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Estimados seæores:

FASE NACIONAL: "DERIVADOS DE
COMO INHIBIDORES MEK"

Damos alcance a la solicitud de patente PCT Fase Nacional presentada ante su Despacho y radicada el dia 30 de Abril del aæo encurso segUn expediente citado en la referencia, con el fin de presentar copias de los siguientes documentos expedidos segün el Tratado en Materia de CooperaciOn de Patentes:

Copia de la publicaciôn internacional No. WO 03/077914 Al de la patente PCT/US03/07864, con su traducción al espaæol.

Copia de informe de büsqueda Internacional SecciOn 18 y normas 43 y 44 segUn PCT/ISA 210, con su traducciªn al espaæol.

En consecuencia, ruego a usted tener en cuenta los anteriores documentos y una vez finiquttado esta dihgencia, ordenar 10 pertinente para que el expediente siga su
curso normal.

Del$ r Jefe,

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(54) Title: N3 ALKYLATIiD BIINZIMIDAZOI.1) DERIVATIVES AS MEK INHIBITORS

R10

H R1

R8 N
(R’

R7

(57) Abstract: Disclosed are compounds of the formula I, and pharmaceutically acceptable salts and prodrugs thereof, wherein W, R’, R2, K7, R5, R9 and R’° are as defined in the specification. Such compounds arc MIlK inhibitors and useful in the treatment of hyperproliferative diseases, such as cancer and inflammation, in mammals, Also disclosed is a method of using such compounds in the treatment of hyperproliicmtivc discases in mammals, and pharmaceutical compositions containing such compounds

WO 03/077914 PCT/US03/07864 N3 A1yiated Benzjmldazole Derivatives as MEK Inhibitors

BACKGROUND OF THE INVENTION Field of the Invention
This invention relates to a series of aikylated (1H-Benzoimidazol-5-yl)-(4-substituted-phcnyl)-arnine derivatives that are useful in the treatment of hyperproliferative diseases, such as cancer and inflammation, in mammals. This invention also relates to a method of using such compounds in the treatment of hyperproliferative diseases in mammals, especially humans, and to pharmaceutical compositions containing such compounds.
Summary of the Related Art
Cell signaling through growth factor receptors and protein kinases is an important regulator of cell growth, proliferation and differentiation. In normal cell growth, growth factors, through receptor activation (i.e. PDGF or EGF and others), activate MAP kinase pathways. One of the most important and most well understood MAP kinase pathways involved in normal and uncontrolled cell growth is the Ras! Raf kinase pathway. Active GTP-bound Ras results in the activation and indirect phosphorylation ofRaf kinase. Raf then phosphorylates MEKI and 2 on two serine residues (S218 and 5222 for MEK1 and S222and S226 for MEK2) (Aim et al., Methods in Enzymology 2001, 332, 417-431). Activated MEK then phosphorylates its only known substrates, the MAP kinases, ERK1 and 2. ERK phosphorylation by MEK occurs on Y204 and T202 for ERK1 and Y185 and T183 for ERK2 (Ahn ci al., Methods in Enzymology 2001, 332, 417-431). Phosphorylated ERK dimerizes and then translocates to the nucleus where it accumulates (Khokhlatchev et al., Cell 1998, 93, 605-615). In the nucleus, ERK is involved in several important cellular functions, including but not limited to nuclear transport, signal transduction, DNA repair, nucleosome assembly and translocation, and mRNA processing and

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translation (Aim et al., Molecular Cell 2000, 6, 1343-1354). Overall, treatment of cells with growth factors leads to the activation of ERK1 and 2 which results in proliferation and, in some cases, differentiation (Lewis et al., Adv. Cancer Re.,. 1998, 74, 49-139).
In proliferative diseases, genetic mutations and/or overexpression of the growth factor receptors, downstream signaling proteins, or protein kinases involved in the ERK kinase pathway lead to uncontrolled cell proliferation and, eventually, tumor formation. For example, some cancers contain mutations which result in the continuous activation of this pathway due to continuous production of growth factors. Other mutations can lead to defects in the deactivation of the activated GTP-bound Ras complex, again resulting in activation of the MAP kinase pathway. Mutated, oncogenic forms of Ras are found in 50% of colon and >90% pancreatic cancers as well as many others types of cancers (Kohl et al., Science 1993, 260, 1834-1837). Recently, bkaf mutations have been identified in more than 60% of malignant melanoma (Davies. H. et al., Nature 2002, 417, 949-954). These mutations in bRafresult in a constitutively active MAP kinase cascade. Studies of primary tumor samples and cell lines have also shown constitutive or overactivation of the MAP kinase pathway in cancers of pancreas, colon, lung, ovary and kidney (Hoshino, R. et al., Oncogene 1999, 18, 813-822). Hence, there is a strong correlation between cancers and an overactive MAP kinase pathway resulting from genetic mutations.
As constitutive or overactivation of MAP kinase cascade plays a pivotal role in
cell proliferation and differentiation, inhibition of this pathway is believed to be beneficial in hyperproliferative diseases. MEK is a key player in this pathway as it is downstream of Ras and Raf. Additionally, it is an attractive therapeutic target because the only known substrates for MEK phosphorylation are the MAP kinases, EEl and 2. Inhibition ofMEK has been shown to have potential therapeutic benefit in several studies. For example, small molecule MEK inhibitors have been shown to inhibit human tumor

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growth in nude mouse xcnografts, (Sebolt-Leopold et al., Nature-Medicine 1999, 5 (7), 810-816; Trachet et al., AACR April 6-10, 2002, Poster 95426; Tecle, H. 2’ International Conference of Protein ICinases, September 9-10, 2002), block static allodynia in animals (WO 01/05390 published January 25, 2001) and inhibit growth of acute myeloid leukemia cells (Milella et at, JCliii Invest 2001, 108 (6), 851-859).
Small molecule inhibitors of IvIEK have been disclosed. At least thirteen patent applications have appeared in the last several years: US 5,525,625 filed January 24, 1995; WO 98/43960 published October 8, 1998; WO 99/01421 published January 14, 1999; WO 99/01426 published January 14, 1999; WO 00/41505 published July 20, 2000; WO 00/42002 published July 20, 2000; WO 00/42003 published July 20, 2000; WO 00/41994 published July 20, 2000; WO 00/42022 published July 20, 2000; WO 00/42029 published July 20, 2000; WO 00/68201 published November 16, 2000; WO 01/6861.9 published September 20, 2001; and WO 02/06213 published January 24, 2002,

WO 031077914 PCT1US03I0764 SUMMARY OF THE INVENTION

This invention provides for alkylated (lH-benzoimdazol-5yl)-4-substituted phenyl)-amine compounds of formula I, and pharmaceutically acceptable salts and prodrugs thereof that are useful in the treatment of hyperprolifcrative diseases. Specifically, the present invention relates to compounds of formula I that act as MEK inhibitors. Also provided is a method for treatment of cancer. Also provided are formulations containing compounds offormula I and methods ofusing the compounds to treat a patient in need thereof. In addition, there are described processes for preparing the inhibitory compounds offormula L
Accordingly, the present invention provides compounds ofthe formula I:

Rio R1

N

?,C R9 RB)a"

and pharmaceutically accepted salts, prodmgs and solvates thereof, wherein:
is an optional bond, provided that one and only one nitrogen of the ring is double-bonded;
R’, R2, R9 and R’° are independently selected from hydrogen, halogen, cyano, nitro, trifluoromethyl, dffluoromethoxy, trifluoromethoxy, azido, -OR3, -C(0)W, -C(0)0R3, NR4C(0)0R6, -OC(0)R3, -NR4S02R6, -S02NR3R4, -NR4C(0)R3,
- C(0)NR3R4, -NR5C(0)NR3R4, -NR5C(NCN)NR3R4, -NR3R4, and

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C1C10 alkyl, C2-C10 alkenyl, C2-C10 alkynyl, C3-C10 cycloalkyl, 3-C10
cycloalkylalkyl, -S(0)J(C1-C6 alkyl), -S(0)j(CR4R5)m-aryl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, heterocyclyl, heterocyclylalkyl, 0(CR4R)m
aryl, -NR4(CR4R)1-aryl, -O(CR4R),heteroaryl, -NR4(CR4R)m-heteroaryl, -0(CR4R)m4ieterocycly1 and -NR4(CR4R5)-heterocyclyl, where each alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl and heterocyclyl portion is optionally substituted with one to five groups independently selected from oxo, halogen, cyano, nitro, trifluoromethyl, difluoromethoxy, trifluoromethoxy, azido, -NR4SO2R6, -S02NR3R4,
- C(0)R3, -C(0)0R3, -OC(0)R3, -NR4C(0)0R6, -NR4C(0)R3,

. C(0)NR3R4, -NR3R4, -NR5C(0)NR3R4, -NR5C(NCN)NR3R4, -OW, aryl,
heteroaryl, arylalkyl, heteroarylalkyl, heterocyclyl, and heterocyclylalkyl;
R3 is selected from hydrogen, trifluoromethyl, and
C1-00 alkyl, C2-C10 alkenyl, C2-C10 alkynyl, C3-C10 cycloalkyl, C3-C,() cycloalkylalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, heterocyclyl,
and heterocyclylalkyl, where each alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl and heterocyclyl portion is optionally substituted with one to
five groups independently selected from oxo, halogen, cyano, intro, trifluoromethyl, difluoromethoxy, trifluoromethoxy, azido, -NRSO2R’"’, -SO2NR’R7,.c(0)R’,.-C(0)OR’, -OC(0)R’, NR’C(0)OR", -NTR’C(0)R’, -C(0)NRR, -SR’, S(0)R" -SO2R", NR’R", -NRC(0)NR"R", - NR’C(NCN)NR"R", -OR’, aryl, heteroaryl, arylalkyl, heteroarylalkyl, heterocyclyl, and heterocyclylalkyl;
R’, R" and R" independently are selected from hydrogen, lower alkyl, lower alkenyl, aryl and arylalkyl;

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K’ "is selected from lower alkyl, lower alkenyl, aryl and arylalkyl; or
Any two of R’, R", R" or R.... can be taken together with the atom to which they are attached to form a 4 to 10 membered carbocycic, heteroaryl or heterocyclic ring,
each of which is optionally substituted with one to three groups independently selected from halogen, cyano, nitro, trifluoromethyl, difluoromethoxy, trifluoromethoxy, azido, aryl, heteroaryl, arylalkyl, heteroarylalkyl, heterocyclyl,
and heterocyclylalkyl; or
R3 and k4 can be taken together with the atom to which they are attached to form a 4 to 10 membered carbocyclic, heteroaryl or heterocyclic ring, each of which is optionally substituted with one to three groups independently selected from halogen, cyano, nitro, trifluoromethyl, difluoromethoxy, trifiuoromethoxy, azido, - NR’S02R"", S02NR’R", -C(0)R, -C(0)OR, -OC(0)R’, -NRC(0)OR, - NR’C(0)R", -C(0)NR’R", -SO2R", -NR’R", -NRC(0)NRR", - NR’C(NCN)NR"R"’, -OR, aryl, heteroaryl, arylalkyl, heteroaiylalkyl, heterocyclyl, and heterocyclylalkyl; or
K4 and K5 independently represent hydrogen or C1-C6 alkyl; or
R4 and R’ together with the atom to which they are attached form a 4 to 10 membered
carbocycic, heteroaryl or heterocyclic ring, each of which is optionally
substituted with one to three groups independently selected from halogen, cyano,
nitro, trifluoromethyl, difluoromethoxy, tnfluoromethoxy, azido, -NR’S02R",
. -SO2NR’R", -C(0)R"", -C(0)OR’, -.00(0)R’, -NR’C(0)OR’"’, -NR’C(0)R", -C(0)NR’R", -SO2R’"’, -NR’R", -NR’C(0)NR"R", -NR’C(NCN)NR"R’, -OR’,
aryl, heteroaryl, arylalkyl, heteroarylalkyl, heterocyclyl, and heterocyclylalkyl;
R6 is selected from trifluoromethyl, and

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Cl-CIO alkyl, C3-C10 cycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, heterocyclyl, heterocyclylalkyl, where each alkyl, cycloalkyl, aryl,
heteroaryl and heterocyclyl portion is optionally substituted with one to
five groups independently selected from oxo, halogen, cyano, nitro, trifluoromethyl, di.fluoromethoxy, trifluorornethoxy, azido, -NR’S02R",
- SO2NRR’, -C(0)R’, -C(0)OR’, -OC(0)R’, -NR C(0)OR’, -NRC(0)R",
-C(0)NR’R", -S02R", -NR’1, -NR’C(0)NR"R", -NR C(NCN)NR R", -
OR, aryl, heteroaryl, arylalkyl, heteroarylalkyl, heterocyclyl, and heterocyclylalkyl;
R7 is selected from hydrogen, and
C1-Cio alkyl, C2-C10 alkenyl, C2-C10 alkynyl, C3-CIO cycloalkyl, C3-C10 cycloalkylalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, heterocyclyl, heterocyclylalkyL where each alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl and heterocyclyl portion is optionally substituted with one to
five groups independently selected from oxo, halogen, cyano, nitro, trifluoromethyl, difluoromethoxy, trifluoromethoxy, azido, -NR4SO2R6,

- SO2NR3R4, -C(0)R3, -C(0)0R3, -OC(0)R3, -NR4C(0)0R6, -NR4C(0)R3,
- C(0)NR3R4, -S02R6, -NR3R4, -NR5C(0)NRR4, -NR5C(NCN)NR3R4, -

OR’, aryl, heteroaryl, arylalkyl, heteroarylalkyl, heterocyclyl, and heterocyclylalkyl;
W is selected from heteroaryl, heterocyclyl, -C(0)OW, -C(0)NR3R4, -C(0)NWW, C(0)R40R3, -C(0)(C3-C10 cycloalkyl), -C(0)(C1-C10 alkyl), -C(0)(aryl), - C(0)(heteroaryl) and -C(0)(hetcrocyclyl), each of which is optionally substituted
with 1-5 groups independently selected from
- NR3R4, -OW, -R2, and

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C1-C10 alkyl, C2-C10 alkenyl, and C2-C10 alkynyl, each of which is
optionally substituted with I or 2 groups independently selected
from NR3R4 and OW;
R8 is selected from hydrogen, -SCF3, -Cl, -13r, -F, cyano, nitro, triftuoromethyl, difluorornethoxy, trifluoromethoxy, azido, -OR3, -C(0)R3, -C(0)0k3,
- NR4C(0)0R6, -OC(0)R, -NR4S02R6, -802NR3R4, -NR4C(0)R3, -C(0)NR3R4, N1.5C(0)NR3R4, -NR3R4, and
CI-CIO alkyl, C2-C10 alkenyl, C2-CIO alkynyl, C3-C10 cycloalkyl, C3-C10 cycloalkylalkyl, S(0)(C1-C6 alkyl), -S(0)j(CR4R5)m-aryl, aryl, arylalkyl,
beteroaryl, heteroarylalkyl, heterocyclyl, heterocyclylalkyl, -O(CR4R5)m
aryl, -NR4(CR4R)m-aryI, 0(CR4R5)mheteroaryl, -NR4(CR4R5)m-heteroaryl, -O(CR4R)m-heterocyclyl and -NR4(CR4R)-heterocycly1, where each alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl and heterocyclyl portion is optionally substituted with one to five groups independently selected from oxo, halogen, cyano, nitro, trifluoromethyl, difluorornethoxy, trifluoromcthoxy, azido, -NR4SO2R, -SO2NR3R4,
- C(0)R3, -C(0)0R3, -OC(0)R3, -NR4C(0)0R6, -WC(0)R3,
- C(0)NR3R4, -NR3R4, -NR5C(0)NR3R4, -NR5C(NCN)NR3R4, -OR’, aryl, heteroaryl, arylallryl, heteroarylailcyl,, heterocyclyl, and heterocycilylalkyl; misO, 1, 2, 3,4or5; and
j is I or 2.

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WO 0310779.14 PCT/LJSO3/O 7864 DETAILED DESCRIPTION OF THE INVENTION

The novel compounds encompassed by the instant invention are those described
by the general formula I set forth above, and the pharmaceutically acceptable salts and prodrugs thereof.
The present invention also provides compounds offormula Tin which R7 is C1 -C10 alkyl, C3-C7 cycloalkyl, C3-C-7 cycloalkylalkyl, C3-C7 beterocycloalkyl or C3-C7 heterocycloalkylalkyl each of which can be optionally substituted with 1 - 3 groups independently selected from oxo, halogen, cyano, nitro, trifluoromethyl, difluoromethoxy, trifluoromethoxy, azido, -NR4SO2R6, -SO2NR3R4, -C(0)R3, -C(0)0R3, -OC(0)R3, 802R3, -WC(0)W, -i&C(o)R3, -C(0)NR3R4, -NR3R4, -NR5C(0)NR3R4, - NR5C(MCN)NR3R4, -OR’, aryl, heteroaryl, arylalkyl, heteroarylalkyl, heterocyclyl, and heterocyclylalkyl.
The present invention also provides compounds offormula I wherein R8 is -OCF3,
- Hr or--Cl, R2 is hydrogen, and R’ is lower alkyl or halogen.
The present invention also provides compounds of formula I wherein R9 is hydrogen or halogen, and R’° is hydrogen.
The present invention also provides compounds of formula I wherein W is

- C(0)0R3 or -C(0)NR4OR3

The present invention also provides compounds of formula II:

R’
U
9

9 R8

() ()
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wherein W, R1, R7, R8, R9 and Pi° are as defined above for formula I.
The present invention also provides compounds of formula TI in which R7 is C1-
Cio alkyl, C3-C7 cycloalkyl or C3-C7 cycloalkylalkyl, each of which can be optionally substituted with 1 - 3 groups independently selected from oxo, halogen cyano, nitro, trifluoromethyl, difluoromethoxy, triflunromethoxy, azido, -NR4SO2k6, -SO2NR3R4, -C(0)R3, C(0)OW, -OC(0)R3, -SO2R3, -NR4C(0)0R6, -N4C(0)R3, -C(0)NR3R4, - NR3R4, -NR5C(0)NR3R4, -NR5C(N(,-N)NR3R4, -OR3, aryl, heteroaryl, arylalkyl, heteroarylalkyl, heterocyclyl, and beterocyclylalkyl.
The present invention also provides compounds of formula II wherein R is - 0CF3. Br orCl, and R1 is lower alkyl or halogen.
The present invention also provides compounds of formula II wherein R9 is hydrogen or halogen, and R’° is hydrogen
The present invention also provides compounds of formula H wherein W is

- C(0)0R3 or -C(0)NR4OR3.

The present invention also provides compounds offormula ifi:

H R1

R7

wherein R1, R2, R7, R8 and R9 are as defined above for formula I, and A is OR3 or - NR’OR3, wherein R3 and R4 are as defined above for formula I.

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WO 03/077914 PCTIUS03/07864 The present invention also provides compounds o. formula III in which R1 is Ci-
C10 ailcyl, C3-C7 cycloalkyl or C3-C7 cycloalkylalkyl, each of which can be optionally substituted with 1 - 3 groups independently selected from oxo, halogen, cyano, intro, trifluorornethyi, difluoroinethoxy, trifluoromethoxy, azido, _NR4SO2R6, -S02NR3R4, ..C(0)R3, -C(0)0R3, -OC(0)R3, -SOW, -NR4C(0)0R6, -NR4C(OR3, -C(0)NR3R4, - NR3R4, -NR5C(0)NR3k4, -NR5CNNNR3R4, -OR3, aryl, heteroaryl, arylalkyl, heteroarylalkyl, heterocyclyl, and heterocyclylalkyl.
The present invention also provides compounds of formula 111 wherein R8 is -OCF3, Br or Cl, R2 is hydrogen, and R1 is lower alkyl or halogen.
The present invention also provides compounds of formula III wherein R9 is hydrogen or halogen.
The present invention also provides compounds of formula ifi wherein R3 is hydrogen or lower alkyl when A is OR3; and R4 is hydrogen when A is NR4OR3.
The present invention also provides compounds of formula lila:
0 A
H R1

R7 R9rll?’ R8
R2

ha

wherein R1, R2, R7, R8 and R9 are as defined above for formula I, and A is OR3 or -NR4OR3, wherein R3 and R4 are as defined above for formula 1.
The present invention also provides compounds offormula ha in which R7 is CI-
CIO alkyl, C3-C7 cycloalkyl or C3-C7 cycloalkylaikyl, each of which can be optionally substituted with I - 3 groups independently selected from oxo, halogen, cyano, nitro,

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trifluoromethyl, difluoromethoxy, trifluioromethoxy, azido, -NR4SO2R6, -SO2NR3R4, -C(0)W, -C(0)0R3, -OC(0)R3, -S02R3, -NIOC(0)OR, -NR4C(0)R3, -C(0)NIR3R4, - NR3R4, -NR5C(0)NR3R4, -NRCNCN)NR3R4, -OW, aryl, heteroaryl, arylalkyl, heteroarylalkyl, heterocyclyl, and heterocyclylalkyl.
The present invention also provides compounds of formula ifia wherein. R, is
- OCF3, Er or Cl, R2 is hydrogen, and R’ is lower alkyl or halogen.
The present invention also provides compounds of formula ha wherein R9 is hydrogen or halogen.
The present invention also provides compounds of formula ma wherein R3 is hydrogen or lower alkyl when A is OR3; and R4 is hydrogen when A is NR4OR3.
The present invention also provides compounds offormula Mb:

R1

Rib

wherein R’, R7, R8 and R9 are as defined above for formula I, and A is OR3 or -NR40R3, wherein R3 and R4 are as defined above for formula T.
The present invention also provides compounds offormula 111b in which R7 is C1 -
C10 alkyl, C3-C7 cycloalkyl or C3-C-1 cycloalkylalkyl, each of which can be optionally substituted with I - 3 groups independently selected from oxo, halogen, cyano, nitro, trifluoromethyl, difluoromethoxy, trifluoromethoxy, azido, -NR4S02R6, -SO2NR3R4,
- C(0)R3, -C(0)0R3, -OC(0)R3, -S02R3, -NR4C(0)0R6, -NR4C(0)R3, -C(0)NR3R4, -

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NR3R4, -NR5C(0)NR3R4, -NR5C(NCN)NTR3R4, -OR’, aryl, heteroaryl, arylalkyl, heteroarylalkyl, hctcrocyelyl, and heterocyclylalkyl.
The present invention also provides compounds of formula l]IIb wherein R8 is
- OCF3, Br orCl, and R1 is lower alkyl or halogen.
The present invention also provides compounds of formula Bib wherein R9 is

fluoro or chioro.

The present invention also provides compounds of formula 111b wherein R3 is hydrogen or lower alkyl when A is --OR3; and R4 is hydrogen when A is NR4OR3. Except as expressly defined otherwise, the following definition of terms is employed throughout this specification.
By "C1-C10 alkyl", "alkyl" and "lower alkyl" in the present invention is meant straight or branched chain alkyl groups having 1-10 carbon atoms, such as, methyl, ethyl, propyl, isopropyl, n-butyl, sec-butyl, tert-butyl, pentyl, 2-pentyl, isopentyl, neopentyl, hexyl, 2-hexyl, 3-hexyl, 3-methylpentyl heptyl, octyl, and the like. Preferred alkyl radicals are C1 alkyl. More preferred alkyl radicals are C3 alkyl.
By "C2-C10 alkenyl", "lower alkenyl" and "alkenyl" means straight and branched hydrocarbon radicals having from 2 to 10 carbon atoms and at least one double bond and includes ethenyl, property1, I -but-3-enyl, 1-pent-3-enyl, 1-hex-5-enyl and the like. More preferred are lower alkenyl having 3-5 carbon atoms.
By "C2-C10 alkynyl", "lower alkynyl" and "alkynyl" means straight and branched hydrocarbon radicals having from 2 to 10 carbon atoms and at least one triple bond and includes ethynyl, propynyl, hutynyl, pentyn-2-yl and the like. More preferred are alkynyl having 3-5 carbon atoms.
By the term "halogen" in the present invention is meant fluorine, bromine, chlorine, and iodine.

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By is meant an aromatic carbocyclic group having a single ring (e.g., phenyl), multiple rings (e.g., biphenyl), or multiple condensed rings in which at least one is aromatic, (e.g., 1,2,3,4-tetrahydronaphthyl, naphthyl), which is optionally mono-, di-, or trisubstituted with, e.g., halogen, lower alkyl, lower alkoxy, trifluoromethyl, aryl, hcteroaryl, and hydroxy,
By "heteroaryl" is meant one or more aromatic ring systems of 5-, 6-, or 7-membered rings which includes fused ring systems (at least one of which is aromatic) of 5-10 atoms containing at least one and up to four heteroatoms selected from nitrogen, oxygen, or sulfur. Examples of heteroaryl groups are pyridinyl, imidazolyl, pyrimidinyl, pyrazolyl, triazolyl, pyrazinyl, tetrazolyl, furyl, thienyl, isoxazolyl, thiazolyl, oxazoiyl, isothiazolyJ, pyrrolyl, quinolinyl, isoquinolinyl, mdolyl, benzirnidazolyl, benzofuranyl, cinnolinyl, indazolyl, iridolizinyl, phthalazinyl, pyridazinyl, triazinyl, isoindolyl, pteridinyl, purinyl, oxadiazolyl, iriazolyl, thiadiazolyl, thiadiazoyl, fnrazanyl
benzofurazanyl, benzothiophenyl, benzothiazolyl, benzoxazolyl, quina.zoli nyl,
quinoxalinyl, naphthyridinyl, and furopyridinyL Spiro moieties are also included within the scope ofthis definition. Heteroaryl groups are optionally mono-, di-, or trisubstituted with, e.g., halogen, lower alkyl, lower alkoxy, haloalkyl, aryl, heteroaryl, and hydroxy. As used herein, the term "carbocycle", "carbocyclyl", "cycloalkyl" or "C3-C10 cycloalkyl" refers to saturated carbocycic radicals having three to ten carbon atoms. The cycloalkyl can be monocyclic, or a polycyclic fused system, and can be fused to an aromatic ring. Examples of such radicals include cyclopropyl, cyclobutyl, cycloperityl and cyclobexyl. The cycloalkyl groups herein are unsubstituted or, as specified, substituted in one or more substitutable positions with various groups. For example, such cycloalkyl groups may be optionally substituted with, for example, CI-C6 alkyl, C1-C6 alkoxy, halogen, hydroxy, cyano, nitro, anino, mono(Cj-C6)alkylamino, di(Ci-
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C6)alkylamino, C2-C6alkenyl, C2-C6alkynyl, C1 -C6 haloalkyl, CI-C6 haloalkoxy, amino(Ci-C6)alkyl, nono(Ci-C6)alkylamino(Ci-C6)alkyl or di(Ci.C)alkyiamino(Ci-C6)alkyi.
By "heterocycle" or "heterocyciyl" is meant one or more carbocyclic ring systems
of 5-, 6-. or 7-membered rings which includes fused ring systems of 4-10 atoms containing at least one and up to four heteroaloms selected from nitrogen, oxygen, or sulfur, and with the proviso that the ring ofthe group does not contain two adjacent 0 or S atoms. A fused system can be a heterocycle fused to an aromatic group. Preferred heterocycles include, but are not limited to, pyrrolidinyl, tetraliydrofuranyl, dihydrofuranyl, tetrahydrothienyl, tetrahydropyranyl, dihydropyranyl, tetrahydrothiopyranyl, piperidino, morpholino, thiomorpholino, thioxanyl, piperazinyl, homopiperazinyl, azetidinyl, oxetanyl, thietanyl, homopiperidinyl, oxepanyl, thiepanyl, oxazepinyl, diazepinyl, thiazepinyl, 1,2,3,6-tetrahydropyridinyl, 2-pyrrolinyL 3-pyLTOilnyl, indolinyl, 2H-pyranyl, 4H-pyranyl, dioxanyl, 1,3-dioxolanyl, pyrazolinyl, dithianyl, dithiolariyl, dihydropyranyl, clihydrothienyl, dihydrofuranyl, pyrazolidinylimidazolinyl, imidazolidinyl, 3-azabicyco[3.1,0]hexanyl, 3-
azabicyclo[4. 1.0]heptanyl, azabicyc1o(2.2.23hcxany1, 3H-indolyl and quinolizinyl. Spiro
moieties are also included within the scope of this definition. The foregoing groups, as
derived from the groups listed above, may he C-attached or N-attached where such is
possible. For instance, a group derived from pyrrole may be pyrrol-1 -yl (N-attached) or
. pyrrol-3-yl (C-attached). Further, a group derived from imidazole may be iniidazol-1-yl (N-attached) or imidazol-3--yl (C-attached). An example of a heterocyclic group wherein
2 ring carbon atoms are substituted with oxo (=0) moieties is 1,1-dioxo-thiomorpholinyl.
The heterocycle groups herein are unsubstituted or, as specified, substituted in one or
more substitutable positions with various groups. For example, such heterocycle groups

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may be optionally substituted with, for example, C1 -C6 alkyl, C1 -C6 alkoxy, halogen, hydroxy, cyano, nitro, amino, mono(Ci-Cs)alkylamiflo, di(Ci-Cs)alkylamino, C2-C6alkenyl, C2-C6alkynyl, C1-05 haloalkyl, C1-C6 haloalkoxy, aniino(C1-C6)alkyl, mono(C1 -C6)alkylamino(Cr-C6)alkyl or di(C1-C6)alkylamino(Ci-Co)alkyl.
The term "arylalkyl" means an alkyl moiety (as defined above) substituted with
one or more aryl moiety (also as defined above). More preferred arylalkyl radicals are aryl-C13--alkyls- Examples include benzyl, phenylethyl, and the like.
The term "heteroarylalkyl" means an alkyl moiety (as defined above) substituted
with a beteroaryl moiety (also as defined above). More preferred heteroarylalkyl radicals are 5- or 6-membered heteroaryl-C13-alkyls. Examples include, oxazolylmethyl, pyridylethyl and the like.
The term "heterocyclylalkyl" means an alkyl moiety (as defined above) substituted with a heterocyclyl moiety (also defined above). More preferred heterocyclylalkyl radicals are 5- or 6-membered heterocyclyl-C13-alkyls. Examples include tetrahydropyranylmethyl.
The term "cycloalkylalkyl" means an alkyl moiety (as defined above) substituted
with a cycloalkyl moiety (also defined above). More preferred heterocyclyl radicals are
5- or 6-membered cycloalkyl-C13-alkyls. Examples include cyclopropylmetbyl.
The term "Me" means methyl, "Et" means ethyl, "Bu" means butyl and "Ac"
means acetyl.
The phrase "pharmaceutically acceptable salt(s)", as used herein, unless otherwise

40 indicated, includes salts of acidic and basic groups which may be present in the
compounds of the present invention. The compounds of the present invention that are
basic in nature are capable of forming a wide variety of salts with various inorganic and
organic acids. The acids that may be used to prepare pharmaceutically acceptable acid

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addition salts of such basic compounds of the present invention are those that form non-toxic acid addition salts, i.e, salts containing pharmaceutically acceptable anions, such as the acetate, benzenesulfonate, benzoate, bicarbonate, bisulfate, bitartrate, borate, bromide, calcium, camsylate, carbonate, chloride, clavulanate, citrate, dihydrochioride, edislyate, estolate, esylate, othylsuccinate, fumarate, gluceptate, gluconate, glutamate, glycollylarsanilate, bexyiresorcinate, hydrabamine, hydrobromide, hydrochloride, iodide, isothionate, lactate, lactobionate, laurate, malate, maicate, mandelate, mesylate, methylsulfate, mucate, napsylate, nitrate, oleate, oxalate, parnoate (embonate), palimitate, pantothenatc,.phosphate/diphospbate, polygalacturonate, salicylate, stearate, subacetate, succinate, tannate, tartrate, teoclate, tosylate, triethiodode, and valerate salts. Since a single compound of the present invention may include more than one acidic or basic moieties, the compounds of the present invention may include mono, di or ni-salts in a single compound.
In the case of an acidic moiety in a compound ofthe present invention, a salt may
be formed by treatment of a compound of the present invention with a basic compound, particularly an inorganic base. Preferred inorganic salts are those formed with alkali and alkaline earth metals such as lithium, sodium, potassium, barium and calcium. Preferred organic base salts include, for example, ammonium, dibenzylammoninm, benzyiarnmonium, 2-hydroxyetliylamnionium, bis(2-hydroxyethyl)annnonium, plrenylethylbenzylamine, dibenzyl-ethylenediamine, and the like salts. Other salts of acidic moieties may include, for example, those salts formed with procaine, quinine and N-methvlgkisoamine, plus salts formed with basic amino acids such as glycine, omithine, histidine, phenyiglycine, lysine and arginine. An especially preferred salt is a sodium or potassium salt of a compound ofthe present invention.

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With respect to basic moieties, a salt is formed by the treatment of a compound of
the present invention with an acidic compound, particularly an inorganic acid. Preferred inorganic salts of this type may include, for example, the hydrochloric, hydrobromic, hydroiodie, sulfuric, phosphoric or the like salts. Preferred organic salts ofthis type, may include, for example, salts formed with formic, acetic, succinic, citric, lactic, maleic, fumaric pailmitic, cholic, pamoic, mucic, 0-glutamic, Dcamphoric, glutaric, glycolic, phtlialic, tartaric, laurie, stearic, salicyclic, methanesulfonic, benzenesulfonic, paratoluenesulfonic, sorbic, puric, benzoic, cinnamic and the like organic acids. An especially preferred salt of this type is a hydrochloride or sulfate salt of a compound of the present invention.
In the compounds of the present invention, where terms such as (CR4R5)m or (CR4R5) are used, R4 and R5 may vary with each iteration of m or t above I. For instance, where m or t is 2, the terms (CR4R5)m or (CR4R5) may equal CFICH2- or - CH(CH3)C(CH2CH3)(CII2CH2CII3)- or any number of similar moieties falling within the scope ofthe definitions ofR4 and R.5.
Certain compounds of the present invention may have asymmetric centers and therefore exist in different onaritiomeric forms. All optical isomers and stereoisomers of the compounds ofthe present invention, and mixtures thereof, are considered to be within the scope of the invention. With respect to the compounds of the present invention, the invention includes the use of a racemate, one or more enantiomeric forms, one or more diastereomeric forms, or mixtures thereof. The compounds ofthe present invention may also exist as tautomers. This invention relates to the use of all such tautomers and mixtures thereof.
The subject invention also includes isotopically-labeled compounds, which are identical to those recited in the present invention, but for the fact that one or more atoms

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are replaced by an atom having an atomic mass or mass number different from the atomic mass or mass number usually found in nature. Examples of isotopes that can be incorporated into compounds of the invention include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorous, sulfur, fluorine and chloride, such as 2H, 3H, ’3C, ’4C, 15N, 180 170 31P, 32P, 35S. 18F, and 36C1, respectively. Compounds of the present invention, prodrugs thereof, and pharmaceutically acceptable salts of said compounds or ofsaid prodrugs which contain the aforementioned isotopes and/or other isotopes of other atoms are within the scope of this invention. Certain isotopically-labeled compounds of the present invention, for example those into which radioactive isotopes such as 3H and 4C are incorporated, are useful in drug and/or substrate tissue distribution assays. Tritiated,, is., 3H and carbon-14, i.e., 14C, isotopes are particularly preferred for their ease of preparation and detectability. Futher, substitution with heavier isotopes such as deuterium, i.e., 2H, can afford certain therapeutic advantages resulting from greater metabolic stability, for example increased in vivo half-life or reduced dosage requirements and, hence, may be preferred in some circumstances. Isotopically labeled
compound of the present invention and prodrugs thereof can generally be prepared by
carrying out procedures disclosed in the Schemes and/or in the Examples and
Preparations below, by substituting a readily available isotopically labeled reagent for a
non-isotopically labeled reagent.
This invention also encompasses pharmaceutical compositions containing a
. compound of formulas 1-ifib and methods oftreating proliferative disorders, or abnormal cell growth, by administering prodrugs of compounds of the the present invention.
Compounds of the present invention having free amino, amido, hydroxy or carboxylic
groups can be converted into prodrugs. Prodrugs include compounds wherein an amino
acid residue, or a polypeptide chain of two or more (e.g., two, three or four) amino acid
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residues is covalently joined through an anjide or ester bond to a free amino, hydroxy or carboxylic acid group of compounds of the present invention. The amino acid residues include but are not limited to the 20 naturally occurring amino acids commonly designated by three letter symbols and also includes 4hydroxyproline, hydroxylysine, demosine, isodemosinc, 3-mcthylhistidine, norvaline, beta-alanine, ganima-aminobutyric acid, cirtulline, homocysteine, bomoserinc, omithine and methioriine sulfone. Additional types of prodrugs are also encompassed. For instance, free carboxyl groups can be derivatized as amides or alkyl esters. Free hydroxy groups may be derivatized using groups including but not limited to hemisuccinates, phosphate esters, dimethylaminoacetates, and phosphoryloxymethyloxycarbonyls, as outlined in Advanced Drug Delivery Reviews l)96, 19, 115. Carbamate prodrugs ofhydroxy and amino groups are also included, as are carbonate prodrugs, sulfonate esters and sulfate esters ofhydroxy groups. Derivatization of hydroxy groups as (acyloxy)methyl and (acyloxy)ethyl ethers wherein the acyl group may be an alkyl ester, optionally substituted with groups including but not limited to ether, amine and carboxylic acid functionalities, or where the acyl group is an amino acid ester as described above, are also encompassed. Prodrugs of this
type are described in J. Med. Chem. 1996, 39, 10. Free amines can also be derivatized as
arnides, sulfonamides or phosphonarnides. All ofthese prodrug moieties may incorporate
groups including but not limited to ether, amine and carboxylic acid functionalities.
It is to be understood that in instances where two or more radicals are used in
succession to define a substituent attached to a structure, the first named radical is

Is considered to be terminal and the last named radical is considered to be attached to the

structure in question. Thus, for example, the radical arylalkyl is attached to the structure
in question by the alkyl group.

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The invention also relates to a pharmaceutical composition for the treatment of a hyperproliferative disorder in a mammal winch comprises a therapeutically effective amount of a compound of the present invention, or a pharmaceutically acceptable salt, prodrug or hydrate thereof, and a pharmaceutically acceptable carrier. In one embodiment, said pharmaceutical composition is for the treatment of cancer such as brain, lung, squamous cell, bladder, gastic, pancreatic, breast, head, neck, renal, kidney, ovarian, prostate, colorectal, esophageal, testicular, gynecological or thyroid cancer. In another embodiment, said pharmaceutical composition is for the treatment of a non-cancerous hyperproliferative disorder such as benign byperplasia of the skin (e.g., psoriasis), restenosis, or prostate (e.g.,benign prostatic hypertrophy (BPH)).
The invention also relates to a pharmaceutical composition for the treatment of pancreatitis or kidney disease (including proliferative glomeruilonephritis and diabetes induced renal disease) or the treatment of pain in a mammal which comprises a therapeutically effective amount of a compound of the present invention, or a pharmaceutically acceptable salt, prodrug or hydrate thereof, and a pharmaceutically acceptable carrier.
The invention also relates to a pharmaceutical composition for the prevention of blastocyte implantation in a manmial which comprises a therapeutically effective amount of a compound ofthe present invention, or a pharmaceutically acceptable salt, prodrug or hydrate thereof, and a pharmaceutically acceptable carrier.
The invention also relates to a pharmaceutical composition for treating a disease related to vasculogenesis or angiogenesis in a mammal which comprises a therapeutically effective amount of a compound of the present invention, or a pharmaceutically acceptable salt, prodrug or hydrate thereof, and a pharmaceutically acceptable carrier. In one embodiment, said pharmaceutical composition is for treating a disease selected from

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the group consisting of tumor angiogenesis, chrome inflammatory disease such as rheumatoid arthritis, atherosclerosis, inflammatory bowel disease, skin diseases such as psoriasis, excema, and scierodenna, diabetes, diabetic retinopathy, retinopathy of prematurity, age-related macular degeneration, hemarigioma, glioma, melanoma, Kaposi’s sarcoma and ovarian, breast, lung, pancreatic, prostate, colon and epidermoid

cancer.

