

Señor

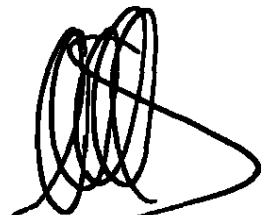
SUPERINTENDENTE DE INDUSTRIA Y COMERCIO
DIVISION DE NUEVAS CREACIONES

E. _____ S. _____ D. _____

Re: P1.-PHARMACIA & UPJOHN COMPANY.-Solicitud de
Patente de Invención Fase Nacional PCT para
"COMPUESTOS PARA EL TRATAMIENTO DE
DESORDENES ADICTIVOS".-Clase A61K 31/00.-Expediente
número 03-021.690.-

1. Me refiero a mi memorial de 3 de Abril de 2003.
2. Anexo me permito presentar a usted documento parcial de Reporte de Búsqueda Internacional junto con sus anexos correspondiente a la solicitud internacional número PCT/US01/25603, actualmente en trámite de Fase Nacional en ese despacho, bajo el número de la referencia.
3. Ruego a usted tomar atenta nota de lo anterior y proceder de conformidad.

Señor Superintendente,


JOSE ANTONIO LLOREDA
T.P. 10.784
Código 231

Anexo a la Forma PCT/ISA/206
COMUNICACIÓN RELACIONADA CON LOS RESULTADOS
DE LA BUSQUEDA PARCIAL INTERNACIONAL

Solicitud Internacional No.
PCT/US 01/25603

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1. La presente comunicación es un Anexo a la invitación a pagar tasas adicionales (Forma PCT/ISA/206). Muestra los resultados de la búsqueda internacional establecida es las partes de la solicitud internacional que se refieren a la invención mencionada primero en las reivindicaciones Nos.:

ver 'Invitación a pagar tasas adicionales'

2. Esta comunicación no es el reporte de búsqueda internacional que será establecido de acuerdo con el Artículo 18 y la Regla 43.

3. Si el solicitante no paga ninguna tasa de búsqueda adicional, la información que aparece en esta comunicación será considerada como el resultado de la búsqueda internacional y será incluida como tal en el reporte de búsqueda internacional.

4. Si el solicitante paga las tasas adicionales, el reporte de búsqueda internacional contendrá la información que aparece en esta comunicación y los resultados de la búsqueda internacional sobre otras partes de la solicitud internacional para los que dichas tasas hayan sido pagadas.

C. DOCUMENTOS CONSIDERADOS RELEVANTES

Categoría *	Citación de documento, con indicación, donde sea apropiado, de los textos relevantes	Relevante a la reivindicación No.
X	US 6 008 233 A (SINAY TERRY G ET AL) 28 de Diciembre de 1999 (1999-12-28) resumen columna 2, línea 35-columna 3, línea 52	1
X	WO 99 24423 A (ELLIOTT MATTHEW JASON; MERCK SHARP & DOHME (GB)) 20 de Mayo de 1999 (1999-05-20) resumen página 8, línea 16-página 9, línea 26	1
X	WO 99 10339 A (LOWE JOHN ADAMS III; PFIZER PROD INC (US)) 4 de Marzo de 1999 (1999-03-04) resumen página 4, línea 19-página 7, línea 35 página 9, línea 13-25; reivindicaciones 1-9	1
X	GARNER, K. J. ET AL: "Análisis de los ligandos Selectivos-del Receptor D2 y D3 en Ratas Entrenadas para Discriminar Cocaína de Sales" PHARMACOLOGY, BIOCHEMISTRY AND BEHAVIOR (1999), 64 (2), 373-378, XP001148424 el documento completo	1-3, 16-25

☒ En el recuadro C se enumeran más documentos.

☒ En el anexo se enumeran miembros de la familia de patentes.

* Categorías especiales de documentos citados:

'A' documento que define el estado general de la técnica el cual no se considera de relevancia particular

'E' documento anterior pero publicado en o después de la fecha de presentación internacional

'L' documento que puede arrojar dudas sobre reivindicaciones de prioridad o que se cita para establecer la fecha de publicación de otra citación u otra razón especial (según se especifica)

'O' documento que se refiere a una revelación oral, uso, exhibición u otros medios

'P' documento publicado antes de la fecha de presentación internacional pero después de la fecha de prioridad reivindicada

'T' documento posterior publicado después de la fecha de presentación internacional o fecha de prioridad y que no está en conflicto con la solicitud pero citado para entender el principio o teoría que sustenta la invención

'X' documento de relevancia particular; la invención reivindicada no puede considerarse nueva o no puede considerarse que comprende un paso inventivo cuando el documento se toma solo

'Y' documento de relevancia particular; la invención reivindicada no puede considerarse que comprende un paso inventivo cuando el documento se combina con uno o más documentos, siendo dicha combinación obvia para una persona experta en la técnica

'Z' documento miembro de la misma familia de patentes

Anexo a la Forma PCT/ISA/206
**COMUNICACIÓN RELACIONADA CON LOS RESULTADOS
DE LA BUSQUEDA PARCIAL INTERNACIONAL**

Solicitud Internacional No.
PCT/US 01/25603

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C. (Continuación) DOCUMENTOS CONSIDERADOS RELEVANTES

000/3

Categoría *	Citación de documento, con indicación, donde sea apropiado, de los textos relevantes	Relevante a la reivindicación No.
X	CAINE S B ET AL: "Prueba in vitro del receptor-D3 predice el decrecimiento de la auto-administración de cocaína en ratas" CHEMABS, XP002168920 resumen	1
A	WO 90 15058 A (UPJOHN CO) 13 de Diciembre de 1990 (1990-12-13) citado en la solicitud el documento completo	1-4, 13-25
A	CALON, F. ET AL: "Disquinesia inducida en levodopa o agonista D2 en monos MPTP: correlación con cambios en receptores de dopamina y GABAA en el complejo estriado-palidal" BRAIN RESEARCH (1995), 680 (1,2), 43-52, XP001148341 el documento completo	1-4, 13-25

INFORMACION ADICIONAL DE PCT/ISA/206

Continuación de la Casilla 3.

Aunque las reivindicaciones 1-4, 13-25 se relacionan con un método de tratamiento del cuerpo humano/animal, la búsqueda se ha llevado a cabo según los supuestos efectos del compuesto/composición.

Defecto(s) adicionales según el Artículo 17(2)(a):

Continuación de la Casilla 3.

Las presentes reivindicaciones 1-4, 13-24 se relacionan con un compuesto/uso definido por referencia a las siguientes expresiones:

síntomas de al menos un desorden seleccionado de los desórdenes adictivos, desórdenes del uso de sustancias psicoactivas, desórdenes de intoxicación, desórdenes de inhalación, adicción al alcohol, adicción al tabaco y adicción a la nicotina.

Se considera que el uso de estos parámetros en el presente contexto lleva a una falta de claridad dentro del significado del Artículo 6 del PCT. Es imposible comparar los parámetros que el solicitante ha escogido para usarse con lo que se expresa en la técnica anterior. La falta de claridad es tal que hace que una búsqueda significativa completa sea imposible.

La fase inicial de la búsqueda reveló un gran número de documentos relevantes para la emisión de la novedad de la reivindicación 1. Se recuperaron tantos documentos que es imposible determinar cuáles partes de la reivindicación puede decirse que definen la materia objeto para la cual pueda buscarse protección legítimamente (Artículo 6 del PCT).

Por consiguiente, la búsqueda se ha restringido al uso de compuestos de la fórmula (I) en relación con un desorden seleccionado de desórdenes adictivos, desórdenes del uso de sustancias psicoactivas, desórdenes de intoxicación, desórdenes de inhalación, adicción al alcohol, adicción al tabaco y adicción a la nicotina.

Se llama la atención del solicitante respecto al hecho de que las reivindicaciones, o partes de las reivindicaciones, relacionadas con invenciones respecto de las cuales no se ha establecido un reporte de búsqueda internacional, no requieren ser el objeto de un examen preliminar internacional (Regla 66.1(e) PCT). También se le notifica al solicitante que la política de la EPO al actuar como Autoridad de Examen Preliminar Internacional normalmente es no llevar a cabo un examen preliminar en materias que no se han buscado. Este es el caso prescindiendo de si las reivindicaciones se enmiendan siguiendo el recibo del reporte de búsqueda o durante cualquier procedimiento del Capítulo II.

Esta Autoridad de Búsqueda Internacional encontró múltiples (grupos de) invenciones en esta solicitud internacional, así:

1. Reivindicaciones: 1, 13-25 (parcialmente) 2-4

Uso de una amina heterocíclica para la preparación de un medicamento para tratar o suprimir los síntomas de al menos un desorden seleccionado de desórdenes adictivos, desórdenes del uso de sustancias psicoactivas, desórdenes de intoxicación, desórdenes de inhalación, adicción al alcohol, adicción al tabaco y adicción a la nicotina.

2. Reivindicaciones: 1, 13-25 (parcialmente) 5-7

Uso de un fenilazacicloalcano para la preparación de un medicamento para tratar o suprimir los síntomas de al menos un desorden seleccionado de desórdenes adictivos, desórdenes del uso de sustancias psicoactivas, desórdenes de intoxicación, desórdenes de inhalación, adicción al alcohol, adicción al tabaco y adicción a la nicotina.

3. Reivindicaciones: 1, 13-25 (parcialmente) 8-9

Uso de una cabergolina para la preparación de un medicamento para tratar o suprimir los síntomas de al menos un desorden seleccionado de desórdenes adictivos, desórdenes del uso de sustancias psicoactivas, desórdenes de intoxicación, desórdenes de inhalación, adicción al alcohol, adicción al tabaco y adicción a la nicotina.

4. Reivindicaciones: 1, 13-16 (parcialmente) 10-12

Uso de una amina bicíclica aromática para la preparación de un medicamento para tratar o suprimir los síntomas de al menos un desorden seleccionado de desórdenes adictivos, desórdenes del uso de sustancias psicoactivas, desórdenes de intoxicación, desórdenes de inhalación, adicción al alcohol, adicción al tabaco y adicción a la nicotina.

Los problemas que hay que resolver por medio de la presente solicitud son proporcionar para el tratamiento o supresión de los síntomas de al menos un desorden seleccionado de desórdenes adictivos, desórdenes del uso de sustancias psicoactivas, desórdenes de intoxicación, desórdenes de inhalación, adicción al alcohol, adicción al tabaco y adicción a la nicotina.

Las soluciones propuestas son el uso de un agente seleccionado del grupo que consiste en una amina heterocíclica, un fenilazacicloalcano, un cabergolina y una amina bicíclica aromática.

US6008233 revela que (1S, 2S)-1-(4-hidroxifenil)-2-(4-hidroxi-4-fenil piperidin-1-ilo)-1-propanol metano sulfonato trihidratado, un fenilazacicloalcano, pueden usarse para tratar desórdenes del sistema nervioso central, tales como adicción a las drogas o al alcohol, síntomas de suspensión del uso de drogas y del alcohol. Ver los pasajes citados en el reporte de búsqueda.

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W09924423 revela el uso de

N-(2-Ciclopropoxi-5-tetrazolil-benzil)-2-fenil-piperidina-3-amina, una amina heterocíclica y un derivado de fenilazacicloalcano para tratar desórdenes relacionados con sustancias que surjan del uso del alcohol, anfetaminas (o sustancias semejantes a las anfetaminas) cafeína, cannabis, cocaína, alucinógenos, propulsores inhalantes o en aerosol, nicotina, opiodes, derivados de fenilglicidina, sedantes, hipnóticos y ansiolíticos, desórdenes relacionados con sustancias que incluyen dependencia y abuso, intoxicación, suspensión, delirio de intoxicación, delirio de suspensión. Ver los pasajes citados en el reporte de búsqueda.

W09910339 revela derivados de 2-Aminopiridina los cuales son aminas bicíclicas aromáticas y aminas heterocíclicas útiles para tratar el sistema nervioso central y otros desórdenes, incluyendo dependencias químicas y adicción (v.g., dependencia de las drogas, alcohol y nicotina). Ver los pasajes citados en el reporte de búsqueda.

Los documentos citados no representan una búsqueda comprensiva para ninguna de las invenciones definidas y deben considerarse únicamente parte de la técnica anterior que pertenece a la idea general que sustenta la presente solicitud.

De conformidad con el Artículo 3(4)(iii) del PCT, una solicitud internacional cumplirá con "los requisitos prescritos de unidad de invención." Esto significa, según se explica en la Regla 13.1 del PCT, que la solicitud se relacionará con una invención únicamente o con un grupo de invenciones así unidas para formar un solo concepto inventivo general.

De los documentos citados anteriormente, parece que el uso de los compuestos de la presente invención en relación con los usos especificados anteriormente y en el tratamiento de las condiciones especificadas anteriormente se conoce en la técnica anterior y no puede cumplir el papel de la técnica característica especial (concepto inventivo general) en el sentido de la Regla 13.2 del PCT.

En la presente solicitud no se puede distinguir una técnica característica adicional que pueda considerarse como una "característica técnica especial" comprendida en la relación técnica entre las diferentes invenciones.

Por consiguiente, a la presente solicitud le falta unidad de invención.

Cada invención es una invención diferente, caracterizada por su propia característica técnica especial, que define la contribución que cada una de las invenciones reivindicadas, consideradas como un todo, hace sobre la técnica anterior.

Puesto que la búsqueda del otro objeto hubiera ocasionado un esfuerzo de búsqueda adicional, únicamente se buscó la primera invención.

La solicitud se relaciona con una pluralidad de invenciones o grupos de invenciones, en el sentido de la Regla 13.1 del PCT. Se han dividido según se define anteriormente. Si el solicitante paga tasas adicionales para uno (o más) grupo(s) de invenciones que no se han buscado aún, entonces la(s) búsqueda(s) adicional(es) pueden revelar técnicas anteriores adicionales que proporcionen evidencia de una falta de unidad adicional 'a posteriori' dentro de uno (o más) del grupo(s) que no se han buscado aún. En dicho caso únicamente la primera invención en este (cada uno de estos) grupo(s) de invenciones, que se considera que le falta unidad de invención, será objeto de búsqueda.

No se emitirá una invitación adicional a pagar tasas adicionales. Esto se debe a que el Artículo 17(3) (a) del PCT estipula que ISA establecerá el Reporte de Búsqueda Internacional en aquellas partes de la solicitud internacional que se relacionan con la invención que se mencionó en primer término en las reivindicaciones ('invención principal') y para aquellas partes que se relacionan con las invenciones respecto de las cuáles se pagaron tasas adicionales. Ni el PCT ni los lineamientos del PCT proporcionan una base legal para invitaciones adicionales a pagar tasas de búsqueda adicionales (W17/00, punto 11 y W1/97, puntos 11-16).

**Annex to Form PCT/ISA/206
COMMUNICATION RELATING TO THE RESULTS
OF THE PARTIAL INTERNATIONAL SEARCH**

International Application No
PCT/US 01/25603

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1. The present communication is an Annex to the invitation to pay additional fees (Form PCT/ISA/206). It shows the results of the international search established on the parts of the international application which relate to the invention first mentioned in claims Nos. *see 'Invitation to pay additional fees'*
2. This communication is not the international search report which will be established according to Article 18 and Rule 43.
3. If the applicant does not pay any additional search fees, the information appearing in this communication will be considered as the result of the international search and will be included as such in the international search report.
4. If the applicant pays additional fees, the international search report will contain both the information appearing in this communication and the results of the international search on other parts of the international application for which such fees will have been paid.

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 6 008 233 A (SINAY TERRY G ET AL) 28 December 1999 (1999-12-28) abstract column 2, line 35 -column 3, line 52	1
X	WO 99 24423 A (ELLIOTT MATTHEW JASON ;MERCK SHARP & DOHME (GB)) 20 May 1999 (1999-05-20) abstract page 8, line 16 -page 9, line 26	1
X	WO 99 10339 A (LOWE JOHN ADAMS III ;PFIZER PROD INC (US)) 4 March 1999 (1999-03-04) abstract page 4, line 19 -page 7, line 35 page 9, line 13-25; claims 1-9	1
X	GARNER, K. J. ET AL: "Analysis of D2 and D3 Receptor-Selective Ligands in Rats Trained to Discriminate Cocaine from Saline" PHARMACOLOGY, BIOCHEMISTRY AND BEHAVIOR (1999), 64(2), 373-378 , XP001148424 the whole document	1-3, 16-25

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☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents.

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- "Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
- "S" document member of the same patent family

**Annex to Form PCT/ISA/206
COMMUNICATION RELATING TO THE RESULTS
OF THE PARTIAL INTERNATIONAL SEARCH**

International Application No
PCT/US 01/25603

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No
X	CAINE S B ET AL: "D3-receptor test in vitro predicts decreased cocaine self-administration in rats" CHEMABS, XP002168920 abstract	1
A	WO 90 15058 A (UPJOHN CO) 13 December 1990 (1990-12-13) cited in the application the whole document	1-4, 13-25
A	CALON, F. ET AL: "Levodopa or D2 agonist induced dyskinesia in MPTP monkeys: correlation with changes in dopamine and GABAA receptors in the striatopallidal complex." BRAIN RESEARCH (1995), 680(1,2), 43-52 , XP001148341 the whole document	1-4, 13-25

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 206

Continuation of Box 3.

Although claims 1-4,13-25 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

Further defect(s) under Article 17(2)(a):

Continuation of Box 3.

Present claims 1-4,13-24 relate to a compound/use defined by reference to the following expressions:
symptoms of at least one disorder selected from addictive disorders, psychoactive substance use disorders, intoxication disorders, inhalation disorders, alcohol addiction, tobacco addiction, and nicotine addiction.

The use of these parameters in the present context is considered to lead to a lack of clarity within the meaning of Article 6 PCT. It is impossible to compare the parameters the applicant has chosen to employ with what is set out in the prior art. The lack of clarity is such as to render a meaningful complete search impossible.

The initial phase of the search revealed a very large number of documents relevant to the issue of novelty of claim 1. So many documents were retrieved that it is impossible to determine which parts of the claim may be said to define subject-matter for which protection might legitimately be sought (Article 6 PCT).

Consequently, the search has been restricted to the use of compounds of formula (I) in relation to a disorder selected from addictive disorders, psychoactive substance use disorders, intoxication disorders, inhalation disorders, alcohol addiction, tobacco addiction, and nicotine addiction.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: 1,13-25 (partially) 2-4

Use of a heterocyclic amine for the preparation of a medicament for treating or suppressing the symptoms of at least one disorder selected from addictive disorders, psychoactive substance use disorders, intoxication disorders, inhalation disorders, alcohol addiction, tobacco addiction, and nicotine addiction.

2. Claims: 1,13-25 (partially), 5-7

Use of a phenylazacycloalkane for the preparation of a medicament for treating or suppressing the symptoms of at least one disorder selected from addictive disorders, psychoactive substance use disorders, intoxication disorders, inhalation disorders, alcohol addiction, tobacco addiction, and nicotine addiction.

3. Claims: 1,13-25 (partially), 8,9

Use of a cabergoline for the preparation of a medicament for treating or suppressing the symptoms of at least one disorder selected from addictive disorders, psychoactive substance use disorders, intoxication disorders, inhalation disorders, alcohol addiction, tobacco addiction, and nicotine addiction.

4. Claims: 1,13-16 (partially), 10-12

Use of a aromatic bicyclic amine for the preparation of a medicament for treating or suppressing the symptoms of at least one disorder selected from addictive disorders, psychoactive substance use disorders, intoxication disorders, inhalation disorders, alcohol addiction, tobacco addiction, and nicotine addiction.

The problems to be solved by the present application are to provide for the treatment or suppressing the symptoms of at least one disorder selected from addictive disorders, psychoactive substance use disorders, intoxication disorders, inhalation disorders, alcohol addiction, tobacco addiction, and nicotine addiction.

The proposed solutions are to use an agent selected from the group consisting of a heterocyclic amine, a phenylazacycloalkane, a cabergoline and an aromatic bicyclic amine.

US6008233 discloses that (1S,2S)-1-(4-hydroxyphenyl)-2-(4-hydroxy-4-phenyl piperidin-1-yl)- 1-propanol methane sulphonate trihydrate, a phenylazacycloalkane, may be used to treat disorders of the central nervous system, a.o. drug and alcohol addiction, drug and alcohol withdrawal symptoms. See the passages cited in the search report.

W09924423 discloses the use of N-(2-Cyclopropoxy-5-tetrazolyl-benzyl)-2-phenyl- piperidine-3-amine, a heterocyclic amine and a phenylazacycloalkane derivative to treat substance-related disorders arising from the use of alcohol, amphetamines (or amphetamine-like substances) caffeine, cannabis, cocaine, hallucinogens, inhalants and aerosol propellants, nicotine, opioids, phenylglycidine derivatives, sedatives, hypnotics, and anxiolytics, which substance-related disorders include dependence and abuse, intoxication, withdrawal, intoxication delirium, withdrawal delirium. See the passages cited in the search report.

W09910339 discloses 2-Aminopyridine derivatives which are aromatic bicyclic amines and heterocyclic amines useful to treat central nervous system and other disorders, including chemical dependencies and addiction (e.g., dependencies on drugs, alcohol and nicotine). See the passages cited in the search report.

The documents cited do not represent a comprehensive search for any of the defined inventions and are to be considered only as part of the prior art pertaining to the general idea underlying the present application.

According to Article 3(4)(iii) PCT, an international application shall comply with "the prescribed requirement of unity of invention". This means, as explained in Rule 13.1 PCT, that the application shall relate to one invention only or to a group of inventions so linked as to form a single general inventive concept.

From the above cited documents, it appears that the use the compounds of the present invention in relation to above specified uses and in the treatment of above specified conditions is known in the prior art and can not fulfil the role of special technical feature (general inventive concept) in the sense of Rule 13.2 PCT.

In the present application no further technical feature can be distinguished that can be regarded as a "special technical feature" involved in the technical relationship among the different inventions.

Consequently the present application lacks unity of invention.

Each of the invention is a distinct invention, characterised by its own special technical feature, defining the contribution which each of the claimed inventions, considered as a whole, makes over the prior art.

As searching the other subject would have caused a major additional searching effort, only the first invention was searched.

The application relates to a plurality of inventions, or groups of inventions, in the sense of Rule 13.1 PCT. They have been divided as defined above. If the applicant pays additional fees for one (or more) not yet searched group(s) of invention(s), then the further search(es) may reveal further prior art that gives evidence of a further lack of unity 'a posteriori' within one (or more) of the not yet searched group(s). In such a case only the first invention in this (each of

these) group(s) of inventions, which is considered to lack unity of invention, will be the subject of a search.

No further invitation to pay further additional fees will be issued. This is because Article 17(3)(a) PCT stipulates that the ISA shall establish the International Search Report on those parts of the international application which relate to the invention first mentioned in the claims ('main invention') and for those parts which relate to inventions in respect of which the additional fees were paid. Neither the PCT nor the PCT guidelines provide a legal basis for further invitations to pay further additional search fees (W17/00, point 11 and W1/97, points 11-16).



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USXXXXX233A

United States Patent [19]

[11] **Patent Number:** **6,008,233**

Andino et al.

[45] **Date of Patent:** **Dec. 28, 1999**

[54] **(1S,2S)-1-(4-HYDROXYPHENYL)-2-(4-HYDROXY-4-PHENYL)PIPERIDIN-1-YL)-1-PROPANOL METHANESULFONATE TRIHYDRATE**

[52] **U.S. Cl.** 514/327; 546 217

[58] **Field of Search** 546 217; 514 327

[56] **References Cited**

U.S. PATENT DOCUMENTS

5,185,343 2-1993 Chenard.

5,272,160 12-1993 Chenard.

FOREIGN PATENT DOCUMENTS

WO 96/06481 2-1996 WIPO.

Primary Examiner—John Kight

Assistant Examiner—Raymond Cowington

Attorney, Agent, or Firm—Peter C. Richardson; Paul H. Ginsburg; Bryan C. Zielinski

[57] **ABSTRACT**

The invention relates to the trihydrate of the mesylate salt of (1S,2S)-1-(4-hydroxyphenyl)-2-(4-hydroxy-4-phenylpiperidin-1-yl)-1-propanol, pharmaceutical compositions containing said compound and methods of treating disorders of the central nervous system by administering said compound.

10 Claims, 2 Drawing Sheets

[75] **Inventors:** **Marta M. Andino, Gales Ferry; Terry G. Slnay, Preston; Eugene F. Flese, Ledyard, all of Conn.**

[73] **Assignee:** **Pfizer Inc., New York, N.Y.**

[21] **Appl. No.:** **09/011,426**

[22] **PCT Filed:** **Jun. 20, 1996**

[86] **PCT No.:** **PCT/IB96/00592**

§ 371 Date: **May 7, 1998**

§ 102(e) Date: **May 7, 1998**

[87] **PCT Pub. No.:** **WO97/07098**

PCT Pub. Date: **Feb. 27, 1997**

Related U.S. Application Data

[60] **Provisional application No. 60/102,236, Aug. 11, 1995.**

[51] **Int. Cl.** **A01N 43/40**

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FIG. 1

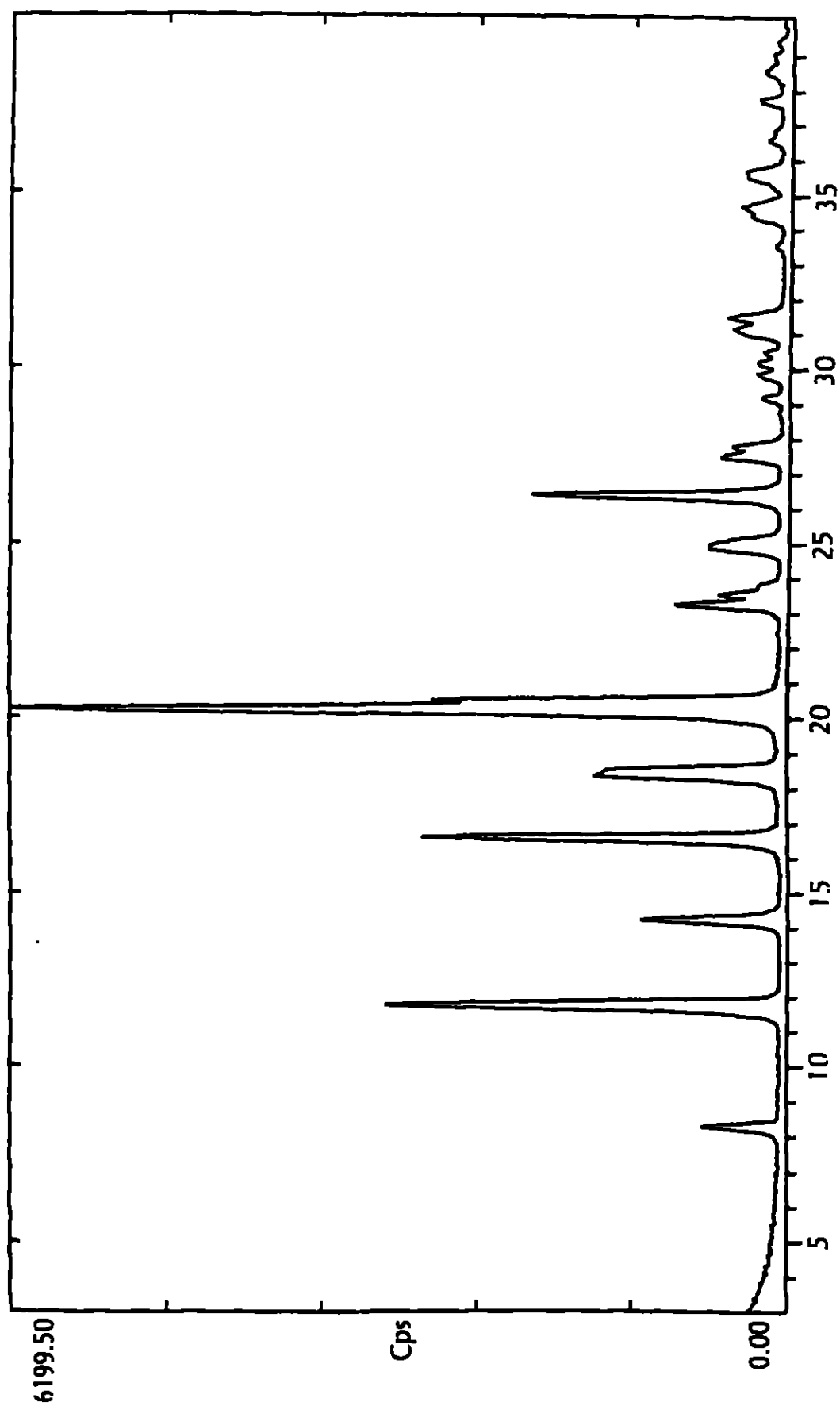
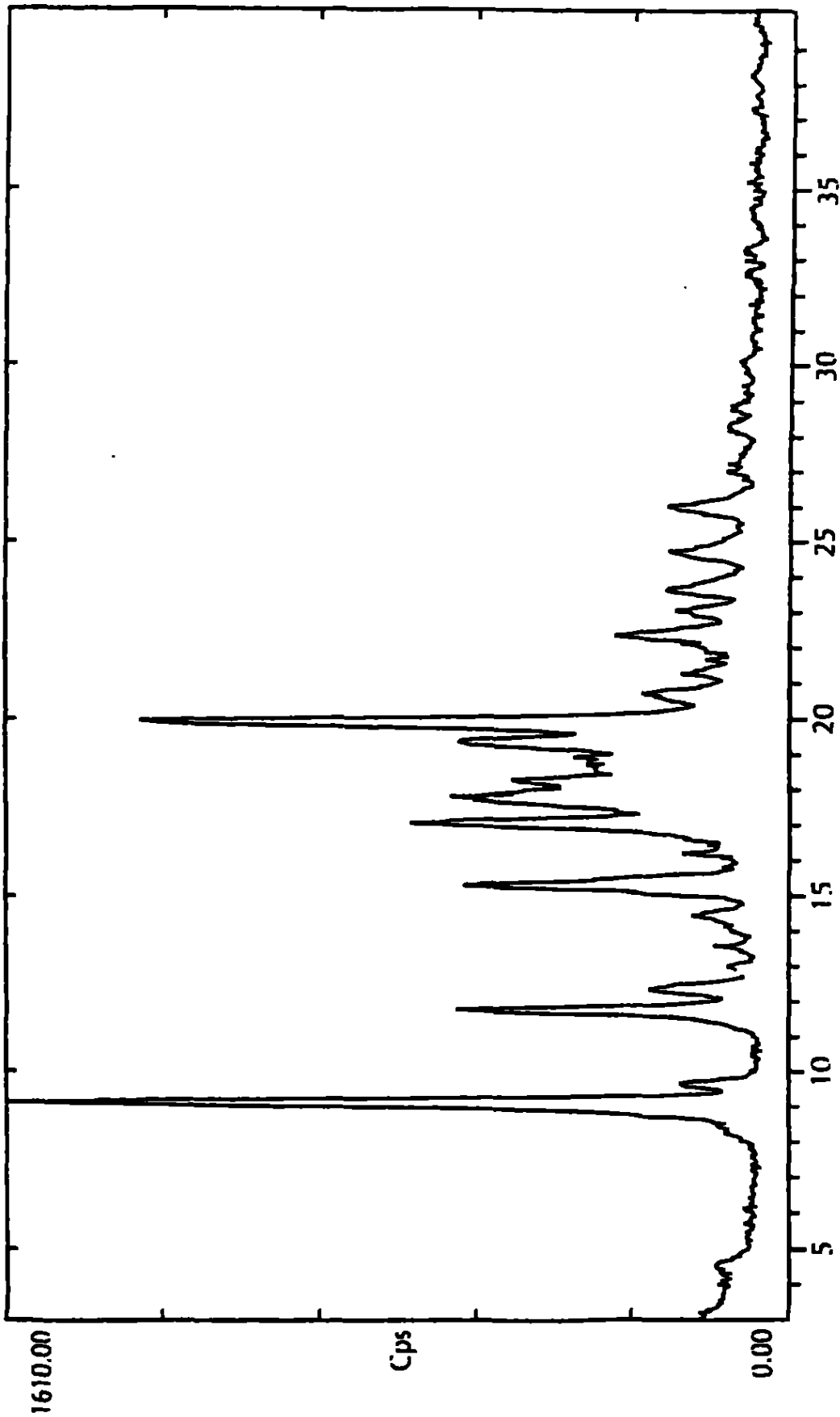


FIG. 2



(1S,2S)-1-(4-HYDROXYPHENYL)-2-(4-HYDROXY-4-PHENYLPYPERIDIN-1-YL)-1-PROPANOL METHANESULFONATE TRIHYDRATE

This application claims benefit of Provisional Application 60/002,238 filed Aug. 11, 1995.

This invention relates to the novel and clinically advantageous trihydrate of the methanesulfonate salt of (1S,2S)-1-(4-hydroxyphenyl)-2-(4-hydroxy-4-phenylpiperidin-1-yl)-1-propanol (hereinafter referred to as "the mesylate salt trihydrate"). This mesylate salt trihydrate, as well as the corresponding anhydrous mesylate salt and free base of (1S,2S)-1-(4-hydroxyphenyl)-2-(4-hydroxy-4-phenylpiperidin-1-yl)-1-propanol (hereinafter referred to, respectively, as "the anhydrous mesylate" and "the free base") exhibit activity as NMDA (N-methyl-D-aspartic acid) receptor antagonists and are useful in the treatment of epilepsy, anxiety, cerebral ischemia, muscular spasms, multifactor dementia, traumatic brain injury, pain, AIDS related dementia, hypoglycemia, migraine, amyotrophic lateral sclerosis, drug and alcohol addiction, drug and alcohol withdrawal symptoms, psychotic conditions, urinary incontinence and degenerative CNS (central nervous system) disorders such as stroke, Alzheimer's disease, Parkinson's disease and Huntington's disease.

The free base, the anhydrous mesylate and methods of preparing them are referred to, generically, in U.S. Pat. No. 5,165,343, which issued on Feb. 9, 1993. They and their use in treating certain of the above disorders are referred to, specifically, in U.S. Pat. No. 5,272,160, which issued on Dec. 21, 1993. Their use in treating the above disorders is referred to in International Patent Application PCT/IL 95/00380, which designates the United States and was filed on May 18, 1995. Their use in combination with a compound capable of enhancing and thus restoring the balance of excitatory feedback from the ventral lateral nucleus of the thalamus into the cortex to treat Parkinson's disease is referred to in International Patent Application PCT/IL 95/00398, which designates the United States and was filed on May 20, 1995. The foregoing U.S. patents and patent applications are incorporated herein by reference in their entireties.

NMDA is an excitatory amino acid. The excitatory amino acids are an important group of neurotransmitters that mediate excitatory neurotransmission in the central nervous system. Glutamic acid and aspartic acid are two endogenous ligands that activate excitatory amino acid (EAA) receptors. There are two types of EAA receptors, ionotropic and metabotropic, which differ in their mode of signal transduction. There are at least three distinct ionotropic EAA receptors characterized by the selective agonist that activates each type: the NMDA, the AMPA (2-amino-3-(5-methyl-3-hydroxyisoxazol-4-yl)propanoic acid) and the kainic acid receptors. The ionotropic EAA receptors are linked to ion channels that are permeable to sodium and, in the case of NMDA receptors, calcium. Metabotropic receptors, linked to phosphoinositide hydrolysis by a membrane associated G-protein, are activated by quisqualic acid, ibotenic acid, and (1S,3R)-1-aminocyclopentane 1,3-dicarboxylic acid.

The NMDA receptor is a macromolecular complex consisting of a number of distinct binding sites that gate on ion channels permeable to sodium and calcium ions. Hansen and Kroeggaard-Larson, *Mol. Res. Rev.*, 10, 55-94 (1990). There are binding sites for glutamic acid, glycine, and polyamines, and a site inside the ion channel where compounds such as phencyclidine (PCP) exert their antagonist effects.

Competitive NMDA antagonists are compounds that block the NMDA receptor by interacting with the glutamate binding site. The ability of a particular compound to competitively bind to the NMDA glutamate receptor may be determined using a radioligand binding assay, as described by Murphy et al., *British J. Pharmacol.*, 95, 932-938 (1988). The antagonists may be distinguished from the agonists using a rat cortical wedge assay, as described by Harrison and Simmonds, *British J. Pharmacol.*, 84, 381-391 (1984). Examples of competitive NMDA antagonists include D-2 amino-5-phosphonopentanoic acid (D-AP5), and D-2-amino-7-phosphonoheptanoic acid, Schaepp et al., *J. Neurotransm.*, 85, 131-143 (1991).

This invention also relates to a method treating of mammals suffering from Parkinson's disease which comprises administering to said mammal (1S,2S)-trans-2-methyl-2-(4-hydroxy-4-phenylpiperidin-1-yl)-1-hydroxy-1-(4-hydroxyphenyl)ethanol methanesulfonate trihydrate and a compound capable of increasing the excitatory feedback from the ventral lateral nucleus of the thalamus into the cortex, such that the balance of the excitatory feedback from the ventral lateral nucleus of the thalamus into the cortex in said mammal suffering from Parkinson's disease is restored. International Patent Application PCT/IL 95/00398, which is referred to above and incorporated herein by reference in its entirety, refers to the use of the free base and the anhydrous mesylate in combination with such an excitatory feedback enhancing agent to treat Parkinson's disease.

The mesylate trihydrate is substantially superior as a therapeutic agent compared to the anhydrous mesylate. It is a more stable crystalline form than the corresponding anhydrous salt, has a substantially longer shelf life and is less subject to breakdown of the crystal structure due to the inclusion of water in the crystal.

SUMMARY OF THE INVENTION

This invention relates to (1S,2S)-1-(4-hydroxyphenyl)-2-(4-hydroxy-4-phenylpiperidin-1-yl)-1-propanol methanesulfonate trihydrate.

This invention also relates to a pharmaceutical composition for the treatment of a disorder selected from degenerative CNS disorders such as stroke, Alzheimer's disease, Parkinson's disease and Huntington's disease; spinal cord trauma, epilepsy, anxiety, cerebral ischemia, muscular spasms, multifactor dementia, traumatic brain injury, pain, AIDS related dementia, hypoglycemia, migraine, amyotrophic lateral sclerosis, drug and alcohol addiction, drug and alcohol withdrawal symptoms, psychotic conditions and urinary incontinence in a mammal, including a human, comprising an NMDA antagonizing amount of (1S,2S)-1-(4-hydroxyphenyl)-2-(4-hydroxy-4-phenylpiperidin-1-yl)-1-propanol methanesulfonate trihydrate and a pharmaceutically acceptable carrier.

