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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 05-001801 - -00007-0000

Fecha: 2007-06-25 16:36:06 Dep. 2020 NUECREACIONES
Tra. 11 PATENTEIYII Eve: 379 FASENACIONALII
Act. 329 CTOINFORMACION Folios: 8

LABORATORIO - URIBE / NOVARTIS AG

Intellectual Property

2768/P

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISION DE NUEVAS CREACIONES
E. S. D.

Re: Expediente No. **05-01801**
Solicitud de patente a nombre de
NOVARTIS AG

Yo, JIMENA ESCOBAR URIBE, identificada como aparece al pie de mi firma, domiciliada en la carrera 11 No. 86-53 Piso 6, obrando como apoderada de la sociedad **NOVARTIS AG.**, domiciliada en Basilea, Suiza, solicitante de la patente de la referencia, me permito manifestar lo siguiente:

1. Con fundamento en la facultad que confiere el artículo 34 de la Decisión 486 al solicitante para modificar la solicitud de patente en cualquier momento del trámite, presento junto con este memorial el capítulo reivindicatorio en el cual se han realizado las siguientes modificaciones:

1.1 Se cancelaron las antiguas reivindicaciones 13 a 14 que hacían referencia a un método para el tratamiento de una enfermedad que responda a la inhibición de la actividad de la quinasas de proteína y al uso del compuesto de fórmula I para la preparación de una composición farmacéutica para el tratamiento de la enfermedad antes mencionada

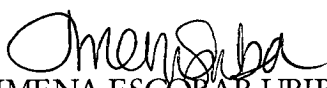
1.2 De otra parte, se limitó el alcance de las reivindicaciones 1 a 10 de la siguiente manera:

Las nuevas reivindicaciones se refieren al compuesto de fórmula I, donde los radicales R_1 , R_2 y R_4 son definidos en los términos expresados en las páginas 33 a 49 de la descripción.

En cuanto a estas modificaciones, me permito decir que las mismas no amplían en ningún sentido la materia objeto de la presente solicitud y se encuentran debidamente sustentadas por la descripción.

Para este efecto, me permito acompañar el recibo No. 07-47,642 de 14 de junio de 2007 con lo cual queda cubierta la tasa correspondiente a la modificación de una solicitud de patente en cuanto a sus reivindicaciones.

Señor Superintendente,


JIMENA ESCOBAR URIBE
C.C.39.779.452 de Usaquén
T.P. 68228
Cód. 5376

+

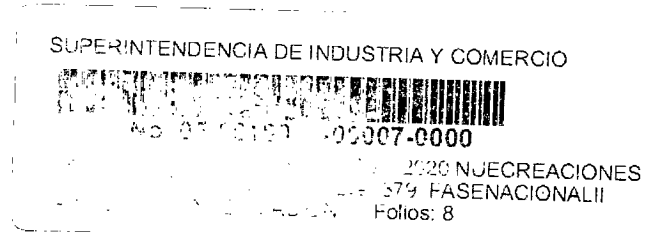
RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____

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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 07 - 47,642
FECHA : JUNIO 14 DE 2007

***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
BOBAR URIBE ASOCIADOS	CONSIGNACION	BANCO POPULAR	050-00110-6	66415405	13/06/2007	2,526,000.00

***** CONCEPTO *****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-03	CAMBIO DE MODALIDAD Y MODIFICA	
		12 MARCAS Y LEMAS COMERCIALES	99,000.00
		TOTAL :	\$ 99,000.00

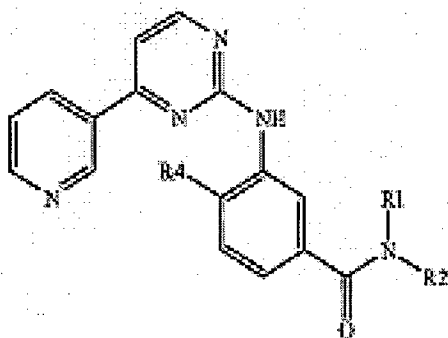
SON: NOVENTA Y NUEVE MIL PESOS

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REIVINDICACIONES

1. Un compuesto de la fórmula I donde :



R1 representa hidrógeno, alquilo inferior, alcoxilo inferior-alquilo inferior, o bencilo;

R2 representa fenilo substituido por uno o más sustituyentes seleccionados del grupo que consiste en alquilo inferior, trifluoro alquilo inferior, hidroxialquilo inferior, aminoalquilo inferior, alquilo inferior-aminoalquilo inferior, di-alquilo inferior aminoalquilo inferior, N-ciclohexilo-N-alquilo inferior-aminoalquilo inferior, alcoxilo inferior- carbonilpiperidinoalquilo inferior, N-alquilo inferior-piperazinoalquilo inferior, alcoxilo inferior-carbonilalquilo inferior, hidroxilo, alcoxilo inferior, trifluoroalcoxilo inferior, 1H-imidazolilalcoxilo inferior, alcanoiloxilo inferior, benzoiloxilo, carboxilo, alcoxilo inferior-carbonilo, carbamoilo, alquilo inferior carbamoilo, amino, alcanilo inferior-amino, benzoilamino, amino mono- ó disustituido por un alquilo inferior, por un hidroxialquilo inferior o por un alcoxilo inferior-alquilo inferior, 1H-imidazolilo, alquilo inferior-1H-imidazolilo, carboxilo-1H-imidazolilo, alquilo inferior estercarboxilo-1H-imidazolilo, pirrolidino, piperidino, piperazino, N-alquilo inferior-piperazino, morfolino, sulfamoílo, alquilo inferior sulfonilo, fenilo, piridilo, halogenílo, ó benzoílo; y

R4 representa hidrógeno, alquilo inferior ó halógeno;

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o un N-óxido o una sal farmacéuticamente aceptable de este compuesto, donde el término "inferior" denota un radical que tiene o incluye un máximo de 7 átomos de carbono, estando los radicales en cuestión en forma lineal o ramificada con una o múltiples ramificaciones.

2. Un compuesto de la fórmula I de acuerdo con la reivindicación 1, en donde:

R_1 representa hidrógeno;

R_2 representa fenilo sustituido por trifluorometilo y opcionalmente un sustituyente adicional seleccionado del grupo que consiste en hidroxialquilo inferior, aminoalquilo inferior, hidroxiaminoalquilo inferior, di-alquiloamina inferior, 1H-imidazolilo, alquilo inferior-1H-imidazolilo, carbamoilo, alquilo inferior carbamoilo, pirrolidino, piperidino, piperazino, alquilo inferior-piperazino, morfolino, alcoxilo inferior, trifluoroalcoxilo inferior, fenilo, piridilo, y halogenilo;

R_4 representa metilo;

o un N-óxido o una sal farmacéuticamente aceptable de este compuesto.

3. Un compuesto de la fórmula I de acuerdo con la reivindicación 1, en donde:

R_1 representa hidrógeno;

R_2 representa fenilo sustituido por trifluorometilo y opcionalmente un sustituyente adicional seleccionado del grupo que consiste de 1-hidroxi-1-metiletilo, metilamino, etilamino, 2-hidroxi-1-propilamino, 2-hidroxi-2-propilamino, dietilamino, 1H-imidazolilo, 2- y 4-metil-1H-imidazolilo, carbamoilo, metilcarbamoilo, pirrolidino, piperidino, piperazino, 4-metilpiperazino, morfolino,

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metoxi, trifluorometoxi, 2,2,2-trifluoroetoxi, fenilo, 2-, 3- y 4-piridilo, cloro, y fluoro;

R₄ representa metilo;

o un N-oxido o una sal farmacéuticamente aceptable de este compuesto.

4. Un compuesto de la fórmula I de acuerdo con la reivindicación 1, en donde:

R₁ representa hidrógeno;

R₂ representa 3-(1-hidroxi-1-metiletil)-5-(trifluorometil) fenilo;

R₄ representa metilo;

o un N-oxido o una sal farmacéuticamente aceptable de este compuesto.

5. Un compuesto de la fórmula I de acuerdo con la reivindicación 1, en donde:

R₁ representa hidrógeno;

R₂ representa fenilo que es mono o di substituido por imidazolalcoxilo inferior, aminoalquilo inferior, trifluorometil, hidroxialquilo inferior, hidroxialquilo inferior amino, bis-(alcoxilo-inferior-alquilo inferior) amino, alquilo inferior piperazinilo, piperidinilo, pirrolidinilo, morfolino, fenilo, piridilo, imidazolilo que está insustituido o mono- ó disustituido por alquilo inferior o por N-alquilo inferior-carbamoílo;

R₄ representa metilo;

o un N-oxido o una sal farmacéuticamente aceptable de este compuesto.

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6. Un compuesto de la fórmula I de acuerdo con la reivindicación 1, en donde:

R₁ representa hidrógeno;

R₂ representa fenilo substituido por 3-trifluorometil y un sustituyente adicional seleccionado del grupo que consiste en 2-metil-1H-imidazolilo y 4-metil-1H-imidazolilo;

R₄ representa metilo;

o un N-oxido o una sal farmacéuticamente aceptable de este compuesto.

7. Un compuesto de la fórmula I de acuerdo con la reivindicación 1, en donde:

R₁ representa hidrógeno;

R₂ representa fenilo substituido por 5-trifluorometil y un sustituyente adicional seleccionado del grupo que consiste en 2,4-dimetil-1H-imidazolilo, 5-metil-1H-imidazolilo, 2-metoximetilamino, propoxi, etoxi, metilaminocarbonilo, benzoílo, 4-metoxi-2-metil, acetilamino 2,4-dimetil-1H-imidazolilo, etil éster de ácido acético, etil éster de ácido carboxílico piperidino;

R₄ representa metilo;

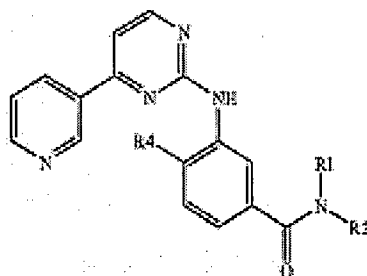
o un N-oxido o una sal farmacéuticamente aceptable de este compuesto.

8. Un compuesto de la fórmula I de acuerdo con la reivindicación 1, en donde el compuesto es 4-metil-3-[[4-(3-piridinil)-2-pirimidinil]amino]-N-[5-(4-metil-1H-

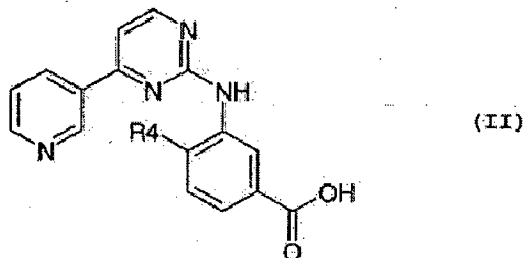
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imidazol-1-il)-3-(trifluorometil) fenil] benzamida o un N-oxido o una sal farmacéuticamente aceptable de este compuesto.

9. Un proceso para la síntesis del compuesto de la fórmula I



o un N-oxido o una sal farmacéuticamente aceptable de este compuesto, donde R1, R2 y R4 son como se definen en la reivindicación 1, caracterizado porque un compuesto de la fórmula II



en donde R4 es como se define para un compuesto de la fórmula I o un derivado del mismo, en donde el grupo carboxilo -COOH está en una forma activada, con una amina de la fórmula III:



en donde R₁ y R₂ son como se definen para un compuesto de la fórmula I, opcionalmente en la presencia de un agente de deshidratación y una base inerte y/o un catalizador adecuado, y opcionalmente en la presencia de un solvente inerte;

en donde los compuestos de partida II y III anteriores también pueden estar presentes con grupos funcionales en una forma protegida si es necesario, y/o en

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la forma de sales, en el entendido de que esté presente un grupo formador de sal y sea posible la reacción en forma de sal;

se remueven cualesquiera grupos protectores en un derivado protegido de un compuesto de la fórmula I;

y si se desea, un compuesto que se pueda obtener de la fórmula I se convierte en otro compuesto de la fórmula I ó en un N-óxido del mismo, un compuesto libre de la fórmula I se convierte en una sal, una sal que se pueda obtener de un compuesto de la fórmula I se convierte en el compuesto libre o en otra sal,

y/o una mezcla de compuestos isómeros de la fórmula I se separa en los isómeros individuales.

10. Una composición farmacéutica que comprende como un ingrediente activo un compuesto de la fórmula I de acuerdo con la reivindicación 1 ó un N-óxido o una sal farmacéuticamente aceptable de este compuesto junto con un vehículo farmacéuticamente aceptable.

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DIVISION DE NUEVAS CREACIONES

RADICACIÓN EXPEDIENTE No 05-1801

EL EXTRACTO DE LA PRESENTE SOLICITUD DE **PATENTE DE INVENCION**

FUE PUBLICADO EN LA GACETA DE PROPIEDAD INDUSTRIAL No **568** DE

FECHA **29 DE SEPTIEMBRE DE 2006** EL TERMINO HABIL SEÑALADO POR

LA LEY EXPIRA EL **29 DE DICIEMBRE DEL 2006**

NOTA: Dentro del plazo de los seis (6) meses siguientes a partir de la fecha de publicación en la gaceta de Propiedad Industrial, deberá solicitar y cancelar el examen de patentabilidad so pena de que la solicitud caiga en abandono, de acuerdo con lo establecido en el Artículo 44 de la Decisión 486/2000.

SE PRESENTARON OPOSICIONES POR PARTE DE TERCEROS.

SI _____

NO ___ _ **X** ___ _



Europäisches Patentamt
European Patent Office
Office européen des brevets



Veröffentlichungsnummer: **0 588 762 A1**

(12)

EUROPÄISCHE PATENTANMELDUNG

(21) Anmeldenummer: **93810595.4**

(51) Int. Cl.⁵: **A61K 31/505**

(22) Anmeldetag: **23.08.93**

(30) Priorität: **31.08.92 CH 2729/92**

(43) Veröffentlichungstag der Anmeldung:
23.03.94 Patentblatt 94/12

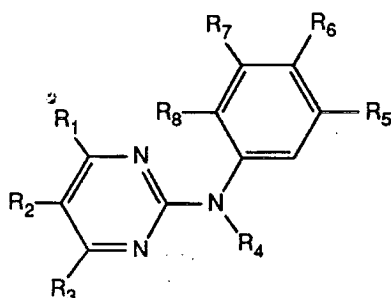
(84) Benannte Vertragsstaaten:
**AT BE CH DE DK ES FR GB GR IE IT LI LU NL
PT SE**

(71) Anmelder: **CIBA-GEIGY AG**
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(54) **Verwendung von Pyrimidinderivaten als Proteinkinase C-Inhibitoren und Antitumormittel.**

(57) Die Erfindung betrifft die Verwendung bekannter N-Phenyl-2-pyrimidinamin-derivate der Formel I zur Hemmung der Proteinkinase C in Warmblütern, d.h. z.B. als Antitumormittel.



(I)

Die Substituenten in Formel I haben die in Anspruch 1 angegebenen Bedeutungen.

EP 0 588 762 A1

Beispiel 6:

Kapseln, enthaltend 10 mg an Wirkstoff, z.B. eine der in den Beispielen 1-2 genannten Verbindungen der Formel I, werden wie folgt auf übliche Weise hergestellt:

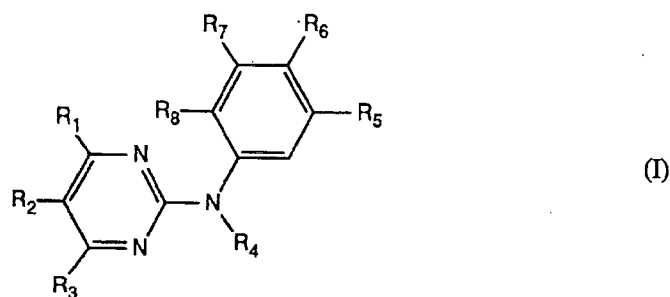
Zusammensetzung:	
Wirkstoff	2500 mg
Talkum	200 mg
Kolloidale Kieselsäure	50 mg

Herstellung:

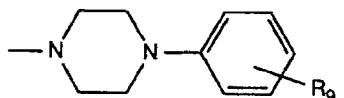
Die aktive Substanz wird mit Talkum und kolloidaler Kieselsäure innig gemischt, das Gemisch durch ein Sieb mit 0,5 mm Maschenweite getrieben und dieses in Portionen von jeweils 11 mg in Hartgelatine-kapseln geeigneter Grösse abgefüllt.

Patentansprüche

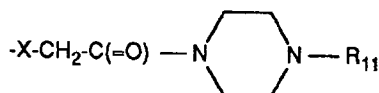
- Verwendung von N-Phenyl-2-pyrimidinamin-derivaten der Formel I,



worin R_1 Wasserstoff oder C_1 - C_3 -Alkyl bedeutet, R_2 Wasserstoff oder C_1 - C_3 -Alkyl bedeutet, R_3 2-Pyridyl, 3-Pyridyl, 4-Pyridyl, 2-Methyl-3-pyridyl, 4-Methyl-3-pyridyl, 2-Furyl, 5-Methyl-2-furyl, 2,5-Dimethyl-3-furyl, 2-Thienyl, 3-Thienyl, 5-Methyl-2-thienyl, 2-Phenothiazinyl, 4-Pyrazinyl, 2-Benzofuryl, N-Oxido-2-pyridyl, N-Oxido-3-pyridyl, N-Oxido-4-pyridyl, 1H-Indol-2-yl, 1H-Indol-3-yl, 1-Methyl-1H-pyrrol-2-yl, 4-Quinoliny, 1-Methyl-pyridinium-4-yl-iodid, Dimethylamino-phenyl oder N-Acetyl-N-methyl-aminophenyl bedeutet, R_4 Wasserstoff, C_1 - C_3 -Alkyl, den Rest $-CO-CO-O-C_2H_5$ oder N,N-Dimethylaminoethyl bedeutet, mindestens einer der Reste R_5 , R_6 , R_7 und R_8 C_1 - C_6 -Alkyl, C_1 - C_3 -Alkoxy, Chlor, Brom, Iod, Trifluormethyl, Hydroxy, Phenyl, Amino, Mono-(C_1 - C_3 -alkyl)-amino, Di-(C_1 - C_3 -alkyl)-amino, C_2 - C_4 -Alkanoyl, Propenyloxy, Carboxy, Carboxy-methoxy, Ethoxycarbonyl-methoxy, Sulfanilamido, N,N-Di-(C_1 - C_3 -alkyl)-sulfanilamido, N-Methyl-piperazinyl, Piperidinyl, 1H-Imidazol-1-yl, 1H-Triazol-1-yl, 1H-Benzimidazol-2-yl, 1-Naphthyl, Cyclopentyl, 3,4-Dimethyl-benzyl oder einen Rest einer der Formeln:
 $-CO_2R$, $-NH-C(=O)-R$, $-N(R)-C(=O)-R$, $-O-(CH_2)_n-N(R)-R$, $-C(=O)-NH-(CH_2)_n-N(R)-R$, $-CH(CH_3)-NH-CHO$, $-C(CH_3)=N-OH$, $-C(CH_3)=N-O-CH_3$, $-C(CH_3)-NH_2$, $-NH-CH_2-C(=O)-N(R)-R$,



$-(CH_2)_m-R_{10}$, $-X-(CH_2)_m-R_{10}$ oder



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bedeutet, worin R für C₁-C₃-Alkyl steht, X für Sauerstoff oder Schwefel steht, m für 1, 2 oder 3 steht, n für 2 oder 3 steht, R₉ für Wasserstoff, C₁-C₃-Alkyl, C₁-C₃-Alkoxy, Chlor, Brom, Iod oder Trifluormethyl steht, R₁₀ für 1H-Imidazol-1-yl oder Morpholinyl steht und R₁₁ für C₁-C₃-Alkyl oder unsubstituiertes oder durch C₁-C₃-Alkyl, Halogen oder Trifluormethyl monosubstituiertes Phenyl steht, und die übrigen der Reste R₅, R₆, R₇ und R₈ Wasserstoff bedeuten, oder von pharmazeutisch verwendbaren Salzen von solchen Verbindungen mit mindestens einer salzbildenden Gruppe zur Herstellung von pharmazeutischen Präparaten zur Anwendung als Hemmer der Proteinkinase C in Warmblütern einschliesslich des Menschen.

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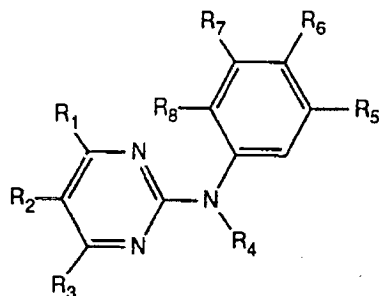
2. Verwendung nach Anspruch 1 zur Herstellung von pharmazeutischen Präparaten zur Anwendung als Antitumormittel in Warmblütern einschliesslich des Menschen.

3. Verwendung nach Anspruch 1 mit Ausnahme einer etwaigen Verwendung gegen Asthma, Allergien, Entzündung und Diabetes.

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4. Verwendung von N-Phenyl-2-pyrimidinamin-derivaten der Formel I,

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(I)

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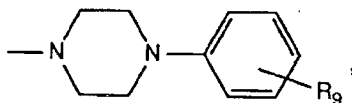
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worin R₁ Wasserstoff oder C₁-C₃-Alkyl bedeutet, R₂ Wasserstoff oder C₁-C₃-Alkyl bedeutet, R₃ 2-Pyridyl, 3-Pyridyl, 4-Pyridyl, 2-Methyl-3-pyridyl, 4-Methyl-3-pyridyl, 2-Furyl, 5-Methyl-2-furyl, 2,5-Dimethyl-3-furyl, 2-Thienyl, 3-Thienyl, 5-Methyl-2-thienyl, 2-Phenothiazinyl, 4-Pyrazinyl, 2-Benzofuryl, N-Oxido-2-pyridyl, N-Oxido-3-pyridyl, N-Oxido-4-pyridyl, 1H-Indol-2-yl, 1H-Indol-3-yl, 1-Methyl-1H-pyrrol-2-yl, 4-Quinolinyl, 1-Methyl-pyridinium-4-yl-iodid, Dimethylamino-phenyl oder N-Acetyl-N-methyl-amino-phenyl bedeutet, R₄ Wasserstoff, C₁-C₃-Alkyl, den Rest -CO-CO-O-C₂H₅ oder N,N-Dimethylaminoethyl bedeutet, mindestens einer der Reste R₅, R₆, R₇ und R₈ C₁-C₆-Alkyl, C₁-C₃-Alkoxy, Chlor, Brom, Iod, Trifluormethyl, Hydroxy, Phenyl, Amino, Mono- (C₁-C₃-alkyl)-amino, Di-(C₁-C₃-alkyl)-amino, C₂-C₄-Alkanoyl, Propenyloxy, Carboxy, Carboxy-methoxy, Ethoxycarbonyl-methoxy, Sulfanilamido, N,N-Di-(C₁-C₃-alkyl)-sulfanilamido, N-Methyl-piperazinyl, Piperidinyl, 1H-Imidazol-1-yl, 1H-Triazol-1-yl, 1H-Benzimidazol-2-yl, 1-Naphthyl, Cyclopentyl, 3,4-Dimethyl-benzyl oder einen Rest einer der Formeln:
-CO₂R, -NH-C(=O)-R, -N(R)-C(=O)-R, -O-(CH₂)_n-N(R)-R, -C(=O)-NH-(CH₂)_n-N(R)-R, -CH(CH₃)-NH-CHO, -C(CH₃)=N-OH, -C(CH₃)=N-O-CH₃, -C(CH₃)-NH₂, -NH-CH₂-C(=O)-N(R)-R,

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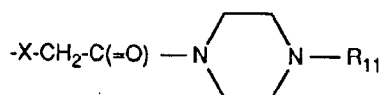
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-(CH₂)_m-R₁₀, -X-(CH₂)_m-R₁₀ oder

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bedeutet, worin R für C₁-C₃-Alkyl steht, X für Sauerstoff oder Schwefel steht, m für 1, 2 oder 3 steht, n für 2 oder 3 steht, R₉ für Wasserstoff, C₁-C₃-Alkyl, C₁-C₃-Alkoxy, Chlor, Brom, Iod oder Trifluormethyl steht, R₁₀ für 1H-Imidazol-1-yl oder Morpholinyll steht und R₁₁ für C₁-C₃-Alkyl oder unsubstituiertes oder durch C₁-C₃-Alkyl, Halogen oder Trifluormethyl monosubstituiertes Phenyl steht, und die übrigen der Reste R₅, R₆, R₇ und R₈ Wasserstoff bedeuten, oder von pharmazeutisch verwendbaren Salzen von solchen Verbindungen mit mindestens einer salzbildenden Gruppe zur Herstellung von pharmazeutischen Präparaten zur Anwendung als Antitumormittel in Warmblütern einschliesslich des Menschen.

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5. Verwendung nach einem der Ansprüche 1-4, worin in der Verbindung der Formel I mindestens zwei der Reste R₅, R₆ und R₈ je für Wasserstoff stehen.

6. Verwendung nach einem der Ansprüche 1-4, worin in der Verbindung der Formel I R₅, R₆ und R₈ je für Wasserstoff stehen.

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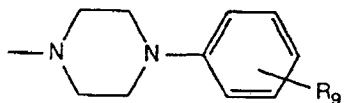
7. Verwendung nach einem der Ansprüche 1-4, worin in der Verbindung der Formel I R₁, R₂, R₄, R₅, R₆ und R₈ je für Wasserstoff stehen, R₃ 2-Pyridyl, 3-Pyridyl, 4-Pyridyl, 2-Methyl-3-pyridyl, 4-Methyl-3-pyridyl, 2-Furyl, 3-Methyl-2-furyl, 2,5-Dimethyl-3-furyl, 2-Thienyl, 3-Thienyl, 5-Methyl-2-thienyl, 2-Phenothiazinyl, 4-Pyrazinyl, 2-Benzofuryl, N-Oxido-2-pyridyl, N-Oxido-3-pyridyl, N-Oxido-4-pyridyl, 1H-Indol-2-yl, 1H-Indol-3-yl, 1-Methyl-1H-pyrrol-2-yl, 4-Quinolinyll, 1-Methyl-pyridinium-4-yl-iodid, Dimethylamino-phenyl oder N-Acetyl-N-methyl-amino-phenyl bedeutet, und R₇ C₁-C₆-Alkyl, C₁-C₃-Alkoxy, Chlor, Brom, Iod, Trifluormethyl, Hydroxy, Phenyl, Amino, Mono-(C₁-C₃-alkyl)-amino, Di-(C₁-C₃-alkyl)-amino, C₂-C₄-Alkanoyl, Propenyloxy, Carboxy, Carboxy-methoxy, Ethoxycarbonyl-methoxy, Sulfanilamido, N,N-Di-(C₁-C₃-alkyl)-sulfanilamido, N-Methyl-piperazinyl, Piperidinyll, 1H-Imidazol-1-yl, 1H-Triazol-1-yl, 1H-Benzimidazol-2-yl, 1-Naphthyl, Cyclopentyl, 3,4-Dimethyl-benzyl oder einen Rest einer der Formeln:

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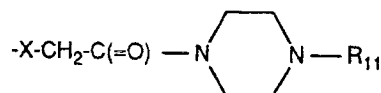
-CO₂R, -NH-C(=O)-R, -N(R)-C(=O)-R, -O-(CH₂)_n-N(R)-R, C(=O)-NH-(CH₂)_n-N(R)-R, -CH(CH₃)-NH-CHO, -C(CH₃)=N-OH, -C(CH₃)=N-O-CH₃, -C(CH₃)-NH₂, -NH-CH₂-C(=O)-N(R)-R,

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-(CH₂)_m-R₁₀, -X-(CH₂)_m-R₁₀ oder

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bedeutet, worin R für C₁-C₃-Alkyl steht, X für Sauerstoff oder Schwefel steht, m für 1, 2 oder 3 steht, n für 2 oder 3 steht, R₉ für Wasserstoff, C₁-C₃-Alkyl, C₁-C₃-Alkoxy, Chlor, Brom, Iod oder Trifluormethyl steht, R₁₀ für 1H-Imidazol-1-yl oder Morpholinyll steht und R₁₁ für C₁-C₃-Alkyl oder unsubstituiertes oder durch C₁-C₃-Alkyl, Halogen oder Trifluor methyl monosubstituiertes Phenyl steht.

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8. Verwendung nach einem der Ansprüche 1-4, worin in der Verbindung der Formel I R₁, R₂, R₄, R₅, R₆ und R₈ je für Wasserstoff stehen, R₃ 3-Pyridyl bedeutet und R₇ 1H-Imidazol-1-yl, Amino, Trifluormethyl, Chlor oder einen Rest der Formel -CO₂R oder -C(=O)-NH-(CH₂)_n-N(R)-R bedeutet, worin R je für Wasserstoff oder Methyl und n für 3 stehen.

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9. Verwendung nach einem der Ansprüche 1-4, worin man als Verbindung der Formel I N-(3-1H-Imidazol-1-yl-phenyl)-4-(3-pyridyl)-2-pyrimidinamin oder ein pharmazeutisch verwendbares Salz davon einsetzt.

10. Verwendung nach einem der Ansprüche 1-4, worin man als Verbindung der Formel I N-(3-Trifluorimethyl-



US005516775A

United States Patent [19] Zimmermann et al.

[11] **Patent Number:** 5,516,775
[45] **Date of Patent:** May 14, 1996

[54] FURTHER USE OF PYRIMIDINE DERIVATIVES

[75] Inventors: **Jürg Zimmermann, Möhlin; Giorgio Caravatti, Allschwil**, both of Switzerland

[73] Assignee: **Ciba-Geigy Corporation**, Tarrytown, N.Y.

[21] Appl. No.: **103,493**

[22] Filed: **Aug. 6, 1993**

[30] Foreign Application Priority Data

Aug. 31, 1992 [CH] Switzerland 2729/92

[51] Int. Cl.⁶ **A61K 31/505; A61K 31/54; A61K 31/535; A61K 31/53**

[52] U.S. Cl. **514/224.2; 514/235.8; 514/241; 514/255; 514/275**

[58] Field of Search **514/275, 224.2, 514/235.8, 241, 255**

[56] References Cited

U.S. PATENT DOCUMENTS

4,816,450 3/1989 Bell et al. 514/25
4,876,252 10/1989 Torley et al. 514/224.8

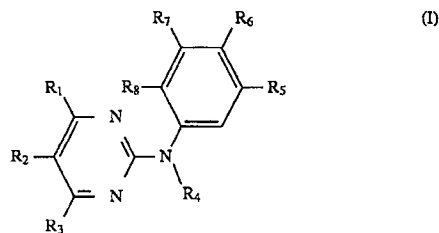
FOREIGN PATENT DOCUMENTS

0164204 12/1985 European Pat. Off. .
0233461 8/1987 European Pat. Off. .
0453731 2/1991 European Pat. Off. .

Primary Examiner—Allen J. Robinson
Assistant Examiner—Mary C. Cebulak
Attorney, Agent, or Firm—Karen G. Kaiser

[57] ABSTRACT

The invention relates to the use of known N-phenyl-2-pyrimidine derivatives for inhibiting protein kinase C in warm-blooded animals as antitumor agents.



The substituents in formula I are as defined in claim 1.

11 Claims, No Drawings

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EQUIVALENT

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FURTHER USE OF PYRIMIDINE DERIVATIVES

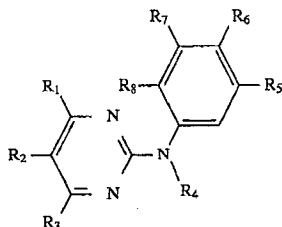
The present invention relates to the use of known N-phenyl-2-pyrimidine derivatives for inhibiting protein kinase C and/or as antitumour agents, and also for the preparation of pharmaceutical compositions for use as inhibitors of protein kinase C and/or as antitumour agents in warm-blooded animals.

European patent application filed under number 87100277.0 and published on Aug. 26, 1987 under publication number 0 233 461, and which is partially equivalent to U.S. Pat. No. 4,876,252, discloses N-phenyl-2-pyrimidinamine derivatives, their preparation and use as antiasthmatic and antiallergic agents owing to their inhibition of histamine release, as well as their use for treating inflammatory conditions and diabetes.

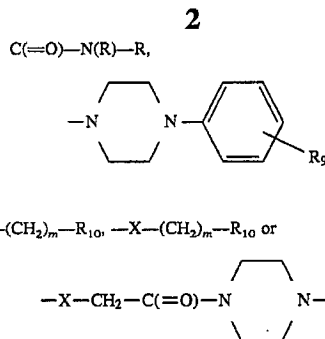
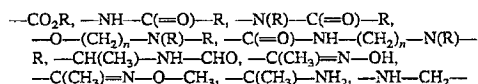
The present invention is based on the observation that some of the N-phenyl-2-pyrimidinamine derivatives disclosed in EP-A-0 233 461 selectively inhibit the protein kinase C enzyme.

Protein kinase C, which is dependent on phospholipids and calcium, occurs within cells in a number of species (distribution of the species tissue-specific) and participates in various fundamental processes such as signal transmission, proliferation and differentiation, as well as the release of hormones and neurotransmitters. This enzyme is activated either by receptor-mediated hydrolysis of phospholipids of the cell membrane or by direct interaction with specific tumour-promoting substances. Cellular functions which are controlled by protein kinase C can be influenced by modulation of the enzymatic activity of protein kinase C.

Specifically, the invention relates to the use of N-phenyl-2-pyrimidinamine derivatives of formula



wherein R₁ is hydrogen or C₁-C₃alkyl, R₂ is hydrogen or C₁-C₃alkyl, R₃ is 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-methyl-3-pyridyl, 4-methyl-3-pyridyl, 2-furyl, 5-methyl-2-furyl, 2,5-dimethyl-3-furyl, 2-thienyl, 3-thienyl, 5-methyl-2-thienyl, 2-phenothiazinyl, 4-pyrazinyl, 2-benzofuryl, N-oxido-2-pyridyl, N-oxido-3-pyridyl, N-oxido-4-pyridyl, 1H-indol-2-yl, 1H-indol-3-yl, 1-methyl-1H-pyrrol-2-yl, 4-quinolinyl, 1-methyl-pyridinium-4-ylidide, dimethylaminophenyl or N-acetyl-N-methyl-aminophenyl, R₄ is hydrogen, C₁-C₃alkyl, —CO—CO—O—C₂H₅ or N,N-dimethylaminoethyl, at least one of R₅, R₆, R₇ and R₈ is C₁-C₆alkyl, C₁-C₃alkoxy, chloro, bromo, iodo, trifluoromethyl, hydroxy, phenyl, amino, mono(C₁-C₃alkyl)amino, di(C₁-C₃alkyl)amino, C₂-C₄alkanoyl, propenyloxy, carboxy, carboxymethoxy, ethoxycarbonylmethoxy, sulfanilamido, N,N-di(C₁-C₃alkyl)sulfanilamido, N-methylpiperazinyl, piperidinyl, 1H-imidazol-1-yl, 1H-triazol-1-yl, 1H-benzimidazol-2-yl, 1-naphthyl, cyclopentyl, 3,4-dimethylbenzyl or a radical of one of the formulae:



wherein R is C₁-C₃alkyl, X is oxygen or sulfur, m is 1, 2 or 3, n is 2 or 3, R₉ is hydrogen, C₁-C₃alkyl, C₁-C₃alkoxy, chloro, bromo, iodo or trifluoromethyl, R₁₀ is 1H-imidazol-1-yl or morpholinyl, and R₁₁ is C₁-C₃alkyl or unsubstituted phenyl or phenyl which is monosubstituted by C₁-C₃alkyl, halogen or trifluoromethyl, and the remaining of the substituents R₅, R₆, R₇ and R₈ are hydrogen, or of pharmaceutically acceptable salts of said compounds containing at least one salt-forming group, for inhibiting protein kinase C and for the preparation of pharmaceutical compositions for use as inhibitors of protein kinase C in warm blooded animals. The novel use of the compounds of formula I as inhibitors of protein kinase C does not extend to their prior claimed use for the treatment of asthma, allergies, inflammatory conditions and diabetes, even if the activity against these diseases should be attributable to the inhibition of protein kinase C.

The compounds of formula I and their preparation are disclosed in EP-A-0 233 461 and in U.S. Pat. 4,876,252.

Salt-forming groups in a compound of formula I are groups or radicals having basic or acidic properties. Compounds having at least one basic group or at least one basic radical, for example a free amino group, a pyrazinyl radical or a pyridyl radical, can form acid addition salts, conveniently with inorganic acids such as hydrochloric acid, sulfuric acid or a phosphoric acid, or with suitable organic carboxylic or sulfonic acids, typically aliphatic mono- or dicarboxylic acids such as trifluoroacetic acid, acetic acid, propionic acid, glycolic acid, succinic acid, maleic acid, fumaric acid, hydroxymaleic acid, malic acid, tartaric acid, citric acid or oxalic acid, or amino acids such as arginine or lysine, aromatic carboxylic acids such as benzoic acid, 2-phenoxybenzoic acid, 2-acetoxybenzoic acid, salicylic acid, 4-aminosalicylic acid, aromatic-aliphatic carboxylic acids such as mandelic acid or cinnamic acid, heteroaromatic carboxylic acids such as nicotinic acid or isonicotinic acid, aliphatic sulfonic acids such as methanesulfonic acid, ethanesulfonic acid or 2-hydroxyethane-sulfonic acid, or aromatic sulfonic acids such as benzenesulfonic acid, p-toluenesulfonic acid or naphthalene-2-sulfonic acid. When several basic groups are present, mono- or polyacid addition salts may be formed.

Compounds of formula I having acidic groups, for example a free carboxyl group, can form metal or ammonium salts such as alkali metal or alkaline earth metal salts, typically sodium, potassium, magnesium or calcium salts, or ammonium salts with ammonia or suitable organic amines such as tertiary monoamines, typically triethylamine or tris(2-hydroxyethyl)amine, or heterocyclic bases such as N-ethylpiperidine or N,N'-dimethylpiperazine.

It has now been found that the compounds of formula I have valuable pharmacological properties that were previously unknown. Inter alia, they selectively inhibit the protein kinase C enzyme.

Protein kinase C from pig brain is used to determine the inhibitory action on protein kinase C. The inhibitory action

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of the compounds of formula I on protein kinase C is determined by the method of D. Fabbro et al, as described in Example 2. In this assay, the compounds of formula I inhibit protein kinase C even at a concentration IC_{50} in the range from c. 0.1 to 30 $\mu\text{mol/liter}$.

In contradistinction thereto, the compounds of formula I only inhibit other enzymes, for example protein kinase A and phosphorylase protein kinase, at far higher concentration, for example 100 times higher. This distinction demonstrates the selectivity of the compounds of formula I.

Owing to their inhibitory action on protein kinase C, the compounds of formula I and their pharmaceutically acceptable salts can be used as tumour-inhibiting, immunomodulating and anti-bacterial drugs and, further, as drugs against atherosclerosis, the immunodeficiency disease AIDS, and diseases of the cardiovascular system and the central nervous system.

As may already be expected in the light of the inhibitory action on protein kinase C described above, the compounds of formula I have antiproliferative properties which can be demonstrated direct, inter alia, in the assay described in Example 1. In this assay, the inhibitory action of compounds of formula I on the growth of human T24 bladder carcinoma cells is determined. The IC_{50} values obtained for the compounds of formula I are from c. 1 to 10 $\mu\text{mol/liter}$.

The antiproliferative properties can also be demonstrated in vivo, as described in Example 3. In the assay described in Example 3, the compounds of formula I, when administered perorally or intraperitoneally, reduce tumour volume to about 35–70% of tumour volume in control animals treated with placebo.

Owing to the described properties, the compounds of formula I can be used in particular as tumour-inhibiting agents, inter alia for the treatment of tumours of the bladder. The invention relates to this utility of the compounds of formula I as antitumour agents irrespective of whether the antitumour activity is directly attributable to the inhibition of protein kinase C or not, and irrespective of whether it can be proved that the antitumour activity is directly attributable to the inhibition of protein kinase C.

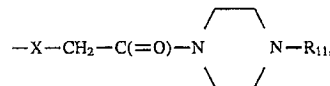
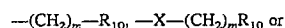
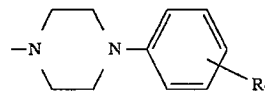
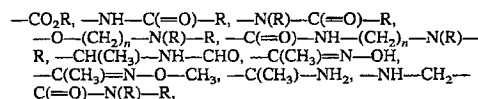
Use of the compounds of formula I in cancer therapy in conjunction with other chemotherapeutic agents prevents the development of resistance (multidrug resistance) or they neutralise an already existing resistance to the other chemotherapeutic agents. In addition, the compounds of formula I are suitable for the other utilities mentioned in connection with protein kinase C modulators, and they can be used in particular for the treatment of diseases that respond to inhibition of protein kinase C. The invention relates to the use of the compounds of formula I for the purposes cited above, with the exception of their prior claimed use against asthma, allergies, inflammatory conditions and diabetes, and for the preparation of pharmaceutical compositions for use for this purpose.

It is preferred to use compounds of formula I, wherein at least two of R_5 , R_6 and R_8 are each hydrogen, more particularly those compounds wherein R_5 , R_6 and R_8 are each hydrogen and the other substituents are as previously defined, and pharmaceutically acceptable salts of said compounds containing at least one salt-forming group.

Principally, compounds of formula I are used wherein R_1 , R_2 , R_4 , R_5 , R_6 and R_8 are each hydrogen, R_3 is 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-methyl-3-pyridyl, 4-methyl-3-pyridyl, 2-furyl, 5-methyl-2-furyl, 2,5-dimethyl-3-pyridyl, 2-thienyl, 3-thienyl, 5-methyl-2-thienyl, 2-phenothiazinyl, 4-pyrazinyl, 2-benzofuryl, N-oxido-2-pyridyl, N-oxido-3-pyridyl, N-oxido-4-pyridyl, 1H-indol-2-yl, 1H-indol-3-yl,

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1-methyl-1H-pyrrol-2-yl, 4-quinoliny, 1-methylpyridinium-4-yl iodide, dimethylaminophenyl or N-acetyl-N-methylaminophenyl, and R_7 is C_1 – C_6 alkyl, C_1 – C_3 alkoxy, chloro, bromo, iodo, trifluoromethyl, hydroxy, phenyl, amino, mono(C_1 – C_3 alkyl)-amino, di(C_1 – C_3 alkyl)amino, C_2 – C_4 alkanoyl, propenyloxy, carboxy, carboxymethoxy, ethoxycarbonylmethoxy, sulfanilamido, N,N-di(C_1 – C_3 alkyl)sulfanilamido, N-methylpiperazinyl, piperidinyl, 1H-imidazol-1-yl, 1H-triazol-1-yl, 1H-benzimidazol-2-yl, 1-naphthyl, cyclopentyl, 3,4-dimethylbenzyl or a radical of one of the formulae:



wherein R is C_1 – C_3 alkyl, X is oxygen or sulfur, m is 1, 2 or 3, n is 2 or 3, R_9 is hydrogen, C_1 – C_3 alkyl, C_1 – C_3 alkoxy, chloro, bromo, iodo or trifluoromethyl, R_m is 1H-imidazol-1-yl or morpholinyl, and R_{11} is C_1 – C_3 alkyl or unsubstituted phenyl or phenyl which is monosubstituted by C_1 – C_3 alkyl, halogen or trifluoromethyl, or of pharmaceutically acceptable salts of said compounds containing at least one salt-forming group.

It is especially preferred to use compounds of formula I, wherein R_1 , R_2 , R_4 , R_5 , R_6 and R_8 are each hydrogen, R_3 is 3-pyridyl, and R_7 is 1H-imidazol-1-yl, amino, trifluoromethyl, chloro or a radical of formula $-\text{CO}_2\text{R}$ or $-\text{C}(=\text{O})-\text{NH}-(\text{CH}_2)_n-\text{N}(\text{R})-\text{R}$, wherein each R is hydrogen or methyl and n is 3, and pharmaceutically acceptable acid addition salts of said compounds.

It is most preferred to use the compounds of formula I cited in the Examples and pharmaceutically acceptable acid addition salts of said compounds.

The invention also relates to a method of treating warm-blooded animals suffering from a tumoral disease, which comprises administering to warm-blooded animals in need of such treatment an effective, tumour-inhibiting amount of a compound of formula I or of a pharmaceutically acceptable salt thereof. The invention further relates to the use of a compound of formula I or of a pharmaceutically acceptable salt thereof for inhibiting protein kinase C in warm-blooded animals or for the preparation of pharmaceutical compositions for use in the therapeutic treatment of the human or animal body. The invention also relates to a method of inhibiting protein kinase C in warm-blooded animals, which comprises administering to a warm-blooded animal in need of such treatment an effective, protein kinase C inhibiting amount of a compound of formula I. It is contemplated that, depending on the species, age, individual condition, mode of administration and the particular clinical picture, daily doses of c. 1–2000 mg, preferably 50–2000 mg, more particularly 500–2000 mg, typically 500–1000 mg, will be administered enterally or parenterally to a warm-blooded animal of 70 kg body weight.

