H)⁺.

Example 103

5 **5-(4-Chlorophenyl)-2-(5-cyano-3-ethylcarbamoyl-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidin-4-yl)-furan-3-carboxylic acid ethyl ester**

Using 3-ethoxycarbonyl-5-(4-chlorophenyl)furan-2-carboxaldehyde and following the procedure of Example 26, intermediate XXIV was obtained in 59 % yield. The title compound was obtained in 42 % yield following the procedure described in Example

10 28.

¹H NMR (DMSO-d₆, 400 MHz): δ 1.02 (t, J = 7.2 Hz, 3H), 1.34 (t, J = 7.1 Hz, 3H), 2.07 (s, 3H), 3.16 (m, 2H), 4.30 (m, 2H), 6.85 (s, 1H), 7.34 (s, 1H), 7.53 (m, 2H), 7.65 (m, 2H), 8.67 (t, J = 5.5 Hz, 1H), 10.76 (s, 1H). MS (ESI) 455 (M-H)⁻. HRMS (ESI) 455.1114 (M-H)⁻.

15

Example 104

5-Cyano-4-methyl-2-oxo-6-(5-pyridin-3-yloxazol-4-yl)-3,6-dihydro-2H-pyrimidine-1-carboxylic acid ethylamide

Using 5-(3-pyridinyl)oxazole-4-carboxaldehyde and following the procedure of

20 Example 26, intermediate XXIV was obtained in 62 % yield. The title compound was obtained in 41 % yield following the procedure described in Example 28.

¹H-NMR (DMSO-d₆, 400 MHz): δ 10.53 (s, 1H), 9.04 (m, 1H), 8.77 (m, 1H), 8.67 (m, 1H), 8.50 (s, 1H), 8.22 (m, 1H), 7.60 (m, 1H), 6.40 (s, 2H), 3.12 (m, 2H), 2.04 (s, 3H), 1.00 (t, 3H, J = 7.2 Hz). ¹³C-NMR (DMSO-d₆, 400 MHz): δ 152.76, 152.52, 25 151.75, 149.97, 149.19, 146.73, 134.73, 133.60, 124.06, 123.45, 116.94, 81.41, 47.81, 34.88, 16.99, 14.63; MS (ESI), 353.18 (M+H)⁺.



70
7**Example 105****5-Cyano-4-methyl-2-oxo-6-(4-phenylthiazol-5-yl)-3,6-dihydro-2H-pyrimidine-1-carboxylic acid ethylamide**

Using 4-phenylthiazole-5-carboxaldehyde and following the procedure of Example 26, intermediate XXIV was obtained in 70 % yield. The title compound was obtained in 27 % yield following the procedure described in Example 28.

¹H-NMR (DMSO-d₆, 400 MHz): δ 10.70 (s, 1H), 9.08 (s, 1H), 8.71 (m, 1H), 7.73 (2H, m), 7.47 (m, 3H), 6.63 (s, 1H), 3.12 (m, 2H), 1.99 (s, 3H), 1.00 (t, 3H, J = 7.2 Hz); ¹³C-NMR (DMSO-d₆, 400 MHz): δ 152.79, 151.97, 151.74, 150.61, 148.43, 133.87, 116.12, 83.68, 34.77, 16.69, 14.39. MS (ESI) 368 (M+H)⁺.

Example 106**[5-Cyano-4-methyl-6-(3-nitrophenyl)-2-oxo-3,6-dihydro-2H-pyrimidin-1-yl]-acetic acid tert-butyl ester**

Using 3-nitrobenzaldehyde and following the procedure of Example 26, intermediate XXIV was obtained in 92 % yield and the title compound was obtained in 52 % yield.

¹H-NMR (MeOH-d₄, 400 MHz): δ 8.28 (m, 1 H), 8.22 (t, 1 H, J = 1.8 Hz), 7.76 (m, 1 H), 7.69 (t, 1 H, J = 7.9 Hz), 7.62 (s, 1 H), 5.31 (s, 1 H), 4.23 (d, 1 H, J = 17.6 Hz), 3.44 (d, 1 H, J = 17.6 Hz), 2.16 (s, 3 H), 1.42 (s, 9 H). LC/MS (ES+) 395 (M+Na)⁺.

20

Example 107**5-Cyano-4-methyl-6-(3-nitrophenyl)-2-oxo-3,6-dihydro-2H-pyrimidine-1-carboxylic acid isopropylamide**

Using 3-nitrobenzaldehyde and following the procedure of Example 26, intermediate XXIV was obtained in 92 % yield. The title compound was obtained in 29 % yield following the procedure described in Example 27.

¹H-NMR (MeOH-d₄, 400 MHz): δ 8.92 (s, 1 H), 8.22 (d, 1 H, J = 8.3 Hz), 8.17 (t, 1 H, J = 1.8 Hz), 7.74 (d, 1 H, J = 6.6 Hz), 7.65 (m, 2 H), 6.31 (s, 1 H), 3.89 (m, 1 H), 2.19 (s, 3 H), 1.20 (d, 3 H, J = 6.6 Hz), 1.16 (d, 3 H, J = 6.6 Hz). LC/MS (ES+) 344 (M+H)⁺, 366 (M+Na)⁺.

30



21
27**Example 108****5-Cyano-4-methyl-6-(3-nitrophenyl)-2-oxo-3,6-dihydro-2H-pyrimidine-1-carboxylic acid propylamide**

Using 3-nitrobenzaldehyde and following the procedure of Example 26, intermediate
5 XXIV was obtained in 92 % yield. The title compound was obtained in 22 % yield
following the procedure described in Example 27.

¹H-NMR (MeOH-d₄, 400 MHz) δ 9.09 (t, 1 H, J = 5.3 Hz), 8.22 (m, 1 H), 8.17 (t, 1 H,
J = 1.8 Hz), 7.75 (d, 1 H, J = 7.9 Hz), 7.65 (t, 1 H, J = 7.9 Hz), 6.30 (s, 1 H), 3.33 (m,
2 H), 2.18 (s, 3 H), 1.54 (m, 2 H), 0.91 (t, 3 H, J = 7.5 Hz). LC/MS (ES+) 344
10 (M+H)⁺, 366 (M+Na)⁺.

Example 109**5-Cyano-4-methyl-6-(3-nitrophenyl)-2-oxo-3,6-dihydro-2H-pyrimidine-1-carboxylic acid phenylamide**

15 Using 3-nitrobenzaldehyde and following the procedure of Example 26, intermediate
XXIV was obtained in 92 % yield. The title compound was obtained in 10 % yield
following the procedure described in Example 27.

¹H-NMR (MeOH-d₄, 400 MHz): δ 11.18 (s, 1 H), 8.23 (m, 2 H), 7.81 (d, 1 H, J = 7.9
Hz), 7.65 (m, 1 H), 7.44 (m, 2 H), 7.31 (t, 2 H, J = 8.3 Hz), 7.11 (t, 1 H, J = 8.3 Hz),
20 6.40 (s, 1 H), 2.23 (s, 3 H). LC/MS (ES+) 378 (M+H)⁺, 400 (M+Na)⁺.

Example 110**5-Cyano-4-methyl-6-(3-nitrophenyl)-2-oxo-3,6-dihydro-2H-pyrimidine-1-carboxylic acid thiazol-2-ylamide**

25 Using 3-nitrobenzaldehyde and following the procedure of Example 26, intermediate
XXIV was obtained in 92 % yield. The title compound was obtained in 33 % yield
following the procedure described in Example 27.

¹H-NMR (MeOH-d₄, 400 MHz): δ 8.23 (m, 2 H), 7.80 (d, 1 H, J = 7.5 Hz), 7.64 (t, 1
H, J = 7.5 Hz), 7.42 (d, 1 H, J = 4.0 Hz), 7.03 (d, 1 H, J = 4.0 Hz), 6.36 (s, 1 H), 2.24
30 (d, 3 H, J = 0.9 Hz). LC/MS (ES+) 385 (M+H)⁺, 407 (M+Na)⁺.



72
13**Example 111****5-Cyano-4-methyl-6-(3-nitrophenyl)-2-oxo-3,6-dihydro-2H-pyrimidine-1-carboxylic acid (2,2,2-trifluoro-ethyl)-amide**

Using 3-nitrobenzaldehyde and following the procedure of Example 26, intermediate
5 XXIV was obtained in 92 % yield. The title compound was obtained in 25 % yield
following the procedure described in Example 27.

¹H-NMR (DMSO-d₆, 500 MHz): δ 10.77 (s, 1 H), 9.23 (t, 1 H, J = 6.0 Hz), 8.21 (m, 1 H), 8.09 (s, 1 H), 7.75 (m, 2 H), 6.26 (s, 1 H), 4.01 (m, 2 H), 2.10 (s, 3 H).

10

Example 112**5-Cyano-4-methyl-6-(3-nitrophenyl)-2-oxo-3,6-dihydro-2H-pyrimidine-1-carboxylic acid cyclopropylamide**

Using 3-nitrobenzaldehyde and following the procedure of Example 26, intermediate
XXIV was obtained in 92 % yield. The title compound was obtained in 19 % yield
15 following the procedure described in Example 27.

¹H-NMR (DMSO-d₆, 500 MHz): δ 10.62 (s, 1 H), 8.58 (s, 1 H), 8.21 (m, 1 H), 8.07 (d, 1 H, J = 1.6 Hz), 7.73 (m, 2 H), 6.22 (s, 1 H), 2.62 (m, 1 H), 2.09 (s, 3 H), 0.64 (m, 2 H), 0.46 (m, 2 H).

20

Example 113**5-Cyano-4-methyl-6-(3-nitrophenyl)-2-oxo-3,6-dihydro-2H-pyrimidine-1-carboxylic acid (2-hydroxy-ethyl)-amide**

Using 3-nitrobenzaldehyde and following the procedure of Example 26, intermediate
XXIV was obtained in 92 % yield. The title compound was obtained in 23 % yield
25 following the procedure described in Example 27.

¹H-NMR (CDCl₃, 500 MHz): δ 8.93 (s, 1 H), 8.15 (d, 1 H, J = 7.9 Hz), 8.07 (s, 1 H), 7.68 (d, 1 H, J = 7.9 Hz), 7.51 (t, 1 H, J = 7.9 Hz), 6.86 (s, 1 H), 6.30 (s, 1 H), 3.67 (m, 2 H), 3.43 (m, 1 H), 3.36 (m, 1 H), 2.18 (s, 3 H). LC/MS (ES+) 346 (M+H)⁺.



73
A
7**Example 114****3-(4,5-Dihydrooxazol-2-yl)-6-methyl-4-(3-nitrophenyl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carbonitrile**

Prepared from the product of Example 113 (Burgess reagent in refluxing
5 tetrahydrofuran) in 71 % yield.

¹H-NMR (MeOH-d₄, 400 MHz): δ 8.10 (m, 2 H), 7.66 (d, 1 H, J = 7.9 Hz), 7.56 (t, 1 H, J = 7.9 Hz), 6.19 (s, 1 H), 4.04 (m, 2 H), 3.50 (m, 1 H), 3.39 (m, 1 H), 2.06 (s, 3 H). LC/MS (ES+) 328 (M+H)⁺.

10

Example 115**5-Cyano-4-methyl-6-(3-nitrophenyl)-2-oxo-3,6-dihydro-2H-pyrimidine-1-carboxylic acid allylamide**

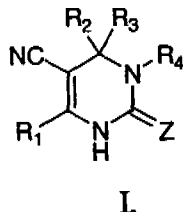
Using 3-nitrobenzaldehyde and following the procedure of Example 26, intermediate
XXIV was obtained in 92 % yield. The title compound was obtained in 36 % yield
15 following the procedure described in Example 27.

¹H-NMR (DMSO-d₆, 500 MHz): δ 10.65 (s, 1 H), 8.92 (t, 1 H, J = 5.5 Hz), 8.21 (m, 1 H), 8.08 (s, 1 H), 7.74 (m, 2 H), 6.24 (s, 1 H), 5.81 (m, 1 H), 5.07 (m, 2 H), 3.78 (m, 2 H), 2.10 (s, 3 H). LC/MS (ES+) 342 (M+H)⁺, 364 (M+Na)⁺.



What is claimed is:

- 5



10

15

20

25

2. The compound of claim 1 wherein R₂ is heteroaryl.

25 X

3. The compound of claim 2 wherein R_3 is H and R_2 is an optionally substituted thiophene, oxazole, isoxazole, or furan.
4. The compound of claim 2 wherein said heteroaryl is substituted with methyl,
5 ethyl, halo, haloalkyl, or aryl.
5. The compound of claim 1 wherein R_3 is H and R_2 is a substituted phenyl
6. The compound of claim 5 wherein said phenyl is substituted with alkyl,
10 alkoxy, alkoxyalkyl, cyano, halo, haloalkyl, nitro, amino CO_2R_5 , $CONR_5R_6$,
alkenyloxy, aryloxy, wherein R_5 and R_6 are, independently, H or alkyl.
7. The compound of claim 6 wherein said phenyl is substituted with methyl,
methoxy, F, Cl, CF_3 , dimethylamino, or ethoxymethyl.
- 15 8. The compound of claim 1 wherein R_1 is alkyl; R_2 is selected from the group
consisting of aryl and heteroaryl; R_3 is H; R_4 is selected from the group consisting of
alkyl, arylalkyl, CO_2R_5 , and $CONR_5R_6$; R_5 and R_6 are independently selected from the
group consisting of H, alkyl, aminoalkyl, hydroxyalkyl, phenylamino and arylalkyl; Z
20 is selected from the group consisting of O, S, and NR_8 ; R_8 is selected from the group
consisting of H and CN.
9. The compound of claim 1 wherein R_4 is selected from the group consisting
of alkyl, arylalkyl, $C(O)R_5$, CO_2R_5 , $C(O)SR_5$ and $CONR_5R_6$.
- 25 10. The compound of claim 1 wherein R_4 is CO_2R_5 ; Z is O; and R_5 is ethyl.
11. The compound of claim 1 wherein R_4 is $CONR_5R_6$; Z is O; R_5 is H and R_6 is
methyl, ethyl, propyl, phenyl, cyclopropyl, hydroxyethyl, thiophene, or 2-propylene. .
- 30 12. The compound of claim 1 wherein R_4 is selected from the group consisting
of alkyl and arylalkyl, and Z is O.

13. The compound of claim 1 wherein R_1 is CH_3 ; R_2 is aryl; R_4 is CO_2R_5 ; R_5 is alkyl; and Z is O.
14. The compound of claim 1 wherein R_1 is CH_3 ; R_2 is aryl; R_4 is $CONR_5R_6$; R_5 is alkyl; R_6 is H and Z is O.
15. The compound of claim 1 wherein R_1 is CH_3 ; R_2 is heteroaryl; R_4 is CO_2R_5 or $CONR_5R_6$; R_6 is H and R_5 is ethyl.
16. A compound selected from the group consisting of:
- 5-cyano-3,6-dihydro-4-methyl-6-(3-nitrophenyl)-2-thioxo-1-(2H)-pyrimidinecarboxylic acid, 1-ethyl ester;
 - 5-cyano-3,6-dihydro-4-methyl-6-(3-nitrophenyl)-2-oxo-1-(2H)-pyrimidinecarboxylic acid, 1-ethyl ester;
 - 5-cyano-3,6-dihydro-4-methyl-6-(3-nitrophenyl)-2-oxo-1-(2H)-pyrimidinecarboxylic acid, 1-ethyl amide;
 - 5-cyano-3,6-dihydro-4-methyl-6-(3-nitrophenyl)-2-oxo-1-(1-oxobutyl)-(2H)-pyrimidine;
 - 5-cyano-3,6-dihydro-4-methyl-6-(3-aminophenyl)-2-oxo-1-(2H)-pyrimidinecarboxylic acid, 1-ethyl ester;
 - 5-cyano-3,6-dihydro-4-methyl-6-(3-(N,N-dimethyl)aminophenyl)-2-oxo-1-(2H)-pyrimidinecarboxylic acid, 1-ethyl ester;
 - 5-cyano-3,6-dihydro-4-methyl-6-(3-trifluoromethylphenyl)-2-oxo-1-(2H)-pyrimidinecarboxylic acid, 1-ethyl ester;
 - 5-cyano-3,6-dihydro-4-methyl-6-(2,3-dichlorophenyl)-2-oxo-1-(2H)-pyrimidinecarboxylic acid, 1-ethyl ester;
 - 5-cyano-3,6-dihydro-4-methyl-6-(3-methoxyphenyl)-2-oxo-1-(2H)-pyrimidinecarboxylic acid, 1-ethyl ester;
 - 5-cyano-3,6-dihydro-4-methyl-6-(3,5-dichlorophenyl)-2-oxo-1-(2H)-pyrimidinecarboxylic acid, 1-ethyl ester;
 - 5-cyano-3,6-dihydro-4-methyl-6-(3,4-dichlorophenyl)-2-oxo-1-(2H)-pyrimidinecarboxylic acid, 1-ethyl ester;

- 5-cyano-3,6-dihydro-4-methyl-6-(3-cyanophenyl)-2-oxo-1-(2H)-pyrimidinecarboxylic acid, 1-ethyl ester;
- 5-cyano-3,6-dihydro-4-methyl-6-(4-methoxyphenyl)-2-oxo-1-(2H)-pyrimidinecarboxylic acid, 1-ethyl ester;
- 5 5-cyano-3,6-dihydro-4-methyl-6-(4-methylphenyl)-2-oxo-1-(2H)-pyrimidinecarboxylic acid, 1-ethyl ester;
- 5-cyano-3,6-dihydro-4-methyl-6-cyclohexyl-2-oxo-1-(2H)-pyrimidinecarboxylic acid, 1-ethyl ester;
- 5-cyano-3,6-dihydro-4-methyl-6-phenyl-2-oxo-1-(2H)-pyrimidinecarboxylic acid, 1-ethyl ester;
- 10 5-cyano-3,6-dihydro-4-methyl-6-(2-methylphenyl)-2-oxo-1-(2H)-pyrimidinecarboxylic acid, 1-ethyl ester;
- 5-cyano-3,6-dihydro-4-methyl-6-(3-chlorophenyl)-2-oxo-1-(2H)-pyrimidinecarboxylic acid, 1-ethyl ester;
- 15 5-cyano-3,6-dihydro-4-methyl-6-(3-fluorophenyl)-2-oxo-1-(2H)-pyrimidinecarboxylic acid, 1-ethyl ester;
- 5-cyano-3,6-dihydro-4-methyl-6-(4-chlorophenyl)-2-oxo-1-(2H)-pyrimidinecarboxylic acid, 1-ethyl ester;
- 5-cyano-3,6-dihydro-4-methyl-6-(4-fluorophenyl)-2-oxo-1-(2H)-pyrimidinecarboxylic acid, 1-ethyl ester; and
- 20 5-cyano-3,6-dihydro-4-methyl-6-(2-fluorophenyl)-2-oxo-1-(2H)-pyrimidinecarboxylic acid, 1-ethyl ester;
- 6-(3,5-Bis-trifluoromethylphenyl)-5-cyano-4-methyl-2-oxo-3,6-dihydro-2H-pyrimidine-1-carboxylic acid ethyl ester;
- 25 6-Butyl-5-cyano-4-methyl-2-oxo-3,6-dihydro-2H-pyrimidine-1-carboxylic acid ethyl ester;
- 5-Cyano-4-methyl-6-(3-nitrophenyl)-2-oxo-3,6-dihydro-2H-pyrimidine-1-carboxylic acid methylamide;
- 5-Cyano-4-methyl-2-oxo-6-phenyl-3,6-dihydro-2H-pyrimidine-1-carboxylic acid ethylamide;
- 30



28


- 5-Cyano-6-(3,5-dichlorophenyl)-4-methyl-2-oxo-3,6-dihydro-2H-pyrimidine-1-carboxylic acid 2-methoxy-ethyl ester;
- 5-Cyano-4-methyl-2-oxo-6-(3-trifluoromethylphenyl)-3,6-dihydro-2H-pyrimidine-1-carboxylic acid ethylamide;
- 5 5-Cyano-6-(3,5-dichlorophenyl)-4-methyl-2-oxo-3,6-dihydro-2H-pyrimidine-1-carboxylic acid ethylamide;
- 3-Butyryl-4-(3,5-dichlorophenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carbonitrile;
- 5-Cyano-4-methyl-2-oxo-6-(3-trifluoromethylphenyl)-3,6-dihydro-2H-pyrimidine-1-carboxylic acid (2-dimethylamino-ethyl)-amide;
- 10 5-Cyano-4-methyl-2-oxo-6-(3-trifluoromethylphenyl)-3,6-dihydro-2H-pyrimidine-1-carbothioic acid S-ethyl ester;
- 5-Cyano-4-methyl-2-oxo-6-(3-trifluoromethylphenyl)-3,6-dihydro-2H-pyrimidine-1-carboxylic acid (2-hydroxy-ethyl)-amide;
- 15 4-(3,5-Dichlorophenyl)-6-methyl-2-oxo-3-(thiophene-2-carbonyl)-1,2,3,4-tetrahydropyrimidine-5-carbonitrile;
- 5-Cyano-6-(3,5-difluorophenyl)-4-methyl-2-oxo-3,6-dihydro-2H-pyrimidine-1-carboxylic acid ethylamide; 5-Cyano-6-(3,5-difluorophenyl)-4-methyl-2-oxo-3,6-dihydro-2H-pyrimidine-1-carboxylic acid ethyl ester
- 20 4-(3,5-Difluorophenyl)-6-methyl-2-oxo-3-(piperidine-1-carbonyl)-1,2,3,4-tetrahydropyrimidine-5-carbonitrile; 4-(3,5-Difluorophenyl)-6-methyl-2-oxo-3-(pyrrolidine-1-carbonyl)-1,2,3,4-tetrahydropyrimidine-5-carbonitrile
- 5-Cyano-4-methyl-6-naphthalen-1-yl-2-oxo-3,6-dihydro-2H-pyrimidine-1-carboxylic acid ethyl ester; 5-Cyano-4-methyl-6-naphthalen-1-yl-2-oxo-3,6-dihydro-2H-pyrimidine-1-carboxylic acid ethylamide; 6-(3-Bromophenyl)-5-cyano-4-methyl-2-oxo-3,6-dihydro-2H-pyrimidine-1-carboxylic acid ethyl ester; 6-(3-Bromophenyl)-5-cyano-4-methyl-2-oxo-3,6-dihydro-2H-pyrimidine-1-carboxylic acid ethylamide; 5-Cyano-4-methyl-2-oxo-6-(2-trifluoromethylphenyl)-3,6-dihydro-2H-pyrimidine-1-carboxylic acid ethyl ester; 5-Cyano-4-methyl-2-oxo-6-(2-trifluoromethylphenyl)-3,6-dihydro-2H-pyrimidine-1-carboxylic acid ethylamide; 5-Cyano-6-(3-methoxycarbonylphenyl)-4-methyl-2-oxo-3,6-dihydro-2H-pyrimidine-1-carboxylic
- 25
- 30

3
10

- acid ethyl ester; 3-(5-Cyano-3-ethylcarbamoyl-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidin-4-yl)-benzoic acid methyl ester
- 6-Butyl-5-cyano-4-methyl-2-oxo-3,6-dihydro-2H-pyrimidine-1-carboxylic acid ethylamide;
- 5 6-(3,5-Bis-trifluoromethylphenyl)-5-cyano-4-methyl-2-oxo-3,6-dihydro-2H-pyrimidine-1-carboxylic acid ethylamide;
- 6-(2,5-Bis-trifluoromethylphenyl)-5-cyano-4-methyl-2-oxo-3,6-dihydro-2H-pyrimidine-1-carboxylic acid ethylamide;
- 6-(2,5-Bis-trifluoromethylphenyl)-5-cyano-4-methyl-2-oxo-3,6-dihydro-2H-pyrimidine-1-carboxylic acid ethyl ester;
- 10 5-Cyano-6-(3-ethylcarbamoylphenyl)-4-methyl-2-oxo-3,6-dihydro-2H-pyrimidine-1-carboxylic acid ethylamide;
- 5-Cyano-6-(3-cyano-4-fluorophenyl)-4-methyl-2-oxo-3,6-dihydro-2H-pyrimidine-1-carboxylic acid ethylamide;
- 15 5-Cyano-6-(3-cyano-4-fluorophenyl)-4-methyl-2-oxo-3,6-dihydro-2H-pyrimidine-1-carboxylic acid ethyl ester;
- 5-Cyano-6-(2,2-dimethylpropyl)-4-methyl-2-oxo-3,6-dihydro-2H-pyrimidine-1-carboxylic acid ethylamide;
- 5-Cyano-6-cyclopropyl-4-methyl-2-oxo-3,6-dihydro-2H-pyrimidine-1-carboxylic acid ethyl ester;
- 20 5-Cyano-6-cyclopropyl-4-methyl-2-oxo-3,6-dihydro-2H-pyrimidine-1-carboxylic acid ethylamide;
- 5-Cyano-6-(2-fluoro-5-trifluoromethylphenyl)-4-methyl-2-oxo-3,6-dihydro-2H-pyrimidine-1-carboxylic acid ethylamide;
- 25 5-Cyano-6-(2-fluoro-5-trifluoromethylphenyl)-4-methyl-2-oxo-3,6-dihydro-2H-pyrimidine-1-carboxylic acid ethyl ester;
- 5-Cyano-6-isopropyl-4-methyl-2-oxo-3,6-dihydro-2H-pyrimidine-1-carboxylic acid ethyl ester;
- 5-Cyano-4-methyl-6-naphthalen-2-yl-2-oxo-3,6-dihydro-2H-pyrimidine-1-carboxylic acid ethyl ester;
- 30



- 5-Cyano-6-[3-(2-hydroxyethylcarbamoyl)-phenyl]-4-methyl-2-oxo-3,6-dihydro-2H-pyrimidine-1-carboxylic acid ethylamide;
- 5-Cyano-6-(2-methoxyphenyl)-4-methyl-2-oxo-3,6-dihydro-2H-pyrimidine-1-carboxylic acid ethyl ester;
- 5 5-Cyano-6-(2-methoxyphenyl)-4-methyl-2-oxo-3,6-dihydro-2H-pyrimidine-1-carboxylic acid ethylamide;
- 6-(2-Allyloxyphenyl)-5-cyano-4-methyl-2-oxo-3,6-dihydro-2H-pyrimidine-1-carboxylic acid ethyl ester;
- 6-(2-Allyloxyphenyl)-5-cyano-4-methyl-2-oxo-3,6-dihydro-2H-pyrimidine-1-carboxylic acid ethylamide;
- 10 6-(2-Bromophenyl)-5-cyano-4-methyl-2-oxo-3,6-dihydro-2H-pyrimidine-1-carboxylic acid ethyl ester;
- 6-(2-Bromophenyl)-5-cyano-4-methyl-2-oxo-3,6-dihydro-2H-pyrimidine-1-carboxylic acid ethylamide
- 15 5-Cyano-6-(3-methoxyphenyl)-4-methyl-2-oxo-3,6-dihydro-2H-pyrimidine-1-carboxylic acid ethylamide
- 6-(2-Benzyloxyphenyl)-5-cyano-4-methyl-2-oxo-3,6-dihydro-2H-pyrimidine-1-carboxylic acid ethyl ester
- 6-Benzyloxymethyl-5-cyano-4-methyl-2-oxo-3,6-dihydro-2H-pyrimidine-1-carboxylic acid ethylamide
- 20 6-Benzyloxymethyl-5-cyano-4-methyl-2-oxo-3,6-dihydro-2H-pyrimidine-1-carboxylic acid ethyl ester;
- 6-(3-Bromo-4-fluorophenyl)-5-cyano-4-methyl-2-oxo-3,6-dihydro-2H-pyrimidine-1-carboxylic acid ethylamide;
- 25 6-(3-Bromo-4-fluorophenyl)-5-cyano-4-methyl-2-oxo-3,6-dihydro-2H-pyrimidine-1-carboxylic acid cyclopropylamide;
- 6-(5-Bromo-2-fluorophenyl)-5-cyano-4-methyl-2-oxo-3,6-dihydro-2H-pyrimidine-1-carboxylic acid ethylamide;
- 6-(5-Bromo-2-fluorophenyl)-5-cyano-4-methyl-2-oxo-3,6-dihydro-2H-pyrimidine-1-carboxylic acid cyclopropylamide;
- 30



81
2
F

- 5-Cyano-6-(3,5-dibromophenyl)-4-methyl-2-oxo-3,6-dihydro-2H-pyrimidine-1-carboxylic acid ethylamide;
- 5-Cyano-4-methyl-6-(3-nitrophenyl)-2-oxo-3,6-dihydro-2H-pyrimidine-1-carboxylic acid cyclopropylmethylamide;
- 5 5-Cyano-4-methyl-2-oxo-6-phenethyloxymethyl-3,6-dihydro-2H-pyrimidine-1-carboxylic acid ethyl ester;
- 5-Cyano-4-methyl-2-oxo-6-phenethyl-3,6-dihydro-2H-pyrimidine-1-carboxylic acid ethylamide;
- 5-Cyano-4-methyl-2-oxo-6-thiophen-3-yl-3,6-dihydro-2H-pyrimidine-1-carboxylic acid ethyl ester;
- 10 5-Cyano-4-methyl-6-(5-methylisoxazol-3-yl)-2-oxo-3,6-dihydro-2H-pyrimidine-1-carboxylic acid ethyl ester;
- 5-Cyano-6-(3,5-dimethylisoxazol-4-yl)-4-methyl-2-oxo-3,6-dihydro-2H-pyrimidine-1-carboxylic acid ethyl ester;
- 15 5-Cyano-4-methyl-2-oxo-6-thiophen-2-yl-3,6-dihydro-2H-pyrimidine-1-carboxylic acid ethyl ester;
- 5-Cyano-4-methyl-6-(3-methylthiophen-2-yl)-2-oxo-3,6-dihydro-2H-pyrimidine-1-carboxylic acid ethylamide;
- 5-Cyano-4-methyl-6-(3-methylthiophen-2-yl)-2-oxo-3,6-dihydro-2H-pyrimidine-1-carboxylic acid ethyl ester;
- 20 5-Cyano-4-methyl-6-(2-methylthiazol-4-yl)-2-oxo-3,6-dihydro-2H-pyrimidine-1-carboxylic acid ethyl ester;
- 6-(4-Bromothiophen-2-yl)-5-cyano-4-methyl-2-oxo-3,6-dihydro-2H-pyrimidine-1-carboxylic acid ethylamide;
- 25 6-(4-Bromothiophen-2-yl)-5-cyano-4-methyl-2-oxo-3,6-dihydro-2H-pyrimidine-1-carboxylic acid ethyl ester;
- 5-Cyano-4-methyl-2-oxo-6-[2-(4-trifluoromethylphenyl)-thiazol-4-yl]-3,6-dihydro-2H-pyrimidine-1-carboxylic acid ethyl ester;
- 6-[5-(4-Chlorophenyl)-oxazol-4-yl]-5-cyano-4-methyl-2-oxo-3,6-dihydro-2H-pyrimidine-1-carboxylic acid ethyl ester;
- 30 6-(2-Bromothiazol-5-yl)-5-cyano-4-methyl-2-oxo-3,6-dihydro-2H-pyrimidine-1-carboxylic acid ethyl ester;



32 

- 5-Cyano-4-methyl-2-oxo-6-(4-phenylthiophen-2-yl)-3,6-dihydro-2H-pyrimidine-1-carboxylic acid ethylamide;
- 6-[5-(4-Chlorophenyl)-furan-2-yl]-5-cyano-4-methyl-2-oxo-3,6-dihydro-2H-pyrimidine-1-carboxylic acid ethylamide;
- 5 5-Cyano-4-methyl-2-oxo-6-(4-trifluoromethylthiazol-5-yl)-3,6-dihydro-2H-pyrimidine-1-carboxylic acid ethyl ester;
- 5-Cyano-4-methyl-2-oxo-6-(4-trifluoromethylthiazol-5-yl)-3,6-dihydro-2H-pyrimidine-1-carboxylic acid ethylamide;
- 5-Cyano-6-[5-(4-methanesulfonylphenyl)-oxazol-4-yl]-4-methyl-2-oxo-3,6-dihydro-2H-pyrimidine-1-carboxylic acid ethylamide;
- 10 6-[5-(4-Chlorophenyl)-oxazol-4-yl]-5-cyano-4-methyl-2-oxo-3,6-dihydro-2H-pyrimidine-1-carboxylic acid ethylamide;
- 5-Cyano-4-methyl-2-oxo-6-[5-(4-trifluoromethylphenyl)-oxazol-4-yl]-3,6-dihydro-2H-pyrimidine-1-carboxylic acid ethylamide;
- 15 5-Cyano-4-methyl-2-oxo-6-(5-phenyloxazol-4-yl)-3,6-dihydro-2H-pyrimidine-1-carboxylic acid ethylamide;
- 5-Cyano-4-methyl-6-[5-(4-nitrophenyl)-oxazol-4-yl]-2-oxo-3,6-dihydro-2H-pyrimidine-1-carboxylic acid ethylamide;
- 5-(4-Chlorophenyl)-2-(5-cyano-3-ethylcarbamoyl-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidin-4-yl)-furan-3-carboxylic acid ethyl ester;
- 20 5-Cyano-4-methyl-2-oxo-6-(5-pyridin-3-yloxazol-4-yl)-3,6-dihydro-2H-pyrimidine-1-carboxylic acid ethylamide;
- 5-Cyano-4-methyl-2-oxo-6-(4-phenylthiazol-5-yl)-3,6-dihydro-2H-pyrimidine-1-carboxylic acid ethylamide;
- 25 [5-Cyano-4-methyl-6-(3-nitrophenyl)-2-oxo-3,6-dihydro-2H-pyrimidin-1-yl]-acetic acid tert-butyl ester;
- 5-Cyano-4-methyl-6-(3-nitrophenyl)-2-oxo-3,6-dihydro-2H-pyrimidine-1-carboxylic acid isopropylamide;
- 5-Cyano-4-methyl-6-(3-nitrophenyl)-2-oxo-3,6-dihydro-2H-pyrimidine-1-carboxylic acid propylamide;
- 30 5-Cyano-4-methyl-6-(3-nitrophenyl)-2-oxo-3,6-dihydro-2H-pyrimidine-1-carboxylic acid phenylamide;



23
X

- 5-Cyano-4-methyl-6-(3-nitrophenyl)-2-oxo-3,6-dihydro-2H-pyrimidine-1-carboxylic acid thiazol-2-ylamide;
- 5-Cyano-4-methyl-6-(3-nitrophenyl)-2-oxo-3,6-dihydro-2H-pyrimidine-1-carboxylic acid (2,2,2-trifluoro-ethyl)-amide;
- 5 5-Cyano-4-methyl-6-(3-nitrophenyl)-2-oxo-3,6-dihydro-2H-pyrimidine-1-carboxylic acid cyclopropylamide;
- 5-Cyano-4-methyl-6-(3-nitrophenyl)-2-oxo-3,6-dihydro-2H-pyrimidine-1-carboxylic acid (2-hydroxy-ethyl)-amide;
- 3-(4,5-Dihydrooxazol-2-yl)-6-methyl-4-(3-nitrophenyl)-2-oxo-1,2,3,4-
- 10 tetrahydropyrimidine-5-carbonitrile; and
- 5-Cyano-4-methyl-6-(3-nitrophenyl)-2-oxo-3,6-dihydro-2H-pyrimidine-1-carboxylic acid allylamide.
17. A pharmaceutical composition comprising a compound of claim 1 and a
- 15 pharmaceutically acceptable carrier.
18. The pharmaceutical composition of claim 17 further comprising at least one other anti-cancer agent formulated as a fixed dose.
- 20 19. A method for treating a proliferative disease via modulation of the Eg5 motor protein comprising administering to a mammalian species in need of such treatment an effective amount of at least one compound of claim 1.
20. The method according to claim 19 further comprising administering to said
- 25 mammalian species at least one other anti-cancer agent.
21. The method according to claim 19 wherein the proliferative disease is cancer.
- 30 22. A method for treating a proliferative disease by inducing apoptosis comprising administering to a mammalian species an effective amount of a compound of claim 1.

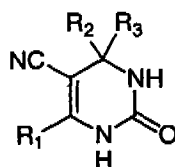


23. The method according to claim 22 further comprising administering to said mammalian species at least one other anti-cancer agent.

5 24. The method according to claim 22 wherein the proliferative disease is cancer.

25. A method of preparing a compound having the formula:

10



XXIV

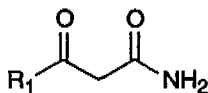
wherein

R_1 is selected from the group consisting of hydrogen, alkyl and cycloalkyl;

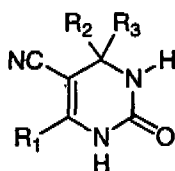
15 R_2 and R_3 are each independently selected from the group consisting of H, alkyl, aryl, heteroaryl, arylalkyl, cycloalkyl, heterocycloalkyl, cycloalkylalkyl, heterocycloalkylalkyl and heteroarylalkyl; or

R_2 and R_3 may also be taken together to form a carbocyclic or heterocyclic ring;

20 comprising contacting a compound having formula R_2COR_3 with a compound having the formula R_1COCH_2CN or a compound having the formula



in the presence of polyphosphate ester and urea to form

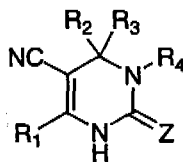


XXIV

25



26. The method of claim 25 further comprising contacting compound XXIV with R_4-X in the presence of a base wherein R_4 is alkyl or acyl, and X is a leaving group, or wherein R_4X is isocyanate or haloformate to yield a compound having formula I

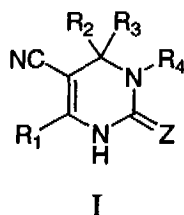


I



Abstract

The present invention provides compounds of formula I



5

and pharmaceutically acceptable salts thereof.

10

The formula I compounds induce mitotic arrest thereby making them useful as anti-cancer agents. The formula I compounds are also useful for the treatment of other diseases which can be treated by inducing mitotic arrest.

