



Señor

SUPERINTENDENTE DE INDUSTRIA Y COMERCIO

E.

S.

D.

REF: EXPEDIENTE 06 078.330

TÍTULO SOLICITADO: COMPUESTOS DERIVADOS DE PIRAZOLO [1,5-A]
PIRIMIDINA COMO INHIBIDORES DE QUINASA
DEPENDIENTE DE CICLINA (CDK)

PUBLICACIÓN: Gaceta 583 del 18/12/2007 número de publicación 708.

SOLICITANTE: SCHERING CORPORATION y PHARMACOEPIA DRUG
DISCOVERY INC.

APODERADO: CARLOS REINALDO OLARTE.

TRÁMITE: RECURSO DE REPOSICION CONTRA LA RESOLUCIÓN
26539 DE 27/04/2012.

JOSÉ LUIS REYES VILLAMIZAR, mayor de edad, identificado como aparece al pie de mi firma, reconocido apoderado de la sociedad **LAFRANCOL S.A.**, en el asunto de la referencia, de manera respetuosa, y dentro de los términos de ley, remito **Recurso de Reposición** contra la Resolución 26539 de 27/04/2012, por la cual se concede a la solicitud **06 078.330** el privilegio de patente de invención. Lo anterior, con el fin de que su Despacho se sirva dar curso a las siguientes

I. **PETICIONES**

PRIMERA. – (PRINCIPAL).- Con base en la información que obra en el expediente, y en aquella que se ha planteado con ocasión del presente recurso, sírvase revocar íntegramente la Resolución 26539 de 27/04/2012, y en su reemplazo, emitir otra que, además de declarar fundada la oposición presentada por el suscrito en nombre de Lafrancol S.A., niegue el privilegio de patente solicitado en el trámite del expediente 06 078.330, ordenando en consecuencia el archivo definitivo del mismo.

SEGUNDA. – (SUBSIDIARIA).- En subsidio de la petición precedente, ruego que en consonancia con recientes decisiones adoptadas por el Despacho, en particular de la proferida mediante Resolución 46284 de 11/09/2009 en el trámite del expediente 05.004.944, se revoque íntegramente la citada Resolución 26539 de 27/04/2012, y se emita otra que en su reemplazo, sin entrar a resolver en este momento el fondo del asunto, revoque la concesión y ordene la devolución del expediente a la Dirección de Nuevas Creaciones, con el fin de que se realice allí un nuevo y profundo examen de patentabilidad basado en el artículo 45 de la Decisión 486 de 2000, en el cual se tengan en cuenta todas las anterioridades y argumentos planteados en la oposición y surgidos con ocasión del presente recurso, para proceder luego a resolver, también negativamente, la solicitud de patente que motiva estas diligencias, ordenando de igual manera el archivo del expediente respectivo.

II. FUNDAMENTOS DEL RECURSO Y MOTIVOS DE INCONFORMIDAD

Además de reiterar que el presente recurso está siendo presentado en la debida oportunidad legal, y con el cumplimiento de todos los requisitos legales aplicables, me permito invocar como fundamento de las peticiones planteadas, la disposición imperativa incluida en el artículo 59, inciso 2º del Código Contencioso Administrativo, según la cual “La decisión (en la vía gubernativa) **resolverá todas las cuestiones** que hayan sido planteadas **y las que aparezcan con motivo del recurso**, así no lo hayan sido antes”. (Paréntesis y negrilla fuera del texto). Paso a plantear a continuación los argumentos del presente recurso:

2.1. Inconsistencias Técnicas y Jurídicas de la Resolución 26539 de 27/04/2012 – Se ha valorado un capítulo reivindicatorio y se ha otorgado otro diferente.

En primer lugar, debo anotar que el capítulo reivindicatorio otorgado fue presentado ante la SIC el 16 de marzo de 2012, en 8 reivindicaciones, al paso que el análisis de patentabilidad y la concesión derivada de éste, se basaron en el documento radicado por el solicitante el 24 de mayo de 2011 en 11 reivindicaciones, circunstancia que de suyo elimina la legalidad de la resolución que nos ocupa, y debería dar lugar a la revocatoria solicitada.

Lo expuesto se hace evidente en el numeral 5.2 de dicha resolución, cuando se expresa que *“por otro lado, respecto al nivel inventivo de la presente solicitud, los solicitantes señalan que el arte previo citado por el opositor no proporcionan enseñanzas concretas que hubiesen conducido a la persona medianamente versada en la materia, justamente al desarrollo de los compuestos reclamados en las nuevas **reivindicaciones 1 a 13**, esperando obtener compuestos activos como inhibidores de CDK.”* (negrilla y subrayado fuera del texto).

Cabe también indicar que dichas “reivindicaciones 1 a 13” resaltadas en el párrafo anterior no hacen referencia a ninguno de los dos capítulos reivindicatorios modificados presentados en este caso, pues **ninguno de los dos consta de dichas 13 reivindicaciones**; ello, habida cuenta de que el capítulo reivindicatorio modificado, de fecha 24 de mayo de 2011 consta de **11** reivindicaciones, y el capítulo reivindicatorio modificado y concedido, de fecha 16 de marzo, consta de **8** reivindicaciones, pero en ningún caso de **13** reivindicaciones.

Así las cosas, en tanto existe un insalvable y determinante error entre los apartes considerativo y resolutivo de la resolución que nos ocupa, y habida cuenta de que dicho error demuestra que la valoración de patentabilidad en este caso fue conducida de manera errónea, ruego se acceda a las peticiones antes formuladas.

2.2. El capítulo reivindicatorio a la postre concedido fue presentado por fuera del término para dar contestación al requerimiento emitido por el Despacho al amparo del artículo 45 de la decisión 486.

Por si la consideración expuesta en el numeral precedente no fuese suficiente para acceder a las peticiones planteadas, debo llamar la atención al hecho igualmente relevante, en el sentido de que el capítulo reivindicatorio modificado, que consta de 11 reivindicaciones, radicado el 24 de mayo de 2011, fue reemplazado por otro presentado el **16 de marzo de 2012** a través de un formulario de correcciones y modificaciones, es decir, once (11) meses después de la contestación al requerimiento de artículo 45 antes referido, **sin que el solicitante, al menos de acuerdo con el sistema público de consultas de la SIC, haya pedido prórroga de términos alguna, ni cancelado el valor de las tasas correspondiente a dicha solicitud de prórroga, circunstancia que, una vez más de suyo, invalida el capítulo reivindicatorio así presentado, y por supuesto, el privilegio de**

patente otorgado –dicho sea de paso, con llamativa celeridad- al amparo del mismo.

- 2.3. Las modificaciones hechas a la solicitud modificaron su naturaleza; por ende, el examen de fondo y la valoración del estado de la técnica eran aplicables a la versión original, pero no a la modificada y a la postre otorgada.**

En primer lugar, se debe tener en cuenta lo expresado por el Manual Andino de Patentes (MAP) –norma superior de aplicación preferente a la Guía de Patentes que viene aplicando la SIC-, cuando expresa que dentro de las funciones del examinador de fondo¹ se encuentran la preclasificación y clasificación de las solicitudes, la búsqueda de antecedentes y el requerimiento de información. Muy respetuosamente se estima que dichas funciones no fueron cumplidas a cabalidad por dicho examinador, de acuerdo con los siguientes argumentos:

- a) En la resolución que concede, dentro de la Clasificación IPC que se hace, aparecen los códigos de clasificación A61K 31/495 (que se refiere a preparaciones medicinales que contienen ingredientes orgánicos activos que tienen ciclos con seis eslabones con dos nitrógenos como únicos heteroátomos de un ciclo) y el código A61P 35/00 (que se refiere a agentes antineoplásicos), y teniendo en cuenta lo que define en el artículo 30 de la Decisión 486 (*“Las reivindicaciones definirán la materia que se desea proteger mediante la patente”*), consideramos que, en primer lugar, dicha clasificación hecha por el examinador y presente en la resolución es incorrecta, dado que lo reivindicado por el capítulo concedido no se refiere a preparaciones medicinales ni mucho menos a agentes antineoplásicos;
- b) en segundo lugar, consideramos que el examinador debió basar su análisis en una nueva búsqueda en el estado de la técnica, de acuerdo con las nuevas características del capítulo reivindicatorio modificado; de acuerdo con el MAP²:

La búsqueda tiene por objetivo establecer el “estado de la técnica” más próximo en la esfera particular propia de la solicitud de patente de invención que se examina y con anterioridad a la fecha de su presentación o de su prioridad validamente invocada, a efecto de poder determinar con base en éste, si la invención es nueva e inventiva.

¹ MAP. Capítulo III, numeral 1.1.

² MAP. Capítulo III. Numeral 7.1

Es decir, haber definido una búsqueda de antecedentes donde ya no se involucraran preparaciones farmacéuticas ni combinaciones farmacológicas ni compuestos con actividades terapéuticas y/o métodos de tratamiento asociados.

- c) En tercer lugar, debió haber requerido información al solicitante de acuerdo con los hallazgos de una nueva búsqueda de antecedentes.
- d) En el mismo sentido, se considera que el título bajo el cual se concedió la solicitud (COMPUESTOS DERIVADOS DE PIRAZOLO [1,5-A] PIRIMIDINA COMO INHIBIDORES DE QUINASA DEPENDIENTE DE CICLINA (CDK)) no corresponde con el contenido del capítulo reivindicatorio concedido, puesto que dicha actividad farmacológica no es una característica que se mencione para los compuestos mencionados en las reivindicaciones concedidas.

2.4. Existen documentos relevantes en el estado de la técnica que fueron ignorados por el examinador de fondo.

- En primer lugar, al hacer búsqueda en bases de datos de patentes, utilizando como palabras claves "pyrazolo*", "pyrimidine*" y "1,5-a"; y restringiendo dicha búsqueda con el código CIP C07D 487/04 (que se refiere a Compuestos heterocíclicos que contienen átomos de nitrógeno como únicos heteroátomos del ciclo en el sistema condensado, no previstos por los grupos C07D 451/00-C07D 477/00, específicamente a Sistemas condensados en orto) que es el código CIP que cita el examinador y que corresponde a una clasificación adecuada de la solicitud, se obtienen los siguientes documentos, que deberían ser tenidos en cuenta por el examinador para su análisis, en especial a lo que se refiere al nivel inventivo del capítulo reivindicatorio modificado:

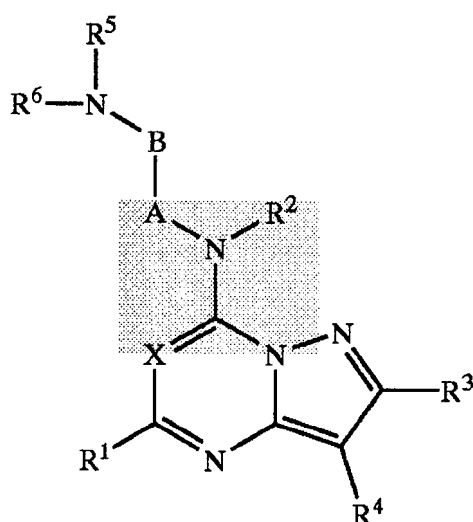
Publicación	Título
US2003134862 (A1)	Compounds
WO03053976 (A1)	PIPAZOLO [1,5-a] PYRIMIDINE DERIVATIV...
DE10223917 (A1)	New 7-amino-6-aryl-pyrazolo-(1,5-a)-p...
US2003069246 (A1)	Certain alkylene diamine-substituted ...
DE10153344 (A1)	Medicaments for treating e.g. epileps...
DE10112197 (A1)	Medicaments for treating e.g. epileps...
US6372749 (B1)	Pyrazolo[1,5-a]pyrimidine derivatives
US6476038 (B1)	Amino substituted pyrazolo[1,5,-a]-1,...
FR2784380 (A1)	New 7-oxy or 7-thio-substituted triaz...
US5985882 (A)	Pyrazolo[1,5-a]pyrimidine derivatives
JP10101671 (A)	NITROGEN MONOXIDE SYNTHASE INHIBITOR
US5843951 (A)	Analgesic composition of pyrazolo(1,5...
JP10218881 (A)	NEW PYRROLOPYRAZOLOPYRIMIDINE DERIVATIVE
US5707997 (A)	Pyrazolo[1,5-a]pyrimidine derivative
US5538977 (A)	3-Substituted-7-[3-(imidazol-1-yl)phe...

Publicación	Título
EP0628559 (A1)	Pyrimidine compounds and their use as...
KR100191774 (B1)	PYRAZOLO(1,5-ALPHA)PYRIMIDINE DERIVAT...
DE4333705 (A1)	Arylmethyl-substituted pyrazolo-azine...
EP0562236 (A1)	Process for the synthesis of 5- not (...)
US5247086 (A)	Process for the synthesis of 5-[(subs...
US5169850 (A)	N-(dialkylamino)methylene)-substitute...
DE4029324 (A1)	HAIR DYES
FI89487 (B)	Process for the preparation of therap...
US5126340 (A)	4-[(substituted)alkylcarbonyl]-4,5-di...
US5059691 (A)	N-((dialkylamino)methylene)-substitut...
WO8906535 (A1)	2-OXO-1-SUBSTITUTED PYRAZOLO[1,5-a]PY...
US4963553 (A)	4-[(substituted) alkylcarbonyl]-4,5-d...
US4870072 (A)	2-oxo-1-substituted pyrazolo[1,5-A]py...
US4859676 (A)	2-Oxo-1-sulfonyl pyrazolo(1,5-a) pyri...
HU203103 (B)	PROCESS FOR PRODUCING PYRAZOLO(1,5-A)...

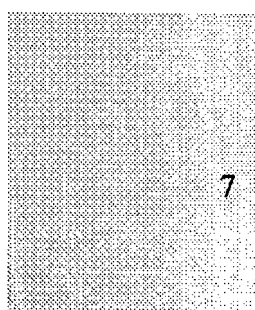
Publicación	Título
HUT47276 (A)	PROCESS FOR PRODUCING PYRAZOLO/1,5-A/...
IL82356 (A)	2-SUBSTITUTED PYRAZOLO(1,5-A)PYRIMIDI...
US4626538 (A)	[7-(3-disubstituted amino)phenyl]pyra...
US4576943 (A)	Pyrazolo[1,5-a]pyrimidines
JP60100581 (A)	PYRAZOLO(1,5-A)PYRIMIDINE DERIVATIVE,...
GB2117764 (A)	Substituted ethenyl derivatives of 1H...
SU1366060 (A3)	METHOD OF OBTAINING SUBSTITUTED 1H-PY...
IE830563 (L)	1H-PYRAZOLO GBP 1,5-a PYRIMIDINES
GB2116971 (A)	1H-pyrazolo [1,5-a] pyrimidines
HU182153 (B)	PROCESS FOR PREPARING SUBSTITUTED PYR...
IE801395 (L)	SUBSTITUTED PYRAZOLO (1, 5-a) PYRIMID...
SU833973 (A1)	METHOD OF PRODUCING 3H-PYRAZOLO/1,5-C...
US4178449 (A)	Pyrazolo[1,5-a]pyrimidines and imidaz...
US4093617 (A)	3,5,7-Trisubstituted pyrazolo{8 1,5-a...
GB1412017 (A)	PYRAZOLO 1,5A PYRIMIDINES
IE36629 (B1)	PYRAZOLO-PYRIMIDINES USEFUL AS ZANTHI...
GB1333311 (A)	N-BRIDGED BICYCLIC HETEROAROMATIC COM...
DE2131790 (A1)	Pyrazolo(1,5-c)pyrimidine derivs - wi...
GB1011048 (A)	Pyrazolopyrimidine derivative and the...
GB835918 (A)	Manufacture of alkylated pyrazolopyri...

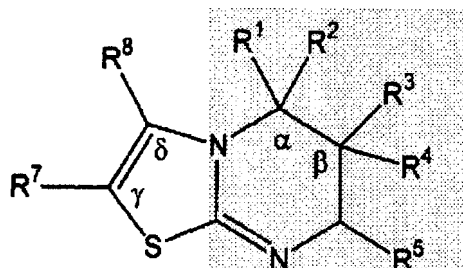
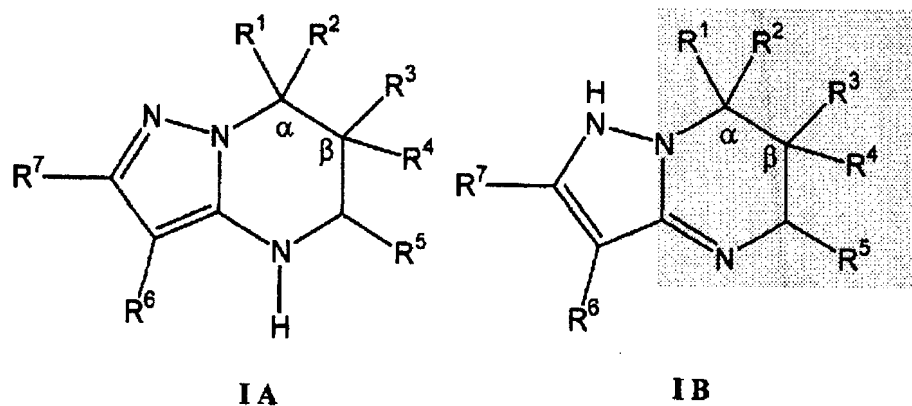
Dentro de estos documentos, son de especial atención los compuestos revelados por las siguientes patentes:

Patente americana US 2003069246 publicada el 10 de abril de 2003, revela compuestos del tipo:

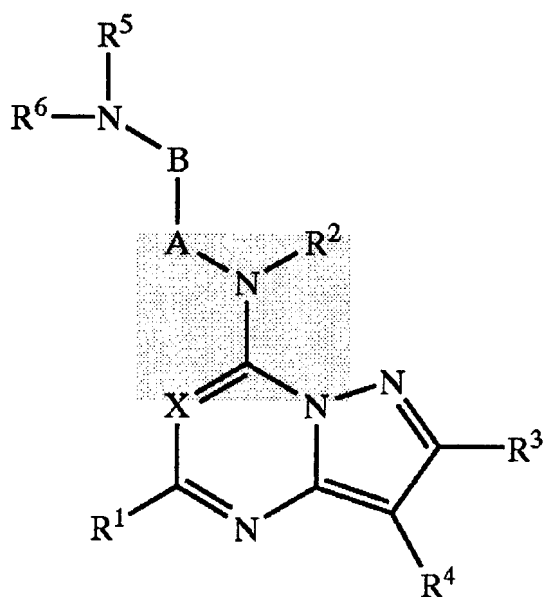


La patente alemana DE 10112197 publicada el 19 de septiembre de 2002, revela compuestos del tipo:

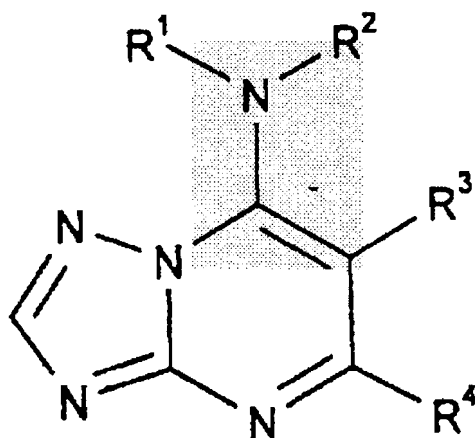




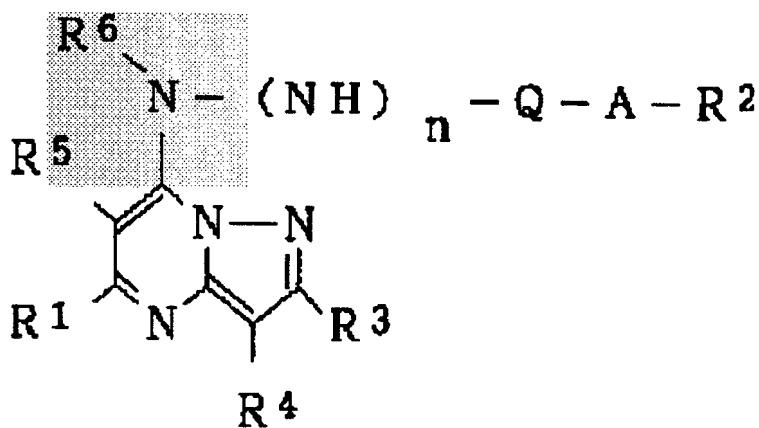
La patente americana US 6476038 publicada el 05 de noviembre de 2002, revela compuestos del tipo:



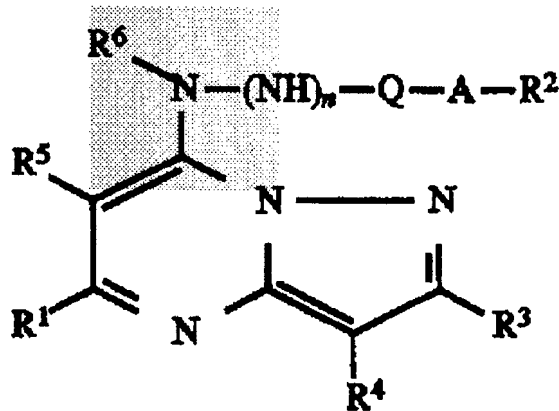
La patente francesa FR 2784380 publicada el 14 de abril de 2000, revela compuestos del tipo:



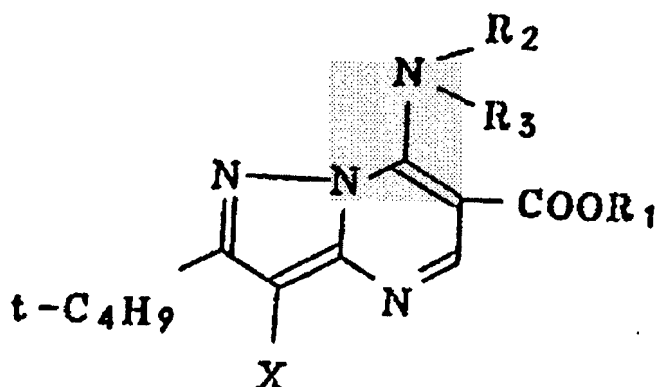
La patente japonesa JP 10101671 publicada el 21 de abril de 1998, revela compuestos del tipo:



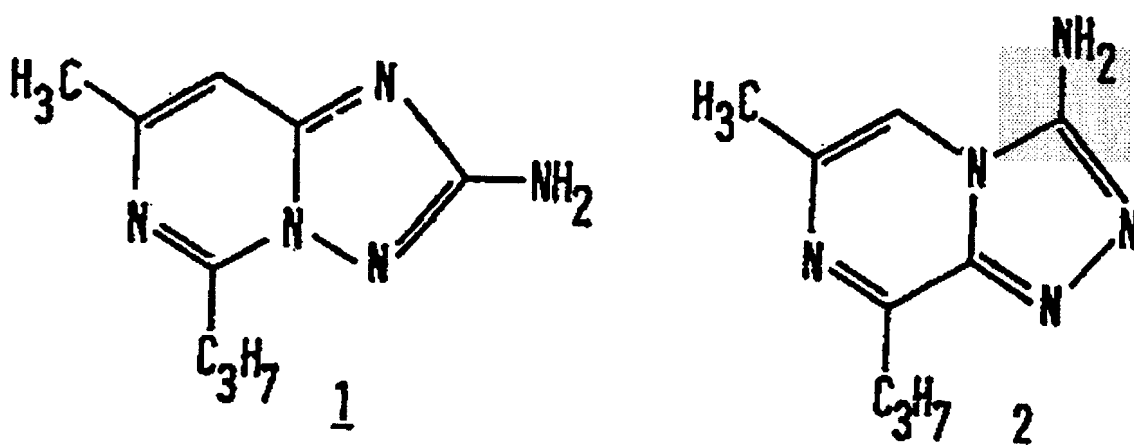
La patente americana US 55707997 publicada el 13 de enero de 1998, revela compuestos del tipo:



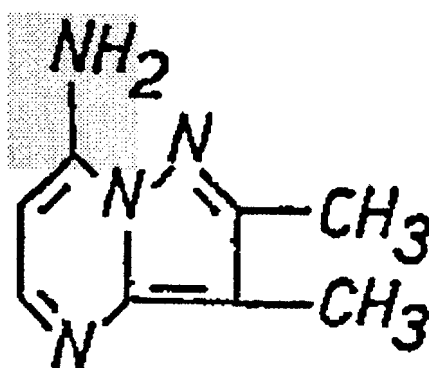
La patente japonesa JP 60100581 publicada el 04 de junio de 1985, revela compuestos del tipo:



La patente británica GB 1412017 publicada el 29 de octubre de 1975, revela compuestos del tipo:



La patente británica GB 1011048 publicada el 24 de noviembre de 1965, revela compuestos del tipo:



Todos estos documento, revelan compuestos sustituidos de pirazolo [1-5-a] pirimidina, con una sustitución en la posición resaltada, que coincide con la misma clase de sustitución y en la misma posición que los compuestos reivindicados por la solicitud concedida, con lo que junto a los conocimientos que cualquier persona versada en asuntos de síntesis química debe conocer, pueden resultar un antecedente relevante y una clara guía, para realizar sustituciones del mismo tipo sobre un núcleo de pirazolo [1-5-a] pirimidina, que no poseen de esta manera nivel inventivo alguno.

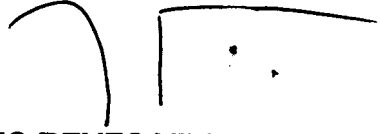
Ruego que se tengan como tales las siguientes, sin perjuicio de aquellas que el Despacho considere oficiosamente, las siguientes:

- Los documentos de patente citados en el numeral 2.4.

IV. NOTIFICACIONES

El suscrito recibirá notificaciones en la secretaría de su Despacho o en mi oficina localizada en la Carrera 17 No. 88-23, Oficina 205, Fax (1) 621.25.42 de esta ciudad. Lafrancol S.A., las recibirá en sus oficinas localizadas en la Carrera 1 N° 46-84 de Cali.

Señor Superintendente,


JOSÉ LUIS REYES VILLAMIZAR

C.C. No. 79.152.473 (Usaquén)

T.P. No. 44655 del C. S. J.

PRESENTACIÓN PERSONAL
NOTARÍA CUARENTA Y DOS (42)
CÍRCULO DE BOGOTÁ - COLOMBIA

JUAN CARLOS VARGAS JARAMILLO
NOTARIO TITULAR EN PROPIEDAD

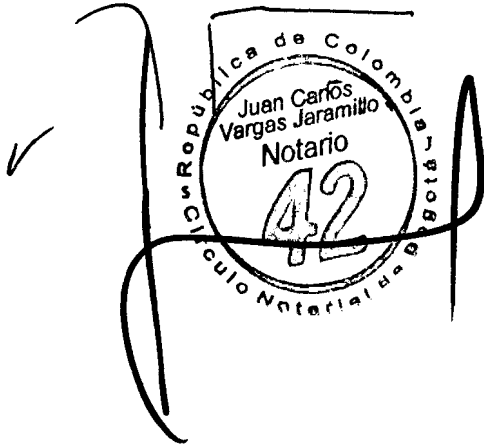
CERTIFICA:

Que REYES VILLAMIZAR JOSE LUIS
quien se identificó con: C.C. 79152473
y con la Tarjeta Profesional No. 44655
presentó personalmente este documento.
En constancia, firma nuevamente.

Bogotá D.C. 18/05/2012

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6





12

⑭ BUNDESREPUBLIK
DEUTSCHLAND



DEUTSCHES
PATENT- UND
MARKENAMT

⑫ **Offenlegungsschrift**
⑩ **DE 101 12 197 A 1**

⑤ Int. Cl.7:
C 07 D 487/04
C 07 D 513/04

⑳ Aktenzeichen: 101 12 197.0
㉔ Anmeldetag: 14. 3. 2001
㉕ Offenlegungstag: 19. 9. 2002

DE 101 12 197 A 1

㉑ Anmelder:
Grünenthal GmbH, 52078 Aachen, DE

㉒ Erfinder:
Gerlach, Matthias, Dr. Dipl.-Chem., 63636 Brachtal,
DE; Maul, Corinna, Dr. Dipl.-Chem., 52066 Aachen,
DE; Jagusch, Utz-Peter, Dipl.-Ing., 52066 Aachen,
DE

㉓ Für die Beurteilung der Patentfähigkeit in Betracht
zu ziehende Druckschriften:

DE 32 26 516 A1
DE 27 01 853 A1
DE 19 38 674 A1
CH 4 82 697
EP 08 36 606 B1
EP 06 18 208 A1

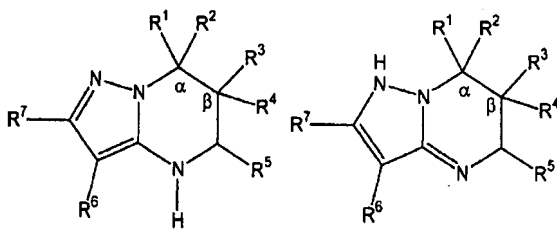
HCAPLUS:
1974:047938;
1988:562901;
1972:059508;
LEESON, Paul D., IVERSEN, Leslie, L.: The Glycine
Site on the NMDA Receptor: Structure-Activity
Relationships and Therapeutic Potential. In:
Journal of Medicinal Chemistry, 1994, Vol. 37,
No. 24, S. 4053-4067;

Die folgenden Angaben sind den vom Anmelder eingereichten Unterlagen entnommen

㉔ Substituierte Pyrazolo- und Thiazolopyrimidine

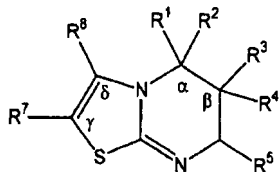
㉕ Die vorliegende Erfindung betrifft substituierte Pyrazolo-
und Thiazolopyrimidine der allgemeinen Struktur (IA),
(IB) und II)

säurespiegel, Hirnödemen, Unterversorgungszuständen
des zentralen Nervensystems, insbesondere bei Hypo-
xien und Anoxien, von AIDs-Demens, von Encephalomy-
elitis, des Tourette-Syndroms, der perinatalen Asphyxie
und/oder bei Tinnitus, sowie diese Verbindungen enthal-
tende pharmazeutische Zusammensetzungen.



IA

IB



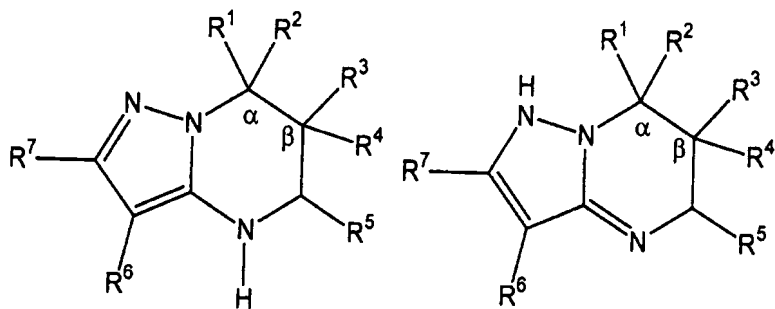
II

Verfahren zu ihrer Herstellung, sie enthaltende Substanz-
bibliotheken, Arzneimittel, die diese Verbindungen ent-
halten, die Verwendung dieser Verbindungen zur Herstel-
lung von Arzneimitteln zur Behandlung von Schmerz, Epi-
lepsie, Schizophrenie, neurodegenerativen Erkrankun-
gen, insbesondere Morbus Alzheimer, Morbus Hunting-
ton und Morbus Parkinson, von cerebralen Ischämien und
Infarkten, von Psychosen bedingt durch erhöhten Amino-

DE 101 12 197 A 1

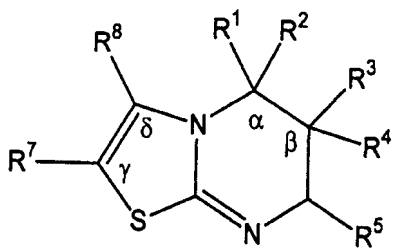
Beschreibung

- [0001] Die vorliegende Anmeldung betrifft substituierte Pyrazolo- und Thiazolopyrimidine, Verfahren zu ihrer Herstellung, die enthaltende Substanzbibliotheken, Arzneimittel, die diese Verbindungen enthalten, die Verwendung dieser Verbindungen zur Herstellung von Arzneimitteln zur Behandlung und/oder Prophylaxe von Schmerz, Epilepsie, Schizophrenie, neurodegenerativen Erkrankungen, insbesondere Morbus Alzheimer, Morbus Huntington und Morbus Parkinson, von cerebralen Ischämien und Infarkten, von Psychosen, bedingt durch erhöhten Aminosäurespiegel, Hirnödemen, Unterversorgungszuständen des zentralen Nervensystems, insbesondere bei Hypoxien und Anoxien, von AIDS-Demenz, von Encephalomyelitis, des Tourette-Syndroms, der perinatalen Asphyxie und/oder bei Tinnitus, sowie diese Verbindungen enthaltende, pharmazeutische Zusammensetzungen.
- [0002] Die Behandlung chronischer und nicht-chronischer Schmerzzustände hat in der Medizin eine große Bedeutung. Es besteht ein weltweiter Bedarf an gut wirksamen Therapien für eine patientengerechte und zielorientierte Behandlung chronischer und nicht-chronischer Schmerzzustände, wobei hierunter die erfolgreiche und zufriedenstellende Schmerzbehandlung für den Patienten zu verstehen ist.
- [0003] Klassische Opioide, wie Morphin, sind bei der Therapie starker bis stärkster Schmerzen gut wirksam. Ihr Einsatz wird jedoch durch die bekannten Nebenwirkungen, wie z. B. Atemdepression, Erbrechen, Sedierung, Obstipation und Toleranzentwicklung, limitiert. Außerdem sind sie bei neuropathischen oder inzidentuellen Schmerzen, unter denen insbesondere Tumorpatienten leiden, weniger wirksam.
- [0004] Opioide entfalten ihre analgetische Wirkung durch Bindung an zellmembranständige Rezeptoren, die zu der Familie der so genannten G-Proteingekoppelten Rezeptoren gehören. Neben diesen gibt es weitere Rezeptoren sowie Ionenkanäle, die wesentlich an dem System der Schmerzentstehung und der Schmerzweiterleitung beteiligt sind, beispielsweise der N-Methyl-D-Aspartat-Ionenkanal (NMDA-Ionenkanal), über den ein wesentlicher Teil der Kommunikation von Synapsen abläuft und durch den der Calcium-Ionenaustausch zwischen einer neuronalen Zelle und ihrer Umgebung gesteuert wird (s. z. B. P. D. Leeson, L. L. Iversen, "J. Med. Chem.", 37 (1994) 4053-4067).
- [0005] Wichtige Erkenntnisse über die physiologische Bedeutung von Ionenkanalselektiven Substanzen sind durch die Entwicklung der "patchclamp"-Technik ermöglicht worden, mit deren Hilfe sich die Wirkung von NMDA-Antagonisten (d. h. Antagonisten des NMDA-Ionenkanals) auf den Calciumhaushalt im Zellinneren nachweisen läßt.
- [0006] Im nichtaktivierten Zustand sind die NMDA-Ionenkanäle jeweils durch einzelne Magnesiumionen verschlossen, die sich im Inneren des Kanals befinden und diesen aufgrund ihrer Größe nicht passieren können. Im aktivierten Zustand können die kleineren Calcium- und Natriumionen den Kanal passieren. Die (+)-MK801-Bindungsstelle des NMDA-Ionenkanals (ionotroper NMDA-Rezeptor) befindet sich ebenfalls im Inneren dieses Membranproteins. Substanzen mit NMDA-antagonistischer Wirkung, wie Phencyclidin (PCP), Ketamin oder MK801, besetzen diese Bindungsstelle (sogenannte "Channelblocker") und verschließen daher den betreffenden NMDA-Ionenkanal.
- [0007] Der vorliegenden Erfindung liegt als eine Aufgabe zugrunde, analgetisch wirksame Verbindungen zur Verfügung zu stellen, die sich zur Schmerztherapie – ggf. auch zur Therapie chronischer und neuropathischer Schmerzen – eignen. Darüber hinaus sollten diese Substanzen möglichst keine der Nebenwirkungen, die üblicherweise bei der Anwendung von Opioiden, wie Morphin, auftreten, wie z. B. Übelkeit, Erbrechen, Abhängigkeit, Atemdepression oder Obstipation, hervorrufen.
- [0008] Diese Aufgabe wird durch die Verbindungen der allgemeinen Struktur (IA), (IB) bzw. (II) gelöst, die analgetisch wirksam sind und an die MK801-Bindungsstelle des NMDA-Rezeptors binden. Bei den erfindungsgemäßen Verbindungen handelt es sich um substituierte Pyrazolo- und Thiazolopyrimidine der allgemeinen Struktur (IA), (IB) bzw. (II):



IA

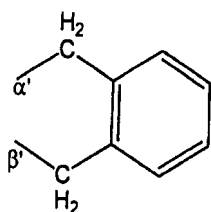
IB



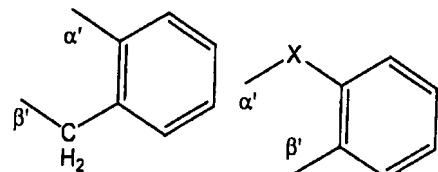
II

worin

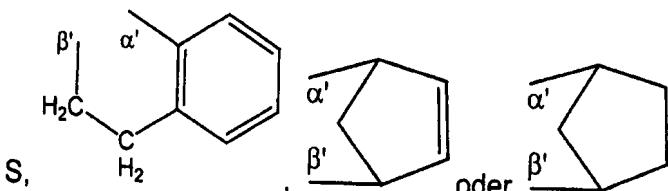
R^1 und R^2 unabhängig voneinander H, O- R^9 , S- R^{10} , C_{1-12} -Alkyl, C_{3-8} -Cycloalkyl, $-CH_2-C_{3-8}$ -Cycloalkyl, Aryl, $-(C_{1-6}$ -Alkyl)-Aryl, Heterocyclyl oder $-(C_{1-6}$ -Alkyl)-Heterocyclyl bedeuten, wobei einer der Reste R^1 und R^2 H ist und der andere Rest von R^1 und R^2 nicht H ist oder für den Fall, daß einer der Reste R^1 und R^2 Aryl bedeutet, der andere Rest von R^1 und R^2 H oder C_{1-12} -Alkyl bedeutet, R^3 und R^4 H, C_{1-12} -Alkyl, C_{3-8} -Cycloalkyl, $-CH_2-C_{3-8}$ -Cycloalkyl, Aryl oder $-(C_{1-6}$ -Alkyl)-Aryl bedeuten, wobei mindestens einer der Reste R^3 und R^4 H ist, oder einer der Reste R^1 und R^2 zusammen mit einem der Reste R^3 und R^4 W bildet, wobei W $\alpha'-(CH_2)_n-\beta'$ mit $n = 3, 4, 5$ oder 6, $\alpha'-CH=CH-CH_2-\beta'$, $\alpha'-CH_2-CH=CH-\beta'$, $\alpha'-CH=CH-CH_2-CH_2-\beta'$, $\alpha'-CH_2-CH=CH-CH_2-\beta'$, $\alpha'-CH_2-CH_2-CH=CH-\beta'$,



$\alpha'-O-(CH_2)_m-\beta'$ mit $m = 2, 3, 4$ oder 5,



mit $X = CH_2, O$ oder



S, bedeutet, das mit α' gekennzeichnete Ende von W mit dem mit α gekennzeichneten Atom der Verbindung der allgemeinen Struktur (IA), (IB) oder (II) verbunden ist und das mit β' gekennzeichnete Ende von W mit dem mit β gekennzeichneten Atom der Verbindung der allgemeinen Struktur (IA), (IB) oder (II) verbunden ist, der andere Rest von R^1 und R^2 H oder C_{1-12} -Alkyl ist und der andere Rest von R^3 und R^4 H oder C_{1-12} -Alkyl ist;

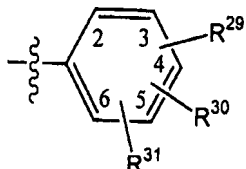
R^5 C_{1-12} -Alkyl, C_{3-8} -Cycloalkyl, $-CH_2-C_{3-8}$ -Cycloalkyl, Aryl, $-(C_{1-6}$ -Alkyl)-Aryl, Heterocyclyl, $-(C_{1-6}$ -Alkyl)-Heterocyclyl oder $C(=O)R^{11}$ bedeutet;

R^6 H, C_{1-8} -Alkyl, -CN, Fluor, Chlor, Brom, Iod, NO_2 , NH_2 , NHR^{12} , $NR^{13}R^{14}$, OR^{15} , $S(O)_pR^{16}$ mit $p = 0, 1$ oder 2, -

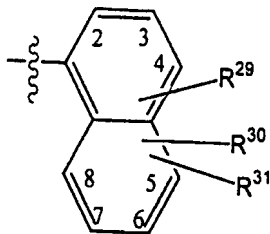
- C(=O)R¹⁷ oder -N=N-Aryl bedeutet;
 R⁷ H, C₁₋₈-Alkyl, Aryl, -CN, Fluor, Chlor, Brom, Iod, NO₂, NH₂, NHR¹², NR¹³R¹⁴, OR¹⁸, S(O)_qR¹⁹ mit q = 0, 1 oder 2 oder C(=O)R²⁰ bedeutet,
 R⁸ H, C₁₋₈-Alkyl oder Aryl bedeutet,
 5 oder
 die Reste R⁷ und R⁸ zusammen Y bilden, wobei Y γ -CR²¹=CR²²-CR²³=CR²⁴- δ bedeutet und das mit γ gekennzeichnete Ende von Y mit dem mit γ gekennzeichneten Atom der allgemeinen Struktur (II) verbunden ist und das mit δ gekennzeichnete Ende von Y mit dem mit δ gekennzeichneten Atom der allgemeinen Struktur (II) verbunden ist;
 R⁹ und R¹⁰ unabhängig voneinander C₁₋₈-Alkyl, C₃₋₈-Cycloalkyl, -CH₂-C₃₋₈-Cycloalkyl, Aryl oder -(C₁₋₆-Alkyl)-Aryl
 10 bedeuten;
 R¹¹ C₁₋₈-Alkyl, C₃₋₈-Cycloalkyl, -CH₂-C₃₋₈-Cycloalkyl, Aryl oder OR²⁵ bedeutet;
 R¹² C₁₋₆-Alkyl oder -CH₂-Aryl bedeutet;
 R¹³ und R¹⁴ gleiches oder verschiedenes C₁₋₆-Alkyl sind oder gemeinsam für -(CH₂)_h- mit h = 4 oder 5 stehen;
 R¹⁵ und R¹⁶ unabhängig voneinander H, C₁₋₈-Alkyl, C₃₋₈-Cycloalkyl, -CH₂-C₃₋₈-Cycloalkyl, Aryl oder -(C₁₋₆-Alkyl)-
 15 Aryl bedeuten;
 R¹⁷ H, C₁₋₈-Alkyl, C₃₋₈-Cycloalkyl, -CH₂-C₃₋₈-Cycloalkyl, Aryl, -(C₁₋₆-Alkyl)-Aryl, NH₂, NHR¹², NR¹³R¹⁴ oder OR²⁶ bedeutet;
 R¹⁸ und R¹⁹ unabhängig voneinander H, C₁₋₈-Alkyl, C₃₋₈-Cycloalkyl, -CH₂-C₃₋₈-Cycloalkyl, Aryl oder -(C₁₋₆-Alkyl)-Aryl bedeuten;
 20 R²⁰ H, C₁₋₈-Alkyl, C₃₋₈-Cycloalkyl, -CH₂-C₃₋₈-Cycloalkyl, Aryl oder -(C₁₋₆-Alkyl)-Aryl oder OR²⁷ bedeutet;
 R²¹, R²², R²³ und R²⁴ unabhängig voneinander H, Fluor, Chlor, Brom, Iod oder OR²⁸ bedeuten;
 R²⁵, R²⁶, R²⁷ und R²⁸ unabhängig voneinander H oder C₁₋₆-Alkyl bedeuten, wobei R²⁵ nicht H bedeutet, wenn zugleich R¹ Aryl und R² Alkyl bedeuten.
 [0009] Die erfindungsgemäßen Verbindungen der allgemeinen Struktur (IA), (IB) oder (II) sowie ihre pharmazeutisch annehmbaren Salze können in Form ihres Racemats, in Form der reinen Enantiomeren oder in Form von Mischungen der Enantiomeren oder Diastereomeren in einem beliebigen Mischungsverhältnis vorliegen. Die erfindungsgemäßen Verbindungen, insbesondere die erfindungsgemäßen Pyrazolopyrimidine (I), können in den tautomeren Formen, im Falle von (I) in den Formen (IA) und (IB) vorliegen, wobei die ggf. bevorzugte, tautomere Form von Verbindung zu Verbindung und z. B. in Abhängigkeit vom Aggregatzustand oder vom gewählten Lösungsmittel variieren kann.
 30 [0010] Folgende Verbindungen der allgemeinen Struktur (IA), (IB) oder (II) sind im Stand der Technik bereits bekannt, ohne daß deren Verwendung in einem Arzneimittel oder zur Herstellung eines Arzneimittels zur Therapie und/oder Prophylaxe von Schmerz, Epilepsie, Schizophrenie, neurodegenerativen Erkrankungen, insbesondere Morbus Alzheimer, Morbus Huntington und Morbus Parkinson, cerebralen Ischämien und Infarkten, Psychosen, bedingt durch erhöhten Aminosäurespiegel, Hirnödemen, Unterversorgungszuständen des zentralen Nervensystems, insbesondere bei Hypoxien
 35 und Anoxien, der AIDS-Demenz, der Encephalomyelitis, des Tourette-Syndroms, der perinatalen Asphyxie und bei Tinnitus beschrieben wird:
 4,5,6,7-Tetrahydro-2-methyl-5,7-diphenyl-pyrazolo[1,5-a]pyrimidin, 4,5,6,7-Tetrahydro-2,5-dimethyl-7-phenyl-pyrazolo[1,5-a]pyrimidin, 4,5,6,7-Tetrahydro-5,7-dimethyl-3-phenyl-pyrazolo[1,5-a]pyrimidin, 4,5,6,7-Tetrahydro-2,5,7-trimethyl-pyrazolo[1,5-a]pyrimidin, 4,5,6,7-Tetrahydro-5,7-dimethyl-2-phenyl-pyrazolo[1,5-a]pyrimidin (B. Koren et al., Tetrahedron (1976) 32, 493-497);
 40 4,5,6,7-Tetrahydro-2-methyl-5,7-di-n-propyl-pyrazolo[1,5-a]pyrimidin-3-carbonitril, 4,5,6,7-Tetrahydro-5-methyl-7-[3-(trifluormethyl)-phenyl]pyrazolo[1,5-a]pyrimidin-3-carbonitril, 7-[4-(Chlor)-phenyl]-4,5,6,7-tetrahydro-5-methyl-pyrazolo[1,5-a]pyrimidin-3-carbonitril, 7-[3-(Chlor)-phenyl]-4,5,6,7-tetrahydro-5-methyl-pyrazolo[1,5-a]pyrimidin-3-carbonitril (EP 0 264 773 A1);
 45 3,4-Dihydro-2-(4-nitrophenyl)-4-phenyl-2H-pyrimido[2,1-b]benzothiazol, 3,4-Dihydro-4-(4-methylphenyl)-2-(4-nitrophenyl)-2H-pyrimido[2,1-b]benzothiazol (M. A. Abdel-Rahman et al., "CA" (1995) 796768 [Rev. Roum. Chim. (1995) 42, 165-172]).
 [0011] Diese Verbindungen sind daher insoweit ebenfalls Gegenstand der vorliegenden Erfindung, als erfindungsgemäße Verfahren zu ihrer Herstellung, sie enthaltende Substanzbibliotheken bzw. Arzneimittel sowie ihre Verwendung
 50 zur Herstellung von Medikamenten zur Behandlung und/oder Prophylaxe von Schmerz, Epilepsie, Schizophrenie, neurodegenerativen Erkrankungen, insbesondere Morbus Alzheimer, Morbus Huntington und Morbus Parkinson, cerebralen Ischämien und Infarkten, Psychosen bedingt durch erhöhten Aminosäurespiegel, Hirnödemen, Unterversorgungszuständen des zentralen Nervensystems, insbesondere bei Hypoxien und Anoxien, der AIDS-Demenz, der Encephalomyelitis, des Tourette-Syndroms, der perinatalen Asphyxie und bei Tinnitus betroffen sind.
 55 [0012] Die Begriffe "Alkyl", "C₁₋₁₂-Alkyl", "C₁₋₈-Alkyl" bzw. "C₁₋₆-Alkyl" umfassen im Sinne dieser Erfindung acyclische, gesättigte oder ungesättigte Kohlenwasserstoffreste, die verzweigt oder geradkettig sowie unsubstituiert oder einfach substituiert oder mehrfach gleich oder verschieden substituiert sein können, mit (wie im Fall von C₁₋₁₂-Alkyl) 1 bis 12 (d. h. 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 oder 12), mit (wie im Fall von C₁₋₁₂-Alkyl) 1 bis 8 (d. h. 1, 2, 3, 4, 5, 6, 7 oder 8) bzw. mit (wie im Fall von C₁₋₆-Alkyl) 1 bis 6 (d. h. 1, 2, 3, 4, 5 oder 6) C-Atomen, d. h. C₁₋₁₂-Alkanyle, C₁₋₈-Alkanyle
 60 bzw. C₁₋₆-Alkanyle, C₂₋₁₂-Alkenyle, C₂₋₈-Alkenyle bzw. C₂₋₆-Alkenyle und C₂₋₁₂-Alkinyle, C₂₋₈-Alkinyle bzw. C₂₋₆-Alkinyle. Dabei weisen "Alkenyle" mindestens eine C-C-Doppelbindung und "Alkinyle" mindestens eine C-C-Dreifachbindung auf. Vorteilhaft ist Alkyl aus der Gruppe ausgewählt, die Methyl, Ethyl, n-Propyl, 2-Propyl, n-Butyl, iso-Butyl, sek.-Butyl, tert.-Butyl, n-Pentyl, iso-Pentyl, neo-Pentyl, n-Hexyl, 2-Hexyl, n-Heptyl, n-Octyl, n-Nonyl, n-Decyl, n-Dodecyl, Ethenyl (Vinyl), Ethinyl, Propenyl (-CH₂CH=CH₂, -CH=CH-CH₃, -C(=CH₂)-CH₃), Propinyl (-CH₂-C $\equiv$ CH, -C $\equiv$ C-CH₃), Butenyl, Butinyl, Pentenyl, Pentinyl, Hexenyl, Hexinyl, Octenyl und Octinyl umfaßt.
 65 [0013] "C₃₋₈-Cycloalkyl" (bzw. "Cycloalkyl") bedeutet im Sinne dieser Erfindung einen cyclischen, gesättigten oder ungesättigten Kohlenwasserstoff-Rest mit 3, 4, 5, 6, 7 oder 8 C-Atomen, wobei der Rest unsubstituiert oder einfach substituiert oder mehrfach gleich oder verschieden substituiert und ggf. benzokondensiert sein kann. Beispielhaft steht Cy-

cloalkyl für Cyclopropyl, Cyclobutyl, Cyclopentyl, Cyclohexyl, Cycloheptyl, Cyclooctyl, Cyclopentenyl, Cyclohexenyl, Cycloheptenyl und Cyclooctenyl. Für die Zwecke der vorliegenden Erfindung besonders bevorzugt sind Cyclopropyl, Cyclopropyl-2-carbonsäure, Cyclopropyl-2-carbonsäureethylester und Cyclohexyl.

[0014] Unter dem Ausdruck "Aryl" ist für die Zwecke der vorliegenden Erfindung ein Rest zu verstehen, der aus der Gruppe, die Phenyl, Naphthyl, Anthracenyl und Biphenyl umfaßt, ausgewählt ist und unsubstituiert oder einfach oder mehrfach gleich oder verschieden substituiert ist. Die Aryl-Reste können auch mit weiteren gesättigten, (partiell) ungesättigten oder aromatischen Ringsystemen kondensiert sein. Jeder Aryl-Rest kann unsubstituiert oder einfach oder mehrfach substituiert vorliegen, wobei die Aryl-Substituenten gleich oder verschieden und in jeder beliebigen Position des Aryls sein können. Vorteilhafterweise steht Aryl für Aryl¹, Aryl² und Aryl³ umfaßt. Dabei steht Aryl¹ für:

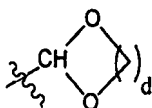


Aryl² für:



und Aryl³ für , wobei R²⁹, R³⁰

und R³¹ unabhängig voneinander H, C₁₋₆-Alkyl, C₃₋₈-Cycloalkyl, -(C₁₋₆-Alkyl)-C₃₋₈-Cycloalkyl, Aryl, -(C₁₋₆-Alkyl)-Aryl, Heterocyclyl, -(C₁₋₆-Alkyl)-Heterocyclyl, F, Cl, Br, I, -CN, -NC, -OR³², -SR³³, -NO, -NO₂, NH₂, NHR³⁴, NR³⁵R³⁶, -N-OH, -N-OC₁₋₆-Alkyl, -NHNH₂, -N=N-Aryl, -(C=O)R³⁷,



mit d = 1, 2 oder 3, oder -(C=S)R³⁷ bedeuten;

R³² und R³³ unabhängig voneinander H, -C₁₋₆-Alkyl, -C₃₋₈-Cycloalkyl, -(C₁₋₆-Alkyl)-C₃₋₈-Cycloalkyl, -Aryl, -(C₁₋₆-Alkyl)-Aryl, -Heterocyclyl, -(C₁₋₆-Alkyl)-Heterocyclyl, (C=O)R³⁸, -[(CH₂)_w-O]_z-H oder -[(CH₂)_w-O]_z-C₁₋₆-Alkyl mit w = 1, 2, 3 oder 4 und z = 1, 2, 3, 4 oder 5 bedeuten;

R³⁴ C₁₋₆-Alkyl, -CH₂-Aryl oder -(C=O)O-tert.-Butyl bedeutet;

R³⁵ und R³⁶ unabhängig voneinander C₁₋₆-Alkyl bedeuten oder gemeinsam für -(CH₂)_g mit g = 4 oder 5 stehen;

R³⁷ H, -C₁₋₆-Alkyl, -C₃₋₈-Cycloalkyl, -(C₁₋₆-Alkyl)-C₃₋₈-Cycloalkyl, -Aryl, -(C₁₋₆-Alkyl)-Aryl, -Heterocyclyl, -(C₁₋₆-Alkyl)-Heterocyclyl, -OR³⁹, -NH₂, -NHR³⁴, -NR³⁵R³⁶ bedeutet;

R³⁸ H, -C₁₋₆-Alkyl, -C₃₋₈-Cycloalkyl, -(C₁₋₆-Alkyl)-C₃₋₆-Cycloalkyl, -Aryl, -(C₁₋₆-Alkyl)-Aryl bedeutet; und

R³⁹ H, C₁₋₆-Alkyl, -C₃₋₈-Cycloalkyl, -(C₁₋₆-Alkyl)-C₃₋₈-Cycloalkyl, -Aryl, -(C₁₋₆-Alkyl)-Aryl, -Heterocyclyl oder -(C₁₋₆-Alkyl)-Heterocyclyl bedeutet.

[0015] Besonders bevorzugte Aryl-Reste sind für die Zwecke der Erfindung Phenyl, 3-Fluor-phenyl, 3-Brom-phenyl, 4-Brom-phenyl, 4-Chlor-phenyl, 4-Fluor-phenyl, 3-Methyl-phenyl, 4-Methyl-phenyl, 4-Hydroxy-phenyl, 4-Methoxy-phenyl, 2,4-Dimethyl-phenyl, 3,4-Dimethoxy-phenyl, 2,3,4-Trimethoxyphenyl, 2-Naphthyl, 4-Trifluorphenyl, 4-Phe-noxy-phenyl, 2-Hydroxy-3-methoxy-phenyl, 4-Hydroxy-3-methoxy-phenyl und 3-Carboxy-2-hydroxy-phenyl.

[0016] Der Ausdruck "Heterocyclyl" steht für einen monocyclischen oder polycyclischen, organischen Rest, in dem mindestens ein Cyclus-1-Heteroatom oder 2, 3, 4 oder 5 gleiche oder verschiedene Heteroatome enthält, das/die aus der Gruppe, die N, O und S enthält, ausgewählt ist/sind, wobei der Rest gesättigt oder ungesättigt ist und unsubstituiert oder einfach substituiert oder mehrfach gleich oder verschieden substituiert ist. Beispiele für Heterocyclyl-Reste im Sinne dieser Erfindung sind monocyclische fünf-, sechs- oder siebengliedrige, organische Reste mit 1 Heteroatom oder 2, 3, 4 oder 5 gleichen oder verschiedenen Heteroatomen, bei dem/denen es sich um Stickstoff, Sauerstoff und/oder Schwefel handelt, und deren benzokondensierte Analoga. Eine Untergruppe der Heterocyclyl-Reste bilden die "Heteroaryl"-Reste, bei denen es sich um solche Heterocyclyle handelt, in denen der mindestens eine Cyclus, der das/die Heteroatom/e enthält, heteroaromatisch ist. Jeder Heteroaryl-Rest kann unsubstituiert oder einfach substituiert oder mehrfach gleich oder verschieden substituiert vorliegen. Beispiele für Heterocyclyl-Reste im Sinne der vorliegenden Erfindung sind Pyrrolidinyl, Tetrahydrofuryl, Piperidinyl, Piperazinyl und insbesondere Morpholinyl. Beispiele für Heterocyclyle, die zugleich Heteroaryl-Reste darstellen, sind Pyrrolyl, Pyrazolyl, Imidazolyl, Pyridazinyl, Pyrimidinyl, Pyrazinyl und insbesondere Furanyl, Thienyl und Pyridinyl sowie deren benzokondensierte Analoga. Alle diese Reste können jeweils unsubstituiert oder einfach oder mehrfach gleich oder verschieden substituiert vorliegen.

[0017] Die Ausdrücke "(C₁₋₆-Alkyl)-C₃₋₈-Cycloalkyl", "(C₁₋₆-Alkyl)-Heterocyclyl" und "(C₁₋₆-Alkyl)-Aryl" bedeuten für die Zwecke der vorliegenden Erfindung, daß der Cycloalkyl-, Heterocyclyl- bzw. Aryl-Rest über eine C₁₋₆-Alkyl-

Gruppe an die mit ihm substituierte Verbindung gebunden ist. Entsprechendes gilt für den Ausdruck " $\text{CH}_2\text{-C}_{3-8}\text{-Cycloalkyl}$ ".

[0018] Im Zusammenhang mit "Alkyl", "Alkanyl", "Alkenyl", "Alkynyl" und "Cycloalkyl" versteht man unter dem Begriff "substituiert" im Sinne dieser Erfindung die Substitution eines Wasserstoffatoms durch beispielsweise F, Cl, Br, I, -CN, -NC, NH_2 , NH-Alkyl, NH-Aryl, NH-Alkyl-Aryl, NH-Heterocyclyl, NH-Alkyl-OH, N(Alkyl)₂, N(Alkyl-Aryl)₂, N(Heterocyclyl)₂, N(Alkyl-OH)₂, NO, NO₂, SH, S-Alkyl, S-Aryl, S-Alkyl-Aryl, S-Heterocyclyl, S-Alkyl-OH, S-Alkyl-SH, OH, O-Alkyl, O-Aryl, O-Alkyl-Aryl, O-Heterocyclyl, O-Alkyl-OH, CHO, C(=O)C₁₋₆-Alkyl, C(=S)C₁₋₆-Alkyl, C(=O)Aryl, C(=S)Aryl, C(=O)C₁₋₆-Alkyl-Aryl, C(=S)C₁₋₆-Alkyl-Aryl, C(=O)-Heterocyclyl, C(=S)-Heterocyclyl, CO₂H, CO₂-Alkyl, CO₂-Alkyl-Aryl, C(=O)NH₂, C(=O)NH-Alkyl, C(=O)NH-Aryl, C(=O)NH-Heterocyclyl, C(=O)N(Alkyl)₂, C(=O)N(Alkyl-Aryl)₂, C(=O)N(Heterocyclyl)₂, SO-Alkyl, SO₂-Alkyl, SO₂-Alkyl-Aryl, SO₂NH₂, SO₃H, SO₃-Alkyl, Cycloalkyl, Aryl oder Heterocyclyl, wobei unter mehrfach substituierten Resten solche Reste zu verstehen sind, die entweder an verschiedenen oder an gleichen Atomen mehrfach, z. B. zwei- oder dreifach, substituiert sind, beispielsweise dreifach am gleichen C-Atom, wie im Falle von CF₃ oder -CH₂CF₃ oder an verschiedenen Stellen, wie im Falle von -CH(OH)-CH=CCl-CH₂Cl. Die Mehrfachsubstitution kann mit dem gleichen oder mit verschiedenen Substituenten erfolgen. Besonders bevorzugt für die Zwecke der vorliegenden Erfindung sind CF₃ und CH₂-CH₂-OH als substituiertes Alkyl sowie Cyclopropyl-2-carbonsäure und Cyclopropyl-2-carbonsäureethylester als substituiertes Cycloalkyl.

[0019] In Bezug auf "Aryl", "Heterocyclyl" sowie "Heteroaryl" versteht man im Sinne dieser Erfindung unter "einfach substituiert" oder "mehrfach substituiert" die ein- oder mehrfache, z. B. zwei-, drei- oder vierfache, Substitution eines oder mehrerer Wasserstoffatome des Ringsystems durch einen geeigneten Substituenten. Soweit die Bedeutung dieser geeigneten Substituenten im Zusammenhang mit "Aryl", "Heterocyclyl" oder "Heteroaryl" nicht an anderer Stelle der Beschreibung oder in den Ansprüchen definiert ist, sind geeignete Substituenten F, Cl, Br, I, -CN, -NC, NH_2 , NH-Alkyl, NH-Aryl, NH-Alkyl-Aryl, NH-Heterocyclyl, NH-Alkyl-OH, N(Alkyl)₂, N(Alkyl-Aryl)₂, N(Heterocyclyl)₂, N(Alkyl-OH)₂, NO, NO₂, SH, S-Alkyl, S-Cycloalkyl, S-Aryl, S-Alkyl-Aryl, S-Heterocyclyl, S-Alkyl-OH, S-Alkyl-SH, OH, O-Alkyl, O-Cycloalkyl, O-Aryl, O-Alkyl-Aryl, O-Heterocyclyl, O-Alkyl-OH, CHO, C(=O)C₁₋₆-Alkyl, C(=S)C₁₋₆-Alkyl, C(=O)Aryl, C(=S)Aryl, C(=O)C₁₋₆-Alkyl-Aryl, C(=S)C₁₋₆-Alkyl-Aryl, C(=O)-Heterocyclyl, C(=S)-Heterocyclyl, CO₂H, CO₂-Alkyl, CO₂-Alkyl-Aryl, C(=O)NH₂, C(=O)NH-Alkyl, C(=O)NH-Aryl, C(=O)NH-Heterocyclyl, C(=O)N(Alkyl)₂, C(=O)N(Alkyl-Aryl)₂, C(=O)N(Heterocyclyl)₂, S(O)-Alkyl, S(O)-Aryl, SO₂-Alkyl, SO₂-Aryl, SO₂NH₂, SO₃H, CF₃, =O, =S; Alkyl, Cycloalkyl, Aryl und/oder Heterocyclyl; an einem oder ggf. verschiedenen Atomen (wobei ein Substituent ggf. seinerseits substituiert sein kann). Die Mehrfachsubstitution erfolgt dabei mit dem gleichen oder mit unterschiedlichen Substituenten.

[0020] "Benzokondensiert" bedeutet für die Zwecke der vorliegenden Erfindung, daß ein Benzol-Ring an einen anderen Cyclus ankondensiert ist.

[0021] Pharmazeutisch annehmbare Salze im Sinne dieser Erfindung sind solche Salze der erfindungsgemäßen Verbindungen gemäß der allgemeinen Struktur I, die bei pharmazeutischer Verwendung physiologisch – insbesondere bei Anwendung am Säugetier und/oder Menschen – verträglich sind. Solche pharmazeutisch annehmbaren Salze können beispielsweise mit anorganischen oder organischen Säuren oder für den Fall, daß die erfindungsgemäßen Verbindungen Carbonsäuren sind, mit Basen gebildet werden.

[0022] Vorzugsweise werden die pharmazeutisch annehmbaren Salze der erfindungsgemäßen Verbindungen gemäß der allgemeinen Struktur (IA), (IB) bzw. (II) mit Salzsäure, Bromwasserstoffsäure, Schwefelsäure, Phosphorsäure, Methansulfonsäure, p-Toluolsulfonsäure, Kohlensäure, Ameisensäure, Essigsäure, Oxalsäure, Bernsteinsäure, Weinsäure, Mandelsäure, Fumarsäure, Milchsäure, Citronensäure, Glutaminsäure oder Asparaginsäure gebildet. Handelt es sich bei den erfindungsgemäßen Verbindungen um Carbonsäuren, können die pharmazeutisch annehmbaren Salze auch durch Umsetzung mit Basen, wie z. B. Natriumhydrogencarbonat oder Natriumcarbonat, gebildet werden. Bei den gebildeten Salzen handelt es sich u. a. um Hydrochloride, Hydrobromide, Phosphate, Carbonate, Hydrogencarbonate, Formiate, Acetate, Oxalate, Succinate, Tartrate, Fumarate, Citrate und Glutamate bzw. um Natrium-Salze. Ebenfalls bevorzugt sind die Hydrate der erfindungsgemäßen Verbindungen, die z. B. durch Kristallisation aus wäßriger Lösung erhalten werden können.

[0023] Alle erfindungsgemäßen Verbindungen enthalten mindestens ein Asymmetriezentrum, nämlich das mit R⁵ substituierte Kohlenstoffatom der Struktur (IA), (IB) bzw. (II). Daher können die erfindungsgemäßen Verbindungen der allgemeinen Struktur (IA), (IB) bzw. (II) in Form ihrer Racemate, in Form der reinen Enantiomeren und/oder Diastereomeren oder in Form von Mischungen dieser Enantiomeren bzw. Diastereomeren vorliegen, und zwar sowohl in Substanz als auch als pharmazeutisch annehmbare Salze dieser Verbindungen. Die Mischungen können in jedem beliebigen Mischungsverhältnis der Stereoisomeren vorliegen. Bevorzugt liegen die Verbindungen der allgemeinen Struktur (IA), (IB) bzw. (II) als enantiomerenreine Verbindungen vor.

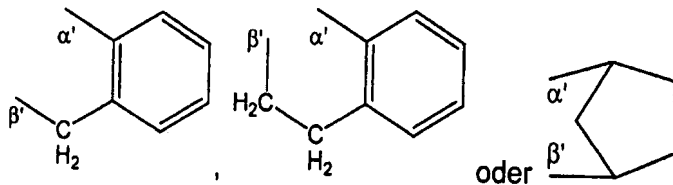
[0024] Bevorzugt sind solche Verbindungen der allgemeinen Formel (IA), (IB) bzw. (II) bzw. deren pharmazeutisch akzeptablen Salze, worin

R¹ und R² unabhängig voneinander H, O-R⁹, S-R¹⁰, C₁₋₆-Alkyl, Aryl' oder -(C₁₋₆-Alkyl)-Aryl', wobei die Aryl'-Substituenten R²⁹, R³⁰ und R³¹ unabhängig voneinander H, C₁₋₆-Alkyl, F, Cl, Br, I, OH, O-C₁₋₆-Alkyl, O-Aryl' oder O-CH₂-Aryl' sind, bedeuten,

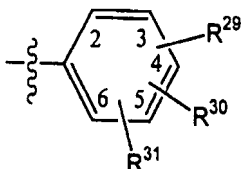
wobei einer der Reste R¹ und R² H ist und der andere Rest von R¹ und R² nicht H ist oder für den Fall, daß einer der Reste R¹ und R² Aryl' bedeutet, der andere Rest von R¹ und R² H oder C₁₋₆-Alkyl bedeutet,

R³ und R⁴ H, unsubstituiertes oder einfach substituiertes oder mehrfach gleich oder verschieden substituiertes Methyl, Ethyl, n-Propyl, 2-Propyl, n-Butyl, iso-Butyl, sek.-Butyl, tert.-Butyl, n-Amyl, iso-Amyl, sek.-Amyl, n-Hexyl, iso-Hexyl, sek.-Hexyl, Aryl' oder -CH₂-Aryl' bedeutet, wobei mindestens einer der Reste R³ und R⁴ H ist, oder

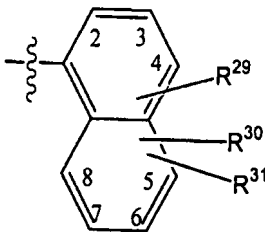
einer der Reste R¹ und R² zusammen mit einem der Reste R³ und R⁴ W bildet, wobei W $\alpha\text{'-CH=CH-CH}_2\text{'}$, $\alpha\text{'-CH=CH-CH}_2\text{'-}\beta\text{'}$, $\alpha\text{'-O-(CH}_2\text{)}_m\text{'-}\beta\text{'}$ mit m = 2, 3, 4 oder 5,



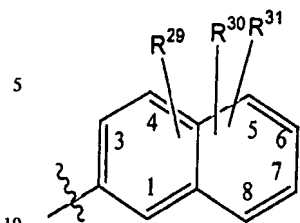
bedeutet, das mit α' gekennzeichnete Ende von W mit dem mit α gekennzeichneten Atom der Verbindung der allgemeinen Struktur (IA), (IB) oder (II) verbunden ist und das mit β' gekennzeichnete Ende von W mit dem mit β gekennzeichneten Atom der Verbindung der allgemeinen Struktur (IA), (IB) oder (II) verbunden ist, der andere Rest von R^1 und R^2 H oder Methyl, Ethyl, n-Propyl, 2-Propyl, n-Butyl, iso-Butyl, sek.-Butyl, tert.-Butyl, n-Amyl, iso-Amyl, sek.-Amyl, n-Hexyl, iso-Hexyl, oder sek.-Hexyl bedeutet und der andere Rest von R^3 und R^4 H oder Methyl, Ethyl, n-Propyl, 2-Propyl, n-Butyl, iso-Butyl, sek.-Butyl, tert.-Butyl, n-Amyl, iso-Amyl, sek.-Amyl, n-Hexyl, iso-Hexyl, sek.-Hexyl bedeutet; R^5 Methyl, Ethyl, n-Propyl, 2-Propyl, n-Butyl, iso-Butyl, sek.-Butyl, tert.-Butyl, n-Amyl, iso-Amyl, sek.-Amyl, n-Hexyl, iso-Hexyl, sek.-Hexyl, Cyclopropyl, Cyclobutyl, Cyclopentyl, Cyclohexyl oder Cycloheptyl, die jeweils unsubstituiert oder einfach substituiert oder mehrfach gleich oder verschieden substituiert sind, Aryl' oder $-(\text{CH}_2)_k\text{-Aryl}'$, wobei $k = 1, 2, 3$ oder 4 ist, Heterocyclyl oder $\text{C}(=\text{O})\text{R}^{11}$ bedeutet; R^6 H, Methyl, Ethyl, -CN, Fluor, Chlor, Brom, Iod, $-\text{C}(=\text{O})\text{R}^{17}$ oder $-\text{N}=\text{N-Aryl}^1$ bedeutet; R^7 H, Aryl', OR^{18} , $\text{S}(\text{O})_q\text{R}^{19}$, wobei $q = 0, 1$ oder 2, oder unsubstituiertes oder einfach substituiertes oder mehrfach gleich oder verschieden substituiertes Methyl, Ethyl, n-Propyl, 2-Propyl, n-Butyl, iso-Butyl, sek.-Butyl, tert.-Butyl, n-Amyl, iso-Amyl, sek.-Amyl, n-Hexyl, iso-Hexyl oder sek.-Hexyl bedeutet, R^8 H oder Aryl' bedeutet, oder die Reste R^7 und R^8 zusammen Y bilden, wobei $Y \gamma\text{-CR}^{21}=\text{CR}^{22}\text{-CR}^{23}=\text{CR}^{24}\text{-}\delta'$ bedeutet und das mit γ gekennzeichnete Ende von Y mit dem mit γ gekennzeichneten Atom der allgemeinen Struktur (II) verbunden ist und das mit δ' gekennzeichnete Ende von Y mit dem mit δ gekennzeichneten Atom der allgemeinen Struktur (II) verbunden ist; R^9 unsubstituiertes oder einfach substituiertes oder mehrfach gleich oder verschieden substituiertes Methyl, Ethyl, n-Propyl, 2-Propyl, n-Butyl, iso-Butyl, sek.-Butyl, tert.-Butyl, n-Amyl, iso-Amyl, sek.-Amyl, n-Hexyl, iso-Hexyl, sek.-Hexyl, Cyclopropyl, Cyclobutyl, Cyclopentyl, Cyclohexyl oder Cycloheptyl bedeutet oder $-(\text{CH}_2)_r\text{-O}_s\text{-H}$ mit $r = 1, 2, 3, 4, 5$ oder 6 und $s = 1, 2, 3, 4, 5$ oder 6 bedeutet; R^{10} Aryl' bedeutet; R^{11} Aryl' oder OR^{25} bedeutet; R^{17} OR^{26} bedeutet; R^{18} H oder Methyl bedeutet; R^{19} H, Aryl' oder jeweils unsubstituiertes, einfach substituiertes oder mehrfach gleich oder verschieden substituiertes Methyl, Ethyl, n-Propyl, 2-Propyl, n-Butyl, iso-Butyl, sek.-Butyl, tert.-Butyl, n-Amyl, iso-Amyl, sek.-Amyl, n-Hexyl, iso-Hexyl oder sek.-Hexyl bedeutet; R^{21} , R^{22} , R^{23} und R^{24} unabhängig voneinander H, Fluor, Chlor, Brom, Iod oder OR^{28} bedeuten; R^{25} H, Methyl, Ethyl, n-Propyl, 2-Propyl, n-Butyl, iso-Butyl, sek.-Butyl, tert.-Butyl, n-Amyl, iso-Amyl, sek.-Amyl, n-Hexyl, iso-Hexyl oder sek.-Hexyl bedeutet, wobei R^{25} nicht H bedeutet, wenn zugleich R^1 Aryl und R^2 Alkyl bedeuten; R^{26} H, Methyl, Ethyl, n-Propyl, 2-Propyl, n-Butyl, iso-Butyl, sek.-Butyl, tert.-Butyl, n-Amyl, iso-Amyl, sek.-Amyl, n-Hexyl, iso-Hexyl oder sek.-Hexyl bedeutet; und R^{28} H, Methyl oder Ethyl bedeutet; Heterocyclyl Furan-2-yl, Furan-3-yl, Thien-2-yl, Thien-3-yl, Pyridin-2-yl-, Pyridin-3-yl oder Pyridin-4-yl, wobei Furan-yl, Thienyl und Pyridinyl jeweils unsubstituiert oder einfach substituiert oder mehrfach gleich oder verschieden substituiert sind, bedeutet; Aryl' Aryl¹, Aryl² oder Aryl³ bedeutet; Aryl¹ für



steht;
Aryl² für



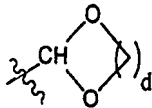
steht;

Aryl³ für

steht;

R²⁹, R³⁰ und R³¹ unabhängig voneinander H, C₁₋₆-Alkyl, C₃₋₈-Cycloalkyl, -(C₁₋₆-Alkyl)-C₃₋₈-Cycloalkyl, Aryl, -(C₁₋₆-Alkyl)-Aryl, Heterocyclyl, -(C₁₋₆-Alkyl)-Heterocyclyl, F, Cl, Br, I, -CN, -NC, -OR³², -SR³³, -NO, -NO₂, NH₂, NHR³⁴, NR³⁵R³⁶, -N-OH, -N-OC₁₋₆-Alkyl, -NHNH₂, -N=N-Aryl, -(C=O)R³⁷,

15



20 mit d = 1, 2 oder 3, oder -(C=S)R³⁷ bedeuten;

R³² und R³³ unabhängig voneinander H, -C₁₋₆-Alkyl, -C₃₋₈-Cycloalkyl, -(C₁₋₆-Alkyl)-C₃₋₈-Cycloalkyl, -Aryl, -(C₁₋₆-Alkyl)-Aryl, -Heterocyclyl, -(C₁₋₆-Alkyl)-Heterocyclyl, (C=O)R³⁸, -[(CH₂)_w-O]_z-H oder -[(CH₂)_w-O]_z-C₁₋₆-Alkyl mit w = 1, 2, 3 oder 4 und z = 1, 2, 3, 4 oder 5 bedeuten;

R³⁴ C₁₋₆-Alkyl, -CH₂-Aryl oder -(C=O)O-tert.-Butyl bedeutet;

25 R³⁵ und R³⁶ unabhängig voneinander C₁₋₆-Alkyl bedeuten oder gemeinsam für -(CH₂)_g- mit g = 4 oder 5 stehen;

R³⁷ H, -C₁₋₆-Alkyl, -C₃₋₈-Cycloalkyl, -(C₁₋₆-Alkyl)-C₃₋₈-Cycloalkyl, -Aryl, -(C₁₋₆-Alkyl)-Aryl, -Heterocyclyl, -(C₁₋₆-Alkyl)-Heterocyclyl, -OR³⁹, -NH₂, -NHR³⁴, -NR³⁵R³⁶ bedeutet;

R³⁸ H, -C₁₋₆-Alkyl, -C₃₋₈-Cycloalkyl, -(C₁₋₆-Alkyl)-C₃₋₈-Cycloalkyl, -Aryl, -(C₁₋₆-Alkyl)-Aryl bedeutet;

und

30 R³⁹ H, C₁₋₆-Alkyl, -C₃₋₈-Cycloalkyl, -(C₁₋₆-Alkyl)-C₃₋₈-Cycloalkyl, -Aryl, -(C₁₋₆-Alkyl)-Aryl, -Heterocyclyl oder -(C₁₋₆-Alkyl)-Heterocyclyl bedeutet.

[0025] Unter diesen Verbindungen sind solche insbesondere bevorzugt, bei denen

R¹ und R² unabhängig voneinander H, O-R⁹, S-R¹⁰, unsubstituiertes oder einfach substituiertes oder mehrfach gleich oder verschieden substituiertes Methyl, Ethyl, n-Propyl, 2-Propyl, n-Butyl, tert.-Butyl oder n-Hexyl, Aryl¹ oder -CH₂-

35 Aryl¹, wobei die Aryl¹-Substituenten R²⁹, R³⁰ und R³¹ unabhängig voneinander H, Methyl, Ethyl, 2-Propyl, n-Butyl, tert.-Butyl, n-Hexyl, F, Cl, Br, I, OH, O-Methyl, O-Ethyl sind, bedeuten,

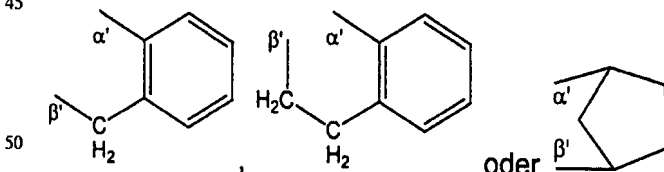
wobei einer der Reste R¹ und R² H ist und der andere Rest von R¹ und R² nicht H ist oder für den Fall, daß einer der Reste R¹ und R² Aryl¹ bedeutet, der andere Rest von R¹ und R² H oder Methyl, Ethyl, n-Propyl, 2-Propyl, n-Butyl, tert.-Butyl oder n-Hexyl bedeutet,

40 R³ und R⁴ H, Methyl oder Aryl¹ bedeutet, wobei die Aryl¹-Substituenten R²⁹, R³⁰ und R³¹ unabhängig voneinander H, Methyl oder O-Methyl sind,

wobei mindestens einer der Reste R³ und R⁴ H ist, oder

einer der Reste R¹ und R² zusammen mit einem der Reste R³ und R⁴ W bildet, wobei W α'-CH=CH-CH₂-β', α'-CH=CH-CH₂-CH₂-β', α'-O-(CH₂)_m-β' mit m = 2, 3, 4 oder 5,

45



bedeutet, das mit α' gekennzeichnete Ende von W mit dem mit α gekennzeichneten Atom der Verbindung der allgemeinen Struktur (IA), (IB) oder (II) verbunden ist und das mit β' gekennzeichnete Ende von W mit dem mit β gekennzeichneten Atom der Verbindung der allgemeinen Struktur (IA), (IB) oder (II) verbunden ist, der andere Rest von R¹ und R²

55 und der andere Rest von R³ und R⁴ jeweils H bedeuten;

R⁵ Methyl, Ethyl, n-Propyl, 2-Propyl, n-Butyl, iso-Butyl, sek.-Butyl, tert.-Butyl, -(CH₂)₄-OH, Cyclopropyl, wobei Cyclopropyl unsubstituiert oder einfach mit C(=O)OH, C(=O)O-Methyl oder C(=O)O-Ethyl substituiert ist, Cyclopentyl, Cyclohexyl, Aryl¹ oder -(CH₂)_k-Aryl¹, wobei die Aryl¹-Substituenten R²⁹, R³⁰ und R³¹ unabhängig voneinander H, -OH, -O-Methyl, O-C₆H₅, CH₃, CF₃ oder C(=O)OH sind und k = 1 oder 2 ist, Heterocyclyl oder C(=O)R¹¹ bedeutet;

60 R⁶ H, -CN, Brom, -C(=O)R¹⁷ oder -N=N-Phenyl bedeutet;

R⁷ H, Aryl¹ mit R²⁹, R³⁰ und R³¹ gleich H, OH, S(O)_qR¹⁹, wobei q = 0 oder 2 ist, oder Methyl, Ethyl, n-Propyl, 2-Propyl, n-Butyl, iso-Butyl, sek.-Butyl oder tert.-Butyl bedeutet,

R⁸ H, Aryl¹, wobei die Aryl¹-Substituenten R²⁹, R³⁰ und R³¹ unabhängig voneinander H, Methyl oder Chlor sind,

oder Aryl³ mit R²⁹, R³⁰ und R³¹ gleich H bedeutet, oder

65 die Reste R¹ und R⁸ zusammen Y bilden, wobei Y γ-CR²¹=CR²²=CR²³=CR²⁴-δ' bedeutet und das mit γ gekennzeichnete Ende von Y mit dem mit γ gekennzeichneten Atom der allgemeinen Struktur (II) verbunden ist und das mit δ' gekennzeichnete Ende von Y mit dem mit δ gekennzeichneten Atom der allgemeinen Struktur (II) verbunden ist;

R⁹ Methyl, Ethyl, n-Propyl, 2-Propyl, n-Butyl, iso-Butyl, sek.-Butyl, tert.-Butyl, n-Amyl, iso-Amyl, sek.-Amyl, n-

Hexyl, iso-Hexyl, sek.-Hexyl, Cyclopropyl, Cyclopentyl oder Cyclohexyl bedeutet oder $-(\text{CH}_2)_r\text{-O})_s\text{-H}$ mit $r = 1, 2$ oder 3 und $s = 1$ oder 2 bedeutet;

R^{10} Aryl¹ bedeutet;

R^{11} Aryl¹ mit R^{29} , R^{30} und R^{31} gleich H oder OR^{25} bedeutet;

R^{17} OR^{26} bedeutet;

R^{19} Methyl oder Aryl¹ bedeutet, wobei einer der Aryl¹-Substituenten R^{29} , R^{30} und R^{31} gleich H oder $-\text{NO}_2$ ist und die beiden anderen Aryl¹-Substituenten von R^{29} , R^{30} und R^{31} H sind,

R^{21} und R^{23} H bedeuten;

R^{22} H, Fluor oder OR^{28} bedeutet;

R^{24} H oder Chlor bedeutet;

R^{25} H, Methyl oder Ethyl bedeutet, wobei R^{25} nicht H bedeutet, wenn zugleich R^1 Aryl und R^2 Alkyl bedeuten;

R^{26} H, Methyl oder Ethyl bedeutet;

R^{28} Methyl oder Ethyl bedeutet; und

Heterocyclyl Furan-2-yl, Furan-3-yl, Thien-2-yl, Thien-3-yl, Pyridin-2-yl, Pyridin-3-yl oder Pyridin-4-yl bedeutet, wobei Furanyl, Thienyl und Pyridinyl jeweils unsubstituiert oder einfach substituiert oder mehrfach gleich oder verschieden mit $-\text{NO}_2$, $-\text{CH}_3$ oder $\text{C}(=\text{O})\text{OH}$ substituiert sind.

[0026] Ganz besonders bevorzugte, erfindungsgemäße Verbindungen der allgemeinen Struktur (IA), (IB) bzw. (II) sind solche, in denen

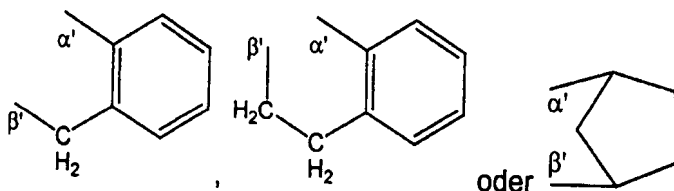
R^1 und R^2 unabhängig voneinander H, $\text{O-CH}_2\text{-CH}_2\text{-OH}$, O-Cyclohexyl , S-Phenyl , Methyl, Phenyl, 3-Fluor-phenyl, 3-Brom-phenyl, 4-Brom-phenyl, 4-Chlor-phenyl, 4-Fluor-phenyl, 3-Methyl-phenyl, 4-Hydroxy-phenyl, 4-Methoxy-phenyl, 2,4-Dimethyl-phenyl, 3,4-Dimethoxy-phenyl, 2,3,4-Trimethoxyphenyl, 2-Naphthyl oder $-\text{CH}_2\text{-Phenyl}$ bedeuten,

R^3 und R^4 H, Methyl oder 4-Methoxy-phenyl bedeuten, wobei mindestens einer der Reste R^3 und R^4 H ist,

oder

einer der Reste R^1 und R^2 zusammen mit einem der Reste R^3 und R^4 W bildet,

wobei W $\alpha'\text{-CH=CH-CH}_2\text{-}\beta'$, $\alpha'\text{-CH=CH-CH}_2\text{-CH}_2\text{-}\beta'$, $\alpha'\text{-O-(CH}_2\text{)}_m\text{-}\beta'$ mit $m = 2, 3, 4$ oder 5 ,



bedeutet, das mit α' gekennzeichnete Ende von W mit dem mit α gekennzeichneten Atom der Verbindung der allgemeinen Struktur (IA), (IB) oder (II) verbunden ist und das mit β' gekennzeichnete Ende von W mit dem mit β gekennzeichneten Atom der Verbindung der allgemeinen Struktur (IA), (IB) oder (II) verbunden ist, der andere Rest von R^1 und R^2 und der andere Rest von R^3 und R^4 jeweils H bedeuten;

R^5 n-Propyl, n-Butyl, tert.-Butyl, $-(\text{CH}_2)_4\text{-OH}$, Cyclopropyl, Cycloprop-2-yl-1-carbonsäureethylester, Cyclohexyl, 4-Trifluorphenyl, 4-Phenoxy-phenyl, 2-Hydroxy-3-methoxy-phenyl, 4-Hydroxy-3-methoxy-phenyl, 3-Carboxy-2-hydroxy-phenyl, $-(\text{CH}_2)_2\text{-Phenyl}$, 5-Carboxy-furan-2-yl, 5-Methyl-furan-2-yl, 5-Nitro-furan-2-yl, 5-Nitro-thien-2-yl, Pyridin-2-yl, Pyridin-3-yl, $\text{C}(=\text{O})\text{Phenyl}$, $\text{C}(=\text{O})\text{OH}$ oder $\text{C}(=\text{O})\text{OEt}$ bedeutet, wobei R^5 nicht $\text{C}(=\text{O})\text{OH}$ bedeutet, wenn zugleich R^1 Aryl und R^2 Alkyl bedeuten;

R^6 H, $-\text{CN}$, Brom, $-\text{C}(=\text{O})\text{OH}$, $-\text{C}(=\text{O})\text{OEt}$ oder $-\text{N=N-Phenyl}$ bedeutet;

R^7 H, Phenyl, OH, $-\text{S-Methyl}$, $-\text{SO}_2\text{-(4-nitrophenyl)}$ oder tert.-Butyl bedeutet,

R^8 4-Chlor-phenyl, 4-Methyl-phenyl oder 2-Naphthyl bedeutet,

oder

die Reste R^7 und R^8 zusammen Y bilden, wobei Y $\gamma\text{-CR}^{21}=\text{CH-CH=CH-}\delta'$ bedeutet und das mit γ gekennzeichnete Ende von Y mit dem mit γ gekennzeichneten Atom der allgemeinen Struktur (II) verbunden ist und das mit δ' gekennzeichnete Ende von Y mit dem mit δ gekennzeichneten Atom der allgemeinen Struktur (II) verbunden ist; und

R^{21} Fluor, Methoxy oder Ethoxy bedeutet.

[0027] Beispielhafte und vorteilhafte Verbindungen der vorliegenden Erfindung sind aus der Gruppe ausgewählt, die

- 3-Brom-5-(5-nitro-furan-2-yl)-7-m-tolyl-tetrahydro-pyrazolo[1,5-a]pyrimidin
- 3-Brom-7-(4-fluor-phenyl)-7-methyl-5-(5-nitro-furan-2-yl)-tetrahydro-pyrazolo[1,5-a]pyrimidin
- 3-Brom-7-naphthalin-2-yl-5-(5-nitro-furan-2-yl)-tetrahydro-pyrazolo[1,5-a]pyrimidin
- 2-(3-Brom-7-m-tolyl-tetrahydro-pyrazolo[1,5-a]pyrimidin-5-yl)-cyclopropan-carbonsäureethylester
- 2-(3-Brom-7-(4-brom-phenyl)-tetrahydro-pyrazolo[1,5-a]pyrimidin-5-yl)-cyclopropan-carbonsäureethylester
- 2-(3-Brom-7-naphthalin-2-yl-tetrahydro-pyrazolo[1,5-a]pyrimidin-5-yl)-cyclopropan-carbonsäureethylester
- 3-Brom-7-(4-fluor-phenyl)-7-methyl-5-(5-methyl-furan-2-yl)-tetrahydro-pyrazolo[1,5-a]pyrimidin
- 3-Brom-7-(3,4-dimethoxy-phenyl)-tetrahydro-pyrazolo[1,5-a]pyrimidin-5-carbonsäureethylester
- 3-Brom-7-(4-methoxy-phenyl)-tetrahydro-pyrazolo[1,5-a]pyrimidin-5-carbonsäureethylester
- 3-Brom-7-(4-methoxy-phenyl)-tetrahydro-pyrazolo[1,5-a]pyrimidin-5-carbonsäure
- 3-Brom-7-(2,4-dimethyl-phenyl)-5-(5-nitro-furan-2-yl)-tetrahydro-pyrazolo[1,5-a]pyrimidin
- 3-Brom-7-(4-methoxy-phenyl)-5-(5-nitro-furan-2-yl)-tetrahydro-pyrazolo[1,5-a]pyrimidin
- 5,5a,6,8a-Tetrahydro-3H-1,4,8b-triaza-as-indacen-3,5-dicarbon-säurediethylester; 5,5a,6,8a-Tetrahydro-4H-1,4,8b-triaza-as-indacen-3,5-dicarbon-säurediethylester
- 2-Hydroxy-3-phenylazo-5,5a,6,8a-tetrahydro-3H-1,4,8b-triaza-as-indacen-5-carbonsäureethylester; 2-Hydroxy-

- 3-phenylazo-5,5a,6,8a-tetrahydro-4H-1,4,8b-triaza-as-indacen-5-carbonsäureethylester
 – 2-tert.-Butyl-5,5a,6,8a-tetrahydro-3H-1,4,8b-triaza-as-indacen-5-carbonsäureethylester; 2-tert.-Butyl-5,5a,6,8a-tetrahydro-3H-1,4,8b-triaza-as-indacen-5-carbonsäureethylester
 – 3-Brom-2-phenyl-5,5a,6,8a-tetrahydro-3H-1,4,8b-triaza-as-indacen-5-carbonsäureethylester; 3-Brom-2-phenyl-5,5a,6,8a-tetrahydro-4H-1,4,8b-triaza-as-indacen-5-carbonsäureethylester
 – 7-(2,3,4-Trimethoxy-phenyl)-tetrahydro-pyrazolo[1,5-a]pyrimidin-3,5-dicarbonssäurediethylester
 – 3-Cyano-2-methylsulfanyl-7-(2,3,4-trimethoxy-phenyl)-tetrahydro-pyrazolo[1,5-a]pyrimidin-5-carbonsäureethylester
 – 2-Hydroxy-7-(4-hydroxy-phenyl)-6-methyl-3-phenylazo-tetrahydro-pyrazolo[1,5-a]pyrimidin-5-carbonsäureethylester
 – 3-Brom-7-(4-hydroxy-phenyl)-6-methyl-2-phenyl-tetrahydro-pyrazolo[1,5-a]pyrimidin-5-carbonsäureethylester
 – 5,5a,6,10b-Tetrahydro-3H-1,4,10c-triaza-cyclopenta[c]fluoren-3,5-dicarbonssäurediethylester; 5,5a,6,10b-Tetrahydro-4H-1,4,10c-triaza-cyclopenta[c]fluoren-3,5-dicarbonssäurediethylester
 – 2-Hydroxy-3-phenylazo-5,5a,6,10b-tetrahydro-3H-1,4,10c-triaza-cyclopenta[c]fluoren-5-carbonsäureethylester; 2-Hydroxy-3-phenylazo-5,5a,6,10b-tetrahydro-4H-1,4,10c-triaza-cyclopenta[c]fluoren-5-carbonsäureethylester
 – 7-Phenylsulfanyl-tetrahydro-pyrazolo[1,5-a]pyrimidin-3,5-dicarbonssäurediethylester
 – 3-Cyano-2-methylsulfanyl-7-phenylsulfanyl-tetrahydro-pyrazolo[1,5-a]pyrimidin-5-carbonsäureethylester
 – 3-Cyano-2-methylsulfanyl-7-(2,3,4-trimethoxy-phenyl)-tetrahydro-pyrazolo[1,5-a]pyrimidin-5-carbonsäureethylester
 – 7-Phenylsulfanyl-tetrahydro-pyrazolo[1,5-a]pyrimidin-3,5-dicarbonssäure-3-ethylester
 – 3-Cyano-7-(2,4-dimethyl-phenyl)-2-methylsulfanyl-tetrahydro-pyrazolo[1,5-a]pyrimidin-5-carbonsäureethylester
 – 3-Cyano-7-(2,4-dimethyl-phenyl)-tetrahydro-pyrazolo[1,5-a]pyrimidin-5-carbonsäureethylester
 – 7-(2,4-Dimethyl-phenyl)-tetrahydro-pyrazolo[1,5-a]pyrimidin-3,5-dicarbonssäure-3-ethylester
 – 3-Brom-7-(2,4-dimethyl-phenyl)-2-phenyl-tetrahydro-pyrazolo[1,5-a]pyrimidin-5-carbonsäureethylester
 – 3-Cyano-7-(2,4-dimethyl-phenyl)-2-methylsulfanyl-tetrahydro-pyrazolo[1,5-a]pyrimidin-5-carbonsäureethylester
 – 3-Cyano-7-(3,4-dimethoxy-phenyl)-2-methylsulfanyl-tetrahydro-pyrazolo[1,5-a]pyrimidin-5-carbonsäureethylester
 – 7-(2,4-Dimethyl-phenyl)-5-(5-nitro-furan-2-yl)-tetrahydro-pyrazolo[1,5-a]pyrimidin-3-carbonsäureethylester
 – 7-(2,4-Dimethyl-phenyl)-5-(5-nitro-furan-2-yl)-3-phenylazo-tetrahydro-pyrazolo[1,5-a]pyrimidin-2-ol
 – 3-Brom-7-(2,4-dimethyl-phenyl)-5-(5-nitro-furan-2-yl)-2-phenyl-tetrahydro-pyrazolo[1,5-a]pyrimidin-3-carbonsäureethylester
 – 7-(2,4-Dimethyl-phenyl)-2-methylsulfanyl-5-(5-nitro-furan-2-yl)-tetrahydro-pyrazolo[1,5-a]pyrimidin-3-carbonsäureethylester
 – 7-(2,4-Dimethyl-phenyl)-5-(2-ethoxycarbonyl-cyclopropyl)-tetrahydro-pyrazolo[1,5-a]pyrimidin-3-carbonsäureethylester
 – 2-[7-(2,4-Dimethyl-phenyl)-2-hydroxy-3-phenylazo-tetrahydro-pyrazolo[1,5-a]pyrimidin-5-yl]-cyclopropan-carbonsäureethylester
 – 2-[2-tert.-Butyl-7-(2,4-dimethyl-phenyl)-tetrahydro-pyrazolo[1,5-a]pyrimidin-5-yl]-cyclopropan-carbonsäureethylester
 – 2-[3-Brom-7-(2,4-dimethyl-phenyl)-2-phenyl-tetrahydro-pyrazolo[1,5-a]pyrimidin-5-yl]-cyclopropan-carbonsäureethylester
 – 2-[3-Cyano-7-(2,4-dimethyl-phenyl)-2-methylsulfanyl-tetrahydro-pyrazolo[1,5-a]pyrimidin-5-yl]-cyclopropan-carbonsäureethylester
 – 5-(2-Ethoxycarbonyl-cyclopropyl)-7-(3-fluor-phenyl)-tetrahydro-pyrazolo[1,5-a]pyrimidin-3-carbonsäureethylester
 – 2-[3-Brom-7-(3-brom-phenyl)-2-phenyl-tetrahydro-pyrazolo[1,5-a]pyrimidin-5-yl]-cyclopropan-carbonsäureethylester
 – 2-[7-(3-Brom-phenyl)-3-cyano-2-methylsulfanyl-tetrahydro-pyrazolo[1,5-a]pyrimidin-5-yl]-cyclopropan-carbonsäureethylester
 – 7-(2,4-Dimethyl-phenyl)-5-(5-nitro-thiophen-2-yl)-3-phenylazo-tetrahydro-pyrazolo[1,5-a]pyrimidin-2-ol
 – 7-(2,4-Dimethyl-phenyl)-2-methylsulfanyl-5-(5-nitro-thiophen-2-yl)-tetrahydro-pyrazolo[1,5-a]pyrimidin-3-carbonsäureethylester
 – 7-(2,4-Dimethyl-phenyl)-5-(5-nitro-thiophen-2-yl)-tetrahydro-pyrazolo[1,5-a]pyrimidin-3-carbonsäureethylester
 – 7-(3,4-Dimethoxy-phenyl)-5-(5-nitro-thiophen-2-yl)-3-phenylazo-tetrahydro-pyrazolo[1,5-a]pyrimidin-2-ol
 – 3-Brom-7-(3,4-dimethoxy-phenyl)-5-(5-nitro-thiophen-2-yl)-2-phenyl-tetrahydro-pyrazolo[1,5-a]pyrimidin-3-carbonsäureethylester
 – 7-(3,4-Dimethoxy-phenyl)-2-methylsulfanyl-5-(5-nitro-thiophen-2-yl)-tetrahydro-pyrazolo[1,5-a]pyrimidin-3-carbonsäureethylester
 – 7-(3,4-Dimethoxy-phenyl)-5-(5-nitro-thiophen-2-yl)-tetrahydro-pyrazolo[1,5-a]pyrimidin-3-carbonsäureethylester
 – 7-(4-Methoxy-phenyl)-5-(5-nitro-thiophen-2-yl)-tetrahydro-pyrazolo[1,5-a]pyrimidin-3-carbonsäureethylester
 – 5-[3-Brom-7-(4-methoxy-phenyl)-2-phenyl-tetrahydro-pyrazolo[1,5-a]pyrimidin-5-yl]-furan-2-carbonsäureethylester
 – 5-Benzoyl-7-(2,4-dimethyl-phenyl)-2-methylsulfanyl-tetrahydro-pyrazolo[1,5-a]pyrimidin-3-carbonsäureethylester
 – 5-Benzoyl-7-(2,4-dimethyl-phenyl)-2-methylsulfanyl-tetrahydro-pyrazolo[1,5-a]pyrimidin-3-carbonsäureethylester
 – 5-Benzoyl-7-(2,4-dimethyl-phenyl)-tetrahydro-pyrazolo[1,5-a]pyrimidin-3-carbonsäureethylester

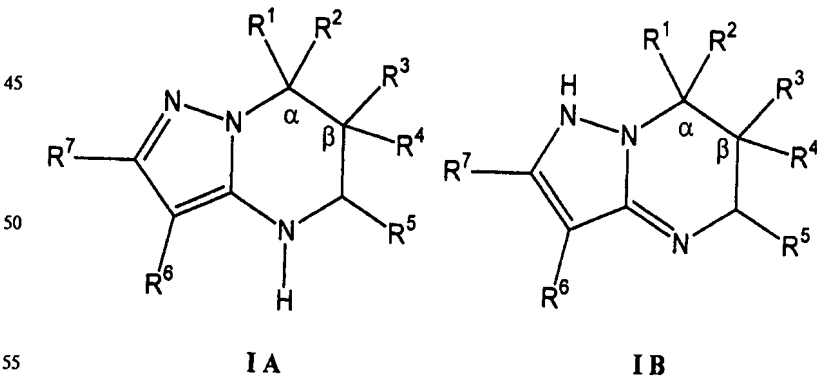
- 5-Benzoyl-7-(3,4-dimethoxy-phenyl)-tetrahydro-pyrazolo[1,5-a]pyrimidin-3-carbonsäureethylester
- [3-Brom-7-(3,4-dimethoxy-phenyl)-2-phenyl-tetrahydro-pyrazolo[1,5-a]pyrimidin-5-yl]-phenyl-methanon
- 5-Benzoyl-7-(3,4-dimethoxy-phenyl)-2-methylsulfanyl-tetrahydro-pyrazolo[1,5-a]pyrimidin-3-carbonitril
- 5-Benzoyl-7-(3,4-dimethoxy-phenyl)-tetrahydro-pyrazolo[1,5-a]pyrimidin-3-carbonitril
- 5-Benzoyl-7-(4-methoxy-phenyl)-tetrahydro-pyrazolo[1,5-a]pyrimidin-3-carbonsäureethylester 5
- 5-Benzoyl-7-(4-methoxy-phenyl)-2-methylsulfanyl-tetrahydro-pyrazolo[1,5-a]pyrimidin-3-carbonitril
- 5-Benzoyl-7-(4-methoxy-phenyl)-tetrahydro-pyrazolo[1,5-a]pyrimidin-3-carbonitril
- 5-Benzoyl-7-(3-fluor-phenyl)-tetrahydro-pyrazolo[1,5-a]pyrimidin-3-carbonsäureethylester
- [3-Brom-7-(3-fluor-phenyl)-2-phenyl-tetrahydro-pyrazolo[1,5-a]pyrimidin-5-yl]-phenyl-methanon
- [3-Brom-7-(3-brom-phenyl)-2-phenyl-tetrahydro-pyrazolo[1,5-a]pyrimidin-5-yl]-phenyl-methanon 10
- 7-(2,4-Dimethyl-phenyl)-5-(4-phenoxy-phenyl)-tetrahydro-pyrazolo[1,5-a]pyrimidin-3-carbonsäureethylester
- 3-Brom-7-(2,4-dimethyl-phenyl)-5-(4-phenoxy-phenyl)-2-phenyl-tetrahydro-pyrazolo[1,5-a]pyrimidin
- 7-(2,4-Dimethyl-phenyl)-2-methylsulfanyl-5-(4-phenoxy-phenyl)-tetrahydro-pyrazolo[1,5-a]pyrimidin-3-carbonitril
- 7-(2,4-Dimethyl-phenyl)-5-(4-phenoxy-phenyl)-tetrahydro-pyrazolo[1,5-a]pyrimidin-3-carbonitril 15
- 7-(3,4-Dimethoxy-phenyl)-5-(4-phenoxy-phenyl)-tetrahydro-pyrazolo[1,5-a]pyrimidin-3-carbonsäureethylester
- 7-(3,4-Dimethoxy-phenyl)-2-methylsulfanyl-5-(4-phenoxy-phenyl)-tetrahydro-pyrazolo[1,5-a]pyrimidin-3-carbonitril
- 3-[3-Cyano-7-(4-hydroxy-phenyl)-6-methyl-tetrahydro-pyrazolo[1,5-a]pyrimidin-5-yl]-2-hydroxy-benzoesäure
- 3-(3-Cyano-5,5a,6,10b-tetrahydro-3H-1,4,10c-triaza-cyclopenta[c]fluoren-5-yl)-2-hydroxy-benzoesäure; 3-(3-Cyano-5,5a,6,10b-tetrahydro-4H-1,4,10c-triaza-cyclopenta[c]fluoren-5-yl)-2-hydroxy-benzoesäure 20
- 3-(3-Cyano-7-phenylsulfanyl-tetrahydro-pyrazolo[1,5-a]pyrimidin-5-yl)-2-hydroxy-benzoesäure
- 3-[2-tert.-Butyl-7-(4-chlor-phenyl)-7-methyl-tetrahydro-pyrazolo[1,5-a]pyrimidin-5-yl]-2-hydroxy-benzoesäure
- 5-(4-Hydroxy-3-methoxy-phenyl)-7-(4-hydroxy-phenyl)-6-methyl-tetrahydro-pyrazolo[1,5-a]pyrimidin-3-carbonsäureethylester 25
- 5-(4-Hydroxy-3-methoxy-phenyl)-7-(4-hydroxy-phenyl)-6-methyl-tetrahydro-pyrazolo[1,5-a]pyrimidin-3-carbonitril
- 5-(4-Hydroxy-3-methoxy-phenyl)-5,5a,6,10b-tetrahydro-3H-1,4,10c-triaza-cyclopenta[c]fluoren-3-carbonsäureethylester; 5-(4-Hydroxy-3-methoxy-phenyl)-5,5a,6,10b-tetrahydro-4H-1,4,10c-triaza-cyclopenta[c]fluoren-3-carbonsäureethylester 30
- 4-(2-tert.-Butyl-5,5a,6,10b-tetrahydro-3H-1,4,10c-triaza-cyclopenta[c]fluoren-5-yl)-2-methoxy-phenol; 4-(2-tert.-Butyl-5,5a,6,10b-tetrahydro-4H-1,4,10c-triaza-cyclopenta[c]fluoren-5-yl)-2-methoxy-phenol
- 5-(4-Hydroxy-3-methoxy-phenyl)-2-methylsulfanyl-5,5a,6,10b-tetrahydro-3H-1,4,10c-triaza-cyclopenta[c]fluoren-3-carbonitril; 5-(4-Hydroxy-3-methoxy-phenyl)-2-methylsulfanyl-5,5a,6,10b-tetrahydro-3H-1,4,10c-triaza-cyclopenta[c]fluoren-3-carbonitril 35
- 5-(4-Hydroxy-3-methoxy-phenyl)-7-phenylsulfanyl-tetrahydro-pyrazolo[1,5-a]pyrimidin-3-carbonsäureethyl-ester
- 4-(2-tert.-Butyl-7-phenylsulfanyl-tetrahydro-pyrazolo[1,5-a]pyrimidin-5-yl)-2-methoxy-phenol
- 4-(3-Brom-2-phenyl-7-phenylsulfanyl-tetrahydro-pyrazolo[1,5-a]pyrimidin-5-yl)-2-methoxy-phenol
- 5-(2-Hydroxy-3-methoxy-phenyl)-7-phenylsulfanyl-tetrahydro-pyrazolo[1,5-a]pyrimidin-3-carbonsäureethyl-ester 40
- 7-(4-Chlor-phenyl)-5-(2-hydroxy-3-methoxy-phenyl)-7-methyl-tetrahydro-pyrazolo[1,5-a]pyrimidin-3-carbonsäureethylester
- 5-(4-Hydroxy-butyl)-5,5a,6,10b-tetrahydro-3H-1,4,10c-triaza-cyclopenta[c]fluoren-3-carbonitril; 5-(4-Hydroxy-butyl)-5,5a,6,10b-tetrahydro-4H-1,4,10c-triaza-cyclopenta[c]fluoren-3-carbonitril 45
- 5-(4-Hydroxy-butyl)-2-methylsulfanyl-7-phenylsulfanyl-tetrahydro-pyrazolo[1,5-a]pyrimidin-3-carbonitril
- 5-(4-Hydroxy-butyl)-7-phenylsulfanyl-tetrahydro-pyrazolo[1,5-a]pyrimidin-3-carbonitril
- 7-(4-Chlor-phenyl)-5-(4-hydroxy-butyl)-7-methyl-tetrahydro-pyrazolo[1,5-a]pyrimidin-3-carbonitril
- 5-Butyl-2-methylsulfanyl-5,5a,6,10b-tetrahydro-3H-1,4,10c-triaza-cyclopenta[c]fluoren-3-carbonitril; 5-Butyl-2-methylsulfanyl-5,5a,6,10b-tetrahydro-4H-1,4,10c-triaza-cyclopenta[c]fluoren-3-carbonitril 50
- 5-Butyl-2-methylsulfanyl-7-phenylsulfanyl-tetrahydro-pyrazolo[1,5-a]pyrimidin-3-carbonitril
- 5-Butyl-7-phenylsulfanyl-tetrahydro-pyrazolo[1,5-a]pyrimidin-3-carbonitril
- 5-Butyl-7-(4-chlor-phenyl)-7-methyl-2-methylsulfanyl-tetrahydro-pyrazolo[1,5-a]pyrimidin-3-carbonitril
- 5-Cyclopropyl-7-(2,4-dimethyl-phenyl)-3-phenylazo-tetrahydro-pyrazolo[1,5-a]pyrimidin-2-ol
- 2-tert.-Butyl-5-cyclopropyl-7-(2,4-dimethyl-phenyl)-tetrahydro-pyrazolo[1,5-a]pyrimidin 55
- 5-Cyclopropyl-7-(2,4-dimethyl-phenyl)-2-methylsulfanyl-tetrahydro-pyrazolo[1,5-a]pyrimidin-3-carbonitril
- 2-tert.-Butyl-5-cyclopropyl-7-(3,4-dimethoxy-phenyl)-tetrahydro-pyrazolo[1,5-a]pyrimidin
- 3-Brom-5-cyclopropyl-7-(3,4-dimethoxy-phenyl)-2-phenyl-tetrahydro-pyrazolo[1,5-a]pyrimidin
- 5-Cyclopropyl-7-(4-methoxy-phenyl)-tetrahydro-pyrazolo[1,5-a]pyrimidin-3-carbonsäureethylester
- 5-Cyclopropyl-3,5,5a,6,7,11b-hexahydro-1,4,11c-triaza-cyclopenta[c]phenanthrene-3-carbonitril 60
- 7-(2,4-Dimethyl-phenyl)-5-pyridin-2-yl-tetrahydro-pyrazolo[1,5-a]pyrimidin-3-carbonsäureethylester
- 7-(2,4-Dimethyl-phenyl)-3-phenylazo-5-pyridin-2-yl-tetrahydro-pyrazolo[1,5-a]pyrimidin-2-ol
- 3-Brom-7-(2,4-dimethyl-phenyl)-2-phenyl-5-pyridin-2-yl-tetrahydro-pyrazolo[1,5-a]pyrimidin
- 7-(2,4-Dimethyl-phenyl)-2-methylsulfanyl-5-pyridin-2-yl-tetrahydro-pyrazolo[1,5-a]pyrimidin-3-carbonitril
- 7-(3,4-Dimethoxy-phenyl)-2-methylsulfanyl-5-phenethyl-tetrahydro-pyrazolo[1,5-a]pyrimidin-3-carbonitril 65
- 7-(3,4-Dimethoxy-phenyl)-5-phenethyl-tetrahydro-pyrazolo[1,5-a]pyrimidin-3-carbonitril
- 5-Cyclopropyl-7-(2-hydroxy-ethoxy)-tetrahydro-pyrazolo[1,5-a]pyrimidin-3-carbonsäureethylester
- 2-(2-tert.-Butyl-5-cyclopropyl-tetrahydro-pyrazolo[1,5-a]pyrimidin-7-yloxy)-ethanol

- 5-Cyclopropyl-3,5,5a,6,7,8a-hexahydro-8-oxa-1,4,8b-triaza-as-indacen-3-carbonsäureethylester; 5-Cyclopropyl-4,5,5a,6,7,8a-hexahydro-8-oxa-1,4,8b-triaza-as-indacen-3-carbonsäureethylester
- 5-Cyclopropyl-3-phenylazo-3,5,5a,6,7,8a-hexahydro-8-oxa-1,4,8b-triaza-as-indacen-2-ol; 5-Cyclopropyl-3-phenylazo-4,5,5a,6,7,8a-hexahydro-8-oxa-1,4,8b-triaza-as-indacen-2-ol
- 7-Cyclohexyloxy-5-cyclopropyl-tetrahydro-pyrazolo[1,5-a]pyrimidin-3-carbonsäureethylester
- 7-Cyclohexyloxy-5-cyclopropyl-2-methylsulfanyl-tetrahydro-pyrazolo[1,5-a]pyrimidin-3-carbonitril
- 7-(4-Chlor-phenyl)-5-cyclohexyl-tetrahydro-pyrazolo[1,5-a]pyrimidin-3-carbonitril
- 5-Cyclohexyl-7-(2-hydroxy-ethoxy)-tetrahydro-pyrazolo[1,5-a]pyrimidin-3-carbonsäureethylester
- 5-Cyclohexyl-3,5,5a,6,7,8a-hexahydro-8-oxa-1,4,8b-triaza-as-indacen-3-carbonsäureethylester; 5-Cyclohexyl-4,5,5a,6,7,8a-hexahydro-8-oxa-1,4,8b-triaza-as-indacen-3-carbonsäureethylester
- 5-Cyclohexyl-7-cyclohexyloxy-tetrahydro-pyrazolo[1,5-a]pyrimidin-3-carbonsäureethylester
- 7-(2,4-Dimethyl-phenyl)-3-phenylazo-5-propyl-tetrahydro-pyrazolo[1,5-a]pyrimidin-2-ol
- 7-(2,4-Dimethyl-phenyl)-2-methylsulfanyl-5-propyl-tetrahydro-pyrazolo[1,5-a]pyrimidin-3-carbonitril
- 5-tert.-Butyl-7-(2,4-dimethyl-phenyl)-tetrahydro-pyrazolo[1,5-a]pyrimidin-3-carbonsäureethylester
- 2,5-Di-tert.-butyl-7-(3,4-dimethoxy-phenyl)-tetrahydro-pyrazolo[1,5-a]pyrimidin
- 3-Brom-5-tert.-butyl-7-(3,4-dimethoxy-phenyl)-2-phenyl-tetrahydro-pyrazolo[1,5-a]pyrimidin
- 2-[3-Cyano-6,7-bis-(4-methoxy-phenyl)-tetrahydro-pyrazolo[1,5-a]pyrimidin-5-yl]-cyclopropan-carbonsäureethylester
- 3-Cyano-6,7-bis-(4-methoxy-phenyl)-tetrahydro-pyrazolo[1,5-a]pyrimidin-5-carbonsäure
- 4-[3-Brom-6-methyl-2-phenyl-5-(4-trifluormethyl-phenyl)-tetrahydro-pyrazolo[1,5-a]pyrimidin-7-yl]-phenol
- 7-(4-Hydroxy-phenyl)-6-methyl-2-methylsulfanyl-5-(4-trifluormethyl-phenyl)-tetrahydro-pyrazolo[1,5-a]pyrimidin-3-carbonitril
- 7-(4-Hydroxy-phenyl)-6-methyl-5-(4-trifluormethyl-phenyl)-tetrahydro-pyrazolo[1,5-a]pyrimidin-3-carbonitril
- 2-(4-Nitro-phenylsulfonyl)-5-phenylsulfanyl-7-pyridin-2-yl-6,7-dihydro-5H-thiazolo[3,2-a]pyrimidin
- 3-(4-Chlor-phenyl)-5-phenylsulfanyl-7-pyridin-2-yl-6,7-dihydro-5H-thiazolo[3,2-a]pyrimidin
- 5-Phenylsulfanyl-7-pyridin-2-yl-3-p-tolyl-6,7-dihydro-5H-thiazolo[3,2-a]pyrimidin
- 7-Methoxy-4-phenylsulfanyl-2-pyridin-2-yl-3,4-dihydro-2H-9-thia-1,4a-diaza-fluoren
- 7-Ethoxy-4-phenylsulfanyl-2-pyridin-2-yl-3,4-dihydro-2H-9-thia-1,4a-diaza-fluoren
- 7-Fluor-4-phenylsulfanyl-2-pyridin-2-yl-3,4-dihydro-2H-9-thia-1,4a-diaza-fluoren
- 3-Naphthalin-2-yl-5-phenylsulfanyl-7-pyridin-2-yl-6,7-dihydro-5H-thiazolo[3,2-a]pyrimidin
- 7-Phenyl-3-phenylazo-5-pyridin-2-yl-3,5,6,7-tetrahydro-pyrazolo[1,5-a]pyrimidin-2-ol
- 7-Phenylsulfanyl-5-pyridin-2-yl-3,5,6,7-tetrahydro-pyrazolo[1,5-a]pyrimidine-3-carbonsäureethylester
- 3-Phenylazo-7-phenylsulfanyl-5-pyridin-2-yl-3,5,6,7-tetrahydro-pyrazolo[1,5-a]pyrimidin-2-ol
- 3-Brom-7-phenylsulfanyl-5-pyridin-2-yl-3,5,6,7-tetrahydro-pyrazolo[1,5-a]pyrimidin
- 7-Phenylsulfanyl-5-pyridin-2-yl-3,5,6,7-tetrahydro-pyrazolo[1,5-a]pyrimidin-3-carbonitril

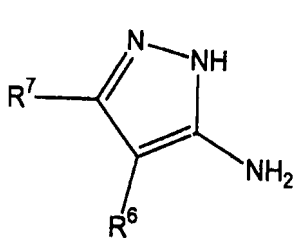
umfaßt sowie ihre pharmazeutisch annehmbaren Salze.

[0028] Die Erfindung betrifft auch Verfahren zur Herstellung der erfindungsgemäßen Verbindungen der Struktur (IA), (IB) und (II).

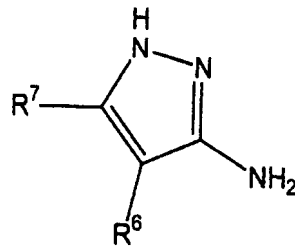
[0029] So sind die Verbindungen der allgemeinen Struktur (IA) und (IB) sowie ihre pharmazeutisch annehmbaren Salze:



worin R^1 , R^2 , R^3 , R^4 , R^5 , R^6 und R^7 wie oben definiert sind, dadurch herstellbar, daß ein Pyrazolamin der allgemeinen Struktur (IIA) und/oder (IIIB):

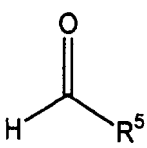


III A



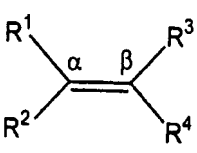
III B

worin R⁶ und R⁷ wie oben definiert sind, mit einem Aldehyd der allgemeinen Struktur (IV):



IV

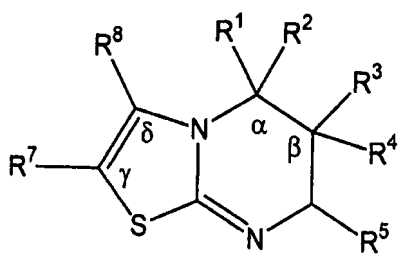
worin R⁵ wie oben definiert ist, und einem Olefin der allgemeinen Struktur (V):



V

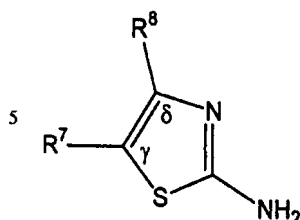
worin R¹, R², R³ und R⁴ wie oben definiert sind mit der Maßgabe, daß, wenn einer der Reste R¹ und R² zusammen mit einem der Reste R³ und R⁴ W bildet, das mit α' gekennzeichnete Ende von W mit dem α-Kohlenstoffatom des Olefins der allgemeinen Struktur (V) und das mit β' gekennzeichnete Ende von W mit dem β-Kohlenstoffatom des Olefins der allgemeinen Struktur (V) verbunden ist, in Gegenwart einer Säure umgesetzt wird.

[0030] Entsprechend sind die erfindungsgemäßen Verbindungen der allgemeinen Struktur (II) sowie ihre pharmazeutisch annehmbaren Salze:



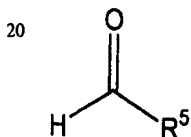
II

worin R¹, R², R³, R⁴, R⁵, R⁷ und R⁸ wie oben definiert sind, dadurch zugänglich, daß ein Thiazolamin der allgemeinen Struktur (VI):



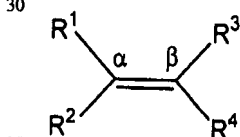
VI

15 worin R^1 und R^8 wie oben definiert sind mit der Maßgabe, daß, wenn R^7 und R^8 Y bilden, das mit γ gekennzeichnete Ende von Y mit dem mit γ gekennzeichneten Atom des Thiazolamins der allgemeinen Struktur (VI) und das mit δ gekennzeichnete Ende von Y mit dem mit δ gekennzeichneten Atom des Thiazolamins der allgemeinen Struktur (VI) verknüpft sind, mit einem Aldehyd der allgemeinen Struktur (IV):



IV

30 worin R^5 wie oben definiert ist, und einem Olefin der allgemeinen Struktur (V):



V

40 worin R^1 , R^2 , R^3 und R^4 wie oben definiert sind mit der Maßgabe, daß, wenn einer der Reste R^1 und R^2 zusammen mit einem der Reste R^3 und R^4 W bildet, das mit α' gekennzeichnete Ende von W mit dem α -Kohlenstoffatom des Olefins der allgemeinen Struktur (V) und das mit β' gekennzeichnete Ende von W mit dem β -Kohlenstoffatom des Olefins der allgemeinen Struktur (V) verbunden ist, in Gegenwart einer Säure umgesetzt wird.

45 [0031] Die erfindungsgemäßen Verfahren werden bevorzugt in einer "Eintopf"-Reaktion durchgeführt, bei der je ein Heterocyclylamin der allgemeinen Struktur (IIA), (IIB) bzw. (VI), je ein Aldehyd der allgemeinen Struktur (IV) und je ein Olefin der allgemeinen Struktur (V) gleichzeitig miteinander umgesetzt werden.

[0032] Bei der eingesetzten Säure handelt es sich um eine anorganische oder organische Protonen- oder Lewis-Säure. Bevorzugt wird die Reaktion in Gegenwart einer organischen Säure, z. B. Essigsäure, Trifluoressigsäure oder Methansulfonsäure, insbesondere Trifluoressigsäure, durchgeführt.

50 [0033] Das erfindungsgemäße Herstellungsverfahren kann in jedem geeigneten Lösungsmittel durchgeführt werden, in dem die Reaktanten sich ausreichend lösen. Bevorzugt sind als Lösungsmittel organische Solventien, z. B. Dichlormethan oder insbesondere Acetonitril.

[0034] Die erfindungsgemäßen Verfahren werden zweckmäßig bei einer Temperatur von 0 bis 100°C, insbesondere bei 15 bis 40°C, durchgeführt. Die Reaktionszeit beträgt vorzugsweise 15 Minuten bis 12 Stunden und kann den jeweiligen Erfordernissen angepaßt werden.

55 [0035] Alle in den erfindungsgemäßen Verfahren eingesetzten Heterocyclylamine der allgemeinen Struktur (III) bzw. (VI), die Aldehyde der allgemeinen Struktur (IV) und die Olefine der allgemeinen Struktur (V) sind käuflich erhältlich (von Acros, Geel; Avocado, Port of Heysham; Aldrich, Deisenhofen; Fluka, Seelze; Lancaster, Mülheim; Maybridge, Tintagel; Merck, Darmstadt; Sigma, Deisenhofen; TCI, Japan) oder können nach im Stand der Technik allgemein bekannten Verfahren hergestellt werden.

60 [0036] Die erfindungsgemäßen Verfahren können auch in semi- oder vollautomatisierter Form als Parallelsynthese einer Gruppe von erfindungsgemäßen Verbindungen der allgemeinen Struktur (IA), (IB) und/oder (II) durchgeführt werden. Somit sind auch Substanzbibliotheken Gegenstand der vorliegenden Erfindung, die mindestens eine Verbindung und vorzugsweise mindestens 48, insbesondere 96 und ganz besonders bevorzugt 384 Verbindungen der allgemeinen und wie oben definierten Struktur (IA), (IB) oder (II) enthalten.

65 [0037] Für die Zwecke der vorliegenden Erfindung wird unter einer "Substanzbibliothek" eine Gruppe von Verbindungen verstanden, die nach dem gleichen Verfahren unter gleichen oder nahezu gleichen Reaktionsbedingungen und unter Variation eines Reagenzes oder mehrerer Reagenzien hergestellt werden. Eine solche Substanzbibliothek kann die Bibliotheksmitglieder sowohl als einzelne, reine Verbindungen als auch als Mischung dieser Verbindungen enthalten. Mit

Hilfe dieser Substanzbibliothek kann beispielsweise ein medizinisches Screening in einem oder mehreren in-nitro-Screening-Verfahren in automatisierter Form durchgeführt werden.

[0038] Die erfindungsgemäßen Verbindungen der allgemeinen Struktur (IA), (IB) oder (II) können sowohl in Substanz als auch als Salz isoliert werden. Die Substanzen der allgemeinen Struktur (IA), (IB) oder (II) werden üblicherweise nach Umsetzung gemäß dem oben dargelegten, erfindungsgemäßen Verfahren und anschließender, herkömmlicher Aufarbeitung erhalten. Die so gewonnenen Verbindungen können dann beispielsweise durch Versetzen mit einer anorganischen oder organischen Säure, vorzugsweise mit Salzsäure, Bromwasserstoffsäure, Schwefelsäure, Phosphorsäure, Methansulfonsäure, p-Toluolsulfonsäure, Kohlensäure, Ameisensäure, Essigsäure, Oxalsäure, Bernsteinsäure, Weinsäure, Mandelsäure, Fumarsäure, Milchsäure, Citronensäure, Glutaminsäure oder Asparaginsäure, in das korrespondierende Salz überführt werden. Bei den gebildeten Salzen handelt es sich u. a. um Hydrochloride, Hydrobromide, Phosphate, Carbonate, Hydrogencarbonate, Formiate, Acetate, Oxalate, Succinate, Tartrate, Fumarate, Citrate und Glutamate. Soweit es sich bei den erfindungsgemäßen Verbindungen der allgemeinen Struktur (IA), (IB) bzw. (II) um Carbonsäuren (z. B. wenn $R^5 = CO_2H$) handelt, kann die Salzbildung durch Zugabe einer physiologisch verträglichen Base, z. B. $NaHCO_3$ oder Natriumcarbonat, herbeigeführt werden; für die Carbonsäuren ist insbesondere die Bildung des Natriumsalzes bevorzugt. Die besonders bevorzugte Hydrochloridbildung kann insbesondere auch durch Versetzen der in einem geeigneten, organischen Lösungsmittel gelösten Base (IA), (IB) bzw. (II) mit Trimethylsilylchlorid (TMSCl) herbeigeführt werden.

[0039] Soweit die Verbindungen der allgemeinen Struktur (IA), (IB) oder (II) in dem erfindungsgemäßen Herstellungsverfahren als Racemate oder als Mischungen ihrer verschiedenen Enantiomeren und/oder Diastereomeren erhalten werden, können diese Mischungen nach im Stand der Technik wohlbekannten Verfahren aufgetrennt werden. Geeignete Methoden sind u. a. chromatographische Trennverfahren, insbesondere Flüssigkeitschromatographie-Verfahren unter Normal- oder erhöhtem Druck, bevorzugt MPLC- und HPLC-Verfahren, sowie Verfahren der fraktionierten Kristallisation. Dabei können insbesondere einzelne Enantiomeren z. B. mittels HPLC an chiraler Phase oder mittels Kristallisation von mit chiralen Säuren, etwa (+)-Weinsäure, (-)-Weinsäure oder (+)-10-Camphersulfonsäure, oder – sofern es sich um Säuren handelt – mit chiralen Basen, etwa Brucin oder (-)-Ephedrin, gebildeten, diastereomeren Salzen voneinander getrennt werden.

[0040] Darüber hinaus ist ein Arzneimittel, das mindestens eine der erfindungsgemäßen und wie oben definierten Verbindungen der allgemeinen Struktur (IA), (IB) oder (II) bzw. ihrer pharmazeutisch annehmbaren Salze umfaßt, Gegenstand der Erfindung. Dabei können die erfindungsgemäßen Verbindungen in dem erfindungsgemäßen Arzneimittel als isomerenreine, insbesondere enantiomerenreine bzw. diastereomerenreine, Verbindungen, aber auch als racemisches oder nicht-racemisches Gemisch vorliegen. Bevorzugt ist dabei, daß das Arzneimittel ein pharmazeutisch annehmbares Salz der erfindungsgemäßen Verbindungen enthält, insbesondere ein Hydrochlorid oder ein Natrium Salz.

[0041] Ein weiterer Gegenstand der Erfindung ist die Verwendung mindestens einer erfindungsgemäßen Verbindung der allgemeinen Struktur (IA), (IB) oder (II), einschließlich ihrer Diastereomeren oder Enantiomeren, auch als Racemate oder Enantiomergemisch, in Form ihrer freien Base oder Säure oder eines mit einer physiologisch verträglichen Säure bzw. Base gebildeten Salzes, insbesondere des Hydrochloridsalzes und des Natriumsalzes, zur Herstellung eines Arzneimittels zur Behandlung von Schmerz. Die erfindungsgemäßen Verbindungen haben sich als analgetisch wirksam erwiesen und binden an die MK801-Bindungsstelle des ionotropen NMDA-Rezeptors.

[0042] Es hat sich aufgrund der Bindung an die MK801-Bindungsstelle auch herausgestellt, daß die erfindungsgemäßen Verbindungen der allgemeinen Struktur (IA), (IB) oder (II) für weitere Indikationen, insbesondere zur Behandlung von Epilepsie, der Schizophrenie, von neurodegenerativen Erkrankungen, insbesondere Morbus Alzheimer, Morbus Huntington und Morbus Parkinson, von cerebralen Ischämien und Infarkten, Psychosen, bedingt durch erhöhten Aminosäurespiegel, Hirnödemen, Unterversorgungszuständen des zentralen Nervensystems, insbesondere bei Hypoxien und Anoxien, von AIDS-Demenz, von Encephalomyelitis, des Tourette-Syndroms, der perinatalen Asphyxie und bei Tinnitus, sehr geeignet sind. Ein weiterer Gegenstand der Anmeldung ist daher die Verwendung mindestens einer erfindungsgemäßen Verbindung der allgemeinen Struktur (IA), (IB) oder (II) einschließlich eines pharmazeutisch annehmbaren Salzes zur Herstellung eines Arzneimittels zur Behandlung und/oder Prophylaxe von Epilepsie, der Schizophrenie, von neurodegenerativen Erkrankungen, insbesondere Morbus Alzheimer, Morbus Huntington und Morbus Parkinson, von cerebralen Ischämien und Infarkten, Psychosen, bedingt durch erhöhten Aminosäurespiegel, Hirnödemen, Unterversorgungszuständen des zentralen Nervensystems, insbesondere bei Hypoxien und Anoxien, von AIDS-Demenz, von Encephalomyelitis, des Tourette-Syndroms, der perinatalen Asphyxie und/oder bei Tinnitus,

[0043] Darüber hinaus sind auch pharmazeutische Zusammensetzungen Gegenstand der vorliegenden Erfindung, die mindestens eine Verbindung der wie oben definierten, allgemeinen Struktur (IA), (IB) oder (II) oder eines ihrer pharmazeutisch annehmbaren Salze und einen oder mehrere pharmazeutische Hilfsstoffe enthalten.

[0044] Die erfindungsgemäßen Arzneimittel und pharmazeutischen Zusammensetzungen können als flüssige, halbfeste oder feste Arzneiformen und in Form von z. B. Injektionslösungen, Tropfen, Säften, Sirupen, Sprays, Suspensionen, Granulaten, Tabletten, Pellets, transdermale therapeutische Systeme, Kapseln, Pflastern, Zäpfchen, Salben, Cremes, Lotionen, Gelen, Emulsionen oder Aerosolen vorliegen und verabreicht werden und enthalten neben mindestens einer erfindungsgemäßen Verbindung der allgemeinen Struktur (IA), (IB) oder (II) je nach galenischer Form pharmazeutische Hilfsstoffe, wie z. B. Trägermaterialien, Füllstoffe, Lösungsmittel, Verdünnungsmittel, oberflächenaktive Stoffe, Farbstoffe, Konservierungsmittel, Sprengmittel, Gleitmittel, Schmiermittel, Aromen und/oder Bindemittel. Diese Hilfsstoffe können beispielsweise sein: Wasser, Ethanol, 2-Propanol, Glycerin, Ethylenglycol, Propylenglycol, Polyethylenglycol, Polypropylenglycol, Glucose, Fructose, Lactose, Saccharose, Dextrose, Melasse, Stärke, modifizierte Stärke, Gelatine, Sorbitol, Inositol, Mannitol, mikrokristalline Cellulose, Methylcellulose, Carboxymethylcellulose, Celluloseacetat, Schellack, Cetylalkohol, Polyvinylpyrrolidon, Paraffine, Wachse, natürliche und synthetische Gummis, Akaziengummi, Alginate, Dextran, gesättigte und ungesättigte Fettsäuren, Stearinsäure, Magnesiumstearat, Zinkstearat, Glycerylstearat, Natriumlaurylsulfat, genießbare Öle, Sesamöl, Kokosnußöl, Erdnußöl, Sojabohnenöl, Lecithin, Natriumlactat, Polyoxyethylen- und -propylenfettsäureester, Sorbitanfettsäureester, Sorbinsäure, Benzoesäure, Citronensäure, Ascorbinsäure, Tanninsäure, Natriumchlorid, Kaliumchlorid, Magnesiumchlorid, Calciumchlorid, Magnesiumoxid, Zinkoxid, Silicium-

dioxid, Titanoxid, Titandioxid, Magnesiumsulfat, Zinksulfat, Calciumsulfat, Pottasche, Calciumphosphat, Dicalciumphosphat, Kaliumbromid, Kaliumiodid, Talkum, Kaolin, Pectin, Crospovidon, Agar und Bentonit.

[0045] Die Auswahl der Hilfsstoffe sowie die einzusetzenden Mengen derselben hängt davon ab, ob das Arzneimittel oral, subkutan, parenteral, intravenös, vaginal, pulmonal, intraperitoneal, transdermal, intramuskulär, nasal, buccal, rektal oder örtlich, zum Beispiel auf Infektionen an der Haut, der Schleimhäute und an den Augen, appliziert werden soll. Für die orale Applikation eignen sich u. a. Zubereitungen in Form von Tabletten, Dragees, Kapseln, Granulaten, Tropfen, Säften und Sirupen, für die parenterale, topische und inhalative Applikation Lösungen, Suspensionen, leicht rekonstituierbare Pulver zur Inhalation sowie Sprays. Erfindungsgemäße Verbindungen der allgemeinen Struktur (IA), (IB) oder (II) in einem Depot in gelöster Form oder in einem Pflaster, gegebenenfalls unter Zusatz von die Hautpenetration fördernden Mitteln, sind geeignete, perkutane Applikationszubereitungen. Rektal, transmucosal, parenteral, oral oder perkutan anwendbare Zubereitungsformen können die erfindungsgemäßen Verbindungen der allgemeinen Struktur (IA), (IB) oder (II) verzögert freisetzen.

[0046] Die Herstellung der erfindungsgemäßen Arzneimittel und pharmazeutischen Zusammensetzungen erfolgt mit Hilfe von im Stand der Technik der pharmazeutischen Formulierung wohlbekannten Mitteln, Vorrichtungen, Methoden und Verfahren, wie sie beispielsweise in "Remington's Pharmaceutical Sciences", Hrsg. A. R. Gennaro, 17. Ed., Mack Publishing Company, Easton, Pa. (1985), insbesondere in Teil 8, Kapitel 76 bis 93, beschrieben sind.

[0047] So kann z. B. für eine feste Formulierung, wie eine Tablette, der Wirkstoff des Arzneimittels, d. h. eine Verbindung der allgemeinen Struktur (IA), (IB) oder (II) oder eines ihrer pharmazeutisch annehmbaren Salze, mit einem pharmazeutischen Träger, z. B. herkömmlichen Tabletteninhaltsstoffen, wie Maisstärke, Lactose, Saccharose, Sorbitol, Talkum, Magnesiumstearat, Dicalciumphosphat oder pharmazeutisch akzeptable Gummis, und pharmazeutischen Verdünnungsmitteln, wie z. B. Wasser, granuliert werden, um eine feste Zusammensetzung zu bilden, die eine erfindungsgemäße Verbindung oder ein pharmazeutisch annehmbares Salz davon in homogener Verteilung enthält. Unter einer homogenen Verteilung wird hier verstanden, daß der Wirkstoff gleichmäßig über die gesamte Zusammensetzung verteilt ist, so daß diese ohne weiteres in gleich wirksame Einheitsdosis-Formen, wie Tabletten, Pillen oder Kapseln, unterteilt werden kann. Die feste Zusammensetzung wird anschließend in Einheitsdosis-Formen unterteilt. Die Tabletten oder Pillen des erfindungsgemäßen Arzneimittels bzw. der erfindungsgemäßen Zusammensetzungen können auch überzogen oder auf andere Weise compoundingiert werden, um eine Dosisform mit verzögerter Freisetzung bereitzustellen. Geeignete Beschichtungsmittel sind u. a. polymere Säuren und Mischungen von polymeren Säuren mit Materialien, wie z. B. Schellack, Cetylalkohol und/oder Celluloseacetat.

[0048] Die an den Patienten zu verabreichende Wirkstoffmenge variiert und ist abhängig vom Gewicht, dem Alter und der Krankheitsgeschichte des Patienten sowie von der Applikationsart, der Indikation und dem Schweregrad der Erkrankung. Üblicherweise werden 0,1 bis 5000 mg/kg, insbesondere 1 bis 500 mg/kg, vorzugsweise 2 bis 250 mg/kg Körpergewicht wenigstens einer erfindungsgemäßen Verbindung der allgemeinen Struktur (IA), (IB) oder (II) appliziert.

[0049] Die nachfolgenden Beispiele dienen zur näheren Erläuterung der vorliegenden Erfindung:

Beispiele

[0050] Die eingesetzten Chemikalien und Lösungsmittel wurden kommerziell von einem der folgenden Anbieter erworben: Acros, Geel; Avocado, Port of Hecyham; Aldrich, Deisenhofen; Fluka, Seelze; Lancaster, Mülheim; Maybridge, Tintagel; Merck, Darmstadt; Sigma, Deisenhofen; TCI, Japan, oder nach allgemeinen, im Stand der Technik bekannten Verfahren hergestellt.

Allgemeine Arbeitsvorschrift AAV (Semiautomatisierte Synthese)

[0051] Ein Rundbodenröhrchen aus Glas (Durchmesser 16 mm, Länge 125 mm) mit Gewinde wurde mit einem Rührer versehen und mit einem Schraubdeckel mit Septum verschlossen. Das Röhrchen wurde in den auf 20°C temperierten Rührblock gestellt. Anschließend wurden nacheinander die folgenden Reagenzien hinzupipettiert:

1. 1 ml einer Lösung, die Trifluoressigsäure und die Heterocyclylamin-Komponente (III) bzw. (VI) jeweils 0,1 M enthält, in Acetonitril;
2. 1 ml einer 0,11-M-Aldehyd(IV)-Lösung in Acetonitril;
3. 1 ml einer 0,3-M-Olefin(V)-Lösung in Acetonitril.

[0052] Das Reaktionsgemisch wurde bei 20°C in einem der Rührblöcke 600 min lang gerührt. Danach wurde die Reaktionslösung an der Filtrations-Station abfiltriert. Das Röhrchen wurde dabei zweimal mit 1,5 ml einer 7,5% NaHCO₃-Lösung gespült. Das Rack mit den Proben wurde manuell auf die Aufarbeitungsanlage gestellt. Das Reaktionsgemisch wurde auf einem Vortexer mit 2 ml Diethylether versetzt und geschüttelt. Zur Ausbildung der Phasengrenze wurde in der Zentrifuge kurz zentrifugiert. Die Phasengrenze wurde optisch detektiert und die organische Phase abpipettiert. Im nächsten Schritt wurde die wäßrige Phase erneut mit 2 ml Diethylether versetzt, geschüttelt, zentrifugiert und die organische Phase abpipettiert. Die vereinigten, organischen Phasen wurden über 2,4 g MgSO₄ (granuliert) getrocknet. Das Lösungsmittel wurde in einer Vakuumzentrifuge entfernt.

[0053] Jede Probe wurde mit ESI-MS und/oder NMR analysiert. Massenspektrometrische Untersuchungen (ESI-MS) wurden mit einem Massenspektrometer der Fa. Finnegan, LCQ Classic durchgeführt. ¹H-NMR-Untersuchungen der erfindungsgemäßen Verbindungen wurden mit einem 300-MHz-DPX-Advance-NMR-Gerät der Fa. Bruker durchgeführt.

[0054] Nach der angegebenen AAV wurden die Beispiels-Verbindungen 1 - 144 (s. Tabelle 1) hergestellt.

Tabelle 1

Beispiel	Name	berechnete Masse	gefundene Masse
1	3-Brom-5-(5-nitro-furan-2-yl)-7-m-tolyl-tetrahydro-pyrazolo[1,5-a]pyrimidin	403.24	403,2/405,1
2	3-Brom-7-(4-fluor-phenyl)-7-methyl-5-(5-nitro-furan-2-yl)-tetrahydro-pyrazolo[1,5-a]pyrimidin	421.23	421,1/423,0
3	3-Brom-7-naphthalin-2-yl-5-(5-nitro-furan-2-yl)-tetrahydro-pyrazolo[1,5-a]pyrimidin	439.27	439,2/441,1
4	2-(3-Brom-7-m-tolyl-tetrahydro-pyrazolo[1,5-a]pyrimidin-5-yl)-cyclopropan-carbonsäure-ethylester	404.31	404,5/406,4
5	2-[3-Brom-7-(4-brom-phenyl)-tetrahydro-pyrazolo[1,5-a]pyrimidin-5-yl]-cyclopropan-carbonsäureethylester	469.18	468,3/470,1/ 472,1
6	2-(3-Brom-7-naphthalin-2-yl-tetrahydro-pyrazolo[1,5-a]pyrimidin-5-yl)-cyclopropan-carbonsäureethylester	440.34	440,5/442,5
7	3-Brom-7-(4-fluor-phenyl)-7-methyl-5-(5-methyl-furan-2-yl)-tetrahydro-pyrazolo[1,5-a]pyrimidin	390.26	390,1/392,0
8	3-Brom-7-(3,4-dimethoxy-phenyl)-tetrahydro-pyrazolo[1,5-a]pyrimidin-5-carbonsäureethylester	410.27	410,3/412,2
9	3-Brom-7-(4-methoxy-phenyl)-tetrahydro-pyrazolo[1,5-a]pyrimidin-5-carbonsäureethylester	380.24	380,2/382,1
10	3-Brom-7-(4-methoxy-phenyl)-tetrahydro-pyrazolo[1,5-a]pyrimidin-5-carbonsäure	352.19	354,2
11	3-Brom-7-(2,4-dimethyl-phenyl)-5-(5-nitro-furan-2-yl)-tetrahydro-pyrazolo[1,5-a]pyrimidin	417.26	417,1/419,0
12	3-Brom-7-(4-methoxy-phenyl)-5-(5-nitro-furan-2-yl)-tetrahydro-pyrazolo[1,5-a]pyrimidin	419.23	419,0/421,0
13	5,5a,6,8a-Tetrahydro-3H-1,4,8b-triaza-as-indacen-3,5-dicarbon-säurediethylester; 5,5a,6,8a-Tetrahydro-4H-1,4,8b-triaza-as-indacen-3,5-dicarbon-säurediethylester;	305.33	306,1
14	2-Hydroxy-3-phenylazo-5,5a,6,8a-tetrahydro-3H-1,4,8b-triaza-as-indacen-5-carbonsäureethylester; 2-Hydroxy-3-phenylazo-5,5a,6,8a-tetrahydro-4H-1,4,8b-triaza-as-indacen-5-carbonsäureethylester	353.38	354,3
15	2-tert-Butyl-5,5a,6,8a-tetrahydro-3H-1,4,8b-triaza-as-indacen-5-carbonsäureethylester; 2-tert-Butyl-5,5a,6,8a-tetrahydro-3H-1,4,8b-triaza-as-indacen-5-carbonsäureethylester	289.37	290,3
16	3-Brom-2-phenyl-5,5a,6,8a-tetrahydro-3H-1,4,8b-triaza-as-indacen-5-carbonsäureethylester; 3-Brom-2-phenyl-5,5a,6,8a-tetrahydro-4H-1,4,8b-triaza-as-indacen-5-carbonsäureethylester	388.26	388,2/390,1
17	7-(2,3,4-Trimethoxy-phenyl)-tetrahydro-pyrazolo[1,5-a]pyrimidin-3,5-dicarbon-säurediethyl ester	433.46	434,4
18	3-Cyano-2-methylsulfanyl-7-(2,3,4-trimethoxy-phenyl)-tetrahydro-pyrazolo[1,5-a]pyrimidin-5-carbonsäureethylester	432.49	433,2

Beispiel	Name	berechnete Masse	gefundene Masse
19	2-Hydroxy-7-(4-hydroxy-phenyl)-6-methyl-3-phenylazo-tetrahydro-pyrazolo[1,5-a]pyrimidin-5-carbonsäureethylester	421.45	422,4
20	3-Brom-7-(4-hydroxy-phenyl)-6-methyl-2-phenyl-tetrahydro-pyrazolo[1,5-a]pyrimidin-5-carbonsäureethylester	456.34	456,4/458,4
21	5,5a,6,10b-Tetrahydro-3H-1,4,10c-triaza-cyclopenta[c]fluoren-3,5-dicarbonssäurediethylester; 5,5a,6,10b-Tetrahydro-4H-1,4,10c-triaza-cyclopenta[c]fluoren-3,5-dicarbonssäurediethylester	355.39	356,2
22	2-Hydroxy-3-phenylazo-5,5a,6,10b-tetrahydro-3H-1,4,10c-triaza-cyclopenta[c]fluoren-5-carbonsäureethylester; 2-Hydroxy-3-phenylazo-5,5a,6,10b-tetrahydro-4H-1,4,10c-triaza-cyclopenta[c]fluoren-5-carbonsäureethylester	403.44	404,3
23	7-Phenylsulfanyl-tetrahydro-pyrazolo[1,5-a]pyrimidin-3,5-dicarbonssäurediethyl ester	375.44	376,2
24	3-Cyano-2-methylsulfanyl-7-phenylsulfanyl-tetrahydro-pyrazolo[1,5-a]pyrimidin-5-carbonsäureethylester	374.48	375,1
25	3-Cyano-2-methylsulfanyl-7-(2,3,4-trimethoxy-phenyl)-tetrahydro-pyrazolo[1,5-a]pyrimidin-5-carbonsäure	404.44	405,2
26	7-Phenylsulfanyl-tetrahydro-pyrazolo[1,5-a]pyrimidin-3,5-dicarbonssäure3-ethyl ester	347.39	348,2
27	3-Cyano-7-(2,4-dimethyl-phenyl)-2-methylsulfanyl-tetrahydro-pyrazolo[1,5-a]pyrimidin-5-carbonsäureethylester	370.47	371,2
28	3-Cyano-7-(2,4-dimethyl-phenyl)-tetrahydro-pyrazolo[1,5-a]pyrimidin-5-carbonsäureethylester	324.38	325,2
29	7-(2,4-Dimethyl-phenyl)-tetrahydro-pyrazolo[1,5-a]pyrimidin-3,5-dicarbonssäure-3-ethyl ester	343.38	344,2
30	3-Brom-7-(2,4-dimethyl-phenyl)-2-phenyl-tetrahydro-pyrazolo[1,5-a]pyrimidin-5-carbonsäure	426.31	426,2/428,1
31	3-Cyano-7-(2,4-dimethyl-phenyl)-2-methylsulfanyl-tetrahydro-pyrazolo[1,5-a]pyrimidin-5-carbonsäure	342.42	343,2
32	3-Cyano-7-(2,4-dimethyl-phenyl)-tetrahydro-pyrazolo[1,5-a]pyrimidin-5-carbonsäure	296.32	297,2
33	3-Cyano-7-(3,4-dimethoxy-phenyl)-2-methylsulfanyl-tetrahydro-pyrazolo[1,5-a]pyrimidin-5-carbonsäure	374.41	376,2
34	7-(2,4-Dimethyl-phenyl)-5-(5-nitro-furan-2-yl)-tetrahydro-pyrazolo[1,5-a]pyrimidin-3-carbonsäureethylester	410.42	411,1
35	7-(2,4-Dimethyl-phenyl)-5-(5-nitro-furan-2-yl)-3-phenylazo-tetrahydro-pyrazolo[1,5-a]pyrimidin-2-ol	458.47	459,3
36	3-Brom-7-(2,4-dimethyl-phenyl)-5-(5-nitro-furan-2-yl)-2-phenyl-tetrahydro-pyrazolo[1,5-a]pyrimidin	493.36	493,2/495,1

Beispiel	Name	berechnete Masse	gefundene Masse
37	7-(2,4-Dimethyl-phenyl)-2-methylsulfanyl-5-(5-nitro-furan-2-yl)-tetrahydro-pyrazolo[1,5-a]pyrimidin-3-carbonitril	409.46	410,1
38	7-(2,4-Dimethyl-phenyl)-5-(5-nitro-furan-2-yl)-tetrahydro-pyrazolo[1,5-a]pyrimidin-3-carbonitril	363.37	364,1
39	3-Brom-7-(3,4-dimethoxy-phenyl)-5-(5-nitro-furan-2-yl)-2-phenyl-tetrahydro-pyrazolo[1,5-a]pyrimidin	525.36	525,4/527,1
40	7-(4-Methoxy-phenyl)-2-methylsulfanyl-5-(5-nitro-furan-2-yl)-tetrahydro-pyrazolo[1,5-a]pyrimidin-3-carbonitril	411.43	412,9
41	7-(2,4-Dimethyl-phenyl)-5-(2-ethoxycarbonyl-cyclopropyl)-tetrahydro-pyrazolo[1,5-a]pyrimidin-3-carbonsäureethylester	411.5	412,5
42	2-[7-(2,4-Dimethyl-phenyl)-2-hydroxy-3-phenylazo-tetrahydro-pyrazolo[1,5-a]pyrimidin-5-yl]-cyclopropancarbonsäureethylester	459.54	460,3
43	2-[2-tert-Butyl-7-(2,4-dimethyl-phenyl)-tetrahydro-pyrazolo[1,5-a]pyrimidin-5-yl]-cyclopropancarbonsäureethylester	395.54	396,5
44	2-[3-Brom-7-(2,4-dimethyl-phenyl)-2-phenyl-tetrahydro-pyrazolo[1,5-a]pyrimidin-5-yl]-cyclopropancarbonsäureethylester	494.43	494,4/496,2
45	2-[3-Cyano-7-(2,4-dimethyl-phenyl)-2-methylsulfanyl-tetrahydro-pyrazolo[1,5-a]pyrimidin-5-yl]-cyclopropancarbonsäureethylester	410.53	411,3
46	5-(2-Ethoxycarbonyl-cyclopropyl)-7-(3-fluor-phenyl)-tetrahydro-pyrazolo[1,5-a]pyrimidin-3-carbonsäureethylester	401.43	402,2
47	2-[3-Brom-7-(3-brom-phenyl)-2-phenyl-tetrahydro-pyrazolo[1,5-a]pyrimidin-5-yl]-cyclopropancarbonsäureethylester	545.28	544,3/546,1/ 548,0
48	2-[7-(3-Brom-phenyl)-3-cyano-2-methylsulfanyl-tetrahydro-pyrazolo[1,5-a]pyrimidin-5-yl]-cyclopropancarbonsäureethylester	461.38	461,2/463,0
49	7-(2,4-Dimethyl-phenyl)-5-(5-nitro-thiophen-2-yl)-3-phenylazo-tetrahydro-pyrazolo[1,5-a]pyrimidin-2-ol	474.54	475,2
50	7-(2,4-Dimethyl-phenyl)-2-methylsulfanyl-5-(5-nitro-thiophen-2-yl)-tetrahydro-pyrazolo[1,5-a]pyrimidin-3-carbonitril	425.53	426,1
51	7-(2,4-Dimethyl-phenyl)-5-(5-nitro-thiophen-2-yl)-tetrahydro-pyrazolo[1,5-a]pyrimidin-3-carbonitril	379.44	380,1
52	7-(3,4-Dimethoxy-phenyl)-5-(5-nitro-thiophen-2-yl)-tetrahydro-pyrazolo[1,5-a]pyrimidin-3-carbonsäureethylester	458.49	459,3
53	7-(3,4-Dimethoxy-phenyl)-5-(5-nitro-thiophen-2-yl)-3-phenylazo-tetrahydro-pyrazolo[1,5-a]pyrimidin-2-ol	506.54	507,2
54	3-Brom-7-(3,4-dimethoxy-phenyl)-5-(5-nitro-thiophen-2-yl)-2-phenyl-tetrahydro-pyrazolo[1,5-a]pyrimidin	541.42	541,4/543,3

Beispiel	Name	berechnete Masse	gefundene Masse
55	7-(3,4-Dimethoxy-phenyl)-2-methylsulfanyl-5-(5-nitro-thiophen-2-yl)-tetrahydro-pyrazolo[1,5-a]pyrimidin-3-carbonitril	457.53	458,1
56	7-(3,4-Dimethoxy-phenyl)-5-(5-nitro-thiophen-2-yl)-tetrahydro-pyrazolo[1,5-a]pyrimidin-3-carbonitril	411.43	412,1
57	7-(4-Methoxy-phenyl)-5-(5-nitro-thiophen-2-yl)-tetrahydro-pyrazolo[1,5-a]pyrimidin-3-carbonsäureethylester	428.46	429,1
58	5-[3-Brom-7-(4-methoxy-phenyl)-2-phenyl-tetrahydro-pyrazolo[1,5-a]pyrimidin-5-yl]-furan-2-carbonsäure	494.34	494,2/496,1
59	5-Benzoyl-7-(2,4-dimethyl-phenyl)-tetrahydro-pyrazolo[1,5-a]pyrimidin-3-carbonsäureethylester	403.48	404,2
60	5-Benzoyl-7-(2,4-dimethyl-phenyl)-2-methylsulfanyl-tetrahydro-pyrazolo[1,5-a]pyrimidin-3-carbonitril	402.51	403,1
61	5-Benzoyl-7-(2,4-dimethyl-phenyl)-tetrahydro-pyrazolo[1,5-a]pyrimidin-3-carbonitril	356.42	355,3/357,2
62	5-Benzoyl-7-(3,4-dimethoxy-phenyl)-tetrahydro-pyrazolo[1,5-a]pyrimidin-3-carbonsäureethylester	435.47	436,2
63	[3-Brom-7-(3,4-dimethoxy-phenyl)-2-phenyl-tetrahydro-pyrazolo[1,5-a]pyrimidin-5-yl]-phenyl-methanon	518.41	518,7/520,2
64	5-Benzoyl-7-(3,4-dimethoxy-phenyl)-2-methylsulfanyl-tetrahydro-pyrazolo[1,5-a]pyrimidin-3-carbonitril	434.51	435,1
65	5-Benzoyl-7-(3,4-dimethoxy-phenyl)-tetrahydro-pyrazolo[1,5-a]pyrimidin-3-carbonitril	388.42	389,1
66	5-Benzoyl-7-(4-methoxy-phenyl)-tetrahydro-pyrazolo[1,5-a]pyrimidin-3-carbonsäureethylester	405.45	406,1
67	5-Benzoyl-7-(4-methoxy-phenyl)-2-methylsulfanyl-tetrahydro-pyrazolo[1,5-a]pyrimidin-3-carbonitril	404.49	405,0
68	5-Benzoyl-7-(4-methoxy-phenyl)-tetrahydro-pyrazolo[1,5-a]pyrimidin-3-carbonitril	358.4	359,0
69	5-Benzoyl-7-(3-fluor-phenyl)-tetrahydro-pyrazolo[1,5-a]pyrimidin-3-carbonsäureethylester	393.41	394,4
70	[3-Brom-7-(3-fluor-phenyl)-2-phenyl-tetrahydro-pyrazolo[1,5-a]pyrimidin-5-yl]-phenyl-methanon	476.35	476,3/478,3
71	[3-Brom-7-(3-brom-phenyl)-2-phenyl-tetrahydro-pyrazolo[1,5-a]pyrimidin-5-yl]-phenyl-methanon	537.26	538,4
72	7-(2,4-Dimethyl-phenyl)-5-(4-phenoxy-phenyl)-tetrahydro-pyrazolo[1,5-a]pyrimidin-3-carbonsäureethylester	467.56	468,2
73	3-Brom-7-(2,4-dimethyl-phenyl)-5-(4-phenoxy-phenyl)-2-phenyl-tetrahydro-pyrazolo[1,5-a]pyrimidin	550.5	550,3/552,2
74	7-(2,4-Dimethyl-phenyl)-2-methylsulfanyl-5-(4-phenoxy-phenyl)-tetrahydro-pyrazolo[1,5-a]pyrimidin-3-carbonitril	466.6	467,1
75	7-(2,4-Dimethyl-phenyl)-5-(4-phenoxy-phenyl)-tetrahydro-pyrazolo[1,5-a]pyrimidin-3-carbonitril	420.51	421,1

Beispiel	Name	berechnete Masse	gefundene Masse
76	7-(3,4-Dimethoxy-phenyl)-5-(4-phenoxy-phenyl)-tetrahydro-pyrazolo[1,5-a]pyrimidin-3-carbonsäureethylester	499.56	500,2
77	7-(3,4-Dimethoxy-phenyl)-2-methylsulfanyl-5-(4-phenoxy-phenyl)-tetrahydro-pyrazolo[1,5-a]pyrimidin-3-carbonitril	498.6	499,1
78	3-[3-Cyano-7-(4-hydroxy-phenyl)-6-methyl-tetrahydro-pyrazolo[1,5-a]pyrimidin-5-yl]-2-hydroxy-benzoesäure	390.39	391,1
79	3-(3-Cyano-5,5a,6,10b-tetrahydro-3H-1,4,10c-triaza-cyclopenta[c]fluoren-5-yl)-2-hydroxy-benzoesäure; 3-(3-Cyano-5,5a,6,10b-tetrahydro-4H-1,4,10c-triaza-cyclopenta[c]fluoren-5-yl)-2-hydroxy-benzoesäure	372.38	373,0
80	3-(3-Cyano-7-phenylsulfanyl-tetrahydro-pyrazolo[1,5-a]pyrimidin-5-yl)-2-hydroxy-benzoesäure	392.43	392,9
81	3-[2-tert-Butyl-7-(4-chlor-phenyl)-7-methyl-tetrahydro-pyrazolo[1,5-a]pyrimidin-5-yl]-2-hydroxy-benzoesäure	439.94	440,2
82	5-(4-Hydroxy-3-methoxy-phenyl)-7-(4-hydroxy-phenyl)-6-methyl-tetrahydro-pyrazolo[1,5-a]pyrimidin-3-carbonsäureethylester	423.46	424,1
83	5-(4-Hydroxy-3-methoxy-phenyl)-7-(4-hydroxy-phenyl)-6-methyl-tetrahydro-pyrazolo[1,5-a]pyrimidin-3-carbonitril	376.41	377,1
84	5-(4-Hydroxy-3-methoxy-phenyl)-5,5a,6,10b-tetrahydro-3H-1,4,10c-triaza-cyclopenta[c]fluoren-3-carbonsäureethylester; 5-(4-Hydroxy-3-methoxy-phenyl)-5,5a,6,10b-tetrahydro-4H-1,4,10c-triaza-cyclopenta[c]fluoren-3-carbonsäureethylester	405.45	406,0
85	4-(2-tert-Butyl-5,5a,6,10b-tetrahydro-3H-1,4,10c-triaza-cyclopenta[c]fluoren-5-yl)-2-methoxy-phenol; 4-(2-tert-Butyl-5,5a,6,10b-tetrahydro-4H-1,4,10c-triaza-cyclopenta[c]fluoren-5-yl)-2-methoxy-phenol	389.49	390,2
86	5-(4-Hydroxy-3-methoxy-phenyl)-2-methylsulfanyl-5,5a,6,10b-tetrahydro-3H-1,4,10c-triaza-cyclopenta[c]fluoren-3-carbonitril; 5-(4-Hydroxy-3-methoxy-phenyl)-2-methylsulfanyl-5,5a,6,10b-tetrahydro-3H-1,4,10c-triaza-cyclopenta[c]fluoren-3-carbonitril	404.49	404,9
87	5-(4-Hydroxy-3-methoxy-phenyl)-7-phenylsulfanyl-tetrahydro-pyrazolo[1,5-a]pyrimidin-3-carbonsäureethylester	425.5	426,0
88	4-(2-tert-Butyl-7-phenylsulfanyl-tetrahydro-pyrazolo[1,5-a]pyrimidin-5-yl)-2-methoxy-phenol	409.55	410,1
89	4-(3-Brom-2-phenyl-7-phenylsulfanyl-tetrahydro-pyrazolo[1,5-a]pyrimidin-5-yl)-2-methoxy-phenol	508.44	508,2/510,0
90	5-(2-Hydroxy-3-methoxy-phenyl)-7-phenylsulfanyl-tetrahydro-pyrazolo[1,5-a]pyrimidin-3-carbonsäureethylester	425.5	425,0

Beispiel	Name	berechnete Masse	gefundene Masse
91	7-(4-Chlor-phenyl)-5-(2-hydroxy-3-methoxy-phenyl)-7-methyl-tetrahydro-pyrazolo[1,5-a]pyrimidin-3-carbonsäureethylester	441.91	441,0
92	5-(4-Hydroxy-butyl)-5,5a,6,10b-tetrahydro-3H-1,4,10c-triaza-cyclopenta[c]fluoren-3-carbonitril; 5-(4-Hydroxy-butyl)-5,5a,6,10b-tetrahydro-4H-1,4,10c-triaza-cyclopenta[c]fluoren-3-carbonitril	308.38	309,3
93	5-(4-Hydroxy-butyl)-2-methylsulfanyl-7-phenylsulfanyl-tetrahydro-pyrazolo[1,5-a]pyrimidin-3-carbonitril	374.52	375,2
94	5-(4-Hydroxy-butyl)-7-phenylsulfanyl-tetrahydro-pyrazolo[1,5-a]pyrimidin-3-carbonitril	328.43	329,2
95	7-(4-Chlor-phenyl)-5-(4-hydroxy-butyl)-7-methyl-tetrahydro-pyrazolo[1,5-a]pyrimidin-3-carbonitril	344.84	345,1
96	5-Butyl-2-methylsulfanyl-5,5a,6,10b-tetrahydro-3H-1,4,10c-triaza-cyclopenta[c]fluoren-3-carbonitril; 5-Butyl-2-methylsulfanyl-5,5a,6,10b-tetrahydro-4H-1,4,10c-triaza-cyclopenta[c]fluoren-3-carbonitril	338.47	339,3
97	5-Butyl-2-methylsulfanyl-7-phenylsulfanyl-tetrahydro-pyrazolo[1,5-a]pyrimidin-3-carbonitril	358.52	359,2
98	5-Butyl-7-phenylsulfanyl-tetrahydro-pyrazolo[1,5-a]pyrimidin-3-carbonitril	312.43	313,1
99	5-Butyl-7-(4-chlor-phenyl)-7-methyl-2-methylsulfanyl-tetrahydro-pyrazolo[1,5-a]pyrimidin-3-carbonitril	374.93	375,3
100	5-Cyclopropyl-7-(2,4-dimethyl-phenyl)-3-phenylazo-tetrahydro-pyrazolo[1,5-a]pyrimidin-2-ol	387.48	388,5
101	2-tert-Butyl-5-cyclopropyl-7-(2,4-dimethyl-phenyl)-tetrahydro-pyrazolo[1,5-a]pyrimidin	323.48	324,6
102	5-Cyclopropyl-7-(2,4-dimethyl-phenyl)-2-methylsulfanyl-tetrahydro-pyrazolo[1,5-a]pyrimidin-3-carbonitril	338.47	339,8
103	2-tert-Butyl-5-cyclopropyl-7-(3,4-dimethoxy-phenyl)-tetrahydro-pyrazolo[1,5-a]pyrimidin	355.48	356,3/357,6
104	3-Brom-5-cyclopropyl-7-(3,4-dimethoxy-phenyl)-2-phenyl-tetrahydro-pyrazolo[1,5-a]pyrimidin	454.37	454,3/456,1
105	5-Cyclopropyl-7-(4-methoxy-phenyl)-tetrahydro-pyrazolo[1,5-a]pyrimidin-3-carbonsäureethylester	341.41	342,7
106	5-Cyclopropyl-3,5,5a,6,7,11b-hexahydro-1,4,11c-triaza-cyclopenta[c]phenanthrene-3-carbonitril	290.36	291,4
107	7-(2,4-Dimethyl-phenyl)-5-pyridin-2-yl-tetrahydro-pyrazolo[1,5-a]pyrimidin-3-carbonsäureethylester	376.45	377,3/378,4
108	7-(2,4-Dimethyl-phenyl)-3-phenylazo-5-pyridin-2-yl-tetrahydro-pyrazolo[1,5-a]pyrimidin-2-ol	424.5	425,3
109	3-Brom-7-(2,4-dimethyl-phenyl)-2-phenyl-5-pyridin-2-yl-tetrahydro-pyrazolo[1,5-a]pyrimidin	459.39	459,7/462,2
110	7-(2,4-Dimethyl-phenyl)-2-methylsulfanyl-5-pyridin-2-yl-tetrahydro-pyrazolo[1,5-a]pyrimidin-3-carbonitril	375.49	376,4
111	7-(3,4-Dimethoxy-phenyl)-2-methylsulfanyl-5-phenethyl-tetrahydro-pyrazolo[1,5-a]pyrimidin-3-carbonitril	434.56	435,3

Beispiel	Name	berechnete Masse	gefundene Masse
112	7-(3,4-Dimethoxy-phenyl)-5-phenethyl-tetrahydro-pyrazolo[1,5-a]pyrimidin-3-carbonitril	388.47	389,2
113	5-Cyclopropyl-7-(2-hydroxy-ethoxy)-tetrahydro-pyrazolo[1,5-a]pyrimidin-3-carbonsäureethylester	295.33	296,2
114	2-(2-tert-Butyl-5-cyclopropyl-tetrahydro-pyrazolo[1,5-a]pyrimidin-7-yloxy)-ethanol	279.38	280,3
115	5-Cyclopropyl-3,5,5a,6,7,8a-hexahydro-8-oxa-1,4,8b-triaza-as-indacen-3-carbonsäureethylester; 5-Cyclopropyl-4,5,5a,6,7,8a-hexahydro-8-oxa-1,4,8b-triaza-as-indacen-3-carbonsäureethylester	277.32	278,3
116	5-Cyclopropyl-3-phenylazo-3,5,5a,6,7,8a-hexahydro-8-oxa-1,4,8b-triaza-as-indacen-2-ol; 5-Cyclopropyl-3-phenylazo-4,5,5a,6,7,8a-hexahydro-8-oxa-1,4,8b-triaza-as-indacen-2-ol	325.37	326,5
117	7-Cyclohexyloxy-5-cyclopropyl-tetrahydro-pyrazolo[1,5-a]pyrimidin-3-carbonsäureethylester	333.43	334,1
118	7-Cyclohexyloxy-5-cyclopropyl-2-methylsulfanyl-tetrahydro-pyrazolo[1,5-a]pyrimidin-3-carbonitril	332.46	333,2
119	7-(4-Chlor-phenyl)-5-cyclohexyl-tetrahydro-pyrazolo[1,5-a]pyrimidin-3-carbonitril	340.85	341,4
120	5-Cyclohexyl-7-(2-hydroxy-ethoxy)-tetrahydro-pyrazolo[1,5-a]pyrimidin-3-carbonsäureethylester	337.41	338,3
121	5-Cyclohexyl-3,5,5a,6,7,8a-hexahydro-8-oxa-1,4,8b-triaza-as-indacen-3-carbonsäureethylester; 5-Cyclohexyl-4,5,5a,6,7,8a-hexahydro-8-oxa-1,4,8b-triaza-as-indacen-3-carbonsäureethylester	319.4	320,3
122	5-Cyclohexyl-7-cyclohexyloxy-tetrahydro-pyrazolo[1,5-a]pyrimidin-3-carbonsäureethylester	375.51	376,2
123	7-(2,4-Dimethyl-phenyl)-3-phenylazo-5-propyl-tetrahydro-pyrazolo[1,5-a]pyrimidin-2-ol	389.5	390,5
124	7-(2,4-Dimethyl-phenyl)-2-methylsulfanyl-5-propyl-tetrahydro-pyrazolo[1,5-a]pyrimidin-3-carbonitril	340.49	341,3
125	5-tert-Butyl-7-(2,4-dimethyl-phenyl)-tetrahydro-pyrazolo[1,5-a]pyrimidin-3-carbonsäureethylester	355.48	356,1
126	2,5-Di-tert-butyl-7-(3,4-dimethoxy-phenyl)-tetrahydro-pyrazolo[1,5-a]pyrimidin	371.52	372,2
127	3-Brom-5-tert-butyl-7-(3,4-dimethoxy-phenyl)-2-phenyl-tetrahydro-pyrazolo[1,5-a]pyrimidin	470.41	470,2/472,1
128	2-[3-Cyano-6,7-bis-(4-methoxy-phenyl)-tetrahydro-pyrazolo[1,5-a]pyrimidin-5-yl]-cyclopropan-carbonsäureethylester	472.54	473,0
129	3-Cyano-6,7-bis-(4-methoxy-phenyl)-tetrahydro-pyrazolo[1,5-a]pyrimidin-5-carbonsäure	404.42	405,0
130	4-[3-Brom-6-methyl-2-phenyl-5-(4-trifluormethyl-phenyl)-tetrahydro-pyrazolo[1,5-a]pyrimidin-7-yl]-phenol	528.37	528,1
131	7-(4-Hydroxy-phenyl)-6-methyl-2-methylsulfanyl-5-(4-trifluormethyl-phenyl)-tetrahydro-pyrazolo[1,5-a]pyrimidin-3-carbonitril	444.47	445,1
132	7-(4-Hydroxy-phenyl)-6-methyl-5-(4-trifluormethyl-phenyl)-tetrahydro-pyrazolo[1,5-a]pyrimidin-3-carbonitril	398.38	399,1

Beispiel	Name	berechnete Masse	gefundene Masse
133	2-(4-Nitro-phenylsulfonyl)-5-phenylsulfonyl-7-pyridin-2-yl-6,7-dihydro-5H-thiazolo[3,2-a]pyrimidin	510,61	511,2
134	3-(4-Chlor-phenyl)-5-phenylsulfonyl-7-pyridin-2-yl-6,7-dihydro-5H-thiazolo[3,2-a]pyrimidin	435,99	436,4
135	5-Phenylsulfonyl-7-pyridin-2-yl-3-p-tolyl-6,7-dihydro-5H-thiazolo[3,2-a]pyrimidin	415,58	416,3
136	7-Methoxy-4-phenylsulfonyl-2-pyridin-2-yl-3,4-dihydro-2H-9-thia-1,4a-diaza-fluoren	405,54	406,3
137	7-Ethoxy-4-phenylsulfonyl-2-pyridin-2-yl-3,4-dihydro-2H-9-thia-1,4a-diaza-fluoren	419,56	420,3
138	7-Fluor-4-phenylsulfonyl-2-pyridin-2-yl-3,4-dihydro-2H-9-thia-1,4a-diaza-fluoren	393,5	394,2
139	3-Naphthalin-2-yl-5-phenylsulfonyl-7-pyridin-2-yl-6,7-dihydro-5H-thiazolo[3,2-a]pyrimidin	451,61	452,5
140	7-Phenyl-3-phenylazo-5-pyridin-2-yl-3,5,6,7-tetrahydro-pyrazolo[1,5-a]pyrimidin-2-ol	396,47	397,4
141	7-Phenylsulfonyl-5-pyridin-2-yl-3,5,6,7-tetrahydro-pyrazolo[1,5-a]pyrimidine-3-carbonsäureethylester	380,5	381,4
142	3-Phenylazo-7-phenylsulfonyl-5-pyridin-2-yl-3,5,6,7-tetrahydro-pyrazolo[1,5-a]pyrimidin-2-ol	428,51	429,6
143	3-Brom-7-phenylsulfonyl-5-pyridin-2-yl-3,5,6,7-tetrahydro-pyrazolo[1,5-a]pyrimidin	387,3	387,2
144	7-Phenylsulfonyl-5-pyridin-2-yl-3,5,6,7-tetrahydro-pyrazolo[1,5-a]pyrimidin-3-carbonitril.	333,41	334,2

Pharmakologische Untersuchungen

[0055] Die Untersuchungen zur Bestimmung der NMDA-antagonistischen Wirkung der erfindungsgemäßen Verbindungen wurden an Hirnmembranhomogenaten (Homogenat von Rattenhirn ohne Cerebellum, Pons und Medulla oblongata von männlichen Wistar-Ratten (Charles River, Sulzfeld, Deutschland)) durchgeführt.