The invention also relates to the use of a compound of formula I or a pharmaceutically acceptable salt thereof for

the preparation of pharmaceutical compositions for use for inhibiting the protein kinase C, inter alia for the treatment of tumour-induced diseases. The novel pharmaceutical compositions contain an effective amount of the active compound, preferably an amount effective for the prophylaxis or therapy of one of the aforementioned diseases, together with pharmaceutically acceptable carriers that are suitable for topical, enteral, for example oral or rectal, or parenteral administration, and which may be inorganic or organic, solid or liquid. For oral administration it is preferred to use tablets or gelatin capsules that contain the active compound together with a diluent such as lactose, dextrose, suchrose, mannitol, sorbitol, cellulose and/or glycerol, and/or glidants, typically diatomaceous earth, talcum, stearic acid or salts thereof such as magnesium or calcium stearate, and/or polyethylene glycol. Tablets may also contain binders such as magnesium aluminium silicate, starches such as maize, corn or rice starch, gelatin, methyl cellulose, sodium carboxymethyl cellulose and/or polyvinyl pyrrolidone and, if desired, disintegrators such as starches, agar, alginic acid or a salt thereof, e.g. sodium alginate, and/or effervescent mixtures, or absorbents, colorants, flavourings and sweeteners. The pharmacologically active compounds of this invention can also be used in the form of compositions for parenteral administration or of infusion solutions. Such solutions are preferably isotonic aqueous solutions or suspensions which, in the case of lyophilised compositions that contain the active compound by itself or together with a carrier such as mannitol, can be prepared before use. The pharmaceutical compositions can be sterilised and/or can contain adjuvants such as preservatives, stabilisers, wetting agents and/or emulsifiers, solubilisers, salts for regulating the osmotic pressure and/or buffers. The novel pharmaceutical compositions which, if desired, may contain further pharmacologically active substances such as antibiotics, are prepared in per se known manner by conventional mixing, granulating, sugar-coating, solution or lyophilising methods and contain from about 1% to 100%, preferably from about 1% to about 20%, of active compound.

The invention is illustrated by the following non-limitative Examples.

ABBREVIATIONS

compound A=N-(3-(1H-imidazol-1-yl)phenyl)-4-(3-pyridyl)-2-pyrimidinamine (=compound of formula I, wherein R_1, R_2, R_4, R_5, R_6 and R_8 are each hydrogen, R_3 is 3-pyridyl and R_7 is 1H-imidazol-1-yl)

compound B=N-(3-(trifluoromethyl)phenyl)-4-(3-pyridyl)-2-pyrimidinamine

compound C=N-(3-chlorophenyl)-4-(3-pyridyl)-2-pyrimidinamine

compound D=N-(3-aminophenyl)-4-(3-pyridyl)-2-pyrimidinamine

compound E=N-(3-methoxycarbonylphenyl)-4-(3-pyridyl)-2-pyrimidinamine

compound F=N-(3-[3-aminopropylaminocarbonyl]phenyl)-4-(3-pyridyl)-2-pyrimidinamine

EXAMPLE 1

Inhibition of the Growth of Human Bladder Carcinoma Cells

Human T24 bladder carcinoma cells are incubated in "Eagle's minimal essential medium", to which 5% (v/v) foetal calf serum has been added, in a humidified incubator

at 37° C. and 5 percent by volume CO₂ in air. The carcinoma cells (1000–1500) are inoculated in 96-well microtitre plates and incubated overnight under the stated conditions. The test compound is added in serial dilutions on day 1. The plates are incubated for 5 days under the stated conditions. During this time the control cultures undergo at least 4 cell divisions. After incubation, the cells are fixed with a 3.3% (g/v) aqueous solution of glutaraldehyde, washed with water and stained with a 0.05% (weight/volume) aqueous solution of methylene blue. After washing, the stain is eluted with 3% (g/v) aqueous hydrochloric acid. Afterwards, the optical density (OD) per well, which is directly proportional to the number of cells, is measured with a photometer (Titertek multiskan) at 665 nm. The IC₅₀ values are computed by a computer system, using the formula

$$\frac{OD_{665}(\text{test}) - \text{minus } OD_{665}(\text{start})}{OD_{665}(\text{control}) - \text{minus } OD_{665}(\text{start})} \times 100$$

The IC₅₀ values are defined as that active compound concentration at which the number of cells per well at the end of the incubation period is only 50% of the number of cells in the control cultures. The following IC₅₀ values are obtained in this assay for the compounds of formula I:

compound	[μmol/litre]
A	2.5
B	7.4
C	5.2
D	7.2

EXAMPLE 2

Determination of the Inhibitory Action on Protein Kinase C

Protein kinase C from pig brain purified in accordance with the procedure described by T. Uchida and C. R. Filburn in J. Biol. Chem. 259, 12311–4 (1984) is used to determine the inhibitory action on protein kinase C. The inhibitory action of the compounds of formula I on protein kinase C is determined by the method of D. Fabro et al., Arch. Biochem. Biophys. 239, 102–111 (1985). The following IC₅₀ values are obtained in this assay for the compounds of formula I:

compound	[μmol/litre]
A	8.8
B	2.5
C	6.3
D	28
E	26
F	28

EXAMPLE 3

Antitumour Activity in Mice

On day 0 a c. 25 mg piece of human T24 bladder carcinoma is transplanted subcutaneously using Trokar under operable "forene" narcosis on female Balb/c nude mice (Balb/c/Balb/c nu/nu, Bomholdgaard, Denmark; six mice per group). On day 6 after the tumour transplantation the average tumour volume is 120–140 mm³ and treatment is commenced. The treatment consists in administering perorally or intraperitoneally once daily over 15 successive

days, i.e. altogether 15 times, 25 ml/kg of the following formulation. This formulation is prepared as follows: 16 mg of a compound of formula I are dissolved in 0.4 ml of dimethyl sulfoxide (100%). Then 0.05 ml of Tween 80 is added to this solution and the batch is mixed. Then 7.6 ml of a 0.9% aqueous solution of sodium chloride are added and the batch is thoroughly mixed. This formulation is prepared fresh daily. The control animals receive a placebo. The placebo is the same formulation without compound of formula I.

24 hours after the last administration, the tumour volume is measured and the ratio [%] of the tumour volume T/C is determined in the treated animals (T) and the control animals treated with placebo (C). The tumour volume in the control animals is defined as 100%, i.e. the smaller the ratio T/C the more effective the formulation.

A ratio T/C of 68% and 53% is obtained after peroral administration of 25 and 50 mg, respectively, of compound B as active ingredient in the above assay. A ratio T/C of 54% and 46% is obtained after intraperitoneal administration of 25 and 50 mg, respectively, of compound B.

EXAMPLE 4

Tablets comprising 20 mg of active ingredient, e.g. one of the compounds of formula I described in Examples 1-2 and having the following composition, are prepared in conventional manner:

Composition:	
active ingredient	20 mg
wheat starch	60 mg
lactose	50 mg
colloidal silicic acid	5 mg
talcum	9 mg
magnesium stearate	1 mg
	145 mg

Preparation: The active ingredient is mixed with a portion of the wheat starch, with the lactose and the colloidal silicic acid and the mixture is forced through a sieve. A further portion of the wheat starch is made into a paste, on a water bath, with five times the amount of water and the powder mixture is kneaded with the paste until a slightly plasticised mass is obtained.

The plasticised mass is passed through a sieve of c. 3 mm mesh size and dried, and the resulting dry granulate is again passed through a sieve. Then the remainder of the wheat starch, the talc and the magnesium stearate are blended in and the mixture is compressed to 145 mg tablets with a breaking notch.

EXAMPLE 5

Tablets comprising 1 mg of active ingredient, e.g. one of the compounds of formula I described in Examples 1-2 and having the following composition, are prepared in conventional manner:

Composition:	
active ingredient	1 mg
wheat starch	60 mg
lactose	50 mg
colloidal silicic acid	5 mg
talcum	9 mg

-continued

Composition:	
magnesium stearate	1 mg
	126 mg

Preparation: The active ingredient is mixed with a portion of the wheat starch, with the lactose and the colloidal silicic acid and the mixture is forced through a sieve. A further portion of the wheat starch is made into a paste, on a water bath, with five times the amount of water and the powder mixture is kneaded with the paste until a slightly plasticised mass is obtained.

The plasticised mass is passed through a sieve of about 3 mm mesh size and dried, and the resulting dry granulate is again passed through a sieve. Then the remainder of the wheat starch, the talc and the magnesium stearate are blended in and the mixture is compressed to 126 mg tablets provided with a breaking notch.

EXAMPLE 6

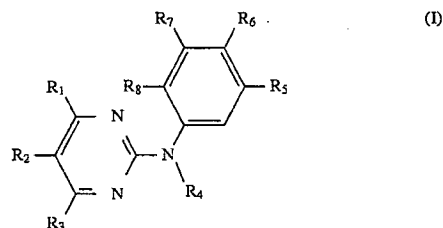
Capsules comprising 10 mg of active ingredient, e.g. one of the compounds of formula I described in Examples 1-2 are prepared in conventional manner as follows:

Composition:	
active ingredient	2500 mg
talcum	200 mg
colloidal silicic acid	50 mg

Preparation: The active ingredient is intimately mixed with the talcum and the colloidal silicic acid and the mixture is forced through a sieve of 0.5 mm mesh size and then filled in 11 mg portions into hard gelatin capsules of suitable size.

What is claimed is:

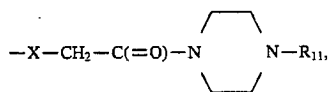
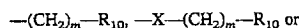
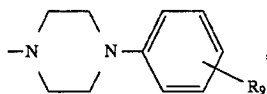
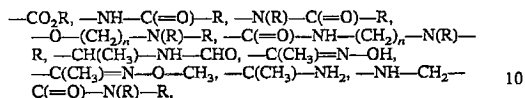
1. A method of treatment of warm-blooded animals suffering from a protein kinase C dependent tumoral disease, which comprises treating warm-blooded animals in need of such treatment with an effective tumor-inhibiting amount of a compound of formula I



wherein R_1 is hydrogen or C_1 - C_3 alkyl, R_2 is hydrogen or C_1 - C_3 alkyl, R_3 is 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-methyl-3-pyridyl, 4-methyl-3-pyridyl, 2-furyl, 5-methyl-2-furyl, 2,5-dimethyl-3-furyl, 2-thienyl, 3-thienyl, 5-methyl-2-thienyl, 2-phenothiazinyl, 4-pyrazinyl, 2-benzofuryl, N-oxido-2-pyridyl, N-oxido-3-pyridyl, N-oxido-4-pyridyl, 1H-indol-2-yl, 1H-indol-3-yl, 1-methyl-1H-pyrrol-2-yl, 4-quinolinyl, 1-methyl-pyridinium-4-yl iodide, dimethylaminophenyl or N-acetyl-N-methylaminophenyl, R_4 is hydrogen, C_1 - C_3 alkyl, $-\text{CO}-\text{CO}-\text{O}-\text{C}_2\text{H}_5$ or N,N-dimethylaminoethyl, at least one of R_5 , R_6 , R_7 and R_8 is C_1 - C_6 alkyl, C_1 - C_3 alkoxy, chloro, bromo, iodo, trifluoromethyl, hydroxy, phenyl, amino, mono- $(C_1$ - C_3 alkyl)amino,

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di(C₁-C₃alkyl)amino, C₂-C₄alkanoyl, propenyloxy, carboxy, carboxymethoxy, ethoxycarbonylmethoxy, sulfanilamido, N,N-di(C₁-C₃alkyl)sulfanilamido, N-methylpiperazinyl, piperidinyl, 1H-imidazol-1-yl, 1H-triazol-1-yl, 1H-benzimidazol-2-yl, 1-naphthyl, cyclopentyl, 3,4-dimethylbenzyl or a radical of one of the formulae:



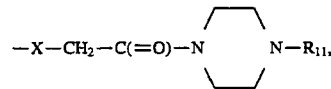
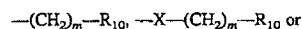
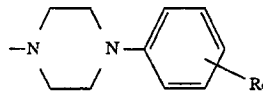
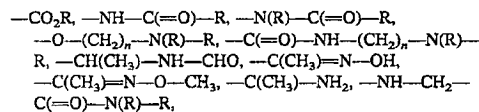
wherein R is C₁-C₃alkyl, X is oxygen or sulfur, m is 1, 2 or 3, n is 2 or 3, R₉ is hydrogen, C₁-C₃alkyl, C₁-C₃alkoxy, chloro, bromo, iodo or trifluoromethyl, R₁₀ is 1H-imidazol-1-yl or morpholinyl, and R₁₁ is C₁-C₃alkyl or unsubstituted phenyl or phenyl which is monosubstituted by C₁-C₃alkyl, halogen or trifluoromethyl, and the other substituents R₅, R₆, R₇ and R₈ are hydrogen, or a pharmaceutically acceptable salt thereof.

2. Method according to claim 1, wherein at least two of the substituents R₅, R₆ and R₈ in the compound of formula I are hydrogen.

3. Method according to claim 1, wherein each of the substituents R₅, R₆ and R₈ in the compound of formula I are hydrogen.

4. Method according to claim 1, wherein R₁, R₂, R₄, R₅, R₆ and R₈ in the compound of formula I are each hydrogen, R₃ is 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-methyl-3-pyridyl, 4-methyl-3-pyridyl, 2-furyl, 5-methyl-2-furyl, 2,5-dimethyl-3-furyl, 2-thienyl, 3-thienyl, 5-methyl-2-thienyl, 2-phenothiazinyl, 4-pyrazinyl, 2-benzofuryl, N-oxido-2-pyridyl, N-oxido-3-pyridyl, N-oxido-4-pyridyl, 1H-indol-2-yl, 1H-indol-3-yl, 1-methyl-1H-pyrrol-2-yl, 4-quinolinyl, 1-methylpyridinium-4-yl iodide, dimethylaminophenyl or N-acetyl-N-methylaminophenyl, and R₇ is C₁-C₆alkyl, C₁-C₃alkoxy, chloro, bromo, iodo, trifluoromethyl, hydroxy, phenyl, amino, mono(C₁-C₃alkyl)-amino, di(C₁-C₃alkyl)amino, C₂-C₄alkanoyl, propenyloxy, carboxy, carboxymethoxy, ethoxycarbonylmethoxy, sulfanilamido, N,N-di(C₁-C₃alkyl)sulfanilamido, N-methylpiperazinyl, piperidinyl, 1H-imidazol-1-yl, 1H-triazol-1-yl, 1H-benzimidazol-2-yl, 1-naphthyl, cyclopentyl, 3,4-dimethylbenzyl or a radical of one of the formulae:

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wherein R is C₁-C₃alkyl, X is oxygen or sulfur, m is 1, 2 or 3, n is 2 or 3, R₉ is hydrogen, C₁-C₃alkyl, C₁-C₃alkoxy, chloro, bromo, iodo or trifluoromethyl, R₁₀ is 1H-imidazol-1-yl or morpholinyl, and R₁₁ is C₁-C₃alkyl or unsubstituted phenyl or phenyl which is monosubstituted by C₁-C₃alkyl, halogen or trifluoromethyl.

5. Method according to claim 1, wherein R₁, R₂, R₄, R₅, R₆ and R₈ are each hydrogen, R₃ is 3-pyridyl, and R₇ is 1H-imidazol-1-yl, amino, trifluoromethyl, chloro or a radical of formula $-\text{CO}_2\text{R}$ or $-\text{C}(=\text{O})-\text{NH}-(\text{CH}_2)_n-\text{N}(\text{R})-\text{R}$, wherein each R is hydrogen or methyl and n is 3.

6. Method according to claim 1, wherein the compound of formula I is N-(3-1H-imidazol-1-ylphenyl)-4-(3-pyridyl)-2-pyrimidinamine or a pharmaceutically acceptable salt thereof.

7. Method according to claim 1, wherein the compound of formula I is N-(3-trifluoromethylphenyl)-4-(3-pyridyl)-2-pyrimidinamine or a pharmaceutically acceptable salt thereof.

8. Method according to claim 1, wherein the compound of formula I is N-(3-chlorophenyl)-4-(3-pyridyl)-2-pyrimidinamine or a pharmaceutically acceptable salt thereof.

9. Method according to claim 1, wherein the compound of formula I is N-(3-aminophenyl)-4-(3-pyridyl)-2-pyrimidinamine or a pharmaceutically acceptable salt thereof.

10. Method according to claim 1, wherein the compound of formula I is N-(3-methoxycarbonylphenyl)-4-(3-pyridyl)-2-pyrimidinamine or a pharmaceutically acceptable salt thereof.

11. Method according to claim 1, wherein the compound of formula I is N-(3-[3-aminopropylaminocarbonyl]phenyl)-4-(3-pyridyl)-2-pyrimidinamine or a pharmaceutically acceptable salt thereof.

* * * * *

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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : C07D 401/04, A61K 31/505	A1	(11) International Publication Number: WO 95/09853
		(43) International Publication Date: 13 April 1995 (13.04.95)

(21) International Application Number: PCT/EP94/03151

(22) International Filing Date: 21 September 1994 (21.09.94)

(30) Priority Data:

2969/93-0 1 October 1993 (01.10.93)
2281/94-2 18 July 1994 (18.07.94)

CH
CH

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(81) Designated States: AM, AU, BB, BG, BR, BY, CA, CN, CZ, EE, FI, GE, HU, JP, KG, KP, KR, KZ, LK, LR, LT, LV, MD, MG, MN, NO, NZ, PL, RO, RU, SI, SK, TJ, TT, UA, US, UZ, VN, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG), ARIPO patent (KE, MW, SD, SZ).

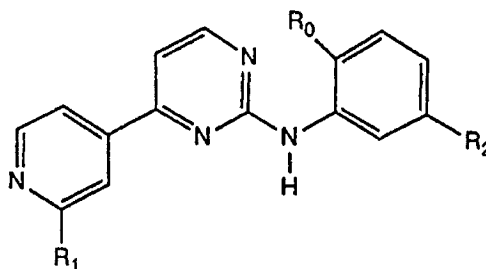
Published

With international search report.

(54) Title: PHARMACOLOGICALLY ACTIVE PYRIDINE DERIVATIVES AND PROCESSES FOR THE PREPARATION THEREOF

(57) Abstract

N-phenyl-2-pyrimidineamine derivatives of formula (I) wherein the substituents are as defined in claim 1 are described. Those compounds can be used, for example, in the treatment of tumour diseases.

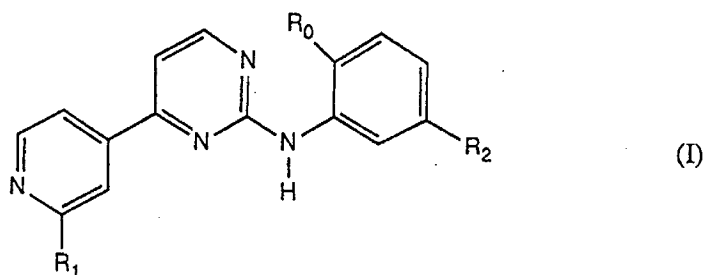


(I)

Pharmacologically active pyridine derivatives and processes for the preparation thereof

The invention relates to N-phenyl-4-(4-pyridyl)-2-pyrimidineamine derivatives, to processes for the preparation thereof, to medicaments comprising those compounds, and to the use thereof in the preparation of pharmaceutical compositions for the therapeutic treatment of warm-blooded animals.

The invention relates to N-phenyl-2-pyrimidineamine derivatives of formula I



wherein

R₀ is hydrogen, halogen, lower alkoxy or lower alkyl,

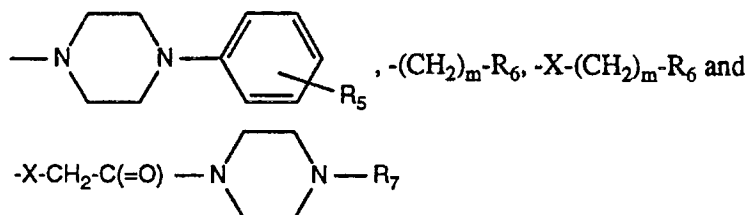
R₁ is

- a) N-(amino-lower alkyl)-carbamoyl,
- b) N-(hydroxy-lower alkyl)-carbamoyl,
- c) hydrazino,
- d) cyclohexyl-amino that is unsubstituted or substituted by amino,
- e) piperazinyl that is unsubstituted or substituted by amino-lower alkyl,
- f) morpholinyl, or
- g) lower alkylamino that is substituted by morpholinyl, hydroxy-lower alkylamino, cyano, imidazolyl, guanidyl, amino, lower alkanoylamino, lower alkylamino-carbonylamino, amidino, di-lower alkylamino-cyclohexyl, carboxy, lower alkoxy-carbonyl, carbamoyl, N-hydroxy-carbamoyl, hydroxy, lower alkoxy, dihydroxyphosphoryloxy, piperazinyl, lower alkanoyl-piperazinyl, formylpiperazinyl, prolylamido or by a radical of the formula H₂N-CH(R)-C(=O)-NH- wherein R is hydrogen, C₁-C₄alkyl, benzyl, hydroxymethyl, 1-hydroxy-ethyl, mercaptomethyl, 2-methylthio-ethyl, indol-3-yl-methyl, phenyl-methyl, 4-hydroxy-phenyl-methyl, carbamoyl-methyl, 2-carbamoyl-ethyl, carboxy-methyl, 2-carboxy-ethyl, 4-amino-butyl, 3-guanidyl-propyl or R is 1H-imidazol-4-yl-methyl, and R₂ is C₁-C₆alkyl, C₁-C₃alkoxy, chlorine, bromine, iodine, trifluoromethyl, hydroxy,

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phenyl, amino, mono(C₁-C₃alkyl)amino, di(C₁-C₃alkyl)amino, C₂-C₄alkanoyl, propen-
yloxy, carboxy, carboxy-methoxy, ethoxycarbonyl-methoxy, sulfanilamido, N,N-di-
(C₁-C₃alkyl)sulfanilamido, N-methyl-piperaziny, piperidinyl, 1H-imidazol-1-yl, 1H-
triazol-1-yl, 1H-benzimidazol-2-yl, 1-naphthyl, cyclopentyl, 3,4-dimethyl-benzyl or a
radical of one of the formulae:

-CO₂R₃, -NH-C(=O)-R₃, -N(R₃)-C(=O)-R₄, -O-(CH₂)_n-N(R₃)-R₄,
-C(=O)-NH-(CH₂)_n-R₄^a, -C(=O)-NH-(CH₂)_n-N(R₃)-R₄, -CH(CH₃)-NH-CHO,
-C(CH₃)=N-OH, -C(CH₃)=N-O-CH₃, -C(CH₃)-NH₂, -NH-CH₂-C(=O)-N(R₃)-R₄,



wherein R₃ and R₄ are each independently of the other C₁-C₃alkyl, R₄^a is hydroxy, amino
or imidazolyl, X is oxygen or sulfur, m is 1, 2 or 3, n is 2 or 3, R₅ is hydrogen, C₁-C₃alkyl,
C₁-C₃alkoxy, chlorine, bromine, iodine or trifluoromethyl, R₆ is 1H-imidazol-1-yl or
morpholinyl and R₇ is C₁-C₃alkyl or is phenyl that is unsubstituted or mono-substituted by
C₁-C₃alkyl, halogen or by trifluoromethyl,
and the salts thereof.

Halogen R₀ is fluorine, bromine, iodine or preferably chlorine.

Lower alkoxy R₀ is preferably methoxy.

Lower alkyl R₀ is preferably methyl.

Amino-lower alkyl in a radical R₁ is preferably ω-amino-C₂-C₃alkyl.

Hydroxy-lower alkyl in a radical R₁ is preferably ω-hydroxy-C₂-C₃alkyl.

Cyclohexyl-amino R₁ substituted by amino is preferably 4-amino-cyclohexyl-amino.

Di-lower alkylamino-cyclohexyl as part of a substituted lower alkyl radical R₁ is
preferably 4-di-lower alkylamino-cyclohexyl, preferably 4-dimethylamino-cyclohexyl.

Piperaziny R₁ is preferably 1-piperaziny. Piperaziny R₁ substituted by amino-lower
alkyl is preferably 4-(2-amino-ethyl)-piperazin-1-yl.

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Morpholinyl R_1 and morpholinyl in a radical R_1 are preferably 4-morpholinyl, wherein the free valency extends from the nitrogen. Lower alkylamino R_1 substituted by morpholinyl is preferably 2-morpholin-4-yl-ethylamino.

Hydroxy-lower alkylamino in a radical R_1 is preferably 2-hydroxy-ethylamino. Lower alkylamino substituted by hydroxy-lower alkylamino is preferably 3-(2-hydroxy-ethyl-amino)-prop-1-ylamino.

Imidazolyl R_4^a in a radical R_2 is preferably 1H-imidazol-4-yl.

Lower alkanoylamino in a radical R_1 is preferably acetylamino.

Lower alkylamino-carbonylamino in a radical R_1 is preferably methylamino-carbonylamino.

Di-lower alkylamino in a radical R_1 is preferably dimethylamino.

Formyl-piperazinyl in a radical R_1 is preferably 4-formyl-piperazinyl.

Lower alkylamino R_1 substituted by cyano, imidazolyl, guanidyl, amino, lower alkanoylamino, lower alkylamino-carbonylamino, amidino, di-lower alkylamino-cyclohexyl, carboxy, lower alkoxy-carbonyl, carbamoyl, N-hydroxy-carbamoyl, hydroxy, lower alkoxy, dihydroxyphosphoryloxy, piperazinyl, lower alkanoyl-piperazinyl, formylpiperazinyl, prolylamido or by a radical of the formula $H_2N-CH(R)-C(=O)-NH-$ is preferably di- or tri-methylamino substituted by those substituents, the substituents preferably being in the ω -position. Lower alkyl R_1 substituted by hydroxy can preferably also be 2-hydroxy-propyl.

A radical of the formula $H_2N-CH(R)-C(=O)-$, wherein R is as defined above, is preferably the acyl radical of any one of the following amino acids which regularly occur in proteins: glycine, alanine, valine, leucine, isoleucine, phenylalanine, serine, threonine, cysteine, methionine, tryptophan, tyrosine, asparagine, glutamine, aspartic acid, glutamic acid, lysine, arginine and histidine, especially in their naturally occurring configuration, preferably the (L)-configuration.

Within the scope of this text, the term "lower" denotes radicals having up to and including

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7, preferably up to and including 4, carbon atoms.

Unless otherwise indicated in the context concerned, lower alkyl is preferably methyl or ethyl.

The compounds of formula I can form acid addition salts, for example with inorganic acids, such as hydrochloric acid, sulfuric acid or a phosphoric acid, or with suitable organic carboxylic or sulfonic acids, for example aliphatic mono- or di-carboxylic acids, such as trifluoroacetic acid, acetic acid, propionic acid, glycolic acid, succinic acid, maleic acid, fumaric acid, hydroxymaleic acid, malic acid, tartaric acid, citric acid, oxalic acid or amino acids, such as arginine or lysine, aromatic carboxylic acids, such as benzoic acid, 2-phenoxy-benzoic acid, 2-acetoxy-benzoic acid, salicylic acid, 4-aminosalicylic acid, aromatic-aliphatic carboxylic acids, such as mandelic acid or cinnamic acid, hetero-aromatic carboxylic acids, such as nicotinic acid or isonicotinic acid, aliphatic sulfonic acids, such as methane-, ethane- or 2-hydroxy-ethane-sulfonic acid, or aromatic sulfonic acids, for example benzene-, p-toluene- or naphthalene-2-sulfonic acid. Mono-, di- or, if other basic groups, such as amino or guanidyl groups, are present in the radical R_1 , poly-acid addition salts can be formed.

Compounds of formula I having acidic groups, for example a free carboxy group in the radical R_1 , can form metal or ammonium salts, such as alkali metal or alkaline earth metal salts, for example sodium, potassium, magnesium or calcium salts, or ammonium salts with ammonia or suitable organic amines, such as tertiary monoamines, for example triethylamine or tri(2-hydroxyethyl)amine, or heterocyclic bases, for example N-ethyl-piperidine or N,N'-dimethyl-piperazine.

Compounds of formula I that possess both acidic and basic groups can form internal salts.

For the purpose of isolation or purification and also in the case of the compounds used further as intermediates, it is also possible to use pharmaceutically unacceptable salts. Only the pharmaceutically acceptable non-toxic salts are used therapeutically, however, and those are therefore preferred.

In view of the close relationship between the novel compounds in free form and in the form of their salts, including also salts that can be used as intermediates, for example in the purification of the novel compounds or in order to identify those compounds, hereinbefore and hereinafter any reference to the free compounds is to be understood as

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including also the corresponding salts, where appropriate and expedient.

The compounds of formula I exhibit valuable pharmacological properties: for example, they inhibit the enzyme protein kinase C with a high degree of selectivity. Phospholipid- and calcium-dependent protein kinase C occurs in cells in a number of forms and participates in various fundamental processes, such as signal transmission, proliferation and differentiation, and also the release of hormones and neurotransmitters. The activation of that enzyme is effected either by receptor-mediated hydrolysis of phospholipids of the cell membrane or by direct interaction with certain tumour-promoting active substances. The sensitivity of the cell to receptor-mediated signal transmission can be substantially influenced by modifying the activity of protein kinase C (as a signal transmitter). Compounds that are capable of influencing the activity of protein kinase C can be used as tumour-inhibiting, antiinflammatory, immunomodulating and antibacterial active ingredients and may even be of value as agents against atherosclerosis and disorders of the cardiovascular system and central nervous system.

Formerly, porcine brain protein kinase C purified in accordance with the procedure described by T. Uchida and C.R. Filburn in *J. Biol. Chem.* 259, 12311-4 (1984) was used to determine the inhibitory action on protein kinase C, and the inhibitory action on protein kinase C was determined in accordance with the procedure of D. Fabbro *et al.*, *Arch. Biochem. Biophys.* 239, 102-111 (1985).

The porcine brain protein kinase C formerly used is a mixture of various sub-types (isotypes) of protein kinase C. If pure recombinant isotypes are used instead of porcine brain protein kinase C in the above test it is found that the compounds of formula I inhibit the "conventional" isotype α preferentially whereas the other "conventional" isotypes β -1, β -2 and γ and especially the "non-conventional" isotypes δ , ϵ and η and the "atypical" isoform ζ are generally inhibited to a lesser extent and in some cases hardly at all.

Recombinant PKC isotypes are cloned, expressed and purified in the following manner:

The production of various proteins with the aid of baculoviruses, and their cloning and isolation from Sf9 insect cells are carried out as described by M.D. Summers and G.E. Smith, "A manual method for baculovirus vectors and insect cell culture procedure", *Texas Agric. Exptl. Station Bull.* (1987), 1555. The construction and isolation of recombinant viruses for the expression of PKC- α (bovine), PKC- β 1 (human), PKC- β 2 (human) and PKC- γ (human/bovine hybrid) in Sf9 cells are effected in the manner

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described by Stabel *et al.* [S. Stabel, M. Liyanage and D. Frith, "Expression of protein kinase C isozymes in insect cells and isolation of recombinant proteins", *Meth. Neurosc.* (1993)]. The production of the PKC isotypes in Sf9 cells is carried out in the manner indicated by Stabel *et al.* (see above), and the purification of the enzymes is effected in accordance with the method described in the publication by McGlynn *et al.* [E. McGlynn, J. Liebetanz, S. Reutener, J. Wood, N.B. Lydon, H. Hofstetter, M. Vanek, T. Meyer and D. Fabbro, "Expression and partial characterization of rat protein kinase C- δ and protein kinase C- ζ in insect cells using recombinant baculovirus", *J. Cell. Biochem.* **49**, 239-250 (1992)]. For the generation of recombinant PKC- δ (rat), PKC- ϵ (rat), PKC- ζ (rat) and PKC- η (mouse), and their expression and purification, the procedure described by Liyanage *et al.* ["Protein kinase C group B members PKC- δ , - ϵ , - ζ and PKC- λ : Comparison of properties of recombinant proteins *in vitro* and *in vivo*", *Biochem. J.* **283**, 781-787 (1992)] and McGlynn *et al.*, respectively, (see above) is followed, with the additional feature that the transfer vector pAc360 is used for the expression of PKC- η [V. Luckow and M.D. Summers, "Trends in the development of baculovirus expression", *Biotechnology* **6**, 47-55 (1988)].

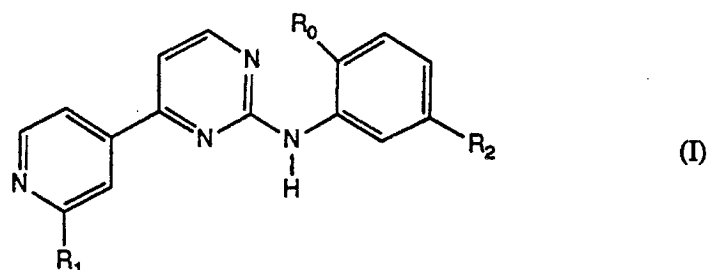
The measurement of the activity of the recombinant PKC isotypes obtained by the above method is carried out in the absence of lipid and calcium (co-factors). Protamine sulfate phosphorylated in the absence of co-factors is used as the substrate. The activity of the enzymes reflects the transfer of ^{32}P from γ -[^{32}P]-ATP to protamine sulfate. Protamine sulfate is a mixture of polypeptides each comprising four C-terminal arginine residues. Phosphate incorporation is measured under the following conditions: 100 μl of the reaction mixture contain in final concentrations 20 mM TRIS-HCl pH 7.4, 10 mM $\text{Mg}[\text{NO}_3]_2$, 0.5 mg/ml of protamine sulfate, 10 μM ATP (0.1 μCi γ -[^{32}P]-ATP; 10 Ci/mol; Amersham, Little Chalfont, United Kingdom), various concentrations of the inhibitory compounds and 0.5-2.5 U (units: a unit is the amount of enzyme that, in one minute and per milligram of protein, transfers one nanomole of ^{32}P from the above-mentioned γ -[^{32}P]-ATP to histone H1 [Sigma, type V-S]) of the enzymes. The reaction is started by the addition of the enzymes and transfer at 32°C. The reaction time is 20 minutes. The reaction is then stopped by dripping aliquots of 50 μl onto P81 chromatography paper (Whatman, Maidstone, United Kingdom). After removing unbound γ -[^{32}P]-ATP and nucleotide fragments by washing operations as described by J.J. Witt and R. Roskoski, "Rapid protein kinase assay using phospho-cellulose-paper absorption", *Anal. Biochem.* **66**, 253-258 (1975), the substrate phosphorylation is determined by scintillation measurement. In that test, the compounds of formula I inhibit the α -isotype of protein kinase C (PKC) at an IC_{50} of as low as approximately from 0.1 to 5.0 $\mu\text{mol/litre}$, generally approximately

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What is claimed is:

1. An N-phenyl-2-pyrimidineamine derivative of formula I



wherein

 R_0 is hydrogen, halogen, lower alkoxy or lower alkyl, R_1 is

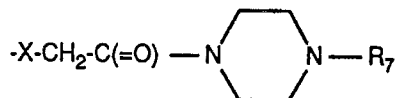
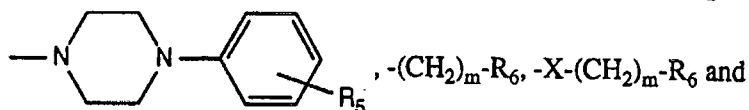
- a) N-(amino-lower alkyl)-carbamoyl,
- b) N-(hydroxy-lower alkyl)-carbamoyl,
- c) hydrazino,
- d) cyclohexyl-amino that is unsubstituted or substituted by amino,
- e) piperazinyl that is unsubstituted or substituted by amino-lower alkyl,
- f) morpholinyl, or
- g) lower alkylamino that is substituted by morpholinyl, hydroxy-lower alkylamino, cyano, imidazolyl, guanidyl, amino, lower alkanoylamino, lower alkylamino-carbonylamino, amidino, di-lower alkylamino-cyclohexyl, carboxy, lower alkoxy-carbonyl, carbamoyl, N-hydroxy-carbamoyl, hydroxy, lower alkoxy, dihydroxyphosphoryloxy, piperazinyl, lower alkanoyl-piperazinyl, formylpiperazinyl, prolylamido or by a radical of the formula $H_2N-CH(R)-C(=O)-NH-$ wherein R is hydrogen, C_1-C_4 alkyl, benzyl, hydroxymethyl, 1-hydroxy-ethyl, mercaptomethyl, 2-methylthio-ethyl, indol-3-yl-methyl, phenyl-methyl, 4-hydroxy-phenyl-methyl, carbamoyl-methyl, 2-carbamoyl-ethyl, carboxy-methyl, 2-carboxy-ethyl, 4-amino-butyl, 3-guanidyl-propyl or R is 1H-imidazol-4-yl-methyl, and R_2 is C_1-C_6 alkyl, C_1-C_3 alkoxy, chlorine, bromine, iodine, trifluoromethyl, hydroxy, phenyl, amino, mono(C_1-C_3 alkyl)amino, di(C_1-C_3 alkyl)amino, C_2-C_4 alkanoyl, propen-yloxy, carboxy, carboxy-methoxy, ethoxycarbonyl-methoxy, sulfanilamido, N,N-di- (C_1-C_3 alkyl)sulfanilamido, N-methyl-piperazinyl, piperidinyl, 1H-imidazol-1-yl, 1H-triazol-1-yl, 1H-benzimidazol-2-yl, 1-naphthyl, cyclopentyl, 3,4-dimethyl-benzyl or a radical of one of the formulae:

 $-CO_2R_3$, $-NH-C(=O)-R_3$, $-N(R_3)-C(=O)-R_4$, $-O-(CH_2)_n-N(R_3)-R_4$,

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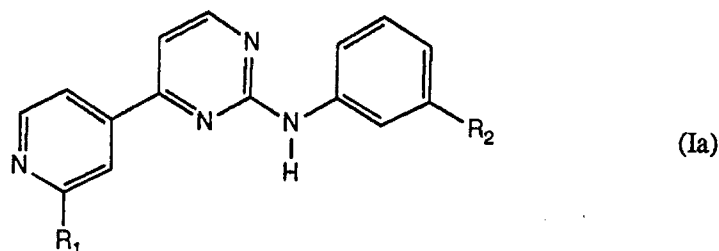
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-C(=O)-NH-(CH₂)_n-R₄^a, -C(=O)-NH-(CH₂)_n-N(R₃)-R₄, -CH(CH₃)-NH-CHO,
-C(CH₃)=N-OH, -C(CH₃)=N-O-CH₃, -C(CH₃)-NH₂, -NH-CH₂-C(=O)-N(R₃)-R₄,



wherein R₃ and R₄ are each independently of the other C₁-C₃alkyl, R₄^a is hydroxy, amino or imidazolyl, X is oxygen or sulfur, m is 1, 2 or 3, n is 2 or 3, R₅ is hydrogen, C₁-C₃alkyl, C₁-C₃alkoxy, chlorine, bromine, iodine or trifluoromethyl, R₆ is 1H-imidazol-1-yl or morpholinyl and R₇ is C₁-C₃alkyl or is phenyl that is unsubstituted or mono-substituted by C₁-C₃alkyl, halogen or by trifluoromethyl, or a salt thereof.

2. An N-phenyl-2-pyrimidineamine derivative according to claim 1 of formula Ia



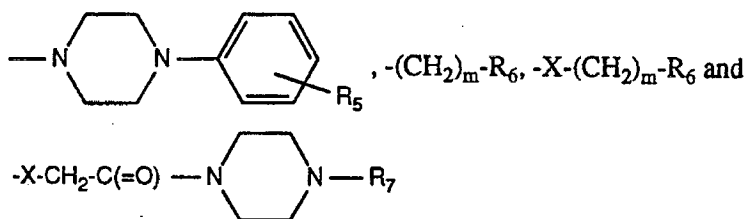
wherein R₁ is

- a) N-(amino-lower alkyl)-carbamoyl,
- b) N-(hydroxy-lower alkyl)-carbamoyl,
- c) hydrazino,
- d) cyclohexyl-amino that is unsubstituted or substituted by amino, or
- e) lower alkylamino that is substituted by cyano, imidazolyl, guanidyl, amino, lower alkanoylamino, lower alkylamino-carbonylamino, amidino, di-lower alkylamino-cyclohexyl, carboxy, lower alkoxy-carbonyl, carbamoyl, N-hydroxy-carbamoyl, hydroxy, lower alkoxy, dihydroxyphosphoryloxy, piperazinyl, lower alkanoyl-piperazinyl, formylpiperazinyl, prolylamido or by a radical of the formula H₂N-CH(R)-C(=O)-NH- wherein R is hydrogen, C₁-C₄alkyl, benzyl, hydroxymethyl, 1-hydroxy-ethyl, mercaptomethyl, 2-methylthio-ethyl, indol-3-yl-methyl, phenyl-methyl, 4-hydroxy-phenyl-methyl, carbamoyl-methyl, 2-carbamoyl-ethyl, carboxy-methyl, 2-carboxy-ethyl, 4-amino-butyl,

3-guanidyl-propyl or R is 1H-imidazol-4-yl-methyl, and

R₂ is C₁-C₆alkyl, C₁-C₃alkoxy, chlorine, bromine, iodine, trifluoromethyl, hydroxy, phenyl, amino, mono(C₁-C₃alkyl)amino, di(C₁-C₃alkyl)amino, C₂-C₄alkanoyl, prop-enyloxy, carboxy, carboxy-methoxy, ethoxycarbonyl-methoxy, sulfanilamido, N,N-di(C₁-C₃alkyl)sulfanilamido, N-methyl-piperaziny, piperidinyl, 1H-imidazol-1-yl, 1H-triazol-1-yl, 1H-benzimidazol-2-yl, 1-naphthyl, cyclopentyl, 3,4-dimethyl-benzyl or a radical of one of the formulae:

-CO₂R₃, -NH-C(=O)-R₃, -N(R₃)-C(=O)-R₄, -O-(CH₂)_n-N(R₃)-R₄,
-C(=O)-NH-(CH₂)_n-N(R₃)-R₄, -CH(CH₃)-NH-CHO, -C(CH₃)=N-OH,
-C(CH₃)=N-O-CH₃, -C(CH₃)-NH₂, -NH-CH₂-C(=O)-N(R₃)-R₄,



wherein R₃ and R₄ are each independently of the other C₁-C₃alkyl, X is oxygen or sulfur, m is 1, 2 or 3, n is 2 or 3, R₅ is hydrogen, C₁-C₃alkyl, C₁-C₃alkoxy, chlorine, bromine, iodine or trifluoromethyl, R₆ is 1H-imidazol-1-yl or morpholinyl and R₇ is C₁-C₃alkyl or is phenyl that is unsubstituted or mono-substituted by C₁-C₃alkyl, halogen or by trifluoromethyl, or a salt thereof.

3. A compound according to claim 1 of formula I, wherein

R₀ is hydrogen, halogen, lower alkoxy or lower alkyl,

R₁ is

- a) N-(amino-lower alkyl)-carbamoyl,
- b) N-(hydroxy-lower alkyl)-carbamoyl,
- c) hydrazino,
- d) piperaziny that is unsubstituted or substituted by amino-lower alkyl,
- e) morpholinyl, or
- f) lower alkylamino that is substituted by morpholinyl, hydroxy-lower alkylamino, imidazolyl, guanidyl, amino, lower alkanoylamino, lower alkylamino-carbonylamino, amidino, carboxy, lower alkoxy-carbonyl, carbamoyl, N-hydroxy-carbamoyl, hydroxy, dihydroxy-phosphoryloxy or by a radical of the formula H₂N-CH(R)-C(=O)-NH- wherein R is hydrogen, and

R₂ is chlorine, trifluoromethyl, carboxy, a radical of the formula -CO₂R₃ wherein R₃ is

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C₁-C₃alkyl, or a radical of the formula -C(=O)-NH-(CH₂)_n-R₄^a wherein n is 2 or 3 and R₄^a is hydroxy, amino or imidazolyl, or a salt thereof.