PCT REQUEST

Original (for SUBMISSION) - printed on 25.03.2002 07:18:48 AM

LD202

0	For receiving Office use only	
0-1	International Application No.	
0-2	International Filing Date	
0-3	Name of receiving Office and "PCT International Application"	
0-4	Form - PCT/RO/101 PCT Request	
0-4-1	Prepared using	PCT-EASY Version 2.92 (updated 01.01.2002)
0-5	Petition The undersigned requests that the present international application be processed according to the Patent Cooperation Treaty	
0-6	Receiving Office (specified by the applicant)	United States Patent and Trademark Office (USPTO) (RO/US)
0-7	Applicant's or agent's file reference	LD202
I	Title of invention	NOVEL CYANO-SUBSTITUTED DIHYDROPYRIMIDINE COMPOUNDS AND THEIR USE TO TREAT DISEASES
II	Applicant	
II-1	This person is:	applicant only
II-2	Applicant for	all designated States except US
II-4	Name	BRISTOL-MYERS SQUIBB COMPANY
II-5	Address:	P.O. BOX 4000 RT. 206 & PROVINCE LINE ROAD PRINCETON, NJ 08543-4000 United States of America
II-6	State of nationality	US
II-7	State of residence	US
II-8	Telephone No.	609-252-3453
II-9	Facsimile No.	609-252-4526
III-1	Applicant and/or inventor	
III-1-1	This person is:	applicant and inventor
III-1-2	Applicant for	US only
III-1-4	Name (LAST, First)	KIMBALL, Spencer, David
III-1-5	Address:	13 Charred Oak Lane East Windsor, NJ 08520 United States of America
III-1-6	State of nationality	US
III-1-7	State of residence	US

4

2

2

PCT REQUEST

Original (for SUBMISSION) - printed on 25.03.2002 07:18:48 AM

III-2	Applicant and/or inventor	
III-2-1	This person is:	applicant and inventor
III-2-2	Applicant for	US only
III-2-4	Name (LAST, First)	LOMBARDO, Louis, J.
III-2-5	Address:	49 West Street Belle Mead, NJ 08502 United States of America
III-2-6	State of nationality	US
III-2-7	State of residence	US
III-3	Applicant and/or inventor	
III-3-1	This person is:	applicant and inventor
III-3-2	Applicant for	US only
III-3-4	Name (LAST, First)	RAWLINS, David, B
III-3-5	Address:	219 Vernon Road Morrisville, PA 19067 United States of America
III-3-6	State of nationality	US
III-3-7	State of residence	US
III-4	Applicant and/or inventor	
III-4-1	This person is:	applicant and inventor
III-4-2	Applicant for	US only
III-4-4	Name (LAST, First)	XIAO, Hai-Yun
III-4-5	Address:	173 Jonathan Dayton Court Princeton, NJ 08540 United States of America
III-4-6	State of nationality	CN
III-4-7	State of residence	US
III-5	Applicant and/or inventor	
III-5-1	This person is:	applicant and inventor
III-5-2	Applicant for	US only
III-5-4	Name (LAST, First)	SCHMIDT, Robert, Joseph
III-5-5	Address:	3 South Deer Place Hainesport, NJ 08036 United States of America
III-5-6	State of nationality	US
III-5-7	State of residence	US
III-6	Applicant and/or inventor	
III-6-1	This person is:	applicant and inventor
III-6-2	Applicant for	US only
III-6-4	Name (LAST, First)	WILLIAMS, David, Kent
III-6-5	Address:	211 Paddock Way Delran, NJ 08075 United States of America
III-6-6	State of nationality	US
III-6-7	State of residence	US



PCT REQUEST

Original (for SUBMISSION) - printed on 25.03.2002 07:18:48 AM

IV-1	Agent or common representative; or address for correspondence The person identified below is hereby/has been appointed to act on behalf of the applicant(s) before the competent International Authorities as:	agent
IV-1-1	Name (LAST, First)	GIBBONS, Maureen
IV-1-2	Address:	BRISTOL-MYERS SQUIBB COMPANY P.O. BOX 4000 RT. 206 & PROVINCE LINE ROAD PRINCETON, NJ 08543-4000 United States of America
IV-1-3	Telephone No.	609-252-3453
IV-1-4	Facsimile No.	609-252-4526
IV-1-5	Agent's registration No.	44,121
IV-2	Additional agent(s)	additional agent(s) with same address as first named agent
IV-2-1	Name(s)	HERMENAU, Ronald; DAVIS, Stephen, B. (26,693); ALGIERI, Aldo; BABAJKO, Suzanne; BABCOCK, Timothy; BUCHHOLZ, Briana; DAMICO, Stephen; DUBOFF, Samuel; FURMAN, Theodore; KILCOYNE, John; KLEIN, Christopher; LANGE, Keith; MAKUJINA, Shah; MORSE, David; O'BRIEN, Maureen; PATEL, Rena; PEIST, Kenneth; PROVOOST, Jonathan; RODNEY, Burton; RYAN, Richard; SHER, Audrey; SWITZER, Joan; WILK-ORESCAN, Rosemarie; WINSLOW, Anastasia; FERGUSON, Blair, Q; BOUDREAUX, Gerald; LARSEN, Scott, K; VANATTEN, Mary, K; DOLAN, Peter, L; BELFIELD, Jing



PCT REQUEST

Original (for SUBMISSION) - printed on 25.03.2002 07:18:48 AM

90
15202

V	Designation of States	
V-1	Regional Patent (other kinds of protection or treatment, if any, are specified between parentheses after the designation(s) concerned)	AP: GH GM KE LS MW MZ SD SL SZ TZ UG ZM ZW and any other State which is a Contracting State of the Harare Protocol and of the PCT EA: AM AZ BY KG KZ MD RU TJ TM and any other State which is a Contracting State of the Eurasian Patent Convention and of the PCT EP: AT BE CH&LI CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE TR and any other State which is a Contracting State of the European Patent Convention and of the PCT OA: BF BJ CF CG CI CM GA GN GQ GW ML MR NE SN TD TG and any other State which is a member State of OAPI and a Contracting State of the PCT
V-2	National Patent (other kinds of protection or treatment, if any, are specified between parentheses after the designation(s) concerned)	AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH&LI CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ OM PH PL PT RO RU SD SE SG SI SK SL TJ TM TN TR TT TZ UA UG US UZ VN YU ZA ZM ZW
V-5	Precautionary Designation Statement In addition to the designations made under items V-1, V-2 and V-3, the applicant also makes under Rule 4.9(b) all designations which would be permitted under the PCT except any designation(s) of the State(s) indicated under item V-6 below. The applicant declares that those additional designations are subject to confirmation and that any designation which is not confirmed before the expiration of 15 months from the priority date is to be regarded as withdrawn by the applicant at the expiration of that time limit.	
V-6	Exclusion(s) from precautionary designations	NONE
VI-1	Priority claim of earlier national application	
VI-1-1	Filing date	29 March 2001 (29.03.2001)
VI-1-2	Number	60/279,956
VI-1-3	Country	US
VI-2	Priority document request The receiving Office is requested to prepare and transmit to the International Bureau a certified copy of the earlier application(s) identified above as item(s):	VI-1

PCT REQUEST

Original (for SUBMISSION) - printed on 25.03.2002 07:18:48 AM

LD202

10-6	Transmittal of search copy delayed until search fee is paid	
------	--	--

FOR INTERNATIONAL BUREAU USE ONLY

11-1	Date of receipt of the record copy by the International Bureau	
------	---	--

PCT (ANNEX - FEE CALCULATION SHEET)Original (for **SUBMISSION**) - printed on 25.03.2002 07:18:48 AM

LD202

(This sheet is not part of and does not count as a sheet of the international application)

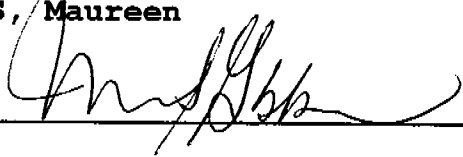
0	For receiving Office use only	
0-1	International Application No.	
0-2	Date stamp of the receiving Office	
0-4	Form - PCT/RO/101 (Annex)	
0-4-1	PCT Fee Calculation Sheet Prepared using	PCT-EASY Version 2.92 (updated 01.01.2002)
0-9	Applicant's or agent's file reference	LD202
2	Applicant	BRISTOL-MYERS SQUIBB COMPANY, et al.
12	Calculation of prescribed fees	fee amount/multiplier Total amounts (USD)
12-1	Transmittal fee T	⇒ 240
12-2-1	Search fee S	⇒ 700
12-2-2	International search to be carried out by	US
12-3	International fee	
	Basic fee	
	(first 30 sheets) b1	407
12-4	Remaining sheets	58
12-5	Additional amount (X)	9
12-6	Total additional amount b2	522
12-7	b1 + b2 = B	929
12-8	Designation fees	
	Number of designations contained in international application	93
12-9	Number of designation fees payable (maximum 5)	5
12-10	Amount of designation fee (X)	88
12-11	Total designation fees D	440
12-12	PCT-EASY fee reduction R	-125
12-13	Total International fee (B+D-R) I	⇒ 1,244
12-14	Fee for priority document	
	Number of priority documents requested	1
12-15	Fee per document (X)	15
12-16	Total priority document fee P	⇒ 15
12-17	TOTAL FEES PAYABLE (T+S+I+P)	⇒ 2,199
12-19	Mode of payment	authorization to charge deposit account
12-20	Deposit account instructions	
	The receiving Office:	United States Patent and Trademark Office (USPTO) (RO/US)
12-20-1	Authorization to charge the total fees indicated above.	✓
12-20-2	Authorization to charge any deficiency or credit any overpayment in the total fees indicated above.	✓



PCT (ANNEX - FEE CALCULATION SHEET)

Original (for SUBMISSION) - printed on 25.03.2002 07:18:48 AM

LD202

12-20-3	Authorization to charge the fee for priority document.	✓
12-21	Deposit account No.	19-3880
12-22	Date	25 March 2002 (25.03.2002)
12-23	Name and signature	GIBBONS, Maureen 

VALIDATION LOG AND REMARKS

13-1-1	Applicant remarks	Abstract contains a chemical formula. Noted in the abstract in brackets [Insert chemical formula here] Power of Attorney enclosed.
13-2-7	Validation messages Contents	Yellow! The power of attorney or a copy of the general power of attorney will need to be furnished unless all applicants sign the request form.
		Green? The international application contains no drawings. Please verify.
13-2-9	Validation messages Payment	Green? Please ensure that you have a valid deposit account with the receiving Office selected.
13-2-10	Validation messages Annotate	Green? All indications that can be made on the Request form are specifically provided for by the software. Please confirm validity of additional indication.

PCT POWER OF ATTORNEY

Printed on 11.02.2002 09:33:53 AM

LD202

0-1	PCT Power of Attorney (for an international application filed under the Patent Cooperation Treaty) (PCT Rule 90.4)	
0-1-1	Prepared using	PCT-EASY Version 2.92 (updated 01.01.2002)
1	The undersigned applicant(s)	BRISTOL-MYERS SQUIBB COMPANY
1-1-1	hereby appoints (appoint) the following person	GIBBONS, Maureen; ALGIERI, Aldo; BABAJKO, Suzanne; BABCOCK, Timothy; BUCHHOLZ, Briana; DAMICO, Stephen; DUBOFF, Samuel; FURMAN, Theodore; KILCOYNE, John; KLEIN, Christopher; LANGE, Keith; MAKUJINA, Shah; MORSE, David; O'BRIEN, Maureen; PATEL, Rena; PEIST, Kenneth; PROVOOST, Jonathan; RODNEY, Burton; RYAN, Richard; SHER, Audrey; SWITZER, Joan; WILK-ORESCAN, Rosemarie; WINSLOW, Anastasia; FERGUSON, Blair, Q; BOUDREAUX, Gerald; LARSEN, Scott, K; VANATTEN, Mary, K; DOLAN, Peter, L; BELFIELD, Jing BRISTOL-MYERS SQUIBB COMPANY P.O. BOX 4000 RT. 206 & PROVINCE LINE ROAD PRINCETON, NJ 08543-4000 United States of America
1-1-2	hereby appoints (appoint) the following person	DAVIS, Stephen, B. BRISTOL-MYERS SQUIBB COMPANY P.O. BOX 4000 RT. 206 & PROVINCE LINE ROAD PRINCETON, NJ 08543-4000 United States of America
1-2	as	agent
1-3	to represent the undersigned before	all the competent International Authorities
1-4	in connection with the international application identified below:	
1-4-1	Title of the invention	NOVEL CYANO-SUBSTITUTED DIHYDROPYRIMIDINE COMPOUNDS AND THEIR USE TO TREAT DISEASES
1-4-2	Applicant's or agent's file reference	LD202
1-4-3	International application number (if already available)	
1-4-4	filed with the following Office as receiving Office	United States Patent and Trademark Office (USPTO) (RO/US)



PCT POWER OF ATTORNEY

Printed on 11.02.2002 09:33:53 AM

96
LD202

1-5	and to make or receive payments on behalf of the undersigned.	
2-1	Signature of applicant	<i>Stephen B. Davis</i>
2-1-1	Name	BRISTOL-MYERS SQUIBB COMPANY
2-1-2	Name of signatory	Stephen B. Davis
2-1-3	Capacity	Patent Counsel
3	Date	11 February 2002 (11.02.2002)

97 2

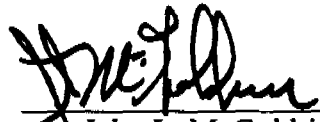
CERTIFICATION

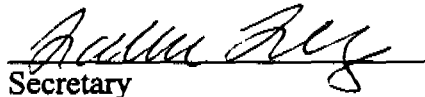
The undersigned, being the Executive Vice President and General Counsel of Bristol-Myers Squibb Company, hereby designates:

Stephen B. Davis
Christopher Klein
Suzanne Babajko
Theodore Furman
David M. Morse
Richard Ryan
Blair Q. Ferguson

(a) to present to the Patent, Trademark, Copyright and similar Government Offices of all countries to or to any competent authority, all original, divisional, continuation and reissue applications, petitions and request in the name of Bristol-Myers Squibb Company and its subsidiary companies, for letters patent for inventions, utility models, industrial models and designs and improvements or additions thereof, trademarks and copyrights; (b) to initial and prosecute oppositions and appeals; (c) to appear before all officers duly authorized, all Ministers, Bureaus, Clerk's Offices and Commissions or Commissioners that may be necessary; (d) to sign and approve on behalf of this corporation all documents and powers of attorney which judgment of the authorized individuals may be necessary or desirable to carry out the powers hereby conferred; (e) to request all proceedings; (f) to pay over or withdraw all taxes, obtain receipts therefor and give discharge; (g) to withdraw applications and all documents relating thereto; (h) to commence proceedings against infringers and assure the defense in infringement actions; and (i) generally to do all that in the judgment of the authorized individual may be necessary to secure granting of the privileges above-mentioned.

IN WITNESS WHEREOF, I have placed my hand and caused the seal of the Company to be affixed hereto on this 25th day of January 2002.


John L. McGoldrick
Executive Vice President
and General Counsel


Secretary

PCT

GENERAL POWER OF ATTORNEY

(for several international applications filed under the Patent Cooperation Treaty)

(PCT Rule 90.5)

The undersigned person(s):

(Family name followed by given name; for a full legal entity, full official designation. The address must include postal code and name of country.)

KIMBALL, Spencer David
13 Charred Oak Lane
East Windsor, NJ 08520
UNITED STATES OF AMERICA

hereby appoint(s) the following person as:

☒ agent

☐ common representative

Name and address

(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)

ALGIERI, Aldo; BABAJKO, Suzanne; BABCOCK, Timothy; BOUDREAUX, Gerald; BUCHHOLZ, Briana; BELFIELD, Jing; DAMICO, Stephen; DAVIS, Stephen; DUBOFF, Samuel; DOLAN, Peter; FERGUSON, Blair; FURMAN, Theodore; GIBBONS, MAUREEN; HERMENA, Ronald; KILCOYNE, John; KLEIN, Christopher; LANGE, Keith; LARSEN, Scott; MAKUJINA, Shah; MORSE, David; O'BRIEN, Maureen; PATEL, Rena; PEIST, Kenneth; PROVOOST, Jonathan; RODNEY, Burton; RYAN, Richard; SHER, Audrey; SWITZER, Joan; VANATTEN, Mary; WILK-ORESCAN, Rosemarie; WINSLOW, Anastasia

to represent the undersigned before

☒ all the competent International Authorities

☐ the International Searching Authority only

☐ the International Preliminary Examining Authority only

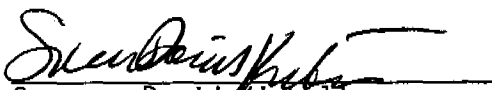
in connection with any and all international applications filed by the undersigned with the following Office

UNITED STATES PATENT AND TRADEMARK OFFICE

as receiving Office

and to make or receive payments on behalf of the undersigned.

Signature(s) (where there are several persons, each of them must sign; next to each signature, indicate the name of the person signing and the capacity in which the person signs, if such capacity is not obvious from reading this power):


Spencer David Kimball

Date:

January 24, 2002

PCT

GENERAL POWER OF ATTORNEY

(for several international applications filed under the Patent Cooperation Treaty)

(PCT Rule 90.5)

The undersigned person(s):

(Family name followed by given name; for a full legal entity, full official designation. The address must include postal code and name of country.)

LOMBARDO, Louis J.
49 West Street
Belle Mead, NJ 08520
UNITED STATES OF AMERICA

hereby appoint(s) the following person as:

☒ agent

☐ common representative

Name and address

(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)

ALGIERI, Aldo; BABAJKO, Suzanne; BABCOCK, Timothy; BOUDREAU, Gerald; BUCHHOLZ, Briana; BELFIELD, Jing; DAMICO, Stephen; DAVIS, Stephen; DUBOFF, Samuel; DOLAN, Peter; FERGUSON, Blair; FURMAN, Theodore; GIBBONS, MAUREEN; HERMENA, Ronald; KILCOYNE, John; KLEIN, Christopher; LANGE, Keith; LARSEN, Scott; MAKUJINA, Shah; MORSE, David; O'BRIEN, Maureen; PATEL, Rena; PEIST, Kenneth; PROVOOST, Jonathan; RODNEY, Burton; RYAN, Richard; SHER, Audrey; SWITZER, Joan; VANATTEN, Mary; WILK-ORESCAN, Rosemarie; WINSLOW, Anastasia

to represent the undersigned before

☒ all the competent International Authorities

☐ the International Searching Authority only

☐ the International Preliminary Examining Authority only

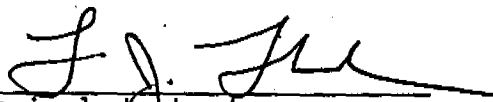
in connection with any and all international applications filed by the undersigned with the following Office

UNITED STATES PATENT AND TRADEMARK OFFICE

as receiving Office

and to make or receive payments on behalf of the undersigned.

Signature(s) (where there are several persons, each of them must sign; next to each signature, indicate the name of the person signing and the capacity in which the person signs, if such capacity is not obvious from reading this power):


Louis J. Lombardo

Date:

January 29, 2002

100
F

PCT

GENERAL POWER OF ATTORNEY

(for several international applications filed under the Patent Cooperation Treaty)

(PCT Rule 90.5)

The undersigned person(s):

(Family name followed by given name; for a full legal entity, full official designation. The address must include postal code and name of country.)

RAWLINS, David B.
219 Vernon Road
Morrisville, PA 19067
UNITED STATES OF AMERICA

hereby appoint(s) the following person as:

☒ agent

☐ common representative

Name and address

(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)

ALGIERI, Aldo; BABAJKO, Suzanne; BABCOCK, Timothy; BOUDREAUX, Gerald; BUCHHOLZ, Briane; BELFIELD, Jing; DAMICO, Stephen; DAVIS, Stephen; DUBOFF, Samuel; DOLAN, Peter; FERGUSON, Blair; FURMAN, Theodore; GIBBONS, MAUREEN; HERMENA, Ronald; KILCOYNE, John; KLEIN, Christopher; LANGE, Keith; LARSEN, Scott; MAKUJINA, Shah; MORSE, David; O'BRIEN, Maureen; PATEL, Rens; PEIST, Kenneth; PROVOOST, Jonathan; RODNEY, Burton; RYAN, Richard; SHER, Audrey; SWITZER, Joan; VANATTEN, Mary; WILK-ORESCAN, Rosemarie; WINSLOW, Anastasia

to represent the undersigned before

☒ all the competent International Authorities

☐ the International Searching Authority only

☐ the International Preliminary Examining Authority only

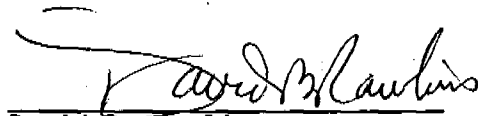
in connection with any and all international applications filed by the undersigned with the following Office

UNITED STATES PATENT AND TRADEMARK OFFICE

as receiving Office

and to make or receive payments on behalf of the undersigned.

Signature(s) (where there are several persons, each of them must sign; next to each signature, indicate the name of the person signing and the capacity in which the person signs, if such capacity is not obvious from reading this power):


David B. Rawlins

Date:

29 JAN 2002

101 ~
TV

PCT

GENERAL POWER OF ATTORNEY

(for several international applications filed under the Patent Cooperation Treaty)

(PCT Rule 90.5)

The undersigned person(s):

(Family name followed by given name; for a full legal entity, full official designation. The address must include postal code and name of country.)

XIAO, Hai-Yun
173 Jonathan Dayton Court,
Princeton, NJ 08540
UNITED STATES OF AMERICA

hereby appoint(s) the following person as:

☒ agent

☐ common representative

Name and address

(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)

ALGIERI, Aldo; BABAJKO, Suzanne; BABCOCK, Timothy; BOUDREAUX, Gerald; BUCHHOLZ, Briana; BELFIELD, Jing; DAMICO, Stephen; DAVIS, Stephen; DUBOFF, Samuel; DOLAN, Peter; FERGUSON, Blair; FURMAN, Theodore; GIBBONS, MAUREEN; HERMENA, Ronald; KILCOYNE, John; KLEIN, Christopher; LANGE, Keith; LARSEN, Scott; MAKUJINA, Shah; MORSE, David; O'BRIEN, Maureen; PATEL, Rena; PEIST, Kenneth; PROVOOST, Jonathan; RODNEY, Burton; RYAN, Richard; SHER, Audrey; SWITZER, Joan; VANATTEN, Mary; WILK-ORESCAN, Rosemarie; WINSLOW, Anastasia

to represent the undersigned before

☒ all the competent International Authorities

☐ the International Searching Authority only

☐ the International Preliminary Examining Authority only

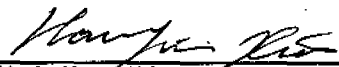
in connection with any and all international applications filed by the undersigned with the following Office

UNITED STATES PATENT AND TRADEMARK OFFICE

as receiving Office

and to make or receive payments on behalf of the undersigned.

Signature(s) (where there are several persons, each of them must sign; next to each signature, indicate the name of the person signing and the capacity in which the person signs, if such capacity is not obvious from reading this power):


Hai-Yun Xiao

Date:

Jan. 29, 2002

PCT

GENERAL POWER OF ATTORNEY

(for several international applications filed under the Patent Cooperation Treaty)

(PCT Rule 90.5)

The undersigned person(s):

(Family name followed by given name; for a full legal entity, full official designation. The address must include postal code and name of country.)

SCHMIDT, Robert Joseph
3 South Deer Place
Hainesport, NJ 08036
UNITED STATES OF AMERICA

hereby appoint(s) the following person as:

☒ agent

☐ common representative

Name and address

(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)

ALGIERI, Aldo; BABAJKO, Suzanne; BABCOCK, Timothy; BOUDREAUX, Gerald; BUCHHOLZ, Briana; BELFIELD, Jing; DAMICO, Stephen; DAVIS, Stephen; DUBOFF, Samuel; DOLAN, Peter; FERGUSON, Blair; FURMAN, Theodore; GIBBONS, MAUREEN; HERMENA, Ronald; KILCOYNE, John; KLEIN, Christopher; LANGE, Keith; LARSEN, Scott; MAKUJINA, Shah; MORSE, David; O'BRIEN, Maureen; PATEL, Rena; PEIST, Kenneth; PROVOOST, Jonathan; RODNEY, Burton; RYAN, Richard; SHER, Audrey; SWITZER, Joan; VANATTEN, Mary; WILK-ORESCAN, Rosemarie; WINSLOW, Anastasia

to represent the undersigned before

☒ all the competent International Authorities

☐ the International Searching Authority only

☐ the International Preliminary Examining Authority only

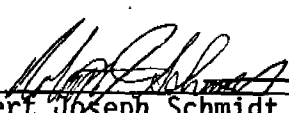
in connection with any and all international applications filed by the undersigned with the following Office

UNITED STATES PATENT AND TRADEMARK OFFICE

as receiving Office

and to make or receive payments on behalf of the undersigned.

Signature(s) (where there are several persons, each of them must sign; next to each signature, indicate the name of the person signing and the capacity in which the person signs, if such capacity is not obvious from reading this power):


Robert Joseph Schmidt

Date:

1/29/02

PCT

GENERAL POWER OF ATTORNEY

(for several international applications filed under the Patent Cooperation Treaty)

(PCT Rule 90.5)

The undersigned person(s):

(Family name followed by given name; for a full legal entity, full official designation. The address must include postal code and name of country.)

WILLIAMS, David Kent
211 Paddock Way
Delran, NJ 08075
UNITED STATES OF AMERICA

hereby appoint(s) the following person as:

☒ agent

☐ common representative

Name and address

(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)

ALGIERI, Aldo; BABAJKO, Suzanne; BABCOCK, Timothy; BOUDREAUX, Gerald; BUCHHOLZ, Briana; BELFIELD, Jing; DAMICO, Stephen; DAVIS, Stephen; DUBOFF, Samuel; DOLAN, Peter; FERGUSON, Blair; FURMAN, Theodore; GIBBONS, MAUREEN; HERMENAU, Ronald; KILCOYNE, John; KLEIN, Christopher; LANGE, Keith; LARSEN, Scott; MAKUJINA, Shah; MORSE, David; O'BRIEN, Maureen; PATEL, Rena; PEIST, Kenneth; PROVOOST, Jonathan; RODNEY, Burton; RYAN, Richard; SHER, Audrey; SWITZER, Joan; VANATTEN, Mary; WILK-ORESCAN, Rosemarie; WINSLOW, Anastasia

to represent the undersigned before

☒ all the competent International Authorities

☐ the International Searching Authority only

☐ the International Preliminary Examining Authority only

in connection with any and all international applications filed by the undersigned with the following Office

UNITED STATES PATENT AND TRADEMARK OFFICE

as receiving Office

and to make or receive payments on behalf of the undersigned.

Signature(s) (where there are several persons, each of them must sign; next to each signature, indicate the name of the person signing and the capacity in which the person signs, if such capacity is not obvious from reading this power):


David Kent Williams

Date:

January 29, 2002

The demand must be filed directly with the competent International Preliminary Examining Authority or, if two or more Authorities are competent, with the one chosen by the applicant. The full name or two-letter code of that Authority may be indicated by the applicant on the line below:

IPEA/ US

PCT

CHAPTER II

DEMAND

under Article 31 of the Patent Cooperation Treaty:
The undersigned requests that the international application specified below be the subject of international preliminary examination according to the Patent Cooperation Treaty and hereby elects all eligible States (except where otherwise indicated).

For International Preliminary Examining Authority use only

Identification of IPEA		Date of receipt of DEMAND	
Box No. I IDENTIFICATION OF THE INTERNATIONAL APPLICATION		Applicant's or agent's file reference LD202 PCT	
International application No. PCT/US02/09497	International filing date (day/month/year) (26.03.02) 26.MARCH.2002	(Earliest) Priority date (day/month/year) (29.03.01) 29.MARCH.01	
Title of invention NOVEL CYANO-SUBSTITUTED DIHYDROPYRIMIDINE COMPOUNDS AND THEIR USE TO TREAT DISEASES			
Box No. II APPLICANT(S)			
Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.) Bristol-Myers Squibb Company P.O. Box 4000 Princeton, NJ 08543-4000 United States of America		Telephone No. 609-252-3453	
		Facsimile No. 609-252-4526	
		Teleprinter No.	
		Applicant's registration No. with the Office	
State (that is, country) of nationality: United States of America		State (that is, country) of residence: United States of America	
Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.) KIMBALL, Spencer, David 13 Charred Oak Lane East Windsor, NJ 08520 UNITED STATES OF AMERICA			
State (that is, country) of nationality: US		State (that is, country) of residence: US	
Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.) LOMBARDO, Louis, J. 49 West Street Belle Mead, NJ 08502 UNITED STATES OF AMERICA			
State (that is, country) of nationality: US		State (that is, country) of residence: US	
☒ Further applicants are indicated on a continuation sheet.			

Continuation of Box No. II APPLICANT(S)

If none of the following sub-boxes is used, this sheet should not be included in the demand.

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

RAWLINS, David, B.
219 Vernon Road
Morrisville, PA 19067
UNITED STATES OF AMERICA

State *(that is, country)* of nationality:
US

State *(that is, country)* of residence:
US

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

XIAO, Hai-Yun
173 Jonathan Dayton Court
Princeton, NJ 08540
UNITED STATES OF AMERICA

State *(that is, country)* of nationality:
CN

State *(that is, country)* of residence:
US

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

SCHMIDT, Robert, Joseph
3 South Deer Place
Hainesport, NJ 08036
UNITED STATES OF AMERICA

State *(that is, country)* of nationality:
US

State *(that is, country)* of residence:
US

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

WILLIAMS, David, Kent
211 Paddock Way
Delran, NJ 08075
UNITED STATES OF AMERICA

State *(that is, country)* of nationality:
US

State *(that is, country)* of residence:
US

☐ Further applicants are indicated on another continuation sheet.

Box No. III AGENT OR COMMON REPRESENTATIVE; OR ADDRESS FOR CORRESPONDENCEThe following person is ☒ agent ☐ common representativeand ☒ has been appointed earlier and represents the applicant(s) also for international preliminary examination.☐ is hereby appointed and any earlier appointment of (an) agent(s)/common representative is hereby revoked.☐ is hereby appointed, specifically for the procedure before the International Preliminary Examining Authority, in addition to the agent(s)/common representative appointed earlier.Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*GIBBONS, Maureen
Bristol-Myers Squibb Company
P.O. Box 4000
Princeton, NJ 08543-4000
United States of America

Telephone No.

609-252-3453

Facsimile No.

609-252-4526

Teleprinter No.

Agent's registration No. with the Office

44,121

☐ Address for correspondence: Mark this check-box where no agent or common representative is/has been appointed and the space above is used instead to indicate a special address to which correspondence should be sent.**Box No. IV BASIS FOR INTERNATIONAL PRELIMINARY EXAMINATION****Statement concerning amendments:***

1. The applicant wishes the international preliminary examination to start on the basis of:

☒ the international application as originally filedthe description ☒ as originally filed☐ as amended under Article 34the claims ☒ as originally filed☐ as amended under Article 19 (together with any accompanying statement)☐ as amended under Article 34the drawings ☒ as originally filed☐ as amended under Article 342. ☐ The applicant wishes any amendment to the claims under Article 19 to be considered as reversed.3. ☐ The applicant wishes the start of the international preliminary examination to be postponed until the expiration of 20 months from the priority date unless the International Preliminary Examining Authority receives a copy of any amendments made under Article 19 or a notice from the applicant that he does not wish to make such amendments (Rule 69.1(d)). *(This check-box may be marked only where the time limit under Article 19 has not yet expired.)*

* Where no check-box is marked, international preliminary examination will start on the basis of the international application as originally filed or, where a copy of amendments to the claims under Article 19 and/or amendments of the international application under Article 34 are received by the International Preliminary Examining Authority before it has begun to draw up a written opinion or the international preliminary examination report, as so amended.

Language for the purposes of international preliminary examination: English.....

☒ which is the language in which the international application was filed.☐ which is the language of a translation furnished for the purposes of international search.☐ which is the language of publication of the international application.☐ which is the language of the translation (to be) furnished for the purposes of international preliminary examination.**Box No. V ELECTION OF STATES**The applicant hereby elects all eligible States *(that is, all States which have been designated and which are bound by Chapter II of the PCT)*

excluding the following States which the applicant wishes not to elect:



Box No. VI CHECK LIST

The demand is accompanied by the following elements, in the language referred to in Box No. IV, for the purposes of international preliminary examination:

- | | | |
|--|---|----------|
| 1. translation of international application | : | 0 sheets |
| 2. amendments under Article 34 | : | 0 sheets |
| 3. copy (or, where required, translation) of amendments under Article 19 | : | 0 sheets |
| 4. copy (or, where required, translation) of statement under Article 19 | : | 0 sheets |
| 5. letter | : | 0 sheets |
| 6. other (specify) | : | 0 sheets |

For International Preliminary
Examining Authority use only

received not received

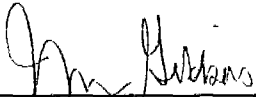
☐	☐
☐	☐
☐	☐
☐	☐
☐	☐
☐	☐

The demand is also accompanied by the item(s) marked below:

- | | |
|--|--|
| 1. ☒ fee calculation sheet | 5. ☐ statement explaining lack of signature |
| 2. ☐ original separate power of attorney | 6. ☐ sequence listing in computer readable form |
| 3. ☐ original general power of attorney | 7. ☐ other (Certification for POA): |
| 4. ☐ copy of general power of attorney; reference number, if any: | |

Box No. VII SIGNATURE OF APPLICANT, AGENT OR COMMON REPRESENTATIVE

Next to each signature, indicate the name of the person signing and the capacity in which the person signs (if such capacity is not obvious from reading the demand).


Maureen Gibbons, Agent

Date: October 26, 2002

For International Preliminary Examining Authority use only

1. Date of actual receipt of DEMAND:

2. Adjusted date of receipt of demand due to CORRECTIONS under Rule 60.1(b):

3. ☐ The date of receipt of the demand is AFTER the expiration of 19 months from the priority date and item 4 or 5, below, does not apply.

☐ The applicant has been informed accordingly.

4. ☐ The date of receipt of the demand is WITHIN the period of 19 months from the priority date as extended by virtue of Rule 80.5.

5. ☐ Although the date of receipt of the demand is after the expiration of 19 months from the priority date, the delay in arrival is EXCUSED pursuant to Rule 82.

For International Bureau use only

Demand received from IPEA on:

These Notes are intended to facilitate the filling in of the demand form and to give some information concerning international preliminary examination under Chapter II of the Patent Cooperation Treaty (PCT). For more detailed information, see the *PCT Applicant's Guide*, a WIPO publication, which is available, together with other PCT related documents, at WIPO's Website: www.wipo.int/pct/en/index.html. The Notes are based on the requirements of the PCT, the Regulations and the Administrative Instructions under the PCT. In case of any discrepancy between these Notes and those requirements, the latter are applicable.

In the demand form and these Notes, "Article", "Rule" and "Section" refer to the provisions of the PCT, the PCT Regulations and the Administrative Instructions, respectively.

Please use a typewriter; check-boxes may be marked by hand with dark ink (Rules 11.9(a) and (b) and 11.14).

The demand form and these Notes may be downloaded from WIPO's Website at the address given above.

IMPORTANT GENERAL INFORMATION

Who May File a Demand? (Article 31(2)(a) and Rule 54): A demand (for international preliminary examination) may only be filed by an applicant who is a national or resident of a PCT Contracting State which is bound by Chapter II of the PCT; furthermore, the international application must have been filed with a receiving Office of, or acting for, a State bound by Chapter II. Where there are two or more applicants (for the same or different elected States) at least one of them must qualify.

Where Must the Demand Be Filed? (Article 31(6)(a)): The demand must be filed with a competent International Preliminary Examining Authority (IPEA). The receiving Office with which the international application was filed will, upon request, give information about the competent IPEA (or see the *PCT Applicant's Guide*, Volume I/B, Annex C). If several IPEAs are competent, the applicant has the choice and the demand must be filed with (and the fees must be paid to) the IPEA chosen by the applicant. The IPEA chosen by the applicant may be identified, preferably by an indication of the name or two-letter code of the IPEA, at the top of the first sheet of the demand in the space provided for that purpose.

When Must the Demand Be Filed? (Article 39(1)): The demand must be filed before the expiration of *19 months from the priority date* in order to extend the time limit for entering the national phase of the PCT procedure from 20 to 30 months from the priority date. *Warning:* if the demand is filed later, the national phase will not be delayed in respect of the elected States and the applicant must enter the national phase before the expiration of the time limit applicable under Article 22 (which is usually 20 months from the priority date).

In Which Language Must the Demand Be Filed? (Rule 55.1): The demand must be filed in the language in which international preliminary examination will be carried out (see Notes to Box No. IV).

What is the Language of Correspondence? (Rules 66.9 and 92.2 and Section 104): Any letter from the applicant to the IPEA must be in the same language as the international application to which it relates. However, where the international preliminary examination will be carried out on the basis of a translation (see Notes to Box No. IV), any letter from the applicant to the IPEA must be in the language of the translation. The IPEA may authorize the use of other languages for letters which do not contain or relate to amendments of the international application. Any letter from the applicant to the International Bureau must be in English or French, at the choice of the applicant. However, if the language of the international application is English, the letter must be in English; if the language of the international application is French, the letter must be in French.

Which Fees Must Be Paid and When? (Rules 57 and 58): Two fees are due in respect of the international preliminary examination: the preliminary examination fee and the handling fee. Both fees must be paid to the IPEA within one month from the date on which the demand is submitted. The Fee Calculation Sheet should be used for that purpose. For details concerning the payment of the fees, see the Notes to that Sheet.

BOX No. I

Applicant's or Agent's File Reference: A file reference may be indicated, if desired. It should not exceed 12 characters. Characters in excess of 12 may be disregarded (Section 109).

Identification of the International Application (Rule 53.6): The international application number must be indicated in Box No. I. Where the demand is filed at a time when the international application number has not yet been notified by the receiving Office, the name of that Office must be indicated instead of the international application number.

International Filing Date and (Earliest) Priority Date (Section 110): Dates must be indicated by the Arabic number of the day, the name of the month and the Arabic number of the year—in that order; after, below or above such indication, the date should be repeated in parentheses, using two-digit Arabic numerals for each of the number of the day, the number of the month and the last two digits of the year, in that order, and separated by periods, slants or hyphens, for example, "20 March 2001 (20.03.01)", "20 March 2001 (20/03/01)" or "20 March 2001 (20-03-01)". Where the international application claims the priority of several earlier applications, the filing date of the earliest application whose priority is claimed must be indicated as the priority date.

Title of the Invention: If a new title has been established by the International Searching Authority, that title must be indicated in Box No. I.

BOX No. II

Applicant(s) (Rule 53.4): All the applicants for the elected States must be indicated in the demand; an applicant named in the request (Form PCT/RO/101) for a State which is not elected need not be named in the demand. It should be noted that the persons named as "inventor only" in the request need not be named in the demand.