[0056] Hierzu wurden frisch präparierte Rattengehirne nach Abtrennen von Cerebellum, Pons und Medulla oblongata in 50 mmol/l Tris/HCl (pH 7,7) mit einem Polytron-Homogenisator (Modell PT3000, Kinematika AG, Littau, Schweiz) bei 6.000 Umdrehungen pro Minute (UPM) für 1 Minute unter Eiskühlung aufgeschlossen und anschließend für 15 Minuten bei 4°C und 60.000 g zentrifugiert. Nach Dekantieren und Verwerfen des Überstandes, erneutem Aufnehmen in 50 mmol/l Tris/HCl (pH 7,7) und Aufschluß des Membranpellets mit einem Homogenisator bei 2.000 UPM für 1 Minute wurde erneut für 15 Minuten bei 4°C und 60.000 g zentrifugiert. Der Überstand wurde wiederum verworfen und das Membranpellet in 50 mmol/l Tris/HCl (pH 7,7) homogenisiert (2.000 UPM für 1 Minute) und aliquotiert bei -70°C eingefroren.

[0057] Für den Rezeptorbindungstest wurden jeweils Aliquote aufgetaut und anschließend für 15 Minuten bei 4°C und 60.000 g zentrifugiert. Nach Dekantieren und Verwerfen des Überstandes wurde das Membranpellet für den Bindungstest mit Bindungstest-Puffer aufgenommen und homogenisiert (2.000 UPM für 1 Minute). Als Bindungstest-Puffer wurden 5 mmol/l Tris/HCl (pH 7,7) supplementiert mit 30 µmol/l Glycin und 100 µmol/l Glutaminsäure verwendet.

[0058] Als radioaktiv markierter Ligand wurde 1 nmol/l (³H)-(+)-MK801 ((5R,10S)-(+)-5-Methyl-10,11-dihydro-5H-dibenzo(a,d)cyclohepten-5,10-imin (NET-972, NEN, Köln, Deutschland)) zugegeben. Der Anteil an unspezifischer Bindung wurde in Anwesenheit von 10 µmol/l nicht radioaktiv markiertem (+)-MK801 (RBI/Sigma, Deisenhofen, Deutschland) bestimmt. In weiteren Ansätzen wurden die jeweiligen erfindungsgemäßen Verbindungen in Konzentrationsreihen zugegeben und die Verdrängung des radioaktiven Liganden aus seiner spezifischen Bindung am NMDA-Rezeptor ermittelt.

[0059] Die Ansätze wurden jeweils für 40 Minuten bei 25°C inkubiert und anschließend zur Bestimmung des an das Hirnmembranhomogenat gebundenen, radioaktiven Liganden mittels Filtration geerntet. Die durch die Filter zurückgehaltene Radioaktivität wurde nach Zugabe von Szintillator (Szintillator "Ready Protein", Beckmann Coulter GmbH, Krefeld, Deutschland) im β-Counter (Packard TRI-CARB Liquid Szintillation Analyzer 2000CA, Packard Instrument, Meriden, CT 06450, USA) vermessen.

[0060] Die resultierende, prozentuale Hemmung der spezifischen Bindung des Liganden (³H)-(+)-MK801 in Gegenwart von je 10 µmol/l der jeweiligen erfindungsgemäßen Verbindung dient als Maß für die Affinität dieser Verbindung zu der (+)-MK801-Bindungsstelle des ionotropen NMDA-Rezeptors. Die Affinität sind in Tabelle 2 als Mittelwerte von Doppelbestimmungen an ausgewählten Beispielen angegeben:

Tabelle 2

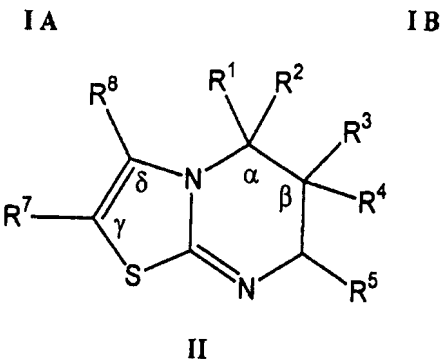
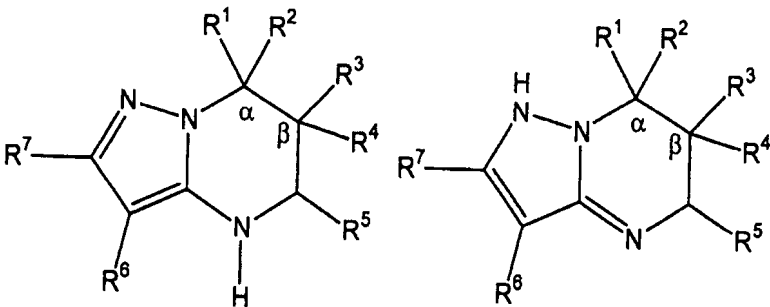
Beispiel	% Hemmung
140	44
141	45
142	75
143	49
144	45

Pharmazeutische Formulierung eines erfindungsgemäßen Arzneimittels

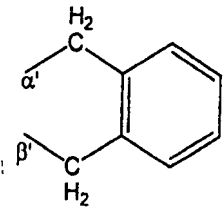
[0061] 1 g des Hydrochlorids von 3-Phenylazo-7-phenylsulfanyl-5-pyridin-2-yl-3,5,6,7-tetrahydro-pyrazolo[1,5-a]pyrimidin-2-ol wurde in 1 l Wasser für Injektionszwecke bei Raumtemperatur gelöst und anschließend durch Zugabe von Natriumchlorid auf isotone Bedingungen eingestellt.

Patentansprüche

1. Verbindung der allgemeinen Struktur (IA), (IB) oder (II) oder eines ihrer pharmazeutisch annehmbaren Salze:



worin
R¹ und R² unabhängig voneinander H, O-R⁹, S-R¹⁰, C₁₋₁₂-Alkyl, C₃₋₈-Cycloalkyl, -CH₂-C₃₋₈-Cycloalkyl, Aryl, -
(C₁₋₆-Alkyl)-Aryl, Heterocyclyl oder -(C₁₋₆-Alkyl)-Heterocyclyl bedeuten,
wobei einer der Reste R¹ und R² H ist und der andere Rest von R¹ und R² nicht H ist oder für den Fall, daß einer der
Reste R¹ und R² Aryl bedeutet, der andere Rest von R¹ und R² H oder C₁₋₁₂-Alkyl ist,
R³ und R⁴ H, C₁₋₁₂-Alkyl, C₃₋₈-Cycloalkyl, -CH₂-C₃₋₈-Cycloalkyl, Aryl oder -(C₁₋₆-Alkyl)-Aryl bedeuten,
wobei mindestens einer der Reste R³ und R⁴ H ist,
oder
einer der Reste R¹ und R² zusammen mit einem der Reste R³ und R⁴ W bildet, wobei W α'-(CH₂)_n-β' mit n = 3, 4, 5
oder 6, α'-CH=CH-CH₂-β', α'-CH₂-CH=CH-β', α'-CH=CH-CH₂-CH₂-β', α'-CH₂-CH=CH-CH₂-β', α'-CH₂-CH₂-
CH=CH-β',



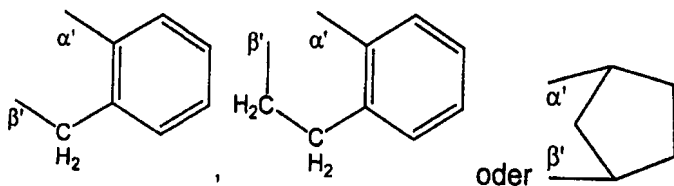
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ist oder für den Fall, daß einer der Reste R^1 und R^2 Aryl¹ bedeutet, der andere Rest von R^1 und R^2 H oder C_{1-12} -Alkyl bedeutet,

R^3 und R^4 H, unsubstituiertes oder einfach substituiertes oder mehrfach gleich oder verschieden substituiertes Methyl, Ethyl, n-Propyl, 2-Propyl, n-Butyl, iso-Butyl, sek.-Butyl, tert.-Butyl, n-Amyl, iso-Amyl, sek.-Amyl, n-Hexyl, iso-Hexyl, sek.-Hexyl, Aryl¹ oder -CH₂-Aryl¹ bedeutet,

wobei mindestens einer der Reste R^3 und R^4 H ist, oder

einer der Reste R^1 und R^2 zusammen mit einem der Reste R^3 und R^4 W bildet, wobei W α' -CH=CH-CH₂- β' , α' -CH=CH-CH₂-CH₂- β' , α' -O-(CH₂)_m- β' mit m = 2, 3, 4 oder 5,



bedeutet, das mit α' gekennzeichnete Ende von W mit dem mit α gekennzeichneten Atom der Verbindung der allgemeinen Struktur (IA), (IB) oder (II) verbunden ist und das mit β' gekennzeichnete Ende von W mit dem mit β gekennzeichneten Atom der Verbindung der allgemeinen Struktur (IA), (IB) oder (II) verbunden ist, der andere Rest von R^1 und R^2 H oder Methyl, Ethyl, n-Propyl, 2-Propyl, n-Butyl, iso-Butyl, sek.-Butyl, tert.-Butyl, n-Amyl, iso-Amyl, sek.-Amyl, n-Hexyl, iso-Hexyl, oder sek.-Hexyl bedeutet und der andere Rest von R^3 und R^4 H oder Methyl, Ethyl, n-Propyl, 2-Propyl, n-Butyl, iso-Butyl, sek.-Butyl, tert.-Butyl, n-Amyl, iso-Amyl, sek.-Amyl, n-Hexyl, iso-Hexyl, sek.-Hexyl bedeutet;

R^5 Methyl, Ethyl, n-Propyl, 2-Propyl, n-Butyl, iso-Butyl, sek.-Butyl, tert.-Butyl, n-Amyl, iso-Amyl, sek.-Amyl, n-Hexyl, iso-Hexyl, sek.-Hexyl, Cyclopropyl, Cyclobutyl, Cyclopentyl, Cyclohexyl oder Cycloheptyl, die jeweils unsubstituiert oder einfach substituiert oder mehrfach gleich oder verschieden substituiert sind, Aryl¹ oder -(CH₂)_k-Aryl¹, wobei k = 1, 2, 3 oder 4 ist, Heterocyclyl oder C(=O)R¹¹ bedeutet;

R^6 H, Methyl, Ethyl, -CN, Fluor, Chlor, Brom, Iod, -C(=O)R¹⁷ oder -N=N-Aryl¹ bedeutet;

R^7 H, Aryl¹, OR¹⁸, S(O)_qR¹⁹, wobei q = 0, 1 oder 2, oder unsubstituiertes oder einfach substituiertes oder mehrfach gleich oder verschieden substituiertes Methyl, Ethyl, n-Propyl, 2-Propyl, n-Butyl, iso-Butyl, sek.-Butyl, tert.-Butyl, n-Amyl, iso-Amyl, sek.-Amyl, n-Hexyl, iso-Hexyl oder sek.-Hexyl bedeutet,

R^8 H oder Aryl¹ bedeutet,

oder

die Reste R^7 und R^8 zusammen Y bilden, wobei Y γ -CR²¹=CR²²-CR²³=CR²⁴- δ' bedeutet und das mit γ gekennzeichnete Ende von Y mit dem mit γ gekennzeichneten Atom der allgemeinen Struktur (II) verbunden ist und das mit δ' gekennzeichnete Ende von Y mit dem mit δ gekennzeichneten Atom der allgemeinen Struktur (II) verbunden ist;

R^9 unsubstituiertes oder einfach substituiertes oder mehrfach gleich oder verschieden substituiertes Methyl, Ethyl, n-Propyl, 2-Propyl, n-Butyl, iso-Butyl, sek.-Butyl, tert.-Butyl, n-Amyl, iso-Amyl, sek.-Amyl, n-Hexyl, iso-Hexyl, sek.-Hexyl, Cyclopropyl, Cyclobutyl, Cyclopentyl, Cyclohexyl oder Cycloheptyl bedeutet oder -[(CH₂)_r-O]_s-H mit r = 1, 2, 3, 4, 5 oder 6 und s = 1, 2, 3, 4, 5 oder 6 bedeutet;

R^{10} Aryl¹ bedeutet;

R^{11} Aryl¹ oder OR²⁵ bedeutet;

R^{17} OR²⁶ bedeutet;

R^{18} H oder Methyl bedeutet;

R^{19} H, Aryl¹ oder jeweils unsubstituiertes, einfach substituiertes oder mehrfach gleich oder verschieden substituiertes Methyl, Ethyl, n-Propyl, 2-Propyl, n-Butyl, iso-Butyl, sek.-Butyl, tert.-Butyl, n-Amyl, iso-Amyl, sek.-Amyl, n-Hexyl, iso-Hexyl oder sek.-Hexyl bedeutet;

R^{21} , R^{22} , R^{23} und R^{24} unabhängig voneinander H, Fluor, Chlor, Brom, Iod oder OR²⁸ bedeuten;

R^{25} H, Methyl, Ethyl, n-Propyl, 2-Propyl, n-Butyl, iso-Butyl, sek.-Butyl, tert.-Butyl, n-Amyl, iso-Amyl, sek.-Amyl, n-Hexyl, iso-Hexyl oder sek.-Hexyl bedeutet, wobei R^{25} nicht H bedeutet, wenn zugleich R^1 Aryl und R^2 Alkyl bedeuten;

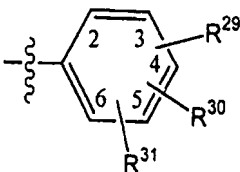
R^{26} H, Methyl, Ethyl, n-Propyl, 2-Propyl, n-Butyl, iso-Butyl, sek.-Butyl, tert.-Butyl, n-Amyl, iso-Amyl, sek.-Amyl, n-Hexyl, iso-Hexyl oder sek.-Hexyl bedeutet; und

R^{28} H, Methyl oder Ethyl bedeutet;

Heterocyclyl Furan-2-yl, Furan-3-yl, Thien-2-yl, Thien-3-yl, Pyridin-2-yl-, Pyridin-3-yl oder Pyridin-4-yl, wobei Furanyl, Thienyl und Pyridinyl jeweils unsubstituiert oder einfach substituiert oder mehrfach gleich oder verschieden substituiert sind, bedeutet;

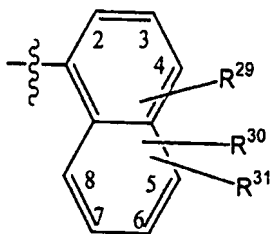
Aryl¹ Aryl¹, Aryl² oder Aryl³ bedeutet;

Aryl¹ für



steht;
Aryl² für

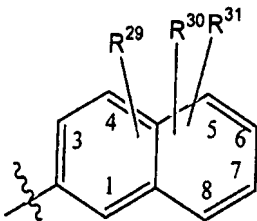
5



10

steht;
Aryl³ für

15



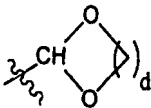
20

steht;

25

R²⁹, R³⁰ und R³¹ unabhängig voneinander H, C₁₋₆-Alkyl, C₃₋₈-Cycloalkyl, -(C₁₋₆-Alkyl)-C₃₋₈-Cycloalkyl, Aryl, -(C₁₋₆-Alkyl)-Aryl, Heterocyclyl, -(C₁₋₆-Alkyl)-Heterocyclyl, F, Cl, Br, I, -CN, -NC, -OR³², -SR³³, -NO, -NO₂, NH₂, NHR³⁴, NR³⁵R³⁶, -N-OH, -N-OC₁₋₆-Alkyl, -NHNH₂, -N=N-Aryl, -(C=O)R³⁷,

30



mit d = 1, 2 oder 3, oder -(C=S)R³⁷ bedeuten;

35

R³² und R³³ unabhängig voneinander H, -C₁₋₆-Alkyl, -C₃₋₈-Cycloalkyl, -(C₁₋₆-Alkyl)-C₃₋₈-Cycloalkyl, -Aryl, -(C₁₋₆-Alkyl)-Aryl, -Heterocyclyl, -(C₁₋₆-Alkyl)-Heterocyclyl, (C=O)R³⁸, -[(CH₂)_w-O]_z-H oder -[(CH₂)_w-O]_z-C₁₋₆-Alkyl mit w = 1, 2, 3 oder 4 und z = 1, 2, 3, 4 oder 5 bedeuten;

R³⁴ C₁₋₆-Alkyl, -CH₂-Aryl oder -(C=O)O-tert.-Butyl bedeutet;

R³⁵ und R³⁶ unabhängig voneinander C₁₋₆-Alkyl bedeuten oder gemeinsam für -(CH₂)_g mit g = 4 oder 5 stehen;

40

R³⁷ H, -C₁₋₆-Alkyl, -C₃₋₈-Cycloalkyl, -(C₁₋₆-Alkyl)-C₃₋₈-Cycloalkyl, -Aryl, -(C₁₋₆-Alkyl)-Aryl, -Heterocyclyl, -(C₁₋₆-Alkyl)-Heterocyclyl, -OR³⁹, -NH₂, -NHR³⁴, -NR³⁵R³⁶ bedeutet;

R³⁸ H, -C₁₋₆-Alkyl, -C₃₋₈-Cycloalkyl, -(C₁₋₆-Alkyl)-C₃₋₈-Cycloalkyl, -Aryl, -(C₁₋₆-Alkyl)-Aryl bedeutet; und

R³⁹ H, C₁₋₆-Alkyl, -C₃₋₈-Cycloalkyl, -(C₁₋₆-Alkyl)-C₃₋₈-Cycloalkyl, -Aryl, -(C₁₋₆-Alkyl)-Aryl, -Heterocyclyl oder -(C₁₋₆-Alkyl)-Heterocyclyl bedeutet.

45

4. Verbindung nach irgendeinem der Ansprüche 1 bis 3 oder ein pharmazeutisch annehmbares Salz davon, dadurch gekennzeichnet, daß

R¹ und R² unabhängig voneinander H, O-R⁹, S-R¹⁰, unsubstituiertes oder einfach substituiertes oder mehrfach gleich oder verschieden substituiertes Methyl, Ethyl, n-Propyl, 2-Propyl, n-Butyl, tert.-Butyl oder n-Hexyl, Aryl' oder -CH₂-Aryl', wobei die Aryl'-Substituenten R²⁹, R³⁰ und R³¹ unabhängig voneinander H, Methyl, Ethyl, 2-Propyl, n-Butyl, tert.-Butyl, n-Hexyl, F, Cl, Br, I, OH, O-Methyl, O-Ethyl sind, bedeuten,

50

wobei einer der Reste R¹ und R² H ist und der andere Rest von R¹ und R² nicht H ist oder für den Fall, daß einer der Reste R¹ und R² Aryl' bedeutet, der andere Rest von R¹ und R² H oder Methyl, Ethyl, n-Propyl, 2-Propyl, n-Butyl, tert.-Butyl oder n-Hexyl bedeutet,

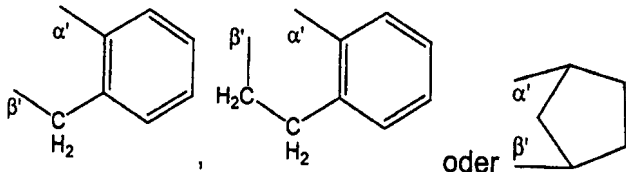
R³ und R⁴ H, Methyl oder Aryl¹ bedeutet, wobei die Aryl¹-Substituenten R²⁹, R³⁰ und R³¹ unabhängig voneinander H, Methyl oder O-Methyl sind,

55

wobei mindestens einer der Reste R³ und R⁴ H ist, oder

einer der Reste R¹ und R² zusammen mit einem der Reste R³ und R⁴ W bildet, wobei W α'-CH=CH-CH₂-β', α'-CH=CH-CH₂-CH₂-β', α'-O-(CH₂)_m-β' mit m = 2, 3, 4 oder 5,

60



oder

65

bedeutet, das mit α' gekennzeichnete Ende von W mit dem mit α gekennzeichneten Atom der Verbindung der allgemeinen Struktur (IA), (IB) oder (II) verbunden ist und das mit β' gekennzeichnete Ende von W mit dem mit β gekennzeichneten Atom der Verbindung der allgemeinen Struktur (IA), (IB) oder (II) verbunden ist, der andere Rest von R¹ und R² und der andere Rest von R³ und R⁴ jeweils H bedeuten;

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R⁵ Methyl, Ethyl, n-Propyl, 2-Propyl, n-Butyl, iso-Butyl, sek.-Butyl, tert.-Butyl, -(CH₂)₄-OH, Cyclopropyl, wobei Cyclopropyl unsubstituiert oder einfach mit C(=O)OH, C(=O)O-Methyl oder C(=O)O-Ethyl substituiert ist, Cyclopentyl, Cyclohexyl, Aryl¹ oder -(CH₂)_k-Aryl¹, wobei die Aryl¹-Substituenten R²⁹, R³⁰ und R³¹ unabhängig voneinander H, -OH, -O-Methyl, O-C₆H₅, CH₃, CF₃ oder C(=O)OH sind und k = 1 oder 2 ist, Heterocyclyl oder C(=O)R¹¹ bedeutet;

R⁶ H, -CN, Brom, -C(=O)R¹⁷ oder -N=N-Phenyl bedeutet;

R⁷ H, Aryl¹ mit R²⁹, R³⁰ und R³¹ gleich H, OH, S(O)_qR¹⁹, wobei q = 0 oder 2 ist, oder Methyl, Ethyl, n-Propyl, 2-Propyl, n-Butyl, iso-Butyl, sek.-Butyl oder tert.-Butyl bedeutet,

R⁸ H, Aryl¹, wobei die Aryl¹-Substituenten R²⁹, R³⁰ und R³¹ unabhängig voneinander H, Methyl oder Chlor sind, oder Aryl³ mit R²⁹, R³⁰ und R³¹ gleich H bedeutet, oder

die Reste R⁷ und R⁸ zusammen Y bilden, wobei Y γ-CR²¹=CR²²-CR²³=CR²⁴-δ' bedeutet und das mit γ gekennzeichnete Ende von Y mit dem mit γ gekennzeichneten Atom der allgemeinen Struktur (II) verbunden ist und das mit δ' gekennzeichnete Ende von Y mit dem mit δ gekennzeichneten Atom der allgemeinen Struktur (II) verbunden ist;

R⁹ Methyl, Ethyl, n-Propyl, 2-Propyl, n-Butyl, iso-Butyl, sek.-Butyl, tert.-Butyl, n-Amyl, iso-Amyl, sek.-Amyl, n-Hexyl, iso-Hexyl, sek.-Hexyl, Cyclopropyl, Cyclopentyl oder Cyclohexyl bedeutet oder -[(CH₂)_r-O]_s-H mit r = 1, 2 oder 3 und s = 1 oder 2 bedeutet;

R¹⁰ Aryl¹ bedeutet;

R¹¹ Aryl¹ mit R²⁹, R³⁰ und R³¹ gleich H oder OR²⁵ bedeutet;

R¹⁷ OR²⁶ bedeutet;

R¹⁹ Methyl oder Aryl¹ bedeutet, wobei einer der Aryl¹-Substituenten R²⁹, R³⁰ und R³¹ gleich H oder -NO₂ ist und die beiden anderen Aryl¹-Substituenten von R²⁹, R³⁰ und R³¹ H sind,

R²¹ und R²³ H bedeuten;

R²² H, Fluor oder OR²⁸ bedeutet;

R²⁴ H oder Chlor bedeutet;

R²⁵ H, Methyl oder Ethyl bedeutet, wobei R²⁵ nicht H bedeutet, wenn zugleich R¹ Aryl und R² Alkyl bedeuten;

R²⁶ H, Methyl oder Ethyl bedeutet;

R²⁸ Methyl oder Ethyl bedeutet, und

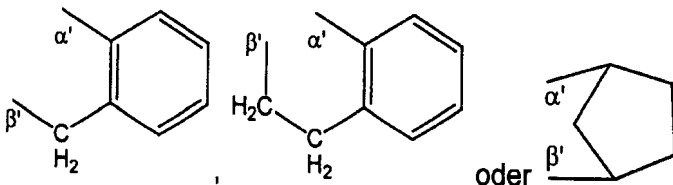
Heterocyclyl Furan-2-yl, Furan-3-yl, Thien-2-yl, Thien-3-yl, Pyridin-2-yl-, Pyridin-3-yl oder Pyridin-4-yl bedeutet, wobei Furanyl, Thienyl und Pyridinyl jeweils unsubstituiert oder einfach substituiert oder mehrfach gleich oder verschieden mit -NO₂, -CH₃ oder C(=O)OH substituiert sind.

5. Verbindung nach irgendeinem der Ansprüche 1 bis 4 oder ein pharmazeutisch annehmbares Salz davon, dadurch gekennzeichnet, daß

R¹ und R² unabhängig voneinander H, O-CH₂-CH₂-OH, O-Cyclohexyl, S-Phenyl, Methyl, Phenyl, 3-Fluor-phenyl, 3-Brom-phenyl, 4-Brom-phenyl, 4-Chlor-phenyl, 4-Fluor-phenyl, 3-Methyl-phenyl, 4-Hydroxy-phenyl, 4-Methoxy-phenyl, 2,4-Dimethyl-phenyl, 3,4-Dimethoxy-phenyl, 2,3,4-Trimethoxyphenyl, 2-Naphthyl oder -CH₂-Phenyl bedeuten,

R³ und R⁴ H, Methyl oder 4-Methoxy-phenyl bedeuten, wobei mindestens einer der Reste R³ und R⁴ H ist, oder

einer der Reste R¹ und R² zusammen mit einem der Reste R³ und R⁴ W bildet, wobei W α'-CH=CH-CH₂-β', α'-CH=CH-CH₂-CH₂-β', α'-O-(CH₂)_m-β' mit m = 2, 3, 4 oder 5,



bedeutet, das mit α' gekennzeichnete Ende von W mit dem mit α gekennzeichneten Atom der Verbindung der allgemeinen Struktur (IA), (IB) oder (II) verbunden ist und das mit β' gekennzeichnete Ende von W mit dem mit β gekennzeichneten Atom der Verbindung der allgemeinen Struktur (IA), (IB) oder (II) verbunden ist,

der andere Rest von R¹ und R² und der andere Rest von R³ und R⁴ jeweils H bedeuten;

R⁵ n-Propyl, n-Butyl, tert.-Butyl, -(CH₂)₄-OH, Cyclopropyl, Cycloprop-2-yl-1-carbonsäureethylester, Cyclohexyl, 4-Trifluorphenyl, 4-Phenoxy-phenyl, 2-Hydroxy-3-methoxy-phenyl, 4-Hydroxy-3-methoxy-phenyl, 3-Carboxy-2-hydroxy-phenyl, -(CH₂)₂-Phenyl, 5-Carboxy-furan-2-yl, 5-Methyl-furan-2-yl, 5-Nitro-furan-2-yl, 5-Nitro-thien-2-yl, Pyridin-2-yl, Pyridin-3-yl, C(=O)Phenyl, C(=O)OH oder C(=O)O-Ethyl bedeutet, wobei R⁵ nicht C(=O)OH bedeutet, wenn zugleich R¹ Aryl und R² Alkyl bedeuten;

R⁶ H, -CN, Brom, -C(=O)OH, -C(=O)O-Ethyl oder -N=N-Phenyl bedeutet;

R⁷ H, Phenyl, OH, -S-Methyl, -SO₂-(4-nitrophenyl) oder tert.-Butyl bedeutet,

R⁸ 4-Chlor-phenyl, 4-Methyl-phenyl oder 2-Naphthyl bedeutet, oder

die Reste R⁷ und R⁸ zusammen Y bilden, wobei Y γ'-CR²¹=CH-CH=CH-δ' bedeutet und das mit γ' gekennzeichnete Ende von Y mit dem mit γ gekennzeichneten Atom der allgemeinen Struktur (II) verbunden ist und das mit δ' gekennzeichnete Ende von Y mit dem mit δ gekennzeichneten Atom der allgemeinen Struktur (II) verbunden ist, und R²¹ Fluor, Methoxy oder Ethoxy bedeutet.

6. Verbindung nach Anspruch 1 oder ein pharmazeutisch annehmbares Salz davon, dadurch gekennzeichnet, daß die Verbindung ausgewählt ist aus:

- 3-Brom-5-(5-nitro-furan-2-yl)-7-m-tolyl-tetrahydro-pyrazolo[1,5-a]pyrimidin

- 3-Brom-7-(4-fluor-phenyl)-7-methyl-5-(5-nitro-furan-2-yl)-tetrahydro-pyrazolo[1,5-a]pyrimidin
- 3-Brom-7-naphthalin-2-yl-5-(5-nitro-furan-2-yl)-tetrahydro-pyrazolo[1,5-a]pyrimidin
- 2-(3-Brom-7-m-tolyl-tetrahydro-pyrazolo[1,5-a]pyrimidin-5-yl)-cyclopropan-carbonsäureethylester
- 5 – 2-[3-Brom-7-(4-brom-phenyl)-tetrahydro-pyrazolo[1,5-a]pyrimidin-5-yl]-cyclopropan-carbonsäureethylester
- 2-(3-Brom-7-naphthalin-2-yl-tetrahydro-pyrazolo[1,5-a]pyrimidin-5-yl)-cyclopropan-carbonsäureethylester
- 3-Brom-7-(4-fluor-phenyl)-7-methyl-5-(5-methyl-furan-2-yl)-tetrahydro-pyrazolo[1,5-a]pyrimidin
- 3-Brom-7-(3,4-dimethoxy-phenyl)-tetrahydro-pyrazolo[1,5-a]pyrimidin-5-carbonsäureethylester
- 10 – 3-Brom-7-(4-methoxy-phenyl)-tetrahydro-pyrazolo[1,5-a]pyrimidin-5-carbonsäureethylester
- 3-Brom-7-(4-methoxy-phenyl)-tetrahydro-pyrazolo[1,5-a]pyrimidin-5-carbonsäure
- 3-Brom-7-(2,4-dimethyl-phenyl)-5-(5-nitro-furan-2-yl)-tetrahydro-pyrazolo[1,5-a]pyrimidin
- 3-Brom-7-(4-methoxy-phenyl)-5-(5-nitro-furan-2-yl)-tetrahydro-pyrazolo[1,5-a]pyrimidin
- 5,5a,6,8a-Tetrahydro-3H-1,4,8b-triaza-as-indacen-3,5-dicarbon-säurediethylester; 5,5a,6,8a-Tetrahydro-4H-1,4,8b-triaza-as-indacen-3,5-dicarbon-säurediethylester;
- 15 – 2-Hydroxy-3-phenylazo-5,5a,6,8a-tetrahydro-3H-1,4,8b-triaza-as-indacen-5-carbonsäureethylester; 2-Hydroxy-3-phenylazo-5,5a,6,8a-tetrahydro-4H-1,4,8b-triaza-as-indacen-5-carbonsäureethylester
- 2-tert.-Butyl-5,5a,6,8a-tetrahydro-3H-1,4,8b-triaza-as-indacen-5-carbonsäureethylester; 2-tert.-Butyl-5,5a,6,8a-tetrahydro-3H-1,4,8b-triaza-as-indacen-5-carbonsäureethylester
- 20 – 3-Brom-2-phenyl-5,5a,6,8a-tetrahydro-3H-1,4,8b-triaza-as-indacen-5-carbonsäureethylester; 3-Brom-2-phenyl-5,5a,6,8a-tetrahydro-4H-1,4,8b-triaza-as-indacen-5-carbonsäureethylester
- 7-(2,3,4-Trimethoxy-phenyl)-tetrahydro-pyrazolo[1,5-a]pyrimidin-3,5-dicarbon-säurediethylester
- 3-Cyano-2-methylsulfanyl-7-(2,3,4-trimethoxy-phenyl)-tetrahydro-pyrazolo[1,5-a]pyrimidin-5-carbon-säureethylester
- 25 – 2-Hydroxy-7-(4-hydroxy-phenyl)-6-methyl-3-phenylazo-tetrahydro-pyrazolo[1,5-a]pyrimidin-5-carbon-säureethylester
- 3-Brom-7-(4-hydroxy-phenyl)-6-methyl-2-phenyl-tetrahydro-pyrazolo[1,5-a]pyrimidin-5-carbonsäureethylester
- 5,5a,6,10b-Tetrahydro-3H-1,4,10c-triaza-cyclopenta[c]fluoren-3,5-dicarbon-säurediethylester; 5,5a,6,10b-Tetrahydro-4H-1,4,10c-triaza-cyclopenta[c]fluoren-3,5-dicarbon-säurediethylester
- 30 – 2-Hydroxy-3-phenylazo-5,5a,6,10b-tetrahydro-3H-1,4,10c-triaza-cyclopenta[c]fluoren-5-carbonsäureethylester; 2-Hydroxy-3-phenylazo-5,5a,6,10b-tetrahydro-4H-1,4,10c-triaza-cyclopenta[c]fluoren-5-carbon-säureethylester
- 7-Phenylsulfanyl-tetrahydro-pyrazolo[1,5-a]pyrimidin-3,5-dicarbon-säurediethylester
- 3-Cyano-2-methylsulfanyl-7-phenylsulfanyl-tetrahydro-pyrazolo[1,5-a]pyrimidin-5-carbonsäureethylester
- 35 – 3-Cyano-2-methylsulfanyl-7-(2,3,4-trimethoxy-phenyl)-tetrahydro-pyrazolo[1,5-a]pyrimidin-5-carbon-säure
- 7-Phenylsulfanyl-tetrahydro-pyrazolo[1,5-a]pyrimidin-3,5-dicarbon-säure3-ethylester
- 3-Cyano-7-(2,4-dimethyl-phenyl)-2-methylsulfanyl-tetrahydro-pyrazolo[1,5-a]pyrimidin-5-carbonsäureethylester
- 40 – 3-Cyano-7-(2,4-dimethyl-phenyl)-tetrahydro-pyrazolo[1,5-a]pyrimidin-5-carbonsäureethylester
- 7-(2,4-Dimethyl-phenyl)-tetrahydro-pyrazolo[1,5-a]pyrimidin-3,5-dicarbon-säure3-ethylester
- 3-Brom-7-(2,4-dimethyl-phenyl)-2-phenyl-tetrahydro-pyrazolo[1,5-a]pyrimidin-5-carbonsäure
- 3-Cyano-7-(2,4-dimethyl-phenyl)-2-methylsulfanyl-tetrahydro-pyrazolo[1,5-a]pyrimidin-5-carbonsäure
- 3-Cyano-7-(2,4-dimethyl-phenyl)-tetrahydro-pyrazolo[1,5-a]pyrimidin-5-carbonsäure
- 45 – 3-Cyano-7-(3,4-dimethoxy-phenyl)-2-methylsulfanyl-tetrahydro-pyrazolo[1,5-a]pyrimidin-5-carbonsäure
- 7-(2,4-Dimethyl-phenyl)-5-(5-nitro-furan-2-yl)-tetrahydro-pyrazolo[1,5-a]pyrimidin-3-carbonsäureethylester
- 7-(2,4-Dimethyl-phenyl)-5-(5-nitro-furan-2-yl)-3-phenylazo-tetrahydro-pyrazolo[1,5-a]pyrimidin-2-ol
- 50 – 3-Brom-7-(2,4-dimethyl-phenyl)-5-(5-nitro-furan-2-yl)-2-phenyl-tetrahydro-pyrazolo[1,5-a]pyrimidin
- 7-(2,4-Dimethyl-phenyl)-2-methylsulfanyl-5-(5-nitro-furan-2-yl)-tetrahydro-pyrazolo[1,5-a]pyrimidin-3-carbonitril
- 7-(2,4-Dimethyl-phenyl)-5-(5-nitro-furan-2-yl)-tetrahydro-pyrazolo[1,5-a]pyrimidin-3-carbonitril
- 3-Brom-7-(3,4-dimethoxy-phenyl)-5-(5-nitro-furan-2-yl)-2-phenyl-tetrahydro-pyrazolo[1,5-a]pyrimidin
- 7-(4-Methoxy-phenyl)-2-methylsulfanyl-5-(5-nitro-furan-2-yl)-tetrahydro-pyrazolo[1,5-a]pyrimidin-3-carbonitril
- 55 – 7-(2,4-Dimethyl-phenyl)-5-(2-ethoxycarbonyl-cyclopropyl)-tetrahydro-pyrazolo[1,5-a]pyrimidin-3-carbonsäureethylester
- 2-[7-(2,4-Dimethyl-phenyl)-2-hydroxy-3-phenylazo-tetrahydro-pyrazolo[1,5-a]pyrimidin-5-yl]-cyclopropan-carbonsäureethylester
- 60 – 2-[2-tert.-Butyl-7-(2,4-dimethyl-phenyl)-tetrahydro-pyrazolo[1,5-a]pyrimidin-5-yl]-cyclopropan-carbonsäureethylester
- 2-[3-Brom-7-(2,4-dimethyl-phenyl)-2-phenyl-tetrahydro-pyrazolo[1,5-a]pyrimidin-5-yl]-cyclopropan-carbonsäureethylester
- 2-[3-Cyano-7-(2,4-dimethyl-phenyl)-2-methylsulfanyl-tetrahydro-pyrazolo[1,5-a]pyrimidin-5-yl]-cyclopropan-carbonsäureethylester
- 65 – 5-(2-Ethoxycarbonyl-cyclopropyl)-7-(3-fluor-phenyl)-tetrahydro-pyrazolo[1,5-a]pyrimidin-3-carbonsäureethylester
- 2-[3-Brom-7-(3-brom-phenyl)-2-phenyl-tetrahydro-pyrazolo[1,5-a]pyrimidin-5-yl]-cyclopropan-carbon-

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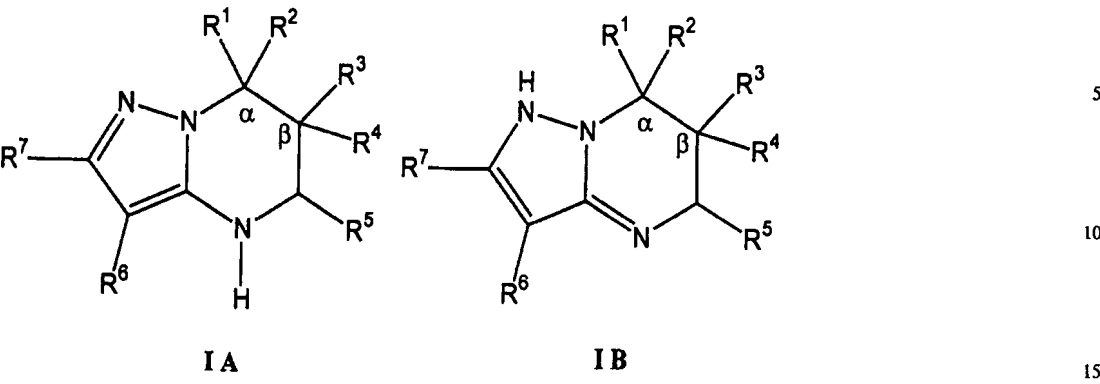
- säureethylester
- 2-[7-(3-Brom-phenyl)-3-cyano-2-methylsulfanyl-tetrahydro-pyrazolo[1,5-a]pyrimidin-5-yl]-cyclopropan-carbonsäureethylester
 - 7-(2,4-Dimethyl-phenyl)-5-(5-nitro-thiophen-2-yl)-3-phenylazo-tetrahydro-pyrazolo[1,5-a]pyrimidin-2-ol
 - 7-(2,4-Dimethyl-phenyl)-2-methylsulfanyl-5-(5-nitro-thiophen-2-yl)-tetrahydro-pyrazolo[1,5-a]pyrimidin-3-carbonitril
 - 7-(2,4-Dimethyl-phenyl)-5-(5-nitro-thiophen-2-yl)-tetrahydro-pyrazolo[1,5-a]pyrimidin-3-carbonitril
 - 7-(3,4-Dimethoxy-phenyl)-5-(5-nitro-thiophen-2-yl)-tetrahydro-pyrazolo[1,5-a]pyrimidin-3-carbonsäureethylester
 - 7-(3,4-Dimethoxy-phenyl)-5-(5-nitro-thiophen-2-yl)-3-phenylazo-tetrahydro-pyrazolo[1,5-a]pyrimidin-2-ol
 - 3-Brom-7-(3,4-dimethoxy-phenyl)-5-(5-nitro-thiophen-2-yl)-2-phenyl-tetrahydro-pyrazolo[1,5-a]pyrimidin
 - 7-(3,4-Dimethoxy-phenyl)-2-methylsulfanyl-5-(5-nitro-thiophen-2-yl)-tetrahydro-pyrazolo[1,5-a]pyrimidin-3-carbonitril
 - 7-(3,4-Dimethoxy-phenyl)-5-(5-nitro-thiophen-2-yl)-tetrahydro-pyrazolo[1,5-a]pyrimidin-3-carbonitril
 - 7-(4-Methoxy-phenyl)-5-(5-nitro-thiophen-2-yl)-tetrahydro-pyrazolo[1,5-a]pyrimidin-3-carbonsäureethylester
 - 5-[3-Brom-7-(4-methoxy-phenyl)-2-phenyl-tetrahydro-pyrazolo[1,5-a]pyrimidin-5-yl]-furan-2-carbonsäure
 - 5-Benzoyl-7-(2,4-dimethyl-phenyl)-tetrahydro-pyrazolo[1,5-a]pyrimidin-3-carbonsäureethylester
 - 5-Benzoyl-7-(2,4-dimethyl-phenyl)-2-methylsulfanyl-tetrahydro-pyrazolo[1,5-a]pyrimidin-3-carbonitril
 - 5-Benzoyl-7-(2,4-dimethyl-phenyl)-tetrahydro-pyrazolo[1,5-a]pyrimidin-3-carbonitril
 - 5-Benzoyl-7-(3,4-dimethoxy-phenyl)-tetrahydro-pyrazolo[1,5-a]pyrimidin-3-carbonsäureethylester
 - [3-Brom-7-(3,4-dimethoxy-phenyl)-2-phenyl-tetrahydro-pyrazolo[1,5-a]pyrimidin-5-yl]-phenyl-methanon
 - 5-Benzoyl-7-(3,4-dimethoxy-phenyl)-2-methylsulfanyl-tetrahydro-pyrazolo[1,5-a]pyrimidin-3-carbonitril
 - 5-Benzoyl-7-(3,4-dimethoxy-phenyl)-tetrahydro-pyrazolo[1,5-a]pyrimidin-3-carbonitril
 - 5-Benzoyl-7-(4-methoxy-phenyl)-2-methylsulfanyl-tetrahydro-pyrazolo[1,5-a]pyrimidin-3-carbonsäureethylester
 - 5-Benzoyl-7-(4-methoxy-phenyl)-tetrahydro-pyrazolo[1,5-a]pyrimidin-3-carbonitril
 - 5-Benzoyl-7-(3-fluor-phenyl)-tetrahydro-pyrazolo[1,5-a]pyrimidin-3-carbonsäureethylester
 - [3-Brom-7-(3-fluor-phenyl)-2-phenyl-tetrahydro-pyrazolo[1,5-a]pyrimidin-5-yl]-phenyl-methanon
 - [3-Brom-7-(3-brom-phenyl)-2-phenyl-tetrahydro-pyrazolo[1,5-a]pyrimidin-5-yl]-phenyl-methanon
 - 7-(2,4-Dimethyl-phenyl)-5-(4-phenoxy-phenyl)-tetrahydro-pyrazolo[1,5-a]pyrimidin-3-carbonsäureethylester
 - 3-Brom-7-(2,4-dimethyl-phenyl)-5-(4-phenoxy-phenyl)-2-phenyl-tetrahydro-pyrazolo[1,5-a]pyrimidin
 - 7-(2,4-Dimethyl-phenyl)-2-methylsulfanyl-5-(4-phenoxy-phenyl)-tetrahydro-pyrazolo[1,5-a]pyrimidin-3-carbonitril
 - 7-(2,4-Dimethyl-phenyl)-5-(4-phenoxy-phenyl)-tetrahydro-pyrazolo[1,5-a]pyrimidin-3-carbonitril
 - 7-(3,4-Dimethoxy-phenyl)-5-(4-phenoxy-phenyl)-tetrahydro-pyrazolo[1,5-a]pyrimidin-3-carbonsäureethylester
 - 7-(3,4-Dimethoxy-phenyl)-2-methylsulfanyl-5-(4-phenoxy-phenyl)-tetrahydro-pyrazolo[1,5-a]pyrimidin-3-carbonitril
 - 3-[3-Cyano-7-(4-hydroxy-phenyl)-6-methyl-tetrahydro-pyrazolo[1,5-a]pyrimidin-5-yl]-2-hydroxy-benzoesäure
 - 3-(3-Cyano-5,5a,6,10b-tetrahydro-3H-1,4,10c-triaza-cyclopenta[c]fluoren-5-yl)-2-hydroxy-benzoesäure;
 - 3-(3-Cyano-5,5a,6,10b-tetrahydro-4H-1,4,10c-triaza-cyclopenta[c]fluoren-5-yl)-2-hydroxy-benzoesäure
 - 3-(3-Cyano-7-phenylsulfanyl-tetrahydro-pyrazolo[1,5-a]pyrimidin-5-yl)-2-hydroxy-benzoesäure
 - 3-[2-tert.-Butyl-7-(4-chlor-phenyl)-7-methyl-tetrahydro-pyrazolo[1,5-a]pyrimidin-5-yl]-2-hydroxy-benzoesäure
 - 5-(4-Hydroxy-3-methoxy-phenyl)-7-(4-hydroxy-phenyl)-6-methyl-tetrahydro-pyrazolo[1,5-a]pyrimidin-3-carbonsäureethylester
 - 5-(4-Hydroxy-3-methoxy-phenyl)-7-(4-hydroxy-phenyl)-6-methyl-tetrahydro-pyrazolo[1,5-a]pyrimidin-3-carbonitril
 - 5-(4-Hydroxy-3-methoxy-phenyl)-5,5a,6,10b-tetrahydro-3H-1,4,10c-triaza-cyclopenta[c]fluoren-3-carbonsäureethylester;
 - 5-(4-Hydroxy-3-methoxy-phenyl)-5,5a,6,10b-tetrahydro-4H-1,4,10c-triaza-cyclopenta[c]fluoren-3-carbonsäureethylester
 - 4-(2-tert.-Butyl-5,5a,6,10b-tetrahydro-3H-1,4,10c-triaza-cyclopenta[c]fluoren-5-yl)-2-methoxy-phenol;
 - 4-(2-tert.-Butyl-5,5a,6,10b-tetrahydro-4H-1,4,10c-triaza-cyclopenta[c]fluoren-5-yl)-2-methoxy-phenol
 - 5-(4-Hydroxy-3-methoxy-phenyl)-2-methylsulfanyl-5,5a,6,10b-tetrahydro-3H-1,4,10c-triaza-cyclopenta[c]fluoren-3-carbonitril;
 - 5-(4-Hydroxy-3-methoxy-phenyl)-2-methylsulfanyl-5,5a,6,10b-tetrahydro-3H-1,4,10c-triaza-cyclopenta[c]fluoren-3-carbonitril
 - 5-(4-Hydroxy-3-methoxy-phenyl)-7-phenylsulfanyl-tetrahydro-pyrazolo[1,5-a]pyrimidin-3-carbonsäureethylester
 - 4-(2-tert.-Butyl-7-phenylsulfanyl-tetrahydro-pyrazolo[1,5-a]pyrimidin-5-yl)-2-methoxy-phenol
 - 4-(3-Brom-2-phenyl-7-phenylsulfanyl-tetrahydro-pyrazolo[1,5-a]pyrimidin-5-yl)-2-methoxy-phenol
 - 5-(2-Hydroxy-3-methoxy-phenyl)-7-phenylsulfanyl-tetrahydro-pyrazolo[1,5-a]pyrimidin-3-carbonsäureethylester

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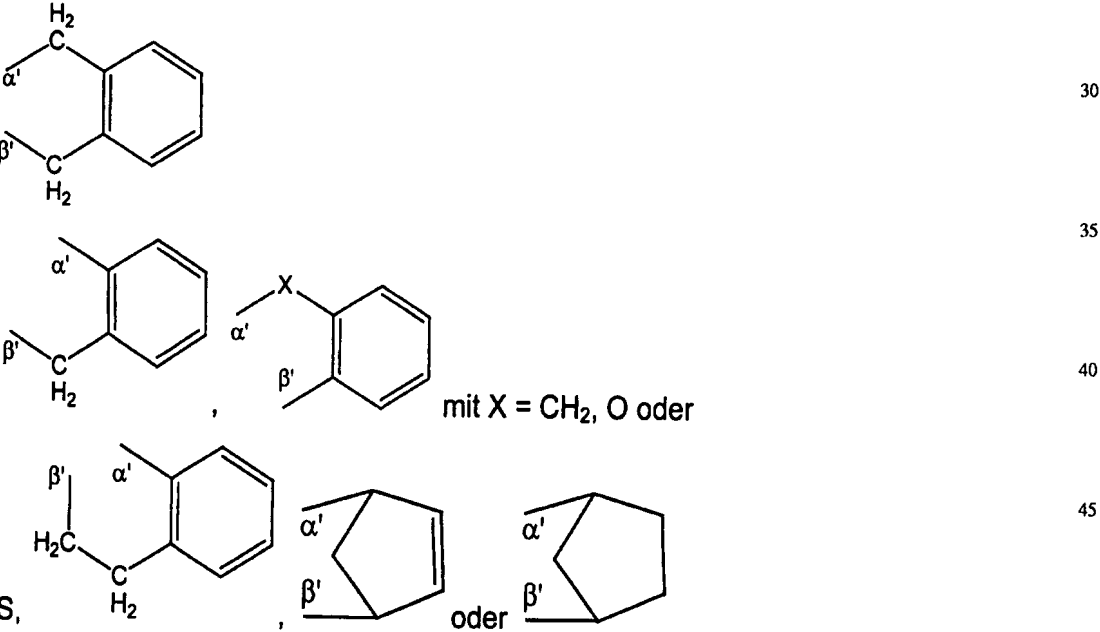
- 7-(4-Chlor-phenyl)-5-(2-hydroxy-3-methoxy-phenyl)-7-methyl-tetrahydro-pyrazolo[1,5-a]pyrimidin-3-carbonsäureethylester
- 5-(4-Hydroxy-butyl)-5,5a,6,10b-tetrahydro-3H-1,4,10c-triaza-cyclopenta[c]fluoren-3-carbonitril; 5-(4-Hydroxy-butyl)-5,5a,6,10b-tetrahydro-4H-1,4,10c-triaza-cyclopenta[c]fluoren-3-carbonitril
- 5 – 5-(4-Hydroxy-butyl)-2-methylsulfanyl-7-phenylsulfanyl-tetrahydro-pyrazolo[1,5-a]pyrimidin-3-carbonitril
- 5-(4-Hydroxy-butyl)-7-phenylsulfanyl-tetrahydro-pyrazolo[1,5-a]pyrimidin-3-carbonitril
- 7-(4-Chlor-phenyl)-5-(4-hydroxy-butyl)-7-methyl-tetrahydro-pyrazolo[1,5-a]pyrimidin-3-carbonitril
- 5-Butyl-2-methylsulfanyl-5,5a,6,10b-tetrahydro-3H-1,4,10c-triaza-cyclopenta[c]fluoren-3-carbonitril; 5-Butyl-2-methylsulfanyl-5,5a,6,10b-tetrahydro-4H-1,4,10c-triaza-cyclopenta[c]fluoren-3-carbonitril
- 10 – 5-Butyl-2-methylsulfanyl-7-phenylsulfanyl-tetrahydro-pyrazolo[1,5-a]pyrimidin-3-carbonitril
- 5-Butyl-7-phenylsulfanyl-tetrahydro-pyrazolo[1,5-a]pyrimidin-3-carbonitril
- 5-Butyl-7-(4-chlor-phenyl)-7-methyl-2-methylsulfanyl-tetrahydro-pyrazolo[1,5-a]pyrimidin-3-carbonitril
- 5-Cyclopropyl-7-(2,4-dimethyl-phenyl)-3-phenylazo-tetrahydro-pyrazolo[1,5-a]pyrimidin-2-ol
- 2-tert.-Butyl-5-cyclopropyl-7-(2,4-dimethyl-phenyl)-tetrahydro-pyrazolo[1,5-a]pyrimidin
- 15 – 5-Cyclopropyl-7-(2,4-dimethyl-phenyl)-2-methylsulfanyl-tetrahydro-pyrazolo[1,5-a]pyrimidin-3-carbonitril
- 2-tert.-Butyl-5-cyclopropyl-7-(3,4-dimethoxy-phenyl)-tetrahydro-pyrazolo[1,5-a]pyrimidin
- 3-Brom-5-cyclopropyl-7-(3,4-dimethoxy-phenyl)-2-phenyl-tetrahydro-pyrazolo[1,5-a]pyrimidin
- 5-Cyclopropyl-7-(4-methoxy-phenyl)-tetrahydro-pyrazolo[1,5-a]pyrimidin-3-carbonsäureethylester
- 20 – 5-Cyclopropyl-3,5,5a,6,7,11b-hexahydro-1,4,11c-triaza-cyclopenta[c]phenanthrene-3-carbonitril
- 7-(2,4-Dimethyl-phenyl)-5-pyridin-2-yl-tetrahydro-pyrazolo[1,5-a]pyrimidin-3-carbonsäureethylester
- 7-(2,4-Dimethyl-phenyl)-3-phenylazo-5-pyridin-2-yl-tetrahydro-pyrazolo[1,5-a]pyrimidin-2-ol
- 3-Brom-7-(2,4-dimethyl-phenyl)-2-phenyl-5-pyridin-2-yl-tetrahydro-pyrazolo[1,5-a]pyrimidin
- 7-(2,4-Dimethyl-phenyl)-2-methylsulfanyl-5-pyridin-2-yl-tetrahydro-pyrazolo[1,5-a]pyrimidin-3-carbonitril
- 25 – 7-(3,4-Dimethoxy-phenyl)-2-methylsulfanyl-5-phenethyl-tetrahydro-pyrazolo[1,5-a]pyrimidin-3-carbonitril
- 7-(3,4-Dimethoxy-phenyl)-5-phenethyl-tetrahydro-pyrazolo[1,5-a]pyrimidin-3-carbonitril
- 5-Cyclopropyl-7-(2-hydroxy-ethoxy)-tetrahydro-pyrazolo[1,5-a]pyrimidin-3-carbonsäureethylester
- 30 – 2-(2-tert.-Butyl-5-cyclopropyl-tetrahydro-pyrazolo[1,5-a]pyrimidin-7-yloxy)-ethanol
- 5-Cyclopropyl-3,5,5a,6,7,8a-hexahydro-8-oxa-1,4,8b-triaza-as-indacen-3-carbonsäureethylester; 5-Cyclopropyl-4,5,5a,6,7,8a-hexahydro-8-oxa-1,4,8b-triaza-as-indacen-3-carbonsäureethylester
- 5-Cyclopropyl-3-phenylazo-3,5,5a,6,7,8a-hexahydro-8-oxa-1,4,8b-triaza-as-indacen-2-ol; 5-Cyclopropyl-3-phenylazo-4,5,5a,6,7,8a-hexahydro-8-oxa-1,4,8b-triaza-as-indacen-2-ol
- 35 – 7-Cyclohexyloxy-5-cyclopropyl-tetrahydro-pyrazolo[1,5-a]pyrimidin-3-carbonsäureethylester
- 7-Cyclohexyloxy-5-cyclopropyl-2-methylsulfanyl-tetrahydro-pyrazolo[1,5-a]pyrimidin-3-carbonitril
- 7-(4-Chlor-phenyl)-5-cyclohexyl-tetrahydro-pyrazolo[1,5-a]pyrimidin-3-carbonitril
- 5-Cyclohexyl-7-(2-hydroxy-ethoxy)-tetrahydro-pyrazolo[1,5-a]pyrimidin-3-carbonsäureethylester
- 5-Cyclohexyl-3,5,5a,6,7,8a-hexahydro-8-oxa-1,4,8b-triaza-as-indacen-3-carbonsäureethylester; 5-Cyclohexyl-4,5,5a,6,7,8a-hexahydro-8-oxa-1,4,8b-triaza-as-indacen-3-carbonsäureethylester
- 40 – 5-Cyclohexyl-7-cyclohexyloxy-tetrahydro-pyrazolo[1,5-a]pyrimidin-3-carbonsäureethylester
- 7-(2,4-Dimethyl-phenyl)-3-phenylazo-5-propyl-tetrahydro-pyrazolo[1,5-a]pyrimidin-2-ol
- 7-(2,4-Dimethyl-phenyl)-2-methylsulfanyl-5-propyl-tetrahydro-pyrazolo[1,5-a]pyrimidin-3-carbonitril
- 5-tert.-Butyl-7-(2,4-dimethyl-phenyl)-tetrahydro-pyrazolo[1,5-a]pyrimidin-3-carbonsäureethylester
- 45 – 2,5-Di-tert.-butyl-7-(3,4-dimethoxy-phenyl)-tetrahydro-pyrazolo[1,5-a]pyrimidin
- 3-Brom-5-tert.-butyl-7-(3,4-dimethoxy-phenyl)-2-phenyl-tetrahydro-pyrazolo[1,5-a]pyrimidin
- 2-[3-Cyano-6,7-bis-(4-methoxy-phenyl)-tetrahydro-pyrazolo[1,5-a]pyrimidin-5-yl]-cyclopropanecarbon-säureethylester
- 3-Cyano-6,7-bis-(4-methoxy-phenyl)-tetrahydro-pyrazolo[1,5-a]pyrimidin-5-carbonsäure
- 50 – 4-[3-Brom-6-methyl-2-phenyl-5-(4-trifluormethyl-phenyl)-tetrahydro-pyrazolo[1,5-a]pyrimidin-7-yl]-phenol
- 7-(4-Hydroxy-phenyl)-6-methyl-2-methylsulfanyl-5-(4-trifluormethyl-phenyl)-tetrahydro-pyrazolo[1,5-a]pyrimidin-3-carbonitril
- 7-(4-Hydroxy-phenyl)-6-methyl-5-(4-trifluormethyl-phenyl)-tetrahydro-pyrazolo[1,5-a]pyrimidin-3-carbonitril
- 55 – 2-(4-Nitro-phenylsulfanyl)-5-phenylsulfanyl-7-pyridin-2-yl-6,7-dihydro-5H-thiazolo[3,2-a]pyrimidin
- 3-(4-Chlor-phenyl)-5-phenylsulfanyl-7-pyridin-2-yl-6,7-dihydro-5H-thiazolo[3,2-a]pyrimidin
- 5-Phenylsulfanyl-7-pyridin-2-yl-3-p-tolyl-6,7-dihydro-5H-thiazolo[3,2-a]pyrimidin
- 7-Methoxy-4-phenylsulfanyl-2-pyridin-2-yl-3,4-dihydro-2H-9-thia-1,4a-diaza-fluoren
- 60 – 7-Ethoxy-4-phenylsulfanyl-2-pyridin-2-yl-3,4-dihydro-2H-9-thia-1,4a-diaza-fluoren
- 7-Fluor-4-phenylsulfanyl-2-pyridin-2-yl-3,4-dihydro-2H-9-thia-1,4a-diaza-fluoren
- 3-Naphthalin-2-yl-5-phenylsulfanyl-7-pyridin-2-yl-6,7-dihydro-5H-thiazolo[3,2-a]pyrimidin
- 7-Phenyl-3-phenylazo-5-pyridin-2-yl-3,5,6,7-tetrahydro-pyrazolo[1,5-a]pyrimidin-2-ol
- 7-Phenylsulfanyl-5-pyridin-2-yl-3,5,6,7-tetrahydro-pyrazolo[1,5-a]pyrimidin-3-carbonsäureethylester
- 65 – 3-Phenylazo-7-phenylsulfanyl-5-pyridin-2-yl-3,5,6,7-tetrahydro-pyrazolo[1,5-a]pyrimidin-2-ol
- 3-Brom-7-phenylsulfanyl-5-pyridin-2-yl-3,5,6,7-tetrahydro-pyrazolo[1,5-a]pyrimidin
- 7-Phenylsulfanyl-5-pyridin-2-yl-3,5,6,7-tetrahydro-pyrazolo[1,5-a]pyrimidin-3-carbonitril.

7. Verfahren zur Herstellung von Verbindungen der allgemeinen Struktur (IA) und/oder (IB) sowie ihrer pharma-

zeitlich annehmbaren Salze:

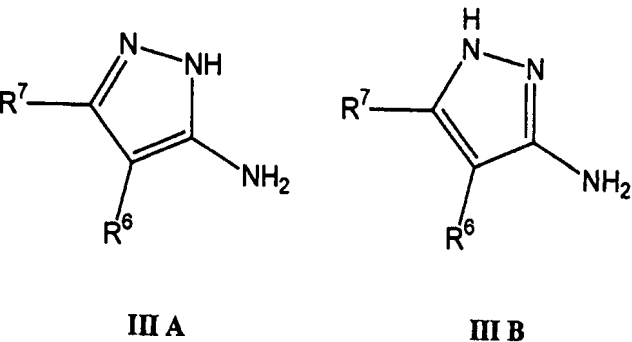


worin
R¹ und R² unabhängig voneinander H, O-R⁹, S-R¹⁰, C₁₋₁₂-Alkyl, C₃₋₈-Cycloalkyl, -CH₂-C₃₋₈-Cycloalkyl, Aryl, -
(C₁₋₆-Alkyl)-Aryl, Heterocyclyl oder -(C₁₋₆-Alkyl)-Heterocyclyl bedeuten,
wobei einer der Reste R¹ und R² H ist und der andere Rest von R¹ und R² nicht H ist oder für den Fall, daß einer der
Reste R¹ und R² Aryl bedeutet, der andere Rest von R¹ und R² H oder C₁₋₁₂-Alkyl bedeutet,
R³ und R⁴ H, C₁₋₁₂-Alkyl, C₃₋₈-Cycloalkyl, -CH₂-C₃₋₈-Cycloalkyl, Aryl oder -(C₁₋₆-Alkyl)-Aryl bedeuten,
wobei mindestens einer der Reste R³ und R⁴ H ist, oder
einer der Reste R¹ und R² zusammen mit einem der Reste R³ und R⁴ W bildet, wobei W α'-(CH₂)_n-β' mit n = 3, 4, 5
oder 6, α'-CH=CH-CH₂-β', α'-CH₂-CH=CH-β', α'-CH=CH-CH₂-CH₂-β', α'-CH₂-CH=CH-CH₂-β', α'-CH₂-CH₂-
CH=CH-β', α'-O-(CH₂)_m-β' mit m = 2, 3, 4 oder 5:

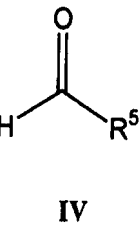


bedeutet, das mit α' gekennzeichnete Ende von W mit dem mit α gekennzeichneten Atom der Verbindung der all-
gemeinen Struktur (IA) oder (IB) verbunden ist und das mit β' gekennzeichnete Ende von W mit dem mit β gekenn-
zeichneten Atom der Verbindung der allgemeinen Struktur (IA) oder (IB) verbunden ist, der andere Rest von R¹ und
R² H oder C₁₋₁₂-Alkyl ist und der andere Rest von R³ und R⁴ H oder C₁₋₁₂-Alkyl ist;
R⁵ C₁₋₁₂-Alkyl, C₃₋₈-Cycloalkyl, -CH₂-C₃₋₈-Cycloalkyl, Aryl, -(C₁₋₆-Alkyl)-Aryl, Heterocyclyl, -(C₁₋₆-Alkyl)-
Heterocyclyl oder C(=O)R¹¹ bedeutet;
R⁶ H, C₁₋₈-Alkyl, -CN, Fluor, Chlor, Brom, Iod, NO₂, NH₂, NHR¹², NR¹³R¹⁴, OR¹⁵, S(O)_pR¹⁶ mit p = 0, 1 oder 2, -
C(=O)R¹⁷ oder -N=N-Aryl bedeutet;
R⁷ H, C₁₋₈-Alkyl, Aryl, -CN, Fluor, Chlor, Brom, Iod, NO₂, NH₂, NHR¹², NR¹³R¹⁴, OR¹⁸, S(O)_qR¹⁹ mit q = 0, 1
oder 2 oder C(=O)R²⁰ bedeutet;
R⁹ und R¹⁰ unabhängig voneinander C₁₋₈-Alkyl, C₃₋₈-Cycloalkyl, -CH₂-C₃₋₈-Cycloalkyl, Aryl oder -(C₁₋₆-Alkyl)-
Aryl bedeuten;
R¹¹ C₁₋₈-Alkyl, C₃₋₈-Cycloalkyl, -CH₂-C₃₋₈-Cycloalkyl, Aryl oder OR²⁵ bedeutet;
R¹² C₁₋₆-Alkyl oder -CH₂-Aryl bedeutet;
R¹³ und R¹⁴ gleiches oder verschiedenes C₁₋₆-Alkyl sind oder gemeinsam für -(CH₂)_h- mit h = 4 oder 5 stehen;
R¹⁵ und R¹⁶ unabhängig voneinander H, C₁₋₈-Alkyl, C₃₋₈-Cycloalkyl, -CH₂-C₃₋₈-Cycloalkyl, Aryl oder -(C₁₋₆-Al-
kyl)-Aryl bedeuten;
R¹⁷ H, C₁₋₈-Alkyl, C₃₋₈-Cycloalkyl, -CH₂-C₃₋₈-Cycloalkyl, Aryl, -(C₁₋₆-Alkyl)-Aryl, NH₂, NHR¹², NR¹³R¹⁴ oder

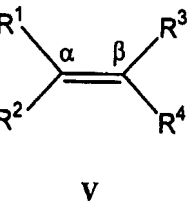
OR²⁶ bedeutet;
R¹⁸ und R¹⁹ unabhängig voneinander H, C₁₋₈-Alkyl, C₃₋₈-Cycloalkyl, -CH₂-C₃₋₈-Cycloalkyl, Aryl oder -(C₁₋₆-Alkyl)-Aryl bedeuten;
R²⁰ H, C₁₋₈-Alkyl, C₃₋₈-Cycloalkyl, -CH₂-C₃₋₈-Cycloalkyl, Aryl oder -(C₁₋₆-Alkyl)-Aryl oder OR²⁷ bedeutet; und
R²⁵, R²⁶ und R²⁷ unabhängig voneinander H oder C₁₋₆-Alkyl bedeuten, wobei R²⁵ nicht H bedeutet, wenn zugleich
R¹ Aryl und R² Alkyl bedeuten;
dadurch gekennzeichnet, daß
ein Pyrazolamin der allgemeinen Struktur (IIIA) oder (IIIB):



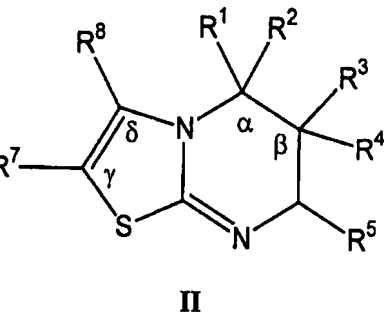
worin
R⁵ und R⁷ wie oben in diesem Anspruch definiert sind, mit einem Aldehyd der allgemeinen Struktur (IV):



worin
R⁵ wie oben in diesem Anspruch definiert ist, und einem Olefin der allgemeinen Struktur (V):



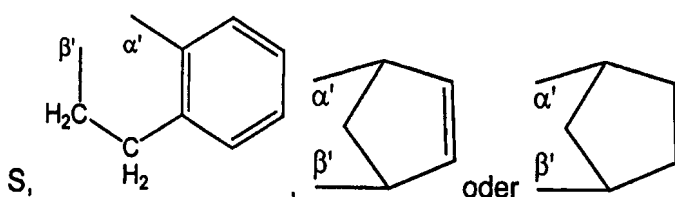
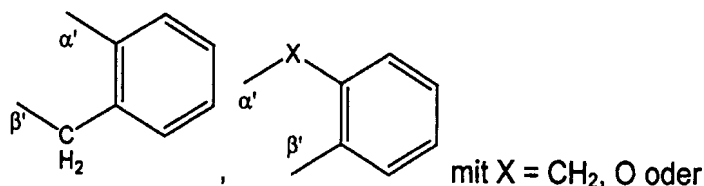
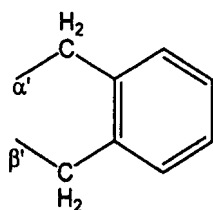
worin
R¹, R², R³ und R⁴ wie oben in diesem Anspruch definiert sind mit der Maßgabe, daß, wenn einer der Reste R¹ und R² zusammen mit einem der Reste R³ und R⁴ W bildet, das mit α' gekennzeichnete Ende von W mit dem α-Kohlenstoffatom des Olefins der allgemeinen Struktur (V) und das mit β' gekennzeichnete Ende von W mit dem β-Kohlenstoffatom des Olefins der allgemeinen Struktur (V) verbunden ist,
in Gegenwart einer Säure umgesetzt wird.
8. Verfahren zur Herstellung von Verbindungen der allgemeinen Struktur (II) oder pharmazeutisch annehmbarer Salze davon:



worin
R¹ und R² unabhängig voneinander H, O-R⁹, S-R¹⁰, C₁₋₁₂-Alkyl, C₃₋₈-Cycloalkyl, -CH₂-C₃₋₈-Cycloalkyl, Aryl, -

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(C₁₋₆-Alkyl)-Aryl, Heterocyclyl oder -(C₁₋₆-Alkyl)-Heterocyclyl bedeuten, wobei einer der Reste R¹ und R² H ist und der andere Rest von R¹ und R² nicht H ist oder für den Fall, daß einer der Reste R¹ und R² Aryl bedeutet, der andere Rest von R¹ und R² H oder C₁₋₁₂-Alkyl bedeutet, R³ und R⁴ H, C₁₋₁₂-Alkyl, C₃₋₈-Cycloalkyl, -CH₂-C₃₋₈-Cycloalkyl, Aryl oder -(C₁₋₆-Alkyl)-Aryl bedeuten, wobei mindestens einer der Reste R³ und R⁴ H ist, oder einer der Reste R¹ und R² zusammen mit einem der Reste R³ und R⁴ W bildet, wobei W α' -(CH₂)_n- β' mit n = 3, 4, 5 oder 6, α' -CH=CH-CH₂- β' , α' -CH₂-CH=CH- β' , α' -CH=CH-CH₂-CH₂- β' , α' -CH₂-CH=CH-CH₂- β' , α' -CH₂-CH₂-CH=CH- β' , α' -O-(CH₂)_m- β' mit m = 2, 3, 4 oder 5:



bedeutet, das mit α' gekennzeichnete Ende von W mit dem mit α gekennzeichneten Atom der Verbindung der allgemeinen Struktur (II) verbunden ist und das mit β' gekennzeichnete Ende von W mit dem mit β gekennzeichneten Atom der Verbindung der allgemeinen Struktur (II) verbunden ist, der andere Rest von R^1 und R^2 H oder C_{1-12} -Alkyl ist und der andere Rest von R^3 und R^4 H oder C_{1-12} -Alkyl ist;

R³ C₁₋₁₂-Alkyl, C₃₋₈-Cycloalkyl, -CH₂-C₃₋₈-Cycloalkyl, Aryl, -(C₁₋₆-Alkyl)-Aryl, Heterocyclyl, -(C₁₋₆-Alkyl)-Heterocyclyl oder C(=O)R¹¹ bedeutet:

R⁷ H, C₁₋₈-Alkyl, Aryl, -CN, Fluor, Chlor, Brom, Iod, NO₂, NH₂, NHR¹², NR¹³R¹⁴, OR¹⁸, S(O)_qR¹⁹ mit q = 0, 1 oder 2 oder C(=O)R²⁰ bedeutet.

R⁸ H, C₁₋₈-Alkyl oder Aryl bedeutet
oder

die Reste R⁷ und R⁸ zusammen Y bilden, wobei Y γ -CR²¹=CR²²-CR²³=CR²⁴- δ bedeutet und das mit γ gekennzeichnete Ende von Y mit dem mit γ gekennzeichneten Atom der allgemeinen Struktur (II) verbunden ist und das mit δ gekennzeichnete Ende von Y mit dem mit δ gekennzeichneten Atom der allgemeinen Struktur (II) verbunden ist;

R⁹ C₁₋₈-Alkyl, C₃₋₈-Cycloalkyl oder -CH₂-C₃₋₈-Cycloalkyl, Aryl oder -(C₁₋₆-Alkyl)-Aryl bedeutet;

R¹⁰ C₁₋₈-Alkyl, C₃₋₈-Cycloalkyl oder -CH₂-C₃₋₈-Cycloalkyl, Aryl oder -(C₁₋₆-Alkyl)-Aryl bedeutet;

R_{12}^{11} C₁₋₈-Alkyl, C₃₋₈-Cycloalkyl oder -CH₂-C₃₋₈-Cycloalkyl, Aryl oder OR²⁵ bedeutet;

R^{12} C₁₋₆-Alkyl, oder -CH₂-Aryl bedeutet;

R^{13} und R^{14} gleiches oder verschiedenes C_{1-6} -Alkyl sind oder gemeinsam für $-(CH_2)_h-$ mit $h = 4$ oder 5 stehen;

R¹⁸ H, C₁₋₈-Älkyl, C₃₋₈-Cycloalkyl, -CH₂-C₃₋₈-Cycloalkyl, Aryl oder -(C₁₋₆-Älkyl)-Aryl bedeutet;

R^{19} C₁₋₈-Alkyl, C₃₋₈-Cycloalkyl, -CH₂-C₃₋₈-Cycloalkyl, Aryl oder -(C₁₋₆-Alkyl)-Aryl bedeutet;

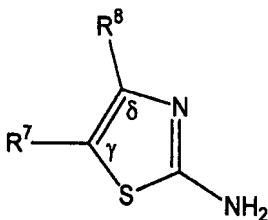
R²⁰ H, C₁₋₈-Alkyl, C₃₋₈-Cycloalkyl, -CH₂-C₃₋₈-Cycloalkyl, Aryl oder -(C₁₋₆-Alkyl)-Aryl oder OR²⁷ bedeutet;

R^{21}, R^{22}, R^{23} und R^{24} unabhängig voneinander H, Fluor, Chlor, Brom, Iod oder OR²⁸ bedeuten;

R²⁵, R²⁶, R²⁷ und R²⁸ unabhängig voneinander H oder C₁₋₆-Alkyl bedeuten, wobei R²⁵ nicht H bedeutet, wenn zugleich R¹ Aryl und R² Alkyl bedeuten;

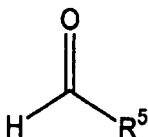
dadurch gekennzeichnet, daß

ein Thiazolamin der allgemeinen Struktur (VI):



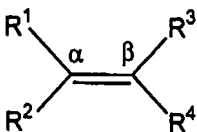
VI

15 worin
R⁷ und R⁸ wie oben in diesem Anspruch definiert sind mit der Maßgabe, daß, wenn R⁷ und R⁸ Y bilden, das mit γ gekennzeichnete Ende von Y mit dem mit γ gekennzeichneten Atom des Thiazolamins der allgemeinen Struktur (VI) und das mit δ' gekennzeichnete Ende von Y mit dem mit δ gekennzeichneten Atom des Thiazolamins der allgemeinen Struktur (VI) verknüpft sind,
20 mit einem Aldehyd der allgemeinen Struktur (IV):



IV

30 worin
R⁵ wie oben in diesem Anspruch definiert ist,
und einem Olefin der allgemeinen Struktur (V):



V

45 worin
R¹, R², R³ und R⁴ wie oben in diesem Anspruch definiert sind mit der Maßgabe, daß, wenn einer der Reste R¹ und R² zusammen mit einem der Reste R³ und R⁴ W bildet, das mit α' gekennzeichnete Ende von W mit dem α-Kohlenstoffatom des Olefins der allgemeinen Struktur (V) und das mit β' gekennzeichnete Ende von W mit dem β-Kohlenstoffatom des Olefins der allgemeinen Struktur (V) verbunden ist,
in Gegenwart einer Säure umgesetzt wird.

50 9. Verfahren nach Anspruch 7 oder 8, dadurch gekennzeichnet, daß die Umsetzung des Heterocyclamins der allgemeinen Struktur (IIIA) oder (IIIB) bzw. (VI) mit dem Aldehyd der allgemeinen Struktur (IV) und dem Olefin der allgemeinen Struktur (V) in einem Eintopf-Verfahren durchgeführt wird.

10. Verfahren nach irgendeinem der Ansprüche 7 bis 9, dadurch gekennzeichnet, daß die Säure Trifluoressigsäure ist.

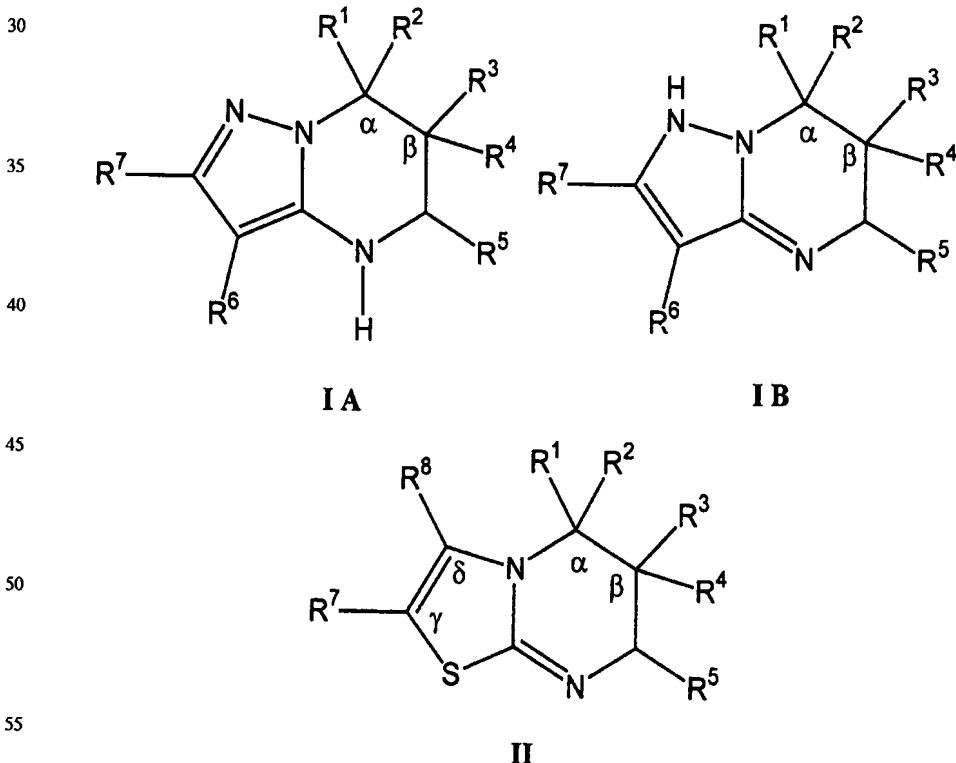
55 11. Verfahren nach irgendeinem der Ansprüche 7 bis 10, dadurch gekennzeichnet, daß die Umsetzung in einem organischen Lösungsmittel bei einer Temperatur von 0 bis 100°C und einer Reaktionszeit von 0,25 bis 12 h durchgeführt wird.

12. Verfahren nach einem der Ansprüche 7 bis 11, dadurch gekennzeichnet, daß die Reaktion bei einer Temperatur von 15 bis 40°C durchgeführt wird.

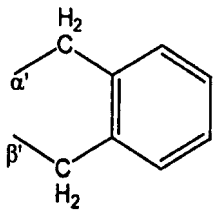
60 13. Substanzbibliothek, enthaltend mindestens eine Verbindung der allgemeinen Struktur (IA), (IB) oder (II):

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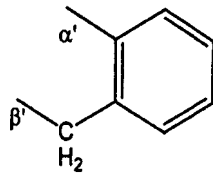
R^5 C₁₋₁₂-Alkyl, C₃₋₈-Cycloalkyl, -CH₂-C₃₋₈-Cycloalkyl, Aryl, -(C₁₋₆-Alkyl)-Aryl, Heterocyclyl, -(C₁₋₆-Alkyl)-Heterocyclyl oder C(=O)R¹¹ bedeutet;
 R^6 C₁₋₈-Alkyl, -CN, Fluor, Chlor, Brom, Iod, NO₂, NH₂, NHR¹², NR¹³R¹⁴, OR¹⁵, S(O)_pR¹⁶ mit p = 0, 1 oder 2, -C(=O)R¹⁷ oder -N=N-Aryl bedeutet;
 R^7 H, C₁₋₈-Alkyl, Aryl, -CN, Fluor, Chlor, Brom, Iod, NO₂, NH₂, NHR¹², NR¹³R¹⁴, OR¹⁸, S(O)_qR¹⁹ mit q = 0, 1 oder 2 oder C(=O)R²⁰ bedeutet,
 R^8 H, C₁₋₈-Alkyl oder Aryl bedeutet, oder
 die Reste R^7 und R^8 zusammen Y bilden, wobei Y γ -CR²¹=CR²²-CR²³=CR²⁴- δ bedeutet und das mit γ gekennzeichnete Ende von Y mit dem mit γ gekennzeichneten Atom der allgemeinen Struktur (II) verbunden ist und das mit δ gekennzeichnete Ende von Y mit dem mit δ gekennzeichneten Atom der allgemeinen Struktur (II) verbunden ist;
 R^9 und R^{10} unabhängig voneinander C₁₋₈-Alkyl, C₃₋₈-Cycloalkyl, -CH₂-C₃₋₈-Cycloalkyl, Aryl oder -(C₁₋₆-Alkyl)-Aryl bedeuten;
 R^{11} C₁₋₈-Alkyl, C₃₋₈-Cycloalkyl, -CH₂-C₃₋₈-Cycloalkyl, Aryl oder OR²⁵ bedeutet;
 R^{12} C₁₋₆-Alkyl oder -CH₂-Aryl bedeutet;
 R^{13} und R^{14} gleiches oder verschiedenes C₁₋₆-Alkyl sind oder gemeinsam für -(CH₂)_h- mit h = 4 oder 5 stehen;
 R^{15} und R^{16} unabhängig voneinander H, C₁₋₈-Alkyl, C₃₋₈-Cycloalkyl, -CH₂-C₃₋₈-Cycloalkyl, Aryl oder -(C₁₋₆-Alkyl)-Aryl bedeuten;
 R^{17} C₁₋₈-Alkyl, C₃₋₈-Cycloalkyl, -CH₂-C₃₋₈-Cycloalkyl, Aryl, -(C₁₋₆-Alkyl)-Aryl, NH₂, NHR¹², NR¹³R¹⁴ oder OR²⁵ bedeutet;
 R^{18} und R^{19} unabhängig voneinander H, C₁₋₈-Alkyl, C₃₋₈-Cycloalkyl, -CH₂-C₃₋₈-Cycloalkyl, Aryl oder -(C₁₋₆-Alkyl)-Aryl bedeuten;
 R^{20} H, C₁₋₈-Alkyl, C₃₋₈-Cycloalkyl, -CH₂-C₃₋₈-Cycloalkyl, Aryl oder -(C₁₋₆-Alkyl)-Aryl oder OR²⁷ bedeutet;
 R^{21} , R^{22} , R^{23} und R^{24} unabhängig voneinander H, Fluor, Chlor, Brom, Iod oder OR²⁸ bedeuten;
 R^{25} , R^{26} , R^{27} und R^{28} unabhängig voneinander H oder C₁₋₆-Alkyl bedeuten, wobei R^{25} nicht H bedeutet, wenn zugleich R^1 Aryl und R^2 Alkyl bedeuten.
 14. Arzneimittel, enthaltend mindestens eine Verbindung der allgemeinen Struktur (IA), (IB) oder (II) oder eines ihrer pharmazeutisch annehmbaren Salze:



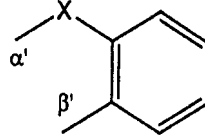
worin
 R^1 und R^2 unabhängig voneinander H, O-R⁹, S-R¹⁰, C₁₋₁₂-Alkyl, C₃₋₈-Cycloalkyl, -CH₂-C₃₋₈-Cycloalkyl, Aryl, -(C₁₋₆-Alkyl)-Aryl, Heterocyclyl oder -(C₁₋₆-Alkyl)-Heterocyclyl bedeuten,
 wobei einer der Reste R^1 und R^2 H ist und der andere Rest von R^1 und R^2 nicht H ist oder für den Fall, daß einer der Reste R^1 und R^2 Aryl bedeutet, der andere Rest von R^1 und R^2 H oder C₁₋₁₂-Alkyl bedeutet,
 R^3 und R^4 H, C₁₋₁₂-Alkyl, C₃₋₈-Cycloalkyl, -CH₂-C₃₋₈-Cycloalkyl, Aryl oder -(C₁₋₆-Alkyl)-Aryl bedeuten,
 wobei mindestens einer der Reste R^3 und R^4 H ist,
 oder
 einer der Reste R^1 und R^2 zusammen mit einem der Reste R^3 und R^4 W bildet, wobei W α' -(CH₂)_n- β' mit n = 3, 4, 5 oder 6, α' -CH=CH-CH₂- β' , α' -CH₂-CH=CH- β' , α' -CH=CH-CH₂-CH₂- β' , α' -CH₂-CH=CH-CH₂- β' , α' -CH₂-CH₂-CH=CH- β' , α' -O-(CH₂)_m- β' mit m = 2, 3, 4 oder 5:



5

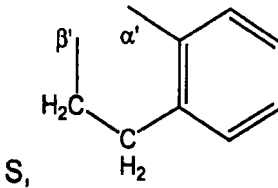


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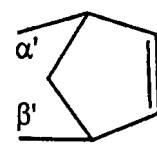


mit X = CH₂, O oder

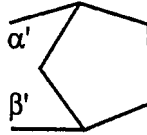
15



20



oder



S,

bedeutet, das mit α' gekennzeichnete Ende von W mit dem mit α gekennzeichneten Atom der Verbindung der allgemeinen Struktur (IA), (IB) oder (II) verbunden ist und das mit β' gekennzeichnete Ende von W mit dem mit β gekennzeichneten Atom der Verbindung der allgemeinen Struktur (IA), (IB) oder (II) verbunden ist, der andere Rest von R^1 und R^2 H oder C_{1-12} -Alkyl ist und der andere Rest von R^3 und R^4 H oder C_{1-12} -Alkyl ist;

25

R^5 C_{1-12} -Alkyl, C_{3-8} -Cycloalkyl, $-CH_2-C_{3-8}$ -Cycloalkyl, Aryl, $-(C_{1-6}$ -Alkyl)-Aryl, Heterocyclyl, $-(C_{1-6}$ -Alkyl)-Heterocyclyl oder $C(=O)R^{11}$ bedeutet;

30

R^6 H, C_{1-8} -Alkyl, $-CN$, Fluor, Chlor, Brom, Iod, NO_2 , NH_2 , NHR^{12} , $NR^{13}R^{14}$, OR^{15} , $S(O)_pR^{16}$ mit $p = 0, 1$ oder 2 , $-C(=O)R^{17}$ oder $-N=N$ -Aryl bedeutet;

R^7 H, C_{1-8} -Alkyl, Aryl, $-CN$, Fluor, Chlor, Brom, Iod, NO_2 , NH_2 , NHR^{12} , $NR^{13}R^{14}$, OR^{18} , $S(O)_qR^{19}$ mit $q = 0, 1$ oder 2 oder $C(=O)R^{20}$ bedeutet;

R^8 H, C_{1-8} -Alkyl oder Aryl bedeutet;

35

oder

die Reste R^7 und R^8 zusammen Y bilden, wobei Y γ - $CR^{21}=CR^{22}-CR^{23}=CR^{24}-\delta$ bedeutet und das mit γ gekennzeichnete Ende von Y mit dem mit γ gekennzeichneten Atom der allgemeinen Struktur (II) verbunden ist und das mit δ gekennzeichnete Ende von Y mit dem mit δ gekennzeichneten Atom der allgemeinen Struktur (II) verbunden ist;

40

R^9 und R^{10} unabhängig voneinander C_{1-8} -Alkyl, C_{3-8} -Cycloalkyl, $-CH_2-C_{3-8}$ -Cycloalkyl, Aryl oder $-(C_{1-6}$ -Alkyl)-Aryl bedeuten;

R^{11} C_{1-8} -Alkyl, C_{3-8} -Cycloalkyl, $-CH_2-C_{3-8}$ -Cycloalkyl, Aryl oder OR^{25} bedeutet;

R^{12} C_{1-6} -Alkyl oder $-CH_2$ -Aryl bedeutet;

R^{13} und R^{14} gleiches oder verschiedenes C_{1-6} -Alkyl sind oder gemeinsam für $-(CH_2)_h-$ mit $h = 4$ oder 5 stehen;

45

R^{15} und R^{16} unabhängig voneinander H, C_{1-8} -Alkyl, C_{3-8} -Cycloalkyl, $-CH_2-C_{3-8}$ -Cycloalkyl, Aryl oder $-(C_{1-6}$ -Alkyl)-Aryl bedeuten;

R^{17} H, C_{1-8} -Alkyl, C_{3-8} -Cycloalkyl, $-CH_2-C_{3-8}$ -Cycloalkyl, Aryl, $-(C_{1-6}$ -Alkyl)-Aryl, NH_2 , NHR^{12} , $NR^{13}R^{14}$ oder OR^{26} bedeutet;

R^{18} und R^{19} unabhängig voneinander H, C_{1-8} -Alkyl, C_{3-8} -Cycloalkyl, $-CH_2-C_{3-8}$ -Cycloalkyl, Aryl oder $-(C_{1-6}$ -Alkyl)-Aryl bedeuten;

50

R^{20} H, C_{1-8} -Alkyl, C_{3-8} -Cycloalkyl, $-CH_2-C_{3-8}$ -Cycloalkyl, Aryl oder $-(C_{1-6}$ -Alkyl)-Aryl oder OR^{27} bedeutet;

R^{21} , R^{22} , R^{23} und R^{24} unabhängig voneinander H, Fluor, Chlor, Brom, Iod oder OR^{28} bedeuten;

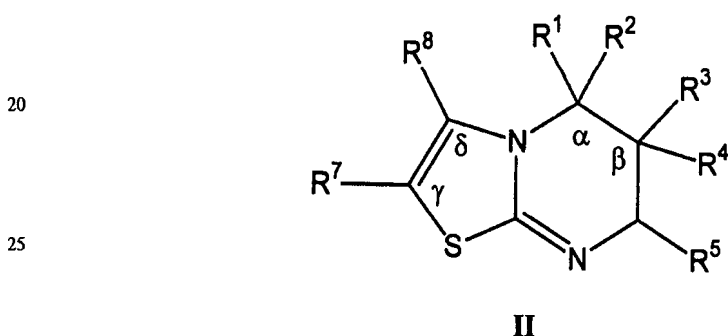
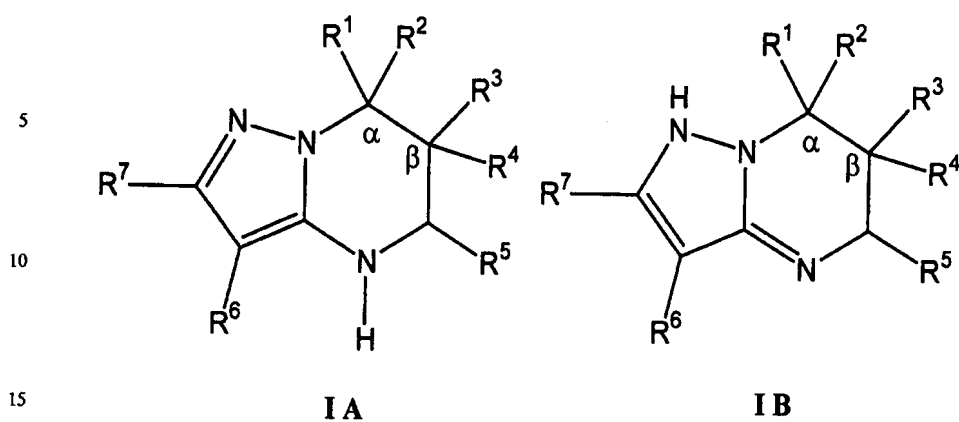
R^{25} , R^{26} , R^{27} und R^{28} unabhängig voneinander H oder C_{1-6} -Alkyl bedeuten, wobei R^{25} nicht H bedeutet, wenn zugleich R^1 Aryl und R^2 Alkyl bedeuten.

55

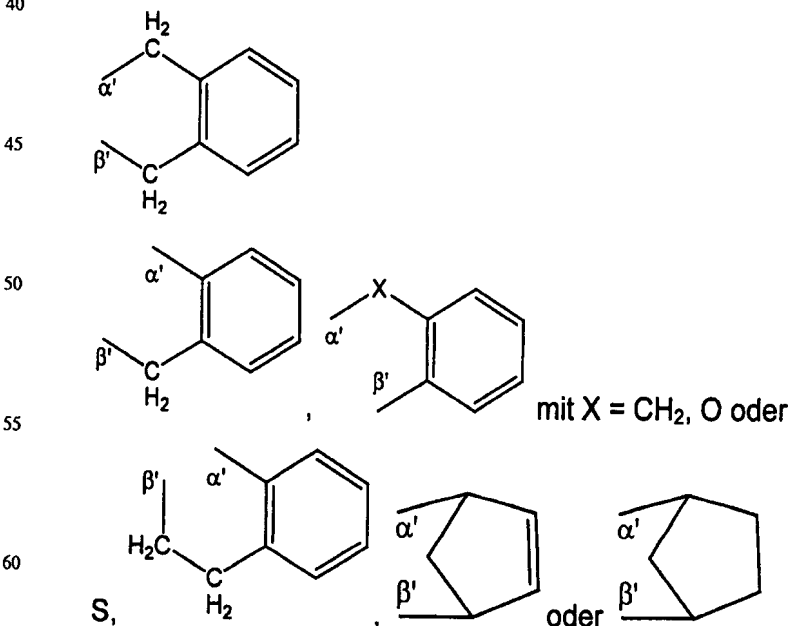
15. Verwendung einer Verbindung der allgemeinen Struktur (IA), (IB) oder (II) oder eines ihrer pharmazeutisch annehmbaren Salze:

60

65



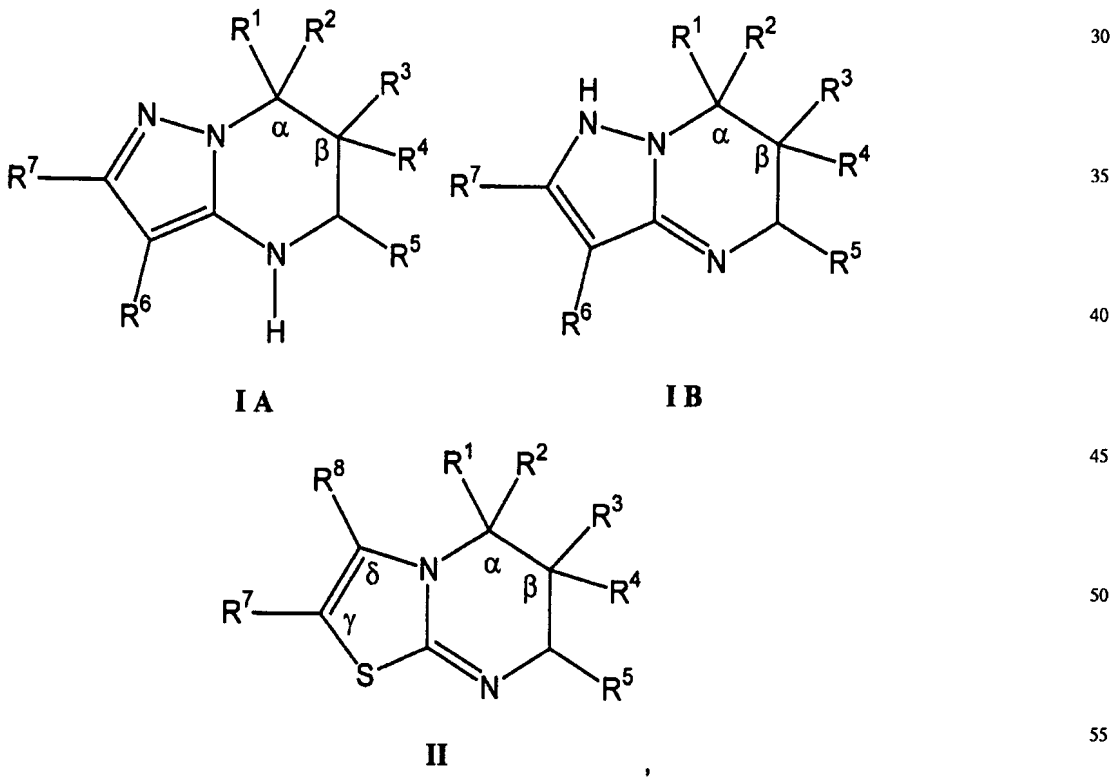
30 worin
 R^1 und R^2 unabhängig voneinander H, O- R^9 , S- R^{10} , C_{1-12} -Alkyl, C_{3-8} -Cycloalkyl, $-CH_2-C_{3-8}$ -Cycloalkyl, Aryl, $-(C_{1-6}$ -Alkyl)-Aryl, Heterocyclyl oder $-(C_{1-6}$ -Alkyl)-Heterocyclyl bedeuten,
wobei einer der Reste R^1 und R^2 H ist und der andere Rest von R^1 und R^2 nicht H ist oder für den Fall, daß einer der
35 Reste R^1 und R^2 Aryl bedeutet, der andere Rest von R^1 und R^2 H oder C_{1-12} -Alkyl bedeutet,
 R^3 und R^4 H, C_{1-12} -Alkyl, C_{3-8} -Cycloalkyl, $-CH_2-C_{3-8}$ -Cycloalkyl, Aryl oder $-(C_{1-6}$ -Alkyl)-Aryl bedeuten,
wobei mindestens einer der Reste R^3 und R^4 H ist, oder
einer der Reste R^1 und R^2 zusammen mit einem der Reste R^3 und R^4 W bildet, wobei W $\alpha'-(CH_2)_n-\beta'$ mit n = 3, 4, 5
oder 6, $\alpha'-CH=CH-CH_2-\beta'$, $\alpha'-CH_2-CH=CH-\beta'$, $\alpha'-CH=CH-CH_2-CH_2-\beta'$, $\alpha'-CH_2-CH=CH-CH_2-\beta'$, $\alpha'-CH_2-CH_2-$
 $CH=CH-\beta'$, $\alpha'-O-(CH_2)_m-\beta'$ mit m = 2, 3, 4 oder 5:



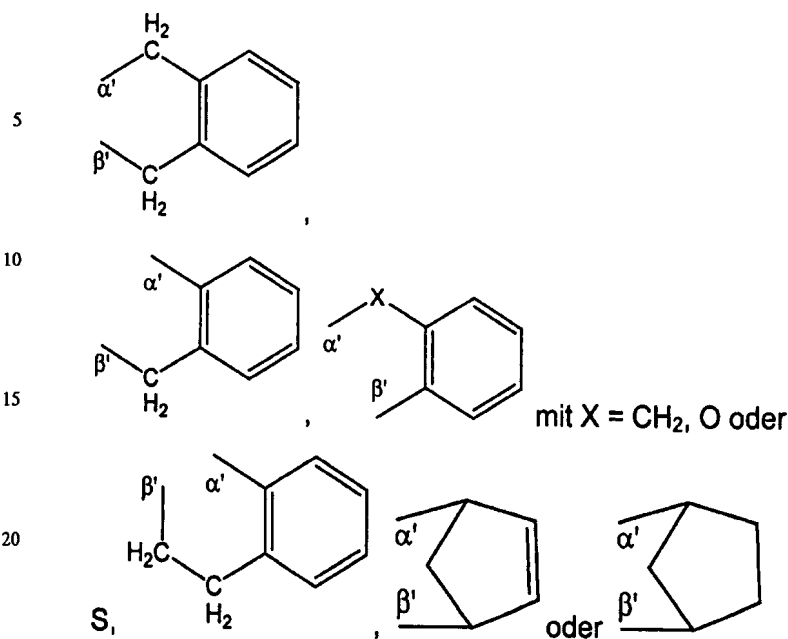
65 bedeutet, das mit α' gekennzeichnete Ende von W mit dem mit α gekennzeichneten Atom der Verbindung der allgemeinen Struktur (IA), (IB) oder (II) verbunden ist und das mit β' gekennzeichnete Ende von W mit dem mit β gekennzeichneten Atom der Verbindung der allgemeinen Struktur (IA), (IB) oder (II) verbunden ist, der andere Rest von R^1 und R^2 H oder C_{1-12} -Alkyl ist und der andere Rest von R^3 und R^4 H oder C_{1-12} -Alkyl ist; C_{1-12} -Alkyl, C_{3-8} -Cycloalkyl, $-CH_2-C_{3-8}$ -Cycloalkyl, Aryl, $-(C_{1-6}$ -Alkyl)-Aryl, Heterocyclyl, $-(C_{1-6}$ -Alkyl)-Hete-

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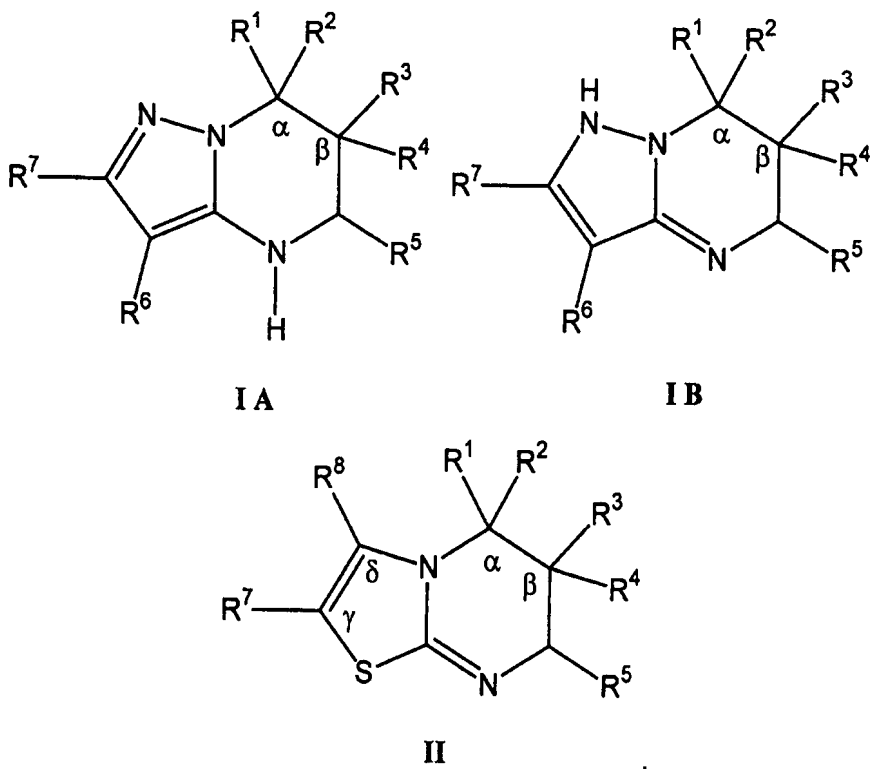
rocyclyl oder C(=O)R¹¹ bedeutet;
R⁶ H, C₁₋₈-Alkyl, -CN, Fluor, Chlor, Brom, Iod, NO₂, NH₂, NHR¹², NR¹³R¹⁴, OR¹⁵, S(O)_pR¹⁶ mit p = 0, 1 oder 2, -
C(=O)R¹⁷ oder -N=N-Aryl bedeutet;
R⁷ H, C₁₋₈-Alkyl, Aryl, -CN, Fluor, Chlor, Brom, Iod, NO₂, NH₂, NHR¹², NR¹³R¹⁴, OR¹⁸, S(O)_qR¹⁹ mit q = 0, 1
oder 2 oder C(=O)R²⁰ bedeutet, 5
R⁸ H, C₁₋₈-Alkyl oder Aryl bedeutet, oder
die Reste R⁷ und R⁸ zusammen Y bilden, wobei Y γ-CR²¹=CR²²-CR²³=CR²⁴-δ' bedeutet und das mit γ' gekenn-
zeichnete Ende von Y mit dem mit γ gekennzeichneten Atom der allgemeinen Struktur (II) verbunden ist und das
mit δ' gekennzeichnete Ende von Y mit dem mit δ gekennzeichneten Atom der allgemeinen Struktur (II) verbunden
ist; 10
R⁹ und R¹⁰ unabhängig voneinander C₁₋₈-Alkyl, C₃₋₈-Cycloalkyl, -CH₂-C₃₋₈-Cycloalkyl, Aryl oder -(C₁₋₆-Alkyl)-
Aryl bedeuten;
R¹¹ C₁₋₈-Alkyl, C₃₋₈-Cycloalkyl, -CH₂-C₃₋₈-Cycloalkyl, Aryl oder OR²⁵ bedeutet;
R¹² C₁₋₆-Alkyl oder -CH₂-Aryl bedeutet;
R¹³ und R¹⁴ gleiches oder verschiedenes C₁₋₆-Alkyl sind oder gemeinsam für -(CH₂)_h- mit h = 4 oder 5 stehen; 15
R¹⁵ und R¹⁶ unabhängig voneinander H, C₁₋₈-Alkyl, C₃₋₈-Cycloalkyl, -CH₂-C₃₋₈-Cycloalkyl, Aryl oder -(C₁₋₆-Al-
kyl)-Aryl bedeuten;
R¹⁷ H, C₁₋₈-Alkyl, C₃₋₈-Cycloalkyl, -CH₂-C₃₋₈-Cycloalkyl, Aryl, -(C₁₋₆-Alkyl)-Aryl, NH₂, NHR¹², NR¹³R¹⁴ oder
OR²⁶ bedeutet;
R¹⁸ und R¹⁹ unabhängig voneinander H, C₁₋₈-Alkyl, C₃₋₈-Cycloalkyl, -CH₂-C₃₋₈-Cycloalkyl, Aryl oder -(C₁₋₆-Al-
kyl)-Aryl bedeuten; 20
R²⁰ H, C₁₋₈-Alkyl, C₃₋₈-Cycloalkyl, -CH₂-C₃₋₈-Cycloalkyl, Aryl oder -(C₁₋₆-Alkyl)-Aryl oder OR²⁷ bedeutet;
R²¹, R²², R²³ und R²⁴ unabhängig voneinander H, Fluor, Chlor, Brom, Iod oder OR²⁸ bedeuten;
R²⁵, R²⁶, R²⁷ und R²⁸ unabhängig voneinander H oder C₁₋₆-Alkyl bedeuten, wobei R²⁵ nicht H bedeutet, wenn zu-
gleich R¹ Aryl und R² Alkyl bedeuten, 25
zur Herstellung eines Arzneimittels zur Behandlung von Schmerz.
16. Verwendung einer Verbindung der allgemeinen Struktur (IA), (IB) oder (II) oder eines ihrer pharmazeutisch an-
nehmbaren Salze:



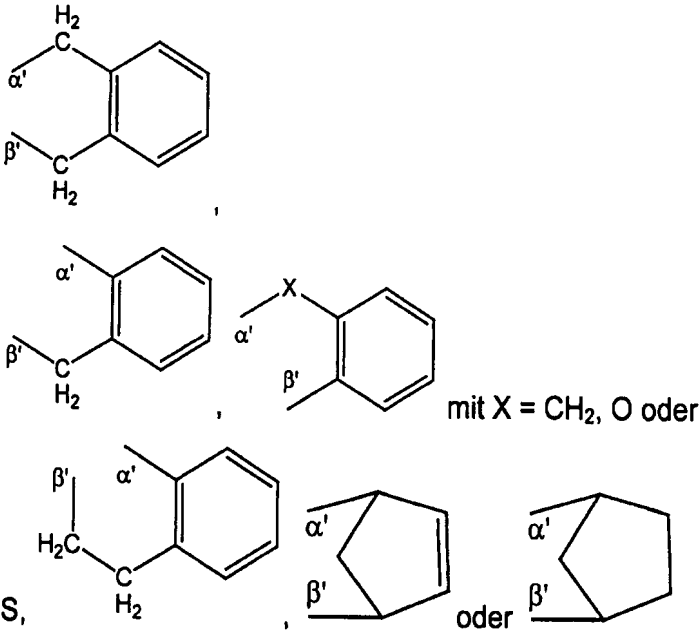
worin
R¹ und R² unabhängig voneinander H, O-R⁹, S-R¹⁰, C₁₋₁₂-Alkyl, C₃₋₈-Cycloalkyl, -CH₂-C₃₋₈-Cycloalkyl, Aryl, -
(C₁₋₆-Alkyl)-Aryl, Heterocyclyl oder -(C₁₋₆-Alkyl)-Heterocyclyl bedeuten, 60
wobei einer der Reste R¹ und R² H ist und der andere Rest von R¹ und R² nicht H ist oder für den Fall, daß einer der
Reste R¹ und R² Aryl bedeutet, der andere Rest von R¹ und R² H oder C₁₋₁₂-Alkyl bedeutet,
R³ und R⁴ H, C₁₋₁₂-Alkyl, C₃₋₈-Cycloalkyl, -CH₂-C₃₋₈-Cycloalkyl, Aryl oder -(C₁₋₆-Alkyl)-Aryl bedeuten,
wobei mindestens einer der Reste R³ und R⁴ H ist, oder
einer der Reste R¹ und R² zusammen mit einem der Reste R³ und R⁴ W bildet, wobei W α'-(CH₂)_n-β' mit n = 3, 4, 5
oder 6, α'-CH=CH-CH₂-β', α'-CH₂-CH=CH-β', α'-CH=CH-CH₂-CH₂-β', α'-CH₂-CH=CH-CH₂-β', α'-CH₂-CH₂-
CH=CH-β', α'-O-(CH₂)_m-β' mit m = 2, 3, 4 oder 5: 65



- bedeutet, das mit α' gekennzeichnete Ende von W mit dem mit α gekennzeichneten Atom der Verbindung der allgemeinen Struktur (IA), (IB) oder (II) verbunden ist und das mit β' gekennzeichnete Ende von W mit dem mit β gekennzeichneten Atom der Verbindung der allgemeinen Struktur (IA), (IB) oder (II) verbunden ist, der andere Rest von R^1 und R^2 H oder C_{1-12} -Alkyl ist und der andere Rest von R^3 und R^4 H oder C_{1-12} -Alkyl ist;
 R^5 C_{1-12} -Alkyl, C_{3-8} -Cycloalkyl, $-CH_2-C_{3-8}$ -Cycloalkyl, Aryl, $-(C_{1-6}$ -Alkyl)-Aryl, Heterocyclyl, $-(C_{1-6}$ -Alkyl)-Heterocyclyl oder $C(=O)R^{11}$ bedeutet;
 R^6 H, C_{1-8} -Alkyl, -CN, Fluor, Chlor, Brom, Iod, NO_2 , NH_2 , NHR^{12} , $NR^{13}R^{14}$, OR^{15} , $S(O)_pR^{16}$ mit $p = 0, 1$ oder 2 , $-C(=O)R^{17}$ oder $-N=N$ -Aryl bedeutet;
 R^7 H, C_{1-8} -Alkyl, Aryl, -CN, Fluor, Chlor, Brom, Iod, NO_2 , NH_2 , NHR^{12} , $NR^{13}R^{14}$, OR^{18} , $S(O)_qR^{19}$ mit $q = 0, 1$ oder 2 oder $C(=O)R^{20}$ bedeutet;
 R^8 H, C_{1-8} -Alkyl oder Aryl bedeutet, oder
die Reste R^7 und R^8 zusammen Y bilden, wobei Y γ - $CR^{21}=CR^{22}-CR^{23}=CR^{24}-\delta$ bedeutet und das mit γ gekennzeichnete Ende von Y mit dem mit γ gekennzeichneten Atom der allgemeinen Struktur (II) verbunden ist und das mit δ gekennzeichnete Ende von Y mit dem mit δ gekennzeichneten Atom der allgemeinen Struktur (II) verbunden ist;
 R^9 und R^{10} unabhängig voneinander C_{1-8} -Alkyl, C_{3-8} -Cycloalkyl, $-CH_2-C_{3-8}$ -Cycloalkyl, Aryl oder $-(C_{1-6}$ -Alkyl)-Aryl bedeuten;
 R^{11} C_{1-8} -Alkyl, C_{3-8} -Cycloalkyl, $-CH_2-C_{3-8}$ -Cycloalkyl, Aryl oder OR^{25} bedeutet;
 R^{12} C_{1-6} -Alkyl oder $-CH_2$ -Aryl bedeutet;
 R^{13} und R^{14} gleiches oder verschiedenes C_{1-6} -Alkyl sind oder gemeinsam für $-(CH_2)_h$ mit $h = 4$ oder 5 stehen;
 R^{15} und R^{16} unabhängig voneinander H, C_{1-8} -Alkyl, C_{3-8} -Cycloalkyl, $-CH_2-C_{3-8}$ -Cycloalkyl, Aryl oder $-(C_{1-6}$ -Alkyl)-Aryl bedeuten;
 R^{17} H, C_{1-8} -Alkyl, C_{3-8} -Cycloalkyl, $-CH_2-C_{3-8}$ -Cycloalkyl, Aryl, $-(C_{1-6}$ -Alkyl)-Aryl, NH_2 , NHR^{12} , $NR^{13}R^{14}$ oder OR^{26} bedeutet;
 R^{18} und R^{19} unabhängig voneinander H, C_{1-8} -Alkyl, C_{3-8} -Cycloalkyl, $-CH_2-C_{3-8}$ -Cycloalkyl, Aryl oder $-(C_{1-6}$ -Alkyl)-Aryl bedeuten;
 R^{20} H, C_{1-8} -Alkyl, C_{3-8} -Cycloalkyl, $-CH_2-C_{3-8}$ -Cycloalkyl, Aryl oder $-(C_{1-6}$ -Alkyl)-Aryl oder OR^{27} bedeutet;
 R^{21} , R^{22} , R^{23} und R^{24} unabhängig voneinander H, Fluor, Chlor, Brom, Iod oder OR^{28} bedeuten;
 R^{25} , R^{26} , R^{27} und R^{28} unabhängig voneinander H oder C_{1-6} -Alkyl bedeuten, wobei R^{25} nicht H bedeutet, wenn zugleich R^1 Aryl und R^2 Alkyl bedeuten;
zur Herstellung eines Arzneimittels zur Behandlung und/oder Prophylaxe von Epilepsie, Schizophrenie, neurodegenerativen Erkrankungen, insbesondere Morbus Alzheimer, Morbus Huntington und Morbus Parkinson, von cerebralen Ischämien und Infarkten, von Psychosen, bedingt durch erhöhten Aminosäurespiegel, Hirnödemen, Unterversorgungszuständen des zentralen Nervensystems, insbesondere bei Hypoxien und Anoxien, von AIDS-Demenz, von Encephalomyelitis, des Tourette-Syndroms, der perinatalen Asphyxie und/oder bei Tinnitus.
17. Pharmazeutische Zusammensetzung, die mindestens eine Verbindung der allgemeinen Struktur (IA), (IB) oder (II) oder eines ihrer pharmazeutisch annehmbaren Salze:



worin
R¹ und R² unabhängig voneinander H, O-R⁹, S-R¹⁰, C₁₋₁₂-Alkyl, C₃₋₈-Cycloalkyl, -CH₂-C₃₋₈-Cycloalkyl, Aryl, -
(C₁₋₆-Alkyl)-Aryl, Heterocyclyl oder -(C₁₋₆-Alkyl)-Heterocyclyl bedeuten,
wobei einer der Reste R¹ und R² H ist und der andere Rest von R¹ und R² nicht H ist oder für den Fall, daß einer der
Reste R¹ und R² Aryl bedeutet, der andere Rest von R¹ und R² H oder C₁₋₁₂-Alkyl bedeutet,
R³ und R⁴ H, C₁₋₁₂-Alkyl, C₃₋₈-Cycloalkyl, -CH₂-C₃₋₈-Cycloalkyl, Aryl oder -(C₁₋₆-Alkyl)-Aryl bedeuten,
wobei mindestens einer der Reste R³ und R⁴ H ist,
oder
einer der Reste R¹ und R² zusammen mit einem der Reste R³ und R⁴ W bildet, wobei W α'-(CH₂)_n-β' mit n = 3, 4, 5
oder 6, α'-CH=CH-CH₂-β', α'-CH₂-CH=CH-β', α'-CH=CH-CH₂-CH₂-β', α'-CH₂-CH=CH-CH₂-β', α'-CH₂-CH₂-
CH=CH-β', α'-O-(CH₂)_m-β' mit m = 2, 3, 4 oder 5:



S,
bedeutet, das mit α' gekennzeichnete Ende von W mit dem mit α gekennzeichneten Atom der Verbindung der all-
gemeinen Struktur (IA), (IB) oder (II) verbunden ist und das mit β' gekennzeichnete Ende von W mit dem mit β ge-
kennzeichneten Atom der Verbindung der allgemeinen Struktur (IA), (IB) oder (II) verbunden ist, der andere Rest
von R¹ und R² H oder C₁₋₁₂-Alkyl ist und der andere Rest von R³ und R⁴ H oder C₁₋₁₂-Alkyl ist;

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- R^5 C_{1-12} -Alkyl, C_{3-8} -Cycloalkyl, $-CH_2-C_{3-8}$ -Cycloalkyl, Aryl, $-(C_{1-6}$ -Alkyl)-Aryl, Heterocyclyl, $-(C_{1-6}$ -Alkyl)-Heterocyclyl oder $C(=O)R^{11}$ bedeutet;
 R^6 H, C_{1-8} -Alkyl, -CN, Fluor, Chlor, Brom, Iod, NO_2 , NH_2 , NHR^{12} , $NR^{13}R^{14}$, OR^{15} , $S(O)_pR^{16}$ mit $p = 0, 1$ oder 2 , $-C(=O)R^{17}$ oder $-N=N$ -Aryl bedeutet;
 R^7 H, C_{1-8} -Alkyl, Aryl, -CN, Fluor, Chlor, Brom, Iod, NO_2 , NH_2 , NHR^{12} , $NR^{13}R^{14}$, OR^{18} , $S(O)_qR^{19}$ mit $q = 0, 1$ oder 2 oder $C(=O)R^{20}$ bedeutet,
 R^8 H, C_{1-8} -Alkyl oder Aryl bedeutet, oder die Reste R^7 und R^8 zusammen Y bilden, wobei Y γ - $CR^{21}=CR^{22}$ - $CR^{23}=CR^{24}$ - δ' bedeutet und das mit γ gekennzeichnete Ende von Y mit dem mit γ gekennzeichneten Atom der allgemeinen Struktur (II) verbunden ist und das mit δ' gekennzeichnete Ende von Y mit dem mit δ gekennzeichneten Atom der allgemeinen Struktur (II) verbunden ist;
 R^9 und R^{10} unabhängig voneinander C_{1-8} -Alkyl, C_{3-8} -Cycloalkyl, $-CH_2-C_{3-8}$ -Cycloalkyl, Aryl oder $-(C_{1-6}$ -Alkyl)-Aryl bedeuten;
 R^{11} C_{1-8} -Alkyl, C_{3-8} -Cycloalkyl, $-CH_2-C_{3-8}$ -Cycloalkyl, Aryl oder OR^{25} bedeutet;
 R^{12} C_{1-6} -Alkyl oder $-CH_2$ -Aryl bedeutet;
 R^{13} und R^{14} gleiches oder verschiedenes C_{1-6} -Alkyl sind oder gemeinsam für $-(CH_2)_h-$ mit $h = 4$ oder 5 stehen;
 R^{15} und R^{16} unabhängig voneinander H, C_{1-8} -Alkyl, C_{3-8} -Cycloalkyl, $-CH_2-C_{3-8}$ -Cycloalkyl, Aryl oder $-(C_{1-6}$ -Alkyl)-Aryl bedeuten;
 R^{17} H, C_{1-8} -Alkyl, C_{3-8} -Cycloalkyl, $-CH_2-C_{3-8}$ -Cycloalkyl, Aryl, $-(C_{1-6}$ -Alkyl)-Aryl, NH_2 , NHR^{12} , $NR^{13}R^{14}$ oder OR^{26} bedeutet;
 R^{18} und R^{19} unabhängig voneinander H, C_{1-8} -Alkyl, C_{3-8} -Cycloalkyl, $-CH_2-C_{3-8}$ -Cycloalkyl, Aryl oder $-(C_{1-6}$ -Alkyl)-Aryl bedeuten;
 R^{20} H, C_{1-8} -Alkyl, C_{3-8} -Cycloalkyl, $-CH_2-C_{3-8}$ -Cycloalkyl, Aryl oder $-(C_{1-6}$ -Alkyl)-Aryl oder OR^{27} bedeutet;
 R^{21} , R^{22} , R^{23} und R^{24} unabhängig voneinander H, Fluor, Chlor, Brom, Iod oder OR^{28} bedeuten;
 R^{25} , R^{26} , R^{27} und R^{28} unabhängig voneinander H oder C_{1-6} -Alkyl bedeuten, wobei R^{25} nicht H bedeutet, wenn zugleich R^1 Aryl und R^2 Alkyl bedeuten,
sowie mindestens einen pharmazeutischen Hilfsstoff enthält.

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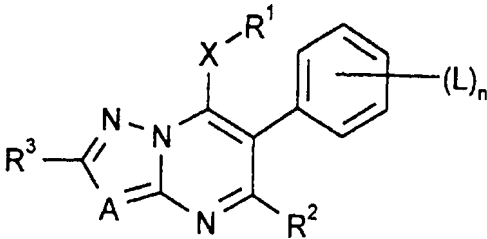
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239:00, 249:00)

12 DEMANDE DE BREVET D'INVENTION A1

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43 Date de mise à la disposition du public de la demande : 14.04.00 Bulletin 00/15.	72 Inventeur(s) : PFRENGLE WALDEMAR FRANZ AUGUSTIN et PEES KLAUS JUERGEN.
56 Liste des documents cités dans le rapport de recherche préliminaire : Ce dernier n'a pas été établi à la date de publication de la demande.	73 Titulaire(s) :
60 Références à d'autres documents nationaux apparentés :	74 Mandataire(s) : CABINET LAVOIX.

54 TRIAZOLOPYRIMIDINES 7-OXY- ET 7-THIO-SUBSTITUEES FONGICIDES.
57 Les nouveaux composés de formule I:



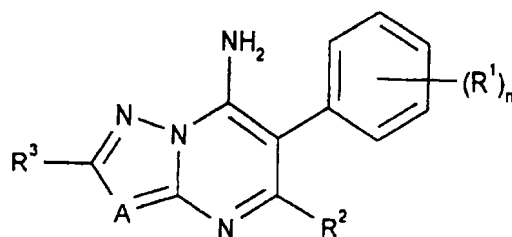
dans laquelle
(R¹, R², R³, A, X, L et n jusqu'à L⁵ sont définis dans la
description) présentent une activité fongicide élevée. Ces
nouveaux composés sont transformés, avec des véhicules
et adjuvants, en des compositions fongicides.

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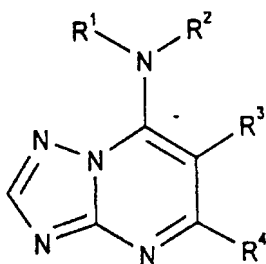
Cette invention se rapporte à certains composés triazolopyrimidine, à un procédé pour les préparer, à des compositions contenant de tels composés, à un procédé pour combattre un champignon en un site, comprenant le traitement du site avec de tels composés, et leur utilisation comme fongicides.

Le document EP-A-0 071 792 revendique des composés de formule générale



5 dans laquelle R^1 représente un groupe alkyle, un atome d'halogène, un groupe alcoxy, cyano, cycloalkyle, aryle, aryloxy, arylthio, aralkyle, arylalkyle, arylalkyloxy ou arylalkylthio, chacun étant éventuellement substitué par un halogène ou un alcoxy; ou bien $(R^1)_n$ représente un benzène, un indane ou un noyau tétrahydronaphtalène soudé à un noyau phénylique, les fractions aromatiques des groupes ci-dessus étant éventuellement substituées par un groupe alkyle, alcoxy, par un atome d'halogène ou par un cyano; n est 1 ou 2, R^2 et R^3 sont chacun un atome d'hydrogène, un groupe alkyle ou aryle, A représente un atome d'azote ou un groupe CR^4 , et R^4 est tel que R^2 mais peut également être un halogène, un cyano ou un alcoxycarbonyle, ou bien conjointement à R^3 il peut former une chaîne alkylène contenant jusqu'à deux doubles liaisons. Ces composés sont considérés comme étant actifs contre différents champignons phytopathogènes, en particulier contre ceux de la classe des phycomycètes. Cependant, une preuve d'activité fongicide n'est apportée, pour ces composés, que contre *Plasmopara viticola*, un membre de la classe des champignons oomycète.

Le brevet US 5,593,996 revendique des composés de formule générale

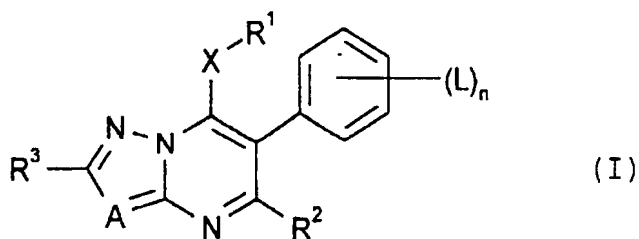


25 dans laquelle R^1 représente un groupe alkyle, alcényle, alcadiényle, cycloalkyle, bicycloalkyle ou hétérocyclyle éventuellement substitué; R^2 représente un atome

d'hydrogène ou un groupe alkyle; ou bien R^1 et R^2 , conjointement à l'atome d'azote intercalé entre eux, représentent un noyau hétérocyclique éventuellement substitué; R^3 représente un groupe phényle ou naphtyle éventuellement substitué; et R^4 représente un atome d'halogène ou un groupe $-NR^5R^6$ où R^5 représente un atome d'hydrogène ou un groupe amino, alkyle, cycloalkyle ou bicycloalkyle et R^6 représente un atome d'hydrogène ou un groupe alkyle.

Le brevet britannique GB 1,148,629 décrit un procédé de préparation de s-triazolo[1,5-a]pyrimidines qui sont substituées en position 7 par un groupe basique, en utilisant des 7-alcoxy ou 7-alkylthio-s-triazolo[1,5-a]pyrimidines comme radical de départ. Cependant, il n'y a pas d'allusion à la description des activités fongicides.

La présente invention fournit un composé de formule I



dans laquelle

R^1 représente un groupe alkyle, alcényle, alcynyle, alcadiényle, aryle, hétéroaryle, cycloalkyle, cycloalcényle, bicycloalkyle, ou hétérocyclyle éventuellement substitué,

R^2 représente un atome d'halogène ou un groupe de formule $-Y-R^4$, dans laquelle Y représente O, S ou NR^5 , R^4 ayant la

signification indiquée pour R^1 , et R^5 étant un atome H ou formant avec R^4 et l'atome d'azote intercalé entre eux un noyau hétérocyclique, ou ayant la signification indiquée pour R^1 ,

5 R^3 représente un atome d'hydrogène ou un groupe alkyle ou aryle,

L représente un atome d'halogène ou un groupe alkyle ou alcoxy éventuellement substitué,

A représente N ou CR^6 , où R^6 a la signification indiquée
10 pour R^3 ,

X représente O ou S, et

n est 0 ou un entier situé entre 1 et 5.

Ces nouveaux composés présentent une excellente activité fongicide sélective pour différentes cultures.

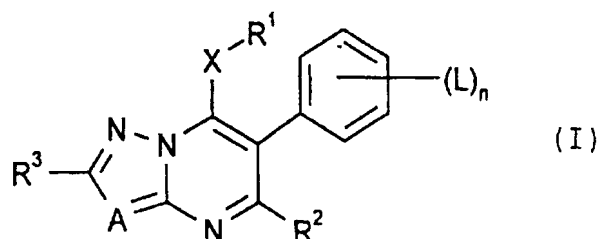
15 Un objectif de la présente invention est de fournir de nouveaux composés fongicides sélectifs.

Un objectif de l'invention est également de fournir des procédés de contrôle d'un champignon indésirable en mettant en contact lesdites plantes avec
20 une quantité efficace à titre de fongicide des nouveaux composés.

Un autre objectif de l'invention est de fournir des compositions fongicides sélectives contenant les nouveaux composés comme principes actifs.

25 Ces objectifs et caractéristiques de l'invention, et d'autres, seront davantage évidents à la lecture de la description détaillée exposée ci-dessous, et à la lecture des revendications jointes.

De façon surprenante, on a trouvé que les
5 composés de formule I



dans laquelle R^1 , R^2 , R^3 , A, L et n ont la signification
indiquée ci-dessus pour la formule I, présentaient une
10 excellente activité fongicide vis à vis d'une large gamme
de champignons.

D'une façon générale, sauf indication contraire,
tel qu'il est utilisé ici le terme atome d'halogène peut
désigner un atome de brome, d'iode, de chlore ou de fluor,
15 et c'est en particulier un atome de brome, de chlore ou de
fluor. Les fractions éventuellement substituées peuvent
être non substituées et comporter de un jusqu'au nombre
maximal possible de substituants. Habituellement, 0 à 2
substituants sont présents.

20 D'une façon générale, sauf indication contraire
ici, les termes alkyle, alcényle, alcynyle, alcadiényle,
tels qu'utilisés ici en ce qui concerne un radical ou à
une fraction, se réfèrent à un radical ou une fraction
ayant une chaîne linéaire ou ramifiée. En règle générale,
25 de tels radicaux possèdent jusqu'à 10, en particulier
jusqu'à 6, atomes de carbone. Une fraction alkyle possède
de manière adéquate de 1 à 10 atomes de carbone, de
préférence de 2 à 6 atomes de carbone. Une fraction alkyle
préférée est un groupe éthyle, ou en particulier un groupe

méthyle. De façon appropriée, une fraction alcényle possède de 2 à 6 atomes de carbone.

D'une façon générale, sauf indication contraire ici, le terme aryle, tel qu'il est utilisé ici en ce qui
5 concerne un radical ou une fraction, se réfère à un groupe aryle possédant 6, 10 ou 14 atomes de carbone, de préférence 6 ou 10 atomes de carbone, en particulier un phényle éventuellement substitué par un ou plusieurs atomes d'halogènes, par un groupe nitro, cyano, alkyle, de
10 préférence alkyle en C₁₋₆, alcoxy, de préférence alcoxy en C₁₋₆, halogénoalkyle, de préférence halogénoalkyle en C₁₋₆, halogénoalcoxy, de préférence halogénoalcoxy en C₁₋₆.

D'une façon générale, sauf indication contraire ici, le terme cycloalkyle ou cycloalcényle, tel qu'il est
15 utilisé ici en ce qui concerne un radical ou une fraction, se réfère à un groupe cycloalkyle possédant 3 à 8 atomes de carbone ou à un groupe cycloalcényle possédant 5 à 8 atomes de carbone, de préférence 5 à 7 atomes de carbone, en particulier un cyclopentyle, un cyclohexyle ou un
20 cyclohexényle éventuellement substitué par un ou plusieurs atomes d'halogènes, par un groupe nitro, cyano, alkyle, de préférence alkyle en C₁₋₆, alcoxy, de préférence alcoxy en C₁₋₆.

D'une façon générale, sauf indication contraire
25 ici, le terme hétéroaryle, tel qu'il est utilisé ici en ce qui concerne un radical ou une fraction, se réfère à un groupe hétérocyclique aromatique possédant 5 ou 6 atomes cycliques, choisis parmi le carbone, l'azote, l'oxygène et le soufre, au moins l'un d'entre eux étant l'azote,
30 l'oxygène ou le soufre, éventuellement substitué par un ou plusieurs atomes d'halogènes, par un groupe nitro, cyano, alkyle, de préférence alkyle en C₁₋₆, alcoxy, de préférence alcoxy en C₁₋₆, en particulier azolyle, triazolyle,

furanyle, oxazolyle, thiényle, thiazolyle, dithiazolyle, pyridyle ou pyrimidyle.

D'une façon générale, sauf indication contraire ici, le terme hétérocyclyle, tel qu'il est utilisé ici pour ce qui concerne un radical ou une fraction, se réfère à un groupe hétérocyclique non aromatique possédant 5 ou 6 atomes cycliques, choisis parmi le carbone, l'azote, l'oxygène et le soufre, au moins l'un d'entre eux étant l'azote, l'oxygène ou le soufre, éventuellement substitué par un ou plusieurs atomes d'halogènes, par un groupe nitro, cyano, alkyle, de préférence alkyle en C₁₋₆, alcoxy, de préférence alcoxy en C₁₋₆, en particulier le tétrahdropyranyle, le tétrahydrofuranyle, le tétrahydrothiényle, le tétrahdropyridyle ou le tétrahdropyrimidyle.

L'invention se rapporte en particulier à des composés de formule générale I dans laquelle toute partie alkyle des groupes R¹ qui peut avoir une chaîne linéaire ou être ramifiée, contient 1 à 10 atomes de carbone, de préférence 2 à 9 atomes de carbone, plus préférentiellement 3 à 6 atomes de carbone, toute partie alcényle, alcynyle ou alcadiényle des substituants R¹ contient 2 à 10 atomes de carbone, de préférence 3 à 9 atomes de carbone, plus préférentiellement 4 à 6 atomes de carbone, toute partie cycloalkyle des substituants R¹ contient de 3 à 10 atomes de carbone, de préférence de 3 à 8 atomes de carbone, plus préférentiellement de 3 à 6 atomes de carbone, et toute partie aryle des substituants R¹ contient 6, 10 ou 14 atomes de carbone, de préférence 6 ou 10 atomes de carbone, dans lesquels chaque groupe éventuellement substitué est indépendamment substitué par un ou plusieurs atomes d'halogènes ou par un groupe nitro, cyano, alkyle, de préférence alkyle en C₁₋₆, cycloalkyle,

de préférence cycloalkyle en C₃₋₆, cycloalcényle, de
préférence cycloalcényle en C₃₋₆, halogénoalkyle, de
préférence halogénoalkyle en C₁₋₆, halogénocycloalkyle, de
préférence halogénocycloalkyle en C₃₋₆, alcoxy, de
5 préférence alcoxy en C₁₋₆, alcanoyloxy, de préférence
alcanoyloxy en C₁₋₆, halogénoalcoxy, de préférence
halogénoalcoxy en C₁₋₆, alkylthio, de préférence alkylthio
en C₁₋₆, phényle, halogéno-, dihalogéno- ou
trihalogénophényle ou pyridyle. N'importe quel groupe
10 alkyle, alcényle ou alcynyle peut être linéaire ou
ramifié. Un atome d'halogène approprié signifie un atome
de fluor, de chlore ou de brome.

Cette invention se rapporte en particulier à des
composés de formule générale I dans laquelle R¹ représente
15 un groupe alkyle en C₁₋₁₀, halogénoalkyle en C₁₋₁₀, en
particulier un groupe alkyle en C₁₋₁₀ fluoré, cycloalkyle
en C₃₋₆, cycloalkyle en C₃₋₈ - alkyle en C₁₋₆, alkyle en C₁₋₆
- cycloalkyle en C₃₋₈, en particulier un groupe
méthylcyclohexyle, cycloalcényle en C₅₋₈, alcoxy en C₁₋₁₀ -
20 alkyle en C₁₋₆, phényle ou mono- ou di-alkyle en C₁₋₆ -
phényle.

L'invention se rapporte en particulier à des
composés de formule générale I dans laquelle R² est un
atome d'halogène, en particulier un atome de chlore, ou un
25 groupe alcoxy, de préférence un alcoxy en C₁₋₅, en
particulier un méthoxy.

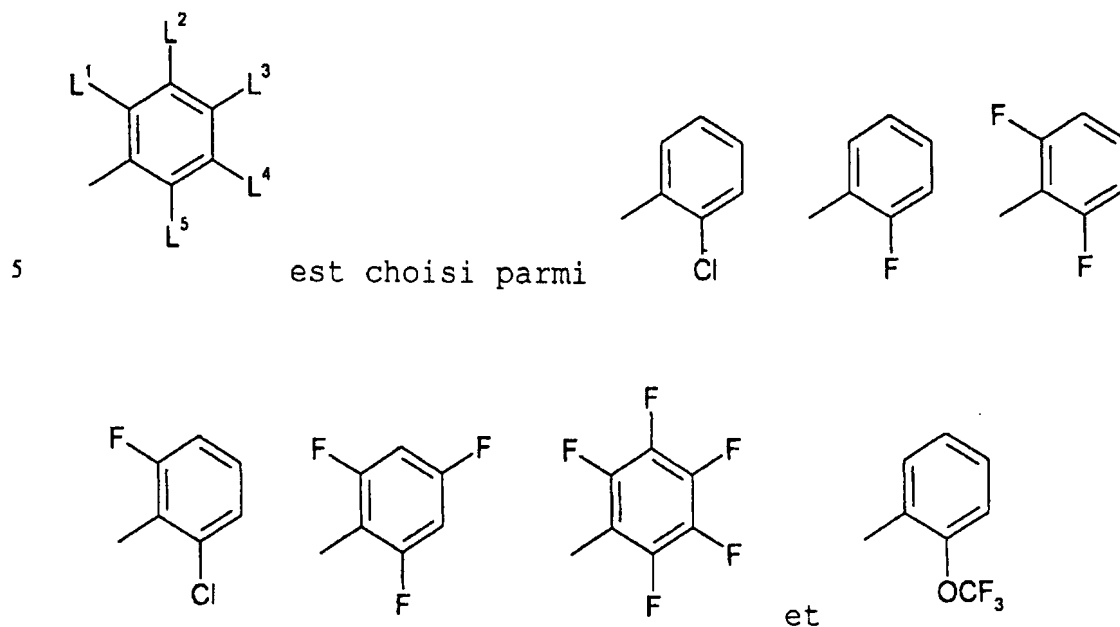
De préférence A représente N et R³ représente un
atome d'hydrogène.

De préférence n est 1, 2 ou 3.

30 De préférence, au moins l'un des substituants L
est un atome de fluor ou de chlore, ou un groupe méthyle,
méthoxy ou trifluorométhoxy. Les autres substituants sont

de préférence choisis entre un atome d'hydrogène ou de fluor.

On préfère en particulier les composés de formule I, dans laquelle le groupe phényle de formule



10 On préfère davantage, le 2-chloro-6-fluorophényle et le 2,4,6-trifluorophényle.

Les composés selon la formule générale I sont des huiles, des gommes, ou des matériaux solides principalement cristallins. Ils sont supérieurs par leurs précieuses propriétés fongicides, en particulier par leur

15 fongitoxité vis à vis d'une large gamme de champignons phytopathogènes. Ils peuvent, par exemple, être utilisés dans l'agriculture ou dans les domaines connexes, pour contrôler les champignons phytopathogènes tels que

20 *Venturia inaequalis*, *Alternaria solani*, *Botrytis cinerea*, *Cercospora beticola*, *Cladosporium herbarum*, *Corticium rolfsii*, *Erysiphe graminis*, *Helminthosporium tritici* *repentis*, *Leptosphaeria nodorum*, *Micronectriella nivalis*, *Monilinia fructigena*, *Mycosphaerella ligulicola*, *Mycosphaerella pinodes*, *Phytophthora infestans*,

Pyricularia grisea f. sp. *oryzae*, *Rhizoctonia solani*,
Monographella nivalis et *Sclerotinia sclerotiorum*, en
particulier pour contrôler *Venturia inaequalis*, *Alternaria*
solani, et *Botrytis cinerea*. Les composés de formule
5 générale I, selon l'invention, possèdent une activité
fongicide élevée dans une large gamme de concentrations,
et peuvent être utilisés dans l'agriculture sans aucune
difficulté.

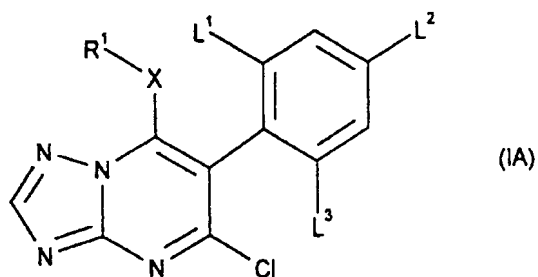
Qui plus est, les composés selon l'invention
10 présentent un contrôle résiduel accru des champignons
comparés aux fongicides classiques.

De bons résultats en termes de contrôle des
champignons phytopathogènes sont obtenus avec un composé
tel que défini dans la formule I dans laquelle:

15 R^2 représente un atome de chlore ou un groupe
méthoxy;

R^1 représente de préférence un alkyle en C_1-C_8 à
chaîne linéaire ou ramifié, en particulier un groupe n-
propyle, iso-propyle, 1- ou 2-méthylpropyle, n-butyle, n-
20 pentyle ou n-hexyle, un cycloalkyle en C_3-7 éventuellement
substitué par un groupe alkyle en C_1-C_8 , en particulier un
cyclopentyle, un cyclohexyle ou un 4-méthylcyclohexyle, un
halogénoalkyle en C_1-C_6 à chaîne linéaire ou ramifié, en
particulier un 3,3,3-trifluoropropyle, ou un phényle
25 éventuellement substitué par au moins un atome d'halogène
ou au moins un groupe alkyle en C_1-C_6 ou alcoxy en C_1-C_6 .

On préfère en particulier les composés de formule
IA,



dans laquelle

R¹ et X ont la signification indiquée, et L¹, L² et L³ représentent chacun indépendamment un atome d'hydrogène, de fluor ou de chlore, un groupe méthyle, trifluorométhoxy, l'un d'entre eux au moins étant différent d'un atome d'hydrogène.

