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Señor

SUPERINTENDENTE DE INDUSTRIA Y COM

E.

S.

D.

REF: Expediente 12-115-817

TÍTULO SOLICITADO: DERIVADOS DE PIRAZOL COMO INHIBIDORES DE JAK.

PUBLICACIÓN: Gaceta 654 de 16/10/2012, N° de publicación 1658.

PRIORIDAD: EP 10382039.5 de 18/02/2010; US 61/306,051 de 19/02/2010; US 61/371,081 de 05/08/2010; EP 10382217.7 de 05/08/2010.

SOLICITANTE: ALMIRALL S.A.

APODERADO: LUZ CLEMENCIA DE PAEZ.

TRÁMITE: SUSTENTACIÓN DE OPOSICION

JOSÉ LUIS REYES VILLAMIZAR, mayor de edad, identificado como aparece al pie de mi firma, abogado en ejercicio, titular de la tarjeta profesional número 44655 del Consejo Superior de la Judicatura, obrando en calidad de apoderado de la sociedad **LAFRANCOL S.A.**, en ejercicio de lo dispuesto por el artículo 42 de la Decisión 486 de 2000, por medio del presente escrito, procedo a sustentar y complementar la oposición presentada, en los siguientes términos:

I. RATIFICACION

La solicitud colombiana en trámite **12-115-817**, referida a nuevos derivados de pirazol de fórmula (I), sus procesos de preparación, las composiciones farmacéuticas que los contienen y sus usos en terapia como inhibidores de Janus kinases (JAK), no reúne los requisitos necesarios para otorgársele el privilegio de

patente de invención, como se demuestra a través de los siguientes argumentos, particularmente en materia de Nivel Inventivo.

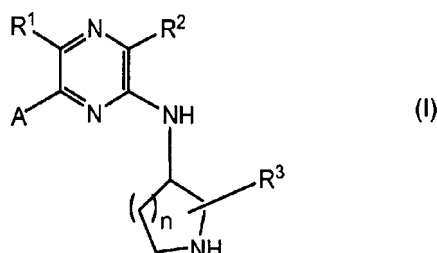
II. COMPLEMENTO DE INFORMACION

En primer lugar, es necesario resaltar que el capítulo reivindicatorio de la solicitud colombiana en curso, específicamente en sus reivindicaciones 29 a 32 se encuentra dirigido a usos del compuesto para ciertas patologías específicas, es decir, métodos de tratamiento, lo cual es inaceptable a la luz de la Decisión 486.

Sin perjuicio de lo anterior, me permito hacer notar que aún si los usos o métodos de tratamiento fueran permitidos en nuestro medio, éstos deberían cumplir necesariamente con los requisitos materiales de patentabilidad, novedad, nivel Inventivo y Aplicación Industrial, siendo éste último de imposible cumplimiento, en tanto la reproducción industrial del uso separado, combinado o secuencial de ingredientes activos es en este caso del resorte de la profesión médica y no de las actividades industriales.

En otro aspecto, y esta vez en relación con la novedad y el nivel inventivo de la solicitud colombiana en trámite, existe un gran número de documentos en los que se revela con anterioridad el mismo tipo de compuestos de fórmula (I) inclusive combinados con otros agentes farmacéuticos, tal como ocurre con la presente solicitud colombiana en trámite.

Por lo tanto el compuesto reivindicado **no es nuevo**, pues ya se conocía, tal y como lo describe la publicación **WO 2010/016005** de febrero 11 de 2010 “**6-SUBSTITUTED 2-HETEROCYCLYLAMINO PYRAZINE COMPOUNDS AS CHK-1 INHIBITORS**”, veamos:

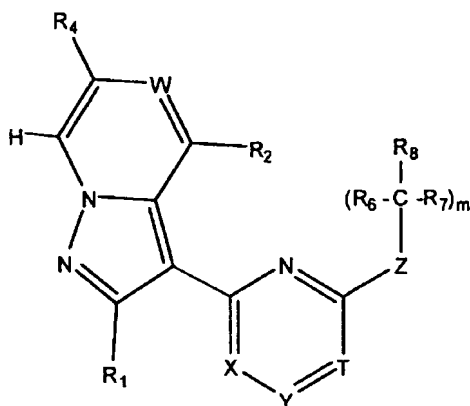


(57) Abstract: The present invention is directed to compounds of formula (I), and pharmaceutically acceptable salts thereof, their synthesis, and their use as CHK-1 inhibitors.

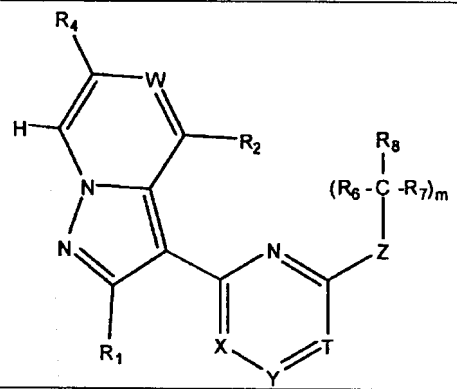
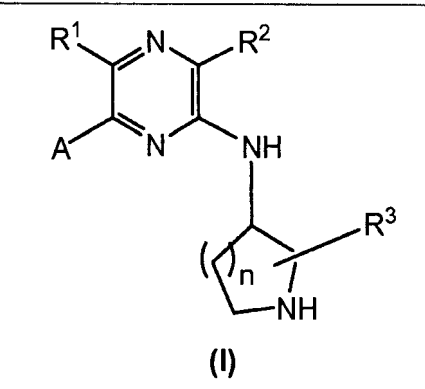
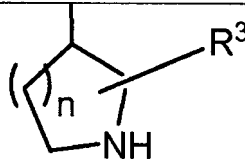
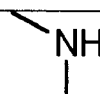
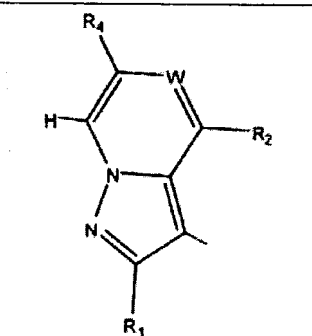
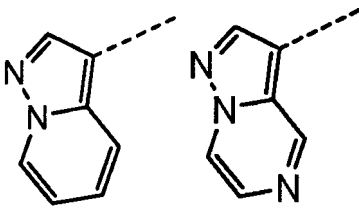
En este documento, claramente se evidencia que el tipo de compuesto de fórmula (I) usado para estados patológicos como por ejemplo estados relacionados con cáncer, tal y como lo reivindica la solicitud colombiana en cuestión, en los cuales se utilizan dichos compuestos en procesos con enfermedades neoplásicas, tumorigenesis, inducción de la apoptosis de células malignas, inhibición de la proliferación y en general inhibición de las quinasas, es ampliamente reconocida en el estado de la técnica.

Ahora bien, si tenemos en cuenta que la reivindicación independiente 1 de la solicitud colombiana en trámite pretende proteger lo siguiente:

1) Un compuesto de fórmula (I) o una sal farmacéuticamente aceptable, o solvato o N-óxido o estereoisómero o derivado deuterado del mismo.



Observamos a simple vista que el compuesto de fórmula (I) no es nuevo ya que en la publicación **WO 2010/016005** antes mencionada, existen compuestos que se superponen con el de la solicitud colombiana en trámite por tener iguales características, como se puede observar a continuación:

CARACTERÍSTICAS DE LA REIVINDICACION 1 CO 12-115817		ANTERIORIDAD WO 2010/016005	
(I)		(I)	
R ₈	5-7 heteroarilo con un heteroátomo O, S y N el cual está a su vez sustituido		 IGUAL Pág 1
m	Igual a cero		- No existe
Z	NR ₅ donde R ₅ = H		 IGUAL Pág 1
Y	N		 IGUAL Pág 1
T	CR ₉ donde R ₉ = H	R ₂	H IGUAL Pág 2
X	CR ₉ donde R ₅ = H	R ₁	H IGUAL Pág 2
	 W= N o CR ₃ Y R ₃ =H R ₁ , R ₂ , R ₄ son H	A	 IGUAL Pág 7, 14

De manera que el objeto de esta solicitud, tal como aparece en la reivindicación independiente 1 no es nuevo, por lo tanto tampoco serían nuevas las reivindicaciones independientes 2 a 35, ni la composición de la reivindicación 36 pues ya se había revelado su forma correcta de preparación, la cual es conocida para cualquier persona medianamente versada en la materia, tal como se observa en el siguiente párrafo tomado de la anterioridad **WO 2010/016005**, tantas veces mencionada:

(Pág 64)

Pharmaceutical compositions suitable for the delivery of compounds of the invention and methods for their preparation will be readily apparent to those skilled in the art. Such compositions and methods for their preparation can be found, for example, in 'Remington's Pharmaceutical Sciences', 19th Edition (Mack Publishing Company, 1995), the disclosure of which is incorporated herein by reference in its entirety.