Make in Box No. II of the demand the required indications as appearing in Boxes Nos. II and III of the request. The Notes to the request apply *mutatis mutandis*. If there are two or more applicants for the States elected in the demand, give the required indications for each of them; if there are more than



three applicants, make the required indications on the "Continuation Sheet".

If different applicants are indicated in the request for different designated States, indicate in Box No. II of the demand only the applicants for the States elected in Box No. V (no indication of the States for which a person is applicant need be made, because those indications have been made in the request).

Applicant's registration number with the Office (Rule 53.4): Where the applicant is registered with the national or regional Office that is acting as International Preliminary Examining Authority, the demand may indicate the number or other indication under which the applicant is so registered.

BOX No. III

Agent or Common Representative (Rules 53.5, 90.1 and 90.2): Mark the applicable check-boxes to indicate *first* whether the person named in this Box is agent or common representative, *then* whether that person *has been appointed earlier* (i.e., during the procedure under Chapter I), or *is appointed in the demand* and any earlier appointment of another person is revoked, or *is appointed specifically for the procedure before the IPEA* (without revocation of any earlier appointment), in addition to the person(s) appointed earlier.

Where an additional person is appointed specifically for the procedure before the IPEA, all notifications issued by the IPEA will be addressed only to that additional person.

A separate power of attorney must be filed with the IPEA, the International Bureau or the receiving Office, if the person appointed at the time the demand is filed (i.e., was not appointed earlier) signs the demand on behalf of the applicant (Rule 90.4).

Agent's registration number with the Office (Rule 53.5): Where the agent is registered with the national or regional Office that is acting as International Preliminary Examining Authority, the demand may indicate the number or other indication under which the agent is so registered.

Address for Correspondence (Rule 4.4(d) and Section 108): Where an agent is appointed, any correspondence intended for the applicant will be sent to the address indicated for that agent (or for the first-mentioned agent, if more than one is appointed). Where one of two or more applicants is appointed as common representative, the address indicated for that applicant in Box No. III will be used.

Where no agent or common representative is appointed, any correspondence will be sent to the address, indicated in Box No. II, of the applicant (if only one person is named as applicant) or of the applicant who is considered to be common representative (if there are two or more persons named as applicants). However, if the applicant wishes correspondence to be sent to a different address in such a case, that address may be indicated in Box No. III instead of the designation of an agent or common representative. In this case, and only in this case, the last check-box of Box No. III must be marked (that is, the last check-box must not be marked if either of the check-boxes "agent" or "common representative" in Box No. III has been marked).

BOX No. IV

Statement Concerning Amendments (Rules 53.2(a)(v), 53.9, 62, 66.1 and 69.1): The international preliminary examination will start on the basis of the international application

as filed or, if amendments have been filed, as amended. Mark the appropriate check-box(es) to enable the IPEA to determine when and on what basis it can start international preliminary examination.

Mark the corresponding check-box(es) under No. 1 where the international preliminary examination should start on the basis of the international application as originally filed or where amendments are to be taken into account, as the case may be. Where amendments are to be taken into account, the applicant must submit *with the demand* a copy of amendments to the claims under Article 19 (Rule 53.9(a)(i)) and/or the amendments of the international application under Article 34 (Rule 53.9(c)), as the case may be. If a check-box is marked but the demand is not accompanied by the documents referred to, the start of international preliminary examination will be delayed until the IPEA receives them.

Mark check-box No. 2 if amendments of the claims under Article 19 have been filed with the International Bureau during the Chapter I procedure, but the applicant does not want these amendments to be taken into account for the purpose of international preliminary examination when the latter starts (Rule 53.9(a)(ii)).

Mark check-box No. 3 where the time limit for filing amendments of the claims under Article 19 has not expired at the time the demand is filed and the applicant wants to keep the option for the filing of such amendments open; the IPEA is thus requested to postpone the start of international preliminary examination (Rules 53.9(b) and 69.1(d)). It should be noted that the examination will start in any event after the expiration of 20 months from the priority date even where the time limit for filing amendments has not yet expired or no amendments have been received by the IPEA.

If no check-box is marked, refer to the footnote at the bottom of the Box.

Language for the Purposes of International Preliminary Examination (Rule 55.2): Where neither the language in which the international application is filed nor the language in which the international application is published is accepted by the IPEA that is to carry out the international preliminary examination, the applicant must furnish with the demand a translation of the international application into a language which is both a language accepted by that Authority and a language of publication.

Where such translation has already been furnished to the International Searching Authority for the purposes of carrying out international search and the IPEA is part of the same Office or intergovernmental organization as the International Searching Authority, the applicant need not furnish another translation. In such a case the international preliminary examination is carried out on the basis of the translation furnished for the purposes of international search.

The language for the purposes of international preliminary examination should be indicated in Box No. IV, on the dotted line, and the corresponding check-box should be marked.

Language of Amendments (Rules 55.3 and 66.9): Amendments and letters relating thereto must be in the same language as that in which the international preliminary examination is carried out, as explained in the preceding paragraphs.



Time Limit for Furnishing Translation of the International Application (Rule 55.2): Any required translation of the international application should be furnished (by the applicant) together with the demand. If it is not so furnished, the IPEA will invite the applicant to furnish it within a time limit which shall not be less than one month from the date of the invitation. That time limit may be extended by the IPEA.

BOX No. V

Election of States (Rule 53.7): Only States which are bound by Chapter II of the PCT *and* which have been designated in the international application (that is, States whose designations have been made under Rule 4.9(a), confirmed under Rule 4.9(c) or considered as having been made under Rule 32.2(a)(i)) can be elected. They are the "eligible States".

For the convenience and protection of applicants, Box No. V contains a statement to the effect that all eligible States are elected. It is only where the applicant does not wish to elect certain eligible States that the name(s) or two-letter code(s) of those States must be indicated after the words "wishes not to elect".

The indication in the demand of the kind of protection or treatment desired for any elected State is not required since it follows the indication made when designating that State in the international application.

BOX No. VI

Check List: It is recommended that this Box be filled in carefully in order for the IPEA to determine as soon as possible whether it is in possession of the documents on the basis of which the applicant wishes international preliminary examination to start.

Where the international application contains disclosure of one or more nucleotide and/or amino acid sequences, and a copy of the sequence listing in computer readable form complying with the standard provided for in the Administrative Instructions is required by the IPEA, the applicant may furnish the listing in computer readable form to the IPEA with the demand. If this is the case, check-box No. 5 must be marked.

BOX No. VII

Signature (Rules 53.8, 90.3(a) and 90.4(a)): The demand must be signed by the applicant or by his agent; if there are two or more applicants, the common representative may sign the demand. If the demand is not signed by (all) the persons who are applicants for the elected States (a person who is applicant only for a State which is not elected need not sign the demand), a power of attorney signed by that (all those) applicant(s) must be filed with the IPEA, with the International Bureau or with the receiving Office unless the agent has previously been appointed.



PCT

CHAPTER II

FEE CALCULATION SHEET

Annex to the Demand

International application No. PCT/US02/09497 Applicant's or agent's file reference LD202 PCT Applicant Bristol-Myers Squibb Company CALCULATION OF PRESCRIBED FEES 1. Preliminary examination fee 490.00 P 2. Handling fee (<i>Applicants from certain States are entitled to a reduction of 75% of the handling fee. Where the applicant is (or all applicants are) so entitled, the amount to be entered at H is 25% of the handling fee.</i>) 146.00 H 3. Total of prescribed fees Add the amounts entered at P and H and enter total in the TOTAL box..... 636.00 TOTAL	For International Preliminary Examining Authority use only Date stamp of the IPEA								
MODE OF PAYMENT <table style="width: 100%;"> <tr> <td>☒ authorization to charge deposit account with the IPEA (see below)</td> <td>☐ cash</td> </tr> <tr> <td>☐ cheque</td> <td>☐ revenue stamps</td> </tr> <tr> <td>☐ postal money order</td> <td>☐ coupons</td> </tr> <tr> <td>☐ bank draft</td> <td>☐ other (specify):</td> </tr> </table>		☒ authorization to charge deposit account with the IPEA (see below)	☐ cash	☐ cheque	☐ revenue stamps	☐ postal money order	☐ coupons	☐ bank draft	☐ other (specify):
☒ authorization to charge deposit account with the IPEA (see below)	☐ cash								
☐ cheque	☐ revenue stamps								
☐ postal money order	☐ coupons								
☐ bank draft	☐ other (specify):								
AUTHORIZATION TO CHARGE (OR CREDIT) DEPOSIT ACCOUNT (<i>This mode of payment may not be available at all IPEAs</i>) <table style="width: 100%;"> <tr> <td style="width: 50%; vertical-align: top;"> ☒ Authorization to charge the total fees indicated above. ☒ (<i>This check-box may be marked only if the conditions for deposit accounts of the IPEA so permit</i>) Authorization to charge any deficiency or credit any overpayment in the total fees indicated above. </td> <td style="width: 50%; vertical-align: top;"> IPEA/ <u>US</u> Deposit Account No.: <u>19-3880</u> Date: <u>October 28, 2002</u> Name: <u>Maureen Gibbons</u> Signature: <u><i>Maureen Gibbons</i></u> </td> </tr> </table>		☒ Authorization to charge the total fees indicated above. ☒ (<i>This check-box may be marked only if the conditions for deposit accounts of the IPEA so permit</i>) Authorization to charge any deficiency or credit any overpayment in the total fees indicated above.	IPEA/ <u>US</u> Deposit Account No.: <u>19-3880</u> Date: <u>October 28, 2002</u> Name: <u>Maureen Gibbons</u> Signature: <u><i>Maureen Gibbons</i></u>						
☒ Authorization to charge the total fees indicated above. ☒ (<i>This check-box may be marked only if the conditions for deposit accounts of the IPEA so permit</i>) Authorization to charge any deficiency or credit any overpayment in the total fees indicated above.	IPEA/ <u>US</u> Deposit Account No.: <u>19-3880</u> Date: <u>October 28, 2002</u> Name: <u>Maureen Gibbons</u> Signature: <u><i>Maureen Gibbons</i></u>								



3ET

NOTES TO THE FEE CALCULATION
(ANNEX TO FORM PCT/IPEA/401)

The purpose of the fee calculation sheet is to help the applicant to identify the prescribed fees and to calculate the amounts to be paid. It is strongly recommended that the applicant complete, by entering the appropriate amounts in the boxes provided, and submit the fee calculation sheet at the time of filing of the demand. This will help the International Preliminary Examining Authority (IPEA) to verify the calculations and to identify any error in them.

CALCULATION OF PRESCRIBED FEES

Two fees must be paid for international preliminary examination:

- (i) the preliminary examination fee for the benefit of the IPEA (Rule 58.1);
- (ii) the handling fee for the benefit of the International Bureau (Rule 57).

Both fees must be paid to the IPEA within one month from the date on which the demand is submitted. The amount payable is the amount applicable on the date of submittal (Rules 57.3 and 58.1(b)). The fees must be paid in a currency acceptable to the IPEA.

Information about the amount of those fees or about equivalent amounts in other currencies can be obtained from the IPEA or the receiving Office. This information is also published in the *PCT Applicant's Guide*, Volume I/B, Annex E, and from time to time in Section IV of the *PCT Gazette*.

Box P: The amount of the preliminary examination fee must be entered in Box P.

Box H: The amount of the handling fee must be entered in Box H.

Reduction of the Handling Fee for Applicants from Certain States: An applicant who is a natural person and who is a national of and resides in a State whose per capita national income is below 3,000 US dollars (according to the average per capita national income figures used by the United Nations for determining its scale of assessments for the contributions payable for the years 1995, 1996 and 1997) is entitled, in accordance with the Schedule of Fees, to a reduction of 75% of certain PCT fees including the handling fee. If there are several applicants, each must satisfy the above-mentioned criteria. The reduction of the handling fee will be automatically available to any applicant (or applicants) who is (or are) so entitled on the basis of the indications of name, nationality and residence given in Box No. II of the demand.

The fee reduction will be available even if one or more of the applicants are not from PCT Contracting States, provided that each of them is a national and resident of a State that meets the above-mentioned requirements and that at least one of the applicants is a national or resident of a PCT Contracting State and thus is entitled to file an international application.

Natural persons who are nationals of and reside in the following PCT Contracting States are eligible: AL Albania, AM Armenia, AZ Azerbaijan, BA Bosnia and Herzegovina, BF Burkina Faso, BG Bulgaria, BJ Benin, BR Brazil,

BY Belarus, BZ Belize, CF Central African Republic, CG Congo, CI Côte d'Ivoire, CM Cameroon, CN China, CO Colombia, CR Costa Rica, CU Cuba, CZ Czech Republic, DM Dominica, DZ Algeria, EC Ecuador, EE Estonia, GA Gabon, GD Grenada, GE Georgia, GH Ghana, GM Gambia, GN Guinea, GW Guinea-Bissau, HR Croatia, HU Hungary, ID Indonesia, IN India, KE Kenya, KG Kyrgyzstan, KP Democratic People's Republic of Korea, KZ Kazakhstan, LC Saint Lucia, LK Sri Lanka, LR Liberia, LS Lesotho, LT Lithuania, LV Latvia, MA Morocco, MD Republic of Moldova, MG Madagascar, MK The former Yugoslav Republic of Macedonia, ML Mali, MN Mongolia, MR Mauritania, MW Malawi, MX Mexico, MZ Mozambique, NE Niger, PL Poland, RO Romania, RU Russian Federation, SD Sudan, SK Slovakia, SL Sierra Leone, SN Senegal, SZ Swaziland, TD Chad, TG Togo, TJ Tajikistan, TM Turkmenistan, TR Turkey, TZ United Republic of Tanzania, UA Ukraine, UG Uganda, UZ Uzbekistan, VN Viet Nam, YU Yugoslavia, ZA South Africa and ZW Zimbabwe. As far as other States are concerned, inquiries should be addressed to the International Bureau.

Calculation of the Handling Fee in Case of Fee Reduction: Where the applicant is (or all applicants are) entitled to a reduction of the handling fee, the total to be entered at Box H is 25% of the handling fee.

Total Box: The total of the amounts inserted in Boxes P and H is the amount which must be paid to the IPEA.

MODE OF PAYMENT

In order to help the IPEA identify the mode of payment of the prescribed fees, it is recommended to mark the applicable check-box(es).

AUTHORIZATION TO CHARGE (OR CREDIT) DEPOSIT ACCOUNT

The applicant should check whether the IPEA allows the use of deposit accounts for payment of PCT fees. In addition, it is recommended that the applicant check what are the specific conditions applicable to the use of deposit accounts with the IPEA since not all IPEAs provide the same services.

Finally, if the IPEA is not the same national Office or intergovernmental organization as that with which the international application was filed, the deposit account with the receiving Office cannot be charged for the purpose of paying the preliminary examination and handling fees due to the IPEA.

The IPEA will not charge fees to deposit accounts unless the deposit account authorization is signed and indicates the deposit account number.



PATENT COOPERATION TREATY

PCT

NOTIFICATION CONCERNING
SUBMISSION OR TRANSMITTAL
OF PRIORITY DOCUMENT

(PCT Administrative Instructions, Section 411)

From the INTERNATIONAL BUREAU

To:

GIBBONS, Maureen
Bristol-Myers Squibb Company
P.O. Box 4000
Rt. 206 & Province Line Road
Princeton, NJ 08543-4000
United States of America

Date of mailing (day/month/year) 06 September 2002 (06.09.02)	IMPORTANT NOTIFICATION
Applicant's or agent's file reference LD202	
International application No. PCT/US02/09497	International filing date (day/month/year) 26 March 2002 (26.03.02)
International publication date (day/month/year) Not yet published	Priority date (day/month/year) 29 March 2001 (29.03.01)
Applicant BRISTOL-MYERS SQUIBB COMPANY et al	

1. The applicant is hereby notified of the date of receipt (except where the letters "NR" appear in the right-hand column) by the International Bureau of the priority document(s) relating to the earlier application(s) indicated below. Unless otherwise indicated by an asterisk appearing next to a date of receipt, or by the letters "NR", in the right-hand column, the priority document concerned was submitted or transmitted to the International Bureau in compliance with Rule 17.1(a) or (b).
2. This updates and replaces any previously issued notification concerning submission or transmittal of priority documents.
3. An asterisk(*) appearing next to a date of receipt, in the right-hand column, denotes a priority document submitted or transmitted to the International Bureau but not in compliance with Rule 17.1(a) or (b). In such a case, **the attention of the applicant is directed** to Rule 17.1(c) which provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.
4. The letters "NR" appearing in the right-hand column denote a priority document which was not received by the International Bureau or which the applicant did not request the receiving Office to prepare and transmit to the International Bureau, as provided by Rule 17.1(a) or (b), respectively. In such a case, **the attention of the applicant is directed** to Rule 17.1(c) which provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.

<u>Priority date</u>	<u>Priority application No.</u>	<u>Country or regional Office or PCT receiving Office</u>	<u>Date of receipt of priority document</u>
29 Marc 2001 (29.03.01)	60/279,956	US	14 June 2002 (14.06.02)

RECEIVED
BMS PATENT LAW

SEP 23 2002

Docketed Item _____
Due Date _____

Attorney The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No. (41-22) 740.14.35	Authorized officer S. Mandallaz Telephone No. (41-22) 338.83.38
--	---



PATENT COOPERATION TREATY

From the INTERNATIONAL SEARCHING AUTHORITY

To:
MAUREEN GIBBONS
BRISTOL-MYERS SQUIBB COMPANY
P.O. BOX 4000
RT.206 & PROVINCE LINE ROAD
PRINCETON, NJ 08543-4000

BMS PATENT LAW

PCT

NOTIFICATION OF TRANSMITTAL OF
THE INTERNATIONAL SEARCH REPORT
OR THE DECLARATION

Docketed Item

US-105

Due Date

10/12/02

(PCT Rule 44.1)

Attorney

(M6)

Date of Mailing
(day/month/year)

12 JUL 2002

Applicant's or agent's file reference
LD202

FOR FURTHER ACTION See paragraphs 1 and 4 below

International application No.
PCT/US02/09497

International filing date
(day/month/year)

26 March 2002 (26.03.2002)

Applicant
BRISTOL-MYERS SQUIBB COMPANY

1. ☒ The applicant is hereby notified that the international search report has been established and is transmitted herewith.

Filing of amendments and statement under Article 19:

The applicant is entitled, if he so wishes, to amend the claims of the international application (see Rule 46):

When? The time limit for filing such amendments is normally two months from the date of transmittal of the international search report.

Where? Directly to the International Bureau of WIPO, 34, chemin des Colombettes
1211 Geneva 20, Switzerland, Facsimile No.: (41-22) 740.14.35

For more detailed instructions, see the notes on the accompanying sheet.

2. ☐ The applicant is hereby notified that no international search report will be established and that the declaration under Article 17(2)(a) to that effect is transmitted herewith.

3. ☐ With regard to the protest against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

- ☐ the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.
☐ no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. **Reminders**

Shortly after 18 months from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau as provided in Rules 90 bis.1 and 90 bis.3, respectively, before the completion of the technical preparations for international publication.

Within 19 months from the priority date, but only in respect of some designated Offices, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase until 30 months from the priority date (in some Offices even later); otherwise the applicant must, within 20 months from the priority date, perform the prescribed acts for entry into the national phase before those designated Offices.

In respect of other designated Offices, the time limit of 30 months (or later) will apply even if no demand is filed within 19 months.

See the Annex to Form PCT/IB/301 and, for details about the applicable time limits, Office by Office, see the *PCT Applicant's Guide*, Volume II, National Chapters and the WIPO Internet site.

Name and mailing address of the ISA/US
Commissioner for Patents
Box PCT
Washington, D.C. 20231
Facsimile No. (703)305-3230

Authorized officer
M. Sund Shah

Telephone No. 703-308-0196

4

1

2

3

4

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference LD202	FOR FURTHER ACTION	see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.
International application No. PCT/US02/09497	International filing date (day/month/year) 26 March 2002 (26.03.2002)	(Earliest) Priority Date (day/month/year) 29 March 2001 (29.03.2001)
Applicant BRISTOL-MYERS SQUIBB COMPANY		

This international search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 2 sheets.



It is also accompanied by a copy of each prior art document cited in this report.

1. Basis of the Report

a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.



the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing:



contained in the international application in written form.



filed together with the international application in computer readable form.



furnished subsequently to this Authority in written form.



furnished subsequently to this Authority in computer readable form.



the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.



the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

2. ☐ Certain claims were found unsearchable (See Box I).

3. ☐ Unity of invention is lacking (See Box II).

4. With regard to the **title**,



the text is approved as submitted by the applicant.



the text has been established by this Authority to read as follows:

5. With regard to the **abstract**,



the text is approved as submitted by the applicant.



the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No. _____



as suggested by the applicant.



because the applicant failed to suggest a figure.



because this figure better characterizes the invention.



None of the figures



INTERNATIONAL SEARCH REPORT

International application No.

PCT/US02/09497

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : C07D 239/42, 409/04, 401/04, 403/12; A61K 31/505, 31/506; A61P 9/14

US CL : 514/274; 544/315, 318

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)

U.S. : 514/274; 544/315, 318

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 practicable, search terms used)
CAS ONLINE, EAST (IS&R)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	Chem. Abstr. Vol. 100, No. 15, TARASOVA, O. A. et al. 'Tetrahydropyrimidine-2-thiones from Tertiary Acetylene Alcohols and Thiourea'. April 1984, page 588, Abstract No. 121004w.	1-26
A	Chem. Abstr. Vol. 100, No. 15, RISE, F. et al. 'Introduction of Carbon Substituents into Pyrimidines by Grignard Reagents'. April 1984, page 588, Abstract No. 121003v.	1-26
A	Chem. Abstr. Vol. 112, No. 17, IBRAHIM, N. S. et al. 'Reaction of Isothiocyanates with Active Methylene Reagent: A New Approach for the Synthesis of Pyrazole, Pyrimidine, and Pyrazolo[1,5-a]pyrimidine Derivatives'. April 1990, page 714, Abstract No. 158194g.	1-26
A	KAPPE, C. O. et al. Synthesis and Reactions of "Biginelli-Compounds". Part I. Journal of Heterocyclic Chemistry, January-February 1989, Vol. 26, No. 1, pages 55-64, especially compounds 24 & 25 on page 59.	1-26

☐ 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	"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
"B" earlier application or patent published on or after the international filing date	"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
"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)	"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
"O" document referring to an oral disclosure, use, exhibition or other means	"&" document member of the same patent family
"P" document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search

22 June 2002 (22.06.2002)

Date of mailing of the international search report

12 JUL 2002

Name and mailing address of the ISA/US

Commissioner of Patents and Trademarks
Box PCT
Washington, D.C. 20231

Facsimile No. (703)305-3230

Authorized officer

Mukund Shah

Telephone No. 703-308-1235

91.727 (3)

PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

RECEIVED
BMS PATENT LAW

PCT

To:
MAUREEN GIBBONS
BRISTOL-MYERS SQUIBB COMPANY
P.O. BOX 4000
RT.206 & PROVINCE LINE ROAD
PRINCETON, NJ 08543-4000

JAN 02 2003

NOTIFICATION OF TRANSMITTAL OF
INTERNATIONAL PRELIMINARY
EXAMINATION REPORT

Docketed Item

Due Date

(PCT Rule 71.1)

Attorney

Date of Mailing
(day/month/year)

26 DEC 2002

Applicant's or agent's file reference

LD202

IMPORTANT NOTIFICATION

International application No.

International filing date (day/month/year)

Priority date (day/month/year)

PCT/US02/09497

26 March 2002 (26.03.2002)

29 March 2001 (29.03.2001)

Applicant

BRISTOL-MYERS SQUIBB COMPANY

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.
2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.
3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.
4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices)(Article 39(1))(see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

Name and mailing address of the IPEA/US
Commissioner of Patents and Trademarks
Box PCT
Washington, D.C. 20231

Facsimile No. (703)305-3230

Authorized officer

Mukund Shah

Telephone No. 703-308-1235

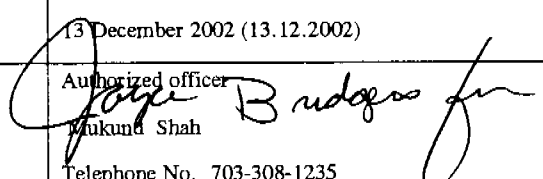
Form PCT/IPEA/416 (July 1992)

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference LD202	FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)	
International application No. PCT/US02/09497	International filing date (day/month/year) 26 March 2002 (26.03.2002)	Priority date (day/month/year) 29 March 2001 (29.03.2001)
International Patent Classification (IPC) or national classification and IPC IPC(7): C07D 239/42, 409/04, 401/04, 403/12; A61K 31/505, 31/506; A61P 9/14. and US Cl.: 514/274; 544/231, 315, 318.		
Applicant BRISTOL-MYERS SQUIBB COMPANY		
1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36. 2. This REPORT consists of a total of <u>3</u> sheets, including this cover sheet. ☐ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT). These annexes consist of a total of <u>0</u> sheets.		
3. This report contains indications relating to the following items: I ☒ Basis of the report II ☐ Priority III ☐ Non-establishment of report with regard to novelty, inventive step and industrial applicability IV ☐ Lack of unity of invention V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement VI ☐ Certain documents cited VII ☐ Certain defects in the international application VIII ☐ Certain observations on the international application		
Date of submission of the demand 28 October 2002 (28.10.2002)	Date of completion of this report 13 December 2002 (13.12.2002)	
Name and mailing address of the IPEA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703)305-3230	Authorized officer  Mukund Shah Telephone No. 703-308-1235	

Form PCT/IPEA/409 (cover sheet)(July 1998)



INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.

PCT/US02/09497

I. Basis of the report

1. With regard to the elements of the international application:*



the international application as originally filed.



the description:

pages 1-69 as originally filed

pages NONE, filed with the demand

pages NONE, filed with the letter of _____.



the claims:

pages 70-81, as originally filed

pages NONE, as amended (together with any statement) under Article 19

pages NONE, filed with the demand

pages NONE, filed with the letter of _____.



the drawings:

pages NONE, as originally filed

pages NONE, filed with the demand

pages NONE, filed with the letter of _____.



the sequence listing part of the description:

pages NONE, as originally filed

pages NONE, filed with the demand

pages NONE, filed with the letter of _____.

2. With regard to the language, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language _____ which is:



the language of a translation furnished for the purposes of international search (under Rule 23.1(b)).



the language of publication of the international application (under Rule 48.3(b)).



the language of the translation furnished for the purposes of international preliminary examination (under Rules 55.2 and/or 55.3).

3. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:



contained in the international application in printed form.



filed together with the international application in computer readable form.



furnished subsequently to this Authority in written form.



furnished subsequently to this Authority in computer readable form.



The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.



The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. ☒ The amendments have resulted in the cancellation of:

the description, pages NONE



the claims, Nos. NONE



the drawings, sheets/fig NONE

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).**

* Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17).

** Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/US02/09497**V. Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement****1. STATEMENT**

Novelty (N)	Claims <u>1-26</u>	YES
	Claims <u>NONE</u>	NO
Inventive Step (IS)	Claims <u>1-26</u>	YES
	Claims <u>NONE</u>	NO
Industrial Applicability (IA)	Claims <u>1-26</u>	YES
	Claims <u>NONE</u>	NO

2. CITATIONS AND EXPLANATIONS

Claims 1-26 meet the criteria set out in PCT Article 33(2)-(4), because the prior art does not teach or fairly suggest compounds of substituted 5-cyano-2-oxo (or thio or amino)-3,6-dihydro-2H-pyrimidine, and their pharmaceutical compositions as well as methods of use. The closest reference, **Kappe et al.** (J. Het. Chem.), discloses an intermediate, compound #25, on page 59. While said intermediate is a substituted 5-cyano-2-oxo-3,6-dihydro-pyrimidine, it lacks a substituent corresponding to the claimed R₄. With no bridging reference, there is no motivation for one skilled in the art to modify Kappe's intermediate. Thus, the instant claims have both novelty and an inventive step.

All claims meet the criteria for industrial applicability since the claimed compounds can be made by pharmaceutical industries, and used to treat proliferative diseases.

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

To:

GIBBONS, Maureen
Bristol-Myers Squibb Company
P.O. Box 4000
Rt. 206 & Province Line Road
Princeton, NJ 08543-4000
ETATS-UNIS D'AMERIQUE

File: LD202 PCT



(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
10 October 2002 (10.10.2002)

PCT

(10) International Publication Number
WO 02/079149 A3

(51) International Patent Classification⁷: **C07D 239/42**,
409/04, 401/04, 403/12, A61K 31/505, 31/506, A61P 9/14

(74) Agents: **GIBBONS, Maureen** et al.; Bristol-Myers
Squibb Company, P.O. Box 4000, Rt. 206 & Province Line
Road, Princeton, NJ 08543-4000 (US).

(21) International Application Number: PCT/US02/09497

(22) International Filing Date: 26 March 2002 (26.03.2002)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/279,956 29 March 2001 (29.03.2001) US

(71) Applicant (for all designated States except US): **BRIS-
TOL-MYERS SQUIBB COMPANY** [US/US]; P.O. Box
4000, Rt. 206 & Province Line Road, Princeton, NJ 08543-
4000 (US).

(72) Inventors; and

(75) Inventors/Applicants (for US only): **KIMBALL,
Spencer, David** [US/US]; 13 Charred Oak Lane, East
Windsor, NJ 08520 (US). **LOMBARDO, Louis, J.**
[US/US]; 49 West Street, Belle Mead, NJ 08502 (US).
RAWLINS, David, B [US/US]; 219 Vernon Road,
Morrisville, PA 19067 (US). **XIAO, Hai-Yun** [CN/US];
173 Jonathan Dayton Court, Princeton, NJ 08540 (US).
SCHMIDT, Robert, Joseph [US/US]; 3 South Deer
Place, Hainesport, NJ 08036 (US). **WILLIAMS, David,
Kent** [US/US]; 211 Paddock Way, Delran, NJ 08075 (US).

(81) Designated States (national): AE, AG, AL, AM, AT, AU,
AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU,
CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH,
GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC,
LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW,
MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG,
SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ,
VN, YU, ZA, ZM, ZW.

(84) Designated States (regional): ARIPO patent (GH, GM,
KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW),
Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM),
European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR,
GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent
(BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR,
NE, SN, TD, TG).

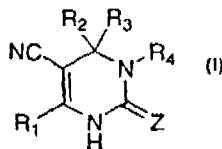
Published:

— with international search report

(88) Date of publication of the international search report:
27 February 2003

For two-letter codes and other abbreviations, refer to the "Guid-
ance Notes on Codes and Abbreviations" appearing at the begin-
ning of each regular issue of the PCT Gazette.

(54) Title: NOVEL CYANO-SUBSTITUTED DIHYDROPYRIMIDINE COMPOUNDS AND THEIR USE TO TREAT DISEASES



(57) Abstract: The present invention provides compounds of formula (I) and pharmaceutically acceptable salts thereof. The formula I compounds induce mitotic arrest thereby making them useful as anti-cancer agents. The formula I compounds are also useful for the treatment of other diseases which can be treated by inducing mitotic arrest.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US02/09497

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : C07D 239/42, 409/04, 401/04, 403/12; A61K 31/505, 31/506; A61P 9/14
US CL : 514/274; 544/315, 318

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)

U.S. : 514/274; 544/315, 318

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 practicable, search terms used)
CAS ONLINE, EAST (IS&R)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	Chem. Abstr. Vol. 100, No. 15, TARASOVA, O. A. et al. 'Tetrahydropyrimidine-2-thiones from Tertiary Acetylene Alcohols and Thiourea'. April 1984, page 588, Abstract No. 121004w.	1-26
A	Chem. Abstr. Vol. 100, No. 15, RISE, F. et al. 'Introduction of Carbon Substituents into Pyrimidines by Grignard Reagents'. April 1984, page 588, Abstract No. 121003v.	1-26
A	Chem. Abstr. Vol. 112, No. 17, IBRAHIM, N. S. et al. 'Reaction of Isothiocyanates with Active Methylene Reagent: A New Approach for the Synthesis of Pyrazole, Pyrimidine, and Pyrazolo[1,5-a]pyrimidine Derivatives'. April 1990, page 714, Abstract No. 158194g.	1-26
A	KAPPE, C. O. et al. Synthesis and Reactions of "Biginelli-Compounds". Part I. Journal of Heterocyclic Chemistry, January-February 1989, Vol. 26, No. 1, pages 55-64, especially compounds 24 & 25 on page 59.	1-26

☐ 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 application or patent published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T"

later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X"

document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y"

document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&"

document member of the same patent family

Date of the actual completion of the international search

22 June 2002 (22.06.2002)

Date of mailing of the international search report

12 JUL 2002

Name and mailing address of the ISA/US

Commissioner of Patents and Trademarks
Box PCT
Washington, D.C. 20231

Facsimile No. (703)305-3230

Authorized officer

Mukund Shah

Telephone No. 703-308-1235



(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
10 October 2002 (10.10.2002)

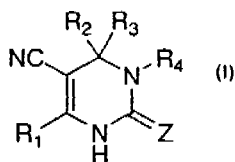
PCT

(10) International Publication Number
WO 02/079149 A2

- (51) International Patent Classification⁷: **C07D**
- (21) International Application Number: PCT/US02/09497
- (22) International Filing Date: 26 March 2002 (26.03.2002)
- (25) Filing Language: English
- (26) Publication Language: English
- (30) Priority Data:
60/279,956 29 March 2001 (29.03.2001) US
- (71) Applicant (for all designated States except US): **BRISTOL-MYERS SQUIBB COMPANY** [US/US]; P.O. Box 4000, Rt. 206 & Province Line Road, Princeton, NJ 08543-4000 (US).
- (72) Inventors; and
- (75) Inventors/Applicants (for US only): **KIMBALL, Spencer, David** [US/US]; 13 Charred Oak Lane, East Windsor, NJ 08520 (US). **LOMBARDO, Louis, J.** [US/US]; 49 West Street, Belle Mead, NJ 08502 (US). **RAWLINS, David, B** [US/US]; 219 Vernon Road, Morrisville, PA 19067 (US). **XIAO, Hai-Yun** [CN/US]; 173 Jonathan Dayton Court, Princeton, NJ 08540 (US). **SCHMIDT, Robert, Joseph** [US/US]; 3 South Deer Place, Hainesport, NJ 08036 (US). **WILLIAMS, David, Kent** [US/US]; 211 Paddock Way, Delran, NJ 08075 (US).
- (74) Agents: **GIBBONS, Maureen** et al.; Bristol-Myers Squibb Company, P.O. Box 4000, Rt. 206 & Province Line Road, Princeton, NJ 08543-4000 (US).
- (81) Designated States (national): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW.
- (84) Designated States (regional): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).
- Published:**
— without international search report and to be republished upon receipt of that report
- For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 02/079149 A2

(54) Title: NOVEL CYANO-SUBSTITUTED DIHYDROPYRIMIDINE COMPOUNDS AND THEIR USE TO TREAT DISEASES



(57) Abstract: The present invention provides compounds of formula (I) and pharmaceutically acceptable salts thereof. The formula I compounds induce mitotic arrest thereby making them useful as anti-cancer agents. The formula I compounds are also useful for the treatment of other diseases which can be treated by inducing mitotic arrest.

**NOVEL CYANO-SUBSTITUTED DIHYDROPYRIMIDINE COMPOUNDS
AND THEIR USE TO TREAT DISEASES**

RELATED APPLICATIONS

5

This application claims the benefit under 35 U.S.C. Section 119(e) of U.S. Provisional Patent Application No. 60/279,956 filed March 29, 2001.

FIELD OF INVENTION

10

This invention relates to novel compounds that interrupt mitosis thereby making the compounds useful for the treatment of proliferative diseases, such as cancer.

15

BACKGROUND

Cell proliferation and programmed cell death play important roles in the growth and development of an organism. In proliferative diseases such as cancer, the processes of cell proliferation and/or programmed cell death are often perturbed. For example, a cancer cell may have unregulated cell division through either the overexpression of a positive regulator of the cell cycle or the loss of a negative regulator of the cell cycle, perhaps by mutation. Alternatively, a cancer cell may have lost the ability to undergo programmed cell death through the overexpression of a negative regulator of apoptosis. Hence, there is a need to develop new
20
25
chemotherapeutic drugs that will restore the processes of checkpoint control and programmed cell death to cancerous cells.

One approach to the treatment of human cancers is to target a protein that is essential for cell cycle progression. In order for the cell cycle to proceed from one phase to the next, certain prerequisite events must be completed. There are
30
checkpoints within the cell cycle that enforce the proper order of events and phases. One such checkpoint is the spindle checkpoint that occurs during the metaphase stage of mitosis. Small molecules that target proteins with essential functions in mitosis may initiate the spindle checkpoint to arrest cells in mitosis. Of the small molecules

that arrest cells in mitosis, those which display anti-tumor activity in the clinic also induce apoptosis, the morphological changes associated with programmed cell death. An effective chemotherapeutic for the treatment of cancer may be one that induces checkpoint control and subsequent programmed cell death.

5 Most compounds known to cause mitotic arrest and apoptosis act as tubulin binding agents. These compounds alter the dynamic instability of microtubules and indirectly alter the function/structure of the mitotic spindle thereby causing mitotic arrest. Because most of these compounds target the tubulin protein, a component of all microtubules, they may also affect normal cellular processes in which
10 microtubules have a role. Hence, a need exists for small molecules that specifically target proteins associated with proliferating cells, such as Eg5.

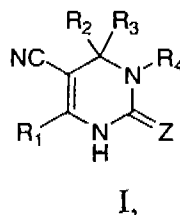
Eg5 is one of several kinesin-like motor proteins that are localized to the mitotic spindle and known to be required for formation and/or function of the bipolar mitotic spindle. Recently, there was a report of a small molecule that disturbs
15 bipolarity of the mitotic spindle (Mayer, T.U. et. al. 1999. Science 286(5441) 971-4). More specifically, the small molecule induced the formation of an aberrant mitotic spindle wherein a monoastral array of microtubules emanated from a central pair of centrosomes, with chromosomes attached to the distal ends of the microtubules. The small molecule was dubbed "monastrol" after the monoastral array. This monoastral
20 array phenotype had been previously observed in mitotic cells that were immunodepleted of the Eg5 motor protein.