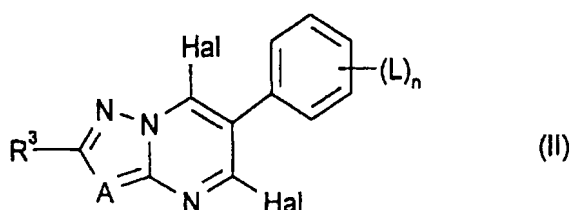
On obtient des résultats particulièrement bons en terme de contrôle des champignons phytopathogènes en utilisant, par exemple, les composés suivants de formule I: la 5-chloro-6-phényl-7-(furfur-2-ylméthylthio)-[1,2,4]triazolo[1,5-a]pyrimidine, 5-chloro-6-phényl-7-(3,4,5,6-tétrahydropyridimid-2-ylthio)-[1,2,4]triazolo[1,5-a]pyrimidine, la 5-chloro-6-(4-méthoxyphényl)-7-(fulfur-2-ylméthylthio)-[1,2,4]triazolo[1,5-a]pyrimidine, la 5-chloro-6-(2-chloro-6-fluorophényl)-7-allylthio-[1,2,4]triazolo[1,5-a]pyrimidine, la 5-chloro-6-(2-chloro-6-fluorophényl)-7-cyclopentylthio-[1,2,4]triazolo[1,5-a]pyrimidine, la 5-chloro-6-(2-chloro-6-fluorophényl)-7-(2,2,2-trifluoroéthylthio)-[1,2,4]triazolo[1,5-a]pyrimidine, la 5-chloro-6-(2-chloro-6-fluorophényl)-7-(isopropylthio)-[1,2,4]triazolo[1,5-a]pyrimidine, la 5-chloro-6-(2-chloro-6-fluorophényl)-7-(1-méthylpropylthio)-[1,2,4]triazolo[1,5-a]pyrimidine, la 5-chloro-6-(2-chloro-6-fluorophényl)-7-propylthio-[1,2,4]triazolo[1,5-a]pyrimidine, la 5-chloro-6-(2-chloro-6-fluorophényl)-7-(2-méthylpropylthio)-[1,2,4]triazolo[1,5-a]pyrimidine, la 5-chloro-6-(2-chloro-6-fluorophényl)-7-cyclohexylthio-

- [1,2,4]triazolo[1,5-a]pyrimidine, la 5-chloro-6-(2-chloro-6-fluorophényl)-7-butylthio-[1,2,4]triazolo[1,5-a]pyrimidine, la 5-chloro-6-(2-chloro-6-fluorophényl)-7-phénylthio-[1,2,4]triazolo[1,5-a]pyrimidine, la 5-chloro-6-(2-chloro-6-fluorophényl)-7-benzylthio-[1,2,4]triazolo[1,5-a]pyrimidine, la 5-chloro-6-(2-chloro-6-fluorophényl)-7-tert-butylthio-[1,2,4]triazolo[1,5-a]pyrimidine, la 5-chloro-6-(2-chloro-6-fluorophényl)-7-méthylthio-[1,2,4]triazolo[1,5-a]pyrimidine, la 5-chloro-6-(2-chloro-6-fluorophényl)-7-éthylthio-[1,2,4]triazolo[1,5-a]pyrimidine, la 5-chloro-6-(2-chloro-6-fluorophényl)-7-(4-chlorophénylthio)-[1,2,4]triazolo[1,5-a]pyrimidine, la 5-chloro-6-(2-chloro-6-fluorophényl)-7-(2-méthylphénylthio)-[1,2,4]triazolo[1,5-a]pyrimidine, la 5-chloro-6-(2-chloro-6-fluorophényl)-7-(2-méthoxyphénylthio)-[1,2,4]triazolo[1,5-a]pyrimidine, la 5-chloro-6-(2-chloro-6-fluorophényl)-7-(4-méthoxyphénylthio)-[1,2,4]triazolo[1,5-a]pyrimidine, la 5-chloro-6-(2-chloro-6-fluorophényl)-7-(2-chlorophénylthio)-[1,2,4]triazolo[1,5-a]pyrimidine, la 5-chloro-6-(2-chloro-6-fluorophényl)-7-éthoxy-[1,2,4]triazolo[1,5-a]pyrimidine, la 5-chloro-6-(2-chloro-6-fluorophényl)-7-cyclopentyloxy-[1,2,4]triazolo[1,5-a]pyrimidine, la 5-chloro-6-(2-chloro-6-fluorophényl)-7-(2,2,2,-trifluoroéthoxy)-[1,2,4]triazolo[1,5-a]pyrimidine, la 5-chloro-7-allylthio-6-(2,4,6-trifluorophényl)-[1,2,4]triazolo[1,5-a]pyrimidine, la 5-chloro-7-cyclopentylthio-6-(2,4,6-trifluorophényl)-[1,2,4]triazolo[1,5-a]pyrimidine, la 5-chloro-7-(2,2,2-trifluoroéthylthio)-6-(2,4,6-trifluorophényl)-[1,2,4]triazolo[1,5-a]pyrimidine, la 5-chloro-7-(isopropylthio)-6-(2,4,6-trifluorophényl)-[1,2,4]triazolo[1,5-a]pyrimidine, la 5-chloro-7-(1-

méthylpropylthio)-6-(2,4,6-trifluorophényl)-
[1,2,4]triazolo[1,5-a]pyrimidine, la 5-chloro-7-
propylthio-6-(2,4,6-trifluorophényl)-[1,2,4]triazolo[1,5-
a]pyrimidine, la 5-chloro-7-(2-méthylpropylthio)-6-(2,4,6-
5 trifluorophényl)-[1,2,4]triazolo[1,5-a]pyrimidine, la 5-
chloro-7-cyclohexylthio-6-(2,4,6-trifluorophényl)-
[1,2,4]triazolo[1,5-a]pyrimidine, la 5-chloro-7-butylthio-
6-(2,4,6-trifluorophényl)-[1,2,4]triazolo[1,5-
a]pyrimidine, la 5-chloro-7-phénylthio-6-(2,4,6-
10 trifluorophényl)-[1,2,4]triazolo[1,5-a]pyrimidine, la 5-
chloro-7-benzylthio-6-(2,4,6-trifluorophényl)-
[1,2,4]triazolo[1,5-a]pyrimidine, la 5-chloro-7-tert-
butylthio-6-(2,4,6-trifluorophényl)-[1,2,4]triazolo[1,5-
a]pyrimidine, la 5-chloro-7-méthylthio-6-(2,4,6-
15 trifluorophényl)-[1,2,4]triazolo[1,5-a]pyrimidine, la 5-
chloro-7-éthylthio-6-(2,4,6-trifluorophényl)-
[1,2,4]triazolo[1,5-a]pyrimidine, la 5-chloro-6-(2,4,6-
trifluorophényl)-7-(4-chlorophénylthio)-
[1,2,4]triazolo[1,5-a]pyrimidine, la [1,2,4]triazolo[1,5-
20 a]pyrimidine, la 5-chloro-6-(2,4,6-trifluorophényl)-7-(2-
méthylphénylthio)-[1,2,4]triazolo[1,5-a]pyrimidine, la 5-
chloro-6-(2,4,6-trifluorophényl)-7-(2-méthoxyphénylthio)-
[1,2,4]triazolo[1,5-a]pyrimidine, la 5-chloro-6-(2,4,6-
trifluorophényl)-7-(4-méthoxyphénylthio)-
25 [1,2,4]triazolo[1,5-a]pyrimidine, la 5-chloro-6-(2,4,6-
trifluorophényl)-7-(2-chlorophénylthio)-
[1,2,4]triazolo[1,5-a]pyrimidine, la 5-chloro-6-(2,4,6-
trifluorophényl)-7-éthoxy-[1,2,4]triazolo[1,5-
a]pyrimidine, la 5-chloro-6-(2,4,6-trifluorophényl)-7-
30 cyclopentyloxy-[1,2,4]triazolo[1,5-a]pyrimidine, la 5-
chloro-6-(2,4,6-trifluorophényl)-7-(2,2,2-
trifluoroéthoxy)-[1,2,4]triazolo[1,5-a]pyrimidine.

La présente invention fournit également un procédé de préparation d'un composé de formule I, qui comprend:

- (a) le traitement de la 5,7-dihalogéno-
5 triazolopyrimidine de formule II,



dans laquelle R^3 , A, L et n ont la signification indiquée pour la formule I et Hal représente un atome d'halogène, avec un composé de formule III



dans laquelle

R^1 et X sont tels que définis pour la formule I, en présence d'une base;

- (b) éventuellement le traitement de la 5-
15 halogénotriazolopyrimidine résultante avec un alcool, ou un thiol ou une amine de formule R^4-YH , dans laquelle R^4 et Y sont tels que définis pour la formule I, en présence d'une base.

La réaction entre les 5,7-dihalogéno-6-aryl-
20 triazolopyrimidines de formule II, qui sont connues du brevet US No. 5,593,996, et le composé de formule III, est commodément réalisée en présence d'un solvant. Les solvants appropriés comprennent les éthers comme le dioxane, l'éther diéthylique et, en particulier, le
25 tétrahydrofurane, les hydrocarbures tels que l'hexane, le cyclohexane ou une huile minérale, et les hydrocarbures aromatiques, par exemple le toluène, ou des mélanges de ces solvants. La réaction est effectuée d'une façon appropriée à une température située dans l'intervalle de

-100°C à +100°C, la température réactionnelle préférée étant de -80°C à +40°C. Il est également préférable que la réaction soit effectuée en présence d'une base forte. Les bases fortes préférées sont les alcanes de métaux alcalins tels que le méthyllithium, le n-butyllithium, le tert-butyllithium, ou les amides de métaux alcalins tels que l'amidure de sodium, le diisopropylamidure de lithium, ou l'hexadiméthylsilazide de potassium ou les hydrures de métaux alcalins tels que l'hydruire de sodium ou de potassium, en particulier l'hydruire de sodium.

On a trouvé que les composés de formule générale I avaient une activité fongicide. Par conséquent, l'invention fournit également une composition fongicide comprenant un principe actif, qui est au moins un composé représenté par la formule I définie ci-dessus, et un ou plusieurs véhicules. On fournit également un procédé pour fabriquer une telle composition qui consiste à amener un composé de formule I, tel que défini ci-dessus, à s'associer avec le(s) véhicule(s). Une telle composition peut contenir un unique principe actif ou un mélange de plusieurs principes actifs selon la présente invention. On envisage également que différents isomères ou mélanges d'isomères puissent avoir différents niveaux ou spectres d'activité, et les compositions peuvent ainsi comprendre des isomères individuels ou des mélanges de tels isomères.

Une composition selon l'invention contient de préférence entre 0,5% et 95% en poids (pds/pds) du principe actif.

Le véhicule, dans une composition selon l'invention, est n'importe quel matériau avec lequel le principe actif est formulé pour faciliter son application sur le site à traiter, lequel peut par exemple être une plante, une graine ou le sol, ou pour faciliter son

stockage, son transport ou sa manipulation. Le véhicule peut être un solide ou un liquide, y compris un matériau qui est normalement un gaz mais qui a été comprimé pour former un liquide.

5 Les compositions peuvent être façonnées, par exemple, en des concentrés en émulsion, des solutions, des émulsions d'huile dans l'eau, des poudres mouillables, des poudres solubles, des concentrés en suspension, des poussières, des granules, des granules dispersables dans
10 l'eau, des micro-capsules, des gels et d'autres types de formulations, grâce aux procédures bien établies. Ces procédures comprennent le mélangeage intensif et/ou le broyage des principes actifs avec d'autres substances telles que des charges, des solvants, des véhicules
15 solides, des composés actifs de surface (tensioactifs), et éventuellement des auxiliaires et/ou adjuvants solides et/ou liquides. La forme d'application, comme la pulvérisation, l'atomisation, la dispersion ou le déversement, peut être choisie comme les compositions en
20 fonction des objectifs souhaités et des circonstances déterminées.

Les solvants peuvent être des hydrocarbures aromatiques, comme par exemple le Solvesso® 200, des naphthalènes substitués, des esters de l'acide phtalique
25 tels que le phtalate de dibutyle ou de dioctyle, des hydrocarbures aliphatiques comme par exemple le cyclohexane ou les paraffines, des alcools et des glycols aussi bien que leurs éthers et esters comme par exemple l'éthanol, l'éther mono- et diméthylique de
30 l'éthylèneglycol, les cétones telles que la cyclohexanone, les solvants fortement polaires tels que la N-méthyl-2-pyrrolidone, ou la γ -butyrolactone, les pyrrolidones d'alkyles supérieurs comme par exemple la n-

octylpyrrolidone ou la cyclohexylpyrrolidone, les esters époxydés d'huiles végétales comme par exemple l'ester méthylé de l'huile de copra ou de soja, et l'eau. Les mélanges de différents liquides sont souvent appropriés.

5 Les véhicules solides, qui peuvent être utilisés pour les poussières, les poudres mouillables, les granules dispersables dans l'eau, ou les granules, peuvent être des charges minérales telles que la calcite, le talc, le kaolin, la montmorillonite ou l'attapulgate. Les
10 propriétés physiques peuvent être améliorées par l'addition de gel de silice ou de polymères hautement dispersés. Les véhicules pour granules peuvent être un matériau poreux comme par exemple la pierre ponce, le kaolin, la sépiolite, la bentonite; les véhicules non
15 adsorbants peuvent être la calcite ou le sable. De plus, on peut utiliser une multitude de matériaux inorganiques ou organiques pré-granulés, tels que la dolomite ou les résidus végétaux broyés.

Les compositions pesticides sont souvent
20 formulées et transportées sous une forme concentrée qui est ensuite diluée par l'utilisateur avant d'être appliquée. La présence de petites quantités d'un véhicule qui est un tensioactif facilite ce procédé de dilution. Ainsi, de préférence au moins un véhicule, dans une
25 composition selon l'invention, est en tensioactif. Par exemple, la composition peut contenir au moins deux ou plusieurs véhicules, dont au moins un est un tensioactif.

Les tensioactifs peuvent être des substances non ioniques, anioniques, cationiques ou zwitterioniques
30 possédant de bonnes propriétés de dispersion, d'émulsification et de mouillage en fonction de la nature du composé selon la formule générale I qui doit être

formulé. Les tensioactifs peuvent également désigner des mélanges de tensioactifs individuels.

Les compositions de l'invention peuvent, par exemple, être formulées sous la forme de poudres

5 mouillables, de granules dispersables dans l'eau, de poussières, de granules, de solutions, de concentrés émulsifiables, d'émulsions, de concentrés en suspension et d'aérosols. Les poudres mouillables contiennent généralement 5 à 90% pds/pds de principe actif et

10 contiennent généralement, en plus du véhicule solide inerte, 3 à 10% pds/pds d'agents dispersants et mouillants et, lorsque nécessaire, 0 à 10% pds/pds de stabilisant(s) et/ou d'autres additifs tels que des agents d'imprégnation ou des agents collants. Les poussières sont généralement

15 formulées sous la forme d'un concentré pulvérulent possédant une composition similaire à celle d'une poudre mouillable mais sans dispersant, et elles peuvent être diluées dans le champ avec un autre véhicule solide pour donner une composition contenant généralement 0,5 à 10%

20 pds/pds de principe actif. Les granules dispersables dans l'eau et les granules sont habituellement préparés de façon à ce qu'ils aient une taille située entre 0,15 mm et 2,0 mm, et ils peuvent être fabriqués selon différentes techniques. Généralement, ce type de granules contiendra

25 0,5 à 90% pds/pds de principe actif et 0 à 20% pds/pds d'additifs tels que des stabilisants, des tensioactifs, des modificateurs à libération lente, et des agents liants. Ce que l'on appelle les "suspensions sèches" sont constituées de granules relativement petits, possédant une

30 concentration relativement élevée en principe actif. Les concentrés émulsifiables contiennent généralement, en plus d'un solvant ou d'un mélange de solvants, 1 à 80% pds/v de principe actif, 2 à 20% pds/v d'émulsifiants et 0 à 20%

pds/v d'autres additifs tels que des stabilisants, des agents d'imprégnation et des inhibiteurs de corrosion. Les concentrés en suspension sont habituellement broyés de façon à obtenir un produit stable, ne sédimentant pas et pouvant s'écouler, et ils contiennent habituellement 5 à 75% pds/v de principe actif, 0,5 à 15% pds/v d'agents dispersants, 0,1 à 10% pds/v d'agents de mise en suspension tels que des colloïdes protecteurs et des agents thixotropes, 0 à 10% pds/v d'autres additifs tels que des dé moussants, des inhibiteurs de corrosion, des stabilisants, des agents d'imprégnation et des agents collants, et de l'eau ou un liquide organique dans lequel le principe actif est pratiquement insoluble; certains solides organiques ou sels inorganiques peuvent être présents à l'état dissous dans la formulation pour aider à éviter la sédimentation et la cristallisation ou en tant qu'agents antigel pour l'eau.

Les dispersions et émulsions aqueuses, par exemple les compositions obtenues en diluant le produit formulé selon l'invention avec de l'eau, se trouvent également dans les limites du domaine d'application de l'invention.

On considère comme étant d'un intérêt particulier pour augmenter la durée de l'activité protectrice des composés de cette invention, l'utilisation d'un véhicule qui fournira une libération lente des composés pesticides dans l'environnement de la plante qui doit être protégée.

L'activité biologique du principe actif peut également être augmentée en incluant un adjuvant dans la dilution à pulvériser. Un adjuvant est défini ici comme étant une substance qui peut augmenter l'activité biologique du principe actif mais qui ne possède pas en elle-même une activité biologique significative.

L'adjuvant peut, soit être inclus dans la formulation en tant qu'agent de co-formulation ou véhicule, soit être ajouté dans le récipient de pulvérisation conjointement à la formulation contenant le principe actif.

5 Par commodité, les compositions peuvent être, de préférence, sous une forme concentrée, bien que l'utilisateur final emploie généralement des compositions diluées. Les compositions peuvent être diluées jusqu'à une concentration aussi faible que 0,001% de principe actif.

10 Les doses sont habituellement situées dans l'intervalle de 0,01 à 10 kg p.i./ha.

Les exemples de formulations selon l'invention sont:

15 Concentré en émulsion (CE)

Principe actif	Composé de l'exemple 7	30% (pds/v)
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Émulsifiant(s)	Atlox® 4856 B / Atlox® 4858B ¹⁾	5% (pds/v)
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(mélange contenant un alkylarylsulfonate de calcium, des éthoxylates d'alcools gras et des aromatiques légers / mélange contenant un alkylarylsulfonate de calcium, des éthoxylates d'alcools gras et des aromatiques légers)

Solvant	Shellsol® A ²⁾	jusqu'à 1000 ml
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(Mélange d'hydrocarbures aromatiques en C₉-C₁₀)

37

Concentré en suspension (CS)

Principe actif	Composé de l'exemple 7	50% (pds/v)
Agent dispersant	Soprophor® FL ³⁾ (sel aminés et de phosphate d'éther polyarylphénylique de polyoxyéthylène)	3% (pds/v)
Agent antimousse	Rhodorsil® 422 ³⁾ (émulsion aqueuse non ionique de polydiméthylsiloxanes)	0,2% (pds/v)
Agent de structure	Kelzan® S ⁴⁾ (gomme de xanthane)	0,2% (pds/v)
Agent antigel	Propylèneglycol	5% (pds/v)
Biocide	Proxel® ⁵⁾ (solution aqueuse de dipropylèneglycol contenant 20% de 1,2-benisohtiazolin-3-one)	0,1% (pds/v)
Eau		jusqu'à 1000 ml

Poudre mouillable (PM)

Principe actif	Composé de l'exemple 7	60% (pds/pds)
Agent mouillant	Atlox® 4995 ¹⁾ (éther alkylique de polyoxyéthylène)	2% (pds/pds)
Agent dispersant	Witcosperse® D-60 ⁶⁾ (mélange de sels de sodium de l'acide naphtalène sulfonique condensé et d'acétates d'alkylarylpolyoxy)	3% (pds/pds)
Véhicule / charge	Kaolin	35% (pds/pds)

Granules dispersables dans l'eau (GE)

Principe actif	Composé de l'exemple 7	50% (pds/pds)
Agent dispersant / liant	Witcosperse® D-450 ⁶⁾ (mélange de sels de sodium de l'acide naphthalène sulfonique condensé et d'alkylsulfonates)	8% (pds/pds)
Agent mouillant	Morwet® EFW ⁶⁾ (produit de la condensation du formaldéhyde)	2% (pds/pds)
Agent antimousse	Rhodorsil® EP 6703 ³⁾ (silicone encapsulé)	1% (pds/pds)
Désagréant	Agrimer® ATF ⁷⁾ (homopolymère réticulé de N-vinyl-2-pyrrolidone)	2% (pds/pds)
Véhicule / charge	Kaolin	35% (pds/pds)

1) disponible dans le commerce auprès de ICI Surfactants

2) disponible dans le commerce auprès de Deutsche Shell AG

5 3) disponible dans le commerce auprès de Rhône Poulenc

4) disponible dans le commerce auprès de Kelco Co.

5) disponible dans le commerce auprès de Zeneca

6) disponible dans le commerce auprès de Witco

7) disponible dans le commerce auprès de International

10 Speciality Products

Les compositions selon cette invention peuvent également comprendre d'autres composés possédant une activité biologique, comme par exemple des composés possédant une activité pesticide similaire ou
 15 complémentaire, ou des composés possédant une activité régulatrice de la croissance végétale, fongicide ou insecticide. Ces mélanges de pesticides peuvent avoir un

spectre d'activité plus large que le composé de formule générale I seul. Qui plus est, l'autre pesticide peut avoir un effet synergique sur l'activité pesticide du composé de formule générale I.

5 Les compositions selon cette invention peuvent également comprendre d'autres composés possédant une activité biologique, comme par exemple des composés possédant une activité fongicide similaire ou complémentaire ou des composés possédant une activité
10 régulant la croissance végétale, herbicide ou insecticide.

Ces mélanges de fongicides peuvent avoir un spectre d'activité plus large que le composé de formule générale I seul. Qui plus est, l'autre fongicide peut avoir un effet synergique sur l'activité fongicide du
15 composé de formule générale I.

Les exemples des autres composés fongicides sont l'anilazine, l'azoxystrobine, le béalaxyle, le bénomyle, le binapacryle, le bitertanol, la blasticidine S, la bouillie bordelaise, le bromuconazole, le bupirimate, le
20 captafol, le captane, le carbendazime, la carboxine, le carpropamide, la chlorbenzthiazole, le chlorothalonil, le chlozolinate, les composés contenant du cuivre tels que l'oxychlorure de cuivre et le sulfate de cuivre, le cycloheximide, le cymoxanil, le cypofurame, le
25 cyproconazole, le cyprodinil, le dichlofluanide, la dichlone, le dichlorane, le diclobutrazol, le diclocymet, la diclomézine, le diéthofencarb, le difénoconazole, le diflumétorime, le diméthirimol, le diméthomorphe, le diniconazole, le dinocap, le ditalimfos, la dithianone, le
30 dodémorphe, la dodine, l'édifènephos, l'époxiconazole, l'étaconazole, l'éthirimol, l'étridiazole, la famoxadone, le fénapanil, le fenarimol, le fenbuconazole, le fenfurame, le fenhexamide, le fencpiclonil, la

fenpropidine, le fenpropimorphe, la fentine, l'acétate de
fentine, l'hydroxyde de fentine, la ferimzone, le
fluaziname, le fludioxonil, le flumétover, le
fluquinconazole, le flusilazole, le flusulfamide, le
5 flutolanil, le flutriafol, le folpet, le fosétyl-
aluminium, le fubéridazole, le furalaxyle, le furametpyr,
la guazatine, l'hexaconazole, l'imazalil, l'iminoctadine,
l'ipconazole, l'iprodione, l'isoprothiolane, la
kasugamycine, la kitazine P, le krésoxime - méthyle, le
10 mancozèbe, le manèbe, le mépanipyrime, le mépronil, le
métalaxyle, le metconazole, le methfuroxame, le
myclobutanil, le néoasozine, le diméthylldithiocarbamate de
nickel, le nitrothalisopropyle, le nuarimol, l'ofurace,
les composés organo-mercuriques, l'oxadixyle,
15 l'oxycarboxine, le penconazole, la pencycurone, l'oxyde de
phénazine, le phtalide, la polyoxine D, le polyrame, le
probenazole, le prochloraze, la procymidione, le
propamocarb, le propiconazole, le propinèbe, le
pyrazophos, le pyrifénox, le pyriméthanil, la pyroquilone,
20 le pyroxyfur, le quinométhionate, le quinoxyfène, le
quintozène, la spiroxamine, le SSF-126, le SSF-129, la
streptomycine, le soufre, le tébuconazole, le
tecloftalame, le tecnazène, le tétraconazole, le
thiabendazole, le thifluzamide, le thiophanate - méthyle,
25 le thirame, le tolclofos-méthyle, le tolylfluamide, la
triadiméfon, le triadiménol, le triazbutil, le
triazoxyde, le tricyclazole, le tridémorphe, le
triflumizole, la triforine, le triticonazole, la
validamycine A, la vinclozoline, le XRD-563, le
30 zarilamide, le zinèbe, le zirame.

De plus, les co-formulations selon l'invention
peuvent contenir au moins un composé de formule I et un
quelconque agent des classes suivantes d'agents de

contrôle biologique tels que les virus, les bactéries, les
nématodes, les champignons et les autres micro-organismes
qui sont appropriés pour le contrôle des insectes, des
mauvaises herbes ou des maladies des plantes, ou pour
5 induire une résistance de l'hôte chez les plantes. Les
exemples de tels agents de contrôle biologiques sont:
Bacillus thuringiensis, *Verticillium lecanii*, *Autographa*
californica NPV, *Beauveria bassiana*, *Ampelomyces*
quisqualis, *Bacillus subtilis*, *Pseudomonas fluorescens*,
10 *Streptomyces griseoviridis* et *Trichoderma harzianum*.

Qui plus est, les co-formulations selon
l'invention peuvent contenir au moins un composé de
formule I et un agent chimique qui induit une résistance
systémique acquise chez les plantes tel que par exemple
15 l'acide nicotinique ou des dérivés de celui-ci, l'acide
2,2-dichloro-3,3-diméthylcyclopropanecarboxylique ou le
BION.

Les composés de formule générale I peuvent être
mélangés avec de la terre, de la tourbe ou d'autres
20 milieux d'enracinement pour protéger les plantes contre
les maladies transmises par les graines, contre les
maladies transmises par le sol ou les maladies fongiques
foliaires.

L'invention fournit en outre aussi l'utilisation
25 comme fongicide d'un composé de formule générale I telle
que défini ci-dessus ou d'une composition telle que
définie ci-dessus, et un procédé pour combattre les
champignons en un site, lequel comprend le fait de traiter
le site, qui peut être par exemple des plantes sujettes ou
30 soumises à une attaque fongique, des graines de telles
plantes ou le milieu dans lequel de telles plantes sont
cultivées ou vont être cultivées, avec un tel composé ou
une telle composition.

La présente invention a une large applicabilité pour la protection des plantes de culture et ornementales contre les attaques fongiques. Les cultures typiques qui peuvent être protégées comprennent les vignes, les
5 cultures de graminées telles que le blé et l'orge, le riz, la betterave sucrière, les fruits supérieurs, les arachides, les pommes de terre et les tomates. La durée de la protection dépend normalement du composé individuel choisi, et également de différents facteurs externes tels
10 que le climat dont l'impact est normalement atténué par l'utilisation d'une formulation appropriée.

Les exemples suivants illustrent davantage la présente invention. Il faut cependant comprendre que l'invention n'est pas limitée uniquement aux exemples
15 particuliers donnés ci-dessous.

Exemple 1

Préparation de la 5-chloro-7-(furfur-2-ylméthylthio)-6-
20 phényl-[1,2,4]-triazolo[1,5a]pyrimidine

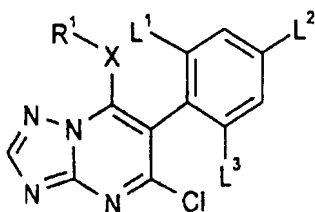
1,2 g (0,01 mol) de fulfurylmercaptan sont ajoutés à une suspension de 1,3 g de NaH (0,01 mol) dans du tétrahydrofurane (THF) et sont chauffés à reflux pendant 2 heures. Le mélange est refroidi jusqu'à la
25 température ambiante, et 2,6 g (0,01 mol) de 5,7-dichloro-6-phényl-[1,2,4]triazolo[1,5a]pyrimidine sont ajoutés. Le mélange résultant est agité pendant 3 heures. Le solvant est évaporé, le résidu est dissous dans de l'acétate d'éthyle, la solution est lavée à l'eau deux fois, et la
30 phase organique est séchée. La solution est filtrée, le solvant est évaporé et le résidu est purifié par chromatographie éclair, ce qui donne le produit sous la forme d'une huile (1,1 g, 32%).

Exemples 2 à 47

Les exemples suivants (Tableau 1; structure et point de fusion) sont synthétisés d'une façon analogue à l'exemple 1.

5

Tableau 1



Exemple	R ¹	X	L ¹	L ²	L ³	Point de fusion (°C)
2	1,4,5,6-tétrahydropyrimid-2-yle	S	H	H	H	212
3	furfur-2-ylméthyle	S	H	OCH ₃	H	huile
4	allyle	S	F	H	Cl	95 - 97
5	cyclopentyle	S	F	H	Cl	105 - 108
6	2,2,2-trifluoroéthyle	S	F	H	Cl	155 - 157
7	isopropyle	S	F	H	Cl	huile
8	1-méthylpropyle	S	F	H	Cl	72 - 75
9	n-propyle	S	F	H	Cl	huile
10	2-méthylpropyle	S	F	H	Cl	93 - 95
11	cyclohexyle	S	F	H	Cl	104 - 105
12	n-butyle	S	F	H	Cl	71 - 72
13	phényle	S	F	H	Cl	129 - 130

14	benzyle	S	F	H	Cl	143 - 146
15	tert-butyle	S	F	H	Cl	104 - 109
16	méthyle	S	F	H	Cl	huile
17	éthyle	S	F	H	Cl	106 - 117
18	4-chlorophényle	S	F	H	Cl	166 - 172
19	2-méthylphényle	S	F	H	Cl	102 - 112
20	2-méthoxyphényle	S	F	H	Cl	136 - 140
21	4-méthoxyphényle	S	F	H	Cl	144 - 148
22	2-chlorophényle	S	F	H	Cl	123 - 127
23	éthyle	O	F	H	Cl	80 - 83
24	cyclopentyle	O	F	H	Cl	106 - 108
25	2,2,2- trifluoroéthyle	O	F	H	Cl	124 - 127
26	allyle	S	F	F	F	
27	cyclopentyle	S	F	F	F	
28	2,2,2- trifluoroéthyle	S	F	F	F	
29	isopropyle	S	F	F	F	
30	1-méthylpropyle	S	F	F	F	
31	n-propyle	S	F	F	F	
32	2-méthylpropyle	S	F	F	F	
33	cyclohexyle	S	F	F	F	
34	n-butyle	S	F	F	F	
35	phényle	S	F	F	F	
36	benzyle	S	F	F	F	
37	tert-butyle	S	F	F	F	
38	méthyle	S	F	F	F	

39	éthyle	S	F	F	F
40	4-chlorophényle	S	F	F	F
41	2-méthylphényle	S	F	F	F
42	2-méthoxyphényle	S	F	F	F
43	4-méthoxyphényle	S	F	F	F
44	2-chlorophényle	S	F	F	F
45	éthyle	O	F	F	F
46	cyclopentyle	O	F	F	F
47	2,2,2-trifluoroéthyle	O	F	F	F

Examens biologiques

Détermination de la concentration minimale inhibitrice pour les composés d'essai par un essai de dilutions

5 successives avec différents champignons phytopathogènes

La valeur de la CMI (Concentration Minimale Inhibitrice), qui indique la concentration la plus faible du principe actif dans le milieu de croissance provoquant une inhibition totale de la croissance mycélienne, est

10 déterminée par des essais de dilutions successives en utilisant des plaques de microtitrage comportant 24 à 48 cupules par plaque. La dilution des composés d'essai dans la solution de nutriments et la distribution dans les cupules sont effectuées par un processeur pour

15 échantillonnage robotisé TECAN RSP 5000. Les concentrations suivantes en composés d'essai sont utilisées: 0,05; 0,10; 0,20; 0,39; 0,78; 1,56; 3,13; 6,25; 12,50; 25,00; 50,00 et 100,00 mg/ml. Pour la préparation de la solution de nutriments, du jus végétal V8 (333 ml)

20 est mélangé avec du carbonate de calcium (4,95 g), puis est centrifugé; le surnageant (200 ml) est dilué avec de

l'eau (800 ml) et mis dans un autoclave à 121°C pendant 30 minutes. Les inocula respectifs (*Alternaria solani*, ALTESO; *Botrytis cinerea*, BOTRCI; *Leptosphaeria nodorum*, LEPTNO; *Phytophthora infestans*, PHYTIN; *Magnaporthe grisea* f.sp. *oryzae*, PYRIOR; *Pyrenophora teres*, PYRNTE; *Rhizoctonia solani*, RHIZSO) sont ajoutées dans les cupules sous la forme de suspensions de spores (50 ml; 5×10^5 /ml) ou sur des tranches de gélose (6 mm) d'une culture sur gélose du champignon. Après 6 à 12 jours d'incubation à des températures appropriées (18 - 25°C), les valeurs de la CMI ont été déterminées par inspection visuelle des plaques (Tableau II; n.t. = non testé).

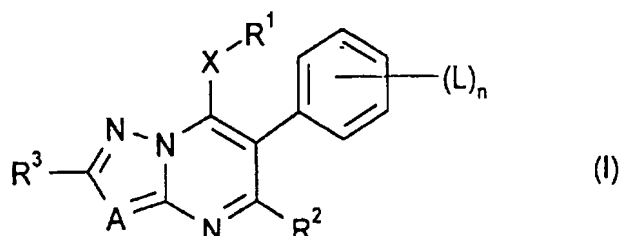
Tableau II

Exemple	ALTESO	BOTRCI	LEPTNO	PHYTIN	PYRIOR	PYRNTE	RHIZSO
4	6,25	12,5	> 100	100	n.t.	100	25
5	1,56	> 100	> 100	> 100	n.t.	> 100	> 100
7	6,25	1,56	> 100	> 100	n.t.	12,5	12,5
8	12,5	3,13	100	> 100	n.t.	> 100	> 100
9	12,5	n.t.	50	> 100	25	> 100	> 100
10	12,5	> 100	25	> 100	25	> 100	> 100
11	12,5	> 100	> 100	50	12,5	> 100	> 100
12	12,5	> 100	25	> 100	25	> 100	> 100
16	> 100	25	100	> 100	25	> 100	> 100
23	25	25	> 100	100	n.t.	50	25
25	25	100	100	1,56	n.t.	12,5	100

REVENDEICATIONS:

5

1. Composé de formule générale I



- R^1 représente un groupe alkyle, alcényle, alcynyle, alcadiényle, aryle, hétéroaryle, cycloaryle, bicycloalkyle ou hétérocyclyle éventuellement substitué,
- R^2 représente un atome d'halogène ou un groupe de formule $-Y-R^4$, où Y représente O, S ou NR^5 ,
- R^3 représente un atome d'hydrogène, ou un groupe alkyle ou aryle,
- R^4 a la signification indiquée pour R^1 ,
- R^5 représente un atome d'hydrogène ou a la signification donnée à R^1 , ou bien R^4 et R^5 , conjointement à l'atome d'azote intercalé entre eux, représente un noyau hétérocyclique,
- L représente un atome d'halogène, ou un groupe alkyle ou alcoxy éventuellement substitué,
- A représente N ou CR^6 , où R^6 a la signification donnée à R^3 ,
- X représente O ou S, et
- n est 0 ou un entier situé entre 1 et 5.

2. Composé selon la revendication 1, dans lequel R^1 représente un groupe alkyle en C_1-C_6 ,

halogénoalkyle en C₁-C₆, ou alcényle en C₂-C₆ ayant une chaîne linéaire ou ramifiée, un cycloalkyle en C₃-C₈ ou un phényle, éventuellement substitué par au moins un substituant choisi dans le groupe constitué d'un atome d'halogène, et d'un groupe alkyle en C₁-C₄ et alcoxy en C₁-C₄.

3. Composé selon la revendication 1, dans lequel R² représente un chlore.

4. Composé selon la revendication 1, dans lequel A est N et R³ est un atome d'hydrogène.

5. Composé selon la revendication 1, choisi dans le groupe constitué:
de la 5-chloro-6-phényl-7-(furfur-2-ylméthylthio)-
[1,2,4]triazolo[1,5a]pyrimidine,
de la 5-chloro-6-phényl-7-(3,4,5,6-tétrahydropyrimid-2-ylthio)-[1,2,4]triazolo[1,5-a]pyrimidine,
de la 5-chloro-6-(4-méthoxyphényl)-7-(furfur-2-ylméthylthio)-[1,2,4]triazolo[1,5-a]pyrimidine,
de la 5-chloro-6-(2-chloro-6-fluorophényl)-7-allylthio-[1,2,4]triazolo[1,5-a]pyrimidine,
de la 5-chloro-6-(2-chloro-6-fluorophényl)-7-cyclopentylthio-[1,2,4]triazolo[1,5-a]pyrimidine,
de la 5-chloro-6-(2-chloro-6-fluorophényl)-7-(2,2,2-trifluoroéthylthio)-[1,2,4]triazolo[1,5-a]pyrimidine,
de la 5-chloro-6-(2-chloro-6-fluorophényl)-7-(isopropylthio)-[1,2,4]triazolo[1,5-a]pyrimidine,

- de la 5-chloro-6-(2-chloro-6-fluorophényl)-7-(1-méthylpropylthio)-[1,2,4]triazolo[1,5-a]pyrimidine,
de la 5-chloro-6-(2-chloro-6-fluorophényl)-7-propylthio[1,2,4]triazolo[1,5-a]pyrimidine,
5 de la 5-chloro-6-(2-chloro-6-fluorophényl)-7-(2-méthylpropylthio)-[1,2,4]triazolo[1,5-a]pyrimidine,
de la 5-chloro-6-(2-chloro-6-fluorophényl)-7-cyclohexylthio-[1,2,4]triazolo[1,5-a]pyrimidine,
de la 5-chloro-6-(2-chloro-6-fluorophényl)-7-butylthio-
10 [1,2,4]triazolo[1,5-a]pyrimidine,
5-chloro-6-(2-chloro-6-fluorophényl)-7-phénylthio-[1,2,4]triazolo[1,5-a]pyrimidine,
de la 5-chloro-6-(2-chloro-6-fluorophényl)-7-tert-butylthio-[1,2,4]triazolo[1,5-a]pyrimidine,
15 de la 5-chloro-6-(2-chloro-6-fluorophényl)-7-méthylthio-[1,2,4]triazolo[1,5-a]pyrimidine,
de la 5-chloro-6-(2-chloro-6-fluorophényl)-7-éthylthio-[1,2,4]triazolo[1,5-a]pyrimidine,
de la 5-chloro-6-(2-chloro-6-fluorophényl)-7-(4-chlorophénylthio)-[1,2,4]triazolo[1,5-a]pyrimidine,
20 de la 5-chloro-6-(2-chloro-6-fluorophényl)-7-(2-méthylphénylthio)-[1,2,4]triazolo[1,5-a]pyrimidine,
de la 5-chloro-6-(2-chloro-6-fluorophényl)-7-(2-méthoxyphénylthio)-[1,2,4]triazolo[1,5-a]pyrimidine,
25 de la 5-chloro-6-(2-chloro-6-fluorophényl)-7-(4-méthoxyphénylthio)-[1,2,4]triazolo[1,5-a]pyrimidine,
de la 5-chloro-6-(2-chloro-6-fluorophényl)-7-(2-chlorophénylthio)-[1,2,4]triazolo[1,5-a]pyrimidine,
de la 5-chloro-6-(2-chloro-6-fluorophényl)-7-éthoxy-
30 [1,2,4]triazolo[1,5-a]pyrimidine,
de la 5-chloro-6-(2-chloro-6-fluorophényl)-7-cyclopentyloxy-[1,2,4]triazolo[1,5-a]pyrimidine,

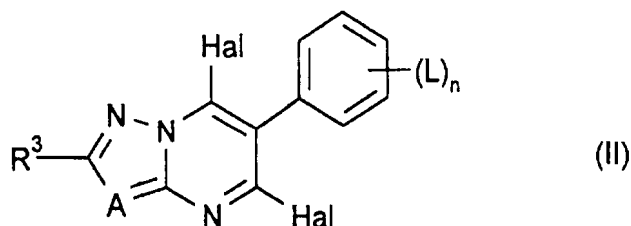
- de la 5-chloro-6-(2-chloro-6-fluorophényl)-7-(2,2,2-trifluoroéthoxy)-[1,2,4]triazolo[1,5-a]pyrimidine,
5-chloro-7-allylthio-6-(2,4,6-trifluorophényl)-[1,2,4]triazolo[1,5-a]pyrimidine,
- 5 de la 5-chloro-7-cyclopentylthio-6-(2,4,6-trifluorophényl)-[1,2,4]triazolo[1,5-a]pyrimidine,
de la 5-chloro-7-(2,2,2-trifluoroéthylthio)-6-(2,4,6-trifluorophényl)-[1,2,4]triazolo[1,5-a]pyrimidine,
de la 5-chloro-7-(isopropylthio)-6-(2,4,6-
- 10 trifluorophényl)-[1,2,4]triazolo[1,5-a]pyrimidine,
de la 5-chloro-7-(1-méthylpropylthio)-6-(2,4,6-trifluorophényl)-[1,2,4]triazolo[1,5-a]pyrimidine,
de la 5-chloro-7-propylthio-6-(2,4,6-trifluorophényl)-[1,2,4]triazolo[1,5-a]pyrimidine,
- 15 de la 5-chloro-7-(2-méthylpropylthio)-6-(2,4,6-trifluorophényl)-[1,2,4]triazolo[1,5-a]pyrimidine,
de la 5-chloro-7-cyclohexylthio-6-(2,4,6-trifluorophényl)-[1,2,4]triazolo[1,5-a]pyrimidine,
de la 5-chloro-7-butylthio-6-(2,4,6-trifluorophényl)-
- 20 [1,2,4]triazolo[1,5-a]pyrimidine,
de la 5-chloro-7-phénylthio-6-(2,4,6-trifluorophényl)-[1,2,4]triazolo[1,5-a]pyrimidine,
de la 5-chloro-7-bentylthio-6-(2,4,6-trifluorophényl)-[1,2,4]triazolo[1,5-a]pyrimidine,
- 25 de la 5-chloro-7-tert-butylthio-6-(2,4,6-trifluorophényl)-[1,2,4]triazolo[1,5-a]pyrimidine,
de la 5-chloro-7-méthylthio-6-(2,4,6-trifluorophényl)-[1,2,4]triazolo[1,5-a]pyrimidine,
de la 5-chloro-7-éthylthio-6-(2,4,6-trifluorophényl)-
- 30 [1,2,4]-triazolo[1,5-a]pyrimidine,
de la 5-chloro-6-(2,4,6-trifluorophényl)-7-(4-chlorophénylthio)-[1,2,4]triazolo[1,5-a]pyrimidine,

de la 5-chloro-6-(2,4,6-trifluorophényl)-7-(2-méthylphénylthio)-[1,2,4]triazolo[1,5-a]pyrimidine,
 de la 5-chloro-6-(2,4,6-trifluorophényl)-7-(2-méthoxyphénylthio)-[1,2,4]triazolo[1,5-a]pyrimidine,
 5 de la 5-chloro-6-(2,4,6-trifluorophényl)-7-(4-méthoxyphénylthio)-[1,2,4]triazolo[1,5-a]pyrimidine,
 de la 5-chloro-6-(2,4,6-trifluorophényl)-7-(2-chlorophénylthio)-[1,2,4]triazolo[1,5-a]pyrimidine,
 de la 5-chloro-6-(2,4,6-trifluorophényl)-7-éthoxy-
 10 [1,2,4]triazolo[1,5-a]pyrimidine,
 de la 5-chloro-6-(2,4,6-trifluorophényl)-7-cyclopentyloxy-[1,2,4]triazolo[1,5-a]pyrimidine, et
 de la 5-chloro-6-(2,4,6-trifluorophényl)-7-(2,2,2-trifluoroéthoxy)-[1,2,4]triazolo[1,5-a]pyrimidine.

15

6. Procédé de préparation d'un composé de formule I tel que défini dans l'une quelconque des revendications précédentes, qui comprend:

20 (a) la mise en réaction d'un composé de formule générale II



dans laquelle R³, A, L et n ont la signification indiquée pour la formule I, et Hal représente un atome d'halogène,
 25 avec un composé de formule III



dans laquelle R¹ et X ont la signification indiquée pour la formule I, en présence d'une base; et

(b) éventuellement le traitement de la 5-halogénotriazolopyrimidine résultante avec un alcool, un thiol ou une amine de formule R^4 -YH, dans laquelle R^4 et Y ont la signification indiquée pour la formule I, en
5 présence d'une base.

7. Composition fongicide qui comprend un véhicule, et comme principe actif, au moins un composé de
10 formule I tel que défini dans l'une quelconque des revendications 1 à 5.

8. Procédé pour combattre les champignons en un
15 site qui comprend le traitement du site avec un composé de formule I, tel que défini dans l'une quelconque des revendications 1 à 5, ou avec une composition telle que définie dans la revendication 7.

PATENT SPECIFICATION

(11) 1 412 017

1 412 017

- (21) Application No. 55587/72 (22) Filed 1 Dec. 1972
- (31) Convention Application No. 206 538 (32) Filed 9 Dec. 1971
- (31) Convention Application No. 245 870 (32) Filed 20 April 1972
- (31) Convention Application No. 273 465 (32) Filed 20 July 1972
- (31) Convention Application No. 299 840 (32) Filed 24 Oct. 1972 in
- (33) United States of America (US)
- (44) Complete Specification published 29 Oct. 1975
- (51) INT CL² C07D 487/02 // A61K 31/505 (C07D 487/02, 231/38, 239/42, 295/00)



- (52) Index at acceptance
- C2C 1400 1407 1532 20Y 214 215 220 226 22Y 246 247
- 250 251 252 25Y 271 280 281 28X 29X 29Y 305
- 30Y 311 313 314 315 31Y 321 322 323 326 327
- 32Y 332 337 342 34Y 350 351 352 355 35Y 360
- 361 364 366 367 368 36Y 373 376 37X 37Y 386
- 43X 440 443 449 451 453 456 45X 45Y 464 470
- 471 500 50Y 551 574 579 601 614 620 621 623
- 624 625 628 62X 62Y 634 650 652 658 65X 670
- 671 672 675 676 677 678 679 680 681 68Y 698
- 708 73Y 744 761 765 776 777 77Y 790 79Y BC
- KF LE LT MD ML NF NG NL NR NT QL
- TN UK WC ZB ZF

(54) PYRAZOLO[1,5a]PYRIMIDINES

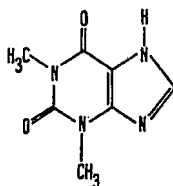
(71) We, ICN PHARMACEUTICALS INC. (previously known as International Chemical & Nuclear Corporation), a Corporation organised and existing under the Laws of the State of California, United States of America, of 171 South Lake Avenue, Pasadena, State of California, United States of America, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to certain pyrazolo (1,5a) pyrimidines and to a process for the production thereof.

As reported by Sutherland et al in "Cyclic AMP", *Am. Rev. Biochem.* 37, 149 (1968), cyclic adenosine monophosphate (C—AMP) has been established as an intracellular "second messenger", mediating many of the actions of a variety of different hormones. According to this theory, first messenger hormones, epinephrine and norepinephrine, influence adenyl cyclase contained at or within cell walls to form intracellular cyclic AMP from adenosine triphosphate upon receipt of the extracellular hormone signal. The formed cyclic AMP in turn functions as a second messenger and stimulates the intracellular functions peculiar to the target cells of the hormone. Cyclic AMP has thus been shown to "activate" protein kinases, which in turn produce physiological effects such as muscle contraction, glycogenolysis, steroidogenesis and dipolysis.

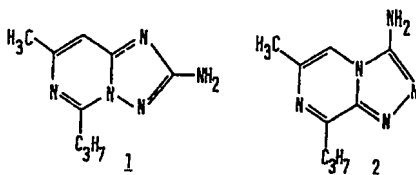
Cyclic AMP is degraded, however *in vivo* by phosphodiesterase enzymes, which catalyze hydrolysis of the cyclic purine nucleotide to 5'-adenosine monophosphate with a consequent loss of function. It has accordingly been suggested that substituted cyclic AMP analogs which are more resistant to phosphodiesterase degradation than the naturally occurring cyclic nucleotide might be administered to aid lagging cellular processes. Synthetic production of such compounds, however, is quite costly. It would be advantageous, therefore, to enhance the beneficial effects of naturally produced cyclic AMP by administering compounds which are capable of inhibiting the undesirable effects of phosphodiesterase enzymes.

Sutherland, et al, in *Circulation* 37, 279 (1968), suggests that the pharmacological effects of theophylline, which has the structure



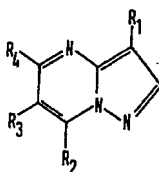
are the result of its ability to inhibit the action of phosphodiesterase enzymes. Theophylline has thus been employed in lieu of the adenylyl cyclase-stimulating hormones, epinephrine and norepinephrine, as a heart stimulant following cardiac arrest and in refractory asthma cases as a bronchial dilator. Theophylline, however, does not selectively inhibit phosphodiesterase, but rather gives general stimulation to the central nervous system. Accordingly, the use of theophylline can make the recipient nervous and irritable and can also create cardiovascular effects, i.e., rapid beating of the heart. By the same token, theophylline is not as potent as phosphodiesterase inhibitor as is desired and consequently has to be used in larger quantities, which, of course, can further the undesirable effects enumerated above.

F. L. Rose et al, in articles appearing in *J. Chem. Soc.* 5642 (1963), 3357 (1965) and 1593 (1969), reported a number of triazolo[2,3c]pyrimidines and triazolo[4,3c]pyrazines (for example, compounds 1 and 2 shown below) which are structurally related to theophylline and capable of protecting animals from histamine-induced bronchospasm.



Pursuing an idea that the pharmacological effects of compounds 1 and 2 might be the result of the same biochemical mechanism as proposed for theophylline, various substituted-pyrazolo[1,5a]pyrimidines were prepared and found to possess the ability to inhibit the enzyme 3',5'-cyclic AMP phosphodiesterase. Further evaluation of these compounds has also revealed that many of these phosphodiesterase inhibitors possess significant pharmacological properties, particularly in the cardiovascular area. For example, 3-bromo-5,7-dimethylpyrazolo[1,5a]pyrimidine and 3-bromo-5-methyl-7-n-propylpyrazolo[1,5a]pyrimidine not only are significantly more active than theophylline against various phosphodiesterase enzymes, but also have the ability to produce a positive inotropic effect in an anesthetized dog without significantly altering heart rate or blood pressure.

According to the present invention there is provided a compound of the structure



wherein R_1 is H, alkoxycarbonyl, alkyl, carbonitrile, halogen, carbamoyl, acyl, aminomethyl, dialkylaminomethyl, nitro, amino, or acetamido; R_2 is alkyl, C_1 to C_8 linear or branched chain alkoxy, C_1 to C_6 alkylthio, SH , or alkyl or dialkylamino, cyclic amino or substituted amino; R_3 is H; and R_4 is H, alkyl, or phenyl; provided that when R_2 and R_4 are methyl, R_1 is not H or carbethoxy; when R_4 is CH_3 and R_2 is methoxy or ethoxy, R_1 is not H; and when R_2 is CH_3 , R_4 and R_1 are not both H; and when R_2 is hydrazino and R_4 is phenyl, R_1 is not H.

Unless otherwise indicated the alkyl substituents preferably contain from 1 to 8 carbon atoms, more preferably from 1 to 6 carbon atoms, and may be branched or linear groups. The alkoxy substituents are C_1 to C_8 , but preferably C_1 to C_4 , linear or branched alkoxy groups. Where R_2 in an alkylthio group, groups having from 1 to 3

carbon atoms are especially preferred. Suitable substituted amino groups are dialkoxyalkylamino, carboxyalkylamino, hydroxyalkylamino, hydrazyl or alkylidenohydrazyl groups, while suitable cyclic amino groups include the morpholino group and the piperidino group.

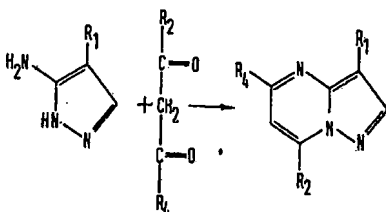
5 The compounds of this invention and the general procedure utilized in preparing the same are illustrated and will be described in conjunction with the schematic drawings which follow. The starting materials utilized in this invention are 3-aminopyrazole (1), 3-amino-4-carbethoxypyrazole (2), 3-amino-4-cyanopyrazole (3), 3-amino-4-pyrazolecarboxamide (4), 3-amino-4-ethylpyrazole (5), 3-amino-4-bromopyrazole (6), and 3-amino-4-nitropyrazole (7). All of these starting materials have been previously reported in the literature with the exception of 3-amino-4-ethylpyrazole (5), which is prepared in the following manner. The base catalyzed condensation of *n*-butyronitrile with ethyl formate affords α -formyl-*n*-butyronitrile, which when treated *in situ* with hydrazine hydrate, affords 3-amino-4-ethylpyrazole (5) as a colorless oil.

10

15 For convenience, only certain compounds related to those of the invention have been included in the description which follows.

15

REACTION SCHEME I



- | | |
|---|--|
| (1) R ₁ = H | (8) R ₂ = R ₄ = CH ₃ ; R ₁ = H |
| (2) R ₁ = COOC ₂ H ₅ | (9) R ₂ = R ₄ = CH ₃ ; R ₁ = COOC ₂ H ₅ |
| (3) R ₁ = C ≡ N | (10) R ₂ = R ₄ = CH ₃ ; R ₁ = C ≡ N |
| (4) R ₁ = CONH ₂ | (11) R ₂ = R ₄ = CH ₃ ; R ₁ = CH ₂ -NH ₂ |
| (5) R ₁ = C ₂ H ₅ | (12) R ₂ = R ₄ = CH ₃ ; R ₁ = CONH ₂ |
| | (13) R ₂ = R ₄ = CH ₃ ; R ₁ = C ₂ H ₅ |
| | (14) R ₂ = R ₄ = C ₂ H ₅ ; R ₁ = H |
| | (15) R ₂ = R ₄ = C ₃ H ₇ ; R ₁ = H |

20 The general procedure for preparation of the 5,7-dialkylpyrazolo[1,5a]pyrimidines follows the work of Y. Makisumi, *Chem. Pharm. Bull.* (Tokyo), 10, 612 (1962), and is depicted in Reaction Scheme I. 3-Aminopyrazole (1) and 3-amino-4-carbethoxypyrazole (2) are condensed with pentane-2,4-dione to provide 5,7-dimethylpyrazolo[1,5a]pyrimidine (8) and the corresponding 3-carbethoxy derivative (9). This reaction has been extended to include the additional 3-amino-4-substituted pyrazoles (3, 4, and 5) to provide the 3-cyano (10), 3-carboxamido (12), and 3-ethyl (13) derivatives of 5,7-dimethylpyrazolo[1,5a]pyrimidine. The catalytic reduction of 3-cyano-5,7-dimethylpyrazolo[1,5a]pyrimidine (10) affords the corresponding 3-amino-ethyl-5,7-dimethylpyrazolo[1,5a]pyrimidine (11). Additionally, it has been found that the condensation of 3-aminopyrazole (1) with heptane-3,5-dione and nonane-4,6-dione affords excellent yields of 5,7-diethylpyrazolo[1,5a]pyrimidine (14) and 5,7-di-*n*-propylpyrazolo[1,5a]pyrimidine (15), respectively.

25

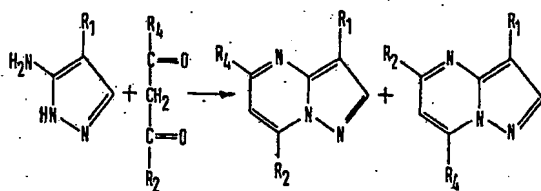
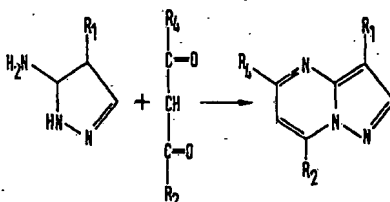
30

The reaction scheme shows the conversion of a 1,2,3,4-tetrahydroquinazolin-2-ylidene derivative to a quinazolin-2-ylidene derivative. The starting material on the left is a bicyclic system with a four-membered ring fused to a six-membered ring. The four-membered ring has a double bond and a nitrogen atom. The six-membered ring has a nitrogen atom at the 2-position and substituents R₁ at the 4-position, R₂ at the 6-position, and R₄ at the 8-position. An arrow points to the product on the right, which is a quinazolin-2-ylidene derivative. The product has a fused bicyclic system with a six-membered ring fused to a five-membered ring. The six-membered ring has a nitrogen atom at the 2-position and substituents R₁ at the 4-position, R₂ at the 6-position, and R₄ at the 8-position. The five-membered ring has a double bond and a nitrogen atom.

- $$\begin{array}{ll}
 (8) \quad R_2 = R_4 = \text{CH}_3; R_1 = \text{H} & (16) \quad R_2 = R_4 = \text{CH}_3; R_1 = \text{Br} \\
 (14) \quad R_2 = R_4 = \text{C}_2\text{H}_5; R_1 = \text{H} & (17) \quad R_2 = R_4 = \text{CH}_3; R_1 = \text{Cl} \\
 (15) \quad R_2 = R_4 = n\text{-C}_3\text{H}_7; R_1 = \text{H} & (18) \quad R_2 = R_4 = \text{CH}_3; R_1 = \text{I} \\
 & (19) \quad R_2 = R_4 = \text{CH}_3; R_1 = \text{F} \\
 & (20) \quad R_2 = R_4 = \text{CH}_3; R_1 = \text{COCH}_3 \\
 & (21) \quad R_2 = R_4 = \text{CH}_3; R_1 = \text{CH}_2\text{-N(CH}_3)_2 \\
 & (22) \quad R_2 = R_4 = \text{CH}_3; R_1 = \text{NO}_2 \\
 & (23) \quad R_2 = R_4 = \text{CH}_3; R_1 = \text{NH}_2 \\
 & (24) \quad R_2 = R_4 = \text{CH}_3; R_1 = \text{NHCOCH}_3 \\
 & (25) \quad R_2 = R_4 = \text{C}_2\text{H}_5; R_1 = \text{Br} \\
 & (26) \quad R_2 = R_4 = n\text{-C}_3\text{H}_7; R_1 = \text{Br}
 \end{array}$$

The 3-unsubstituted-5,7-dialkylpyrazolo[1,5a]pyrimidines (8, 14, and 15) readily undergo electrophilic attack at the 3-position as shown in Reaction Scheme II. The treatment of the 5,7-dialkylpyrazolo[1,5a]pyrimidines (8, 14, or 15) with N-bromosuccinimide results in the formation of 3-bromo-5,7-dialkylpyrazolo[1,5a]pyrimidines (16, 25, 26). Additionally, it has been found that the treatment of (8) with N-chlorosuccinimide or with iodine monochloride results in the formation of the 3-chloro (17) and the 3-iodo (18) derivatives of 5,7-dimethylpyrazolo[1,5a]pyrimidine. The reaction of 5,7-dimethylpyrazolo[1,5a]pyrimidine (8) with trifluoroacetic acid and boron trifluoride etherate has been found to afford 5,7-dimethyl-3-fluoro-pyrazolo[1,5a]pyrimidine (19). Friedel-Crafts acylation of 5,7-dimethylpyrazolo[1,5a]pyrimidine (8) affords 3-acetyl-5,7-dimethylpyrazolo[1,5a]pyrimidine (20) in 61% yields. When compound 8 is treated with an aqueous solution of dimethylamine and formalin solution, 5,7-dimethyl-3-dimethylaminomethylpyrazolo[1,5a]pyrimidine (21) is obtained. Finally, nitration of compound 8 affords the expected 5,7-dimethyl-3-nitropyrazolo[1,5a]pyrimidine (22). Reduction of compound 22 with palladium or charcoal catalyst affords the corresponding 3-amino-5,7-dimethylpyrazolo[1,5a]pyrimidine (23), which when treated with acetic anhydride results in the formation of the 3-acetamido derivative (24). The site of electrophilic attack at position 3 in these 5,7-dialkylpyrazolo[1,5a]pyrimidines has been proven by the proton magnetic resonance spectra, since the up-field proton at 6.60% (which is coupled to the proton at 8.11%; $J=0.0066\%$) found in 5,7-dimethylpyrazolo[1,5a]pyrimidine (8) is absent in these 3-substituted derivatives.

REACTION SCHEME III

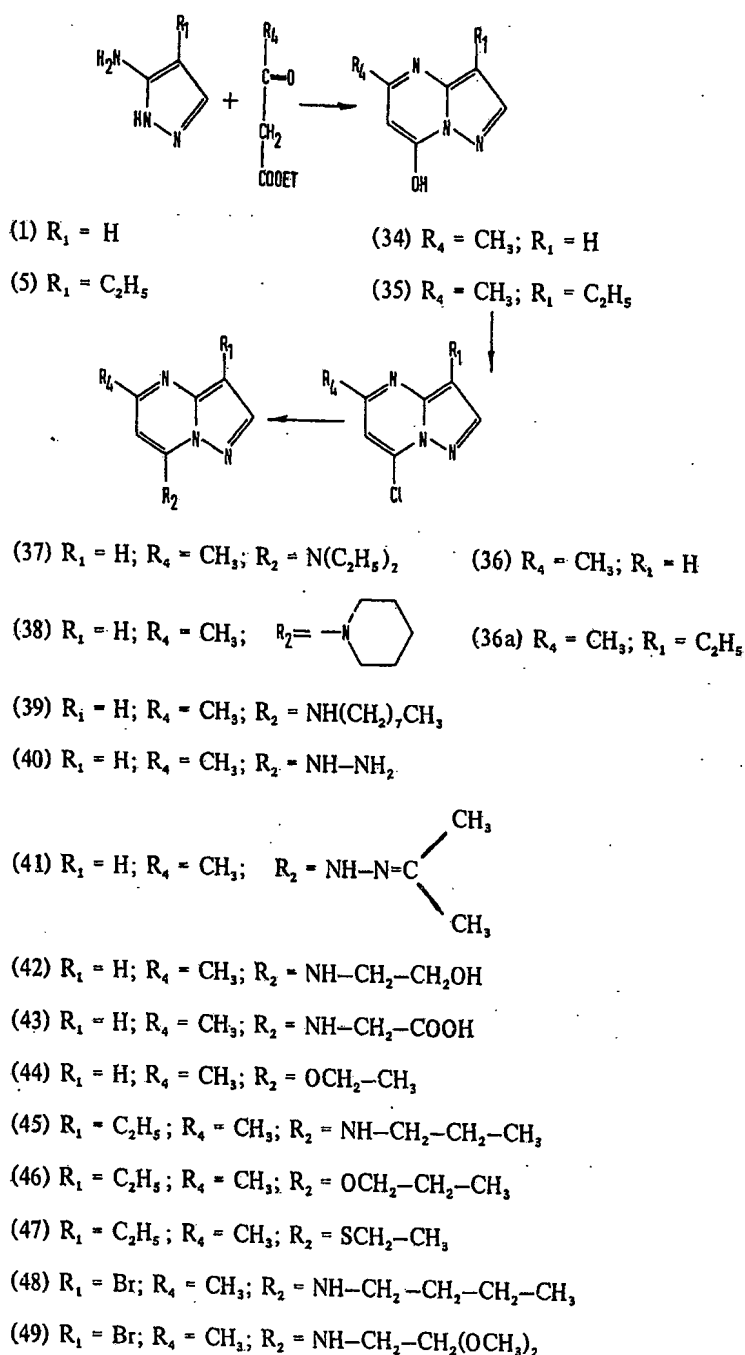
(1) $R_1 = H$ (27a) $R_2 = CH_3$; $R_4 = C_2H_5$; $R_1 = H$ (27b) $R_2 = CH_3$; $R_4 = C_3H_7$; $R_1 = H$ (28a) $R_2 = C_2H_5$; $R_4 = CH_3$; $R_1 = H$ (28b) $R_2 = n-C_3H_7$; $R_4 = CH_3$; $R_1 = H$ (2) $R_1 = COOC_2H_5$ (29) $R_2 = C_2H_5$; $R_4 = CH_3$; $R_1 = Br$ (30) $R_2 = n-C_3H_7$; $R_4 = CH_3$; $R_1 = Br$ (31) $R_2 = C_2H_5$; $R_4 = CH_3$; $R_1 = NO_2$ (32) $R_2 = C_2H_5$; $R_4 = CH_3$; $R_1 = COOC_2H_5$ (33) $R_2 = CH_3$; $R_4 = C_6H_5$; $R_1 = H$

The condensation of 3-aminopyrazole (1) with unsymmetrical β -diketones is shown in Reaction Scheme III. The reaction of 3-aminopyrazole (1) with hexane-2,4-dione affords a mixture of the isomers 27a and 28a. Because of similarity of the physical properties of these two isomers, separation is difficult and for that reason the crude isomeric mixture of 27a and 28a was converted into higher melting derivatives (29) and (31), which may be isolated by column chromatography and fractional recrystallization techniques. Similarly, condensation of 3-aminopyrazole (1) with heptane-2,4-dione affords a mixture of the isomers 27b and 28b, which, when treated with N-bromosuccinimide, affords 3-bromo-5-methyl-7-n-propylpyrazolo[1,5a]pyrimidine (30) which is purified by chromatography. The condensation of 3-amino-4-carboxypyrazole (2) with hexane-2,4-dione results in a mixture of isomeric products; however, 3-carboxy-7-ethyl-5-methylpyrazolo[1,5a]pyrimidine (32) has been found to be the predominate isomer. By the same token, condensation of 1-phenyl-1,3-butane-dione with 3-aminopyrazole (1) yields an isomeric product which may be recrystallized without chromatography to yield 7-methyl-5-phenylpyrazolo[1,5a]pyrimidine (33). That this isomer was obtained rather than 5-methyl-7-phenylpyrazolo[1,5a]pyrimidine was demonstrated by comparison of physical data (proton magnetic resonance spectra, ultra-violet spectra, and melting point) with the 5-methyl isomer that was previously reported by H. Dorn et al, *J. Prakt. Chem.*, 313, 969 (1971).

5 The structural assignment of compounds 29—32 is based on the proton magnetic
resonance spectra of the well separated C₅ and C₇ methyl signals. It has been demon-
strated [H. Reimlinger, *Chem. Ber.*, 103, 1900 and 3252 (1970), 104, 2232 and 2237
(1971)] that in 5,7-dimethylpyrazolo[1,5a]pyrimidine (8) the C₇ methyl signal,
10 being adjacent to the bridgehead nitrogen, is deshielded to a greater extent than the
C₅ methyl signal (adjacent the N₄ nitrogen) and thus occurs at a lower field. The
assignments are 2.568 for C₅-methyl and 2.738 for the C₇-methyl in deuteriochloroform.
Since the replacement of a longer alkyl chain (e.g. ethyl or propyl) for one methyl
group at either C₅ or C₇ would not be expected to change the chemical shift of the
15 remaining methyl group, the 5-methyl-7-alkyl isomer can be distinguished from the
7-methyl-5-alkyl isomer via pmr (in deuteriochloroform) and the percentage of each
isomer in the isomeric mixture can be estimated from the integration of the signals.
Similarly, the C₅-methyl signal occurs at 2.608 and the C₇-methyl signal at 2.728
(in deuteriochloroform) for the pmr of 3-bromo-5,7-dimethylpyrazolo[1,5a]pyrimidine
(16), thus permitting identification of the separated products 29 and 30 from the
bromination (and subsequent chromatography) of the isomeric mixtures 27a and
28b or 27b and 28b.

20 The condensation of 3-amino-4-substitutedpyrazoles with β -ketoesters is shown
in Reaction Scheme IV. Following the procedure described by Y. Makisumi, *Chem.*
Pharm. Bull. (Tokyo), 10, 612 and 620 (1962), 3-aminopyrazole (1) was condensed
with acetoacetic ester to obtain 5-methyl-7-hydroxypyrazolo[1,5a]pyrimidine (34)
which, when treated with phosphorus oxychloride, results in the formation of 7-chloro-
5-methylpyrazolo[1,5a]pyrimidine (36). These reactions have been extended to 3-
25 amino-4-ethylpyrazole (5) to afford 3-ethyl-7-hydroxy-5-methylpyrazolo[1,5a]pyr-
imidine (35) and the corresponding 7-chloro-3-ethyl-5-methylpyrazolo[1,5a]-
pyrimidine 36a. The chloro moieties of compounds 36 and 36a are quite susceptible
to nucleophilic displacement when treated with various nucleophilic reagents.

REACTION SCHEME IV



Thus, the treatment of compounds 36 or 37 with various amines, sodium alkoxides, and sodium alkylmercaptides results in the formation of the 7-substituted derivatives 37 to 40 and 42 to 47. The reaction of 7-hydrazino-5-methylpyrazolo[1,5a]pyrimidine (40) with acetone in ethanolic hydrogen chloride results in the formation of the isopropylidene derivative (41). These 5-methyl-7-substitutedpyrazolo[1,5a]pyrimidines readily undergo electrophilic attack at the 3 position. Thus, in this manner, the 3-bromo-5-methyl-7-substitutedaminopyrazolo[1,5a]pyrimidines (48) and (49) have been prepared.

The invention will now be further described and illustrated in the following Examples (aside from Example I which merely serves to illustrate the preparation of one starting material, 3-amino-4-ethylpyrazole) in which all parts and percentages are by weight and all temperatures in degrees Centigrade unless otherwise indicated. Melting points were taken on a Thomas-Hoover melting point apparatus and are uncorrected. Infra-red and nuclear magnetic resonance spectra were determined on a Perkin-Elmer 257 grating infra-red spectrophotometer and on a Hitachi Perkin-Elmer R-20A high resolution nuclear magnetic resonance spectrophotometer, respectively. (Hitachi is a Registered Trade Mark). Hydrogenations were carried out on a Parr hydrogenator at room temperature and at a starting pressure of 42 lbs/in² of hydrogen. All samples displayed a single spot on thin layer chromatography and were analyzed by the Heterocyclic Chemical Corporation of Harrisonville, Missouri. Where analyses are indicated only by symbols of the elements or functions, analytical results obtained for those elements or functions were within $\pm 0.4\%$ of the theoretical values.

Examples XXV to XXIX relate to the preparation of intermediate derivatives.

EXAMPLE I.

Preparation of 3-Amino-4-ethylpyrazole (5)

A suspension of sodium metal [53.0g; 2.31 formula weights] in 1500 ml of anhydrous ether was stirred at 20° while a mixture of ethyl formate [180.0g; 2.43 moles] and *n*-butyronitrile [158.0g; 2.31 moles] was added dropwise over a period of two hours. After the addition was complete, the mixture was stirred at 20–25° for two days at which time the sodium metal was completely reacted. The reaction mixture was cooled to 10° and neutralized by the dropwise addition of glacial acetic acid [138.0g; 2.31 moles]. The temperature of the mixture during neutralization was maintained at 10–15°. The solids were separated by filtration and the filtrate evaporated to dryness at reduced keeping the temperature below 20°. The resulting crude α -formyl *n*-butyronitrile was utilized directly for the formation of 3-amino-4-ethylpyrazole (7) without further purification.

The crude α -formyl *n*-butyronitrile was dissolved in 200 ml of ethanol and treated with 85% hydrazine hydrate [118g; 2.0 formula weights] and 36 ml of glacial acetic acid. The resulting solution was heated at reflux for two hours and then evaporated to dryness. The residual oil was purified by distillation at 0.2mm (Hg.). The fraction that had a boiling point of 120–4° was collected. This fraction weighed 55.2g (21%) and was found to be analytically pure 3-amino-4-ethylpyrazole (7). Analysis corresponds to that calculated for C₈H₉N₃: (C, H).

EXAMPLE II.

5-7-Dimethyl pyrazolo[1,5a]pyrimidine-3-carbonitrile (10)

A solution of 7.25g (0.067 moles) 3-amino-4-cyanopyrazole [R.K. Robins, J.A.C.S. 78, 788 (1956)], acetylacetone [7.00 g (0.07 moles)], piperidine (10 drops) in 100 ml of EtOH was heated at reflux. After refluxing 6 hrs. the solution was allowed to cool slowly, whereupon crystallization occurred. The product was separated by filtration and recrystallized from EtOH to afford 6.00 g. (52%) of analytically pure product; mp 165–7°.

Anal. corresponds to that calculated for (C₉H₈N₄) C, H, N.

IR. (KBr) 2250 cm⁻¹ (CN)

EXAMPLE III.

3-Aminomethyl-5,7-dimethyl pyrazolo[1,5a]pyrimidine hydrochloride (II)

To a solution of the carbonitrile product of Example II (1.00 g) in 150 ml of EtOH was added 5 ml of HCl (12N) and 0.25g of 10% Pd/C catalyst. The resulting mixture was hydrogenated at room temperature for 16 hrs. The mixture was filtered through Celite and evaporated to dryness at reduced pressure. (Celite is a Registered Trade Mark). The gummy semi-solid was dissolved in water (25 ml), made basic by the addition of NaOH solution (1N), and extracted into CHCl₃ solution, and after drying, was chromatographed on basic alumina. Evaporation of the CHCl₃ eluant afforded a colorless solid (mp 119–20°) that rapidly became colored. The hydrochloride of the solid was prepared by dissolving the same in Et₂O and adding HCl gas; mp 265–7° (dec).

Anal. Corresponds to that calculated for (C₉H₁₂N₄ · HCl) C, H, N.

EXAMPLE IV.

5,7-Dimethyl pyrazolo[1,5a]pyrimidine-3-carboxamide (12)

A mixture of 1.00g (5.7 mmoles) 3-amino-4-carbamoylpyrazole, hemisulfate [R.K. Robins, J.A.C.S. 78, 788 (1956)], acetylacetone [0.60g (6.0 mmoles)], piperidine (1.5g) in 40 ml of EtOH was heated at reflux. After refluxing 16 hrs. the solution was allowed to cool. The crystalline product was recrystallized from EtOH to yield 0.90g (83%) of analytically pure product; mp 247—8° (dec).

Anal. Corresponds to that calculated for (C₉H₁₀N₄O) C, H, N.

IR. (KBr) 1665 cm⁻¹ (CONH₂)

NMR. (d₆-DMSO) singlets in a ratio of 3:3:1:2:1, with chemical shifts of 2.62δ (CH₃), 2.75δ (CH₃), 7.1δ and 8.52δ (ring protons), and 7.50δ (broad, NH₂ of amide).

EXAMPLE V.

Preparation of 5,7-Dimethyl-3-Ethylpyrazolo[1,5a]Pyrimidine (13)

A solution of 3-amino-4-ethylpyrazole (1) [1.0g; 10 mmoles], 2,4-pentanedione [1.0g; 9 mmoles], and 3 drops of piperidine in 5 ml of absolute ethanol was heated at reflux for 12 hours. The resulting solution was evaporated to dryness, and the residual oil was purified by column chromatography on silica gel (50g) utilizing a mixture of 30—60° petroleum ether: chloroform (7:3) as the solvent. Evaporation of the solvent afforded 1.3g (82%) of analytically pure 5,7-dimethyl-3-ethylpyrazolo[1,5a]pyrimidine (5) as a colorless oil.

Anal. Corresponds to that calculated for (C₁₀H₁₃N₃) C, H, N

EXAMPLE VI.

5,7-Diethylpyrazolo[1,5a]pyrimidine (14)

This compound was prepared from 6.5 g (0.05 mol) of heptane-3,5-dione and the yield of chromatographed material (white needles, m.p. 43—44°C from petroleum ether was 6.3 g (72%).

Anal. calcd for C₁₀H₁₃N₃ (MW 175): C, 68.54; H, 7.48; N, 23.98;

Found: C, 68.52; H, 7.58; N, 24.25

NMR(CDCl₃) m, 1.4δ (both C₆-ethyl and C₇-ethyl triplets); m, 3.1δ (both C₆-ethyl and C₇-ethyl quartets); s, 6.58δ (C₅-H); s, 6.6δ (C₈-H) and s, 8.1δ (C₂-H), the latter two protons being coupled with J_{2,8}=1.9 cps.

EXAMPLE VII.

5,7-Di-n-propylpyrazolo[1,5a]pyrimidine (15)

This compound was synthesized from nonane-4,6-dione (15.6 g, 0.10 mole) to give 17.0 g (84%) of a pale yellow oil, after chromatography.

Anal. calcd for C₁₂H₁₇N₃ (MW 203): C, 70.93; H, N, 20.69. Found: C. 71.16; H, 8.25; N, 20.85. b.p. 155—158°/0.1mm

EXAMPLE VIII.

3-Bromo 5,7-dimethyl pyrazolo[1,5a]pyrimidine (16)

To a solution of 2.0g (13.6 mmoles) 5,7-dimethyl pyrazolo[1,5a]pyridine [Y. Makisumi, Chem. Pharm. Bull. (Tokyo) 10, 612 (1962)] in CHCl₃ (25 ml) was added N-bromosuccinimide (NBS) [2.42g (13.6 mmoles)]. This mixture was heated on the steam bath for 10 minutes, and then allowed to cool to room temperature. The clear yellow solution was then added to an ice cold solution of potassium hydroxide (50 ml, 2N) with vigorous stirring. The CHCl₃ layer was dried over Na₂SO₄, then chromatographed on basic alumina. Evaporation on the CHCl₃ eluant afforded a white solid which was further purified by recrystallization from petroleum ether (30—60°) to give 1.7g (56%) of analytically pure product; mp 115—6°.

Anal. Corresponds to that calculated for (C₈H₈N₃Br) C, H, N.

NMR (CDCl₃) four singlets in a ratio of 3:3:1:1 at 2.60δ (CH₃), 2.72δ (CH₃), 6.62δ (H at 6 position), and 8.10δ (H at 2 position). The spectrum of the starting material exhibited peaks at 2.56δ (CH₃ at C₇), 2.73δ (CH₃ at C₅), 6.58δ (C₆-H), 6.60δ (C₈-H), and 8.11δ (C₂-H) (protons at C₂ and C₃ were coupled, J=2.1cps).

EXAMPLE IX.

3-chloro-5,7-dimethyl pyrazolo[1,5a]pyrimidine (17)

In a manner similar to the preparation of Example VIII the treatment of 5,7-dimethyl pyrazolo[1,5a]pyrimidine [1.20g (8.15 mmoles)] with N-chlorosuccinimide (NCS) [1.33g (10.0 mmoles)] afforded 963 mg (65%) of analytically pure product; mp 89—90°.

Anal. Corresponds to that calculated for (C₈H₈N₃Cl) C, H, N.

EXAMPLE X.

5,7-dimethyl 3-iodo pyrazolo[1,5a]pyrimidine (18)

5 A solution of ICl [5.0g (27 mmoles)] in CHCl₃ (50 ml) was added to a stirred
solution of 5,7-dimethyl pyrazolo[1,5a]pyrimidine [2.96g (20 mmoles)] in CHCl₃
(50 ml). Within a few minutes, the mixture became warm and crystals of the hydro- 5
chloride salt of the subject compound began to separate. The mixture was warmed
on the steam bath for 2—3 min to complete the reaction, and then refrigerated over-
night. The yellow hydrochloride salt was separated by filtration, washed with Et₂O,
and the air dried. The yellow solid, which weighed 4.4g, was dissolved in water 10
(100 ml) and this solution was made alkaline by the addition of NaOH solution
(2.5N). The alkaline solution was extracted with CHCl₃ 3(25 ml), and the CHCl₃
extracts were dried over Na₂SO₄. The CHCl₃ extract was chromatographed on basic 10
alumina, and the CHCl₃ eluant evaporated to dryness. The residue was recrystallized
from petroleum ether (30—60°) to afford 2.02g (37%) of analytically pure product;
mp 120—2°. 15

Anal. Corresponds to that calculated for (C₈H₈N₃I) C, H, N. 15

EXAMPLE XI.

5,7-Dimethyl 3-Fluoro pyrazolo[1,5a]pyrimidine (19)

20 A mixture of 5,7-dimethyl pyrazolo[1,5a]pyrimidine [1.47g (10 mmoles)], tri-
fluoroacetic anhydride (2.0 ml), and boron trifluoride etherate (2.0 ml) in CH₂Cl₂
(30 ml) was heated at reflux for 24 hours. At the end of this time the red solution
was cooled and added to an ice cold solution of NaOH (30 ml, 2N). The organic
layer was separated and the alkaline layer extracted with CH₂Cl₂ 3(20 ml). The
combined CH₂Cl₂ extracts were washed with water 2(20 ml) and dried over Na₂SO₄. 25
The CH₂Cl₂ extract was evaporated and the residue covered with n-pentane and
chilled. The yellow white crystalline plates were separated by filtration, and recrystal-
lized from n-heptane to yield and analytically pure product; mp 129—30°. 25

Anal. Corresponds to that calculated for (C₈H₈N₃F) C, H, N, F. 25

30 NMR (CDCl₃) four singlets in a ratio of 3:3:1:1 at 2.55δ (CH₃), 2.60δ (CH₃),
6.60δ (H at 6 position) and 8.60δ (H at 2 position). 30

EXAMPLE XII.

3-Acetyl-5,7-dimethyl pyrazolo[1,5a]pyrimidine (20)

35 With good stirring, a solution of SnCl₄ [5.21 g (20 mmoles)] in CH₂Cl₂ (10 ml)
was added dropwise to a solution of 5,7-dimethyl pyrazolo [1,5a]pyrimidine [2.94 g
(20 mmoles)] and acetyl chloride [1.56 g (20 mmoles)] in CH₂Cl₂ (10 ml). After 35
the addition was complete, the mixture was heated at reflux for 12 hrs., cooled, and
then added to dilute HCl (100 ml, 3N). The organic layer was separated and the
acidic solution extracted with CH₂Cl₂ 2(20 ml). The combined CH₂Cl₂ extracts were
dried over Na₂SO₄ and evaporated to dryness. The residue was dissolved in benzene 40
and chromatographed on basic alumina, and the benzene eluant evaporated to dryness.
Recrystallization of the crystalline residue from a benzene-heptane mixture afforded
2.32 g (61%) of analytically pure product; mp 179—80°. 40

Anal. Corresponds to that calculated for (C₁₀H₁₁N₃O) C, H, N. 40

EXAMPLE XIII.

3-Dimethylaminomethyl-5,7-dimethyl pyrazolo[1,a]pyrimidine,
dihydrochloride (21)

45 An aqueous solution of dimethylamine (4.0 ml, 40%) was added slowly to
HOAc (4.5 ml) keeping the temperature below 10°. After the addition was complete,
formalin solution (3.0 ml, 37%) was added to the solution. The resulting solution 45
was allowed to stir for 20 min., and then 5,7-dimethyl pyrazolo[1,5a]pyrimidine
[2.0 g (13.6 mmoles)] was added in small portions. The resulting mixture was then
stirred at room temperature for 12 hrs. and then added to cold NaOH solution (50 ml,
2.5 N). This basic mixture was then extracted with CHCl₃ 3(50 ml), and the
combined CHCl₃ extracts were dried over Na₂SO₄, and evaporated to dryness. 50
The resulting oil, which did not solidify, was dissolved in Et₂O and the dihydrochloride
salt of the product was precipitated by adding HCl gas. This crude product was
purified by recrystallization from EtOH—EtOAc to obtain an analytically pure product;
mp 194—5°. 55

Anal. Corresponds to that calculated for (C₂₂H₁₆N₄ · 2HCl) C, H, N. 55

60 NMR (free amine, CDCl₃) seven singlets in a ratio of 3:3:3:3:2:1:1 at 2.21δ,
2.30δ (N—CH₃ groups), 2.59δ, 2.72δ (CH₃), 3.70δ (CH₂) 6.59 (H at 6 position),
and 8.10δ (H at 2 position). 60

EXAMPLE XIV.

5,7-Dimethyl-3-nitro pyrazolo[1,5a]pyrimidine (22)

5,7-dimethyl pyrazolo[1,5a]pyrimidine [1.0 g (6.8 mmoles)] was dissolved in H_2SO_4 (10 ml) keeping the temperature below 5° . Fuming HNO_3 [4 ml; sp. gr. 1.5] was added dropwise to the cold H_2SO_4 solution, with good stirring. The temperature during this addition was maintained below 10° . After the addition was complete the solution was stirred at room temperature for 45min. and then added to 100 g of ice. The precipitated product was separated by filtration, washed well with H_2O , and dried. Recrystallization from CH_3OH afforded 0.75 g (57%) of analytically pure product; mp $156-7^\circ$.

Anal. Corresponds to that calculated for $\text{C}_8\text{H}_8\text{N}_4\text{O}_2$: C, H, N.

NMR (CDCl_3) singlets in a ratio of 3:3:1:1 at 2.80δ (CH_3), 2.85δ (CH_3), 7.04δ (H at 6 position), and 8.76δ (H at 2 position).

EXAMPLE XV.

3-Amino-5,7-dimethyl pyrazolo[1,5a]pyrimidine (23)

To a solution of the nitro derivative of Example XXII [5.0 g (26 mmoles)] in EtOH (50 ml) was added HOAc (5 ml) and 0.25 g of 10% Pd/C catalyst. The resulting mixture was hydrogenated at room temperature for 16 hours. The mixture was filtered through Celite and evaporated to dryness at reduced pressure. The oil residue was dissolved in water (100 ml), made basic with NH_4OH , and then extracted into CHCl_3 3(35 ml). The combined CHCl_3 extracts were dried over Na_2SO_4 , and chromatographed on basic alumina. Evaporation of the CHCl_3 eluant afforded 2.7 g (64%) of red crystalline product; mp $133-5^\circ$ (dec).

Anal. Corresponds to that calculated for $(\text{C}_8\text{H}_{10}\text{N}_4)$ C, H, N.

EXAMPLE XVI.

3-Acetamido-5,7-dimethyl pyrazolo[1,5a]pyrimidine (24)

A solution of the 3-amino derivative of Example XV [2.6 g (16 mmoles)] in Ac_2O (50 ml) was heated on the steam bath for ten minutes and then allowed to cool to room temperature. The crystalline product was separated by filtration, washed with H_2O and dried. Recrystallization from H_2O afforded 2.6 g (80%) of analytically pure product; mp $175-6^\circ$.

Anal. Corresponds to that calculated for $(\text{C}_{10}\text{H}_{12}\text{N}_4\text{O})$ C, H, N.

EXAMPLE XVII.

3-Bromo-5,7-diethylpyrazolo[1,5a]pyrimidine (25)

This compound was prepared by bromination of 1.75 g (0.01 mole) of the dialkyl compound. Chromatography on basic alumina with chloroform gave 2.0 g (79%) of white needles, m.p. $64-65^\circ\text{C}$.

Anal. calcd for $\text{C}_{10}\text{H}_{12}\text{N}_4\text{Br}$ (MW 254): C, 47.24; H, 4.72; N, 16.53. Found: C, 47.10; H, 4.63; N, 16.71.

NMR (CDCl_3) t, 1.35δ and t, 1.43δ (from C_5 - and C_7 -ethyl); q, 2.98δ and q, 3.10δ from C_5 - and C_7 -ethyl); s, 6.63δ (C_6 -H) and s, 8.08δ (C_2 -H) integration 3:3:2:2:1:1. No coupling was observed for singlets at 6.63δ and 8.08δ .

EXAMPLE XVIII.

3-Bromo-5,7-di-n-propylpyrazolo[1,5a]pyrimidine (26)

This compound was prepared by brominating 4.06 g (0.02 mol) of the 5,7-di-n-propyl parent compound to yield 3.5 g (62%) of white needles, m.p. $66-67^\circ\text{C}$ after chromatography on basic alumina (chloroform) and recrystallization from petroleum ether.

Anal. calcd for $\text{C}_{12}\text{H}_{16}\text{N}_4\text{Br}$ (MW 282): C, 51.06; H, 5.67; N, 14.89. Found: C, 50.85; H, 5.92; N, 15.11.

NMR (CDCl_3) propyl groups appear as overlapping multiplets at 1.2δ , 1.8δ and 3.0δ ; s, 6.60δ (C_6 -H); s, 8.08 ($\text{C}-\text{H}$). Integration 6:4:4:1:1.

EXAMPLE XIX.

5-Methyl(ethyl)-7-ethyl(methyl)pyrazolo[1,5a]pyrimidine (27a & 28a)

The compound was prepared, as described above, from 3-aminopyrazole (8.3 g) and hexane-2,4-dione (11.4 g) in ethanol with a catalytic amount of piperidine. The product was isolated as a colorless oil (14.0 g, 87% yield) via chromatography on basic alumina with benzene. Oil, b.p. $173-177^\circ/0.1\text{mm}$. Mass spectrum $M^+ = 161$.

Anal. Calcd. for $\text{C}_9\text{H}_{11}\text{N}_3$ (MW 161): C, 67.08; H, 6.83; N, 26.08. Found: C, 66.88; H, 6.94; N, 26.22.

5 NMR (CDCl₃) indicated two isomers, 5-ethyl-7-methyl and 5-methyl-7-ethyl, with the dominant (65.35) being the latter isomer: m, 1.4δ (two triplets from the 5-ethyl and the 7-ethyl), m, 3.1δ (two quartets from the 5-ethyl and the 7-ethyl), s, 2.56δ (C₅-CH₃) and s, 2.73δ (C₇-CH₃), s, 6.58δ (C₆-H) and coupled s, 6.60δ (C₈-H) with coupled s, 8.11δ (C₂-H) and J_{2,3}=1.9 cps. 5

EXAMPLE XX.

10 5-Methyl(n-propyl)-7-n-propyl(methyl)pyrazolo[1,5a]pyrimidine (27b & 28b)
This compound was prepared from heptane-2,4-dione (8.2 g, 0.064 mole) and the dominant isomer was found to be the 5-methyl-7-n-propyl. Yield: 15 g mixed isomers (86%) colorless, semisolid, mp 40-45°, b.p. 165-169°/0.1 mm. Mass spectrum M⁺=175. 10
Anal. calcd for C₁₉H₂₃N₃ (MW 175): C, 68.54; H, 7.48; N, 23.98.
Found: C, 68.31; H, 7.56; N, 23.79.
15 NMR (CDCl₃) m, 1.2δ (C₅, C₇-propyl); m, 1.8δ (C₅, C₇-propyl); m, 3.0δ (C₅, C₇-propyl); s, 2.58δ (C₅-CH₃) and s, 2.72δ (C₇-CH₃); s, 6.58δ (C₆-H) and coupled s, 6.63δ (C₈-H) with coupled s, 8.10δ (C₂-H) J_{2,3}=1.9 cps. 15

EXAMPLE XXI.

20 3-Bromo-7-ethyl-5-methylpyrazolo[1,5a]pyrimidine (29)
This compound was prepared from 2.6δ (0.063 mole) of the isomeric mixture of dialkyl compound to yield 2.5 g (64%) of the pure 7-ethyl-5-methyl isomer, m.p. 78-79°C. 20
Anal. Calcd for C₉H₁₀N₄Br (MW 240): C, 45.00; H, 4.16; N, 17.50.
Found: C, 44.79; H, 4.38; N, 17.40.
25 NMR (CDCl₃) t, 1.43δ (ethyl); s, 2.6δ (C₅-CH₃); q, 3.10δ (ethyl); s, 6.63δ (C₆-H); s, 8.10δ (C₂-H). 25
The establishment of the isomer which was isolated, is based on the nmr data of 3-bromo-5,7-dimethylpyrazolo[1,5a]pyrimidine, which consist of methyl peaks at 2.60δ and at 2.72δ. The peak at 2.60δ is attributed to the C₅-CH₃, i.e., the methyl group closest to the N₄-nitrogen not involved in the bridgehead. The peak at 2.72δ is attributed to the C₇-CH₃, i.e., the methyl group closest to the bridgehead nitrogen by virtue of its greater deshielding effect, which is in accord with similar studies by other authors [Y. Makisumi, et al, *Chem. Pharm. Bull.*, 12, 204 (1964)]. 30

EXAMPLE XXII.

35 3-bromo-5-methyl-7-n-propylpyrazolo[1,5a]pyrimidine (30)
This compound was prepared from 1.75 g (0.01 mole) of the 5,7-dialkyl compound (mixed isomers), which was purified by chromatography on basic alumina with chloroform. A colorless oil was obtained and this soon solidified to white crystals, which upon recrystallization from benzene-petroleum ether (1:25) gave white needles, m.p. 88-89°C, 1.20 g (48%). 35
Anal. calcd for C₁₉H₂₁N₃Br (MW 254): C, 47.24; H, 4.72; N, 16.53.
Found: C, 47.30; H, 4.81; N, 16.60.
40 NMR (CDCl₃) t, 1.05δ (propyl); m, 1.8δ (propyl); s, 2.64δ (C₅-CH₃); t, 3.10δ (propyl); s, 6.59δ (C₆-H); s, 8.05δ (C₂-H). 40

EXAMPLE XXIII.

45 7-Ethyl-5-methyl-3-nitropyrazolo[1,5a]pyrimidine (31)
Concentrated sulfuric acid (10 ml, sp. gr. 1.94) was cooled via ice bath and 3.2 g (0.02 mole) of the isomeric 7-(5)-ethyl-5(7)-methyl compound was cautiously added, with stirring. When the temperature remained at +15°C, concentrated nitric acid (7 ml, sp. gr. 1.35) was added dropwise, maintaining the temperature at +15°C throughout the addition. Then the solution was allowed to warm to room temperature and stirring was continued for 15-20 hours (overnight). The yellow solution was then cautiously poured over 200 g of ice, with stirring and the product precipitated. Filtration was difficult, so the product was extracted from the aqueous phase with methylene chloride (100 ml) and the organic layer was washed with water (100 ml) and dried (Na₂SO₄). Evaporation of the solvent yielded a dark semi-solid, fractionally recrystallized several times from methanol water to give 1.30 g of the pure 7-ethyl-5-methyl-3-nitro isomer, yellow needles, m.p. 127-128°C. 50
Anal. calcd for C₉H₁₀N₄O₂ (MW 206): C, 52.42; H, 4.85; N, 27.18.
Found: C, 52.45; H, 5.11; N, 27.11.
55 NMR (DMSO-d₆) t, 1.40δ (C₇-ethyl); s, 2.70δ (C₅-methyl); q, 3.2δ (C₇-ethyl); s, 7.35δ (C₆-H); s, 8.98δ (C₂-H). 55
60 60

EXAMPLE XXIV.

3-Carboethoxy-7-ethyl-5-methylpyrazolo[1,5a]pyrimidine (32)

This compound was prepared by refluxing 3.15 g (0.02 mole) of 3-amino-4-carboethoxypyrazole [C. C. Cheng, *J. Het. Chem.*, 5, (1968) and J. Druey, P. Schmidt, *Chem. Abst.*, 53 10262e] and 2.3 g (0.02 mole) of hexane-2, 4-dione in ethanol (20 ml) with a catalytic amount of piperidine (2 drops) for 15—20 hours. The solvent was removed by distillation at reduced pressure (water aspirator) and the colorless oil remaining was triturated with ether-pentane, the solvent decanted, and the insoluble oil taken up in chloroform and chromatographed on basic alumina with chloroform. A colorless oil was obtained on evaporation of the solvent, and upon trituration with petroleum ether (30—60°) and ice bath cooling, white crystals, m.p. 33—38°C were obtained. The nmr spectrum (CDCl_3) indicated that both isomers were present, as suspected from the low, broad range of the melting point. Recrystallization several times from benzene gave 1.3 gm of the 7-ethyl-5-methyl isomer, free of the 7-methyl-5-ethyl isomer, m.p. 67—68°C.

Anal. calcd for $\text{C}_{12}\text{H}_{13}\text{N}_3\text{O}_2$ (MW 233): C, 61.78; H, 6.48; N, 18.02.
Found: C, 61.95; H, 6.60; N, 18.23.

NMR (CDCl_3) τ , 1.43 (both terminal CH_3 of ethyl group and ethyl ester superimposed); s, 2.78 ($\text{C}_6\text{—CH}_3$); q, 4.458 (ethyl ester); s, 6.758 ($\text{C}_6\text{—H}$); s, 8.508 ($\text{C}_2\text{—H}$)

EXAMPLE XXV.

7-Methyl-5-phenylpyrazolo[1,5a]pyrimidine (33)

This compound was prepared from 1-phenylbutane-1,3-dione (8.1 g, 0.05 mol) in the usual manner, to give a crude product which was chromatographed on basic alumina with ether-chloroform (9:2) yielding white plates, 1.3 g (12.7%), m.p. 70—71° after recrystallization from petroleum ether. This product was demonstrated to be the pure 7-methyl-5-phenyl isomer by nmr.

Anal. calcd for $\text{C}_{13}\text{H}_{11}\text{N}_3$ (MW 209.3): C, 74.62; H, 5.30; N, 20.08.
Found: C, 74.77; H, 5.20; N, 20.21.

NMR (CDCl_3): s, 2.828 ($\text{C}_6\text{—CH}_3$); coupled s, 6.718 ($\text{C}_6\text{—H}$); s, 7.108 ($\text{C}_8\text{—H}$) m, 7.808 and 8.158 ($\text{C}_7\text{—phenyl ABX pattern}$) and coupled s, 8.038 ($\text{C}_2\text{—H}$). $J_{2,3}=2.1$ cps.

EXAMPLE XXVI.

5-Methyl-7-hydroxypyrazolo[1,5a]pyrimidine (34)

This compound was prepared from 3-aminopyrazole (1) and ethylacetoacetate, refluxing in ethanol with a catalytic amount of piperidine, in the same method as described by Y. Makisumi [*Chem. and Pharm. Bull. Japan*, 10, 612 (1962)]. Yield: 80%, white powder, m.p. 297—298°C (lit. 298°C).

EXAMPLE XXVII.

3-Ethyl-7-hydroxy-5-methylpyrazolo[1,5a]pyrimidine (35)

A solution of ethyl acetoacetate [14.6 g (0.112 moles)] and 3-amino-4-ethylpyrazole (compound 5) [12.0g; 0.108 moles] was stirred at room temperature for 10 minutes and then diluted by adding 100 ml of glacial acetic acid. The resulting mixture was stirred and heated at reflux for 3 hours and then allowed to cool to room temperature. The mixture was added to 200 ml of ethyl acetate and the products separated by filtration. The solid products were separated by filtration and purified by recrystallization from aqueous ethanol to afford 14.7 g (77%), the analytically pure product that had a melting point of 290—2°.

Anal. Corresponds to that calc'd for ($\text{C}_{13}\text{H}_{11}\text{N}_3\text{O}_2$) C, H, N.

EXAMPLE XXVIII.

5-Methyl-7-chloropyrazolo[1,5a]pyrimidine (36)

This compound was prepared from the corresponding 7-hydroxy derivative in refluxing phosphorus oxychloride, in the prescribed manner of Y. Makisumi (ibid.) The product was purified by sublimation and recrystallization from petroleum ether. Yield: 20% on a large scale (0.5 mole) chlorination, colorless needles with a musty odor, m.p. 39—40°C. (lit. 40°C).

EXAMPLE XXIX.

7-Chloro-3-ethyl-5-methylpyrazolo[1,5a]pyrimidine (36a)

A suspension of 3-ethyl-7-hydroxy-5-methylpyrazolo[1,5a]pyrimidine (35)

[8.85 g (50 mmoles)] and 10 ml of N,N-dimethylaniline in 100 ml of phosphorous oxychloride was stirred and heated at reflux for 1 hour. At the end of this time, the excess phosphorous oxychloride was removed *in vacuo*, utilizing the steam bath as the source of heat. The residual syrup was added slowly with good stirring to 200g of crushed ice. The resulting solution was extracted with absolute ether 3(150 ml), and the combined ethereal extracts were washed with sodium bicarbonate solution 3(100 ml) and then with water (100 ml). The ethereal extract was dried over anhydrous sodium sulfate and then evaporated to dryness. The resulting crude chloro derivative were purified by recrystallization from *n*-heptane and then by vacuum sublimation at 120–140° (0.1mm) to afford 8.6 g (90%) of analytically pure product that had a melting point of 61–2°.

Anal. Corresponds to that calc'd (C₉H₁₀N₃Cl) N.

EXAMPLE XXX.

7-Diethylamino-5-methylpyrazolo[1,5a]pyrimidine (37)

This compound was prepared from 840 mg (0.005 mole) of the 7-chloro compound (36) and 730 mg (0.010 mole) of diethylamine. The product was isolated in the usual manner to yield 700 mg (69%) yellowish plates, m.p. 75–77°C from methanol-water.

Anal. Calcd for C₁₁H₁₆N₄ (MW 204.27) C, 64.67; H, 7.90; N, 27.43.
Found: C, 64.31; H, 8.05; N, 27.22.

EXAMPLE XXXI.

5-Methyl-7-piperidinopyrazolo[1,5a]pyrimidine (38)

This compound was prepared from 840 mg (0.005 mole) of the 7-chloro precursor (36) and 840 mg (0.010 mole) piperidine to yield 840 mg (78% yield) ivory colored platelets, m.p. 78–79°C from ethanol-water.

Anal. Calcd for C₁₂H₁₆N₄ (MW 216.28) C, 66.64; H, 7.46; N, 25.91.
Found: C, 66.93; H, 7.52; N, 26.14.

Mass Spectrum M⁺=216 UV (MeOH) λ max (log ε max) at 225 (4.50), 280* (3.64), 290* (3.73), 320 (3.94) mμ.

EXAMPLE XXXII.

5-Methyl-7-n-Octylaminopyrazolo[1,5a]pyrimidine (39)

This compound was prepared from 840 mg (0.005 mole) of the analogous 7-chloro-5-methyl compound (36) and 1.30 g (0.010 mole) of n-octylamine to yield 255 mg (38%) white platelets, m.p. 48–50°C.

Anal. Calcd for C₁₈H₂₄N₄ (MW 260.37) C, 69.19; H, 9.29; N, 21.52.
Found: C, 69.28; H, 9.31; N, 21.71.

EXAMPLE XXXIII.

7-Hydrazino-5-methylpyrazolo[1,5a]pyrimidine (40)

This compound was prepared from 1.0 g of the 7-chloro derivative (36), which was refluxed in 30 ml ethanol containing 6 ml of 85% hydrazine hydrate. After 2 hours of reflux, the solution was concentrated to 10 ml (rotovap) whereupon the product separated as crystals. The material was washed with 5 ml cold ethanol to yield 420 mg of white plates, m.p. 228–230° dec. An analytical product was recrystallized from ethanol.

Anal. Calcd for C₇H₈N₅ (MW 163.16) C, 51.50; H, 5.57; N, 42.92.
Found: C, 51.55; H, 5.61; N, 43.20.

NMR (d₆-DMSO) s, 2.44δ (CH₃—CH₃); s, 4.72δ (hydrazino NH); 2, 6.26δ coupled (C₃—H) to s, 8.03δ (C₂—H); s, 6.33δ (C₆—H); broad s, 8.82δ (hydrazino NH). Coupling constant J_{2,3}=2.5 cps.

EXAMPLE XXXIV.

7-(2-N,N'-Isopropylidenehydrazino-5-methylpyrazolo[1,5a]pyrimidine (41)

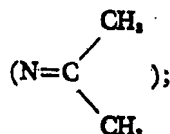
A mixture of 1.1 g of the corresponding 7-hydrazino compound (40), 100 ml reagent grade acetone, and 20 ml of ethanolic hydrogen chloride was refluxed for 4 hours. Upon cooling, the insoluble material was filtered off and recrystallized from ethanol, m.p. 257–258°C (yield 20%).

Anal. Calcd for C₂₀H₂₇N₁₀Cl (MW 442.5) hemihydrochloride C, 54.23; H, 6.10; N, 31.63; Cl, 8.02.

Found: C, 54.01; H, 6.32; N, 31.44; Cl, 7.86.

NMR (trifluoroacetic acid): s, 2.58δ (C₃—H); s, 2.88δ

* shoulder



s, 7.6 δ (C₃—H) coupled to s, 8.6 δ (C₂—H); s, 7.2 δ (C₆—H). J_{2,3}=2.5 cps.

EXAMPLE XXXV.

7-B-Hydroxyethylamino-5-methylpyrazolo[1,5a]pyrimidine (42)

This compound was prepared from 3000 mg of the corresponding 7-chloro compound (36), refluxed for 3 hours in 10 ml ethanol containing 100 mg of 2-aminoethanol (monoethanolamine). Evaporation of the solution (rotovap) and recrystallization of the solid residue from methanolether affords 175 mg of yellow-white cubes, m.p. 162—163°C. The compound was found to be quite hygroscopic.

Anal. Calcd for C₉H₁₂N₄O (MW 164.20) C, 65.83; H, 7.37; N, 17.06.

Found: C, 65.37; H, 7.42; N, 17.23
NMR (d₆-DMSO) s, 2.40 δ (C₅—CH₃); m, 3.4 δ to 3.75 δ (—CH₂—CH₂— of amine function); broad s, 5.0 δ (OH); s, 6.12 δ (C₆—H); s, 6.31 δ (C₃—H) coupled to s, 8.05 δ (C₂—H); broad s, 7.55 δ (NH).

EXAMPLE XXXVI.

N-[5-methylpyrazolo[1,5a]pyrimidine-7-yl] glycine (43)

300 mg of the 7-chloro precursor (36) was dissolved in 10 ml of ethanol and mixed with 130 mg of glycine (18 mmol) dissolved in an aqueous solution of 200 mg sodium carbonate (19 mmol) in 20 ml water. The mixture was refluxed for 3 hours, then chilled to produce 200 mg of white platelets. Recrystallization from dimethylformamide-methanol gave crystals with m.p. 305—305.5° dec.

Anal. Calcd for C₉H₁₀N₄O₂ (MW 206.20) C, 52.42; H, 4.89; N, 27.17.
Found: C, 52.30; H, 4.98; N, 26.92.

EXAMPLE XXXVII.

3-Ethyl-5-methyl-7-n-propylaminopyrazolo[1,5a]pyrimidine (45)

A solution of 7-chloro-3-ethyl-5-methylpyrazolo[1,5a]pyrimidine (37) [0.585 g, (3 mmoles)] and *n*-propylamine [0.35 g; 6 mmoles] in 20 ml of absolute ethanol was stirred at room temperature for 2 hours. At the end of this time, the solution was evaporated to dryness and the residue titrated with 30 ml of water. Recrystallization of the residue from aqueous ethanol afforded 0.425 g (64%) the analytically pure product that had a melting point of 46—8°.

Anal. Corresponds to that calcd for (C₁₂H₁₈N₄) C, H, N.

EXAMPLE XXXVIII.

3-Ethyl-5-methyl-7-*n*-propoxypropyrazolo[1,5a]pyrimidine (46)

A solution of sodium *n*-propoxide was prepared by dissolving sodium metal [0.165 g; 0.0072 formula weights] in 40 ml of *n*-propanol. This solution was stirred at room temperature and the 7-chloro-3-ethyl-5-methylpyrazolo[1,5a]pyrimidine (37) [1.29 g, (6.6 mmoles)] was added. The resultant solution was stirred at room temperature for 1 hour and then evaporated to dryness *in vacuo* at room temperature. The residue was extracted with boiling 60—90° petroleum ether 3 (15 ml), and the combined extracts were evaporated to dryness to yield crude 3-ethyl-7-(*n*-propoxy)-5-methylpyrazolo[1,5a]pyrimidine (46). The produce was purified by column chromatography on silica gel (100g), utilizing a solvent system of 60—90° petroleum ether: ethyl acetate (8:2) to afford 1.11 g (77%) the analytically pure product that had a melting point of 92—4°.

Anal. Corresponds to that calcd for (C₁₂H₁₇N₃O) C, H, N.

EXAMPLE XXXIX.

3-Ethyl-7-ethylthio-5-methylpyrazolo 1,5a pyrimidines (47)

Ethanethiol [0.5g; 8.06 mmoles] was added to a solution of sodium metal [0.165g; 0.0072 formula weights] in 15 ml of anhydrous methanol. The resulting solution was stirred at room temperature for 20 minutes, and then the 7-chloro-3-ethyl-5-methylpyrazolo[1,5a]pyrimidine (37) [1.29 g (6.6 mmoles)] was added. The resulting solution was stirred at room temperature and then evaporated to dryness *in vacuo* at 25°C. The residue was extracted with boiling 60—90° petroleum ether

3(10 ml), and the combined extracts were evaporated to yield crude 3-ethyl-7-ethylthio-5-methylpyrazolo[1,5a]pyrimidine (47). The produce was purified by column chromatography on silica gel (100g), utilizing a solvent system of 60—90° petroleum ether:ethyl acetate (9:1) to yield the analytically pure product that was isolated as an oil.

Anal. Corresponds to that calcd for $(C_{11}H_{16}N_2S)$ C, H, N.

EXAMPLE XL.

3-Bromo-7-n-butylamino-5-methylpyrazolo[1,5a]pyrimidine (48)

The 7-n-butylamino-5-methylpyrazolo[1,5a]pyrimidine was prepared from 1.68 g (0.01 mole) of the corresponding 7-chloro-5-methyl compound and 1.46 g (0.02 mole) n-butylamine, and the oil obtained on work-up was utilized for bromination without further identification (other than spectra). The bromination procedure was the same as that employed for the 5,7-dialkylpyrazolo[1,5a]pyrimidines and upon work-up in the usual manner, with recrystallization from ether-petroleum ether, the 3-bromo compound was obtained as white platelets, m.p. 99—100°C, 1.41 g (50%).

Anal. Calcd for $C_{11}H_{18}N_4O_2Br$ (MW 315.21) C, 41.90; H, 4.76; N, 17.77; Br, 25.39.

Found: C, 42.16; H, 4.85; N, 17.92; Br, 25.11.

NMR ($CDCl_3$) exhibits peaks at δ , 2.58 δ (C_5-CH_3); s, 5.87 δ (C_6-H); s, 7.92 δ (C_2-H).

EXAMPLE XLI.

3-Bromo-7-(2,2'-dimethoxyethylamino)-5-methylpyrazolo[1,5a]pyrimidine (49)

This compound was prepared in a manner similar to that of the preceding compound, by reacting the 7-chloro-5-methyl derivative (1.68 g, 0.01 mole) with aminoacetaldehyde dimethylacetal (2.3 g, 0.021 mole) in ethanol, isolating the liquid 7-(2,2'-dimethoxyethylamino) derivative and brominating the oil with N-bromosuccinimide (1.78 g, 0.01 mole) in 50 ml chloroform and isolating the product as in the preceding example. Recrystallization of the chromatographed solid (chloroform on Merck basic alumina) gave pale ivory colored cubettes, 2.5 g, (79%), m.p. 134—135°C from petroleum ether (MERCK is a Registered Trade Mark).

Anal. Calcd for $C_{11}H_{18}N_4O_2Br$ (MW 315.21) C, 41.90; H, 4.76; N, 17.77; Br, 25.39.

Found: C, 42.16; H, 4.85; N, 17.92; Br, 25.11.

NMR ($CDCl_3$) exhibits peaks at δ , 2.58 δ (C_5-CH_3); s, 5.87 δ (C_6-H); s, 7.92 δ (C_2-H).

EXAMPLE XLII.

The compounds of the invention were tested for inhibition of phosphodiesterase by the following procedure.

3',5'-Cyclic-AMP phosphodiesterase (PDE) was isolated and purified from three different tissues in the following manner. Homogenates of rabbit kidney, rabbit lung and beef heart are made in sucrose-Tris-magnesium buffer and are subjected to centrifugation at low speed to remove nuclei and cell debris. The supernatants are then centrifuged at 105,000 x g for 30 minutes, and the 105,000 x g supernatants are then fractionated using $(NH_4)_2SO_4$. The precipitation which forms at 0—30% saturation is collected by centrifugation at 20,000 x g, dissolved in Tris-magnesium buffer, and dialyzed overnight against the same buffer. A second $(NH_4)_2SO_4$ fraction is obtained by raising the concentration of the first supernatant to 50%. These two $(NH_4)_2SO_4$ fractions as well as the supernatant from the 30—50% cut were then assayed for PDE activity using the method of Appleman, *Biochem. 10*, 311 (1971). The first fraction obtained from both kidney and lung tissue contains a PDE with low affinity for 3',5'-c-AMP (high K_m). The second fraction exhibits a bisphasic curve when the Lineweaver-Burk method of analysis is used. This indicates either the presence of two separate enzymes, one having a high and the other a low affinity for C-AMP, or one protein with two separate sites. Appleman, *supra*, indicates that extracts of brain yield two separate enzymes (a high K_m and a low K_m) which can be separated by sepharose gel chromatography.

The inhibitory studies reported in Tables I and II were performed with the low affinity (Fraction I, high K_m) enzyme obtained from rabbit kidney or rabbit lung. The studies reported in Tables III—VI were performed with the high affinity (Fraction II, low K_m) enzyme obtained from rabbit lung or kidney and beef heart. I_{50} values

5 were calculated in some instances from a plot of long I vs. percent I in experiments in which inhibitor concentration is varied over a wide range, at a constant 3',5'-cyclic AMP concentration of approximately $5 \times 10^{-4}M$ (Tables I and II) or $1.6 \times 10^{-7}M$ (Tables III and IV). The relative inhibitory activity of each compound as compared with theophylline is expressed as an α value. This value is obtained by dividing the I_{50} value obtained for the particular compound being evaluated. 5

In most instances, α values were calculated from an inhibition study performed with a single concentration of test compound as long as the inhibition produced by that concentration was from 20—80%. In this instance an α value was calculated as

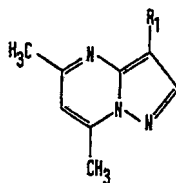
10
$$\alpha = \frac{\text{concentration of theophylline giving (X\%) inhibition}}{\text{concentration of test substance giving the same (X\%) inhibition}}$$
 10

The validity of this method has been checked by comparing α values obtained by (1) measurements at a single concentration of inhibitor and (2) measurements at four concentrations of inhibitor (I_{50} determinations). α values compared in this way have been found to agree to within 10% of each other.

15 The basic incubation mixture contained the following substances (amounts in μ moles): ^3H -cAMP (specific activity $\sim 2,180$ cmp/pmole), .00016; Tris pH 7.5, 40; $MgCl_2$, 0.5; Enzyme (cAMP phosphodiesterase), 5—50 μg protein; and 10^{-4} to 10^{-6} molar concentration of the inhibitor; incubation time 10 minutes at 30°C. At the end of incubation, the mixtures are heated to 90°C for 2 minutes and 100 μg of snake venom phosphodiesterase from Crotalus atrox was added and the tubes incubated for 10 minutes at 30°C. The mixture was then cooled and 1 ml of Dowex 1—2X, 200—400 mesh suspension, prepared by mixing 100 g of the resin in 200 G H_2O , was added and the mixture centrifuged. (DOWEX is a Registered Trade Mark.) An aliquot of the supernatant was used to determine counts per minute using a liquid scintillation spectrometer. Zero time values were obtained using incubations in which the cAMP phosphodiesterase was omitted from the first incubation. 25

TABLE I

Inhibition of 3', 5'-Cyclic AMP
Phosphodiesterase (PDE)
Isolated from Rabbit Kidney

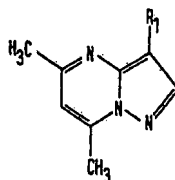


R_1	I_{50} [M]	I_{50} (theophylline) [M]	$\alpha = \frac{I_{50} \text{ (theophylline)}}{I_{50} \text{ (compound)}}$
			$\frac{[M]}{[M]}$
H*	8×10^{-4}	1.6×10^{-4}	0.20
COOC ₂ H ₅ *	1×10^{-3}	2.2×10^{-4}	0.22
COMPOUND 1*	1.6×10^{-3}	2.2×10^{-4}	0.14
CN	2.5×10^{-4}	2.2×10^{-4}	0.88
CONH ₂	3.4×10^{-4}	2.2×10^{-4}	0.65
CH ₂ NH ₂	6×10^{-3}	2.2×10^{-4}	0.04
Br	1.0×10^{-4}	2.2×10^{-4}	2.20
Cl	2.4×10^{-4}	3.2×10^{-4}	1.33
I	1.3×10^{-4}	1.6×10^{-4}	1.23
COCH ₃	2.8×10^{-4}	1.6×10^{-4}	0.57
CH ₂ N(CH ₃) ₂	4.3×10^{-4}	2.6×10^{-4}	0.61
NO ₂	1.3×10^{-4}	2.2×10^{-4}	0.17
NH ₂	2.5×10^{-3}	2.2×10^{-4}	0.09
NHCOCH ₃	6×10^{-3}	2.2×10^{-4}	0.04

*For comparison only.

TABLE II

Inhibition of 3', 5'-Cyclic AMP Phosphodiesterase
(PDE) Isolated from Rabbit Lung

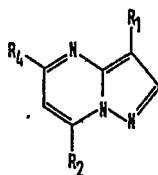


R_1	I_{50} [M]	I_{50} (Theophylline) [M]	I_{50} (Theophylline) [M]
			$= \frac{I_{50}(\text{Compound})}{I_{50}(\text{Theophylline})}$
H*	2.0×10^{-3}	6.4×10^{-4}	0.32
CN	9.5×10^{-4}	6.5×10^{-4}	0.68
CONH ₂	2.0×10^{-3}	6.5×10^{-4}	0.32
Br	2.7×10^{-4}	6.4×10^{-4}	2.4
Cl	2.1×10^{-4}	6.5×10^{-4}	3.1
I	2.1×10^{-4}	7.4×10^{-4}	3.5
COCH ₃	5.0×10^{-4}	7.4×10^{-4}	1.5
CH ₂ N(CH ₃) ₂	1.3×10^{-3}	7.4×10^{-4}	0.57

*For comparison only.

TABLE III

5,7-dialkyl-3-substituted pyrazolo[1,5a]pyrimidines

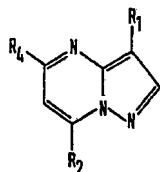


R ₄	R ₂	R ₁	α Lung	α Heart
CH ₃	CH ₃	H*	0.3	0.2
CH ₃	CH ₃	COOEt*	0.6	0.4
CH ₃	CH ₃	CONH ₂	0.5	0.4
CH ₃	CH ₃	CH ₂ NH ₂		
CH ₃	CH ₃	Br	0.7	1.7
CH ₃	CH ₃	Cl	2.2	1.7
CH ₃	CH ₃	I	3.5	1.5
CH ₃	CH ₃	COOCH ₃	1.0	0.4
CH ₃	CH ₃	CH ₂ N(CH ₃) ₂	0.3	0.3
CH ₃	CH ₃	NO ₂	0.4	0.2
CH ₃	CH ₃	NH ₂		
CH ₃	CH ₃	NHCOCH ₃	0.1	0.1
CH ₃	CH ₃	C ₂ H ₅	2.2	
CH ₃	CH ₂ -CH ₂ -CH ₃	H	2.1	1.1
CH ₃	-CH ₂ -CH ₂ -CH ₃	Br	7.5	6.5
CH ₂ -CH ₃	-CH ₂ -CH ₃	H	3.0	1.1
CH ₃	-CH ₂ -CH ₃	COOC ₂ H ₅	1.5	0.5
CH ₂ -CH ₃	CH ₂ -CH ₃	Br	7.4	6.0
CH ₂ -CH ₂ -CH ₃	-CH ₂ -CH ₂ -CH ₃	Br	5.5	3.0
CH ₃	CH ₂ -CH ₃	Br	7.5	4.0
CH ₃	CH ₂ -CH ₃	NO ₂	2.5	0.5
C ₆ H ₅	CH ₃	H	3.4	2.4
CH ₂ -CH ₂ -CH ₃	CH ₂ -CH ₂ -CH ₃	H		

* For comparison only.

TABLE IV

5-Alkyl-3,7-disubstituted pyrazolo[1,5a] pyrimidines



R ₄	R ₂	R ₁	PDE αLung	PDE αHeart
CH ₃	NH-CH ₂ -CH ₂ -CH ₃	C ₂ H ₅	9.4	—
CH ₃	O-CH ₂ -CH ₂ -CH ₃	C ₂ H ₅	5.4	—
CH ₃	S-CH ₂ -CH ₃	C ₂ H ₅	8.9	—
CH ₂	NH-CH ₂ -CH ₂ -CH ₂ -CH ₃	Br	1.5	6.0
CH ₃	NH-CH ₂ -CH ₂ (OCH ₃) ₂	Br	6.8	4.5
CH ₃	N(C ₂ H ₅) ₂	H	3.2	1.7
CH ₃		H	2.4	1.5
CH ₃	NH(CH ₂) ₇ -CH ₃	H	9.0	3.0
CH ₃	NH-NH ₂	H	1.5	0.5
CH ₃		H	—	—
CH ₃	NH-CH ₂ -CH ₂ OH	H	0.5	3.7
CH ₃	NH-CH ₂ -COOH	H	0.2	2.1
CH ₃	-O-CH ₂ -CH ₃ *	H	1.4	1.0

* For comparison only.

5 The results shown in the foregoing Tables indicate that several of the compounds of this invention are several times more effective as inhibitors of phosphodiesterase enzyme than theophylline. By the same token, the results indicate that these compounds are capable of selective inhibition. It should also be noted that other examples could be given of compounds within the scope of the present invention, as for example, compounds where R₁ is an alkyl other than ethyl (in which case, the compounds would be prepared by the procedure of the foregoing corresponding Examples, using another alkyl nitrile as a starting material in place of *n*-butyronitrile or ethyl benzoyl-acetate in place of ethyl acetoacetate) with similar satisfactory results to be obtained. For the sake of brevity of disclosure, however, additional example will not be provided herein.

10 In general, the phosphodiesterase inhibitors of the invention may find employment in the treatment of disorders responsive to the administration of epinephrine or norepinephrine, since in either case the result is maintenance of greater levels of C—AMP — in the first instance by retarding C—AMP degradation and in the second by stimulating its production.

15

Several compounds of the invention have been tested *in vivo* and reveal a variety of activities indicative of selective transport to specific tissues. Thus 3-cyano-5,7-dimethyl pyrazolo[1,5a]pyrimidine has been shown to significantly inhibit ADP-induced platelet aggregation. The corresponding 3-nitro analog exhibits anti-pregnancy effect at 25 and 12.5 mg/kg orally, appreciable anti-edema activity, and some inhibition of ADP-induced platelet aggregation. The 3-carboxamido analog of these compounds similarly demonstrated an anti-edema effect and was very active against ADP-induced platelet aggregation. 5,7-Dimethyl-3-bromo pyrazolo[1,5a]pyrimidine exhibited anti-edema and ADP-induced platelet aggregation inhibitory effects, and additionally had muscle relaxant properties at 300 mg/kg 3 hours after administration. This compound also exhibits a positive inotropic effect on the heart. It is interesting to note that the known compound 5,7 - dimethyl - 3 - carbethoxy pyrazole [1,5a]pyrimidine was an anticonvulsant at 100 mg/kg, as well as an inhibitor of ADP-induced platelet aggregation.

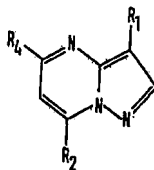
Preliminary pharmacological evaluation has revealed that 5,7-dimethylpyrazolo[1,5a]pyrimidine - 3 - carboxamide, 5,7 - dimethyl - 3 - iodopyrazolo[1,5a]pyrimidine, 3 - bromo - 5,7 - dimethylpyrazolo[1,5a]pyrimidine, and 5 - isopropylpyrazolo[1,5a]pyrimidin - 7 - ol possess significant cardiovascular properties. In the isolated Langendorf heart preparation, these compounds bring about coronary dilation and/or produce a positive inotropic effect at concentrations of 2.5 mg/ml.

When administered orally to rats at a dose of 50 mg/kg of body weight, 5,7-dimethylpyrazolo[1,5a]pyrimidine - 3 - carboxamide, 3 - bromo - 5,7 - dimethylpyrazolo[1,5a]pyrimidine, 5,7 - dimethyl - 3 - iodopyrazolo[1,5a]pyrimidine, and 5 - isopropylpyrazolo[1,5a]pyrimidin - 7 - ol significantly lowered blood pressure (10% or more). At an oral dose of 25 mg/kg, 5,7 - dimethyl - 3 - iodopyrazolo[1,5a]pyrimidine lowered blood pressure by 10% for periods of up to six hours.

In anesthetized dogs, 3 - bromo - 5,7 - dimethylpyrazolo[1,5a] pyrimidine [5 mg/kg; i.v. infusion] caused a significant increase in the cardiac output at both 30 and 60 minutes following the start of infusion (p 0.05). The increased output was 21% and 20% respectively. The cardiac output was maintained above baseline values for two hours after the infusion was stopped. A similar increase (p=0.005) was observed in stroke volume during the same time. No significant changes were noted in the arterial pressure, central venous pressure, or heart rate.

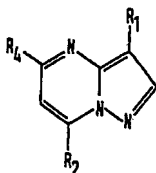
Additional pharmacological evaluation has revealed that 5,7 - dimethyl - 3 - nitro-pyrazolo[1,5a] pyrimidine and 7 - hydrazino - 5 - methylpyrazolo[1,5a] pyrimidine possess anti-pregnancy activity in mice at an oral dose of 12.5 mg/kg of body weight.

Numerous of the 3,5,7-trisubstitutedpyrazolo[1,5a] pyrimidines have shown anti-inflammatory (anti-edema) activity when evaluated by the methods described by C. A. Winter, et al, in *Proc. Exper. Biol. Med.*, 111, 544 (1962). In this test procedure significance is associated with compounds that bring about at least a 30% reduction in foot volume when administered orally to rats at an oral dose of 100 mg/kg of body weight. The following table illustrated the activity possessed by various compounds of the present invention.



R ₄	R ₂	R ₁	Dose mg/kg	Inhibition of foot volume (%)
CH ₃	CH ₃	NO ₂	100	30
CH ₃	CH ₃	CONH ₂	100	38
"	"	"	50	0
CH ₃	CH ₃	Br	100	38
"	"	"	50	10
CH ₃	CH ₃	I	100	75
"	"	"	50	54
"	"	"	25	0
CH ₃	NH-C ₄ H ₉ (n)	Br	100	50
"	"	"	50	0

5 Numerous of these 3,5,7-trisubstitutedpyrazolo[1,5a]pyrimidines are classified as smooth muscle relaxants as evidenced by the fact that relaxation of isolated guinea pig uteri preparations is observed on administration of such a compound. The following table illustrates the activity that various compounds of the present invention possess (Significance is associated with a + response at concentrations of 10 mg/ml or less).

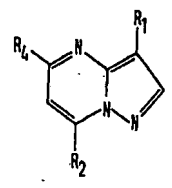


R ₄	R ₂	R ₁	Conc. μg/ml	Response
CH ₃	CH ₃	I	10	+
"	"	"	2	+
"	"	"	0.4	-
CH(CH ₃) ₂	OH	H	10	+
"	"	"	2	-
C ₆ H ₅	CH ₃	H	10	+
"	"	"	2	+
"	"	"	0.4	-
C ₃ H ₇ (n)	C ₃ H ₇ (n)	H	10	+
"	"	"	2	+
"	"	"	0.4	-
C ₂ H ₅	C ₂ H ₅	H	10	+
"	"	"	2	-
CH ₃	C ₃ H ₇ (n)	Br	10	+
"	"	"	2	+
"	"	"	0.4	-
C ₃ H ₇ (n)	C ₃ H ₇ (n)	Br	10	+
"	"	"	2	-

5

Numerous of the 3,5,7-trisubstitutedpyrazolo[1,5a]pyrimidines have also been found to significantly inhibit ADP induced platelet aggregation as determined by the method of M. H. Pindell, et al, described in *Microvasc. Research*, 1, 374 (1969). Significance in this test system is associated with compounds that possess the ability to inhibit 50% or greater at a concentration of 100 mg/ml. The following table illustrates the activity that various compounds of the present invention possess.

5



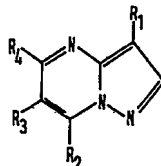
R ₄	R ₂	R ₁	Conc. μg/ml	(%) Inhibition
CH ₃	CH ₃	C≡N	100	79
"	"	"	50	62
"	"	"	25	31
CH ₃	CH ₃	NO ₂	100	54
"	"	"	50	41
CH ₃	CH ₃	CONH ₂	100	100
"	"	"	10	51
"	"	"	5	41
CH ₃	CH ₃	COOEt*	100	59
"	"	" *	50	21
CH ₃	CH ₃	Br	100	75
"	"	"	50	50
CH ₃	C ₂ H ₅	NO ₂	100	72
"	"	"	50	16

* For comparison only.

- 5
- When 3 - ethyl - 5 - methyl - 7 - n - propylaminopyrazolo[1,5a]pyrimidine was administered orally to rats at a dose of 100 mg/kg, it was observed that this compound possessed significant anti-inflammatory activity. Following the protocol of C. A. Winter, et al, described in *Proc. Exper. Biol. Med.*, 111, 544—7 (1962), this compound brought about a 30—40% decrease in foot volume as adjudged 4 hours after dosing.
- 5
- 10
- A. B. Richards, et al, described in *Curr. Ther. Res.*, 11, 587—93 (1963) a method for evaluating compounds for their antinauseant activities. Following this protocol, it has been found that 5,7 - dimethyl - 3 - ethylpyrazolo[1,5a]pyrimidin-7 - yl) - N,N - dimethyl hydrazine possess significant antinauseant activity when administered by intraperitoneal injection to guinea pigs at a dose of 100 mg/kg of body weight.
- 10
- 15
- When 5,7 - dimethyl - 3 - ethylpyrazolo[1,5a]pyrimidine was administered orally to rats at a dose of 25 mg/kg, it was observed that this compound possessed the ability to inhibit stress induced ulcer formation. Following the procedures described by D. A. Brodie, et al, in *Journal of Neuropsychiatry*, 4, 388—408 (1968), this compound inhibited stress induced ulcers by 60—70% six hours after dosing.
- 15
- 20
- Preliminary pharmacological evaluation has revealed also that several 3-alkyl substituted compounds of the present invention possess the ability to bring about
- 20

smooth muscle relaxation. Following the protocol described by B. Levy and S. Tozzi in *Journal of Pharmacology and Experimental Therapeutics*, 142, 178—84 (1963), it has been found that several of the compounds bring about relaxation of isolated guinea pig uteri at low concentrations. The results of these studies are summarized in Table VIII.

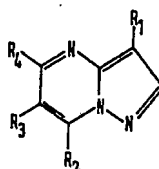
TABLE VIII



R ₄	R ₃	R ₂	R ₁	Minimum Effective Concentration (μg/ml)
CH ₃	H	CH ₃	C ₂ H ₅	10
CH ₃	H	NH—CH ₂ —CH ₂ —CH ₃	C ₂ H ₅	2
CH ₃	H	O—CH ₂ —CH ₂ —CH ₃	C ₂ H ₅	10
CH ₃	H	S—CH ₂ —CH ₃	C ₂ H ₅	10

WHAT WE CLAIM IS:—

1. A compound of the structure



- 10 wherein R₁ is H, alkoxycarbonyl, alkyl, carbonitrile, halogen, carbamoyl, acyl, amino-methyl, dialkylaminomethyl, nitro, amino, or acetamido; R₂ is alkyl, C₁ to C₈ linear or branched chain alkoxy, C₁ to C₈ alkylthio, SH, or alkyl or dialkylamino, cyclic amino or substituted amino; R₃ is H; and R₄ is H, alkyl, or phenyl; provided that
- 15 when R₂ and R₄ are methyl, R₁ is not H or carbethoxy; when R₄ is CH₃ and R₂ is methoxy or ethoxy, R₁ is not H; when R₂ is CH₃, R₄ and R₁ are not both H; and when R₂ is hydrazine and R₄ is phenyl, R₁ is not H.
2. A compound as claimed in claim 1, wherein there is at least one alkyl sub-
- 20 stituent having from 1 to 8 carbon atoms.
3. A compound as claimed in claim 1 or claim 2, wherein there is at least one alkoxy substituent having from 1 to 4 carbon atoms.
4. A compound as claimed in any one of claims 1 to 3, wherein R₂ is an alkylthio group having from 1 to 3 carbon atoms.
5. A compound as claimed in any one of claims 1 to 3, wherein R₂ is dialkoxy-
- 25 alkylamino, carboxyalkylamino, hydroxyalkylamino, hydrazyl, alkylidenohydrazyl, morpholino or piperidino.
6. A compound as claimed in any one of claims 1 to 3, wherein R₂ and R₄ are alkyl and R₁ is halogen.
7. A compound as claimed in claim 6, wherein R₂ and R₄ are methyl and R₁ is bromine, chlorine or iodine.
- 30 8. A compound as claimed in claim 6, wherein R₄ is methyl, R₂ is propyl, and R₁ is halogen.
9. A compound as claimed in claim 8, wherein R₁ is bromine.
10. A compound as claimed in any one of claims 1 to 3, wherein R₂ and R₄ are alkyl and R₁ is H.

11. A compound as claimed in claim 10, wherein R₂ and R₄ are ethyl.
12. A compound as claimed in claim 6, wherein R₂ and R₄ are both ethyl or propyl and R₁ is bromine.
13. A compound as claimed in claim 6, wherein R₂ is ethyl, and R₁ is bromine.
14. A compound as claimed in any one of claims 1 to 3, wherein R₂ and R₄ are alkyl and R₁ is nitro.
15. A compound as claimed in claim 14, wherein R₄ is methyl and R₂ is ethyl.
16. A compound as claimed in any one of claims 1 to 3, wherein R₄ is phenyl, R₂ is alkyl and R₁ is H.
17. A compound as claimed in claim 16, wherein R₂ is methyl.
18. A compound as claimed in any one of claims 1 to 3, wherein R₄ is alkyl, R₂ is alkylamino and R₁ is halogen.
19. A compound as claimed in claim 18, wherein R₄ is methyl, R₂ is butylamino and R₁ is bromine.
20. A compound as claimed in any one of claims 1 to 3, wherein R₄ is alkyl, R₂ is alkylamino or dialkylamino, and R₁ is H.
21. A compound as claimed in claim 20, wherein R₄ is methyl and R₂ is diethylamino.
22. A compound as claimed in claim 21, wherein R₄ is methyl and R₂ is octylamino.
23. A compound as claimed in any one of claims 1 to 3 or 5, wherein R₄ is alkyl, R₂ is substituted amino and R₁ is halogen.
24. A compound as claimed in claim 23, wherein R₄ is methyl, R₂ is dialkoxyalkylamino, and R₁ is bromine.
25. A compound as claimed in claim 24, wherein R₂ is dimethoxyethylamino.
26. A compound as claimed in any one of claims 1 to 3 or 5, wherein R₄ is alkyl, R₂ is cyclic amino or substituted amino and R₁ is H.
27. A compound as claimed in claim 26, wherein R₄ is methyl and R₂ is piperidino or hydroxyalkylamino.
28. A compound as claimed in claim 27, wherein R₂ is hydroxyethylamino.
29. A compound as claimed in any one of claims 1 to 3, wherein R₄ is ethyl.
30. A compound as claimed in claim 29, wherein R₂ and R₄ are methyl.
31. A compound as claimed in claim 29, wherein R₄ is methyl and R₂ is alkylamino.
32. A compound as claimed in claim 31, wherein R₂ is propylamino.
33. A compound as claimed in claim 29, wherein R₄ is methyl and R₂ is propoxy or ethylthio.
34. A process for preparing the 3,5,7 trisubstitutedpyrazolo[1,5a]pyrimidines defined in claim 1, which process comprises reacting a 3-aminopyrazole derivative with a symmetrical β-diketone or an unsymmetrical β-diketone.
35. A process as claimed in claim 34, wherein a 3-unsubstituted compound is obtained in the reaction involving a 3-amino-pyrazole derivative which 3-unsubstituted compound is subsequently reacted with an electrophilic reagent to obtain a 3,5,7-trisubstitutedpyrazolo [1,5a] pyrimidine.
36. A process as claimed in claim 35, wherein the electrophilic reagent is N-bromosuccinimide, N-chlorosuccinimide, iodine monochloride, trifluoroacetic acid and boron trifluoride etherate, a friedelcrafts acylation system, a nitrating reagent, or an aqueous solution of dimethylamine and formalin solution.
37. A process for preparing the 3,5,7-trisubstitutedpyrazolo[1,5-a]-pyrimidines defined in claim 1 which process comprises reacting a 3-aminopyrazole derivative with a β-keto ester, treating the resulting 7-hydroxy substituted compound with phosphorus oxychloride to obtain the 7-chloro-3,5-disubstituted pyrazolo [1,5-a] pyrimidine, which is then reacted with a nucleophilic reagent to provide the said 7-amino-, 7-alkoxy- or 7-alkylthio- derivatives.
38. A process as claimed in claim 37, wherein the nucleophilic reagent is an amine, a sodium alkoxide or a sodium alkylmercaptide.
39. A process as claimed in claim 34, substantially as hereinbefore described.
40. A process as claimed in claim 34, substantially as hereinbefore described in any one of the specific Examples.
41. A compound as claimed in claim 1, whenever prepared by a process as claimed in any one of claims 34 to 40.