4. A compound according to claim 1 of formula I, wherein

R₀ is hydrogen,

R₁ is

a) N-(amino-lower alkyl)-carbamoyl,

b) N-(hydroxy-lower alkyl)-carbamoyl,

c) hydrazino or

d) lower alkylamino that is substituted by imidazolyl, guanidyl, amino, lower alkanoyl-amino, lower alkylamino-carbonylamino, amidino, carboxy, lower alkoxy carbonyl, carbamoyl, N-hydroxy-carbamoyl, hydroxy, dihydroxyphosphoryloxy or by a radical of the formula H₂N-CH(R)-C(=O)-NH- wherein R is hydrogen, and

R₂ is chlorine or trifluoromethyl,

or a salt thereof.

5. A compound according to claim 1 of formula I, wherein

R₀ is hydrogen, chlorine, lower alkyl or lower alkoxy,

R₁ is N-(ω-amino-C₂-C₃alkyl)-carbamoyl, N-(ω-hydroxy-C₂-C₃alkyl)-carbamoyl,

hydrazino, 2-hydroxy-propylamino or linear C₂-C₃alkylamino that is substituted in the ω-position by morpholinyl, ω-hydroxy-lower alkylamino, imidazolyl, guanidyl, amino, lower alkanoylamino, amidino, carboxy, lower alkoxy carbonyl, carbamoyl, N-hydroxy-carbamoyl, hydroxy or by dihydroxyphosphoryloxy, and

R₂ is chlorine, trifluoromethyl, carboxy, a radical of the formula -CO₂R₃ wherein R₃ is C₁-C₃alkyl, or a radical of the formula -C(=O)-NH-(CH₂)_n-R₄^a wherein n is 2 or 3 and R₄^a is hydroxy, amino or imidazolyl,

or a salt thereof.

6. A compound according to claim 1 of formula I, wherein

R₀ is hydrogen,

R₁ is N-(ω-amino-C₂-C₃alkyl)-carbamoyl, N-(ω-hydroxy-C₂-C₃alkyl)-carbamoyl,

hydrazino, 2-hydroxy-propylamino or linear C₂-C₃alkylamino that is substituted in the ω-position by imidazolyl, guanidyl, amino, lower alkanoylamino, amidino, carboxy, lower alkoxy carbonyl, carbamoyl, N-hydroxy-carbamoyl, hydroxy or by dihydroxyphosphoryloxy, and

R₂ is chlorine or trifluoromethyl,

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or a salt thereof.

7. A compound according to claim 1 of formula I, wherein

R_0 is hydrogen, chlorine, methyl or methoxy,

R_1 is N-(ω -amino- C_2 - C_3 alkyl)-carbamoyl, N-(ω -hydroxy- C_2 - C_3 alkyl)-carbamoyl, hydrazino, 2-hydroxy-propylamino or linear C_2 - C_3 alkylamino that is substituted in the ω -position by 4-morpholinyl, ω -hydroxy-ethylamino, 1H-imidazol-1-yl, 1H-imidazol-4-yl, guanidyl, amino, acetylamino, amidino, carboxy, ethoxycarbonyl, carbamoyl, N-hydroxy-carbamoyl, hydroxy or dihydroxyphosphoryloxy, and

R_2 is chlorine, trifluoromethyl, carboxy, a radical of the formula $-CO_2R_3$ wherein R_3 is methyl, or a radical of the formula $-C(=O)-NH-(CH_2)_n-R_4^a$ wherein n is 2 or 3 and R_4^a is hydroxy, amino or 1H-imidazol-4-yl,

or a salt thereof.

8. N-(3-chloro-phenyl)-4-[2-(3-hydroxy-propyl-amino)-4-pyridyl]-2-pyrimidineamine or a pharmaceutically acceptable salt thereof according to claim 1.

9. A compound according to claim 1 of formula I or a pharmaceutically acceptable salt thereof, selected from

N-(3-trifluoromethyl-phenyl)-4-[2-(3-hydroxy-propyl-amino)-4-pyridyl]-2-pyrimidine-amine,

N-(3-chloro-phenyl)-4-[2-(2-amino-ethyl-amino)-4-pyridyl]-2-pyrimidineamine,

N-(3-trifluoromethyl-phenyl)-4-[2-(2-amino-ethyl-amino)-4-pyridyl]-2-pyrimidineamine,

N-[3-chloro-phenyl]-4-[2-(N-{2-amino-ethyl}-aminocarbonyl)-4-pyridyl]-2-pyrimidine-amine,

N-[3-chloro-phenyl]-4-[2-(N-{2-hydroxy-ethyl}-aminocarbonyl)-4-pyridyl]-2-pyrimidine-amine,

N-[3-chloro-phenyl]-4-[2-(N-{3-hydroxy-propyl}-aminocarbonyl)-4-pyridyl]-2-pyrimidineamine,

N-[3-chloro-phenyl]-4-[2-(N-{3-amino-prop-1-yl}-aminocarbonyl)-4-pyridyl]-2-pyrimidineamine,

N-[3-chloro-phenyl]-4-[2-(2-hydroxy-ethyl-amino)-4-pyridyl]-2-pyrimidineamine,

N-[3-carboxy-phenyl]-4-[2-(3-hydroxy-propyl-amino)-4-pyridyl]-2-pyrimidineamine,

N-[3-methoxycarbonyl-phenyl]-4-[2-(3-hydroxy-propyl-amino)-4-pyridyl]-2-pyrimidine-amine,

N-[3-chloro-phenyl]-4-[2-(4-hydroxy-butyl-amino)-4-pyridyl]-2-pyrimidineamine,

N-[3-chloro-phenyl]-4-[2-[2-(imidazol-4-yl)-ethyl-amino]-4-pyridyl]-2-pyrimidineamine,

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N-[3-methyl-phenyl]-4-[2-(3-hydroxy-propyl-amino)-4-pyridyl]-2-pyrimidineamine,
N-[3-chloro-phenyl]-4-[2-(5-hydroxy-pentyl-amino)-4-pyridyl]-2-pyrimidineamine,
N-[3-{N-(3-hydroxy-propyl)amino-carbonyl}-phenyl]-4-[2-(3-hydroxy-propyl-amino)-4-pyridyl]-2-pyrimidineamine,
N-[3-{N-(3-amino-propyl)aminocarbonyl}-phenyl]-4-[2-(3-hydroxy-propyl-amino)-4-pyridyl]-2-pyrimidineamine,
N-[3-{N-(2-imidazol-4-yl-ethyl)-aminocarbonyl}-phenyl]-4-[2-(3-hydroxy-propyl-amino)-4-pyridyl]-2-pyrimidineamine,
N-[3-chloro-6-methyl-phenyl]-4-[2-(3-hydroxy-propyl-amino)-4-pyridyl]-2-pyrimidineamine,
N-[3,6-dichloro-phenyl]-4-[2-(3-hydroxy-propyl-amino)-4-pyridyl]-2-pyrimidineamine,
N-[3-chloro-6-methoxy-phenyl]-4-[2-(3-hydroxy-propyl-amino)-4-pyridyl]-2-pyrimidineamine,
N-[3-chloro-phenyl]-4-[2-(1-piperazinyl)-4-pyridyl]-2-pyrimidineamine,
N-[3-chloro-phenyl]-4-[2-{2-[4-morpholinyl]ethyl-amino}-4-pyridyl]-2-pyrimidineamine,
N-[3-chloro-phenyl]-4-[2-[4-(2-amino-ethyl)-piperazin-1-yl]-4-pyridyl]-2-pyrimidineamine,
N-[3-chloro-phenyl]-4-[2-[3-(2-hydroxy-ethyl-amino)-propylamino]-4-pyridyl]-2-pyrimidineamine and
N-[3-chloro-phenyl]-4-[2-(4-morpholinyl)-4-pyridyl]-2-pyrimidineamine
and from the pharmaceutically acceptable salts thereof.

10. A compound of formula I according to any one of claims 1 to 9 or a pharmaceutically acceptable salt of such a compound having at least one salt-forming group for use in a method for the therapeutic treatment of the human or animal body.

11. A pharmaceutical composition comprising a compound of formula I according to any one of claims 1 to 9 or a pharmaceutically acceptable salt of such a compound having at least one salt-forming group together with a pharmaceutical carrier.

12. A pharmaceutical composition for the treatment of tumours in warm-blooded animals including humans, comprising a dose effective against tumours of a compound of formula I according to any one of claims 1 to 9 or a pharmaceutically acceptable salt of such a compound having at least one salt-forming group together with a pharmaceutical carrier.

13. The use of a compound of formula I according to any one of claims 1 to 9 or of a

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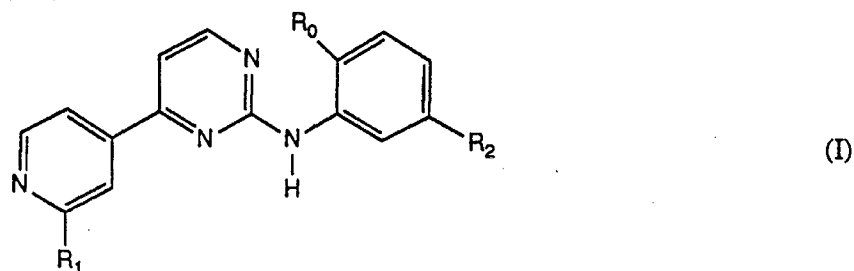
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pharmaceutically acceptable salt of such a compound having at least one salt-forming group in the preparation of a pharmaceutical composition for use in the chemotherapy of tumours.

14. The use of a compound of formula I according to any one of claims 1 to 9 or of a pharmaceutically acceptable salt of such a compound having at least one salt-forming group in the chemotherapy of tumours.

15. A method of treating a warm-blooded animal including a human, which comprises administering to such a warm-blooded animal suffering from a tumour disease a dose effective against tumours of a compound of formula I according to any one of claims 1 to 9 or of a pharmaceutically acceptable salt of such a compound having at least one salt-forming group.

16. A process for the preparation of an N-phenyl-2-pyrimidineamine derivative of formula I



wherein

R₀ is hydrogen, halogen, lower alkoxy or lower alkyl,

R₁ is

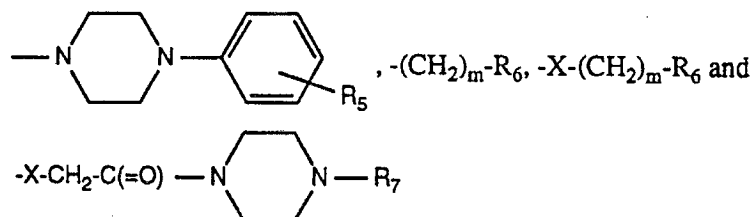
- a) N-(amino-lower alkyl)-carbamoyl,
- b) N-(hydroxy-lower alkyl)-carbamoyl,
- c) hydrazino,
- d) cyclohexyl-amino that is unsubstituted or substituted by amino,
- e) piperazinyl that is unsubstituted or substituted by amino-lower alkyl,
- f) morpholinyl, or
- g) lower alkylamino that is substituted by morpholinyl, hydroxy-lower alkylamino, cyano, imidazolyl, guanidyl, amino, lower alkanoylamino, lower alkylamino-carbonylamino, amidino, di-lower alkylamino-cyclohexyl, carboxy, lower alkoxycarbonyl, carbamoyl, N-hydroxy-carbamoyl, hydroxy, lower alkoxy, dihydroxyphosphoryloxy, piperazinyl,

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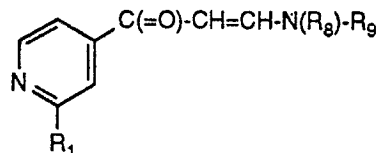
lower alkanoyl-piperazinyl, formylpiperazinyl, prolylamido or by a radical of the formula $H_2N-CH(R)-C(=O)-NH-$ wherein R is hydrogen, C_1-C_4 alkyl, benzyl, hydroxymethyl, 1-hydroxy-ethyl, mercaptomethyl, 2-methylthio-ethyl, indol-3-yl-methyl, phenyl-methyl, 4-hydroxy-phenyl-methyl, carbamoyl-methyl, 2-carbamoyl-ethyl, carboxy-methyl, 2-carboxy-ethyl, 4-amino-butyl, 3-guanidyl-propyl or R is 1H-imidazol-4-yl-methyl, and R_2 is C_1-C_6 alkyl, C_1-C_3 alkoxy, chlorine, bromine, iodine, trifluoromethyl, hydroxy, phenyl, amino, mono(C_1-C_3 alkyl)amino, di(C_1-C_3 alkyl)amino, C_2-C_4 alkanoyl, propen-yloxy, carboxy, carboxy-methoxy, ethoxycarbonyl-methoxy, sulfanilamido, N,N-di- (C_1-C_3 alkyl)sulfanilamido, N-methyl-piperazinyl, piperidinyl, 1H-imidazol-1-yl, 1H-triazol-1-yl, 1H-benzimidazol-2-yl, 1-naphthyl, cyclopentyl, 3,4-dimethyl-benzyl or a radical of one of the formulae:

$-CO_2R_3$, $-NH-C(=O)-R_3$, $-N(R_3)-C(=O)-R_4$, $-O-(CH_2)_n-N(R_3)-R_4$,
 $-C(=O)-NH-(CH_2)_n-R_4^a$, $-C(=O)-NH-(CH_2)_n-N(R_3)-R_4$, $-CH(CH_3)-NH-CHO$,
 $-C(CH_3)=N-OH$, $-C(CH_3)=N-O-CH_3$, $-C(CH_3)-NH_2$, $-NH-CH_2-C(=O)-N(R_3)-R_4$,



wherein R_3 and R_4 are each independently of the other C_1-C_3 alkyl, R_4^a is hydroxy, amino or imidazolyl, X is oxygen or sulfur, m is 1, 2 or 3, n is 2 or 3, R_5 is hydrogen, C_1-C_3 alkyl, C_1-C_3 alkoxy, chlorine, bromine, iodine or trifluoromethyl, R_6 is 1H-imidazol-1-yl or morpholinyl and R_7 is C_1-C_3 alkyl or is phenyl that is unsubstituted or mono-substituted by C_1-C_3 alkyl, halogen or by trifluoromethyl, or a salt thereof, wherein

a) a compound of formula II

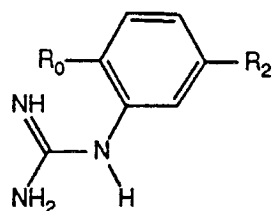


(II),

wherein R_8 and R_9 are each independently of the other lower alkyl and R_1 is as defined above, functional groups present in a compound of formula II, with the exception of the groups participating in the reaction, being, if necessary, in protected form, or a salt of such a compound is reacted with a compound of formula III

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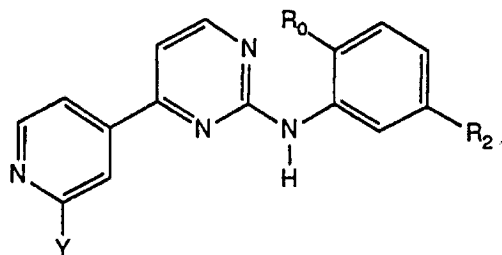
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(III),

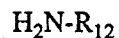
wherein R_0 and R_2 are as defined above, functional groups present in a compound of formula III, with the exception of the guanidino group participating in the reaction, being, if necessary, in protected form, or with a salt of such a compound, and any protecting groups present are removed, or

b) for the preparation of a compound of formula I wherein R_1 has the above-mentioned meaning c), d) or g) and R_0 and R_2 each have any one of the above-mentioned meanings, a compound of formula IV



(IV),

wherein Y is a leaving group and R_0 and R_2 are as defined above, functional groups present in a compound of formula IV, with the exception of the leaving group participating in the reaction, being, if necessary, in protected form, or a salt of such a compound is reacted with an amine of the formula

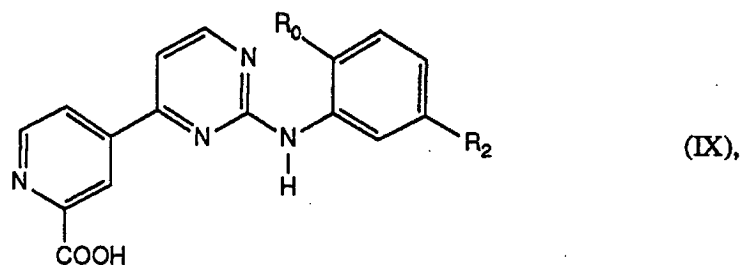


(V)

wherein R_{12} is amino or unsubstituted or amino-substituted cyclohexyl, or is lower alkyl that is substituted by morpholinyl, hydroxy-lower alkylamino, cyano, imidazolyl, guanidyl, amino, lower alkanoylamino, lower alkylamino-carbonylamino, amidino, di-lower alkylamino-cyclohexyl, carboxy, lower alkoxy-carbonyl, carbamoyl, N-hydroxy-carbamoyl, hydroxy, lower alkoxy, dihydroxyphosphoryloxy, piperazinyl, lower alkanoyl-piperazinyl, formylpiperazinyl, prolylamido or by a radical of the formula $H_2N-CH(R)-C(=O)-NH-$ wherein R is hydrogen, C_1-C_4 alkyl, benzyl, hydroxymethyl, 1-

hydroxy-ethyl, mercaptomethyl, 2-methylthio-ethyl, indol-3-yl-methyl, phenyl-methyl, 4-hydroxy-phenyl-methyl, carbamoyl-methyl, 2-carbamoyl-ethyl, carboxy-methyl, 2-carboxy-ethyl, 4-amino-butyl, 3-guanidyl-propyl or R is 1H-imidazol-4-yl-methyl, functional groups present in R₁₂ being, if necessary, in protected form, and any protecting groups present are removed, or

c) for the preparation of a compound of formula I wherein R₁ is N-(amino-lower alkyl)-carbamoyl or N-(hydroxy-lower alkyl)-carbamoyl and R₀ and R₂ each have any one of the above-mentioned meanings, a carboxylic acid of formula IX

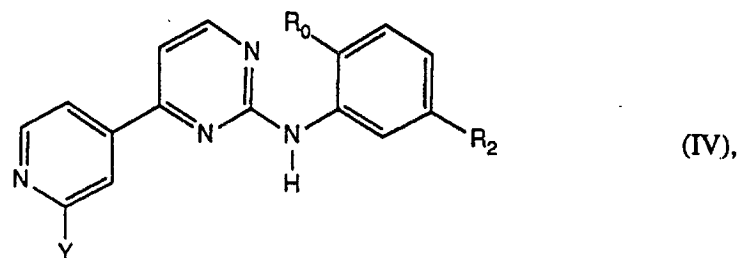


wherein R₀ and R₂ each have any one of the above-mentioned meanings, functional groups present in R₂ being, if necessary, in protected form, or a reactive acid derivative thereof is reacted with an amine of formula X



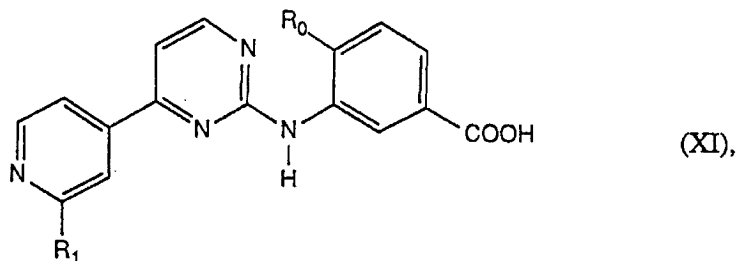
wherein R₁₃ is amino-lower alkyl or hydroxy-lower alkyl, the amino or hydroxy group being, if necessary, in protected form, and any protecting groups present are removed, or

d) for the preparation of a compound of formula I wherein R₁ is morpholinyl, or is piperazinyl that is unsubstituted or substituted by amino-lower alkyl and R₀ and R₂ each have any one of the above-mentioned meanings, a compound of formula IV



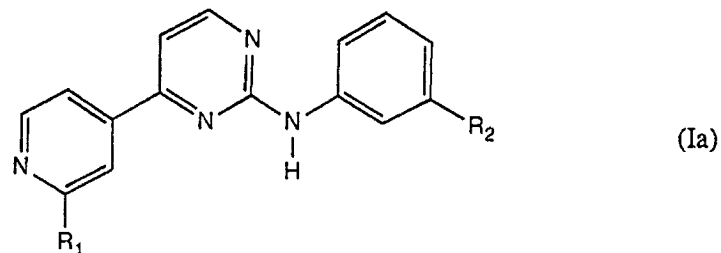
wherein Y is a leaving group and R_0 and R_2 are as defined above, functional groups present in a compound of formula IV, with the exception of the leaving group participating in the reaction, being, if necessary, in protected form, or a salt of such a compound is reacted with morpholine, or with piperazine that is unsubstituted or substituted by amino-lower alkyl, and any protecting groups present are removed, or

e) for the preparation of a compound of formula I wherein R_2 is $-\text{CO}_2\text{R}_3$, $-\text{C}(=\text{O})-\text{NH}-(\text{CH}_2)_n-\text{R}_4^a$ or $-\text{C}(=\text{O})-\text{NH}-(\text{CH}_2)_n-\text{N}(\text{R}_3)-\text{R}_4$, wherein the symbols and substituents are each as defined above, a carboxylic acid of formula XI



wherein R_0 and R_1 are as defined above, functional groups present therein being, if necessary, in protected form, or a reactive carboxylic acid derivative thereof is esterified or amidated in an appropriate manner and any protecting groups present are removed, and, if desired, a compound of formula I obtained in accordance with any one of Processes a-e is converted into its salt, or an obtained salt of a compound of formula I is converted into the free compound.

17. A process according to claim 16 for the preparation of a compound of formula Ia



wherein R_1 is

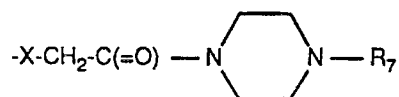
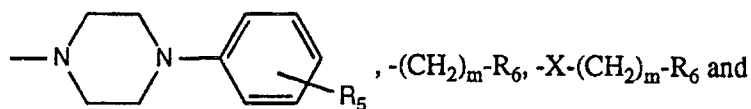
a) N-(amino-lower alkyl)-carbamoyl,

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- b) N-(hydroxy-lower alkyl)-carbamoyl,
 c) hydrazino,
 d) cyclohexyl-amino that is unsubstituted or substituted by amino, or
 e) lower alkylamino that is substituted by cyano, imidazolyl, guanidyl, amino, lower alkanoylamino, lower alkylamino-carbonylamino, amidino, di-lower alkylamino-cyclohexyl, carboxy, lower alkoxy-carbonyl, carbamoyl, N-hydroxy-carbamoyl, hydroxy, lower alkoxy, dihydroxyphosphoryloxy, piperazinyl, lower alkanoyl-piperazinyl, formylpiperazinyl, prolylamido or by a radical of the formula $H_2N-CH(R)-C(=O)-NH-$ wherein R is hydrogen, C_1-C_4 alkyl, benzyl, hydroxymethyl, 1-hydroxy-ethyl, mercaptomethyl, 2-methylthio-ethyl, indol-3-yl-methyl, phenyl-methyl, 4-hydroxy-phenyl-methyl, carbamoyl-methyl, 2-carbamoyl-ethyl, carboxy-methyl, 2-carboxy-ethyl, 4-amino-butyl, 3-guanidyl-propyl or R is 1H-imidazol-4-yl-methyl, and
 R_2 is C_1-C_6 alkyl, C_1-C_3 alkoxy, chlorine, bromine, iodine, trifluoromethyl, hydroxy, phenyl, amino, mono(C_1-C_3 alkyl)amino, di(C_1-C_3 alkyl)amino, C_2-C_4 alkanoyl, propenyloxy, carboxy, carboxy-methoxy, ethoxycarbonyl-methoxy, sulfanilamido, N,N-di(C_1-C_3 alkyl)sulfanilamido, N-methyl-piperazinyl, piperidinyl, 1H-imidazol-1-yl, 1H-triazol-1-yl, 1H-benzimidazol-2-yl, 1-naphthyl, cyclopentyl, 3,4-dimethyl-benzyl or a radical of one of the formulae:

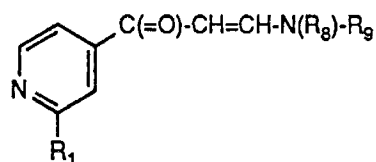
$-CO_2R_3$, $-NH-C(=O)-R_3$, $-N(R_3)-C(=O)-R_4$, $-O-(CH_2)_n-N(R_3)-R_4$,
 $-C(=O)-NH-(CH_2)_n-N(R_3)-R_4$, $-CH(CH_3)-NH-CHO$, $-C(CH_3)=N-OH$,
 $-C(CH_3)=N-O-CH_3$, $-C(CH_3)-NH_2$, $-NH-CH_2-C(=O)-N(R_3)-R_4$,



wherein R_3 and R_4 are each independently of the other C_1-C_3 alkyl, X is oxygen or sulfur, m is 1, 2 or 3, n is 2 or 3, R_5 is hydrogen, C_1-C_3 alkyl, C_1-C_3 alkoxy, chlorine, bromine, iodine or trifluoromethyl, R_6 is 1H-imidazol-1-yl or morpholinyl, and R_7 is C_1-C_3 alkyl or is phenyl that is unsubstituted or mono-substituted by C_1-C_3 alkyl, halogen or by trifluoromethyl,

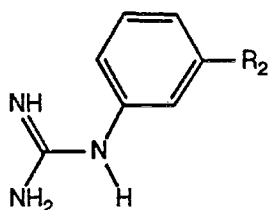
or a salt thereof, wherein

- a) a compound of formula II



(II),

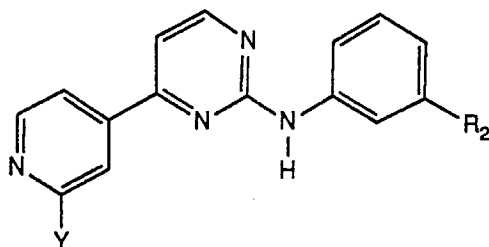
wherein R_8 and R_9 are each independently of the other lower alkyl and R_1 is as defined above, functional groups present in a compound of formula II, with the exception of the groups participating in the reaction, being, if necessary, in protected form, or a salt of such a compound is reacted with a compound of formula IIIa



(IIIa),

wherein R_2 is as defined above, functional groups present in a compound of formula IIIa, with the exception of the guanidino group participating in the reaction, being, if necessary, in protected form, or with a salt of such a compound, and any protecting groups present are removed, or

b) for the preparation of a compound of formula Ia wherein R_1 has any one of the above-mentioned meanings c) to e) and R_2 has any one of the above-mentioned meanings, a compound of formula IVa

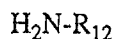


(IVa),

wherein Y is a leaving group and R_2 is as defined above, functional groups present in a compound of formula IVa, with the exception of the leaving group participating in the reaction, being, if necessary, in protected form, or a salt of such a compound is reacted with an amine of the formula

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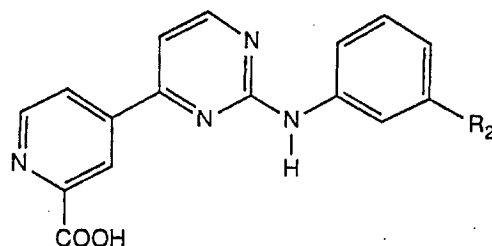
- 59 -



(V)

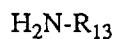
wherein R_{12} is amino or unsubstituted or amino-substituted cyclohexyl, or is lower alkyl that is substituted by cyano, imidazolyl, guanidyl, amino, lower alkanoylamino, lower alkylamino-carbonylamino, amidino, di-lower alkylamino-cyclohexyl, carboxy, lower alkoxy-carbonyl, carbamoyl, N-hydroxy-carbamoyl, hydroxy, lower alkoxy, dihydroxy-phosphoryloxy, piperazinyl, lower alkanoyl-piperazinyl, formylpiperazinyl, prolylamido or by a radical of the formula $\text{H}_2\text{N}-\text{CH}(\text{R})-\text{C}(=\text{O})-\text{NH}-$ wherein R is hydrogen, C_1-C_4 alkyl, benzyl, hydroxymethyl, 1-hydroxy-ethyl, mercaptomethyl, 2-methylthio-ethyl, indol-3-yl-methyl, phenyl-methyl, 4-hydroxy-phenyl-methyl, carbamoyl-methyl, 2-carbamoyl-ethyl, carboxy-methyl, 2-carboxy-ethyl, 4-amino-butyl, 3-guanidyl-propyl or R is 1H-imidazol-4-yl-methyl, functional groups present in R_{12} being, if necessary, in protected form, and any protecting groups present are removed, or

c) for the preparation of a compound of formula Ia wherein R_1 is N-(amino-lower alkyl)-carbamoyl or N-(hydroxy-lower alkyl)-carbamoyl and R_2 has any one of the above-mentioned meanings, a carboxylic acid of formula IXa



(IXa),

wherein R_2 has any one of the above-mentioned meanings, or a reactive acid derivative thereof is reacted with an amine of formula X



(X),

wherein R_{13} is amino-lower alkyl or hydroxy-lower alkyl, the amino or hydroxy group being, if necessary, in protected form, and any protecting groups present are removed, and, if desired, a compound of formula I obtained in accordance with any one of Processes a-c is converted into its salt or an obtained salt of a compound of formula I is converted into the free compound.

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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISION DE NUEVAS CREACIONES
E. S. D.

Re: Expediente No. **05-001.801**
Solicitud de patente a nombre de **NOVARTIS AG.**

Yo, JIMENA ESCOBAR URIBE, identificada como aparece al pie de mi firma, domiciliada en la carrera 11 A No. 86-53, piso 6, obrando como apoderada de la sociedad **NOVARTIS AG**, domiciliada en Basilea Suiza solicitante de la patente de la referencia, en respuesta al oficio No. 14538 notificado por fijación en lista el 14 de noviembre de 2008, relacionado con el concepto técnico de fondo No. 2656, me permito presentar ante ese despacho los siguientes documentos que fueron requeridos con fundamento en el artículo 46 de la Decisión 486: :

- ✓ ZIMMERMANN J ET AL: "Potent and selective inhibitors of the Abl-kinase: phenylamino-pyrimidine (PAP) derivatives" BIORGANIC & MEDICAL CHEMISTRY LETTERS, OXFORD, GB, Vol. 7, No. 2, 21 January 1997 (1997-01-21), páginas 187-192, XP004135990. ISSN: 0960-894X, ejemplos 17,24; tabla 1.
- ✓ ZIMMERMANN J ET AL: "Phenylamino-pyrimidine (PAP)- derivatives: a new class of potent and highly selective PDGF-receptor autophosphorylation inhibitors" BIORGANIC & MEDICAL CHEMISTRY LETTERS, OXFORD, GB, Vol. 6, No. 11, 4 June 1996 (1996-06-04), páginas 1221-1226, XP004134858. ISSN: 0960-894X, ejemplos 3, 11; tabla 1.
- ✓ PAUL R ET AL: "Preparation of substituted N-phenyl-4-aril-2-pyrimidinamines as mediator release inhibitors" JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY. WASHINGTON, US, Vol. 36, no. 19, 17 september 1993 (1993-09-17),

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páginas 2716-2725, XP002134022, ISSN: 0022-2623, ejemplos 2-7, 2-22, tabla II.

Sobre este particular, me permito manifestar que con la presentación de estos tres documentos queda totalmente atendido el requerimiento de ese despacho fundamentado en el artículo 46 de la Decisión 486.

Señor Superintendente,



JIMENA ESCOBAR URIBE

C.C.39.779.452 de Usaquén

T.P. 68228

Cód. 5376

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POTENT AND SELECTIVE INHIBITORS OF THE ABL-KINASE: PHENYLAMINO-PYRIMIDINE (PAP) DERIVATIVES

Jürg Zimmermann*, Elisabeth Buchdunger, Helmut Mett, Thomas Meyer, and Nicholas B. Lydon
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Ciba-Geigy Limited, CH-4002 Basel, Switzerland

Abstract: Due to its relatively clear etiology, Chronic myelogenous leukemia (CML) represents an ideal disease target for a therapy using a selective inhibitor of the Bcr-Abl tyrosine protein kinase. Extensive optimization of the class of phenylamino-pyrimidines yielded highly potent and selective Bcr-Abl kinase inhibitors. Compound 1 shows high potency ($IC_{50} = 38$ nM) and selectivity for the Abl tyrosine protein kinase at the *in vitro* level. © 1997, Elsevier Science Ltd. All rights reserved.

INTRODUCTION. Chronic myelogenous leukemia (CML) is a hematological stem cell disorder associated with a specific chromosomal translocation known as the Philadelphia (Ph) chromosome which is detected in 95% of patients with CML and 20% with acute lymphocytic leukemia (ALL)[1]. The molecular consequence of the translocation is the fusion of the *abl* protooncogene to the *bcr* gene resulting in the production of an activated form of the Abl tyrosine protein kinase[2]. The Bcr-Abl protein is capable of inducing leukemia's in mice[3], implicating the protein as the cause of these diseases. As the tyrosine kinase activity of the Bcr-Abl protein is essential to its transforming ability, a specific, well tolerated inhibitor of the Abl tyrosine protein kinase would be a highly attractive therapy for these disorders. This approach could yield a selective anti cancer agent that would be useful for *in vitro* bone marrow purging in preparation for autologous bone marrow transplantation of Bcr-Abl positive leukemia's and for the *in vivo* therapy of these leukemia's. The concept is supported by the fact that inactivation of the *bcr-abl* oncogen by an antisense approach selectively kills leukemia cells harboring this gene[4]. Inhibition of the Abl kinase activity has been reported by low molecular weight compounds such as arylvinylamide, 2-oxindole[5], homophthalimides, benzoisothiazoline-2,2-dioxides, catechols, (for a review of these classes see [6]), tyrphostins[7] and benzopyranones[8]. However, most compounds showed either limited selectivity or low potency. In this communication we enclose our preliminary findings on a series of new phenylamino-pyrimidine (PAP)-derivatives capable of inhibiting phosphorylation by the v-Abl kinase at nanomolar concentrations.

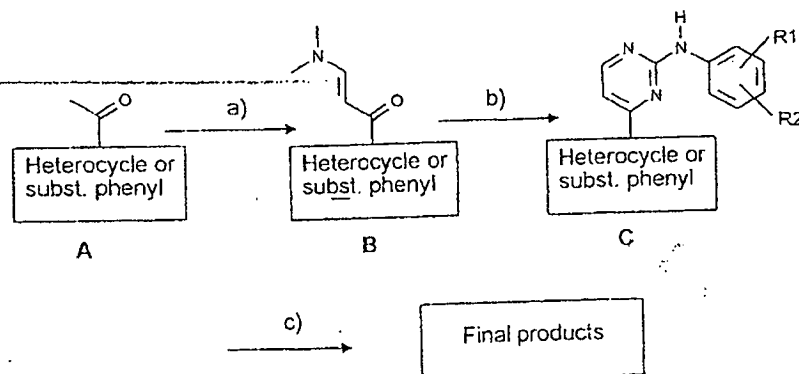
CHEMISTRY. Synthesis of the phenylamino-pyrimidines was started from acetyl-substituted heterocycles or aryl-derivatives A which were converted to the enamines B using N,N-dimethyl-formamide dimethylacetal. The heterocyclic ring system C (10, 20, 22, 25, 26, 29, 31, 34-37) was constructed by the reaction of the substituted phenylguanidines with the enamines B. The optional functional group transformation of substituents attached at the phenyl ring included hydrogenation (H_2 , Pd/C) of the nitro group to give the anilines 16, 17, and 24. Acylation with the required acid chlorides yielded the amides 1-8, 11-15, 18, 19, 21, 23, 27, 28 (phthalic anhydride was used as the acylation reagent), 30 and 32. Alkaline hydrolysis of the ester 31

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give the carboxylic acid 33. Synthesis of the required guanidines for the preparation of 20 and 29 are described elsewhere.^[9] Synthesis of 9 is depicted in scheme 2.

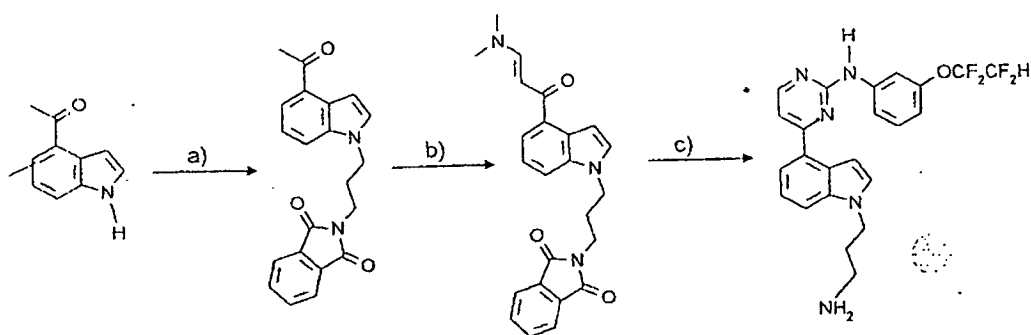
The physicochemical properties of the generally poorly soluble pyrimidine-derivatives can be improved by attachment of hydrophilic substituents on the phenyl ring. For example compound 1^[10] is a polyvalent base (pK_a,1 : 8.07; pK_a,2 : 3.73; pK_a,3 : 2.56, pK_a,4 : 1.52), the corresponding methane sulfonate shows good solubility in water (> 100 g/l), yielding an acidic solution (pH: 4.2). The solubility at pH 7.4 however is much lower (49 mg/l). At pH 7.4, the methane sulfonate of 1 is rather lipophilic with a log P of 1.99.

Scheme 1: General synthesis of the PAP's



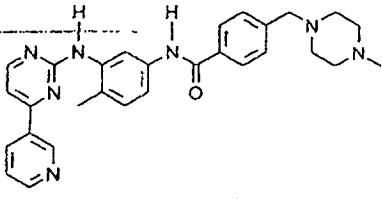
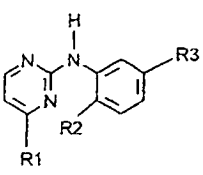
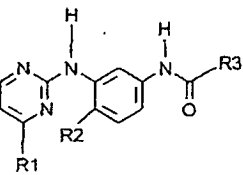
a) Dimethyl-formamide dimethylacetal (neat). b) subst. phenylguanidine, i-propanol, reflux.
c) Optional functional-group transformation of R1/R2.

Scheme 2: Synthesis of compound 9



a) N-(3-Bromopropyl)phthalimide, NaH. b) N,N-Dimethylformamide dimethylacetal.
c) 1:3-Tetrafluoroethoxyphenylguanidine, i-propanol, rf. ii: Hydrazine hydrate in ethanol

Table 1: Compounds prepared

		
1	A	B

No.	Form.	R1	R2	R3	mp [°C]
1	I	see above	"	"	207-212
2	B	3-pyridyl	H	identical as in compound 1	198-201
3	B	3-pyridyl	H	3-pyridyl	217-220
4	B	3-pyridyl	CH ₃	4-methylphenyl	102-106
5	B	3-pyridyl	H	pentyl	180-184
6	B	3-pyridyl	CH ₃	2-naphthyl	97-101
7	B	3-pyridyl	H	4-fluorophenyl	215-216
8	B	3-pyridyl	H	2-thiophenyl	139-141
9	A	see scheme 2	"	tetrafluoroethoxy	amorph.
10	A	3-indolyl	H	tetrafluoroethoxy	140-142
11	B	3-pyridyl	H	phenyl	207-209
12	B	3-pyridyl	CH ₃	phenyl	179-180
13	A	3-pyridyl	H	3-aminopropylaminocarbonyl	142-146
14	B	3-pyridyl	H	cyclohexyl	205-206
15	B	3-pyridyl	H	4-pyridyl	224-226
16	A	4-pyridyl	H	amino	200-202
17	A	3-pyridyl	H	amino	58-68
18	B	3-pyridyl	CH ₃	2-methoxyphenyl	88-92
19	B	3-pyridyl	CH ₃	4-chlorophenyl	216-219
20	A	3-pyridyl	H	2-(1-imidazolyl)ethoxy	amorph.
21	B	3-pyridyl	H	4-methylphenyl	214-216
22	A	2-pyridyl	H	nitro	213-219
23	B	3-pyridyl	H	4-cyanophenyl	220-222
24	A	3-pyridyl	CH ₃	amino	143-144
25	A	3-pyridyl	H	chloro	146-147
26	A	3-pyridyl	H	hydrogen	143-144
27	B	3-pyridyl	H	2-methoxyphenyl	147-150
28	B	3-pyridyl	H	2-carboxyphenyl	206-209

29	A	3-pyridyl	H	1-imidazolyl	132-134
30	B	3-pyridyl	H	2-pyridyl	187-190
31	A	3-pyridyl	H	methoxycarbonyl	192-195
32	B	3-pyridyl	CH ₃	methyl	220-222
33	A	3-pyridyl	H	carboxy	292-294
34	A	3-pyridyl	H	nitro	212-213
35	A	4-chlorophenyl	H	tetrafluoroethoxy	133-135
36	A	4-pyridyl	H	nitro	282-284
37	A	4-pyridyl	H	tetrafluoroethoxy	193-194

RESULTS AND DISCUSSION. The compounds were assayed for the inhibition of four tyrosine kinases (v-Abl, PDGFR-kinase, EGFR-kinase and c-Src) and three serine/threonine kinases (PKC α , PKC δ and PKA) [10], see table 2. The optimization aimed at potent inhibition of the phosphorylation by the v-Abl kinase whereas the six other kinases tested served as selectivity criteria. Compounds 1-19 inhibited the v-Abl-kinase *in vitro* with the IC₅₀ values of less than 1 μ M, the most active compound being tested was derivative 1 (IC₅₀ = 38 nM). The most potent compounds on the inhibition of the v-Abl kinase (IC₅₀ < 300 nM) are members of the structural class B, e.g. containing an amide function on the phenyl ring. The nature of the acyl-substituent is of minor importance: substituted phenyl (1,4,6 and 7), heterocycles (3 and 8) and alkyl (5) are tolerated. The 3-pyridyl moiety in 4-position of the pyrimidine can be replaced by an indoyl moiety. In this case the amide function on the phenyl ring (structure type B) is not required any more (9, 10) for efficient inhibitory activity. In this indoyl-series, improvement of the aqueous solubility can be accomplished by attachment of a salt forming group on the indole side chain (10). The benzamide moiety in structural type B can be replaced by an 3-aminopropylaminocarbonyl moiety (13) and with the corresponding amine although with a slight decrease of potency (16, 17).

The compounds were further screened for selectivity. None of the PAP's showed inhibition (IC₅₀ > 1 μ M) of the protein kinase A and the EGFR kinase with the exception of compound 9. The c-Src catalyzed phosphorylation was inhibited by only a few derivatives. The inhibition of the PDGFR-kinase autophosphorylation however was found to be similar to the activity measured for the v-Abl kinase. But also here it is possible to gain selectivity: e.g. the potent v-abl kinase inhibitor 3 was devoid of PDGF activity. The selectivity against PKC- α and - δ was not very difficult to achieve within this series, compound 1 was not inhibiting PKC at all and the v-Abl inactive derivative 37 showed a selective PKC- α inhibition. The methyl-group in 6-position of the phenyl-ring helps to improve on selectivity: compounds 1, 4 and 6 bearing this "flag-methyl" do not inhibit PKC- α and - δ to a significant extent, whereas compounds lacking this group are dual inhibitors (e.g. 3).

Remarkable is compound 9, it showed absolutely no selectivity at all against the seven kinases tested. It is interesting to note that the class of the PAP's can also serve as leads for other kinases (PKC, PKA, c-src, EGF-R-K, PDGF-R-K): compound 9 inhibited the EGF-R autophosphorylation and c-Src with an IC₅₀ of 0.53 μ M and 0.5 respectively. The very potent (IC₅₀: 0.01 μ M) PDGF-R inhibitors 4 and 19 and the PKC- α inhibitors 9, 10, 23, 27, 34, 35 and 37 could serve as starting points for the respective projects whereas for the PKC- δ and specially PKA projects none of the tested members of this class could serve as a promising lead.