The distinctive monoastral array phenotype facilitated identification of monastrol as a potential inhibitor of Eg5. Indeed, monastrol was further shown to inhibit the Eg5 motor-driven motility of microtubules in an *in vitro* assay.
25 Furthermore, monastrol had no apparent effect upon the related kinesin motor or upon the motor(s) responsible for golgi apparatus movement within the cell. Cells that display the monoastral array phenotype, either through immunodepletion of Eg5 or monastrol inhibition of Eg5, arrest in M-phase of the cell cycle. Unfortunately, however, the mitotic arrest induced by either of these mechanisms is transient.
30 (Kapoor, 2000. *J. Cell. Biol.* 150(5) 975-80). Both the monoastral array phenotype and the monastrol induced cell cycle arrest in mitosis are reversible. Cells recover to form a normal bipolar mitotic spindle, to complete mitosis, and to proceed through the

cell cycle and normal cell proliferation. This suggests that a small molecule inhibitor of Eg5 that induced a transient mitotic arrest may not be effective for the treatment of cancer cell proliferation. Nonetheless, the discovery that monastrol causes mitotic arrest is intriguing and hence there is a need to further study and identify compounds that can be used to modulate the Eg5 motor protein in a manner that would be effective in the treatment of human cancers. There is also a need to explore the use of these compounds in combination with other antineoplastic agents.

SUMMARY

The compounds of the invention cause the interruption of mitosis, and as such, can be used to treat proliferative diseases. For example, the compounds of the instant invention can be used as antiproliferatives and anticancer agents. More specifically, the invention comprises a compound of formula I



its enantiomers, diastereomers, pharmaceutically acceptable salts, prodrugs and solvates thereof, wherein

R₁ is selected from the group consisting of hydrogen, alkyl and cycloalkyl;

R₂ and R₃ are each independently selected from the group consisting of H, alkyl, aryl, heteroaryl, arylalkyl, cycloalkyl, heterocycloalkyl, cycloalkylalkyl, heterocycloalkylalkyl and heteroarylalkyl; or

R₂ and R₃ may also be taken together to form a carbocyclic or heterocyclic ring;

R₄ is selected from the group consisting of alkyl, arylalkyl, cycloalkylalkyl, heteroarylalkyl, heterocycloalkyl, aminoalkyl, heterocycloalkylalkyl, CN, C(O)R₅, CO₂R₅, C(O)SR₅ and CONR₅R₆;

R₅ and R₆ are each independently selected from the group consisting of H, alkyl, cycloalkyl, hydroxyalkyl, alkenyl, alkoxy, thioalkoxy, alkoxyalkyl, haloalkyl,

aryl, heteroaryl, arylalkyl, cycloalkylalkyl, heteroarylalkyl and heterocycloalkylalkyl or N-R₅R₆ together form a heterocycloalkyl

Z is selected from the group consisting of O, S and NR₈;

R₈ is selected from the group consisting of H, CN, sulfonamido, OR₇, alkyl, cycloalkyl, aryl, arylalkyl, heterocyclyl, heteroaryl and heteroarylalkyl; and

R₇ is selected from the group consisting of H, alkyl, arylalkyl, cycloalkylalkyl, heterocycloalkylalkyl and heteroarylalkyl.

In a preferred embodiment, R₂ is a heteroaryl, such as an optionally substituted thiophene, oxazole, isoxazole, or furan. Preferred substituents include methyl, ethyl, halo, haloalkyl, or aryl groups.

According to one embodiment, R₃ is H and R₂ is an optionally substituted phenyl wherein the substituents are selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, cyano, halo, haloalkyl, nitro, amino CO₂R₅, CONR₅R₆, alkenyloxy, aryloxy, wherein R₅ and R₆ are, independently, H or alkyl. Preferred substituents include methyl, methoxy, F, Cl, CF₃, dimethylamino, and ethoxymethyl, for example.

According to one embodiment of the present invention, R₁ is alkyl; R₂ is selected from the group consisting of aryl and heteroaryl; R₃ is H; R₄ is selected from the group consisting of alkyl, arylalkyl, CO₂R₅, and CONR₅R₆; R₅ and R₆ are independently selected from the group consisting of H, alkyl, aminoalkyl, hydroxyalkyl, phenylamino and arylalkyl; Z is selected from the group consisting of O, S, and NR₈; R₈ is selected from the group consisting of H and CN.

In a preferred embodiment, R₄ is selected from the group consisting of alkyl, arylalkyl, C(O)R₅, CO₂R₅, C(O)SR₅ and CONR₅R₆.

According to one embodiment, R₄ is CO₂R₅; Z is O; and R₅ is ethyl.

In another embodiment, R₄ is CONR₅R₆; Z is O; R₅ is H and R₆ is methyl, ethyl, propyl, phenyl, cyclopropyl, hydroxyethyl, thiophene, or 2-propylene.

In one embodiment of the present invention, R₄ is selected from the group consisting of alkyl and arylalkyl, and Z is O. In another embodiment R₁ is CH₃; R₂ is aryl; R₄ is CO₂R₅; R₅ is alkyl; and Z is O. In still another embodiment R₁ is CH₃; R₂ is aryl; R₄ is CONR₅R₆; R₅ is alkyl; R₆ is H and Z is O. In yet another embodiment, R₁ is CH₃; R₂ is heteroaryl; R₄ is CO₂R₅ or CONR₅R₆; R₆ is H and R₅ is ethyl.

The present invention also provides methods for preparing intermediates and compounds having Formula I.

The present invention also provides methods for treating a proliferative disease, such as cancer, via modulation of the Eg5 motor protein comprising
5 administering to a mammalian species in need of such treatment an effective amount of at least one compound of formula I, as defined above.

DESCRIPTION

The present invention provides for compounds of formula I, as defined above,
10 pharmaceutical compositions employing such compounds and methods of using such compounds.

Listed below are definitions of various terms used to describe the compounds of the instant invention. These definitions apply to the terms as they are used throughout the specification (unless they are otherwise limited in specific instances)
15 either individually or as part of a larger group.

The term "alkyl" herein alone or as part of another group refers to a monovalent alkane (hydrocarbon) derived radical containing from 1 to 12 carbon atoms unless otherwise defined. An alkyl group is an optionally substituted straight, branched or cyclic saturated hydrocarbon group. When substituted, alkyl groups may
20 be substituted with up to four substituent groups, R as defined, at any available point of attachment. When the alkyl group is said to be substituted with an alkyl group, this is used interchangeably with "branched alkyl group". Exemplary unsubstituted such groups include methyl, ethyl, propyl, isopropyl, n-butyl, t-butyl, isobutyl, pentyl, hexyl, isohexyl, heptyl, 4,4-dimethylpentyl, octyl, 2,2,4-trimethylpentyl, nonyl, decyl,
25 undecyl, dodecyl, and the like. Exemplary substituents may include but are not limited to one or more of the following groups: aryl, halo (such as F, Cl, Br, I), haloalkyl (such as CCl₃ or CF₃), alkoxy, alkylthio, hydroxy, carboxy (-COOH), alkyloxycarbonyl (-C(O)R), alkylcarbonyloxy (-OCOR), amino (-NH₂), carbamoyl (-NHCOOR- or -OCONHR-), urea (-NHCONHR-) or thiol (-SH). Alkyl groups as
30 defined may also comprise one or more carbon to carbon double bonds or one or more carbon to carbon triple bonds.

The term "alkenyl" herein alone or as part of another group refers to a hydrocarbon radical straight, branched or cyclic containing from 2 to 12 carbon atoms and at least one carbon to carbon double bond.

The term "alkynyl" herein alone or as part of another group refers to a hydrocarbon radical straight, branched or cyclic containing from 2 to 12 carbon atoms and at least one carbon to carbon triple bond.

The numbers in the subscript after the symbol "C" define the number of carbon atoms a particular group can contain. For example "C₁₋₆ alkyl" means a straight or branched saturated carbon chain having from one to six carbon atoms; examples include methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, isobutyl, t-butyl, n-pentyl, sec-pentyl, isopentyl, and n-hexyl. Depending on the context, "C₁₋₆ alkyl" can also refer to C₁₋₆ alkylene which bridges two groups; examples include propane-1,3-diyl, butane-1,4-diyl, 2-methyl-butane-1,4-diyl, etc. "C₂₋₆ alkenyl" means a straight or branched carbon chain having at least one carbon-carbon double bond, and having from two to six carbon atoms; examples include ethenyl, propenyl, isopropenyl, butenyl, isobutenyl, pentenyl, and hexenyl. Depending on the context, "C₂₋₆ alkenyl" can also refer to C₂₋₆ alkenediyl which bridges two groups; examples include ethylene-1,2-diyl (vinylene), 2-methyl-2-butene-1,4-diyl, 2-hexene-1,6-diyl, etc. "C₂₋₆ alkynyl" means a straight or branched carbon chain having at least one carbon-carbon triple bond, and from two to six carbon atoms; examples include ethynyl, propynyl, butynyl, and hexynyl.

The term "cycloalkyl" herein alone or as part of another group is a specie of alkyl containing from 3 to 15 carbon atoms, without alternating or resonating double bonds between carbon atoms. It may contain from 1 to 4 rings. Exemplary unsubstituted such groups include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, adamantyl, etc. Exemplary substituents include one or more of the following groups: halogen, alkyl, alkoxy, alkyl hydroxy, amino, nitro, cyano, thiol and/or alkylthio.

The terms "alkoxy" or "alkylthio" herein alone or as part of another group denote an alkyl group as described above bonded through an oxygen linkage (-O-) or a sulfur linkage (-S-), respectively.

The term "alkyloxycarbonyl" herein alone or as part of another group denotes an alkoxy group bonded through a carbonyl group. An alkoxycarbonyl radical is represented by the formula: $-C(O)OR$, where the R group is a straight or branched C_{1-6} alkyl group.

5 The term "alkylcarbonyl" herein alone or as part of another group refers to an alkyl group bonded through a carbonyl group.

The term "alkylcarbonyloxy" herein alone or as part of another group denotes an alkylcarbonyl group which is bonded through an oxygen linkage.

10 The term "arylalkyl" herein alone or as part of another group denotes an aromatic ring bonded to an alkyl group as described above.

The term "aryl" herein alone or as part of another group refers to monocyclic or bicyclic aromatic rings, e.g. phenyl, substituted phenyl and the like, as well as groups which are fused, e.g., naphthyl, phenanthrenyl and the like. An aryl group thus contains at least one ring having at least 6 atoms, with up to five such rings being
15 present, containing up to 22 atoms therein, with alternating (resonating) double bonds between adjacent carbon atoms or suitable heteroatoms. Aryl groups may optionally be substituted with one or more groups including, but not limited to halogen, alkyl, alkoxy, hydroxy, carboxy, carbamoyl, alkyloxycarbonyl, nitro, alkenyloxy, trifluoromethyl, amino, cycloalkyl, cyano, alkyl $S(O)_m$ ($m=O, 1, 2$), or thiol.

20 The term "amino" herein alone or as part of another group refers to $-NH_2$. An "amino" may optionally be substituted with one or two substituents, which may be the same or different, such as alkyl, aryl, arylalkyl, alkenyl, alkynyl, heteroaryl, heteroarylalkyl, cycloheteroalkyl, cycloheteroalkylalkyl, cycloalkyl, cycloalkylalkyl, haloalkyl, hydroxyalkyl, alkoxyalkyl, thioalkyl, carbonyl or carboxyl. These
25 substituents may be further substituted with a carboxylic acid, any of the alkyl or aryl substituents set out herein. In some embodiments, the amino groups are substituted with carboxyl or carbonyl to form N-acyl or N-carbamoyl derivatives

The term "carbocyclic ring" herein alone or as part of another group refers to stable, saturated or partially unsaturated monocyclic ring hydrocarbyls of 3 to 7
30 carbon atoms such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl. The carbocyclic ring may be optionally substituted meaning that the carbocyclic ring may be substituted at one or more substitutable ring positions by one

or more groups independently selected from alkyl (preferably lower alkyl), alkoxy (preferably lower alkoxy), nitro, monoalkylamino (preferably a lower alkylamino), dialkylamino (preferably a di[lower]alkylamino), cyano, halo, haloalkyl (preferably trifluoromethyl), alkanoyl, aminocarbonyl, monoalkylaminocarbonyl, dialkylaminocarbonyl, alkyl amido (preferably lower alkyl amido), alkoxyalkyl (preferably a lower alkoxy[lower]alkyl), alkoxycarbonyl (preferably a lower alkoxycarbonyl), alkylcarbonyloxy (preferably a lower alkylcarbonyloxy) and aryl (preferably phenyl), said aryl being optionally substituted by halo, lower alkyl and lower alkoxy groups.

The term "cycloalkyl" herein alone or as part of another group refers to fully saturated and partially unsaturated hydrocarbon rings of 3 to 9, preferably 3 to 7 carbon atoms. Further, a cycloalkyl may be substituted. A substituted cycloalkyl refers to such rings having one, two, or three substituents, preferably one, selected from the group consisting of halo, alkyl, substituted alkyl, alkenyl, alkynyl, nitro, cyano, oxo ($=O$), hydroxy, alkoxy, thioalkyl, $-CO_2H$, $-C(=O)H$, CO_2 -alkyl, $-C(=O)alkyl$, keto, $=N-OH$, $=N-O-alkyl$, aryl, heteroaryl, heterocyclo, a five or six membered ketal (*i.e.* 1,3-dioxolane or 1,3-dioxane), $-NR'R''$, $-C(=O)NR'R''$, $-CO_2NR'R''$, $-C(=O)NR'R''$, $-NR'CO_2R''$, $-NR'C(=O)R''$, $-SO_2NR'R''$, and $-NR'SO_2R''$, wherein each of R' and R'' is independently selected from hydrogen, alkyl, substituted alkyl, and cycloalkyl, or R' and R'' together form a heterocyclo or heteroaryl ring.

The term "heteroaryl" herein alone or as part of another group refers to substituted and unsubstituted aromatic 5 or 6 membered monocyclic groups, 9 or 10 membered bicyclic groups, and 11 to 14 membered tricyclic groups which have at least one heteroatom (O, S or N) in at least one of the rings. Each ring of the heteroaryl group containing a heteroatom can contain one or two oxygen or sulfur atoms and/or from one to four nitrogen atoms provided that the total number of heteroatoms in each ring is four or less and each ring has at least one carbon atom. The fused rings completing the bicyclic and tricyclic groups may contain only carbon atoms and may be saturated, partially saturated, or unsaturated. The nitrogen and sulfur atoms may optionally be oxidized and the nitrogen atoms may optionally be quaternized. Heteroaryl groups which are bicyclic or tricyclic must include at least

one fully aromatic ring but the other fused ring or rings may be aromatic or non-aromatic. The heteroaryl group may be attached at any available nitrogen or carbon atom of any ring. The heteroaryl ring system may contain zero, one, two or three substituents selected from the group consisting of halo, alkyl, substituted alkyl, alkenyl, alkynyl, aryl, nitro, cyano, hydroxy, alkoxy, thioalkyl, -CO₂H, -C(=O)H, -CO₂-alkyl, -C(=O)alkyl, phenyl, benzyl, phenylethyl, phenyloxy, phenylthio, cycloalkyl, substituted cycloalkyl, heterocyclo, heteroaryl, -NR'R'', -C(=O)NR'R'', -CO₂NR'R'', -C(=O)NR'R'', -NR'CO₂R'', -NR'C(=O)R'', -SO₂NR'R'', and -NR'SO₂R'', wherein each of R' and R'' is independently selected from hydrogen, alkyl, substituted alkyl, and cycloalkyl, or R' and R'' together form a heterocyclo or heteroaryl ring.

Exemplary monocyclic heteroaryl groups include pyrrolyl, pyrazolyl, pyrazolinyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl, thiadiazolyl, isothiazolyl, furanyl, thienyl, oxadiazolyl, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, triazinyl and the like.

Exemplary bicyclic heteroaryl groups include indolyl, benzothiazolyl, benzodioxolyl, benzoxazolyl, benzothienyl, quinolinyl, tetrahydroisoquinolinyl, isoquinolinyl, benzimidazolyl, benzopyranyl, indolizinyl, benzofuranyl, chromonyl, coumarinyl, benzopyranyl, cinnolinyl, quinoxalinyl, indazolyl, pyrrolopyridyl, furopyridinyl, dihydroisoindolyl, tetrahydroquinolinyl and the like.

Exemplary tricyclic heteroaryl groups include carbazolyl, benzidolyl, phenanthroline, acridinyl, phenanthridinyl, xanthenyl and the like.

The term "heterocycloalkyl" herein alone or as part of another group refers to a cycloalkyl group (nonaromatic) in which one of the carbon atoms in the ring is replaced by a heteroatom selected from O, S or N, and in which up to three additional carbon atoms may be replaced by said heteroatoms.

The term "heterocyclic ring" herein alone or as part of another group refers to a stable, saturated, or partially unsaturated monocyclic ring system containing 5 to 7 ring members of carbon atoms and other atoms selected from nitrogen, sulfur and/or oxygen. Preferably, a heterocyclic ring is a 5 or 6-membered monocyclic ring and contains one, two, or three heteroatoms selected from nitrogen, oxygen and/or sulfur. The heterocyclic ring may be optionally substituted which means that the heterocyclic

ring may be substituted at one or more substitutable ring positions by one or more groups independently selected from alkyl (preferably lower alkyl), alkoxy (preferably lower alkoxy), nitro, monoalkylamino (preferably a lower alkylamino), dialkylamino (preferably a di[lower]alkylamino), cyano, halo, haloalkyl (preferably trifluoromethyl), alkanoyl, aminocarbonyl, monoalkylaminocarbonyl, dialkylaminocarbonyl, alkyl amido (preferably lower alkyl amido), alkoxyalkyl (preferably a lower alkoxy[lower]alkyl), alkoxycarbonyl (preferably a lower alkoxycarbonyl), alkylcarbonyloxy (preferably a lower alkylcarbonyloxy) and aryl (preferably phenyl), said aryl being optionally substituted by halo, lower alkyl and lower alkoxy groups. Examples of such heterocyclic rings are isoxazolyl, imidazoliny, thiazoliny, imidazolidiny, pyrrolyl, pyrroliny, pyranly, pyraziny, piperidy, morpholiny and triazolyl. The heterocyclic ring may be attached to the parent structure through a carbon atom or through any heteroatom of the heterocycl that results in a stable structure.

The term "heterocycl" herein alone or as part of another group as used herein refers to a stable, saturated, or partially unsaturated, monocyclic, bridged monocyclic, bicyclic, and spiro ring system containing carbon atoms and other atoms selected from nitrogen, sulfur and/or oxygen. Preferably, a heterocycl is a 5 or 6-membered monocyclic ring or an 8-11 membered bicyclic ring which consists of carbon atoms and contains one, two, or three heteroatoms selected from nitrogen, oxygen and/or sulfur. The term "optionally substituted" as it refers to "heterocycl" herein indicates that the heterocycl group may be substituted at one or more substitutable ring positions by one or more groups independently selected from alkyl (preferably lower alkyl), alkoxy (preferably lower alkoxy), nitro, monoalkylamino (preferably a lower alkylamino), dialkylamino (preferably a di[lower]alkylamino), cyano, halo, haloalkyl (preferably trifluoromethyl), alkanoyl, aminocarbonyl, monoalkylaminocarbonyl, dialkylaminocarbonyl, alkyl amido (preferably lower alkyl amido), alkoxyalkyl (preferably a lower alkoxy[lower]alkyl), alkoxycarbonyl (preferably a lower alkoxycarbonyl), alkylcarbonyloxy (preferably a lower alkylcarbonyloxy) and aryl (preferably phenyl), said aryl being optionally substituted by halo, lower alkyl and lower alkoxy groups. Examples of such heterocycl groups are isoxazolyl, imidazoliny, thiazoliny, imidazolidiny, pyrrolyl, pyrroliny, pyranly, pyraziny,

piperidyl, morpholinyl and triazolyl. The heterocyclyl group may be attached to the parent structure through a carbon atom or through any heteroatom of the heterocyclyl that results in a stable structure.

The term "heteroatom" means O, S or N, selected on an independent basis. It should be noted that any heteroatom with unsatisfied valences is assumed to have the hydrogen atom to satisfy the valences.

The term "halogen" or "halo" refers to chlorine, bromine, fluorine or iodine selected on an independent basis.

When a functional group is termed "protected", this means that the group is in modified form to preclude undesired side reactions at the protected site. Suitable protecting groups for the compounds of the present invention will be recognized from the present application taking into account the level of skill in the art, and with reference to standard textbooks, such as Greene, T. W. et al., *Protective Groups in Organic Synthesis*, Wiley, N.Y. (1991).

As used herein, the term "patient" encompasses all mammalian species.

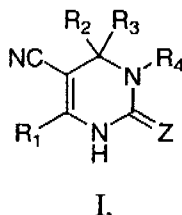
Suitable examples of salts of the compounds according to the invention with inorganic or organic acids are hydrochloride, hydrobromide, sulfate, methanesulfonate, maleate, fumarate, and phosphate. Salts which are unsuitable for pharmaceutical uses but which can be employed, for example, for the isolation or purification of free compounds I or their pharmaceutically acceptable salts, are also included.

All stereoisomers of the compounds of the instant invention are contemplated, either in admixture or in pure or substantially pure form. The definition of the compounds according to the invention embraces all possible stereoisomers and their mixtures. It very particularly embraces the racemic forms and the isolated optical isomers having the specified activity. The racemic forms can be resolved by physical methods, such as, for example, fractional crystallization, separation or crystallization of diastereomeric derivatives or separation by chiral column chromatography. The individual optical isomers can be obtained from the racemates by conventional methods, such as, for example, salt formation with an optically active acid followed by crystallization.

It should be understood that the present invention includes prodrug forms of the compounds of formula I. Various forms of prodrugs are well known in the art. For examples of such prodrug derivatives, see:

- (a) Design of Prodrugs, edited by H. Bundgaard (Elsevier, 1985); and Methods in
5 Enzymology, Vol. 42, pp. 309-396, edited by K. Widder et al., (Academic Press, 1985);
(b) A Textbook of Drug Design and Development, edited by Krosgaard-Larsen and H. Bundgaard, Chapter 5, "Design and Application of Prodrugs," by H. Bundgaard, pp. 113-191 (1991);
10 (c) H. Bundgaard, Advanced Drug Deliver Reviews, 8, pp. 1-38 (1992);
(d) H. Bundgaard et al., Journal of Pharmaceutical Sciences, 77, 285 (1988); and
(e) N. Kayeka et al., Chem. Phar. Bull., 32, 692 (1984).

In general, the instant invention comprises a compound of formula I



its enantiomers, diastereomers, pharmaceutically acceptable salts, prodrugs and solvates thereof. R₁ is hydrogen, alkyl or cycloalkyl. R₂ and R₃ are each
20 independently H, alkyl, aryl, heteroaryl, arylalkyl, cycloalkylalkyl, heterocycloalkylalkyl or heteroarylalkyl. Alternatively, R₂ and R₃ may be taken together to form either a carbocyclic or heterocyclic ring. R₄ is alkyl, arylalkyl, cycloalkylalkyl, heteroarylalkyl, heterocycloalkylalkyl, CN, COR₅, CO₂R₅ or CONR₅R₆. R₅ and R₆ are each independently H, alkyl, arylalkyl, cycloalkylalkyl,
25 heteroarylalkyl or heterocycloalkylalkyl. Z is O, S or NR₈; R₈ is H, CN, sulfonamido, OR₇, alkyl, cycloalkyl, aryl, arylalkyl, heterocyclyl, heteroaryl or heteroarylalkyl. R₇ is H, alkyl, arylalkyl, cycloalkylalkyl, heterocycloalkylalkyl, or heteroarylalkyl.

One preferred embodiment of the instant invention are compounds of formula
30 I, as defined above, wherein R₁ is alkyl; R₂ is selected from the group consisting of

aryl and heteroaryl; R_3 is H; R_4 is selected from the group consisting of alkyl, arylalkyl, CO_2R_5 and CONR_5R_6 ; R_5 and R_6 are independently selected from the group consisting of H, alkyl and arylalkyl; Z is selected from the group consisting of O, S and NR_8 ; and R_8 is selected from the group consisting of H and CN.

5 In another preferred embodiment, the invention comprises compounds of formula I, as defined above, wherein R_4 is selected from the group consisting of alkyl, arylalkyl, CO_2R_5 and CONR_5R_6 .

In yet another preferred embodiment, the instant invention comprises the compounds of formula I, as defined above, wherein R_4 is CO_2R_5 or CONR_5R_6 and Z
10 is O.

In yet a further preferred embodiment, the instant invention comprises the compounds of formula I, as defined above, wherein R_4 is selected from the group consisting of alkyl and arylalkyl, and Z is O.

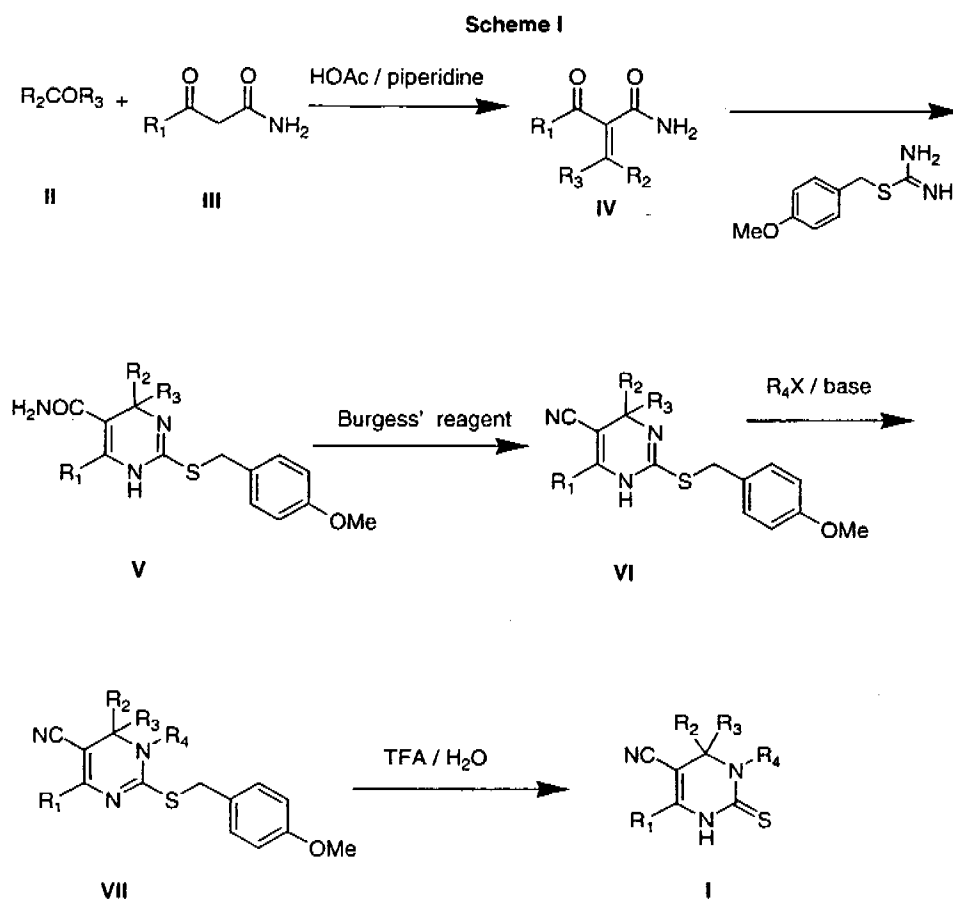
In still yet another preferred embodiment, the instant invention comprises the
15 compounds of formula I, as defined above, wherein R_1 is CH_3 ; R_2 is aryl; R_4 is CO_2R_5 ; R_5 is alkyl; and Z is O.

In still yet another preferred embodiment, the instant invention comprises the compounds of formula I, as defined above, wherein R_1 is CH_3 ; R_2 is aryl; R_4 is CONR_5R_6 ; R_5 is alkyl, R_6 is H; and Z is O.

20 The invention further provides a pharmaceutical composition comprising a compound of formula I, as defined above, and a pharmaceutically acceptable carrier. Optionally the pharmaceutical composition may further comprise at least one other anti-cancer agent formulated as a fixed dose.

The invention also provides a method for treating a proliferative disease via
25 modulation of the Eg5 motor protein, and/or, inducing apoptosis comprising administering to a mammalian species in need of such treatment an effective amount of at least one compound of formula I, as defined above. In another embodiment, the invention provides a method for treating a proliferative disease via modulation of the Eg5 motor protein comprising administering to a mammalian species in need of such
30 treatment an effective amount of at least one compound of formula I, as defined above, in combination (simultaneously or sequentially) with at least one other anti-cancer agent. In a preferred embodiment, the proliferative disease is cancer.

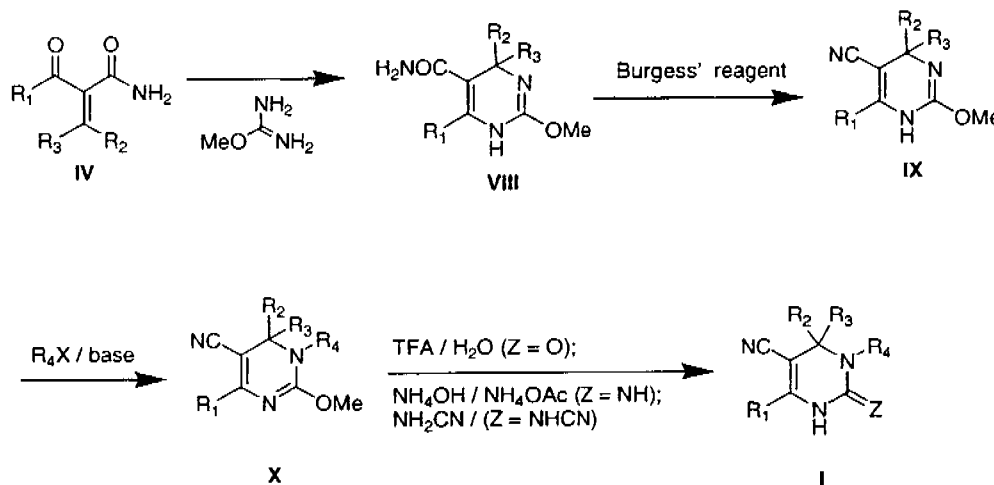
Certain compounds of formula I may generally be prepared according to the following schemes and the knowledge of one skilled in the art. Solvates (e.g., hydrates) of the compounds of formula I are also within the scope of the present invention. Methods of solvation are generally known in the art. Accordingly, the compounds of the instant invention may be in the free or hydrate form, and may be obtained by methods exemplified by the following schemes below.



Compounds of formula I where Z is S may be made in accordance with Scheme I. A ketone or an aldehyde I (e.g., benzaldehyde, where R_2 is phenyl and R_3 is H), is condensed with an acetoacetamide III to give a Knoevenagel product IV as a mixture of isomers. Reaction with S-paramethoxybenzyl thiourea provides the protected dihydropyrimidine thione V. The primary amido group of V is dehydrated to the cyano substituent in VI using a dehydrating agent such as Burgess' reagent (methoxycarbonylsulfamoyl)triethylammonium hydroxide, inner salt. The N3 substituent is introduced by reaction with R_4X where R_4 is alkyl or acyl, and X is a

leaving group, or where R_4X is an isocyanate or haloformate. The protecting group is removed by treatment with acid in the presence of water to give compounds of formula I where Z is S.

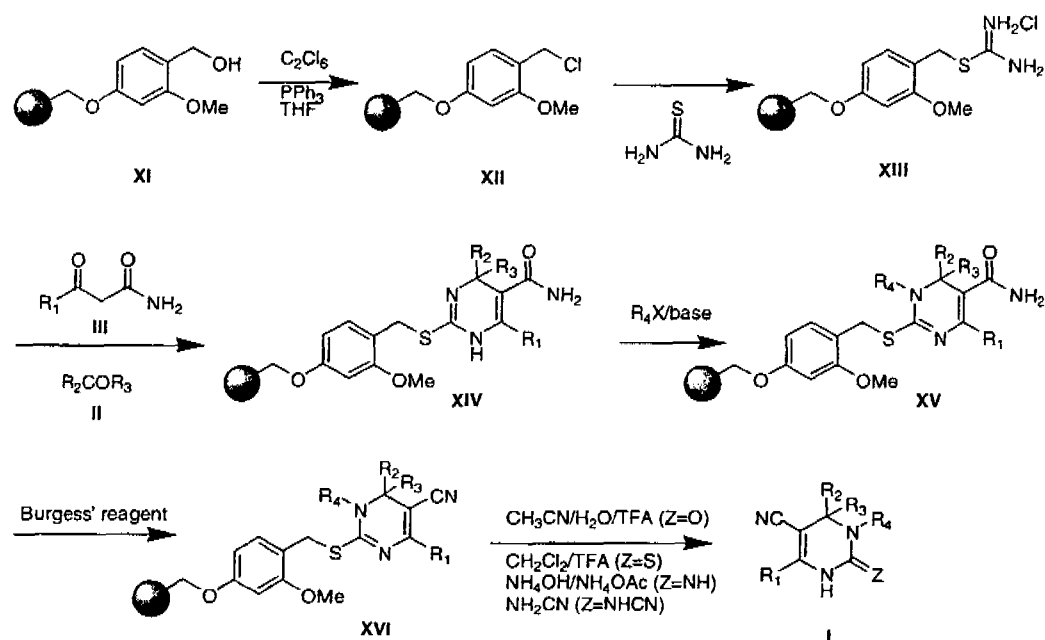
Scheme II



Compounds of formula I where Z is O, NH, or NR_8 are prepared from the reaction of Knoevenagel products IV with O-methyl isourea to provide the O-methyl dihydropyrimidines VIII. The primary amide is converted to a nitrile group using a dehydrating agent such as Burgess' reagent. The N3 substituent is introduced by reaction with R_4X where R_4 is alkyl or acyl, and X is a leaving group, or where R_4X is an isocyanate or haloformate. The methyl ether protecting group is removed by treatment with acid in the presence of water to give compounds of formula I where Z is O. Alternatively, treatment of compounds of formula X with ammonium hydroxide in the presence of ammonium acetate, or cyanamide in ethanol, provides compounds of formula I where Z is NH or NR_8 .

Compounds of formula I may also be prepared using the Bignelli reaction (D. J. Brown in *The Pyrimidines*, Wiley: New York, 1962, 440).

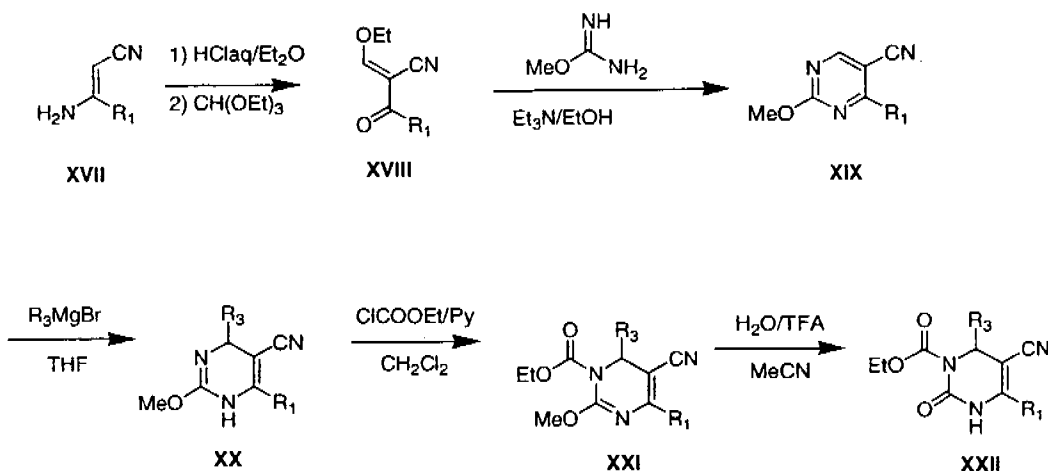
Scheme III
SOLID PHASE SYNTHESIS



Compounds of formula I could be prepared on solid support as outlined in Scheme III. Starting compound XI denotes a resin-bound benzyl alcohol used for solid support synthesis which is prepared from a Merrifield resin denoted as $\bullet$, and 2-methoxy-4-hydroxybenzaldehyde, followed by reduction of the aldehyde with reducing agents such as NaBH_4 . The benzyl alcohol is converted into the benzyl chloride using agents such as hexachloroethane and triphenylphosphine in THF to form resins of formula XII. The chloride is displaced with thiourea to form the isothiourethane resin XIII. The resulting resin is treated with excess of ketoamides like acetoamide (III, R_1 is CH_3), in the presence of ketones of formula R_2COR_3 or aldehydes of formula R_2CHO to form the resin-bound pyrimidinethiones of formula XIV. The N3 substituent is introduced using R_4X , where X is a leaving group and R_4 is alkyl or acyl, or R_4X is an isocyanate, or haloformate, in the presence of base to form structures of formula XV. The primary amide can be dehydrated to the cyano group using reagents such as Burgess' reagent to form compounds of formula XVI. The products can be cleaved from the resin using a variety of conditions to form compounds of formula I, where Z is determined by the cleavage method employed. Cleavage in the presence of aqueous acid will form compounds of formula I with Z

being O, whereas cleavage under anhydrous acid conditions will form compounds of formula I with Z being S. Alternatively, treatment of resins with structure XVI with ammonium hydroxide in the presence of ammonium acetate will form compounds of formula I with Z being NH, while treatment with cyanamide, provides compounds of
5 formula I with Z being NHCN.