De otro lado, las reivindicaciones 37 y 38 que pretenden proteger el compuesto de fórmula (I) combinándolo con uno o dos principios activos diferentes, el cual a su vez es seleccionado de entre dos listas de posibilidades que contienen 34 y 29 grupos farmacológicos respectivamente, tampoco sería nuevo ni inventivo ya que la misma anterioridad según lo descrito en la página 64 y siguientes, revelan posibilidades exageradamente amplias de compuestos que pueden combinarse con el compuesto de fórmula (I), que como ya lo discutimos, tampoco es nuevo ni inventivo. Veamos:

(Pág 64)

The compounds can be administered alone or in combination with one or more other compounds of the invention, or in combination with one or more other drugs (or as any combination thereof). Generally, they will be administered as a formulation in association with one or more pharmaceutically acceptable excipients. The term

(pág 75)

Other anti-tumor agents include Pfizer's MEK1/2 inhibitor PD325901, Array Biopharm's MEK inhibitor ARRY-142886, Bristol Myers' CDK2 inhibitor BMS-387,032, Pfizer's CDK inhibitor PD0332991 and AstraZeneca's AXD-5438, and combinations thereof.

The following cytotoxic agents, e.g., one or more selected from the group consisting of epirubicin (Ellence), docetaxel (Taxotere), paclitaxel, Zinecard (dexrazoxane), rituximab (Rituxan) imatinib mesylate (Gleevec), and combinations thereof, may be used in combination with a compound of the present invention and pharmaceutical compositions disclosed herein.

(pág 76)

Antimetabolites include but are not limited to, methotrexate, 6-mercaptopurine riboside, mercaptopurine, 5-fluorouracil (5-FU) alone or in combination with leucovorin, tegafur, UFT, doxifluridine, carmofur, cytarabine, cytarabine ocfosfate, enocitabine, S-1, Alimta (premetrexed disodium, LY231514, MTA), Gemzar (gemcitabine, Eli Lilly), fludarabin, 5-azacitidine, capecitabine, cladribine, clofarabine, decitabine, eflornithine, ethynylcytidine, cytosine arabinoside, hydroxyurea, TS-1, melphalan, nelarabine, nolatrexed, ocfosfate, disodium premetrexed, pentostatin, pelitrexol, raltitrexed, triapine, trimetrexate, vidarabine, vincristine, vinorelbine; 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-oxoquinazolin-6-ylmethyl)-N-methylamino]-2-thenoyl)-L-glutamic acid and combinations thereof.

(pág 77)

Immunologicals include interferons and numerous other immune enhancing agents. Interferons include interferon alpha, interferon alpha-2a, interferon, alpha-2b, interferon beta, interferon gamma-1a, interferon gamma-1b (Actimmune), or interferon gamma-n1 and combinations thereof. Other agents include filgrastim, lentinan, sizofilan, TheraCys, ubenimex, WF-10, aldesleukin, alemtuzumab, BAM-002, dacarbazine, daclizumab, denileukin, gemtuzumab ozogamicin, ibritumomab, imiquimod, lenograstim, lentinan, melanoma vaccine (Corixa), molgramostim, OncoVAX-CL, sargramostim, tasonermin, tecleukin, thymalasin, tositumomab, Virulizin, Z-100, epratuzumab, mitumomab, oregovomab, pentumomab (Y-muHMG1), Provenge (Dendreon) and combinations thereof.

Other anticancer agents that can be used in combination with a compound of the present invention include alitretinoin, ampligen, atrasentan bexarotene, bortezomib, Bosentan, calcitriol, exisulind, finasteride, fotemustine, ibandronic acid, miltefosine, mitoxantrone, l-asparaginase, procarbazine, dacarbazine, hydroxycarbamide, pegaspargase, pentostatin, tazarotne, Telcyta (TLK-286, Telik Inc.), Velcade (bortemazib, Millenium), tretinoin, and combinations thereof.

Como se observa a simple vista además de que el *compuesto de fórmula (I)* y sus dependientes 2 a 35 carecen de total novedad, *composiciones* como las de la reivindicación 36 y *combinaciones* de otros fármacos de diferentes entidades farmacológicas con el compuesto de fórmula (I) como las que se pretenden proteger en las reivindicaciones 37 y 38 ya habían sido consideradas en el arte previo mencionado, por lo cual tampoco son nuevas.

En conclusión la solicitud colombiana en trámite incumple los requisitos fundamentales para otorgársele el privilegio de patente de invención primero, porque pretende atribuirse exclusividad sobre "métodos de tratamiento" al relacionar el uso sobre todo tipo de patologías en sus reivindicaciones; segundo, porque su composición tal y como se reivindica carece totalmente de novedad y tercero porque sus combinaciones ya eran conocidas, por lo tanto carecería también de todo indicio de nivel inventivo puesto que pretende utilizar prácticas comunes en el estado de la técnica y sus posibles variantes tales como realizar modificaciones moleculares o utilizar otros compuestos diferentes en combinación con el compuesto de fórmula (I), serían obvias para una persona medianamente versada en la materia que conozca y se guíe por el documento WO 2010/016005.

Así las cosas, y con fundamento en los argumentos expuestos a lo largo del presente escrito, respetuosamente reitero la solicitud para que su despacho se abstenga de conceder el privilegio de patente solicitado, y ordene en consecuencia el archivo del expediente respectivo.

IV. ANEXOS

- Publicación Internacional WO 2010/016005 "6 substituted 2-heterocyclylamino pyrazine compounds as CHK-1 inhibitors" págs. 1, 2, 14, 64, 75, 76, 77.

Señor Superintendente,



JOSÉ LUIS REYES VILLAMIZAR

C.C. 79'152.473 de Usaqué

T.P.A. 44.655 del C.S.J.

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PCT

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C07D 471/04 (2006.01) A61K 31/437 (2006.01)
C07D 487/04 (2006.01) A61P 35/00 (2006.01)

(21) International Application Number:

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4 August 2009 (04.08.2009)

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English

(26) Publication Language:

English

(30) Priority Data:

61/086,732 6 August 2008 (06.08.2008) US
61/229,428 29 July 2009 (29.07.2009) US

(71) Applicant (for all designated States except US): PFIZER INC. [US/US]; 235 East 42nd Street, New York, NY 10017 (US).

(72) Inventors; and

(75) Inventors/Applicants (for US only): NINKOVIC, Sacha [CA/US]; Pfizer Global Research & Development, 10777 Science Center Drive, San Diego, California 92121 (US). BRAGANZA, John Frederick [CA/US]; Pfizer Global Research & Development, 10777 Science Center Drive, San Diego, California 92121 (US). COLLINS, Michael Raymond [US/US]; Pfizer Global Research & Development, 10777 Science Center Drive, San Diego, California 92121 (US). KATH, John Charles [US/US]; Pfizer Global Research & Development, 10777 Science Center Drive, San Diego, California 92121 (US). LI, Hui [CN/US]; Pfizer Global Research & Development, 10777 Science Center Drive, San Diego, California 92121 (US). RICHTER, Daniel Tyler [US/US]; Pfizer Global Research & Development, 10777 Science Center Drive, San Diego, California 92121 (US).

(74) Agent: BENSON, Gregg C.; Pfizer Inc. 235 East 42nd Street, New York, New York 10017 (US).