This invention also relates to a pharmaceutical composition for the treatment of a disorder selected from degenerative CNS disorders such as stroke, Alzheimer's disease, Parkinson's disease and Huntington's disease; epilepsy, anxiety, cerebral ischemia, muscular spasms, multifactor dementia, traumatic brain injury, pain, AIDS related dementia, hypoglycemia, migraine, amyotrophic lateral sclerosis, drug and alcohol addiction, drug and alcohol withdrawal symptoms, psychotic conditions and urinary incontinence in a mammal, including a human, comprising an amount of (1S,2S)-1-(4-hydroxyphenyl)-2-(4-hydroxy-4-phenylpiperidin-1-yl)-1-propanol methanesulfonate trihydrate that is effective in treating such disorder, and a pharmaceutically acceptable carrier.

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This invention also relates to a method of treating a disorder selected from degenerative CNS disorders such as stroke, Alzheimer's disease, Parkinson's disease and Huntington's disease; epilepsy, anxiety, cerebral ischemia, muscular spasms, multiinfarct dementia, traumatic brain injury, pain, AIDS related dementia, hypoglycemia, migraine, amyotrophic lateral sclerosis, drug and alcohol addiction, drug and alcohol withdrawal symptoms, psychotic conditions and urinary incontinence in a mammal, including a human, comprising administering to said mammal an amount of (1S,2S)-1-(4-hydroxyphenyl)-2-(4-hydroxy-4-phenylpiperidin-1-yl)-1-propanol methane-sulfonate trihydrate that is effective in treating such disorder.

This invention also relates to a method of treating a disorder selected from degenerative CNS disorders such as stroke, Alzheimer's disease, Parkinson's disease and Huntington's disease; epilepsy, anxiety, cerebral ischemia, muscular spasms, multiinfarct dementia, traumatic brain injury, pain, AIDS related dementia, hypoglycemia, migraine, amyotrophic lateral sclerosis, drug and alcohol addiction, drug and alcohol withdrawal symptoms, psychotic conditions and urinary incontinence in a mammal, including a human, comprising administering to said mammal an NMDA antagonizing amount of (1S,2S)-1-(4-hydroxyphenyl)-2-(4-hydroxy-4-phenylpiperidin-1-yl)-1-propanol methanesulfonate trihydrate.

This invention relates to a method of treating Parkinson's disease in a mammal, including a human, comprising administering to said mammal a Parkinson's disease treating effective amount of a synergistic combination of (1S,2S)-1-(4-hydroxyphenyl)-2-(4-hydroxy-4-phenylpiperidin-1-yl)-1-propanol methanesulfonate trihydrate and an agent capable of restoring the balance of the excitatory feedback from the ventral lateral nucleus of the thalamus into the cortex.

This invention also relates to a method of treating Parkinson's disease in a mammal, including a human, comprising treating said mammal with a Parkinson's disease treating effective amount of a synergistic combination of the trihydrate of (1S,2S)-1-(4-hydroxyphenyl)-2-(4-hydroxy-4-phenylpiperidin-1-yl)-1-propanol methanesulfonate trihydrate and an excitatory feedback enhancing agent selected from the group consisting of dopamine agonists, dopamine D1 agonists, dopamine D2 agonists, dopamine β -adrenergic receptor agonists, dopamine 5-HT uptake inhibitor 5-HT-1A agonists, dopamine opiate agonists, adrenoceptor agonists, α 2-adrenergic antagonist dopamine agonists, α 2-adrenergic dopamine D2 agonists, dopamine uptake inhibitors, monoamine oxidase inhibitors, monoamine oxidase-B inhibitors, catecholamethyl transferases (COMT) inhibitors and levodopa.

DESCRIPTION OF THE DRAWINGS

FIG. 1 depicts the X-ray powder diffraction spectrum of the mesylate trihydrate (taken on a Siemens D 5000 diffractometer after equilibration of the anhydrous mesylate at 81% relative humidity ("RH")), expressed as intensity (CPS) versus diffraction angle (two-theta degrees).

FIG. 2 depicts the X-ray powder diffraction spectrum of the anhydrous mesylate, taken on a Siemens D 5000 diffractometer and expressed as intensity (CPS) versus diffraction angle (two-theta degrees).

Tables 1 and 2 below identify selected peaks from the spectra of FIGS. 1 and 2, respectively, by diffraction angle (two-theta), d-spacing (d), relative intensity (rel. int.) and maximum intensity (max. int.).

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Table 1

X-RAY POWDER DIFFRACTION DATA FOR THE MESYLATE TRIHYDRATE

TABLE 1

X-RAY POWDER DIFFRACTION DATA FOR THE MESYLATE TRIHYDRATE			
Two-Theta (degrees)	D-spacing (degrees)	Max. Int. (counts/sec)	Rel. Int. (%)
8.290	10.6563	666.50	10.78
11.795	7.5026	3202.00	51.64
14.267	6.2027	1100.00	18.71
16.618	5.3302	2000.00	46.94
18.473	4.7989	1512.00	24.41
20.261	4.3792	6190.50	100.00
23.272	3.6190	800.50	14.41
23.630	3.5634	400.50	7.94
24.965	3.3608	633.50	10.21
26.980	3.1257	2042.50	32.94
27.755	3.0116	445.50	7.19
29.165	2.8094	214.00	3.45
29.830	2.7019	290.50	4.39
30.100	2.6607	286.50	4.14
30.400	2.6002	207.50	3.34
31.106	2.5728	440.50	7.24
31.400	2.5305	403.50	7.06
33.564	2.2678	125.50	2.02
34.630	2.1667	300.00	5.26
35.574	2.1216	359.00	6.77
36.568	2.0553	093.50	1.12
37.080	2.0053	254.50	4.11
38.907	1.8660	215.00	3.47
39.920	1.7121	158.00	2.44
40.350	1.6804	120.00	2.08

Table 2

X-RAY POWDER DIFFRACTION DATA FOR THE ANHYDROUS MESYLATE

TABLE 2

X-RAY POWDER DIFFRACTION DATA FOR THE ANHYDROUS MESYLATE			
Two-Theta (degrees)	D-spacing (degrees)	Max. Int. (counts/sec)	Rel. Int. (%)
4.295	19.6446	140.50	9.20
9.098	9.7116	1600.00	100.00
9.656	9.1524	221.00	13.71
11.233	7.5362	682.50	42.39
12.374	7.1472	264.50	17.67
12.976	6.8167	123.00	7.64
13.564	6.5229	149.50	9.29
14.120	6.2671	130.50	8.11
14.464	6.1106	096.00	12.17
15.113	5.7814	667.00	41.43
16.268	5.4449	212.50	13.26
17.006	5.1647	777.00	48.26
17.799	4.9000	634.00	43.11
18.264	4.8534	569.50	38.17
18.916	4.6876	440.00	27.33
19.468	4.5791	679.50	42.29
19.932	4.4496	1332.50	82.76
20.743	4.2787	206.50	18.42
21.167	4.1971	216.50	13.45
22.410	3.9641	354.50	22.02
23.066	3.8444	230.50	14.32
23.672	3.7544	280.50	18.46
24.725	3.5078	243.00	15.09
26.024	3.2111	246.00	15.26
27.088	3.0800	127.00	7.89

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Table 3

TABLE 2-continued

X-RAY POWDER DIFFRACTION DATA FOR THE ANHYDROUS MESYLATE			
Two Theta (degrees)	Spacing (degrees)	Max. Int. (counts/sec)	Ref. Int. (%)
25.276	3.1535	126.90	7.86
26.820	3.0953	121.00	7.52
30.083	2.9681	103.00	6.30
32.611	2.8435	97.00	6.02
33.272	2.8005	100.50	6.24
34.202	2.7628	83.50	5.19
35.186	2.7268	87.50	5.43

DETAILED DESCRIPTION OF THE
INVENTION

The mesylate salt trihydrate is a white crystalline solid that exhibits well defined, narrowed X-ray diffraction peaks (FIG. 1), in contrast to the anhydrous mesylate, which exhibits poor diffraction pattern resolution, a raised background and lack of diffraction peaks at 2θ>26° (FIG. 2). Only one crystalline form has been observed for the trihydrate mesylate. This crystalline form has good solubility in water (25 and 15 mg/ml in pH 3 and 7 aqueous buffered solutions, respectively).

The mesylate salt trihydrate can be prepared by the following method. The free base is dissolved in water at 40° C. To this solution is added at least 1 equivalent of methane sulfonic acid and the resulting mixture is warmed to 60-65° C. The warm solution can be filtered to render it particulate free. The solution is concentrated to approximately 40% of the initial volume, cooled below 10° C., isolated by filtration and dried to a water content (measured Karl Fischer titration) of approximately 11.3%. The resulting crystalline mesylate salt trihydrate can be further purified by recrystallization.

The anhydrous mesylate, when equilibrated in an 81% RH environment, will convert to the mesylate salt trihydrate.

The free base and anhydrous mesylate can be prepared as described in U.S. Pat. No. 5,272,160, which is referred to above and incorporated herein by reference in its entirety. The resolution of racemic 1-(4-hydroxyphenyl)-2-(4-hydroxy-4-phenylpiperidin-1-yl)-1-propanol to form the free base and corresponding (1R,2R) enantiomer is exemplified in Example 1. An alternate method of preparing the free base is described in Example 2, which also exemplifies the synthesis of the mesylate salt trihydrate.

The hygroscopicity of the mesylate salt trihydrate was studied at 0%, 52% and 98% controlled relative humidities (RH's), and under ambient laboratory conditions (24-27° C., 31-64% RH's). No weight change was observed at 52% and 98% RH's or under ambient conditions. Loss of waters of hydration is observed at 0% RH. The weight loss observed at 0% RH was reversible; the anhydrous form quickly equilibrated to the hydrated form when exposed to higher humidities. Weight loss was also observed in bulk stability samples stored in polyethylene bags at 40° C., 30% RH (>10% of weight was lost in 9 months).

By contrast, a substantial weight gain was observed for the anhydrous mesylate at ambient conditions, as shown in Table 3 below.

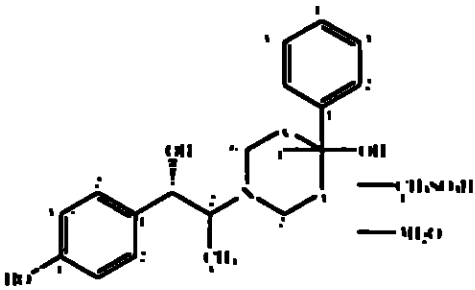
HYGROSCOPICITY AT AMBIENT
CONDITIONS OF THE ANHYDROUS
MESYLATE SALT

TABLE 3

HYGROSCOPICITY AT AMBIENT CONDITIONS OF THE ANHYDROUS MESYLATE SALT			
Weight of Sample	% Difference from Prev. Weighing	% Difference from Initial	Time Since Initial
0.4972 g	—	—	—
0.4972 g	0.06	0.06	1 hours
0.4972 g	0.09	0.06	3 hours
0.4990 g	0.26	0.32	22 hours
0.5002 g	0.24	0.56	30.5 hours
0.5076 g	1.36	1.93	48 hours
0.5102 g	0.53	2.47	68 hours
0.5175 g	1.33	3.83	130 hours
0.5176 g	0.00	3.83	132 hours
0.5171 g	0.02	3.86	218 hours
0.5184 g	0.25	4.12	246 hours
0.5203 g	0.37	4.50	362 hours
0.5193 g	-0.19	4.30	408 hours
0.5193 g	0.00	4.30	413 hours

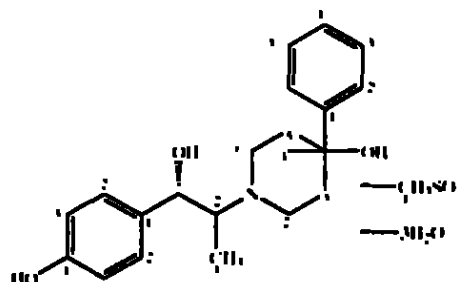
Proton and Carbon Nuclear Magnetic Resonance (NMR)
Spectra of the Mesylate Salt Trihydrate

The proton and carbon NMR spectra of the mesylate salt trihydrate are described below. Chemical shift assignments in (1D,1D) (relative to tetramethylsilane (TMS)) were made on the basis of ¹H-¹H Correlated Spectroscopy (COSY), ¹H-¹³C Distortionless Enhancement by Polarization Transfer (DELPT), and ¹H-¹³C Heteronuclear Chemical Shift Correlation (HETCOR) two-dimensional NMR experiments. The tentative proton and carbon peak assignments are given below and are consistent with the structure of the mesylate salt trihydrate.



Assignment	¹³ C (δ, ppm)	# Protons	¹ H (δ, ppm)
3	159.2	0	—
1*	146.2	0	—
1	132.6	0	—
2	129.8	2	7.50 (m)
3*	129.5	2	7.50 (m)
4*	126.4	1	7.50 (m)
2*	125.6	2	7.50 (m)
3	116.5	2	6.84 (d)
1	71.5	1	4.66 (d)
4*	69.8	0	—
2	68.3	1	3.58 (m)
6*/1*	48.8	2	3.12 (d), 3.72 (d)
2*/1*	43.2	2	3.58 (m)
4	36.5	3	2.70 (s)

-continued



Assignment	δ (ppm)	# Protons	δ (ppm)
4' (2)	76.6	2	2.64 (t, 1.98 td)
3' (2)	76.4	2	2.42 (t, 1.98 td)
1	6.7	1	1.12 (d)

(1) The 6' and 2' positions are not chemically equivalent, the assignments may be interchangeable.

(2) The 4' and 3' positions are not chemically equivalent the assignments may be interchangeable. The proton splitting pattern at 1.98-2.00 ppm appears as two doublets when acquired on a high-field instrument (500 MHz), but only as a triplet when acquired with a lower field (300 MHz) instrument. This is believed to be due to a salt effect arising from the mesylate.

The mesylate salt trihydrate, similar to the anhydrous mesylate and free base, possesses selective neuroprotective activity, based upon its antischemic activity and ability to block excitatory amino acid receptors. The preferred procedure for evaluating the neuroprotective activity of this compound is that described by Ismail A. Shalaby, et al., in *J. Pharm. and Experimental Therapeutics*, 260, 925 (1992). This article is incorporated herein by reference in its entirety and described below.

Cell culture. Seventeen day fetal rat (C1), (Charles River Breeding Laboratories, Inc., Wilmington, Mass.) hippocampal cells are cultured on PRIMARIA culture plates (Becton Dickinson Co., Lincoln Park, N.J.) for 2 to 3 weeks in serum containing culture medium (minimum essential medium with nonessential amino acids, containing 2 mM glutamine, 21 mM glucose, penicillin streptomycin (5000 U each), 10% fetal bovine serum (days 1-7) and 10% horse serum (days 1-21). Cells are either plated on 96-well microtiter plates at a density of 80,000 cells per well or on 24-well culture plates at a density of 250,000 cells per well. Cultures are grown at 37° C. in a humidified CO₂ tissue culture incubator containing 5% CO₂/95% air. Proliferation of nonneuronal cells is controlled by adding 20 μ M uridine and 20 μ M 5-fluoro-2-deoxyuridine (Sigma Chemical Co., St. Louis, Mo.) from days 6 to 8 of culture. Culture media is exchanged every 2 to 3 days with fresh stock.

Glutamate toxicity. The cultures are assessed for glutamate toxicity 2 to 3 weeks from initial plating. Culture media is removed and cultures rinsed twice with a CSS (in millimolar): NaCl, 12; KCl, 5.4; MgCl₂, 0.8; CaCl₂, 1.8; glucose, 15; and 4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid, 25 mM (pH 7.4). Cultures are then exposed for 15 min (37° C.) to various concentrations of glutamate. After this incubation, cultures are rinsed 3 times with glutamate-free CSS and twice with fresh culture medium without serum. The cultures are then incubated for 20 to 24 hr in serum-free culture medium. The compound being tested is added 2 min before and during the 15-min exposure to glutamate. In some experiments, the compound is added at different times after the glutamate exposure and for the following 20 to 24 hr.

Cell viability is routinely assessed 20 to 24 hours after the excitotoxin exposure by measuring the activity of the cyto-

solic enzyme LDH. LDH activity is determined from the culture medium of each of the 96 wells of the microtiter plates. A 50- μ l sample of the media is added to an equal volume of sodium-phosphate buffer (0.1 M, pH 7.4) containing 1.32 mM sodium pyruvate and 2.9 mM NADH. The 340 nm absorbance of the total reaction mixture for each of the 96 wells is monitored every 5 sec for 2 min by an automated spectrophotometric microtiter plate reader (Molecular Devices; Menlo Park, Calif.). The rate of absorbance is automatically calculated using an IBM S01/Tmax program (version 1.01; Molecular Devices) and is used as the index of LDH activity.

Morphological assessment of neuronal viability is determined using phase contrast microscopy. The 96-well culture plates do not permit good phase-contrast imagery, so cells cultured on 24-well plates are used for this purpose. Quantitatively, both culture platings are equally sensitive to glutamate toxicity, and display 2- to 3-fold increases in LDH activity 24 hours after exposure to 0.1 to 1.0 mM glutamate.

Reagents. DTG can be purchased from Aldrich (Chemical Company (Milwaukee, Wis.), and haloperidol from Research Biochemicals Inc. (Natick, Mass.). Spermine can be purchased from Sigma (Chemical Co. (St. Louis, Mo.). Horse and fetal bovine serum can be purchased from Hyclone (Logan, Utah). Culture medium, glutamine and penicillin streptomycin can be purchased from Gibco (Grand Island, N.Y.).

Data analysis. Neurotoxicity can be quantified by measuring the activity of LDH present in the culture medium 20 to 24 hours after glutamate exposure. The increased LDH activity in the culture media correlates with destruction and degeneration of neurons (Koh and Choi, 1987). Because actual levels of LDH vary from different cultures, data are routinely expressed relative to buffer-treated sister wells of the same culture plate. To obtain an index of LDH activity from glutamate and drug-treated cultures, the LDH values from control cultures are subtracted from that of the treatment groups. Data for drug treatments is expressed as a percentage of the increase in LDH induced by 1 mM glutamate (or NMDA) for each experiment. Concentrations of NMDA antagonists required to reverse 50% of the LDH increase induced by excitotoxins (IC₅₀) are calculated using log-probit analysis from the pooled results of three independent experiments.

The selective neuroprotective antischemic and excitatory amino acid blocking activities of the mesylate salt trihydrate of this invention render it useful in the treatment of disorders selected from degenerative CNS disorders such as stroke, Alzheimer's disease, Parkinson's disease and Huntington's disease; epilepsy, anxiety, cerebral ischemia, muscular spasms, multiinfarct dementia, traumatic brain injury, pain, AIDS related dementia, hypoglycemia, migraine, amyotrophic lateral sclerosis, drug and alcohol addiction, drug and alcohol withdrawal symptoms, psychotic conditions and urinary incontinence.

In the systemic treatment of such disorders, the dosage is typically from about 0.02 to 250 mg/kg/day (0.001-12.5 g/day in a typical human weighing 50 kg) in single or divided doses, regardless of the route of administration. A more preferred dosage range is from about 0.15 mg/kg/day to about 250 mg/kg/day. Of course, depending upon the exact nature of the illness and the condition of the patient, doses outside this range may be prescribed by the attending physician. The oral route of administration is generally preferred. However, if the patient is unable to swallow, or oral absorption is otherwise impaired, the preferred route of administration will be parenteral (i.m., i.v.) or topical.

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The mesylate salt trihydrate may be administered in the form of pharmaceutical compositions together with a pharmaceutically acceptable vehicle or diluent. Such compositions are generally formulated in a conventional manner utilizing solid or liquid vehicles or diluents as appropriate to the mode of desired administration: for oral administration, in the form of tablets, hard or soft gelatin capsules, suspensions, granules, powders and the like; for parenteral administration, in the form of injectable solutions or suspensions, and the like; and for topical administration, in the form of solutions, lotions, ointments, salves and the like.

EXAMPLE 1

Enantiomeric (1S,2S)- and (1R,2R)-1-(4-(4-hydroxyphenyl)-2-(4-hydroxy-4-phenylpiperidin-1-yl)-1-propanol

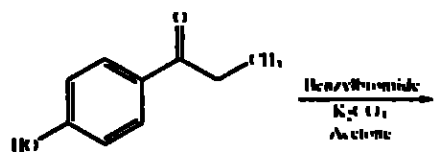
(+)-tartaric acid (300 mg, 2 mmol) was dissolved in 30 ml warm methanol. Racemic 1S,2S-1-(4-(4-hydroxyphenyl)-2-(4-hydroxy-4-phenylpiperidin-1-yl)-1-propanol (655 mg, 2 mmol) was added all at once. With stirring and gentle warming a colorless homogeneous solution was obtained. Upon standing at ambient temperature 24 hours, 319 mg (66%) of a fluffy white precipitate was obtained. This product was recrystallized from methanol to give 263 mg of the (+)-tartrate salt of levorotatory title product as a white solid; mp 206.5-207.5° C.; [α]_D²⁵ = -36.2°. This salt (115 mg) was added to 50 ml. of saturated NaHCO₃. Ethyl acetate (5 ml.) was added and the mixture was vigorously stirred 30 minutes. The aqueous phase was repeatedly extracted with ethyl acetate. The organic layers were combined and washed with brine, dried over calcium sulfate, and concentrated. The tan residue was recrystallized from ethyl acetate-hexane to give 32 mg (39%) of white, levorotatory title product; mp 203-204° C.; [α]_D²⁵ = -56.9°. Anal. Calcd. for C₂₅H₂₇N₃O₃: C, 73.37; H, 7.70; N, 4.28. Found: C, 72.61; H, 7.45; N, 4.21.

The filtrate from the (+)-tartrate salt preparation above was treated with 100 ml. saturated aqueous NaHCO₃ and extracted well with ethyl acetate. The combined organic extracts were washed with brine, dried over calcium sulfate and concentrated to give 380 mg of recovered starting material (partially resolved). This material was treated with (-)-tartaric acid (174 mg) in 30 ml. of methanol as above. After standing for 24 hours, filtration gave 320 mg (66%) of product which was further recrystallized from methanol to produce 239 mg of the (-)-tartrate salt of dextrorotatory title product; mp 206.5-207.5° C.; [α]_D²⁵ = +33.9°. The latter was converted to dextrorotatory title product in the manner above in 49% yield; mp 204-205° C.; [α]_D²⁵ = +58.4°. Anal. found: C, 72.94; H, 7.64; N, 4.24.

EXAMPLE 2

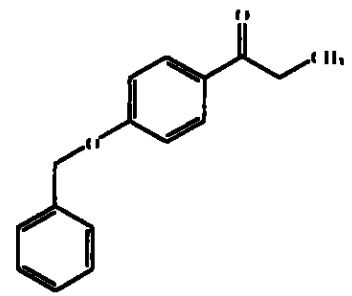
(1S,2S)-1-(4-(4-hydroxyphenyl)-2-(4-hydroxy-4-phenylpiperidin-yl)-1-propanol Methanesulfonate Trihydrate

STEP 1



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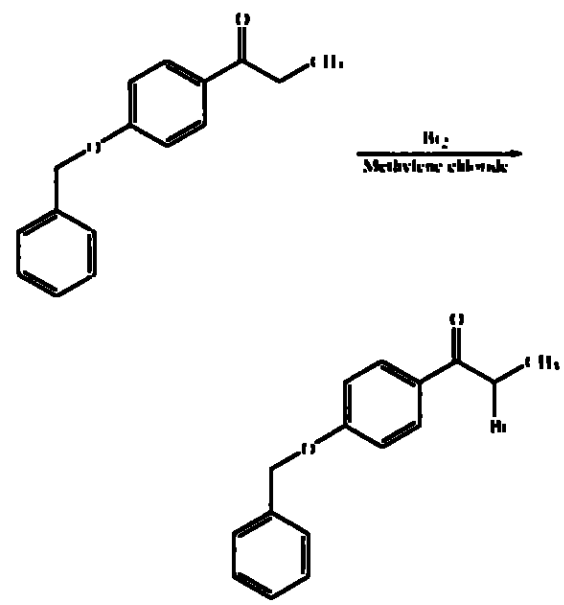
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A 50 gallon glass lined reactor was charged with 17.1 gallons of acetone, 8.65 kilograms (kg) (57.7 mol) of 4'-hydroxypropiophenone, 9.95 kg (72.0 mol) of potassium carbonate and 6.8 liters (l) (57.7 mol) of benzylbromide. The mixture was heated to reflux (56° C.) for 20 hours. Analysis of thin layer chromatography (TLC) revealed that the reaction was essentially complete. The suspension was atmospherically concentrated to a volume of 10 gallons and 17.1 gallons of water were charged. The suspension was granulated at 25° C. for 1 hour. The product was filtered on a 30" Lapp and washed with 4.6 gallons of water followed by a mixture of 6.9 gallons of hexane and 2.3 gallons of isopropanol. After vacuum drying at 45° C., this yielded 13.35 kg (96.4%) of the above-depicted product.

A second run was carried out with 9.8 kg (65.25 mol) of 4'-hydroxypropiophenone using the procedure described above. After drying 15.1 kg (96.3%) of the above-depicted product was obtained.

STEP 2



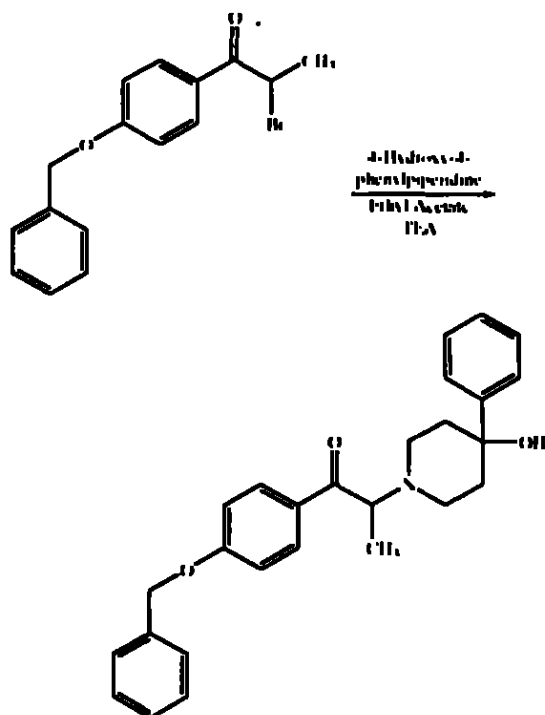
Under a nitrogen atmosphere, a 100 gallon glass lined reactor was charged with 75 gallons of methylene chloride and 28.2 kg (117.5 mol) of the product from Step 1. The solution was stirred five minutes and then 18.8 kg of bromine was charged. The reaction was stirred for 0.5 hours at 22° C. Analysis of TLC revealed that the reaction was essentially complete. To the solution was charged 37 gallons of water and the mixture was stirred for 15 minutes. The methylene chloride was separated and washed with 18.5 gallons of saturated aqueous sodium bicarbonate. The meth-

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ylene chloride was separated, atmospherically concentrated to a volume of 40 gallons and 60 gallons of isopropanol was charged. The concentration was continued until a pot temperature of 80° C. and final volume of 40 gallons were obtained. The suspension was cooled to 20° C. and granulated for 18 hours. The product was filtered on a 30" Lapp and washed with 10 gallons of isopropanol. After vacuum drying at 45° C., this yielded 29.1 kg (77.6%) of the above-depicted product.

STEP 3

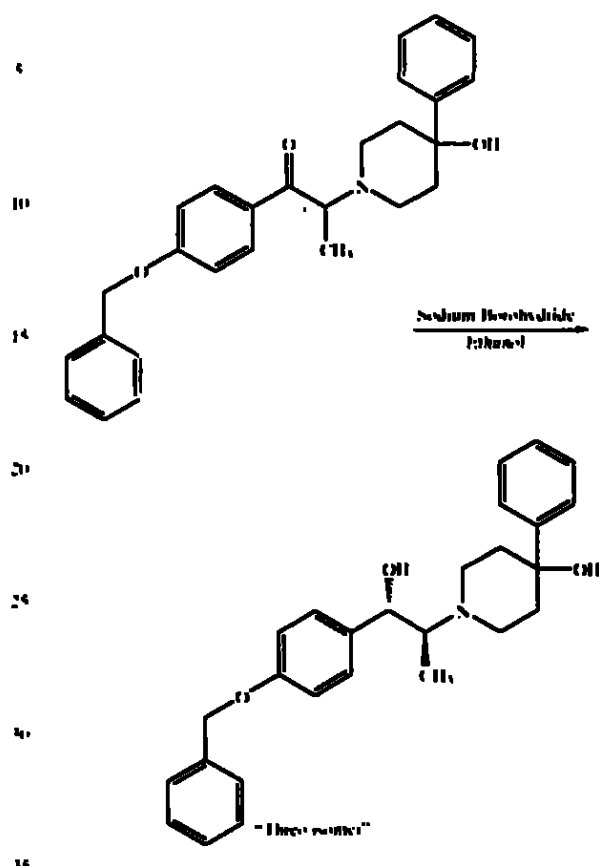


Under a nitrogen atmosphere, a 20 gallon glass lined reactor was charged with 4.90 kg (15.3 mol) of the product from step 2, 7.0 gallons of ethyl acetate, 2.70 kg (15.3 mol) of 4-hydroxy-4-phenylpiperidine and 1.54 kg of triethylamine (15.3 mol). The solution was heated to reflux (77° C.) for 18 hours. The resulting suspension was cooled to 20° C. Analysis by 'H.C.' revealed that the reaction was essentially complete. The byproduct (triethylamine hydrobromide salt) was filtered on a 30" Lapp and washed with 4 gallons of ethyl acetate. The filtrate was concentrated under vacuum to a volume of 17 liters. The concentrate was charged to 48 liters of hexane and the resulting suspension granulated for 2 hours at 20° C. The product was filtered on a 30" Lapp and washed with 4 gallons of hexane. After vacuum drying at 50° C., this yielded 4.9 kg (77%) of the above-depicted product.

A second run was carried out with 3.6 kg (11.3 mol) of the product from step 2 using the procedure described above. After drying 4.1 kg (87%) of the above-depicted product was obtained.

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STEP 4



Under a nitrogen atmosphere, a 100 gallon glass lined reactor was charged with 87.0 gallons of 2B ethanol and 1.7 kg (45.2 mol) of sodium borohydride. The resulting solution was stirred at 25° C. and 9.4 kg (22.6 mol) of the product from step 3 was charged. The suspension was stirred for 18 hours at 25-30° C. Analysis by 'H.C.' revealed that the reaction was essentially complete to the desired three diastereoisomer. To the suspension was charged 7.8 liters of water. The suspension was concentrated under vacuum to a volume of 40 gallons. After granulating for 1 hour, the product was filtered on a 30" Lapp and washed with 2 gallons of 2B ethanol. The wet product, 9.4 gallons of 2B ethanol and 8.7 gallons of water were charged to a 100 gallon glass lined reactor. The suspension was stirred at reflux (78° C.) for 16 hours. The suspension was cooled to 25° C., filtered on 30" Lapp and washed with 7 gallons of water followed by 4 gallons of 2B ethanol. After air drying at 50° C., this yielded 8.2 kg (86.5%) of the above-depicted product. This material was recrystallized in the following manner.

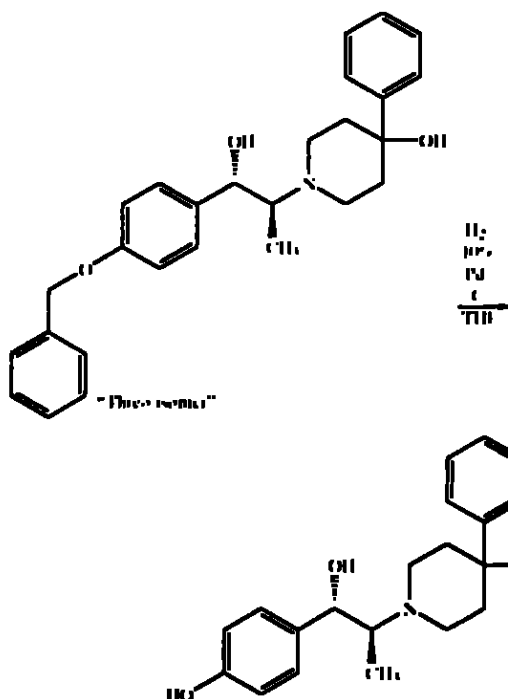
A 100 gallon glass lined reactor was charged with 7.9 kg (18.9 mol) of the product from step 3, 20 gallons of 2B ethanol and 4 gallons of acetone. The suspension was heated to 70° C. producing a solution. The solution was concentrated atmospherically to a volume of 15 gallons. The suspension was cooled to 25° C. and granulated for 1 hour. The product was filtered on a 30" Lapp. The wet product and 11.7 gallons of 2B ethanol was charged to a 100 gallon glass lined reactor. The suspension was heated to reflux (78° C.) for 18 hours. The suspension was cooled to 25° C., filtered on a 30" Lapp and washed with 2 gallons of 2B ethanol. After air drying at 50° C. this yielded 5.6 kg (70.6%) of the above-depicted product.

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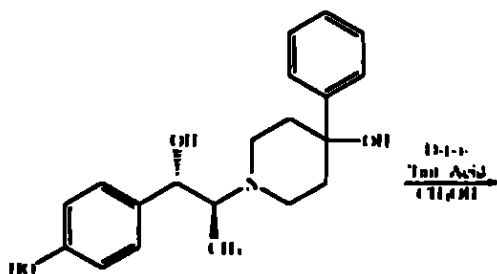
STEP 5

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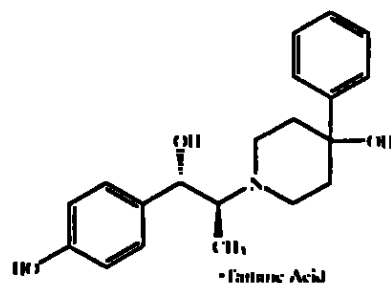
Under a nitrogen atmosphere, a 50 gallon glass lined reactor was charged with 825 g of 10% palladium on carbon (50% water wet), 5.5 kg (13.2 mol) of the product from step 4 and 15.5 gallons of tetrahydrofuran (THF). The mixture was hydrogenated between 40-50° C. for 2 hours. At this time, analysis by TLC revealed that the reduction was essentially complete. The reaction was filtered through a 14" sparkler prepacked with Celite and washed with 8 gallons of THF. The filtrate was transferred to a clean 100 gallon glass lined reactor, vacuum concentrated to a volume of 7 gallons and 21 gallons of ethyl acetate were charged. The suspension was atmospherically concentrated to a volume of 10 gallons and a pot temperature of 72° C. The suspension was cooled to 10° C., filtered on a 30" Lapp and washed with 2 gallons of ethyl acetate. After air drying at 55° C. this yielded a 3.9 kg (90%) of the above-depicted product (i.e., the free base).

STEP 6



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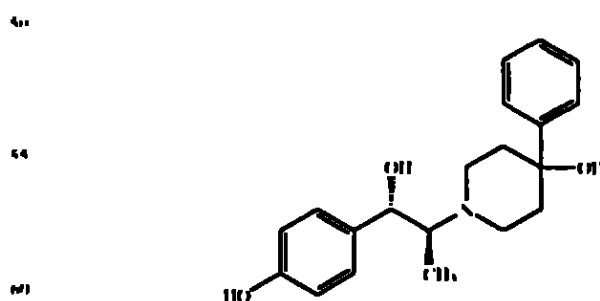
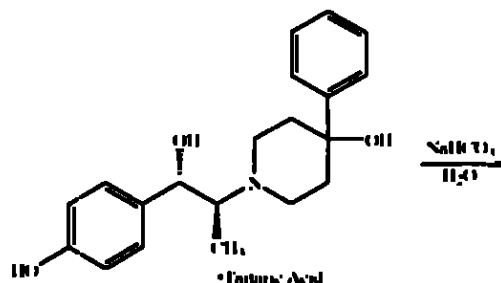
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A 100 gallon glass lined reactor was charged with 20 gallons of methanol and 3.7 kg (11.4 mol) of the product from step 5 (i.e., the free base). The suspension was heated to 60° C. and 1.7 kg (11.4 mol) of D-(-)-tartaric acid were charged. The resulting solution was heated to reflux (65°) for 3 hours after which a suspension formed. The suspension was cooled to 35° C., filtered on a 30" Lapp and washed with 1 gallon of methanol. The wet solids were charged to a 100 gallon glass lined reactor with 10 gallons of methanol. The suspension was stirred for 18 hours at 25° C. The suspension was filtered on a 30" Lapp and washed with 2 gallons of methanol. After air drying at 50° C. this yielded 2.7 kg (100%) of the above-depicted product (i.e., the tartaric acid salt of the free base (R-(-)-enantiomer)). This material was purified in the following manner:

A 100 gallon glass lined reactor was charged with 10.6 gallons of methanol and 2.67 kg (5.6 mol) of the above tartaric acid salt. The suspension was heated to reflux (80° C.) for 18 hours. The suspension was cooled to 30° C., filtered on a 30" Lapp and washed with 4 gallons of methanol. After air drying at 50° C., this yielded 2.05 kg (76.7%) of the above-depicted product (i.e., the tartaric acid salt of the free base).

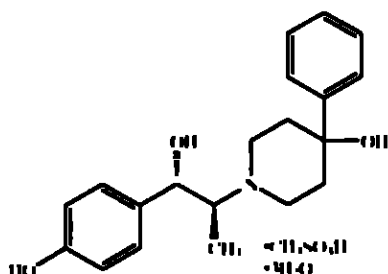
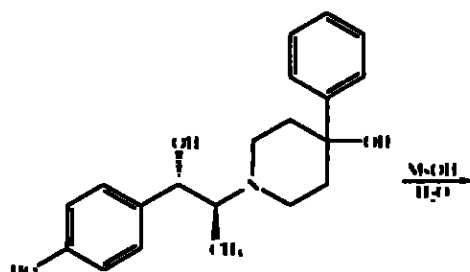
STEP 7



A 55 liter nalgene tub was charged with 30 liters of water and 1056 g (12.6 mol) of sodium bicarbonate at 20° C. To the resulting solution was charged 2.0 kg (4.2 mol) of the product from step 6 (i.e., the tartaric acid salt of the free base). The suspension was stirred for 4 hours during which

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a great deal foaming occurred. After the foaming ceased, the suspension was filtered on a 32 cm funnel and washed with 1 gallon of water. After air drying at 50° C., this yielded 1.28 kg (93.5%) of the above-depicted product (i.e., the free base) STLP's



A 22 liter flask was charged with 1277 g (3.9 mol) of product from step 7 and 14 liters of water. The suspension was warmed to 30° C. and 375 g (3.9 mol) of methane sulfonic acid were charged. The resulting solution was warmed to 60° C., clarified by filtering through Celite and washed with 2 liters of water. The speck-free filtrate was concentrated under vacuum to a volume of 6 liters. The suspension was cooled to 0-5° C. and granulated for 1 hour. The product was filtered on a 18" filter funnel and washed with 635 ml of speck-free water. After air drying at 25° C. for 18 hours, this yielded 1646 g (88%) of the above-depicted product (i.e., the mesylate salt trihydrate).