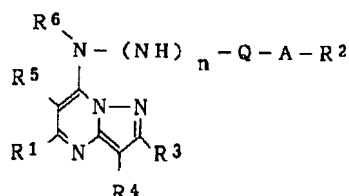
I.C.N. PHARMACEUTICALS INC.,
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【特許請求の範囲】

【請求項1】 一般式

【化1】



〔式中、R¹ は水素原子、置換基としてチエニル基、低級アルコキシ基、低級アルキルチオ基、オキシ基又はヒドロキシル基を有することのある低級アルキル基、シクロアルキル基、チエニル基、フリル基、低級アルケニル基又は置換基として低級アルキル基、低級アルコキシ基、フェニルチオ基及びハロゲン原子から選ばれる基の1～3個を有することのあるフェニル基を、R² はナフチル基、シクロアルキル基、フリル基、チエニル基、ハロゲン原子で置換されることのあるピリジル基、ハロゲン原子で置換されることのあるフェノキシ基又は置換基として低級アルキル基、低級アルコキシ基、ハロゲン原子、ニトロ基、ハロゲン置換低級アルキル基、ハロゲン置換低級アルコキシ基、低級アルコキシカルボニル基、ヒドロキシル基、フェニル低級アルコキシ基、アミノ基、シアノ基、低級アルカノイルオキシ基、フェニル基及び低級アルコキシホスホリル低級アルキル基から選ばれる基の1～3個を有することのあるフェニル基を、R³ は水素原子、フェニル基又は低級アルキル基を、R⁴ は水素原子、低級アルキル基、低級アルコキシカルボニル基、フェニル低級アルキル基、置換基としてフェニルチオ基を有することのあるフェニル基又はハロゲン原子を、R⁵ は水素原子又は低級アルキル基を、R⁶ は水素原子、低級アルキル基、フェニル低級アルキル基又は置換基として低級アルコキシ基、ハロゲン置換低級アルキル基及びハロゲン原子から選ばれる基の1～3個を有するベンゾイル基を示し、またR¹ 及びR⁵ は互いに結合して低級アルキレン基を形成してもよく、Qはカルボニル基又はスルホニル基を、Aは単結合、低級アルキレン基又は低級アルケニレン基をそれぞれ示し、nは0又は1を示す。〕で表わされるピラゾロ〔1, 5-a〕ピリミジン誘導体を有効成分として、その有効量を、無毒性担体と共に含有することを特徴とする一酸化窒素合成酵素阻害剤。

【請求項2】 有効成分が、請求項1に記載の一般式中、R⁵ 及びR⁶ がそれぞれ水素原子で、Qがカルボニル基で、Aが単結合で、nが0である化合物である請求項1に記載の一酸化窒素合成酵素阻害剤。

【請求項3】 有効成分が、請求項1に記載の一般式中、R¹ がフェニル基又は置換基としてヒドロキシル基又は低級アルコキシ基を有することのある低級アルキル基で、R² が置換基として低級アルコキシ基、ハロゲン

置換低級アルキル基及びハロゲン原子から選ばれる基の1～3個を有するフェニル基で、R⁴ が水素原子又はフェニル基である化合物である請求項2に記載の一酸化窒素合成酵素阻害剤。

【請求項4】 有効成分が、請求項1に記載の一般式中、R¹ がフェニル基、メチル基、エチル基、n-ブチル基又はn-ペンチル基で、R² が4-エトキシ-3, 5-ジメトキシフェニル基、3, 4, 5-トリメトキシフェニル基、2-メトキシフェニル基、2, 4-ジクロロフェニル基又は2-トリフルオロメチルフェニル基である化合物である請求項2に記載の一酸化窒素合成酵素阻害剤。

【請求項5】 有効成分が、5-n-ブチル-7-(3, 4, 5-トリメトキシベンゾイルアミノ)ピラゾロ〔1, 5-a〕ピリミジン、5-フェニル-7-(3, 4, 5-トリメトキシベンゾイルアミノ)ピラゾロ〔1, 5-a〕ピリミジン及び5-n-ブチル-7-(2-トリフルオロメチルベンゾイルアミノ)ピラゾロ〔1, 5-a〕ピリミジンから選ばれる化合物である請求項4に記載の一酸化窒素合成酵素阻害剤。

【請求項6】 有効成分が、5-n-ブチル-7-(3, 4, 5-トリメトキシベンゾイルアミノ)ピラゾロ〔1, 5-a〕ピリミジンである請求項5に記載の一酸化窒素合成酵素阻害剤。

【請求項7】 誘導型一酸化窒素合成酵素を選択的に阻害する請求項1～6のいずれかに記載の一酸化窒素合成酵素阻害剤。

【請求項8】 請求項1に記載のピラゾロ〔1, 5-a〕ピリミジン誘導体の有効量を、無毒性担体と共に含有することを特徴とする敗血症予防及び治療剤。

【請求項9】 請求項1に記載のピラゾロ〔1, 5-a〕ピリミジン誘導体の有効量を、無毒性担体と共に含有することを特徴とするエンドトキシンショック改善剤。

【発明の詳細な説明】

【0001】

【発明の属する技術分野】本発明は新規なNO（一酸化窒素）合成酵素阻害剤、より詳しくは誘導型NO合成酵素の誘導を阻害する薬剤に関する。

【0002】

【従来の技術】1980年代前半、生体内における窒素酸化物の研究過程で、NO（一酸化窒素）が生体内で産生していることが初めて見出された。その発見をきっかけに、NOは多くの研究者の注目を集め、1987年には、NOが血管内皮由来弛緩因子の本体であるとの報告がなされた。そして、現在では、循環、免疫、神経系等広い分野で、NOの生理機能や病態との関連が明らかにされている。

【0003】そのうち、例えば、体内で常時産生しているNOは、循環動態の恒常性を維持する重要な役割を担

っていることが解明されている。また一方、敗血症においては、エンドトキシンにより活性化されたサイトカインの働きにより、大量のNOが産生され、これが内皮細胞障害、心筋収縮力低下等のエンドトキシンショック状態を引き起こすといわれている。

【0004】NOは、NO合成酵素（NOS）によってL-アルギニンから産生される。そして、その酵素には、大きく分けて病態時のNO産生に係わる誘導型NOS（iNOS）と、常時発現している構成型NOS（cNOS）とがある。

【0005】上記したように、NOは敗血症等の種々の疾患に関与しているので、そのメカニズムの解明、惹いてはそれら疾患の治療薬への応用等を目的として、NO阻害剤の研究が進められており、その代表例としては、N- ω -ニトロ-L-アルギニン等のアルギニン類縁体が挙げられる。

【0006】しかしながら、上記代表例を含む従来公知のNOS阻害剤は、iNOSだけでなく、cNOSをも阻害してしまうものが殆どであり、之等の治療薬としての利用によれば、恒常的な循環動態の調節までもが抑制されてしまい、血圧上昇、臓器血流減少等の副作用を回避することはできない。更に、之等の利用時には、中枢神経系への影響やインポテンツ等の問題も懸念される。

【0007】以上のように、従来知られているNOS阻害剤は、医薬品として評価できるものではなく、之等に代わって、iNOSを選択的に阻害することのできる新しい物質の提供が当業界で要望されている。

【0008】

【発明が解決しようとする課題】従って、本発明の目的は、当業界で要望されているiNOSのみを選択的に阻害できる物質及びこれを利用した一酸化窒素合成酵素阻害剤を提供することにある。

【0009】本発明者らの研究グループは、かねてより医薬製剤有効成分化合物の開発を目的として、種々の化合物の合成及びそれらの有する薬理作用の研究、解明等を行なってきたが、その過程で、先に、強力な鎮痛作用を有する一連のピラゾロピリミジン誘導体の合成に成功し、この化合物に係わる発明を特許出願した〔WO95/35298〕。

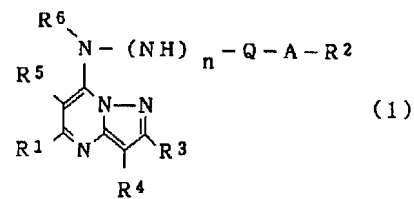
【0010】引き続き研究において、本発明者らは、上記一連の化合物が、先に見出された鎮痛作用とは別個に、しかも該作用とは無関係に、iNOSの誘導阻害作用を有するという事実を新たに見出し、ここに本発明を完成するに至った。

【0011】

【課題を解決するための手段】即ち、本発明によれば、下記一般式（1）で表わされるピラゾロ〔1, 5-a〕ピリミジン誘導体を有効成分とする一酸化窒素合成酵素阻害剤が提供される。

【0012】

【化2】



【0013】上記一般式（1）中、R¹ は水素原子、置換基としてチエニル基、低級アルコキシ基、低級アルキルチオ基、オキソ基又はヒドロキシル基を有することのある低級アルキル基、シクロアルキル基、チエニル基、フリル基、低級アルケニル基又は置換基として低級アルキル基、低級アルコキシ基、フェニルチオ基及びハロゲン原子から選ばれる基の1～3個を有することのあるフェニル基を、R² はナフチル基、シクロアルキル基、フリル基、チエニル基、ハロゲン原子で置換されることのあるピリジル基、ハロゲン原子で置換されることのあるフェノキシ基又は置換基として低級アルキル基、低級アルコキシ基、ハロゲン原子、ニトロ基、ハロゲン置換低級アルキル基、ハロゲン置換低級アルコキシ基、低級アルコキシカルボニル基、ヒドロキシル基、フェニル低級アルコキシ基、アミノ基、シアノ基、低級アルカノイルオキシ基、フェニル基及び低級アルコキシホスホリル低級アルキル基から選ばれる基の1～3個を有することのあるフェニル基を、R³ は水素原子、フェニル基又は低級アルキル基を、R⁴ は水素原子、低級アルキル基、低級アルコキシカルボニル基、フェニル低級アルキル基、置換基としてフェニルチオ基を有することのあるフェニル基又はハロゲン原子を、R⁵ は水素原子又は低級アルキル基を、R⁶ は水素原子、低級アルキル基、フェニル低級アルキル基又は置換基として低級アルコキシ基、ハロゲン置換低級アルキル基及びハロゲン原子から選ばれる基の1～3個を有するベンゾイル基を示し、またR¹ 及びR⁵ は互いに結合して低級アルキレン基を形成してもよく、Qはカルボニル基又はスルホニル基を、Aは単結合、低級アルキレン基又は低級アルケニレン基をそれぞれ示し、nは0又は1を示す。

【0014】上記一般式（1）で表わされる誘導体は、一酸化窒素合成阻害作用、殊に誘導型一酸化窒素合成酵素（iNOS）を選択的に阻害する作用を有しており、従って、血圧上昇、臓器血流減少、中枢神経系への悪影響等の副作用を殆ど示さない点において特徴づけられる。

【0015】本発明一酸化窒素合成酵素阻害剤の有効成分を表わす上記一般式（1）中の各基としては、例えば次の各基を例示できる。即ち、低級アルキル基としては、メチル、エチル、プロピル、イソプロピル、ブチル、イソブチル、tert-ブチル、ペンチル、ヘキシル基等の直鎖又は分枝鎖状低級アルキル基を例示できる。

【0016】シクロアルキル基としては、シクロプロピ

ル、シクロブチル、シクロペンチル、シクロヘキシル、シクロヘプチル、シクロオクチル基等を例示できる。

【0017】低級アルコキシ基としては、メトキシ、エトキシ、プロポキシ、イソプロポキシ、ブトキシ、ペンチルオキシ、ヘキシルオキシ基等を例示できる。

【0018】低級アルキルチオ基としては、メチルチオ、エチルチオ、プロピルチオ、ブチルチオ、ペンチルチオ、ヘキシルチオ基等を例示できる。

【0019】ハロゲン原子には、弗素、塩素、臭素及び沃素原子が含まれる。

【0020】ハロゲン置換低級アルキル基としては、トリフルオロメチル、ペンタフルオロエチル、ヘプタフルオロプロピル、ノナフルオロブチル、ウンデカフルオロペンチル、トリデカフルオロヘキシル基等を例示できる。

【0021】ハロゲン置換低級アルコキシ基としては、トリフルオロメトキシ、ペンタフルオロエトキシ、ヘプタフルオロプロポキシ、ノナフルオロブトキシ、ウンデカフルオロペンチルオキシ、トリデカフルオロヘキシルオキシ基等を例示できる。

【0022】低級アルコキシカルボニル基としては、メトキシカルボニル、エトキシカルボニル、プロポキシカルボニル、イソプロポキシカルボニル、ブトキシカルボニル、ペンチルオキシカルボニル、ヘキシルオキシカルボニル基等を例示できる。

【0023】ジ低級アルコキシホスホリル低級アルキル基としては、ジメトキシホスホリルメチル、ジエトキシホスホリルメチル、ジプロポキシホスホリルメチル、ジイソプロポキシホスホリルメチル、ジブトキシホスホリルメチル、ジペンチルオキシホスホリルメチル、ジヘキシルオキシホスホリルメチル、2-（ジメトキシホスホリル）エチル、2-（ジエトキシホスホリル）エチル、3-（ジエトキシホスホリル）プロピル基等を例示できる。

【0024】ナフチル基には、1-ナフチル、2-ナフチル基が含まれる。

【0025】低級アルキレン基としては、メチレン、エチレン、トリメチレン、テトラメチレン、ペンタメチレン、ヘキサメチレン基等を例示できる。

【0026】低級アルケニレン基としては、ビニレン、プロペニレン基等を例示できる。

【0027】ハロゲン原子で置換されることのあるピリジル基としては、2-ピリジル、3-ピリジル、4-ピリジル、6-クロロ-2-ピリジル、5-クロロ-2-ピリジル、4-クロロ-2-ピリジル、3-クロロ-2-ピリジル、6-クロロ-3-ピリジル、5-クロロ-3-ピリジル、4-クロロ-3-ピリジル、2-クロロ-3-ピリジル、2-クロロ-4-ピリジル、3-クロロ-4-ピリジル、6-フルオロ-3-ピリジル、6-ブromo-3-ピリジル、6-ヨード-3-ピリジル基等

を例示できる。

【0028】ハロゲン原子で置換されることのあるフェノキシ基としては、フェノキシ、2-クロロフェノキシ、3-クロロフェノキシ、4-クロロフェノキシ、4-フルオロフェノキシ、4-ブromofenoxi、4-ヨードフェノキシ基等を例示できる。

【0029】チエニル基には、2-チエニル及び3-チエニル基が含まれ、またフリル基には、2-フリル及び3-フリル基が含まれる。

【0030】低級アルケニル基としては、ビニル、アリル、イソプロペニル、1-ブテニル、2-ブテニル、3-ブテニル、1-ペンテニル、2-ペンテニル、3-ペンテニル、4-ペンテニル、1-ヘキセニル、2-ヘキセニル、3-ヘキセニル、4-ヘキセニル、5-ヘキセニル基等を例示できる。

【0031】フェニル低級アルキル基としては、ベンジル、1-フェニルエチル、2-フェニルエチル、3-フェニルプロピル、4-フェニルブチル、5-フェニルペンチル、6-フェニルヘキシル基等を例示できる。

【0032】フェニル低級アルコキシ基としては、ベンジルオキシ、2-フェニルエトキシ、3-フェニルプロポキシ、4-フェニルブトキシ、5-フェニルペンチルオキシ、6-フェニルヘキシルオキシ基等を例示できる。

【0033】低級アルカノイルオキシ基としては、アセトキシ、プロピオニルオキシ、ブチリルオキシ、バレリルオキシ、ピバロイルオキシ、ヘキサノイルオキシ、ヘプタノイルオキシ基等を例示できる。

【0034】置換基としてチエニル基、低級アルコキシ基、低級アルキルチオ基、オキソ基又はヒドロキシル基を有することのある低級アルキル基としては、上記無置換の低級アルキル基に加えて、2-チエニルメチル、3-チエニルメチル、1-（2-チエニル）エチル、1-（3-チエニル）エチル、2-（2-チエニル）エチル、2-（3-チエニル）エチル、3-（2-チエニル）プロピル、4-（2-チエニル）ブチル、5-（2-チエニル）ペンチル、6-（2-チエニル）ヘキシル、メトキシメチル、エトキシメチル、プロポキシメチル、ブトキシメチル、ペンチルオキシメチル、ヘキシルオキシメチル、1-メトキシエチル、2-メトキシエチル、3-メトキシプロピル、4-メトキシブチル、5-メトキシペンチル、6-メトキシヘキシル、ヒドロキシメチル、1-ヒドロキシエチル、2-ヒドロキシエチル、1-ヒドロキシプロピル、2-ヒドロキシプロピル、3-ヒドロキシプロピル、3-ヒドロキシブチル、4-ヒドロキシペンチル、5-ヒドロキシヘキシル、メチルチオメチル、エチルチオメチル、プロピルチオメチル、ブチルチオメチル、ペンチルチオメチル、ヘキシルチオメチル、2-メチルチオエチル、3-メチルチオプロピル、4-メチルチオブチル、5-メチルチオペンチル

ル、6-メチルチオヘキシル、ホルミル、ホルミルメチル、アセチル、2-ホルミルエチル、2-オキソプロピル、プロピオニル、3-ホルミルプロピル、3-オキソブチル、2-オキソブチル、ブチリル、4-ホルミルブチル、4-オキソペンチル、3-オキソペンチル、2-オキソペンチル、バレリル、5-ホルミルペンチル、5-オキソヘキシル、4-オキソヘキシル、3-オキソヘキシル、2-オキソヘキシル、ヘキサノイル基等を例示できる。

【0035】置換基として低級アルキル基、低級アルコキシ基、フェニルチオ基及びハロゲン原子から選ばれる基の1~3個を有することのあるフェニル基としては、フェニル、2-メチルフェニル、3-メチルフェニル、4-メチルフェニル、4-エチルフェニル、4-プロピルフェニル、4-ブチルフェニル、4-tert-ブチルフェニル、4-ペンチルフェニル、4-ヘキシルフェニル、2,3-ジメチルフェニル、2,4-ジメチルフェニル、2,5-ジメチルフェニル、2,6-ジメチルフェニル、3,4-ジメチルフェニル、3,5-ジメチルフェニル、2-メトキシフェニル、3-メトキシフェニル、4-メトキシフェニル、4-エトキシフェニル、4-プロポキシフェニル、4-ブトキシフェニル、4-ペンチルオキシフェニル、4-ヘキシルオキシフェニル、2,3-ジメトキシフェニル、2,4-ジメトキシフェニル、2,5-ジメトキシフェニル、2,6-ジメトキシフェニル、3,4-ジメトキシフェニル、3,5-ジメトキシフェニル、3,4,5-トリメトキシフェニル、2-クロロフェニル、3-クロロフェニル、4-クロロフェニル、4-ブロモフェニル、4-ヨードフェニル、4-フルオロフェニル、4-(フェニルチオ)フェニル、3-(フェニルチオ)フェニル、2-(フェニルチオ)フェニル基等を例示できる。

【0036】置換基として低級アルキル基、低級アルコキシ基、ハロゲン原子、ニトロ基、ハロゲン置換低級アルキル基、ハロゲン置換低級アルコキシ基、低級アルコキシカルボニル基、ヒドロキシル基、フェニル低級アルコキシ基、アミノ基、シアノ基、低級アルカノイルオキシ基、フェニル基及び低級アルコキシホスホリル低級アルキル基から選ばれる基の1~3個を有することのあるフェニル基としては、次の各基を例示できる。

【0037】即ち、フェニル、2-メチルフェニル、3-メチルフェニル、4-メチルフェニル、4-エチルフェニル、4-プロピルフェニル、4-ブチルフェニル、4-tert-ブチルフェニル、4-ペンチルフェニル、4-ヘキシルフェニル、2-メトキシフェニル、3-メトキシフェニル、4-メトキシフェニル、4-エトキシフェニル、4-プロポキシフェニル、4-ブトキシフェニル、4-ペンチルオキシフェニル、4-ヘキシルオキシフェニル、2,3-ジメトキシフェニル、2,4-ジメトキシフェニル、2,5-ジメトキシフェニル、2,6-

ジメトキシフェニル、3,4-ジメトキシフェニル、3,5-ジメトキシフェニル、2,3,4-トリメトキシフェニル、2,3,5-トリメトキシフェニル、2,3,6-トリメトキシフェニル、2,4,5-トリメトキシフェニル、2,4,6-トリメトキシフェニル、3,4,5-トリメトキシフェニル、3,4,5-トリエトキシフェニル、2-フルオロフェニル、3-フルオロフェニル、4-フルオロフェニル、2-クロロフェニル、3-クロロフェニル、4-クロロフェニル、2-ブロモフェニル、3-ブロモフェニル、4-ブロモフェニル、4-ヨードフェニル、2,3-ジクロロフェニル、2,4-ジクロロフェニル、2-ニトロフェニル、3-ニトロフェニル、4-ニトロフェニル、2-トリフルオロメチルフェニル、3-トリフルオロメチルフェニル、4-トリフルオロメチルフェニル、4-ペンタフルオロエチルフェニル、4-ヘプタフルオロプロピルフェニル、4-ノナフルオロブチルフェニル、4-ウンデカフルオロペンチルフェニル、4-トリデカフルオロヘキシルフェニル、2-メトキシカルボニルフェニル、3-メトキシカルボニルフェニル、4-メトキシカルボニルフェニル、4-エトキシカルボニルフェニル、4-プロポキシカルボニルフェニル、4-ブトキシカルボニルフェニル、4-ペンチルオキシカルボニルフェニル、4-ヘキシルオキシカルボニルフェニル、2-ビフェニル、3-ビフェニル、4-ビフェニル、2-(ジエトキシホスホリルメチル)フェニル、3-(ジエトキシホスホリルメチル)フェニル、4-(ジエトキシホスホリルメチル)フェニル、4-(ジイソプロポキシホスホリルメチル)フェニル、3,5-ジメトキシ-4-エトキシフェニル、3,5-ジメトキシ-4-プロポキシフェニル、4-ブトキシ-3,5-ジメトキシフェニル、3,5-ジメトキシ-4-ペンチルオキシフェニル、3,5-ジメトキシ-4-ヘキシルオキシフェニル、2,3-ビス(トリフルオロメチル)フェニル、2,4-ビス(トリフルオロメチル)フェニル、2,5-ビス(トリフルオロメチル)フェニル、2,6-ビス(トリフルオロメチル)フェニル、3,4-ビス(トリフルオロメチル)フェニル、3,5-ビス(トリフルオロメチル)フェニル、3,5-ジメトキシ-4-ヒドロキシフェニル、3,5-ジエトキシ-4-ヒドロキシフェニル、4-ベンジルオキシ-3,5-ジメトキシフェニル、4-ベンジルオキシ-3,5-ジエトキシフェニル、3,5-ジメトキシ-4-(2-フェニルエトキシ)フェニル、4-アセトキシ-3,5-ジメトキシフェニル、3,5-ジメトキシ-4-プロピオニルオキシフェニル、2-クロロ-3,5-ジメトキシフェニル、4-クロロ-3,5-ジメトキシフェニル、4-ブロモ-3,5-ジメトキシフェニル、3,5-ジメトキシ-4-ヨードフェニル、3,5-

ージクロロ-4-メトキシフェニル、3, 5-ジクロロ-4-エトキシフェニル、2-アミノフェニル、3-アミノフェニル、4-アミノフェニル、2-シアノフェニル、3-シアノフェニル、4-シアノフェニル、4-トリフルオロメトキシフェニル、3-トリフルオロメトキシフェニル、2-トリフルオロメトキシフェニル、4-ペンタフルオロエトキシフェニル、4-ヘプタフルオロプロボキシフェニル、4-ノナフルオロブトキシフェニル、4-ウンデカフルオロペンチルオキシフェニル、4-トリデカフルオロヘキシルオキシフェニル、3, 5-ビス(トリフルオロメトキシ)フェニル、3, 4, 5-トリス(トリフルオロメトキシ)フェニル基等を例示できる。

【0038】置換基としてフェニルチオ基を有することのあるフェニル基としては、フェニル、4-(フェニルチオ)フェニル、3-(フェニルチオ)フェニル、2-(フェニルチオ)フェニル基等を例示できる。

【0039】置換基として低級アルコキシ基、ハロゲン置換低級アルキル基及びハロゲン原子から選ばれる基の1~3個を有するベンゾイル基としては、2-クロロベンゾイル、3-クロロベンゾイル、4-クロロベンゾイル、2-フルオロベンゾイル、2-ブロモベンゾイル、2-ヨードベンゾイル、2, 4-ジクロロベンゾイル、3, 4-ジクロロベンゾイル、2, 5-ジクロロベンゾイル、2, 6-ジクロロベンゾイル、2-トリフルオロメチルベンゾイル、3-トリフルオロメチルベンゾイル、4-トリフルオロメチルベンゾイル、3, 5-ビス(トリフルオロメチル)ベンゾイル、3, 4, 5-トリス(トリフルオロメチル)ベンゾイル、2-メトキシベンゾイル、3-メトキシベンゾイル、4-メトキシベンゾイル、2, 3-ジメトキシベンゾイル、2, 4-ジメトキシベンゾイル、3, 5-ジメトキシベンゾイル、3, 4, 5-トリメトキシベンゾイル、2-エトキシベンゾイル、2-プロボキシベンゾイル、2-ブトキシベンゾイル、2-ペンチルオキシベンゾイル、2-ヘキシルオキシベンゾイル基等を例示できる。

【0040】上記一般式(1)で表わされるピラゾロ〔1, 5-a〕ピリミジン誘導体は、一酸化窒素合成酵素阻害剤、特に誘導型一酸化窒素合成酵素(iNOS)を選択的に阻害する薬剤として、敗血症、エンドトキシンショック、慢性関節リウマチ等の治療及び予防に有用であり、従来の一酸化窒素合成酵素阻害剤にみられる如き副作用が非常に少ない利点がある。

【0041】上記一酸化窒素合成酵素阻害剤として好ましいピラゾロ〔1, 5-a〕ピリミジン誘導体としては、前記一般式(1)中、 R^4 及び R^5 がそれぞれ水素原子で、Qがカルボニル基で、Aが単結合で、nが0である化合物を例示できる。該化合物の内でも、特に R^1 がフェニル基又は置換基としてヒドロキシル基又は低級アルコキシ基を有することのある低級アルキル基で、 R^2

が置換基として低級アルコキシ基、ハロゲン置換低級アルキル基及びハロゲン原子から選ばれる基の1~3個を有するフェニル基で、 R^4 が水素原子又はフェニル基である化合物、より具体的には R^1 がフェニル基、メチル基、エチル基、n-ブチル基又はn-ペンチル基で、 R^2 が4-エトキシ-3, 5-ジメトキシフェニル基、3, 4, 5-トリメトキシフェニル基、2-メトキシフェニル基、2, 4-ジクロロフェニル基又は2-トリフルオロメチルフェニル基である化合物は、好適である。

【0042】之等好適なピラゾロ〔1, 5-a〕ピリミジン誘導体の具体例としては、例えば5-n-ブチル-7-(3, 4, 5-トリメトキシベンゾイルアミノ)ピラゾロ〔1, 5-a〕ピリミジン、5-フェニル-7-(3, 4, 5-トリメトキシベンゾイルアミノ)ピラゾロ〔1, 5-a〕ピリミジン及び5-n-ブチル-7-(2-トリフルオロメチルベンゾイルアミノ)ピラゾロ〔1, 5-a〕ピリミジンを例示することができ、この内でも5-n-ブチル-7-(3, 4, 5-トリメトキシベンゾイルアミノ)ピラゾロ〔1, 5-a〕ピリミジンは最適である。

【0043】上記一般式(1)で表わされる本発明有効成分化合物は、各種の方法により製造することができ、その具体例としては、前記WO95/35298号公報に記載の方法を例示することができる。

【0044】代表的には、該方法は、適当なカルボン酸エステルと3-アミノピラゾールイルとを縮合反応させて、7-ヒドロキシピラゾロ〔1, 5-a〕ピリミジン類を得、次いでこれをハロゲン化して、7-ハロゲノピラゾロ〔1, 5-a〕ピリミジン類とし、更にこれをアンモニア水又はヒドラジンで処理して7-アミノ体に変換し、これに酸ハロゲン化物を反応させることにより実施できる。

【0045】かかる方法に従い得られる本発明有効成分化合物の具体例としては、後記第1表~第5表に実施例No. 1~134として示す各化合物を例示することができる。

【0046】上記一般式(1)で表わされる化合物は、医薬的に許容される酸付加塩とすることができ、之等の塩も本発明一酸化窒素合成酵素阻害剤の有効成分化合物に包含される。上記酸付加塩を形成させ得る酸としては、例えば塩酸、臭化水素酸、硫酸等の無機酸、シュウ酸、フマル酸、マレイン酸、酒石酸、クエン酸等の有機酸を例示でき、この酸付加塩の形成反応は常法に従うことができる。

【0047】また、上記一般式(1)で表わされる化合物中、 R^6 が水素原子であるものは、これを常法に従ってアルカリ金属塩、例えばナトリウム塩、カリウム塩等、アルカリ土類金属塩、例えばカルシウム塩、マグネシウム塩等、その他銅塩等とすることができ、之等の塩類も本発明一酸化窒素合成酵素阻害剤有効成分化合物に

包含される。

【0048】尚、一般式(1)で表わされる化合物中、Aがアルケニレン基である化合物及びR1が低級アルケニル基である化合物の一部は、シス、トランス異性体構造をとることができ、本発明一酸化窒素合成酵素阻害剤は之等のいずれをも有効成分とすることができる。

【0049】また、一般式(1)で表わされる化合物中の一部の化合物は、炭素原子を不斉中心とした光学異性体が存在し、本発明一酸化窒素合成酵素阻害剤は、かかる光学活性体及びラセミ体のいずれをも有効成分とすることができる。

【0050】本発明一酸化窒素合成酵素阻害剤は、上記一般式(1)で表わされる化合物を有効成分として、これを、適当な無毒性製剤担体と共に用いて、一般的な医薬製剤組成物の形態とされ実用される。

【0051】本発明医薬製剤に利用される上記製剤担体としては、製剤の使用形態に応じて、通常使用される充填剤、増量剤、結合剤、付湿剤、崩壊剤、表面活性剤、滑沢剤等の希釈剤あるいは賦形剤を例示でき、これらは得られる製剤の投与単位形態に応じて適宜選択使用される。

【0052】上記医薬製剤の投与単位形態としては、各種の形態が治療目的に応じて選択でき、その代表的なものとしては錠剤、丸剤、散剤、液剤、懸濁剤、乳剤、顆粒剤、カプセル剤、坐剤、注射剤(液剤、懸濁剤等)、軟膏剤等が挙げられる。

【0053】錠剤の形態に成形するに際しては、上記製剤担体として例えば乳糖、白糖、塩化ナトリウム、ブドウ糖、尿素、デンプン、炭酸カルシウム、カオリン、結晶セルロース、ケイ酸、リン酸カリウム等の賦形剤、水、エタノール、プロパノール、単シロップ、ブドウ糖液、デンプン液、ゼラチン溶液、カルボキシメチルセルロース、ヒドロキシプロピルセルロース、メチルセルロース、ポリビニルピロリドン等の結合剤、カルボキシメチルセルロースナトリウム、カルボキシメチルセルロースカルシウム、低置換度ヒドロキシプロピルセルロース、乾燥デンプン、アルギン酸ナトリウム、カンテン末、ラミナラン末、炭酸水素ナトリウム、炭酸カルシウム等の崩壊剤、ポリオキシエチレンソルビタン脂肪酸エステル類、ラウリル硫酸ナトリウム、ステアリン酸モノグリセリド等の界面活性剤、白糖、ステアリン、カカオバター、水素添加油等の崩壊抑制剤、第4級アンモニウム塩基、ラウリル硫酸ナトリウム等の吸収促進剤、グリセリン、デンプン等の保湿剤、デンプン、乳糖、カオリン、ベントナイト、コロイド状ケイ酸等の吸着剤、精製タルク、ステアリン酸塩、ホウ酸末、ポリエチレングリコール等の滑沢剤等を使用できる。更に錠剤は必要に応じて通常の剤皮を施した錠剤、例えば糖衣錠、ゼラチン被包錠、腸溶被錠、フィルムコーティング錠あるいは二重錠、多層錠とすることができる。

【0054】丸剤の形態に成形するに際しては、製剤担体として例えばブドウ糖、乳糖、デンプン、カカオ脂、硬化植物油、カオリン、タルク等の賦形剤、アラビアゴム末、トラガント末、ゼラチン、エタノール等の結合剤、ラミナラン、カンテン等の崩壊剤等を使用できる。

【0055】坐剤の形態に成形するに際しては、製剤担体として例えばポリエチレングリコール、カカオ脂、高級アルコール、高級アルコールのエステル類、ゼラチン、半合成グリセライド等を使用できる。

【0056】カプセル剤は、常法に従い通常本発明の有効成分化合物を上記で例示した各種の製剤担体と混合して硬質ゼラチンカプセル、軟質カプセル等に充填して調整される。

【0057】液剤、乳剤、懸濁剤等の注射剤として調製される場合、之等は殺菌され且つ血液と等張であるのが好ましく、之等の形態に成形するに際しては、希釈剤として例えば水、エチルアルコール、マクロゴール、プロピレングリコール、エトキシ化イソステアリルアルコール、ポリオキシ化イソステアリルアルコール、ポリオキシエチレンソルビタン脂肪酸エステル類等を使用できる。尚、この場合等張性の溶液を調整するに充分な量の食塩、ブドウ糖あるいはグリセリンを本発明薬剤中に含有させてもよく、また通常の溶解補助剤、緩衝剤、無痛化剤等を添加してもよい。

【0058】更に、本発明薬剤中には、必要に応じて着色剤、保存剤、香料、風味剤、甘味剤等や他の医薬品を含有させることもできる。

【0059】ペースト、クリーム、ゲル等の軟膏剤の形態に成形するに際しては、希釈剤として例えば白色ワセリン、パラフィン、グリセリン、セルロース誘導体、ポリエチレングリコール、シリコン、ベントナイト等を使用できる。

【0060】本発明薬剤中に含有されるべき一般式(1)で表わされる有効成分化合物の量は、特に限定されず広範囲より適宜選択されるが、通常医薬製剤中に約1~70重量%程度含有されるものとするのがよい。

【0061】上記医薬製剤の投与方法は特に制限がなく、各種製剤形態、患者の年齢、性別その他の条件、疾患の程度等に応じて決定される。例えば錠剤、丸剤、液剤、懸濁剤、乳剤、顆粒剤及びカプセル剤は経口投与され、注射剤は単独で又はブドウ糖、アミノ酸等の通常の補液と混合して静脈内投与され、更に必要に応じ単独で筋肉内、皮内、皮下もしくは腹腔内投与され、坐剤は直腸内投与される。

【0062】上記医薬製剤の投与量は、その用法、患者の年齢、性別その他の条件、疾患の程度等により適宜選択されるが、通常有効成分である本発明化合物の量が1日当たり体重1kg当たり約0.5~20mg程度とするのがよく、該製剤は1日に1~4回に分けて投与することができる。

【0063】
【実施例】以下、本発明を更に詳しく説明するため、本発明一酸化窒素合成酵素阻害剤の調製例を製剤例として挙げ、次いで薬理試験例を挙げる。

【0064】

【製剤例1】 カプセル剤の調製

有効成分化合物	250g
結晶セルロース（日本薬局方品）	30g
コーンスターチ（日本薬局方品）	17g
タルク（日本薬局方品）	2g
ステアリン酸マグネシウム（日本薬局方品）	1g

即ち、上記処方に従い、各成分を細かく粉末にし、均一な混合物となるように混和後、所望の寸法を有する経口投与用ゼラチンカプセルに充填して、目的のカプセル剤を調製した。

【0066】

【製剤例2】 錠剤の調製

有効成分化合物	600g
乳糖（日本薬局方品）	67g
コーンスターチ（日本薬局方品）	33g
カルボキシメチルセルロースカルシウム（日本薬局方品）	25g
メチルセルロース（日本薬局方品）	12g
ステアリン酸マグネシウム（日本薬局方品）	3g

即ち、上記処方に従い、有効成分化合物、乳糖、コーンスターチ及びカルボキシメチルセルロースカルシウムを充分混合し、メチルセルロース水溶液を用いて混合物を顆粒化し、24メッシュの篩を通し、これをステアリン酸マグネシウムと混合して、錠剤にプレスして、目的の錠剤を得た。

【0068】

有効成分化合物	400g
結晶セルロース（日本薬局方品）	60g
コーンスターチ（日本薬局方品）	34g
タルク（日本薬局方品）	4g
ステアリン酸マグネシウム（日本薬局方品）	2g

即ち、上記処方に従い、各成分を細かく粉末にし、均一な混合物となるように混和した後、所望の寸法を有する経口投与用ゼラチンカプセルに充填して、目的のカプセル剤を得た。

【0070】

【製剤例4】 錠剤の調製

有効成分化合物	600g
乳糖（日本薬局方品）	67g
コーンスターチ（日本薬局方品）	33g
カルボキシメチルセルロースカルシウム（日本薬局方品）	25g
メチルセルロース（日本薬局方品）	12g
ステアリン酸マグネシウム（日本薬局方品）	3g

即ち、上記処方に従い、有効成分化合物、乳糖、コーンスターチ及びカルボキシメチルセルロースカルシウムを充分混合し、メチルセルロース水溶液を用いて混合物を

有効成分化合物として5-n-ブチル-7-(3, 4, 5-トリメトキシベンゾイルアミノ)ピラゾロ〔1, 5-a〕ピリミジンを用いて、1カプセル当りその250mgを含有する硬質ゼラチンカプセル（1000個）を、次の処方により調製した。

【0065】

250g
30g
17g
2g
1g

有効成分として5-n-ブチル-7-(3, 4, 5-トリメトキシベンゾイルアミノ)ピラゾロ〔1, 5-a〕ピリミジンを用いて、1錠当りその300mgを含有する錠剤（2000錠）を、次の処方により調製した。

【0067】

600g
67g
33g
25g
12g
3g

【製剤例3】 カプセル剤の調製

有効成分として5-n-ブチル-7-(2-トリフルオロメチルベンゾイルアミノ)ピラゾロ〔1, 5-a〕ピリミジンを用いて、1カプセル当りその200mgを含有する硬質ゼラチンカプセル（2000個）を、次の処方により調製した。

【0069】

400g
60g
34g
4g
2g

有効成分として5-n-ブチル-7-(2-トリフルオロメチルベンゾイルアミノ)ピラゾロ〔1, 5-a〕ピリミジンを用いて、1錠当りその300mgを含有する錠剤（2000錠）を、次の処方により調製した。

【0071】

顆粒化し、24メッシュの篩を通し、これをステアリン酸マグネシウムと混合して、錠剤にプレスして、目的の錠剤を得た。

【0072】

【薬理試験例1】ウィスター (Wistar) 系雄性ラット (8週齢、200～250g) を頸椎脱臼により屠殺し、直ちに胸部大動脈を摘出し、周囲の結合組織を剥離した。次に、血管内皮細胞に存在するcNOSの影響をなくすため、血管内腔を綿糸にて擦過して内皮細胞を除去し、これを2mm長さに切り分け、リング状標本とした。この標本を、クレブス・ヘンゼライト液 (NaCl 118mM、KCl 4.7mM、CaCl₂ 2.5mM、KH₂PO₄ 1.2mM、MgSO₄ 1.2mM、NaHCO₃ 25mM、グルコース11mM) を10ml入れた臓器浴中に1gの圧力下で懸垂し、O₂/CO₂ (95%/5%) 混合ガスを連続的に通気した。

【0073】まず、この標本について、フェニレフリン 3×10^{-7} M添加して血管を収縮させた後、アセチルコリン 10^{-5} Mを加えた場合及びL-アルギニン 10^{-5} Mを加えた場合のいずれでも弛緩が起きないこと、即ちcNOSとiNOSの両者が欠如していることを確認した。

【0074】次に、上記標本にリボポリサッカライド (LPS) 300ng/mlを加え、8時間後にL-アルギニン 10^{-5} Mを加えて、血管の弛緩及びサイクリックGMP (cGMP) 濃度を測定した (対照群)。

【0075】一方、LPSを添加する30分前に、5-n-ブチル-7- (3, 4, 5-トリメトキシベンゾイルアミノ) ピラゾロ [1, 5-a] ピリミジン (第1表中実施例1の化合物) の 3×10^{-5} Mを臓器浴中に添加しておき、L-アルギニン添加後の血管の弛緩及びcGMP濃度を上記と同様にして測定した (本発明群)。

【0076】尚、血管の収縮及び弛緩は、アイソトニックトランスデューサー (isotonic transducer, 日本光電製、TD-111T) にて測定し、レコーダー (NIHON DENSI KAGAKU, U-228) で記録した。また、cGMP濃度は、市販のラジオイムノアッセイキット (Amersham, cGMP [¹²⁵I] アッセイシステム) で測定した。

【0077】その結果、本発明群では、血管の弛緩が対照群と比較して70%抑制された。また、cGMP濃度も、本発明群では対照群と比較して80%抑制された。

【0078】このことから、本発明有効成分化合物は、LPSによるiNOSの誘導を阻害していることが明らかである。

【0079】

【薬理試験例2】ウィスター (Wistar) 系雄性ラット (8週齢、200～250g) を頸椎脱臼により屠殺し、直ちに胸部大動脈を摘出し、周囲の結合組織を剥離した。血管を、コラーゲナーゼ238U/ml、エステラーゼ22.5U/ml、ウシ血清アルブミン0.2%を含有するHEPES・ハanks液 (CaCl₂・H₂O 185.5mg/l、KCl 400.0mg/l、KH₂PO₄ 60.0mg/l、MgSO₄ 97.7mg

/l、NaCl 8000.0mg/l、NaHCO₃ 350.0mg/l、Na₂HPO₄ 47.5mg/l、グルコース 1000mg/l) 中で37℃にて45分間インキュベートした。

【0080】次に、HEPES・ハanks液中、この血管から内皮細胞と外膜を剥離して中膜平滑筋のみを取り出し、細切りにして、上記と同様のコラーゲナーゼ、エステラーゼ及びウシ血清アルブミンを含有するHEPES・ハanks液中で37℃にて70分間インキュベートし、酵素消化させた。これを、ウシ胎児血清を10%含有するダルベッコ変法イーグル培地 (MgSO₄・7H₂O 200.0mg/l、NaCl 6400mg/l、NaHCO₃ 3700.0mg/l、NaH₂PO₄ 125.5mg/l、Fe (NO₃)₃・9H₂O 0.1mg/l、フェノールレッド 15.0mg/l、葉酸 4.0mg/l、ニコチンアミド 4.0mg/l、パントテン酸カルシウム 4.0mg/l、ピリドキサル・HCl 4.0mg/l、リボフラビン 0.4mg/l、チアミン・HCl 4.0mg/l、塩化コリン 4.0mg/l、グルコース 1000mg/l、1-イノシトール 7.0mg/l、ビルビン酸ナトリウム 110.0mg/l) に浮遊させ、数回洗浄し、 2×10^5 個/mlの割合でシャーレに接種した。細胞がコンフエクトになった時点で継代し、4代目で次の実験に使用した。

【0081】即ち、上記培養細胞にL-アルギニン 10^{-5} Mを加え、更にLPS 300ng/ml或いはインターロイキン-1β (IL-1β) 10ng/mlを加えて24時間放置し、蓄積したNO₂の量を測定した (対照群)。

【0082】一方、LPS或いはIL-1βを添加する30分前に、5-n-ブチル-7- (3, 4, 5-トリメトキシベンゾイルアミノ) ピラゾロ [1, 5-a] ピリミジン (第1表中実施例1の化合物、本発明群1) の 3×10^{-5} M或いは5-n-ブチル-7- (2-トリフルオロメチルベンゾイルアミノ) ピラゾロ [1, 5-a] ピリミジン (第1表中実施例32の化合物、本発明群2) の 3×10^{-5} Mを臓器浴中に添加しておき、L-アルギニン或いはIL-1β添加24時間後の蓄積したNO₂の量を上記と同様にして測定した (本発明群)。

【0083】尚、NO₂の量は、培養上清に等量のGriess試薬 (0.1%N- (1-ナフチル) エチレンジアミン・ジハイドロクロライド/H₂O + 1%スルファニルアミン/2.5%H₃PO₄) を加え、570nmにおける吸光度を測定することにより定量した。

【0084】結果を図1及び図2に示す。

【0085】尚、図1は、LPSを添加した場合のデータを、図2はIL-1βを添加した場合のデータをそれぞれ示す。また、それぞれの図には、コントロールとして何も添加しなかった群のデータを併記する。

【0086】図1及び図2より、本発明有効成分化合物は、LPS及びIL-1 β によるiNOSの誘導を阻害していることが明らかである。

【0087】

【薬理試験例3】スプラークダウリユー (Sprague Dawley) 系雄性ラット (6~9週齢、200~250g) を頸椎脱臼により屠殺し、直ちに胸部大動脈を摘出し、周囲の結合組織を剥離した。次に、これを5~7個に輪切りに分割し、それぞれ縦に切り開いた後、血管内皮細胞に存在するcNOSの影響をなくすため、血管内腔を洗浄綿棒にて擦過して内皮細胞を除去して、標本を調製した。

【0088】30 μ M濃度に調製した本発明有効成分化合物 (供試化合物) のジメチルスルホキシド溶液を添加し、更に400 μ M濃度となるようにL-アルギニンを添加したクレブス・ヘンゼライト液 (薬理試験例1で用いたものと同一組成) 中に、上記標本を入れ、37℃で30分間インキュベートした。続いて、リボポリサッカライド (LPS) を1000ng/mlの濃度で添加し、37℃で24時間インキュベートした (供試化合物を用いた実験群、本発明群)。

【0089】次に、上清を96穴プレートに取り、文献 [新生化学実験講座10、血管、内皮と平滑筋、135頁、日本生化学会編、東京化学同人、1993年] に記載のNO₂測定法に従い、NO₂をグリース (Griess) 液

で発色させ、バイオカイネチックスリーター (Biokinetics reader, BIO-TEK Instruments 社製、EL-340型) で測定して、蓄積されたNO₂量を算出した。

【0090】また、標本の血管片を、1N水酸化ナトリウム水溶液に溶解させ、バイオラッドDCプロテインアッセイキット (Bio-Rad DC protein assay kit, Bio-Rad Laboratories社製) で発色させ、スペクトロフォトメーター (Spectrophotometer, HITACHI社製、U-3000型) で測定して、蛋白量を算出した。そして、之等の値より、蛋白1mg当たりのNO₂生成量を求めた。

【0091】一方、供試化合物の代わりにジメチルスルホキシドを加えた対照群、及びLPSも加えないコントロール群について、同一試験を繰り返した。

【0092】以上のようにして求められた各群における蛋白1mg当たりのNO₂生成量より、iNOS誘導阻害率を下式に従い求めた。

【0093】阻害率 (%) = { 1 - [(本発明群値) - (コントロール群値)] / [(対照群値) - (コントロール群値)] } × 100

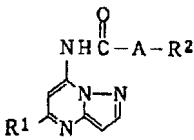
得られた結果を第6表に示す。

【0094】第6表より、本発明有効成分化合物は、LPSによるiNOSの誘導を阻害していることが明らかである。

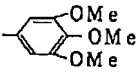
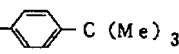
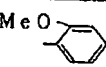
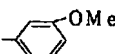
【0095】

【表1】

第 1 表



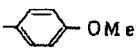
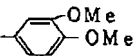
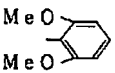
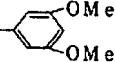
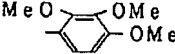
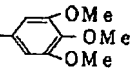
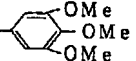
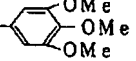
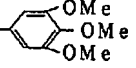
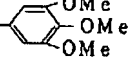
Me:メチル基、Et:エチル基、nPr:n-プロピル基、
nBu:n-ブチル基、nPe:n-ペンチル基、Ph:フェニル基

実施 例No.	R1	R2	A	融 点 (℃) (再結晶溶媒)
1	nBu		単 結 合	127~129 (ジエチルエーテル-n-ヘキサン)
2	nBu	Ph	単 結 合	83~85 (酢酸エチル-n-ヘキサン)
3	nBu		単 結 合	102~104 (n-ヘキサン)
4	nBu		単 結 合	94~95 (n-ヘキサン)
5	nBu		単 結 合	83~84 (n-ヘキサン)
6	nBu		単 結 合	¹ H-NMR (CDCl ₃) 0.97(3H,t,J=7.3), 1.37(9H,s), 1.4-1.5(2H,m), 1.7-1.9(2H,m), 2.86(2H,t,J=7.8), 6.57(1H,d,J=2.3), 7.58(1H,d,J=8.7), 7.77(1H,s), 7.97(1H,d,J=8.7), 8.03(1H,d,J=2.3), 10.0(1H,brs)
7	nBu		単 結 合	82~84 (n-ヘキサン)
8	nBu		単 結 合	49~51 (n-ヘキサン)

【0096】

【表2】

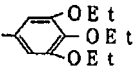
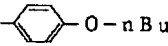
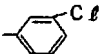
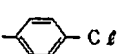
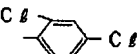
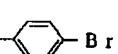
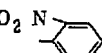
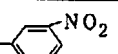
第 1 表 (続 き)

実施 例No	R ¹	R ²	A	融 点 (℃) (再結晶溶媒)
9	nBu		単 結 合	108~109 (n-ヘキサン)
10	nBu		単 結 合	129~132 (n-ヘキサン)
11	nBu		単 結 合	143~144 (ジエチルエーテル-n-ヘキサン)
12	nBu		単 結 合	101~103 (ジエチルエーテル-n-ヘキサン)
13	nBu		単 結 合	92~94 (ジエチルエーテル-n-ヘキサン)
14	nBu		単 結 合	115~117 (酢酸エチル-n-ヘキサン)
15	Et		単 結 合	141~143 (酢酸エチル-n-ヘキサン)
16	nPr		単 結 合	119~121 (ジエチルエーテル-n-ヘキサン)
17			単 結 合	198~201 (酢酸エチル-n-ヘキサン)
18	nPe		単 結 合	116~118 (n-ヘキサン)
19	Ph		単 結 合	185~187 (酢酸エチル-n-ヘキサン)

【0097】

【表3】

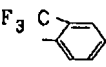
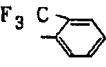
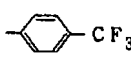
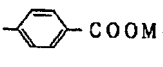
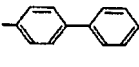
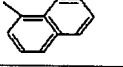
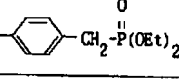
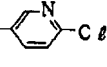
第 1 表 (続 き)

実施 例No	R ¹	R ²	A	融 点 (℃) (再結晶溶媒)
20	nBu		単 結 合	100~102 (ジエチルエーテル-n-ヘキサン)
21	nBu		単 結 合	87~90 (n-ヘキサン)
22	nBu		単 結 合	99~100 (n-ヘキサン)
23	nBu		単 結 合	107~109 (ジエチルエーテル)
24	nBu		単 結 合	81~82 (n-ヘキサン)
25	nBu		単 結 合	92~94 (ジエチルエーテル)
26	nBu		単 結 合	97~99 (n-ヘキサン)
27	nBu		単 結 合	93~95 (n-ヘキサン)
28	nBu		単 結 合	97~99 (n-ヘキサン)
29	nBu		単 結 合	133~135 (酢酸エチル-n-ヘキサン)
30	nBu		単 結 合	143~145 (酢酸エチル-n-ヘキサン)

【0098】

【表4】

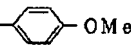
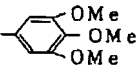
第 1 表 (続 き)

実施 例No	R ¹	R ²	A	融 点 (℃) (再結晶溶媒)
31	Et		単 結 合	125~127 (ジエチルエーテル-n-ヘキサン)
32	nBu		単 結 合	84~87 (n-ヘキサン)
33	nBu		単 結 合	95~97 (n-ヘキサン)
34	nBu		単 結 合	122~123 (n-ヘキサン)
35	nBu		単 結 合	139~141 (酢酸エチル-n-ヘキサン)
36	nBu		単 結 合	119~121 (酢酸エチル-n-ヘキサン)
37	nBu		単 結 合	57~60 (酢酸エチル-n-ヘキサン)
38	nBu		単 結 合	82~84 (ジエチルエーテル-n-ヘキサン)
39	nBu		単 結 合	103~105 (酢酸エチル-n-ヘキサン)
40	nBu		単 結 合	92~93 (ジエチルエーテル-n-ヘキサン)
41	nBu	Ph		80~82 (ジエチルエーテル-n-ヘキサン)

【0099】

【表5】

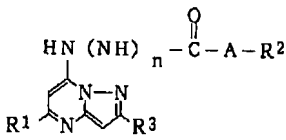
第 1 表 (続 き)

実施 例No.	R ¹	R ²	A	融 点 (°C) (再結晶溶媒)
42	nBu		-CH ₂ -	73~75 (酢酸エチル-n-ヘキサン)
43	nBu	Ph	-C ₂ H ₄ -	¹ H-NMR (CDCl ₃) 0.95(3H,t,J=7.3), 1.3-1.5 (2H,m), 1.7-1.8(2H,m), 2.80 (2H,t,J=7.8), 2.88(2H,t,J= 7.5), 3.09(2H,t,J=7.5), 6.53 (1H,d,J=2.2), 7.2-7.3(5H,m), 7.60(1H,s), 7.95(1H,d,J=2.2), 9.23(1H,brs)
44	nBu	PhO-	-CH ₂ -	108~109 (n-ヘキサン)
45	nBu		-CH ₂ -	140~142 (酢酸エチル-n-ヘキサン)
46	nBu		-CH=CH-	134~137 (酢酸エチル-n-ヘキサン)

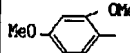
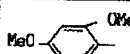
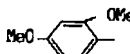
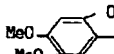
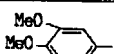
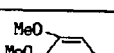
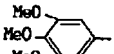
【0100】

【表6】

第 2 表



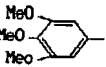
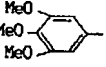
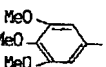
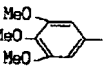
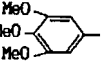
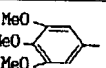
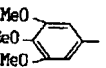
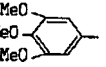
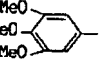
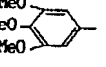
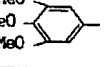
Me:メチル基、Et:エチル基、nPr:n-プロピル基、
nBu:n-ブチル基、tBu:t-ブチル基、nPe:n-ペンチル基、
Ph:フェニル基、Ac:アセチル基

実施 例No	R ¹	R ²	R ³	A	n	融 点 (°C) (再結晶溶媒)
47	nBu		H	単 結 合	0	¹ H-NMR (CDCl ₃) 0.95(3H,t,J=7.4), 1.2-2.1 (14H,m), 2.4-2.6(1H,m), 2.81 (2H,t,J=7.8), 6.54(1H,d,J= 2.2), 7.62(1H,s), 8.00(1H,d, J=2.2), 9.29(1H,brs)
48	nBu		H	単 結 合	0	141~142 (エタノール-n-ヘキサン)
49			H	単 結 合	0	209~211 (塩化メチレン-酢酸エチル)
50			H	単 結 合	0	206~208 (塩化メチレン-酢酸エチル)
51	nBu		H	単 結 合	0	136~137 (エタノール-n-ヘキサン)
52	Me		H	単 結 合	0	173~175 (エタノール-n-ヘキサン)
53	nBu		Me	単 結 合	0	127~129 (エタノール-n-ヘキサン)
54	CH ₂ =CH-C ₂ H ₄ -		H	単 結 合	0	104~106 (酢酸エチル-n-ヘキサン)

【0101】

【表7】

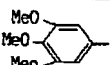
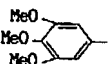
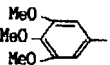
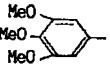
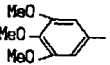
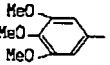
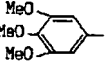
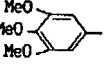
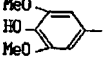
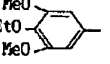
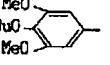
第 2 表 (続 き)

実施 例No	R1	R2	R3	A	n	融 点 (°C) (再結晶溶媒)
55	Et-O-CH ₂ -		H	単 結 合	0	138~140 (酢酸エチル-n-ヘキサン)
56			H	単 結 合	0	163~165 (クロロホルム-酢酸エチル)
57			H	単 結 合	0	166~168 (酢酸エチル-n-ヘキサン)
58			H	単 結 合	0	193~195 (塩化メチレン-ジエチルエーテル)
59			H	単 結 合	0	174~176 (塩化メチレン-ジエチルエーテル)
60			H	単 結 合	0	203~205 (塩化メチレン-ジエチルエーテル)
61			H	単 結 合	0	175~177 (塩化メチレン-酢酸エチル)
62			H	単 結 合	0	192~194 (塩化メチレン-ジエチルエーテル)
63			H	単 結 合	0	181~183 (塩化メチレン-ジエチルエーテル)
64			H	単 結 合	0	224~226 (塩化メチレン-ジエチルエーテル)
65			H	単 結 合	0	214~216 (塩化メチレン-ジエチルエーテル)

【0102】

【表8】

第 2 表 (続 き)

実施 例No	R ¹	R ²	R ³	A	n	融 点 (°C) (再結晶溶媒)
66			H	単 結 合	0	190~192 (塩化メチレン-ジエチルエーテル)
67			H	単 結 合	0	222~224 (クロロホルム-酢酸エチル)
68			H	単 結 合	0	193~195 (クロロホルム-酢酸エチル)
69			H	単 結 合	0	189~191 (塩化メチレン-ジエチルエーテル)
70			H	単 結 合	0	174~176 (塩化メチレン-酢酸エチル)
71			H	単 結 合	0	191~193 (塩化メチレン-ジエチルエーテル)
72			H	単 結 合	0	198~200 (塩化メチレン-酢酸エチル)
73			H	単 結 合	0	157~159 (酢酸エチル)
74	nBu		H	単 結 合	0	159~161 (エタノール-n-ヘキサン)
75	nBu		H	単 結 合	0	79~81 (ジエチルエーテル-n-ヘキサン)
76	nBu		H	単 結 合	0	98~100 (n-ヘキサン)

【0103】

【表9】

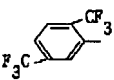
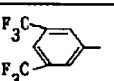
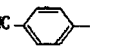
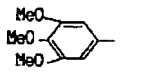
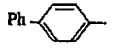
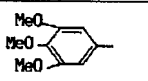
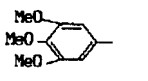
第 2 表 (続 き)

実施 例No	R ¹	R ²	R ³	A	n	融 点 (°C) (再結晶溶媒)
77	nBu		H	単 結 合	0	82~85 (エタノール-n-ヘキサン)
78	nBu		H	単 結 合	0	158~160 (酢酸エチル-n-ヘキサン)
79	nBu		H	単 結 合	0	182~184 (酢酸エチル-n-ヘキサン)
80	nBu		H	単 結 合	0	132~135 (酢酸エチル-n-ヘキサン)
81	nBu		H	単 結 合	0	111~113 (ジエチルエーテル-n-ヘキサン)
82	Me		H	単 結 合	0	154~155 (エタノール-n-ヘキサン)
83	nPr		H	単 結 合	0	139~141 (ジエチルエーテル-n-ヘキサン)
84			H	単 結 合	0	102~104 (n-ヘキサン)
85	nPe		H	単 結 合	0	93~95 (n-ヘキサン)
86	Ph		H	単 結 合	0	143~145 (ジエチルエーテル-n-ヘキサン)
87	nBu		H	単 結 合	0	46~48 (酢酸エチル-n-ヘキサン)

【0104】

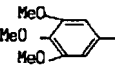
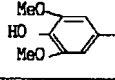
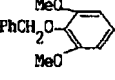
【表10】

第 2 表 (続 き)

実施 例No	R ¹	R ²	R ³	A	n	融 点 (℃) (再結晶溶媒)
88	nBu		H	単結合	0	108~110 (n-ヘキサン)
89	nBu		H	単結合	0	92.5~94.5 (n-ヘキサン)
90	nBu		H	単結合	0	106~108 (n-ヘキサン)
91	nBu		H	単結合	0	123~125 (エタノール-n-ヘキサン)
92	nBu		H	単結合	0	123~125 (ジエチルエーテル-n-ヘキサン)
93	nBu		H	単結合	0	139~140 (エタノール-n-ヘキサン)
94	nBu		H	CH ₂	0	121~123 (酢酸エチル-n-ヘキサン)
95	nBu		H	CH-CH	0	194~196 (エタノール-n-ヘキサン)
96	nBu		H	単結合	1	222 (分解) (エタノール-n-ヘキサン)
97	Ph		H	単結合	1	250 (分解) (メタノール-n-ヘキサン)
98	nBu		H	単結合	1	247 (分解) (エタノール-n-ヘキサン)

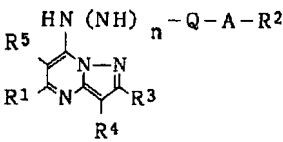
【0105】 【表11】

第 2 表 (続 き)

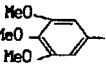
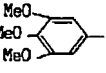
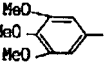
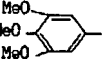
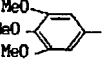
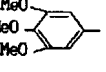
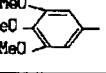
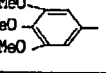
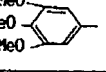
実施 例No	R ¹	R ²	R ³	A	n	融 点 (℃) (再結晶溶媒)
99	Ph		H	単結合	1	263 (分解) (エタノール-n-ヘキサン)
100	$\text{CH}_3-\underset{\text{OH}}{\text{CH}}-\text{C}_2\text{H}_4-$		H	単結合	0	128~130 (塩化メチレン-n-ヘキサン)
101	$\text{CH}_3-\underset{\text{OH}}{\text{CH}}-\text{C}_2\text{H}_4-$		H	単結合	0	153~155 (エタノール-n-ヘキサン)
102	$\text{CH}_3-\underset{\text{OH}}{\text{CH}}-\text{C}_2\text{H}_4-$		H	単結合	0	127~129 (酢酸エチル-n-ヘキサン)

【0106】 【表12】

第 4 表



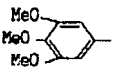
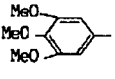
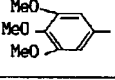
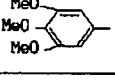
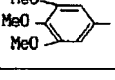
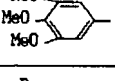
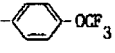
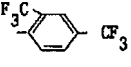
Me : メチル基、Et : エチル基、nBu : n-ブチル基、Ph : フェニル基

実施 例No	R ¹	R ⁵	R ²	R ³	R ⁴	Q	A	n	融 点 (°C) (再結晶溶媒)
107	H	H		H	H	$\text{O}=\text{C}$	単結合	0	185~187 (塩化メチレン- n-ヘキサン)
108	nBu	H		Me	$\text{O}=\text{C}-\text{OEt}$	$\text{O}=\text{C}$	単結合	0	138~140 (酢酸エチル- n-ヘキサン)
109	nBu	H		nBu	H	$\text{O}=\text{C}$	単結合	0	95~97 (酢酸エチル- n-ヘキサン)
110	nBu	H		nBu	Me	$\text{O}=\text{C}$	単結合	0	96~98 (酢酸エチル- n-ヘキサン)
111	nBu	H		Ph	H	$\text{O}=\text{C}$	単結合	0	190~192 (塩化メチレン- ジエチルエーテル)
112	nBu	H		Ph	PhCH_2-	$\text{O}=\text{C}$	単結合	0	149~151 (酢酸エチル- n-ヘキサン)
113	nBu	H		Ph		$\text{O}=\text{C}$	単結合	0	111~113 (酢酸エチル- n-ヘキサン)
114	nBu	H		H	nBu	$\text{O}=\text{C}$	単結合	0	81~83 (n-ヘキサン)
115	nBu	H		H	Ph	$\text{O}=\text{C}$	単結合	0	139~141 (酢酸エチル- n-ヘキサン)

【0108】

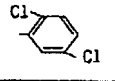
【表14】

第 4 表 (続 き)

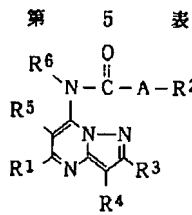
実施 例No	R ¹	R ⁵	R ²	R ³	R ⁴	Q	A	n	融 点 (°C) (再結晶溶媒)
116	nBu	Me		H	H	$\begin{smallmatrix} O \\ \\ C \end{smallmatrix}$	単結合	0	145~147 (塩化メチレン- n-ヘキサン)
117	$-\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2-$			H	H	$\begin{smallmatrix} O \\ \\ C \end{smallmatrix}$	単結合	0	102~104 (塩化メチレン- n-ヘキサン)
118	$\begin{smallmatrix} \text{Me}-\text{C}-\text{CH}_2\text{CH}_2- \\ \\ \text{O} \end{smallmatrix}$	H		H	H	$\begin{smallmatrix} O \\ \\ C \end{smallmatrix}$	単結合	0	115~117 (塩化メチレン- n-ヘキサン)
119	$\text{Et}-\text{S}-\text{CH}_2-$	H		H	H	$\begin{smallmatrix} O \\ \\ C \end{smallmatrix}$	単結合	0	80~82 (酢酸エチル- n-ヘキサン)
120	$\text{MeS}-\text{CH}_2\text{CH}_2-$	H		H	H	$\begin{smallmatrix} O \\ \\ C \end{smallmatrix}$	単結合	0	113~115 (塩化メチレン- ジエチルエーテル)
121	$\text{PhS}-\text{C}_6\text{H}_4-$	H		H	H	$\begin{smallmatrix} O \\ \\ C \end{smallmatrix}$	単結合	0	179~181 (塩化メチレン- ジエチルエーテル)
122	nBu	H		H	H	$\begin{smallmatrix} O \\ \\ C \end{smallmatrix}$	単結合	0	98~100 (ジエチルエーテル)
123	nBu	H		H	H	$\begin{smallmatrix} O \\ \\ C \end{smallmatrix}$	単結合	0	73~75 (n-ヘキサン)
124	nBu	H		H	H	$\begin{smallmatrix} O \\ \\ C \end{smallmatrix}$	単結合	0	129~131 (n-ヘキサン)
125	nBu	H		H	H	$\begin{smallmatrix} O \\ \\ C \end{smallmatrix}$	単結合	0	91~93 (ジエチルエーテル n-ヘキサン)
126	nBu	H		H	H	$\begin{smallmatrix} O \\ \\ C \end{smallmatrix}$	単結合	0	91~93 (n-ヘキサン)

【0109】 【表15】

第 4 表 (続 き)

実施 例No	R ¹	R ⁵	R ²	R ³	R ⁴	Q	A	n	融 点 (°C) (再結晶溶媒)
127	nBu	H	Ph	H	H	SO ₂	単結合	0	300℃以上 (酢酸エチル- n-ヘキサン)
128	nBu	H		H	H	SO ₂	単結合	0	300℃以上 (酢酸エチル- n-ヘキサン)

【0110】 【表16】



Me : メチル基、n Bu : n-ブチル基

実施例No	R ¹	R ⁵	R ²	R ³	R ⁴	R ⁶	A	融点 (°C) (再結晶溶媒)
129	nBu	H		H	H	Me	単結合	93~95 (酢酸エチル- n-ヘキサン)
130	nBu	H		H	H	Ph-CH ₂ -	単結合	¹ H-NMR(CDCl ₃) 0.76(3H, t, J=7.2), 0.9-1.1(2H, m), 1.3- 1.4(2H, m), 2.51(2H, t, J=7.4), 3.47(6H, s), 3.74(3H, s), 5.33(2H, brs), 5.83 (1H, s), 6.60(2H, s), 6.68(1H, d, J=2.0), 7.1-7.3(5H, m), 8.24(1H, d, J=2.0)
131	nBu	H		H	H		単結合	127~129 (酢酸エチル- n-ヘキサン)
132	nBu	H		H	H		単結合	119~121 (ジエチルエーテル- n-ヘキサン)
133	Me	H		H	H		単結合	180~182 (塩化メチレン- n-ヘキサン)
134	nBu	H		H	H		単結合	111~113 (ジエチルエーテル- n-ヘキサン)

【0111】
【表17】

第 6 表

供試化合物(実施例番号)	阻害率 (%)
7	74.6
15	66.9
16	44.7
18	58.0
19	83.0
23	43.1
26	62.3
52	64.7
53*	48.9
55	44.5
75	66.7
100	44.9
111**	32.2
115	57.2

* ; 化合物濃度 = 10 μM、

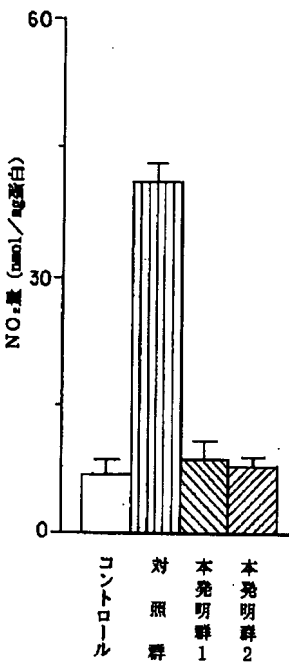
** ; 化合物濃度 = 3 μM、

【図面の簡単な説明】

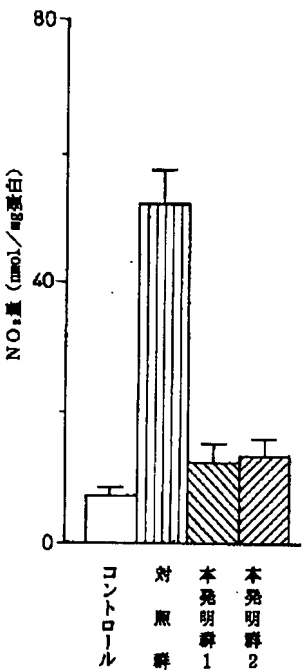
【図1】薬理試験例2に従い求められた本発明有効成分化合物のLPSによるiNOS誘導の阻害効果を示すグラフである。

【図2】薬理試験例2に従い求められた本発明有効成分化合物のIL-1βによるiNOS誘導の阻害効果を示すグラフである。

【図1】



【図2】



⑩ 日本国特許庁 (JP) ⑪ 特許出願公開
⑫ 公開特許公報 (A) 昭60-100581

⑬ Int. Cl. 4 識別記号 庁内整理番号 ⑭ 公開 昭和60年(1985)6月4日
C 07 D 487/04 1 4 2 8115-4C
A 01 N 43/90 1 0 4 7215-4H
審査請求 未請求 発明の数 7 (全17頁)

⑮ 発明の名称 ピラゾロ〔1, 5-a〕ピリミジン誘導体、それらを含有する農園
芸用殺菌剤及びそれらの製造方法

⑯ 特 願 昭58-207583
⑰ 出 願 昭58(1983)11月7日

⑱ 発 明 者 磯 野 卓 東京都大田区多摩川2丁目24番25号 株式会社エス・デ
ー・エスバイオテック東京研究所内
⑲ 発 明 者 小 島 一 弘 東京都大田区多摩川2丁目24番25号 株式会社エス・デ
ー・エスバイオテック東京研究所内
⑳ 発 明 者 安 江 敏 郎 東京都大田区多摩川2丁目24番25号 株式会社エス・デ
ー・エスバイオテック東京研究所内
㉑ 出 願 人 株式会社エス・デ ー・エスバイオテック 東京都港区東新橋2丁目12番7号
㉒ 代 理 人 弁理士 菊地 精一
最終頁に続く

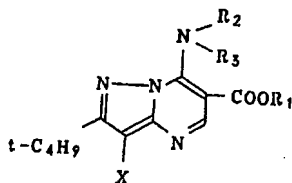
明 細 書

1. 発明の名称

ピラゾロ〔1, 5-a〕ピリミジン誘導体、それ
らを含有する農園芸用殺菌剤 X 、及びそれら
の製造方法

2. 特許請求の範囲

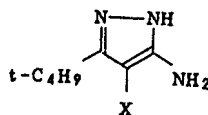
1) 式



〔式中、 R_1 は水素原子、又は炭素数1ないし4のアルキル基を表わし、 R_2 及び R_3 は各々が互いに独立して水素原子、炭素数1ないし4のアルキル基、シクロアルキル基、アラルキル基、シアルキルアミノアルキル基、又はフェニル基(塩素原子、メトキシ基、又はメチル基で置換されていてもよい)を表わし、場合によっては R_2 と R_3 とで炭素環、又は酸素原子を含む炭素環を形成してもよい。

X は水素原子、塩素原子、又は臭素原子を表わす。〕
で表わされるピラゾロ〔1, 5-a〕ピリミジン誘導体

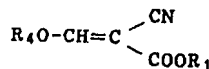
2) 式



〔式中、 X は水素原子、塩素原子、又は臭素原子を表わす。〕

で表わされる3-アミノ-4- t -ブチルピラゾールと、

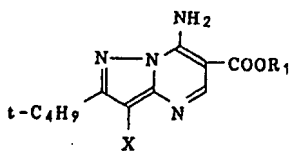
式



〔式中、 R_1 は炭素数1ないし4のアルキル基を表わし、 R_4 はメチル基又はエチル基を表わし、 X は水素原子、塩素原子、又は臭素原子を表わす〕
で表わされるシアノ酢酸エステル誘導体とを反応させることを特徴とする

特開昭60-100581(2)

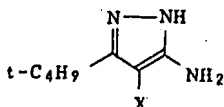
式



〔式中、R₁は炭素数1ないし4のアルキル基を表わし、Xは水素原子、塩素原子、又は臭素原子を表わす。〕

で表わされるピラゾロ〔1,5-a〕ピリミジン誘導体の製法。

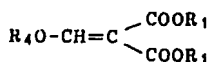
3) 式



〔式中、Xは水素原子、塩素原子、又は臭素原子を表わす。〕

で表わされる3-アミノ-4-tert-ブチルピラゾールと

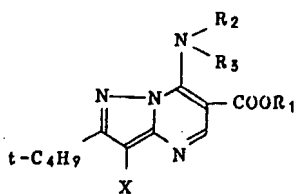
式



炭素数1ないし4のアルキル基、シクロアルキル基、アラルキル基、ジアルキルアミノアルキル基、又はフェニル基（塩素原子、メトキシ基、又はメチル基で置換されていてもよい）を表わし、場合によってはR₂とR₃とで炭素環、又は酸素原子を含む炭素環を形成してもよい。〕

で表わされる化合物とを反応させることを特徴とする、

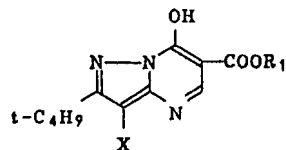
式



〔式中R₁は炭素数1ないし4のアルキル基を表わし、R₂及びR₃は各々が互いに独立して水素原子、炭素数1ないし4のアルキル基、シクロアルキル基、アラルキル基、ジアルキルアミノアルキル基、又はフェニル基（塩素原子、メトキシ基、又はメチル基で置換されていてもよい）

〔式中、R₁は炭素数1ないし4のアルキル基を表わし、R₄はメチル基、又はエチル基を表わす。〕
で表わされるマロン酸エステル誘導体とを反応させることにより得られる

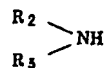
式



〔式中、R₁は炭素数1ないし4のアルキル基を表わし、Xは水素原子、塩素原子、又は臭素原子を表わす。〕

で表わされる7-ヒドロキシピラゾロ〔1,5-a〕ピリミジン誘導体をオキシ塩化リンと反応させることによって得られる7-クロロピラゾロ〔1,5-a〕ピリミジン誘導体を

式

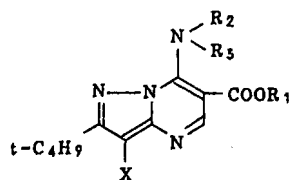


〔式中、R₂及びR₃は各々が独立して水素原子、

を表わし、場合によってはR₂とR₃とで炭素環、又は酸素原子を含む炭素環を形成してもよい。Xは水素原子、塩素原子、又は臭素原子を表わす。〕

で表わされるピラゾロ〔1,5-a〕ピリミジン誘導体の製法。

4) 式



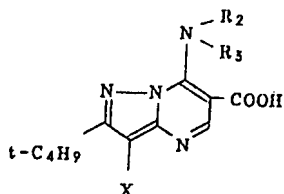
〔式中、R₁は炭素数1ないし4のアルキル基を表わしR₂及びR₃は各々が互いに独立して水素原子、炭素数1ないし4のアルキル基、シクロアルキル基、アラルキル基、ジアルキルアミノアルキル基、又はフェニル基（塩素原子、メトキシ基、又はメチル基で置換されていてもよい）を表わし、場合によってはR₂とR₃とで炭素環、又は酸素原子を含む炭素環を形成してもよい。〕

特開昭60-100581(3)

Xは水素原子、塩素原子、又は酸素原子を表わす。]

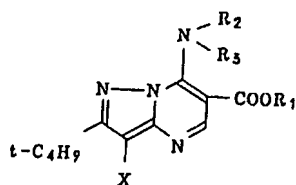
で表わされる6-アルコキシカルボニルピラゾロ〔1,5-a〕ピリミジン誘導体を加水分解反応させることを特徴とする、

式



[式中、R₂及びR₃は各々が互いに独立して水素原子、炭素数1ないし4のアルキル基、シクロアルキル基、アラルキル基、ジアルキルアミノアルキル基、又はフェニル基(塩素原子、メトキシ基、又はメチル基で置換されていてもよい)を表わし、場合によってはR₂とR₃とで炭素環、又は酸素原子を含む炭素環を形成してもよい。Xは水素原子、塩素原子、又は酸素原子を表わす。]

式

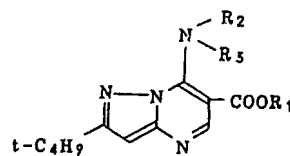


[式中、R₁は水素原子、又は炭素数1ないし4のアルキル基を表わし、R₂及びR₃は各々が互いに独立して水素原子、炭素数1ないし4のアルキル基、シクロアルキル基、アラルキル基、ジアルキルアミノアルキル基、又はフェニル基(塩素原子、メトキシ基、又はメチル基で置換されていてもよい)を表わし、場合によってはR₂とR₃とで炭素環、又は酸素原子を含む炭素環を形成してもよい。Xは水素原子、塩素原子、又は酸素原子を表わす。]

で表わされるピラゾロ〔1,5-a〕ピリミジン誘導体の製法。

で表わされるピラゾロ〔1,5-a〕ピリミジン-6-カルボン酸誘導体の製法。

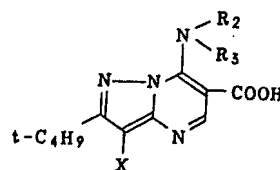
5) 式



[式中、R₁は水素原子、又は炭素数1ないし4のアルキル基を表わし、R₂及びR₃は各々が互いに独立して水素原子、炭素数1ないし4のアルキル基、シクロアルキル基、アラルキル基、ジアルキルアミノアルキル基、又はフェニル基(塩素原子、メトキシ基、又はメチル基で置換されていてもよい)を表わし、場合によってはR₂とR₃とで炭素環、又は酸素原子を含む炭素環を形成してもよい。]

で表わされるピラゾロ〔1,5-a〕ピリミジン誘導体をハロゲン化反応させることを特徴とする、

6) 式



[式中、R₂及びR₃は各々が互いに独立して水素原子、炭素数1ないし4のアルキル基、シクロアルキル基、アラルキル基、ジアルキルアミノアルキル基、又はフェニル基(塩素原子、メトキシ基、又はメチル基で置換されていてもよい)を表わし、場合によってはR₂とR₃とで炭素環、又は酸素原子を含む炭素環を形成してもよい。Xは水素原子、塩素原子、又は酸素原子を表わす。]

で表わされるピラゾロ〔1,5-a〕ピリミジン-6-カルボン酸と、

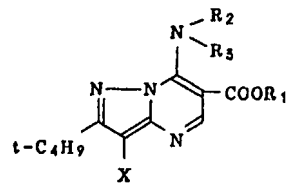
式 R₁-OH

[式中、R₁は炭素数1ないし4のアルキル基を表わす]

で表わされるアルコールと酸触媒、又は脱水縮合

剤と反応させることを特徴とする、

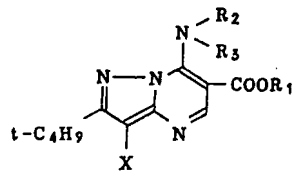
式



〔式中、R₁は炭素数1ないし4のアルキル基を表わし、R₂及びR₃は各々が互いに独立して水素原子、炭素数1ないし4のアルキル基、シクロアルキル基、アラルキル基、ジアルキルアミノアルキル基、又はフェニル基（塩素原子、メトキシ基、又はメチル基で置換されていてもよい）を表わし、場合によってはR₂とR₃とで炭素環、又は酸素原子を含む炭素環を形成してもよい。Xは水素原子、塩素原子、又は臭素原子を表わす。〕

で表わされる6-アルコキシカルボニルピラゾロ〔1,5-a〕ピリミジン誘導体の製法。

7) 式

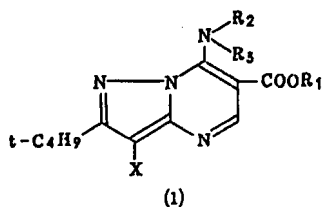


〔式中、R₁は水素原子、又は炭素数1ないし4のアルキル基を表わし、R₂及びR₃は各々が互いに独立して水素原子、炭素数1ないし4のアルキル基、シクロアルキル基、アラルキル基、ジアルキルアミノアルキル基、又はフェニル基（塩素原子、メトキシ基、又はメチル基で置換されていてもよい）を表わし、場合によってはR₂とR₃とで炭素環、又は酸素原子を含む炭素環を形成してもよい。Xは水素原子、塩素原子、又は臭素原子を表わす。〕

で表わされるピラゾロ〔1,5-a〕ピリミジン誘導体を有効成分として含有することを特徴とする農園芸用殺菌剤。

3. 発明の詳細な説明

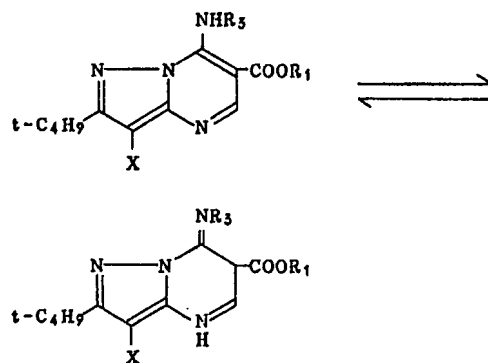
本発明は、下記一般式(1)で表わされる新規なピラゾロ〔1,5-a〕ピリミジン誘導体、それらの製法、及びそれらを有効成分として含有することを特徴とする農園芸用殺菌剤に関するものである。



〔式中、R₁は水素原子、又は炭素数1ないし4のアルキル基を表わし、R₂及びR₃は各々が互いに独立して水素原子、炭素数1ないし4のアルキル基、シクロアルキル基、アラルキル基、ジアルキルアミノアルキル基、又はフェニル基（塩素原子、メトキシ基、又はメチル基で置換されていてもよい）を表わし、場合によってはR₂とR₃とで炭素環、又は酸素原子を含む炭素環を形成してもよい。さらにXは水素原子、塩素原子、又は臭素

原子を表わす〕

なお、本化合物はR₂、又はR₃のうち、少くとも一方、例えばR₂が水素原子の場合は、次のような互変異性体としても表示できる。



〔式中、R₁、R₃、Xは前記のとおりである〕

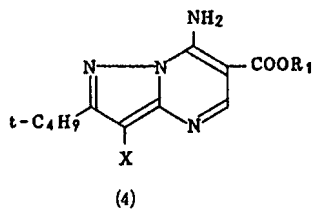
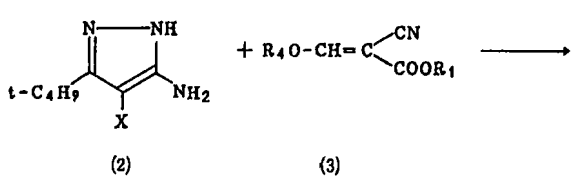
従来、6-アルコキシカルボニル-7-アミノ-又は6-アルコキシカルボニル-7-置換アミノ-ピラゾロ〔1,5-a〕ピリミジン誘導体については医薬、又は合成中間体等として知られている。例えば、特公告昭37-7982号、特公告昭40-

8556号公報では医薬、制ガン剤、合成中間体、写真乳化剤の安定剤と記載されている。又、特公開昭48-64097号公報ではホスホジエステラーゼ酵素に対する作用、陽性筋衰力作用を惹起する能力について記載されている。しかし、これらの文献には農園芸用殺菌剤についての記載はなく、しかも、2位にターシャリー・ブチル基(tert-ブチル)の導入された化合物例はない。

本発明者らは作物を病害から保護することは収量の安定化、品質保持、あるいは増収の面から重要な課題であると認識し、新しい農園芸用殺菌剤の開発を目標に、ピラゾロ〔1,5-a〕ピリミジン誘導体を合成し、広くスクリーニングをおこなった。その結果、前記一般式(1)で表わされる化合物が、新規物質で、しかも、農園芸用殺菌剤として、特に穀物、野菜、果樹、花卉等のうどんと病に特異的に作用して殺菌作用を有することを見出し、本発明をなすに至った。

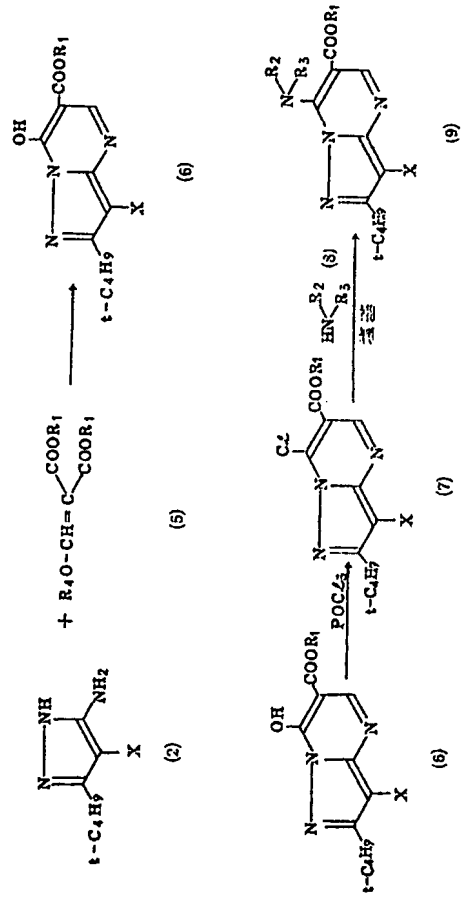
本発明による化合物の一般的製法を以下の図式と関連させて説明する。

反応図式 1



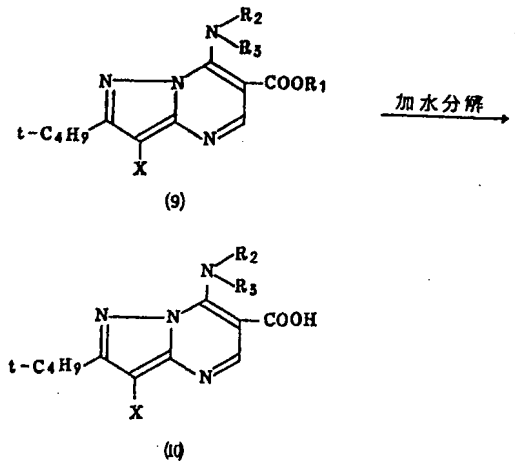
〔式中、Xは前記のとおりであり、R₁は炭素数1ないし4のアルキル基を表わし、R₄はメチル基、又はエチル基を表わす〕

反応図式 2



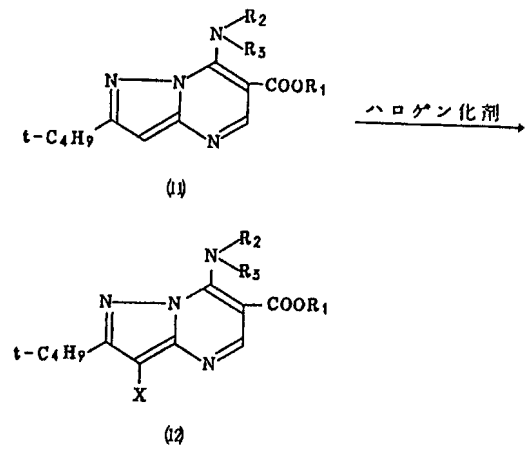
〔式中、R₁は炭素数1ないし4のアルキル基を表わし、R₂、R₃、R₄及びXは前記のとおりである〕

反応図式 3



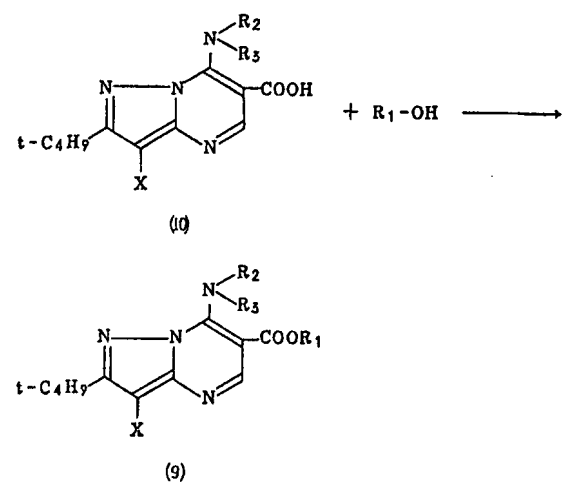
〔式中、R₁は炭素数1ないし4のアルキル基を表わし、R₂、R₃及びXは前記のとおりである〕

反応図式 4



〔式中、Xは塩素原子、又は臭素原子を表わし、
R₁は水素原子、又は炭素数1ないし4のアルキル基を表わし、R₂及びR₃は前記のとおりである〕

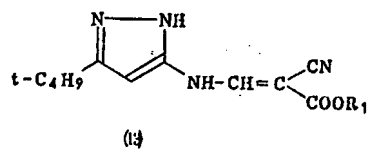
反応図式 5



〔式中、Xは水素原子、塩素原子、又は臭素原子を表わし、R₁は炭素数1ないし4のアルキル基を表わし、R₂及びR₃は前記のとおりである〕

反応図式1では原料物質(2)及び(3)を溶媒中、若しくは無溶媒下で加熱することにより、目的物(4)が得られる。本反応は好ましくは酸性条件下で行なわれるが、緩和な条件、ことに中性媒質中では

中間体(4)



〔式中、R₁は炭素数1ないし4のアルキル基を表わす〕
を単離後、酸性条件下で加熱しても良く、又、ナトリウムアルコキシドのようなアルカリの存在下で行なっても良い。反応溶媒としては好ましくはメタノール、エタノールのような低級アルコール類、酢酸などが使用されるが、その他の有機非反応性溶媒から適当に選択して使用されても良い。又、反応系を酸性条件にするためには塩酸、硫酸などの鉱酸や酢酸などの有機酸が使用される。反応温度は室温から150℃であるが、好ましくは70℃から120℃である。原料物質(2)に対して(3)の使用モル比は0.5から2までであるが、好ましくは0.9から1.1までである。原料物質(2)に

対して添加される酸、又はアルカリの使用モル比は0.1から10までであるが、好ましくは0.5から2までである。

反応図式2では原料物質(2)及び(5)を溶媒中、若しくは無溶媒下に加温することにより、合成中間体(6)が得られる。ここに反応溶媒とは好ましくはメタノール、エタノールのような低級アルコール類、酢酸などが使用されるが、その他の有機非反応性溶媒から適当に選択して使用されても良い。又、塩酸、硫酸などの鉱酸や酢酸などの有機酸のような酸やナトリウムアルコキシドのようなアルカリを添加することにより反応は促進される。反応温度は室温から150℃であるが、好ましくは70℃から120℃である。原料物質(2)に対して(5)の使用モル比は0.5から2までであるが好ましくは0.9から1.1までである。原料物質(2)に対して添加される酸又はアルカリの使用モル比は0.1から10までであるが好ましくは0.5から2までである。

合成中間体(6)はN,N-ジメチルアニリンのよう

な第3級アミンの存在下で過剰のオキシ塩化リンと加熱還流すると合成中間体(7)が得られる。この反応で使用される第3級アミンは(6)に対して等モルから10倍モルまでであるが好ましくは等モルから2倍モルまでである。

合成中間体(7)は溶媒中、又は無溶媒で塩基の存在下で各種のアミン(8)と容易に求核置換されて、目的物(9)が得られる。この求核置換反応で使用される塩基としてはトリエチルアミン、ピリジン、N,N-ジエチルアニリンのような第3級アミン、あるいは反応試剤(8)そのものが使用できる。反応温度は-10℃から150℃であるが、好ましくは0℃から120℃である。反応溶媒としては好ましくはメタノール、エタノールのような低級アルコール類、ジクロロメタン、クロロホルム、四塩化炭素などが使用されるが、その他の有機非反応性溶媒から適当に選択して使用されても良い。

反応図式3では(9)を酸又はアルカリによって加水分解することにより、容易に目的物(10)が得られる。酸としては10%ないし25%の塩酸、又は

これと同程度の酸性度を有する鉍酸の水溶液が使用される。アルカリとしては5%ないし25%の水酸化ナトリウム水溶液、又はこれと同程度の塩基性を有するアルカリ水溶液が使用される。場合によってはメタノール、エタノールのような低級アルコールなどを酸又はアルカリの水溶液とともに溶媒として使用することができる。反応温度は40℃から使用される溶媒の還流温度までが好ましい。

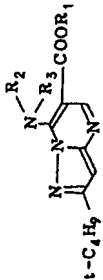
反応図式4では(11)を溶媒中、ハロゲン化剤と反応させることにより、目的物(12)が得られる。ハロゲン化剤としては、塩素化反応には塩素、塩化スルフルル、N-クロロスクシンイミドなど、又、臭素化反応には臭素、N-ブロモスクシンイミドなどが使用できる。反応溶媒としてはハロゲン化反応に通常使用される溶媒から適当に選択して使用できるが、好ましくは四塩化炭素などのハロアルカン類である。反応温度は-10℃から150℃であるが、好ましくは0℃から使用される溶媒の還流温度までである。

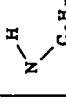
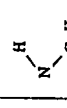
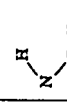
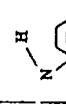
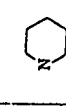
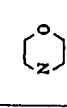
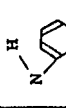
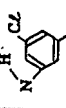
反応図式5では(10)を、エステル化させようとするアルコール(R_1-OH)と適当な酸触媒、又は脱水縮合剤の存在下で反応させて、目的物(9)が得られる。酸触媒として、無水塩化水素、トリフルオロボロンエチレートなどが使用され、脱水縮合剤としてジシクロヘキシルカルボジイミド(DCC)などが使用される。反応温度は0℃から150℃までであるが、好ましくは室温から120℃までである。

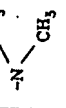
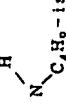
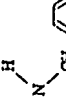
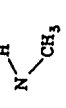
本発明の化合物の代表的なものを具体的に例示すれば、例えば、第1表及び第2表に示す通りである。なお、表中の化合物番号は以下の合成例、実施例および試験例においても参照される。表中、性状は室温に於ける性状を示し、融点(mp)はReichert Kofler式ホットペンチで測定したが、未修正値である。赤外吸収スペクトル(IR)は日本分光A-102型赤外分光光度計で測定し、かつ、カルボニル基の伸縮振動による特性吸収値を示す。屈折率(n_D)はAtago Abbo屈折計で測定した値を示す。さらに、核磁気共鳴スペクトル(NMR)は

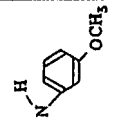
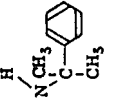
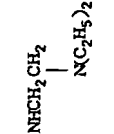
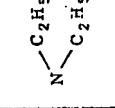
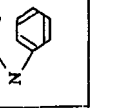
日本分光JMN-FX200型核磁気共鳴分光光度計で測定し、テトラメチルシランを内部標準として使用し、ppm値で示す。()内は溶媒である。s, d, t, q, m及びbrは各々、一重線、二重線、三重線、四重線、多重線、及び広巾線を示し、Jはカップリング定数を示す。

第 1 表

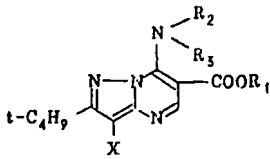


8	C ₂ H ₅		粘質性油状。IR(液膜) $\nu_{C=O}$ 1673 cm ⁻¹ NMR(CDCl ₃) 1.25(3H, t, J=7Hz), 1.37(9H, s), 1.39(2H, t, J=7Hz), 4.33(2H, q, J=7Hz), 4.37(2H, q, J=7Hz), 6.27(1H, s), 8.61(1H, s), 9.50(1H, br, s)
9	C ₂ H ₅		粘質性油状。n _D ²⁵ 1.5563, IR(液膜) $\nu_{C=O}$ 1668 cm ⁻¹ NMR(CDCl ₃) 1.03(3H, t, J=7Hz), 1.37(9H, s), 1.39(3H, t, J=7Hz), 1.5~2.0(2H, m), 4.1~4.4(2H, m), 4.33(2H, q, J=7Hz), 6.27(1H, s), 8.62(1H, s)
10	C ₂ H ₅		結晶性。IR(液膜) $\nu_{C=O}$ 1667 cm ⁻¹ NMR(CDCl ₃) 1.38(3H, t, J=7Hz), 1.39(9H, s), 1.74(9H, s), 4.34(2H, q, J=7Hz), 6.30(1H, s), 8.66(1H, s)
11	C ₂ H ₅		結晶性。IR(液膜) $\nu_{C=O}$ 1664 cm ⁻¹ NMR(CDCl ₃) 1.37(9H, s), 1.39(3H, t, J=7Hz), 1.13~2.2(10H, m), 4.33(2H, q, J=7Hz), 5.20(1H, m), 6.27(1H, s), 8.52(1H, s)
12	C ₂ H ₅		結晶性。IR(液膜) $\nu_{C=O}$ 1700 cm ⁻¹ NMR(CDCl ₃) 1.40(9H, s), 1.38(3H, t, J=7Hz), 1.6~2.0(6H, m), 3.5~3.7(2H, m), 4.36(2H, q, J=7Hz), 6.40(1H, s), 8.60(1H, s)
13	C ₂ H ₅		結晶性。IR(液膜) $\nu_{C=O}$ 1705 cm ⁻¹ NMR(CDCl ₃) 1.38(9H, s), 1.40(3H, t, J=7Hz), 3.73(4H, t, J=7Hz), 3.95(4H, t, J=7Hz), 4.37(2H, q, J=7Hz), 6.43(1H, s), 8.65(1H, s)
14	C ₂ H ₅		結晶性 mp 85℃, IR(KBr) $\nu_{C=O}$ 1667 cm ⁻¹ NMR(CDCl ₃) 1.14(9H, s), 1.36(3H, t, J=7Hz), 4.30(2H, q, J=7Hz), 6.33(1H, s), 7.1~7.4(5H, m), 8.75(1H, s)
15	C ₂ H ₅		結晶性, mp 139℃, IR(KBr) $\nu_{C=O}$ 1662 cm ⁻¹ NMR(CDCl ₃) 1.20(9H, s), 1.42(3H, t, J=7Hz), 4.39(2H, q, J=7Hz), 6.39(1H, s), 7.0~7.3(3H, m), 8.78(1H, s), 10.8(1H, br, s)

化合物 番 号	R ₁	-N ^{R₂} _{R₃}	熔点 (mp), 屈折率 (n _D), 赤外線吸収スペクトル (IR) 後継類共鳴スペクトル (NMR), 性状
1	C ₂ H ₅	-NH ₂	結晶性, mp 146℃, IR(KBr) $\nu_{C=O}$ 1683 cm ⁻¹ NMR(CDCl ₃) 1.38(3H, t, J=7Hz), 1.39(9H, s), 4.39(2H, q, J=7Hz), 6.39(1H, s), 7.0(1H, br), 8.4(1H, br), 8.71(1H, s)
2	C ₂ H ₅		粘質性油状, n _D ²⁵ 1.5666, IR(液膜) $\nu_{C=O}$ 1712 cm ⁻¹ NMR(CDCl ₃) 1.39(9H, s), 1.40(3H, t, J=7Hz), 3.33(6H, s), 4.36(2H, q, J=7Hz), 6.38(1H, s), 8.58(1H, s)
3	H	NH ₂	結晶性, mp 250℃以上, IR(KBr) $\nu_{C=O}$ 1675 cm ⁻¹ NMR(CDCl ₃ +D ₂ SO-d ₆) 1.40(9H, s), 6.32(1H, s), 7.6(1H, br), 8.5(1H, br), 8.62(1H, s)
4	C ₂ H ₅		粘質性油状, n _D ²⁵ 1.5510, IR(液膜) $\nu_{C=O}$ 1670 cm ⁻¹ NMR(CDCl ₃) 1.02(6H, d, J=7Hz), 1.37(9H, s), 1.8~2.2(1H, m), 4.17(2H, m), 4.34(2H, q, J=7Hz), 6.28(1H, s), 8.63(1H, s)
5	C ₂ H ₅		粘質性油状, n _D ²⁵ 1.5895, IR(液膜) $\nu_{C=O}$ 1670 cm ⁻¹ NMR(CDCl ₃) 1.34(9H, s), 1.37(3H, t, J=7Hz), 3.83(2H, d, J=8Hz), 4.31(2H, q, J=7Hz), 6.29(1H, s), 7.1~7.4(5H, m), 8.63(1H, s)
6	CH ₃	NH ₂	結晶性, mp 144℃, IR(KBr) $\nu_{C=O}$ 1688 cm ⁻¹ NMR(CDCl ₃) 1.39(9H, s), 3.92(3H, s), 6.40(1H, s), 7.0(1H, br), 8.3(1H, br), 8.70(1H, s)
7	C ₂ H ₅		結晶性; IR(液膜) $\nu_{C=O}$ 1672 cm ⁻¹ NMR(CDCl ₃) 1.37(9H, s), 1.39(3H, t, J=7Hz), 3.80(3H, d, J=5Hz), 4.33(2H, q, J=7Hz), 6.27(1H, s), 8.60(1H, s)

16	C ₂ H ₅		結晶性，mp 114～115℃，IR(KBr) $\nu_{\text{C=O}}$ 1663cm ⁻¹ NMR(CDCl ₃) 1.17(9H, s), 1.34(3H, t, J=7Hz), 3.77(3H, s), 4.29(2H, q, J=7Hz), 6.34(1H, s), 6.7～7.3(4H, m), 8.74(1H, s), 10.5(1H, br, s)
17	C ₂ H ₅		粘質性油状， n_D^{25} 1.5542，IR(液膜) $\nu_{\text{C=O}}$ 1668cm ⁻¹ NMR(CDCl ₃) 0.98(9H, s), 1.44(3H, t, J=7Hz), 2.00(6H, s), 4.41(2H, q, J=7Hz), 6.11(1H, s), 7.0～7.4(5H, m), 8.69(1H, s)
18	C ₂ H ₅		粘質性油状， n_D^{25} 1.5572，IR(液膜) $\nu_{\text{C=O}}$ 1670cm ⁻¹ NMR(CDCl ₃) 1.03(6H, t, J=7Hz), 1.15(3H, t, J=7Hz), 2.59(4H, q, J=7Hz), 2.72(2H, q, J=7Hz), 3.33 (2H, m), 4.33(2H, q, J=7Hz), 6.27(1H, s), 8.63 (1H, s)
19	C ₃ H ₇ -n	NH ₂	結晶性，mp 148℃，IR(KBr) $\nu_{\text{C=O}}$ 1685cm ⁻¹ NMR(CDCl ₃ +DMSO-d ₆) 1.03(3H, t, J=7Hz), 1.3～ 1.6(2H, m), 1.39(9H, s), 4.37(2H, t, J=7Hz), 6.36(1H, s), 8.67(1H, s), 7.2(1H, br), 8.4(1H, br)
20	C ₄ H ₉ -n	NH ₂	結晶性，mp 115℃，IR(KBr) $\nu_{\text{C=O}}$ 1685cm ⁻¹ NMR(CDCl ₃) 0.99(3H, t, J=7Hz), 1.2～1.9(4H, m), 1.39(9H, s), 4.33(2H, t, J=7Hz), 6.39(1H, s), 7.0(1H, br), 8.4(1H, br), 8.70(1H, s)
21	C ₂ H ₅		粘質性油状， n_D^{25} 1.5670，IR(液膜) $\nu_{\text{C=O}}$ 1715cm ⁻¹ NMR(CDCl ₃) 1.21(6H, t, J=7Hz), 1.38(3H, t, J=7Hz), 1.40(9H, s), 3.73(4H, q, J=7Hz), 4.36(2H, q, J=7Hz), 6.42(1H, s), 8.64(1H, s)
22	C ₂ H ₅		結晶性，IR(KBr) $\nu_{\text{C=O}}$ 1690cm ⁻¹ NMR(CDCl ₃) 1.32(3H, t, J=7Hz), 1.36(9H, s), 3.63(3H, s), 3.94(2H, q, J=7Hz), 6.56(1H, s), 8.68(1H, s)

第 2 表



化合物番号	R ₁	-N $\begin{smallmatrix} R_2 \\ R_3 \end{smallmatrix}$	X	融点 (mp)，赤外線吸収スペクトル (IR) 核磁気共鳴スペクトル (NMR)，性状
23	C ₂ H ₅	NH ₂	Cl	結晶性，mp 145℃，IR(KBr) $\nu_{\text{C=O}}$ 1683cm ⁻¹ NMR(CDCl ₃) 1.45(3H, t, J=7Hz), 1.49(9H, s) 4.39(2H, q, J=7Hz), 7.0(1H, br), 8.5(1H, br), 8.75(1H, s)
24	C ₂ H ₅	NH ₂	Br	結晶性，mp 152℃，IR(KBr) $\nu_{\text{C=O}}$ 1683cm ⁻¹ NMR(DMSO-d ₆) + CDCl ₃) 1.40(3H, t, J=7Hz), 1.50(9H, s), 4.38(2H, q, J=7Hz), 7.7(1H, br), 8.5(1H, br), 8.72(1H, s)

次に本発明に於ける製造法についての具体例を示す。

合成例 1

7-アミノ-2-*tert*-ブチル-6-エトキシカルボニルピラゾロ〔1,5-a〕ピリミジン(化合物1)

3-アミノ-5-*tert*-ブチルピラゾール50.6gを氷酢酸200mlに溶解し、室温で攪拌下エチルエトキシメチレンシアノ酢酸62.3gを少しずつ添加する。添加後、加熱還流を4時間おこない、溶媒を減圧で留去する。残渣に水を注ぎ析出する粗結晶を回収し、よく水洗する。この粗結晶を含水エタノールより再結晶化させると目的の化合物1が82.3g得られる。

合成例 2

2-*tert*-ブチル-7-ジメチルアミノ-6-エトキシカルボニルピラゾロ〔1,5-a〕ピリミジン(化合物2)

3-アミノ-5-*tert*-ブチルピラゾール65.0gを氷酢酸200mlに溶解し、室温で攪拌下ジエチルエトキシメチレンマロネート100gを20

分で滴加する。滴加後30分室温で攪拌し、その後、加熱還流を2時間おこなう。冷後、析出している粗結晶を回収し、水、シクロヘキサンの順に洗滌する。減圧下で加熱乾燥し、融点250℃以上の2-*tert*-ブチル-6-エトキシカルボニル-7-ヒドロキシピラゾロ〔1,5-a〕ピリミジン96.4gを得る。この得られた7-ヒドロキシ体52.7gにオキシ塩化リン500ml及びN,N-ジエチルアニリン55mlを加え、攪拌下加熱還流を4時間おこなう。過剰のオキシ塩化リンを減圧留去し、シロップ状の残渣にジクロロメタン200mlを加え、砕いた氷800gに十分攪拌しながら注ぐ。ジクロロメタン層を分液し、水層はジクロロメタン100mlで抽出する。得られたジクロロメタン層を冷水、炭酸水素ナトリウム飽和水溶液、冷水の順に洗滌する。塩化カルシウム(無水物)で乾燥後、溶媒を減圧留去すると2-*tert*-ブチル-7-クロロ-6-エトキシカルボニルピラゾロ〔1,5-a〕ピリミジンを主成分として含有するシロップ75gが得られる。この7-クロロ体は

精製せずに次の反応に供する。7-クロロ体を10ミリモル含有するシロップの無水エタノール溶液20mlを無水ジメチルアミン1.0g含有する無水エタノール10mlの溶液に室温下に加え、2時間攪拌をおこなう。反応後、エタノールを減圧下で留去し、ジクロロメタンを加え、水、0.5N塩酸、水の順に洗滌する。溶媒を留去後得られた粗製の化合物2をトルエン/酢酸エチル(3:1)の溶媒系を使ってシリカゲルカラムクロマトグラフィー処理をおこなうことにより精製すると粘質性油状物質として目的の化合物2が2.4g得られる。

合成例 3

7-アミノ-2-*tert*-ブチル-6-カルボキシピラゾロ〔1,5-a〕ピリミジン(化合物3)

合成例1で得られた化合物1 2.6gに水酸化ナトリウム0.5gを含む水2mlとエタノール10mlの溶液を加え、2時間加熱還流をおこなう。反応液からエタノールを減圧留去した後、酢酸で酸性にすると結晶が析出する。この結晶を回収して、

含水エタノールより再結晶化すると目的の化合物3が2.1g得られる。

合成例 4

7-アニリノ-2-*tert*-ブチル-6-エトキシカルボニルピラゾロ〔1,5-a〕ピリミジン(化合物14)

合成例2で得られた2-*tert*-ブチル-7-クロロ-6-エトキシカルボニルピラゾロ〔1,5-a〕ピリミジンを10ミリモル含有する無水エタノール溶液20mlをアニリン0.93g、トリエチルアミン1.1gに加え、室温で1時間攪拌した後、2時間加熱還流する。反応後、溶媒を減圧留去し、得られた残渣にクロロホルムと水を加え、クロロホルム層を分液し、クロロホルム層を水、0.5N塩酸、1N炭酸ナトリウム水溶液、水の順に洗滌する。芒硝で乾燥後、溶媒を留去する。得られた残渣をジクロロメタンを溶媒としてフロリジルカラムクロマトグラフィー処理で精製すると目的の化合物14が結晶として3.5g得られる。

合成例 5

2-ヒ-ブチル-7-メチルアミノ-6-エトキシカルボニルピラゾロ[1,5-a]ピリミジン
(化合物7)

合成例2で得られた2-ヒ-ブチル-7-クロロ-6-エトキシカルボニルピラゾロ[1,5-a]ピリミジンを10ミリモル含有するジクロロメタン溶液20mlを氷水浴で冷却し、攪拌しながら、40%メチルアミン水溶液2.0gを滴加する。滴加後、反応温度を室温に上げ、8時間攪拌を行なう。一晩放置後、水を加え、ジクロロメタン層を分液し、水洗を行なう。芒硝で乾燥後、フロリジルカラムクロマトグラフィー、シリカゲルカラムクロマトグラフィーの順に精製処理すると目的の化合物7が白色結晶として1.9g得られる。

合成例6

n-ブチル 7-アミノ-2-ヒ-ブチルピラゾロ[1,5-a]ピリミジン-6-カルボキシレート(化合物20)

3-アミノ-5-ヒ-ブチルピラゾール3.7gを氷酢酸20mlに溶解し、室温で攪拌下、n-ブ

る。

合成例8

7-アミノ-3-プロモ-2-ヒ-ブチル-6-エトキシカルボニルピラゾロ[1,5-a]ピリミジン(化合物24)

3-アミノ-5-ヒ-ブチルピラゾール13.9gを酢酸30mlに溶解し、室温で攪拌させながら臭素16.3gを含む酢酸20mlの溶液を2時間で滴加する。滴加後、6時間攪拌を続け、反応を完了させる。不溶固体を除去した母液にジクロロメタンを加え、水、10%炭酸ナトリウム水溶液、水の順に洗滌し、芒硝で乾燥後、フロリジルカラムクロマトグラフィーで処理すると、3-アミノ-4-プロモ-5-ヒ-ブチルピラゾールが結晶性物質として16.7g得られる。この物質の核磁気共鳴スペクトル(重クロロホルム溶媒、テトラメチルシラン内部標準)は0ppmから9ppmまでに1.358ppmに一重線があるのみである。

上記の3-アミノ-4-プロモ-5-ヒ-ブチルピラゾール2.2gとエチルエトキシメチレンシ

チルエトキシメチレンシアノ酢酸5.2gを滴加する。滴加後、加熱還流を3時間おこない、溶媒を減圧で留去する。残渣に氷水を注ぎ、析出する粗結晶を濾取し、よく水洗する。この粗結晶を含水エタノールより再結晶化させると目的の化合物20が6.8g得られる。

合成例7

7-アミノ-2-ヒ-ブチル-3-クロロ-6-エトキシカルボニルピラゾロ[1,5-a]ピリミジン(化合物23)

合成例1により得られる7-アミノ-2-ヒ-ブチル-6-エトキシカルボニルピラゾロ[1,5-a]ピリミジン(化合物1)6.6gを四塩化炭素60mlに溶解し、室温で攪拌下、塩化スルフリル3.4gの四塩化炭素10mlの溶液を15分で滴加し、滴加後、室温のまま2時間攪拌を続ける。反応後、炭酸水素ナトリウム水溶液を加え、中和する。ジクロロメタンで抽出の後、水洗し、溶媒を減圧留去する。得られた粗結晶をエタノールより再結晶化し、目的の化合物23が4.1g得られ

アノ酢酸1.7gとを、合成例1と同様に反応させると、目的の化合物24が2.2g得られる。

合成例9

n-プロピル 7-アミノ-2-ヒ-ブチルピラゾロ[1,5-a]ピリミジン-6-カルボキシレート(化合物19)

合成例3により得られる7-アミノ-2-ヒ-ブチル-6-カルボキシピラゾロ[1,5-a]ピリミジン4.8gとn-プロパノール3.0gの混合物にトリフルオロエチレート11.3gを少しづつ加え、室温で1時間攪拌を行なった後、加熱還流を3時間行なう。反応混合物を氷浴で冷却しながら、10%炭酸ナトリウム水溶液で塩基性にした後、ジクロロメタンで抽出し、10%炭酸ナトリウム、水の順に洗滌し、芒硝で乾燥する。溶媒を減圧留去し、得られる粗結晶をシクロヘキサン-エタノールより再結晶化すると目的の化合物19が白色結晶として1.8g得られる。

合成例10

7-アミノ-2-ヒ-ブチル-6-エトキシカ

ルポニルピラゾロ〔1,5-a〕ピリミジン(化合物1)

エチルメトキシメチレンシアノ酢酸3.2gのエタノール10mlの溶液を室温で攪拌させながら、3-アミノ-5-ヒープチルピラゾール2.8gのエタノール5mlの溶液を滴加する。滴加後、室温で3時間攪拌を続ける。一晩放置後、析出している結晶を濾取し、冷エタノールで洗滌後、乾燥すると白色結晶として、 α -(5-ヒープチルピラゾール-3-イル)アミノメチレン-シアノ酢酸エチルが3.0g得られる。

NMR (CDCl₃ 溶媒、TMS 内部標準) ppm

- 1.34 (9H, s); 1.36 (3H, t, J=7 Hz);
- 4.30 (2H, q, J=7 Hz); 5.96 (1H, s);
- 8.28 (1H, d, J=15 Hz); 11.31 (1H, brs);
- 11.75 (1H, d, J=15 Hz);

上記の α -(5-ヒープチルピラゾール-3-イル)アミノメチレン-シアノ酢酸エチル2.0gを酢酸10ml中で加熱還流を45分行ない、以下、合成例1と同様に処理して、目的の化合物1が

1.5g得られる。
前記一般式(1)の本発明化合物は前述したように良好な殺菌作用を有し、寄主植物に被害を与えることなく、植物の病気に対して治療的、かつ保護的な効果を示す。
適用される作物、ならびに病害は、例えば、表3に示すとおりである。

表 3

作物	病 害
水 稲	いもち病、ごま葉枯病
大 麦	うどんこ病
小 麦	うどんこ病
インゲン	うどんこ病
小 豆	うどんこ病
タバコ	うどんこ病
ナ ス	うどんこ病
ピーマン	うどんこ病
キュウリ	うどんこ病、つる枯病
スイカ	うどんこ病、つる枯病
メロン	うどんこ病、つる枯病
イチゴ	うどんこ病
ば ら	うどんこ病
柿	うどんこ病
リンゴ	うどんこ病
アボウ	うどんこ病

本発明の化合物は、担体および必要に応じて他の補助剤と混合して、農園芸用殺菌剤として通常用いられる製剤形態、たとえば、粉剤、粗粉剤、微粒剤、粒剤、水和剤、乳剤、水溶液剤、水溶剤、油懸濁剤等に調製されて使用される。ここでいう担体とは、処理すべき部位へ有効成分化合物の到達性を助け、また、有効成分化合物の貯蔵、輸送あるいは取り扱いを容易にするために、農園芸用殺菌剤中に混合される合成または天然の無機または有機物質を意味する。

適当な固体担体としては、カオリナイト群、モンモリロナイト群あるいはアタパルジャイト群等で代表されるクレイ類、タルク、雲母、葉ロウ石、蛭石、パーミュキライト、石こう、炭酸カルシウム、ドロマイト、けいそう土、マグネシウム石灰、りん灰石、セオライト、無水ケイ酸、合成ケイ酸カルシウム、等の無機物質、大豆粉、タバコ粉、クルミ粉、小麦粉、木粉、でんぷん、結晶セルロース等の植物性有機物質、タマロン樹脂、石油樹脂、アルキド樹脂、ポリ塩化ビニル、ポリアルキ

レングリコール、ケトン樹脂、エステルガム、コーバルガム、ダンマルガム等の合成または天然の高分子化合物、カルナバロウ、密ロウ等のワックス類、あるいは尿素等があげられる。
適当な液体担体としては、ケロシン、鉱油、スピンドル油、ホワイトオイル等のパラフィン系もしくはナフテン系炭化水素、ベンゼン、トルエン、キシレン、エチルベンゼン、クメン、メチルナフタリン等の芳香族炭化水素、四塩化炭素、クロロホルム、トリクロルエチレン、モノクロルベンゼン、 α -クロルトルエン等の塩素化炭化水素、ジオキサン、テトラヒドロフランのようなエーテル類、アセトン、メチルエチルケトン、ジイソブチルケトン、シクロヘキサノン、アセトフェノン、イソホロン等のケトン類、酢酸エチル、酢酸アミル、エチレングリコールアセテート、ジエチレングリコールアセテート、マレイン酸ジブチル、コハク酸ジエチル等のエステル類、メタノール、 n -ヘキサノール、エチレングリコール、ジエチレングリコール、シクロヘキサノール、ベンジルアルコール等のア

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ルコール類、エチレングリコールエチルエーテル、エチレングリコールフェニルエーテル、ジエチレングリコールエチルエーテル、ジエチレングリコールブチルエーテル等のエーテルアルコール類、ジメチルホルムアミド、ジメチルスルホキシド等の極性溶媒あるいは水等があげられる。

乳化、分散、湿潤、拡張、結合、崩壊性調節、有効成分安定化、流動性改良、防錆等の目的で使用される界面活性剤は、非イオン性、陰イオン性、陽イオン性および両性イオン性のいずれのものをも使用しうるが、通常は非イオン性および(または)陰イオン性のものが使用される。適当な非イオン性界面活性剤としては、たとえば、ラウリルアルコール、ステアリルアルコール、オレイルアルコール等の高級アルコールにエチレンオキシドを重合付加させたもの、イソオクチルフェノール、ノニルフェノール等のアルキルフェノールにエチレンオキシドを重合付加させたもの、ブチルナフトール、オクチルナフトール等のアルキルナフトールにエチレンオキシドを重合付加させたもの、パルミチン酸、ステア

リン酸、オレイン酸等の高級脂肪酸にエチレンオキシドを重合付加させたもの、ステアリルりん酸、ジラウリルりん酸等のモノもしくはジアルキルりん酸にエチレンオキシドを重合付加させたもの、ドデシルアミン、ステアリン酸アミド等のアミンにエチレンオキシドを重合付加させたもの、ソルビタン等の多価アルコールの高級脂肪酸エステルおよびそれにエチレンオキシドを重合付加させたもの、エチレンオキシドとプロピレンオキシドを重合付加させたもの等があげられる。適当な陰イオン性界面活性剤としては、たとえば、ラウリル硫酸ナトリウム、オレイルアルコール硫酸エステルアミン塩等のアルキル硫酸エステル塩、スルホはく酸ジオクチルエステルナトリウム、2-エチルヘキセンスルホン酸ナトリウム等のアルキルスルホン酸塩、イソプロピルナフタレンスルホン酸ナトリウム、メチレンビスナフタレンスルホン酸ナトリウム、リグニンスルホン酸ナトリウム、ドデシルベンゼンスルホン酸ナトリウム等のアリールスルホン酸塩等があげられる。

さらに本発明の農園芸用殺菌剤には製剤の性状を改善し、生物効果を高める目的で、カゼイン、ゼラチン、アルブミン、ニカリ、アルギン酸ソーダ、カルボキシメチルセルロース、メチルセルロース、ヒドロキシエチルセルロース、ポリビニルアルコール等の高分子化合物や他の補助剤を併用することもできる。

上記の担体および種々の補助剤は製剤の剤型、適用場面等を考慮して、目的に応じてそれぞれ単独にあるいは組合わせて適宜使用される。

粉剤は、例えば有効成分化合物を通常1ないし25重量部含有し、残部は固体担体である。

水和剤は、例えば有効成分化合物を通常25ないし30重量部含有し、残部は固体担体、分散湿潤剤であって、必要に応じて保護コロイド剤、チキントロビー剤、消泡剤等が加えられる。

粒剤は、例えば有効成分化合物を通常1ないし35重量部含有し、残部は大部分が固体担体である。有効成分化合物は固体担体と均一に混合されているか、あるいは固体担体の表面に均一に固着

もしくは吸着されており、粒の径は約0.2ないし1.5mm程度である。

乳剤は、例えば有効成分化合物を通常5ないし50重量部含有しており、これに約5ないし20重量部の乳化剤が含まれ、残部は液体担体であり、必要に応じて防錆剤が加えられる。

このようにして種々の剤型に調製された本発明の農園芸用殺菌剤を、たとえば、水田または畑地において農作物に病気の発生する前または発生後に作物の茎葉に散布、または土壌もしくは水面に施用するときは、10aあたり有効成分として10ないし5000g好ましくは100~2000gを投ずることにより、有効に病害を防除することができる。

また、本発明の農園芸用殺菌剤を種子処理、たとえば種子粉衣剤として使用するとき、種子重量あたり有効成分として0.1%~2%好ましくは0.2~0.5%を粉衣することにより、有効に土壌もしくは種子伝染性病害を防除できる。

本発明の農園芸用殺菌剤は、殺菌スペクトラム

を広げるために他の農園芸用殺菌剤が配合されることは好ましく、場合によっては相乗効果を期待することもできる。

本発明の農園芸用殺菌剤はまた植物生長調節剤、除草剤、殺虫剤または肥料と配分して使用できる。

本発明の農園芸用殺菌剤の製剤例を次にあげる。文中、単に部とあるのは全て重量部を意味する。

製剤例 1. 粉 剤

化合物番号2の化合物5部、タルク50部、カオリン45部を均一に混合して粉剤を得た。

製剤例 2. 水和剤

化合物番号7の化合物50部、クレ-29部、佳藻土10部、ホワイトカーボン5部、リグニンスルホン酸ナトリウム3部、ニューコール110G（日本乳化剤社商品名）2部およびポリビニルアルコール1部を混合機中で均一に混合し、ハンマーミルで3回粉砕して水和剤を得た。

製剤例 3. 粒 剤

化合物番号14の化合物70部を微細に粉砕し、これにクレ-30部を加えて混合機中で混和して

プレミックスとした。このプレミックス10部をクレ-60部およびペントナイト30部と共に混合機中で均一に混和した。このものに適当量の水を加え、ニーダー中で捏和し、直径0.8mmのスクリーンより押し出し、50℃の通風乾燥機中で乾燥した。このものをシフターによって整粒して粒剤を得た。

製剤例 4. 乳 剤

化合物番号21の化合物5部、ポリエチレングリコールエーテル系界面活性剤10部、n-ブタノール45部、およびキシレン40部をよく混合して乳剤を得た。

このようにして調製された本発明の農園芸用殺菌剤の実施例を次にあげる。なお、供試薬剤は前記製剤例2に準じて製造し、本発明の有効成分化合物を50%含有する水和剤を用いた。

以下の試験のために公知の比較有効物質として以下の化合物を使用した。

S,S-6-メチルキノキサリン-2,3-ジイルジチオカーボネート（モレスタン）

4,5,6,7-テトラクロロフタリド（ラブサイド）
ジイソプロピル1,3-ジチオラン-3-イリテ
ン-マロネート（フジワン）

また、日本特許（特公告昭37-7982号、昭40-8556号）記載の公知物質と本発明化合物との殺菌効果の比較のために、以下の化合物を使用した。

7-アミノ-6-エトキシカルボニルピラゾロ〔1,5-a〕ピリミジン（化合物A）

7-アミノ-6-エトキシカルボニル-2-メチルピラゾロ〔1,5-a〕ピリミジン（化合物B）

試験例1 稲いもち病防除効果試験

＜方法＞

径15cmの素焼鉢で生育させた3葉期の稲（品種：十石）にスプレーガンで、500ppmに希釈した薬液の200ℓ/10a相当量を散布した後温室で風乾した。風乾後、顕微鏡100倍1視野当り50個の分生胞子になるように調整したいもち病菌（Pyricularia oryzae）の胞子懸濁液を噴霧接種した。接種後直ちに、温度23℃湿度100

%の温室条件下に2日間保った後に8日間温室内に放置し、以下の調査規準に従い、各鉢当り40葉の第3葉の発病程度を調査した。但し、連数は3連とし、120葉について調査した。

調査規準

発病指数	0	1	2	3	4
1葉当り病斑数(個)	0	1~3	4~6	7~10	11~

$$\text{発病率(\%)} = \frac{\text{発病葉数}}{\text{総調査葉数}} \times 100$$

$$\text{発病度} = \frac{\sum (\text{発病指数} \times \text{発病指数別葉数})}{4 \times \text{総調査葉数}} \times 100$$

結果

濃度

ppm

発病程度別株数

0

1

2

3

4

総調査株数

発病率(%)

発病度害

1	500	120	85	26	8	1	0	29.1	9.4
2	"	"	120	0	0	0	0	0	0
6	"	"	71	30	16	3	0	40.8	14.8
7	"	"	82	25	11	2	0	31.7	11.0
8	"	"	88	24	7	1	0	26.7	8.5
9	"	"	80	22	16	2	0	33.3	12.5
19	"	"	104	11	5	0	0	13.3	4.4
20	"	"	63	31	18	8	0	47.5	19.0
21	"	"	90	18	10	2	0	25.0	9.2
A	"	"	3	20	44	32	11	97.5	51.7
B	"	"	1	34	38	36	21	99.2	60.8
ラフサイド	"	"	120	0	0	0	0	0	0
フジワ	"	"	99	13	7	1	0	17.5	6.3
無処理	-	"	0	20	32	54	14	100	62.9

<結果>

試験例2 大根萎黄病防除効力試験

<方法>

あらかじめ大根萎黄病菌 (*Fusarium oxysporum* f. *raphani*) で汚染させた畑土を径15cmの素焼鉢につめ、大根の種子(品種:青首宮重)を鉢当り15粒播種し、あらかじめ大根萎黄病菌で汚染させた畑土で覆土した。表面より軽く水を均一に灌水した後、500ppmに調整した薬液の3ℓ/m²の相当量を表面に均一に灌注した。灌注後、しばらく静置した後温室内に放置した。本薬展開後に各鉢当り10本の株になるように間引いた。試験期間中の灌水は適宜行ない、処理60日後に立枯本数、導管褐変本数を調べた。但し、連数は5連とし50株について調査した。

発病株率(%) = $\frac{(\text{立枯株数} + \text{導管褐変株数})}{\text{総調査株数}} \times 100$

発病度 = $\frac{1 \times \text{立枯株数} + 0.5 \times \text{導管褐変株数}}{1 \times \text{総調査株数}} \times 100$

<結果>

化合物	濃度 (a.i. ppm)	総調査 株数	発病株数		発病率(%)	発病度 害
			立枯株数	導管褐変株数		
5	500	50	1	4	10	6
11	500	50	0	0	0	0
12	500	50	0	0	0	0
14	500	50	0	0	0	0
17	500	50	0	0	0	0
22	500	50	0	0	0	0
ベンレート	-	50	0	0	0	0
無処理	-	50	18	34	100	63

試験例3 きゅうりうどんと病防除効果試験(1)

<方法>

径15cmの素焼鉢にあらかじめ芽出したきゅうりの種子(品種:相模半白)を鉢当り5粒播種した。1葉期にスプレーガンで125ppmに希釈した薬液の200ℓ/10a相当量を散布した。風乾後にきゅうりうどんと病菌 (*Sphaerotheca fuliginea*) の分生胞子を均一になるように軽く接種した。接種後、温室内に放置し接種12日後に第1葉に生じた病斑数を調査した。

但し、連数は3連とし15葉について調査した。

<結果>

化合物	濃度調査 (a.i. ppm)	葉数	総病斑数	1葉当り 病斑数	薬害
1	125	15	1	0.07	-
5	"	15	13	0.87	-
7	"	15	2	0.13	-
9	"	15	4	0.27	-
10	"	15	0	0	-
12	"	15	3	0.20	-
14	"	15	15	1.00	-
19	"	15	4	0.27	-
24	"	15	3	0.20	-
モレスタン	125	15	3	0.20	±
無処理	-	15	363	24.2	-
2	125	15	3	0.20	-
8	"	15	3	0.20	-
21	"	15	4	0.27	-

試験例4 きゅうりうどんと病防除効果試験(2)

<方法>

径15cmの素焼鉢にあらかじめ芽出ししたきゅうりの種子(品種:相模半白)を鉢当り5粒播種した。1葉期にスプレーガンで62.5ppmに希釈した薬液の200ℓ/10a相当量を散布した。風乾後にきゅうりうどんと病菌(*Sphaerotheca fuliginea*)の分生胞子を均一になるように軽く接種した。接種後温室内に放置し、接種12日後に第1葉に生じた病斑数を調査した。但し、連数は3連とし15葉について調査した。

<結果>

化合物	濃度調査 (a.i. ppm)	葉数	総病斑数	1葉当り 病斑数	薬害
1	62.5	15	1	0.07	-
2	62.5	15	2	0.13	-
7	62.5	15	1	0.07	-
9	62.5	15	2	0.13	-
19	62.5	15	3	0.20	-
モレスタン	125	15	3	0.20	-
無処理	-	15	348	23.2	-
8	62.5	15	2	0.13	-
20	62.5	15	4	0.26	-
21	62.5	15	4	0.26	-

なるように、きゅうりうどんと病菌

(*Sphaerotheca fuliginea*)の分生胞子を噴霧接種した。接種後病斑の形成されるまで室内に保った後に、スプレーガンで125ppmに希釈した薬液の充分量を噴霧散布した。風乾後温室内に放置し、薬散10日後に第1本葉の病斑面積を調査した。但し、連数は3連とし15葉について調査した。

<結果>

化合物	濃度 (a.i. ppm)	調査葉数	平均病斑面積(%)	薬害
1	125	15	0.2	-
2	125	15	0.4	-
7	125	15	1.6	-
8	125	15	2.1	-
19	125	15	1.6	-
モレスタン	125	15	1.3	±
無処理	-	15	73.2	-
9	125	15	2.3	-
21	125	15	2.1	-

試験例5 きゅうりうどんと病防除効果試験(3)

<方法>

径15cmの素焼鉢にあらかじめ芽出ししたきゅうりの種子(品種:相模半白)を鉢当り5粒播種した。第1本葉の展開期にスプレーガンで均一に

第1頁の続き

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- [54] **PYRAZOLO[1,5-A]PYRIMIDINE DERIVATIVE**
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- [22] **PCT Filed:** **Jun. 5, 1995**
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- [87] **PCT Pub. No.:** **WO95/35298**
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- [51] **Int. Cl.⁶** **A61K 31/505; C07D 403/02**
- [52] **U.S. Cl.** **514/258; 544/281**
- [58] **Field of Search** **544/281; 514/258**

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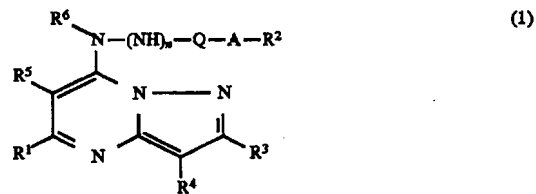
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[57] **ABSTRACT**

The invention provides a pyrazolo[1,5-a]pyrimidine derivative of the following formula (1):



wherein R^1 , R^3 , R^4 , R^5 , R^6 , Q, A and n are defined in the description; and R^2 is naphthyl, cycloalkyl, furyl, thienyl, optionally halogen-substituted pyridyl, optionally halogen-substituted phenoxy, or phenyl which may have 1 to 3 substituents selected from the group consisting of lower alkyl, lower alkoxy, halogen, nitro, halogen-substituted lower alkyl, halogen-substituted lower alkoxy, lower alkoxy-carbonyl, hydroxyl, phenyl(lower)alkoxy, amino, cyano, lower alkanoyloxy, phenyl and di(lower)alkoxyphosphoryl(lower)alkyl. This derivative is useful as a potent analgesic.

10 Claims, No Drawings

**PYRAZOLO[1,5-A]PYRIMIDINE
DERIVATIVE**

This is a national stage application, filed under 35 USC 371, of PCT/JP95/01104, filed Jun. 5, 1995.

TECHNICAL FIELD

The present invention relates to novel pyrazolo[1,5-a]pyrimidine derivatives.

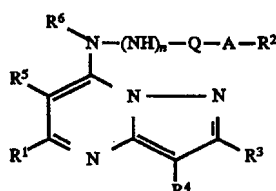
PRIOR ART

The pyrazolo[1,5-a]pyrimidine derivatives of the invention are novel compounds which have never been published in the literature.

DISCLOSURE OF THE INVENTION

The object of the invention is to provide compounds of value as medicines as will be described hereinafter.

The present invention provides a novel pyrazolo[1,5-a]pyrimidine derivative of the following formula (1):



wherein R¹ is hydrogen, lower alkyl which may have thienyl, lower alkoxy, lower alkylthio, oxo or hydroxyl as a substituent, cycloalkyl, thienyl, furyl, lower alkenyl, or phenyl which may have 1 to 3 substituents selected from the group consisting of lower alkyl, lower alkoxy, phenylthio and halogen; R² is naphthyl, cycloalkyl, furyl, thienyl, optionally halogen-substituted pyridyl, optionally halogen-substituted phenoxy, or phenyl which may have 1 to 3 substituents selected from the group consisting of lower alkyl, lower alkoxy, halogen, nitro, halogen-substituted lower alkyl, halogen-substituted lower alkoxy, lower alkoxycarbonyl, hydroxyl, phenyl(lower)alkoxy, amino, cyano, lower alkanoyloxy, phenyl and di(lower)alkoxyphosphoryl(lower)alkyl; R³ is hydrogen, phenyl or lower alkyl; R⁴ is hydrogen, lower alkyl, lower alkoxycarbonyl, phenyl (lower)alkyl, optionally phenylthio-substituted phenyl, or halogen; R⁵ is hydrogen or lower alkyl; R⁶ is hydrogen, lower alkyl, phenyl(lower)alkyl, or benzoyl having 1 to 3 substituents selected from the group consisting of lower alkoxy, halogen-substituted lower alkyl and halogen; R¹ and R⁵ may conjointly form lower alkylene; Q is carbonyl or sulfonyl; A is a single bond, lower alkylene or lower alkenylene; and n is 0 or 1.

Examples of the groups in the above formula (1) are as follows. The lower alkyl group includes straight- or branched-chain lower alkyl groups such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert-butyl, pentyl, hexyl, and the like.

The cycloalkyl group includes cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, and the like.

The lower alkoxy group includes methoxy, ethoxy, propoxy, isopropoxy, butoxy, pentyloxy, hexyloxy, and the like.

The lower alkylthio group includes methylthio, ethylthio, propylthio, butylthio, pentylthio, hexylthio, and the like.

The halogen atom includes fluorine, chlorine, bromine and iodine.

The halogen-substituted lower alkyl group includes trifluoromethyl, pentafluoroethyl, heptafluoropropyl, nonafluorobutyl, undecafluoropentyl, tridecafluorohexyl, and the like.

5 The halogen-substituted lower alkoxy group includes trifluoromethoxy, pentafluoroethoxy, heptafluoropropoxy, nonafluorobutoxy, undecafluoropentyloxy, tridecafluorohexyloxy, and the like.

The lower alkoxycarbonyl group includes methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, isopropoxycarbonyl, butoxycarbonyl, pentyloxycarbonyl, hexyloxycarbonyl, and the like.

10 The di(lower)alkoxyphosphoryl(lower)alkyl group includes dimethoxyphosphorylmethyl, diethoxyphosphorylmethyl, dipropoxyphosphorylmethyl, diisopropoxyphosphorylmethyl, dibutoxyphosphorylmethyl, dipentyloxyphosphorylmethyl, dihexyloxyphosphorylmethyl, 2-(dimethoxyphosphoryl)ethyl, 2-(diethoxyphosphoryl)ethyl, 3-(diethoxyphosphoryl)propyl, and the like.

20 The naphthyl group includes 1-naphthyl, 2-naphthyl, and the like.

The lower alkylene group includes methylene, ethylene, trimethylene, tetramethylene, pentamethylene, hexamethylene, and the like.

25 The lower alkenylene group includes vinylene, propenylene, and the like.

The optionally halogen-substituted pyridyl group includes 2-pyridyl, 3-pyridyl, 4-pyridyl, 6-chloro-2-pyridyl, 5-chloro-2-pyridyl, 4-chloro-3-pyridyl, 3-chloro-2-pyridyl, 6-chloro-3-pyridyl, 5-chloro-3-pyridyl, 4-chloro-3-pyridyl, 2-chloro-3-pyridyl, 2-chloro-4-pyridyl, 3-chloro-4-pyridyl, 6-fluoro-3-pyridyl, 6-bromo-3-pyridyl, 6-iodo-3-pyridyl, and the like.

30 The optionally halogen-substituted phenoxy group includes phenoxy, 2-chlorophenoxy, 3-chlorophenoxy, 4-chlorophenoxy, 4-fluorophenoxy, 4-bromophenoxy, 4-iodophenoxy, and the like.

The thienyl group includes 2-thienyl and 3-thienyl, and the furyl group includes 2-furyl and 3-furyl.

40 The lower alkenyl group includes vinyl, allyl, isopropenyl, 1-butenyl, 2-butenyl, 3-butenyl, 1-pentenyl, 2-pentenyl, 3-pentenyl, 4-pentenyl, 1-hexenyl, 2-hexenyl, 3-hexenyl, 4-hexenyl, 5-hexenyl, and the like.

The phenyl(lower)alkyl group includes benzyl, 1-phenylethyl, 2-phenylethyl, 3-phenylpropyl, 4-phenylbutyl, 5-phenylpentyl, 6-phenylhexyl, and the like.

The phenyl(lower)alkoxy group includes benzyloxy, 2-phenylethoxy, 3-phenylpropoxy, 4-phenylbutoxy, 5-phenylpentyloxy, 6-phenylhexyloxy, and the like.

50 The lower alkanoyloxy group includes acetoxy, propionyloxy, butyryloxy, valeryloxy, pivaloyloxy, hexanoyloxy, heptanoyloxy, and the like.

The lower alkyl group which may have thienyl, lower alkoxy, lower alkylthio, oxo or hydroxyl as a substituent includes not only the above-mentioned non-substituted lower alkyl groups but also 2-thienylmethyl, 3-thienylmethyl, 1-(2-thienyl)ethyl, 1-(3-thienyl)ethyl, 2-(2-thienyl)ethyl, 2-(3-thienyl)ethyl, 3-(2-thienyl)propyl, 4-(2-thienyl)butyl, 5-(2-thienyl)pentyl, 6-(2-thienyl)hexyl, methoxymethyl, ethoxymethyl, propoxymethyl, butoxymethyl, pentyloxymethyl, hexyloxymethyl, 1-methoxyethyl, 2-methoxyethyl, 3-methoxypropyl, 4-methoxybutyl, 5-methoxypentyl, 6-methoxyhexyl, hydroxymethyl, 1-hydroxyethyl, 2-hydroxyethyl, 1-hydroxypropyl, 2-hydroxypropyl, 3-hydroxypropyl, 3-hydroxybutyl, 4-hydroxypentyl, 5-hydroxyhexyl, methylthiomethyl, ethylthiomethyl, propylthiomethyl, and the like.

butylthiomethyl, pentylthiomethyl, hexylthiomethyl, 2-methylthioethyl, 3-methylthiopropyl, 4-methylthiobutyl, 5-methylthiopentyl, 6-methylthiohexyl, formyl, formylmethyl, acetyl, 2-formylethyl, 2-oxopropyl, propionyl, 3-formylpropyl, 3-oxobutyl, 2-oxobutyl, butyryl, 4-formylbutyl, 4-oxopentyl, 3-oxopentyl, 2-oxopentyl, valeryl, 5-formylpentyl, 5-oxohexyl, 4-oxohexyl, 3-oxohexyl, 2-oxohexyl, hexanoyl, and the like.

The phenyl group which may have 1 to 3 substituents selected from the group consisting of lower alkyl, lower alkoxy, phenylthio and halogen includes phenyl, 2-methylphenyl, 3-methylphenyl, 4-methylphenyl, 4-ethylphenyl, 4-propylphenyl, 4-butylphenyl, 4-*t*-butylphenyl, 4-pentylphenyl, 4-hexylphenyl, 2,3-dimethylphenyl, 2,4-dimethylphenyl, 2,5-dimethylphenyl, 2,6-dimethylphenyl, 3,4-dimethylphenyl, 3,5-dimethylphenyl, 2-methoxyphenyl, 3-methoxyphenyl, 4-methoxyphenyl, 4-ethoxyphenyl, 4-propoxyphenyl, 4-butoxyphenyl, 4-pentyloxyphenyl, 4-hexyloxyphenyl, 2,3-dimethoxyphenyl, 2,4-dimethoxyphenyl, 2,5-dimethoxyphenyl, 2,6-dimethoxyphenyl, 3,4-dimethoxyphenyl, 3,5-dimethoxyphenyl, 3,4,5-trimethoxyphenyl, 2-chlorophenyl, 3-chlorophenyl, 4-chlorophenyl, 4-bromophenyl, 4-iodophenyl, 4-fluorophenyl, 4-(phenylthio)phenyl, 3-(phenylthio)phenyl, 2-(phenylthio)phenyl, and the like.

The phenyl group which may have 1 to 3 substituents selected from the group consisting of lower alkyl, lower alkoxy, halogen, nitro, halogen-substituted lower alkyl, halogen-substituted lower alkoxy, lower alkoxycarbonyl, hydroxyl, phenyl(lower)alkoxy, amino, cyano, lower alkanoxyloxy, phenyl and di(lower)alkoxyphosphoryl-(lower)alkyl include the following groups:

phenyl, 2-methylphenyl, 3-methylphenyl, 4-methylphenyl, 4-ethylphenyl, 4-propylphenyl, 4-butylphenyl, 4-*t*-butylphenyl, 4-pentylphenyl, 4-hexylphenyl, 2-methoxyphenyl, 3-methoxyphenyl, 4-methoxyphenyl, 4-ethoxyphenyl, 4-propoxyphenyl, 4-butoxyphenyl, 4-pentyloxyphenyl, 4-hexyloxyphenyl, 2,3-dimethoxyphenyl, 2,4-dimethoxyphenyl, 2,5-dimethoxyphenyl, 2,6-dimethoxyphenyl, 3,4-dimethoxyphenyl, 3,5-dimethoxyphenyl, 2,3,4-trimethoxyphenyl, 2,3,5-trimethoxyphenyl, 2,3,6-trimethoxyphenyl, 2,4,5-trimethoxyphenyl, 2,4,6-trimethoxyphenyl, 3,4,5-trimethoxyphenyl, 3,4,5-triethoxyphenyl, 2-fluorophenyl, 3-fluorophenyl, 4-fluorophenyl, 2-chlorophenyl, 3-chlorophenyl, 4-chlorophenyl, 2-bromophenyl, 3-bromophenyl, 4-bromophenyl, 4-iodophenyl, 2,3-dichlorophenyl, 2,4-dichlorophenyl, 2-nitrophenyl, 3-nitrophenyl, 4-nitrophenyl, 2-trifluoromethylphenyl, 3-trifluoromethylphenyl, 4-trifluoromethylphenyl, 4-pentafluoroethylphenyl, 4-heptafluoropropylphenyl, 4-nonafluorobutylphenyl, 4-undecafluoropentylphenyl, 4-tridecafluorohexylphenyl, 2-methoxycarbonylphenyl, 3-methoxycarbonylphenyl, 4-methoxycarbonylphenyl, 4-ethoxycarbonylphenyl, 4-propoxycarbonylphenyl, 4-butoxycarbonylphenyl, 4-pentyloxycarbonylphenyl, 4-hexyloxycarbonylphenyl, 2-biphenyl, 3-biphenyl, 4-biphenyl, 2-(diethoxyphosphorylmethyl)phenyl, 3-(diethoxyphosphorylmethyl)phenyl, 4-(diethoxyphosphorylmethyl)phenyl, 4-(dimethoxyphosphorylmethyl)phenyl, 4-(diisopropoxyphosphorylmethyl)phenyl, 3,5-dimethoxy-4-ethoxyphenyl, 3,5-dimethoxy-4-propoxyphenyl, 4-butoxy-3,5-dimethoxyphenyl, 3,5-dimethoxy-4-pentyloxyphenyl, 3,5-dimethoxy-4-hexyloxyphenyl, 2,3-bis

(trifluoro-methyl)phenyl, 2,4-bis(trifluoromethyl)phenyl, 2,5-bis(trifluoromethyl)phenyl, 2,6-bis(trifluoromethyl)phenyl, 3,4-bis(trifluoromethyl)phenyl, 3,5-bis(trifluoromethyl)phenyl, 3,5-dimethoxy-4-hydroxyphenyl, 3,5-diethoxy-4-hydroxyphenyl, 3,5-dipropoxy-4-hydroxyphenyl, 4-benzyloxy-3,5-dimethoxyphenyl, 4-benzyloxy-3,5-diethoxyphenyl, 3,5-dimethoxy-4-(2-phenylethoxy)phenyl, 4-acetoxy-3,5-dimethoxyphenyl, 3,5-dimethoxy-4-propionyloxyphenyl, 2-chloro-3,5-dimethoxyphenyl, 4-chloro-3,5-dimethoxyphenyl, 4-bromo-3,5-dimethoxyphenyl, 3,5-dimethoxy-4-iodophenyl, 3,5-dichloro-4-methoxyphenyl, 3,5-dichloro-4-ethoxyphenyl, 2-aminophenyl, 3-aminophenyl, 4-aminophenyl, 2-cyanophenyl, 3-cyanophenyl, 4-cyanophenyl, 4-trifluoromethoxyphenyl, 3-trifluoromethoxyphenyl, 2-trifluoromethoxyphenyl, 4-pentafluoroethoxyphenyl, 4-heptafluoropropoxyphenyl, 4-nonafluorobutoxyphenyl, 4-undecafluoropentyloxyphenyl, 4-tridecafluorohexyloxyphenyl, 3,5-bis(trifluoromethoxy)phenyl, 3,4,5-tris(trifluoromethoxy)phenyl, and the like.

The optionally phenylthio-substituted phenyl group includes phenyl, 4-(phenylthio)phenyl, 3-(phenylthio)phenyl, 2-(phenylthio)phenyl, and the like.

The benzoyl group having 1 to 3 substituents selected from the group consisting of lower alkoxy, halogen-substituted lower alkyl and halogen include 2-chlorobenzoyl, 3-chlorobenzoyl, 4-chlorobenzoyl, 2-fluorobenzoyl, 2-bromobenzoyl, 2-iodobenzoyl, 2,4-dichlorobenzoyl, 3,4-dichlorobenzoyl, 2,5-dichlorobenzoyl, 2,6-dichlorobenzoyl, 2-trifluoromethylbenzoyl, 3-trifluoromethylbenzoyl, 4-trifluoromethylbenzoyl, 3,5-bis(trifluoromethyl)benzoyl, 3,4,5-tris(trifluoromethyl)benzoyl, 2-methoxybenzoyl, 3-methoxybenzoyl, 4-methoxybenzoyl, 2,3-dimethoxybenzoyl, 2,4-dimethoxybenzoyl, 3,5-dimethoxybenzoyl, 3,4,5-trimethoxybenzoyl, 2-ethoxybenzoyl, 2-propoxybenzoyl, 2-butoxybenzoyl, 2-pentyloxybenzoyl, 2-hexyloxybenzoyl, and the like.

The pyrazolo[1,5-*a*]pyrimidine derivatives of formula (1) according to the invention have potent analgesic effects and are useful as analgesics to relieve pains such as postoperative pain, migraine, gout, cancer pain, chronic pain and neuropathic pain. Furthermore, the derivatives of the invention are free of side effects typical of conventional analgesics, do not cause hallucination or derangement and are not addictive.

Examples of preferred pyrazolo[1,5-*a*]pyrimidine derivatives of the invention for use as the analgesics are: compounds of formula (1) wherein Q is carbonyl and n is 0; compounds wherein Q is carbonyl, n is 1, R¹ is lower alkyl or phenyl, R² is phenyl having 1 to 3 substituents selected from the group consisting of lower alkoxy and halogen-substituted lower alkyl, R³, R⁴, R⁵ and R⁶ are each hydrogen, and A is a single bond; and compounds wherein Q is sulfonyl, n is 0, R¹ is lower alkyl, R² is phenyl which may have 1 to 3 halogens, R³, R⁴, R⁵ and R⁶ are each hydrogen, and A is a single bond.

Of these preferred pyrazolo[1,5-*a*]pyrimidine derivatives, the following compounds are more preferable.

(1) Compounds wherein R¹ is optionally lower alkylthio-substituted lower alkyl or optionally phenylthio-substituted phenyl, R² is phenyl having 1 to 3 substituents selected from the group consisting of lower alkoxy, halogen and halogen-substituted lower alkyl, R³ is hydrogen or phenyl, R⁴ is hydrogen, halogen or phenyl, R⁵ is hydrogen, R⁶ is hydrogen or benzoyl having halogen-substituted lower alkyl as a substituent, Q is carbonyl and A is a single bond;

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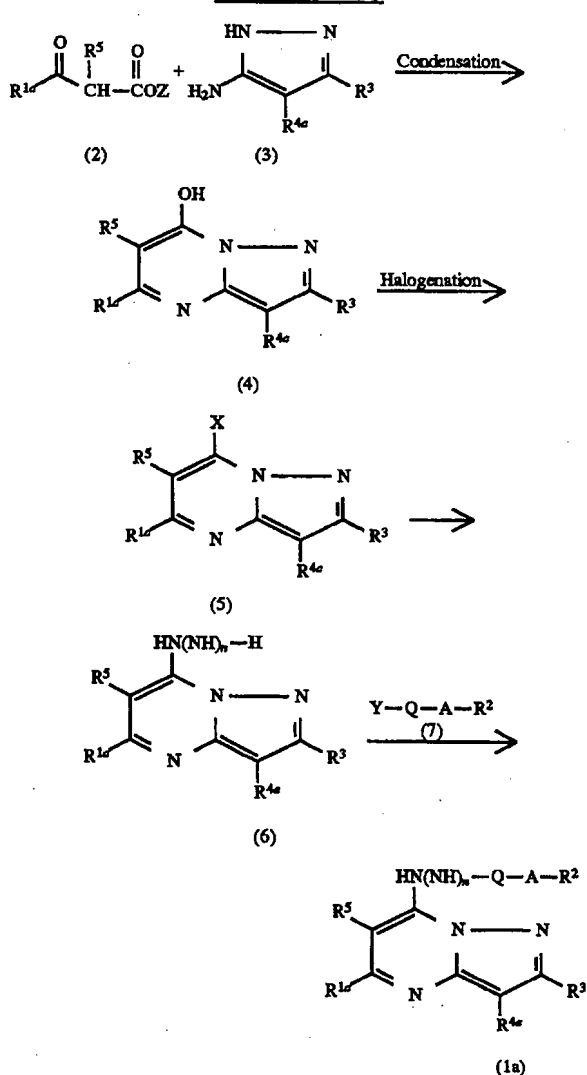
(2) compounds wherein R^3 , R^4 and R^6 are each hydrogen, n is 0, R^1 is n -butyl and R^2 is phenyl having either 2 to 3 lower alkoxy groups or 1 to 2 halogen-substituted lower alkyl groups, or R^1 is phenyl and R^2 is phenyl having 3 lower alkoxy groups; and

(3) compounds wherein R^2 is 2,4-dimethoxyphenyl, 3,4,5-trimethoxyphenyl, 2-trifluoromethylphenyl or 2,5-bis(trifluoromethyl)phenyl.

Examples of most preferred pyrazolo[1,5-a]pyrimidine derivatives of the invention are 5- n -butyl-7-(3,4,5-trimethoxybenzoylamino)pyrazolo[1,5-a]pyrimidine and 5- n -butyl-7-(2-trifluoromethylbenzoylamino)pyrazolo[1,5-a]pyrimidine.

The derivatives of formula (1) according to the invention can be produced by various processes. Some exemplary processes are schematically shown hereinafter.

[Reaction Scheme-1]



wherein R^2 , R^3 , R^5 , n , Q and A are as defined above, R^{1a} is hydrogen, lower alkyl which may have thienyl, lower alkoxy or lower alkylthio as a substituent, cycloalkyl, thienyl, furyl, lower alkenyl, or phenyl which may have 1 to 3 substituents selected from the group consisting of lower alkyl, lower alkoxy, phenylthio and halogen, R^{1a} and R^5 may jointly form lower alkylene, R^{4a} is hydrogen, lower alkyl, lower alkoxy, carbonyl, phenyl(lower)alkyl, or optionally

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phenylthio-substituted phenyl, X and Y are each halogen, and Z is lower alkyl.

The condensation of the compounds (2) and (3) in Reaction Scheme-1 is carried out in a suitable inert solvent at room temperature to the boiling point of the solvent. Examples of useful inert solvents are acetic acid, ethanol, benzene, toluene, xylene and tetrahydrofuran (THF). The compounds (2) and (3) are preferably used in an approximately equimolar proportion. The reaction is carried out for about 2-5 hours to provide the desired compound (4).

The subsequent halogenation of the compound (4) is carried out using a halogenating agent such as phosphorus oxychloride and phosphorus oxybromide in the presence of a suitable acid acceptor such as N,N -dimethylaniline, N,N -diethylaniline and triethylamine. Since the said halogenating agents also function as solvents, there is no need to use other solvents in this reaction but an inert solvent such as benzene, toluene and xylene may be optionally used. The acid acceptor is preferably used in an amount of about 1-10 equivalents relative to the compound (4). The reaction is carried out at approximately room temperature to $150^\circ C$. for about 0.5-12 hours.

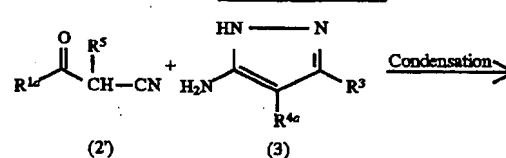
The halide (5) obtained by this reaction is treated with aqueous ammonia or hydrazine to convert the halide into the compound (6). This treatment requires no solvents and is generally carried out by heating the compound (5) with an excess of aqueous ammonia at about $100^\circ-150^\circ C$. for about 1-12 hours or treating the compound (5) with an excess of hydrazine at about $0^\circ C$. to room temperature for about 5-30 hours.

The compound (6) thus obtained is reacted with acid halide (7) to convert the compound (6) into the compound (1) of the invention. This reaction can be carried out in a suitable solvent in the presence of an acid acceptor. Examples of useful solvents are aromatic or aliphatic hydrocarbons such as benzene, toluene, xylene and petroleum ether; chain or cyclic ethers such as diethylether, dimethoxyethane, tetrahydrofuran (THF) and 1,4-dioxane; ketones such as acetone, ethylmethylketone and acetophenone; hydrocarbon halides such as dichloromethane, chloroform, carbon tetrachloride and 1,2-dichloroethane. Examples of useful acid acceptors are tertiary amines such as triethylamine, N,N -diethylaniline, N -methylmorpholine, pyridine and 4-methylaminopyridine.

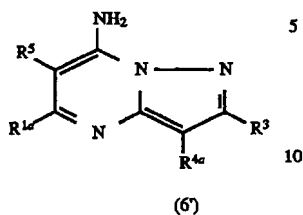
There is no specific limitation on the amounts of the acid halide (7) and the acid acceptor relative to the compound (6) in this reaction. It is, however, preferable that the acid halide be used in an approximately equimolar proportion and the acid acceptor in an approximately equimolar to excessive amount. The reaction goes to completion at room temperature to reflux temperature of the solvent in about 0.5-20 hours.

Compound (6'), i.e., the compound (6) wherein $n=0$ can be produced by the process shown in Reaction Scheme-1'.

[Reaction Scheme-1']



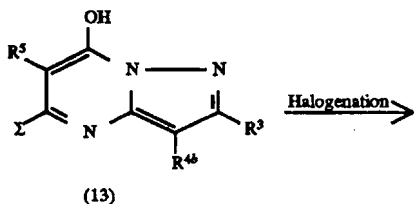
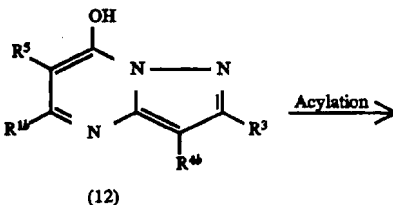
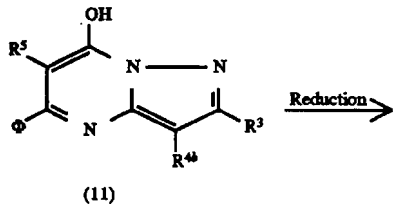
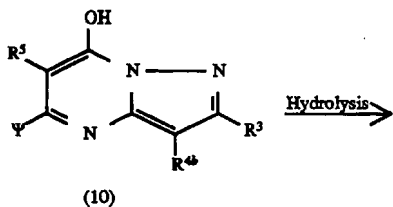
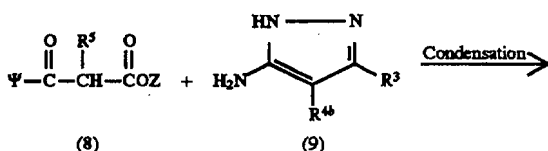
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[Reaction Scheme-1']



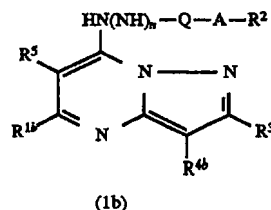
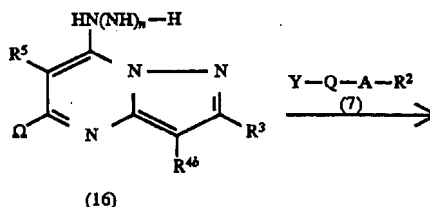
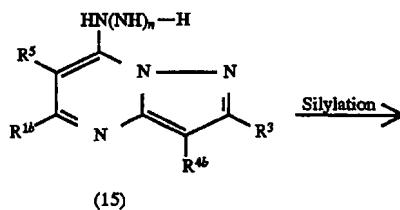
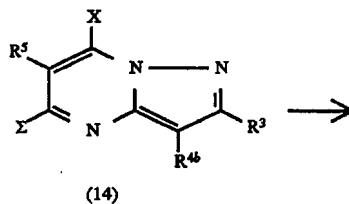
wherein R^{1a}, R³, R^{4a} and R⁵ are as defined above

The condensation of the nitrile derivative (2') and the compound (3) in this scheme is carried out in an inert solvent such as benzene, toluene, xylene, acetic acid and ethanol at room temperature to reflux temperature of the solvent for about 2-10 hours. These two compounds are generally used in an approximately equimolar proportion.

[Reaction Scheme-2]



8
-continued
[Reaction Scheme-2]



wherein R², R³, R⁵, X, Y, A, Q, Z and n are as defined above, Ψ is lower alkyl having protected oxo, Φ is lower alkyl having oxo, Σ is lower alkyl having acyloxy, Ω is lower alkyl having tri(lower)alkyl-silyloxy, R^{1b} is hydroxy(lower)alkyl, R^{4b} is hydrogen, lower alkyl, phenyl(lower)alkyl or optionally phenylthio-substituted phenyl.

The condensation of the compounds (8) and (9) in Reaction Scheme-2 can be carried out in the same manner as the condensation of the compounds (2) and (3) in Reaction Scheme-1.

Examples of the lower alkyl having protected oxo and represented by Ψ in the compound (8) include lower alkyl groups having as protected oxo the residue of di(lower)alkyl acetal such as dimethylacetal, methylethylacetal, diethylacetal, dipropylacetal, dibutylacetal, dipentylacetal and dihexylacetal or the residue of cyclic acetal such as ethylene acetal, trimethylene acetal and tetramethylene acetal.

The subsequent hydrolysis of the compound (10) according to Reaction Scheme-2 can be carried out using an organic acid such as acetic acid, propionic acid and p-toluenesulfonic acid. Of these organic acids, carboxylic acids such as acetic acid and propionic acid function as solvents. When such a carboxylic acid is used, no other solvents are necessary. Other suitable inert solvents such as benzene, toluene and xylene may be optionally used even when a carboxylic acid is used as the organic acid. The reaction goes to completion at approximately room temperature to reflux temperature of the solvent for about 10-80 hours to provide the compound (11).

Examples of the lower alkyl having oxo and represented by Φ in the compound (11) include those prepared by

eliminating protective groups from the corresponding "lower alkyl having protected oxo" and represented by Ψ . Specific examples are formyl, formylmethyl, acetyl, 2-formylethyl, 2-oxopropyl, propionyl, 3-formylpropyl, 3-oxobutyl, 2-oxobutyl, butyryl, 4-formylbutyl, 4-oxopentyl, 3-oxopentyl, 2-oxopentyl, valeryl, 5-formylpentyl, 5-oxohexyl, 4-oxohexyl, 3-oxohexyl, 2-oxohexyl, hexanoyl, and the like.

The subsequent reduction of the compound (11) can be carried out using a suitable reducing agent in an inert solvent. Examples of useful reducing agents are borohydride compounds such as sodium borohydride, potassium borohydride, lithium borohydride, sodium cyanoborohydride and sodium triethylborohydride, and lithium aluminum hydride compounds such as lithium aluminum hydride and lithium tri-*n*-butoxyaluminumhydride. When a borohydride compound is used as the reducing agent, the inert solvent is preferably either an alcohol solvent such as methanol and ethanol or a mixed solvent of said alcohol and another solvent such as dichloromethane and diethyl ether. When a lithium aluminum hydride compound is used as the reducing agent, the solvent is preferably diethyl ether, THF or like ethers. The reducing agent is preferably used in at least approximately equimolar proportion relative to the compound (11). The reaction goes to completion at approximately 0° C. to room temperature in about 0.5–3 hours.

Acylation of the compound (12) thus obtained can be carried out using an acylating agent in the absence of solvents or in an inert solvent such as pyridine, lutidine, *N,N*-dimethylformamide (DMF) and *N,N*-dimethylacetamide (DMA). Examples of useful acylating agents are acid anhydrides such as acetic anhydride, propionic anhydride, butyric anhydride, valeric anhydride, hexanoic anhydride and heptanoic anhydride. These are generally used in an amount of 1–10 equivalents relative to the compound (12). In order not to acylate hydroxyl at 7 position of the compound (12), the reaction conditions are preferably selected within the ranges of approximately 0° C. to room temperature and of about 0.5 to 2 hours.

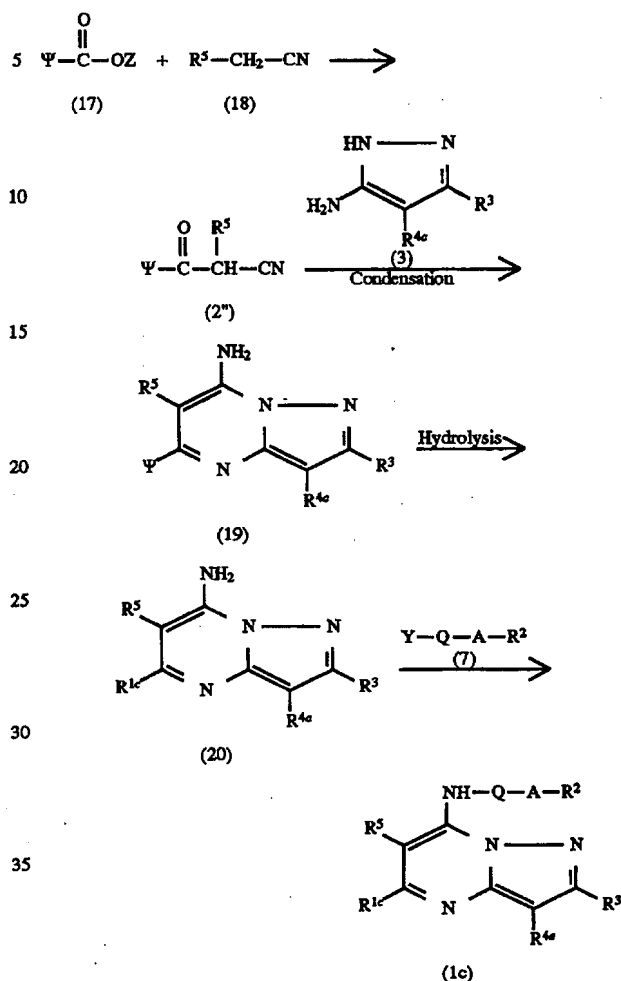
Halogenation of the compound (13) thus obtained can be carried out in the same manner as the halogenation of the compound (4) in Reaction Scheme-1.

Conversion of the compound (14) thus obtained to the compound (15) can be carried out under the same conditions as in the conversion of the compound (5) to the compound (6) in Reaction Scheme-1. The lower alkyl having acyloxy and represented by Σ in the compound (14) is hydrolyzed to form hydroxy(lower)alkyl by this reaction.

Silylation of the compound (15) thus obtained can be carried out using halotrialkylsilane in the presence of an acid acceptor in a suitable inert solvent such as THF and dichloromethane. Examples of useful acid acceptors are sodium carbonate, potassium carbonate, triethylamine and *N,N*-dimethylaminopyridine. Examples of useful halotrialkylsilane are chlorotrimethylsilane, chlorotriethylsilane, chlorotripropylsilane, chlorotributylsilane and chlorobutyldiethylsilane. These are normally used in an approximately equimolar to excessive amount relative to the compound (15). The reaction goes to completion at approximately room temperature in about 5–30 hours.

Lastly the compound (16) thus obtained is reacted with acid halide (7) to provide the desired compound (1b) of the invention. This reaction can be carried out in the same manner as the reaction using acid halide (7) in Reaction Scheme-1. The substituent Ω at position 5 of the compound (16) can be easily converted to the corresponding R^b group (hydroxy(lower)alkyl) by this reaction or the subsequent hydrolysis.

[Reaction Scheme-3]



wherein R^2 , R^3 , R^{4a} , R^5 , X , Y , Z , Q , A , n and Ψ are as defined above and R^k is lower alkyl having oxo.

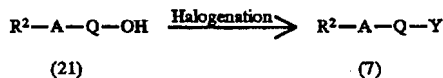
The reaction of the compound (17) and the nitrile derivative (18) in Reaction Scheme-3 can be carried out in an inert solvent such as DMF, DMA and dimethyl sulfoxide (DMSO) in the presence of a base such as sodium hydride and potassium hydride. The nitrile derivative (18) and the base are preferably used in an amount of 1 to an excessive equivalent relative to the compound (17) respectively. The reaction goes to completion at approximately 0° C. to room temperature in 2–10 hours.

The subsequent condensation of the compounds (2'') and (3) can be carried out in the same manner as the condensation in Reaction Scheme-1'.

Hydrolysis of the compound (19) can be carried out in the same manner as the hydrolysis in Reaction Scheme-2.

The reaction of the compounds (20) and (7) can be carried out in the same manner as the reaction in Reaction Scheme-1.

[Reaction Scheme-4]

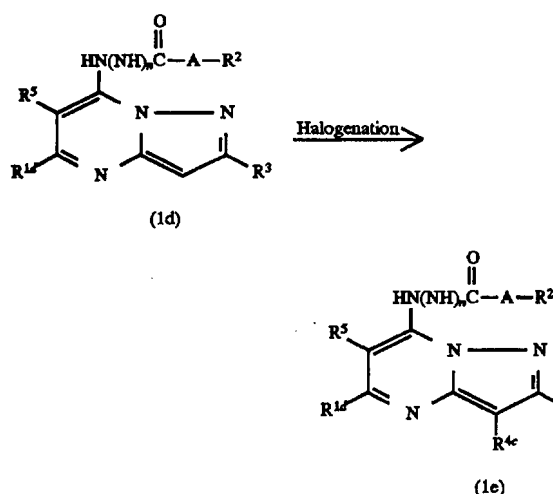


wherein R^2 , A , Q and Y are as defined above.

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As shown in Reaction Scheme-4, acid halide (7) to be used in Reaction Schemes-1, 2 and 3 can be prepared by halogenating the compound (21). The halogenation can be carried out by a conventional method. For example, the compound (21) is reacted with a halogenating agent such as thionyl chloride and thionyl bromide in the absence of solvents or in an inert solvent such as chloroform and diethylether. In this method, an excess of the halogenating agent is generally used. The reaction can be carried out at approximately room temperature to 150° C. for about 0.5-5 hours.

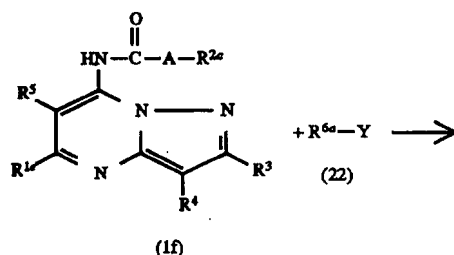
[Reaction Scheme-5]



wherein R^2 , R^3 , R^5 , A and n are as defined above, R^{1d} is hydrogen, lower alkyl which may have lower alkoxy or lower alkylthio as a substituent, cycloalkyl, thienyl, furyl, or phenyl which may have 1-3 substituents selected from the group consisting of lower alkyl, lower alkoxy, phenylthio and halogen, R^{1d} and R^5 may conjointly form lower alkylene and R^{4c} is halogen.

The halogenation of the compound (1d) in Reaction Scheme-5 can be carried out using a halogenating agent such as N-bromosuccinimide (NBS) and N-chlorosuccinimide (NCS) in an inert solvent such as benzene, carbon tetrachloride and chloroform. The halogenating agent is normally used in an amount of 1 equivalent to a slightly excessive amount relative to the compound (1d). The reaction can be carried out at approximately room temperature to reflux temperature of the solvent for 0.5-5 hours.

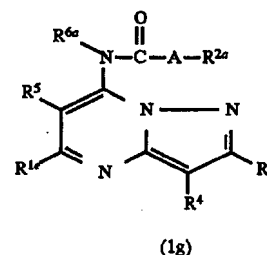
[Reaction Scheme-6]



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-continued

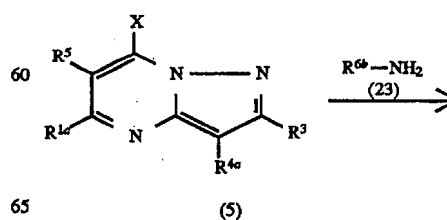
[Reaction Scheme-6]



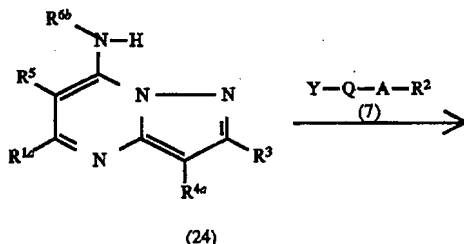
wherein R^3 , R^4 , R^5 and Y are as defined above, R^{1e} is hydrogen, lower alkyl which may have thienyl, lower alkoxy, lower alkylthio or oxo as a substituent, cycloalkyl, thienyl, furyl, lower alkenyl, or phenyl which may have 1-3 substituents selected from the group consisting of lower alkyl, lower alkoxy, phenylthio and halogen, R^{1e} and R^5 may conjointly form lower alkylene, R^{2a} is naphthyl, cycloalkyl, furyl, thienyl, optionally halogen-substituted pyridyl, optionally halogen-substituted phenoxy, or phenyl which may have 1-3 substituents selected from the group consisting of lower alkyl, lower alkoxy, halogen, nitro, halogen-substituted lower alkyl, halogen-substituted lower alkoxy, lower alkoxy carbonyl, phenyl(lower)alkoxy, cyano, lower alkanoyloxy, phenyl and di(lower)alkoxyphosphoryl-(lower)alkyl, and R^{6a} is phenyl(lower)alkyl, or benzoyl having 1-3 substituents selected from the group consisting of lower alkoxy, halogen-substituted lower alkyl and halogen.

In Reaction Scheme-6, the compound (1f) is reacted with the compound (22) in an inert solvent in the presence of a base to provide the compound (1g). When R^{6a} is a phenyl (lower)alkyl, suitable inert solvents are DMF, DMA, DMSO, etc. and suitable bases are sodium hydride, potassium hydride, etc. When R^{6a} is a benzoyl having 1-3 substituents selected from the group consisting of lower alkoxy, halogen-substituted lower alkyl and halogen, suitable inert solvents are chloroform, dichloromethane, etc. and suitable bases are triethylamine, N,N-dimethylaniline, etc. The compound (22) is normally used in an amount of 1 to a slightly excessive equivalent. The base is preferably used in an amount of 1 to an excessive equivalent. The reaction is carried out at approximately 0° C. to room temperature for 3-30 hours.

[Reaction Scheme-7]



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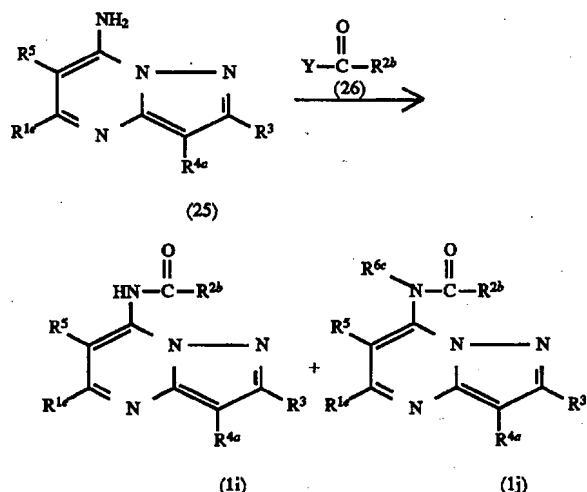
-continued
[Reaction Scheme-7]

wherein R^{1a} , R^2 , R^3 , R^{4a} , R^5 , X , Y , Q and A are as defined above and R^{6a} is lower alkyl or phenyl(lower)alkyl.

The reaction of the compounds (5) and (23) in Reaction Scheme-7 is carried out in an inert solvent such as methanol and ethanol in the presence of an acid acceptor such as sodium hydrogen carbonate, sodium carbonate and potassium carbonate at reflux temperature of the solvent for about 1-5 hours.

The reaction of the compounds (24) and (7) can be carried out in the same manner as the corresponding reaction in Reaction Scheme-1, thus giving the compound (1h).

[Reaction Scheme-8]



wherein R^{1a} , R^3 , R^{4a} , R^5 , and Y are as defined above, R^{2b} is phenyl having 1-3 substituents selected from the group consisting of lower alkoxy, halogen, halogen-substituted lower alkyl and R^{6a} is benzoyl having 1 to 3 substituents selected from the group consisting of lower alkoxy, halogen-substituted lower alkyl and halogen.

The reaction of the compounds (25) and (26) in Reaction Scheme-8 can be carried out in the same manner as the reaction of the compounds (6) and (7) in Reaction Scheme-1. A by-product (1j) is obtained together with the main product (1i) by this reaction.

The compounds of the invention can be formed into pharmaceutically acceptable acid addition salts, which are

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also included among the compounds of the invention. The acid for use to form such salts includes inorganic acids such as hydrochloric acid, hydrobromic acid and sulfuric acid and organic acids such as oxalic acid, fumaric acid, maleic acid, tartaric acid and citric acid. The reaction for forming such salts can be performed by conventional methods.

The object compound in each of the above processes can be easily isolated by conventional separation and purification means. Examples of useful isolation means include various conventional means such as adsorption chromatography, preparative thin-layer chromatography, recrystallization and solvent extraction.

Some compounds of formula (1) according to the invention, wherein A is alkenylene or R^1 is lower alkenyl, may be cis- or trans-isomers. Of course, these isomers are included in the invention.

Compounds of the formula (1) according to the invention may exist as optical isomers having a carbon atom as a stereogenic center. Such optically active substances and racemic derivatives are included in the invention.

The compound of the invention can be made into usual dosage forms of pharmaceutical compositions using suitable non-toxic pharmaceutically acceptable carriers. The present invention provides such pharmaceutical compositions, especially analgesics.

Examples of useful pharmaceutically acceptable carriers include conventional diluents or excipients such as fillers, volume builders, binders, humectants, disintegrators, surfactants, lubricants, and the like. These carriers are selectively used according to the desired unit dosage form.

The unit dosage form of said pharmaceutical composition can be selected from a broad variety of forms according to the intended medical treatment. Typical examples are tablets, pills, powders, solutions, suspensions, emulsions, granules, capsules, suppositories, injections (solutions, suspensions, etc.), ointments, and the like.