(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PE, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

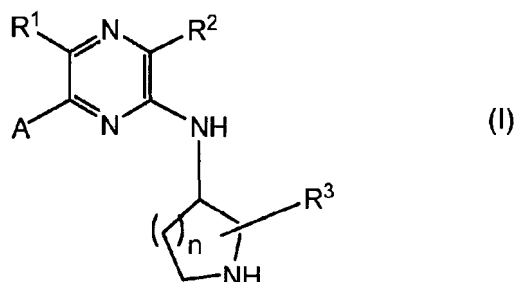
Declarations under Rule 4.17:

- as to the identity of the inventor (Rule 4.17(i))
- as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))
- as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))
- of inventorship (Rule 4.17(iv))

Published:

- with international search report (Art. 21(3))

(54) Title: 6 SUBSTITUTED 2-HETEROCYCLYLAMINO PYRAZINE COMPOUNDS AS CHK-1 INHIBITORS



(57) Abstract: The present invention is directed to compounds of formula (I), and pharmaceutically acceptable salts thereof, their synthesis, and their use as CHK-1 inhibitors.

6 SUBSTITUTED 2- HETEROCYCLYLAMINO PYRAZINE COMPOUNDS AS CHK-1 INHIBITORS

This application claims the benefit of United States Provisional Patent
Application Nos. 61/086,732, filed August 6, 2008, and 61/229,428, filed July 29,
2009, the disclosures of which are hereby incorporated by reference in their
entireties.

Field of the Invention

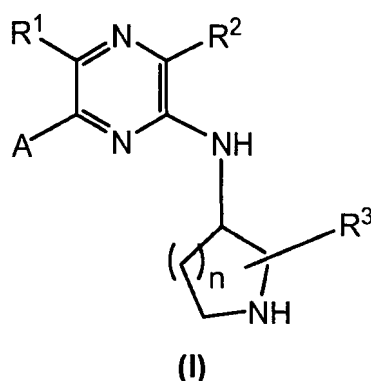
The present invention is directed to compounds, and pharmaceutically
acceptable salts thereof, their synthesis, and their use as modulators or inhibitors of
check point kinase 1 (CHK-1). The compounds of the present invention are useful for
modulating (e.g. inhibiting) CHK-1 activity and for treating diseases or conditions
mediated by CHK-1, such as for example, disease states associated with abnormal
cell growth such as cancer.

Background

It has been well known in the art that check point kinase 1 (CHK-1) is one of
the important enzymes that are involved in maintaining the order and fidelity of events
in the cell cycle and CHK-1 inhibitors have been proposed for cancer therapy.
(*Science*, 277, 1501-1505 (1997); *Science*, 277, 1497-1501 (1997)). (*Cell*, 91, 865-
867 (1997); *Science*, 277, 1450-1451 (1997); *Nature*, 363, 368-371 (1993); *Molec.*
Biol. Cell, 5, 147-160 (1994)). Flagg, G. et. al. (1997) *Current Biology* 7:977-986;
U.S. Patent Nos. 6,967,198, 6,413,755, 6,383,744 and 6,211,164; and International
Publication Nos. WO 01/16306, WO 01/21771, WO 00/16781, and WO 02/070494).

Summary of Invention

The current invention is directed to a compound of formula (I)

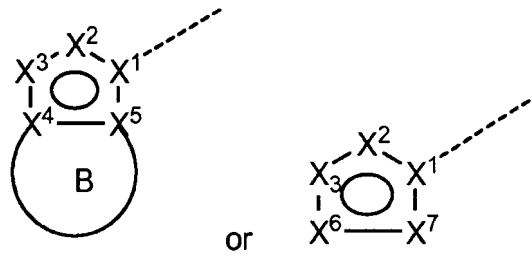


wherein,

- 2 -

n is 0, 1 or 2; preferably n is 1 or 2, more preferably, n is 2;

A is of the structure



and A is optionally further substituted with 1-6 R^4 ;

5 X^1 , X^2 , X^3 , X^4 and X^5 form a 5 member heteroaryl having 1-4 nitrogen ring atoms;

X^1 , X^2 , X^3 , X^6 and X^7 form a 5 member heteroaryl having 1-4 nitrogen ring atoms;

10 X^1 is N or C; X^2 is N, NH or CH; X^3 is N; each of X^4 and X^5 is independently N or C; each of X^6 and X^7 is independently N, NH or CH;

B together with X^4 and X^5 form a ring selected from phenyl, 5-6 member heteroaryl, 5-6 member heterocyclyl, C_5 - C_6 cycloalkyl and C_5 - C_6 cycloalkenyl, each of the said 5-6 member heteroaryl and 5-6 member heterocyclyl has 1-3 ring heteroatoms selected from N, O and S;

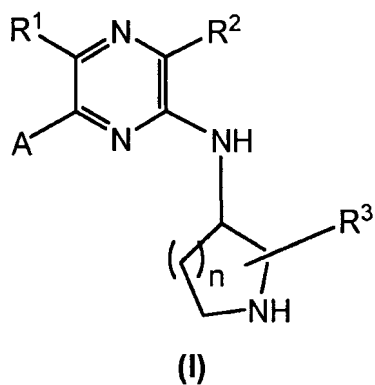
15 each of R^1 and R^2 is independently selected from hydrogen, fluorine, chlorine, -CN, $-OR^b$, $-N(R^b)_2$, and C_1 - C_3 alkyl optionally substituted with 1-6 groups selected from fluorine, chlorine and -CN;

R^3 represents 1-6 optional substituents independently selected from the group consisting of -oxo- and R^0 ;

20 two R^3 attached to the same ring atom, together with the ring atom attached to, may form a ring selected from C_3 - C_6 cycloalkyl, C_5 - C_6 cycloalkenyl and 3-6 member heterocyclyl; each of the said C_3 - C_6 cycloalkyl, C_5 - C_6 cycloalkenyl and 3-6 member heterocyclyl is optionally further substituted with 1-5 groups selected from -oxo- and R^w ;

25 two R^3 attached to two adjacent ring atoms, together with the ring atoms attached to, may form a fused ring selected from C_3 - C_6 cycloalkyl, C_5 - C_6 cycloalkenyl, 3-6 member heterocyclyl, phenyl and 5-6 member heteroaryl; the said C_3 - C_6 cycloalkyl, C_5 - C_6 cycloalkenyl, 3-6 member heterocyclyl, phenyl and 5-6 member heteroaryl is optionally further substituted with 1-5 groups selected from oxo and R^w ;