The invention also relates to a method oftreating a hyperproliferative disorder in a mammal that comprises administering to said mammal a therapeutically effective amount of a compound ofthe present invention, or a pharmaceutically acceptable salt, prodrug or hydrate thereof. In one embodiment, said method relates to the treatment of cancer such as brain, lung, squamous cell, bladder, gastic, pancreatic, breast, head, neck, renal, kidney, ovarian, prostate, colorectal, esophageal, testicular, gynecological or thyroid cancer. In another embodiment, said method relates to the treatment of a non-cancerous hyperproliferative disorder such as benign hyperplasia of the skin (e.g., psoriasis), restenosis, or prostate (e.g.,benigu prostatic hypertrophy (BPH)).
The invention also relates to a method for the treatment of a hyperproliferative disorder in a mammal that comprises administering to said mammal a therapeutically effective amount of a compound of the present invention, or a pharmaceutically acceptable salt, prodrug or hydrate thereof, in combination with an anti-tumor agent selected from the group consisting of mitotic inhibitors, alkylating agents, anti-metabolites, intercalating antibiotics, growth factor inhibitors, cell cycle inhibitors, enzyme inhibitors, topoisomerase inhibitors, biological response modifiers, anti-hormones, angiogenesis inhibitors, and anti-androgens.
The invention also relates to a method oftreating pancreatitis or kidney disease in
a mammal that comprises administering to said mammal a therapeutically effective

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amount of a compound of the present invention, or a pharmaceutically acceptable salt, prodrug or hydrate thereof.
The invention also relates to a method of preventing blastocyte implantation in a mammal that comprises administering to said mammal a therapeutically effective amount of a compound ofthe present invention, or a pharmaceutically acceptable salt, prodrug or hydrate thereof.
The invention also relates to a method of treating diseases related to vasculogenesis or angiogenesis in a mammal that comprises administering to said mammal a therapeutically effective amount of a compound of the present invention, or a pharmaceutically acceptable salt, prodrug or hydrate thereof. In one embodiment, said method is for treating a disease selected from the group consisting oftumor angiogcnesis, chronic inflammatory disease such as rheumatoid Arthritis, atherosclerosis, inflammatory bowel disease, skin diseases such as psoriasis, excema, and scleroderma, diabetes, diabetic retinopathy, retinopathy of prematurity, age-related macular degeneration, hemangioma, glioma, melanoma, Kaposi’s sarcoma and ovarian, breast, lung, pancreatic, prostate, colon and epidermoid cancer.
Patients that can be treated with compounds of the present invention, or pharmaceutically acceptable salts, prodrugs and hydrates ofsaid compounds, according to the methods of this invention include, for example, patients that have been diagnosed as having psoriasis, restenosis, atherosclerosis, BPH, lung cancer, boric cancer, CMML, pancreatic cancer, skin cancer, cancer of the head and neck, cutaneous or intraocular melanoma, uterine cancer, ovarian cancer, rectal cancer, cancer of the anal region, stomach cancer, colon cancer, breast cancer, testicular, gynecologic tumors (e.g., uterine sarcomas, carcinoma ofthe fallopian tubes, carcinoma of the endometrium, carcinoma of the cervix, carcinoma ofthe vagina or carcinoma ofthe vulva), Hodgkin’s disease, cancer

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of the esophagus, Cancer of the small intestine, cancer of the endocrine system (e.g., cancer of the thyroid, parathyroid or adrenal glands), sarcomas of soft tissues, cancer of the urethra, cancer ofthe penis, prostate cancer, chronic or acute leukemia, solid tumors of childhood, lymphocytic lymphomas, cancer of the bladder, cancer of the kidney or ureter (e.g., renal cell carcinoma, carcinoma of the renal pelvis), or neoplasms of the central nervous system (e.g., primary CNS lymphona, spinal axis tumors, brain stem gliomas or pituitary adenomas).
This invention also relates to a pharmaceutical composition for inhibiting abnormal cell growth in a mammal which comprises an amount of a compound of the present invention, or a pharmaceutically acceptable salt or solvate or prodrug thereof, in combination with an amount of a chemotherapeutic, wherein the amounts of the compound, salt, solvate, or prodrug, and ofthe chemotherapeutic are together effective in inhibiting abnormal cell growth. Many chernotherapeutics are presently known in the art. In one embodiment, the chemotherapeutic is selected from the group consisting ofmitotic inhibitors, alkylating agents, anti-metabolites, intercalating antibiotics, growth factor inhibitors, cell cycle inhibitors, enzymes, topoisomerase inhibitors, biological response modifiers, anti-hormones, angiogenesis inhibitors, and anti-androgens.
This invention further relates to a method for inhibiting abnormal cell growth in a mammal or treating a hyperprdliferative disorder which method comprises administering to the mammal an amount of a compound ofthe present invention, or a pharmaceutically acceptable salt or solvate or prodrug thereof, in combination with radiation therapy, wherein the amounts of the compound, salt, solvate, or prodrug, is in combination with the radiation therapy effective in inhibiting abnormal cell growth or treating the hyperproliferative disorder in the mammal. Techniques for administering radiation therapy are known in the art, and these techniques can be used in the combination therapy

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WO 03/077914 PCTIIJS03/07864 described herein. The administration of the compound of the invention in this combination therapy can be determined as described herein.
It is believed that the compounds of the present invention can render abnormal
cells more sensitive to treatment with radiation for purposes of killing and/or inhibiting the growth of such cells. Accordingly, this invention further relates to a method for sensitizing abnormal cells in a mammal to treatment with radiation which comprises administering to the mammal an amount of a compound of the present invention or pharmaceutically acceptable salt or solvate or prodrug thereof, which amount is effective is sensitizing abnormal cells to treatment with radiation. The amount of the compound, salt, or solvate in this method can be determined according to the means for ascertaining effective amounts ofsuch compounds described herein.
The invention also relates to a method of and to a pharmaceutical composition of inhibiting abnormal cell growth in a mammal which comprises an amount of a compound of the present invention, or a pharmaceutically acceptable salt or solvate thereof, a prodrug thereof, or an isotopically-labeled derivative thereof, and an amount of one or more substances selected from anti-angiogenesis agents, signal transduction inhibitors, and antiproliferative agents.
Anti-angiogenesis agents, such as MMP-2 (matrix-metalloprotienase 2) inhibitors, MAP-9 (matrix-metalloprotienase 9) inhibitors, and COX-Il (cyclooxygenase U) inhibitors, can be used in conjunction with a compound of the present invention and pharmaceutical compositions described herein. Examples of useful COX-11 inhibitors include CELEBRE)C (alecoxib), valdecoxib, and rofecoxib. Examples ofuseful matrix rnetalloprotienase inhibitors are described in WO 96/33172 (published October 24, 1996), WO 96/27583 (published March 7, 1996), European Patent Application No. 97304971.1 (filed July 8, 1997), European Patent Application No. 99308617,2 (filed October 29,

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1999), WO 98/07697 (published February 26, 1998), WO 98/03516 (published January 29, 1998), WO 98/34918 (published August 13, 1998), WO 98/34915 (published August 13, 1998), WO 98/33768 (published August 6, 1998), WO 98/30566 (published July 16, 1998), European Patent Publication 606,046 (published July 13, 1994), European Patent Publication 931,788 (published July 28, 1999), WO 90/05719 (published May 31, 1990), WO 99/52910 (published October 21, 1999), WO 99/52889 (published October 21, 1999), WO 99/29667 (published June 17, 1999), PCT International Application No. PCTJIB98/01113 (filed July 21, 1998), European Patent Application No. 99302232.1 (filed March 25, 1999), Great Britain Patent Application No. 9912961.1 (filed June 3, 1999), United States Provisional Application No. 60/148,464 (filed August 12, 1999), United States Patent 5,863,949 (issued January 26, 1999), United States Patent 5,861,510 (issued January 19, 1999), and European Patent Publication 780,386 (published June 25, 1997), all of which are incorporated herein in their entireties by reference. Preferred MIvIP-2 and MMP-9 inhibitors are those that have little or no activity inhibiting MMP-1. More preferred, are those that selectively inhibit MMP-2 and/or MMP-9 relative to the other matrix-metalloproteinases (i.e., MM:P-1, M"-3, MMP-4, MMP-5, MMP-6, MW-7, M2VIP-8, MMP- 10, MMP-1 1, MMP-12, and MMP-1 3).
Some specific examples of MMP inhibitors useful in the present invention are AG-3340, RO 32-3555, and RS 13-0830.
The terms "abnormal cell growth" and "hyperproliferative disorder" are used interchangeably in this application.
"Abnormal cell growth", as used herein, unless otherwise indicated, refers to cell growth that is independent of normal regulatory mechanisms (e.g., loss of contact inhibition). This includes, for example, the abnormal growth of (1) tumor cells (tumors) that proliferate by expressing a mutated tyrosine kinase or overexpression of a receptor

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tyrosine kinase; (2) benign and malignant cells of other proliferative diseases in which aberrant tyrosine kinase activation occurs; (3) any tumors that proliferate by receptor tyrosine kinases; (4) any tumors that proliferate by aberrant serine/threonine kinase activation; and (5) benign and malignant cells of other proliferative diseases in which aberrant serine/theroine kinase activation occurs.
The term "treating", as used herein, unless otherwise indicated,
alleviating, inhibiting the progress of, or preventing the disorder or condition to which such term applies, or one or more symptoms of such disorder or condition. The term "treatment", as used herein, unless otherwise indicated, refers to the act of treating as "treating" is defined immediately above.
Representative compounds of the present invention, which are encompassed by
the present invention include, but are not limited to the compounds of the examples and their pharmaceutically acceptable acid or base addition salts or prodrugs thereof.
The examples presented below are intended to illustrate particular embodiments of
the invention, and are not intended to limit the scope of the specification or the claims in any way.

An illustration ofthe preparation of compounds ofthe present invention is shown
in Schemes 1-4.

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Scheme 1

CO2H CO2H CO2H
F

02N 02N F

Fj F NI-i2
2 3

CO2Me H R1

) 02N ()2N Fy?

NH2NH2 R2

4 5

H R1 H R1

/D

H2N N;
NH2 R H

6

0 Ri
H R1

110 0
H

HN
N

-- NH R2 R N R2

8

H

HO 0 0

0

1

0JJH Rl
H R

FR

I

H (8 FIN F

R

N
N

R<N R2

10

11

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Scheme la

0

CO2Me MeO 4F 4NH
02N 02N

NH2 NH2

MeO

N,a

HNF

Me0° Me00

HN F R8 HN F

/28

MeO 0
NR

HNrVR8

Me00 HO0

HN’t F R8 HNf’ F R8
R’ R7N
9 10

29

HN 0
hyrdoxyl H
amine N1

HN j F Ra

R7 N

29

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Scheme 2

CO2Me 7OO

H R1

0,N F 02N F
NH2 NH2 R2

4 12

I H R1

H2NyF
NH2 R2

13
70 0

N/F/R8

R" R

7O0
I H R’
N

N’F R8/
’--NH 14R2

HO 0

H Rl JN

N F R8 /
RyJN R2
10
H
H R1

N’F /

11

30

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Scheme 3

H H 0NO
H

›JtN; F
R2 HOnN N
15 OH

H
N

V0 I

1

flN’ R8 0
R2

17

S

31

HR _

16

H
0NQ
H R1

al? I 8

)Nit R2

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Scheme 4

N
H R HO

ON L.
R-N’F / R8 Y H R1

R2

21
R-N1F
R2

r-i /22

H R1 H2N H R1

R7-N F R7--N F R R2 2
19 20\

I

P

25

32

R

R7

23
H2N

o,N
H R1

11 R8
R2

24

R8

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PA

Scheme 5

H R1

HO
H

HN , F/ R8 HN

R2
R7 9 R7 30

R OH
H R1

HNF;?--?R8
R2
R7 32

I H R1
Na

HNF J% N R2
R7 33

I H

HN F
R2
R7 31

General synthetic methods which may be referred to for preparing some of the compounds of the present invention are provided in PCT published application number WO 00/42022 (published July 20, 2000). The foregoing patent application is incorporated herein by reference in its entirety.
The examples presented below are intended to illustrate particular embodiments of
the invention, and are not intended to limit the scope ofthe specification Or the claims in

any way.

An illustration of the preparation of compounds ofthe present invention is shown

. in Schemes 1-4.
Scheme 1 illustrates the synthesis of compounds of the present invention. In step
I, the acid is nitrated using standard conditions preferable finning nitric acid in 112504. In step 2, the aniline is prepared by fluoride displacement with NE40H at room

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Ic;

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temperature in water followed by careful acidification with concentrated mineral acid to pH near 0. In step 3, the ester is prepared by standard methods including by not limited to Fisher Esteriflcation (MeOH, H2SO4), and reaction with TMSCHN2 in suitable organic solvents like PhMeIMeOH or TIIF/MeOH. In step 4, the dianilino derivative is prepared by heating (60 to 200 °C) the ester with an excess ofthe appropriate aniline neat or in an organic solvent like xylenes. For example, when R’ = Me and R2 = H the preferred method is stirring the ester with 10 equivalents aniline in xylenes at reflux until complete reaction. In step 5, the nitro arene is reduced to produce the diamine by standard reduction conditions, including by not limited to 112, and Pd/C or Pd(OH)2/C or Raney Nickel in organic solvent like EtOH or TIIF, Fe in AcOH, Zn in AcOH or Zn, NH4C1 (aq) in MeOH. In step 6, the diamine is cycization by heating with formic acid neat or fomiamidine acetate in an appropriate solvent like litOH. Alternatively, when R1 or R2 does not equal halo the nitro arene can he converted directly to the beuzimidazole in step 7 by heating in formic acid with Pd(OH)2/C or other palladium source like Pd/C. In step 8, a halide can he incorporated by standard methods, including but not limited to NBS or
NCS and pTsOH in organic cosolvents like T}IF and MeOH. In step 9, the
benzimidazolc is alkylated to give a near equal mixture ofNi and N3 products which are
separable by standard techniques, including, for example, chromatography and trituration.
The alkylation is accomplished by use of an alkylating agent like an alkyl halide and base
like NaH, or K2CO3 in suitable organic solvent like OMF or TIIF at temperatures ranging
. from 0 to 80 °C. R7 can be further modified by various synthetic methods known in the art, as exemplified below. In step 10, the ester is hydrolysiied by standard saponification
methods. The acid is then converted to the desired hydroxamate in step 11 by standard
coupling procedures including but not limited to EDCI, HOBt or PyBOP and the

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WO 031077914 PCI..(tJS0I)7864 appropriate hydroxytamine in suitable organic solvents like DMF, THF or methylene

chloride.

Scheme 2 illustrates an example in which the R8 substituent is on the aniline prior
to the coupling procedure with the intro ester. The reaction description is exactly like that for Scheme 1 except that there is no need to incorporated R8 as it is present in the aniline from the beginning,
in Scheme 3, the preparation of N3 alkyl amino benzimidazole derivatives is illustrated. In step 1, the terminal alkene ofthe N3 alkylated benzimidazole hydroxamate is clihydroxylated using a suitable oxidant like 0s04 in suitable solvent or KMn04 or 12, AgOAc, AeOH, water. The diol is then further oxidized in step 2 by Na104 or Pb(OAc)4 in suitable bipbasic mixture to give the aldehyde. Alternatively (step 3), the alkene can be directly converted to the aldehyde by standard methods including but not limited to ozonefMe2S, Na10410s04 or KMnO4. In step 4, the amine is prepared by reductive amination using standard methods such as Na(CN)BH3, Na(OAc)BH, NMe4BH(OAc)3 with or without AcOH in a suitable solvent such as methylene chloride, acetonitrile or
THF. The preferable reduction amination is to treat the aldehyde with amine,
Me4NBH(OAc)3 and acetic acid in MeCN at room temperature.
Scheme 4 illustrates the preparation of compounds ofthe present invention where
W is heterocyclic. In step 1, the methyl ester is converted to the hydrazide by stirring
with hydrazine in a suitable solvent like EtOH at temperatures from 50 to 100 T. The
. desired heterocyclic derivative is then prepared by cycization with the appropriate reagent. For oxadiazole 21 the hydrazide is treated with an orthoformate like triethyl
orthoformate, and an acid catalyst like pTsOH in a suitable organic solvent like EtOH at
elevated temperatures (50 - 100 °C). For hydroxy oxadiazole 22 the hydrazide can be
cyclized with phosgene or a phosgene equivalent like triphosgene or carbonyl diimidazole

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in a suitable organic solvent like toluene at temperatures ranging from 50 to 120 T. The mercapto oxadizaole 23 can be prepared by reaction with carbon disulfide, and base like KOH in suitable organic solvent like EIOH at elevated temperatures (50 - 100 °C). The amino oxadiazok 24 can be made by reaction with &CN and base like NaHCO, in a suitable biphasic solvent system like dioxane and water at room temperature. Finally, the substituted amino oxadiazole 25 can be prepared by first reacting the bydrazide with an appropriate isothiocyanate in a suitable organic solvent like DMF or THF at temperatures ranging from 25 to 100 T. The intermediate can be isolated or can be cyclized directly with the treatment of EDCI or other carbodiimide in suitable organic solvent like THF or ME at temperatures ranging from room temperature to 80°C.
In Scheme 5, the preparation of keto benzimidazole derivatives are illustrated. In
step 1, the methyl ester is converted to the benzyl alcohol by standard reductive methods, preferably LAH in TIfF at 0 °C or NaBH4 in EtOH:THF at room temperature. Oxidation to the aldehyde can be accomplished in step 2 using Mn02 in acetone:THF at 50 T. In step 3, organometallic reageants, such as organolithiurn reagents and Grignard reagents, can be added to the aldehyde in THF at low temperature (e.g., -78 °C) to give the substituted benzyl alcohol. The keto derivatives can be prepared in step 4 by oxidation of the benyzi alcohol under standard conditions such as Swem or Dess-Martin oxidation. The compounds of the present invention may have asymmetric carbon atoms. Diastereomeric mixtures can be separated into their individual diastereomers on the basis of their physical chemical differences by methods known to those skilled in the art, for example, by chromatography or fractional crystallization. Enantiomers can be separated by converting the enantiomer mixture into a diastereomeric mixture by reaction with an appropriate optically active compound (e.g., alcohol), separating the diastereomers and converting (e.g., hydrolyzing) the individual diastereomers to the corresponding pure

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enantioniers- All such isomers, including diastereomeric mixtures and pure enantiomers are considered as part ofthe invention.
The activity ofthe compounds of the present invention may be determined by the following procedure. N-terminal 6 His-tagged, constitutively active MEK1 (2-393) is expressed in B. coil and protein is purified by conventional methods (Ahn et al., Science 1994, 265, 966-970). The activity of MEK1 is assessed by measuring the incorporation ofy-33P-pbosphate from y-33P-ATP onto N-terminal His tagged ERK2, which is expressed in B. ccli and is purified by conventional methods, in the presence of MEK1. The assay is carried out in 96-well polypropylene plate. The incubation niixture (100 L) comprises of 25 mM Hepes pH 7.4, 10 MM M902, S mM 3-g1ycero1phosphate, 100 4M Na-orthovanadate, 5 mM DTT, 5 uM IVIEK1, and 1 1tM ERK2. Inhibitors are suspended in DMSO, and all reactions, including controls are performed at a final concentration of 1%

DMSO. Reactions are initiated by the addition of 10 tM ATP (with 0.5 pCi y-33p-ATP/well) and incubated at ambient temperature for 45 minutes. Equal volume of 25% TCA is added to stop the reaction and precipitate the proteins. Precipitated proteins are trapped onto glass fiber B filterplates, and excess labeled ATP washed off using a Tomtec MACH III harvestor. Plates are allowed to air-thy prior to adding 30 ilJwcll of Packard Microscint 20, and plates are counted using a Packard TopCount. In this assay, compounds ofthe invention exhibited an IC50 ofless than 50 micromolar.
The following compounds exemplify compounds ofsuch activity.

8n
lib
lie
18i
29c
29i

91

37

WO 03/077914 PCTIUS03107864 29s
29t
29bb
29111
29mnnn

Administration ofthe compounds ofthe present invention (hereinafter the "active compound(s)") can be effected by any method that enables delivery ofthe compounds to the site of action. These methods include oral routes, intraduodenal routes, parentcral injection (including intravenous, subcutaneous, intramuscular, intravascular or infusion), topical, and rectal administration.
The amount ofthe active compound administered will be dependent on the subject being treated, the severity of the disorder or condition, the rate of administration, the disposition ofthe compound and the discretion ofthe prescribing physician. However, an effective dosage is in the range of about 0.001 to about 100 mg per kg body weight per day, preferably about 1 to about 35 mg/kg/day, in single or divided doses. For a 70 kg human, this would amount to about 0.05 to 7 g/day, preferably about 0.05 to about 2.5 g/day. In some instances, dosage levels below the lower limit ofthe aforesaid range may be more than adequate, while in other cases still larger doses may be employed without causing any harmful side effect, provided that such larger doses are first divided into several small doses for administration throughout the day.
The active compound may be applied as a sole therapy or may involve one or more other anti-tumor substances, for example those selected from, for example, mitotic inhibitors, for example vinbiastine; alkylating agents, for example cis-platin, carboplatin and cyclopbosphamide; anti-metabolites, for example 5fluorouraci1, cytosine arabinside and hydroxyurea, or, for example, one of the preferred anti-metabolites disclosed in European Patent Application No. 239362 such as N-(5-[N-(3,4-dihydro-2-methyl-4-

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inhibitors; cell cycle inhibitors; intercalating antibiotics, for example adriamycin and bleomycin; enzymes, for example, interferon; and anti-hormones, for example anti-estrogens such as NolvadexTM (tamoxifen) or, for example anti-androgens such as CasodexTM ’-

(trifluoromethyl)propionanilide). Such conjoint treatment may be achieved by way ofthe simultaneous, sequential or separate dosing ofthe individual components oftreatment. The pharmaceutical composition may, for example, be in a form suitable for oral administration as a tablet, capsule, pill, powder, sustained release formulations, solution, suspension, for parenteral injection as a sterile solution, suspension or emulsion, for topical administration as an ointment or cream or for rectal administration as a suppository. The pharmaceutical composition may be in unit dosage forms suitable for single administration of precise dosages. The pharmaceutical composition will include a conventional pharmaceutical carrier or excipient and a compound according to the invention as an active ingredient. In addition, it may include other medicinal or pharmaceutical agents, carriers, adjuvants, etc.
Exemplary parenteral administration forms include solutions or suspensions of active compounds in sterile aqueous solutions, for example, aqueous propylene glycol or dextrose solutions. Such dosage forms can be suitably buffered, ifdesired.
Suitable pharmaceutical earners include inert diluents or fillers, water and various organic solvents. The pharmaceutical compositions may, if desired, contain additional ingredients such as flavorings, binders, excipients and the like. Thus for oral administration, tablets containing various excipients, such as citric acid may be employed together with various disintegrants such as starch, alginic acid and certain complex silicates and with binding agents such as sucrose, gelatin and acacia. Additionally,

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lubricating agents such as magnesium stearate, sodium lauryl sulfate and talc are often useful for tabletirig purposes. Solid compositions of a similar type may also be employed in soft and hard filled gelatin capsules. Preferred materials, therefore, include lactose or milk sugar and high molecular weight polyethylene glycols. When aqueous suspensions or elixirs arc desired for oral administration the active compound therein may be combined with various sweetening or flavoring agents, coloring matters or dyes and, if desired, emulsifying agents or suspending agents, together with diluents such as water, ethanol, propylene glycol, glycerin, or combinations thereof.
Methods of preparing various pharmaceutical compositions with a specific amount of active compound are known, or will be apparent, to those skilled in this art. For examples, see npgton’s Pharmaceutical Sciences, Mack Publishing Company,

Ester, Pa., 15th Edition (1975).
The examples and preparations provided below further illustrate and exemplify
the compounds ofthe present invention and methods ofpreparing such compounds. It is to be understood that the scope of the present invention is not limited in any way by the scope of the following examples and preparations. In the following examples molecules with a single chiral center, unless otherwise noted, exist as a racemic mixture. Those molecules with two or more chiral centers, unless otherwise noted, exist as a racemic mixture of diastereomers. Single enantiomersldiastereomcrs maybe obtained by methods known to those skilled in the art.

The disclosures in this application of all articles and references, including patents,
are incorporated herein by reference.
The invention is illustrated further by the following examples which are not to be construed as limiting the invention in scope or spirit to the specific procedures described in them.
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The starting materials and various intermediates may be obtained from commercial sources, prepared from commercially available organic compounds, or prepared using well known synthetic methods.
Representative examples of methods for preparing intermediates of the invention

are set forth below.

S

fl

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Examples

Example:t

H. N O
Y

HN i F Br
7-Fluoro-6-(4-bromo-2-rnethyl-phenylarnino)-311-benzolrnidazole-5-carboxylk acid cyclopropylmethoxy-amide (Ha)
Step A: 2,3, 4-Trfiuoro--5-nitro-benzoic acid 2
A 3 liter three neck round bottom flask is charged with 125 ml H2SO4. Fuming nitric acid is added (8.4 ml, 199 mmol) and the mixture gently stirred. 2,3,4-Trifluorobenzoic acid 1 (25 g, 142 nunol) is added in 5 g portions over 90 minutes. The dark brownish yellow solution is stirred for 60 min at which time the reaction is complete. The reaction mixture is poured into 1 liter of an ice:water mixture and extracted with diethyl ether (3 x 600 ml). The combined organic extracts are dried (MgSO4) and concentrated under reduced pressure to give a yellow solid. The solid is suspended in hexanes and stirred for 30 min after which time it is filtered to give 29 g (92%) of clean

desired product as an off-yellow solid: MS APCI (-) m/z 220 (M-1) detected,

40 Step E: 4.-Amino-2,3-dfluoro-5-nitro-benzoic acid 3

Ammonium hydroxide solution (30% in water) (35 ml, 271 mntol) is added to a solution of 2,3,4-triffuoro-5-nitro-benzoic acid 2 (15 g, 67.8 minol) in 30 nil water at 0 °C with stirring. Upon completion of ammonium hydroxide addition the reaction mixture is

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warmed to room temperature with stirring. After 2.5 h, the reaction mixture is cooled to C) ° C and concentrated HCI is carefully added until pH ofreaction mixture is near 0. The reaction mixture is diluted with water (30 ml) and extracted with diethyl ether (3 x 50 ml). The combined organic extracts are dried (MgSO4) and concentrated under reduced pressure to give 14 g (9501a) of pure desired product: MS APCI (-) in/z 217 (M-1)

detected.

Step C: 4-Amino-2, 3dfluoro-5-nitrobenzoic acid methyl ester 4
A 2 M solution ofTMS diazomethane in hexanes (6.88 ml, 13.75 mmol) is added
to a suspension of 4-amino-2,3-difluoro-5-nitro-benzoic acid 3 (2.00 g, 917 mmol) in 25 nil of 4:1 THF:MeOH at 0 °C under nitrogen atmosphere. Upon completion of addition, reaction mixture is warmed to room temperature. After 0.5 11, excess TMS diazomethane is destroyed by the careful addition of acetic acid. The reaction is then concentrated under reduced pressure and dried in vacuo to give 1.95 g (92%) of pure desired product:
MS APCI (-) rn/z 231 (M-l) detected.

Step D: 4-Amino-3-fluoro-5-nitro-2-o-tolylamino--benzoic acid methyl ester Sa 4-Arnino-2,3-difluoro-5nitro-benzoic acid methyl ester 4 (12.0 g, 51.7 mmol) is
suspended in xylen.es (60 nil) and ortho-toluidine is added (55.2 ml, 517 mmol). The
reaction mixture is heated to refiux with stirring under a nitrogen atmosphere. After 36 h,
. the reaction mixture is cooled to room temperature, diluted with diethyl ether and washed with 10% aqueous TIC] solution. The aqueous washings are extracted with diethyl ether.
The combined organic extracts are concentrated under reduced pressure. The residue is
dissolved in methylene chloride and filtered through silica gel in a fitted funnel, rinsing

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with methylene chloride. Three fractions are recovered. The first (2 liter) is nearly clean by IIPLC. The second (1 liter) and third (1 liter) fractions are only partially pure. The first fraction is concentrated wider reduced pressure and triturated with diethyl ether to give 11.2 g (68%) of clean desired product as a bright yellow solid: MS APCI () rn/s 318 (M-1) detected.

Step E: 7-Fluoro-6-o-tolylarnino--1H-benzoimidazole5-carboxylic acid methyl ester 7a 4-Anino3-fluoro--5-nitro-2-o-to1ylamino-benzoic acid methyl ester Sa (1.57 g,
4.92 mmol), formic acid (25 ml, 26.5 mrnol) and 20% Pd(OH)2/C (1.57 g, 2.95 mmol) in 25 ml EtOH are beating with stirring to 95 T. After 16 h, the reaction mixture is cooled to room temperature and 0.5 g 20% Pd(OH)2/C and 10 ml formic acid added. The reaction mixture is heated to 95 °C with stirring. After 16 ii, the reaction mixture is cooled to room temperature and filtered through Celite rinsing with EtOH. The filtrate is concentrated under reduced pressure until the desired product precipitates. The desired product is collected by filtration. The filtrate is concentrated again until more desired product precipitates. The product is collected by filtration. Repeated EtOH concentration, product filtration several times. Recovered 1.09 g (74%) pure desired product: MS APCI (1-) rn/s 300 (M+1) detected; MS APCI () rn/s 298 (M-1) detected.

Step F. 7-Fluoro-6.(4-broino-2-rnetiiyl-phen),larnino)-JH-benzoirnidazole-5--carboxylic acid methyl ester 8a
7-Fluoro-6-o-tolylami.no- 1H-benzoimidazole-5-carboxylic acid methyl ester 7a
(2.00 g, 6.68 mmol) is suspended in 1:1 THE:MeOH mixture (60 ml) and cooled to --78 ° C under a nitrogen atmosphere. A solution of NBS (1.20 g, 6.75 mmol) in 1:1

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THF/McOH (5 nil) is added followed by a Me011 (5 ml) solution of TsOHH20 (1.9 g, 10.0 mmol). After 30 minutes, the reaction mixture is warmed to 0 °C and then after 1 h warmed to rt. After 16 h, more NBS (0.12 g, 0.67 mmol) is added and the reaction mixture is allowed to stir for 3 h. The reaction mixture is quenched by the addition of 10% Na2S204 solution. After 30 mm the reaction mixture is diluted with water and ethyl acetate and the layers separated. The aqueous layer is extracted with ethyl acetate. The combined organic extracts are dried (Na2SO4) and concentrated under reduced pressure. The recovered solid is triturated with methylene chloride to give 2.00 g (79%) pure desired product: MS APCI (+) rn/z 380, 378 (M+1 Br pattern) detected.

Step G: 7Ffuoro-6-(4bronw-2-inethyl-phenyla1nino)-1H-beflzoifllidazole-5-carboXYliC

.

acid IOa

7-Fluoro-6-(4-bromo-2-methyl-phenylamino)- 1H-benzoimidazole-5-carboxylic
acid methyl ester 8a (63 mg, 0.167 mmol) is suspended in MeOH (1.5 ml) and 20% NaOH (400 il) is added. After 16 h, the reaction mixture is cooled to 0 °C and 1 N HCl solution is added dropwise until p11 is 2 to 3. The reaction mixture is diluted with ethyl acetate and water and the layers separated. The organic layer is washed with brine, dried (Na2SO4) and concentrated under reduced pressure to give 58 mg (95%) of desired product: MS APCI (-1-),n/z 366, 364 (M+1 Br pattern) detected; MS APCI (-) in/z 364, 362 (M4 Br pattern) detected.

Step H. 7Fiuoro_6-(4-hromo-2-nzethylphenylarnino1H-benzoirnidazole-5-CarboJ9’1ic acid cyciopropylmethoxy-ainide ha 7-Fluoro-6-(4-bromo-2-methyl-phenylamino)-1H-benzoimidazole-5-carboxylic acid lOa

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Ids

WO 03/077914 PCTIUS03/07864 (48 mg, 0.132 mmol) is dissolved in 1:1 THF: methylene’chloride (1 ml) and Ilunig’s base (0.23 p.1, 1.32 mmol) is added followed by PyBOP (82 mg, 0.158 mmol). After a few minutes, cyclopropyl methyl hydroxylamine hydrochloride (20 mg, 0.158 nmrol) (WO 0042022) is added. After the reaction is complete, the mixture is partitioned between methylene chloride and saturated NaHCO3 solution. The layers are separated and the organic layer is washed with saturated NaLIC03 and brine. The organic layer is dried (Na2SO4) and concentrated under reduced pressure. After purification by FCC (elute with 20:1 methlene chlonde:MeOfl), 25 mg (45%) of pure desired product is isolated: MS EST (+) rn/z 435, 433 (M-I-1 Br pattern) detected; MS EST (-) in/z 433, 431 (M-1 Br pattern) detected; 1H NME. (400MHz, CDC13) 8.15 (s, 111), 8.02 (s, 1H), 7.28 (s, 111), 7.43 (d, 1H, 7.07 (dd, lH, 6.36 m, 1H, 3.70 2H), 2,38 (s, 3H), 0.86 (ni,

111), 0.41 (m, 2H), 0.13 (in, 2H); 19 NMR (376MHz, DC13) 134.05 (s).

Example 2

OOCH3

7-Fluoro6-plienyliunino-31I-benzoimidazole.-5-carboxylic acid methyl ester (270) Step A: 4-A,nino-3-fluoro-5--nitro-2phenylainino-benzoic acid methyl ester 26a 4-Ammo-2,3-difluoro-5-nitro-benzoic acid methyl ester 4 (23.48 g, 101.1 mmol),
the product ofExample 1, Step C, is suspended in xylenes (125 mL) aM aniline (92 mL, 1011 mmol) is added. The reaction mixture is stirred at 125 °C for 16 hours under N2. The reaction mixture is cooled to room temperature and solids precipitate out ofsolution. The solids are collected by filtration and are washed with xylenes and then diethyl ether.

EEO

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1q

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Recovered 22.22 g (72.78 mmol) of yellow solid which is pure desired product. The filtrate is concentrated under reduced pressure, redissolved in methylene chloride and flushed through a plug of silica gel eluting with methylene chloride. The desired fractions are concentrated under reduced pressure to give a brown solid which is triturated with diethyl ether to give 5.47 g (17.91 mmol) of yellow solid which is pure desired product. Combined product yield is 27.69 g (90%). MS APCI (-) m/z 304 (l’1-1)

detected.

Step B: 7Fluoro-6-pheny1a;nhw-3H-benzoiinidazole-5-carboxylic acid methyl

ester 27a

4-Amino-3-fluoro-5-nitro-2-phenylamino-benzoic acid methyl ester 26a (16.70 g,
54.71 mmol), formic acid (250 mL, 6.63 mot) and 20% Pd(Off)2/C (9.00 g, 16.91 mmol) in ethanol (250 niL) are stirred at 40 °C for two hours under N2 and then at 95 °C for 16 hours. The reaction mixture is cooled to room temperature and filtered through Celite rinsing with ethyl acetate. The filtrate is concentrated under reduced pressure to give a yellow solid. The solid is triturated with diethyl ether to give 13.47 g (869/0) of the desired product as a tan solid. MS APCI (+) iw’z 286 (M+1) detected; MS APCI () m/z 284 (M-1) detected.

Example 3

OOCH3

I H
ii

N

NN’YF Br

6-(4-Bromu-2-chloro-phenylainiiio)-7-fluoro-311-benzoimi4azole-5-carboxylic acid methyl ester (8b)

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Step A: 6-(4-Bromo-phenyla1nino)- 7fluoro3Th-benzoimidazole-5-carbOXYIiC acid methyl

ester 28a

7F1uorophenyiamino3HbenzoimidaZOle-5-carb0XYhC acid methyl ester 27a
(4.99 g, 17.51 rurnol) is dissolved in NN-dimethylformamide (275 mL). N-bromosuccinimide (3.15 g, 17.70 mmol) is added as a solid and the reaction mixture is stirred at room temperature under N2. After 30 min, the reaction mixture is quenched by the addition of aqueous saturated sodium bisulfite solution. The reaction mixture is then poured into a separatory funnel, diluted with water and ethyl acetate and the layers separated. The aqueous layer is extracted with ethyl acetate. The combined organic extracts are washed three times with water, once with brine and then are dried (Na2SO4) and concentrated under reduced pressure to yield 6.38 g (100%) of the pure desired product as a tan solid. MS ESI (+) m/z 364,366 (M+ Br pattern) detected.

Step B: 6-(4Bromo-2-chlora-pheny1amino)-7-fluoro-3H-benzOimidaZOle-5-carboxylic acid methyl ester 8b
6-(4Bromo-phenylamino)-7-fiuoro-3H-benzoimidazOle-5-carbOXylic acid methyl
ester 28a (6.38 g, 17.51 mmol) is dissolved in N,N-dimethylformamide (275 mL). N chlorosuceinimide (2.36 g, 17.70 mmol) is added as a solid and the reaction mixture is stirred at room temperature under N2 until the reaction is (5-6 days). The reaction quenched by the addition of aqueous saturated sodium bisulfite solution to give a suspension. The resulting solids are collected by filtration, washed with water and diethyl ether and dried under reduced pressure to yield 6.07 g (87%) ofthe pure desired product as a beige solid. MS ESI (+) rn/z 398, 400 (M4- Br pattern) detected,

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0 OCH3

HNFOCI

6-(2,4-DicI:loro-phenylarnino)- 7-fluoro-3H-beiszoimidazole-5-carboxylic acid
methyl ester (Rc)
7F1uoro6..phenyiamino-3H-benzoimidazo1e-5-carbOXY1iC acid methyl ester 272
(1.00 g, 3.51 mmol) is suspended in 1:1 tetrahydroftiran/methanol (20 niL) and cooled to
 78 °C under N2. TsOHH20 (3.00 g, 10.50 minol) is added followed by N-chiorosuccinimide (0.95 g, 7.08 mmol). After 10 minutes, the reaction mixture is warmed
to 0 °C to give a solution and then 30 min later warmed to room temperature. After Sstirringfor 16 hours, the reaction is complete. The reaction mixture is quenched by the addition of aqueous saturated sodium bisulfite solution and diluted with ethyl acetate and
water and the layers separated. The aqueous layer is extracted with ethyl acetate. The
combined organic extracts are washed with brine, dried (Na2SO4) and concentrated under
reduced pressure. The resulting solid residue is triturated with methylcnc chloride to
yield a white solid which is collected by filtration to yield 1.05 g (85%) of the pure
desired product. MS ESI (+) mlz 355, 357 (’M+ Cl pattern) detected.

Example 5

0 OCH3
F

HNFBr

6_(4-Broino-2-fluoro-phenylarnino)-7-fluoro-3H-benzoiniidazole-5-carboxyliC acid

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WO 03/077914 PCTIUS03/07864 methyl ester (8d)

Step A: 4-Amino-3-fluoro-2-(’2-fluoro-phenylamino)-5-nitro-benzoic acid methyl ester 5b 4-Amino-2,3-difluoro-5-nitro-benzoic acid methyl ester 4 (1.50 g, 6.46 mmol) is suspended in xyienes (7.5 rnL) and 2-fluoro-phenylamine (6.24 mL, 64.6 mrnol) is added. The reaction mixture is stirred at 140 °C under N2. After stirring for 6 days, the reaction is complete. The reaction mixture is cooled to room temperature and diluted with methylene chloride and filtered through a silica gel plug eluting with methylene chloride (IL) to give an orange filtrate. The filtrate is concentrated to dryness and then triturated with diethyl ether to yield a bright yellow solid. The trituration is repeated. The yellow solid is collected to yield 1.08 g (52%) of the pure desired product. MS APCI (-) m/z 322 (M-l) detected.

Step B: 6-(4-Brorno-2fiuoro-phenylainino)-7fiuoro-3H-benzoirnidazole-5-carboxylic acid methyl ester Sd
4-Amino-3-fluoro-2-(2-fluoro-phenylamino).-5-nitro-benzoic acid methyl ester 5b
is converted by the reduction/cyclization and bromination procedures already described to yield the desired product. MS ESI (+) m/z 382, 384 (M+ Br pattern) detected.

Example 6

H3CO.-O
H

HN F CI
6-(4-Cizloro-2-methyl-p/ienylanzino)-7-Jluoro-311-benzoimidazo/e-5-carboxyljc acid methyl ester (Se)
7-Fluoro-6-o-tolylarnino-311-benzoimidazole-5-carboxylic acid methyl ester 7a is
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converted by the procedure already described for bromination, except N-chiorosuccinimide is used instead of N-bromosuccinimide, to yield the desired product. MS ESI (+) mhz 334, 336 (M+, Cl pattern) detected.