The tablets can be molded using as pharmaceutically acceptable carriers excipients such as lactose, sucrose, sodium chloride, glucose, urea, starch, calcium carbonate, kaolin, crystalline cellulose, silicic acid and potassium phosphate, binders such as water, ethanol, propanol, simple syrup, glucose syrup, starch solution, gelatin solution, carboxymethyl cellulose, hydroxypropyl cellulose, methyl cellulose and polyvinyl pyrrolidone, disintegrators such as sodium carboxymethyl cellulose, calcium carboxymethyl cellulose, low-substituted hydroxypropyl cellulose, dry starch, sodium alginate, agar powder, laminaran powder, sodium hydrogen carbonate and calcium carbonate, surfactants such as polyoxyethylene sorbitan fatty acid ester, sodium lauryl sulfate and stearyl monoglyceride, disintegration inhibitors such as sucrose, stearin, cacao butter and hydrogenated oil, absorption promoters such as quaternary ammonium base and sodium lauryl sulfate, humectants such as glycerin and starch, adsorbents such as starch, lactose, kaolin, bentonite and colloidal silicic acid, and lubricants such as purified talc, stearic acid salt, boric acid powder and polyethylene glycol. Furthermore, such tablets may be optionally coated to provide sugar-coated tablets, gelatin-coated tablets, enteric tablets, film-coated tablets, etc. or be processed into double-layer or multiple-layer tablets.

The pills can be molded using as pharmaceutically acceptable carriers excipients such as glucose, lactose, starch, cacao butter, hydrogenated vegetable oil, kaolin and talc, binders such as gum arabic powder, tragacanth powder, gelatin and ethanol, and disintegrators such as laminaran and starch.

The suppositories can be molded using as pharmaceutically acceptable carriers polyethylene glycol, cacao butter,

higher alcohols or their esters, gelatin, semisynthetic glycerides, and the like.

The capsules can be manufactured by mixing the active ingredient compound of the invention with pharmaceutically acceptable carriers as mentioned above and filling the mixture into hard gelatin capsule shells, soft capsule shells, etc. according to conventional methods.

The injections in the form of solutions, emulsions, suspensions, etc. can be manufactured using diluents such as water, ethyl alcohol, macrogol, propylene glycol, ethoxylated isostearyl alcohol, polyoxyisostearyl alcohol and polyoxyethylene sorbitan fatty acid ester and are preferably sterilized and rendered isotonic with respect to the blood. In order to provide such an isotonic solution, a sufficient amount of sodium chloride, glucose or glycerin may be added to the pharmaceutical composition of the invention. Conventional solubilizers, buffers, local anesthetics, etc. may also be added.

Further, coloring agents, preservatives, perfumes, flavors, sweeteners, or other pharmaceutical compositions may be optionally incorporated in the pharmaceutical compositions of the invention.

The ointments in the form of paste, cream, gel, etc. can be manufactured using diluents such as white vaseline, paraffin, glycerin, cellulose derivatives, polyethylene glycol, silicone and bentonite.

The proportion of the active ingredient compound of formula (1) of the invention in the pharmaceutical composition of the invention is not so critical but can be liberally selected from a broad range. Generally, the active ingredient compound preferably accounts for about 1 to 70 weight % of the final composition.

There is no specific limitation on the administration method for the pharmaceutical composition of the invention. The proper method can be determined according to the dosage form, patient's age, sex or other conditions, severity of disease, etc. For example, the tablets, pills, solutions, suspensions, emulsions, granules and capsules are orally administered. The injections are intravenously administered singly or in admixture with a conventional infusion such as glucose and amino acid, and optionally administered singly by the intramuscular, intradermal, subcutaneous or intraperitoneal route. The suppositories are intrarectally administered.

The dosage of the pharmaceutical composition is suitably selected according to the administration method, patient's age, sex or other conditions, severity of disease, etc. The dosage of the compound of the invention as the active ingredient is preferably about 0.5–20 mg per kg body weight a day and this amount can be administered once or in 2–4 divided doses.

BEST MODE FOR PRACTICING THE INVENTION

Preparation examples for starting compounds to produce compounds of the invention are given below as Reference Examples, and preparation examples for compounds of the invention are given below as Examples to clarify the present invention in more detail.

REFERENCE EXAMPLE 1

Preparation of 7-amino-5-n-butylpyrazolo[1,5-a]pyrimidine

Step (1)

A solution of 100 g of 3-aminopyrazole and 190 g of methyl 3-oxoheptanoate in 120 ml of toluene was refluxed

with heating at 100° C. for 3 hours and then cooled. Toluene was distilled off under reduced pressure and diethyl ether was added to the residue. The crystals precipitated were collected and washed with diethyl ether and acetonitrile to provide 184 g of 5-n-butyl-7-hydroxypyrazolo[1,5-a]pyrimidine as colorless crystals.

Step (2)

Phosphorus oxychloride (80 ml) and triethylamine (44 ml) were added to a toluene suspension (400 ml) containing 40 g of the crystals obtained in step (1). The reaction mixture was refluxed with heating for 4 hours. After completion of the reaction, the reaction mixture was concentrated under reduced pressure and the residue was poured into ice water. The mixture was neutralized with sodium acetate and extracted with ethyl acetate. The organic layer was collected, washed with a saturated saline solution, dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (eluent: ethyl acetate: n-hexane=1:9) to provide 41 g of 5-n-butyl-7-chloropyrazolo[1,5-a]pyrimidine as a light yellow oily compound.

Step (3)

The compound prepared in the above step (2) (21 g) and 25% aqueous ammonia (100 ml) were enclosed in a stainless steel sealed tube, heated at 110° C. for 12 hours and cooled. The crystals precipitated were collected by filtration, washed with water and recrystallized from chloroform-n-hexane to provide 18.4 g of 7-amino-5-n-butylpyrazolo[1,5-a]pyrimidine as colorless crystals (melting point: 124°–126° C.).

The following compounds were prepared in the same manner as above.

- (1) 7-Amino-5-ethylpyrazolo[1,5-a]pyrimidine (melting point: 175°–177° C., recrystallization solvent: ethyl acetate-n-hexane)
- (2) 7-Amino-5-n-propylpyrazolo[1,5-a]pyrimidine (melting point: 138°–140° C., recrystallization solvent: ethyl acetate-n-hexane)
- (3) 7-Amino-5-cyclopropylpyrazolo[1,5-a]pyrimidine (melting point: 206°–209° C., recrystallization solvent: chloroform-n-hexane)
- (4) 7-Amino-5-n-pentylpyrazolo[1,5-a]pyrimidine (melting point: 125°–126° C., recrystallization solvent: ethyl acetate-n-hexane)
- (5) 7-Amino-5-phenylpyrazolo[1,5-a]pyrimidine (melting point: 207°–209° C., recrystallization solvent: ethyl acetate-n-hexane)
- (6) 7-Amino-5-(4-methoxyphenyl)pyrazolo[1,5-a]pyrimidine (melting point: 194°–196° C., recrystallization solvent: ethanol-n-hexane)
- (7) 7-Amino-5-(2-thienyl)pyrazolo[1,5-a]pyrimidine (melting point: 227°–229° C., recrystallization solvent: ethanol-n-hexane)
- (8) 7-Amino-5-(3-thienyl)pyrazolo[1,5-a]pyrimidine (melting point: 203°–205° C., recrystallization solvent: ethanol-n-hexane)
- (9) 7-Amino-5-methylpyrazolo[1,5-a]pyrimidine (melting point: 220°–222° C., recrystallization solvent: chloroform-n-hexane)
- (10) 7-Amino-5-n-butyl-2-methylpyrazolo[1,5-a]pyrimidine (melting point: 176°–178° C., recrystallization solvent: chloroform-n-hexane)
- (11) 7-Amino-5-(2,4-dimethylphenyl)pyrazolo[1,5-a]pyrimidine (melting point: 168°–170° C., recrystallization solvent: chloroform-n-hexane)
- (12) 7-Amino-5-(3,5-dimethylphenyl)pyrazolo[1,5-a]pyrimidine (melting point: 180°–182° C., recrystallization solvent: ethanol-n-hexane)

- (13) 7-Amino-5-(2-methoxyphenyl)pyrazolo[1,5-a]pyrimidine (melting point: 201°–203° C., recrystallization solvent: ethanol-n-hexane)
- (14) 7-Amino-5-(3-methoxyphenyl)pyrazolo[1,5-a]pyrimidine (melting point: 195°–197° C., recrystallization solvent: ethanol-n-hexane)
- (15) 7-Amino-5-(3,4,5-trimethoxyphenyl)pyrazolo[1,5-a]pyrimidine (melting point: 198°–200° C., recrystallization solvent: ethanol-n-hexane)
- (16) 7-Amino-5-(2-chlorophenyl)pyrazolo[1,5-a]pyrimidine (melting point: 208°–210° C., recrystallization solvent: chloroform-n-hexane)
- (17) 7-Amino-5-(2-furyl)pyrazolo[1,5-a]pyrimidine (melting point: 204°–206° C., recrystallization solvent: ethanol-n-hexane)
- (18) 7-Amino-5-(3-furyl)pyrazolo[1,5-a]pyrimidine (melting point: 208°–210° C., recrystallization solvent: ethanol-n-hexane)
- (19) 7-Amino-5-(2-thienylmethyl)pyrazolo[1,5-a]pyrimidine (melting point: 188°–190° C., recrystallization solvent: ethanol-n-hexane)
- (20) 7-Amino-5-(3,5-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidine (melting point: 207°–209° C., recrystallization solvent: ethanol-n-hexane)
- The following compounds were also prepared in the same manner as above.
- (21) 7-Amino-5-(3-butenyl)pyrazolo[1,5-a]pyrimidine
- (22) 7-Amino-5-ethoxymethylpyrazolo[1,5-a]pyrimidine
- (23) 7-Amino-5-(2-methylphenyl)pyrazolo[1,5-a]pyrimidine
- (24) 7-Amino-5-(3-methylphenyl)pyrazolo[1,5-a]pyrimidine
- (25) 7-Amino-5-(4-methylphenyl)pyrazolo[1,5-a]pyrimidine
- (26) 7-Amino-5-(3-chlorophenyl)pyrazolo[1,5-a]pyrimidine
- (27) 7-Amino-5-(4-chlorophenyl)pyrazolo[1,5-a]pyrimidine
- (28) 7-Aminopyrazolo[1,5-a]pyrimidine
- (29) 7-Amino-5-n-butyl-3-ethoxycarbonyl-2-methylpyrazolo[1,5-a]pyrimidine (melting point: 178°–180° C., recrystallization solvent: methylene chloride-n-hexane)
- (30) 7-Amino-2,5-di-n-butyl-3-methylpyrazolo[1,5-a]pyrimidine (melting point: 123°–125° C., recrystallization solvent: diethyl ether-n-hexane)
- (31) 7-Amino-5-n-butyl-2-phenylpyrazolo[1,5-a]pyrimidine (melting point: 206°–208° C., recrystallization solvent: ethyl acetate-n-hexane)
- (32) 7-Amino-3-benzyl-5-n-butyl-2-phenylpyrazolo[1,5-a]pyrimidine (melting point: 106°–108° C., recrystallization solvent: chloroform-n-hexane)
- (33) 7-Amino-5-n-butyl-2-phenyl-3-[4-(phenylthio)phenyl]pyrazolo[1,5-a]pyrimidine (melting point: 139°–141° C., recrystallization solvent: diethyl ether-n-hexane)
- (34) 7-Amino-3,5-di-n-butylpyrazolo[1,5-a]pyrimidine (melting point: 58°–60° C., recrystallization solvent: ethyl acetate-n-hexane)
- (35) 7-Amino-5-n-butyl-3-phenylpyrazolo[1,5-a]pyrimidine (melting point: 113°–115° C., recrystallization solvent: ethyl acetate-n-hexane)
- (36) 7-Amino-5-[(ethylthio)methyl]pyrazolo[1,5-a]pyrimidine (melting point: 109°–111° C., recrystallization solvent: chloroform-n-hexane)
- (37) 7-Amino-5-[2-(methylthio)ethyl]pyrazolo[1,5-a]pyrimidine (melting point: 77°–79° C., recrystallization solvent: ethyl acetate-n-hexane)
- (38) 7-Amino-5-[4-(phenylthio)phenyl]pyrazolo[1,5-a]pyrimidine (melting point: 182°–184° C., recrystallization solvent: chloroform-diethyl ether)

- (39) 9-Amino-5,6,7,8-tetrahydropyrazolo[5,1-b]quinazoline (melting point: 230°–233° C., recrystallization solvent: ethyl acetate-n-hexane)
- (40) 7-Amino-2,5-di-n-butylpyrazolo[1,5-a]pyrimidine (melting point: 105°–107° C., recrystallization solvent: diethyl ether-n-hexane)

REFERENCE EXAMPLE 2

Preparation of 5-n-butyl-7-hydrazinopyrazolo[1,5-a]pyrimidine

Hydrazine monohydrate (50 ml) was slowly added dropwise to 21.0 g of 5-n-butyl-7-chloropyrazolo[1,5-a]pyrimidine prepared in step (2) of Reference Example 1 at room temperature and stirred at room temperature for 10 hours. After completion of the reaction, the crystals precipitated were collected, washed with water and recrystallized from chloroform-n-hexane to provide 12.6 g of the object compound as colorless crystals (melting point: 126°–129° C.).

7-Hydrazino-5-phenylpyrazolo[1,5-a]pyrimidine was prepared in the same manner as above.

REFERENCE EXAMPLE 3

Preparation of 7-amino-5-(3-oxobutyl)pyrazolo[1,5-a]pyrimidine

An acetonitrile solution (10 ml) containing 5.0 g of methyl 2-methyl-1,3-dioxolane-2-propionate was added dropwise to 10 ml of a DMF suspension containing 2.3 g of 60% sodium hydride, and stirred at room temperature for 4 hours. The reaction mixture was poured into ice water, acidified with a saturated citric acid solution and extracted with ethyl acetate. The organic layer was washed with water and a saturated saline solution and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (eluent: n-hexane:ethyl acetate=3:2) to provide 3.0 g of 2-methyl-β-oxo-1,3-dioxolane-2-pentanenitrile as oil.

Subsequently, a toluene solution (1.6 ml) containing 3.0 g of the compound thus obtained and 1.4 g of 3-aminopyrazole was stirred at 115° C. for 10 hours. The reaction mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (eluent: chloroform:methanol=20:1) and recrystallized from chloroform-n-hexane to provide 2.1 g of 7-amino-5-[2-(2-methyl-1,3-dioxolane-2-yl)ethyl]pyrazolo[1,5-a]pyrimidine as colorless crystals.

Then 1.0 g of the crystals thus obtained were dissolved in 500 ml of acetic acid-water (4:1) and stirred at 80° C. overnight. After completion of the reaction, the reaction mixture was concentrated under reduced pressure. The remaining acetic acid-water was azeotropically distilled off with benzene. The residue was recrystallized from ethanol-n-hexane to provide 0.7 g of the title object compound as colorless crystals.

Melting point: 164°–166° C., recrystallization solvent: ethanol-n-hexane

REFERENCE EXAMPLE 4

Preparation of 7-amino-5-n-butyl-6-methylpyrazolo[1,5-a]pyrimidine

A toluene solution (2.5 ml) containing 1.8 g of 3-aminopyrazole and 3 g of 2-methyl-3-oxoheptanenitrile

was heated at 115° C. for 3.5 hours. Toluene was distilled off under reduced pressure and the residue was recrystallized from ethyl acetate and washed with diethyl ether to provide 2.4 g of the title object compound as colorless crystals.

Melting point: 153°–155° C., recrystallization solvent: ethyl acetate

EXAMPLE 1

Preparation of 5-n-butyl-7-(3,4,5-trimethoxybenzoylamino) pyrazolo[1,5-a]pyrimidine

7-Amino-5-n-butylpyrazolo[1,5-a]pyrimidine (1.90 g) and pyridine (20 ml) were dissolved in 20 ml of dry dichloromethane. A dry dichloromethane solution (10 ml) containing 2.6 g of 3,4,5-trimethoxybenzoyl chloride was slowly added dropwise thereto and stirred at room temperature for 10 hours. After addition of 50 ml of a 10% aqueous sodium hydrogen carbonate solution, the reaction mixture was extracted with chloroform. The organic layer was collected, washed with 10% aqueous hydrochloric acid and water, dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (eluent: ethyl acetate: n-hexane=1:2) and recrystallized from diethyl ether-n-hexane to provide 2.4 g of the object compound as colorless crystals. Table 1 shows the structure and melting point of the compound obtained.

EXAMPLES 2–46

The compounds set forth in Table 1 were prepared in the same manner as in Example 1. The structures and melting points of the compounds are also shown in Table 1. As to the oily compounds, data on the results of ¹H-NMR analysis are shown.

EXAMPLES 47–99

The compounds set forth in Table 2 were prepared in the same manner as in Example 1. The structures and melting points of the compounds are also shown in Table 2. As to the oily compounds, data on the results of ¹H-NMR analysis are shown.

EXAMPLE 100

Preparation of 5-(3-hydroxybutyl)-7-(3,4,5-trimethoxybenzoylamino) pyrazolo[1,5-a]pyrimidine

Step (1)

A toluene solution (2 ml) containing 0.90 g of 3-aminopyrazole and 1.90 g of methyl 2-methyl-β-oxo-1,3-dioxolane-2-valerate was refluxed with heating at 115° C. for 1 hour, allowed to cool and then concentrated under reduced pressure. Diethyl ether was added to the residue. The crystals precipitated were collected and washed with diethyl ether to provide 1.85 g of 7-hydroxy-5-[2-(2-methyl-1,3-dioxolane-2-yl)ethyl]pyrazolo[1,5-a]pyrimidine as colorless crystals.

Step (2)

The crystals thus obtained (2.2 g) were dissolved in 500 ml of acetic acid-water (4:1) and stirred at 50° C. for 3 days. After completion of the reaction, the reaction mixture was concentrated under reduced pressure and the remaining acetic acid-water was azeotropically distilled off with benzene. The residue was recrystallized from ethanol-n-hexane to provide 11.0 g of 7-hydroxy-5-(3-oxobutyl)pyrazolo[1,5-a]pyrimidine as colorless crystals.

Step (3)

The crystals obtained in step (2) (5.7 g) were dissolved in 120 ml of methanol. Sodium borohydride (0.53 g) was added under ice-cooling and stirred at 0° C. for 2 hours. After completion of the reaction, the reaction mixture was acidified by adding dilute aqueous hydrochloric acid dropwise and then extracted with chloroform. The organic layer was collected, washed with a saturated saline solution, dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was recrystallized from ethanol-n-hexane to provide 4.16 g of 7-hydroxy-5-(3-hydroxybutyl) pyrazolo[1,5-a]pyrimidine as colorless crystals.

Step (4)

The crystals obtained in step (3) (4.16 g) were dissolved in 40 ml of acetic anhydride and 40 ml of pyridine and stirred at room temperature for 30 minutes. After completion of the reaction, the reaction mixture was concentrated under reduced pressure and the residue was recrystallized from methanol-diethyl ether to provide 4.2 g of 5-(3-acetoxybutyl)-7-hydroxypyrazolo[1,5-a]pyrimidine as colorless crystals.

Step (5)

Phosphorus oxychloride (6.4 ml) and triethylamine (3.5 ml) were added to 40 ml of a toluene suspension containing 4.2 g of the crystals obtained in step (4), and the mixture was refluxed with heating for 6 hours. After completion of the reaction, the reaction mixture was concentrated under reduced pressure and the residue was poured into ice water. The mixture was neutralized with sodium acetate and extracted with ethyl acetate. The organic layer was collected, washed with a saturated saline solution, dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (eluent: ethyl acetate: n-hexane=4:1) to provide 4.3 g of 5-(3-acetoxybutyl)-7-chloropyrazolo[1,5-a]pyrimidine as a light yellow oily compound.

Step (6)

The compound prepared in step (5) (4.3 g) and 25% aqueous ammonia (50 ml) were enclosed in a stainless steel sealed tube, heated at 105° C. for 14 hours and allowed to cool. The crystals precipitated were collected by filtration, washed with water and dried to provide 3.2 g of 7-amino-5-(3-hydroxybutyl)pyrazolo[1,5-a]pyrimidine as light yellow crystals.

Step (7)

Triethylamine (400 μl) and chlorotrimethylsilane (680 μl) were added to 5 ml of a THF solution containing 500 mg of the crystals obtained in step (6), and the mixture was stirred at room temperature for 12 hours. After completion of the reaction, a saturated aqueous NaHCO₃ solution was added and the reaction mixture was extracted with dichloromethane. The organic layer was collected, washed with water and a saturated saline solution, dried over anhydrous sodium sulfate and concentrated under reduced pressure. n-Hexane was added to the residue. The crystals precipitated were collected by filtration to provide 520 mg of 7-amino-5-(3-trimethylsilyloxybutyl) pyrazolo[1,5-a]pyrimidine as colorless crystals.

¹H-NMR (δ:ppm) [CDCl₃] 0.12 (9H, s), 1.20 (3H, d, J=5.9), 1.8–1.9 (2H, m), 2.6–2.9 (2H, m), 3.8–3.9 (1H, m), 5.61 (2H, brs), 5.99 (1H, s), 6.41 (1H, d, J=2.0), 7.99 (1H, d, J=2.0)

Step (8)

A dry dichloromethane solution (5 ml) containing 650 mg of 3,4,5-trimethoxybenzoyl chloride was slowly added dropwise to 5 ml of a pyridine solution containing 520 mg of the

crystals obtained in step (7), and stirred at room temperature for 2 hours. After completion of the reaction, a saturated aqueous NaHCO₃ solution was added and the reaction mixture was extracted with dichloromethane. The organic layer was collected and washed with a 1N aqueous hydrochloric acid until the pH of the water layer became about 1. The organic layer was allowed to stand for 2 hours, washed with water and a saturated saline solution, dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was recrystallized from dichloromethane-n-hexane to provide 480 mg of the object compound as colorless crystals. Table 2 shows the structure and melting point of the compound obtained.

EXAMPLES 101 and 102

The compounds set forth in Table 2 were prepared in the same manner as in Example 100. The structures and melting points of the compounds are also shown in Table 2.

EXAMPLE 103

Preparation of 5-n-butyl-3-chloro-2-methyl-7-(3,4,5-trimethoxybenzoylamino) pyrazolo[1,5-a]pyrimidine

5-n-Butyl-2-methyl-7-(3,4,5-trimethoxybenzoyl-amino) pyrazolo[1,5-a]pyrimidine (the compound of Example 53; 0.78 g) was dissolved in 10 ml of chloroform. After addition of 0.28 g of NCS, the mixture was refluxed with heating for 1 hour and allowed to cool. After addition of some water, the reaction mixture was extracted with chloroform. The organic layer was collected, dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (eluent: ethyl acetate:n-hexane=1:2) and recrystallized from ethanol-n-hexane to provide 0.61 g of the object compound as colorless crystals. Table 3 shows the structure and melting point of the compound obtained.

EXAMPLES 104-106

The compounds set forth in Table 3 were prepared in the same manner as in Example 103. The structures and melting points of the compounds are also shown in Table 3.

EXAMPLES 107-128

The compounds set forth in Table 4 were prepared in the same manner as in Example 1. The structures and melting points of the compounds are also shown in Table 4.

EXAMPLE 129

Preparation of 5-n-butyl-7-[N-methyl-N-(3,4,5-trimethoxybenzoyl) amino]pyrazolo[1,5-a]pyrimidine

5-n-Butyl-7-chloropyrazolo[1,5-a]pyrimidine (the compound prepared in step (2) of Reference Example 1; 8.60 g), sodium hydrogen carbonate (3.44 g) and 40% methylamine (3.18 g) were added to 50 ml of ethanol and heated at 120° C. for 2 hours. After completion of the reaction, ethanol was distilled off under reduced pressure. After addition of some

water, the residue was extracted with ethyl acetate. The organic layer was collected, dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (eluent: ethyl acetate:n-hexane=1:2) to provide 2.33 g of 5-n-butyl-7-methylaminopyrazolo[1,5-a]pyrimidine as crystals.

The object compound was prepared using the crystals thus obtained and 3,4,5-trimethoxybenzoyl chloride in the same manner as in Example 1. The structure and melting point of the compound obtained are shown in Table 5.

EXAMPLE 130

The compound set forth in Table 5 was prepared in the same manner as in Example 129. The structure and melting point of the compound are also shown in Table 5.

EXAMPLE 131

Preparation of 5-n-butyl-7-[N,N-bis(3,4,5-trimethoxybenzoyl) amino]pyrazolo[1,5-a]pyrimidine

The compound prepared in Example 1 (1.92 g) and triethylamine (1.02 g) were dissolved in 10 ml of chloroform. A chloroform solution (10 ml) containing 1.28 g of 3,4,5-trimethoxybenzoyl chloride was added to the solution at room temperature and the mixture was stirred at room temperature for 10 hours. After completion of the reaction, the organic layer was washed with dilute aqueous hydrochloric acid, dried over anhydrous sodium sulfate and concentrated. The residue was purified by silica gel column chromatography (eluent: ethyl acetate:n-hexane=1:2) and recrystallized from ethyl acetate-n-hexane to provide 1.10 g of the object compound as colorless crystals.

The structure and melting point of the compound obtained are shown in Table 5.

EXAMPLE 132

Preparation of 5-n-butyl-7-[N,N-bis(2-chlorobenzoyl) amino]pyrazolo[1,5-a]pyrimidine

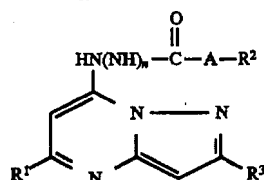
The former fractions obtained by silica gel column chromatography in Example 23 were purified by silica gel column chromatography again (eluent: dichloromethane), and recrystallized to provide the object compound as colorless crystals. Table 5 shows the structure and melting point of the compound obtained.

EXAMPLES 133-134

The former fractions obtained by silica gel column chromatography in Examples 32 and 52 were treated in the same manner as in Example 132, thus giving the compounds shown in Table 5. The structures and melting points of the compounds are also shown in Table 5.

The former fractions obtained by silica gel column chromatography in Example 1 were treated likewise, giving the same compound as in Example 131.

TABLE 2



Me: methyl group, Et: ethyl group, nPr: n-propyl group,
nBu: n-butyl group, tBu: t-butyl group, nPe: n-pentyl group,
Ph: phenyl group, Ac: acetyl group

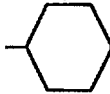
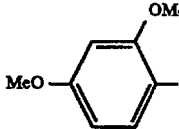
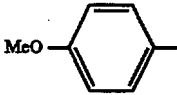
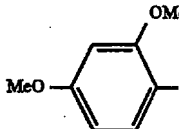
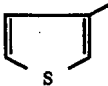
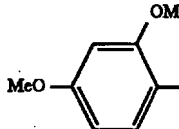
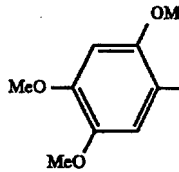
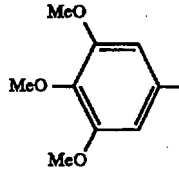
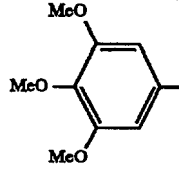
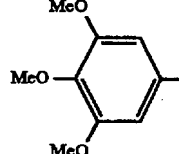
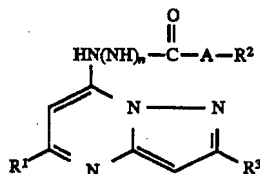
No.	R ¹	R ²	R ³	A	n	Melting point (°C.) (Recrystallization solvent)
47	nBu		H	Singlebond	0	¹ H-NMR(CDCl ₃)0.95(3H, t, J=7.4), 1.2-2.1(14H, m), 2.4-2.6(1H, m), 2.81(2H, t, J=7.8), 6.54(1H, d, J=2.2), 7.62(1H, s), 8.00(1H, d, J=2.2), 9.29(1H, brs)
48	nBu		H	Singlebond	0	141-142 (Ethanol-n-hexane)
49			H	Singlebond	0	209-211 (Methylene chloride-ethyl acetate)
50			H	Singlebond	0	206-208 (Methylene chloride-ethyl acetate)
51	nBu		H	Singlebond	0	136-137 (Ethanol-n-hexane)
52	Me		H	Singlebond	0	173-175 (Ethanol-n-hexane)
53	nBu		Me	Singlebond	0	127-129 (Ethanol-n-hexane)
54	CH ₂ =CH-C ₂ H ₄ -		H	Singlebond	0	104-106 (Ethyl acetate-n-hexane)

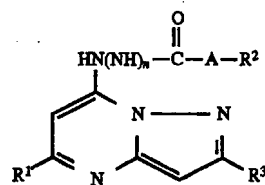
TABLE 2-continued



Me: methyl group, Et: ethyl group, nPr: n-propyl group,
nBu: n-butyl group, tBu: t-butyl group, nPe: n-pentyl group,
Ph: phenyl group, Ac: acetyl group

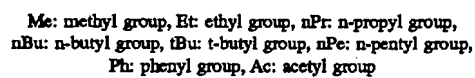
No.	R ¹	R ²	R ³	A	n	Melting point (°C.) (Recrystallization solvent)
55	Et-O-CH ₂ -		H	Singlebond	0	138-140 (Ethyl acetate-n-hexane)
56			H	Singlebond	0	163-165 (Chloroform-ethyl acetate)
57			H	Singlebond	0	166-168 (Ethyl acetate-n-hexane)
58			H	Singlebond	0	193-195 (Methylene chloride-diethyl ether)
59			H	Singlebond	0	174-176 (Methylene chloride-diethyl ether)
60			H	Singlebond	0	203-205 (Methylene chloride-diethyl ether)
61			H	Singlebond	0	175-177 (Methylene chloride-ether acetate)

TABLE 2-continued



Me: methyl group, Et: ethyl group, nPr: n-propyl group,
nBu: n-butyl group, tBu: t-butyl group, nPe: n-pentyl group,
Ph: phenyl group, Ac: acetyl group

No.	R ¹	R ²	R ³	A	n	Melting point (°C.) (Recrystallization solvent)
62			H	Singlebond	0	192-194 (Methylene chloride-diethyl ether)
63			H	Singlebond	0	181-183 (Methylene chloride-diethyl ether)
64			H	Singlebond	0	224-226 (Methylene chloride-diethyl ether)
65			H	Singlebond	0	214-216 (Methylene chloride-diethyl ether)
66			H	Singlebond	0	190-192 (Methylene chloride-diethyl ether)
67			H	Singlebond	0	222-224 (Chloroform-ethyl acetate)
68			H	Singlebond	0	193-195 (Chloroform-ethyl acetate)



No.	R ¹	R ²	R ³	A	n	Melting point (°C.) (Recrystallization solvent)
69			H	Singlebond	0	189–191 (Methylene chloride-diethyl ether)
70			H	Singlebond	0	174–176 (Methylene chloride-ethyl acetate)
71			H	Singlebond	0	191–193 (Methylene chloride-diethyl ether)
72			H	Singlebond	0	198–200 (Methylene chloride-ethyl acetate)
73			H	Singlebond	0	157–159 (Ethyl acetate)
74	nBu		H	Singlebond	0	159–161 (Ethanol-n-hexane)
75	nBu		H	Singlebond	0	79–81 (Diethyl ether-n-hexane)

$$\begin{array}{c}
 \text{O} \\
 \parallel \\
 \text{HN}(\text{NH})_m - \text{C} - \text{A} - \text{R}^2 \\
 | \\
 \text{C} = \text{C} \\
 | \quad \quad | \\
 \text{R}^1 \quad \quad \text{N} \text{---} \text{N} \\
 \quad \quad \quad | \quad \quad | \\
 \quad \quad \quad \text{C} = \text{C} \\
 \quad \quad \quad | \quad \quad | \\
 \quad \quad \quad \text{R}^3 \quad \quad \text{R}^4
 \end{array}$$

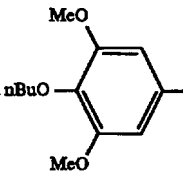
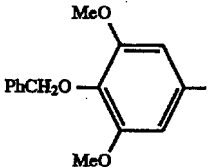
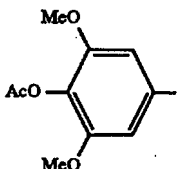
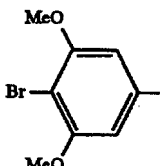
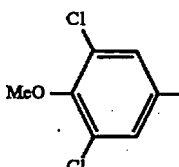
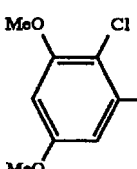
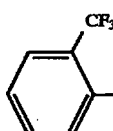
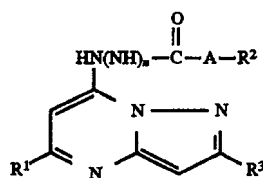
No.	R ¹	R ²	R ³	A	n	Melting point (°C.) (Recrystallization solvent)
76	nBu		H	Singlebond	0	98-100 (n-Hexane)
77	nBu		H	Singlebond	0	82-85 (Ethanol-n-hexane)
78	nBu		H	Singlebond	0	158-160 (Ethyl acetate-n-hexane)
79	nBu		H	Singlebond	0	182-184 (Ethyl acetate-n-hexane)
80	nBu		H	Singlebond	0	132-135 (Ethyl acetate-n-hexane)
81	nBu		H	Singlebond	0	111-113 (Diethyl ether-n-hexane)
82	Me		H	Singlebond	0	154-155 (Ethanol-n-hexane)

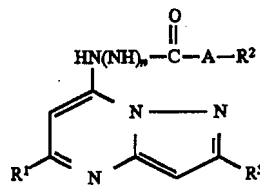
TABLE 2-continued



Me: methyl group, Et: ethyl group, nPr: n-propyl group,
nBu: n-butyl group, tBu: t-butyl group, nPe: n-pentyl group,
Ph: phenyl group, Ac: acetyl group

No.	R^1	R^2	R^3	A	n	Melting point (°C.) (Recrystallization solvent)
83	nPr		H	Singlebond	0	139-141 (Diethyl ether-n-hexane)
84			H	Singlebond	0	102-104 (n-Hexane)
85	nPe		H	Singlebond	0	93-95 (n-Hexane)
86	Ph		H	Singlebond	0	143-145 (Diethyl ether-n-hexane)
87	nBu		H	Singlebond	0	46-48 (Ethyl acetate-n-hexane)
88	nBu		H	Singlebond	0	108-110 (n-Hexane)
89	nBu		H	Singlebond	0	92.5-94.5 (n-Hexane)
90	nBu		H	Singlebond	0	106-108 (n-Hexane)

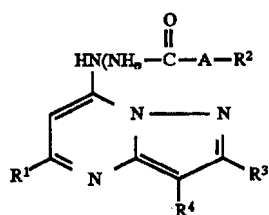
TABLE 2-continued



Me: methyl group, Et: ethyl group, nPr: n-propyl group,
nBu: n-butyl group, tBu: t-butyl group, nPe: n-pentyl group,
Ph: phenyl group, Ac: acetyl group

No.	R ¹	R ²	R ³	A	n	Melting point (°C.) (Recrystallization solvent)
91	nBu		H	Singlebond	0	123-125 (Ethanol-n-hexane)
92	nBu		H	Singlebond	0	123-125 (Diethyl ether-n-hexane)
93	nBu		H	Singlebond	0	139-140 (Ethanol-n-hexane)
94	nBu		H	CH ₂	0	121-123 (ethyl acetate-n-hexane)
95	nBu		H	-CH=CH-O		194-196 (Ethanol-n-hexane)
96	nBu		H	Singlebond	1	222 (Decomposition) (Ethanol-n-hexane)
97	Ph		H	Singlebond	1	250 (Decomposition) (Methanol-n-hexane)
98	nBu		H	Singlebond	1	247 (Decomposition) (Ethanol-n-hexane)
99	Ph		H	Singlebond	1	263 (Decomposition) (Ethanol-n-hexane)

TABLE 3-continued



Me: methy group, nBu: n-butyl group

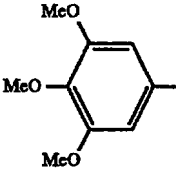
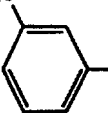
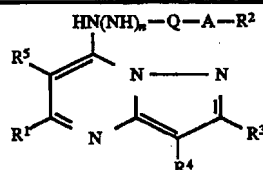
Ex.	R ¹	R ²	R ³	R ⁴	A	n	Recrystallization solvent	Melting point (°C.)
105	nBu		H	Br	Single-bond	0	146-148	(Ethanol-n-hexane)
106	nBu		H	Cl	Single-bond	0	133-135	(Diethyl ether-n-hexane)

TABLE 4



Me: methyl group, Et: ethyl group, nBu: n-butyl group, Ph: phenyl group

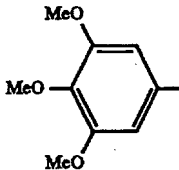
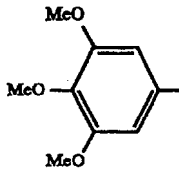
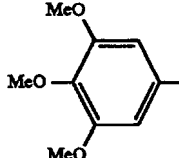
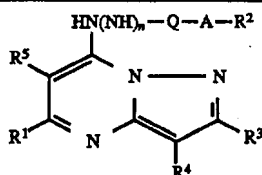
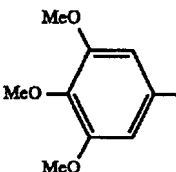
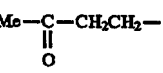
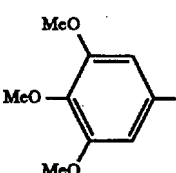
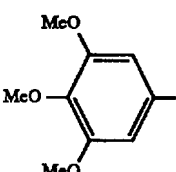
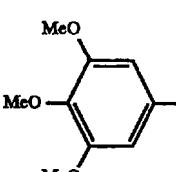
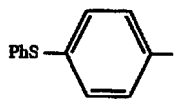
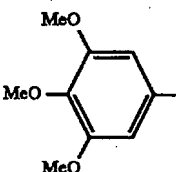
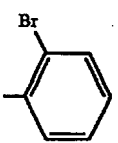
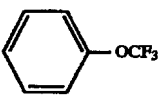
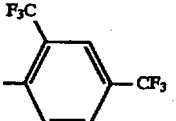
Ex. No.	R ¹	R ⁵	R ²	R ³	R ⁴	Q	A*	n	Melting point (°C.) (recrystallization solvent)
107	H	H		H	H	$\begin{array}{c} \text{O} \\ \\ \text{C} \end{array}$	SB	0	185-187 (Methylene chloride-n-hexane)
108	nBu	H		Me	$\begin{array}{c} \text{O} \\ \\ -\text{COEt} \end{array}$	$\begin{array}{c} \text{O} \\ \\ \text{C} \end{array}$	SB	0	138-140 (Ethyl acetate-n-hexane)
109	nBu	H		nBu	H	$\begin{array}{c} \text{O} \\ \\ \text{C} \end{array}$	SB	0	95-97 (Ethyl acetate-n-hexane)

TABLE 4-continued



Me: methyl group, Et: ethyl group, nBu: n-butyl group, Ph: phenyl group

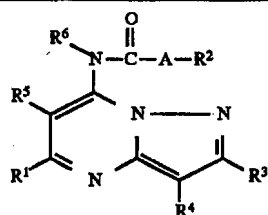
Ex. No.	R ¹	R ²	R ³	R ⁴	Q	A*	n	Melting point (°C.) (recrystallization solvent)
117	-CH ₂ CH ₂ CH ₂ CH ₂ -		H	H		SB	0	102-104 (Methylene chloride-n-hexane)
118			H	H		SB	0	115-117 (Methylene chloride-n-hexane)
119	Et-S-CH ₂ -		H	H		SB	0	80-82 (Ethyl acetate-n-hexane)
120	MeS-CH ₂ CH ₂ -		H	H		SB	0	113-115 (Methylene chloride-diethyl ether)
121			H	H		SB	0	179-181 (Methylene chloride-diethyl ether)
122	nBu		H	H		SB	0	98-100 (Diethyl ether)
123	nBu		H	H		SB	0	73-75 (n-Hexane)
124	nBu		H	H		SB	0	129-131 (n-Hexane)

Ex. No.	R ¹	R ²	R ³	R ⁴	Q	A*	n	Melting point (°C.) (recrystallization solvent)
125	nBu		H	H	$\begin{matrix} O \\ \\ C \end{matrix}$	SB	0	91-93 (Diethyl ether-n-hexane)
126	nBu		H	H	$\begin{matrix} O \\ \\ C \end{matrix}$	SB	0	91-93 (n-Hexane)
127	nBu	Ph	H	H	SO ₂	SB	0	>300° C. (Ethyl acetate-n-hexane)
128	nBu		H	H	SO ₂	SB	0	>300° C. (Ethyl acetate-n-hexane)

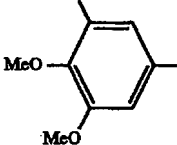
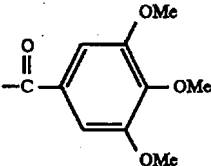
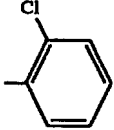
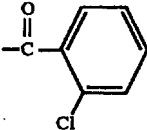
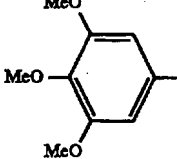
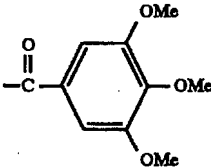
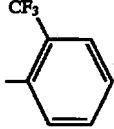
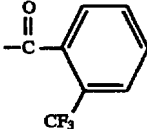
Me: methyl group, nBu: n-butyl group

Ex. No.	R ¹	R ⁵	R ²	R ³	R ⁴	R ⁶	A*	Melting point (°C.) (Recrystallization solvent)
129	nBu	H		H	H	Me	SB	93-95 (Ethyl acetate-n-hexane)
130	nBu	H		H	H	Ph-CH ₂ -	SB	¹ H-NMR(CDCl ₃) 0.76(3H, t, J=7.2), 0.9-1.1(2H, m), 1.3- 1.4(2H, m), 2.51(2H, t, J=7.4), 3.47(6H, s), 3.74(3H, s), 5.33(2H, brs), 5.83 (1H, s), 6.60(2H, s), 6.68(1H, d, J=2.0), 7.1-7.3(5H, m), 8.24(1H, d, J=2.0)

TABLE 5-continued



Me: methyl group, nBu: n-butyl group

Ex. No.	R ¹	R ²	R ³	R ⁴	R ⁶	A*	Melting point (°C.) (Recrystallization solvent)
131	nBu	H	MeO	H	H	SB	127-129 (Ethyl acetate-n-hexane)
							
							
132	nBu	H	Cl	H	H	SB	119-121 (Diethyl ether-n-hexane)
							
							
133	Me	H	MeO	H	H	SB	180-182 (Methylene chloride-n-hexane)
							
							
134	nBu	H	CF ₃	H	H	SB	111-113 (Diethyl ether-n-hexane)
							
							

*In column A, "SB" means "Single bond".

Given below are Pharmacological Test Examples for the compounds of the invention and Formulation Examples for pharmaceutical compositions containing the compounds of the invention.

Pharmacological Test Example 1

Six-week-old male Wistar rats were used as subjects (each group: 7 rats). The pain threshold of each rat's left hind paw was measured using Analgesy-Meter (Unicom) based on the method of Randall-Selitto [Randall, L. O. and Selitto, J. J., Arch. Int. Pharmacodyn., 111, 409 (1957)]. The value thus obtained was termed "pre-value"

After one hour from the measurement, 0.1 ml of a 20% yeast suspension was subcutaneously injected to the left hind paw of each rat. Immediately after the injection, a 5% gum arabic suspension containing the compound of the invention was orally given to the rats of test group in an amount of 10 ml/kg, whereas a 5% gum arabic suspension (free of the compound of the invention) was given to the rats of control group likewise.

The pain threshold of each rat's left hind paw was measured in the same manner as mentioned above every one 65 hour after the yeast injection. The value thus obtained was termed "post-value".

The recovery rate of the pain threshold was calculated from these values (post-values) and the pre-values of the rats in each group, by means of the following formula.

Recovery rate of pain threshold (%) =

$$\frac{(\text{Test group average post-value}) - (\text{Control group average post-value})}{(\text{Control group average pre-value}) - (\text{Control group average post-value})} \times 100$$

Table 6 shows the results (the highest recovery rates).

TABLE 6

Ex. No.	Recovery rate (%)	Dosage (mg/kg)	Time to measure (hours later)
1	41.5	3	3
7	44.1	3	4
14	51.6	3	4
19	53.9	3	3
21	54.0	3	4
23	45.1	3	1
32	43.0	3	3

TABLE 6-continued

Ex. No.	Recovery rate (%)	Dosage (mg/kg)	Time to measure (hours later)
36	32.7	1	3
48	52.2	1	3
52	79.6	3	3
54	55.7	1	4
55	73.7	3	3
69	38.7	1	3
70	36.8	1	3
74	43.9	1	2
76	57.6	1	2
77	41.6	1	3
79	32.1	1	3
88	76.4	3	4
92	39.7	1	3
93	32.6	1	4
94	31.3	1	3
96	35.0	1	2
97	51.5	1	4
104	78.5	3	3
111	62.0	3	4
115	61.0	3	4
120	63.8	3	4
121	46.2	3	3
127	36.4	1	3
134	115.4	3	3

PHARMACOLOGICAL TEST EXAMPLE 2

Using 6-week-old male Wistar rats (each group: 7 rats), the pain threshold of each rat's left hind paw was measured using Analgesy-Meter (Unicom) based on the method of Randall-Selitto [Randall, L. O. and Selitto, J. J., Arch. Int. Pharmacodyn., 111, 409 (1957)]. The value thus obtained was termed "pre-value".

After one hour from the measurement, a 5% gum arabic suspension containing the compound of the invention was orally given to the rats of test group in an amount of 10 ml/kg so that the dosage of the compound of the invention was 1 mg/kg, whereas a 5% gum arabic suspension (free of the compound of the invention) was given to the rats of control group likewise. One hour later, a physiological saline solution containing substance P (25 ng/0.1 ml) was subcutaneously injected to the left hind paw of each rat.

The pain threshold of each rat's left hind paw was measured in the same manner as above at a certain time after the injection of substance P. The value thus obtained was termed "post-value".

The recovery rate of the pain threshold was calculated from these values (post-values) and the pre-values of the rats in each group, by means of the following formula.

Recovery rate of pain threshold (%) =

$$\frac{\frac{(\text{Test group average post-value}) - (\text{Control group average post-value})}{(\text{Control group average pre-value}) - (\text{Control group average post-value})} \times 100}{}$$

Table 7 shows the results (the highest recovery rates).

TABLE 7

Ex. No.	Recovery rate (%)	Time to measure	Ex. No.	Recovery rate (%)	Time to measure
1	72.3	60 min. later	23	52.9	30 min. later
2	40.2	60 min. later	24	41.3	60 min. later
3	33.3	30 min. later	25	46.0	15 min. later
5	51.9	30 min. later	26	55.8	60 min. later
7	52.3	60 min. later	29	56.2	30 min. later
8	83.9	60 min. later	32	86.6	60 min. later
9	56.2	60 min. later	33	90.1	30 min. later
11	48.8	60 min. later	34	58.2	60 min. later
12	58.8	60 min. later	35	102.5	60 min. later
13	32.7	15 min. later	38	67.2	15 min. later
14	69.5	15 min. later	41*	67.4	30 min. later
16	35.1	30 min. later	42	51.8	66 min. later
17	95.9	60 min. later	44	44.1	30 min. later
19	91.7	60 min. later	45	54.8	15 min. later
20	33.8	30 min. later	46	109.0	30 min. later
21	81.3	60 min. later	48	80.4	60 min. later
22	54.4	60 min. later	50	53.0	30 min. later
52	65.1	30 min. later	113	44.4	15 min. later
53	58.7	30 min. later	115	55.6	30 min. later
65	32.0	30 min. later	117	37.2	30 min. later
80	30.4	15 min. later	118	33.5	30 min. later
81	31.2	15 min. later	119	38.1	15 min. later
88	59.5	60 min. later	120	71.4	60 min. later
89	33.3	15 min. later	121	73.3	60 min. later
90	53.1	30 min. later	122	30.6	60 min. later
91	53.1	30 min. later	123	32.5	30 min. later
95	38.4	15 min. later	124	53.8	15 min. later
96	102.0	60 min. later	125	33.7	30 min. later
103	35.0	30 min. later	129	39.7	60 min. later
104	63.5	60 min. later	133	36.4	60 min. later
111	62.1	30 min. later	134	100.7	60 min. later
112	37.9	15 min. later			

*: dosage = 10 mg/kg

As shown in Tables 6 and 7, the compounds of the invention produce excellent analgesic effects.

FORMULATION EXAMPLE 1

Manufacture of Tablets

Using the compound of the invention obtained in Example 1 as an active ingredient, tablets (2000 tables) each containing 300 mg of the active ingredient were manufactured according to the following formula:

Compound of Example 1	600 g
Lactose (product of Japanese pharmacopoeia: JP)	67 g
Corn starch (JP)	33 g
Calcium carboxymethyl cellulose (JP)	25 g
Methyl cellulose (JP)	12 g
Magnesium stearate (JP)	3 g

More specifically, the compound of Example 1, lactose, corn starch and calcium carboxymethyl cellulose according to the above formula were fully blended and granulated using an aqueous solution of methyl cellulose. The granulated mixture was passed through a 24-mesh sieve and the granules under the sieve were mixed with magnesium stearate and compression-molded into tablets to provide the object tablets.

FORMULATION EXAMPLE 2

Manufacture of Capsules

Using the compound of the invention obtained in Example 32 as an active ingredient, hard gelatin capsules

(2000 units) each containing 200 mg of the active ingredient were manufactured according to the following formula:

Compound of Example 32	400 g
Crystalline cellulose (JP)	60 g
Corn starch (JP)	34 g
Talc (JP)	4 g
Magnesium stearate (JP)	2 g

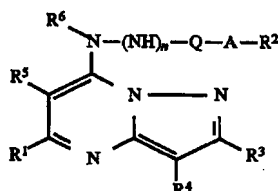
More specifically, the ingredients according to the above formula were finely pulverized and blended to give a homogeneous composition. This composition was filled into proper-sized gelatin capsule shells for oral administration to provide the object capsules.

INDUSTRIAL APPLICABILITY

The pyrazolo[1,5-a]pyrimidine derivatives according to the present invention have potent analgesic effects and are useful as analgesics.

What is claimed is:

1. A pyrazolo[1,5-a]pyrimidine derivative of the following formula (1):



wherein R^1 is hydrogen, lower alkyl which may have thienyl, lower alkoxy, lower alkylthio, oxo or hydroxyl as a substituent, cycloalkyl, thienyl, furyl, lower alkenyl, or R^1 phenyl, said R^1 phenyl having 1 to 3 substituents selected from the group consisting of lower alkyl, lower alkoxy, phenylthio and halogen; R^2 is naphthyl, cycloalkyl, furyl, thienyl, pyridyl, halogen-substituted pyridyl, phenoxy, halogen-substituted phenoxy, or phenyl which may have 1 to 3 substituents selected from the group consisting of lower alkyl, lower alkoxy, halogen, nitro, halogen-substituted lower alkyl, halogen-substituted lower alkoxy, lower alkoxycarbonyl, hydroxyl, phenyl(lower)alkoxy, amino, cyano, lower alkanoyloxy, phenyl and di(lower)alkoxyphosphoryl(lower)alkyl; R^3 is hydrogen, phenyl or lower alkyl; R^4 is hydrogen, lower alkyl, lower alkoxycarbonyl, phenyl(lower)alkyl, phenyl, phenylthio-substituted phenyl, or halogen; R^5 is hydrogen or lower alkyl; R^6 is hydrogen, lower alkyl, phenyl(lower)alkyl, or an R^6 benzoyl, said R^6 benzoyl having 1 to 3 substituents selected from the group consisting of lower alkoxy, halogen-substituted lower alkyl and halogen; R^1 and R^3 may con-

jointly form lower alkylene; Q is carbonyl or sulfonyl; A is a single bond, lower alkylene or lower alkenylene; and n is 0 or 1.

2. A pyrazolo[1,5-a]pyrimidine derivative according to
5 claim 1 which is selected from the group consisting of
compounds of formula (1) wherein Q is carbonyl and n is 0,
compounds wherein Q is carbonyl, n is 1, R¹ is lower alkyl
or phenyl, R² is phenyl having 1 to 3 substituents selected
from the group consisting of lower alkoxy and halogen-
10 substituted lower alkyl, R³, R⁴, R⁵ and R⁶ are each
hydrogen, and A is a single bond; and compounds wherein
Q is sulfonyl, n is 0, R¹ is lower alkyl, R² is phenyl which
may have 1 to 3 halogens, R³, R⁴, R⁵ and R⁶ are each
hydrogen, and A is a single bond.

15 3. A pyrazolo[1,5-a]pyrimidine derivative according to claim 2 wherein R¹ is optionally lower alkylthio-substituted lower alkyl or optionally phenylthio-substituted phenyl, R² is phenyl having 1 to 3 substituents selected from the group consisting of lower alkoxy, halogen and halogen-substituted
20 lower alkyl, R³ is hydrogen or phenyl, R⁴ is hydrogen, halogen or phenyl; R⁵ is hydrogen; R⁶ is hydrogen or benzoyl having halogen-substituted lower alkyl as a substituent, Q is carbonyl and A is a single bond.

(1) 25 4. A pyrazolo[1,5-a]pyrimidine derivative according to claim 3 wherein R^3 , R^4 and R^6 are each hydrogen, n is 0, R^1 is n -butyl and R^2 is phenyl having either 2 to 3 lower alkoxy groups or 1 to 2 halogen-substituted lower alkyl groups, or R^1 is phenyl and R^2 is phenyl having 3 lower alkoxy groups.

5. A pyrazolo[1,5-a]pyrimidine derivative according to claim 4 wherein R² is 2,4-dimethoxyphenyl, 3,4,5-trimethoxyphenyl, 2-trifluoromethylphenyl or 2,5-bis(trifluoromethyl)phenyl.

6. A pyrazolo[1,5-a]pyrimidine derivative according to claim 5 which is selected from 5-n-butyl-7-(3,4,5-trimethoxybenzoylamino)pyrazolo[1,5-a]pyrimidine and 5-n-butyl-7-(2-trifluoromethylbenzoyl-amino) pyrazolo[1,5-a]pyrimidine.

7. A pyrazolo[1,5-a]pyrimidine derivative according to claim 6 which is 5-n-butyl-7-(3,4,5-trimethoxybenzoylamino)pyrazolo[1,5-a]pyrimidine.

8. An analgesic composition which comprises an effective amount of a pyrazolo[1,5-a]pyrimidine derivative defined in one of claims, 2-7 and 1 and a pharmaceutically acceptable carrier.

45 9. An analgesic composition which comprises an effective amount of 5-n-butyl-7-(3,4,5-trimethoxybenzoylamino)-pyrazolo[1,5-a]pyrimidine as an active ingredient and a pharmaceutically acceptable carrier.

10. A method for relieving pain, which comprises administering to a patient an effective amount of the pyrazolo[1,5-a]pyrimidine derivative defined in claim 1.

* * * * *



US006476038B1

(12) **United States Patent**
Darrow et al.

(10) **Patent No.:** **US 6,476,038 B1**
(45) **Date of Patent:** **Nov. 5, 2002**

(54) **AMINO SUBSTITUTED PYRAZOLO[1,5-A]-1,5-PYRIMIDINES AND PYRAZOLO[1,5-A]-1,3,5-TRIAZINES**

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(73) **Assignees:** **Neurogen Corporation**, Branford, CT (US); **Pfizer Inc.**, New York, NY (US)

(*) **Notice:** Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) **Appl. No.:** **09/676,972**

(22) **Filed:** **Sep. 29, 2000**

Related U.S. Application Data

(60) **Provisional application No.** 60/156,868, filed on Sep. 30, 1999.

(51) **Int. Cl.⁷** **C07D 487/04**; A61K 31/519; A61P 3/04; A61P 9/12

(52) **U.S. Cl.** **514/258**; 544/281

(58) **Field of Search** 544/281; 514/258

(56) **References Cited**

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WO 9803510 1/1998

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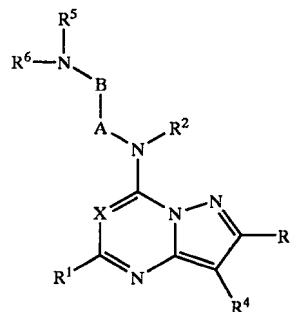
Primary Examiner—Mark L. Berch

Assistant Examiner—H Kahsay Habte

(74) **Attorney, Agent, or Firm**—Ladas & Parry

(57) **ABSTRACT**

Disclosed are compounds of the formula:



where R^1 , R^2 , R^3 , R^4 , R^5 , R^6 , and X are defined herein. These compounds are selective modulators of NPY1 receptors. These compounds are useful in the treatment of a number of CNS disorders, metabolic disorders, and peripheral disorders, particularly eating disorders and hypertension. Methods of treatment of such disorders and well as packaged pharmaceutical compositions are also provided.

Compounds of the invention are also useful as probes for the localization of NPY1 receptors and as standards in assays for NPY1 receptor binding. Methods of using the compounds in receptor localization studies are given.

31 Claims, No Drawings

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AMINO SUBSTITUTED PYRAZOLO[1,5-A]-1,5-PYRIMIDINES AND PYRAZOLO[1,5-A]-1,3,5-TRIAZINES

RELATED APPLICATION

This application claims priority from provisional application 60/156868 filed on Sep. 30, 1999, which is incorporated herein by reference.

FIELD OF THE INVENTION

This invention relates to certain amino substituted pyrazolo[1,5-a]-1,5-pyrimidines and pyrazolo[1,5-a]-1,3,5-triazines, preferably those which selectively and/or potentially bind mammalian neuropeptide Y (NPY) receptors. This invention also relates to pharmaceutical compositions comprising such compounds. It further relates to the use of such compounds in treating physiological disorders associated with an excess of neuropeptide Y, especially feeding disorders, some psychiatric disorders, and certain cardiovascular diseases.

BACKGROUND OF THE INVENTION

Neuropeptide Y (NPY) is a 36 amino acid peptide first isolated in 1982 and subsequently found to be largely conserved across species. It belongs to a large family of peptides that includes, among others, peptide YY (PYY) and pancreatic peptide (PP). NPY is believed to be the most abundant peptide in the mammalian brain. It is also found in sympathetic neurons, and NPY-containing fibers have been found in peripheral tissues, such as around the arteries in the heart, the respiratory tract, the gastrointestinal tract, and the genitourinary tract. Central injection of NPY elicits a multitude of physiological responses, such as stimulation of feeding, increase in fat storage, elevation of blood sugar and insulin, anxiolytic behaviors, reduction in locomotor activity, hormone release, increase in blood pressure, reduction in body temperature, and catalepsy. In the cardiovascular system, NPY is believed to be involved in the regulation of coronary tone, while in the gastrointestinal tract, PYY is reported to cause inhibition of gastric acid secretion, pancreatic exocrine secretion, and gastrointestinal motility. These effects appear to be selectively mediated by various NPY receptors which currently include the Y₁, Y₂, Y₃, Y₄, Y₅, and Y₆ subtypes, in addition to the hypothetical Y_{1-like} subtype. Selective peptidic agonists and antagonists have been identified for most of the subtypes, but few selective non-peptidic antagonists have been reported. The Y₁ and Y₅ receptor subtypes appear to be involved in appetite regulation, but their relative contribution to the modulation of food intake and energy expenditure remains unclear. The discovery of non-peptidic antagonists of the Y₁ and/or Y₅ receptor provides novel therapeutic agents, that are less prone to the shortcomings of the peptide antagonists, namely, for example, poor metabolic stability, low oral bioavailability, and poor brain permeability, for the treatment of obesity and cardiovascular diseases. Recently, a few of such agents have been reported, some of which having demonstrated pharmacological efficacy in pre-clinical animal models. The present invention provides a novel class of potent non-peptidic antagonists of the NPY receptors, in particular, the Y₁ receptor.

Insofar as is known, aminoalkyl substituted pyrazolo[1,5-a]-1,5-pyrimidines and pyrazolo[1,5-a]-1,3,5-triazines have not been previously reported as NPY receptor antagonists useful in the treatment of feeding and cardiovascular disorders. However, this general class of compounds has

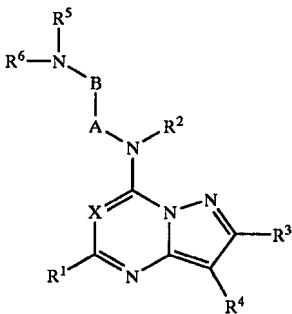
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been described for other uses by virtue of different mechanisms of action, e.g., as antagonists of the corticotropin releasing factor (CRF₁). For example International Patent Publication WO 98/03510 describes certain pyrazolotriazines and pyrazolopyrimidines as being of use as corticotropin releasing factors.

SUMMARY OF THE INVENTION

Compounds that interact with the Y₁ receptor and inhibit the activity of neuropeptide Y at those receptors are useful in treating physiological disorders associated with an excess of neuropeptide Y, including eating disorders, such as, for example, obesity and bulimia, and certain cardiovascular diseases, for example, hypertension.

This invention relates to a method of treating a physiological disorder associated with an excess of neuropeptide Y, which method comprises administering to a mammal in need of said treatment an effective amount of an amino substituted pyrazolo[1,5-a]-1,5-pyrimidine or a pyrazolo[1,5-a]-1,3,5-triazine of the formula I:



Formula I

or a pharmaceutically acceptable salt or prodrug thereof, wherein the compound exhibits a K_i of 5 micromolar or less in an assay of NPY receptor binding, and

- X is N or CR¹⁴;
- R¹ is selected from H, C₁-C₆ alkyl, C₃-C₁₀ cycloalkyl, (C₃-C₁₀ cycloalkyl) C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, cyano, halo, C₁-C₆ haloalkyl, OR⁷, C₁-C₆ alkyl-OR⁷, C₁-C₆ cyanoalkyl, NR⁸R⁹, and C₁-C₆ alkyl-NR⁸R⁹;
- R² is
 - H,
 - C₁-C₆ alkyl which optionally forms a C₃-C₆ aminocarbocycle or a C₂-C₅ aminoheterocycle with A or B, each of which is optionally substituted with R⁷,
 - C₃-C₁₀ cycloalkyl, or
 - (C₃-C₁₀ cycloalkyl) C₁-C₆ alkyl; or
- R² and R⁶ jointly form with the 2 nitrogen atoms to which they are bound a C₂-C₅ aminoheterocycle optionally substituted with R⁷;
- A is (CH₂)_m where m is 1,2 or 3 and is optionally mono- or di-substituted at each carbon atom with C₁-C₆ alkyl, C₃-C₁₀ cycloalkyl, (C₃-C₁₀ cycloalkyl) C₁-C₆ alkyl, C₁-C₆ alkenyl, C₁-C₆ alkynyl, cyano, halogen, C₁-C₆ haloalkyl, OR⁷, C₁-C₆ alkyl-OR⁷, C₁-C₆ cyanoalkyl, NR⁸R⁹, or C₁-C₆ alkyl-NR⁸R⁹, or
- A and B jointly form a C₃-C₆ carbocycle, which is optionally substituted at each carbon atom with R⁷, or
- A and R² jointly form a C₃-C₆ aminocarbocycle, which is optionally substituted at each carbon atom with R⁷;

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B is (CH₂)_n, where n is 0, 1, 2, or 3 and is optionally substituted at each carbon atom with C₁-C₆ alkyl, C₃-C₁₀ cycloalkyl, (C₃-C₁₀ cycloalkyl) C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, cyano, halogen, C₁-C₆ haloalkyl, OR⁷, C₁-C₆ alkyl-OR⁷; C₁-C₆ cyanoalkyl, NR⁸R⁹, or C₁-C₆ alkyl-NR⁸R⁹, or

B and R² jointly form a C₃-C₆ aminocarbocycle, which is optionally substituted at each carbon atom with R⁷, or

B and R⁶ jointly form a C₃-C₆ aminocarbocycle, which is optionally substituted at each carbon atom with R⁷;

R³ is selected from H, C₁-C₆ alkyl, C₃-C₁₀ cycloalkyl, (C₃-C₁₀ cycloalkyl) C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, cyano, halo, C₁-C₆ haloalkyl, OR⁷, C₁-C₆ alkyl-OR⁷, C₁-C₆ cyanoalkyl, NR⁸R⁹, and C₁-C₆ alkyl-NR⁸R⁹;

R⁴ is selected from aryl or heteroaryl, each optionally substituted with 1 to 5 substituents independently selected at each occurrence from C₁-C₆ alkyl, C₃-C₁₀ cycloalkyl, C₃-C₁₀ cycloalkenyl, (C₃-C₁₀ cycloalkyl) C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, halogen, C₁-C₆ haloalkyl, trifluoromethylsulfonyl, OR⁷, C₁-C₆ alkyl-OR⁷, NR⁸R⁹, C₁-C₆ alkyl-NR⁸R⁹, CONR⁸R⁹, C₁-C₆ alkyl-CONR⁸R⁹, COOR⁷, C₁-C₆ alkyl-COOR⁷, CN, C₁-C₆ alkyl-CN, SO₂NR⁸R⁹, SO₂R⁷, aryl, heteroaryl, heterocycloalkyl, and 3-, 4-, or 5-(2-oxy-1, 3-oxazolidinyl), with the proviso that at least one of the positions ortho or para to the point of attachment of the aryl or heteroaryl ring to the pyrazole is substituted;

R⁵ and R⁶ are independently selected from H, C₁-C₆ alkyl, C₃-C₁₀ cycloalkyl, (C₃-C₁₀ cycloalkyl) C₁-C₆ alkyl, C₂-C₆ alkenyl, and C₂-C₆ alkynyl;

R⁷ is H, C₁-C₆ alkyl, C₃-C₁₀ cycloalkyl, C₃-C₁₀ cycloalkenyl, (C₃-C₁₀ cycloalkyl) C₁-C₆ alkyl, C₁-C₃ haloalkyl, or heterocycloalkyl, C₁-C₈ alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, C₁-C₈ alkanoyl, aroyl, heteroaroyl, aryl, heteroaryl, C₁-C₆ arylalkyl or C₁-C₆ heteroarylalkyl each of which is optionally substituted with 1 to 5 substituents independently selected at each occurrence from halogen, C₁-C₆ haloalkyl, OR¹³, NR⁸R⁹, C₁-C₆ alkyl-OR¹³, C₁-C₆ alkyl-NR⁸R⁹, CONR⁸R⁹, COOR¹³, CN, SO₂NR⁸R⁹, SO₂R¹³, with the proviso that for SO₂R⁷, R⁷ cannot be H;

R⁸ and R⁹ are independently selected at each occurrence from H, C₁-C₆ alkyl, C₃-C₁₀ cycloalkyl, C₂-C₆ alkenyl, C₃-C₁₀ cycloalkenyl, C₂-C₆ alkynyl, heterocycloalkyl, C₁-C₈ alkanoyl, aroyl, heteroaroyl, aryl, heteroaryl, C₁-C₆ arylalkyl or C₁-C₆ heteroarylalkyl, or R⁸ and R⁹, taken together, can form a C₃-C₆ aminocarbocycle or a C₂-C₅ aminoheterocycle each optionally substituted at each occurrence with C₁-C₆ alkyl, C₃-C₁₀ cycloalkyl, C₃-C₁₀ cycloalkenyl, (C₃-C₁₀ cycloalkyl) C₁-C₆ alkyl, C₁-C₃ haloalkyl, or heterocycloalkyl, C₁-C₈ alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, C₁-C₈ alkanoyl, aroyl, heteroaroyl, aryl, heteroaryl, C₁-C₆ arylalkyl or C₁-C₆ heteroarylalkyl;

R¹¹ is selected from H, C₁-C₆ alkyl, C₃-C₁₀ cycloalkyl, (C₃-C₁₀ cycloalkyl) C₁-C₆ alkyl;

R¹² is selected from H, aryl, heteroaryl, C₁-C₆ alkyl, C₃-C₁₀ cycloalkyl, (C₃-C₁₀ cycloalkyl) C₁-C₆ alkyl, optionally substituted with OR⁷, NR⁸R⁹, C₃-C₆ aminocarbocycle, or C₂-C₅ aminoheterocycle;

R¹³ is independently selected at each occurrence from H, C₁-C₆ alkyl, C₃-C₁₀ cycloalkyl, (C₃-C₁₀ cycloalkyl)

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C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ haloalkyl, with the proviso that when R⁷ is SO₂R¹³, R¹³ cannot be H; and

R¹⁴ is H, C₁-C₆ alkyl, C₃-C₁₀ cycloalkyl, (C₃-C₁₀ cycloalkyl) C₁-C₆ alkyl, C₂-C₄ alkenyl, C₂-C₄ alkynyl, halo, or CN.

Preferred compounds of Formula I exhibit a 20-fold or more greater affinity for the NPY₁ receptor than for the CRF₁ receptor. Preferred compounds of Formula I also do not exhibit high affinity for the CRF₁ receptor.

This invention also encompasses, in additional embodiments, the novel compounds of formula I, and the salts and solvates thereof, as well as pharmaceutical formulations comprising a compound of formula I, or a pharmaceutically acceptable salt or solvate thereof in combination with one or more pharmaceutically acceptable carriers, excipients, or diluents thereof.

This invention also encompasses methods to treat physiological disorders associated with an excess of neuropeptide Y, such as eating and cardiovascular disorders, which method comprises administering to a mammal in need of said treatment an effective amount of a compound of the formula I.

This invention also encompasses methods of selectively inhibiting binding of NPY to NPY₁ receptors, which comprises contacting a compound of formula I with neuronal cells, wherein the compound is present in an amount effective to produce a concentration sufficient to inhibit binding of NPY to NPY₁ receptors in vitro.

DETAILED DESCRIPTION OF THE INVENTION

The current invention includes a novel group of aminoalkyl substituted 4-amino pyrazolopyrimidines and 7-amino pyrazolo triazines, those of formula I. Preferred aminoalkyl substituted 4-amino pyrazolopyrimidines and 7-amino pyrazolo triazines bind with high affinity to the NPY₁ receptor and more preferably act as antagonists of NPY binding to the NPY₁ receptor. Preferred compounds of the invention bind with high selectivity to the NPY₁ receptor, particularly such compounds do not bind with high affinity to CRF₁ receptors. Without wishing to be bound to any particular theory, it is believed that the interaction of the compounds of Formula I with the NPY₁ receptor results in the pharmaceutical utility of these compounds.

The invention further comprises methods of treating patients in need of such treatment with an amount of a compound of the invention sufficient to alter the symptoms of a eating disorder or cardiovascular disorder.

The present invention also pertains to methods of inhibiting the binding of NPY receptor ligands, such as NPY or PYY, to the NPY₁ receptors which methods involve contacting a compound of the invention with cells expressing NPY₁ receptors, wherein the compound is present at a concentration sufficient to inhibit the binding of NPY receptor Ligands to NPY₁ receptors in vitro. This method includes inhibiting the binding of NPY receptor ligands to NPY₁ receptors in vivo, e.g., in a patient given an amount of a compound of Formula I that would be sufficient to inhibit the binding of NPY receptor ligands to NPY receptors in vitro. The amount of a compound that would be sufficient to inhibit the binding of a NPY receptor ligand to the NPY₁ receptor may be readily determined via an NPY₁ receptor binding assay, such as the assay described in Example 94A. The NPY₁ receptors used to determine in vitro binding may be obtained from a variety of sources, for example from

preparations of rat brain or from cells expressing cloned human NPY₁ receptors.

The present invention also pertains to methods for altering the signal-transducing activity of NPY₁ receptors, said method comprising exposing cells expressing such receptors to an effective amount of a compound of the invention. This method includes altering the signal-transducing activity of NPY₁ receptors in vivo, e.g., in a patient given an amount of a compound of Formula I that would be sufficient to alter the signal-transducing activity of NPY₁ receptors in vitro. The amount of a compound that would be sufficient to alter the signal-transducing activity of NPY₁ receptors may be determined via a NPY₁ receptor signal transduction assay, such as the assay described in Example 93B.

The NPY₁ receptor ligands provided by this invention and labeled derivatives thereof are also useful as standards and reagents in determining the ability of a potential pharmaceutical to bind to the NPY₁ receptor.

Radiolabeled derivatives the NPY₁ receptor ligands provided by this invention are also useful for mapping the location of NPY₁ receptors (e.g., in tissue sections via autoradiography) and as radiotracers for positron emission tomography (PET) imaging, single photon emission computerized tomography (SPECT), and the like, to characterize such receptors in living subjects.

In addition to compounds of Formula I, the invention also provides as preferred compounds, compounds of Formula I wherein

X is N or CH; and

R¹ is H, C₁-C₆ alkyl, C₃-C₁₀ cycloalkyl, or (C₃-C₁₀ cycloalkyl) C₁-C₆ alkyl. Such compounds will be referred to as compounds of Formula Ia.

Other preferred compounds of Formula I are those compounds wherein

X is N or CH; R¹ is C₁-C₆ alkyl; R² is H or C₁-C₆ alkyl; and

R³ is C₁-C₆ alkyl, trifluoromethyl, or C₁-C₆alkyl-O C₁-C₆alkyl. Such compounds will be referred to as compounds of Formula Ib.

In another embodiment the invention provides compounds of Formula I, wherein

X is N or CH; R¹ is H, C₁-C₆ alkyl, C₃-C₁₀ cycloalkyl, or (C₃-C₁₀ cycloalkyl) C₁-C₆ alkyl;

R² is H or C₁-C₆ alkyl; R³ is C₁-C₆ alkyl, trifluoromethyl, or C₁-C₆alkyl-O C₁-C₆alkyl; and

R⁵ is H. Such compounds will be referred to as compounds of Formula Ic.

Further provided are compounds wherein:

X is N or CH; R¹ is C₁-C₆ alkyl; R² is H or C₁-C₆ alkyl;

R³ is C₁-C₆ alkyl, trifluoromethyl, or C₁-C₆alkyl-O C₁-C₆alkyl; R⁴ is phenyl, mono-, di-, or tri-substituted

C₁-C₆ alkyl, C₃-C₁₀ cycloalkyl, C₃-C₁₀ cycloalkenyl, (C₃-C₁₀ cycloalkyl) C₁-C₆ alkyl, C₁-C₆ alkenyl,

halogen, C₁-C₆ haloalkyl, trifluoromethylsulfonyl, OR⁷, C₁-C₆ alkyl-OR⁷, NR⁸R⁹, C₁-C₆ alkyl-NR⁸R⁹,

CONR⁸R⁹, C₁-C₆ alkyl-CONR⁸R⁹, COOR⁷, C₁-C₆ alkyl-COOR⁷, CN, C₁-C₆ alkyl-CN, SO₂NR⁸R⁹,

SO₂R⁷, aryl, heteroaryl, heterocycloalkyl, 3-, 4-, or 5-(2-oxo-1,3-oxazolidinyl), wherein at least one of the

positions ortho or para to the point of attachment of the aryl or heteroaryl ring to the pyrazole is substituted;

and R⁷, R⁸, and R⁹ are as defined for Formula I. Such compounds will be referred to as compounds of Formula Id.

In yet another embodiment the invention provides compounds of Formula I wherein X is N or CH; R¹ is C₁-C₆

alkyl; R² is H or C₁-C₆ alkyl; R³ is C₁-C₆ alkyl, trifluoromethyl, or C₁-C₆ alkyl-O C₁-C₆alkyl; and R⁴ is phenyl, mono-, di-, or trisubstituted with C₁-C₆ alkyl, C₃-C₁₀ cycloalkyl, C₃-C₁₀ cycloalkenyl, (C₃-C₁₀ cycloalkyl) C₁-C₆ alkyl, C₁-C₆ alkenyl, halogen, C₁-C₆ haloalkyl, trifluoromethylsulfonyl, OR⁷, C₁-C₆ alkyl-OR⁷, NR⁸R⁹, C₁-C₆ alkyl-NR⁸R⁹, CONR⁸R⁹, C₁-C₆ alkyl-CONR⁸R⁹, COOR⁷, C₁-C₆ alkyl-COOR⁷, CN, C₁-C₆ alkyl-CN, SO₂NR⁸R⁹, SO₂R⁷, aryl, heteroaryl, heterocycloalkyl, 3-, 4-, or 5-(2-oxo-1,3-oxazolidinyl), wherein at least one of the positions ortho or para to the point of attachment of the aryl or heteroaryl ring to the pyrazole is substituted; R⁵ is H; and R⁶ is H, C₁-C₆ alkyl, C₃-C₁₀ cycloalkyl, or (C₃-C₁₀ cycloalkyl) C₁-C₆ alkyl. Such compounds will be referred to as compounds of Formula Ie.

Additionally the invention provides compounds of Formula I wherein X is N or CH; R¹ is C₁-C₆ alkyl; R² is H or C₁-C₆ alkyl; R³ is C₁-C₆ alkyl, trifluoromethyl, or C₁-C₆alkyl-O C₁-C₆alkyl; and R⁴ is phenyl, mono-, di-, or trisubstituted with C₁-C₆ alkyl, C₃-C₁₀ cycloalkyl, C₃-C₁₀ cycloalkenyl, (C₃-C₁₀ cycloalkyl) C₁-C₆ alkyl, C₁-C₆ alkenyl, halogen, C₁-C₆ haloalkyl, trifluoromethylsulfonyl, OR⁷, C₁-C₆ alkyl-OR⁷, NR⁸R⁹, C₁-C₆ alkyl-NR⁸R⁹, CONR⁸R⁹, C₁-C₆ alkyl-CONR⁸R⁹, COOR⁷, C₁-C₆ alkyl-COOR⁷, CN, C₁-C₆ alkyl-CN, SO₂NR⁸R⁹, SO₂R⁷, aryl, heteroaryl, heterocycloalkyl, 3-, 4-, or 5-(2-oxo-1,3-oxazolidinyl), wherein at least one of the positions ortho or para to the point of attachment of the aryl or heteroaryl ring to the pyrazole is substituted; and R⁶ is H, C₁-C₆ alkyl, C₃-C₁₀ cycloalkyl, or (C₃-C₁₀ cycloalkyl) C₁-C₆ alkyl. Such compounds will be referred to as compounds of Formula If.

Particularly preferred are compounds of Formula I wherein R⁵ is H, and R⁶ is cycloalkyl or (cycloalkyl)alkyl. (Compounds of Formula Ig)

For each of Formula Ia-Ig compounds that exhibits a K_i of 5 micromolar or less in an assay of NPY receptor binding are preferred. Also preferred are compounds of Formula I, and Formula Ia-Ig that do not exhibit a K_i or IC₅₀ of 5 micromolar or less, or more preferably that do not exhibit a K_i or IC₅₀ of 1 micromolar or less, for the CRF1 receptor in an assay of CRF1 receptor binding. An assay of CRF receptor binding is given in Example 94.

In certain situations, the compounds of formula I may contain one or more asymmetric carbon atoms, so that the compounds can exist in different stereoisomeric forms. These compounds can be, for example, racemates or optically active forms. In these situations, the single enantiomers, i.e., optically active forms, can be obtained by asymmetric synthesis or by resolution of the racemates. Resolution of the racemates can be accomplished, for example, by conventional methods such as crystallization in the presence of a resolving agent, or chromatography, using, for example a chiral HPLC column.

Representative compounds of the present invention, which are encompassed by formula I, include, but are not limited to the compounds in Examples 1-87 and their pharmaceutically acceptable acid addition salts. In addition, if the compound of the invention is obtained as an acid addition salt, the free base can be obtained by basifying a solution of the acid salt. Conversely, if the product is a free base, an addition salt, particularly a pharmaceutically acceptable addition salt, may be produced by dissolving the free base in a suitable organic solvent and treating the solution with an acid, in accordance with conventional procedures for preparing acid addition salts from base compounds.

Non-toxic pharmaceutical salts include salts of acids such as hydrochloric, phosphoric, hydrobromic, sulfuric, sulfonic, formic, toluenesulfonic, methanesulfonic, nitric, benzoic, citric, tartaric, maleic, hydroiodic, alkanolic such as acetic, $\text{HOOC}-(\text{CH}_2)_n-\text{COOH}$ where n is 0-4, and the like. Those skilled in the art will recognize a wide variety of non-toxic pharmaceutically acceptable addition salts.

The present invention also encompasses the acylated prodrugs of the compounds of formula I. "Prodrugs" are considered to be any covalently bonded carriers which release the active parent drug of formula I in vivo when such prodrug is administered to a mammalian subject. Prodrugs of the compounds of the invention are prepared by modifying functional groups present in the compounds in such a way that the modifications are cleaved, either in routine manipulation or in vivo to the parent compounds. Prodrugs include compounds wherein hydroxy, amine, or sulfhydryl groups are bonded to any group that, when administered to a mammalian subject, cleaves to form a free hydroxyl, amino, or sulfhydryl group, respectively. Examples of prodrugs include, but are not limited to, acetate, formate, and benzoate derivatives of alcohol and amine functional groups in the compounds of formula I; and the like. Those skilled in the art will recognize various synthetic methodologies which may be employed to prepare non-toxic pharmaceutically acceptable addition salts and acylated prodrugs of the compounds encompassed by formula I.

Where a compound exists in various tautomeric forms, the invention is not limited to any one of the specific tautomers. The invention includes all tautomeric forms of a compound.

By "heteroatom" in the present invention is meant oxygen or sulfur, or a nitrogen atom optionally substituted by C_1-C_6 lower alkyl, C_1-C_6 arylalkyl, C_1-C_{10} cycloalkyl, C_3-C_{10} cycloalkyl) C_1-C_6 alkyl, C_2-C_8 alkanoyl, C_1-C_6 sulfonyl.

By "alkyl", "lower alkyl", or " C_1-C_6 alkyl" in the present invention is meant straight or branched chain alkyl groups having 1-6 carbon atoms, such as, for example, methyl, ethyl, propyl, isopropyl, n-butyl, sec-butyl, tert-butyl, pentyl, 2-pentyl, isopentyl, neopentyl, hexyl, 2-hexyl, 3-hexyl, and 3-methylpentyl.

By "cycloalkyl", or " C_3-C_{10} cycloalkyl" in the present invention is meant alkyl groups having 3-10 carbon atoms forming a mono-, bi-, or polycyclic ring system, such as, for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, norbornyl, and the like.

By "(cycloalkyl)alkyl", "lower (cycloalkyl)alkyl", or (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl in the present invention is meant a straight or branched alkyl substituent formed of 1 to 6 carbon atoms attached to a mono-, bi-, or polycyclic ring system having 3-10 carbon atoms, such as, for example, cyclopropylmethyl, cyclobutylmethyl, cyclopentylmethyl, cyclohexylmethyl, cycloheptylmethyl, and the like.

The term " C_2-C_6 alkenyl" in the present invention means hydrocarbon chains having 2 to 6 carbons in a straight or branched arrangement and containing one or more unsaturated carbon-carbon double bonds which may occur in any stable point along the chain, such as, for example, ethenyl, allyl, isopropenyl, and the like.

By "cycloalkenyl" or " C_3-C_{10} cycloalkenyl" in the present invention is meant alkyl groups having 3-10 carbon atoms forming a mono-, bi-, or polycyclic ring system having 3-10 carbon atoms and containing one or more carbon-carbon double bonds which may occur in any stable point in the ring, such as, for example, cyclopentenyl, cyclohexenyl, or cycloheptenyl.

The term " C_2-C_6 alkynyl" in the present invention means hydrocarbon chains having 2 to 6 carbons in a straight or

branched arrangement and containing one or more unsaturated carbon-carbon triple bonds which may occur in any stable point along the chain, such as, for example, ethynyl, propargyl, and the like.

The term "aryl" in the present invention means a monocyclic or bicyclic aromatic group having preferably 6 to 10 carbon atoms, such as, for example, phenyl or naphthyl.

The term "heteroaryl" in the present invention means an aryl group in which one or more of the ring(s) carbon atoms have been replaced with a heteroatom. Such groups preferably have 4 to 10 carbon atoms and 1 to 4 heteroatoms, such as, for example, pyridyl, pyrimidinyl, triazinyl, imidazolyl, oxazolyl, isoxazolyl, indolyl, pyrrolyl, pyrazolyl, quinolinyl, isoquinolinyl, thiazolyl, benzothiadiazolyl, triazolyl, triazinyl, pyrazinyl, furanyl, thienyl, benzothienyl, benzofuranyl, tetrazolyl.

The term "heterocyclyl", "heterocycle" or "heterocycloalkyl" in the present invention means a saturated or partially saturated heteroaryl group.

By " C_1-C_6 arylalkyl" or " C_1-C_6 heteroarylalkyl" in the present invention is meant a branched or straight-chain alkyl group having 1-6 carbon atoms and substituted on one of the carbon atoms by an optionally substituted aryl or heteroaryl ring, such as, for example, benzyl, phenethyl, methylpyridyl, ethylpyridyl, and the like.

By " C_5-C_8 arylcycloalkyl" in the present invention is meant cycloalkyl groups having 5-8 carbon atoms and fused to an aryl group, such as, for example, 1,2,3,4 tetrahydronaphthalenyl, 2,3-dihydrobenzothienyl, or 2,3-dihydrobenzofuranyl.

By " C_5-C_8 heteroarylalkyl" in the present invention is meant cycloalkyl groups having 5-8 carbon atoms fused to a heteroaryl group, such as, for example, 1,2,3,4 tetrahydroquinolyl, 2,3-dihydrobenzothienyl, 2,3-dihydrobenzofuranyl, or indolinyl.

By "alkoxy", " C_1-C_6 alkoxy", or " C_1-C_6 alkyloxy" in the present invention is meant straight or branched chain alkoxy groups having 1-6 carbon atoms, such as, for example, methoxy, ethoxy, propoxy, isopropoxy, n-butoxy, sec-butoxy, tert-butoxy, pentoxy, 2-pentyl, isopentoxy, neopentoxy, hexoxy, 2-hexoxy, 3-hexoxy, and 3-methylpentoxy.

By "cycloalkoxy", " C_3-C_{10} cycloalkoxy", or " C_3-C_{10} cycloalkyloxy" in the present invention is meant a group formed by an oxygen atom attached to a mono-, bi-, or polycyclic ring system having 3-10 carbon atoms, such as, for example, cyclopropoxy, cyclobutoxy, cyclopentoxy, cyclohexoxy, or cycloheptoxy.

By "(cycloalkyl)alkyloxy", "(C_3-C_{10} cycloalkyl) C_1-C_6 alkoxy", or "(C_3-C_{10} cycloalkyl) C_1-C_6 alkyloxy" in the present invention is meant a group formed by an oxygen atom attached to a 1-6 carbon chain linked to a mono-, bi-, or polycyclic ring system having 3-10 carbon atoms, such as, for example, cyclopropylmethyloxy, cyclobutylmethyloxy, cyclopentylmethyloxy, cyclohexylmethyloxy, cycloheptylmethyloxy, and the like.

By " C_3-C_6 aminocarbocycle" is meant a cyclic amino group formed by a nitrogen contained in a ring having 3 to 6 carbon atoms, such as, for example, azetidino, pyrrolidino, piperidino, perhydroazepino.

By " C_2-C_5 aminoheterocycle" is meant a cyclic amino group formed by a nitrogen contained in a ring having 2 to 5 carbon atoms and one other heteroatom, such as, for example, morpholino, thiomorpholino, piperazino.

By the terms "halo" or "halogen" in the present invention is meant fluoro, chloro, bromo, and iodo.

"Haloalkyl" is intended to include both branched and straight-chain alkyl having the specified number of carbon atoms substituted with 1 or more halogens.

The term "C₂-C₈ alkanoyl" means an acyl group with 2 to 8 carbon atoms in a linear, branched, or C₃-C₁₀ cycloalkyl arrangement, optionally substituted with 1 to 5 substituents independently selected at each occurrence from halogen, trifluoromethyl, OR⁷, NR⁸R⁹, CONR⁸R⁹, COOR⁷, or CN.

The term "C₁-C₆ alkyl sulfonyl" means an alkylsulfonyl group containing 1 to 6 carbon atoms in a linear, branched, or C₃-C₇ cycloalkyl arrangement.

The term "substituted" means that one or more hydrogen on the designated atom is replaced by the specified group, provided that the valence on the designated atom is not exceeded, and that a chemically stable compound results from the substitution.

A stable compound is defined herein as one that can be isolated, characterized, and tested for biological activity.

The term "oxo" (i.e. =O) indicates that two germinal hydrogen atoms are replaced by a double-bond oxygen group.

The term "hydroximino" (i.e. =N—OH) indicates that two germinal hydrogen atoms are replaced by a double-bond nitrogen atom substituted with a hydroxyl group.

The term "C₁-C₆ alkoximino" (i.e. =N—O-Alkyl) indicates that two germinal hydrogen atoms are replaced by a double-bond nitrogen atom substituted with a C₁-C₂ alkoxy group, such as, for example, methoximino (=N—OMe).

In the present invention, the term "potent" in the context of NPY₁ receptor antagonists qualifies a binding affinity with a K_i of less than 10 micromolar, preferably less than 1 micromolar, and more preferably less than 100 nanomolar in the human NPY₁ binding assay.

In the present invention, the term "selective" in the context of NPY₁ receptor antagonists qualifies a binding affinity with a K_i in the human NPY₁ binding assay that is 10-fold or 20-fold, preferably 100-fold, and more preferably 1000-fold, less than the K_i of the same compound measured in another receptor binding assay, in particular the NPY₅ and CRF₁ receptor binding assays. Binding assays for the NPY₅ and CRF₁ receptors have been described, for example, in *J. Clin. Invest.*, 102, 2136 (1998) and in *Endocrinology* 116, 1653 (1985), respectively. A CRF₁ receptor binding assay is also given in Example 94.

As the compounds of formula I are selective antagonists of the Y₁ receptor, they are of value in the treatment of a wide variety of clinical conditions which are characterized by the presence of an excess of neuropeptide Y. Thus, the invention provides methods for the treatment or prevention of a physiological disorder associated with an excess of neuropeptide Y, which method comprises administering to a mammal in need of said treatment an effective amount of a compound of formula I or a pharmaceutically acceptable salt, solvate or prodrug thereof. The term "physiological disorder associated with an excess of neuropeptide Y" encompasses those disorders associated with an inappropriate stimulation of neuropeptide Y receptors, regardless of the actual amount of neuropeptide Y present locally. These physiological disorders may include: disorders or diseases pertaining to the heart, blood vessels or the renal system, such as vasospasm, heart failure, shock, cardiac hypertrophy increased blood pressure, angina, myocardial infarction, sudden cardiac death, arrhythmia, peripheral vascular disease, and abnormal renal conditions such as impaired

flow of fluid, abnormal mass transport, or renal failure; conditions related to increased sympathetic nerve activity for example, during or after coronary artery surgery, and operations and surgery in the gastrointestinal tract; cerebral diseases and diseases related to the central nervous system, such as cerebral infarction, neurodegeneration, epilepsy, stroke, and conditions related to stroke, cerebral vasospasm and hemorrhage, depression, anxiety, schizophrenia, and dementia; conditions related to pain or nociception; diseases related to abnormal gastrointestinal motility and secretion, such as different forms of ileus, urinary incontinence, and Crohn's disease; abnormal drink and food intake disorders, such as obesity, anorexia, bulimia, and metabolic disorders; diseases related to sexual dysfunction and reproductive disorders; conditions or disorders associated with inflammation; respiratory diseases, such as asthma and conditions related to asthma and bronchoconstriction; and diseases related to abnormal hormone release, such as leutinizing hormone, growth hormone, insulin, and prolactin.

Pharmaceutical Preparations

The compounds of general Formula I may be administered orally, topically, parenterally, by inhalation or spray or rectally in dosage unit formulations containing conventional non-toxic pharmaceutically acceptable carriers, adjuvants and vehicles. The term parenteral as used herein includes subcutaneous injections, intravenous, intramuscular, intrastemal injection or infusion techniques. In addition, there is provided a pharmaceutical formulation comprising a compound of general Formula I and a pharmaceutically acceptable carrier. One or more compounds of general Formula I may be present in association with one or more non-toxic pharmaceutically acceptable carriers and/or diluents and/or adjuvants and if desired other active ingredients. The pharmaceutical compositions containing compounds of general Formula I may be in a form suitable for oral use, for example, as tablets, troches, lozenges, aqueous or oily suspensions, dispersible powders or granules, emulsion, hard or soft capsules, or syrups or elixirs. Compositions intended for oral use may be prepared according to any method known to the art for the manufacture of pharmaceutical compositions and such compositions may contain one or more agents selected from sweetening agents, flavoring agents, coloring agents and preserving agents in order to provide pharmaceutically elegant and palatable preparations. Tablets contain the active ingredient in admixture with non-toxic pharmaceutically acceptable excipients which are suitable for the manufacture of tablets. These excipients may be for example, inert diluents, such as calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate; granulating and disintegrating agents, for example, corn starch, or alginic acid; binding agents, for example starch, gelatin or acacia, and lubricating agents, for example magnesium stearate, stearic acid or talc. The tablets may be uncoated or they may be coated by known techniques to delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monostearate or glyceryl distearate may be employed.

Formulations for oral use may also be presented as hard gelatin capsules wherein the active ingredient is mixed with

an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules wherein the active ingredient is mixed with water or an oil medium, for example peanut oil, liquid paraffin or olive oil.

Aqueous suspensions contain the active materials in admixture with excipients suitable for the manufacture of aqueous suspensions. Such excipients are suspending agents, for example sodium carboxymethylcellulose, methylcellulose, hydropropylmethylcellulose, sodium alginate, polyvinyl-pyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents may be a naturally-occurring phosphatide, for example, lecithin, or condensation products of an alkylene oxide with fatty acids, for example polyoxyethylene stearate, or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethyleneoxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, for example polyethylene sorbitan monooleate. The aqueous suspensions may also contain one or more preservatives, for example ethyl, or n-propyl p-hydroxybenzoate, one or more coloring agents, one or more flavoring agents, and one or more sweetening agents, such as sucrose or saccharin.

Oily suspensions may be formulated by suspending the active ingredients in a vegetable oil, for example arachid oil, olive oil, sesame oil or coconut oil, or in a mineral oil such as liquid paraffin. The oily suspensions may contain a thickening agent, for example beeswax, hard paraffin or cetyl alcohol. Sweetening agents such as those set forth above, and flavoring agents may be added to provide palatable oral preparations. These compositions may be preserved by the addition of an anti-oxidant such as ascorbic acid.

Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water provide the active ingredient in admixture with a dispersing or wetting agent, suspending agent and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those already mentioned above. Additional excipients, for example sweetening, flavoring and coloring agents, may also be present.

Pharmaceutical compositions of the invention may also be in the form of oil-in-water emulsions. The oily phase may be a vegetable oil, for example olive oil or arachid oil, or a mineral oil, for example liquid paraffin or mixtures of these. Suitable emulsifying agents may be naturally-occurring gums, for example gum acacia or gum tragacanth, naturally-occurring phosphatides, for example soy bean, lecithin, and esters or partial esters derived from fatty acids and hexitol, anhydrides, for example sorbitan monooleate, and condensation products of the said partial esters with ethylene oxide, for example polyoxyethylene sorbitan monooleate. The emulsions may also contain sweetening and flavoring agents.

Syrups and elixirs may be formulated with sweetening agents, for example glycerol, propylene glycol, sorbitol or sucrose. Such formulations may also contain a demulcent, a preservative and flavoring and coloring agents. The pharmaceutical compositions may be in the form of a sterile

injectable aqueous or oleaginous suspension. This suspension may be formulated according to the known art using those suitable dispersing or wetting agents and suspending agents which have been mentioned above. The sterile injectable preparation may also be sterile injectable solution or suspension in a non-toxic parentally acceptable diluent or solvent, for example as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectables.

The compounds of general Formula I may also be administered in the form of suppositories for rectal administration of the drug. These compositions can be prepared by mixing the drug with a suitable non-irritating excipient which is solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum to release the drug. Such materials are cocoa butter and polyethylene glycols. Compounds of general Formula I may be administered parenterally in a sterile medium. The drug, depending on the vehicle and concentration used, can either be suspended or dissolved in the vehicle. Advantageously, adjuvants such as local anesthetics, preservatives and buffering agents can be dissolved in the vehicle. Dosage levels of the order of from about 0.1 mg to about 50 mg per kilogram of body weight per day are useful in the treatment of the above-indicated conditions (about 0.5 mg to about 3 g per patient per day), although higher amounts, for example up to 140 mg/kg/day may be appropriate in some circumstances. The amount of active ingredient that may be combined with the carrier materials to produce a single dosage form will vary depending upon the host treated and the particular mode of administration. Dosage unit forms will generally contain between from about 1 mg to about 500 mg of an active ingredient.

Frequency of dosage may also vary depending on the compound used and the particular disease treated. However, for treatment of most eating disorders, a dosage regimen of 4 times daily or less is preferred. For the treatment of stress and depression a dosage regimen of 1 or 2 times daily is particularly preferred.

It will be understood, however, that the specific dose level for any particular patient will depend upon a variety of factors including the activity of the specific compound employed, the age, body weight, general health, sex, diet, time of administration, route of administration, and rate of excretion, drug combination and the severity of the particular disease undergoing therapy.

Preferred compounds of the invention will have certain pharmacological properties. Such properties include, but are not limited to oral bioavailability, low toxicity, low serum protein binding and desirable in vitro and in vivo half-lives. Penetration of the blood brain barrier for compounds used to treat CNS disorders is necessary, while low brain levels of compounds used to treat peripheral disorders are often preferred.

Assays may be used to predict these desirable pharmacological properties. Assays used to predict bioavailability

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include transport across human intestinal cell monolayers, including Caco-2 cell monolayers. Toxicity to cultured hepatocytes may be used to predict compound toxicity. Penetration of the blood brain barrier of a compound in humans may be predicted from the brain levels of the compound in laboratory animals given the compound intravenously.

Serum protein binding may be predicted from albumin binding assays. Such assays are described in a review by Oravcová, et al. (*Journal of Chromatography B* 1996, 677, 1-27).

Compound half-life is inversely proportional to the frequency of dosage of a compound. In vitro half-lives of compounds may be predicted from assays of microsomal half-life as described by Kuhnz and Gieschen (*Drug Metabolism and Disposition* 1998, 26, 1120-1127).

As discussed above, preferred compounds of the invention exhibit good activity in standard in vitro NPY receptor binding assays, specifically the assay as specified in Example 93A, which follows. References herein to "standard in vitro NPY receptor binding assay" are intended to refer to that protocol as defined in Example 93A which follows. Generally preferred compounds of the invention exhibit a K_i of about 1 micromolar or less, still more preferably and K_i of about 100 nanomolar or less even more preferably an K_i of about 10 nanomolar or less or even 1 nanomolar or less in such a defined standard in vitro NPY receptor binding assay as exemplified by Example 93A which follows. In appropriate case, the compounds of the invention may be employed in combination with other active agents. The invention therefore also provides pharmaceutical combination compositions comprising a therapeutically effective amount of a composition comprising: (a) first compound, said first compound being a compound as described above a prodrug thereof, or a pharmaceutically acceptable salt of said compound or of said prodrug; and (b) a second compound, said second compound being a β_3 agonist, a thyromimetic, an eating behavior modifying agent or a NPY antagonist; and a pharmaceutical carrier, vehicle or diluent. To this end therefore the invention also provides a kit comprising: (a) first compound, said first compound being a compound as described above, a prodrug thereof, or a pharmaceutically acceptable salt of said compound or of said prodrug; (b) a second compound, said second compound being a β_3 agonist, a thyromimetic, an eating behavior modifying agent or a NPY antagonist; and a pharmaceutical carrier, vehicle, diluent; and (c) means for containing said first and second unit dosage forms wherein the amounts of the first and second compounds result in a therapeutic effect.

Synthetic Schemes

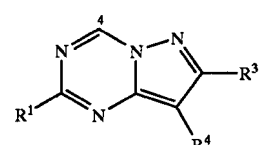
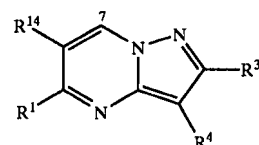
Preparation of Amino Substituted Pyrazolo[1,5-a]-1,5-Pyrimidines and Pyrazolo[1,5-a]-1,3,5-Triazines Derivatives

An illustration of preparation methods of compounds of the present invention is given in the Schemes below. In particular displacement of a leaving group Z, as in formula 10 (Scheme 1) by the appropriate substituted amine provides a method to convert the heterocyclic cores of the present invention, i.e. aryl or heteroaryl substituted pyrazolo[1,5-a]-1,5-pyrimidines and pyrazo[1,5-a]-1,3,5-triazines, into compounds that potently interact with the NPY1 receptor. Such transformations may require several consecutive chemical steps. Those having skill in the art will recognize that the starting materials may be varied and additional steps employed to produce compounds encompassed by the present invention. The disclosures of all articles and refer-

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ences mentioned in this application, including patents, are incorporated herein by reference. Unless otherwise specified the variable R^1 , R^2 , R^3 , R^4 , R^5 , R^6 , and X are as defined for Formula I.

One general approach is to convert a heterocyclic core A and or a heterocyclic core B



to a compound that exhibits a K_i of 5 micromolar or less in an assay of NPY receptor binding, wherein

R^1 is selected from H, C_1 - C_6 alkyl, C_3 - C_{10} cycloalkyl, (C_3 - C_{10} cycloalkyl) C_1 - C_6 alkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, cyano, halo, C_1 - C_6 haloalkyl, OR^7 , C_1 - C_6 alkyl- OR^7 , C_1 - C_6 cyanoalkyl, NR^8R^9 , and C_1 - C_6 alkyl- NR^8R^9 ;

R^3 is selected from H, C_1 - C_6 alkyl, C_3 - C_{10} cycloalkyl, (C_3 - C_{10} cycloalkyl) C_1 - C_6 alkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, cyano, halo, C_1 - C_6 haloalkyl, OR^7 , C_1 - C_6 alkyl- OR^7 , C_1 - C_6 cyanoalkyl, NR^8R^9 , and C_1 - C_6 alkyl- NR^8R^9 ;

R^4 is selected from aryl or heteroaryl, each optionally substituted with 1 to 5 substituents independently selected at each occurrence from C_1 - C_6 alkyl, C_3 - C_{10} cycloalkyl, C_3 - C_{10} cycloalkenyl, (C_3 - C_{10} cycloalkyl) C_1 - C_6 alkyl, C_1 - C_6 alkenyl, halogen, C_1 - C_6 haloalkyl, trifluoromethylsulfonyl, OR^7 , C_1 - C_6 alkyl- OR^7 , NR^8R^9 , C_1 - C_6 alkyl- NR^8R^9 , $CONR^8R^9$, C_1 - C_6 alkyl- $CONR^8R^9$, $COOR^7$, C_1 - C_6 alkyl- $COOR^7$, CN , C_1 - C_6 alkyl- CN , $SO_2NR^8R^9$, SO_2R^7 , aryl, heteroaryl, heterocycloalkyl, and 3-, 4-, or 5-(2-oxo-1,3-oxazolidinyl), with the proviso that at least one of the positions ortho or para to the point of attachment of the aryl or heteroaryl ring to the pyrazole is substituted;

R^{14} is H, C_1 - C_6 alkyl, C_3 - C_{10} cycloalkyl, (C_3 - C_{10} cycloalkyl) C_1 - C_6 alkyl, C_2 - C_4 alkenyl, C_2 - C_4 alkynyl, halo, or CN ; by substituting the 7-position of the heterocyclic core A or the 4-position of the heterocyclic core B with a diamine group $-N[R^2]-A-B-N[R^6]-R^5$

wherein:

R^2 is

H,

C_1 - C_6 alkyl which optionally forms a C_3 - C_6 aminocarbocycle or a C_2 - C_5 aminoheterocycle with A or B, each of which is optionally substituted with R^7 ,

C_3 - C_{10} cycloalkyl, or

(C_3 - C_{10} cycloalkyl) C_1 - C_{10} alkyl; or

R^2 and R^6 jointly form with the 2 nitrogen atoms to which they are bound a C_2 - C_5 aminoheterocycle optionally substituted with R^7 ;

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A is $(CH_2)_m$, where m is 1, 2 or 3 and is optionally mono- or di-substituted at each carbon atom with C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, $(C_3-C_{10}$ cycloalkyl) C_1-C_6 alkyl, C_1-C_6 alkenyl, C_1-C_6 alkynyl, cyano, halogen, C_1-C_6 haloalkyl, OR^7 , C_1-C_6 alkyl- OR^7 , C_1-C_6 cyanoalkyl, NR^8R^9 , or C_1-C_6 alkyl- NR^8R^9 , or

A and B jointly form a C_3-C_6 carbocycle, which is optionally substituted at each carbon atom with R^7 , or

A and R^2 jointly form a C_3-C_6 aminocarbocycle, which is optionally substituted at each carbon atom with R^7 .

B is $(CH_2)_n$, where n is 0, 1, 2, or 3 and is optionally substituted at each carbon atom with C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, $(C_3-C_{10}$ cycloalkyl) C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, cyano, halogen, C_1-C_6 haloalkyl, OR^7 , C_1-C_6 alkyl- OR^7 , C_1-C_6 cyanoalkyl, NR^8R^9 , or C_1-C_6 alkyl- NR^8R^9 , or

B and R^2 jointly form a C_3-C_6 aminocarbocycle, which is optionally substituted at each carbon atom with R^7 , or

B and R^6 jointly form a C_3-C_6 aminocarbocycle, which is optionally substituted at each carbon atom with R^7 ;

R^5 and R^6 are independently selected from H, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, $(C_3-C_{10}$ cycloalkyl) C_1-C_6 alkyl, C_2-C_6 alkenyl, and C_2-C_6 alkynyl;

R^7 is H, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, C_3-C_{10} cycloalkenyl, $(C_3-C_{10}$ cycloalkyl) C_1-C_6 alkyl, C_1-C_3 haloalkyl, or heterocycloalkyl, C_1-C_8 alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, C_1-C_8 alkanoyl, aroyl, heteroaroyl, aryl, heteroaryl, C_1-C_6 arylalkyl or C_1-C_6 heteroarylalkyl each of which is optionally substituted with 1 to 5 substituents independently selected at each occurrence from halogen, C_1-C_6 haloalkyl, OR^{13} , NR^8R^9 , C_1-C_6 alkyl- OR^{13} , C_1-C_6 alkyl- NR^8R^9 , $CONR^8R^9$, $COOR^{13}$, CN, $SO_2NR^8R^9$, SO_2R^{13} , with the proviso that for SO_2R^7 , R^7 cannot be H;

R^8 and R^9 are independently selected at each occurrence from H, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_3-C_{10} cycloalkenyl, C_2-C_6 alkynyl, heterocycloalkyl, C_1-C_8 alkanoyl, aroyl, heteroaroyl, aryl, heteroaryl, C_1-C_6 arylalkyl or C_1-C_6 heteroarylalkyl, or R^8 and R^9 , taken together, can form a C_3-C_6 aminocarbocycle or a C_2-C_5 aminoheterocycle each optionally substituted at each occurrence with C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, C_3-C_{10} cycloalkenyl, $(C_3-C_{10}$ cycloalkyl) C_1-C_6 alkyl, C_1-C_3 haloalkyl, or heterocycloalkyl, C_1-C_8 alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, C_1-C_8 alkanoyl, aroyl, heteroaroyl, aryl, heteroaryl, C_1-C_6 arylalkyl or C_1-C_6 heteroarylalkyl;

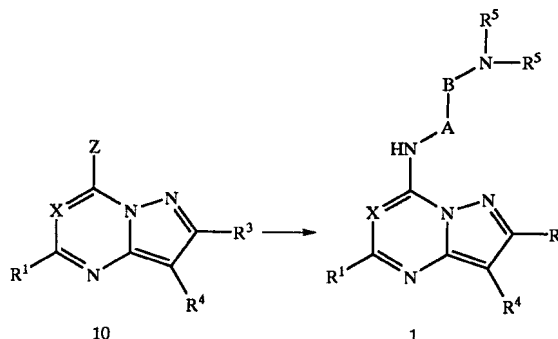
R^{11} is selected from H, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, $(C_3-C_{10}$ cycloalkyl) C_1-C_6 alkyl;

R^{12} is selected from H, aryl, heteroaryl, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, $(C_3-C_{10}$ cycloalkyl) C_1-C_6 alkyl, optionally substituted with OR^7 , NR^8R^9 , C_3-C_6 aminocarbocycle, or C_2-C_5 aminoheterocycle; and

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R^{13} is independently selected at each occurrence from H, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, $(C_3-C_{10}$ cycloalkyl) C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 haloalkyl, with the proviso that when R^7 is SO_2R^{13} , R^{13} cannot be H. More specifically the following schemes may be used.

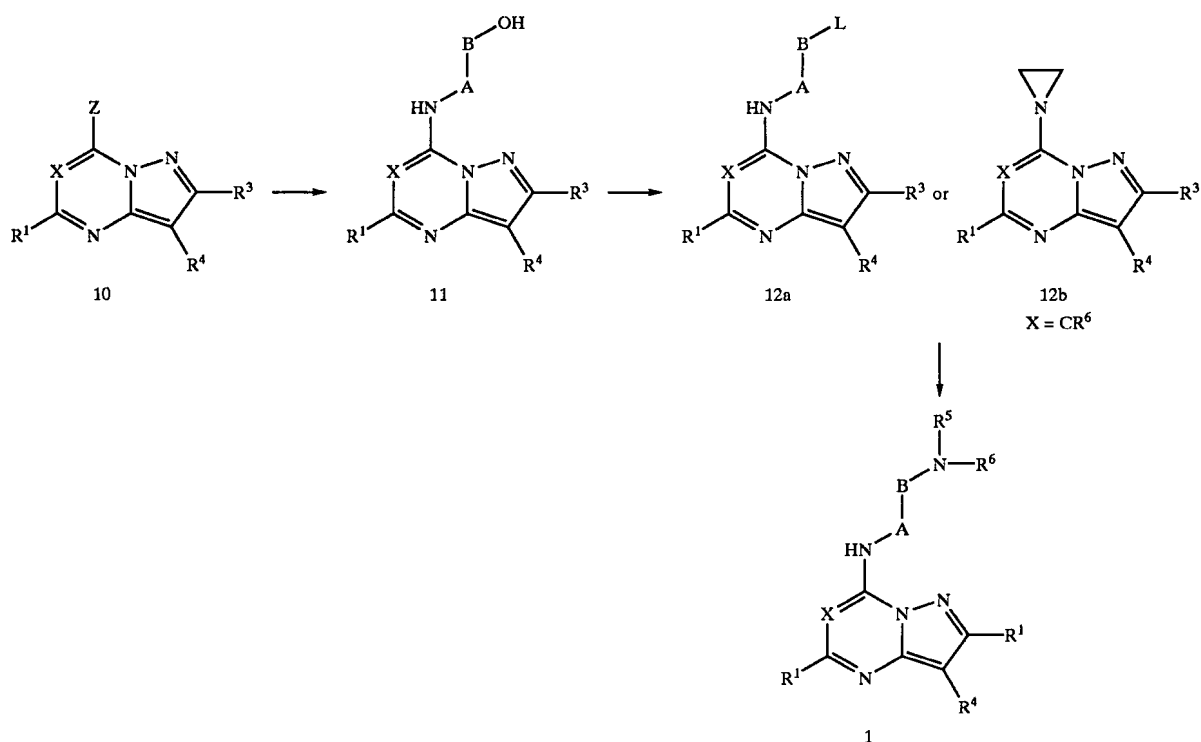
SCHEME 1



As illustrated in Scheme 1, compounds of formula I can be prepared from intermediate compounds of formula 10, where Z is halogen (preferably chloro or bromo), alkane sulfonyloxy, aryl sulfonyloxy or haloalkane sulfonyloxy, and X, R^1 , R^3 and R^4 are defined above, using the procedures outlined below.

Compounds of formula 10 react with an amine of formula $H_2N-A-B-N[R^6]-R^5$, where A, B, R^5 and R^6 are defined as above, in the presence or absence of a base in the presence or absence of an inert solvent at reaction temperatures ranging from $-78^\circ C.$ to $250^\circ C.$ to generate compounds of formula I. Bases may include, but are not limited to, alkali metal hydrides (preferably sodium hydride), alkali metal alkoxides (1-6 carbons) (preferably sodium methoxide, sodium ethoxide, or sodium tert-butoxide), alkaline earth metal hydrides, alkali metal dialkylamides (preferably lithium diisopropylamide), alkali metal carbonates, alkali metal bicarbonates, alkali metal bis-(trialkylsilyl)amides (preferably lithium or sodium (trimethylsilyl)amide), trialkylamines (preferably N,N-diisopropyl-N-ethyl amine or triethylamine), arylamines (preferably 4-dimethyl aniline), or heteroaromatic amines (preferably pyridine). Inert solvents may include, but are not limited to, alkyl alcohols (1-8 carbons) (preferably methanol, ethanol, or tert-butanol), lower alkanenitriles (1-6 carbons) (preferably acetonitrile), dialkyl ethers (preferably diethyl ether), cyclic ethers (preferably tetrahydrofuran or 1,4-dioxane), N,N-dialkylformamides (preferably dimethyl formamide), N,N-dialkylacetamides (preferably dimethyl acetamide), cyclic amides (preferably N-methylpyrrolidin-2-one), dialkylsulfoxides (preferably dimethylsulfoxide), aromatic hydrocarbons (preferably benzene or toluene), or haloalkanes (1-10 carbons and 1-10 halogens) (preferably dichloromethane). Preferred reaction temperatures range from $0^\circ C.$ to $140^\circ C.$

SCHEME 2



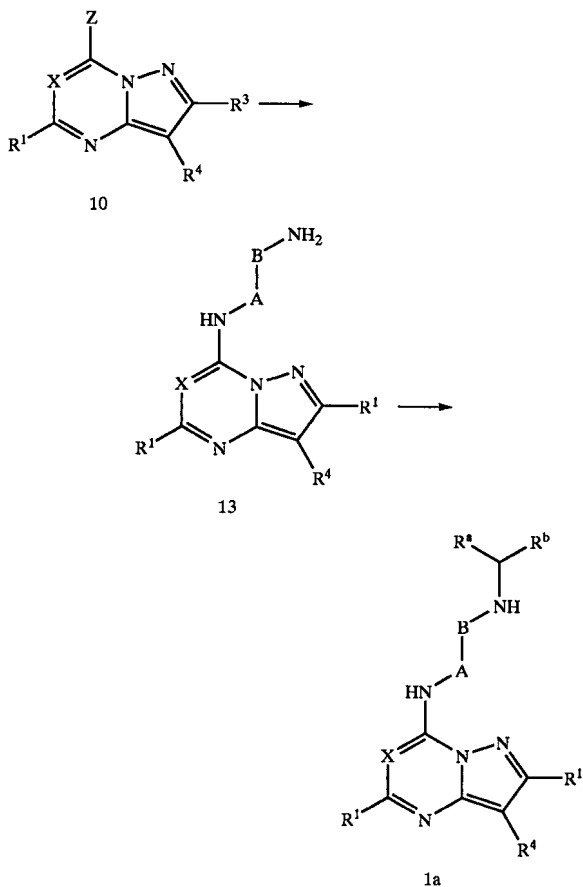
Alternatively, as shown in Scheme 2, compounds of formula I can be obtained by first reacting a compound of formula 10 with an amino alcohol of formula $H_2N-A-B-OH$, where A and B are defined as above, in the presence or absence of a base in the presence or absence of an inert solvent at reaction temperatures ranging from $-78^\circ C.$ to $250^\circ C.$ to generate intermediates of formula 11. Reacting a compound of formula 11 with a halogenating agent or sulfonylating agent in the presence or absence of a base in the presence or absence of an inert solvent at reaction temperatures ranging from $-78^\circ C.$ to $250^\circ C.$ to afford products of formula 12a (where Z is halogen, alkane sulfonyloxy, aryl sulfonyloxy or haloalkane sulfonyloxy) or 12b when A and B are both CH_2 and X is CR^{14} . Halogenating agents include, but are not limited to, $SOCl_2$, $POCl_3$, PCl_3 , PCl_5 , $POBr_3$, PBr_3 , PBr_5 , CCl_4/PPh_3 . Sulfonylating agents include, but are not limited to, alkanesulfonyl halides or anhydrides (preferably methanesulfonyl chloride or methanesulfonic anhydride), aryl sulfonyl halides or anhydrides (such as p-toluenesulfonyl chloride or anhydride), or haloalkylsulfonyl halides or anhydrides (preferably trifluoromethanesulfonyl chloride or anhydride). Bases may include, but are not limited to, trialkylamines (preferably N,N-di-isopropyl-N-ethyl amine or triethylamine), bicyclic amidines (preferably DBU), anilines (preferably N-dimethyl aniline), or heteroaromatic amines (preferably pyridine). Inert solvents may include, but are not limited to, lower alkanenitriles (1–6 carbons) (preferably acetonitrile), dialkyl ethers (preferably diethyl ether), cyclic ethers (preferably tetrahydrofuran or 1,4-dioxane), N,N-dialkylformamides (preferably dimethyl formamide), N,N-dialkylacetamides (preferably dimethyl acetamide), cyclic amides (preferably N-methylpyrrolidin-2-one), dialkylsulfoxides (preferably

dimethylsulfoxide), aromatic hydrocarbons (preferably benzene or toluene), or haloalkanes with 1–10 carbons and 1–10 halogens (preferably dichloromethane). Preferred reaction temperatures range from $-20^\circ C.$ to $100^\circ C.$ Compounds of formula 12a or 12b can then be reacted with an amine of formula $HN[R^5]-R^6$, where R^5 and R^6 are defined as above, to give a compound of formula I. Bases may include, but are not limited to, alkali metal hydrides (preferably sodium hydride), alkali metal alkoxides (1–6 carbons) (preferably sodium methoxide, sodium ethoxide, or sodium tert-butoxide), alkaline earth metal hydrides, alkali metal dialkylamides (preferably lithium diisopropylamide), alkali metal carbonates, alkali metal bicarbonates, alkali metal bis-(trialkylsilyl)amides (preferably lithium or sodium (trimethylsilyl)amide), trialkylamines (preferably N,N-diisopropyl-N-ethyl amine or triethylamine), arylamines (preferably 4-dimethyl aniline), or heteroaromatic amines (preferably pyridine). Inert solvents may include, but are not limited to, alkyl alcohols (1–8 carbons) (preferably methanol, ethanol, or tert-butanol), lower alkanenitriles (1–6 carbons) (preferably acetonitrile), dialkyl ethers (preferably diethyl ether), cyclic ethers (preferably tetrahydrofuran or 1,4-dioxane), N,N-dialkylformamides (preferably dimethyl formamide), N,N-dialkylacetamides (preferably dimethyl acetamide), cyclic amides (preferably N-methylpyrrolidin-2-one), dialkylsulfoxides (preferably dimethylsulfoxide), aromatic hydrocarbons (preferably benzene or toluene), or haloalkanes (1–10 carbons and 1–10 halogens) (preferably dichloromethane). Preferred reaction temperatures range from $0^\circ C.$ to $140^\circ C.$

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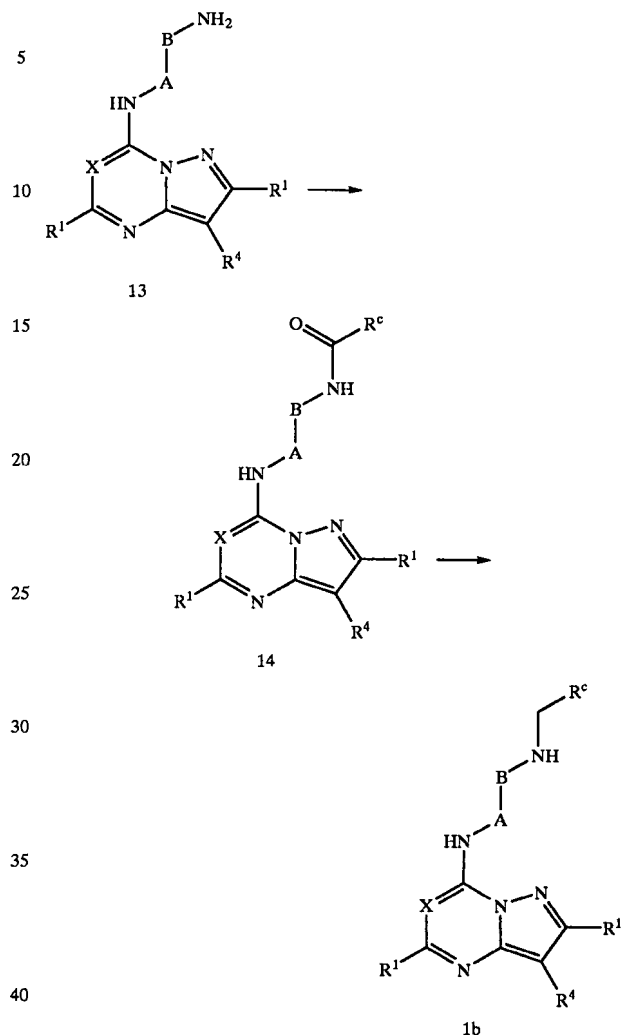
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SCHEME 3



A subset of compounds of formula I, described under formula Ia, can be obtained by first reacting a compound of formula 10 with a diamine of formula $H_2N-A-B-NH_2$, where A and B are defined as above, in the presence or absence of a base in the presence or absence of an inert solvent at reaction temperatures ranging from $-78^\circ C.$ to $250^\circ C.$ to generate intermediates of formula 13. Reaction of a compound of formula 13 with an aldehyde or ketone of Formula $R^a-C(=O)-R^b$ in the presence of a reducing agent provides a compound of formula Ia, where the grouping R^a-CH-R^b corresponds to R^5 in formula I, as defined above. Reducing agents include, but are not limited to, alkali metal or alkaline earth metal borohydrides (preferably lithium or sodium borohydride), borane (preferably complexed with dimethyl sulfide or tetrahydrofuran), dialkylboranes (such as di-isoamylborane), alkali metal aluminum hydrides (preferably lithium aluminum hydride), alkali metal (trialkoxo)aluminum hydrides (such as triethoxyaluminum hydride), dialkyl aluminum hydrides (such as di-isobutyl aluminum hydride), alane (preferably complexed with dimethyl amine). Inert solvents may include, but are not limited to, alkyl alcohols (1-6 carbons) (preferably methanol, ethanol, or tert-butanol), dialkyl ethers (preferably diethyl ether), cyclic ethers (preferably tetrahydrofuran or 1,4-dioxane), aromatic hydrocarbons (preferably benzene or toluene). Preferred reaction temperatures range from $-78^\circ C.$ to $100^\circ C.$

SCHEME 4

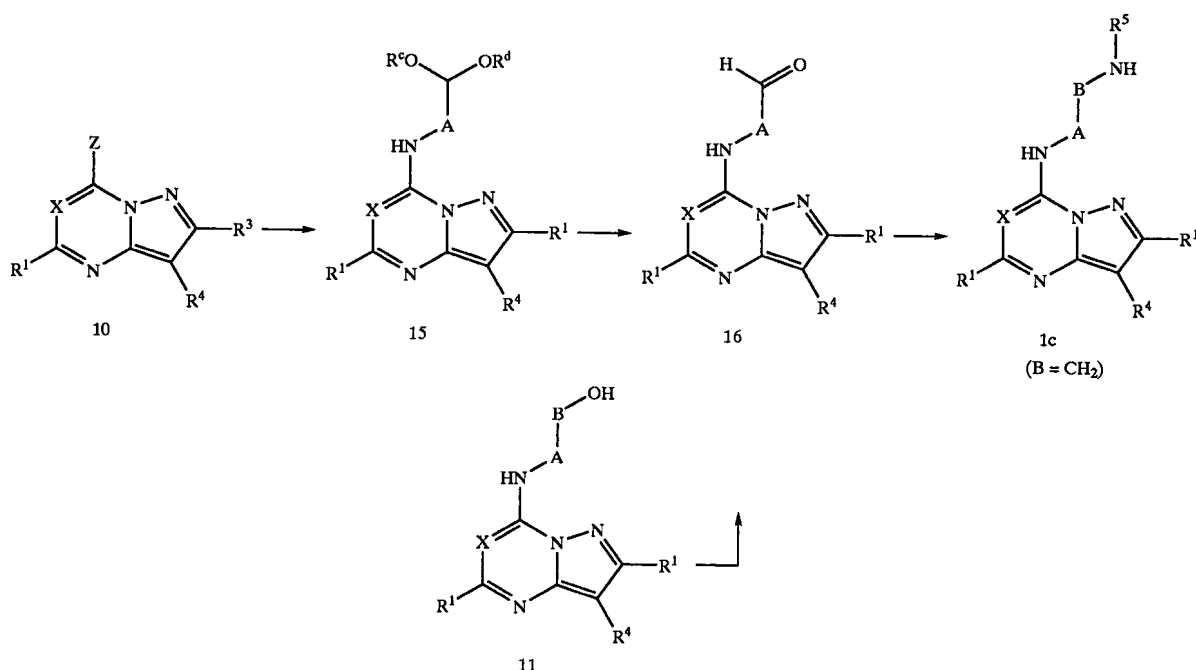


Alternatively, a subset of compounds of formula I, described under formula Ib, can be obtained by first reacting a compound of formula 13 with an activated acid of formula $R^c-C(=O)-Z$, where Z is halo (preferably chloro), O-acyl (preferably $O-C(=O)-R^c$), in the presence or absence of a base in the presence or absence of an inert solvent at reaction temperatures ranging from $-78^\circ C.$ to $250^\circ C.$ to generate an amide intermediate of formula 14. Reaction of a compound of formula 14 with a reducing agent provides a compound of formula Ib, where the grouping R^c-CH_2 corresponds to R^5 in formula I, as defined above. Reducing agents include, but are not limited to, alkali metal or alkaline earth metal borohydrides (preferably lithium or sodium borohydride), borane (preferably complexed with dimethyl sulfide or tetrahydrofuran), dialkylboranes (such as di-isoamylborane), alkali metal aluminum hydrides (preferably lithium aluminum hydride), alkali metal (trialkoxo)aluminum hydrides (such as triethoxyaluminum hydride), dialkyl aluminum hydrides (such as di-isobutyl aluminum hydride), alane (preferably complexed with dimethyl amine). Inert solvents may include, but are not limited to, alkyl alcohols (1-6 carbons) (preferably methanol, ethanol, or tert-butanol), dialkyl ethers (preferably diethyl ether), cyclic ethers (preferably tetrahydrofuran or 1,4-dioxane), aromatic hydrocarbons (preferably benzene or

toluene). Preferred reaction temperatures range from -78° C. to 100° C.

vents may include, but are not limited to dialkyl ethers (preferably diethyl ether), cyclic ethers (preferably tetrahydrofuran or 1,4-dioxane), aromatic hydrocarbons (preferably benzene or toluene), or haloalkanes (1–10 carbons and 1–10 halogens) (preferably dichloromethane). Protic acids include, but are not limited to, formic acid, acetic acid, trifluoroacetic acid, hydrochloric acid, methane sulfonic acid. Alternatively, compounds of formula 16 can be obtained by oxidation of compounds of formula 11 where $B=CH_2$. Oxidizing agents include, but are not limited to, transition metal oxides, such as CrO_3 or MnO_2 , pyridine-chromium complexes, such as $CrO_3 \cdot C_5H_5N$, pyridinium dichromate or pyridinium chlorochromate, or an oxalyl chloride-DMSO-triethylamine reagent (Swern oxidation). Compounds of formula 16 react with amines of formula H_2N-R^5 , where R^5 is defined above, in the presence of a reducing agent in the presence or absence of an inert solvent in the presence or absence of a protic acid at temperatures ranging from -78° C. to 100° C., to give compounds of formula 1c. Reducing agents include, but are not limited to, alkali metal or alkaline earth metal borohydrides (preferably lithium or sodium borohydride), borane (preferably complexed with dimethyl sulfide or tetrahydrofuran), dialkylboranes (such as di-isoamylborane), alkali metal aluminum hydrides (preferably lithium aluminum hydride), alkali metal (trialkoxo)aluminum hydrides (such as triethoxyaluminum hydride), dialkyl aluminum hydrides (such as di-isobutyl aluminum hydride), alane (preferably complexed with dimethyl amine). Inert solvents may include, but are not limited to, alkyl alcohols (1–6 carbons) (preferably methanol, ethanol, or tert-butanol), dialkyl ethers (preferably diethyl ether), cyclic ethers (preferably tetrahydrofuran or 1,4-dioxane), aromatic hydrocarbons (preferably benzene or toluene).

SCHEME 5

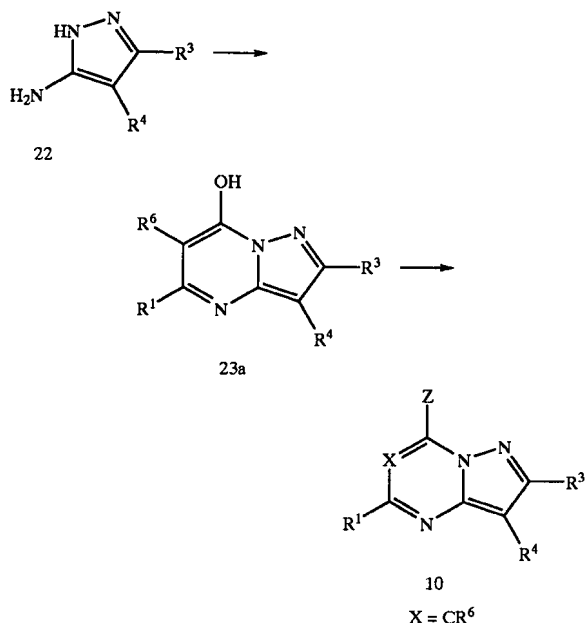


Alternatively, a subset of compounds of formula I, described under formula 1c, can be obtained by first reacting a compound of formula 10 with an amine of formula $H_2N-A-CH(OR^c)(OR^d)$, where A is defined above, and R^c and R^d are C_1-C_6 lower alkyls or, taken together, complete a ketal group, such as, for example a dioxane or dioxolane group, in the presence or absence of a base in the presence or absence of an inert solvent at reaction temperatures ranging from -78° C. to 250° C. to generate compounds of formula 15. Bases may include, but are not limited to, alkali metal hydrides (preferably sodium hydride), alkali metal alkoxides (1–6 carbons) (preferably sodium methoxide, sodium ethoxide, or sodium tert-butoxide), alkaline earth metal hydrides, alkali metal dialkylamides (preferably lithium diisopropylamide), alkali metal carbonates, alkali metal bicarbonates, alkali metal bis-(trialkylsilyl)amides (preferably lithium or sodium (trimethylsilyl)amide), trialkylamines (preferably N,N-di-isopropyl-N-ethyl amine or triethylamine), arylamines (preferably 4-dimethyl aniline), or heteroaromatic amines (preferably pyridine). Inert solvents may include, but are not limited to, alkyl alcohols (1–8 carbons) (preferably methanol, ethanol, or tert-butanol), lower alkanenitriles (1–6 carbons) (preferably acetonitrile), dialkyl ethers (preferably diethyl ether), cyclic ethers (preferably tetrahydrofuran or 1,4-dioxane), N,N-dialkylformamides (preferably dimethyl formamide), N,N-dialkylacetamides (preferably dimethyl acetamide), cyclic amides (preferably N-methylpyrrolidin-2-one), dialkylsulfoxides (preferably dimethylsulfoxide), aromatic hydrocarbons (preferably benzene or toluene), or haloalkanes (1–10 carbons and 1–10 halogens) (preferably dichloromethane). Compounds of formula 15 react with a protic acid in the presence or absence of an inert solvent at reaction temperatures ranging from -78° C. to 250° C., followed by aqueous work-up to generate compounds of formula 16. Inert sol-

vents may include, but are not limited to, dialkyl ethers (preferably diethyl ether), cyclic ethers (preferably tetrahydrofuran or 1,4-dioxane), aromatic hydrocarbons (preferably benzene or toluene), or haloalkanes (1–10 carbons and 1–10 halogens) (preferably dichloromethane). Protic acids include, but are not limited to, formic acid, acetic acid, trifluoroacetic acid, hydrochloric acid, methane sulfonic acid. Alternatively, compounds of formula 16 can be obtained by oxidation of compounds of formula 11 where $B=CH_2$. Oxidizing agents include, but are not limited to, transition metal oxides, such as CrO_3 or MnO_2 , pyridine-chromium complexes, such as $CrO_3 \cdot C_5H_5N$, pyridinium dichromate or pyridinium chlorochromate, or an oxalyl chloride-DMSO-triethylamine reagent (Swern oxidation). Compounds of formula 16 react with amines of formula H_2N-R^5 , where R^5 is defined above, in the presence of a reducing agent in the presence or absence of an inert solvent in the presence or absence of a protic acid at temperatures ranging from -78° C. to 100° C., to give compounds of formula 1c. Reducing agents include, but are not limited to, alkali metal or alkaline earth metal borohydrides (preferably lithium or sodium borohydride), borane (preferably complexed with dimethyl sulfide or tetrahydrofuran), dialkylboranes (such as di-isoamylborane), alkali metal aluminum hydrides (preferably lithium aluminum hydride), alkali metal (trialkoxo)aluminum hydrides (such as triethoxyaluminum hydride), dialkyl aluminum hydrides (such as di-isobutyl aluminum hydride), alane (preferably complexed with dimethyl amine). Inert solvents may include, but are not limited to, alkyl alcohols (1–6 carbons) (preferably methanol, ethanol, or tert-butanol), dialkyl ethers (preferably diethyl ether), cyclic ethers (preferably tetrahydrofuran or 1,4-dioxane), aromatic hydrocarbons (preferably benzene or toluene).

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SCHEME 6

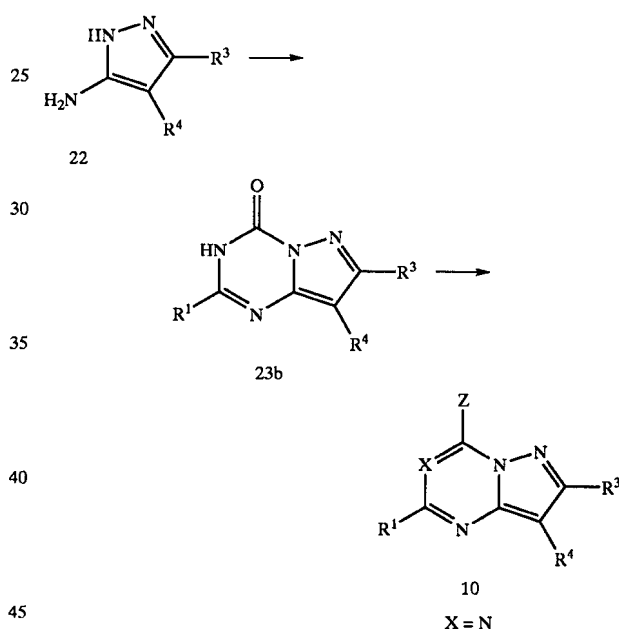


When X is CR¹⁴, as defined above, compounds of formula 10 may be obtained from compounds of formula 22. Compounds of formula 22 can be reacted with compounds of formula R¹-C=O-CH(R¹⁴)-C=O-R^c, where R¹ and R¹⁴ are defined above, and R^c is halogen, cyano, lower alkoxy (1-6 carbons), or lower alkanoyloxy (1-6 carbons), in the presence or absence of a base in an inert solvent at reaction temperatures ranging from -50° C. to 250° C. to afford compounds of formula 23a. Bases may include, but are not limited to, alkali metal hydrides (preferably sodium hydride), alkali metal alkoxides (1-6 carbons) (preferably sodium methoxide, sodium ethoxide, or sodium tert-butoxide), alkaline earth metal hydrides, alkali metal dialkylamides (preferably lithium diisopropylamide), alkali metal carbonates, alkali metal hydroxides, alkali metal bis-(trialkylsilyl)amides (preferably lithium or sodium (trimethylsilyl)amide), trialkylamines (preferably N,N-diisopropyl-N-ethyl amine or triethylamine), bicyclic amidines (preferably DBU), or heteroaromatic amines (preferably pyridine). Inert solvents may include, but are not limited to, alkyl alcohols (1-8 carbons) (preferably methanol, ethanol, or tert-butanol), lower alkanenitriles (1-6 carbons) (preferably acetonitrile), water, dialkyl ethers (preferably diethyl ether), cyclic ethers (preferably tetrahydrofuran or 1,4-dioxane), N,N-dialkylformamides (preferably dimethyl formamide), N,N-dialkylacetamides (preferably dimethyl acetamide), cyclic amides (preferably N-methylpyrrolidin-2-one), dialkylsulfoxides (preferably dimethylsulfoxide), aromatic hydrocarbons (preferably benzene or toluene). Compounds of formula 23a can then be reacted with a halogenating agent or sulfonylating agent in the presence or absence of a base in the presence or absence of an inert solvent at reaction temperatures ranging from -78° C. to 250° C. to afford products of formula 10 (where Z is halogen, alkane sulfonyloxy, aryl sulfonyloxy or haloalkane sulfonyloxy and X is CR¹⁴). Halogenating agents include, but are not limited to, SOCl₂, POCl₃, PCl₃, PCl₅, POBr₃, PBr₃, or PBr₅. Sulfonylating agents include, but are not limited to, alkanesulfonyl halides or anhydrides (preferably methanesulfonyl chloride or methanesulfonic

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anhydride), aryl sulfonyl halides or anhydrides (such as p-toluenesulfonyl chloride or anhydride), or haloalkylsulfonyl halides or anhydrides (preferably trifluoromethanesulfonic anhydride). Bases may include, but are not limited to, trialkylamines (preferably N,N-di-isopropyl-N-ethyl amine or triethylamine), bicyclic amidines (preferably DBU), anilines (preferably N-dimethyl aniline), or heteroaromatic amines (preferably pyridine). Inert solvents may include, but are not limited to, lower alkanenitriles (1-6 carbons) (preferably acetonitrile), dialkyl ethers (preferably diethyl ether), cyclic ethers (preferably tetrahydrofuran or 1,4-dioxane), N,N-dialkylformamides (preferably dimethyl formamide), N,N-dialkylacetamides (preferably dimethyl acetamide), cyclic amides (preferably N-methylpyrrolidin-2-one), dialkylsulfoxides (preferably dimethylsulfoxide), aromatic hydrocarbons (preferably benzene or toluene), or haloalkanes with 1-10 carbons and 1-10 halogens (preferably dichloromethane). Preferred reaction temperatures range from -20° C. to 100° C.

SCHEME 7

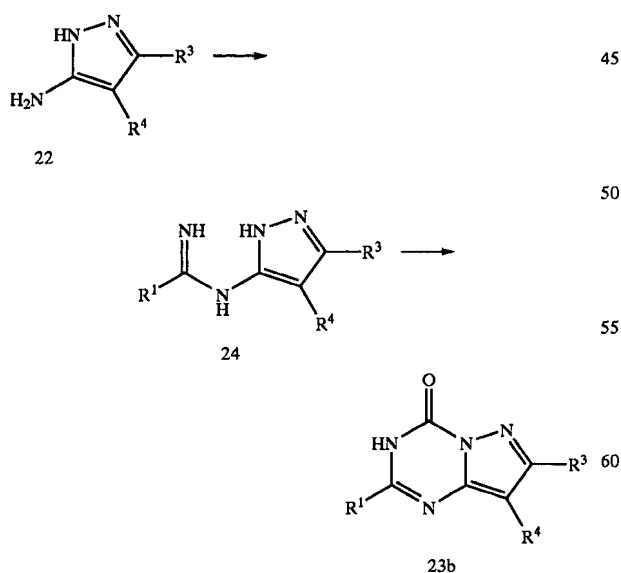


When X is N, compounds of formula 22 can be reacted with compounds of formula R¹-C=N(COOR^g)-OR^f, where R¹ is defined above, and R^g is lower alkyl (1-6 carbons), and R^f is halogen, cyano, lower alkoxy (1-6 carbons), or lower alkanoyloxy (1-6 carbons), in the presence or absence of a base in an inert solvent at reaction temperatures ranging from -50° C. to 250° C. to afford compounds of formula 23b. Bases may include, but are not limited to, alkali metal hydrides (preferably sodium hydride), alkali metal alkoxides (1-6 carbons) (preferably sodium methoxide, sodium ethoxide, or sodium tert-butoxide), alkaline earth metal hydrides, alkali metal dialkylamides (preferably lithium diisopropylamide), alkali metal carbonates, alkali metal hydroxides, alkali metal bis-(trialkylsilyl)amides (preferably lithium or sodium (trimethylsilyl)amide), trialkylamines (preferably N,N-diisopropyl-N-ethyl amine or triethylamine), bicyclic amidines (preferably DBU), or heteroaromatic amines (preferably pyridine). Inert solvents may include, but are not limited to, alkyl alcohols (1-8 carbons) (preferably

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methanol, ethanol, or tert-butanol), lower alkanenitriles (1–6 carbons) (preferably acetonitrile), water, dialkyl ethers (preferably diethyl ether), cyclic ethers (preferably tetrahydrofuran or 1,4-dioxane), N,N-dialkylformamides (preferably dimethyl formamide), N,N-dialkylacetamides (preferably dimethyl acetamide), cyclic amides (preferably N-methylpyrrolidin-2-one), dialkylsulfoxides (preferably dimethylsulfoxide), aromatic hydrocarbons (preferably benzene or toluene), heteroaromatic hydrocarbons (preferably pyridine). Compounds of formula 23b can then be reacted with a halogenating agent or sulfonylating agent in the presence or absence of a base in the presence or absence of an inert solvent at reaction temperatures ranging from -78°C . to 250°C . to afford products of formula 10 (where Z is halogen, alkane sulfonyloxy, aryl sulfonyloxy or haloalkane sulfonyloxy and X is N). Halogenating agents include, but are not limited to, SOCl_2 , POCl_3 , PCl_3 , PCl_5 , POBr_3 , PBr_3 , or PBr_5 . Sulfonylating agents include, but are not limited to, alkanesulfonyl halides or anhydrides (preferably methanesulfonyl chloride or methanesulfonic anhydride), aryl sulfonyl halides or anhydrides (such as p-toluenesulfonyl chloride or anhydride), or haloalkylsulfonyl halides or anhydrides (preferably trifluoromethanesulfonic anhydride). Bases may include, but are not limited to, trialkylamines (preferably N,N-di-isopropyl-N-ethyl amine or triethylamine), bicyclic amidines (preferably DBU), anilines (preferably N-dimethyl aniline), or heteroaromatic amines (preferably pyridine). Inert solvents may include, but are not limited to, lower alkanenitriles (1–6 carbons) (preferably acetonitrile), dialkyl ethers (preferably diethyl ether), cyclic ethers (preferably tetrahydrofuran or 1,4-dioxane), N,N-dialkylformamides (preferably dimethyl formamide), N,N-dialkylacetamides (preferably dimethyl acetamide), cyclic amides (preferably N-methylpyrrolidin-2-one), dialkylsulfoxides (preferably dimethylsulfoxide), aromatic hydrocarbons (preferably benzene or toluene), or haloalkanes with 1–10 carbons and 1–10 halogens (preferably dichloromethane). Preferred reaction temperatures range from -20°C . to 100°C .

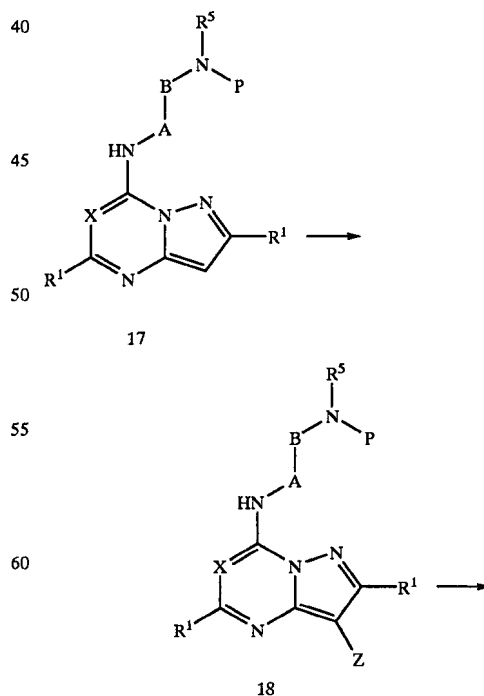
SCHEME 8



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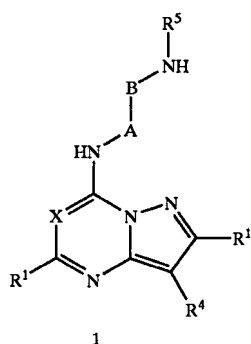
Alternatively, compounds of formula 23b can be obtained by first reacting compounds of formula 22 with compounds of the formula $\text{R}^1-(\text{C}=\text{NH})-\text{OR}^h$, where R^1 is defined above and R^h is a lower alkyl group (preferably methyl or ethyl), in the presence or absence of an acid in an inert solvent to give an intermediate of formula 24. Compounds of formula 24 react with a compound of formula $\text{R}^i-\text{C}=\text{O}-\text{R}^j$, where R^i and R^j are each or independently lower alkoxy (preferably methoxy or ethoxy), 1-imidazolyl, halo, aryloxy (preferably 4-nitrophenoxy) in the presence or absence of an inert solvent to afford compounds of formula 23b. Bases may include, but are not limited to, alkali metals (preferably sodium), alkali metal hydrides (preferably sodium hydride), alkali metal alkoxides (1–6 carbons) (preferably sodium methoxide, sodium ethoxide, or sodium tert-butoxide), alkaline earth metal hydrides, alkali metal dialkylamides (preferably lithium diisopropylamide), alkali metal carbonates, alkali metal hydroxides, alkali metal bis-(trialkylsilyl)amides (preferably lithium or sodium (trimethylsilyl)amide), trialkylamines (preferably N,N-diisopropyl-N-ethyl amine or triethylamine), bicyclic amidines (preferably DBU), or heteroaromatic amines (preferably pyridine). Inert solvents may include, but are not limited to, alkyl alcohols (1–8 carbons) (preferably methanol, ethanol, or tert-butanol), lower alkanenitriles (1–6 carbons) (preferably acetonitrile), water, dialkyl ethers (preferably diethyl ether), cyclic ethers (preferably tetrahydrofuran or 1,4-dioxane), N,N-dialkylformamides (preferably dimethyl formamide), N,N-dialkylacetamides (preferably dimethyl acetamide), cyclic amides (preferably N-methylpyrrolidin-2-one), dialkylsulfoxides (preferably dimethylsulfoxide), aromatic hydrocarbons (preferably benzene or toluene).

SCHEME 9



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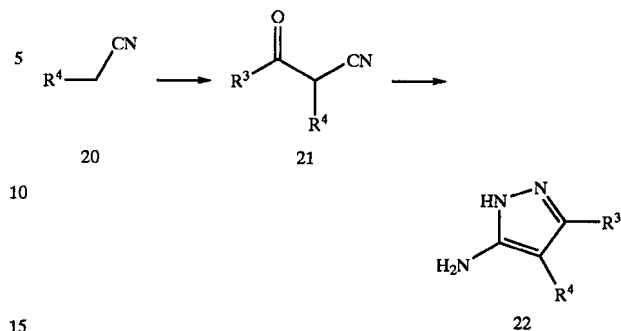
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SCHEME 10



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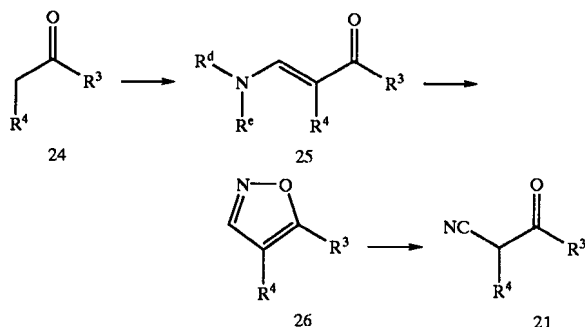
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Compounds of formula I can also be prepared from compounds of formula 17 (prepared using the methods applicable to the synthesis of compounds of formula I), where P is H or an appropriate amino protecting group. Such groups, known in the art of organic synthesis for the protection of amines, include those listed in "Protective Groups in Organic Synthesis", by Greene and Wuts [John Wiley & Sons, NY, 1991]. Examples of amine protecting groups include, but are not limited to, acyl types (such as formyl, trifluoroacetyl, phthalyl, and p-toluenesulfonyl), carbamate types (such as benzyloxycarbonyl, t-butoxycarbonyl, 9-fluorenylmethyloxycarbonyl, allyloxycarbonyl, and 2,2,2-trichloroethyloxycarbonyl), alkyl types (such as benzyl and triphenylmethyl). Reacting compounds of formula 17 with a halogenating agent provides compounds of formula 18 where X is Br, Cl, or I. Compounds of formula 18 react with a compound of formula R^4M (where M is alkali metal, ZnCl, ZnBr, MgBr, MgCl, MgI, CeCl₂, CeBr₂, copper halides, B(OH)₂, B(O-lower alkyl)₂, or Sn(lower alkyl)₃) in the presence or absence of an organometallic catalyst in the presence or absence of a base in an inert solvent at temperatures ranging from -100° C. to 200° C. to give compounds of formula I (or their N-protected forms which can then be deprotected). Similar conditions have been described in WO 98/54093. Those skilled in the art will recognize that the reagents R^4M may be generated in situ. Organometallic catalysts include but are not limited to, palladium phosphine complexes (such as Pd(PPh₃)₄), palladium halides or alkanoates (such as PdCl₂(PPh₃)₂ or Pd(OAc)₂), or nickel complexes (such as NiCl₂(PPh₃)₂). Bases may include, but are not limited to, alkali metal alkoxides (1-6 carbons) (preferably sodium methoxide, sodium ethoxide, or sodium tert-butoxide), alkali metal carbonates or bicarbonates, alkali metal hydroxides, alkali metal phosphates, or trialkylamines (preferably N,N-di-isopropyl-N-ethyl amine or triethylamine). Inert solvents may include, but are not limited to, lower alkanenitriles (1-6 carbons) (preferably acetonitrile), water, dialkyl ethers (preferably diethyl ether), cyclic ethers (preferably tetrahydrofuran or 1,4-dioxane), N,N-dialkylformamides (preferably dimethyl formamide), N,N-dialkylacetamides (preferably dimethyl acetamide), cyclic amides (preferably N-methylpyrrolidin-2-one), dialkylsulfoxides (preferably dimethylsulfoxide), aromatic hydrocarbons (preferably benzene or toluene).

Compounds of formula 22 may be obtained from compounds of formula 20, where R^4 is defined as above. Compounds of formula 20 are reacted with compounds of formula $R^3-C=O-R^c$, where R^3 is defined above and R^c is halogen, cyano, lower alkoxy (1-6 carbons), or lower alkanoyloxy (1-6 carbons), in the presence of a base in an inert solvent at reaction temperatures ranging from -78° C. to 200° C. to afford compounds of formula 21. Bases may include, but are not limited to, alkali metal hydrides (preferably sodium hydride), alkali metal alkoxides (1-6 carbons) (preferably sodium methoxide, sodium ethoxide, or sodium tert-butoxide), alkaline earth metal hydrides, alkali metal dialkylamides (preferably lithium diisopropylamide), alkali metal carbonates, alkali metal hydroxides, alkali metal bis-(trialkylsilyl)amides (preferably lithium or sodium (trimethylsilyl)amide), trialkylamines (preferably N,N-diisopropyl-N-ethyl amine or triethylamine), bicyclic amidines (preferably DBU), or heteroaromatic amines (preferably pyridine). Inert solvents may include, but are not limited to, alkyl alcohols (1-8 carbons) (preferably methanol, ethanol, or tert-butanol), lower alkanenitriles (1-6 carbons) (preferably acetonitrile), water, dialkyl ethers (preferably diethyl ether), cyclic ethers (preferably tetrahydrofuran or 1,4-dioxane), N,N-dialkylformamides (preferably dimethyl formamide), N,N-dialkylacetamides (preferably dimethyl acetamide), cyclic amides (preferably N-methylpyrrolidin-2-one), dialkylsulfoxides (preferably dimethylsulfoxide), aromatic hydrocarbons (preferably benzene or toluene). Alternatively, compounds of formula 20 may be reacted with a solvent of formula $R^3-C=O-R^c$, where R^3 is defined above and R^c is lower alkoxy (1-6 carbons), in the presence of an alkali metal (preferably sodium) at reaction temperatures ranging from -78° C. to 200° C. to afford compounds of formula 21. Compounds of formula 21 may be reacted with hydrazine (hydrate or hydrochloride salt) in an inert solvent, at reaction temperatures ranging from 0° C. to 200° C., preferably 70° C. to 150° C., to afford compounds of formula 22. Inert solvents may include, but are not limited to, water, lower alkanic acids (preferably formic, acetic, or trifluoro acetic acid), alkyl alcohols (1-8 carbons) (preferably methanol or ethanol), lower alkanenitriles (1-6 carbons) (preferably acetonitrile), cyclic ethers (preferably tetrahydrofuran or 1,4-dioxane), N,N-dialkylformamides (preferably dimethyl formamide), N,N-dialkylacetamides (preferably dimethyl acetamide), cyclic amides (preferably N-methylpyrrolidin-2-one), dialkylsulfoxides (preferably dimethylsulfoxide), aromatic hydrocarbons (preferably benzene or toluene).

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SCHEME 11



Alternatively, compounds of formula 21 can be obtained by first reacting compounds of formula 24 with dialkyl formamide dialkyl acetal of formula $(\text{R}^d\text{R}^e)\text{N}-\text{CH}(\text{OR}^f)_2$ where R^d , R^e , and R^f are each or independently $\text{C}_1\text{--C}_6$ lower alkyl (preferably methyl) in the presence or absence of an inert solvent at reaction temperatures ranging from 0°C . to 250°C ., preferably between 70°C . and 150°C . to provide compounds of formula 25. Inert solvents may include, but are not limited to, lower alkanenitriles (1–6 carbons) (preferably acetonitrile), dialkyl ethers (preferably diethyl ether), cyclic ethers (preferably tetrahydrofuran or 1,4-dioxane), N,N-dialkylformamides (preferably dimethyl formamide), N,N-dialkylacetamides (preferably dimethyl acetamide), cyclic amides (preferably N-methylpyrrolidin-2-one), dialkylsulfoxides (preferably dimethylsulfoxide), aromatic hydrocarbons (preferably benzene or toluene), or haloalkanes with 1–10 carbons and 1–10 halogens (preferably dichloromethane). Compounds of formula 25 can be reacted with hydroxylamine salt (preferably hydrochloride) in the presence or absence of an inert solvent at reaction temperatures ranging from 0°C . to 250°C ., preferably between 70°C . and 200°C . to provide oxazoles of formula 26. Inert solvents may include, but are not limited to, alkyl alcohols (1–8 carbons) (preferably methanol, ethanol, or tert-butanol), lower alkanenitriles (1–6 carbons) (preferably acetonitrile), water, dialkyl ethers (preferably diethyl ether), cyclic ethers (preferably tetrahydrofuran or 1,4-dioxane), N,N-dialkylformamides (preferably dimethyl formamide), N,N-dialkylacetamides (preferably dimethyl acetamide), cyclic amides (preferably N-methylpyrrolidin-2-one), dialkylsulfoxides (preferably dimethylsulfoxide), aromatic hydrocarbons (preferably benzene or toluene). Oxazole intermediates of formula 26 can be reacted with a base in the presence or absence of an inert solvent at reaction temperatures ranging from 0°C . to 200°C . Bases may include, but are not limited to, alkali hydroxides (preferably sodium or potassium hydroxide), alkali metal hydrides (preferably sodium hydride), alkali metal alkoxides (1–6 carbons) (preferably sodium methoxide, sodium ethoxide, or sodium tert-butoxide), alkaline earth metal hydrides, alkali metal dialkylamides (preferably lithium diisopropylamide), alkali metal carbonates, alkali metal hydroxides, alkali metal bis-(trialkylsilyl)amides (preferably lithium or sodium (trimethylsilyl)amide), trialkylamines (preferably N,N-diisopropyl-N-ethyl amine or triethylamine), bicyclic amidines (preferably DBU), or heteroaromatic amines (preferably pyridine). Inert solvents may include, but are not limited to, alkyl alcohols (1–8 carbons) (preferably methanol, ethanol, or tert-butanol), lower alkanenitriles (1–6 carbons) (preferably acetonitrile), water, dialkyl ethers (preferably diethyl ether), cyclic ethers (preferably tetrahy-

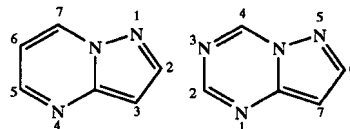
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drofuran or 1,4-dioxane), N,N-dialkylformamides (preferably dimethyl formamide), N,N-dialkylacetamides (preferably dimethyl acetamide), cyclic amides (preferably N-methylpyrrolidin-2-one), dialkylsulfoxides (preferably dimethylsulfoxide), aromatic hydrocarbons (preferably benzene or toluene).

EXAMPLES

The following examples listed in the TABLE are provided to describe the invention in further details. These examples can be prepared by one or more of the above-mentioned method and are intended to illustrate and not to limit the invention.