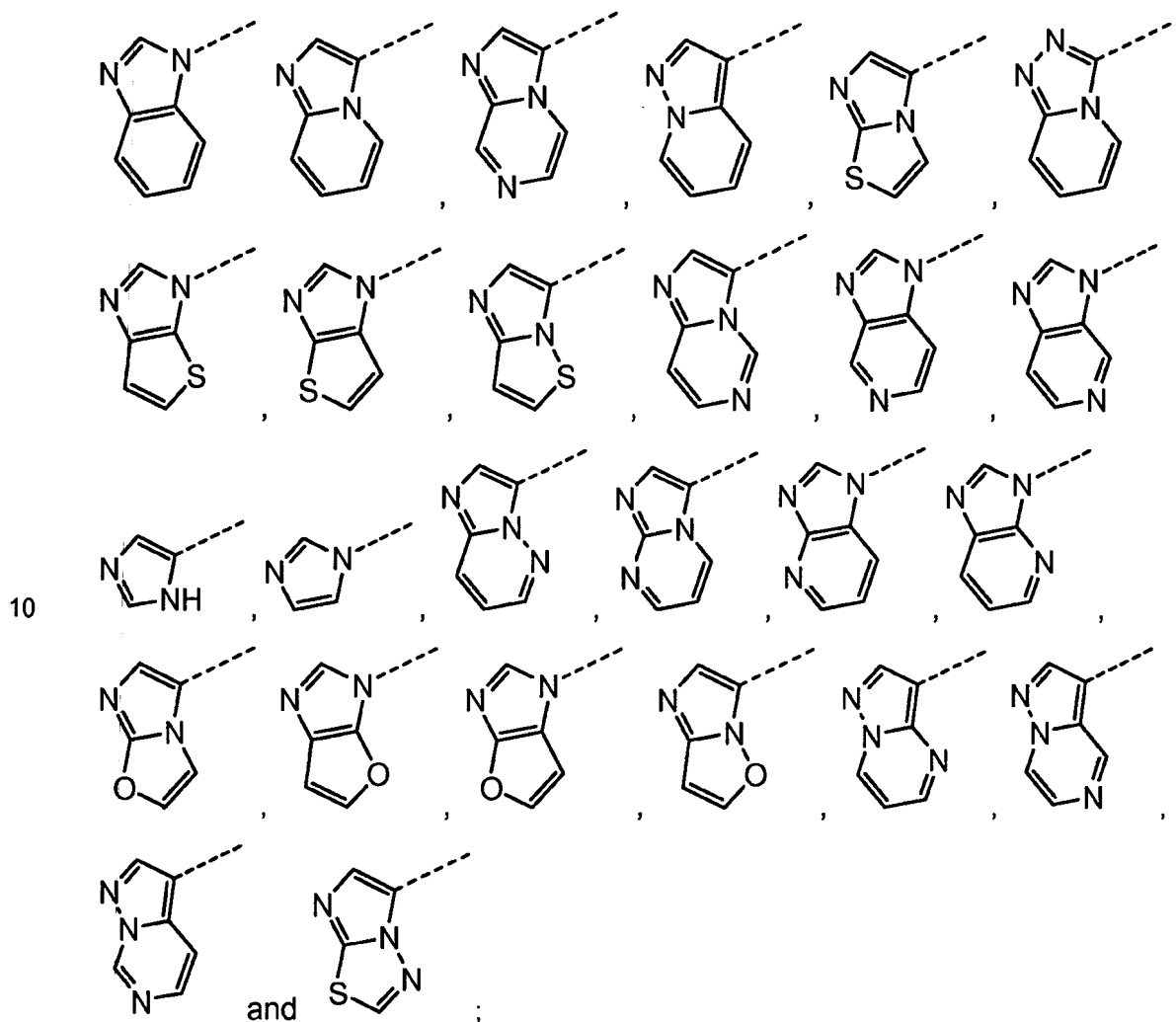
In another preferred embodiment, the invention provides compound of formula I,



wherein,

5 n is 1 or 2, preferably n is 2;

A is a heteroaryl selected from the group consisting of



A is optionally further substituted with 1-5 R^4 ;

R^1 is hydrogen;

- 64 -

(iv) where the compounds of the present invention contain a secondary amino group, a primary derivative thereof (e.g. $\text{-NHR}^1 \rightarrow \text{-NH}_2$);

(v) where the compounds of the present invention contain a phenyl moiety, a phenol derivative thereof (e.g. $\text{-Ph} \rightarrow \text{-PhOH}$); and

5 (vi) where the compounds of the present invention contain an amide group, a carboxylic acid derivative thereof (e.g. $\text{-CONH}_2 \rightarrow \text{COOH}$).

Compounds of the invention intended for pharmaceutical use may be administered as crystalline or amorphous products, or mixtures thereof. They may be obtained, for example, as solid plugs, powders, or films by methods such as precipitation, crystallization, freeze drying, spray drying, or evaporative drying.
10 Microwave or radio frequency drying may be used for this purpose.

The compounds can be administered alone or in combination with one or more other compounds of the invention, or in combination with one or more other drugs (or as any combination thereof). Generally, they will be administered as a formulation in association with one or more pharmaceutically acceptable excipients. The term
15 "excipient" is used herein to describe any ingredient other than the compound(s) of the invention. The choice of excipient will to a large extent depend on factors such as the particular mode of administration, the effect of the excipient on solubility and stability, and the nature of the dosage form.

20 Pharmaceutical compositions suitable for the delivery of compounds of the invention and methods for their preparation will be readily apparent to those skilled in the art. Such compositions and methods for their preparation can be found, for example, in 'Remington's Pharmaceutical Sciences', 19th Edition (Mack Publishing Company, 1995), the disclosure of which is incorporated herein by reference in its
25 entirety.

Oral Administration

The compounds of the invention may be administered orally. Oral administration may involve swallowing, so that the compound enters the gastrointestinal tract, or buccal or sublingual administration may be employed by which the compound enters
30 the blood stream directly from the mouth.

Formulations suitable for oral administration include solid formulations such as tablets, capsules containing particulates, liquids, or powders, lozenges (including

- 65 -

liquid-filled), chews, multi- and nano-particulates, gels, solid solution, liposome, films (including muco-adhesive), ovules, sprays and liquid formulations.

Liquid formulations include suspensions, solutions, syrups and elixirs. Such formulations may be used as fillers in soft or hard capsules and typically include a carrier, for example, water, ethanol, polyethylene glycol, propylene glycol, methylcellulose, or a suitable oil, and one or more emulsifying agents and/or suspending agents. Liquid formulations may also be prepared by the reconstitution of a solid, for example, from a sachet.

The compounds of the invention may also be used in fast-dissolving, fast-disintegrating dosage forms such as those described in Expert Opinion in Therapeutic Patents, 11 (6), 981-986 by Liang and Chen (2001), the disclosure of which is incorporated herein by reference in its entirety.

For tablet dosage forms, depending on dose, the drug may make up from 1 wt% to 80 wt% of the dosage form, more typically from 5 wt% to 60 wt% of the dosage form. In addition to the drug, tablets generally contain a disintegrant. Examples of disintegrants include sodium starch glycolate, sodium carboxymethyl cellulose, calcium carboxymethyl cellulose, croscarmellose sodium, crospovidone, polyvinylpyrrolidone, methyl cellulose, microcrystalline cellulose, lower alkyl-substituted hydroxypropyl cellulose, starch, pregelatinized starch and sodium alginate. Generally, the disintegrant will comprise from 1 wt% to 25 wt%, preferably from 5 wt% to 20 wt% of the dosage form.

Binders are generally used to impart cohesive qualities to a tablet formulation. Suitable binders include microcrystalline cellulose, gelatin, sugars, polyethylene glycol, natural and synthetic gums, polyvinylpyrrolidone, pregelatinized starch, hydroxypropyl cellulose and hydroxypropyl methylcellulose. Tablets may also contain diluents, such as lactose (monohydrate, spray-dried monohydrate, anhydrous and the like), mannitol, xylitol, dextrose, sucrose, sorbitol, microcrystalline cellulose, starch and dibasic calcium phosphate dihydrate.

Tablets may also optionally include surface active agents, such as sodium lauryl sulfate and polysorbate 80, and glidants such as silicon dioxide and talc. When present, surface active agents are typically in amounts of from 0.2 wt% to 5 wt% of the tablet, and glidants typically from 0.2 wt% to 1 wt% of the tablet.

- 66 -

Tablets also generally contain lubricants such as magnesium stearate, calcium stearate, zinc stearate, sodium stearyl fumarate, and mixtures of magnesium stearate with sodium lauryl sulphate. Lubricants generally are present in amounts from 0.25 wt% to 10 wt%, preferably from 0.5 wt% to 3 wt% of the tablet.

5 Other conventional ingredients include anti-oxidants, colorants, flavoring agents, preservatives and taste-masking agents.

Exemplary tablets contain up to about 80 wt% drug, from about 10 wt% to about 90 wt% binder, from about 0 wt% to about 85 wt% diluent, from about 2 wt% to about 10 wt% disintegrant, and from about 0.25 wt% to about 10 wt% lubricant.

10 Tablet blends may be compressed directly or by roller to form tablets. Tablet blends or portions of blends may alternatively be wet-, dry-, or melt-granulated, melt congealed, or extruded before tableting. The final formulation may include one or more layers and may be coated or uncoated; or encapsulated.

The formulation of tablets is discussed in detail in "Pharmaceutical Dosage
15 Forms: Tablets, Vol. 1", by H. Lieberman and L. Lachman, Marcel Dekker, N.Y., N.Y., 1980 (ISBN 0-8247-6918-X), the disclosure of which is incorporated herein by reference in its entirety.

Solid formulations for oral administration may be formulated to be immediate and/or modified release. Modified release formulations include delayed-, sustained-,
20 pulsed-, controlled-, targeted and programmed release.

