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54 TITULO

COMPUESTOS DE DIHIDROPIRIMIDINA CIANO-SUSTITUIDA Y SU USO PARA
TRATAR ENFERMEDADES

51 CLASIFICACION INTERNACIONAL

C07D239/42, A61K31/505

71 SOLICITANTE

BRISTOL - MYERS SQUIBB COMPANY

DOMICILIO

PRINCETON NEW JERSEY ESTADOS UNIDOS DE AMERICA

74 APODERADO

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PCT

ENTRADA EN FASE NACIONAL

1

SOLICITUD DE



Patente de Invención



Patente de Modelo de Utilidad



Capítulo I



Capítulo II

2

SOLICITANTE
(71)

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IDENTIFICACION

CC ☐ NIT ☐

CE ☐ Otro ☐

Cual _____

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Número 170 322 TP 1003

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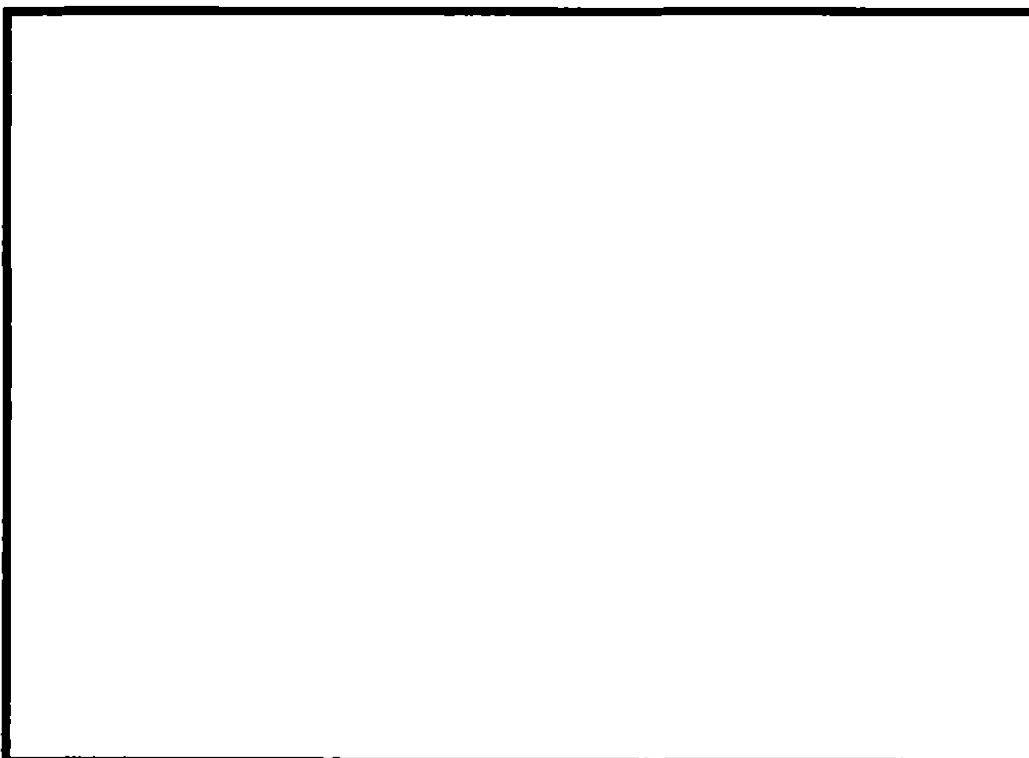
Instrucciones para el diligenciamiento del presente formulario ver reverso de esta página

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ANEXOS

- ☒ Comprobante de pago de la tasa de presentación de la solicitud \$400.000
- ☐ Documento que acredite 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 170322 de Bogotá T.P 1003 del G.S.J.

Instrucciones para la presentación de los anexos, ver reverso de esta página

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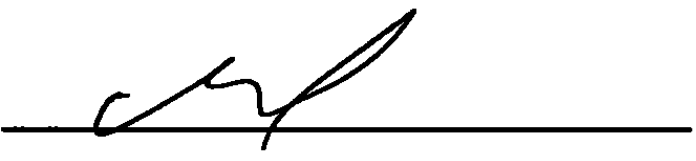
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***** C O N C E P T O *****

CANT	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
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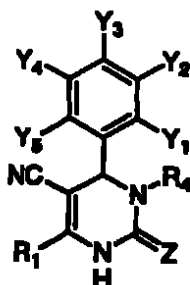
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(54) Title CYANO-SUBSTITUTED DIHYDROPYRIMIDINE COMPOUNDS AND THEIR USE TO TREAT DISEASES



(I)

(57) Abstract The present invention provides compounds of formula (I), 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 02/079169 A1

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

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

BACKGROUND

 Cell proliferation and programmed cell death play important roles in the
15 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
20 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
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
25 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
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
30 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

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 microtubules have a role. Hence, a need exists for small molecules that specifically target proteins associated with proliferating cells, such as Eg5

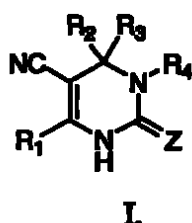
Eg5 is one of several kinesin-like motor proteins that are localized to the mitotic spindle and known to be required for formation and/or function of the bipolar mitotic spindle. Recently there was a report of a small molecule that disturbs bipolarity of the mitotic spindle (Mayer, T U et al 1999 Science 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 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. 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. (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:

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

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, $C(O)R_5$, CO_2R_5 , $C(O)SR_5$ and $CONR_5R_6$;

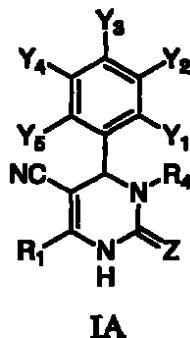
R_5 and R_6 are each independently selected from the group consisting of H, alkyl, cycloalkyl, hydroxyalkyl, alkenyl, alkoxy, thioalkoxy, alkoxyalkyl, haloalkyl, aryl, heteroaryl, arylalkyl, cycloalkylalkyl, heteroarylalkyl and heterocycloalkylalkyl, or $N-R_5R_6$ together form a heterocycloalkyl;

Z is selected from the group consisting of O, S and NR_8 .

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

- 5 According to one embodiment, compounds of the present invention include those having formula IA



10

- its enantiomers diastereomers pharmaceutically acceptable salts prodrugs and solvates thereof wherein Y_1 , Y_2 , Y_3 , Y_4 and Y_5 are independently selected from the group consisting of H halogen lower alkyl O-alkyl O aryl NH-alkyl, NH-aryl, N-alkylalkyl, N-alkylaryl, N-arylarlyl with the proviso that at least one of Y_1 , Y_2 , Y_3 , Y_4 and Y_5 is aryl or heteroaryl and the remaining groups are as defined above.

- The present invention also provides methods for treating a proliferative disease, such as cancer 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 formula I or IA, as defined above

20

DESCRIPTION

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

25

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) 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 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, 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), alkylloxycarbonyl (-C(O)R), alkylcarbonyloxy (-OCOR), amino (-NH₂), carbamoyl (-NHCOOR- or -OCONHR-), urea (-NHCONHR-) or thiol (-SH). Alkyl groups as 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

A
7

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 species 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 alkyloxycarbonyl radical is represented by the formula, -C(O)OR, where the R group is a straight or branched C₁₋₆ alkyl group.

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.

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 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, aryl, heteroaryl, cyano alkyl $S(O)_m$ ($m=O, 1, 2$) or thiol

- 5 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
- 10 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
- 15 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),
- 20 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
- 25 (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
- 30 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'', -
 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,
 5 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
 10 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
 15 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
 20 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'', -
 25 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,
 alkyl, substituted alkyl and cycloalkyl, or R and R' together form a heterocyclo or
 heteroaryl ring

Exemplary monocyclic heteroaryl groups include pyrrolyl, pyrazolyl
 30 pyrazolinyl, imidazolyl, oxazolyl, diazolyl, 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 quinolyl, tetrahydroisoquinolyl, isoquinolyl, benzimidazolyl benzopyranyl indolizyl benzofuranyl chromonyl, coumarinyl, benzopyranyl cannolyl, quinoxalyl, indazolyl, pyrrolopyridyl, furopyridinyl, dihydroisoindolyl, tetrahydroquinolyl 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 heterocyclyl 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, 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, 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

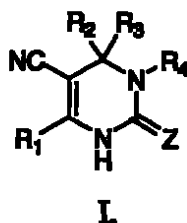
Suitable examples of salts of the compounds according to the invention with inorganic or organic acids are hydrochloride, hydrobromide, sulfate, methanesulfonate, maleate, fumarate, and phosphate. Salts which are unsuitable for pharmaceutical uses but which can be employed, for example, for the isolation 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 R_1 is hydrogen, alkyl or cycloalkyl R_2 and R_3 are each
 5 independently H, alkyl aryl, heteroaryl arylalkyl, cycloalkylalkyl, heterocycloalkylalkyl or heteroarylalkyl Alternatively R_2 and R_3 may be taken together to form either a carbocyclic or heterocyclic ring. R_4 is alkyl, arylalkyl, cycloalkylalkyl, aminoalkyl, heteroarylalkyl heterocycloalkylalkyl, CN COR_5 , CO_2R_5 or $CONR_5R_6$ R_5 and R_6 are each independently H, alkyl arylalkyl
 10 cycloalkylalkyl, heteroarylalkyl or heterocycloalkylalkyl or $N-R_5R_6$ together form a heterocycloalkyl Z is O S or NR_8 , R_8 is H, CN, sulfonamido, OR_7 , alkyl cycloalkyl aryl, arylalkyl, heterocyclyl, heteroaryl or heteroarylalkyl R_7 is H alkyl, arylalkyl, cycloalkylalkyl, heterocycloalkylalkyl or heteroarylalkyl

One preferred embodiment of the instant invention includes compounds of
 15 formula I, as defined above 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 is selected from the group consisting of O S and NR_8 , and R_8 is selected from the
 20 group consisting of H and CN

In one preferred embodiment, the invention comprises compounds of formula I wherein R_2 is heteroaryl Preferred heteroaryl groups include optionally substituted thiophenyl, oxazolyl, isoxazolyl and furanyl Preferred substituents include methyl ethyl halo, haloalkyl such as CF_3 or aryl groups such as phenyl or substituted
 25 phenyl Preferred phenyl substituents include alkyl groups, such as methyl alkoxy groups such as methoxy halo (F Cl, or Br) haloalkyl such as CF_3 amino groups such as dimethylamino or alkoxyalkyl groups such as ethoxymethyl groups

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 $CONR_5R_6$
 30

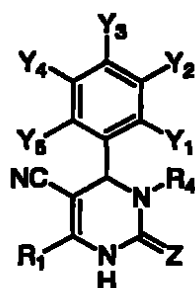
In yet another preferred embodiment, the instant invention comprises the compounds of formula I, as defined above, wherein R_4 is CO_2R_5 , Z is O and R_5 is ethyl

In yet a further preferred embodiment, the instant invention comprises the compounds of formula I, as defined above, wherein R_4 is $CONR_5R_6$, Z is O, R_5 is H, and R_6 is methyl, ethyl, propyl, phenyl cyclopropyl, hydroxyethyl thiophenyl, or 2-propylene.

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 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

According to one embodiment, the instant invention comprises compounds of formula IA



1A

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

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

Y_1 , Y_2 , Y_3 , Y_4 and Y_5 are independently selected from the group consisting of H halogen lower alkyl O alkyl O aryl NH alkyl NH aryl N alkyl alkyl N alkyl aryl, N aryl aryl with the proviso that at least one of Y_1 , Y_2 , Y_3 , Y_4 and Y_5 is aryl or heteroaryl

R_4 is selected from the group consisting of alkyl arylalkyl cycloalkylalkyl aminoalkyl, heteroarylalkyl heterocycloalkylalkyl CN, COR_5 , CO_2R_5 and $CONR_5R_6$

R₅ and R₆ are independently selected from the group consisting of H, alkyl haloalkyl, cycloalkyl arylalkyl cycloalkylalkyl heteroarylalkyl, and heterocycloalkylalkyl,

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

5 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

10 In some preferred embodiments Y₂ is aryl or heteroaryl. In preferred embodiments Y₂ is an optionally substituted phenyl, pyridyl thiazolyl, pyrrolyl, or diazolyl Preferred substituents include Br, Cl, F methyl ethyl, or CF₃

According to one embodiment of the instant invention compounds comprise Formula IA, wherein R₄ is alkyl arylalkyl, CO₂R₅ or CONR₅R₆

15 According to another embodiment, the instant invention comprises compounds having formula IA wherein R₁ is alkyl 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 haloalkyl cycloalkyl 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

20 According to another embodiment, the instant invention comprises compounds of Formula IA wherein R₄ is CO₂R₅ or CONR₅R₆ and Z is O

In other embodiments, the instant invention comprises compounds of formula IA wherein R₄ is selected from the group consisting of alkyl and arylalkyl, and Z is O

25 In still further embodiments the instant invention comprises compounds of formula IA wherein R₁ is CH₃ R₄ is CO₂R₅ R₅ is alkyl and Z is O

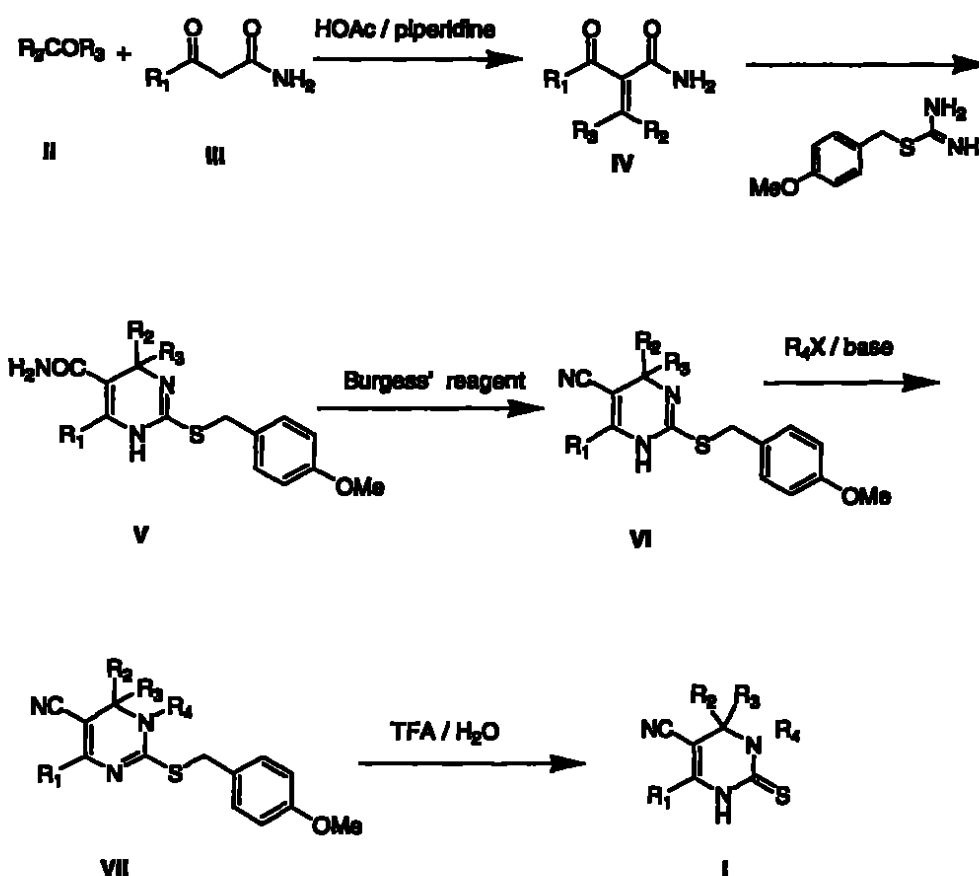
The invention further provides a pharmaceutical composition comprising a compound of formula I or IA as defined above, and a pharmaceutically acceptable carrier Optionally the pharmaceutical composition may further comprise at least one other anti-cancer agent formulated as a fixed dose.

30 The invention also provides a method for treating a proliferative disease via 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 treatment an effective amount of at least one compound of formula I or Ia, as defined
 5 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 and Ia are also within the scope of the
 10 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

Scheme I

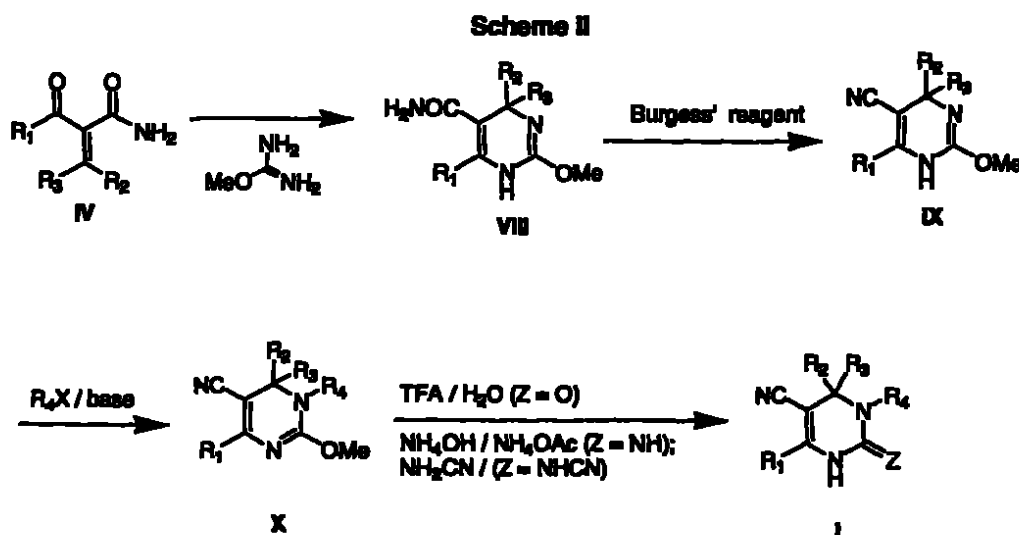


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Compounds of formula I where Z is S may be made in accordance with Scheme I. A ketone or an aldehyde I (e.g. benzaldehyde, where R_2 is phenyl and R_3

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

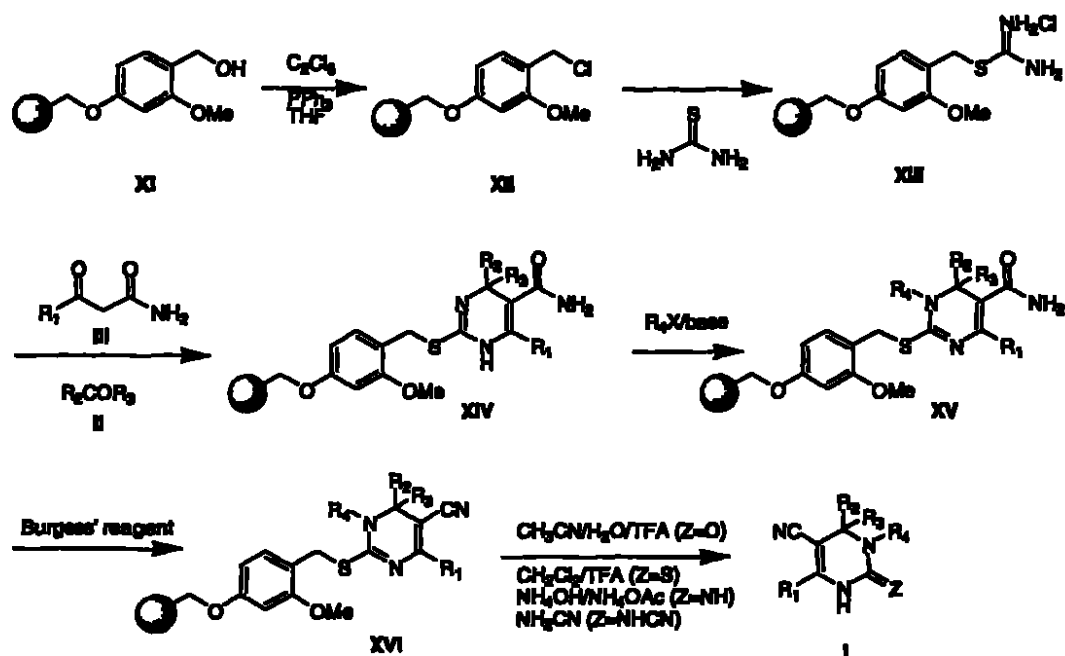
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Compounds of formula I where Z is O, NH, or NR_3 are prepared from the reaction of Knoevenagel products IV with O-methyl isourea to provide the O-methyl dihydropyrimidines VIII. The primary amide is converted to a nitrile group using a dehydrating 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_3 .

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

Scheme II
SOLID PHASE SYNTHESIS

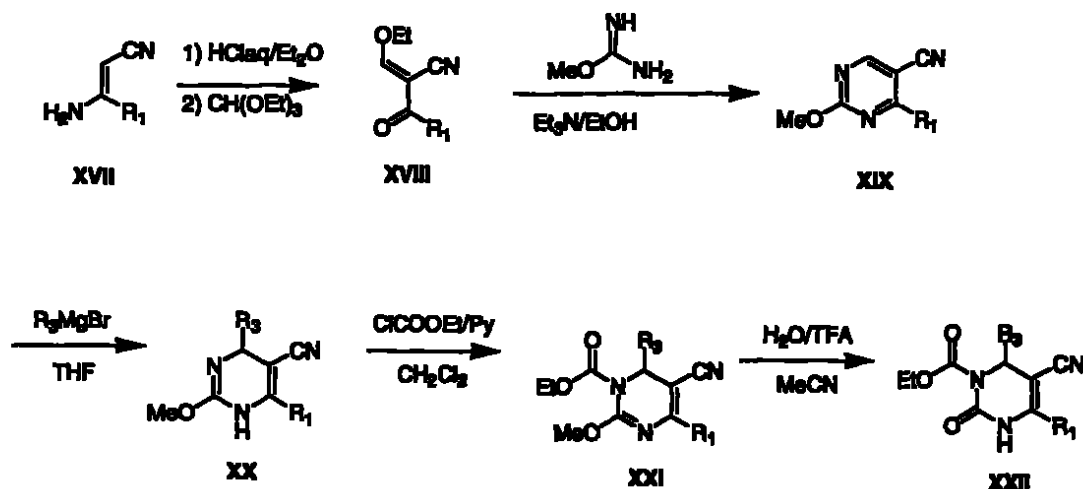


Compounds of formula I could be prepared on solid support as outlined in Scheme III. Starting compound XI denotes a resin-bound benzyl alcohol used for solid support synthesis which is prepared from a Merrifield resin denoted as ●, and 2-methoxy-4-hydroxybenzaldehyde, followed by reduction of the aldehyde 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 isothiurea 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 formula I with Z being NHCN

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Scheme IV



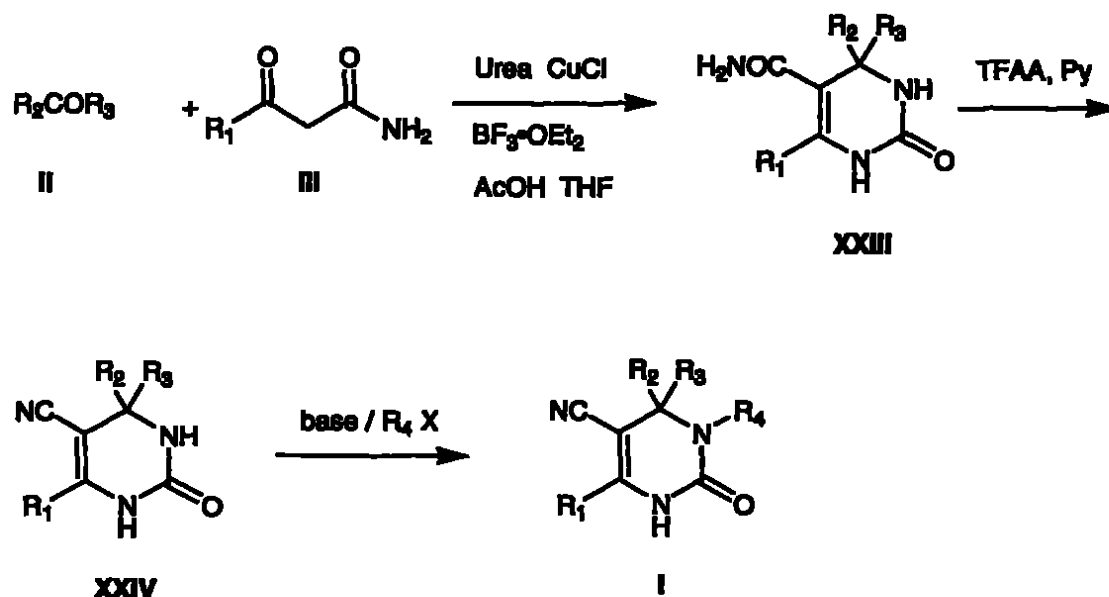
Compounds of formula XVIII may be prepared from a 3-amino-3-alkyl acrylonitrile XVII using the methods illustrated in Scheme IV. Reaction of a compound of formula XVII with aqueous acid, such as hydrochloric acid, followed by treatment with triethyl orthoformate, provides a compound of formula XVIII. 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 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 1998 63 3454-3457) a carbonyl compound of formula Ia 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.

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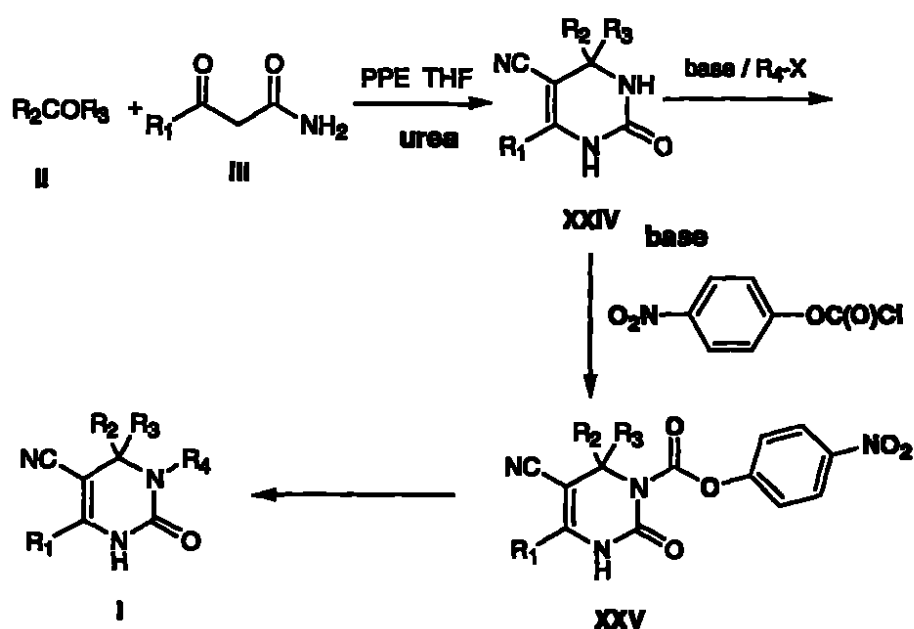
Scheme V



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.

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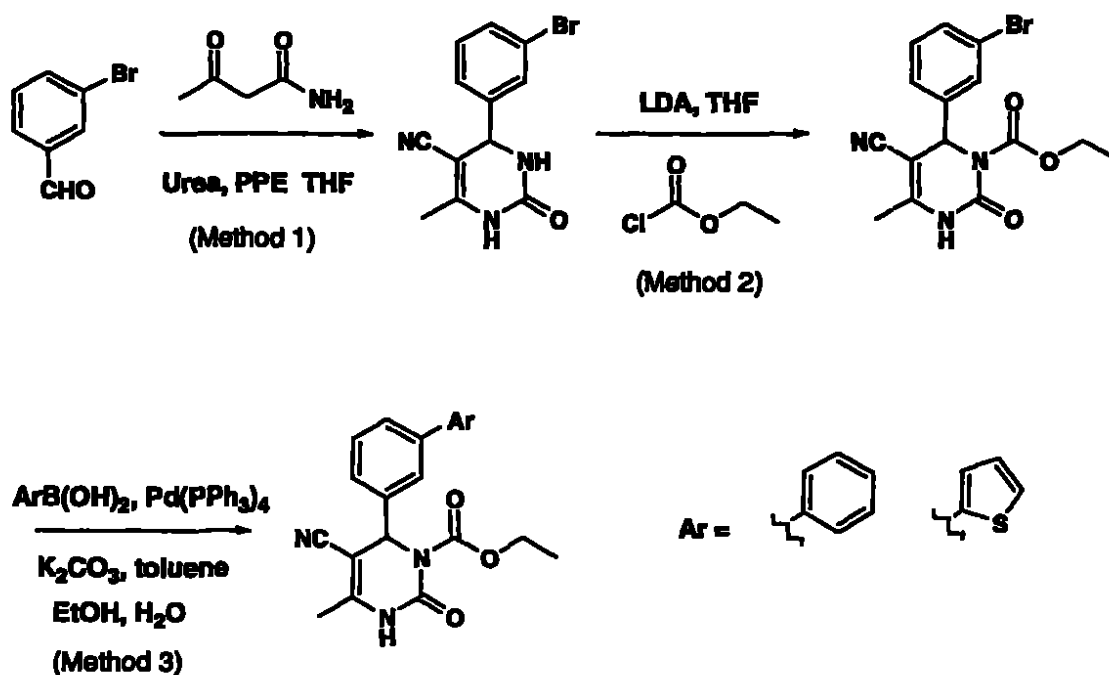
Scheme VI



In all of the above schema, a 2-acyl acetonitrile derivative, i.e., R_1COCH_2CN may be substituted for a compound of formula III. schemes below

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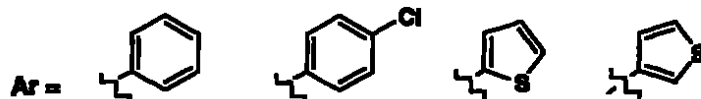
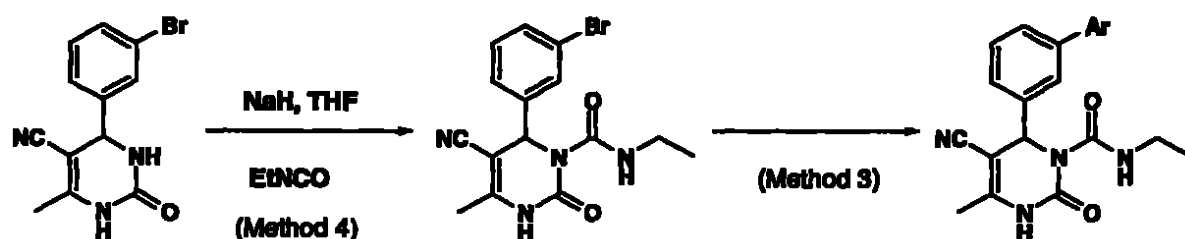
Scheme VII (Examples 116-117)



Compounds of formula Ia where R₄ is a carbamate may be made in accordance with Scheme VII. Following the procedure of Method 1, an appropriate aldehyde may be condensed with acetoacetamide and urea in the presence of polyphosphoric ester (PPE) to give a dihydropyrimidone product in high yield.

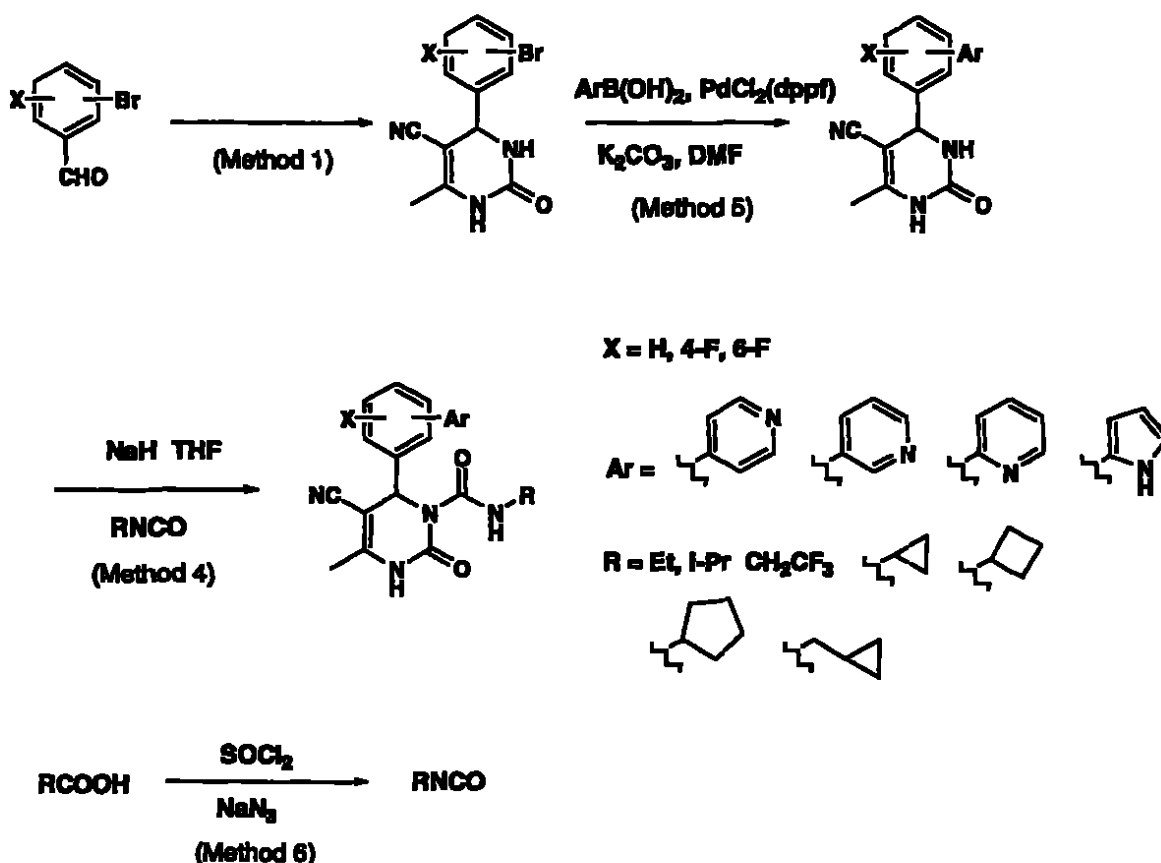
- 5 Reaction of this compound with lithium diisopropylamide and ethyl chloroformate following the procedure of Method 2 provides predominately the N-1 carbamate, which then undergoes a palladium-catalyzed Suzuki coupling reaction with an aryl or heteroaryl boronic acid to give compounds of the present invention as described by Method 3

Scheme VIII (Examples 118-121)



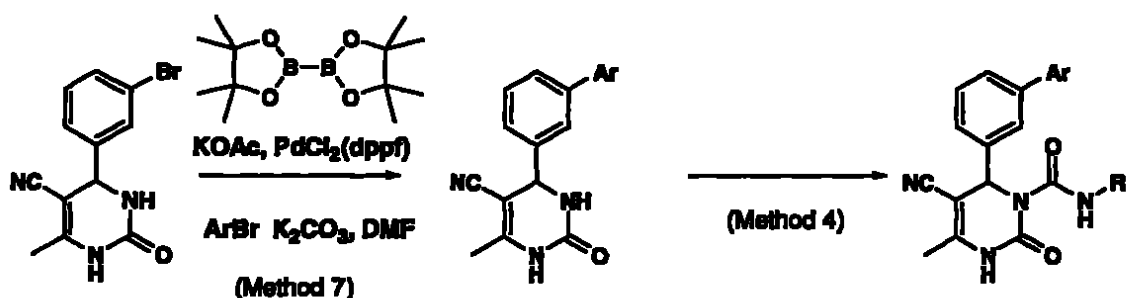
Similarly compounds of formula Ia where R₄ is a urea may be made in accordance with Scheme VIII. Reaction of a dihydropyrimidone compound obtained following the procedure of Method 1 with sodium hydride and ethyl isocyanate following the procedure of Method 4 provides exclusively the N-1 urea, which then undergoes a palladium-catalyzed Suzuki coupling reaction with an aryl or heteroaryl boronic acid to give compounds of the present invention as described by Method 3

Scheme IX (Examples 122-139, 144-145)



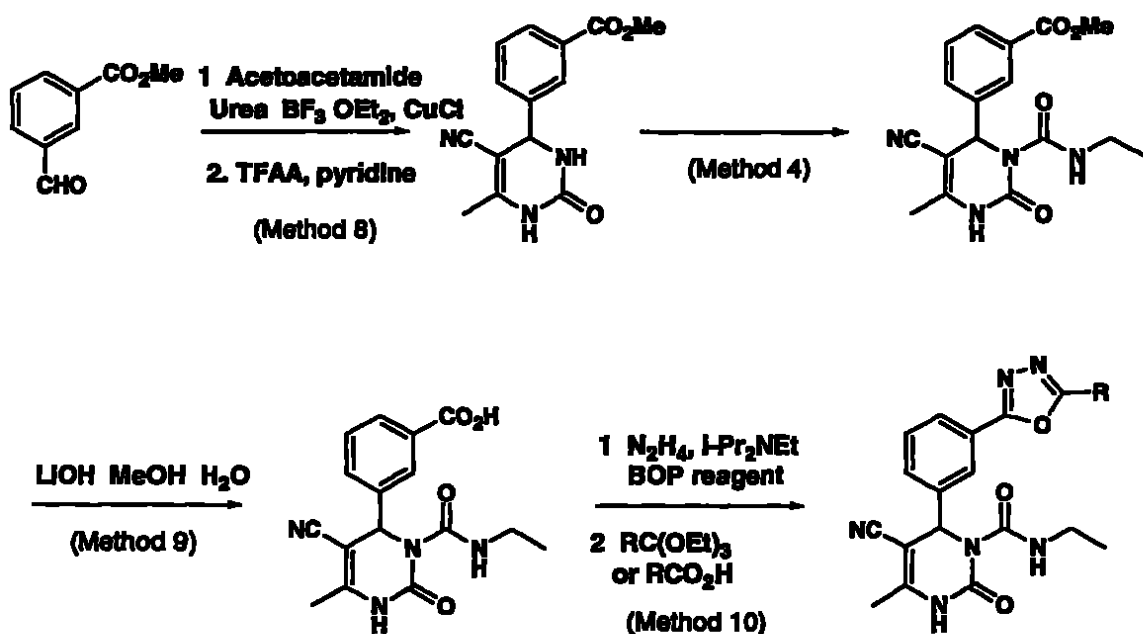
An alternative reaction sequence is described in Scheme IX, wherein a
 palladium-catalyzed coupling reaction may be performed prior to addition of the
 5 exocyclic urea moiety at the N-1 position on the dihydropyrimidone ring. Thus, the
 dihydropyrimidone product of Method 1 may be reacted with an appropriate aryl or
 heteroaryl boronic acid in the presence of a palladium catalyst following Method 5 to
 afford a biaryl product. Subsequent reaction with an isocyanate in the presence of
 sodium hydride following the procedure of Method 4 affords the compounds of the
 10 present invention in good yield. A variety of isocyanate reagents may be prepared from
 corresponding carboxylic acid precursors by treatment with thionyl chloride and
 sodium azide using Method 6.

Scheme X (Examples 140-141)



A variation of the process of Scheme IX involves formation of the boronic acid derivative of the dihydropyrimidinone prepared by Method 1 and is described in Scheme X. This boronic acid derivative may be prepared by reaction of an appropriate aryl halide with bis(pinacolato)diboron in the presence of a palladium catalyst. Subsequent reaction with an appropriate aryl halide in the presence of additional palladium catalyst affords the desired biaryl compound following the procedure of Method 7. Subsequent reaction with an isocyanate in the presence of sodium hydride following the procedure of Method 4 affords the compounds of the present invention in good yield.

Scheme XI (Examples 142-143)



Oxadiazole-substituted compounds of formula IA may be prepared in accordance with Scheme X. Following the procedure of Method 8 an appropriate aryl aldehyde may be condensed with acetoacetamide and urea in the presence of boron trifluoride, followed by dehydration with trifluoroacetic anhydride to give a dihydropyrimidone compound. Reaction of this dihydropyrimidone with an isocyanate and sodium hydride following the procedure of Method 4 affords the N-1 substituted urea, which may be further reacted with lithium hydroxide to provide a carboxylic acid as described by Method 9. Treatment of the carboxylic acid with hydrazine and BOP reagent affords the corresponding acyl hydrazide which undergoes cyclization with triethyl orthoacetate or an alkyl acid to afford compounds of the present invention as described by Method 10.

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 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 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,
- 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 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 astrocytoma, neuroblastoma, glioma and schwannomas, and
- f) other tumors, including melanoma, seminoma, teratocarcinoma, osteosarcoma, xenoderma pigmentosum, keratocanthoma, thyroid follicular cancer and Kaposi's sarcoma.

Due to the key role of motor proteins in the regulation of cellular proliferation 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 adenomatous polyposis, neurofibromatosis, atherosclerosis, pulmonary fibrosis, arthritis, psoriasis, glomerulonephritis, restenosis following angioplasty or vascular surgery, hypertrophic scar

formation inflammatory bowel disease, transplantation rejection endotoxemic shock, and fungal infections

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

Compounds of formula I and Ia may be 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.

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-B, 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
5 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
10 inhibitors such as etoposide, topoisomerase I inhibitors such as CPT-11 or topotecan, tubulin interacting agents, such as paclitaxel docetaxel or the epothilones, either naturally occurring or synthetic hormonal agents such as tamoxifen, thymidilate synthase inhibitors such as 5-fluorouracil and anti-metabolites such as methotrexate.

15 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 formulae I and Ia may also be administered sequentially with known anticancer or cytotoxic agents when a combination formulation is inappropriate. The
20 invention is not limited in the sequence of administration compounds of formulae I and Ia may be administered either prior to or after administration of the known anticancer or cytotoxic agent(s)

ASSAYS

25 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 formulae I and Ia exhibited antiproliferative activity. Preferred compounds exhibit IC_{50} values less than or equal
30 to about 10 μ M

9
18Cell Culture

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

72-Hour Proliferation Assay

5 Cells were plated at a density of 3,000-6,000 cells/well, depending upon the cell line used, in a 96-well plate. The cultures were 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 μM .

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 formulae I and IA exhibited activity in the clonogenicity assay.

Combination Studies - Clonogenic Growth Assays

Combination studies to examine the use of the Eg5 inhibitors of formulae I and Ia in combination with other antineoplastic agents were conducted essentially the same as the standard colony growth assay with the exception of compound treatment.

5 In the combination studies the cells were treated with both a compound of formulae I and Ia 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

10 survival fractions of combination treatments with those of single drug treatments

Cell Cycle Analysis

The cell cycle profile of cells treated with compounds of formulae I and Ia was monitored by flow cytometry. Briefly, A2780 ovarian carcinoma cells were seeded at

15 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 formulae I and Ia 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

20 apoptosis including, for example, anti-phospho-ThreonineProline, anti-M Phase Phosphoprotein 2 (MMP2), and anti-p85 PARP. The compounds of formulae I and Ia 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 and II, separately at concentrations of 100 nM to 50 μ M for 4 to 30 hours, fixed and

30 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

19
imaged by fluorescent and confocal fluorescent microscopy The compounds of formulae I and IA 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 formula I or IA as defined above or at least one of its pharmacologically acceptable acid addition salts and the use of a compound of the formula I or IA 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 70 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 Step 4

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 = 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 7.48 g 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)

30

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 1 h, 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, 4 ml/min, monitoring at 220 nm)

Example 5

- enantiomer 5* Cyano-3,6-dihydro-4-methyl-6-(3-nitrophenyl)-2-oxo-1-(2H)-pyrimidinecarboxylic acid, 1-ethyl ester (enantiomer A)
- 15 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 x 250
- 20 mm, 10% MeOH / 10% EtOH / Heptane, 1.0 ml/min monitoring at 220 nm, 94.7% ee)

Example 6

- enantiomer 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 x 250 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

23
22**Example 10**

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

- 5 HPLC-HI 100% at 3.2 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 $[M-H]^- = 352$

Example 11

- 10 **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 methanol over 4 minutes containing 0.1% of TFA, 4 ml/min, monitoring at 220 nm)
MS $[M+H]^+ = 316$

- 15 **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 methanol over 4 minutes containing 0.1% of TFA, 4 ml/min, monitoring at 220 nm)

- 20 MS $[M-H]^- = 352$

Example 13

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

- 25 HPLC-HI 100% at 3.197 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 $[M-H]^- = 352$

Example 14

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

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-1,2,3,4-tetrahydropyrimidinecarboxylic 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-1,2,3,4-tetrahydropyrimidinecarboxylic 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/2 mm 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.

23

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)

5

Example 17

**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 -
10 44°C under argon the reaction was slowly warmed to room temperature, and stirred
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
15 mixture was stirred at room temperature for 30 min, stirred for another 10 min after
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
20 were added, the aqueous layer was separated and extracted with EtOAc, and the
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
25 220 nm)

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

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29

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 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), 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 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)-pyrimidin-9-carboxylic 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 at 220 nm).

25

Example 20

5-Cyano-3,6-dihydro-4-methyl-6-(3-chlorophenyl)-2-oxo-1-(2H)-pyrimidin-9-carboxylic acid, 1-ethyl ester

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).

30

Example 21

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

- 5 MS (M+H)⁺ = 304 HPLC RT = 1.29 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 22

- 10 **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, 10-90 % 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

- 20 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 monitoring at 220 nm)

Example 24

- 25 **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, 10-90% aqueous methanol over 4 minutes containing 0.2% phosphoric acid, 4 ml/min, monitoring at 220 nm)

26
25**Example 25****6-(3,5-Bis-trifluoromethylphenyl)-5-cyano-4 methyl-2-oxo-3,6-dihydro-2H-pyrimidine-1-carboxylic acid ethyl ester****5 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),
10 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%)

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
20 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 □L, 0 20 mmol) was added via a syringe The reaction mixture was stirred at -78 °C for
30 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

5 (M+Na)⁺

Example 26

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

10 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 15 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 20 (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.

B. Step 2

25 **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 (5 mL) 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 30 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.

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)⁺

Example 27

5-Cyano-4-methyl-6-(3-nitrophenyl)-2-oxo-3,6-dihydro-2H-pyrimidine-1-carboxylic acid methylamide

A. Step 1

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 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 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

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 µL, 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

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)⁺

Example 28

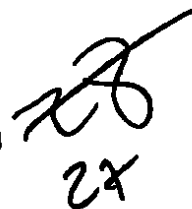
5-Cyano-4-methyl-2-oxo-6-phenyl-3,6-dihydro-2H-pyrimidine-1-carboxylic acid ethylamide. To a solution of 6-Methyl-2-oxo-4-phenyl-1,2,3,4-tetrahydropyrimidine-5-carbonitrile (100 mg, 0.47 mmole, obtained in 65 % yield by the procedure described in Example 26 Step 1) in 4 mL of tetrahydrofuran under argon 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)⁺

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)⁺

30

**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) δδ 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) δδ 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**20 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) δδ 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**30 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.

20 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

28

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 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.

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

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 H), 2.14 (s, 3 H), 1.84 (m, 4 H), 1.28 (m, 4H). LC/MS (ES+) 361 (M+H)⁺

25

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 procedure described in Example 2. The title compound was obtained in 18 % yield following the procedure of Example 3.

30

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, 1 H), 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 7 % 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 **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 8.85 (t, 3 H, $J = 6.7$), 1.07 (t, 3 H, $J = 7.2$), 1.23-1.29 (m, 4 H), 1.44-1.60 (m, 2 H), 2.05 (s, 3 H), 3.17-3.32 (m, 2 H), 5.04 (t, 1 H, $J = 6.0$), 8.70 (t, 1 H, $J = 5.5$), 10.30 (s, 1 H) 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)
- 20 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)
- 30 LC/MS (ES+) 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 carbodumide 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)⁺

2
3 31**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) δδ 0.92 (s, 9H), 1.06 (t, 3H, J = 7.15 Hz), 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) δδ 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, 2H), 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) δδ 0.36-0.51 (m, 4H), 1.05-1.09 (m, 4H), 2.06 (s, 3H), 3.20-3.23 (m, 2H), 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)⁺

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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

32

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,
5 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)⁺

10

Example 63**5-Cyano-6-[3-(2-hydroxyethylcarbamoyl)-phenyl]-4-methyl 2-oxo-3,6-dihydro-2H pyrimidine-1-carboxylic acid ethylamide**

15 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 carbodumide 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
20 = 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)⁺

25

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
30 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)⁺

5

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

10

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)⁺

15

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

20

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)⁺

25

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

30

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)⁺

5

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

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

10

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)⁺

15

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,

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

20

¹H-NMR (MeOH-d₄, 500 MHz) δ 7.55 (m, 1H), 7.30 (m, 2H), 7.15 (m, 1H), 6.46 (s, 1H), 3.14 (m, 2H), 2.04 (s, 3H), 1.04 (t, 3H, J = 7.1 Hz). LC/MS (ES+) 364 (M+H)⁺

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 62 % yield following the procedure described in Example 28.