The numbering system used to describe the compounds of the present invention is as follows:



Commercial reagents were used without further purification. THF refers to tetrahydrofuran. LDA refers to lithium diisopropylamide and DBU refers to 1,8-diazabicyclo[5.4.0]undec-7-ene. Room or ambient temperature refers to 20°C . to 25°C . Concentration implies the use of a rotary evaporator. TLC refers to thin layer chromatography. Mass spectral data were obtained either by CI or APCI methods. Other commonly used abbreviations are: Ph is phenyl, Me is methyl, Et is ethyl, Pr is n-propyl, iPr is isopropyl, Bu is butyl, iBu is isobutyl ($\text{CH}_2\text{--CHMe}_2$), tBu is tert-butyl, cBu is cyclobutyl, Pent is n-pentyl, cPent is cyclopentyl, cHex is cyclohexyl, Py is pyridyl, MeOH means methanol, EtOH means ethanol, EtOAc means ethyl acetate, Et₂O means diethyl ether, CH_2Cl_2 means methylene chloride, DMSO means dimethyl sulfoxide, NMP means N-methyl pyrrolidone, THF means tetrahydrofuran, DMF means dimethyl formamide, EX means example,

Example 1

Preparation of 7-(2-(cyclohexylamino)ethylamino)-2,5-dimethyl-3-(4-chloro-2,6-dimethylphenyl)-pyrazolo[1,5-a] pyrimidine

(formula I where X is CH_3 , R^1 is CH_3 , R^2 is H, A is CH_2 , B is CH_2 , R_3 is CH_3 , R^4 is 2,6-dimethyl-4-chlorophenyl, R^5 is cyclohexyl)

A. 4-Bromo-3,5-dimethyl chlorobenzene

Slurry 2,6-dimethyl-4-chloroaniline hydrochloride (23 g, 193.11 g/mol) in CH_2Cl_2 (100 ml) and wash with saturated NaHCO_3 to generate the free base. Dry over Na_2SO_4 , filter and evaporate down to a violet oil. Slurry up in 120 mL 6.0 N H_2SO_4 and stir vigorously at ambient temperature to break up larger pieces of solid. Cool to 0°C . in an ice/water bath, then portionwise over 15 min add a clear colorless solution of NaNO_2 in 50 mL H_2O . Maintain temperature 15°C . over course of addition, stirring under dry N_2 . After 1 hour, carefully pour the cold reaction solution (solution A) into a second solution (solution B) containing 31.7 g CuBr in 33 mL aqueous HBr (48%) at ambient temperature. Let stand at ambient temperature until gas evolution ceases, then heat to 110°C . under N_2 while stirring. Stir for 3 h, then cool to rt. Extract the aqueous layer with a (2:1) mixture of

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hexanes and Et₂O (2×500 mL), then dry the combined organic layers over Na₂SO₄, filter and evaporate down to a brown oil. Triturate the oil with hexanes (100 mL), filter out the remaining solids and wash with copious amounts of hexanes. Evaporate the hexane layers to concentrate then flush through a pad of silica to remove baseline material, using hexanes as eluent. Evaporate to a clear colorless oil (13.5 g).

B. 4-Chloro-2,6-dimethyl benzaldehyde

Dissolve 4-bromo-3,5-dimethyl chlorobenzene (6.5 g) in 50 mL anhydrous THF and cool to -78° C. (dry ice/acetone) under N₂. Dropwise over 5 min add a solution of butyllithium (12.50 mL, 2.5M in hexanes) to the stirring solution of aryl bromide at -78° C. After 2 h, dropwise add anhydrous DMF (5.0 mL) to the orange/red reaction solution and allow to warm to ambient temperature overnight while stirring under N₂. Evaporate the yellow solution down to a yellow oil and partition between H₂O (100 mL) and CH₂Cl₂ (100 mL). Extract the aqueous layer once with CH₂Cl₂, then pool the organic layers and dry over Na₂SO₄, filter and evaporate down to 5.0 g of yellow oil. Use without further purification. LCMS=169.6 (MH⁺).

C. 4-Chloro-2,6-dimethyl benzyl alcohol

Dissolve 4-chloro-2,6-dimethyl benzaldehyde (5.0 g, 168.64 g/mol) in 100 mL dry MeOH. Cool to 0° C. while stirring under N₂. Portionwise add powdered NaBH₄ (0.76 g, 37.85 g/mol) over 5 min. Stir at 0° C. for 2 h, monitoring by TLC until aldehyde consumed, then evaporate to a yellow oil. Add H₂O (50 mL) and bring to pH 7.0 by addition of saturated NH₄Cl. Extract the neutral aqueous layer with CH₂Cl₂ (3×75 mL) and dry the pooled organic layers over Na₂SO₄. Filter and concentrate to a yellow oil. Flush through a pad of silica to remove baseline material, then evaporate to a yellow solid (3.0 g) which can be used without further purification. LCMS=171.6 (MH⁺), 169.6 (M⁻).

D. 4-Chloro-2,6-dimethyl phenyl acetonitrile

Dissolve 4-chloro-2,6-dimethyl benzyl alcohol (2.8 g, 170.66 g/mol) in CH₂Cl₂ (25 mL) and cool to 0° C. under N₂. Dropwise add thionyl chloride (2.4 mL, 3.90 g, 118.9 g/mol) in 10 mL CH₂Cl₂ while stirring under N₂. After 2 h, monitoring by TLC (alcohol Rf=0.35, chloride Rf=1.0; using 20% EtOAc/80% hexanes as eluent), quench the reaction carefully by addition of saturated NaHCO₃ (100 mL) and stir until gas evolution ceases. Separate layers, then extract the aqueous layer with CH₂Cl₂ (100 mL). Pool the organic layers, dry over Na₂SO₄, filter and evaporate to a pale yellow oil. Take up in DMSO (25 mL), add solid NaCN (1.25 g, 49.011 g/mol) and heat to 60° C. while stirring under N₂. Stir 2 h until chloride consumed (TLC; chloride Rf=1.0, nitrile Rf=0.6; using 20% EtOAc/80% hexanes as eluent), then cool to rt. Add 2.0 N NaOH (150 mL) and stir until orange precipitate forms, then filter and wash solid with H₂O. Dissolve solid in CH₂Cl₂, wash with H₂O, the dry over Na₂SO₄. Filter the organic layer and evaporate to an orange oil which crystallizes upon standing at ambient temperature. (2.3 g). LCMS=180.2 (MH⁺), 178.2 (M⁻).

E. 2-(4-Chloro-2,6-dimethylphenyl)-3-oxobutanenitrile

Dissolve 4-chloro-2,6-dimethyl phenyl acetonitrile (2.3 g, 179.2 g/mol) in 15 mL EtOAc and add sodium metal (0.35

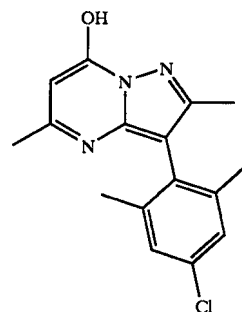
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g, pea-sized fragments). Heat to reflux (90° C. bath temperature) under N₂ overnight. Evaporate down to solid and slurry up in Et₂O (100 mL); stir vigorously to break up fragments. Filter and wash solid with copious amounts of Et₂O. Dissolve solid in H₂O to form a clear yellow solution, and add 1.0 N HCl (100 mL) to pH 1. Extract the resulting cloudy solution with CH₂Cl₂ (3×100 mL) until aqueous layer is clear. Pool and dry the organic layers over Na₂SO₄, filter and evaporate to yellow oil (1.8 g). TLC: Rf=0.2 using 20% EtOAc/80% hexanes as eluent. LCMS=222.3 (MH⁺); 220.2 (M⁻).

F. 5-Amino-4-(4-chloro-2,6-dimethylphenyl)-3-methylpyrazole

Dissolve anhydrous hydrazine (0.91 g, 0.90 mL) in 20 mL toluene. Add glacial acetic acid (2.25 mL) and allow to stand at ambient temperature for 10 min until solution becomes cloudy white. Add a solution of 2-(4-chloro-2,6-dimethylphenyl)-3-oxobutanenitrile in 10 toluene, rinsing out the ketonitrile flask with an additional 5 mL toluene. Heat to reflux under N₂ (130° C.) with Dean-Stark trap attached. Water will begin to accumulate after 10 min or so. After 2 h, evaporate down and partition between 1.0 N NaOH (100 mL) and EtOAc (100 mL). Extract aqueous layer with EtOAc (2×100 mL), then pool the organic layers and dry over Na₂SO₄. Filter and evaporate to yellow oil (1.75 g). Use without further purification. LCMS=236.5 (MH⁺); 234.5 (M⁻).

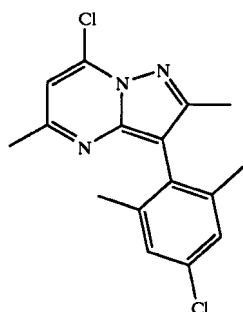
G. 7-Hydroxy-2,5-dimethyl-3-(4-chloro-2,6-dimethylphenyl)-pyrazolo[1,5-a]pyrimidine



Dissolve 5-amino-4-(4-chloro-2,6-dimethylphenyl)-3-methylpyrazole in 20 mL glacial acetic acid at ambient temperature, and add ethyl acetoacetate (2.0 mL, 1.99 g). Heat to reflux (130° C.) under N₂ overnight. Evaporate down to concentrate and add 200 mL Et₂O to precipitate out product. Stir at ambient temperature for 1 hour, then filter and wash the resulting white solid (1.25 g) with copious amounts of Et₂O. LCMS=302.2 (MH⁺); 300.2 (M⁻).

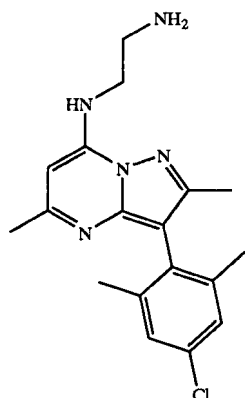
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H. 7-Chloro-2,5-dimethyl-3-(4-chloro-2,6-dimethylphenyl)-pyrazolo[1,5-a]pyrimidine



Slurry 7-hydroxy-2,5-dimethyl-3-(4-chloro-2,6-dimethylphenyl)-pyrazolo[1,5-a] pyrimidine in 10 mL POCl_3 and reflux at 130°C . under N_2 . After 2 h, monitoring by TLC (alcohol $R_f=0.5$, chloride $R_f=1.0$; EtOAc as eluent), quench the reaction carefully at ambient temperature by diluting with 50 mL CH_2Cl_2 and pouring slowlyj into non-stirring saturated NaHCO_3 . Adjust stirring speed to control rate of quenching of residual POCl_3 and stir until gas evolution ceases. Separate the layers and extract the aqueous layer with CH_2Cl_2 (2x50 mL). Pool the organic layers and dry over Na_2SO_4 . Filter and evaporate to yellow oil, which is used directly without further purification.

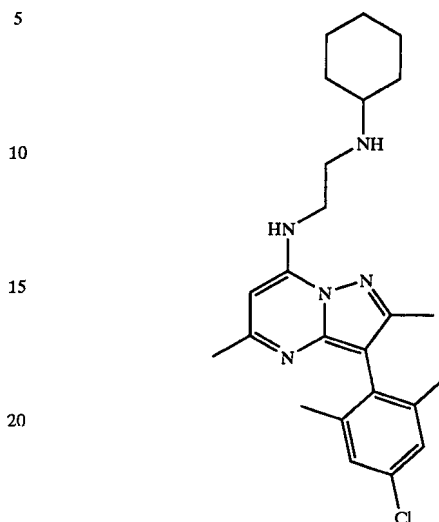
I. 7-(2-aminoethylamino)-2,5-dimethyl-3-(4-chloro-2,6-dimethylphenyl)-pyrazolo[1,5-a] pyrimidine



Dissolve 7-chloro-2,5-dimethyl-3-(4-chloro-2,6-dimethylphenyl)-pyrazolo[1,5-a] pyrimidine in 25 mL CH_3CN , then add excess ethylenediamine (5 mL) and heat to 80°C . for 3–6 h under N_2 with attached reflux condenser. (TLC; product diamine $R_f=0.5$, aryl chloride $R_f=1.0$; [10% (2.0M NH_3 in MeOH)/90% CH_2Cl_2] as eluent). Cool to ambient temperature and evaporate to yellow oil. Partition between CH_2Cl_2 (50 mL) and 1.0 N NaOH (50 mL), and extract aqueous layer 2x30 mL CH_2Cl_2 . Pool organic layers, dry over Na_2SO_4 , filter and evaporate to yellow-white foam (1.25 g). Use without further purification. LCMS=344.4 (MH^+); 342.3 (M^-).

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J. 7-(2-(Cyclohexylamino)ethylamino)-2,5-dimethyl-3-(4-chloro-2,6-dimethylphenyl)-pyrazolo[1,5-a] pyrimidine



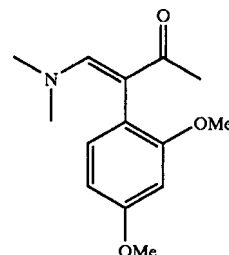
Dissolve 7-(2-aminoethylamino)-2,5-dimethyl-3-(4-chloro-2,6-dimethylphenyl)-pyrazolo [1,5-a] pyrimidine (0.183 g, 5.4×10^{-4} mol, 339.2 g/mol) in dichloroethane (5 mL) and add cyclohexanone (100.12 g/mol) and sodium triacetoxyborohydride (0.172 g, 211.94 g/mol). To the resultant slurry, add glacial acetic acid (0.032 mL, 5.4×10^{-4} mol) and stir at ambient temperature under N_2 for 3 h. Partition between CH_2Cl_2 (3 mL) and 1.0 N NaOH (10 mL), then separate the layers and chromatograph the CH_2Cl_2 layer using [10% (2.0M NH_3 in MeOH)/90% CH_2Cl_2] as eluent. Obtained 0.16 g white solid-foam upon evaporation.

Example 2

Preparation of 7-(2-(cyclopentylamino)ethylamino)-3-(2,4-dimethoxyphenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidine

(formula I where X is CH_3 , R^1 is CH_3 , R^2 is H, A is CH_2 , B is CH_2 , R^3 is CH_3 , R^4 is 2,4-dimethoxyphenyl, R^5 is cyclopentyl)

A. (3E)-3-(2,4-dimethoxyphenyl)-4-(dimethylamino)but-3-en-2-one



Dissolve 1-(2,4-dimethoxyphenyl)acetone (1.0 g, 5.15 mmol, 194.23 g/mol) in DMF-diethyl acetal (4.5 mL, 25.7 mmol, 147.22 g/mol) and stir under N_2 at 100°C . overnight. TLC using 20% EtOAc/80% hexanes; (ketone $R_f=0.25$, product $R_f=0.0$). Evaporate to thick oil, dissolve in EtOAc (25 mL) and wash with H_2O (3x25 mL). Extract pooled H_2O

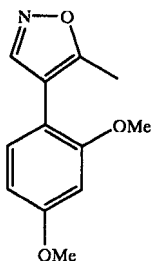
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layers with EtOAc. Dry pooled organic layers over Na_2SO_4 , filter and evaporate to thick oil which solidifies upon standing at ambient temperature (0.98 g). Use without further purification. LCMS=250.2 (MH^+); 248.2 (M^-).

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B. 4-(2,4-Dimethoxyphenyl)-5-methyl-isoxazole



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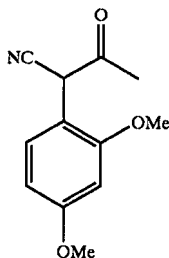
Dissolve (3E)-3-(2,4-dimethoxyphenyl)-4-(dimethylamino)but-3-en-2-one (5.1 g, 20.6 mmol) in EtOH (50 mL) and add $\text{NH}_2\text{OH}\cdot\text{HCl}$ (3.05 g, 44.0 mmol). Heat to reflux under N_2 for 20 min. Cool and evaporate to red-brown oil. Dissolve in CH_2Cl_2 , dry over Na_2SO_4 , filter and concentrate to red-brown oil (4.4 g). Use without further purification. LCMS=220.2 (MH^+); 218.2 (M^-).

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C. 2-(2,4-Dimethoxyphenyl)-3-oxobutanenitrile

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Slurry 4-(2,4-dimethoxyphenyl)-5-methyl-isoxazole (4.4 g) in 1.0 N NaOH (35 mL) and add 35 mL MeOH to dissolve. Heat at 60°C under N_2 for 1 hour, then cool to

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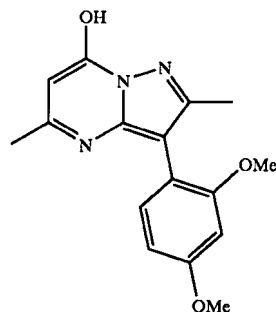
D. 5-Amino-4-(2,4-dimethoxyphenyl)-3-methylpyrazole

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This compound was prepared as described in Example 1F.

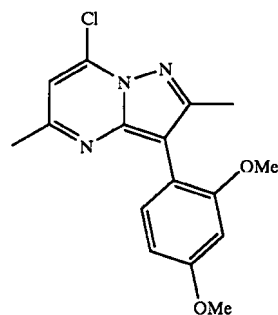
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E. 7-Hydroxy-2,5-dimethyl-3-(2,4-dimethoxyphenyl)-pyrazolo[1,5-a]pyrimidine



This compound was prepared as described in Example 1G.

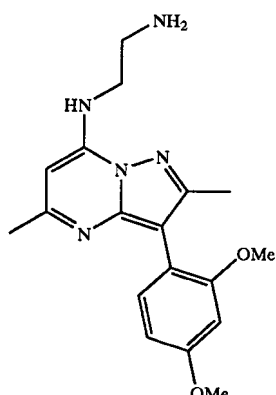
F. 7-Chloro-2,5-dimethyl-3-(2,4-dimethoxyphenyl)-pyrazolo[1,5-a]pyrimidine



Slurry 7-hydroxy-2,5-dimethyl-3-(2,4-dimethoxyphenyl)-pyrazolo[1,5-a] pyrimidine in 10 mL POCl_3 and reflux at 130°C under N_2 . After 2 h, monitoring by TLC (alcohol Rf =0.5, chloride Rf =1.0; EtOAc as eluent), quench the reaction carefully at ambient temperature by diluting with 50 mL CH_2Cl_2 and pouring slowly into non-stirring saturated NaHCO_3 . Adjust stirring speed to control rate of quenching of residual POCl_3 and stir until gas evolution ceases. Separate the layers and extract the aqueous layer with CH_2Cl_2 (2x50 mL). Pool the organic layers and dry over Na_2SO_4 . Filter and evaporate to yellow oil, which is used directly without further purification.

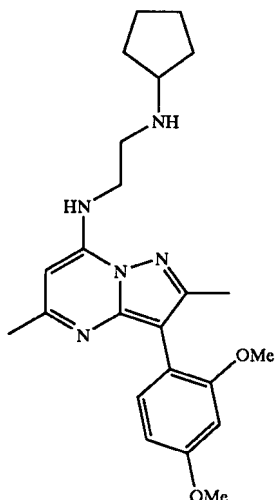
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G. 7-(2-aminoethylamino)-2,5-dimethyl-3-(2,4-dimethoxyphenyl)-pyrazolo[1,5-a] pyrimidine



Dissolve 7-chloro-2,5-dimethyl-3-(2,4-dimethoxyphenyl)-pyrazolo[1,5-a] pyrimidine in 25 mL CH₃CN, then add excess ethylenediamine (5 mL) and heat to 80° C. for 3–6 h under N₂ with attached reflux condenser. (TLC: [10% (2.0M NH₃ in MeOH)/90% CH₂Cl₂] as eluent). Cool to ambient temperature and evaporate to yellow oil. Partition between CH₂Cl₂ (50 mL) and 1.0 N NaOH (50 mL), and extract aqueous layer 2x30 mL CH₂Cl₂. Pool organic layers, dry over Na₂SO₄, filter and evaporate to yellow-white foam. Use without further purification.

H. 7-(2-(cyclopentylamino)ethylamino)-3-(2,4-dimethoxyphenyl)-2,5-dimethyl-pyrazolo[1,5-a] pyrimidine



This compound was prepared as described in Example 1J.

Example 3

Preparation of 7-(2-(cyclopentylamino)ethylamino)-2,5-dimethyl-3-(2,6-dimethyl-4-methoxyphenyl)-pyrazolo[1,5-a] pyrimidine

(formula I where X is CH, R¹ is CH₃, R² is H, A is CH₂, B is CH₂, R³ is CH₃, R⁴ is 2,4-dimethyl-4-methoxyphenyl, R⁵ is cyclopentyl)

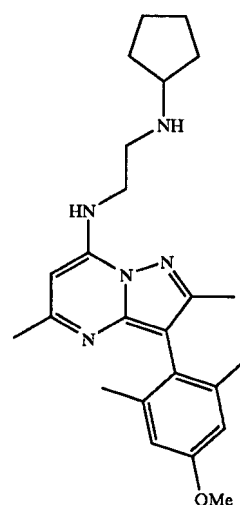
A. 4-Methoxy-2,6-dimethyl phenyl acetonitrile

Dropwise add a solution of chlorotrimethylsilane (20 mL) in CH₂Cl₂ (40 mL) to a stirred solution cooled to 0° C. of

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4-methoxy-2,6-dimethyl benzyl alcohol (approx. 74 mmol) in 300 mL CH₂Cl₂. Solution changes color from colorless to yellow and then to purple over the course of the reaction. After 2 h, monitoring by TLC (alcohol R_f=0.25, chloride R_f=0.95; using 20% EtOAc/80% hexanes as eluent), evaporate down to a yellow oil. Dissolve in dry DMF (50 mL) and cool to 0° C. under N₂. Add freshly ground NaCN (7.0 g) portionwise over 5 minute (exothermic) to the stirring reaction, forming a yellow/white slurry. Stir for 5–8 h at 0° C. until no starting material remains, as determined by TLC (nitrile R_f=0.5; using 20% EtOAc/80% hexanes as eluent). Partition the reaction solution between EtOAc (100 mL) and 0.1 N NaOH (300 mL). Dry the EtOAc layer over Na₂SO₄, filter and evaporate to yellow oil. Chromatograph in 10% EtOAc/90% hexanes on silica to remove residual chloride and evaporate to 2.1 g yellow solid; clean by TLC. LCMS= 176.5 (MII⁺), 174.4 (M⁺).

B. 7-(2-(Cyclopentylamino)ethylamino)-2,5-dimethyl-3-(2,6-dimethyl-4-methoxyphenyl)-pyrazolo[1,5-a] pyrimidine



7-(2-(cyclopentylamino)ethylamino)-2,5-dimethyl-3-(2,6-dimethyl-4-methoxyphenyl)-pyrazolo[1,5-a] pyrimidine is obtained from 4-methoxy-2,6-dimethyl phenyl acetonitrile using the procedures described in EXAMPLE 1 E, F, G, H, I, and J.

Example 4

Preparation of 7-(2-(cyclopentylamino)ethylamino)-2-trifluoromethyl-5-methyl-3-(2,4-dichlorophenyl)-pyrazolo[1,5-a] pyrimidine

(formula I where X is CH, R¹ is CH₃, R² is H, A is CH₂, B is CH₂, R³ is CF₃, R⁴ is 2,4-dichlorophenyl, R⁵ is cyclopentyl)

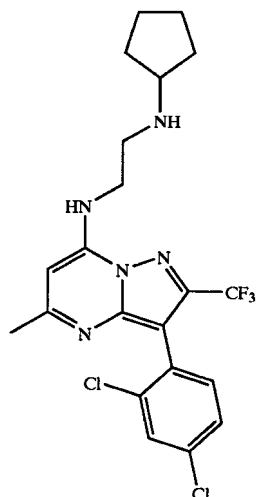
A. 2-(2,4-Dichlorophenyl)-4,4,4-trifluoro-3-oxobutanenitrile

Slurry 2,4-dichlorophenylacetonitrile (I) (5.0 g, 26.9 mmol, 186.04 g/mol) in ethyl trifluoroacetate (6.4 mL, 7.6 g, 142.08 g/mol) and add 20 mL anhydrous THF. Portionwise at ambient temperature add NaH (1.88 g, 47.1 mmol, 60% in mineral oil) over 5 min. Heat reaction to reflux (90° C. bath temperature) overnight. Evaporate to thick red-brown oil and partition between Et₂O (100 mL) and H₂O (60 mL).

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Separate layers and extract H₂O with Et₂O (2×75 mL). Acidify the aqueous layer with 1.0 N HCl to pH 1 (becomes cloudy white suspension) and extract aqueous layer with CH₂Cl₂ (3×100 mL). Dry pooled CH₂Cl₂ layers over Na₂SO₄, filter and concentrate to yellow oil (7.5 g, 26.5 mmol). Use without further purification. LCMS=281.9 (MH⁺); 279.8 (M⁻).

B. 7-(2-(Cyclopentylamino)ethylamino)-2-trifluoromethyl-2-methyl-3-(2,4-dichlorophenyl)-pyrazolo[1,5-a] pyrimidine



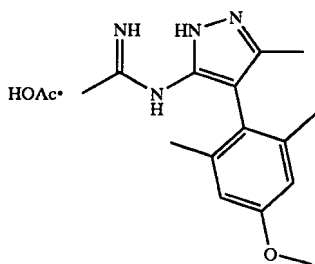
7-(2-(Cyclopentylamino)ethylamino)-2-trifluoromethyl-5-methyl-3-(2,4-dichlorophenyl)-pyrazolo[1,5-a] pyrimidine is obtained from 2-(2,4-dichlorophenyl)-4,4,4-trifluoro-3-oxobutanenitrile using the procedures described in EXAMPLE 1 F, G, H, I, and J.

Example 5

Preparation of 7-(2-(cyclopentylamino)ethylamino)-2,5-dimethyl-3-(4-methoxy-2,6-dimethylphenyl)-[1,5-a]-pyrazolo-1,3,5-triazine

(formula I where X is N, R¹ is CH₃, R² is H, A is CH₂, B is CH₂, R³ is CH₃, R⁴ is 2,6-dimethyl-4-methoxyphenyl, R⁵ is cyclopentyl)

A. (Iminoethyl)[4-(4-methoxy-2,6-dimethylphenyl)-3-methylpyrazol-5-yl]amine acetate salt

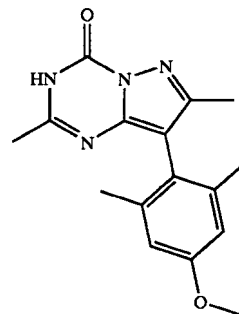


To a solution of 5-amino-4-(4-methoxy-2,6-dimethylphenyl)-3-methylpyrazole (1.89 g) in acetonitrile (30 mL) add ethylacetimidate (free base, 1.8 mL) followed by acetic acid (0.47 mL). Collect the precipitate that formed

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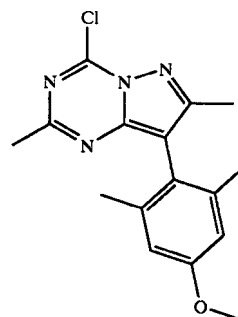
upon stirring overnight by filtration. Wash the solid with dry ether and dry to afford 2.61 g of (iminoethyl)[4-(4-methoxy-2,6-dimethylphenyl)-3-methylpyrazol-5-yl]amine acetate salt as a white powder.

B. 2,6-Dimethyl-7-(2,6-dimethyl-4-methoxyphenyl)-3H-[1,5-c]-pyrazolo-1,3,5-triazin-4-one



Add sodium pieces (1.81 g) to a flask containing anhydrous ethanol and equipped with a reflux condenser. Allow the mixture to stir until all the sodium is consumed and then add the amidine (2.61 g as the acetate salt) from step A in one portion. Add diethyl carbonate (7.6 mL) and reflux the mixture overnight. Concentrate the mixture under reduced pressure, dissolve the residue in water (75 mL) and adjust the pH to 5 with 3N HCl. Extract the aqueous mixture with EtOAc and wash the extracts with brine, dry over anhydrous sodium sulfate, and concentrate in vacuo to obtain a foam. Stir the residue with hexanes for 20 min and collect the solid by filtration, then wash with hexanes to obtain 2.01 g of 2,6-dimethyl-7-(2,6-dimethyl-4-methoxyphenyl)-3H-[1,5-c]-pyrazolo-1,3,5-triazin-4-one as a yellow powder: MS 299 (M+H).

C. 4-Chloro-2,6-dimethyl-7-(2,6-dimethyl-4-methoxyphenyl) [1,5-a]-pyrazolo-1,3,5-triazine

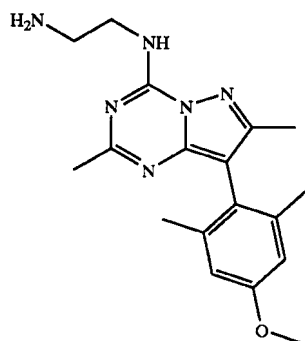


Dissolve 2,6-dimethyl-7-(2,6-dimethyl-4-methoxyphenyl)-3H-[1,5-c]-pyrazolo-1,3,5-triazin-4-one from step B (1 g) in POCl₃ (50 mL) and add N,N-dimethylaniline (0.55 mL). Reflux the reaction mixture under a dry nitrogen atmosphere for 18 h at which time concentrate the mixture under reduced pressure. Dissolve the residue in EtOAc and wash with a saturated aqueous NaHCO₃ solution, then with brine. Dry the organic layer over anhydrous sodium sulfate, filter and concentrate under reduced pressure to obtain 4-chloro-2,6-dimethyl-7-(2,6-dimethyl-4-methoxyphenyl) [1,5-a]-pyrazolo-1,3,5-triazine as a dark oil. MS 317 (M+H).

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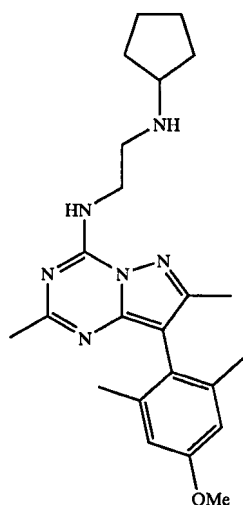
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D. 2,6-Dimethyl-7-(2,6-dimethyl-4-methoxyphenyl)-4-(2-aminoethyl)amino-[1,5-a]-pyrazolo-1,3,5-triazine



Dissolve 4-chloro-2,6-dimethyl-7-(2,6-dimethyl-4-methoxyphenyl) [1,5-a]-pyrazolo-1,3,5-triazine in dry toluene (10 mL) to form a stock solution of the chloride (~0.34 M). Add a portion of this solution (8 mL) dropwise into a stirring solution of ethylenediamine (3.6 mL) in acetonitrile (50 mL) which is heated to 60° C. After 3 h at 60° C., cool the solution, concentrate under reduced pressure, dilute with 10% NaOH and extract with EtOAc. Wash the combined extracts with brine, dry over anhydrous sodium sulfate and concentrate under reduced pressure to obtain a yellow residue. Triturate the residue with 20% EtOAc/hexanes and collect the resulting solid by filtration to obtain 0.72 g of 2,6-dimethyl-7-(2,6-dimethyl-4-methoxyphenyl)-4-(2-aminoethyl)amino-[1,5-a]-pyrazolo-1,3,5-triazine as a yellow solid: MS 341 (M+H).

E. 7-(2-(Cyclopentylamino)ethylamino)-2,5-dimethyl-3-(4-methoxy-2,6-dimethylphenyl)-[1,5-a]-pyrazolo-1,3,5-triazine



Dissolve 2,6-dimethyl-7-(2,6-dimethyl-4-methoxyphenyl)-4-(2-aminoethyl)amino-[1,5-a]-pyrazolo-1,3,5-triazine from step D (0.211 g) in dry dichloroethane (15 mL) and add cyclopentanone (1 equiv). Add acetic acid (35 μ L) followed by sodium triacetoxyborohydride (0.184 g) and stir the resulting homogeneous mixture overnight at ambient temperature. Dilute the reaction mixture with 4 volumes of CH_2Cl_2 , wash with brine, dry over anhydrous

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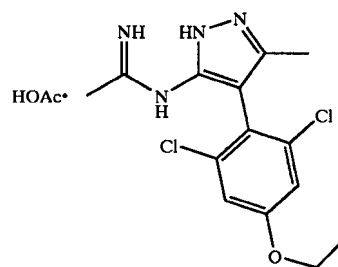
sodium sulfate, and concentrate under reduced pressure to obtain a yellow solid. Purify using preparative thin-layer chromatography [10% MeOH(2N NH_3)/ CH_2Cl_2] to obtain 7-(2-(cyclopentylamino)ethylamino)-2,5-dimethyl-3-(4-methoxy-2,6-dimethylphenyl)-[1,5-a]-pyrazolo-1,3,5-triazine.

Example 6

Preparation of 7-(2-(cyclopentylamino)ethylamino)-2,5-dimethyl-3-(4-ethoxy-2,6-dichlorophenyl)-[1,5-a]-pyrazolo-1,3,5-triazine

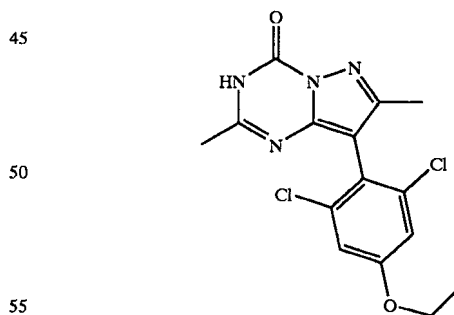
formula I where X is N, R^1 is CH_3 , R^2 is H, A is CH_2 , B is CH_2 , R^3 is CH_3 , R^4 is 2,6-dichloro-4-ethoxyphenyl, R^5 is cyclopentyl

A. (Iminoethyl)[4-(4-ethoxy-2,6-dichlorophenyl)-3-methylpyrazol-5-yl]amine acetate salt



To a solution of 5-amino-4-(4-ethoxy-2,6-dichlorophenyl)-3-methylpyrazole (4.8 g) in acetonitrile (50 mL) add ethylacetimidate (free base, 2.3 mL) followed by acetic acid (0.96 mL). Collect the precipitate that formed upon stirring overnight by filtration. Wash the solid with dry ether and dry to afford 5.02 g of (iminoethyl)[4-(4-ethoxy-2,6-dichlorophenyl)-3-methylpyrazol-5-yl]amine acetate salt as a white powder.

B. 2,6-Dimethyl-7-(2,6-dichloro-4-ethoxyphenyl)-3H-[1,5-c]-pyrazolo-1,3,5-triazin-4-one



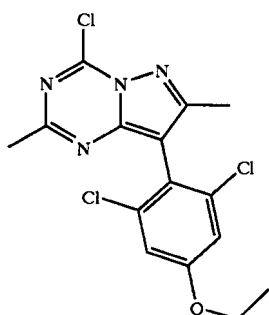
Add sodium pieces (2.98 g) to a flask containing anhydrous ethanol and equipped with a reflux condenser. Allow the mixture to stir until all the sodium is consumed and then add the amidine (5.02 g as the acetate salt) from step A in one portion. Add diethyl carbonate (12.6 mL) and reflux the mixture for four h. Concentrate the mixture under reduced pressure, dissolve the residue in water (75 mL) and adjust the pH to 5 with 3N HCl. Extract the aqueous mixture with EtOAc and wash the extracts with brine, dry over anhydrous sodium sulfate, and concentrate in vacuo to obtain a foam.

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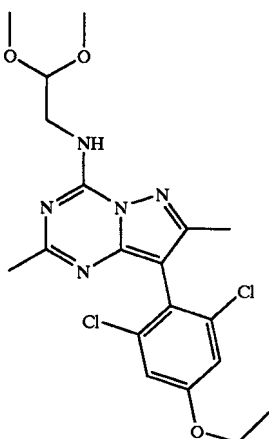
Stir the residue with hexanes for 20 min and collect the solid by filtration, then wash with hexanes to obtain 4.41 g of 2,6-dimethyl-7-(2,6-dichloro-4-ethoxyphenyl)-3H-[1,5-c]-pyrazolo-1,3,5-triazin-4-one as a beige solid: MS 353 (M+H).

C. 4-Chloro-2,6-dimethyl-7-(2,6-dichloro-4-ethoxyphenyl) [1,5-a]-pyrazolo-1,3,5-triazine



Dissolve 2,6-dimethyl-7-(2,6-dichloro-4-ethoxyphenyl)-3H-[1,5-c]-pyrazolo-1,3,5-triazin-4-one from step B (1.05 g) in POCl₃ (50 mL) and add 2,6-lutidine (0.45 mL). Reflux the reaction mixture under a dry nitrogen atmosphere for 48 h and then concentrate the mixture under reduced pressure. Dissolve the residue in EtOAc and wash with a saturated aqueous NaHCO₃ solution, then with brine. Dry the organic layer over anhydrous sodium sulfate, filter and concentrate under reduced pressure to obtain an oil which crystallizes upon standing. Wash the solid with hexanes to remove residual 2,6-lutidine and collect the solid on a sintered glass funnel yielding 4-chloro-2,6-dimethyl-7-(2,6-dichloro-4-ethoxyphenyl) [1,5-a]-pyrazolo-1,3,5-triazine. MS 372 (M+H).

D. 2,6-Dimethyl-7-(2,6-dichloro-4-ethoxyphenyl)-4-(2,2-dimethoxyethyl)amino-[1,5-a]-pyrazolo-1,3,5-triazine

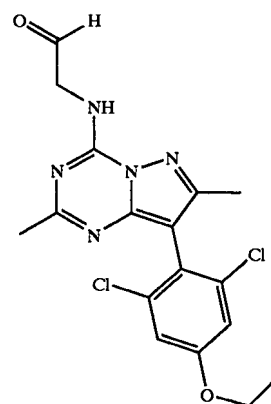


Dissolve the product from step C in dry acetonitrile and then add 2.1 equivalents of aminoacetaldehyde dimethyl acetal. Heat the solution to 60° C. and stir under a dry nitrogen atmosphere for 2–6 h. Remove the solvent under reduced pressure, dilute with 10% NaOH and extract with EtOAc. Wash the combined extracts with brine, dry over anhydrous sodium sulfate and concentrate under reduced

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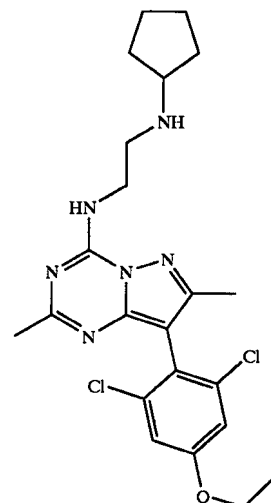
pressure to obtain a yellow oil which crystallizes upon standing. The product, 2,6-dimethyl-7-(2,6-dichloro-4-ethoxyphenyl)-4-(2,2-dimethoxyethyl)amino-[1,5-a]-pyrazolo-1,3,5-triazine, is used without further purification. MS (M+H).

E. 2-[[7-(2,6-dichloro-4-ethoxyphenyl)-2,5,6-trimethyl-3-pyrazolino[2,3-a]1,3,5-triazin-4-yl]amino]ethanal



Dissolve the product obtained from step D in neat trifluoroacetic acid (25 mL). After allowing the mixture to stand at ambient temperature for 0.5 h, concentrate the mixture under reduced pressure. Add saturated aqueous sodium bicarbonate and stir the resulting heterogeneous mixture for 0.5 h. Extract the aqueous solution with EtOAc, wash the EtOAc extracts with brine and then dry over anhydrous sodium sulfate. Evaporation of the solvent under reduced pressure yields the aldehyde as an off-white foam. ¹H NMR (CDCl₃): δ 9.79 (s, 1H, CHO).

F. 7-(2-(Cyclopentylamino)ethylamino)-2,5-dimethyl-3-(4-ethoxy-2,6-dichlorophenyl)-[1,5-a]-pyrazolo-1,3,5-triazine



Dissolve the aldehyde (62 mg, 0.16 mmol) obtained from step E in dry dichloroethane (4 mL). Add 1.1 equivalents of cyclopentylamine followed by 1 equivalent of acetic acid. After the addition of sodium triacetoxyborohydride (1.4 eq), stir the solution at ambient temperature for several h. Dilute

the reaction mixture with 4 volumes of CH_2Cl_2 then wash the mixture with brine (1x), dry over anhydrous Na_2SO_4 . Concentrate under reduced pressure. Preparative thin layer chromatography [10% $\text{MeOH}(2\text{N } \text{NH}_3)/\text{CH}_2\text{Cl}_2$] of the oily residue yields 7-(2-(cyclopentylamino)ethylamino)-2,5-dimethyl-3-(4-ethoxy-2,6-dichlorophenyl)-[1,5-a]-pyrazolo-1,3,5-triazine.

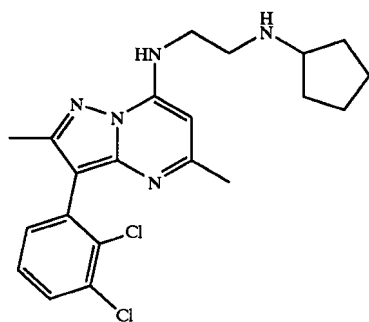
The preparation of the compounds of the present invention by the above-mentioned methods is illustrated further by the following examples, delineated in the TABLE which are not to be construed as limiting the invention in scope or spirit to the specific procedures and compounds described in them. Commonly used abbreviations are: Ph is phenyl, Me is methyl, Et is ethyl, Pr is n-propyl, iPr is isopropyl, cPr is cyclopropyl, Bu is butyl, iBu is isobutyl ($\text{CH}_2\text{---CHMe}_2$), tBu is tert-butyl, cBu is cyclobutyl, Pent is n-pentyl, cPent is cyclopentyl, cHex is cyclohexyl, Py is pyridyl, Bn is benzyl (CH_2Ph), Ac is acetyl ($\text{CH}_3\text{---(C=O)}$), tBOC is tert-butyloxycarbonyl (tBuO---(C=O)). EX means example.

By way of further exemplification, details of the preparation used in Example 14 which is included in the Table are as follows:

Example 14

Preparation of N-cyclopentyl-N'-[3-(2,3-dichlorophenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-yl]-ethane-1,2-diamine hydrochloride salt

formula I where X is CH, R^1 is CH_3 , R^2 is H, A is CH_2 , B is CH_2 , R^3 is CH_3 , R^4 is 2,3-dichloro-4-ethoxyphenyl, R^5 is cyclopentyl, R^6 is H



A. 7-Chloro-2,5-dimethyl-pyrazolo[1,5-a]pyrimidine

2,5-Dimethyl-4H-pyrazolo[1,5-a]pyrimidin-7-one (3.5 g, 21 mmol) in phosphorus oxychloride (20 mL) was stirred at reflux. After 3 hours the dark purple reaction was cooled and then extracted from ice water with ethyl acetate. The combined organic layers were washed with water and saturated aqueous sodium bicarbonate, dried (Na_2SO_4) and then concentrated under reduced pressure to give the title compound (3.0 g, 77%) as a brown solid: +APCI MS ($\text{M}+1$)⁺ 182; ^1H NMR (CDCl_3) δ : 6.74 (s, 1H), 6.42 (s, 1H), 2.55 (s, 3H), 2.53 (s, 3H).

B. N-(2,5-Dimethyl-pyrazolo[1,5-a]pyrimidin-7-yl)-ethane-1,2-diamine

To a stirred solution of 7-chloro-2,5-dimethyl-pyrazolo[1,5-a]pyrimidine (3.0 g, 16.5 mmol) in ethanol (60 mL) was added ethylene diamine (4 mL, 60 mmol). After refluxing 18 hours the reaction was cooled, poured into saturated aqueous

sodium bicarbonate, and then washed with ethyl acetate. The aqueous layer was then extracted with 3:7 isopropyl alcohol/chloroform, the combined extracts were dried (Na_2SO_4) and then concentrated under reduced pressure to give the title compound as an amorphous brown solid (3.2 g, 94%): +APCI MS ($\text{M}+1$)⁺ 206; ^1H NMR (methanol- d_4) δ : 6.05 (s, 1H), 6.00 (s, 1H), 3.45 (m, 2H), 2.91 (m, 2H).

C. N-Cyclopentyl-N'-(2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-yl)-ethane-1,2-diamine

To a stirred solution of N-(2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-yl)-ethane-1,2-diamine (3.2 g, 16 mmol) and cyclopentanone (2.7 mL, 30 mmol) in methanol (30 mL)/acetic acid (3 mL) was added sodium cyanoborohydride (0.94 g, 15 mmol), portionwise. After stirring 1 hour the reaction was concentrated under reduced pressure and then extracted from saturated aqueous sodium bicarbonate with ethyl acetate. The combined extracts were dried (Na_2SO_4), concentrated under reduced pressure to give the crude product as a brown oil (5.6 g): +APCI MS ($\text{M}+1$)⁺ 274; ^1H NMR (CDCl_3) δ : 6.11 (s, 1H), 6.76 (s, 1H), 3.21 (t, 2H), 3.21 (m, 1H), 3.04 (t, 1H), 2.42 (s, 3H), 2.40 (s, 3H).

D. Cyclopentyl-[2-(2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-ylamino)-ethyl]-carbamic acid tert-butyl ester

To a stirred solution of the crude N-cyclopentyl-N'-(2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-yl)-ethane-1,2-diamine (5.6 g) in methylene chloride (24 mL)/methanol (2 mL) was added di-tert-butyl dicarbonate (5.1 g, 23 mmol) and then 4-dimethylaminopyridine (0.6 g, 4.9 mmol). After stirring 5 hours the reaction was concentrated under reduced pressure and then chromatographed (1:1 ethyl acetate/hexanes) to afford the title compound as an orange glass (2.3 g 39% from B): +APCI MS ($\text{M}+1$)⁺ 374; ^1H NMR (CDCl_3) δ : 6.16 (s, 1H), 5.78 (s, 1H), 4.25-4.15 (br s, 1H), 3.47 (m, 4H), 2.47 (s, 3H), 2.41 (s, 3H), 1.51 (s, 9H).

E. Cyclopentyl-[2-(3-iodo-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-ylamino)-ethyl]-carbamic acid tert-butyl ester

To a 0° C. stirred solution of cyclopentyl-[2-(2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-ylamino)-ethyl]-carbamic acid tert-butyl ester (89 mg, 0.24 mmol) in chloroform (5 mL) was added N-iodosuccinimide (54 mg, 0.24 mmol). After stirring 30 minutes the reaction was extracted from saturated aqueous sodium thiosulfate with chloroform. The combined extracts were dried (Na_2SO_4), concentrated under reduced pressure to give the product as a slightly yellowed glass (102 mg, 85%): +APCI MS ($\text{M}+1$)⁺ 500; ^1H NMR (CDCl_3) δ : 5.82 (s, 1H), 4.25-4.10 (br s, 1H), 3.46 (s, 4H), 2.51 (s, 3H), 2.41 (s, 3H), 1.50 (s, 9H).

F. Cyclopentyl-[2-[3-(2,3-dichloro-phenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-ylamino]-ethyl]-carbamic acid tert-butyl ester

A suspension of cyclopentyl-[2-(3-iodo-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-ylamino)-ethyl]-carbamic acid tert-butyl ester (38 mg, 0.076 mmol) and 2,3-dichlorobenzeneboronic acid in toluene (0.5 mL)/ethanol (0.5 mL)/2 M aqueous sodium carbonate (0.22 mL) was degassed (3x) by alternately pulling a vacuum followed by repressurization with nitrogen. Tetrakis(triphenylphosphine) palladium (10 mg, 0.009 mmol) was added, and the mixture was degassed (3x) again. The mixture was stirred for 2.5

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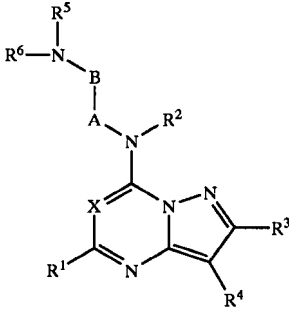
hours at 100° C., concentrated under reduced pressure, and then chromatographed (4:1 hexanes/ethyl acetate) to give the product as colorless oil (24 mg, 60%): +APCl MS (M+1)⁺ 518; ¹H NMR (CDCl₃) δ 7.42 (dd, 1 H), 7.30 (dd, 1H), 7.22 (t, 1H), 5.84 (s, 1H), 4.25–4.10 (br s, 1H), 3.49 (s, 4H), 2.44 (s, 3H), 2.32 (s, 3H), 1.52 (s, 9H).

G. N-Cyclopentyl-N'-[3-(2,3-dichloro-phenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-yl]-ethane-1,2-diamine hydrochloride salt

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The cyclopentyl-{2-[3-(2,3-dichloro-phenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-ylamino]-ethyl}-carbamic acid tert-butyl ester (21 mg, 0.040 mmol) was stirred for 1 hour in 2:1 ethanol/concentrated aqueous hydrochloric acid (1.5 mL), concentrated under reduced pressure, and then concentrated 2 additional times from ethanol to give the title compound (17 mg, 94%): +APCl MS (M+1)⁺ 418; ¹H NMR (methanol-d₄) δ: 7.69 (d, 1H), 7.50–7.40 (m, 2H), 6.78 (s, 1H), 4.06 (br s, 2H), 3.63 (br m, 1H), 3.42 (br s, 2H), 2.60 (s, 3H), 2.34 (s, 3H).

Table of Examples



EX	X	R ¹	R ²	R ³	R ⁴	A-B-N[R ⁶]-R ⁵	MW
7.	CH	Me	H	Me	2-Cl-4-F-Ph	(CH ₂) ₂ -NH-cHex	415.93
8.	CH	Me	H	Me	2-Cl-4-F-Ph	(CH ₂) ₂ -NH-cPent	401.92
9.	CH	Me	H	Me	2-Cl-4-OEt-Ph	(CH ₂) ₂ -NH-cPent	427.98
10.	CH	Me	H	Me	2-Cl-6-F-Ph	(CH ₂) ₂ -NH-cPent	401.91
11.	CH	Me	H	Me	2-Cl-Ph	(CH ₂) ₂ -NH-cPent	383.93
12.	CH	Me	H	Me	2-F-4-Br-Ph	(CH ₂) ₂ -NH-cPent	482.83
13.	CH	Me	H	Me	2-F-Ph	(CH ₂) ₂ -NH-cPent	367.47
14.	CH	Me	H	Me	2,3-diCl-Ph	(CH ₂) ₂ -NH-cPent	418.37
15.	CH	Me	H	Me	2,4-diCl-6-OMe-Ph	(CH ₂) ₂ -NH-cPent	448.4
16.	CH	Me	H	Me	2,4-diCl-Ph	(CH ₂) ₂ -NH-cBu	404.24
17.	CH	Me	H	Me	2,4-diCl-Ph	(CH ₂) ₂ -NH-CH ₂ -cPr	404.34
18.	CH	Me	H	Me	2,4-diCl-Ph	(CH ₂) ₂ -NH-cHex	432.39
19.	N	Me	H	Me	2,4-diCl-Ph	(CH ₂) ₂ -NH-cHex	433.4
20.	CH	Me	H	Me	2,4-diCl-Ph	(CH ₂) ₂ -NH-cPent	418.36
21.	N	Me	H	Me	2,4-diCl-Ph	(CH ₂) ₂ -NH-cPent	419.4
22.	CH	Me	H	Me	2,4-diF-6-OEt-Ph	(CH ₂) ₂ -NH-cPent	465.98
23.	CH	Me	H	Me	2,4-diF-Ph	(CH ₂) ₂ -NH-cHex	399.48
24.	CH	Me	H	Me	2,4-diF-Ph	(CH ₂) ₂ -NH-cPent	385.45
25.	CH	Me	H	Me	2,4-diOMe-6Cl-Ph	(CH ₂) ₂ -NH-cPent	443.98
26.	CH	Me	H	Me	2,4-diOMe-6Cl-Ph	(CH ₂) ₂ -NH ₂	375.9
27.	CH	Me	H	Me	2,4-diOMe-Ph	(CH ₂) ₂ -NH-cHex	423.55
28.	CH	Me	H	Me	2,4,6-triF-Ph	(CH ₂) ₂ -NH-cPent	439.91
29.	CH	Me	H	Me	2,4,6-triMe-Ph	CH ₂ -(2-Me-piperidin-6-yl)	391.6
30.	CH	Me	H	Me	2,4,6-triMe-Ph	(CH ₂) ₂ -NH-cBu	377.53
31.	CH	Me	H	Me	2,4,6-triMe-Ph	(CH ₂) ₂ -NH-CH ₂ -cPr	377.53
32.	CH	Me	H	Me	2,4,6-triMe-Ph	(CH ₂) ₂ -NH-cHex	405.59
33.	CH	Et	H	Me	2,4,6-triMe-Ph	(CH ₂) ₂ -NH-cHex	419.61
34.	CH	Me	H	Me	2,4,6-triMe-Ph	(CH ₂) ₂ -NH-cPent	391.55
35.	CH	Me	H	CF ₃	2,4,6-triMe-Ph	(CH ₂) ₂ -NH-cPent	445.52
36.	N	Me	H	Me	2,4,6-triMe-Ph	(CH ₂) ₂ -NH-cPent	392.5
37.	CH	Et	H	Me	2,4,6-triMe-Ph	(CH ₂) ₂ -NH-cPent	405.59
38.	CH	Me	H	Me	2,4,6-triMe-Ph	(CH ₂) ₂ -NH-iBu	379.55
39.	CH	Me	H	Me	2,4,6-triMe-Ph	(CH ₂) ₂ -NH-iPr	365.52
40.	CH	Me	H	Me	2,4,6-triMe-Ph	(CH ₂) ₂ -NH-tBu	379.54
41.	CH	Me	H	Me	2,4,6-triMe-Ph	(CH ₂) ₂ -NH-cPent	405.59
42.	CH	Me	H	Me	2,5-diCl-Ph	(CH ₂) ₂ -NH-cPent	418.37
43.	CH	Me	H	Me	2,5-diF-Ph	(CH ₂) ₂ -NH-cHex	385.46
44.	N	Me	H	Me	2,5-diMe-4-OMe-Ph	(CH ₂) ₂ -NH-cHex	422.6
45.	CH	Me	H	Me	2,5-diMe-4-OMe-Ph	(CH ₂) ₂ -NH-cHex	421.59
46.	N	Me	H	Me	2,5-diMe-4-OMe-Ph	(CH ₂) ₂ -NH-cPent	408.5
47.	CH	Me	H	Me	2,6-diCl-4-OEt-Ph	(CH ₂) ₂ -NH-(CH ₂) ₂ -NH ₂	394.31
48.	CH	Me	H	Me	2,6-diCl-4-OEt-Ph	(CH ₂) ₂ -NH-CH ₂ -CMe ₂ -NH ₂	422.36
49.	N	Me	H	Me	2,6-diCl-4-OEt-Ph	(CH ₂) ₂ -NH ₂	395.3
50.	CH	Me	H	Me	2,6-diCl-4-OEt-Ph	CH ₂ -CHMe-NH ₂	408.33

amplification. Each 1 ml volume of recombinant baculovirus (at passage 0) is used to infect a separate T25 flask containing 2×10^6 Sf9 cells in 5 mls of insect medium. After five days of incubation at 27° C., supernatant medium is harvested from each of the T25 infections for use as passage 1 inoculum. Recombinant baculoviral clones are then subjected to a second round of amplification, using 1 ml of passage 1 stock to infect 1×10^8 cells in 100 ml of insect medium divided into 2 T175 flasks. Forty-eight hours post infection, passage 2 medium is harvested from each 100 ml prep and plaque assayed for titer. The cell pellets from the second round of amplification are assayed for affinity binding of radiolabeled ligand (see below) to verify recombinant receptor expression. A third round of amplification is then initiated using an M.O.I. of 0.1 to infect a liter of Sf9 cells. Forty hours post-infection the supernatant medium is harvested to yield passage 3 baculoviral stock and the cell pellet assayed for affinity binding. Titer of the passage 3 baculoviral stock is determined by plaque assay and an M.O.I. and Incubation Time Course experiment is carried out to determine conditions for optimal receptor expression.

Log-phase Sf9 cells are infected with stocks of recombinant baculovirus encoding the proteins of interest (e.g., human NPY1 and three g-proteins), followed by culturing in insect medium at 27° C. 72 hours post-infection, a sample of cell suspension is analyzed for viability by trypan blue dye exclusion, and the remaining Sf9 cells are harvested via centrifugation (3000 rpm/10 min/ 4° C.).

Preparation of purified membranes: Sf9 cell pellets are resuspended in homogenization buffer (10 mM HEPES, 250 mM sucrose, 0.5 $\square$ g/ml leupeptin, 2 $\square$ g/ml Aprotinin, 200 $\square$ M PMSF, and 2.5 mM EDTA, pH 7.4) and homogenized using a POLYTRON homogenizer (setting 5 for 30 seconds). The homogenate is centrifuged (536 $\times$ g/10 min/4° C.) to pellet the nuclei. The supernatant containing isolated membranes is decanted to a clean centrifuge tube, centrifuged (48,000 $\times$ g/30 min, 4° C.) and resuspended in 30 ml, or preferably 20 ml of homogenization buffer. This centrifugation and resuspension step is repeated twice. The final pellet is resuspended in ice cold Dulbecco's PBS containing 5 mM EDTA and stored in frozen aliquots until needed at -80° C. The protein concentration of the resulting membrane preparation is measured using the Bradford protein assay (Bio-Rad Laboratories, Hercules, Calif.). By this measure, a 1-liter culture of cells typically yields 50–100 mg of total membrane protein.

CO-infection for GTP γ ³⁵S binding assay: Four baculoviral expression vector stocks are used to infect a culture of Sf9 cells with an MOI of 1:1:1:1. These four consisted of one vector encoding the human NPY1 receptor and a different commercially obtained baculoviral expression vector stock encoding each of the three subunits of a heterotrimeric G-protein, in particular, the G-protein-encoding virus stocks are obtained from BIOSIGNAL Inc., Montreal, and are 1) a G α_{12} G-protein-encoding virus stock (either the rat G α_{12} G-protein-encoding virus stock BIOSIGNAL #V5J008 or the rat G α_{12} G-protein-encoding virus stock BIOSIGNAL #V5H010), 2) a bovine β 1 G-protein-encoding virus stock (BIOSIGNAL #V5H012), and 3) a human γ 2 G-protein-encoding virus stock (BIOSIGNAL #V6B003). Agonist-stimulated GTP γ ³⁵S binding on purified membranes is assessed using hNPY 1–36 (American Peptide Co., Sunnyvale, Calif.) as agonist in order to ascertain functional activity as measured by GTP γ ³⁵S binding.

B. GTP γ ³⁵S binding assay: Purified Sf9 cell membranes are resuspended by Dounce homogenization (tight pestle) in GTP γ ³⁵S binding assay buffer (50 mM Tris pH 7.0, 120 mM

NaCl, 2 mM MgCl₂, 2 mM EGTA, 0.1% BSA, 0.1 mM bacitracin, 100KIU/mL Aprotinin, 5 μ M GDP) and added to reaction tubes at a concentration of 30 μ g/reaction tube. After adding increasing doses of the agonist hNPY 1–36 (American Peptide Co., Sunnyvale, Calif.), reactions are initiated by the addition of 100 pM GTP γ ³⁵S. Following a 30-minute incubation at ambient temperature, the reactions are terminated by vacuum filtration over GF/C filters (pre-soaked in wash buffer, 0.1% BSA) followed by washing with ice-cold wash buffer (50 mM Tris pH 7.0, 120 mM NaCl). Bound GTP γ ³⁵S is determined by liquid scintillation spectrometry of the washed filters. Non-specific binding is determined using 10 mM GTP γ S. Data are generally expressed as % maximal response and are derived by determining the maximal agonist stimulated % above basal stimulation. Computer analysis may be conveniently used to calculate estimated EC₅₀, IC₅₀ and K_i values from GTP γ ³⁵S binding experiment data, e.g., using SigmaPlot software. The binding affinity for the preferred compounds of the invention, expressed as K_i values, ranges from about 0.1 nanomolar to about 5 micromolar. Particularly preferred compounds yield a K_i value of less than 100 nanomolar, most preferably less than 10 nanomolar.

Assay for affinity binding of radiolabeled ligand: Purified membranes are washed with PBS and re-suspended by gentle pipetting in binding buffer (50 mM Tris(HCl), 5 mM KCl, 120 mM NaCl, 2 mM CaCl₂, 1 mM MgCl₂, 0.1% bovine serum albumin (BSA), pH 7.4). Membranes (5 μ g) are added to siliconized (Sigmacote, Sigma) polypropylene tubes in addition to 0.050 nM [125I]NPY (porcine, New England Nuclear Corp., Boston, Mass.) for competition analysis or 0.010–0.500 nM [125I]NPY (porcine) for saturation analysis. For evaluation of guanine nucleotide effects on receptor affinity, GTP is added at a final concentration of 100 μ M. Cold displacers are added at concentrations ranging from 10–12 M to 10–6 M to yield a final volume of 0.250 mL. Nonspecific binding is determined in the presence of 1 μ M NPY (human, American Peptide Co., Sunnyvale, Calif.) and accounts for less than 10% of total binding. Following a 2-hour incubation at ambient temperature, the reaction is terminated by rapid vacuum filtration. Samples are filtered over presoaked GF/C Whatman filters (1.0% polyethyleneimine for 2 hours) and rinsed 2 times with 5 mL cold binding buffer lacking BSA. Remaining bound radioactivity is measured by gamma counting. To estimate the B_{max}, K_d and K_i, the results of binding experiments are analyzed using SigmaPlot software (SPSS Science, Chicago, Ill.). The binding affinity for the compounds of the invention, expressed as a K_i value, ranges from about 0.1 nanomolar to about 10 micromolar. The most preferred compounds of the invention have a K_i of less than 100 nanomolar and a binding selectivity of >100-fold relative to other G-protein coupled receptors, including NPY₅ and CRF1₁ receptors.

C. In vivo Analysis—Food Deprivation

Subjects. Experimentally naive and experienced male Sprague-Dawley rats (Sasco, St. Louis, Mo.) weighing 210–300 g at the beginning of the experiment are used. Animals are triple-housed in stainless steel hanging cages in a temperature (22 C. $\pm$ 2) and humidity (40–70% RH) controlled animal facility with a 12:12 hour light-dark cycle. Food (Standard Rat Chow, PMI Feeds Inc., #5012) and water are available ad libitum.

Apparatus. Consumption data is collected while the animals are housed in Nalgene Metabolic cages (Model #650-0100). Each cage is comprised of subassemblies made of clear polymethylpentene (PMP), polycarbonate (PC), or stainless steel (SS). All parts disassemble for quick and

accurate data collection and for cleaning. The entire cylinder-shaped plastic and SS cage rests on a SS stand and houses one animal.

The animal is contained in the round Upper Chamber (PC) assembly (12 cm high and 20 cm in diameter) and rests on a SS floor. Two subassemblies are attached to the Upper Chamber. The first assembly consists of a SS feeding chamber (10 cm long, 5 cm high and 5 cm wide) with a PC feeding drawer attached to the bottom. The feeding drawer has two compartments: a food storage compartment with the capacity for approximately 50 g of pulverized rat chow, and a food spillage compartment. The animal is allowed access to the pulverized chow by an opening in the SS floor of the feeding chamber. The floor of the feeding chamber does not allow access to the food dropped into the spillage compartment. The second assembly includes a water bottle support, a PC water bottle (100 ml capacity) and a graduated water spillage collection tube. The water bottle support funnels any spilled water into the water spillage collection tube.

The lower chamber consists of a PMP separating cone, PMP collection funnel, PMP fluid (urine) collection tube, and a PMP solid (feces) collection tube. The separating cone is attached to the top of the collection funnel, which in turn is attached to the bottom of the Upper Chamber. The urine runs off the separating cone onto the walls of the collection funnel and into the urine collection tube. The separating cone also separates the feces and funnels it into the feces collection tube.

Food consumption, water consumption, and body weight may be measured with an Ohaus Portable Advanced scale (± 0.1 g accuracy).

Procedure. Prior to the day of testing, animals are habituated to the testing apparatus by placing each animal in a Metabolic cage for 1 hour. On the day of the experiment, animals that have been food deprived the previous night are weighed and assigned to treatment groups. Assignments are made using a quasi-random method utilizing the body weights to assure that the treatment groups had similar average body weight. Animals are then administered either vehicle (0.5% methyl cellulose) or drug (a compound of the invention). At that time, the feeding drawer is filled with pulverized chow, the filled water bottle, and the empty urine and feces collection tubes are weighed. Two hours after drug treatment, each animal is weighed and placed in a Metabolic Cage. Following a one-hour test session, animals are removed and body weight obtained. The food and water containers are then weighed and the food and water consumption data recorded.

Drugs. Drug suspended in vehicle, or vehicle alone as a control, is administered orally (PO) using a gavage tube connected to a 3 or 5 ml syringe at a volume of 10 ml/kg. Drug is made into a homogenous suspension by stirring and ultrasonication for at least 1 hour prior to dosing.

Statistical Analyses. The means and standard errors of the mean (SEM) for food consumption, water consumption, and body weight change are obtained. One-way analysis of variance using Systat (5.2.1) is used to test for group differences. A significant effect is defined as having a p value of < 0.05 .

The following parameters are defined: Body weight change is the difference between the body weight of the animal immediately prior to placement in the metabolic cage and its body weight at the end of the one hour test session. Food consumption is the difference in the weight of the food drawer prior to testing and the weight following the 1-hour test session. Water consumption is the difference in the weight of the water bottle prior to testing and the weight

following the 1-hour test session. Preferred compounds of the invention reduce food intake and body weight gain, preferably to a statistically significant degree as determined by standard parametric analysis such as a student's T-test.

Example 95

Assay for CRF Receptor Binding Activity

As discussed above, the following assay is defined herein as a standard in vitro CRF receptor binding assay. The assay may be used to demonstrate CRF1 receptor-binding activity. The CRF receptor binding is performed using a modified version of the assay described by Grigoriadis and De Souza (*Methods in Neurosciences*, Vol. 5, 1991). IMR-32 human neuroblastoma cells, a cell-line that naturally expresses the CRF1 receptor, are grown to confluency in DMEM containing FBS.

To prepare receptor-containing membranes, cells are homogenized in wash buffer (50 mM Tris HCl, 10 mM $MgCl_2$, 2 mM EGTA, pH 7.4) and centrifuged at 48,000 g for 10 min at 4° C. The pellet is re-suspended in wash buffer and the homogenization and centrifugation steps are performed two additional times.

Membrane pellets containing CRF receptors are re-suspended in 50 mM Tris buffer pH 7.7 containing 10 mM $MgCl_2$ and 2 mM EDTA and centrifuged for 10 min at 48000xg. Membranes are washed again and brought to a final concentration of 1500 mg/ml in binding buffer (Tris buffer above with 0.1% BSA, 15 mM bacitracin and 0.01 mg/ml aprotinin.). For the binding assay, 100 ml of the membrane preparation are added to 96 well microtube plates containing 100 ml of ^{125}I -CRF (SA 2200 Ci/mmol, final concentration of 100 pM) and 50 ml of test compound. Binding is carried out at ambient temperature for 2 h. Plates are then harvested on a Brandel 96 well cell harvester and filters are counted for gamma emissions on a Wallac 1205 Betaplate liquid scintillation counter. Non specific binding is defined by 1 mM cold CRF. IC_{50} values are calculated with the non-linear curve fitting program RS/1 (BBN Software Products Corp., Cambridge, Mass.). The binding affinity for a compound of Formula I expressed as an IC_{50} value generally ranges from about 0.5 nanomolar to about 10 micromolar.

Example 96

Preparation of Radiolabeled Probe Compounds of the Invention

The compounds of the invention are prepared as radiolabeled probes by carrying out their synthesis using precursors comprising at least one atom that is a radioisotope. The radioisotope is preferably selected from of at least one of carbon (preferably ^{14}C), hydrogen (preferably ^3H), sulfur (preferably ^{35}S), or iodine (preferably ^{125}I). Such radiolabeled probes are conveniently synthesized by a radioisotope supplier specializing in custom synthesis of radiolabeled probe compounds. Such suppliers include Amersham Corporation, Arlington Heights, Ill.; Cambridge Isotope Laboratories, Inc. Andover, Mass.; SRI International, Menlo Park, Calif.; Wizard Laboratories, West Sacramento, Calif.; ChemSyn Laboratories, Lexena, Kans.;

Example 97

Preparation of Radiolabeled Probe Compounds of the Invention

The compounds of the invention are prepared as radiolabeled probes by carrying out their synthesis using precursors comprising at least one atom that is a radioisotope. The radioisotope is preferably selected from of at least one of carbon (preferably ^{14}C), hydrogen (preferably ^3H), sulfur

221
222

222
223

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(preferably ³⁵S), or iodine (preferably ¹²⁵I). Such radiolabeled probes are conveniently synthesized by a radioisotope supplier specializing in custom synthesis of radiolabeled probe compounds. Such suppliers include Amersham Corporation, Arlington Heights, Ill.; Cambridge Isotope Laboratories, Inc. Andover, Mass.; SRI International, Menlo Park, Calif.; Wizard Laboratories, West Sacramento, Calif.; ChemSyn Laboratories, Lexena, Kans.; American Radiolabeled Chemicals, Inc., St. Louis, Mo.; and Moravak Biochemicals Inc., Brea, Calif.

Tritium labeled probe compounds are also conveniently prepared catalytically via platinum-catalyzed exchange in tritiated acetic acid, acid-catalyzed exchange in tritiated trifluoroacetic acid, or heterogeneous-catalyzed exchange with tritium gas. Such preparations are also conveniently carried out as a custom radiolabeling by any of the suppliers listed in the preceding paragraph using the compound of the invention as substrate. In addition, certain precursors may be subjected to tritium-halogen exchange with tritium gas,

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tritium gas reduction of unsaturated bonds, or reduction using sodium borotritide, as appropriate.

Example 98

Receptor Autoradiography
Receptor autoradiography (receptor mapping) is carried out in vitro as described by Kuhar in sections 8.1.1 to 8.1.9 of Current Protocols in Pharmacology (1998) John Wiley & Sons, New York, using radiolabeled compounds of the invention prepared as described in the preceding Example.
The invention and the manner and process of making and using it, are now described in such full, clear, concise and exact terms as to enable any person skilled in the art to which it pertains, to make and use the same. It is to be understood that the foregoing describes preferred embodiments of the present invention and that modifications may be made therein without departing from the spirit or scope of the present invention as set forth in the claims. To particularly point out and distinctly claim the subject matter regarded as invention, the following claims conclude this specification.

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<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 1

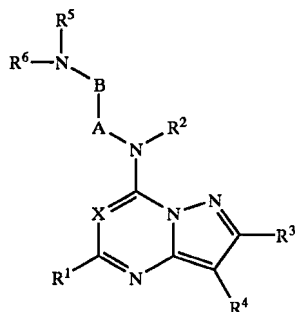
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What is claimed is:

1. A compound of the formula



or a pharmaceutically acceptable salt or an acylated derivative wherein a free hydroxyl or amino group has been acylated to form a compound capable of acting as a prodrug thereof, wherein the compound exhibits a K_i of 5 micromolar or less in a NPY1 receptor binding assay as determined by displacement of radiolabeled [^{125} I] NPY1 from the NPY receptor coded for by SEQ ID NO: 1 in which said radiolabeled [^{125} I] NPY was bound to, and

X is CR^{14} ;

R^1 is selected from H, C_1 - C_6 alkyl, C_3 - C_{10} cycloalkyl, (C_3 - C_{10} cycloalkyl) C_1 - C_6 alkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, cyano, halo, C_1 - C_6 haloalkyl, OR^7 , C_1 - C_6 alkyl- OR^7 , C_1 - C_6 cyanoalkyl, NR^8R^9 , and C_1 - C_6 alkyl- NR^8R^9 ;

 R^2 is

H,

C_1 - C_6 alkyl which optionally forms a C_3 - C_6 aminocarbocycle or a C_2 - C_5 aminoheterocycle with A or B, each of which is optionally substituted with R^7 ,

C_3 - C_{10} cycloalkyl, or
(C_3 - C_{10} cycloalkyl) C_1 - C_6 alkyl; or

R^2 and R^6 jointly form with the 2 nitrogen atoms to which they are bound a C_2 - C_5 aminoheterocycle optionally substituted with R^7 ;

A is $(CH_2)_m$ where m is 1, 2 or 3 and is optionally mono- or di-substituted at each carbon atom with C_1 - C_6 alkyl, C_3 - C_{10} cycloalkyl, (C_3 - C_{10} cycloalkyl) C_1 - C_6 alkyl, C_1 - C_6 alkenyl, C_1 - C_6 alkynyl, cyano, halogen, C_1 - C_6 haloalkyl, OR^7 , C_1 - C_6 alkyl- OR^7 , C_1 - C_6 cyanoalkyl, NR^8R^9 , or C_1 - C_6 alkyl- NR^8R^9 , or

A and B jointly form a C_3 - C_6 carbocycle, which is optionally substituted at each carbon atom with R^7 , or

A and R^2 jointly form a C_3 - C_6 aminocarbocycle, which is optionally substituted at each carbon atom with R^7 ;

B is $(CH_2)_n$ where n is 0, 1, 2, or 3 and is optionally substituted at each carbon atom with C_1 - C_6 alkyl,

C_3 - C_{10} cycloalkyl, (C_3 - C_{10} cycloalkyl) C_1 - C_6 alkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, cyano, halogen, C_1 - C_6 haloalkyl, OR^7 , C_1 - C_6 alkyl- OR^7 , C_1 - C_6 cyanoalkyl, NR^8R^9 , or C_1 - C_6 alkyl- NR^8R^9 , or

B and R^2 jointly form a C_3 - C_6 aminocarbocycle, which is optionally substituted at each carbon atom with R^7 , or

B and R^6 jointly form a C_3 - C_6 aminocarbocycle, which is optionally substituted at each carbon atom with R^7 ;

R^3 is selected from H, C_1 - C_6 alkyl, C_3 - C_{10} cycloalkyl, (C_3 - C_{10} cycloalkyl) C_1 - C_6 alkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, cyano, halo, C_1 - C_6 haloalkyl, OR^7 , C_1 - C_6 alkyl- OR^7 , C_1 - C_6 cyanoalkyl, NR^8R^9 , and C_1 - C_6 alkyl- NR^8R^9 ;

R^4 is selected from aryl or heteroaryl, each optionally substituted with 1 to 5 substituents independently selected at each occurrence from C_1 - C_6 alkyl, C_3 - C_{10} cycloalkyl, C_3 - C_{10} cycloalkenyl, (C_3 - C_{10} cycloalkyl) C_1 - C_6 alkyl, C_1 - C_6 alkenyl, halogen, C_1 - C_6 haloalkyl, trifluoromethylsulfonyl, OR^7 , C_1 - C_6 alkyl- OR^7 , NR^8R^9 , C_1 - C_6 alkyl- NR^8R^9 , $CONR^8R^9$, C_1 - C_6 alkyl- $CONR^8R^9$, $COOR^7$, C_1 - C_6 alkyl- $COOR^7$, CN, C_1 - C_6 alkyl-CN, $S_2NR^8R^9$, SO_2R^7 , aryl, heteroaryl, heterocycloalkyl, and 3-, 4-, or 5-(2-oxo-1,3-oxazolidinyl), with the proviso that at least one of the positions ortho or para to the point of attachment of the aryl or heteroaryl ring to the pyrazole is substituted;

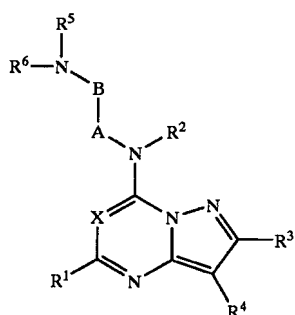
R^5 and R^6 are independently selected from H, C_1 - C_6 alkyl, C_3 - C_{10} cycloalkyl, (C_3 - C_{10} cycloalkyl) C_1 - C_6 alkyl, C_2 - C_6 alkenyl, and C_2 - C_6 alkynyl,

R^7 is H, C_1 - C_6 alkyl, C_3 - C_{10} cycloalkyl, C_3 - C_{10} cycloalkenyl, (C_3 - C_{10} cycloalkyl) C_1 - C_6 alkyl, C_1 - C_3 haloalkyl, or heterocycloalkyl, C_1 - C_8 alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, C_1 - C_8 alkanoyl, aroyl, heteroaroyl, aryl, heteroaryl, C_1 - C_6 arylalkyl or C_1 - C_6 heteroarylalkyl each of which is optionally substituted with 1 to 5 substituents independently selected at each occurrence from halogen, C_1 - C_6 haloalkyl, OR^{13} , NR^8R^9 , C_1 - C_6 alkyl- OR^{13} , C_1 - C_6 alkyl- NR^8R^9 , $CONR^8R^9$, $COOR^{13}$, CN, $SO_2NR^8R^9$, SO_2R^{13} , with the proviso that for SO_2R^7 , R^7 cannot be H;

R^8 and R^9 are independently selected at each occurrence from H, C_1 - C_6 alkyl, C_3 - C_{10} cycloalkyl, C_2 - C_6 alkenyl, C_3 - C_{10} cycloalkenyl, C_2 - C_6 alkynyl, heterocycloalkyl, C_1 - C_8 alkanoyl, aroyl, heteroaroyl, aryl, heteroaryl, C_1 - C_6 arylalkyl or C_1 - C_6 heteroarylalkyl, or R^8 and R^9 , taken together, can form a C_3 - C_6 aminocarbocycle or a C_2 - C_5 aminoheterocycle each optionally substituted at each occurrence with R^7 ;

R^{11} is selected from H, C_1 - C_6 alkyl, C_3 - C_{10} cycloalkyl, (C_3 - C_{10} cycloalkyl) C_1 - C_6 alkyl;

- R^{12} is selected from H, aryl, heteroaryl, C_1 - C_6 alkyl, C_3 - C_{10} cycloalkyl, (C_3 - C_{10} cycloalkyl) C_1 - C_6 alkyl, optionally substituted with OR^7 , NR^8R^9 , C_3 - C_6 aminocarbocycle, or C_2 - C_5 aminoheterocycle;
- R^{13} is independently selected at each occurrence from H, C_1 - C_6 alkyl, C_3 - C_{10} cycloalkyl, (C_3 - C_{10} cycloalkyl) C_1 - C_6 alkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, C_1 - C_6 haloalkyl, with the proviso that for SO_2R^{13} , R^{13} cannot be H; and
- R^{14} is H, C_1 - C_6 alkyl, C_3 - C_{10} cycloalkyl, (C_3 - C_{10} cycloalkyl) C_1 - C_6 alkyl, C_2 - C_4 alkenyl, C_2 - C_4 alkynyl, halo, or CN.
2. A compound according to claim 1, wherein X is CH.
3. A compound according to claim 1, wherein X is CH; and
- R^1 is H, C_1 - C_6 alkyl, C_3 - C_{10} cycloalkyl, or (C_3 - C_{10} cycloalkyl) C_1 - C_6 alkyl.
4. A compound according to claim 1, wherein X is CH;
- R^1 is H, C_1 - C_6 alkyl;
- R^2 is H or C_1 - C_6 alkyl; and
- R^3 is C_1 - C_6 alkyl, trifluoromethyl, or C_1 - C_6 alkyl-O C_1 - C_6 alkyl.
5. A compound according to claim 1 wherein the compound exhibits a 20-fold greater affinity for the NPY1 receptor in the NPY1 receptor binding assay than for the CRF1 receptor in an assay of CRF1 receptor as determined by binding to a radiolabeled ligand.
6. A compound according to claim 1 wherein the compound exhibits a 100-fold greater affinity for the NPY1 receptor in the NPY1 receptor binding assay than for the CRF1 receptor in an assay of CRF1 receptor as determined by binding to a radiolabeled ligand.
7. A method for treating eating disorders comprising administering to a patient suffering from an eating disorder a compound according to claim 1.
8. A method for treating obesity or bulimia nervosa which comprises administering an effective amount of a compound according to claim 1 to a patient in need thereof.
9. A compound of the formula



or a pharmaceutically acceptable salt or an acylated derivative wherein a free hydroxyl or amino group has been acylated to form a compound capable of acting as a prodrug thereof, wherein the compound exhibits a K_i of 5 micromolar or less in a NPY1 receptor binding assay as determined by displacement of radiolabeled [^{125} I] NPY from the NPY1 receptor coded for by SEQ ID NO.: 1 in which said radiolabeled [^{125} I] NPY was bound to, and

X is CR^{14} ;

R^1 is selected from H, C_1 - C_6 alkyl, C_3 - C_{10} cycloalkyl, (C_3 - C_{10} cycloalkyl) C_1 - C_6 alkyl, C_2 - C_6 alkenyl,

C_2 - C_6 alkynyl, cyano, halo, C_1 - C_6 haloalkyl, OR^7 , C_1 - C_6 alkyl- OR^7 , C_1 - C_6 cyanoalkyl, NR^8R^9 , and C_1 - C_6 alkyl- NR^8R^9 ;

R^2 is

H,

C_1 - C_6 alkyl which optionally forms a C_3 - C_6 aminocarbocycle or a C_2 - C_5 aminoheterocycle with A or B, each of which is optionally substituted with R^7 ,

C_3 - C_{10} cycloalkyl, or

(C_3 - C_{10} cycloalkyl) C_1 - C_6 alkyl; or

R^2 and R^6 jointly form with the 2 nitrogen atoms to which they are bound a C_2 - C_5 aminoheterocycle optionally substituted with R^7 ;

A is $(CH_2)_m$ where m is 1, 2 or 3 and is optionally mono- or di-substituted at each carbon atom with C_1 - C_6 alkyl, C_3 - C_{10} cycloalkyl, (C_3 - C_{10} cycloalkyl) C_1 - C_6 alkyl, C_1 - C_6 alkenyl, C_1 - C_6 alkynyl, cyano, halogen, C_1 - C_6 haloalkyl, OR^7 , C_1 - C_6 alkyl- OR^7 ; C_1 - C_6 cyanoalkyl, NR^8R^9 , or C_1 - C_6 alkyl- NR^8R^9 , or

A and B jointly form a C_3 - C_6 carbocycle, which is optionally substituted at each carbon atom with R^7 , or

A and R^2 jointly form a C_3 - C_6 aminocarbocycle, which is optionally substituted at each carbon atom with R^7 ;

B is $(CH_2)_n$ where n is 0, 1, 2, or 3 and is optionally substituted at each carbon atom with C_1 - C_6 alkyl, C_3 - C_{10} cycloalkyl, (C_3 - C_{10} cycloalkyl) C_1 - C_6 alkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, cyano, halogen, C_1 - C_6 haloalkyl, OR^7 , C_1 - C_6 alkyl- OR^7 ; C_1 - C_6 cyanoalkyl, NR^8R^9 , or C_1 - C_6 alkyl- NR^8R^9 , or

B and R^2 jointly form a C_3 - C_6 aminocarbocycle, which is optionally substituted at each carbon atom with R^7 , or

B and R^6 jointly form a C_3 - C_6 aminocarbocycle, which is optionally substituted at each carbon atom with R^7 ;

R^3 is selected from H, C_1 - C_6 alkyl, C_3 - C_{10} cycloalkyl, (C_3 - C_{10} cycloalkyl) C_1 - C_6 alkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, cyano, halo, C_1 - C_6 haloalkyl, OR^7 , C_1 - C_6 alkyl- OR^7 , C_1 - C_6 cyanoalkyl, NR^8R^9 , and C_1 - C_6 alkyl- NR^8R^9 ;

R^4 is selected from aryl or heteroaryl, each optionally substituted with 1 to 5 substituents independently selected at each occurrence from C_1 - C_6 alkyl, C_3 - C_{10} cycloalkyl, C_3 - C_{10} cycloalkenyl, (C_3 - C_{10} cycloalkyl) C_1 - C_6 alkyl, C_1 - C_6 alkenyl, halogen, C_1 - C_6 haloalkyl, trifluoromethylsulfonyl, OR^7 , C_1 - C_6 alkyl- OR^7 , NR^8R^9 , C_1 - C_6 alkyl- NR^8R^9 , $CONR^8R^9$, C_1 - C_6 alkyl- $CONR^8R^9$, $COOR^7$, C_1 - C_6 alkyl- $COOR^7$, CN, C_1 - C_6 alkyl-CN, $SO_2NR^8R^9$, SO_2R^7 , aryl, heteroaryl, heterocycloalkyl, and 3-, 4-, or 5-(2-oxo-1,3-oxazolidinyl), with the proviso that at least one of the positions ortho or para to the point of attachment of the aryl or heteroaryl ring to the pyrazole is substituted;

R^5 is H;

R^6 and C_3 - C_{10} cycloalkyl, (C_3 - C_{10} cycloalkyl) C_1 - C_6 alkyl;

R^7 is H, C_1 - C_6 alkyl, C_3 - C_{10} cycloalkyl, C_3 - C_{10} cycloalkenyl, (C_3 - C_{10} cycloalkyl) C_1 - C_6 alkyl, C_1 - C_3 haloalkyl, or heterocycloalkyl, C_1 - C_8 alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, C_1 - C_8 alkanoyl, aroyl, heteroaroyle, aryl, heteroaryl, C_1 - C_6 arylalkyl or C_1 - C_6 heteroarylalkyl each of which is optionally substituted with 1 to 5 substituents independently selected at each occurrence from halogen, C_1 - C_6 haloalkyl, OR^{13} , NR^8R^9 , C_1 - C_6 alkyl- OR^{13} , C_1 - C_6

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alkyl-NR⁸R⁹, CONR⁸R⁹, COOR¹³, CN, SO₂NR⁸R⁹, SO₂R¹³, with the proviso that for SO₂R⁷, R⁷ cannot be H;

R⁸ and R⁹ are independently selected at each occurrence from H, C₁-C₆ alkyl, C₃-C₁₀ cycloalkyl, C₂-C₆ alkenyl, C₃-C₁₀ cycloalkenyl, C₂-C₆ alkynyl, heterocycloalkyl, C₁-C₈ alkanoyl, aroyl, heteroaroyl, aryl, heteroaryl, C₁-C₆ arylalkyl or C₁-C₆ heteroarylalkyl, or R⁸ and R⁹, taken together, can form a C₃-C₆ aminocarbocycle or a C₂-C₅ aminoheterocycle each optionally substituted at each occurrence with R⁷;

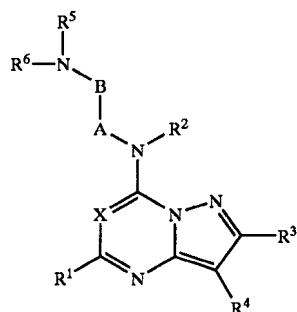
R¹¹ is selected from H, C₁-C₆ alkyl, C₃-C₁₀ cycloalkyl, (C₃-C₁₀ cycloalkyl) C₁-C₆ alkyl;

R¹² is selected from H, aryl, heteroaryl, C₁-C₆ alkyl, C₃-C₁₀ cycloalkyl, (C₃-C₁₀ cycloalkyl) C₁-C₆ alkyl, optionally substituted with OR⁷, NR⁸R⁹, C₃-C₆ aminocarbocycle, or C₂-C₅ aminoheterocycle;

R¹³ is independently selected at each occurrence from H, C₁-C₆ alkyl, C₃-C₁₀ cycloalkyl, (C₃-C₁₀ cycloalkyl) C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ haloalkyl, with the proviso that for SO₂R¹³, R¹³ cannot be H; and

R¹⁴ is H, C₁-C₆ alkyl, C₃-C₁₀ cycloalkyl, (C₃-C₁₀ cycloalkyl) C₁-C₆ alkyl, C₂-C₄ alkenyl, C₂-C₄ alkynyl, halo, or CN.

10. A compound of the formula



or a pharmaceutically acceptable salt or an acylated derivative wherein a free hydroxyl or amino group has been acylated to form a compound capable of acting as a prodrug thereof, wherein the compound exhibits a K_i of 5 micromolar or less in a NPY₁ receptor binding assay as determined by displacement of radiolabeled [125 I] NPY from the NPY₁ receptor coded for by SEQ ID NO.: 1 in which said radiolabeled [125 I] NPY was bound to, and

X is CR¹⁴;

R¹ is selected from H, C₁-C₆ alkyl, C₃-C₁₀ cycloalkyl, (C₃-C₁₀ cycloalkyl) C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, cyano, halo, C₁-C₆ haloalkyl, OR⁷, C₁-C₆ alkyl-OR⁷, C₁-C₆ cyanoalkyl, NR⁸R⁹, and C₁-C₆ alkyl-NR⁸R⁹;

R² is

H,

C₁-C₆ alkyl which optionally forms a C₃-C₆ aminocarbocycle or a C₂-C₅ aminoheterocycle with A or B, each of which is optionally substituted with R⁷, C₃-C₁₀ cycloalkyl, or (C₃-C₁₀ cycloalkyl) C₁-C₆ alkyl; or

R² and R⁶ jointly form with the 2 nitrogen atoms to which they are bound a C₂-C₅ aminoheterocycle optionally substituted with R⁷;

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A is (CH₂)_m where m is 1,2 or 3 and is optionally mono- or di-substituted at each carbon atom with C₁-C₆ alkyl, C₃-C₁₀ cycloalkyl, (C₃-C₁₀ cycloalkyl) C₁-C₆ alkyl, C₁-C₆ alkenyl, C₁-C₆ alkynyl, cyano, halogen, C₁-C₆ haloalkyl, OR⁷, C₁-C₆ alkyl-OR⁷; C₁-C₆ cyanoalkyl, NR⁸R⁹, or C₁-C₆ alkyl-NR⁸R⁹, or

A and B jointly form a C₃-C₆ carbocycle, which is optionally substituted at each carbon atom with R⁷, or

A and R² jointly form a C₃-C₆ aminocarbocycle, which is optionally substituted at each carbon atom with R⁷;

B is (CH₂)_n where n is 0, 1, 2, or 3 and is optionally substituted at each carbon atom with C₁-C₆ alkyl, C₃-C₁₀ cycloalkyl, (C₃-C₁₀ cycloalkyl) C₁-C₆ alkyl, C₁-C₆ alkenyl, C₂-C₆ alkynyl, cyano, halogen, C₁-C₆ haloalkyl, OR⁷, C₁-C₆ alkyl-OR⁷; C₁-C₆ cyanoalkyl, NR⁸R⁹, or C₁-C₆ alkyl-NR⁸R⁹, or

B and R² jointly form a C₃-C₆ aminocarbocycle, which is optionally substituted at each carbon atom with R⁷, or

B and R⁶ jointly form a C₃-C₆ aminocarbocycle, which is optionally substituted at each carbon atom with R⁷;

R³ is selected from H, C₁-C₆ alkyl, C₃-C₁₀ cycloalkyl, (C₃-C₁₀ cycloalkyl) C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, cyano, halo, C₁-C₆ haloalkyl, OR⁷, C₁-C₆ alkyl-OR⁷, C₁-C₆ cyanoalkyl, NR⁸R⁹, and C₁-C₆ alkyl-NR⁸R⁹;

R⁴ is selected from aryl or heteroaryl, each optionally substituted with 1 to 5 substituents independently selected at each occurrence from C₁-C₆ alkyl, C₃-C₁₀ cycloalkyl, halogen, C₁-C₆ haloalkyl, CN, alkylsulfonyl, OR⁷, NR⁸R⁹, CONR⁸R⁹, COOR⁷, SO₂NR⁸R⁹, COR⁷, SO₂R⁷;

R⁵ and R⁶ are independently selected from H, C₁-C₆ alkyl, C₃-C₁₀ cycloalkyl, (C₃-C₁₀ cycloalkyl) C₁-C₆ alkyl;

R⁷ is H, C₁-C₆ alkyl, C₃-C₁₀ cycloalkyl, C₃-C₁₀ cycloalkenyl, (C₃-C₁₀ cycloalkyl) C₁-C₆ alkyl, C₁-C₃ haloalkyl, or heterocycloalkyl, C₁-C₈ alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, C₁-C₈ alkanoyl, aroyl, heteroaroyl, aryl, heteroaryl, C₁-C₆ arylalkyl or C₁-C₆ heteroarylalkyl each of which is optionally substituted with 1 to 5 substituents independently selected at each occurrence from halogen, C₁-C₆ haloalkyl, OR¹³, NR⁸R⁹, C₁-C₆ alkyl-OR¹³, C₁-C₆ alkyl-NR⁸R⁹, CONR⁸R⁹, COOR¹³, CN, SO₂NR⁸R⁹, SO₂R¹³, with the proviso that for SO₂R⁷, R⁷ cannot be H;

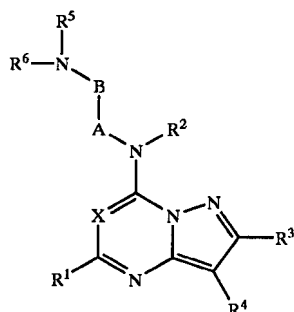
R⁸ and R⁹ are independently selected at each occurrence from H, C₁-C₆ alkyl, C₃-C₁₀ cycloalkyl, C₂-C₆ alkenyl; C₃-C₁₀ cycloalkenyl, C₂-C₆ alkynyl, heterocycloalkyl, C₁-C₈ alkanoyl, aroyl, heteroaroyl, aryl, heteroaryl, C₁-C₆ arylalkyl or C₁-C₆ heteroarylalkyl, or R⁸ and R⁹, taken together, can form a C₃-C₆ aminocarbocycle or a C₂-C₅ aminoheterocycle each optionally substituted at each occurrence with C₁-C₆ alkyl, C₃-C₁₀ cycloalkyl, C₃-C₁₀ cycloalkenyl, (C₃-C₁₀ cycloalkyl) C₁-C₆ alkyl, C₁-C₃ haloalkyl, or heterocycloalkyl, C₁-C₈ alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, C₁-C₈ alkanoyl, aroyl, heteroaroyl, aryl, heteroaryl, C₁-C₆ arylalkyl or C₁-C₆ heteroarylalkyl;

R¹¹ is selected from H, C₁-C₆ alkyl, C₃-C₁₀ cycloalkyl, (C₃-C₁₀ cycloalkyl) C₁-C₆ alkyl;

R¹² is selected from H, aryl, heteroaryl, C₁-C₆ alkyl, C₃-C₁₀ cycloalkyl, (C₃-C₁₀ cycloalkyl) C₁-C₆ alkyl,

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- optionally substituted with OR⁷, NR⁸R⁹, C₃-C₆ aminocarbocycle, or C₂-C₅ aminoheterocycle;
- R¹³ is independently selected at each occurrence from H, C₁-C₆ alkyl, C₃-C₁₀ cycloalkyl, (C₃-C₁₀ cycloalkyl) C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ haloalkyl, with the proviso that for SO₂R¹³, R¹³ cannot be H; and
- R¹⁴ is H, C₁-C₆ alkyl, C₃-C₁₀ cycloalkyl, (C₃-C₁₀ cycloalkyl) C₁-C₆ alkyl, C₂-C₄ alkenyl, C₂-C₄ alkynyl, halo, or CN.
11. A compound of the formula



or a pharmaceutically acceptable salt or an acylated derivative wherein a free hydroxyl or amino group has been acylated to form a compound capable of acting as a prodrug thereof, wherein:

- X is CR¹⁴;
- R¹ is selected from H, C₁-C₆ alkyl, C₃-C₁₀ cycloalkyl, (C₃-C₁₀ cycloalkyl) C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, cyano, halo, C₁-C₆ haloalkyl, OR⁷, C₁-C₆ alkyl-OR⁷, C₁-C₆ cyanoalkyl, NR⁸R⁹, and C₁-C₆ alkyl-NR⁸R⁹;
- R² is
- H,
- C₁-C₆ alkyl which optionally forms a C₃-C₆ aminocarbocycle or a C₂-C₅ aminoheterocycle with A or B, each of which is optionally substituted with R⁷,
- C₃-C₁₀ cycloalkyl, or
- (C₃-C₁₀ cycloalkyl) C₁-C₆ alkyl; or
- R² and R⁶ jointly form with the 2 nitrogen atoms to which they are bound a C₂-C₅ aminoheterocycle optionally substituted with R⁷;
- A is (CH₂)_m where m is 1,2 or 3 and is optionally mono- or di-substituted at each carbon atom with C₁-C₆ alkyl, C₃-C₁₀ cycloalkyl, (C₃-C₁₀ cycloalkyl) C₁-C₆ alkyl, C₂-C₆ alkenyl, C₁-C₆ alkynyl, cyano, halogen, C₁-C₆ haloalkyl, OR⁷, C₁-C₆ alkyl-OR⁷, C₁-C₆ cyanoalkyl, NR⁸R⁹, or C₁-C₆ alkyl-NR⁸R⁹, or
- A and B jointly form a C₃-C₆ carbocycle, which is optionally substituted at each carbon atom with R⁷, or
- A and R² jointly form a C₃-C₆ aminocarbocycle, which is optionally substituted at each carbon atom with R⁷;
- B is (CH₂)_n where n is 0, 1, 2, or 3 and is optionally substituted at each carbon atom with C₁-C₆ alkyl, C₃-C₁₀ cycloalkyl, (C₃-C₁₀ cycloalkyl) C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, cyano, halogen, C₁-C₆ haloalkyl, OR⁷, C₁-C₆ alkyl-OR⁷, C₁-C₆ cyanoalkyl, NR⁸R⁹, or C₁-C₆ alkyl-NR⁸R⁹, or
- B and R² jointly form a C₃-C₆ aminocarbocycle, which is optionally substituted at each carbon atom with R⁷, or
- B and R⁶ jointly form a C₃-C₆ aminocarbocycle, which is optionally substituted at each carbon atom with R⁷;

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- R³ is selected from H, C₁-C₆ alkyl, C₃-C₁₀ cycloalkyl, (C₃-C₁₀ cycloalkyl) C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, cyano, halo, C₁-C₆ haloalkyl, OR⁷, C₁-C₆ alkyl-OR⁷, C₁-C₆ cyanoalkyl, NR⁸R⁹, and C₁-C₆ alkyl-NR⁸R⁹;
- R⁴ is selected from aryl or heteroaryl, each substituted with aryl, heteroaryl, heterocycloalkyl, and 3-, 4-, or (5-(2-oxo-1,3-oxazolidinyl), heterocycloalkyl, cyclopentenyl, cyclohexenyl, C₁-C₆ alkenyl, C₁-C₆ alkynyl, (C₃-C₁₀ cycloalkyl) C₁-C₆ alkyl, trifluoromethylsulfonyl, C₁-C₆ alkyl-NR⁸R⁹, C₁-C₆ alkyl-CN, C₁-C₆ alkyl-CONR⁸R⁹, C₁-C₆ alkyl-OR⁷, C₁-C₆ alkyl-COOR⁷ and optionally substituted with 1 to 4 substituents independently selected at each occurrence from C₁-C₆ alkyl, (C₃-C₁₀ cycloalkyl) C₁-C₆ alkyl, halogen, C₁-C₆ haloalkyl, trifluoromethylsulfonyl, OR⁷, C₁-C₆ alkyl-OR⁷, NR⁸R⁹, C₁-C₆ alkyl-NR⁸R⁹, CONR⁸R⁹, C₁-C₆ alkyl-CONR⁸R⁹, COOR⁷, C₁-C₆ alkyl-COOR⁷, CN, C₁-C₆ alkyl-CN, SO₂NR⁸R⁹, SO₂R⁷;
- R⁵ and R⁶ are independently selected from H, C₁-C₆ alkyl, C₃-C₁₀ cycloalkyl, (C₃-C₁₀ cycloalkyl) C₁-C₆ alkyl;
- R⁷ is H, C₁-C₆ alkyl, C₃-C₁₀ cycloalkyl, C₃-C₁₀ cycloalkenyl, (C₃-C₁₀ cycloalkyl) C₁-C₆ alkyl, C₁-C₃ haloalkyl, or heterocycloalkyl, C₁-C₈ alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, C₁-C₈ alkanoyl, aroyl, heteroaroyl, aryl, heteroaryl, C₁-C₆ arylalkyl or C₁-C₆ heteroarylalkyl each of which is optionally substituted with 1 to 5 substituents independently selected at each occurrence from halogen, C₁-C₆ haloalkyl, OR¹³, NR⁸R⁹, C₁-C₆ alkyl-OR¹³, C₁-C₆ alkyl-NR⁸R⁹, CONR⁸R⁹, COOR¹³, CN, SO₂NR⁸R⁹, SO₂R¹³, with the proviso that when R⁷ is SO₂R¹³, R¹³ cannot be H;
- R⁸ and R⁹ are independently selected at each occurrence from H, C₁-C₆ alkyl, C₃-C₁₀ cycloalkyl, C₂-C₆ alkenyl, C₃-C₁₀ cycloalkenyl, C₂-C₆ alkynyl, heterocycloalkyl, C₁-C₈ alkanoyl, aroyl, heteroaroyl, aryl, heteroaryl, C₁-C₆ arylalkyl or C₁-C₆ heteroarylalkyl, or R⁸ and R⁹, taken together, can form a C₃-C₆ aminocarbocycle or a C₂-C₅ aminoheterocycle each optionally substituted at each occurrence with C₁-C₆ alkyl, C₃-C₁₀ cycloalkyl, C₃-C₁₀ cycloalkenyl, (C₃-C₁₀ cycloalkyl) C₁-C₆ alkyl, C₁-C₃ haloalkyl, or heterocycloalkyl, C₁-C₈ alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, C₁-C₈ alkanoyl, aroyl, heteroaroyl, aryl, heteroaryl, C₁-C₆ arylalkyl or C₁-C₆ heteroarylalkyl;
- R¹¹ is selected from H, C₁-C₆ alkyl, C₃-C₁₀ cycloalkyl, (C₃-C₁₀ cycloalkyl) C₁-C₆ alkyl;
- R¹² is selected from H, aryl, heteroaryl, C₁-C₆ alkyl, C₃-C₁₀ cycloalkyl, (C₃-C₁₀ cycloalkyl) C₁-C₆ alkyl, optionally substituted with OR⁷, NR⁸R⁹, C₃-C₆ aminocarbocycle, or C₂-C₅ aminoheterocycle;
- R¹³ is independently selected at each occurrence from H, C₁-C₆ alkyl, C₃-C₁₀ cycloalkyl, (C₃-C₁₀ cycloalkyl) C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ haloalkyl, with the proviso that for SO₂R¹³, R¹³ cannot be H; and
- R¹⁴ is H, C₁-C₆ alkyl, C₃-C₁₀ cycloalkyl, (C₃-C₁₀ cycloalkyl) C₁-C₆ alkyl, C₂-C₄ alkenyl, C₂-C₄ alkynyl, halo, or CN.
12. A compound according to claim 10, wherein
- X is CH;
- R¹ is H, C₁-C₆ alkyl, C₃-C₁₀ cycloalkyl, or (C₃-C₁₀ cycloalkyl) C₁-C₆ alkyl;

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R² is H;

R³ is C₁-C₆ alkyl, trifluoromethyl, or C₁-C₆alkyl-O C₁-C₆alkyl;

R⁴ is phenyl, mono-, di-, or tri-substituted C₁-C₆ alkyl, halogen, C₁-C₆ haloalkyl, or

OR⁷;

R⁵ is H;

R⁷ is methyl, ethyl, isopropyl, or propyl.

13. A compound of claim 12 wherein the compound has the structure N-cyclohexyl-N'-[3-(2,6-dichloro-4-methoxy-phenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-yl]-ethane-1,2-diamine; N-cyclohexyl-N'-[2,5-dimethyl-3-(2,4,6-trimethyl-phenyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-ethane-1,2-diamine; N-cyclopentyl-N'-[2,5-dimethyl-3-(2,4,6-trimethyl-phenyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-ethane-1,2-diamine; or N-cyclopentyl-N'-[3-(2,6-dichloro-4-methoxy-phenyl)-2,5-dimethyl-pyrazolo [1,5-a]pyrimidin-7-yl]-ethane-1,2-diamine.

14. A compound according to claim 11, wherein R¹⁴ is H, C₁-C₄ alkyl.

15. A compound according to claim 14 wherein

R² is H; R⁶ is H;

X is CH;

A is CH₂, optionally substituted with one or two of the following: F, CF₃, or methyl, ethyl, isopropyl;

B is CH₂, optionally substituted with one or two of the following: F, CF₃, or methyl, ethyl, isopropyl.

16. A compound according to claim 15 wherein

R⁵ is C₁-C₇ alkyl, C₁-C₆ cycloalkyl, or C₁-C₆ cycloalkyl C₁-C₂ alkyl;

A, B is CH₂.

17. A compound according to claim 15 wherein

R⁴ is selected from aryl or heteroaryl, each substituted with aryl, heteroaryl, heterocycloalkyl, and 3-, 4-, or 5-(2-oxo-1,3-oxazolidinyl), heterocycloalkyl, cyclopentenyl, cyclohexenyl, C₁-C₆ alkenyl, C₁-C₆ alkynyl, (C₃-C₁₀ cycloalkyl) C₁-C₆ alkyl, trifluoromethylsulfonyl, C₁-C₆ alkyl-NR⁸R⁹, C₁-C₆ alkyl-CN, C₁-C₆ alkyl-CONR⁸R⁹, (C₁-C₄)alkyl-OR⁷, C₁-C₆ alkyl-COOR⁷ and optionally substituted with 1 to 4 substituents independently selected at each occurrence from C₁-C₆ alkyl, (C₃-C₁₀ cycloalkyl) C₁-C₆ alkyl, halogen, C₁-C₆ haloalkyl, trifluoromethylsulfonyl, OR⁷, C₁-C₆ alkyl-OR⁷, NR⁸R⁹, C₁-C₆ alkyl-NR⁸R⁹, CONR⁸R⁹, C₁-C₆ alkyl.

18. A compound of claim 17 wherein

R⁴ is phenyl substituted with acetylene, cyclopentenyl, cyclohexenyl, (C₁-C₄)alkyl-OR⁷, C₁-C₃ alkynyl, and optionally substituted with 1 to 2 substituents independently selected at each occurrence from methyl, F, Cl, CF₃, OR⁷;

R⁷ is H, methyl, ethyl.

19. A compound of claim 18 where the structure is N-cyclohexyl-N'-[3-(2,6-dichloro-4-ethynyl-phenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-yl]-ethane-1,2-diamine; N-cyclopentyl-N'-[3-(2,6-dichloro-4-ethynyl-phenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-yl]-

ethane-1,2-diamine; N-cyclopentyl-N'-[3-(2,6-dichloro-4-cyclopent-1-enyl-phenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-yl]-ethane-1,2-diamine; or N-cyclohexyl-N'-[3-(2,6-dichloro-4-cyclopent-1-enyl-phenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-yl]-ethane-1,2-diamine.

20. A compound according to claim 10 wherein the compound exhibits a 20-fold greater affinity for the NPY1 receptor in the NPY1 receptor binding assay than for the CRF receptor in an assay of CRF receptor as determined by binding to a radiolabeled ligand.

21. A compound according to claim 10 wherein the compound exhibits a 100-fold greater affinity for the NPY1 receptor in the NPY1 receptor binding assay than for the CRF receptor in an assay of CRF receptor as determined by binding to a radiolabeled ligand.

22. A method for treating eating disorders comprising administering to a patient suffering from an eating disorder a compound according to claim 10.

23. A pharmaceutical composition comprising a compound according to claim 10 and a pharmaceutically acceptable carrier.

24. A packaged pharmaceutical composition comprising the pharmaceutical composition of claim 10 in a container and comprising instructions for using the composition to treat a patient suffering from an eating disorder or hypertension.

25. A method for treating obesity or bulimia nervosa which comprises administering an effective amount of a compound according to claim 10 to a patient in need thereof.

26. A method of treating obesity comprising administering to a mammal in need of such treatment a therapeutically effective amount of a compound of formula as defined in claim 11 or a prodrug thereof or a pharmaceutically acceptable salt of said compound or of said prodrug.

27. A method as recited in claim 26 wherein the amount of the compound in Formula I as defined in claim 11 is about 0.01 mg/kg/day to about 50 mg/kg/day.

28. A method as recited in claim 27 wherein the mammal is female or male human.

29. A pharmaceutical composition which comprises a therapeutically effective amount of compound of claim 11 or a prodrug thereof or a pharmaceutically acceptable salt of said compound or of said prodrug and a pharmaceutically acceptable carrier, vehicle or diluent.

30. A pharmaceutical composition for the treatment of obesity which comprises a therapeutically effective amount of compound of claim 11 or a prodrug thereof or a pharmaceutically acceptable salt of said compound or of said prodrug and a pharmaceutically acceptable carrier, vehicle or diluent.

31. A pharmaceutical composition comprising a compound as defined in claim 11 and a pharmaceutically acceptable carrier for the treatment of disorders or disease states caused by eating disorders, of obesity, bulimia nervosa, dislipidemia, memory loss, epileptic seizures, migraine, sleep disorders, pain, sexual/reproductive disorders, depression, anxiety, cerebral hemorrhage, shock, nasal congestion or diarrhea.

* * * * *

**CERTAIN ALKYLENE DIAMINE-SUBSTITUTED
PYRAZOLO[1,5-A]-1,5-PYRIMIDINES AND
PYRAZOLO [1,5-A]-1,3,5-TRIAZINES**

**CROSS REFERENCE TO RELATED
APPLICATION**

[0001] This application claims priority from Provisional Application No. 60/15869, filed on Sep. 30, 1999, which is incorporated herein by reference.

FIELD OF THE INVENTION

[0002] This invention relates to certain alkylene diamine-substituted pyrazolo[1,5-a]-1,5-pyrimidines and pyrazolo [1,5-a]-1,3,5-triazines which selectively and potently bind mammalian neuropeptide Y (NPY) receptors. This invention also relates to pharmaceutical compositions comprising such compounds. It further relates to the use of such compounds in treating physiological disorders associated with an excess of neuropeptide Y, especially feeding disorders, some psychiatric disorders, and certain cardiovascular diseases.

BACKGROUND OF THE INVENTION

[0003] Neuropeptide Y (NPY) is a 36 amino acid peptide first isolated in 1982 [K. Tatemoto, M. Carlquist, V. Mutt, *Nature*, 296, 659, (1982)] and subsequently found to be largely conserved across species. It belongs to a large family of peptides which includes, among others, peptide YY (PYY) and pancreatic peptide (PP). NPY is the most abundant peptide in the mammalian brain, but is also localized in sympathetic neurons and NPY-containing fibers have been found in peripheral tissues, such as around the arteries in the heart, the respiratory tract, the gastrointestinal tract, and the genitourinary tract. Central injection of NPY elicits a multitude of physiological responses, such as stimulation of feeding, increase in fat storage, elevation of blood sugar and insulin, anxiolytic behaviors, reduction in locomotor activity, hormone release, increase in blood pressure, reduction in body temperature, and catalepsy. In the cardiovascular system, NPY is believed to be involved in the regulation of coronary tone, while in the gastrointestinal tract, PYY is reported to cause inhibition of gastric acid secretion, pancreatic exocrine secretion, and gastrointestinal motility. These effects are selectively mediated by various NPY receptors which currently include the Y₁, Y₂, Y₃, Y₄, and Y₅ subtypes, in addition to the hypothetical Y_{1-like} subtype [C. Wahlestedt, D. Reis, *Ann. Rev. Pharmacol. Toxicol.*, 33, 309 (1993); D. Gehlert, P. Hipskind, *Curr. Pharm. Design*, 1, 295 (1995); M. C. Michel et al., *Pharmacol. Rev.*, 50, 143 (1998)]. Selective peptidic agonists and antagonists have been identified for most of the subtypes, but few selective non-peptidic antagonists have been reported [B. A. Zimanyi, Z. Fathi, G. S. Pointdexter, *Curr. Pharm. Design*, 4, 349 (1998)]. The Y₁ and Y₅ receptor subtypes appear to be involved in appetite regulation, but their relative contribution to the modulation of food intake and energy expenditure remains unclear [D. R. Gehlert, P. A. Hipskind, *Exp. Opin. Invest. Drugs*, 6, 1827, (1997)]. The discovery of non-peptidic antagonists of the Y₁ and/or Y₅ receptor, would provide novel therapeutic agents, devoid of the shortcomings of the peptide antagonists, namely, for example, poor metabolic stability, low oral bioavailability, poor brain permeability, for the treatment of obesity and cardiovascular diseases. Recently, a few of those agents have been reported [D. R. Gehlert, P. A. Hipskind, *Exp. Opin. Invest. Drugs*, 6, 1827, (1997); P. Hipskind et al., *J. Med. Chem.*, 40, 3712 (1997); M. Muller et al., *Arch. Pharm. Pharm. Med. Chem.*,

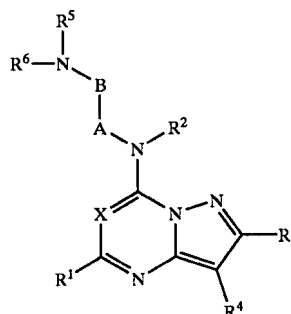
330, 333 (1997); H. Zarrinmayeh, et al., *J. Med. Chem.*, 41, 2709 (1998); H. A. Wieland et al., *Br. J. Pharmacol.*, 125, 549 (1998); Y. Shigeri et al., *Pharmacol. Letters*, 63, PL 151 (1998); D. M. Zimmerman et al., *Bioorg. Med. Chem. Letters*, 8, 473, (1998); L. Criscione, *J. Clin. Invest.*, 102, 12, 2136 (1998); Y. Murakami, et al., *J. Med. Chem.*, 42, 2621 (1999); T. C. Britton et al., *Bioorg. Med. Chem. Letters*, 9, 475, (1999); H. Zarrinmayeh, et al., *Bioorg. Med. Chem. Letters*, 9, 647, (1999)], some of which having demonstrated pharmacological efficacy in pre-clinical animal models. The present invention provides a novel class of potent non-peptidic antagonists of the NPY receptors, in particular, the Y₁ receptor.

[0004] Insofar as is known, aminoalkyl substituted pyrazolo[1,5-a]-1,5-pyrimidines and pyrazolo[1,5-a]-1,3,5-triazines have not been previously reported as NPY receptor(s) antagonists useful in the treatment of feeding and cardiovascular disorders. However, this general class of compounds has been described for other uses by virtue of different mechanisms of action. For instance, WO 98/03510 and WO 99/38868 (Du Pont Pharmaceuticals) discloses pyrazolo[1,5-a]-1,5-pyrimidines and pyrazolo [1,5-a]-1,3,5-triazines as antagonists of the corticotropin releasing factor (CRF). Therein, other prior art relative to pyrazolo[1,5-a]-1,5-pyrimidines and pyrazolo[1,5-a]-1,3,5-triazines is also described. Similar compounds have also been described in WO 97/29109, 98/08847, and D. J. Wustrow et al., *Bioorg. Med. Chem. Lett.* 8, 2067 (1998).

SUMMARY OF THE INVENTION

[0005] Compounds that interact with the Y₁ receptor and inhibit the activity of neuropeptide Y at those receptors are useful in treating physiological disorders associated with an excess of neuropeptide Y, including eating disorders, such as, for example, obesity and bulimia, and certain cardiovascular diseases, for example, hypertension.

[0006] This invention relates to novel compounds, compositions, and methods for the treatment of physiological disorders associated with an excess of neuropeptide Y. The novel compounds encompassed by the present invention are those of formula I



[0007] wherein:

[0008] X is N or CR¹⁴;

[0009] R¹ is selected from H, C₁-C₆ alkyl, C₃-C₁₀ cycloalkyl, (C₃-C₁₀ cycloalkyl) C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, cyano, halo, C₁-C₆ haloalkyl, OR⁷, C₁-C₆ alkyl-OR⁷; C₁-C₆ cyanoalkyl, NR⁸R⁹, C₁-C₆ alkyl-NR⁸R⁹;

[0010] R is H,

[0011] C₁-C₆ alkyl which optionally forms a C₃-C₆ aminocarbocycle or a C₂-C₅ aminoheterocycle with A or B, each optionally substituted at each occurrence with R⁷,

[0012] C₃-C₁₀ cycloalkyl, or

[0013] (C₃-C₁₀ cycloalkyl) C₁-C₆ alkyl;

[0014] or R₂ and R⁶ jointly form with the 2 nitrogen atoms to which they are bound a C₂-C₅ aminoheterocycle optionally substituted at each occurrence with R⁷;

[0015] A is (CH₂)_m where m is 1,2 or 3 and is optionally mono- or di-substituted on each occurrence with C₁-C₆ alkyl, C₃-C₁₀ cycloalkyl, (C₃-C₁₀ cycloalkyl) C₁-C₆ alkyl, C₁-C₆ alkenyl, C₁-C₆ alkynyl, cyano, halo, C₁-C₆ haloalkyl, OR⁷, C₁-C₆ alkyl-OR⁷; C₁-C₆ cyanoalkyl, NR⁸R⁹, C₁-C₆ alkyl-NR⁸R⁹,

[0016] or A and B jointly form a C₃-C₆ carbocycle, optionally substituted at each occurrence with R⁷,

[0017] or, as mentioned above, A and R² jointly form a C₃-C₆ aminocarbocycle or a C₂-C₅ aminoheterocycle optionally substituted at each occurrence with R⁷;

[0018] B is (CH₂)_n where n is 1,2 or 3 and is optionally mono- or di-substituted on each occurrence with C₁-C₆ alkyl, C₃-C₁₀ cycloalkyl, (C₃-C₁₀ cycloalkyl) C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, cyano, halo, C₁-C₆ haloalkyl, OR⁷, C₁-C₆ alkyl-OR⁷; C₁-C₆ cyanoalkyl, NR⁸R⁹, C₁-C₆ alkyl-NR⁸R⁹, or, as mentioned above, B and A jointly form a C₃-C₆ carbocycle, optionally substituted at each occurrence with R⁷

[0019] or, as mentioned above, B and R² jointly form a C₃-C₆ aminocarbocycle or a C₂-C₅ aminoheterocycle optionally substituted at each occurrence with R⁷;

[0020] R³ is selected from H, C₁-C₆ alkyl, C₃-C₁₀ cycloalkyl, (C₃-C₁₀ cycloalkyl) C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, cyano, halo, C₁-C₆ haloalkyl, OR⁷, C₁-C₆ alkyl-OR⁷, C₁-C₆ cyanoalkyl, NR⁸R⁹, C₁-C₆ alkyl-NR⁸R⁹;

[0021] R⁴ is selected from aryl or heteroaryl, each optionally substituted with 1 to 5 substituents independently selected at each occurrence from C₁-C₆ alkyl, C₃-C₁₀ cycloalkyl, C₃-C₁₀ cycloalkenyl, (C₃-C₁₀ cycloalkyl) C₁-C₆ alkyl, C₁-C₆ alkenyl, C₁-C₆ alkynyl, halogen, C₁-C₆ haloalkyl, trifluoromethylsulfonyl, OR⁷, C₁-C₆ alkyl-OR⁷, NR⁸R⁹, C₁-C₆ alkyl-NR⁸R⁹, CONR⁸R⁹, C₁-C₆ alkyl-CONR⁸R⁹, COOR⁷, C₁-C₆ alkyl-COOR⁷, CN, C₁-C₆ alkyl-CN, SO₂NR⁸R⁹, SO₂R⁷, aryl, heteroaryl, heterocycloalkyl, 3-, 4-, or 5-(2-oxo-1,3-oxazolidinyl), with the proviso that at least one of the positions ortho or para to the point of attachment of the aryl or heteroaryl ring to the pyrazole is substituted;

[0022] R⁵ is selected from:

[0023] C₁-C₆ alkyl, (C₃-C₁₀ cycloalkyl) C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, each of which is substituted with 1 to 5 groups independently selected at each

occurrence from halo, C₁-C₂ haloalkyl, OR⁷, cyano, NR⁸R⁹, CONR⁸R⁹, COOR⁷, SO₂NR⁸R⁹, SO₂R⁷, NR¹¹COR², NR¹¹SO₂R⁷;

[0024] C₁-C₆ arylalkyl, C₁-C₆ heteroarylalkyl, C₅-C₈ arylcycloalkyl, or C₅-C₈ heteroarylalkyl, where aryl is phenyl or naphthyl, and heteroaryl is 2-,3-, or 4-pyridyl, 2-, 4- or 5-pyrimidinyl, triazinyl, 1-, 2- or 4-imidazolyl, 2-, 4-, or 5-oxazolyl, isoxazolyl, indolyl, pyrazolyl, quinolyl, isoquinolyl, 2-, 4-, or 5-thiazolyl, benzothiadiazolyl, 1-, 3- or 4-pyrazolyl, 1-, 3- or 4-triazolyl, 2-triazinyl, 2-pyrazinyl, 2-, or 3-furanyl, 2-, or 3-thienyl, 2-, or 3-benzothienyl, or 1-, 2- or 5-tetrazolyl, each of which is optionally substituted with 1 to 5 substituents independently selected at each occurrence from C₁-C₆ alkyl, C₃-C₁₀ cycloalkyl, C₃-C₁₀ cycloalkenyl, (C₃-C₁₀ cycloalkyl) C₁-C₆ alkyl, C₁-C₆ alkenyl, halogen, C₁-C₆ haloalkyl, trifluoromethylsulfonyl, OR⁷, NR⁸R⁹, C₁-C₆ alkyl-OR⁷, C₁-C₆ alkyl-NR⁸R⁹, CONR⁸R⁹, COOR⁷, CN, SO₂NR⁸R⁹, SO₂R⁷, aryl, heteroaryl, heterocycloalkyl, 3-, 4-, or 5-(2-oxo-1,3-oxazolidinyl), with the proviso that 2 adjacent substituents can optionally form together a C₃-C₁₀ cycloalkyl ring, a C₃-C₁₀ cycloalkenyl ring or a heterocycloalkyl ring;

[0025] C₃-C₁₀ cycloalkyl substituted with 1 to 6 substituents independently selected at each occurrence from C₁-C₆ alkyl, C₃-C₁₀ cycloalkyl, C₃-C₁₀ cycloalkenyl, (C₃-C₁₀ cycloalkyl) C₁-C₆ alkyl, C₁-C₆ alkenyl, halogen, C₁-C₆ haloalkyl, OR⁷, NR⁸R⁹, with the proviso that when two OR⁷ or NR⁸R⁹ substituents are geminally located on the same carbon R⁷ is not H and they can form together a C₂-C₄ ketal, oxazoline, oxazolidine, imidazoline, or imidazolidine heterocycle, C₁-C₆ alkyl-OR⁷, C₁-C₆ alkyl-NR⁸R⁹, CONR⁸R⁹, COOR⁷, CN, oxo, hydroximino, C₁-C₆ alkoximino, SO₂NR⁸R⁹, SO₂R⁷, heterocycloalkyl, aryl, heteroaryl, where aryl or heteroaryl is optionally substituted with 1 to 5 substituents independently selected at each occurrence from C₁-C₆ alkyl, C₃-C₁₀ cycloalkyl, C₃-C₁₀ cycloalkenyl, (C₃-C₁₀ cycloalkyl) C₁-C₆ alkyl, C₁-C₆ alkenyl, halogen, C₁-C₆ haloalkyl, trifluoromethylsulfonyl, OR⁷, NR⁸R⁹, C₁-C₆ alkyl-OR⁷, C₁-C₆ alkyl-NR⁸R⁹, CONR⁸R⁹, COOR⁷, CN, SO₂NR⁸R⁹, SO₂R⁷, aryl, heteroaryl, heterocycloalkyl, 3-, 4-, or 5-(2-oxo-1,3-oxazolidinyl), with the proviso that 2 adjacent substituents can optionally form together a C₃-C₁₀ cycloalkyl ring, a C₃-C₁₀ cycloalkenyl ring or a heterocycloalkyl ring;

[0026] aryl or heteroaryl, optionally substituted with 1 to 5 substituents independently selected at each occurrence from halogen, C₁-C₆ alkyl, C₃-C₁₀ cycloalkyl, C₃-C₁₀ cycloalkenyl, (C₃-C₁₀ cycloalkyl) C₁-C₆ alkyl, C₁-C₆ alkenyl, halogen, C₁-C₆ haloalkyl, trifluoromethylsulfonyl, OR⁷, NR⁸R⁹, C₁-C₆ alkyl-OR⁷, C₁-C₆ alkyl-NR⁸R⁹, CONR⁸R⁹, COOR⁷, CN, SO₂NR⁸R⁹, SO₂R⁷, aryl, heteroaryl, heterocycloalkyl, 3-, 4-, or 5-(2-oxo-1,3-oxazolidinyl), with the proviso that 2

adjacent substituents can optionally form together a C₃-C₁₀ cycloalkyl ring, a C₃-C₁₀ cycloalkenyl ring or a heterocycloalkyl ring; or

[0027] 3- or 4-piperidinyl, 3-pyrrolidinyl, 3- or 4-tetrahydropyranyl, 3-tetrahydrofuranyl, 3- or 4-tetrahydropyranyl, 3-tetrahydrofuranyl, 3- or 4-tetrahydrothiopyranyl, 3- or 4-(1,11-dioxo) tetrahydrothiopyranyl, 1-azabicyclo[4.4.0]decyl, 8-azabicyclo[3.2.1]octanyl, norbornyl, quinuclidinyl, indolin-2-one-3-yl, 2-(methoximino)-perhydroazepin-6-yl, each optionally substituted with 1 to 5 substituents independently selected at each occurrence from R⁷, C₁-C₆ alkyl-OR⁷, C₁-C₆ alkyl-NR⁸R⁹, CONR⁸R⁹, CN, COOR⁷, SO₂NR⁸R⁹, SO₂R⁷;

[0028] R⁶ is selected from H, C₁-C₆ alkyl, C₃-C₁₀ cycloalkyl, (C₃-C₁₀ cycloalkyl) C₁-C₆ alkyl, C₂-C₄ alkenyl, C₁-C₆ arylalkyl, C₁-C₆ heteroarylalkyl where aryl or heteroaryl are optionally substituted with 1 to 5 substituents independently selected at each occurrence from halogen, C₁-C₆ haloalkyl, OR¹³, NR⁸R⁹, C₁-C₆ alkyl-OR¹³, C₁-C₆ alkyl-NR⁸R⁹, CONR⁸R⁹, COOR⁷, CN, SO₂NR⁸R⁹, SO₂R⁷, or R⁶ and R², as mentioned above, jointly form, with the 2 nitrogen atoms to which they are bound, a C₂-C₅ aminoheterocycle optionally substituted at each occurrence with R⁷;

[0029] R⁷ is H, C₁-C₆ alkyl, C₃-C₁₀ cycloalkyl, C₃-C₁₀ cycloalkenyl, (C₃-C₁₀ cycloalkyl) C₁-C₆ alkyl, C₁-C₃ haloalkyl,

[0030] or heterocycloalkyl, C₁-C₈ alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, C₁-C₈ alkanoyl, aroyl, heteroaroyl, aryl, heteroaryl, C₁-C₆ arylalkyl or C₁-C₆ heteroarylalkyl each optionally substituted with 1 to 5 substituents independently selected at each occurrence from halogen, C₁-C₆ haloalkyl, OR¹³, NR⁸R⁹, C₁-C₆ alkyl-OR¹³, C₁-C₆ alkyl-NR⁸R⁹, CONR⁸R⁹, COOR¹³, CN, SO₂NR⁸R⁹, SO₂R¹³, with the proviso that for SO₂R¹³, R¹³ cannot be H;

[0031] R⁸ and R⁹ are independently selected at each occurrence from H, C₁-C₆ alkyl, C₃-C₁₀ cycloalkyl, C₂-C₆ alkenyl, C₃-C₁₀ cycloalkenyl, C₂-C₆ alkynyl, heterocycloalkyl, C₁-C₈ alkanoyl, aroyl, heteroaroyl, aryl, heteroaryl, C₁-C₆ arylalkyl or C₁-C₆ heteroarylalkyl, or R⁸ and R⁹, taken together, can form a C₃-C₆ aminocarbocycle or a C₂-C₅ aminoheterocycle each optionally substituted at each occurrence with C₁-C₆ alkyl, C₃-C₁₀ cycloalkyl, C₃-C₁₀ cycloalkenyl, (C₃-C₁₀ cycloalkyl) C₁-C₆ alkyl, C₁-C₃ haloalkyl, or heterocycloalkyl, C₁-C₈ alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, C₁-C₈ alkanoyl, aroyl, heteroaroyl, aryl, heteroaryl, C₁-C₆ arylalkyl or C₁-C₆ heteroarylalkyl;

[0032] R¹¹ is selected from H, C₁-C₆ alkyl, C₃-C₁₀ cycloalkyl, (C₃-C₁₀ cycloalkyl) C₁-C₆ alkyl;

[0033] R¹² is selected from H, aryl, heteroaryl, C₁-C₆ alkyl, C₃-C₁₀ cycloalkyl, (C₃-C₁₀ cycloalkyl) C₁-C₆ alkyl, optionally substituted with OR⁷, NR⁸R⁹, C₃-C₆ aminocarbocycle, or C₂-C₅ aminoheterocycle;

[0034] R¹³ is independently selected at each occurrence from H, C₁-C₆ alkyl, C₃-C₁₀ cycloalkyl, (C₃-C₁₀

cycloalkyl) C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ haloalkyl, with the proviso that when R⁷ is SO₂R¹³, R¹³ cannot be H;

[0035] R¹⁴ is H, C₁-C₆ alkyl, C₃-C₁₀ cycloalkyl, (C₃-C₁₀ cycloalkyl) C₁-C₆ alkyl, C₂-C₄ alkenyl, C₂-C₄ alkynyl, halo, or CN;

[0036] or a pharmaceutically acceptable salt, hydrate, or prodrug thereof.

[0037] Preferred compounds of the present invention are those of formula I where X is N or CH, R¹ is H, C₁-C₆ alkyl, C₃-C₁₀ cycloalkyl, or (C₃-C₁₀ cycloalkyl) C₁-C₆ alkyl; R⁶ is H, C₁-C₆ alkyl, C₃-C₁₀ cycloalkyl, or (C₃-C₁₀ cycloalkyl) C₁-C₆ alkyl.

[0038] This invention also encompasses, in additional embodiments, the novel compounds of formula I, and the salts and solvates thereof, as well as pharmaceutical formulations comprising a compound of formula I, or a pharmaceutically acceptable salt or solvate thereof, in combination with one or more pharmaceutically acceptable carriers, excipients, or diluents therefor.

[0039] This invention also encompasses methods to treat physiological disorders associated with an excess of neuropeptide Y, such as eating and cardiovascular disorders, which method comprises administering to a mammal in need of said treatment an effective amount of a compound of the formula I.

[0040] This invention also encompasses methods of selectively inhibiting binding of NPY₁ receptor s, which comprises contacting a compound of formula I with neuronal cells, wherein the compound is present in an amount effective to produce a concentration sufficient to inhibit binding of NPY₁ receptors in vitro.

DETAILED DESCRIPTION OF THE INVENTION

[0041] The current invention concerns the discovery that a select group of aminoalkyl substituted 4-amino pyrazolopyrimidines and 7-amino pyrazolo triazines, those of formula I, which are novel and useful neuropeptide Y receptor antagonists.

[0042] In certain situations, the compounds of formula I may contain one or more asymmetric carbon atoms, so that the compounds can exist in different stereoisomeric forms. These compounds can be, for example, racemates or optically active forms. In these situations, the single enantiomers, i.e., optically active forms, can be obtained by asymmetric synthesis or by resolution of the racemates. Resolution of the racemates can be accomplished, for example, by conventional methods such as crystallization in the presence of a resolving agent, or chromatography, using, for example a chiral HPLC column.

[0043] Representative compounds of the present invention, which are encompassed by formula I, include, but are not limited to the compounds in Examples 1-306 and their pharmaceutically acceptable acid addition salts. In addition, if the compound of the invention is obtained as an acid addition salt, the free base can be obtained by basifying a solution of the acid salt. Conversely, if the product is a free base, an addition salt, particularly a pharmaceutically acceptable addition salt, may be produced by dissolving the

free base in a suitable organic solvent and treating the solution with an acid, in accordance with conventional procedures for preparing acid addition salts from base compounds.

[0044] Non-toxic pharmaceutical salts include salts of acids such as hydrochloric, phosphoric, hydrobromic, sulfuric, sulfonic, formic, toluenesulfonic, methanesulfonic, nitric, benzoic, citric, tartaric, maleic, hydroiodic, alkanic such as acetic, $\text{HOOC}-(\text{CH}_2)_n-\text{COOH}$ where n is 0-4, and the like. Those skilled in the art will recognize a wide variety of non-toxic pharmaceutically acceptable addition salts.

[0045] The present invention also encompasses the acylated prodrugs of the compounds of formula I. "Prodrugs" are considered to be any covalently bonded carriers which release the active parent drug of formula I in vivo when such prodrug is administered to a mammalian subject. Prodrugs of the compounds of the invention are prepared by modifying functional groups present in the compounds in such a way that the modifications are cleaved, either in routine manipulation or in vivo to the parent compounds. Prodrugs include compounds wherein hydroxy, amine, or sulfhydryl groups are bonded to any group that, when administered to a mammalian subject, cleaves to form a free hydroxyl, amino, or sulfhydryl group, respectively. Examples of prodrugs include, but are not limited to, acetate, formate, and benzoate derivatives of alcohol and amine functional groups in the compounds of formula I; and the like. Those skilled in the art will recognize various synthetic methodologies which may be employed to prepare non-toxic pharmaceutically acceptable addition salts and acylated prodrugs of the compounds encompassed by formula I.

[0046] Where a compound exists in various tautomeric forms, the invention is not limited to any one of the specific tautomers. The invention includes all tautomeric forms of a compound.

[0047] By "heteroatom" in the present invention is meant oxygen or sulfur, or a nitrogen atom optionally substituted by $\text{C}_1\text{-C}_6$ lower alkyl, $\text{C}_1\text{-C}_6$ arylalkyl, $\text{C}_1\text{-C}_{10}$ cycloalkyl, ($\text{C}_2\text{-C}_{10}$ cycloalkyl) $\text{C}_1\text{-C}_6$ alkyl, $\text{C}_2\text{-C}_8$ alkanoyl, $\text{C}_1\text{-C}_6$ sulfonyl.

[0048] By "alkyl", "lower alkyl", or " $\text{C}_1\text{-C}_6$ alkyl" in the present invention is meant straight or branched chain alkyl groups having 1-6 carbon atoms, such as, for example, methyl, ethyl, propyl, isopropyl, n-butyl, sec-butyl, tert-butyl, pentyl, 2-pentyl, isopentyl, neopentyl, hexyl, 2-hexyl, 3-hexyl, and 3-methylpentyl.

[0049] By "cycloalkyl", or " $\text{C}_3\text{-C}_{10}$ cycloalkyl" in the present invention is meant alkyl groups having 3-10 carbon atoms forming a mono-, bi-, or polycyclic ring system, such as, for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, norbornyl, and the like.

[0050] By "(cycloalkyl)alkyl", "lower (cycloalkyl)alkyl", or ($\text{C}_3\text{-C}_{10}$ cycloalkyl) $\text{C}_1\text{-C}_6$ alkyl in the present invention is meant a straight or branched alkyl substituent formed of 1 to 6 carbon atoms attached to a mono-, bi, or polycyclic ring system having 3-10 carbon atoms, such as, for example, cyclopropylmethyl, cyclobutylmethyl, cyclopentylmethyl, cyclohexylmethyl, cycloheptylmethyl, and the like.

[0051] The term " $\text{C}_2\text{-C}_6$ alkenyl" in the present invention means hydrocarbon chains having 2 to 6 carbons in a straight

or branched arrangement and containing one or more unsaturated carbon-carbon double bonds which may occur in any stable point along the chain, such as, for example, ethenyl, allyl, isopropenyl, and the like.

[0052] By "cycloalkenyl" or " $\text{C}_3\text{-C}_{10}$ cycloalkenyl" in the present invention is meant alkyl groups having 3-10 carbon atoms forming a mono-, bi, or polycyclic ring system having 3-10 carbon atoms and containing one or more carbon-carbon double bonds which may occur in any stable point in the ring, such as, for example, cyclopentenyl, cyclohexenyl, or cycloheptenyl.

[0053] The term " $\text{C}_2\text{-C}_6$ alkynyl" in the present invention means hydrocarbon chains having 2 to 6 carbons in a straight or branched arrangement and containing one or more unsaturated carbon-carbon triple bonds which may occur in any stable point along the chain, such as, for example, ethynyl, propargyl, and the like.

[0054] The term "aryl" in the present invention means a monocyclic or bicyclic aromatic group having preferably 6 to 10 carbon atoms, such as, for example, phenyl or naphthyl.

[0055] The term "heteroaryl" in the present invention means an aryl group in which one or more of the ring(s) carbon atoms have been replaced with a heteroatom. Such groups preferably have 4 to 10 carbon atoms and 1 to 4 heteroatoms, such as, for example, pyridyl, pyrimidinyl, triazinyl, imidazolyl, oxazolyl, isoxazolyl, indolyl, pyrrolyl, pyrazolyl, quinolinyl, isoquinolinyl, thiazolyl, benzothiadiazolyl, triazolyl, triazinyl, pyrazinyl, furanyl, thienyl, benzothienyl, benzofuranyl, tetrazolyl.

[0056] The term "heterocyclyl", "heterocycle" or "heterocycloalkyl" in the present invention means a saturated or partially saturated heteroaryl group.

[0057] By " $\text{C}_1\text{-C}_6$ arylalkyl" or " $\text{C}_1\text{-C}_6$ heteroarylalkyl" in the present invention is meant a branched or straight-chain alkyl group having 1-6 carbon atoms and substituted on one of the carbon atoms by an optionally substituted aryl or heteroaryl ring, such as, for example, benzyl, phenethyl, methylpyridyl, ethylpyridyl, and the like.

[0058] By " $\text{C}_5\text{-C}_8$ arylcycloalkyl" in the present invention is meant cycloalkyl groups having 5-8 carbon atoms fused to an aryl group, such as, for example, 1,2,3,4 tetrahydronaphthalenyl, 2,3-dihydrobenzothienyl, or 2,3-dihydrobenzofuranyl.

[0059] By " $\text{C}_5\text{-C}_8$ heteroarylalkyl" in the present invention is meant cycloalkyl groups having 5-8 carbon atoms fused to a heteroaryl group, such as, for example, 1,2,3,4 tetrahydroquinolyl, 2,3-dihydrobenzothienyl, 2,3-dihydrobenzofuranyl, or indolyl.

[0060] By "alkoxy", " $\text{C}_1\text{-C}_6$ alkoxy", or " $\text{C}_1\text{-C}_6$ alkyloxy" in the present invention is meant straight or branched chain alkoxy groups having 1-6 carbon atoms, such as, for example, methoxy, ethoxy, propoxy, isopropoxy, n-butoxy, sec-butoxy, tert-butoxy, pentoxy, 2-pentyl, isopentoxy, neopentoxy, hexoxy, 2-hexoxy, 3-hexoxy, and 3-methylpentoxy.

[0061] By "cycloalkoxy", " $\text{C}_3\text{-C}_{10}$ cycloalkoxy", or " $\text{C}_3\text{-C}_{10}$ cycloalkyloxy" in the present invention is meant a group formed by an oxygen atom attached to a mono-, bi, or

polycyclic ring system having 3-10 carbon atoms, such as, for example, cyclopropoxy, cyclobutoxy, cyclopentoxy, cyclohexoxy, or cycloheptoxy.

[0062] By “(cycloalkyl)alkyloxy”, “(C₃-C₁₀ cycloalkyl) C₁-C₆ alkoxy”, or “(C₃-C₁₀ cycloalkyl) C₁-C₆ alkyloxy” in the present invention is meant a group formed by an oxygen atom attached to a 1-6 carbon chain linked to a mono-, bi, or polycyclic ring system having 3-10 carbon atoms, such as, for example, cyclopropylmethyloxy, cyclobutylmethyloxy, cyclopentylmethyloxy, cyclohexylmethyloxy, cycloheptylmethyloxy, and the like.

[0063] By “C₃-C₆ aminocarbocycle” is meant a cyclic amino group formed by a nitrogen contained in a ring having 3 to 6 carbon atoms, such as, for example, azetidino, pyrrolidino, piperidino, perhydroazepino.

[0064] By “C₂-C₅ aminoheterocycle” is meant a cyclic amino group formed by a nitrogen contained in a ring having 2 to 5 carbon atoms and one other heteroatom, such as, for example, morpholino, thiomorpholino, piperazino.

[0065] By the terms “halo” or “halogen” in the present invention is meant fluoro, chloro, bromo, and iodo.

[0066] “Haloalkyl” is intended to include both branched and straight-chain alkyl having the specified number of carbon atoms substituted with 1 or more halogens.

[0067] The term “C₂-C₈ alkanoyl” means an acyl group with 2 to 8 carbon atoms in a linear, branched, or C₃-C₁₀ cycloalkyl arrangement, optionally substituted with 1 to 5 substituents independently selected at each occurrence from halogen, trifluoromethyl, OR⁷, NR⁸R⁹, CONR⁸R⁹, COOR⁷, or CN.

[0068] The term “C₁-C₆ alkyl sulfonyl” means an alkyl-sulfonyl group containing 1 to 6 carbon atoms in a linear, branched, or C₃-C₇ cycloalkyl arrangement.

[0069] The term “substituted” means that one or more hydrogen on the designated atom is replaced by the specified group, provided that the valence on the designated atom is not exceeded, and that a chemically stable compound results from the substitution.

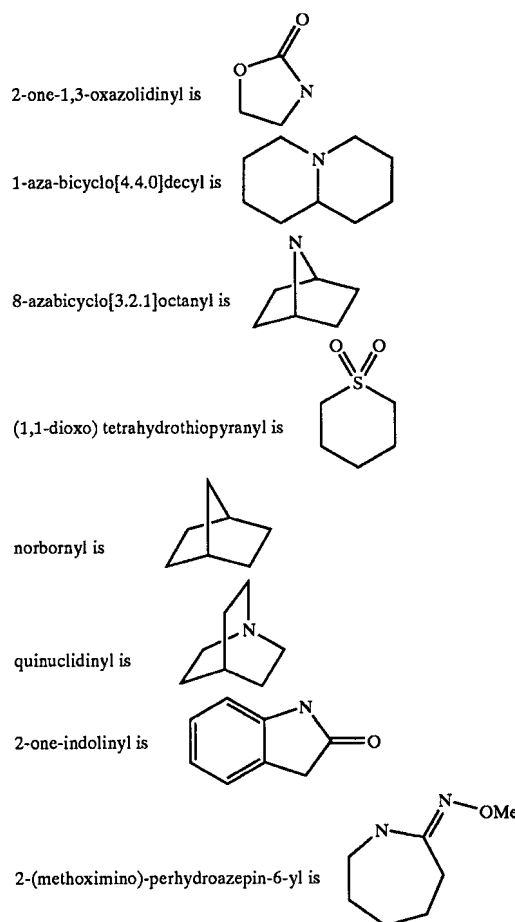
[0070] A stable compound is defined herein as one that can be isolated, characterized, and tested for biological activity.

[0071] The term “oxo” (i.e. =O) indicates that two geminal hydrogen atoms are replaced by a double-bond oxygen group.

[0072] The term “hydroximino” (i.e. =N—OH) indicates that two geminal hydrogen atoms are replaced by a double-bond nitrogen atom substituted with a hydroxyl group.

[0073] The term “C₁-C₆ alkoximino” (i.e. =N—O-Alkyl) indicates that two geminal hydrogen atoms are replaced by a double-bond nitrogen atom substituted with a C₁-C₂ alkoxy group, such as, for example, methoximino (=N—OMe).

[0074] In the present invention, some of the groups specifically mentioned above are defined as follows:



[0075] Unless specified, the point of attachment may occur in any stable point along the above-mentioned rings.

[0076] In the present invention, the term “potent” in the context of NPY₁ receptor antagonists qualifies a binding affinity with a K_i of less than 10 micromolar, preferably less than 1 micromolar, and more preferably less than 100 nanomolar in the human NPY₁ binding assay.

[0077] In the present invention, the term “selective” in the context of NPY₁ receptor antagonists qualifies a binding affinity with a K_i in the human NPY₁ binding assay that is 10-fold, preferably 100-fold, and more preferably 1000-fold, less than the K_i of the same compound measured in another receptor binding assay, in particular the NPY₅ and the CRF₁ receptor binding assays. Binding assays for the NPY₅ and CRF₁ receptors have been described, for example, in *J. Clin. Invest.*, 102 2136 (1998) and in *Endocrinology* 116, 1653 (1985), respectively.

[0078] As the compounds of formula I are selective antagonists of the Y₁ receptor, they are of value in the treatment of a wide variety of clinical conditions which are characterized by the presence of an excess of neuropeptide Y. Thus, the invention provides methods for the treatment or

prevention of a physiological disorder associated with an excess of neuropeptide Y, which method comprises administering to a mammal in need of said treatment an effective amount of a compound of formula I or a pharmaceutically acceptable salt, solvate or prodrug thereof. The term "physiological disorder associated with an excess of neuropeptide Y" encompasses those disorders associated with an inappropriate stimulation of neuropeptide Y receptors, regardless of the actual amount of neuropeptide Y present locally. These physiological disorders may include: disorders or diseases pertaining to the heart, blood vessels or the renal system, such as vasospasm, heart failure, shock, cardiac hypertrophy increased blood pressure, angina, myocardial infarction, sudden cardiac death, arrhythmia, peripheral vascular disease, and abnormal renal conditions such as impaired flow of fluid, abnormal mass transport, or renal failure; conditions related to increased sympathetic nerve activity for example, during or after coronary artery surgery, and operations and surgery in the gastrointestinal tract; cerebral diseases and diseases related to the central nervous system, such as cerebral infarction, neurodegeneration, epilepsy, stroke, and conditions related to stroke, cerebral vasospasm and hemorrhage, depression, anxiety, schizophrenia, and dementia; conditions related to pain or nociception; diseases related to abnormal gastrointestinal motility and secretion, such as different forms of ileus, urinary incontinence, and Crohn's disease; abnormal drink and food intake disorders, such as obesity, anorexia, bulimia, and metabolic disorders; diseases related to sexual dysfunction and reproductive disorders; conditions or disorders associated with inflammation; respiratory diseases, such as asthma and conditions related to asthma and bronchoconstriction; and diseases related to abnormal hormone release, such as leutinizing hormone, growth hormone, insulin, and prolactin.

[0079] The compounds of general formula I may be administered orally, topically, parenterally, by inhalation or spray or rectally in dosage unit formulations containing conventional non-toxic pharmaceutically acceptable carriers, adjuvants and vehicles. The term parenteral as used herein includes subcutaneous injections, intravenous, intramuscular, intrasternal injection or infusion techniques. In addition, there is provided a pharmaceutical formulation comprising a compound of general formula I and a pharmaceutically acceptable carrier. One or more compounds of general formula I may be present in association with one or more non-toxic pharmaceutically acceptable carriers and/or diluents and/or adjuvants and if desired other active ingredients. The pharmaceutical compositions containing compounds of general formula I may be in a form suitable for oral use, for example, as tablets, troches, lozenges, aqueous or oily suspensions, dispersible powders or granules, emulsion, hard or soft capsules, or syrups or elixirs.

[0080] Compositions intended for oral use may be prepared according to any method known to the art for the manufacture of pharmaceutical compositions and such compositions may contain one or more agents selected from the group consisting of sweetening agents, flavoring agents, coloring agents and preserving agents in order to provide pharmaceutically elegant and palatable preparations. Tablets contain the active ingredient in admixture with non-toxic pharmaceutically acceptable excipients which are suitable for the manufacture of tablets. These excipients may be for example, inert diluents, such as calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate;

granulating and disintegrating agents, for example, corn starch, or alginic acid; binding agents, for example starch, gelatin or acacia, and lubricating agents, for example magnesium stearate, stearic acid or talc. The tablets may be uncoated or they may be coated by known techniques to delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monostearate or glyceryl distearate may be employed.

[0081] Formulations for oral use may also be presented as hard gelatin capsules wherein the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules wherein the active ingredient is mixed with water or an oil medium, for example peanut oil, liquid paraffin or olive oil. Aqueous suspensions contain the active materials in admixture with excipients suitable for the manufacture of aqueous suspensions. Such excipients are suspending agents, for example sodium carboxymethylcellulose, methylcellulose, hydropropylmethylcellulose, sodium alginate, polyvinylpyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents may be a naturally-occurring phosphatide, for example, lecithin, or condensation products of an alkylene oxide with fatty acids, for example polyoxyethylene stearate, or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethyleneoxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, for example polyethylene sorbitan monooleate. The aqueous suspensions may also contain one or more preservatives, for example ethyl, or n-propyl p-hydroxybenzoate, one or more coloring agents, one or more flavoring agents, and one or more sweetening agents, such as sucrose or saccharin.

[0082] Oily suspensions may be formulated by suspending the active ingredients in a vegetable oil, for example arachid oil, olive oil, sesame oil or coconut oil, or in a mineral oil such as liquid paraffin. The oily suspensions may contain a thickening agent, for example beeswax, hard paraffin or cetyl alcohol. Sweetening agents such as those set forth above, and flavoring agents may be added to provide palatable oral preparations. These compositions may be preserved by the addition of an anti-oxidant such as ascorbic acid.

[0083] Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water provide the active ingredient in admixture with a dispersing or wetting agent, suspending agent and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those already mentioned above. Additional excipients, for example sweetening, flavoring and coloring agents, may also be present.

[0084] Pharmaceutical compositions of the invention may also be in the form of oil-in-water emulsions. The oily phase may be a vegetable oil, for example olive oil or arachid oil, or a mineral oil, for example liquid paraffin or mixtures of

these. Suitable emulsifying agents may be naturally-occurring gums, for example gum acacia or gum tragacanth, naturally-occurring phosphatides, for example soy bean, lecithin, and esters or partial esters derived from fatty acids and hexitol, anhydrides, for example sorbitan monooleate, and condensation products of the said partial esters with ethylene oxide, for example polyoxyethylene sorbitan monooleate. The emulsions may also contain sweetening and flavoring agents.

[0085] Syrups and elixirs may be formulated with sweetening agents, for example glycerol, propylene glycol, sorbitol or sucrose. Such formulations may also contain a demulcent, a preservative and flavoring and coloring agents. The pharmaceutical compositions may be in the form of a sterile injectable aqueous or oleaginous suspension. This suspension may be formulated according to the known art using those suitable dispersing or wetting agents and suspending agents which have been mentioned above. The sterile injectable preparation may also be sterile injectable solution or suspension in a non-toxic parenterally acceptable diluent or solvent, for example as a solution in 1,3-butenediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectables.

[0086] The compounds of general formula I may also be administered in the form of suppositories for rectal administration of the drug. These compositions can be prepared by mixing the drug with a suitable non-irritating excipient which is solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum to release the drug. Such materials are cocoa butter and polyethylene glycols.

[0087] Compounds of general formula I may be administered parenterally in a sterile medium. The drug, depending on the vehicle and concentration used, can either be suspended or dissolved in the vehicle. Advantageously, adjuvants such as local anesthetics, preservatives and buffering agents can be dissolved in the vehicle.

[0088] Dosage levels of the order of from about 0.1 mg to about 50 mg per kilogram of body weight per day are useful in the treatment of the above-indicated conditions (about 0.5 mg to about 3 g per patient per day), although higher amounts for example up to 140 mg/kg/day may be appropriate in some circumstances. The amount of active ingredient that may be combined with the carrier materials to produce a single dosage form will vary depending upon the host treated and the particular mode of administration. Dosage unit forms will generally contain between from about 1 mg to about 500 mg of an active ingredient.

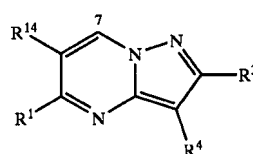
[0089] It will be understood, however, that the specific dose level for any particular patient will depend upon a

variety of factors including the activity of the specific compound employed, the age, body weight, general health, sex, diet, time of administration, route of administration, and rate of excretion, drug combination and the severity of the particular disease undergoing therapy.

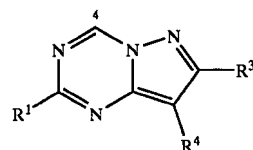
[0090] In appropriate cases, the compounds of the invention may be employed in combination with other active agents. The invention therefore also provides pharmaceutical combination compositions comprising a therapeutically effective amount of a composition comprising: (a) first compound, said first compound being a compound of the type described above a prodrug thereof, or a pharmaceutically acceptable salt of said compound or of said prodrug; and (b) a second compound, said second compound being a gonist, a thyromimetic, an eating behavior modifying agent or a NPY antagonist; and a pharmaceutical carrier, vehicle, diluent. Combinations may, for example comprise (a) first compound, said first compound being a compound as described above a prodrug thereof, or a pharmaceutically acceptable salt of said compound or of said prodrug; (b) a second compound, said second compound being an aldose reductase inhibitor, a glycogen phosphorylase inhibitor, a sorbitol dehydrogenase inhibitor, insulin metformin, acarbose, a thiazolidinedione, a glitazone, rosiglitazone, a sulfonylurea, glipazide, glyburide, or chlorpropamide; (c) a pharmaceutical carrier, vehicle, or diluent. In other cases, a kit may be appropriate comprising: (a) first compound, said first compound being a compound of claim 24 or 25, a prodrug thereof, or a pharmaceutically acceptable salt of said compound or of said prodrug; (b) a second compound, said second compound being a P3 agonist, a thyromimetic, an eating behavior modifying agent or a NPY antagonist; and a pharmaceutical carrier, vehicle, diluent; and (c) means for containing said first and second unit dosage forms wherein the amounts of the first and second compounds result in a therapeutic effect.

[0091] Preparation of Aminoalkyl Substituted Pyrazolo[1,5-a]-1,5-Pyrimidines and Pyrazolo[1,5-a]-1,3,5-Triazines Derivatives

[0092] One general approach is to convert a heterocyclic core A and or a heterocyclic core B



A



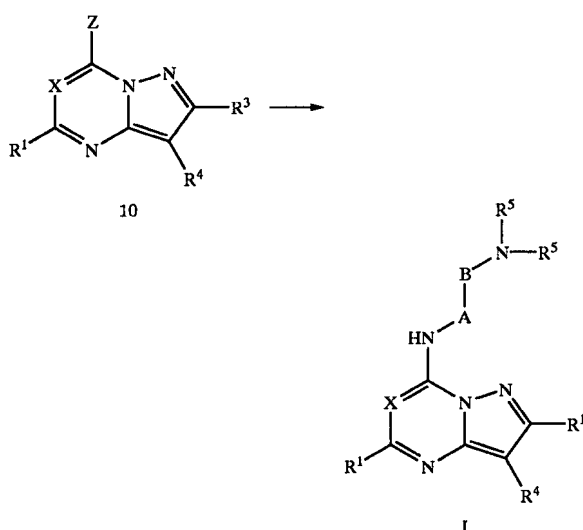
B

[0093] to a compound that exhibits a K_i of 5 micromolar or less in an assay of NPY receptor binding, wherein the

substituents are as defined above by substituting the 7-position of the heterocyclic core A or the 4-position of the heterocyclic core B with a diamine group $\text{—N[R}^2\text{]—A—B—N[R}^6\text{]—R}^5$.

[0094] An illustration of preparation methods of compounds of the present invention is given in the Schemes below. In particular displacement of a leaving group Z, as in formula 10 (Scheme 1) by the appropriate substituted amine provides a method to convert the heterocyclic cores of the present invention, i.e. aryl or heteroaryl substituted pyrazolo [1,5-a]-1,5-pyrimidines and pyrazolo[1,5-a]-1,3,5-triazines, into compounds that potentially interact with the NPY1 receptor. Such transformations may require several consecutive chemical steps. Those having skill in the art will recognize that the starting materials may be varied and additional steps employed to produce compounds encompassed by the present invention. The disclosures of all articles and references mentioned in this application, including patents, are incorporated herein by reference.

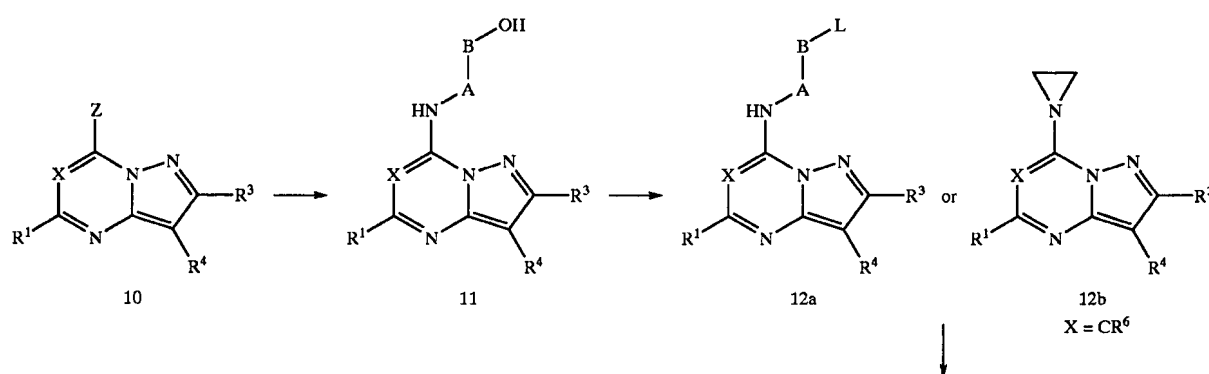
SCHEME 1



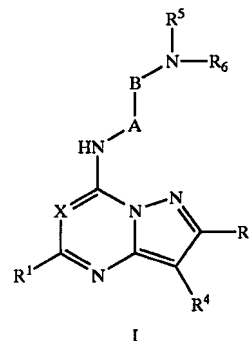
[0095] As illustrated in Scheme 1, compounds of formula I can be prepared from intermediate compounds of formula 10, where Z is halogen (preferably chloro or bromo), alkane sulfonyloxy, aryl sulfonyloxy or haloalkane sulfonyloxy, and X, R¹, R³ and R⁴ are defined above, using the procedures outlined below.