Example 7

H3C 0

HNF0CF3

7Fluoro6(2_rnethyl-4trifluoromedwxy-pheflyla1fliflO)-3II-beflZOimidaZOIe-S-carboxylic acid methyl ester (81)
Step A. 4-Amino-3-fluoro-2-(’2-rnethyl-4-trYluoromethoxy-pheflYlarfliflO)-5-flitro-benzoic acid methyl ester 12a
4-Amino-2,3-difluoro-5-nitro-benzoic acid methyl ester 4 (0,50 g, 2.15 rnmol) is suspended in xylenes (3 mL) and 2-methyl-4-trifluoromethoxy-phenylamine (1.00 g, 5.23 mmol) is added. The reaction mixture is stirred at 140 °C under N2. After stirring for 7 days, the reaction is a mixture of starting material and product. The reaction mixture is cooled to room temperature. The reaction mixture is poured into a separatory funnel and diethyl ether and 10% aqueous HC1 are added and the layers separated. The aqueous phase is extracted with three portions of diethyl ether. The combined diethyl ether layers are dried (MgSO4) and concentrated under reduced pressure. The residue is redissolved in methylene chloride and flushed through a plug of silica gel eluting with methylene chloride. The filtrate is concentrated under reduced pressure to give a bright yellow solid. The solid is washed with diethyl ether and the filtrate is concentrated under reduced pressure and the residue is further purified by FCC (eluting with 100% methylene chloride) to yield 0.39 g (45%) ofthe desired pure product as a yellow solid. MS APCI (-

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) nilz 402 (M-1) detected.

Step B. 7Fluoro-6-(2-,net/zyi-4-/rfluoromethoxy-phenylamiflO)-3H-benzoimidazole-5-carboxylic acid methyl ester 8f 4Amjno3fiuoro-2(2-methy1-4-trifluoromethOXy-PbeflY1amm0)-5-mtr0-beflZ0iC
acid methyl ester 12a is converted by the reduction/cyclization procedure already described to yield the desired product. MS APCI (+) n/z 384 (M+1) detected; MS APCI () m/z 382 (M-1) detected.

Example 8
Preparation ofHydroxylamines

IJydroxylamines useful for synthesizing compounds ofthe present invention may
be prepared as follows
(i) 0-(2-Methoxy-cthyl)-hydroxylamine
Step A: 2-(2-Methoxy-et/zoxy)’isoindole-1, 3-dione
DEAD (10 mL, 63 mmol) is added to a mixture of 2-methoxyethanol (5.0 mL, 63 mmol), PPh3 (17 g, 63 mmol), and N-hydroxyphthalimide (10 g, 62 mmol) in THF (170 mL). The resulting orange solution is stirred 16 h at room temperature. The reaction mixture is concentrated in vacuo, and the solids are filtered washing with CHCI3. The filtrate is concentrated again, and the solids are filtered washing with CHC13. This process is repeated until no precipitate forms. The final yellowish solids are recrystallized from EtOH to give the desired product (7.7 g, 55
Step B: 0-2-Methoxy-ethyl)-vdroxylamine
To a solution of 2-(2-rnethoxy-ethoxy)-’isoindole-1,3-dione (7.7 g, 35 mmol) in CH2C12 (30 niL) at room temperature is added methylhydrazine (2.0 mL, 36 mmol). The

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resulting solution is stirred for 16 h at room temperature. The white solids are filtered off. The solvent is carefully distilled off under reduced pressure, then the concentrate is distilled under vacuum (20 torr, 57-58 °C) to afford the desired product (2.2 g, 68%).

(ii) The following hydroxylamincs are prepared as described above using the appropriate alcohols. The isoindole-13-dionc intermediates are purified by flash chromatography.
NH2

02-obutoxy-ethyl)-hydroxamine is used directly without
purification.

<DN,,,,,’,O, NH2 0-(2-Po1idin-1-yl-ethyl)-hydrolamine is used directly without

purification.

CN--’-??O NH2 0(2-Pipetidiu-1-yl-ethyl)-hydroxyline is purified by Kugebohr

distillation (chamber temperature 140 °C, 1 torr). 0-(2-Methylsuifanyl-ethyl)-hydroxylaminc is purified by vacuum
distillation (76-78 °C, 20 ton).

Ph NH2

0-(2-Phcnylsulfanyl-ethyl)-hydroxylamine is used directly without
purification.

so NH2 0-(3-Methylsulfanyl-propyl)hydroxy1amine is used directly without

Spurification.

(iii) The following hydroxylamines are prepared from the appropriate isoindole-1,3-dione by oxidation using oxone (Tefrahedron Lett. 1981, 22, 1287), and then

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00\ 4,,S-0NH2 0(2Methanesu1fony1ethyl)-bYdIOXYIarnme is used directly without
purification.
0\ II0
PK&0..-NH2 0(2BenzenesuIfony1-ethyl)bydroXylaIflifle is purified by flash chromatography (1% MeOH in CH202).

d’ ’b 0(3Methanesu1fonyl-propy1)--bydrOXYaITIifle is used directly without purification.

Ph^,,-0.NH2 0-(3-Phenylsulfanyl-propyl)-hydroxylainine is prepared from PhSCH2CH2CH2Br and N-hydroxyphthaliniide by the patent procedure WO 0018790 and then is deprotected by the procedure described above and used directly without purification.

NH2

(iv) c’ ’b 043-flenzenesnlfonyl-propyl)-hydroxylamine is prepared from the above isoindole- 1,3-dione through its oxidation with oxone followed by deprotection as described above and is purified by flash chromatography (100% CH202 to 2% MeOH in CH2Cl2).

(v) 0_(2Morpho1in-4-y1-ethyI)-hydroxy1amine dihydrochloride
Step A: 0-(’2-Brconoethyl)-hydroxylamine J2ydrobrornide 2-(2-Bromo-ethoxy)4soindole-1,3-dione is prepared from 1,2-dibromoethane and N-hydroxyphthalimide as described in WO 0018790, and is then subjected to the procedure in J Org. Chem. 1963, 28, 1604 to yield the desired product.
Step B: (’2-Bromo-ethoxy)-carbarnic add tertbutyl ester

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To a solution of 0-(2-bromoeth.yl)-hydroxy1afltifle bydrobrornide (100 mg, 0.45 mmol) and di-t-butyl dicarbonate (110 mg, 0.49 inmol) in CH202 (1 mL) at room temperature is added Et3N (0.08 mL, 0.56 mmol). The resulting suspension is stirred for 16 h room temperature. The reaction mixture is diluted with EtOAc, washed with 1 N aq HCI and brine, dried over MgSO4, filtered, concentrated, and purified by flash chromatography (100% CH202) to give the desired product (81 mg, 75%).
Step C. (’2-Morpholizz4-yi-etho.xy,)carbamic acid tert-butyl ester
To a solution of (2-bromo-ethoxy-carbamic acid tert-butyl ester (252 mg, 1.05
mmol) in DIvIF (2 mL) at room temperature is added morpholine (0.14 mL, 1.6 mmol).
The reaction mixture is stirred for 7h at 50 T. The reaction mixture is diluted with
EtOAc, and washed with water. The organic layer is dried over MgSO4, filtered,

40 concentrated, and purified by flash chromatography (2% MeOH in CH202) to give the
desired product (I 18 mg, 46%): MS APCI (+) rn/z 247 detected.
Step D: 0-(2-Morpholin-4-yl-ethyl)-hydroxylarnine dihydrochloride
To a solution of (2-morpholin-4-yl-ethoxy)-carbanaic acid tert-butyl ester (118
mg, 0,48 mmol) in MeOH (1 mL) is added 4 M dioxane solution of HC1 (2.4 mL, 9.60
mmol) at room temperature. The resulting solution is stirred for 16 h at room
temperature. After addition of additional HCI (2.4 mL) followed by stirring for 4 h, the reaction mixture is concentrated in vacuo to give yellow solids (82 mg, 78%).

(vi) The isoiudole- 1,3-dione intermediates ofthe following hydroxylamines are prepared from the appropriate alkyl halide and N-bydroxyphtbalimide by the procedure described within J Heterocyclic Chem. 2000, 37, 827-830. The isoindole- 1,3-diones are deprotected by the procedure described above: 0-but-3-enyl-hydroxylamine; 0-

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(tetrahydro-furan-2-ylmethyl)-hydroXylamhle; 0(3methoxy-propy1)-hydroxylamine; and 0-(3-benzyloxy-propyl)-hydroxYlamine.

(vii) The following hydroxylamines are prepared as described in WO 0206213: 0(2-viny1oxy-ethyl)-hydroXY1amine; 2-aminooxy-2-methyl-propafl- 1-01; 1 -aminooxy-2-methyl-propan-2-ol; 3-aminooxy-propan-1 -ol; and (2-arninooxy-ethyl)-methyl-carbamic acid tert-butyl ester.

Example 9

H
0

HN/FÆBr

6(4_Bromo_2_chloro-phenylanh1w)- 7-fluoro-3H-benzoirnidazole-5-carbOXYliC acid cyclopropylniethoxy-arnide (’Jib)

Step A: 4Amino2-(2-chloro-phflYlamiflO)-3-flUOrO-517itr0-befl201c acid methyl ester 5b 4Aniino-2,3-difluoro-5-nitro-benZOiC acid methyl ester 4 (2.00 g, 8.62 minol) is suspended in xylcnes (15 ml) and 2-chioro aniline (9.06 ml, 86.15 mmol) is added. The reaction mixture is heated to 140 °C under a nitrogen atmosphere. After 6 days, the reaction mixture is cooled to room temperature, and diluted with ethyl acetate. The reaction mixture is washed with water, bob HC1 solution and brine. The organic layer is dried (MgSO4) and concentrated under reduced pressure. The crude product is triturated

Is

with diethyl ether, twice, to give 0.35 g (12%) pure desired product as a brownish solid.

Step B: 4, 5-Diamino-2-(2-chloro--phenylamiflo)-3-fiUOrO-benzoic acid methyl ester 6a 4-Amino-2-2-chloro-phenylamiflo)-3-f1uoro-5-nitro-henzoic acid methyl ester 5b

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(0.30 g, 0.88 mmol) is suspended in AcOH (5 ml) and zinc dust (0.29 g, 4.42 mmol) is added. After 15 minutes, the reaction is complete. The reaction mixture is diluted with ethyl acetate and filtered through Celite. The filtrate is washed with water, saturated NaHC01, 10% K2CO3 and brine. The organic layer is dried (MgSO4) and concentrated under reduced pressure to give 0.13 g (481/o) pure desired product as an whitish brown

foam.

Step C: 6-(2*Ch1oro-phenylamiflo)-7-flUOro-3NbeiZ01midZOle5cath0XY acid methyl ester 7b
4,5_Diamino2-(2-ch1oro-phenylarniflO)-3-f1UOrO-bcflZOic acid methyl ester 6a

(0.125 g, 0.404 mmol) is suspended in Et011 (2 ml) and formamidine acetate (63 mg, 0.605 mmol) is added. The reaction mixture is heated to reflux. Alter 16 hours, the reaction mixture is cooled to rt and diluted with ethyl acetate. The organic layer is washed with water, saturated NaI-1CO3, 10% K2CO3 and brine. The organic layer is dried
(MgSO4) and concentrated under reduced pressure to give 0.109 g (851/6) pure desired
product.

Step D: 6(’4-Bromo-2-chloro-phenylamino)-7--fluoro-3H-benzOimidazole-5-CarbOXYliC
acid methyl ester 8b
6-(2Cb1oro_pheny1amino)-7-tluoro-3H-benzoimidazo1e-5-carboxyliC acid methyl
. ester 7b (55 mg, 0.172 mmol) is dissolved in 1:1 THF:MeOH (2 ml) and cooled to 78 °C under an atmosphere of nitrogen. TsOH’H20 (49 mg, 0.258 mmol) is added followed by
NBS (31 mg, 0,174 mmol). After 10 minutes, the reaction mixture is warmed to 0 °C and
then 2 hours later warmed to A. After 16 hours, the reaction mixture is quenched by the

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Step E: 6-(4Bromo2-chloro-phenylamino)-7-fluoro3H-benzoimidazole-5-carboxvtic acid lOb
6-(4--Bromo--2-chloro-phenylamino)-7-fluoro-3H-benzoimidazole-5-cai-boxylic
acid methyl ester 8b (58 rug, 0.146 mmol) is suspended in FtOH (2 ml) and 1 ml 2 N NaOH is added. After 16 hours, the reaction mixture is diluted with ethyl acetate, water, and 10% HCJ solution. The layers are separated and the organic layer is washed with brine. The organic layer is dried (MgSO4) and concentrated under reduced pressure. Trituration with McOH gives 22 mg (39%) pure desired product.

Step F: 6-(4-Bromo-2chloro-pheuylamino)-7-fluoro-3Hbenzoimidazo1&5..carboxylie
acid cyclopropyimethoxy.-amide (lib) 6-(4-Bromo-2-ch1oro-phenyIaino)-7-fluom-3H-benzoimidazo1e5cari,,oxyljc
acid lOb (22 mg, 0.057 mmol) is dissolved in DMF (1 ml) and HOBt (9 mg, 0.062 mmol)
followed by triethyl amine (18 jil, 0.132 mmol) is added. Cyclopropyl methyl
. hydroxylamine hydrochloride (8 rug, 0.062 mmol) is added followed by EDCI (14 rug, 0.074 mmol). After 16 hours, the reaction mixture is diluted with ethyl acetate and water
and the layers separated. The organic layer is washed with saturated NH.C1, brine,
saturated NaI-1CO3, water and brine. The organic layer is dried (MgSO4) and

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S

concentrated under reduced pressure to give 23 mg (89%) pure desired product. MS

APCI (+) rn/z 455, 453 (M+ Br pattern) detected; MS APCI (-) m/z 453, 451 (M- Br

pattern) detected; ’FT NMR (400Mflz, DM50-d6) 3 11.69 (broad s, 1ff), 8.43 (s, 1E1),

7.62 (d 1H), 7.28 (dd, iJi), 6.42 (in, III), 3.63 (d, 2H), 1.03 (in, 111), 0.48 (m, 2H), 0.19

(m, 2ff); 19F NMR (376MHIz, DM50-d6) 1 3295 (s).

The following compounds are prepared by methods similar to those described in

Example 1 and in this Example 9 by using the appropriate carboxylic acid and the

appropriate hydroxylarnine:

H

-

HN F C!

H

/ HN’F

8h H 1i

H1’
HN ’7F CI

81 HO -0.N 0
H CI

HN F16-Cl

8i
H

O?Iy N

6

HN F CI

8m 0N0

__

H

H
N

HN’fF 0CF3

-i-- __________________________

>çii 0
H

’’CJ

8n 0
H C1

HNLYF HN’YF Br

H00Jt.O
H

(LN):

NF Br

Example 10

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6-(4-Brorno-2-chloro-phenyla,nino)-7-fluoro-3-rnethyl-3H-benzolmlda2,ole-5-carboxylic acid (2-lij’droxy-ethoxy)-amide (29c)
Step A. 6-’4-Bromo-2-chloro-p1zenylamino)-7-fluoro--3-inethyl--3H-benzoimidazole-5-carboxylic acid methyl ester 9a and 6-(4-Broino-2-chloro-phenylamino)- 7-fluoro-]- inethyl-1R-benzoimidawle-5-carboxylic acid methyl ester
A solution of 6-(4-bromo-2-cbloro-phenylamino)-7-fluoro-3F1-benzoimidazole-5-earboxylic acid methyl ester 8b (150 mg. 0.38 mmol), iodomethanc (28.tL, 0.45 mmol) and potassium. carbonate (78 mg, 0.56 mmol) in dimethylformamide (1.5 mL) is stirred at 75 °C for one hour. The reaction mixture is diluted with ethyl acetate, washed with saturated aqueous potassium carbonate (2x), brine, and dried (Na2SO4. Flash column chromatography (20:1 methylene chloride/ethyl acetate) provides 56 mg (36%) of the more mobile 6-4-bromo-2--ch1oro-pheny1amino)-7-fiuioro-3-methy1-3H-bezoimidazole-5 -carboxylic acid methyl ester 9a as a white solid. F NIMR (376 MHz, CD3OD) 133.5 (s). MS APCI (+) m/z 412, 414 (M+, Br pattern) detected. Also isolated is 54 mg (35%) of 6-(4-bromo-2-chloro-phenylamino)--7-fluoro- 1 -methyl- 1 H-benzoimidazole.-5-carboxylic acid methyl ester as a white solid. 19p NMIR (376 MHz, CD30D) 139.9 (s). MS APCI (1-) ni/r 412, 414 (M+, Br pattern) detected.

Step B. 6-(’4-Bromo-.2-chloro--phenylamino)-.7fiuoro-3-methyl-.3H--benzoimidazole-5-carhoxylic acid lOc
6-(4-Bromo-2-chioro-phenylamino)-7-fluoro-3-methyl-3H-benzoiniidazole-5-carboxylic acid methyl ester 9a (56 mg, 0.14 mmol) is dissolved into 2:1 THF/water (3 mL) and NaOH (0.55 mL, 1.0 M aqueous solution, 0.55 mmol) is added. After stirring for two hours the reaction is reduced to one quarter initial volume via rotary evaporation and the remainder diluted to 50 mL with water. The aqueous solution is acidified to pH 2

ZE

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by the addition of 1.0 M aqueous JIC1 and extracted with 1:1 tetrahydrofuran/ethyl acetate (3x), dried (Na2SO4) and concentrated under reduced pressure to provide 43 mg (79%) pure carboxylic acid as an off white solid. MS ESI (+) m/z 397, 398 (’M+, Br pattern)

detected.

Step C,’
carboxylic acid (’2-viny1oxyethoxy)-amide 29a 6(4-Bromo-2-ch1oro-pheny1amino)-7-f1uoro-3-mcthyl-3H-beflzOi1flidaZOle-5-carboxylic acid lOc (2.00 g, 5.0 mmcl), 0(2-vinyloxy-ethyl)-hydroxylaxnine (0.776 g, 7.5 mmcl), HOBt (0.88 g, 6.5 mmol), triethylainine (1,61 inL, 2.3 mmol) and EDCT (1.3 g 6.5 mmcl) are dissolved in dimethylformamidc (52 inL) and stirred at room temperature for 48 hours. The reaction mixture is diluted with ethyl acetate, washed with water (3x), saturated potassium, carbonate (2x), saturated ammonium chloride (2x), brine, dried (Na2SO4) and concentrated under reduced pressure to an off-white solid. Trituration ofthe solid with diethyl ether provides 2.18 g (90%) desired product as an off-white solid. MS ESI (-i-) m/z 483, 485 (M+ Br pattern) detected.

Step D: 6-(4-Bromo-2-chloro-phenylamino)-7-fluoro-3methy1-3H-benzoimidazole-5-carboxylic acid (2.-hydroxy-ethoxy)-amide 29c
Hydrochloric acid (14 mL, 1.0 M aqueous solution, 14 mmcl) is added to a
suspension of 6-(4-brorno-2-clhloro-phenylainino)-7-fluoro-3 -rnethyl-3H-benzoimidazole -5-carboxylic acid (2-vinyloxy-ethoxy)-amide 29a (2.18 g. 4.50 mmcl) in ethanol (50 niL) and the reaction mixture allowed to stir for 24 hours. The reaction mixture is concentrated to dryness by rotary evaporation and the solids partitioned between 3:1 ethyl

M.

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acetate/tetrahydrofuran and saturated potassium carbonate. The aqueous phase is extracted with 3:1 ethyl acetate/tetrahydrofuran (3x), the combined organics dried (Na?SO4), and concentrated to provide 2.11 g (100%) 6-(4-bromo-2-cbioro-phenylamino)-7-fluoro-3-methyl-3H-benzoimidazole-5-carboxyhc acid (2-hydroxy-ethoxy)-amide as an off-white solid. MS ESI (+) m/z 457, 459 (M+, Br pattern) detected.
’H NMR (400 MIElz, MeOH-d.1) 8.26 (s, 111), 7.78 (s, 1H), 7.57 (4, 1H), 7.24 (dd, 1ff),
6.40 (dd, 111), 3.86 (s, 3H), 3.79 (in, 2H), 3.49 (in, 2H). ’9F NMR (376 MHz, MeOH-d4)
 133.68 (s).

Example 11

The following compounds are prepared by methods similar to those described in SExample 10 by using methyl ester Sb and the appropriate aTkylating agent (Step A) and the appropriate hydroxylamine (Step C):
29d H
HO.,NO
H

NFBr

29ff
01

H
H

NF Br
N
29eN 0
H

"-N F Br

29gg

FI: Br
29f H

4F5Br

29hh 0

N"fF L,,,1
_ Br
C1

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F Br

29ii
ci

L.L

O0NO
Hcl

2 9 h S i r

H Cl 29jj

- N\ - NN) t l F Br

N’f’F Sir

29i

o NH

NH

cl

29kk

N_(

N ’ FBr N F Br

29j)iOH

o NH
CI

2911 H
SQNO
H Cl
Nj[

N’fF Br
\--N
- Nj F

29k HO0
H Ci
N

- (I

29m
Ph
H Ci

LL. N F Br L L N"F Sr

291 H

N Br

29

H

Br

H

N_(H

LJBr
1

(F

B r_ :

13___ ___ ’N’tF

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11

S

29n H

CfN\.--N

F Br

29pp

N_(

Br

290 29qq PhsoN0

N F-6Br N F Br

N 0 ci

F Br
\--N

H00NO

NF>Br
\--N

29

29q H0VQNO
00 I H

I I

N Jt’ Br N F Br

29r 50H

0 NH

FBr

0
H

 N F Br

29s HO -0N0

F -f: ’Sr

29uu H

0N

Fr
N

64

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fl

29t H

HO0NO

CI H

- N;

Br

N

H
0NO

H CI

Ql xc?

\--- N ?N Br
\--N

29u H
HO 0NQ ci
N_(

29ww BOC H
N0N 0

d1

H

L?N; N F Br L

F Br

29v HO0NO

O

29xx H

HOc l H Cl

NI /N’FBr F Br
0

29W HO,

H

H

NL

Br
\ \---N

29yy H
HON0 CI

F3C/NN

FB

__ Q

29x H
N 0

H CL

29zz H

HO-0NO

H Cl

Br

F Br N

29y H

0N0

H Ci

29aaa

H Cl
Nt?

F Br

_____ ’FBr

MeON

65

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29z 0N0
H CI

H
HO - 0 NO

H Cl

N’F Br
N FB
N

EtO =N

29aa

H CI

H
CI

14 Br
N"YF Br
ç N

OH

MeO

__29bb H 0N0
H cl
N_(

29ddd H 0NO H ClN

N/XF Dr
N ’ F

TOMe

29cc H

H
N

29eee H
CI

’16-Br
N BrEtO

5-0

29dd ,NO H29fff
CI 0N0 0 ci

N/LYF ’Br
N F Br

29ee H

NO ci 2Qo /Th H \NH_6 0.N0 cl

_ /N]F Br N F Br

604

WO 93/077914 PCTIUS03/97 Example 12

H
OH

N’T’F LBr

6.-(4-Rrwno-2-chloro-pheiiylwnino)-7-fluoro..3-rnethyl-3H-benzoiinidazole-5-carboxyllc acid (2,3-diiydroxy-propoxy)-amide (291sh1i) To a solution of 6-(4-bromo-2-chloro-phcnylamino)-7-tluoro.-3-methyl-3H-benzoimidazole-5-carboxylic acid allyloxy-amide 29tt (20 mg, 0.04 mmol) in 0.50 rnL
4:1 tetrahydrofurärilwater is added 0s04 (41 pL, 0.054 M solution in t-BuOH, 0.002
mmol) followed by NrvIO (7 mg. 0.06 mmol). The solution is stirred at room temperature
for eight hours after which time 1{PLC analysis showed complete conversion to product. SThe solution is then stirred with saturated NaHS03 and diluted with ethyl acetate. The organic phase is dried (Na2SO4). Purification by FCC (DCM -> 20:1 DCMII\4e0H)
provided 16 mg desired product as an off-white solid. MS ESI (-I-) m/z 487, 489 (M+, Br
pattern) detected.

Example 13

OH
I H
HO0. NO

H CI N_d
N, F Br

6-(4-.Rrorno-2-chloro-phenylamino)- 7-fluoro-3-snethyl-3H-banzoimidazole-5-carboxylic acid (3,4-dihydroxy-butoxy)-arnide (29W) 6-(4-brorno-2-cbloro-phenylamino)-7-fluoro-3 -methyl-3H-benzoirnidazolc-5-

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Ar

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carboxylic acid but-3-enyloxy-amide 29uu is subjected to the dihydroxylation method

described in Example 12. MS APCI (+);n/z 501, 503 (M+ Br pattern) detected.

Example 14

H H
H

CF3CO2H <LNTL

N F ’Sr

6-(4-Brorno-2-cl:loro-phenylainiiw)-7-fluoro-3-rnethyl-3H-benzoimidazole-5-carboxylic acid (2-mcthylamiiw-ethoxy).-amide TFA salt (29j,:j)
Prepared from (2 ([6-(4-bromo-2-chloro-phenylarniiio)-7-fluoro-3 -methyl-3H-benzoimidazole-5-carbonyl]-axninooxy} -ethyl)-methyl-carbaiuic acid tert-butyl ester 29ww by tritluoroacetic acid deprotection in methylene chloride. MS APCI (+) m/z 470, 472 (M+, Br pattern) detected; 1H NMR (400 MHz, CD30D) 8 8.31 (s, 1H), 7.74 (a, 111), 7.51 (d, 111), 7.19 (dd, 1H), 6.39 (dd, 1H), 4.11 (m, 2H), 3.97 (a, 3ff), 3.12 (m, 2H), 2.72 (s, 311); ’F NM1R (376 MHz, CD30D) 77.41 (s, 3F), 134.79 (s, IF).

Example 15
The following compounds are prepared by methods similar to those described in

Example 10 by using methyl ester 8a and the appropriate alkylating agent (Step A) and

the appropriate hydroxylaxmne (Step C):

lic H Ile H

F ’Br NF Br

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TIT H TIT H
- N 0N 0
Nj[N

NF Br N1 F Br

Example 16
The following compounds are prepared by methods similar to those described in Example 10 by using methyl ester Se and the appropriate alkylating agent (Step A) and the appropriate hydroxylarnine (Step C):

hg H

F CI

i-il-

0
H

N’F CI

0_ H

N F CI

H

H I

0
H,&CI

N F Cl
I

Example 17
The following compounds are prepared by methods similar to those described in

Example 10 by using methyl ester Sc and the appropriate alkylaling agent (Step A) and the appropriate hydroxylainine (Step C):

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H -
1 IM N 0HO N 0
V0 CI H CI

N 4 F C I
 N Ft?cl _______

Example 18
The following compounds are prepared by methods similar to those described in Example 10 by using methyl ester 3d and the appropriate alkylating agent (Step A) and the appropriate hydroxylamine (Step C):

29111 HO ’ 0 29 H0.> i o

 N] F Br N F Br

Example 19

H
NO

NYF Br

6-(4-Bro1no-2-rnethy1-phenyIamüIo)-7-fluoro-3-.f4-(4-methy-ppera7jr,-i-yl)-bu1ylJ-3H-benzoimidazole-5-carbcxylic acid cyclopropylmethexy-amide (1 Jo)
Step A: 6-(4-Broino-2-rnethyl--phenylarnino)-7-fluoro-3-pent-4-enyl-3H-benzoimidazo1e-5-carboxylic acid methyl ester 9b
7-Fluoro-6-(4-bromo-2-inethyl-phenylamino)4H-benzoimidazole-5-carboxylic
acid methyl ester 8a (0.915 g, 2.419 mmol) is suspended in DMF (18 ml) under an atmosphere of nitrogen. Bromopentene (0.430 ml, 3.629 mmol) and K2CO3 (0.502 g,

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3.629 mmol) are added and the reaction mixture was warmed to 80 °C. After 1 hour, the reaction mixture is cooled to room temperature and poured into 100 ml of 1:1 ethyl acetate:diethyi ether. The organic layer is washed with water and brine, dried (Na2SO4) and concentrated under reduced pressure. The N3 and Ni alkylated products are separated by flash column chromatography, eluted with 20:1 methylene chloride:ethyl acetate. Complete separation of the isomers is obtained by performing two chromatographic separations. The higher Rf product is the N3 product 9b, while the lower R1 product is the Ni product. The recovery of the N3 product 9b is 0.415 g (38%): LC/MS EST (+) rn/z 448, 446 (M+1 Br pattern) detected. The recovery ofthe Ni product was 0.486 g (45%): LC/MS ESI (+) m/z 448, 446 (M+1 Br pattern) detected.

Step B: 6-(’4-Brorno-2-inethyl-pheny1arnino)- 7-fluoro-3-pen/--4-enyl-3H-henzoiinidazoie-5-carboxylic acid lOd
6-(4-.Bromo-2-methyl-phenylamino)-7-fluoro-3-pcnt-4-enyl-3H-bcnzoimidazole-5-carboxylic acid methyl ester 9b is dissolved in 1:1 TJ]F:MeOH (10 ml) and 1 N NaOH solution (2.3 ml) is added. After 5h, the organic solvents are removed under reduced pressure and the residue diluted with water and 100 nil 1:1 THF:ethyl acetate. The layers are separated and the aqueous layer extracted with ethyl acetate. The combined organic extracts are dried (Na2SO4) and concentrated tinder reduced pressure to afford 0.39 g (100%) clean desired product as a light yellow solid.

Step C: 6-(4Bromo-2-methyl-phenylamino)-7.-ftuoro-3-pent-4-enyl_3H-benzoimidazole-5-carboxylic acid cyclopropyhnethoxy-amide 111 6-(4-Bromo-2-methyl-phenylnino)-7-fluoro-3-pent-4--enyl-3H-benzoimidazole-

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5-carboxylic acid 10d (0.390 g, 0.902 mmol) is dissolved in 1:1 THF:methylene chloride (6 ml) and Hunig’s base (0.346 ml, 1.985 rnmol) is added followed by PyBOP (0.563 g, 1.083 mrnol). After 10 minutes, cyclopropyl methyl hydroxylarnine hydrochloride (0.134 g, 1.083 mniol) is added. After 16 hours, the reaction mixture is diluted with ethyl acetate and washed with 0.1 N HCl, saturated NaHCO3, and brine. The organic layer is dried
(Na2SO4) and concentrated under reduced pressure. The crude yellow residue is purified
by FCC eluted with ethyl acetate to give 0.315 g (70%) pure desired product as a yellow
solid: MS APCT (-I-),n/z 503, 501 (MI-i Br pattern) detected.

Step I):
benzoirnidazole-5-carboxylic acid cyclopropylmethay-amide Jim
. 6-(4-Brorno2-methyl-phenylamino)-7-fluOrO-3-peflt-4-eflyl-3H-be11ZOifludaZOle-5-carboxylic acid cyclopropylmethoxy-amide 111(0.307 g, 0.612 rnmol) is dissolved in
4:1 THF:water (8 ml) and 1.134 ml (0.061 mmol) of an 0.054M. 0s04 solution in r-
BuOH has added followed by NMO (0.093 g, 0.796 mmol). Alter 5h, the reaction
mixture is quenched by the addition of 10% NaHS203 solution. After 10 the
reaction mixture is filtered through Celite rinsing with ethyl acetate and methylene
chloride. The filtrate is diluted with ethyl acetate and washed with 0.01 N HCl, and brine. The organic layer is dried (Na2SO4) and concentrated under reduced pressure. The crude product is purified by FCC eluted with 9:1 ethyl acetate:MeOH to give 0.244 g (74%) pure desired product.

Step 6-(4-Bromo-2-methyl-phenplarnino)-7-fluoro-3-(4-oxo-butyl)-3H benzoiinidazole-5-carboxylic acid cyclopropylnethoxy-ainide liii

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WO 03/077914 PCTIUS03/07864 To a mixture of 6(4-brorno-2-methyl-pheny1amino)-3-(4,5-dihydr0xy-penty1)-7-fluoro-3H-benzoimidazole-5-carboxylic acid cyclopropylmethoxy-amide 1 im (0.244 g, 0.456 mmol), THF (5 ml) and pH 7 phosphate buffer (3 ml) is added sodium periodate (0.195 g, 0.911 mmol). After 16 hours, the reaction mixture is diluted with ethyl acetate and washed with NaHCO3, and brine. The organic layer is dried (Na2SO4) and concentrated under reduced pressure to give an orange solid. Purification by FCC eluted with 4:1 methylene chloride:MeOH yields 0.189 g (82%) pure desired product as a yellow solid: MS APCI (+) rn/i 505, 503 (M+1 Br pattern) detected; MS APCI (-) rn/i 503, 501 (M-1 Br pattern) detected.

Step F. 6-(4-Bromo-2-methyl-phenylarnino)-7-fluoro-3-[4-(4-rnethyl-piperazin-1-yl)-- butylJ-3ff-benzoirnidazole-5-carboxyhc acid cyclopropylmethoxy-amide lb 6-(4-Bromo-2-metbyl-phenylamino).-7-fluoro-3-(4-oxo--butyl)-3H benzoimidazole-5-carboxylic acid cyclopropylmethoxy-amide tin (15 mg, 0.030 mmol) is dissolved in MeCN (500 d) and methylpiperazine (10 p.1, 0.089 mmol) is added followed by AcOH (5 p.1, 0.089 mmol). After 5 tetramethylainmonium triacetoxyborohydride (12 mg, 0.045 rnmol) is added. After 5 the reaction mixture is diluted with ethyl acetate and washed with NaHCO3 and brine. The organic layer is dried (Na2SO4) and concentrated under reduced pressure to give 12 mg (691/o) ofpure desired product as a white solid. MS APCI (-) rn/i 587, 585 (M-1 Br pattern) detected; 1H NIl’1IR (400 MHz, CDC13) 7.99 (s, 1ff), 7.98 (s, 111), 7.30 (d, IM, 7.08 (dd, 111), 6.30 (d, 111), 6.1 (broad singlet, 111), 4.26 (t, 2ff), 3.64 (d, 211’), 3.37 (s, 111), 2.45 (broad, 8H), 2.41 (a, 3H), 2.38 (t, 2H), 2.28 (a, 311), 1.95 (quin, 211), 1.55 (quirt, 211), 0.98 (m, 111), 0.50 (qt, 2F1), 0.22 (qt, 211).

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Example 20
The following compounds are prepared by methods similar to those described in

Example 19 by using the appropriate alkenyl substituted benzimidazole and the

appropriate amine in the reductive amination (step F):

T- HO, 0’HC1 0
N_jC

180 OA
71’?

7"

H_6

C F CA

HO)’N

Br

H

HJr

HO F B

18 H

NO
H I

N j F CI

18q
H

I

N_6CI

H

I F

6CI

_ /__/?N /

HO OH
H 18r

ocl

CI
HOCN

011
\ll?ONO H

CF

18s H

N O

o_ Hj:ICj

NJtLF
CI

HO))

/

_

HO
74

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H

- &

18t H
7Of0H

-61,- F Br
F Br 0’N

18g H

NO iSu

0H

F

H N F Br N’N

H

I g hH

N

iSv
7°H_6W

F Br

HN HC)
181 H
OIN

I

18w H

QNO
H"&

F Br

F Br CN-/--/N
181 H

OIN 0

H1H, P-N

18x H

F Cl
F Br /N

H iSy H
H

N
F Br

\= N

181 H 18z H

N

F Cl
Br
SONNN

F

75

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I

H

H -6\-Br

Cl

- N F

I-1

N,,6F

18b CI

N N FBT

Example 21

i-i

0
N FI: Br

6-(’4-BroIno-2-methy1-pheny1arnino)-3-f4-(’1,1-dlOxo-1)’-thiomorpholin-4-y)-bu1ylj-7-fluuro-3H-benzolmidazole-5-carboxylte acid cyclopropylmethoxy-amide (18cc)
To a solution of 6-(4-bromo-2-methylphenyIamino)-7-fluoro-3-(4-thiomorpho1in-4-yI-buty-3H-benzoimidazo1e-5-carboxyIic acid cyclopropylmethoxy-amide 181 (8 mg, 0.014 rnmol) in 1:1:1 water/acetonefMeOH (1 mL) is added NMO (1,6 mg, 0.014 nimol) and osmium tetroxide (250 jiL, 0.054 M solution in tBuO1-T, 0.014 mniol). After stirring for 24 hours, the solution is diluted with saturated sodium thiosulfate, stirred for 10 minutes and diluted with ethyl acetate. The solution is washed with brine (2x), dried (Na2SO4) and concentrated under reduced pressure to a grey solid. FCC (10:1 dichioromethane/methanol) provides 6 mg (71%) desired product as an off-white solid. MS ESI (+) m/z 622, 624 M+, Br pattern) detected.

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., WO 93/077914 PCTItJS03/07864 Example 22

6-(4-Brorno-2-c/iloro-’phenylwnino)- 7-fluoro-3-[4-(4-inethyl-plperazin-1-yl)-buty!J-3H-
henzoimidazole-S-carboxyli.c acid cydopropylmethoxy-amide (18dd)
A solution of 6-(4-hromo-2-chioro-phenylamiio)-3-(4-ch1oro-hutyl)-7-fluoro-3H-
. beiuoirnidazole-5-carboxylic acid cyclopropyhnethoxy-amide lSee (10 mg, 0.018 mmoO, sodium iodide (14 mg, 0.092 mmol), and 1-methy1piperazine (10 tL, 0.092 rnmol) are
stirred at 85 °C for three hours. The reaction mixture is diluted with ethyl acetate and
washed three times with water, washed twice with saturated aqueous potassium
carbonate, dried (Na2SO4) and concentrated under reduced pressure to a yellow oil. Flash
column chromatography (1:1 dichioromethane/methanol followed by methanol followed
by 20:1 methanolltriethylamine) yields clean product (8 mg, 72%) as an off-white foam. MS ESI (+) m/z 607, 609 (M+, Br pattern) detected. ’H NM (400 MHz, DMSO-d6) 8.37 (S. 111), 7.71 (s, 111), 7.49 (d, 1H). 7.18 (dd, 111), 6.40 (dd, 111), 4.38 (1, 211), 3.62 (d, 2131), 2.45 (broad, 811), 2.41 (t, 21-1),2.28 (s, 311), 1.96 (m, 211’), 1.54 (m, 211), 1.07 (m, 111), 0.50 (d, 211), 0.22 ((1,211’).

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C

Example 23

The following compounds are prepared by methods similar to those described in

Example 22, using an appropriate amine and primary alkyl chloride.

18ff

N_6 H

l8tt o

- N1

11
Br

Br

l8gg l8uu
CI H

N F

NI F Br
NJ

OJ

l8bh

01 H Cl H,&

Br
, NJ

l8ii ,__p

N

_I L l8ww I-I ---.----- NO

N,&,,(
I

x N E

Br

l S j j H Cl
N

ISXX H

Sr

0 F o9

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H

ci

1 8
H CI

7-N

F Br

/N
HJ

1811 H lSzz - ______

V0

NO

Br

HN X F H
18M
m H

1 8aaa cl H

F Br
N

H
ci

l8bbb

N

SSKFBr N

l800 H

N

::?

1 8ccc 0N
H CI

11

N_(?

F

Br CN_/N;

18pp H
0,; H Ci

- 6Br

l8cldd H

NO
- HG!

CO F ==N
HN"

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I

18qq -- H 0

F Br

ISeec 0NOIN cl H

l8rr H

Br
O

Tsfff H

ci

HO (LO

NNF

l8ss H

HO-0NO

NF-TC Sr

Example 24

6-(4-Chloro-2-methyl-phenyiamiiw)- 7-fluoro-3-oxazol-5-ylrnethyl-311-benzoirnidazole-5-carboxylic acid cyclopropylmethoxy-amide (18ggg) 6-(4-Chloro-2-methyl-phenylamino)-7-fluoro-3-(2-oxo-ethyl)-3H-benzoimidazole-5-carboxylic acid cyclopropylmethoxy-amide (0.020 g, 0.046 mmol) is dissolved in inethanol (2 mL). Potassium carbonate (0.013 g, 0.093 mmol) and 1-isocyanomethanesulfonyl-4-methyl-benzene (0.010 g, 0.051 mmol) are added. The reaction mixture is stirred at reflux for 16 hours under N2, then concentrated under reduced pressure. The residue is dissolved in ethyl acetate and poured into a separatory funnel and washed with water and brine. The combined aqueous layers are reextracted

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with ethyl acetate (2x). The combined ethyl acetate layers are dried (Na2SO4,) and concentrated under reduced pressure. The resulting solid was purified by flash column chromatography (elating with 15:1 methylene ehloride:rnethanol) to yield 0.011 g (50%) of the desired product. MS APCI (+) m/z 470, 472 (M+ Cl pattern) detected; 111 NMR (400 MHz, CDCI3) 8 10.51 (br s, 1H), 8.07 (s, ill), 8.02 (s, 1H), 7,89 (s, 11-1), 7.23 (s, 111), 7.15 (d, 1H), 6.92 (dd, 111), 6.31 (d, lii), 6.11 (br s, 111), 5.45 (s, 211), 3.62 (d, 2E1), 2.40 (s, 3H) 0.87 (in, 111, 0.49 (rn, 2H), 0.20 (m, 211). ’F NW (376 MHz, CDC13) - 134.54(s).