We claim:

1. (1S,2S)-1-(4-hydroxyphenyl)-2-(4-hydroxy-4-phenylpiperidin-1-yl)-1-propanol methanesulfonate trihydrate.

2. A pharmaceutical composition for the treatment of a disorder selected from degenerative CNS disorders such as stroke, Alzheimer's disease, Parkinson's disease and Huntington's disease; epilepsy, anxiety, cerebral ischemia, muscular spasms, multiinfarct dementia, traumatic brain injury, pain, AIDS related dementia, hypoglycemia, migraine, amyotrophic lateral sclerosis, drug and alcohol addiction, drug and alcohol withdrawal symptoms, psychotic conditions and urinary incontinence in a mammal, comprising an NMDA antagonizing effective amount of the trihydrate mesylate salt according to claim 1 and a pharmaceutically acceptable carrier.

3. A pharmaceutical composition for the treatment of a disorder selected from degenerative CNS disorders such as stroke, Alzheimer's disease, Parkinson's disease and Hun-

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tington's disease; epilepsy, anxiety, cerebral ischemia, muscular spasms, multiinfarct dementia, traumatic brain injury, pain, AIDS related dementia, hypoglycemia, migraine, amyotrophic lateral sclerosis, drug and alcohol addiction, drug and alcohol withdrawal symptoms, psychotic conditions and urinary incontinence in a mammal, comprising an amount of the trihydrate mesylate salt according to claim 1 that is effective in treating each disorder and a pharmaceutically acceptable carrier.

4. A method of treating a disorder selected from degenerative CNS disorders such as stroke, Alzheimer's disease, Parkinson's disease and Huntington's disease; epilepsy, anxiety, cerebral ischemia, muscular spasms, multiinfarct dementia, traumatic brain injury, pain, AIDS related dementia, hypoglycemia, migraine, amyotrophic lateral sclerosis, drug and alcohol addiction, drug and alcohol withdrawal symptoms, psychotic conditions and urinary incontinence in a mammal, comprising administering to said mammal an amount of the trihydrate mesylate salt according to claim 1 that is effective in treating such disorder.

5. A method of treating a disorder selected from degenerative CNS disorders such as stroke, Alzheimer's disease, Parkinson's disease and Huntington's disease; epilepsy, anxiety, cerebral ischemia, muscular spasms, multiinfarct dementia, traumatic brain injury, pain, AIDS related dementia, hypoglycemia, migraine, amyotrophic lateral sclerosis, drug and alcohol addiction, drug and alcohol withdrawal symptoms, psychotic conditions and urinary incontinence in a mammal, comprising administering to said mammal an NMDA antagonizing amount of the trihydrate mesylate salt according to claim 1.

6. A method of treating Parkinson's disease in a mammal, comprising administering to said mammal a Parkinson's disease treating effective amount of a synergistic combination of the mesylate salt trihydrate according to claim 1 of (1S,2S)-1-(4-hydroxyphenyl)-2-(4-hydroxy-4-phenylpiperidin-1-yl)-1-propanol and an agent capable of restoring the balance of the excitatory feedback from the ventral lateral nucleus of the thalamus into the cortex.

7. A method of treating Parkinson's disease in a mammal, comprising treating said mammal with a Parkinson's disease treating effective amount of a synergistic combination of the mesylate salt trihydrate according to claim 1 and an excitatory feedback from enhancing agent selected from the group consisting of dopamine agonists, dopamine D1 agonists, dopamine D2 agonists, dopamine β -adrenergic receptor agonists, dopamine 5-HT uptake inhibitor 5-HT-1A agonists, dopamine opiate agonists, adrenoceptor agonists, α 2-adrenergic antagonist dopamine agonists, α 2-adrenergic dopamine D2 agonists, dopamine uptake inhibitors, monoamine oxidase inhibitors, monoamine oxidase-B inhibitors, COMT inhibitors and levodopa.

8. A method of claim 7 wherein said excitatory feedback enhancing agent is levodopa.

9. A method according to claim 4, wherein the disorder being treated is Parkinson's disease.

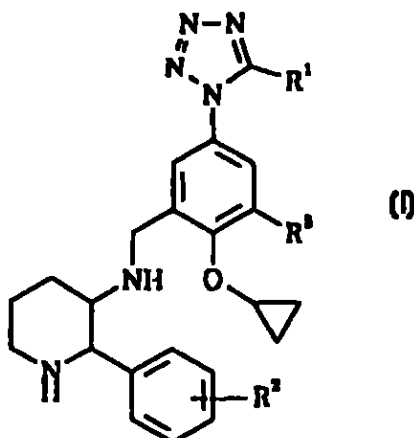
10. A method according to claim 4, wherein the disorder being treated is traumatic brain injury or cerebral ischemia.



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(21) International Application Number: PCT/GB98/03299 (22) International Filing Date: 4 November 1998 (04.11.98) (30) Priority Data: 9723544.4 7 November 1997 (07.11.97) GB (71) Applicant (for all designated States except US): MERCK SHARP & DOHME LIMITED (GB/GB); Hertford Road, Huddersdon, Hertfordshire EN11 9BU (GB). (72) Inventor; and (75) Inventor/Applicant (for US only): ELLIOTT, Matthew, Jason (GB/GB); Terlings Park, Eastwick Road, Harlow, Essex CM20 2QR (GB). (74) Agent: HISCOCK, I. J.; Merck & Co., Inc., European Patent Dept., Terlings Park, Eastwick Road, Harlow, Essex CM20 2QR (GB).	(N1) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GR, GD, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Euraasin patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG). Published With international search report.	

(54) Title: PIPERIDINE DERIVATIVES AND THEIR USE AS TACHYKININ ANTAGONISTS



(57) Abstract

Substituted piperidine derivatives of structural formula (I), wherein R^1 represents a hydrogen atom or a methyl or trifluoromethyl group; R^2 represents a hydrogen or halogen atom; and R^3 represents a hydrogen or halogen atom; and pharmaceutically acceptable salts thereof are tachykinin receptor antagonists of use, for example, in the treatment or prevention of pain, inflammation, migraine, emesis, postherpetic neuralgia, depression and anxiety.

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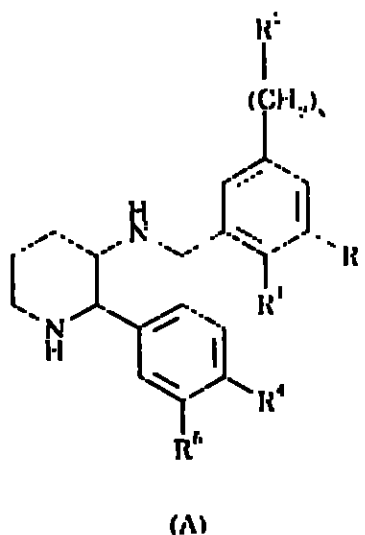
PIPERIDINE DERIVATIVES AND THEIR USE AS TACHYKININ ANTAGONISTS

This invention relates to piperidine derivatives and their use as
 5 tachykinin antagonists, and in particular as neurokinin-1 receptor
 antagonists.

We have now found a class of piperidine derivatives which are
 potent receptor antagonists of tachykinins, especially of the neurokinin-1
 (substance P) receptor. In addition, the compounds of the present
 10 invention exhibit a high level of hepatic stability as measured by, for
 example, conventional liver microsome analysis.

International Patent Specification Nos. WO 95/08549 and WO
 96/29326 disclose NK-1 receptor antagonists of the general structural
 formula (A)

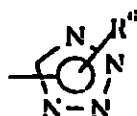
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wherein

R¹ is a C₁₋₄alkoxy group;

20 R² is



R^3 is a hydrogen or halogen atom;

R^4 and R^5 may each independently represent a hydrogen or halogen atom, or a C_{1-4} alkyl, C_{1-4} alkoxy or trifluoromethyl group;

R^6 is a halogen atom, or a C_{1-4} alkyl, $(CH_2)_m$ cyclopropyl, $-S(O)_n C_{1-4}$ alkyl,

5 phenyl, NR^7R^8 , $CH_2C(O)CF_3$ or trifluoromethyl group;

R^7 and R^8 may each independently represent a halogen atom, or a C_{1-4} alkyl or acyl group;

x is zero or 1;

n is zero, 1 or 2; and

10 m is zero or 1.

International Patent Specification No. WO 96/21661 discloses NK-1 receptor antagonists of the structural formula (A) wherein R^2 - R^8 , x, n and m are essentially as previously defined, and R^1 is $-O-(CH_2)_p C_{3-7}$ cycloalkyl (wherein p is zero or 1), $-O-C_{1-7}$ fluoroalkyl, or $-O-(CH_2)_n X$ (wherein n is 1 or 15 2); where X is selected from $C(O)NR^7R^8$, $C(O)R^9$, NR^7R^8 , $SO_2NR^7R^8$, $NHSO_2R^9$, $S(O)_2R^9$, OC_{1-4} alkyl, NO_2 , CO_2H , CO_2C_{1-4} alkyl, CN or, when n is 2, X may also represent OH, SH or NH_2 .

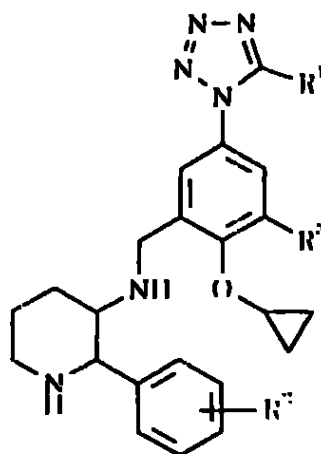
WO 96/21661 defines an $-O-(CH_2)_n C_{3-7}$ cycloalkyl group as being, for example, cyclopropyloxy, cyclopropylmethoxy, cyclobutyloxy, 20 cyclobutylmethoxy, cyclopentyloxy, cyclohexyloxy or cycloheptyloxy. A preferred class of compound in WO 96/21661 is defined as compounds wherein the group R^1 is a cyclopropylmethoxy, cyclopentyloxy, difluoromethoxy, trifluoromethoxy, 2,2,2-trifluoroethoxy or, more preferably, a fluoromethoxy group.

25 From within the general class of compound disclosed by the aforementioned patent specifications, we have now identified a novel subclass of compound which, by virtue of their unique cyclopropyl ether moiety, possess a high degree of oral bioavailability together with a high affinity for the human NK-1 receptor. A further advantage of the 30 compounds of the present invention is their enhanced duration of action.

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Preferably, the compounds of the present invention possess both a high degree of oral bioavailability and an enhanced duration of action.

The present invention accordingly provides the compounds of the formula (I):



(I)

wherein

R^1 represents a hydrogen atom or a methyl or trifluoromethyl group;

R^2 represents a hydrogen or halogen atom; and

R^3 represents a hydrogen or halogen atom;

or a pharmaceutically acceptable salt thereof.

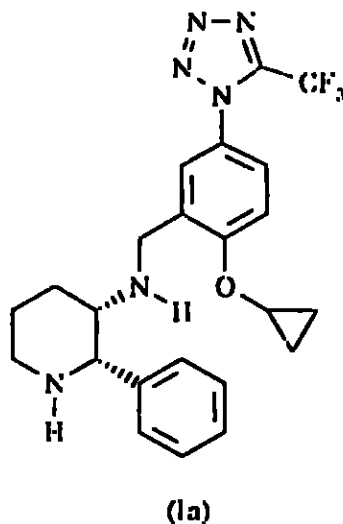
Particularly preferred compounds of formula (I) are those wherein R^1 represents a hydrogen atom or a trifluoromethyl group. Most especially, R^1 represents a trifluoromethyl group.

Further preferred compounds of formula (I) are those wherein R^2 represents a hydrogen, fluorine or chlorine atom. Especially preferred are those compounds of formula (I) wherein R^2 is a hydrogen atom or a 4-fluorine atom. Most especially, R^2 is a hydrogen atom or a 4-fluorine atom.

Also preferred are compounds of formula (I) wherein R^3 represents a hydrogen, fluorine or chlorine atom. Especially preferred are those compounds wherein R^3 is a hydrogen or fluorine atom, in particular, a hydrogen atom.

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A particularly preferred compound of the present invention is the ~~001~~ compound of formula (Ia)



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or a salt thereof, especially a pharmaceutically acceptable acid addition salt thereof. Most aptly the compounds of the formula (I) and (Ia) are the (2S,3S) stereoisomer.

Specific compounds of the present invention include:

- 10 *N*-{[2-cyclopropoxy-5-(5-trifluoromethyltetrazol-1-yl)phenyl]methyl}-2-phenylpiperidin-3-amine;
(2S,3S)-*N*-{[2-cyclopropoxy-5-(5-trifluoromethyltetrazol-1-yl)phenyl]methyl}-2-phenylpiperidin-3-amine;
N-{[2-cyclopropoxy-5-(5-trifluoromethyltetrazol-1-yl)phenyl]methyl}-2-(4-
- 15 fluorophenyl)piperidin-3-amine;
or a pharmaceutically acceptable salt thereof.

In a further aspect of the present invention, the compounds of formula (I) may be prepared in the form of a pharmaceutically acceptable salt, especially an acid addition salt.

- 20 For use in medicine, the salts of the compounds of formula (I) will be non-toxic pharmaceutically acceptable salts. Other salts may, however, be useful in the preparation of the compounds according to the invention or of their non-toxic pharmaceutically acceptable salts. Suitable

pharmaceutically acceptable salts of the compounds of this invention include acid addition salts which may, for example, be formed by mixing a solution of the compound according to the invention with a solution of a pharmaceutically acceptable acid such as hydrochloric acid, fumaric acid, 5 p-toluenesulphonic acid, maleic acid, succinic acid, acetic acid, citric acid, tartaric acid, carbonic acid, phosphoric acid or sulphuric acid. Salts of amine groups may also comprise quaternary ammonium salts in which the amino nitrogen atom carries a suitable organic group such as an alkyl, alkenyl, alkynyl or aralkyl moiety.

10 The salts may be formed by conventional means, such as by reacting the free base form of the product with one or more equivalents of the appropriate acid in a solvent or medium in which the salt is insoluble, or in a solvent such as water which is removed *in vacuo* or by freeze drying or by exchanging the anions of an existing salt for another anion on a 15 suitable ion exchange resin.

The present invention includes within its scope solvates of the compounds of formula (I) and salts thereof, for example, hydrates.

The compounds according to the invention have at least two asymmetric centres, and may accordingly exist both as enantiomers and as 20 diastereoisomers. It is to be understood that all such isomers and mixtures thereof are encompassed within the scope of the present invention. The 2S,3S stereoisomer is particularly preferred.

The present invention further provides pharmaceutical compositions comprising one or more compounds of formula (I) in 25 association with a pharmaceutically acceptable carrier or excipient.

Preferably the compositions according to the invention are in unit dosage forms such as tablets, pills, capsules, wafers, powders, granules, solutions or suspensions, or suppositories, for oral, parenteral or rectal administration, or administration by inhalation or insufflation. Oral 30 compositions such as tablets, pills, capsules or wafers, are particularly preferred.

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For preparing solid compositions such as tablets, the principal active ingredient is mixed with a pharmaceutical carrier, e.g. conventional tableting ingredients such as corn starch, lactose, sucrose, sorbitol, talc, stearic acid, magnesium stearate, dicalcium phosphate or gums, and other pharmaceutical diluents, e.g. water, to form a solid preformulation composition containing a homogeneous mixture of a compound of the present invention, or a non-toxic pharmaceutically acceptable salt thereof. When referring to these preformulation compositions as homogeneous, it is meant that the active ingredient is dispersed evenly throughout the composition so that the composition may be readily subdivided into equally effective unit dosage forms such as tablets, pills and capsules. This solid preformulation composition is then subdivided into unit dosage forms of the type described above containing from 0.1 to about 500 mg of the active ingredient of the present invention. The tablets or pills of the novel composition can be coated or otherwise compounded to provide a dosage form affording the advantage of prolonged action. For example, the tablet or pill can comprise an inner dosage and an outer dosage component, the latter being in the form of an envelope over the former. The two components can be separated by an enteric layer which serves to resist disintegration in the stomach and permits the inner component to pass intact into the duodenum or to be delayed in release. A variety of materials can be used for such enteric layers or coatings, such materials including a number of polymeric acids and mixtures of polymeric acids with such materials as shellac, cetyl alcohol and cellulose acetate.

The liquid forms in which the novel compositions of the present invention may be incorporated for administration orally or by injection include aqueous solutions, suitably flavoured syrups, aqueous or oil suspensions, and flavoured emulsions with edible oils such as cottonseed oil, sesame oil, coconut oil or peanut oil, as well as elixirs and similar pharmaceutical vehicles. Suitable dispersing or suspending agents for aqueous suspensions include synthetic and natural gums such as

tragacanth, acacia, alginate, dextran, sodium carboxymethylcellulose, 00107
methylcellulose, polyvinyl-pyrrolidone or gelatin.

Preferred compositions for administration by injection include those comprising a compound of formula (I), as the active ingredient, in
5 association with a surface-active agent (or wetting agent or surfactant) or in the form of an emulsion (as a water-in-oil or oil-in-water emulsion).

Suitable surface-active agents include, in particular, non-ionic agents, such as polyoxyethylenesorbitans (e.g. Tween™ 20, 40, 60, 80 or 85) and other sorbitans (e.g. Span™ 20, 40, 60, 80 or 85). Compositions
10 with a surface-active agent will conveniently comprise between 0.05 and 5% surface-active agent, and preferably between 0.1 and 2.5%. It will be appreciated that other ingredients may be added, for example mannitol or other pharmaceutically acceptable vehicles, if necessary.

Suitable emulsions may be prepared using commercially available
15 fat emulsions, such as Intralipid™, Liposyn™, Infonyl™, Lipofundin™ and Lipiphysan™. The active ingredient may be either dissolved in a pre-mixed emulsion composition or alternatively it may be dissolved in an oil (e.g. soybean oil, safflower oil, cottonseed oil, sesame oil, corn oil or almond oil) and an emulsion formed upon mixing with a phospholipid (e.g. egg
20 phospholipids, soybean phospholipids or soybean lecithin) and water. It will be appreciated that other ingredients may be added, for example glycerol or glucose, to adjust the tonicity of the emulsion. Suitable emulsions will typically contain up to 20% oil, for example, between 5 and 20%. The fat emulsion will preferably comprise fat droplets between 0.1
25 and 1.0µm, particularly 0.1 and 0.5µm, and have a pH in the range of 5.5 to 8.0.

Particularly preferred emulsion compositions are those prepared by mixing a compound of formula (I) with Intralipid™ or the components thereof (soybean oil, egg phospholipids, glycerol and water).

30 Compositions for inhalation or insufflation include solutions and suspensions in pharmaceutically acceptable, aqueous or organic solvents.

or mixtures thereof, and powders. The liquid or solid compositions may contain suitable pharmaceutically acceptable excipients as set out above. Preferably the compositions are administered by the oral or nasal respiratory route for local or systemic effect. Compositions in preferably
5 sterile pharmaceutically acceptable solvents may be nebulised by use of inert gases. Nebulised solutions may be breathed directly from the nebulising device or the nebulising device may be attached to a face mask, tent or intermittent positive pressure breathing machine. Solution, suspension or powder compositions may be administered, preferably orally
10 or nasally, from devices which deliver the formulation in an appropriate manner.

The present invention further provides a process for the preparation of a pharmaceutical composition comprising a compound of formula (I), which process comprises bringing a compound of formula (I) into
15 association with a pharmaceutically acceptable carrier or excipient.

The compounds of formula (I) are of value in the treatment of a wide variety of clinical conditions which are characterised by the presence of an excess of tachykinin, in particular substance P, activity.

Thus, for example, an excess of tachykinin, and in particular
20 substance P, activity is implicated in a variety of disorders of the central nervous system. Such disorders include mood disorders, such as depression or more particularly depressive disorders, for example, single episodic or recurrent major depressive disorders and dysthymic disorders, or bipolar disorders, for example, bipolar I disorder, bipolar II disorder and
25 cyclothymic disorder; anxiety disorders, such as panic disorder with or without agoraphobia, agoraphobia without history of panic disorder, specific phobias, for example, specific animal phobias, social phobias, obsessive-compulsive disorder, stress disorders including post-traumatic stress disorder and acute stress disorder, and generalised anxiety
30 disorders; schizophrenia and other psychotic disorders, for example, schizophreniform disorders, schizoaffective disorders, delusional disorders,

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brief psychotic disorders, shared psychotic disorders and psychotic disorders with delusions or hallucinations; delerium, dementia, and amnesic and other cognitive or neurodegenerative disorders, such as Alzheimer's disease, senile dementia, dementia of the Alzheimer's type, 5 vascular dementia, and other dementias, for example, due to HIV disease, head trauma, Parkinson's disease, Huntington's disease, Pick's disease, Creutzfeldt-Jakob disease, or due to multiple aetiologies; Parkinson's disease and other extra-pyramidal movement disorders such as medication-induced movement disorders, for example, neuroleptic-induced parkinsonism, neuroleptic malignant syndrome, neuroleptic-induced acute 10 dystonia, neuroleptic-induced acute akathisia, neuroleptic-induced tardive dyskinesia and medication-induced postural tremour; substance-related disorders arising from the use of alcohol, amphetamines (or amphetamine-like substances) caffeine, cannabis, cocaine, hallucinogens, inhalants and aerosol propellants, nicotine, opioids, phenylglycidine derivatives, 15 sedatives, hypnotics, and anxiolytics, which substance-related disorders include dependence and abuse, intoxication, withdrawal, intoxication delerium, withdrawal delerium, persisting dementia, psychotic disorders, mood disorders, anxiety disorders, sexual dysfunction and sleep disorders; 20 epilepsy; Down's syndrome; demyelinating diseases such as MS and ALS and other neuropathological disorders such as peripheral neuropathy, for example diabetic and chemotherapy-induced neuropathy, and postherpetic neuralgia, trigeminal neuralgia, segmental or intercostal neuralgia and other neuralgias; and cerebral vascular disorders due to acute or chronic 25 cerebrovascular damage such as cerebral infarction, subarachnoid haemorrhage or cerebral oedema.

Tachykinin, and in particular substance P, activity is also involved in nociception and pain. The compounds of the present invention will therefore be of use in the prevention or treatment of diseases and 30 conditions in which pain predominates, including soft tissue and peripheral damage, such as acute trauma, osteoarthritis, rheumatoid

arthritis, musculo-skeletal pain, particularly after trauma, spinal pain, myofascial pain syndromes, headache, episiotomy pain, and burns; deep and visceral pain, such as heart pain, muscle pain, eye pain, orofacial pain, for example, odontalgia, abdominal pain, gynaecological pain, for
5 example, dysmenorrhoea, and labour pain; pain associated with nerve and root damage, such as pain associated with peripheral nerve disorders, for example, nerve entrapment and brachial plexus avulsions, amputation, peripheral neuropathies, tic douloureux, atypical facial pain, nerve root damage, and arachnoiditis; pain associated with carcinoma, often referred
10 to as cancer pain; central nervous system pain, such as pain due to spinal cord or brain stem damage; low back pain; sciatica; ankylosing spondylitis, gout; and scar pain.

Tachykinin, and in particular substance P, antagonists may also be of use in the treatment of respiratory diseases, particularly those
15 associated with excess mucus secretion, such as chronic obstructive airways disease, bronchopneumonia, chronic bronchitis, cystic fibrosis and asthma, adult respiratory distress syndrome, bronchospasm and cough; inflammatory diseases such as inflammatory bowel disease, psoriasis, fibrositis, osteoarthritis, rheumatoid arthritis, pruritis and sunburn;
20 allergies such as eczema and rhinitis; hypersensitivity disorders such as poison ivy; ophthalmic diseases such as conjunctivitis, vernal conjunctivitis, and the like; ophthalmic conditions associated with cell proliferation such as proliferative vitreoretinopathy; cutaneous diseases such as contact dermatitis, atopic dermatitis, urticaria, and other
25 eczematoid dermatitis.

Tachykinin, and in particular substance P, antagonists may also be of use in the treatment of neoplasms, including breast tumours, neuroganglioblastomas and small cell carcinomas such as small cell lung cancer.

30 Tachykinin, and in particular substance P, antagonists may also be of use in the treatment of gastrointestinal (GI) disorders, including

inflammatory disorders and diseases of the GI tract such as gastritis, gastroduodenal ulcers, gastric carcinomas, gastric lymphomas, disorders associated with the neuronal control of viscera, ulcerative colitis, Crohn's disease, irritable bowel syndrome and emesis, including acute, delayed or
5 anticipatory emesis such as emesis induced by chemotherapy, radiation, toxins, viral or bacterial infections, pregnancy, vestibular disorders, for example, motion sickness, vertigo, dizziness and Meniere's disease, surgery, migraine, variations in intracranial pressure, gastro-oesophageal reflux disease, acid indigestion, over indulgence in food or drink, acid
10 stomach, waterbrash or regurgitation, heartburn, for example, episodic, nocturnal or meal-induced heartburn, and dyspepsia.

Tachykinin, and in particular substance P, antagonists may also be of use in the treatment of a variety of other conditions including stress related somatic disorders; reflex sympathetic dystrophy such as
15 shoulder/hand syndrome; adverse immunological reactions such as rejection of transplanted tissues and disorders related to immune enhancement or suppression such as systemic lupus erythematosus; plasma extravasation resulting from cytokine chemotherapy, disorders of bladder function such as cystitis, bladder detrusor hyper-reflexia and
20 incontinence; fibrosing and collagen diseases such as scleroderma and eosinophilic fasciitis; disorders of blood flow caused by vasodilation and vasospastic diseases such as angina, vascular headache, migraine and Reynaud's disease; and pain or nociception attributable to or associated with any of the foregoing conditions, especially the transmission of pain in
25 migraine.

The compounds of formula (I) are also of value in the treatment of a combination of the above conditions, in particular in the treatment of combined post-operative pain and post-operative nausea and vomiting.

The compounds of formula (I) are particularly useful in the
30 treatment of emesis, including acute, delayed or anticipatory emesis, such as emesis induced by chemotherapy, radiation, toxins, pregnancy,

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vestibular disorders, motion, surgery, migraine, and variations in
intracranial pressure. Most especially, the compounds of formula (I) are of
use in the treatment of emesis induced by antineoplastic (cytotoxic)
agents, including those routinely used in cancer chemotherapy, and emesis
5 induced by other pharmacological agents, for example, rolipram.

Examples of such chemotherapeutic agents include alkylating
agents, for example, nitrogen mustards, ethylenimine compounds, alkyl
sulphonates and other compounds with an alkylating action such as
nitrosoureas, cisplatin and dacarbazine; antimetabolites, for example, folic
10 acid, purine or pyrimidine antagonists; mitotic inhibitors, for example,
vinca alkaloids and derivatives of podophyllotoxin; and cytotoxic
antibiotics.

Particular examples of chemotherapeutic agents are described, for
instance, by D. J. Stewart in *Nausea and Vomiting: Recent Research and*
15 *Clinical Advances*, Eds. J. Kucharczyk *et al*, CRC Press Inc., Boca Raton,
Florida, USA (1991) pages 177-203, especially page 188. Commonly used
chemotherapeutic agents include cisplatin, dacarbazine (DTIC),
dactinomycin, mechlorethamine (nitrogen mustard), streptozocin,
cyclophosphamide, carmustine (BCNU), lomustine (CCNU), doxorubicin
20 (adriamycin), daunorubicin, procarbazine, mitomycin, cytarabine,
etoposide, methotrexate, 5-fluorouracil, vinblastine, vincristine, bleomycin
and chlorambucil [R. J. Gralla *et al* in *Cancer Treatment Reports* (1984)
68(1), 163-172].

The compounds of formula (I) are also of use in the treatment of
25 emesis induced by radiation including radiation therapy such as in the
treatment of cancer, or radiation sickness; and in the treatment of post-
operative nausea and vomiting.

It will be appreciated that the compounds of formula (I) may be
presented together with another therapeutic agent as a combined
30 preparation for simultaneous, separate or sequential use for the relief of

emesis. Such combined preparations may be, for example, in the form of a twin pack.

A further aspect of the present invention comprises the compounds of formula (I) in combination with a 5-HT₃ antagonist, such as ondansetron, granisetron or tropisetron, or other anti-emetic medicaments, for example, a dopamine antagonist such as metoclopramide or domperidone or GABA_B receptor agonists such as baclofen.

Additionally, a compound of formula (I), either alone or in combination with one or more other anti-emetic therapeutic agents, may be

administered in combination with an anti-inflammatory corticosteroid, such as dexamethasone, betamethasone, triamcinolone, triamcinolone acetonide, flunisolide, budesonide, or others such as those disclosed in US patent nos. 2,789,118, 2,990,401, 3,048,581, 3,126,375, 3,929,768, 3,996,359, 3,928,326 and 3,749,712. Dexamethasone (Decadron™) is particularly preferred. Furthermore, a compound of formula (I) may be administered in combination with a chemotherapeutic agent such as an alkylating agent, antimetabolite, mitotic inhibitor or cytotoxic antibiotic, as described above. In general, the currently available dosage forms of the known therapeutic agents for use in such combinations will be suitable.

When tested in the ferret model of cisplatin-induced emesis described by F. D. Tattersall *et al*, in *Eur. J. Pharmacol.*, (1993) 250, R5-R6, the compounds of the present invention were found to attenuate the retching and vomiting induced by cisplatin.

The compounds of formula (I) are also particularly useful in the treatment of pain or nociception and/or inflammation and disorders associated therewith such as, for example, neuropathy, such as diabetic and chemotherapy-induced neuropathy, postherpetic and other neuralgias, asthma, osteoarthritis, rheumatoid arthritis and headache, including migraine, acute or chronic tension headache, cluster headache, temporomandibular pain, and maxillary sinus pain.

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The compounds of formula (I) are also particularly useful in the treatment of depression including depressive disorders, for example, single episodic or recurrent major depressive disorders, and dysthymic disorders, depressive neurosis, and neurotic depression; melancholic depression including anorexia, weight loss, insomnia and early morning waking, and psychomotor retardation; atypical depression (or reactive depression) including increased appetite, hypersomnia, psychomotor agitation or irritability, anxiety and phobias; seasonal affective disorder; or depression.

The present invention further provides a compound of formula (I) for use in therapy.

According to a further or alternative aspect, the present invention provides a compound of formula (I) for use in the manufacture of a medicament for the treatment of physiological disorders associated with an excess of tachykinins, especially substance P.

The present invention also provides a method for the treatment or prevention of physiological disorders associated with an excess of tachykinins, especially substance P, which method comprises administration to a patient in need thereof of a tachykinin reducing amount of a compound of formula (I) or a composition comprising a compound of formula (I).

According to a further aspect of the present invention, it may be desirable to treat any of the aforementioned conditions with a combination of a compound according to the present invention and one or more other pharmacologically active agents suitable for the treatment of the specific condition. The compound of formula (I) and the other pharmacologically active agent(s) may be administered to a patient simultaneously, sequentially or in combination.

Thus, for example, for the treatment of respiratory diseases such as asthma, a compound of formula (I) may be used in conjunction with a bronchodilator, such as a β_2 -adrenergic receptor agonist or tachykinin antagonist which acts at NK-2 receptors. The compound of formula (I) and

the bronchodilator may be administered to a patient simultaneously, sequentially or in combination.

Likewise, a compound of the present invention may be employed with a leukotriene antagonists, such as a leukotriene D₄ antagonist such
5 as a compound selected from those disclosed in European patent specification nos. 0 480 717 and 0 604 114 and in US patent nos. 4,859,692 and 5,270,324. This combination is particularly useful in the treatment of respiratory diseases such as asthma, chronic bronchitis and cough.

The present invention accordingly provides a method for the
10 treatment of a respiratory disease, such as asthma, which method comprises administration to a patient in need thereof of an effective amount of a compound of formula (I) and an effective amount of a bronchodilator.

The present invention also provides a composition comprising a
15 compound of formula (I), a bronchodilator, and a pharmaceutically acceptable carrier.

It will be appreciated that for the treatment or prevention of migraine, a compound of the present invention may be used in conjunction with other anti-migraine agents, such as ergotamines or 5-HT₁ agonists,
20 especially sumatriptan, naratriptan, zolmatriptan or rizatriptan.

Likewise, for the treatment of behavioural hyperalgesia, a compound of the present invention may be used in conjunction with an antagonist of N-methyl D-aspartate (NMDA), such as dizocilpine.

For the treatment or prevention of inflammatory conditions in the
25 lower urinary tract, especially cystitis, a compound of the present invention may be used in conjunction with an anti-inflammatory agent such as a bradykinin receptor antagonist.

The present invention also provides a composition comprising a compound of formula (I), a bronchodilator, and a pharmaceutically
30 acceptable carrier.

It will be appreciated that for the treatment or prevention of pain or nociception, a compound of the present invention may be used in conjunction with other analgesics, such as acetaminophen (paracetamol), aspirin and other NSAIDs and, in particular, opioid analgesics, especially morphine. Specific anti-inflammatory agents include diclofenac, ibuprofen, indomethacin, ketoprofen, naproxen, piroxicam and sulindac. Suitable opioid analgesics of use in conjunction with a compound of the present invention include morphine, codeine, dihydrocodeine, diacetylmorphine, hydrocodone, hydromorphone, levorphanol, oxymorphone, alfentanil, buprenorphine, butorphanol, fentanyl, sufentanyl, meperidine, methadone, nalbuphine, propoxyphene and pentazocine; or a pharmaceutically acceptable salt thereof. Preferred salts of these opioid analgesics include morphine sulphate, morphine hydrochloride, morphine tartrate, codeine phosphate, codeine sulphate, dihydrocodeine bitartrate, diacetylmorphine hydrochloride, hydrocodone bitartrate, hydromorphone hydrochloride, levorphanol tartrate, oxymorphone hydrochloride, alfentanil hydrochloride, buprenorphine hydrochloride, butorphanol tartrate, fentanyl citrate, meperidine hydrochloride, methadone hydrochloride, nalbuphine hydrochloride, propoxyphene hydrochloride, propoxyphene napsylate (2-naphthalenesulphonic acid (1:1) monohydrate), and pentazocine hydrochloride.

Therefore, in a further aspect of the present invention, there is provided a pharmaceutical composition comprising a compound of the present invention and an analgesic, together with at least one pharmaceutically acceptable carrier or excipient.

In a further or alternative aspect of the present invention, there is provided a product comprising a compound of the present invention and an analgesic as a combined preparation for simultaneous, separate or sequential use in the treatment or prevention of pain or nociception.

It will be appreciated that for the treatment of depression or anxiety, a compound of the present invention may be used in conjunction with other anti-depressant or anti-anxiety agents.

Suitable classes of anti-depressant agent include norepinephrine reuptake inhibitors, selective serotonin reuptake inhibitors (SSRIs), monoamine oxidase inhibitors (MAOIs), reversible inhibitors of monoamine oxidase (RIMAs), serotonin and noradrenaline reuptake inhibitors (SNRIs), corticotropin releasing factor (CRF) antagonists, α -adrenoreceptor antagonists and atypical anti-depressants.

Suitable norepinephrine reuptake inhibitors include tertiary amine tricyclics and secondary amine tricyclics. Suitable examples of tertiary amine tricyclics include: amitriptyline, clomipramine, doxepin, imipramine and trimipramine, and pharmaceutically acceptable salts thereof. Suitable examples of secondary amine tricyclics include: amoxapine, desipramine, maprotiline, nortriptyline and protriptyline, and pharmaceutically acceptable salts thereof.

Suitable selective serotonin reuptake inhibitors include: fluoxetine, fluvoxamine, paroxetine and sertraline, and pharmaceutically acceptable salts thereof.

Suitable monoamine oxidase inhibitors include: isocarboxazid, phenelzine, tranylecypromine and selegiline, and pharmaceutically acceptable salts thereof.

Suitable reversible inhibitors of monoamine oxidase include: moclobemide, and pharmaceutically acceptable salts thereof.

Suitable serotonin and noradrenaline reuptake inhibitors of use in the present invention include: venlafaxine, and pharmaceutically acceptable salts thereof.

Suitable CRF antagonists include those compounds described in International Patent Specification Nos. WO 94/13643, WO 94/13644, WO 94/13661, WO 94/13676 and WO 94/13677.

Suitable atypical anti-depressants include: bupropion, lithium, nefazodone, trazodone and viloxazine, and pharmaceutically acceptable salts thereof.

5 Suitable classes of anti-anxiety agent include benzodiazepines and 5-HT_{1A} agonists or antagonists, especially 5-HT_{1A} partial agonists, and corticotropin releasing factor (CRF) antagonists.

Suitable benzodiazepines include: alprazolam, chlordiazepoxide, clonazepam, chlorazepate, diazepam, halazepam, lorazepam, oxazepam and prazepam, and pharmaceutically acceptable salts thereof.

10 Suitable 5-HT_{1A} receptor agonists or antagonists include, in particular, the 5-HT_{1A} receptor partial agonists buspirone, flesinoxan, gepirone and ipsapirone, and pharmaceutically acceptable salts thereof.

Therefore, in a further aspect of the present invention, there is provided a pharmaceutical composition comprising a compound of the
15 present invention and an anti-depressant or anti-anxiety agent, together with at least one pharmaceutically acceptable carrier or excipient.

In a further or alternative aspect of the present invention, there is provided a product comprising a compound of the present invention and an
20 anti-depressant or anti-anxiety agent as a combined preparation for simultaneous, separate or sequential use for the treatment or prevention of depression and/or anxiety.

It will be appreciated that for the treatment or prevention of eating disorders, including obesity, bulimia nervosa and compulsive eating disorders, a compound of the present invention may be used in conjunction
25 with other anorectic agents.

The present invention accordingly provides the use of a compound of formula (I) and an anorectic agent for the manufacture of a medicament for the treatment or prevention of eating disorders.

30 The present invention also provides a method for the treatment or prevention of eating disorders, which method comprises administration to a patient in need of such treatment an amount of a compound of formula

(I) and an amount of an anorectic agent, such that together they give effective relief.

In a further aspect of the present invention, there is provided a pharmaceutical composition comprising a compound of formula (I) and an anorectic agent, together with at least one pharmaceutically acceptable carrier or excipient.

It will be appreciated that the compound of formula (I) and anorectic agent may be present as a combined preparation for simultaneous, separate or sequential use for the treatment or prevention of eating disorders. Such combined preparations may be, for example, in the form of a twin pack.

In a further or alternative aspect of the present invention, there is therefore provided a product comprising a compound of formula (I) and an anorectic agent as a combined preparation for simultaneous, separate or sequential use in the treatment or prevention of eating disorders.