Suitable modified release formulations are described in U.S. Patent No. 6,106,864. Details of other suitable release technologies such as high energy dispersions and osmotic and coated particles can be found in Verma *et al*, Pharmaceutical Technology On-line, 25(2), 1-14 (2001). The use of chewing gum to
25 achieve controlled release is described in WO 00/35298. The disclosures of these references are incorporated herein by reference in their entireties.

Parenteral Administration

The compounds of the invention may also be administered directly into the blood stream, into muscle, or into an internal organ. Suitable means for parenteral
30 administration include intravenous, intraarterial, intraperitoneal, intrathecal, intraventricular, intraurethral, intrasternal, intracranial, intramuscular and subcutaneous. Suitable devices for parenteral administration include needle (including microneedle) injectors, needle-free injectors and infusion techniques.

- 67 -

Parenteral formulations are typically aqueous solutions which may contain excipients such as salts, carbohydrates and buffering agents (preferably to a pH of from 3 to 9), but, for some applications, they may be more suitably formulated as a sterile non-aqueous solution or as a dried form to be used in conjunction with a suitable vehicle such as sterile, pyrogen-free water.

The preparation of parenteral formulations under sterile conditions, for example, by lyophilization, may readily be accomplished using standard pharmaceutical techniques well known to those skilled in the art.

The solubility of compounds of the invention used in the preparation of parenteral solutions may be increased by the use of appropriate formulation techniques, such as the incorporation of solubility-enhancing agents.

Formulations for parenteral administration may be formulated to be immediate and/or modified release. Modified release formulations include delayed-, sustained-, pulsed-, controlled-, targeted and programmed release. Thus compounds of the invention may be formulated as a solid, semi-solid, or thixotropic liquid for administration as an implanted depot providing modified release of the active compound. Examples of such formulations include drug-coated stents and PGLA microspheres.

Topical Administration

The compounds of the invention may also be administered topically to the skin or mucosa, that is, dermally or transdermally. Typical formulations for this purpose include gels, hydrogels, lotions, solutions, creams, ointments, dusting powders, dressings, foams, films, skin patches, wafers, implants, sponges, fibers, bandages and microemulsions. Liposomes may also be used. Typical carriers include alcohol, water, mineral oil, liquid petrolatum, white petrolatum, glycerin, polyethylene glycol and propylene glycol. Penetration enhancers may be incorporated; see, for example, J Pharm Sci, 88 (10), 955-958 by Finnin and Morgan (October 1999). Other means of topical administration include delivery by electroporation, iontophoresis, phonophoresis, sonophoresis and microneedle or needle-free (e.g. Powderject™, Bioject™, etc.) injection. The disclosures of these references are incorporated herein by reference in their entireties.

- 68 -

Formulations for topical administration may be formulated to be immediate and/or modified release. Modified release formulations include delayed-, sustained-, pulsed-, controlled-, targeted and programmed release.

Inhaled/Intranasal Administration

5 The compounds of the invention can also be administered intranasally or by inhalation, typically in the form of a dry powder (either alone, as a mixture, for example, in a dry blend with lactose, or as a mixed component particle, for example, mixed with phospholipids, such as phosphatidylcholine) from a dry powder inhaler or as an aerosol spray from a pressurized container, pump, spray, atomizer (preferably
10 an atomizer using electrohydrodynamics to produce a fine mist), or nebulizer, with or without the use of a suitable propellant, such as 1,1,1,2-tetrafluoroethane or 1,1,1,2,3,3,3-heptafluoropropane. For intranasal use, the powder may include a bioadhesive agent, for example, chitosan or cyclodextrin.

15 The pressurized container, pump, spray, atomizer, or nebulizer contains a solution or suspension of the compound(s) of the invention comprising, for example, ethanol, aqueous ethanol, or a suitable alternative agent for dispersing, solubilizing, or extending release of the active, a propellant(s) as solvent and an optional surfactant, such as sorbitan trioleate, oleic acid, or an oligolactic acid.

20 Prior to use in a dry powder or suspension formulation, the drug product is micronized to a size suitable for delivery by inhalation (typically less than 5 microns). This may be achieved by any appropriate comminuting method, such as spiral jet milling, fluid bed jet milling, supercritical fluid processing to form nanoparticles, high pressure homogenisation, or spray drying.

25 Capsules (made, for example, from gelatin or HPMC), blisters and cartridges for use in an inhaler or insufflator may be formulated to contain a powder mix of the compound of the invention, a suitable powder base such as lactose or starch and a performance modifier such as *L*-leucine, mannitol, or magnesium stearate. The lactose may be anhydrous or in the form of the monohydrate, preferably the latter. Other suitable excipients include dextran, glucose, maltose, sorbitol, xylitol, fructose,
30 sucrose and trehalose.

 A suitable solution formulation for use in an atomizer using electrohydrodynamics to produce a fine mist may contain from 1µg to 20mg of the compound of the invention per actuation and the actuation volume may vary from 1µL

- 69 -

to 100 μ L. A typical formulation includes a compound of the invention, propylene glycol, sterile water, ethanol and sodium chloride. Alternative solvents which may be used instead of propylene glycol include glycerol and polyethylene glycol.

Suitable flavors, such as menthol and levomenthol, or sweeteners, such as saccharin or saccharin sodium, may be added to those formulations of the invention intended for inhaled/intranasal administration.

Formulations for inhaled/intranasal administration may be formulated to be immediate and/or modified release using, for example, poly(DL-lactic-co-glycolic acid (PGLA). Modified release formulations include delayed-, sustained-, pulsed-, controlled-, targeted and programmed release.

In the case of dry powder inhalers and aerosols, the dosage unit is determined by means of a valve which delivers a metered amount. Units in accordance with the invention are typically arranged to administer a metered dose or "puff" containing a desired amount of the compound of the invention. The overall daily dose may be administered in a single dose or, more usually, as divided doses throughout the day.

Rectal/Intravaginal Administration

Compounds of the invention may be administered rectally or vaginally, for example, in the form of a suppository, pessary, or enema. Cocoa butter is a traditional suppository base, but various alternatives may be used as appropriate.

Formulations for rectal/vaginal administration may be formulated to be immediate and/or modified release. Modified release formulations include delayed-, sustained-, pulsed-, controlled-, targeted and programmed release.

Ocular Administration

Compounds of the invention may also be administered directly to the eye or ear, typically in the form of drops of a micronized suspension or solution in isotonic, pH-adjusted, sterile saline. Other formulations suitable for ocular and aural administration include ointments, biodegradable (e.g. absorbable gel sponges, collagen) and non-biodegradable (e.g. silicone) implants, wafers, lenses and particulate or vesicular systems, such as niosomes or liposomes. A polymer such as cross-linked polyacrylic acid, polyvinylalcohol, hyaluronic acid, a cellulosic polymer, for example, hydroxypropylmethylcellulose, hydroxyethylcellulose, or methyl cellulose, or a heteropolysaccharide polymer, for example, gelatin gum, may be incorporated

- 70 -

together with a preservative, such as benzalkonium chloride. Such formulations may also be delivered by iontophoresis.

Formulations for ocular/aural administration may be formulated to be immediate and/or modified release. Modified release formulations include delayed-, sustained-,
5 pulsed-, controlled-, targeted, or programmed release.

Other Technologies

Compounds of the invention may be combined with soluble macromolecular entities, such as cyclodextrin and suitable derivatives thereof or polyethylene glycol-containing polymers, in order to improve their solubility, dissolution rate, taste-
10 masking, bioavailability and/or stability for use in any of the aforementioned modes of administration.

Drug-cyclodextrin complexes, for example, are found to be generally useful for most dosage forms and administration routes. Both inclusion and non-inclusion complexes may be used. As an alternative to direct complexation with the drug, the
15 cyclodextrin may be used as an auxiliary additive, *i.e.* as a carrier, diluent, or solubilizer. Most commonly used for these purposes are alpha-, beta- and gamma-cyclodextrins, examples of which may be found in PCT Publication Nos. WO 91/11172, WO 94/02518 and WO 98/55148, the disclosures of which are incorporated herein by reference in their entireties.