Table 2: Enzymatic profile, IC₅₀ (μM)

No	v-Abl-K	EGFR	c-Src	PDGFR	PKA	PKCα	PKCδ
1	0.038	>100	>100	0.05	>500	>100	>100
2	0.1	>100	7.8	0.2	475	n.d.	n.d.
3	0.15	>100	9	50	>500	1.7	17
4	0.2	>100	>100	0.01	>100	>100	>500
5	0.2	>100	3.7	0.6	n.d.	2.0	19
6	0.2	>100	>100	0.05	>100	>100	>500
7	0.2	>50	>100	3	>500	n.d.	n.d.
8	0.3	>50	3	20	>500	n.d.	n.d.
9	0.35	0.53	0.5	5	2	0.18	4.4
10	0.37	1.8	2.2	>10	73	0.29	1.4
11	0.4	>50	15.7	5	>500	1.2	23
12	0.4	65	>100	0.1	>500	72	>500
13	0.4	45	9.8	>10	n.d.	n.d.	n.d.
14	0.45	>100	46	0.8	>500	n.d.	n.d.
15	0.5	>100	78	>100	>500	1.3	24
16	0.6	n.d.	16	>10	n.d.	n.d.	n.d.
17	0.7	50	14	>100	6.0	210	>500
18	0.8	>100	>100	0.3	>500	80	>100
19	0.8	>100	>100	0.01	>100	>100	>100
20	1.0	7.1	4.9	>10	340	1.5	34
21	1.0	>100	>100	0.8	>500	n.d.	n.d.
22	1.2	>100	>100	>100	>500	2.5	>500
23	1.3	>100	>100	1.5	>500	0.35	>500
24	1.5	>100	>100	>10	>500	240	>500
25	1.5	>100	>100	>10	>500	1.6	23
26	1.8	100	>100	>10	>500	10.5	39
27	1.9	100	>100	1.0	>500	0.32	>500
28	2.0	n.d.	44	>100	>500	n.d.	n.d.
29	3.3	>100	1.6	18	>500	1.0	21
30	3.8	n.d.	90	>100	>500	n.d.	n.d.
31	5.1	n.d.	90	>10	>500	2.5	39
32	5.8	>100	>100	50	>500	500	>500
33	8.0	n.d.	126	>10	n.d.	45	>100
34	34	100	93	>100	>500	0.79	>500
35	>50	>100	>100	>10	>500	0.85	>100
36	61	>100	>100	>100	>500	2.6	>500
37	>100	>100	>100	>10	>500	0.3	>100

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The selectivity of compound 1 on the enzymatic assays for Abl- and PDGFR-kinase could be translated to the cellular and *in vivo* situation: *v-abl*- and *v-sis* transformed BALB/c 3T3 cells were inhibited *in vitro* and *in vivo* [11]. The reported findings with compound 1 suggest that it may be a development candidate for use in the treatment of Philadelphia chromosome-positive leukemia's [12]. Additional potential applications for compound 1 may include proliferative diseases that involve abnormal PDGF receptor activation.

ACKNOWLEDGMENT. We thank B. Adams, J.M. Groell, C. Loretan, N. Martin, E. Seeber and R. Vogelsanger for skillful experimental assistance.

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(Received in Belgium 21 August 1996; accepted 11 December 1996)





Pergamon

Bioorganic & Medicinal Chemistry Letters, Vol. 6, No. 11, pp. 1221-1226, 1996

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0960-894X/96 \$15.00 + 0.00

PII: S0960-894X(96)00197-7

PHENYLAMINO-PYRIMIDINE (PAP) - DERIVATIVES: A NEW CLASS OF POTENT AND HIGHLY SELECTIVE PDGF-RECEPTOR AUTOPHOSPHORYLATION INHIBITORS

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Abstract: Phenylamino-pyrimidines represent a novel class of inhibitors of the PDGF-receptor autophosphorylation with a high degree of selectivity versus other tyrosine and serine/threonine kinases. Optimum activity of ca 10 nM (IC₅₀) was observed when the phenylamino-group which is attached to the pyrimidine carries a benzamide-moiety with a lipophilic substituent in 4-position.

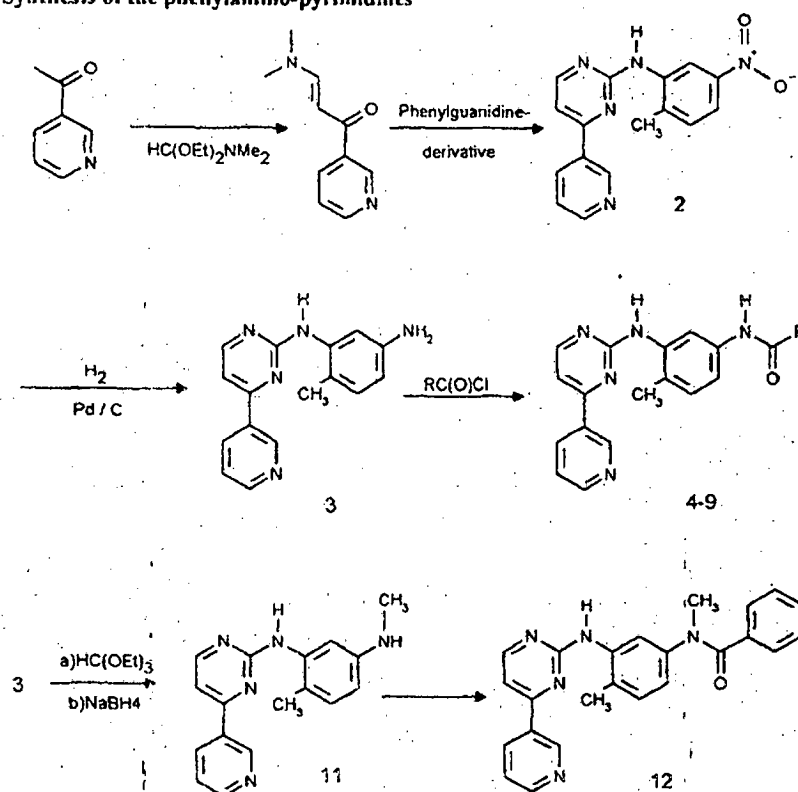
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INTRODUCTION. Platelet-derived growth factor (PDGF) is a potent mitogen and chemotactic factor for a variety of cells of mesenchymal origin such as fibroblasts, vascular smooth muscle cells and brain glial cells¹. There are three isoforms of PDGF^{2,3} which bind with different affinities to two related tyrosine kinase receptors (PDGF-R)^{4,5}. Binding of PDGF to the extracellular part of either receptor type leads to dimerization of receptor molecules, followed by activation of the receptor tyrosine protein kinase⁶ and generation of phosphorylation mediated signals which initiate the biological response^{7,8}. Much of the interest in PDGF emanates from the finding that the *v-sis* oncogene of the simian sarcoma virus is a retroviral homolog of the cellular gene encoding the B-chain of PDGF^{9,10}. Gene transfer experiments have shown that overexpression of the normal human PDGF B-chain gene (*c-sis* protooncogene) causes the generation of fibrosarcomas¹¹. Evidence for the involvement of an autocrine mechanism in the transformation of cultured cells by the *sis* oncogene has emerged from the finding that agents preventing the interaction between PDGF and its receptor such as PDGF antibodies¹² or suramin¹³ revert the transformed phenotype. Furthermore, dominant-negative mutants of PDGF have been shown to break the autocrine loop and to revert the transformed phenotype of both, PDGF-transformed BALB/c 3T3 cells and human astrocytoma cell lines¹⁴. The hypothesis that unscheduled production of PDGF may contribute to the growth of spontaneous tumors is supported by the finding that PDGF is frequently produced by cell lines from human tumors (reviewed in¹⁵). Furthermore, PDGF has been implicated in the pathogenesis of several non-malignant proliferative diseases including fibrosis, atherosclerosis¹⁶ and restenosis following vascular angioplasty^{17,18}.

The accumulating evidence for the involvement of PDGF in human proliferative disorders has led to a search for specific inhibitors of the PDGF receptor tyrosine protein kinase. Inhibition of the PDGF receptor kinase activity has been reported for low molecular weight compounds from the staurosporine¹⁹⁻²¹, tyrphostin²²⁻²⁴ and quinoline²⁵ classes of compounds. However, most compounds showed either limited selectivity or limited potency at the cellular level. In this Letter we enclose our preliminary findings on a series of new phenylamino-pyrimidine (PAP)-derivatives which are capable of inhibiting cellular PDGF-receptor autophosphorylation at nanomolar concentration. Potential clinical applications of these inhibitors include their use as anticancer agents, as well as a drug for the treatment of conditions characterized by inappropriate fibroblast and vascular intimal hyperplasia.

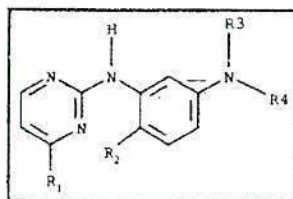
CHEMISTRY. Phenylamino-pyrimidines (PAP) were prepared via the classical route²⁶ for the synthesis of the pyrimidine-ring system. The acetyl derivatives of different heterocycles were converted into the enaminones using *N,N*-dimethylformamide-diethylacetal which were then brought in reaction with the corresponding guanidines to give phenylamino-pyrimidines²⁷. Catalytic hydrogenation of the nitro group in 2 resulted in the amine 3, which was acylated with the corresponding acid chlorides to give the amides 4-9, vigorous conditions yielded the diamide 10. The methylation of the aniline-group in 3 turned out to be rather difficult. However treatment with ethyl-ortho-formate followed by reduction with sodiumborohydride was finally successful. The methyl-derivative 11 could be isolated in 35% overall yield. The benzylation with benzoylchloride in pyridine afforded 12. Oxidation of 4 with *m*-chloro perbenzoic acid gave the pyridine-*N*-oxide 13; mild conditions have to be used to avoid oxidation of the pyrimidine-nitrogens. For the synthesis of 14-16, the same methodology was applied starting either with 3-acetylthiophene or using differently substituted guanidine-derivatives.

Scheme 1: Synthesis of the phenylamino-pyrimidines



In general, the compounds show poor solubility in water (e.g. 4: 1.9 mg/l), but are soluble under acidic conditions (4: HCl 0.1N = 3.3 g/l). The crystalline derivatives are slightly basic (e.g. 4: $pK_a = 3.77$) and are rather lipophilic (e.g. 4: $\log P = 3.57$).

Table 1. Data for the compounds tested



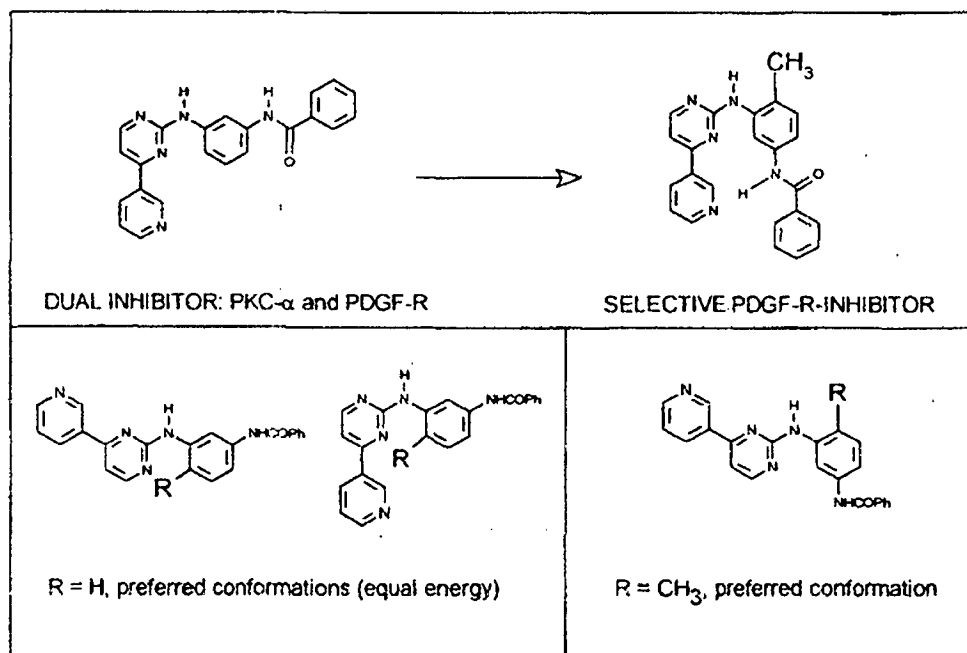
No	R1	R2	R3	R4	FAB-MS	mp[°C]
1	3-pyridyl	H	H	C(O)C ₆ H ₅	368	207-209
2	3-pyridyl	CH ₃	O	O	308	195-198
3	3-pyridyl	CH ₃	H	H	278	138-140
4	3-pyridyl	CH ₃	H	C(O)C ₆ H ₅	382	179-180
5	3-pyridyl	CH ₃	H	C(O)-(o-OCH ₃)C ₆ H ₄	412	88-92
6	3-pyridyl	CH ₃	H	C(O)-(p-CH ₃)C ₆ H ₄	396	102-106
7	3-pyridyl	CH ₃	H	C(O)-(p-Cl)C ₆ H ₄	416	216-219
8	3-pyridyl	CH ₃	H	C(O)CH ₃	320	220-222
9	3-pyridyl	CH ₃	H	C(O)-2-naphthyl	432	97-101
10	3-pyridyl	CH ₃	C(O)C ₆ H ₅	C(O)C ₆ H ₅	488	255-258
11	3-pyridyl	CH ₃	CH ₃	H	292	120-122
12	3-pyridyl	CH ₃	CH ₃	C(O)C ₆ H ₅	396	amorph.
13	3-pyridyl-N-oxide	CH ₃	H	C(O)C ₆ H ₅	398	238-241
14	2-thiophenyl	CH ₃	H	C(O)C ₆ H ₅	387	206-207
15	3-pyridyl	Cl	H	C(O)C ₆ H ₅	402	221-222
16	3-pyridyl	OCH ₃	H	C(O)C ₆ H ₅	398	222-223

RESULTS AND DISCUSSION. The compounds were assayed for the inhibition of three tyrosine kinases (PDGF-receptor, EGF-receptor and c-Src) and three serine/threonine kinases (PKC- α , PKC- δ and PKA)²⁸. The IC₅₀'s are the average of at least two independent experiments, the standard deviation is $\pm$ 10%.

At the onset of our work in the PDGF-program the phenylamino-pyrimidine 1 was identified as an attractive lead. However this compound is a dual inhibitor, acting on PKC- α and PDGF-R in the submicromolar range. With the introduction of a methyl group in 6-position of the phenyl-ring, the inhibition of PKC- α was lost, whereas the potency for inhibition of the PDGF-receptor autophosphorylation was enhanced. The dramatic loss of activity on PKC- α can either be explained by the forced change of the preferred conformation upon the introduction of this flag-methyl (scheme 2). Either the required shape of the inhibitor for a tight binding is then not achievable or the flag-methyl group severely clashes with the wall of the ATP-binding pocket within the protein kinase C family²⁹. This "flag-methyl" effect works reliably, the nitro- and amino-derivatives without this substituent are potent PKC- α inhibitors (IC₅₀: 1-5 μ M; data not shown) but upon introduction of this flag-methyl (2,3), inhibition of PKC is lost. Compounds 2,3,4,6,7 and 9 were also tested on PKC- β 1, β 2, γ , ϵ , and η (data not shown), which were not inhibited (IC₅₀ > 100 μ M).

Table 2: Enzymatic Profile, IC₅₀ [μM]

No.	PDGF-R	EGF-R	c-Src	PKC-α	PKC-δ	PKA
1	5	>50	15.7 —	1.2	23	>500
2	>100	>100	>100	>500	>500	>500
3	>10	>100	>100	>100	>500	>500
4	0.1	>100	>100	72	>500	>500
5	0.3	>100	>100	>100	>500	>500
6	0.01	>100	>100	>100	>500	>100
7	0.01	>100	>100	>100	>500	>100
8	50	>100	>100	>100	>500	>500
9	0.05	>100	>100	>100	>500	>100
10	2.5	75	n.d.	>100	>100	>500
11	>10	>100	n.d.	71	>100	>500
12	>100	49	n.d.	85	>100	>500
13	>10	>100	n.d.	>100	>100	>500
14	>10	>100	>100	>100	>100	>500
15	0.15	>100	n.d.	>100	>100	>500
16	>10	>100	n.d.	10	>100	>500

Scheme 2: Increase of selectivity and analysis of the conformation³⁰

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12

The pharmacophore of this class for inhibition of PDGF-receptor can be defined as follows: phenylamino-pyrimidine with a pyridine attached in 4-position of the pyrimidine ring system. The substitution pattern of the phenyl group has to be as follows: a methyl- or chloro-substituent in 6-position ($R_2 = \text{CH}_3$ or Cl) and a substituted benzamide ($R_4 = \text{C}(\text{O})\text{-phenyl}$) with a free NH -group ($R_3 = \text{H}$) in 3-position. The benzamide is preferentially substituted again with a small lipophilic substituent (chlorine or methyl) in 4-position of the benzamide moiety (comp. 6 and 7).

Despite the sequence homology in the ATP-binding region among serine/threonine and tyrosine kinases,³¹ these results show that ATP-competitive compounds have the potential to be potent and selective inhibitors of individual protein kinases. A possible explanation for the observed high selectivity lies in the fact, that ATP is only weakly bound, so minor changes of amino acids in the ATP-binding pocket do not change the already low affinity for ATP but do alter the affinity of inhibitors. In summary, PAP-derivatives represent a novel class of inhibitors of the PDGF-R family of protein kinases with high selectivity and potency at the enzymatic and cellular level. Furthermore, they are efficiently taken up by the cells. Experimental data show that this high selectivity can be translated into a very specific PDGF-dependent tumor-growth inhibition *in vivo*.³²

Acknowledgment: We thank B. Adams, J.M. Groell, C. Loretan, N. Martin, E. Seeber and R. Vogelsanger for skillful experimental assistance.

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(Received in Belgium 27 December 1995; accepted 24 April 1996)

P: 2717/09/1993
P: 2716/2725

Preparation of Substituted *N*-Phenyl-4-aryl-2-pyrimidinamines as Mediator Release Inhibitors XP-002134022

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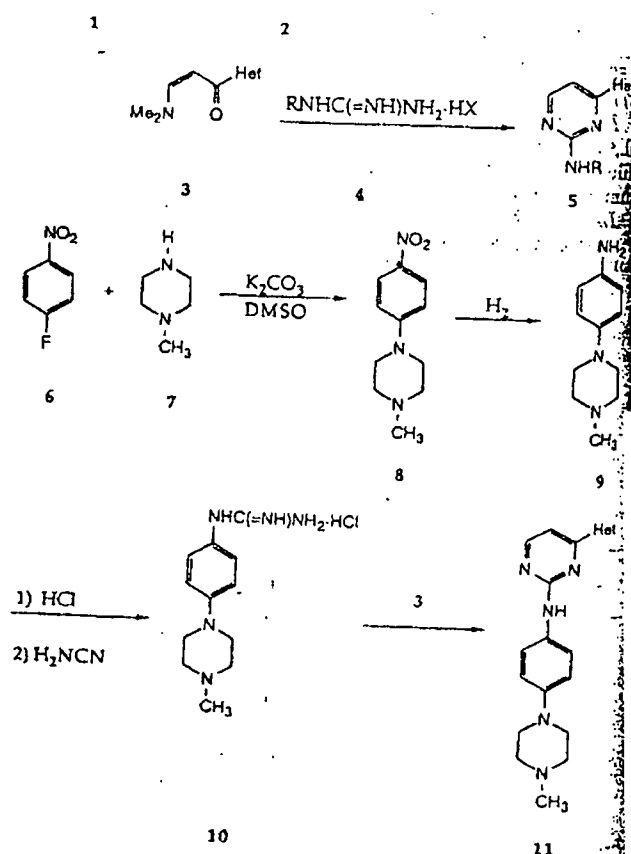
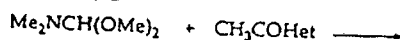
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Received February 19, 1993*

The role of immunologically released mediators, such as histamine, leukotrienes, and platelet-activating factor, is well-established for asthma and other allergic disorders. Developing therapeutic agents which would block mediator release from mast cells and other relevant cell types would provide a rational approach to asthma therapy. Using human basophil as a screen, a series of 4-aryl-2-(phenylamino)pyrimidines was found which inhibited mediator release. These compounds were prepared by condensing acetyl heterocycles with dimethylformamide dimethyl acetal to form enaminones which are cyclized with aryl guanidines to give pyrimidines. After examining a large number of analogs, *N*-[3-(1*H*-imidazol-1-yl)phenyl]-4-(2-pyridinyl)-2-pyrimidinamine (1-27) was chosen for toxicological evaluation.

In the currently accepted explanation for the events leading to an asthmatic attack,^{1,2} antigens cross-link the E antibodies (IgE) attached to the human lung mast cells. On cross-linking, the IgE triggers the mast cell to release preformed mediators plus substances which, in turn, are converted to other mediators. The various mediators, such as histamine, leukotrienes, eosinophil chemotactic factors, and platelet-activating factor, induce the asthmatic attack. With one of the major treatments, the use of β -agonists, being increasingly questioned³ and with death rates from asthma in industrial countries on the rise,⁴ there is an urgent need for new therapy. There are a number of approaches for finding an antiasthma compound. One can search for receptor antagonists for specific mediators⁵ or one can search for compounds which inhibit the release of mediators from mast cells.⁶ As it is probably unlikely that one mediator causes all the symptoms of asthma,⁷ the latter approach is the one we have been pursuing for a number of years.⁸ Since human mast cells, the most desirable test cells, are difficult to obtain in the quantities needed for a screening program, a substitute was sought. Circulating basophils resemble mast cells in having IgE attached to their surface. On antigen challenge, the basophil releases mediators similar to those released by the mast cell. Thus, if one could find a compound which would inhibit the release of mediators from human basophils, this compound might also inhibit mediator release from human mast cells and consequently be useful as a prophylaxis for asthma and/or allergy. Human basophils, separated from leukocytes, were incubated with test compounds and challenged with anti-IgE or antigen, by the method of Lichtenstein.⁹ Histamine release was measured vs controls and blanks. It was assumed that histamine release was indicative of all the mediators released. A later study, using a radioimmunoassay for leukotrienes, verified this assumption. With the basophil as a screen, 2-aminopyrimidines 5 were identified as antiasthma compounds and a synthetic program was undertaken to improve their activity.

Scheme I



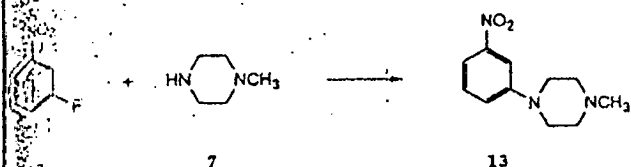
Chemistry

The general method of Brederick¹⁰ was used for the synthesis of pyrimidines which involved reacting *N,N*-dimethylformamide dimethyl acetal (1), with an aromatic, generally heterocyclic, acetyl derivative 2, to give the enaminone 3. Reaction of 3 with a guanidine derivative 4 gave

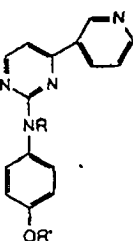
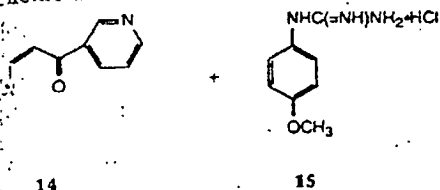
* Abstract published in *Advances in Chemistry* 250, 1-10 (1993).

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Scheme II

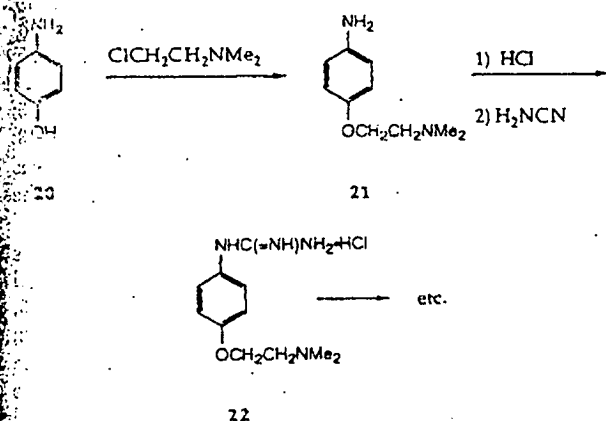


Scheme III



- 16 R = H, R' = CH₃
 17 R = H, R' = H
 18 R = H, R' = CH₂CH₂NEt₂
 19 R, R' = CH₂CH₂NEt₂

Scheme IV

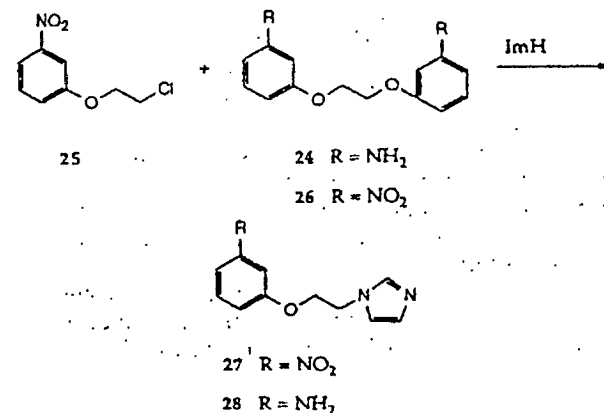


guanidines were used for preparing pyrimidines. When it was found that adding amino groups to the R substituent, when R was phenyl, increased the activity in the basophil assay, new guanidines were prepared. Some of these syntheses will be described.

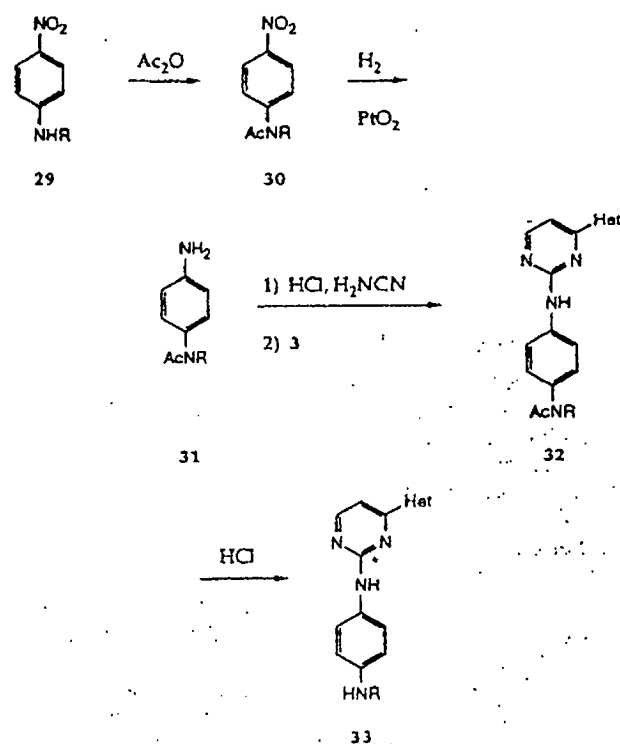
4-Fluoronitrobenzene (6) reacted with *N*-methylpiperazine (7) to give 8, in good yield. Hydrogenation reduced the nitro group to amine 9, which was converted to its hydrochloride and then was fused with cyanamide to give guanidine 10 (Scheme I). If the guanidine could be obtained in crystalline form, the subsequent cyclization frequently gave 60–70% yields. In the more usual case, the guanidine 4 was a syrup and had to be used in crude form, reducing the yield of 5 to around 30%.

Since the fluoro displacement went well, and the product was readily isolated (poured into water, collected crystals), it was decided to prepare the 3-substituted compound 13 (Scheme II). While no resonance effects could be invoked

Scheme V



Scheme VI



here, inductive effects were sufficient to bring about a similar reaction, although higher temperatures were necessary.

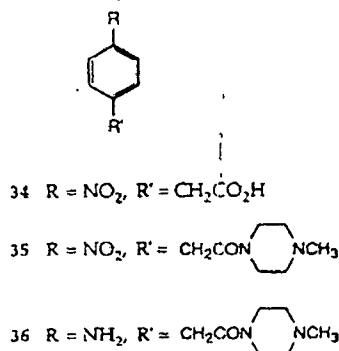
Initially aminoethers of the type 18 were prepared by coupling enaminone 14 with commercially available 15 to give 16 (Scheme III). Cleavage with 48% HBr gave 17 which could be converted by alkylation to a variety of ethers similar to 18. Unfortunately, ether formation was usually accompanied by a small amount of *N*-alkylated product, 19, which was a nuisance to remove. The alternative approach to making the ether first (Scheme IV), cleanly gave 21. These amines, which could be distilled and stored in the freezer, were converted to guanidines and then to pyrimidines, in much better overall yield.

Since the amino ethers, such as 18, were quite active in the basophil assay, it was decided to try to replace the amine by imidazole. Attempts to prepare 1-chloroethylimidazole from imidazole and 2-chloroethyl *p*-toluenesulfonate (23) gave only 1-vinylimidazole, while attempts to prepare 3-(2-chloroethoxy)benzenamine from 3-hydroxyaniline and 23 gave 3,3'-(1,2-ethanediylbis(oxy))bis[benzenamine] (24) (¹H NMR). To avoid these problems,

the known compound 25 was prepared from 3-nitrophenol and 23. Some contamination of 25 by 26 was noted (^1H NMR) but upon conversion of 25 to 27, 26 was lost during workup. Next, hydrogenation of 27 gave 28, which was converted to the pyrimidine as previously described (Scheme V).

Amino and monomethylamino substituents were prepared by the general procedure of acylation of the appropriate nitro amine, **29**, to give **30**. Hydrogenation, followed by the usual pyrimidine synthesis gave **32**, which upon acid hydrolysis gave **33** (Scheme VI).

Finally, 2-(4-nitrophenoxy)acetic acid (34) was converted to 35 using *N,N'*-carbonyldiimidazole and *N*-methylpiperazine and reduced with Pd black and formic acid¹¹ to 36.



Structure-Activity Relationships

When the pyrimidines were first screened in the basophil assay, a compound was considered active if it lowered histamine release by 50% (IC_{50}) at a concentration of 48 μ M. As more active compounds were found, the IC_{50} for acceptable activity was lowered to 24, 12, 6, and finally 3 μ M. Results from the basophil assay largely guided the synthetic effort. Further evaluation was done in the mouse passive cutaneous anaphylaxis assay (PCA), monkey cutaneous anaphylaxis, and rat lung fragment assays.

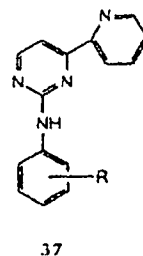
In general, the 2-, 3-, and 4-pyridinyl, 2-furyl, and 2-thienyl groups in the pyrimidine 4-position gave the best activity. Table VIII, which lists 4-substituents other than the above five, reveals a lack of outstanding activity (basophil < 1). Examining the thiophene ring in position 4 (Tables IV and VI) reveals that 2-thienyl was generally more active than 3-thienyl; compare 4-7 to 6-4, 4-3 to 6-3, 4-6 to 6-2, 4-1 to 6-1, 4-12 to 6-6, 4-7 to 6-4, and 4-14 to 6-7. The only exception was 4-8 vs 6-5. Substituents on the thiophene ring lowered activity; compare 4-7 to 6-11 and 6-16, 4-9 to 6-12 and 6-17, 4-3 to 6-9, 4-1 to 6-8 and 6-13, and 4-12 to 6-10 and 6-15. There was some indication that substitution near the point of attachment to the pyrimidine ring decreased the activity more than remote substituents; hence, 5-methyl-2-thienyl groups were more active than 3-methyl-2-thienyl groups (6-16 vs 6-11, 6-17 vs 6-12, 6-15 vs 6-10).

In the case of a furyl group in the pyrimidine 4-position, unsubstituted 2-furyl was more potent than 5-methyl-2-furyl four times (5-17 vs 7-5, 5-6 vs 7-2, 5-14 vs 7-4, 5-1 vs 7-1) and the same once (5-10 vs 7-3). Comparing 2-furyl to 2,5-dimethyl-3-furyl showed that the unsubstituted 2-furyl was more active five times (5-17 vs 7-12, 5-10 vs 7-11, 5-6 vs 7-9, 5-14 vs 7-10, 5-4 vs 7-8) and less active twice (5-1 vs 7-6, 5-3 vs 7-7). Examining the effect of adding substituents on the pyrimidine ring led to the conclusion that activity was generally lowered. For 5-substitution,

activity was lowered in two cases (5-17 vs 5-18, and 5-4 vs 5-5) and raised in one (5-1 vs 5-2). In the case of 6-substitution, nine examples showed reduced activity (1-37 vs 1-38, 1-12 vs 1-13, 2-45 vs 2-46, 3-1 vs 3-4, 3-7 vs 3-8, 3-15 vs 3-16, 3-28 vs 3-29, 3-34 vs 3-35, 3-38 vs 3-39) while two examples displayed slightly increased activity (1-1 vs 1-2, 6-13 vs 6-14).

Only two significant cases of 2-amino N-alkylation were examined. In both, activity was lost (2-15 vs 2-16, 3-1 vs 3-3). An attempt at making a prodrug reduced the basophil activity slightly, as expected, but did not lead to significantly longer activity when tested in the mouse PCA (3-2 vs 3-1). Eliminating the 2-amino group (1-39, 3-49) or substituting a methylene group for it (1-40, 3-50) gave little or no activity, as did replacing phenyl with cyclohexyl (3-48) or cyclopentyl (3-47).

The most significant improvement in basophil activity was produced by substituents on the phenyl ring attached to the 2-amino group. In the case where the pyrimidine



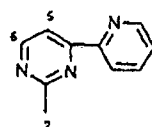
4-substituent was 2-pyridine (37), neither electron-donating nor -withdrawing substituents seemed to make any difference. However, *meta* substitution on the phenyl ring gave better activity than *ortho* or *para*, while the unsubstituted phenyl, 1-1, was inactive. Compare 1-3 and 1-18; 1-5, 1-21, and 1-34; 1-6 and 1-22; 1-7 and 1-23; 1-8 and 1-24; 1-9 and 1-25 (although 1-9 is a salt); 1-12 and 1-26; 1-15 and 1-30; 1-14 and 1-27; 1-16 and 1-31; 1-17 and 1-33; and 1-19 and 1-35. Even *m,m*-disubstitution (1-37) was more effective than *m,p*-disubstitution (1-36) while the rest of the disubstituted compounds were inactive.

In the case of 4-(3-pyridinyl)pyrimidines, the results were less clear cut. In seven cases *meta*-substituted phenyls were more active than *para* or *ortho* phenyls (2-3, 2-23, and 2-39; 2-4 and 2-27; 2-9 and 2-31; 2-12 and 2-32; 2-14 and 2-34; 2-15, 2-35, and 2-40; 2-22 and 2-38), while in five cases the *para* substitution was equal to or more active than the *meta* (2-6 and 2-28; 2-7 and 2-29; 2-8 and 2-30; 2-13 and 2-33; 2-20, 2-36, and 2-42). When available, the *ortho*-substituted compound was always the least active. In the case of the (dialkylamino)alkyl ethers, diethyl was more active than dimethyl, while diisopropyl (2-18, 2-20 and 2-21) was the least active.

Lengthening the chain (2-19 vs 2-18) of the ether had no effect. Only free bases can be compared, as salts, and even the type of salts make a difference, compare 2-1 to 2-2, and 2-24 to 2-25 and 2-26. *m,m*-Dimethyl was more active than other dimethyl substitution (2-45, 2-44). Unlike the 2-pyridinyl series, in the 3-pyridinyl case, the unsubstituted phenyl was active (2-1, 1-1).

In the 4-pyridinyl case, there were six examples of *meta*-substituted phenyls being more active than *para* ones (3-5 and 3-27, 3-20 and 3-38, 3-10 and 3-32, 3-18 and 3-36, 3-12 and 3-33, 3-9 and 3-31) and three where the *para* were slightly more active (3-7, 3-30 and 3-43; 3-15, 3-34 and 3-44; 3-25 and 3-40). In one case, *o*-phenyl substitution

Table I. 2-Pyridinylpyrimidines



substituents ^a		basophil ^b	formula ^c	% yield	recryst solvent ^d	mp, °C	start mat. ^{e,f}
theophylline		309 ± 55 (17)					
Na ₂ chromoglycate		1000					
NHPh		I	C ₁₅ H ₁₂ N ₄	65	CH ₂ Cl ₂ -Me ₂ CO	190.5-192	comm
NHPh	Me	26.8 (1)	C ₁₆ H ₁₄ N ₄	33	EtOH	94-98	comm ^g
NHC ₆ H ₄ -4-F		I	C ₁₅ H ₁₁ FN ₄	64	2-PrOH	207-209	comm
NHC ₆ H ₄ -4-Cl		I	C ₁₅ H ₁₁ ClN ₄	54	MeOCH ₂ CH ₂ OH	220-222	comm
NHC ₆ H ₄ -4-Me		I	C ₁₆ H ₁₃ N ₄	51	MeOCH ₂ CH ₂ OH	179-181	comm
NHC ₆ H ₄ -4-Et		2.1 (1)	C ₁₇ H ₁₅ N ₄	53	Me ₂ CO-hex	148.5-149.5	comm
NHC ₆ H ₄ -4-SO ₂ NH ₂		4.6 ± 0.1 (2)	C ₁₆ H ₁₃ N ₄ O ₂ S	26	MeOCH ₂ CH ₂ OH	274-277	amine
NHC ₆ H ₄ -4-NHAc		1.5 ± 0.8 (3)	C ₁₇ H ₁₅ N ₄ O	55	MeOCH ₂ CH ₂ OH	254-255	amine
NHC ₆ H ₄ -4-NH ₂		1.5 ± 0.2 (4)	C ₁₆ H ₁₃ N ₄ ·2HCl·1/2H ₂ O	77	EtOH-H ₂ O	285-288	1-8 ^h
NHC ₆ H ₄ -4-NAcMe		1.8 ± 0.13 (4)	C ₁₆ H ₁₃ N ₄ O	38	EtOH	179-181	comm
NHC ₆ H ₄ -4-NHMe		1.4 (1)	C ₁₆ H ₁₃ N ₄ ·1/2H ₂ O	59	EtOH	110-112	1-10 ^h
NHC ₆ H ₄ -4-NMe ₂		3.3 ± 1.6 (6)	C ₁₇ H ₁₇ N ₄ ·1/2H ₂ O	31	EtOH	171-174	amine
NHC ₆ H ₄ -4-NMe ₂	Me	31.9 (3)	C ₁₈ H ₁₉ N ₄ ·1/2H ₂ O	7		145-148	amine ^g
NHC ₆ H ₄ -4-(1-Im)		1.4 ± 0.2 (3)	C ₁₆ H ₁₃ N ₆	63	EtOH	204-206	39
NHC ₆ H ₄ -4-OMe		8.3 ± 0.3 (2)	C ₁₆ H ₁₃ N ₄ O	55	MeOCH ₂ CH ₂ OH	162-164	comm
NHC ₆ H ₄ -4-OCH ₂ CH ₂ NEt ₂		>3	C ₂₁ H ₂₅ N ₆ O	9	Et ₂ O-hex	106-108	amine ^g
NHC ₆ H ₄ -4-COOMe		I	C ₁₇ H ₁₅ N ₄ O ₂	44	EtOAc-MeOH	231.5-233.5	amine
NHC ₆ H ₄ -3-F		1.0 ± 0.3 (5)	C ₁₆ H ₁₃ FN ₄	44	EtOH	162-164	amine
NHC ₆ H ₄ -3-CF ₃		2.9 ± 1.7 (3)	C ₁₆ H ₁₁ F ₃ N ₄	49	MeOCH ₂ CH ₂ OH	126-128	comm
NHC ₆ H ₄ -3-CF ₃		0.4 ± 0.4 (2)	C ₁₆ H ₁₁ F ₃ N ₄ ·H ₂ SO ₄	93	EtOH	208-211	1-19
NHC ₆ H ₄ -3-Me		0.7 ± 0.5 (6)	C ₁₆ H ₁₃ N ₄	62		135-137	comm
NHC ₆ H ₄ -3-Et		1.4 (1)	C ₁₇ H ₁₅ N ₄	65	EtOH	101-104	amine
NHC ₆ H ₄ -3-SO ₂ NH ₂		0.5 ± 0.3 (2)	C ₁₆ H ₁₃ N ₄ O ₂ S	26	MeOCH ₂ CH ₂ OH	223-225	amine
NHC ₆ H ₄ -3-NHAc		0.3 ± 0.2 (4)	C ₁₇ H ₁₅ N ₄ O	50	MeOCH ₂ CH ₂ OH	190-192	amine
NHC ₆ H ₄ -3-NH ₂		0.3 ± 0.1 (2)	C ₁₆ H ₁₃ N ₄	57	MeOCH ₂ CH ₂ OH	153-156	1-24 ^h
NHC ₆ H ₄ -3-NMe ₂		0.4 ± 0.3 (2)	C ₁₇ H ₁₇ N ₄	18	EtOH	109-111	amine
NHC ₆ H ₄ -3-(1-Im)		0.3 ± 0.1 (5)	C ₁₈ H ₁₉ N ₆	33	EtOH	205.5-206.5	43
NHC ₆ H ₄ -3-(1-Im)			C ₁₈ H ₁₉ N ₆ ·HCl	83	EtOH	232.5-234	1-27
NHC ₆ H ₄ -3-(1-Im)		0.2 ± 0.1 (11)	C ₁₈ H ₁₉ N ₆ ·2HCl·1/2H ₂ O	100		119-126	1-27
NHC ₆ H ₄ -3-OMe		0.2 (1)	C ₁₆ H ₁₃ N ₄ O	52	EtOH	110-113	amine
NHC ₆ H ₄ -3-OCH ₂ CH ₂ NEt ₂		1.2 ± 0.5 (3)	C ₂₁ H ₂₅ N ₆ O	9	Et ₂ O-hex	64-66	k
NHC ₆ H ₄ -3-(OCH ₂ CH ₂ -1-Im)		0.4 ± 0.1 (3)	C ₂₀ H ₂₃ N ₆ O	16	EtOH	149-151.5	l
NHC ₆ H ₄ -3-COOEt		3.0 ± 0.3 (3)	C ₁₈ H ₁₉ N ₄ O ₂ ·1/2H ₂ O	16	EtOH	156-158	amine
NHC ₆ H ₄ -2-Me		I	C ₁₆ H ₁₃ N ₄	55	EtOH	111-113	comm
NHC ₆ H ₄ -2-CF ₃		I	C ₁₆ H ₁₁ F ₃ N ₄	22		106-110	comm
NHC ₆ H ₄ -3,4-Me ₂		5.9 (1)	C ₁₇ H ₁₅ N ₄	52	Me ₂ CO-hex	130-133.5	comm
NHC ₆ H ₄ -3,5-Me ₂		0.1 ± 0.01 (2)	C ₁₇ H ₁₅ N ₄	47	EtOH	114-119	amine
NHC ₆ H ₄ -3,5-Me ₂	Me	>24	C ₁₈ H ₁₇ N ₄	38	EtOH	110-112	amine ^g
Ph		I	C ₁₅ H ₁₁ N ₃	27	EtOH	70-72	comm
CH ₂ Ph		I	C ₁₆ H ₁₃ N ₃	7	EtOH-H ₂ O	65-67	amine
NHC ₆ H ₄ -4-(4-MePip)		1.9 ± 1.5 (2)	C ₂₀ H ₂₀ N ₆	43	EtOH	192-193	amine ^g

^a Substituents in the 2-position of the pyrimidine are defined as NHPh = phenylamino, NHC₆H₄-4-(1-Im) = [(4-(1H-imidazol-1-yl)phenyl)amino], NMorph = 4-morpholinyl, (4-MePip) = 4-methylpiperidin-1-yl, (1-(4-Me)Im) = 4-methylimidazol-1-yl. ^b IC₅₀ in μ M as means $\pm$ SEM. The numbers in parentheses indicate the number of dose responses carried out. ^c The elements cited were within 0.4% of the theoretical values (except O). ^d In some cases, filtration of the hot reaction mixture to remove inorganic material, followed by cooling, caused the product to crystallize out of the reaction mixture in pure form. Hence, no recrystallization solvent is listed. ^e "Comm" means the guanidine was commercially available. "Amine" means the guanidine was prepared, without isolation, from a commercially available amine. ^f Used enaminone 3-(dimethylamino)-1-(2-pyridinyl)-2-propen-1-one (ref 16), unless otherwise noted, with method A. ^g Used enaminone 3-(dimethylamino)-1-(2-pyridinyl)-2-buten-1-one, mp 68-70 °C, method H. ^h Method B. ⁱ Kaye, I. A.; Burlant, W. J.; Price, L. Thiocyanation of p-Dialkylaminoalkoxyanilines. *J. Org. Chem.* 1951, 16, 1421-1426. ^j C: calcd, 73.89; found, 74.57. ^k Prepared from 3-aminophenol by method D. ^l Prepared from 42 by method L. ^m N: calcd, 17.71; found, 18.5. ⁿ Reference 15.

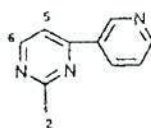
was more active than *meta* or *para* substitution (3-6, 3-28, 3-42). Since the unsubstituted phenyl (3-1) was very active, many substituents lowered activity. Lengthening the chain of a 4-amino ether lowered activity, as did substituting S for O (3-25, 3-24, 3-26). Replacing the dialkylamino group of 3-40 with imidazole gave a very active compound (3-41).