In a further embodiment of the present invention there is provided the use of a compound of formula (I) and an anorectic agent for the manufacture of a medicament for the treatment or prevention of obesity.

The present invention also provides a method for the treatment or prevention of obesity, which method comprises administration to a patient in need of such treatment an amount of a compound of formula (I) and an amount of an anorectic agent, such that together they give effective relief.

In an alternative embodiment of the present invention there is provided the use of a compound of formula (I) and an anorectic agent for the manufacture of a medicament for the treatment or prevention of bulimia nervosa.

The present invention also provides a method for the treatment or prevention of bulimia nervosa, which method comprises administration to a patient in need of such treatment an amount of a compound of formula (I) and an amount of an anorectic agent, such that together they give effective relief.

In a further embodiment of the present invention there is provided the use of a compound of formula (I) and an anorectic agent for the manufacture of a medicament for the treatment or prevention of compulsive eating disorders.

5 The present invention also provides a method for the treatment or prevention of compulsive eating disorders, which method comprises administration to a patient in need of such treatment an amount of a compound of formula (I) and an amount of an anorectic agent, such that together they give effective relief.

10 In an alternative embodiment of the present invention there is provided the use of a compound of formula (I) and an anorectic agent for the manufacture of a medicament for reducing the total body fat mass in an obese mammal, especially a human.

15 The present invention also provides a method for reducing the total body fat mass in an obese mammal, especially a human, which method comprises administration to a patient in need of such treatment an amount of a compound of formula (I) and an amount of an anorectic agent, such that together they give effective relief.

20 Suitable anorectic agents of use in combination with a compound of the present invention include, but are not limited to, aminorex, amphetchloral, amphetamine, benzphetamine, chlorphentermine, clobenzorex, cloforex, clominorex, clortermine, cyclexedrine, dexfenfluramine, dextroamphetamine, diethylpropion, diphemethoxidine, N-ethylamphetamine, fenbutrazate, fenfluramine, fenisorex, fenproporex, 25 fludorex, fluminorex, furfurylmethylamphetamine, levamfetamine, levophacetoperane, mazindol, mefenorex, metamfepramone, methamphetamine, norpseudoephedrine, pentorex, phendimetrazine, phenmetrazine, phentermine, phenylpropanolamine, picilorex and sibutramine; and pharmaceutically acceptable salts thereof.

30 Particularly preferred anorectic agents include amphetamine and derivatives thereof such as amphetamine, benzphetamine.

chlorphentermine, clobenzorex, cloforex, clotermine, dexfenfluramine, dextroamphetamine, diethylpropion, *N*-ethylamphetamine, fenfluramine, fenproporex, furfurylmethylamphetamine, levamfetamine, mefenorex, metamfepramone, methamphetamine, norpseudoephedrine, pentorex, phendimetrazine, phenmetrazine, phentermine, phenylpropanolamine, picilorex and sibutramine; and pharmaceutically acceptable salts thereof.

A particularly suitable class of anorectic agent are the halogenated amphetamine derivatives, including chlorphentermine, cloforex, clotermine, dexfenfluramine, fenfluramine, picilorex and sibutramine; and pharmaceutically acceptable salts thereof.

Particularly preferred halogenated amphetamine derivatives of use in combination with a compound of the present invention include: fenfluramine and dexfenfluramine, and pharmaceutically acceptable salts thereof.

It will be appreciated that for the treatment or prevention of obesity, the compounds of the present invention may also be used in combination with a selective serotonin reuptake inhibitor (SSRI).

The present invention accordingly provides the use of a compound of formula (I) and an SSRI for the manufacture of a medicament for the treatment or prevention of obesity.

The present invention also provides a method for the treatment or prevention of obesity, which method comprises administration to a patient in need of such treatment an amount of a compound of formula (I) and an amount of an SSRI, such that together they give effective relief.

In a further aspect of the present invention, there is provided a pharmaceutical composition for the treatment or prevention of obesity comprising a compound of formula (I) and an SSRI, together with at least one pharmaceutically acceptable carrier or excipient.

It will be appreciated that the compound of formula (I) and SSRI may be present as a combined preparation for simultaneous, separate or

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sequential use for the treatment or prevention of obesity. Such combined preparations may be, for example, in the form of a twin pack.

In a further or alternative aspect of the present invention, there is therefore provided a product comprising a compound of formula (I) and an SSRI as a combined preparation for simultaneous, separate or sequential use in the treatment or prevention of obesity.

In an alternative embodiment of the present invention, there is provided the use of a compound of formula (I) and an SSRI for the manufacture of a medicament for reducing the total body fat mass in an obese mammal, especially a human.

The present invention also provides a method for reducing the total body fat mass in an obese mammal, especially a human, which method comprises administration to the mammal an amount of a compound of formula (I) and an amount of an SSRI, such that together they give effective relief.

In a further aspect of the present invention, there is provided a pharmaceutical composition for reducing the total body fat mass in an obese mammal, especially a human, comprising a compound of formula (I) and an SSRI, together with at least one pharmaceutically acceptable carrier or excipient.

Suitable selective serotonin reuptake inhibitors of use in combination with a compound of the present invention include: fluoxetine, fluvoxamine, paroxetine and sertraline, and pharmaceutically acceptable salts thereof.

As used herein "obesity" refers to a condition whereby a mammal has a Body Mass Index (BMI), which is calculated as weight per height squared (kg/m^2), of at least 25.9. Conventionally, those persons with normal weight, have a BMI of 19.9 to less than 25.9.

The obesity herein may be due to any cause, whether genetic or environmental. Examples of disorders that may result in obesity or be the cause of obesity include overeating and bulimia, polycystic ovarian

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disease, craniopharyngioma, the Prader-Willi Syndrome, Frohlich's syndrome, Type II diabetes, GH-deficient subjects, normal variant short stature, Turner's syndrome, and other pathological conditions showing reduced metabolic activity or a decrease in resting energy expenditure as a percentage of total fat-free mass, e.g. children with acute lymphoblastic leukemia.

"Treatment" (of obesity) refers to reducing the BMI of the mammal to less than about 25.9, and maintaining that weight for at least 6 months. The treatment suitably results in a reduction in food or caloric intake by the mammal.

"Prevention" (of obesity) refers to preventing obesity from occurring if the treatment is administered prior to the onset of the obese condition. Moreover, if treatment is commenced in already obese subjects, such treatment is expected to prevent, or to prevent the progression of, the medical sequelae of obesity, such as, e.g., arteriosclerosis, Type II diabetes, polycystic ovarian disease, cardiovascular diseases, osteoarthritis, dermatological disorders, hypertension, insulin resistance, hypercholesterolemia, hypertriglyceridemia, and cholelithiasis.

Thus, in one aspect, this invention relates to the inhibition and/or complete suppression of lipogenesis in obese mammals, i.e., the excessive accumulation of lipids in fat cells, which is one of the major features of human and animal obesity, as well as loss of total body weight. In another aspect, the invention ameliorates the conditions that are a consequence of the disease, such as preventing or arresting the progression of polycystic ovarian disease so that the patient is no longer infertile, and increasing the insulin sensitivity and/or decreasing or eliminating the need or usage of insulin in a diabetic patient, e.g., one with adult-onset diabetes or Type II diabetes.

A further aspect of the present invention comprises the use of a compound of formula (I) for achieving a chronobiologic (circadian rhythm phase-shifting) effect and alleviating circadian rhythm disorders in a

mammal. The present invention is further directed to the use of a compound of formula (I) for blocking the phase-shifting effects of light in a mammal.

5 The present invention further relates to the use of a compound of formula (I) for enhancing or improving sleep quality, in particular by increasing sleep efficiency and augmenting sleep maintenance, as well as for preventing and treating sleep disorders and sleep disturbances, in a mammal.

10 In a preferred embodiment, the present invention provides a method for the phase advance or phase delay in the circadian rhythm of a subject which comprises administering to the subject an appropriate amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof.

15 In the treatment of the conditions associated with an excess of tachykinins, a suitable dosage level is about 0.001 to 50 mg/kg per day, in particular about 0.01 to about 25 mg/kg, such as from about 0.05 to about 10 mg/kg per day.

For example, in the treatment of conditions involving the neurotransmission of pain sensations, a suitable dosage level is about 0.001 to 25 mg/kg per day, preferably about 0.005 to 10 mg/kg per day, and especially about 0.005 to 5 mg/kg per day. The compounds may be administered on a regimen of 1 to 4 times per day, preferably once or twice per day.

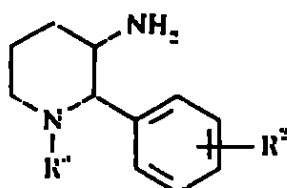
25 In the treatment of emesis using an injectable formulation, a suitable dosage level is about 0.001 to 10 mg/kg per day, preferably about 0.005 to 5 mg/kg per day, and especially 0.01 to 1 mg/kg per day. The compounds may be administered on a regimen of 1 to 4 times per day, preferably once or twice per day.

30 It will be appreciated that the amount of a compound of formula (I) required for use in any treatment will vary not only with the particular compounds or composition selected but also with the route of administration, the nature of the condition being treated, and the age and

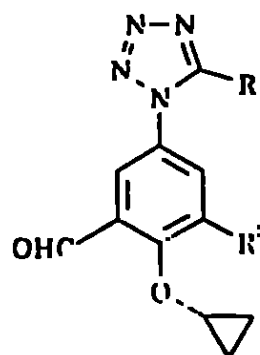
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condition of the patient, and will ultimately be at the discretion of the attendant physician.

The compounds according to the present invention may be prepared by a process (A) which comprises reacting a compound of formula (II) with
5 a compound of formula (III) in the presence of a reducing agent:



(II)

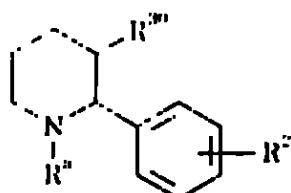


(III)

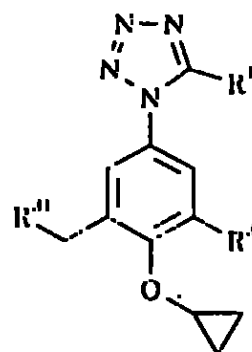
wherein R^1 , R^2 and R^3 are as defined for formula (I), and R^a is a hydrogen
10 atom or a nitrogen protecting group, followed where necessary by N-deprotection.

Suitable reducing agents for use in this reaction include, for example, sodium borohydride, sodium cyanoborohydride or sodium triacetoxyborohydride. The reaction is conveniently effected in a suitable
15 solvent such as acetic acid, methanol or 1,2-dichloroethane at a temperature between 0°C and 50°C, conveniently at about room temperature.

According to another process (B), the compounds according to the present invention may be prepared by reacting a compound of formula (IV)
20 with a compound of formula (V):



(IV)



(V)

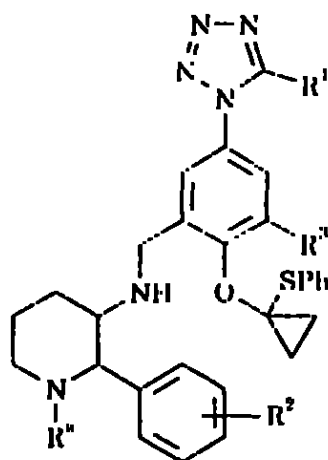
wherein R^1 , R^2 and R^3 are as defined for formula (I), R^a is a hydrogen atom or a nitrogen protecting group, and one of R^{30} and R^{31} represents a leaving group and the other of R^{30} and R^{31} represents NH_2 ; in the presence of a base, followed by deprotection, if required.

Suitably R^{30} represents NH_2 and R^{31} represents a leaving group.

Suitable leaving groups include halogen atoms, e.g. chlorine, bromine or iodine, or sulphonate derivatives such as tosylate, mesylate or triflate.

The reaction is conveniently carried out in a suitable organic solvent, such as an ether, e.g. 1,2-dimethoxyethane, at a temperature in the region of $0^\circ C$. Favoured bases of use in the reaction include alkali metal amides and hydrides, such as potassium bis(trimethylsilyl)amide or potassium hydride. Suitably, sodium hydride is used.

According to another general process (C), compounds of formula (I) may be prepared from a compound of formula (VI)

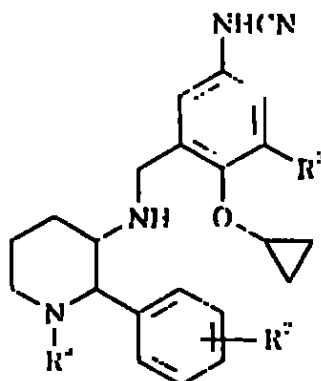


(VI)

wherein R¹, R² and R³ are as defined for formula (I). R³ is a hydrogen atom or a nitrogen protecting group, and Ph is a phenyl ring, by reaction with lithium naphthalenide in tetrahydrofuran, followed where necessary by N-deprotection. The reaction is preferably effected at reduced temperature, for example at about -78°C.

According to another general process (D), compounds of formula (I) may be prepared from a compound of formula (VII)

10



Am,

wherein R² and R³ are as defined for formula (I) and R⁴ is a hydrogen atom or a nitrogen protecting group, by reaction with ammonium chloride and sodium azide at elevated temperature, followed where necessary by

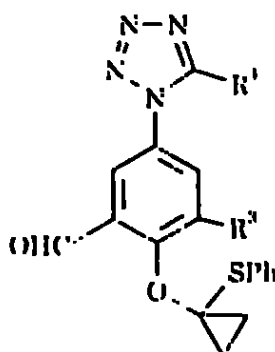
N-deprotection. The reaction is conveniently effected in a solvent such as dimethylformamide.

Further details of suitable procedures will be found in the accompanying Examples.

- 5 Suitable amino protecting groups include alkoxycarbonyl groups such as *tert*-butoxycarbonyl and trichloroethoxycarbonyl, aralkyloxycarbonyl groups such as benzyloxycarbonyl, or aralkyl groups such as benzyl. Removal of the protecting group is effected by conventional procedures thus, for example, *tert*-butoxycarbonyl groups
- 10 may be removed under acidic conditions using, for example, trifluoroacetic acid; benzyloxycarbonyl and benzyl groups, may also be removed by hydrogenolysis in the presence of a catalyst, for example, palladium; and trichloroethoxycarbonyl groups may be removed with zinc dust.

- Methods for the preparation of intermediates of formula (II) and
- 15 (IV) are well known in the art (see, for instance, European Patent Specification No. 0 436 334-A).

Intermediates of formula (III) may be prepared from a compound of formula (VIII)

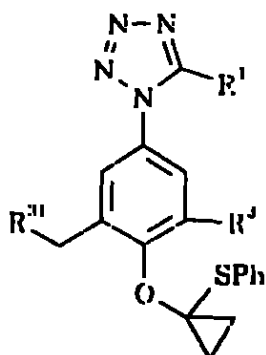


(VIII)

using the method of general process (C), above.

Similarly, intermediates of formula (V) may be prepared from a compound of formula (IX)

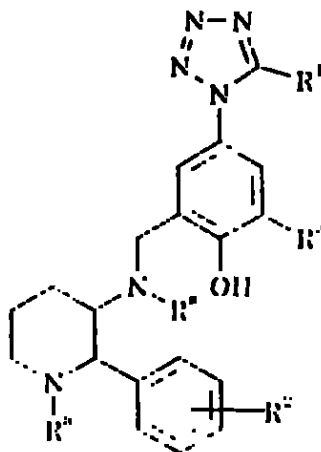
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(IX)

according to the method of general process (C).

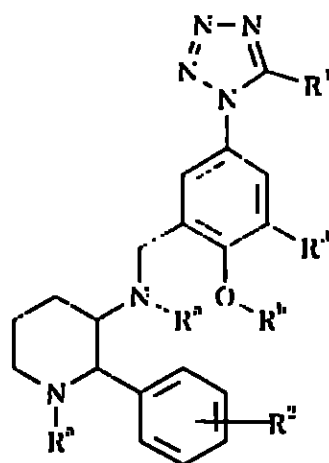
Intermediates of formula (VI) may be prepared from a compound of
5 formula (X)



(X)

wherein R¹ and R² are as defined for formula (I) and R³ is a hydrogen atom
10 or a nitrogen protecting group, by reaction with (1-iodo-cycloprop-1-yl)phenylsulphide in the presence of silver carbonate.

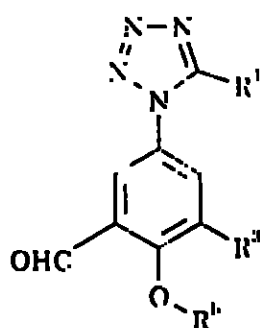
Compounds of formula (X) may be prepared from a compound of
formula (XI)



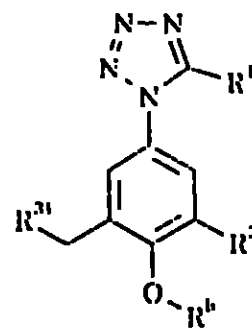
(XI)

where R⁶ is a suitable hydroxy protecting group, for example an aralkyl group such as benzyl, by hydrogenation under conventional conditions.

- 5 Compounds of formula (XI) may be prepared by either of the methods of general process (A) or (B), above, using a suitable protected phenolic precursor of formula (XIIa) or (XIIb)



(XIIa)



(XIIb)

10

in place of the compound of formula (III) or (V), respectively.

- Compounds of formulae (VIII) and (IX) may be prepared by reacting the corresponding phenolic precursors with (1-iodo-cycloprop-1-yl)phenylsulphide in the presence of silver carbonate. The phenolic precursors of compounds of formulae (VIII), (IX), (XIIa) and (XIIb) are
- 15

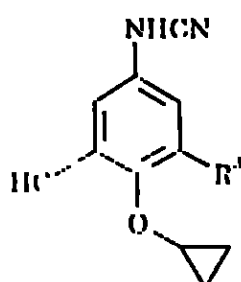
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known compounds or may be prepared from known compounds by methods readily apparent to one skilled in the art.

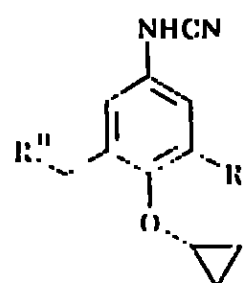
Alternatively, intermediates of formula (III) may be prepared by carbonylation of the corresponding aryl iodide using conventional methodology, for example, by treatment with carbon monoxide in the presence of tetrakis(triphenylphosphine)palladium (0) and tributyl tin hydride.

The aryl iodide precursor may be prepared from the corresponding aniline derivative using, for example, the methodology described herein.

Intermediates of formula (VII) may be prepared by either of the methods of general process (A) or (B), above, using a suitable cyanamide precursor of formula (XIIIa) or (XIIIb)



(XIIIa)



(XIIIb)

in place of the compound of formula (III) or (IV), respectively.

Compounds of formula (XIIIa) and (XIIIb) may be prepared by reacting the corresponding compounds of formula (III) or (IV) wherein R¹ is hydrogen, or a protected derivative thereof, with n-butyl lithium in a suitable solvent such as tetrahydrofuran.

During any of the above synthetic sequences it may be necessary and/or desirable to protect sensitive or reactive groups on any of the molecules concerned. This may be achieved by means of conventional protecting groups, such as those described in *Protective Groups in Organic Chemistry*, ed. J.F.W. McOmie, Plenum Press, 1973; and T.W. Greene and P.G.M. Wuts, *Protective Groups in Organic Synthesis*, John Wiley & Sons.

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1991. The protecting groups may be removed at a convenient subsequent stage using methods known from the art.

The stereoisomers of the compounds of formula (I) may be separated by procedures known in the art to obtain the preferred (2S,3S)

5' stereoisomers.

The exemplified compounds of this invention were tested by the methods set out at pages 36 to 39 of International Patent Specification No. WO 93/01165. The compounds were found to be active with IC₅₀ at the NK₁ receptor of less than 1nM on said test method. Thus, for instance, the
10 compounds of Examples 1 and 2 were found to have an IC₅₀ at the human NK₁ receptor of 0.08nM and 0.13nM, respectively.

The following non-limiting Examples serve to illustrate the preparation of compounds of the present invention:

15

DESCRIPTION 1

5-Nitro-2-(1-phenylthiocycloprop-1-yl)oxybenzenemethanol

Silver carbonate (20g, 72.2mmol) was added to a solution of 2-hydroxy-5-nitrobenzaldehyde (6.5g, 40.1mmol) and (1-iodocycloprop-1-yl)phenylsulfide (Cohen T. and Matz J. R., *J. Am.*
20 *Chem. Soc.* 1980, 102, 6902) (20g, 72.2mmol) in toluene (60ml) and the mixture was stirred at 40°C for 24 hours. The mixture was cooled, diluted with ethyl acetate and filtered, washing well with ethyl acetate. The mixture was washed with aqueous sodium hydroxide (3 x 100ml) and brine (100ml), dried (MgSO₄) and the solvent was evaporated under
25 reduced pressure. The residue was dissolved in ethanol (15ml), cooled in ice and sodium borohydride (0.74g, 19.6mmol) was added. The mixture was stirred at room temperature for 1 hour, then water (10ml) was added. The mixture was extracted with ethyl acetate and the combined organic fractions were dried (MgSO₄) and the solvent was evaporated under
30 reduced pressure. The residue was purified by flash column chromatography on silica gel, eluting with hexane/ethyl acetate (95:5

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increasing to 50:50), to give the title compound as a yellow solid (5g, 40%).
¹H NMR (360MHz, CDCl₃) δ 1.48-1.50 (4H, m), 1.80 (1H, t), 4.60-4.62 (2H, d), 7.26-7.45 (6H, m), 8.21-8.29 (1H, dd), and 8.30 (1H, d).

5

DESCRIPTION 2

5-Amino-2-(1-phenylthiocycloprop-1-yl)oxybenzenemethanol

Iron powder (7.1g, 126.2mmol) was added to a mixture of
5-nitro-2-(1-phenylthiocycloprop-1-yl)oxybenzenemethanol (Description 1;
5g, 15.8mmol) and acetic acid (50ml) in water (150ml) and the mixture
10 was heated to 80°C and stirred overnight. The mixture was cooled and
filtered through Celite™, washing the residue thoroughly with ethyl
acetate, and the solvent was evaporated under reduced pressure. The
residue was dissolved in ethyl acetate and washed with aqueous sodium
hydroxide (1M, 3x100ml). The organic layer was dried (MgSO₄) and the
15 solvent was evaporated under reduced pressure. The residue was purified
by flash column chromatography on silica gel, eluting with
CH₂Cl₂/MeOH/NH₃(Aq.) (96:4:0.4) to give the title compound as an orange
oil (2.8g, 62%). ¹H NMR (360MHz, CDCl₃) δ 1.32-1.50 (4H, m), 3.32 (3H, br
s), 4.47 (2H, s), 6.65 (2H, m), 7.13 (1H, d, *J* 8.4 Hz), 7.20-7.34 (3H, m), and
20 7.46 (2H, m).

DESCRIPTION 3

5-Amino-2-cyclopropoxybenzenemethanol

Lithium naphthalenide (0.7M solution in THF), was added dropwise
25 to a stirred, cooled (-78°C) solution of 5-amino-2-(1-phenylthiocycloprop-1-
yl)oxybenzenemethanol (Description 2; 2.8g, 9.8mmol) in tetrahydrofuran
(30ml) until a dark green color persisted. The mixture was stirred at
-78°C for 30 minutes, then water (25ml) was added and the mixture was
warmed to room temperature. The mixture was extracted with ethyl
30 acetate and the combined organic fractions were dried (MgSO₄) and the
solvent was evaporated under reduced pressure. The residue was purified

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by flash column chromatography on silica gel, eluting with $\text{CH}_2\text{Cl}_2/\text{MeOH}/\text{NH}_3(\text{Aq.})$ (97:3:0.3) to give the title compound as a yellow solid (1.34g, 77%). ^1H NMR (360MHz, CDCl_3) δ 0.74-0.75 (4H, d, J 4.5 Hz), 2.41-2.50 (1H, br s), 3.42-3.46 (2H, br s), 3.69-3.71 (1H, m), 4.55 (2H, s), 6.59 (1H, dd, J 8.5, 2.9 Hz), 6.65 (1H, d, J 2.9 Hz), and 7.03-7.06 (1H, d, J 8.5 Hz).

DESCRIPTION 4

N-[4-Cyclopropoxy-3-(hydroxymethyl)phenyl]trifluoroacetamide

10 Trifluoroacetic anhydride (3.5ml, 24.7mmol), was added dropwise to a stirred, cooled (-78°C) solution of 5-amino-2-cyclopropoxybenzenemethanol (Description 3; 1.34g, 7.49mmols), and triethylamine, (4.7ml, 33.7mmol) in dichloromethane (20ml), such that that the temperature of the mixture did not exceed 15 -65°C . The mixture was stirred at -78°C for 45 minutes, then warmed to room temperature and the solvent was evaporated under reduced pressure. The residue was dissolved in methanol and the mixture was heated under reflux for 20 minutes. The mixture was cooled and the solvent was evaporated under reduced pressure. The residue was 20 dissolved in ethyl acetate, washed with aqueous citric acid (10%, 3x50ml), aqueous sodium hydrogen carbonate (saturated, 3x50ml) and brine (50ml), dried (MgSO_4), and the solvent was evaporated under reduced pressure to give the title compound as a brown solid (1.74g, 84%). ^1H NMR (360MHz, CDCl_3) δ 0.78-0.84 (4H, m), 2.18 (1H, br s), 3.76-3.81 (1H, m), 4.63 (2H, s), 25 7.26 (1H, d, J 8.7 Hz), 7.40-7.41 (1H, d, J 2.7 Hz), 7.54-7.57 (1H, dd, J 8.7, 2.7 Hz), and 7.87 (1H, br s).

DESCRIPTION 5

2-(Cyclopropoxy)-5-(trifluoroacetylaminophenyl)methyl Benzoate

30 Benzoyl chloride (637 μL , 5.5mmol) was added to a stirred, cooled (0°C) solution of

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N-[4-cyclopropoxy-3-(hydroxymethyl)phenyl]trifluoroacetamide
(Description 4; 1.5g, 5.5mmol) and pyridine (884 μ L, 10.9mmol) in
dichloromethane (20ml) and the mixture was allowed to warm to room
temperature and stirred for 2 hours. The mixture was poured into
5 aqueous sodium hydrogen carbonate (saturated, 75ml) and extracted with
ethyl acetate. The combined organic fractions were washed with aqueous
sodium hydrogen carbonate (saturated, 3x70ml), aqueous citric acid (10%,
3x70ml) and brine (70ml), dried (Na_2SO_4) and the solvent was evaporated
under reduced pressure. The residue was purified by flash column
10 chromatography on silica gel, eluting with hexane/ethyl acetate (90:10), to
give the title compound as a pale yellow solid (1.81g, 88%). ^1H NMR
(360MHz, CDCl_3) δ 0.78-0.82 (4H, m), 3.79-3.81 (1H, m), 5.35 (2H, s), 7.28
(1H, d, J 8.8 Hz), 7.44-7.48 (3H, m), 7.58 (1H, m), 7.63 (1H, dd, J 8.8, 2.7
Hz), 7.77 (1H, br s), and 8.07 (2H, d, J 7.6 Hz).

15

DESCRIPTION 6

2-(Cyclopropoxy)-5-[5-(trifluoromethyl)tetrazol-1-yl]phenylmethyl Benzoate

Triphenylphosphine (1.88g, 7.16mmol) was added to a suspension of
20 2-(cyclopropoxy)-5-(trifluoroacetylamino)phenylmethyl benzoate
(Description 5; 1.81g, 4.78mmol) in carbon tetrachloride (30ml) and the
mixture was heated under reflux overnight. The mixture was cooled and
the solvent was evaporated under reduced pressure. The residue was
dissolved in dimethylformamide (20ml) and added slowly to a suspension
25 of sodium azide (466mg, 7.16mmol) in dimethylformamide (10ml). The
mixture was stirred at room temperature for 30 minutes, poured into
water (100ml) and extracted with ethyl acetate. The combined organic
fractions were washed with water (4x100ml) and brine (100ml), dried
(Na_2SO_4) and the solvent was evaporated under reduced pressure. The
30 residue was purified by flash column chromatography on silica gel, eluting
with hexane/ethyl acetate (85:15), to give the title compound as a yellow

oil (1.57g, 81%). ^1H NMR (360MHz, CDCl_3) δ 0.86-0.91 (4H, m), 3.86-3.90 (1H, m), 5.41 (2H, s), 7.41-7.48 (4H, m), 7.54-7.61 (2H, m), and 8.04-8.07 (2H, dd, J 8.4, 1.3 Hz).

5

DESCRIPTION 7

2-(Cyclopropoxy)-5-[5-(trifluoromethyl)tetrazol-1-yl]benzenemethanol

Aqueous lithium hydroxide (1M, 20ml, 20mmol) was added to a solution of

2-(cyclopropoxy)-5-[5-(trifluoromethyl)tetrazol-1-yl]phenylmethyl benzoate
(Description 6; 1.57g, 3.9mmol) in methanol (20ml) and the mixture was
stirred at room temperature for 1 hour. The mixture was poured into
aqueous sodium hydrogen carbonate (saturated, 100ml) and extracted
with ethyl acetate (2x100ml). The combined organic fractions were
washed with aqueous sodium hydrogen carbonate (saturated, 3x100ml)
and brine (100ml), dried (Na_2SO_4), and the solvent was evaporated under
reduced pressure to give the title compound as a yellow oil (1.13g, 97%). ^1H
NMR (360MHz, CDCl_3) δ 0.83-0.92 (4H, m), 2.06 (1H, t, J 6.0 Hz),
3.84-3.89 (1H, m), 4.72 (2H, d, J 6.0 Hz), 7.34 (1H, dd, J 8.8, 2.4 Hz), 7.42
(1H, d, J 8.8 Hz), and 7.51 (1H, d, J 2.4 Hz).

20

DESCRIPTION 8

2-(Cyclopropoxy)-5-[5-(trifluoromethyl)tetrazol-1-yl]benzaldehyde

Sulfur trioxide pyridine complex (2.16g, 13.6mmol) was added to a solution of 2-(cyclopropoxy)-5-[5-(trifluoromethyl)tetrazol-

1-yl]benzenemethanol (Description 7; 1.13g, 3.8mmol) and triethylamine,
(3.7ml, 26.4mmol) in dimethylsulfoxide and the mixture was stirred at
room temperature for 45 minutes. The mixture was poured into aqueous
citric acid (10%, 70ml) and extracted with ethyl acetate. The combined
organic fractions were washed with aqueous citric acid (10%, 4x70ml),
water (3x70ml) and brine (70ml), dried (Na_2SO_4), and the solvent was
evaporated under reduced pressure to give the title compound as a yellow

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solid (0.459g, 41%). ^1H NMR (360MHz, CDCl_3) δ 0.96-0.98 (4H, m), 3.95-3.99 (1H, m), 7.62 (1H, d, J 8.9 Hz), 7.66 (1H, dd, J 8.9, 2.7 Hz), 7.94 (1H, d, J 2.7 Hz), and 10.42 (1H, s).

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EXAMPLE 1(2S,3S)-N-((2-Cyclopropoxy-5-[5-(trifluoromethyl)tetrazol-1-yl]phenyl)methyl)-2-phenylpiperidin-3-amine Dihydrochloride

Sodium triacetoxyborohydride (411mg, 1.94mmol) was added to a mixture of 2-(cyclopropoxy)-5-[5-(trifluoromethyl)tetrazol-1-yl]benzaldehyde (Description 8; 0.459g, 1.54mmol),
10 (2S,3S)-2-phenylpiperidin-3-amine (prepared by the method described in WO 95/08549; 0.407g, 2.3mmol) and acetic acid (0.246ml, 4.62mmol) in 1,2-dichloroethane (3ml) and the mixture was stirred at room temperature for 45 minutes. The mixture was poured into aqueous sodium hydrogen
15 carbonate (satd.) and extracted with ethyl acetate. The combined organic fractions were washed with aqueous sodium hydrogen carbonate (satd., 2x70ml) and brine (70ml), dried (Na_2SO_4) and the solvent was evaporated under reduced pressure. The residue was purified by MPLC on silica gel, eluting with $\text{CH}_2\text{Cl}_2/\text{MeOH}/\text{NH}_3(\text{Aq.})$ (97:3:0.3). The residue was dissolved
20 in ethanol (3ml) and ethereal hydrogen chloride (1M, 2.5ml) was added. The solvent was evaporated under reduced pressure and the residue was recrystallised from ethanol/water (6:1). The solid was collected and dried *in vacuo* to give the title compound as a colorless solid (0.25g, 30%). ^1H NMR (360MHz, D_2O) δ 0.55-0.58 (1H, m), 0.72-0.75 (1H, m), 0.81-0.86 (2H, m), 2.10-2.11 (2H, m), 2.28 (1H, m), 2.47-2.50 (1H, m), 3.29-3.37 (1H, m), 3.69-3.72 (1H, m), 3.76-3.79 (1H, m), 3.96 (1H, m), 4.06 (1H, d, J 13.7 Hz), 4.34 (1H, d, J 13.7 Hz), 4.96 (1H, d, J 3.8 Hz), 7.32 (2H, m), 7.48-7.55 (5H, m), and 7.69-7.72 (1H, dd, J 8.9, 2.6 Hz). m/z (ES $^+$) 459 (M+1).

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EXAMPLE 2

(±)-(2*R*3*R*,2*S*3*S*)-N-(2-Cyclopropoxy-5-[5-(trifluoromethyl)tetrazol-1-yl]phenyl)methyl)-2-(4-fluorophenyl)piperidin-3-amine Dihydrochloride

Prepared from the compound of Description 8 and

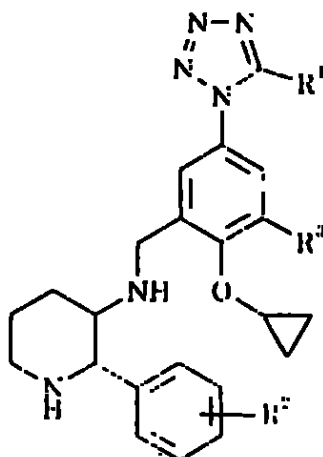
- 5 (±)-(2*R*3*R*,2*S*3*S*)-2-(4-fluorophenyl)piperidin-3-amine (prepared by the method described in WO 95/08549) according to the method of Example 1.
- ¹H NMR (360MHz, D₂O) δ 0.59 (1H, m), 0.72-0.75 (1H, m), 0.83-0.86 (2H, m), 2.07 (2H, m), 2.25 (1H, m), 2.43 (1H, m), 3.31-3.34 (1H, m), 3.64-3.68 (1H, m), 3.81-3.82 (1H, m), 3.89 (1H, m), 4.05 (1H, d, *J* 13.7 Hz), 4.31 (1H, d, *J* 13.7 Hz), 4.94 (1H, d, *J* 3.8 Hz), 7.24-7.28 (2H, m), 7.35-7.39 (2H, m), 7.50 (1H, d, *J* 2.6 Hz), 7.54 (1H, d, *J* 8.9 Hz), and 7.70 (1H, dd, *J* 8.9, 2.6 Hz). m/z (ES⁺) 477 (M+1).
- 10

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CLAIMS:

1. A compound of the formula (I):



(I)

wherein

R¹ represents a hydrogen atom or a methyl or trifluoromethyl group;

R² represents a hydrogen or halogen atom; and

R³ represents a hydrogen or halogen atom;

or a pharmaceutically acceptable salt thereof.

2. A compound as claimed in claim 1 wherein R¹ represents a hydrogen atom or a trifluoromethyl group.

3. A compound as claimed in claim 2 wherein R¹ represents a trifluoromethyl group.

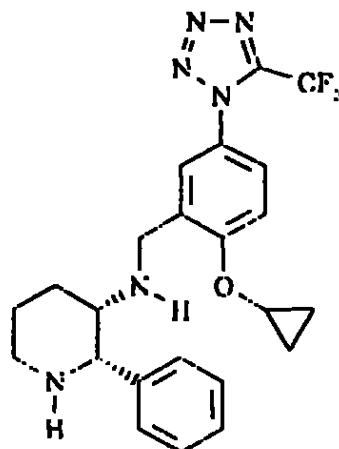
4. A compound as claimed in any one of claims 1 to 3 wherein R² represents a hydrogen, fluorine or chlorine atom.

5. A compound as claimed in claim 4 wherein R² is a hydrogen atom or a 4-fluorine atom.

6. A compound as claimed in any one of claims 1 to 5 wherein R^3 represents a hydrogen, fluorine or chlorine atom.

5 7. A compound as claimed in claim 6 wherein R^3 is a hydrogen or fluorine atom.

8. A compound as claimed in claim 1 which has the formula (1a)



(1a)

or a salt thereof.

9. The compound as claimed in claim 8 in the form of a
15 pharmaceutically acceptable acid addition salt.

10. A compound as claimed in any one of claims 1 to 9 in the form of its (2S,3S) stereoisomer.

20 11. A compound as claimed in claim 1 selected from:
N-{[2-cyclopropoxy-5-(5-(trifluoromethyl)tetrazol-1-yl)phenyl]methyl}-2-phenylpiperidin-3-amine;

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- (2S,3S)-N-([2-cyclopropoxy-5-(5-trifluoromethyltetrazol-1-yl)phenyl)methyl]-2-phenylpiperidin-3-amine;
N-([2-cyclopropoxy-5-(5-trifluoromethyltetrazol-1-yl)phenyl)methyl]-2-(4-fluorophenyl)piperidin-3-amine;
5 or a pharmaceutically acceptable salt thereof.

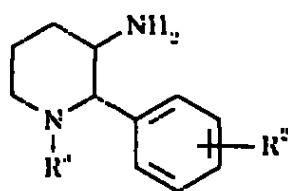
12. A compound as claimed in any preceding claim for use in therapy.
- 10 13. A pharmaceutical composition comprising a compound as claimed in any one of claims 1 to 11, together with at least one pharmaceutically acceptable carrier or excipient.
- 15 14. A method for the treatment or prevention of physiological disorders associated with an excess of tachykinins, which method comprises administration to a patient in need thereof of a tachykinin reducing amount of a compound according to claim 1.
- 20 15. A method according to claim 14 for the treatment or prevention of pain or inflammation, migraine, emesis, postherpetic neuralgia, depression or anxiety.
- 25 16. The use of a compound as claimed in any one of claims 1 to 11 for the manufacture of a medicament for the treatment or prevention of a physiological disorder associated with an excess of tachykinins.
- 30 17. The use of a compound as claimed in any one of claims 1 to 11 for the manufacture of a medicament for the treatment or prevention of pain or inflammation, migraine, emesis, postherpetic neuralgia, depression or anxiety.