The amount of the active compound administered will be dependent on the
20 subject being treated, the severity of the disorder or condition, the rate of administration, the disposition of the compound and the discretion of the prescribing physician. However, an effective dosage is typically in the range of about 0.001 to about 100 mg per kg body weight per day, preferably about 0.01 to about 35
25 mg/kg/day, in single or divided doses. For a 70 kg human, this would amount to about 0.07 to about 7000 mg/day, preferably about 0.7 to about 2500 mg/day. In some instances, dosage levels below the lower limit of the aforesaid range may be more than adequate, while in other cases still larger doses may be used without causing any harmful side effect, with such larger doses typically divided into several
30 smaller doses for administration throughout the day.

This invention also relates to a method for the treatment of abnormal cell growth in a mammal which comprises administering to said mammal an amount of a compound of the present invention, or a salt or solvate thereof, that is effective in

- 71 -

treating abnormal cell growth 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, enzymes, topoisomerase inhibitors, biological response modifiers, antibodies, cytotoxics, anti-
5 hormones, and anti-androgens.

In one embodiment of the present invention the anti-tumor agent used in conjunction with a compound of the present invention and pharmaceutical compositions described herein is an anti-angiogenesis agent, kinase inhibitor, pan kinase inhibitor or growth factor inhibitor. Preferred pan kinase inhibitors include
10 Sutent™ (sunitinib), described in U.S. Patent No. 6,573,293 (Pfizer, Inc, NY, USA). Anti-angiogenesis agents, include but are not limited to the following agents, such as EGF inhibitors, EGFR inhibitors, VEGF inhibitors, VEGFR inhibitors, TIE2 inhibitors, IGF1R inhibitors, COX-II (cyclooxygenase II) inhibitors, MMP-2 (matrix-metalloprotenase 2) inhibitors, and MMP-9 (matrix-metalloprotenase 9) inhibitors.

Preferred VEGF inhibitors, include for example, Avastin (bevacizumab), an anti-VEGF monoclonal antibody of Genentech, Inc. of South San Francisco, California. Additional VEGF inhibitors include CP-547,632 (Pfizer Inc., NY, USA), AG13736 (Pfizer Inc.), ZD-6474 (AstraZeneca), AEE788 (Novartis), AZD-2171, VEGF Trap (Regeneron/Aventis), Vatalanib (also known as PTK-787, ZK-222584: Novartis &
20 Schering AG), Macugen (pegaptanib octasodium, NX-1838, EYE-001, Pfizer Inc./Gilead/Eyetech), IM862 (Cytran Inc. of Kirkland, Washington, USA); and angiozyme, a synthetic ribozyme from Ribozyme (Boulder, Colorado) and Chiron (Emeryville, California) and combinations thereof.

VEGF inhibitors useful in the practice of the present invention are described in
25 US Patent No. 6,534,524 and 6,235,764, both of which are incorporated in their entirety for all purposes. Additional VEGF inhibitors are described in, for example in WO 99/24440, in WO 95/21613, WO 99/61422, U.S. Patent 5,834,504, WO 98/50356, U.S. Patent 5,883,113 U.S. Patent 5,886,020, U.S. Patent 5,792,783, U.S. Patent 6,653,308, WO 99/10349, WO 97/32856, WO 97/22596, WO 98/54093, WO 98/02438,
30 WO 99/16755, and WO 98/02437, all of which are herein incorporated by reference in their entirety.

Other anti-angiogenic compounds include acitretin, fenretinide, thalidomide, zoledronic acid, angiostatin, aplidine, cilengtide, combretastatin A-4, endostatin,

- 72 -

halofuginone, rebimastat, removab, Revlimid, squalamine, ukrain, Vitaxin and combinations thereof.

Other antiproliferative agents that may be used in combination with the compounds of the present invention include inhibitors of the enzyme farnesyl protein transferase and inhibitors of the receptor tyrosine kinase PDGFr, including the compounds disclosed and claimed in the following: U.S. Patent 6,080,769; U.S. Patent 6,194,438; U.S. Patent 6,258,824; U.S. Patent 6,586,447; U.S. Patent 6,071,935; U.S. Patent 6,495,564; and U.S. Patent 6,150,377; U.S. Patent 6,596,735; U.S. Patent 6,479,513; WO 01/40217; U.S. 2003-0166675. Each of the foregoing patents and patent applications is herein incorporated by reference in their entirety.

PDGFr inhibitors include but are not limited to those disclosed in international patent application publication numbers WO01/40217 and WO2004/020431, the contents of which are incorporated in their entirety for all purposes. Preferred PDGFr inhibitors include Pfizer's CP-673,451 and CP-868,596 and its salts.

Preferred GARF inhibitors include Pfizer's AG-2037 (pelitrexol and its salts). GARF inhibitors useful in the practice of the present invention are disclosed in US Patent No. 5,608,082 which is incorporated in its entirety for all purposes.

Examples of useful COX-II inhibitors which can be used in conjunction with a compound of Formula (I) and pharmaceutical compositions disclosed herein include CELEBREXTM (celecoxib), parecoxib, deracoxib, ABT-963, MK-663 (etoricoxib), COX-189 (Lumiracoxib), BMS 347070, RS 57067, NS-398, Bextra (valdecoxib), paracoxib, Vioxx (rofecoxib), SD-8381, 4-Methyl-2-(3,4-dimethylphenyl)-1-(4-sulfamoyl-phenyl)-1H-pyrrole, 2-(4-Ethoxyphenyl)-4-methyl-1-(4-sulfamoylphenyl)-1H-pyrrole, T-614, JTE-522, S-2474, SVT-2016, CT-3, SC-58125 and Arcoxia (etoricoxib). Additionally, COX-II inhibitors are disclosed in U.S. Patent Applications US 2005-0148627 and US 2005-0148777, the contents of which are incorporated in their entirety for all purposes.

In a particular embodiment the anti-tumor agent is celecoxib (U.S. Patent No. 5,466,823), valdecoxib (U.S. Patent No. 5,633,272), parecoxib (U.S. Patent No. 5,932,598), deracoxib (U.S. Patent No. 5,521,207), SD-8381 (U.S. Patent No. 6,034,256, Example 175), ABT-963 (WO 2002/24719), rofecoxib (CAS No. 162011-90-7), MK-663 (or etoricoxib) as disclosed in WO 1998/03484, COX-189 (Lumiracoxib) as disclosed in WO 1999/11605, BMS-347070 (U.S. Patent 6,180,651),

- 73 -

NS-398 (CAS 123653-11-2), RS 57067 (CAS 17932-91-3), 4-Methyl-2-(3,4-dimethylphenyl)-1-(4-sulfamoyl-phenyl)-1H-pyrrole, 2-(4-Ethoxyphenyl)-4-methyl-1-(4-sulfamoylphenyl)-1H-pyrrole, or meloxicam.

Other useful inhibitors as anti-tumor agents used in combination with a compound of the present invention and pharmaceutical compositions disclosed herein include aspirin, and non-steroidal anti-inflammatory drugs (NSAIDs) which inhibit the enzyme that makes prostaglandins (cyclooxygenase I and II), resulting in lower levels of prostaglandins, include but are not limited to the following, Salsalate (Amigesic), Diflunisal (Dolobid), Ibuprofen (Motrin), Ketoprofen (Orudis), Nabumetone (Relafen), Piroxicam (Feldene), Naproxen (Aleve, Naprosyn), Diclofenac (Voltaren), Indomethacin (Indocin), Sulindac (Clinoril), Tolmetin (Tolectin), Etodolac (Lodine), Ketorolac (Toradol), Oxaprozin (Daypro) and combinations thereof.

Preferred COX-I inhibitors include ibuprofen (Motrin), nuprin, naproxen (Aleve), indomethacin (Indocin), nabumetone (Relafen) and combinations thereof.

Targeted agents used in combination with a compound of the present invention and pharmaceutical compositions disclosed herein include EGFr inhibitors such as Iressa (gefitinib, AstraZeneca), Tarceva (erlotinib or OSI-774, OSI Pharmaceuticals Inc.), Erbitux (cetuximab, Imclone Pharmaceuticals, Inc.), EMD-7200 (Merck AG), ABX-EGF (Amgen Inc. and Abgenix Inc.), HR3 (Cuban Government), IgA antibodies (University of Erlangen-Nuremberg), TP-38 (IVAX), EGFR fusion protein, EGF-vaccine, anti-EGFr immunoliposomes (Hermes Biosciences Inc.) and combinations thereof. Preferred EGFr inhibitors include Iressa, Erbitux, Tarceva and combinations thereof.