SCHEME IV



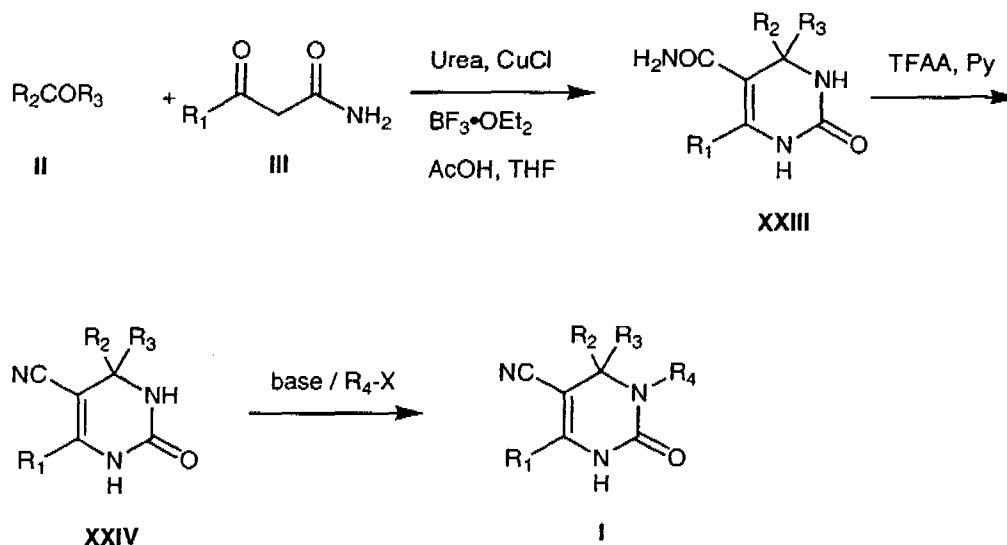
Compounds of formula XVIII may be prepared from a 3-amino-3-alkyl acrylonitrile XVII using the methods illustrated in Scheme IV. Reaction of a compound of formula XVII with aqueous acid, such as hydrochloric acid, followed by
10 treatment with triethyl orthoformate, provides a compound of formula XVIII. Reaction of a compound of formula XVIII with O-methyl isourea in the presence of a base such as triethylamine, provides a pyrimidine of formula XIX. Pyrimidines of formula XIX may be reacted with organometallic species such as a Grignard reagent, R_3MgBr , in a solvent such as ether or tetrahydrofuran, to give a pyrimidine of formula
15 XX, which is a compound of formula IX wherein R_2 is H. In analogy with Scheme II, a compound of formula XX may be converted into a compound of formula XXII, which is a compound of formula I in which R_4 is ethoxycarbonyl and R_2 is H.

Alternatively, compounds of formula I, wherein $Z = O$, may be prepared in accordance with Scheme V. Following the procedure of E.H. Hu *et al* (J. Org. Chem,
20 1998, 63, 3454-3457), a carbonyl compound of formula II is condensed with an acylacetamide of formula III in the presence of urea, cuprous chloride and borontrifluoride etherate to give intermediate XXIII. Dehydration with trifluoroacetic anhydride in pyridine affords nitrile XXIV. The N3 substituent is introduced by

reaction with R_4X where R_4 is alkyl or acyl, and X is a leaving group, or where R_4X is an isocyanate or haloformate to give compounds of formula I. Deprotonation is effected with a base such as sodium hydride or LDA in aprotic solvents such as dimethylformamide or tetrahydrofuran.

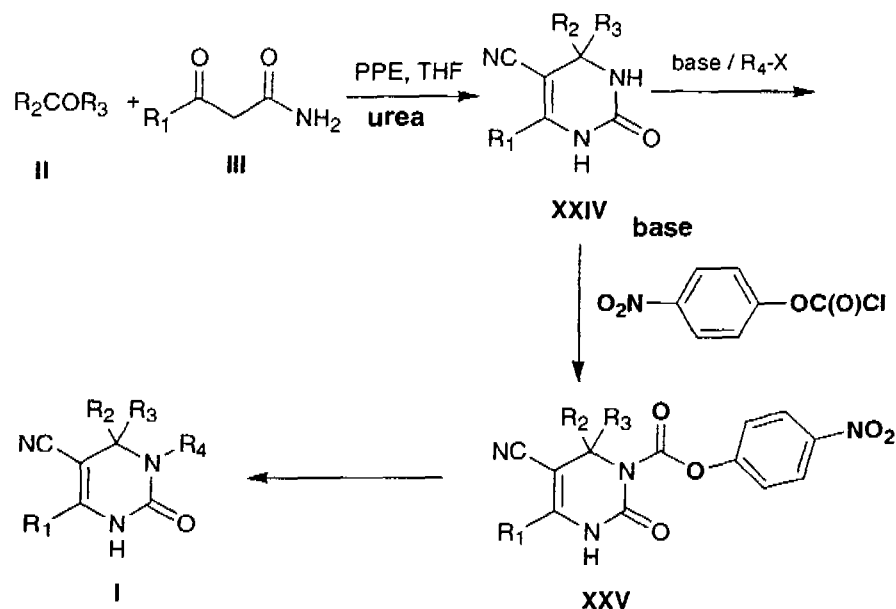
5

Scheme V



In yet another procedure, compounds of formula I, wherein $Z = O$, may be prepared in accordance with Scheme VI. A carbonyl compound of formula II is condensed with an acylacetamide of formula III in the presence of urea and polyphosphate ester to directly afford nitrile XXIV. Introduction of the N3 substituent follows the procedure as described in Scheme V. Compounds of formula I, where R_4 is aminocarbonyl, may also be obtained by first forming a reactive intermediate such as a nitrophenylcarbamate of formula XXV, which is subsequently reacted with an amine.

Scheme VI



In all of the above schema, a 2-acyl acetonitrile derivative, i.e., $\text{R}_1\text{COCH}_2\text{CN}$, may be substituted for a compound of formula III.

As discussed in the background section, Eg5 is a kinesin-like motor protein that facilitates spindle bipolarity during mitosis of the cell cycle. More specifically, the Eg5 protein acts to sort and bundle microtubules of the mitotic spindle during mitosis. Accordingly, Eg5 participates in cell cycle regulation through the spindle checkpoint during the M phase of the cycle. While not wishing to be bound by any theory, it is believed that the compounds of the instant invention act as Eg5 inhibitors.

This is theorized because the compounds of the instant invention induce a monopolar astral array of microtubules (the monoastral phenotype) and it has been shown that when Eg5 activity is absent, the monoastral phenotype forms. Regardless of the mechanism of action, the compounds of the instant invention have been shown to cause disruption of the bipolar spindle, spindle checkpoint initiation, mitotic arrest, programmed cell death and tumor cell proliferation inhibition. Furthermore, the compounds of the invention induce a cell cycle arrest in mitosis that is not transient but rather which progresses into programmed cell death. The compounds also exhibit high potency, inducing mitotic arrest and apoptosis in human cells *in vitro* at concentrations in the low or sub μM range. Additionally, in contrast to microtubule agents, the compounds do not disrupt the dynamic instability of microtubules. The instant invention may therefore more specifically target the mitotic spindle of

proliferating cells, which may provide for different toxicity profiles than those of existing anti-cancer drugs.

The compounds according to the invention have pharmacological properties; in particular, the compounds of formula I induce mitotic arrest and are believed to be
5 Eg5 inhibitors. The novel compounds of formula I are thus useful in the therapy of a variety of proliferative diseases (including but not limited to diseases associated with the Eg5 motor protein) such as cancer, autoimmune diseases, viral diseases, fungal diseases, neurodegenerative disorders and cardiovascular disease.

More specifically, the compounds of formula I are useful in the treatment of a
10 variety of cancers, including, but not limited to, the following:

- a) carcinoma, including that of the bladder, breast, colon, kidney, liver, lung, including small cell lung cancer, esophagus, gall bladder, ovary, pancreas, stomach, cervix, thyroid, prostate, and skin, including squamous cell carcinoma;
- 15 b) hematopoietic tumors of lymphoid lineage, including leukemia, acute lymphocytic leukemia, acute lymphoblastic leukemia, B-cell lymphoma, T-cell lymphoma, Hodgkins lymphoma, non-Hodgkins lymphoma, hairy cell lymphoma and Burkett's lymphoma;
- c) hematopoietic tumors of myeloid lineage, including acute and
20 chronic myelogenous leukemias, myelodysplastic syndrome and promyelocytic leukemia;
- d) tumors of mesenchymal origin, including fibrosarcoma and rhabdomyosarcoma;
- e) tumors of the central and peripheral nervous system, including
25 astrocytoma, neuroblastoma, glioma and schwannomas; and
- f) other tumors, including melanoma, seminoma, teratocarcinoma, osteosarcoma, xenoderoma pigmentosum, keratocanthoma, thyroid follicular cancer and Kaposi's sarcoma.

Due to the key role of motor proteins in the regulation of cellular proliferation
30 in general, inhibitors could act as reversible cytostatic agents which may be useful in the treatment of any disease process which features abnormal cellular proliferation, e.g., benign prostatic hyperplasia, familial adenomatosis polyposis, neuro-

20135

fibromatosis, atherosclerosis, pulmonary fibrosis, arthritis, psoriasis, glomerulonephritis, restenosis following angioplasty or vascular surgery, hypertrophic scar formation, inflammatory bowel disease, transplantation rejection, endotoxic shock, and fungal infections.

5 Compounds of formula I induce apoptosis. The apoptotic response is aberrant in a variety of human diseases. Compounds of formula I, as modulators of apoptosis, will be useful in the treatment of cancer (including but not limited to those types mentioned herein above), viral infections (including but not limited to herpesvirus, poxvirus, Epstein-Barr virus, Sindbis virus and adenovirus), prevention of AIDS
10 development in HIV-infected individuals, autoimmune diseases (including but not limited to systemic lupus, erythematosus, autoimmune mediated glomerulonephritis, rheumatoid arthritis, psoriasis, inflammatory bowel disease, and autoimmune diabetes mellitus), neurodegenerative disorders (including but not limited to Alzheimer's disease, AIDS-related dementia, Parkinson's disease, amyotrophic lateral sclerosis,
15 retinitis pigmentosa, spinal muscular atrophy and cerebellar degeneration), myelodysplastic syndromes, aplastic anemia, ischemic injury associated with myocardial infarctions, stroke and reperfusion injury, arrhythmia, atherosclerosis, toxin-induced or alcohol related liver diseases, hematological diseases (including but not limited to chronic anemia and aplastic anemia), degenerative diseases of the
20 musculoskeletal system (including but not limited to osteoporosis and arthritis) aspirin-sensitive rhinosinusitis, cystic fibrosis, multiple sclerosis, kidney diseases and cancer pain.

 Compounds of formula I may modulate the level of cellular RNA and DNA synthesis. These agents would therefore be useful in the treatment of viral infections
25 (including but not limited to HIV, human papilloma virus, herpesvirus, poxvirus, Epstein-Barr virus, Sindbis virus and adenovirus).

 Compounds of formula I are useful in the chemoprevention of cancer. Chemoprevention is defined as inhibiting the development of invasive cancer by either blocking the initiating mutagenic event or by blocking the progression of pre-
30 malignant cells that have already suffered an insult or inhibiting tumor relapse.

 Compounds of formula I may also be useful in inhibiting tumor angiogenesis and metastasis.

The instant invention may also inhibit other motor proteins, for example, including but not limited to: those human motor proteins that correspond to, Xklp2, MKLP1, CHO1, chromokinesins, Nod, Cenp-E, MCAK, members of the BimC family, and members of the Kar3 family. Additionally, compounds used in the methods of the instant invention may also act as inhibitors of other kinesin or kinesin-like proteins and thus be effective in the treatment of diseases associated with other kinesin or kinesin-like proteins.

The compounds of this invention may also be useful in combination (administered together or sequentially) with known anti-cancer treatments such as radiation therapy or with cytostatic or cytotoxic agents, such as for example, but not limited to, DNA interactive agents, such as cisplatin or doxorubicin; topoisomerase II inhibitors, such as etoposide; topoisomerase I inhibitors such as CPT-11 or topotecan; tubulin interacting agents, such as paclitaxel, docetaxel or the epothilones; hormonal agents, such as tamoxifen; thymidilate synthase inhibitors, such as 5-fluorouracil; and anti-metabolites, such as methotrexate.

If formulated as a fixed dose, such combination products employ the compounds of this invention within the dosage range described below and the other pharmaceutically active agent or treatment within its approved dosage range. Compounds of formula I may also be administered sequentially with known anticancer or cytotoxic agents when a combination formulation is inappropriate. The invention is not limited in the sequence of administration; compounds of formula I may be administered either prior to or after administration of the known anticancer or cytotoxic agent(s).

25 ASSAYS

The pharmacological properties of the compounds of this invention may be confirmed by a number of pharmacological assays. The exemplified pharmacological assays which follow have been carried out with the compounds according to the invention and their salts. The compounds of formula I exhibited antiproliferative activity. Preferred compounds exhibit IC_{50} values less than or equal to about 10 μ M.

Cell Culture

Cell lines are maintained in RPMI-1640 plus 10% fetal bovine serum.

72-Hour Proliferation Assay

- 5 Cells are plated at a density of 3,000-6,000 cells/well, depending upon the cell line used, in a 96-well plate. The cultures are grown overnight. Cells were then treated in triplicate with a seven concentration dose-response curve. The maximum concentration of DMSO never exceeded 0.5%. Cells were exposed to compound for 72 hours. Proliferation was measured using XTT or MTS from Promega. The ovarian, breast, prostate, lung, leukemia, and colorectal human cancer cell lines used in this assay included but were not limited to, for example, A2780S, SKBR3, MDA-MB-231, PC3, LX-1, K562, HT-29, WiDr, HCT-15 and HCT116. The compounds of formula I exhibited activity in the 72-hour cell proliferation assay, inhibiting cell proliferation in one or more of the cell lines listed above with at an IC_{50} less than or equal to about 10 μ M.

15

Clonogenic Growth Assay

- Colony growth inhibition was measured for A2780 ovarian carcinoma cells using a standard clonogenic assay. Briefly, 200 cells/well were seeded into 6-well tissue culture plates (Falcon, Franklin Lakes, NJ) and allowed to attach for 18 hours. Assay medium consisted of RPMI-1640 plus 10% fetal bovine serum. Cells were then treated in duplicate with a six concentration dose-response curve. The maximum concentration of DMSO never exceeded 0.25%. Cells were exposed to compound for 4, 8 or 24 hours. Compound was then removed and the cells were washed with 2 volumes of PBS. The normal growth medium was then replaced. Colonies were fed with fresh media every third day. Colony number was scored on day 10-14 using a Optimax imaging station. The compound concentration required to inhibit 50% or 90% of colony formation (IC_{50} or IC_{90} , respectively) was determined by non-linear regression analysis. The coefficient of variance ($SD/mean$, $n=3$) = 30%. When exposed to cells for 24 hours, the compounds of formula I exhibited activity in the clonogenicity assay.
- 20
- 25
- 30

Combination Studies - Clonogenic Growth Assays

Combination studies to examine the use of the Eg5 inhibitors of formula I in combination with other antineoplastic agents were conducted essentially the same as the standard colony growth assay with the exception of compound treatment. In the
5 combination studies, the cells were treated with both a compound of formula I and another antineoplastic agent. The compounds were administered simultaneously or sequentially; both the order of sequence and length of treatment (1 to 24 hours) were varied. Data evaluation was based upon the isobologram analysis and the envelope of additivity, using the line of multiplicity which compares the survival fractions of
10 combination treatments with those of single drug treatments.

Cell Cycle Analysis

The cell cycle profile of cells treated with compounds of formula I was monitored by flow cytometry. Briefly, A2780 ovarian carcinoma cells were seeded at a density of 2
15 $\times 10^5$ per well in standard 6 well culture plates and permitted to grow for 17 hours. Cells were then exposed to compounds of formula I at varying concentrations for 2 to 24 hours. Following exposure, cell populations were harvested, stained with propidium iodide to determine DNA content and also stained with the appropriate immunological reagent for protein biomarkers of mitosis and apoptosis, including, for
20 example, anti-phospho-ThreonineProline, anti-M Phase Phosphoprotein 2 (MMP2), and anti-p85 PARP. The compounds of formula I exhibited activity in the cell cycle profile analysis assay, producing significant increases in mitotic and apoptotic fractions of the cell population.

25 Immunocytochemistry Assays

A2780 ovarian carcinoma cells or PTK2 kangaroo rat kidney epithelial cells were plated at a density of 200 to 2000 cells per well in 4 chamber glass slides and allowed to attach overnight. Cells were then treated with compounds of formula I at concentrations of 100 nM to 50 μ M for 4 to 30 hours, fixed and permeabilized for
30 subsequent staining. Stain reagents included, for example, propidium iodide, DAPI, rhodamine phalloidin, anti- α tubulin, anti- β tubulin, anti- γ tubulin, and the appropriate

fluorescent-tagged secondary antibodies. Cells were imaged by fluorescent and confocal fluorescent microscopy. The compounds of formula I inhibited bipolar spindle formation and induced a monoastral array of microtubules.

Further subject matter of the invention also includes pharmaceuticals for use as described above including controlling cancer, inflammation and arthritis, which contain at least one compound of the formula I as defined above or at least one of its pharmacologically acceptable acid addition salts, and the use of a compound of the formula I as defined above for the preparation of a pharmaceutical having activity against proliferative diseases as described previously including against cancer, inflammation and/or arthritis.

The following examples and preparations describe the manner and process of making and using the invention and are illustrative rather than limiting. It should be understood that there may be other embodiments which fall within the spirit and scope of the invention as defined by the claims appended hereto.

Example 1

5-Cyano-3,6-dihydro-4-methyl-6-(3-nitrophenyl)-2-thioxo-1-(2H)-pyrimidinecarboxylic acid, 1-ethyl ester

A. Step 1

A mixture of 6.42 g of acetoacetamide, 8.0 g of 3-nitrobenzaldehyde, 0.61 ml of acetic acid, and 0.21 ml of piperidine in 30 ml of toluene was heated to reflux. A Dean Stark trap was used to azeotrope the water produced. After refluxed for 2 h, the reaction mixture was cooled to room temperature, with a lot of solid appeared, it was treated with a solution of 300 ml of EtOAc and 25 ml MeOH, the solid was then filtered off, rinsed with 15 ml of EtOAc twice to give 3.1 g of desired product in 25% yield.

B. Step 2

A mixture of 200 mg of the compound of Example 1, Step 1, 198 mg of 2-(4-methoxybenzyl)-2-thiopseudourea HCl salt, 84 mg of sodium acetate in 3.6 ml DMF was heated at 85 °C for 15 h, then cooled to room temperature. The resulting reaction mixture was purified by preparative HPLC using a (YMC S5 ODS 20 X 100 mm)

column, the desired fraction was concentrated to dryness. Saturated NaHCO_3 (50 ml) was added and extracted with EtOAc (3 x 50 ml), combined EtOAc extracts were washed with 30 ml of brine, dried with MgSO_4 , filtered and concentrated under vacuum to give 126.1 mg desired product in 36% yield.

5

C. Step 3

A mixture of the compound of Example 1, Step 2 (86.5 mg) and Burgess reagent (150 mg) in 7.0 ml of anhydrous THF was stirred at room temperature for 1 h, concentrated under vacuum, then purified by preparative HPLC using a YMC S5 (10 ODS 20 X 100 mm) column to give 80.8 mg of desired product in 87% yield.

D. Step4

To a solution of the compound of Example 1, Step 3 (60 mg) and pyridine (0.1 ml) in 0.6 ml of CH_2Cl_2 , 17 μl of ethylchloroformate was added, after stirring for 2.5 h, 15 another 22 μl of ethylchloroformate was added, the reaction mixture was stirred for 2 h, then 0.3 ml of trifluoroacetic acid was added, the resulting mixture was stirred for another 1 h, and concentrated under vacuum, diluted with DMF, MeOH and a little CH_2Cl_2 , filtered, then purified by preparative HPLC using a (YMC S5 ODS 20 X 100 mm) column to give 22.5 mg of product in 42.7% yield. MS $(\text{M}-\text{H})^+ = 345$. HPLC RT 20 = 2.85 min (YMC S5 ODS column 4.6 x 50 mm, 10-90% aqueous methanol over 4 minutes containing 0.2% phosphoric acid, 4ml/min, monitoring at 220 nm)

Example 2

25 5-Cyano-3,6-dihydro-4-methyl-6-(3-nitrophenyl)-2-oxo-1-(2H)-pyrimidinecarboxylic acid, 1-ethyl ester

A. Step 1

10.92 g of NaHCO_3 was added portionwise to a solution of 7.83 g of the compound of Example 1, Step 1 and 7.48g of o-methylisourea hydrogen sulfate in DMF (100 ml), there was gas evolved. The reaction mixture was stirred for 2 h, then heated at 65°C 30 overnight, cooled to room temperature, diluted with 800 ml of EtOAc, washed with water (2 x 100 ml) and brine (1 x 100 ml). The organic layer was dried MgSO_4 .

filtered and concentrated under vacuum. The resulting residue was triturated in EtOAc-CH₂Cl₂-hexane to give 5.48 g of desired product as solid (56%).

B. Step 2

- 5 A mixture of the compound of Example 2, Step 1 (209 mg) and Burgess reagent (274.5 mg) in CH₂Cl₂ (5 ml) and THF (10 ml) was stirred overnight. The reaction mixture was concentrated under vacuum, diluted with 150 ml of EtOAc, then washed with saturated NaHCO₃ (2 x 30 ml) and brine (1 x 30 ml), dried with MgSO₄, concentrated under vacuum. The resulting residue was purified silica gel
10 chromatography to give 136 mg (69.4%) of desired product.

C. Step 3

- 1.23 ml of pyridine was added to a solution of 2.075 g of the compound of Example 2, Step 2 in CH₂Cl₂ (30 ml) under argon at 0 °C, then 0.87 ml of ethyl chloroformate
15 was added slowly. The reaction mixture was warmed to room temperature and stirred for 3 h, diluted with a mixture of saturated of NaHCO₃ (50 ml) and brine (50 ml), extracted with EtOAc three times, the combined layers were washed with brine and dried with MgSO₄, filtered and concentrated under vacuum, purified by silica gel chromatography to give 2.57 g (98%) of desired product.

20

D. Step 4

- 2.5 ml of TFA was added to a solution of 1.44 g of the compound of Example 2, Step 3 in CH₃CN (25 ml) and H₂O (2.5 ml), the reaction mixture was stirred for 2 h, a lot of white solid appeared. The solid was filtered off, rinsed with CH₃CN (3 x 20 ml)
25 and hexane (2 x 20 ml), dried in air to give 860 mg (62.2%) desired product. The filtrate was concentrated under vacuum, the solid was recrystallized in CH₃CN to give another 320 mg (23.2%) of product. MS (M-H)⁺ = 329. HPLC RT = 2.53 min (YMC S5 ODS column 4.6 x 50 mm, 10-90% aqueous methanol over 4 minutes containing 0.2% phosphoric acid, 4ml/min, monitoring at 220 nm)

Example 3

5-Cyano-3,6-dihydro-4-methyl-6-(3-nitrophenyl)-2-oxo-1-(2H)-pyrimidinecarboxylic acid, 1-ethyl amide.

A. Step 1

- 5 To a solution of the compound of Example 2, Step 2 (100 mg; 0.37 mmol) and pyridine (0.74 mmol; 18 μ L) in dichloroethane (40 mL) was added 4-nitrophenyl chloroformate (81 mg; 0.40 mmol) and the resulting solution was stirred at room temperature for 1.5 hours. The reaction mixture was diluted with saturated NaHCO₃ (30 mL), extracted with ethyl acetate (3 x 50 mL), dried (MgSO₄) and concentrated in
10 vacuo to afford a white foam. Purification by chromatography (SiO₂: 20% EtOAc/hexane) afforded the desired compound as a colorless foam (99 mg; 62%)

B. Step 2

- To a solution of the compound of Example 3, Step 1 (12 mg; 27 μ mol) in THF (0.1
15 mL) was added 2M ethylamine in THF solution (15 μ L; 30 mmol) in one portion at room temperature and the resulting yellow solution was stirred 30 minutes. Dilution of the reaction mixture with methanol (1.8 mL) afforded a yellow solid which was collected by suction filtration and purified by preparative HPLC to afford the title compound as a white solid (20 mg; 22%).

20

In contrast to the method of Example 2 above, in this case the 2-methoxy group hydrolyzed during isolation and purification to afford the dihydropyrimidinone ring without the need for treatment with TFA (Example 2, Step 4).

25

Example 4

5-Cyano-3,6-dihydro-4-methyl-6-(3-nitrophenyl)-2-oxo-1-(1-oxobutyl)-(2H)-pyrimidine

A. Step 1

- 23.7 μ L of butyryl chloride was added to a solution of 52 mg of the compound of
30 Example 2, Step 2 and 0.15 mL of pyridine in 0.6 mL of anhydrous CH₂Cl₂, the reaction mixture was stirred for 1h, then 24 μ L of butyryl chloride was added, the

reaction was stirred for 1.5 h, purified by preparative HPLC using a YMC S5 (ODS 20 x 100 mm) column to give 30 mg desired product.

B. Step 2

- 5 A solution of 30 mg of the compound of Example 4, Step 1, 0.2 ml of H₂O and 0.2 ml of TFA in 1.2 ml CH₃CN was stirred for 1.5 h, it was added another 0.1 ml of TFA and stirred for another 2.5 h. The reaction mixture was concentrated under vacuum, and purified by preparative HPLC using a YMC S5 (ODS 20 x 100 mm) column to give 11.8 mg desired product. MS (M-H)⁺ = 327. HPLC RT = 3.06 min (YMC S5
- 10 ODS column 4.6 x 50 mm, 10-90% aqueous methanol over 4 minutes containing 0.2% phosphoric acid, 4ml/min, monitoring at 220 nm)

Example 5

- enantio 5-Cyano-3,6-dihydro-4-methyl-6-(3-nitrophenyl)-2-oxo-1-(2H)-*
15 *pyrimidinecarboxylic acid, 1-ethyl ester (enantiomer A)*

53 mg of the compound of Example 2, Step 4 was dissolved in absolute EtOH, preparative chiral separation was carried out using a Chiralcel OD-H S5 (4.6 x 250 mm) column, 20 mg of enantiomer A and 27 mg of enantiomer B were obtained. MS (M-H)⁺ = 329. HPLC-Chiral RT = 10.44 min (Chiralcel OD-H, S5, column 4.6 x250

20 mm, 10% MeOH / 10% EtOH /Heptane, 1.0 ml /min, monitoring at 220 nm, 94.7% ee)

Example 6

- enantio 5-Cyano-3,6-dihydro-4-methyl-6-(3-nitrophenyl)-2-oxo-1-(2H)-*
pyrimidinecarboxylic acid, 1-ethyl ester (enantiomer B)
- 25 MS (M-H)⁺ = 329. HPLC-Chiral RT = 12.92 min (Chiralcel OD-H, S5, column 4.6 x250 mm, 10% MeOH / 10% EtOH /Heptane, 1.0 ml /min, monitoring at 220 nm, 99.64% ee)

Example 7

- 30 *5-Cyano-3,6-dihydro-4-methyl-6-(3-aminophenyl)-2-oxo-1-(2H)-*
pyrimidinecarboxylic acid, 1-ethyl ester

A solution of 12 mg of the compound of Example 1, Step 4 in ethanol was treated with 100 mg of tin (II) chloride and heated to reflux under argon for 90 min., the reaction was cooled down and quenched with saturated NaHCO₃ solution and extracted with EtOAc (3 x 50 ml). The combined organic layer was washed with H₂O, dried with Na₂SO₄ and concentrated under vacuum. It was triturated with hexane and ether to give 8 mg of crude product, which was further purified by preparative HPLC to afford 3 mg of desired product as TFA salt. MS (M+H)⁺ = 301. HPLC RT = 1.685 min (YMC S5 ODS column 4.6 x 50 mm, 10-90% aqueous methanol over 4 minutes containing 0.1% of TFA, 4ml/min, monitoring at 220 nm)

10

Example 8

5-Cyano-3,6-dihydro-4-methyl-6-(3-(N,N-dimethyl)aminophenyl)-2-oxo-1-(2H)-pyrimidinecarboxylic acid, 1-ethyl ester

A solution of 12 mg of the compound of Example 7 in CH₃CN (1 ml) was added paraformaldehyde (40 mg), sodium cyanoborohydride (30 mg) followed by 2 drops of acetic acid. The reaction mixture was stirred at room temperature for 2 h, then quenched with saturated NaHCO₃ solution and extracted with EtOAc three times. The combined organic layer was washed with brine, dried with Na₂SO₄ and concentrated under vacuum. The resulting residue was purified by preparative HPLC to yield 3.2 mg of desired product as TFA salt. MS (M+H)⁺ = 329. HPLC RT = 1.76 min (YMC S5 ODS column 4.6 x 50 mm, 10-90% aqueous methanol over 4 minutes containing 0.1% of TFA, 4ml/min, monitoring at 220 nm)

Examples 9 through 15 were prepared using the methods of Example 2 with the substitution of an appropriate benzaldehyde in Step 1.

Example 9

5-Cyano-3,6-dihydro-4-methyl-6-(3-trifluoromethylphenyl)-2-oxo-1-(2H)-pyrimidinecarboxylic acid, 1-ethyl ester

HPLC-HI 100% at 2.84 min (YMC S5 ODS column 4.6 x 50 mm, 10 - 90% aqueous methanol over 4 minutes containing 0.1% of TFA , 4 ml/min, monitoring at 220 nm). MS: [M+H]⁺ = 354.

30

11/11/160

Example 10

5-Cyano-3,6-dihydro-4-methyl-6-(2,3-dichlorophenyl)-2-oxo-1-(2H)-pyrimidinecarboxylic acid, 1-ethyl ester

HPLC-HI 100% at 3.2 min (YMC S5 ODS column 4.6 x 50 mm, 10 - 90% aqueous
5 methanol over 4 minutes containing 0.1% of TFA , 4 ml/min, monitoring at 220 nm).
MS: $[M-H]^- = 352$.

Example 11

5-Cyano-3,6-dihydro-4-methyl-6-(3-methoxyphenyl)-2-oxo-1-(2H)-pyrimidinecarboxylic acid, 1-ethyl ester

10 HPLC-HI 100% at 2.42 min (YMC S5 ODS column 4.6 x 50 mm, 10 - 90% aqueous
methanol over 4 minutes containing 0.1% of TFA , 4 ml/min, monitoring at 220 nm).
MS: $[M+H]^+ = 316$.

Example 12

15 **5-Cyano-3,6-dihydro-4-methyl-6-(3,5-dichlorophenyl)-2-oxo-1-(2H)-pyrimidinecarboxylic acid, 1-ethyl ester**

HPLC-HI 87% at 3.26 min (YMC S5 ODS column 4.6 x 50 mm, 10 - 90% aqueous
methanol over 4 minutes containing 0.1% of TFA , 4 ml/min, monitoring at 220 nm).
MS: $[M-H]^- = 352$.

20

Example 13

5-Cyano-3,6-dihydro-4-methyl-6-(3,4-dichlorophenyl)-2-oxo-1-(2H)-pyrimidinecarboxylic acid, 1-ethyl ester

HPLC-HI 100% at 3.197 min (YMC S5 ODS column 4.6 x 50 mm, 10 - 90% aqueous
25 methanol over 4 minutes containing 0.1% of TFA , 4 ml/min, monitoring at 220 nm).
MS: $[M-H]^- = 352$.

Example 14

5-Cyano-3,6-dihydro-4-methyl-6-(3-cyanophenyl)-2-oxo-1-(2H)-pyrimidinecarboxylic acid, 1-ethyl ester

30

HPLC-HI 93% at 2.32 min (YMC S5 ODS column 4.6 x 50 mm, 10 - 90% aqueous methanol over 4 minutes containing 0.1% of TFA , 4 ml/min, monitoring at 220 nm).
MS: $[M+H]^+ = 311$.

5

Example 15

5-Cyano-3,6-dihydro-4-methyl-6-(4-methoxyphenyl)-2-oxo-1-(2H)-pyrimidinecarboxylic acid, 1-ethyl ester

HPLC-HI 100% at 2.55 min (YMC S5 ODS column 4.6 x 50 mm, 10 - 90% aqueous methanol over 4 minutes containing 0.1% of TFA , 4 ml/min, monitoring at 220 nm).

10 MS: $[M+H]^+ = 316$.**Example 16**

5-Cyano-3,6-dihydro-4-methyl-6-(4-methylphenyl)-2-oxo-1-(2H)-pyrimidinecarboxylic acid, 1-ethyl ester

15 A. Step 1

A cloudy solution of 3-aminocrotononitrile (41 g, 0.5 mol) in Et₂O (500 ml) was added dropwise to the 15% HCl solution (115 ml) at 0°C over 30 min with vigorous stirring, and the reaction mixture was stirred at 0°C for 15 min. The aqueous solution was then separated, extracted with Et₂O (2 x 125 ml), the combined organic phases
20 dried with Na₂SO₄. Triethyl orthoformate (83 ml) in a 500 ml three-neck flask equipped with addition funnel and distillation set was stirred in 60°C-65°C oil bath, the above ether solution was added dropwise such that the rate of addition was equal to the rate of distillation. An additional 83 ml of triethyl orthoformate was added to the reaction when the addition of the ether solution was half complete, the oil bath
25 temperature was slowly raised to 100°C, and the reaction mixture was then stirred for 5 h. Distillation gave 26.6 g (38%) of desired red solid product at 150-155°C/ 2mm Hg.

B. Step 2

30 To a mixture of O-methylisourea sulfate (9.9 g, 80 mmol), the compound of Example 16, Step 1 (7.4 g, 53 mmol) and ethanol (90 ml) was added Et₃N (11 ml, 80 mmol). The mixture was stirred at room temperature for 15 min, then stirred at 66°C for 3 h,

and concentrated to remove EtOH. EtOAc (80 ml) and H₂O (80 ml) were added, the aqueous layer were separated and extracted with EtOAc (2 x 80 ml), the combined organic layer were dried with Na₂SO₄, concentrated to give brown solid, which was dissolved in EtOAc, filtered through a silica gel pad, washed with EtOAc/heptane (1/1) to remove dark color, and the combined filtrate was concentrated. The solid thus obtained was recrystallized in heptane / EtOAc to give yellow crystal 5.18 g in 65% yield.

C. Step 3

10 A solution of p-tolylmagnesium bromide in ether (1M, 1 ml, 1 mmol) was added dropwise to a solution of the compound of Example 16, Step 2 (75 mg, 0.5 mmol) in THF (2 ml) at 0°C under argon. The reaction mixture was stirred at the temperature for 1.5 h, another 3 ml of Grignard reagent was added at -78°C, the reaction was slowly warmed to room temperature and stirred for 2 min. Saturated NH₄Cl (5 ml) and H₂O (5 ml) were added, the mixture was extracted with EtOAc (2 x 15 ml), the combined organic layer was dried, concentrated and chromatographed on silica gel to give 45.6 mg of desired product in 91% yield.

D. Step 4

20 To a solution of the compound of Example 16, Step 3 (109 mg, 0.45 mmol) was added pyridine (0.2 ml, 2.5 mmol) in dry CH₂Cl₂ (5 ml) followed by ethyl chloroformate (0.1 ml, 1.05 mmol), and the resulting reaction mixture was stirred at room temperature overnight. MeOH was added, the resulting mixture was stirred for 15 min, concentrated, and chromatographed on silica gel column to give 100 mg desired product as colorless oil (71%).

E. Step 5

A mixture of the compound of Example 15, Step 4 (100 mg, 0.32 mmol), H₂O (0.7 ml), CH₃CN (0.5 ml) and TFA (7 ml) was stirred at room temperature for 2 h. The solution was then concentrated to remove CH₃CN, saturated NaHCO₃ was added to make the mixture basic, the white solid precipitate was filtered, washed with H₂O, and dried to give the desired product (64 mg). The crude product was dried and recrystallized from EtOH / H₂O to give another 20 mg desired product as white solid.

MS (M+H)⁺ = 300. HPLC RT = 3.40 min (YMC S5 ODS column 4.6 x 50 mm, 10-90% aqueous methanol over 4 minutes containing 0.2% phosphoric acid, 4 ml/min, monitoring at 220 nm)

Example 17

5 **5-Cyano-3,6-dihydro-4-methyl-6-cyclohexyl-2-oxo-1-(2H)-pyrimidinecarboxylic acid, 1-ethyl ester**

To a solution of the compound of Example 16, Step 2 (30 mg, 0.2 mmol) in THF (1.2 ml) was added cyclohexylmagnesium chloride (2 M in ether, 1.0 ml, 2 mmol) at -44°C under argon, the reaction was slowly warmed to room temperature, and stirred
10 for 10 min. Saturated NH₄Cl was added, the resulting mixture was extracted several times with EtOAc, the combined organic layer dried, filtered through a silica gel pad, and concentrated to give yellow oil. The oil was dissolved in CH₂Cl₂ (2 ml), then pyridine (80 µl, 0.9 mmol) and ethyl chloroformate (50 µl, 0.5 mmol) were added, the mixture was stirred at room temperature for 30 min, stirred for another 10 min after
15 which H₂O (25 µl) and EtOAc were added, and the mixture dried over Na₂SO₄, filtered through a silica gel pad, and concentrated to give yellow oil. The oil was dissolved in CH₃CN (2 ml), H₂O (0.3 ml) and TFA (0.2 ml) were added, and the mixture stirred at room temperature for 2 h. Saturated NaHCO₃ solution and EtOAc were added, the aqueous layer was separated and extracted with EtOAc, and the
20 combined organic layer was dried over Na₂SO₄, concentrated and chromatographed on silica gel to give 35 mg of desired product as yellow foam (60%). MS (M+H)⁺ = 392. HPLC RT = 3.60 min (YMC S5 ODS column 4.6 x 50 mm, 10-90% aqueous methanol over 4 minutes containing 0.2% phosphoric acid, 4 ml/min, monitoring at 220 nm)

25

Example 18

5-Cyano-3,6-dihydro-4-methyl-6-phenyl-2-oxo-1-(2H)-pyrimidinecarboxylic acid, 1-ethyl ester

To a solution of the compound of Example 16, Step 2 (55 mg, 0.37 mmol) in dry THF
30 (2 ml) was added phenylmagnesium bromide (2 M in THF, 2 ml, 4 mmol) dropwise at -78°C under argon. After addition, the reaction was slowly warmed to room

temperature and stirred for about 10 min, until starting material disappeared. Saturated NH_4Cl solution and H_2O were added, the mixture was extracted with EtOAc for two times, and the combined organic layer was dried over Na_2SO_4 , concentrated and chromatographed on silica gel to give solid intermediate. The solid
5 was dissolved in CH_2Cl_2 (5 ml), pyridine (0.15 ml, 1.8 mmol) and ethyl chloroformate (0.1 ml, 1 mmol) were added, and the reaction mixture was stirred at room temperature for 0.5 h. The reaction was quenched with 50 μl of H_2O , diluted with 5 ml of EtOAc, the resulting mixture was dried over Na_2SO_4 , filtered through silica gel column to give the intermediate as an oil. The oil was dissolved in CH_3CN (5 ml),
10 H_2O (0.5 ml) and TFA (0.4 ml) were added, the reaction mixture stirred for 1.5 h, and concentrated in vacuo. Saturated NaHCO_3 solution was added to neutralize the mixture, and the precipitate was then filtered and air dried. Recrystallization in EtOAc / heptane to give 70 mg solid product in 66% yield. MS $(\text{M}+\text{H})^+ = 286$. HPLC RT = 1.28 min. (Phenom-Prime S5 C18 4.6 x 30 mm, 10-90 % aqueous methanol over 2
15 minutes containing 0.1 % TFA, 5 ml/min, monitoring at 220 nm)

Examples 19 through 24 were prepared using the method of Example 18 with the substitution of an appropriate arylmagnesiumhalide.