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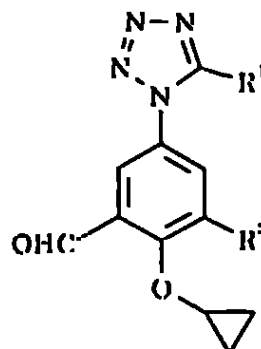
18. A process for the preparation of a compound as claimed in claim 1 which comprises:

(A) reacting a compound of formula (II) with a compound of formula (III) in the presence of a reducing agent:

5



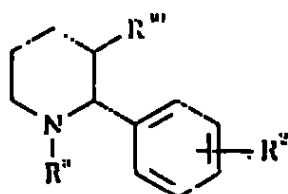
(II)



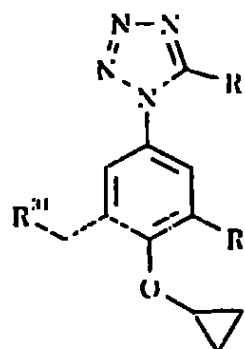
(III)

wherein R^1 , R^2 and R^3 are as defined in claim 1, and R^a is a hydrogen atom or a nitrogen protecting group; or

10 (B) reacting a compound of formula (IV) with a compound of formula (V):



(IV)

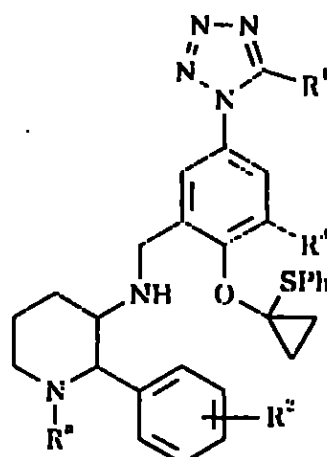


(V)

15 wherein R^1 , R^2 and R^3 are as defined in claim 1, R^a is a hydrogen atom or a nitrogen protecting group, and one of R^w and R^{31} represents a leaving group and the other of R^w and R^{31} represents NH_2 ; in the presence of a base; or

(C) reacting a compound of formula (V')

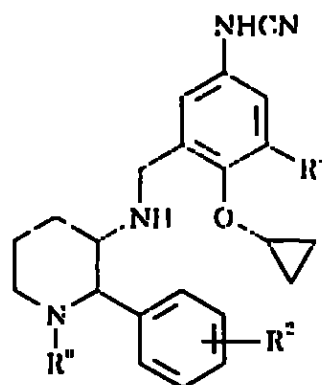
001/141



(VI)

wherein R¹, R² and R³ are as defined in claim 1, R^a is a hydrogen atom or a
 5 nitrogen protecting group, and Ph is a phenyl ring; with lithium
 naphthalenide in tetrahydrofuran; or

(D) reacting a compound of formula (VII)



(VII)

10

wherein R² and R³ are as defined in claim 1, and R^a is a hydrogen atom or
 a nitrogen protecting group; with ammonium chloride and sodium azide;

each process being followed, where necessary, by the removal of any
 protecting group where present;

~~CC-4~~

and when the compound of formula (I) is obtained as a mixture of enantiomers or diastereoisomers, optionally resolving the mixture to obtain the desired enantiomer;

- and/or, if desired, converting the resulting compound of formula (I)
- 5 or a salt thereof, into a pharmaceutically acceptable salt thereof.

INTERNATIONAL SEARCH REPORT

International Application No. 2

PCT/GB 98/03299

143

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D401/12 A61K31/445

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 95 08549 A (GLAXO GROUP LTD ;ARMOUR DUNCAN ROBERT (GB); EVANS BRIAN (GB); GIBL) 30 March 1995 cited in the application see claim 1 ---	1-18
Y	WO 96 29326 A (GLAXO GROUP LTD ;GIBLIN GERARD MARTIN PAUL (GB); SHARRATT PETER JO) 26 September 1996 cited in the application see claim 1 ---	1-18
X	WO 96 21661 A (GLAXO GROUP LTD ;ARMOUR DUNCAN ROBERT (GB); GIBLIN GERALD MARTIN P) 18 July 1996 cited in the application see claims 1,3 ---	1-18
-/-		

☒ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

* Special categories of cited documents

A document defining the general state of the art which is not considered to be of particular relevance

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L document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

O document referring to an oral disclosure, use, exhibition or other means

P document published prior to the international filing date but later than the priority date claimed

T later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

X document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

Y document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is considered with one or more other such documents, such combination being obvious to a person skilled in the art

A document member of the same patent family

Date of the actual completion of the international search

2 February 1999

Date of making of the international search report

10.02.99

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentean 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 spa nl,
Fax: (+31-70) 340-2016

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Gettins, M

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page 1 of 2

INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB 98/03299

144

C.(Continuation)- DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 97 21702 A (MERCK SHARP & DOHME ;BAKER RAYMOND (GB); ELLIOTT JASON (GB); SWAIN) 19 June 1997 see claim 1 -----	1-18

INTERNATIONAL SEARCH REPORT

International application No
PCT/GB 98/03299

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons

- 1 ☒ Claims Nos
because they relate to subject matter not required to be searched by this Authority, namely

Although claims 14 and 15 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
- 2 ☐ Claims Nos
because they relate to parts of the International Application that do not comply with the presented requirements to such an extent that no meaningful International Search can be carried out, specifically
- 3 ☐ Claims Nos
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6 4(a)

Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows

- 1 ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims
- 2 ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee
- 3 ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos
- 4 ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims, it is covered by claims Nos

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest
- ☐ No protest accompanied the payment of additional search fees

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/GB 98/03299

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9508549 A	30-03-1995	AP 495 A AT 173255 T AU 681190 B AU 7697494 A BG 100487 A CN 1135218 A CZ 9600830 A DE 69414590 D EP 0720609 A FI 961270 A HR 940575 A HU 75648 A JP 9505275 T NO 961156 A NZ 273614 A PL 313619 A SG 52644 A SK 38396 A US 5703240 A US 5843966 A ZA 9407291 A	28-05-1996 15-11-1998 21-08-1997 10-04-1995 31-12-1996 06-11-1996 11-09-1996 17-12-1998 10-07-1996 03-05-1996 28-02-1997 28-05-1997 27-05-1997 21-05-1996 22-09-1997 08-07-1996 28-09-1998 05-02-1997 30-12-1997 01-12-1998 31-05-1995
WO 9629326 A	26-09-1996	AU 5333596 A EP 0815104 A	08-10-1996 07-01-1998
WO 9621661 A	18-07-1996	AU 4437896 A EP 0802912 A JP 10511973 T	31-07-1996 29-10-1997 17-11-1998
WO 9721702 A	19-06-1997	AU 1037897 A CA 2238711 A EP 0866790 A	03-07-1997 19-06-1997 30-09-1998

Form PCT/ISA/210 (patent family annex) (July 1992)

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : C07D 401/10, A61K 31/495, 31/44, 31/445, 31/47, C07D 405/10, 213/73, 413/10, A61K 31/535, C07D 401/12, 405/12, 405/14, 453/02, 491/04	A1	(11) International Publication Number: WO 99/10339 (43) International Publication Date: 4 March 1999 (04.03.99)
(21) International Application Number: PCT/IB98/01229 (22) International Filing Date: 11 August 1998 (11.08.98) (30) Priority Data: 60/057,094 27 August 1997 (27.08.97) US (71) Applicant (for all designated States except US): PFIZER PRODUCTS INC. (US/US); Eastern Point Road, Groton, CT 06340 (US). (72) Inventor; and (75) Inventor/Applicant (for US only): LOWE, John, Adams, III [US/US]; 28 Covese Lane, Stonington, CT 06378 (US). (74) Agents: SPIEGEL, Allen, J.; c/o SIMPSON, Alison, Urquhart-Dykes & Lord, 91 Wimpole Street, London W1M 8AH (GB) et al.		(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i>
(54) Title: 2-AMINOPYRIDINES CONTAINING FUSED RING SUBSTITUENTS AS NOS INHIBITORS		
(57) Abstract The present invention relates to 2-aminopyridine derivatives of formula (I) wherein G, R¹ and R² are defined as in the specification, that exhibit activity as nitric oxide synthase (NOS) inhibitors, in pharmaceutical compositions containing them and to their use in the treatment and prevention of central nervous system and other disorders. (I)		

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5 2-AMINOPYRIDINES CONTAINING FUSED RING SUBSTITUENTS AS NOS INHIBITORS

The present invention relates to certain 2-aminopyridines containing fused ring substituents that exhibit activity as nitric oxide synthase (NOS) inhibitors, to pharmaceutical compositions containing them and to their use in the treatment and prevention of central nervous system disorders, inflammatory disorders, septic shock and other disorders.

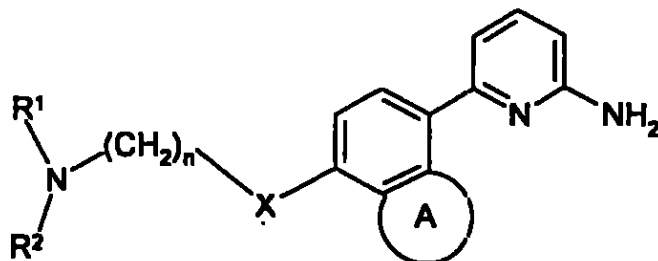
There are three known isoforms of NOS - an inducible form (I-NOS) and two constitutive forms referred to as, respectively, neuronal NOS (N-NOS) and endothelial NOS (E-NOS). Each of these enzymes carries out the conversion of arginine to citrulline while producing a molecule of nitric oxide (NO) in response to various stimuli. It is believed that excess nitric oxide (NO) production by NOS plays a role in the pathology of a number of disorders and conditions in mammals. For example, NO produced by I-NOS is thought to play a role in diseases that involve systemic hypotension such as toxic shock and therapy with certain cytokines. It has been shown that cancer patients treated with cytokines such as Interleukin 1 (IL-1), interleukin 2 (IL-2) or tumor necrosis factor (TNF) suffer cytokine-induced shock and hypotension due to NO produced from macrophages, i.e., inducible NOS (I-NOS), see Chemical & Engineering News, Dec. 20, p. 33, (1993). I-NOS inhibitors can reverse this. It is also believed that I-NOS plays a role in the pathology of diseases of the central nervous system such as ischemia. For example, inhibition of I-NOS has been shown to ameliorate cerebral ischemic damage in rats, see Am. J. Physiol., 268, p. R286 (1995)). Suppression of adjuvant induced arthritis by selective inhibition of I-NOS is reported in Eur. J. Pharmacol., 273, p. 15-24 (1995).

NO produced by N-NOS is thought to play a role in diseases such as cerebral ischemia, pain, and opiate tolerance. For example, inhibition of N-NOS decreases infarct volume after proximal middle cerebral artery occlusion in the rat, see J. Cerebr. Blood Flow Metab., 14, p. 924-929 (1994). N-NOS inhibition has also been shown to be effective in antinociception, as evidenced by activity in the late phase of the formalin-induced hindpaw licking and acetic acid-induced abdominal constriction assays, see Br. J. Pharmacol., 110, p. 219-224 (1993). In addition, subcutaneous injection of Freund's adjuvant in the rat induces an increase in NOS-positive neurons in the spinal cord that is manifested in increased sensitivity to pain, which can be treated with NOS inhibitors, see Japanese Journal of Pharmacology, 75, p. 327-335 (1997). Finally, opioid withdrawal in rodents has been reported to be reduced by N-NOS inhibition, see Neuropsychopharmacol., 13, p. 269-293 (1995).

5

Summary of the Invention

This invention relates to compounds of the formula



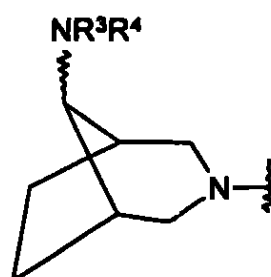
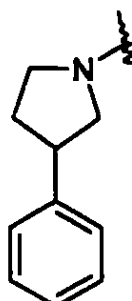
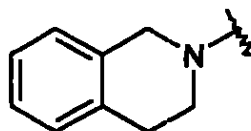
wherein ring A is a fused 5-7 membered saturated or unsaturated ring wherein from zero to two of the ring members are heteroatoms selected, independently, from nitrogen, oxygen and sulfur, with the proviso that no two adjacent ring members can both be heteroatoms;

X is oxygen or a bond;

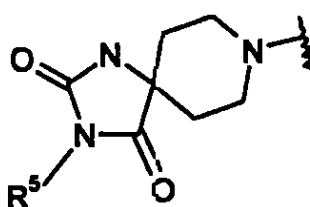
n is an interger from two to six; and

R¹ and R² are selected, independently, from (C₁-C₆) alkyl, aryl, tetrahydronaphthalene and aralkyl, wherein said aryl and the aryl moiety of said aralkyl is phenyl or naphthyl and the alkyl moiety is straight or branched and contains from 1 to 6 carbon atoms, and wherein said (C₁-C₆) alkyl, said aryl, said tetrahydronaphthalene and the aryl moiety of said aralkyl may optionally be substituted with from one to three substituents, preferably from zero to two substituents, that are selected, independently, from halo (e.g., chloro, fluoro, bromo, iodo), nitro, hydroxy, cyano, amino, (C₁-C₄) alkoxy, and (C₁-C₄) alkylamino;

or R¹ and R² form, together with the nitrogen to which they are attached, a piperazine, azetidine, piperidine or pyrrolidine ring or an azabicyclic ring containing from 6 to 14 ring members, from 1 to 3 of which are nitrogen and the rest of which are carbon, wherein examples of said azabicyclic rings are the following



and



5

also R^1 or R^2 may be connected onto the $(CH_2)_n$ group to form a ring of from 4 to 7 members;

5 wherein R^3 and R^4 are selected from hydrogen, (C_1-C_6) alkyl, phenyl, naphthyl, (C_1-C_6) alkyl- $C(=O)-$, $HC(=O)-$, (C_1-C_6) alkoxy- $C(=O)-$, phenyl- $C(=O)-$, naphthyl- $C(=O)-$, and $R^6R^7NC(=O)-$ wherein R^6 and R^7 are selected, independently, from hydrogen and (C_1-C_6) alkyl;

R^5 is selected from hydrogen, (C_1-C_6) alkyl, phenyl, naphthyl, phenyl- (C_1-C_6) alkyl- and naphthyl- (C_1-C_6) alkyl-;

10 and wherein said piperazine, azetidine, piperidine and pyrrolidine rings may optionally be substituted with one or more substituents, preferably with from zero to two substituents that are selected, independently, from (C_1-C_6) alkyl, amino, (C_1-C_6) alkylamino, $[di-(C_1-C_6)alkyl]amino$, phenyl substituted 5 to 6 membered heterocyclic rings containing from 1 to 4 rings nitrogen atoms, benzoyl, benzoylmethyl, benzylcarbonyl, phenylaminocarbonyl, phenylethyl and phenoxycarbonyl,
15 and wherein the phenyl moieties of any of the foregoing substituents may optionally be substituted with one or more substituents, preferably with from zero to two substituents, that are selected, independently, from halo, (C_1-C_3) alkyl, (C_1-C_3) alkoxy, nitro, amino, cyano, CF_3 and OCF_3 ;

and the pharmaceutically acceptable salts of such compounds.

The following compounds are preferred compounds of the invention:

- 20 6-[4-(2-Dimethylamino-ethoxy)-naphthalen-1-yl]-pyridin-2-ylamine;
6-[4-(2-Pyrrolidin-1-yl-ethoxy)-naphthalen-1-yl]-pyridin-2-ylamine;
6-[4-(2-[(Benzo[1,3]dioxol-5-ylmethyl)-amino]-ethoxy)-naphthalen-1-yl]-pyridin-2-ylamine;
6-[4-(2-(6,7-Dimethoxy-3,4-dihydro-1H-isoquinolin-2-yl)-ethoxy)-naphthalen-1-yl]-pyridin-2-ylamine;
25 3-[2-[4-(6-Amino-pyridin-2-yl)-naphthalen-1-yloxy]-ethyl]-3-aza-bicyclo[3.1.0]hex-6-ylamine;
6-[4-(2-(4-Phenethyl-piperazin-1-yl)-ethoxy)-naphthalen-1-yl]-pyridin-2-ylamine;
6-[4-(2-(3-Amino-pyrrolidin-1-yl)-ethoxy)-naphthalen-1-yl]-pyridin-2-ylamine;
30 6-[4-(1-Benzyl-piperidin-4-yloxy)-naphthalen-1-yl]-pyridin-2-ylamine;
6-[4-(1-Benzyl-pyrrolidin-3-yloxy)-naphthalen-1-yl]-pyridin-2-ylamine;
6-[4-(Piperidin-4-yloxy)-naphthalen-1-yl]-pyridin-2-ylamine;
6-[4-(Pyrrolidin-3-yloxy)-naphthalen-1-yl]-pyridin-2-ylamine;
6-[4-(1-Isobutyl-piperidin-4-yloxy)-naphthalen-1-yl]-pyridin-2-ylamine;
35 6-[4-(1-Furan-2-ylmethyl-piperidin-4-yloxy)-naphthalen-1-yl]-pyridin-2-ylamine;
6-[4-(1-Isobutyl-pyrrolidin-3-yloxy)-naphthalen-1-yl]-pyridin-2-ylamine;
6-[4-(1-Furan-2-ylmethyl-pyrrolidin-3-yloxy)-naphthalen-1-yl]-pyridin-2-ylamine;
6-[4-(2-Morpholin-4-yl-ethoxy)-naphthalen-1-yl]-pyridin-2-ylamine;
6-[4-(2-Diisopropylamino-ethoxy)-naphthalen-1-yl]-pyridin-2-ylamine;

- 5 6-[4-(1-Methyl-piperidin-4-yloxy)-naphthalen-1-yl]-pyridin-2-ylamine;
6-[4-(1-Methyl-pyrrolidin-3-yloxy)-naphthalen-1-yl]-pyridin-2-ylamine;
6-[4-(3-Dimethylamino-propoxy)-naphthalen-1-yl]-pyridin-2-ylamine;
6-[4-(1-Aza-bicyclo[2.2.2]oct-3-yloxy)-naphthalen-1-yl]-pyridin-2-ylamine;
6-[4-(2-Piperidin-1-yl-ethoxy)-naphthalen-1-yl]-pyridin-2-ylamine
- 10 6-[4-[2-(3,4-Dihydro-1H-isoquinolin-2-yl)-ethoxy]-naphthalen-1-yl]-pyridin-2-ylamine;
6-[4-[2-(4-Dimethylamino-piperidin-1-yl)-ethoxy]-naphthalen-1-yl]-pyridin-2-ylamine;
6-[4-[2-(tert-Butyl-methyl-amino)-ethoxy]-naphthalen-1-yl]-pyridin-2-ylamine;
6-[4-[2-(4-Methyl-piperazin-1-yl)-ethoxy]-naphthalen-1-yl]-pyridin-2-ylamine;
6-[4-[2-(4-Phenyl-piperidin-1-yl)-ethoxy]-naphthalen-1-yl]-pyridin-2-ylamine;
- 15 6-[4-[2-(7,8-Dihydro-5H-[1,3]dioxolo[4,5-g]isoquinolin-6-yl)-ethoxy]-naphthalen-1-yl]-
pyridin-2-ylamine;
6-[4-(Piperidin-2-ylmethoxy)-naphthalen-1-yl]-pyridin-2-ylamine;
6-[4-(1-Methyl-piperidin-2-ylmethoxy)-naphthalen-1-yl]-pyridin-2-ylamine;
6-[4-(1-Methyl-piperidin-3-ylmethoxy)-naphthalen-1-yl]-pyridin-2-ylamine;
- 20 6-[4-(2-Amino-cyclohexyloxy)-naphthalen-1-yl]-pyridin-2-ylamine;
6-[4-(Piperidin-3-ylmethoxy)-naphthalen-1-yl]-pyridin-2-ylamine;
6-[4-(1-Isobutyl-azetidin-3-yloxy)-naphthalen-1-yl]-pyridin-2-ylamine;
6-[4-(1-Furan-2-ylmethyl-azetidin-3-yloxy)-naphthalen-1-yl]-pyridin-2-ylamine;
6-[4-(8-Methyl-8-aza-bicyclo[3.2.1]oct-3-yloxy)-naphthalen-1-yl]-pyridin-2-ylamine;
- 25 6-[4-(Azetidin-3-yloxy)-naphthalen-1-yl]-pyridin-2-ylamine;
6-[4-(1-Methyl-pyrrolidin-2-ylmethoxy)-naphthalen-1-yl]-pyridin-2-ylamine;
6-[4-(Azetidin-2-ylmethoxy)-naphthalen-1-yl]-pyridin-2-ylamine;
6-[7-(2-Dimethylamino-ethoxy)-indan-4-yl]-pyridin-2-ylamine;
6-[7-(2-Pyrrolidin-1-yl-ethoxy)-indan-4-yl]-pyridin-2-ylamine;
- 30 6-[7-[2-(Benzyl-methyl-amino)-ethoxy]-indan-4-yl]-pyridin-2-ylamine;
6-[7-[2-(4-Phenethyl-piperazin-1-yl)-ethoxy]-indan-4-yl]-pyridin-2-ylamine;
6-[7-[2-(4-Isobutyl-piperazin-1-yl)-ethoxy]-indan-4-yl]-pyridin-2-ylamine;
6-[7-(2-Morpholin-4-yl-ethoxy)-indan-4-yl]-pyridin-2-ylamine;
6-[7-(2-Diisopropylamino-ethoxy)-indan-4-yl]-pyridin-2-ylamine;
- 35 6-[7-[2-(7,8-Dihydro-5H-[1,3]dioxolo[4,5-g]isoquinolin-6-yl)-ethoxy]-indan-4-yl]-pyridin-
2-ylamine;
6-[7-[2-(4-Methyl-piperazin-1-yl)-ethoxy]-indan-4-yl]-pyridin-2-ylamine;
6-[7-[2-(tert-Butyl-methyl-amino)-ethoxy]-indan-4-yl]-pyridin-2-ylamine;
6-[7-[2-(4-Dimethylamino-piperidin-1-yl)-ethoxy]-indan-4-yl]-pyridin-2-ylamine;

- 5 6-[8-(2-Dimethylamino-ethoxy)-1,2,3,4-tetrahydro-1,4-methano-naphthalen-5-yl]-
pyridin-2-ylamine;
 6-[8-(2-Pyrrolidin-1-yl-ethoxy)-1,2,3,4-tetrahydro-1,4-methano-naphthalen-5-yl]-pyridin-
2-ylamine;
 6-[4-(2-Dimethylamino-ethoxy)-5,6,7,8-tetrahydro-naphthalen-1-yl]-pyridin-2-ylamine;
10 6-[4-(2-Pyrrolidin-1-yl-ethoxy)-5,6,7,8-tetrahydro-naphthalen-1-yl]-pyridin-2-ylamine;
 6-[4-(2-(tert-Butyl-methyl-amino)-ethoxy)-5,6,7,8-tetrahydro-naphthalen-1-yl]-pyridin-2-
ylamine;
 6-[4-(2-Diisopropylamino-ethoxy)-5,6,7,8-tetrahydro-naphthalen-1-yl]-pyridin-2-ylamine;
 6-[4-(2-Diethylamino-ethoxy)-5,6,7,8-tetrahydro-naphthalen-1-yl]-pyridin-2-ylamine;
15 6-[4-(2-(3,4-Dihydro-1H-isoquinolin-2-yl)-ethoxy)-5,6,7,8-tetrahydro-naphthalen-1-yl]-
pyridin-2-ylamine;
 6-[4-(2-Piperidin-1-yl-ethoxy)-5,6,7,8-tetrahydro-naphthalen-1-yl]-pyridin-2-ylamine;
 6-[4-(2-Morpholin-4-yl-ethoxy)-5,6,7,8-tetrahydro-naphthalen-1-yl]-pyridin-2-ylamine;
20 6-[4-(2-(7,8-Dihydro-5H-[1,3]dioxolo[4,5-g]isoquinolin-6-yl)-ethoxy)-5,6,7,8-tetrahydro-
naphthalen-1-yl]-pyridin-2-ylamine;
 6-[4-(2-(4-Methyl-piperazin-1-yl)-ethoxy)-5,6,7,8-tetrahydro-naphthalen-1-yl]-pyridin-2-
ylamine;
 6-[4-(2-(4-Dimethylamino-piperidin-1-yl)-ethoxy)-5,6,7,8-tetrahydro-naphthalen-1-yl]-
pyridin-2-ylamine;
25 6-[4-(2-(7,8-Dihydro-5H-[1,3]dioxolo[4,5-g]isoquinolin-6-yl)-ethoxy)-5,6,7,8-tetrahydro-
naphthalen-1-yl]-pyridin-2-ylamine;
 6-[4-(1-Isobutyl-piperidin-3-ylmethoxy)-5,6,7,8-tetrahydro-naphthalen-1-yl]-pyridin-2-
ylamine;
 6-[4-(1-Methyl-piperidin-3-ylmethoxy)-5,6,7,8-tetrahydro-naphthalen-1-yl]-pyridin-2-
30 ylamine;
 6-[4-(2-(2-Diethylamino-ethoxy)-ethoxy)-5,6,7,8-tetrahydro-naphthalen-1-yl]-pyridin-2-
ylamine;
 6-[4-(Piperidin-3-ylmethoxy)-5,6,7,8-tetrahydro-naphthalen-1-yl]-pyridin-2-ylamine;
 6-[4-(2-Amino-cyclohexyloxy)-5,6,7,8-tetrahydro-naphthalen-1-yl]-pyridin-2-ylamine;
35 6-[4-(Pyrrolidin-2-ylmethoxy)-5,6,7,8-tetrahydro-naphthalen-1-yl]-pyridin-2-ylamine; and
 6-[4-(2-Dimethylamino-ethoxy)-6,7,8,9-tetrahydro-5H-benzocyclohepten-1-yl]-pyridin-2-
ylamine;

and the pharmaceutically acceptable salts of the foregoing compounds.

The following are additional examples of compounds of this invention:

- 5 6-[4-(2-Amino-cyclopentyloxy)-5,6,7,8-tetrahydro-naphthalen-1-yl]-pyridin-2-ylamine;
 6-[4-(2-Amino-cyclobutyloxy)-5,6,7,8-tetrahydro-naphthalen-1-yl]-pyridin-2-ylamine;
 6-[4-(2-Amino-cyclopropyloxy)-5,6,7,8-tetrahydro-naphthalen-1-yl]-pyridin-2-ylamine;
 6-[4-(3-Amino-cyclohexyloxy)-5,6,7,8-tetrahydro-naphthalen-1-yl]-pyridin-2-ylamine;
 6-[4-(3-Amino-cyclopentyloxy)-5,6,7,8-tetrahydro-naphthalen-1-yl]-pyridin-2-ylamine;
 10 6-[4-(3-Amino-cyclobutyloxy)-5,6,7,8-tetrahydro-naphthalen-1-yl]-pyridin-2-ylamine;
 6-[4-(4-Amino-cyclohexyloxy)-5,6,7,8-tetrahydro-naphthalen-1-yl]-pyridin-2-ylamine;
 6-[4-(2-Amino-cyclopentyloxy)-naphthalen-1-yl]-pyridin-2-ylamine;
 6-[4-(2-Amino-cyclobutyloxy)-naphthalen-1-yl]-pyridin-2-ylamine;
 6-[4-(2-Amino-cyclopropyloxy)-naphthalen-1-yl]-pyridin-2-ylamine;
 15 6-[4-(3-Amino-cyclohexyloxy)-naphthalen-1-yl]-pyridin-2-ylamine;
 6-[4-(3-Amino-cyclopentyloxy)-naphthalen-1-yl]-pyridin-2-ylamine;
 6-[4-(3-Amino-cyclobutyloxy)-naphthalen-1-yl]-pyridin-2-ylamine;
 6-[4-(4-Amino-cyclohexyloxy)-naphthalen-1-yl]-pyridin-2-ylamine;
 6-[4-(2-Amino-cyclopentyloxy)-indan-4-yl]-pyridin-2-ylamine;
 20 6-[4-(2-Amino-cyclobutyloxy)-indan-4-yl]-pyridin-2-ylamine;
 6-[4-(2-Amino-cyclopropyloxy)-indan-4-yl]-pyridin-2-ylamine;
 6-[4-(3-Amino-cyclohexyloxy)-indan-4-yl]-pyridin-2-ylamine;
 6-[4-(3-Amino-cyclopentyloxy)-indan-4-yl]-pyridin-2-ylamine;
 6-[4-(3-Amino-cyclobutyloxy)-indan-4-yl]-pyridin-2-ylamine;
 25 6-[4-(4-Amino-cyclohexyloxy)-indan-4-yl]-pyridin-2-ylamine;
 6-[4-Piperidin-3-ylmethoxy)-6,7,8,9-tetrahydro-5H-benzocyclohepten-1-yl]-pyridin-2-ylamine;
 6-[4-(2-Pyrrolidinyl-ethoxy)-6,7,8,9-tetrahydro-5H-benzocyclohepten-1-yl]-pyridin-2-ylamine;
 30 6-[4-(2-Amino-cyclohexyloxy)-6,7,8,9-tetrahydro-5H-benzocyclohepten-1-yl]-pyridin-2-ylamine;
 6-[4-(2-(4-Dimethylamino-piperidin-1-yl)-ethoxy)-6,7,8,9-tetrahydro-5H-benzocyclohepten-1-yl]-pyridin-2-ylamine; and
 6-[4-(2-(4-Methyl-piperazin-1-yl)-ethoxy)-6,7,8,9-tetrahydro-5H-benzocyclohepten-1-yl]-pyridin-2-ylamine.
 35

The present invention also relates to the pharmaceutically acceptable acid addition salts of compounds of the formula I. The acids which are used to prepare the pharmaceutically acceptable acid addition salts of the aforementioned base compounds of this invention are those which form non-toxic acid addition salts, i.e., salts containing pharmacologically acceptable anions, such as the hydrochloride, hydrobromide, hydroiodide, nitrate, sulfate, bisulfate,

5 phosphate, acid phosphate, acetate, lactate, citrate, acid citrate, tartrate, bitartrate, succinate, maleate, fumarate, gluconate, saccharate, benzoate, methanesulfonate, ethanesulfonate, benzenesulfonate, p-toluenesulfonate and pamoate [i.e., 1,1-methylene-bis-(2-hydroxy-3-naphthoate)] salts.

10 The term "alkyl", as used herein, unless otherwise indicated, includes saturated monovalent hydrocarbon radicals having straight, branched or cyclic moieties or combinations thereof.

The term "one or more substituents", as used herein, refers to a number of substituents that equals from one to the maximum number of substituents possible based on the number of available bonding sites.

15 The terms "halo" and "halogen", as used herein, unless otherwise indicated, include chloro, fluoro, bromo and iodo.

Examples of more specific embodiments of the present invention include:

- (a) compounds of the formula I wherein ring A is pyrrolo;
- (b) compounds of the formula I wherein ring A is pyrido;
- 20 (c) compounds of the formula I wherein X is a bond;
- (d) compounds of the formula I wherein ring A is pyrimido;
- (e) compounds of the formula I wherein n is 2 or 3;
- (f) compounds of the formula I wherein X is oxygen;
- (g) compounds of the formula I wherein R¹ and R² are selected, independently, from
- 25 (C₁-C₆)alkyl;
- (h) compounds of the formula I wherein R¹ and R² do not form a ring with the nitrogen to which they are attached;
- (i) compounds of the formula I wherein R¹ and R² form, together with the nitrogen to which they are attached, a piperazine, azetidine, piperidine or pyrrolidine ring;
- 30 (j) compounds of the formula I wherein R¹ is selected from (C₁-C₆)alkyl and R² is selected from aryl, tetrahydronaphthalene and aralkyl; and
- (k) compounds of the formula I wherein ring A is thieno or thiazolo.

The present invention also relates to a pharmaceutical composition for treating or preventing a condition selected from the group consisting of migraine inflammatory diseases (e.g.,

35 asthma), stroke, acute and chronic pain, hypovolemic shock, traumatic shock, reperfusion injury, Crohn's disease, ulcerative colitis, septic shock, multiple sclerosis, AIDS associated dementia, neurodegenerative diseases, neuron toxicity, depression (e.g., major depressive disorder and dysthymia, Parkinson's disease, Alzheimer's disease, chemical dependencies and addiction (e.g.,

5 dependencies on drugs, alcohol and nicotine), emesis, epilepsy, anxiety, psychosis, head trauma, adult respiratory distress syndrome (ARDS), morphine induced tolerance and withdrawal symptoms, inflammatory bowel disease, osteoarthritis, rheumatoid arthritis, ovulation, dilated cardiomyopathy, acute spinal cord injury, Huntington's disease, glaucoma, macular degeneration, diabetic neuropathy, diabetic nephropathy and cancer in a mammal, including a
10 human, comprising an amount of a compound of the formula I, or a pharmaceutically acceptable salt thereof that is effective in treating or preventing such condition, and a pharmaceutically acceptable carrier.

The present invention also relates to a method of treating or preventing a condition selected from the group consisting of migraine inflammatory diseases (e.g., asthma), stroke, acute
15 and chronic pain, hypovolemic shock, traumatic shock, reperfusion injury, Crohn's disease, ulcerative colitis, septic shock, multiple sclerosis, AIDS associated dementia, neurodegenerative diseases, neuron toxicity, depression (e.g., major depressive disorder and dysthymia), Parkinson's disease, Alzheimer's disease, chemical dependencies and addictions (e.g., dependencies on drugs, alcohol and nicotine), emesis, epilepsy, anxiety, psychosis, head trauma,
20 adult respiratory distress syndrome (ARDS), morphine induced tolerance and withdrawal symptoms, inflammatory bowel disease, osteoarthritis, rheumatoid arthritis, ovulation, dilated cardiomyopathy, acute spinal cord injury, Huntington's disease, glaucoma, macular degeneration, diabetic neuropathy, diabetic nephropathy and cancer in a mammal, including a human, comprising administering to said mammal an amount of a compound of the formula I, or a
25 pharmaceutically acceptable salt thereof, that is effective in treating or preventing such condition.

The present invention also relates to a pharmaceutical composition for inhibiting nitric oxide synthase (NOS) in a mammal, including a human, comprising an NOS inhibiting effective amount of a compound of the formula I, or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier.

30 The present invention also relates to a method of inhibiting NOS in a mammal, including a human, comprising administering to said mammal a NOS inhibiting effective amount of a compound of the formula I, or a pharmaceutically acceptable salt thereof.

The present invention also relates to a pharmaceutical composition for treating or preventing a condition selected from the group consisting of migraine, inflammatory diseases
35 (e.g., asthma), stroke, acute and chronic pain, hypovolemic shock, traumatic shock, reperfusion injury, Crohn's disease, ulcerative colitis, septic shock, multiple sclerosis, AIDS associated dementia, neurodegenerative diseases, neuron toxicity, depression (e.g., major depressive disorder and dysthymia), Parkinson's disease, Alzheimer's disease, chemical dependencies and addictions (e.g., dependencies on drugs, alcohol and nicotine), emesis, epilepsy, anxiety,
40 psychosis, head trauma, adult respiratory distress syndrome (ARDS), morphine induced tolerance

5 and withdrawal symptoms, inflammatory bowel disease, osteoarthritis, rheumatoid arthritis, ovulation, dilated cardiomyopathy, acute spinal cord injury, Huntington's disease, glaucoma, macular degeneration, diabetic neuropathy, diabetic nephropathy and cancer in a mammal, including a human, comprising a NOS inhibiting effective amount of a compound of the formula I, or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier.

10 The present invention also relates to a method of treating or preventing a condition selected from the group consisting of migraine, inflammatory diseases (e.g., asthma), stroke, acute and chronic pain, hypovolemic shock, traumatic shock, reperfusion injury, Crohn's disease, ulcerative colitis, septic shock, multiple sclerosis, AIDS associated dementia, neurodegenerative diseases, neuron toxicity, depression (e.g., major depressive disorder and dysthymia),
15 Parkinson's disease, Alzheimer's disease, chemical dependencies and addictions (e.g., dependencies on drugs, alcohol or nicotine), emesis, epilepsy, anxiety, psychosis, head trauma, adult respiratory distress syndrome (ARDS), morphine induced tolerance and withdrawal symptoms, inflammatory bowel disease, osteoarthritis, rheumatoid arthritis, ovulation, dilated cardiomyopathy, acute spinal cord injury, Huntington's disease, glaucoma, macular
20 degeneration, diabetic neuropathy, diabetic nephropathy and cancer in a mammal, including a human, comprising administering to said mammal a NOS inhibiting effective amount of a compound of the formula II, or a pharmaceutically acceptable salt thereof.

Compounds of formula I may contain chiral centers and therefore may exist in different enantiomeric and diastereomeric forms. This invention relates to all optical isomers and all
25 stereoisomers of compounds of the formula I and mixtures thereof, and to all pharmaceutical compositions and methods of treatment defined above that contain or employ them, respectively.