30

¹H-NMR (DMSO-d₆, 500 MHz) δ 10.49 (s, 1H), 8.79 (t, 1H, J = 5.5 Hz), 7.32 (t, 1H, J = 7.7 Hz), 6.92 (m, 1H), 6.81 (d, 1H, J = 7.7 Hz), 6.75 (s, 1H), 6.06 (s, 1H),

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⁺)

Example 71

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

Using 2-benzoyloxybenzaldehyde and following the procedure of Example 26 intermediate XXIV was obtained in 47 % yield and the title compound was obtained in 54 % yield

10 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)⁺

Example 72

15 **6-Benzoyloxymethyl-5-cyano-4-methyl 2-oxo-3,6-dihydro-2H pyrimidine-1-carboxylic acid ethylamide**

Using 2-benzoyloxyacetaldehyde and following the procedure of Example 26 intermediate XXIV was obtained in 45 % yield The title compound was obtained in 30 % yield following the procedure described in Example 28

20 ¹H-NMR (DMSO-d₆) δδ 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)

Example 73

25 **6-Benzoyloxymethyl-5-cyano-4-methyl 2-oxo-3,6-dihydro 2H-pyrimidine-1-carboxylic acid ethyl ester**

Using 2-benzoyloxyacetaldehyde and following the procedure of Example 26 intermediate XXIV was obtained in 45 % yield and the title compound was obtained in 80 % yield

30 ¹H-NMR (DMSO-d₆) δδ 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)

34

Example 74

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

- 5 Using 3-bromo-4-fluorobenzaldehyde and following the procedure of Example 26, 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

- 15 Using 3-bromo-4-fluorobenzaldehyde and following the procedure of Example 26, 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

- 25 Using 5-bromo-2-fluorobenzaldehyde and following the procedure of Example 26, 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)
- 30

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)⁺

6
35**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) δ 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) δ 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**

25 Using thiophene-3-carboxaldehyde and following the procedure of Example 26 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⁺)
30 292 (M+H)⁺

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)

36

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), 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), 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)

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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 1.053 (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)⁺

38

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, 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)⁺

10

Example 93

- 15 **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, 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)⁺

20

Example 94

- 25 **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) δδ 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) δδ 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

15 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 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 (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, 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). ¹³C-NMR (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, 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

39

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) δδ 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) δδ 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) □□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

- 5 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) □□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

- 15 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, 1H), 8.22 (t, 1H, J = 1.8 Hz), 7.76 (m, 1H), 7.69 (t, 1H, J = 7.9 Hz), 7.62 (s, 1H), 5.31 (s, 1H), 4.23 (d, 1H, J = 17.6 Hz), 3.44 (d, 1H, J = 17.6 Hz), 2.16 (s, 3H), 1.42 (s, 9H). 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

- 25 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, 1H), 8.22 (d, 1H, J = 8.3 Hz), 8.17 (t, 1H, J = 1.8 Hz), 7.74 (d, 1H, J = 6.6 Hz), 7.65 (m, 2H), 6.31 (s, 1H), 3.89 (m, 1H), 2.19 (s, 3H), 1.20 (d, 3H, J = 6.6 Hz), 1.16 (d, 3H, 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 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 (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**

- 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), 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**

- 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 (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)

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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

15 XXIV was obtained in 92 % yield. The title compound was obtained in 19 % yield 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)

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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

25 XXIV was obtained in 92 % yield. The title compound was obtained in 23 % yield 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)⁺

42
41**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)⁺

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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 8.10 (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)⁺

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Example 116**6-(3-Bromophenyl)-5-cyano-3,6-dihydro-4-methyl-2-oxo-(2H)-pyrimidine****Method 1**

A mixture of 3-bromobenzaldehyde (13.0 g, 70 mmol), acetoacetamide (7.08 g, 70 mmol), urea (5.26 g, 87.5 mmol), polyphosphate ester (9.1 g, 21 mmol) and THF (150 mL) was heated in a sealed tube for 18 h at 75 °C. This mixture was cooled to room temperature, more polyphosphate ester (60.6 g, 140 mmol) was added and heating resumed for another 5 h. The reaction mixture was cooled to room temperature, poured into water (800 mL) and stirred for 18 h. The resulting precipitates were

30 collected by vacuum filtration, washed with water and with ether, and air dried to yield 6-(3-bromophenyl)-5-cyano-3,6-dihydro-4-methyl-2-oxo-(2H)-pyrimidine as a light yellow solid (16.25 g, 79%). ¹H NMR (DMSO-d₆, 400 MHz) δ 9.60 (s, 1 H)

7 87 (s, 1 H) 7 55 (m, 1 H) 7 48 (m, 1 H) 7 39 (t, 1 H, $J = 7.9$ Hz), 7 32 (d, 1 H $J = 7.9$ Hz), 5 14 (s, 1 H) 2 02 (s 3 H)

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

Method 2

To a solution of 6-(3-bromophenyl)-5-cyano-3,6-dihydro-4-methyl-2-oxo-(2H)-pyrimidine (0.29 g, 1 mmol) in THF (5 mL) chilled to -78°C was added LDA (0.55 mL, 1.1 mmol 2.0 M in THF). The resulting yellow suspension was stirred for 0.5 h, warmed to -20°C for 0.5 h and recooled to -78°C then ethyl chloroformate (0.14 mL, 1.5 mmol) was added via syringe. The reaction mixture was stirred for 20 min, warmed to room temperature and quenched with EtOAc. This mixture was washed with aqueous NaHCO_3 solution and with brine, dried (Na_2SO_4) and concentrated in vacuo. The residue was purified by flash column chromatography (10% to 30% EtOAc/hexanes) to give, after evaporation of solvent, 6-(3-bromophenyl)-5-cyano-3,6-dihydro-4-methyl-2-oxo-1-(2H)-pyrimidinecarboxylic acid, 1-ethyl ester as a colorless solid (0.29 g, 80%). ^1H NMR (CDCl_3 , 400 MHz) δ 7.48 (m, 2 H) 7.28 (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 ($\text{M} + \text{H}^+$)

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

25 Method 3

A mixture of 6-(3-bromophenyl)-5-cyano-3,6-dihydro-4-methyl-2-oxo-1-(2H)-pyrimidinecarboxylic acid, 1-ethyl ester (36 mg, 0.1 mmol), phenylboronic acid (24 mg, 0.2 mmol), potassium carbonate (110 mg, 0.8 mmol), EtOH (2 mL), water (1 mL) and toluene (4 mL) was flushed with nitrogen gas several times before palladium tetrakis(triphenylphosphine) (5 mg) was introduced. The reaction mixture was heated at reflux under nitrogen for 1 h, cooled to room temperature, and diluted with EtOAc. This mixture was washed with water, dried (Na_2SO_4) and concentrated in vacuo. The residue was purified by flash column chromatography (50% to 70%

EtOAc/hexanes) to give, after evaporation of solvent, the title compound as a colorless solid (26 mg, 72%) ¹H NMR (MeOH-d₄, 400 MHz) δ 7.48 (m, 4 H), 7.35 (m, 3 H), 7.23 (m, 2 H), 5.84 (s, 1 H), 4.15 (m, 2 H), 2.04 (s, 3 H), 1.15 (t, 3 H, J = 7.0 Hz). LC/MS (ES+) 362 (M+H⁺)

5

Example 117

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

Following the procedure of Method 3 the title compound was obtained from 6-(3-bromophenyl)-5-cyano-3,6-dihydro-4-methyl-2-oxo-1-(2H)-pyrimidinecarboxylic acid, 1-ethyl ester and 2-thiopheneboronic acid as a light brown solid in 85% yield. ¹H NMR (MeOH-d₄, 400 MHz) δ 7.52 (m, 2 H), 7.33 (d, 1 H, J = 7.9 Hz), 7.29 (m, 2 H), 7.15 (d, 1 H, J = 7.9 Hz), 6.99 (m, 1 H), 5.81 (s, 1 H), 4.16 (m, 2 H), 2.05 (s, 3 H), 1.17 (t, 3 H, J = 7.0 Hz). LC/MS (ES+) 368 (M+H⁺), 390 (M+Na⁺)

15

Example 118

6-(3-Bromophenyl)-5-cyano-3,6-dihydro-4-methyl-2-oxo-1-(2H)-pyrimidinecarboxylic acid, 1-ethyl amide

20 Method 4

To a solution of 6-(3-bromophenyl)-5-cyano-3,6-dihydro-4-methyl-2-oxo-(2H)pyrimidine (2.92 g, 10 mmol) in THF (30 mL) was added 95% sodium hydride (0.30 g, 12 mmol). After gas evolution ceased ethyl isocyanate (0.44 mL, 12 mmol) was added via syringe. The reaction mixture was stirred for 0.5 h, quenched with water and extracted twice with EtOAc. The combined extracts were washed with 0.5 N aqueous NaOH, with water and with brine, dried (MgSO₄) and concentrated in vacuo. The residue was purified by flash column chromatography (25% to 35% EtOAc/hexane) to give, after evaporation of solvent, 6-(3-bromophenyl)-5-cyano-3,6-dihydro-4-methyl-2-oxo-1-(2H)-pyrimidinecarboxylic acid, 1-ethyl amide as a colorless solid (2.91 g, 80%). ¹H NMR (CDCl₃, 400 MHz) δ 8.65 (t, 3 H, J = 5.3 Hz), 7.91 (s, 1 H), 7.39 (m, 1 H), 7.35 (m, 1 H), 7.21 (m, 1 H), 7.15 (d, 1 H, J = 7.9 Hz),

30

6.24 (s, 1 H), 3.25 (m, 2 H), 2.10 (s, 3 H), 1.10 (t, 3 H, $J = 7.0$ Hz) LC/MS (ES+) 363 ($M+H^+$)

5 6-(3-Biphenyl)-5-cyano-3,6-dihydro-4-methyl-2-oxo-1-(2H)-pyrimidinecarboxylic acid, 1-ethyl amide

Following the procedure of Method 3 the title compound was obtained from 6-(3-bromophenyl)-5-cyano-3,6-dihydro-4-methyl-2-oxo-1-(2H)-pyrimidinecarboxylic acid, 1-ethyl amide and phenylboronic acid as a light yellow solid in 44% yield. ^1H NMR ($CDCl_3$, 400 MHz) δ 8.70 (t, 1 H, $J = 5.3$ Hz), 7.55 (m, 4 H), 7.43 (m, 3 H), 7.36 (m, 1 H), 7.29 (d, 1 H, $J = 7.5$ Hz), 7.19 (s, 1 H), 6.39 (s, 1 H), 3.34 (m, 2 H), 2.18 (s, 3 H), 1.17 (t, 3 H, $J = 7.0$ Hz), LC/MS (ES+) 361 ($M+H^+$)

Example 119

15 6-(3-(4-Chlorophenyl)phenyl)-5-cyano-3,6-dihydro-4-methyl-2-oxo-1-(2H)-pyrimidinecarboxylic acid, 1-ethyl amide

Following the procedure of Method 3 the title compound was obtained from 6-(3-bromophenyl)-5-cyano-3,6-dihydro-4-methyl-2-oxo-1-(2H)-pyrimidinecarboxylic acid, 1-ethyl amide and 4-chlorophenylboronic acid as a brownish solid in 42% yield. ^1H NMR ($MeOH-d_4$, 400 MHz) δ 7.57 (m, 3 H), 7.51 (s, 1 H), 7.45 (m, 3 H), 7.29 (d, 1 H, $J = 7.5$ Hz), 6.21 (s, 1 H), 3.25 (m, 2 H), 2.13 (s, 3 H), 1.12 (t, 3 H, $J = 7.0$ Hz) LC/MS (ES+) 395 ($M+H^+$)

Example 120

25 5-Cyano-3,6-dihydro-4-methyl-2-oxo-6-(3-(2-thienyl)phenyl)-1-(2H)-pyrimidinecarboxylic acid, 1-ethyl amide

Following the procedure of Method 3 the title compound was obtained from 6-(3-bromophenyl)-5-cyano-3,6-dihydro-4-methyl-2-oxo-1-(2H)-pyrimidinecarboxylic acid, 1-ethyl amide and 2-thiopheneboronic acid as a light yellow solid in 58% yield. ^1H NMR ($CDCl_3$, 400 MHz) δ 8.70 (t, 1 H, $J = 5.3$ Hz), 7.54 (m, 2 H), 7.37 (t, 1 H, $J = 7.9$ Hz), 7.30 (m, 2 H), 7.23 (d, 1 H, $J = 7.9$ Hz), 7.12 (s, 1 H), 7.08 (m, 1 H), 6.37 (s, 1 H), 3.32 (m, 2 H), 2.18 (s, 3 H), 1.17 (t, 3 H, $J = 7.0$ Hz) LC/MS (ES+) 367 ($M+H^+$)

43

Example 121

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

- 5 Following the procedure of Method 3 the title compound was obtained from 6-(3-bromophenyl)-5-cyano-3,6-dihydro-4-methyl-2-oxo-1-(2H)-pyrimidinecarboxylic acid, 1-ethyl amide and 3-thiopheneboronic acid as a colorless solid in 14% yield. ¹H NMR (MeOH-d₄, 400 MHz) δ 7.52 (m, 2 H), 7.46 (s, 1 H), 7.39 (m, 1 H), 7.31 (m, 2 H), 7.11 (d, 1 H, *J* = 7.5 Hz), 6.11 (s, 1 H), 3.17 (m, 2 H), 2.05 (s, 3 H), 1.03 (t, 3 H, *J* = 7.0 Hz), LC/MS (ES+) 367 (M+H⁺)
- 10

Example 122

5-Cyano-3,6-dihydro-4-methyl-2-oxo-6-(3-(4-pyridyl)phenyl)-(2H)-pyrimidine

15 **Method 5**

- A mixture of 6-(3-bromophenyl)-5-cyano-3,6-dihydro-4-methyl-2-oxo-(2H)-pyrimidine (1.62 g, 5.5 mmol), pyridine-4-boronic acid (0.75 g, 6.1 mmol), potassium carbonate (2.28 g, 16.5 mmol) and DMF (10 mL) was flushed with nitrogen gas several times before [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium (50 mg) was introduced. The reaction mixture was heated at 95 °C under nitrogen for 64 h, cooled to room temperature and filtered through Celite. The filtrate was diluted with MeOH and stirred with AG 50W-X2 Resin for 10 min. The resin was collected by vacuum filtration, washed with MeOH and then eluted with 2 M NH₃ in MeOH. This NH₃-MeOH solution was concentrated in vacuo to give 5-cyano-3,6-dihydro-4-methyl-2-oxo-6-(3-(4-pyridyl)phenyl)-(2H)-pyrimidine as a brown solid (1.61 g, 32%). ¹H NMR (DMSO-d₆, 400 MHz) δ 9.58 (s, 1 H), 8.66 (d, 2 H, *J* = 2.2 Hz), 7.88 (s, 1 H), 7.77 (d, 1 H, *J* = 7.9 Hz), 7.69 (m, 3 H), 7.57 (m, 1 H), 7.41 (d, 1 H, *J* = 7.9 Hz), 5.22 (s, 1 H), 2.03 (d, 3 H, *J* = 2.2 Hz)
- 20
- 25

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

Following the procedure of Method 4 the HCl salt of the title compound was obtained from 5-cyano-3,6-dihydro-4-methyl-2-oxo-6-(3-(4-pyridyl)phenyl)-(2H)-pyrimidine and ethyl isocyanate as a light yellow solid in 26% yield LC/MS (ES+) 362 (M+H⁺)

5

Example 123

2,2,2-Trifluoroethyl isocyanate

Method 6

- 10 A mixture of 3,3,3-trifluoropropionic acid (10.2 g, 80 mmol) and thionyl chloride (5.8 mL, 80 mmol) was heated at reflux for 3 h and cooled to room temperature. Distillation of this mixture afforded 3,3,3-trifluoropropionyl chloride as a colorless liquid (7.12 g, 61%). A mixture of 3,3,3-trifluoropropionyl chloride (6.3 g, 43 mmol), sodium azide (2.8 g, 43 mmol) and toluene (10 mL) was stirred for 18 h at room
- 15 temperature, heated at reflux for 1.5 h and cooled to room temperature to give a solution of 2,2,2-trifluoroethyl isocyanate in toluene (approximately 1.2 M by titration using benzylamine) which was used as such in subsequent reactions

20 5-Cyano-3,6-dihydro-4-methyl-2-oxo-6-(3-(4-pyridyl)phenyl)-1-(2H)-pyrimidinecarboxylic acid, 1-(2,2,2-trifluoroethyl)amide

- Following the procedure of Method 4 the TFA salt of the title compound was obtained from 5-cyano-3,6-dihydro-4-methyl-2-oxo-6-(3-(4-pyridyl)phenyl)-(2H)-pyrimidine and 2,2,2-trifluoroethyl isocyanate as an off-white solid in 45% yield ¹H NMR (MeOH-d₄, 500 MHz) δδ 9.51 (t, 1 H, J = 6.6 Hz), 8.86 (d, 2 H, J = 6.6 Hz), 8.30 (d, 2 H, J = 6.6 Hz), 7.93 (d, 1 H, J = 7.7 Hz), 7.90 (s, 1 H), 7.67 (t, 1 H, J = 7.7 Hz), 7.59 (d, 1 H, J = 7.7 Hz), 6.29 (s, 1 H), 3.97 (m, 2 H), 2.18 (s, 3 H). LC/MS (ES+) 416 (M+H⁺)
- 25

Example 124

- 30 5-Cyano-3,6-dihydro-4-methyl-2-oxo-6-(3-(4-pyridyl)phenyl)-1-(2H)-pyrimidinecarboxylic acid, 1-isopropyl amide

Following the procedure of Method 4, the TFA salt of the title compound was obtained from 5-cyano-3,6-dihydro-4-methyl-2-oxo-6-(3-(4-pyridyl)phenyl)-(2H)-pyrimidine and isopropyl isocyanate as a colorless solid in 44% yield ¹H NMR (MeOH-d₄, 400 MHz) δ 8.87 (d, 2 H, J = 7.0 Hz), 8.34 (d, 2 H, J = 7.0 Hz), 7.94 (d, 1 H, J = 7.5 Hz), 7.89 (s, 1 H), 7.68 (t, 1 H, J = 7.5 Hz), 7.58 (d, 1 H, J = 7.5 Hz), 6.27 (s, 1 H), 3.86 (m, 1 H), 2.16 (s, 3 H), 1.18 (d, 3 H, J = 6.6 Hz), 1.12 (d, 3 H, J = 6.6 Hz), LC/MS (ES+) 376 (M+H⁺)

Example 125

10 **5-Cyano-3,6-dihydro-4-methyl-2-oxo-6-(3-(4-pyridyl)phenyl)-1-(2H)-pyrimidinecarboxylic acid, 1-cyclopropyl amide**

Following the procedure of Method 4 the TFA salt of the title compound was obtained from 5-cyano-3,6-dihydro-4-methyl-2-oxo-6-(3-(4-pyridyl)phenyl)-(2H)-pyrimidine and cyclopropyl isocyanate (prepared from cyclopropanecarbonyl chloride using the procedure of Method 6) as a colorless solid in 42% yield ¹H NMR (MeOH-d₄, 500 MHz) δ 8.51 (d, 2 H, J = 6.0 Hz), 7.64 (d, 1 H, J = 7.7 Hz), 7.60 (m, 3 H), 7.46 (t, 1 H, J = 7.7 Hz), 7.32 (d, 1 H, J = 7.7 Hz), 6.15 (s, 1 H), 2.54 (m, 1 H), 2.05 (s, 3 H), 0.62 (m, 2 H), 0.43 (m, 1 H), 0.36 (m, 1 H), LC/MS (ES+) 374 (M+H⁺)

20 Example 126

5-Cyano-3,6-dihydro-4-methyl-2-oxo-6-(3-(3-pyridyl)phenyl)-(2H)-pyrimidine

Following the procedure of Method 5 5-cyano-3,6-dihydro-4-methyl-2-oxo-6-(3-(3-pyridyl)phenyl)-(2H)-pyrimidine was obtained from 6-(3-bromophenyl)-5-cyano-3,6-dihydro-4-methyl-2-oxo-(2H)-pyrimidine and pyridine-3-boronic acid 1,3-propanediol cyclic ester as an off-white solid in 76% yield ¹H NMR (DMSO-d₆, 400 MHz) δ 9.51 (s, 1 H), 8.81 (d, 1 H, J = 2.6 Hz), 8.53 (m, 1 H), 7.99 (m, 1 H), 7.82 (s, 1 H), 7.64 (d, 1 H, J = 7.9 Hz), 7.57 (d, 1 H, J = 1.8 Hz), 7.50 (t, 1 H, J = 7.9 Hz), 7.45 (m, 1 H), 7.30 (d, 1 H, J = 2.6 Hz), 5.15 (s, 1 H), 1.97 (s, 3 H)

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

Following the procedure of Method 4 the HCl salt of the title compound was obtained from 5-cyano-3,6-dihydro-4-methyl-2-oxo-6-(3-(3-pyridyl)phenyl)-(2H)-pyrimidine and ethyl isocyanate as a light yellow solid in 53% yield ¹H NMR (MeOH-d₄, 400 MHz) δ 9.18 (s, 1 H), 8.92 (m, 1 H), 8.86 (d, 2 H, J = 5.3 Hz), 8.19 (m, 1 H), 7.78 (m, 2 H), 7.64 (t, 1 H, J = 7.5 Hz), 7.51 (d, 1 H, J = 7.5 Hz), 6.24 (s, 1 H), 3.24 (m, 2 H), 2.15 (s, 3 H), 1.11 (t, 3 H, J = 7.0 Hz) LC/MS (ES+) 362 (M+H⁺)

Example 127

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

Following the procedure of Method 4 the TFA salt of the title compound was obtained from 5-cyano-3,6-dihydro-4-methyl-2-oxo-6-(3-(3-pyridyl)phenyl)-(2H)-pyrimidine and 2,2,2-trifluoroethyl isocyanate as a colorless solid in 40% yield ¹H NMR (MeOH-d₄, 400 MHz) δ 9.51 (s, 1 H), 9.07 (s, 1 H), 8.79 (s, 1 H), 8.71 (d, 1 H, J = 6.6 Hz), 8.04 (m, 1 H), 7.76 (d, 1 H, J = 7.7 Hz), 7.73 (s, 1 H), 7.62 (m, 1 H), 7.49 (d, 1 H, J = 7.7 Hz), 6.27 (s, 1 H), 3.98 (m, 2 H), 2.17 (d, 3 H, J = 2.7 Hz) LC/MS (ES+) 416 (M+H⁺)

Example 128

5-Cyano-3,6-dihydro-4-methyl-2-oxo-6-(3-(3-pyridyl)phenyl)-1-(2H)-pyrimidinecarboxylic acid, 1-isopropyl amide

Following the procedure of Method 4, the TFA salt of the title compound was obtained from 5-cyano-3,6-dihydro-4-methyl-2-oxo-6-(3-(3-pyridyl)phenyl)-(2H)-pyrimidine and isopropyl isocyanate as a colorless solid in 46% yield ¹H NMR (MeOH-d₄, 400 MHz) δ 9.09 (d, 1 H, J = 1.8 Hz), 8.79 (d, 1 H, J = 5.3 Hz), 8.74 (m, 1 H), 8.05 (m, 1 H), 7.76 (d, 1 H, J = 7.9 Hz), 7.73 (d, 1 H, J = 1.8 Hz), 7.62 (t, 1 H, J = 7.9 Hz), 7.48 (d, 1 H, J = 7.9 Hz), 6.24 (s, 1 H), 3.86 (m, 1 H), 2.15 (s, 3 H), 1.18 (d, 3 H, J = 6.6 Hz), 1.12 (d, 3 H, J = 6.6 Hz) LC/MS (ES+) 376 (M+H⁺)

Example 129

5-Cyano-3,6-dihydro-4-methyl-2-oxo-6-(3-(3-pyridyl)phenyl)-1-(2H)-pyrimidinecarboxylic acid, 1-cyclopropyl amide

Following the procedure of Method 4, the HCl salt of the title compound was obtained from 5-cyano-3,6-dihydro-4-methyl-2-oxo-6-(3-(3-pyridyl)phenyl)-(2H)-pyrimidine and cyclopropyl isocyanate as an off-white solid in 40% yield. ¹H NMR (MeOH-d₄, 500 MHz) δ 9.08 (s, 1 H), 8.80 (d, 1 H, J = 8.2 Hz), 8.77 (d, 1 H, J = 5.5 Hz), 8.09 (m, 1 H), 7.70 (d, 1 H, J = 7.7 Hz), 7.67 (s, 1 H), 7.55 (t, 1 H, J = 7.7 Hz), 7.41 (d, 1 H, J = 7.7 Hz), 6.15 (s, 1 H), 2.53 (m, 1 H), 2.06 (s, 3 H), 0.62 (m, 2 H), 0.43 (m, 1 H), 0.36 (m, 1 H). LC/MS (ES+) 374 (M+H⁺)

Example 130

10 **5 Cyano-3,6-dihydro-4-methyl-2-oxo-6-(3-(3-pyridyl)phenyl) 1-(2H)-pyrimidinecarboxylic acid, 1-cyclobutyl amide**

Following the procedure of Method 4, the TFA salt of the title compound was obtained from 5-cyano-3,6-dihydro-4-methyl-2-oxo-6-(3-(3-pyridyl)phenyl)-(2H)-pyrimidine and cyclobutyl isocyanate (prepared from cyclobutanecarbonyl chloride using the procedure of Method 6) as an off-white solid in 88% yield. ¹H NMR (MeOH-d₄, 500 MHz) δ 8.99 (s, 1 H), 8.69 (d, 1 H, J = 4.9 Hz), 8.63 (d, 1 H, J = 8.2 Hz), 7.95 (m, 1 H), 7.66 (d, 1 H, J = 7.7 Hz), 7.62 (s, 1 H), 7.52 (t, 1 H, J = 7.7 Hz), 7.38 (d, 1 H, J = 7.7 Hz), 6.12 (s, 1 H), 4.09 (m, 1 H), 2.18 (m, 2 H), 2.06 (s, 3 H), 1.82 (m, 2 H), 1.63 (m, 2 H). LC/MS (ES+) 388 (M+H⁺)

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Example 131

5 Cyano-3,6-dihydro-4-methyl-2-oxo-6-(3-(3-pyridyl)phenyl) 1-(2H)-pyrimidinecarboxylic acid, 1-cyclopentyl amide

Following the procedure of Method 4, the TFA salt of the title compound was obtained from 5-cyano-3,6-dihydro-4-methyl-2-oxo-6-(3-(3-pyridyl)phenyl)-(2H)-pyrimidine and cyclopentyl isocyanate as an off-white solid in 46% yield. LC/MS (ES+) 402 (M+H⁺)

25

Example 132

30 **5 Cyano-3,6-dihydro-4-methyl-2-oxo-6-(3-(3-pyridyl)phenyl) 1-(2H)-pyrimidinecarboxylic acid, 1-cyclopropylmethyl amide**

Following the procedure of Method 4 the TFA salt of the title compound was obtained from 5-cyano-3,6-dihydro-4-methyl-2-oxo-6-(3-(3-pyridyl)phenyl)-(2H)-pyrimidine and cyclopropylmethyl isocyanate (prepared from cyclopropylacetic acid using the procedure of Method 6) as an off-white solid in 62% yield LC/MS (ES+)

5 (M+H⁺)

Example 133

5-Cyano-3,6-dihydro-4-methyl-2-oxo-6-(3-(2-pyridyl)phenyl)-(2H)-pyrimidine

Following the procedure of Method 5, 5-cyano-3,6-dihydro-4-methyl-2-oxo-6-(3-(2-pyridyl)phenyl)-(2H)-pyrimidine was obtained from 6-(3-bromophenyl)-5-cyano-3,6-dihydro-4-methyl-2-oxo-(2H)-pyrimidine and 2-tributylstannylpyridine as an off-white solid in 26% yield ¹H NMR (MeOH-d₄, 500 MHz) 8.71 (d, 1 H, J = 5.0 Hz) 8.25 (m, 1 H) 8.09 (d, 1 H, J = 7.7 Hz) 7.93 (m, 2 H) 7.67 (m, 1 H) 7.63 (d, 1 H, J = 8.2 Hz) 7.57 (d, 1 H, J = 7.7 Hz), 5.29 (s, 1 H), 2.13 (s, 3 H) LC/MS (ES+) 291

10 15 (M+H⁺)

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

Following the procedure of Method 4 the title compound was obtained from 5-cyano-3,6-dihydro-4-methyl-2-oxo-6-(3-(2-pyridyl)phenyl)-(2H)-pyrimidine and ethyl isocyanate as a colorless solid in 25% yield ¹H NMR (MeOH-d₄, 400 MHz) 8.61 (m, 1 H) 7.90 (m, 3 H) 7.82 (d, 1 H, J = 7.9 Hz), 7.51 (m, 1 H) 7.38 (m, 2 H) 6.25 (s, 1 H), 3.25 (m, 2 H), 2.15 (s, 3 H), 1.11 (t, 3 H, J = 7.0 Hz), LC/MS (ES+) 362

20 25 (M+H⁺)

Example 134

5-Cyano-3,6-dihydro-4-methyl-2-oxo-6-(3-(2-t-butoxycarbonylpyrrole)phenyl)-(2H)-pyrimidine

Following the procedure of Method 5 5-cyano-3,6-dihydro-4-methyl-2-oxo-6-(3-(2-t-butoxycarbonylpyrrole)phenyl)-(2H)-pyrimidine was obtained from 6-(3-bromophenyl)-5-cyano-3,6-dihydro-4-methyl-2-oxo-(2H)-pyrimidine and 1-(t-butoxycarbonyl)pyrrole-2-boronic acid as a light yellow foamy solid in 43% yield ¹H

30

NMR (DMSO- d_6 , 400 MHz) δ 9.52 (s, 1 H), 7.84 (s, 1 H), 7.39 (t, 1 H, $J = 7.9$ Hz), 7.34 (m, 1 H), 7.28 (d, 1 H, $J = 7.9$ Hz), 7.23 (d, 1 H, $J = 7.9$ Hz), 7.19 (s, 1 H), 6.28 (m, 1 H), 6.21 (m, 1 H), 5.09 (s, 1 H), 2.00 (s, 3 H), 1.28 (s, 9 H)

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

Following the procedure of Method 4 and subsequent treatment with TFA in CH_2Cl_2 for 3 h, the title compound was obtained from 5-cyano-3,6-dihydro-4-methyl-2-oxo-6-(3-(2-*t*-butoxycarbonylpyrrole)phenyl)-(2H)-pyrimidine and ethyl isocyanate as a light brown solid in 21% yield. ^1H NMR (MeOH- d_4 , 400 MHz) δ 7.49 (m, 2 H), 7.32 (t, 1 H, $J = 7.9$ Hz), 7.06 (d, 1 H, $J = 7.9$ Hz), 6.80 (s, 1 H), 6.43 (s, 1 H), 6.14 (m, 2 H), 3.25 (m, 2 H), 2.14 (s, 3 H), 1.12 (t, 3 H, $J = 7.0$ Hz). LC/MS (ES+) 350 ($M+H^+$)

Example 135

15 6-(3-Bromo-4-fluorophenyl)-5-cyano-3,6-dihydro-4-methyl-2-oxo-(2H)-pyrimidine

Following the procedure of Method 1, 6-(3-bromo-4-fluorophenyl)-5-cyano-3,6-dihydro-4-methyl-2-oxo-(2H)-pyrimidine was obtained from 3-bromo-4-fluorobenzaldehyde, urea and acetoacetamide as a light yellow solid in 99% yield. ^1H NMR (DMSO- d_6 , 400 MHz) δ 9.62 (s, 1 H), 7.86 (s, 1 H), 7.62 (d, 1 H, $J = 6.6$ Hz), 7.44 (t, 1 H, $J = 8.8$ Hz), 7.38 (m, 1 H), 5.18 (s, 1 H), 2.03 (s, 3 H)

5 Cyano-3,6-dihydro-6-(4-fluoro-3-(3-pyridyl)phenyl)-4-methyl-2-oxo-(2H)-pyrimidine

25 Following the procedure of Method 5, 5-cyano-3,6-dihydro-6-(4-fluoro-3-(3-pyridyl)phenyl)-4-methyl-2-oxo-(2H)-pyrimidine was obtained from 6-(3-bromo-4-fluorophenyl)-5-cyano-3,6-dihydro-4-methyl-2-oxo-(2H)-pyrimidine and pyridine-3-boronic acid, 1,3-propanediol cyclic ester as a dark brown solid in 44% yield. ^1H NMR (DMSO- d_6 , 400 MHz) δ 9.58 (s, 1 H), 8.74 (s, 1 H), 8.62 (m, 1 H), 7.97 (m, 1 H), 7.86 (s, 1 H), 7.53 (m, 2 H), 7.42 (m, 1 H), 7.40 (s, 1 H), 5.23 (s, 1 H), 2.02 (s, 3 H)

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

Following the procedure of Method 4 the TFA salt of the title compound was obtained from 5-cyano-3,6-dihydro-6-(4-fluoro-3-(3-pyridyl)phenyl)-4-methyl-2-oxo-
 5 (2H)-pyrimidine and ethyl isocyanate as a colorless solid in 52% yield ¹H NMR (MeOH-d₄ 400 MHz) δδ 8.95 (s, 1 H), 8.74 (d, 1 H, J = 4.9 Hz), 8.58 (d, 1 H, J = 7.7 Hz), 7.98 (m, 1 H), 7.54 (m, 1 H), 7.43 (m, 1 H), 7.28 (m, 1 H), 6.14 (s, 1 H), 2.06 (s, 3 H), 1.02 (t, 3 H, J = 7.1 Hz), LC/MS (ES+) 380 (M+H⁺)

10

Example 136

5-Cyano-3,6-dihydro-6-(4-fluoro-3-(3-pyridyl)phenyl)-4-methyl-2-oxo-1-(2H)-pyrimidinecarboxylic acid, 1-(2,2,2-trifluoroethyl) amide

Following the procedure of Method 4 the TFA salt of the title compound was obtained from 5-cyano-3,6-dihydro-6-(4-fluoro-3-(3-pyridyl)phenyl)-4-methyl-2-oxo-
 15 (2H)-pyrimidine and 2,2,2-trifluoroethyl isocyanate as a colorless solid in 31% yield ¹H NMR (MeOH-d₄ 500 MHz) □ ¹H NMR (MeOH-d₄, 400 MHz) δδ 9.48 (m, 1 H), 8.99 (s, 1 H), 8.80 (s, 1 H), 8.57 (d, 1 H, J = 8.2 Hz), 8.00 (m, 1 H), 7.63 (m, 1 H), 7.53 (m, 1 H), 7.38 (m, 1 H), 6.26 (s, 1 H), 3.97 (m, 2 H), 2.17 (d, 3 H, J = 1.6 Hz), LC/MS (ES+) 434 (M+H⁺)

20

Example 137

5-Cyano-3,6-dihydro-6-(4-fluoro-3-(3-pyridyl)phenyl)-4-methyl-2-oxo-1-(2H)-pyrimidinecarboxylic acid, 1-cyclopropyl amide

Following the procedure of Method 4 the TFA salt of the title compound was
 25 obtained from 5-cyano-3,6-dihydro-6-(4-fluoro-3-(3-pyridyl)phenyl)-4-methyl-2-oxo-(2H)-pyrimidine and cyclopropyl isocyanate as an off-white solid in 39% yield LC/MS (ES+) 392 (M+H⁺)

Example 138

30 **6-(5-Bromo-2-fluorophenyl)-5-cyano-3,6-dihydro-4-methyl-2-oxo-(2H)-pyrimidine**

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Following the procedure of Method 1, 6 (5-bromo-2-fluorophenyl)-5-cyano-3,6-dihydro-4-methyl-2-oxo (2H)-pyrimidine was obtained from 5-bromo-2-fluorobenzaldehyde, urea and acetoacetamide as a yellow solid in 72% yield. ¹H NMR (DMSO-d₆, 400 MHz) δ 9.66 (s, 1 H), 7.81 (s, 1 H), 7.61 (m, 1 H), 7.54 (m, 1 H), 7.27 (m, 1 H), 5.36 (s, 1 H), 2.02 (d, 3 H, J = 3.1 Hz)

5-Cyano-3,6-dihydro-6-(2-fluoro-5-(3-pyridyl)phenyl)-4-methyl-2-oxo-(2H)-pyrimidine

Following the procedure of Method 5, 5-cyano-3,6-dihydro-6-(2-fluoro-5-(3-pyridyl)phenyl)-4-methyl-2-oxo-(2H)-pyrimidine was obtained from 6 (5-bromo-2-fluorophenyl)-5-cyano-3,6-dihydro-4-methyl-2-oxo-(2H)-pyrimidine and pyridine-3-boronic acid 1,3-propanediol cyclic ester as an off-white solid in 59% yield. ¹H NMR (DMSO-d₆, 400 MHz) δ 9.62 (s, 1 H), 8.86 (d, 1 H, J = 1.8 Hz), 8.58 (m, 1 H), 8.04 (m, 1 H), 7.81 (s, 1 H), 7.77 (m, 1 H), 7.69 (m, 1 H), 7.50 (m, 1 H), 7.38 (m, 1 H), 5.41 (s, 1 H), 2.01 (d, 3 H, J = 0.9 Hz)

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

Following the procedure of Method 4, the HCl salt of the title compound was obtained from 5-cyano-3,6-dihydro-6-(2-fluoro-5-(3-pyridyl)phenyl)-4-methyl-2-oxo-(2H)-pyrimidine and ethyl isocyanate as a slightly yellow solid in 34% yield. ¹H NMR (MeOH-d₄, 500 MHz) δ 9.20 (s, 1 H), 8.91 (d, 1 H, J = 8.2 Hz), 8.86 (d, 1 H, J = 4.4 Hz), 8.19 (m, 1 H), 7.84 (m, 2 H), 7.40 (m, 1 H), 6.29 (s, 1 H), 3.20 (m, 2 H), 2.12 (d, 3 H, J = 2.2 Hz), 1.09 (m, 3 H), LC/MS (ES+) 380 (M+H⁺)

Example 139

5-Cyano-3,6-dihydro-6-(2-fluoro-5-(3-pyridyl)phenyl)-4-methyl-2-oxo-1-(2H)-pyrimidinecarboxylic acid, 1-cyclopropyl amide

Following the procedure of Method 4, the HCl salt of the title compound was obtained from 5-cyano-3,6-dihydro-6-(2-fluoro-5-(3-pyridyl)phenyl)-4-methyl-2-oxo-(2H)-pyrimidine and cyclopropyl isocyanate as a light yellow solid in 32% yield. ¹H

NMR (MeOH-d₄, 500 MHz) δ 9.19 (s, 1 H), 8.91 (d, 1 H, $J = 8.2$ Hz), 8.85 (d, 1 H, $J = 5.5$ Hz), 8.17 (m, 1 H), 7.84 (m, 2 H), 7.40 (m, 1 H), 6.28 (s, 1 H), 2.58 (m, 1 H), 2.11 (s, 3 H), 0.69 (m, 2 H), 0.51 (m, 1 H), 0.42 (m, 1 H). LC/MS (ES+) 392 (M+H⁺)

5

Example 140**5 Cyano-3,6-dihydro-4-methyl-6-(3-(4-methyl-3-pyridyl)phenyl)-2-oxo-(2H)-pyrimidine**Method 7

- 10 A mixture of 6-(3-bromophenyl)-5-cyano-3,6-dihydro-4-methyl-2-oxo-(2H)-pyrimidine (1.46 g, 5 mmol), bis(pinacolato)diboron (1.40 g, 5.5 mmol), potassium acetate (1.47 g, 16.5 mmol) and DMF (5 mL) was flushed with nitrogen gas several times before [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium (50 mg) was introduced. The reaction mixture was heated at 95 °C under nitrogen for 18 h, cooled to room temperature and filtered through Celite. The filtrate was diluted with EtOAc, washed with water and with brine, dried (Na₂SO₄) and concentrated to give a dark viscous oil. This material was re-dissolved in DMF (5 mL) and reacted under nitrogen with 5-bromo-2-methylpyridine (0.66 g, 3.8 mmol), [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium (50 mg) and potassium carbonate (2.07 g, 15 mmol) at 95 °C for 18 h. The reaction mixture was cooled to room temperature, diluted with MeOH and stirred with AG 50W-X2 Resin for 5 min. The resin was collected by vacuum filtration, washed with MeOH and then eluted with 2 M NH₃ in MeOH. This NH₃-MeOH solution was concentrated in vacuo to give 5-cyano-3,6-dihydro-4-methyl-6-(3-(4-methyl-3-pyridyl)phenyl)-2-oxo-(2H)-pyrimidine as a brown solid (0.69 g, 45%). ¹H NMR (DMSO-d₆, 400 MHz) δ 9.55 (s, 1 H), 8.72 (s, 1 H), 7.92 (d, 1 H, $J = 6.2$ Hz), 7.85 (s, 1 H), 7.64 (d, 1 H, $J = 7.5$ Hz), 7.57 (s, 1 H), 7.51 (t, 1 H, $J = 7.5$ Hz), 7.33 (m, 2 H), 5.18 (s, 1 H), 2.49 (s, 3 H), 2.01 (s, 3 H).

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

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Following the procedure of Method 4, the HCl salt of the title compound was obtained from 5-cyano-3,6-dihydro-4-methyl-6-(3-(4-methyl-3-pyridyl)phenyl)-2-oxo-(2H)-pyrimidine and ethyl isocyanate as a slightly yellow solid in 33% yield. ¹H NMR (MeOH-d₄, 500 MHz) δ 8.99 (d, 1 H, J = 2.2 Hz), 8.75 (m, 1 H), 8.01 (d, 1 H, J = 8.2 Hz), 7.76 (d, 1 H, J = 7.7 Hz), 7.73 (s, 1 H), 7.62 (t, 1 H, J = 7.7 Hz), 7.49 (d, 1 H, J = 7.7 Hz), 6.23 (s, 1 H), 3.25 (m, 2 H), 2.84 (s, 3 H), 2.15 (s, 3 H), 1.12 (t, 3 H, J = 7.1 Hz), LC/MS (ES+) 376 (M+H⁺).

Example 141

10 5-Cyano-3,6-dihydro-4-methyl-6-(3-(4-methyl-3-pyridyl)phenyl)-2-oxo-1-(2H)-pyrimidinecarboxylic acid, 1-cyclopropyl amide

Following the procedure of Method 4, the TFA salt of the title compound was obtained from 5-cyano-3,6-dihydro-4-methyl-6-(3-(4-methyl-3-pyridyl)phenyl)-2-oxo-(2H)-pyrimidine and cyclopropyl isocyanate as a colorless solid in 17% yield. ¹H NMR (MeOH-d₄, 400 MHz) δ 8.95 (s, 1 H), 8.66 (d, 1 H, J = 8.3 Hz), 7.93 (d, 1 H, J = 8.3 Hz), 7.75 (d, 1 H, J = 7.9 Hz), 7.72 (s, 1 H), 7.61 (t, 1 H, J = 7.9 Hz), 7.47 (d, 1 H, J = 7.9 Hz), 6.23 (s, 1 H), 2.81 (s, 3 H), 2.63 (m, 1 H), 2.15 (s, 3 H), 0.71 (m, 2 H), 0.51 (m, 1 H), 0.46 (m, 1 H), LC/MS (ES+) 388 (M+H⁺).

20

Example 142

6-(3-Carbomethoxyphenyl)-5-cyano-3,6-dihydro-4-methyl-2-oxo-(2H)-pyrimidine

Method 8

25 A mixture of 3-carbomethoxybenzaldehyde (4.15 g, 25.3 mmol), acetoacetamide (2.56 g, 25.3 mmol), urea (2.28 g, 38.0 mmol), boron trifluoride etherate (0.25 mL), copper chloride (0.25 g, 2.5 mmol), acetic acid (0.1 mL) and THF (50 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 7.48 g of an off-white solid.

30 To a mixture of this solid and pyridine (100 mL) at 0 °C was added trifluoroacetic anhydride (10.6 mL, 7.5 mmol) slowly via syringe. The resulting brown solution was stirred for 2.5 h and poured into water to result in precipitation. The precipitates were

collected by vacuum filtration, washed with water and with CH_2Cl_2 , and air dried to give 6-(3-carbomethoxyphenyl)-5-cyano-3,6-dihydro-4-methyl-2-oxo-(2H)-pyrimidine as a light tan solid (4.57 g, 67%) ^1H NMR ($\text{DMSO}-d_6$, 400 MHz) δ 9.62 (s, 1 H), 7.94 (m, 2 H), 7.90 (s, 1 H), 7.58 (m, 2 H), 5.24 (s, 1 H), 3.87 (s, 3 H), 2.02 (s, 3 H)

5

6-(3-Carbomethoxyphenyl)-5-cyano-3,6-dihydro-4-methyl-2-oxo-1-(2H)-pyrimidinecarboxylic acid, 1-ethyl amide

Following the procedure of Method 4, 6-(3-carbomethoxyphenyl)-5-cyano-3,6-dihydro-4-methyl-2-oxo-1-(2H)-pyrimidinecarboxylic acid, 1-ethyl amide was obtained from 6-(3-carbomethoxyphenyl)-5-cyano-3,6-dihydro-4-methyl-2-oxo-(2H)-pyrimidine and ethyl isocyanate as a colorless solid in 52% yield ^1H NMR ($\text{MeOH}-d_4$, 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 ($\text{M}+\text{H}^+$) 365 ($\text{M}+\text{Na}^+$)

15

6-(3-Carboxyphenyl)-5-cyano-3,6-dihydro-4-methyl-2-oxo-1-(2H)-pyrimidinecarboxylic acid, 1-ethyl amide

Method 9

To a mixture of 6-(3-carbomethoxyphenyl)-5-cyano-3,6-dihydro-4-methyl-2-oxo-1-(2H)-pyrimidinecarboxylic acid, 1-ethyl amide (0.34 g, 1.0 mmol), MeOH (9 mL) and water (3 mL) at 0 °C was added lithium hydroxide (0.84 g, 20.0 mmol). The reaction mixture was stirred for 1 h, acidified to pH 2 with 1 N HCl and extracted with EtOAc. The extract was dried (MgSO_4) and concentrated in vacuo to give 6-(3-carboxyphenyl)-5-cyano-3,6-dihydro-4-methyl-2-oxo-1-(2H)-pyrimidinecarboxylic acid, 1-ethyl amide as a colorless solid (0.30 g, 92%) ^1H NMR ($\text{MeOH}-d_4$, 400 MHz) δ 8.98 (s, 1 H), 7.89 (m, 2 H), 7.46 (d, 1 H, $J = 7.5$ Hz), 7.42 (t, 1 H, $J = 7.5$ Hz), 6.12 (s, 1 H), 3.16 (m, 2 H), 2.06 (s, 3 H), 1.03 (t, 3 H, $J = 7.0$ Hz)

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

20
49**Method 10**

A mixture of 6-(3-carboxyphenyl)-5-cyano-3,6-dihydro-4-methyl-2-oxo-1-(2H)-pyrimidinecarboxylic acid, 1-ethyl amide (0.03 g, 0.1 mmol) BOP reagent (0.07 g, 0.15 mmol) diisopropylethylamine (0.03 mL, 0.15 mmol) hydrazine (5 μ L, 0.15 mmol) and THF (1 mL) was stirred for 1 h and concentrated in vacuo. The residue was heated with triethyl orthoacetate (1 mL) at 80 °C for 18 h to give a light red solution. This solution was concentrated in vacuo, purification of the residue was carried out using preparative HPLC. Appropriate fractions were combined and concentrated in vacuo to give the title compound as an off-white solid (0.02 g, 55%).
¹H NMR (DMSO-d₆, 500 MHz) δ 10.54 (s, 1 H), 8.80 (t, 1 H, $J = 5.5$ Hz), 7.93 (d, 1 H, $J = 7.9$ Hz), 7.84 (s, 1 H), 7.64 (t, 1 H, $J = 7.9$ Hz), 7.50 (d, 1 H, $J = 7.9$ Hz), 6.18 (s, 1 H), 3.16 (m, 2 H), 2.09 (s, 3 H), 1.03 (t, 3 H, $J = 7.1$ Hz), LC/MS (ES+) 367 (M+H⁺) 399 (M+Na⁺)

15

Example 143**5-Cyano-3,6-dihydro-4-methyl 6-(3 (5-oxa-4 trifluoromethyl-2,3-diazole)phenyl) 2-oxo-1 (2H)-pyrimidinecarboxylic acid, 1-ethyl amide**

Following the procedure of Method 10 the title compound was obtained from 6-(3-carboxyphenyl)-5-cyano-3,6-dihydro-4-methyl-2-oxo-1-(2H)-pyrimidinecarboxylic acid, 1-ethyl amide, hydrazine and trifluoroacetic acid as a colorless solid in 42% yield. ¹H NMR (DMSO-d₆, 500 MHz) δ 10.54 (s, 1 H), 8.79 (t, 1 H, $J = 5.5$ Hz), 7.84 (d, 1 H, $J = 7.7$ Hz), 7.75 (s, 1 H), 7.57 (t, 1 H, $J = 7.7$ Hz), 7.51 (d, 1 H, $J = 7.7$ Hz), 6.13 (s, 1 H), 3.16 (m, 2 H), 2.09 (s, 3 H), 1.03 (t, 3 H, $J = 7.1$ Hz). ¹⁹F NMR (DMSO-d₆, 500 MHz) δ -73.35

25

Example 144**6-(2-Bromophenyl)-5-cyano-3,6-dihydro-4-methyl-2-oxo-(2H)-pyrimidine**

Following the procedure of Method 1 6-(2-bromophenyl)-5-cyano-3,6-dihydro-4-methyl-2-oxo-(2H) pyrimidine was obtained from 2-bromobenzaldehyde, acetoactamide and urea as a light yellow solid in 85% yield. ¹H NMR (DMSO-d₆,

30

400 MHz) δ 9.64 (s, 1 H) 7.81 (s, 1 H) 7.63 (d, 1 H, $J = 7.9$ Hz), 7.44 (m, 2 H) 7.29 (m, 1 H), 5.51 (s, 1 H) 2.01 (s, 3 H)

5 6-(2-(4-Chlorophenyl)phenyl)-5-cyano-3,6-dihydro-4-methyl-2-oxo-(2H)-pyrimidine

Following the procedure of Method 5 6-(2-(4-chlorophenyl)phenyl)-5-cyano-3,6-dihydro-4-methyl-2-oxo-(2H)-pyrimidine was obtained from 6-(2-bromophenyl)-5-cyano-3,6-dihydro-4-methyl-2-oxo-(2H)-pyrimidine and 4-chlorophenylboronic acid as a colorless solid in 53% yield.