Few comparisons of phenyl substitution were available in the 4-(2-thienyl)pyrimidine series. However, there were still more cases (three: 4-6, 4-12; 4-5, 4-11; 4-2, 4-7) where *meta* derivatives were more active than there were in which *para* ones were more active (two: 4-3, 4-9; 4-4, 4-10). Since

substitution improved the activity. The imidazolylethoxy group (4-13) again gave the best activity of the 2-thienyl series.

When the pyrimidine 4-substituent was a 2-furyl, the unsubstituted phenyl compound 5-1 was essentially inactive. Only four valid comparisons of phenyl substitution are available. For the ethyl and imidazolyl groups, *meta* was more active than *para* (5-3, 5-11; 5-8, 5-13). The amino ethers were equal (5-9, 5-15), while the *p*-isomer of the methylpiperazinyl analog was more active (5-7, 5-12). Going from one *meta* substituent to two (5-10, 5-17) increased activity. Thus for the five main types of 4-heteroaryl-

Table II. 3-Pyridinylpyrimidines



substituents ^a		basophil	formula ^b	% yield	recryst solvent	mp, °C	start. mat.
2	5						
2-1	NHPh	0.9 (1)	C ₁₅ H ₁₂ N ₄	24	CH ₂ Cl ₂ -hex.	147-148	comm
2-2	NHPh	1.3 ± 0.8 (3)	C ₁₅ H ₁₂ N ₄ ·H ₂ SO ₄ ·H ₂ O ^d	87		167-187	2-1
2-3	NHC ₆ H ₄ -4-Cl	I	C ₁₆ H ₁₁ ClN ₄	56	MeOCH ₂ CH ₂ OH	183-184	comm
2-4	NHC ₆ H ₄ -4-Me	I	C ₁₆ H ₁₁ N ₄	77	2-PrOH	135-136	comm
2-5	NHC ₆ H ₄ -4- <i>t</i> -Bu	0.6 ± 0.2 (3)	C ₁₉ H ₂₀ N ₄ ·1/8 C ₂ H ₆ O	8	EtOH-H ₂ O	130-133	amine
2-6	NHC ₆ H ₄ -4-SO ₂ NH ₂	0.2 ± 0.1 (3)	C ₁₆ H ₁₃ N ₆ O ₂ ·S ^{7/8} ·H ₂ O	30	MeOCH ₂ CH ₂ OH	224-225	amine
2-7	NHC ₆ H ₄ -4-COMe	0.8 (1)	C ₁₇ H ₁₄ N ₄ O	78	MeOCH ₂ CH ₂ OH	181-183	amine
2-8	NHC ₆ H ₄ -4-NHAc	3.6 (1)	C ₁₇ H ₁₅ N ₄ O·3/4 H ₂ O	40	MeOCH ₂ CH ₂ OH	192-195	amine
2-9	NHC ₆ H ₄ -4-NH ₂	2.8 ± 1.1 (4)	C ₁₆ H ₁₃ N ₆ ·2HCl	67	H ₂ O	296-301	2-3 ^e
2-10	NHC ₆ H ₄ -4-NAcMe	0.9 ± 0.1 (3)	C ₁₈ H ₁₇ N ₆ O	49	EtOH	194-197	comm
2-11	NHC ₆ H ₄ -4-NHMe	2.1 ± 0.8 (2)	C ₁₆ H ₁₅ N ₆	53	EtOH	164-166	2-10 ^e
2-12	NHC ₆ H ₄ -4-NMe ₂	2.8 ± 1.8 (2)	C ₁₇ H ₁₇ N ₆	30	EtOH	165-166	amine
2-13	NHC ₆ H ₄ -4-(4-MePip)	0.5 (2)	C ₂₀ H ₂₂ N ₆	70	EtOH	174-175	g
2-14	NHC ₆ H ₄ -4-(1-Im)	1.3 ± 1.2 (4)	C ₁₈ H ₁₄ N ₆	41	MeOH	170-172	39
2-15	NHC ₆ H ₄ -4-OMe	1.7 (1)	C ₁₆ H ₁₄ N ₄ O	60	2-PrOH	121-122	comm
2-16	NMeC ₆ H ₄ -4-OMe	>24	C ₁₇ H ₁₆ N ₄ O	48	Et ₂ O-hex.	88-90	comm
2-17	NHC ₆ H ₄ -4-OH	5.1 ± 0.7 (5)	C ₁₆ H ₁₂ N ₄ O·1/2 H ₂ O	80	EtOH	221-223	2-15 ^e
2-18	NHC ₆ H ₄ -4-OCH ₂ CH ₂ NMe ₂	0.7 ± 0.2 (3)	C ₁₉ H ₂₁ N ₆ O·1/2 H ₂ O ^e	37	CHCl ₃ -hex.	108-110	2-17 ^e
2-19	NHC ₆ H ₄ -4-OCH ₂ CH ₂ CH ₂ NMe ₂	0.6 ± 0.4 (2)	C ₂₀ H ₂₃ N ₆ O·1/18 H ₂ O	41	Et ₂ O-hex.	85-87	2-17 ^e
2-20	NHC ₆ H ₄ -4-OCH ₂ CH ₂ NEt ₂	0.2 ± 0.2 (3)	C ₂₁ H ₂₅ N ₆ O·1/2 H ₂ O ^e	47	Et ₂ O-hex.	87-89	2-17 ^e
2-21	NHC ₆ H ₄ -4-OCH ₂ CH ₂ N(iPr) ₂	4.6 (1)	C ₂₃ H ₂₉ N ₆ O·1/2 H ₂ O ^e	13	Et ₂ O-hex.	122-124	2-17 ^e
2-22	NHC ₆ H ₄ -4-COOEt	12.4 (1)	C ₁₈ H ₁₆ N ₄ O ₂	15	EtOH	197-202	amine
2-23	NHC ₆ H ₄ -3-Cl	1.5 ± 0.4 (2)	C ₁₅ H ₁₁ ClN ₄ ·1/2 H ₂ O	64	MeOCH ₂ CH ₂ OH	146-148	comm
2-24	NHC ₆ H ₄ -3-CF ₃	I	C ₁₆ H ₁₁ F ₃ N ₄	61	CHCl ₃ -hex.	181-183	comm
2-25	NHC ₆ H ₄ -3-CF ₃	0.7 (1)	C ₁₆ H ₁₁ F ₃ N ₄ ·7/8 HCl	65		220-223	2-24
2-26	NHC ₆ H ₄ -3-CF ₃	2.1 (2)	C ₁₆ H ₁₁ F ₃ N ₄ ·H ₂ SO ₄ ·1/4 H ₂ O	55		196-199	2-24
2-27	NHC ₆ H ₄ -3-Me	1.5 (1)	C ₁₆ H ₁₄ N ₄	34	MeOCH ₂ CH ₂ OH	103-104	comm
2-28	NHC ₆ H ₄ -3-SO ₂ NH ₂	0.2 ± 0.9 (3)	C ₁₆ H ₁₃ N ₆ O ₂ S	36	MeOCH ₂ CH ₂ OH	278-280	amine
2-29	NHC ₆ H ₄ -3-COMe	4.1 (1)	C ₁₇ H ₁₄ N ₄ O·1/2 H ₂ O ^m	36	CHCl ₃ -hex.	166-168	amine
2-30	NHC ₆ H ₄ -3-NHAc	3.6 ± 2.7 (3)	C ₁₇ H ₁₆ N ₄ O	54	MeOCH ₂ CH ₂ OH	239-241	comm
2-31	NHC ₆ H ₄ -3-NH ₂	0.5 ± 0.1 (2)	C ₁₆ H ₁₃ N ₆ ·2HCl	23	EtOH-H ₂ O	279-284	2-30 ^e
2-32	NHC ₆ H ₄ -3-NMe ₂	1.8 ± 0.8 (4)	C ₁₇ H ₁₆ N ₆	29	EtOH	123-125	amine
2-33	NHC ₆ H ₄ -3-(4-MePip)	1.2 ± 0.3 (3)	C ₂₀ H ₂₂ N ₆	29	EtOAc, MeCOEt	132-133.5	n
2-34	NHC ₆ H ₄ -3-(1-Im)	0.2 ± 0.04 (3)	C ₁₈ H ₁₄ N ₆ ·3/4 H ₂ O ^e	20	MeCOEt	58-130	43
2-35	NHC ₆ H ₄ -3-OMe	0.3 (2)	C ₁₆ H ₁₄ N ₄ O	31	EtOH	126-127	amine
2-36	NHC ₆ H ₄ -3-OCH ₂ CH ₂ NEt ₂	2.9 ± 1.3 (3)	C ₂₁ H ₂₅ N ₆ O·1/2 CH ₃ OH ^p	28	chrom	79-82	amine
2-37	NHC ₆ H ₄ -3-(OCH ₂ CH ₂ -1-Im)	0.1 ± 0.04 (3)	C ₂₀ H ₁₈ N ₆ O	24	MeCOEt	135-137.5	amine
2-38	NHC ₆ H ₄ -3-COOEt	10.5 ± 7.4 (5)	C ₁₈ H ₁₆ N ₄ O ₂ ·H ₂ O	20	EtOH	95-103	amine
2-39	NHC ₆ H ₄ -2-Cl	I	C ₁₅ H ₁₁ ClN ₄ ·1/4 H ₂ O	54	MeOCH ₂ CH ₂ OH	103-104	comm
2-40	NHC ₆ H ₄ -2-OMe	9.8 ± 9.8 (2)	C ₁₆ H ₁₄ N ₄ O	77	Et ₂ O	99-101	amine
2-41	NHC ₆ H ₄ -2-OH	23.5 (1)	C ₁₅ H ₁₂ N ₄ O ^e	54	EtOH	166-168	2-40 ^e
2-42	NHC ₆ H ₄ -2-OCH ₂ CH ₂ NEt ₂	>6	C ₂₁ H ₂₅ N ₆ O ^e	30	chrom	gum	2-41 ^e
2-43	NHC ₆ H ₄ -2,6-F ₂	21.0 (2)	C ₁₅ H ₁₀ F ₂ N ₄ ·1/6 H ₂ O	17	EtOH	163-166	amine
2-44	NHC ₆ H ₄ -2,4-Me ₂	I	C ₁₇ H ₁₆ N ₄	43	CH ₂ Cl ₂ -hex.	113-115	comm
2-45	NHC ₆ H ₄ -3,5-Me ₂	0.8 ± 0.1 (2)	C ₁₇ H ₁₆ N ₄ ·1/8 H ₂ O	52	EtOH	122-126	amine
2-46	NHC ₆ H ₄ -3,5-Me ₂	Me >24	C ₁₈ H ₁₈ N ₄	11	EtOH	136-140	amine

^a See footnotes a, b, and d of Table I. ^b See footnote c of Table I. ^c Used enaminone 3-(dimethylamino)-1-(3-pyridinyl)-2-propen-1-one (ref. 16) unless otherwise noted. ^d C: calcd, 49.44; found, 48.48. ^e Method B. / C: calcd, 67.70; found, 65.82. ^f Reference 15. ^g Method C. ^h MS M⁺: calcd, 335; found, 335. ⁱ Method D. ^j MS M⁺: calcd, 363; found, 363. ^k MS M⁺: calcd, 391; found, 391. ^l MS M⁺: calcd, 290; found, 290. ^m 1-Fluoro-3-nitrobenzene was converted to 1-methyl-4-(3-nitrophenyl)piperazine by method J and then to (1-piperazinyl)benzamine hydrochloride by method L. ⁿ MS M⁺: calcd, 313; found, 313. ^o MS M⁺: calcd, 363; found, 363. ^p Prepared from 3-aminophenol by method D. ^q Prepared from 42 by method L. ^r MS M⁺: calcd, 264; found, 264. ^s MS M⁺: calcd, 363; found, 363. ^t Used enaminone 3-(dimethylamino)-2-methyl-1-(3-pyridinyl)-2-propen-1-one (Dusza, J. P.; Tomcufcik, A. S.; Albright, J. D. Eur. Pat. Appl. EP 129847; Chem. Abstr. 1985, 102, 220889m; Aryl and Heteroaryl[7-(aryl and heteroaryl)pyrazolo[1,5-a]pyrimidin-3-yl]methanones. US 4,521,422, 1985).

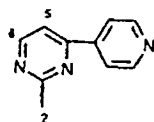
furan), *meta*-substitution of the 2-anilino group usually gave the highest activity. *N*-[3-(1*H*-imidazol-1-yl)phenyl]-4-(2-pyridinyl)-2-pyrimidinamine (1-27) was picked as one of the most active compounds and was evaluated in several other tests.

Since the basophil assay measured only *in vitro* cell histamine release inhibition and since it had been assumed that this measurement was indicative of total mediator release inhibition, it was desirable to demonstrate that at least another important mediator, leukotriene C₄ (LTC₄), was inhibited by 1-27. Using a radioimmunoassay¹² for LTC₄ release from basophils and measuring histamine release simultaneously on a second portion of the same

cells gave IC₅₀ (LTC₄) = 205 ± 48 nM (*n* = 5) for 1-27 while IC₅₀ (histamine) = 311 ± 133 nM (*n* = 5).

To demonstrate *in vivo* activity, 1-27 was tested in the mouse passive cutaneous anaphylaxis (PCA) test,¹³ where an ID₅₀ of ca. 50 mg/kg at times of 0.5-41 min following oral dosing was found. Compound 1-27 at doses of 400 μg/kg caused a 0.5-2 log shift (*n* = 4) in dose-response curves to anti-IgE in a cutaneous anaphylaxis assay in rhesus monkeys with a natural sensitivity to *Ascaris* antigen. Finally an acute LD₅₀ in mice of approximately 800 mg/kg was found for 1-27. Compound 1-27 has been chosen for further studies as a potential antiasthma agent.

Table III. 4-Pyridinylpyrimidines



	substituent ^a		basophil	formula ^b	% yield	recryst solvent	mp, °C	start. mat. ^c
	2	6						
3-1	NHPh		0.9 ± 0.4 (5)	C ₁₅ H ₁₂ N ₄	75	EtOH	153-154	comm
3-2	N(COOCOOEt)Ph		2.2 ± 1.3 (3)	C ₁₉ H ₁₆ N ₄ O ₃	35	EtOH	139-140	3-1 ^d
3-3	NMePh		>24	C ₁₅ H ₁₄ N ₄ ·1/2H ₂ O	45	EtOH	105-107	amine
3-4	NHPh	Me	I	C ₁₆ H ₁₄ N ₄	35	CH ₂ Cl ₂ -Me ₂ CO	207-210	comm ^e
3-5	NHC ₆ H ₄ -4-F		1.9 ± 0.5 (2)	C ₁₅ H ₁₁ FN ₄	66	MeOCH ₂ CH ₂ OH	186-188	comm
3-6	NHC ₆ H ₄ -4-Me		I	C ₁₆ H ₁₂ N ₄	68	MeOCH ₂ CH ₂ OH	198-199	comm
3-7	NHC ₆ H ₄ -4-Et		7.7 ± 3.5 (3)	C ₁₇ H ₁₄ N ₄	70	CH ₂ Cl ₂ -hex.	138-140	comm
3-8	NHC ₆ H ₄ -4-Et	Me	I	C ₁₈ H ₁₆ N ₄	29	Me ₂ CO-hex.	149-151	comm ^e
3-9	NHC ₆ H ₄ -4-SO ₂ NH ₂		5.1 ± 0.3 (4)	C ₁₆ H ₁₃ N ₄ O ₂ S	21	MeOCH ₂ CH ₂ OH	225-228	amine
3-10	NHC ₆ H ₄ -4-NHAc		5.3 ± 1.4 (2)	C ₁₇ H ₁₅ N ₄ O	58	EtOH	294-296	amine
3-11	NHC ₆ H ₄ -4-NH ₂		2.9 ± 0.7 (6)	C ₁₆ H ₁₃ N ₆ ·3/2HCl·1/2H ₂ O	96	EtOH-H ₂ O	292-296	3-10 ^f
3-12	NHC ₆ H ₄ -4-NH ₂		2.4 ± 2.1 (2)	C ₁₅ H ₁₃ N ₆ ·1/2H ₂ O		EtOH	178-180 ^g	3-11
3-13	NHC ₆ H ₄ -4-NAcMe		0.5 ± 0.2 (3)	C ₁₈ H ₁₇ N ₄ O	81	MeOCH ₂ CH ₂ OH	233-234	comm
3-14	NHC ₆ H ₄ -4-NHMe	h		C ₁₆ H ₁₅ N ₆ ·2HCl	9	EtOH	285-287	3-13 ^h
3-15	NHC ₆ H ₄ -4-NMe ₂		3.7 ± 1.4 (10)	C ₁₇ H ₁₇ N ₆	14	EtOH	164-166	amine
3-16	NHC ₆ H ₄ -4-NMe ₂	Me	>24	C ₁₈ H ₁₉ N ₆	73	EtOH	153-154	amine ^e
3-17	NHC ₆ H ₄ -4-(4-MePip)		0.6 (1)	C ₂₀ H ₂₂ N ₆	58	DMF	248-250	39
3-18	NHC ₆ H ₄ -4-(1-Im)		7.6 ± 2.3 (5)	C ₁₈ H ₁₅ N ₆ ·1/2HCON(CH ₃) ₂ ⁱ	53	EtOH	244-245.5	amine ⁱ
3-19	NHC ₆ H ₄ -4-[1-(4-Me)Im]		>3	C ₁₉ H ₁₇ N ₆	73	MeOCH ₂ CH ₂ OH	174-175	comm
3-20	NHC ₆ H ₄ -4-OMe		4.2 (1)	C ₁₆ H ₁₄ N ₄ O	21	Et ₂ O-hex.	124-126	3-20 ^m
3-21	NMeC ₆ H ₄ -4-OMe		>24	C ₁₇ H ₁₅ N ₄ O	15	EtOH-Et ₂ O	163-165	44
3-22	NHC ₆ H ₄ -4-OCH ₂ CO(4-MePip)		0.3 ± 0.2 (3)	C ₂₂ H ₂₄ N ₆ O ₂	41	DMF-EtOH	249-252d	3-20 ⁿ
3-23	NHC ₆ H ₄ -4-OH		3.3 ± 1.3 (3)	C ₁₅ H ₁₂ N ₄ O·1/2EtOAc·1/2H ₂ O ⁿ	27	CHCl ₃ -hex.	123-124.5	3-23 ^p
3-24	NHC ₆ H ₄ -4-O(CH ₂) ₃ NEt ₂		1.3 ± 0.8 (4)	C ₂₀ H ₂₃ N ₆ O	10	Et ₂ O-hex.	85-87	3-23 ^p
3-25	NHC ₆ H ₄ -4-OCH ₂ CH ₂ NEt ₂		0.2 ± 0.2 (2)	C ₂₁ H ₂₅ N ₆ O·1/2H ₂ O ^o	13	EtOAc-hex.	84-87	amine ^e
3-26	NHC ₆ H ₄ -4-SCH ₂ CH ₂ NEt ₂		1.0 ± 0.3 (3)	C ₂₁ H ₂₅ N ₆ S ^r	39	EtOH	155-162	amine
3-27	NHC ₆ H ₄ -3-F		0.7 ± 0.1 (2)	C ₁₅ H ₁₁ FN ₄	60	CH ₂ Cl ₂ -Me ₂ CO	185-188.5	comm ^e
3-28	NHC ₆ H ₄ -3-Me		8.8 ± 2.6 (3)	C ₁₆ H ₁₄ N ₄	53	EtOH	126-128	amine
3-29	NHC ₆ H ₄ -3-Me	Me	I	C ₁₇ H ₁₆ N ₄	34	MeOCH ₂ CH ₂ OH	262-264	amine
3-30	NHC ₆ H ₄ -3-Et		10.6 (1)	C ₁₇ H ₁₈ N ₄	63	MeOCH ₂ CH ₂ OH	267-270	comm
3-31	NHC ₆ H ₄ -3-SO ₂ NH ₂		0.5 ± 0.02 (2)	C ₁₆ H ₁₃ N ₆ O ₂ S·1/2H ₂ O	77	MeOCH ₂ CH ₂ OH	199-202	3-32 ^q
3-32	NHC ₆ H ₄ -3-NHAc		2.7 ± 1.1 (3)	C ₁₇ H ₁₇ N ₆	25	EtOH	165-168	amine
3-33	NHC ₆ H ₄ -3-NH ₂		1.0 ± 0.3 (3)	C ₁₆ H ₁₃ N ₆ ·3/2H ₂ O	10	MeOCH ₂ CH ₂ OH	200-201	amine ^e
3-34	NHC ₆ H ₄ -3-NMe ₂		3.7 ± 2 (5)	C ₁₇ H ₁₇ N ₆	24	EtOH	237-239	43
3-35	NHC ₆ H ₄ -3-NMe ₂	Me	>24	C ₁₈ H ₁₉ N ₆	66	EtOH-Et ₂ O	259-266	3-36
3-36	NHC ₆ H ₄ -3-(1-Im)		0.6 ± 0.2 (2)	C ₁₈ H ₁₄ N ₆ ·1/2H ₂ O ^u	33	EtOH	159-160	amine
3-37	NHC ₆ H ₄ -3-(1-Im)		3.9 ± 3.6 (2)	C ₁₈ H ₁₄ N ₆ ·1/2HCl·5/8H ₂ O	13	EtOH	187-189	amine ^e
3-38	NHC ₆ H ₄ -3-OMe		0.4 ± 0.3 (3)	C ₁₆ H ₁₄ N ₄ O	45	CH ₃ CN	138-140	amine ^u
3-39	NHC ₆ H ₄ -3-OMe	Me	>24	C ₁₇ H ₁₆ N ₄ O	62	EtOH	129-130.5	comm
3-40	NHC ₆ H ₄ -3-OCH ₂ CH ₂ NEt ₂		0.6 ± 0.2 (2)	C ₂₁ H ₂₅ N ₆ O	25	Me ₂ CO	228-231	amine
3-41	NHC ₆ H ₄ -3-(OCH ₂ CH ₂ -1-Im)		0.2 ± 0.1 (5)	C ₂₀ H ₁₈ N ₆ O·1/2CH ₃ CN ^w	8	EtOH	114-119	amine
3-42	NHC ₆ H ₄ -2-Me		3.9 ± 0.1 (2)	C ₁₆ H ₁₄ N ₄	16	EtOH	239-242	z
3-43	NHC ₆ H ₄ -2-Et	I		C ₁₇ H ₁₆ N ₄ ·2HCl	45	EtOH	132-136	amine
3-44	NHC ₆ H ₄ -2-NMe ₂		36.2 (1)	C ₁₇ H ₁₇ N ₆ ·5/8C ₂ H ₄ O ₂ ^y	9	EtOH	122-124	comm
3-45	NHC ₆ H ₄ -3-CF ₃ , 4-(1-Im)		0.4 ± 0.2 (4)	C ₁₉ H ₁₃ F ₃ N ₆	42	EtOH	143-146	amine
3-46	NHCH ₂ C ₆ H ₄ -3,4-Me ₂	I		C ₁₆ H ₁₄ N ₄	47	EtOH-H ₂ O	232-237	comm
3-47	NH-cyclopentyl	I		C ₁₆ H ₁₄ N ₄			79-119	amine
3-48	NH-cyclohexyl	I		C ₁₆ H ₁₄ N ₄				
3-49	Ph	I	13.9 (1)	C ₁₆ H ₁₄ N ₄ ·1/2H ₂ O				
3-50	CH ₂ Ph	I		C ₁₆ H ₁₃ N ₆ ·5/8C ₂ H ₄				

^a See footnotes a, b, and d of Table I. ^b See footnote c of Table I. ^c The enaminone was 3-(dimethylamino)-1-(4-pyridinyl)-2-propen-1-one (ref 10) unless otherwise noted. ^d Method E. ^e Used enaminone 3-(dimethylamino)-1-(4-pyridinyl)-2-buten-1-one (footnote u Table II). ^f Method B. ^g Dimorphic, the second form had mp 192-193.5 °C. ^h Compound interfered with the histamine assay. ⁱ N: calcd, 22.93; found, 21.32. ^j Reference 15. ^k MS M⁺: calcd, 314; found, 314. DMF detected in the ¹H NMR. ^l Roberts, D. A.; Campbell, S. F. Heteroarylquinolone Inotropic Agents. Eur. Pat. Appl. EP 166533 1986; Chem. Abstr. 1986, 105, 115061z. ^m Method F. ⁿ MS M⁺: calcd, 264; found, 264. ^o Method C. ^p Method D. ^q MS M⁺: calcd, 363; found, 363. ^r C: calcd, 66.46; found, 65.86. S: calcd, 8.45; found, 8.90. MS M⁺: calcd, 379; found, 379. ^s Buechi, J.; Enezi, J.; Enezi, G. Congr. Sci. Pharm. 1959, 317-328; Synthesis and Activity of Some Local Anesthetics. Derivatives of Procaine. Chem. Abstr. 1962, 56, 1534h. Bp 113 °C/0.1 mm. ^t C: calcd, 73.26; found, 71.77. ^u MS M⁺: calcd, 314; found, 314. ^v Footnote q of Table II. ^w MS M⁺: calcd, 358; found, 358. ^x Prepared from 42 by method L. ^y Maleate. ^z Prepared from 2-fluoro-5-nitrobenzotrifluoride via method J to 1-[4-nitro-2-(trifluoromethyl)phenyl]-1H-imidazole and reduction to 4-(1H-imidazol-1-yl)-3-(trifluoromethyl)benzamine by method L.

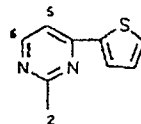
Experimental Section

Melting points were obtained on a standardized Mel-Temp apparatus and are uncorrected. Infrared spectra were taken on a Nicolet FT-IR spectrophotometer and ultraviolet spectra on a Hewlett-Packard 4050A. A Varian FT80 was used for ¹H NMR, and spectra are given in ppm downfield from a TMS internal standard with coupling constants in hertz. For mass spectra, a Finnigan-MHT CH7 was used. Column chromatography was

carried out by evaporating a MeOH solution of impure material onto a small amount of silica gel. The dried gel was placed on top of a wet (CCl₄) silica gel column. The column was eluted with CHCl₃, followed by 1% increments of MeOH to 10% MeOH/CHCl₃. TLC was carried out on silica gel plates, using MeOH/CHCl₃ (1:3 or 1:9).

Basophil Mediator Release. This test has been described in detail.²⁶

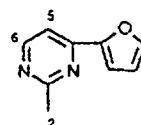
Table IV. 2-Thienylpyrimidines



	2-substituent ^a	basophil	formula ^b	% yield	recryst solvent	mp, °C	start. mat.
4-1	NHPh	31.7 (1)	C ₁₄ H ₁₁ N ₃ S	66		137-139	comm
4-2	NHC ₆ H ₄ -4-Me	I	C ₁₆ H ₁₃ N ₃ S	65	MeOCH ₂ CH ₂ OH	179-181	comm
4-3	NHC ₆ H ₄ -4-NMe ₂	0.9 ± 0.3 (4)	C ₁₆ H ₁₅ N ₃ S·1/2H ₂ O	29	MeOCH ₂ CH ₂ OH	174-175	amine
4-4	NHC ₆ H ₄ -4-(4-MePip)	0.4 ± 0.3 (2)	C ₁₉ H ₂₁ N ₆ S	60	CHCl ₃	215.5-216.5	d
4-5	NHC ₆ H ₄ -4-(1-Im)	4.3 ± 1.5 (3)	C ₁₇ H ₁₃ N ₆ S	62	MeOH	210.5-212	39
4-6	NHC ₆ H ₄ -4-OMe	3.9 (1)	C ₁₅ H ₁₃ N ₃ OS	53		158-160	comm
4-7	NHC ₆ H ₄ -3-Me	0.3 (1)	C ₁₅ H ₁₃ N ₃ S	54	EtOH	112.5-114.5	comm
4-8	NHC ₆ H ₄ -3-Et	I	C ₁₆ H ₁₅ N ₃ S	59	EtOH	114-116	amine
4-9	NHC ₆ H ₄ -3-NMe ₂	2.4 ± 0.7 (2)	C ₁₆ H ₁₇ N ₃ S	37	EtOH	118-120	amine
4-10	NHC ₆ H ₄ -3-(4-MePip)	3.5 ± 0.3 (3)	C ₁₉ H ₂₁ N ₆ S	49	EtOAc	125-126.5	e
4-11	NHC ₆ H ₄ -3-(1-Im)	0.3 ± 0.06 (4)	C ₁₇ H ₁₃ N ₆ S	31	EtOH	183-184.5	43
4-12	NHC ₆ H ₄ -3-OMe	0.9 ± 0.9 (2)	C ₁₅ H ₁₃ N ₃ OS	36	EtOH	151-153	amine
4-13	NHC ₆ H ₄ -3-(OCH ₂ CH ₂ -1-Im)	0.1 ± 0.01 (3)	C ₁₉ H ₁₇ N ₆ OS·1/2C ₂ H ₄ O	35	EtOH	118	g
4-14	NHC ₆ H ₃ -3,5-Me ₂	4.3 ± 1.0 (2)	C ₁₆ H ₁₅ N ₃ S	56	EtOH	152-155	amine

^a See footnotes a, b, and d of Table I. ^b See footnote c of Table I. ^c Used enaminone 3-(dimethylamino)-1-(2-thienyl)-2-propen-1-one (Wagner, R. M.; Jutz, C. *Chem. Ber.* 1971, 104, 2375-2983). ^d Reference 15. ^e Footnote u of Table II. ^f MS M⁺: calcd, 363; found, 363. ^g Prepared from 42 by method L.

Table V. 2-Furylpyrimidines



	substituent ^a		basophil	formula ^b	% yield	recryst solvent	mp, °C	start. mat.
	2	6						
5-1	NHPh		32.0 (1)	C ₁₄ H ₁₁ N ₃ O	70	EtOH	144-145	comm
5-2	NHPh	Me	17.7 (1)	C ₁₆ H ₁₃ N ₃ O	45	CH ₂ Cl ₂ -hex.	141-142	comm ^d
5-3	NHC ₆ H ₄ -4-Et		I	C ₁₆ H ₁₅ N ₃ O	56	EtOH	152-155	comm
5-4	NHC ₆ H ₄ -4-NMe ₂		1.9 (2)	C ₁₆ H ₁₇ N ₃ O	33	EtOH	166-167	amine
5-5	NHC ₆ H ₄ -4-NMe ₂	Me	5.9 (1)	C ₁₇ H ₁₉ N ₃ O	21	EtOH	146-148	amine ^d
5-6	NHC ₆ H ₄ -4-NEt ₂		8.7 (2)	C ₁₈ H ₂₁ N ₃ O	33	EtOH	132-133	amine
5-7	NHC ₆ H ₄ -4-(4-MePip)		1.8 ± 1.8 (2)	C ₁₉ H ₂₃ N ₆ O	68	EtOH	193-195	e
5-8	NHC ₆ H ₄ -4-(1-Im)		2.2 ± 0.9 (3)	C ₁₇ H ₁₃ N ₆ O	42	MeOH	211.5-213.5	39
5-9	NHC ₆ H ₄ -4-OCH ₂ CH ₂ NEt ₂		1.3 ± 0.5 (3)	C ₂₀ H ₂₄ N ₆ O ₂	21	Et ₂ O	114-116	amine ^f
5-10	NHC ₆ H ₄ -3-Me		2.1 ± 0.3 (9)	C ₁₆ H ₁₃ N ₃ O	56	EtOH	98-99.5	comm
5-11	NHC ₆ H ₄ -3-Et		9.7 (1)	C ₁₆ H ₁₅ N ₃ O	56	EtOH	95-98	amine
5-12	NHC ₆ H ₄ -3-(4-MePip)		5.0 ± 3.5 (3)	C ₁₉ H ₂₃ N ₆ O	36	EtOAc	134.5-136	g
5-13	NHC ₆ H ₄ -3-(1-Im)		0.8 ± 0.04 (2)	C ₁₇ H ₁₃ N ₆ O	26	EtOH	174-175.5	43
5-14	NHC ₆ H ₄ -3-OMe		0.4 ± 0.4 (3)	C ₁₆ H ₁₃ N ₃ O	44	EtOH	114-116	amine
5-15	NHC ₆ H ₄ -3-OCH ₂ CH ₂ NEt ₂		1.4 ± 0.6 (2)	C ₂₀ H ₂₄ N ₆ O ₂	47	chrom	gum	amine ^h
5-16	NHC ₆ H ₄ -3-(OCH ₂ CH ₂ -1-Im)		0.2 ± 0.05 (3)	C ₁₉ H ₁₇ N ₆ O ₂	29	EtOH	136-137	i
5-17	NHC ₆ H ₃ -3,5-Me		0.7 ± 0.2 (3)	C ₁₆ H ₁₅ N ₃ O	58	EtOH	126-129	amine
5-18	NHC ₆ H ₃ -3,5-Me ₂	Me	>24	C ₁₇ H ₁₇ N ₃ O	42	MeOCH ₂ CH ₂ OH	155-158	amine ^d

^a See footnotes a, b, and d of Table I. ^b See footnote c of Table I. ^c Used enaminone 3-(dimethylamino)-1-(2-furyl)-2-propen-1-one, (Verachchagiri, L. I.; Korshunov, S. P.; Timokhin, B. V.; Kakevich, R. I. *Probl. Poluprod. Prom-si. OrgSin.* 1967, 223-227; Furfalkynes IX. Some transformations of Furfylethynylcarbinol and its Derivatives. *Chem. Abstr.* 1968, 68, 21756v.) See also footnote c of Table I. ^d Used crude enaminone 3-(dimethylamino)-1-(2-furyl)-2-methyl-2-propen-1-one, method H. ^e Reference 15. ^f Footnote i of Table I. ^g Footnote u of Table II. ^h Footnote k of Table I. ⁱ Prepared from 42 by method L. ^j C: calcd, 72.43; found, 73.22.

Monkey Cutaneous Anaphylaxis. Female Rhesus monkeys sensitive to *Ascaris* were anesthetized with ketamine and restrained supine. An iv line was established in a leg vein and 2 mL/kg of a 1% Evans blue dye in saline was infused through a sterile filter. Replicate serial log dilutions of -3, -4, -5, -6, and -7 of the *Ascaris* protein (Greer Laboratories, B33-8-1A4) were injected id into the right flank of the animal, 0.1 mL/spot. On occasion, anti-human IgE was injected at serial dilutions and utilized in an identical manner to *Ascaris* antigen. Twenty minutes later, the lesion areas were read as in PCA studies. Compound 1-27 at 400 µg/kg was dosed intravenously. After an additional 5 min for absorption and distribution, a repeat of the anti-IgE injection was done on the left side and read as before. Activity was established by a reduction in lesion size at all levels of anti-human IgE.

Mouse PCA.¹³ This assay has been described in detail.^{ab}

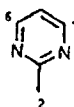
In Vitro Histamine Release--Rat Lung Tissue. (a) **Passive Sensitization of Lung Tissue.** The lungs from male

Sprague-Dawley rats were removed, cut into small portions, with care taken to remove all visible blood vessels, and finally cut into fine rectangular bits (10-15 mg) with iris scissors. The tissue was repeatedly washed in Tyrode's buffer until all visible traces of blood were removed and the washed fragments were placed in an appropriate dilution of IgE solution and incubated for 18 h at 4 °C or 3 h at 37 °C. After incubation, the tissue was washed twice in Tyrode's buffer and drained well, and ca. 15 tissue fragments (150-250 mg) were used for each sample to be assayed.

(b) **Challenge of Passively Sensitized Lung Tissue.** Reaction tubes containing 990 µL of Tyrode's buffer alone or buffer containing the desired concentration of drug were placed in a 37 °C water bath. Three additional reaction tubes were prepared containing 1000 µL of buffer. These served as spontaneous histamine release samples. Fragments of sensitized tissue were added to each tube and allowed to incubate for 10 min. Then, 10 µL of buffer containing 40 µg of anti-IgE was added to each tube, with the exception of the spontaneous release samples.

285 298

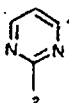
Table VI. Miscellaneous Thienylpyrimidines



substituent ^a		basophil	formula ^b	% yield	recryst solvent	mp, °C	start. mat.		
2	4								
6-1	NHPh	3-thienyl	I	C ₁₄ H ₁₁ N ₂ S	44	EtOH	142-143	comm ^c	
6-2	NHC ₆ H ₄ -4-OMe	3-thienyl	15.6 (1)	C ₁₆ H ₁₃ N ₂ OS	61	Me ₂ CO-hex.	158-160.5	comm ^c	
6-3	NHC ₆ H ₄ -4-NMe ₂	3-thienyl	2.1 ± 0.9 (2)	C ₁₆ H ₁₅ N ₄ S	33	EtOH	173-174	amine ^c	
6-4	NHC ₆ H ₄ -3-Me	3-thienyl	3.8 (1)	C ₁₅ H ₁₃ N ₂ S	27	EtOH	104.5-105.5	comm ^c	
6-5	NHC ₆ H ₄ -3-Et	3-thienyl	1.1 (1)	C ₁₇ H ₁₅ N ₂ OS·1/2H ₂ O	60	EtOH	86-89	amine ^c	
6-6	NHC ₆ H ₄ -3-OMe	3-thienyl	1.8 ± 1.2 (2)	C ₁₆ H ₁₃ N ₂ OS·1/2H ₂ O	40	EtOH	142-145	amine ^c	
6-7	NHC ₆ H ₃ -3,5-Me ₂	3-thienyl	I	C ₁₅ H ₁₃ N ₂ S	56	EtOH	140-142	amine ^c	
6-8	NHPh	3-Me-2-thienyl	I	C ₁₅ H ₁₃ N ₂ S	64	EtOH	137-140	comm ^d	
6-9	NHC ₆ H ₄ -4-NMe ₂	3-Me-2-thienyl	1.8 ± 0.5 (2)	C ₁₇ H ₁₅ N ₄ S	36	EtOH	145-148	amine ^d	
6-10	NHC ₆ H ₄ -3-OMe	3-Me-2-thienyl	>24	C ₁₆ H ₁₃ N ₂ OS	40	EtOH	120-123	amine ^d	
6-11	NHC ₆ H ₄ -3-Me	3-Me-2-thienyl	I	C ₁₆ H ₁₃ N ₂ S	56	EtOH	130-133	comm ^d	
6-12	NHC ₆ H ₄ -3-NMe ₂	3-Me-2-thienyl	I	C ₁₇ H ₁₅ N ₄ S	30	EtOH	140-142	amine ^d	
6-13	NHPh	5-Me-2-thienyl	I	C ₁₆ H ₁₃ N ₂ S	54	EtOH	144-145	comm ^e	
6-14	NHPh	5-Me-2-thienyl	Me	24.8 (1)	C ₁₆ H ₁₃ N ₂ S	34	EtOH	133-135	comm ^e
6-15	NHC ₆ H ₄ -3-OMe	5-Me-2-thienyl	2.3 ± 2.3 (2)	C ₁₆ H ₁₃ N ₂ OS	31	EtOH	149-151	amine ^e	
6-16	NHC ₆ H ₄ -3-Me	5-Me-2-thienyl	1.4 ± 0.9 (2)	C ₁₆ H ₁₃ N ₂ S·1/2H ₂ O	50	EtOH	114-116	amine ^e	
6-17	NHC ₆ H ₄ -3-NMe ₂	5-Me-2-thienyl	5.7 (1)	C ₁₇ H ₁₅ N ₄ S	33	EtOH	130-133	amine ^e	

^a See footnotes a, b, and d of Table I. ^b See footnote c of Table I. ^c Enaminone 3-(dimethylamino)-1-(3-thienyl)-2-propen-1-one. (Dusza, J. P.; Albright, J. D. Substituted Pyrazolo[1,5-a]pyrimidines and their Use as Anxiolytic Agents. US 4,281,000 1981; Chem. Abstr. 1981, 95, 187293z.) ^d Enaminone 3-(dimethylamino)-1-(3-methyl-2-thienyl)-2-propen-1-one, mp 45-49 °C, method H. ^e Enaminone 3-(dimethylamino)-1-(5-methyl-2-thienyl)-2-propen-1-one. (Dusza, J. P.; Albright, J. D. 7-Heteroaryl[1,2,4]-triazolo[1,5-a]pyrimidines. US 4,444,774 1984; Chem. Abstr. 1984, 101, 38474z.) ^f Enaminone 3-(dimethylamino)-1-(5-methyl-2-thienyl)-2-buten-1-one, mp 123-126 °C method H.

Table VII. Miscellaneous Furylpyrimidines



substituents ^a		basophil	formula ^b	% yield	recryst solvent	mp, °C	start. mat.	
2	4							
7-1	NHPh	5-Me-2-furyl	I	C ₁₅ H ₁₃ N ₂ O	60	EtOH	155-156	comm ^c
7-2	NHC ₆ H ₄ -4-NEt ₂	5-Me-2-furyl	28.0 (1)	C ₁₉ H ₂₁ N ₄ O	27	EtOH	118-119	amine ^c
7-3	NHC ₆ H ₄ -3-Me	5-Me-2-furyl	2.0 (1)	C ₁₆ H ₁₅ N ₂ O	51	EtOH	119-121	comm ^c
7-4	NHC ₆ H ₄ -3-OMe	5-Me-2-furyl	1.5 ± 0.4 (5)	C ₁₆ H ₁₅ N ₂ O ₂	24	EtOH	95-97	amine ^c
7-5	NHC ₆ H ₃ -3,5-Me ₂	5-Me-2-furyl	I	C ₁₇ H ₁₇ N ₂ O	26	EtOH	182-185	amine ^c
7-6	NHPh	2,5-Me ₂ -3-furyl	2.0 ± 0.2 (2)	C ₁₆ H ₁₃ N ₂ O	48	EtOH	116-118	comm ^d
7-7	NHC ₆ H ₄ -4-Et	2,5-Me ₂ -3-furyl	19.2 (1)	C ₁₈ H ₁₉ N ₂ O·1/2H ₂ O	26	EtOH	93-96	comm ^d
7-8	NHC ₆ H ₄ -4-NMe ₂	2,5-Me ₂ -3-furyl	4.9 ± 0.7 (2)	C ₁₈ H ₂₁ N ₄ O·1/2C ₂ H ₅ O	24	EtOH	126-129	amine ^d
7-9	NHC ₆ H ₄ -4-NEt ₂	2,5-Me ₂ -3-furyl	>24	C ₂₀ H ₂₃ N ₄ O	22	EtOH	133-134	amine ^d
7-10	NHC ₆ H ₄ -3-OMe	2,5-Me ₂ -3-furyl	5.8 ± 3.2 (2)	C ₁₇ H ₁₇ N ₂ O ₂	25	EtOH	124-125	amine ^d
7-11	NHC ₆ H ₄ -3-Me	2,5-Me ₂ -3-furyl	28.5 (1)	C ₁₇ H ₁₇ N ₂ O·1/2H ₂ O	45	EtOH	144-146	comm ^e
7-12	NHC ₆ H ₃ -3,5-Me ₂	2,5-Me ₂ -3-furyl	4.1 ± 2.5 (2)	C ₁₈ H ₁₉ N ₂ O	36	EtOH	149-152	amine ^e

^a See footnotes a, b, and d of Table I. ^b See footnote c of Table I. ^c Used enaminone 3-(dimethylamino)-1-(5-methyl-2-furyl)-2-propen-1-one, mp 126-128 °C, method H. ^d Used 38.

and allowed to incubate for 60 min. Afterward, the buffer was carefully removed from each sample and 0.2 mL of 8% HClO₄ was added to it. After centrifuging for 15 min at 2000 rpm to remove the precipitated protein, the supernatants were decanted and assayed fluorometrically for histamine content.

After removal of the incubation fluid, the lung fragments were resuspended in 2 mL of buffer and boiled for 10 min in capped tubes to release the remaining histamine. The tubes were then removed from the bath and allowed to cool, and a 1-mL aliquot of each sample was placed in a tube containing 0.2 mL of 8% HClO₄. After centrifugation at 2000 rpm for 15 min, the supernatant was decanted from the precipitated protein and analyzed for histamine¹⁴ with the full-scale response of the histamine autoanalyzer adjusted to 400 ng of histamine; the threshold sensitivity was then approximately 25 ng.

(c) Calculation of Results. Calculations were made as described for the basophil test except the percent release (R) was calculated using the total histamine release from each sample rather than a mean. This was necessary since the weight of tissue varied from sample to sample, and the total histamine was proportional to that weight. For 1-27 the IC₅₀ was 26.2 ± 19.8 μM (n = 2).