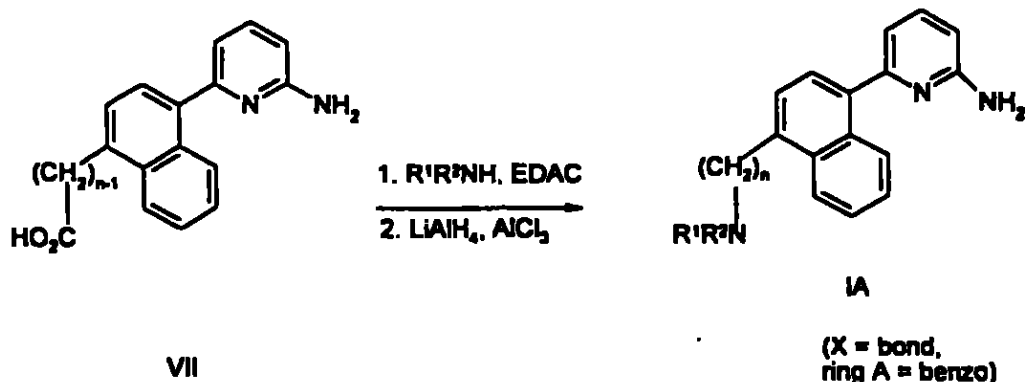
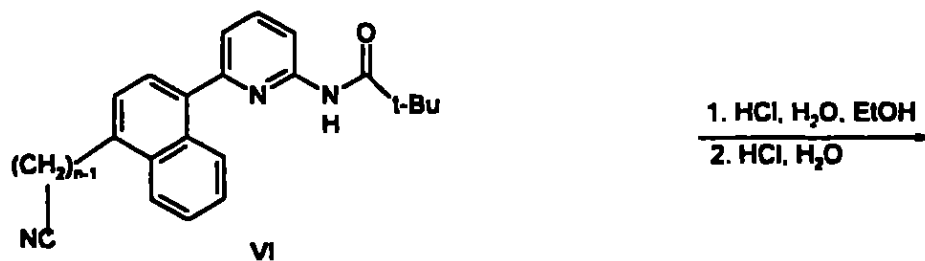
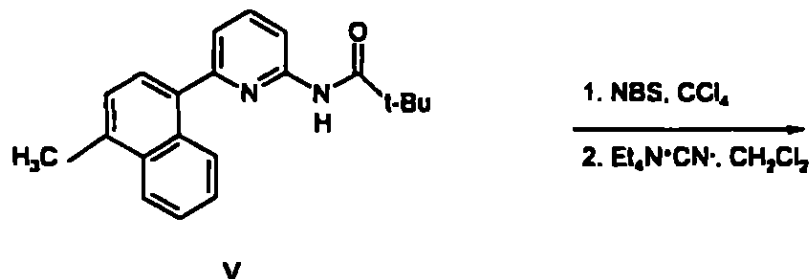
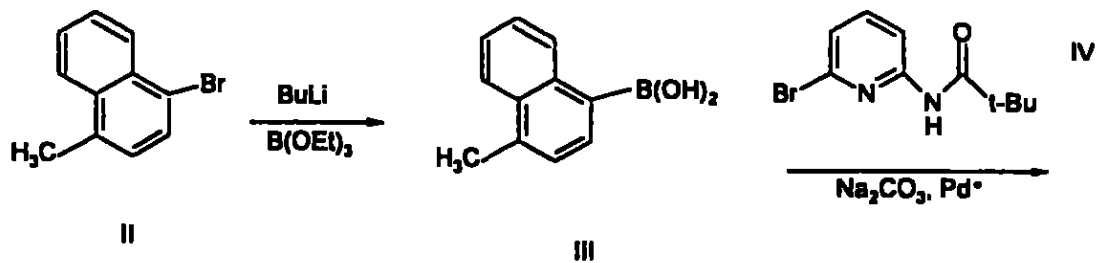
Formula I above includes compounds identical to those depicted but for the fact that one or more hydrogen, carbon or other atoms are replaced by isotopes thereof. Such compounds may be useful as research and diagnostic tools in metabolism pharmacokinetic studies and in binding
30 assays.

Detailed Description of the Invention

The compounds of the formula I may be prepared as described in the following reaction schemes and discussion. Unless otherwise indicated, ring A, X, n, R¹, R², R³, R⁴, R⁵, R⁶ and R⁷ and structural formula I in the reaction schemes and discussion that follow are defined as above.

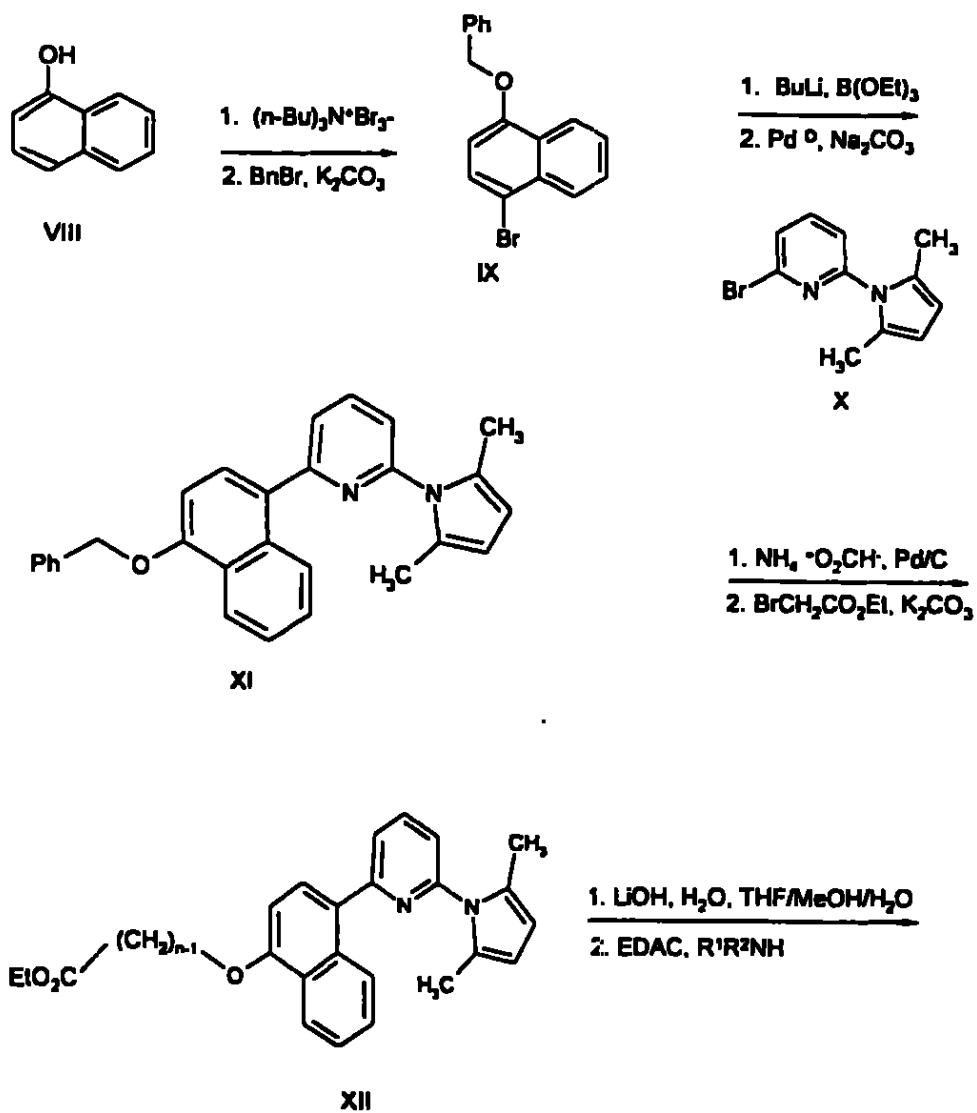
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SCHEME 1

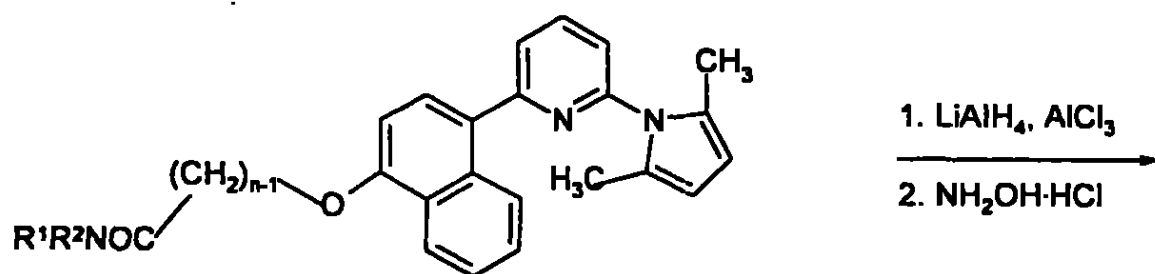


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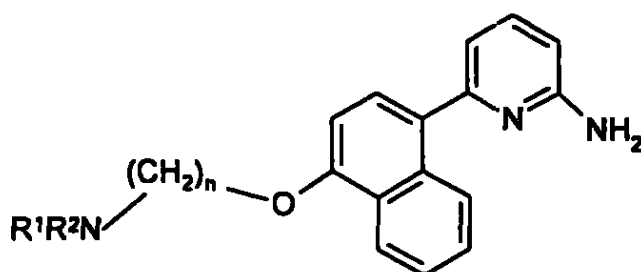
Scheme 2



5

Scheme 2 continued

XIII



IB

(X = O, ring A = benzo)

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5 Scheme 1 illustrates a method of preparing compounds of the formula I wherein X is a bond and ring A is benzo. Schemes 2 and 3 illustrate methods of preparing compounds of the formula I wherein X is oxygen and ring A is benzo. The starting materials used in the procedures of Schemes 1 and 2 are either commercially available, known in the art or readily obtainable from known compounds by methods that will be apparent to those skilled in the art.

10 Referring to Scheme 1, the compound of formula II is cooled to about -70°C in dry tetrahydrofuran (THF), and then a solution of n-butyl lithium is added to it. The resulting solution is then treated with triethyl borate and allowed to warm to room temperature to form the compound of formula III.

15 The compound of formula III is reacted with the compound of formula IV to form the compound of formula V. This reaction is generally carried out in an aqueous ethanol solvent, in the presence of sodium carbonate and tetrakis(triphenylphosphine) palladium, at about the reflux temperature.

20 The compound of the formula VI can be formed in the following manner. First, the compound of formula V is reacted with N-bromosuccinimide (NBS) and bis-(1-cyano-1-aza)-cyclohexane in carbon tetrachloride and refluxed for about 8 hours, with additional portions of the initiator being added at about 1, 2 and 4 hours. After evaporation of the solvent, the product of this reaction is reacted with triethylammonium cyanide in methylene chloride at about room temperature to form the compound of formula VI.

25 Saturation of a solution of the compound of formula VI in ethanol with hydrogen chloride, followed by refluxing the mixture and then heating in aqueous hydrochloric acid, yields the compound of formula VII.

30 The compound of the formula VII that is formed in the preceding step can be converted into the compound of formula IA in the following manner. First, the compound of formula VII is reacted with the appropriate compound of the formula R^2R^1NH and N-ethyl-N-dimethylaminopropyl carbodiimide (EDAC) in the presence of a base. Examples of suitable bases are those selected from trialkylamines, alkali metal carbonates and alkaline earth metal carbonates. This reaction is typically conducted in a solvent such as acetonitrile, methylene chloride or N,N-dimethylformamide (DMF), at a temperature from about room temperature to about 100°C, preferably at about room temperature. Preferably, the reaction is conducted in the presence of a catalytic additive such as N-hydroxysuccinamide or hydroxybenzotriazole.

35 The product of the foregoing reaction is then reduced using methods well known to those of skill in the art. For example, the reduction can be carried out using lithium aluminum hydride in tetrahydrofuran, with or without aluminum chloride, or using borane methyl sulfide in tetrahydrofuran, at a temperature of about -78°C to about 0°C, preferably at about -70°C, to yield
40 the desired compound of formula IA.

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5 Referring to scheme 2, the compound of formula VIII is reacted with tetrabutylammonium tribromide in 1,2-dichloroethane at about room temperature. The product of this reaction is then treated with benzyl bromide and potassium carbonate in a solvent such as acetonitrile, at about the reflux temperature of the reaction mixture, to form the compound of formula IX.

10 The compound of formula IX is then converted into 1-benzyloxy-naphthalene-4-boronic acid by the procedure described above for preparing the boronic acid derivative of formula III in Scheme 1.

Reaction of 1-benzyloxy-naphthalene-4-boronic acid with the compound of formula X in an ethanol solvent, in the presence of sodium carbonate and tetrakis(triphenyl) palladium, at about the reflux temperature of the reaction mixture, yields the compound of formula XI.

15 The compound of formula XI can be converted into the compound of formula XIII using the following two step process. The compound of formula XI is reacted with ammonium formate and ten percent palladium on carbon, in an ethanol solvent, at about the reflux temperature of the reaction mixture, to yield the analogous compound to that having formula XI, wherein the benzyloxy group of formula XI is replaced with a hydroxy group. The compound of formula XII is then formed by reacting the above hydroxy derivative with 2-bromoethylacetate and potassium carbonate in acetonitrile at about the reflux temperature of the reaction mixture.

25 Basic hydrolysis of the compound of formula XII, followed by reaction with N-ethyl-N-3-dimethylaminopropylcarbodiimide (EDAC) and the appropriate compound having the formula R^1R^2NH yields the desired compound of the formula XIII. The base hydrolysis is typically carried out using an alkali metal or alkaline earth metal hydroxide in a mixture of THF, methanol and water at about room temperature. The reaction with R^1R^2NH and EDAC is generally carried out using the procedure described above for the preparation of compounds of the formula IA from those of formula VII in Scheme 1.

30 The compound of formula XIII can be converted into the desired compound of formula IB as follows. The compound of formula XIII is reduced to form the corresponding compound wherein the carbonyl group is replaced by a methylene group, after which the 2,5-dimethylpyrrolyl protecting group is removed. The reduction can be carried out using methods well known to those of skill in the art, for example, using lithium aluminum hydride in tetrahydrofuran, with or without aluminum chloride, or using borane methyl sulfide in tetrahydrofuran, at a temperature of about 35 -78°C to about 0°C, preferably at about -70°C.

Removal of the 2,5-dimethylpyrrolyl protecting group can be accomplished by reaction with hydroxylamine hydrochloride. This reaction is generally carried out in an alcoholic or aqueous alcoholic solvent, at a temperature from about room temperature to about the reflux temperature of the reaction mixture, preferably at about the reflux temperature, for about 8 to 40 about 72 hours.

5 Compounds of the formula I that are identical to those of formula IB but for the fact that ring A is other than benzo can be prepared in an analogous fashion, starting with the appropriate compound that is analogous to that of formula VIII, wherein the unsubstituted benzo ring of formula VIII is replaced by a ring other than benzo that is within the definition of ring A.

 Referring to Scheme 3, the known 1-fluoronaphthalene (XIV) is brominated with
10 bromine in acetic acid at a temperature from about room temperature to about the reflux temperature of the reaction mixture for about 1 to about 48 hours, and the bromide cooled to about -70°C in dry tetrahydrofuran (THF), and then a solution of n-butyl lithium is added to it. The resulting solution is then treated with triethyl borate and allowed to warm to room temperature to form the compound of formula XV. The compound of formula XV is reacted with the compound of
15 formula IV to form the compound of formula XVI. This reaction is generally carried out in an aqueous ethanol solvent, in the presence of sodium carbonate and tetrakis(triphenylphosphine) palladium, at about the reflux temperature. The compound of formula XVI is then treated with an alkali metal alkoxide prepared from a compound of the formula $\text{HO}(\text{CH}_2)_n\text{NR}^1\text{R}^2$ and sodium hydride in a polar solvent such as dimethylformamide, at a temperature from room temperature to
20 140°C for about 1 to about 48 hours. This reaction produces the corresponding compound of formula XVII, which is then deblocked to remove the 2,5-dimethylpyrrolyl protecting group by reaction with hydroxylamine hydrochloride. This reaction is generally carried out in an alcoholic or aqueous alcoholic solvent, at a temperature from about room temperature to about the reflux temperature of the reaction mixture, preferably at about the reflux temperature, for about 8 to
25 about 72 hours.

 Compounds of the formula I that are identical to those of formula IA and IB but for the fact that ring A is other than benzo can be prepared in an analogous fashion, starting with the appropriate starting materials that are analogous to those of formulas VIII and XIV, on Schemes 1, 2 and 3 respectively, wherein the unsubstituted benzo ring of such starting materials is replaced
30 by a ring other than benzo that is within the definition of ring A.

 The preparation of other compounds of the formula I not specifically described in the foregoing experimental section can be accomplished using combinations of the reactions described above that will be apparent to those skilled in the art.

 In each of the reactions discussed or illustrated above, pressure is not critical unless
35 otherwise indicated. Pressures from about 0.5 atmospheres to about 5 atmospheres are generally acceptable, and ambient pressure, i.e., about 1 atmosphere, is preferred as a matter of convenience.

 The compounds of formulae I ("the active compounds of this invention") which are basic in nature are capable of forming a wide variety of different salts with various inorganic and organic
40 acids. Although such salts must be pharmaceutically acceptable for administration to animals, it is

5 often desirable in practice to initially isolate a compound of the formula I from the reaction mixture as a pharmaceutically unacceptable salt and then simply convert the latter back to the free base compound by treatment with an alkaline reagent and subsequently convert the latter free base to a pharmaceutically acceptable acid addition salt. The acid addition salts of the active base compounds of this invention are readily prepared by treating the base compound with a
10 substantially equivalent amount of the chosen mineral or organic acid in an aqueous solvent medium or in a suitable organic solvent, such as methanol or ethanol. Upon careful evaporation of the solvent, the desired solid salt is readily obtained.

The active compounds of this invention and their pharmaceutically acceptable salts are useful as NOS inhibitors i.e., they possess the ability to inhibit the NOS enzyme in mammals, and
15 therefore they are able to function as therapeutic agents in the treatment of the aforementioned disorders and diseases in an afflicted mammal.

The active compounds of this invention and their pharmaceutically acceptable salts can be administered via either the oral, parenteral or topical routes. In general, these compounds are most desirably administered in dosages ranging from about 0.01 to about 250 mg per day, in
20 single or divided doses (i.e., from 1 to 4 doses per day), although variations will necessarily occur depending upon the species, weight and condition of the subject being treated and the particular route of administration chosen. However, a dosage level that is in the range of about 0.07 mg to about 21 mg per kg of body weight per day is most desirably employed. Variations may nevertheless occur depending upon the species of animal being treated and its individual
25 response to said medicament, as well as on the type of pharmaceutical formulation chosen and the time period and interval at which such administration is carried out. In some instances, dosage levels below the lower limit of the aforesaid range may be more than adequate, while in other cases still larger doses may be employed without causing any harmful side effect, provided that such larger doses are first divided into several small doses for administration throughout the
30 day.

The active compounds of the invention may be administered alone or in combination with pharmaceutically acceptable carriers or diluents by either of the three routes previously indicated, and such administration may be carried out in single or multiple doses. More particularly, the novel therapeutic agents of this invention can be administered in a wide variety of different dosage
35 forms, i.e., they may be combined with various pharmaceutically acceptable inert carriers in the form of tablets, capsules, lozenges, troches, hard candies, powders, sprays, creams, salves, suppositories, jellies, gels, pastes, lotions, ointments, aqueous suspensions, injectable solutions, elixirs, syrups, and the like. Such carriers include solid diluents or fillers, sterile aqueous media and various non-toxic organic solvents, etc. Moreover, oral pharmaceutical compositions can be
40 suitably sweetened and/or flavored. In general, the therapeutically-effective compounds of this

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5 invention are present in such dosage forms at concentration levels ranging from about 5.0% to about 70% by weight.

For oral administration, tablets containing various excipients such as microcrystalline cellulose, sodium citrate, calcium carbonate, dicalcium phosphate and glycine may be employed along with various disintegrants such as starch (and preferably corn, potato or tapioca starch),
10 alginic acid and certain complex silicates, together with granulation binders like polyvinylpyrrolidone, sucrose, gelatin and acacia. Additionally, lubricating agents such as magnesium stearate, sodium lauryl sulfate and talc are often very useful for tableting purposes. Solid compositions of a similar type may also be employed as fillers in gelatin capsules; preferred materials in this connection also include lactose or milk sugar as well as high molecular weight
15 polyethylene glycols. When aqueous suspensions and/or elixirs are desired for oral administration, the active ingredient may be combined with various sweetening or flavoring agents, coloring matter or dyes, and, if so desired, emulsifying and/or suspending agents as well, together with such diluents as water, ethanol, propylene glycol, glycerin and various like combinations thereof.

20 For parenteral administration, solutions of an active compound of the present invention in either sesame or peanut oil or in aqueous propylene glycol may be employed. The aqueous solutions should be suitably buffered (preferably pH greater than 8) if necessary and the liquid diluent first rendered isotonic. These aqueous solutions are suitable for intravenous injection purposes. The oily solutions are suitable for intraarticular, intramuscular and subcutaneous
25 injection purposes. The preparation of all these solutions under sterile conditions is readily accomplished by standard pharmaceutical techniques well known to those skilled in the art.

Additionally, it is also possible to administer the active compounds of the present invention topically when treating inflammatory conditions of the skin and this may be done by way of creams, jellies, gels, pastes, patches, ointments and the like, in accordance with standard
30 pharmaceutical practice.

The ability of compounds of the formulae I to inhibit NOS may be determined using procedures described in the literature. The ability of compounds of the formulae I to inhibit endothelial NOS may be determined by using the procedures described by Schmidt *et al.* in Proc. Natl. Acad. Sci. U.S.A., 88, pp. 365-369 (1991) and by Pollock *et al.* in Proc. Natl. Acad. Sci. U.S.A., 88, pp. 10480-10484 (1991). The ability of compounds of the formulae I to inhibit inducible
35 NOS may be determined using the procedures described by Schmidt *et al.* in Proc. Natl. Acad. Sci. U.S.A., 88 pp. 365-369 (1991) and by Garvey *et al.* in J. Biol. Chem., 269, pp. 26669-26676 (1994). The ability of the compounds of the formulae I to inhibit neuronal NOS may be determined using the procedure described by Bredt and Snyder in Proc. Natl. Acad. Sci. U.S.A., 87, 682-685
40 (1990).

5 Of sixteen compounds of the formula I that were tested, all exhibited an $IC_{50} < 10 \mu M$ for inhibition of either inducible or neuronal NOS.

The present invention is illustrated by the following examples. It will be understood, however, that the invention is not limited to the specific details of these examples. Melting points are uncorrected. Proton nuclear magnetic resonance spectra (1H NMR) and ^{13}C nuclear magnetic
10 resonance spectra were measured for solutions in deuteriochloroform ($CDCl_3$) or in CD_3OD or CD_3SOCD_3 and peak positions are expressed in parts per million (ppm) downfield from tetramethylsilane (TMS). The peak shapes are denoted as follows: s, singlet; d, doublet; t, triplet; q, quartet, m, multiplet, b, broad.

EXAMPLE 1

15 6-[4-[2-(4-Phenethyl-piperazin-1-yl)-ethyl]-naphthalen-1-yl]-pyridin-2-ylamine
N-t-Butylcarbonyl-5-bromo-pyridyl-2-amine

To a 125 mL round-bottomed flask equipped with N_2 inlet were added 0.865 g (5 mmol) 6-bromo-2-aminopyridine, 0.677 mL (5.5 mmol) trimethylacetyl chloride, 15 mL dry acetonitrile, and 1.045 mL (7.5 mmol) triethylamine. The reaction was stirred at room temperature for 14
20 hours, poured into water, and stirred until a solid precipitate had formed. The solid was filtered, washed with water, and dried to afford 1.04 g (81%), mp 87-90°C.

1H -NMR (δ , $CDCl_3$): 1.28 (s, 9H), 7.17 (d, J=8, 1H), 7.52 (t, J=8, 1H), 8.00 (bs, 1H), 8.19 (d, J=8, 1H).

^{13}C -NMR (δ , $CDCl_3$): 27.3, 39.8, 112.2, 123.3, 139.0, 140.5, 151.6, 177.1.

25 B. 4-Methylnaphthalene-1-boronic acid

To a 125 mL round-bottomed flask equipped with N_2 inlet were added 1.78 g (11.4 mmol) 1-bromo-4-methylnaphthalene and 20 mL dry tetrahydrofuran. The solution was cooled to -70°C, and 5.49 mL (13.7 mmol) of a 2.5M solution of n-butyl lithium in hexane was added over 5 minutes, and the reaction stirred at -70°C for 10 minutes. The solution was then treated
30 with 2.34 mL (13.7 mmol) triethyl borate, stirred 5 minutes at -70°C, then warmed to room temperature and stirred 40 hours. The reaction was quenched with aqueous ammonium chloride solution, poured into 0.5 N hydrochloric acid, and extracted into ethyl acetate. The organic layer was washed with brine, dried over sodium sulfate, and evaporated to a white solid after trituration with hexane, mp 224-228°C, 1.9 g (90%).

35 1H -NMR (δ , $CDCl_3$): 2.63 (s, 3H), 7.25 (m, 1H), 7.3-7.5 (m, 3H), 7.75 (m, 1H), 7.95 (m, 1H).

^{13}C -NMR (δ , $CDCl_3$): 19.4, 124.5, 125.5, 125.7, 126.0, 128.5, 128.9, 129.9, 131.6, 134.9, 135.3.

C. N-t-Butylcarbonyl-6-(4-methylnaphthalen-1-yl)-pyridin-2-ylamine

5 To a 100 mL round-bottomed flask equipped with condenser and N₂ inlet were added 975 mg (3.795 mmol) N-t-butylcarbonyl-6-bromo-pyridyl-2-amine, 706 mg (3.795 mmol) 4-methylnaphthalene-1-boronic acid, 1.61 g (15.18 mmol) sodium carbonate, 50 mg (0.04 mmol) tetrakis(triphenylphosphine) palladium, 18 mL ethanol, and 2 mL water, and the reaction heated at 80°C for 13 hours. TLC showed a major spot at R_f = 0.2 in 15% ethyl acetate in hexane, and
10 LCMS showed a major peak at P+1 = 319. The reaction was cooled, poured into water, and extracted into ethyl acetate. The organic layer was washed with water and brine, dried over sodium sulfate, and evaporated. The residue was chromatographed on silica gel using hexane/ethyl acetate as eluant to afford 1.25 g (~100%) of a foam.

¹H-NMR (δ, CDCl₃): 1.32 (s, 9H), 2.73 (s, 3H), 7.25 (m, 1H), 7.3-7.5 (m, 4H), 7.81 (t, J=8, 1H), 8.00 (d, J=8, 1H), 8.05 (d, J=8, 1H), 8.145 (bs, 1H), 8.31 (d, J=8, 1H).
15

¹³C-NMR (δ, CDCl₃): 19.7, 27.5, 60.4, 112.1, 121.1, 124.4, 125.8, 126.08, 126.11, 126.16, 126.9, 131.1, 132.9, 135.3, 1338.7, 151.3, 157.8, 177.3.

MS (%): 319 (parent+1, 100).

D. N-t-Butylcarbonyl-6-(4-cyanomethylnaphthalen-1-yl)-pyridin-2-ylamine

20 To a 100 mL round-bottomed flask equipped with condenser and N₂ inlet were added 1.21 g (3.795 mmol) N-t-butylcarbonyl-6-(4-methylnaphthalen-1-yl)-pyridin-2-ylamine, 810 mg (4.554 mmol) N-bromosuccinimide, 35 mL carbon tetrachloride, and 10 mg bis-(1-cyano-1-azo)-cyclohexane. The reaction was heated at reflux for a total of 8 hours as additional portions of initiator were added at 1, 2, and 4 hours. The reaction was cooled, filtered with carbon
25 tetrachloride, and evaporated. The red oil, 2.5 g, was used directly.

¹H-NMR (δ, CDCl₃): 1.33 (s, 9H), 5.00 (s, 2H), 7.26 (d, J=7.5, 1H), 7.49 (m, 2H), 7.63 (m, 2H), 7.84 (t, J=8, 1H), 8.02 (d, J=8, 1H), 8.115 (bs, 1H), 8.22 (d, J=8, 1H), 8.36 (d, J=7.5, 1H).

¹³C-NMR (δ, CDCl₃): 27.6, 31.6, 39.9, 112.6, 121.0, 124.1, 126.6, 126.7, 127.3, 131.5,
30 131.7, 134.1, 138.8, 139.5, 151.4, 157.1, 177.35.

MS (%): 397/399 (parent+1, 100).

The above oil was taken up in 35 mL dry methylene chloride and treated with 593 mg (3.795 mmol) tetraethylammonium cyanide, and reaction stirred at room temperature for 13 hours. LCMS showed a major peak at P+1 = 344 and TLC showed a major spot at R_f = 0.6 in
35 10% ethyl acetate in methylene chloride. The reaction was evaporated, and the residue chromatographed on silica gel using ethyl acetate in methylene chloride as eluant to afford 1.00 g (77%) of a foam.

¹H-NMR (δ, CDCl₃): 1.32 (s, 9H), 4.18 (s, 3H), 7.26 (d, J=7.5, 1H), 7.53 (m, 2H), 7.63 (m, 2H), 7.84 (t, J=8, 1H), 7.92 (d, J=8, 1H), 8.04 (d, J=8.5, 1H), 8.10 (bs, 1H), 8.34 (d, J=8,
40 1H).

5 ¹³C-NMR (δ, CDCl₃): 22.0, 27.5, 39.9, 112.6, 121.0, 122.75, 126.0, 126.7, 126.9, 127.2, 131.2, 131.4, 138.9, 139.1, 151.4, 156.9, 177.35.

MS (%): 344 (parent+1, 100).

E. 6-(4-Carboxymethylnaphthalen-1-yl)-pyridin-2-ylamine

To a 100 mL round-bottomed flask equipped with condenser and N₂ inlet were added
10 1.00 g (2.915 mmol) N-t-butylcarbonyl-6-(4-cyanomethylnaphthalen-1-yl)-pyridin-2-ylamine and 35 mL ethanol. The solution was saturated with HCl and refluxed 14 hours, adding two drops of water once it had reached reflux. The reaction (LCMS showed P+1 = 391) was cooled and evaporated, and the residue taken up in ethyl acetate, washed with aqueous sodium bicarbonate solution, water, and brine, dried over sodium sulfate, and evaporated to an oil, 1.09
15 g (96%), which was used directly.

¹H-NMR (δ, CDCl₃): 1.21 (t, J=7, 3H), 1.31 (s, 9H), 4.09 (s, 2H), 4.13 (q, J=7, 2H), 7.25 (d, J=7.5, 1H), 7.4-7.6 (m, 4H), 7.82 (t, J=7.5, 1H), 7.99 (d, J=8, 1H), 8.06 (d, J=8, 1H), 8.13 (bs, 1H), 8.31 (d, J=8, 1H).

¹³C-NMR (δ, CDCl₃): 14.2, 27.5, 39.5, 60.4, 61.0, 112.3, 121.1, 124.2, 126.3, 126.4,
20 126.8, 127.5, 131.4, 131.7, 132.5, 137.8, 138.7, 151.3, 157.5, 171.4, 177.3.

MS (%): 391 (parent+1, 100).

The above oil was taken up in 25 mL 6 N hydrochloric acid, and heated at 95-100°C for 12 hours. LCMS showed P+1 = 279. The reaction was cooled, washed with ether, and evaporated, finally dried under vacuum, to a white solid, 0.85 g (93% overall) of the product as
25 the hydrochloride salt.

MS (%): 279 (parent+1, 100).

F. 6-(4-(4-(2-Phenylethyl)piperazinylcarbonyl)-methylnaphthalen-1-yl)-pyridin-2-ylamine

To a 100 mL round-bottomed flask equipped with condenser and N₂ inlet were added
157 mg (0.50 mmol) 6-(4-carboxymethylnaphthalen-1-yl)-pyridin-2-ylamine, 95 mg (0.50 mmol)
30 N-phenethylpiperazine, 96 mg (0.50 mmol) N-ethyl, N-3-dimethylaminopropyl-carbodiimide, 0.230 mL (1.65 mmol) triethylamine, 10 mg N-hydroxybenzotriazole, and 7 mL dry acetonitrile. The reaction was stirred at room temperature 12 hours (LCMS showed P+1 = 451 and TLC showed R_f = 0.3 in 10% methanol/methylene chloride), then evaporated and the residue chromatographed on silica gel using methanol/methylene chloride as eluant to afford the
35 product as a foam, 230 mg (~100%).

¹H-NMR (δ, CDCl₃): 2.37 (m, 2H), 2.52 (m, 2H), 2.59 (m, 2H), 2.76 (m, 2H), 3.46 (m, 2H), 3.76 (m, 2H), 4.17 (s, 2H), 4.73 (bs, 2H, NH₂), 6.46 (d, J=8, 1H), 6.83 (d, J=7.5, 1H), 7.1-7.6 (m, 10H), 7.98 (d, J=8, 1H), 8.14 (d, J=8.5, 1H).

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5 ^{13}C -NMR (δ , CDCl_3): 33.4, 38.5, 41.8, 46.1, 52.8, 53.2, 60.2, 137.2, 115.2, 123.5, 125.6, 126.1, 126.2, 126.3, 126.5, 127.0, 128.5, 128.7, 131.6, 132.2, 138.1, 138.5, 139.9, 157.4, 158.3, 169.7.

MS (%): 451 (parent+1, 100).

G. 6-[4-[2-(4-Phenethyl-piperazin-1-yl)-ethyl]-naphthalen-1-yl]-pyridin-2-ylamine

10 To a 100 mL round-bottomed flask equipped with condenser and N_2 inlet were added 200 mg aluminum chloride and 5 mL dry tetrahydrofuran. The solution was cooled to 0°C . and 3.50 mL (3.50 mmol) of a 1.0 M solution of lithium aluminum hydride in tetrahydrofuran was added. Stirring was continued at room temperature for 20 minutes, then the solution was cooled to -70°C , and a solution of 225 mg (0.50 mmol) 6-[4-(2-phenylethyl)piperazinylcarbonyl]-methylnaphthalen-1-yl-pyridin-2-ylamine in 7 mL dry
15 tetrahydrofuran was added. Stirring was continued 1 hour at -70°C , then 2 hours at room temperature (LCMS showed $\text{P}+1 = 437$), followed by careful quenching with 5 mL 1 N hydrochloric acid. After stirring for 20 minutes (min.), the reaction was treated with 6 mL 6 N aqueous sodium hydroxide solution, and extracted with several portions of methylene chloride.
20 The organic phase was dried over sodium sulfate and evaporated to afford an oil, which was converted to the hydrochloride salt using HCl in ether, affording the product, 175 mg (64%) as a white solid, mp $80-105^\circ\text{C}$.

^1H -NMR (δ , CDCl_3): 2.65 (m, 6H), 2.76 (m, 4H), 2.84 (m, 4H), 3.33 (m, 2H), 4.68 (bs, 2H, NH_2), 6.44 (d, $J=8$, 1H), 6.85 (d, $J=7$, 1H), 7.1-7.6 (m, 10H), 8.11 (m, 2H).

25 ^{13}C -NMR (δ , CDCl_3): 30.9, 33.7, 53.3, 59.7, 60.6, 106.9, 115.2, 123.9, 125.77, 125.83, 126.1, 126.7, 126.9, 128.4, 128.7, 131.4, 132.3, 136.9, 137.8, 138.0, 140.4, 157.9, 158.2.

MS (%): 437 (parent+1, 100).

Anal. Calc'd. for $\text{C}_{28}\text{H}_{32}\text{N}_4\cdot\text{Cl}\cdot 3/2\text{H}_2\text{O}\cdot 1/2(\text{C}_4\text{H}_{10}\text{O})$: C 69.32, H 7.69, N 10.43. Found: C 69.46, H 7.35, N 10.36.

30

EXAMPLE 2

3-[2-[4-(6-Amino-pyridin-2-yl)-naphthalen-1-yl]-ethyl]-3-aza-bicyclo[3.1.0]hex-6-ylamine

Prepared as in Example 1, with an extra deblocking step using trifluoroacetic acid in methylene chloride to remove a t-butoxycarbonyl protecting group, in 71% yield, mp $250-260^\circ\text{C}$, as the hydrochloride salt.

35 ^1H -NMR (δ , CDCl_3): 1.24 (bs, 2H), 1.36 (bs, 1H), 2.43 (m, 2H), 2.72 (m, 2H), 3.1-3.2 (m, 4H), 4.63 (bs, 2H, NH_2), 6.45 (d, $J=8$, 1H), 6.83 (d, $J=7$, 1H), 7.3-7.6 (m, 5H), 8.07 (m, 2H).

^{13}C -NMR (δ , CDCl_3): 25.8, 29.7, 32.7, 55.0, 56.7, 106.8, 115.2, 123.9, 125.7, 125.9, 126.6, 126.8, 131.5, 132.2, 137.1, 137.6, 138.0, 157.9, 158.1.

MS (%): 345 (parent+1, 100).

- 5 Anal. Calc'd. for $C_{22}H_{24}N_4 \cdot 7/4HCl \cdot (C_4H_{10}O)$: C 64.74, H 7.47, N 11.61. Found: C 64.34, H 6.94, N 11.20.

EXAMPLE 3

6-[4-[2-(4-Benzhydryl-piperidin-1-yl)-ethyl]-naphthalen-1-yl]-pyridin-2-ylamine

Prepared as in Example 1, in 74% yield, mp 225-235°C, as the hydrochloride salt.

- 10 1H -NMR (δ , $CDCl_3$): 1.32 (m, 1H), 1.64 (m, 1H), 2.07 (m, 2H), 2.17 (m, 1H), 2.70 (m, 2H), 3.06 (m, 2H), 3.31 (m, 2H), 3.55 (d, J=8, 1H), 3.75 (m, 2H), 4.64 (bs, 2H, NH_2), 6.45 (d, J=8, 1H), 6.85 (d, J=7, 1H), 7.16 (m, 1H), 7.2-7.6 (m, 14H), 8.10 (m, 2H).

- ^{13}C -NMR (δ , $CDCl_3$): 25.7, 31.0, 31.5, 39.7, 54.0, 59.0, 60.1, 68.0, 106.8, 115.2, 123.9, 125.7, 125.8, 126.1, 126.2, 126.7, 126.9, 128.1, 128.6, 131.6, 132.3, 137.1, 137.7, 138.0, 143.9, 15

MS (%): 498 (parent+1, 100).

- Anal. Calc'd. for $C_{35}H_{35}N_3 \cdot 2HCl$: C 73.67, H 6.54, N 7.36. Found: C 73.86, H 6.97, N 7.04.

EXAMPLE 4

- 20 6-[4-[2-(6,7-Dimethoxy-3,4-dihydro-1H-isoquinolin-2-yl)-ethyl]-naphthalen-1-yl]-pyridin-2-ylamine

Prepared as in Example 1, in 56.5% yield, mp 172-176°C.

- 1H -NMR (δ , $CDCl_3$): 2.87 (m, 6H), 3.41 (m, 2H), 3.71 (m, 2H), 3.826 (s, 3H), 3.831 (s, 3H), 4.80 (bs, 2H, NH_2), 6.47 (d, J=8, 1H), 6.56 (s, 1H), 6.60 (s, 1H), 6.84 (d, J=7.5, 1H), 7.4-25 7.6 (m, 5H), 8.12 (m, 2H).

^{13}C -NMR (δ , $CDCl_3$): 28.7, 31.3, 51.1, 55.7, 55.80, 55.83, 59.3, 106.8, 109.4, 111.3, 115.15, 123.8, 125.67, 125.74, 126.0, 126.5, 126.8, 131.5, 132.2, 136.8, 137.7, 138.0, 147.1, 147.4, 157.8, 158.0.

MS (%): 440 (parent+1, 100).

- 30 Anal. Calc'd. for $C_{28}H_{29}N_3O_2 \cdot 1/4H_2O$: C 75.73, H 6.70, N 9.46. Found: C 75.66, H 6.54, N 9.17.

EXAMPLE 5

6-[4-[2-(6-Methoxy-1,3,4,9-tetrahydro- β -carbolin-2-yl)-ethyl]-naphthalen-1-yl]-pyridin-2-ylamine

- 35 Prepared as in Example 1, in 60% yield, mp 132-138°C.