Example 25

H
H
N

OX N F Sr

6-(4-Brorno-2-chloro-phenylwnino)-7-fluoro-3-(3-oxo-3-pyrrolidin-1-yl-propyl)-3H-benzoirnidazole-5-carboxylic acid cyeiopropylmethoxy-amide (18lthh)
Step A: 6-4-Bromo2-chloro--phenylamino)-3-’2-ter.-butoxycarbonyl-ethy)-7-fluoro-3H-benzoirnidazole-5-carboxylic acid methyl ester 6-(4-Bromo-2-chloro-phenylamino)-7-fluoro-3H-benzoimidazole-5-carboxylic
acid methyl ester 8b (0.50 g, 1.25 mm.ol) is dissolved in DMF (8 ml) under N2 and K2CO3 (0.26 g, 1.88 mmol) is added followed by t-butyl acrylate (1.84 ml, 12.54 rmnol). The reaction mixture is heated to 90 °C with stirring. After 4 h, the reaction mixture is cooled to rt and diluted with ethyl acetate. The organic layer is washed with water (3x) and brine, dried (MgSO4) and concentrated under reduced pressure. Purification by flash column chromatography eluted with 19:1 methylene chloride:ethyl acetate gives 0.41 g

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S

(62%) desired product.

Step B: 6(4-Bromo-2-chloro-phenylarnino)-3(’2-carbOXY-ethyl)- 7-fluoro-3H-benzoimidazole-5-carboxylic acid methyl ester TFA salt

benzoiniidazole-5-carboxylic acid methyl ester (0.050 g, 0.095 mmol) is dissolved in methylene chloride (0.5 ml) and TFA (0,5 ml) is added. After 45 the reaction mixture is concentrated to dryness to give 0.49 g (88%)desired product: LC/MS ESI (-I-) m/z 472, 470 (M+ Br pattern) detected; ’H NMR (400MHz, DMSO-d6) 8.51 (s, 1H), 8.20 (s, 111), 8.13 (s, 111), 7.64 (d, 111), 7.29 (dd, 111), 6.45 (dd, 111), 4.55 (t, 2H), 2.89 (t. 2H).

Step C 6-(443romo2-chloro-phenylamino)-7-fluOro3-(3-oxa--3-pyrrOlidifl-1--Yl--PrOPYl)- 3H-benzoiinidazole-5-carboxylic acid methyl ester
To solution of 6-(4-bromo-2-chloro-phenylamino)-3-(2-carboxy-ethyl)-7-fluoro-3H-benzoimidazoie-5-carboxylic acid methyl ester (60 mg, 0.13 mmol) in DMF (1.8 mL) is added H013t-H20 (24 mg, 0.16 mrnol), Et3N (0.043 mL, 0.31 mmol), pyrrolidine (0.011 mL, 0.13 mmol), and EDCI (34 mg, 0.18 mmol) at A. The resulting yellow solution is stirred 16 h at rt. The reaction mixture is diluted with EtOAc and water, washed with sat’d aq NH4C1, brine, sat’d aq NaHCO3, and brine. The organic layer is dried over MgSO4, filtered, and concentrated in vacua to give a crude material which is purified by flash chromatography (3% MeOH in CH202) to afford 45 mg (67%) of the desired product: MS APCI (+),n/z 523, 525 (M–, Br pattern) detected.

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WO 03/077914 PCTIUS03/07864 Step Dr 6-(4--Bromo-2-chloro-pheny1amino)-7-fluoro-3-(3-oxo-3-pyrrolidin-1-yl--prop)il,)_ 3Hbenzofrnidazole-5carboxylic acid
To a solution of 6-(4-bromo2-chIoro-pheny1amino)-7-fluoro-3-(3-oxo-3-pyrrolidin- 1 -yl-propyl)-3H-benzoimidazole-5-carboxylic acid methyl ester (41 mg, 0.079 nirnol) in TLIF/H20 (1.5 mJJ0.75 mL) is added 0.20 mL (0.20 mmol) of! N aq LiOH at rt. The resulting solution is stirred 16 11. The reaction mixture is acidified with 1 N aq HC1 (pH 2 to 3) and diluted with fitOAc. The organic layer is dried over M9SO4, filtered, and concentrated in vacuo to give a crude product (42 mg) which is directly used without further purification.

Step Er
3H-benzoirnidazole-5-carhoxylic acid cyclopropylmethoxy-amide 18IzIth
The title compound is prepared from 6-(4-bromo-2-chloro-phenylamino)-7-fluoro-3-(3-oxo-3-pyrrolidin- 1-yl-propyl)-3H-benzoirnidazole-5-carboxylic acid and 0-cyclopropyhnethyl-hydroxylamine hydrochloride by the standard coupling procedure described in Step A: MS APCI (+) in/z 578, 580 (M+, Br pattern) detected; ’H NMR (400 MBz, DMSO-46) 11.66 (s, 111), 8.42 (s, 111), 8.01 (s, 1H), 7.76 (s, 111), 7.62 (s, 111), 7.28 (d, 111), 6.39 (in, 1H), 4.52 (t, 211), 3.66 (d, 2ff), 3.33 (t, 2H), 3.28 (t, 2H), 2.89 (t, 2H), 1.83 (m, 211), 1.76 (in, 211), 1.06 (m, 111), 0.49 (m, 211), 0.22 (m, 2H); 19i N.tvIR (376 MHz, DMSO-d6) 132.94 (s, IF).

E

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C

Example 26
The following compounds are prepared by methods similar to those described in Example 25 using methyl ester Sb and the appropriate amines:

_l8iii H
O’J H CI

I

NH F Br

l8kkk- H
HO0.NO

H ci

NH II F Br

HO, -)i0 ci

QN; TTÆL

F Br

Example 27

H
0NO

H CI

F Br

6-(4-Iiroino-2-chloro-plsenylamino)- 7-flrwro-3-(tetrahydro-pyrau-2-ylmethyl)-3H_ benzoimidazole-5--carboxylic acid (2-hydroxy-etlwxy)-amide (lip)
Step A: 6-(4Bromo-2-chioro--phenylamino)- 7-fluoro-3-(tetravdro-pyran-2-ylmethyl)- 3H-benzoimidazole-5-carbo%ylic acid methyl ester llq 6-(4-Bromo-2-chloro-phenylainino)-7-fluoro-3H-benzoiniidazole-5-carboxylic
. acid methyl ester Sb (0.25 g, 0.63 mmol) is dissolved in NN-dimethylformaniide (5 mL). 2-Bromomethyl-tetrahydropyran (0.34 g, 1.88 rnmol) and potassium carbonate (0.26 g,
1.88 mrnol) are added and the reaction mixture is stirred at 60 °C for 12 hours under N2.
The reaction mixture is poured into a separatory funnel, diluted with ethyl acetate and

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water and the layers separated. The ethyl acctate layer is washed with water and brine, dried (Na2SO4) and concentrated under reduced pressure. The resulting solid residue is triturated with diethyl ether to yield a pale yellow solid (N3 regioisomer by NMR) and a yellow filtrate (mixture of Ni and N3 regioisomers by NMR). The solids are collected
and washed with diethyl ether to yield 0.12 g (37%) ofthe pure desired N3 regioisomeric
product as a pale yellow solid. MS ESI (+) rn/z 496, 498 (M+, Br pattern) detected.

Step B:
3Hbenzoimidazole-5-carhoxylic acid hr

3H-benzoiniidazole-5-carbOXylic acid methyl ester liq is suspended in 4:1 Itetrahydrofuran/water(25 mL) and aqueous 1 M L1OH is added (2.5 mL). Alter stirring at room temperature for 16 hours, the reaction mixture is homogeneous and the reaction is
complete. The reaction mixture is cooled to 0 °C, diluted with water and aqueous 2 M
HC1 is added dropwise until the pH of the solution is 1-2, at which time it turns to a
suspension. The reaction mixture is poured into a scparatory funnel and diluted with
ethyl acetate/tetrahydrofuran and water and the layers separated. The aqueous layer is
extracted with ethyl acetate. The combined organic layers are washed with brine, dried (Na2SO4) and concentrated under reduced pressure to yield 0.11 g (100%) of the pure desired product as a white solid. MS ESI (+) rn/z 482, 484 (M+, Br pattern) detected.

Step C: 6-(4-Brotno-2-chloro-phenylainino)- 7-fluoro.-3-(tetrahydro-pyran-2-ylmethyl)- 3H-benoimidazole-5--carboxylic acid (2-vinylaxy-ethoxy)-amide his

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3H-benzoimidazole-5-carboxylic acid 11r (0.11 g, 0.23 mmol) is dissolved in N,N-dimethylformamide (2 rnL). HOBT (0.037 g, 0.27 mmol) and triethylamine (0.094 mL, 0.68 nimol) are added. Then 0-(2-vinyloxy-ethyl)-hydroxYlamine (0.028 g, 0.27 mmol) and EDCI (0.056 g, 0.29 mmol) are added and the reaction mixture is stirred at room temperature under N2 until HPLC shows the reaction is complete (2-3 days). The reaction mixture is poured into a separatory funnel, diluted with ethyl acetate and water and the layers separated. The ethyl acetate layer is washed successively with aqueous saturated NH4CI (2x), brine (lx), aqueous saturated sodium bicarbonate (2x), water (lx), and brine (lx), dried (Na2SO4) and concentrated under reduced pressure. The resulting solid is purified by FCC (eluting with 15:1 methylene chloride:methanol) to yield 0.039 g (79%) of the pure desired product as an off-white solid. MS £51 (+) m/z 567, 569 (M+, Br pattern) detected.

Step D: ó-(4-Brorno-2-c/2loro-p/zenylamino).7-jluoro-3-(tetrahydro-pyran-2-ylmethyl)- 3H-benzoimidazole-5-carboxylic acid (2-hydroxy-etizoxy)-amide lip 6(4-Bromo-2-chloro-phenylaniino)-7-fIuoro-3-(tetrahydro-pyran-2yJrnethy1)- 3H-benzoimidazole-5-carboxylic acid (2-vinyloxy-etboxy)-amide 11 s (0039 g, 0.068 mmol) is dissolved in ethanol (2 niL) and aqueous 2 M HC1 (200uL) is added. The reaction mixture is stirred at room temperature for 30 minutes. The reaction mixture is diluted with water and then neutralized with aqueous 2 M NaOH (’-200 uL) until pH 7 and concentrated under reduced pressure. The residue is partitioned between ethyl acetate and brine in a separatory funnel and the layers separated. The ethyl acetate layer is dried (Na2SO4) and concentrated under reduced pressure to yield 0.034 g (91%) ofthe pure desired product as an off-white solid. MS EST (+) rn/z 541, 543 (M+, Br pattern)

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detected; ’H NMR (400 Maz, CD30D) 6 8.29 (s, 111), 7.75 (s, 111), 7.49 (d, 1ff), 7.18

(dd, 111), 6.40 (dd, I H), 4.40 (dd, A of ABX pattern, 1ff), 4.28 (dd, B of ABX pattern, 111), 3.92 (m, X of ABX pattern, 111), 3.66 (t, 211), 3.35 (in, 111), 1.89 (m, 111), 1.76

111), 2.28 (s, 311), 1.54 (in, 311), 1.30 (m, 1H). ’9F NUR (376 MHz, CD30D) 134.87 (s).

Example 28
The following compounds are prepared by methods similar to that described in

Example 27 by using the appropriate methyl ester and alkylating agent (Step A) and the

appropriate hydroxylamine in (Step Q.

iEiiiT
H CI

N] F Hr

lix HO -’...0N 0

N F Br

0 -i-i-i;:- \--N 6

HO-0ii 0

H C1

F Br

ilY HO0Ji

N I F Br

00-

H J

____ liz ox

OH

0 JH CI
N F r
"-N

HN--./)-.L,/N F Br

11w HO, -0ii
H CI

F
CI N " "

Llaa H
0NOH

F Br

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H
CI

C)O,1tL. /N / F Br

6-(4-Bromo-2.chloro-phenyIarnino)-7-fluoro-3-(’2-rnethwiesu1fony!-ethyl)-3H-
benzoiinWaole-5-carbo.xylic acid cyclopropylmethoxy-amide (llbb)
Step A: 6-(4-Bromo-2-chloro-phenylamino)-7’-fiuoro-3(2-inetJzanesulfonyl-et/zyl)-3H-benzoimidazole5carboxylic acid methyl ester 11cc 6-(4-Bromo-2-ch1oropheny1arnino)-7-fluoro-3H-benzoimidazole-5-carboxylic
acid methyl ester Sb (1.55 g, 3.89 mmol) is dissolved in 15 ml DMF under N2. K2CO3 (0,70 g, 5.06 mrnol) is added followed by methyl vinyl sulfone (0.41 ml, 4.67 nimol). After stirring 16 h at room temperature, the reaction mixture is diluted with ethyl acetate and water. The layers are separated and the organic layer is washed with water (3x) and brine. The combined aqueous washes are extracted with ethyl acetate. The combined organic extracts are dried (MgSO4) and concentrated under reduced. Purification by dissolving the residue in methylene chloride and precipitating with diethyl ether, repeated several times, gives 1.16 g (59%) pure desired product as a yellow solid: MS APCI (+) mhz 506, 504 (M+ Br pattern) and 400, 398 (M methyl ethyl sulfone Br pattern).

Step B: 6-(4-Bromo-2-chloro.phenylamnino)-’7-fluoro-3-(2-methanesulfonyl-ethyl)-3H-benzoimidazole-5-carboxylic acid cyclopropylmethoxy-amide 111mb 6-(4-Bromo-2-ehloro-pbenylamino)-7-fluoro-3-(2-methanesulfonyl-ethyl)-3H-benzoimidazo1e5-carboxylic acid methyl ester 11cc is subjected to methods previously described to give 6-(4-bromo-2-cbloro-phenylamino)-7-fluoro-3-(2-methanesulfonyl-

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I

ethyl)-311-benzoimidazole-5-Carboxylic acid cyclopropyhnethoxy-amide: MS APCI (+)

m/.z 561, 559 (M+ Br pattern) and MS APCI (-) mlz 559, 557 (M- Br pattern) detected; 1H

NMR (400MHz, DMSO-d6) 311.75 (s, 1H), 8.47 (s, IH), 8.04 (s, 1H), 7.77 (s, 1H), 7.62

(d, 1H), 7.28 (dd, 111), 6.40 (dd, 111), 4.78 (t, 211’), 3.82 (t, 2H), 3.62 (d, 211), 3.07 (s, 311),

1.02 (m, IH), 0.49 (m, 211), 0.21 (m, 211); 19FNMR (376MHz, DMSO-d6) 132.66 (s).

Example 30
The following compounds were prepared similarly using the appropriate methyl

ester and Michael acceptor and methods described previously.

11 d HO

H ci

N H

-

o

j:

1 ljj H
ONO

NF Bt -6 / \ O $ NF" Br
MCC H
H2N H

N_q:N’YF

jj.jj HO,O

N’F LBr
Br

11ff NH2

ri j)
H C1

iii H
H
I

N_6

0

O
N F Br
NFBr

llgg H HO0..N0 of

i 1mm

_____

H_

VII?

0’ N 0
H__6

F Br NC N((" F Br

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U U

H__6 nn OO(L116 Br

O4NF Br

NCNF
HO

HJ:5Br

Example 31

H2N
1=N
0,N

HNF Br

[6-(5-Amino-[1,3,4]oxadiazol-2-y1)-4-fluoro-1Ji-benzoimidazol-5-y1](4-bromo-2-meth)l-phenyl)-amine (24a)
Step A: 6-(4-Bromo-2-me/hy1pheny1arnino)- 7-fluoro-3H-benzoimidazo1e-5carboxylic acid hydrazide 20a
6-(4-Bromo-2-methyl-phenylamino)-7-fluoro-3F1-beuzoixnidazole-5 -carboxylie
acid methyl ester 8a (0.051 g, 0.135 mmol) is suspended in EtOH (5 ml) and hydrazine hydrate (0.118 g, 2.023 rmnol) is added. The reaction mixture is heated at reflux for 16 hours. The reaction mixture is concentrated wider reduced pressure and purified by FCC eluted with 97:3 ethyl acetate:MeOI-I to give 0.041 g (81%) of clean desired product: LC/MS ESI (+) rn/z 378, 380 (M+ Br pattern) detected.

Step B: [6-(5Amino-[J,3,4]oxadiazol-2-yl)--4-fluoro-]H-benzoimidazol-5-yl]-(4bromo-2-inethyl-phenyl)-amine 24a

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acid hydrazide 20a (0.041 g, 0.109 mniol) is suspended in 1,4-dioxane (1.5 ml) and 36 j.tI of a 3 M solution of cyanogen bromide in methylene chloride is added. NaBC03 (9 mg, 0.109 mmol) in water (1.5 ml) is then added. After 16 hours, the reaction mixture is diluted with water and brine and extracted with TRY. The combined organic extracts are dried (Na2SO4) and concentrated under reduced pressure. Purification by FCC eluted with 98:2 ethyl acetate:MeOH gives 24 mg (55%) of pure desired product as a yellow solid: LC/MS ESI (+) rn/z 403, 405 (M+ Br pattern) detected; ’H-NMR (400 Mhz, DMSO-d6) 5 12.97 (s, IH), 8.42 (s, 1H, 7.94 (s, IM, 7.74 (s, llT, 7.36 (s, 21-1), 7,33 d, 111), 7.15 (d, 1H), 6.40 (bs, IH), 2.34 (s, 3H).

.

Example 32

NH2

N\ 0 Me

HNFbCI

[6-(5-Amino-[1,3,4]oxadiazol-2-yl)-4-Jluoro-1H-benzoirnidazol-5-ylJ-(4--chloro-2-methyl-p/ienyl)-amine (24b)
[6-(5-Amino-[1,3,4]oxadiazol-2-yl)-4-fluoro- 1 H-benzoimidazo1-5-yl]-(4chloro-2-methyl-phenyl)-arnine 24b is prepared as described in example 31 starting with 6-(4-chloro-2-methyl-phenylarnino)-7-fluoro-3H-benzoimidazole-5-carboxylic acid methyl ester 8e. LC/MS ESI (+) mlz 359, 361 (M+ Cl pattern) detected; ’H NIMIR (400MHz, DMSO-d6) 8.42 (s, IH), 8.00 (bs, 111), 7.78 (bs, 111) 7.48 (s, 211), 7.22 (s, 11-1), 7.04 (d, 111’), 6.48 (bs, 111), 2.37 (s, 3H).

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Example 33

chloro-phenyO-amine (24c)
{6(5-Amino-[1,3,4]oxadiazo1-2-yl)-4-fluoro-1H-benzoimidaZOl-5-Y1]-(4-brOmO-

2-ch1oro-pheriyl)-amine 24c is prepared as described in example 31 starting with 6-(4-bromo-2-chloro-phenylamino)-7-fluoro-3H-berlzOiflhidaZOlC-5-CarbOXYliC acid methyl ester 8b. MS APCI (+) m/z 425, 423 (M+ Br pattern) and MS APCI (-)m/z 423, 421 (M-Br pattern) detected.

Example 34

N H2
HN 0
Me

HNFCI

6-(4-Chloro-2-methyl-phenylamlno)-7-fluoro-3H-benwimidazole-5-carboxylic acid Iiydrazide (20b)
6-(4-Cbloro-2-methyl-phenylaniino)-7-fluoro-3H-benzoiflhidazole-5-CarbOXyliC
acid hydrazide 20b is prepared as described in example 31, step A from 6-(4-chloro-2-methyl-phenylamino)-7-fluoro-3H-benzoimidazole-5-carboxylic acid methyl ester Se. LC/MS ESI (+) m/z 334, 336 (M+ Cl pattern) detected; ’H NMR (400MHz, DMSO-d6)

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8 13.09 (bs, 111), 9.98 (a. 1ff), 8.40 (s, 11-1), 8.17 (bs, IH), 7.64 (bs, 1131), 7.20 (s, IF!), 7.03 (d, iF!). 6.41 (bs, 111), 4.49 (s, 2H, 2.23 (s, 3H.

Example 35

5_[6(4_C1zloro-2_methy1-phenylaniino)-7-fluoro-3H-benzoimidazo1-5-y1]- f1,3,4Joxadiazol-2-ol (22a)
6-(4--Chloro-2-methyl-phenylamino)-7-fluoro-311-benzoimidazole-5-carboxyliC
acid hydrazide 20b (0.050 g, 0.150 rnmol) is suspended in PhMe (2 ml) and a 20% phosgene solution in PhMe (0.24 ml, 0,45 mmol) is added. The reaction mixture is stirred at reflux under N2 for lh and then cooled to rt. The reaction mixture is quenched by the addition of a 1:1 mixture of TBF and 10% HC1 (20 ml). The layers are separated and the aqueous layer is extracted with THF (3x). The combined organic layer is washed with brine, dried (Na2804) and concentrated under reduced pressure to give 54 mg (99%) of desired product as a yellow solid: LC/MS ESI (-F) in/z 360, 362 (M+ Cl pattern) detected; ’H NMIR (400MHz, DMSO-d) 8 12.64 (s, lH), 8.83 (s, 1H), 7.88 (s, 1H), 7.30 (s, iF!), 7.20 (d, IF!), 7,00 (dd, 1H), 6,38 (dd, iF!), 2.30 (s, 31-1).

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0
Me

HNFCI

(4_Ch1oro2methylpIsenyl)-(4_fltWro6-[1,3,4]oXadiaOl-2-Yl-1H4eflZOimühZZOl-S’Yl)
amine (21a)

acid hydrazidc 20b (0.048 g, 0.144 mmol) is suspended in 3 ml absolute EtOH and HC(OEt)3 (0.60 ml, 3.54 mmol) is added followed by catalytic pTsOHJi20. The reaction mixture is heated to reflux under N2. After 2h, the reaction mixture is cooled to room temperature and concentrated under reduced pressure. Purification by flash column chromatography (97:3 ethyl acetate:MeOH) gives 36 mg (73%) desired product as a light

yellow solid. LC/MS ESJ (+) m/z 344,346 (M+ Cl pattern) detected; 1{ NMR (400MHz,
DMSO-d) 13.10 (bs, 114), 9.39 (s, 11-1), 8.49 (s, 111), 8.10 (bs, IH), 7.78 (bs, 111), 7.20 (d. 1H), 7.00 (dd, 111), 6.41 (bs, IH), 2.18 (s, 3H).

Example 37

SH

N... 0
YH Me

(r
HN iyLP L’c1

5-f6-(4-Chloro-2-inethyl-pheuylarniiw)- 7-fluoro-31I-benzoiinidazol-5-yIJ-[1,3,41axadiazoie-2-thiol (23a)

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acid hydrazide 20b (0,050 g, 0.150 mmol) is suspended in 3 ml absolute EtOfi and cooled to 0°C under N2. CS2 is added (26 mg, 0.346 mmol) followed by powdered KOH (8 mg, 0.150 rnrnol). After stirring at 0 OC for 30 mini the reaction mixture is heated to reflux. After 3.5 h, the reaction mixture is quenched by the addition of water, followed by the addition of ethyl acetate and IN Rd. The layers are separated and the aqueous layer is extracted with ethyl acetate. The combined organic extracts are dried (Na2SO4) and concentrated under reduced pressure to give the desired product as a yellow solid: LC/MS ESI (+) in/z 376, 378 (M+ Cl pattern) detected; ’H NMR (400MELz, DMSO-d6) 8.51 (s, 111), 7.92 (s, 1H), 7.19 (a, 111), 7.12 (s, 111). 6.98 (d, 114), 6.29 (d, l}’l), 2.28 (a, 31-1).

isExample38

H Cl
HN;Br

6-(4-Brorno-2-chloro-pltenylarnino)-7-fluora-3H-.beuzoimidazole-5-carboxy/ic acid methylumide (iloo)
6-(4-Brorno-2-chloro-phenylamino)-7-fluoro-3H-benzoiniidazole-5-carboxylic
acid lOc (0.029 g, 0.076 mmol) is dissolved in NN-dimethylformarnide (1.lmL). HOBT (0.016 g, 0.10 mmol), triethylamine (0.028 rnL, 0.20 mmol), methylamine (0.059 mL, 0.12 mmol, 2 M solution in tetrahydrofuran), and EDCI (0.019 g, 0.10 mmol) are added consecutively to the reaction mixture at room temperature. The solution is stirred at room temperature for 16 hours under N2. The reaction mixture is poured into a separatory funnel and diluted with ethyl acetate and water and the layers separated. The ethyl acetate layer is washed successively with aqueous saturated N1=4C1 (2x), brine (lx), aqueous

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S

saturated sodium bicarbonate (2x), water (lx), and brine (lx), dried and concentrated under reduced pressure. The resulting solid is purified by FCC (eluting with 19:1 methylene chloride:rnethanol) to yield 0.013 g (42%) of the pure desired product. MS APCI (+) m/z 397, 399 (M+, Br pattern) detected; ’H NMR (400 MHz, t)MSO-d6) 8.76 (broads, 1H), 8.69 (m, 1H), 8.41 (s, 1H), 776 (s, 1ff), 7.63 (d, 111), 7.30 (dd, 111), 6.50 (dd, 1ff), 2.76 and 2.75 Cs and s, 3ff total, amide rotainers). ’F NMR (376 MHz, DMSO-d6) 132.69 (s).

Example 39
The following compounds are prepared using methods similar to that described above in Example 38 by using the appropriate carboxylic acid and amine. In those cases that contain two amine functionalities, the appropriate mono Boc protected amine is used in the coupling reaction and the Boc group is later removed in a final step under standard TFA deprotection conditions.

llpp (NH
ON)
I H
HN"TF

lluu H
0

HNfF

H2N llvv H

I I HN F CI HN FBr
1 in
ii

1 lww 1çs

ONH

I H CI
HN; FBr
HN"1F Br

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liss

L NO N NH

H

HNTF Br
HNYF Br
11’N 0

HN/F CI

Example 40

HNFtLBr 4 [6-(4-Bronio-2-chloro-p/zenylamhw)-7-fluora-3H-benzoisnidazol-5-ylJ-metlzanol(lOe)

6-(4-Bromo-2-cbloro-phenylamino)7-fluoro.-3Hbenzoimidazole-5-carboxylic
acid methyl ester 8b (1.06 g, 2.65 nmiol) is suspended in tetrahydrofuran (25 mL) and cooled to -78 T. Lithium aluminum hydride (8.03 mL, 8.03 rrnnol, 1M solution in tetrahydrofuran) is added dropwise to the reaction mixture. After stirring for 10 minutes at 78 °C, the reaction mixture is warmed to 0 °C and becomes a homogeneous solution. The reaction mixture is stirred for 5 minutes at 0 °C and then cooled again to -78 °C. The reaction mixture is quenched with MeOH, diluted with Rochelle’s salt, warmed to room temperature and stirred for 1 hour. The reaction mixture is then poured into a separatory fmmel, diluted with ethyl acetate, and the layers separated. The aqueous phase is extracted with ethyl acetate. The combined ethyl acetate layers are dried (Na2804) and concentrated under reduced pressure to yield 0.98 g (100%) of the pure desired product as a pale yellow solid. MS ESI (+) mlz 370, 372 (M-t-, Br pattern) detected.

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Example 41

I

N_(

HNF Br

5(4Brorno_2_ch1oro.pheIlylW1zi1zo)_7_fiUOrO-3H_beflZO(midaZOle’5"CarbaldehYde (JOf) [6(4Brorno2-chloro-pbenylan1ino)-7-flu0rO-3R-benZOimidaZO1-5-yl]methanO1
lOe (0,96 g, 2.58 mmol) is dissolved in tetrahydrofuran/acetone (1:1, 15 mL), and Mn02 (2.24 g, 25.8 mmol) is added. The reaction mixture is stirred at 50 °C for 10 hours under N2. The reaction mixture is filtered through silica gel and eluted with methylene chloride/methanol (10:1, 1 L). The filtrate is concentrated under reduced pressure to a small volume and then filtered through an Acrodisc syringe filter to remove small amounts of Mn02 that passed through the silica gel. The filtrate is concentrated under reduced pressure and the residue is purified by flash column chromatography (eluting with 20:1 methylene chloride:methanol) to yield 0.81 g (85%) ofthe pure desired product as a bright yellow solid. MS ESI (+) m/z 368, 370 (M-I-, Br pattern) detected.

1_/6-(4_Jiromo-2-chloro-phenylarnino)-7-fluoro-3-rnethyl-311-beflZOimidazol-5-y1]-2-hydroxy-et/tanoaae (lOg)
Step A: l[6-(4-Bromo-2-ch1oro-pheny1amino).7-fluoro-3-methyl-31Lbenzoirnidazo1-5-yl]-2-mthoxymet1zoxy-et1zanol IN

li

C4
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To a solution of tributyl-methoxyrnetboxymethyl-stannane (864 mg, 2.37 mmcl,
prepared by the procedure reported in.L Oig. Chen. 1988, 53, 4131) in TLIF (S mL) at -
78 °C is added n-BuLi (0.94 mL, 2.35 rnmol, 2.5 M solution in hexane). After stirring for
3 a solution of 6-(4--bromo-2-chloro-phenylamino)-7-fluoro-3-methyl-3H-benzoimidazole-5-carbaldehyde lOb (59 mg, 0.15 mmol) in THF (2 mL) is added at -78
T. After stirring for 40 min at -78 °C, the reaction is quenched with saturated aqueous N1LCl at -78 °C, warmed to room temperature, and diluted with EtOAc. The organic layer is washed with brine, dried over M9SO4, filtered, concentrated, and purified by flash chromatography (1.5 % MeOH in CH202) to give the desired product (45 mg, 64%): MS MCI (+) rn/z 458,460 (M--, Br pattern) detected.

Step B: i-[6-(4-Bromo-2-chloro-phenylwniizo)-7--fluoro-3-methyl-3H-benzoirnidazol-5-yIJ-2-rnetharymethoxy-ethanone 1Oj
A solution of 1-[6-(4-bromo-2-chloro-phenylamino)-7--fluoro--3-rnethyl3FI-benzoimidazol-5-ylJ-2-methoxymethoxy-ethanol iOi (44 mg, 0.096 mmol) and the Dess-Martin periodinane (49 mg, 0.12 mrnol) in CH2Cl2 (1.5 mL) is stirred for 1.5 h at A. The reaction mixture is diluted with ether (3 mL). Saturated aqueous NaHCO3 (1 mL) containing sodium thiosulfate pentahydrate (74 mg) is added. The resulting mixture is stirred for 10 min and diluted with EtOAc. The organic layer is washed with saturated aqueous NaHCO3 and brine, dried over MgSO4, filtered, and concentrated in i’acuo to give a crude material which is purified by flash chromatography (1.5% MeOH in CH2C12) to afford the desired product (31 mg, 71%): MS APCI (+) m/z 456, 458 (M+, Br pattern) detected.

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Step C: 1-[6-(4-Broino-2-chloro-phenylamino)-?-fluoro-3-methyl-3H-benzoimidazol-5-ylJ-2-hydroxy-ethanone lOg
A mixture of 1-[6-(4bromo-2ch1oro-pheny1amiflO)-7-f-1UOrO-3-methYl-3H-benzoirnidazol-5-yl]-2-rnethoxyrnethoxy-ethaflOfle 1 Oj (15 mg, 0.033 nunol), 10% aqueous HCl (0.3 mL), methanol (0.01 mL), and water (0.05 mL) is stirred for 3 days at
11. The reaction mixture is neutralized with saturated aqueous NaHCO3, and diluted with EtOAc. The organic layer is washed with brine, dried over MgSO4, filtered, concentrated in vacuo, and purified by flash chromatography (1.5% MeOR in CH202) to afford the desired prouduct (7.3 mg, 54%): MS APCI (+) rn/z 412, 414 (M+, Br pattern) detected;

1fl NIvIR (400 MHz, acetone-d6) 8.64 (s, 1R), 8.34 (s, in), 8.16 (s, 111), 7.58 (d, 1H),
7.31 (dd, 1H), 6.59 (dd, 11-1), 4.94 (s, 2H), 4.06 (s, 3H); 19F NIVIR (376 MHz, acetone-d6)  132.45 (s, IF).

Example 43

-HN

o

t1’Br

1[6(4-Bromo-2-chloro-phenyIamino)-7-fluoro-3H-benzoi.1nidazo1-5-yI]-2-hydrOxfr ethaiwne (10k)
Step A: 76(4Brorno-2-chloro-phenylwnino)-7-fluoro-3H-benzoimidazol-5-y/j-2-rnethoxyinethoxy-ethanol 101
6.-(4Bromo-2-ch1oro-pheny1amino)-7-fiuoro-3H-benzoimidazo1e-5-caIirn1dehYde
lOt is treated with tributyl-methoxyrnethoxymethyl-statmane according to the procedure

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described in Example 42, Step A to yield compound 101. MS APCI (+) rn/z 444, 446 (M+, Br pattern) detected.

Step B: J_6-(’4Brorno2--ehloro-phenylarnino)-7-fluoro-3JI-benzoimidazoI-5-y1J-2-methoxymethoxy-ethanone lOin
To a solution of oxaiyl chloride (0. 11 mL, 0.22 mmol) in CH202 (1 mL) at -78 °C
is added DMSO (0.016 mL, 0.22 mmcl), After stirring for 3 a solution of l-[6-(4-bromo-2-ehloro-pbenylaniino)-7-fluoro-3H-benzoirnidazol-5-yl]-2-methoxymethoxy-ethanol 101 (25 mg, 0.056 mrnol) in methylene chloride (lmL) is added. The resulting solution is stirred for 30 rain at -78 T. TEA (0.1 mL, 0.71 mmcl) is added. The reaction mixture is slowly warmed to room temperature, stirred for 5 nun at room temperature, and diluted with water and CH202. The organic layer is separated, dried over MgSO4, filtered, and concentrated to give the crude product which is directly used without further purification.

Step C:]-[6-(4-Bromo-2-chloro-phenylarnino)-7-fluoro-3lLbenzoimidazol-5-ylj-2-hydroxy-ethanone 10k
1 -[6-(4-Bromo-2-chloro-pheny1amino)7-fluoro-3H-benzoimidazol-5-yi2.- methoxymethoxy-ethanone tOrn is deprotected according to the procedure described in Example 42, Step C to yield compound 10k. MS APC1 (+) rn/z 398, 400 (M+, Br pattern) detected; ’H NMR (400 MHz, CDuOD) 5 8.38 (s, iLl), 8.04 (s, 1H), 7.52 (d, 1H), 7.22 (dd, iLl), 6.53 (dd, 11, 4.90 rn, 21; 19F NMR (376 MHz, CD30D) 133.96 (s, IF).

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0

HNFbBr

1-[6-(4-Bronw-2..dzloro-plienylamiiW)- 7_fluoro-3H-benzoimidazol-5-Y112’ethOXY ethanone (IOn)
Step A: 1[6_(4_Bromo2_chloro-p1zenylarnino)-7-flUOrO-3H-be2ZOi?flida0lS-YlJ2 ethoxy-ethanol lOo
To a solution of lithiomathyl ethyl ether in THF (6 mL) (prepared from 4,4’.di-tert-butylbiphenyl (585 mg, 2.20 mmol), Li (18 mg. 2.59 mmol), and EtOCIi2CI (0.20 mL, 2.05 mmol) by the procedure reported in Tetrahedron 1996, 52, 1643) is added a solution of 6(4-bromo-2-chIoro-phenylamino)-7-uluorO-3H-beflZ0rn11daZO1e-5-carbaldehyde lOf (29 mg, 0.080 mmol) in THF (1 mL) at -78 °C. The resulting solution is stirred for 1 h and then quenched with saturated aqueous NM4CI at -78 °C, warmed to room temperature, and extracted with EtOAc. The organic layer is washed with brine, dried over MgSO4, filtered, concentrated in vacuo, and purified by flash chromatography (100% CH202 to 3% to 5% MeOH in C11202) to give the desired product (15 mg, 44%): MS APCI (+) rn/z 428, 430 (M+, Br pattern) detected.

Step B:
etizoxy-ethanone iOn
The title compound is prepared from 1-[6(4-bromo-2-ch1oro-pheny1amirio)7-fluoro-3Hbenzoimidazol-5-yl]-2-ethOXY-ethaflOI lOo according to the procedure describcd in Example 42, Step B except that the reaction mixture is not treated with saturated aqueous NaHCO3 containing sodium thiosulfate pentahydrate. MS APCI (i-)

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?n/z 426, 428 (M+, Br pattern) detected; 1H NMR (400 MHz, CD30D) 6 8.36 (s, 111), 8.04 (s, 111), 7.51 (d, 111), 7.21 (dcl, 111), 6.51 (dd, 1B), 4.76 (s, 211), 3.57 (q, 211), 1.19 (t,
313) 19F NIVLR (376 MHz, CD30D) 133.96 (s).

Example 45

FOBr

l-[6-(4-Bromo-2-clzioro-phenylamilto)- 7-fluoro-311-benzoimidazol-5-ylj-2-methoxy-

ethanone

1-6-(4-Bromo-2-ch1oro-phenylamino)-7-f1uoro-3H-benZoimidaZO1-5-yl]-2-methoxy-ethanone is prepared from 6-(4-bromo-2-chloro-phenylamino)-7-fluoro-3H-benzoimidazole-5-carbaldehyde JOf and lithiomcthyl methyl ether by the procedures described in Example 44. MS APCI (+) m/z 412,414 (M+, Br pattern) detected.

Example 46

BnO 1-01
H C1

I N):5,

HNFBr

2Benr,y1oxy_l_f6-(4bromo-2chloro-p1ienyla,ninO)-7-flUOro-3JJ-benzOimidaZOl-5-Y1J-

.

ethanone (I 0q)
Step A: 2-Benzyloxy-1-[6-(4-bromo-2-chloro-phen.vlamino)-7-fluoro-3H-benzoiinidazol-5-yl]-ethaiwl]Or

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To a solution of benzyloxymethyllithium in THF (2 mL, prepared from n-Bu3SnCII2OBn (505 mg, 1.23 minol) and n-BuLi (0.49 mL, 1.22 mmol, 2.5 M solution in hexane) by the procedure reported in J. Am. Chem. Soc. 1978, 100, 1481) is added a solution of 6-(4-bromo-2-chtoro-phenylaniino)-7-fluoro--31-I-benzoimidazole-5-carbaldehyde 101 (51 mg, 0.14 rnmol) in TIfF (3 mL) at 78 °C. The resulting solution is stirred for 1 h at -78 T. The reaction is quenched with saturated aqueous NthC1, and extracted with EtOAc. The organic layer is dried over MgSO4, filtered, concentrated in vacuo, and purified by flash chromatography (100% CH2C12 to 3% MeOR in CH202) to afford the desired product (46 mg, 68%): MS APCI (+) m/z 490, 492 (M+, Br pattern)

detected.

Step B: 2-Ben2yloxy-1-’[6-(4-brorno-2-chloro-phenylarnino)-7-fluoro-3H-benzonnidazol-5-yl]-ethanone lOq
The title compound is prepared from 2-henzyloxy- 1 -[6-(4-bromo-2-chloro-phenylamino)-7-fluoro-3H-benzoftnidazol-5-yl]-ethanol lOr by the procedure describcd in Example 42, Step B except that the reaction mixture is not treated with saturated aqueous NaHCO3 containing sodium thiosulfate pentahydrate: MS APCI (+) nilz 488, 490 (M+, Br pattern) detected; ’H NMR (400 MHz, CD30D) 8.37 (s, II), 8.02 (s, 1R), 7,51 (d, 1H), 7.26 (m, 5H), 7.19 (dd iB), 6.46 (dd, 1H), 4.77 (s, 2H), 4.58 (s, 211; 9F NMR (376 MHz, CD30D) -134.52 (s).