Other anti-tumor agents include those selected from pan erb receptor inhibitors or ErbB2 receptor inhibitors, such as CP-724,714 (Pfizer, Inc.), CI-1033 (canertinib, Pfizer, Inc.), Herceptin (trastuzumab, Genentech Inc.), Omitarg (2C4, pertuzumab, Genentech Inc.), TAK-165 (Takeda), GW-572016 (lonafarnib, GlaxoSmithKline), GW-282974 (GlaxoSmithKline), EKB-569 (Wyeth), PKI-166 (Novartis), dHER2 (HER2 Vaccine, Corixa and GlaxoSmithKline), APC8024 (HER2 Vaccine, Dendreon), anti-HER2/neu bispecific antibody (Decof Cancer Center), B7.her2.IgG3 (Agensys), AS HER2 (Research Institute for Rad Biology & Medicine), trifunctional bispecific antibodies (University of Munich) and mAB AR-209 (Aronex Pharmaceuticals Inc) and mAB 2B-1 (Chiron) and combinations thereof.

- 74 -

Preferred erb selective anti-tumor agents include Herceptin, TAK-165, CP-724,714, ABX-EGF, HER3 and combinations thereof. Preferred pan erbb receptor inhibitors include GW572016, CI-1033, EKB-569, and Omitarg and combinations thereof.

5 Additional erbB2 inhibitors include those disclosed in WO 98/02434, WO 99/35146, WO 99/35132, WO 98/02437, WO 97/13760, WO 95/19970, U.S. Patent 5,587,458, and U.S. Patent 5,877,305, each of which is herein incorporated by reference in its entirety. ErbB2 receptor inhibitors useful in the present invention are also disclosed in U.S. Patents 6,465,449, and 6,284,764, and in WO 2001/98277 each of which are
10 herein incorporated by reference in their entirety.

Additionally, other anti-tumor agents may be selected from the following agents, BAY-43-9006 (Onyx Pharmaceuticals Inc.), Genasense (augmerosen, Genta), Panitumumab (Abgenix/Amgen), Zevalin (Schering), Bexxar (Corixa/GlaxoSmithKline), Abarelix, Alimta, EPO 906 (Novartis), discodermolide (XAA-296), ABT-510 (Abbott),
15 Neovastat (Aeterna), enzastaurin (Eli Lilly), Combrestatin A4P (Oxigene), ZD-6126 (AstraZeneca), flavopiridol (Aventis), CYC-202 (Cyclacel), AVE-8062 (Aventis), DMXAA (Roche/Antisoma), Thymitaq (Eximias), Temodar (temozolomide, Schering Plough) and Revlimid (Celegene) and combinations thereof.

Other anti-tumor agents may be selected from the following agents, CyPat (cyproterone acetate), Histerelin (histrelin acetate), Plenaixis (abarelix depot),
20 Atrasentan (ABT-627), Satraplatin (JM-216), thalomid (Thalidomide), Theratope, Temilifene (DPPE), ABI-007 (paclitaxel), Evista (raloxifene), Atamestane (Biomed-777), Xyotax (polyglutamate paclitaxel), Targetin (bexarotene) and combinations thereof.

Additionally, other anti-tumor agents may be selected from the following agents,
25 Trizaone (tirapazamine), Aposyn (exisulind), Nevastat (AE-941), Ceplene (histamine dihydrochloride), Orathecin (rubitecan), Virulizin, Gastrimmune (G17DT), DX-8951f (exatecan mesylate), Onconase (ranpirnase), BEC2 (mitumoab), Xcytrin (motexafin gadolinium) and combinations thereof.

Further anti-tumor agents may be selected from the following agents, CeaVac (CEA),
30 NeuTrexin (trimetresate glucuronate) and combinations thereof. Additional anti-tumor agents may be selected from the following agents, OvaRex (oregovomab), Osidem (IDM-1), and combinations thereof. Additional anti-tumor agents may be selected from the following agents, Advexin (ING 201), Tirazone (tirapazamine), and

- 75 -

combinations thereof. Additional anti-tumor agents may be selected from the following agents, RSR13 (efaproxiral), Cotara (131I chTNT 1/b), NBI-3001 (IL-4) and combinations thereof. Additional anti-tumor agents may be selected from the following agents, Canvaxin, GMK vaccine, PEG Interon A, Taxoprexin (DHA/paclitaxel), and combinations thereof.

Other anti-tumor agents include Pfizer's MEK1/2 inhibitor PD325901, Array Biopharm's MEK inhibitor ARRY-142886, Bristol Myers' CDK2 inhibitor BMS-387,032, Pfizer's CDK inhibitor PD0332991 and AstraZeneca's AXD-5438, and combinations thereof.

Additionally, mTOR inhibitors may also be utilized such as CCI-779 (Wyeth) and rapamycin derivatives RAD001 (Novartis) and AP-23573 (Ariad), HDAC inhibitors, SAHA (Merck Inc./Aton Pharmaceuticals) and combinations thereof. Additional anti-tumor agents include aurora 2 inhibitor VX-680 (Vertex), and Chk1/2 inhibitor XL844 (Exelixis).

The following cytotoxic agents, e.g., one or more selected from the group consisting of epirubicin (Ellence), docetaxel (Taxotere), paclitaxel, Zinecard (dexrazoxane), rituximab (Rituxan) imatinib mesylate (Gleevec), and combinations thereof, may be used in combination with a compound of the present invention and pharmaceutical compositions disclosed herein.

The invention also contemplates the use of the compounds of the present invention together with hormonal therapy, including but not limited to, exemestane (Aromasin, Pfizer Inc.), leuporelin (Lupron or Leuplin, TAP/Abbott/Takeda), anastrozole (Arimidex, Astrazeneca), gosrelin (Zoladex, AstraZeneca), doxercalciferol, fadrozole, formestane, tamoxifen citrate (tamoxifen, Nolvadex, AstraZeneca), Casodex (AstraZeneca), Abarelix (Praecis), Trelstar, and combinations thereof.

The invention also relates to the use of the compounds of the present invention together with hormonal therapy agents such as anti-estrogens including, but not limited to fulvestrant, toremifene, raloxifene, lasofoxifene, letrozole (Femara, Novartis), anti-androgens such as bicalutamide, flutamide, mifepristone, nilutamide, Casodex™(4'-cyano-3-(4-fluorophenylsulphonyl)-2-hydroxy-2-methyl-3'-(trifluoromethyl) propionanilide, bicalutamide) and combinations thereof.

Further, the invention provides a compound of the present invention alone or in combination with one or more supportive care products, e.g., a product selected from

- 76 -

the group consisting of Filgrastim (Neupogen), ondansetron (Zofran), Fragmin, Procrit, Aloxi, Emend, or combinations thereof.

Particularly preferred cytotoxic agents include Camptosar, Erbitux, Iressa, Gleevec, Taxotere and combinations thereof.

5 The following topoisomerase I inhibitors may be utilized as anti-tumor agents: camptothecin; irinotecan HCl (Camptosar); edotecarin; orathecin (Supergen); exatecan (Daiichi); BN-80915 (Roche); and combinations thereof. Particularly preferred topoisomerase II inhibitors include epirubicin (Ellence).

Alkylating agents include, but are not limited to, nitrogen mustard N-oxide, cyclophosphamide, ifosfamide, melphalan, busulfan, mitobronitol, carboquone, thiotepa, ranimustine, nimustine, temozolomide, AMD-473, altretamine, AP-5280, apaziquone, brostallicin, bendamustine, carmustine, estramustine, fotemustine, glufosfamide, ifosfamide, KW-2170, mafosfamide, and mitolactol; platinum-coordinated alkylating compounds include but are not limited to, cisplatin, Paraplatin (carboplatin), eptaplatin, lobaplatin, nedaplatin, Eloxatin (oxaliplatin, Sanofi) or satraplatin and combinations thereof. Particularly preferred alkylating agents include Eloxatin (oxaliplatin).