20

Example 19

5-Cyano-3,6-dihydro-4-methyl-6-(2-methylphenyl)-2-oxo-1-(2H)-pyrimidinecarboxylic acid, 1-ethyl ester

MS $(\text{M}+\text{H})^+ = 300$. HPLC RT = 1.41 min. (Phenom-Prime S5 C18 4.6 x 30 mm, 10-90 % aqueous methanol over 2 minutes containing 0.1 % TFA, 5 ml/min, monitoring
25 at 220 nm)

Example 20

5-Cyano-3,6-dihydro-4-methyl-6-(3-chlorophenyl)-2-oxo-1-(2H)-pyrimidinecarboxylic acid, 1-ethyl ester

30 MS $(\text{M}+\text{H})^+ = 320$. HPLC RT = 1.43 min. (Phenom-Prime S5 C18 4.6 x 30 mm, 10-90 % aqueous methanol over 2 minutes containing 0.1 % TFA, 5 ml/min, monitoring at 220 nm)

Example 21

5-Cyano-3,6-dihydro-4-methyl-6-(3-fluorophenyl)-2-oxo-1-(2H)-pyrimidinecarboxylic acid, 1-ethyl ester

MS (M+H)⁺ = 304. HPLC RT = 1.29 min. (Phenom-Prime S5 C18 4.6 x 30 mm, 10-
5 90 % aqueous methanol over 2 minutes containing 0.1 % TFA, 5 ml/min, monitoring
at 220 nm)

Example 22

5-Cyano-3,6-dihydro-4-methyl-6-(4-chlorophenyl)-2-oxo-1-(2H)-pyrimidinecarboxylic acid, 1-ethyl ester

MS (M+H)⁺ = 320. HPLC RT = 1.44 min. (Phenom-Prime S5 C18 4.6 x 30 mm, 10-
10 90 % aqueous methanol over 2 minutes containing 0.1 % TFA, 5 ml/min, monitoring
at 220 nm)

Example 23

5-Cyano-3,6-dihydro-4-methyl-6-(4-fluorophenyl)-2-oxo-1-(2H)-pyrimidinecarboxylic acid, 1-ethyl ester

MS (M+H)⁺ = 304. HPLC RT = 3.21 min (YMC S5 ODS column 4.6 x 50 mm, 10-
90% aqueous methanol over 4 minutes containing 0.2% phosphoric acid, 4 ml/min,
15 20 monitoring at 220 nm)

Example 24

5-Cyano-3,6-dihydro-4-methyl-6-(2-fluorophenyl)-2-oxo-1-(2H)-pyrimidinecarboxylic acid, 1-ethyl ester

MS (M+H)⁺ = 304. HPLC RT = 3.05 min (YMC S5 ODS column 4.6 x 50 mm, 10-
25 90% aqueous methanol over 4 minutes containing 0.2% phosphoric acid, 4 ml/min,
monitoring at 220 nm)

Example 25

6-(3,5-Bis-trifluoromethylphenyl)-5-cyano-4-methyl-2-oxo-3,6-dihydro-2H-pyrimidine-1-carboxylic acid ethyl ester

30

163

A. Step 1

4-(3,5-Bis-trifluoromethylphenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid amide. A mixture of 3,5-bis(trifluoromethyl)benzaldehyde (2.42 g, 10.0 mmol), acetoacetamide (1.01 g, 10.0 mmol), urea (0.90 g, 15.0 mmol), copper chloride (0.1 g, 1.0 mmol), boron trifluoride etherate (0.09 mL), AcOH (0.04 mL), and THF (20 mL) was heated at 65 °C for 18 h and cooled to room temperature. The resulting precipitates were collected by vacuum filtration, washed with THF, and air dried to give the title compound as an off-white solid (1.33 g, 36%).

10 B. Step 2

4-(3,5-Bis-trifluoromethylphenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydro-pyrimidine-5-carbonitrile. To a mixture of compound from Step 1 (1.10 g, 3.0 mmol) and pyridine (12 mL) at 0 °C was added trifluoroacetic anhydride (1.3 mL, 9.0 mmol) slowly over 10 min. The reaction mixture became a clear brown solution and was stirred for 18 h, then poured into water. The resulting off-white precipitates were collected by vacuum filtration, washed with water, and air dried to give the title compound as a light brown solid (1.06 g, 100%).

C. Step 3

6-(3,5-Bis-trifluoromethylphenyl)-5-cyano-4-methyl-2-oxo-3,6-dihydro-2H-pyrimidine-1-carboxylic acid ethyl ester. To a solution of compound from Step 2 (60.0 mg, 0.17 mmol) in THF (2 mL) chilled to -78 °C was added LDA (0.15 mL, 0.30 mmol, 2.0 M in hexanes). The resulting mixture was stirred at -78 °C for 15 min, warmed to -25 °C for 15 min, recooled to -78 °C and ethyl chloroformate (20 µL, 0.20 mmol) was added via a syringe. The reaction mixture was stirred at -78 °C for 15 min, gradually warmed to room temperature and stirred for 1 h, quenched with MeOH and concentrated in vacuo. The residue was purified by preparative HPLC (methanol/water); product fractions were combined and concentrated in vacuo to afford the title compound as an off-white solid (28.4 mg, 40%).

¹H-NMR (DMSO-d₆, 400 MHz): δ 10.64 (s, 1 H), 8.19 (s, 1 H), 7.93 (s, 2 H), 6.15 (s, 1 H), 4.17 (m, 2 H), 2.10 (s, 3 H), 1.17 (t, 3 H, J = 7.0 Hz). LC/MS (ES+) 444 (M+Na)⁺.

Example 26**6-Butyl-5-cyano-4-methyl-2-oxo-3,6-dihydro-2H-pyrimidine-1-carboxylic acid ethyl ester**

5

A. Step 1**4-Hexyl-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carbonitrile.**

Polyphosphate ester (1.15 g, 3.89 mmol, 0.30 eq) was added to a sealed tube containing a solution of urea (1.17 g, 19.4 mmol), valeraldehyde (1.38 ml, 12.9 mmol) and acetoacetamide (1.31 g, 12.9 mmol) in THF (15 mL) under argon and heated at 75°C for three hours. The reaction mixture was cooled to room temperature, polyphosphate ester (8.80 g, 29.8 mmol) was added and the reaction mixture was heated at 85°C for four hours. The reaction mixture was cooled to room temperature and poured on ice. The aqueous solution was neutralized with 1N NaOH and extracted with chloroform (3X100 mL). The combined organic layers were dried (Na₂SO₄), filtered and concentrated under vacuum to give the title compound (0.940 g, 97%); HRMS 192.1143 (M-H)⁺. The product was used in the next step without further purification.

20 **B. Step 2**

6-Butyl-5-cyano-4-methyl-2-oxo-3,6-dihydro-2H-pyrimidine-1-carboxylic acid ethyl ester. LDA (0.585 mL, 1.17 mmol, 2.0 M in hexane) was added dropwise to a solution of compound from Step 1 (0.150 g, 0.777 mmol) in THF (5mL) at -78°C. The reaction mixture was stirred at -78°C for twenty minutes and ethyl chloroformate (0.111 mL, 1.17 mmol) was added in one portion. The reaction mixture was allowed to warm to room temperature and was stirred for sixteen hours. The reaction mixture was quenched with saturated ammonium chloride (35 ml) and the solution was extracted with chloroform (3X100 ml). The combined organic layers were dried (Na₂SO₄), filtered and concentrated under vacuum. The residue was purified by flash chromatography (eluting 2/1 ethyl acetate/hexanes) to afford the title compound (0.110 g, 53%) as a solid.

30

¹H-NMR (DMSO-d₆, 400 MHz): δ 0.86 (t, 3 H, J = 6.79), 1.21-1.33 (m, 7H), 1.54-1.65 (m, 2H), 2.04 (s, 3H), 4.17-4.23 (m, 2H), 4.68 (t, 1H, J = 6.42), 10.33 (s, 1H). MS 264 (M-H)⁻. HRMS 266.1506 (M+H)⁺.

5

Example 27**5-Cyano-4-methyl-6-(3-nitrophenyl)-2-oxo-3,6-dihydro-2H-pyrimidine-1-carboxylic acid methylamide**

A. Step 1

10 **5-Cyano-4-methyl-6-(3-nitrophenyl)-2-oxo-3,6-dihydro-2H-pyrimidine-1-carboxylic acid 4-nitrophenyl ester.** To a suspension of 6-Methyl-4-(3-nitrophenyl)-2-oxo-1,2,3,4-tetrahydro-pyrimidine-5-carbonitrile (0.43 g, 1.7 mmol, prepared by the method described in Example 26, Step 1, in 77 % yield) in THF (15 mL) at -78 °C was added LDA (1.25 mL, 2.5 mmol, 2.0 M in hexanes). The resulting
15 mixture was stirred at -78 °C for 15 min, warmed to -25 °C for 15 min, re-cooled to -78 °C and 4-nitrophenyl chloroformate (0.50 g, 2.5 mmol) was added in one portion. The reaction mixture was stirred at -78 °C for 15 min, gradually warmed to room temperature, quenched with water and extracted with ethyl acetate. The organic extract was washed with brine, dried (MgSO₄) and concentrated in vacuo. The
20 residue was purified by flash column chromatography on silica gel using 50% to 70% ethyl acetate-hexane as eluant to give the title compound as a light yellow solid (0.38 g, 53%).

B. Step 2

25 **5-Cyano-4-methyl-6-(3-nitrophenyl)-2-oxo-3,6-dihydro-2H-pyrimidine-1-carboxylic acid methylamide.** To a solution of compound from Step 1 (12.5 mg, 0.03 mmol) in THF (1 mL) was added methylamine (4.1 uL, 0.033 mmol, 8 M in EtOH). The reaction mixture was stirred for 2 h and concentrated in vacuo. The residue was purified by preparative HPLC (methanol/water). Product fractions were
30 combined, concentrated in vacuo and lyophilized to give the title compound as a colorless solid (8.2 mg, 87%).

¹H-NMR (MeOH-d₄, 400 MHz): δ 8.22 (m, 1 H), 8.17 (t, 1 H, J = 1.8 Hz), 7.76 (m, 1 H), 7.65 (t, 1 H, J = 7.9 Hz), 6.30 (s, 1 H), 2.82 (s, 3 H), 2.18 (s, 3 H). LC/MS (ES+) 338 (M+Na)⁺.

5

Example 28

5-Cyano-4-methyl-2-oxo-6-phenyl-3,6-dihydro-2H-pyrimidine-1-carboxylic acid ethylamide. To a solution 6-Methyl-2-oxo-4-phenyl-1,2,3,4-tetrahydropyrimidine-5-carbonitrile (100 mg, 0.47 mmole, obtained in 65 % yield by the procedure described in Example 26, Step 1) in 4 mL of tetrahydrofuran under argon at room temperature
10 was added oil free sodium hydride (17 mg, 0.70 mmole). After stirring for ten minutes, ethyl isocyanate (50 mg, 0.70 mmole) was added. The reaction mixture was diluted with ethyl acetate and washed with dilute citric acid, water and saturated brine. The dried (anhydrous magnesium sulfate) organic extract was concentrated *in vacuo* and the product purified by flash chromatography on silica gel, eluting with
15 ethyl acetate/hexanes (3:2) to give 100 mg (75 %) of title compound as a white solid. ¹H-NMR (DMSO-d₆, 400 MHz) δ 10.51 (br s, 1 H); 8.79 (t, J = 5.4 Hz, 1 H); 7.22-7.48 (m, 5 H); 6.09 (s, 1 H); 3.10-3.25 (m, 2 H); 2.08 (s, 3 H); 1.03 (t, J = 7.2 Hz, 3 H). LC/MS (ES+) 285 (M+H)⁺.

20

Example 29

5-Cyano-6-(3,5-dichlorophenyl)-4-methyl-2-oxo-3,6-dihydro-2H-pyrimidine-1-carboxylic acid 2-methoxy-ethyl ester

Using 3,5-dichlorobenzaldehyde and following the procedure described in Example 2, the title compound was obtained in 3 % overall yield.

25 ¹H-NMR (DMSO-d₆, 500 MHz): δ 10.59 (s, 1 H), 7.66 (t, 1 H, J = 1.6 Hz), 7.31 (d, 2 H, J = 1.6 Hz), 5.90 (s, 1 H), 4.26 (m, 2 H), 3.54 (m, 2 H), 3.25 (s, 3 H), 2.11 (s, 3 H). LC/MS (ES+) 384 (M+H)⁺.

145
165**Example 30****5-Cyano-4-methyl-2-oxo-6-(3-trifluoromethylphenyl)-3,6-dihydro-2H-pyrimidine-1-carboxylic acid ethylamide**

Using 3-trifluoromethylbenzaldehyde and following a modification of the procedure described in Example 2, the title compound was obtained in 3 % overall yield.

¹H-NMR (CDCl₃, 400 MHz): δ 8.68 (s, 1 H), 7.60 (m, 2 H), 7.53 (m, 2 H), 6.37 (s, 1 H), 3.30 (m, 2 H), 2.08 (s, 3 H), 1.17 (t, 3 H, J = 7.0 Hz). LC/MS (ES+) 353 (M+H)⁺, 375 (M+Na)⁺.

10

Example 31**5-Cyano-6-(3,5-dichlorophenyl)-4-methyl-2-oxo-3,6-dihydro-2H-pyrimidine-1-carboxylic acid ethylamide**

Using 3,5-dichlorobenzaldehyde and following a modification of the procedure described in Example 2, the title compound was obtained in 5 % overall yield.

¹H-NMR (DMSO-d₆, 400 MHz): δ 10.56 (s, 1 H), 8.76 (t, 1 H, J = 5.3 Hz), 7.63 (t, 1 H, J = 1.8 Hz), 7.27 (d, 2 H, J = 1.8 Hz), 6.10 (s, 1 H), 3.16 (m, 2 H), 2.09 (s, 3 H), 1.03 (t, 3 H, J = 7.0 Hz). LC/MS (ES+) 353 (M+H)⁺, 375 (M+Na)⁺.

Example 32**3-Butyryl-4-(3,5-dichlorophenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carbonitrile**

Using 3,5-dichlorobenzaldehyde and following the procedure described in Example 2, the title compound was obtained in 7 % overall yield.

¹H-NMR (DMSO-d₆, 500 MHz): δ 10.63 (s, 1 H), 7.63 (t, 1 H, J = 1.6 Hz), 7.26 (d, 2 H, J = 1.6 Hz), 6.04 (s, 1 H), 2.95 (m, 1 H), 2.74 (m, 1 H), 1.54 (m, 2 H), 2.11 (s, 3 H), 0.86 (t, 3 H, J = 7.1 Hz).

Example 33**5-Cyano-4-methyl-2-oxo-6-(3-trifluoromethylphenyl)-3,6-dihydro-2H-pyrimidine-1-carboxylic acid (2-dimethylamino-ethyl)-amide**

Using 3-trifluoromethylbenzaldehyde and following the procedure described in Example 2, the title compound was obtained in 8 % overall yield.

¹H-NMR (MeOH-d₄, 400 MHz): δ 7.64 (m, 1 H), 7.59 (m, 3 H), 6.25 (s, 1 H), 3.43 (m, 1 H), 3.38 (m, 1 H), 2.56 (t, 1 H, J = 6.2 Hz), 2.32 (s, 6 H), 2.15 (d, 3 H, J = 0.9 Hz); LC/MS (ES+) 396 (M+H)⁺.

5

Example 34**5-Cyano-4-methyl-2-oxo-6-(3-trifluoromethylphenyl)-3,6-dihydro-2H-pyrimidine-1-carbothioic acid S-ethyl ester**

Using 3-trifluoromethylbenzaldehyde and following a modification of the procedure described in Example 2, the title compound was obtained in 3 % overall yield.

10 ¹H-NMR (CDCl₃, 400 MHz): δ 8.21 (s, 1 H), 7.61 (m, 1 H), 7.52 (m, 3 H), 6.24 (s, 1 H), 2.87 (m, 2 H), 2.26 (d, 3 H, J = 0.9 Hz), 1.26 (t, 3 H, J = 7.5 Hz). LC/MS (ES+) 392 (M+Na)⁺.

Example 35

15 **5-Cyano-4-methyl-2-oxo-6-(3-trifluoromethylphenyl)-3,6-dihydro-2H-pyrimidine-1-carboxylic acid (2-hydroxy-ethyl)-amide**

Using 3-trifluoromethylbenzaldehyde and following a modification of the procedure described in Example 2, the title compound was obtained in 15 % overall yield.

¹H-NMR (MeOH-d₄, 400 MHz): δ 7.63 (m, 1 H), 7.58 (m, 3 H), 6.25 (s, 1 H), 3.58 (m, 2 H), 3.35 (m, 2 H), 2.15 (s, 3 H). LC/MS (ES+) 369 (M+H)⁺.

Example 36**4-(3,5-Dichlorophenyl)-6-methyl-2-oxo-3-(thiophene-2-carbonyl)-1,2,3,4-tetrahydropyrimidine-5-carbonitrile**

25 Using 3,5-dichlorobenzaldehyde and following the procedure described in Example 2, the title compound was obtained in 5 % overall yield

¹H-NMR (DMSO-d₆, 400 MHz): δ 10.78 (s, 1 H), 7.96 (d, 1 H, J = 4.8 Hz), 7.72 (d, 1 H, J = 3.1 Hz), 7.64 (t, 1 H, J = 1.8 Hz), 7.36 (d, 2 H, J = 1.8 Hz), 7.17 (m, 1 H), 5.92 (s, 1 H), 2.82 (s, 3 H), 2.18 (s, 3 H). LC/MS (ES+) 415 (M+Na)⁺.

30

11/16/02

Example 37**5-Cyano-6-(3,5-difluorophenyl)-4-methyl-2-oxo-3,6-dihydro-2H-pyrimidine-1-carboxylic acid ethylamide**

Intermediate IX was obtained using 3,5-difluorobenzaldehyde and following the
5 procedure described in Example 2. The title compound was obtained in 28 % yield
following the procedure of Example 3.

¹H-NMR (CD₃Cl, 400 MHz): δ 6.77 (m, 2 H), 6.67 (m, 1 H), 6.21 (s, 1 H), 3.27 (m, 2
H), 2.15 (s, 3 H), 1.12 (t, 3H, J = 10.4 Hz). LC/MS (ES+) 321 (M+H)⁺.

10

Example 38**5-Cyano-6-(3,5-difluorophenyl)-4-methyl-2-oxo-3,6-dihydro-2H-pyrimidine-1-carboxylic acid ethyl ester**

Using 3,5-difluorobenzaldehyde and following the procedure described in Example 2,
the title compound was obtained in 36 % yield for the final two steps.

15 ¹H-NMR (CD₃Cl, 400 MHz): δ 8.26 (s, 1 H), 6.83 (m, 2 H), 6.73 (m, 1 H), 5.80 (s, 1
H), 4.27 (m, 2 H), 2.15 (s, 3 H), 1.26 (t, 3H, J = 10.4 Hz). LC/MS (ES+) 322 (M+H)⁺.

Example 39**4-(3,5-Difluorophenyl)-6-methyl-2-oxo-3-(piperidine-1-carbonyl)-1,2,3,4-tetrahydropyrimidine-5-carbonitrile**

20

Intermediate IX was obtained using 3,5-difluorobenzaldehyde and following the
procedure described in Example 2. The title compound was obtained in 30 % yield
following the procedure of Example 3.

25 ¹H-NMR (CD₃OD, 400 MHz): δ 7.01 (m, 3 H), 5.62(s, 1 H), 5.48 (s, 1 H), 3.37 (m, 2 H), 3.24 (m, 2
H), 2.14 (s, 3 H), 1.84 (m, 4), 1.28 (m, 4H). LC/MS (ES+) 361 (M+H)⁺.

Example 40**4-(3,5-Difluorophenyl)-6-methyl-2-oxo-3-(pyrrolidine-1-carbonyl)-1,2,3,4-tetrahydropyrimidine-5-carbonitrile**

Intermediate IX was obtained using 3,5-difluorobenzaldehyde and following the
30 procedure described in Example 2. The title compound was obtained in 18 % yield
following the procedure of Example 3.

¹H-NMR (CD₃OD, 400 MHz): δ 8.25 (s, 1 H), 8.24 (d, 1 H, J = 7.9 Hz), 7.82 (d, 1 H, J = 7.9 Hz), 7.67 (t, 2 H, J = 7.9 Hz), 5.77 (s, 1H), 2.29-3.30 (m, 4 H), 2.16 (s, 3 H), 1.77 (m, 4). LC/MS (ES+) 355 (M+H)⁺.

5

Example 41**5-Cyano-4-methyl-6-naphthalen-1-yl-2-oxo-3,6-dihydro-2H-pyrimidine-1-carboxylic acid ethyl ester**

Using naphthalene-1-carboxaldehyde and following the procedure of Example 25, intermediate XXIV was obtained in 44 % yield and the title compound was obtained in 22 % yield.

¹H-NMR (DMSO-d₆, 400 MHz): δ 10.57 (s, 1 H), 8.40 (d, 1 H, J = 8.4 Hz), 7.98 (d, 1 H, J = 7.9 Hz), 7.94 (d, 1 H, J = 8.4 Hz), 7.61 (m, 2 H), 7.55 (t, 1 H, J = 7.0 Hz), 7.39 (d, 1 H, J = 7.0 Hz), 6.73 (s, 1 H), 4.04 (m, 2 H), 2.05 (s, 3 H), 1.00 (t, 3 H, J = 7.0 Hz). LC/MS (ES+) 336 (M+H)⁺.

15

Example 42**5-Cyano-4-methyl-6-naphthalen-1-yl-2-oxo-3,6-dihydro-2H-pyrimidine-1-carboxylic acid ethylamide**

Using naphthalene-1-carboxaldehyde and following the procedure of Example 25, intermediate XXIV was obtained in 44 % yield. The title compound was obtained in 67 % yield following the procedure described in Example 28.

¹H-NMR (CDCl₃, 400 MHz): δ 8.83 (t, 1 H, J = 5.3 Hz), 8.43 (d, 1 H, J = 8.4 Hz), 7.96 (s, 1 H), 7.84 (m, 2 H), 7.61 (m, 1 H), 7.52 (t, 1 H, J = 7.0 Hz), 7.42 (t, 1 H, J = 7.9 Hz), 7.36 (d, 1 H, J = 6.2 Hz), 7.14 (s, 1 H), 3.30 (m, 1 H), 3.21 (m, 1 H), 1.92 (s, 3 H), 1.11 (t, 3 H, J = 7.5 Hz). LC/MS (ES+) 335 (M+H)⁺, 357 (M+Na)⁺.

25

Example 43**6-(3-Bromophenyl)-5-cyano-4-methyl-2-oxo-3,6-dihydro-2H-pyrimidine-1-carboxylic acid ethyl ester**

Using 3-bromobenzaldehyde and following the procedure of Example 25, intermediate XXIV was obtained in 25 % yield and the title compound was obtained in 80 % yield.

30

¹H-NMR (CDCl₃, 400 MHz): δ 7.48 (m, 2 H), 7.27 (m, 2 H), 5.87 (s, 1 H), 4.33 (m, 2 H), 2.22 (s, 3 H), 1.33 (t, 3 H, J = 7.0 Hz). LC/MS (ES+) 364 (M+H)⁺.

Example 44

5 **6-(3-Bromophenyl)-5-cyano-4-methyl-2-oxo-3,6-dihydro-2H-pyrimidine-1-carboxylic acid ethylamide**

Using 3-bromobenzaldehyde and following the procedure of Example 25, intermediate XXIV was obtained in 25 % yield. The title compound was obtained in 88 % yield following the procedure described in Example 28.

10 ¹H-NMR (CDCl₃, 400 MHz): δ 8.65 (t, 1 H, J = 5.3 Hz), 7.91 (s, 1 H), 7.84 (m, 1 H), 7.38 (m, 1 H), 7.19 (m, 2 H), 6.24 (s, 1 H), 3.24 (m, 2 H), 2.10 (s, 3 H), 1.10 (t, 3 H, J = 7.0 Hz). LC/MS (ES+) 363 (M+H)⁺.

Example 45

15 **5-Cyano-4-methyl-2-oxo-6-(2-trifluoromethylphenyl)-3,6-dihydro-2H-pyrimidine-1-carboxylic acid ethyl ester**

Using 2-trifluoromethylbenzaldehyde and following the procedure of Example 25, intermediate XXIV was obtained in 43 % yield and the title compound was obtained in 30 % yield.

20 ¹H-NMR (DMSO-d₆, 400 MHz) δ 10.58 (s, 1 H), 7.77 (m, 2 H), 7.58 (t, 1 H, J = 7.5 Hz), 7.51 (d, 1 H, J = 8.4 Hz), 6.06 (d, 1 H, J = 0.9 Hz), 4.06 (m, 2 H), 2.05 (d, 3 H, J = 0.9 Hz), 1.05 (t, 3 H, J = 7.0 Hz). LC/MS (ES+) 354 (M+H)⁺, 376 (M+Na)⁺.

Example 46

25 **5-Cyano-4-methyl-2-oxo-6-(2-trifluoromethylphenyl)-3,6-dihydro-2H-pyrimidine-1-carboxylic acid ethylamide**

Using 2-trifluoromethylbenzaldehyde and following the procedure of Example 25, intermediate XXIV was obtained in 43 % yield. The title compound was obtained in 26 % yield following the procedure described in Example 28.

30 ¹H-NMR (MeOH-d₄, 400 MHz): δ 9.07 (s, 1 H), 7.69 (d, 1 H, J = 7.9 Hz), 7.64 (d, 1 H, J = 7.9 Hz), 7.54 (d, 1 H, J = 7.9 Hz), 7.49 (t, 1 H, J = 7.9 Hz), 6.48 (s, 1 H), 3.17

(m, 2 H), 2.11 (s, 3 H), 1.06 (t, 3 H, $J = 7.0$ Hz). LC/MS (ES+) 353 (M+H)⁺, 375 (M+Na)⁺.

Example 47

5 **5-Cyano-6-(3-methoxycarbonylphenyl)-4-methyl-2-oxo-3,6-dihydro-2H-pyrimidine-1-carboxylic acid ethyl ester**

Using methyl 3-formylbenzoate and following the procedure of Example 25, intermediate XXIV was obtained in 30 % yield and the title compound was obtained in 50 % yield.

10 ¹H-NMR (MeOH-d₄, 400 MHz): δ 8.02 (m, 2 H), 7.60 (m, 1 H), 7.52 (m, 1 H), 5.93 (s, 1 H), 4.28 (m, 2 H), 3.92 (s, 3 H), 2.18 (s, 3 H), 1.29 (t, 3 H, $J = 7.0$ Hz). LC/MS (ES+) 344 (M+H)⁺, 366 (M+Na)⁺.

Example 48

15 **3-(5-Cyano-3-ethylcarbamoyl-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidin-4-yl)-benzoic acid methyl ester**

Using methyl 3-formylbenzoate and following the procedure of Example 25, intermediate XXIV was obtained in 30 % yield. The title compound was obtained in 40 % yield following the procedure described in Example 28.

20 ¹H-NMR (MeOH-d₄, 400 MHz): δ 8.94 (s, 1 H), 7.89 (m, 2 H), 7.48 (d, 1 H, $J = 7.9$ Hz), 7.40 (t, 1 H, $J = 7.9$ Hz), 6.15 (s, 1 H), 3.83 (s, 3 H), 3.17 (m, 2 H), 2.07 (s, 3 H), 1.05 (t, 3 H, $J = 7.0$ Hz). LC/MS (ES+) 343 (M+H)⁺, 365 (M+Na)⁺.

Example 49

25 **BMS-511181 6-Butyl-5-cyano-4-methyl-2-oxo-3,6-dihydro-2H-pyrimidine-1-carboxylic acid ethylamide**

Using 1-butanaldehyde and following the procedure of Example 26, intermediate XXIV was obtained in 97 % yield. The title compound was obtained in 55 % yield following the procedure described in Example 28.

30 ¹H-NMR (DMSO-d₆, 400 MHz): δ 0.85 (t, 3 H, $J = 6.7$), 1.07 (t, 3H, $J = 7.2$), 1.23-1.29 (m, 4H), 1.44-1.60 (m, 2H), 2.05 (s, 3H), 3.17-3.32 (m, 2H), 5.04 (t, 1H, $J = 6.0$), 8.70(t, 1H, $J = 5.5$), 10.30 (s, 1H). MS 263 (M-H)⁻.

165

Example 50**6-(3,5-Bis-trifluoromethylphenyl)-5-cyano-4-methyl-2-oxo-3,6-dihydro-2H-pyrimidine-1-carboxylic acid ethylamide**

- 5 Using 3,5-bis-trifluoromethylbenzaldehyde and following the procedure of Example 25, intermediate XXIV was obtained in 100 % yield. The title compound was obtained in 50 % yield following the procedure described in Example 28.

¹H-NMR (CDCl₃, 400 MHz): δ 8.68 (t, 1 H, J = 5.3 Hz), 7.86 (s, 1 H), 7.77 (s, 2 H), 7.48 (s, 1 H), 6.46 (s, 1 H), 3.31 (m, 2 H), 2.24 (s, 3 H), 1.17 (t, 3 H, J = 7.0 Hz).

- 10 LC/MS (ES+) 421 (M+H)⁺.

Example 51**6-(2,5-Bis-trifluoromethylphenyl)-5-cyano-4-methyl-2-oxo-3,6-dihydro-2H-pyrimidine-1-carboxylic acid ethylamide**

- 15 Using 2,5-bis-trifluoromethylbenzaldehyde and following the procedure of Example 25, intermediate XXIV was obtained in 25 % yield. The title compound was obtained in 38 % yield following the procedure described in Example 28.

¹H-NMR (MeOH-d₄, 400 MHz): δ 7.94 (d, 1 H, J = 8.4 Hz), 7.84 (d, 1 H, J = 8.4 Hz), 7.75 (s, 1 H), 6.50 (s, 1 H), 3.17 (m, 2 H), 2.12 (d, 3 H, J = 0.9 Hz), 1.05 (t, 3 H, J =

- 20 7.0 Hz). LC/MS (ES+) 421 (M+H)⁺, 443 (M+Na)⁺.

Example 52**6-(2,5-Bis-trifluoromethylphenyl)-5-cyano-4-methyl-2-oxo-3,6-dihydro-2H-pyrimidine-1-carboxylic acid ethyl ester**

- 25 Using 2,5-bis-trifluoromethylbenzaldehyde and following the procedure of Example 25, intermediate XXIV was obtained in 25 % yield and the title compound was obtained in 55 % yield

¹H-NMR (CDCl₃, 400 MHz): δ 8.43 (s, 1 H), 7.88 (m, 1 H), 7.76 (m, 2 H), 6.25 (s, 1 H), 4.23 (q, 2 H, J = 7.0 Hz), 2.22 (s, 3 H), 1.19 (t, 3 H, J = 7.0 Hz). LC/MS (ES+)

- 30 422 (M+H)⁺.

Example 53**5-Cyano-6-(3-ethylcarbamoylphenyl)-4-methyl-2-oxo-3,6-dihydro-2H-pyrimidine-1-carboxylic acid ethylamide**

Starting with the product of Example 48, the title compound was obtained in 57 %
5 yield by ester hydrolysis (lithium hydroxide in aqueous methanol) and coupling of the resulting carboxylic acid with ethylamine (water soluble carbodiimide and hydroxybenzotriazole in acetonitrile).

¹H-NMR (MeOH-d₄, 400 MHz): δ 8.97 (s, 1 H), 7.68 (d, 1 H, J = 1.8 Hz), 7.65 (m, 1 H), 7.38 (m, 2 H), 6.10 (s, 1 H), 3.30 (m, 2 H), 3.13 (m, 2 H), 2.05 (s, 3 H), 1.12 (t, 3
10 H, J = 7.0 Hz), 1.01 (t, 3 H, J = 7.0 Hz). LC/MS (ES+) 356 (M+H)⁺.

Example 54**5-Cyano-6-(3-cyano-4-fluorophenyl)-4-methyl-2-oxo-3,6-dihydro-2H-pyrimidine-1-carboxylic acid ethylamide**

15 Using 3-cyano-4-fluorobenzaldehyde and following the procedure of Example 25, intermediate XXIV was obtained in 62 % yield. The title compound was obtained in 51 % yield following the procedure described in Example 28.

¹H-NMR (CDCl₃, 500 MHz) δ 8.66 (s, 1 H), 7.74 (s, 1 H), 7.65 (m, 1 H), 7.57 (m, 1 H), 7.22 (t, 1 H, J = 8.2 Hz), 6.32 (s, 1 H), 3.29 (m, 2 H), 2.22 (s, 3 H), 1.16 (t, 3 H, J
20 = 7.2 Hz). LC/MS (ES+) 328 (M+H)⁺, 350 (M+Na)⁺.

Example 55**5-Cyano-6-(3-cyano-4-fluorophenyl)-4-methyl-2-oxo-3,6-dihydro-2H-pyrimidine-1-carboxylic acid ethyl ester**

25 Using 3-cyano-4-fluorobenzaldehyde and following the procedure of Example 25, intermediate XXIV was obtained in 62 % yield and the title compound was obtained in 30 % yield.

¹H-NMR (MeOH-d₄, 400 MHz): δ 7.71 (m, 2 H), 7.38 (t, 1 H, J = 8.3 Hz), 5.93 (s, 1 H), 4.32 (m, 2 H), 2.20 (d, 3 H, J = 0.9 Hz), 1.32 (t, 3 H, J = 7.0 Hz). LC/MS (ES+)
30 329 (M+H)⁺.

149
469
17**Example 56****5-Cyano-6-(2,2-dimethylpropyl)-4-methyl-2-oxo-3,6-dihydro-2H-pyrimidine-1-carboxylic acid ethylamide**

Using 2,2-dimethylpropionaldehyde and following the procedure of Example 26,
5 intermediate XXIV was obtained in 57 % yield. The title compound was obtained in 54 % yield following the procedure described in Example 28.

¹H-NMR (DMSO-d₆, 400 MHz): δ 0.92 (s, 9H), 1.06 (t, 3H, J = 7.15Hz), 1.43-1.47 (m, 2H), 2.05 (s, 3H), 3.21 (m, 2H), 5.20 (m, 1H), 8.60 (m, 1H), 10.42 (s, 1H). MS 277 (M-H)⁻.

10

Example 57**5-Cyano-6-cyclopropyl-4-methyl-2-oxo-3,6-dihydro-2H-pyrimidine-1-carboxylic acid ethyl ester**

Using cyclopropanecarboxaldehyde and following the procedure of Example 26,
15 intermediate XXIV was obtained in 83 % yield and the title compound was obtained in 36 % yield.

¹H-NMR (DMSO-d₆, 400 MHz): δ 0.35-0.65 (m, 4H), 1.10-1.21 (m, 1H), 1.23 (t, 3H, J = 7.09 Hz), 2.05 (s, 3H), 4.18-4.21 (m, 2 H), 4.33 (d, 1H, J = 8.13 Hz), 10.36 (s, 1H). MS 248 (M-H)⁻.

20

Example 58**5-Cyano-6-cyclopropyl-4-methyl-2-oxo-3,6-dihydro-2H-pyrimidine-1-carboxylic acid ethylamide**

Using cyclopropanecarboxaldehyde and following the procedure of Example 26,
25 intermediate XXIV was obtained in 83 % yield. The title compound was obtained in 15 % yield following the procedure described in Example 28.

¹H-NMR (DMSO-d₆, 400 MHz): δ 0.36-0.51 (m, 4H), 1.05-1.09 (m, 4H), 2.06 (s, 3H), 3.20-3.23 (m, 2 H), 4.66 (d, 1H, J = 8.30 Hz), 8.74 (m, 1H), 10.36 (s, 1H). MS 247 (M-H)⁻. HRMS 247.1195 (M-H)⁻.

30

Example 59**5-Cyano-6-(2-fluoro-5-trifluoromethylphenyl)-4-methyl-2-oxo-3,6-dihydro-2H-pyrimidine-1-carboxylic acid ethylamide**

Using 2-fluoro-5-trifluoromethylbenzaldehyde and following the procedure of

- 5 Example 25, intermediate XXIV was obtained in 41 % yield. The title compound was obtained in 75 % yield following the procedure described in Example 28.

¹H-NMR (CDCl₃, 400 MHz): δ 8.68 (t, 1 H, J = 4.8 Hz), 7.60 (m, 2 H), 7.37 (s, 1 H), 7.22 (t, 1 H, J = 9.2 Hz), 6.41 (s, 1 H), 3.30 (m, 1 H), 3.24 (m, 1 H), 2.18 (d, 3 H, J = 0.9 Hz), 1.14 (t, 3 H, J = 7.0 Hz). LC/MS (ES+) 371 (M+H)⁺, 393 (M+Na)⁺.

10

Example 60**5-Cyano-6-(2-fluoro-5-trifluoromethylphenyl)-4-methyl-2-oxo-3,6-dihydro-2H-pyrimidine-1-carboxylic acid ethyl ester**

Using 2-fluoro-5-trifluoromethylbenzaldehyde and following the procedure of

- 15 Example 25, intermediate XXIV was obtained in 41 % yield and the title compound was obtained in 38 % yield.

¹H-NMR (CDCl₃, 400 MHz): δ 8.27 (s, 1 H), 7.65 (m, 1 H), 7.58 (m, 1 H), 7.25 (t, 1 H, J = 9.2 Hz), 6.03 (s, 1 H), 4.28 (m, 2 H), 2.20 (d, 3 H, J = 0.9 Hz), 1.29 (t, 3 H, J = 7.0 Hz). LC/MS (ES+) 372 (M+H)⁺, 394 (M+Na)⁺.

20

Example 61**5-Cyano-6-isopropyl-4-methyl-2-oxo-3,6-dihydro-2H-pyrimidine-1-carboxylic acid ethyl ester**

Using cyclopropanecarboxaldehyde and following the procedure of Example 26,

- 25 intermediate XXIV was obtained in 76 % yield and the title compound was obtained in 23 % yield.