10

6-(2-(4-Chlorophenyl)phenyl)-5-cyano-3,6-dihydro-4-methyl-2-oxo-1-(2H)-pyrimidinecarboxylic acid, 1-ethyl amide

Following the procedure of Method 4, the title compound was obtained from 6-(2-(4-chlorophenyl)phenyl)-5-cyano-3,6-dihydro-4-methyl-2-oxo-(2H)-pyrimidine and ethyl isocyanate as a colorless solid in 47% yield. ^1H NMR (MeOH- d_4 , 400 MHz) 7.47 (m, 2 H) 7.35 (m, 5 H) 7.12 (d, 1 H, $J = 6.6$ Hz) 6.17 (s, 1 H) 3.16 (m, 2 H) 1.95 (s, 3 H), 1.05 (m, 3 H, $J = 7.0$ Hz), LC/MS (ES+) 395 ($M+H^+$)

Example 145

20 5-Cyano-3,6-dihydro-4-methyl-2-oxo-6-(2-(3-pyridyl)phenyl)-(2H)-pyrimidine

Following the procedure of Method 5 5-cyano-3,6-dihydro-4-methyl-2-oxo-6-(2-(3-pyridyl)phenyl)-(2H)-pyrimidine was obtained from 6-(2-bromophenyl)-5-cyano-3,6-dihydro-4-methyl-2-oxo-(2H)-pyrimidine and pyridine-3-boronic acid 1,3-propanediol cyclic ester as a colorless viscous oil in 29% yield. ^1H NMR (MeOH- d_4 , 400 MHz) δ 8.44 (m, 2 H) 7.74 (m, 1 H) 7.45 (m, 4 H) 7.14 (d, 1 H, $J = 7.5$ Hz) 5.12 (s, 1 H) 1.88 (d, 3 H, $J = 1.3$ Hz)

25 5-Cyano-3,6-dihydro-4-methyl-2-oxo-6-(2-(3-pyridyl)phenyl)-1-(2H)-pyrimidinecarboxylic acid, 1-ethyl amide

Following the procedure of Method 4 the TFA salt of the title compound was obtained from 5-cyano-3,6-dihydro-4-methyl-2-oxo-6-(2-(3-pyridyl)phenyl)-(2H)-

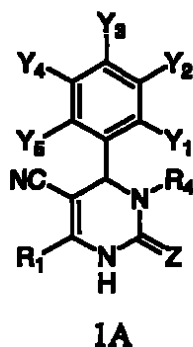
pyrimidine and ethyl isocyanate as a light yellow solid in 53% yield LC/MS (ES+)
362 (M+H⁺)

50

Claims

What is claimed is

1 A compound of formula IA



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

Y_1 , Y_2 , Y_3 , Y_4 and Y_5 are independently selected from the group consisting of H, halogen, lower alkyl, O alkyl, O aryl, NH alkyl, NH aryl, N alkyl alkyl, N alkyl aryl, N aryl aryl with the proviso that at least one of Y_1 , Y_2 , Y_3 , Y_4 and Y_5 is aryl or heteroaryl

15 R_4 is selected from the group consisting of alkyl, arylalkyl, cycloalkylalkyl, heteroarylalkyl, heterocycloalkylalkyl, CN, COR_5 , CO_2R_5 and $CONR_5R_6$

R_5 and R_6 are independently selected from the group consisting of H, alkyl, haloalkyl, cycloalkyl, aminoalkyl, arylalkyl, cycloalkylalkyl, heteroarylalkyl and heterocycloalkylalkyl,

20 Z is selected from the group consisting of O, S and NR_8

R_8 is selected from the group consisting of H, CN, sulfonamido, OR_7 , 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

25

2 The compound of claim 1 wherein Y_2 is aryl or heteroaryl



- 3 The compound of claim 2 wherein Y_2 is an optionally substituted phenyl pyridyl thiazolyl, pyrrolyl or diazolyl
- 4 The compound of claim 3 wherein said substituent is halo, alkyl, or haloalkyl.
- 5 The compound of claim 4 wherein said substituent is Br Cl, F, methyl, ethyl or CF_3
- 6 The compound of claim 1 wherein R_4 is alkyl arylalkyl CO_2R_5 or $CONR_5R_6$
- 10 The compound of claim 1 wherein R_1 is alkyl 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, haloalkyl, cycloalkyl, and arylalkyl Z is selected from the group consisting of O, S and NR_8 , R_8 is selected from the group consisting of H and CN
- 15 The compound of claim 1 wherein R_4 is CO_2R_5 and Z is O
- 8 The compound of claim 1 wherein R_4 is $CONR_5R_6$ and Z is O
- 9 The compound of claim 1 wherein R_4 is selected from the group consisting of alkyl and arylalkyl, and Z is O
- 20 The compound of claim 1 wherein R_1 is CH_3 R_4 is CO_2R_5 R_5 is alkyl and Z is O
- 25 A compound selected from the group consisting of 6-(3-biphenyl)-5-cyano-3,6-dihydro-4-methyl-2-oxo-1-(2H)-pyrimidinecarboxylic acid, 1-ethyl ester, 5-cyano-3,6-dihydro-4-methyl-2-oxo-6-(3-(2-thienyl)phenyl) 1-(2H)-pyrimidinecarboxylic acid, 1-ethyl ester
- 30

- 6-(3-biphenyl)-5-cyano-3,6-dihydro-4-methyl-2-oxo-1-(2H)-pyrimidinecarboxylic acid, 1-ethyl amide,
- 6 (3-(4-chlorophenyl)phenyl)-5-cyano-3 6-dihydro-4-methyl-2-oxo-1-(2H)-pyrimidinecarboxylic acid, 1-ethyl amide,
- 5 5-cyano-3,6-dihydro-4-methyl-2-oxo-6-(3-(2-thienyl)phenyl)-1-(2H)-pyrimidinecarboxylic acid, 1-ethyl amide,
- 5-cyano-3 6-dihydro-4-methyl-2-oxo-6-(3-(3-thienyl)phenyl)-1-(2H)-pyrimidinecarboxylic acid, 1-ethyl amide,
- 5-cyano-3 6-dihydro-4-methyl-2-oxo-6-(3-(4-pyridyl)phenyl)-1-(2H)-pyrimidinecarboxylic acid, 1-ethyl amide
- 10 5-cyano-3 6-dihydro-4-methyl-2-oxo-6-(3-(4-pyridyl)phenyl)-1-(2H)-pyrimidinecarboxylic acid, 1-(2,2,2-trifluoro)ethyl amide,
- 5-cyano-3 6-dihydro-4-methyl-2-oxo-6-(3-(4-pyridyl)phenyl)-1-(2H)-pyrimidinecarboxylic acid, 1-isopropyl amide
- 15 5-cyano-3 6-dihydro-4-methyl-2-oxo-6-(3-(4-pyridyl)phenyl)-1-(2H)-pyrimidinecarboxylic acid, 1-cyclopropyl amide,
- 5-cyano-3 6-dihydro-4-methyl-2-oxo-6-(3-(3-pyridyl)phenyl)-1-(2H)-pyrimidinecarboxylic acid, 1-ethyl amide
- 5-cyano-3 6-dihydro-4-methyl-2-oxo-6-(3-(3-pyridyl)phenyl)-1-(2H)-pyrimidinecarboxylic acid, 1-(2,2,2-trifluoro)ethyl amide,
- 20 5-cyano-3 6-dihydro-4-methyl-2-oxo-6-(3-(3-pyridyl)phenyl)-1-(2H)-pyrimidinecarboxylic acid, 1-isopropyl amide,
- 5-cyano-3 6-dihydro-4-methyl-2-oxo 6 (3-(3-pyridyl)phenyl)-1-(2H)-pyrimidinecarboxylic acid, 1-cyclopropyl amide
- 25 5-cyano-3 6-dihydro-4-methyl-2-oxo-6-(3-(3-pyridyl)phenyl)-1-(2H)-pyrimidinecarboxylic acid, 1 cyclobutyl amide
- 5-cyano-3 6-dihydro-4-methyl-2-oxo-6-(3-(3-pyridyl)phenyl)-1-(2H)-pyrimidinecarboxylic acid, 1-cyclopentyl amide
- 5-cyano 3 6-dihydro-4-methyl-2-oxo-6-(3-(3-pyridyl)phenyl)-1-(2H)-pyrimidinecarboxylic acid, 1-cyclopropylmethyl amide,
- 30 5-cyano-3 6-dihydro-4-methyl-2-oxo-6-(3-(2-pyridyl)phenyl)-1-(2H)-pyrimidinecarboxylic acid, 1-ethyl amide,

- 5-cyano-3,6-dihydro-4-methyl-2-oxo-6-(3-(2-pyrrole)phenyl)-1-(2H)-pyrimidinecarboxylic acid, 1-ethyl amide,
 5-cyano-3,6-dihydro-6-(4-fluoro-3-(3-pyridyl)phenyl)-4-methyl-2-oxo-1-(2H)-pyrimidinecarboxylic acid, 1-ethyl amide
 5 5-cyano-3,6-dihydro-6-(4-fluoro-3-(3-pyridyl)phenyl)-4-methyl-2-oxo-1-(2H)-pyrimidinecarboxylic acid, 1-(2,2,2-trifluoro)ethyl amide
 5-cyano-3,6-dihydro-6-(4-fluoro-3-(3-pyridyl)phenyl)-4-methyl-2-oxo-1-(2H)-pyrimidinecarboxylic acid, 1-cyclopropyl amide
 5-cyano-3,6-dihydro-6-(2-fluoro-5-(3-pyridyl)phenyl)-4-methyl-2-oxo-1-(2H)-pyrimidinecarboxylic acid, 1-ethyl amide,
 10 5-cyano-3,6-dihydro-6-(2-fluoro-5-(3-pyridyl)phenyl)-4-methyl-2-oxo-1-(2H)-pyrimidinecarboxylic acid, 1-cyclopropyl amide,
 5-cyano-3,6-dihydro-4-methyl-6-(3-(4-methyl-3-pyridyl)phenyl)-2-oxo-1-(2H)-pyrimidinecarboxylic acid, 1-ethyl amide,
 15 5-cyano-3,6-dihydro-4-methyl-6-(3-(4-methyl-3-pyridyl)phenyl)-2-oxo-1-(2H)-pyrimidinecarboxylic acid, 1-cyclopropyl amide,
 5-cyano-3,6-dihydro-4-methyl-6-(3-(4-methyl-5-oxa-2,3-diazole)phenyl)-2-oxo-1-(2H)-pyrimidinecarboxylic acid, 1-ethyl amide,
 5-cyano-3,6-dihydro-4-methyl-6-(3-(5-oxa-4-trifluoromethyl-2,3-diazole)phenyl)-2-oxo-1-(2H)-pyrimidinecarboxylic acid 1-ethyl amide
 20 6-(2-(4-chlorophenyl)phenyl)-5-cyano-3,6-dihydro-4-methyl-2-oxo-1-(2H)-pyrimidinecarboxylic acid, 1-ethyl amide and
 5-cyano-3,6-dihydro-4-methyl-2-oxo-6-(2-(3-pyridyl)phenyl)-1-(2H)-pyrimidinecarboxylic acid, 1-ethyl amide.

25

13 A method for treating a proliferative disease via inducing mitotic arrest comprising administering to a mammalian species an effective amount of a compound of claim 1

30

14 The method according to claim 13 further comprising administering to the patient at least one other anti-cancer agent in combination with said compound

15 The method according to claim 14 wherein said anticancer agent is cisplatin
doxorubicin topoisomerase II inhibitors, etoposide, topoisomerase I inhibitors CPT-
11 topotecan, paclitaxel, docetaxel epothilone, tamoxifen, thymidilate synthase
inhibitors and anti-metabolites

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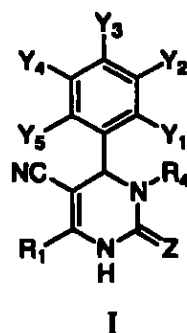
16 The method according to claim 11 wherein the proliferative disease is
cancer

17 A method for treating a disease associated with the Eg5 motor protein
10 comprising administering to a mammalian species in need of such treatment an
effective amount of a compound of claim 1

Abstract

The present invention provides compounds of formula I

5



and pharmaceutically acceptable salts thereof. The formula I compounds induce
10 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.

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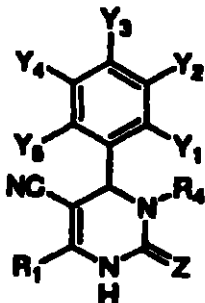
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(54) Título COMPUESTOS DE DIHIDROPIRIMIDINA CIANO-SUSTITUIDA Y SU USO PARA TRATAR ENFERMEDADES



(I)

57) Extracto La presente invención provee compuestos de fórmula (I) y sus sales de aceptación farmacéutica. Los compuestos de fórmula I inducen detención mitótica haciéndolos así útiles como agentes anti-cáncer. Los compuestos de fórmula I son asimismo útiles para el tratamiento de otras enfermedades que pueden tratarse induciendo detención mitótica.

WO 02/079169 A1

COMPUESTOS DE DIHIDROPIRIMIDINA CIANO-SUSTITUIDA Y SU USO PARA TRATAR ENFERMEDADES

SOLICITUDES RELACIONADAS

Esta solicitud reclama el beneficio bajo 35 U S C Sección 119(e) de la Solicitud de Patente Provisional de los Estados Unidos No 60/279,956 presentada el 29 de marzo de 2001

CAMPO DE LA INVENCION

Esta invencion se relaciona con compuestos novedosos que interrumpen la mitosis, haciendo así los compuestos utiles para el tratamiento de enfermedades proliferativas, tales como cancer

ANTECEDENTES

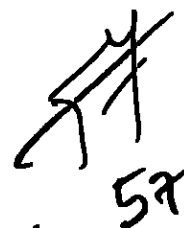
La proliferación y la muerte programada de la celula juegan papeles importantes en el crecimiento y desarrollo de un organismo En enfermedades proliferativas tales como cáncer, los procesos de proliferacion celular y/o muerte celular programada se encuentran a menudo perturbados Por ejemplo, una celula cancerosa puede tener una division celular no regulada sea mediante la sobreexpresion de un regulador positivo del ciclo celular o la perdida de un regulador negativo del ciclo celular, probablemente por mutacion Alternativamente, una celula cancerosa puede haber perdido la habilidad de experimentar muerte celular programada mediante la sobreexpresion de un regulador negativo de apoptosis Por lo tanto, existe la necesidad de desarrollar nuevos farmacos quimioterapeuticos que restauren los procesos de control de punto de inspección y muerte celular programada en las células cancerosas

Un enfoque en el tratamiento de cánceres humanos es tomar como blanco de accion una proteina que es esencial para la progresión del ciclo

celular Con el fin de que el ciclo celular avance de una fase a la siguiente, tienen que cumplirse ciertos eventos pre-requeridos Existen puntos de inspeccion en el ciclo celular que ponen en ejecucion el orden adecuado de eventos y fases Un punto tal de inspeccion es el punto de inspeccion del huso que ocurre durante la etapa de metafase de la mitosis Pequeñas moléculas que toman como blanco de acción proteínas con funciones esenciales en la mitosis pueden iniciar el punto de inspeccion del huso para detener células en mitosis De dichas moléculas pequeñas que detienen células en mitosis, aquellas que despliegan actividad anti-tumoral en la clínica inducen igualmente apoptosis, los cambios morfológicos asociados con la muerte programada de la célula Un quimioterapéutico efectivo para el tratamiento de cáncer puede ser uno que induzca control de punto de inspeccion y la subsiguiente muerte celular programada

La mayoría de los compuestos conocidos por causar detención mitótica y apoptosis actúan como agentes enlazantes de tubulina Estos compuestos alteran la inestabilidad dinámica de microtubulos e indirectamente alteran la función/estructura del huso mitótico causando así detención mitótica Debido a que la mayoría de estos compuestos toman como blanco de acción la proteína tubulina, un componente de todos los microtubulos, ellos pueden también afectar procesos celulares normales en los cuales los microtubulos juegan un papel Por lo tanto, existe una necesidad de moléculas pequeñas que específicamente tomen como blanco de acción proteínas asociadas con células proliferantes, tales como Eg5

Eg5 es una de las varias proteínas motoras similares a la quinesina que se localizan en el huso mitótico y se conocen por requerirse para la formación y/o función del huso mitótico bipolar Recientemente, hubo un informe de una pequeña molécula que trastorna la bipolaridad del huso mitótico (Mayer, T U y colaboradores, 1999 Science 286 (5441) 971-4) Mas específicamente, la pequeña molécula inducía la formación de un huso mitótico aberrante en donde un arreglo monoastral de microtubulos emanaba de un par central de centrosomas, con cromosomas unidos a los extremos distales de los microtubulos La pequeña molécula fue



denominada "monastrol" segun el arreglo monoastral Este fenotipo de arreglo monoastral se había observado previamente en celulas mitóticas que estaban inmunoagotadas de la proteina motora Eg5

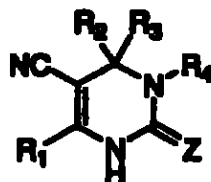
El fenotipo de arreglo monoastral distintivo facilitó la identificación de monastrol como un inhibidor potencial de Eg5 En efecto, se comprobó además que monastrol inhibia la motilidad producida por la motora Eg5 de microtubulos en un ensayo *in vitro* Mas aun, monastrol no tuvo efecto aparente sobre la motora quinesina relacionada o sobre la motora(s) responsable del movimiento del aparato de Golgi en la celula Celulas que despliegan el fenotipo de arreglo monoastral, mediante inmunoagotamiento de Eg5 o inhibición de monastrol de Eg5, se detienen en la M fase del ciclo celular Desafortunadamente, sin embargo, la detencion mitótica inducida por cualquiera de estos mecanismos es transitoria. (Kapoor, 2000 *J Cell Biol* 150(5) 975-80) Tanto el fenotipo de arreglo monoastral como la detencion del ciclo celular inducido por monastrol en mitosis son reversibles Las células se recuperan para formar un huso mitotico bipolar normal, para completar la mitosis, y para proseguir a través del ciclo celular y la proliferación normal de la célula Esto sugiere que un inhibidor de molécula pequeña de Eg5 que indujo una detención mitótica transitoria puede no ser efectivo para el tratamiento de proliferacion celular cancerosa No obstante, el descubrimiento que el monastrol ocasiona detención mitótica es intrigante y, por consiguiente, existe la necesidad de estudiar aun mas e identificar compuestos que pueden usarse para modular la proteína motora Eg5 en una forma que sea efectiva en el tratamiento de canceres humanos Existe igualmente una necesidad de explorar el uso de estos compuestos en combinacion con otros agentes neoplásicos

SUMARIO

Los compuestos de la invención causan la interrupción de mitosis, y como tales, pueden emplearse para tratar enfermedades proliferativas Por ejemplo, los compuestos de la presente invencion pueden usarse como

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antiproliferativos y agentes anticancer Mas específicamente, la invención comprende un compuesto de fórmula I



I,

sus enantiómeros, diastereómeros, sales de aceptación farmacéutica, profarmacos y solvatos de los mismos, en donde

R_1 se selecciona del grupo conformado por hidrógeno, alquilo y cicloalquilo,

R_2 y R_3 se seleccionan cada uno independientemente del grupo conformado por H, alquilo, arilo, heteroarilo, arilalquilo, cicloalquilo, heterocicloalquilo, cicloalquilalquilo, heterocicloalquilalquilo y heteroarilalquilo, o

R_2 y R_3 pueden también tomarse juntos para formar un anillo carboxílico o heterocíclico,

R_4 se selecciona del grupo conformado por alquilo, arilalquilo, cicloalquilalquilo, heteroarilalquilo, heterocicloalquilo, aminoalquilo, heterocicloalquilalquilo, CN, $C(O)R_5$, CO_2R_5 , $C(O)SR_5$ y $CONR_5R_6$,

R_5 y R_6 se seleccionan cada uno independientemente del grupo conformado por H, alquilo, cicloalquilo, hidroxialquilo, alqueno, alcoxi, tioalcoxi, alcoxialquilo, haloalquilo, arilo, heteroarilo, arilalquilo, cicloalquilalquilo, heteroarilalquilo y heterocicloalquilalquilo o $N-R_5R_6$ juntos forman un heterocicloalquilo,

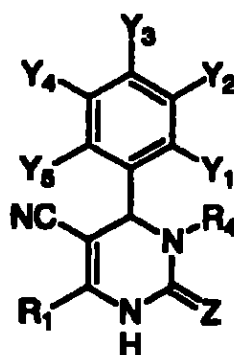
Z se selecciona del grupo conformado por O, S y NR_8 ,

R_8 se selecciona del grupo conformado por H, CN, sulfonamido, OR_7 , alquilo, cicloalquilo, arilo, arilalquilo, heterociclilo, heteroarilo y heteroarilalquilo, y

R_7 se selecciona del grupo conformado por H, alquilo, arilalquilo, cicloalquilalquilo, heterocicloalquilalquilo y heteroarilalquilo

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De acuerdo con una incorporacion, compuestos de la presente invencion incluyen aquellos que tienen la formula IA



IA

sus enantiómeros, diastereómeros, sales de aceptación farmacéutica, profármacos y solvatos de las mismas, en donde Y₁, Y₂, Y₃, Y₄ y Y₅ se seleccionan independientemente del grupo conformado por H, halógeno, alquilo inferior, O-alquilo, O-arilo, NH-alquilo, NH-arilo, N-alquilalquilo, N-alquilarilo, N-arilarilo con la condición que por lo menos uno de Y₁, Y₂, Y₃, Y₄ y Y₅ es arilo o heteroarilo, y los grupos restantes son como se definen mas arriba.

La presente invención provee además métodos para tratar una enfermedad proliferativa, tal como cáncer, por medio de la modulación de la proteína motora Eg5 que comprende administrar a una especie mamífera necesitada de dicho tratamiento una cantidad efectiva de por lo menos un compuesto de fórmula I o IA, como se define anteriormente

DESCRIPCIÓN

La presente invención hace posibles compuestos de fórmula I y IA, como se define más arriba, composiciones farmacéuticas que emplean dichos compuestos y métodos de usar dichos compuestos

Enumeradas a continuación se encuentran definiciones de varios términos usados para describir los compuestos de la presente invención. Estas definiciones se aplican a los términos tal como se usan de principio a

fin de la especificacion (a menos que se limiten en otra forma en casos especificos) individualmente o como parte de un grupo mas grande

El termino "alquilo" aqui solo o como parte de otro grupo se refiere a un radical derivado (hidrocarburo) alcano monovalente que contiene de 1 a 12 atomos de carbono a menos que se defina lo contrario. Un grupo alquilo es un grupo hidrocarburo saturado, recto, ramificado opcionalmente sustituido. Cuando sustituidos, los grupos alquilo pueden sustituirse con hasta cuatro grupos sustituyentes, R como se define, en cualquier punto disponible de unión. Cuando se dice que el grupo alquilo se sustituye con un grupo alquilo, esto se usa intercambiabilmente con "grupo alquilo ramificado". Tales grupos ejemplares no sustituidos incluyen metilo, etilo, propilo, isopropilo, n-butilo, t-butilo, isobutilo, pentilo, hexilo, isohexilo, heptilo, 4,4-dimetilpentilo, octilo, 2,2,4-trimetilpentilo, nonilo, decilo, undecilo, dodecilo, y similares. Sustituyentes ejemplares pueden incluir pero no se limitan a uno o mas de los siguientes grupos: arilo, halo (tal como F, Cl, Br, I), haloalquilo (tal como CCl_3 o CF_3), alcoxi, alquiltio, hidroxilo, carboxilo ($-\text{COOH}$), alquiloilcarbonilo ($-\text{C(O)R}$), alquiloilcarboniloxilo ($-\text{OCOR}$), amino ($-\text{NH}_2$), carbamoilo ($-\text{NHCOOR}-$ o $-\text{OCONHR}-$), urea ($-\text{NHCONHR}-$) o tiol ($-\text{SH}$). Grupos alquilo, como se define, pueden comprender igualmente uno o mas enlaces dobles carbono a carbono o uno o mas enlaces triples carbono a carbono.

El término "alquenoilo" aqui solo o como parte de otro grupo se refiere a un radical hidrocarburo recto, ramificado o ciclico que contiene de 2 a 12 átomos de carbono y por lo menos un doble enlace carbono a carbono.

El termino "alquinoilo" aqui solo o como parte de otro grupo se refiere a un radical hidrocarburo recto, ramificado o cíclico que contiene de 2 a 12 atomos de carbono y por lo menos un triple enlace carbono a carbono.

Los numeros en el subíndice después del símbolo "C" definen el numero de atomos de carbono que puede contener un grupo particular. Por ejemplo " C_{1-6} alquilo" significa una cadena de carbono saturado recta o ramificada que tiene de uno a seis átomos de carbono, ejemplos incluyen metilo, etilo, n-propilo, isopropilo, n-butilo, sec-butilo, isobutilo, t-butilo, n-

pentilo, sec-pentilo, isopentilo, y n-hexilo. Dependiendo del contexto, "C₁₋₆ alquilo" puede también referirse a C₁₋₆ alquileo que puentea dos grupos, ejemplos incluyen propan-1,3-diilo, butan-1,4-diilo, 2-metil-butan-1,4-diilo, etc. "C₂₋₆ alquenoilo" significa una cadena carbono recta o ramificada que tiene por lo menos un doble enlace carbono-carbono, y que tiene de dos a seis átomos de carbono, ejemplos incluyen etenilo, propenilo, isopropenilo, butenilo, isobutenilo, pentenilo, y hexenilo. Dependiendo del contexto, "C₂₋₆ alquenoilo" puede referirse igualmente a C₂₋₆ alqueno-diilo que puentea dos grupos, ejemplos incluyen etilen-1,2-diilo (vinileno), 2-metil-2-buten-1,4-diilo, 2-hexen-1,6-diilo, etc. "C₂₋₆ alquinoilo" significa una cadena carbono recta o ramificada que tiene por lo menos un triple enlace carbono-carbono, y de dos a seis átomos de carbono, ejemplos incluyen etinilo, propinilo, butinilo, y hexinilo.

El término "cicloalquilo" aquí solo o como parte de otro grupo es una especie de alquilo que contiene de 3 a 15 átomos de carbono, sin alternar o resonar dobles enlaces entre átomos de carbono. Puede contener de 1 a 4 anillos. Dichos grupos ejemplares no sustituidos incluyen ciclopropilo, ciclobutilo, ciclopentilo, ciclohexilo, adamantilo, etc. Sustituyentes ejemplares incluyen uno o más de los siguientes grupos: halógeno, alquilo, alcoxi, alquil hidroxilo, amino, nitro, ciano, tiol y/o alquiltio.

Los términos "alcoxi" o "alquiltio" aquí solos o como parte de otro grupo denotan un grupo alquilo como se describe más arriba unidos mediante un enlace oxígeno (-O-) o un enlace azufre (-S-), respectivamente.

El término "alquiloxicarbonilo" aquí solo o como parte de otro grupo denota un grupo alcoxi unido mediante un grupo carbonilo. Un radical alquiloxicarbonilo se representa por la fórmula -C(O)OR, en donde el grupo R es un grupo C₁₋₆ alquilo recto o ramificado.

El término "alquilcarbonilo" aquí solo o como parte de otro grupo se refiere a un grupo alquilo unido mediante un grupo carbonilo.

El término "alquilcarboniloxi" aquí solo o como parte de otro grupo denota un grupo alquilcarbonilo que se une mediante un enlace oxígeno.

El termino "arilalquilo" aquí solo o como parte de otro grupo denota un anillo aromático unido a un grupo alquilo como se describe mas arriba

El termino "arilo" aquí solo o como parte de otro grupo se refiere a anillos aromaticos monociclicos o biciclicos, por ejemplo, fenilo, fenilo sustituido y similares, así como grupos que son fusionados, por ejemplo, naftilo, fenantrenilo y similares. Por consiguiente un grupo arilo contiene por lo menos un anillo que tiene por lo menos 6 átomos, estando presentes hasta cinco dichos anillos, que contienen hasta 22 átomos en ellos, con dobles enlaces alternantes (resonantes) entre átomos adyacentes de carbono o heteroátomos apropiados. Grupos arilo pueden sustituirse opcionalmente con uno o mas grupos incluyendo, pero no limitados, a halogeno, alquilo, alcoxi, hidroxilo, carboxilo, carbamilo, alquiloxicarbonilo, nitro, alquilenilo, trifluorometilo, amino, cicloalquilo, arilo, heteroarilo, ciano, alquil S(O)_m (m=O, 1, 2), o tiol

El termino "amino" aquí solo o como parte de otro grupo se refiere a -NH₂. Un "amino" puede sustituirse opcionalmente con uno o dos sustituyentes, que pueden ser los mismos o diferentes, tal como alquilo, arilo, arilalquilo, alqueno, alquino, heteroarilo, heteroarilalquilo, cicloheteroalquilo, cicloheteroalquilalquilo, cicloalquilo, cicloalquilalquilo, haloalquilo, hidroxialquilo, alcoxialquilo, tioalquilo, carbonilo o carboxilo. Estos sustituyentes pueden sustituirse adicionalmente con un ácido carboxílico, cualquiera de los sustituyentes alquilo o arilo expuestos aquí. En algunas incorporaciones, los grupos amino se sustituyen con carboxilo o carbonilo para formar derivados N-acilo o N-carbamilo.

El termino "anillo carbocíclico" aquí solo o como parte de otro grupo se refiere a hidrocarburos de anillo monocíclico estables, saturados o parcialmente insaturados de 3 a 7 átomos de carbono tal como ciclopropilo, ciclobutilo, ciclopentilo, ciclohexilo y cicloheptilo. El anillo carbocíclico puede sustituirse opcionalmente significando que el anillo carbocíclico puede sustituirse en una o más posiciones de anillo sustituibles por uno o más grupos independientemente seleccionados de alquilo (preferiblemente alquilo inferior), alcoxi (preferiblemente alcoxi inferior), nitro,

monoalquilamino (preferiblemente un alquilamino inferior), dialquilamino (preferiblemente a di[inferior]alquilamino), ciano, halo, haloalquilo (preferiblemente trifluorometilo), alcanilo, aminocarbonilo, monoalquilaminocarbonilo, dialquilaminocarbonilo, alquilamido (preferiblemente alquilamido inferior), alcohalquilo (preferiblemente un alcohal[inferior]alquilo inferior), alcoxycarbonilo (preferiblemente un alcoxycarbonilo inferior), alquilcarbonilo (preferiblemente un alquilcarbonilo inferior) y arilo (preferiblemente fenilo), sustituyendose dicho arilo opcionalmente por grupos, alquilo inferior y alcox inferior

El termino "cicloalquilo" aquí solo o como parte de otro grupo se refiere a anillos hidrocarburos completamente saturados y parcialmente insaturados de 3 a 9, preferiblemente 3 a 7 átomos de carbono. Además, puede sustituirse un cicloalquilo. Un cicloalquilo sustituido se refiere a aquellos anillos que tienen uno, dos, o tres sustituyentes, preferiblemente uno, seleccionados del grupo conformado por halo, alquilo, alquilo sustituido, alqueno, alquino, nitro, ciano, oxo (=O), hidrox, alcox, tioalquilo, -CO₂H, -C(=O)H, CO₂-alquilo, -C(=O)alquilo, ceto, =N-OH, =N-O-alquilo, arilo, heteroarilo, heterociclo, un acetal de cinco o seis miembros (*es decir*, 1,3-dioxolano o 1,3-dioxano), -NR'R", -C(=O)NR'R", -CO₂NR'R", -C(=O)NR'R", -NR'CO₂R", -NR'C(=O)R", -SO₂NR'R", y -NR'SO₂R", en donde cada uno de R' y R" se selecciona independientemente de hidrogeno, alquilo, alquilo sustituido, y cicloalquilo, o R' y R" juntos forman un anillo heterociclo o heteroarilo

El término "heteroarilo" aquí solo o como parte de otro grupo se refiere a grupos monociclicos de 5 o 6 miembros, aromaticos, sustituidos y no sustituidos, grupos biciclicos de 9 ó 10 miembros, y grupos tricíclico de 11 a 14 miembros que tienen por lo menos un heteroátomo (O, S o N) en por lo menos uno de los anillos. Cada anillo del grupo heteroarilo que contiene un heteroátomo puede incluir uno o dos átomos de oxigeno o azufre y/o de uno a cuatro átomos de nitrógeno con la condicion que el

numero total de heteroatomos en cada anillo es cuatro o menos y cada anillo tiene por lo menos un atomo de carbono. Los anillos fusionados que completan los grupos bicíclicos y tricíclicos pueden contener unicamente átomos de carbono y pueden ser saturados, parcialmente saturados, o insaturados. Los átomos de nitrógeno y azufre pueden oxidarse opcionalmente y los átomos de nitrógeno pueden cuaternizarse opcionalmente. Grupos heteroarilo que son bicíclicos o tricíclicos tienen que incluir por lo menos un anillo completamente aromático pero el otro anillo fusionado o anillos puede ser aromático o no aromático. El grupo heteroarilo pueden unirse en cualquier atomo de nitrógeno o carbono disponible de cualquier anillo. El sistema de anillo heteroarilo puede contener cero, uno, dos o tres sustituyentes seleccionados del grupo conformado por halo, alquilo, alquilo sustituido, alquenilo, alquinilo, arilo, nitro, ciano, hidroxilo, alcoxi, tioalquilo, $-CO_2H$, $-C(=O)H$, $-CO_2$ -alquilo, $-C(=O)$ alquilo, fenilo, benzilo, feniletilo, feniloxi, feniltio, cicloalquilo, cicloalquilo sustituido, heterociclo, heteroarilo, $-NR'R''$, $-C(=O)NR'R''$, $-CO_2NR'R''$, $-C(=O)NR'R''$, $-NR'CO_2R''$, $-NR'C(=O)R''$, $-SO_2NR'R''$, y $-NR'SO_2R''$, en donde cada uno de R' y R'' se selecciona independientemente de hidrógeno, alquilo, alquilo sustituido, y cicloalquilo, o R' y R'' juntos forman un anillo heterociclo o heteroarilo.

Grupos heteroarilo monocíclico ejemplares incluyen pirrolilo, pirazolilo, pirazolinilo, imidazolilo, oxazolilo, diazolilo, isoxazolilo, tiazolilo, tiadiazolilo, isotiazolilo, furanilo, tienilo, oxadiazolilo, piridilo, pirazinilo, pirimidinilo, piridazinilo, triazinilo y similares.

Grupos heteroarilo bicíclico ejemplares incluyen indolilo, benzotiazolilo, benzodioxolilo, benzoxazolilo, benzotienilo, quinolinilo, tetrahydroisoquinolinilo, isoquinolinilo, benzimidazolilo, benzopirranilo, indolizinilo, benzofuranilo, cromonilo, cumarinilo, benzopirranilo, cinnolinilo, quinoxalinilo, indazolilo, pirrolopiridilo, furopiridinilo, dihydroisoindolilo, tetrahydroquinolinilo y similares.



Grupos heteroarilo tricíclico ejemplares incluyen carbazolilo, benzidolilo, fenantrolinilo, acridinilo, fenantridinilo, xantenilo y similares

El término "heterocicloalquilo" aquí solo o como parte de otro grupo se refiere a un grupo cicloalquilo (no aromático) en el cual uno de los átomos de carbono en el anillo se reemplaza por un heteroátomo seleccionado de O, S o N, y en el cual hasta tres átomos adicionales de carbono pueden reemplazarse por dichos heteroátomos

El término "anillo heterocíclico" aquí solo o como parte de otro grupo se refiere a un sistema de anillo monocíclico estable, saturado, o parcialmente insaturado que contiene 5 a 7 miembros de anillo de átomos de carbono y otros átomos seleccionados de nitrógeno, azufre y/o oxígeno. Preferiblemente, un heterociclilo es un anillo monocíclico de 5 o 6 miembros y contiene uno, dos, o más heteroátomos seleccionados de nitrógeno, oxígeno y/o azufre. El anillo heterocíclico puede ser opcionalmente sustituido lo cual significa que el anillo heterocíclico puede sustituirse en una o más posiciones de anillo sustituibles por uno o más grupos independientemente seleccionados de alquilo (preferiblemente alquilo inferior), alcoxi (preferiblemente alcoxi inferior), nitro, monoalquilamino (preferiblemente un alquilamino inferior), dialquilamino (preferiblemente un di[inferior]alquilamino), ciano, halo, haloalquilo (preferiblemente trifluorometilo), alcanilo, aminocarbonilo, monoalquilaminocarbonilo, dialquilaminocarbonilo, alquilamido (preferiblemente alquilamido inferior), alcoxi alquilo (preferiblemente un alcoxi[inferior]alquilo inferior), alcoxicarbonilo (preferiblemente un alcoxicarbonilo inferior), alquilcarbonilo (preferiblemente un alquilcarbonilo inferior) y arilo (preferiblemente fenilo), siendo dicho arilo opcionalmente sustituido por grupos halo, alquilo inferior y alcoxi inferior. Ejemplos de dichos anillos heterocíclicos son isoxazolilo, imidazolinilo, tiazolinilo, imidazolidinilo, pirrolilo, pirrolinilo, piranilo, pirazinilo, piperidilo, morfolinilo y triazolilo. El anillo heterocíclico puede estar unido a la estructura origen a través de un átomo de carbono o a través

de cualquier heteroátomo de heterociclilo que resulte en una estructura estable

El término "heterociclilo" aquí solo o como parte de otro grupo como se usa aquí se refiere a un sistema de anillo estable, saturado, o parcialmente insaturado, monocíclico, monocíclico puenteado, bicíclico, y espiro que contiene átomos de carbono y otros átomos seleccionados de nitrógeno, azufre y/o oxígeno. Preferiblemente, un heterociclilo es un anillo monocíclico de 5 o 6 miembros o un anillo bicíclico de 8-11 miembros que consta de átomos de carbono y contiene uno, dos, o tres heteroátomos seleccionados de nitrógeno, oxígeno y/o azufre. El término "opcionalmente sustituido" en la medida en que se refiera a un "heterociclilo" aquí indica que el grupo heterociclilo puede sustituirse en una o más posiciones de anillo sustituibles por uno o más grupos independientemente seleccionados de alquilo (preferiblemente alquilo inferior), alcoxi (preferiblemente alcoxi inferior), nitro, monoalquilamino (preferiblemente un alquilamino inferior), dialquilamino (preferiblemente un di[inferior]alquilamino), ciano, halo, haloalquilo (preferiblemente trifluorometilo), alcanilo, aminocarbonilo, monoalquilaminocarbonilo, dialquilaminocarbonilo, alquilamido (preferiblemente alquilamido inferior), alcoxi alquilo (preferiblemente un alcoxi[inferior]alquilo inferior), alcoxicarbonil (preferiblemente un alcoxicarbonilo inferior), alquilcarbonilo (preferiblemente un alquilcarbonilo inferior) y arilo (preferiblemente fenilo), siendo dicho arilo opcionalmente sustituido por grupos halo, alquilo inferior y alcoxi inferior. Ejemplos de dichos grupos heterociclilo son isoxazolilo, imidazolinilo, tiazolinilo, imidazolidinilo, pirrolilo, pirrolinilo, piranilo, pirazinilo, piperidilo, morfolinilo y triazolilo. El grupo heterociclilo puede estar unido a la estructura original a través de un átomo de carbono o a través de cualquier heteroátomo del heterociclilo que resulte en una estructura estable.

El termino "heteroátomo" significa O, S o N, seleccionados sobre una base independiente. Debe anotarse que se asume que cualquier heteroátomo con valencias no satisfechas tiene el átomo de hidrogeno para satisfacer las valencias.

El término "halógeno" o "halo" se refiere a cloro, bromo, fluor o yodo seleccionados sobre una base independiente.

Cuando un grupo funcional se designa "protegido", esto significa que el grupo se encuentra en forma no modificada para evitar reacciones colaterales indeseadas en el sitio protegido. Grupos protectores adecuados para los compuestos de la presente invencion se reconocerán de la presente solicitud tomando en cuenta el nivel de habilidad en el arte, y con referencia a libros de texto estándar, tal como Greene, T W y colaboradores, *Protective Groups in Organic Synthesis* Wiley, N Y (1991).

Tal como se usa aqui, el termino "paciente" abarca todas las especies mamíferas.

Ejemplos apropiados de sales de los compuestos de acuerdo con la invención con ácidos organicos o inorganicos son clorhidrato, bromhidrato, sulfato, metanosulfonato, maleato, fumarato, y fosfato. Sales que son inapropiadas para usos farmacéuticos pero que pueden emplearse, por ejemplo, para el aislamiento o purificación de compuestos libres o sus sales de aceptación farmaceutica, se incluyen igualmente.

Se contemplan todos los estereoisómeros de los compuestos de la presente invencion, en mezcla o en forma pura o sustancialmente pura. La definicion de los compuestos de acuerdo con la invencion abarca todos los posibles estereoisómeros y sus mezclas. Incluye muy particularmente las formas racémicas y los isómeros opticos aislados que tienen la actividad especificada. Las formas racémicas pueden resolverse por metodos fisicos, tales como, por ejemplo, cristalización fraccionaria, separacion o cristalización de derivados diastereomericos o separacion por cromatografía de columna quiral. Los isómeros ópticos individuales pueden obtenerse de los racematos por metodos convencionales, tales como, por ejemplo,

formacion de sales con un ácido optimamente activo seguida por cristalización

Debe entenderse que la presente invencion incluye formas de profármacos de los compuestos de fórmula I. Varias formas de profarmacos son bien conocidas en el arte. Para ejemplos de dichos derivados de profármacos, véase

- (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)

En general, la presente invención comprende un compuesto de formula I



I,

sus enantiómeros, diastereómeros, sales de aceptación farmaceutica, profarmacos y solvatos de los mismos. R₁ es hidrogeno, alquilo o cicloalquilo. R₂ y R₃ son cada uno independientemente H, alquilo, arilo, heteroarilo, arilalquilo, cicloalquilalquilo, heterocicloalquilalquilo o heteroarilalquilo. Alternativamente, R₂ y R₃ pueden tomarse juntos para formar un anillo carbociclico o heterociclico. R₄ es alquilo, arilalquilo, cicloalquilalquilo, aminoalquilo, heteroarilalquilo, heterocicloalquilalquilo,

CN, COR₅, CO₂R₅ ó CONR₅R₆ R₅ y R₆ son cada uno independientemente H, alquilo, arilalquilo, cicl alquilalquilo, heteroarilalquilo o heterocicloalquilalquilo o N-R₅R₆ juntos forman un heterocicloalquilo, Z es O, S o NR₈, R₈ es H, CN, sulfonamido, OR₇, alquilo, cicloalquilo, arilo, arilalquilo, heterociclilo, heteroarilo o heteroarilalquilo R₇ es H, alquilo, arilalquilo, cicloalquilalquilo, heterocicloalquilalquilo, o heteroarilalquilo

Una incorporacion preferida de la presente invención incluye compuestos de formula I, como se define más arriba, en donde R₁ es alquilo, R₂ se selecciona del grupo conformado por arilo y heteroarilo, R₃ es H, R₄ se selecciona del grupo conformado por alquilo, arilalquilo, CO₂R₅ y CONR₅R₆, R₅ y R₆ se seleccionan independientemente del grupo conformado por H, alquilo, aminoalquilo, hidroxialquilo, fenilamino y arilalquilo, Z se selecciona del grupo conformado por O, S y NR₈, y R₈ se selecciona del grupo conformado por H y CN

En una incorporacion preferida, la invencion comprende compuestos de fórmula I en donde R₂ es heteroarilo Grupos heteroarilo preferidos incluyen tiofenilo opcionalmente sustituido, oxazolilo, isoxazolilo, y furanilo Sustituyentes preferidos incluyen metilo, etilo, halo, haloalquilo, tales como grupos CF₃ o arilo, tales como fenilo o fenilo sustituido Sustituyentes fenilo preferidos incluyen grupos alquilo, tales como metilo, grupos alcoxi, tales como metoxi, halo, (F, Cl, o Br), haloalquilo, tales como, CF₃, grupos amino, tales como dimetilamino, o grupos alcoxialquilo, tales como grupos etoximetilo

En otra incorporación preferida, la invención comprende compuestos de fórmula I, como se define mas arriba, en donde R₄ se selecciona del grupo conformado por alquilo, arilalquilo, CO₂R₅ y CONR₅R₆

En todavía otra incorporacion preferida, la presente invencion comprende los compuestos de fórmula I, como se define más arriba, en donde R₄ es CO₂R₅, Z es O, y R₅ es etilo

En todavía una incorporación adicional preferida, la presente invención comprende los compuestos de formula I, como se define más

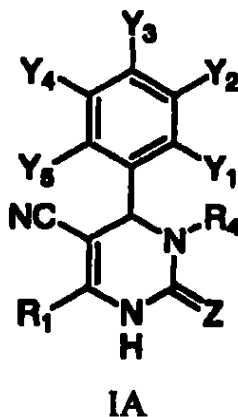
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arriba, en donde R_4 es CONR_5R_6 , Z es O, R_5 es H, y R_6 es metilo, etilo, propilo, fenilo, ciclopropilo, hidroxietilo, tiofenilo, o 2-propileno

En todavia otra incorporación preferida, la presente invencion comprende los compuestos de fórmula I, como se define mas arriba, en donde R_1 es CH_3 , R_2 es arilo, R_4 es CO_2R_5 , R_5 es alquilo, y Z es O

En todavía otra incorporacion preferida, la presente invencion comprende los compuestos de fórmula I, como se define mas arriba, en donde R_1 es CH_3 , R_2 es arilo, R_4 es CONR_5R_6 , R_5 es alquilo, R_6 es H, y Z es O

De acuerdo con una incorporacion, la presente invencion comprende compuestos de formula IA



e incluyen sus enantiomeros, diastereomeros, sales de aceptacion farmaceutica , profármacos y solvatos de las mismas, en donde

R_1 se selecciona del grupo conformado por hidrogeno, alquilo y cicloalquilo,

Y_1 Y_2 Y_3 , Y_4 y Y_5 se seleccionan independientemente del grupo conformado por H, halógeno, alquilo inferior, O alquilo, O arilo, NH alquilo, NH arilo, N alquil alquilo, N alquil arilo, N aril arilo, con la condicion que por lo menos uno de Y_1 , Y_2 , Y_3 , Y_4 y Y_5 es arilo o heteroarilo,

R_4 se selecciona del grupo conformado por alquilo, arilalquilo, cicloalquilalquilo, aminoalquilo, heteroarilalquilo, heterocicloalquilalquilo, CN, COR_5 , CO_2R_5 y CONR_5R_6 ,

R_3 y R_6 se seleccionan independientemente del grupo conformado por H, alquilo, haloalquilo, cicloalquilo, arilalquilo, cicloalquilalquilo, heteroarilalquilo, y heterocicloalquilalquilo,

Z se selecciona del grupo conformado por O, S y NR_8 ,

R_8 se selecciona del grupo conformado por H, CN, sulfonamido, OR_7 , alquilo, cicloalquilo, arilo, arilalquilo, heterociclilo, heteroarilo y heteroarilalquilo, y

R_7 se selecciona del grupo conformado por H, alquilo, arilalquilo, cicloalquilalquilo, heterocicloalquilalquilo, y heteroarilalquilo

En algunas incorporaciones preferidas, Y_2 es arilo o heteroarilo En incorporaciones preferidas, Y_2 es un fenilo opcionalmente sustituido, piridilo, tiazolilo, pirrolilo, o diazolilo Sustituyentes preferidos incluyen Br, Cl, F, metilo, etilo, o CF_3

De acuerdo con una incorporación de la presente invención, compuestos comprenden Formula IA, en donde R_4 es alquilo, arilalquilo, CO_2R_5 ó $CONR_5R_6$

De acuerdo con otra incorporación, la presente invención comprende compuestos que tienen la fórmula IA en donde R_1 es alquilo, R_4 se selecciona del grupo conformado por alquilo, arilalquilo, CO_2R_5 , y $CONR_5R_6$, R_3 y R_6 se seleccionan independientemente del grupo conformado por H, alquilo, haloalquilo, cicloalquilo, y arilalquilo, Z se selecciona del grupo conformado por O, S, y NR_8 , R_8 se selecciona del grupo conformado por H y CN

De acuerdo con otra incorporación, la presente invención comprende compuestos de Formula IA en donde R_4 es CO_2R_5 ó $CONR_5R_6$ y Z es O

En otras incorporaciones, la presente invención comprende compuestos de formula IA en donde R_4 se selecciona del grupo conformado por alquilo y arilalquilo, y Z es O

En todavía mas incorporaciones, la presente invención comprende compuestos de fórmula IA en donde R_1 es CH_3 , R_4 es CO_2R_5 , R_5 es alquilo, y Z es O

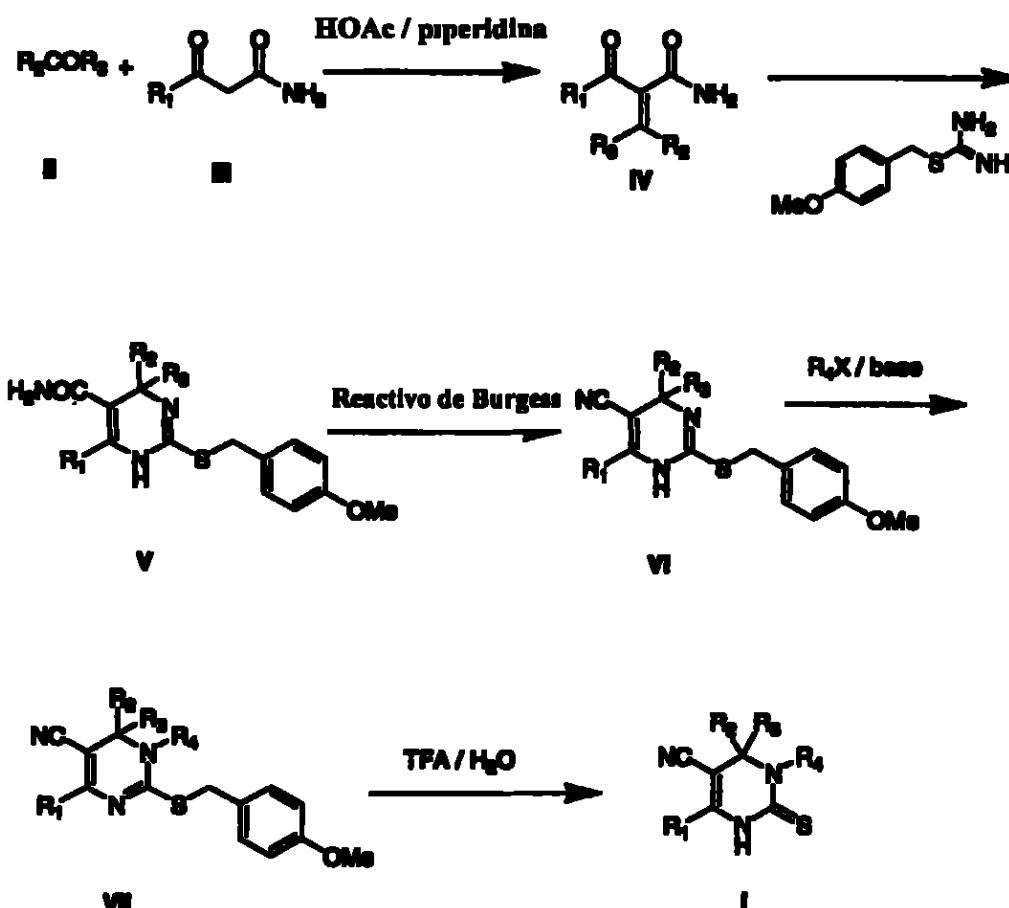
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La invencion provee además una composicion farmaceutica que comprende un compuesto de fórmula I o IA, como se define más arriba, y un vehiculo portador de aceptacion farmaceutica Opcionalmente la composición farmacéutica puede comprender adicionalmente por lo menos otro agente anti-cancer formulado como una dosis fija.