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3L.Y
WO 93/077914 PCT/US03/07864 Example 47

methanesulfonyl-etharione (]ON)
Step A: J[6(4-Brorno-2-chloro-phenylarnino)-7-flUOrO-3H-beflZOimidaZ0l-5Yi]-2-
methanesuifonyl-ethanol 101
To a solution of methyl sulfone (65 mg, 0.68 mmol) in THF (1.5 mL) is added a
solution of n-BuLl (0.27 mL, 0.68 mmol, 2.5 M solution in hexane) at -78 T. After
stirring for 5 nun, HMPA (0,1 mL) is added. After stirring for additional 10 min, a

40 solution of 6-(4-bromo-2-chloro-phenylamino)-7-flUOrO-3H-beflZ011mdaZOlC-5-
carbaldehyde 101(26 mg, 0.069 mmol) in THF (1 mL) is added. The resulting solution
is stirred for 1.5 h at -’-78 T. The reaction is quenched with saturated aqueous NI-14C1,
warmed to room temperature, and diluted with EtOAc. The organic layer is washed with
water, dried over MgSO4, filtered, concentrated in vacuo, and purified by flash
chromatography (3% MeOH in C11202) to give the crude desired product (31 mg, 96%)
which is used directly without further purification: MS APCI (+) rnlz 462, 464 (M+, & pattern) detected,

Step B: 1[6-(4-.Bromo--2-chloro-phenylamino)-7-fluOr0-3H-benzoimidaZOl-5--YlJ-2-
rnethanesu1fonplethanone lOs
The title compound is prepared from I -[6-(4--bromo-2-chloro-phenylamino)-7-fluoro-31-I-benzoimidazol-5-yl]-2-methanesulfonyl-ethaliOl lOt by the procedure described in Example 42, Step B except that the reaction mixture is not treated with

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LI

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saturated aqueous Na1CO3 containing sodium thiosulfate pentahydrate: MS APCI (+) ,n/z 460, 462 (M+, Br pattern) detected; ’H NIv1R (400 MHz, acetone-d6) 8 8.44 (s, 1H), 8,33 (s, lii), 7.59 (s, 111), 7.32 (d, 1H), 6.68 (dd, lii), 5.00 (s, 111), 3.15 (s, 31-I); 19F NMR (376 MHz, acetone-d6) 132.97 (a).

Example 48

HO

OH

HNct5er

1-[6-(4-Broino-2-chloro-pheny!arnlno)-7-fluoro-3H-benzoirnidazol-5-yl]-ethane-1,2-diol (lOu)
Step A: l-[6-(4-Bromo-2-c/zloro-phenylamino)-7-fluoro-3H-benzoimidazol-5-yl]-2-(eopropoxydimethyl-si1an>’l)ethano1 iCy
To a solution of the Grignard reagent prepared from Mg and chioroniethyl dimethylisopropoxy silane (Org. Synth. 1992, 69, 96) [4.4 mL, 3.26 nimol, 0.74 M solution (based on 90% purity)] in TI-IF, is added a solution of 6-(’4-.bromo-2-chloro-phenylamino)-7-fluoro3H-benzoimidazole-5--carbaldehyde lOf (200 mg, 0.54 mmol) in TI-IF (1 mL) at -78 T. Alter stirring for I h at 78 °C, the reaction is quenched with saturated aqueous NH4CI, and extracted with EtOAc. The organic layer is dried over M9SO4, filtered, concentrated in vacuo to afford the crude desired product which is directly used without further purification.

Step B: l-[6-(4-Bromo--2-chloro-phenylamino)- 7-fluoro-3H.-benzoimidazol-5-ylJ-ethane-1,2-’diol IOu

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, J
WO 03/077914 PCT/US03/07864 To the crude 1
5-yl]-2-(isopropoxy-dimethyl-silanyl)-ethanol lOv in MeOH-THF (5 mL-5 mL) is added KRC03 (54 mg, 0.54 mmol), and KF (74 mg, 1.27 mmol), and 30% aqueous H202 (0.20 mL) at it After stirring for 3.5 h at room temperature, the reaction mixture is diluted with water, and extracted with EtOAc. The organic layer is dried over MgSO4, filtered, concentrated in vacuo, and purified by flash chromatography (8% to 10 % MeOH in C112C12) to give the desired product (74 mg, 341/o): MS APCI (+) m/z 400, 402 (M–, Br pattern) detected; ’H NMR (400 MHz, CD30D) 8 8.20 (s, 11-1), 7.62 (broad s, 1H), 7,47 (d, 1H), 7.14 (dd, 1H), 6.30 (d, 1H), 4.96 (t, 1H), 3.64 (m, 2H); 19F NIvIIR (376 MHz, CD3OD) -136.87 (s).

Example 49

CI

’ N’7’F ’Br

f6-(4-Bromo-.2-chloro-phenylarnino)-7-fluoro-3-melhyl-3H-benzoimidazol-S-vl]- pyridin-2-yl-rnethanol (IOw)
To a solution of 2-bromopyridine (0.10 mL, 1.04 mmol) in THE (3 mL) at -78 °C
is added n-fluLi (0.39 mL, 0.98 mmol, 2.5 M solution in hexane). After stirring for 10 min at -78 °C, a solution of 6-(4-bromo-2-chloro-phenylaruino)-7-fluoro-3-methyl-3H-benzoimidazole-5-carbaidehyde lOb (25 mg, 0.064 mmol) in TIIF (1 mL) is added. The resulting reaction mixture is stirred for 1.5 h at -78 °C, quenched with saturated aqueous NII4C1, and extracted with EtOA.o. The organic layer is dried over M9SO4, filtered, concentrated in vacuo, and purified by flash chromatography (2.5% MeOH in CH202) to

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afford the desired product (18 mg, 62%): MS APCI (+) m/z 461, 463 (M+, Br pattern) detected; 1H NMR (400 MHz, CDTOD) 8 8.31 (d, 1ff), 8.16 (s, 1H), 7.65 (in, 311), 7.38 (d, 111), 7.10 (m, 1ff), 7.00 (dd, 11-1), 6.11 (dd, 111), 6.05 (s, 111’), 3.94 (s, 311); F N1vIR (376 Ivfflz, CD30D) 135.79 (s).

Example 50

HN: FbBr

(4-Brorno-2-cliloro-plzeny!)-(4-fluoro-6-oxazol-5-yl-JH-benzoimidazol-5-yI)-arnine (lOX)
Step A: [6-(4-Brorno2chloro-phenylamino)-7-fluoro-3(2-rnethanesulftrnyl-ethy1)-3H-benzoimidazol-5-yI]-methanol 10y
6-(4Bromo2-ch1oro-phenylamiuo)-7-fluoro-3-(2-methanesulfony1..ethyl).3H-benzoimidazole-5-carboxyiic acid methyl ester lIce (0.3 00 g, 0.594 mrnol) is suspended in a mixture of EtOH (6 ml) and TIfF (4 ml) under N2. NaBI11 (0.112 g. 2.97 mmol) is added. After approximately 4 days stirring, reaction mixture is quenched by the addition of AcOH until the reaction mixture reaches pH 7. The reaction mixture is concentrated to dryness under reduced pressure and the residue partitioned between ethyl acetate and water. The layers are separated and the organic layer is washed with water (3x), brine, and dried (Na2SO4). The organic layer is concentrated under reduced pressure until a white precipitate forms which is collected by filtration to give 0.225 g (79%) clean desired product: LC/MS BSJ (+) m/z 478,476 (M+ Br pattern) detected.

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Step B:
benzoimidazole-5--Carbaldel1yde JOz

benzoimidazol-5-yl]-methanol lOy (0.050, 0.105 mmol) is dissolved in 11 THF:acetone (2 ml) under N2 and Mn02 (0.046 g, 0.524 mmol) is added. The reaction mixture is stirred at room temperature for 16 h, and then at 55 °C for 5 h. Additional Mn02 (0.046 g, 0.524 mmol) is added and the reaction mixture stirred at 55 °C for 2 h. The reaction mixture is concentrated to dryness and the residue dissolved in 10:1 methylene chloride:MeOH. The solution is filtered through a silica gel plug eluted with 10:1 methylene chloride:MeOH. The resulting filtrate is concentrated under reduced pressure to give 41 mg (82%) desired product as a bright yellow solid.

Step C: (4-Broino2-ch1oro-pheny1)-(4-fluoro-6-Qxazol-5--Yl-1I!-be1lZOitflidaz0l-$Yl)- amine lQx
6-(4-Bromo-2-chlom-pbenylaminO)-7-flUOrO-3-(2-methah1eSUlfOflyl-ethy1)-3H benzoimidazole-5--carbaldehyde lOz (0.025 g, 0.053 mmol) is suspended in MeOH (2 ml) and K2CO3 (0-015 g, 0.105 mmol) is added followed by tosylmethyl isocyanide (0.011 g, 0.058 mmol). The reaction mixture is heated to reflux under N2 for 16 h. After cooling, additional tosyirnethyl isocyanide (0.011 g, 0.058 mmol) is added and the reaction mixture heated to reflux under N2 for 16 h. The reaction mixture is cooled to room temperature, concentrated under reduced pressure and dissolved in ethyl acetate. The organic solution is washed with water and brine. The combined aqueous washes are extracted with ethyl acetate. The combined organic extracts are dried (Na2SO4) and concentrated under reduced pressure. Purification by flash column chromatography eluted with 20:1 methylene chloride:MeOH gives 4 mg (18%) desired product lOx and I 109

-, WO 03/077914 PCTIUS03/07864 mg (4%) (4-brorno-2-chloro-phenyl)-.[4-fluoro-l-(2-metbanesu1fony1-ethy1)-6-oxazol-5-
yl- 1H-benzoiniidazol-5-yl]-amine.
(4-Bromo-2-chloro-phenyl)-(4-fluoro-6-oxazol-5-Yl-I H-benzoimidazol-5-yl)-
amine lOx. LC/MS ESI (+) m/z 409, 407 (M+ Br pattcm) detected; ’11 NMR (400MHz,
McOH-d4) 8.33 (s, 1H), 8.24 (s, 111), 7.94 (bs, 111), 7.51 (d, lH, 7.33 (s, 111), 7.07 (dd,
lIT), 6.14 (dd, 111).
(4-Bromo-2-chloro-phenyl)-[4-fluoro-1 -(2-methanesulfonyl-ethyl)-6-oxazol-5-yl-1H-benzoimidazo15-y1]-aniine. LCIMS £51 (1) rn/z 515, 513 (M+ Br pattern) detected; l1 NMR (400MH7, MeOH-d4) 8.39 (s, 111), 8.28 (s, 11-1), 8.03 (s, II1, 7.52 (d, III), 7.37 (s, 111), 7.07 (m, 114). 6.14 (dd, 111), 3.83 (t, 211), 2.99 (s, 3111), 1.18 (t, 211).

Example 51

(4-Brorno-2-chloro-phenyl)-[4-fluoro-6-(311-imidazo/-4-y!)-1H-be,izoirnidazol-5-yl/- amine (lOaa)
Step A: (’4-Bromo-2-chloro-phenvl)-{4-fluoro-1-(2-rnethanesulfony1-ethyl)-6-[4-(’to1uene-4-sulfonyl)-4,5-dihydro-oxazol-5-yl]-JH-benzoirnidazo%-5-yJ}-arnine lObb 6-(4-Bromo-2-chioro-phenylamino)-7-fluoro-3-(2-methanesulfonyl-ethyl)-311-benzoimidazole-5-carbaldebyde lOz (0050 g, 0.107 nimol) is suspended in EtOH (0.5 ml) under N2 and tosylmethyl isocyariide (0.020 g, 0.105 mmol) is added followed by catalytic NaCN (-4 mg). After 2 Ii, 2 ml TUF is added to assist with solubility. After stirring for 16 h at room temperature, a second equivalent of tosylmethyl isocyanicle

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(0.020 g, 0.105 mmol) is added. After 8 h, the reaction mixture is concentrated under reduced pressure and used as is in the next reaction: LC/MS ES1 (+) rnlz 671, 669 (M+ Br pattern) detected.

Step B:
yl]-ainine lOaa
(4-Bromo-2-chloro-phcnyl)- {44luoro- 1-(2-rnethanesulfonyl-ethy1)-6-[4-(toluene 4sufonyl)4,5dihydro-oxazo15-yl]-1H-benZoitflidaZ0l-5-Y1} -amine lObb (0072 g, 0.107 minol) is treated with 2.4 ml of a 2.0 M NH3 in Me011 solution in a sealed pressure tube. The reaction mixture is then heated to 90 °C with stirring for 20 b and furthered stirred at room temperature for 3 days. The reaction mixture is transferred to a round bottom flask and concentrated under reduced pressure. Purification by flash column chromatography, twice, eluted with 10:1 methylene chloride:MeOH, followed by successive trituations with methylene chloride and then diethyl ether gives 3 mg (7%) desired product: LC/MS ESI (-I-) m/z 408, 406 (M+ Br pattern) detected; 1E1 NMR (400MHz, MeOJ{-d4) 8.23 Cs, lH. 7.87 (s, 1H), 7.74 (s, 1H, 7.46 m, 111), 7.32 (d, 111), 7.05 (in, 111), 6.20 (dd, 111).

Example 52

H
N 0

H C1

C’6Br

6-(4-Bro,no-2-cbloro-phenylwnino)-7-cI:loro-3-metlsyl-3H-benzoisnidazok-5-carboxylic acid (2-J:ydroxy-ethoxy.)-arnide (lOcc)

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Step A: 3-Cltloro-2,4-djfluoro-5-nitro-benzoic acid 2a
3-Chloro-2,4-difluoro-benzoic acid la (3.00 g, 15.6 mmoJ) is added to a stirred solution of concentrated H2SO4 (16 mL) and fuming nitric acid (0.85 mL, 20.3 mrnol). After 3 hours a precipitate forms. The yellow slurry is poured onto ice water (100 mL). The aqueous mixture is extracted with diethyl ether (3x). The organic extracts are dried (Na2SO4) and concentrated wider reduced pressure to give 3.50 g (95%) of clean desired product as a pale yellow solid.

Step B: 4-Arnino-3-ch1oro-2-fluoro-5-nitrohenzoic acid 3a
Ammonium hydroxide solution (6.88 g, -30% in water, 58.9 mmol) is added to a solution of 3-chloro-2,4-dffluoro-5-nitro-benzoic acid 2a (3.5 g, 14.7 mmol) in water (16 mL) at 0 °C with stirring. Upon completion of the ammonium hydroxide addition the reaction mixture is warmed to room temperature. After 5 hours the reaction mixture is cooled to 0 °C and concentrated HC1 is carefully added until the pH of the reaction mixture is near zero. The solid is collected by filtration and washed with water and diethyl ether. The solids are transferred to a round bottom flask as a solution in MeOH and EtOAc and concentrated under reduced pressure to give 2.96 g of a yellow solid. The filtrate is partitioned between diethyl ether and water and the organic layer is washed with brine. The combined organic extracts are dried (Na2SO4) and concentrated under reduced pressure to give 0.65 g of product. Recovered a total of 3.61 g (104%) of pure desired product, that is carried forward without further purification.

Step C: 4-Arnino--3-chloro-2-fluoro-5-nitro-benzoic acid methyl ester 4a

To a stirred solution of 4-amino-3cbloro-2-fluoro-5-nitro-benzojc acid 3a (3.61 g,
15.4 rnmol) in TIfF (30 mL) and MeOH (10 mL), TMS diazomcthane (9.23 mL, 2.0 M

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solution in hexanes, 18.5 mmol) is added. After completion of reaction, the reaction mixture is concentrated via rotary evaporation with acetic acid in the trap. The recovered oily solid is triturated with diethyl ether to provide 1.51 g of a yellow solid. The filtrate is concentrated and triturated with diethyl ether to give an additional 0.69 g of yellow solid. A total of 220 g (57%) ofpure desired product is recovered.

Step D: 4-Amino-3-chloro-5nitro-2-phenylarnino-benzoic acid methyl ester 5c 4-Arnino3-ch1oro-2’fluoro5-nitro-’benzoic acid methyl ester 4a (2.20 g, 8.84 nmiol) is suspended in MeOH (9A mL) and aniline (3.22 mL, 35.4 minol) is added. The reaction mixture is heated to reflux with stirring under a nitrogen atmosphere. After 19 hours, the reaction is complete. Distilled water (3.22 mL) is added to the reaction mixture and refluxing is continued for one hour. The reaction mixture is cooled to 0 °C in an ice bath for 20 minutes. The reaction mixture is filtered and washed with 3:10 distilled water/MeOH (65 mL total) and then with MeOH. The solid is dissolved with CH202 and concentrated under reduced pressure to give 2.40 g (84%) of pure desired product. MS APCI (-) m/z 320.3 M1) detected.

Step E. 4,5-Diamino-3-chloro-2-phezylamino-henzoic acid methyl ester 6b 4-Amino-3-chloro-5-nitro-2-phenylamino-benzoic acid methyl ester Sv (0.50 g,
1.55 mmol) is dissolved into 2:1 EtOHJMeOH (15.5 mL). Saturated aqueous NH4C1 (15 mL), Zn powder (1.02 g, 15.6 mmofl, and TIfF (10 mL) are added. After stirring for 20 hours, the reaction mixture is diluted with CH2Cl2/Tl{F and water. The organic layer is washed with water (3x). The combined organic extracts are dried (Na2SO4) and concentrated under reduced pressure. The solids are triturated with ether to give 0.32 g (70%) clean desired product.
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Step F. acid methyl

ester 7c

acid methyl ester 6b (0.32 g, 1.09
mmol) and formamidine acetate (72 rug, 1.64 mmol) in EtOH (36 mL) are heated, with
stirring, to 80°C. After 44 hours, the reaction mixture is cooled to room temperature and
diluted with EtOAc and washed with water (3x), saturated NaHCO3, and brine. The
combined organic extracts are dried (Na2SO4) and concentrated under reduced pressure to
give 033 g (99%) clean desired product as a solid. MS APCI (+) m/z 302.3 (M--1)

detected.

40 Step G: 6-(’4-Brono--phenyla7nino)- 7-chloro-3H-benzoimidazole-5-carboxylic acid methyl
ester 89

7Cli1oro6-pheny1amino-3H-beflzOimidaZOle-5-CarboXYliC acid methyl. ester 7c

(0.327 g, 108 mmol) is dissolved into DMF (16 mL) and NBS (0.193 g, 1.08 mmol) is
added. After one hour, the reaction mixture is quenched by the addition of saturated
aqueous NailS03. The reaction mixture is then partitioned between EtOAc/TIE[F and
water. The organic layer is washed with water and brine. The combined organic extracts are dried (Na2SO4) and concentrated under reduced pressure. The recovered solid is triturated with ether to give 0.225 g (54%) pure desired product. MS ESI (+) m/z 382, 384 (M+, Br pattern) detected.

Step H:
acid methyl ester lOdd

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o-(4-Bromo-phenylamino)-7-chloro-3H-bcnzoimidazole-5-carboxylic acid methyl
ester 8g (0.225 g, 0391 mmol) is dissolved in DMF (2 mL) and NCS (79 mg, 0.591 mmol) is added. After the NCS is in solution concentrated HCI (0.005 mL, 0.059 mmol) is added. After 2 hours, sodium bicarbonate, water and NaHS03 are added to the reaction mixture. Solids are filtered and washed with water and ether to give 0.141 g (57%) of
clean desired product as a tan solid. MS MCI (-) in/z 414, 416 (M-, Br pattern) detected.

Step I: 6(4-Bromo-2-chloro-phenylarnino_7-chloro-3-methvl3H_f,enzojmjdazo1e_5
carboxylic acid methyl ester 1 Qee
6-(4-Bromo-2-chloro-pbenylarnino)-7-chloro-3H-benzoiniidazole-5-carboxylic
acid methyl ester lOdd (0.141 g, 0.34 mmol), potassium carbonate (0.141 g, 1.02 rnmol),
. and lodomethane (0.063 mL, 1.02 mmol) are dissolved in dirnethylfonnanuide (3 mL. After 20 hours, the reaction mixture is diluted with fitOAc and washed with water (3x),
potassium carbonate, and brine. The organic layer is dried (Na2SO4) and concentrated to
a brown oil. The N3 and NI alkylated regioisomers are separated by flash
chromatography (EtOAc). The rccovery of the N3 alkylated regioisomer is 20.4 mg
(28%). MS ESI (4-) m/z 428,430 (M+, Br pattern) detected.

Step.1: 6-(4-Rromo-2--chioro-phenylarnino)-7chloro3,nethyl_3Hbe,jzo1mjdazole5 cczrboxy(ic acid 10ff

carboxylic acid methyl ester lOee (21 rug, 0.048 mmol) is dissolved into 2:1 T[JF/water (1.2 mL) and NaOI-I (0.190 mL, 1.0 M aqueous solution, 0.190 nrmol) is added. After stirring for 4 hours the reaction is diluted with water and acidified to pH 2 by addition of 1.0 M HC1. The mixture is then extracted with 3:1 EtOAc/TH1F (3x), dried (Na2SO4) and

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Step K: 6-’4-Bromo--2-chloro-phenylamino)-7-chloro-3-methyl-3H-.benzoimidazole-S-carboxylic acid (2-vinylox),ethoxy)-arnide lOgg 6-(4-Bromo2-ch1oro-phenylamino)-7-chloro-3-methyl-3H-benzoimidazo1e-5-
carboxylic acid 10ff (32 mg, 0.077 mmol), 0-(2--vinyloxy-ethyl)-hydroxylamine (0.010
mL, 0.092 minol), HOBt (13 mg, 0.093 mmol), tziethylaniinc (0.011 mL, 0.077 mmol),
and EDCI (19 mg, 0.10 mmol) are dissolved into dimetbylfonnamide (1.0 niL) and
allowed to stir under a nitrogen atmosphere at room temperature for 24 hours- The
reaction mixture is diluted with EtOAc, washed with water (3x), 10% potassium
. carbonate (2x), saturated ammonium chloride, brine, dried (Na2SO4), and concentrated under reduced pressure to give 39 mg of 85% pure material. MS APCI (-) m/z 497, 501
(M-, Br pattern) detected.

Step L: 6-(4-Bromo-2-cliloro-phenplainino).. 7-chloro-3-methyl-3H-benzoirnidazole-5-
carboxylic acid (2-hydroxy--erhoxy)-a,nide 10cc
Hydrochloric acid (0.78 mL, 1.0 M aqueous solution, 0.78 rnmol) is added to a
suspension of
benzoimidazole-5-carboxylic acid lOgg (2viny1oxy-ethoxy)-amide (39 mg, 0.078 mn’iol) in MeOH (1 mL). After one hour, the reaction mixture is neutralized to pH 7 and concentrated under reduced pressure. The solids are dissolved in EtOAc, washed with brine, dried (Na2SO4), and concentrated under reduced pressure. Flash chromatography (20:1 CH2C12JMeOH) provides 9 mg (23%) of pure product: MS APCI (–) m/z 473, 475

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(M+, Br pattern) detected; ’H NMR (400 MHz, CDCl) 8.30 (s, 1H), 8.08 (s, 111), 7.57 d, 1H), 7.15 (dd, 111), 6.21 (d, 1H, 3.97 (s, 311) 3.86 (m, 21-1),3.57 (m, 211).

Example 53

H

HN,CI Br

6(4_Bromo_2..ch1oro_pheny1amino)-3IfbeizzoirnidaZote-5-CarbO).y1iC acid (2-1zydroy-ethoxy)-amide (1111th)
The above compound is prepared in an analogous fashion to Example 52 except
that Step I is eliminated. MS APCI (-) m/z 457, 461 (M-, Br pattern) detected; ’H NIvIR (400 MHz, CD30D) 8.40 (s, 1H), 7.85 (s, 1H), 7.50 (d, 111), 7.14 (dd, 111), 6.21 (d, IH), 3.84 (m, 211), 3.61 (m, 211).

Example 54

OH
H

F

H

. 6-(4-Brono-2-chloro-phenyLainlno)-7-fluoro-2-rnethyl-3H-benzoimidazaIe-5-carboxyIk acid (2-hydroxy-ethoxy)-amide (IOU) Step A: 4, 5-Diarnino-3--fluoro-2-phenylarnino-benzoic acid methyl ester 6c 4-Amino-3-fluoro-5-nitro-2-pheriylarnino-benzoic acid methyl ester 26a (11.44 g,
37.48 rumol) is suspended in ethanol (400 niL) and ammonium formate (11.80 g, 187,0

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mniol) and 20 % Pd(OH)ilC (10.00 g, 18.79 mmol) are added. The reaction mixture is stirred at 95 °C under N2 for 30 minutes. The reaction mixture is cooled to room temperature and then filtered through celite, rinsing with ethanol. The filtrate is concentrated under reduced pressure to give 9.63g (93 %) ofthe pure desired product as a purple/red solid. MS ESI (+) m/z 276 (M+1) detected.

Step B: 7-Fluoro2-methyl-6-phenylainino-3H_bcnzoimidazole-5-carboxyljc acid methyl

ester 31a

4,5-Dianuno3-fJuoro-2-phenylamino-henzoic acid methyl ester 6c (0.20 g, 0.73 mmol) is suspended in ethanol (3 mL) and 5 M aqueous HCI (1 mL., 5.00 mmol) is added. The reaction mixture is brought to reflux under N2 and then 2,4-pentanedione (0.150 mL, 1.45 mmol) is added. The reaction mixture is stirred at reflux for 60 minutes. The reaction mixture is cooled to room temperature and treated with saturated aqueous NaHCO3 until the pH of the reaction mixture is pH 7 and is then concentrated under reduced pressure to dryness. The residue is diluted with ethyl acetate and water, poured into a separatory funnel and the layers separated. The ethyl acetate layer is washed with brine, dried (Na2SO4) and concentrated under reduced pressure. The red solid residue is triturated with diethyl ether to yield a light brown solid and a red filtrate. The solid is collected and washed with diethyl ether to yield 0.20 g (91 %) ofthe pure desired product as a light brown solid. MS ESI (+) m/z 300 (M+1) detected.

Step C:
carbatylic acid (2-hydroxy-ethoxy)-amide 1011 7-Fluoro-2-methyl..ô-pbenylaino3Wbenzoimidazole.5carboxyljc acid methyl
ester 31a is converted by the bromination, chlorination, hydrolysis, coupling, and

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hydrolysis procedures already described to yield the pure desired product as an off-white solid. MS }3S1 (+) m/z 457, 459 (M+, Br pattern) detected; ’H NMR (400 MHz, CD30D) 7.58 (s, 1H), 7.49 (d, Iii), 7.18 (dd, IH), 6.41 (m, 111), 3.91 (t, 2H), 3.65 (t, 2H), 2.61 (s, 311), 19F NMR (376 MHz, CD30D) 435.84 (s).

Example 55

H

HLN rLF

6-(4-Cyano-2-methyl-plaenylamino)-7-fluoro-3H-benzoimidazole-5-carboxylic acid cyclopropylmeEhyoxy-amide (llyy)
Step A: 7-Fluoro-6-(4-iodo-2-methyl-phenylamino)-JH-benzoiinidazole-5-carboxylic acid methyl ester 10ff
7-Fluoro-6-o--tolylamino-1H-benzoirnidazole-5-carboxylic acid methyl ester 7a
(1.47 g, 4.92 mmol) is suspended in 1:1 THF:MeOH mixture (44 ml) and cooled to- -78 ° C under a nitrogen atmosphere. A solution of NIS (1,66 g, 7.39 minol) in THIF (2 ml) is added followed by a MeOH (2 ml) solution of TsOIFH20 (1.87 g, 9,84 mniol). After 30 minutes, the reaction mixture is warmed to 0 °C and I ml methylene chloride is added. The reaction is slowly allowed to warm to room temperature with stirring over 16 hours. The reaction mixture is quenched by the addition of 10% Na2S204 solution. The reaction mixture is then diluted with water and ethyl acetate and the layers separated. The aqueous layer is extracted with ethyl acetate. The combined organic extracts are dried (Na2SO4) and concentrated under reduced pressure. The recovered solid is triturated with

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MeOH to give 1.45 g (69%) pure desired product: MS ESI (+) m/z 426 (M+l) detected; MS ESI (-) m/z 424 M-l) detected.

Step B: 7-Fluoro-6-.(4iodo-2methyl-p1i.envlamino)-(’2.-trimethylsilanyl-ethoxyrnethyl)- benzoimidazole-5-carborylie acid methyl ester lOkk 7-Fluoro-6-(4-iodo-2-methyl-phcnylamino).1H-benzoimidazol e-5-carboxylic acid methyl ester lOjj (0.200 g, 0.470 mmol) is suspended in DMF (2 ml) under N2 and cooled to 0°C in an ice-water bath. NaH (60% dispersion in oil, 0.018 g, 0.470 mmol) is added. After 10 mm, the reaction mixture is warmed to room temperature and stirred for 30 After cooling to 0 C, SEMC1 (0.087 ml, 0.494 mmol) is added and the reaction is allowed to warm to room temperature with stirring overnight. The reaction mixture is quenched by the addition ofwater and brine. The reaction mixture is extracted with ethyl acetate. The combined organic extracts are washed with water and brine, and dried (MgSO4) and concentrated under reduced pressure. Purification by flash column chromatography eluted with 1:1 hexanes:ethyl acetate gives 0.182 g (70%) of desired product as a 1:1 mixture ofNl and N3 isomers as a white foam.

Step C: 6-4-cyano-2-metlzyl-pheny1amino)- 7-fluoro-(2-trimethylsilanyi.-ethoxymethyQ_ benzoimidazole-5-carboxylic acid methyl ester 1011
To a stirred solution of a 1:1 mixture of NI:N3 isomers of 7-fluoro-6-(4.-iodo-2

acid methyl ester lQjj (0.060 g, 0.108 mmol) in 1 ml DMF at room temperature under N2 is added dppf(2 mg, 0.004 inmol) followed by Pd2dba (2 mg, 0.002 mmol) and Zn(CN)2 (8 mg, 0.065 mmol) (Tetrahedron Lett. 1999, 40, 8193-8195). The reaction mixture is heated to 120 °C for 45 min. The reaction mixture is cooled to room temperature and

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pressure. Purification by flash column chromatography eluted with 1:1 hexanes:ethyi
acetate gives 38 mg (77%) of desired product as a 1:1 mixture of Ni and N3 isomers: APCI MS (-1-) m,’z 455 (M+l) detected.

Step D: 6-(4-Cyano-2-methyl-phenylamino)-7.fluoro--(2-trimethylsilanyl-ethoxymethyl)- benzoimidazole-5-carboxylic acid 1 0mm
A 1:1 mixture of Ni:N3 isomers of 6-(4-cyano-2-methylphenylamino)-7-fluoro-(2-trirnethyisi1anyl-ethoxymethyl)beiizoimidazole-5-carboxylic acid methyl ester
(31 mg, 0.068 mmol) is hydrolyzed with aqueous sodium hydroxide as described previously to give 26 mg (87%) ofdesired product.

Step E. 6-(4-Cyano-2-methyl-Phenylarnino)-7-fiuoro-(2-trimerhylsilanyletho.ymethy/)- benzoiinidazoie-5.-carboxylic acid cyclopropylmethyoxy-amide llzz
A 1:1 mixture of Ni:N3 isomers of 6-(4-cyano-2-methyl-phenylarnino)-7-fluoro-(2-trimethylsilanyl-etiioxymethyi)-benzoirnidazole-5-carboxylic acid 10mm (26 mg, 0.059 mmol) is coupled with EDCI and cyclopropyl methyl hydroxylamine hydrochloride as described previously to give 28 mg (93%) of desired product: APCI MS (+) m/z 510 (M-J-1) detected.

Step F: 6-(4-Gvano--2-rnethy1-pheiwlamino)--7-fluoro-3Hbenzoimidazole-5-car,axyljc acid cyclopropylrnet/zym.y-arnide llyy

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WO 03/077914 PCT/US03/07864 To a slurry of a 1:1 mixture of N1:N3 isomers 6-(4-cyano-2-methyl-phenylmino)-7-fluoro-(2-trimethylsilanyl-ethoxymethyl)-benzoirnidazole-5-carboxylic acid cyclopropylmethyoxy-amide fizz (28 mg, 0.055 mmol) in 0.5 ml EtOH is added 0.5 ml 10% 1-ICI. The reaction mixture is heated to 50 °C with stirring overnight (Whitten et al., JOC 1986, 51, 1891-1894). An additional 0.5 ml 10% HCI is added and the reaction

mixture stirred at 70 UC overnight. The reaction mixture Is cooled to room temperature and neutralized fo pH -8 with 1.5 ml IN NaOH. The reaction mixture is extracted with ethyl acetate, dried (MgSO4) and concentrated under reduced pressure to give 14 mg (60%) of 90% pure product as a mixture of rotatomem: MS APCI (-I-) rn/z 380 (M–1) detected; MS APCI (-),n/z 378 (M-1) detected; 111 NIvIR (400MHz, MeOH-d4) 8 8.41 (bs, 111), 7.75 (m, 1H), 7.50 (s, 111), 7.38 (ci, 1H), 6.51 (m, 111), 3.72 (d, 0.5 11, 3.65 (d, 1.5 H), 2.41 (s, 311), 0.98 (111, m), 0.58 (ci, 1.5 H), 0.40 (ci, 0.5 H), 0.25 (d, 1.5 H), 0.19 (d,0.5H).

Example 56

H
-0N.O
I

NIC??

6-(4-Ethynyl-2-inethyl-phcnylmino)-7-fluoro-3f1_benzoi,nidazole_5..czjrboxylw acid cyclopropylrn&ioxy-arnide llaaa
Step A. 7-Fluoro-6-(2-rnethyl-4.-trimethylsi1anylethynyl-phenylarnjno3H benzoirnidazole-5-carboxylic acid cyclopropylmethox-y-amjde llbbb 7-Fluoro-6-(4-iodo-2-metbyl-phenylamino)-3H-heuroimidazole-5-carboxyljc acid cyclopropylmethoxy-amide 1 lccc (0.025 g, 0.052 mmol) is dissolved in 1:1 acetonitrile/triethylamine (0.50 mL). Ethynyl-trimethylsilane (0.013 mL, 0.092 mmol),

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Rc

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Pd(PPh3)2C12 (0.004 g, 0.006 mmol), and Oil (0.002 g, 0.011 mmol) are added consecutively and the reaction mixture is stirred at 60 °C for 1 hour under N2. The reaction mixture is cooled to room temperature and concentrated under reduced pressure. The residue is purified by FCC (eluting with 20:1 methylene chloride:methanol) to yield 0.020 g (87%) ofthe desired product.

Step B:
acid cyclopropylmethoxy-wnide llaaa 7Fluoro-6(2methy1-4-trimethylsilany1ethyfly1-phefly1aflhiflO)-3H-benzoimidazole-5-carboxylic acid cyclopropylmethoxy-aniide llbbb (0.020 g, 0.044 mmol) is dissolved in tetrahydrofuran (0.50 mL) and the reaction solution is cooled to 0 ° C. TBAF (50 uL, 0.050 mmol, 1 M solution in tetrahydrofuran) is added. The reaction mixture is warmed to room temperature and additional TBAF (25 uL, 0,025 mmol, 1 M solution in tetrahydrofuran) is added. The reaction mixture is stirred at 50 °C for 2 hours under N2. The reaction mixture is cooled to room temperature, a few drops of H20 are added and then it is concentrated under reduced pressure. The residue is purified by FCC (eluting with 20:1 methylene chloride:methanol) to yield 0.011 g (65%) of the pure

desired product. MS APCI (-) m/z 377 (M-1) detected; ljj NMR (400 MHz, COd3)

10.56 (broad 8, 11-1), 8.12 (s, IH), 7.99 (s, 111), 7.28 (s, 1ff), 7.11 (d, 111), 6.42 (broad, 114), 3.70 (br s, 211), 2.96 (d, IH), 2.37 (s, 3H), 0.85 (in, 1H), 0.50 (in, 2H), 0.22 (m, 2ff).

The invention and the manner and process of making and using it, are now described in such fail, clear, concise and exact terms as to enable any person skilled in the art to which it pertains, to make and use the same. It is to be understood that the

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foregoing describes preferred embodiments of the present invention and that modifications may be made therein without departing from the spirit or scope of the present invention as set forth in the claims. To particularly point out and distinctly claim the subject matter regarded as invention, the following claims conclude this specification.