¹H-NMR (DMSO-d₆, 400 MHz): δ 0.88-0.92 (m, 6H), 1.23 (t, 3H, J = 7.10 Hz), 1.90-1.95 (m, 1H), 2.07 (s, 3H), 4.16-4.22 (m, 2H), 4.51 (d, 1H, J = 6.82 Hz), 10.37 (s, 1H). MS: 250 (M-H)⁻.

30

Example 62**5-Cyano-4-methyl-6-naphthalen-2-yl-2-oxo-3,6-dihydro-2H-pyrimidine-1-carboxylic acid ethyl ester**

Using naphthalene-2-carboxaldehyde and following the procedure of Example 25, intermediate XXIV was obtained in 64 % yield and the title compound was obtained in 39 % yield.

¹H-NMR (DMSO-d₆, 400 MHz): δ 10.54 (s, 1 H), 7.96 (m, 3 H), 7.78 (s, 1 H), 7.56 (m, 2 H), 7.44 (d, 1 H, J = 8.3 Hz), 5.98 (s, 1 H), 4.18 (q, 2 H, J = 7.0 Hz), 2.12 (s, 3 H), 1.20 (t, 3 H, J = 7.0 Hz). LC/MS (ES+) 336 (M+H)⁺.

Example 63

5-Cyano-6-[3-(2-hydroxyethylcarbamoyl)-phenyl]-4-methyl-2-oxo-3,6-dihydro-2H-pyrimidine-1-carboxylic acid ethylamide

Starting with the product of Example 48, the title compound was obtained in 60 % yield by ester hydrolysis (lithium hydroxide in aqueous methanol) and coupling of the resulting carboxylic acid with 2-aminoethanol (water soluble carbodiimide and hydroxybenzotriazole in acetonitrile).

¹H-NMR (CDCl₃, 400 MHz): δ 8.73 (t, 1 H, J = 5.3 Hz), 8.03 (s, 1 H), 7.75 (t, 1 H, J = 1.8 Hz), 7.68 (m, 1 H), 7.51 (d, 1 H, J = 7.5 Hz), 7.39 (t, 1 H, J = 7.5 Hz), 7.00 (t, 1 H, J = 4.8 Hz), 6.29 (s, 1 H), 3.80 (t, 2 H, J = 4.8 Hz), 3.59 (q, 2 H, J = 4.8 Hz), 3.31 (m, 1 H), 3.22 (m, 1 H), 2.18 (s, 3 H), 1.13 (t, 3 H, J = 7.0 Hz). LC/MS (ES+) 372 (M+H)⁺, 394 (M+Na)⁺.

Example 64

5-Cyano-6-(2-methoxyphenyl)-4-methyl-2-oxo-3,6-dihydro-2H-pyrimidine-1-carboxylic acid ethyl ester

Using 2-methoxybenzaldehyde and following the procedure of Example 26,

intermediate XXIV was obtained in 17 % yield and the title compound was obtained in 28 % yield.

¹H-NMR (400 MHz, CDCl₃): δ 1.27 (t, J = 7.0 Hz, 3H), 2.12 (d, J = 0.6 Hz, 3H), 3.86 (s, 3H), 4.25 (m, 2H), 6.04 (s, 1H), 6.93 (m, 2H), 7.06 (s, 1H), 7.2 (m, 1H), 7.33 (m, 1H). MS 316 (M+H)⁺.

Example 65**5-Cyano-6-(2-methoxyphenyl)-4-methyl-2-oxo-3,6-dihydro-2H-pyrimidine-1-carboxylic acid ethylamide**

Using 2-methoxybenzaldehyde and following the procedure of Example 26,

- 5 intermediate XXIV was obtained in 17 % yield. Using the procedure of Example 27, the title compound was obtained in 8 % yield.

¹H-NMR (400 MHz, CDCl₃): δ 1.13 (t, J = 7.0 Hz, 3H), 2.1 (s, 3H), 3.25 (m, 1H), 3.33 (m, 1H), 3.86 (s, 3H), 6.47 (s, 1H), 6.62 (s, 1H), 6.9 (m, 2H), 7.2 (dd, J₁ = 1.5 Hz, J₂ = 7.6 Hz, 1H), 7.3 (dt, J₁ = 1.7 Hz, J₂ = 7.2 Hz, 1H), 8.7 (bs, 1H). MS 315 (M+H)⁺.

10

Example 66**6-(2-Allyloxyphenyl)-5-cyano-4-methyl-2-oxo-3,6-dihydro-2H-pyrimidine-1-carboxylic acid ethyl ester**

Using 2-allyloxybenzaldehyde and following the procedure of Example 26,

- 15 intermediate XXIV was obtained in 33 % yield and the title compound was obtained in 43 % yield.

¹H-NMR (400 MHz, CDCl₃): δ 1.26 (t, J = 7.0 Hz, 3H), 2.1 (s, 3H), 4.25 (m, 2H), 4.6 (m, 2H), 5.30(d, J = 10.4 Hz, 1H), 5.36 (d, J = 16.0 Hz), 6.0 (s, 1H), 6.1 (m, 1H), 6.9 (m, 3H), 7.25 (m, 2H). MS 342 (M+H)⁺.

20

Example 67**6-(2-Allyloxyphenyl)-5-cyano-4-methyl-2-oxo-3,6-dihydro-2H-pyrimidine-1-carboxylic acid ethylamide**

Using 2-allyloxybenzaldehyde and following the procedure of Example 26,

- 25 intermediate XXIV was obtained in 33 % yield. Using the procedure of Example 27, the title compound was obtained in 23 % yield.

¹H-NMR (400 MHz, CDCl₃): δ 1.12 (t, J = 7.0 Hz, 3H), 2.1 (s, 3H), 3.2 (m, 1H), 3.3 (m, 1H), 4.6 (m, 2H), 5.35 (m, 2H), 6.1 (m, 1H), 6.38 (s, 1H), 6.50 (s, 1H), 6.9 (m, 2H), 7.25 (m, 2H), 8.7 (bs, 1H). MS 341 (M+H)⁺.

30

171

Example 68**6-(2-Bromophenyl)-5-cyano-4-methyl-2-oxo-3,6-dihydro-2H-pyrimidine-1-carboxylic acid ethyl ester**

Using 2-bromobenzaldehyde and following the procedure of Example 25,
5 intermediate XXIV was obtained in 50 % yield and the title compound was obtained in 31 % yield.

¹H-NMR (400 MHz, CDCl₃): δ 1.24 (t, J = 7.2 Hz, 3H), 2.16 (s, 3H), 4.24 (q, J = 7.1 Hz, 2H), 6.33 (s, 1H), 7.20 (m, 1H), 7.33 (m, 3H), 7.6 (d, J = 8.0 Hz, 1H). MS 364 (M+H)⁺.

10

Example 69**6-(2-Bromophenyl)-5-cyano-4-methyl-2-oxo-3,6-dihydro-2H-pyrimidine-1-carboxylic acid ethylamide**

Using 2-bromobenzaldehyde and following the procedure of Example 25,
15 intermediate XXIV was obtained in 50 % yield. The title compound was obtained in 46 % yield following the procedure described in Example 28.

¹H-NMR (MeOH-d₄, 500 MHz): δ 7.55 (m, 1 H), 7.30 (m, 2 H), 7.15 (m, 1 H), 6.46 (s, 1 H), 3.14 (m, 2 H), 2.04 (s, 3 H), 1.04 (t, 3 H, J = 7.1 Hz). LC/MS (ES⁺) 364 (M+H⁺).

20

Example 70**5-Cyano-6-(3-methoxyphenyl)-4-methyl-2-oxo-3,6-dihydro-2H-pyrimidine-1-carboxylic acid ethylamide**

Using 3-methoxybenzaldehyde and following the procedure of Example 25,
intermediate XXIV was obtained in 66 % yield. The title compound was obtained in
25 62 % yield following the procedure described in Example 28.

¹H-NMR (DMSO-d₆, 500 MHz): δ 10.49 (s, 1 H), 8.79 (t, 1 H, J = 5.5 Hz), 7.32 (t, 1 H, J = 7.7 Hz), 6.92 (m, 1 H), 6.81 (d, 1 H, J = 7.7 Hz), 6.75 (s, 1 H), 6.06 (s, 1 H), 3.74 (s, 3 H), 3.17 (m, 2 H), 2.07 (s, 3 H), 1.04 (t, 3 H, J = 7.1 Hz). LC/MS (ES⁺) 315 (M+H⁺).

30

Example 71**6-(2-Benzyloxyphenyl)-5-cyano-4-methyl-2-oxo-3,6-dihydro-2H-pyrimidine-1-carboxylic acid ethyl ester**

Using 2-benzyloxybenzaldehyde and following the procedure of Example 26,

- 5 intermediate XXIV was obtained in 47 % yield and the title compound was obtained in 54 % yield.

¹H-NMR (CDCl₃, 400 MHz): δ 1.25 (t, J = 7.0 Hz, 3H), 1.82 (d, J = 0.9 Hz, 3H), 4.21 (m, 2H), 5.04 (dd, J₁ = 10.5 Hz, J₂ = 31.2 Hz, 2H), 5.71 (s, 1H), 5.84 (s, 1H), 6.96 (m, 2H), 7.30 (m, 2H), 7.45 (m, 5H). MS 392 (M+H)⁺.

10

Example 72**6-Benzyloxymethyl-5-cyano-4-methyl-2-oxo-3,6-dihydro-2H-pyrimidine-1-carboxylic acid ethylamide**

Using 2-benzyloxyacetaldehyde and following the procedure of Example 26,

- 15 intermediate XXIV was obtained in 45 % yield. The title compound was obtained in 30 % yield following the procedure described in Example 28.

¹H-NMR (DMSO-d₆): δ 1.10 (t, 3H, J = 7.33 Hz), 2.07 (s, 3H), 3.22-3.26 (m, 2H), 3.49-3.52 (m, 2H), 4.51 (s, 2H), 5.29 (m, 1H), 7.27-7.34 (m, 5H), 7.90 (br m, 1H), 8.75 (br m, 1H). MS: 327 (M-H)⁻. HRMS 327.1450 (M-H)⁻.

20

Example 73**6-Benzyloxymethyl-5-cyano-4-methyl-2-oxo-3,6-dihydro-2H-pyrimidine-1-carboxylic acid ethyl ester**

Using 2-benzyloxyacetaldehyde and following the procedure of Example 26,

- 25 intermediate XXIV was obtained in 45 % yield and the title compound was obtained in 80 % yield.

¹H-NMR (DMSO-d₆): δ 1.28 (t, 3H, J = 7.13), 2.05 (s, 3H), 3.58-3.70 (m, 2H), 4.29-4.35 (m, 2H), 4.53 (s, 3H), 4.97-4.99 (m, 1H), 7.25-7.35 (m, 5H). MS: 328 (M-H)⁻. 328.1297 HRMS (M-H)⁻.

30

152
172**Example 74****6-(3-Bromo-4-fluorophenyl)-5-cyano-4-methyl-2-oxo-3,6-dihydro-2H-pyrimidine-1-carboxylic acid ethylamide**

Using 3-bromo-4-fluorobenzaldehyde and following the procedure of Example 26,
5 intermediate XXIV was obtained in 99 % yield. The title compound was obtained in 69 % yield following the procedure described in Example 28.

¹H-NMR (DMSO-d₆, 400 MHz): δ 10.55 (s, 1 H), 8.75 (t, 1 H, J = 5.3 Hz), 7.55 (m, 1 H), 7.42 (t, 1 H, J = 8.8 Hz), 7.33 (m, 1 H), 6.10 (s, 1 H), 3.16 (m, 2 H), 2.09 (s, 3 H), 1.03 (t, 3 H, J = 7.0 Hz). LC/MS (ES+) 381 (M+H⁺).

10

Example 75**6-(3-Bromo-4-fluorophenyl)-5-cyano-4-methyl-2-oxo-3,6-dihydro-2H-pyrimidine-1-carboxylic acid cyclopropylamide**

Using 3-bromo-4-fluorobenzaldehyde and following the procedure of Example 26,
15 intermediate XXIV was obtained in 99 % yield. The title compound was obtained in 54 % yield following the procedure described in Example 28.

¹H-NMR (MeOH-d₄, 500 MHz): δ 7.46 (m, 1 H), 7.25 (m, 1 H), 7.14 (t, 1 H, J = 8.8 Hz), 6.04 (s, 1 H), 2.54 (m, 1 H), 2.05 (s, 3 H), 0.63 (m, 2 H), 0.42 (m, 1 H), 0.37 (m, 1 H). LC/MS (ES+) 393 (M+H⁺).

20

Example 76**6-(5-Bromo-2-fluorophenyl)-5-cyano-4-methyl-2-oxo-3,6-dihydro-2H-pyrimidine-1-carboxylic acid ethylamide**

Using 5-bromo-2-fluorobenzaldehyde and following the procedure of Example 26,
25 intermediate XXIV was obtained in 71 % yield. The title compound was obtained in 70 % yield following the procedure described in Example 28.

¹H-NMR (MeOH-d₄, 500 MHz): δ 7.50 (m, 1 H), 7.43 (m, 1 H), 7.10 (m, 1 H), 6.22 (s, 1 H), 3.22 (m, 2 H), 2.11 (d, 3 H, J = 2.2 Hz), 1.11 (m, 3 H).

Example 77**6-(5-Bromo-2-fluorophenyl)-5-cyano-4-methyl-2-oxo-3,6-dihydro-2H-pyrimidine-1-carboxylic acid cyclopropylamide**

Using 5-bromo-2-fluorobenzaldehyde and following the procedure of Example 26,

5 intermediate XXIV was obtained in 71 % yield. The title compound was obtained in 70 % yield following the procedure described in Example 28.

¹H-NMR (MeOH-d₄, 500 MHz): δ 7.51 (m, 1 H), 7.44 (m, 1 H), 7.11 (m, 1 H), 6.21 (s, 1 H), 2.60 (m, 1 H), 2.10 (d, 3 H, J = 1.6 Hz), 0.70 (m, 2 H), 0.51 (m, 1 H), 0.44 (m, 1 H).

10

Example 78**5-Cyano-6-(3,5-dibromophenyl)-4-methyl-2-oxo-3,6-dihydro-2H-pyrimidine-1-carboxylic acid ethylamide**

Using 3,5-dibromobenzaldehyde and following the procedure of Example 26,

15 intermediate XXIV was obtained in 46 % yield. The title compound was obtained in 83 % yield following the procedure described in Example 28.

¹H-NMR (DMSO-d₆, 400 MHz) δ 10.60 (br s, 1 H); 8.77 (t, J = 5.4 Hz, 1 H); 7.85 (t, J = 1.6 Hz, 1 H); 7.42 (d, J = 1.7 Hz, 2 H); 6.08 (s, 1 H); 3.18-3.26 (m, 2 H); 2.08 (s, 3 H), 1.03 (t, J = 7.1 Hz, 3 H). LC/MS (ES+) 441 (M+H)⁺.

20

Example 79**5-Cyano-4-methyl-6-(3-nitrophenyl)-2-oxo-3,6-dihydro-2H-pyrimidine-1-carboxylic acid cyclopropylmethanamide**

Using 3-nitrobenzaldehyde and following the procedure of Example 26, intermediate

25 XXIV was obtained in 92 % yield. The title compound was obtained in 53 % yield following the procedure described in Example 28.

¹H-NMR (MeOH-d₄, 500 MHz): δ 9.15 (s, 1 H), 8.21 (m, 1 H), 8.17 (d, 1 H, J = 1.6 Hz), 7.76 (d, 1 H, J = 7.7 Hz), 7.66 (t, 1 H, J = 7.7 Hz), 6.29 (s, 1 H), 3.68 (d, 1 H, J = 7.1 Hz), 3.09 (m, 2 H), 2.17 (s, 3 H), 0.98 (m, 1 H), 0.48 (m, 2 H), 0.20 (m, 2 H).

30 LC/MS (ES+) 356 (M+H⁺).

33
77**Example 80****5-Cyano-4-methyl-2-oxo-6-phenethyloxymethyl-3,6-dihydro-2H-pyrimidine-1-carboxylic acid ethyl ester**

Using 2-phenethyloxyacetaldehyde and following the procedure of Example 26,
5 intermediate XXIV was obtained in 38 % yield and the title compound was obtained in 18 % yield.

¹H-NMR (DMSO-d₆, 400MHz): 1.23 (t, 3H, J = 7.1 Hz), 2.00 (s, 3H), 2.75 (t, 2H, J = 6.7 Hz), 3.59-3.85 (m, 4H), 4.18-4.20 (m, 2H), 4.81 (br m, 1H), 7.19-7.27 (m, 5H), 10.26 (s, 1H). MS 342 (M-H)⁻. HRMS 342.1458 (M-H)⁻.

10

Example 81**5-Cyano-4-methyl-2-oxo-6-phenethyl-3,6-dihydro-2H-pyrimidine-1-carboxylic acid ethylamide**

Using 3-phenylpropionaldehyde and following the procedure of Example 26,
15 intermediate XXIV was obtained in 58 % yield. The title compound was obtained in 42 % yield following the procedure described in Example 28.

¹H-NMR (DMSO-d₆, 400 MHz): 1.07 (t, 3H, J = 7.1 Hz), 1.80-2.03 (m, 2H), 2.06 (s, 3H), 2.51-2.75 (m, 2H), 3.19-3.22 (m, 2H), 5.12 (br m, 1H), 7.18-7.30 (m, 5H), 8.70 (br m, 1H), 10.36 (s, 1H). MS 311 (M-H)⁻. HRMS 311.1493 (M-H)⁻.

20

Example 82**5-Cyano-4-methyl-2-oxo-6-thiophen-3-yl-3,6-dihydro-2H-pyrimidine-1-carboxylic acid ethyl ester**

Using thiophene-3-carboxaldehyde and following the procedure of Example 26,
25 intermediate XXIV was obtained in 50 % yield and the title compound was obtained in 30 % yield.

¹H-NMR (DMSO-d₆, 400 MHz): δ 1.23 (t, J = 7.1 Hz, 3H), 2.10 (s, 3H), 4.21 (m, 2H), 5.87 (s, 1H), 7.03 (m, 1H), 7.44 (s, 1H), 7.60 (m, 1H), 10.48 (s, 1H). MS 292 (ES⁺): 292 (M+H)⁺.

30

Example 83**5-Cyano-4-methyl-6-(5-methylisoxazol-3-yl)-2-oxo-3,6-dihydro-2H-pyrimidine-1-carboxylic acid ethyl ester**

Using 5-methylisoxazole-3-carboxaldehyde and following the procedure of Example 26, intermediate XXIV was obtained in 27 % yield and the title compound was obtained in 67 % yield.

¹H-NMR (DMSO-d₆, 400 MHz): δ 10.52 (s, 1H), 6.20 (s, 1H), 5.95 (s, 1H), 4.21 (q, 2H, J = 7.0 Hz), 2.40 (s, 3H), 2.05 (s, 3H), 1.22 (t, 3H, J = 7.0 Hz). ¹³C-NMR (DMSO-d₆, 400 MHz): δ 170.87, 161.63, 151.86, 150.57, 147.09, 116.44, 99.35, 81.29, 63.08, 49.55, 16.85, 13.68, 11.56. MS (ESI), 291 (M+H)⁺.

Example 84**5-Cyano-6-(3,5-dimethylisoxazol-4-yl)-4-methyl-2-oxo-3,6-dihydro-2H-pyrimidine-1-carboxylic acid ethyl ester**

Using 3,5-dimethylisoxazole-4-carboxaldehyde and following the procedure of Example 26, intermediate XXIV was obtained in 74 % yield and the title compound was obtained in 47 % yield.

¹H-NMR (DMSO-d₆, 400 MHz): δ 10.56 (s, 1H), 5.82 (s, 1H), 4.15 (q, 2H, J = 7.0 Hz), 2.38 (s, 3H), 2.14 (s, 1H), 2.07 (s, 3H), 1.17 (t, 3H, J = 7.0 Hz). ¹³C-NMR (DMSO-d₆, 400 MHz): δ 167.03, 157.45, 152.17, 147.60, 146.95, 116.44, 113.45, 81.58, 62.96, 48.58, 16.77, 13.64, 10.50, 9.57. MS (ESI), 305 (M+H)⁺.

Example 85**5-Cyano-4-methyl-2-oxo-6-thiophen-2-yl-3,6-dihydro-2H-pyrimidine-1-carboxylic acid ethyl ester**

Using thiophene-2-carboxaldehyde and following the procedure of Example 26, intermediate XXIV was obtained in 41 % yield and the title compound was obtained in 58 % yield.

¹H-NMR (DMSO-d₆, 400 MHz): δ 1.25 (t, J = 7.1 Hz, 3H), 2.12 (s, 3H), 4.24 (m, 2H), 6.08 (s, 1H), 7.02 (m, 1H), 7.07 (d, J = 3.4 Hz, 1H), 7.56 (m, 1H), 10.58 (s, 1H). MS (ESI) 290 (M-H)⁻.

HRMS (ESI) 290.0598 (M-H)⁻.

153
174**Example 86****5-Cyano-4-methyl-6-(3-methylthiophen-2-yl)-2-oxo-3,6-dihydro-2H-pyrimidine-1-carboxylic acid ethylamide**

- 5 Using 3-methylthiophene-2-carboxaldehyde and following the procedure of Example 26, intermediate XXIV was obtained in 33 % yield. The title compound was obtained in 17 % yield following the procedure described in Example 28.

¹H NMR (DMSO-d₆, 400 MHz): δ 1.03 (t, J = 7.2 Hz, 3H), 2.05 (s, 3H), 3.15 (m, 2H), 3.33 (s, 3H), 6.41 (s, 1H), 6.82 (d, J = 5.1 Hz, 1H), 7.35 (d, J = 5.1 Hz, 1H),
10 8.73 (t, J = 5.6 Hz, 1H), 10.62 (s, 1H).

MS (ESI) 303 (M-H)⁻. HRMS (ESI) 303.0927 (M-H)⁻.

Example 87**5-Cyano-4-methyl-6-(3-methylthiophen-2-yl)-2-oxo-3,6-dihydro-2H-pyrimidine-1-carboxylic acid ethyl ester**

- 15 Using 3-methylthiophene-2-carboxaldehyde and following the procedure of Example 26, intermediate XXIV was obtained in 33 % yield and the title compound was obtained in 14 % yield.

¹H-NMR (DMSO-d₆, 400 MHz): δ 1.20 (t, J = 7.1 Hz, 3H), 2.05 (s, 3H), 3.33 (s, 3H), 4.17 (q, J = 7.1 Hz, 2H), 6.14 (s, 1H), 6.84 (d, J = 5.1 Hz, 1H), 7.38 (d, J = 5.1 Hz, 1H), 10.61 (s, 1H). MS (ESI) 304 (M-H). HRMS (ESI) 304.0746 (M-H).

Example 88**5-Cyano-4-methyl-6-(2-methylthiazol-4-yl)-2-oxo-3,6-dihydro-2H-pyrimidine-1-carboxylic acid ethyl ester**

- 25 Using 2-methylthiazole-4-carboxaldehyde and following the procedure of Example 26, intermediate XXIV was obtained in 26 % yield and the title compound was obtained in 16 % yield.

¹H-NMR (CDCl₃, 400 MHz): δ 7.96 (s, 1H), 7.11 (s, 1H), 5.93 (s, 1H), 4.31 (m, 2H),
30 2.67 (s, 3H), 2.16 (s, 3H), 1.32 (t, 3H, J = 6.9 Hz); ¹³C-NMR (CDCl₃, 400 MHz): δ 168.13, 152.34, 151.77, 149.06, 147.71, 116.31, 115.88, 85.39, 64.24, 35.87, 19.17, 17.81, 14.09. MS (ESI) 307 (M+H)⁺.

Example 89**6-(4-Bromothiophen-2-yl)-5-cyano-4-methyl-2-oxo-3,6-dihydro-2H-pyrimidine-1-carboxylic acid ethylamide**

- 5 Using 4-bromothiophene-2-carboxaldehyde and following the procedure of Example 26, intermediate XXIV was obtained in 68 % yield. The title compound was obtained in 49 % yield following the procedure described in Example 28. ¹H-NMR (DMSO-d₆, 400 MHz): δ 1.07 (t, J = 7.1 Hz, 3H), 2.15 (s, 3H), 3.22 (m, 2H), 6.36 (s, 1H), 7.06 (s, 1H), 7.67 (s, 1H), 8.68 (t, J = 5.6 Hz, 1H), 10.64 (s, 1H). MS (ES⁺) 369 (M+H)⁺.
10 HRMS (ESI): 366.9876 (M-H)⁻.

Example 90**6-(4-Bromothiophen-2-yl)-5-cyano-4-methyl-2-oxo-3,6-dihydro-2H-pyrimidine-1-carboxylic acid ethyl ester**

- 15 Using 4-bromothiazole-2-carboxaldehyde and following the procedure of Example 26, intermediate XXIV was obtained in 68 % yield and the title compound was obtained in 45 % yield. ¹H-NMR (DMSO-d₆, 400 MHz): δ 1.25 (t, J = 7.1 Hz, 3H), 2.14 (s, 3H), 4.24 (m, 2H), 6.09 (s, 1H), 7.10 (s, 1H), 7.71 (s, 1H), 10.63 (s, 1H). MS (ESI) 368 [M-H]⁻. HRMS (ESI) 367.9697 (M-H)⁻.

20

Example 91**5-Cyano-4-methyl-2-oxo-6-[2-(4-trifluoromethylphenyl)-thiazol-4-yl]-3,6-dihydro-2H-pyrimidine-1-carboxylic acid ethyl ester**

- Using 2-(4-trifluoromethylphenyl)thiazole-4-carboxaldehyde and following the
25 procedure of Example 26, intermediate XXIV was obtained in 17 % yield and the title compound was obtained in 31 % yield.
¹H-NMR (DMSO-d₆, 400 MHz): δ 10.53 (s, 1H), 8.08 (d, 2H, J = 8.2 Hz), 7.89 (d, 2H, J = 8.1 Hz), 7.78 (s, 1H), 5.96 (s, 1H), 4.20 (m, 2H), 2.07 (s, 3H), 1.22 (t, 3H, J = 7.1 Hz); ¹³C-NMR (DMSO-D₆, 400 MHz): δ 166.18, 154.51, 152.00, 149.60, 142.48,
30 135.79, 130.05, 129.78, 126.45, 125.96, 124.71, 122.30, 117.75, 116.84, 82.69, 62.83, 52.82, 16.87, 13.66. MS (ESI), 437 (M+H)⁺.

Example 92**6-[5-(4-Chlorophenyl)-oxazol-4-yl]-5-cyano-4-methyl-2-oxo-3,6-dihydro-2H-pyrimidine-1-carboxylic acid ethyl ester**

Using 5-(4-Chlorophenyl)oxazole-4-carboxaldehyde and following the procedure of

- 5 Example 26, intermediate XXIV was obtained in 22 % yield and the title compound was obtained in 16 % yield.

¹H-NMR (DMSO-d₆, 400 MHz): δ 10.48 (s, 1H), 8.47 (m, 1H), 7.79 (d, 2H, J= 8.6 Hz), 7.64 (d, 2H, J= 8.6 Hz), 6.14 (s, 1H), 4.01 (q, 2H, J= 7.1 Hz), 2.05 (s, 3H), 0.96 (t, 3H, J = 7.1 Hz); ¹³C-NMR (DMSO-D₆, 400 MHz): δ 152.07, 151.98, 149.50, 10
147.60, 143.20, 133.40, 133.20, 129.01, 127.58, 125.33, 116.82, 81.25, 62.71, 49.80, 16.80, 13.20. MS (ESI), 387 (M+H)⁺.

Example 93**6-(2-Bromothiazol-5-yl)-5-cyano-4-methyl-2-oxo-3,6-dihydro-2H-pyrimidine-1-carboxylic acid ethyl ester**

- 15 Using 2-Bromothiazole-5-carboxaldehyde and following the procedure of Example 26, intermediate XXIV was obtained in 44 % yield and the title compound was obtained in 41 % yield

¹H-NMR (DMSO-d₆, 400 MHz): δ 10.67 (s, 1H), 7.72 (s, 1H), 6.15 (s, 1H), 4.26 (m, 20
2H), 2.15 (s, 3H), 1.27 (t, 3H, J = 7.1 Hz); ¹³C-NMR (DMSO-D₆, 400 MHz): δ 152.49, 151.78, 147.11, 141.99, 140.14, 137.93, 116.70, 82.49, 63.91, 50.06, 17.52, 14.18. MS (ESI), 371.0 (M+H)⁺.

Example 94**5-Cyano-4-methyl-2-oxo-6-(4-phenylthiophen-2-yl)-3,6-dihydro-2H-pyrimidine-1-carboxylic acid ethylamide**

- Using 4-bromothiophene-2-carboxaldehyde and following the procedure of Example 26, intermediate XXIV was obtained in 68 % yield. The 4-bromothiophenyl intermediate was converted to 4-phenylthienyl intermediate by the Suzuki reaction in 91 % yield
- 30 The title compound was obtained in 33 % yield following the procedure described in Example 28.

¹H-NMR (DMSO-d₆, 400 MHz): δ 1.07 (t, J = 7.1 Hz, 3H), 2.17 (s, 3H), 3.23 (m, 2H), 6.42 (s, 1H), 7.30 (t, J = 5.1 Hz, 1H), 7.41-7.43 (m, 3H), 7.66-7.68 (m, 2H), 7.83 (s, 1H), 8.71 (t, J = 5.6 Hz, 1H), 10.61 (s, 1H). MS (ESI) 365 (M-H)⁻. HRMS (ESI) 365.1064(M-H)⁻.

5

Example 95

6-[5-(4-Chlorophenyl)-furan-2-yl]-5-cyano-4-methyl-2-oxo-3,6-dihydro-2H-pyrimidine-1-carboxylic acid ethylamide

Using 5-(4-Chlorophenyl)furan-2-carboxaldehyde and following the procedure of

- 10 Example 26, intermediate XXIV was obtained in 16 % yield. The title compound was obtained in 43 % yield following the procedure described in Example 28.

¹H-NMR (DMSO-d₆, 400 MHz): δ 1.07 (t, J = 7.1 Hz, 3H), 2.12 (s, 3H), 3.22 (m, 2H), 6.27 (s, 1H), 6.46 (d, J = 3.4 Hz, 1H), 6.97 (d, J = 3.4 Hz, 1H), 7.51 (m, 2H), 7.63 (m, 2H), 8.70 (t, J = 5.5 Hz, 1H), 10.62 (s, 1H). MS (ESI) 383 (M-H)⁻. HRMS (ESI) 383.0913 (M-H)⁻.

15

Example 96

5-Cyano-4-methyl-2-oxo-6-(4-trifluoromethylthiazol-5-yl)-3,6-dihydro-2H-pyrimidine-1-carboxylic acid ethyl ester

- 20 Using 4-trifluoromethylthiazole-5-carboxaldehyde and following the procedure of Example 26, intermediate XXIV was obtained in 63 % yield and the title compound was obtained in 52 % yield.

¹H-NMR (DMSO-d₆, 400 MHz): δ 10.84 (s, 1H), 9.22 (s, 1H), 6.45 (s, 1H), 4.15 (q, 2H, J = 5.7 Hz), 2.06 (s, 3H), 1.16 (t, 3H, J = 5.7 Hz). ¹³C-NMR (DMSO-D₆, 400
25 MHz): δ 165.51, 151.90, 149.88, 146.79, 142.70, 138.70, 116.10, 83.68, 63.78, 50.42, 17.44, 13.94; MS (ESI) 361 (M+H)⁺.

25

Example 97

5-Cyano-4-methyl-2-oxo-6-(4-trifluoromethylthiazol-5-yl)-3,6-dihydro-2H-pyrimidine-1-carboxylic acid ethylamide

30

Using 4-trifluoromethylthiazole-5-carboxaldehyde and following the procedure of Example 26, intermediate XXIV was obtained in 63 % yield. The title compound was obtained in 59 % yield following the procedure described in Example 28.

¹H-NMR (DMSO-d₆, 400 MHz): δ 10.84 (s, 1H), 9.19 (s, 1H), 8.69 (m, 1H), 6.68 (s, 1H), 3.15 (m, 1H), 2.06 (s, 3H), 1.01 (t, 3H, J = 7.0 Hz); ¹³C-NMR (DMSO-d₆, 400 MHz): δ 155.54, 151.46, 150.25, 149.38, 143.23, 138.70, 115.63, 82.55, 47.93, 34.83, 16.87, 14.34. MS (ESI) 360 (M+H)⁺.

Example 98

10 5-Cyano-6-[5-(4-methanesulfonylphenyl)-oxazol-4-yl]-4-methyl-2-oxo-3,6-dihydro-2H-pyrimidine-1-carboxylic acid ethylamide

Using 5-(4-methanesulfonylphenyl)oxazole-4-carboxaldehyde and following the procedure of Example 26, intermediate XXIV was obtained in 22 % yield. The title compound was obtained in 63 % yield following the procedure described in Example 28.

¹H-NMR (DMF-d₇, 400 MHz): δ 10.60 (s, 1H), 8.96 (t, J = 4.8 Hz, 1H), 8.62 (s, 1H), 8.25 (d, J = 8.3 Hz, 2H), 8.18 (d, J = 8.3 Hz, 2H), 6.67 (s, 1H), 3.37 (s, 3H), 3.25 (m, 2H), 2.21 (s, 3H), 1.07 (t, J = 7.4 Hz, 3H). MS (ESI) 430 (M+H)⁺.

20 Example 99

6-[5-(4-Chlorophenyl)-oxazol-4-yl]-5-cyano-4-methyl-2-oxo-3,6-dihydro-2H-pyrimidine-1-carboxylic acid ethylamide

Using 5-(4-chlorophenyl)oxazol-4-carboxaldehyde and following the procedure of Example 26, intermediate XXIV was obtained in 40 % yield. The title compound was obtained in 58 % yield following the procedure described in Example 28.

¹H-NMR (DMSO-d₆, 400 MHz): δ 10.51 (s, 1H), 8.78 (m, 1H), 8.43 (s, 1H), 7.85 (d, 2H, J = 8.5 Hz), 7.62 (d, 2H, J = 8.5 Hz), 6.38 (s, 1H), 3.11 (m, 2H), 2.02 (s, 3H), 0.99 (t, 3H, J = 7.2 Hz). ¹³C-NMR (DMSO-D₆, 400 MHz): δ 152.99, 152.51, 152.11, 149.30, 143.70, 134.17, 129.52, 128.13, 126.40, 117.20, 81.80, 48.09, 35.17, 17.28, 14.95. MS (ESI), 386 (M+H)⁺.

Example 100**5-Cyano-4-methyl-2-oxo-6-[5-(4-trifluoromethylphenyl)-oxazol-4-yl]-3,6-dihydro-2H-pyrimidine-1-carboxylic acid ethylamide**

Using 5-(4-trifluoromethylphenyl)oxazole-4-carboxaldehyde and following the
5 procedure of Example 26, intermediate XXIV was obtained in 31 % yield. The title
compound was obtained in 52 % yield following the procedure described in Example
28.

¹H-NMR (DMSO-d₆, 400 MHz): δ 10.54 (s, 1H), 8.78 (m, 1H), 8.50 (s, 1H), 8.06 (d,
2H, J = 8.1 Hz), 7.91 (d, 2H, J = 8.1 Hz), 6.46 (s, 1H), 3.10 (m, 2H), 2.03 (s, 3H), 0.99
10 (t, 3H, J = 7.2 Hz); ¹³C-NMR (DMSO-d₆, 400 MHz): δ 152.53, 152.31, 151.52,
149.03, 142.70, 134.96, 130.69, 126.41, 125.88, 116.62, 81.03, 47.69, 34.65, 16.75,
14.41; MS (ESI), 420.13 (M+H)⁺.

Example 101**5-Cyano-4-methyl-2-oxo-6-(5-phenyloxazol-4-yl)-3,6-dihydro-2H-pyrimidine-1-carboxylic acid ethylamide**

Catalytic reduction (10 % Pd/C, ammonium formate in refluxing acetonitrile) of the
product of Example 99 gave the title compound in 45 % yield.

¹H-NMR (CDCl₃, 400 MHz): δ 8.69 (m, 1H), 7.87 (m, 3H), 7.50 (m, 2H), 7.41 (m,
20 1H), 7.00 (s, 1H), 6.63 (s, 1H), 3.30 (m, 2H), 2.18 (s, 3H), 1.13 (t, 3H, J = 7.2 Hz).
¹³CNMR (CDCl₃, 400 MHz): δ 152.40, 152.13, 150.25, 146.90, 132.60, 129.50,
129.12, 126.79, 116.57, 80.93, 48.25, 35.70, 17.87, 14.72; MS (ESI), 352.16 (M+H)⁺.

Example 102**5-Cyano-4-methyl-6-[5-(4-nitrophenyl)-oxazol-4-yl]-2-oxo-3,6-dihydro-2H-pyrimidine-1-carboxylic acid ethylamide**

Using 5-(4-nitrophenyl)oxazole-4-carboxaldehyde and following the procedure of
Example 26, intermediate XXIV was obtained in 36 % yield. The title compound was
obtained in 70 % yield following the procedure described in Example 28.

¹H-NMR (DMSO-d₆, 400 MHz): δ 10.56 (s, 1H), 8.79 (m, 1H), 8.56 (s, 1H), 8.38 (m,
30 2H), 8.13 (m, 2H), 6.50 (s, 1H), 3.12 (m, 2H), 2.03 (s, 3H), 0.99 (t, 3H, J = 7.2 Hz).
¹³C-NMR (DMSO-d₆, 400 MHz): δ 153.04, 152.37, 151.51, 149.13, 146.97, 136.16,

132.85, 126.72, 124.19, 116.57, 80.93, 47.87, 34.70, 16.81, 14.45. MS (ESI) 397 (M+H)⁺.

Example 103

5 **5-(4-Chlorophenyl)-2-(5-cyano-3-ethylcarbamoyl-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidin-4-yl)-furan-3-carboxylic acid ethyl ester**

Using 3-ethoxycarbonyl-5-(4-chlorophenyl)furan-2-carboxaldehyde and following the procedure of Example 26, intermediate XXIV was obtained in 59 % yield. The title compound was obtained in 42 % yield following the procedure described in Example 10 28.

¹H NMR (DMSO-d₆, 400 MHz): δ 1.02 (t, J = 7.2 Hz, 3H), 1.34 (t, J = 7.1 Hz, 3H), 2.07 (s, 3H), 3.16 (m, 2H), 4.30 (m, 2H), 6.85 (s, 1H), 7.34 (s, 1H), 7.53 (m, 2H), 7.65 (m, 2H), 8.67 (t, J = 5.5 Hz, 1H), 10.76 (s, 1H). MS (ESI) 455 (M-H)⁻. HRMS (ESI) 455.1114 (M-H)⁻.