La invención provee igualmente un metodo para tratar una enfermedad proliferativa mediante modulacion de la proteina motora Eg5, y/o, inducir apoptosis que comprende administrar a una especie mamifera necesitada de dicho tratamiento una cantidad efectiva de por lo menos un compuesto de fórmula I, como se define más arriba En otra incorporacion, la invención provee un metodo para tratar una enfermedad proliferativa mediante modulacion de la proteína motora Eg5 que comprende administrar a una especie mamifera necesitada de dicho tratamiento una cantidad efectiva de por lo menos un compuesto de formula I o IA, como se define mas arriba, en combinacion (simultánea o secuencialmente) con por lo menos otro agente anti-cancer En una incorporacion preferida, la enfermedad proliferativa es cáncer

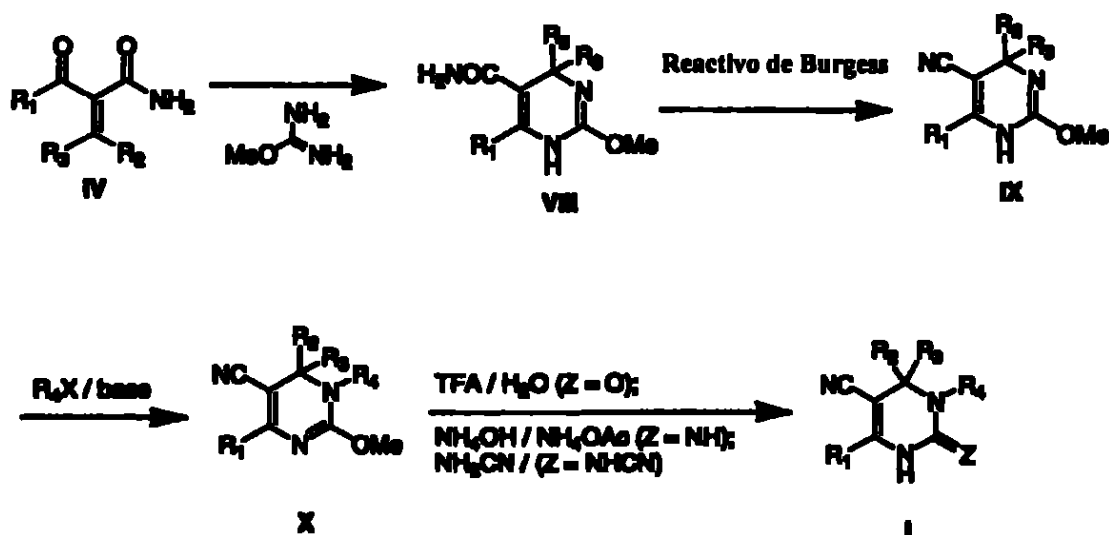
Ciertos compuestos de fórmula I pueden prepararse generalmente de acuerdo con los siguientes esquemas y el conocimiento de un experto en el arte Solvatos (por ejemplo, hidratos) de los compuestos de formula I y IA se encuentran también dentro de la orbita de la presente invencion Métodos de solvatación se conocen por lo general en el arte En consecuencia, los compuestos de la presente invencion pueden estar en forma libre o de hidrato, y pueden obtenerse por metodos ejemplificados los siguientes esquemas incluidos a continuación

Esquema I



con Esquema I Una cetona o un aldehído I (por ejemplo, benzaldehído, donde R_2 es fenilo y R_3 es H), se condensa con una acetoacetamida III para producir un producto de Knoevenagel IV como una mezcla de isómeros. La reacción con S-parametoxibencil tiourea proporciona la dihidropirimidina tiona V protegida. El grupo amido primario de V se deshidrata al sustituyente ciano en VI usando un agente deshidratador tal como reactivo de Burgess (metoxycarbonilsulfamoyl)triethylhidroxido de amonio, sal interna. El sustituyente N3 se introduce por reacción con R_4X donde R_4 es alquilo o acilo, y X es un grupo saliente, o donde R_4X es un isocianato o haloformato. El grupo protector se retira por tratamiento con ácido en la presencia de agua para producir compuestos de fórmula I donde Z es S.

Esquema II



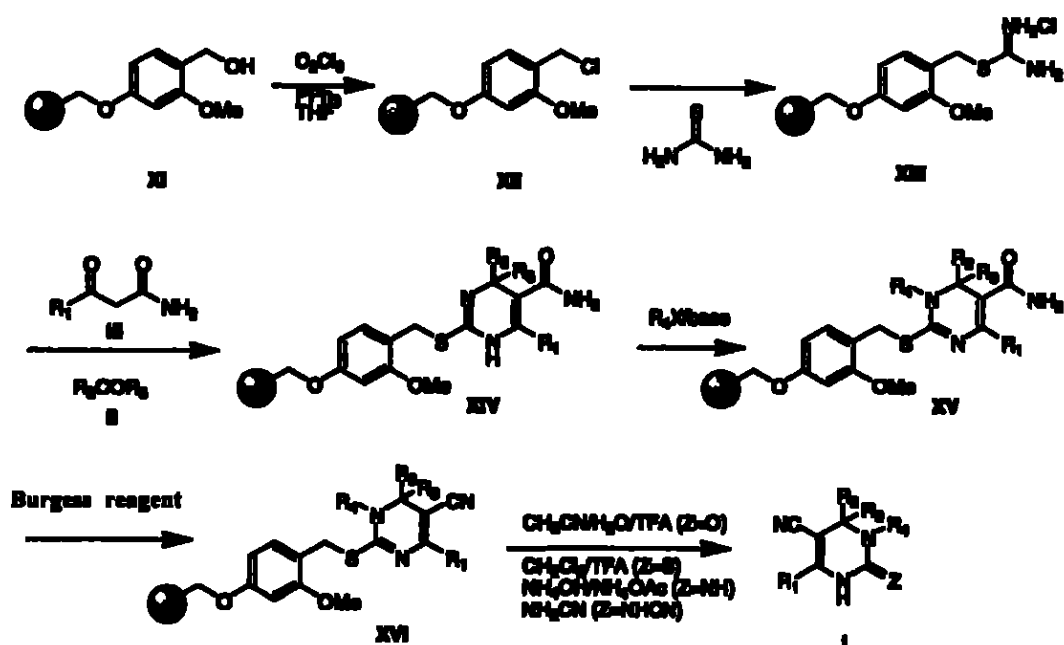
Compuestos de formula I donde Z es O, NH, o NR_8 se preparan de la reaccion de productos de Knoevenagel IV con O-metil isourea para proporcionar las O-metil dihidropirimidinas VIII. La amida primaria se convierte en un grupo nitrilo usando un agente deshidratante tal como reactivo de Burgess. El sustituyente N3 se introduce por reacción con R_4X donde R_4 es alquilo o acilo, y X es un grupo saliente, o donde R_4X es un isocianato o haloformato. El grupo protector metil éster se retira por tratamiento con ácido en la presencia de agua para producir compuestos de formula I donde Z es O. Alternativamente, tratamiento de compuestos de formula X con hidroxido de amonio en la presencia de acetato de amonio, o cianamida en etanol, provee compuestos de fórmula I donde Z es NH o NR_8 .

Compuestos de formula I pueden prepararse igualmente usando la reaccion de Bignelli (D J Brown in *The Pyrimidines*, Wiley New York, 1962, 440).

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Esquema III

SÍNTESIS DE FASE SÓLIDA

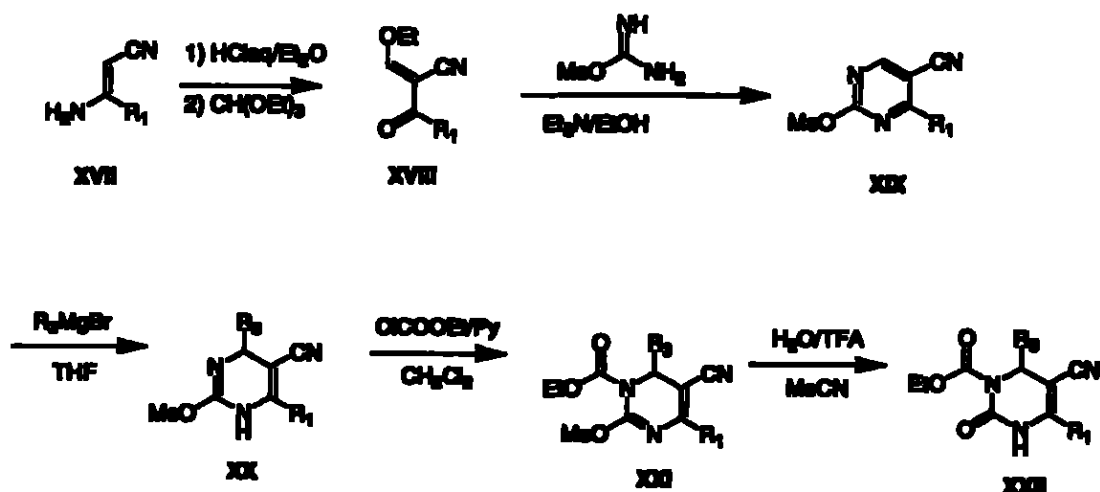


Compuestos de formula I pudieron prepararse sobre un soporte solido como se esboza en Esquema III. El compuesto inicial XI denota un alcohol bencilico ligado a resina usado para sintesis de soporte sólido que se prepara a partir de una resina Merrifield denotada como $\bullet$, y 2-metoxi-4-hidroxibenzaldehído, seguida por reduccion del aldehído con agentes reductores tales como NaBH_4 . El alcohol bencilico se convierte en el cloruro de bencilo usando agentes tales como hexacloroetano y trifenilfosfina en THF para formar resinas de fórmula XII. El cloruro se desplaza con tiourea para formar la resina de isotiourea XIII. La resina resultante se trata con exceso de cetoamidas como acetoamida (III, R_1 es CH_3), en la presencia de cetonas de formula R_2COR_3 o aldehidos de formula R_2CHO para formar las pirimidinas ligadas a resina de formula XIV. El sustituyente N3 se introduce usando R_4X , donde X es un grupo saliente y R_4 es alquilo o acilo, o R_4X es un isocianato, o haloformato, en la presencia de una base para formar estructuras de fórmula XV. La

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amida primaria puede deshidratarse al grupo ciano usando reactivos tales como el reactivo de Burgess para formar compuestos de fórmula XVI. Los productos pueden escindirse de la resina usando una variedad de condiciones para formar compuestos de fórmula I, donde Z se determina por el método de escisión empleado. Escisión cleavage en la presencia de ácido acuoso formará compuestos de fórmula I con Z siendo O, mientras que escisión bajo condiciones de ácido anhidro formará compuestos de fórmula I con Z siendo S. Alternativamente, el tratamiento de resinas con estructura XVI con hidróxido de amonio en la presencia de acetato de amonio formará compuestos de fórmula I con Z siendo NH, mientras que el tratamiento con cianamida provee compuestos de fórmula I con Z siendo NHCN.

ESQUEMA IV

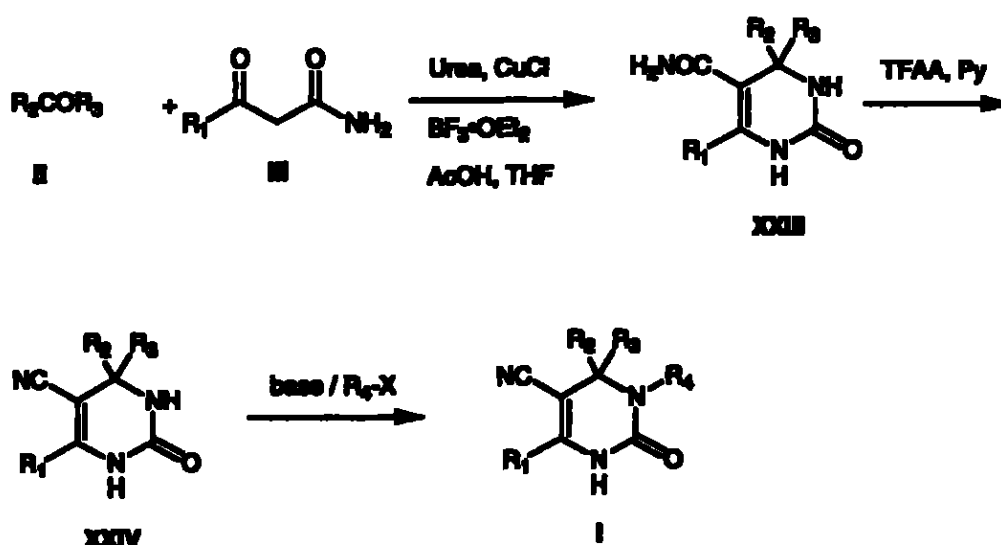


Compuestos de fórmula XVIII pueden prepararse de un 3-amino-3-alkil acrilonitrilo XVII usando los métodos ilustrados en Esquema IV. La reacción de un compuesto de fórmula XVIII con ácido acuoso, tal como ácido clorhídrico, seguido por tratamiento con trietil ortoformato, provee un compuesto de fórmula XVIII. La reacción de un compuesto de fórmula XVIII con O-metil isourea en la presencia de una base tal como trietilamina, provee una pirimidina de fórmula XIX. Pirimidinas de fórmula XIX pueden hacerse reaccionar con especies organometálicas tales como un

reactivo de Grignard, R_3MgBr , en un solvente tal como éter o tetrahidrofurano, para producir una pirimidina de fórmula XX, que es un compuesto de fórmula IX en donde R_2 es H. En analogía con Esquema II, un compuesto de fórmula XX puede convertirse en un compuesto de fórmula XXII, que es un compuesto de fórmula I en la cual R_4 es etoxicarbonilo y R_2 es H.

Alternativamente, compuestos de fórmula I, en donde $Z = O$, pueden prepararse de acuerdo con Esquema V. Siguiendo el procedimiento de E H Hu y colaboradores (J Org Chem, 1998, 63 3454-3457), un compuesto carbonilo de fórmula Ia se condensa con una acilacetamida de fórmula III en la presencia de urea, cloruro cuproso y etearato de borotrifluoruro para producir intermedio XXIII. La deshidratación con anhídrido trifluoroacético en piridina produce nitrilo XXIV. El sustituyente $N3$ se introduce por reacción con R_4X donde R_4 es alquilo o acilo, y X es un grupo saliente, o donde R_4X es un isocianato o haloformato para producir compuestos de fórmula I. La desprotonación se efectúa con una base tal como hidruro de sodio o LDA en solventes aproticos tales como dimetilformamida o tetrahidrofurano.

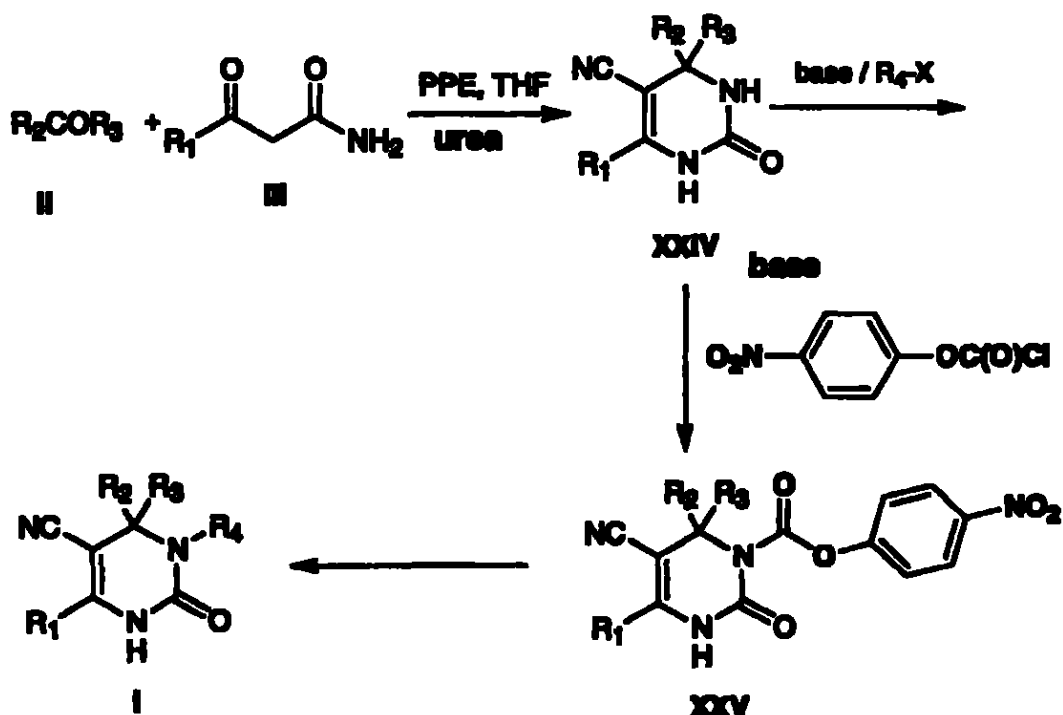
Esquema V



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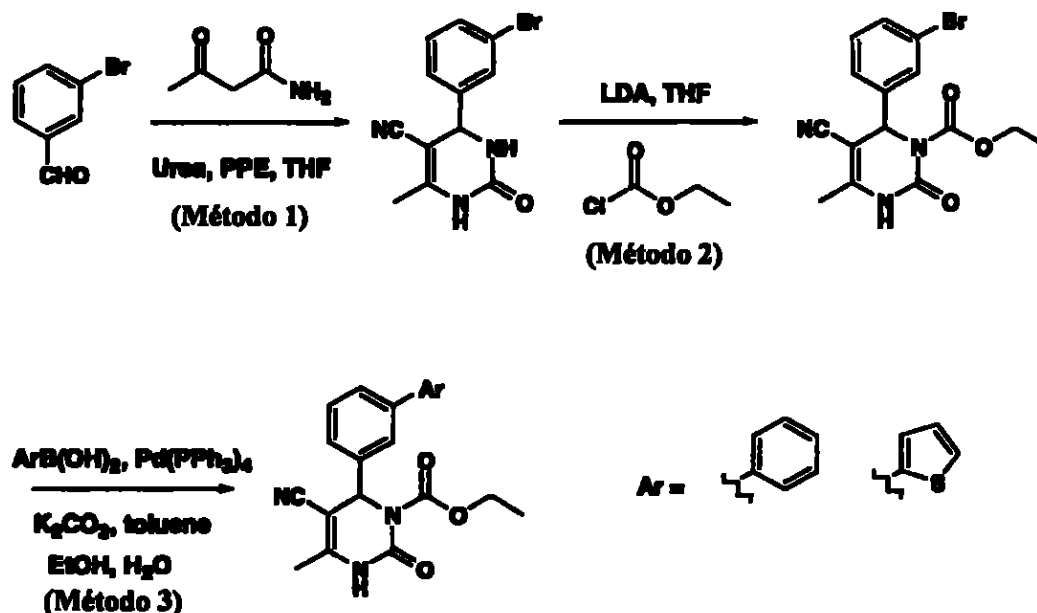
En todavía otro procedimiento, compuestos de fórmula I, en donde Z = O, pueden prepararse de acuerdo con Esquema VI. Un compuesto carbonilo de fórmula II se condensa con una acilacetamida de fórmula III en la presencia de urea y ester de polifosfato para producir directamente nitrilo XXIV. La introducción del sustituyente N3 sigue el procedimiento como se describe en Esquema V. Compuestos de fórmula I, donde R₄ es aminocarbonilo, pueden obtenerse asimismo formando primero un intermedio reactivo tal como un nitrofenilcarbarnato de fórmula XXV, que subsiguientemente se hace reaccionar con una amina.

Esquema VI



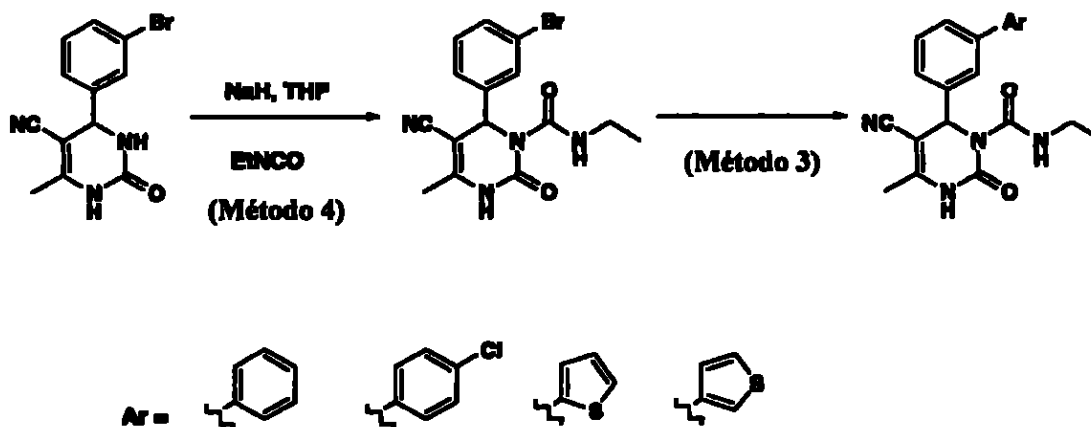
En todos los esquemas anteriores, un derivado de 2-acil acetonitrilo, es decir, R_1COCH_2CN , puede sustituirse por un compuesto de fórmula III, esquemas a continuación

Esquema VII (Ejemplos 116-117)



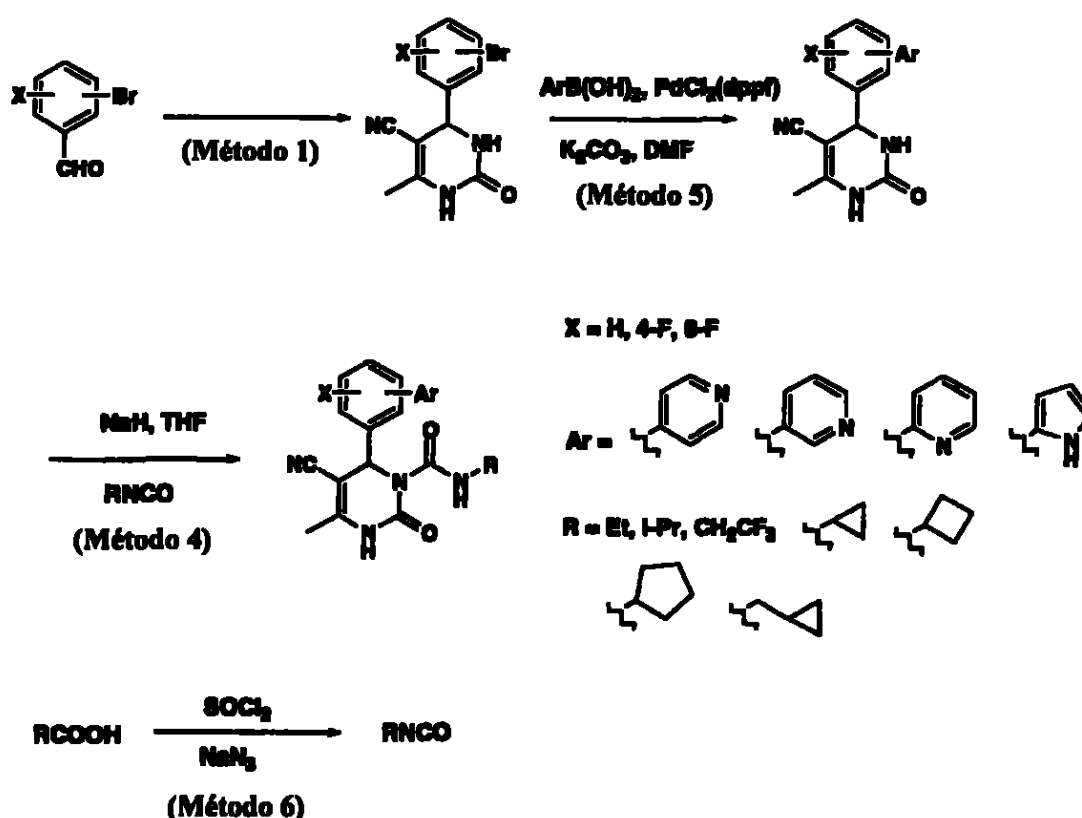
Compuestos de formula Ia donde R₄ es un carbamato pueden elaborarse de acuerdo con Esquema VII Siguiendo el procedimiento de Metodo 1, puede condensarse un aldehído apropiado con acetoacetamida y urea en la presencia de ester polifosforico (PPE) para proporcionar un producto dihidropirimidona en alto rendimiento La reacción de este compuesto con diisopropilamida de litio y cloroformato de etilo siguiendo el procedimiento de Matodo 2 provee predominantemente el N-1 carbamato, el cual experimenta luego una reaccion de acoplamiento de Suzuki catalizada por paladio con un ácido aril o heteroaril bórico para producir compuestos de la presente invención como se describe por el Método 3

Esquema VIII (Ejemplos 118-121)



Similarmente, compuestos de fórmula Ia donde R₄ es urea pueden elaborarse de acuerdo con Esquema VIII. La reacción de un compuesto de dihidropirimidona obtenido siguiendo el procedimiento de Método 1 con hidruro de sodio e isocianato de etilo siguiendo el procedimiento de Método 4 provee exclusivamente la N-1 urea, que entonces experimenta una reacción de acoplamiento de Suzuki catalizada por paladio con un ácido aril o heteroaril bórico para producir compuestos de la presente invención como se describe por Método 3.

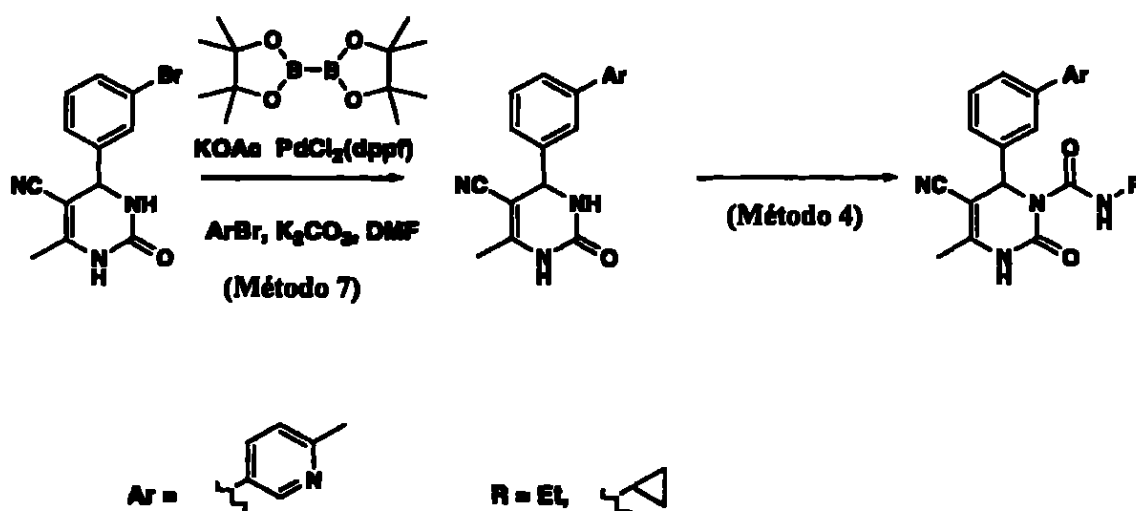
Esquema IX (Ejemplos 122-139, 144-145)



Una secuencia de reacción alternativa se describe en Esquema IX, en donde una reacción de acoplamiento catalizada por paladio puede llevarse a cabo antes de la adición de la fracción de urea exocíclica en la posición N-1 en el anillo de dihidropirimidona. Por consiguiente, el producto de dihidropirimidona de Método 1 puede hacerse reaccionar con un ácido aril o heteroaril bórico en la presencia de un catalizador de paladio siguiendo

Metodo 5 para proporcionar un producto biarilico La subsiguiente reaccion con un isocianato en la presencia de hidruro de sodio siguiendo el procedimiento de Metodo 4 proporciona los compuestos de la presente invencion en buen rendimiento Una variedad de reactivos de isocianato pueden prepararse de los precursores correspondientes de acido carboxilico por tratamiento con cloruro de tionilo y azida de sodio usando Metodo 6

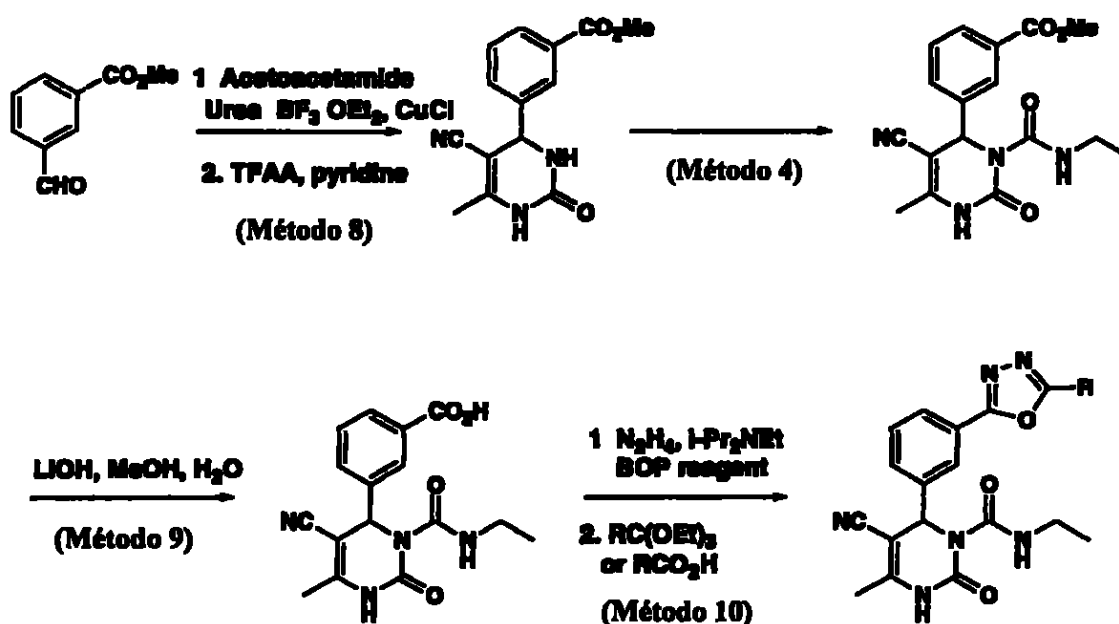
Esquema X (Ejemplos 140-141)



Una variación del proceso de Esquema IX implica la formación del derivado de ácido bórico de la dihidropirimidona preparada por Método 1 y se describe en Esquema X Este derivado de ácido bórico puede prepararse mediante reacción de un halogenuro de arilo apropiado con bis(pinacolato)diboro en la presencia de un catalizador de paladio La subsiguiente reacción con un halogenuro de arilo en la presencia de catalizador de paladio adicional proporciona el compuesto biarilico deseado siguiendo el procedimiento de Método 7 La subsiguiente reacción con un isocianato en la presencia de hidruro de sodio siguiendo el procedimiento de Metodo 4 proporciona los compuestos de la presente invención en buen rendimiento

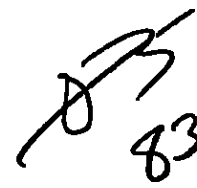


Esquema XI (Ejemplos 142-143)



Compuestos oxadiazol-sustituídos de fórmula IA pueden prepararse de acuerdo con Esquema X. Siguiendo el procedimiento de Método 8, puede condensarse un aldehído de arilo apropiado con acetoacetamida y urea en la presencia de trifluoruro de boro, seguido por deshidratación con anhídrido trifluoroacético para producir un compuesto de dihidropirimidona. La reacción de esta dihidropirimidona con un isocianato e hidruro de sodio siguiendo el procedimiento de Método 4 proporciona la urea N-1 sustituida, la cual puede hacerse reaccionar adicionalmente con hidróxido de litio para proporcionar un ácido carboxílico como se describe por Método 9. El tratamiento del ácido carboxílico con hidrazina y reactivo BOP proporciona la correspondiente hidrazida de acilo, que experimenta ciclización con ortoacetato de trietilo o un ácido alquílico para proporcionar compuestos de la presente invención como se describe por Método 10.

Como se discutió en la sección Antecedentes, Eg5 es una proteína motora similar a la quinesina que facilita la bipolaridad del huso durante la mitosis del ciclo celular. Más específicamente, la proteína Eg5 actúa para seleccionar y juntar microtubulos del huso mitótico durante la mitosis. En



consecuencia, Eg5 participa en la regulacion del ciclo celular a traves del punto de inspección del huso durante la M fase del ciclo Aunque no se quiere comprometerse con ninguna teoría, se cree que los compuestos de la presente invención actúan como inhibidores de Eg5 Esto se teoriza porque los compuestos de la presente invencion inducen un arreglo astral monopolar de microtubulos (el fenotipo monoastral) y se ha demostrado que cuando está ausente la actividad Eg5, se forma el fenotipo monoastral Sin importar el mecanismo de accion, se ha demostrado que los compuestos de la presente invención causan ruptura del huso bipolar, iniciación del punto de inspeccion del huso, detención mitotica, muerte celular programada e inhibición de la proliferación de las celulas tumorales Mas aun, los compuestos de la invencion inducen una detencion del ciclo celular en la mitosis que no es transitorio sino que mas bien avanza hacia la muerte celular programada Los compuestos exhiben ademas gran potencia, induciendo detención mitotica y apoptosis en células humanas *in vitro* en concentraciones en el rango μM bajo o por debajo de el Adicionalmente, en contraste con agentes microtubulares, los compuestos no desestabilizan la inestabilidad dinámica de los microtubulos Por lo tanto, la presente invencion puede tomar como blanco de acción mas especificamente el huso mitotico de las celulas proliferantes, lo cual puede permitir diferentes perfiles de toxicidad que los de los farmacos anti-cáncer existentes

Los compuestos de acuerdo con la invención tienen propiedades farmacológicas, en particular, los compuestos de formula I inducen detencion mitótica y se cree que son inhibidores de Eg5 Los novedosos compuestos de fórmula I son así utiles en la terapia de una variedad de enfermedades proliferativas (incluyendo pero sin limitarse a las enfermedades asociadas con la proteina motora Eg5) tales como cancer, enfermedades autoinmunes, enfermedades virales, enfermedades fungales, trastornos neurodegenerativos y enfermedad cardiovascular

Más específicamente, los compuestos de formula I son utiles en el tratamiento de una variedad de canceres, incluyendo, pero no limitados a, los siguientes

a) carcinoma, incluyendo el cáncer de vejiga, mama, colon, riñón, hígado, pulmon, incluyendo cancer de pulmon de celulas pequeñas, esofago, vesicula biliar, ovario, pancreas, estomago, cuello del utero, tiroides, prostata, y piel, incluyendo carcinoma de celulas escamosas,

b) tumores hematopoyéticos de linaje linfoide, incluyendo leucemia, leucemia linfocítico grave, leucemia linfoblástica grave, linfoma de células B, linfoma de células T, linfoma de Hodgkins, linfoma no-Hodgkins, linfoma de celulas pilosas y linfoma de Burkett,

c) tumores hematopoyeticos de linaje mieloide, incluyendo leucemias mielogenas graves y crónicas, síndrome mielodisplasico y leucemia promielocitica,

d) tumores de origen mesenquimatico, incluyendo fibrosarcoma y rabdomiosarcoma,

e) tumores del sistema nervioso central y periférico, incluyendo astrocitoma, neuroblastoma, glioma y schwannomas, y

f) otros tumores, incluyendo melanoma, seminoma, teratocarcinoma, osteosarcoma, xenoderoma pigmentosum, queratoacantoma, cáncer folicular tiroideo y sarcoma de Kaposi

Debido al papel clave de las proteínas motoras en la regulacion de proliferación celular en general, inhibidores podrian actuar como agentes citostáticos reversibles que pueden ser utiles en el tratamiento de cualquier proceso patologico que caracteriza proliferacion celular anormal, por ejemplo, hiperplasia prostatica benigna, poliposis adenomatosis familiar,

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neurofibromatosis, aterosclerosis, fibrosis pulmonar, artritis, psoriasis, glomerulonefritis, restenosis a raíz de angioplastia o cirugía vascular, formación de heridas hipertroficas, enfermedad intestinal inflamatoria, rechazo de transplantes, choque endotoxico, e infecciones fungales

Compuestos de formulas I y la inducen apoptosis La respuesta apoptótica es aberrante en una variedad de enfermedades humanas Compuestos de fórmula I, como moduladores de apoptosis, serán útiles en el tratamiento de cancer (incluyendo pero sin limitarse a aquellos tipos mencionados aquí anteriormente), infecciones virales (incluyendo pero sin limitarse a herpesvirus, poxvirus, virus Epstein-Barr, virus Sindbis y adenovirus), prevención del desarrollo del SIDA en individuos afectados por VIH, enfermedades autoinmunes (incluyendo pero sin limitarse a lupus sistémico, eritematoso, glomerulonefritis mediada autoinmune, artritis reumatoide, psoriasis, enfermedad intestinal inflamatoria, y diabetes mellitus autoinmune), trastornos neurodegenerativos (incluyendo pero sin limitarse a enfermedad de Alzheimer, demencia relacionada con SIDA, mal de Parkinson, esclerosis lateral amiotrófica, retinitis pigmentosa, atrofia muscular espinal y degeneración cerebelar), síndrome mielodisplásico, anemia aplásica, lesión isquémica asociada con infartos del miocardio, apoplejia y daño por reperfusión, arritmia, aterosclerosis, enfermedades hepáticas relacionadas con el alcohol o inducidas por toxinas, enfermedades hematológicas (incluyendo pero sin limitarse a anemia crónica y anemia aplásica), enfermedades degenerativas del sistemas musculoesquelético (incluyendo pero sin limitarse a osteoporosis y artritis) rinosinusitis sensible a la aspirina, fibrosis quística, esclerosis múltiple, enfermedades renales y dolor producido por cancer

Compuestos de fórmula I y la pueden modular el nivel de síntesis de ADN y ARN celular Estos agentes serían por lo tanto útiles en el tratamiento de infecciones virales (incluyendo pero sin limitarse a VIH, virus de papiloma humano, herpesvirus, poxvirus, virus de Epstein-Barr, virus Sindbis y adenovirus)

Compuestos de formula I y Ia pueden ser utiles en la quimioprevencion del cáncer. Quimioprevencion se define como inhibicion del desarrollo de cáncer invasivo bloqueando el evento mutagenico inicial o bloqueando la progresion de células pre-malignas que ya han sufrido un insulto o inhibiendo la reincidencia del tumor.

Compuestos de fórmula I pueden ser igualmente utiles en inhibir angiogenesis tumoral y metastasis.

La presente invención puede inhibir igualmente otras proteínas motoras, por ejemplo, incluyendo pero sin limitarse a aquellas proteínas motoras humanas que corresponden a Xklp2, MKLP1, CHO1, cromokuinesinas, Nod, Cenp-E, MCAK, miembros de la familia BimC, y miembros de la familia Kar3. Adicionalmente, compuestos usados en los metodos de la presente invencion pueden actuar también como inhibidores de otras proteínas quinesina o similares a quinesina y, así, ser efectivos en el tratamiento de enfermedades asociadas con otras proteínas quinesina o similares a quinesina.

Los compuestos de esta invención pueden ser asimismo utiles en combinacion (administrados juntos o secuencialmente) con tratamientos anti-cáncer conocidos tales como terapia de radiacion o con agentes citotóxicos o citostaticos, tales como por ejemplo, pero no limitados a, agentes interactivos de ADN, tales como cisplatino o doxorubicina, inhibidores de topoisomerasa II, tales como etoposido, inhibidores de topoisomerasa I tales como CPT-11 o topotecan, agentes interactuantes de tubulina, tales como paclitaxel, docetaxel o las epotilonas, de ocurrencia natural o sintetica, agentes hormonales, tales como tamoxifen, inhibidores de sintasa timidilato, tales como 5-fluorouracil, y anti-metabolitos, tales como metotrexato.

Si se formula como una dosis fija, dichos productos de combinacion emplean los compuestos de esta invención en el rango de dosificacion descrito mas adelante y el otro agente farmacéuticamente activo o tratamiento en el rango de dosificación aprobada. Compuestos de fórmulas



I y la pueden administrarse tambien secuencialmente con agentes citotoxicos o anticancer conocidos cuando es inapropiada una formulacion de combinacion La invencion no se limita en la secuencia de administracion, compuestos de formulas I y la pueden administrarse antes o despues de la administracion del agente(s) citotoxico o anti-cancer conocido

ENSAYOS

Las propiedades farmacologicas de los compuestos de esta invencion pueden confirmarse por un numero de ensayos farmacologicos Los ensayos farmacologicos ejemplificados que siguen se han llevado a cabo con los compuestos de acuerdo con la invencion y sus sales Los compuestos de formulas I y la exhibieron actividad antiproliferativa Compuestos preferidos exhiben valores IC_{50} menores o iguales a alrededor de $10 \mu M$

Cultivo de Células

Líneas celulares se mantuvieron en RPMI-1640 mas 10% suero bovino fetal

Ensayo de Proliferacion de 72 Horas

Las células se ponen a una densidad de 3,000-6,000 células /pozo, dependiendo de la línea de célula usada, en una placa de 96 pozos Los cultivos crecieron durante la noche Luego las células se trataron en triplicado curva respuesta-dosis concentracion de siete La concentracion maxima de DMSO nunca excedio 0.5% Las células se expusieron al compuesto durante 72 horas La proliferación se cuantifico usando XTT o MTS de Promega Las líneas celulares de cancer humano de ovario, mama, prostata, pulmon, leucemia, y colorrectal usadas en este ensayo incluían pero no se limitaban a, por ejemplo, A2780S, SKBR3, MDA-MB-231, PC3, LX-1, K562, HT-29, WiDr, HCT-15 y HCT116 Los compuestos de

DZ
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formula I exhibieron actividad en el ensayo de proliferacion celular de 72 horas, inhibiendo la proliferacion celular en una o más de las lineas celulares enumeradas anteriormente con un IC_{50} menor que o igual a alrededor de 10 μM

Ensayo de Crecimiento Clonogenico

La inhibicion de crecimiento de colonias se cuantificó para células de carcinoma de ovario A2780 usando un ensayo clonogénico estandar. Brevemente, 200 células/pozo se sembraron en placas de cultivo de tejido de 6 pozos (Falcon, Franklin Lakes, NJ) y se dejaron unirse durante 18 horas. El medio de ensayo consistía de RPMI-1640 mas 10% suero bovino fetal. A continuacion las celulas se trataron en duplicado con una curva de respuesta-dosis concentración de seis. La concentración máxima de DMSO nunca excedio 0.25%. Las celulas se expusieron al compuesto durante 4, 8 ó 24 horas. A continuacion se retiro el compuesto y las celulas se lavaron con 2 volúmenes de PBS (salina tamponada con fosfato). Seguidamente se reemplazó el medio de crecimiento normal. Las colonias se alimentaron con medio fresco cada tercer día. El numero de colonias se anotaron el dia 10-14 usando una estación de imágenes Optimax. La concentracion de compuesto requerida para inhibir 50% o 90% de formacion de colonias (IC_{50} ó IC_{90} , respectivamente) se determino por analisis de regresión no lineal. El coeficiente de varianza (Desviacion Estandar (SD)/media, $n=3$) = 30%. Cuando se expusieron a células durante 24 horas, los compuestos de formulas I y IA exhibieron actividad en el ensayo de clonogenicidad.

Estudios de Combinacion – Ensayos de Crecimiento Clonogenico

Estudios de combinacion para examinar el uso de los inhibidores de Eg5 de formulas I y Ia en combinacion con otros agentes neoplásicos se llevaron a cabo en esencialmente la misma forma que el ensayo de crecimiento de colonias estándar con la excepcion del tratamiento del compuesto. En los estudios de combinación, las celulas se trataron con un

compuesto de formulas I y Ia y otro agente antineoplásico Los compuestos se administraron simultanea o secuencialmente, tanto el orden de secuencia como la duración del tratamiento (1 a 24 horas) se variaron La evaluacion de los datos se baso en el análisis de isoblograma y la cubierta externa de aditividad, usando la línea de multiplicidad que compara las fracciones de supervivencia de tratamientos de combinación con los de tratamientos de farmaco unico

Analisis de Ciclo Celular

El perfil del ciclo celular de células tratadas con compuestos de formulas I y Ia se monitoreó mediante citometria de flujo Brevemente, celulas de carcinoma de ovario A2780 se sembraron a una densidad de 2×10^5 por pozo en placas estándar de cultivo de 6 pozos y se dejaron crecer durante 17 horas A continuacion las células se expusieron a compuestos de formulas I y Ia a concentraciones variables durante 2 a 24 horas Luego de la exposicion, las poblaciones de celulas se recolectaron, se tiñeron con yoduro de propidio para determinar el contenido de ADN y se tiñeron tambien con el reactivo inmunologico apropiado para biomarcadores de proteinas de mitosis y apoptosis, incluyendo, por ejemplo, anti-fosfo-TreoninaProlina, anti-M Fase Fosfoproteína 2 (MMP2), y anti-p85 PARP Los compuestos de fórmulas I y IA exhibieron actividad en el ensayo de analisis de perfil del ciclo celular, produciendo aumentos significativos en fracciones mitoticas y apoptóticas de la poblacion celular

Ensayos de Inmunocitoquimica

Células de carcinoma de ovario A2780 o células epiteliales de riñon de rata canguro PTK2 se pusieron a una densidad de 200 a 2000 células por pozo en platinas de vidrio de 4 cámaras y se dejaron unir durante la noche Las celulas se trataron con compuestos de formula I y II a concentraciones de 100 nM a 50 μ M durante 4 a 30 horas, se fijaron y permeabilizaron para la tinción subsiguiente Los reactivos de tincion incluan, por ejemplo,

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yoduro de propidio, DAPI, rodamina faloidina, anti- α tubulina, anti- β tubulina, anti- γ tubulina, y los anticuerpos secundarios apropiados marcados fluorescentemente. Se hicieron imágenes de las células mediante microscopia fluorescente y fluorescente confocal. Los compuestos de formulas I y la inhibieron la formación del huso bipolar e indujeron un arreglo monoastral de microtúbulos.

Otro tema de la invención incluye además farmacéuticos para uso como se describe anteriormente incluyendo los que controlan cáncer, inflamación y artritis, que contienen por lo menos un compuesto de la fórmula I o IA como se define más arriba o por lo menos una de sus sales de ácido de aceptación farmacéutica, y el uso de un compuesto de la fórmula I o IA como se define más arriba para la preparación de un fármaco que posee actividad contra enfermedades proliferativas como se describió previamente incluyendo actividad contra cáncer, inflamación y/o artritis.

Los siguientes ejemplos y preparaciones describen la manera y el proceso de elaborar y usar la invención y son ilustrativos más bien que limitantes. Debe entenderse que puede haber otras incorporaciones que caen dentro del espíritu y órbita de la invención como se define por las reivindicaciones adjuntas aquí.

Ejemplo 1

Ácido 5-ciano-3,6-dihidro-4-metil-6-(3-nitrofenil)-2-tio-1-(2H)-pirimidinacarboxílico, 1-etil éster

A Paso 1

Una mezcla de 6.42 g de acetoacetamida, 8.0 g de 3-nitrobenzaldehído, 0.61 ml de ácido acético, y 0.21 ml de piperidina en 30 ml de tolueno se calentó a reflujo. Se utilizó una trampa Dean Stark para mezclar azeotrópicamente el agua producida. Luego de refluirla durante 2 horas, la mezcla de reacción se enfrió a temperatura ambiente, con la aparición de gran cantidad de sólido blanco, se trató con una solución de 300 ml de EtOAc y 25 ml

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MeOH, luego el sólido se extrajo por filtración, se enjuagó con 15 ml de EtOAc dos veces para producir 3.1 g de producto deseado en un rendimiento del 25%

B Paso 2

Una mezcla de 200 mg del compuesto de Ejemplo 1, Paso 1, 198 mg de sal HCl de 2-(4-metoxibencil)-2-tiopseudourea, 84 mg de acetato de sodio en 3.6 ml DMF se calentó a 85 °C durante 15 horas, luego se enfrió a temperatura ambiente. La mezcla de reacción resultante se purificó por HPLC preparativa usando una columna (YMC S5 ODS 20 X 100 mm), la fracción deseada se concentró a sequedad. Se agregó NaHCO₃ saturado (50 ml) y se extrajo con EtOAc (3 x 50 ml), los extractos EtOAc combinados se lavaron con 30 ml de salmuera, se secaron MgSO₄, se filtraron y se concentraron bajo vacío para producir 126.1 mg producto deseado en un rendimiento del 36%

C Paso 3

Una mezcla de el compuesto de Ejemplo 1, Paso 2 (86.5 mg) y reactivo de Burgess (150 mg) en 7.0 ml de THF anhidro se agitó a temperatura ambiente durante 1 hora, se concentró bajo vacío, luego se purificó por HPLC preparativa usando una columna YMC S5 (ODS 20 X 100 mm) para producir 80.8 mg de producto deseado en un rendimiento del 87%

D Paso 4

A una solución del compuesto de Ejemplo 1, Paso 3 (60 mg) y piridina (0.1 ml) en 0.6 ml de CH₂Cl₂, se agregaron 17 µl de etilcloroformato, después de agitar durante 2.5 horas se agregaron otros 22 µl de etilcloroformato, la mezcla de reacción se agitó durante 2 horas, seguidamente se agregó 0.3 ml de ácido trifluoroacético, la mezcla resultante se agitó durante 1 hora más, y se concentró bajo vacío, se diluyó con DMF, MeOH y un poco de CH₂Cl₂,

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se filtró, luego se purificó por HPLC preparativa usando una columna (YMC S5 ODS 20 X 100 mm) para producir 22.5 mg de producto en un rendimiento del 42.7%. MS (M-H)⁺ = 345. HPLC RT (Temperatura Ambiente) = 2.85 min (columna YMC S5 ODS 4.6 x 50 mm, 10-90% metanol acuoso durante 4 minutos que contenía 0.2% ácido fosfórico, 4 ml/min, monitoreando a 220 nm).