Method A. N-[4-(4-Methyl-1-piperazinyl)phenyl]-4-(2-pyridinyl)-2-pyrimidinamine (1-41). A mixture of 7.71 g (0.0250 mol) of [4-(4-methyl-1-piperazinyl)phenyl]guanidine hydrochloride,¹⁶ 4.40 g (0.0250 mol) of 3-(dimethylamino)-1-(2-pyridinyl)-2-propen-1-one,¹⁶ 6.90 g (0.050 mol) of K₂CO₃, and 125 mL of 2-methoxyethanol was stirred and refluxed gently. An air-cooled condenser was used to avoid having the dimethylammonium carbonate which evolved plug up the condenser. After 25 h of reflux, the solvent was permitted to evaporate, and the residue was triturated with aqueous K₂CO₃ and collected to give, on air-drying, 4.51 g of a black solid, mp 190-191 °C. The product was dissolved in 300 mL of hot EtOH and filtered through a pad of hydrous magnesium silicate, and the filtrate was boiled down to 200 mL. Cooling gave 3.76 g (43%) of yellow crystalline 1-41: mp 192-193 °C; MS (M+) 346; ¹H NMR (DMSO-d₆) δ 9.55 (s, 1H, 2-NH), 8.82 (d, 1H, J = 4.5, 6'-H), 8.65 (d, 1H, J = 6, 6-H), 8.45 (d, 1H, J = 8.5, 3'-H), 8.11 (m, 1H, 4'-H), 7.72 (d, 1H, J = 6, 5-H), 7.65 (d, 1H, J = 8.5, J = 4.5, 5'-H), 7.00 (d, 2H, J = 8.5, ArH), 7.75 (d, 2H, J = 8.5, ArH), 3.15 (m, 4H, 2(N-CH₂)), 2.55 (m, 4H, 2(N-CH₂)) 2.30 (s, 3H, CH₃). Anal. C, H, N.

Method B. N-[4-(2-Pyridinyl)-2-pyrimidinyl]-1,4-benzenediamine Dihydrochloride (1-9). After refluxing of a

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Table VIII. Miscellaneous 4-Heterocyclic Pyrimidines



substituent ^a		basophil	formula ^b	% yield	recryst solvent	mp, °C	start. mat.	eneaminone
2	4							
8-1	NHC ₆ H ₄ -4-Et	2-pyrazinyl	1.9 ± 0.9 (3)	C ₁₆ H ₁₄ N ₆	55	Me ₂ CO-hex.	157.5-159	comm
8-2	NHC ₆ H ₄ -3-OMe	2-benzofuranyl	2.8 ± 1.1 (4)	C ₁₉ H ₁₆ N ₂ O ₂	51	MeOCH ₂ CH ₂ OH	132-134	amine
8-3	NHC ₆ H ₄ -4-Et	4-phenothiazinyl	I	C ₂₄ H ₂₀ N ₄ S	29	EtOH	154-164	comm
8-4	NHPh	3-indolyl	3.0 (1)	C ₁₈ H ₁₄ N ₄	64	EtOH	188-190	comm
8-5	NHC ₆ H ₄ -3-Me	2-pyrrolyl	8.5 ± 2.6 (2)	C ₁₅ H ₁₁ N ₄	40	EtOH	128.5-130	comm
8-6	NHPh	1-Me-2-pyrrolyl	I	C ₁₅ H ₁₁ N ₄	63	EtOH	118-120	comm
8-7	NHC ₆ H ₄ -3-Me	3-indolyl	2.2 (1)	C ₁₉ H ₁₆ N ₄	52	EtOH	164-167	comm
8-8	NHC ₆ H ₄ -4-Et	4-quinolyl	4.0 (1)	C ₂₁ H ₁₈ N ₄	55	EtOH	176-178	comm
8-9	NHC ₆ H ₄ -4-OMe	1-Me-4-pyridinium	33.3 ± 18 (3)	C ₁₇ H ₁₇ N ₄ O	73	EtOH	282-284	3-20

^a See footnotes a, b, and d of Table I. ^b See footnote c of Table I. ^c 3-(Dimethylamino)-1-(2-pyrazinyl)-2-propen-1-one, mp 132-133 °C, method H. ^d 1-(2-Benzofuranyl)-3-(dimethylamino)-2-propen-1-one, mp 137-138.5 °C, method H. ^e 3-(Dimethylamino)-1-(2-phenothiazinyl)-2-propen-1-one, mp 240-246 °C, method H. ^f 3-(Dimethylamino)-1-(3-indolyl)-2-propen-1-one, mp 237-239 °C, method H. ^g 3-(Dimethylamino)-1-(1H-pyrrol-2-yl)-2-propen-1-one, mp 192-193 °C, method H. ^h 3-(Dimethylamino)-1-(1-methyl-1H-pyrrol-2-yl)-2-propen-1-one, mp 92.5-94.5 °C, method H. ⁱ 3-(Dimethylamino)-1-(4-quinolyl)-2-propen-1-one, used crude, method H. ^j Method G.

mixture of 12.86 g (0.0421 mol) of *N*-[4-[[4-(2-pyridinyl)-2-pyrimidinyl]amino]phenyl]acetamide (1-8) and 80 mL of 6 N HCl for 30 min, the solution was cooled. A solid was collected which was recrystallized from EtOH-H₂O to give 10.84 g (77%) of 1-9, mp 285-288 °C. Anal. C, H, N, Cl.

Method C. 4-[[4-(3-Pyridinyl)-2-pyrimidinyl]amino]phenol (2-17). *N*-(4-Methoxyphenyl)-4-(3-pyridinyl)-2-pyrimidinamine (2-15) (25.0 g, 0.0899 mol) was dissolved in 60 mL of 48% HBr and refluxed 7 h. After concentrating under vacuum, the residue was dissolved in 2.5 mL of H₂O and the pH adjusted to 9 with saturated aqueous KHCO₃. The resulting solid was collected, washed with H₂O and Et₂O, and then dried. Recrystallization from EtOH gave 19.1 g (80%) of yellow crystals, mp 223-225 °C. A small amount was recrystallized from CHCl₃-EtOAc (filtered through a hydrous magnesium silicate pad) for analysis, mp 221-223 °C. Anal. C, H, N.

Method D. *N*-[4-(2-(Dimethylamino)ethoxy)phenyl]-4-(3-pyridinyl)-2-pyrimidinamine (2-18). After drying of 1.10 g (4.03 mmol) of 4-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]phenol (2-17) in a vacuum oven at 50 °C overnight, the phenol was dissolved in 25 mL of DMF, and 213 mg (4.43 mmol) of 50% NaH in oil was added. The mixture was stirred at room temperature, protected from moisture, until all the hydride had reacted (45 min). 2-(Dimethylamino)ethyl chloride hydrochloride (ca. 2 g) was partitioned between 1 N NaOH and Et₂O. Upon drying of the organic extract (MgSO₄), it was concentrated in a rotary evaporator (60 °C/13 mm) to approximately 600 mg of free amine, of which 480 mg (4.43 mmol) was added to the reaction mixture. Stirring was continued overnight, whereupon the solvent was removed at 60 °C under vacuum. The residual brown gum was partitioned between EtOAc and brine. After two more extractions of the aqueous phase with EtOAc, the extracts were combined and washed with 1 N NaOH. The organic phase was dried (MgSO₄) and concentrated under vacuum, producing 900 mg of gum. This gum crystallized from CHCl₃-hexane to give 400 mg of 2-18 as beige crystals, mp 108-110 °C. A second crop of 100 mg (37%), mp 107-109 °C, was obtained upon partial evaporation of the mother liquors. Anal. C, H, N.

Method E. Oxo[phenyl[4-(4-pyridinyl)-2-pyrimidinyl]amino]acetic Acid Ethyl Ester (3-2). To a 4.08 g (0.0164 mol) portion of 2-anilino-4-(4-pyridinyl)pyrimidine (3-1) dissolved in 20 mL of 3A-sieve-dried DMF was added 0.80 g (0.0167 mol) of 50% NaH/oil with stirring, with 10 mL of DMF used as a wash. After the deep red mixture ceased effervescing, a solution of 2.23 mL (2.73 g, 0.0200 mol) of ethyl oxalyl chloride in 10 mL of DMF was cautiously added dropwise. The reaction was stirred overnight and then concentrated under vacuum. The residue was distributed between CHCl₃ and aqueous KHCO₃, and the organic layer was separated and passed through a pad of hydrous magnesium silicate. After evaporation to dryness, the residue was recrystallized four times from EtOH to give 1.98 g of off-white, crystalline 3-2: mp 139-140 °C; yield 35%. Anal. C, N,

Method F. *N*-(4-Methoxyphenyl)-*N*-methyl-4-(4-pyridinyl)-2-pyrimidinamine (3-21). To a solution of 2.78 g (10.0 mmol) of 2-(4-methoxyphenyl)-4-(4-pyridinyl)pyrimidine (3-20) in 30 mL of DMF was added 0.528 g (11.0 mmol) of 50% NaH/oil under anhydrous conditions. After the effervescence had subsided (45 min), 1.70 g (12.0 mmol) of iodomethane was added and the reaction stirred at ambient temperature overnight. The solvent was removed under vacuum and the residue partitioned between CHCl₃ and H₂O. After separation of the organic phase, it was dried (MgSO₄), filtered through a pad of silica gel, and evaporated to 1.3 g of crude product. Recrystallization from Et₂O-hexane gave 0.51 g (32%) of product 3-21 as yellow crystals, mp 119-121 °C.

Method G. 4-[2-[(4-Methoxyphenyl)amino]-4-pyrimidinyl]-1-methylpyridinium Iodide (8-9).

A solution of 2.0 g (7.2 mmol) of 2-(4-methoxyphenyl)-4-(4-pyridinyl)pyrimidine (3-20) in 550 mL of EtOH and 10 mL of iodomethane was refluxed for 4 h. An additional 10 mL of iodomethane was added and the solution refluxed overnight. On standing at room temperature for several hours, product crystallized out which was collected and washed with EtOH to give 2.2 g (73%) of purple crystals: mp 282-284 °C; MS (M⁺) 278 (-CH₃I); if the amino nitrogen had been alkylated, M⁺ of 292 would have been found. Anal. C, H, N, I.

Method H. 3-(Dimethylamino)-1-(2,5-dimethyl-3-furanyl)-2-propen-1-one (38). 3-Acetyl-2,5-dimethylfuran (6.91 g, 0.0500 mol) and 15 mL of dimethylformamide dimethyl acetal were heated on a steam bath in an open flask, for 30 h. The residue was dissolved in CH₂Cl₂ and passed through a pad of hydrous magnesium silicate. After dilution of the filtrate with hexane, it was evaporated to about 25 mL. Cooling gave crystals which were recrystallized from heptane to give 5.09 g (53%) of enaminone 38, mp 91-95 °C. Anal. C, H, N.

Method I. [4-(1*H*-imidazol-1-yl)phenyl]guanidine Dihydrochloride (39). To 1.59 g (0.0100 mol) of 4-(1*H*-imidazol-1-yl)benzenamine¹⁷ (40) was added 2.5 mL of 10 N HCl, giving a new solid, and then 1.05 g (0.025 mol) of cyanamide was added followed by 1 mL of H₂O. Upon warming on a steam bath, a solution formed which, on further heating, bubbled vigorously. After 15 min, the solution was cooled to room temperature and 2.5 mL of concentrated HCl was added. Cooling to -10 °C for several days gave a precipitate which was collected and washed with ice-cold EtOH and then Et₂O, leaving 2.33 g of pinkish crystals, mp 318-328 °C dec. The guanidine was boiled with 25 mL of EtOH and the insoluble (while hot) solid collected to give 2.28 g (83%) of 39 as a 2.1HCl-0.125Et₂O salt: mp 318-324 °C; ¹H NMR (H₂O-d₆) δ 9.23 (s, 1H, 2-Im-H), 7.93 (s, 1H, 1m-H), 7.78 (d, 2H, J = 8.7, Ar-H), 7.68 (s, 1H, 1m-H), 7.59 (d, 2H, J = 8.7, Ar-H). Anal. C, H, N.

Method J. 1-(3-Nitrophenyl)-1*H*-imidazole (41). A mixture of 289.0 g (4.25 mol) of imidazole, 292 g (2.12 mol) of K₂CO₃, 3 L of DMSO, and 300.0 g (2.12 mol) of 1-fluoro-3-nitrobenzene

reaction was poured into 6 L of water and cooled in the refrigerator over the weekend. After collecting the crystalline product, it was washed with 1 L of water and air-dried to give 15.6 g of solid, mp 107.5–109.5 °C. Next the solid was taken up in 2.4 L of EtOAc and the hot solution passed through a pad of hydrous magnesium silicate. Boiling the filtrate down to 1.5 L and cooling gave a precipitate which was collected and washed with 200 mL of EtOAc, to leave 151.7 g of off-white crystals, mp 107.5 °C. Evaporation of the mother liquors and recrystallization from EtOAc gave a second crop (59.7 g), mp 107–108.5 °C. Concentration again of the mother liquors followed by two recrystallizations from EtOAc gave a third crop (30.9 g), mp 108.5–110 °C; total yield = 60%. ¹H-NMR (CDCl₃) δ 8.29 (m, 2H, Ar-H), 7.96 (s, 1H, Im-H), 7.71 (m, 2H, Ar-H), 7.38 (s, 1H, Im-H), 7.15 (s, 1H, Im-H). Anal. C, H, Cl, N.

Method K. 1-[2-(3-Nitrophenoxy)ethyl]-1H-imidazole (42). To 40.64 g (0.597 mol) of imidazole in 300 mL of DMF was added 19.2 g (0.400 mol) of 1:1 NaH/oil. When the effervescence subsided, 79.95 g (0.3965 mol) of 3-(2-chloroethoxy)benzenesulfonate was added to the gray solution. After 0.5 h, the reaction turned dark orange-brown. Upon standing over the weekend, the reaction was washed with hexane to remove the immiscible oil. The reaction was then concentrated under vacuum. Water was added to the residue and the product extracted into CHCl₃. The organic extract was back-washed with water and then concentrated under vacuum. Next, the residue was taken up in 200 mL of water and 100 mL of concentrated HCl and then washed (3X) with CHCl₃. The aqueous layer was slowly dripped onto solid K₂CO₃. More water was added, and the product was extracted into CHCl₃. After drying (Na₂SO₄), the solution was concentrated in vacuum to an oil, which slowly solidified. The residue was boiled with CCl₄ and then triturated with 2-propyl acetate. Recrystallization from 2-propyl acetate followed through hydrous magnesium silicate gave 30.80 g of product (42), mp 51.5–56 °C. Concentration of the mother liquors gave two additional crops (25.76 g, mp 47–52 °C; 23.39 g, 80%, mp 52–54 °C). Anal. C, H, N.

Method L. 3-(1H-Imidazol-1-yl)benzenamine (43). In a Parr hydrogenation bottle was placed 75.00 g of 1-(3-nitrophenyl)-1H-imidazole, 10.70 g of PtO₂, and 250 mL of EtOH. The mixture was shaken in a Parr hydrogenation apparatus until no more hydrogen was taken up. This process was repeated until 241.63 g (1.2778 mol) of nitro compound had been reduced. For each batch, the catalyst was filtered off and the solvent removed under vacuum. The residues were combined to give 207.2 g of gray crystalline amine, mp 108.5–111 °C. Recrystallization of the amine from 530 mL of 2-PrOH gave 156.4 g of off-white crystals, mp 111–113 °C. Two recrystallizations of the mother liquor residues from 2-PrOH gave an additional 32.6 g (96%) of 43: ¹H-NMR (DMSO-*d*₆) δ 8.06 (s, 1H, Im-H), 7.55 (s, 1H, Im-H), 6.72 (m, 2H, Ar-H), 6.57 (m, 2H, Ar-H), 6.54 (d, 1H, Im-H), 5.39 (s, 2H, NH₂). Anal. C, H, N.

Method M. 1-[(4-Aminophenoxy)acetyl]-4-methylpiperazine (44). After preparation of a solution of 10.88 g (0.039 mol) of 1-methyl-4-[(4-nitrophenoxy)acetyl]piperazine²⁰ (12–8) in 160 mL of MeOH, 10.61 g (0.150 mol) of HCO₂Na and 6.90 mL (8.42 g, 0.156 mol) of 96% HCO₂H were added to it.¹¹ Next 0.827 g (7.80 mmol) of Pd black was added with stirring. The reaction mixture began to effervesce vigorously and it was cooled in a water bath. Stirring was continued for 2 h. After filtration of the reaction mixture, the filtrate was evaporated and the residual pink gum partitioned between CHCl₃ and saturated aqueous KHCO₃. The organic phase was separated, dried (MgSO₄), and passed through a pad of hydrous magnesium silicate. Evaporation gave 8.40 g (86%) of pink crystals, mp 80–82 °C, which gave one spot on TLC. Anal. C, H, N.

Acknowledgment. We thank Dr. J. James and his group for the microanalyses and Dr. J. M. Baldoni and his staff for the spectra. We also thank Mr. G. Morton for the ¹H-NMR interpretations.

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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 05-001801 - 00011-0000

Fecha: 2009-02-09 15:52:31 Dep. 2020 NUECREACIONI
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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISION DE NUEVAS CREACIONES
E. S. D.

Re: Expediente No. **05-001.801**
Solicitud de patente a nombre de **NOVARTIS AG.**

Yo, JIMENA ESCOBAR URIBE, identificada como aparece al pie de mi firma, domiciliada en la carrera 11 A No. 86-53, piso 6, obrando como apoderada de la sociedad **NOVARTIS AG**, domiciliada en Basilea Suiza solicitante de la patente de la referencia, en respuesta al oficio No. 14537 notificado por fijación en lista el 14 de noviembre de 2008, relacionado con el concepto técnico de fondo No. 2656, me permito informar lo siguiente:

1. Con fundamento en la facultad que confiere el artículo 34 de la Decisión 486 al solicitante para modificar la solicitud de patente en cualquier momento del trámite, presento junto con este memorial nuevo pliego reivindicatorio que consta de 9 reivindicaciones, en donde se realizaron las siguientes modificaciones:

1.1 Se canceló la antigua reivindicación 9 que hacía mención al proceso para la síntesis de compuestos de la fórmula (I).

1.2 De otra parte, se reemplazó el término "linear" por la expresión correcta "lineal" en la página 136 y se cambió la expresión "N-alquiler inferior" por la expresión correcta "N-alquiler inferior" dentro del juego de reivindicaciones presentadas con mi memorial del 25 de junio de 2007.

Sobre este particular me permito decir que las modificaciones anteriores no involucran ampliación alguna de la materia originalmente presentada en la solicitud y se proporcionan con el ánimo de superar las objeciones de claridad y novedad señaladas por el examinador.

Para este efecto, me permito acompañar el recibo No 09-2,762; 09-2,862; 09-2,720 del 13 de enero de 2009, con los cuales, queda cubierta la tasa correspondiente a la modificación de una solicitud de patente.

2. Claridad

Respecto a la objeción plantada por el examinador, me permito decir que con las correcciones anteriormente expuestas queda superada cualquier posible carencia de claridad del nuevo juego de reivindicaciones.

3. Novedad

En cuanto a este requisito, atentamente me permito decir que es deseo del solicitante desistir de la antigua reivindicación 9, con lo cual se subsana la novedad de la solicitud en estudio.

4. Nivel Inventivo

Sobre este particular, me permito citar el artículo 18 de la Decisión 486 donde se pone de manifiesto que: *"Se considerará que una invención tiene nivel inventivo, si para una persona del oficio normalmente versada en la materia técnica correspondiente, esa invención no hubiese resultado obvia ni se hubiese derivado de manera evidente del estado de la técnica."*(El subrayado es nuestro).

La norma anteriormente citada, lo que quiere indicar es que el nivel inventivo radica en que no resulte obvia para una persona medianamente versada en la materia y que la invención no se derive de manera evidente del estado de la técnica. Resulta entonces claro que lo que exige el legislador es la demostración de la obviedad o que se deriva de manera evidente del estado de la técnica, imponiéndose el deber en cabeza de la administración para que se evidencien estos dos hechos.

En ningún momento es acertado concluir que la presente invención no tiene un efecto técnico inesperado partiendo de una comparación entre el estado del arte citado y la invención en estudio, porque entonces estaríamos ante un escenario de un estudio de novedad, el cual sí está basado en semejanzas y diferencias. Es más, no resulta acertado manifestar que la única diferencia entre la invención en estudio y el documento D1 esté en la presencia de un radical -C(O)-NR1R2 para el sustituyente R2 en los compuestos de fórmula (I) de la solicitud en estudio.

Al respecto, me permito recordarle al señor examinador los presupuestos y reglas de valoración del nivel inventivo. El requisito de nivel inventivo comprende varios aspectos que deben ser considerados al momento de realizar dicho examen sobre una invención. En efecto, es necesario enfatizar que dicho análisis le corresponderá realizarlo a una persona versada en la materia que se presume es *"una persona con formación técnica, que ha hecho un aprendizaje o estudios en el dominio general al que se refiere la invención"*¹.

También es menester recordar que la persona versada en la materia, quien es la encargada de realizar el examen de nivel inventivo, ha de desvirtuar la falta del mismo,

¹ "GUIA PARA LOS PAISES EN DESARROLLO SOBRE EL EXAMEN DE LAS SOLICITUDES DE PATENTES". Organización Mundial de Propiedad Intelectual, Ginebra, 1982., página 40.

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ya que la carga de la prueba de demostrar el no cumplimiento de este requisito por parte de la invención en estudio corresponde a dicha persona. Para tal fin, ella determinará *“cuál era el estado de la técnica en la fecha de presentación o de prioridad, citando los hechos y los medios de prueba que lo respalden (documentos, testimonios, etc); debe, además, mostrar lo que para la persona del oficio deriva de manera evidente de ese estado de la técnica, y por qué razones.”*²

Adicionalmente, esta persona versada en la materia, al analizar las pruebas que eventualmente desvirtúan el nivel inventivo, confrontará dichas anterioridades con la invención en estudio de tal forma que encuentre las características que distinguen la invención frente a lo que era conocido en la anterioridad más cercana, en este caso D1. De esta forma, *“es entonces (y sólo entonces) cuando se debe examinar también si, en el contexto general de la reivindicación que se examina, las diferencias son sólo variantes u otras modificaciones evidentes para la persona del oficio que procura innovaciones o, por el contrario, presentan la necesaria originalidad”*.³

Sobre este particular, respetuosamente manifiesto que la Superintendencia de Industria y Comercio ignoró esta regla, puesto que aunque hizo una comparación, basó su examen de nivel inventivo únicamente en la diferencia antes mencionada sin prestar mayor atención a otras diferencias relevantes entre los compuestos reivindicados y la anterioridad D1, que no habrían sido evidentes para una persona medianamente versada en la técnica.

En este sentido, me permito señalar que los compuestos de la invención en estudio son estructuralmente diferentes de los mostrados en la anterioridad D1 en al menos cuatro características que no habrían sido evidentes a partir de D1, las cuales son:

- (1) La característica de tener una parte fenólica sustituida anexa al grupo aminocarbonilo en los compuestos reclamados de fórmula (I), es decir, la definición de R2 de la solicitud en estudio que no es enseñada ni sugerida por D1.
- (2) La característica de una parte 3-piridil en los compuestos reclamados;
- (3) La característica de la parte carbonilamino unida al grupo fenilo central en los compuestos de fórmula (I) de la invención en estudio;
- (4) La característica de un grupo halógeno o alquilo unido al grupo fenilo central en los compuestos reclamados.

Sobre este particular, cabe señalar que si bien el documento D1 dentro de sus muchas posibilidades para los radicales R3 y R5 a R8, enseñan de manera general, sustituyentes para estas posiciones, también es cierto que la combinación de la primera característica novedosa antes señalada y las otras 3 características específicas, no habría podido ser derivada de manera evidente por una persona normalmente versada en la técnica a

² Ob cit, pág 40.

³ Ibídem.

partir de lo mencionado en D1, toda vez que al hacer una estimación del total de posibles combinaciones de las sustituciones sugeridas para los distintos radiales de D1, habrían unas 38.400 posibilidades de combinar dichas sustituciones.

Esto a todas luces, demuestra que las cuatro características diferenciadoras mostradas en los compuestos de la presente invención, no habrían podido ser alcanzadas de manera evidente por una persona de conocimientos promedio en la técnica a partir de un universo de sustituciones tan vasto, como el mostrado en D1.

Sobre este particular, es necesario señalar que ese despacho ha debido preguntarse: si estaba una persona del oficio de nivel medio en condiciones de plantearse el problema, de resolverlo (en la forma que se reivindica) y de prever el resultado?. Es evidente que el examinador en este caso no se planteó dichos interrogantes ya que su análisis de nivel inventivo se limitó a afirmar, sin sustento alguno, la obviedad de esta invención a partir del hallazgo de una sola diferencia entre los compuestos reclamados y aquellos mostrados por D1, dejando de lado características como las mostradas anteriormente y sin considerar que el documento D1 no brinda sugerencia o indicio de alguna forma similar de solucionar el problema resuelto por la presente invención.

En efecto, es posible que una persona medianamente versada en la técnica lograra identificar la necesidad de compuestos alternativos de la fórmula (I) que fueran útiles en la inhibición de la proteína quinasa en la enfermedad de la leucemia. Sin embargo, dicha persona no habría encontrado ninguna sugerencia o motivación en el documento D1 para solucionar dicho problema, ya que dicha anterioridad no hace referencia alguna a que variaciones específicas en los compuestos allí planteados, podrían inhibir la actividad de proteínas tan determinadas como c-Abl quinasa y KDR. De hecho, D1 se encuentra más enfocado a describir inhibidores de PKC. Es más, se proporciona en la página 6 de dicho documento una tabla de pruebas para el tratamiento de carcinoma de vejiga.

En este orden de ideas, nada de lo revelado en D1 podría conducir de manera evidente a una persona medianamente versada en la técnica a los compuestos de la invención en estudio, pues ni la manera de resolver el problema técnico ni los resultados obtenidos en la presente invención habrían podido ser derivados de manera evidente a partir de un documento como D1 que se encuentra dirigido a solucionar otro problema como es el de proporcionar compuestos para tratamientos de carcinoma de vejiga.

De lo anterior, se concluye que la presente invención sí tiene altura inventiva, ya que la respuesta es negativa para dos de los tres interrogantes, en el presente caso y según la "Guía para los Países en Desarrollo sobre el Examen de las Solicitudes de Patentes" de la OMPI de 1982, basta con que una de las tres respuestas sea negativa para que exista la actividad inventiva.

De otra parte, el examinador en el folio 262 señala que: "no se observa algún efecto sorprendente o superioridad con respecto a lo conocido pues los resultados presentados son pocos con

respecto a todo lo que la descripción insinúa haber ensayado y además no se presentan resultados que evidencien las ventajas o el salto tecnológico de los compuestos con respecto al estado de la técnica y/o una mejora comparativa en los niveles de actividad"

Con relación a estos argumentos, me permito decir que los novedosos compuestos de la solicitud en estudio muestran efectos sorprendentes, toda vez que gracias a las modificaciones planteadas en la estructura de la fórmula (I), el solicitante logra compuestos con doble actividad, es decir, con actividad de inhibición para las proteínas Abl quinasa y KDR, actividades totalmente diferentes y no sugeridas por D1 y que se encuentran en porcentajes bastante notorios, como los mostrados en las páginas 132 a 134 de la memoria descriptiva para compuestos representativos de la solicitud.

En procura de afianzar aún más el nivel inventivo de la invención y lo inesperado de las actividades reportadas por los compuestos de la invención, es deseo del solicitante poner en conocimiento de ese despacho un artículo científico divulgado en "Cancer Research", publicado en junio de 2005, esto es, varios años después de la presentación de la solicitud en estudio, en el cual se documenta de manera adicional que el compuesto del Ejemplo '92 que corresponde a 4-metil-3-[[4-(3-piridinil)-2-pirimidinil] amino]-N-[5-(4-metil-1H-imidazol-1-il)-3-(trifluorometil) fenil]benzamida (denominado AMN107) presenta una gran capacidad para tratar la LMC (Leucemia Mielógena Crónica).

Finalmente, en cuanto a la afirmación que los resultados "son pocos" en comparación a lo mencionado en la descripción, respetuosamente me permito decir que esta afirmación resulta ambigua y carente de sustento en la normativa andina, pues los resultados proporcionados en la memoria descriptiva son ejemplos de la mejor forma conocida por el solicitante para llevar a cabo la invención, como así se exigen en el artículo 28 de la Decisión 486. Adicionalmente, en ninguna parte de dicha Decisión se establece cuando los ejemplos proporcionados por el solicitante, deban ser considerados como "pocos". En consecuencia, respetuosamente se solicita a ese despacho retirar esta objeción que no resulta procedente a la luz de la Decisión 486.

En relación con lo anterior y en cuanto a la objeción que indica que tampoco "*se presentan resultados que evidencien las ventajas o el salto tecnológico de los compuestos con respecto al estado de la técnica y/o una mejora comparativa en los niveles de actividad.*", atentamente me permito decir que teniendo en cuenta que los compuestos revelados en D1 muestran una actividad totalmente diferente a los compuestos reclamados en la solicitud en estudio y que además dicha anterioridad no sugiere modificaciones que pudieran llevar a las actividades mostradas por la invención en estudio, resulta claro que para el solicitante y para cualquier persona versada en la materia, previo a la presentación de esta solicitud, no resultaba relevante llevar a cabo experimentos comparativos con la técnica anterior citada, pues no existe indicio alguno en D1 que sugiriera que los compuestos allí reportados pudieran mostrar actividad diferente a la inhibición de la PKC. Así las cosas, también resulta improcedente requerir esta clase de pruebas

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adicionales que, entre otras cosas, tampoco se encuentran consideradas como obligatorias a la luz de la Decisión 486.

En consecuencia, me permito manifestar que la presente invención cumple cabalmente con los requisitos de patentabilidad, especialmente con el requerimiento de nivel inventivo sobre las enseñanzas del documento D1. Por tanto, solicito de manera atenta se tengan en cuenta los argumentos y la información suministrada por el solicitante y se otorgue el privilegio de patente de invención a la solicitud en estudio.

En consecuencia, solicitamos a ese despacho pronunciarse en relación con todos los argumentos presentados en este memorial dando estricta aplicación al principio del debido proceso consagrado en el artículo 29 de la Constitución Nacional. De igual forma, si el examinador considera que subsisten razones para objetar la presente invención ruego expedir otro examen de fondo con los debidos motivos y razones que sustenten su objeción con el fin de que mi mandante tenga la posibilidad de exponer sus argumentos con base en la interpretación de los artículos 45 de la Decisión 486 -el cual otorga la facultad al examinador para emitir los exámenes de fondo-, 35 y 59 del Código Contencioso Administrativo que señala que: *"habiéndose dado oportunidad a los interesados para expresar sus opiniones, y con base en las pruebas e informes disponibles, se tomará la decisión que será motivada al menos en forma sumaria si afecta a particulares"* y *"(..) deberá proferirse la decisión definitiva. Esta se motivará en sus aspectos de hecho y de derecho, y en los de conveniencia si es el caso"*, respectivamente (el subrayado es nuestro).

Señor Superintendente,


JIMENA ESCOBAR URIBE

C.C.39.779.452 de Usaquén

T.P. 68228

Cód. 5376

In vitro Activity of Bcr-Abl Inhibitors AMN107 and BMS-354825 against Clinically Relevant Imatinib-Resistant Abl Kinase Domain Mutants

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Abstract

Imatinib, a Bcr-Abl tyrosine kinase inhibitor, is a highly effective therapy for patients with chronic myelogenous leukemia (CML). Despite durable responses in most chronic phase patients, relapses have been observed and are much more prevalent in patients with advanced disease. The most common mechanism of acquired imatinib resistance has been traced to Bcr-Abl kinase domain mutations with decreased imatinib sensitivity. Thus, alternate Bcr-Abl kinase inhibitors that have activity against imatinib-resistant mutants would be useful for patients who relapse on imatinib therapy. Two such Bcr-Abl inhibitors are currently being evaluated in clinical trials: the improved potency, selective Abl inhibitor AMN107 and the highly potent dual Src/Abl inhibitor BMS-354825. In the current article, we compared imatinib, AMN107, and BMS-354825 in cellular and biochemical assays against a panel of 16 kinase domain mutants representing >90% of clinical isolates. We report that AMN107 and BMS-354825 are 20-fold and 325-fold more potent than imatinib against cells expressing wild-type Bcr-Abl and that similar improvements are maintained for all imatinib-resistant mutants tested, with the exception of T315I. Thus, both inhibitors hold promise for treating imatinib-refractory CML. (Cancer Res 2005; 65(11): 4500-5)

Introduction

Imatinib (STI571, Gleevec), an Abl kinase inhibitor, is now the first line treatment for patients with chronic myelogenous leukemia (CML; ref. 1). Its success is predicated on the efficient inhibition of the deregulated, oncogenic tyrosine kinase Bcr-Abl, which plays a critical role in the pathogenesis of CML (2, 3). Most newly diagnosed CML patients with chronic phase disease treated with imatinib achieve durable responses (4); however, a small percentage of these patients and most advanced-phase patients relapse on imatinib therapy (4-6).

In patients who relapse on imatinib therapy, the Bcr-Abl kinase is reactivated, emphasizing the importance of the kinase activity of this protein to disease pathogenesis. The most common mechanism of resistance, occurring in 60% to 90% of patients who acquire

imatinib resistance, involves specific mutations in the kinase domain of Bcr-Abl that interfere with imatinib binding without eliminating ATP binding or kinase activity (reviewed in refs. 7, 8). Clinically observed mutations identified within the Bcr-Abl kinase domain span a range of residual imatinib sensitivities (IC₅₀: 900-4,400 nmol/L) and encompass several functionally distinct kinase domain regions, including the nucleotide binding P-loop, imatinib contact residues, and the activation loop (7, 9, 10).

An understanding of the mechanism of imatinib resistance has prompted the search for alternate Bcr-Abl inhibitors that are effective against clinically observed Bcr-Abl mutants. Two promising new Bcr-Abl inhibitors for treating imatinib-resistant CML are currently being evaluated in clinical trials: the selective Abl inhibitor AMN107 and the dual Src/Abl inhibitor BMS-354825 (Fig. 1A, top). AMN107 was developed by rational drug design based on the crystal structure of an Abl-imatinib complex, whereas BMS-354825 is a Src inhibitor that was found to exhibit Abl inhibitory properties.

The crystal structure of the Abl kinase domain in complex with imatinib indicates that few changes to the imatinib scaffold are likely to be tolerated (7, 11). Imatinib binds to the canonical ATP site lining the groove between the N and C lobes of the protein. The drug penetrates into the central cleft of the kinase and the high topological congruency between the aniline-pyrimidine substructure and the surface of the distorted ATP-binding pocket suggest that making changes within this region of imatinib might not be very productive. However, the methylpiperazinyl group of imatinib (Fig. 1A, top) lies along a surface-exposed pocket of the Abl kinase and is potentially more amenable to modification. Replacement of this heterocycle and further rational design to optimize drug-like properties led to the discovery of AMN107 (Novartis Pharmaceuticals, Basel, Switzerland; Fig. 1A), which, as predicted, possesses substantially increased binding affinity and selectivity for the Abl kinase compared with imatinib (12).

Another approach to counteract imatinib resistance is to use inhibitors that bind Bcr-Abl with less stringent conformational requirements than imatinib. Imatinib selectively targets an inactive conformation of the Abl kinase domain in which the activation loop is in a nonphosphorylated, closed position that is incompatible with substrate binding (13). Specific differences between the inactive conformations of Abl and Src provide a structural basis for the initially surprising finding that Src family kinases are not imatinib targets, despite a high degree of sequence homology (11). The Abl and Src active conformations are more similar and many inhibitors that bind to the active conformation of Src are also capable of inhibiting Abl (11). BMS-354825 is a dual Src-Abl kinase

Note: Supplementary data for this article are available at Cancer Research Online (<http://cancerres.aacrjournals.org/>).

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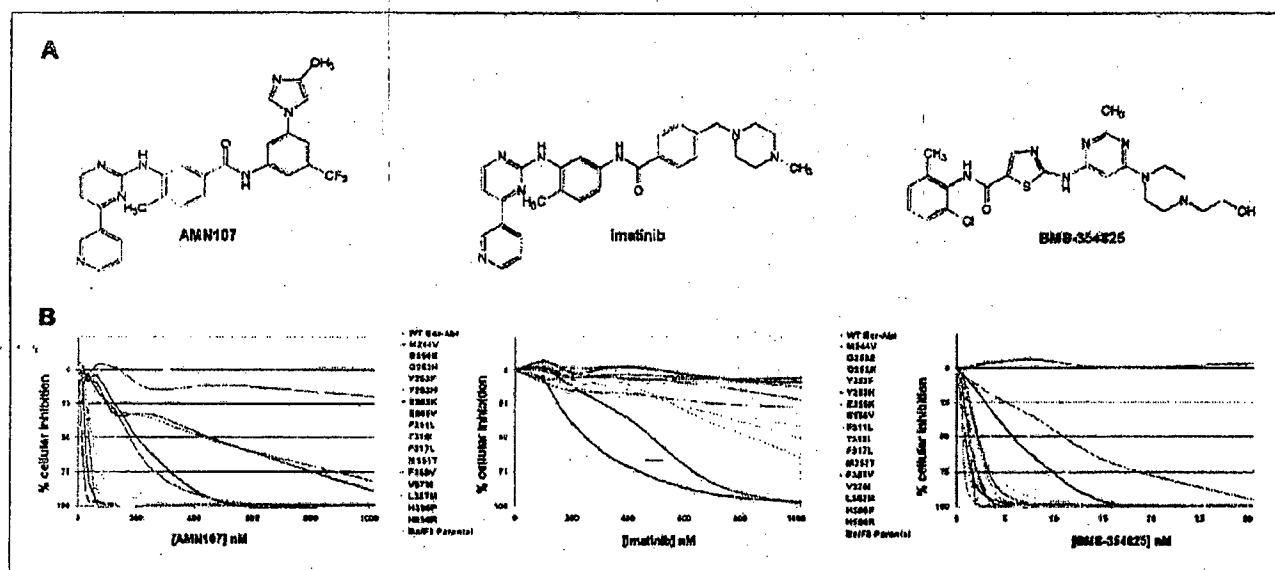


Figure 1. AMN107 and BMS-354825 are more effective than imatinib in inhibiting proliferation of Ba/F3 cells expressing wild-type Bcr-Abl or all Bcr-Abl mutants except T315I. **A**, structures of AMN107, imatinib, and BMS-354825. **B**, Ba/F3 cells supplemented with IL-3 or Ba/F3 cells expressing wild-type or mutant Bcr-Abl protein were plated in quadruplicate at 5×10^3 cells/well in 96-well plates with escalating concentrations of imatinib (0–2,000 nmol/L), AMN107 (0–2,000 nmol/L), or BMS-354825 (0–32 nmol/L) included in the media. Results from day 3 methanethiosulfonate assays were used to construct best-fit curves and calculate the cellular IC_{50} and IC_{90} values. For imatinib, only the IC_{50} value is reported. The mean based on four replicates was calculated in the absence of inhibitor and for each concentration of inhibitor. Means $\pm$ SE were generated from three independent experiments and reported as the percentage inhibition of cellular proliferation relative to control. Error bars are omitted for clarity. Note that the scale of the abscissa for the BMS-354825 cellular proliferation graph differs from that of imatinib and AMN107.

inhibitor that inhibits all tested Bcr-Abl kinase domain mutants observed in relapsed patients with the exception of T315I. The drug was also highly effective in a mouse model of imatinib-resistant, Bcr-Abl-dependent disease (14).

Although some data regarding the ability of AMN107 to inhibit various imatinib-resistant mutants is available, a number of the common mutants have not been included in the published data. Further, given differences in cell lines used, variations in levels of Bcr-Abl expression, and differing assay conditions, a direct comparison of AMN107 and BMS-354825 based on published results is not possible. Given that both of these drugs are in clinical trials, knowledge of the relative sensitivity of a particular mutant could assist in determining which drug would be more appropriate for a particular patient. Therefore, in this report, we present a complete profile of AMN107 against imatinib-resistant mutants and a direct cellular and biochemical comparison between imatinib, AMN107, and BMS-354825.

Materials and Methods

Reagents. BMS-354825 (*N*-(2-chloro-6-methylphenyl)-2-[[6-[4-(2-hydroxyethyl)-1-piperazinyl]-2-methyl-4-pyrimidinyl]amino]-5-thiazolecarboxamide) was synthesized by Bristol-Myers Squibb (New York, NY; ref. 14). AMN107 (NVP-AMN107-AA; 4-methyl-*N*-(3-(4-methyl-1*H*-imidazol-5-(trifluoromethyl)phenyl)-3-(3-pyridinyl)-2-pyridinyl)amino benzamide, hydrochloride) was synthesized by Novartis Pharmaceuticals (12). Imatinib was purchased from the Oregon Health and Science University pharmacy. Each compound was prepared as a 10 mmol/L stock in DMSO and experiments were done with dilutions of the stock solutions.

Cell lines. Ba/F3 transfectants (expressing full-length wild-type Bcr-Abl or Bcr-Abl with kinase domain point mutations) were generated, selected, and maintained as previously described (10). Parental Ba/F3 cells were supplemented with interleukin-3 (IL-3).

Kinase autophosphorylation assays with glutathione *S*-transferase-Abl kinase domains. Kinase assays using wild-type and mutant glutathione *S*-transferase (GST)-Abl fusion proteins (c-Abl amino acids 220–498) were done as described, with minor alterations (15). GST-Abl fusion proteins were released from glutathione-Sepharose beads before use; the concentration of ATP was 5 μ mol/L. Immediately before use in kinase autophosphorylation and *in vitro* peptide substrate phosphorylation assays, GST-Abl kinase domain fusion proteins were treated with LAR tyrosine phosphatase according to the manufacturer's instructions (New England Biolabs, Beverly, MA). After 1-hour incubation at 30°C, LAR phosphatase was inactivated by addition of sodium vanadate (1 mmol/L). Immunoblot analysis comparing untreated GST-Abl kinase to dephosphorylated GST-Abl kinase was routinely done using phosphotyrosine-specific antibody 4G10 to confirm complete (>95%) dephosphorylation of tyrosine residues and c-Abl antibody CST 2862 to confirm equal loading of GST-Abl kinase. The inhibitor concentration ranges for IC_{50} determinations were 0 to 5,000 nmol/L (imatinib and AMN107) or 0 to 32 nmol/L (BMS-354825). The BMS-354825 concentration range was extended to 1,000 nmol/L for mutant T315I. These same inhibitor concentrations were used for the *in vitro* peptide substrate phosphorylation assays. The three inhibitors were tested over these same concentration ranges against GST-Src kinase (Cell Signaling Technology, Boulder, CO) and GST-Lyn kinase (Stressgen, Victoria, BC, Canada).

***In vitro* peptide substrate phosphorylation assays with glutathione *S*-transferase-Abl kinase domains.** The effects of imatinib (0–5,000 nmol/L), AMN107 (0–5,000 nmol/L), and BMS-354825 (0–32 nmol/L) on the catalytic activity of unphosphorylated GST-Abl kinase were assessed using a synthetic, NH_2 -terminal biotin-linked peptide substrate (biotin-EATYAAPFAKKK-amide; ref. 16). Assays were carried out at 30°C for 5 minutes in 25 μ L of reaction mixture consisting of kinase buffer [25 mmol/L Tris-HCl (pH 7.5), 5 mmol/L β -glycerophosphate, 2 mmol/L DTT, 0.1 mmol/L Na_3VO_4 , 10 mmol/L $MgCl_2$; Cell Signaling Technology], 50 μ mol/L peptide substrate, 10 nmol/L wild-type or mutant GST-Abl kinase, and 50 μ mol/L ATP/[γ - ^{32}P]ATP (5,000 cpm/pmol). Reactions were terminated by addition of guanidine hydrochloride to a final concentration of 2.5 mol/L.

A portion of each terminated reaction mixture was transferred to a streptavidin-coated membrane (SAM² biotin capture membrane; Promega, Madison, WI), washed, and dried according to the manufacturer's instructions; phosphate incorporation was determined by scintillation counting. Results were corrected for background binding to the membranes as determined by omitting peptide substrate from the kinase reaction. Time course experiments to establish the linear range of enzymatic activity preceded kinase assays. Similar *in vitro* peptide substrate phosphorylation assays were conducted with two Src family kinases: GST-Src kinase (Cell Signaling Technology) and GST-Lyn kinase (Stressgen). For Src family kinases, SignaTECT PTK biotinylated peptide substrate 2 (Promega) was the peptide substrate; all other conditions were as described for the GST-Abl kinase assays.