15

Example 104

5-Cyano-4-methyl-2-oxo-6-(5-pyridin-3-yloxazol-4-yl)-3,6-dihydro-2H-pyrimidine-1-carboxylic acid ethylamide

Using 5-(3-pyridinyl)oxazole-4-carboxaldehyde and following the procedure of Example 26, intermediate XXIV was obtained in 62 % yield. The title compound was 20 obtained in 41 % yield following the procedure described in Example 28.

¹H-NMR (DMSO-d₆, 400 MHz): δ 10.53 (s, 1H), 9.04 (m, 1H), 8.77 (m, 1H), 8.67 (m, 1H), 8.50 (s, 1H), 8.22 (m, 1H), 7.60 (m, 1H), 6.40 (s, 2H), 3.12 (m, 2H), 2.04 (s, 3H), 1.00 (t, 3H, J = 7.2 Hz). ¹³C-NMR (DMSO-d₆, 400 MHz): δ 152.76, 152.52, 25 151.75, 149.97, 149.19, 146.73, 134.73, 133.60, 124.06, 123.45, 116.94, 81.41, 47.81, 34.88, 16.99, 14.63; MS (ESI), 353.18 (M+H)⁺.

Example 105**5-Cyano-4-methyl-2-oxo-6-(4-phenylthiazol-5-yl)-3,6-dihydro-2H-pyrimidine-1-carboxylic acid ethylamide**

Using 4-phenylthiazole-5-carboxaldehyde and following the procedure of Example 26, intermediate XXIV was obtained in 70 % yield. The title compound was obtained in 27 % yield following the procedure described in Example 28.

¹H-NMR (DMSO-d₆, 400 MHz): δ 10.70 (s, 1H), 9.08 (s, 1H), 8.71 (m, 1H), 7.73 (2H, m), 7.47 (m, 3H), 6.63 (s, 1H), 3.12 (m, 2H), 1.99 (s, 3H), 1.00 (t, 3H, J = 7.2 Hz); ¹³C-NMR (DMSO-d₆, 400 MHz): δ 152.79, 151.97, 151.74, 150.61, 148.43, 133.87, 116.12, 83.68, 34.77, 16.69, 14.39. MS (ESI) 368 (M+H)⁺.

Example 106**[5-Cyano-4-methyl-6-(3-nitrophenyl)-2-oxo-3,6-dihydro-2H-pyrimidin-1-yl]-acetic acid tert-butyl ester**

Using 3-nitrobenzaldehyde and following the procedure of Example 26, intermediate XXIV was obtained in 92 % yield and the title compound was obtained in 52 % yield.

¹H-NMR (MeOH-d₄, 400 MHz): δ 8.28 (m, 1 H), 8.22 (t, 1 H, J = 1.8 Hz), 7.76 (m, 1 H), 7.69 (t, 1 H, J = 7.9 Hz), 7.62 (s, 1 H), 5.31 (s, 1 H), 4.23 (d, 1 H, J = 17.6 Hz), 3.44 (d, 1 H, J = 17.6 Hz), 2.16 (s, 3 H), 1.42 (s, 9 H). LC/MS (ES⁺) 395 (M+Na)⁺.

Example 107**5-Cyano-4-methyl-6-(3-nitrophenyl)-2-oxo-3,6-dihydro-2H-pyrimidine-1-carboxylic acid isopropylamide**

Using 3-nitrobenzaldehyde and following the procedure of Example 26, intermediate XXIV was obtained in 92 % yield. The title compound was obtained in 29 % yield following the procedure described in Example 27.

¹H-NMR (MeOH-d₄, 400 MHz): δ 8.92 (s, 1 H), 8.22 (d, 1 H, J = 8.3 Hz), 8.17 (t, 1 H, J = 1.8 Hz), 7.74 (d, 1 H, J = 6.6 Hz), 7.65 (m, 2 H), 6.31 (s, 1 H), 3.89 (m, 1 H), 2.19 (s, 3 H), 1.20 (d, 3 H, J = 6.6 Hz), 1.16 (d, 3 H, J = 6.6 Hz). LC/MS (ES⁺) 344 (M+H)⁺, 366 (M+Na)⁺.

Example 108**5-Cyano-4-methyl-6-(3-nitrophenyl)-2-oxo-3,6-dihydro-2H-pyrimidine-1-carboxylic acid propylamide**

Using 3-nitrobenzaldehyde and following the procedure of Example 26, intermediate

- 5 XXIV was obtained in 92 % yield. The title compound was obtained in 22 % yield following the procedure described in Example 27.

¹H-NMR (MeOH-d₄, 400 MHz) δ 9.09 (t, 1 H, J = 5.3 Hz), 8.22 (m, 1 H), 8.17 (t, 1 H, J = 1.8 Hz), 7.75 (d, 1 H, J = 7.9 Hz), 7.65 (t, 1 H, J = 7.9 Hz), 6.30 (s, 1 H), 3.33 (m, 2 H), 2.18 (s, 3 H), 1.54 (m, 2 H), 0.91 (t, 3 H, J = 7.5 Hz). LC/MS (ES+) 344

- 10 (M+H)⁺, 366 (M+Na)⁺.

Example 109**5-Cyano-4-methyl-6-(3-nitrophenyl)-2-oxo-3,6-dihydro-2H-pyrimidine-1-carboxylic acid phenylamide**

- 15 Using 3-nitrobenzaldehyde and following the procedure of Example 26, intermediate XXIV was obtained in 92 % yield. The title compound was obtained in 10 % yield following the procedure described in Example 27.

¹H-NMR (MeOH-d₄, 400 MHz): δ 11.18 (s, 1 H), 8.23 (m, 2 H), 7.81 (d, 1 H, J = 7.9 Hz), 7.65 (m, 1 H), 7.44 (m, 2 H), 7.31 (t, 2 H, J = 8.3 Hz), 7.11 (t, 1 H, J = 8.3 Hz),

- 20 6.40 (s, 1 H), 2.23 (s, 3 H). LC/MS (ES+) 378 (M+H)⁺, 400 (M+Na)⁺.

Example 110**5-Cyano-4-methyl-6-(3-nitrophenyl)-2-oxo-3,6-dihydro-2H-pyrimidine-1-carboxylic acid thiazol-2-ylamide**

- 25 Using 3-nitrobenzaldehyde and following the procedure of Example 26, intermediate XXIV was obtained in 92 % yield. The title compound was obtained in 33 % yield following the procedure described in Example 27.

¹H-NMR (MeOH-d₄, 400 MHz): δ 8.23 (m, 2 H), 7.80 (d, 1 H, J = 7.5 Hz), 7.64 (t, 1 H, J = 7.5 Hz), 7.42 (d, 1 H, J = 4.0 Hz), 7.03 (d, 1 H, J = 4.0 Hz), 6.36 (s, 1 H), 2.24

- 30 (d, 3 H, J = 0.9 Hz). LC/MS (ES+) 385 (M+H)⁺, 407 (M+Na)⁺.

Example 111**5-Cyano-4-methyl-6-(3-nitrophenyl)-2-oxo-3,6-dihydro-2H-pyrimidine-1-carboxylic acid (2,2,2-trifluoro-ethyl)-amide**

Using 3-nitrobenzaldehyde and following the procedure of Example 26, intermediate

- 5 XXIV was obtained in 92 % yield. The title compound was obtained in 25 % yield following the procedure described in Example 27.

¹H-NMR (DMSO-d₆, 500 MHz): δ 10.77 (s, 1 H), 9.23 (t, 1 H, J = 6.0 Hz), 8.21 (m, 1 H), 8.09 (s, 1 H), 7.75 (m, 2 H), 6.26 (s, 1 H), 4.01 (m, 2 H), 2.10 (s, 3 H).

10

Example 112**5-Cyano-4-methyl-6-(3-nitrophenyl)-2-oxo-3,6-dihydro-2H-pyrimidine-1-carboxylic acid cyclopropylamide**

Using 3-nitrobenzaldehyde and following the procedure of Example 26, intermediate XXIV was obtained in 92 % yield. The title compound was obtained in 19 % yield

- 15 following the procedure described in Example 27.

¹H-NMR (DMSO-d₆, 500 MHz): δ 10.62 (s, 1 H), 8.58 (s, 1 H), 8.21 (m, 1 H), 8.07 (d, 1 H, J = 1.6 Hz), 7.73 (m, 2 H), 6.22 (s, 1 H), 2.62 (m, 1 H), 2.09 (s, 3 H), 0.64 (m, 2 H), 0.46 (m, 2 H).

20

Example 113**5-Cyano-4-methyl-6-(3-nitrophenyl)-2-oxo-3,6-dihydro-2H-pyrimidine-1-carboxylic acid (2-hydroxy-ethyl)-amide**

Using 3-nitrobenzaldehyde and following the procedure of Example 26, intermediate XXIV was obtained in 92 % yield. The title compound was obtained in 23 % yield

- 25 following the procedure described in Example 27.

¹H-NMR (CDCl₃, 500 MHz): δ 8.93 (s, 1 H), 8.15 (d, 1 H, J = 7.9 Hz), 8.07 (s, 1 H), 7.68 (d, 1 H, J = 7.9 Hz), 7.51 (t, 1 H, J = 7.9 Hz), 6.86 (s, 1 H), 6.30 (s, 1 H), 3.67 (m, 2 H), 3.43 (m, 1 H), 3.36 (m, 1 H), 2.18 (s, 3 H). LC/MS (ES+) 346 (M+H)⁺.

109

Example 114**3-(4,5-Dihydrooxazol-2-yl)-6-methyl-4-(3-nitrophenyl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carbonitrile**

Prepared from the product of Example 113 (Burgess reagent in refluxing
5 tetrahydrofuran) in 71 % yield.

¹H-NMR (MeOH-d₄, 400 MHz): δ 8.10 (m, 2 H), 7.66 (d, 1 H, J = 7.9 Hz), 7.56 (t, 1 H, J = 7.9 Hz), 6.19 (s, 1 H), 4.04 (m, 2 H), 3.50 (m, 1 H), 3.39 (m, 1 H), 2.06 (s, 3 H). LC/MS (ES+) 328 (M+H)⁺.

10

Example 115**5-Cyano-4-methyl-6-(3-nitrophenyl)-2-oxo-3,6-dihydro-2H-pyrimidine-1-carboxylic acid allylamide**

Using 3-nitrobenzaldehyde and following the procedure of Example 26, intermediate
XXIV was obtained in 92 % yield. The title compound was obtained in 36 % yield
15 following the procedure described in Example 27.

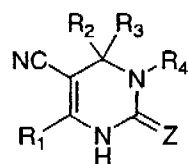
¹H-NMR (DMSO-d₆, 500 MHz): δ 10.65 (s, 1 H), 8.92 (t, 1 H, J = 5.5 Hz), 8.21 (m, 1 H), 8.08 (s, 1 H), 7.74 (m, 2 H), 6.24 (s, 1 H), 5.81 (m, 1 H), 5.07 (m, 2 H), 3.78 (m, 2 H), 2.10 (s, 3 H). LC/MS (ES+) 342 (M+H)⁺, 364 (M+Na)⁺.

Claims

What is claimed is:

1. A compound of formula I

5



I,

its enantiomers, diastereomers, pharmaceutically acceptable salts, prodrugs and solvates thereof, wherein

10 R_1 is selected from the group consisting of hydrogen, alkyl and cycloalkyl;

R_2 and R_3 are each independently selected from the group consisting of H, alkyl, aryl, heteroaryl, arylalkyl, cycloalkyl, heterocycloalkyl, cycloalkylalkyl, heterocycloalkylalkyl and heteroarylalkyl; or

15 R_2 and R_3 may also be taken together to form a carbocyclic or heterocyclic ring;

R_4 is selected from the group consisting of alkyl, arylalkyl, cycloalkylalkyl, heteroarylalkyl, heterocycloalkyl, aminoalkyl, heterocycloalkylalkyl, CN, C(O) R_5 , CO₂ R_5 , C(O)SR₅ and CONR₅ R_6 ;

20 R_5 and R_6 are each independently selected from the group consisting of H, alkyl, cycloalkyl, hydroxyalkyl, alkenyl, alkoxy, thioalkoxy, alkoxyalkyl, haloalkyl, aryl, heteroaryl, arylalkyl, cycloalkylalkyl, heteroarylalkyl and heterocycloalkylalkyl or N- R_5R_6 together form a heterocycloalkyl

Z is selected from the group consisting of O, S and NR₈;

25 R_8 is selected from the group consisting of H, CN, sulfonamido, OR₇, alkyl, cycloalkyl, aryl, arylalkyl, heterocyclyl, heteroaryl and heteroarylalkyl; and

R_7 is selected from the group consisting of H, alkyl, arylalkyl, cycloalkylalkyl, heterocycloalkylalkyl and heteroarylalkyl.

2. The compound of claim 1 wherein R_2 is heteroaryl.

3. The compound of claim 2 wherein R_3 is H and R_2 is an optionally substituted thiophene, oxazole, isoxazole, or furan.
4. The compound of claim 2 wherein said heteroaryl is substituted with methyl,
5 ethyl, halo, haloalkyl, or aryl.
5. The compound of claim 1 wherein R_3 is H and R_2 is a substituted phenyl
6. The compound of claim 5 wherein said phenyl is substituted with alkyl,
10 alkoxy, alkoxyalkyl, cyano, halo, haloalkyl, nitro, amino CO_2R_5 , CONR_5R_6 ,
alkenyloxy, aryloxy, wherein R_5 and R_6 are, independently, H or alkyl.
7. The compound of claim 6 wherein said phenyl is substituted with methyl,
methoxy, F, Cl, CF_3 , dimethylamino, or ethoxymethyl.
- 15
8. The compound of claim 1 wherein R_1 is alkyl; R_2 is selected from the group
consisting of aryl and heteroaryl; R_3 is H; R_4 is selected from the group consisting of
alkyl, arylalkyl, CO_2R_5 , and CONR_5R_6 ; R_5 and R_6 are independently selected from the
group consisting of H, alkyl, aminoalkyl, hydroxyalkyl, phenylamino and arylalkyl; Z
20 is selected from the group consisting of O, S, and NR_8 ; R_8 is selected from the group
consisting of H and CN.
9. The compound of claim 1 wherein R_4 is selected from the group consisting
of alkyl, arylalkyl, $\text{C}(\text{O})\text{R}_5$, CO_2R_5 , $\text{C}(\text{O})\text{SR}_5$ and CONR_5R_6 .
- 25
10. The compound of claim 1 wherein R_4 is CO_2R_5 ; Z is O; and R_5 is ethyl.
11. The compound of claim 1 wherein R_4 is CONR_5R_6 , Z is O; R_5 is H and R_6 is
methyl, ethyl, propyl, phenyl, cyclopropyl, hydroxyethyl, thiophene, or 2-propylene.
- 30
12. The compound of claim 1 wherein R_4 is selected from the group consisting
of alkyl and arylalkyl, and Z is O.

13. The compound of claim 1 wherein R_1 is CH_3 ; R_2 is aryl; R_4 is CO_2R_5 ; R_5 is alkyl; and Z is O.
14. The compound of claim 1 wherein R_1 is CH_3 ; R_2 is aryl; R_4 is $CONR_5R_6$; R_5 is alkyl; R_6 is H and Z is O.
15. The compound of claim 1 wherein R_1 is CH_3 ; R_2 is heteroaryl; R_4 is CO_2R_5 or $CONR_5R_6$; R_6 is H and R_5 is ethyl.
16. A compound selected from the group consisting of:
- 5-cyano-3,6-dihydro-4-methyl-6-(3-nitrophenyl)-2-thioxo-1-(2H)-pyrimidinecarboxylic acid, 1-ethyl ester;
- 5-cyano-3,6-dihydro-4-methyl-6-(3-nitrophenyl)-2-oxo-1-(2H)-pyrimidinecarboxylic acid, 1-ethyl ester;
- 5-cyano-3,6-dihydro-4-methyl-6-(3-nitrophenyl)-2-oxo-1-(2H)-pyrimidinecarboxylic acid, 1-ethyl amide;
- 5-cyano-3,6-dihydro-4-methyl-6-(3-nitrophenyl)-2-oxo-1-(1-oxobutyl)-(2H)-pyrimidine;
- 5-cyano-3,6-dihydro-4-methyl-6-(3-aminophenyl)-2-oxo-1-(2H)-pyrimidinecarboxylic acid, 1-ethyl ester;
- 5-cyano-3,6-dihydro-4-methyl-6-(3-aminophenyl)-2-oxo-1-(2H)-pyrimidinecarboxylic acid, 1-ethyl ester;
- 5-cyano-3,6-dihydro-4-methyl-6-(3-(N,N-dimethyl)aminophenyl)-2-oxo-1-(2H)-pyrimidinecarboxylic acid, 1-ethyl ester;
- 5-cyano-3,6-dihydro-4-methyl-6-(3-trifluoromethylphenyl)-2-oxo-1-(2H)-pyrimidinecarboxylic acid, 1-ethyl ester;
- 5-cyano-3,6-dihydro-4-methyl-6-(2,3-dichlorophenyl)-2-oxo-1-(2H)-pyrimidinecarboxylic acid, 1-ethyl ester;
- 5-cyano-3,6-dihydro-4-methyl-6-(3-methoxyphenyl)-2-oxo-1-(2H)-pyrimidinecarboxylic acid, 1-ethyl ester;
- 5-cyano-3,6-dihydro-4-methyl-6-(3,5-dichlorophenyl)-2-oxo-1-(2H)-pyrimidinecarboxylic acid, 1-ethyl ester;
- 5-cyano-3,6-dihydro-4-methyl-6-(3,4-dichlorophenyl)-2-oxo-1-(2H)-pyrimidinecarboxylic acid, 1-ethyl ester;

- 5-cyano-3,6-dihydro-4-methyl-6-(3-cyanophenyl)-2-oxo-1-(2H)-pyrimidinecarboxylic acid, 1-ethyl ester;
- 5-cyano-3,6-dihydro-4-methyl-6-(4-methoxyphenyl)-2-oxo-1-(2H)-pyrimidinecarboxylic acid, 1-ethyl ester;
- 5 5-cyano-3,6-dihydro-4-methyl-6-(4-methylphenyl)-2-oxo-1-(2H)-pyrimidinecarboxylic acid, 1-ethyl ester;
- 5-cyano-3,6-dihydro-4-methyl-6-cyclohexyl-2-oxo-1-(2H)-pyrimidinecarboxylic acid, 1-ethyl ester;
- 5-cyano-3,6-dihydro-4-methyl-6-phenyl-2-oxo-1-(2H)-pyrimidinecarboxylic acid, 1-ethyl ester;
- 10 5-cyano-3,6-dihydro-4-methyl-6-(2-methylphenyl)-2-oxo-1-(2H)-pyrimidinecarboxylic acid, 1-ethyl ester;
- 5-cyano-3,6-dihydro-4-methyl-6-(3-chlorophenyl)-2-oxo-1-(2H)-pyrimidinecarboxylic acid, 1-ethyl ester;
- 15 5-cyano-3,6-dihydro-4-methyl-6-(3-fluorophenyl)-2-oxo-1-(2H)-pyrimidinecarboxylic acid, 1-ethyl ester;
- 5-cyano-3,6-dihydro-4-methyl-6-(4-chlorophenyl)-2-oxo-1-(2H)-pyrimidinecarboxylic acid, 1-ethyl ester;
- 5-cyano-3,6-dihydro-4-methyl-6-(4-fluorophenyl)-2-oxo-1-(2H)-pyrimidinecarboxylic acid, 1-ethyl ester; and
- 20 5-cyano-3,6-dihydro-4-methyl-6-(2-fluorophenyl)-2-oxo-1-(2H)-pyrimidinecarboxylic acid, 1-ethyl ester;
- 6-(3,5-Bis-trifluoromethylphenyl)-5-cyano-4-methyl-2-oxo-3,6-dihydro-2H-pyrimidine-1-carboxylic acid ethyl ester;
- 25 6-Butyl-5-cyano-4-methyl-2-oxo-3,6-dihydro-2H-pyrimidine-1-carboxylic acid ethyl ester;
- 5-Cyano-4-methyl-6-(3-nitrophenyl)-2-oxo-3,6-dihydro-2H-pyrimidine-1-carboxylic acid methylamide;
- 5-Cyano-4-methyl-2-oxo-6-phenyl-3,6-dihydro-2H-pyrimidine-1-carboxylic acid ethylamide;
- 30

- 5-Cyano-6-(3,5-dichlorophenyl)-4-methyl-2-oxo-3,6-dihydro-2H-pyrimidine-1-carboxylic acid 2-methoxy-ethyl ester;
- 5-Cyano-4-methyl-2-oxo-6-(3-trifluoromethylphenyl)-3,6-dihydro-2H-pyrimidine-1-carboxylic acid ethylamide;
- 5 5-Cyano-6-(3,5-dichlorophenyl)-4-methyl-2-oxo-3,6-dihydro-2H-pyrimidine-1-carboxylic acid ethylamide;
- 3-Butyryl-4-(3,5-dichlorophenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carbonitrile;
- 5-Cyano-4-methyl-2-oxo-6-(3-trifluoromethylphenyl)-3,6-dihydro-2H-pyrimidine-1-
- 10 carboxylic acid (2-dimethylamino-ethyl)-amide;
- 5-Cyano-4-methyl-2-oxo-6-(3-trifluoromethylphenyl)-3,6-dihydro-2H-pyrimidine-1-carbothioic acid S-ethyl ester;
- 5-Cyano-4-methyl-2-oxo-6-(3-trifluoromethylphenyl)-3,6-dihydro-2H-pyrimidine-1-carboxylic acid (2-hydroxy-ethyl)-amide;
- 15 4-(3,5-Dichlorophenyl)-6-methyl-2-oxo-3-(thiophene-2-carbonyl)-1,2,3,4-tetrahydropyrimidine-5-carbonitrile;
- 5-Cyano-6-(3,5-difluorophenyl)-4-methyl-2-oxo-3,6-dihydro-2H-pyrimidine-1-carboxylic acid ethylamide; 5-Cyano-6-(3,5-difluorophenyl)-4-methyl-2-oxo-3,6-dihydro-2H-pyrimidine-1-carboxylic acid ethyl ester
- 20 4-(3,5-Difluorophenyl)-6-methyl-2-oxo-3-(piperidine-1-carbonyl)-1,2,3,4-tetrahydropyrimidine-5-carbonitrile; 4-(3,5-Difluorophenyl)-6-methyl-2-oxo-3-(pyrrolidine-1-carbonyl)-1,2,3,4-tetrahydropyrimidine-5-carbonitrile
- 5-Cyano-4-methyl-6-naphthalen-1-yl-2-oxo-3,6-dihydro-2H-pyrimidine-1-carboxylic acid ethyl ester; 5-Cyano-4-methyl-6-naphthalen-1-yl-2-oxo-3,6-dihydro-2H-
- 25 pyrimidine-1-carboxylic acid ethylamide; 6-(3-Bromophenyl)-5-cyano-4-methyl-2-oxo-3,6-dihydro-2H-pyrimidine-1-carboxylic acid ethyl ester; 6-(3-Bromophenyl)-5-cyano-4-methyl-2-oxo-3,6-dihydro-2H-pyrimidine-1-carboxylic acid ethylamide; 5-Cyano-4-methyl-2-oxo-6-(2-trifluoromethylphenyl)-3,6-dihydro-2H-pyrimidine-1-carboxylic acid ethyl ester; 5-Cyano-4-methyl-2-oxo-6-(2-trifluoromethylphenyl)-3,6-
- 30 dihydro-2H-pyrimidine-1-carboxylic acid ethylamide; 5-Cyano-6-(3-methoxycarbonylphenyl)-4-methyl-2-oxo-3,6-dihydro-2H-pyrimidine-1-carboxylic

- acid ethyl ester; 3-(5-Cyano-3-ethylcarbamoyl-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidin-4-yl)-benzoic acid methyl ester
- 6-Butyl-5-cyano-4-methyl-2-oxo-3,6-dihydro-2H-pyrimidine-1-carboxylic acid ethylamide;
- 5 6-(3,5-Bis-trifluoromethylphenyl)-5-cyano-4-methyl-2-oxo-3,6-dihydro-2H-pyrimidine-1-carboxylic acid ethylamide;
- 6-(2,5-Bis-trifluoromethylphenyl)-5-cyano-4-methyl-2-oxo-3,6-dihydro-2H-pyrimidine-1-carboxylic acid ethylamide;
- 6-(2,5-Bis-trifluoromethylphenyl)-5-cyano-4-methyl-2-oxo-3,6-dihydro-2H-pyrimidine-1-carboxylic acid ethyl ester;
- 10 5-Cyano-6-(3-ethylcarbamoylphenyl)-4-methyl-2-oxo-3,6-dihydro-2H-pyrimidine-1-carboxylic acid ethylamide;
- 5-Cyano-6-(3-cyano-4-fluorophenyl)-4-methyl-2-oxo-3,6-dihydro-2H-pyrimidine-1-carboxylic acid ethylamide;
- 15 5-Cyano-6-(3-cyano-4-fluorophenyl)-4-methyl-2-oxo-3,6-dihydro-2H-pyrimidine-1-carboxylic acid ethyl ester;
- 5-Cyano-6-(2,2-dimethylpropyl)-4-methyl-2-oxo-3,6-dihydro-2H-pyrimidine-1-carboxylic acid ethylamide;
- 5-Cyano-6-cyclopropyl-4-methyl-2-oxo-3,6-dihydro-2H-pyrimidine-1-carboxylic acid ethyl ester;
- 20 5-Cyano-6-cyclopropyl-4-methyl-2-oxo-3,6-dihydro-2H-pyrimidine-1-carboxylic acid ethylamide;
- 5-Cyano-6-(2-fluoro-5-trifluoromethylphenyl)-4-methyl-2-oxo-3,6-dihydro-2H-pyrimidine-1-carboxylic acid ethylamide;
- 25 5-Cyano-6-(2-fluoro-5-trifluoromethylphenyl)-4-methyl-2-oxo-3,6-dihydro-2H-pyrimidine-1-carboxylic acid ethyl ester;
- 5-Cyano-6-isopropyl-4-methyl-2-oxo-3,6-dihydro-2H-pyrimidine-1-carboxylic acid ethyl ester;
- 5-Cyano-4-methyl-6-naphthalen-2-yl-2-oxo-3,6-dihydro-2H-pyrimidine-1-carboxylic acid ethyl ester;
- 30

- 5-Cyano-6-[3-(2-hydroxyethylcarbamoyl)-phenyl]-4-methyl-2-oxo-3,6-dihydro-2H-pyrimidine-1-carboxylic acid ethylamide;
- 5-Cyano-6-(2-methoxyphenyl)-4-methyl-2-oxo-3,6-dihydro-2H-pyrimidine-1-carboxylic acid ethyl ester;
- 5 5-Cyano-6-(2-methoxyphenyl)-4-methyl-2-oxo-3,6-dihydro-2H-pyrimidine-1-carboxylic acid ethylamide;
- 6-(2-Allyloxyphenyl)-5-cyano-4-methyl-2-oxo-3,6-dihydro-2H-pyrimidine-1-carboxylic acid ethyl ester;
- 6-(2-Allyloxyphenyl)-5-cyano-4-methyl-2-oxo-3,6-dihydro-2H-pyrimidine-1-
- 10 carboxylic acid ethylamide;
- 6-(2-Bromophenyl)-5-cyano-4-methyl-2-oxo-3,6-dihydro-2H-pyrimidine-1-carboxylic acid ethyl ester;
- 6-(2-Bromophenyl)-5-cyano-4-methyl-2-oxo-3,6-dihydro-2H-pyrimidine-1-carboxylic acid ethylamide
- 15 5-Cyano-6-(3-methoxyphenyl)-4-methyl-2-oxo-3,6-dihydro-2H-pyrimidine-1-carboxylic acid ethylamide
- 6-(2-Benzyloxyphenyl)-5-cyano-4-methyl-2-oxo-3,6-dihydro-2H-pyrimidine-1-carboxylic acid ethyl ester
- 6-Benzyloxymethyl-5-cyano-4-methyl-2-oxo-3,6-dihydro-2H-pyrimidine-1-
- 20 carboxylic acid ethylamide
- 6-Benzyloxymethyl-5-cyano-4-methyl-2-oxo-3,6-dihydro-2H-pyrimidine-1-carboxylic acid ethyl ester;
- 6-(3-Bromo-4-fluorophenyl)-5-cyano-4-methyl-2-oxo-3,6-dihydro-2H-pyrimidine-1-carboxylic acid ethylamide;
- 25 6-(3-Bromo-4-fluorophenyl)-5-cyano-4-methyl-2-oxo-3,6-dihydro-2H-pyrimidine-1-carboxylic acid cyclopropylamide;
- 6-(5-Bromo-2-fluorophenyl)-5-cyano-4-methyl-2-oxo-3,6-dihydro-2H-pyrimidine-1-carboxylic acid ethylamide;
- 6-(5-Bromo-2-fluorophenyl)-5-cyano-4-methyl-2-oxo-3,6-dihydro-2H-pyrimidine-1-
- 30 carboxylic acid cyclopropylamide;

- 5-Cyano-6-(3,5-dibromophenyl)-4-methyl-2-oxo-3,6-dihydro-2H-pyrimidine-1-carboxylic acid ethylamide;
- 5-Cyano-4-methyl-6-(3-nitrophenyl)-2-oxo-3,6-dihydro-2H-pyrimidine-1-carboxylic acid cyclopropylmethylamide;
- 5 5-Cyano-4-methyl-2-oxo-6-phenethyloxymethyl-3,6-dihydro-2H-pyrimidine-1-carboxylic acid ethyl ester;
- 5-Cyano-4-methyl-2-oxo-6-phenethyl-3,6-dihydro-2H-pyrimidine-1-carboxylic acid ethylamide;
- 5-Cyano-4-methyl-2-oxo-6-thiophen-3-yl-3,6-dihydro-2H-pyrimidine-1-carboxylic acid ethyl ester;
- 10 5-Cyano-4-methyl-6-(5-methylisoxazol-3-yl)-2-oxo-3,6-dihydro-2H-pyrimidine-1-carboxylic acid ethyl ester;
- 5-Cyano-6-(3,5-dimethylisoxazol-4-yl)-4-methyl-2-oxo-3,6-dihydro-2H-pyrimidine-1-carboxylic acid ethyl ester;
- 15 5-Cyano-4-methyl-2-oxo-6-thiophen-2-yl-3,6-dihydro-2H-pyrimidine-1-carboxylic acid ethyl ester;
- 5-Cyano-4-methyl-6-(3-methylthiophen-2-yl)-2-oxo-3,6-dihydro-2H-pyrimidine-1-carboxylic acid ethylamide;
- 5-Cyano-4-methyl-6-(3-methylthiophen-2-yl)-2-oxo-3,6-dihydro-2H-pyrimidine-1-carboxylic acid ethyl ester;
- 20 5-Cyano-4-methyl-6-(2-methylthiazol-4-yl)-2-oxo-3,6-dihydro-2H-pyrimidine-1-carboxylic acid ethyl ester;
- 6-(4-Bromothiophen-2-yl)-5-cyano-4-methyl-2-oxo-3,6-dihydro-2H-pyrimidine-1-carboxylic acid ethylamide;
- 25 6-(4-Bromothiophen-2-yl)-5-cyano-4-methyl-2-oxo-3,6-dihydro-2H-pyrimidine-1-carboxylic acid ethyl ester;
- 5-Cyano-4-methyl-2-oxo-6-[2-(4-trifluoromethylphenyl)-thiazol-4-yl]-3,6-dihydro-2H-pyrimidine-1-carboxylic acid ethyl ester;
- 6-[5-(4-Chlorophenyl)-oxazol-4-yl]-5-cyano-4-methyl-2-oxo-3,6-dihydro-2H-pyrimidine-1-carboxylic acid ethyl ester;
- 30 6-(2-Bromothiazol-5-yl)-5-cyano-4-methyl-2-oxo-3,6-dihydro-2H-pyrimidine-1-carboxylic acid ethyl ester;

- 5-Cyano-4-methyl-2-oxo-6-(4-phenylthiophen-2-yl)-3,6-dihydro-2H-pyrimidine-1-carboxylic acid ethylamide;
- 6-[5-(4-Chlorophenyl)-furan-2-yl]-5-cyano-4-methyl-2-oxo-3,6-dihydro-2H-pyrimidine-1-carboxylic acid ethylamide;
- 5 5-Cyano-4-methyl-2-oxo-6-(4-trifluoromethylthiazol-5-yl)-3,6-dihydro-2H-pyrimidine-1-carboxylic acid ethyl ester;
- 5-Cyano-4-methyl-2-oxo-6-(4-trifluoromethylthiazol-5-yl)-3,6-dihydro-2H-pyrimidine-1-carboxylic acid ethylamide;
- 5-Cyano-6-[5-(4-methanesulfonylphenyl)-oxazol-4-yl]-4-methyl-2-oxo-3,6-dihydro-10 2H-pyrimidine-1-carboxylic acid ethylamide;
- 6-[5-(4-Chlorophenyl)-oxazol-4-yl]-5-cyano-4-methyl-2-oxo-3,6-dihydro-2H-pyrimidine-1-carboxylic acid ethylamide;
- 5-Cyano-4-methyl-2-oxo-6-[5-(4-trifluoromethylphenyl)-oxazol-4-yl]-3,6-dihydro-2H-pyrimidine-1-carboxylic acid ethylamide;
- 15 5-Cyano-4-methyl-2-oxo-6-(5-phenyloxazol-4-yl)-3,6-dihydro-2H-pyrimidine-1-carboxylic acid ethylamide;
- 5-Cyano-4-methyl-6-[5-(4-nitrophenyl)-oxazol-4-yl]-2-oxo-3,6-dihydro-2H-pyrimidine-1-carboxylic acid ethylamide;
- 5-(4-Chlorophenyl)-2-(5-cyano-3-ethylcarbamoyl-6-methyl-2-oxo-1,2,3,4-20 tetrahydropyrimidin-4-yl)-furan-3-carboxylic acid ethyl ester;
- 5-Cyano-4-methyl-2-oxo-6-(5-pyridin-3-yloxazol-4-yl)-3,6-dihydro-2H-pyrimidine-1-carboxylic acid ethylamide;
- 5-Cyano-4-methyl-2-oxo-6-(4-phenylthiazol-5-yl)-3,6-dihydro-2H-pyrimidine-1-carboxylic acid ethylamide;
- 25 [5-Cyano-4-methyl-6-(3-nitrophenyl)-2-oxo-3,6-dihydro-2H-pyrimidin-1-yl]-acetic acid tert-butyl ester;
- 5-Cyano-4-methyl-6-(3-nitrophenyl)-2-oxo-3,6-dihydro-2H-pyrimidine-1-carboxylic acid isopropylamide;
- 5-Cyano-4-methyl-6-(3-nitrophenyl)-2-oxo-3,6-dihydro-2H-pyrimidine-1-carboxylic acid propylamide;
- 30 5-Cyano-4-methyl-6-(3-nitrophenyl)-2-oxo-3,6-dihydro-2H-pyrimidine-1-carboxylic acid phenylamide;

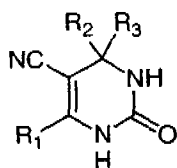
- 5-Cyano-4-methyl-6-(3-nitrophenyl)-2-oxo-3,6-dihydro-2H-pyrimidine-1-carboxylic acid thiazol-2-ylamide;
- 5-Cyano-4-methyl-6-(3-nitrophenyl)-2-oxo-3,6-dihydro-2H-pyrimidine-1-carboxylic acid (2,2,2-trifluoro-ethyl)-amide;
- 5 5-Cyano-4-methyl-6-(3-nitrophenyl)-2-oxo-3,6-dihydro-2H-pyrimidine-1-carboxylic acid cyclopropylamide;
- 5-Cyano-4-methyl-6-(3-nitrophenyl)-2-oxo-3,6-dihydro-2H-pyrimidine-1-carboxylic acid (2-hydroxy-ethyl)-amide;
- 3-(4,5-Dihydrooxazol-2-yl)-6-methyl-4-(3-nitrophenyl)-2-oxo-1,2,3,4-
- 10 tetrahydropyrimidine-5-carbonitrile; and
- 5-Cyano-4-methyl-6-(3-nitrophenyl)-2-oxo-3,6-dihydro-2H-pyrimidine-1-carboxylic acid allylamide.
17. A pharmaceutical composition comprising a compound of claim 1 and a
- 15 pharmaceutically acceptable carrier.
18. The pharmaceutical composition of claim 17 further comprising at least one other anti-cancer agent formulated as a fixed dose.
- 20 19. A method for treating a proliferative disease via modulation of the Eg5 motor protein comprising administering to a mammalian species in need of such treatment an effective amount of at least one compound of claim 1.
20. The method according to claim 19 further comprising administering to said
- 25 mammalian species at least one other anti-cancer agent.
21. The method according to claim 19 wherein the proliferative disease is cancer.
- 30 22. A method for treating a proliferative disease by inducing apoptosis comprising administering to a mammalian species an effective amount of a compound of claim 1.

23. The method according to claim 22 further comprising administering to said mammalian species at least one other anti-cancer agent.

5 24. The method according to claim 22 wherein the proliferative disease is cancer.

25. A method of preparing a compound having the formula:

10



XXIV

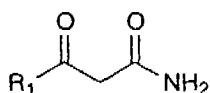
wherein

R_1 is selected from the group consisting of hydrogen, alkyl and cycloalkyl;

15 R_2 and R_3 are each independently selected from the group consisting of H, alkyl, aryl, heteroaryl, arylalkyl, cycloalkyl, heterocycloalkyl, cycloalkylalkyl, heterocycloalkylalkyl and heteroarylalkyl; or

R_2 and R_3 may also be taken together to form a carbocyclic or heterocyclic ring;

20 comprising contacting a compound having formula R_2COR_3 with a compound having the formula R_1COCH_2CN or a compound having the formula



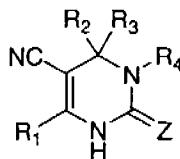
in the presence of polyphosphate ester and urea to form



XXIV

25

26. The method of claim 25 further comprising contacting compound XXIV with R_4 -X in the presence of a base wherein R_4 is alkyl or acyl, and X is a leaving group, or wherein R_4 X is isocyanate or haloformate to yield a compound having formula I



I