Ejemplo 2

Ácido 5-ciano-3,6-dihidro-4-metil-6-(3-nitrofenil)-2-oxo-1-(2H)-pirimidinacarboxílico, 1-etil éster

A Paso 1

10.92 g de NaHCO₃ se agregaron en porciones a una solución de 7.83 g del compuesto de Ejemplo 1, Paso 1 y 7.48 g de sulfato hidrogenado de O-metilisourea en DMF (100 ml), hubo evolución de gas. La mezcla de reacción se agitó durante 2 horas, luego se calentó a 65°C durante la noche, se enfrió a temperatura ambiente, se diluyó con 800 ml de EtOAc, se lavó con agua (2 x 100 ml) y salmuera (1 x 100 ml). La capa orgánica se secó con MgSO₄, se filtró y se concentró bajo vacío. El residuo resultante se trituró en EtOAc-CH₂Cl₂-hexano para producir 5.48 g de producto deseado como un sólido (56%).

B Paso 2

Una mezcla del compuesto de Ejemplo 2, Paso 1 (209 mg) y reactivo de Burgess (274.5 mg) en CH₂Cl₂ (5 ml) y THF (10 ml) se agitó durante la noche. La mezcla de reacción se concentró bajo vacío, se diluyó con 150 ml de EtOAc, luego se lavó con NaHCO₃ saturado (2 x 30 ml) y salmuera (1 x 30 ml), se secó con MgSO₄, se concentró bajo vacío. El residuo resultante se purificó por cromatografía de gel de sílice para producir 136 mg (69.4%) de producto deseado.

C Paso 3

Se agrego 1.23 ml de piridina a una solución de 2.075 g del compuesto de Ejemplo 2, Paso 2 en CH₂Cl₂ (30 ml) bajo argon a 0 °C, luego se agregó lentamente 0.87 ml de cloroformato de etilo. La mezcla de reacción se calentó a temperatura ambiente y se agitó durante 3 horas, se diluyó con una mezcla de NaHCO₃ saturado (50 ml) y salmuera (50 ml), se extrajo con EtOAc tres veces, las capas combinadas se lavaron con salmuera y se secaron MgSO₄, se filtraron y se concentraron bajo vacío, se purificaron por cromatografía de gel de sílice para producir 2.57 g (98%) de producto deseado.

D Paso 4

Se agregaron 2.5 ml de TFA a una solución de 1.44 g del compuesto de Ejemplo 2, Paso 3 en CH₃CN (25 ml) y H₂O (2.5 ml), la mezcla de reacción se agitó durante 2 horas, apareció gran cantidad de sólido blanco. El sólido se extrajo por filtración, se enjuagó con CH₃CN (3 x 20 ml) y hexano (2 x 20 ml), se secó en aire para producir 860 mg (62.2%) del producto deseado. El filtrado se concentró bajo vacío, el sólido se recrystalizó en CH₃CN para producir otros 320 mg (23.2%) de producto. MS (M-H)⁺ = 329. HPLC RT = 2.53 min (columna YMC S5 ODS 4.6 x 50 mm, 10-90% metanol acuoso durante 4 minutos que contenía 0.2% ácido fosfórico, 4 ml/min, monitoreando a 220 nm).

Ejemplo 3

Acido 5-ciano-3,6-dihidro-4-metil-6-(3-nitrofenil)-2-oxo-1-(2H)-pirimidinacarboxílico, 1-etil amida

A Paso 1

A una solución del compuesto de Ejemplo 2, Paso 2 (100 mg, 0.37 mmol) y piridina (0.74 mmol, 18 µL) en dicloroetano (40 mL) se agregó 4-nitrofenil cloroformato (81 mg, 0.40 mmol) y la solución resultante se agitó a

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temperatura ambiente durante 1 5 horas La mezcla de reacción se diluyo con NaHCO_3 saturado (30 mL), se extrajo con acetato de etilo (3 x 50 mL), se secó (MgSO_4) y se concentro in vacuo para proporcionar una espuma blanca Purificación por cromatografía (SiO_2 20% EtOAc/hexano) produjo el compuesto deseado como una espuma incolora (99 mg, 62%)

B Paso 2

A una solución del compuesto de Ejemplo 3, Paso 1 (12 mg, 27 μmol) en THF (0 1 mL) se agrego 2M etilamina en solución de THF (15 μl , 30 mmol) en una porción a temperatura ambiente y la solución amarilla resultante se agitó 30 minutos Dilución de la mezcla de reacción con metanol (1 8 mL) produjo un sólido amarillo que se recogió por filtración con succión y se purificó por HPLC preparativa para proporcionar el compuesto del título como un sólido blanco (20 mg, 22%)

En contraste con el método de Ejemplo 2 anterior, en este caso el grupo 2-metoxi se hidrolizo durante el aislamiento y la purificación para proporcionar el anillo dihidropirimidinona sin necesidad de tratamiento con TFA (Ejemplo 2, Paso 4)

Ejemplo 4

5-Ciano-3,6-dihidro-4-metil-6-(3-nitrofenil)-2-oxo-1-(1-oxobutil)-(2H)-pirimidina

A Paso 1

23 7 μl de cloruro de butirilo se agregaron a una solución de 52 mg del compuesto de Ejemplo 2, Paso 2 y 0 15 ml de piridina en 0 6 ml de CH_2Cl_2 anhidro, la mezcla de reacción se agitó durante 1 hora, luego se agregaron 24 μl de cloruro de butirilo, la reacción se agito durante 1 5 horas, se purifico por HPLC preparativa usando una columna YMC S5 (ODS 20 x 100 mm) para producir 30 mg del producto deseado

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95**B Paso 2**

Una solución de 30 mg del compuesto de Ejemplo 4, Paso 1, 0.2 ml de H₂O y 0.2 ml de TFA en 1.2 ml CH₃CN se agitó durante 1.5 hora, se agregó otro 0.1 ml de TFA y se agitó durante 2.5 horas más. La mezcla de reacción se concentró bajo vacío, y se purificó por HPLC preparativa usando una columna YMC S5 (ODS 20 x 100 mm) para producir 11.8 mg del producto deseado. MS (M-H)⁺ = 327. HPLC RT = 3.06 minutos (columna YMC S5 ODS 4.6 x 50 mm, 10-90% metanol acuoso durante 4 minutos que contenía 0.2% ácido fosfórico, 4 ml/min, monitoreando a 220 nm).

Ejemplo 5

enantiómero Ácido 5-ciano-3,6-dihidro-4-metil-6-(3-nitrofenil)-2-oxo-1-(2H)-pirimidinacarboxílico, 1-etil ester (enantiómero A)

53 mg del compuesto de Ejemplo 2, Paso 4 se disolvieron en EtOH absoluto, separación quiral preparativa se llevó a cabo usando una columna Chiralcel OD-H S5 (4.6 x 250 mm), se obtuvieron 20 mg de enantiómero A y 27 mg de enantiómero B. MS (M-H)⁺ = 329. HPLC-Chiral RT = 10.44 minutos (Chiralcel OD-H, S5, columna 4.6 x 250 mm, 10% MeOH / 10% EtOH / Heptano, 1.0 ml/min, monitoreando a 220 nm, 94.7% ee).

Ejemplo 6

enantiómero Ácido 5-ciano-3,6-dihidro-4-metil-6-(3-nitrofenil)-2-oxo-1-(2H)-pirimidinacarboxílico, 1-etil ester (enantiómero B)

MS (M-H)⁺ = 329. HPLC-Chiral RT = 12.92 min (Chiralcel OD-H, S5, columna 4.6 x 250 mm, 10% MeOH / 10% EtOH / Heptano, 1.0 ml/min, monitoreando a 220 nm, 99.64% ee).

Ejemplo 7

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Acido 5-ciano-3,6-dihidro-4-metil-6-(3-aminofenil)-2-oxo-1-(2H)-pirimidinacarboxílico, 1-etil éster

Una solución de 12 mg del compuesto de Ejemplo 1, Paso 4 en etanol se trató con 100 mg de cloruro de estaño (II) y se calentó a reflujo bajo argón durante 90 minutos, la reacción se enfrió y se extinguió con solución de NaHCO_3 saturado y se extrajo con EtOAc (3 x 50 ml) La capa orgánica combinada se lavó con H_2O , se secó Na_2SO_4 y se concentró bajo vacío Se trituró con hexano y éter para producir 8 mg de producto crudo, el cual se purificó adicionalmente por HPLC preparativa para proporcionar 3 mg de producto deseado como sal de TFA MS $(\text{M}+\text{H})^+ = 301$ HPLC RT = 1.685 minutos (columna YMC S5 ODS 4.6 x 50 mm, 10-90% metanol acuoso durante 4 minutos que contenía 0.1% de TFA, 4 ml/min, monitoreando a 220 nm)

Ejemplo 8**Ácido 5-ciano-3,6-dihidro-4-metil-6-(3-(N,N-dimetil)aminofenil)-2-oxo-1-(2H)-pirimidinacarboxílico, 1-etil éster**

A una solución de 12 mg del compuesto de Ejemplo 7 en CH_3CN (1 ml) se agregó paraformaldehído (40 mg), cianoborohidruro de sodio (30 mg) seguido por 2 gotas de ácido acético La mezcla de reacción se agitó a temperatura ambiente durante 2 horas, luego se extinguió con solución de NaHCO_3 saturado y se extrajo con EtOAc tres veces La capa orgánica combinada se lavó con salmuera, se secó Na_2SO_4 y se concentró bajo vacío El residuo resultante se purificó por HPLC preparativa para producir 3.2 mg de producto deseado como sal de TFA MS $(\text{M}+\text{H})^+ = 329$ HPLC RT = 1.76 minutos (columna YMC S5 ODS 4.6 x 50 mm, 10-90% metanol acuoso durante 4 minutos que contenía 0.1% de TFA, 4 ml/min, monitoreando a 220 nm)

y 7

Ejemplos 9 a 15 se prepararon usando los métodos de Ejemplo 2 con la sustitución de un benzaldehído apropiado en Paso 1

Ejemplo 9

Ácido 5-ciano-3,6-dihidro-4-metil-6-(3-trifluorometilfenil)-2-oxo-1-(2H)-pirimidinacarboxílico, 1-etil éster

HPLC-HI 100% a 2.84 min (columna YMC S5 ODS 4.6 x 50 mm, 10 - 90% metanol acuoso durante 4 minutos que contenía 0.1% de TFA, 4 ml/min, monitoreando a 220 nm) MS $[M+H]^+ = 354$

Ejemplo 10

Ácido 5-ciano-3,6-dihidro-4-metil-6-(2,3-diclorofenil)-2-oxo-1-(2H)-pirimidinacarboxílico, 1-etil éster

HPLC-HI 100% a 3.2 min (columna YMC S5 ODS 4.6 x 50 mm, 10 - 90% metanol acuoso durante 4 minutos que contenía 0.1% de TFA, 4 ml/min, monitoreando a 220 nm) MS $[M-H] = 352$

Ejemplo 11

Ácido 5-ciano-3,6-dihidro-4-metil-6-(3-metoxifenil)-2-oxo-1-(2H)-pirimidinacarboxílico, 1-etil éster

HPLC-HI 100% a 2.42 min (columna YMC S5 ODS 4.6 x 50 mm, 10 - 90% metanol acuoso durante 4 minutos que contenía 0.1% de TFA, 4 ml/min, monitoreando a 220 nm) MS $[M+H]^+ = 316$

Ejemplo 12

Ácido 5-ciano-3,6-dihidro-4-metil-6-(3,5-diclorofenil)-2-oxo-1-(2H)-pirimidinacarboxílico, 1-etil éster

HPLC-HI 87% a 3.26 min (columna YMC S5 ODS 4.6 x 50 mm, 10 - 90% metanol acuoso durante 4 minutos que contenía 0.1% de TFA, 4 ml/min, monitoreando a 220 nm) MS $[M-H] = 352$

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98**Ejemplo 13**

Acido 5-ciano-3,6-dihidro-4-metil-6-(3, 4-diclorofenil)-2-oxo-1-(2H)-pirimidinacarboxílico, 1-etil éster

HPLC-HI 100% a 3 197 min (columna YMC S5 ODS 4 6 x 50 mm, 10 - 90% metanol acuoso durante 4 minutos que contenía 0 1% de TFA, 4 ml/min, monitoreando a 220 nm) MS [M-H] = 352

Ejemplo 14

Ácido 5-ciano-3,6-dihidro-4-metil-6-(3-cianofenil)-2-oxo-1-(2H)-pirimidinacarboxílico, 1-etil éster

HPLC-HI 93% a 2 32 min (columna YMC S5 ODS 4 6 x 50 mm, 10 - 90% metanol acuoso durante 4 minutos que contenía 0 1% de TFA, 4 ml/min, monitoreando a 220 nm) MS [M+H]⁺ = 311

Ejemplo 15

Acido 5-ciano-3,6-dihidro-4-metil-6-(4-metoxifenil)-2-oxo-1-(2H)-pirimidinacarboxílico, 1-etil éster

HPLC-HI 100% a 2 55 min (columna YMC S5 CDS 4 6 x 50 mm, 10- 90% metanol acuoso durante 4 minutos que contenía 0 1% de TFA , 4 ml/min monitbreando a 220nm) MS [M+H]⁺ = 316

Ejemplo 16

Acido 5-ciano-3,6-dihidro-4-metil-6-(4-metilfenil)-2-oxo-1-(2H)-pirimidinacarboxílico, 1-etil éster

A Paso 1

Una solución turbia de 3-aminocrotononitrilo (41 g, 0 5 mol) en Et₂O (500 ml) se agrego gota a gota a la solución 15% HCl (115 ml) a 0°C durante 30 minutos con agitación vigorosa, y la mezcla de reacción se agito a 0°C

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durante 15 minutos. Seguidamente se separó la solución acuosa, se extrajo con Et₂O (2 x 125 ml), se secaron las fases orgánicas combinadas Na₂SO₄. Trietil ortoformato (83 ml) en un matraz de tres cuellos de 500 ml equipado con embudo de adición y juego de destilación se agitó en baño de aceite a 60°C - 65°C, la anterior solución de éter se agregó gota a gota de modo que la tasa de adición fuera igual a la tasa de destilación. Se agregaron 83 ml adicionales de trietil ortoformato a la reacción cuando la adición de la solución de éter estaba semiconcluida, se incrementó lentamente la temperatura del baño de aceite a 100°C, y la mezcla de reacción se agitó luego durante 5 horas. La destilación produjo 26.6 g (38%) del producto sólido rojo deseado a 150- 155°C/ 2mm Hg.

B Paso 2

A una mezcla de O-metilisourea sulfato (9.9 g, 80 mmol), se agregó el compuesto de Ejemplo 16, Paso 1 (7.4 g, 53 mmol) y etanol (90 ml). Et₃N (11 ml, 80 mmol). La mezcla se agitó a temperatura ambiente durante 15 minutos, luego se agitó a 66°C durante 3 horas, y se concentró para retirar el EtOH. Se agregaron EtOAc (80 ml) y H₂O (80 ml), la capa acuosa se separó y se extrajo con EtOAc (2 x 80 ml), la capa orgánica combinada se secó Na₂SO₄, concentró para producir un sólido café, que se disolvió en EtOAc, se filtró a través de una almohadilla de gel de sílice, se lavó con EtOAc/heptano (1/1) para eliminar el color oscuro, y el filtrado combinado se concentró. El sólido así obtenido se recrystalizó en heptano / EtOAc para producir 5.18 g de un cristal amarillo en un rendimiento del 65%.

C Paso 3

Una solución de bromuro de p-tolilmagnesio en éter (1M, 1 ml, 1 mmol) se agregó gota a gota a una solución del compuesto de Ejemplo 16, Paso 2 (75 mg, 0.5 mmol) en THF (2 ml) a 0°C bajo argón. La mezcla de reacción se agitó a la temperatura durante 1.5 horas, se agregaron otros 3 ml de reactivo

de Grignard a -78°C , la reacción se calentó lentamente a temperatura ambiente y se agitó durante 2 minutos. Se agregaron NH_4Cl saturado (5 ml) H_2O (5 ml), la mezcla se extrajo con EtOAc (2 x 15 ml), la capa orgánica combinada se secó, concentró y cromatografió en gel de sílice para producir 45.6 mg de producto deseado en un rendimiento del 91%.

D Paso 4

A una solución del compuesto de Ejemplo 16, Paso 3 (109 mg, 0.45 mmol) se agregó piridina (0.2 ml, 2.5 mmol) en CH_2Cl_2 seco (5 ml) seguido por cloroformato de etilo (0.1 ml, 1.05 mmol), y la mezcla de reacción resultante se agitó a temperatura ambiente durante la noche. Se agregó MeOH, la mezcla resultante se agitó durante 15 minutos, se concentró, y cromatografió en columna de gel de sílice para producir 100 mg del producto deseado como un aceite incoloro (71%).

E Paso 5

Una mezcla de el compuesto de Ejemplo 15, Paso 4 (100 mg, 0.32 mmol) H_2O (0.7 ml), CH_3CN (0.5 ml) y TFA (7 ml) se agitó a temperatura ambiente durante 2 horas. La solución se concentró luego para retirar CH_3CN , se agregó NaHCO_3 saturado para hacer básica la mezcla, se filtró el precipitado sólido blanco, se lavó con H_2O , y se secó para producir el producto deseado (64 mg). El producto crudo se secó y recristalizó a partir de EtOH / H_2O para producir otros 20 mg producto deseado como un sólido blanco. MS $(\text{M}+\text{H})^+ = 300$ HPLC RT = 3.40 min (columna YMC S5 ODS 4.6 x 50 mm, 10-90% metanol acuoso durante 4 minutos que contenía 0.2% ácido fosfórico, 4 ml/min, monitoreando a 220 nm).

Ejemplo 17

Ácido **5-ciano-3,6-dihidro-4-metil-6-ciclohexil-2-oxo-1-(2H)-pirimidinacarboxílico, 1-etil éster**

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A una solución del compuesto de Ejemplo 16, Paso 2 (30 mg, 0.2 mmol) en THF (1.2 ml) se agregó cloruro de ciclohexilmagnesio (2 M en éter, 1.0 ml, 2 mmol) a -44°C bajo argón, la reacción se calentó lentamente a temperatura ambiente, y se agitó durante 10 minutos. Se agregó NH_4Cl saturado, la mezcla resultante se extrajo varias veces con EtOAc, la capa orgánica combinada se secó, se filtró a través de una almohadilla de gel de sílice, y se concentró para producir aceite amarillo. El aceite se disolvió en CH_2Cl_2 (2 ml), luego se agregaron piridina (80 μl , 0.9 mmol) y cloroformato de etilo (50 μl , 0.5 mmol), la mezcla se agitó a temperatura ambiente durante 30 minutos, se agitó durante otros 10 minutos tras lo cual se agregaron H_2O (25 μl) y EtOAc, y la mezcla se secó sobre Na_2SO_4 , se filtró a través de una almohadilla de gel de sílice, y se concentró para producir aceite amarillo. El aceite se disolvió en CH_3CN (2 ml), se agregaron H_2O (0.3 ml) y TFA (0.2 ml), y la mezcla se agitó a temperatura ambiente durante 2 horas. Se agregaron solución de NaHCO_3 saturado y EtOAc, la capa acuosa se separó y se extrajo con EtOAc, y la capa orgánica combinada se secó sobre Na_2SO_4 , se concentró y se cromatógrafo en gel de sílice para producir 35 mg del producto deseado como espuma amarilla (60%). MS $(\text{M}+\text{H})^+ = 392$ HPLC RT = 3.60 min (columna YMC S5 ODS 4.6 x 50 mm, 10-90% metanol acuoso durante 4 minutos que contenía 0.2% ácido fosfórico, 4 ml/min, monitoreando a 220 nm)

Ejemplo 18

Ácido 5-ciano-3,6-dihidro-4-metil-6-fenil-2-oxo-1-(2H)-pirimidina carboxílico, 1-etil ester

A una solución del compuesto de Ejemplo 16, Paso 2 (55 mg, 0.37 mmol) en THF seco (2 ml) se agregó bromuro de fenilmagnesio (2 M en THF, 2 ml, 4 mmol) gota a gota a -78°C bajo argón. Luego de la adición, la reacción se calentó lentamente a temperatura ambiente y se agitó durante alrededor de 10 minutos, hasta la desaparición del material inicial. Se

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agregaron solución de NH_4Cl saturado y H_2O , la mezcla se extrajo con EtOAc durante dos veces, y la capa orgánica combinada se seco sobre Na_2SO_4 , se concentró y se cromatógrafo en gel de sílice para producir un intermedio sólido. El sólido se disolvió en CH_2Cl_2 (5 ml), se agregaron piridina (0.15 ml, 1.8 mmol) y cloroformato de etilo (0.1 ml, 1 mmol), y la mezcla de reacción se agitó a temperatura ambiente durante 0.5 horas. La reacción se extinguió con 50 μl de H_2O , se diluyó con 5 ml de EtOAc, la mezcla resultante se seco sobre Na_2SO_4 , se filtró a través de una columna de gel de sílice para producir el intermedio como un aceite. El aceite se disolvió en CH_3CN (5 ml), se agregó H_2O (0.5 ml) y TFA (0.4 ml), la mezcla de reacción se agitó durante 1.5 horas, y se concentró in vacuo. Se agregó solución de NaHCO_3 saturado para neutralizar la mezcla, y el precipitado se filtró luego y se secó por aire. Recristalización en EtOAc / heptano para producir 70 mg de producto sólido en rendimiento del 66%. MS $(\text{M}+\text{H})^+ = 286$ HPLC RT = 1.28 min (Phenom-Prime S5 C18 4.6 x 30 mm, 10-90 % metanol acuoso durante 2 minutos que contenía 0.1 % TFA, 5 ml/min, monitoreando a 220 nm).

Ejemplos 19 a 24 se prepararon usando el método de Ejemplo 18 con la sustitución de un halogenuro de arilmagnesio apropiado.

Ejemplo 19

Ácido **5-ciano-3,6-dihidro-4-metil-6-(2-metilfenil)-2-oxo-1-(2H)-pirimidinacarboxílico, 1-etil éster**

MS $(\text{M}+\text{H})^+ = 300$ HPLC RT = 1.41 min (Phenom-Prime S5 C18 4.6 x 30 mm, 10-90 % metanol acuoso durante 2 minutos que contenía 0.1 % TFA, 5 ml/min, monitoreando a 220 nm).

Ejemplo 20

Ácido **5-ciano-3,6-dihidro-4-metil-6-(3-clorofenil)-2-oxo-1-(2H)-pirimidinacarboxílico, 1-etil éster**

MS (M+H)⁺ = 320 HPLC RT = 1.43 min (Phenom-Prime S5 C18 4.6 x 30 mm, 10-90 % metanol acuoso durante 2 minutos que contenía 0.1 % TFA, 5 ml/min, monitoreando a 220 nm)

Ejemplo 21

Ácido 5-ciano-3,6-dihidro-4-metil-6-(3-fluorofenil)-2-oxo-1-(2H)-pirimidinacarboxílico, 1-etil éster

MS (M+H)⁺ = 304 HPLC RT = 1.29 min (Phenom-Prime S5 C18 4.6 x 30 mm, 10-90 % metanol acuoso durante 2 minutos que contenía 0.1 % TFA, 5 ml/min, monitoreando a 220 nm)

Ejemplo 22

Ácido 5-ciano-3,6-dihidro-4-metil-6-(4-clorofenil)-2-oxo-1-(2H)-pirimidinacarboxílico, 1-etil éster

MS (M+H)⁺ = 320 HPLC RT = 1.44 min (Phenom-Prime S5 C18 4.6 x 30 mm, 10-90 % metanol acuoso durante 2 minutos que contenía 0.1 % TFA, 5 ml/min, monitoreando a 220 nm)

Ejemplo 23

Ácido 5-ciano-3,6-dihidro-4-metil-6-(4-fluorofenil)-2-oxo-1-(2H)-pirimidinacarboxílico, 1-etil éster

MS (M+H)⁺ = 304 HPLC RT = 3.21 min (YMC S5 ODS columna 4.6 x 50 mm, 10-90% metanol acuoso durante 4 minutos que contenía 0.2% ácido fosfórico, 4 ml/min, monitoreando a 220 nm)

Ejemplo 24

Ácido 5-ciano-3,6-dihidro-4-metil-6-(2-fluorofenil)-2-oxo-1-(2H)-pirimidinacarboxílico, 1-etil éster

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MS (M+H)⁺ = 304 HPLC RT = 3.05 min (columna YMC S5 ODS 4.6 x 50 mm 10-90% metanol acuoso durante 4 minutos que contenia 0.2% ácido fosforico, 4 ml/min, monitoreando a 220 nm)

Ejemplo 25

Acido 6-(3,5-bis-trifluorometilfenil)-5-ciano-4-metil-2-oxo-3,6-dihidro-2H-pirimidina-1-carboxílico etil éster

A Paso 1

Amida de ácido 4-(3,5-bis-trifluorometilfenil)-6-metil-2-oxo-1,2,3,4-tetrahidropirimidina-5-carboxílico Una mezcla de 3,5-bis(trifluorometil)benzaldehído (2.42 g, 10.0 mmol), acetoacetamida (1.01 g, 10.0 mmol), urea (0.90 g, 15.0 mmol), cloruro de cobre (0.1 g, 1.0 mmol), eterato de trifluoruro de boro (0.09 mL), AcOH (0.04 mL), y THF (20 mL) se calentó a 65 °C durante 18 horas y se enfrió a temperatura ambiente. Los precipitados resultantes se recogieron mediante filtración de vacío, se lavaron con THF, y se secaron con aire para producir el compuesto del título como un sólido blancuzco (1.33 g, 36%)

B Paso 2

4-(3,5-Bis-trifluorometilfenil)-6-metil-2-oxo-1,2,3,4-tetrahidropirimidina-5-carbonitrilo A una mezcla de compuesto de Paso 1-(1.10 g, 3.0 mmol) y piridina (12 mL) a 0 °C se agregó anhídrido trifluoroacético (1.3 mL, 9.0 mmol) lentamente durante 10 minutos. La mezcla de reacción se volvió una solución café claro y se agitó durante 18 horas, luego se vertió en agua. Los precipitados blancuzcos resultantes se recogieron mediante filtración de vacío, se lavaron con agua, y se secaron con aire para producir el compuesto del título como un sólido café claro (1.06 g, 100%)

C Paso 3

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Ácido 6-(3,5-bis-trifluorometilfenil)-5-ciano-4-metil-2-oxo-3,6-dihidro-2H-pirimidina-1-carboxílico etil ester A una solución de compuesto de Paso 2 (60 0 mg, 0 17 mmol) en THF (2 mL) enfriada a -78 °C se agrego LDA (0 15 mL, 0 30 mmol, 2 0 M en hexanos) La mezcla resultante se agito a -78 °C durante 15 minutos, se calentó a -25 °C durante 15 minutos, se volvió a enfriar a -78 °C y se agregó cloroformato de etilo (20 µl, 0 20 mmol) mediante una jeringa. La mezcla de reacción se agito a -78 °C durante 15 minutos, se calentó gradualmente a temperatura ambiente y se agitó durante 1 hora, se extinguió con MeOH y se concentró in vacuo El residuo se purificó por HPLC preparativa (metanol/agua), se combinaron fracciones del producto y se concentraron in vacuo para proporcionar el compuesto del título como un sólido blancuzco (28 4 mg, 40%) ¹H-NMR (DMSO-d₆, 400 MHz) δ 10 64 (s, 1 H), 8 19 (s, 1 H), 7 93 (s, 2H), 6 15 (s, 1 H), 4 17 (m, 2H), 2 10 (s, 3 H), 1 17 (t, 3 H, J= 7 0 Hz) LC/MS (ES+) 444 (M+Na)⁺

Ejemplo 26

Ácido 6-butil-5-ciano-4-metil-2-oxo-3,6-dihidro-2H-pirimidina-1-carboxílico etil ester

A Paso 1

4-Hexil-6-metil-2-oxo-1,2,3,4-tetrahidropirimidina-5-carbonitrilo

Ester de polifosfato (1 15 g, 3 89 mmol, 0 30 eq) se agrego a un tubo sellado que contenía una solución de urea (1 17 g, 19 4 mmol), valeraldehído (1 38 ml, 12 9 mmol) y acetoacetamida (1 31 g, 12 9 mmol) en THF (15 mL) bajo argón y se calentó a 75°C durante tres horas La mezcla de reacción se enfrió a temperatura ambiente, se agregó éster de polifosfato (8 80 g, 29 8 mmol) y la mezcla de reacción se calentó a 85°C durante cuatro horas La mezcla de reacción se enfrió a temperatura ambiente y se vertió en hielo La solución acuosa se neutralizó con 1N

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NaOH y se extrajo con cloroformo (3X100 mL) Las capas orgánicas combinadas se secaron (Na_2SO_4), se filtraron y concentraron bajo vacío para producir el compuesto del título (0 940 g, 97%) HRMS 192 1143 (M-H) El producto se utilizó en el siguiente paso sin purificación adicional

B Paso 2

Ácido 6-butir-5-ciano-4-metil-2-oxo-3,6-dihidro-2H-pirimidina-1-carboxílico etil éster LDA (0 585 mL, 1 17 mmol, 2 0 M en hexano) se agregó gota a gota a una solución de compuesto de Paso 1 (0 150 g, 0 777 mmol) en THF (5mL) a -78°C La mezcla de reacción se agitó a -78°C durante veinte minutos y se agregó cloroformato de etilo (0 111 mL, 1 17 mmol) en una porción La mezcla de reacción se dejó calentar a temperatura ambiente y se agitó durante dieciséis horas La mezcla de reacción se extinguió con cloruro de amonio saturado (35 ml) y la solución se extrajo con cloroformo (3X100 ml) Las capas orgánicas combinadas se secaron (Na_2SO_4), se filtraron y se concentraron bajo vacío El residuo se purificó por cromatografía de destello (eluyendo 2/1 acetato de etilo/hexanos) para proporcionar el compuesto del título (0 110 g, 53%) como un sólido

$^1\text{H-NMR}$ (DMSO-d_6 , 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) $^+$

Ejemplo 27

Ácido 5-ciano-4-metil-6-(3-nitrofenil)-2-oxo-3,6-dihidro-2H-pirimidina-1-carboxílico metilamida

A Paso 1

Ácido 5-ciano-4-metil-6-(3-nitrofenil)-2-oxo-3,6-dihidro-2H-pirimidina-1-carboxílico 4-nitrofenil éster A una detención de 6-metil-4-(3-nitro-

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fenil)-2-oxo-1,2,3,4-tetrahidro-pirimidina-5-carbonitrilo (0.43 g, 1.7 mmol, preparada por el metodo descrito en Ejemplo 26, Paso 1, en 77 % de rendimiento) en THF (15 mL) a -78 °C se agregó LDA (1.25 mL, 2.5 mmol, 2.0 M en hexanos). La mezcla resultante se agito a -78 °C durante 15 min, se calentó a -25 °C durante 15 minutos, se volvió a enfriar a -78 °C y se agregó 4-nitrofenil cloroformato (0.50 g, 2.5 mmol) en una porcion. La mezcla de reacción se agito a -78 °C durante 15 minutos, se calentó gradualmente a temperatura ambiente, se extinguió con agua y se extrajo con acetato de etilo. El extracto orgánico se lavó con salmuera, se seco (MgSO₄) y se concentro in vacuo. El residuo se purifico por cromatografía de columna de destello en gel de sílice usando 50% a 70% acetato de etilo-hexano como eluyente para producir el compuesto del titulo como un sólido amarillo claro (0.38 g, 53%).

B Paso 2

Ácido 5-ciano-4-metil-6-(3-nitrofenil)-2-oxo-3,6-dihidro-2H-pirimidina-1-carboxílico metilamida A una solución de compuesto del Paso 1 (12.5 mg, 0.03 mmol) en THF (1 mL) se agregó metilamina (4.1 µL, 0.033 mmol, 8 M en EtOH). La mezcla de reacción se agito durante 2 horas y se concentró in vacuo. El residuo se purifico por HPLC preparativa (metanol/agua). Se combinaron fracciones del producto, se concentraron in vacuo y liofilizaron para producir el compuesto del título como un sólido incoloro (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)⁺

Ejemplo 28

Ácido 5-ciano-4-metil-2-oxo-6-fenil-3,6-dihidro-2H-pirimidina-1-carboxílico etilamida A una solución de 6-metil-2-oxo-4-fenil-1,2,3,4-

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tetrahidropirimidina-5-carbonitrilo (100 mg, 0.47 mmoles, obtenida en rendimiento del 65 % por el procedimiento descrito en Ejemplo 26, Paso 1) en 4 mL de tetrahidrofurano bajo argón a temperatura ambiente se agregó hidruro de sodio libre de aceite (17 mg, 0.70 mmoles). Después de agitar durante diez minutos, se agregó isocianato de etilo (50 mg, 0.70 mmoles). La mezcla de reacción se diluyó con acetato de etilo y se lavó con ácido cítrico diluido, agua y salmuera saturada. El extracto orgánico (sulfato de magnesio anhidro) seco se concentró *in vacuo* y el producto se purificó por cromatografía de destello en gel de sílice, eluyendo con acetato de etilo/hexano (3/2) para producir 100 mg (75 %) del compuesto del título como un sólido blanco. 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, 2H), 2.08 (s, 3 H), 1.03 (t, J = 7.2 Hz, 3 H). LC/MS (ES+) 285 (M+H)⁺

Ejemplo 29

Ácido 5-ciano-6-(3,5-diclorofenil)-4-metil-2-oxo-3,6-dihidro-2H-pirimidina-1-carboxílico 2-metoxi-etil éster

Usando 3,5-diclorobenzaldehído y siguiendo el procedimiento descrito en Ejemplo 2, se obtuvo el compuesto del título en un rendimiento total del 3 %. 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, 2H), 3.54 (m, 2H), 3.25 (s, 3 H), 2.11 (s, 3 H). LC/MS (ES+) 384 (M+H)⁺

Ejemplo 30

Ácido 5-ciano-4-metil-2-oxo-6-(3-trifluorometilfenil)-3,6-dihidro-2H-pirimidina-1-carboxílico etilamida

Usando 3-trifluorometilbenzaldehído y siguiendo una modificación del procedimiento descrito en Ejemplo 2, se obtuvo el compuesto del título en un rendimiento general del 3 %.

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

Ejemplo 31

Ácido 5-ciano-6-(3,5-diclorofenil)-4-metil-2-oxo-3,6-dihidro-2H-pirimidina-1-carboxílico etilamida

Usando 3,5-diclorobenzaldehído y siguiendo una modificación del procedimiento descrito en Ejemplo 2, se obtuvo el compuesto del título en un rendimiento general del 5 %

¹H-NMR (DMSO-d₆, 400 MHz) δδ 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, 2H), 2.09 (s, 3 H), 1.03 (t, 3 H, J = 7.0 Hz) LC/MS (ES+) 353 (M+H)⁺, 375 (M+Na)⁺

Ejemplo 32

3-Butiril-4-(3,5-diclorofenil)-6-metil-2-oxo-1,2,3,4-tetrahidropirimidina-5-carbonitrilo

Usando 3,5-diclorobenzaldehído y siguiendo el procedimiento descrito en Ejemplo 2, se obtuvo el compuesto del título en un rendimiento general del 7 %

¹H-NMR (DMSO-d₆, 500 MHz) δδ 10.63 (s, 1 H), 7.63 (t, 1H, 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, 2H), 2.11 (s, 3H), 0.86 (t, 3H, J=7.1 Hz)

Ejemplo 33

Ácido 5-ciano-4-metil-2-oxo-6-(3-trifluorometilfenil)-3,6-dihidro-2H-pirimidina-1-carboxílico (2-dimetilamino-etil)-amida

Usando 3-trifluorometilbenzaldehído y siguiendo el procedimiento descrito en Ejemplo 2, se obtuvo el compuesto del título en un rendimiento general del 8 %

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)⁺

Ejemplo 34

Ácido 5-ciano-4-metil-2-oxo-6-(3-trifluorometilfenil)-3,6-dihidro-2H-pirimidina-1-carboxílico S-etil ester

Usando 3-trifluorometilbenzaldehído y siguiendo una modificación del procedimiento descrito en Ejemplo 2, se obtuvo el compuesto del título en un rendimiento general del 3 %

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, 2H), 2.26 (d, 3 H, J = 0.9 Hz), 1.26 (t, 3 H, J = 7.5 Hz) LC/MS (ES⁺) 392 (M+Na)⁺

Ejemplo 35

Ácido 5-ciano-4-metil-2-oxo-6-(3-trifluorometilfenil)-3,6-dihidro-2H-pirimidina-1-carboxílico (2-hidroxi-etil)-amida

Usando 3-trifluorometilbenzaldehído y siguiendo una modificación del procedimiento descrito en Ejemplo 2, se obtuvo el compuesto del título en un rendimiento general del 15 %

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, 2H), 3.35 (m, 2H), 2.15 (s, 3 H) LC/MS (ES⁺) 369 (M+H)⁺

Ejemplo 36

4-(3,5-Diclorofenil)-6-metil-2-oxo-3-(tiofeno-2-carbonil)-1,2,3,4-tetrahidropirimidina-5-carbonitrilo

/ / /

Usando 3,5-diclorobenzaldehído y siguiendo el procedimiento descrito en Ejemplo 2, se obtuvo el compuesto del título en un rendimiento general del 5 %

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)⁺

Ejemplo 37

Acido 5-ciano-6-(3,5-difluorofenil)-4-metil-2-oxo-3,6-dihidro-2H-pirimidina-1-carboxílico etilamida

Intermedio IX se obtuvo usando 3,5-difluorobenzaldehído y siguiendo el procedimiento descrito en Ejemplo 2. Se obtuvo el compuesto del título en un rendimiento del 28 % siguiendo el procedimiento de Ejemplo 3.

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

Ejemplo 38

Ácido 5-ciano-6-(3,5-difluorofenil)-4-metil-2-oxo-3,6-dihidro-2H-pirimidina-1-carboxílico etil ester

Usando 3,5-difluorobenzaldehído y siguiendo el procedimiento descrito en Ejemplo 2, se obtuvo el compuesto del título en un rendimiento del 36 % para los dos pasos finales.

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

Ejemplo 39

4-(3,5-Difluorofenil)-6-metil-2-oxo-3-(piperidina-1-carbonil)-1,2,3,4-tetrahidropirimidina-5-carbonitrilo

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Intermedio IX se obtuvo usando 3,5-difluorobenzaldehído y siguiendo el procedimiento descrito en Ejemplo 2. Se obtuvo el compuesto del título en un rendimiento del 30 % siguiendo el procedimiento de Ejemplo 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, 2H), 3.24 (m, 2H), 2.14 (s, 3 H), 1.84 (m, 4), 1.28 (m, 4H)
LC/MS (ES+) 361 (M+H)⁺

Ejemplo 40

4-(3,5-Difluorofenil)-6-metil-2-oxo-3-(pirrolidina-1-carbonil)-1,2,3,4-tetrahidropirimidina-5-carbonitrilo

Intermedio IX se obtuvo usando 3,5-difluorobenzaldehído y siguiendo el procedimiento descrito en Ejemplo 2. Se obtuvo el compuesto del título en un rendimiento del 18 % siguiendo el procedimiento de Ejemplo 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)⁺

Ejemplo 41

Ácido 5-ciano-4-metil-6-naftalen-1-il-2-oxo-3,6-dihidro-2H-pirimidina-1-carboxílico etil éster

Usando naftaleno-1-carboxaldehído y siguiendo el procedimiento de Ejemplo 25, se obtuvo intermedio XXIV en un rendimiento del 44 % y el compuesto del título se obtuvo en un rendimiento del 22 %.

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, 2H), 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, 2H), 2.05 (s, 3 H), 1.00 (t, 3 H, J = 7.0 Hz) LC/MS (ES+) 336 (M+H)⁺

Ejemplo 42

Acido 5-ciano-4-metil-6-naftalen-1-il-2-oxo-3,6-dihidro-2H-pirimidina

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-1-carboxílico etilamida

Usando naftaleno-1-carboxaldehído y siguiendo el procedimiento de Ejemplo 25, se obtuvo intermedio XXIV en un rendimiento del 44 %. Se obtuvo el compuesto del título en un rendimiento del 67 % siguiendo el procedimiento descrito en Ejemplo 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, 2H), 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)⁺

Ejemplo 43**Ácido 6-(3-bromofenil)-5-ciano-4-metil-2-oxo-3,6-dihidro-2H-pirimidina-1-carboxílico etil ester**

Usando 3-bromobenzaldehído y siguiendo el procedimiento de Ejemplo 25, se obtuvo intermedio XXIV en un rendimiento del 25 % y se obtuvo el compuesto del título en un rendimiento del 80 %

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

Ejemplo 44**Ácido 6-(3-Bromofenil)-5-ciano-4-metil-2-oxo-3,6-dihidro-2H-pirimidina-1-carboxílico etilamida**

Usando 3-bromobenzaldehído y siguiendo el procedimiento de Ejemplo 25, se obtuvo intermedio XXIV un rendimiento del 25 %. Se obtuvo el compuesto del título en un rendimiento del 88 % siguiendo el procedimiento descrito en Ejemplo 28 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, 2H), 6.24 (s, 1 H), 3.24 (m, 2H), 2.10 (s, 3 H), 1.10 (t, 3 H, J = 7.0 Hz) LC/MS (ES⁺) 363 (M+H)⁺

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Ejemplo 45

Ácido 5-ciano-4-metil-2-oxo-6-(2-trifluorometilfenil)-3,6-dihidro-2H-pirimidina-1-carboxílico etil éster

Usando 2-trifluorometilbenzaldehído y siguiendo el procedimiento de Ejemplo 25, se obtuvo intermedio XXIV en un rendimiento del 43 % y se obtuvo el compuesto del título en un rendimiento del 30 %

¹H-NMR (DMSO-d₆, 400 MHz) δ 10.58 (s, 1 H), 7.77 (m, 2H), 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, 2H), 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)⁺

Ejemplo 46

Acido 5-ciano-4-metil-2-oxo-6-(2-trifluorometilfenil)-3,6-dihidro-2H-pirimidina-1-carboxílico etilamida

Usando 2-trifluorometilbenzaldehído y siguiendo el procedimiento de Ejemplo 25, se obtuvo intermedio XXIV en un rendimiento del 43 % Se obtuvo el compuesto del título en un rendimiento del 26 % siguiendo el procedimiento descrito en Ejemplo 28

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

Ejemplo 47

Acido 5-ciano-6-(3-metoxycarbonilfenil)-4-metil-2-oxo-3,6-dihidro-2H-pirimidina-1-carboxílico etil éster

Usando metil 3-formilbenzoato y siguiendo el procedimiento de Ejemplo 25, se obtuvo intermedio XXIV en un rendimiento del 30 % y se obtuvo el compuesto del título en un rendimiento del 50 %

¹H-NMR (MeOH-d₄, 400 MHz) δ 8.02 (m, 2H), 7.60 (m, 1 H), 7.52 (m, 1 H), 5.93 (s, 1 H), 4.28 (m, 2H), 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)⁺

Ejemplo 48

Ácido 3-(5-ciano-3-etilcarbamoyl-6-metil-2-oxo-1,2,3,4-tetrahidropirimidin-4-il)-benzoico metil éster

Usando metil 3-formilbenzoato y siguiendo el procedimiento de Ejemplo 25, se obtuvo intermedio XXIV en un rendimiento del 30 %. Se obtuvo el compuesto del título en un rendimiento del 40 % siguiendo el procedimiento descrito en Ejemplo 28. ¹H-NMR (MeOH-d₄, 400 MHz) δ 8.94 (s, 1 H), 7.89 (m, 2H), 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, 2H), 2.07 (s, 3 H), 1.05 (t, 3 H, J = 7.0 Hz) LC/MS (ES+) 343 (M+H)⁺, 365 (M+Na)⁺

Ejemplo 49

Ácido BMS-511181 6-butil-5-ciano-4-metil-2-oxo-3,6-dihidro-2H-pirimidina-1-carboxílico etilamida

Usando 1-buteraldehído y siguiendo el procedimiento de Ejemplo 26, se obtuvo intermedio XXIV en un rendimiento del 97 %. Se obtuvo el compuesto del título en un rendimiento del 55 % siguiendo el procedimiento descrito en Ejemplo 28.