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1. A compound ofthe formula

Ri

R7

W
H

R2

and pharmaceutically accepted salts, prodrugs and solvates thereof, wherein:
is an optional bond, provided that one and only one nitrogen of the ring is double-bonded;
R1, R, R9 and R1° are independently selected from hydrogen, halogen, cyano, nitro, trifluoroinethyl, dffluoromethoxy, trifluoromethoxy, azido, -OR3, -C(0)R3,
- C(0)0R3, WC(0)W, -OC(0)R3, -NR4SO2R6, -SO2NR3R4, -NR4C(0)R3,
- C(0)NR3R4, -NR5C(0)NR3R4, -NR5C(NCN)NR3R4, -N3R4, and
C1 -C10 alkyl, C2-C10 alkenyl, C2-C10 alkynyl, C3-C10 cycloalkyl, C3-C10 cycloalkylalkyl, -S(0)(C -C6 alkyl), -S(0)j(CR4R5)m-aryl, aryl, arylalkyl,
heteroaryl, beteroarylalkyl, heterocyclyl, heterocyclylalkyl, -O(CR4R5)m-
aryl, -NR4(CR4R5)rn-aryl, O(CR4R)m-heteroaryl, -NR4(CR4R5)m heteroaryl, 0(CR4R5)mheterocyclyl and -NR4(CR4R5)m-heterocyclyl, whore each alkyl, atkenyl, alkynyl, cycloalkyl, aryl, heteroaryl and heterocyclyl portion is optionally substituted with one to five groups independently selected from oxo, halogen, cyano, intro, trifluoromethyl, difluoromethoxy, trifluoromethoxy, azido, -NR4SO2R6, -S02NR3R4,

-C(0)R3, _C(0)OW, -OC(0)R3, NR4C(0)OR6, -NR4C(0)R3,

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-CO)NR3R4, NR3R4, -NRC(0)NR3R4, -NR5CNCN)NR3R4, -OR3, aryl,
heteroaryl, arylalkyl, heteroarylalkyl, heterocyclyl, and heterocyclylalkyl;
R3 is selected from hydrogen, trifluoromethyl, and
CI-CIO alkyl, C2-C10 alkenyl, C2-C10 alkynyl, C3-C10 cycloalkyl, C3-CIO cycloalkylalkyl, aryl, arylalkyl, heteroaryl, betcroarylalkyl, heterocyclyl,
and heterocyclylalkyl, where each alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl and heterocyclyl portion is optionally substituted with one to
five groups independently selected from oxo, halogen, cyano, nitro, trifluoromethyl, difluoromethoxy, trifluoromethoxy, azido, -NR’SO2R",
- SO2NRR", -C(0)R’, -C(0)OR’, -OC(0)R’, -NR’C(0)OR", -NR’C(0)R", -C(0)NRR", -SW, -S(0)R", -S02R...., -NR’R’, -NRC(0)NIR."R..., - NR’C(NCN)NR"R’, -OR, aryl, heteroaryl, arylalkyl, heteroarylalkyl, heterocyclyl, and heterocyclylalkyl;
It’, R" and R" independently are selected from hydrogen, lower alkyl, lower alkenyl, aryl and arylalkyl;
R" is selected from lower alkyl, lower alkenyl, aryl and arylalkyl; or
Any two of R’, R", It" or R" can be taken together with the atom to which they are
attached to form a 4 to 10 membered carbocycic, heteroaryl or heterocyclic ring,
each of which is optionally substituted with one to three groups independently
selected from halogen, cyano, nitro, trifluoromethyl, difluoromethoxy,
. trifluoromethoxy, azido, aryl, heteroaryl, arylalkyl, heteroarylalkyl, heterocyclyl, and heterocyclylalkyl; or
R3 and It4 can be taken together with the atom to which they are attached to form a 4 to
10 membered carbocyclic, heteroaryl or heterocyclic ring, each of which is
optionally substituted with one to three groups independently selected from

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WO (3/077914 PCTIUS03/07864 halogen, cyano, intro, trifluoromethyl, difluoromethoxy, trifluorornethoxy, azido, - NR’S02R", -SO2NR’R", -C(0)R, -C(0)OR’ -OC(0)R’, -NR’C(0)OR", - NRC(0)R", -C(0)NR’R", -S02R’"’, -NR’R", -NR’C(0)NR"R", - NR’C(NCN)NIR"R, -OR, aryl, tieteroaryl, arylalkyl, heteroarylalkyl, heterocyclyl, and heterocyclylalkyl; or
R4 and R5 independently represent hydrogen or C1-C6 alkyl; or
R4 and R.5 together with the atom to which they are attached form a 4 to 10 membered carbocyclic, heteroaryl or heterocycic ring, each of which is optionally substituted with one to three groups independently selected from halogen, cyano, nitro, trifluoromethyl, difluoromethoxy, tri–luoromethoxy, azido, -NR’S02R"’, -SO2NP’R", -C(0)R", -C(0)OR’, -OC(0)R’, -NR’C(0)OR", -NR’C(0)R", -C(0)NR’R", -SOR", -NR’R", -NR’C(0)NTR’R", -NR’C(NCN)NR"R", -OR’,
aryl, heteroaryl, arylalkyl, heteroarylalkyl, heterocyclyl, and heterocyclylalkyl;
R6 is selected from trifluoromethyl, and
C -C10 alkyl, C3-C10 cycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyJ, heterocyclyl, heterocyclylalkyl, where each alkyl, cycloalkyl, aryl, heteroaryl and heterocyclyl portion is optionally substituted with one to
five groups independently selected from oxo, halogen, cyano, intro, trifluoromethyl, difluoromethoxy, trifluoromethoxy, azido, -NRSO2R’",
- SO2Mt’R", -C(0)R’, -C(0)OR’, -OC(0)R’, -NR’C(0)OR", -NR’C(0)R’, -C(0)NR’R", -S02R", -NR’R’, -NR’C(0)NR"R", -NR’C(NCN)NR"R". - OR’, aryl, heteroaryl, arylalkyl, beteroarylalkyl, heterocyclyl, and heterocyclylaikyl;
R7 is selected from hydrogen,, and

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C1-C30 alkyl, C2-C10 alkenyl, C2-C10 alkynyl, C3-C10 cycloalkyl, C3-CIO cycloalkylalkyi, aryl, arylalkyl, heteroaryl, heteroarylalkyl, heterocyclyl, heterocyclylalkyl, where each alkyl, alkenyl, alkynyl, cycloalkyl, aryl,
heteroaryl and heterocyclyl portion is optionally substituted with one to
five groups independently selected from oxo, halogen, cyano, intro, trifluoromethyl, difluoromethoxy, trifiuoron3ethoxy, azido, -NR4SO2R6,
- SO2NR3R4, -C(0)W, -C(0)0R3, -OC(0)R3, -NR4C(0)0R6, NR4C(0)R3,
- C(0)NR3R4,.S02R6, -NR3R4, -NR5C(0)NR3R4, -NR5C(NCN)NR3R4, -
OR3, aryl, heteroaryl, arylalkyl, heteroarylalkyl, heterocyclyl, and beterocyclylalkyl;
W is selected from heteroaryl, heterocyclyl, -C(0)0R3, -C(0)NR3R4, -C(0)NR4OR3, - C(0)R40R3, -C(0)(C3-C10 cycloalkyl), -C(0)(Ci-C10 alkyl), -C(0)(aryl), - C(0)(heteroaryl) and. C(0)(heterocyciyl), each of which is optionally substituted
with 1-5 groups independently selected from
- NR3R4, -OR3, -R2, and
C1-C10 alkyl, C2-C10 alkenyl, and C2-C10 alkynyl, each of which is
optionally substituted with 1 or 2 groups independently selected
from - NR3R4 and OW;
R8 is selected from hydrogen, -SCF3, -Cl, -Br, -F, cyano, nitro, trifluoromethyl, difluorometboxy, trifluorornethoxy, azido, -OR3, -C(0)R3, -C(0)OR3,
. NR4C(0)0R6, -OC(0)R3, -NR4S02R6, -SO2NR3R4, -WC(0)R3, C(0)NRR4,
- NRC(0)NR3R4, -NR3R4, and
CA -CID alkyl, C2-C10 aikenyl, C2-C10 alkynyl, C3-C10 cycloalkyl, C1-00
cycloalkylalkyl, -S(0)J(C3-C6 alkyl), -S(0)j(CR4R5)m-aryl, aryl, arylalkyl,
heteroaryl, heteroarylaikyl, heterocyclyl, heterocyclylailcyl, -O(CR4R5)m
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heteroaryl, _O(CR4R5)heterocyc1yl and -NR4(R4R5)m-heterocyc1yi,
where each alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl and heterocyclyl portion is optionally substituted with one to five groups independently selected from oxo, halogen, cyano, nitro, trifluoromethyl, difluoromethoxy, trifluoromethoxy, azido, -NR4S02R6, -S02NR3R4,

- C(0)R3, -C(0)0R3, -OC(0)R3, -NR4C(0)OR6, -NR4C(0)R3,

- C(0)NRR4, -NRR4, -NR5C(0)NRR4, -NR5CNcN)NR3R4, -OR3, aryl, heteroaryl, arylalkyl, beteroarylalkyl, heterocyclyl, and heterocyclylaikyl;
inisO, 1,2,3,4or5;and
j is 1 or 2.

2. A compound ofthe formula

R1

and pharmaceutically accepted salts, prodrugs and solvates thereof, wherein:
is an optional bond, provided that one and only one nitrogen of the ring is double-bonded;
R’, R9 and R’° are independently selected from hydrogen, halogen, cyano, nitro, trifjuoron,ethyl, difhioromethoxy, trifluoromethoxy, azido, -OR3, -C(0)R3, -C(0)0R3, NR4C(0)0R6, -OC(0)R3, -NR4SO2R6, -SO2NR3R4, -WC(0)R,
- C(0)NR3R4, -NIR5C(0)NR3R4, -NR5C(NCN)NR3R4, -NR3R4, and
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WO 03/077914 PCT/US03I07864 rn CI -CIO alkyl, C2-CIO alkenyl, C2-C10 alkynyl, C3-CIO cycloalkyl, C3-CIO
cycloalkylaikyl, -S(0)(C -C6 alkyl, -S(0)j(CR4R5)m-aryl, aryl, arylaJkyl, heteroaryl, heteroarylaikyl, heterocyclyl, heterocyclylalkyl, -O(CR4R5)m-
aryl, NR4(CR4R5)maryl, 0(CR4R5)miieteroaryl, -NR4(CR4R5)m-heteroaryl, -O(CR4R5)m-heterocyclyl and -NR4(CR4R5)m-beterocyclyl, where each alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl and
heterocyclyl portion is optionally substituted with one to five groups
independently selected from oxo, halogen, cyano, intro, tri–luoromethyl,
difluoromethoxy, trifluorornethoxy, azido, -NR4SO2R6, -SO2NIR3R4,
-C(0)W, -C(0)0R3, -OC(0)R3, -WC(0)0R6, -WC(0)R’,
- C(0)NR3R4, -NR3R4, -NR5C(0)NR3R4, -NR5C(NCN)NR3R4, -OW, aryl,
. heteroaryl, arylalkyl, heteroarylalkyl, heterocyclyl, and heterocyclylalkyl; R3 is selected from hydrogen, hifluoromethyl, and
C1-00 allcyl, C2-CIO alkenyl, CrCio alkynyl, C3-C10 cycloalkyl, C3-C10
cycloalkylalkyl, aryl, arylaikyl, heteroaryl, heteroarylalkyl, heterocyclyl,
and heterocyclylalkyl, where each alkyl, alkenyl, alkynyl, cycloalkyl, aryl,
heteroaryl and heterocyclyl portion is optionally substituted with one to
five groups independently selected from oxo, halogen, cyano, nitro, trifluoromethyl, difluoromethoxy, trifluoromethoxy, azido, -NR’S02R",
-SO2NR’R", -C(0)R’, -C(0)OR’, -OC(0)R’, -NR’C(0)OR"", -NR’C(0)R", -C(0)NR’R’, -SR’, -S(0)R", -SO2R", -NR’R", -NR’C(0)NR"R", - NR’C(NCN)NR"R", -OR’, aryl, heteroaryl, aiylalkyl, heteroarylalkyl, heterocyclyl, and heterocyclylalkyl;
R’, R" and R" independently are selected from hydrogen, lower alkyl, lower alkenyl, aryl and arylailcyl;
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’is selected from lower aikyl, lower alkenyl, aryl and arylalkyl; or
Any two of R’, R", R"’ or R" can be taken together with the atom to which they are attached to form a 4 to 10 membered carbocyclic, heteroaryl or heterocyclic ring,
each of which is optionally substituted with one to three groups independently selected from halogen, cyano, nitro, trifluoromethyl, difluoromethoxy, trifluorornethoxy, azido, aryl, heteroaryl, arylalkyl, heteroarylalkyl, heterocyclyl,
and heterocyclylalkyl; or
R3 and R4 can be taken together with the atom to which they are attached to form a 4 to 10 membered carbocyclic, heteroaryl and heterocyclic ring, each of which is optionally substituted with one to three groups independently selected from halogen, cyano, nitro, trifluoromethyl, difluoromethoxy, trifluoromethoxy, azido, - NR’SO2R’, -SO2NR’R", -C(0)R, -C(0)OR’, -OC(0)R’, -NRC(0)OR", - NR’C(0)R", -C(0)NR’R", -S02R", -NR’R", -NR’C(0)NR"R", - NR’C(NCN)NR"R", -OR, aryl, heteroaryl, arylalkyl, heteroarylalkyl, heterocyclyl, and heterocyclylalkyl; or
R4 and R5 independently represent hydrogen or C1-C6 alkyl; or
R’ and R5 together with the atom to which they are attached form a 4 to 10 membered
carbocyclic, heteroaryl or heterocyclic ring, each of which is optionally
substituted with one to three groups independently selected from halogen, cyano,
intro, trifluoromethyl, difluoromethoxy, trifluoromethoxy, azido, -NR’SO2R".
. -SO2NR’R", -C(0)R, -C(0)OR’. -OC(0)R’, -NR’C(0)OR", -NR’C(0)R", -C(0)NRR, -SO2R, -NR’R’, -NR’C(0)NR"R"’, -NR’C(NCN)NR"R’", -OR’,
aryl, heteroaryl, arylalkyl, heteroarylalkyl, heterocyclyl, and heterocyclylalkyl;
R6 is selected from trifluoromethyl, and

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C1-C10 alkyl, C3-C)0 cycloalkyl, aryl, arylalkyl, beteraryl, heteroarylalkyl, heterocyclyt, and heterocyclylalkyl, where each alkyl, cycloalkyl, aryl,
heteroaryl and heterocyclyl portion is optionally substituted with one to
five groups independently selected from oxo, halogen, cyano, nitro, ti-ifluorornethyl, difluorometboxy, trifluoromethoxy, azido, -NIt’S02R",
- SO2NR’R", -C(0)R’, -C(0)OR’, -OC(0)R’, -NR’C(0)OR"", -NR’C(0)R",
-C(0)NR’R", -SO2R", -NR’R’, -NR’C(0)NR R", -NR’C(NCN)NR R", -
OR’, aryl, heteroaryl, arylalkyl, heteroarylalkyl, heterocyclyl, and heterocyclylalkyl;
R7 is selected from hydrogen, and
C1 -C10 alkyl, C2-C10 alkenyl, C2-C10 alkynyl, C3-C10 cycloalkyl, C3-C10
cycloalkylalkyl, aryl, arylalkyl, heteroaryl, beteroarylalkyl, heterocyclyl,
and heterocyclylalkyl, where each alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl and heterocyclyl portion is optionally substituted with one to
five groups independently selected from oxo, halogen, cyano, nitro,
tn fluoromethyl, difluoromethoxy, trifluoromethoxy, azido, -NR4SO2R6,
- S02NR3R4, -C(0)R3,.-C(0)0R3, -OC(0)R3, -NR4C(0)0R6, -NR4C(0)R3,
- C(0)NR3R4, -S02R5, -NR3R4, -NR5C(0)NR3R4, -NR5C(NCN)NR3R4,

OR’, aryl, heteroaryl, arylalkyl, heteroarylalkyl, heterocyclyl, and
heterocyclylalkyl;
. W is selected from heteroaryl, heterocyclyl, -C(0)0R3, -C(0)NR3R4, -C(0)NR4OR3, C(0)WOW, -C(0)(C3-C10 cycloalkyl), -C(0)(C1-Cio alkyl), -C(0)(aryl),
C(0)(heteroaryl) and -C(0)(heterocyclyl), each of which is optionally substituted
with 1-5 groups independently selected from
- NR3R4, -OW, -R2, and

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C1-C10 alkyl, C2-C10 alkenyl, and C2-C10 alkynyl, each of which is
optionally substituted with 1 or 2 groups independently selected
from - NR3R4 andOW;
R8 is selected from hydrogen, -SCF3, -Cl, -Br, -F, cyano, nitro, trifluoromethyl, difluoroinethoxy, tritluoromethoxy, azido, -OW, -.C(0)R3, -C(0)0R3,
- NR4C(o)0R6, -OC(0)R3, -NR4SO2R6, -SO2NR3R4, -WC(0)R3, -C(0)NR1R4,
- NR5C(0)NR3R4, -NR3R4, and

C1 -C10 alkyl, C2-C10 alkenyl, C2-C alkynyl, C3-C10 cycloaikyl, C3-C10
cycloalkylalkyl, -S(0)(C1-C6 alkyl), -S(0)J(CR4R)fl)-aryl, aryl, arylalkyl,
heteraryl, heteroarylalkyl, heterocyclyl, heterocyclylalky!, -0(CR4R5)TTI-
aryl, NR4(CR4R5)maryl, -O(CR4R)m-heteroaryl, NR4(CR4R5)m lieteroaryl, 0(CR4R5)mheterocyclyl and -NR4(CR4R)m-heterocyclyl, where each alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl and heterocyclyl portion is optionally substituted with one to five groups independently selected from oxo, halogen, cyano, nitro, trifluoromethyl, difluoromethoxy, trifluoromethoxy, azido, -NR4S02R, -SO2NR3R4,
- C(0)R3, -C(0)0R3, -OC(0)R3, -NR4C(0)0R6, -NR4C(0)k3,
- C(0)N1?R4, -NR3R4, -NR5C(0)N3R4, -.NIR5qNCN)NR3R4, -OR, aryl,
heteroaryl, arylalkyl, heteroarylalkyl, heterocyclyl, and heterocyclylalkyl; inisO,1,2,3, 4or5; and
j is 1 or 2.

3. A compound ofthe formula

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H RI

R9 R8

R7 R2

and pharmaceutically accepted salts, prodnigs and solvates thereof, wherein:
R’, R2, and R9 are independently selected from hydrogen, halogen, cyano, nitro, trifluoromethyl, difluoromethoxy, trifluoromethoxy, azido, -OW, -C(0)W, -C(0)0R3, NR4C(0)0R6, -OC(0)R3, -NR4S02R6, -SO2NR3R4, -NIt4C(0)R3,
- C(0)NR3R4, -NR5C(0)NR3R4, -NR5C(NCN)NR3R4, -NR3R, and
C1-C10 alkyl, C2-C10 alkenyl, CrCio alkynyl, C3-C10 cycloalkyl, C3-C10 cycloalkylalkyl, -S(0)(C1-C6 alkyl), -S(0)3(CR4R5),,-aryl, aryl, arylakyl,
heteroaryl, heteroarylalkyl, heterocyclyl, heterocyclylalkyl, O(CR4R.5)m-
aryl, -NR4(CR4R)m-aryl, -O(CR4R5)m-heteroaryl,-NR4(CR4R5)m heteroaryl, -O(CR4R5),,-heterocyclyl and -NR4(CR4R5)m-hetcrocyclyl, where each alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl and heterocyclyl portion is optionally substituted with one to five groups independently selected from oxo, halogen, cyano, nitro, trifluoromethyl, difluorometboxy, trifluoromethoxy, azido, -NR4SO2R, -SO2NR3R4, -C(0)W, -C(0)0R3, -OC(0)R3, -NR4C(0)0R6, -NR4C(0)R.3,
- C(0)NR3R4, -NR3R4, -NR5C(0)NR3R4, -NR5C(NCN)NR3R4, -.0R3, aryl, heteroaryl, arylalkyl, heteroarylalkyl, heterocyclyl, and heterocyclylaikyl;
R3 is selected from hydrogen, trifluoromethyl, and
C1 -C10 alkyl, C2-CIO alkyenyl, C2-C10 alkynyl, C3-C10 cycloalkyl, C3-C10 cycloalkylalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, heterocyclyl,

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and heterocyclylalkyl, where each alkyl, alkenyl, alkynyl, cycloa]kyl, aryl,
heteroaryl and heterocyclyl portion is optionally substituted with one to
five groups independently selected from oxo, halogen, cyano, nitro, trifluorometbyl, clifluoromethoxy, irifluoroniethoxy, azido, -NR’SO2R"", -SO2NR’R", -C(0)R’, -C(0)OR’, -OC(0)R’, -NR’C(0)OR›’, -NR’C(0)R’, -C(0)NR’R", -SR", -S(0)R", -SO2R, -NR’R", -NR’C(0)NR"R’’, NRC(NCN)NRR, -OR’, aryl, heteroaryl, arylalkyl, heteroarylalkyl, heterocyclyl, and heterocyclylalkyl;
R’, R" and R" independently are selected from hydrogen, lower alkyl, lower alkenyl, aryl and arylalkyl;
P." is selected from lower alkyl, lower alkenyl, aryl and arylalkyl; or
Any two of P.’, R", R" or P." can be taken together with the atom to which they are attached to form a 4 to 10 membered carbocyclic, heteroaryl or heterocyclic ring,
each of which is optionally substituted with one to three groups independently selected from halogen, cyano, nitro, trifluoromethyl, difluoromethoxy,
tnfluoromethoxy, azido, aryl, heteroaryl, arylalkyl, heteroarylalkyl, heterocyclyl,
and heterocyclylalkyl; or
R3 and P.4 can be taken together with the atom to which they are attached to form a 4 to
10 membered carbocydhc, heteroaryl or heterocyclic ring, each of which is
optionally substituted with one to three groups independently selected from
. halogen, cyano, nitro, triuluoromethyl, ditluoromethoxy, trifluoromethoxy, azido, - NR’S02R", -SO2NR’R", -C(0)R’, -C(0)OR’, -OC(0)R’, -NRC(0)OR", -
NR’C(0)R", -C(0)NR’R", -SOR", -NR’R", -NR’C(0)NR"R", -
NR’C(NCN)NR"R", -OR’, aryl, heteroaryl, arylalkyl, heteroarylalkyl,
heterocyclyl, and heterocyclylalkyl; or
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R4 and R5 independently represent hydrogen or C1-C6 alkyl; or
R4 and R5 can be taken together with the atom to which they are attached to form a 4 to 10 membered carbocyclic, heteroaryl or heterocyclic ring, each of which is optionally substituted with one to three groups independently selected from halogen, cyano, nitro, irifluorometbyl, difluoromethoxy, trifluoromethoxy, azido, - NR’S0211", -SO2NRR", -C(0)R’, -C(0)OR’, -OC(0)R’, -NR’C(0)OR’"’, - NR’C(0)R", -C(0)NR’R", -SO2R",.-NR’R", -NRC(0)NR’R", - NR’C(NCN)NR"R", -OR’, aryl, heteroaryl, arylalkyl, heteroarylalkyl, heterocyclyl, and heterocyclylalkyl;
R6 is selected from trifluoromethyl, and
C1-00 alkyl, C3-C10 cycloalkyl, aryl, arylalkyl, heteroaryl, hcteroarylaikyl, heterocyclyl, and heterocyclylalkyl, where each alkyl, cycloalkyl, aryl, heteroaryl and heterocyclyl portion is optionally substituted with one to
five groups independently selected from oxo, halogen, cyano, nitro, trifluoromcthyl, difiuoromethoxy, trifluoromethoxy, azido, -NR’S02R"’,
- SO2NR’R", -C(0)R’, -C(0)OR’, -OC(0)R’, -NR’C(0)OR", -NR’C(0)R",
-C(0)NR’R", -SO2R", -NRR’, -NR’C(0)NR’’R", -NR’C(NCN)NR"R", -
OR, aryl, heteroaryl, arylalkyl, heteroarylalkyl, heterocyclyl, and
heterocyclylalkyl;
R7 is selected from hydrogen, and
CrCio alkyl, C2-C10 alkenyl, C2-C10 alkynyl, C3-C10 cycloalkyl, C3-C10

W cycloalkylaikyl, aryl. arylalkyl, heteroaryl, heteroarylalkyl, heterocyclyl,

and heterocyclylalkyl, where each alkyl, alkenyl, alkynyl, cycloalkyl, aryl,
heteroaryl and heterocyclyl portion is optionally substituted with one to
live groups independently selected from oxo, halogen, cyano, nitro,

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WO 031077914 PCT/US03/0764 trifluoromethyl, difluoroniethoxy, trifluoromethoxy, azido, -NR4SO2R6,

- S02NR3R4, -C(0)R3, -C(0)0R3, -OC(0)R3, -NR4C(0)0R6, -NIR4C(0)R3,
- C(0)NR3R4, -S02R6, -NR3R4, -NR5C(0)NTR3E4, -NR5C(NCN)NR3R4, -

OW, aryl, heteroaryl, arylalkyl, heteroarylalkyl, heterocyclyl, and heterocyclylalkyl;
A is selected from -C(0)0R3 or.-C(0)NR4OR3;
R8 is selected from hydrogen, -SCF3, -Cl, -Br, -F, cyano, nitro, trifluoromethyl, difluoromcthoxy, trifluoromethoxy, azido, -OR3, -C(0)R3, -C(0)0R3,

- NR4C(o)0R6, -OC(0)R3, -NR4802R6, -SO2NR3R4, -WC(0)R3, -C(0)NR3R4,
- NR5C(0)NR3R4, -NR3R4, and
C1 -C10 alkyl, C2-C10 alkenyl, C2-C10 alkynyl, C3-C10 cycloalkyl, C3-C10
cycloalkylailcyl, -S(0)1(C1-C6 alkyl), S(0)j(CR4R5)maryl, aryl, arylalkyl,
heteroaryl, heteroarylailcyl, heterocyclyl, heterocyclylalkyl, O(CR4R)m-
aryl, -NR4(CR4R5)m-aryl, -O(CR4R5)m-heteroaryl, -NR4(CR4R5)m-heteroaryl, -O(CR4R5)m-heteroeyclyl and -NR4(CR4R5)m-hetcrocyclyl, where each alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl and heterocyclyl portion is optionally substituted with one to five groups independently selected from oxo, halogen, cyano, nitro, trifluoromethyl, difluorornethoxy, trifluoromethoxy, azido, -NR4SO2R6, -SO2NR3R4,

-C(0)W, -C(0)0R3, -OC(0)R3, -N1.4C(0)OR6, -WC(0)R?,
- C(0)NR3R4, -NR3R4, -NT(5C(0)NR3R4, -NR5C(NCN)NR3R4, -OR, aryl,
heteroaryl, arylalkyl, heteroarylaikyl, heterocyclyl, and heterocyclylalkyl; misO, 1, 2, 3,4or 5; and
j is 1 or 2.

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C)

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4. A compound according to claim 3 which is

R

5. A compound according to claim 4 wherein
R7 is C1 -C10 alkyl, C3-C7 cycloalkyl, C3-C7 cycloalkylalkyl, C3-C7 heterocycloalicyl or C3-
C7 heterocycloalkylalkyl, each of which can be optionally substituted with 1 - 3
groups independently selected from oxo, halogen, cyano, nitro, tn fluonomethyl,
. difluorornethoxy, trifluoromethoxy, azido, -NR4SOR6, -S02NR3R4, -C(0)W, - C(0)0R3, -OC(0)R3, -SO2R, -WC(0)0R6, -NR4C(0)R3, -C(0)NR-3R4, -
NR3R4, -NR5C(0)NR3R4, -NR5C(NCN)NR3R4, -OR3, aryl, beteroaryl, arylalkyl,
heteroarylaikyl, heterocyclyl, and heterocyclylalkyl;
R9 is hydrogen or halogen;
R1 is lower alkyl or halogen; and
R8 is OCF3 or halogen.

6. A compound according to claim 5 wherein R9 is fluoro.

S 7. A compound according to claim 6 wherein R’ is methyl or chioro.

8. A compound according to claim 7 wherein R8 is chioro or bromo.

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9. A compound according to claim 5 wherein A is -C(0)NR40R3,

10. A compound according to claim I wherein
R7 is C1-C10 alkyl, C3-C7 cycloalkyl, C3 -C7 cycloalkyla]kyl, C3-C7 heterocycloalkyl or C3-C7 heterocycloalkylailcyl, each of which can be optionally substituted with 1 3 groups independently selected from oxo, halogen, cyano, nitro, trifluorornethyl, difluoromethoxy, trifluoroniethoxy, azido, NR4S02R6, SO2NR3R4, -C(0)W, - C(0)0R3, -OC(0)R3, -S02R6. -NR4C(0)0R6, -NR4C(0)R3, -C(0)NR3R4, -

NR3R4, -NR5C(0)NR3R4, -NR5C(NCN)NR3R4, -OR3, aryl, heteroaryl, arylalkyl, lieteroarylalkyl, heterocyclyl, and heterocyclylalkyl;
R8 is -OCF3, Br or Cl, R2 is hydrogen, and R1 is lower alkyl or halogen;

40 R9 is hydrogen or halogen;
R10 is hydrogen; and
W is -C(0)0R3 or -C(0)NR4OR3.

11. A compound according to claim 10 wherein W is -C(0)NR4OR3.

12. A compound according to claim 2 wherein
R7 is C1-C10 alkyl, C3-C7 cycloalky or C3-C7 cycloalkylalkyi, each of which can be optionally substituted with 1 - 3 groups independently selected from oxo, halogen, cyano, nitro, trifluoromethyl, difluoromethoxy, trifluorom.ethoxy, azido, - NR4SO2R6, -SO2NR3R4, -C(0)W, -C(0)0R3, -OC(0)R3, -S02R3, -NR4C(0)0R6,
- NR4C(0)R3, -C(0)NR3R4, -NR3R4, -NR5C(0)NR3R4, -NR5C(NCN)NR3R4, -OR3,

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i(is hydrogen or halogen;
R’° is hydrogen; and
W is-C(0)OR’ or C(0)NR40R3.

13. A compound according to claim 12 wherein W is -C(0)NR4OR3.

14. A compound according to claim 1 which is selected from 7-F1uoro-6-(4bromo-2-methyhpheny1amino)-3II-benzoimidazo1e-5-carhoxyiic acid cyclopropylmethoxy-amide;
6-(4-Brorno-2-chloro-phenylamino)-7-fluoro-3H-benzoimidazole-5-carboxylic acid cyclopropylmethoxy-amide;
. 6-(4-Bromo-2chloro-pbenyIamino)-7-fluoro-3-methyl-3H-benzoimidazole5-carboxylic acid (2-hydroxy-ethoxy)-amide;
6-(4-Bromo-2-chloro-phenyiamino)-7-fluoro-3-methyl-3H-benzoimidazole5..carboxylic
acid (2,3-dihydroxy-propoxy)-ainide; 6-(4-Bromo-2.ch1oro-phenylamino)-7-fluoro-3-(terahydro-pyran-2.y1rnethy1)3H benzoimidazole-5-carboxylic acid (2-hydroxy-ethoxy)-amide; [6.(5-Arnino-[1.3,4]oxadiazo1-2-yl)-4-fluoro-1H-benzoirnidazo15-yl]-(4-bromo-2 melhyl-phenyl)-amine;
1 -L6-(4-Brorno-2-ch1oro-phenylamino)-7-fluoro-3-methy1-3H-benzoimidazo1.5yl}2 hydroxy-ethanone;
1 -{6-(4-Bromo-2-chloro-phenylamx1o)-7-fluoro-3H-benzoimidazo15yl]2methoxy ethanone;
-(4-Bromo-2-c1oro-pheny1amino)-7-fluoro_3-methyl_3H-benzoimidazo1e.5carxyJic acid (2-hydroxy- 1,1 -dimethyl-ethoxy)--amide;

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6-(4-Bromo-2-chloro-phenylamino)-7-fIuoro-3-(tetrahydro-fiiran-2yhnethyl)-3H-benzoimidazole-5-carboxylic acid (2-hydroxy.ethoxy)-amide;
Ô -(4-Bromo-2-chloro-phenylamino)-7-fluoro-3H-benzoimidazole-5-carboxylic acid (2-hydroxy-ethoxy)-amide;
6-(4-Brorno2-fluoro-phenylamino)-7-fluoro-3--rnethy1-3H-benzoimidazo1e-5-carboxylic acid (2-hydroxy--ethoxy)-amide; and 6-(2,4-Dichloro-phenylamino)-7-fluoro-3.-mcthyl-3H-benzoimidazole-5-carboxyiic acid (2-hydroxy-ethoxy)-amide.

15. A composition comprising a compound of claim I and a pharmaceutically
acceptable carrier.

16. A method of inhibiting MC activity in a mammal comprising
administrating an effective amount of a compound of claim I to the marrunal,

17. A method for treatment of a hperproJifcrative disorder in a mammal
comprising administrating an effective amount of a compound of claim 1 to the mammal.

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(54) Titulo: Derivados de Benzimidazol a1cui1ado N3 como
Inhibidores de MEK

10

H R1

R N

R9
R2
NH
R7

frE1

4

(57) Resumeri: Se revelan los compuestos de la FOrrrtula I, y sales y profÆrmacos farmacØuticamente aceptables de Ia misma, danae IN, R’, R2, R’, R, R9 y R’ son coma se aefineri en la memoria descriptiva Dichos compuestos sari inhibiIores de MEK y son eficaces en el tratamiento de enfermedades hiperproliferativas, coma cancer e infiamación, en mamiferos. AaemÆs se revela un mØtodo para utilizar dichos compuestos en el tratamienta de enfermedades hiperproliferativas en masüferos, i compasiciones farmacØuticas que cantienen dichos compuestos.

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Derivados de Benzimidazol aiquilado N3 como Inhibidores de MEK

ANTECEDNTS DE LP INVENCTON

Campo de la Invención

La presente invención se relaciona con una serie de derivados aiquilados de (1H-Benzoimidazol-5-il)-(fenilo sustituido en posición 4)-amina que son eficaces en el tratamiento de enfermedades hiperproliferativas, corno el cØncer y la –nflarnación, en mamIferos. La invención ademÆs se relaciona con un mØtodo para utilizar dichos compuestos en el tratamiento de enfermedades hiperproliferativas en mamiferos, especialmente en humanos, y con composiciones farmacØuticas que contienen dichos compuestos.

Resuinen del Arte Relacionado

La sefialización celular a travØs de receptores de factor
de crecimiento y cinasas de proteirias es un regulador importante del crecimiento, proliferación y diferenciaciôn celLular. En crecimiento normal de la cØlula, los factores de crecimiento, a travØs de activación de receptor (por ejernplo,

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PUCE a ECF y otros), activan los carninos de cinasa MAP. Uno de
los caminos de la cinasa MAP mÆs conocidos e importantes relacionados con el crecimiento celular normal y no controlacio es el carnino de cinasa Ras/ Raf. Ras unido a CTP activo da como resultado la activación y fosforilación indirecta y la activación de la cinasa Raf. Rat entonces fosforila MEKJ. y 2 sabre dos residuos de serina (3218 y 3222 para MEK1 y 3222 y
3226 para MEK2) (Ahn et aJ., Metods in Enzymology 2001, 332,
417-431). MEI< activado entonces fosforila sus substratos
conocidos, las cinasas MAP, ERK1 y 2. La fosforilac.ión ERK
mediante MEK tiene lugar sobre Y204 y T202 pare ERK1 e Y185 y
T183 para ERK2 (Ahn et al., Methods in Enzyrnoloqy 2001, 332,
417-431). ERR fosforilada dirneriza y luego se transloca al
nOclea donde se acumula (Khokhlatchev et a]., Ce]] 1998, 93,
605-615). En el nücleo, ERK se relaciona en varies funciones celulares importantes, incluyendo pero sin limitarse al transporte nuclear, transducciôn de setial, reparación del ADN, reunion y translocaciOn de nucleosoma, y traducción y procesamiento de ARNm (Ahn et a]., Molecular Cell 2000, 6,
1343-1354). En general, el tratamiento de las cØlu.las con
factores de crecimiento ileva a la activación de ERK1 y 2 la
cual da coma resultacio la pro].iferación, y en algunos casos, la
diferenciación (Lewis et a]., Adv. Cancer Res, 1998, 74, 49-

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En las enfermedades proliferativas, las mutaciones genØticas y/ o la sobreexpresión de los receptores del factor de crecirniento, proteinas de sealización descendente, o las cinasas de proteinas involucradas en el camino de cinasa ERK ilevan a una proliferación celular descontrolada, y eventualmente a la forrnación del tumor. Por ejemplo, algunos tipos de cÆnceres contienen mutaciones que dan como resultado la activación continua de este camino debido a la producc–ón continua de los factores de crecimiento. Otras mutaciones pueden producir defectos en la desactivaclón del complejo Ras activado unido a GTP, dando como resultado nuevamente la activación del camino de cinasa MAP. Las formas oncogØnicas mutadas de Ras se encuentran en un 50% de cancer de colon y >90% de pØncreas asi como tamblØn muchas otras clases de cancer (Kohl et a1, Science 1993, 260, 1834-837) Recientemente, las mutaciones bRaf han sido identificadas en rnÆs de 60% de melanoma maligno (Davies, H. et a]., Nature 2002, 417, 949-954). Estas mutaciones en bRaf dan como resultado una cascada de cinasa MAP activa constitutivamente. Los estudios de las muestras de tumor primarias y las lIneas celulares ademÆs han mostrado sobre activación del camino de cinasa MAP en cancer de

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pncreas, colon, pulmôn, ovario e higado (Hoshino, R. et a].,
Oncogene 1999, 18, 813-822). Pot consiguiente, hay una
. importante correlación entre diferentes tipos de cancer y un
camino de cinasa MAP sobre activo dando como resultado
mutaciones genØticas.

Dado que la sobre activación de cascada de cinasa MAP juega un importante papel en la proliferación y diferenciación celular, la inhihición de este camino se cree es beneficiosa para las enfermedades hiperproliferativas. MEN juega un papel irnportante en este camino ya que es el camino descendiente de Ras y Raf. AdemÆs, es un objetivo terapØutico atractivo porque los nicos substratos conocidos para la fosforilación de MEN
son las cinasa MAP, ERK1 y 2. La inhibición de MEN ha mostrado
tenet un potencial beneficia terapØutico en muchos estudios. Pot ejemplo, los inhibidores de rnolØcula pequeæa MEN han
mostrado inhibit el crecimiento del tumor humano en
xenoinjertos de ratones sin pelos, (Sebolt-Leopold et a].,
Nature -Medicine 1999, 5 (7), 810-816; Trachet et al., AACR
Abril 6-10, 2002, Poster #5426; Tecle, H. IBC 2° International Conference of Protein Kinases, Septiembre 9-10, 2002), bloquear alodinia estÆtica en animales (WO 01/05390 publicada el 25 de enero, 2001) e inhibit el crecimiento de cØlulas con leucenüa

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mieloidea aguda (Milella et a1, J Clin Invest 2001, 108 (6), 851-859) -

Algunos inhibidores de molØcula pequefla de MEF(han sido revelados. Al rnenos trece solicitudes han aparecido en los ltimos aæos; patente de Estados Unidos 5.525,625 presentada el 24 de enero, 1995; WO 98/43960 publicada el 8 de octubre, 1998; 99/01421 publicada ci 14 de enero, 1999; WO 99/01426 publicada el 14 de enero, 1999; WO 00/41505 publicada ci 20 de julio, 2000; WO 00/42002 publicada el 20 de julio, 2000; WO 00/42003 publicada el 20 de julio, 2000; WO 00/41994 publicada el 20 de julio, 2000; WO 00/42022 publicada el 20 de julio, 2000; WO 00/42029 publicada ci 20 de julio 2000; WO 00/68201 publicada el 16 de noviembre, 2000; WO 01/68619 publicada el 20 de septiembre, 2001; y WO 02/06213 publicada ci 24 de enero,

2002.
RSUMEN DE IJ INVENCION

La presente invención proporciona compuestos de aiquilada (lH-benzoirnidazol-5--il) (4-susti.tuido fenilo) -arni.na de la formula I, y sales y profÆrmnacos farmacØuticamente aceptables de los mismos que son eficaces en el tratamiento de enfermedades proliferativas. Especialmnente, la presente

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invenclón se relaciona con compuestos de la f6rrnu1 I que acttan como inhibidores MEK. Aderns se proporciona un mØtodo para el tratamiento del cancer. AdemÆs se proporcionan formulaciones que contieneri compuestos de la formula I y mØtodos para utilizar los compuestos para tratar a un paciente que lo necesite. AdemÆs, se describen procesos para la preparaciOn de compuestos inhibitorios de la formula I.