1H -NMR (δ , $CDCl_3$): 2.81 (m, 2H), 2.91 (m, 4H), 3.31 (m, 2H), 3.51 (bs, 2H), 3.83 (s, 3H), 4.61 (bs, 2H, NH_2), 6.46 (d, J=8, 1H), 6.75 (dd, J=2.5, 8.7, 1H), 6.84 (d, J=7, 1H), 6.92 (d, J=2.5, 1H), 7.08 (d, J=8, 1H), 7.36 (d, J=7, 1H), 7.4-7.6 (m, 3H), 8.08 (d, J=8, 1H), 8.13 (dd, J=1.8, 1H), 8.39 (bs, 1H).

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5 ^{13}C -NMR (δ , CDCl_3): 25.5, 50.2, 51.1, 55.8, 58.7, 67.9, 100.2, 103.9, 107.8, 110.7, 111.3, 115.2, 123.8, 125.7, 125.8, 126.1, 126.6, 126.8, 127.5, 131.1, 131.6, 132.1, 132.8, 136.8, 137.6, 138.1, 153.7, 157.7, 158.0.

MS (%): 449 (parent+1, 100).

Anal. Calc'd. for $\text{C}_{29}\text{H}_{29}\text{N}_4\text{O} \cdot (\text{C}_4\text{H}_{10}\text{O})$: C 75.83, H 7.33, N 10.72. Found: C 75.80, H 7.00, N 11.33.

EXAMPLE 6

6-(4-[2-((Benzo[1,3]dioxol-5-ylmethyl)-amino)-ethyl]-naphthalen-1-yl)-pyridin-2-ylamine

Prepared as in Example 1, in 77% yield, mp 80-110°C, as the hydrochloride salt.

15 ^1H -NMR (δ , CDCl_3): 3.00 (t, J=7, 2H), 3.31 (t, J=7, 2H), 3.70 (s, 2H), 4.62 (bs, 2H, NH_2), 5.90 (s, 2H), 6.48 (d, J=8, 1H), 6.72 (s, 1H), 6.73 (m, 1H), 6.81 (m, 1H), 6.85 (d, J=7, 1H), 7.4-7.6 (m, 5H), 8.09 (m, 2H).

^{13}C -NMR (δ , CDCl_3): 33.7, 49.7, 53.7, 100.9, 106.9, 108.1, 108.7, 115.2, 121.2, 123.9, 125.76, 125.80, 126.1, 126.5, 126.8, 131.7, 132.3, 134.2, 136.5, 137.8, 138.1, 146.5, 147.7, 157.8, 158.1.

20 MS (%): 398 (parent+1, 100).

Anal. Calc'd. for $\text{C}_{25}\text{H}_{23}\text{N}_3\text{O}_2 \cdot 2\text{HCl} \cdot \text{H}_2\text{O} \cdot 1/2(\text{C}_4\text{H}_{10}\text{O})$: C 61.72, H 6.14, N 8.00. Found: C 61.81, H 5.97, N 7.56.

EXAMPLE 7

6-(4-[2-(3,4-Difluoro-benzylamino)-ethyl]-naphthalen-1-yl)-pyridin-2-ylamine

25 Prepared as in Example 1, in 91% yield, mp 70-80°C, as the hydrochloride salt.

^1H -NMR (δ , CDCl_3): 2.93 (t, J=7, 2H), 3.315 (t, J=7, 2H), 3.70 (s, 2H), 4.76 (bs, 2H, NH_2), 6.47 (d, J=8, 1H), 6.81 (d, J=7, 1H), 7.0-7.2 (m, 3H), 7.4-7.6 (m, 5H), 8.06 (m, 2H).

30 ^{13}C -NMR (δ , CDCl_3): 32.9, 49.2, 52.2, 107.1, 115.0, 117.1, 123.7, 124.2, 125.9, 126.1, 126.4, 126.7, 131.6, 132.0, 135.8, 137.8, 138.1, 148.1, 148.3, 148.8, 149.0, 150.6, 150.7, 151.3, 151.4, 157.4, 158.1.

MS (%): 390 (parent+1, 100).

Anal. Calc'd. for $\text{C}_{24}\text{H}_{21}\text{N}_3\text{F}_2 \cdot 3/2\text{HCl} \cdot 1/2\text{H}_2\text{O} \cdot (\text{C}_4\text{H}_{10}\text{O})$: C 63.78, H 6.40, N 7.97. Found: C 63.94, H 5.95, N 7.89.

EXAMPLE 8

6-(4-[2-(3,4,5-Trimethoxy-benzylamino)-ethyl]-naphthalen-1-yl)-pyridin-2-ylamine

35 Prepared as in Example 1, in 80% yield, mp 75-95°C, as the hydrochloride salt.

^1H -NMR (δ , CDCl_3): 3.02 (t, J=7, 2H), 3.34 (t, J=7, 2H), 3.73 (s, 2H), 3.78 (s, 6H), 3.795 (s, 3H), 4.655 (bs, 2H, NH_2), 6.46 (d, J=8, 1H), 6.49 (s, 2H), 6.82 (d, J=7.5, 1H), 7.4-7.6 (m, 5H), 8.08 (m, 2H).

5 ^{13}C -NMR (δ , CDCl_3): 33.5, 49.7, 54.0, 55.9, 60.7, 104.7, 106.9, 115.0, 123.8, 125.4, 125.70, 125.74, 126.1, 126.4, 126.7, 131.6, 132.1, 135.8, 136.3, 136.6, 137.8, 138.0, 153.1, 157.6, 158.1.

MS (%): 444 (parent+1, 100).

Anal. Calc'd. for $\text{C}_{27}\text{H}_{29}\text{N}_3\text{O}_2 \cdot 2\text{HCl} \cdot (\text{C}_4\text{H}_{10}\text{O})$: C 63.05, H 7.00, N 7.11. Found: C 63.04, H 6.70, N 6.96.

EXAMPLE 9

6-[4-[2-(3-Chloro-benzylamino)-ethyl]-naphthalen-1-yl]-pyridin-2-ylamine

Prepared as in Example 1, using as a precursor 3,4-dichlorobenzylamine. In this case, the lithium aluminum hydride/aluminum chloride reduction removed one of the chlorine atoms, affording the 3-chlorobenzyl compound. The final product was prepared in 73% yield, mp 60-75°C, as the hydrochloride salt.

^1H -NMR (δ , CDCl_3): 2.99 (t, J=7, 2H), 3.30 (t, J=7, 2H), 3.73 (bs, 2H), 4.675 (bs, 2H, NH_2), 6.46 (d, J=8, 1H), 6.83 (d, J=7, 1H), 7.2-7.6 (m, 9H), 8.07 (m, 2H).

20 ^{13}C -NMR (δ , CDCl_3): 33.6, 49.7, 68.0, 107.0, 115.1, 123.9, 125.8, 126.1, 126.5, 126.8, 128.5, 129.5, 131.7, 132.2, 136.3, 137.8, 138.1, 157.7, 158.2.

MS (%): 388 (parent+1, 100).

Anal. Calc'd. for $\text{C}_{24}\text{H}_{22}\text{N}_3\text{Cl} \cdot \text{HCl} \cdot \text{H}_2\text{O} \cdot 1/2(\text{C}_4\text{H}_{10}\text{O})$: C 65.13, H 6.31, N 8.76. Found: C 64.84, H 6.25, N 8.35.

EXAMPLE 10

6-[4-[2-[(Furan-2-ylmethyl)-amino]-ethyl]-naphthalen-1-yl]-pyridin-2-ylamine

Prepared as in Example 1, in 44% yield, mp 185-205°C, as the hydrochloride salt.

^1H -NMR (δ , CDCl_3): 3.00 (d, J=7, 2H), 3.285 (d, J=7, 2H), 3.79 (s, 2H), 4.68 (bs, 2H, NH_2), 6.13 (bs, 1H), 6.26 (bs, 1H), 6.45 (d, J=8, 1H), 6.83 (d, J=7.5, 1H), 7.3-7.6 (m, 6H), 8.08 (m, 2H).

30 ^{13}C -NMR (δ , CDCl_3): 33.4, 46.1, 49.5, 106.9, 107.0, 110.0, 115.05, 123.8, 125.7, 126.0, 126.4, 126.7, 131.6, 132.1, 136.2, 137.7, 138.0, 141.75, 153.5, 157.6, 158.1.

MS (%): 344 (parent+1, 100).

Anal. Calc'd. for $\text{C}_{22}\text{H}_{21}\text{N}_3\text{O} \cdot \text{HCl} \cdot 3/2\text{H}_2\text{O}$: C 64.23, H 6.25, N 10.21. Found: C 64.42, H 6.04, N 9.86.

EXAMPLE 11

6-[4-[2-(3,4-Dichloro-benzylamino)-ethyl]-naphthalen-1-yl]-pyridin-2-ylamine

Prepared as in Example 1, using borane methyl sulfide in place of the lithium aluminum hydride/aluminum chloride reduction in the final step. The final product was prepared in 88.5% yield, mp 145-170°C, as the hydrochloride salt.

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5 $^1\text{H-NMR}$ (δ , CDCl_3): 2.98 (t, $J=7$, 2H), 3.295 (t, $J=7$, 2H), 3.71 (s, 2H), 4.60 (bs, 2H, NH_2), 6.49 (d, $J=8$, 1H), 6.85 (d, $J=7.5$, 1H), 7.2-7.6 (m, 7H), 8.08 (m, 2H).

$^{13}\text{C-NMR}$ (δ , CDCl_3): 33.6, 49.7, 52.7, 107.0, 115.3, 123.8, 125.8, 125.9, 126.2, 126.5, 126.9, 127.3, 127.4, 129.9, 130.0, 130.2, 130.7, 131.7, 132.2, 132.3, 136.2, 138.1, 140.7, 157.8, 158.1.

10 MS (%): 388 (parent+1, 100).

Anal. Calc'd. for $\text{C}_{24}\text{H}_{21}\text{N}_3\text{Cl}_2\cdot\text{HCl}\cdot 2\text{H}_2\text{O}\cdot 1/2(\text{C}_4\text{H}_{10}\text{O})$: C 58.71, H 5.87, N 7.90. Found: C 58.35, H 5.92, N 6.62.

EXAMPLE 12

6-[4-(2-Dimethylamino-ethoxy)-naphthalen-1-yl]-pyridin-2-ylamine

15 Referring to Scheme 2

A. 4-Bromo-1-benzyloxy-naphthalene:

To a 250 mL round-bottomed flask equipped with addition funnel and N_2 inlet were added 2.88 g (20 mmol) 1-naphthol and 50 mL 1,2-dichloroethane, and with stirring a solution of 9.64 g (20 mmol) tetrabutylammonium tribromide in 30 mL 1,2-dichloroethane dropwise over 10
20 minutes. After stirring an additional 10 minutes at room temperature, the solution was washed with dilute aqueous sodium bisulfite and water, dried over sodium sulfate, and evaporated. The mixture of product and tributylammonium salts was used directly.

$^1\text{H-NMR}$ (δ , CDCl_3): 7.22 (d, $J=8$, 1H), 7.43 (m, 2H), 7.50 (dt, $J=1.8$, 1H), 8.05 (d, $J=8$, 1H), 8.18 (d, $J=8$, 1H).

25 $^{13}\text{C-NMR}$ (δ , CDCl_3): 109.8, 111.4, 122.7, 125.3, 126.25, 126.7, 137.4, 129.9, 132.5, 153.0.

The above oil was dissolved in 100 mL acetonitrile, and treated with 3.57 mL (30 mmol) benzyl bromide and 5.53 g (40 mmol) potassium carbonate, the refluxed 14 hours. TLC showed a major spot at $R_f = 0.2$ in 5% methylene chloride/hexane. The reaction was cooled,
30 poured into dilute aqueous hydrochloric acid/ethyl acetate, and the organic layer separated, washed with water and brine, dried over sodium sulfate, and evaporated. The residue was chromatographed on silica gel using methylene chloride/hexane as eluant to afford 5.8 g (93%) of an oil.

$^1\text{H-NMR}$ (δ , CDCl_3): 5.22 (s, 2H), 6.74 (d, $J=8$, 1H), 7.4-7.7 (m, 8H), 8.21 (d, $J=8$, 1H),
35 8.39 (d, $J=8$, 1H).

$^{13}\text{C-NMR}$ (δ , CDCl_3): 70.3, 105.9, 113.6, 122.7, 126.1, 126.9, 127.0, 127.4, 127.9, 128.1, 128.7, 129.5, 132.6, 136.7, 154.3.

MS (%): 314 (parent+1, 100).

B. 1-Benzyloxy-naphthalene-4-boronic acid

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5 Using the procedure in Example 1A, 5.95 g (19 mmol) of 4-bromo-1-benzyloxy-naphthalene was converted to the product in 55% yield as a white solid, mp 149-152°C.

¹H-NMR (δ, CDCl₃): 5.18 (s, 2H), 6.82 (m, 1H), 7.2-7.8 (m, 8H), 8.28 (m, 2H).

¹³C-NMR (δ, CDCl₃): 69.9, 104.5, 104.7, 122.2, 122.4, 124.8, 125.0, 126.5, 126.6, 127.6, 127.7, 127.9, 128.0, 128.5, 130.9, 132.9, 136.9.

10 C. 2-(2,5-Dimethylpyrrolyl)-6-(4-benzyloxy-1-naphthyl)-pyridine

Prepared as in Example 1B, in ~100% yield as an oil.

¹H-NMR (δ, CDCl₃): 2.25 (s, 6H), 5.29 (s, 2H), 5.92 (s, 2H), 6.95 (d, J=8, 1H), 7.21 (d, J=7.5, 1H), 7.3-7.6 (m, 9H), 7.89 (t, J=8, 1H), 8.14 (m, 1H), 8.45 (m, 1H).

¹³C-NMR (δ, CDCl₃): 13.5, 70.1, 104.8, 106.8, 119.7, 122.5, 123.4, 125.2, 125.3, 125.9, 15 126.4, 126.9, 127.3, 127.9, 128.2, 128.6, 130.5, 132.0, 136.9, 138.0, 151.8, 155.0, 159.1.

MS (%): 405 (parent+1, 100).

D. 2-(2,5-Dimethylpyrrolyl)-6-(4-hydroxy-1-naphthyl)-pyridine

To a 125 mL round-bottomed flask equipped with condenser and N₂ inlet were added 1.53 g (3.795 mmol) 2-(2,5-dimethylpyrrolyl)-6-(4-benzyloxy-1-naphthyl)-pyridine, 1.20 g 20 (18.975 mmol) ammonium formate, 100 mg 10% palladium-on-carbon, and 30 mL ethanol. The reaction was refluxed 4 hours, with additional catalyst and formate added at 2 and 3 hours, then cooled and filtered through Cellite with ethanol and methylene chloride. The filtrate was evaporated and the residue taken up in ethyl acetate/aqueous sodium bicarbonate solution. The organic layer was washed with brine, dried over sodium sulfate, and evaporated to a light 25 brown solid, 1.21 g (~100%).

¹H-NMR (δ, CDCl₃): 2.105 (s, 6H), 5.775 (s, 2H), 6.66 (d, J=8, 1H), 7.04 (d, J=8, 1H), 7.29 (m, 2H), 7.38 (d, J=8, 1H), 7.72 (t, J=8, 1H), 7.95 (m, 1H), 8.18 (m, 1H).

¹³C-NMR (δ, CDCl₃): 13.8, 106.7, 106.8, 107.6, 119.6, 122.55, 124.5, 124.7, 125.0, 126.5, 128.4, 128.5, 128.7, 132.0, 138.2, 151.5, 153.9, 159.3.

30 MS (%): 315 (parent+1, 100).

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5 E. 2-(2,5-Dimethylpyrrolyl)-6-(4-(2-carboethoxymethyloxy)-1-naphthyl)-pyridine

To a 125 mL round-bottomed flask equipped with condenser and N₂ inlet were added 1.19 g (3.795 mmol) 2-(2,5-dimethylpyrrolyl)-6-(4-hydroxy-1-naphthyl)-pyridine, .505 mL (4.554 mmol) ethyl bromoacetate, 1.05 g (7.59 mmol) potassium carbonate, and 25 mL acetonitrile. The mixture was refluxed 12 hours, cooled (TLC R_f = 0.6 in 1/1-ethyl acetate/hexane), poured
10 into water, and extracted into ethyl acetate. The organic layer was washed with brine, dried over sodium sulfate, and evaporated. The residue was chromatographed on silica gel using hexane/ethyl acetate as eluant to afford 2.05 g (~100%) of an oil.

¹H-NMR (δ, CDCl₃): 1.31 (t, J=7, 3H), 2.26 (s, 6H), 4.29 (q, J=7, 2H), 4.82 (s, 2H), 5.94 (s, 2H), 6.78 (d, J=8, 1H), 7.20 (d, J=8, 1H), 7.5-7.6 (m, 5H), 7.87 (t, J=8, 1H), 8.15 (m, 1H),
15 8.50 (m, 1H).

¹³C-NMR (δ, CDCl₃): 13.6, 14.2, 61.4, 65.7, 104.6, 107.0, 119.9, 122.6, 123.6, 125.3, 125.6, 125.8, 127.2, 128.0, 128.6, 131.4, 132.1, 138.3, 151.8, 154.3, 158.9, 168.6.

MS (%): 401 (parent+1, 100).

F. 2-(2,5-Dimethylpyrrolyl)-6-(4-(2-carboxymethyloxy)-1-naphthyl)-pyridine

20 To a 125 mL round-bottomed flask equipped with condenser and N₂ inlet were added 1.52 g (3.795 mmol) of 2-(2,5-dimethylpyrrolyl)-6-(4-(2-carboethoxymethyloxy)-1-naphthyl)-pyridine, 15 mL tetrahydrofuran, and 478 mg (11.385 mmol) lithium hydroxide hydrate in 15 mL water, with additional methanol to maintain a solution. The reaction was stirred at room temperature for 12 hours, (LCMS P+1 = 373), poured into dilute aqueous hydrochloric acid, and
25 extracted into ethyl acetate. The organic layer was washed with brine, dried over sodium sulfate, and evaporated to a solid, 1.27 g (90%).

¹H-NMR (δ, CDCl₃): 2.20 (s, 6H), 4.74 (s, 2H), 5.89 (s, 2H), 6.765 (d, J=8, 1H), 7.20 (d, J=8, 1H), 7.4-7.6 (m, 4H), 7.885 (t, J=8, 1H), 8.04 (m, 1H), 8.44 (m, 1H).

¹³C-NMR (δ CDCl₃): 13.3, 65.3, 104.5, 106.9, 120.3, 122.6, 124.0, 125.0, 125.6, 125.7,
30 127.2, 128.0, 128.7, 130.8, 132.0, 138.6, 151.7, 154.3, 158.9, 170.9.

MS (%): 373 (parent+1, 100).

G. 2-(2,5-Dimethylpyrrolyl)-6-(4-(2-(dimethylaminocarbonyl)methyloxy)-1-naphthyl)-pyridine

Prepared as in Example 1D in ~100% yield as an oil.

35 ¹H-NMR (δ, CDCl₃): 2.225 (s, 6H), 2.97 (s, 3H), 3.10 (s, 3H), 4.90 (s, 2H), 5.89 (s, 2H), 6.93 (d, J=8, 1H), 7.21 (d, J=8, 1H), 7.4-7.6 (m, 4H), 7.90 (t, J=8, 1H), 8.09 (m, 1H), 8.38 (m, 1H).

¹³C-NMR (δ, CDCl₃): 13.5, 35.8, 36.8, 67.9, 104.7, 106.8, 119.9, 122.2, 123.5, 125.4, 125.56, 125.63, 127.1, 128.1, 128.6, 131.2, 132.1, 138.2, 151.8, 154.1, 159.0, 167.7.

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5 MS (%): 400 (parent+1, 100).

H. 2-(2,5-Dimethylpyrrolyl)-6-(4-(2-(2-dimethylaminoethyl)methoxy)-1-naphthyl)-pyridine

Prepared as in Example 1E in ~100% yield as an oil.

¹H-NMR (δ, CDCl₃): 2.24 (s, 6H), 2.42 (s, 6H), 2.915 (t, J=6, 2H), 4.30 (t, J=6, 2H),
10 5.91 (s, 2H), 6.90 (d, J=8, 1H), 7.20 (d, J=8, 1H), 7.5-7.7 (m, 4H), 7.89 (t, J=8, 1H), 8.13 (m, 1H), 8.37 (m, 1H).

¹³C-NMR (δ, CDCl₃): 13.5, 46.2, 58.2, 67.0, 104.3, 106.8, 119.7, 122.5, 123.5, 125.2, 125.3, 123.8, 126.9, 128.3, 138.6, 130.4, 132.0, 138.1, 151.8, 155.3, 159.1.

MS (%): 386 (parent+1, 100).

15 I. 6-[4-(2-Dimethylamino-ethoxy)-naphthalen-1-yl]-pyridin-2-ylamine

To a 100 mL round-bottomed flask equipped with condenser and N₂ inlet were added 155 mg (0.403 mmol) 2-(2,5-dimethylpyrrolyl)-6-(4-(2-(2-dimethylaminoethyl)methoxy)-1-naphthyl)-pyridine, 500 mg hydroxylamine hydrochloride, 9 mL ethanol, and 1 mL water. The solution was refluxed 40 h (LCMS P+1 = 308), cooled, poured into dilute aqueous hydrochloric
20 acid, and washed with ethyl acetate. The aqueous layer was adjusted to pH 12 with 6 N aqueous sodium hydroxide solution and extracted with several portions of methylene chloride. The organic layer was dried over sodium sulfate and evaporated to a solid, 81 mg (85%), mp 98-106°C.

¹H-NMR (δ, CDCl₃): 2.395 (s, 6H), 2.89 (t, J=8, 2H), 4.27 (t, J=6, 2H), 4.65 (bs, 2H, NH₂), 6.43 (d, J=8, 1H), 6.84 (m, 2H), 7.4-7.6 (m, 4H), 8.10 (m, 1H), 8.32 (m, 1H).

¹³C-NMR (δ, CDCl₃): 46.2, 58.2, 66.9, 104.2, 106.6, 115.2, 122.2, 125.1, 125.7, 125.8, 126.7, 127.2, 131.4, 132.2, 138.0, 154.7, 157.8, 158.2.

MS (%): 308 (parent+1, 100).

Anal. Calc'd. for C₁₈H₂₁N₃O•1/4H₂O: C 73.17, H 6.95, N 13.47. Found: C 73.18, H
30 7.00, N 13.43.

EXAMPLE 13

6-[4-(2-Pyrrolidin-1-yl-ethoxy)-naphthalen-1-yl]-pyridin-2-ylamine

Prepared as in Example 12, in 69% yield, mp 245-255°C, as the hydrochloride salt.

¹H-NMR (δ, CDCl₃): 1.79 (bs, 4H), 2.685 (bs, 2H), 3.035 (t, J=6, 2H), 4.30 (t, J=6, 2H),
35 4.68 (bs, 2H, NH₂), 6.41 (d, J=8, 1H), 6.82 (m, 2H), 7.4-7.6 (m, 4H), 8.10 (m, 1H), 8.31 (m, 1H).

¹³C-NMR (δ, CDCl₃): 23.6, 54.9, 55.0, 67.8, 104.2, 106.6, 115.1, 122.2, 125.0, 125.7, 125.8, 126.6, 127.3, 131.4, 132.2, 138.0, 154.7, 157.7, 158.2.

MS (%): 334 (parent+1, 100).

Anal. Calc'd. for C₂₁H₂₃N₃O•2HCl•1/2(C₄H₁₀O): C 63.30, H 6.82, N 9.48. Found: C
40 62.23, H 6.41, N 9.56.

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EXAMPLE 14

6-{4-[2-[(Benzo[1,3]dioxol-5-ylmethyl)-amino]-ethoxy]-naphthalen-1-yl}-pyridin-2-ylamine

Prepared as in Example 12, in 75% yield, mp 60-80°C, as the hydrochloride salt.

¹H-NMR (δ, CDCl₃): 3.12 (t, J=6, 2H), 3.81 (s, 2H), 4.25 (t, J=6, 2H), 5.91 (s, 2H), 6.41 (d, J=8, 1H), 6.7-6.8 (m, 4H), 6.89 (s, 1H), 7.4-7.5 (m, 4H), 8.10 (m, 1H), 8.28 (m, 1H).

¹³C-NMR (δ, CDCl₃): 47.9, 53.5, 67.7, 100.9, 104.4, 106.6, 108.1, 108.7, 115.1, 121.3, 122.0, 125.1, 125.7, 125.8, 126.7, 127.3, 131.5, 132.2, 134.1, 138.0, 146.6, 147.8, 154.6, 157.6, 158.3.

MS (%): 414 (parent+1, 100).

Anal. Calc'd. for C₂₃H₂₃N₃O₃·HCl·3/2H₂O: C 62.96, H 5.71, N 8.81. Found: C 63.17, H 5.63, N 8.48.

EXAMPLE 15

6-{4-[2-(6,7-Dimethoxy-3,4-dihydro-1H-isoquinolin-2-yl)-ethoxy]-naphthalen-1-yl}-pyridin-2-ylamine

Prepared as in Example 12, in 81% yield, mp 130-150°C, as the hydrochloride salt.

¹H-NMR (δ, CDCl₃): 2.83 (m, 2H), 2.90 (m, 2H), 3.105 (t, J=6, 2H), 3.74 (s, 2H), 3.78 (s, 3H), 3.80 (s, 3H), 4.37 (t, J=6, 2H), 4.69 (bs, 2H, NH₂), 6.39 (d, J=8, 1H), 6.49 (s, 1H), 6.57 (s, 1H), 6.84 (m, 2H), 7.4-7.5 (m, 4H), 8.11 (m, 1H), 8.33 (m, 1H).

¹³C-NMR (δ, CDCl₃): 28.6, 51.6, 55.9, 56.1, 56.8, 67.0, 104.3, 106.6, 109.5, 111.3, 115.1, 122.2, 125.1, 125.7, 125.8, 125.9, 126.4, 126.7, 127.3, 147.2, 147.5, 154.6, 157.6, 158.2.

MS (%): 456 (parent+1, 100).

Anal. Calc'd. for C₂₈H₂₈N₃O₅·2HCl·H₂O: C 61.54, H 6.09, N 7.69. Found: C 61.77, H 6.04, N 7.35.

EXAMPLE 16

3-{2-[4-(6-Amino-pyridin-2-yl)-naphthalen-1-yloxy]-ethyl}-3-aza-bicyclo[3.1.0]hex-6-ylamine

Prepared as in Example 12, in 63% yield (following a deblocking step with trifluoroacetic acid in methylene chloride to remove a t-butoxycarbonyl protecting group), mp 140-155°C, as the hydrochloride salt.

¹H-NMR (δ, CDCl₃): 1.35 (bs, 2H), 1.41 (s, 1H), 2.53 (bs, 2H), 2.93 (t, J=6, 2H), 3.11 (m, 4H), 4.185 (t, J=6, 2H), 4.67 (bs, 2H, NH₂), 6.42 (d, J=8, 1H), 6.81 (m, 2H), 7.4-7.5 (m, 4H), 8.10 (m, 1H), 8.29 (m, 1H).

¹³C-NMR (δ, CDCl₃): 25.8, 32.6, 54.0, 55.6, 67.7, 104.2, 106.6, 115.2, 122.2, 125.1, 125.7, 125.9, 126.6, 127.3, 132.1, 133.7, 138.0, 154.7, 157.7, 158.2.

5 MS (%): 361 (parent+1, 100).

Anal. Calc'd. for $C_{22}H_{24}N_4O \cdot 2HCl \cdot 1/2(C_4H_{10}O)$: C 61.28, H 8.64, N 11.91. Found: C 61.89, H 6.44, N 11.83.

EXAMPLE 17

6-[4-[2-(4-Phenethyl-piperazin-1-yl)-ethoxy]-naphthalen-1-yl]-pyridin-2-ylamine

10 Prepared as in Example 12, in 78% yield, mp 45-80°C, as the hydrochloride salt.

1H -NMR (δ , $CDCl_3$): 2.5-2.9 (m, 12H), 3.00 (t, J=6, 2H), 4.325 (t, J=6, 2H), 4.62 (bs, 2H), 6.47 (d, J=8, 1H), 6.84 (d, J=8, 1H), 6.85 (d, J=7, 1H), 7.20 (m, 3H), 7.28 (m, 2H), 7.46 (m, 4H), 8.10 (m, 1H), 8.31 (m, 1H).

15 ^{13}C -NMR (δ , $CDCl_3$): 33.53, 53.14, 53.64, 57.135, 60.43, 66.61, 104.26, 106.49, 115.165, 122.10, 125.04, 125.43, 125.61, 125.94, 126.57, 127.15, 128.29, 128.61, 131.41, 132.40, 137.92, 140.23, 154.61, 157.67, 158.03.

MS (%): 453 (parent+1, 100).

Anal. Calc'd. for $C_{29}H_{32}N_4O \cdot 3HCl \cdot 3/2H_2O \cdot (C_4H_{10}O)$: C 59.77, H 7.30, N 8.45. Found: C 59.42, H 7.19, N 8.05.

EXAMPLE 18

6-[4-[2-(3-Amino-pyrrolidin-1-yl)-ethoxy]-naphthalen-1-yl]-pyridin-2-ylamine

Prepared as in Example 12, in 59% yield, mp 70-90°C, as the hydrochloride salt.

25 1H -NMR (δ , $CDCl_3$): 1.25 (m, 2H), 2.5 (m, 1H), 2.6 (m, 1H), 2.88 (m, 2H), 3.035 (t, J=6, 2H), 4.30 (t, J=6, 2H), 4.59 (bs, 2H), 6.47 (d, J=8, 1H), 6.85 (m, 2H), 7.4-7.6 (m, 4H), 8.09 (m, 1H), 8.31 (m, 1H).

^{13}C -NMR (δ , $CDCl_3$): 35.14, 50.90, 53.95, 54.71, 64.63, 67.60, 104.19, 106.45, 115.21, 122.12, 125.00, 125.60, 126.54, 126.72, 127.16, 137.92, 142.45, 147.38, 154.66, 156.33, 157.92.

MS (%): 349 (parent+1, 100).

30 Anal. Calc'd. for $C_{21}H_{24}N_4O \cdot 2HCl \cdot 2(C_4H_{10}O) \cdot 1/3(CH_2Cl_2)$: C 58.92, H 7.87, N 9.37. Found: C 58.93, H 7.84, N 7.77.

EXAMPLE 19

6-[4-(2-Diisopropylamino-ethoxy)-naphthalen-1-yl]-pyridin-2-ylamine:

Prepared as in Example 12, in 97.5% yield, as an amorphous solid.

35 1H -NMR (δ , $CDCl_3$): 1.09 (d, J=6.6, 12H), 3.01 (t, J=7, 2H), 3.11 (m, 2H), 4.12 (t, J=7, 2H), 4.62 (bs, 2H), 6.43 (d, J=8, 1H), 6.86 (m, 2H), 7.47 (m, 4H), 8.14 (m, 1H), 8.35 (m, 1H).

^{13}C -NMR (δ , $CDCl_3$): 20.94, 44.49, 49.61, 69.61, 104.27, 106.50, 115.22, 124.97, 125.70, 125.86, 126.59, 127.34, 131.20, 132.17, 137.96, 154.93, 157.90, 158.14.

MS (%): 364 (parent+1, 100).

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5 HRMS Calc'd. for $C_{23}H_{30}N_3O$: 364.2389. Found: 364.2383.

EXAMPLE 20

6-[4-(2-Morpholin-4-yl-ethoxy)-naphthalen-1-yl]-pyridin-2-ylamine

Prepared as in Example 12, in 60% yield, as an amorphous solid.

$^1\text{H-NMR}$ (δ , CDCl_3): 2.66 (m, 4H), 2.96 (t, $J=6$, 2H), 3.74 (m, 4H), 4.32 (t, $J=6$, 2H),
10 4.60 (bs, 2H), 6.48 (d, $J=8$, 1H), 6.86 (m, 2H), 7.46 (m, 4H), 8.11 (m, 1H), 8.30 (m, 1H).

$^{13}\text{C-NMR}$ (δ , CDCl_3): 54.10, 57.55, 66.54, 66.94, 104.32, 106.49, 115.19, 122.02,
125.07, 125.61, 125.78, 126.60, 127.13, 131.42, 132.10, 137.97, 154.56, 157.59, 157.93.

MS (%): 350 (parent+1, 100).

Anal. Calc'd. for $C_{21}H_{23}N_3O_2 \cdot 1/4\text{H}_2\text{O}$: C 72.18, H 6.63, N 12.03. Found: C 71.62, H
15 6.67, N 11.69.

EXAMPLE 21

6-[4-(2-Piperidin-1-yl-ethoxy)-naphthalen-1-yl]-pyridin-2-ylamine

Prepared as in Example 12, in 68% yield, as an amorphous solid as the hydrochloride
salt.

$^1\text{H-NMR}$ (δ , CDCl_3): 1.45 (m, 2H), 1.60 (m, 4H), 2.58 (m, 4H), 2.93 (t, $J=6$, 2H), 4.30 (t,
20 $J=6$, 2H), 4.66 (bs, 2H), 6.38 (d, $J=8$, 1H), 6.82 (m, 2H), 7.45 (m, 4H), 8.11 (m, 1H), 8.32 (m,
1H).

$^{13}\text{C-NMR}$ (δ , CDCl_3): 24.19, 26.07, 55.08, 57.91, 66.66, 104.33, 106.54, 115.09,
122.22, 125.07, 125.75, 125.86, 126.62, 127.18, 131.46, 132.17, 137.94, 154.71, 157.75,
25 158.24.

MS (%): 348 (parent+1, 100).

Anal. Calc'd. for $C_{22}H_{25}N_3O \cdot 2\text{HCl} \cdot 3\text{H}_2\text{O} \cdot 1/4(\text{C}_6\text{H}_{10}\text{O})$: C 56.04, H 7.26, N 8.52. Found:
C 56.20, H 7.11, N 8.27.

EXAMPLE 22

30 6-[4-[2-(3,4-Dihydro-1H-isoquinolin-2-yl)-ethoxy]-naphthalen-1-yl]-pyridin-2-ylamine

Prepared as in Example 12, in 26% yield, as an amorphous solid as the hydrochloride
salt.

$^1\text{H-NMR}$ (δ , CDCl_3): 2.96 (m, 4H), 3.16 (t, $J=6$, 2H), 3.87 (m, 2H), 4.42 (t, $J=6$, 2H),
4.58 (bs, 2H), 6.48 (d, $J=8$, 1H), 6.88 (m, 2H), 7.01 (m, 1H), 7.11 (m, 3H), 7.50 (m, 4H), 8.12
35 (m, 1H), 8.36 (m, 1H).

$^{13}\text{C-NMR}$ (δ , CDCl_3): 28.96, 51.46, 56.43, 56.79, 66.94, 104.34, 106.45, 115.21,
122.10, 125.04, 125.57, 125.64, 125.84, 126.11, 126.52, 126.57, 127.16, 128.61, 131.46,
132.13, 133.98, 134.48, 137.92, 154.63, 157.73, 157.88.

MS (%): 396 (parent+1, 100).

5 HRMS Calc'd. for $C_{28}H_{28}N_3O$: 396.2076. Found: 396.2080.

EXAMPLE 23

6-[4-[2-(4-Dimethylamino-piperidin-1-yl)-ethoxy]-naphthalen-1-yl]pyridin-2-ylamine:

Prepared as in Example 12, in 73% yield, as an amorphous solid as the hydrochloride salt.

10 1H -NMR (δ , $CDCl_3$): 1.56 (m, 2H), 1.80 (m, 2H), 2.18 (m, 3H), 2.26 (s, 6H), 4.28 (t, J=6, 2H), 3.10 (m, 2H), 4.28 (t, J=6, 2H), 4.58 (bs, 2H), 6.43 (d, J=8, 1H), 6.83 (m, 2H), 7.44 (m, 4H), 8.09 (m, 1H), 8.29 (m, 1H).

^{13}C -NMR (δ , $CDCl_3$): 28.33, 29.70, 41.61, 53.85, 57.12, 62.11, 66.77, 76.76, 104.33, 106.51, 115.22, 122.15, 125.09, 125.70, 125.85, 126.64, 127.23, 131.49, 132.15, 137.97, 154.65, 157.80, 158.08.

MS (%): 391 (parent+1, 100).

Anal. Calc'd. for $C_{24}H_{30}N_4O \cdot 3HCl \cdot 3H_2O \cdot 1/2(C_6H_{10}O)$: C 52.84, H 7.50, N 9.48. Found: C 52.65, H 7.78, N 9.38.

HRMS Calc'd. for $C_{24}H_{31}N_4O$: 391.2498. Found: 391.2485.

20 EXAMPLE 24

6-[4-(1-Benzyl-piperidin-4-yloxy)-naphthalen-1-yl]-pyridin-2-ylamine

A 4-Bromo-1-fluoronaphthalene

To a 50 mL round-bottomed flask equipped with condenser and N_2 inlet were added 3.75 mL (5.0 g, 34.25 mmol) 1-fluoronaphthalene and 10 mL carbon tetrachloride, followed by dropwise addition of 1.7 mL (5.5 g, 34.375 mmol) bromine over 3 min. The reaction was heated to 50-60°C as HBr was evolved for 2 hours, then cooled and concentrated. The residue was dissolved in methanol and kept overnight at 0°C. After filtration with cold methanol, the product, with mp close to room temperature, was 4.62 g (60%) of a yellow oil.

30 1H -NMR (δ , $CDCl_3$): 7.02 (t, J=8, 1H), 7.6-7.7 (m, 3H), 8.10 (d, J=8.5, 1H), 8.20 (d, J=8.5, 1H).

GCMS (%): 224/226 (parent, Br^{79}/Br^{81} 100).

B. 4-Fluoronaphthalene-1-boronic acid

To a 250 mL three-necked round-bottomed flask equipped with septum and N_2 inlet were added 4.62 g (20.53 mmol) 4-bromo-1-fluoronaphthalene and 100 mL dry tetrahydrofuran. The solution was cooled to -70°C, and 15.4 mL (24.64 mmol) of a 1.6 M solution of butyl lithium in hexane was added dropwise over 5 min. The reaction was stirred at -70°C for 10 min, then 4.2 mL (3.59 g, 24.64 mmol) triethyl borate was added, and the reaction stirred at -70°C for 20 min and warmed to room temperature. After stirring overnight at room temperature, the reaction was quenched with saturated aqueous ammonium chloride solution, acidified with 1 N hydrochloric acid, and extracted into ethyl acetate (twice). The combined organic layer was

5 washed with brine, dried over sodium sulfate, and evaporated. The residue was triturated with hexane to give an off-white powder, 1.97 g (51%), as a mixture of monoaryl and diaryl boronic acids.

¹H-NMR (δ, CDCl₃): 7.2-7.4 (m, 1H), 7.5-7.7 (m, 3H), 8.0-8.5 (m, 1H), 8.5 and 9.2 (m, 1H).