¹H-NMR (DMSO-d₆, 400 MHz) δ 8.85 (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)

Ejemplo 50

Ácido 6-(3,5-bis-trifluorometilfenil)-5-ciano-4-metil-2-oxo-3,6-dihidro-2H-pirimidina-1-carboxílico etilamida

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Usando 3,5-bis-trifluorometilbenzaldehído y siguiendo el procedimiento de Ejemplo 25, se obtuvo intermedio XXIV en un rendimiento del 100 %. Se obtuvo el compuesto del título en un rendimiento del 50 % siguiendo el procedimiento descrito en Ejemplo 28

$^1\text{H-NMR}$ (CDCl_3 , 400 MHz) δ 8.68 (t, 1 H, $J = 5.3$ Hz), 7.86 (s, 1 H), 7.77 (s, 2H), 7.48 (s, 1 H), 6.46 (s, 1 H), 3.31 (m, 2H), 2.24 (s, 3 H), 1.17 (t, 3 H, $J = 7.0$ Hz) LC/MS (ES+) 421 (M+H) $^+$

Ejemplo 51

Ácido 6-(2,5-bis-trifluorometilfenil)-5-ciano-4-metil-2-oxo-3,6-dihidro-2H-pirimidina-1-carboxílico etilamida

Usando 2,5-bis-trifluorometilbenzaldehído y siguiendo el procedimiento de Ejemplo 25, se obtuvo intermedio XXIV en un rendimiento del 25 % de rendimiento. Se obtuvo el compuesto del título en un rendimiento del 38 % siguiendo el procedimiento descrito en Ejemplo 28

$^1\text{H-NMR}$ (MeOH-d_4 , 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, 2H), 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) $^+$

Ejemplo 52

Ácido 6-(2,5-bis-trifluorometilfenil)-5-ciano-4-metil-2-oxo-3,6-dihidro-2H-pirimidina-1-carboxílico etil éster

Usando 2,5-bis-trifluorometilbenzaldehído y siguiendo el procedimiento de Ejemplo 25, se obtuvo intermedio XXIV en un rendimiento del 25 % y se obtuvo el compuesto del título en un rendimiento del 55 %

$^1\text{H-NMR}$ (CDCl_3 , 400 MHz) δ 8.43 (s, 1 H), 7.88 (m, 1 H), 7.76 (m, 2H), 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+) 422 (M+H) $^+$

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Ejemplo 53**Ácido 5-ciano-6-(3-etilcarbamoilfenil)-4-metil-2-oxo-3,6-dihidro-2H-pirimidina-1-carboxílico etilamida**

Comenzando con el producto de Ejemplo 48, se obtuvo el compuesto del título en un rendimiento del 57 % por hidrólisis de éster (hidróxido de litio en metanol acuoso) y acoplamiento del ácido carboxílico resultante con etilamina (carbodiimida soluble en agua e hidroxibenzotriazol en acetonitrilo)

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, 2H), 6.10 (s, 1 H), 3.30 (m, 2H), 3.13 (m, 2H), 2.05 (s, 3 H), 1.12 (t, 3 H, J = 7.0 Hz), 1.01 (t, 3 H, J = 7.0 Hz) LC/MS (ES+) 356 (M+H)⁺

Ejemplo 54**Ácido 5-ciano-6-(3-ciano-4-fluorofenil)-4-metil-2-oxo-3,6-dihidro-2H-pirimidina-1-carboxílico etilamida**

Usando 3-ciano-4-fluorobenzaldehído y siguiendo el procedimiento de Ejemplo 25, se obtuvo intermedio XXIV en un rendimiento del 62 %. Se obtuvo el compuesto del título en un rendimiento del 51 % siguiendo el procedimiento descrito en Ejemplo 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, 2H), 2.22 (s, 3 H), 1.16 (t, 3 H, J = 7.2 Hz) LC/MS (ES+) 328 (M+H)⁺ 350 (M+Na)⁺

Ejemplo 55**Acido 5-ciano-6-(3-ciano-4-fluorofenil)-4-metil-2-oxo-3,6-dihidro-2H-pirimidina-1-carboxílico etil éster**

Usando 3-ciano-4-fluorobenzaldehído y siguiendo el procedimiento de Ejemplo 25, se obtuvo intermedio XXIV en un rendimiento del 62 % y se obtuvo el compuesto del título en un rendimiento del 30 %

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

Ejemplo 56

Ácido 5-ciano-6-(2,2-dimetilpropil)-4-metil-2-oxo-3,6-dihidro-2H-pirimidina-1-carboxílico etilamida

Usando 2,2-dimetilpropionaldehído y siguiendo el procedimiento de Ejemplo 26, se obtuvo intermedio XXIV en un rendimiento del 57 % de Se obtuvo el compuesto del título en un rendimiento del 54 % siguiendo el procedimiento descrito en Ejemplo 28

¹H-NMR (DMSO-d₆, 400 MHz) δ 8.02 (s, 9H), 1.06 (t, 3H, J = 7.15 Hz), 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)

Ejemplo 57

Ácido 5-ciano-6-ciclopropil-4-metil-2-oxo-3,6-dihidro-2H-pirimidina-1-carboxílico etil éster

Usando ciclopropanocarboxaldehído y siguiendo el procedimiento de Ejemplo 26, se obtuvo intermedio XXIV en un rendimiento del 83 % y se obtuvo el compuesto del título en un rendimiento del 36 %

¹H-NMR (DMSO-d₆, 400 MHz) δ 8.035-8.065 (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, 2H), 4.33 (d, 1H, J = 8.13 Hz), 10.36 (s, 1H) MS 248 (M-H)

Ejemplo 58

Ácido 5-ciano-6-ciclopropil-4-metil-2-oxo-3,6-dihidro-2H-pirimidina-1-carboxílico etilamida

Usando ciclopropanocarboxaldehído y siguiendo el procedimiento de Ejemplo 26, se obtuvo intermedio XXIV en un rendimiento del 83 % Se

obtuvo el compuesto del título en un rendimiento del 15 % siguiendo el procedimiento descrito en Ejemplo 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, 2H), 4.66 (d, 1H, J = 8.30 Hz), 8.74 (m, 1H), 0.36 (s, 1H) MS 247 (M-H)⁻ HRMS 247.1195 (M-H)⁻

Ejemplo 59

Ácido 5-ciano-6-(2-fluoro-5-trifluorometilfenil)-4-metil-2-oxo-3,6-dihidro-2H-pirimidina-1-carboxílico etilamida

Usando 2-fluoro-5-trifluorometilbenzaldehído y siguiendo el procedimiento de Ejemplo 25, se obtuvo intermedio XXIV en un rendimiento del 41 %. Se obtuvo el compuesto del título en un rendimiento del 75 % siguiendo el procedimiento descrito en Ejemplo 28

¹H-NMR (CDCl₃, 400 MHz) δ 8.68 (t, 1 H, J = 4.8 Hz), 7.60 (m, 2H), 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)⁺

Ejemplo 60

Ácido 5-ciano-6-(2-fluoro-5-trifluorometilfenil)-4-metil-2-oxo-3,6-dihidro-2H-pirimidina-1-carboxílico etil éster

Usando 2-fluoro-5-trifluorometilbenzaldehído y siguiendo el procedimiento de Ejemplo 25, se obtuvo intermedio XXIV en un rendimiento del 41 % y se obtuvo el compuesto del título en un rendimiento del 38 %

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, 2H), 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)⁺

Ejemplo 61

Ácido 5-ciano-6-isopropil-4-metil-2-oxo-3,6-dihidro-2H-pirimidina-1-carboxílico etil éster

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Usando ciclopropanocarboxaldehído y siguiendo el procedimiento de Ejemplo 26, se obtuvo intermedio XXIV en un rendimiento del 76 % de rendimiento y se obtuvo el compuesto del título en un rendimiento del 23 %

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)

Ejemplo 62

Ácido 5-ciano-4-metil-6-naftalen-2-il-2-oxo-3,6-dihidro-2H-pirimidina-1-carboxílico etil éster

Usando naftaleno-2-carboxaldehído y siguiendo el procedimiento de Ejemplo 25, se obtuvo intermedio XXIV en un rendimiento del 64 % de rendimiento y se obtuvo el compuesto del título en un rendimiento del 39 %

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, 2H), 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)⁺

Ejemplo 63

Acido 5-ciano-6-[3-(2-hidroxiethylcarbamoil)-fenil]-4-metil-2-oxo-3,6-dihidro-2H-pirimidina-1-carboxílico etilamida

Comenzando con el producto de Ejemplo 48, se obtuvo el compuesto del título en un rendimiento del 60 % mediante hidrólisis de ester (hidroxido de litio en metanol acuoso) y acoplado el ácido carboxílico resultante con 2-aminoetanol (carbodiimida soluble en agua e hidroxibenzotriazol en acetonitrilo)

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)⁺

Ejemplo 64

Ácido 5-ciano-6-(2-metoxifenil)-4-metil-2-oxo-3,6-dihidro-2H-pirimidina-1-carboxílico etil éster

Usando 2-metoxibenzaldehído y siguiendo el procedimiento de Ejemplo 26, Se obtuvo intermedio XXIV en un rendimiento del 17 % y se obtuvo el compuesto del título en un rendimiento del 28 %

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)⁺

Ejemplo 65

Ácido 5-ciano-6-(2-metoxifenil)-4-metil-2-oxo-3,6-dihidro-2H-pirimidina-1-carboxílico etilamida

Usando 2-metoxibenzaldehído y siguiendo el procedimiento de Ejemplo 26, Se obtuvo intermedio XXIV en un rendimiento del 17 % Usando el procedimiento de Ejemplo 27, se obtuvo el compuesto del título en un rendimiento del 8 %

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)⁺

Ejemplo 66

Ácido 6-(2-allyloxfenil)-5-ciano-4-metil-2-oxo-3,6-dihidro-2H-pirimidina-1-carboxílico etil ester

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Usando 2-aliloxibenzaldehído y siguiendo el procedimiento de Ejemplo 26, se obtuvo intermedio XXIV en un rendimiento del 33 % y se obtuvo el compuesto del título en un rendimiento del 43 %

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)⁺

Ejemplo 67

Ácido 6-(2-aliloxifenil)-5-ciano-4-metil-2-oxo-3,6-dihidro-2H-pirimidina-1-carboxílico etilamida

Usando 2-aliloxibenzaldehído y siguiendo el procedimiento de Ejemplo 26, se obtuvo intermedio XXIV en un rendimiento del 33 %. Usando el procedimiento de Ejemplo 27, se obtuvo el compuesto del título en un rendimiento del 23 %

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)⁺

Ejemplo 68

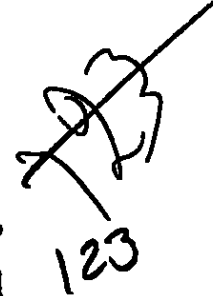
6-(2-Bromofenil)-5-ciano-4-metil-2-oxo-3,6-dihidro-2H-pirimidina-1-carboxílico acid etil éster

Usando 2-bromobenzaldehído y siguiendo el procedimiento de Ejemplo 25, se obtuvo intermedio XXIV en un rendimiento del 50 % y se obtuvo el compuesto del título en un rendimiento del 31 %

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)⁺

Ejemplo 69

Ácido 6-(2-bromofenil)-5-ciano-4-metil-2-oxo-3,6-dihidro-2H-pirimidina-1-carboxílico etilamida



Usando 2-bromobenzaldehído y siguiendo el procedimiento de Ejemplo 25, se obtuvo intermedio XXIV en un rendimiento del 50 %. Se obtuvo el compuesto del título en un rendimiento del 46 % siguiendo el procedimiento descrito en Ejemplo 28

¹H-NMR (MeOH-d₄, 500 MHz) δ 7.55 (m, 1 H), 7.30 (m, 2H), 7.15 (m, 1 H), 6.46 (s, 1 H), 3.14 (m, 2H), 2.04 (s, 3 H), 1.04 (t, 3 H, J = 7.1 Hz)
LC/MS (ES⁺) 364 (M+H⁺)

Ejemplo 70

Ácido 5-ciano-6-(3-metoxifenil)-4-metil-2-oxo-3,6-dihidro-2H-pirimidina-1-carboxílico etilamida

Usando 3-metoxibenzaldehído y siguiendo el procedimiento de Ejemplo 25, Se obtuvo intermedio XXIV en un rendimiento del 66 %. Se obtuvo el compuesto del título en un rendimiento del 62 % siguiendo el procedimiento descrito en Ejemplo 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, 2H), 2.07 (s, 3 H), 1.04 (t, 3 H, J = 7.1 Hz) LC/MS (ES⁺) 315 (M+H⁺)

Ejemplo 71

Acido 6-(2-benciloxifenil)-5-ciano-4-metil-2-oxo-3,6-dihidro-2H-pirimidina-1-carboxílico etil éster

Usando 2-benciloxibenzaldehído y siguiendo el procedimiento de Ejemplo 26, se obtuvo intermedio XXIV en un rendimiento del 47 % y se obtuvo el compuesto del título en un rendimiento del 54 %

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)⁺

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Ejemplo 72

Ácido 6-benciloximetil-5-ciano-4-metil-2-oxo-3,6-dihidro-2H-pirimidina-1-carboxílico etilamida

Usando 2-benciloxiacetaldehído y siguiendo el procedimiento de Ejemplo 26, se obtuvo intermedio XXIV en un rendimiento del 45 %. Se obtuvo el compuesto del título en un rendimiento del 30 % siguiendo el procedimiento descrito en Ejemplo 28

¹H-NMR (DMSO-d₆) δδ 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)

Ejemplo 73

Ácido 6-Benciloximetil-5-ciano-4-metil-2-oxo-3,6-dihidro-2H-pirimidina-1-carboxílico etil éster

Usando 2-benciloxiacetaldehído y siguiendo el procedimiento de Ejemplo 26, se obtuvo intermedio XXIV en un rendimiento del 45 % y se obtuvo el compuesto del título en un rendimiento del 80 %

¹H-NMR (DMSO-d₆) δδ 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)

Ejemplo 74

Ácido 6-(3-bromo-4-fluorofenil)-5-ciano-4-metil-2-oxo-3,6-dihidro-2H-pirimidina-1-carboxílico etilamida

Usando 3-bromo-4-fluorobenzaldehído y siguiendo el procedimiento de Ejemplo 26, se obtuvo intermedio XXIV en un rendimiento del 99 %. Se obtuvo el compuesto del título en un rendimiento del 69 % siguiendo el procedimiento descrito en Ejemplo 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, 2H), 2.09 (s, 3 H), 1.03 (t, 3 H, $J = 7.0$ Hz) LC/MS (ES+) 381 (M+H⁺)

Ejemplo 75

Ácido 6-(3-bromo-4-fluorofenil)-5-ciano-4-metil-2-oxo-3,6-dihidro-2H-pirimidina-1-carboxílico ciclopropilamida

Usando 3-bromo-4-fluorobenzaldehído y siguiendo el procedimiento de Ejemplo 26, se obtuvo intermedio XXIV en un rendimiento del 99 %. Se obtuvo el compuesto del título en un rendimiento del 54 % siguiendo el procedimiento descrito en Ejemplo 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, 2H), 0.42 (m, 1 H), 0.37 (m, 1 H) LC/MS (ES+) 393 (M+H⁺)

Ejemplo 76

Ácido 6-(5-bromo-2-fluorofenil)-5-ciano-4-metil-2-oxo-3,6-dihidro-2H-pirimidina-1-carboxílico etilamida

Usando 5-bromo-2-fluorobenzaldehído y siguiendo el procedimiento de Ejemplo 26, se obtuvo intermedio XXIV en un rendimiento del 71 % de rendimiento. Se obtuvo el compuesto del título en un rendimiento del 70 % siguiendo el procedimiento descrito en Ejemplo 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, 2H), 2.11 (d, 3 H, $J = 2.2$ Hz), 1.11 (m, 3 H)

Ejemplo 77

Ácido 6-(5-bromo-2-fluorofenil)-5-ciano-4-metil-2-oxo-3,6-dihidro-2H-pirimidina-1-carboxílico ciclopropilamida

Usando 5-bromo-2-fluorobenzaldehído y siguiendo el procedimiento de Ejemplo 26, se obtuvo intermedio XXIV en un rendimiento del 71 %. Se

obtuvo el compuesto del título en un rendimiento del 70 % siguiendo el procedimiento descrito en Ejemplo 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, 2H), 0.51 (m, 1 H), 0.44 (m, 1 H)

Ejemplo 78

Ácido 5-ciano-6-(3,5-dibromofenil)-4-metil-2-oxo-3,6-dihidro-2H-pirimidina-1-carboxílico etilamida

Usando 3,5-dibromobenzaldehído y siguiendo el procedimiento de Ejemplo 26, se obtuvo intermedio XXIV en un rendimiento del 46 %. Se obtuvo el compuesto del título en un rendimiento del 83 % siguiendo el procedimiento descrito en Ejemplo 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, 2H), 6.08 (s, 1 H), 3.18-3.26 (m, 2H), 2.08 (s, 3 H), 1.03 (t, J = 7.1 Hz, 3 H). LC/MS (ES⁺) 441 (M+H)⁺

Ejemplo 79

Ácido 5-ciano-4-metil-6-(3-nitrofenil)-2-oxo-3,6-dihidro-2H-pirimidina-1-carboxílico ciclopropilmetilamida

Usando 3-nitrobenzaldehído y siguiendo el procedimiento de Ejemplo 26, se obtuvo intermedio XXIV en un rendimiento del 92 %. Se obtuvo el compuesto del título en un rendimiento del 53 % siguiendo el procedimiento descrito en Ejemplo 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, 2H), 2.17 (s, 3 H), 0.98 (m, 1 H), 0.48 (m, 2H), 0.20 (m, 2H). LC/MS (ES⁺) 356 (M+H)⁺

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Ejemplo 80

Acido **5-ciano-4-metil-2-oxo-6-fenetiloximetil-3,6-dihidro-2H-pirimidina-1-carboxílico etil éster**

Usando 2-fenetiloxiacetaldehído y siguiendo el procedimiento de Ejemplo 26, se obtuvo intermedio XXIV en un rendimiento del 38 % y se obtuvo el compuesto del título 18 % de rendimiento

¹H-NMR (DMSO-d₆, 400MHz) δ 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)

Ejemplo 81

Acido **5-ciano-4-metil-2-oxo-6-fenetil-3,6-dihidro-2H-pirimidina-1-carboxílico etilamida**

Usando 3-fenilpropionaldehído y siguiendo el procedimiento de Ejemplo 26, se obtuvo intermedio XXIV en un rendimiento del 58 %. Se obtuvo el compuesto del título en un rendimiento del 42 % siguiendo el procedimiento descrito en Ejemplo 28

¹H-NMR (DMSO-d₆, 400 MHz) δ 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)

Ejemplo 82

Ácido **5-ciano-4-metil-2-oxo-6-tiofen-3-il-3,6-dihidro-2H-pirimidina-1-carboxílico etil éster**

Usando tiofeno-3-carboxaldehído y siguiendo el procedimiento de Ejemplo 26, se obtuvo intermedio XXIV en un rendimiento del 50 % de rendimiento y se obtuvo el compuesto del título en un rendimiento del 30 %

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$^1\text{H-NMR}$ (DMSO-d_6 , 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 ($\text{M}+\text{H}$) $^+$

Ejemplo 83

Ácido 5-ciano-4-metil-6-(5-metilisoxazol-3-il)-2-oxo-3,6-dihidro-2H-pirimidina-1-carboxílico etil éster

Usando 5-metilisoxazol-3-carboxaldehído y siguiendo el procedimiento de Ejemplo 26, se obtuvo intermedio XXIV en un rendimiento del 27 % y se obtuvo el compuesto del título en un rendimiento del 67 %

$^1\text{H-NMR}$ (DMSO-d_6 , 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)
 $^{13}\text{C-NMR}$ (DMSO-d_6 , 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 ($\text{M}+\text{H}$) $^+$

Ejemplo 84

Ácido 5-ciano-6-(3,5-dimetilisoxazol-4-il)-4-metil-2-oxo-3,6-dihidro-2H-pirimidina-1-carboxílico etil éster

Usando 3,5-dimetilisoxazol-4-carboxaldehído y siguiendo el procedimiento de Ejemplo 26, se obtuvo intermedio XXIV en un rendimiento del 74 % y se obtuvo el compuesto del título en un rendimiento del 47 %

$^1\text{H-NMR}$ (DMSO-d_6 , 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)
 $^{13}\text{C-NMR}$ (DMSO-d_6 , 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 ($\text{M}+\text{H}$) $^+$

Ejemplo 85

Ácido 5-ciano-4-metil-2-oxo-6-tiofen-2-il-3,6-dihidro-2H-pirimidina-1-carboxílico etil éster

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Usando tiofeno-2-carboxaldehído y siguiendo el procedimiento de Ejemplo 26, se obtuvo intermedio XXIV en un rendimiento del 41 % y se obtuvo el compuesto del título en un rendimiento del 58 %

$^1\text{H-NMR}$ (DMSO- d_6 , 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)

Ejemplo 86

Ácido 5-ciano-4-metil-6-(3-metiltiofen-2-il)-2-oxo-3,6-dihidro-2H-pirimidina-1-carboxílico etilamida

Usando 3-metiltiofeno-2-carboxaldehído y siguiendo el procedimiento de Ejemplo 26, se obtuvo intermedio XXIV en un rendimiento del 33 % Se obtuvo el compuesto del título en un rendimiento del 17 % siguiendo el procedimiento descrito en Ejemplo 28

$^1\text{H-NMR}$ (DMSO- d_6 , 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), 8.73 (t, $J = 5.6$ Hz, 1H), 10.62 (s, 1H)

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

Ejemplo 87

Ácido 5-ciano-4-metil-6-(3-metiltiofen-2-il)-2-oxo-3,6-dihidro-2H-pirimidina-1-carboxílico etil ester

Usando 3-metiltiofeno-2-carboxaldehído y siguiendo el procedimiento de Ejemplo 26, se obtuvo intermedio XXIV en 33 % de rendimiento y se obtuvo el compuesto del título en un rendimiento del 14 %

$^1\text{H-NMR}$ (DMSO- d_6 , 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)

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Ejemplo 88

Acido 5-ciano-4-metil-6-(2-metiltiazol-4-il)-2-oxo-3,6-dihidro-2H-pirimidina-1-carboxílico etil ester

Usando 2-metiltiazol-4-carboxaldehído y siguiendo el procedimiento de Ejemplo 26, se obtuvo intermedio XXIV en un rendimiento del 26 % y se obtuvo el compuesto del título en un rendimiento del 16 %

$^1\text{H-NMR}$ (CDCl_3 , 400 MHz) δ 7.96 (s, 1H), 7.11 (s, 1H), 5.93 (s, 1H), 4.31 (m, 2H), 2.67 (s, 3H), 2.16 (s, 3H), 1.32 (t, 3H, $J = 6.9$ Hz), $^{13}\text{C-NMR}$ (CDCl_3 , 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 ($\text{M}+\text{H}$) $^+$

Ejemplo 89

Ácido 6-(4-bromotiofen-2-il)-5-ciano-4-metil-2-oxo-3,6-dihidro-2H-pirimidina-1-carboxílico etilamida

Usando 4-bromotiofeno-2-carboxaldehído y siguiendo el procedimiento de Ejemplo 26, se obtuvo intermedio XXIV en un rendimiento del 68 % Se obtuvo el compuesto del título en un rendimiento del 49 % siguiendo el procedimiento descrito en Ejemplo 28 $^1\text{H-NMR}$ (DMSO-d_6 , 400 MHz) δ 8.107 (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 ($\text{M}+\text{H}$) $^+$ HRMS(ESI) 366.9876 ($\text{M}-\text{H}$)

Ejemplo 90

Ácido 6-(4-bromotiofen-2-il)-5-ciano-4-metil-2-oxo-3,6-dihidro-2H-pirimidina-1-carboxílico etil éster

Usando 4-bromotiazol-2-carboxaldehído y siguiendo el procedimiento de Ejemplo 26, se obtuvo intermedio XXIV en un rendimiento del 68% de rendimiento y se obtuvo el compuesto del título en un rendimiento del 45 % $^1\text{H-NMR}$ (DMSO-d_6 , 400 MHz) δ 8.125 (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 [$\text{M}-\text{H}$] HRMS (ESI) 367.9697 ($\text{M}-\text{H}$)

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Ejemplo 91

Ácido 5-ciano-4-metil-2-oxo-6-[2-(4-trifluorometilfenil) tiazol-4-il]-3,6-dihidro-2H-pirimidina-1-carboxílico etil éster

Usando 2-(4-trifluorometilfenil)tiazol-4-carboxaldehído y siguiendo el procedimiento de Ejemplo 26, se obtuvo intermedio XXIV en un rendimiento del 17 % de rendimiento y se obtuvo el compuesto del título en un rendimiento del 31 %

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, 52.82, 16.87, 13.66 MS (ESI), 437 (M+H)⁺

Ejemplo 92

Ácido 6-[5-(4-clorofenil) oxazol-4-il]-5-ciano-4-metil-2-oxo-3,6-dihidro-2H-pirimidina-1-carboxílico etil éster

Usando 5-(4-clorofenil)oxazol-4-carboxaldehído y siguiendo el procedimiento de Ejemplo 26, se obtuvo intermedio XXIV en un rendimiento del 22 % de rendimiento y se obtuvo el compuesto del título en un rendimiento del 16 %

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, 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)⁺

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Ejemplo 93

Ácido 6-(2-bromotiazol-5-il) 5-ciano-4-metil-2-oxo-3,6-dihidro-2H-pirimidina-1-carboxílico etil ester

Usando 2-bromotiazol-5-carboxaldehído y siguiendo el procedimiento de Ejemplo 26, se obtuvo intermedio XXIV en un rendimiento del 44 % y se obtuvo el compuesto del título en un rendimiento del 41 %

¹H-NMR (DMSO-d₆, 400 MHz) δ 10.67 (s, 1H), 7.72 (s, 1H), 6.15 (s, 1H), 4.26 (m, 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)⁺

Ejemplo 94

Ácido 5-ciano-4-metil-2-oxo-6-(4-feniltiofen-2-il) 3,6-dihidro-2H-pirimidina-1-carboxílico etilamida

Usando 4-bromotiofeno-2-carboxaldehído y siguiendo el procedimiento de Ejemplo 26, se obtuvo intermedio XXIV en un rendimiento del 68 % de rendimiento. El intermedio 4-bromotienilo se convirtió en intermedio 4-feniltienilo mediante la reacción de Suzuki en un rendimiento del 91 %. Se obtuvo el compuesto del título en un rendimiento del 33 % siguiendo el procedimiento descrito en Ejemplo 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)

Ejemplo 95

Acido 6-[5-(4-clorofenil) furan-2-il]-5-ciano-4-metil-2-oxo-3,6-dihidro-2H-pirimidina-1-carboxílico etilamida

Usando 5-(4-clorofenil)furan-2-carboxaldehído y siguiendo el procedimiento de Ejemplo 26, se obtuvo intermedio XXIV en un

rendimiento del 16 % Se obtuvo el compuesto del título en un rendimiento del 43 % siguiendo el procedimiento descrito en Ejemplo 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)

Ejemplo 96

Acido 5-ciano-4-metil-2-oxo-6-(4-trifluorometiltiazol-5-il) 3,6-dihidro-2H-pirimidina-1-carboxílico etil éster

Usando 4-trifluorometiltiazol-5-carboxaldehído y siguiendo el procedimiento de Ejemplo 26, se obtuvo intermedio XXIV en un rendimiento del 63 % y se obtuvo el compuesto del título en un rendimiento del 52 %

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)⁺

Ejemplo 97

Ácido 5-ciano-4-metil-2-oxo-6-(4-trifluorometiltiazol-5-il) 3,6-dihidro-2H-pirimidina-1-carboxílico etilamida

Usando 4-trifluorometiltiazol-5-carboxaldehído y siguiendo el procedimiento de Ejemplo 26, se obtuvo intermedio XXIV en un rendimiento del 63 % Se obtuvo el compuesto del título en un rendimiento del 59 % siguiendo el procedimiento descrito en Ejemplo 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)⁺

Ejemplo 98

Ácido 5-ciano-6-[5-(4-metanosulfonilfenil) oxazol-4-il]-4-metil-2-oxo-3,6-dihidro-2H-pirimidina-1-carboxílico etilamida

Usando 5-(4-metanosulfonilfenil)oxazol-4-carboxaldehído y siguiendo el procedimiento de Ejemplo 26, se obtuvo intermedio XXIV en un rendimiento del 22 %. Se obtuvo el compuesto del título en un rendimiento del 63 % siguiendo el procedimiento descrito en Ejemplo 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)⁺

Ejemplo 99

Ácido 6-[5-(4-clorofenil) oxazol-4-il]-5-ciano-4-metil-2-oxo-3,6-dihidro-2H-pirimidina-1-carboxílico etilamida

Usando 5-(4-clorofenil)oxazol-4-carboxaldehído y siguiendo el procedimiento de Ejemplo 26, se obtuvo intermedio XXIV en un rendimiento del 40 %. Se obtuvo el compuesto del título en un rendimiento del 58 % siguiendo el procedimiento descrito en Ejemplo 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)⁺

Ejemplo 100

Ácido 5-ciano-4-metil-2-oxo-6-[5-(4-trifluorometilfenil) oxazol-4-il]-3,6-dihidro-2H-pirimidina-1-carboxílico etilamida

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Usando 5-(4-trifluorometilfenil)oxazol-4-carboxaldehído y siguiendo el procedimiento de Ejemplo 26, se obtuvo intermedio XXIV en un rendimiento del 31 %. Se obtuvo el compuesto del título en un rendimiento del 52 % siguiendo el procedimiento descrito en Ejemplo 28

$^1\text{H-NMR}$ (DMSO-d_6 , 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 (t, 3H, $J = 7.2$ Hz), $^{13}\text{C-NMR}$ (DMSO-d_6 , 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 ($\text{M}+\text{H}$) $^+$

Ejemplo 101

Ácido 5-ciano-4-metil-2-oxo-6-(5-feniloxazol-4-il) 3,6-dihidro-2H-pirimidina-1-carboxílico etilamida

Reduccion catalitica (10 % Pd/C, formato de amonio en acetonitrilo en reflujo) del producto de Ejemplo 99 produjo el compuesto del titulo en un rendimiento del 45 %

$^1\text{H-NMR}$ (CDCl_3 , 400 MHz) δ 8.69 (m, 1H), 7.87 (m, 3H), 7.50 (m, 2H), 7.41 (m, 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) $^{13}\text{CNMR}$ (CDCl_3 , 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 ($\text{M}+\text{H}$) $^+$

Ejemplo 102

Ácido 5-ciano-4-metil-6-[5-(4-nitrofenil) oxazol-4-il]-2-oxo-3,6-dihidro-2H-pirimidina-1-carboxílico etilamida

Usando 5-(4-nitrofenil)oxazol-4-carboxaldehído y siguiendo el procedimiento de Ejemplo 26, se obtuvo intermedio XXIV en un

rendimiento del 36 % Se obtuvo el compuesto del título en un rendimiento del 70 % siguiendo el procedimiento descrito en Ejemplo 28

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)⁺

Ejemplo 103

Ácido 5-(4-clorofenil)-2-(5-ciano-3-etilcarbamoyl-6-metil-2-oxo-1,2,3,4-tetrahidropirimidina-4-il) furan-3-carboxílico etil éster

Usando 3-etoxycarbonil-5-(4-clorofenil)furan-2-carboxaldehído y siguiendo el procedimiento de Ejemplo 26, se obtuvo intermedio XXIV en un rendimiento del 59 % Se obtuvo el compuesto del título en un rendimiento del 42 % siguiendo el procedimiento descrito en Ejemplo 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)

Ejemplo 104

Ácido 5-ciano-4-metil-2-oxo-6-(5-piridin-3-iloxazol-4-il)-3,6-dihidro-2H-pirimidina-1-carboxílico etilamida

Usando 5-(3-piridinil)oxazol-4-carboxaldehído y siguiendo el procedimiento de Ejemplo 26, se obtuvo intermedio XXIV en un rendimiento del 62 % Se obtuvo el compuesto del título en un rendimiento del 41 % siguiendo el procedimiento descrito en Ejemplo 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) $\delta\delta$ 152 76, 152 52, 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)⁺

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Ejemplo 105

Ácido 5-ciano-4-metil-2-oxo-6-(4-feniltiazol-5-il)3,6-dihidro-2H-pirimidina-1-carboxílico etilamida

Usando 4-feniltiazol-5-carboxaldehído y siguiendo el procedimiento de Ejemplo 26, se obtuvo intermedio XXIV en un rendimiento del 70 %. Se obtuvo el compuesto del título en un rendimiento del 27 % siguiendo el procedimiento descrito en Ejemplo 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) $\delta\delta$ 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)⁺

Ejemplo 106

Acido [5-ciano-4-metil-6-(3-nitrofenil)2-oxo-3,6-dihidro-2H-pirimidin-1-il]-acético tert-butil éster

Usando 3-nitrobenzaldehído y siguiendo el procedimiento de Ejemplo 26, se obtuvo intermedio XXIV en un rendimiento del 92 % y se obtuvo el compuesto del título en un rendimiento del 52 % ¹H-NMR (MeOH-d₄, 400 MHz) δ 8 28 (m, 1H), 8 22 (t, 1H, J = 1 8 Hz), 7 76 (m, 1H), 7 69 (t, 1 H, J = 7 9 Hz), 7 62 (s, 1H), 5 31 (s, 1H), 4 23 (d, 1H, J = 17 6 Hz), 3 44 (d, 1H, J = 17 6 Hz), 2 16 (s, 3 H), 1 42 (s, 9 H) LC/MS (ES+) 395 (M+Na)⁺

Ejemplo 107

Ácido 5-ciano-4-metil-6-(3-nitrofenil)2-oxo-3,6-dihidro-2H-pirimidina-1-carboxílico isopropilamida

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Usando 3-nitrobenzaldehído y siguiendo el procedimiento de Ejemplo 26, se obtuvo intermedio XXIV en un rendimiento del 92 %. Se obtuvo el compuesto del título en un rendimiento del 29 % siguiendo el procedimiento descrito en Ejemplo 27 $^1\text{H-NMR}$ (MeOH-d_4 , 400 MHz) δ 8.92 (s, 1H), 8.22 (d, 1H, $J = 8.3$ Hz), 8.17 (t, 1H, $J = 1.8$ Hz), 7.74 (d, 1H, $J = 6.6$ Hz), 7.65 (m, 2H), 6.31 (s, 1H), 3.89 (m, 1H), 2.19 (s, 3H), 1.20 (d, 3H, $J = 6.6$ Hz), 1.16 (d, 3H, $J = 6.6$ Hz) LC/MS (ES+) 344 ($\text{M}+\text{H}$) $^+$ 366 ($\text{M}+\text{Na}$) $^+$

Ejemplo 108

Ácido 5-ciano-4-metil-6-(3-nitrofenil) 2-oxo-3,6-dihidro-2H-pirimidina-1-carboxílico propilamida

Usando 3-nitrobenzaldehído y siguiendo el procedimiento de Ejemplo 26, se obtuvo intermedio XXIV en un rendimiento del 92 % de rendimiento. Se obtuvo el compuesto del título en un rendimiento del 22 % siguiendo el procedimiento descrito en Ejemplo 27 $^1\text{H-NMR}$ (MeOH-d_4 , 400 MHz) δ 9.09 (t, 1H, $J = 5.3$ Hz), 8.22 (m, 1H), 8.17 (t, 1H, $J = 1.8$ Hz), 7.75 (d, 1H, $J = 7.9$ Hz), 7.65 (t, 1H, $J = 7.9$ Hz), 6.30 (s, 1H), 3.33 (m, 2H), 2.18 (s, 3H), 1.54 (m, 2H), 0.91 (t, 3H, $J = 7.5$ Hz) LC/MS (ES+) 344 ($\text{M}+\text{H}$) $^+$, 366 ($\text{M}+\text{Na}$) $^+$

Ejemplo 109

Ácido 5-ciano-4-metil-6-(3-nitrofenil) 2-oxo-3,6-dihidro-2H-pirimidina-1-carboxílico fenilamida

Usando 3-nitrobenzaldehído y siguiendo el procedimiento de Ejemplo 26, se obtuvo intermedio XXIV en un rendimiento del 92 % de rendimiento. Se obtuvo el compuesto del título en un rendimiento del 10 % siguiendo el procedimiento descrito en Ejemplo 27 $^1\text{H-NMR}$ (MeOH-d_4 , 400 MHz) δ 11.18 (s, 1H), 8.23 (m, 2H), 7.81 (d, 1H, $J = 7.9$ Hz), 7.65 (m, 1H), 7.44 (m,

2H), 7.31 (t, 2 H, J = 8.3 Hz), 7.11 (t, 1H, J = 8.3 Hz), 6.40 (s, 1H), 2.23 (s, 3H) LC/MS (ES+) 378 (M+H)⁺, 400 (M+Na)⁺

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Ejemplo 110

Ácido 5-ciano-4-metil-6-(3-nitrofenil)-2-oxo-3,6-dihidro-2H-pirimidina-1-carboxílico tiazol-2-ilamida

Usando 3-nitrobenzaldehído y siguiendo el procedimiento de Ejemplo 26, se obtuvo intermedio XXIV en un rendimiento del 92 %. Se obtuvo el compuesto del título en un rendimiento del 33 % siguiendo el procedimiento descrito en Ejemplo 27. ¹H-NMR (MeOH-d₄, 400 MHz) δ 8.23 (m, 2H), 7.80 (d, 1H, J = 7.5 Hz), 7.64 (t, 1H, J = 7.5 Hz), 7.42 (d, 1H, J = 4.0 Hz), 7.03 (d, 1H, J = 4.0 Hz), 6.36 (s, 1H), 2.24 (d, 3H, J = 0.9 Hz) LC/MS (ES+) 385 (M+H)⁺, 407 (M+Na)⁺

Ejemplo 111

Ácido 5-ciano-4-metil-6-(3-nitrofenil)-2-oxo-3,6-dihidro-2H-pirimidina-1-carboxílico (2,2,2-trifluoro-etil) amina

Usando 3-nitrobenzaldehído y siguiendo el procedimiento de Ejemplo 26, se obtuvo intermedio XXIV en un rendimiento del 92 %. Se obtuvo el compuesto del título en un rendimiento del 25 % siguiendo el procedimiento descrito en Ejemplo 27. ¹H-NMR (DMSO-d₆, 500 MHz) δ 10.77 (s, 1H), 9.23 (t, 1H, J = 6.0 Hz), 8.21 (m, 1H), 8.09 (s, 1H), 7.75 (m, 2H), 6.26 (s, 1H), 4.01 (m, 2H), 2.10 (s, 3H)

Ejemplo 112

Ácido 5-ciano-4-metil-6-(3-nitrofenil)-2-oxo-3,6-dihidro-2H-pirimidina-1-carboxílico ciclopropilamida

Usando 3-nitrobenzaldehído y siguiendo el procedimiento de Ejemplo 26, se obtuvo intermedio XXIV en un rendimiento del 92 %. Se obtuvo el compuesto del título en un rendimiento del 19 % siguiendo el

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procedimiento descrito en Ejemplo 27 $^1\text{H-NMR}$ (DMSO-d_6 , 500 MHz) δ 10.62 (s, 1H), 8.58 (s, 1H), 8.21 (m, 1H), 8.07 (d, 1H, $J = 1.6$ Hz), 7.73 (m, 2H), 6.22 (s, 1H), 2.62 (m, 1H), 2.09 (s, 3H), 0.64 (m, 2H), 0.46 (m, 2H)

Ejemplo 113

Ácido 5-ciano-4-metil-6-(3-nitrofenil)-2-oxo-3,6-dihidro-2H-pirimidina-1-carboxílico (2-hidroxi-etil)-amida

Usando 3-nitrobenzaldehído y siguiendo el procedimiento de Ejemplo 26, se obtuvo intermedio XXIV en un rendimiento del 92 %. Se obtuvo el compuesto del título en un rendimiento del 23 % siguiendo el procedimiento descrito en Ejemplo 27 $^1\text{H-NMR}$ (CDCl_3 , 500 MHz) δ 8.93 (s, 1H), 8.15 (d, 1H, $J = 7.9$ Hz), 8.07 (s, 1H), 7.68 (d, 1H, $J = 7.9$ Hz), 7.51 (t, 1H, $J = 7.9$ Hz), 6.86 (s, 1H), 6.30 (s, 1H), 3.67 (m, 2H), 3.43 (m, 1H), 3.36 (m, 1H), 2.18 (s, 3H) LC/MS (ES+) 346 (M+H)⁺

Ejemplo 114

3-(4,5-Dihidrooxazol-2-il) 6-metil-4-(3-nitrofenil)-2-oxo-1,2,3,4-tetrahidropirimidina-5-carbonitrilo

Preparada del producto de Ejemplo 113 (reactivo de Burgess en tetrahidrofurano a reflujo) en un rendimiento del 71 %

$^1\text{H-NMR}$ (MeOH-d_4 , 400 MHz) δ 8.10 (m, 2H), 7.66 (d, 1H, $J = 7.9$ Hz), 7.56 (t, 1H, $J = 7.9$ Hz), 6.19 (s, 1H), 4.04 (m, 2H), 3.50 (m, 1H), 3.39 (m, 1H), 2.06 (s, 3H) LC/MS (ES+) 328 (M+H)⁺

Ejemplo 115

Ácido 5-ciano-4-metil-6-(3-nitrofenil)-2-oxo-3,6-dihidro-2H-pirimidina-1-carboxílico alilamida

Usando 3-nitrobenzaldehído y siguiendo el procedimiento de Ejemplo 26, se obtuvo intermedio XXIV en un rendimiento del 92 %. Se obtuvo el compuesto del título en un rendimiento del 36 % siguiendo el procedimiento descrito en Ejemplo 27 $^1\text{H-NMR}$ (DMSO-d_6 , 500 MHz) δ

10 65 (s, 1H), 8 92 (t, 1H, $J = 5.5$ Hz), 8 21 (m, 1H), 8 08 (s, 1H), 7 74 (m, 2H), 6 24 (s, 1H), 5 81 (m, 1H), 5 07 (m, 2H), 3 78 (m, 2H), 2 10 (s, 3H)
 LC/MS (ES+) 342 (M+H)⁺, 364 (M+Na)⁺

Ejemplo 116

6-(3-Bromofenil)-5-ciano-3,6-dihidro-4-metil-2-oxo-(2H)-pirimidina

Método 1

Una mezcla de 3-bromobenzaldehído (13 0 g, 70 mmol), acetoacetamida (7 08 g, 70 mmol), urea (5 26 g, 87 5 mmol), ester de polifosfato (9 1 g, 21 mmol) y THF (150 mL) se calentó en un tubo sellado durante 18 horas a 75 °C. Esta mezcla se enfrió a temperatura ambiente, se agregó más ester de polifosfato (60 6 g, 140 mmol) y se reanudó el calentamiento durante otras 5 horas. La mezcla de reacción se enfrió a temperatura ambiente, se vertió en agua (800 mL) y se agitó durante 18 horas. Los precipitados resultantes se recogieron por filtración de vacío, se lavaron con agua y con éter, y se secaron con aire para producir 6-(3-bromofenil)-5-ciano-3,6-dihidro-4-metil-2-oxo-(2H)-pirimidina como un sólido amarillo claro (16 25 g, 79%).
¹H NMR (DMSO-d₆, 400 MHz) δ 9 60 (s, 1H), 7 87 (s, 1H), 7 55 (m, 1H), 7 48 (m, 1H), 7 39 (t, 1H, $J = 7.9$ Hz), 7 32 (d, 1H, $J = 7.9$ Hz), 5 14 (s, 1H), 2 02 (s, 3H)

Ácido 6-(3-bromofenil)-5-ciano-3,6-dihidro-4-metil-2-oxo-1-(2H)-pirimidinacarboxílico, 1-etil éster

Método 2

A una solución de 6-(3-bromofenil)-5-ciano-3,6-dihidro-4-metil-2-oxo-(2H)-pirimidina (0 29 g, 1 mmol) en THF (5 mL) enfriado a -78 °C se agregó LDA (0 55 mL, 1 1 mmol, 2 0 M en THF). La detención amarilla resultante se agitó durante 0 5 horas, se calentó a -20 °C durante 0 5 horas y se volvió a enfriar a -78 °C, luego se agregó cloroformato de etilo (0 14 mL, 1 5 mmol) mediante una jeringa. La mezcla de reacción se agitó

durante 20 minutos, se calentó a temperatura ambiente y se extinguió con EtOAc. Esta mezcla se lavó con solución de NaHCO_3 acuoso y con salmuera, se seco (Na_2SO_4), y se concentró in vacuo. El residuo se purificó por cromatografía de columna de destello (10% a 30% EtOAc/hexanos) para producir, tras la evaporación del solvente, ácido 6-(3-bromofenil)-5-ciano-3,6-dihidro-4-metil-2-oxo-1-(2H)-pirimidinacarboxílico, 1-etil éster como un sólido incoloro (0.29 g, 80%) ^1H NMR (CDCl_3 , 400 MHz) δ 7.48 (m, 2H), 7.28 (m, 2H), 5.87 (s, 1H), 4.33 (m, 2H), 2.22 (s, 3H), 1.33 (t, 3H, $J = 7.0$ Hz), LC/MS (ES+) 364 ($\text{M} + \text{H}^+$)

Acido 6-(3-bifenil)-5-ciano-3,6-dihidro-4-metil-2-oxo-1-(2H)-pirimidina carboxílico, 1-etil éster

Metodo 3

Una mezcla de ácido 6-(3-bromofenil)-5-ciano-3,6-dihidro-4-metil-2-oxo-1-(2H)-pirimidinacarboxílico, 1-etil éster (36 mg, 0.1 mmol), ácido fenilbórico (24 mg, 0.2 mmol), carbonato de potasio (110 mg, 0.8 mmol), EtOH (2 mL), agua (1 mL), y tolueno (4 mL) se enjuaga con gas nitrógeno varias veces antes que se introdujera tetrakis(trifenilfosfina) de paladio (5 mg). La mezcla de reacción se calentó a reflujo bajo nitrógeno durante 1 hora, se enfrió a temperatura ambiente, y se diluyó con EtOAc. Esta mezcla se lavó con agua, se seco (Na_2SO_4), y se concentró in vacuo. El residuo se purificó por cromatografía de columna de destello (50% a 70% EtOAc/hexanos) para producir, tras la evaporación del solvente, el compuesto del título como un sólido incoloro (26 mg, 72%) ^1H NMR (MeOH-d_4 , 400 MHz) δ 7.48 (m, 4H), 7.35 (m, 3H), 7.23 (m, 2H), 5.84 (s, 1H), 4.15 (m, 2H), 2.04 (s, 3H), 1.15 (t, 3H, $J = 7.0$ Hz), LC/MS (ES+) 362 ($\text{M} + \text{H}^+$)

Ejemplo 117

Acido 5-ciano-3,6-dihidro-4-metil-2-oxo-6-(3-(2-tienil)fenil)-1-(2H)-pirimidinacarboxílico, 1-etil éster

Siguiendo el procedimiento de Método 3, se obtuvo el compuesto del título de ácido 6-(3-bromofenil)-5-ciano-3,6-dihidro-4-metil-2-oxo-1-(2H)-pirimidinacarboxílico, 1-etil ester y ácido 2-tiofenobórico como un sólido café claro en un rendimiento del 85% ^1H NMR (MeOH- d_4 , 400 MHz) δ 7.52 (m, 2H), 7.33 (d, 1H, $J = 7.9$ Hz), 7.29 (m, 2H), 7.15 (d, 1H, $J = 7.9$ Hz), 6.99 (m, 1H), 5.81 (s, 1H), 4.16 (m, 2H), 2.05 (s, 3H), 1.17 (t, 3H, $J = 7.0$ Hz), LC/MS (ES+) 368 ($\text{M} + \text{H}^+$), 390 ($\text{M} + \text{Na}^+$)

Ejemplo 118

Acido 6-(3-bromofenil)-5-ciano-3,6-dihidro-4-metil-2-oxo-1-(2H)-pirimidinacarboxílico, 1-etil amida

Método 4

A una solución de 6-(3-bromofenil)-5-ciano-3,6-dihidro-4-metil-2-oxo-(2H)-pirimidina (2.92 g, 10 mmol) en THF (30 mL) se agregó 95% hidruro de sodio (0.30 g, 12 mmol). Una vez cesó la evolución, se agregó isocianato de etilo (0.44 mL, 12 mmol) a través de una jeringa. La mezcla de reacción se agitó durante 0.5 hora, se extinguió con agua y se extrajo dos veces con EtOAc. Los extractos combinados se lavaron con 0.5 N NaOH acuoso, con agua y con salmuera, se seco (MgSO_4) y se concentró in vacuo. El residuo se purificó por cromatografía de columna de destello (25% a 35% EtOAc/hexano) para producir, tras la evaporación del solvente, ácido 6-(3-bromofenil)-5-ciano-3,6-dihidro-4-metil-2-oxo-1-(2H)-pirimidinacarboxílico, 1-etil amida como un sólido incoloro (2.91 g, 80%) ^1H NMR (CDCl_3 , 400 MHz) δ 8.65 (t, 3H, $J = 5.3$ Hz), 7.91 (s, 1H), 7.39 (m, 1H), 7.35 (m, 1H), 7.21 (m, 1H), 7.15 (d, 1H, $J = 7.9$ Hz), 6.24 (s, 1H), 3.25 (m, 2H), 2.10 (s, 3H), 1.10 (t, 3H, $J = 7.0$ Hz), LC/MS (ES+) 363 ($\text{M} + \text{H}^+$)

Acido 6-(3-bifenil)-5-ciano-3,6-dihidro-4-metil-2-oxo-1-(2H)-pirimidinacarboxílico, 1-etil amida

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Siguiendo el procedimiento de Metodo 3, se obtuvo el compuesto del título de ácido 6-(3-bromofenil)-5-ciano-3,6-dihidro-4-metil-2-oxo-1-(2H)-pirimidinacarboxílico, 1-etil amida y ácido fenilbórico como un solido amarillo clareen un rendimiento del 44% ^1H NMR (CDCl_3 , 400 MHz) δ 8.70 (t, 1H, $J = 5.3$ Hz), 7.55 (m, 4H), 7.43 (m, 3H), 7.36 (m, 1H), 7.29 (d, 1H, $J = 7.5$ Hz), 7.19 (s, 1H), 6.39 (s, 1H), 3.34 (m, 2H), 2.18 (s, 3H), 1.17 (t, 3H, $J = 7.0$ Hz), LC/MS (ES+) 361 ($\text{M} + \text{H}^+$)

Ejemplo 119

Ácido 6-(3-(4-clorofenil)fenil)-5-ciano-3,6-dihidro-4-metil-2-oxo-1-(2H)-pirimidinacarboxílico, 1-etil amida

Siguiendo el procedimiento de Método 3, se obtuvo el compuesto del título de ácido 6-(3-bromofenil)-5-ciano-3,6-dihidro-4-metil-2-oxo-1-(2H)-pirimidinacarboxílico, 1-etil amida y ácido 4-clorofenilbórico como un solido parduzco en un rendimiento del 42% ^1H NMR ($\text{MeOH}-d_4$, 400 MHz) δ 7.57 (m, 3H), 7.51 (s, 1H), 7.45 (m, 3H), 7.29 (d, 1H, $J = 7.5$ Hz), 6.21 (s, 1H), 3.25 (m, 2H), 2.13 (s, 3H), 1.12 (t, 3H, $J = 7.0$ Hz), LC/MS (ES+) 395 ($\text{M} + \text{H}^+$)

Ejemplo 120

Ácido 5-ciano-3,6-dihidro-4-metil-2-oxo-6-(3-(2-tienil)fenil)-1-(2H)-pirimidinacarboxílico, 1-etil amida

Siguiendo el procedimiento de Método 3, se obtuvo el compuesto del título de ácido 6-(3-bromofenil)-5-ciano-3,6-dihidro-4-metil-2-oxo-1-(2H)-pirimidinacarboxílico, 1-etil amida y ácido 2-tiofenoborico como un solido amarillo claro en un rendimiento del 58% ^1H NMR (CDCl_3 , 400 MHz) δ 8.70 (t, 1H, $J = 5.3$ Hz), 7.54 (m, 2H), 7.37 (t, 1H, $J = 7.9$ Hz), 7.30 (m, 2H), 7.23 (d, 1H, $J = 7.9$ Hz), 7.12 (s, 1H), 7.08 (m, 1H), 6.37 (s, 1H), 3.32 (m, 2H), 2.18 (s, 3H), 1.17 (t, 3H, $J = 7.0$ Hz), LC/MS (ES+) 367 ($\text{M} + \text{H}^+$)

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Ejemplo 121

Ácido 5-ciano-3,6-dihidro-4-metil-2-oxo-6-(3-(3-tienil)fenil)-1-(2H)-pirimidinacarboxílico, 1-etil amida

Siguiendo el procedimiento de Metodo 3, se obtuvo el compuesto del título de ácido 6-(3-bromofenil)-5-ciano-3,6-dihidro-4-metil-2-oxo-1-(2H)-pirimidinacarboxílico, 1-etil amida y ácido 3-tiofenobórico como un sólido incoloro en un rendimiento del 14% ¹H NMR (MeOH-d₄, 400 MHz) δ 7.52 (m, 2H), 7.46 (s, 1H), 7.39 (m, 1H), 7.31 (m, 2H), 7.11 (d, 1H, J=7.5 Hz), 6.11 (s, 1H), 3.17 (m, 2H), 2.05 (s, 3H), 1.03 (t, 3H, J = 7.0 Hz), LC/MS (ES+) 367 (M+H⁺)

Ejemplo 122

5-Ciano-3,6-dihidro-4-metil-2-oxo-6-(3-(4-piridil)fenil)-(2H)-pirimidina

Metodo 5

Una mezcla de 6-(3-bromofenil)-5-ciano-3,6-dihidro-4-metil-2-oxo-(2H)-pirimidina (1.62 g, 5.5 mmol), ácido piridina-4-bórico (0.75 g, 6.1 mmol), carbonato de potasio (2.28 g, 16.5 mmol) y DMF (10 mL) se lavó con gas de nitrógeno varias veces antes de introducir [1,1'-bis(difenilfosfino)ferroceno]dicloropaladio (50 mg). La mezcla de reacción se calentó a 95 °C bajo nitrógeno durante 64 horas, se enfrió a temperatura ambiente y se filtró a través de celita. El filtrado se diluyó con MeOH y se agitó con Resina AG 50W-X2 durante 10 minutos. La resina se recogió por filtración de vacío, se lavó con MeOH y luego se eluyó 2 M NH₃ en MeOH. Esta solución NH₃-MeOH se concentró en vacío para producir 5-ciano-3,6-dihidro-4-metil-2-oxo-6-(3-(4-piridil)fenil)-(2H)-pirimidina como un sólido marrón (1.61 g, 32%) ¹H NMR (DMSO-d₆, 400 MHz) δ 9.58 (s, 1H), 8.66 (d, 2H, J = 2.2 Hz), 7.88 (s, 1H), 7.77 (d, 1H, J = 7.9 Hz), 7.69 (m, 3H), 7.57 (m, 1H), 7.41 (d, 1H, J = 7.9 Hz), 5.22 (s, 1H), 2.03 (d, 3H, J = 2.2 Hz)

Ácido 5-ciano-3,6-dihidro-4-metil-2-oxo-6-(3-(4-piridil)fenil)-1-(2H)-pirimidinacarboxílico, 1-etil amida

Siguiendo el procedimiento de Metodo 4, se obtuvo la sal HCl del compuesto del título a partir de 5-ciano-3,6-dihidro-4-metil-2-oxo-6-(3-(4-piridil)fenil)-(2H)-pirimidina e isocinato de etilo como un sólido amarillo claro en un rendimiento del 26% LC/MS (ES+) 362 (M+H⁺)

Ejemplo 123

2,2,2-Trifluoroetil isocianato

Metodo 6

Una mezcla de ácido 3,3,3-trifluoropropiónico (10.2 g, 80 mmol) y cloruro de tionilo (5.8 mL, 80 mmol) se calentó a reflujo durante 3 horas y se enfrió a temperatura ambiente. La destilación de esta mezcla produjo cloruro de 3,3,3-trifluoropropionilo como un líquido incoloro (7.12 g, 61%). Una mezcla de cloruro de 3,3,3-trifluoropropionilo (6.3 g, 43 mmol), azida de sodio (2.8 g, 43 mmol) y tolueno (10 mL) se agitó durante 18 horas a temperatura ambiente, se calentó a reflujo durante 1.5 horas y se enfrió a temperatura ambiente para producir una solución de isocianato de 2,2,2-trifluoroetilo en tolueno (aproximadamente 1.2 M por titulación usando bencilamina) la cual se utilizó como tal en reacciones subsiguientes.