Antimetabolites include but are not limited to, methotrexate, 6-mercaptopurine riboside, mercaptopurine, 5-fluorouracil (5-FU) alone or in combination with leucovorin, tegafur, UFT, doxifluridine, carmofur, cytarabine, cytarabine ocfosfate, enocitabine, S-1, Alimta (premetrexed disodium, LY231514, MTA), Gemzar (gemcitabine, Eli Lilly), fludarabin, 5-azacitidine, capecitabine, cladribine, clofarabine, decitabine, eflornithine, ethynylcytidine, cytosine arabinoside, hydroxyurea, TS-1, melphalan, nelarabine, nolatrexed, ocfosfate, disodium premetrexed, pentostatin, pelitrexol, raltitrexed, triapine, trimetrexate, vidarabine, vincristine, vinorelbine; 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-oxoquinazolin-6-ylmethyl)-N-methylamino]-2-thenoyl)-L-glutamic acid and combinations thereof.

Antibiotics include intercalating antibiotics and include, but are not limited to: aclarubicin, actinomycin D, amrubicin, annamycin, adriamycin, bleomycin, daunorubicin, doxorubicin, elsamitracin, epirubicin, galarubicin, idarubicin, mitomycin C, nemorubicin, neocarzinostatin, peplomycin, pirarubicin, rebeccamycin, stimalamer, streptozocin, valrubicin, zinostatin and combinations thereof.

- 77 -

Plant derived anti-tumor substances include for example those selected from mitotic inhibitors, for example vinblastine, docetaxel (Taxotere), paclitaxel and combinations thereof.

Cytotoxic topoisomerase inhibiting agents include one or more agents selected from the group consisting of aclarubicin, amonafide, belotecan, camptothecin, 10-hydroxycamptothecin, 9-aminocamptothecin, diflomotecan, irinotecan HCl (Camptosar), edotecarin, epirubicin (Ellence), etoposide, exatecan, gimatecan, lurtotecan, mitoxantrone, pirarubicin, pixantrone, rubitecan, sobuzoxane, SN-38, tafluposide, topotecan, and combinations thereof.

Preferred cytotoxic topoisomerase inhibiting agents include one or more agents selected from the group consisting of camptothecin, 10-hydroxycamptothecin, 9-aminocamptothecin, irinotecan HCl (Camptosar), edotecarin, epirubicin (Ellence), etoposide, SN-38, topotecan, and combinations thereof.

Immunologicals include interferons and numerous other immune enhancing agents. Interferons include interferon alpha, interferon alpha-2a, interferon, alpha-2b, interferon beta, interferon gamma-1a, interferon gamma-1b (Actimmune), or interferon gamma-n1 and combinations thereof. Other agents include filgrastim, lentinan, sizofilan, TheraCys, ubenimex, WF-10, aldesleukin, alemtuzumab, BAM-002, dacarbazine, daclizumab, denileukin, gemtuzumab ozogamicin, ibritumomab, imiquimod, lenograstim, lentinan, melanoma vaccine (Corixa), molgramostim, OncoVAX-CL, sargramostim, tasonermin, tecleukin, thymalasin, tositumomab, Virulizin, Z-100, epratuzumab, mitumomab, oregovomab, pentumomab (Y-muHMFG1), Provenge (Dendreon) and combinations thereof.

Biological response modifiers are agents that modify defense mechanisms of living organisms or biological responses, such as survival, growth, or differentiation of tissue cells to direct them to have anti-tumor activity. Such agents include krestin, lentinan, sizofiran, picibanil, ubenimex and combinations thereof.

Other anticancer agents that can be used in combination with a compound of the present invention include alitretinoin, ampligen, atrasentan bexarotene, bortezomib, Bosentan, calcitriol, exisulind, finasteride, fotemustine, ibandronic acid, miltefosine, mitoxantrone, l-asparaginase, procarbazine, dacarbazine, hydroxycarbamide, pegaspargase, pentostatin, tazarotne, Telcyta (TLK-286, Telik Inc.), Velcade (bortemazib, Millenium), tretinoin, and combinations thereof.

- 78 -

Platinum-coordinated compounds include but are not limited to, cisplatin, carboplatin, nedaplatin, oxaliplatin, and combinations thereof.

Camptothecin derivatives include but are not limited to camptothecin, 10-hydroxycamptothecin, 9-aminocamptothecin, irinotecan, SN-38, edotecarin, topotecan and combinations thereof.

Other antitumor agents include mitoxantrone, l-asparaginase, procarbazine, dacarbazine, hydroxycarbamide, pentostatin, tretinoin and combinations thereof.

Anti-tumor agents capable of enhancing antitumor immune responses, such as CTLA4 (cytotoxic lymphocyte antigen 4) antibodies, and other agents capable of blocking CTLA4 may also be utilized, such as MDX-010 (Medarex) and CTLA4 compounds disclosed in U.S. Patent 6,682,736; and anti-proliferative agents such as other farnesyl protein transferase inhibitors, for example the farnesyl protein transferase inhibitors. Additionally, specific CTLA4 antibodies that can be used in combination with compounds of the present invention include those disclosed in U.S. Patents 6,682,736 and 6,682,736 both of which are herein incorporated by reference in their entirety.

Specific IGF1R antibodies that can be used in the combination methods of the present invention include those disclosed in WO 2002/053596, which is herein incorporated by reference in its entirety.

Specific CD40 antibodies that can be used in the present invention include those disclosed in WO 2003/040170 which is herein incorporated by reference in its entirety.

Gene therapy agents may also be employed as anti-tumor agents such as TNFerade (GeneVec), which express TNFalpha in response to radiotherapy.

In one embodiment of the present invention statins may be used in combination with a compound of the present invention and pharmaceutical compositions thereof. Statins (HMG-CoA reductase inhibitors) may be selected from the group consisting of Atorvastatin (Lipitor™, Pfizer Inc.), Pravastatin (Pravachol™, Bristol-Myers Squibb), Lovastatin (Mevacor™, Merck Inc.), Simvastatin (Zocor™, Merck Inc.), Fluvastatin (Lescol™, Novartis), Cerivastatin (Baycol™, Bayer), Rosuvastatin (Crestor™, AstraZeneca), Lovostatin and Niacin (Advicor™, Kos Pharmaceuticals), derivatives and combinations thereof.

- 79 -

In a preferred embodiment the statin is selected from the group consisting of Atovorstatin and Lovastatin, derivatives and combinations thereof. Other agents useful as anti-tumor agents include Caduet.

Inasmuch as it may be desirable to administer a combination of active compounds, for example, for the purpose of treating a particular disease or condition, it is within the scope of the present invention that two or more pharmaceutical compositions, at least one of which contains a compound in accordance with the invention, may conveniently be combined in the form of a kit suitable for coadministration of the compositions. Thus the kit of the invention includes two or more separate pharmaceutical compositions, at least one of which contains a compound of the invention, and means for separately retaining said compositions, such as a container, divided bottle, or divided foil packet. An example of such a kit is the familiar blister pack used for the packaging of tablets, capsules and the like.

The kit of the invention is particularly suitable for administering different dosage forms, for example, oral and parenteral, for administering the separate compositions at different dosage intervals, or for titrating the separate compositions against one another. To assist compliance, the kit typically includes directions for administration and may be provided with a memory aid.

Examples

In the following examples and preparations, "BOC", "Boc" or "boc" means N-*tert*-butoxycarbonyl, CBZ means carbobenzyloxy, DCM means CH₂Cl₂, DIPEA or DIEA means diisopropyl ethyl amine, DMA means N,N-dimethylacetamide, "DMF" means dimethylformamide, "DMSO" means dimethylsulfoxide, "DPPP" means 1,3-bis(diphenylphosphino)propane, "HOAc" means acetic acid, "IPA" means isopropyl alcohol, "MTBE" means methyl *t*-butyl ether, "NMP" means 1-methyl 2-pyrrolidinone, TEA means triethyl amine, TFA means trifluoro acetic acid.

Specific examples

Example 1 (Method B): 6-(1H-benzimidazol-1-yl)-N-[(3R)-piperidin-3-yl]pyrazin-2-amine