Cellular proliferation assays. Ba/F3 cell lines were plated in triplicate and incubated with escalating concentrations of imatinib, AMN107, or BMS-354825 for 72 hours. Proliferation was measured using a methanethiosulfonate-based viability assay (CellTiter96 Aqueous One Solution Reagent; Promega). IC₅₀ and IC₉₀ values are reported as the mean of three independent experiments done in quadruplicate. The inhibitor concentration ranges for IC₅₀ and IC₉₀ determinations were 0 to 2,000 nmol/L (imatinib and AMN107) or 0 to 32 nmol/L (BMS-354825). The imatinib concentration range was extended to 6,400 nmol/L for mutants with IC₅₀ >2,000 nmol/L. The BMS-354825 concentration range was extended to 200 nmol/L for mutant T315I.

Immunoblotting. Ba/F3 cell lines (1×10^6 cells) were incubated for 3 hours in media containing escalating doses of either imatinib or AMN107. Cells were collected by centrifugation and lysed in SDS sample buffer.

Following SDS-PAGE, proteins were transferred to Immobilon-P membranes (Millipore Corp., Bedford, MA) for immunoblotting. Tyrosine-phosphorylated Bcr-Abl was detected with mouse monoclonal phosphotyrosine antibody 4G10 (Supplementary Fig. S1). Bcr-Abl expression was detected using rabbit c-Abl antibody CST 2862 (Cell Signaling Technology).

Apoptosis assays. Ba/F3 cell lines (6×10^4 cells/well) were incubated in 1 mL media containing vehicle, imatinib (300 nmol/L, 1,500 nmol/L), or AMN107 (30, 300, and 1,500 nmol/L) for 72 hours. Detection of apoptosis was done using a Guava Nexin apoptosis kit (Annexin V-phycoerythrin and 7-amino-actinomycin D; Guava Technologies, Hayward, CA) and a Guava Technologies PCA instrument. Results based on three independent experiments are reported as the mean $\pm$ SE (Supplementary Fig. S2).

Results and Discussion

In this study, we compared the activity of imatinib and two promising Bcr-Abl inhibitors, AMN107 and BMS-354825, against wild-type Bcr-Abl and imatinib-resistant Bcr-Abl mutants. Biochemical assays with purified, dephosphorylated wild-type GST-Abl kinase showed that AMN107 inhibited Abl-catalyzed peptide substrate phosphorylation with ~20-fold higher potency than imatinib (IC₅₀: 15 versus 280 nmol/L), whereas BMS-354825 had a two-log (~325-fold) increased potency relative to imatinib (IC₅₀: 0.6 versus 280 nmol/L). Corresponding experiments with mutant Abl kinase domains revealed that the ~20-fold improved potency of AMN107 compared with imatinib is also seen with the imatinib-resistant mutants (Table 1). The one exception was the Abl mutant

Table 1. Imatinib, AMN107, and BMS-354825 IC₅₀ values (nmol/L) for purified GST-Abl kinase and purified GST-Src kinase autophosphorylation and peptide substrate phosphorylation assays

Purified GST-Abl kinase and GST-Src kinase assays												
Peptide substrate phosphorylation						Autophosphorylation						
Imatinib		AMN107		BMS-354825		Imatinib		AMN107		BMS-354825		
IC ₅₀ (nmol/L)	Fold change	IC ₅₀ (nmol/L)	Fold change	IC ₅₀ (nmol/L)	Fold change	IC ₅₀ (nmol/L)	Fold change	IC ₅₀ (nmol/L)	Fold change	IC ₅₀ (nmol/L)	Fold change	
WT Abl	280	1	15	1	0.6	1	300	1	7	1	0.8	1
M244V	220	0.8	19	1.3	0.8	1.3	380	1.3	13	2	0.9	1.1
G250E	1,650	6	36	2	0.3	0.5	1,000	3	35	5	2.0	3
Q252H	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd
Y253F	4,300	15	28	2	0.4	0.6	>5,000	>17	55	8	3.1	4
Y253H	>5,000	>18	400	27	1.8	3	>5,000	>17	190	27	1.4	2
E255K	>5,000	>18	59	4	0.2	0.3	2,800	9	110	16	1.5	2
E255V	3,700	13	160	11	0.6	1	>5,000	>17	275	39	1.7	2
F311L	800	3	57	4	0.9	1.5	775	3	17	2	0.5	0.6
T315I	>5,000	>18	>5,000	>333	>10,000	>16,667	>5,000	>17	>5,000	>714	>1,000	>1,250
F317L	800	3	29	2	0.9	1.5	900	3	20	3	1.15	1.4
M351T	440	2	12	0.8	0.1	0.2	820	3	9	1.3	1.6	2
F359V	900	3	170	11	0.5	0.8	4,700	16	35	5	1.7	2
V379I	950	3	21	1.4	0.7	1.2	800	3	50	7	2.25	3
I387M	825	3	18	1.2	0.5	0.8	1,500	5	50	7	3.7	5
H396P	2,000	7	9	0.6	0.5	0.8	800	3	55	8	3.0	4
H396R	1,400	5	28	2	0.8	1.3	1,950	7	31	4	2.0	3
Src	>5,000	na	>5,000	na	0.8	1.3	>5,000	na	>5,000	na	6	8
Lyn	>5,000	na	>5,000	na	2.8	4.67	>5,000	na	>5,000	na	4.4	5.5

NOTE: Fold change refers to the fold difference in the IC₅₀, relative to wild type, which is set to 1. Abbreviations: WT, wild type; na, not applicable; nd, not determined.

T315I, which was completely insensitive to AMN107 (highest concentration tested: 5,000 nmol/L). To facilitate comparisons within Table 1, the IC₅₀ data are also expressed as fold change relative to a baseline of one for wild-type Abl kinase. By viewing the data in this way, it is apparent that the overall pattern of mutant sensitivity to AMN107 closely parallels that of imatinib. Because imatinib and AMN107 are predicted to share an absolute requirement for a specific inactive Bcr-Abl conformation and to bind in very similar ways, it is logical to expect largely the same pattern of effectiveness for AMN107 as for imatinib, but with the range of effectiveness shifted to a value more than an order of magnitude lower than that of imatinib. In contrast, BMS-354825 potently inhibited wild-type Abl kinase and all mutants except T315I over a narrow range (IC₅₀ ≤ 1.7 nmol/L). We also did a complete set of Abl kinase autophosphorylation assays with each of the inhibitors and obtained similar results to those from peptide substrate assays (Table 1). Thus, biochemical assays establish that AMN107 and BMS-354825 directly target wild-type and mutant Abl kinase domains and inhibit autophosphorylation and substrate phosphorylation in a concentration-dependent manner. Similar assays with the Src family kinases Src and Lyn (17, 18), which is expressed at high levels in primary CML blast crisis cells, showed that BMS-354825 is a potent inhibitor of these Src family kinases, whereas imatinib and AMN107 are inactive against these kinases (Table 1).

To extend the results with isolated kinase domains into a cellular context, we carried out cellular proliferation assays using Ba/F3 cells expressing wild-type or kinase domain mutants of Bcr-Abl. Similar to the data using isolated kinase domains, AMN107 inhibited the growth of cells expressing wild-type Bcr-Abl with 20-fold higher potency than imatinib (IC₅₀: 13 versus 260 nmol/L); BMS-354825 (IC₅₀: 0.8 nmol/L) displayed 325-fold greater potency compared with imatinib against cells expressing wild-type Bcr-Abl (Fig. 1; Table 2). For both inhibitors, similar improvements were maintained for all imatinib-resistant mutants tested, with the notable exception of T315I. We have previously reported that inhibition of Bcr-Abl by imatinib or the Src/Abl inhibitor AP23464 results in the accumulation of cells expressing WT Bcr-Abl in the G₀-G₁ cell cycle phase (19). We confirmed that this is also the case for AMN107 in the current study (data not shown).

The data for AMN107 is summarized in Fig. 2, which shows a model of AMN107 in complex with Abl kinase mutant M351T, and shows that the sensitivity of Bcr-Abl mutants to AMN107 segregates into four categories: high (IC₅₀ ≤ 70 nmol/L: M244V, G250E, Q252H, F311L, F317L, M351T, V379I, L387M, H396P, H396R), medium (IC₅₀ ≤ 200 nmol/L: Y253F, E255K, F359V), low (IC₅₀ ≤ 450 nmol/L: Y253H, E255V), and insensitive (IC₅₀ > 2 μmol/L: T315I). This pattern is highly reminiscent of the corresponding ranking of imatinib sensitivities (Table 2) and expected given the highly related structures of these two compounds and the binding

Table 2. Imatinib, AMN107, and BMS-354825 IC₅₀ values (nmol/L) for cellular proliferation and cellular Bcr-Abl tyrosine phosphorylation assays

Ba/F3 cellular assays									
Cellular proliferation						Bcr-Abl tyrosine phosphorylation			
Imatinib		AMN107		BMS-354825		Imatinib	AMN107	BMS-354825*	
IC ₅₀ (nmol/L)	Fold change	IC ₅₀ (nmol/L)	Fold change	IC ₅₀ (nmol/L)	Fold change	IC ₅₀ (nmol/L)	IC ₅₀ (nmol/L)	IC ₅₀ (nmol/L)	
WT Bcr-Abl	260	1	13 (28) [†]	1	0.8 (2.6) [†]	1	280	10	<10
M244V	2,000	8	38 (56)	3	1.3 (1.8)	2	500	8	<10
G250E	1,350	5	48 (152)	4	1.8 (3)	2	1,000	7	10-100
Q252H	1,325	5	70 (156)	5	3.4 (11.2)	4	1,500	15	<10
Y253F	3,475	13	125 (215)	10	1.4 (3)	2	4,200	55	<10
Y253H	>6,400	>25	450 (1,024)	35	1.3 (3)	2	>5,000	155	<10
E255K	5,200	20	200 (415)	15	5.6 (12.8)	7	5,000	70	10-100
E255V	>6,400	>25	430 (2,000)	33	11 (27)	14	>5,000	250	<10
F311L	480	2	23 (48)	2	1.3 (2.8)	2	600	44	nd
T315I	>6,400	>25	>2,000	>154	>200	>250	>5,000	>5,000	>1,000
F317L	1,050	4	50 (116)	4	7.4 (15)	9	400	47	<10
M351T	880	3	15 (31)	1.2	1.1 (3)	1.4	500	8	<10
F359V	1,825	7	175 (385)	13	2.2 (4.8)	3	3,100	43	10-100
V379I	1,630	6	51 (115)	4	0.8 (1.6)	1	800	15	nd
L387M	1,000	4	49 (115)	4	2 (4)	3	2,700	33	nd
H396P	850	3	41 (69)	3	0.6 (1.2)	0.8	2,700	70	nd
H396R	1,750	7	41 (73)	3	1.3 (2.7)	2	1,000	22	<10
Parental Ba/F3	>6,400	>25	>2,000	>154	>200	>250	ns	ns	nd

NOTE: Fold change refers to the fold difference in the IC₅₀, relative to wild type, which is set to 1.
Abbreviation: ns, no signal detected. Bcr-Abl not expressed.
*Estimated from ref. (14).
[†] Values in parentheses are IC₉₀ values, given for AMN107 and BMS-354825 only.

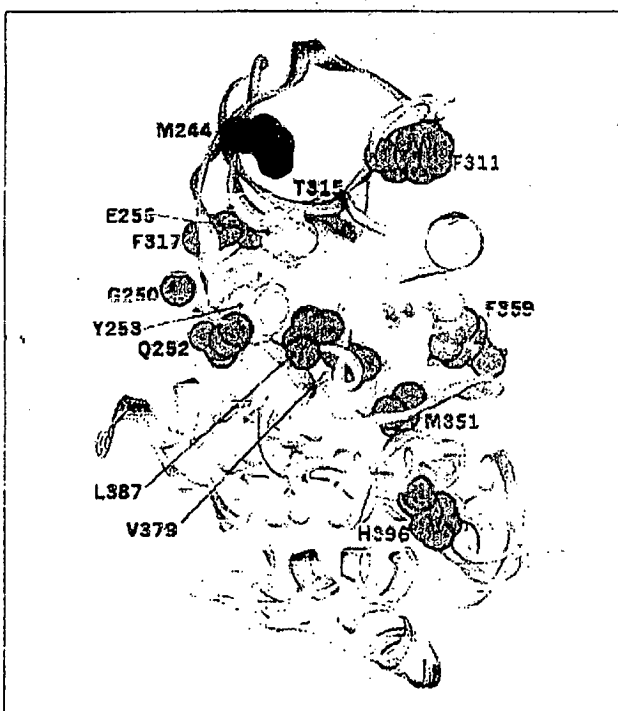


Figure 2. AMN107 in complex with kinase domain of Abl mutant M351T. Schematic diagram showing the locations of residues on Abl kinase corresponding to imatinib-resistant mutant forms of Bcr-Abl detected in patients. The residues are color coded according to their sensitivity to inhibition by AMN107, which is shown as a tube representation with a transparent yellow surface, as bound in a crystal structure of M351T Abl kinase (light blue). Mutations of residues shaded in red are highly sensitive to AMN107 ($IC_{50} \leq 70$ nmol/L: M244V, G250E, Q252H, F311L, F317L, M351T, V379I, L387M, H396P, H396R). Residues in orange show medium sensitivity ($IC_{50} \leq 200$ nmol/L: Y253F, E255K, F359V). Residues in green show low sensitivity ($IC_{50} \leq 450$ nmol/L: Y253H, E255V), and the blue residue (T315I) is insensitive to AMN107 ($IC_{50} > 2$ μ mol/L). Note that the level of AMN107 sensitivity at positions 253 and 255 (green) is dependent on the specific amino acid substitution. Thus, mutants Y253F and E255K fall in the medium (orange) classification, whereas Y253H and E255V comprise the low (green) category.

constraints they share. However, there are a few differences in the fold differences in sensitivities of the mutants to imatinib and AMN107. This is particularly noteworthy for M351T. Due to the structural differences between AMN107 and imatinib, this residue comes in close proximity to imatinib, but is less critical for coordinating binding of AMN107. BMS-354825, on the other hand, was found to be an extremely potent inhibitor of proliferation in cells expressing all mutants except T315I. As in the biochemical assays, the range of IC_{50} values for cells treated with BMS-354825 was narrow (0.8–11 nmol/L), in line with the proposal that the Bcr-Abl structural requirements for binding BMS-354825 are much less stringent than for imatinib family members.

Cellular Bcr-Abl tyrosine phosphorylation immunoblot analysis confirmed that AMN107 is much more potent than imatinib in reducing Bcr-Abl tyrosine phosphorylation levels in cells expressing wild-type Bcr-Abl and all imatinib-resistant mutants except T315I (Table 2; Supplementary Fig. S1). As a basis of comparison, published values for BMS-354825 are included in Table 2 (14). With respect to AMN107, the highly imatinib-resistant mutants Y253H (AMN107 IC_{50} : 155 nmol/L) and E255V (AMN107 IC_{50} : 250 nmol/L) were the least sensitive mutants. For all other mutants, treatment

with 250 nmol/L AMN107 resulted in complete (>95%) inhibition of the phosphorylated Bcr-Abl tyrosine kinase signal (Supplementary Fig. S1). As expected, T315I was completely insensitive to AMN107 treatment ($IC_{50} > 5,000$ nmol/L) and no Bcr-Abl signal was detected in lysates from untransfected, parental Ba/F3 cells (data not shown).

In agreement with cellular proliferation and tyrosine phosphorylation assay results, AMN107 induced apoptosis at significantly lower concentrations than imatinib in cells expressing wild-type Bcr-Abl or any of the kinase domain mutants except T315I (Supplementary Fig. S2). At the highest AMN107 concentration tested (1.5 μ mol/L), >90% of the cells were Annexin positive except in the cases of Y253H (65%), E255V (65%), and T315I (3%). Parental Ba/F3 cells and Ba/F3 cells expressing Bcr-Abl mutant T315I did not undergo apoptosis above vehicle-treated control levels in response to either inhibitor.

A conservative estimate for imatinib steady-state trough levels in patients treated with 400 mg imatinib per day is 1.5 μ mol/L (2, 20). The pharmacokinetic profile and maximum tolerated dose for AMN107 have not been reported, and its effectiveness as a therapy for imatinib-resistant CML will depend on the concentration that can be reached in humans. Preliminary findings from the phase I/II study indicate that orally administered AMN107 at 200 mg per day is well tolerated with biological and marrow effects in some patients (21). Taking inhibition at or above the IC_{50} value (Table 2) as a benchmark for clinical benefit, AMN107 at a trough level of 1.5 μ mol/L would be predicted to be an effective single agent therapeutic for cells expressing wild-type Bcr-Abl and all mutants tested except T315I. If a trough level of only 500 nmol/L is achievable, three mutants (Y253H, E255V, and T315I) are predicted to be substantially resistant.

BMS-354825 is ~325-fold more potent than imatinib and 16-fold more potent than AMN107 against wild-type Bcr-Abl. Again, invoking inhibition at or above the IC_{50} value (Table 2) as an indicator of clinical benefit, BMS-354825 would be predicted to be an effective single agent therapeutic for cells expressing wild-type Bcr-Abl and all mutants tested except T315I at a trough level of 50 nmol/L. Establishing and utilizing the minimum effective concentration may be especially important in the case of dual Src/Abl inhibitors, such as BMS-354825 due to concerns pertaining to off-target effects.

In summary, the cellular and biochemical experiments directly comparing AMN107 and BMS-354825 to imatinib show that both inhibitors are more potent than imatinib against all cell lines and purified Abl kinase domains tested except T315I. The mutants, other than T315I, that were least responsive to AMN107 in all three cellular assays were Y253H and E255V (Fig. 2). Analogous to imatinib, the extent of sensitivity to AMN107 depended on the specific substitution at a given position (e.g., E255V less sensitive than E255K to AMN107).

Both AMN107 and BMS-354825 hold promise for treating patients with imatinib-resistant CML except when the disease is driven by Bcr-Abl mutant T315I. Although both inhibitors efficiently block Bcr-Abl tyrosine kinase catalytic activity, they do so by binding to distinct, partially overlapping sites in the kinase domain and by placing different conformational requirements on the Abl kinase domain. If results of clinical trials and pharmacokinetic studies indicate that AMN107 and BMS-354825 are safe and effective, the feasibility of using these drugs in combination should be evaluated. In support of this approach, we recently investigated the use of imatinib in combination with BMS-354825 as a strategy for confronting drug resistance in

CML.⁶ Specifically, treating Ba/F3 cells expressing wild-type or imatinib-resistant Bcr-Abl kinase domain mutants with various combinations of imatinib and BMS-354825 produced additive inhibitory effects. Even at imatinib concentrations above clinically achievable levels, no antagonism of the Src/Abl inhibitor was observed. A particularly appealing therapeutic option is to use a Bcr-Abl inhibitor cocktail containing these inhibitors as well as an as yet undiscovered T315I inhibitor. Advantages of combinatorial therapy are that clones resistant to one of the Bcr-Abl inhibitors may be vulnerable to another component of the cocktail (22), the potential to eliminate a wider spectrum of mutants, including those that predate therapeutic intervention (23), and eradication

of a higher proportion of residual leukemic cells (8). Therefore, using Bcr-Abl inhibitor combinations to treat newly diagnosed, chronic-phase CML patients may represent the best strategy to prevent or significantly delay the onset of acquired drug resistance. In addition, these Bcr-Abl kinase inhibitors could also increase response rates and duration of response due to their increased potency.

Acknowledgments

Received 1/25/2005; revised 3/28/2005; accepted 4/7/2005.

Grant support: National Cancer Institute, The Leukemia and Lymphoma Society, Burroughs Wellcome Foundation, and Howard Hughes Medical Institute (BJ. Druker). The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked *advertisement* in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

We thank Amie Corbin for providing the GST-Abl kinase domain constructs used for enzymatic assays.

⁶ T. O'Hare, et al. Combined Abl inhibitor therapy for minimizing drug resistance in CML: Src/Abl inhibitors are compatible with imatinib, submitted for publication.

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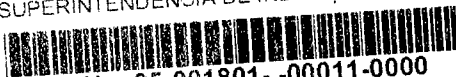
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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

CERTIFICACION DE EXCEDENTE : 09 - 2,862
FECHA : ENERO 13 DE 2009

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 05-001801- -00011-0000

Fecha: 2009-02-09 15:52:31 Dep. 2020 NUECREACION
Tra. 11 PATENTE IYII Eve: 379 FASE NACIONAL II
Act. 444 RESPUESTA REQUE Folios: 22

***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
CLARKE MODET Y CO. COLOMB	CONSIGNACION	BANCO DE BOGOTA	062754387	107995683	13/01/2009	40,435,000.00

***** CONCEPTO *****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-09	OTROS SERVICIOS DE PROPIEDAD I	
		99 OTROS SERVCIOS ADMINISTRATIVOS	100,000.00
		TOTAL :	\$ 100,000.00

SON: CIENTO MIL PESOS

RESPONSABLE :

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____

ESTA CERTIFICACION DE EXCEDENTE DE PAGO SOLO PODRA SER UTILIZADA
COMO PARTE DE LA CANCELACION DE UNA TARIFA VIGENTE Y NO PODRA SER
SUSTITUIDA POR NINGUN RECIBO.

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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

CERTIFICACION DE EXCEDENTE : 09 - 2,720
FECHA : ENERO 13 DE 2009



***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PAGO	Vr. PAGO
CLARKE MODET Y CO. COLOMB	CONSIGNACION	BANCO DE BOGOTA	062754387	107995683	13/01/2009	40,435,000.00

***** CONCEPTO *****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-09	OTROS SERVICIOS DE PROPIEDAD I	
		99 OTROS SERVICIOS ADMINISTRATIVOS	5,000.00
		TOTAL :	\$ 5,000.00

SON: CINCO MIL PESOS

RESPONSABLE : _____

TBO DE CAJA APLICADO AL EXPEDIENTE No. _____

ESTA CERTIFICACION DE EXCEDENTE DE PAGO SOLO PODRA SER UTILIZADA
COMO PARTE DE LA CANCELACION DE UNA TARIFA VIGENTE Y NO PODRA SER
SUSTITUIDA POR NINGUN RECIBO.

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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

CERTIFICACION DE EXCEDENTE : 09 - 2,719
FECHA : ENERO 13 DE 2009

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 05-001801- -00011-0000

Fecha: 2009-02-09 15:52:31 Dep. 2020 NUECREACION
Tra. 11 PATENTEYII Eve: 379 FASENACIONALII
Act. 444 RESPUESTAREQUE Folios: 22

***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PAGO	Vr. PAGO
CLARKE MODET Y CO. COLOMB	CONSIGNACION	BANCO DE BOGOTA	062754387	107995683	13/01/2009	40,435,000.00

***** CONCEPTO *****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-09	OTROS SERVICIOS DE PROPIEDAD I	
		99 OTROS SERVICIOS ADMINISTRATIVOS	5,000.00
		TOTAL :	\$ 5,000.00

SON: CINCO MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____

ESTA CERTIFICACION DE EXCEDENTE DE PAGO SOLO PODRA SER UTILIZADA
COMO PARTE DE LA CANCELACION DE UNA TARIFA VIGENTE Y NO PODRA SER
SUSTITUIDA POR NINGUN RECIBO.

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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

CERTIFICACION DE EXCEDENTE : 09 - 2,762
FECHA : ENERO 13 DE 2009



***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
CLARKE MODET Y CO. COLOMB	CONSIGNACION	BANCO DE BOGOTA	062754387	107995683	13/01/2009	40,435,000.00

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

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-09	OTROS SERVICIOS DE PROPIEDAD I	
		99 OTROS SERVICIOS ADMINISTRATIVOS	1,000.00
		TOTAL :	\$ 1,000.00

SON: MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____

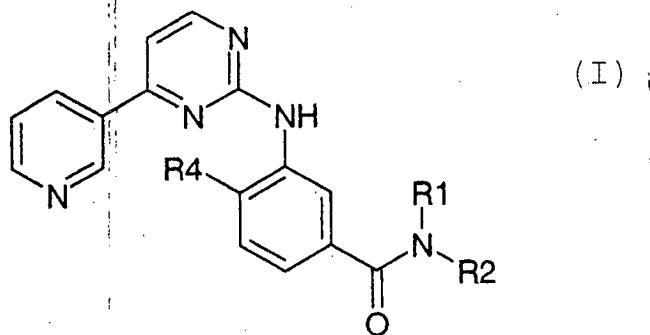
ESTA CERTIFICACION DE EXCEDENTE DE PAGO SOLO PODRA SER UTILIZADA
COMO PARTE DE LA CANCELACION DE UNA TARIFA VIGENTE Y NO PODRA SER
SUSTITUIDA POR NINGUN RECIBO.

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REIVINDICACIONES

1. Un compuesto de la fórmula:



R1 representa hidrógeno, alquilo inferior, alcoxilo inferior-alquilo inferior, o bencilo;

R2 representa fenilo substituido por uno o más sustituyentes seleccionados del grupo que consiste de alquilo inferior, trifluoro-alquilo inferior, hidroxialquilo inferior, aminoalquilo inferior, alquilo inferior-aminoalquilo inferior, di-alquilo inferior aminoalquilo inferior, N-ciclohexilo-N-alquilo inferior-aminoalquilo inferior, alcoxilo inferior-carbonil-piperidin-alquilo inferior, N-alquilo inferior-piperazin-alquilo inferior, alcoxilo inferior-carbonilalquilo inferior, hidroxilo, alcoxilo inferior, trifluoroalcoxilo inferior, 1H-imidazolilalcoxilo inferior, alcanoiloxilo inferior, benzoiloxilo, carboxilo, alcoxilo inferior-carbonilo, carbamoilo, alquilo inferior carbamoilo, amino, alcanoil inferior-

amino, benzoilamino, amino mono- ó disustituido por un alquilo inferior, por un hidroxialquilo inferior o por un alcóxilo inferior-alquilo inferior, 1H-imidazolilo, alquilo inferior-1H-imidazolilo, carboxilo-1H-imidazolilo, alquilo inferior estercarboxilo-1H-imidazolilo, pirrolidino, piperidino, piperazino, N-alquilo inferior-piperazino, morfolino, sulfamóilo, alquilo inferior sulfonilo, fenilo, piridilo, halogenílo, ó benzoílo; y

R4 representa hidrógeno, alquilo inferior ó halógeno;

o un N-óxido o una sal farmacéuticamente aceptable de este compuesto, donde el término "inferior" denota un radical que tiene o incluye un máximo de 7 átomos de carbono, estando los radicales en cuestión en forma lineal o ramificada con una o múltiples ramificaciones.

2. Un compuesto de la fórmula I de acuerdo con la reivindicación 1, en donde:

R1 representa hidrógeno;

R2 representa fenilo substituido por trifluorometilo y opcionalmente un sustituyente adicional seleccionado del grupo que consiste de hidroxialquilo inferior, aminoalquilo inferior,

hidroxiaminoalquilo inferior, di-alquiloamina inferior, 1H-imidazolilo, alquilo inferior-1H-imidazolilo, carbamoilo, alquilo inferior carbamoilo, pirrolidino, piperidino, piperazino, alquilo inferior-piperazino, morfolino, alcoxilo inferior, trifluoroalcoxilo inferior, fenilo, piridilo, y halogenilo;

R4 representa metilo;

o un N-oxido o una sal farmacéuticamente aceptable de este compuesto.

3. Un compuesto de la fórmula I de acuerdo con la reivindicación 1, en donde:

R1 representa hidrógeno;

R2 representa fenilo substituido por trifluorometilo y opcionalmente un sustituyente adicional seleccionado del grupo que consiste de 1-hidroxi-1-metiletilo, metilamino, etilamino, 2-hidroxi-1-propilamino, 2-hidroxi-2-propilamino, dietilamino, 1H-imidazolilo, 2- y 4-metil-1H-imidazolilo, carbamoilo, metilcarbamoilo, pirrolidino, piperidino, piperazino, 4-metilpiperazino, morfolino, metoxi, trifluorometoxi, 2,2,2-trifluoroetoxi, fenilo, 2-, 3- y 4-piridilo, cloro, y fluoro;

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R4 representa metilo;

o un N-oxido o una sal farmacéuticamente aceptable de este compuesto.

4. Un compuesto de la fórmula I de acuerdo con la reivindicación 1, en donde:

R1 representa hidrógeno;

R2 representa 3-(1-hidroxi-1-metiletíl)-5-(trifluorometíl) fenilo;

R4 representa metilo;

o un N-oxido o una sal farmacéuticamente aceptable de este compuesto.

5. Un compuesto de la fórmula I de acuerdo con la reivindicación 1, en donde:

R1 representa hidrógeno;

R2 representa fenilo que es mono o di substituido por imidazolalcoxilo inferior, aminoalquilo inferior, trifluorometíl, hidroxialquilo inferior, hidroxialquilo inferior amino, bis-(alcoxilo-inferior-alquilo inferior)amino, alquilo inferior piperazinilo, piperidinilo, pirrolidinilo,

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morfolino, fenilo, piridilo, imidazolilo que está insustituido o mono- ó disustituido por alquilo inferior o por N-alquilo inferior-carbamoílo;

R4 representa metilo;

o un N-oxido o una sal farmacéuticamente aceptable de este compuesto.

6. Un compuesto de la fórmula I de acuerdo con la reivindicación 1, en donde:

R1 representa hidrógeno;

R2 representa fenilo substituido por 3-trifluorometil y un sustituyente adicional seleccionado del grupo que consiste en 2-metil-1H-imidazolilo y 4-metil-1H-imidazolilo;

R4 representa metilo;

o un N-oxido o una sal farmacéuticamente aceptable de este compuesto.

7. Un compuesto de la fórmula I de acuerdo con la reivindicación 1, en donde:

R1 representa hidrógeno;

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R2 representa fenilo substituido por 5-trifluorometil y un sustituyente adicional seleccionado del grupo que consiste de 2,4-dimetil-1H-imidazolilo, 5-metil-1H-imidazolilo, 2-metoximetilamino, propoxi, etoxi, metilaminocarbonilo, benzoílo, 4-metoxi-2-metil, acetilamino 2,4-dimetil-1H-imidazolilo, etil éster del ácido acético, etil éster del ácido carboxílico piperidino;

R4 representa metilo;

o un N-óxido o una sal farmacéuticamente aceptable de este compuesto.

8. Un compuesto de la fórmula I de acuerdo con la reivindicación 1, en donde el compuesto es 4-metil-3-[[4-(3-piridinil)-2-pirimidinil]amino]-N-[5-(4-metil-1H-imidazol-1-il)-3-(trifluorometil)fenil]benzamida

o un N-óxido o una sal farmacéuticamente aceptable de este compuesto.

9. Una composición farmacéutica que comprende como un ingrediente activo un compuesto de la fórmula I de acuerdo con la reivindicación 1 o un N-óxido o una sal farmacéuticamente aceptable de este compuesto junto con un vehículo farmacéuticamente aceptable.

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**SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISION DE NUEVAS CREACIONES**

Radicación No. 05001801

Clasificación Internacional (IPC): A61K 31/506

Concepto Técnico No. 708

Patente de Invención ☐ Patente de Modelo de Utilidad ☐

Vía Nacional ☐

Vía PCT (fase nacional) ☐ Cap. I ☐ Cap. II ☐

No. Sol. Internacional PCT/EP2003/007198

Fecha de Presentación Internal. 4/07/2003

Como resultado del examen definitivo, realizado con fundamento en el artículo 48 de la Decisión 486 de la Comisión de la Comunidad Andina, se le comunica:

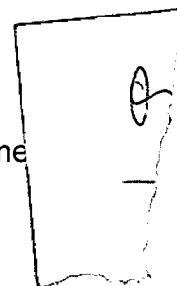
1. Documentos estudiados

Descripción: Folios: 6 a 140

Reivindicaciones: Folios 141 a 157 como se radicó inicialmente
Folios 219 a 224 modificadas en fase nacional
Folios 304 a 309 modificadas como respuesta al primer examen de fondo

Rta. del Solicitante: Folios: 288 a 293

Prioridad: Fecha: 5/07/2002, 20/12/2002, país: UK y número 0215676.8, 0229893.3



2. Objeto de la invención

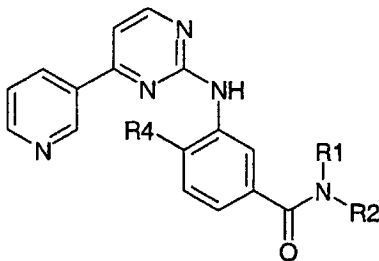
Título sugerido de la solicitud: Pirimidinilaminobenzamidas sustituidas como inhibidores de cinasas de tirosina.

El problema planteado en esta solicitud es la necesidad de compuestos útiles para la terapia de una enfermedad que responda a la inhibición de la actividad de la cinasa de proteína en especial una enfermedad neoplástica, en particular leucemia.

Para solucionar este problema técnico la solicitud en estudio proporciona novedosas pirimidinilaminobenzamidas sustituidas.

Clasificación Internacional de Patentes (IPC.): A61K 31/506

Reivindicaciones 1 - 8: compuestos de la fórmula general (I).



Reivindicación 9: Composición que comprende un ingrediente activo de fórmula (I) junto con un vehículo farmacéuticamente aceptable.

3. De la solicitud de Patente (según el caso)

Descripción (artículo 28 D. 486)

- La descripción cumple con el requisito de claridad o comprensión de acuerdo al art. 28 de la Decisión 486.

Reivindicaciones (artículo 30 D 486)

- Realizadas las modificaciones al capítulo reivindicatorio según los requerimientos establecidos en el art. 45 es claro y conciso y además está lo suficientemente sustentado por la descripción por lo tanto cumple con el requisito de definición claridad, concisión o sustento por la descripción de acuerdo al art. 30 de la Decisión 486.

4. Determinación del Estado de la Técnica

La fecha que se ha tenido en cuenta para determinar el Estado de la Técnica es:

Fecha de presentación de la solicitud prioritaria 5/07/2002

Teniendo en cuenta la fecha indicada se realizó la búsqueda en el estado de la técnica de documentos relacionados con la solicitud encontrándose los siguientes documentos más relevantes:

Nº	Documento	Título	Fecha de publicación*
D ₁	EP 0588762	FURTHER USE OF PYRIMIDINE DERIVATIVES	1996/05/14
D ₂		POTENT AND SELECTIVE INHIBITORS OF THE ABL-KINASE: PHENYLAMINO-PYRIMIDINE (PAP) DERIVATIVES	1997/01/21
D ₃		PHENYLAMINO-PYRIMIDINE (PAP) – DERIVATIVES: A NEW CLASS OF POTENT AND HIGHLY SELECTIVE PKGF-RECEPTOR AUTOPHOSPHORYLATION INHIBITORS	1996/06/04

5. Respuesta a los argumentos del solicitante:

- Se considera subsanada la objeción por falta de novedad de la antigua reivindicación 9 correspondiente al proceso, al ser eliminada.
- Con respecto a la observación del solicitante que sugiere que el estudio de nivel inventivo se basó en solo una diferencia sin tener en cuenta otras cuatro diferencias no evidentes para una persona versada en la técnica, se desea aclarar que:
 1. La **definición de R2** que reclama como diferente, hace parte del sustituyente que en efecto se evidencia como "diferente" en el primer examen de fondo.
 2. La característica de **una parte 3-piridil** en los compuestos reclamados no se tomó como "diferente" con respecto a la anterioridad debido a que según el folio 227 línea 38 página 8 de la anterioridad es una de las posibilidades que igualmente puede tomar la anterioridad, así que esta característica se evidencia como "igual" a la solicitud tal como se indica en el primer examen de fondo.
 3. La característica **carbonilamino unida al grupo fenilo** central en los compuestos de fórmula (I) que también reclama como diferente, también hace parte del sustituyente que se evidencia como "diferente" en el primer examen de fondo, incluidas todas sus ramificaciones.
 4. La característica de **un grupo halógeno o alquilo** unido al grupo fenilo central en los compuestos reclamados, correspondiente al radical R4 no se tomó como "diferente" con respecto a la anterioridad debido a que según el folio 227 línea 43 página 8 de la anterioridad pertenecen a las posibilidades que de la misma forma puede tomar la anterioridad, así que esta característica se evidencia como "igual" a la solicitud tal como se indica en el primer examen de fondo.

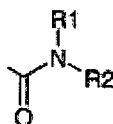
6. Análisis de patentabilidad (según requisito) (artículo 14 D486)

Novedad (artículo 16 D486)

- No se encontró dentro del estado de la técnica, documento alguno que evidenciara la existencia de la invención.
- Por lo tanto es novedoso de acuerdo a lo estipulado en el art. 16 de la Decisión 486 de la Comisión de la Comunidad Andina.

Nivel inventivo (artículo 18 D486)

El problema técnico planteado en esta solicitud el cual es la necesidad de compuestos útiles para la terapia de una enfermedad que responda a la inhibición de la actividad de la cinasa de proteína en especial la leucemia, no resultaba obvio mediante lo conocido en el estado de la técnica ya que la



sustitución en el fenilo de tipo $\text{N}(\text{R1})(\text{R2})\text{C}(=\text{O})$ reivindicada no fue sugerida por ninguna de las anterioridades encontradas, obteniéndose además una mejora de los niveles de actividad evidenciada en los estudios adjuntados, por el ejemplo 92 denominado AMN107 (4-metil-3-[[4-(3-piridinil)-2-pirimidinil]amino]-N-[5-(4-metil-1H-imidazol-1-il)-3-(trifluorometil) fenil] enzamida.

306

- Por lo tanto los compuestos reivindicados tienen nivel inventivo de acuerdo a lo estipulado en el art. 18 de la Decisión 486 de la Comisión de la Comunidad Andina.

7. Conclusión:

En consecuencia y por todo lo expuesto anteriormente, se recomienda **Conceder** las reivindicaciones: 304 a 309 (folios: 1 - **9**).

Bogotá, D.C.,

CONCEPTO TECNICO No. 708	EXAMINADOR TECNICO Código No. 202087
------------------------------------	--

**REPUBLICA DE COLOMBIA
SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO**

RESOLUCION Nº 2 2 0 0 9

Por la cual se otorga una patente de invención

CERTIFICADO 94

Rad. PCT/ 05-1801

EL SUPERINTENDENTE DE INDUSTRIA Y COMERCIO
en ejercicio de sus facultades legales, en especial de las que se confirieron en el artículo
4, numeral 5 del decreto 2153 de 1992, y

CONSIDERANDO:

PRIMERO: Que la solicitud internacional PCT/EP 2003/007198 de fecha 04 de julio del 2003, correspondiente a la patente de invención titulada "INHIBIDORES DE CINASAS DE TIROSINA", fue radicada en esta Superintendencia el 12 de enero del 2005 bajo el número 05001801, para los efectos de que se dé comienzo a la fase nacional en virtud del Tratado de Cooperación en Materia de Patentes (PCT).

SEGUNDO: Que el extracto de esta solicitud fue publicado en la Gaceta de la Propiedad Industrial Nº 568 del 29 de septiembre del 2006, sin que se hubieran presentado oposiciones por parte de terceros.

TERCERO: Que realizado el examen de fondo se requirió al solicitante en los términos del artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, para que presentara respuesta a las observaciones de carácter técnico visibles a folios 259 a 263 del cuaderno administrativo, relacionadas con la patentabilidad o cumplimiento de los requisitos establecidos por esta Decisión, para la concesión de la patente.

CUARTO: Que el solicitante mediante escrito radicado bajo el número 05-001801-00010-0000 del 09 de febrero del 2009, atendió oportunamente el requerimiento formulado, presentando nuevos folios 304 a 309 con el texto de las reivindicaciones que reemplazan las originalmente presentadas, atendiendo de esta manera las observaciones efectuadas en el examen de fondo. El nuevo capítulo reivindicatorio se acepta, como quiera que se ajusta a las prescripciones contenidas en el artículo 34 de la Decisión 486.

QUINTO: Que en virtud de lo dispuesto en el artículo 14 de la Decisión 486 expedida por la Comisión de La Comunidad Andina se otorgarán patentes "*...para las invenciones, sean de producto o de procedimiento, en todos los campos de la tecnología, siempre que sean nuevas, tengan nivel inventivo y sean susceptibles de aplicación industrial*".

REPUBLICA DE COLOMBIA
SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

RESOLUCION

Nº 2 2 0 0 9

Por la cual se otorga una patente de invención

CERTIFICADO 94

Rad. PCT/ 05-1801

SEXTO: Que en el presente caso cumplen los requisitos indicados en el numeral anterior las reivindicaciones 1 a 9 contenidas en los folios 304 a 309, razón por la cual este Despacho encuentra procedente conceder para las mismas el privilegio de patente solicitado.

SEPTIMO: Que de acuerdo con el objeto concedido se modifica el título de la invención, el cual quedará de la siguiente manera: "PIRIMIDINILAMINO BENZAMIDAS SUSTITUIDAS COMO INHIBIDORES DE CINASAS DE TIROSINA".

RESUELVE:

ARTICULO PRIMERO: Otorgar el privilegio de patente de invención a la solicitud que entró en fase nacional en virtud del Tratado de Cooperación en Materia de Patentes (PCT), para la creación denominada:

**" PIRIMIDINILAMINO BENZAMIDAS SUSTITUIDAS COMO INHIBIDORES DE
CINASAS DE TIROSINA "**

Clasificación IPC: A 61 K 31/506.

Reivindicación(es): 1 a 9 **Folio(s):** 304 a 309.

Titular(es): NOVARTIS AG.

Domicilio(s): Basilea, Suiza.

Inventor(es): Werner Breitenstein, Pascal Furet, Sandra Jacob y Paul William Manley.

Prioridad Nº: 0215676.8 **Fecha:** 05 de julio del 2002 **País:** GB.
0229893.3 20 de diciembre del 2002 GB.

REPUBLICA DE COLOMBIA
SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

RESOLUCION **Nº 2 2 0 0 9**

Por la cual se otorga una patente de invención

CERTIFICADO

94

Rad. PCT/ 05-1801

Solicitud Internacional N°: PCT/EP 2003/007198 Fecha: 04 de julio del 2003

Vigente desde: 04 de julio del 2003

Hasta: 04 de julio del 2023

ARTICULO SEGUNDO: El titular tendrá los derechos y las obligaciones establecidos en la Decisión 486 de la Comisión de la Comunidad Andina y demás disposiciones legales vigentes sobre propiedad industrial, precisando que para mantener vigente la patente se deberá cancelar la tasa anual de mantenimiento conforme lo dispone el artículo 80 de la referida norma comunitaria.

ARTICULO TERCERO: Entregar al titular copia auténtica de esta resolución y el certificado de patente, previas las anotaciones en los libros de registro.

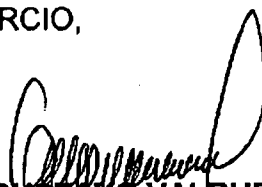
ARTICULO CUARTO: Notificar el contenido de la presente resolución a la doctora Jimena Escobar Uribe, en su calidad de apoderada de Novartis AG., o a quien haga sus veces, entregándole copia de la misma, advirtiéndole que contra ella procede el recurso de reposición ante el Superintendente de Industria y Comercio, del cual podrá hacer uso al momento de la notificación personal o dentro de los 5 días hábiles siguientes a ella.

NOTIFÍQUESE Y CUMPLASE

Dada en Bogotá, D.C., a los

3 0 ABR. 2009

EL SUPERINTENDENTE DE INDUSTRIA Y COMERCIO,


GUSTAVO VALBUENA QUIÑONES

Doctora

JIMENA ESCOBAR URIBE

Carrera 11 N° 86 – 53, Piso 6.

Bogotá D.C.

317
310

Clarke, Modet & Cº

COLOMBIA

Doctor

GIANCARLO MARCENARO JIMÉNEZ

Superintendente Delegado para la Propiedad Industrial

EXPEDIENTE : **05.001.801**

SOLICITUD : ENTREGA DE TITULO

ASUNTO : 2768/p



Estimado doctor Marcenaro:

Yo, DILIA RODRÍGUEZ D´ALEMAN, identificada como aparece al pie de mi firma, domiciliada en Bogotá, en la Carrera 11 No. 86-53 Piso 6, obrando como apoderada sustituta de este asunto, mediante resolución No.22009 de 30 de abril de 2009, se concedió el registro de la patente denominada **"PIRIMIDINILAMINO BENZAMIDAS SUSTITUIDAS COMO INHIBIDORES DE CINASAS DE TIROSINA"** a favor de mi mandante. Ya me fue entregada copia íntegra, auténtica y gratuita de dicha resolución.