[0096] Compounds of formula 10 react with an amine of formula $\text{H}_2\text{N—A—B—N[R}^6\text{]—R}^5$, where A, B, R⁵ and R⁶ are defined as above, in the presence or absence of a base in the presence or absence of an inert solvent at reaction temperatures ranging from -78°C . to 250°C . to generate compounds of formula I. Bases may include, but are not limited to, alkali metal hydrides (preferably sodium hydride), alkali metal alkoxides (1-6 carbons) (preferably sodium methoxide, sodium ethoxide, or sodium tert-butoxide), alkaline earth metal hydrides, alkali metal dialkylamides (preferably lithium diisopropylamide), alkali metal carbonates, alkali metal bicarbonates, alkali metal bis-(trialkylsilyl)amides (preferably lithium or sodium (trimethylsilyl)amide), trialkylamines (preferably N,N-di-isopropyl-N-ethyl amine or triethylamine), arylamines (preferably 4-dimethyl aniline), or heteroaromatic amines (preferably pyridine). Inert solvents may include, but are not limited to, alkyl alcohols (1-8 carbons) (preferably methanol, ethanol, or tert-butanol), lower alkanenitriles (1-6 carbons) (preferably acetonitrile), dialkyl ethers (preferably diethyl ether), cyclic ethers (preferably tetrahydrofuran or 1,4-dioxane), N,N-dialkylformamides (preferably dimethyl formamide), N,N-dialkylacetamides (preferably dimethyl acetamide), cyclic amides (preferably N-methylpyrrolidin-2-one), dialkylsulfoxides (preferably dimethylsulfoxide), aromatic hydrocarbons (preferably benzene or toluene), or haloalkanes (1-10 carbons and 1-10 halogens) (preferably dichloromethane). Preferred reaction temperatures range from 0°C . to 140°C .

SCHEME 2



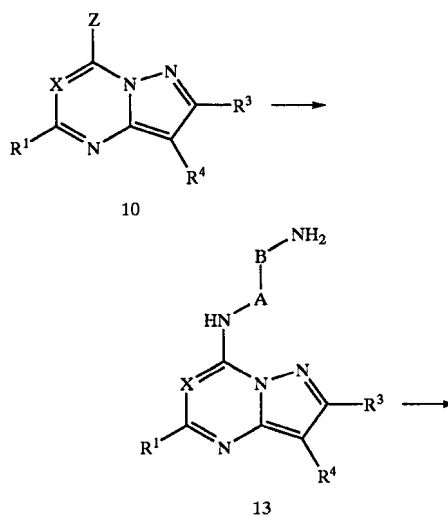
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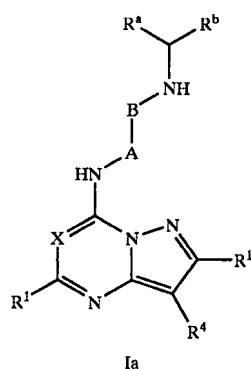
[0097] Alternatively, as shown in Scheme 2, compounds of formula I can be obtained by first reacting a compound of formula 10 with an amino alcohol of formula $H_2N-A-B-OH$, where A and B are defined as above, in the presence or absence of a base in the presence or absence of an inert solvent at reaction temperatures ranging from $-78^\circ C.$ to $250^\circ C.$ to generate intermediates of formula 11. Reacting a compound of formula 11 with a halogenating agent or sulfonylating agent in the presence or absence of a base in the presence or absence of an inert solvent at reaction temperatures ranging from $-78^\circ C.$ to $250^\circ C.$ to afford products of formula 12a (where Z is halogen, alkane sulfonyloxy, aryl sulfonyloxy or haloalkane sulfonyloxy) or 12b when A and B are both CH_2 and X is CR^{14} . Halogenating agents include, but are not limited to, $SOCl_2$, $POCl_3$, PCl_3 , PCl_5 , $POBr_3$, PBr_3 , PBr_5 , CCl_4/PPh_3 . Sulfonylating agents include, but are not limited to, alkanesulfonyl halides or anhydrides (preferably methanesulfonyl chloride or methanesulfonic anhydride), aryl sulfonyl halides or anhydrides (such as p-toluenesulfonyl chloride or anhydride), or haloalkylsulfonyl halides or anhydrides (preferably trifluoromethanesulfonic anhydride). Bases may include, but are not limited to, trialkylamines (preferably N,N-di-isopropyl-N-ethyl amine or triethylamine), bicyclic amidines (preferably DBU), anilines (preferably N-dimethyl aniline), or heteroaromatic amines (preferably pyridine). Inert solvents may include, but are not limited to, lower alkanenitriles (1-6 carbons) (preferably acetonitrile), dialkyl ethers (preferably diethyl ether), cyclic ethers (preferably tetrahydrofuran or 1,4-dioxane), N,N-dialkylformamides (preferably dimethyl formamide), N,N-dialkylacetamides (preferably dimethyl acetamide), cyclic amides (preferably N-methylpyrrolidin-2-one), dialkylsulfoxides (preferably dimethylsulfoxide), aromatic hydrocarbons (preferably benzene or toluene), or haloalkanes with 1-10 carbons and 1-10 halogens (preferably dichloromethane). Preferred reaction temperatures range from $-20^\circ C.$ to $100^\circ C.$ Compounds of formula 12a or 12b can then be reacted with an amine of formula $HN[R^6]-R^5$, where R^5 and R^6 are defined as above, to give a compound of formula I. Bases may include, but are not limited to, alkali metal hydrides (preferably sodium hydride), alkali metal alkoxides (1-6 carbons) (preferably sodium methoxide, sodium ethoxide, or sodium tert-butox-

ide), alkaline earth metal hydrides, alkali metal dialkylamides (preferably lithium diisopropylamide), alkali metal carbonates, alkali metal bicarbonates, alkali metal bis-(trialkylsilyl)amides (preferably lithium or sodium (trimethylsilyl)amide), trialkylamines (preferably N,N-di-isopropyl-N-ethyl amine or triethylamine), arylamines (preferably 4-dimethyl aniline), or heteroaromatic amines (preferably pyridine). Inert solvents may include, but are not limited to, alkyl alcohols (1-8 carbons) (preferably methanol, ethanol, or tert-butanol), lower alkanenitriles (1-6 carbons) (preferably acetonitrile), dialkyl ethers (preferably diethyl ether), cyclic ethers (preferably tetrahydrofuran or 1,4-dioxane), N,N-dialkylformamides (preferably dimethyl formamide), N,N-dialkylacetamides (preferably dimethyl acetamide), cyclic amides (preferably N-methylpyrrolidin-2-one), dialkylsulfoxides (preferably dimethylsulfoxide), aromatic hydrocarbons (preferably benzene or toluene), or haloalkanes (1-10 carbons and 1-10 halogens) (preferably dichloromethane). Preferred reaction temperatures range from $0^\circ C.$ to $140^\circ C.$

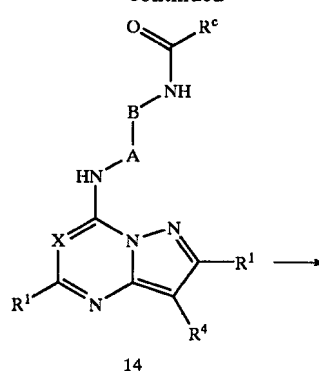
SCHEME 3



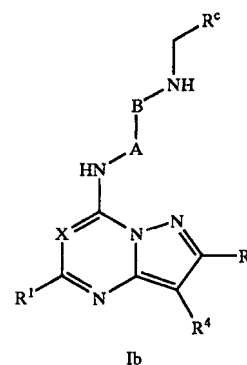
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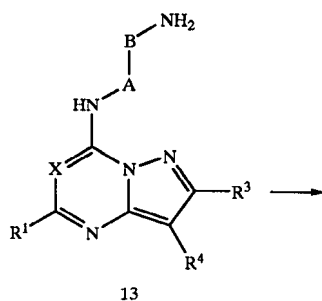


[0098] A subset of compounds of formula I, described under formula Ia in Scheme 3, can be obtained by first reacting a compound of formula 10 with a diamine of formula $H_2N-A-B-NH_2$, where A and B are defined as above, in the presence or absence of a base in the presence or absence of an inert solvent at reaction temperatures ranging from $-78^\circ C.$ to $250^\circ C.$ to generate intermediates of formula 13. Reaction of a compound of formula 13 with a ketone of Formula $Re-C=O-Re$ or an aldehyde of Formula $R^a-C=O-R^b$ where $R^b=H$, in the presence of a reducing agent provides a compound of formula Ia, where the grouping R^a-CH-R^b corresponds to R^5 in formula I, as defined above. Reducing agents include, but are not limited to, alkali metal or alkaline earth metal borohydrides (preferably lithium or sodium borohydride), borane (preferably complexed with dimethyl sulfide or tetrahydrofuran), dialkylboranes (such as di-isoamylborane), alkali metal aluminum hydrides (preferably lithium aluminum hydride), alkali metal (trialkoxo)aluminum hydrides (such as triethoxyaluminum hydride), dialkyl aluminum hydrides (such as di-isobutyl aluminum hydride), alane (preferably complexed with dimethylethylamine). Inert solvents may include, but are not limited to, alkyl alcohols (1-6 carbons) (preferably methanol, ethanol, or tert-butanol), dialkyl ethers (preferably diethyl ether), cyclic ethers (preferably tetrahydrofuran or 1,4-dioxane), aromatic hydrocarbons (preferably benzene or toluene). Preferred reaction temperatures range from $-78^\circ C.$ to $100^\circ C.$



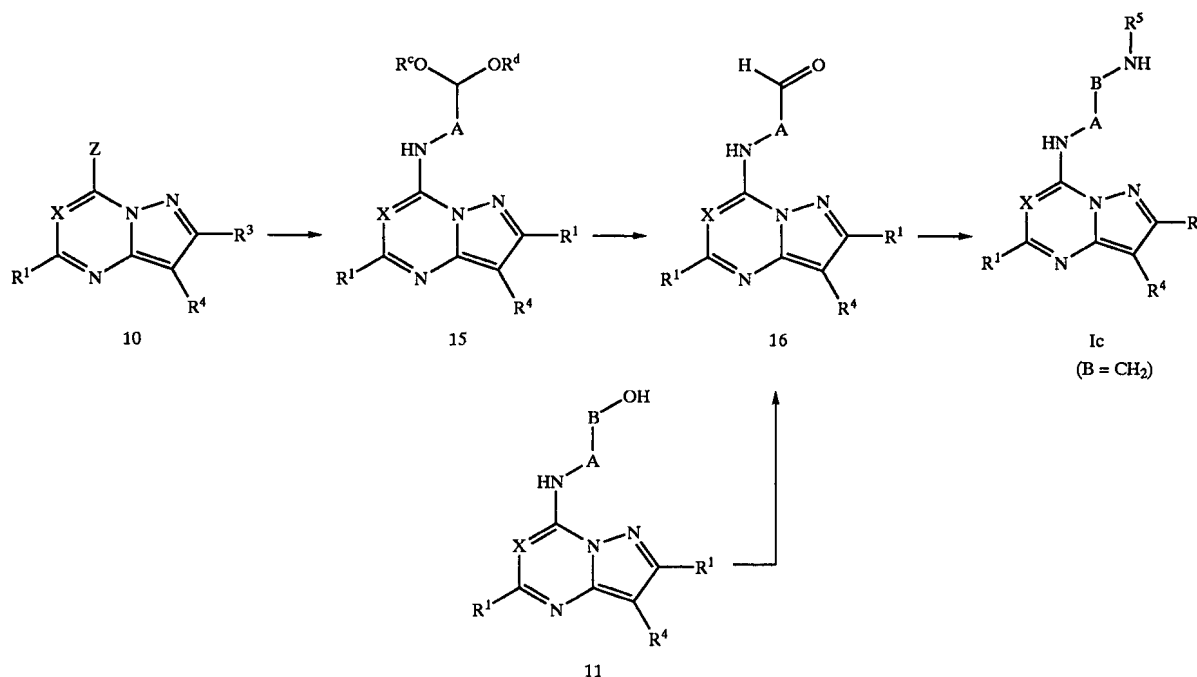
[0099] Alternatively, as illustrated in Scheme 4, a subset of compounds of formula I, described under formula Ib, can be obtained by first reacting a compound of formula 13 with an activated acid of formula $R^c-C=O-Z$, where Z is halo (preferably chloro), O-acyl (preferably $O-C=O-R^c$), in the presence or absence of a base in the presence or absence of an inert solvent at reaction temperatures ranging from $-78^\circ C.$ to $250^\circ C.$ to generate an amide intermediate of formula 14. Reaction of a compound of formula 14 with a reducing agent provides a compound of formula Ib, where the grouping R^c-CH_2 corresponds to R^5 in formula I, as defined above. Reducing agents include, but are not limited to, alkali metal or alkaline earth metal borohydrides (preferably lithium or sodium borohydride), borane (preferably complexed with dimethyl sulfide or tetrahydrofuran), dialkylboranes (such as di-isoamylborane), alkali metal aluminum hydrides (preferably lithium aluminum hydride), alkali metal (trialkoxo)aluminum hydrides (such as triethoxyaluminum hydride), dialkyl aluminum hydrides (such as di-isobutyl aluminum hydride), alane (preferably complexed with dimethylethylamine). Inert solvents may include, but are not limited to, alkyl alcohols (1-6 carbons) (preferably methanol, ethanol, or tert-butanol), dialkyl ethers (preferably diethyl ether), cyclic ethers (preferably tetrahydrofuran or 1,4-dioxane), aromatic hydrocarbons (preferably benzene or toluene). Preferred reaction temperatures range from $-78^\circ C.$ to $100^\circ C.$

SCHEME 4



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SCHEME 5



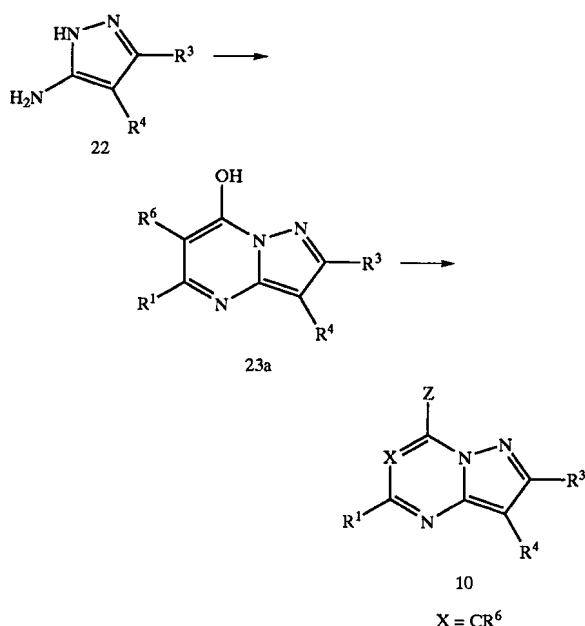
[0100] Alternatively, a subset of compounds of formula I, described under formula Ic in Scheme 5, can be obtained by first reacting a compound of formula 10 with an amine of formula $\text{H}_2\text{N}-\text{A}-\text{CH}(\text{OR}^c)(\text{OR}^d)$, where A is defined above, and R^c and R^d are C_1 - C_6 lower alkyls or, taken together, complete a ketal group, such as, for example a dioxane or dioxolane group, in the presence or absence of a base in the presence or absence of an inert solvent at reaction temperatures ranging from -78°C . to 250°C . to generate compounds of formula 15. Bases may include, but are not limited to, alkali metal hydrides (preferably sodium hydride), alkali metal alkoxides (1-6 carbons) (preferably sodium methoxide, sodium ethoxide, or sodium tert-butoxide), alkaline earth metal hydrides, alkali metal dialkylamides (preferably lithium diisopropylamide), alkali metal carbonates, alkali metal bicarbonates, alkali metal bis-(tri-alkylsilyl)amides (preferably lithium or sodium (trimethylsilyl)amide), trialkylamines (preferably N,N-di-isopropyl-N-ethyl amine or triethylamine), arylamines (preferably 4-dimethyl aniline), or heteroaromatic amines (preferably pyridine). Inert solvents may include, but are not limited to, alkyl alcohols (1-8 carbons) (preferably methanol, ethanol, or tert-butanol), lower alkanenitriles (1-6 carbons) (preferably acetonitrile), dialkyl ethers (preferably diethyl ether), cyclic ethers (preferably tetrahydrofuran or 1,4-dioxane), N,N-dialkylformamides (preferably dimethyl formamide), N,N-dialkylacetamides (preferably dimethyl acetamide), cyclic amides (preferably N-methylpyrrolidin-2-one), dialkylsulfoxides (preferably dimethylsulfoxide), aromatic hydrocarbons (preferably benzene or toluene), or haloalkanes (1-10 carbons and 1-10 halogens) (preferably dichloromethane). Compounds of formula 15 react with a protic acid in the presence or absence of an inert solvent at reaction

temperatures ranging from -78°C . to 250°C ., followed by aqueous work-up to generate compounds of formula 16. Inert solvents may include, but are not limited to dialkyl ethers (preferably diethyl ether), cyclic ethers (preferably tetrahydrofuran or 1,4-dioxane), N,N-dialkylformamides (preferably dimethyl formamide), N,N-dialkylacetamides (preferably dimethyl acetamide), cyclic amides (preferably N-methylpyrrolidin-2-one), dialkylsulfoxides (preferably dimethylsulfoxide), aromatic hydrocarbons (preferably benzene or toluene), or haloalkanes (1-10 carbons and 1-10 halogens) (preferably dichloromethane). Protic acids include, but are not limited to, formic acid, acetic acid, trifluoroacetic acid, hydrochloric acid, methane sulfonic acid. Alternatively, compounds of formula 16 can be obtained by oxidation of compounds of formula 11 where $\text{B}=\text{CH}_2$. Oxidizing agents include, but are not limited to, transition metal oxides, such as CrO_3 or MnO_2 , pyridine-chromium complexes, such as $\text{CrO}_3\cdot\text{C}_5\text{H}_5\text{N}$, pyridinium dichromate or pyridinium chlorochromate, or an oxalyl chloride-DMSO-triethylamine reagent (Swern oxidation). Compounds of formula 16 react with amines of formula $\text{H}_2\text{N}-\text{R}^5$, where R^5 is defined above, in the presence of a reducing agent in the presence or absence of an inert solvent in the presence or absence of a protic acid at temperatures ranging from -78°C . to 100°C ., to give compounds of formula Ic. Reducing agents include, but are not limited to, alkali metal or alkaline earth metal borohydrides (preferably lithium or sodium borohydride), borane (preferably complexed with dimethyl sulfide or tetrahydrofuran), dialkylboranes (such as di-isoamylborane), alkali metal aluminum hydrides (preferably lithium aluminum hydride), alkali metal (trialkoxo)aluminum hydrides (such as triethoxyalu-

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minum hydride), dialkyl aluminum hydrides (such as diisobutyl aluminum hydride), alane (preferably complexed with dimethylethylamine). Inert solvents may include, but are not limited to, alkyl alcohols (1-6 carbons) (preferably methanol, ethanol, or tert-butanol), dialkyl ethers (preferably diethyl ether), cyclic ethers (preferably tetrahydrofuran or 1,4-dioxane), aromatic hydrocarbons (preferably benzene or toluene).

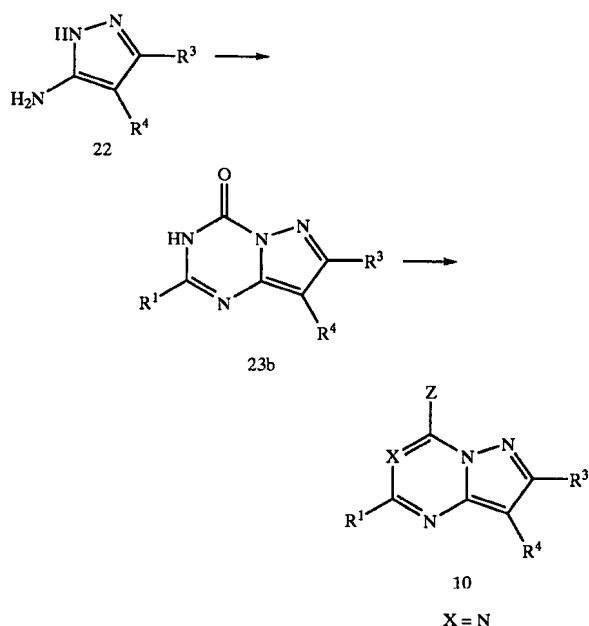
SCHEME 6



[0101] When X is CR^{14} , as defined above, compounds of formula 10 may be obtained from compounds of formula 22, as shown in Scheme 6. Compounds of formula 22 can be reacted with compounds of formula $R-C(=O)-CH(R^{14})C(=O)-R^c$, where R^1 and R^{14} are defined above, and R^c is halogen, cyano, lower alkoxy (1-6 carbons), or lower alkanoyloxy (1-6 carbons), in the presence or absence of a base in an inert solvent at reaction temperatures ranging from $-50^\circ C.$ to $250^\circ C.$ to afford compounds of formula 23a. Bases may include, but are not limited to, alkali metal hydrides (preferably sodium hydride), alkali metal alkoxides (1-6 carbons) (preferably sodium methoxide, sodium ethoxide, or sodium tert-butoxide), alkaline earth metal hydrides, alkali metal dialkylamides (preferably lithium diisopropylamide), alkali metal carbonates, alkali metal hydroxides, alkali metal bis-(trialkylsilyl)amides (preferably lithium or sodium (trimethylsilyl)amide), trialkylamines (preferably N,N -di-isopropyl- N -ethyl amine or triethylamine), bicyclic amidines (preferably DBU), or heteroaromatic amines (preferably pyridine). Inert solvents may include, but are not limited to, alkyl alcohols (1-8 carbons) (preferably methanol, ethanol, or tert-butanol), lower alkanenitriles (1-6 carbons) (preferably acetonitrile), water, dialkyl ethers (preferably diethyl ether), cyclic ethers (preferably tetrahydrofuran or 1,4-dioxane), N,N -dialkylformamides (preferably dimethyl formamide), N,N -dialkylacetamides (preferably dimethyl acetamide), cyclic amides (preferably N -methylpyrrolidin-2-one), dialkylsulfoxides (preferably dimethylsulfoxide), aromatic hydrocarbons (preferably benzene or toluene), or haloalkanes with 1-10 carbons and 1-10 halogens (preferably dichloromethane). Preferred reaction temperatures range from $-20^\circ C.$ to $100^\circ C.$

zene or toluene). Compounds of formula 23a can then be reacted with a halogenating agent or sulfonylating agent in the presence or absence of a base in the presence or absence of an inert solvent at reaction temperatures ranging from $-78^\circ C.$ to $250^\circ C.$ to afford products of formula 10 (where Z is halogen, alkane sulfonyloxy, aryl sulfonyloxy or haloalkane sulfonyloxy and X is CR^{14}). Halogenating agents include, but are not limited to, $SOCl_2$, $POCl_3$, PCl_3 , PCl_5 , $POBr_3$, PBr_3 , or PBr_5 . Sulfonylating agents include, but are not limited to, alkanesulfonyl halides or anhydrides (preferably methanesulfonyl chloride or methanesulfonic anhydride), aryl sulfonyl halides or anhydrides (such as p -toluenesulfonyl chloride or anhydride), or haloalkylsulfonyl halides or anhydrides (preferably trifluoromethanesulfonic anhydride). Bases may include, but are not limited to, trialkylamines (preferably N,N -di-isopropyl- N -ethyl amine or triethylamine), bicyclic amidines (preferably DBU), anilines (preferably N -dimethyl aniline), or heteroaromatic amines (preferably pyridine). Inert solvents may include, but are not limited to, lower alkanenitriles (1-6 carbons) (preferably acetonitrile), dialkyl ethers (preferably diethyl ether), cyclic ethers (preferably tetrahydrofuran or 1,4-dioxane), N,N -dialkylformamides (preferably dimethyl formamide), N,N -dialkylacetamides (preferably dimethyl acetamide), cyclic amides (preferably N -methylpyrrolidin-2-one), dialkylsulfoxides (preferably dimethylsulfoxide), aromatic hydrocarbons (preferably benzene or toluene), or haloalkanes with 1-10 carbons and 1-10 halogens (preferably dichloromethane). Preferred reaction temperatures range from $-20^\circ C.$ to $100^\circ C.$

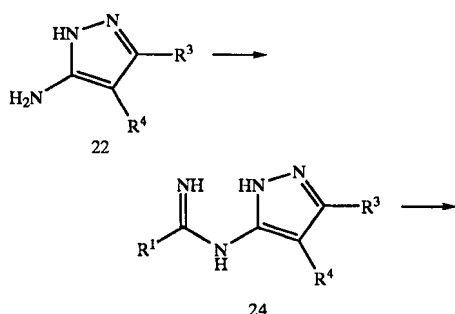
SCHEME 7



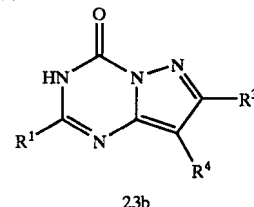
[0102] As shown in Scheme 7, when X is N , compounds of formula 22 can be reacted with compounds of formula $R-C(=N(COOR^g))OR^f$, where R^1 is defined above, and R^g is lower alkyl (1-6 carbons), and R^f is halogen, cyano, lower alkoxy (1-6 carbons), or lower alkanoyloxy (1-6 carbons), in the presence or absence of a base in an inert solvent at reaction temperatures ranging from $-50^\circ C.$ to $250^\circ C.$ to afford compounds of formula 23b. Bases may

include, but are not limited to, alkali metal hydrides (preferably sodium hydride), alkali metal alkoxides (1-6 carbons) (preferably sodium methoxide, sodium ethoxide, or sodium tert-butoxide), alkaline earth metal hydrides, alkali metal dialkylamides (preferably lithium diisopropylamide), alkali metal carbonates, alkali metal hydroxides, alkali metal bis-(trialkylsilyl)amides (preferably lithium or sodium (trimethylsilyl)amide), trialkylamines (preferably N,N-di-isopropyl-N-ethyl amine or triethylamine), bicyclic amidines (preferably DBU), or heteroaromatic amines (preferably pyridine). Inert solvents may include, but are not limited to, alkyl alcohols (1-8 carbons) (preferably methanol, ethanol, or tert-butanol), lower alkanenitriles (1-6 carbons) (preferably acetonitrile), water, dialkyl ethers (preferably diethyl ether), cyclic ethers (preferably tetrahydrofuran or 1,4-dioxane), N,N-dialkylformamides (preferably dimethyl formamide), N,N-dialkylacetamides (preferably dimethyl acetamide), cyclic amides (preferably N-methylpyrrolidin-2-one), dialkylsulfoxides (preferably dimethylsulfoxide), aromatic hydrocarbons (preferably benzene or toluene), heteroaromatic hydrocarbons (preferably pyridine). Compounds of formula 23b can then be reacted with a halogenating agent or sulfonylating agent in the presence or absence of a base in the presence or absence of an inert solvent at reaction temperatures ranging from -78°C . to 250°C . to afford products of formula 10 (where Z is halogen, alkane sulfonyloxy, aryl sulfonyloxy or haloalkane sulfonyloxy and X is N). Halogenating agents include, but are not limited to, SOCl_2 , POCl_3 , PCl_3 , PCl_5 , POBr_3 , PBr_3 , or PBr_5 . Sulfonylating agents include, but are not limited to, alkanesulfonyl halides or anhydrides (preferably methanesulfonyl chloride or methanesulfonic anhydride), aryl sulfonyl halides or anhydrides (such as p-toluenesulfonyl chloride or anhydride), or haloalkylsulfonyl halides or anhydrides (preferably trifluoromethanesulfonic anhydride). Bases may include, but are not limited to, trialkylamines (preferably N,N-di-isopropyl-N-ethyl amine or triethylamine), bicyclic amidines (preferably DBU), anilines (preferably N-dimethyl aniline), or heteroaromatic amines (preferably pyridine). Inert solvents may include, but are not limited to, lower alkanenitriles (1-6 carbons) (preferably acetonitrile), dialkyl ethers (preferably diethyl ether), cyclic ethers (preferably tetrahydrofuran or 1,4-dioxane), N,N-dialkylformamides (preferably dimethyl formamide), N,N-dialkylacetamides (preferably dimethyl acetamide), cyclic amides (preferably N-methylpyrrolidin-2-one), dialkylsulfoxides (preferably dimethylsulfoxide), aromatic hydrocarbons (preferably benzene or toluene), or haloalkanes with 1-10 carbons and 1-10 halogens (preferably dichloromethane). Preferred reaction temperatures range from -20°C . to 100°C .

SCHEME 8

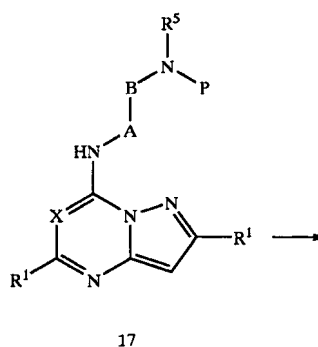


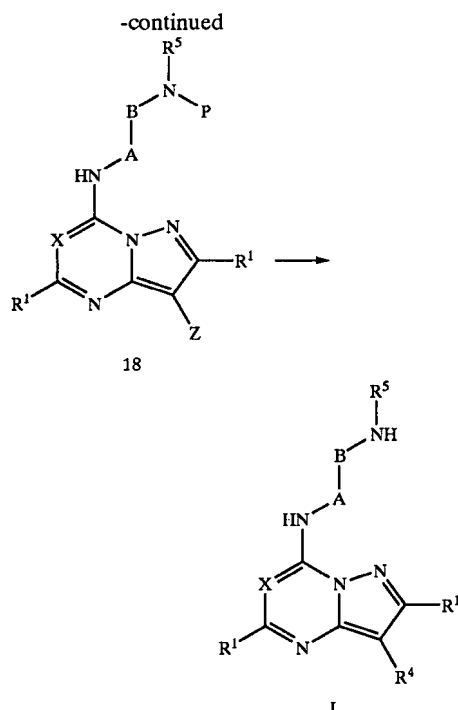
-continued



[0103] Alternatively, as illustrated in Scheme 8, compounds of formula 23b can be obtained by first reacting compounds of formula 22 with compounds of the formula $\text{R}^1\text{—}(\text{C}=\text{NH})\text{—OR}^i$, where R^1 is defined above and R^i is a lower alkyl group (preferably methyl or ethyl), in the presence or absence of an acid in an inert solvent to give an intermediate of formula 24. Compounds of formula 24 react with a compound of formula $\text{R}^i\text{—C}=\text{O—R}^1$, where R^1 and R^i are each or independently lower alkoxy (preferably methoxy or ethoxy), 1-imidazolyl, halo, aryloxy (preferably 4-nitrophenoxy) in the presence or YES absence of an inert solvent to afford compounds of formula 23b. Bases may include, but are not limited to, alkali metals (preferably sodium), alkali metal hydrides (preferably sodium hydride), alkali metal alkoxides (1-6 carbons) (preferably sodium methoxide, sodium ethoxide, or sodium tert-butoxide), alkaline earth metal hydrides, alkali metal dialkylamides (preferably lithium diisopropylamide), alkali metal carbonates, alkali metal hydroxides, alkali metal bis-(trialkylsilyl)amides (preferably lithium or sodium (trimethylsilyl)amide), trialkylamines (preferably N,N-di-isopropyl-N-ethyl amine or triethylamine), bicyclic amidines (preferably DBU), or heteroaromatic amines (preferably pyridine). Inert solvents may include, but are not limited to, alkyl alcohols (1-8 carbons) (preferably methanol, ethanol, or tert-butanol), lower alkanenitriles (1-6 carbons) (preferably acetonitrile), water, dialkyl ethers (preferably diethyl ether), cyclic ethers (preferably tetrahydrofuran or 1,4-dioxane), N,N-dialkylformamides (preferably dimethyl formamide), N,N-dialkylacetamides (preferably dimethyl acetamide), cyclic amides (preferably N-methylpyrrolidin-2-one), dialkylsulfoxides (preferably dimethylsulfoxide), aromatic hydrocarbons (preferably benzene or toluene).

SCHEME 9

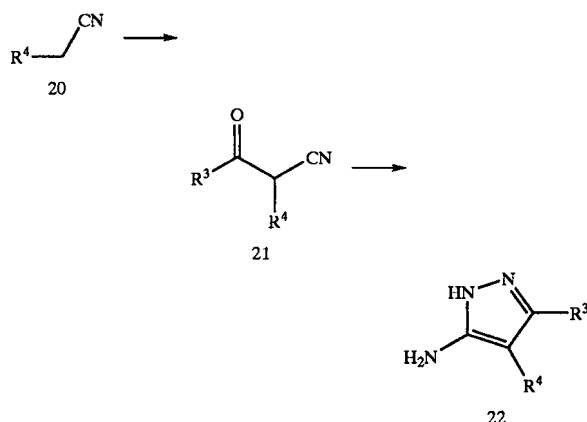




[0104] According to Scheme 9, compounds of formula I can also be prepared from compounds of formula 17 (prepared using the methods applicable to the synthesis of compounds of formula I), where P is H or an appropriate amino protecting group. Such groups, known in the art of organic synthesis for the protection of amines, include those listed in "Protective Groups in Organic Synthesis", by Greene and Wuts [John Wiley & Sons, NY, 1991]. Examples of amine protecting groups include, but are not limited to, acyl types (such as formyl, trifluoroacetyl, phthalyl, and p-toluenesulfonyl), carbamate types (such as benzyloxycarbonyl, t-butoxycarbonyl, 9-fluorenylmethyloxycarbonyl, allyloxycarbonyl, and 2,2,2-trichloroethyloxycarbonyl), alkyl types (such as benzyl and triphenylmethyl). Reacting compounds of formula 17 with a halogenating agent provides compounds of formula 18 where X is Br, Cl, or I. Compounds of formula 18 react with a compound of formula R^4M (where M is alkali metal, ZnCl, ZnBr, MgBr, MgCl, MgI, CeCl₂, CeBr₂, copper halides, B(OH)₂, B(O-lower alkyl)₂, or Sn(lower alkyl)₃) in the presence or absence of an organometallic catalyst in the presence or absence of a base in an inert solvent at temperatures ranging from -100° C. to 200° C. to give compounds of formula I (or their N-protected forms which can then be deprotected). Similar conditions have been described in WO 98/54093. Those skilled in the art will recognize that the reagents R^4M may be generated in situ. Organometallic catalysts include but are not limited to, palladium phosphine complexes (such as Pd(PPh₃)₄), palladium halides or alkanoates (such as PdCl₂(PPh₃)₂ or Pd(OAc)₂), or nickel complexes (such as NiCl₂(PPh₃)₂). Bases may include, but are not limited to, alkali metal alkoxides (1-6 carbons) (preferably sodium methoxide, sodium ethoxide, or sodium tert-butoxide), alkali metal carbonates or bicarbonates, alkali metal hydroxides, alkali metal phosphates, or trialkylamines (preferably

N,N-di-isopropyl-N-ethyl amine or triethylamine). Inert solvents may include, but are not limited to, lower alkanenitriles (1-6 carbons) (preferably acetonitrile), water, dialkyl ethers (preferably diethyl ether), cyclic ethers (preferably tetrahydrofuran or 1,4-dioxane), N,N-dialkylformamides (preferably dimethyl formamide), N,N-dialkylacetamides (preferably dimethyl acetamide), cyclic amides (preferably N-methylpyrrolidin-2-one), dialkylsulfoxides (preferably dimethylsulfoxide), aromatic hydrocarbons (preferably benzene or toluene).

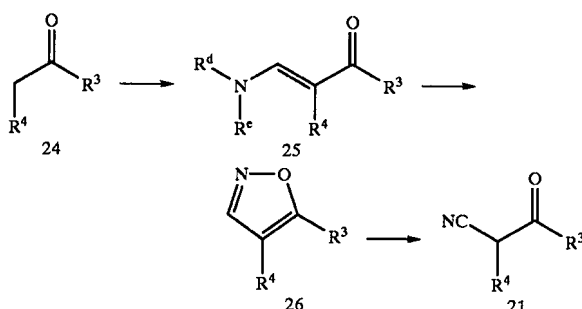
SCHEME 10



[0105] As shown in Scheme 10, compounds of formula 22 may be obtained from compounds of formula 20, where R^4 is defined as above. Compounds of formula 20 are reacted with compounds of formula $R^3-C=OR^c$, where R^3 is defined above and R^c is halogen, cyano, lower alkoxy (1-6 carbons), or lower alkanoyloxy (1-6 carbons), in the presence of a base in an inert solvent at reaction temperatures ranging from -78° C. to 200° C. to afford compounds of formula 21. Bases may include, but are not limited to, alkali metal hydrides (preferably sodium hydride), alkali metal alkoxides (1-6 carbons) (preferably sodium methoxide, sodium ethoxide, or sodium tert-butoxide), alkaline earth metal hydrides, alkali metal dialkylamides (preferably lithium diisopropylamide), alkali metal carbonates, alkali metal hydroxides, alkali metal bis-(trialkylsilyl)amides (preferably lithium or sodium (trimethylsilyl)amide), trialkylamines (preferably N,N-di-isopropyl-N-ethyl amine or triethylamine), bicyclic amidines (preferably DBU), or heteroaromatic amines (preferably pyridine). Inert solvents may include, but are not limited to, alkyl alcohols (1-8 carbons) (preferably methanol, ethanol, or tert-butanol), lower alkanenitriles (1-6 carbons) (preferably acetonitrile), water, dialkyl ethers (preferably diethyl ether), cyclic ethers (preferably tetrahydrofuran or 1,4-dioxane), N,N-dialkylformamides (preferably dimethyl formamide), N,N-dialkylacetamides (preferably dimethyl acetamide), cyclic amides (preferably N-methylpyrrolidin-2-one), dialkylsulfoxides (preferably dimethylsulfoxide), aromatic hydrocarbons (preferably benzene or toluene). Alternatively, compounds of formula 20 may be reacted with a solvent of formula $R^3-C=O-R^c$, where R^3 is defined above and R^c is lower alkoxy (1-6 carbons), in the presence of an alkali metal (preferably sodium) at reaction temperatures ranging from

-78° C. to 200° C. to afford compounds of formula 21. Compounds of formula 21 may be reacted with hydrazine (hydrate or hydrochloride salt) in an inert solvent, at reaction temperatures ranging from 0° C. to 200° C., preferably 70° C. to 150° C., to afford compounds of formula 22. Inert solvents may include, but are not limited to, water, lower alkanolic acids (preferably formic, acetic, or trifluoro acetic acid), alkyl alcohols (1-8 carbons) (preferably methanol or ethanol), lower alkanenitriles (1-6 carbons) (preferably acetonitrile), cyclic ethers (preferably tetrahydrofuran or 1,4-dioxane), N,N-dialkylformamides (preferably dimethyl formamide), N,N-dialkylacetamides (preferably dimethyl acetamide), cyclic amides (preferably N-methylpyrrolidin-2-one), dialkylsulfoxides (preferably dimethylsulfoxide), aromatic hydrocarbons (preferably benzene or toluene).

SCHEME 11



[0106] Alternatively, compounds of formula 21 can be obtained, as illustrated in Scheme 11, by first reacting compounds of formula 24 with dialkyl formamide dialkyl acetal of formula $(R^d R^e)N-CH(OR^f)_2$ where R^d , R^e , and R^f are each or independently C_1 - C_6 lower alkyl (preferably methyl) in the presence or absence of an inert solvent at reaction temperatures ranging from 0° C. to 250° C., preferably between 70° C. and 150° C. to provide compounds of formula 25. Inert solvents may include, but are not limited to, lower alkanenitriles (1-6 carbons) (preferably acetonitrile), dialkyl ethers (preferably diethyl ether), cyclic ethers (preferably tetrahydrofuran or 1,4-dioxane), N,N-dialkylformamides (preferably dimethyl formamide), N,N-dialkylacetamides (preferably dimethyl acetamide), cyclic amides (preferably N-methylpyrrolidin-2-one), dialkylsulfoxides (preferably dimethylsulfoxide), aromatic hydrocarbons (preferably benzene or toluene), or haloalkanes with 1-10 carbons and 1-10 halogens (preferably dichloromethane). Compounds of formula 25 can be reacted with hydroxylamine salt (preferably hydrochloride) in the presence or absence of an inert solvent at reaction temperatures ranging from 0° C. to 250° C., preferably between 70° C. and 200° C. to provide oxazoles of formula 26. Inert solvents may include, but are not limited to, alkyl alcohols (1-8 carbons) (preferably methanol, ethanol, or tert-butanol), lower alkanenitriles (1-6 carbons) (preferably acetonitrile), water, dialkyl ethers (preferably diethyl ether), cyclic ethers (preferably tetrahydrofuran or 1,4-dioxane), N,N-dialkylformamides (preferably dimethyl formamide), N,N-dialkylacetamides (preferably dimethyl acetamide), cyclic amides (preferably N-methylpyrrolidin-2-one), dialkylsulfoxides (preferably dimethylsulfoxide), aromatic hydrocarbons (preferably benzene or toluene). Oxazole intermediates of formula 26 can be reacted with a base in the presence or

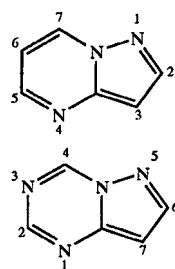
absence of an inert solvent at reaction temperatures ranging from 0° C. to 200° C. Bases may include, but are not limited to, alkali hydroxides (preferably sodium or potassium hydroxide), alkali metal hydrides (preferably sodium hydride), alkali metal alkoxides (1-6 carbons) (preferably sodium methoxide, sodium ethoxide, or sodium tert-butoxide), alkaline earth metal hydrides, alkali metal dialkylamides (preferably lithium diisopropylamide), alkali metal carbonates, alkali metal hydroxides, alkali metal bis-(trialkylsilyl)amides (preferably lithium or sodium (trimethylsilyl)amide), trialkylamines (preferably N,N-di-isopropyl-N-ethyl amine or triethylamine), bicyclic amidines (preferably DBU), or heteroaromatic amines (preferably pyridine). Inert solvents may include, but are not limited to, alkyl alcohols (1-8 carbons) (preferably methanol, ethanol, or tert-butanol), lower alkanenitriles (1-6 carbons) (preferably acetonitrile), water, dialkyl ethers (preferably diethyl ether), cyclic ethers (preferably tetrahydrofuran or 1,4-dioxane), N,N-dialkylformamides (preferably dimethyl formamide), N,N-dialkylacetamides (preferably dimethyl acetamide), cyclic amides (preferably N-methylpyrrolidin-2-one), dialkylsulfoxides (preferably dimethylsulfoxide), aromatic hydrocarbons (preferably benzene or toluene).

EXAMPLES

[0107] The following examples are provided to describe the invention in further details. These examples, which set forth the best mode presently contemplated for carrying the invention, are intended to illustrate and not to limit the invention.

[0108] Commercial reagents were used without further purification. THF refers to tetrahydrofuran. LDA refers to lithium diisopropylamide and DBU refers to 1,8-diazabicyclo[5.4.0]undec-7-ene. Room or ambient temperature refers to 20° C. to 25° C. Concentration implies the use of a rotary evaporator. TLC refers to thin layer chromatography. Mass spectral data were obtained either by CI or APCI methods. Other commonly used abbreviations are: Ph is phenyl, Me is methyl, Et is ethyl, Pr is n-propyl, iPr is isopropyl, Bu is butyl, iBu is isobutyl (CH_2-CHMe_2), tBu is tert-butyl, cBu is cyclobutyl, Pent is n-pentyl, cPent is cyclopentyl, chex is cyclohexyl, Py is pyridyl, MeOH means methanol, EtOH means ethanol, EtOAc means ethyl acetate, Et₂O means diethyl ether, CH_2Cl_2 means methylene chloride, DMSO means dimethyl sulfoxide, NMP means N-methyl pyrrolidone, THF means tetrahydrofuran, DMF means dimethyl formamide, EX means example.

[0109] The numbering system used to describe the compounds of the present invention is as follows:



Example 1

Preparation of 7-(2-(perhydro-2H-pyran-4-ylamino)ethylamino)-2,5-dimethyl-3-(4-chloro-2,6-dimethylphenyl)-pyrazolo[1,5-a] pyrimidine

Formula I where X is CH, R¹ is CH₃, R² is H, A is CH₂, B is CH₂, R³ is CH₃, R⁴ is 2,6-dimethyl-4chlorophenyl, R⁵ is perhydro-2H-pyran-4-yl

[0110] A. 4-Bromo-3,5-dimethyl chlorobenzene

[0111] Slurry 2,6-dimethyl-4chloroaniline hydrochloride (23g, 193.11 g/mol) in CH₂Cl₂ (100 ml) and wash with saturated NaHCO₃ to generate the free base. Dry over Na₂SO₄, filter and evaporate down to a violet oil. Slurry up in 120 mL 6.0 N H₂SO₄ and stir vigorously at ambient temperature to break up larger pieces of solid. Cool to 0° C. in an ice/water bath, then portionwise over 15 minutes add a clear colorless solution of NaNO₂ in 50 mL H₂O. Maintain temperature 15° C. over course of addition, stirring under dry N₂. After 1 hour, carefully pour the cold reaction solution (solution A) into a second solution (solution B) containing 31.7 g CuBr in 33 mL aqueous HBr (48%) at ambient temperature. Let stand at ambient temperature until gas evolution ceases, then heat to 110° C. under N₂ while stirring. Stir for 3 hours, then cool to rt. Extract the aqueous layer with a (2:1) mixture of hexanes and Et₂O (2x500 mL), then dry the combined organic layers over Na₂SO₄, filter and evaporate down to a brown oil. Triturate the oil with hexanes (100 mL), filter out the remaining solids and wash with copious amounts of hexanes. Evaporate the hexane layers to concentrate then flush through a pad of silica to remove baseline material, using hexanes as eluent. Evaporate to a clear colorless oil (13.5g).

[0112] B. 4-Chloro-2,6-dimethyl benzaldehyde

[0113] Dissolve 4-bromo-3,5-dimethyl chlorobenzene (6.5 g) in 50 mL anhydrous THF and cool to -78° C. (dry ice/acetone) under N₂. Dropwise over 5 minutes add a solution of butyllithium (12.50 mL, 2.5M in hexanes) to the stirring solution of aryl bromide at -78° C. After 2 hours, dropwise add anhydrous DMF (5.0 mL) to the orange/red reaction solution and allow to warm to ambient temperature overnight while stirring under N₂. Evaporate the yellow solution down to a yellow oil and partition between H₂O (100 mL) and CH₂Cl₂ (100 mL). Extract the aqueous layer once with CH₂Cl₂, then pool the organic layers and dry over Na₂SO₄, filter and evaporate down to 5.0 g of yellow oil. Use without further purification. LCMS=169.6 (MEN)

[0114] C. 4-Chloro-2,6-dimethyl benzyl alcohol

[0115] Dissolve 4-chloro-2,6-dimethyl benzaldehyde (5.0 g, 168.64 g/mol) in 100 mL dry methanol. Cool to 0° C. while stirring under N₂. Portionwise add powdered NaBH₄ (0.76g, 37.85 g/mol) over 5 minutes. Stir at 0° C. for 2 hours, monitoring by TLC until aldehyde consumed, then evaporate to a yellow oil. Add H₂O (50 mL) and bring to pH 7.0 by addition of saturated NH₄Cl. Extract the neutral aqueous layer with CH₂Cl₂ (3x75 mL) and dry the pooled organic

layers over Na₂SO₄. Filter and concentrate to a yellow oil. Flush through a pad of silica to remove baseline material, then evaporate to a yellow solid (3.0 g) which can be used without further purification. LCMS=171.6 (MH⁺), 169.6 (M⁻).

[0116] D. 4-Chloro-2,6-dimethyl phenyl acetonitrile

[0117] Dissolve 4-chloro-2,6-dimethyl benzyl alcohol (2.8g, 170.66 g/mol) in CH₂Cl₂ (25 mL) and cool to 0° C. under N₂. Dropwise add thionyl chloride (2.4 mL, 3.90 g, 118.9 g/mol) in 10 mL CH₂Cl₂ while stirring under N₂. After 2 hours, monitoring by TLC (alcohol Rf=0.35, chloride Rf=1.0; using 20% EtOAc/80% hexanes as eluent), quench the reaction carefully by addition of saturated NaHCO₃ (100 mL) and stir until gas evolution ceases. Separate layers, then extract the aqueous layer with CH₂Cl₂ (100 mL). Pool the organic layers, dry over Na₂SO₄, filter and evaporate to a pale yellow oil. Take up in DMSO (25 mL), add solid NaCN (1.25 g, 49.011 g/mol) and heat to 60° C. while stirring under N₂. Stir 2 hours until chloride consumed (TLC; chloride Rf=1.0, nitrile Rf=0.6; using 20% EtOAc/80% hexanes as eluent), then cool to rt. Add 2.0 N NaOH (150 mL) and stir until orange precipitate forms, then filter and wash solid with H₂O. Dissolve solid in CH₂Cl₂, wash with H₂O, the dry over Na₂SO₄. Filter the organic layer and evaporate to an orange oil which crystallizes upon standing at rt. (2.3 g). LCMS=180.2 (MH⁺), 178.2 (M⁻).

[0118] E. 2-(4-Chloro-2,6-dimethylphenyl)-3-oxobutanenitrile

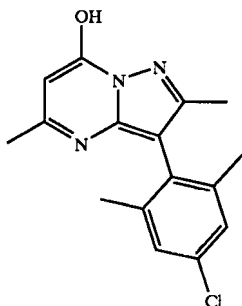
[0119] Dissolve 4-chloro-2,6-dimethyl phenyl acetonitrile (2.3 g, 179.2 g/mol) in 15 mL EtOAc and add sodium metal (0.35 g, pea-sized fragments). Heat to reflux (90° C. bath temperature) under N₂ overnight. Evaporate down to solid and slurry up in Et₂O (100 mL); stir vigorously to break up fragments. Filter and wash solid with copious amounts of Et₂O. Dissolve solid in H₂O to form a clear yellow solution, and add 1.0 N HCl (100 mL) to pH 1. Extract the resulting cloudy solution with CH₂Cl₂ (3x100 mL) until aqueous layer is clear. Pool and dry the organic layers over Na₂SO₄, filter and evaporate to yellow oil (1.8g). TLC: Rf=0.2 using 20% EtOAc/80% hexanes as eluent. LCMS=222.3 (MH⁺); 220.2 (M⁻).

[0120] F. 5-Amino-4-(4-chloro-2,6-dimethylphenyl)-3-methylpyrazole

[0121] Dissolve anhydrous hydrazine (0.91g, 0.90 mL) in 20 mL toluene. Add glacial acetic acid (2.25 mL) and allow to stand at ambient temperature for 10 minutes until solution becomes cloudy white. Add a solution of 2-(4-chloro-2,6-dimethylphenyl)-3-oxobutanenitrile in 10 mL toluene, rinsing out the ketonitrile flask with an additional 5 mL toluene. Heat to reflux under N₂ (130° C.) with Dean-Stark trap attached. Water will begin to accumulate after 10 minutes or so. After 2 hours, evaporate down and partition between 1.0 N NaOH (100 mL) and EtOAc (100 mL). Extract aqueous layer with EtOAc (2x100 mL), then pool the organic layers and dry over Na₂SO₄. Filter and evaporate to yellow oil (1.75 g). Use without further purification. LCMS=236.5 (MH⁺); 234.5 (M⁻).

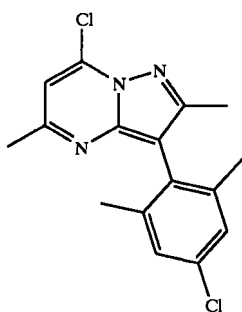
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[0122] G. 7-Hydroxy-2,5-dimethyl-3-(4-chloro-2,6-dimethylphenyl)-pyrazolo[1,5-a]pyrimidine



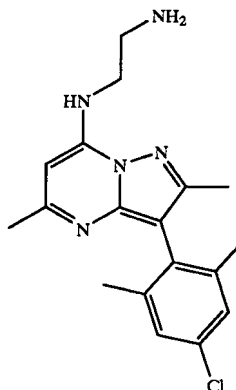
[0123] Dissolve 5-amino-4-(4-chloro-2,6-dimethylphenyl)-3-methylpyrazole in 20 mL glacial acetic acid at ambient temperature, and add ethyl acetoacetate (2.0 mL, 1.99 g). Heat to reflux (130° C.) under N₂ overnight. Evaporate down to concentrate and add 200 mL Et₂O to precipitate out product. Stir at ambient temperature for 1 hour, then filter and wash the resulting white solid (1.25 g) with copious amounts of Et₂O. LCMS=302.2 (MH⁺); 300.2 (M⁻).

[0124] H. 7-Chloro-2,5-dimethyl-3-(4-chloro-2,6-dimethylphenyl)-pyrazolo [1,5-a]pyrimidine



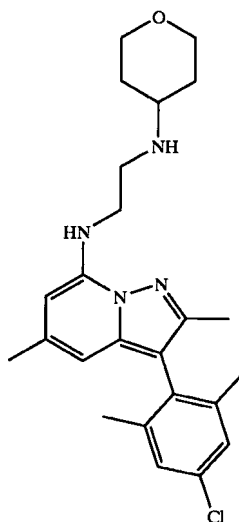
[0125] Slurry 7-hydroxy-2,5-dimethyl-3-(4-chloro-2,6-dimethylphenyl)-pyrazolo[1,5-a] pyrimidine in 10 mL POCl₃ and reflux at 130° C. under N₂. After 2 hours, monitoring by TLC (alcohol R_f=0.5, chloride R_f=1.0; EtOAc as eluent), quench the reaction carefully at ambient temperature by diluting with 50 mL CH₂Cl₂ and pouring slowly into non-stirring saturated NaHCO₃. Adjust stirring speed to control rate of quenching of residual POCl₃ and stir until gas evolution ceases. Separate the layers and extract the aqueous layer with CH₂Cl₂ (2x50 mL). Pool the organic layers and dry over Na₂SO₄. Filter and evaporate to yellow oil, which is used directly without further purification.

[0126] I. 7-(2-aminoethylamino)-2,5-dimethyl-3-(4-chloro-2,6-dimethylphenyl)-pyrazolo[1,5-a] pyrimidine



[0127] Dissolve 7-chloro-2,5-dimethyl-3-(4-chloro-2,6-dimethylphenyl)-pyrazolo[1,5-a] pyrimidine in 25 mL CH₃CN, then add excess ethylenediamine (5 mL) and heat to 80° C. for 3-6 hours under N₂ with attached reflux condenser. (TLC; product diamine R_f=0.5, aryl chloride R_f=1.0; [10% (2.0M NH₃ in MeOH)/90% CH₂Cl₂] as eluent). Cool to ambient temperature and evaporate to yellow oil. Partition between CH₂Cl₂ (50 mL) and 1.0 N NaOH (50 mL), and extract aqueous layer 2x30 mL CH₂Cl₂. Pool organic layers, dry over Na₂SO₄, filter and evaporate to yellow-white foam (1.25 g). Use without further purification. LCMS=344.4 (MH⁺); 342.3 (M⁻).

[0128] J. 7-(2-(perhydro-2H-pyran-4-ylamino)ethylamino)-2,5-dimethyl-3-(4-chloro-2,6-dimethylphenyl)-pyrazolo[1,5-a] pyrimidine



[0129] Dissolve 7-(2-aminoethylamino)-2,5-dimethyl-3-(4-chloro-2,6-dimethylphenyl)-pyrazolo[1,5-a] pyrimidine (0.183g, 5.4x10⁻⁴ mol, 339.2 g/mol) in dichloroethane (5 mL) and add tetrahydro-4H-pyran-4-one (0.068 g, 0.060 mL, 100.12 g/mol) and sodium triacetoxyborohydride (0.172 g,

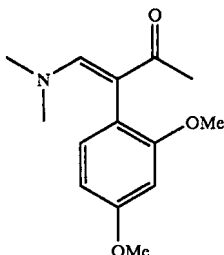
211.94 g/mol). To the resultant slurry, add glacial acetic acid (0.032 mL, 5.4×10^{-4} mol) and stir at ambient temperature under N_2 for 3 hours. Partition between CH_2Cl_2 (3 mL) and 1.0 N NaOH (10 mL), then separate the layers and chromatograph the CH_2Cl_2 layer using [10% (2.0M NH_3 in MeOH)/90% CH_2Cl_2] as eluent. Obtained 0.16 g white solid-foam upon evaporation. TLC: Rf=0.65. LCMS=422.5 (MH^+); 420.5 (M^-). H-NMR ($CDCl_3$): 6.67 (s, 2H); 5.79 (d, 1H, J=8.8 Hz); 3.98 (br. d, 2H, J=12 Hz); 3.78 (s, 3H); 3.52 (t, 2H, J=6 Hz); 3.39 (br. t, 2H, J=12 Hz); 3.37 (s, 1H); 3.04 (t, 2H, J=6 Hz); 2.75-2.81 (m, 2H); 2.40 (s, 3H); 2.18 (s, 3H); 2.00 (s, 6H); 1.89 (br. d, 2H, J=12 Hz); 1.47-1.53 (m, 2H).

Example 2

Preparation of 7-(2-(2-(4-ethoxy-3-methoxyphenyl)ethylamino)ethylamino)-3-(2,4-dimethoxyphenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidine

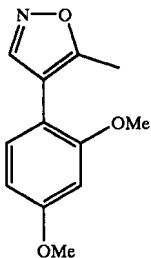
Formula I where X is CH_2 , R^1 is CH_3 , R^2 is H, A is CH_2 , B is CH_2 , R^3 is CH_3 , R^4 is 2,4-dimethoxyphenyl, R^5 is 2-(4-ethoxy-3-methoxyphenyl)ethylamino)ethyl

[0130] A. (3E)-3-(2,4-dimethoxyphenyl)-4-(dimethylamino)but-3-en-2-one



[0131] Dissolve 1-(2,4-dimethoxyphenyl)acetone (1.0 g, 5.15 mmol, 194.23 g/mol) in DMF-diethyl acetal (4.5 mL, 25.7 mmol, 147.22 g/mol) and stir under N_2 at 100° C. overnight. TLC using 20% EtOAc/80% hexanes; (ketone Rf=0.25, product Rf=0.0). Evaporate to thick oil, dissolve in EtOAc (25 mL) and wash with H_2O (3x25 mL). Extract pooled H_2O layers with EtOAc. Dry pooled organic layers over Na_2SO_4 , filter and evaporate to thick oil which solidifies upon standing at ambient temperature (0.98 g). Use without further purification. LCMS=250.2 (NH^+); 248.2 (M^-).

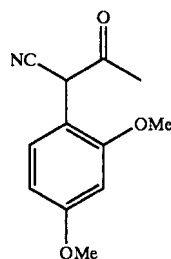
[0132] B. 4-(2,4-Dimethoxyphenyl)-5-methyl-isoxazole



[0133] Dissolve (3E)-3-(2,4-dimethoxyphenyl)-4-(dimethylamino)but-3-en-2-one (5.1 g, 20.6 mmol) in EtOH (50 mL) and add $NH_4OH.HCl$ (3.05 g, 44.0 mmol). Heat to

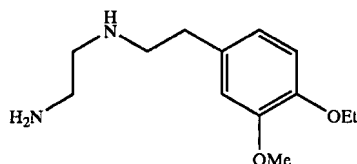
reflux under N_2 for 20 minutes. Cool and evaporate to red-brown oil. Dissolve in CH_2Cl_2 , dry over Na_2SO_4 , filter and concentrate to red-brown oil (4.4 g). Use without further purification. LCMS=220.2 (MH^+); 218.2 (M^-).

[0134] C. 2-(2,4-Dimethoxyphenyl)-3-oxobutanenitrile.



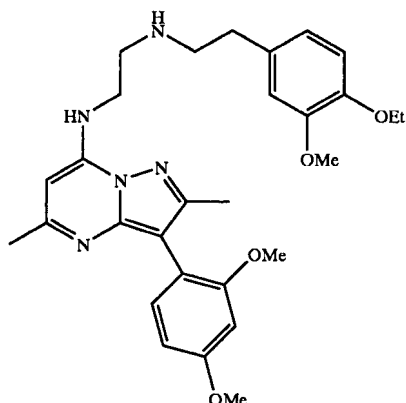
[0135] Slurry 4-(2,4-dimethoxyphenyl)-5-methyl-isoxazole (4.4 g) in 1.0 N NaOH (35 mL) and add 35 mL MeOH to dissolve. Heat at 60° C. under N_2 for 1 hour, then cool to clear brown solution. Add 1.0 N HCl to acidify to pH 1, then filter the resulting white solid precipitate. Dissolve solid in EtOAc, dry over Na_2SO_4 , filter and concentrate to red oil. Use without further purification. LCMS=220.2 (MH^+); 218.2 (M^-).

[0136] D. N-(4-Ethoxy-3-methoxy-phenethyl)-ethylene-diamine.



[0137] Dissolve 4-ethoxy-3-methoxy-phenyl acetic acid (26 g, 119 mol) in dichloroethane (300 mL, anhydrous) and cool to 0° C. Dropwise add oxalyl chloride (130 mL, 2.0 M in CH_2Cl_2) and DMF (2 mL), then allow to warm to ambient temperature overnight. Evaporate down and chase with CH_2Cl_2 , then evaporate to a tan oil. Dissolve in 200 mL dichloroethane and cool to 0° C. while stirring under N_2 . Dropwise, over 45 minutes, add a second solution of N-tBOC-ethylenediamine (20 g) and triethylamine (20 mL) in 100 mL dichloroethane. Partition between CH_2Cl_2 (500 mL) and 1.0 N HCl (200 mL), then separate the layers and wash the organic layer with 1.0 N HCl (200 mL). Wash the organic layer with saturated K_2CO_3 (2 x 200 mL), then dry the CH_2Cl_2 layer over Na_2SO_4 , filter and evaporate to tan solid. Triturate with 200 mL Et_2O and stir vigorously to fragment solid, then filter and wash copiously with Et_2O to obtain 20.5 g white solid. Dissolve white solid (3.0 g, 8.52 mmol) in 10 mL (1:1 trifluoroacetic acid: CH_2Cl_2) and stir at ambient temperature 1 hour. Evaporate down and partition between CH_2Cl_2 (25 mL) and 1.0 N NaOH (25 mL), then separate the layers and extract the aqueous layer with CH_2Cl_2 (25 mL). Pool the organic layers, dry over Na_2SO_4 , filter and evaporate to a white solid (1.75 g).

[0138] E. 7-(2-(2-(4-ethoxy-3-methoxyphenyl)ethylamino)ethylamino)-3-(2,4-dimethoxyphenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidine.



[0139] Dissolve 7-chloro-2,5-dimethyl-3-(2,4-dimethoxyphenyl)-pyrazolo[1,5-a]pyrimidine (prepared from 2-(2,4-dimethoxyphenyl)-3-oxobutanenitrile according to the methods of EXAMPLE 1 F, G and H) (0.2 g, 6.31 $\times$ 10⁻⁴ mol) in dichloroethane (10 mL), then add the N-(4-ethoxy-3-methoxy-phenethyl)-ethylenediamine from step D (0.10 g, 4.2 $\times$ 10⁻⁴ mol) and diisopropylethylamine (0.1 mL, 6 $\times$ 10⁻⁴ mol) and stir under N₂ at 80° C. overnight. Wash the organic layer with saturated NaHCO₃ (10 mL), then evaporate the organic layer down to a yellow oil. Chromatograph using [10% (2.0 M NH₃ in MeOH)/90% CH₂Cl₂] and evaporate to obtain 50 mg pale yellow solid. LCMS=520.3 (MH⁺); 518.3 (M⁻). H-NMR (CDCl₃): 7.35 (d, 1H, J=8.4 Hz); 6.71-6.8 (m, 3H); 6.56-6.61 (m, 2H); 6.47 (t, 1H, J=5.6 Hz); 5.75 (s, 1H); 4.05 (quart., 2H, J=6.8 Hz); 3.82-3.88 (m, 5H); 3.77 (s, 3H); 3.42 (quart., 2H, J=5.6 Hz); 2.97 (t, 2H, J=6 Hz); 2.90 (t, 2H, J=6 Hz); 2.76 (t, 2H, J=7.2 Hz); 2.44 (s, 3H); 2.35 (s, 3H) 1.43 (t, 3H, J=6.8 Hz).

Example 3

Preparation of 7-(2-(perhydro-2H-pyran-4-ylamino)ethylamino)-2,5-dimethyl-3-(2,6-dimethyl-4-methoxyphenyl)-pyrazolo[1,5-a] pyrimidine

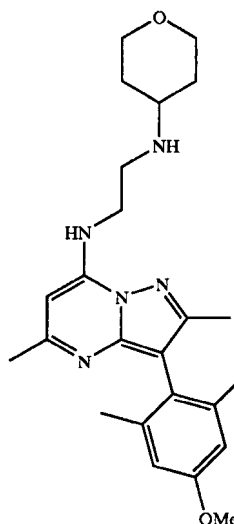
Formula I where X is CH, R¹ is CH₃, R² is H, A is CH₂, B is CH₂, R³ is CH₃, R⁴ is 2,4-dimethyl-4-methoxyphenyl, R⁵ is perhydro-2H-pyran-4-yl

[0140] A. 4-Methoxy-2,6-dimethyl phenyl acetonitrile

[0141] Dropwise add a solution of chlorotrimethylsilane (20 mL) in CH₂Cl₂ (40 mL) to a stirred solution cooled to 0° C. of 4-methoxy-2,6-dimethyl benzyl alcohol (approx. 74 mmol) in 300 mL CH₂Cl₂. Solution changes color from colorless to yellow and then to purple over the course of the reaction. After 2 hours, monitoring by TLC (alcohol Rf=0.25, chloride Rf=0.95; using 20% EtOAc/80% hexanes as eluent), evaporate down to a yellow oil. Dissolve in dry DMF (50 mL) and cool to 0° C. under N₂. Add freshly ground NaCN (7.0 g) portionwise over 5 minute (exothermic) to the stirring reaction, forming a yellow/white slurry. Stir for 5-8 hours at 0° C. until no starting material remains, as determined by TLC (nitrile Rf=0.5; using 20% EtOAc/

80% hexanes as eluent). Partition the reaction solution between EtOAc (100 mL) and 0.1 N NaOH (300 mL). Dry the EtOAc layer over Na₂SO₄, filter and evaporate to yellow oil. Chromatograph in 10% EtOAc/90% hexanes on silica to remove residual chloride and evaporate to 2.1 g yellow solid; clean by TLC. LCMS=176.5 (MH⁺), 174.4 (M⁻).

[0142] B. 7-(2-(Perhydro-2H-pyran-4-ylamino)ethylamino)-2,5-dimethyl-3-(2,6-dimethyl-4-methoxyphenyl)-pyrazolo[1,5-a] pyrimidine



[0143] 7-(2-(Perhydro-2H-pyran-4-ylamino)ethylamino)-2,5-dimethyl-3-(2,6-dimethyl-4-methoxyphenyl)-pyrazolo[1,5-a] pyrimidine is obtained from 4-methoxy-2,6-dimethyl phenyl acetonitrile using the procedures described in EXAMPLE 1 E, F, G, H, I, J.

Example 4

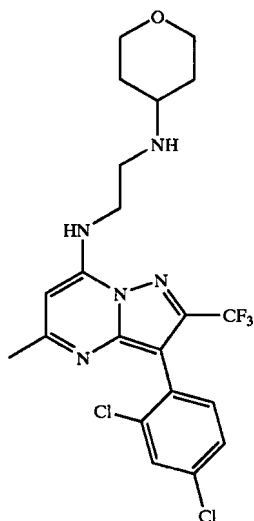
Preparation of 7-(2-(perhydro-2H-pyran-4-ylamino)ethylamino)-2-trifluoromethyl-5-methyl-3-(2,4-dichlorophenyl)-pyrazolo[1,5-a] pyrimidine

Formula I where X is CH, R¹ is CH₃, R² is H, A is CH₂, B is CH₂, R³ is CF₃, R⁴ is 2,4-dichlorophenyl, R⁵ is perhydro-2H-pyran-4-yl

[0144] A. 2-(2,4-Dichlorophenyl)-4,4,4-trifluoro-3-oxobutanenitrile

[0145] Slurry 2,4-dichlorophenylacetonitrile (I) (5.0 g, 26.9 mmol, 186.04 g/mol) in ethyl trifluoroacetate (6.4 mL, 7.6 g, 142.08 g/mol) and add 20 mL anhydrous THE. Portionwise at ambient temperature add NaH (1.88 g, 47.1 mmol, 60% in mineral oil) over 5 minutes. Heat reaction to reflux (90° C. bath temperature) overnight. Evaporate to thick red-brown oil and partition between Et₂O (100 mL) and H₂O (60 mL). Separate layers and extract H₂O with Et₂O (2 $\times$ 75 mL). Acidify the aqueous layer with 1.0 N HCl to pH 1 (becomes cloudy white suspension) and extract aqueous layer with CH₂Cl₂ (3 $\times$ 100 mL). Dry pooled CH₂Cl₂ layers over Na₂SO₄, filter and concentrate to yellow oil (7.5 g, 26.5 mmol). Use without further purification. LCMS=281.9 (MH⁺); 279.8 (M⁻).

[0146] B. 7-(2-(Perhydro-2H-pyran-4-ylamino)ethylamino)-2-trifluoromethyl-5-methyl-3-(2,4-dichlorophenyl)-pyrazolo[1,5-a] pyrimidine



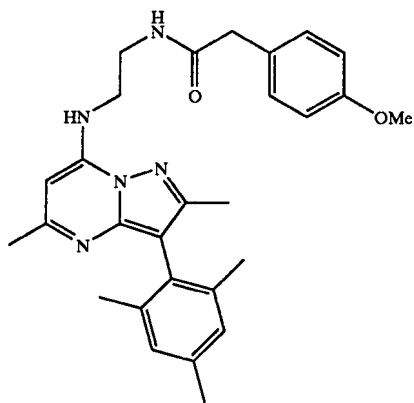
[0147] 7-(2-(Perhydro-2H-pyran-4-ylamino)ethylamino)-2-trifluoromethyl-5-methyl-3-(2,4-dichlorophenyl)-pyrazolo[1,5-a] pyrimidine is obtained from 2-(2,4-dichlorophenyl) 4,4,4-trifluoro-3-oxobutanenitrile using the procedures described in EXAMPLE 1 F, G, H, J.

Example 5

Preparation of 7-(2-(2-(4-methoxyphenyl)ethylamino)ethylamino)-3-(2,4,6-trimethylphenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidine

Formula I where X is CH, R¹ is CH₃, R² is H, A is CH₂, B is CH₂, R³ is CH₃, R⁴ is 2,4,6-trimethylphenyl, R⁵ is 2-(4-methoxyphenyl)ethylamino)ethyl

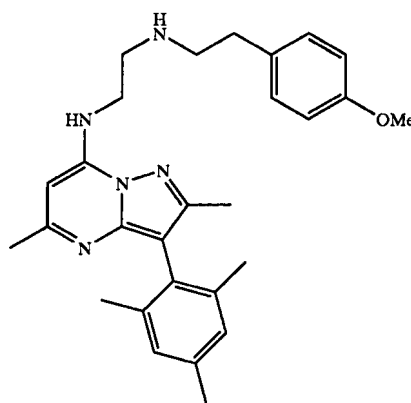
[0148] A. N-(3-(2,4,6-trimethylphenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-yl)-2-(4-methoxyphenyl)acetamide



[0149] Dissolve 7-chloro-2,5-dimethyl-3-(2,4,6-trimethylphenyl)-pyrazolo[1,5-a]pyrimidine (0.26 g, 8.69×10⁻⁴ mol) in 2 mL N-methylpyrrolidine, and add N-(2-aminoethyl)-2-(4-methoxyphenyl)acetamide (0.75 g, 3.6 mmol).

Heat to 80° C. overnight under N₂. Partition between EtOAc (50 mL) and H₂O (50 mL), then separate layers and wash EtOAc layer successively with 0.1 N NaOH (25 mL), H₂O (25 mL), and brine. Pool aqueous layers and extract with EtOAc (25 mL). Pool EtOAc layers, dry over Na₂SO₄, filter and concentrate to yellow oil. Chromatograph on silica gel eluting with EtOAc and evaporate to obtain 0.30 g of N-(3-(2,4,6-trimethylphenyl)-2,5-dimethyl-pyrazolo[1,5-a] pyrimidin-7-yl)-2-(4-methoxyphenyl)acetamide as a clear pale yellow oil. LCMS=472.3 (MH⁺); 470.2 (M⁻). ¹H-NMR (CDCl₃): 7.10 (d, 2H, J=10.2 Hz); 6.39 (s, 2H); 6.81 (d, 2H, J=10.2 Hz); 6.46 (t, 1H, J=6.0 Hz); 6.16 (t, 1H, J=6.0 Hz); 5.79 (s, 1H); 3.76 (s, 3H); 3.45-3.50 (mn, 6H); 2.38 (s, 3H); 2.30 (s, 3H); 2.20 (s, 3H); 2.02 (s, 6H).

[0150] B. 7-(2-(2-(4-methoxyphenyl)ethylamino)ethylamino)-3-(2,4,6-trimethylphenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidine



[0151] Dissolve N-(3-(2,4,6-trimethylphenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-yl)-2-(4-methoxyphenyl)acetamide (0.15 g, 3.2×10⁻⁴ mol) in 5 mL anhydrous THF and stir under N₂. Add borane-dimethylsulfide complex (0.25 mL, 10.0 M in THF) and heat to reflux overnight. Quench by careful addition of MeOH until gas evolution ceases, then evaporate to oil. Add HCl in Et₂O (2 TnL, 1.0 M) and MeOH to solubilize (5 mL), then reflux 1 hour and evaporate. Dissolve in CH₂Cl₂ (20 mL) and wash with saturated NaHCO₃ (20 mL). Evaporate CH₂Cl₂ layer and chromatograph on silica gel eluting with EtOAc (Rf=0.15), then evaporate down to a clear oil (0.10 g). LCMS=458.3 (MH⁺), 456.4 (M⁻). ¹H-NMR (CD₃Cl): 7.13 (d, 2H, J=8.8 Hz); 6.94 (s, 3H); 6.84 (d, 2H, J=8.8 Hz); 6.57 (t, 1H, J=5.6 Hz); 5.77 (s, 1H); 3.78 (s, 3H); 3.44 (quartet, 2H, J=5.6 Hz); 3.00 (t, 2H, J=6.0 Hz); 2.92 (t, 2H, J=6.8 Hz); 2.78 (t, 2H, J=6.8 Hz); 2.41 (s, 3H); 2.31 (s, 3H); 2.22 (s, 3H); 2.01 (s, 6H).

[0152] Alternatively, the reduction can be carried out as follows: dissolve N-(3-(2,4,6-trimethylphenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-yl)-2-(4-methoxyphenyl)acetamide (0.15g, 3.2×10⁻⁴ mol) in 5 mL anhydrous THF. Add a fresh solution of alanine-dimethylethylamine complex in toluene (2.25 mL, 9.6×10⁻⁴ mol) and heat to 50° C. overnight under dry N₂. Quench reaction by addition of solid Na₂CO₃·10H₂O (0.5 g) and stir vigorously until gas evolution ceases. Filter through celite to remove solid and evaporate.

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250

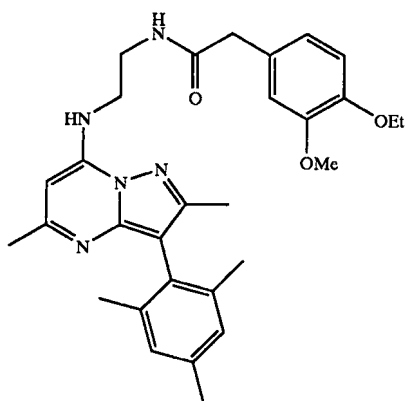
rate the filtrate down to a clear pale yellow oil. Chromatograph on silica gel eluting with EtOAc ($R_f=0.15$), then evaporate down to a clear oil (0.10 g).

Example 6

Preparation of 7-(2-(2-(4-ethoxy-3-methoxyphenyl)ethylamino)ethylamino)-3-(2,4,6-trimethylphenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidine

Formula I where X is CH, R^1 is CH₃, R^2 is H, A is CH₂, B is CH₂, R^3 is CH₃, R^4 is 2,4,6-trimethylphenyl, R^5 is 2-(4-ethoxy-3-methoxyphenyl)ethylamino)ethyl

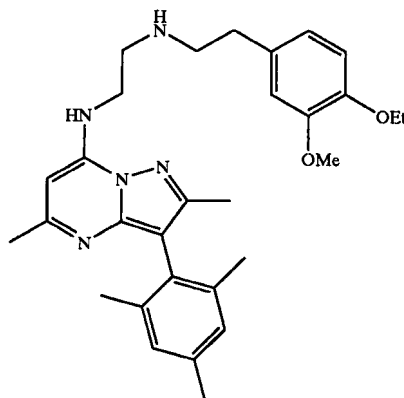
[0153] A. N-(3-(2,4,6-trimethylphenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-yl)-2-(4-ethoxy-3-methoxyphenyl)acetamide



[0154] Dissolve 7-(2-aminoethylamino)-2,5-dimethyl-3-(2,4,6-trimethylphenyl)-pyrazolo[1,5-a] pyrimidine (91 mg, 2.8×10^{-4} mol) in N-methyl pyrrolidine (2 mL) and add 2-(4-ethoxy-3-methoxyphenyl)acetic acid (65 mg, 3.1×10^{-4} mol). Add triethylamine (85 mg, 0.117 mL, 8.46×10^{-4} mol) and BOP-Cl (0.15 g, 3.4×10^{-4} mol), then stir at ambient temperature under N₂ overnight. Partition between H₂O (10 mL) and EtOAc (10 mL), then separate layers and wash EtOAc layer with 1.0 N NaOH (10 mL). Dry the EtOAc layer over Na₂SO₄, filter and evaporate to oil. Use without further purification. LCMS=516.3 (MH⁺); 514.2 (M⁻).

[0155] Alternatively, N-(2-aminoethyl)-2-(4-ethoxy-3-methoxyphenyl)acetamide can be prepared as follows: dissolve 2-(4-ethoxy-3-methoxyphenyl)acetic acid in (26 g, 119 mol) in dichloroethane (300 mL, anhydrous) and cool to 0° C. Dropwise add oxalyl chloride (130 mL, 2.0 M in CH₂Cl₂) and DMF (2 mL), then allow to warm to ambient temperature overnight. Evaporate down and chase with CH₂Cl₂, then evaporate to a tan solid. Dissolve a portion of the tan solid acid chloride (80 mg, 3.5×10^{-4} mol) in N-methyl pyrrolidine (2 mL) and cool to 0° C. Add 7-(2-aminoethylamino)-2,5-dimethyl-3-(2,4,6-trimethylphenyl)-pyrazolo[1,5-a] pyrimidine (100 mg, 3.1×10^{-4} mol) and triethylamine (85 mg, 0.117 mL, 8.46×10^{-4} mol), then stir at ambient temperature under N₂ overnight. Partition between H₂O (10 mL) and EtOAc (10 mL), then separate layers and wash EtOAc layer with 1.0 N NaOH (10 mL). Dry the EtOAc layer over Na₂SO₄, filter and evaporate to oil. Use without further purification.

[0156] B 7-(2-(2-(4-Ethoxy-3-methoxyphenyl)ethylamino)ethylamino)-3-(2,4,6-trimethylphenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidine.



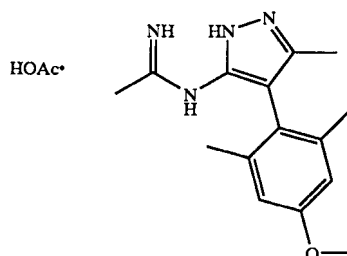
[0157] Reduction of N-(3-(2,4,6-trimethylphenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-yl)-2-(4-ethoxy-3-methoxyphenyl)acetamide with borane-dimethylsulfide complex, according to the procedure of EXAMPLE 5, yields 7-(2-(2-(4-ethoxy-3-methoxyphenyl)ethylamino)ethylamino)-3-(2,4,6-trimethylphenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidine. LCMS=502.3 (MH⁺); 500.4 (M⁻).

Example 7

Preparation of 7-(2-(perhydro-2H-pyran-4-ylamino)ethylamino)-2,5-dimethyl-3-(4-methoxy-2,6-dimethylphenyl)-[1,5-a]-pyrazolo-1,3,5-triazine.

Formula I where X is N, R^1 is CH₃, R^2 is H, A is CH₂, B is CH₂, R^3 is CH₃, R^4 is 2,6-dimethyl-4-methoxyphenyl, R^5 is perhydro-2H-pyran-4-yl

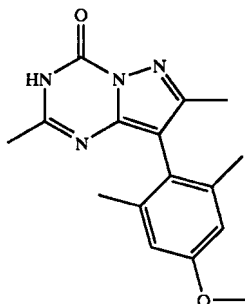
[0158] A. (Iminoethyl) [4-(4-methoxy-2,6-dimethylphenyl)-3-methylpyrazol-5-yl]amine acetate salt.



[0159] To a solution of 5-amino-4-(4-methoxy-2,6-dimethylphenyl)-3-methylpyrazole (1.89 g) (prepared from 4-methoxy-2,6-dimethyl benzaldehyde according to Example 1 C—F) in acetonitrile (30 mL) add ethylacetimidate (free base, 1.8 mL) followed by acetic acid (0.47 mL). Collect the precipitate that formed upon stirring overnight by filtration. Wash the solid with dry ether and dry to afford 2.61 g of (iminoethyl)[4-(4-methoxy-2,6-dimethylphenyl)-3-methylpyrazol-5-yl]amine acetate salt as a white powder.

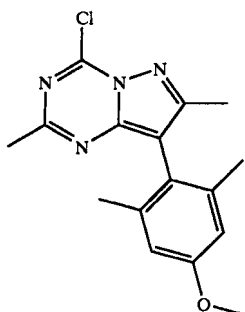
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[0160] B. 2,6-Dimethyl-7-(2,6-dimethyl-4-methoxyphenyl)-3H-[1,5-c]-pyrazolo-1,3,5-triazin-4-one.



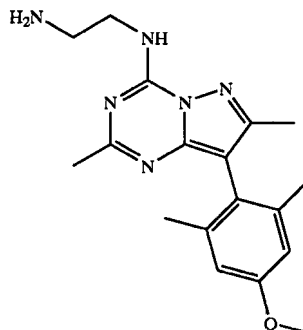
[0161] Add sodium pieces (1.81 g) to a flask containing anhydrous ethanol and equipped with a reflux condenser. Allow the mixture to stir until all the sodium is consumed and then add the amidine (2.61 g as the acetate salt) from step A in one portion. Add diethyl carbonate (7.6 mL) and reflux the mixture overnight. Concentrate the mixture under reduced pressure, dissolve the residue in water (75 mL) and adjust the pH to 5 with 3N HCl. Extract the aqueous mixture with ethyl acetate and wash the extracts with brine, dry over anhydrous sodium sulfate, and concentrate in vacuo to obtain a foam. Stir the residue with hexanes for 20 minutes and collect the solid by filtration, then wash with hexanes to obtain 2.01 g of 2,6-dimethyl-7-(2,6-dimethyl-4-methoxyphenyl)-3H-[1,5-c]-pyrazolo-1,3,5-triazin-4-one as a yellow powder: MS 299 (M+H).

[0162] C. 4-Chloro-2,6-dimethyl-7-(2,6-dimethyl-4-methoxyphenyl) [1,5-a]-pyrazolo-1,3,5-triazine.



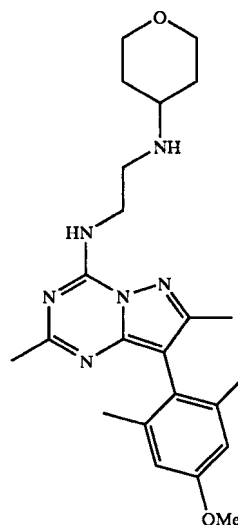
[0163] Dissolve 2,6-dimethyl-7-(2,6-dimethyl-4-methoxyphenyl)-3H-[1,5-c]-pyrazolo-1,3,5-triazin-4-one from step B (1 g) in POCl₃ (50 mL) and add N,N-dimethylaniline (0.55 mL). Reflux the reaction mixture under a dry nitrogen atmosphere for 18h at which time concentrate the mixture under reduced pressure. Dissolve the residue in ethyl acetate and wash with a saturated aqueous NaHCO₃ solution, then with brine. Dry the organic layer over anhydrous sodium sulfate, filter and concentrate under reduced pressure to obtain 4-chloro-2,6-dimethyl-7-(2,6-dimethyl-4-methoxyphenyl) [1,5-a]-pyrazolo-1,3,5-triazine as a dark oil. MS 317 (M+H).

[0164] D. 2,6-Dimethyl-7-(2,6-dimethyl-4-methoxyphenyl)-4-(2-aminoethyl)amino-[1,5-a]-pyrazolo-1,3,5-triazine.



[0165] Dissolve 4-chloro-2,6-dimethyl-7-(2,6-dimethyl-4-methoxyphenyl) [1,5-a]-pyrazolo-1,3,5-triazine in dry toluene (10 mL) to form a stock solution of the chloride (0.34 M). Add a portion of this solution (8 mL) dropwise into a stirring solution of ethylenediamine (3.6 mL) in acetonitrile (50 mL) which is heated to 60° C. After 3h at 60° C., cool the solution, concentrate under reduced pressure, dilute with 10% NaOH and extract with ethyl acetate. Wash the combined extracts with brine, dry over anhydrous sodium sulfate and concentrate under reduced pressure to obtain a yellow residue. Triturate the residue with 20% ethyl acetate/hexanes and collect the resulting solid by filtration to obtain 0.72 g of 2,6-dimethyl-7-(2,6-dimethyl-4-methoxyphenyl)-4-(2-aminoethyl)amino-[1,5-a]-pyrazolo-1,3,5-triazine as a yellow solid: MS 341 (M+H).

[0166] E. 2,6-Dimethyl-7-(2,6-dimethyl-4-methoxyphenyl)-4-(2-(perhydro-2H-pyran-4-ylamino)ethylamino)-[1,5-a]-pyrazolo-1,3,5-triazine.



[0167] Dissolve 2,6-dimethyl-7-(2,6-dimethyl-4-methoxyphenyl)-4-(2-aminoethyl)amino-[1,5a]-pyrazolo-1,3,5-triazine from step D (0.211 g) in dry dichloroethane (15 mL) and add tetrahydro-4-H-pyran-4-one (57 µL). Add acetic acid

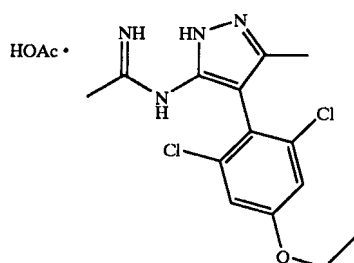
(35 μ L) followed by sodium triacetoxyborohydride (0.184 g) and stir the resulting homogeneous mixture overnight at ambient temperature. Dilute the reaction mixture with 4 volumes of dichloromethane, wash with brine, dry over anhydrous sodium sulfate, and concentrate under reduced pressure to obtain a yellow solid. Purify using preparative thin-layer chromatography [10% MeOH(2N NH₃)/CH₂Cl₂] to obtain 2,6-dimethyl-7-(2,6-dimethyl-4-methoxyphenyl)-4-(2-(perhydro-2H-pyran-4-ylamino)ethylamino)-[1,5-a]-pyrazolo-1,3,5-triazine (0.165 g) as a light-yellow solid: MS 425 (M+H).

Example 8

Preparation of 2-[(2-{[7-(2,6-dichloro-4-ethoxyphenyl)-2,6-dimethylpyrazolo[1,5-a]1,3,5-triazin-4-yl]amino}ethyl)amino]-2-methylpropan-1-ol

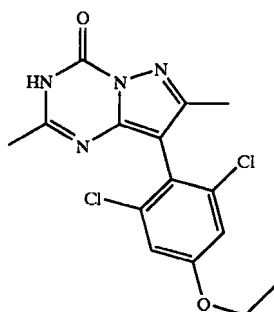
Formula I where X is N, R¹ is CH₃, R² is H, A is CH₂, B is CH₂, R³ is CH₃, R⁴ is 2,6-dichloro-4-ethoxyphenyl, R⁵ is C(CH₃)₂CH₂OH

[0168] A. Iminoethyl[4-(4-ethoxy-2,6-dichlorophenyl)-3-methylpyrazol-5-yl]amine acetate salt.



[0169] To a solution of 5-amino-4-(4-ethoxy-2,6-dichlorophenyl)-3-methylpyrazole (4.8 g) (prepared from 4-ethoxy-2,6-dichloro benzaldehyde according to Example 1 C-F) in acetonitrile (50 mL) add ethylacetimidate (free base, 2.3 mL) followed by acetic acid (0.96 mL). Collect the precipitate that formed upon stirring overnight by filtration. Wash the solid with dry ether and dry to afford 5.02 g of (iminoethyl)[4-(4-ethoxy-2,6-dichlorophenyl)-3-methylpyrazol-5-yl]amine acetate salt as a white powder.

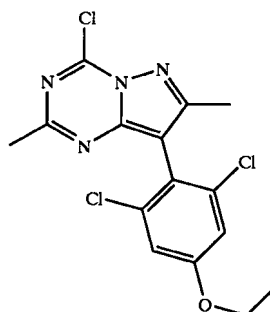
[0170] B. 2,6-Dimethyl-7-(2,6-dichloro-4-ethoxyphenyl)-3H-[1,5-c]-pyrazolo-1,3,5-triazin-4-one.



[0171] Add sodium pieces (2.98 g) to a flask containing anhydrous ethanol and equipped with a reflux condenser. Allow the mixture to stir until all the sodium is consumed and then add the amidine (5.02 g as the acetate salt) from step A in one portion. Add diethyl carbonate (12.6 mL) and reflux the mixture for four hours. Concentrate the mixture

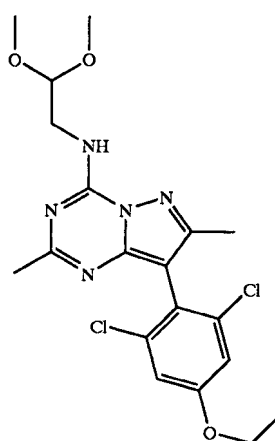
under reduced pressure, dissolve the residue in water (75 mL) and adjust the pH to 5 with 3N HCl. Extract the aqueous mixture with ethyl acetate and wash the extracts with brine, dry over anhydrous sodium sulfate, and concentrate in vacuo to obtain a foam. Stir the residue with hexanes for 20 minutes and collect the solid by filtration, then wash with hexanes to obtain 4.41 g of 2,6-dimethyl-7-(2,6-dichloro-4-ethoxyphenyl)-3H-[1,5-c]-pyrazolo-1,3,5-triazin-4-one as a beige solid: MS 353 (M+H).

[0172] C. 4-Chloro-2,6-dimethyl-7-(2,6-dichloro-4-ethoxyphenyl)-[1,5-a]-pyrazolo-1,3,5-triazine.



[0173] Dissolve 2,6-dimethyl-7-(2,6-dichloro-4-ethoxyphenyl)-3H-[1,5-c]-pyrazolo-1,3,5-triazin-4-one from step B (1.05 g) in POCl₃ (50 mL) and add 2,6-lutidine (0.45 mL). Reflux the reaction mixture under a dry nitrogen atmosphere for 48 h and then concentrate the mixture under reduced pressure. Dissolve the residue in ethyl acetate and wash with a saturated aqueous NaHCO₃ solution, then with brine. Dry the organic layer over anhydrous sodium sulfate, filter and concentrate under reduced pressure to obtain an oil which crystallizes upon standing. Wash the solid with hexanes to remove residual 2,6-lutidine and collect the solid on a sintered glass funnel yielding 4-chloro-2,6-dimethyl-7-(2,6-dichloro-4-ethoxyphenyl)-[1,5-a]-pyrazolo-1,3,5-triazine. MS 372 (M+H).

[0174] D. 2,6-Dimethyl-7-(2,6-dichloro-4-ethoxyphenyl)-4-(2,2-dimethoxyethyl)amino-[1,5-a]-pyrazolo-1,3,5-triazine.

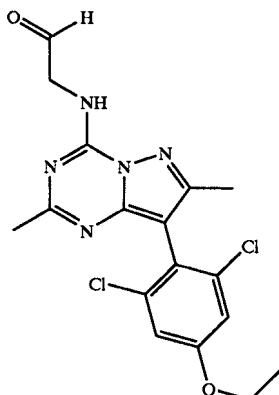


[0175] Dissolve the product from step C in dry acetonitrile and then add 2.1 equivalents of aminoacetaldehyde dimethyl

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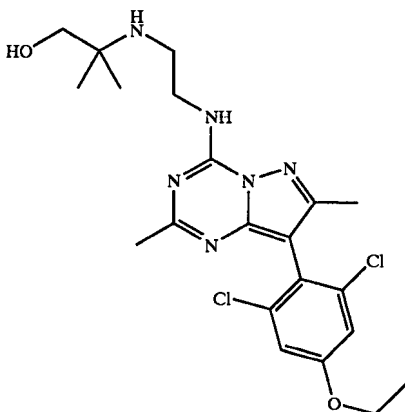
acetal. Heat the solution to 60° C. and stir under a dry nitrogen atmosphere for 2-6 hours. Remove the solvent under reduced pressure, dilute with 10% NaOH and extract with ethyl acetate. Wash the combined extracts with brine, dry over anhydrous sodium sulfate and concentrate under reduced pressure to obtain a yellow oil which crystallizes upon standing. The product, 2,6-dimethyl-7-(2,6-dichloro-4-ethoxyphenyl)-4-(2,2-dimethoxyethyl)amino-[1,5-a]-pyrazolo-1,3,5-triazine, is used without further purification. MS (M+H).

[0176] B. 2-[[7-(2,6-dichloro-4-ethoxyphenyl)-2,5,6-trimethyl-3-pyrazolino[2,3-a]1,3,5-triazin-4-yl]amino]ethanal.



[0177] Dissolve the product obtained from step D in neat trifluoroacetic acid (25 mL). After allowing the mixture to stand at ambient temperature for 0.5 h, concentrate the mixture under reduced pressure. Add saturated aqueous sodium bicarbonate and stir the resulting heterogeneous mixture for 0.5 h. Extract the aqueous solution with EtOAc, wash the EtOAc extracts with brine and then dry over anhydrous sodium sulfate. Evaporation of the solvent under reduced pressure yields the aldehyde as an off-white foam. ¹H NMR (CDCl₃): δ 9.79 (s, 1H, CHO).

[0178] F. 2-[(2-[[7-(2,6-dichloro-4-ethoxyphenyl)-2,6-dimethylpyrazolo[1,5-a]1,3,5-triazin-4-yl]amino]ethyl)amino]-2-methylpropan-1-ol.



[0179] Dissolve the aldehyde (62 mg, 0.16 mmol) obtained from step E in dry dichloroethane (4 mL). Add 1.1 equivalents of 2-amino-2-methyl-1-propanol (15 μL) followed by 1 equivalent of acetic acid. After the addition of

sodium triacetoxyborohydride (1.4 eq), stir the solution at ambient temperature for several hours. Dilute the reaction mixture with 4 volumes of methylene chloride then wash the mixture with brine (1×), dry over anhydrous Na₂SO₄. Concentrate under reduced pressure. Preparative thin layer chromatography [10% MeOH(2N NH₃)/CH₂Cl₂] of the oily residue yields 2-[(2-[[7-(2,6-dichloro-4-ethoxyphenyl)-2,6-dimethylpyrazolo[1,5-a]1,3,5-triazin-4-yl]amino]ethyl)amino]-2-methylpropan-1-ol.

[0180] The preparation of the compounds of the present invention by the above-mentioned methods is illustrated further by the following examples, delineated in the TABLE which are not to be construed as limiting the invention in scope or spirit to the specific procedures and compounds described in them. Commonly used abbreviations are: Ph is phenyl, Me is methyl, Et is ethyl, Pr is n-propyl, iPr is isopropyl, cPr is cyclopropyl, Bu is butyl, iBu is isobutyl (CH₂-CHMe₂), tBu is tert-butyl, cBu is cyclobutyl, Pent is n-pentyl, cPent is cyclopentyl, chex is cyclohexyl, Py is pyridyl, Bn is benzyl (CH₂Ph), Ac is acetyl (CH₃-C(=O)), tBOC is tert-butyloxycarbonyl (tBuO-C(=O)). EX means example.

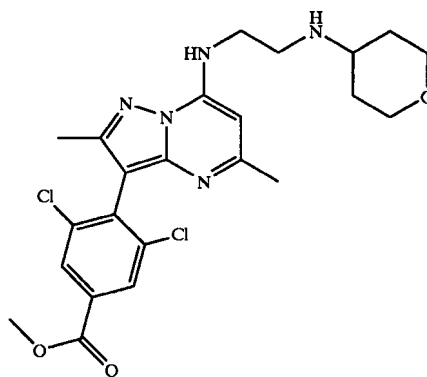
[0181] Further experimental details of the methods of Examples 119, 132, 133, 134, 277, 279, 382 and 522 are set out below.

Example 119

Preparation of 3,5-dichloro-4-{2,5-dimethyl-7-[2-(tetrahydro-pyran-4-ylamino)-ethylamino]-pyrazolo[1,5a]pyrimidin-3-yl}-benzoic acid methyl ester

Formula I where X is CH, R¹ is CH₃, R² is H, A is CH₂, B is CH₂, R³ is CH₃, R⁴ is 2,6-dichloro-4-methoxycarbonylphenyl, R⁵ is tetrahydropyranyl

[0182]



[0183] A. 4-(7-{2-[tert-Butoxycarbonyl-(tetrahydro-pyran-4-yl)-amino]-ethylamino}-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-3-yl)-3,5-dichloro-benzoic acid methyl ester

[0184] A suspension of methanesulfonic acid 4-(7-{2-[tert-butoxycarbonyl-(tetrahydro-pyran-4-yl)-amino]-ethylamino}-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-3-yl)-3,5-dichloro-phenyl ester (188 mg, 0.276 mmol) from Example

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134, step B, 1,3-bis(diphenylphosphino)propane (30 mg 0.073 mmol), triethylamine (0.10 mL), and palladium (II) acetate (25 mg, 0.11 mmol) in methanol (3.5 mL)/dimethylsulfoxide (3.5 mL) was degassed with a stream of carbon monoxide and then shaken for 4 hours at 70° C. under 40 psi carbon monoxide. The mixture was filtered through Celite, diluted with ethyl acetate and washed with water, dried (Na₂SO₄), concentrated under reduced pressure, and chromatographed (3:1 to 1:1 hexanes/ethyl acetate) to afford the product (144 mg, 88%): +APCI MS (M+1)⁺592; ¹H NMR (CDCl₃) δ: 8.04 (s, 2H), 5.83 (br s, 1H), 3.92 (s, 3H), 2.43 (s, 3H), 2.24 (s, 3H), 1.53 (s, 9H).

[0185] B. 3,5-Dichloro-4-{2,5-dimethyl-7-[2-(tetrahydro-pyran-4-ylamino)-ethylamino]-pyrazolo[1,5-a]pyrimidin-3-yl}-benzoic acid methyl ester

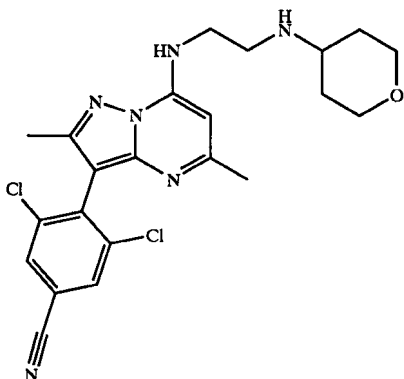
[0186] To {2-[3-(2,6-Dichloro-4-cyano-phenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-ylamino]-ethyl}-(tetrahydro-pyran-4-yl)-carbamic acid tert-butyl ester (74 mg, 0.12 mmol) was added 2:1 ethanol/concentrated aqueous hydrochloric acid (1 mL). The reaction was stirred 3 hours at room temperature, concentrated under reduced pressure, and then concentrated 3 additional times from ethanol to give a solid that was extracted from saturated sodium bicarbonate with methylene chloride, the combined extracts were dried (CDCl₃) and concentrated under reduced pressure to give the title compound (47 mg, 80%): +APCI MS (M+1)⁺492; ¹H NMR (methanol-d₄) δ: 8.04 (s, 2H), 5.82 (s, 1H), 3.93 (s, 3H), 2.43 (s, 3H), 2.27 (s, 3H).

Example 132

Preparation of 3,5-dichloro-4-{2,5-dimethyl-7-[2-(tetrahydro-pyran-4-ylamino)-ethylamino]-pyrazolo[1,5-a]pyrimidin-3-yl}-benzonitrile hydrochloride salt

Formula I where X is CH, R¹ is CH₃, R² is H, A is CH₂, B is CH₂, R³ is CH₃, R⁴ is 2,6-dichloro-4-cyanophenyl, R⁵ is tetrahydropyranyl

[0187]



[0188] A. {2-[2-[3-(2,6-Dichloro-4-cyano-phenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-ylamino]-ethyl}-(tetrahydro-pyran-4-yl)-carbamic acid tert-butyl ester

[0189] A suspension of methanesulfonic acid 4-(7-{2-[tert-butoxycarbonyl-(tetrahydro-pyran-4-yl)-amino]-ethy-

lamino}-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-3-yl)-3,5-dichlorophenyl ester (10 mg, 0.015 mmol) from Example 134, step B, zinc cyanide (2.7 mg 0.023 mmol), and palladium tetrakis(triphenylphosphine) (1.5 mg, 0.0013 mmol) in dimethylformamide (0.35 mL) was degassed with a stream of nitrogen and then stirred for 2 hours at 90° C. The mixture was extracted from saturated aqueous sodium bicarbonate with ethyl acetate, the combined extracts were washed with water, dried (Na₂SO₄), concentrated under reduced pressure, and chromatographed (9:1 to 5:3 to 0:1 hexanes/ethyl acetate) to afford the product (10 mg, quantitative): +APCI MS (M+1)⁺559; ¹H NMR (CDCl₃) δ: 7.68 (s, 2H), 5.85 (br s, 1H), 2.44 (s, 3H), 2.25 (s, 3H), 1.53 (s, 9H).

[0190] B. 3,5-Dichloro-4-{2,5-dimethyl-7-[2-(tetrahydro-pyran-4-ylamino)-ethylamino]-pyrazolo[1,5-a]pyrimidin-3-yl}-benzonitrile hydrochloride salt

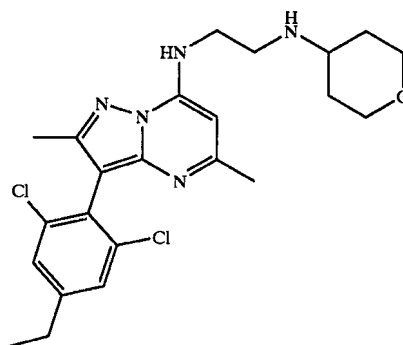
[0191] To {2-[3-(2,6-Dichloro-4-cyano-phenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-ylamino]-ethyl}-(tetrahydro-pyran-4-yl)-carbamic acid tert-butyl ester (10 mg, 0.015 mmol) was added 2:1 ethanol/concentrated aqueous hydrochloric acid (1 mL). The reaction was stirred 3 hours at room temperature, concentrated under reduced pressure, and then concentrated 3 additional times from ethanol to give a solid that was triturated from ether to afford the title compound (10 mg, quantitative): +APCI MS (M+1)⁺459; ¹H NMR (methanol-d₄) δ: 8.06 (s, 2H), 6.90 (s, 1H), 2.62 (s, 3H), 2.32 (s, 3H).

Example 133

Preparation of N-13-(2,6-dichloro-4-ethyl-phenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-yl]-N'-(tetrahydro-pyran-4-yl)-ethane-1,2-diamine hydrochloride salt

Formula I where X is CH, R¹ is CH₃, R² is H, A is CH₂, B is CH₂, R³ is CH₃, R⁴ is 2,6-dichloro-4-ethylphenyl, R⁵ is tetrahydropyranyl

[0192]



[0193] A. {2-[3-(2,6-Dichloro-4-ethyl-phenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-ylamino]-ethyl}-(tetrahydro-pyran-4-yl)-carbamic acid tert-butyl ester

[0194] To a suspension of methanesulfonic acid 4-(7-{2-[tert-butoxycarbonyl-(tetrahydro-pyran-4-yl)-amino]-ethylamino}-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-3-yl)-3,5-dichlorophenyl ester (1.0 g, 1.5 mmol) from Example 134,

step B, powdered K_3PO_4 (39 mg 0.18 mmol), and dichloro[bis(diphenylphosphino)ferrocene]palladium (60 mg, 0.085 mmol) in tetrahydrofuran (7.5 mL) was added triethylborane (1 M in THF, 2.9 mL, 2.9 mmol). The mixture was degassed with a stream of nitrogen and then stirred for 2.5 hours at 75° C. The mixture was concentrated under reduced pressure, extracted from saturated aqueous sodium bicarbonate with methylene chloride, dried (Na_2SO_4), and concentrated under reduced pressure to give crude product (1.07 g). Analysis by MS and ^1H NMR spectroscopy indicated a 1:1 mixture of product and starting material. A portion of the crude material (408 mg) was then resubjected to the above reaction conditions for 2.5 hours, then worked up as before. Chromatography (2:1 hexanes/ethyl acetate) afforded product (176 mg, 56%): +APCI MS ($M+1$)⁺ 562; ^1H NMR (methanol- d_4) δ : 7.33 (s, 2H), 6.04 (br s, 1H), 2.66 (q, 2H), 2.37 (s, 3H), 2.20 (s, 3H), 1.42 (s, 9H), 1.25 (t, 3H).

[0195] B. N-[3-(2,6-Dichloro-4-ethyl-phenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-yl]-N'-(tetrahydro-pyran-4-yl)-ethane-1,2-diamine hydrochloride salt

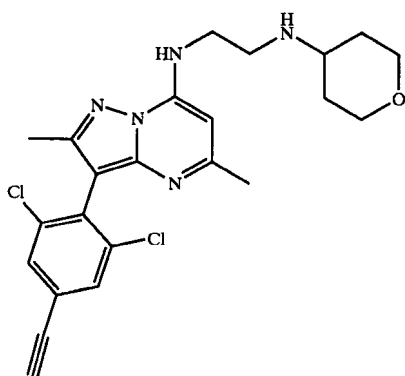
[0196] To {2-[3-(2,6-dichloro-4-ethyl-phenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-ylamino]-ethyl}-(tetrahydro-pyran-4-yl)-carbamic acid tert-butyl ester (0.18 g, 0.31 mmol) 2:1 ethanol/concentrated aqueous hydrochloric acid (3 mL). The reaction was stirred 15 minutes at 50° C., concentrated under reduced pressure, and then concentrated 3 additional times from ethanol to give a solid that was triturated from ether to afford the title compound (0.15 g, quantitative): +APCI MS ($M+1$)⁺ 462; ^1H NMR (methanol- d_4) δ : 7.48 (s, 2H), 6.81 (s, 1H), 2.72 (q, 2H), 2.60 (s, 3H), 2.30 (s, 3H), 1.28 (t, 3H).

Example 134

Preparation of N-[3-(2,6-Dichloro-4-ethynyl-phenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-yl]-N'-(tetrahydro-pyran-4-yl)-ethane-1,2-diamine

Formula I where X is CH, R^1 is CH_3 , R^2 is H, A is CH_2 , B is CH_2 , R^3 is CH_3 , R^4 is 2,6-dichloro-4-ethynylphenyl, R^5 is tetrahydropyranyl

[0197]



[0198] A. {2-[3-(2,6-Dichloro-4-hydroxy-phenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-ylamino]-ethyl}-(tetrahydro-pyran-4-yl)-carbamic acid tert-butyl ester

[0199] A stirred suspension of the crude 3,5-Dichloro-4-{2,5-dimethyl-7-[2-(tetrahydro-pyran-4-ylamino)-ethylamino]-pyrazolo[1,5-a]pyrimidin-3-yl}-phenol hydrobromide salt (8.7 mmol) from Example 382, step A in methylene chloride (100 mL) was adjusted to pH 9.5 with triethyl amine, di-tert-butyl-dicarbonate (3.0 g, 14 mmol) was added and the mixture was stirred for 2 days. The reaction then extracted from saturated aqueous sodium bicarbonate with methylene chloride, the combined organic layers were dried (Na_2SO_4) and then concentrated under reduced pressure to give the carbamate in which the phenol had been partially acylated. To a stirred solution of the residue in methanol (50 mL) was added 0.5 M sodium methoxide in methanol (30 mL, 15 mmol). After 1 hour the reaction was concentrated and then extracted from pH 7 buffer with methylene chloride. The combined extracts were dried (Na_2SO_4), concentrated under reduced pressure and then chromatographed (10:1 ethyl acetate/methanol) to give the product (2.8 g, 58%) as a beige foam: +APCI MS ($M+1$)⁺ 550; ^1H NMR ($CDCl_3$) δ : 6.70 (s, 2H), 5.84 (s, 1H), 2.51 (s, 3H), 2.24 (s, 3H), 1.54 (s, 9H).

[0200] B. Methanesulfonic acid 4-(7-{2-[tert-butoxycarbonyl-(tetrahydro-pyran-4-yl)-amino]-ethylamino}-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-3-yl)-3,5-dichloro-phenyl ester

[0201] To a 0° C. stirred solution of {2-[3-(2,6-Dichloro-4-hydroxy-phenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-ylamino]-ethyl}-(tetrahydro-pyran-4-yl)-carbamic acid tert-butyl ester (2.0 g, 3.6 mmol) and 2,6-lutidine (1.2 mL, 11 mmol) in methylene chloride was added trifluoromethanesulfonic anhydride, dropwise. After 15 minutes the reaction was extracted from saturated aqueous sodium bicarbonate with methylene chloride, the combined organic layers were dried (Na_2SO_4), concentrated under reduced pressure, concentrated again from toluene to remove the lutidine, and then chromatographed (2:1 to 3:1 ethyl acetate/hexanes) to give the product (1.7 g, 69%) as an off-white foam: +APCI MS ($M+1$)⁺ 682; ^1H NMR ($CDCl_3$) δ : 7.37 (s, 2H), 5.84 (s, 1H), 2.45 (s, 3H), 2.25 (s, 3H), 1.53 (s, 9H).

[0202] C. {2-[3-(2,6-Dichloro-4-trimethylsilanylethynyl-phenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-ylamino]-ethyl}-(tetrahydro-pyran-4-yl)-carbamic acid tert-butyl ester

[0203] A suspension of methanesulfonic acid 4-(7-{2-[tert-butoxycarbonyl-(tetrahydro-pyran-4-yl)-amino]-ethylamino}-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-3-yl)-3,5-dichlorophenyl ester (1.5 g, 2.2 mmol) in acetonitrile (5 mL)/triethylamine (1.9 mL) was degassed (3x) by alternately pulling a vacuum followed by repressurization with nitrogen. Trimethylsilylacetylene (0.50 mL, 3.6 mmol), dichlorobis(triphenylphosphine)palladium (65 mg, 0.093 mmol), and copper(I) iodide (42 mg, 0.22 mmol) were added, and the mixture was degassed (3X) again. The

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mixture was stirred for 4 hours at 65° C., the black mixture was extracted from saturated aqueous sodium bicarbonate with methylene chloride, dried (Na₂SO₄), filtered through Celite, concentrated under reduced pressure, and then chromatographed (7:3 hexanes/ethyl acetate) to give the product as a light brown foam (1.2 g, 89%): +APCI MS (M+1)⁺ 630; ¹H NMR (CDCl₃) δ: 7.51 (s, 2H), 5.82 (s, 1H), 2.44 (s, 3H), 2.23 (s, 3H), 1.53 (s, 9H), 0.24 (s, 9H).

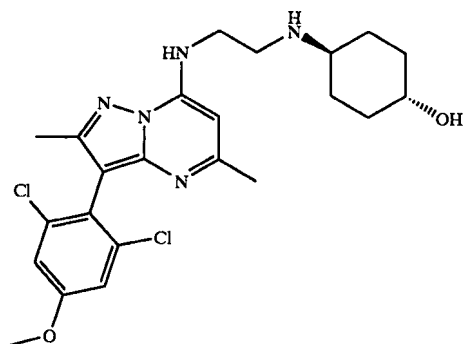
[0204] D. N-[3-(2,6-Dichloro-4-ethynyl-phenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-yl]-N'-(tetrahydro-pyran-4-yl)-ethane-1,2-diamine

[0205] To a stirred solution of {2-[3-(2,6-dichloro-4-trimethylsilyl-ethynyl-phenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-ylamino]-ethyl}-(tetrahydro-pyran-4-yl)-carbamic acid tert-butyl ester (1.2 g, 2.0 mmol) in ethanol (2 mL) was added KOH (0.2 g, 8 mmol). After 1 hour, the reaction was cooled to 0° C. and 1:1 ethanol/concentrated aqueous hydrochloric acid (4 mL) was added and the mixture was allowed to warm to room temperature. After 1 day, the reaction was concentrated under reduced pressure, extracted from saturated aqueous sodium bicarbonate with methylene chloride, the combined extracts were dried (Na₂SO₄), concentrated under reduced pressure, and then chromatographed (4:1 to 10:3 to 3:2 ethyl acetate/methanol) to afford the title compound (0.70 g, 78%) as an off-white solid: +APCI MS (M+1)⁺ 458; ¹H NMR (methanol-d₄) δ: 7.58 (d, 1H), 6.10 (s, 1H), 3.76 (s, 1H), 2.39 (s, 3H), 2.23 (s, 3H).

Example 277

4-{2-[3-(2,6-Dichloro-4-methoxy-phenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-ylamino]-ethyl}-amino}-cyclohexanol

[0206]



[0207] A. Preparation of [2-(4-hydroxy-cyclohexylamino)-ethyl]-carbamic acid tert-butyl ester: A mixture of N-tert-butoxycarbonylglycinal (5 g, 31.4 mmol), trans 4-amino-cyclohexanol (3.6 g, 31.4 mmol), sodium cyanoborohydride (1.98 g, 314 mmol) in 1:20 HOAc/MeOH

(105 mL) was stirred at room temperature for 72 h. The reaction mixture was diluted with EtOAc and was washed with sat'd aq NaHCO₃, sat aq NaCl, dried, and concentrated in vacuo to give 3.7 g of an oily residue. MS 259 (MH⁺).

[0208] B. Preparation of 4-(2-amino-ethylamino)-cyclohexanol: The product obtained in step A was treated with 1:1 conc HCl/MeOH (40 mL) and was stirred for 1 hr. The reaction mixture was concentrated in vacuo to give 3.3 g of the desired product. MS 159 (MH⁺).

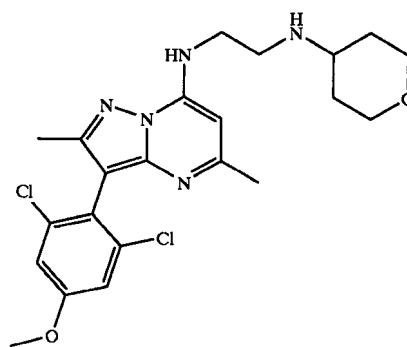
[0209] C. A solution of 7-chloro-3-(2,6-dichloro-4-methoxy-phenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidine (5.1 g, 14.3 mmol), triethylamine (15 mL) and the product from step B (3.3 g, 14.3 mmol) was heated under reflux for 17 h. The reaction mixture was cooled to room temperature and the solvent was removed under vacuum. The residue was dissolved in EtOAc, washed with sat'd aq NaHCO₃, sat'd aq NaCl, dried and concentrated. The crude residue was purified on SiO₂-gel using a gradient of 100% EtOAc to 10% Et₂NH/EtOAc to give 400 mg of the desired product. A portion of the product (20 mg) was treated with 4 M HCl (1 mL) in dioxane (5 mL) and the reaction mixture was concentrated in vacuo to give the HCl salt. ¹H NMR (Unity-400, CD₃OD): δ 7.2 (s), 6.8 (s), 4.08 (m), 3.65 (s), 3.4 (m), 2.6 (s), 2.3 (s), 2.2 (d), 2.05 (d), 1.6-1.3 (m). MS 478 (MH⁺), 480 (MH⁺).

Example 279

Preparation of N-[3-(2,6-dichloro-4-methoxy-phenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-yl]-N'-(tetrahydro-pyran-4-yl)-ethane-1,2-diamine hydrochloride salt

Formula I where X is CH, R¹ is CH₃, R² is H, A is CH₂, B is CH₂, R³ is CH₃, R⁴ is 2,6-dichloro-4-methoxyphenyl, R⁵ is tetrahydropyranyl

[0210]



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[0211] A. (2,6-Dichloro-4-methoxy-phenyl)-acetonitrile and (2,4-Dichloro-6-methoxy-phenyl)-acetonitrile

[0212] A solution of 1,3-dichloro-2-chloromethyl-5-methoxy-benzene (5.0 g, 22 mmol), contaminated with the corresponding 4-chloromethyl and di-(chloromethyl) isomers (*J. Med. Chem.*, 31, 72 (1988)) in refluxing dichloromethane (30 mL) was treated with tetraethylammonium cyanide in four portions over 25 minutes. Ten minutes after the final addition the reaction was cooled and then extracted from saturated aqueous sodium bicarbonate with ethyl acetate. The combined organic layers were dried (Na_2SO_4), concentrated under reduced pressure, and then chromatographed (6:1 hexanes/ethyl acetate) to give the title compounds (2:1 ratio, 3.4 g, 71%) as a colorless solid. (2,6-Dichloro-4-methoxy-phenyl)-acetonitrile: ^1H NMR (CDCl_3) δ : 6.91 (s, 2H), 3.91 (s, 2H), 3.79 (s, 3H). (2,4-Dichloro-6-methoxy-phenyl)-acetonitrile: ^1H NMR (CDCl_3) δ : 7.06 (d, 1H), 6.82 (d, 1H), 3.89 (s, 2H), 3.79 (s, 3H).

[0213] B. 4-(2,6-Dichloro-4-methoxy-phenyl)-5-methyl-2H-pyrazol-3-ylamine

[0214] To a stirred solution of the (2,6-dichloro-4-methoxy-phenyl)-acetonitrile and (2,4-dichloro-6-methoxy-phenyl)-acetonitrile (20 g, 96 mmol) in ethyl acetate (95 mL) was added sodium ethoxide in ethanol (21 wt. %, 95 mL, 0.25 mol). The reaction was heated at reflux for 4 hours, and then cooled, diluted with water and washed with diethyl ether. The aqueous layer was acidified to pH 4 with 1 M HCl and then extracted with methylene chloride. The combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure to give a brown oil (20 g, 83%). To a solution of the brown oil in benzene (150 mL) was added acetic acid (16 mL), which caused the formation of a colorless precipitate. Hydrazine hydrate was added (7.6 mL, 0.16 mol) and the reaction was heated to reflux, at which point the reaction became homogeneous. After 16 hours, an additional portion of hydrazine hydrate was added (5 mL, 0.10 mmol) and the mixture was heated for 24 more hours. The reaction was cooled and then extracted with 1 M HCl. The combined aqueous layers were adjusted to pH 8 with aqueous ammonium hydroxide (cooled in an ice bath) and then extracted with methylene chloride. The combined organic layers were dried (Na_2SO_4), concentrated under reduced pressure, and then chromatographed (10:1:0.1 ethyl acetate/diethylamine/methanol) to give the title compound (6 g, 29% from A) as a colorless solid: ^1H NMR (CDCl_3) δ : 6.98 (s, 2H), 3.81 (s, 3H), 2.16 (s, 3H).

[0215] C. 3-(2,6-Dichloro-4-methoxy-phenyl)-2-methyl-4H-pyrazolo[1,5-a]pyrimidin-7-one

[0216] To a solution of 4-(2,6-dichloro-4-methoxy-phenyl)-5-methyl-2H-pyrazol-3-ylamine (10.1 g, 39 mmol) in acetic acid (17 mL) was added methyl acetoacetate. After the mixture was heated at reflux for 3 hours it was cooled and then diluted with diethyl ether (50 mL) to generate a colorless precipitate. The solid was collected by vacuum filtration and washed with additional ether to afford the title compound as a colorless solid (10.3 g, 77%): +APCI MS

($\text{M}+1$)⁺ 338; ^1H NMR (methanol- d_4) δ : 7.14 (s, 2H), 5.68 (s, 1H), 3.86 (s, 3H), 2.30 (s, 3H), 2.16 (s, 3H).

[0217] D. 7-Chloro-3-(2,6-dichloro-4-methoxy-phenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidine

[0218] A suspension of 3-(2,6-dichloro-4-methoxy-phenyl)-2-methyl-4H-pyrazolo[1,5-a]pyrimidin-7-one (10.3 g, 31 mmol) in phosphorus oxychloride (60 mL) was stirred at reflux. After 2 hours the homogeneous red solution was concentrated under reduced pressure and then extracted from saturated sodium bicarbonate with chloroform. The combined organic layers were dried (Na_2SO_4) and then concentrated under reduced pressure to give the title compound (10.2 g, 94%) as a red solid: +APCI MS ($\text{M}+1$)⁺ 356; ^1H NMR (CDCl_3) δ : 7.05 (s, 2H), 6.84 (s, 1H), 3.886 (s, 3H), 2.59 (s, 3H), 2.42 (s, 3H).

[0219] E N-[3-(2,6-Dichloro-4-methoxy-phenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-yl]-ethane-1,2-diamine

[0220] To a stirred solution of ethylene diamine (19 mL, 0.28 mol) in ethanol (40 mL) was added a solution of 7-chloro-3-(2,6-dichloro-4-methoxy-phenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidine (9.9 g, 28 mmol) in methylene chloride (30 mL), dropwise over 1 hour. After refluxing 2 hours the reaction was concentrated under reduced pressure, extracted from saturated aqueous sodium bicarbonate with chloroform, the combined extracts were dried (Na_2SO_4) and then concentrated under reduced pressure to give the title compound as a yellow solid (10.42 g, 98%): +APCI MS ($\text{M}+1$)⁺ 380; ^1H NMR (CDCl_3) δ : 6.97 (s, 2H), 5.81 (s, 1H), 3.80 (s, 3H), 3.45 (m, 2H), 3.07 (t, 2H), 2.44 (s, 3H), 2.26 (s, 3H).

[0221] F N-[3-(2,6-Dichloro-4-methoxy-phenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-yl]-N'-(tetrahydro-pyran-4-yl)-ethane-1,2-diamine hydrochloride salt

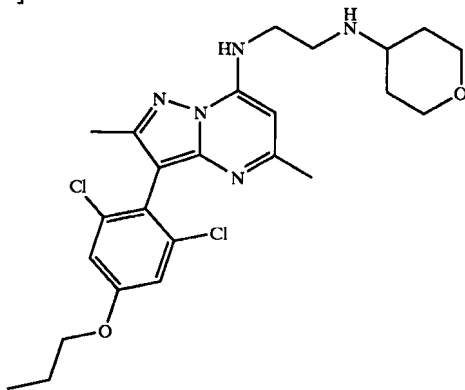
[0222] To a stirred solution of N-[3-(2,6-dichloro-4-methoxy-phenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-yl]-ethane-1,2-diamine (3.32 g, 8.7 mmol) and tetrahydro-4H-pyran-4-one (1.8 g, 18 mmol) in methanol (60 mL)/acetic acid (1.6 g) was added sodium cyanoborohydride (1.1 g, 17 mmol), portionwise. After stirring 1 hour the reaction was concentrated under reduced pressure and then extracted from saturated aqueous sodium bicarbonate with ethyl acetate. The combined extracts were dried (Na_2SO_4), concentrated under reduced pressure to give the crude product as a colorless foam (4.1 g, quant). A solution of the product in ether (150 mL) was treated with 1 M ethereal HCl which generated a precipitate that was collected by vacuum filtration to give the title compound (4.1 g, 94%) as a pink solid: +APCI MS ($\text{M}+1$)⁺ 464; ^1H NMR (methanol- d_4) δ : 7.14 (s, 2H), 6.38 (s, 1H), 4.03 (dd, 2H), 3.94 (br t, 2H), 3.86 (s, 3H), 3.50-3.38 (m, 5H), 2.51 (s, 3H), 2.26 (s, 3H), 2.05 (m, 2H), 1.68 (qd, 2H).

Example 382

Preparation of N-[3-(2,6-dichloro-4-propoxy-phenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-yl]-N'-(tetrahydro-pyran-4-yl)-ethane-1,2-diamine hydrochloride salt

Formula I where X is CH, R¹ is CH₃, R² is H, A is CH₂, B is CH₂, R³ is CH₃, R⁴ is 2,6-dichloro-4-propoxyphenyl, R⁵ is tetrahydropyranyl

[0223]



[0224] A. 3,5-Dichloro-4-{2,5-dimethyl-7-[2-(tetrahydro-pyran-4-ylamino)-ethylamino]-pyrazolo[1,5-a]pyrimidin-3-yl}-phenol hydrobromide salt

[0225] A suspension of N-[3-(2,6-dichloro-4-methoxy-phenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-yl]-N'-(tetrahydro-pyran-4-yl)-ethane-1,2-diamine (4.1 g, 8.2 mmol), from Example 279, step F, in concentrated aqueous HBr (30 mL) was stirred at reflux. After 5 hours the reaction was concentrated under reduced pressure at 70° C. to give the hydrogen bromide salt as a brown oil (7.35 g). A small portion was triturated from ether to give the product as a brown solid: +APCl MS (M+1)⁺ 450; ¹H NMR (methanol-d₄) δ: 7.00 (s, 2H), 6.85 (s, 1H), 4.11 (t, 2H), 4.02 (dd, 2H), 3.60-3.40 (m, 5H), 2.61 (s, 3H), 2.29 (s, 3H), 2.095 (m, 2H), 1.74 (qd, 2H).

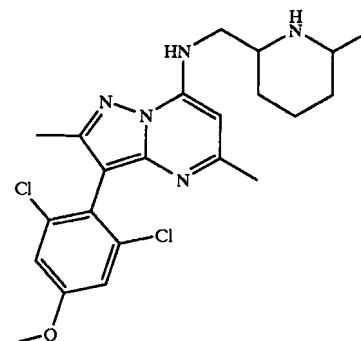
[0226] B. N-[3-(2,6-Dichloro-4-propoxy-phenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-yl]-N'-(tetrahydro-pyran-4-yl)-ethane-1,2-diamine hydrochloride salt

[0227] A solution of crude 3,5-Dichloro-4-{2,5-dimethyl-7-[2-(tetrahydro-pyran-4-ylamino)-ethylamino]-pyrazolo[1,5-a]pyrimidin-3-yl}-phenol hydrobromide salt (8.7 mmol) from step A in isopropyl alcohol (50 mL) was adjusted to pH 12 with 6 M aqueous NaOH. Propyl iodide (1.3 mL, 14 mmol) was added and the reaction was heated at reflux for 4 hours. The reaction was cooled and then extracted from saturated aqueous sodium bicarbonate with methylene chloride, dried (Na₂SO₄), concentrated under reduced pressure, and then chromatographed (10:1:0.1 methylene chloride/methanol/ammonium hydroxide) to give the product (2.0 g, 47%). A solution of the product in ethanol was treated with 1 M ethereal HCl (1 eq., 4.1 mmol), the mixture was concentrated to give a solid which was repurled from 1:1 ethanol/ether. The solids were collected to give the title compound (700 mg) as a colorless solid. The mother liquor was concentrated and then repurled from ether to give the remainder of the product as an off-white solid (1.3 g): +APCl MS (M+1)⁺ 492; ¹H NMR (methanol-d₄) δ: 7.21 (s, 2H), 6.67 (s, 1H), 2.61 (s, 3H), 2.33 (s, 3H), 1.10 (t, 3H).

Example 522

[3-(2,6-Dichloro-4-methoxy-phenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-yl]-(6-methyl-piperidin-2-ylmethyl)-amine

[0228]



[0229] A. Preparation of methanesulfonic acid 6-methyl-pyridin-2-yl ester: Methanesulfonyl chloride (0.94 mL, 12.18 mmol) was added to a solution of 6-methyl-2-pyridinemethanol (1g, 8.12 mmol) and triethylamine (1.7 mL, 12.18 mmol) in THF (20 mL) at 0° C. The reaction mixture was stirred for 40 min, then was quenched with sat'd aq NaHCO₃ and extracted with EtOAc. The combined organic extracts were washed with sat'd aq NaCl, dried and concentrated in vacuo. The crude residue was chromatographed on SiO₂-gel using 50% EtOAc/hexane to give the product as an oil. ¹H NMR (Unity-400, CDCl₃): δ 7.6 (t), 7.26 (d), 7.15 (d), 5.28 (s), 3.1 (s), 2.5 (s).

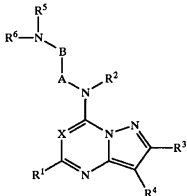
[0230] B. Preparation of 2-azidomethyl-6-methyl-pyridine: A mixture of the mesylate (1.0 g, 9.45 mmol) and sodium azide (610 mg, 9.45 mmol) in DM80 (40 mL) was stirred for 1 hr at room temperature. The reaction mixture was poured into EtOAc and was washed with sat'd aq NaCl, dried and concentrated in vacuo. The crude residue was purified using silica gel chromatography (25% EtOAc/hexanes) to give 936 mg of desired product. ¹H NMR (Unity-400, CDCl₃): δ 7.6 (t), 7.1 (d), 7.08 (d), 4.43 (s), 2.54 (s).

[0231] C. Preparation of (6-methyl-piperidin-2-yl)-methylamine: A mixture of the product obtained in Step B (860 mg) and PtO₂ (86 mg) in acetic acid (20 mL) was hydrogenated in a Paar Shaker at 40 psi for 17 h. The reaction mixture was filtered and the filtrate was concentrated under vacuum to give 2 g of the desired product. ¹H NMR (Unity-400, CD₃OD): δ 3.1, 1.93 (s), 1.88 (m), 1.55 (m), 1.28 (dd, 3 H).

[0232] D. Preparation of [3-(2,6-dichloro-4-methoxy-phenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-yl]-(6-methyl-piperidin-2-ylmethyl)-amine: A solution of 7-chloro-3-(2,6-dichloro-4-methoxy-phenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidine (50 mg, 0.11 mmol), triethylamine (1 mL) and the product from step C (42 mg, 0.22 mmol) in EtOH (3 mL) was heated under reflux for 17 h. The reaction was concentrated under vacuum. The residue was diluted with sat'd aq NaHCO₃ and the aqueous solution was extracted with EtOAc (3×), dried and concentrated in vacuo. The crude residue was purified on a prep TLC plate using 1.5% Et₂NH/EtOAc to give 36 mg of the desired product. ¹H NMR (Unity-400, CDCl₃): δ 7.0 (s, 2H), 5.94 (s, 1H), 3.8 (s, 3H), 3.53 (m), 3.05 (m), 2.8 (m), 2.44 (s, 3H), 2.27 (s, 3H), 1.9 (m), 1.7 (m). MS 448 (M).

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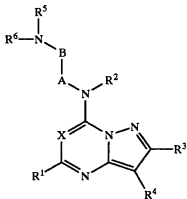
Table of Additional Examples



Ex	X	R ¹	R ²	R ³	R ⁴	A-B-N[R ⁵]-R ⁶	MW
9.	N	Me	H	Me	2-Br-4,5-diOMe-Ph	(CH ₂) ₂ -NH-(CH ₂) ₂ -(3-OMe-4-EO-Ph)	599.53
10.	CH	Me	H	Me	2-Br-6-Cl-Ph	(CH ₂) ₂ -NH-(tetrahydropyran-4-yl)	478.8
11.	CH	Me	H	Me	2-Cl-Ph	(CH ₂) ₂ -NH-(CH ₂) ₂ -(4-OMe-Ph)	486.44
12.	CH	Me	H	Me	2-OMe-4-OB-6-F-Ph	(CH ₂) ₂ -NH-(tetrahydropyran-4-yl)	457.54
13.	CH	Me	H	Me	2,4-diCl-6-(OSO ₂ CF ₃)-Ph	(CH ₂) ₂ -NH-(tetrahydropyran-4-yl)	528.43
14.	CH	Me	H	Me	2,4-diCl-6-OEt-Ph	(CH ₂) ₂ -NH-(1-(pyrimidin-2-yl)-piperidin-4-yl)	555.5
15.	CH	Me	H	Me	2,4-diCl-6-OEt-Ph	(CH ₂) ₂ -NH-(4-ethyleneketal-cHex)	534.48
16.	CH	Me	H	Me	2,4-diCl-6-OEt-Ph	(CH ₂) ₂ -NH-(tetrahydropyran-4-yl)	478.4
17.	CH	Me	H	Me	2,4-diCl-6-OEt-Ph	(CH ₂) ₂ -NH-(tetrahydropyran-4-yl)	478.41
18.	CH	Me	H	Me	2,4-diCl-6-OH-Ph	(CH ₂) ₂ -NH-(tetrahydropyran-4-yl)	450.4
19.	CH	Me	H	Me	2,4-diCl-6-OMe-Ph	(CH ₂) ₂ -NH-(1-Bn-piperidin-4-yl)	553.5
20.	CH	Me	H	Me	2,4-diCl-6-OMe-Ph	(CH ₂) ₂ -NH-(4-ethoxyimino-cHex)	519.5
21.	CH	Me	H	Me	2,4-diCl-6-OMe-Ph	(CH ₂) ₂ -NH-(4-ethyleneketal-cHex)	520.5
22.	CH	Me	H	Me	2,4-diCl-6-OMe-Ph	(CH ₂) ₂ -NH-(4-isobutoxyimino-cHex)	547.5
23.	CH	Me	H	Me	2,4-diCl-6-OMe-Ph	(CH ₂) ₂ -NH-(4-methoxyimino-cHex)	505.5
24.	CH	Me	H	Me	2,4-diCl-6-OMe-Ph	(CH ₂) ₂ -NH-(4-OH-cHex)	478.43
25.	CH	Me	H	Me	2,4-diCl-6-OMe-Ph	(CH ₂) ₂ -NH-(7-methoxyimino-azepan-3-yl)	520.5
26.	CH	Me	H	Me	2,4-diCl-6-OMe-Ph	(CH ₂) ₂ -NH-(CH ₂) ₂ -OH	424.33
27.	CH	Me	H	Me	2,4-diCl-6-OMe-Ph	(CH ₂) ₂ -NH-(tetrahydropyran-4-yl)	464.4
28.	CH	Me	H	Me	2,4-diCl-6-OMe-Ph	(CH ₂) ₂ -NH-cyclohexan-4-one	491.42
29.	CH	iPr	H	Me	2,4-diCl-Ph	(CH ₂) ₂ -NH-(1-(pyrimidin-2-yl)-piperidin-4-yl)	539.52
30.	N	Me	H	Me	2,4-diCl-Ph	(CH ₂) ₂ -NH-(1-(pyrimidin-2-yl)-piperidin-4-yl)	512.44
31.	CH	Me	H	Me	2,4-diCl-Ph	(CH ₂) ₂ -NH-(1-Bn-piperidin-4-yl)	523.51
32.	N	Me	H	Me	2,4-diCl-Ph	(CH ₂) ₂ -NH-(1-Bn-piperidin-4-yl)	524.5
33.	CH	Me	H	CF ₃	2,4-diCl-Ph	(CH ₂) ₂ -NH-(1-Bn-piperidin-4-yl)	577.48
34.	CH	Me	H	Me	2,4-diCl-Ph	(CH ₂) ₂ -NH-(2-Cl-cHex)	466.84
35.	CH	Me	H	Me	2,4-diCl-Ph	(CH ₂) ₂ -NH-(2-Cl-cPent)	452.82
36.	CH	Me	H	Me	2,4-diCl-Ph	(CH ₂) ₂ -NH-(2-Me-cHex)	446.42
37.	CH	Me	H	Me	2,4-diCl-Ph	(CH ₂) ₂ -NH-(2-OH-cHex)	448.39
38.	CH	Me	H	Me	2,4-diCl-Ph	(CH ₂) ₂ -NH-(2-OMe-cHex)	462.42
39.	N	Me	H	Me	2,4-diCl-Ph	(CH ₂) ₂ -NH-(2F-cPent)	436.3

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Table of Additional Examples



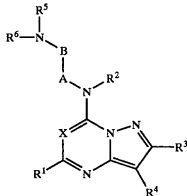
Ex	X	R ¹	R ²	R ³	R ⁴	A-B-N[R ⁵]-R ⁶	MW
40.	CH	Me	H	Me	2,4-diCl—Ph	(CH ₂) ₂ —NH-(3-Me-cyclohex-2-enyl)	444.41
41.	CH	iPr	H	Me	2,4-diCl—Ph	(CH ₂) ₂ —NH-(4-CF ₃ -cHex)	528.45
42.	N	Me	H	Me	2,4-diCl—Ph	(CH ₂) ₂ —NH-(4-methoximino-cHex)	476.4
43.	CH	Me	H	Me	2,4-diCl—Ph	(CH ₂) ₂ —NH-(4,4-diMe-cyclohex-2-enyl)	458.43
44.	CH	Me	H	Me	2,4-diCl—Ph	(CH ₂) ₂ —NH—(CH ₂) ₂ -(2-OMe—Ph)	484.42
45.	N	Me	H	Me	2,4-diCl—Ph	(CH ₂) ₂ —NH—(CH ₂) ₂ -(3-OMe-4-OBn—Ph)	529.47
46.	CH	Me	H	Me	2,4-diCl—Ph	(CH ₂) ₂ —NH—(CH ₂) ₂ -(3-OMe-4-OBn—Ph)	528.47
47.	CH	Me	H	Me	2,4-diCl—Ph	(CH ₂) ₂ —NH—(CH ₂) ₂ -(4-OMe—Ph)	484.42
48.	CH	iPr	H	Me	2,4-diCl—Ph	(CH ₂) ₂ —NH-(cis-4-CF ₃ -cHex)	528.45
49.	CH	iPr	H	Me	2,4-diCl—Ph	(CH ₂) ₂ —NH-(tetrahydropyran-4-yl)	462.43
50.	CH	Me	H	Me	2,4-diCl—Ph	(CH ₂) ₂ —NH-(tetrahydropyran-4-yl)	450.44
51.	CH	Me	H	Me	2,4-diCl—Ph	(CH ₂) ₂ —NH-(tetrahydropyran-4-yl)	434.37
52.	N	Me	H	Me	2,4-diCl—Ph	(CH ₂) ₂ —NH-2-norbornyl	445.4
53.	N	Me	H	Me	2,4-diCl—Ph	(CH ₂) ₂ —NH—CHMe—(CH ₂) ₂ —NEt ₂	478.5
54.	N	Me	H	Me	2,4-diCl—Ph	(CH ₂) ₂ —NH—CHMe—CH ₂ —NEt ₂	464.4
55.	CH	Me	H	Me	2,4-diCl—Ph	(CH ₂) ₂ —NH-cyclohex-2-enyl	430.38
56.	CH	Me	H	Me	2,4-diCl—Ph	(CH ₂) ₂ —NH-piperidin-4-yl	433.38
57.	CH	Me	H	Me	2,4-diCl—Ph	CHMe—CH ₂ —OH	422.36
58.	CH	Me	H	Me	2,4-diF—Ph	(CH ₂) ₂ —NH—(CH ₂) ₂ -(3-OMe-4-OBn—Ph)	495.57
59.	CH	Et	H	Me	2,4-diMe—Ph	(CH ₂) ₂ —NH-(1-pyrimidin-2-yl)-piperidin-4-yl	484.7
60.	CH	nPr	H	Me	2,4-diMe—Ph	(CH ₂) ₂ —NH-(1-pyrimidin-2-yl)-piperidin-4-yl	498.7
61.	CH	Et	H	Me	2,4-diMe—Ph	CH ₂ —CHMe—NH-(1-pyrimidin-2-yl)-piperidin-4-yl	498.7
62.	CH	nPr	H	Me	2,4-diMe—Ph	CH ₂ —CHMe—NH-(1-pyrimidin-2-yl)-piperidin-4-yl	512.7
63.	CH	Me	H	Me	2,4-diOMe-6-Cl—Ph	(CH ₂) ₂ —NH-(1-(5-Et-pyrimidin-2-yl)-piperidin-4-yl)	565.11
64.	CH	Me	H	Me	2,4-diOMe-6-Cl—Ph	(CH ₂) ₂ —NH-(1-pyrimidin-2-yl)-piperidin-4-yl	537.1
65.	CH	Me	H	Me	2,4-diOMe-6-Cl—Ph	(CH ₂) ₂ —NH-(1-Ac-piperidin-4-yl)	501.02
66.	CH	Me	H	Me	2,4-diOMe-6-Cl—Ph	(CH ₂) ₂ —NH-(1-SO ₂ Me-piperidin-4-yl)	531.0
67.	CH	Me	H	Me	2,4-diOMe-6-Cl—Ph	(CH ₂) ₂ —NH-(1-(NH-iBu)-cHex)	537.08
68.	CH	Me	H	Me	2,4-diOMe-6-Cl—Ph	(CH ₂) ₂ —NH-(1-(NH-iBu)-cHex)	529.12
69.	CH	Me	H	Me	2,4-diOMe-6-F—Ph	(CH ₂) ₂ —NH-(1-Ac-piperidin-4-yl)	484.57
70.	CH	Me	H	Me	2,4-diOMe-6-F—Ph	(CH ₂) ₂ —NH-(1-Bn-piperidin-4-yl)	532.65
71.	CH	Me	H	Me	2,4-diOMe-6-F—Ph	(CH ₂) ₂ —NH-(4-ethyleneketal-cHex)	499.58

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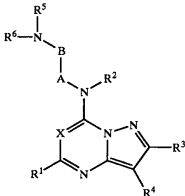


Ex	X	R ¹	R ²	R ³	R ⁴	A-B-N[R ⁵]-R ⁵	MW
72.	CH	Me	H	Me	2,4-diOMe-6-F-Ph	(CH2)2-NH-(4-oxo-cHex)	455.23
73.	CH	Me	H	Me	2,4-diOMe-6Cl-Ph	(CH2)2-NH-(1-Bn-piperidin-4-yl)	549.1
74.	CH	Me	H	Me	2,4-diOMe-6Cl-Ph	(CH2)2-NH-(1-tBoc-piperidin-4-yl)	559.1
75.	CH	Me	H	Me	2,4-diOMe-6Cl-Ph	(CH2)2-NH-(4-ethyleneketal-cHex)	516
76.	CH	Me	H	Me	2,4-diOMe-6Cl-Ph	(CH2)2-NH-(4-oxo-cHex)	471.99
77.	CH	Me	H	Me	2,4-diOMe-6Cl-Ph	(CH2)2-NH-(tetrahydropyran-4-yl)	459.98
78.	CH	Me	H	Me	2,4-diOMe-6Cl-Ph	(CH2)2-NH-piperidin-4-yl)	458.99
79.	CH	Me	H	Me	2,4,6-triCl-Ph	(CH2)2-NH-(4-(1-morpholino)-cHex)	533.51
80.	CH	Me	H	Me	2,4,6-triCl-Ph	(CH2)2-NH-(4-ethyleneketal-cHex)	524.9
81.	CH	Me	H	Me	2,4,6-triCl-Ph	(CH2)2-NH-(4-NHMe-cHex)	477.44
82.	CH	Me	H	Me	2,4,6-triCl-Ph	(CH2)2-NH-(tetrahydropyran-4-yl)	468.8
83.	CH	Me	H	Me	2,4,6-triCl-Ph	CH2-CHMe-NH-(4-NHMe-cHex)	491.47
84.	CH	Me	H	Me	2,4,6-triMe-Ph	(CH2)2-3-pyridyl	428.58
85.	CH	Et	H	Me	2,4,6-triMe-Ph	(CH2)2-NH-(1-(pyrimidin-2-yl)-piperidin-4-yl)	498.7
86.	CH	Et	H	Me	2,4,6-triMe-Ph	(CH2)2-NH-(1-(pyrimidin-2-yl)-piperidin-4-yl)	512.7
87.	CH	nPr	H	Me	2,4,6-triMe-Ph	(CH2)2-NH-(1-(pyrimidin-2-yl)-piperidin-4-yl)	512.7
88.	CH	Me	H	Me	2,4,6-triMe-Ph	(CH2)2-NH-(1-(pyrimidin-2-yl)-piperidin-4-yl)	484.7
89.	CH	Me	H	Me	2,4,6-triMe-Ph	(CH2)2-NH-(1-(pyrimidin-2-yl)-piperidin-4-yl)	484.64
90.	CH	Et	H	Me	2,4,6-triMe-Ph	(CH2)2-NH-(1-Ac-piperidin-4-yl)	462.6
91.	CH	Me	H	Me	2,4,6-triMe-Ph	(CH2)2-NH-(1-COOEt-piperidin-4-yl)	478.64
92.	CH	Et	H	Me	2,4,6-triMe-Ph	(CH2)2-NH-(1,2,3,4-tetrahydro-naphthalen-2-yl)	467.7
93.	CH	Me	H	Me	2,4,6-triMe-Ph	(CH2)2-NH-(CH2)2-(1-Me-pyrrolidin-2-yl)	434.63
94.	CH	Et	H	Me	2,4,6-triMe-Ph	(CH2)2-NH-(CH2)2-(3-OMe-4-EO-Ph)	515.70
95.	CH	CH3	H	Et	2,4,6-triMe-Ph	(CH2)2-NH-(CH2)2-(3-OMe-4-EO-Ph)	515.70
96.	CH	iPr	H	Me	2,4,6-triMe-Ph	(CH2)2-NH-(CH2)2-(3-OMe-4-EO-Ph)	529.73
97.	CH	nPr	H	Me	2,4,6-triMe-Ph	(CH2)2-NH-(CH2)2-(3-OMe-4-EO-Ph)	529.73
98.	CH	Ph	H	Me	2,4,6-triMe-Ph	(CH2)2-NH-(CH2)2-(3-OMe-4-EO-Ph)	563.74
99.	CH	Me	H	Me	2,4,6-triMe-Ph	(CH2)2-NH-(trans-4-COOEt-cHex)	477.64
100.	CH	Me	H	Me	2,4,6-triMe-Ph	(CH2)2-NH-(trans-4-COOH-cHex)	449.59
101.	CH	Et	H	Me	2,4,6-triMe-Ph	(CH2)2-NH-CHMe-Ph	441.6
102.	CH	Me	H	CH2-OMe	2,4,6-triMe-Ph	(CH2)2-NH-cPent	421.59
103.	CH	Me	H	Me	2,4,6-triMe-Ph	(CH2)2-NH-cyclohex-3-enyl	403.6

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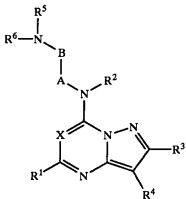
Table of Additional Examples



Ex	X	R ¹	R ²	R ³	R ⁴	A-B-N[R ⁵]-R ⁵	MW
104.	CH	Me	H	Me	2,4,6-triMe-Ph	(CH ₂) ₃ -NH-CH ₂ -(3,4-diOMe-Ph)	487.64
105.	CH	Me	H	Me	2,4,6-triMe-Ph	(CH ₂) ₃ -NH-CH ₂ -(4-OMe-Ph)	457.61
106.	CH	nPr	H	Me	2,4,6-triMe-Ph	CH ₂ -CHMe-NH-(1-(pyrimidin-2-yl)-piperidin-4-yl)	526.73
107.	CH	Et	H	Me	2,4,6-triMe-Ph	CH ₂ -CHMe-NH-(1-Ac-piperidin-4-yl)	476.7
108.	CH	Et	H	Me	2,4,6-triMe-Ph	CH ₂ -CHMe-NH-(1,2,3,4-tetrahydro-naphthalen-2-yl)	481.7
109.	CH	Et	H	Me	2,4,6-triMe-Ph	CH ₂ -CHMe-NH-CHMe-Ph	455.65
110.	CH	Me	H	Me	2,4,6-triMe-Ph	CHiBu-CH ₂ -NH-(tetrahydropyran-4-yl)	463.7
111.	CH	Me	H	Me	2,6-diCl-4-(2-oxo-oxazolidin-3-yl)-Ph	(CH ₂) ₂ -NH-(tetrahydropyran-4-yl)	519.4
112.	CH	Me	H	Me	2,6-diCl-4-(3,5-dimethyl-isoxazol-4-yl)-Ph	(CH ₂) ₂ -NH-(tetrahydropyran-4-yl)	529.47
113.	CH	Me	H	Me	2,6-diCl-4-(4,5-dihydro-oxazol-2-yl)-Ph	(CH ₂) ₂ -NH-(tetrahydropyran-4-yl)	503.4
114.	CH	Me	H	Me	2,6-diCl-4-(4H-[1,2,4]triazol-3-yl)-Ph	(CH ₂) ₂ -NH-(tetrahydropyran-4-yl)	502.41
115.	CH	Me	H	Me	2,6-diCl-4-(C=O)-1'-pyrrolidine)-Ph	(CH ₂) ₂ -NH-(tetrahydropyran-4-yl)	531.49
116.	CH	Me	H	Me	2,6-diCl-4-(C=O)-N-Et)-Ph	(CH ₂) ₂ -NH-(tetrahydropyran-4-yl)	505.45
117.	CH	Me	H	Me	2,6-diCl-4-(CH(OH)Me ₂)	(CH ₂) ₂ -NH-(tetrahydropyran-4-yl)	492.45
118.	CH	Me	H	Me	2,6-diCl-4-(CH ₂ OH)-Ph	(CH ₂) ₂ -NH-(tetrahydropyran-4-yl)	464.40
119.	CH	Me	H	Me	2,6-diCl-4-(CO ₂ Me)-Ph	(CH ₂) ₂ -NH-(tetrahydropyran-4-yl)	492.41
120.	CH	Me	H	Me	2,6-diCl-4-(COOEt)-Ph	(CH ₂) ₂ -NH-(tetrahydropyran-4-yl)	506.44
121.	CH	Me	H	Me	2,6-diCl-4-(COOH)-Ph	(CH ₂) ₂ -NH-(tetrahydropyran-4-yl)	478.38
122.	CH	Me	H	Me	2,6-diCl-4-(pEnt-1-ene)-Ph	(CH ₂) ₂ -NH-(tetrahydropyran-4-yl)	500.48
123.	CH	Me	H	Me	2,6-diCl-4-(isopropene)-Ph	(CH ₂) ₂ -NH-(tetrahydropyran-4-yl)	474.44
124.	CH	Me	H	Me	2,6-diCl-4-(O(CH ₂) ₂ -NMe ₂)-Ph	(CH ₂) ₂ -NH-(tetrahydropyran-4-yl)	521.5
125.	CH	Me	H	Me	2,6-diCl-4-CH ₂ OMe-Ph	(CH ₂) ₂ -NH-(tetrahydropyran-4-yl)	478.4
126.	CH	Me	H	Me	2,6-diCl-4-CHO-Ph	(CH ₂) ₂ -NH-(tetrahydropyran-4-yl)	477.40
127.	CH	Me	H	Me	2,6-diCl-4-CN-Ph	(CH ₂) ₂ -NH-(1-(pyrimidin-2-yl)-piperidin-4-yl)	536.5
128.	CH	Me	H	Me	2,6-diCl-4-CN-Ph	(CH ₂) ₂ -NH-(1-(SO ₂ -N-(Me) ₂)-piperidin-4-yl)	565.53
129.	CH	Me	H	Me	2,6-diCl-4-CN-Ph	(CH ₂) ₂ -NH-(1-Bn-piperidin-4-yl)	548.52
130.	CH	Me	H	Me	2,6-diCl-4-CN-Ph	(CH ₂) ₂ -NH-(1-propanoyl-piperidin-4-yl)	514.46
131.	CH	Me	H	Me	2,6-diCl-4-CN-Ph	(CH ₂) ₂ -NH-(1-SO ₂ Me-piperidin-4-yl)	536.5
132.	CH	Me	H	Me	2,6-diCl-4-CN-Ph	(CH ₂) ₂ -NH-(tetrahydropyran-4-yl)	459.38
133.	CH	Me	H	Me	2,6-diCl-4-Et-Ph	(CH ₂) ₂ -NH-(tetrahydropyran-4-yl)	462.42
134.	CH	Me	H	Me	2,6-diCl-4-ethynyl-Ph	(CH ₂) ₂ -NH-(tetrahydropyran-4-yl)	458.4
135.	CH	Me	H	Me	2,6-diCl-4-ethynyl-Ph	CH ₂ -CHMe-NH-(1-(pyrimidin-2-yl)-piperidin-4-yl)	535.5

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Table of Additional Examples

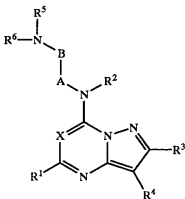


Ex	X	R ¹	R ²	R ³	R ⁴	A-B-N[R ⁵] ₂ R ⁵	MW
136.	CH	Me	H	Me	2,6-diCl-4-OEt-Ph	(CH ₂) ₂ -NH-(1-(pyrimidin-2-yl)-piperidin-4-yl)	555.22
137.	N	Me	H	Me	2,6-diCl-4-OEt-Ph	(CH ₂) ₂ -NH-(1-(pyrimidin-2-yl)-piperidin-4-yl)	556.5
138.	CH	Me	H	Me	2,6-diCl-4-OEt-Ph	(CH ₂) ₂ -NH-(1-Ac-piperidin-4-yl)	519.5
139.	N	Me	H	Me	2,6-diCl-4-OEt-Ph	(CH ₂) ₂ -NH-(1-Ac-piperidin-4-yl)	520.5
140.	CH	Me	H	Me	2,6-diCl-4-OEt-Ph	(CH ₂) ₂ -NH-(1-benzoyl-piperidin-4-yl)	567.6
141.	N	Me	H	Me	2,6-diCl-4-OEt-Ph	(CH ₂) ₂ -NH-(1-COOEt-piperidin-4-yl)	550.5
142.	CH	Me	H	Me	2,6-diCl-4-OEt-Ph	(CH ₂) ₂ -NH-(1-propanoyl-piperidin-4-yl)	533.5
143.	CH	Me	H	Me	2,6-diCl-4-OEt-Ph	(CH ₂) ₂ -NH-(1-SO ₂ Me-piperidin-4-yl)	555.5
144.	N	Me	H	Me	2,6-diCl-4-OEt-Ph	(CH ₂) ₂ -NH-(1-SO ₂ Me-piperidin-4-yl)	556.5
145.	CH	Me	H	Me	2,6-diCl-4-OEt-Ph	(CH ₂) ₂ -NH-(1-SO ₂ Me-piperidin-4-yl)	555.52
146.	CH	Me	H	Me	2,6-diCl-4-OEt-Ph	(CH ₂) ₂ -NH-(1-SO ₂ Me ₂ -piperidin-4-yl)	584.6
147.	N	Me	H	Me	2,6-diCl-4-OEt-Ph	(CH ₂) ₂ -NH-(1-tBoc-piperidin-4-yl)	578.53
148.	CH	Me	H	Me	2,6-diCl-4-OEt-Ph	(CH ₂) ₂ -NH-(2-Me-tetrahydro-furan-3-yl)	478.43
149.	CH	Me	H	Me	2,6-diCl-4-OEt-Ph	(CH ₂) ₂ -NH-(2-OEt-cHex)	520.51
150.	CH	Me	H	Me	2,6-diCl-4-OEt-Ph	(CH ₂) ₂ -NH-(2-OH-cHex)	492.45
151.	CH	Me	H	Me	2,6-diCl-4-OEt-Ph	(CH ₂) ₂ -NH-(2-oxo-pyrrolidin-4-yl)	447.4
152.	N	Me	H	Me	2,6-diCl-4-OEt-Ph	(CH ₂) ₂ -NH-(2F-cPent)	481.40
153.	CH	Me	H	Me	2,6-diCl-4-OEt-Ph	(CH ₂) ₂ -NH-(4-COOEt-cHex)	548.52
154.	CH	Me	H	Me	2,6-diCl-4-OEt-Ph	(CH ₂) ₂ -NH-(4-ethyleneketal-cHex)	534.5
155.	N	Me	H	Me	2,6-diCl-4-OEt-Ph	(CH ₂) ₂ -NH-(4-ethyleneketal-cHex)	535.47
156.	N	Me	H	Me	2,6-diCl-4-OEt-Ph	(CH ₂) ₂ -NH-(4-NHSO ₂ Me-cHex)	570.5
157.	CH	Me	H	Me	2,6-diCl-4-OEt-Ph	(CH ₂) ₂ -NH-(4-OH-cHex)	492.5
158.	N	Me	H	Me	2,6-diCl-4-OEt-Ph	(CH ₂) ₂ -NH-(4-oxo-cHex)	493.43
159.	CH	Me	H	Me	2,6-diCl-4-OEt-Ph	(CH ₂) ₂ -NH-(4-oxo-cHex)	490.5
160.	N	Me	H	Me	2,6-diCl-4-OEt-Ph	(CH ₂) ₂ -NH-(4-oxo-cHex)	491.41
161.	CH	Me	H	Me	2,6-diCl-4-OEt-Ph	(CH ₂) ₂ -NH-(4,4-Me ₂ -lacton-3-yl)	506.4
162.	CH	Me	H	Me	2,6-diCl-4-OEt-Ph	(CH ₂) ₂ -NH-(6-azabicyclo(4.4.0)dec-3-yl)	531.53
163.	CH	Me	H	Me	2,6-diCl-4-OEt-Ph	(CH ₂) ₂ -NH-(7-oxo-azepan-3-yl)	505.45
164.	N	Me	H	Me	2,6-diCl-4-OEt-Ph	(CH ₂) ₂ -NH-(CH ₂) ₂ -OH	439.3
165.	N	Me	H	Me	2,6-diCl-4-OEt-Ph	(CH ₂) ₂ -NH-(CH ₂) ₃ -OH	453.4
166.	N	Me	H	Me	2,6-diCl-4-OEt-Ph	(CH ₂) ₂ -NH-(CH ₂) ₃ -OMe	467.4
167.	N	Me	H	Me	2,6-diCl-4-OEt-Ph	(CH ₂) ₂ -NH-(CH ₂) ₃ -(R)-CHMe-OH	453.4