Dc tal manera, la presente invenciOn proporciona compuestos de la formula I:

H 10 N

R2
R7

y sales, profÆrmacos y solvatos de la misma farmacØuticamente aceptados, caracterizados porque:

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es un enlace opcional, si solo un nitrógeno del anillo tiene un enlace doble;

R1, R R y R1J son seleccionados independientemente de hidróqeno, halóqeno, ciano, nitro, trifluorometilo, difluorometoxi, trifluorometoxi, azido, -OR, -C(0)R,
OR’, NR4C (0) 0R, -CC (0) R, -NRS02R, -S0NRR1,
NRC (0) (0) NR3R4, -NR5C (0) NR-R% -NR5C (NCN) NRR4, -NR3R,

aiquilo, CL,-C aiquenilo, CC1 aiquinil, C3C11,
cicloalquilo, C -C c–cloalquilaiquilo, -8(0) i (CI-CII
alquilo), (0) i (CR4R) mrilo, ari lo, arilalquilo,
heteroarilo, heteroarilalquiio, heterociclilo,
heterociclilaiquilo, 0(CR4R))rn-arilo, NR4(CRRj-arilo, -O(CRR)1-heteroarlo,
heteroarilo, -0(CR4R5)m-heterocicliio y
heterociclilo, donde cada porción de aiquilo, alquenilo, aiquinilo, cicloalquilo, arilo, heteroarilo y heteroc.iclilo es opc.ionalmente sutituida por uno a cinco grupos independientemente
selecciona.ios de oxo, halógeno, ciano, nitro,
trifluorometilo, difluorometoxi, trifluorometoxi,
azido, -NR430R, -S0NRR, -C (0) R, -C (0) 0R,

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- 00(0) R3, -NR4C (0) 0R, -NR4C (0) R3, (0) NR3R!, -NR’R4,
- NR’5C (0) NR3R4, -NRc (NON) NR3R4, -OR3, arilo,
heteroarilo, arilaiquilo, heteroarilaiquilo,
heterociclilo, y heterociclilaiquilo;

R3 es se1ecciondo de hidrógeno, trifluorometilo, y
C -C1 aiquilo, C2 -C1 aiquenilo, C7-C1u aiquinilo, C3Ci,
cicloalquilo, C3-010 cicloalquiloalquilo, arilo,
arilaiquilo, heteroarilo, heteroarilaiquilo,
heterociclilo, y heterociolilaiquilo, donde cada aiquilo, aiquenilo, aiquinil, cicloalquilo, arilo,
heteroarilo y porción de heterociclilo es
opcionalmente sustituida por uno a cinco grupos independientemente seleccionados de oxo, haiógeno, ciano, nitro, trifluorometilo, difluorometoxi, trifluorometoxi, azido, -NR’S02R", -S02NRR",
- C(0)R’, -C(0)OR’, -OC(0)R’, -NR’C(0)OR", -
NRC (0) R", -0(0) NR’R’, -SR’, (0) R’’’’, -502R
NR’R", -NR’C(0)NR’’R", -NR’C(NCN)NR"R", -OR, arilo,
heteroarilo, arilaiquilo, heteroarilaiquilo,
heterociclilo, y heterociclilaiquilo;

R’, R’’ y R’’’ independientemente son seleccionados de

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hiUróqeno, aiquilo inferior, aiquenilo inferior, ariio y
a r ii a 1 q Ul 10;

R’’’’ es seleccionado de aiquilo inferior, aiquenilo inferior
, arilo y arilalquilo. 0

Dos cualesquiera de R’, R’’, R’’’ o R’’’’ pueden ser tomados con ci Ætomo al cual se unen para formar un carbociclo de
4 a 10 miembros, heteroarilo o aniiio heterociclico, cada
uno de los cuales es opcionalmente sustituido por uno a
tres grupos independientemente seiecc.ionados de halógeno,
ciano, nitro, trifluorometilo, difluorometoxi, trifluorometoxi, azido, ariio, heteroariio, ari.ialquiio, heteroarilaiquilo, heterociclilo, y heterociciiiaiquiio; o

R3 y R4 pueden ser tomados con ci Ætomo al cual se unen para formar un carbociclo de 4 a 10 miembros, heteroarilo 0 anillo heterociciico, cada uno de los cuales es opciorialmente sustituido por uno a tres grupos independientemente seieccionados de haiógeno, ciano, nitro, trifluorometilo, difluorometoxi, trifluorometoxi, azido, -NRSO2R, -SONR’R", -C(0)R’, -C(0)OR’, -OC(0)R,
- NR’C(0)OR", -NR C(0)R, -CO)NRR, -SOR, -NR R,

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- NR’C (0) NR’ ’R", -NR’C (NON) NR’ ’R", -OR’, arilo,
heteroarilo, arilaiquilo, heteroarilaiquilo, heterociclilo, y heterociclilaiqullo; o

R4 y R independientemente representan hidrógeno o aiquilo; 0

R4 y R5 junto con el Ætorno al cual se unen para formar un carbociclo de 4 a 10 miembros, heteroarilo o anillo heterociclico, cada uno de los cuales es opcionalmente sustituido por uno a tres grupos independientemente seleccionados de halôgeno, ciano, nitro, trifluorometilo, difluorometoxi, trifluorometoxi, azido, -NR’SO2R"’,
- SO2NR’R", -C(0)R"’’, -C(0)OR’, -OC (0) R, -NR’C (0) OR", -
NR’C (0) R", -C (0) NR’R", -S02R’ ", -NR’ R", -NR’ C (0) NR’ R", - NR’C(NCN)NR"R’, -OR’, arilo, heteroarilo, arilaiquilo, heteroarilaiquilo, heterociclilo, y heterociclilaiquilo;
es seleccionado de trifluorornetilo, y

C1 -C aiquilo, C3 -C- cicloalquilo, arilo, arilaiquilo, heteroarilo, heteroarilalquilo, heterociclilo, heterociclilaiquilo, donde cada porción de alquilo, cicloalquiio, arilo, heteroarilo y heterociclilo es

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opalonalmente 5ustituida par uno a cnaa grupos
independientemente seleccionada5 de oxo, halógeno,
ciano, nitro, triiuorometiia, difluorametoxi, trifluorometoxi, azido, -NRSOR, -SO:NR’R,
(0) R, (0) OR’, -OC (0) R, -NRC (0) OR", -
NR’C(0)R", -C(0)NRR", -SOR", -NR’R’,
-NRC(0) NR›R, -NR’C(NCN)NR"R", -OR’, arilo,
heteroaiilo, arilaiquilo, heteroarilaiquilo,
heteroaiciiio, y heterociclilaiquilo;

R es seleccionado de hidróqeno, y
Cr-Cj,, alLquiio, C2 -C1 aiquenilo, C --C, aiquinil, C:C cicloalquIlo, C."-Clf, cicloaiquiialquiio, arilo,
ari1aiquio, heteroarilo, heteroarilaiquilo,
heterociclilo, heterociclilaJquilo, donde cada aiquilo, aiquenilo, aiquinil, cicloaiquilo, arilo, heteroarilo y porción de heterocc1ilo es opcionalmente sustituida par uno a cinco grupos
independientemente seleccionados de oxo, halógeno,
ciano, nitro, trif.iuorometiio, dif.iuorometoxi, trifluorometoxi, azido, -NR4SO-R, -SONR3R, -C(0)R3,
- C(0)0R3, -OO(0)R, -NR4C(0)OR, -NRC(0)R3,
C (0) NR3R4, SO:R, NR3R’, NR5C (0) NR3R1, -

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NR5C(NCN)NRR4, -OR3, arilo, heteroarilo1 arilaiquilo,
heteroarilaiquilo, heteroic1i1o, y
he t e r o ci c lila 1 qu i 1 o;

es seleccionado de heteroarilo, heterocdclilo, -C(0)OR, -
C(0)NR3R, -C(0)NR4OR, -C(0)R’OR3, -CO) (C3 -C1
cicloalquilo), (0) (C. -C aiquilo), (0) (arilo), -
C(0) (heteroarilo) y -C(0) (heterociclilo), cada uno de los
cuales es opcionalrnente sustituldo por 1-5 grupos independientemente seleccionados de
- NRR4, -OR, -R2, y

C1 -C1) alquilo, C2 -C10 aiquenilo, y C2-Ci aiquinil,
cada uno do los cuales es opcionalmente
sustituido por 1 6 2 grupos indeperidientemente
seleccionados do - NRR4 y

es seleccionado de hidrógeno, -SCF3, -Cl, -Br, -F, ciano,
nitro, trifluorometulo, difluorometoxi, trifluororaetoxi,
azido, -OR3, -C (0) R3, -C (0) OR, -NR4C (0) ORB, -OC (0) B3, -
NR4S02R, -SO2NR3R4, -NR4C (0) R, -C (0) NR3R4, -NR5C (0) NRR4, -

NR3R4, y

C1-Ci aiquilo, C:, -CI!, alquenilo, C.--CI,. aiquinil, CCjj

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alqutlo), -S(0)(CR1R)rr-ar.i1o, artlo, arilaiquilo,
heeroari1o, heteroarilaiquilo, heterooicdilo,
heterociclilaiquilo, -0(CR’R)-ari1o, -NR (CRP)
arilo, -O(CRR)-heteroari1o,
heteroarilo, _O(CRdR5)r-heterooLclilo y -NR’ (CRR5)1-
heterooiclilo, donde cada porción de alqUilo, alquenilo, aiquirill, cicicaiquilo, arilo, heteroarilo y heteroc.icliio es opcionalmente sutituida por uno a cinco grupos independientemente seleccionados de oxo,
haiógeno, ciano, nitro, tr ifluorometilo,
difiuoromeoxi, trifluorometoxi, azido, -NRSOR, -
SONRR4, -C(0)R’, -C(0)OR’, -00(0) R3, -NR-’C(0)OR’, -
NR’0 (0) R3, -C (0) NR3R4, -NR3R4, -NR’(’- (0) NR3R4,
- NR5C(NCN)NRR, -OR3, ariio, heteroarilo,
a rila 1 q u ilo, het e roar i 1 a 1 q ui lo, he t e r 0 C I ci i lo, y
he t e r ocic lila 1 q ui lo;
m es 0, 1, 2, 3, 4 o 5; y
j es 1 0 2.

DESCRIPCION DETALLADA DE LA INVENCION

Los corripuestos nuevos de la presente invenciIn son

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aquellos descritos pot la fôrmula I anteriormente mencionada, y las sales y profÆrrnacos farmacØuticamente aceptables de la

mi sma

La presente invención proporciona compuestos de la formula
I en la cual R es Ci-Ci alquilo, C3 -C cicloalquilo, CCT
cicloalquilalquilo, C3 -C’: heterocicloalquilo o C3 -C
heterocicloalquilalquilo cada uno de los cuales puede ser opcionalmente sustituido pot 1 - 3 grupos independientemente seleccionados de oxo, halógeno, ciano, nitro, trifluorometilo, difluorometoxi, trifluorometoxi, azido, NR4SO7Re, -S02NR3R4,
- C(0)R°, -C(0)0R3, -OC(0)R3, -S02R3, _NRIC(0)ORC, -NRO(0)R3,
- C(0)NR3

R’, NR3R4,-NR50 (0) NR3R4, -NR5C (NCN) NR3R4, -OR’, arilo, heteroarilo, arilalquilo, heteroarilalquilo, heterociclilo, y heterociclilaiquilo.

La presente invención ademÆs proporciona compuestos de la fOrmula I caracterizada porque RC es -OCF3, -Br o -Cl, R2 es hidrógeno, y R es alqu–lo inferior o halógeno.

La presente invención ademÆs proporciona compuestos de la
formula I caracterizada porque R9 es hidrOqeno o halógeno, y RI 2
es hidrógeno.

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La presente invención ademÆs proporciona compuestos de la formula I caracterizada porque W es -C(0)OR’ a -C(0)NR4OR.

La presente invención ademÆs proporciona compuestos de la

fOrmula II:

w
R10

RQ [???RB

II

caracterizada porque W, R, R, R1, R9 y RI C, son coma se define

anteriorrnente para la formula I.

La presente invención ademÆs proporciona compuestos de la
formula II en la cual R es C1 -C aiquilo, C3 -C- cicloalquilo a
C3 -C. cicloalquilalquilo, cada uno de los cuales puede set opcionalmente sustituido par 1 - 3 grupos independientemente
seleccionados de oxo, halOgeno, ciano, nitro,
trifluorometilo, difluorometoxi, trifluorametoxi, azido, -

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NR4SO2R, -SO7NR3R, -C (0) R3, -C (0) ORS, -CC (0) R, -S0R3, -
N R4 C (0) OR’, -NR4C(0) R3, -C (0)NR3R, -NR-R’, -NR3C (0) NR3R4, -
NR5C (NCN)NR3R’, -OR, arilo, heteroarilo, arilaiquilo, heteroarilaiquilo, heterociclilo, y heterocic1i1a1qui10

La presente invención ademÆs proporciona compuestos de la
formula II caracterizada porque RB es -OCF’., -Br o -Cl, y R es
aiquilo inferior o halOqeno.

La presente invención ademÆs proporciona compuestos de la formula II caracterizada porque R es hidrógeno o halOqeno, y R’° es hidrogeno.

La presente invención ademÆs proporciona compuestos de la

formula II caracterizada porque W es -C(0)0R3 o -C(0)NR4 OR-?.

La presente invenciOn ademÆs proporciona compuestos de la
formula III:

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0 A
H R1

R9 R N R2

caracterizada porque R1, R2, R, RG y R’ son como se define
anteriormente para la f6rmula I, y A es a -NR4OR,
caracterizada porque R3 y R’ son como se define anteriorrnente para la formula 1.

La presente invención adernÆs proporciona compuestos de la formula III en la cual R es Cl-C,,, alquilo, C3 -C cicloalquilo a
C3 -C-1 cicloalquilalquilo, cada uno de los cuales puede ser
opcionalmente sustituido par 1 - 3 qrupos independientemnente
seleccionados de oxo, halógeno, ciano, nitro, trifluorometilo,
difluorometoxi, trifluorometox.i, azido, -NRSOR’, -SONRR4,
- C(0)R, -C(o)0R3, -OC(0)R3, SO: R, NR1C(0)OR, NR4C(0)R3,
(0) NR3R4, -NR3R1 -NR5C (0) NRR4, -NRC (NCN) NR3R, -0R, arilo, heteroarilo, arilaiquilo, heteroarilaiquilo, heterociclilo, y heterociclilaiquilo.

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La presente invención ademÆs proporciona compuestos de la
formula III caracterizada porque R1 es -CCF3, -Br o -Cl, R7 es
hidrógeno, y R1 es aiquilo inferior o halógeno.

La presente invencióri ademÆs proporciona compuestos de la
fOrmula III caracterizada porque R9 es hidrogeno o halOgeno.

La presente invención ademÆs proporciona compuestos de la formula III caracterizada porque R3 es hidrOqeno o aiquilo inferior cuando A es -OR3; y R4 es hidrógeno cuando A es -

NR OR.

La presente invención ademÆs proporciona compuestos de la formula lila:

lila

caracterizada porque R’, B2, R, Ru y R9 son como se define

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anteriormente Para la fórmula I, y A es -OR3 o -NR4OR3,
caracterizada porque R y R1 son como se define anteriormente

Para la formula I.

La presente invención ademÆs proporciona compuestos de la
fOrmula lila en la cual R es C -C, alqu:iio, C., -C. cicloalquilo
C:3 -C- cic.loalquiloalquilo, ca(ia uno de los cuales puede ser
opcionalmente sustituido por 1 - 3 grupos independientemente
seleccionados de oxo, halógeno, ciano, nitro, trif]uorometilo,
difluorometoxi, tiifluorometoxi, azido, -NR4SOR, -SO2NR3R,
(0) (0) OR, -OC (0) R3, -SOR3, -NR1C (0) OR, -NR4C (0) R,
(0) NRR’, -NR3R, -NR5C (0) NR3R, -NR5C (NCN)NR3R’, -OR3, arilo,
heteroarilo, arilalquilo, heteroarilalquilo, heterociclilo, y heterociclilalquilo.

La presente invenc.ión ademÆs proporciona compuestos de la
fOrmula lila caracterizada porque RB es -OCF’., -Br o -Cl, R2 es
hidrógeno, y es alquilo inferior o halOgeno.

La presente invención ademÆs proporciona compuestos de la formula lila caracterizada porque R9 es hidróqeno o halOqeno.

La presente invención ademÆs proporciona compuestos de la

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fórmula lila caracterizacla porque R3 es hidrógeno o aiquilo inferior cuando A es -OR3; y R’1 es hidrógeno cuando A es -

NR OR3.

La presente.invención ademÆs proporciona compuestos de la

formula Tub:

II lb

caracterizada porgue R’, R, R y R son como se define anteriormente para la formula I, y A es -OR3 NRaOR, caracterizada porque R3 y R4 son como se define anteriormente para la formula I.

0
La presente invenciOn ademÆs proporciona compuestos de la formula Ilib en la cual R es C-I-Cjt, aiquilo, C3 -C- cicloalquilo 0 C3-Cl cicloalquilalquilo, cada uno de los cuales puede ser opcionalmente sustituido por 1 - 3 grupos independientemente

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seleccionados de oxo, halOgeno, ciano, nitro, trifluorometilo, difluorometoxi, tr.ifluorometoxi, azido, -NR4SOR, _SO?NRR,
- C(0)R3, -C(0)OR, -OC(0)R, -SOR3, -NR’C(0)OR, -NRC(0)R,
(0) NRR’, -NR-R", -NR3C (0) NR3R4, -NRC (NON) NR3R, -OR, arilo, heteroarilo, ariLEllquilo, heteroari11qui1o, heterociclilo, y heterociclilaiquilo.

La presente invenciórl ademÆs proporciona compuestos de la fórmula Ilib caracterizada porque R es -OCF3, -Br o -Cl, y R1 es a.lquilo inferior 0 haiógeno.

La presente invención ademas proporciona compuestos de la formula Tub caracterizada porque R9 es fluoro o cloro.

La presente invención adeniÆs proporciona compuestos de la formula Ilib caracterizada porque R3 es hicirOgeno o aiquilo inferior cuando A es -OR3; y R4 es hidróqeno cuando A es -

NR4 OR3.

Excepto que se defina expresamente lo contraria, la siguiente definiciOn de tOrminos se utiliza en la presente memoria descriptiva.

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Par ’C -C1 aiquilo", ’a1qui1a" y ’a1qui10 inferior" en la
presente invención se entiende grupos aiquilo de cadena ramificada a lisa que tienen 1-10 Ætomos de carbono, como, metilo, etilLo, propilo, isopropilo, n-butilo, sec-butilo, ter-butilo, pentilo, 2-pentila, isopentilo, neopentilo, hexilo, 2-hexilo, 3-hexilo, 3-metilpentilo, heptilo, octilo, y similares. Los radicales aiquilo preferidos son C1 aiquilo. Radicales aiquilo particularmente preferidos son C -i-3 aiquilo.

Por "C2-C aiquenilo", ’a1queni10 inferior" y ’alqueni1o"
se entiende radicales de hidrocarburo lisos o ramificados que tienen de 2 a 10 Ætomos de carbono y al menos un enlace doble e incluye etenilo, propenilo, 1-but-3-enilo, 1-pent---3--enilo, 1-hex-5-enilo y similares. Se prefiere aiquenilo inferior que tiene de 3-5 Ætomos de carbono.

Par C2(-10 aiquinil", "alquinil inferior" y ’alquini1" se
entiende radicales de hidrocarburo ramificados a lisos que tienen de 2 a 10 Ætomos de carbono y al menos un enlace triple e incluye etinilo, propinilo, butinilo, pentin-2-il y
similares. Se prefiere aiquinil que tiene de 3-5
Ætomos de carbono.

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Par el tØrmino "halóqeno" en la presente invención se entiende flior, bramo, clara, y yado.

Por "arilo" se entiende un grupo carbocIclica aramÆtico
que tiene un anillo ünica (par ejempla, fenfl.a), anillas
multiples (par ejempla, bifenilo), a anillos mltip1e3
condensadas en las cuales al menas una es ararnÆtica, (par
ejempla, 1,2,3,4-tetrahidronaftila, naftilo), que es opcionalmente mono-, di-, a trisustituida can, par ejempla,

10 halógena, aiquilo inferior, alcoxi inferior, trifluarametilo,
arila, heteraarila, e hidraxi.

Par "heteraarilo" se entiende una a mÆs sistemas de
anillas aramÆticas de 5-, 6-, 6 7-miembras que incluyen
sistemas de anillas fusianadas (al menas una de las cuales es
aramÆtica) de 5-10 Ætomas que cantienen al menas una y hasta
cuatra heteraÆtomos seleccionados de nitrógena, axigeno, o azufre. Ejemplas de grupos heteraarilos son piridinila, imidazalilo, pirimidinilo, pirazolilo, triazolila, pirazinilo, tetrazolila, furila, tienila, isaxazalila, tiazalila, oxazalila, isotiazolilo, pirrolilo, quinolinilo, isaquinolinila, indalila, benzimidazalila, benzofuranila, cinnolinilo, indazolilo, indolizinilo, ftalazinilo,

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piridazinilo, triazinilo, isoindolilo, pteridinilo, purinilo, oxadiazolilo, triazolilo, tiadiazo.1–lo, tiadiazolilo, furazanilo, benzofurazanilo, bonzotioferiilo, benzotiazolilo, benzoxazolilo, quinazolinilo, quinoxalinilo, naftiridinilo, y furopiridinilo. Las porciones espiro tairibiØn se encuentran
cjentro del alcance de la presente definición. Los grupos
heteroarilos son opcionalLmente mono-, di-, o trisustituidos por, por ejemplo, halógeno, aiquilo inferior, alcoxi inferior, haloalquilo, arilo, heteroarilo, e hidroxi.

Como se utiliza en la presente, el termino ’carbociclo",
"carbociclilo", "cicloalquilo" o ’C3 -C1 cicloalquilo" se
refiere a los radicales carbociclicos saturados que tienen tres a diez Ætomos de carbono. El cicloalquilo puede ser un sistema monociclico, o un sistema policiclico fusionado, y puede fusionarse con un ariillo aromÆtico. Ejemplos de dichos radicales incluyen, ciclopropilo, ciclobutilo, ciclopentilo y ciclohexilo. Los grupos cicloalquilo en la presente no estÆn sustituidos, o como se especifica, sustituidos en uno o rnÆs posiciones con varios grupos. Por ejemplo, dichos grupos cicloalquilo pueden ser opcionalmente sustituidos por, por
ejemplo, Ci-CF, aiquilo, C1 -C aicoxi, halógeno, hidroxi, ciano,
nitro, amino, mono (C:i.-C)alquiloamino, di(C1-C6)alquiloamino,

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C2-Clquenilo, C7-Calquinilo, C-0 hloalqullo, haloalcoxi, amino (C1-C)a1quilo, mono (CI -C)a1quiloamino(C-0)alquilo o di(C-C)a1qui1oamino(C1-C)a1quilo.

Por ’heterocic1o" o "heterociclilo" se entiende uno o mÆs sistemas de anillos carbociclicos de 5-, 6-, 6 7-miembros que incluye sistemas de anillos fusionados de 4-10 Ætomos que contienen al menos uno y hasta cuatro heterotomos seleccionados de nitrÆqerio, oxigeno, o azufre, siempre que el anillo del grupo no contenga dos 0 adyacentes o Ætornos S. Un sisterna fusionado puede ser un heterociclo fusionado aun grupo arornÆtico. Heterociclos preferidos incluyen, poro sin limitarse, pirrolidinilo, tetrahidrofuranilo, dihidrofuranilo, tetrahidrotienilo, tetrahidropiranilo, dihidropiranilo, tetrahidrotiopiranilo, piperidino, rnorfolino, tiomorfolino, tioxanilo, piperazinilo, homopiperazinilo, azetidinilo, oxetanilo, tietanilLo, homopiperidinilo, oxepanhlo, tieparxiio, oxazepinilo, diazepinilo, tiazepinilo, 1,2,3,6-tetrahidropiridinilo, 2-pirro.iinilo, 3-pirrolinilo, indo] inilo, 2H-piranilo, 4H-piranilo, dioxanilo, 1, 3-dioxolanilo, pirazolinilo, ditianilo, ditiolanilo, dihidropiranilo, dihidrotienilo, dihidrofuranilo, pirazolidinilimidazolinilo, imidazolidinilo, 3-azahicico [3.1. 0]hexaniio, 3-

f)j

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azabiciclo[4.1.0]heptanilo, azabiciclo[2.2.2]hexanilo, 3H-
indolil y quinolizini10 Las porciones espiro tambiØn estªn
incluidas dentro del alcance de la presente definición. Los mencionadas grupos, coma derivan de los grupos mencionados anteriormente, pueden estar unidos a C a unidos a N cuando dichas un–ones son posibles. Par ejemplo, un grupo derivado de pirrolo puede ser pirrol-1-il (unido a N) a pirrol-3--ii (unido a C). AdemÆs, un qrupo derivado de imiciazol puede ser imidazal-1-il (unido a N) a imidazol-3-il (unido a C) - Un ejemplo de un
grupo heterociclico donde Ætomos de carbono de dos anillos son
sustituidos por porciones oxo (=0) es 1,1-dioxo--tiomorfolinilo. Los grupos heterocicla en la presente no estÆn sustituidos, a segun se especifica, son sustituidos en una a mÆs posiciones adecuadas par varios grupos. Par ejemplo, cada grupa heterocicla puede ser opcionalmente sustituido par, por
ejemplo, C1 -C6 aiquilo, C1 -C6 alcoxi, halógeno, hidroxi, ciano,
nitro, amino, mono (C1-C)alquilamino, di(C1-C)alqui1amino, C7-
C6alquenilo, C7-C6alquinilo, Cl-C6 haloalquilo, C1 -C haLoalcoxi, amino (C1-05)alquilo, mono (Ci-C)alquilaamino(Ca-C)alqui10 0 di (C -C6) aiquiloamino (C1 -C6) aiquilo.

El tØrmino "arilaiquilo" significa una pardon de aiquilo (coma se define anteriormente) sustituida con una a mÆs

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porciones de arilo (tamblØn definido anteriarmente) Radicles arialquilo particularmente preferidos son aril-C1-.3-alquilos. Los ejemplos incluyen bencila, feniloetilo, y similares.

El tØrmino ’heteraarilalqui1o" significa un porciOn aiquila (coma se define anteriarmente) substituida par una pardon heteroarilo (tambiØn coma se define anteriormente). Los radicales heteroarilaiquilo aun mÆs preferidos son heteroaril-C-aiquiio de 5- 0 6 miembros. Los ejemplos incluyen, axazolilmetilo, pirdileti1a y similares.

El tØrmino "heterociclilalquiio" significa una porción alquila (coma se define anteriormente) sustituida par una porción heterociclila (tambiØn definida anteriormente) Los radicales heteraciclilalguilo aun mÆs preferidos son heterocic.iii-C,.-alquilo de 5 6 6 miembros. Los ejemplos incluyen tetrahidropiranilmetilo.

El tØrmino "cicloalquiloalquilo" significa una porción aiquilo (coma se define anteriarmente) susttuida par una porción cicloalqui].o (tambiØn definida anteriormente). Los radicales heteraciclila aun mÆs preferidos son cicloalquila-C: 3-alquilo de 5 0 6 miembros. Los ejemplos incluyen

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ciclopropilmetilo.

El tØrrnino "Me" significa metilo, ’’Et" significa etilo,
"Bu" significa butilo y "Ac" significa acetilo.

La frase ’’sal(es) farmacØuticamente aceptable(s)", como se
usa en la presente, a menos que se indique lo contrario, incluye sales de grupos Æcidos y bsicos que pueden estar presentes en los compuestos de la presente invención. Los compuestos de la presente invención que son bÆsicos per naturaleza son capaces de formar una amplia variedad de sales con varios Æcidos orgÆnicos e inorgÆnicos. Los Æcidos que pueden ser utilizados para preparar sales de adición farmacØut–camente aceptables de dichos compuestos bÆsicos de la presente inverición son aquellos que forman sales de adición no tóxicas, es decir, sales que contienen aniones farmacØuticarnente aceptables, comb sales de acetato, bencensulfonato, benzoato, bicarbonato, bisulfato, bitartrato, borato, bromo, calcio, camsilato, carbonato, cloruro, clavulanato, citrate, dihidrocloruro, edisliato, estolato, esilato, etilosuccinato, fumnarato, gluceptato, gluconato, glutamato, glicollilarsanilato, hexilresorcinato, hidrabamina, hidrobromo, hidrocloruro, yoduro, isotionato, lactato,

all-
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lactobionato, Laurato, malato, maleato, mielato, rnesilato, met ilLosulfato, mucato, napsilato, nitrato, oleato, oxalato, pamoato (embonato), palimitato, pantotenato, fosfato/difosfato, poligalacturonato, salicilato, estearato, subacetato, succinato, tanato, tartrato, teoclato, tosilato, trietiodode, y valerato. Ya un compuesto simple de l& presente invención puede incluir ms de una porciOn Æcida o bÆsica, 105 compuestos do la presente invención tambien pueden incluir mono, di o tn-sales en un compuesto ünico.

En el caso de la porción Æcida en un compuesto de la presente invención, una sal puede formarse mediante tratamiento de un compuesto de la presente invención, con un compuesto bÆsico, particularmente una base inorgÆnica. Las sales inorgÆnicas prefenidas son aquellas formadas con metales alcalinos y alcalinotØrreos como el litio, sodio, potasio, bario y calcio. Las sales de base orqÆnica preferidas incluyen por ejemplo, amonio, dibencilamonio, bencilamonio, 2-hidroxietiloamonio, bis(2-hidroxietilo)amonio, feniletilbencilamina, dibencil-etilendiamina, y sales similares. Otras sales de porciones Æcidas pueden incluir, por ejemplo, aquellas sales formadas con procaina, quinina, y N-metiloglusoamina, mÆs sales formadas con aminoÆcidos bÆsicos

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corno glicina, ornit.ina, hlstliina, fenilylicina, lisina y arginina. Una sal especialmente preferida es una sal de sdio o de potasio de un compuesto de la presente invención.

Con respecto a las porciones bÆs.icas, una sal es formada rnecLLante tratamiento de un compuesto de la presente invención con un compuesto Æcido, particularmente un Æcido inorgÆnico. Las sales inorgÆnicas preferidas de este tipo –ncluyen, por ejemplo, sales de hidrocloruro, de hidrobromo, de hidroyoduro, de azufre o fosfóricas, o sales similares. Las sales orgÆnicas preferidas de este tipo, pueden incluir, por ejemplo, sales forrnadas con Æcido fórmico, acØtico, succinico, cItrico, lÆctico, maleico, fumÆrico, palmitico, cólico, pamoico, rndcico, D-glutÆmico, L-camfórico, glutÆrico, glicólico, ftÆlico, tartÆrico, laurico, esteÆrico, saliciclico, metanosulfónico, bencenosulfónico, paratoluenosulfónico, sdrbico, pdrico, benzoico, cinnÆrriico y Æc.idos orgÆnicos similares. Una sal especialmente preferida de esta clase es una sal de hidrocloruro o sal de sulfato de un compuesto de la presente invencidn -

En los compuestos de la presente invención, donde se utilizan tØrminos como CRR3) 0 C}R), R y R5 pueden

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variar con cada iteración de m a t sabre 1. Par ejemplo, donde
m a t es 2, los tØrminos (CR4R)rn a (CR4R) pueden igual
CH7CH2- a -Cli (OH.3) C (CHCH:3) ((’H7CH-CH3) - a cualquier nÆmea de
parciofles sirnilares que se encuentran dentro del &lcance de las definicianes de R4 y R.

Ciertos campuestos de la presente invención pueden tener centras asimØtricas y par la tanta existen en diferentes farrnas enantiamØrricas. Se cansidera que todos las isómeras y estereaisórneras ópticas de las campuestos de la presente
invención, y mezclas de las nusmos, estÆn dentro del alcance de
la presente invención. Can respecta a las carnpuestas de la presente invención, la invención incluye el usa de un racemato, una a mÆs farrnas enantiamØricas, una a mÆs farmas diastereamØricas, a rnezcla de las mismas. Los cornpuestos de la presente invenciOn pueden existir adernÆs coma tautómeras. La presente invenc.ión se relaciana con el usa de tados las tautórneras y mezolas de las mismas.

La presente invención tambiØn incluye compuestos etiquetados isotópicamente, que son idØnticas a las mencianadas en la presente invención, excepto par el hecha de que una a mds Ætamas son reemplazadas par un Ætama que tiene una masa

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atórnica o un ntrnero de masa diferente de la masa atómica o del nimero de masa usualmente encontrado en in nnturaleza Ejemplos de isótopos que pueden set incorporados en los compuestos de in invención inciuyen isótopos de hidrógeno, carbono, nitrógeno, oxIqeno, fósforo, azufre, fluor y cioruro,

como pot ejemplo 2F1, 3H, 13C, a4C, 1N, 0, 10, ulp, uup, 3g,
y Cl, respectivamente. Los compuestos de in presente
invención, profÆrmacos de los rnismos, y sales farmacØuticamente aceptabies de dichos compuestos o de dichos profÆrmacos que contienen los isótopos anteriormente mencionados y/ u otros isótopos de otros Ætomos, estÆn dentro del alcance de in presente invención. Ciertos compuestos etiquetados isotópicnmente de la presente invención, pot ejemplo aquellos en los cuales se incorporan isótopos radioactivOs como 3H y

ill C,
son eficaces en ensayos de distribución de droga y/ o tejido de substrato. Isótopos triturados, es decir, 3H y carbono-14, es decir, O, son particularmente preferidos par su fÆcii preparación y detectabilidad. AdemÆs, in sustitución con isótopos mÆs pesados como el deuterio, es decir, 2H, puede proporcionar ciertas ventajas terapØuticas que dan como resultado mayor estabilidaci metabóiica, pot ejemplo vida media in vivo incrementada o requerimierito de dosis reducida, y pot lo tanto, pueden set preferida en aigunas circunstancias. El

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compuesto etiquetado isotópicamente de la presente invención y los profÆrmacos del misrno pueden generalmente ser preparados realizando procedimientos revelados en los Esquemas y/ o en los Ejemplos y Preparaciones que se encuentran a coritinuación, mediante sustitucibn de un reactivo disponible rÆpidamente etiquetado isotópicamente para un reactivo etiquetado no isotópicamente.

La presente invención ademÆs comprende composiciones farmacØuticas que contienen un compuesto de las fórmulas 1-Ilib y mØtodos para tratar enfermedades proliferativas, o crecimiento celular anormal, administrando profÆrmacos de compuestos de la presente invención. Los compuestos de la presente invención que tierien grupos libres amino, amido, hidroxi o carboxulico pueden ser convertidos en profÆrmacos. Los profÆrmacos incluyen compuestos caracterizados porque un residuo de amino Æcido, o una cadena de polipØptidos de dos o mÆs (por ejemplo, dos, tres o cuatro) residuos de amino Æcido es unido en forma covalente a travØs de una union de amida o ester a un amino libre, hidroxi o grupo de Æcido carboxilico de compuestos de la presente invención. Los residuos de amino Æcidos incluyen, pero sin limitarse, los 20 aminodcidos que ocurren naturalrnente comOnmente designados por sirribolos de tres

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letras y ademÆs incluyen 4-hidroxiprolina, hidroxilisina, demosina, isodernosina, 3-metilohistidina, norvalina, beta-alaniria, 6cido gamma-aminobutirico, cirtu].lina, homocisteina, homoserina, ornitina y metionina sulfona. TambiØn se incluyen clases adicionales de profÆrmacos. Por ejemplo, grupos carboxilo libre pueden ser derivados coma amidas a aiquilo Østeres. Crupos hidroxi libre pueden ser derivados utilizando grupos iracluyendo pero sin limitar, hemisuccinatos, Østeres de fosfato, dimetilaminoacetatos, y fosforiloximetiloxicarbonilos,
coma se delineó en Advanced Drug Delivery Reviews 1996, 29,
115. Los profÆrmacos de carbamato de grupos hidroxi y amino
tambiØn se incluyen, coma lo son los profÆrmacos de carbonato, Østeres de sulfonato y Østeres de sulfonato de grupos hidroxi. TambiØn se incluye derivación de grupos hidroxi coma Østeres(aciloxi)metIlico y (aciloxi)etilico donde el grupo acilo puede ser un ester aiquilo, opcionalrnente sustituido por grupos que incluyen, pero sin limitar, funcionalidades de Øter,
amnina y Æcido carboxIlico, a donde el qrupo acilo es un ester
aminoÆcjdo coma se describió anteriormente. ProfÆrmacos de este
tipo se describen en J. Med. Chem. 1996, 39, 10. Las aminas
libres tambiØn pueden ser derivadas coma amidas, suifonamidas o
fasfanamidas. Tocias estas porciones de profÆrmacos pueden
incorporar grupos incluyendo, pero sin limitar, funcionalidades

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de Øter, amina, y Æcido carboxilico.

Se entiende que cuando dos o mÆs radicales son utilizados
en suceslón para definir un sustituyente unido a una estructura, el primer radical nombrado es considerado terminal y el iitimo radical nombrado es considerado estar unido a la estructura en cuestión. De esta manera, por ejempio, el radical arilaiquilo estÆ unido a la estructura en cuestión medi.ante un qrupo alquilo.

La presente invención tamhiØn se relaciona con una composirión farmacØutica para el tratamiento de una enfermedad hiperproliferativa en un mamifero que comprende una cantidad terapØuticamente efectiva de un compuesto de la presente invenciOn, o una sal o profÆrmaco o hidrato farmacØuticamente efectivos, y un portador farmacØuticamente aceptable. En una realización, dicha composición farmacØutica se utiliza para el tratamiento del cancer como cancer de cerebro, de pulmón, de cØlula escamosa, de vejiga, de estómago, de pancreas, de mamas, de cabeza, de cuello, renal, de riæón, de ovario, de próstata, colorectal, de esófaqo, de testiculo, ginecológico o de tiroides. En otra realización, dicha composicibn farmacØutica se utiliza para el tratamiento de enfermedades

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hiperproliferativas no cancerigenas coma hiperplasia benigna de
la piel (par ejemplo, psoriasis), restenosis, a próstata (par
ejernplo, hipertrofia prostÆtica benigna (BPH)

La presente invención ademas se relaciona can una
cornposición farmacØutica para el tratamiento de pancreatitis
a enfermedades renales (incluyendo glomerulonefritis proliferativa y enfermedad renal.inducida par diabetes) a el tratamiento del dolor en an mamifera que comprende una cantidad teraputicamente efectiva de an cornpuesto de la presente invención, a una sal, profÆrmaco a hidrato farmacØuticamente aceptables y an portador farmacØuticamerite aceptable.

La presente invención ademÆs se relaciona con una compasición farmacØutica para la prevención de la implantación de blastocitas en un rnamifero que comprende una cantidad terapØuticamente efectiva de an compuesto de la presente invención, a una sal, prafÆrmaco a hidrato farmacØuticamente aceptables y an portador farmacØuticamente aceptable.

La presente invención ademÆs se relaciona con una composición para el tratamiento de una enfermedad relacionada con vasculaqØnesis a angiogenesis en un mamifero que comprende

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una cantidad terapØuticamente efectiva de un compuesta de la presente invención, a una sal, pratdrmaco a hidrato farmacØuticamente aceptables y un partadar faimacØut.icamente aceptable. En una realización, dicha composición farmacØutica
se utiliza para el tratamiento de una enfermedad selecconadas
del grupa formado par angiogenesis de tumor, enfermedades inflamatarias crdnicas coma artritis reumataide, aterosclerosis, enfermedad inflamatoria del intestino grueso, enfermedades de piel, coma psoriasis, eczema, y sclerade.tma, diabetes, retinopatIa diabØtica, retinopatia de prematurita, deqeneración macular senil, hemanqiama, qliama, melanoma, sarcoma de Kaposi y cancer de avario, de mamas, de pulmón, de
pancreas, de próstata, de colon, y de epidermis.

La presente invención tambiØri se relaciona can un mØtodo
para el tratamiento de una enfermedad hiperpraliferativa en un
mamifero que comprende administrar a dicho rnamifero una
cantidad terapØuticamente efectiva de un compuesta de la ispresente invención, a una sal a profÆrmaco a hidrato farmacØuticamente efectivas, y un portador farmacØuticamente
aceptable. En una reaiización, dicho mØtodo se relaciona co el
tratamiento del cancer coma cancer de cerebra, de pulmón, de
cØlula escamasa, de vejiga, de estOmago, de pancreas, de mamas,

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de cabeza, de cuello, renal, de riæón, de ovarlo, de próstata, colorectal, de esófago, de testIculo, qinecológico o de tiro–des. En otra realización, dicho rnØtodo se relaciona con el tratamiento de enfermedades hiperproliferativas no cancerigenas como hiperplasia benigna de la piel (pot ejernplo, psoriasis), restenosis, o próstata (pot ejemplo, hipertrofia prostÆtica benigna (BPH))

La presente invención tamblØn se relaciona con un mØtodo
para el tratamiento de una enfermedad hiperproliferativa en un mamifero que comprende adrrünistrar a d–cho mamifero una cantidad terapØuticamente efectiva de un compuesto de la presente invención, o una sal o profÆrmaco o hidrato farmacØuticamente aceptables, en combinación con un agente anti- tumor seleccionado del grupo forrnado por inhibidores mitóticos, agentes de alquilación, anti-metabolitos, antihióticos intercambiables, inhibidores de factor de crecimiento, inhibidores del ciclo celular, inhibidores de enzimas, inhibidores topoisomerasa, modIficadores de la respuesta biológica, anti hormonas, inhibidores angiogenesis y anti-andrógenos.

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La presente invención tambiØn se relaciona con un mØtodo
para el tratamiento de pancreatitis o enfermedad renal en un marnifero que comprende arninistrar una cantidad terapØuticamente efectiva de un compuesto de la presente invención, o una sal, un profdrmaco o un hidrato farmacØuticamente aceptables del misrno.

La presente invenci.ón tambi.Øn se relaciona con un mØtodo para la prevención de implantación de blastocito en un rnamifero
que comprende la adrninistración de una cantidad
terapØut.icamente efectiva de un compuesto de la presente invención, o una sal, un profÆrmaco o un hidrato farmacØut–carnente aceptables del rnismo.

La presente invención tambiØn se relaciona con un mØtodo
para el tratamiento de enfermedacies relacionadas con vasculogØnesis o angiogØnesis en un marnifero que comprende la adrninistración a dicho marnifero de una cantidad

10 terapØuticamente efectiva de un compuesto de la presente

invención, o una sal, un profdrmaco 0 Ufl hidrato
farmacØuticamente aceptables del mismo. En una realización,
dicho mØtodo se utiliza para el tratamiento de enfermedades seleccionadas del grupo forrnado por angiogØnesis de tumor,

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enfermedad inflamatoria crónica como artritis reumatoide, aterosclerosis, enfermedad inflamatoria del intestino, enfermedades de la piel como psoriasis, eczema, y escieroderma, diabetes, retinopatia diabØtica, retinopatia de prematurita, degeneración macular senil, hernangioma, glioma, melanoma, sarcoma de Kaposi y cancer de ovario, de mamas, de pulmón, de pancreas, de próstata, de colon y de piel.