Solicito que **se proceda a numerar el certificado de la patente y se ordene la entrega del título correspondiente.**

Cordialmente,

DILIA MARÍA RODRÍGUEZ D´ALEMAN
C.C. 41.654.882 de Bogotá.
T.P. 20824 CSJ

Superintendencia de Industria y Comercio

Otorga la Patente de Invención a:

Novartis AG

Basilea, Suiza

A la Creación denominada:

"Pirimidinilaminobenzamidas sustituidas como inhibidores de cinasas de tirosina"

Inventor(es):

Werner Breitenstein

Pascal Furet

Pandra Jacob

Paul William Manley

Certificado No. 94

Solicitud Internacional No.: PCT/EP2003/007198

Clasificación Internacional: A61K 31/506

de Patentes

9 Reivindicaciones

Vigente Desde: 04/07/2003

Hasta: 04/07/2023

Prioridad No.: GB 0215676.8 05/07/2002

GB 0229893.3 20/12/2002

Que la solicitud de Patente de Invención No. 5 1801 cumple con los requisitos previstos en las disposiciones legales vigentes, Resolución No. 22009 de 30/04/2009, en testimonio de ello se estampa la forma del funcionario competente y el sello de esta Entidad.

Superintendente de Industria y Comercio

AVISO DE NOTIFICACION
CORREO CERTIFICADO319
312

Radicación :	5-1801- -13-0	Fecha:	2009-05-05 08:15:43
Trámite :	11 PATENTEIYII		
Evento :	379 FASENACIONALI		
Actuación :	432 COMUNICACTOADM		
Destinatario :	JIMENA ESCOBAR URIBE Folios 1		

Señor (a) (es)
JIMENA ESCOBAR URIBE
CARRERA 11 NO. 86-53 PISO 6
BOGOTA D.C.

Referencia RESOLUCION : 22009
Fecha : 30/04/2009
Expediente : 5-1801
Trámite : 11 PCT-PATENTE DE INVENCION CAPITULOS I Y II
Evento : 379 FASE NACIONAL INCLUIDO CAPITULO II
Actuación : 432 COMUNICACION ACTO ADMINISTRATIVO

Comendidamente le solicito presentarse a este Despacho ubicado en la Carrera 13 No. 27 - 00 Piso Quinto (5), de la ciudad de Bogotá D.C., dentro del término de cinco (5) días hábiles contados a partir del envío de la presente citación, en horario de 8:00 a.m. a 4:30 p.m. jornada continua, con el fin de notificarle personalmente el contenido de la resolución de la referencia proferida dentro del expediente tramitado con el número de radicación citado en el asunto.

De no hacerse presente en el término indicado anteriormente, la providencia en mención se notificará por edicto, el cual se fijará por el término de diez (10) días en el Centro de Documentación e Información.

Para su comodidad el texto completo de la resolución se encontrará disponible en la página web de la Entidad desde el día hábil siguiente al de su notificación, la cual podrá ser consultada desde un computador con acceso a Internet, en la página www.sic.gov.co, con el número de resolución a través de la opción servicios en línea bases de datos - otros servicios - consulta actos administrativos.

En caso de que se haya notificado, haga caso omiso de este aviso.

Secretaría General
SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

Al contestar favor indique el número de
radicación consignado en el sticker

Sede Centro: Carrera 13 No. 27-00 pisos 2, 5, 7 y 10 PBX: 5870000
Sede CAN: Av. Carrera 50 No. 26- 55 int. 2 Tel 5880070
Call Center 5232695. Línea 01800-910165
Web: www.sic.gov.co e-mail: info@sic.gov.co
Bogotá D.C. Colombia

**REPUBLICA DE COLOMBIA
SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO**

RESOLUCION Nº 2 2 0 0 9

Por la cual se otorga una patente de invención

CERTIFICADO

Rad. PCT/ 05-1801

EL SUPERINTENDENTE DE INDUSTRIA Y COMERCIO

en ejercicio de sus facultades legales, en especial de las que se confirieron en el artículo 4, numeral 5 del decreto 2153 de 1992, y

CONSIDERANDO:

PRIMERO: Que la solicitud internacional PCT/EP 2003/007198 de fecha 04 de julio del 2003, correspondiente a la patente de invención titulada "INHIBIDORES DE CINASAS DE TIROSINA", fue radicada en esta Superintendencia el 12 de enero del 2005 bajo el número 05001801, para los efectos de que se dé comienzo a la fase nacional en virtud del Tratado de Cooperación en Materia de Patentes (PCT).

SEGUNDO: Que el extracto de esta solicitud fue publicado en la Gaceta de la Propiedad Industrial Nº 568 del 29 de septiembre del 2006, sin que se hubieran presentado oposiciones por parte de terceros.

TERCERO: Que realizado el examen de fondo se requirió al solicitante en los términos del artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, para que presentara respuesta a las observaciones de carácter técnico visibles a folios 259 a 263 del cuaderno administrativo, relacionadas con la patentabilidad o cumplimiento de los requisitos establecidos por esta Decisión, para la concesión de la patente.

CUARTO: Que el solicitante mediante escrito radicado bajo el número 05-001801-00010-0000 del 09 de febrero del 2009, atendió oportunamente el requerimiento formulado, presentando nuevos folios 304 a 309 con el texto de las reivindicaciones que reemplazan las originalmente presentadas, atendiendo de esta manera las observaciones efectuadas en el examen de fondo. El nuevo capítulo reivindicatorio se acepta, como quiera que se ajusta a las prescripciones contenidas en el artículo 34 de la Decisión 486.

QUINTO: Que en virtud de lo dispuesto en el artículo 14 de la Decisión 486 expedida por la Comisión de La Comunidad Andina se otorgarán patentes "...para las invenciones, sean de producto o de procedimiento, en todos los campos de la tecnología, siempre que sean nuevas, tengan nivel inventivo y sean susceptibles de aplicación industrial".

REPUBLICA DE COLOMBIA
SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

RESOLUCION

Nº 2 2 0 0 9

Por la cual se otorga una patente de invención

CERTIFICADO

Rad. PCT/ 05-1801

SEXTO: Que en el presente caso cumplen los requisitos indicados en el numeral anterior las reivindicaciones 1 a 9 contenidas en los folios 304 a 309, razón por la cual este Despacho encuentra procedente conceder para las mismas el privilegio de patente solicitado.

SEPTIMO: Que de acuerdo con el objeto concedido se modifica el título de la invención, el cual quedará de la siguiente manera: "PIRIMIDINILAMINO BENZAMIDAS SUSTITUIDAS COMO INHIBIDORES DE CINASAS DE TIROSINA".

RESUELVE:

ARTICULO PRIMERO: Otorgar el privilegio de patente de invención a la solicitud que entró en fase nacional en virtud del Tratado de Cooperación en Materia de Patentes (PCT), para la creación denominada:

**" PIRIMIDINILAMINO BENZAMIDAS SUSTITUIDAS COMO INHIBIDORES DE
CINASAS DE TIROSINA "**

Clasificación IPC: A 61 K 31/506.

Reivindicación(es): 1 a 9 **Folio(s):** 304 a 309.

Titular(es): NOVARTIS AG.

Domicilio(s): Basilea, Suiza.

Inventor(es): Werner Breitenstein, Pascal Furet, Sandra Jacob y Paul William Manley.

Prioridad Nº: 0215676.8 **Fecha:** 05 de julio del 2002 **País:** GB.
0229893.3 20 de diciembre del 2002 GB.

REPUBLICA DE COLOMBIA
SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

RESOLUCION **Nº 2 2 0 0 9**

Por la cual se otorga una patente de invención

CERTIFICADO

Rad. PCT/ 05-1801

Solicitud Internacional N°: PCT/EP 2003/007198 Fecha: 04 de julio del 2003

Vigente desde: 04 de julio del 2003 Hasta: 04 de julio del 2023

ARTICULO SEGUNDO: El titular tendrá los derechos y las obligaciones establecidos en la Decisión 486 de la Comisión de la Comunidad Andina y demás disposiciones legales vigentes sobre propiedad industrial, precisando que para mantener vigente la patente se deberá cancelar la tasa anual de mantenimiento conforme lo dispone el artículo 80 de la referida norma comunitaria.

ARTICULO TERCERO: Entregar al titular copia auténtica de esta resolución y el certificado de patente, previas las anotaciones en los libros de registro.

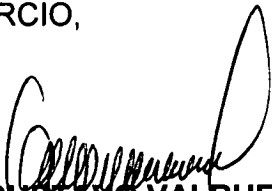
ARTICULO CUARTO: Notificar el contenido de la presente resolución a la doctora Jimena Escobar Uribe, en su calidad de apoderada de Novartis AG., o a quien haga sus veces, entregándole copia de la misma, advirtiéndole que contra ella procede el recurso de reposición ante el Superintendente de Industria y Comercio, del cual podrá hacer uso al momento de la notificación personal o dentro de los 5 días hábiles siguientes a ella.

NOTIFÍQUESE Y CUMPLASE

Dada en Bogotá, D.C., a los

30 ABR. 2009

EL SUPERINTENDENTE DE INDUSTRIA Y COMERCIO,


GUSTAVO VALBUENA QUIÑONES

Doctora
JIMENA ESCOBAR URIBE
Carrera 11 N° 86 – 53, Piso 6.
Bogotá D.C.

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

EL SECRETARIO GENERAL

Certifica que la Resolución 22009 de fecha 30/04/2009

fué notificado mediante listado número 82

fijado el 13/05/2009 y desfijado el 27/05/2009



No. 05-001801- -00015-0001

Fecha: 2009-07-06 15:11:56 Dep. 2020 NUECREACION
Tra. 11 PATENTEIYII Eve: 323 ANUALIDADES
Act. 411 PRESENTACION Folios: 3**Clarke, Modet & Cº**

COLOMBIA

**SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISIÓN DE NUEVAS CREACIONES**

EXPEDIENTE : 05.001.801
CERTIFICADO : 94
ASUNTO : Pago de tasa anual de mantenimiento

Yo, DILIA RODRÍGUEZ D'ALEMAN, domiciliada en Bogotá, D.C., en la carrera 11 No. 86-53, piso 6, identificada como aparece al pie de mi firma, obrando como apoderada sustituta en nombre y representación de la sociedad NOVARTIS AG., domiciliada en Basilea, Suiza, según poder cuyos particulares obran en el expediente de la referencia, manifiesto y pido a usted lo siguiente:

1. De conformidad con lo prescrito por el artículo 1 (Actuaciones Posteriores a la Concesión-Numeral 1.1.1.3.2) de la resolución No. 36155 de 28 de diciembre de 2006, adjunto el recibo No. 09-30,680 de 23 de abril de 2009, por valor de \$280.000, correspondiente al pago de la tasa anual de mantenimiento para el período de 30 de julio de 2009 a 30 de julio de 2010.

2. Ruego a usted expedir y ordenar que se me entregue el acto administrativo o constancia oficial de pago de la tasa anual de mantenimiento atrás mencionada y aquí cubierta.

Señor Superintendente,

DILIA RODRÍGUEZ D'ALEMAN

C.C. 41.654.882 Bogotá

T.P. 20824

2768/p

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 09 - 30,680
FECHA : ABRIL 23 DE 2009

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 05-001801- -00015-0001

Fecha: 2009-07-06 15:11:56 Dep. 2020 NUECREACIONE
Tra. 11 PATENTEIYII Eve: 323 ANUALIDADES
Act. 411 PRESENTACION Folios: 3

***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	Nº. PAGO	FECHA PGO	Vr. PAGO
CLARKE MODEY Y CO. COLOMB	CONSIGNACION	BANCO DE BOGOTA	062754387	111781530	23/04/2009	69,685,000.00

***** CONCEPTO *****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-09	OTROS SERVICIOS DE PROPIEDAD I *** TASA ANUAL AÑOS 4 a 8 PARA MANTEN	280,000.00

TOTAL : \$ 280,000.00

SON: DOSCIENTOS OCHENTA MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____

P-1891

325
318

Clarke, Modet & C^o

COLOMBIA

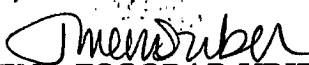
SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISION DE NUEVAS CREACIONES

REF:

EXPEDIENTE No. 05.001.801

SOLICITUD DE PATENTE A NOMBRE DE NOVARTIS AG

Yo, **JIMENA ESCOBAR URIBE**, identificada como aparece al pie de mi firma, domiciliada en la Carrera 11 No. 86-53 Piso 6, atentamente digo a usted que sustituyo el poder con que obro a la doctora **DILIA RODRIGUEZ D'ALEMAN**, domiciliada en Bogotá, D.C., portadora de la tarjeta profesional No. 20.824, con las mismas facultades con que me fueron conferidas para este caso.


JIMENA ESCOBAR URIBE

C.C. 39.779.452 de Usaquén

T.P. 68.228

Acepto sustitución


DILIA RODRIGUEZ D'ALEMAN

C.C. 41.654.882 de Bogotá

T.P. 20.824

PRESENTACION PERSONAL

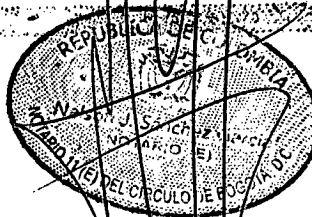
El anterior escrito fue presentado ante el
NOTARIO ONCE (E) DEL CIRCULO DE BOGOTA D.C.
personalmente por **JIMENA GONZALEZ**

quien exhibió la c.c. **377452**
y Tarjeta Profesional No. **188228** C.S.J.

Firma **30 JUN 2009**

Fecha **30 JUN 2009**

Nelson J. Sánchez García
NOTARIO (E)



SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO-SISTEMA DE NUEVAS CREACIONES
-ANUALIDADES-

Martes 8 de Septiembre de 2009 11:24:45

Enlaces

RADICACIÓN

Total Datos: 2 / 2

Expediente Año 2005 Número 1801 Control Sec-Even 2 Cons-Radi 16

Fecha Dia 11 Mes Agosto Año 2009 Hora 16:37:05 Certificado 94

Rad.

Trámite PCT-PATENTE DE INVENCION CAPITULOS I Y II

Evento ANUALIDADES

Estado PEND.APLICAC.DESGLOS
Act.

Siguiente PEND.APLICAC.DESGLOS

NUEVA CREACIÓN estado actual: CONCESION

Titulo PIRIMIDINILAMINOBENZAMIDAS SUSTITUIDAS COMO INHIBIDORES DE CINASAS DE TIROSINA

Sector (QF) QUIMICA FARMACEUTICA

Clasificación A61K 31/506 AC;

Vigencia Desde(dd/mm/aaaa):04/07/2003 Hasta: 04/07/2023 Libro: Folio: Tipo concesión: TOTAL Presentación 2005-01-12 16:43:47

Concesion 2009-04-30 16:05:21

PERSONA QUE EFECTUA EL PAGO

CC 79462057 CASTILLO BONILLA JERONIMO

Domicilio CALLE 93 A N.O. 14-17 OFICINA 311, BOGOTA D.C., COLOMBIA

OTRA INFORMACIÓN

Recibos	Año	Número recibo	Valor
	9	57908	350000.0
	Total		350000

Desde (dd/mm/aaaa): Hasta (dd/mm/aaaa):

Observac.

Si desea que esta consulta mejore, por favor reporte sus comentarios a la Oficina de Sistemas Oficina de Sistemas



Bogotá D.C.,
2020

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

RAD: 05-001801--0018 0002 Fecha: 2009-09-08 11:25:29
DEP: 20 NUECREACIONES
TRA: 11 PATENTEIYII EVE: 323 ANUALIDADES
ACT: 440 RESPUESTA Folios: 2

Doctor(a)

CASTILLO BONILLA JERONIMO

CALLE 93 A NO. 14-17 OFICINA 311
BOGOTA D.C.

Asunto: Radicación: 5 1801
Trámite: 11
Evento: 323
Actuación: 440
Folios: 2

Apreciado(a) doctor(a):

En atención al contenido de las comunicaciones relacionadas con el expediente citado en el asunto, adjunto le remito la certificación con la información de los pagos de la(s) tasa(s) de mantenimiento del certificado de Pct-patente de Invención Capítulos I Y II número 94.

Es de anotar que la aplicación de los pagos se hace de acuerdo a la fecha de presentación y al período solicitado en tal escrito. En el caso de presentar en la casilla período/estado: PENDIENTE APLICACIÓN O DESGLOSE; se solicita informe a esta oficina si desea que sea aplicado para el siguiente período, de ser así, deberá manifestarlo por escrito como complemento de información a la anualidad. Lo anterior debe hacerse de acuerdo a lo dispuesto en el artículo 80 de la Decisión 486/00 y la resolución de tarifas vigente.

En el evento de no aceptar la aplicación indicada en el párrafo anterior, si lo estima conveniente podrá solicitar por escrito el desglose del(los) mencionado(s) pago(s).

Atentamente,

MARIA CONSUELO CASIJ REY
Secretaría General Ad Hoc

RAD.:5 1801

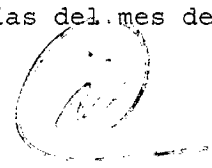
Secretaría General Ad Hoc

CERTIFICA

Que de conformidad con lo dispuesto en el artículo 80 de la Decisión 486 de la Comisión de la Comunidad Andina y las resoluciones de las tasas aplicables; se allegaron los siguientes recibos oficiales de caja, correspondientes a las tasas de mantenimiento del certificado de Pct-patente de Invención Capítulos I Y II número 94:

Recibo	Fecha Radicado	Presentado Por	Período o Estado (AAAA/MM/DD)
9-30680	2009/07/06	RODRIGUEZ D` ALEMAN DILIA MARIA	2009/07/04 al 2010/07/04
9-57908	2009/08/11	CASTILLO BONILLA JERONIMO	Pendiente aplicación o desglose

Se expide en Bogotá D.C., a los 08 días del mes de Septiembre de 2009


MARIA CONSUELO CASIJ REY

mbuitrag

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
División de Nuevas Creaciones
E. S. D.



Ref: PAGO DE ANUALIDAD-EXPEDIENTE No.05-001801
Solicitud de Patente de Invención a nombre de **NOVARTIS AG.**
Certificado 94

Por Resolución No.22009 del 30 de Abril de 2009 ese Despacho concedió el privilegio de Patente de Invención para PIRIMIDINILAMINO BENZAMIDAS SUSTITUIDAS COMO INHIBIDORES DE CINASAS DE TIROSINA, certificado 94 a nombre de NOVARTIS AG.

Para cumplir con lo dispuesto por el artículo 80 de la Decisión 486 de la Comisión de la Comunidad Andina, adjunto el recibo N° por concepto de la tasa anual para el mantenimiento de la patente, correspondiente al periodo comprendido entre el 04 de Julio de 2013 y el 04 de Julio de 2014.

Atentamente,

JERONIMO CASTILLO BONILLA
C.C. 79.462.057 Bogotá
T.P. 104167 C.S. Judicatura

323

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800.176.089-2

- / -



Industria y Comercio
SUPERINTENDENCIA

RECIBO DE CAJA

No. 13 - 0074761

Bogotá D.C., Julio 26 de 2013 - 16:13:35

RECIBIDO DE : CASTILLO PINEDA SAS

NI 860.046.502

***** Soporte del Pago *****

TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PAGO	VR PAGO
CONSIGNACION	BANCO DE BOGOTA	062754387	598172433	26/07/2013	51.111.000.00

***** Conceptos Pagados *****

CANT.	RENTISTICO	CONCEPTO	Vr.UNDITARIO	Vr.CONCEPTO
1	50005-01-09 OTROS SERVICIOS DE PROPIEDAD INDUSTRIAL	1612 TASA ANUAL A#OS 9 a 12 CUATRENIO PARA MANTENIMINETO DE	480.000.00	480.000.00
				\$480.000.00

SON: **CUATROCIENTOS OCHENTA MIL PESOS MONEDA CORRIENTE***

Responsable:

Recibo de Caja Aplicado al Expediente No. _____

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 05-001801- -00023-0006

Fecha: 2013-07-29 16:35:42 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 323 ANUALIDADES
Act. 411 PRESENTACION Folios: 2

Sede Centro: Carrera 13 No. 27 - 00 Pisos 3,4,5 y 10 Bogotá, D.C.- Colombia

Web: www.sic.gov.co e-mail: info@sic.gov.co Conmutador: (571) 5870000 Fax: (571) 5870284 Línea: 018000-910165 Call Center: (571) 6513240

Julio 26 de 2013 - 16:13:42

**SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISIÓN DE NUEVAS CREACIONES**

2020
Bogotá, D.C.,

Doctora
JIMENA ESCOBAR URIBE
Apoderada

ASUNTO	Radicación	05-1801
	Trámite	002
	Evento	001
	Actuación	430
	Oficio	Nº 1 4 5 3 8
	Folios	002

Como resultado del examen de búsqueda de anterioridades y con fundamento en el artículo 46 de la Decisión 486 de la Comisión de la Comunidad Andina, se le comunica:

1. SOLICITUD DE SUMINISTRO DE INFORMACIÓN

El artículo 46 de la Decisión 486 de la Comisión de la Comunidad Andina establece que: "La Oficina Nacional competente podrá requerir el informe de expertos o de organismos científicos o tecnológicos que se consideren idóneos, para que emitan opinión sobre la patentabilidad de la invención. Asimismo, cuando lo estime conveniente, podrá requerir informes de otras oficinas de propiedad industrial. De ser necesario, a efectos del examen de patentabilidad y a requerimiento de la oficina nacional competente, el solicitante proporcionará, en un plazo que no excederán de 3 meses, uno o más de los siguientes documentos relativos a una o más de las solicitudes extranjeras referidas total o parcialmente a la misma invención que se examina: ... b) copia de los resultados de exámenes de novedad o de patentabilidad efectuados respecto a esa solicitud extranjera; ... Si el solicitante no presentara los documentos requeridos dentro del plazo señalado en el presente artículo la oficina nacional competente denegará la patente".

Como consecuencia de la búsqueda de anterioridades de materia relacionada con la de la presente invención, se determinó que existen en el estado de la técnica los siguientes documentos, que eventualmente afectarían los requisitos de patentabilidad de esta solicitud:

- ZIMMERMANN J ET AL : « Potent and selective inhibitors of the Abl-kinase : phenylamino-pyrimidine (PAP) derivatives » BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, OXFORD, GB, vol. 7, no. 2, 21 January 1997 (1997-01-21), pages 187-192, XP004135990. ISSN : 0960-894X, examples 17, 24 ; table 1.
- ZIMMERMANN J ET AL : « phenylamino-pyrimidine (PAP) – derivatives : a new class of potent and highly selective PDGF-receptor autophosphorylation inhibitors » BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, OXFORD, GB, vol. 6, no. 11, 4 june 1996 (1996-06-04), pages 1221 – 1226, XP004134858, ISSN : 0960-894X, examples 3, 11 ; table 1.
- PAUL R ET AL : « Preparation of substituted N-phenyl-4-aryl-2-pyrimidinamines as mediator release inhibitors » JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY. WASHINGTON, US, vol. 36, no. 19, 17 September 1993

325

(1993-09-17), pages 2716-2725, XP002134022, ISSN : 0022-2623, examples 2-7, 2-22 ; table II.

Siendo que las publicaciones referenciadas hacen parte del resultado del examen de búsqueda realizado para la solicitud WO equivalente a esta solicitud colombiana aquí estudiada, y no siendo viable la consecución de dichos artículos por este despacho, se requiere que el solicitante, en virtud de lo establecido en el artículo 46 de la Decisión 486 de la Comisión de la Comunidad Andina, proporcione las publicaciones completas, con lo que podrá realizarse un análisis absoluto de la patentabilidad de la invención correspondiente a la presente solicitud.

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto (5), del título primero de la circular única N° 10 de 2001.

ALIX CARMENZA CÉSPEDES DE VERGEL
Jefe de la División de Nuevas Creaciones

El anterior requerimiento fue notificado por fijación en lista, de fecha 14 NOV. 2008

CONCEPTO TÉCNICO Nº: 2656	EXAMINADOR TÉCNICO Código Nº: 202087	EXAMINADOR JURÍDICO Código Nº:
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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISIÓN DE NUEVAS CREACIONES

2020
Bogotá, D.C.,

Abogada
JIMENA ESCOBAR URIBE
Apoderada

ASUNTO	Radicación	05001801
	Trámite	011
	Evento	379
	Actuación	430
	Oficio	Nº 1 4 5 3 7
	Folios	263

Patente de Invención ☐ Patente de Modelo de Utilidad ☐

Vía Nacional ☐

Vía PCT (fase nacional) ☐ Cap. I ☐ Cap. II ☐

No. Sol. Internacional PCT/EP2003/007198
Fecha de Presentación Internal. 4/07/2003

Como resultado del examen de fondo, realizado con fundamento en el artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se le comunica:

1. Documentos estudiados

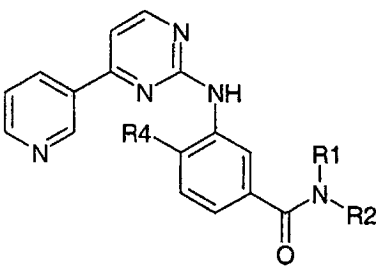
- 1.1. Descripción: Folios: 6 a 140
- 1.2. Reivindicaciones: Folios 141 a 157 como se radicó inicialmente
Folios 219 a 224 modificadas en fase nacional.
- 1.3. Prioridad: Fecha: 5/07/2002, 20/12/2002, país: UK y número:
0215676.8, 0229893.3

2. Objeto de la invención

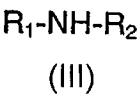
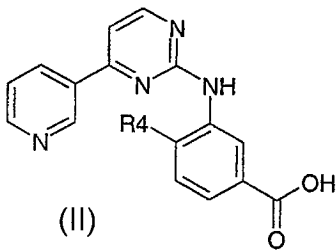
- Título de la solicitud: **INHIBIDORES DE CINASAS DE TIROSINA**. Número de folio: 1

El objeto de la presente solicitud de patente de invención consiste en:

Reivindicaciones 1 - 8: compuestos de la fórmula general (I) con sus respectivos sustituyentes y diferentes posibilidades estructurales.



Reivindicación 9: proceso (folio 155 y 223) para la síntesis de compuestos de la fórmula general (I) caracterizado porque un compuesto (II) que tiene un grupo carboxilo –COOH en forma activada reacciona con una amina (III) opcionalmente en la presencia de un agente de deshidratación y una base inerte y/o un catalizador adecuado y opcionalmente un solvente inerte.



Reivindicación 10: Composición que comprende un ingrediente activo de fórmula (I) junto con un vehículo farmacéuticamente aceptable.

El problema planteado en esta solicitud es la necesidad de compuestos útiles para la terapia de una enfermedad que responda a la inhibición de la actividad de la cinasa de proteína en especial una enfermedad neoplástica, en particular leucemia.

Para solucionar este problema técnico la solicitud en estudio proporciona novedosas pirimidinilaminobenzamidas sustituidas.

Clasificación Internacional de Patentes (IPC.): A61K 31/506

3. **Determinación del Estado de la Técnica**

La fecha que se ha tenido en cuenta para determinar el Estado de la Técnica es:

Fecha de presentación de la solicitud prioritaria 5/07/2002

Teniendo en cuenta la fecha indicada se realizó la búsqueda en el estado de la técnica de documentos relacionados con la solicitud encontrándose los siguientes documentos más relevantes:

Nº	Documento	Título	Fecha de publicación*
D ₁	EP 0588762	FURTHER USE OF PYRIMIDINE DERIVATIVES	14/05/1996
D ₂	WO 95/09853	PHARMACOLOGICALLY ACTIVE PYRIDINE DERIVATIVES AND PROCESSES FOR THE PREPARATION THEREOF	13/04/1995

4. De la solicitud de Patente

4.1. Reivindicaciones (artículo 30 D 486)

Una vez revisado el capítulo reivindicatorio esta dependencia encuentra:

- Al parecer existe un error de redacción en la página 139. Se requiere al solicitante realizar las correcciones necesarias para dar claridad a lo que se pretende proteger.

5. Análisis de patentabilidad (artículo 14 D486)

5.1. Novedad (artículo 16 D486)

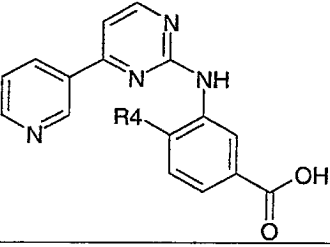
Reivindicación 9: proceso para la síntesis de compuestos de la fórmula general (I) caracterizado porque un compuesto (II) que tiene un grupo carboxilo –COOH en forma activada reacciona con una amina (III).

D2 enseña (ver folio 236 y siguientes) procesos para derivados de N-fenil-2-pirimidinamina de fórmula (I) para ser usados en el tratamiento de enfermedades tumorales.

Así las cosas el proceso reivindicado se superpone con el proceso del documento D2, por lo tanto no es novedoso, pues ya se conocía en el estado de la técnica (ver folios 249 - 251).

- ♦ Las dos etapas característicos del proceso reivindicado es decir: **un compuesto con un grupo carboxilo que reacciona en forma activada con una amina** habían sido divulgados previamente en el Estado de la Técnica (según la tabla siguiente:

TABLA 1

CARACTERÍSTICAS REIVINDICADAS	D ₂
	Si
R ₁ -NH-R ₂	Si

De manera que el objeto de la reivindicación 9 no es nuevo.

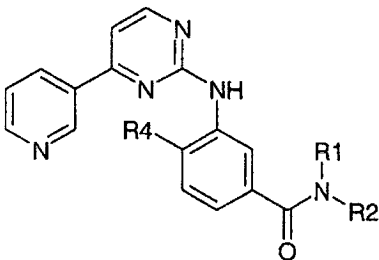
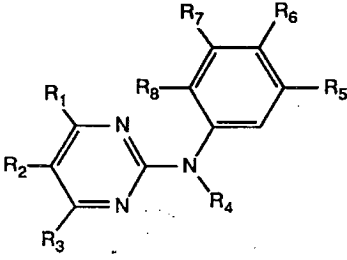
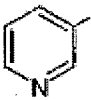
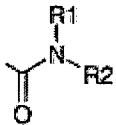
5.2. Nivel inventivo (artículo 18 D486)

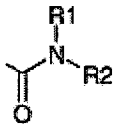
La presente Solicitud de Patente reivindica (de 1 - 8) un compuesto de fórmula general I y (10) una composición que está conformada por dicho compuesto:

Dicho compuesto se ve afectado por el siguiente documento más cercano del Estado de la Técnica:

D₁ que enseña el uso de derivados conocidos N-fenil-2-pirimidina para inhibir la proteína quinasa C o como agentes antitumorales (Ver folios: 226-235).

TABLA 2

SOLICITUD		ANTERIORIDAD (D ₁)		Comparación
(I)		(1)		
		R ₃	3-píridil	IGUAL
		R ₁ , R ₂	H	IGUAL
	H	R ₄	H	IGUAL
R ₄	Alquilo, halógeno	R ₈	Alquilo, halógeno	IGUAL
		R ₅	-NH-C(=O)-R	DIFERENTE

La única **diferencia con D₁** es que esta solicitud **posee un radical**  como sustituyente adicional en R₂ pero esta diferencia no parece conceder un efecto técnico inesperado ya que a pesar de que el capítulo descriptivo muestra mediante protocolos de ensayos y anexando algunos resultados que hacen referencia que una selección de los compuestos reivindicados parecen ser activos contra algunas cinasas (folios 23 - 31) no se observa algún efecto sorprendente o superioridad con respecto a lo conocido pues los resultados presentados son pocos con respecto a todo lo que la descripción insinúa haber ensayado y además no se presentan resultados que evidencien las ventajas o el salto tecnológico de los compuestos con respecto al estado de la técnica y/o una mejora comparativa en los niveles de actividad.

De esta forma el Problema Técnico Objetivo fundamental de la Invención Reivindicada no puede definirse y los compuestos y composiciones reivindicados se consideran tan solo una alternativa, sin algún salto tecnológico que lo haga superior a **lo previamente conocido**.

Por consiguiente, de acuerdo a las consideraciones expuestas anteriormente, resultaría obvio el diseño de este tipo de compuestos y composiciones para un experto en la materia.

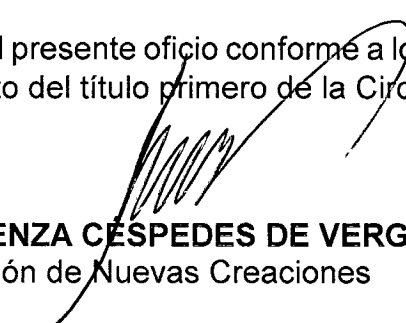
6. Conclusión:

Los requisitos de patentabilidad de la presente solicitud se encuentran afectados así:

N°	Documento N°	Reivindicaciones afectadas	Requisito que afecta
D ₁	EP0588762	1-8, 10	NIVEL INVENTIVO
D ₂	WO 95/09853	9	NOVEDAD

En cumplimiento del artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se le indica que debe dar respuesta dentro del término de 60 días contados a partir de la fecha de notificación de la presente comunicación. En caso de no dar respuesta al presente requerimiento, o si a pesar de la respuesta subsistieran los impedimentos para la concesión, se denegará la patente.

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del título primero de la Circular Única N° 10 de 2001.


ALIX CARMENZA CÉSPEDES DE VERGEL
Jefe de División de Nuevas Creaciones

El anterior requerimiento fue notificado por fijación en lista, de fecha 11 4 NOV. 2008

CONCEPTO TÉCNICO No. 2656	EXAMINADOR TÉCNICO Código No. 202087
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SUPERINTENDENCIA DE INDUSTRIA Y COM
División de Nuevas Creaciones
E. S. D.



Ref: PAGO DE ANUALIDAD-EXPEDIENTE No.05-001801
Solicitud de Patente de Invención a nombre de **NOVARTIS AG.**
Certificado 94

Por Resolución No.22009 del 30 de Abril de 2009 ese Despacho concedió el privilegio de Patente de Invención para PIRIMIDINILAMINOBENZAMIDAS SUSTITUIDAS COMO INHIBIDORES DE CINASAS DE TIROSINA, certificado 94 a nombre de NOVARTIS AG.

Para cumplir con lo dispuesto por el artículo 80 de la Decisión 486 de la Comisión de la Comunidad Andina, adjunto el recibo N° por concepto de la tasa anual para el mantenimiento de la patente, correspondiente al periodo comprendido entre el 04 de Julio de 2014 y el 04 de Julio de 2015.

Atentamente,

JERONIMO CASTILLO BONILLA
C.C. 79.462.057 Bogotá
T.P. 104167 C.S. Judicatura

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800.176.089-2

- / -

297
332Industria y Comercio
SUPERINTENDENCIA

RECIBO DE CAJA

No. 14 - 0078190

Bogotá D.C., Julio 23 de 2014 - 15:08:06

RECIBIDO DE : CASTILLO PINEDA SAS

NI 860.046.502

*** Soporte del Pago ***

TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PAGO	VR PAGO
CONSIGNACION	BANCO DE BOGOTA	062754387	686794942	23/07/2014	63.647.000.00

*** Conceptos Pagados ***

CANT.	RENTISTICO	CONCEPTO	Vr.UNDITARIO	Vr.CONCEPTO
1	50005-01-09 OTROS SERVICIOS DE PROPIEDAD INDUSTRIAL	1612 TASA ANUAL A#OS 9 a 12 CUATRENIO PARA MANTENIMINETO DE	494.000.00	494.000.00
				\$494.000.00

SON: **CUATROCIENTOS NOVENTA Y CUATRO MIL PESOS MONEDA CORRIENTE**

Responsable: _____

Recibo de Caja Aplicado al Expediente No. _____

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 05-001801- -00025-0008

Fecha: 2014-07-25 12:56:22
Tra. 11 PATENTEIYII
Act. 411 PRESENTACIONDep. 2020 DIR.NUEVASCR
Eve: 323 ANUALIDADES
Folios: 2

Sede Centro: Carrera 13 No. 27 - 00 Pisos 3,4,5 y 10 Bogotá, D.C.- Colombia

Web: www.sic.gov.co e-mail: Info@sic.gov.co Conmutador: (571) 5870000 Fax: (571) 5870284 Línea: 018000-910165 Call Center: (571) 6513240

Julio 23 de 2014 - 15:08:22

Pedro Castillo Pineda & Asociados
ABOGADOS

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
División de Nuevas Creaciones
E. S. D.

2927
333

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

No. 05-001801- -00027-0009

Fecha: 2015-07-30 09:39:42 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 323 ANUALIDADES
Act. 411 PRESENTACION Folios: 2

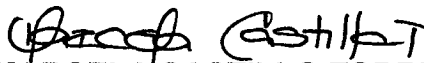
61

Ref: PAGO DE ANUALIDAD-EXPEDIENTE No.05-001801
Solicitud de Patente de Invención a nombre de **NOVARTIS AG.**
Certificado 94

Por Resolución No.22009 del 30 de Abril de 2009 ese Despacho concedió el privilegio de Patente de Invención para PIRIMIDINILAMINOBENZAMIDAS SUSTITUIDAS COMO INHIBIDORES DE CINASAS DE TIROSINA, certificado 94 a nombre de NOVARTIS AG.

Para cumplir con lo dispuesto por el artículo 80 de la Decisión 486 de la Comisión de la Comunidad Andina, adjunto el recibo N° por concepto de la tasa anual para el mantenimiento de la patente, correspondiente al periodo comprendido entre el 04 de Julio de 2015 y el 04 de Julio de 2016.

Atentamente,


MARCELA CASTILLO TORRES
T.P. 80331 C.S. Judicatura
C.C. 39.784.109 Usaquén

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800.176.089-2

- / -

334



Industria y Comercio

SUPERINTENDENCIA

RECIBO DE CAJA

No. 15 - 0082204

Bogotá D.C., Julio 24 de 2015 - 09:39:40

RECIBIDO DE : CASTILLO PINEDA SAS

NI 860.046.502

*** Soporte del Pago ***

TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PAGO	VR. PAGO
CONSIGNACION	BANCO DE BOGOTA	062754387	699629862	23/07/2015	70.001.000.00

*** Conceptos Pagados ***

CANT.	RENTISTICO	CONCEPTO	Vr.UNDITARIO	Vr.CONCEPTO
1	50005-01-09 OTROS SERVICIOS DE PROPIEDAD INDUSTRIAL	1613 TASA ANUAL A#OS 13 a 16 PARA MANTENIMINETO DE PATENTE D	790.000.00	790.000.00
				\$790.000.00

SON: **SETECIENTOS NOVENTA MIL PESOS MONEDA CORRIENTE**

Responsable: _____

Recibo de Caja Aplicado al Expediente No. _____

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 05-001801- -00027-0009

Fecha: 2015-07-30 09:39:42 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 323 ANUALIDADES
Act. 411 PRESENTACION Folios: 2

Sede Centro: Carrera 13 No. 27 - 00 Pisos 3,4,5 y 10 Bogotá, D.C.- Colombia

Web: www.sic.gov.co e-mail: info@sic.gov.co Conmutador: (571) 5870000 Fax: (571) 5870284 Línea: 018000-910165 Call Center: (571) 6513240

Julio 24 de 2015 - 09:40:06

Pedro Castillo Pineda & Asociados
ABOGADOS

Superintendencia de Industria y Comercio
Radicado: 05001801 009027 Folios: 2
Dependencia: Desc Fecha: 2016-07-29 17:33:33
Tipo aplicación: Documentos independientes

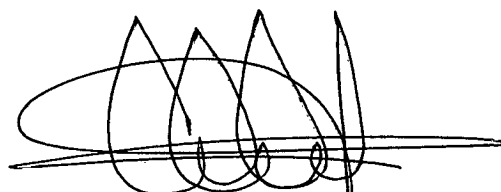
SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
División de Nuevas Creaciones
E. S. D.

Superintendencia de Industria y Comercio
Radicado: 05001801 009027 Folios: 2
Dependencia: 2020 Fecha: 2016-07-29 17:33:48
Tipo aplicación: Documento independiente

Ref: PAGO DE ANUALIDAD-EXPEDIENTE No.05-001801
Solicitud de Patente de Invención a nombre de **NOVARTIS AG.**
Certificado 94

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Atentamente,



JERONIMO CASTILLO BONILLA
C.C. 79.462.057 Bogotá
T.P. 104167 C.S. Judicatura

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800.176.089-2

- / -

336



RECIBO DE CAJA

No. 16 - 0074373

Bogotá D.C., Julio 29 de 2016 - 16:18:59

RECIBIDO DE : CASTILLO PINEDA SAS

NI 860.046.502

*** Soporte del Pago ***

TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PAGO	VR PAGO
CONSIGNACION	BANCO DE BOGOTA	062754387	854503296	29/07/2016	18.076.000.00

*** Conceptos Pagados ***

CANT.	RENTISTICO	CONCEPTO	Vr.UNDITARIO	Vr.CONCEPTO
1	50005-01-09 OTROS SERVICIOS DE PROPIEDAD INDUSTRIAL	1613 TASA ANUAL A#OS 13 a 16 PARA MANTENIMIENTO DE PATENTE DE INVENCIÓN	983.000.00	983.000.00
			=====	\$983.000.00

SON: **NOVECIENTOS OCHENTA Y TRES MIL PESOS MONEDA CORRIENTE***

Responsable: _____

Recibo de Caja Aplicado al Expediente No. _____

Superintendencia de Industria y Comercio



Radicado: 05001801 009027 **Folios:** 2
Dependencia: Desc **Fecha:** 2016-07-29 17:33:33
Tipo aplicación: Documentos independientes

Superintendencia de Industria y Comercio



Radicado: 05001801 009027 **Folios:** 2
Dependencia: 2020 **Fecha:** 2016-07-29 17:33:48
Tipo aplicación: Documento independiente

Sede Centro: Carrera 13 No. 27 - 00 Pisos 3,4,5 y 10 Bogotá, D.C.- Colombia

Web: www.sic.gov.co e-mail: info@sic.gov.co Conmutador: (571) 5870000 Fax: (571) 5870284 Línea: 018000-910165 Call Center: (571) 6513240

Julio 29 de 2016 - 16:19:01

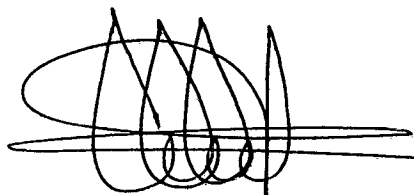
SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
División de Nuevas Creaciones
E. S. D.



Ref: PAGO DE ANUALIDAD-EXPEDIENTE No.05-001801
Solicitud de Patente de Invención a nombre de **NOVARTIS AG.**
Certificado 94

Para cumplir con lo dispuesto por el artículo 80 de la Decisión 486 de la Comisión de la Comunidad Andina, adjunto el recibo N° por concepto de la tasa anual para el mantenimiento de la patente, correspondiente al periodo comprendido entre el 04 de Julio de 2017 y el 04 de Julio de 2018.

Atentamente,



JERONIMO CASTILLO BONILLA
C.C. 79.462.057 Bogotá
T.P. 104167 C.S. Judicatura

338 297

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800.176.089-2

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RECIBO DE CAJA

No. 17 - 0057825

Bogotá 1/2 D.C., Julio 24 de 2017 - 16:18:55

RECIBIDO DE : CASTILLO PINEDA SAS

NI.860.046.502

*** Soporte del Pago ***

TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PAGO	VR. PAGO
CONSIGNACION	BANCO DE BOGOTA	062754387	794005925	24/07/2017	101.945.000.00

*** Conceptos Pagados ***

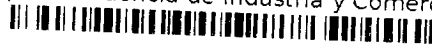
CANT.	RENTISTICO	CONCEPTO	Vr.UNITARIO	Vr.CONCEPTO
1	50005-01-09 OTROS SERVICIOS DE PROPIEDAD INDUSTRIAL	1613.TASA ANUAL A#OS 13 a 16 PARA MANTENIMIENTO DE PATENTE DE INVENCIÓN	1.050.000.00	1.050.000.00
				\$1.050.000.00

SON: **UN MILLON CINCUENTA MIL PESOS MONEDA CORRIENTE**

Responsable: _____

Recibo de Caja Aplicado al Expediente No. _____

Superintendencia de Industria y Comercio



Radicado: NC2017/0007653 Folios 2
Dependencia: 2020 Fecha: 2017-07-28 9:44:7
Tipo aplicación: Anualidad
Número referenciado: 05001801

Sede Centro: Carrera 13 No. 27 - 00 Pisos 3,4,5 y 10 Bogotá 1/2, D.C.- Colombia

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Julio 24 de 2017 - 16:19:16

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