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-continued

Table of Additional Examples



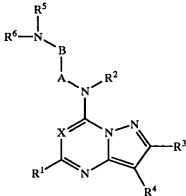
Ex	X	R ¹	R ²	R ³	R ⁴	A-B-N[R ⁵] ₂ R ⁶	MW
168.	N	Me	H	Me	2,6-diCl-4-OEt-Ph	(CH ₂) ₂ -NH-(S)-CHMe-CH ₂ -OH	453.4
169.	CH	Me	H	Me	2,6-diCl-4-OEt-Ph	(CH ₂) ₂ -NH-(tetrahydropyran-4-yl)	478.4
170.	CH	Et	H	Me	2,6-diCl-4-OEt-Ph	(CH ₂) ₂ -NH-(tetrahydropyran-4-yl)	492.5
171.	N	Me	H	Me	2,6-diCl-4-OEt-Ph	(CH ₂) ₂ -NH-(tetrahydropyran-4-yl)	479.4
172.	N	Me	H	Me	2,6-diCl-4-OEt-Ph	(CH ₂) ₂ -NH-(trans-4-COOEt-cHex)	549.49
173.	N	Me	H	Me	2,6-diCl-4-OEt-Ph	(CH ₂) ₂ -NH-(trans-4-OH-piperidin-4-yl)	493.4
174.	CH	Me	H	Me	2,6-diCl-4-OEt-Ph	(CH ₂) ₂ -NH-CH ₂ -(1-tBoc-piperidin-4-yl)	591.59
175.	CH	Me	H	Me	2,6-diCl-4-OEt-Ph	(CH ₂) ₂ -NH-CH ₂ -(piperidin-4-yl)	491.47
176.	CH	Me	H	Me	2,6-diCl-4-OEt-Ph	(CH ₂) ₂ -NH-CH ₂ -CF ₃	476.33
177.	CH	Me	H	Me	2,6-diCl-4-OEt-Ph	(CH ₂) ₂ -NH-CH ₂ -CHOH-CH ₂ OH	468.39
178.	CH	Me	H	Me	2,6-diCl-4-OEt-Ph	(CH ₂) ₂ -NH-CHMe-(1-tBoc-piperidin-4-yl)	547.5
179.	CH	Me	H	Me	2,6-diCl-4-OEt-Ph	(CH ₂) ₂ -NH-CHMe-(1-tBoc-piperidin-4-yl)	605.61
180.	CH	Me	H	Me	2,6-diCl-4-OEt-Ph	(CH ₂) ₂ -NH-CHMe-(piperidin-4-yl)	505.49
181.	CH	Me	H	Me	2,6-diCl-4-OEt-Ph	(CH ₂) ₂ -NH-cyclohex-3-enyl	475.4
182.	CH	Me	H	Me	2,6-diCl-4-OEt-Ph	(CH ₂) ₂ -NH-cyclohex-3-enyl	474.4
183.	CH	Me	H	Me	2,6-diCl-4-OEt-Ph	(CH ₂) ₂ -NH-cyclohexan-4-oxime	505.5
184.	N	Me	H	Me	2,6-diCl-4-OEt-Ph	(CH ₂) ₂ -NH-piperidin-4-yl	480.43
185.	CH	Me	H	Me	2,6-diCl-4-OEt-Ph	CH ₂ -CHMe-NH-(1-(pyrimidin-2-yl)-piperidin-4-yl)	569.54
186.	CH	Me	H	Me	2,6-diCl-4-OEt-Ph	CH ₂ -CHMe-NH-(4-ethyleneketal-cHex)	548.52
187.	CH	Me	H	Me	2,6-diCl-4-OEt-Ph	CH ₂ -CHMe-NH-(4-OH-cHex)	506.48
188.	CH	Me	H	Me	2,6-diCl-4-OEt-Ph	CH ₂ -CHMe-NH-(tetrahydropyran-4-yl)	492.45
189.	CH	Me	H	Me	2,6-diCl-4-OEt-Ph	CH ₂ -CMe ₂ -NH-(tetrahydropyran-4-yl)	506.48
190.	CH	Me	H	Me	2,6-diCl-4-OEt-Ph	CHMe-CH ₂ -NH-(tetrahydropyran-4-yl)	492.45
191.	CH	Me	H	Me	2,6-diCl-4-OH-Ph	(CH ₂) ₂ -NH-(1-tBoc-piperidin-4-yl)	539.51
192.	CH	Me	H	Me	2,6-diCl-4-OH-Ph	(CH ₂) ₂ -NH-(1-Ph-pyrrolidin-3-yl)	511.46
193.	CH	Me	H	Me	2,6-diCl-4-OH-Ph	(CH ₂) ₂ -NH-(4-ethyleneketal-cHex)	506.44
194.	CH	Me	H	Me	2,6-diCl-4-OH-Ph	(CH ₂) ₂ -NH-(4-oxo-cHex)	462.38
195.	CH	Me	H	Me	2,6-diCl-4-OH-Ph	(CH ₂) ₂ -NH-(6-azabicycl[4.4.0]dec-3-yl)	503.48
196.	CH	Me	H	Me	2,6-diCl-4-OH-Ph	(CH ₂) ₂ -NH-(tetrahydropyran-4-yl)	450.4
197.	CH	Et	H	Me	2,6-diCl-4-OH-Ph	(CH ₂) ₂ -NH-(tetrahydropyran-4-yl)	464.4
198.	CH	Me	H	Me	2,6-diCl-4-OH-Ph	(CH ₂) ₂ -NH-CHMe-CH ₂ -(3-OMe-4-OEt-Ph)	530.46
199.	CH	Me	H	Me	2,6-diCl-4-OH-Ph	(CH ₂) ₂ -NH-CHMe-CH ₂ -NMe ₂	451.4

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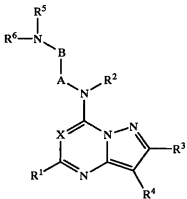
Table of Additional Examples



Ex	X	R ¹	R ²	R ³	R ⁴	A-B-N[R ⁵]-R ⁵	MW
200.	CH	Me	H	Me	2,6-diCl-4-OH—Ph	CH ₂ —CHMe—NH-(4-(1-morpholino)-cHex)	547.53
201.	CH	Me	H	Me	2,6-diCl-4-OH—Ph	CH ₂ —CHMe—NH-(tetrahydropyran-4-yl)	464.4
202.	CH	Me	H	Me	2,6-diCl-4-OH—Ph	CHMe—CHMe—NH-(tetrahydropyran-4-yl)	478.43
203.	CH	Me	H	Me	2,6-diCl-4-OPr—Ph	(CH ₂) ₂ —NH-(tetrahydropyran-4-yl)	492.45
204.	CH	Me	H	Me	2,6-diCl-4-OMe—Ph	2-(NH-(1-Bn-piperidin-4-yl))-cHex	607.63
205.	CH	Me	H	Me	2,6-diCl-4-OMe—Ph	2-(NH-(1-Bn-piperidin-4-yl))-cHex	607.63
206.	CH	Me	H	Me	2,6-diCl-4-OMe—Ph	2-(NH-(tetrahydropyran-4-yl))-cHex	518.49
207.	CH	Me	H	Me	2,6-diCl-4-OMe—Ph	2-(NH-(tetrahydropyran-4-yl))-cHex	518.49
208.	CH	Me	H	Me	2,6-diCl-4-OMe—Ph	3-(NH-(1-Bn-piperidin-4-yl))-cHex	607.63
209.	CH	Me	H	Me	2,6-diCl-4-OMe—Ph	3-(NH-(tetrahydropyran-4-yl))-cHex	518.49
210.	CH	Me	H	Me	2,6-diCl-4-OMe—Ph	4-(NH-(tetrahydropyran-4-yl))-cHex	518.49
211.	CH	Me	H	Me	2,6-diCl-4-OMe—Ph	(CH ₂) ₂ —CHMe—NH-(1-Bn-piperidin-4-yl)	595.62
212.	CH	Me	H	Me	2,6-diCl-4-OMe—Ph	(CH ₂) ₂ —CHMe—NH-(tetrahydropyran-4-yl)	506.48
213.	CH	iPr	H	Me	2,6-diCl-4-OMe—Ph	(CH ₂) ₂ —CHMe—NH-(tetrahydropyran-4-yl)	534.5
214.	CH	Me	H	Me	2,6-diCl-4-OMe—Ph	(CH ₂) ₂ —N((CH ₂) ₃ —CF ₃) ₂	600.44
215.	CH	Me	H	Me	2,6-diCl-4-OMe—Ph	(CH ₂) ₂ —N(CH ₂ -2-(CH ₂ OH)-furan-5-yl) ₂	600.51
216.	CH	Me	H	Me	2,6-diCl-4-OMe—Ph	(CH ₂) ₂ —N(CH ₂ -2-pyridyl)-(1-(CH ₂ -2-pyridyl)-piperidin-4-yl)	645.64
217.	CH	Me	H	Me	2,6-diCl-4-OMe—Ph	(CH ₂) ₂ —N(CH ₂ -3-pyridyl)-(1-(CH ₂ -3-pyridyl)-piperidin-4-yl)	645.64
218.	CH	Me	H	Me	2,6-diCl-4-OMe—Ph	(CH ₂) ₂ —N(CH ₂ —CHOH—CH ₂ OH) ₂	528.44
219.	CH	Me	H	Me	2,6-diCl-4-OMe—Ph	(CH ₂) ₂ -N-propanoyl-(1-propanoyl-piperidin-4-yl)	575.54
220.	CH	Me	H	Me	2,6-diCl-4-OMe—Ph	(CH ₂) ₂ -NEt-(tetrahydropyran-4-yl)	492.45
221.	CH	Me	H	Me	2,6-diCl-4-OMe—Ph	(CH ₂) ₂ —NH-(1-(CH ₂ -2-pyridyl)-piperidin-4-yl)	554.53
222.	CH	Me	H	Me	2,6-diCl-4-OMe—Ph	(CH ₂) ₂ —NH-(1-(CH ₂ -3-pyridyl)-piperidin-4-yl)	554.53
223.	CH	Me	H	Me	2,6-diCl-4-OMe—Ph	(CH ₂) ₂ —NH-(1-(CH ₂ -4-pyridyl)-piperidin-4-yl)	554.53
224.	CH	Me	H	Me	2,6-diCl-4-OMe—Ph	(CH ₂) ₂ —NH-(1-(pyrimidin-2-yl)-piperidin-4-yl)	541.5
225.	CH	Et	H	Me	2,6-diCl-4-OMe—Ph	(CH ₂) ₂ —NH-(1-(pyrimidin-2-yl)-piperidin-4-yl)	555.52
226.	CH	Me	H	Me	2,6-diCl-4-OMe—Ph	(CH ₂) ₂ —NH-(1-Ac-piperidin-4-yl)	504.46
227.	CH	Me	Me	Me	2,6-diCl-4-OMe—Ph	(CH ₂) ₂ —NH-(1-Bn-piperidin-4-yl)	519.5
228.	CH	Me	H	Me	2,6-diCl-4-OMe—Ph	(CH ₂) ₂ —NH-(1-Bn-piperidin-4-yl)	553.5
229.	CH	Me	H	Me	2,6-diCl-4-OMe—Ph	(CH ₂) ₂ —NH-(1-Et-piperidin-3-yl)	491.5
230.	CH	Me	H	Me	2,6-diCl-4-OMe—Ph	(CH ₂) ₂ —NH-(1-Et-piperidin-4-yl)	491.5
231.	CH	Me	H	Me	2,6-diCl-4-OMe—Ph	(CH ₂) ₂ —NH-(1-Pr-piperidin-4-yl)	505.5

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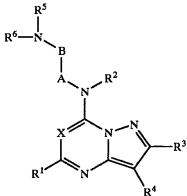
Table of Additional Examples



Ex	X	R ¹	R ²	R ³	R ⁴	A-B-N[R ⁵]-R ⁶	MW
232.	CH	Me	H	Me	2,6-diCl-4-OMe-Ph	(CH ₂) ₂ -NH-(1-Me-piperidin-4-yl)	477.44
233.	CH	Me	H	Me	2,6-diCl-4-OMe-Ph	(CH ₂) ₂ -NH-(1-Ph-pyrrolidin-3-yl)	525.49
234.	CH	Me	H	Me	2,6-diCl-4-OMe-Ph	(CH ₂) ₂ -NH-(1-phenylethyl)-pyrrolidin-2-one-4-yl)	567.52
235.	CH	Me	H	Me	2,6-diCl-4-OMe-Ph	(CH ₂) ₂ -NH-(1-phenylethyl-piperidin-4-yl)	567.57
236.	CH	Me	H	Me	2,6-diCl-4-OMe-Ph	(CH ₂) ₂ -NH-(1-propanoyl-piperidin-4-yl)	519.5
237.	CH	Me	H	Me	2,6-diCl-4-OMe-Ph	(CH ₂) ₂ -NH-(1-SO ₂ Me-piperidin-4-yl)	541.5
238.	CH	Me	H	Me	2,6-diCl-4-OMe-Ph	(CH ₂) ₂ -NH-(2-Me-tetrahydrofuran-3-yl)	570.5
239.	CH	Et	H	Me	2,6-diCl-4-OMe-Ph	(CH ₂) ₂ -NH-(1,2,3,4-tetrahydro-naphthalen-2-yl)	524.5
240.	CH	Me	H	Me	2,6-diCl-4-OMe-Ph	(CH ₂) ₂ -NH-(2-CF ₃ -cHex)	530.4
241.	CH	Me	H	Me	2,6-diCl-4-OMe-Ph	(CH ₂) ₂ -NH-(2-Me-tetrahydrofuran-3-yl)	464.40
242.	CH	Me	H	Me	2,6-diCl-4-OMe-Ph	(CH ₂) ₂ -NH-(2-oxo-pyrrolidin-4-yl)	463.37
243.	CH	Me	H	Me	2,6-diCl-4-OMe-Ph	(CH ₂) ₂ -NH-(2,2,6,6-tetramethyl-piperidin-4-yl)	519.5
244.	CH	Me	H	Me	2,6-diCl-4-OMe-Ph	(CH ₂) ₂ -NH-(2F-cHex)	480.4
245.	CH	Me	H	Me	2,6-diCl-4-OMe-Ph	(CH ₂) ₂ -NH-(4-(1-azetidin)-cHex)	517.51
246.	CH	Me	H	Me	2,6-diCl-4-OMe-Ph	(CH ₂) ₂ -NH-(4-(1-morpholino)-cHex)	547.53
247.	CH	Me	H	Me	2,6-diCl-4-OMe-Ph	(CH ₂) ₂ -NH-(4-(1-piperidino)-cHex)	545.56
248.	CH	Me	H	Me	2,6-diCl-4-OMe-Ph	(CH ₂) ₂ -NH-(4-(1-pyrrolidino)-cHex)	531.53
249.	CH	Me	H	Me	2,6-diCl-4-OMe-Ph	(CH ₂) ₂ -NH-(4-(NH-CH ₂ -2-pyridyl)-cHex)	568.55
250.	CH	Me	H	Me	2,6-diCl-4-OMe-Ph	(CH ₂) ₂ -NH-(4-(NH-CH ₂ -CH ₂ -CH ₂ OH)-cHex)	521.49
251.	CH	Me	H	Me	2,6-diCl-4-OMe-Ph	(CH ₂) ₂ -NH-(4-(NH ₂)-cHex)	477.44
252.	CH	Me	H	Me	2,6-diCl-4-OMe-Ph	(CH ₂) ₂ -NH-(4-(NHAc)-cHex)	519.48
253.	CH	Me	H	Me	2,6-diCl-4-OMe-Ph	(CH ₂) ₂ -NH-(4-(NHCO ₂ Me)-cHex)	555.53
254.	CH	Me	H	Me	2,6-diCl-4-OMe-Ph	(CH ₂) ₂ -NH-(4-CF ₃ -cHex)	530.42
255.	CH	Me	H	Me	2,6-diCl-4-OMe-Ph	(CH ₂) ₂ -NH-(4-CF ₃ -cHex)	530.4
256.	CH	iPr	H	Me	2,6-diCl-4-OMe-Ph	(CH ₂) ₂ -NH-(4-CF ₃ -cHex)	558.5
257.	CH	Et	H	Me	2,6-diCl-4-OMe-Ph	(CH ₂) ₂ -NH-(4-CF ₃ -cHex)	544.5
258.	CH	Me	H	Me	2,6-diCl-4-OMe-Ph	(CH ₂) ₂ -NH-(4-ethyleneketal-cHex)	520.5
259.	CH	Me	H	Me	2,6-diCl-4-OMe-Ph	(CH ₂) ₂ -NH-(4-hydroxyimino-cHex)	491.42
260.	CH	Me	H	Me	2,6-diCl-4-OMe-Ph	(CH ₂) ₂ -NH-(4-NHCO ₂ Me-cHex)	535.5
261.	CH	Me	H	Me	2,6-diCl-4-OMe-Ph	(CH ₂) ₂ -NH-(4-NHEt-cHex)	505.50
262.	CH	Me	H	Me	2,6-diCl-4-OMe-Ph	(CH ₂) ₂ -NH-(4-NH <i>i</i> Bu-cHex)	533.55
263.	CH	Me	H	Me	2,6-diCl-4-OMe-Ph	(CH ₂) ₂ -NH-(4-NHMe-cHex)	491.47

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cHex

Table of Additional Examples

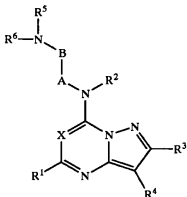


Ex	X	R ¹	R ²	R ³	R ⁴	A-B-N[R ⁶]-R ⁵	MW
264.	CH	Me	H	Me	2,6-diCl-4-OMe-Ph	(CH2)2-NH-(4-NHpropanoyl-cHex)	533.5
265.	CH	Me	H	Me	2,6-diCl-4-OMe-Ph	(CH2)2-NH-(4-OH-cHex)	478.43
266.	CH	Et	H	Me	2,6-diCl-4-OMe-Ph	(CH2)2-NH-(4,4-Dimethyl-2-oxo-tetrahydro-furan-3-yl)	506.44
267.	CH	Me	H	Me	2,6-diCl-4-OMe-Ph	(CH2)2-NH-(5-Cl-iodan-1-yl)	530.89
268.	CH	Me	H	Me	2,6-diCl-4-OMe-Ph	(CH2)2-NH-(5-fluoriodolin-2-one-3-yl)	529.41
269.	CH	Me	H	Me	2,6-diCl-4-OMe-Ph	(CH2)2-NH-(6-azabicyclo[4.4.0]dec-3-yl)	517.51
270.	CH	Me	H	Me	2,6-diCl-4-OMe-Ph	(CH2)2-NH-(6-OMe-1,2,3,4-tetrahydro-naphthalen-1-yl)	540.5
271.	CH	Me	H	Me	2,6-diCl-4-OMe-Ph	(CH2)2-NH-(7-methoxyimino-azepan-3-yl)	520.47
272.	CH	Me	H	Me	2,6-diCl-4-OMe-Ph	(CH2)2-NH-(CH2)2-CF3	476.3
273.	CH	Me	H	Me	2,6-diCl-4-OMe-Ph	(CH2)2-NH-(CH2)2-OH	424.33
274.	CH	Me	H	Me	2,6-diCl-4-OMe-Ph	(CH2)2-NH-(CH2)3-CF3	490.336
275.	CH	Me	H	Me	2,6-diCl-4-OMe-Ph	(CH2)2-NH-(cis-2F-cHex)	480.4
276.	CH	Me	H	Me	2,6-diCl-4-OMe-Ph	(CH2)2-NH-(cis-4-NHtBu-cHex)	533.55
277.	CH	Me	H	Me	2,6-diCl-4-OMe-Ph	(CH2)2-NH-(trans-4-OH-cHex)-#277a (CH2)2-NH-(cis-4OH-cHex)-#277b	478.43
278.	CH	Me	H	Me	2,6-diCl-4-OMe-Ph	(CH2)2-NH-(turan-2-one-4-yl)	464.36
279.	CH	Me	H	Me	2,6-diCl-4-OMe-Ph	(CH2)2-NH-(tetrahydropyran-4-yl)	464.4
280.	CH	Et	H	Me	2,6-diCl-4-OMe-Ph	(CH2)2-NH-(tetrahydropyran-4-yl)	478.4
281.	CH	tBu	H	Me	2,6-diCl-4-OMe-Ph	(CH2)2-NH-(tetrahydropyran-4-yl)	506.5
282.	CH	nPr	H	Me	2,6-diCl-4-OMe-Ph	(CH2)2-NH-(tetrahydropyran-4-yl)	492.5
283.	CH	iPr	H	Me	2,6-diCl-4-OMe-Ph	(CH2)2-NH-(tetrahydropyran-4-yl)	492.5
284.	CH	CF3	H	Me	2,6-diCl-4-OMe-Ph	(CH2)2-NH-(tetrahydropyran-4-yl)	518.4
285.	N	Me	H	Me	2,6-diCl-4-OMe-Ph	(CH2)2-NH-(tetrahydropyran-4-yl)	465.38
286.	CH	Me	H	Me	2,6-diCl-4-OMe-Ph	(CH2)2-NH-(trans-2F-cHex)	480.4
287.	CH	Me	H	Me	2,6-diCl-4-OMe-Ph	(CH2)2-NH-(trans-4-NHtBu-cHex)	533.55
288.	CH	Me	H	Me	2,6-diCl-4-OMe-Ph	(CH2)2-NH-(trans-4-OH-piperidin-4-yl)	478.4
289.	CH	Me	H	Me	2,6-diCl-4-OMe-Ph	(CH2)2-NH-Bn	470.41
290.	CH	Me	H	Me	2,6-diCl-4-OMe-Ph	(CH2)2-NH-CH-CH-(CH2OH)2	454.36
291.	CH	Me	H	Me	2,6-diCl-4-OMe-Ph	(CH2)2-NH-CH2-(1-tBoc-piperidin-4-yl)	577.56
292.	CH	Me	H	Me	2,6-diCl-4-OMe-Ph	(CH2)2-NH-CH2-(2-Me-oxetan-2-yl)	464.4
293.	CH	Me	H	Me	2,6-diCl-4-OMe-Ph	(CH2)2-NH-CH2-(piperidin-4-yl)	477.44
294.	CH	Me	H	Me	2,6-diCl-4-OMe-Ph	(CH2)2-NH-CH2-2-(CH2OH)-furan-5-yl	490.39

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Table of Additional Examples



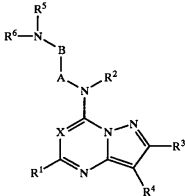
Ex	X	R ¹	R ²	R ³	R ⁴	A-B-N[R ⁶]-R ⁵	MW
295.	CH	Et	H	Me	2,6-diCl-4-OMe-Ph	(CH2)2-NH-CH2-2-CF3-Ph	552.43
296.	CH	Me	H	Me	2,6-diCl-4-OMe-Ph	(CH2)2-NH-CH2-2-pyridyl	471.39
297.	CH	Et	H	Me	2,6-diCl-4-OMe-Ph	(CH2)2-NH-CH2-3-CF3-Ph	552.43
298.	CH	Me	H	Me	2,6-diCl-4-OMe-Ph	(CH2)2-NH-CH2-3-pyridyl	471.39
299.	CH	Et	H	Me	2,6-diCl-4-OMe-Ph	(CH2)2-NH-CH2-4-CF3-Ph	552.43
300.	CH	Et	H	Me	2,6-diCl-4-OMe-Ph	(CH2)2-NH-CH2-4-Cl-Ph	518.88
301.	CH	Et	H	Me	2,6-diCl-4-OMe-Ph	(CH2)2-NH-CH2-4-OCF3-Ph	568.43
302.	CH	Et	H	Me	2,6-diCl-4-OMe-Ph	(CH2)2-NH-CH2-4-OMe-Ph	514.46
303.	CH	Me	H	Me	2,6-diCl-4-OMe-Ph	(CH2)2-NH-CH2-4-pyridyl	471.39
304.	CH	Me	H	Me	2,6-diCl-4-OMe-Ph	(CH2)2-NH-CH2-CF3	462.31
305.	CH	Me	H	Me	2,6-diCl-4-OMe-Ph	(CH2)2-NH-CH2-CHOH-CH2OH	454.36
306.	CH	Me	H	Me	2,6-diCl-4-OMe-Ph	(CH2)2-NH-CH2-CHOH-Me	438.36
307.	CH	Me	H	Me	2,6-diCl-4-OMe-Ph	(CH2)2-NH-CH2CHF2	444.3
308.	CH	Me	H	Me	2,6-diCl-4-OMe-Ph	(CH2)2-NH-CH2CHFPb	502.4
309.	CH	Me	H	Me	2,6-diCl-4-OMe-Ph	(CH2)2-NH-CHPr-CH2OH	452.39
310.	CH	Me	H	Me	2,6-diCl-4-OMe-Ph	(CH2)2-NH-CHPr-Ph	498.46
311.	CH	Et	H	Me	2,6-diCl-4-OMe-Ph	(CH2)2-NH-CHPr-Ph	512.49
312.	CH	nPr	H	Me	2,6-diCl-4-OMe-Ph	(CH2)2-NH-CHPr-Ph	526.51
313.	CH	Me	H	Me	2,6-diCl-4-OMe-Ph	(CH2)2-NH-CHMe-(1-Et-piperidin-4-yl)	533.51
314.	CH	Me	H	Me	2,6-diCl-4-OMe-Ph	(CH2)2-NH-CHMe-(1-SO2Me-piperidin-4-yl)	569.6
315.	CH	Me	H	Me	2,6-diCl-4-OMe-Ph	(CH2)2-NH-CHMe-(1-Boc-piperidin-4-yl)	591.59
316.	CH	Me	H	Me	2,6-diCl-4-OMe-Ph	(CH2)2-NH-CHMe-(CH2)3-NEt2	521.54
317.	CH	Me	H	Me	2,6-diCl-4-OMe-Ph	(CH2)2-NH-CHMe-(piperidin-4-yl)	491.47
318.	CH	Et	H	Me	2,6-diCl-4-OMe-Ph	(CH2)2-NH-CHMe-4-Cl-Ph	532.90
319.	CH	Et	H	Me	2,6-diCl-4-OMe-Ph	(CH2)2-NH-CHMe-4-F-Ph	516.45
320.	CH	Me	H	Me	2,6-diCl-4-OMe-Ph	(CH2)2-NH-CHMe-CH2-F	440.4
321.	CH	Me	H	Me	2,6-diCl-4-OMe-Ph	(CH2)2-NH-CHMe-CH2-NEt2	493.48
322.	CH	Me	H	Me	2,6-diCl-4-OMe-Ph	(CH2)2-NH-CHMe-CH2-NMe2	465.43
323.	CH	Me	H	Me	2,6-diCl-4-OMe-Ph	(CH2)2-NH-CHMe-Ph	484.43
324.	CH	Et	H	Me	2,6-diCl-4-OMe-Ph	(CH2)2-NH-CHMe-Ph	498.46
325.	CH	Me	H	Me	2,6-diCl-4-OMe-Ph	(CH2)2-NH-CHMe-piperidin-4-yl	477.44
326.	CH	Me	H	Me	2,6-diCl-4-OMe-Ph	(CH2)2-NH-cyclohex-3-enyl	460.4

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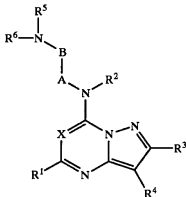
Table of Additional Examples



Ex	X	R ¹	R ²	R ³	R ⁴	A-B-N[R ⁵] ₂ R ⁶	MW
327.	CH	nPr	H	Me	2,6-diCl-4-OMe-Ph	(CH ₂) ₂ -NH-cyclohex-3-enyl	488.5
328.	CH	Et	H	Me	2,6-diCl-4-OMe-Ph	(CH ₂) ₂ -NH-cyclohex-3-enyl	474.4
329.	CH	Me	Me	Me	2,6-diCl-4-OMe-Ph	(CH ₂) ₂ -NH-cyclohex-3-enyl	474.4
330.	CH	Me	H	Me	2,6-diCl-4-OMe-Ph	(CH ₂) ₂ -NH-cyclopent-3-enyl	446.38
331.	CH	Me	H	Me	2,6-diCl-4-OMe-Ph	(CH ₂) ₂ -NH-piperidin-4-yl	463.41
332.	CH	Me	H	Me	2,6-diCl-4-OMe-Ph	(CH ₂) ₂ -NH-tropin-3-yl	488.4
333.	CH	Me	Et	Me	2,6-diCl-4-OMe-Ph	(CH ₂) ₂ -NHEt	436.39
334.	CH	Me	H	Me	2,6-diCl-4-OMe-Ph	(CH ₂) ₂ -NMe-(1-Ac-piperidin-4-yl)	519.5
335.	CH	Me	Me	Me	2,6-diCl-4-OMe-Ph	(CH ₂) ₂ -NMe-(tetrahydropyran-4-yl)	533.51
336.	CH	Me	H	Me	2,6-diCl-4-OMe-Ph	(CH ₂) ₂ -NMe-(tetrahydropyran-4-yl)	478.4
337.	CH	Me	Me	Me	2,6-diCl-4-OMe-Ph	(CH ₂) ₂ -NMe-cyclohex-3-enyl	488.5
338.	CH	Me	H	Me	2,6-diCl-4-OMe-Ph	(CH ₂) ₂ -NMe-cyclohex-3-enyl	474.4
339.	CH	Me	H	Me	2,6-diCl-4-OMe-Ph	(CH ₂) ₃ -NH-(1-Bn-piperidin-4-yl)	567.57
340.	CH	Me	H	Me	2,6-diCl-4-OMe-Ph	(CH ₂) ₃ -NH-tetrahydropyran-4-yl	478.43
341.	CH	Me	H	Me	2,6-diCl-4-OMe-Ph	(CH ₂) ₄ -NH-(tetrahydropyran-4-yl)	492.45
342.	CH	Me	H	Me	2,6-diCl-4-OMe-Ph	CH ₂ -(S)-pyrrolidin-2-yl	420.34
343.	CH	Me	H	Me	2,6-diCl-4-OMe-Ph	CH ₂ -CH(CH ₂ -imidazol-1-yl)-NH-(1-Bn-piperidin-4-yl)	633.63
344.	CH	Me	H	Me	2,6-diCl-4-OMe-Ph	CH ₂ -CH(CH ₂ -imidazol-1-yl)-NH-(tetrahydropyran-4-yl)	544.49
345.	CH	Me	H	Me	2,6-diCl-4-OMe-Ph	CH ₂ -CHEt-NH-(1-Ac-piperidin-4-yl)	533.5
346.	CH	Me	H	Me	2,6-diCl-4-OMe-Ph	CH ₂ -CHEt-NH-(tetrahydropyran-4-yl)	492.5
347.	CH	Me	H	Me	2,6-diCl-4-OMe-Ph	CH ₂ -CHiBu-NH-(tetrahydropyran-4-yl)	520.52
348.	CH	Me	H	Me	2,6-diCl-4-OMe-Ph	CH ₂ -CHiPr-NH-(tetrahydropyran-4-yl)	506.5
349.	CH	iPr	H	Me	2,6-diCl-4-OMe-Ph	CH ₂ -CHMe-NH-(1-(pyrimidin-2-yl)-piperidin-4-yl)	583.57
350.	CH	nPr	H	Me	2,6-diCl-4-OMe-Ph	CH ₂ -CHMe-NH-(1-(pyrimidin-2-yl)-piperidin-4-yl)	583.57
351.	CH	Et	H	Me	2,6-diCl-4-OMe-Ph	CH ₂ -CHMe-NH-(1-(pyrimidin-2-yl)-piperidin-4-yl)	569.54
352.	CH	Me	H	Me	2,6-diCl-4-OMe-Ph	CH ₂ -CHMe-NH-(4-(1-morpholino)-cHex)	561.56
353.	CH	Me	H	Me	2,6-diCl-4-OMe-Ph	CH ₂ -CHMe-NH-(4-(1-morpholino)-cHex)	575.59
354.	CH	Me	H	Me	2,6-diCl-4-OMe-Ph	CH ₂ -CHMe-NH-(4-ethyleneketal-cHex)	534.49
355.	CH	Me	H	Me	2,6-diCl-4-OMe-Ph	CH ₂ -CHMe-NH-(4-NHMe-cHex)	505.50
356.	CH	Me	H	Me	2,6-diCl-4-OMe-Ph	CH ₂ -CHMe-NH-(4-OH-cHex)	492.45
357.	CH	Me	H	Me	2,6-diCl-4-OMe-Ph	CH ₂ -CHMe-NH-(4-oxo-cHex)	490.44
358.	CH	Me	H	Me	2,6-diCl-4-OMe-Ph	CH ₂ -CHMe-NH-(tetrahydropyran-4-yl)	478.4

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Table of Additional Examples

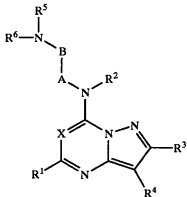


Ex	X	R ¹	R ²	R ³	R ⁴	A-B-N[R ⁵]-R ⁶	MW
359.	CH	Et	H	Me	2,6-diCl-4-OMe-Ph	CH ₂ -CHMe-NH-(tetrahydropyran-4-yl)	492.5
360.	CH	iPr	H	Me	2,6-diCl-4-OMe-Ph	CH ₂ -CHMe-NH-(tetrahydropyran-4-yl)	506.48
361.	CH	nPr	H	Me	2,6-diCl-4-OMe-Ph	CH ₂ -CHMe-NH-(tetrahydropyran-4-yl)	506.5
362.	CH	Me	H	Me	2,6-diCl-4-OMe-Ph	CH ₂ -CHNH ₂ -CH ₂ -imidazol-1-yl	460.37
363.	CH	Me	H	Me	2,6-diCl-4-OMe-Ph	CH ₂ -CHOH-CH ₂ -NH-(1-Bn-piperidin-4-yl)	583.57
364.	CH	Me	H	Me	2,6-diCl-4-OMe-Ph	CH ₂ -CHOH-CH ₂ -NH-(tetrahydropyran-4-yl)	494.43
365.	CH	Me	H	Me	2,6-diCl-4-OMe-Ph	CH ₂ -CHOH-CH ₂ -NH ₂	410.31
366.	CH	Me	H	Me	2,6-diCl-4-OMe-Ph	CH ₂ -CMe ₂ -CH ₂ -NH-(1-Bn-piperidin-4-yl)	595.62
367.	CH	Me	H	Me	2,6-diCl-4-OMe-Ph	CH ₂ -CMe ₂ -CH ₂ -NH-(tetrahydropyran-4-yl)	506.48
368.	CH	Me	H	Me	2,6-diCl-4-OMe-Ph	CH ₂ -CMe ₂ -NH-(1-Bn-piperidin-4-yl)	581.59
369.	CH	Me	H	Me	2,6-diCl-4-OMe-Ph	CH ₂ -CMe ₂ -NH-(tetrahydropyran-4-yl)	492.45
370.	CH	Me	Me	Me	2,6-diCl-4-OMe-Ph	CH ₂ -NH-(tetrahydropyran-4-yl)	478.4
371.	CH	Me	H	Me	2,6-diCl-4-OMe-Ph	CHEt-CH ₂ -NH-(1-Ac-piperidin-4-yl)	533.5
372.	CH	Me	H	Me	2,6-diCl-4-OMe-Ph	CHEt-CH ₂ -NH-(tetrahydropyran-4-yl)	492.5
373.	CH	Me	H	Me	2,6-diCl-4-OMe-Ph	CHiBu-CH ₂ -NH-(tetrahydropyran-4-yl)	520.52
374.	CH	Me	H	Me	2,6-diCl-4-OMe-Ph	CHMe-CHMe-NH-(1-COOEt-piperidin-4-yl)	563.5
375.	CH	Me	H	Me	2,6-diCl-4-OMe-Ph	CHMe-CHMe-NH-(tetrahydropyran-4-yl)	492.45
376.	CH	Me	H	Me	2,6-diCl-4-OMe-Ph	CHMe-CHMe-NH-(tetrahydropyran-4-yl)	506.48
377.	CH	Et	H	Me	2,6-diCl-4-OMe-Ph	CHMe-CHMe-NH-(tetrahydropyran-4-yl)	506.5
378.	CH	Me	H	Me	2,6-diCl-4-OMe-Ph	CMe ₂ -CH ₂ -NH-(pyrimidin-2-yl)-piperidin-4-yl)	569.5
379.	CH	Me	H	Me	2,6-diCl-4-OMe-Ph	CMe ₂ -CH ₂ -NH-(tetrahydropyran-4-yl)	492.5
380.	CH	Me	H	Me	2,6-diCl-4-OMe-Ph	CMe ₂ -CH ₂ -NH-C(Me) ₂ -CH ₂ -OH	480.4
381.	CH	Me	H	Me	2,6-diCl-4-OMe-Ph	quinuclidin-3-yl	446.38
382.	CH	Me	H	Me	2,6-diCl-4-OPr-Ph	(CH ₂) ₂ -NH-(tetrahydropyran-4-yl)	492.45
383.	CH	Me	H	Me	2,6-diCl-4-OSO ₂ CF ₃ -Ph	(CH ₂) ₂ -NH-(tetrahydropyran-4-yl)	582.43
384.	CH	Et	H	Me	2,6-diCl-Ph	(CH ₂) ₂ -NH-(1-(pyrimidin-2-yl)-piperidin-4-yl)	525.5
385.	CH	iPr	H	Me	2,6-diCl-Ph	(CH ₂) ₂ -NH-(1-(pyrimidin-2-yl)-piperidin-4-yl)	539.5
386.	CH	CF ₃	H	Me	2,6-diCl-Ph	(CH ₂) ₂ -NH-(1-(pyrimidin-2-yl)-piperidin-4-yl)	565.43
387.	CH	nPr	H	Me	2,6-diCl-Ph	(CH ₂) ₂ -NH-(1-(pyrimidin-2-yl)-piperidin-4-yl)	539.5
388.	CH	Me	H	Me	2,6-diCl-Ph	(CH ₂) ₂ -NH-(1-benzoyl-piperidin-4-yl)	646.88
389.	CH	Me	H	Me	2,6-diCl-Ph	(CH ₂) ₂ -NH-(1-Bn-piperidin-4-yl)	523.51
390.	N	Me	H	Me	2,6-diCl-Ph	(CH ₂) ₂ -NH-(1-Bn-piperidin-4-yl)	524.5

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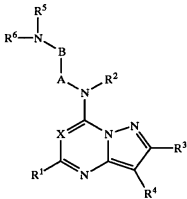
Table of Additional Examples



Ex	X	R ¹	R ²	R ³	R ⁴	A-B-N[R ⁶]-R ⁵	MW
391.	CH	Me	H	Me	2,6-diCl-Ph	(CH ₂) ₂ -NH-(1-Bu-pyrrolidin-3-yl)	509.49
392.	CH	Me	H	Me	2,6-diCl-Ph	(CH ₂) ₂ -NH-(1-Et-piperidin-3-yl)	461.4
393.	CH	Me	H	Me	2,6-diCl-Ph	(CH ₂) ₂ -NH-(1-Et-piperidin-4-yl)	534.36
394.	CH	Me	H	Me	2,6-diCl-Ph	(CH ₂) ₂ -NH-(1-Me-piperidin-4-yl)	447.41
395.	CH	Me	H	Me	2,6-diCl-Ph	(CH ₂) ₂ -NH-(4-(1-azetidino)-cHex)	487.5
396.	CH	Me	H	Me	2,6-diCl-Ph	(CH ₂) ₂ -NH-(4-(1-morpholino)-cHex)	503.5
397.	CH	Me	H	Me	2,6-diCl-Ph	(CH ₂) ₂ -NH-(4-(1-piperidino)-cHex)	515.5
398.	CH	Me	H	Me	2,6-diCl-Ph	(CH ₂) ₂ -NH-(4-(1-pyrrolidino)-cHex)	647.35
399.	CH	Me	H	Me	2,6-diCl-Ph	(CH ₂) ₂ -NH-(4-(NH-(CH ₂) ₂ -OH)-cHex)	491.47
400.	CH	Me	H	Me	2,6-diCl-Ph	(CH ₂) ₂ -NH-(4-(NH-(CH ₂ -2-pyridyl)-cHex)	538.53
401.	CH	Me	H	Me	2,6-diCl-Ph	(CH ₂) ₂ -NH-(4-(NH-iBu)-cHex)	503.52
402.	CH	Me	H	Me	2,6-diCl-Ph	(CH ₂) ₂ -NH-(4-(NHEt)-cHex)	460.4
403.	CH	Me	H	Me	2,6-diCl-Ph	(CH ₂) ₂ -NH-(4-(NHMe)-cHex)	607.28
404.	CH	iPr	H	Me	2,6-diCl-Ph	(CH ₂) ₂ -NH-(4-CF ₃ -cHex)	528.5
405.	CH	Me	H	Me	2,6-diCl-Ph	(CH ₂) ₂ -NH-(4-ethyleneketal-cHex)	490.44
406.	CH	Me	H	Me	2,6-diCl-Ph	(CH ₂) ₂ -NH-(4-OH-cHex)	448.4
407.	CH	Me	H	Me	2,6-diCl-Ph	(CH ₂) ₂ -NH-(4-oxo-cHex)	446.38
408.	N	Me	H	Me	2,6-diCl-Ph	(CH ₂) ₂ -NH-(4-trans-OH-cHex)	449.4
409.	CH	Me	H	Me	2,6-diCl-Ph	(CH ₂) ₂ -NH-(6,7-diOMe-1,2,3,4-tetrahydronaphthalen-2-yl)	540.5
410.	CH	Me	H	Me	2,6-diCl-Ph	(CH ₂) ₂ -NH-(8-aza-8-methylbicyclo[3.2.1]octan-3-yl)	459.43
411.	CH	Me	H	Me	2,6-diCl-Ph	(CH ₂) ₂ -NH-(tetrahydropyran-4-yl)	434.37
412.	CH	iPr	H	Me	2,6-diCl-Ph	(CH ₂) ₂ -NH-(tetrahydropyran-4-yl)	462.4
413.	CH	CF ₃	H	Me	2,6-diCl-Ph	(CH ₂) ₂ -NH-(tetrahydropyran-4-yl)	488.34
414.	CH	CF ₃	H	Me	2,6-diCl-Ph	(CH ₂) ₂ -NH-(trans-1-CF ₃ -cyclohexan-4-yl)	554.37
415.	CH	Me	H	Me	2,6-diCl-Ph	(CH ₂) ₂ -NH-2,2,6,6-tetramethylpiperidin-4-yl	489.5
416.	CH	Me	H	Me	2,6-diCl-Ph	(CH ₂) ₂ -NH-CHMe-CH ₂ -(3-OMe-4-(O-(CH ₂) ₂ -NMe ₂)-Ph)	585.6
417.	CH	Me	H	Me	2,6-diCl-Ph	(CH ₂) ₂ -NH-CHMe-CH ₂ -(3-OMe-4-OH-Ph)	514.46
418.	N	Me	H	Me	2,6-diCl-Ph	(CH ₂) ₂ -NH-cPent	449.4
419.	CH	Me	H	Me	2,6-diCl-Ph	(CH ₂) ₂ -NH-piperidin-4-yl	433.4
420.	CH	Me	H	Me	2,6-diCl-Ph	(CH ₂) ₂ -NH-quinolin-2-yl	477.40
421.	CH	Me	H	Me	2,6-diCl-Ph	(CH ₂) ₂ -NH-quinolidin-3-yl	459.4
422.	CH	Me	H	Me	2,6-diCl-Ph	CH ₂ -CHEt-NH-(1-Ac-piperidin-4-yl)	503.48

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Table of Additional Examples



Ex	X	R ¹	R ²	R ³	R ⁴	A-B-N[R ⁶]-R ⁵	MW
423.	CH	Me	H	Me	2,6-diCl-Ph	CH ₂ -CHEt-NH-(tetrahydropyran-4-yl)	462.43
424.	CH	nPr	H	Me	2,6-diCl-Ph	CH ₂ -CHMe-NH-(1-(pyrimidin-2-yl)-piperidin-4-yl)	553.5
425.	CH	Et	H	Me	2,6-diCl-Ph	CH ₂ -CHMe-NH-(1-(pyrimidin-2-yl)-piperidin-4-yl)	539.5
426.	CH	Me	H	Me	2,6-diCl-Ph	CH ₂ -CHMe-NH-(1-Bn-piperidin-4-yl)	537.53
427.	CH	Me	H	Me	2,6-diCl-Ph	CH ₂ -CHMe-NH-(tetrahydropyran-4-yl)	448.4
428.	CH	Me	H	Me	2,6-diCl-Ph	CHEt-CH ₂ -NH-(tetrahydropyran-4-yl)	462.4
429.	CH	Me	H	Me	2,6-diCl-Ph	CHEt-CH ₂ -NH-(tetrahydropyran-4-yl)	503.5
430.	CH	Me	H	Me	2,6-diCl-Ph	CHMe-CHMe-NH-(1-Bn-piperidin-4-yl)	551.57
431.	CH	Me	H	Me	2,6-diCl-Ph	CHMe-CHMe-NH-(tetrahydropyran-4-yl)	462.43
432.	CH	Me	H	Me	2,6-diMe-3,5-diBr-4-OCF ₃ -Ph	(CH ₂) ₂ -NH-(tetrahydropyran-4-yl)	634.6
433.	CH	Me	H	Me	2,6-diMe-4-Cl-Ph	(CH ₂) ₂ -NH-(1-pyrimidin-2-yl)-piperidin-4-yl)	505.06
434.	CH	Me	H	Me	2,6-diMe-4-Cl-Ph	(CH ₂) ₂ -NH-(1-Bn-piperidin-4-yl)	517.12
435.	CH	Me	H	Me	2,6-diMe-4-Cl-Ph	(CH ₂) ₂ -NH-(1-COOEt-piperidin-4-yl)	499.0
436.	CH	Me	H	Me	2,6-diMe-4-Cl-Ph	(CH ₂) ₂ -NH-(4-COOH-cHex)	470.01
437.	CH	Me	H	Me	2,6-diMe-4-CN-Ph	(CH ₂) ₂ -NH-(tetrahydropyran-4-yl)	418.53
438.	CH	Me	H	Me	2,6-diMe-4-OCF ₃ -5-Br-Ph	(CH ₂) ₂ -NH-(tetrahydropyran-4-yl)	556.4
439.	CH	Me	H	Me	2,6-diMe-4-OCF ₃ -Ph	(CH ₂) ₂ -NH-(1-(5-Et-pyrimidin-2-yl)-piperidin-4-yl)	582.66
440.	CH	Me	H	Me	2,6-diMe-4-OCF ₃ -Ph	(CH ₂) ₂ -NH-(1-pyrimidin-2-yl)-piperidin-4-yl)	554.61
441.	CH	Me	H	Me	2,6-diMe-4-OCF ₃ -Ph	(CH ₂) ₂ -NH-(1-pyrimidin-2-yl)-piperidin-4-yl)	536.62
442.	CH	Me	H	Me	2,6-diMe-4-OCF ₃ -Ph	(CH ₂) ₂ -NH-(2F-cPent)	479.53
443.	CH	Me	H	Me	2,6-diMe-4-OCF ₃ -Ph	(CH ₂) ₂ -NH-(tetrahydropyran-4-yl)	477.52
444.	CH	Me	H	Me	2,6-diMe-4-OCF ₃ -Ph	(CH ₂) ₂ -NH-(1-(2-Cl-pyrimidin-5-yl)-piperidin-4-yl)	459.53
445.	CH	Me	H	Me	2,6-diMe-4-OEt-Ph	(CH ₂) ₂ -NH-(1-(2-Cl-pyrimidin-5-yl)-piperidin-4-yl)	549.11
446.	CH	Me	H	Me	2,6-diMe-4-OEt-Ph	(CH ₂) ₂ -NH-(1-(2-F-pyridin-6-yl)-piperidin-4-yl)	531.67
447.	CH	Me	H	Me	2,6-diMe-4-OEt-Ph	(CH ₂) ₂ -NH-(1-(2-Ome-pyridin-5-yl)-piperidin-4-yl)	543.70
448.	CH	Me	H	Me	2,6-diMe-4-OEt-Ph	(CH ₂) ₂ -NH-(1-(3,6-diMe-pyrazin-2-yl)-piperidin-4-yl)	542.72
449.	CH	Me	H	Me	2,6-diMe-4-OEt-Ph	(CH ₂) ₂ -NH-(1-(4-Me-pyridin-2-yl)-piperidin-4-yl)	527.70
450.	CH	Me	H	Me	2,6-diMe-4-OEt-Ph	(CH ₂) ₂ -NH-(1-(4-Ome-pyrimidin-2-yl)-piperidin-4-yl)	544.69
451.	CH	Me	H	Me	2,6-diMe-4-OEt-Ph	(CH ₂) ₂ -NH-(1-(5-CF ₃ -pyridin-2-yl)-piperidin-4-yl)	581.68
452.	CH	Me	H	Me	2,6-diMe-4-OEt-Ph	(CH ₂) ₂ -NH-(1-(5-F-pyrimidin-2-yl)-piperidin-4-yl)	532.66

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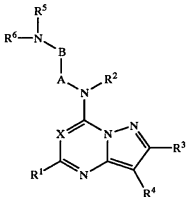
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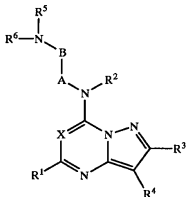
Table of Additional Examples



Ex	X	R ¹	R ²	R ³	R ⁴	A-B-N[R ⁶]-R ⁵	MW
453.	CH	Me	H	Me	2,6-diMe-4-OEt—Ph	(CH2)2—NH-(1-(6-Cl-pyridazin-3-yl)-piperidin-4-yl)	549.11
454.	CH	Me	H	Me	2,6-diMe-4-OEt—Ph	(CH2)2—NH-(1-(6-Me-pyridin-2-yl)-piperidin-4-yl)	527.70
455.	CH	Me	H	Me	2,6-diMe-4-OEt—Ph	(CH2)2—NH-(1-(6-O-Me-pyridin-2-yl)-piperidin-4-yl)	543.70
456.	CH	Me	H	Me	2,6-diMe-4-OEt—Ph	(CH2)2—NH-(1-(pyridin-2-yl)-piperidin-4-yl)	513.68
457.	CH	Me	H	Me	2,6-diMe-4-OEt—Ph	(CH2)2—NH-(1-(pyrimidin-2-yl)-piperidin-4-yl)	514.67
458.	CH	Me	H	Me	2,6-diMe-4-OEt—Ph	(CH2)2—NH-(1-(pyrimidin-5-yl)-piperidin-4-yl)	542.72
459.	CH	Me	H	Me	2,6-diMe-4-OEt—Ph	(CH2)2—NH-(1-(pyrimidin-5-yl)-piperidin-4-yl)	514.67
460.	CH	Me	H	Me	2,6-diMe-4-OEt—Ph	(CH2)2—NH-(1-(thiazol-2-yl)-piperidin-4-yl)	519.71
461.	CH	Me	H	Me	2,6-diMe-4-OEt—Ph	(CH2)2—NH-(4-ethylencetol-cHex)	493.64
462.	CH	Me	H	Me	2,6-diMe-4-OEt—Ph	(CH2)2—NH-(4-oxo-cHex)	449.59
463.	CH	Me	H	Me	2,6-diMe-4-OH—Ph	(CH2)2—NH-(1-(2-F-pyridin-6-yl)-piperidin-4-yl)	503.61
464.	CH	Me	H	Me	2,6-diMe-4-OMe—Ph	(CH2)2—NH-(1-(2-OMe-pyridin-6-yl)-piperidin-4-yl)	529.68
465.	CH	Me	H	Me	2,6-diMe-4-OMe—Ph	(CH2)2—NH-(1-(4-CF3-pyrimidin-2-yl)-piperidin-4-yl)	568.64
466.	CH	Me	H	Me	2,6-diMe-4-OMe—Ph	(CH2)2—NH-(1-(5-Et-pyrimidin-2-yl)-piperidin-4-yl)	528.7
467.	CH	Me	H	Me	2,6-diMe-4-OMe—Ph	(CH2)2—NH-(1-(5-F-pyrimidin-2-yl)-piperidin-4-yl)	518.63
468.	CH	Me	H	Me	2,6-diMe-4-OMe—Ph	(CH2)2—NH-(1-(6-F-2-pyridyl)-piperidin-4-yl)	517.64
469.	CH	Me	H	Me	2,6-diMe-4-OMe—Ph	(CH2)2—NH-(1-(pyrimidin-2-yl)-piperidin-4-yl)	500.64
470.	CH	Me	H	Me	2,6-diMe-4-OMe—Ph	(CH2)2—NH-(1-(pyrimidin-2-yl)-piperidin-4-yl)	486.61
471.	N	Me	H	Me	2,6-diMe-4-OMe—Ph	(CH2)2—NH-(1-(pyrimidin-2-yl)-piperidin-4-yl)	501.63
472.	CH	Me	H	Me	2,6-diMe-4-OMe—Ph	(CH2)2—NH-(1-(thiazol-2-yl)-piperidin-4-yl)	512.7
473.	CH	Me	H	Me	2,6-diMe-4-OMe—Ph	(CH2)2—NH-(1-Bn-piperidin-4-yl)	505.68
474.	CH	Me	H	Me	2,6-diMe-4-OMe—Ph	(CH2)2—NH-(1-COOEt-piperidin-4-yl)	493.64
475.	CH	Me	H	Me	2,6-diMe-4-OMe—Ph	(CH2)2—NH-(1-Et-piperidin-4-yl)	450.62
476.	CH	Me	H	Me	2,6-diMe-4-OMe—Ph	(CH2)2—NH-(1-Et-piperidin-4-yl)	450.4
477.	CH	Me	H	Me	2,6-diMe-4-OMe—Ph	(CH2)2—NH-(1-formyl-piperidin-4-yl)	451.3
478.	CH	Me	H	Me	2,6-diMe-4-OMe—Ph	(CH2)2—NH-(1-Me-piperidin-4-yl)	436.4
479.	CH	Me	H	Me	2,6-diMe-4-OMe—Ph	(CH2)2—NH-(1-SO2Me-piperidin-4-yl)	500.66
480.	CH	Me	H	Me	2,6-diMe-4-OMe—Ph	(CH2)2—NH-(2-Me-tetrahydrofuran-3-yl)	423.55
481.	CH	Me	H	Me	2,6-diMe-4-OMe—Ph	(CH2)2—NH-(2F-cPent)	425.6
482.	CH	Me	H	Me	2,6-diMe-4-OMe—Ph	(CH2)2—NH-(4-(1-morpholino)-cHex)	520.71

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Table of Additional Examples

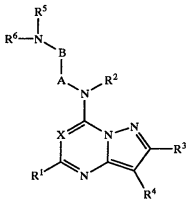


Ex	X	R ¹	R ²	R ³	R ⁴	A-B-N[R ⁶]-R ⁵	MW
483.	CH	Me	H	Me	2,6-diMe-4-OMe-Ph	(CH ₂) ₂ -NH-(4-(1-piperidino)-cHex)	518.74
484.	CH	Me	H	Me	2,6-diMe-4-OMe-Ph	(CH ₂) ₂ -NH-(4-(1-pyrrolidino)-cHex)	490.68
485.	CH	Me	H	Me	2,6-diMe-4-OMe-Ph	(CH ₂) ₂ -NH-(4-(1-pyrrolidino)-cHex)	504.71
486.	CH	Me	H	Me	2,6-diMe-4-OMe-Ph	(CH ₂) ₂ -NH-(4-(NH-CH ₂ -2-pyridyl)-cHex)	541.73
487.	CH	Me	H	Me	2,6-diMe-4-OMe-Ph	(CH ₂) ₂ -NH-(4-(NH-CH ₂ -4-pyridyl)-cHex)	541.73
488.	CH	Me	H	Me	2,6-diMe-4-OMe-Ph	(CH ₂) ₂ -NH-(4-(NH-iBu)-cHex)	492.70
489.	CH	Me	H	Me	2,6-diMe-4-OMe-Ph	(CH ₂) ₂ -NH-(4-NiBu-NSO ₂ -Me)-cHex)	570.79
490.	CH	Me	H	Me	2,6-diMe-4-OMe-Ph	(CH ₂) ₂ -NH-(4-(NMe-NiBu)-cHex)	506.73
491.	CH	Me	H	Me	2,6-diMe-4-OMe-Ph	(CH ₂) ₂ -NH-(4-ethyl-eneketal-cHex)	479.61
492.	CH	Me	H	Me	2,6-diMe-4-OMe-Ph	(CH ₂) ₂ -NH-(4-NH-iBu-cHex)	506.73
493.	CH	Me	H	Me	2,6-diMe-4-OMe-Ph	(CH ₂) ₂ -NH-(4-NHSO ₂ -Me-cHex)	514.68
494.	CH	Me	H	Me	2,6-diMe-4-OMe-Ph	(CH ₂) ₂ -NH-(4-oxo-cHex)	435.4
495.	CH	Me	H	Me	2,6-diMe-4-OMe-Ph	(CH ₂) ₂ -NH-(4,4-diMe-cHex)	449.63
496.	CH	Me	H	Me	2,6-diMe-4-OMe-Ph	(CH ₂) ₂ -NH-(4,4-dioxo-tetrahydrothian-yl)	471.62
497.	CH	Me	H	Me	2,6-diMe-4-OMe-Ph	(CH ₂) ₂ -NH-(tetrahydropyran-4-yl)	439.63
498.	N	Me	H	Me	2,6-diMe-4-OMe-Ph	(CH ₂) ₂ -NH-(trans-4-COOEt-cHex)	494.63
499.	CH	Me	H	Me	2,6-diMe-4-OMe-Ph	(CH ₂) ₂ -NH-(trans-4-COOEt-cHex)	493.64
500.	CH	Me	H	Me	2,6-diMe-4-OMe-Ph	(CH ₂) ₂ -NH-(trans-4-COOH-cHex)	465.59
501.	CH	Me	H	Me	2,6-diMe-4-OMe-Ph	(CH ₂) ₂ -NH-cyclohex-3-enyl	419.57
502.	CH	Me	H	Me	2,6-diMe-4-OMe-Ph	(CH ₂) ₂ -NH-piperidin-4-yl	422.5
503.	CH	Me	H	Me	2,6-diMe-4-OMe-Ph	CH ₂ -CHMe-NH-(1-(5-Et-pyrimidin-2-yl)-piperidin-4-yl)	542.70
504.	CH	Me	H	Me	2,6-diMe-4-OMe-Ph	CH ₂ -CHMe-NH-(1-(pyrimidin-2-yl)-piperidin-4-yl)	514.68
505.	CH	Me	H	Me	2,6-diMe-4-OMe-Ph	CH ₂ -CHMe ₂ -NH-(1-(5-Et-pyrimidin-2-yl)-piperidin-4-yl)	556.7
506.	CH	Me	H	Me	2,6-diMe-4-iBu-Ph	(CH ₂) ₂ -NH-(tetrahydropyran-4-yl)	449.64
507.	CH	Et	H	Me	2,6-diMe-Ph	(CH ₂) ₂ -NH-(1-pyrimidin-2-yl)-piperidin-4-yl)	484.65
508.	CH	Et	H	Me	2,6-diMe-Ph	(CH ₂) ₂ -NH-(1-pyrimidin-2-yl)-piperidin-4-yl)	484.65
509.	CH	aPr	H	Me	2,6-diMe-Ph	(CH ₂) ₂ -NH-(1-pyrimidin-2-yl)-piperidin-4-yl)	498.7
510.	CH	Me	H	Me	2,6-diMe-Ph	(CH ₂) ₂ -NH-(1-pyrimidin-2-yl)-piperidin-4-yl)	470.6
511.	CH	Et	H	Me	2,6-diMe-Ph	(CH ₂) ₂ -NH-(1-Ac-piperidin-4-yl)	448.62
512.	CH	Et	H	Me	2,6-diMe-Ph	(CH ₂) ₂ -NH-(1,2,3,4-tetrahydro-asphthalen-2-yl)	453.6

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Table of Additional Examples



Ex	X	R ¹	R ²	R ³	R ⁴	A-B-N[R ⁵] ₂ R ⁶	MW
513.	CH	Et	H	Me	2,6-diMe-Ph	CH ₂ -CHMe-NH-(1-(4-pyrimidin-2-yl)-piperidin-4-yl)	498.7
514.	CH	nPr	H	Me	2,6-diMe-Ph	CH ₂ -CHMe-NH-(1-(4-pyrimidin-2-yl)-piperidin-4-yl)	512.7
515.	CH	me	H	Me	2,6-diMe-Ph	CH ₂ -CHMe-NH-(1-(4-pyrimidin-2-yl)-piperidin-4-yl)	484.7
516.	CH	Et	H	Me	2,6-diMe-Ph	CH ₂ -CHMe-NH-(1,2,3,4-tetrahydro-naphthalen-2-yl)	467.7
517.	CH	Me	H	Me	2,6-diOMe-Ph	(CH ₂) ₂ -NH-(1-Et-piperidin-4-yl)	452.4
518.	CH	Me	H	Me	2,6-diOMe-Ph	(CH ₂) ₂ -NH-(4-ethyleneketal-cHex)	481.59
519.	CH	Me	H	Me	2,6-diOMe-Ph	(CH ₂) ₂ -NH-(4-oxo-cHex)	437.3
520.	CH	Me	H	Me	2,6-diOMe-Ph	(CH ₂) ₂ -NH-(tetrahydropyran-4-yl)	425.52

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[0233] The pharmaceutical utility of compounds of this invention are indicated by the following assays for human NPY-1 receptor activity.

[0234] Assay for Human NPY-1 Receptor Binding Activity

[0235] Compounds are assayed for activity using the following method: Baculovirus-infected Sf9 cells expressing recombinant human NPY-1 receptors are harvested at 42-48 hours at which time batches of 500 mL of cell suspension are pelleted by centrifugation. Each pellet is re-suspended in 30 mL of lysis buffer (10 mM HEPES, 250 mM sucrose, 0.5 gg/mL leupeptin, 2 μ g/mL Aprotinin, 200 μ M PMSF and 2.5 mM EDTA, pH 7.4) and gently homogenized by 50 strokes using a dounce homogenizer. The homogenate is centrifuged at 4° C. for 10 minutes at 536x g to pellet the nuclei. The supernatant is collected into a fresh tube and centrifuged twice in the same buffer at 48,000x g for 40 minutes. The final pellet was re-suspended in 10 mL of PBS containing 5 mM EDTA by dounce homogenization and stored in aliquots at -80° C.

[0236] Purified membranes are washed by PBS and re-suspended by gentle pipetting in binding buffer (50 mM Tris(HCl), 5 mM KCl, 120 mM NaCl, 2 mM CaCl₂, 1 mM MgCl₂, 0.1% bovine serum albumin (BSA), pH 7.4). Membranes (5 μ g) are added to siliconized (Sigmacote, Sigma) polypropylene tubes in addition to 0.050 nM [¹²⁵I]NPY (porcine) for competition analysis or 0.010-0.500 nM [¹²⁵I]NPY (porcine) for saturation analysis. For evaluation of guanine nucleotide effects on receptor affinity, GTP is added at a final concentration of 100 μ M. Cold displacers are added at concentrations ranging from 10⁻¹² M to 10⁻⁶ M to yield a final volume of 0.250 mL. Nonspecific binding is determined in the presence of 1 μ M NPY (human) and accounts for less than 10% of total binding. Following a 2 hour incubation at room temperature, the reaction is terminated by rapid vacuum filtration. Samples are filtered over pre-soaked GF/C Whatman filters (1.0% polyethyleneimine for 2 hours) and rinsed 2 times with 5 mL cold binding buffer lacking BSA. Remaining bound radioactivity is measured by gamma counting. To estimate the B_{max}, K_d and K_i, the results of binding experiments are analyzed using SigmaPlot software (Jandel). The binding affinity for the compounds of the invention, expressed as a K_i value, ranges from about 0.1 nanomolar to about 10 micromolar. The most active compounds of the invention have a K_i of less than 100 nanomolar and a binding selectivity of >100-fold relative to other G-protein coupled receptors, including NPY₅ and CRF₁ receptors.

[0237] hNPY 1-36 Induced GTP γ ³⁵S Binding at Human NPY Y1 Receptors Co-Expressed With G α i2, G β 11 and G γ 2 in Sf9 Cells.

[0238] Agonist induced GTP γ ³⁵S binding by G-protein coupled receptors (GPCR) provides a functional measure of G-protein activation. This assay has been widely used for many GPCR's and offers the possibility to distinguish agonists from antagonists and to determine potency and efficacy of agonists for a given GPCR [Thomas et al., 1995; O'Boyle and Lawler, 1995]. GTP γ ³⁵S binding activity was measured using a modification of a previously described method [Wieland and Jacobs, 1994]. Log-phase Sf9 cells were co-infected with separate baculoviral stocks encoding the hNPY Y1 receptor and the G-protein subunits α i2, β 1,

and γ 2 followed by culturing in Hink's TNM-FH insect medium supplemented Grace's with 4.1 mM L-Gln, 3.3 g/L LAH, 3.3 g/L ultrafiltered yeastolate and 10% heat-inactivated fetal bovine serum at 27° C. 72 hours post infection, a sample of cell suspension was analyzed for viability by trypan blue dye exclusion, and the remaining Sf9 cells were harvested via centrifugation (3000 rpm/10 min/4° C.). Each pellet was re-suspended in homogenization buffer (10 mM HEPES, 250 mM sucrose, 0.5 μ g/ml leupeptin, 2 μ g/ml Aprotinin, 200 μ M PMSF and 2.5 mM EDTA, pH 7.4) and homogenized using a Polytron (setting 5 for 30 seconds). The homogenate was centrifuged at 4° C. for 10 minutes at 536x g to pellet the nuclei. The supernatant was collected into a fresh tube and centrifuged twice in the same buffer at 48,000x g for 40 minutes. The final pellet for each membrane preparation was re-suspended in DPBS containing 5 mM EDTA and stored in aliquots at -80° C. On the day of the assay, thawed membrane homogenates were re-suspended in assay buffer (50 mM Tris pH 7.0, 120 mM NaCl, 2 mM MgCl₂, 2 mM EGTA, 0.1% BSA, 0.1 mM bacitracin, 100 KIU/mL Aprotinin, 5 μ M GDP) and added to reaction tubes at a concentration of 30 μ g/reaction tube. After adding test compounds at concentrations ranging from 10⁻¹¹M to 10⁻⁵M, reactions were initiated by the addition of both 100 pM GTP γ ³⁵S and hNPY1-36 ranging in concentration from 0.001 nM to 1.0 μ M (final volume of 0.250 ml). Following a 30 minute incubation at RT°, the reaction was terminated by vacuum filtration over GF/C filters (Pre-soaked in wash buffer, 0.1% BSA) with ice-cold wash buffer (50 mM Tris pH 7.0, 120 mM NaCl). Bound GTP γ ³⁵S was determined by liquid scintillation spectrometry. Non-specific binding was defined by 10 FM GTP γ ³⁵S and represented less than 5 percent of total binding. To estimate the EC₅₀, IC₅₀ and K_i, the results of GTP γ ³⁵S binding experiments were analyzed using SigmaPlot software (Jandel). The binding affinity for the compounds of the invention, expressed as a K_i value, ranges from about 0.1 nanomolar to about 10 micromolar. The most active compounds of the invention have a K_i of less than 100 nanomolar.

[0239] Food Deprivation Model

[0240] Subjects.

[0241] Experimentally naive and experienced male Sprague-Dawley rats (Sasco, St. Louis, Mo.) weighing 210-300g at the beginning of the experiment were used. Animals were id triple-housed in stainless steel hanging cages in a temperature (22 C $\pm$ 2) and humidity (40-70% RH) controlled animal facility with a 12:12 hour light-dark cycle. Food (Standard Rat Chow, PMI Feeds Inc., #5012) and water were available ad libitum.

[0242] Apparatus.

[0243] Consumption data was collected while the animals were housed in Nalgene Metabolic cages (Model #650-0100). Each cage was comprised of subassemblies made of clear polymethylpentene (PMP), polycarbonate (PC), or stainless steel (SS). All parts disassemble for quick and accurate data collection and for cleaning. The entire cylinder-shaped plastic and SS cage rests on a SS stand and houses one animal.

[0244] The animal is contained in the round Upper Chamber (PC) assembly (12 cm high and 20 cm in diameter) and rests on a SS floor. Two subassemblies are attached to the

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Upper Chamber. The first assembly consists of a SS feeding chamber (10 cm long, 5 cm high and 5 cm wide) with a PC feeding drawer attached to the bottom. The feeding drawer has two compartments: a food storage compartment with the capacity for approximately 50 g of pulverized rat chow, and a food spillage compartment. The animal is allowed access to the pulverized chow by an opening in the SS floor of the feeding chamber. The floor of the feeding chamber does not allow access to the food dropped into the spillage compartment.

[0245] The second assembly includes a water bottle support, a PC water bottle (100 ml capacity) and a graduated water spillage collection tube. The water bottle support funnels any spilled water into the water spillage collection tube.

[0246] The lower chamber consists of a PMP separating cone, PMP collection funnel, PMP fluid (urine) collection tube, and a PMP solid (feces) collection tube. The separating cone is attached to the top of the collection funnel, which in turn is attached to the bottom of the Upper Chamber. The urine runs off the separating cone onto the walls of the collection funnel and into the urine collection tube. The separating cone also separates the feces and funnels it into the feces collection tube.

[0247] Food consumption, water consumption, and body weight were measured with an Ohaus Portable Advanced scale (± 0.1 g accuracy).

[0248] Procedure.

[0249] Prior to the day of testing, animals were habituated to the testing apparatus by placing each animal in a Metabolic cage for 1 hour. On the day of the experiment, animals that were food deprived the previous night were weighed and assigned to treatment groups. Assignments were made using a quasi-random method utilizing the body weights to assure that the treatment groups had similar average body weight. Animals were then administered either vehicle (0.5% methyl cellulose, MC) or drug. At that time, the feeding drawer filled with pulverized chow, the filled water bottle, and the empty urine and feces collection tubes were

weighed. Two hours after drug treatment, each animal was weighed and placed in a Metabolic Cage. Following a one hour test session, animals were removed and body weight obtained. The food and water containers were then weighed and the data recorded.

[0250] Drugs.

[0251] Drug (suspended in 0.5% MC) or 0.5% MC was administered orally (PO) using a gavage tube connected to a 3 or 5ml syringe at a volume of 10 ml/kg. Drug was made into a homogenous suspension by stirring and ultrasonication for at least 1 hour prior to dosing.

[0252] Statistical Analyses.

[0253] The means and standard errors of the mean (SEM) for food consumption, water consumption, and body weight change are presented. One-way analysis of variance using Systat (5.2.1) was used to test for group differences. A significant effect is defined as having a p value of < 0.05 .

[0254] The following parameters are defined: Body weight change is the difference between the body weight of the animal immediately prior to placement in the metabolic cage and its body weight at the end of the one hour test session. Food consumption is the difference in the weight of the food drawer prior to testing and the weight following the 1 hour test session. Water consumption is the difference in the weight of the water bottle prior to testing and the weight following the 1 hour test session. The most potent compounds of the invention significantly reduce food intake and body weight gain.

[0255] The invention and the manner and process of making and using it, are now described in such full, clear, concise and exact terms as to enable any person skilled in the art to which it pertains, to make and use the same. It is to be understood that the foregoing describes preferred embodiments of the present invention and that modifications may be made therein without departing from the spirit or scope of the present invention as set forth in the claims. To particularly point out and distinctly claim the subject matter regarded as invention, the following claims conclude this specification.

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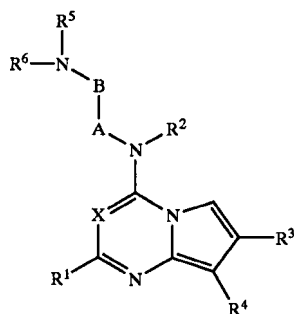
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tggggttgaa atcatttgaa aatgactaag attttcttgt cttgcttttt actgcttttg	1500
ttgtagtgtg cataaattaca ttggaacaa aaggtgtggg ctttgggggc ttctggaaat	1560
agttttgacc agacatcttt gaagtgtttt ttgtgaattt accag	1605

What is claimed is:

1. A compound of the formula



or a pharmaceutically acceptable salt, hydrate, or prodrug thereof, wherein:

X is N or CR¹⁴;R¹ is selected from H, C₁-C₆ alkyl, C₃-C₁₀ cycloalkyl, (C₃-C₁₀ cycloalkyl) C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, cyano, halo, C₁-C₆ haloalkyl, OR⁷, C₁-C₆ alkyl-OR⁷, C₁-C₆ cyanoalkyl, NR⁸R⁹, C₁-C₆ alkyl-NR⁸R⁹;P² is H,C₁-C₆ alkyl which optionally forms a C₃-C₆ aminocarbocycle or a C₂-C₅ aminoheterocycle with A or B, each of which is optionally substituted with R⁷,C₃-C₁₀ cycloalkyl, or(C₃-C₁₀ cycloalkyl) C₁-C₆ alkyl; orR² and R⁶ jointly with the 2 nitrogen atoms to which they are bound, form a C₂-C₅ aminoheterocycle optionally substituted with R⁷, orR² and A jointly form a C₃-C₆ aminocarbocycle or a C₂-C₅ aminoheterocycle optionally substituted with R⁷;A represents an alkyl chain of 1,2, or 3 carbon atoms which is optionally mono- or di-substituted at each carbon with substituents independently selected from C₁-C₆ alkyl, C₃-C₁₀ cycloalkyl, (C₃-C₁₀ cycloalkyl) C₁-C₆ alkyl, C₁-C₆ alkenyl, C₁-C₆ alkynyl, cyano, halo, C₁-C₆ haloalkyl, OR⁷, C₁-C₆ alkyl-OR⁷, C₁-C₆ cyanoalkyl, NR⁸R⁹, and C₁-C₆ alkyl-NR⁸R⁹, orA and B jointly form a C₃-C₆ carbocycle, optionally substituted at each atom with R⁷;

B represents an alkyl chain of 1,2 or 3 carbons atoms, which is optionally mono- or di-substituted at each carbon with substituents independently selected from C₁-C₆ alkyl, C₃-C₁₀ cycloalkyl, (C₃-C₁₀ cycloalkyl) C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, cyano, halo, C₁-C₆ haloalkyl, OR⁷, C₁-C₆ alkyl-OR⁷, C₁-C₆ cyanoalkyl, NR⁸R⁹, and C₁-C₆ alkyl-NR⁸R⁹, or

B and R² jointly form a C₃-C₆ aminocarbocycle, which is optionally substituted at each atom with R⁷, or

B and R⁶ jointly form a C₃-C₆ aminocarbocycle, which is optionally substituted at each atom with R⁷;

R³ is selected from H, C₁-C₆ alkyl, C₃-C₁₀ cycloalkyl, (C₃-C₁₀ cycloalkyl) C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, cyano, halo, C₁-C₆ haloalkyl, OR⁷, C₁-C₆ alkyl-OR⁷, C₁-C₆ cyanoalkyl, NR⁸R⁹, C₁-C₆ alkyl-NR⁸R⁹;

R⁴ is selected from aryl or heteroaryl, each of which is substituted with 1 to 5 substituents independently selected from C₁-C₆ alkyl, C₃-C₁₀ cycloalkyl, C₃-C₁₀ cycloalkenyl, (C₃-C₁₀ cycloalkyl) C₁-C₆ alkyl, C₁-C₆ alkenyl, C₁-C₆ alkynyl, halogen, C₁-C₆ haloalkyl, trifluoromethylsulfonyl, OR⁷, C₁-C₆ alkyl-OR⁷, NR⁸R⁹, C₁-C₆ alkyl-NR⁸R⁹, CONR⁸R⁹, C₁-C₆ alkyl-CONR⁸R⁹, COOR⁷, C₁-C₆ alkyl-COOR⁷, CN, C₁-C₆ alkyl-CN, SO₂NR⁸R⁹, SO₂R⁷, aryl, heteroaryl, heterocycloalkyl, 3-, 4-, or 5-(2-oxo-1,3-oxazolidinyl), wherein at least one of the positions ortho or para to the point of attachment of the aryl or heteroaryl ring to the pyrazole is substituted;

R⁵ is selected from:

C₁-C₆ alkyl, (C₃-C₁₀ cycloalkyl) C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, each of which is substituted with 1 to 5 groups independently selected at each occurrence from halo, C₁-C₂ haloalkyl, oxo, OR⁷, cyano, NR⁸R⁹, CONR⁸R⁹, COOR⁷, SO₂NR⁸R⁹, SO₂R⁷, NR¹¹COR¹², NR¹¹SO₂R⁷;

Aryl(C₁-C₆)alkyl, heteroaryl(C₁-C₆)alkyl, aryl(C₅-C₈)cycloalkyl, or heteroaryl(C₅-C₈)cycloalkyl, each of which is optionally substituted with 1 to 5 substituents independently selected at each occurrence from C₁-C₆ alkyl, C₃-C₁₀ cycloalkyl, C₃-C₁₀ cycloalkenyl, (C₃-C₁₀ cycloalkyl) C₁-C₆ alkyl, C₁-C₆ alkenyl, halogen, C₁-C₆ haloalkyl, trifluoromethylsulfonyl, OR⁷, NR⁸R⁹, C₁-C₆ alkyl-OR⁷, C₁-C₆ alkyl-NR⁸R⁹, CONR⁸R⁹, COOR⁷, CN, SO₂NR⁸R⁹, SO₂R⁷, aryl, heteroaryl, heterocycloalkyl, 3-, 4-, or 5-(2-oxo-1,3-oxazolidinyl), wherein any 2 adjacent substituents may be taken together to form a C₃-C₁₀ cycloalkyl ring, a C₃-C₁₀ cycloalkenyl ring or a heterocycloalkyl ring;

C₃-C₁₀ cycloalkyl or C₂-C₉ heterocycloalkyl containing one, two, or three O, S, or N atoms, each of which is optionally substituted with 1 to 6 substituents independently selected from C₁-C₆ alkyl, C₃-C₁₀ cycloalkyl, C₃-C₁₀ cycloalkenyl, (C₃-C₁₀ cycloalkyl) C₁-C₆ alkyl, C₁-C₆ alkenyl, oxo, halogen, C₁-C₆ haloalkyl, OR⁷, NR⁸R⁹, (with the proviso that when two OR⁷ or NR⁸R⁹ substituents are geminally located on the same carbon R⁷ is not H and the geminally located OR⁷ or NR⁸R⁹ substituents can

be taken together to form a C₂-C₄ ketal, oxazoline, oxazolidine, imidazoline, or imidazolidine heterocycle), C₁-C₆ alkyl-OR⁷, C₁-C₆ alkyl-NR⁸R⁹, CONR⁸R⁹, COOR⁷, CN, oxo, hydroximino, C₁-C₆ alkoximino, SO₂NR⁸R⁹, SO₂R⁷, heterocycloalkyl, aryl, heteroaryl, where aryl or heteroaryl is optionally substituted with 1 to 5 substituents independently selected at each occurrence from C₁-C₆ alkyl, C₃-C₁₀ cycloalkyl, C₃-C₁₀ cycloalkenyl, (C₃-C₁₀ cycloalkyl) C₁-C₆ alkyl, C₁-C₆ alkenyl, halogen, C₁-C₆ haloalkyl, trifluoromethylsulfonyl, OR⁷, NR⁸R⁹, C₁-C₆ alkyl-OR⁷, C₁-C₆ alkyl-NR⁸R⁹, CONR⁸R⁹, COOR⁷, CN, SO₂NR⁸R⁹, SO₂R⁷, aryl, heteroaryl, heterocycloalkyl, 3-, 4-, or 5-(2-oxo-1,3-oxazolidinyl), with the proviso that 2 adjacent substituents can optionally form together a C₃-C₁₀ cycloalkyl ring, a C₃-C₁₀ cycloalkenyl ring or a heterocycloalkyl ring;

aryl or heteroaryl, optionally substituted with 1 to 5 substituents independently selected at each occurrence from halogen, C₁-C₆ alkyl, C₃-C₁₀ cycloalkyl, C₃-C₁₀ cycloalkenyl, (C₃-C₁₀ cycloalkyl) C₁-C₆ alkyl, C₁-C₆ alkenyl, halogen, C₁-C₆ haloalkyl, trifluoromethylsulfonyl, OR⁷, NR⁸R⁹, C₁-C₆ alkyl-OR⁷, C₁-C₆ alkyl-NRR⁹, CONR⁸R⁹, COOR⁷, CN, SO₂NR⁸R⁹, SO₂R⁷, aryl, heteroaryl, heterocycloalkyl, 3-, 4-, or 5-(2-oxo-1,3-oxazolidinyl), wherein any 2 adjacent substituents may be taken together to form a C₃-C₁₀ cycloalkyl ring, a C₃-C₁₀ cycloalkenyl ring or a heterocycloalkyl ring; or

3- or 4-piperidinyl, 3-pyrrolidinyl, 3- or 4-tetrahydropyran-2-yl, 3-tetrahydrofuran-2-yl, 3- or 4-tetrahydropyran-2-yl, 3-tetrahydrofuran-2-yl, 3- or 4-tetrahydrothiopyran-2-yl, 3- or 4-(1,1-dioxo) tetrahydrothiopyran-2-yl, 1-azabicyclo[4.4.0]decyl, 8-azabicyclo[3.2.1]octan-2-yl, norbornyl, quinuclidinyl, indolin-2-one-3-yl, 2-(methoximino)-perhydroazepin-6-yl, each optionally substituted with 1 to 5 substituents independently selected at each occurrence from R⁷, C₁-C₆ alkyl-OR⁷, C₁-C₆ alkyl-NR⁸R⁹, CONR⁸R⁹, CN, COOR⁷, SO₂NR⁸R⁹, and SO₂R⁷;

R⁶ is selected from H, C₁-C₆ alkyl, C₃-C₁₀ cycloalkyl, (C₃-C₁₀ cycloalkyl) C₁-C₆ alkyl, C₂-C₄ alkenyl, aryl(C₁-C₆)alkyl, heteroaryl(C₁-C₆)alkyl each of which is optionally substituted with 1 to 5 substituents independently from halogen, C₁-C₆ haloalkyl, OR¹³, NR⁸R⁹, C₁-C₆ alkyl-OR¹³, C₁-C₆ alkyl-NR⁸R⁹, CONR⁸R⁹, COOR⁷, CN, SO₂NR⁸R⁹, and SO₂R⁷;

R⁷ is independently selected at each occurrence from H, C₁-C₆ alkyl, C₃-C₁₀ cycloalkyl, C₃-C₁₀ cycloalkenyl, (C₃-C₁₀ cycloalkyl) C₁-C₆ alkyl, C₁-C₃ haloalkyl, or heterocycloalkyl, C₁-C₈ alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, C₁-C₈ alkanoyl, aroyl, heteroaroyl, aryl, heteroaryl, C₁-C₆ arylalkyl or C₁-C₆ heteroarylalkyl each optionally substituted with 1 to 5 substituents independently selected from halogen, C₁-C₆ haloalkyl, OR¹³, NR⁸R⁹, C₁-C₆ alkyl-OR¹³, C₁-C₆ alkyl-NR⁸R⁹, CONR⁸R⁹, COOR¹³, CN, SO₂NR⁸R⁹, and SO₂R¹³, with the proviso that when R⁷ is SO₂R¹³, R¹³ cannot be H

R⁸ and R⁹ are independently selected at each occurrence from H, C₁-C₆ alkyl, C₃-C₁₀ cycloalkyl, C₂-C₆

alkenyl, C₃-C₁₀ cycloalkenyl, C₂-C₆ alkynyl, hetero-cycloalkyl, C₁-C₈ alkanoyl, aroyl, heteroaroyl, aryl, heteroaryl, C₁-C₆ arylalkyl or C₁-C₆ heteroarylalkyl, or R⁸ and R⁹, taken together, can form a C₃-C₆ aminocarbocycle or a C₂-C₅ aminoheterocycle each of which is optionally substituted with C₁-C₆ alkyl, C₃-C₁₀ cycloalkyl, C₃-C₁₀ cycloalkenyl, (C₃-C₁₀ cycloalkyl) C₁-C₆ alkyl, C₁-C₃ haloalkyl, or hetero-cycloalkyl, C₁-C₈ alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, C₁-C₈ alkanoyl, aroyl, heteroaroyl, aryl, heteroaryl, C₁-C₆ arylalkyl or C₁-C₆ heteroaryl-alkyl;

R¹¹ is selected from H, C₁-C₆ alkyl, C₃-C₁₀ cycloalkyl, (C₃-C₁₀ cycloalkyl) C₁-C₆ alkyl;

R¹² is selected from H, aryl, heteroaryl, C₁-C₆ alkyl, C₃-C₁₀ cycloalkyl, (C₃-C₁₀ cycloalkyl) C₁-C₆ alkyl, optionally substituted with OR⁷, NR⁸R⁹, C₃-C₆ aminocarbocycle, or C₂-C₅ aminoheterocycle;

R¹³ is independently selected at each occurrence from H, C₁-C₆ alkyl, C₃-C₁₀ cycloalkyl, (C₃-C₁₀ cycloalkyl) C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ haloalkyl, with the proviso that when R⁷ is SO₂R¹³, R¹³ cannot be H; and

R¹⁴ is H, C₁-C₆ alkyl, C₃-C₁₀ cycloalkyl, (C₃-C₁₀ cycloalkyl) C₁-C₆ alkyl, C₂-C₄ alkenyl, C₂-C₄ alkynyl, halo, or CN.

2. A compound according to claim 1, wherein

R⁵ is phenyl, naphthyl, 2,3-, or 4-pyridyl, 2-, 4- or 5-pyrimidinyl, triazinyl, 1-, 2- or 4-imidazolyl, 2-, 4-, or 5-oxazolyl, isoxazolyl, indolyl, pyrazolyl, quinolyl, isoquinolyl, 2-, 4-, or 5-thiazolyl, benzothiadiazolyl, 1-, 3- or 4-pyrazolyl, 1-, 3- or 4-triazolyl, 2-triazinyl, 2-pyrazinyl, 2-, or 3-furanyl, 2-, or 3-thienyl, 2-, or 3-benzothieryl, or 1-, 2- or 5-tetrazolyl each of which is optionally substituted with 1 to 5 substituents independently selected from C₁-C₆ alkyl, C₃-C₁₀ cycloalkyl, C₃-C₁₀ cycloalkenyl, (C₃-C₁₀ cycloalkyl) C₁-C₆ alkyl, C₁-C₆ alkenyl, halogen, C₁-C₆ haloalkyl, trifluoromethylsulfonyl, OR⁷, NR⁸R⁹, C₁-C₆ alkyl-OR⁷, C₁-C₆ alkyl-NR⁸R⁹, CONR⁸R⁹, COOR⁷, CN, SO₂NR⁸R⁹, SO₂R⁷, aryl, heteroaryl, heterocycloalkyl, 3-, 4-, or oxo-1,3-oxazolidinyl, wherein 2 adjacent substituents may be taken together to form a cycloalkyl ring, a C₃-C₁₀ cycloalkenyl ring or a heterocycloalkyl ring.

3. A compound according to claim 1, wherein

X is NR¹ is H, C₁-C₆ alkyl, C₃-C₁₀ cycloalkyl, or (C₃-C₁₀ cycloalkyl) C₁-C₆ alkyl; and

R⁶ is H, C₁-C₆ alkyl, C₃-C₁₀ cycloalkyl, or (C₃-C₁₀ cycloalkyl) C₁-C₆ alkyl.

4. A compound according to claim 1, wherein

X is N;

R¹ is C₁-C₆ alkyl;

R² is H or C₁-C₆ alkyl;

R³ is C₁-C₆ alkyl, trifluoromethyl, or C₁-C₆alkyl-O C₁-C₆alkyl; and

R⁶ is H, C₁-C₆ alkyl, C₃-C₁₀ cycloalkyl, or (C₃-C₁₀ cycloalkyl) C₁-C₆ alkyl.

5. A compound according to claim 1, wherein;

X is N;

R¹ is C₁-C₆ alkyl;

R² is H or C₁-C₆ alkyl;

R³ is C₁-C₆ alkyl, trifluoromethyl, or C₁-C₆alkyl-O C₁-C₆alkyl;

R⁴ is phenyl, mono, di, or trisubstituted with C₁-C₆ alkyl, C₃-C₁₀ cycloalkyl, C₃-C₁₀ cycloalkenyl, (C₃-C₁₀ cycloalkyl) C₁-C₆ alkyl, C₁-C₆ alkenyl, halogen, C₁-C₆ haloalkyl, trifluoromethylsulfonyl, OR⁷, C₁-C₆ alkyl-OR⁷, NR⁸R⁹, C₁-C₆ alkyl-NR⁸R⁹, CONR⁸R⁹, C₁-C₆ alkyl-CONR⁸R⁹, COOR⁷, C₁-C₆ alkyl-COOR⁷, CN, C₁-C₆ alkyl-CN, SO₂NR⁸R⁹, SO₂R⁷, aryl, heteroaryl, heterocycloalkyl, 3-, 4-, or 5-(2-oxo-1,3-oxazolidinyl), wherein at least one of the positions ortho or para to the point of attachment of the aryl or heteroaryl ring to the pyrazole is substituted,

R⁶ is H, C₁-C₆ alkyl, C₃-C₁₀ cycloalkyl, or (C₃-C₁₀ cycloalkyl) C₁-C₆ alkyl; and R⁷, R⁸, and R⁹ are as defined in claim 1.

6. A compound according to claim 1, wherein:

X is N;

R¹ is C₁-C₆ alkyl;

R² is H or C₁-C₆ alkyl;

R³ is C₁-C₆ alkyl, trifluoromethyl, or C₁-C₆alkyl-O C₁-C₆alkyl;

R⁴ is phenyl, mono, di, or trisubstituted with C₁-C₆ alkyl, C₃-C₁₀ cycloalkyl, C₃-C₁₀ cycloalkenyl, (C₃-C₁₀ cycloalkyl) C₁-C₆ alkyl, C₁-C₆ alkenyl, halogen, C₁-C₆ haloalkyl, trifluoromethylsulfonyl, OR⁷, C₁-C₆ alkyl-OR⁷, NR⁸R⁹, C₁-C₆ alkyl-NR⁸R⁹, CONR⁸R⁹, C₁-C₆ alkyl-CONR⁸R⁹, COOR⁷, C₁-C₆ alkyl-COOR⁷, CN, C₁-C₆ alkyl-CN, SO₂NR⁸R⁹, SO₂R⁷, aryl, heteroaryl, heterocycloalkyl, 3-, 4-, or 5-(2-oxo-1,3-oxazolidinyl), wherein at least one of the positions ortho or para to the point of attachment of the aryl or heteroaryl ring to the pyrazole is substituted,

R is

C₁-C₆ alkyl, C₃-C₁₀cycloalkyl, (C₃-C₁₀ cycloalkyl) C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, each of which is substituted with 1 to 5 groups independently selected at each occurrence from halo, C₁-C₂ haloalkyl, OR⁷, cyano, NR⁸R⁹, CONR⁸R⁹, COOR⁷, SO₂NR⁸R⁹, SO₂R⁷, NR¹¹COR¹², NR¹¹SO₂R⁷; or

3- or 4-piperidinyl, 3-pyrrolidinyl, 3- or 4-tetrahydro-pyranyl, 3-tetrahydrofuran-3-yl, 3- or 4-tetrahydrothiopyran-3-yl, 3- or 4-(1,1-dioxo) tetrahydrothiopyran-3-yl, 1-azabicyclo[4.4.0]decyl, 8-azabicyclo[3.2.1]octan-8-yl, norbornyl, quinuclidinyl, indolin-2-one-3-yl, 2-(methoximino)-perhydroazepin-6-yl, each optionally substituted with 1 to 5 substituents independently selected at each occurrence from R⁷, C₁-C₆ alkyl-OR⁷, C₁-C₆ alkyl-NR⁸R⁹, CONR⁸R⁹, CN, COOR⁷, SO₂NR⁸R⁹, and SO₂R⁷;

R⁶ is H, C₁-C₆ alkyl, C₃-C₁₀ cycloalkyl, or (C₃-C₁₀ cycloalkyl) C₁-C₆ alkyl; and

R⁷, R⁸, R⁹, R¹¹, and R¹² are as defined in claim 1.

7. A compound according to claim 1, wherein;

X is CH;

R¹ is H, C₁-C₆ alkyl, C₃-C₁₀ cycloalkyl, or (C₃-C₁₀ cycloalkyl) C₁-C₆ alkyl; and

R⁶ is H, C₁-C₆ alkyl, C₃-C₁₀ cycloalkyl, or (C₃-C₁₀ cycloalkyl) C₁-C₆ alkyl.

8. A compound according to claim 1, wherein:

X is CH;

R¹ is C₁-C₆ alkyl;

R² is H or C₁-C₆ alkyl;

R³ is C₁-C₆ alkyl, trifluoromethyl, or C₁-C₆alkyl-O C₁-C₆alkyl; and

R⁶ is H, C₁-C₆ alkyl, C₃-C₁₀ cycloalkyl, or (C₃-C₁₀ cycloalkyl) C₁-C₆ alkyl.

9. A compound according to claim 1, wherein;

X is CH;

R¹ is C₁-C₆ alkyl;

R² is H or C₁-C₆ alkyl;

R³ is C₁-C₆ alkyl, trifluoromethyl, or C₁-C₆alkyl-O C₁-C₆alkyl;

R⁴ is phenyl, mono, di, or trisubstituted with C₁-C₆ alkyl, C₃-C₁₀ cycloalkyl, C₃-C₁₀ cycloalkenyl, (C₃-C₁₀ cycloalkyl) C₁-C₆ alkyl, C₁-C₆ alkenyl, halogen, C₁-C₆ haloalkyl, trifluoromethylsulfonyl, OR⁷, C₁-C₆ alkyl-OR⁷, NR⁸R⁹, C₁-C₆ alkyl-NR⁸R⁹, CONRR⁹, C₁-C₆ alkyl-CONRR⁹, COOR⁷, C₁-C₆ alkyl-COOR⁷, CN, C₁-C₆ alkyl-CN, SO₂NRR⁹, SO₂R⁷, aryl, heteroaryl, heterocycloalkyl, 3-, 4-, or 5-(2-oxo-1,3-oxazolidinyl), wherein at least one of the positions ortho or para to the point of attachment of the aryl or heteroaryl ring to the pyrazole is substituted,

R⁶ is H, C₁-C₆ alkyl, C₃-C₁₀ cycloalkyl, or (C₃-C₁₀ cycloalkyl) C₁-C₆ alkyl; and

R⁷, R⁸, and R⁹ are as defined in claim 1.

10. A compound according to claim 1, wherein:

X is CH;

R¹ is C₁-C₆ alkyl;

R² is H or C₁-C₆ alkyl;

R³ is C₁-C₆ alkyl, trifluoromethyl, or C₁-C₆alkyl-O C₁-C₆alkyl;

R⁴ is phenyl, mono, di, or trisubstituted with C₁-C₆ alkyl, C₃-C₁₀ cycloalkyl, C₃-C₁₀ cycloalkenyl, (C₃-C₁₀ cycloalkyl) C₁-C₆ alkyl, C₁-C₆ alkenyl, halogen, C₁-C₆ haloalkyl, trifluoromethylsulfonyl, OR⁷, C₁-C₆ alkyl-OR⁷, NR⁸R⁹, C₁-C₆ alkyl-NR⁸R⁹, CONR⁸R⁹, C₁-C₆ alkyl-CONR⁸R⁹, COOR⁷, C₁-C₆ alkyl-COOR⁷, CN, C₁-C₆ alkyl-CN, SO₂NRR⁹, SO₂R⁷, aryl, heteroaryl, heterocycloalkyl, 3-, 4-, or 5-(2-oxo-1,3-oxazolidinyl), wherein at least one of the positions ortho or para to the point of attachment of the aryl or heteroaryl ring to the pyrazole is substituted,

R⁵ is

C₁-C₆ alkyl, C₃-C₁₀cycloalkyl, (C₃-C₁₀ cycloalkyl) C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, each of which is substituted with 1 to 5 groups independently selected at each occurrence from halo, C₁-C₂ haloalkyl, OR⁷, cyano, NR⁸R⁹, CONR⁸R⁹, COOR⁷, SO₂NR⁸R⁹, SO₂R⁷, NR¹¹COR¹², NR¹¹SO₂R⁷; or

3- or 4-piperidinyl, 3-pyrrolidinyl, 3- or 4-tetrahydropyranyl, 3-tetrahydrofuranyl, 3- or 4- tetrahydropyranyl, 3-tetrahydrofuranyl, 3- or 4-tetrahydrothiopyranyl, 3- or 4-(1,1 -dioxo) tetrahydrothiopyranyl, 1-azabicyclo[4.4.0]decyl, 8-H azabicyclo[3.2.1]octanyl, norbomyl, quinuclidinyl, indolin-2-one-3-yl, 2-(methoximino)-perhydroazepin-6-yl, each optionally substituted with 1 to 5 substituents independently selected at each occurrence from R⁷, C₁-C₆ alkyl-OR⁷, C₁-C₆ alkyl-NR⁸R⁹, CONR⁸R⁹, CN, COOR⁷ SO₂NR⁸R⁹, and SO₂R⁷;

R⁶ is H, C₁-C₆ alkyl, C₃-C₁₀ cycloalkyl, or (C₃-C₁₀ cycloalkyl) C₁-C₆ alkyl; and

R⁷, R⁸, R⁹, R¹¹, and R¹² are as defined in claim 1.

11. A method for treating eating disorders and cardiovascular disorders comprising administering to a patient suffering from an eating disorder or cardiovascular disorder a compound according to claim 1.

12. A pharmaceutical composition comprising a compound according to claim 1 and a pharmaceutically acceptable carrier.

13. A packaged pharmaceutical composition comprising the pharmaceutical composition of claim 12 in a container and comprising instructions for using the composition to treat a patient suffering from an eating disorder or hypertension.

14. A method for localizing NPY receptors in tissue section samples comprising:

contacting with a sample of tissue a detectably-labeled compound of claim 1 under conditions that permit binding of the compound to the sample of tissue; washing the tissue sample to remove unbound compound; and detecting the bound compound.

15. The method of claim 14, wherein the compound is radiolabeled.

16. A method of inhibiting the binding of NPY to the NPY1 receptor, which method comprises contacting, in the presence of NPY, a solution comprising a compound of claim 1 with cells expressing the NPY1 receptor, wherein the compound is present in the solution at a concentration sufficient to reduce levels of NPY binding to cells expressing the NPY1 receptor in vitro.

17. A method for altering the signal-transducing activity of a cell surface NPY1 receptor, said method comprising contacting cells expressing such a receptor with a solution comprising a compound according to claim 1, wherein the compound is present in the solution at a concentration sufficient to reduce levels of NPY binding to cells expressing the NPY1 receptor in vitro.

18. A compound according to any one of claim 1 wherein in an assay of NPY binding the compound exhibits an K_i of 1 micromolar or less.

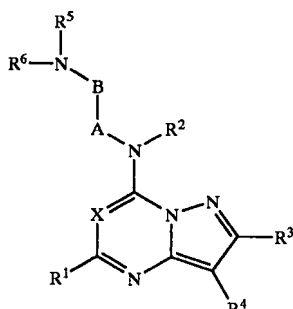
19. A compound according to any one of claim 1 wherein in an assay of NPY binding the compound exhibits an K_i of 100 nanomolar or less.

20. A compound according to any one of claim 1 wherein in an assay of NPY binding the compound exhibits an K_i of 100 nanomolar 10 nanomolar or less.

21. A method for treating obesity or bulimia nervosa which comprises administering an effective amount of a compound according to claim 1 to a patient in need thereof.

22. A method for treating hypertension which comprises administering an effective amount of a compound according to claim 1 to a patient in need thereof.

23. A compound in accordance with formula I



wherein:

X is N or CR¹⁴;

R¹ is selected from H, C₁-C₆ alkyl, C₃-C₆ cycloalkyl, (C₃-C₁₀ cycloalkyl) C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, cyano, halo, C₁-C₆ haloalkyl, OR⁷, C₁-C₆ alkyl-OR⁷, C₁-C₆ cyanoalkyl, NR⁸R⁹, C₁-C₆ alkyl-NR⁸R⁹;

R² is H,

C₁-C₆ alkyl which optionally forms a C₃-C₆ aminocarbocycle or a C₂-C₅ aminoheterocycle with A or B, each optionally substituted at each occurrence with R⁷,

C₃-C₁₀ cycloalkyl, or

(C₃-C₁₀ cycloalkyl) C₁-C₆ alkyl;

or R² and R⁶ jointly form with the 2 nitrogen atoms to which they are bound form a C₂-C₅ aminoheterocycle optionally substituted at each occurrence with R⁷;

A is (CH₂)_m, where m is 1,2 or 3 and is optionally mono- or di-substituted on each occurrence with C₁-C₆ alkyl, C₃-C₁₀ cycloalkyl, (C₃-C₁₀ cycloalkyl) C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, cyano, halo, C₁-C₆ haloalkyl, OR⁷, C₁-C₆ alkyl-OR⁷, C₁-C₆ cyanoalkyl, NR⁸R⁹, C₁-C₆ alkyl-NR⁸R⁹, or A and B jointly form a C₃-C₆ carbocycle, optionally substituted at each occurrence with R⁷,

or, A and R² jointly form a C₃-C₆ aminocarbocycle or a C₂-C₅ aminoheterocycle optionally substituted at each occurrence with R⁷;

aminoheterocycle optionally substituted at each occurrence with R⁷;

B is (CH₂)_n, where n is 1,2 or 3 and is optionally mono- or di-substituted on each occurrence with C₁-C₆ alkyl, C₃-C₁₀ cycloalkyl, (C₃-C₁₀ cycloalkyl) C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, cyano, halo, C₁-C₆

haloalkyl, OR⁷, C₁-C₆ alkyl-OR⁷, C₁-C₆ cyanoalkyl, NR⁸R⁹, and C₁-C₆ alkyl-NR⁸R⁹;

or, as mentioned above, B and A jointly form a C₃-C₆ carbocycle, optionally substituted at each occurrence with R⁷

or, as mentioned above, B and R² jointly form a C₁-C₆ aminocarbocycle or a C₂-C₅ aminoheterocycle optionally substituted at each occurrence with R⁷;

R³ is selected from H, C₁-C₆ alkyl, C₃-C₁₀ cycloalkyl, (C₃-C₁₀ cycloalkyl) C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, cyano, halo, C₁-C₆ haloalkyl, OR⁷, C₁-C₆ alkyl-OR⁷, C₁-C₆ cyanoalkyl, NR⁸R⁹, C₁-C₆ alkyl-NR⁸R⁹;

R⁴ is selected from aryl or heteroaryl, each of which is substituted with 1 to 5 substituents independently selected from C₁-C₆ alkyl, C₃-C₁₀ cycloalkyl, C₃-C₁₀ cycloalkenyl, (C₃-C₁₀ cycloalkyl) C₁-C₆ alkyl, C₁-C₆ alkenyl, C₁-C₆ alkynyl, halogen, C₁-C₆ haloalkyl, trifluoromethylsulfonyl, OR⁷, C₁-C₆ alkyl-OR⁷, NR⁸R⁹, C₁-C₆ alkyl-NR⁸R⁹, CONR⁸R⁹, C₁-C₆ alkyl-CONR⁸R⁹, COOR⁷, C₁-C₆ alkyl-COOR⁷, CN, C₁-C₆ alkyl-CN, SO₂NR⁸R⁹, SO₂R⁷, aryl, heteroaryl, heterocycloalkyl, 3-, 4-, or 5-(2-oxo-1,3-oxazolidinyl), wherein at least one of the positions ortho or para to the point of attachment of the aryl or heteroaryl ring to the pyrazole is substituted;

R⁵ is selected from:

C₁-C₆ alkyl, (C₃-C₁₀ cycloalkyl) C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, each of which is substituted with 1 to 5 groups independently selected at each occurrence from halo, C₁-C₂ haloalkyl, oxo, OR⁷, cyano, NR⁸R⁹, CONR⁸R⁹, COOR⁷, SO₂NR⁸R⁹, SO₂R⁷, NR¹¹COR¹², NR¹¹SO₂R⁷;

Aryl(C₁-C₆)alkyl, heteroaryl(C₁-C₆)alkyl, aryl(C₃-C₆)cycloalkyl, or heteroaryl(C₃-C₆)cycloalkyl, where aryl is phenyl or naphthyl, and heteroaryl is 2-, 3- or 4-pyridyl, 2-, 4-, or 5-pyrimidinyl, triazinyl, 1-, 2-, or 4-imidazolyl, 2-, 4-, or 5-oxazolyl, isoxazolyl, indolyl, pyrazolyl, quinolyl, isoquinolyl, 2-, 4-, or 5-thiazolyl, benzothiadiazolyl, 1-, 3- or 4-pyrazolyl, 1-, 3- or 4-triazolyl, 2-triazinyl, 2-pyrazinyl, 2-, or 3-furanyl, 2-, or 3-thienyl, 2-, or 3-benzothienyl, or 1-, 2- or 5-tetrazolyl, each of which is optionally substituted with 1 to 5 substituents independently selected at each occurrence from C₁-C₆ alkyl, C₃-C₁₀ cycloalkyl, C₃-C₁₀ cycloalkenyl, (C₃-C₁₀ cycloalkyl) C₁-C₆ alkyl, C₁-C₆ alkenyl, halogen, C₁-C₆ haloalkyl, trifluoromethylsulfonyl, OR⁷, NR⁸R⁹, C₁-C₆ alkyl-OR⁷, C₁-C₆ alkyl-NR⁸R⁹, CONR⁸R⁹, COOR⁷, CN, SO₂NR⁸R⁹, SO₂R⁷, aryl, heteroaryl, heterocycloalkyl, 3-, 4-, or 5-(2-oxo-1,3-oxazolidinyl), wherein any 2 adjacent substituents may be taken together to form a C₃-C₁₀ cycloalkyl ring, a C₃-C₁₀ cycloalkenyl ring or a heterocycloalkyl ring;

C₃-C₁₀ cycloalkyl optionally substituted with 1 to 6 substituents independently selected from C₁-C₆ alkyl, C₃-C₁₀ cycloalkyl, C₃-C₁₀ cycloalkenyl, (C₃-C₁₀ cycloalkyl) C₁-C₆ alkyl, C₁-C₆ alkenyl, oxo, halogen, C₁-C₆ haloalkyl, OR⁷, NR⁸R⁹, (with the proviso that when two OR⁷ or NR⁸R⁹ substituents are geminally

located on the same carbon R^7 is not H and the geminally located OR^7 or NR^8R^9 substituents can be taken together to form a C_2-C_4 ketal, oxazoline, oxazolidine, imidazoline, or imidazolidine heterocycle), C_1-C_6 alkyl- OR^7 , C_1-C_6 alkyl- NR^8R^9 , $CONRR^9$, $COOR^7$, CN, oxo, is hydroximino, C_1-C_6 alkoximino, $SO_2NR^8R^9$, SO_2R^7 , heterocycloalkyl, aryl, heteroaryl, where aryl or heteroaryl is optionally substituted with 1 to 5 substituents independently selected at each occurrence from C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, C_3-C_{10} cycloalkenyl, (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl, C_1-C_6 alkenyl, halogen, C_1-C_6 haloalkyl, trifluoromethylsulfonyl, OR^7 , NR^8R^9 , C_1-C_6 alkyl- OR^7 , C_1-C_6 alkyl- NR^8R^9 , $CONRR^9$, $COOR^7$, CN, $SO_2NR^8R^9$, SO_2R^7 , aryl, heteroaryl, heterocycloalkyl, 3-, 4-, or 5-(2-oxo-1,3-oxazolidinyl), with the proviso that 2 adjacent substituents can optionally form together a C_3-C_{10} cycloalkyl ring, a C_3-C_{10} cycloalkenyl ring or a heterocycloalkyl ring;

aryl or heteroaryl, optionally substituted with 1 to 5 substituents independently selected at each occurrence from halogen, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, C_3-C_{10} cycloalkenyl, (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl, C_1-C_6 alkenyl, halogen, C_1-C_6 haloalkyl, trifluoromethylsulfonyl, OR^7 , NR^8R^9 , C_1-C_6 alkyl- OR^7 , C_1-C_6 alkyl- NR^8R^9 , $CONRR^9$, $COOR^7$, CN, $SO_2NR^8R^9$, SO_2R^7 , aryl, heteroaryl, heterocycloalkyl, 3-, 4-, or 5-(2-oxo-1,3-oxazolidinyl), wherein any 2 adjacent substituents may be taken together to form a C_3-C_{10} cycloalkyl ring, a C_3-C_{10} cycloalkenyl ring or a heterocycloalkyl ring; or

3- or 4-piperidinyl, 3-pyrrolidinyl, 3- or 4-tetrahydropyran-1-yl, 3-tetrahydrofuran-2-yl, 3- or 4-tetrahydropyran-2-yl, 3-tetrahydrofuran-3-yl, 3- or 4-tetrahydrothiopyran-2-yl, 3- or 4-(1,1-dioxo) tetrahydrothiopyran-2-yl, 1-azabicyclo[4.4.0]decyl, 8-azabicyclo[3.2.1]octyl, norbornyl, quinuclidinyl, indolin-2-one-3-yl, 2-(methoximino)-perhydroazepin-6-yl, each optionally substituted with 1 to 5 substituents independently selected at each occurrence from R^7 , C_1-C_6 alkyl- OR^7 , C_1-C_6 alkyl- NR^8R^9 , $CONRR^9$, CN, $COOR^7$, $SO_2NR^8R^9$, and SO_2R^7 ;

R^6 is selected from H, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl, C_2-C_4 alkenyl, aryl, (C_1-C_6 alkyl, heteroaryl, (C_1-C_6 alkyl) each of which is optionally substituted with 1 to 5 substituents independently from halogen, C_1-C_6 haloalkyl, OR^{13} , NR^8R^9 , C_1-C_6 alkyl- OR^{13} , C_1-C_6 alkyl- NR^8R^9 , $CONRR^9$, $COOR^{13}$, CN, $SO_2NR^8R^9$, and SO_2R^{13} ;

or R^6 and R^2 jointly form with the two nitrogens to which they are bound a C_2-C_5 aminocarbocycle optionally substituted at each occurrence by R^7 ;

R^7 is independently selected at each occurrence from H, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, C_3-C_{10} cycloalkenyl, (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl, C_2-C_4 alkenyl, or heterocycloalkyl, C_1-C_8 alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, C_1-C_8 alkanoyl, aroyl, heteroaryloxy, aryl, heteroaryl, C_1-C_6 arylalkyl or C_1-C_6 heteroarylalkyl each optionally substituted with 1 to 5 substituents independently selected from halogen, C_1-C_6 haloalkyl, OR, NR^8R^9 , C_1-C_6 alkyl- OR^{13} , C_1-C_6 alkyl- NR^8R^9 , $CONRR^9$, $COOR^{13}$, CN, $SO_2NR^8R^9$, and SO_2R^{13} , with the proviso that when R^7 is SO_2R^{13} , R^{13} cannot be H;

R^8 and R^9 are independently selected at each occurrence from H, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_3-C_{10} cycloalkenyl, C_2-C_6 alkynyl, heterocycloalkyl, C_1-C_8 alkanoyl, aroyl, heteroaryloxy, aryl, heteroaryl, C_1-C_6 arylalkyl or C_1-C_6 heteroarylalkyl, or R^8 and R^9 , taken together, can form a C_3-C_6 aminocarbocycle or a C_2-C_5 aminoheterocycle each of which is optionally substituted with C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, C_3-C_{10} cycloalkenyl, (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl, C_1-C_3 haloalkyl, or heterocycloalkyl, C_1-C_8 alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, C_1-C_8 alkanoyl, aroyl, heteroaryloxy, aryl, heteroaryl, C_1-C_6 arylalkyl or C_1-C_6 heteroarylalkyl;

R^{11} is selected from H, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl;

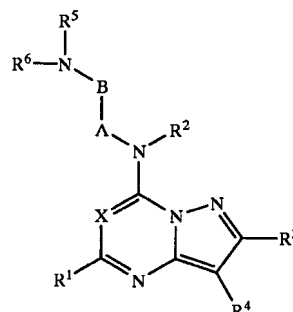
R^{12} is selected from H, aryl, heteroaryl, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl, optionally substituted with OR^7 , NR^8R^9 , C_3-C_6 aminocarbocycle, or C_2-C_5 aminoheterocycle;

R^{13} is independently selected at each occurrence from H, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 haloalkyl, with the proviso that when R^7 is SO_2R^{13} , R^{13} cannot be H; and

R^{14} is H, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl, C_2-C_4 alkenyl, C_2-C_4 alkynyl, halo, or CN.

or a pharmaceutically acceptable salt, hydrate or prodrug thereof.

24. A compound in accordance with formula I



or a pharmaceutically acceptable salt, hydrate or prodrug thereof wherein:

X is N or CR^{14} ;

R^1 is selected from H, C_1-C_6 alkyl, C_3-C_6 cycloalkyl, (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, cyano, halo, C_1-C_6 haloalkyl, OR^7 , C_1-C_6 alkyl- OR^7 , C_1-C_6 cyanoalkyl, NR^8R^9 , C_1-C_6 alkyl- NR^8R^9 ;

R is H, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl or (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl, wherein each alkyl or cycloalkyl group may be optionally substituted with 1 to 3 R^7 groups;

R^2 may optionally join with R^5 and the two and the 2 nitrogen atoms to which they are bound to form a 6 to 10 membered heterocyclic ring optionally substituted

at each carbon with R⁷ or R² and A may optionally join to form a 3 to 8 membered heterocyclic ring optionally substituted at each carbon with R^{7a}; or

or R¹ and B optionally join to form a 4 to 10 membered heterocyclic ring optionally substituted at each carbon with R⁷¹ or

A represents an alkyl chain of 1, 2 or 3 carbon atoms which is optionally mono- or di-substituted at each carbon with substituents independently selected from C₁-C₆ alkyl, C₃-C₁₀ cycloalkyl, (C₃-C₁₀ cycloalkyl) C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, cyano, halo, C₁-C₆ haloalkyl, OR⁷, C₁-C₆ alkyl-OR⁷, C₁-C₆ cyanoalkyl, NR^{8R9}, C₁-C₆ alkyl-NR^{8R9}, or A and B jointly form a C₃-C₆ carbocycle, optionally substituted at each occurrence with R^{7a};

B represents an alkyl chain of 1, 2 or 3 carbons atoms, which is optionally mono- or di-substituted at each carbon with substituents independently selected from

B represents an alkyl chain of 1, 2 or 3 carbons atoms, which is optionally mono- or di-substituted at each carbon with substituents independently selected from C₁-C₆ alkyl, C₃-C₁₀ cycloalkyl, (C₃-C₁₀ cycloalkyl) C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, cyano, halo, C₁-C₆ haloalkyl, OR⁷, C₁-C₆ alkyl-OR⁷, C₁-C₆ cyanoalkyl, NR^{8R9}, and C₁-C₆ alkyl-NR^{8R9}, or

B and R⁵ may jointly form a 4 to 7 membered heterocyclic ring, which is optionally substituted at each atom with R^{7a};

R³ is selected from H, C₁-C₆ alkyl, C₃-C₁₀ cycloalkyl, (C₃-C₁₀ cycloalkyl) C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, cyano, halo, C₁-C₆ haloalkyl, OR⁷, C₁-C₆ alkyl-OR⁷, C₁-C₆ cyanoalkyl, NR^{8R9}, C₁-C₆ allyl-NR^{8R9};

R⁴ is selected from aryl or heteroaryl, each of which is substituted with 1 to 5 substituents independently selected from C₁-C₆ alkyl, C₃-C₁₀ cycloalkyl, C₃-C₁₀ cycloalkenyl, (C₃-C₁₀ cycloalkyl) C₁-C₆ alkyl, C₁-C₆ alkenyl, C₁-C₆ alkynyl, halogen, C₁-C₆ haloalkyl, trifluoromethylsulfonyl, OR⁷, C₁-C₆ alkyl-OR⁷, NR^{8R9}, C₁-C₆ alkyl-NR^{8R9}, CONR^{8R9}, C₁-C₆ alkyl-CONR^{8R9}, COOR⁷, C₁-C₆ alkyl-COOR⁷, CN, C₁-C₆ alkyl-CN, SO₂NR^{8R9}, SO₂R⁷, aryl, heteroaryl, heterocycloalkyl, 3-, 4-, or 5-(2-oxo-1,3-oxazolidinyl), C₂-C₄ alkynyl wherein at least one of the positions ortho or para to the point of attachment of the aryl or heteroaryl ring to the pyrazole is substituted;

R⁵ is selected from:

C₁-C₆ alkyl, (C₃-C₁₀ cycloalkyl) C₁-C₆ alkyl, each of which is substituted with 1 to 5 groups independently selected at each occurrence from C₁-C₆ alkyl, C₃-C₁₀ cycloalkyl, C₃-C₁₀ cycloalkenyl, (C₃-C₁₀ cycloalkyl) C₁-C₆ alkyl, C₂-C₆ alkenyl, halogen, C₁-C₆ haloalkyl, OR⁷, NR^{8R9}, (with the proviso that when two OR⁷ or NR^{8R9} substituents are geminally located on the same carbon R⁷ is not H and the geminally located OR⁷ or NR^{8R9} substituents can be taken together to form a C₂-C₄ ketal, oxazoline, oxazolidine, imidazoline, or imidazolidine heterocycle), C₁-C₆ alkyl-OR⁷, C₁-C₆ alkyl-NR^{8R9}, CONR^{8R9}, COOR⁷, CN, oxo, hydroximino, C₁-C₆ alkoximino, SO₂NR^{8R9}, SO₂R⁷, hetero-

cycloalkyl, aryl, heteroaryl, where aryl or heteroaryl is optionally substituted with 1 to 5 substituents independently selected at each occurrence from C₁-C₆ alkyl, C₃-C₁₀ cycloalkyl, C₃-C₁₀ cycloalkenyl, (C₃-C₁₀ cycloalkyl) C₁-C₆ alkyl, C₂-C₆ alkenyl, halogen, C₁-C₆ haloalkyl, trifluoromethylsulfonyl, OR⁷, NR^{8R9}, C₁-C₆ alkyl-OR⁷, C₁-C₆ alkyl-NR^{8R9}, CONR^{8R9}, COOR⁷, CN, SO₂NR^{8R9}, SO₂R⁷, aryl, heteroaryl, heterocycloalkyl, 3-, 4-, or 5-(2-oxo-1,3-oxazolidinyl), with the proviso that 2 adjacent substituents can optionally form together a C₃-C₁₀ cycloalkyl ring, a C₃-C₁₀ cycloalkenyl ring or a heterocycloalkyl ring; with the proviso that C₁-C₆ alkyl group is substituted with a C₁-C₆ alkyl group to give a C₇-C₁₀ alkyl group

Aryl(C₁-C₆) alkyl, heteroaryl(C₁-C₆)alkyl, aryl(C₃-C₁₀)cycloalkyl, or heteroaryl(C₃-C₁₀)cycloalkyl, each of which is optionally substituted with 1 to 5 substituents independently selected at each occurrence from C₁-C₆ alkyl, C₃-C₁₀ cycloalkyl, C₃-C₁₀ cycloalkenyl, (C₃-C₁₀ cycloalkyl) C₁-C₆ alkyl, C₁-C₆ alkenyl, halogen, C₁-C₆ haloalkyl, trifluoromethylsulfonyl, OR⁷, NR^{8R9}, C₁-C₆ alkyl-OR⁷, C₁-C₆ alkyl-NR^{8R9}, CONR^{8R9}, COOR⁷, CN, SO₂NR^{8R9}, SO₂R⁷, aryl, heteroaryl, heterocycloalkyl, 3-, 4-, or 5-(2-oxo-1,3-oxazolidinyl), wherein any 2 adjacent substituents may be taken together to form a C₃-C₁₀ cycloalkyl ring, a C₃-C₁₀ cycloalkenyl ring or a heterocycloalkyl ring;

C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₃-C₁₀ cycloalkenyl, or a 3 to 10 membered mono- or bicyclic heterocycle containing 1-3 O, S or N atoms, each of which is optionally substituted with 1 to 6 substituents independently selected from C₁-C₆ alkyl, C₃-C₁₀ cycloalkyl, C₃-C₁₀ cycloalkenyl, (C₃-C₁₀ cycloalkyl) C₁-C₆ alkyl, C₂-C₆ alkenyl, halogen, C₁-C₆ haloalkyl, OR⁷, NR^{8R9}, (with the proviso that when two OR⁷ or NR^{8R9} substituents are geminally located on the same carbon R⁷ is not H and the geminally located OR⁷ or NR^{8R9} substituents can be taken together to form a C₂-C₄ ketal, oxazoline, oxazolidine, imidazoline, or imidazolidine heterocycle), C₁-C₆ alkyl-OR⁷, C₁-C₆ alkyl-NR^{8R9}, CONR^{8R9}, COOR⁷, CN, oxo, hydroximino, C₁-C₆ alkoximino, SO₂NR^{8R9}, SO₂R⁷, COR⁷, heterocycloalkyl, aryl, C₁-C₆ alkylaryl, heteroaryl, C₁-C₆ alkylheteroaryl where aryl or heteroaryl is optionally substituted with 1 to 5 substituents independently selected at each occurrence from C₁-C₆ alkyl, C₃-C₁₀ cycloalkyl, C₃-C₁₀ cycloalkenyl, (C₃-C₁₀ cycloalkyl) C₁-C₆ alkyl, C₂-C₆ alkenyl, halogen, C₁-C₆ haloalkyl, trifluoromethylsulfonyl, OR⁷, NR^{8R9}, C₁-C₆ alkyl-OR⁷, C₁-C₆ alkyl-NR^{8R9}, CONR^{8R9}, COOR⁷, CN, SO₂NR^{8R9}, SO₂R⁷, aryl, heteroaryl, heterocycloalkyl, 3-, 4-, or 5-(2-oxo-1,3-oxazolidinyl), with the proviso that 2 adjacent substituents can optionally form together a C₃-C₁₀ cycloalkyl ring, a C₃-C₁₀ cycloalkenyl ring or a heterocycloalkyl ring; or

aryl or heteroaryl, optionally substituted with 1 to 5 substituents independently selected at each occurrence from halogen, C₁-C₆ alkyl, C₃-C₁₀ cycloalkyl, C₃-C₁₀ cycloalkenyl, (C₃-C₁₀ cycloalkyl) C₁-C₆ alkyl, C₂-C₆ alkenyl, halogen, C₁-C₆ haloalkyl, trifluoromethylsulfonyl, OR⁷, NR^{8R9}, C₁-C₆ alkyl-OR⁷, C₁-C₆ alkyl-NR^{8R9}, CONR^{8R9}, COOR⁷, CN, SO₂NR^{8R9}, SO₂R⁷, aryl, heteroaryl, heterocycloalkyl, 3-, 4-, or 5-(2-oxo-

- 1,3-oxazolidinyl), wherein any 2 adjacent substituents may be taken together to form a C₃-C₁₀ cycloalkyl ring, a C₃-C₁₀ cycloalkenyl ring or a heterocycloalkyl ring;
- R⁶ is selected from H, C₁-C₆ alkyl, C₃-C₁₀ cycloalkyl, (C₃-C₁₀ cycloalkyl) C₁-C₆ alkyl, C₂-C₄ alkenyl, aryl(C₁-C₆)alkyl, heteroaryl(C₁-C₆)alkyl each of which is optionally substituted with 1 to 5 substituents independently from halogen, C₁-C₆ haloalkyl, OR¹³, NR⁸R⁹, C₁-C₆ alkyl-OR³, C₁-C₆ alkyl-NR⁸R⁹, CONR⁸R⁹, COOR⁷, CN, SO₂NR⁸R⁹, and SO₂R⁷;
- R⁷ is independently selected at each occurrence from H, C₁-C₆ alkyl, C₃-C₁₀ cycloalkyl, C₃-C₁₀ cycloalkenyl, (C₃-C₁₀ cycloalkyl) C₁-C₆ alkyl, C₁-C₃ haloalkyl, or heterocycloalkyl, aryl, heteroaryl, C₁-C₆ arylalkyl or C₁-C₆ heteroarylalkyl each optionally substituted with 1 to 5 substituents independently selected from halogen, C₁-C₆ haloalkyl, OR¹³, NR⁸R⁹, C₁-C₆ alkyl-OR¹³, C₁-C₆ alkyl-NR⁸R⁹, CONR⁸R⁹, COOR¹³, CN, SO₂NR⁸R⁹, and SO₂R¹³;
- R^{7a} is independently selected at each occurrence from H, C₁-C₆ alkyl, C₃-C₁₀ cycloalkyl, C₃-C₁₀ cycloalkenyl, (C₃-C₁₀ cycloalkyl) C₁-C₆ alkyl, C₁-C₃ haloalkyl, or heterocycloalkyl, C₁-C₈ alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, C₁-C₈ alkanoyl, aroyl, heteroaroyl, aryl, heteroaryl, C₁-C₆ arylalkyl or C₁-C₆ heteroarylalkyl each optionally substituted with 1 to 5 substituents independently selected from halogen, C₁-C₆ haloalkyl, OR¹³, NR⁸R⁹, C₁-C₆ alkyl-OR¹³, C₁-C₆ alkyl-NR⁸R⁹, CONR⁸R⁹, COOR¹³, CN, SO₂NR⁸R⁹, and SO₂R¹³, with the proviso that when R^{7a} is SO₂R¹³, R cannot be H;
- R⁸ and R⁹ are independently selected at each occurrence from H, C₁-C₆ alkyl, C₃-C₁₀ cycloalkyl, C₂-C₆ alkenyl, C₃-C₁₀ cycloalkenyl, C₂-C₆ alkynyl, heterocycloalkyl, C₁-C₈ alkanoyl, aroyl, heteroaroyl, aryl, heteroaryl, C₁-C₆ arylalkyl or C₁-C₆ heteroarylalkyl, or R⁸ and R⁹ taken together, can form a C₃-C₆ aminocarbocycle or a C₂-C₅ aminoheterocycle each of which is optionally substituted with C₁-C₆ alkyl, C₃-C₁₀ cycloalkyl, C₃-C₁₀ cycloalkenyl, (C₃-C₁₀ cycloalkyl) C₁-C₆ alkyl, C₁-C₃ haloalkyl, or heterocycloalkyl, C₁-C₈ alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, C₁-C₈ alkanoyl, aroyl, heteroaroyl, aryl, heteroaryl, C₁-C₆ arylalkyl or C₁-C₆ heteroarylalkyl;
- R¹¹ is selected from H, C₁-C₆ alkyl, C₃-C₁₀ cycloalkyl, (C₃-C₁₀ cycloalkyl) C₁-C₆ alkyl;
- R¹² is selected from H, aryl, heteroaryl, C₁-C₆ alkyl, C₃-C₁₀ cycloalkyl, (C₃-C₁₀ cycloalkyl) C₁-C₆ alkyl, optionally substituted with OR⁷, NR⁸R⁹, C₃-C₆ aminocarbocycle, or C₂-C₅ aminoheterocycle;
- R¹³ is independently selected at each occurrence from H, C₁-C₆ alkyl, C₃-C₁₀ cycloalkyl, (C₃-C₁₀ cycloalkyl) C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ haloalkyl, with the proviso that when R⁷ is for SO₂R¹³, R¹³ cannot be H; and
- R¹⁴ is H, C₁-C₆ alkyl, C₃-C₁₀ cycloalkyl, (C₃-C₁₀ cycloalkyl) C₁-C₆ alkyl, C₂-C₄ alkenyl, C₂-C₄ alkynyl, halo, or CN.
25. A compound according to claim 24, wherein
- R¹⁴ is H, C₁-C₄ alkyl, F or Cl.
26. A Compound according to claim 25, wherein
- R¹⁴ is H, C₁-C₄ alkyl, (C₃-C₆ cycloalkyl) C₁-C₂ alkyl, where the alkyl and cycloalkyl groups are optionally substituted with 1-3 fluorines.
- R³ is H, C₁-C₄ alkyl, (C₃-C₆ cycloalkyl) C₁-C₂ alkyl, where the alkyl and cycloalkyl groups are optionally substituted with 1-3 fluorines.
- A is CH₂, optionally substituted with one or two of the following: F, CF₃, or C₁-C₃ alkyl;
- B is a 1, 2 or 3 carbon chain, optionally substituted with one or two of the following: F, CF₃, or C₁-C₃ alkyl.
27. A Compound according to claim 26, wherein
- R⁴ is phenyl, substituted with 2 or 3 substituents independently selected from C₁-C₃ alkyl, C₃-C₆ cycloalkyl, C₃-C₆ cycloalkenyl, (C₃-C₅ cycloalkyl) C₁-C₂ alkyl, C₃-C₆ alkenyl, F, Cl, C₁-C₂ fluoroalkyl, OR⁷, C₁-C₃ alkyl-OR⁷, NR⁸R⁹, C₁-C₆ alkyl-NR⁸R⁹, CONR⁸R⁹, C₁-C₃ alkyl-CONR⁸R⁹, COOR⁷, C₂-C₆ alkynyl, wherein the phenyl ring is minimally 2,4 disubstituted.
27. A Compound according to claim 26, wherein
- R₂ is H;
- R⁶ is H;
- R⁴ is phenyl, substituted with 2 or 3 substituents independently selected from C₁-C₃ alkyl, C₃-C₆ cycloalkyl, C₃-C₆ cycloalkenyl, C₂-C₄ alkenyl, F, Cl, CF₃, CHF₂, CH₂CF₃, OMe, OCF₃, OEt, OPr, OiPr, C₂-C₄ alkyl OH, C₂-C₆ alkynyl, wherein the phenyl ring is minimally 2,4 di-substituted.
28. A Compound according to claim 27, wherein
- A is CH₂;
- B is CH₂;
- B and R₅ form a 5 to 7 membered heterocyclic ring, substituted on carbon with R^{7a}.
- R^{7a} is independently selected at each occurrence from H, C₁-C₃ alkyl, C₃-C₆ cycloalkyl, C₃-C₆ cycloalkenyl, (C₃-C₆ cycloalkyl) C₁-C₂ alkyl, C₁-C₂ fluoroalkyl, heterocycloalkyl, C₁-C₄ alkanoyl, aroyl, heteroaroyl, aryl, heteroaryl, C₁-C₂ arylalkyl or C₁-C₂ heteroarylalkyl each optionally substituted with 1 to 3 substituents independently selected from F, Cl, CF₃, OR¹³, NR⁸R⁹, C₁-C₂ alkyl-OR¹³, C₁-C₂ alkyl-NR⁸R⁹, CONR⁸R⁹, COOR¹³, and CN;
- R⁸ is H, C₁-C₃ alkyl, CF₃ or CH₂CF₃.
- R⁹ is H or C₁-C₃ alkyl.
- R¹³ is H, C₁-C₃ alkyl, CF₃ or CH₂CF₃.
29. A Compound according to claim 27, wherein
- A is CH₂, optionally substituted with one or two of the following: F, CF₃, or methyl, ethyl, isopropyl;
- B is CH₂, optionally substituted with one or two of the following: F, CF₃, methyl, ethyl, or Isopropyl.
30. A Compound according to claim 29, wherein
- R⁵ is C₁-C₇, alkyl, C₃-C₆cycloalkyl, or C₃-C₆ cycloalkyl C₁-C₂ alkyl, substituted with F, CF₃, OR⁷ or NR⁸R⁹;
- A is CB₂, optionally substituted with methyl;

B is CH₂, optionally substituted with methyl;

X is N or CH.

31. A compound according to claim 30, wherein

R⁷ is H, C₁-C₃ alkyl, CF₃ or CH₂CF₃;

R⁸ is H, C₁-C₃ alkyl, CF₃ or CH₂CF₃;

R⁹ is H or C₁-C₃ alkyl or NR⁸R⁹ taken together to form a pyrrolidine, piperidine or morpholine ring.

32. A Compound according to claim 29, wherein

R⁵ is 3- or 4-tetrahydropyranyl, 3-tetrahydrofuranyl, 3- or 4-tetrahydrothiopyranyl, 3- or 4-cyclohexenyl, or 3-cyclopentenyl, optionally substituted with 1 or 2 substituents selected from C₁-C₃ alkyl;

A is CH₂, optionally substituted with methyl;

B is CH₂ optionally substituted with methyl; and

X is Nor CH.

33. A Compound according to claim 29, wherein

R⁵ is 3- or 4-piperidinyl or 3-pyrrolidinyl, optionally substituted on 1 or 2 carbons with C₁-C₃ alkyl, and one substituent on nitrogen from H, C₁-C₆ alkyl, C₃-C₆ cycloalkyl, C₃-C₆ cycloalkenyl, (C₃-C₆ cycloalkyl) C₁-C₂ alkyl, C₁-C₄ alkenyl, C₁-C₃ fluoroalkyl, C₂-C₄ alkyl-OR⁷, C₂-C₄ alkyl-NR⁸R⁹, heterocycloalkyl, CO-C₁-C₄ alkyl, aryl, C₁-C₃ alkylaryl, heteroaryl, C₁-C₃ alkylheteroaryl where aryl or heteroaryl is optionally substituted with 1 to 3 substituents independently selected at each occurrence from C₁-C₃ alkyl F, Cl, C₁-C₂ fluoroalkyl, OR⁷, NR⁸R⁹, C₁-C₂ all-OR⁷, C₁-C₂ alkyl-NR⁸R⁹, CONR⁸R⁹, COOR⁷, CN, SO₂NR⁸R⁹, SO₂R⁷, aryl, heteroaryl, heterocycloalkyl, 3-, 4-, or 5-(2-oxo-1,3-oxazolidinyl).

34. A Compound according to claim 33, wherein

R⁵ is 3- or 4-piperidinyl or 3-pyrrolidinyl, optionally substituted on nitrogen with H, C₁-C₃ alkyl, CH₂CF₃, acetyl, pyridyl, benzyl, methylenepyridyl, pyrimidinyl, or pyrazinyl, where the aryl or heteroaryl group is optionally substituted with 1 to 2 substituents independently selected at each occurrence from C₁-C₃ alkyl, F, Cl, CF₃, OR, NR⁸R⁹.

R⁷ is H, C₁-C₂ alkyl, CF₃ or CH₂CF₃.

R⁸ is H, C₁-C₂ alkyl, CF₃ or CH₂CF₃.

R⁹ is H or C₁-C₂ alkyl.

A is CH₂, optionally substituted methyl;

B is CH₂, optionally substituted with methyl;

X is N or CH.

35. A compound according to claim 29, wherein

R⁵ is C₁-C₂ arylalkyl, C₁-C₂ heteroarylalkyl, C₃-C₄ arylcycloalkyl, or C₃-C₄ heteroarylalkyl, where aryl is phenyl or naphthyl, and heteroaryl is 2-, 3-, or 4-pyridyl, 2-, 4- or 5 pyrimidinyl, triazinyl, 1-, 2- or 4-imidazolyl, 2-, 4-, or 5-oxazolyl, isoxazolyl, indolyl, pyrazolyl, quinolyl, isoquinolyl, 2-, 4-, or 5-thiazolyl, benzothiadiazolyl, 1-, 3- or 4 pyrazolyl, 1-, 3- or 4-triazolyl, 2-triazinyl, 2-pyr, ziny, 2-, or 3-furanyl, 2-, or 3-thienyl, 2-, or 3-benzothienyl, or 1-, 2- or 5-tetrazolyl, each of which is optionally substituted with 1 to 3 substituents independently selected at each occur-

rence from C₁-C₃ alkyl, C₃-C₆ cycloalkyl, C₃-C₆ cycloalkenyl, (C₃-C₆ cycloalkyl) C₁-C₂ alkyl, C₁-C₆ alkenyl, F, Cl, C₁-C₂ fluoroalkyl, OR⁷, NRR⁹, C₁-C₂ alkyl-OR⁷, C₁-C₂ alkyl-NR⁸R⁹ or CN.

36. A compound according to claim 35, wherein

R⁵ is phenethyl, pyridinylethyl, or 2-tetrahydronaphthyl, each of which is optionally substituted with 1 to 2 substituents independently selected at each occurrence from C₁-C₂ alkyl, F, Cl, CF₃, OR⁷, NR⁸R⁹.

R⁷ is H, C₁-C₂ alkyl, CF₃ or CH₂CF₃.

R⁸ is H, C₁-C₂ alkyl, CF₃ or CH₂CF₃.

R⁹ is H or C₁-C₂ alkyl.

A is CH, optionally substituted with methyl;

B is CH₂, optionally substituted with methyl;

X is N or CH.

37. A compound according to claim 28, where the structure is [3-(2,6-dichloro-4-methoxy-phenyl)-2,5-dimethylpyrazolo [1,5-a]pyrimidin-7-yl]-(6-methyl-piperidin-2-ylmethyl)-amine.

38. A compound according to claim 31, where the compound is selected from the group consisting of:

2-[2-[3-(2,6-dichloro-4-methoxy-phenyl)-2,5-dimethylpyrazolo[1,5-a]pyrimidin-7-ylamino]-ethylamino]-butan-1-ol;

N-{2-[3-(2,6-dichloro-4-methoxy-phenyl)-2,5-dimethylpyrazolo[1,5-a]pyrimidin-7-ylamino]-ethyl}-N'-methyl-cyclohexane-1,4-diamine;

N-{2-[3-(2,6-dichloro-4-methoxy-phenyl)-2,5-dimethylpyrazolo[1,5-a]pyrimidin-7-ylamino]-ethyl}-N'-ethyl-cyclohexane-1,4-diamine;

N-[3-(2,6-dichloro-4-methoxy-phenyl)-2,5-dimethylpyrazolo[1,5-a]pyrimidin-7-yl]-N'-(4-morpholin-4-yl-cyclohexyl)-ethane-1,2-diamine;

4-{2-[3-(2,6-dichloro-4-methoxy-phenyl)-2,5-dimethylpyrazolo[1,5-a]pyrimidin-7-ylamino]-ethylaminol}-cyclohexanol;

3-{2-[3-(2,6-dichloro-4-methoxy-phenyl)-2,5-dimethylpyrazolo[1,5-a]pyrimidin-7-ylamino]-ethylamino}-propane-1,2-diol;

N-[2-[3-(2,6-dichloro-4-methoxy-phenyl)-2,5-dimethylpyrazolo[1,5-a]pyrimidin-7-ylamino]-ethyl]-N'-isobutyl-cyclohexane-1,4-diamine;

N-[2-[3-(2,6-dichloro-4-methoxy-phenyl)-2,5-dimethylpyrazolo[1,5-a]pyrimidin-7-ylamino]-ethyl]-N'-isobutyl-cyclohexane-1,4-diamine;

4-{2-[3-(2,6-dichloro-4-methoxy-phenyl)-2,5-dimethylpyrazolo[1,5-a]pyrimidin-7-ylamino]-1-methyl-ethylamino}-cyclohexanol;

2-{2-[3-(2,6-dichloro-4-methoxy-phenyl)-2,5-dimethylpyrazolo[1,5-a]pyrimidin-7-ylamino]-ethylamino}-cyclohexanol;

N-[3-(2,6-dichloro-4-methoxy-phenyl)-2,5-dimethylpyrazolo [1,5-a]pyrimidin-7-yl]-N'-(4,4,4-trifluorobutyl)-ethane-1,2-diamine;

- N-[3-(2,6-dichloro-4-ethoxy-phenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-yl]-N'-(2,2,2-trifluoro-ethyl)-ethane-1,2-diamine;
- N-[3-(2,6-dichloro-4-methoxy-phenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-yl]-N'-(2-trifluoromethyl-cyclohexyl)-ethane-1,2-diamine;
- N-[3-(2,6-dichloro-4-methoxy-phenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-yl]-N'-(4-trifluoromethyl-cyclohexyl)-ethane-1,2-diamine;
- N-[3-(2,6-dichloro-4-methoxy-phenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-yl]-N'-(2,2-difluoro-ethyl)-ethane-1,2-diamine;
- N-[3-(2,6-dichloro-4-methoxy-phenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-yl]-N'-(2-fluoro-1-methyl-ethyl)-ethane-1,2-diamine;
- N-[3-(2,6-dichloro-4-methoxy-phenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-yl]-N'-(2-fluoro-cyclohexyl)-ethane-1,2-diamine.
39. A compound of claim 32, where the compound is selected from the group consisting of N-[3-(2,6-dichloro-phenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-yl]-N'-(tetrahydro-pyran-4-yl)-ethane-1,2-diamine; N-[3-(2,4-dichloro-6-methoxy-phenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-yl]-N'-(tetrahydro-pyran-4-yl)-ethane-1,2-diamine; N-[3-(2,6-dichloro-4-methoxy-phenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-yl]-N'-(tetrahydro-pyran-4-yl)-ethane-1,2-diamine; N-[3-(2,6-dichloro-phenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-yl]-N'-(1-methyl-piperidin-4-yl)-ethane-1,2-diamine; N-[3-(2,6-dichloro-4-methoxy-phenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-yl]-N'-(2-methyl-tetrahydro-furan-3-yl)-ethane-1,2-diamine; N-[3-(2,6-dichloro-4-ethoxy-phenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-yl]-N'-(tetrahydro-pyran-4-yl)-ethane-1,2-diamine; 3,5-dichloro-4-[2,5-dimethyl-7-[2-(tetrahydro-pyran-4-ylamino)-ethylamino]-pyrazolo[1,5-a]pyrimidin-3-yl]-benzonitrile; N-[3-(2,6-dichloro-4-propoxy-phenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-yl]-N'-(tetrahydro-pyran-4-yl)-ethane-1,2-diamine; 2-(3,5-dichloro-4-(2,5-dimethyl-7-[2-(tetrahydro-pyran-4-ylamino)-ethylamino]-pyrazolo[1,5-a]pyrimidin-3-yl)-phenyl)-propan-2-ol; N-[3-(2,6-dichloro-4-cyclopent-1-enyl-phenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-yl]-N-(tetrahydro-pyran-4-yl)-ethane-1,2-diamine; N-[8-(2,6-dichloro-4-ethoxy-phenyl)-2,7-dimethyl-pyrazolo[1,5-a][1,3,5]triazin-4-yl]-N'-(tetrahydro-pyran-4-yl)-ethane-1,2-diamine; (3,5-dichloro-4-(2,5-dimethyl-7-[2-(tetrahydro-pyran-4-ylamino)-ethylamino]-pyrazolo[1,5-a]pyrimidin-3-yl)-phenyl)-methanol; N-[3-(2,6-dichloro-4-ethoxy-phenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-yl]-N-(2-methyl-tetrahydro-furan-3-yl)-ethane-1,2-diamine; N-[5-tert-butyl-3-(2,6-dichloro-4-methoxy-phenyl)-2-methyl-pyrazolo[1,5-a]pyrimidin-7-yl]-N'-(tetrahydro-pyran-4-yl)-ethane-1,2-diamine; N-[3-(2,6-dichloro-4-ethoxy-phenyl)-5-ethyl-2-methyl-pyrazolo[1,5-a]pyrimidin-7-yl]-N-(tetrahydro-pyran-4-yl)-ethane-1,2-diamine; N-cyclohex-3-enyl-N'-[3-(2,6-dichloro-4-methoxy-phenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-yl]-ethane-1,2-diamine; N-cyclohex-3-enyl-N'-[8-(2,6-dichloro-4-ethoxy-phenyl)-2,7-dimethyl-pyrazolo[1,5-a][1,3,5]triazin-4-yl]-ethane-1,2-diamine; N-cyclopent-3-enyl-N'-[3-(2,6-dichloro-4-methoxy-phenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-yl]-ethane-1,2-diamine.
40. A compound of claim 34 where the structure is selected from the group consisting of
- N-[3-(2,6-dichloro-phenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-yl]-N'-(1-ethyl-piperidin-5-yl)-pyrimidin-7-yl]-N'-(2,2,6,6-tetramethyl-piperidin-4-yl)-ethane-1,2-diamine;
- N-[3-(2,6-dichloro-phenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-yl]-N'-19-piperidin-4-yl)-ethane-1,2-diamine;
- N-[3-(2,6-dichloro-phenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-yl]-N-(1-ethyl-piperidin-3-yl)-ethane-1,2-diamine;
- N-(1-benzyl-pyrrolidin-3-yl)-N'-[3-(2,6-dichloro-phenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-yl]-ethane-1,2-diamine;
- N-[3-(2,6-dichloro-phenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-yl]-N-pyrimidin-2-yl)-ethane-1,2-diamine;
- N-(1-benzylpiperidin-4-yl)-N-[3-(2,4-dichloro-6-methoxy-phenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-yl]-ethane-1,2-diamine;
- N-(1-benzyl-piperidin-4-yl)-N-[3-(2,6-dichloro-4-methoxy-phenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-yl]-ethane-1,2-diamine;
- N-[3-(2,6-dichloro-4-methoxy-phenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-yl]-N'-(1'-methyl-piperidin-4-yl)-ethane-1,2-diamine;
- N-[3-(2,6-dichloro-4-methoxy-phenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-yl]-N-(1-ethyl-piperidin-4-yl)-ethane-1,2-diamine;
- N-[3-(2,6-dichloro-4-methoxy-phenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-yl]-N'-(1-isopropyl-piperidin-4-yl)-ethane-1,2-diamine;
- N-[3-(2,6-dichloro-4-methoxy-phenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-yl]-N'-(2,2,6,6-tetramethyl-piperidin-4-yl)-ethane-1,2-diamine;
- N-[3-(2,6-dichloro-4-methoxy-phenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-yl]-N'-(1-ethyl-piperidin-3-yl)-ethane-1,2-diamine;
- N-[3-(2,6-dichloro-4-methoxy-phenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-yl]-N'-piperidin-4-yl)-ethane-1,2-diamine;
- N²-(1-Benzyl-piperidin-4-yl)-N'-[3-(2,6-dichloro-phenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-yl]-propane-1,2-diamine;
- N-[3-(2,6-Dichloro-4-methoxy-phenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-yl]-N'-(1-pyridin-3-ylmethyl-piperidin-4-yl)-ethane-1,2-diamine;
- N-[3-(2,6-Dichloro-4-methoxyphenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-yl]-N'-(1-pyridin-4-ylmethyl-piperidin-4-yl)-ethane-1,2-diamine;
- 3,5-Dichloro-4-[2,5-dimethyl-7-[2-(1-phenyl-pyrrolidin-3-ylamino)-ethylamino]-pyrazolo[1,5-a]pyrimidin-3-yl]-phenol;

- N-[3-(2,6-dichloro-4-methoxy-phenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-yl]-N'-(1-pyridin-2-ylmethyl-piperidin-4-yl)-ethane-1,2-diamine;
- 3,5-dichloro-4-(2,5-dimethyl-7-[2-(1-pyrimidin-2-yl-piperidin-4-ylamino)-ethylamino]-pyrazolo[1,5-a]pyrimidin-3-yl)-benzonitrile;
- N-[3-(2,6-dichloro-4-ethoxy-phenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-yl]-N'-(1-pyrimidin-2-yl-piperidin-4-yl)-ethane-1,2-diamine;
- N-[3-(2,6-dichloro-4-methoxy-phenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-yl]-N'-(1-pyrimidin-2-yl-piperidin-4-yl)-ethane-1,2-diamine;
- N-(1-benzyl-piperidin-4-yl)-N'-[3-(2,6-dichloro-4-ethoxy-phenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-yl]-ethane-1,2-diamine;
- N-[3-(2,6-dichloro-phenyl)-5-ethyl-2-methyl-pyrazolo[1,5-a]pyrimidin-7-yl]-N'-(1-pyrimidin-2-yl-piperidin-4-yl)-ethane-1,2-diamine;
- N-[3-(2,6-dichloro-phenyl)-5-isopropyl-2-methyl-pyrazolo[1,5-a]pyrimidin-7-yl]-N'-(1-pyrimidin-2-yl-piperidin-4-yl)-ethane-1,2-diamine;
- N-[3-(2,4-dichloro-phenyl)-5-isopropyl-2-methyl-pyrazolo[1,5-a]pyrimidin-7-yl]-N'-(1-pyrimidin-2-yl-piperidin-4-yl)-ethane-1,2-diamine;
- N'-[3-(2,6-dichloro-4-ethoxy-phenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-yl]-N²-(1-pyrimidin-2-yl-piperidin-4-yl)-propane-1,2-diamine;
- N'-[3-(2,6-dichloro-4-methoxy-phenyl)-5-isopropyl-2-methyl-pyrazolo[1,5-a]pyrimidin-7-yl]-N²-(1-pyrimidin-2-yl-piperidin-4-yl)-propane-1,2-diamine;
- N-[3-(2,6-dichloro-4-methoxy-phenyl)-5-ethyl-2-methyl-pyrazolo[1,5-a]pyrimidin-7-yl]-N'-(1-pyrimidin-2-yl-piperidin-4-yl)-ethane-1,2-diamine;
- N'-[3-(2,6-dichloro-4-methoxy-phenyl)-2-methyl-5-propyl-pyrazolo[1,5-a]pyrimidin-7-yl]-N²-(1-pyrimidin-2-yl-piperidin-4-yl)-propane-1,2-diamine;
- N'-[3-(2,6-dichloro-4-methoxy-phenyl)-5-ethyl-2-methyl-pyrazolo[1,5-a]pyrimidin-7-yl]-N²-(1-pyrimidin-2-yl-piperidin-4-yl)-propane-1,2-diamine;
- N-[3-(2,6-dichloro-phenyl)-2-methyl-5-propylpyrazolo[1,5-a]pyrimidin-7-yl]-N'-(1-pyrimidin-2-yl-piperidin-4-yl)-ethane-1,2-diamine;
- N-[3-(2,6-dichloro-phenyl)-2-methyl-5-propyl-pyrazolo[1,5-a]pyrimidin-7-yl]-N²-(1-pyrimidin-2-yl-piperidin-4-yl)-propane-1,2-diamine;
- N'-[3-(2,6-dichloro-phenyl)-5-ethyl-2-methyl-pyrazolo[1,5-a]pyrimidin-7-yl]-N²-(1-pyrimidin-2-yl-piperidin-4-yl)-propane-1,2-diamine;
- N-[5-ethyl-2-methyl-3-(2,4,6-trimethyl-phenyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-N'-(1-pyrimidin-2-yl-piperidin-4-yl)-ethane-1,2-diamine;
- N'-[5-ethyl-2-methyl-3-(2,4,6-trimethyl-phenyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-N²-(1-pyrimidin-2-yl-piperidin-4-yl)-propane-1,2-diamine; N-[3-(2,6-dichloro-4-ethynyl-phenyl)-2,5-dimethylpyrazolo[1,5-a]pyrimidin-7-yl]-N-(1-pyrimidin-2-yl-piperidin-4-yl)-ethane-1,2-diamine;
- N-[2-methyl-5-propyl-3-(2,4,6-trimethyl-phenyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-N'-(1-pyrimidin-2-yl-piperidin-4-yl)-ethane-1,2-diamine;
- N'-[2,5-dimethyl-3-(2,4,6-trimethylphenyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-N'-(1-pyrimidin-2-yl-piperidin-4-yl)-ethane-1,2-diamine;
- N'-[3-(2,6-Dimethyl-phenyl)-5-ethyl-2-methyl-pyrazolo[1,5-a]pyrimidin-7-yl]-N'-(1-pyrimidin-2-yl-piperidin-4-yl)-propane-1,2-diamine;
- N-[3-(2,6-dimethyl-phenyl)-2-methyl-5-propyl-pyrazolo[1,5-a]pyrimidin-7-yl]-N'-(1-pyrimidin-2-yl-piperidin-4-yl)-ethane-1,2-diamine;
- N'-[3-(2,6-Dimethyl-phenyl)-2-methyl-5-propyl-pyrazolo[1,5-a]pyrimidin-7-yl]-N²-(1-pyrimidin-2-yl-piperidin-4-yl)-propane-1,2-diamine;
- N'-[3-(2,6dimethyl-phenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-yl]-N²-(1-pyrimidin-2-ylpiperidin-4-yl)-propane-1,2-diamine;
- N-[3-(2,4-dimethyl-phenyl)-5-ethyl-2-methyl-pyrazolo[1,5-a]pyrimidin-7-yl]-N-(1-pyrimidin-2-yl-piperidin-4-yl)-ethane-1,2-diamine;
- N-[3-(2,4-dimethyl-phenyl)-2-methyl-5-propyl-pyrazolo[1,5-a]pyrimidin-7-yl]-N'-(1-pyrimidin-2-yl-piperidin-4-yl)-ethane-1,2-diamine; and
- 1-[4-(1-[3-(2,6-dichloro-4-methoxyphenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-ylamino]-methyl)-propylamino]piperidin-1-yl]-ethanone.
- 41 A compound of claim 37 where the structure is selected from the group consisting of
- N-[2,5-dimethyl-3-(2,4,6-trimethylphenyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-N-[2-(4-methoxy-phenyl)-ethyl]-ethane-1,2diamine;
- N-[3-(2,6-dichloro-4-methoxy-phenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-yl]-N'-[2-(4-methoxy-phenyl)-ethyl]-ethane-1,2-diamine;
- N-[3-(2,6-dichloro-4-methoxy-phenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-yl]-N'-[2-(3-ethoxy-4-methoxy-phenyl)-ethyl]-ethane-1,2-diamine;
- N-[3-(2,6-dichloro-4-methoxy-phenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-yl]-N'-[2-(4-ethoxy-3-methoxy-phenyl)-ethyl]ethane-1,2-diamine; N-[3-(2,6-dichloro-4-methoxy-phenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-yl]-N'-(1,2,3,4-tetrahydro-naphthalen-2-yl)-ethane-1,2-diamine;
- N-[3-(2,6-dichloro-4-methoxy-phenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-yl]-N'-(2-pyridin-2-yl-ethyl)-ethane-1,2-diamine;
- N-[3-(2,6-dichloro-4-methoxy-phenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-yl]-N'-(2-pyridin-3-yl-ethyl)-ethane-1,2-diamine; and
- N-[3-(2,6-dichloro-4-methoxy-phenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-yl]-N'-(2-pyridin-4-yl-ethyl)-ethane-1,2-diamine.

42. A method of treating obesity comprising administering to a mammal in need of such treatment a therapeutically effective amount of a compound of claim 23 or 24 or a prodrug thereof or a pharmaceutically acceptable salt of said compound or of said prodrug.
43. A method as recited in claim 42 wherein the amount of said compound administered is about 0.01 mg/kg/day to about 50 mg/kg/day.
44. A method as recited in claim 42 wherein the mammal is female or male human.
45. A pharmaceutical composition which comprises a therapeutically effective amount of compound of claim 24 or a prodrug thereof or a pharmaceutically acceptable salt of said compound or of said prodrug and a pharmaceutically acceptable carrier, vehicle or diluent.
46. A pharmaceutical composition for the treatment of obesity which comprises a therapeutically effective amount of compound of claim 24 or a prodrug thereof or a pharmaceutically acceptable salt of said compound or of said prodrug and a pharmaceutically acceptable carrier, vehicle or diluent.
47. A pharmaceutical combination composition comprising a therapeutically effective amount of a composition comprising: (a) first compound, said first compound being a compound of claim 24, a prodrug thereof, or a pharmaceutically acceptable salt of said compound or of said prodrug; and (b) a second compound, said second compound being a β_3 agonist, a thyromimetic, an eating behavior modifying agent or a NPY antagonist; and a pharmaceutical carrier, vehicle, diluent.
48. A method of treating obesity comprising administering to a mammal in need of such treatment: (a) first compound, said first compound being a compound of claim 24, a prodrug thereof, or a pharmaceutically acceptable salt of said compound or of said prodrug; and (b) a second compound, said second compound being a β_3 agonist, a thyromimetic, an eating behavior modifying agent or a NPY antagonist; and a pharmaceutical carrier, vehicle, diluent; (and (c) wherein the amounts of the first and second compounds result in a therapeutic effect.

49. A kit comprising: (a) first compound, said first compound being a compound of claim 24 or 25, a prodrug thereof, or a pharmaceutically acceptable salt of said compound or of said prodrug; (b) a second compound, said second compound being a β_3 agonist, a thyromimetic, an eating behavior modifying agent or a NPY antagonist; and a pharmaceutical carrier, vehicle, diluent; and (c) means for containing said first and second unit dosage forms wherein the amounts of the first and second compounds result in a therapeutic effect,
50. A pharmaceutical combination composition comprising a therapeutically effective amount of a composition comprising (a) first compound, said first compound being a compound of claim 23 or 24, a prodrug thereof, or a pharmaceutically acceptable salt of said compound or of said prodrug; (b) a second compound, said second compound being an aldose reductase inhibitor, a glycogen phosphorylase inhibitor, a sorbitol dehydrogenase N inhibitor, insulin metformin, acarbose, a thiazolidinedione, a glitazone, rosiglitazone, troglitazone, a sulfonylurea, glipazide, glyburide, or chlorpropamide; (c) a pharmaceutical carrier, vehicle, or diluent.
51. A pharmaceutical composition according to claim 24 for the treatment of disorders or disease states caused by eating disorders, of obesity, bulimia nervosa, diabetes, dyslipidemia, hypertension, memory loss, epileptic seizures, migraine, sleep disorders, pain, sexual/reproductive disorders, depression, anxiety, cerebral hemorrhage, shock, congestive heart failure, nasal congestion or diarrhea.
52. A method of selectively inhibiting binding of NPY receptors, which comprises contacting a compound of claim 1 with neuronal cells, wherein the compound is present in an amount effective to produce a concentration sufficient to selectively inhibit binding of NPY peptides to NPY₁ receptors in vitro.

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