Ácido 5-ciano-3,6-dihidro-4-metil-2-oxo-6-(3-(4-piridil)fenil)-1-(2H)-pirimidinacarboxílico, 1-(2,2,2-trifluoro)etil amida

Siguiendo el procedimiento de Método 4, se obtuvo la sal TFA del compuesto del título a partir de 5-ciano-3,6-dihidro-4-metil-2-oxo-6-(3-(4-piridil)fenil)-(2H)-pirimidina e isocianato de 2,2,2-trifluoroetilo como un sólido blancuzco en un rendimiento del 45%. ¹H NMR (MeOH-d₄, 500 MHz) δδ 9.51 (t, 1H, J = 6.6 Hz), 8.86 (d, 2H, J = 6.6 Hz), 8.30 (d, 2H, J = 6.6 Hz), 7.93 (d, 1H, J = 7.7 Hz), 7.90 (s, 1H), 7.67 (t, 1H, J = 7.7 Hz), 7.59 (d, 1H, J = 7.7 Hz), 6.29 (s, 1H), 3.97 (m, 2H), 2.18 (s, 3H), LC/MS (ES+) 416 (M+H⁺)

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Ejemplo 124

Acido 5-ciano-3,6-dihidro-4-metil-2-oxo-6-(3-(4-piridil)fenil)-1-(2H)-pirimidinacarboxílico, 1-isopropil amida

Siguiendo el procedimiento de Metodo 4, se obtuvo la sal TFA del compuesto del título a partir de 5-ciano-3,6-dihidro-4-metil-2-oxo-6-(3-(4-piridil)fenil)-(2H)-pirimidina y un isocianato de isopropilo como un sólido incoloro en un rendimiento del 44% ¹H NMR (MeOH-d₄, 400 MHz) δ 8.87 (d, 2H, J = 7.0 Hz), 8.34 (d, 2H, J = 7.0 Hz), 7.94 (d, 1H, J = 7.5 Hz), 7.89 (s, 1H), 7.68 (t, 1H, J = 7.5 Hz), 7.58 (d, 1H, J = 7.5 Hz), 6.27 (s, 1H), 3.86 (m, 1H), 2.16 (s, 3H), 1.18 (d, 3H, J = 6.6 Hz), 1.12 (d, 3H, J = 6.6 Hz), LC/MS (ES+) 376 (M+H⁺)

Ejemplo 125

Ácido 5-ciano-3,6-dihidro-4-metil-2-oxo-6-(3-(4-piridil)fenil)-1-(2H)-pirimidinacarboxílico, 1-ciclopropil amida

Siguiendo el procedimiento de Método 4, se obtuvo la sal TFA del compuesto del título a partir de 5-ciano-3,6-dihidro-4-metil-2-oxo-6-(3-(4-piridil)fenil)-(2H)-pirimidina e isocianato de ciclopropilo (preparado de cloruro de ciclopropanocarbonilo usando el procedimiento de Método 6) como un sólido incoloro en un rendimiento del 42% ¹H NMR (MeOH-d₄, 500 MHz) δ 8.51 (d, 2H, J = 6.0 Hz), 7.64 (d, 1H, J = 7.7 Hz), 7.60 (m, 3H), 7.46 (t, 1H, J = 7.7 Hz), 7.32 (d, 1H, J = 7.7 Hz), 6.15 (s, 1H), 2.54 (m, 1H), 2.05 (s, 3H), 0.62 (m, 2H), 0.43 (m, 1H), 0.36 (m, 1H), LC/MS (ES+) 374 (M+H⁺)

Ejemplo 126

5-Ciano-3,6-dihidro-4-metil-2-oxo-6-(3-(3-piridil)fenil)-(2H)-pirimidina

Siguiendo el procedimiento de Método 5, se obtuvo 5-ciano-3,6-dihidro-4-metil-2-oxo-6-(3-(3-piridil)fenil)-(2H)-pirimidina a partir de 6-(3-bromofenil)-5-ciano-3,6-dihidro-4-metil-2-oxo-(2H)-pirimidina y ácido piridina-3-bórico, éster ciclico de 1,3-propanodiol como un sólido

blancuzco en un rendimiento del 76% ^1H NMR (DMSO- d_6 , 400 MHz) δ 9.51 (s, 1H), 8.81 (d, 1H, $J = 2.6$ Hz), 8.53 (m, 1H), 7.99 (m, 1H), 7.82 (s, 1H), 7.64 (d, 1H, $J = 7.9$ Hz), 7.57 (d, 1H, $J = 1.8$ Hz), 7.50 (t, 1H, $J = 7.9$ Hz), 7.45 (m, 1H), 7.30 (d, 1H, $J = 2.6$ Hz), 5.15 (s, 1H), 1.97 (s, 3H)

Ácido 5-ciano-3,6-dihidro-4-metil-2-oxo-6-(3-(3-piridil)fenil)-1-(2H)-pirimidinacarboxílico acid, 1-etil amida

Siguiendo el procedimiento de Método 4, se obtuvo la sal HCl del compuesto del título a partir de 5-ciano-3,6-dihidro-4-metil-2-oxo-6-(3-(3-piridil)fenil)-(2H)-pirimidina e isocianato de etilo como un sólido amarillo claro en un rendimiento del 53% ^1H NMR (MeOH- d_4 , 400 MHz) δ 9.18 (s, 1H), 8.92 (m, 1H), 8.86 (d, 2H, $J = 5.3$ Hz), 8.19 (m, 1H), 7.78 (m, 2H), 7.64 (t, 1H, $J = 7.5$ Hz), 7.51 (d, 1H, $J = 7.5$ Hz), 6.24 (s, 1H), 3.24 (m, 2H), 2.15 (s, 3H), 1.11 (t, 3H, $J = 7.0$ Hz), LC/MS (ES+) 362 ($M+H^+$)

Ejemplo 127

Acido 5-ciano-3,6-dihidro-4-metil-2-oxo-6-(3-(3-piridil)fenil)-1-(2H)-pirimidinacarboxílico, 1-(2,2,2-trifluoro)etil amida

Siguiendo el procedimiento de Metodo 4, se obtuvo la sal TFA del compuesto del título a partir de 5-ciano-3,6-dihidro-4-metil-2-oxo-6-(3-(3-piridil)fenil)-(2H)-pirimidina e isocianato de 2,2,2-trifluoroetilo como un sólido incoloro en un rendimiento del 40% ^1H NMR (MeOH- d_4 , 400 MHz) δ 9.51 (s, 1H), 9.07 (s, 1H), 8.79 (s, 1H), 8.71 (d, 1H, $J = 6.6$ Hz), 8.04 (m, 1H), 7.76 (d, 1H, $J = 7.7$ Hz), 7.73 (s, 1H), 7.62 (m, 1H), 7.49 (d, 1H, $J = 7.7$ Hz), 6.27 (s, 1H), 3.98 (m, 2H), 2.17 (d, 3H, $J = 2.7$ Hz), LC/MS (ES+) 416 ($M+H^+$)

Ejemplo 128

Acido 5-ciano-3,6-dihidro-4-metil-2-oxo-6-(3-(3-piridil)fenil)-1-(2H)-pirimidinacarboxílico, 1-isopropil amida

Siguiendo el procedimiento de Metodo 4, se obtuvo la sal TFA del compuesto del título a partir de 5-ciano-3,6-dihidro-4-metil-2-oxo-6-(3-(3-

piridil)fenil)-(2H)-pirimidina e isocianato de isopropilo como un sólido incoloro en un rendimiento del 46% ¹H NMR (MeOH-d₄, 400 MHz) δ 9.09 (d, 1H, *J* = 1.8 Hz), 8.79 (d, 1H, *J* = 5.3 Hz), 8.74 (m, 1H), 8.05 (m, 1H), 7.76 (d, 1H, *J* = 7.9 Hz), 7.73 (d, 1H, *J* = 1.8 Hz), 7.62 (t, 1H, *J* = 7.9 Hz), 7.48 (d, 1H, *J* = 7.9 Hz), 6.24 (s, 1H), 3.86 (m, 1H), 2.15 (s, 3H), 1.18 (d, 3H, *J* = 6.6 Hz), 1.12 (d, 3H, *J* = 6.6 Hz), LC/MS (ES+) 376 (M+H⁺)

Ejemplo 129

Ácido 5-ciano-3,6-dihidro-4-metil-2-oxo-6-(3-(3-piridil)fenil)-1-(2H)-pirimidinacarboxílico, 1-ciclopropil amida

Siguiendo el procedimiento de Metodo 4, se obtuvo la sal HCl del compuesto del título a partir de 5-ciano-3,6-dihidro-4-metil-2-oxo-6-(3-(3-piridil)fenil)-(2H)-pirimidina e isocianato de ciclopropilo como un sólido blancuzco en un rendimiento del 40% ¹H NMR (MeOH-d₄, 500 MHz) δ 9.08 (s, 1H), 8.80 (d, 1H, *J* = 8.2 Hz), 8.77 (d, 1H, *J* = 5.5 Hz), 8.09 (m, 1H), 7.70 (d, 1H, *J* = 7.7 Hz), 7.67 (s, 1H), 7.55 (t, 1H, *J* = 7.7 Hz), 7.41 (d, 1H, *J* = 7.7 Hz), δ 1.5 (s, 1H), 2.53 (m, 1H), 2.06 (s, 3H), 0.62 (m, 2H), 0.43 (m, 1H), 0.36 (m, 1H), LC/MS (ES+) 374 (M+H⁺)

Ejemplo 130

Ácido 5-ciano-3,6-dihidro-4-metil-2-oxo-6-(3-(3-piridil)fenil)-1-(2H)-pirimidinacarboxílico, 1-ciclobutil amida

Siguiendo el procedimiento de Método 4, se obtuvo la sal TFA del compuesto del título a partir de 5-ciano-3,6-dihidro-4-metil-2-oxo-6-(3-(3-piridil)fenil)-(2H)-pirimidina e isocianato de ciclobutilo (preparado de cloruro de ciclobutanocarbonilo usando el procedimiento de Metodo 6) como un sólido blancuzco en un rendimiento de 88% ¹H NMR (MeOH-d₄, 500 MHz) δ 8.99 (s, 1H), 8.69 (d, 1H, *J* = 4.9 Hz), 8.63 (d, 1H, *J* = 8.2 Hz), 7.95 (m, 1H), 7.66 (d, 1H, *J* = 7.7 Hz), 7.62 (s, 1H), 7.52 (t, 1H, *J* = 7.7 Hz), 7.38 (d, 1H, *J* = 7.7 Hz), 6.12 (s, 1H), 4.09 (m, 1H), 2.18 (m, 2H), 2.06 (s, 3H), 1.82 (m, 2H), 1.63 (m, 2H), LC/MS (ES+) 388 (M+H⁺)

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17**Ejemplo 131**

Ácido 5-ciano-3,6-dihidro-4-metil-2-oxo-6-(3-(3-piridil)fenil)-1-(2H)-pirimidinacarboxílico, 1-ciclopentil amida

Siguiendo el procedimiento de Metodo 4, se obtuvo la sal TFA del compuesto del título a partir de 5-ciano-3,6-dihidro-4-metil-2-oxo-6-(3-(3-piridil)fenil)-(2H)-pirimidina e isocianato de ciclopentilo como un sólido blancuzco en un rendimiento de 46% LC/MS (ES+) 402 (M+H⁺)

Ejemplo 132

Ácido 5-ciano-3,6-dihidro-4-metil-2-oxo-6-(3-(3-piridil)fenil)-1-(2H)-pirimidinacarboxílico, 1-ciclopropilmetil amida

Siguiendo el procedimiento de Método 4, se obtuvo la sal TFA del compuesto del título a partir de 5-ciano-3,6-dihidro-4-metil-2-oxo-6-(3-(3-piridil)fenil)-(2H)-pirimidina e isocianato de ciclopropilmetilo (preparado de ácido ciclopropilacético usando el procedimiento de Metodo 6) como un sólido blancuzco en un rendimiento de 62% LC/MS (ES+) (M+H⁺)

Ejemplo 133

5-Ciano-3,6-dihidro-4-metil-2-oxo-6-(3-(2-piridil)fenil)-(2H)-pirimidina

Siguiendo el procedimiento de Método 5, se obtuvo 5-ciano-3,6-dihidro-4-metil-2-oxo-6-(3-(2-piridil)fenil)-(2H)-pirimidina a partir de 6-(3-bromofenil)-5-ciano-3,6-dihidro-4-metil-2-oxo-(2H)-pirimidina y 2-tributilstannilpiridina como un sólido blancuzco en un rendimiento de 26% ¹H NMR (MeOH-d₄, 500 MHz) 8.71 (d, 1H, J = 5.0 Hz), 8.25 (m, 1H), 8.09 (d, 1H, J = 7.7 Hz), 7.93 (m, 2H), 7.67 (m, 1H), 7.63 (d, 1H, J = 8.2 Hz), 7.57 (d, 1H, J = 7.7 Hz), 5.29 (s, 1H), 2.13 (s, 3H), LC/MS (ES+) 291 (M+H⁺)

Acido 5-ciano-3,6-dihidro-4-metil-2-oxo-6-(3-(2-piridil)fenil)-1-(2H)-pirimidinacarboxílico, 1-etil amida

Siguiendo el procedimiento de Método 4, se obtuvo el compuesto del título a partir de 5-ciano-3,6-dihidro-4-metil-2-oxo-6-(3-(2-piridil)fenil)-(2H)-

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pirimidina e isocianato de etilo como un sólido incoloro en un rendimiento del 25% ^1H NMR (MeOH- d_4 , 400 MHz) δ 8.61 (m, 1H), 7.90 (m, 3H), 7.82 (d, 1H, $J = 7.9$ Hz), 7.51 (m, 1H), 7.38 (m, 2H), 6.25 (s, 1H), 3.25 (m, 2H), 2.15 (s, 3H), 1.11 (t, 3H, $J = 7.0$ Hz), LC/MS (ES+) 362 ($\text{M} + \text{H}^+$)

Ejemplo 134

5-Ciano-3,6-dihidro-4-metil-2-oxo-6-(3-(2-t-butoxicarbonilpirrol) fenil)-(2H)-pirimidina

Siguiendo el procedimiento de Metodo 5, se obtuvo 5-ciano-3,6-dihidro-4-metil-2-oxo-6-(3-(2-t-butoxicarbonilpirrol)fenil)-(2H)-pirimidina a partir de 6-(3-bromofenil)-5-ciano-3,6-dihidro-4-metil-2-oxo-(2H)-pirimidina y ácido 1-(t-butoxicarbonil)pirrol-2-bórico como un sólido espumoso amarillo claro en un rendimiento del 43% ^1H NMR (DMSO- d_6 , 400 MHz) δ 9.52 (s, 1H), 7.84 (s, 1H), 7.39 (t, 1H, $J = 7.9$ Hz), 7.34 (m, 1H), 7.28 (d, 1H, $J = 7.9$ Hz), 7.23 (d, 1H, $J = 7.9$ Hz), 7.19 (s, 1H), 6.28 (m, 1H), 6.21 (m, 1H), 5.09 (s, 1H), 2.00 (s, 3H), 1.28 (s, 9 H)

Ácido 5-ciano-3,6-dihidro-4-metil-2-oxo-6-(3-(2-pirrol)fenil)-1-(2H)-pirimidinacarboxílico, 1-etil amida

Siguiendo el procedimiento de Metodo 4 y el tratamiento subsiguiente con TFA en CH_2Cl_2 durante 3 horas, se obtuvo el compuesto del título de 5-ciano-3,6-dihidro-4-metil-2-oxo-6-(3-(2-t-butoxicarbonilpirrol)fenil)-(2H)-pirimidina e isocianato de etilo como un sólido café claro en un rendimiento del 21% ^1H NMR (MeOH- d_4 , 400 MHz) δ 7.49 (m, 2H), 7.32 (t, 1H, $J = 7.9$ Hz), 7.06 (d, 1H, $J = 7.9$ Hz), 6.80 (s, 1H), 6.43 (s, 1H), 6.14 (m, 2H), 3.25 (m, 2H), 2.14 (s, 3H), 1.12 (t, 3H, $J = 7.0$ Hz), LC/MS (ES+) 350 ($\text{M} + \text{H}^+$)

Ejemplo 135

6-(3-Bromo-4-fluorofenil)-5-ciano-3,6-dihidro-4-metil-2-oxo-(2H)-pirimidina

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Siguiendo el procedimiento de Método 1, se obtuvo 6-(3-bromo-4-fluorofenil)-5-ciano-3,6-dihidro-4-metil-2-oxo-(2H)-pirimidina a partir de 3-bromo-4-fluorobenzaldehído, urea y acetoacetamida como un sólido amarillo claro en un rendimiento del 99% ^1H NMR (DMSO- d_6 , 400 MHz) δ 9.62 (s, 1H), 7.86 (s, 1H), 7.62 (d, 1H, $J = 6.6$ Hz), 7.44 (t, 1H, $J = 8.8$ Hz), 7.38 (m, 1H), 5.18 (s, 1H), 2.03 (s, 3H)

5-Ciano-3,6-dihidro-6-(4-fluoro-3-(3-piridil)fenil)-4-metil-2-oxo-(2H)-pirimidina

Siguiendo el procedimiento de Método 5, se obtuvo 5-ciano-3,6-dihidro-6-(4-fluoro-3-(3-piridil)fenil)-4-metil-2-oxo-(2H)-pirimidina a partir de 6-(3-bromo-4-fluorofenil)-5-ciano-3,6-dihidro-4-metil-2-oxo-(2H)-pirimidina y ácido piridina-3-bórico, éster cíclico de 1,3-propanodiol como un sólido café oscuro en un rendimiento del 44% ^1H NMR (DMSO- d_6 , 400 MHz) δ 9.58 (s, 1H), 8.74 (s, 1H), 8.62 (m, 1H), 7.97 (m, 1H), 7.86 (s, 1H), 7.53 (m, 2H), 7.42 (m, 1H), 7.40 (s, 1H), 5.23 (s, 1H), 2.02 (s, 3H)

Ácido 5-ciano-3,6-dihidro-6-(4-fluoro-3-(3-piridil)fenil)-4-metil-2-oxo-1-(2H)-pirimidinacarboxílico, 1-etil amida

Siguiendo el procedimiento de Método 4, se obtuvo la sal TFA del compuesto del título a partir de 5-ciano-3,6-dihidro-6-(4-fluoro-3-(3-piridil)fenil)-4-metil-2-oxo-(2H)-pirimidina e isocianato de etilo como un sólido incoloro en un rendimiento del 52% ^1H NMR (MeOH- d_4 , 400 MHz) δ 8.95 (s, 1H), 8.74 (d, 1H, $J = 4.9$ Hz), 8.58 (d, 1H, $J = 7.7$ Hz), 7.98 (m, 1H), 7.54 (m, 1H), 7.43 (m, 1H), 7.28 (m, 1H), 6.14 (s, 1H), 2.06 (s, 3H), 1.02 (t, 3H, $J = 7.1$ Hz), LC/MS (ES+) 380 ($M+H^+$)

Ejemplo 136

Ácido 5-ciano-3,6-dihidro-6-(4-fluoro-3-(3-piridil)fenil)-4-metil-2-oxo-1-(2H)-pirimidinacarboxílico, 1-(2,2,2-trifluoro)etil amida

Siguiendo el procedimiento de Método 4, se obtuvo la sal TFA del compuesto del título a partir de 5-ciano-3,6-dihidro-6-(4-fluoro-3-(3-

piridil)fenil)-4-metil-2-oxo-(2H)-pirimidina e isocianato de 2,2,2-trifluoroetilo como un sólido incoloro en un rendimiento del 31% ¹H NMR (MeOH-d₄, 500 MHz) δ ¹H NMR (MeOH-d₄, 400 MHz) δδ 9.48 (m, 1H), 8.99 (s, 1H), 8.80 (s, 1H), 8.57 (d, 1H, *J* = 8.2 Hz), 8.00 (m, 1H), 7.63 (m, 1H), 7.53 (m, 1H), 7.38 (m, 1H), 6.26 (s, 1H), 3.97 (m, 2H), 2.17 (d, 3H, *J* = 1.6 Hz), LC/MS (ES⁺) 434 (M+H⁺)

Ejemplo 137

Ácido 5-ciano-3,6-dihidro-6-(4-fluoro-3-(3-piridil)fenil)-4-metil-2-oxo-1-(2H)-pirimidinacarboxílico, 1-ciclopropil amida

Siguiendo el procedimiento de Metodo 4, se obtuvo la sal TFA del compuesto del título a partir de 5-ciano-3,6-dihidro-6-(4-fluoro-3-(3-piridil)fenil)-4-metil-2-oxo-(2H)-pirimidina e isocianato de ciclopropilo como un sólido blancuzco en un rendimiento de 39%

LC/MS (ES⁺) 392 (M+H⁺)

Ejemplo 138

6-(5-Bromo-2-fluorofenil)-5-ciano-3,6-dihidro-4-metil-2-oxo-(2H)-pirimidina

Siguiendo el procedimiento de Metodo 1, se obtuvo 6-(5-bromo-2-fluorofenil)-5-ciano-3,6-dihidro-4-metil-2-oxo-(2H)-pirimidina a partir de 5-bromo-2-fluorobenzaldehído, urea y acetoacetamida como un sólido amarillo en un rendimiento del 72% ¹H NMR (DMSO-d₆, 400 MHz) δ 9.66 (s, 1H), 7.81 (s, 1H), 7.61 (m, 1H), 7.54 (m, 1H), 7.27 (m, 1H), 5.36 (s, 1H), 2.02 (d, 3H, *J* = 3.1 Hz)

5-Ciano-3,6-dihidro-6-(2-fluoro-5-(3-piridil)fenil)-4-metil-2-oxo-(2H)-pirimidina

Siguiendo el procedimiento de Metodo 5, se obtuvo 5-ciano-3,6-dihidro-6-(2-fluoro-5-(3-piridil)fenil)-4-metil-2-oxo-(2H)-pirimidina a partir de 6-(5-bromo-2-fluorofenil)-5-ciano-3,6-dihidro-4-metil-2-oxo-(2H)-pirimidina y ácido piridina-3-bórico, éster cíclico 1,3-propanodiol como un sólido

blancuzco en un rendimiento de 59% ^1H NMR (DMSO- d_6 , 400 MHz) δ 9.62 (s, 1H), 8.86 (d, 1H, $J = 1.8$ Hz), 8.58 (m, 1H), 8.04 (m, 1H), 7.81 (s, 1H), 7.77 (m, 1H), 7.69 (m, 1H), 7.50 (m, 1H), 7.38 (m, 1H), 5.41 (s, 1H), 2.01 (d, 3H, $J = 0.9$ Hz)

Acido 5-ciano-3,6-dihidro-6-(2-fluoro-5-(3-piridil)fenil)-4-metil-2-oxo-1-(2H)-pirimidinacarboxílico, 1-etil amida

Siguiendo el procedimiento de Metodo 4, se obtuvo la sal HCl del compuesto del título a partir de 5-ciano-3,6-dihidro-6-(2-fluoro-5-(3-piridil)fenil)-4-metil-2-oxo-(2H)-pirimidina e isocianato de etilo como un sólido ligeramente amarillo en un rendimiento del 34% ^1H NMR (MeOH- d_4 , 500 MHz) δ 9.20 (s, 1H), 8.91 (d, 1H, $J = 8.2$ Hz), 8.86 (d, 1H, $J = 4.4$ Hz), 8.19 (m, 1H), 7.84 (m, 2H), 7.40 (m, 1H), 6.29 (s, 1H), 3.20 (m, 2H), 2.12 (d, 3H, $J = 2.2$ Hz), 1.09 (m, 3H), LC/MS (ES+) 380 ($\text{M}+\text{H}^+$)

Ejemplo 139

Acido 5-ciano-3,6-dihidro-6-(2-fluoro-5-(3-piridil)fenil)-4-metil-2-oxo-1-(2H)-pirimidinacarboxílico, 1-ciclopropil amida

Siguiendo el procedimiento de Método 4, se obtuvo la sal HCl del compuesto del título a partir de 5-ciano-3,6-dihidro-6-(2-fluoro-5-(3-piridil)fenil)-4-metil-2-oxo-(2H)-pirimidina e isocianato de ciclopropilo como un sólido amarillo claro en un rendimiento del 32% ^1H NMR (MeOH- d_4 , 500 MHz) δ 9.19 (s, 1H), 8.91 (d, 1H, $J = 8.2$ Hz), 8.85 (d, 1H, $J = 5.5$ Hz), 8.17 (m, 1H), 7.84 (m, 2H), 7.40 (m, 1H), 6.28 (s, 1H), 2.58 (m, 1H), 2.11 (s, 3H), 0.69 (m, 2H), 0.51 (m, 1H), 0.42 (m, 1H), LC/MS (ES+) 392 ($\text{M}+\text{H}^+$)

Ejemplo 140

5-Ciano-3,6-dihidro-4-metil-6-(3-(4-metil-3-piridil)fenil)-2-oxo-(2H)-pirimidina

Metodo 7

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Una mezcla de 6-(3-bromofenil)-5-ciano-3,6-dihidro-4-metil-2-oxo-(2H)-pirimidina (1 46 g, 5 mmol), bis(pinacolato)diboro (1 40 g, 5 5 mmol), acetato de potasio (1 47 g, 16 5 mmol) y DMF (5 mL) se lavo con gas nitrógeno varias veces antes de introducir [1,1'-bis(difenilfosfino)ferroceno]dicloropaladio (50 mg) La mezcla de reacción se calentó a 95 °C bajo nitrógeno durante 18 horas, se enfrió a temperatura ambiente y se filtró a través de celita. El filtrado se diluyó con EtOAc, se lavo con agua y con salmuera, se seco (Na_2SO_4) y se concentró para producir un aceite viscoso oscuro Este material se disolvió nuevamente en DMF (5 mL) y se hizo reaccionar bajo nitrógeno con 5-bromo-2-metilpiridina (0 66 g, 3 8 mmol), [1,1'-bis(difenilfosfino)ferroceno]dicloropaladio (50 mg) y carbonato de potasio (2 07 g, 15 mmol) a 95 °C durante 18 horas La mezcla de reacción se enfrió a temperatura ambiente, se diluyó con MeOH y se agitó con Resina AG 50W-X2 durante 5 minutos La resina se recogió por filtración de vacío, se lavó con MeOH y luego se eluyó con 2 M NH_3 in MeOH Esta solución NH_3 -MeOH se concentró en vacío para producir 5-ciano-3,6-dihidro-4-metil-6-(3-(4-metil-3-piridil)fenil)-2-oxo-(2H)-pirimidina como un sólido café (0 69 g, 45%) ^1H NMR ($\text{DMSO}-d_6$, 400 MHz) δ 9 55 (s, 1H), 8 72 (s, 1H), 7 92 (d, 1H, $J = 6 2$ Hz), 7 85 (s, 1H), 7 64 (d, 1H, $J = 7 5$ Hz), 7 57 (s, 1H), 7 51 (t, 1H, $J = 7 5$ Hz), 7 33 (m, 2H), 5 18 (s, 1H), 2 49 (s, 3H), 2 01 (s, 3H)

Ácido 5-ciano-3,6-dihidro-4-metil-6-(3-(4-metil-3-piridil)fenil)-2-oxo-1-(2H)-pirimidinacarboxílico, 1-etil amida

Siguiendo el procedimiento de Método 4, se obtuvo la sal HCl del compuesto del título a partir de 5-ciano-3,6-dihidro-4-metil-6-(3-(4-metil-3-piridil)fenil)-2-oxo-(2H)-pirimidina e isocianato de etilo como un sólido ligeramente amarillo en un rendimiento del 33% ^1H NMR ($\text{MeOH}-d_4$, 500 MHz) δ 8 99 (d, 1H, $J = 2 2$ Hz), 8 75 (m, 1H), 8 01 (d, 1H, $J = 8 2$ Hz), 7 76 (d, 1H, $J = 7 7$ Hz), 7 73 (s, 1H), 7 62 (t, 1H, $J = 7 7$ Hz), 7 49 (d, 1H,

$J = 7.7$ Hz), 6.23 (s, 1H), 3.25 (m, 2H), 2.84 (s, 3H), 2.15 (s, 3H), 1.12 (t, 3H, $J = 7.1$ Hz), LC/MS (ES+) 376 (M+H⁺)

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Ejemplo 141

Ácido 5-ciano-3,6-dihidro-4-metil-6-(3-(4-metil-3-piridil)fenil)-2-oxo-1-(2H)-pirimidinacarboxílico, 1-ciclopropil amida

Seguendo el procedimiento de Metodo 4, se obtuvo la sal TFA del compuesto del título a partir de 5-ciano-3,6-dihidro-4-metil-6-(3-(4-metil-3-piridil)fenil)-2-oxo-(2H)-pirimidina e isocianato de ciclopropilo como un sólido incoloro en un rendimiento del 17%. ¹H NMR (MeOH-d₄, 400 MHz) δδ 8.95 (s, 1H), 8.66 (d, 1H, $J = 8.3$ Hz), 7.93 (d, 1H, $J = 8.3$ Hz), 7.75 (d, 1H, $J = 7.9$ Hz), 7.72 (s, 1H), 7.61 (t, 1H, $J = 7.9$ Hz), 7.47 (d, 1H, $J = 7.9$ Hz), 6.23 (s, 1H), 2.81 (s, 3H), 2.63 (m, 1H), 2.15 (s, 3H), 0.71 (m, 2H), 0.51 (m, 1H), 0.46 (m, 1H), LC/MS (ES+) 388 (M+H⁺)

Ejemplo 142

6-(3-Carbometoxifenil)-5-ciano-3,6-dihidro-4-metil-2-oxo-(2H)-pirimidina

Método 8

Una mezcla de 3-carbometoxibenzaldehído (4.15 g, 25.3 mmol), acetoacetamida (2.56 g, 25.3 mmol), urea (2.28 g, 38.0 mmol), etearato de trifluoruro de boro (0.25 mL), cloruro de cobre (0.25 g, 2.5 mmol), ácido acético (0.1 mL) y THF (50 mL) se calentó a 65 °C durante 18 horas y se enfrió a temperatura ambiente. Los precipitados resultantes se recogieron por filtración de vacío, se lavaron con THF y se secaron por aire para producir 7.48 g de un sólido blancuzco. A una mezcla de este sólido y piridina (100 mL) a 0 °C se agregó anhídrido trifluoroacético (10.6 mL, 7.5 mmol) lentamente a través de una jeringa. La solución café resultante se agitó durante 2.5 horas y se vertió en agua para resultar en precipitación. Los precipitados se recogieron por filtración de vacío, se lavaron con agua y con CH₂Cl₂, y se secaron por aire para producir 6-(3-carbometoxifenil)-5-

ciano-3,6-dihidro-4-metil-2-oxo-(2H)-pirimidina como un solido marrón claro (4.57 g, 67%) ^1H NMR (DMSO- d_6 , 400 MHz) δ 9.62 (s, 1H), 7.94 (m, 2H), 7.90 (s, 1H), 7.58 (m, 2H), 5.24 (s, 1H), 3.87 (s, 3H), 2.02 (s, 3H)

Ácido 6-(3-carbometoxifenil)-5-ciano-3,6-dihidro-4-metil-2-oxo-1-(2H)-pirimidinacarboxílico, 1-etil amida

Siguiendo el procedimiento de Método 4, se obtuvo ácido 6-(3-carbometoxifenil)-5-ciano-3,6-dihidro-4-metil-2-oxo-1-(2H)-pirimidinacarboxílico, 1-etil amida a partir de 6-(3-carbometoxifenil)-5-ciano-3,6-dihidro-4-metil-2-oxo-(2H)-pirimidina e isocianato de etilo como un solido incoloro en un rendimiento del 52% ^1H NMR (MeOH- d_4 , 400 MHz) δ 8.94 (s, 1H), 7.89 (m, 2H), 7.48 (d, 1H, $J = 7.9$ Hz), 7.40 (t, 1H, $J = 7.9$ Hz), 6.15 (s, 1H), 3.83 (s, 3H), 3.17 (m, 2H), 2.07 (s, 3H), 1.05 (t, 3H, $J = 7.0$ Hz), LC/MS (ES+) 343 ($M+H^+$), 365 ($M+Na^+$)

Acido 6-(3-carboxifenil)-5-ciano-3,6-dihidro-4-metil-2-oxo-1-(2H)-pirimidinacarboxílico, 1-etil amida

Método 9

A una mezcla de 6-(3-carbometoxifenil)-5-ciano-3,6-dihidro-4-metil-2-oxo-1-(2H)-pirimidinacarboxílico, 1-etil amida (0.34 g, 1.0 mmol), MeOH (9 mL) y agua (3 mL) a 0 °C se agrego hidroxido de litio (0.84g, 20.0 mmol). La mezcla de reacción se agito durante 1 hora, se acidifico a pH 2 con 1 N HCl y se extrajo con EtOAc. El extracto se seco ($MgSO_4$) y se concentro in vacuo para producir ácido 6-(3-carboxifenil)-5-ciano-3,6-dihidro-4-metil-2-oxo-1-(2H)-pirimidinacarboxílico, 1-etil amida como un solido incoloro (0.30 g, 92%) ^1H NMR (MeOH- d_4 , 400 MHz) δ 8.98 (s, 1H), 7.89 (m, 2H), 7.46 (d, 1H, $J = 7.5$ Hz), 7.42 (t, 1H, $J = 7.5$ Hz), 6.12 (s, 1H), 3.16 (m, 2H), 2.06 (s, 3H), 1.03 (t, 3H, $J = 7.0$ Hz)

Ácido 5-ciano-3,6-dihidro-4-metil-6-(3-(4-metil-5-oxa-2,3-diazol) fenil)-2-oxo-1-(2H)-pirimidinacarboxílico, 1-etil amida



Método 10

Una mezcla de ácido 6-(3-carboxifenil)-5-ciano-3,6-dihidro-4-metil-2-oxo-1-(2H)-pirimidinacarboxílico, 1-etil amida (0.03 g, 0.1 mmol), reactivo BOP (0.07 g, 0.15 mmol), diisopropiletilamina (0.03 mL, 0.15 mmol), hidrazina (5 mL, 0.15 mmol) y THF (1 mL) se agitó durante 1 hora y se concentró in vacuo. El residuo se calentó con ortoacetato de trietilo (1 mL) a 80 °C durante 18 horas para producir una solución roja clara. Esta solución se concentró in vacuo, la purificación del residuo se llevó a cabo usando HPLC preparativa. Fracciones apropiadas se combinaron y se concentraron in vacuo para producir el compuesto del título como un sólido blancuzco (0.02 g, 55%). ¹H NMR (DMSO-d₆, 500 MHz) δδ 10.54 (s, 1H), 8.80 (t, 1H, J = 5.5 Hz), 7.93 (d, 1H, J = 7.9 Hz), 7.84 (s, 1H), 7.64 (t, 1H, J = 7.9 Hz), 7.50 (d, 1H, J = 7.9 Hz), 6.18 (s, 1H), 3.16 (m, 2H), 2.09 (s, 3H), 1.03 (t, 3H, J = 7.1 Hz), LC/MS (ES+) 367 (M+H⁺), 399 (M+Na⁺)

Ejemplo 143

Ácido 5-ciano-3,6-dihidro-4-metil-6-(3-(5-oxa-4-trifluorometil-2,3-diazol)fenil)-2-oxo-1-(2H)-pirimidinacarboxílico, 1-etil amida

Siguiendo el procedimiento de Método 10, se obtuvo el compuesto del título a partir de 6-(3-carboxifenil)-5-ciano-3,6-dihidro-4-metil-2-oxo-1-(2H)-pirimidinacarboxílico, 1-etil amida, hidracina y ácido trifluoroacético como un sólido incoloro en un rendimiento del 42%. ¹H NMR (DMSO-d₆, 500 MHz) δδ 10.54 (s, 1H), 8.79 (t, 1H, J = 5.5 Hz), 7.84 (d, 1H, J = 7.7 Hz), 7.75 (s, 1H), 7.57 (t, 1H, J = 7.7 Hz), 7.51 (d, 1H, J = 7.7 Hz), 6.13 (s, 1H), 3.16 (m, 2H), 2.09 (s, 3H), 1.03 (t, 3H, J = 7.1 Hz), ¹⁹F NMR (DMSO-d₆, 500 MHz) δδ -73.35

Ejemplo 144

6-(2-Bromofenil)-5-ciano-3,6-dihidro-4-metil-2-oxo-(2H)-pirimidina

Siguiendo el procedimiento de Método 1, se obtuvo 6-(2-bromofenil)-5-ciano-3,6-dihidro-4-metil-2-oxo-(2H)-pirimidina a partir de 2-

bromobenzaldehído, acetoactamida y urea como un sólido amarillo claro en un rendimiento del 85% ^1H NMR (DMSO- d_6 , 400 MHz) δ 9.64 (s, 1H), 7.81 (s, 1H), 7.63 (d, 1H, $J = 7.9$ Hz), 7.44 (m, 2H), 7.29 (m, 1H), 5.51 (s, 1H), 2.01 (s, 3H)

6-(2-(4-Clorofenil)fenil)-5-ciano-3,6-dihidro-4-metil-2-oxo-(2H)-pirimidina

Siguiendo el procedimiento de Metodo 5, se obtuvo 6-(2-(4-chlorofenil)fenil)-5-ciano-3,6-dihidro-4-metil-2-oxo-(2H)-pirimidina a partir de 6-(2-bromofenil)-5-ciano-3,6-dihidro-4-metil-2-oxo-(2H)-pirimidina y ácido 4-clorofenilbórico como un sólido incoloro en un rendimiento del 53%

Ácido 6-(2-(4-clorofenil)fenil)-5-ciano-3,6-dihidro-4-metil-2-oxo-1-(2H)-pirimidinacarboxílico, 1-etil amida

Siguiendo el procedimiento de Método 4, se obtuvo el compuesto del título de 6-(2-(4-chlorofenil)fenil)-5-ciano-3,6-dihidro-4-metil-2-oxo-(2H)-pirimidina e isocianato de etilo como un sólido incoloro en un rendimiento del 47% ^1H NMR (MeOH- d_4 , 400 MHz) 7.47 (m, 2H), 7.35 (m, 5H), 7.12 (d, 1H, $J = 6.6$ Hz), 6.17 (s, 1H), 3.16 (m, 2H), 1.95 (s, 3H), 1.05 (m, 3H, $J = 7.0$ Hz), LC/MS (ES+) 395 (M+H $^+$)

Ejemplo 145

5-Ciano-3,6-dihidro-4-metil-2-oxo-6-(2-(3-piridil)fenil)-(2H)-pirimidina

Siguiendo el procedimiento de Metodo 5, se obtuvo 5-ciano-3,6-dihidro-4-metil-2-oxo-6-(2-(3-piridil)fenil)-(2H)-pirimidina a partir de 6-(2-bromofenil)-5-ciano-3,6-dihidro-4-metil-2-oxo-(2H)-pirimidina y ácido piridina-3-bórico, éster cíclico de 1,3-propanodiol como un aceite viscoso incoloro en un rendimiento del 29% ^1H NMR (MeOH- d_4 , 400 MHz) δ 8.44 (m, 2H), 7.74 (m, 1H), 7.45 (m, 4H), 7.14 (d, 1H, $J = 7.5$ Hz), 5.12 (s, 1H), 1.88 (d, 3H, $J = 1.3$ Hz)

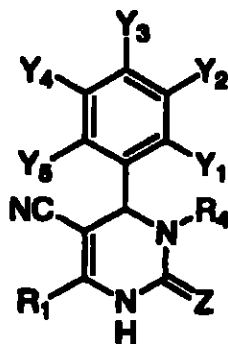
**Ácido 5-ciano-3,6-dihidro-4-metil-2-oxo-6-(2-(3-piridil)fenil)-1-(2H)-
pirimidinacarboxílico, 1-etil amida**

Siguiendo el procedimiento de Metodo 4, se obtuvo la sal TFA del compuesto del título a partir de 5-ciano-3,6-dihidro-4-metil-2-oxo-6-(2-(3-piridil)fenil)-(2H)-pirimidina e isocianato de etilo como un solido amarillo claro en un rendimiento del 53% LC/MS (ES+) 362 (M+H⁺)

Reivindicaciones

Lo que se reivindica es

1 Compuesto de formula IA



IA

sus enantiomeros, diastereomeros, sales de aceptación farmaceutica, profarmacos y solvatos de los mismos, en donde

R_1 se selecciona del grupo conformado por hidrogeno, alquilo y cicloalquilo,

Y_1 , Y_2 , Y_3 , Y_4 y Y_5 se seleccionan independientemente del grupo conformado por H, halogeno, alquilo inferior, O alquilo, O arilo, NH alquilo, NH arilo, N alquilalquilo, N alquilarilo, N arilarilo con la condicion que por lo menos uno de Y_1 , Y_2 , Y_3 , Y_4 y Y_5 es arilo o heteroarilo,

R_4 se selecciona del grupo conformado por alquilo, arilalquilo, cicloalquilalquilo, heteroarilalquilo, heterocicloalquilalquilo, CN, COR_5 , CO_2R_5 , y $CONR_5R_6$,

R_5 y R_6 , se seleccionan independientemente del grupo conformado por H, alquilo, haloalquilo, cicloalquilo, aminoalquilo, arilalquilo, cicloalquilalquilo, heteroarilalquilo y heterocicloalquilalquilo,

Z se selecciona del grupo conformado por O, S y NR_8 ,

R_8 se selecciona del grupo conformado por H, CN, sulfonamido, OR_7 , alquilo, cicloalquilo, arilo, arilalquilo, heterociclilo, heteroarilo y heteroarilalquilo, y

R_7 se selecciona del grupo conformado por H, alquilo, arilalquilo, cicloalquilalquilo, heterocicloalquilalquilo y heteroarilalquilo

- 2 El compuesto de reivindicación 1 en donde Y_2 es anillo o heteroanillo
- 3 El compuesto de reivindicación 2 en donde Y_2 es un fenilo, piridilo, thiazolilo, pirrolilo, o diazolilo opcionalmente sustituido
- 4 El compuesto de reivindicación 3 en donde dicho sustituyente es halo, alquilo, o haloalquilo
- 5 El compuesto de reivindicación 4 en donde dicho sustituyente es Br, Cl, F, metilo, etilo, o CF_3
- 6 El compuesto de reivindicación 1 en donde R_4 es alquilo, arilalquilo, CO_2R_5 ó $CONR_5R_6$
- 7 El compuesto de reivindicación 1 en donde R_1 es alquilo, R_4 se selecciona del grupo conformado por alquilo, arilalquilo, CO_2R_5 , y $CONR_5R_6$, R_5 y R_6 se seleccionan independientemente del grupo conformado por H, alquilo, haloalquilo, cicloalquilo, y arilalquilo, Z se selecciona del grupo conformado por O, S, y NR_8 , R_8 se selecciona del grupo conformado por H y CN
- 8 El compuesto de reivindicación 1 en donde R_4 es CO_2R_5 , y Z es O
- 9 El compuesto de reivindicación 1 en donde R_4 es $CONR_5R_6$ y Z es O
- 10 El compuesto de reivindicación 1 en donde R_4 se selecciona del grupo conformado por alquilo y arilalquilo, y Z es O
- 11 El compuesto de reivindicación 1 en donde R_1 es CH_3 , R_4 es CO_2R_5 , R_5 es alquilo, y Z es O

12 Un compuesto seleccionado del grupo conformado por

ácido 6-(3-bifenil)-5-ciano-3,6-dihidro-4-metil-2-oxo-1-(2H)-
pirimidinacarboxílico, 1-etil ester;

ácido 5-ciano-3,6-dihidro-4-metil-2-oxo-6-(3-(2-tienil)fenil)-1-(2H)-
pirimidinacarboxílico, 1-etil ester,

ácido 6-(3-bifenil)-5-ciano-3,6-dihidro-4-metil-2-oxo-1-(2H)-
pirimidinacarboxílico, 1-etil amida,

ácido 6-(3-(4-clorfenil)fenil)-5-ciano-3,6-dihidro-4-metil-2-oxo-1-(2H)-
pirimidinacarboxílico, 1-etil amida,

ácido 5-ciano-3,6-dihidro-4-metil-2-oxo-6-(3-(2-tienil)fenil)-1-(2H)-
pirimidinacarboxílico, 1-etil amida,

ácido 5-ciano-3,6-dihidro-4-metil-2-oxo-6-(3-(3-tienil)fenil)-1-(2H)-
pirimidinacarboxílico, 1-etil amida,

ácido 5-ciano-3,6-dihidro-4-metil-2-oxo-6-(3-(4-píridil)fenil)-1-(2H)-
pirimidinacarboxílico, 1-etil amida,

ácido 5-ciano-3,6-dihidro-4-metil-2-oxo-6-(3-(4-píridil)fenil)-1-(2H)-
pirimidinacarboxílico, 1-(2,2,2-trifluoro)etil amida,

ácido 5-ciano-3,6-dihidro-4-metil-2-oxo-6-(3-(4-píridil)fenil)-1-(2H)-
pirimidinacarboxílico, 1-isopropil amida,

ácido 5-ciano-3,6-dihidro-4-metil-2-oxo-6-(3-(4-píridil)fenil)-1-(2H)-
pirimidinacarboxílico, 1-ciclopropil amida,

ácido 5-ciano-3,6-dihidro-4-metil-2-oxo-6-(3-(3-píridil)fenil)-1-(2H)-
pirimidinacarboxílico, 1-etil amida,

ácido 5-ciano-3,6-dihidro-4-metil-2-oxo-6-(3-(3-píridil)fenil)-1-(2H)-
pirimidinacarboxílico, 1-(2,2,2-trifluoro)etil amida,

ácido 5-ciano-3,6-dihidro-4-metil-2-oxo-6-(3-(3-píridil)fenil)-1-(2H)-
pirimidinacarboxílico, 1-isopropil amida,

ácido 5-ciano-3,6-dihidro-4-metil-2-oxo-6-(3-(3-píridil)fenil)-1-(2H)-
pirimidinacarboxílico, 1-ciclopropil amida,

ácido 5-ciano-3,6-dihidro-4-metil-2-oxo-6-(3-(3-píridil)fenil)-1-(2H)-
pirimidinacarboxílico, 1-ciclobutil amida,

acido 5-ciano-3,6-dihidro-4-metil-2-oxo-6-(3-(3-piridil)fenil)-1-(2H)-
 pirimidinacarboxílico, 1-ciclopentil amida,

acido 5-ciano-3,6-dihidro-4-metil-2-oxo-6-(3-(3-piridil)fenil)-1-(2H)-
 pirimidinacarboxílico, 1-ciclopropilmetil amida,

acido 5-ciano-3,6-dihidro-4-metil-2-oxo-6-(3-(2-piridil)fenil)-1-(2H)-
 pirimidinacarboxílico, 1-etil amida,

ácido 5-ciano-3,6-dihidro-4-metil-2-oxo-6-(3-(2-pirrol)fenil)-1-(2H)-
 pirimidinacarboxílico, 1-etil amida,

ácido 5-ciano-3,6-dihidro-6-(4-fluoro-3-(3-piridil)fenil)-4-metil-2-oxo-1-
 (2H)-pirimidinacarboxílico, 1-etil amida,

acido 5-ciano-3,6-dihidro-6-(4-fluoro-3-(3-piridil)fenil)-4-metil-2-oxo-1-
 (2H)-pirimidinacarboxílico, 1-(2,2,2-trifluoro)etil amida,

acido 5-ciano-3,6-dihidro-6-(4-fluoro-3-(3-piridil)fenil)-4-metil-2-oxo-1-
 (2H)-pirimidinacarboxílico, 1-ciclopropil amida,

acido 5-ciano-3,6-dihidro-6-(2-fluoro-5-(3-piridil)fenil)-4-metil-2-oxo-1-
 (2H)-pirimidinacarboxílico, 1-etil amida,

ácido 5-ciano-3,6-dihidro-6-(2-fluoro-5-(3-piridil)fenil)-4-metil-2-oxo-1-
 (2H)-pirimidinacarboxílico, 1-ciclopropil amida,

acido 5-ciano-3,6-dihidro-4-metil-6-(3-(4-metil-3-piridil)fenil)-2-oxo-1-
 (2H)-pirimidinacarboxílico, 1-etil amida,

acido 5-ciano-3,6-dihidro-4-metil-6-(3-(4-metil-3-piridil)fenil)-2-oxo-1-
 (2H)-pirimidinacarboxílico, 1-ciclopropil amida,

ácido 5-ciano-3,6-dihidro-4-metil-6-(3-(4-metil-5-oxa-2,3-diazol)fenil)-2-
 oxo-1-(2H)-pirimidinacarboxílico, 1-etil amida,

ácido 5-ciano-3,6-dihidro-4-metil-6-(3-(5-oxa-4-trifluorometil-2,3-
 diazole)fenil)-2-oxo-1-(2H)-pirimidinacarboxílico, 1-etil amida,

ácido 6-(2-(4-Clorofenil)fenil)-5-ciano-3,6-dihidro-4-metil-2-oxo-1-(2H)-
 pirimidinacarboxílico, 1-etil amida, y

acido 5-ciano-3,6-dihidro-4-metil-2-oxo-6-(2-(3-piridil)fenil)-1-(2H)-
 pirimidinacarboxílico, 1-etil amida

13 Un método para tratar una enfermedad proliferativa a través de la inducción de detención mitótica que comprende administrar a una especie mamífera una cantidad efectiva de un compuesto de reivindicación 1

14 El método de acuerdo con reivindicación 13 que comprende además administrar al paciente por lo menos otro agente anti-cáncer en combinación con dicho compuesto

15 El método de acuerdo con reivindicación 14 en donde dicho agente anticancer es cisplatino, doxorubicina, inhibidores de topoisomerasa II, etopósido, inhibidores de topoisomerasa I, CPT-11, topotecano, paclitaxel, docetaxel, epotilona, tamoxifen, inhibidores de timidilato sintasa, y anti-metabolitos

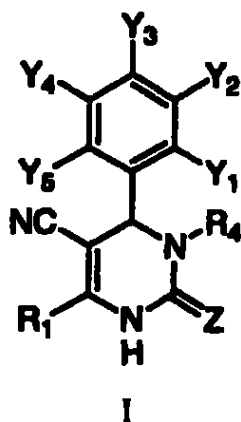
16 El método de acuerdo con reivindicación 11 en donde la enfermedad proliferativa es cáncer

17 Un método para tratar una enfermedad asociada con la proteína motora Eg5 que comprende administrar a una especie mamífera necesitada de dicho tratamiento una cantidad efectiva de un compuesto de reivindicación 1

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Extracto

La presente invencion provee compuestos de fórmula I



y sus sales de aceptación farmacéutica Los compuestos de fórmula I inducen detención mitotica y, por lo tanto, los hacen utiles como agentes anti-cáncer Los compuestos de fórmula I son tambien utiles para el tratamiento de otras enfermedades que pueden tratarse induciendo detención mitótica

PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To
MAUREEN CIBBONS
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
INTERNATIONAL PRELIMINARY
EXAMINATION REPORT

Docketed Item

(PCT Rule 71.1)

Due Date

Attorney

Date of Mailing
(day/month/year)

19 DEC 2002

Applicant's or agent's file reference

LD0300

IMPORTANT NOTIFICATION

International application No

International filing date (day/month/year)

Priority date (day/month/year)

PCT/US02/09494

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

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Facsimile No (703)305-3230

Form PCT/IPEA/416 (July 1992)

Authorized officer

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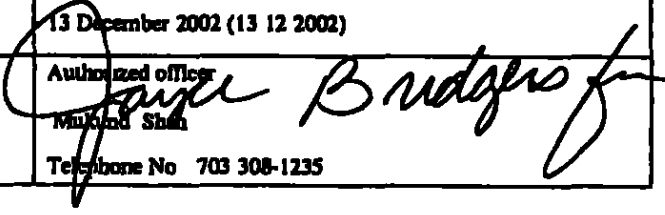
7-67

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference LD0300	FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)	
International application No PCT/US02/09494	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, 544/315, 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 29 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)

I Basis of the report

1 With regard to the elements of the international application *

- ☒ the international application as originally filed
- ☒ the description
pages 1-92 as originally filed
pages NONE filed with the demand
pages NONE filed with the letter of _____
- ☒ the claims
pages 93-97 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/US02/09494

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V Reasoned statement under Rule 66 2(a)(II) with regard to novelty inventive step or industrial applicability; citations and explanations supporting such statement

I STATEMENT

Novelty (N)

Claims 1-17 YES

Claims NONE NO

Inventive Step (IS)

Claims 1-17 YES

Claims NONE NO

Industrial Applicability (IA)

Claims 1-17 YES

Claims NONE NO

2 CITATIONS AND EXPLANATIONS

Claims 1-17 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-4-phenyl-3,6-dihydro-pyrimidine. The closest reference, Kappe et al. (J. Het. Chem.) discloses an intermediate compound #24. Said intermediate differs from the claimed compound by not having a substituent on the ring N that is equivalent to the claimed R₄. With no bridging reference, there is no motivation for one skilled in the art to modify the compound of Kappe et al. Thus, the instant invention has both novelty and an inventive step.