Los pacientes que pueden ser tratados con compuestos de la presente invención, sales, profÆrmacos y hidratos farmacØuticamente aceptables de dichos cornpuestos, de acuerdo con los mØtodos de la presente invención, incluyen por ejemplo, pacientes a los que se les ha diagnosticado psoriasis,
restenosis, aterosclerosis, BPH, cancer de pulrndn, cancer de
huesos, CMNL, cancer de pancreas, de piel, de cabeza y cuello,
melanoma cutÆneo o intraocular, melanoma, cancer uterino, de
ovario, cancer rectal, cancer de la region anal, de estómago,
de colon, de mamas, de testiculo, tumores ginecolOgicos (por

16 ejemplo, sarcomas uterinos, carcinoma de trompas de Falopio,
carcinoma del endometrio, carcinoma del cuello del Otero,
carcinoma vaginal o carcinoma de vulva), mal de Hodgkin, cancer
de esófago, cancer de intestino delgado, cancer de sistema
endocrino (por ejemplo, cancer de tiroides, paratiroides o

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glÆndulas adrenales), sarcomas de tejidos blandos, cancer de uretra, de pene, de próstata, leucemia crónica a aquada, tumores sólidos de nifez, linfomas linfoclticos, cancer de vejiga, cancer de riæón, a ureter (por ejemplo, carcinoma celular renal, carcinoma de pelvis renal) o neoplasmas del sistema nervioso central (par ejemplo, linfoma primaria SNO, tumores en columna vertebral, gLioma de tallo cerebral o adenoma pituitario)

La presente invención ademÆs se relaciona con una compazición farmacØutica para inhibir el crecimiento celular anorrnai en un mamifero que comprende una cantidad del compuesto
de la presente invención, a una sal, solvato a profÆrmaco farmacØuticamente aceptables, en combinaciÆn con una cantidad
de quimioterapia de radiación, caracterizada porque las
cantidades del compuesto, sal, solvato o profÆrmaco y de la quimioterapia son juntas efectivas en la inhibición del

10 crecimiento celular anormal. Muchos quimioterapedticos son

actualmente conocidos en la materia. En una realización, el quimioterapØutico es seleccionado del grupo formado por
inhibidores mitóticos, agentes de alquilación, anti-
metabolitos, antibióticos intercamb.iables, inhihidores del

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factor de crecimiento, inhibidores del ciclo celular, enzimas, inhibidores de topoisomeraza, moclifloadores de la respuesta biológica, anti-hormonas, inhibidores de angiogenØsis, y anti-andrdgenos.

La presente invención ademÆs se relaciona con un mØtodo para inhibir el crecimiento celular anormal en un mamIfero o para tratar una enfermedad hiperproliferativa cuyo mØtodo comprende administrar a dicho mamIfero una cantidad del compuesto de la presente invención, o una sal, solvato o profÆrmaco farmacØuticamente aceptables, en combinación con una terapia de radiación, caracterizada porque las cantidades del
compuesto, sal, solvato a profÆrmaco estªn en comhinación con
la terapia de radiación efectiva en la inhibición del crecimiento celular anormal a en ci tratamiento de la enfermedad proi.iferativa en el mamIfero. Las tØcnicas para administrar terapia de radiación son conocidas en 1 materia, y estas tØcnicas pueden ser utilizadas en la terapia de
combinación coma se menciona en la presente. La admnistración
del compuesto de la invención en la terapia de combinación puede ser determinada como se describe en la presente.

Se cree que los compuestos de la presente invención pueden

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hacer que las cØlulas anormales se vuelvan mÆs sensibles al tratamiento con radiación para matar y/ o Jnhibir el crecimiento de dichas cØlulas. De tal manera, esta invención ademÆs se relaciona con un mØtodo para sensibiliar las cØlulas anormales en un mamifero para el tratamiento con radiación que comprende aciministrar a un mamifero una cantidad del compuesto de la presente invención o una sal, o solvato a profÆrmaco del mismo farmacØuticamente aceptable cuya cantidad es efectiva para sensibilizar cØlu].as anormales para el tratamiento con radiación. La cantidad del compuesto, sal, o solvato en este mØtodo puede set determinada de acuerdo con el medio para determinar cantidades efectivas de dichos compuestos descritos en la presente.

La presente invención ademØs se relaciona con un mØtodo y
una composición farmacØutica de inhibición del crecimienta celular anormal en un mamifero que comprende una cantidad de un compuesto de la presente invención, a una sal a solvato a profÆrniaco del mismo farmacØuticamente aceptable, 0 Ufl derivado etiquetado isotópicamente del mismo, y una cantidad de una o mÆs sustancias seleccioriadas de agentes anti-’angiogØnesis, jnFijbidores de transducción de seæal, y agentes antiproliferativos.

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Los agentes anti-anqiogØnesis, coma los inhibidores de
MMP-2 (matriz-metaioprotienasa 2), inhibidores de MMP-9
(matriz-meta11oprotienasa 9), e inhib.idores de COX -IT
(ciclooxigenasa II), pueden ser utilizados en conjunción con un compuesto de la presente invencOn y composiciones farmacØuticas descriptas en la presente. Eljempios de
inhibidores de COX -IT eficaces incluyen CELEBRI8X’ (alecoxib)
valdecoxib, y rofecoxib. Ejemplos de inhibidores de
metalloprotienasa de matriz eficaces se describen en
96/33172 (publicada el 24 de octubre, 1996), O 96/27583
(publicada el 7 de marzo, 1996), Solicitud de Patente Europea No. 9730497.1.1 (presentada el 8 de julio, 1997), Solicitud de Patente Europea No. 99308617.2 (presentada el 29 de octubre, 1999), WO 98/07697 (publicada el 26 de febrero, 1998), WO 98/03516 (publicada el 29 de enero, 1998), WO 98/34918
(publicada el 13 de agosto, 1998), WO 98/34915 (publica el 13
de agosto, 1998), WO 98/33768 (publicada ci 6 de agosto, 1998) WO 98/30566 (publicada el 16 de julio, 1998), publicación de Patente Europea 606,046 (publicada el 13 de julio, 1994), Pubiicación de Patente Europea 931,788 (publicada el 28 de
julio, 1999), WO 90/05719 (publicada el 31 de rrLayO, 1990), WO
99/52910 (publicada el 21 de octubre, 1999), WO 99/52889

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(publicada el 21 de octubre, 1999), O 99/29667 (publicada el
17 de junio, 1999), Solicitud Internacional por PCT No. PCT/1B98/01113 (presentada el 21 de julio, 1998), Solicitud de Patente Europea No. 99302232.1 (presentada el 25 de marzo, 1999), Solicitud de Patente de Gran Bretafia No, 9912961.1 (presentada el 3 de junio, 1999), Solicitud Provisional de Estados Unidos No. 60/148,464 (presentada el 12 de agosto, 1999), Patente de Estados Unidos 5,863,949 (concedida el 26 de
enero, 1999), Patente de Estados Unidos 5,861,510 (concedida el
19 de enero, 1999), y Publicación de Patente Europea 780,386 (publicada el 25 de junio, 1997), las cuales se incorporan en

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la presente por referencia en su totaliclaci. Inhibidores de MMP-2 y MMP-9 prefericlos son aquellos que tienen poca actividad inhibidora de I4MP-1 o que ni siquiera poseen dicha actividad. MÆs prefereritemente se encuentran aquellos que inhiben selectivamente MMP-2 y/ o MMP-9 en relaciOn con las otras
metalloproteinasas de matriz (por ejernplo, MMP-IL, MMP-3, MMP-4,
MMP-5, MMP-6, MMP-7, MMP-8, MMP-10, MMP-11, NMP--12, y HMP-13)

Algunos ejemplos especIficos de inhibidores de MMP eficaces en la presente invención son AG -3340, RO 32-3555, y RS

13-0830.

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Los tØrminos "crecimiento celular anormal" y ’enfermedad hiperproliferativa" se utilizan de manera intercambiable en la presente solicitud.

"Crecimiento celular anarmal", coma se utiliza en la presente, a menos que se indique lo contraric, se refiere al crecimiento celular que es independiente de los mecan–smas reguladores normales (par ejemplo, pØrdida de inhibición al contacto). Esto incluye, por ejemplo, el crecimiento anormal de
(1) cØlulas tumorosas (tumores) que proliferan mediante la expresión de tirosin cinasa mutada a sobre expresión de una tirosin cinasa receptora; (2) cØlulas malignas y benignas de otras enfermedades proliferativas en las cuales se produce la sabre activación de tirosin cinasa; (3) cualquier tumor que prolifera por tirosin cinasa receptores; (4) cualquier tumor que prolifera por sobre activación de serif/ tirosin cinasa y
(5) cØlulas benignas y malignas de otras enfermedades proliferativas en las cuales se produce la sabre activación de serin/ tirosin cinasa.

El tØrmino "tratar", coma se utiliza en la presente, a menos que se indique lo contraria, significa revertir, aliviar,
inhibir el progreso de la eniermedad a evitar dicha enfermedad

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o mal para la cuEd se aplica este terrnino, 0 Ufl() o mÆs sintomas de dicha enfermedad o mal. El tØrmi.no "tratarniento", como se utiliza en la presente, a ruenos que se indique lo contrario, se refiere Ed acto de tratar como ya se ha definiclo dicho tØrmino "tratar".

Los compuestos representativos de la presente invención,
que se encuentran abarcados en la presente invención, incluyeri pero sin limitar, los compuestos de los ejemplos y sus sales de adición base a Æcidas farmacØuticamente aceptables o profÆrmacos de los rnismos.

Los ejemplos presentados mÆs adelante pretenden ilustrar realizaciones particulares de la invención y de ninguna rnariera intentan limitar el alcance de la rnemoria descriptiva o de sus reivindicaciones.

En los Esquemas 1-4 se muestra una ilustración de la preparación de los compuestos de la invención.
Esquerna 1

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H R1

S

N

H2N...-, F /....
NH2 R2

6

. O 0 H Ri
N

B

N . F /
- NH R2

8

HO...
H R1

HN. F [R8

R2

10

11

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CO2Me

...F

02N......

NH2

4

H R1

N /

N, 7 F/ R8
R2
R7

9

Esquema 2

H R1
N.

... 02N F i-.

NH2 R2

12

H
N

N F /....

- - NH 14

R

HO. .0
H R1
N,.

N I F
R2
R
10

H
H

NT

11/
.. R8

R2
R

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N.

17 H R1

J.
/R8
R2
15

H

V H R1
,N.

F R8

17

Esqueua 3

N.O
Ri

HO/H\N

F

/16

Ra
Nn......F 7..

R2

18

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S

S

H R1

N .’

R-. N F
R2

19

Esquema 4

H2N
N
ON
H R1

N ../

1..
R7-- N

...:........F /.......
N

24

2co

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Esquema 5

OO HO H0

H R1 H R1 H

FciR8

N N

R8 - HN / HN"Y’ F / R HN 7F / j
R2)/N R2 R2
R7 9 R7 30 R7 31

R,,OH
I H R1 1-4 R1

HN*F/ HN1 /
R2 N

F R3
R2

R7 32 R7 33

Los mØtodos sintØticos generales que pueden ser

mencionados para la preparación de algunos compuestos de la

presente invención se proporcionan en la solicituci PCT nürnero

WO 00/42022 (publicada el 20 de julio, 2000) La mencionada

solicitud de patente se incorpora en la presente pot referencia

en su totalidad.

Los ejemplos presentados mÆs adelante pretenden ilustrar

realizaciones particulares de la invención y no pretenden de

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ninguna manera limitar el alcance de la memoria descriptiva o
de las reivindicaciones.

En los Esquemas 1-4 se muestra una ilustración de la
preparación de compuestos do la presente invención.

El Esquema 1 ilustra la sintes.is de los compuestos de la
presente invención. En el paso 1 el Æcido es riltrado uti.lizando condiciones generales preferentemente despiciiendo Æcido nitrico en H7SO1. En el paso 2, la anilina es preparada mediante desplazamiento de fluoruro con NHOH a temperatura ambiente en agua sequido de una meticulosa acidificación con Æcido mineral
concentrado a un pH cercano a 0. En el paso 3, el ester es
preparado mediante mØtodos estÆndares iricluyendo pero sin
limitar a Øste, el mØtodo Fisher Esterification (Me0H, H7304),
y reacción con TMSCHN2 en solventes orgÆnicos adecuados como
PhMe/Me0H o T1-IF/MeOH. En el paso 4, el derivado de dianilina
es preparado mediante calentamiento(60 a 200 CC) del ester con un exceso de la apropiada anilina buena o en un solvente orgÆnico como xilenos. Por ejemplo, cuando Rc = Me y RL = H el mØtodo preferido es mezclar el ester con 10 anilinas equivalentes en xilenos al reflujo hasta que se corrpleta La
reaccióri. En el paso 5, el nitro areno es reducido para
producir la diamina mediante condiciones de reducción

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estÆndares, incluyendo, pero sin limitarse a Østos, H2, y Pd/c
o Pd(OH)21C o Raney Nickel en un solvente orqÆnico coma EtOH
o THF, Fe en AcOH, Zn en AcOH o Zn, NHCl (aq) en MeOH.
En el Paso 6, la diamina es ciclada mediante calentarniento con
Æcido fórmico bueno a acetato de formamidina un solvente
apropiado como EtCH. Alternativamente, cuando R1 a R2 no
iguala a halo, el nitro areno puede ser convertido directamente
a benzimidazol en el Paso 7 mediante calentamiento en Æcido
fórndc.o con Pd(OH)2/C u otra fuente de paladia como Pd/C. En
el Paso 8, un haluro puede ser incorporado mediante mØtodos
estÆndares, incluyendo Pero sin limitar, NBS a NCS y pTsOH en
cosolventes orgÆnicos como THF y MeCH. En el Paso 9,
benzimidazol es aiquilado Para proporcionar una mezcla casi igual de los productos Ni y N3 que son separables mediante tØcnicas estÆndares, incluyendo, par ejemplo, cromatografia y
trittiración La alquilación se realiza mediante el uso de un
agente de alquilación coma aiquilo haluro y base coma NaH, o K2CO3 en un solvente orgÆnico coma DMF a THE a temperaturas que
oscilan entre 0 y 80 >C. R puede ser ademÆs rnodificado
mediante varios mØtodos s.intØticos conocidos en la materia, como se ejemplifica mÆs adelante. En el Paso 10, el ester es hidrolizado mediante mØtodos de saponificación estÆndares. El Æcida es entonces convertido en el hidroxamato deseado en el

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Paso 11 mediante procedimientos de union estÆndares incluyendo
Pero sin limitase a Østos, EDCI, HOBt o PyBOP y la hidroxilamina apropiada en solventes orgÆnicos adecuados como
DMF, THF o cloruro de metileno.

El Esquema 2 ilustra un ejemplo en el cual el sustituyente
RB estÆ en anilina antes del procedimiento de union con nitro ester. La descripción de la reacción es exactamente comb aquella Para el Esquema 1 excepto que no se necesita incorporar R ya que estÆ presente en la anilina descie el comienzo.

En el Esquema 3, se ilustra la preparaciOn de derivados N3
aiquilo amino benzimidazol. En el paso 1, el aiqueno terminal
de hidroxamato de N3 aiquilado benzimidazol es dihidroxilado utilizando un oxidante adecuado como OsO en un solvente
adecuado o KMnO4 o 12, AgoAc, AcOH, aqua. El diol es entonces
oxidado en el paso 2 por Na104 or Pb(OAc)4 en una mezcla
bifÆsica adecuada para proporcionar ci aldehIdo. Alternativamente (paso 3), el alqueno puede ser directamente convertido en aldehido mediante mØtoclos estÆndares incluyendo Pero sin limitase a Østos, ozono/Me2S, NaIO/Os04 o KMn04. En
ci paso 4, la amina es preparada mediante aminación
reduccionista utilizando mØtodos estÆndares como Na(CN)8H3,

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Na(OAc)36H, NMe4BH(OAc)3 con o sin AcOH en un solvente adecuado
coma cioruro de metileno, acetonitrilo a THF. La aminación de
reducción preferida es tratar ci aldehdo con amina,
Me4NBH(OAc) y Æcido acØtico en NeCN a temperatura ambiente.

El Esquema 4 ilustra la preparación de compuestos de la presente invención donde VQ es heterocIclico. En el paso 1, ci ester metIlico es convertido en hidrazida mezciando con hidrazina en un solvente adecuado coma EtOH a temperaturas
desde 50 a 100 -C. El derivado heterociclico deseado es
entonces preparado mediante ciclización con ci reactiva apropiado. Para oxadiazol 21 la hidrazida es tratada con un ortoformata coma artoformato de trietUo, y un catalizador
Æcido coma pTsOH en un solvente orgÆnico adecuado como EtOH a
temperaturas elevadas (50 - 100 C) Para hidraxi oxadiazol 22
la hidrazida puede set ciclada con fosgeno o con un fosgeno equivalente coma trifosgeno a carbonil diimidazoi en un solvente adecuado coma tolueno a temperaturas que oscilan entre 50 y 120C. El mercapta oxadizaol 23 puede ser preparado
mediante reacción con disulfuro de carbono, ’ base coma KOH en
solvente orgÆnico adecuado coma EtOH a temperaturas eievadas (50 100 °C). El amino oxadiazol 24 puede ser reaiizado mediante
reacción con BrCN y base coma NaHCO, en un sistema de solvente

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bifÆsico corno dioxano y aqua a temperatura ambiente. Finalmente, el amino oxadiazol sustituido 25 puede ser preparado en primer lugar mediante la reacción de hidrazida con un isotiocianato apropiado en un solvente orgÆnico adecuado como DMF o THE’ a temperaturas que oscilan entre 25 y 100 00. EL intermedio puede ser separacio o puede ser ciclado
directamente con el trataniiento de EDCI u otra carbodiiinida en
solvente orgnico adecuado como THE’ o DMF a teinperaturas que
oscilan entre temperatura ambiente y 80 C.

En el Esquema 5, se ilustra la preparación de derivados de
ceto benzirnidazol. En el paso 1, el ester metilico es
convertido en alcohol bencilico mediante mØtodos de reducción estÆndares, preferenternente LAH en THE’ a 0 00 a NaBH4 en
EtOH:THF a temperatura ambiente. La oxidación del aldehIdo
puede ser realizada en el paso 2 utilizando MnO.,en acetona:THF
a 50 00. En el paso 3, los reactivos organometÆlicos, como
los reactivos organilitio y Grignard, pueden ser agregados al
aldehido en THE’ a baja temperatura (par ejemplo, -78 0ç)

para

proporcionar el alcohol bencilico sustituido. Los derivados de
ceto pueden ser preparados en el paso 4 mediante oxidación del
alcohol bencilico bajo condiciones estndares corno oxidación
Swern a Dess-Martin.

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Los compuestos de la pre5ente invención pueden tener Ætomos de carbono asimØtricos. Las mezclas diastereomØricas pueden ser separadas en sus diastereómeros individuales sabre la base de sus ciiferencias.fisico quimicas mediante mØtodos conocidos par los expertos en la materia, par ejemplo, cromatografia o cristalización fraccional. Los enantiómeros pueden ser separados mediante conversion de la rnezcla de enantiómero en rnezcla diastereomØrica mediante la reacoión con una compuesto activo ópticamente apropiado (por ejemplo, alcohol), separando los diastereOmeros y oonvirtiendo(por ejemplo, hidrolizando) los diastereómeros individuales en los corresponWientes enantiOmeros puros. Todos estos isómeros, incluyendo mezolas diastereomØricas y enantiómeros puros son considerados parte do la invención.

La actividad de los compuestos de la presente invenciôn puede ser determinada par el siquiente procedirniento. N - terminal 6 His-etiquetada, MEK1 (2-393) activo es expresado en E. coli y la proteina es purificada mediante mØtodos convencionales (Ahn et a]., Science 1994, 265, 966-970). La actividad de MEK1 es evaluada mediante mediciOn de la incorporaciOn de y-33P-fosfato desde y-33P -ATP en N -terminal His

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etiquetacia ERK2, que se expresa en E. colt y se purifica mediante mØtodos convencionales, en presencia de MEK1. EL ensayo es realLizado en on plato de polipropileno de 96
aberturas. La mezcla de la incubaciôn (100 pL) comprende 25 mM
Hepes, pH 7,4, 10 mM MgC17, 5 mM J3-glicerolfosfato, 100 pi’i Na-
ortovanadato, 5 mM DTT, 5 nM MEK1, y 1 pM ERK2. Los
inhibidores son suspendidos en DM50, y todas las reacciones, incluyendo los controles se realizan en una concentración final
de 1% de DM50. Se cornienzan las reacciones agregando 10 pM ATP
(con 0,5 pCi y-3P-ATP/ abertura) y se incuhan a temperatura
ambiente durante 45 minutos. Se agrega igual volumen de 25% TCA
para detener la reacción y precipitar las protelnas. Las protelnas precipitadas son atrapadas en las placas de filtro de fibra de vidrio B y el exceso de ATP etiquetado es lavado
utilizando un cosechador Tomtec MACH III. Se permite que las
placas sean secadas per aire antes de aqreqar 30 pL/ abertura de Packard Microscint 20, y se cuentan las placas utilizando Packard TopCount. En este ensayo, los compuestos de la invención mostraron un IC de menos de 50 micromolares.

Los siguientes compuestos ejemplifican compuestos de dicha actividad -

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Conuesto #
8n
lib
110

lip
181
2 9c
291
29s
29t
 2 9-b
29111
29mrnm

La administtaciôn de los cornpuestos de la presente Invención (de ahora en adelante vcompuesto(s) activo(s)") puede ser efectuada por cualquier mØtodo que perrnita la liberación de los compuestos al lucjar de acción. Estos mØtodos incluyen vias orales, vIas intraduodenales, inyección parenteral(incluyendo intravenosa, subcutÆnea, intramuscular, intravascular a Infusion), tOpicas, y administración rectal.

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La cantidad del compuesto adrninistrado dependerÆ del
paciente, de la gravedad del mal o enfermedad, del promedlo de
admInistración, la forma del compuesto y criterio del medico
que lo receta. Sin embargo, una dosis efectiva se encuentra
entre 0,001 y 100 mg por kilo de peso corporal par dia,
preferentemente entre 1 35 mg/kg/dia, en dosis Onica5 a divididas. Para una persona de 70 kg, esta cantidad serla aproximadamente entre 0,05 y 7 g/dla, preferentemente entre 0,05 y 2,5 g/dia. En alguno casos, los niveles de dosis debajo de los limites inferiores anteriormente mencionados son mÆs que suficientes, rnientras que en otros casos dosis mayores pueden ser utilizadas sin causar ningün efecto colateral peligroso, si dichas dosis mayores se dividen en primer lugar en varias dosis pequeæas para su administración durante el dia.
El compuesto activo puede ser aplicado coma terapia ünica
o puede abarcar una o mâs sustancias anti- tumorales, por ejemplo, inhibidores mitóticos, por ejemplo vinbiastina; agentes de alquilación, par ejemplo cis-platin, carboplatin ciclofosfamida; anti-metabolitos, por ejemplo 5-fluorouracil, citosina arabinsida e hiciroxiurea, o, par ejemplo, uno de los anti- metabolitos preferidos revelados en la Solicitud de Patente Europea Na. 239362 coma Æcido N-(5-[N-(3,4-dihidro-2-metil-4 -oxoquinazolin-6-ilmetil) -N-metilamino] -2--tenoil) -L-

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qlutÆrnico; inhibidores de factor de crecim.iento; inhibidores de ciclo celular, antibióticos intercarnbiables, por ejemplo adriamicin y bleomicin; enzimas, por ejemplo, interferon; y anti-hormorias, per ejemplo anti-e5tr6genos comb NolvadexTM (tamoxifen) o, par ejemplo anti-andrógenos como CasodexTM (4’- ciano-3- (4-fluorofenilsulfonil) -2-hidroxi-2-mnetil-3’ - (trifluoromnetil)propionanilida) Dicho tratamiento conjunto puede ser logrado mnediante dosifi cación simultÆnea, secuencial a separada de]os componentes individuales del tratamiento.

La compo5ici6n farmacØutica puede, por ejemplo, estar en
una forma adecuada para la admninistración oral como una pastilla, cÆpsula, pildora, polvo, formulaciones de liberaciOn sostenida, soluciOn, suspensión o emulsión, para la administraciOn tópica coma on unqUento o crema, a para la adrninistración rectal, coma on supositoria. La composición farmanØutica puede ser fommnas de dasis en unidad adecuada para la administración individual de dosis precisas. La composición farmnacØutica incluirÆ on portador farmacØutico convencianal a excipiente y on comnpuesto de acuerdo con la invención coma on inqmediente activo. AdernÆs, puede incluir otros agentes rnedicinales a farrnacØuticos, portadares, auxiliares, etc.

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Las formas de administración parenteral ejemplares
incluyen soluciones a suspensiones de compuestos activos en soluciones acuosas estØriles, por ejemplo, soluciones de
dextrosa o propilenglicol acuoso. Dichas formas de dosis pueden
ser adecuadamente amortiguadas si asi se lo desease.

Los portadores farmacØuticos adecuados incluyen cliluyentes inertes o rellenos, aqua y varios solventes orgÆnicos. Las composiciones farmacØuticas pueden, si se desease, contener ingredientes adicionales como saborizantes, aglutinantes excipientes y similares. De esta manera, Para la administración oral, se pueden utilizar pastillas que contienen varios excipientes, como el Æcicio citrico, junta con varios desintegrantes como almidón, Æcido alginico, y ciertos silicatos complejos y con agentes de union coma sacarosa, gelatina y acacia. Adicionalmente, los aqentes lubricantes como estereato de maqnesio, sulfato lauril de sodio y talco son frecuentemente eficaces para las pastillas. Las composiciones sOlidas de uria clase similar pueden ademÆs ser utilizadas en cÆpsulas de gelatina rellenas duras y blandas. Los materiales preferidos, ademÆs, incluyen lactosa a azücar de leche, y polietilengligoles de alto peso molecular. Cuando las suspensiones acuosas a elixires son deseados Para la

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administración oral el compuesto activo puede estar combinado con varios agentes edulcorantes a saborizantes, tinturas 0 colarantes, si se desea, agentes emulsianantes a agentes de suspension, junta con diluyentes coma agua, etanol, propilen glicol, glicerina, a carnbinaciones de los mismos.

Los mØtodos para la preparación de composiciones
farmacØiticas con una cantidad especIfica del compuesto activo, son bien conocidas a se vuelven evidentes para los expertos en
la materia. Como ejemplos, vease Remington’s Farrnaceutica].
Sciences, Mack Publishing Company, Ester, Pa., 15E1 Edition (1975)

Los ejemplos y las preparaciones proporcionados a continuaciOn ademÆs ilustrari y ejemplifican los compuestos de la presente invención y mØtodas de preparación de dichos campuestos. Se entiende que el alcance de la presente invención no estÆ limitado de ninguna manera por el alcance de los ejemplos y de las preparaciones. En los siguientes ejemplos, a menos que se exprese lo contrario, existen malØculas can un centro quiral dnico coma una mezcla racØmica. Aquellas molØculas con dos a mÆs centros quirales, a menos que se exprese lo contraria, existen coma una mezcla racØmica de

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diastereómeros. Los enantiómeros/diastereómeros simples pueden
ser obtenidos rriediante mØtodos conocidos por los expertos en la
materia.

Las revelaciones en la presente solicitud de todos los
articulos y referencias, incluyendo patentes, se incorporan en
la presente por referenda.

La invención se ilustra adems mecliante los siguientes ejemplos que no pretenden lirnitar la invención en el alcance o espiritu de los procedimientos especIficos en ellos descritos.

Los materiales de partida y varios intermediarios pueden
ser obtenidos en fuentes comerciales, preparados a partir de compuestos orgÆriicos cornercialmente disponibles o preparados utilizando inØtodos sintØticos conocidos.

A continuaciôn se encuentran los ejemplos representativos
de mØtodos para preparar intermedios de la invencidn.

Ej emp10

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Ejemplo 1

H
N
H
N

HN F Br

Acido 7-Iluoro-6- (4-broino-2-raetil--ferzilarnino) -3H-behzoimidazol-5-carboxilico c1clopropi2Lmetoxi-azriida (ha)

Paso A: Æcido 2,3,4-Trifluoro-5-nitro-benz6ico 2

Un balón do tres cuellos con base redonda de 3 litros es

cargado con 125 ml H2501. Acido nitrico fumante es agreqado (8,4 ml, 199 mmol) y la rnezcla es mezclada ligeramente. Acido 2,3,4-triflucrobenz6ico 1 (25 g, 142 mmol) es agreqado en porciones de 5 g durante mds de 90 minutos. La soluciOn amarillenta castaæo oscuro es mezclada durante 60 min en cuyo tiempo se compieta la reacción. La mezclLa de la reacción es vertida en un ILitro de una mezcla hielo:agua y extraida con dietil Øter (3 x 600 ml). Los extractos orgÆnicos combinados

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son secados (MgSO) y concentrados a presión reducida para proporcionar un sólido amarillo. El sólido es susperidido en hexanos y mezclado durante 30 minutos y despuØs de dicho tiernpo
es filtrado para proporcionar 29 g (92%) del producto limpio
deseado como un sólido color amarillento: MS APCJ1 (-) m/z 220 (M-1) detectado.

Paso B: Æcido 4-aminc,--2,3-difluoro-5-nitro-benz6ico 3

Una solución de hidróxido de amonio (30% en agua) (35
ml, 271 mmol) es agregada a una solucióri do Æcido 2,3,4-
trifluoro-5--n–tro-benz6ico 2 (15 g, 67,8 mmol) en 30 ml de agua
a 0 00 mientras se mezcla. Una vez que se termina de agreqar
hidróx–do de amonlo, la mezcla do la reacción es entibiada a
temperatura ambiente mientras se mezcla. Luego de 2,5 h, la
mezcla de la reacción es enfriada a 0 -’0 y HC1 concentrado es
cuidadosamente agregado hasta que el pH de la mezcla de la
reacción es cercano a 0. La mezcla de la reacción es diluida
con agua (30 ml) y extralda con dietil Øter (3 x 50 ml) Los
extractos orgÆnicos combinados son secados (Mg504) y concentrados bajo presión reducida para proporcionar 14 g (95%)
del producto deseado puro: MS APCI (--) m/z 217 (M-1) detectado.

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Paso C: ester metilico del dcidn 4-Arnino2,3-diflro-5-nitro
benzóico 4

Una saluclón de 2 N de TMS diazometana en hexanos (6,88
ml, 13,75 mmcl) es agreqada a una suspension de 6cido 4-amino-
2,3-difluoro--5-nitro-benz6ico 3 (2,00 g, 9,17 mmcl) en 25 ml de
4:1 THF:MeOH a 0 °C baja atmósfera de nitrOqeno. Una vez que
finaliza la adición, la mezcla de reacciOn es entihi.ada a
temperatura ambiente. Luego de 0,5 horas, el exceso de TMS
diazometano es destruido mediante cuidadosa adición de Æcido
acØtico. La reaccidn es entonces concentrada baja presión
reducida y secada in vacuo para proporcionar 1,95 g (92) del
producto deseado puro: MS APCI (-) m/z 231 (N-i) detentado.

Paso D: ester net.ilico del Acido 4-amino-3-fluoro5-nitro-2-a
tolilamino-benzdico 5a

Ester metilic.o del 6cido 4-amino-2,3-dif1uoro-5-nitro
benzóico 4 (12,0 g, 51,7 mmcl) es suspendida en xilenos (60 ml)
y se agrega arto-toluidino (55,2 ml, 517 mmofl. La mezcla de
in reacciOn es calentada a reflujo mediante mezclado baja una
atmósfera de nitrOgeno. Luego de 36 h, In mezcla de in
reacción es enfriada a temperatura ambiente, dilulda can

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dietil Øter y lavada con 10% de solución acuosa HC1. Los
lavados acuosos son extraidos con dietil Øter. Los extractos orgÆnicos combinados son concentratados bajo presion reducida.
El residua es disuelto en cloruro de metileno y filtrado a
travØs de gel de sIlice por un embudo enjuagando con cloruro de metileno. Se recubren tres fracciones. La primera (2 litros)
estÆ casi limpia por HPLC. La segunda (1 litro) y la tercera
(1 litro) son solo parcialmente puras. La primera fracciOn es concentrada bajo presión reducida y triturada con dietil Øter para proporcionar 11,2 g (68%) del producto limpio deseado
coma un sólido amarillo brillante: MS APCI (-) m/z 318 (M-1)

detectado.

Paso E: ester inetilico del Æcido 7-fluoro-6-otolilamino-lH
benzoimidazol-5-carboxilico 7a

Ester rnetIiico del Æcido 4-amino-3--f1uoro--5---nitro-2-0-

tolilamino-benz6ico 5a (1,57 g, 4,92 mmol), Æcido fórmico (25
ml, 26,5 mmol) y 20% Pd(OH)7/C (1,57 g, 2,95 mmol) en 25 ml
EtOH son calentados mediante mezclado a 95 °C. Luego de 16 h,
la mezcla de la reacción es enfriada a temperatura ambiente y
se agrega 0,5 g 20% Pd(O1-1)2/C y 10 ml de Æcido fórmico. La
mezcla de la reacciOn es calentada a 95 °C mediante rnezclado.

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Luego de 16 h, la mezcla de la reacción es erifriada a
temperatura ambiente and filtracia par Ceiite enjuagando can EtOH. El filtrado es concentrado baja presión reducida hasta que ci producto deseado se p.recipita. El producto deseado es
recolectado mediante filtraciôn. El filtrado Cs nuevamente
concentrada hasta que se precipita un producto mÆs deseado. Una
concentraciôn de EtOH repetida, filtración del producto varias
Se recupera 1,09 g (74w;) de producto puro deseado: MS
APCI (+) in/z 300 (M+1) detectado; MS APCI (-) m/z 298 (M -l)

detectado.

Paso F: ester rnetllico del Æc.ido 7-fluaro--6-(4-.bromo-2-nietil-- fenilamino)-2H-benzolmidazal-5-carboxiJica Ba

Ester metilico del Æc:ido 7-Fluoro-6-o--tolilamino--lH-- henzoimi.dazol-5--carbox.Ilico 7a (2,00 g, 6,68 mmol) es
suspendido en una mezcla de 1:1 THF:MeOH (60 ml) y enfriado a -
78 °C baja una atrnósfera de nitrógeno. Una solución de NES

10 (1,20 g, 6,75 mmol) en 1:1 THF/MeOl-i (5 ml) es agregada seguido
par una solucióri MeCH (5 ml) de TsOHHO (1,9 g, 10,0 mmol)
Luego de 30 minutos, la mezcla de la reacción es entibiada 0
° C y lueqo de 1 h entibiada a rt. Luego de 16 h, es
agregado màs NBS (0,12 g, 0,67 rnrnoi) y la mezcla de la reacción

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se deja mezclar durarite 3 h. La mezcla de la reacción es
suspendida mediante la adición do solución 10% NaS204. Luego
do 30 la mezcla de la reacción es diluida con aqua y
acetato do etilo y las capas son separadas. La capa acuosa
se extrae con acetato de etilo. Los extractos orgÆnicos
combinados se secan (Na2SO4) y se concentran bajo presión
reducida. El sólido recuperado se tritura con cloruro do
rnetileno para proporcionar 2,00 g (79%) del producto puro
deseado: MS APCI (+) in/z 380, 378 (modelo M+1 Br) detectado.
Paso G: Acido 7-fluoro--6-(4-hromo--2-metiJ-fenilamioa)--1H-
benzoimidazol -5--carboxilico lOa

Ester metili.co del Æcido 7-fluoro--6-(4-bromo-2-metil-fenilamino)-1H-benzoimidazol-5-carboxilico 8a (63 mg, 0,167
mrnol) se suspende en MeOH (1,5 ml) y se agrega 20% NaOH (400
p1). Luego de 16 h, la mezcla de la reacción se enfria a 0
UC y una solución do 1 N HC1 se agrega gota a gota hasta quo
el pH es 2 a 3. La mezcla de la reacción se diluye con acetato

do etilo y aqua y las capas so separan. La capa orgÆnica se
lava con salmuera, se seca (Na7SO1) y se concentra bajo presión
reducida para proporcionar 58 mg (95%) del producto deseado: MS
APCI (-H m/z 366, 364 (modelo M+1 Br) detectado; MS APCI (--)
m/z 364, 362 (modelo M-1 Br) detectado.

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Paso H: cicloprop22metQY-aJT1Jda del Æcido 7-fiucro-6-(4-hromo-
2-rnetil-fenilazmino)--IH-benzollnidazo.l-5-CarhOXiliCO 21a

El Æcidc 7f1ucro-6- (4-bromo-2-metil-fenilaminc) -lH-
benzoimidazoi-5---carboxIlico lOa (48 my, 0,132 mmcl) se d.isuelve
en 1:1 THF: cloruro de metilenc (1 ml) y se aqreqa base de
Hunig (0,23 p1, 1,32 mmcl) seguido par PyBOP (82 my, 0,158
mmcl). Luego de unos pacos minutos, se aqrega hidi.oclorurc de
ciciopropil metil hidroxilamina (20 my, 0,158 mmcl) (WO
0042022). Luego de que se completa la reacción, la mezcla se
divide entre una solución de cloruro de metileno y NaHCO
saturado. Las capas se separan y la capa orgÆnica se lava con
NaHCO3 saturado y salmuera. La capa orgÆnica se seca (Na7SO4)
y se concentra baja presión reducida. Luego de purificación
par FCC (eluir con 20:1 cloruro de metileno:MeOH), 25 my (45%)
del producto deseado puro se separa: MS ESI (+) m1z 435, 433
(modelo M+1 Br) detectado; MS ESI (-) in/z 433, 431 (inodelo M-1
Br) detectado; H RMN (400MH2, CDCl) 5 8,15 (s, 1H), 8,02
(s, 11-1), 7,28 (s, il-), 7,43 (d, 11-1), 7,07 (dd, 11-1), 6,36 (in, 1H), 3,70 (d, 2H), 2,38 (s, 3H), 0,86 (m, lH), 0,41 (m, 2H),
0,13 (in, 2H); F RMN (376MHz, CIDC1:d -134,05 (s)

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Ejemplo 2

OCH3

HN F

is ter metulico del Æcido 7-fluoro-6-fenilamino-3H-
benzo–znidazol -5-carboxIlico (27a)

AIbL Paso A: ester metilico del Æcido 4-amino-3-fluoro-5-nitro--2-
fenilarnirio-benz6ico 26a

Ester metlllco del Æcido 4-amino-2.,3-dif1uoro-5-riitro-
benz6ico 4 (23,48 g, 101,1 mmol), el producto del Ejemplo 1,
Paso C, se suspende en xilenos (125 mL) y se agrega anilina
(92 mL, 1011 mmol) La mezola de la reacción se mezola a 125
00 durante 16 horas bajo N2. La rnezcla de la reacción se
enfrIa a temperatura arnbiente y los sôlidos se precipitan
fuera de la solución. Los sólidos se colectan medlante

filtración y se lavan con xilenos y luego con dietil Øter.
22,22 g (72,78 minol) recuperados del sôlido amarillo que es el
producto puro deseado. El filtrado se concentra bajo presión
reducida, se disuelve nuevamente en cloruro de metilerio y se

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purga a travØs de un tapón de gel de sllice lavando con cloruro
de rnetileno. Las fracciones deseadas se concentran baja
presión reducida para proporcionar un sólido castaflo que se
tritura con dietil Øter para proporcionar 5,47 g (17,91 mmol)
de sólido amarillo que es el producto puro deseado. El
rendimiento del producto combinado es 27,69 g (90%) MS APCI
(-) jn/ 304 (M -l) detectado.

Paso B: ester metilico del Æcido 7-fluoro-6--fenilamino--
3Fi-benzoimidazol-5-carboxilico 27a

Ester metilico del Æcido 4-amino-3---fluoro-5-nitro-2-
fenilamino-benz6ico 26a (16,70 g, 54,71 mmol), Æcido fórmico
(250 mL, 6,63 mol) y 20% Pd(OH)7/C (9,00 g, 16,91 mmol) en
etanol (250 mL) se mezclan a 40 °C durante dos horas baja N y
luego a 95 °C durante 16 horas. La mezcla de la reacción se
enfrIa a temperatura ambiente y se filtra mediante Celite
enjuagando con acetato de etilo. El filtrado se concentra
Sbajo presión reducida para proporcionar un sólido amarillo. El
sólido se tritura con dietil Øter para proporcionar 13,47 g
(86%) del producto deseado como un sólido oscuro. MS APCI (+)
m/z 286 (M+1) detectado; MS APCI (-) m/z 284 (M -l) detectado.

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Ejemplo 3

OCH3
N
HN F Br
_--.-,N

Ester raetIlico del Æcido 6-(4-brorno-2-cloro-fenilaraino)-7-fluoro-3H--benzo2jidazol-5-carboxIlico (Sb)

Paso A: ester metilico dcl Æcido 6-(4-b.romo-fenilam.ino)--7-fluoro-3H--benzoimidazol -5-carboxilico 28a

Ester metIlico del Æcida 7-fluaro-6-fenilarnino-3H---
benzoimidazol-5--carboxilico 27a (4,99g, 17,51 mmol) se disuelve
en N,N-ciimetilformarnida (275 mL) N-bromosuccinimida (3,15 q,
17,70 mmol) se agreqa coma un sóiido y la mezcla de la reacción
se mezcla a ternperatura ambiente baja N:. Luego de 30 mm,
la mezcla de la reacción es suspendida mediante adición de
saluclón de bisulfito sódico saturada acuaso. La mezcla de la
reacción es entonces vertida en un embudo de separación,
dilulcia con aqua y acetato de etilo y las capas separadas. La