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

TRATADO SOBRE COOPERACIÓN INTERNACIONAL
EN MATERIA DE PATENTES

171
H

Remitente

OFICINA ENCARGADA DEL EXAMEN PRELIMINAR INTERNACIONAL

A

MAUREN GIBBONS
BRISTOL MYERS SQUIBB COMPANY
P O BOX 4000
RT 206 & PROVINCE LINE ROAD
PRINCETON NJ 08543-4000

PCT

COMUNICACIÓN SOBRE EL ENVÍO DEL
INFORME DE EXAMEN PRELIMINAR
INTERNACIONAL

(Regla 71.1 PCT)

Fecha de envío
(Día/Mes/Año)

19 DIC 2002

No. de Expediente del Solicitante o Apoderado

LD0300

COMUNICACIÓN IMPORTANTE

No. de Solicitud Internacional

PCT/US02/09494

Fecha Internacional de Presentación
(día/mes/año)

28 de Marzo de 2002 (28 03 2002)

Fecha de Prioridad (día/mes/año)

29 de Marzo de 2001 (29 03 2001)

Solicitante

BRISTOL-MYERS SQUIBB COMPANY

1. Se comunica al solicitante que la oficina encargada del examen preliminar internacional le envía con el presente el informe de examen preliminar internacional elaborado para la solicitud internacional en caso dado con los anexos correspondientes.

2. Una copia del informe, en caso dado con los anexos correspondientes, se hace llegar a la Oficina Internacional para su envío posterior a todas las oficinas seleccionadas.

3. A solicitud de una oficina seleccionada la Oficina Internacional preparará una traducción del informe (pero no de los anexos) al inglés y la remitirá a esta oficina.

4. RECORDATORIO

Para ingresar en la fase nacional el solicitante, dentro de los 30 meses a partir de la fecha de prioridad (o en algunas oficinas incluso después), tiene que realizar ante cada oficina seleccionada ciertos actos (entrega de traducciones y desembolso de honorarios nacionales) (Artículo 39 (1)) (véase también la información remitida por la Oficina Internacional en el Formulario PCT/IB/301).

Si se tiene que enviar a una oficina seleccionada una traducción de la solicitud internacional, entonces esta traducción tiene que incluir traducciones de todos los anexos al informe de examen preliminar internacional. Es obligación del solicitante elaborar dichas traducciones y hacerlas llegar directamente a las oficinas seleccionadas respectivas.

Mayores detalles en cuanto a los plazos normativos y los requisitos de las oficinas seleccionadas se desprenden del Volumen II de la guía PCT para solicitantes.

Nombre y dirección postal de la Oficina Encargada del
Examen Preliminar Internacional (IPEA/US)

Comisionado de Patentes Y Marcas
Box PCT
Washington, D C 20231

Empleado Autorizado

Mukund Shah

Fax No (703) 305 - 3230

Teléfono No 703-308-1235

Formulario PCT/IPEA/418 (Julio 1992)

TRATADO SOBRE COOPERACIÓN INTERNACIONAL
EN MATERIA DE PATENTES

PCT

INF RME DE EXAMEN PRELIMINAR INTERNACIONAL
(Artículo 36 y Regla 70 PCT)

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No de Expediente del Solicitante o Apoderado LD0300	PROCEDIMIENTO POSTERIOR Véase comunicación sobre el envío del Informe de examen preliminar internacional (Formulario PCT/IPEA/416)	
No Solicitud Internacional PCT/US02/09494	Fecha Internacional de Presentación (día/mes/año) 26 de Marzo de 2002 (26 03 2002)	Fecha de Prioridad (día/mes/año) 29 de Marzo de 2001 (29 03 2001)
Clasificación Internacional de Patente (IPC) o Clasificación Nacional e IPC IPC(7) C07D 239/42 409/04 401/04 403/12 A61K 31/505 31/508 A61P 9/14 y US Cl 514/274 544/315 318		
Solicitante BRISTOL-MYERS SQUIBB COMPANY		

1	Este Informe de examen preliminar internacional fue elaborado por la Oficina Encargada del Examen Preliminar Internacional y se envía al solicitante según Artículo 36.
2	Este INFORME comprende un total de <u>3</u> hojas. Incluye esta portada. ☐ Además se adjuntan ANEXOS al Informe en este caso se trata de hojas con descripciones reivindicaciones y/o dibujos que se modificaron y que sirven de base a este Informe y/o hojas con correcciones efectuadas por esta oficina (véase Regla 70 16 y Sección 607 de las Instrucciones administrativas al PCT) Estos anexos comprenden en total de <u>0</u> hojas.
3	Este Informe contiene datos con respecto a los siguientes puntos. I ☒ Base del Informe II ☐ Prioridad III ☐ Sin elaboración de un dictamen sobre novedad, actividad inventiva y posibilidad de aplicación industrial IV ☐ Uniformidad deficiente de la invención V ☒ Declaración justificada según Artículo 35(2) con respecto a la novedad la actividad inventiva y la posibilidad de aplicación industrial documentos y explicaciones que sustentan esta declaración VI ☐ Ciertos documentos enumerados VII ☐ Ciertas deficiencias del registro internacional VIII ☐ Ciertas observaciones relacionadas con la solicitud internacional

Fecha de presentación de la petición 29 de Octubre de 2002 (28 10 2002)	Fecha de la preparación de este informe 13 de Diciembre de 2002 (13 12 2002)
Nombre y dirección postal de la Oficina Encargada del Examen Preliminar Internacional (IPEA/US) Comisionado de Patentes Y Marcas Box PCT Washington D C 20231	Empleado Autorizado Mukund Shah
Fax No (703) 305 – 3230	Teléfono No 703-308-1235

Formulario PCT/IPEA/409 (portada) (Julio 1998)

INFORME DE EXAMEN PRELIMINAR INTERNACIONAL		Solicitud Internacional No PCT/US02/09494
I Base del Informe		
1	Con respecto a los elementos de la solicitud internacional * ☒ la solicitud internacional tal como se radicó originalmente ☒ la descripción páginas <u>1-92</u> como se radicaron originalmente páginas <u>NINGUNA</u> radicadas con la petición páginas <u>NINGUNA</u> radicadas con la carta de _____ ☒ las reivindicaciones Páginas <u>93-97</u> como se radicaron originalmente páginas <u>NINGUNA</u> como se modificaron (junto con cualquier declaración) bajo artículo 19 páginas <u>NINGUNA</u> radicadas con la petición páginas <u>NINGUNA</u> radicadas con la carta de _____ ☒ los dibujos páginas <u>NINGUNA</u> como se radicaron originalmente páginas <u>NINGUNA</u> radicadas con la petición páginas <u>NINGUNA</u> radicadas con la carta de _____ ☐ la parte del listado de secuencias de la descripción páginas <u>NINGUNA</u> como se radicaron originalmente páginas <u>NINGUNA</u> radicadas con la petición páginas <u>NINGUNA</u> radicadas con la carta de _____	
2	En lo concerniente al idioma todos los elementos indicados más arriba estuvieron a disposición de la oficina o le fueron enviados en el idioma en el cual se radicó la solicitud internacional salvo indicación en contrario consignada bajo este punto Estos elementos estuvieron a disposición de la oficina o le fueron enviados en el idioma siguiente que es ☐ el idioma de una traducción enviada para efectos de la búsqueda internacional (según la regla 23 1 (b)) ☐ el idioma de publicación de la solicitud internacional (según la regla 48 3 (b)) ☐ el idioma de la traducción enviada para efectos del examen preliminar internacional (según la regla 55 2 y/o 55 3)	
3	En lo que concierne a la secuencia de nucleótidos y/o aminoácidos divulgados en la solicitud internacional (en caso dado) el examen preliminar internacional se llevó a cabo sobre la base del listado de secuencias ☐ contenido en la solicitud internacional por escrito ☐ radicado con la solicitud internacional en formato de lectura por computador ☐ remitido posteriormente a la oficina por escrito ☐ remitido posteriormente a la oficina en formato de lectura por computador ☐ se ha prestado la declaración según la cual el listado de secuencias por escrito y suministrado posteriormente no va más allá de la divulgación hecha en la solicitud tal como se radicó ☐ se ha prestado la declaración según la cual las informaciones registradas en formato de lectura por computador son idénticas a las de los listados de secuencias presentados por escrito	
4	☒ Las modificaciones han acarreado la anulación ☒ de la descripción páginas <u>NINGUNA</u> ☒ de las reivindicaciones Nos <u>NINGUNA</u> ☒ de los dibujos hojas/fg- <u>NINGUNA</u>	
5	☐ El presente informe se preparó sin tener en cuenta (algunas de) las modificaciones que se consideraron que van más allá de la exposición de la invención tal como se radicó según se indica a continuación en el Cuadro Suplementario (regla 70 2 (c)) **	
<i>Hojas intercambiables, que se presentaron a la Oficina de Radicación con base en una solicitud según Artículo 14 se consideran en el marco de este informe como "presentadas inicialmente" y no se le adjuntan porque no contienen ningún tipo de modificaciones (Reglas 70.16 y 70.17)</i> <i>Toda hoja intercambiable que incluya modificaciones de esta índole debe indicarse en el punto 1 y anexarse al presente informe</i>		

INFORME DE EXAMEN PRELIMINAR INTERNACIONAL

Solicitud Internacional No

PCT/US02/09494

V Declaración motivada bajo Regla 68 2(a)(II) en cuanto a la novedad la actividad inventiva y la posibilidad de aplicación industrial, citas y explicaciones que sustentan esta declaración

1 DECLARACIÓN

Novedad (N)	Reivindicaciones <u>1 17</u>	SÍ
	Reivindicaciones <u>NINGUNA</u>	NO
Actividad Inventiva (IS)	Reivindicaciones <u>1 17</u>	SÍ
	Reivindicaciones <u>NINGUNA</u>	NO
Posibilidad de Aplicación Industrial (IA)	Reivindicaciones <u>1 17</u>	SÍ
	Reivindicaciones <u>NINGUNA</u>	NO

2 CITAS Y EXPLICACIONES

Reivindicaciones 1 17 satisfacen los criterios expuestos en el Artículo 33(2)-(4) PCT porque el arte previo no enseña o medianamente sugiere compuestos de 5-ciano-4-fenil-3,6-dihidro-pirimidina sustituida. La referencia más próxima Kappe y colaboradores (J. Het. Chem.) divulga un intermedio compuesto #24. Dicho intermedio difiere del compuesto reivindicado por no tener un sustituyente en el anillo N que sea equivalente al R₄ reivindicado. Sin una referencia puente, no existe motivación para una persona experta en el arte de modificar el compuesto de Kappe y colaboradores. Por lo tanto, la presente invención posee tanto novedad como actividad inventiva.

Todas las reivindicaciones satisfacen los criterios de posibilidad de aplicación industrial porque los compuestos reivindicados pueden prepararse por industrias farmacéuticas y usarse para tratar enfermedades proliferativas.

PCT REQUEST

Original (for SUBMISSION) printed on 22.03.2002 01:28:34 PM

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/ROH01 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	LD0300
I	Title of Invention	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.	609-2525781
II-9	Facsimile No.	609-252-4526
II-11	Applicant's registration No. with the Office	34,620
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)	LOMBARDO, Louis, J
III-1-6	Address.	49 West Street Belle Mead, NJ 08502 United States of America
III-1-8	State of nationality	US
III-1 7	State of residence	US

PCT REQUEST

Duplicate of original printed on 30 03 2002 01 28 34 PM

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)	WU, Laurence, I
III-2-5	Address	43 Nathan Court Newtown, PA 18940 United States of America
III-2-6	State of nationality	US
III-2-7	State of residence	US
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, BOUDREAU, Gerald, LARSEN, Scott, K, VANATTEN, Mary, K DOLAN, Peter, L, BELFIELD, Jing

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LD0360

PCT REQUEST

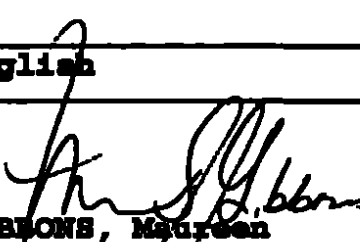
Duplicate of original printed on 30 03 2002 01:28:34 PM

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 CE 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 claim of earlier national application	
VI-2-1	Filing date	22 March 2002 (22 03 2002)
VI-2-2	Number	
VI-2-3	Country	US

PCT REQUEST

LD0300

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VI-3	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, VI-2	
VII-1	International Searching Authority Chosen	United States Patent and Trademark Office (USPTO) (ISA/US)	
VIII	Declarations	Number of declarations	
VIII-1	Declaration as to the identity of the inventor	-	
VIII-2	Declaration as to the applicant's entitlement, as at the international filing date, to apply for and be granted a patent	-	
VIII-3	Declaration as to the applicant's entitlement, as at the international filing date, to claim the priority of the earlier application	-	
VIII-4	Declaration of inventorship (only for the purposes of the designation of the United States of America)	-	
VIII-5	Declaration as to non-prejudicial disclosures or exceptions to lack of novelty	-	
IX	Check list	number of sheets	electronic file(s) attached
IX-1	Request (including declaration sheets)	5	-
IX-2	Description	98	-
IX-3	Claims	5	-
IX-4	Abstract	1	EZABST00 TXT
IX-5	Drawings	0	-
IX-7	TOTAL	109	
	Accompanying items	paper document(s) attached	electronic file(s) attached
IX-8	Fee calculation sheet	✓	-
IX-9	Original separate power of attorney	✓	-
IX-10	Original general power of attorney	✓	-
IX-17	PCT-EASY diskette	-	Diskette
IX-18	Figure of the drawings which should accompany the abstract		
IX-20	Language of filing of the international application	English	
X-1	Signature of applicant, agent or common representative		
X-1-1	Name (LAST First)	GIBBONS, Maureen	

FOR RECEIVING OFFICE USE ONLY

10-1	Date of actual receipt of the purported international application	
10-2	Drawings	
10-2-1	Received	
10-2-2	Not received	

PCT REQUEST

Original (for SUBMISSION) printed on 22.03.2002 01:28:34 PM

10-3	Corrected date of actual receipt due to later but timely received papers or drawings completing the purported International application	
10-4	Date of timely receipt of the required corrections under PCT Article 11(2)	
10-5	International Searching Authority	ISA/US
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	
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PCT (ANNEX - FEE CALCULATION SHEET)

LD0300

Original (for SUBMISSION) printed on 22.03.2002 01:28:34 PM

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

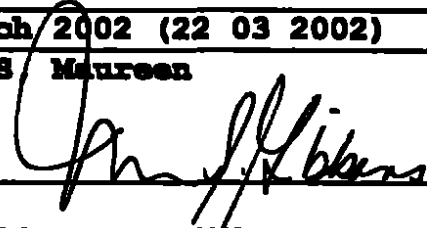
0	For receiving Office use only			
0-1	International Application No.			
0-2	Date stamp of the receiving Office			
0-4	Form PCT/ROH01 (Annex)			
0-4-1	PCT Fee Calculation Sheet Prepared using	PCT-EASY Version 2 92 (updated 01 01 2002)		
0-9	Applicant's or agent's file reference	LD0300		
2	Applicant	BRISTOL-MYERS 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	79		
12-5	Additional amount (X)	9		
12-6	Total additional amount b2	711		
12-7	b1 + b2 = B	1,118		
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 fee D	440		
12-12	PCT-EASY fee reduction R	-125		
12-13	Total international fee (B+D-R) I	⇒	1,433	
12-14	Fee for priority document			
	Number of priority documents requested	2		
12-15	Fee per document (X)	15		
12-16	Total priority document fee P	⇒	30	
12-17	TOTAL FEES PAYABLE (T+S+B+P)	⇒	2,403	
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 22.03.2002 01:26 34 PM

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LD0309

12-20-3	Authorization to charge the fee for priority document.	✓
12-21	Deposit account No.	19-3880
12-22	Date	22 March 2002 (22 03 2002)
12-23	Name and signature	GIBBONS Maureen 

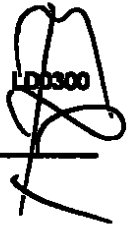
VALIDATION LOG AND REMARKS

13-1-1	Applicant remarks	Abstract contains a chemical formula Noted in the abstract in brackets "INSERT CHEMICAL FORMULA HERE" Second priority serial number not yet available
13-2-4	Validation messages Priority	Yellow Priority 2 Application No is missing Green? Priority 2 Priority date and today's computer generated date are the same Please verify
13-2-7	Validation messages Contents	Green? The international application contains no drawings Please verify
13-2-8	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.

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LD0300

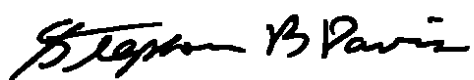
0-1	PCT Power of Attorney (for an International application filed under the Patent Cooperation Treaty) (PCT Rule 90.4)	
0-1-1	Prepared using	PCT-EASY Version 2 92 (updated 01 01 2002)
1	The undersigned applicant(s)	BRISTOL-MYERS SQUIBB COMPANY
1-1-1	hereby appoints (appoint) the following person	GIBBONS, Maureen, DAVIS, Stephen, B , 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
1-2	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	CYANO-SUBSTITUTED DIHYDROPYRIMIDINE COMPOUNDS AND THEIR USE TO TREAT DISEASES
1-4-2	Applicant's or agent's file reference	LD0300
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)
1-5	and to make or receive payments on behalf of the undersigned.	

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LD0300


PCT POWER OF ATTORNEY

Printed on 01 03 2002 09:45:37 AM

2-1	Signature of applicant	
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	01 March 2002 (01 03 2002)

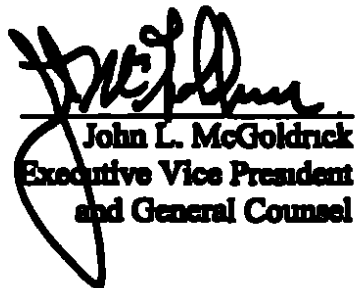
CERTIFICATION

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

Stephen B. Davis
Christopher Klein
Suzanne Babayko
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)

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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 08502
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, Bryan; BELFIELD, Jing; DAMICO, Stephen; DAVIS, Stephen; DUBOFF, Samuel; DOLAN, Peter; FERGUSON, Blair; FURMAN, Theodore; GIBBONS, MAUREEN; HERMENAUI, Ronald; KILCOYNE, John; KLEIN, Christopher; LANGE, Keith; LARSEN, Scott; MAKUJINA, Shah; MORSE, David; O'BRIEN, Maureen; PATEL, Rana; 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:

February 27, 2002

PCT

GENERAL POWER OF ATTORNEY

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

(PCT Rule 90.5)

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The undersigned person(s):

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

WU, Laurence I
43 Nathan Court
Newtown, PA 18940
UNITED STATES OF AMERICA

I hereby appoint(s) the following person as:

☒ agent

☐ common representative

Name and address

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

ALGERI, Aldo; BABAKO, Suzanne; BABCOCK, Timothy; BOUDREAUX, Gerald; BUCHHOLZ, Brynne; BELFIELD, Jing; DAMICO, Stephen; DAVIS, Stephen; DUBOFF, Samuel; DOLAN, Peter; FERGUSON, Blair; FURMAN, Theodore; GIBBONS, MAUREEN; HERMENAU, Ronald; KILCOYNE, John; KLEIN, Christopher; LANGE, Kelly; LARSEN, Scott; MAKUJINA, Shah; MORSE, David; O'BRIEN, Maureen; PATEL, Rana; PEIST, Kenneth; PROVOOST, Jonathan; RODNEY Birtton; RYAN, Richard; SHER, Audrey; SWITZER, Joan; VANATTEN, Mary; WELK-OREDCAN, 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):


Laurence I Wu

Date:

March 14, 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

DEMAND

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CHAPTER II

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 LD0300 PCT
International application No. PCT/US02/09494	International filing date (day/month/year) (28 03.02) 28 MARCH 2002	(Earliest) Priority date (day/month/year) (29 03.01) 29 MARCH 01
Title of invention 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.) 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
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.) WU, Laurence, I 43 Nathan Court Newtown, PA 18940 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.		

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 earlierName 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 28, 2002
Maureen Gibbons

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 60.5.

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(8)(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 68.9 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.

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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

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International application No. PCT/US02/09494	For International Preliminary Examining Authority use only	
Applicant's or agent's file reference LD0300 PCT	Date stamp of the IPEA	
Applicant Bristol-Myers Squibb Company		
CALCULATION OF PRESCRIBED FEES		
1 Preliminary examination fee - - - - -	490 00	P
2 Handling fee (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.) - - - - -	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		
MODE OF PAYMENT		
☒ 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>		
☒ Authorization to charge the total fees indicated above	IPEA/ <u>US</u>	
☒ (This check-box may be marked only if the conditions for deposit accounts of the IPEA so permit) Authorization to charge any deficiency or credit any overpayment in the total fees indicated above.	Deposit Account No <u>19-3880</u>	
	Date: <u>October 24, 2002</u>	
	Name: <u>Maureen Gibbons</u>	
	Signature: <u>[Signature]</u>	

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NOTES TO THE FEE CALCULATION JT
(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 1985, 1986 and 1987) 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

From the RECEIVING OFFICE

PCT

To:
BRISTOL-MYERS SQUIBB COMPANY
P O BOX 4000
RT 208 & PROVINCE LINE ROAD
PRINCETON NEW JERSEY 08543-4000

RECEIVED
BMS PATENT LAW

17 MAY 28 2002

Docketed Item *0A*

INVITATION TO CORRECT PRIORITY CLAIM
PCT Rules 4.10, 26bis.1, 26bis.2(a) and (b))

Date of mailing (day/month/year)	22 May 2002
Applicant's or agent's file Date 2/19/02 Attorney <i>MC</i>	REPLY DATE See item 1
International application No. PCT/US02/08494	International filing date (day/month/year) 28 Mar 2002
Applicant BRISTOL-MYERS SQUIBB COMPANY	

The applicant is hereby invited, within the time limit indicated below, to correct, by a notice submitted to this receiving Office, defects in the priority claim(s), as indicated in the Annex.

- Time limit to respond to this invitation (Rule 26bis.1(a)):-
 - within 16 months from the (earliest) priority date; or
 - if the (earliest) priority date is changed as a result of the correction or addition of the (earliest) priority claim, within 16 months from that (earliest) priority date so changed,
 whichever expires first, provided that such a notice may, in any event, be submitted until the expiration of four months from the international filing date.

Failure to respond to this invitation within the prescribed time limit may result in the priority claim concerned to be considered, for the purposes of the procedure under the PCT, not to have been made (Rule 26bis.2(b)).

- In the case where multiple priorities have been claimed, this invitation relates to the following priority claim(s):

- A copy of this invitation is being sent to the International Bureau.

Name and mailing address of the receiving Office Assistant Commissioner for Patent, Box PCT Washington, D.C. 20231 Attn RO/US	Authorized officer Hallet Saunders
Facsimile No. 703-305-3230	Telephone No. 703-305-3663

195
[Handwritten signature]

196
/

This receiving Office has found the following defects in the priority claim(s)

1 Failure to Comply with the Requirements of Rule 4.10

a. ☒ National application

- ☐ Missing indication of the filing date of the earlier application.
- ☐ Filing date indicated for the earlier application does not fall within the period of 12 months preceding the international filing date.
- ☒ Missing indication of the number of the earlier application.*
- ☐ Missing indication of the country party to the Paris Convention for the Protection of Industrial Property or of the Member of the World Trade Organization that is not party to that Convention, in which the earlier national application was filed.
- ☐ The country indicated is neither a party to the Paris Convention for the Protection of Industrial Property nor a Member of the World Trade Organization.

b. ☐ Regional application

- ☐ Missing indication of the filing date of the earlier application.
- ☐ Filing date indicated for the earlier application does not fall within the period of 12 months preceding the international filing date.
- ☐ Missing indication of the number of the earlier application.*
- ☐ Missing indication of the authority entrusted with the granting of regional patents under the applicable regional patent treaty.
- ☐ The authority indicated as the authority entrusted with the granting of regional patents does not grant regional patents.
- ☐ The priority claim in relation to the ARIPO application does not indicate either at least one country party to the Paris Convention for the Protection of Industrial Property or at least one Member of the World Trade Organization, for which the earlier application was filed.

c. ☐ International application

- ☐ Missing indication of the filing date of the earlier application.
- ☐ Filing date indicated for the earlier application does not fall within the period of 12 months preceding the international filing date.
- ☐ Missing indication of the number of the earlier application.*
- ☐ Missing indication of the receiving Office with which it was filed.

2. Inconsistency with the Corresponding Indications in the Priority Document*

a. ☐ Inconsistency with regard to the filing date of the earlier application:

The request indicates:
The priority document indicates:

b. ☐ Inconsistency with regard to the number of the earlier application:

The request indicates:
The priority document indicates:

c. ☐ Inconsistency with regard to the country party to the Paris Convention for the Protection of Industrial Property or the Member of the World Trade Organization in which the national application was filed.

The request indicates:
The priority document indicates:

d. ☐ Inconsistency with regard to the authority entrusted with the granting of regional patents under the applicable regional patent treaty:

The request indicates:
The priority document indicates:

e. ☐ Inconsistency with regard to the receiving Office with which the international application was filed.

The request indicates:
The priority document indicates:

* Even if this defect is not corrected in response to this invitation, the priority claim concerned will not be considered not to have been made (Rule 26bis.2(b)).

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27/0

Docket No LD0300

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

International Application No PCT/US02/09494
International Filing Date 26 March 2002
Priority Date 29 March 2001
Applicant. Bristol-Myers Squibb Company

For Cyano Substituted Dihydropyrimidine Compounds And Their
Use To Treat Diseases

Box PCT
Assistant Commissioner for Patents
Washington, D C 20231

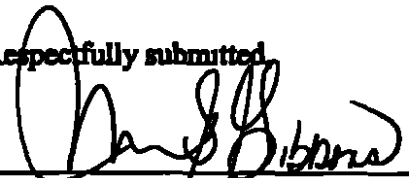
RESPONSE TO INVITATION TO CORRECT DEFECTS
IN THE INTERNATIONAL APPLICATION

SIR

In response to the Invitation to Correct Defects in the International Application noted above, please note the application number for the priority patent application is 10/104,382

No fee is believed due. However in the event a fee is due it is requested that the payment be charged to Deposit Account 19-3880

Respectfully submitted



Maureen S Gibbons
Reg No 44,121
Bristol-Myers Squibb Company
P O Box 4000
Princeton, New Jersey 08543-4000
(609) 252 3453

Express Mail mailing label number EY001829709US

Date of Deposit June 18, 2002

I hereby certify that this paper correspondence is being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service on the date indicated above and is addressed to the Assistant Commissioner of Patents and Trademarks, (Box PCT) Washington, D C. 20231

Halda Franco

(Typed or printed name of person mailing paper or fee)



(Signature of Person mailing paper or fee)

PATENT COOPERATION TREATY

PCT

NOTIFICATION RELATING TO PRIORITY CLAIM

(PCT Rules 26bis 1 and 26bis 2 and Administrative Instructions Sections 402 and 409)

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 February 2003 (06 02 03)

FEB 24 2003

Docketed Item

Applicant's or agent's file reference
LD0300

Due Date

Attorney

IMPORTANT NOTIFICATION

International application No
PCT/US02/09494

International filing date (day/month/year)
26 March 2002 (26 03 02)

Applicant

BRISTOL MYERS SQUIBB COMPANY et al

The applicant is hereby notified of the following in respect of the priority claim(s) made in the international application

- 1 ☒ Correction of priority claim. In accordance with the applicant's notice received on 18 June 2002 (18 06 02) the following priority claim has been corrected to read as follows

US 22 March 2002 (22 03 02) 10/104 382

- ☐ or though the indication of the number of the earlier application is missing
☐ even though the following indication in the priority claim is not the same as the corresponding indication appearing in the priority document

- 2 ☐ Addition of priority claim. In accordance with the applicant's notice received on the following priority claim has been added

- ☐ even though the indication of the number of the earlier application is missing
☐ even though the following indication in the priority claim is not the same as the corresponding indication appearing in the priority document

- 3 ☐ As a result of the correction and/or addition of (a) priority claim(s) under items 1 and/or 2 the (earliest) priority date is

- 4 ☐ Priority claim considered not to have been made.

- ☐ The applicant failed to respond to the invitation under Rule 26bis.2(a) (Form PCT/IB/318) within the prescribed time limit.
☐ The applicant's notice was received after the expiration of the prescribed time limit under Rule 26bis.1(a)
☐ The applicant's notice failed to correct the priority claim so as to comply with the requirements of Rule 4.10.

The applicant may before the technical preparations for international publication have been completed and subject to the payment of a fee request the International Bureau to publish together with the international application information concerning the priority claim See Rule 26bis.2(c) and the PCT Applicant's Guide Volume I Annex B2(II)

- 5 ☐ In case where multiple priorities have been claimed the above item(s) relate to the following priority claim(s)

- 6 A copy of this notification has been sent to the receiving Office and

- ☐ to the international Searching Authority (where the international search report has not yet been issued)
☒ the designated Offices (which have already been notified of the receipt of the record copy)

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No. (41 22) 740.14.35

Authorized officer

Dominique DELMAS

Telephone No. (41 22) 338.83.38

PATENT COOPERATION TREATY

1997

From the INTERNATIONAL SEARCHING AUTHORITY

PCT

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

RECEIVED
BAIS PATENT LAW

NOTIFICATION OF TRANSMITTAL OF
THE INTERNATIONAL SEARCH REPORT
OR THE DECLARATION

(PCT Rule 44.1)

Docketed Item US-105

Date of Mailing
(day/month/year)

31 JUL 2002

Due Date

10/31/02

Applicant's or agent's file reference
LD0300

Attorney

(MG)

FOR FURTHER ACTION See paragraphs 1 and 4 below

International application No
PCT/US02/09494

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 30 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
Richard Shah

Telephone No 703-308-0196

Form PCT/ISA/220 (April 2002)

(See notes on accompanying sheet)

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

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H
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Applicant's or agent's file reference LD0300	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/US02/09494	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 3 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/US02/09494

2d

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	WO 00/78731 A1 (CELL TECH CHIROSCIENCE LIMITED) 28 December 2000 (28 12 00) especially page 60 Examples 31 & 32	1 17
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 compound #27 on page 59	1 17
A	REHWALD M et al Synthesis of Thieno[2,3-d]pyrimidines and Amino-pyrimidines from 2-Alkoxy-5-cyano-thioxypyrimidine Intermediates Heterocycles June 1998 Vol 48 No 6 pages 1157 1167 especially compound #6 on page 1159	1 17
A	AGARWAL, N et al Suitably Functionalised Pyrimidines as Potential Antimycotic Agents Bioorganic & Medicinal Chemistry Letters 2000 Vol 10 pages 703-706 especially page 705	1 17
A	Chem Abstr Vol 114 No 9 RAM V J et al Chemotherapeutic Agents XI Synthesis of Pyrimidines and Azolopyrimidines as Leishmanicides 04 March 1991 Abstract No 114 81744L	1 17
☒ Further documents are listed in the continuation of Box C ☐ See patent family annex		
Special categories of cited documents:		
A	document defining the general state of the art which is not considered to be of particular relevance	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
E	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 doubt 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	
P*	document published prior to the international filing date but later than the priority date claimed	& document member of the same patent family
Date of the actual completion of the international search		Date of mailing of the international search report
22 June 2002 (22 06 2002)		31 JUL 2002
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D C 20531		Authorized officer Mustund Shah
Facsimile No (703)305 3230		Telephone No 703-308 1235

INTERNATIONAL SEARCH REPORT

International application No

PCT/US02/09494

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C (Continuation) 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 127 No 12 KLEIDERNIGG O P et al Synthesis and Reactions of Biginelli Compounds 8 Separation of enantiomers of 4-Aryldihydropyrimidines by Direct Enantioselective HPLC A Critical Comparison of Chiral Stationary Phases 22 September 1997 page 664 Abstract No 127 161790p	1 17
A	Chem Abstr Vol 133 No 7 AL-AFALEQ et al Heterocyclic Synthesis via Enaminonitriles An Efficient One Step Synthesis of Some Novel Azolo[1 5-a]pyrimidine Pyrimido[1 2-a]benzimidazole Pyrido[1 2-a]benzimidazole Pyrimidine and Pyrazole Derivatives 14 August 2000 pages 671-672 Abstract No 133 89496b	1 17
A	Chem Abstr Vol 129 No 15 REHWALD M et al Synthesis of Thieno[2 3-d]pyrimidines and Aminopyrimidines from 2-Alkoxy 5-cyano-4-thioxopyrimidine Intermediates 12 October 1998 page 662 Abstract No 129 189296x	1 17

PATENT COOPERATION TREATY

91755

203
22

From the
INTERNATIONAL PRELIMINARY EXAMINING 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
INTERNATIONAL PRELIMINARY
EXAMINATION REPORT

Docketed Item _____

(PCT Rule 71.1)

Due Date _____

Attorney MC

Date of Mailing
(day/month/year)

19 DEC 2002

Applicant's or agent's file reference

LD0300

IMPORTANT NOTIFICATION

International application No

PCT/US02/09494

International filing date (day/month/year)

26 March 2002 (26 03 2002)

Priority date (day/month/year)

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

Form PCT/IPEA/416 (July 1992)

Authorized officer

James Bridges
Mansur Shah

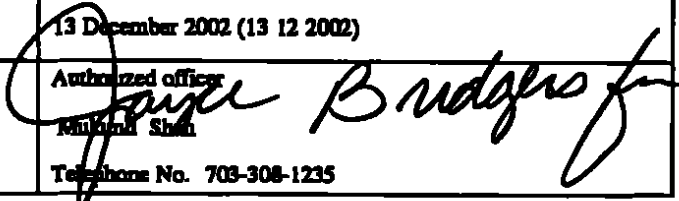
Telephone No. 703-308-1235

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference LD0300	FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)	
International application No PCT/US02/09494	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 514/274 544/315 318		
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 29 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 Comptroller of Patents and Trademarks Box PCT Washington, D.C. 20531 Facsimile No (703)305-3230	Authorized officer  Rhonda Shah Telephone No. 703-308-1235	

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

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No

PCT/US02/09494

105

I Basis of the report

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

- ☒ the international application as originally filed
- ☒ the description.
pages 1-92 as originally filed
pages NONE filed with the demand
pages NONE filed with the letter of _____
- ☒ the claims
pages 93-97 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/US02/09494

206

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 17</u>	YES
	Claims <u>NONE</u>	NO
Inventive Step (IS)	Claims <u>1 17</u>	YES
	Claims <u>NONE</u>	NO
Industrial Applicability (IA)	Claims <u>1 17</u>	YES
	Claims <u>NONE</u>	NO

2 CITATIONS AND EXPLANATIONS

Claims 1 17 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-4-phenyl 3,6-dihydro-pyrimidine. The closest reference, Kappe et al. (J. Het. Chem.) discloses an intermediate compound #24. Said intermediate differs from the claimed compound by not having a substituent on the ring N that is equivalent to the claimed R₄. With no bridging reference there is no motivation for one skilled in the art to modify the compound of Kappe et al. Thus the instant invention has both novelty and an inventive step.

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

INTERNATIONAL SEARCH REPORT

International application No

PCT/US02/09494

207

A CLASSIFICATION OF SUBJECT MATTER		
IPC(7)	C07D 239/4.. 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	WO 00/78731 A1 (CELL TECH CHIROSCIENCE LIMITED) 28 December 2000 (28 12 00) especially page 60 Examples 31 & 32	1 17
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 compound #27 on page 59	1 17
A	REHWALD M et. al Synthesis of Thieno[2,3-d]pyrimidines and Amino-pyrimidines from 2-Alkoxy-5-cyano-thioxopyrimidine Intermediates Heterocycles June 1998 Vol. 48 No 6 pages 1157 1167 especially compound #6 on page 1159	1 17
A	AGARWAL N et al. Suitably Functionalised Pyrimidines as Potential Antimycotic Agents Bioorganic & Medicinal Chemistry Letters 2000 Vol 10 pages 703-706 especially page 705	1 17
A	Chem. Abstr Vol 114 No 9 RAM V J et al Chemotherapeutic Agents XI Synthesis of Pyrimidines and Azolopyrimidines as Leishmanicides 04 March 1991 Abstract No 114 81744t.	1 17
☒ Further documents are listed in the continuation of Box C ☐ See patent family annex		
Special categories of cited documents.		
A	documents 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
E	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	documents which may throw doubts on priority claim(s) or which is used 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	
P	document published prior to the international filing date but later than the priority date claimed	& 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 31 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 Mujibund Shah Telephone No 703-308-1235

208

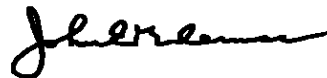
APOSTILLE

(CONVENTION DE LA HAYE DU 5 OCTOBRE 1961)

- 1 COUNTRY UNITED STATES OF AMERICA
2 THIS PUBLIC DOCUMENT HAS BEEN SIGNED BY
DIANE C BARTRAM
3 ACTING IN THE CAPACITY OF
NOTARY PUBLIC OF NEW JERSEY
4 BEARS THE SEAL/STAMP OF
DIANE C BARTRAM NOTARY

CERTIFIED

- 5 AT TRENTON NEW JERSEY
6 THE 19TH DAY OF AUGUST 2003
7 BY John E McCormac CPA NEW JERSEY TREASURER
8 NO A179516
9 SEAL/STAMP 10 SIGNATURE



209 

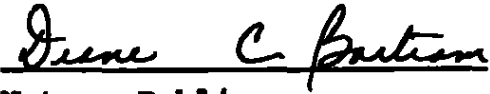
USSN 10/104,382-LD0300

I, Stephen B Davis, Patent Counsel, Patent Department,
BRISTOL-MYERS SQUIBB COMPANY, do hereby certify that this
document is a notarized true and original signed by the
inventor


Stephen B Davis

STATE OF NEW JERSEY)
)
COUNTY OF MERCER)

Subscribed and sworn to before me this
6th day of August, 2003


Notary Public

DIANE C. BARTRAM
Notary Public of New Jersey
My Commission Expires March 9, 2008

SEAL



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APPLICATION NUMBER	FLING DATE	GRP ART UNIT	FL FEE REGD	ATTY DOCKET NO	DRAWINGS	TOT CLAIMS	IND CLAIMS
10/104 382	83/22/2002	1614	740	LD0300 NP		17	2

CONFIRMATION NO 7050

23814

STEPHEN B DAVIS

BRISTOL-MYERS SQUIBB COMPANY

PATENT DEPARTMENT

**PARENTS GET
P O BOX 4000**

PRINCETON NJ 08543-4000

FILING RECEIPT

Data Mailed 05/01/2002

Receipt is acknowledged of this nonprovisional Patent Application. It will be considered in its order and you will be notified as to the results of the examination. Be sure to provide the U.S. APPLICATION NUMBER, FILING DATE, NAME OF APPLICANT, and TITLE OF INVENTION when inquiring about this application. Fees transmitted by check or draft are subject to collection. Please verify the accuracy of the data presented on this receipt. If an error is noted on this Filing Receipt, please write to the Office of Initial Patent Examination's Filing Receipt Corrections, facsimile number 703-746-9195. Please provide a copy of this Filing Receipt with the changes noted thereon. If you received a "Notice to File Missing Parts" for this application, please submit any corrections to this Filing Receipt with your reply to the Notice. When the USPTO processes the reply to the Notice, the USPTO will generate another Filing Receipt incorporating the requested corrections (if appropriate).

Applicant(s)

Louis J Lombardo Belle Mead NJ
Laurence I Wu Newton PA

Domestic Priority data as claimed by applicant

THIS APPLN CLAIMS BENEFIT OF 60/279 956 03/29/2001

Foreign Applications

If Required, Foreign Filing License Granted 05/01/2002

Projected Publication Date 10/03/2002

Non-Publication Request No

Early Publication Request No

Title

Cyano-substituted dihydropyrimidine compounds and their use to treat diseases

Preliminary Class

514

21

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ASSIGNMENT

We,

Louis J Lombardo residing at **49 West Street
Belle Mead, New Jersey 08502
United States of America**

Laurence I Wu residing at **43 Nathan Court
Newton, Pennsylvania 18940
United States of America,**

pureuant to contractual obligations heretofore assumed by us and/or for good and valuable consideration, the receipt and adequacy of which is hereby acknowledged, do hereby sell and assign to Bristol-Myers Squibb Company, a Delaware corporation, having a place of business at Lawrenceville-Princeton Road, Princeton, NJ 08543-4000, its successors, assigns and legal representatives, all our right, title and interest, which includes the right to and full benefit of such priorities as may now or hereafter be granted to us by local laws or by treaty, including any international convention for the protection of industrial property, in and for all countries of the world including the United States and its territories and possessions, in and to the invention entitled

CYANO-SUBSTITUTED DIHYDROPYRIMIDINE COMPOUNDS AND THEIR USE TO TREAT DISEASES

Invented by us and described in the non-provisional United States patent application executed on even date herewith including said non-provisional United States patent application and any application claiming priority from said non-provisional application, filed in any country, and any patents which may be issued and/or granted thereon, and all divisions, continuations, reissues, reexamination certificates and extensions thereof in all countries, the said interest being the entire ownership of said invention and all of said applications, patents (including reissue patents), extensions and reexamination certificates to be held and enjoyed by the said Bristol-Myers Squibb Company and its successors and assigns to the full end of the terms to which said patents (including reissue patents), extensions and reexamination certificates may be granted and/or issued, as fully and entirely as the same would have been held and enjoyed by us if this sale, assignment and transfer had not been made,

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And we hereby agree to communicate to said assignee or its representatives any facts known to us respecting said invention, to testify in any legal proceedings, to sign and/or execute any further documents and/or instruments which may be necessary, lawful and proper in and/or for the filing and/or prosecution of all applications, including divisional, continuation and reissue applications, extensions and reexamination certificates and/or the granting and/or issuance thereof and/or to otherwise secure title to said invention and all of said applications, patents (including reissue patents, extensions and reexamination certificates in said assignee, and in general to do everything possible to aid said assignee, its successors and assigns to obtain and enforce proper protection for said invention in all countries

Signed this 21 day of March, 2002 by


Louie J. Lombardo

State of New Jersey

County of Mercer

There appeared before me the person above-named and acknowledged that they executed the same, of their own free will for the purpose set forth on this 21 day of March, 2002


Notary Public
Hilda Franco
Notary Public of New Jersey
My Commission Expires January 5, 2005

Signed this 21 day of March, 2002 by


Laurence I. Wu

State of New Jersey

County of Mercer

There appeared before me the person above-named and acknowledged that they executed the same, of their own free will for the purpose set forth on this 21 day of March, 2002.


Notary Public
Hilda Franco
Notary Public of New Jersey
My Commission Expires January 5, 2005

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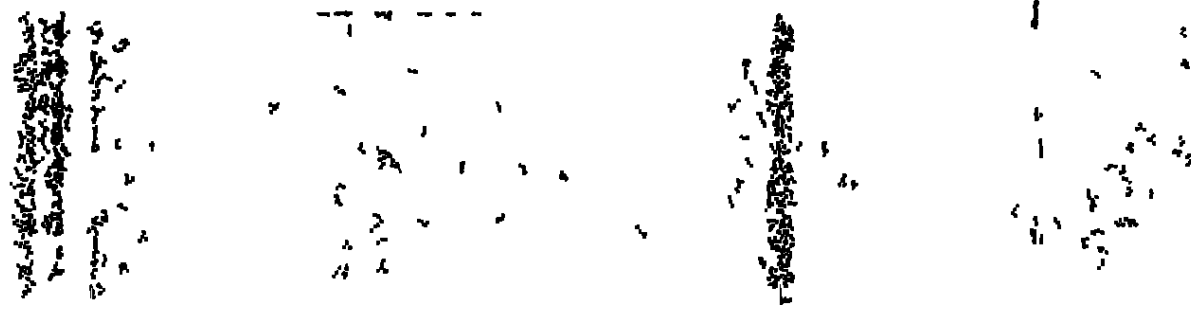
SUPERINDUSTRIA Y COMERCIO
Radicación : 03085451 00000000 Folios: 212
Fecha (HUB): 2003-09-25 16:38 02
Trámite 011 PCT-PATENT 379 FASE NDCI 411 PRESENTAC
Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

REQUISITOS NECESARIOS PARA PRESENTACION Y AGILIZACION DEL
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	USUARIO	RADICADOR
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Datos de identificación del solicitante o de la persona que se presenta la solicitud.	~~()~~	()
Descripción de la invención	~~()~~	()
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Comprobante de pago de las tasas establecidas	()	()
COMPLETA ()	INCOMPLETA ()	()

Firma Responsable *Andrés Posse*

Fecha



03 0854511

SUPERINDUSTRIA Y COMERCIO

SISTEMA DE REGISTRO I

| Fecha 29/10/2003 |

| MANTENIMIENTO DE PROTOCOLOS |

|Numero 19358 |

|Fecha 07/05/1999 |

|Conferido BRISTOL-MYERS SQUIBB COMPANY |

|Pais US ESTADOS UNIDOS DE AMERICA |

|Ciudad 82 PRINCETON NEW JERSEY |

|Represent. S Sustituir S Desistir S |

|No. Radicacion 03 085451 Clase 0 Secv 0 Seac 0 |

|IsenciaCodigo Ctr Nombre |

| 1 340 A CASTRO DUQUE RAMIRO |

| 2 3002 GOMEZ MEJIA HECTOR |

| Encontrados (1/1) registro(s)@



2020
Bogotá DC

Doctor(a)
RAMIRO CASTRO DUQUE
Apoderado(a)
BRISTOL MYERS SQUIBB COMPANY

REFERENCIA.	Radicación No	03 085451
	Solicitud Internacional	PCT/US02/09494
	Fecha inicio fase nacional	29/10/03
	Trámite	011
	Evento	379
	Actuación	416
	Oficio No	1305
	Folios	001

Teniendo en cuenta que la solicitud de privilegio de patente que se tramita bajo el expediente indicado en la referencia reúne los requisitos de forma establecidos en la Decisión 486 de la Comisión de la Comunidad Andina el Tratado de Cooperación en Materia de Patentes (PCT), el Reglamento y la Circular Unica de la Superintendencia de Industria y Comercio, se envía el extracto de la solicitud a la Oficina de Comunicaciones para efecto de su publicación en la Gaceta de Propiedad Industrial

Cúmplase
Dado en Bogotá DC

30 ENE 2004

ALIX CARMENZA CÉSPEDES DE VERGEL
Jefe de la División de Nuevas Creaciones

202055