10 APCI (-) (%): 189 (parent-1, 60).

C. 2-(2,5-Dimethylpyrrolyl)-6-(4-fluoro-naphth-1-yl)pyridine

To a 50 mL round-bottomed flask equipped with condenser and N₂ inlet were added 404 mg (2.13 mmol) 4-fluoronaphthalene-1-boronic acid, 534 mg (2.13 mmol) 2-(2,5-dimethylpyrrolyl)-6-bromopyridine, 902 mg (8.51 mmol) sodium carbonate, 150 mg
15 tetrakis(triphenyl)phosphine, 10 mL ethanol, and 2 mL water. The reaction was refluxed overnight, cooled, poured into water, and extracted into ethyl acetate. After combining with another run on a larger scale, the combined organic layer was washed with brine, dried over sodium sulfate, and evaporated. The residue was chromatographed on silica gel using hexane/ethyl acetate as eluant to afford 4.72 g (85%) of an oil.

20 ¹H-NMR (δ, CDCl₃): 2.25 (s, 6H), 5.92 (s, 2H), 7.1-7.2 (m, 2H), 7.4-7.6 (m, 4H), 7.95 (t, J=8, 1H), 8.12 (d, J=8, 1H), 8.19 (d, J=8, 1H).

¹³C-NMR (δ, CDCl₃): 13.41, 106.97, 108.82, 109.02, 120.18, 120.78, 120.84, 123.42, 123.81, 123.96, 125.48, 126.20, 127.32, 127.68, 127.76, 128.56, 132.35, 133.90, 138.22, 151.87, 157.82, 158.30, 160.34.

25 MS (%): 317 (parent+1, 100).

HRMS Calc'd. for C₂₁H₁₈N₂F (parent+1): 317.1454. Found: 317.1462.

D. 2-(2,5-Dimethylpyrrolyl)-6-(4-((N-benzyl)-4-piperidinyloxy)-naphth-1-yl)pyridine

To a 20 mL round-bottomed flask equipped with condenser and N₂ inlet were added 121 mg (0.633 mmol) 4-hydroxy-N-benzylpiperidine and 5 mL dry dimethylformamide, followed
30 by 32 mg (0.791 mmol) sodium hydride (60% in oil). The reaction was heated to 70°C to ensure complete formation of the alkoxide, and then 100 mg (0.316 mmol) 2-(2,5-dimethylpyrrolyl)-6-(4-fluoro-naphth-1-yl)pyridine in 2 mL dry dimethylformamide was added, and the reaction was heated at 80°C for 10 min. The reaction was cooled, poured into water, and extracted into ethyl acetate. After combining with another run on a larger scale, the
35 combined organic layer was washed with brine, dried over sodium sulfate, and evaporated. The residue was chromatographed on silica gel using methanol/methylene chloride as eluant to afford 489 mg (54%) of an oil.

40 ¹H-NMR (δ, CDCl₃): 2.04 (m, 2H), 2.10 (m, 2H), 2.25 (s, 6H), 2.44 (m, 2H), 2.79 (m, 2H), 3.58 (s, 2H), 4.65 (m, 1H), 5.91 (s, 2H), 6.92 (d, J=8, 1H), 7.2-7.6 (m, 7H), 7.90 (t, J=8, 1H), 8.12 (m, 1H), 8.39 (m, 1H).

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- 5 ^{13}C -NMR (δ , CDCl_3): 13.55, 30.69, 50.43, 63.19, 72.54, 105.94, 106.84, 119.72, 122.68, 123.50, 125.22, 126.69, 126.90, 127.08, 128.27, 128.32, 128.67, 129.09, 129.19, 130.12, 132.22, 138.09, 138.40, 151.83, 153.75, 159.16.
- MS (%): 488 (parent+1, 100).
- HRMS Calc'd. for $\text{C}_{33}\text{H}_{34}\text{N}_3\text{O}$ (parent+1): 488.2702. Found: 488.2703.
- 10 E. 6-[4-(1-Benzyl-piperidin-4-yloxy)-naphthalen-1-yl]-pyridin-2-ylamine
- Prepared as in Example 12I, in 93% yield, mp 265-285°C (dec.), as the hydrochloride salt.
- ^1H -NMR (δ , CDCl_3): 1.9-2.1 (m, 4H), 2.41 (m, 2H), 2.77 (m, 2H), 4.61 (m, 1H), 4.68 (bs, 2H, NH), 6.42 (d, J=8, 1H), 6.86 (m, 2H), 7.2-7.5 (m, 9H), 8.12 (m, 1H), 8.37 (m, 1H).
- 15 ^{13}C -NMR (δ , CDCl_3): 30.65, 50.37, 63.10, 72.53, 106.05, 106.49, 115.08, 122.37, 124.97, 125.67, 126.52, 126.70, 126.97, 127.12, 128.16, 129.11, 131.24, 132.38, 137.89, 138.35, 153.16, 157.66, 158.16.
- MS (%): 410 (parent+1, 100).
- Anal. Calc'd. for $\text{C}_{27}\text{H}_{27}\text{N}_3\text{O} \cdot 2\text{HCl} \cdot 5/3\text{H}_2\text{O}$: C 63.28, H 6.36, N 8.20. Found: C 63.18,
- 20 H 6.40, N 7.88.

EXAMPLE 256-[4-(1-Benzyl-pyrrolidin-3-yloxy)-naphthalen-1-yl]-pyridin-2-ylamine

Prepared as in Example 24, in 98% yield, mp 160-170°C, as the hydrochloride salt.

- ^1H -NMR (δ , CDCl_3): 2.15 (m, 1H), 2.36 (m, 1H), 2.67 (m, 1H), 2.79 (m, 1H), 2.87 (m, 1H), 3.12 (m, 1H), 3.69 (AB_q, J=13, Dn=20, 2H), 4.74 (bs, 2H), 5.00 (m, 1H), 6.37 (d, J=8, 1H), 6.72 (d, J=8, 1H), 6.83 (d, J=8, 1H), 7.2-7.6 (m, 9H), 8.14 (m, 1H), 8.38 (m, 1H).
- ^{13}C -NMR (δ , CDCl_3): 32.37, 52.84, 60.17, 60.35, 77.0, 105.32, 106.52, 114.95, 122.40, 125.02, 125.70, 126.11, 126.62, 127.03, 127.12, 128.28, 128.82, 131.33, 132.28, 137.88, 138.70, 153.59, 157.59, 158.26.
- 30 MS (%): 396 (parent+1, 100).
- Anal. Calc'd. for $\text{C}_{28}\text{H}_{25}\text{N}_3\text{O} \cdot 2\text{HCl} \cdot 5/3\text{H}_2\text{O}$: C 62.65, H 6.13, N 8.43. Found: C 62.73, H 6.06, N 8.40.

EXAMPLE 266-[4-(4-Dimethylamino-butoxy)-naphthalen-1-yl]-pyridin-2-ylamine

Prepared as in Example 24, in 71% yield, mp 78-80°C, as the hydrochloride salt.

- ^1H -NMR (δ , CDCl_3): 1.75 (m, 2H), 1.94 (m, 2H), 2.23 (s, 6H), 2.37 (m, 2H), 4.16 (t, J=6, 2H), 4.63 (bs, 2H), 6.43 (d, J=8, 1H), 6.83 (m, 2H), 7.4-7.6 (m, 4H), 8.08 (m, 1H), 8.32 (m, 1H).
- ^{13}C -NMR (δ , CDCl_3): 24.33, 27.12, 45.31, 59.34, 67.90, 104.06, 106.44, 115.11, 122.09, 124.91, 125.57, 125.83, 126.49, 127.17, 131.12, 132.08, 137.88, 154.86, 157.73,
- 40 158.06.

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5 MS (%): 336 (parent+1, 100).

Anal. Calc'd. for $C_{21}H_{25}N_3O \cdot 2HCl \cdot 1/2(H_2CO_3) \cdot 5/4H_2O$: C 55.91, H 6.66, N 9.10.

Found: C 55.89, H 6.89, N 8.80.

EXAMPLE 27

6-[4-(Piperidin-4-yloxy)-naphthalen-1-yl]-pyridin-2-ylamine

10 Prepared as in Example 24, in 88% yield, mp 65-75°C as the free base, and mp 205-220°C, as the hydrochloride salt.

1H -NMR (δ , $CDCl_3$): 1.80 (m, 2H), 2.01 (m, 2H), 2.72 (m, 2H), 3.12 (m, 2H), 4.59 (m, 1H), 4.71 (bs, 2H), 6.38 (d, J=8, 1H), 6.82 (m, 2H), 7.4-7.6 (m, 4H), 8.10 (m, 1H), 8.34 (m, 1H).

^{13}C -NMR (δ , $CDCl_3$): 32.01, 43.63, 73.20, 106.09, 106.44, 114.95, 122.30, 124.94,
15 125.66, 126.49, 126.67, 127.05, 131.32, 132.35, 137.84, 153.03, 157.64, 158.19.

MS (%): 320 (parent+1, 100).

Anal. Calc'd. for $C_{20}H_{21}N_3O \cdot 3/4(C_6H_8O_2) \cdot 1/2H_2O$: C 70.03, H 7.15, N 10.65. Found: C 70.30, H 6.77, N 10.99.

EXAMPLE 28

20 6-[4-(Pyrrolidin-3-yloxy)-naphthalen-1-yl]-pyridin-2-ylamine: Prepared as in Example 24, in 75% yield, mp 60-70°C as the free base, and 180-200°C as the hydrochloride salt.

1H -NMR (δ , $CDCl_3$): 2.05 (m, 2H), 2.87 (m, 1H), 3.05 (m, 1H), 3.14 (m, 1H), 3.25 (m, 1H), 4.73 (bs, 2H), 4.94 (m, 1H), 6.37 (d, J=8, 1H), 6.74 (d, J=8, 1H), 6.79 (d, J=7, 1H), 7.42 (m, 4H), 8.10 (m, 1H), 8.24 (m, 1H).

25 ^{13}C -NMR (δ , $CDCl_3$): 33.44, 46.13, 53.62, 76.81, 105.43, 106.47, 114.91, 122.06, 124.98, 125.70, 126.13, 126.54, 127.00, 131.35, 132.23, 137.82, 153.29, 157.56, 158.23.

MS (%): 306 (parent+1, 100).

HRMS Calc'd. for $C_{19}H_{20}N_3O$: 306.1606. Found: 306.1608.

EXAMPLE 29

6-[4-(1-Isobutyl-piperidin-4-yloxy)-naphthalen-1-yl]-pyridin-2-ylamine

30 Prepared as in Example 24, in 38% yield, mp 198-210°C, as the hydrochloride salt.

1H -NMR (δ , $CDCl_3$): 0.92 (d, J=7, 6H), 1.81 (m, 1H), 2.01 (m, 2H), 2.12 (m, 2H), 2.16 (d, J=7, 2H), 2.39 (m, 2H), 2.75 (m, 2H), 4.59 (m, 3H), 6.46 (d, J=8, 1H), 6.87 (m, 2H), 7.4-7.6 (m, 4H), 8.09 (m, 1H), 8.33 (m, 1H).

35 ^{13}C -NMR (δ , $CDCl_3$): 20.92, 25.59, 30.46, 50.83, 66.81, 72.56, 106.06, 106.42, 115.16, 122.30, 124.92, 125.63, 126.49, 126.70, 127.07, 131.24, 132.33, 137.89, 153.14, 157.76, 158.00.

MS (%): 376 (parent+1, 100).

Anal. Calc'd. for $C_{24}H_{29}N_3O \cdot 2HCl \cdot 3/2H_2O$: C 60.63, H 7.21, N 8.84. Found: C 60.77,

40 H 7.30, N 8.48.

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EXAMPLE 306-[4-(1-Furan-2-ylmethyl-piperidin-4-yloxy)-naphthalen-1-yl]-pyridin-2-ylamine

Prepared as in Example 24, in 38% yield, mp 178-195°C, as the hydrochloride salt.

¹H-NMR (δ, CDCl₃): 2.07 (m, 4H), 2.48 (m, 2H), 2.76 (m, 2H), 3.59 (s, 2H), 4.5 (bs, 2H), 4.62 (m, 1H), 6.21 (m, 1H), 6.31 (m, 1H), 6.45 (d, J=8, 1H), 6.85 (m, 2H), 7.4-7.6 (m, 5H),
10 8.09 (m, 1H), 8.32 (m, 1H).

¹³C-NMR (δ, CDCl₃): 30.42, 49.93, 54.93, 72.00, 106.08, 106.44, 108.69, 109.98, 115.16, 122.30, 124.95, 125.61, 126.49, 126.70, 127.05, 131.29, 132.33, 137.89, 142.07, 151.74, 153.06, 157.73, 158.02.

MS (%): 400 (parent+1, 100).

15 Anal. Calc'd. for C₂₅H₂₅N₃O₂•2HCl•9/4H₂O: C 58.54, H 6.19, N 8.19. Found: C 58.66, H 6.13, N 8.04.

EXAMPLE 316-[4-(1-Isobutyl-pyrrolidin-3-yloxy)-naphthalen-1-yl]-pyridin-2-ylamine

Prepared as in Example 24, in 45% yield, mp 78-85°C, as the hydrochloride salt.

20 ¹H-NMR (δ, CDCl₃): 0.94 (d, J=7, 6H), 1.76 (m, 1H), 2.14 (m, 1H), 2.2-2.4 (m, 3H), 2.6-2.9 (m, 3H), 3.10 (m, 1H), 4.59 (bs, 2H), 5.03 (m, 1H), 6.45 (d, J=8, 1H), 6.75 (d, J=8, 1H), 6.85 (d, J=8, 1H), 7.4-7.6 (m, 4H), 8.10 (m, 1H), 8.33 (m, 1H).

¹³C-NMR (δ, CDCl₃): 20.35, 21.02, 27.31, 32.20, 53.31, 60.50, 64.82, 105.29, 106.42, 115.15, 122.37, 124.92, 125.56, 126.16, 126.56, 127.05, 131.20, 132.21, 137.88, 153.66,
25 157.73, 158.03.

MS (%): 362 (parent+1, 100).

HRMS Calc'd. for C₂₃H₂₈N₃O: 362.2232. Found: 362.2217.EXAMPLE 326-[4-(1-Furan-2-ylmethyl-pyrrolidin-3-yloxy)-naphthalen-1-yl]-pyridin-2-ylamine

30 Prepared as in Example 24, in 46% yield, mp 140-160°C, as the hydrochloride salt.

¹H-NMR (δ, CDCl₃): 2.15 (m, 1H), 2.38 (m, 1H), 2.7-2.9 (m, 3H), 3.21 (m, 1H), 3.72 (AB_q, J=7, Dn=20, 2H), 4.60 (bs, 2H), 5.03 (m, 1H), 6.21 (m, 1H), 6.31 (m, 1H), 6.44 (d, J=8, 1H), 6.72 (d, J=8, 1H), 6.84 (d, J=7, 1H), 7.37 (m, 1H), 7.44 (m, 4H), 8.10 (m, 1H), 8.32 (m, 1H).

¹³C-NMR (δ, CDCl₃): 32.34, 51.72, 52.53, 59.80, 76.70, 105.19, 106.47, 107.98, 110.03, 115.12, 122.37, 124.95, 125.57, 126.06, 126.59, 127.02, 131.30, 132.21, 137.89,
35 141.98, 152.21, 153.53, 157.67, 158.05.

MS (%): 386 (parent+1, 100).

Anal. Calc'd. for C₂₄H₂₃N₃O₂•2HCl•9/4H₂O: C 57.78, H 5.96, N 8.42. Found: C 57.96, H 5.98, N 8.14.

5

EXAMPLE 336-[4-(1-Methyl-piperidin-4-yloxy)-naphthalen-1-yl]-pyridin-2-ylamine

Prepared as in Example 24, in 90% yield, mp 179-187°C, as the hydrochloride salt.

¹H-NMR (δ, CDCl₃): 2.00 (m, 4H), 2.26 (s, 3H), 2.33 (m, 2H), 2.645 (m, 2H), 4.54 (m, 1H), 4.76 (bs, 2H), 6.35 (d, J=8, 1H), 6.78 (d, J=7, 1H), 6.81 (d, J=8, 1H), 7.41 (m, 4H), 8.09 (m, 1H), 8.33 (m, 1H).

10

¹³C-NMR (δ, CDCl₃): 30.46, 46.13, 52.35, 71.64, 105.93, 106.51, 114.88, 122.27, 124.95, 125.66, 126.47, 126.59, 127.07, 131.26, 132.32, 137.84, 153.02, 157.47, 158.26.

MS (%): 334 (parent+1, 100).

Anal. Calc'd. for C₂₁H₂₃N₃O•2HCl•H₂O•(C₄H₈O): C 60.48, H 7.11, N 8.46. Found: C

15 60.19, H 7.61, N 9.94.

EXAMPLE 346-[4-(1-Methyl-pyrrolidin-3-yloxy)-naphthalen-1-yl]-pyridin-2-ylamine

Prepared as in Example 24, in 77% yield, mp 138-145°C, as the hydrochloride salt.

¹H-NMR (δ, CDCl₃): 2.10 (m, 1H), 2.35 (m, 1H), 2.395 (s, 3H), 2.55 (m, 1H), 2.79 (m, 1H), 2.89 (m, 1H), 2.99 (m, 1H), 4.69 (bs, 2H), 5.01 (m, 1H), 6.41 (d, J=8, 1H), 6.70 (d, J=8, 1H), 6.81 (d, J=8, 1H), 7.43 (m, 4H), 8.07 (m, 1H), 8.32 (m, 1H).

20

¹³C-NMR (δ, CDCl₃): 32.97, 42.10, 55.09, 62.34, 77.39, 105.13, 106.51, 115.04, 122.39, 124.84, 125.54, 126.03, 126.57, 126.99, 131.26, 132.21, 137.88, 153.53, 157.57, 158.15.

25

MS (%): 320 (parent+1, 100).

Anal. Calc'd. for C₂₀H₂₁N₃O•2HCl•3H₂O: C 53.82, H 6.55, N 9.41. Found: C 54.02, H 6.45, N 9.13.

EXAMPLE 356-[4-(3-Dimethylamino-propoxy)-naphthalen-1-yl]-pyridin-2-ylamine

Prepared as in Example 24, in 91.5% yield, mp 105-120°C, as the hydrochloride salt.

30

¹H-NMR (δ, CDCl₃): 2.08 (m, 2H), 2.26 (s, 6H), 2.54 (t, J=7, 2H), 4.18 (t, J=6, 2H), 4.72 (bs, 2H), 6.40 (d, J=8, 1H), 6.81 (m, 2H), 7.45 (m, 4H), 8.08 (m, 1H), 8.32 (m, 1H).

¹³C-NMR (δ, CDCl₃): 27.47, 45.41, 56.52, 66.39, 104.16, 106.47, 115.01, 122.03, 124.91, 125.63, 125.77, 126.47, 127.20, 131.17, 132.08, 137.85, 154.78, 157.63, 158.17.

35

MS (%): 322 (parent+1, 100).

Anal. Calc'd. for C₂₀H₂₃N₃O•2HCl•7/2H₂O: C 52.52, H 7.05, N 9.19. Found: C 52.62, H 6.77, N 8.73.

EXAMPLE 366-[4-(1-Aza-bicyclo[2.2.2]oct-3-yloxy)-naphthalen-1-yl]-pyridin-2-ylamine

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5 Prepared as in Example 24, in 89% yield, mp 220-228°C, as the hydrochloride salt.

¹H-NMR (δ, CDCl₃): 1.41 (m, 1H), 1.54 (m, 1H), 1.71 (m, 1H), 2.09 (m, 1H), 2.27 (m, 1H), 2.78 (m, 3H), 2.96 (m, 2H), 3.30 (m, 1H), 4.56 (m, 1H), 4.71 (bs, 2H), 6.39 (d, J=8, 1H), 6.70 (d, J=8, 1H), 6.81 (d, J=7, 1H), 7.43 (m, 4H), 8.09 (m, 1H), 8.32 (m, 1H).

¹³C-NMR (δ, CDCl₃): 19.61, 24.37, 25.15, 46.53, 47.33, 55.73, 73.44, 105.38, 106.47,
10 114.95, 122.07, 125.01, 125.73, 126.24, 126.54, 127.05, 131.29, 132.33, 137.84, 153.00, 157.56, 158.20.

MS (%): 346 (parent+1, 100).

Anal. Calc'd. for C₂₂H₂₃N₃O•2HCl•5/2H₂O: C 57.02, H 6.52, N 9.07. Found: C 57.07, H 6.27, N 8.88.

15

EXAMPLE 37

6-[4-(2-Dimethylamino-ethoxy)-5,6,7,8-tetrahydro-naphthalen-1-yl]-pyridin-2-ylamine

A. 4-Bromo-5,6,7,8-tetrahydro-1-benzyloxynaphthalene

To a 250 mL round-bottomed flask equipped with addition funnel and N₂ inlet were added 2.96 g (20 mmol) 5,6,7,8-tetrahydro-naphthalen-1-ol and 50 mL 1,2-dichloroethane, and with stirring a solution of 9.64 g (20 mmol) tributylammonium tribromide in 30 mL 1,2-dichloroethane dropwise over 10 min. After stirring an additional 10 min at room temperature, the solution was washed with water, dilute aqueous sodium bisulfite, and water, dried over sodium sulfate, and evaporated. The mixture of product and tributylammonium bromide was used directly.

25 ¹H-NMR (δ, CDCl₃): 1.70 (m, 4H), 2.56 (t, J=6, 2H), 2.61 (t, J=6, 2H), 7.02 (AB, 2H), 8.0 (bs, 1H, OH).

¹³C-NMR (δ, CDCl₃): 22.2, 22.9, 23.8, 30.5, 114.0, 114.7, 126.6, 129.0, 136.7, 154.1.

The above oil was dissolved in 100 mL acetonitrile, and treated with 3.57 mL (30 mmol) benzyl bromide and 5.53 g (40 mmol) potassium carbonate, the refluxed 14 h. TLC showed a major spot at R_f = 0.3 in 10% methylene chloride/hexane (with benzyl bromide at R_f=0.4). The reaction was cooled, poured into dilute aqueous hydrochloric acid/ethyl acetate, and the organic layer separated, washed with water and brine, dried over sodium sulfate, and evaporated. The residue was chromatographed on silica gel using methylene chloride/hexane as eluant to afford 4.0 g (63%) of an oil.

35 ¹H-NMR (δ, CDCl₃): 1.77 (m, 4H), 2.75 (m, 4H), 5.045 (s, 2H), 6.62 (d, J=9, 1H), 7.3-7.5 (m, 6H).

¹³C-NMR (δ, CDCl₃): 22.2, 22.9, 24.0, 30.7, 69.9, 109.8, 116.7, 127.1, 127.9, 128.6, 129.1, 129.3, 137.2, 137.5, 155.6.

B. 5,6,7,8-tetrahydro-1-benzyloxynaphthalene-4-boronic acid

5 Prepared as in Example 12B as a white solid after trituration with hexane, mp 199-205°C, in 72% yield.

¹H-NMR (δ, CDCl₃): 1.72 (m, 4H), 2.70 (m, 4H), 5.005 (s, 2H), 6.66 (m, 1H), 7.01 (d, J=8, 1H), 7.2-7.4 (m, 5H).

¹³C-NMR (δ, CDCl₃): 22.6, 22.9, 23.4, 30.0, 107.8, 125.9, 127.0, 127.6, 128.4, 131.1,
10 137.5, 140.8, 156.9.

C. 2-(2,5-Dimethylpyrrolyl)-6-[4-benzyloxy-5,6,7,8-tetrahydro-naphthalen-1-yl]-pyridine

Prepared as in Example 12C in 100% yield as an oil.

¹H-NMR (δ, CDCl₃): 1.81 (m, 2H), 1.91 (m, 2H), 2.29 (s, 6H), 2.93 (m, 4H), 5.19 (s, 2H),
6.02 (s, 2H), 6.91 (d, J=8, 1H), 7.21 (d, J=8, 1H), 7.32 (d, J=8, 1H), 7.4-7.6 (m, 6H), 7.89 (t,
15 J=8, 1H).

¹³C-NMR (δ, CDCl₃): 13.5, 22.5, 23.0, 24.0, 28.9, 69.8, 106.8, 108.2, 119.6, 123.1,
126.8, 127.2, 127.8, 12.9, 128.6, 128.7, 132.8, 136.8, 137.6, 138.0, 151.4, 156.8, 160.4.

MS (%): 409 (parent+1, 100).

D. 2-(2,5-Dimethylpyrrolyl)-6-[4-hydroxy-5,6,7,8-tetrahydro-naphthalen-1-yl]-pyridine

20 Prepared as in Example 12D in 100% yield as an low melting solid.

¹H-NMR (δ, CDCl₃): 1.67 (m, 2H), 1.77 (m, 2H), 2.16 (s, 6H), 2.63 (m, 2H), 2.73 (m,
2H), 5.89 (s, 2H), 6.3 (bs, 1H, OH), 6.51 (d, J=8, 1H), 7.02 (d, J=8, 1H), 7.13 (d, J=8, 1H), 7.35
(d, J=8, 1H), 7.83 (t, J=8, 1H).

¹³C-NMR (δ, CDCl₃): 13.3, 22.3, 22.8, 23.3, 28.6, 106.6, 112.1, 119.7, 123.3, 124.2,
25 127.8, 128.7, 131.9, 136.6, 138.1, 151.2, 154.4, 160.5.

MS (%): 319 (parent+1, 100).

E. 2-(2,5-Dimethylpyrrolyl)-6-[4-carboethoxymethoxy-5,6,7,8-tetrahydro-naphthalen-1-yl]-pyridine

Prepared as in Example 12E in 83.5% yield as an oil.

30 ¹H-NMR (δ, CDCl₃): 1.31 (t, J=7, 3H), 1.71 (m, 2H), 1.83 (m, 2H), 2.19 (s, 6H), 4.26 (q,
J=7, 2H), 4.66 (s, 2H), 5.90 (s, 2H), 6.64 (d, J=8, 1H), 7.12 (d, J=8, 1H), 7.20 (d, J=8, 1H), 7.35
(d, J=8, 1H), 7.82 (t, J=8, 1H).

¹³C-NMR (δ, CDCl₃): 13.4, 14.2, 22.3, 22.9, 23.7, 28.7, 61.2, 65.5, 106.7, 107.8, 119.6,
123.0, 126.9, 127.7, 128.5, 133.4, 137.0, 138.1, 151.3, 156.0, 160.1, 169.0.

35 MS (%): 405 (parent+1, 100).

F. 2-(2,5-Dimethylpyrrolyl)-6-[4-carboxymethoxy-5,6,7,8-tetrahydro-naphthalen-1-yl]-pyridine

Prepared as in Example 12F in 100% yield as a solid, mp 199-208°C.

5 ¹H-NMR (δ, CDCl₃): 1.62 (m, 2H), 1.72 (m, 2H), 2.08 (s, 6H), 2.66 (m, 2H), 2.75 (m, 2H), 4.56 (s, 2H), 5.81 (s, 2H), 6.58 (d, J=8, 1H), 7.09 (m, 2H), 7.31 (d, J=8, 1H), 7.80 (t, J=8, 1H).

¹³C-NMR (δ, CDCl₃): 12.95, 22.1, 22.6, 23.4, 28.4, 65.0, 106.5, 107.7, 119.9, 123.3, 126.7, 127.4, 128.5, 132.8, 136.6, 138.3, 151.1, 155.9, 160.1, 171.2.

10 MS (%): 377 (parent+1, 100).

G. 2-(2,5-Dimethylpyrrolyl)-6-[4-(N,N-dimethylcarboxamido)methoxy]-5,6,7,8-tetrahydro-naphthalen-1-yl]-pyridine

Prepared as in Example 12G in 100% yield as an oil.

15 ¹H-NMR (δ, CDCl₃): 1.67 (m, 2H), 1.77 (m, 2H), 2.14 (s, 6H), 2.76 (m, 4H), 2.96 (s, 3H), 3.08 (s, 3H), 4.71 (s, 2H), 5.86 (s, 2H), 6.75 (d, J=8, 1H), 7.11 (d, J=8, 1H), 7.16 (d, J=8, 1H), 7.34 (d, J=8, 1H), 7.82 (t, J=8, 1H).

¹³C-NMR (δ, CDCl₃): 13.3, 22.2, 22.8, 23.6, 28.6, 35.7, 36.7, 67.7, 106.5, 107.7, 119.6, 122.9, 126.5, 127.8, 128.6, 133.2, 136.8, 138.0, 151.2, 155.9, 160.2, 168.1.

MS (%): 404 (parent+1, 100).

20 H. 2-(2,5-Dimethylpyrrolyl)-6-[4-(N,N-dimethylaminoethoxy)-5,6,7,8-tetrahydro-naphthalen-1-yl]-pyridine

Prepared as in Example 12H in 93% yield as an oil.

25 ¹H-NMR (δ, CDCl₃): 1.69 (m, 2H), 1.78 (m, 2H), 2.16 (s, 6H), 2.36 (s, 6H), 2.73 (t, J=7, 2H), 2.78 (m, 4H), 4.11 (t, J=7, 2H), 5.88 (s, 2H), 6.74 (d, J=8, 1H), 7.11 (d, J=8, 1H), 7.20 (d, J=8, 1H), 7.36 (d, J=8, 1H), 7.81 (t, J=8, 1H).

¹³C-NMR (δ, CDCl₃): 13.3, 22.3, 22.9, 23.7, 28.7, 46.2, 58.4, 66.6, 106.6, 107.6, 119.5, 122.95, 126.5, 127.7, 128.6, 132.4, 136.6, 137.9, 151.2, 156.9, 160.35.

MS (%): 390 (parent+1, 100).

30 I. 6-[4-(N,N-Dimethylamino-ethoxy)-5,6,7,8-tetrahydro-naphthalen-1-yl]-pyridin-2-ylamine

Prepared as in Example 12I in 57% yield as the hydrochloride salt, mp 239-242°C from methanol/isopropyl ether.

35 ¹H-NMR (δ, CDCl₃): 1.64 (m, 2H), 1.71 (m, 2H), 2.33 (s, 6H), 2.67 (m, 4H), 2.74 (t, J=6, 2H), 4.07 (t, J=6, 2H), 4.55 (bs, 2H), 6.36 (d, J=8, 1H), 6.62 (d, J=8, 1H), 6.67 (d, J=8, 1H), 7.07 (d, J=8, 1H), 7.40 (t, J=8, 1H).

¹³C-NMR (δ, CDCl₃): 22.3, 22.8, 23.6, 28.1, 46.0, 58.2, 66.4, 106.0, 107.4, 114.3, 126.2, 126.8, 133.5, 136.2, 137.6, 156.3, 157.6, 158.8.

MS (%): 312 (parent+1, 100).

40 Anal. Calc'd. for C₁₉H₂₅N₃O•2HCl•1/4H₂O: C 58.69, H 7.13, N 10.81. Found: C 58.72, H 7.14, N 10.79.

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5 6-[4-(N,N-Dimethylamino-ethoxy)-5,6,7,8-tetrahydro-naphthalen-1-yl]-pyridin-2-ylamine
may also be prepared by the following method:

J. 4-Bromo-1-(N,N-dimethylaminoethoxy)-5,6,7,8-tetrahydro-naphthalene

 To a 1 L round-bottomed flask equipped with condenser and N₂ inlet were added 10.0 g
(44 mmol) 4-bromo-5,6,7,8-tetrahydro-naphthalen-1-ol (Example 37A), 19 g (130 mmol) 2-
10 dimethylaminoethyl chloride hydrochloride, 30.3 g (220 mmol) powdered potassium carbonate,
and 600 mL acetonitrile. The reaction was refluxed 60 hours, followed by an additional portion
of the chloride and continued refluxing for 24 hours. The reaction was cooled, filtered and
concentrated. The residue was chromatographed on silica gel using methanol/methylene
chloride as eluant to afford 8.55 g (85%) of a light brown oil.

15 ¹H-NMR (δ, CDCl₃): 1.72 (m, 4H), 2.33 (s, 6H), 2.63 (m, 2H), 2.68 (m, 2H), 2.73 (t, J=6,
2H), 4.01 (t, J=6, 2H), 6.53 (d, J=8, 1H), 7.28 (d, J=8, 1H).

¹³C-NMR (δ, CDCl₃): 22.1, 22.8, 23.7, 30.5, 46.0, 538.2, 66.6, 109.2, 116.4, 128.8,
129.2, 137.2, 155.6.

 MS : 298/300 (parent+1).

20 K. 1-(N,N-Dimethylaminoethoxy)-5,6,7,8-tetrahydro-naphthalene-4-boronic acid

 To a 1 L 3N round-bottomed flask equipped with septum and N₂ inlet were added 8.55
g (28.7 mmol) 4-bromo-1-(2-dimethylaminoethoxy)-5,6,7,8-tetrahydro-naphthalene and 300 mL
dry tetrahydrofuran. The solution was cooled to -70°C, and 13.8 mL (34.4 mmol) of a 2.5 M
solution of butyl lithium in hexanes was added. The reaction was stirred at -70°C for 1 h, then
25 5.9 mL (34.4 mmol) triethyl borate was added, and the reaction stirred at -70°C for 2 h and
warmed to room temperature overnight. The reaction was quenched with aqueous saturated
ammonium chloride solution and extracted three times with ethyl acetate. The organic layer
was washed with brine, dried over sodium sulfate, and evaporated. The residue was triturated
with hexane to a white solid, 6.3 g (83.5%).

30 ¹H-NMR (δ, CDCl₃): 1.79 (m, 4H), 2.44 (s, 6H), 2.68 (m, 2H), 2.89 (m, 2H), 3.32 (m,
2H), 4.19 (m, 2H), 6.74 (d, J=8, 1H), 8.03 (d, J=8, 1H).

L. 2-(2,5-Dimethylpyrrolyl)-6-[4-(N,N-dimethylaminoethoxy)-5,6,7,8-tetrahydro-
naphthalen-1-yl]-pyridine

 To a 500 mL round-bottomed flask equipped with condenser and N₂ inlet were added
35 6.3 g (23.4 mmol) 1-(N,N-dimethylaminoethoxy)-5,6,7,8-tetrahydro-naphthalene-4-boronic acid,
6.0 g (23.4 mmol) 6-bromo-2-(2,5-dimethylpyrrolyl)pyridine, 10.1 g (95.6 mmol) sodium
carbonate, 552 mg tetrakis(triphenylphosphine) palladium, 200 mL ethanol and 20 mL water.
The reaction was refluxed for 20 hours, cooled, and filtered. The filtrate was concentrated,
taken up in 1N sodium hydroxide solution, and extracted three times into ethyl acetate. The
40 organic layer was washed with saturated aqueous sodium bicarbonate solution and brine, dried

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5 over sodium sulfate, and evaporated. The residue was chromatographed on silica gel using methanol/methylene chloride as eluant to afford 7.67 g (82%) of the product as an oil.

$^1\text{H-NMR}$ (δ , CDCl_3): 1.69 (m, 2H), 1.78 (m, 2H), 2.16 (s, 6H), 2.36 (s, 6H), 2.73 (t, J=7, 2H), 2.78 (m, 4H), 4.11 (t, J=7, 2H), 5.88 (s, 2H), 6.74 (d, J=8, 1H), 7.11 (d, J=8, 1H), 7.20 (d, J=8, 1H), 7.36 (d, J=8, 1H), 7.81 (t, J=8, 1H).

10 $^{13}\text{C-NMR}$ (δ , CDCl_3): 13.3, 22.3, 22.9, 23.7, 28.7, 46.2, 58.4, 66.6, 106.6, 107.6, 119.5, 122.95, 126.5, 127.7, 128.6, 132.4, 136.6, 137.9, 151.2, 156.9, 160.35.

MS (%): 390 (parent+1, 100).

This material was then converted to 6-[4-(N,N-dimethylamino-ethoxy)-5,6,7,8-tetrahydro-naphthalen-1-yl]-pyridin-2-ylamine by the method given in Example 37I in 83% yield.

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EXAMPLE 38

6-[4-(2-Pyrrolidin-1-yl-ethoxy)-5,6,7,8-tetrahydro-naphthalen-1-yl]-pyridin-2-ylamine

Prepared as in Example 37, in 58% yield, as a hygroscopic solid as the hydrochloride salt.

20 $^1\text{H-NMR}$ (δ , CDCl_3): 1.64 (m, 2H), 1.74 (m, 2H), 1.77 (m, 4H), 2.62 (m, 4H), 2.68 (m, 4H), 2.89 (t, J=6, 2H), 4.10 (t, J=6, 2H), 4.52 (bs, 2H), 6.37 (d, J=8, 1H), 6.63 (d, J=8, 1H), 6.65 (d, J=8, 1H), 7.07 (d, J=8, 1H), 7.40 (t, J=8, 1H).

$^{13}\text{C-NMR}$ (δ , CDCl_3): 22.4, 22.9, 23.5, 23.7, 28.2, 54.9, 55.0, 67.4, 106.1, 107.5, 114.4, 126.3, 126.9, 133.5, 136.3, 137.7, 156.4, 157.7, 158.9.

MS (%): 338 (parent+1, 100).

25 Anal. Calc'd. for $\text{C}_{21}\text{H}_{27}\text{N}_3\text{O} \cdot 2\text{HCl} \cdot 3\text{H}_2\text{O}$: C 54.31, H 7.60, N 9.05. Found: C 54.00, H 7.83, N 9.19.

EXAMPLE 39

6-[4-[2-(tert-Butyl-methyl-amino)-ethoxy]-5,6,7,8-tetrahydro-naphthalen-1-yl]-pyridin-2-ylamine

30 Prepared as in Example 37, in 93% yield, mp 65-80°C, as the hydrochloride salt.

$^1\text{H-NMR}$ (δ , CDCl_3): 1.08 (s, 9H), 1.64 (m, 2H), 1.74 (m, 2H), 2.325 (s, 3H), 2.68 (m, 4H), 2.79 (t, J=6, 2H), 4.01 (t, J=6, 2H), 4.50 (bs, 2H), 6.37 (d, J=8, 1H), 6.64 (d, J=8, 1H), 6.68 (d, J=8, 1H), 7.08 (d, J=8, 1H), 7.41 (t, J=8, 1H).

35 $^{13}\text{C-NMR}$ (δ , CDCl_3): 22.44, 22.89, 23.72, 26.07, 28.24, 36.67, 50.50, 67.89, 106.05, 107.50, 114.52, 126.21, 126.88, 133.32, 136.19, 137.73, 156.56, 157.65, 158.97.

MS (%): 354 (parent+1, 100).

Anal. Calc'd. for $\text{C}_{22}\text{H}_{31}\text{N}_3\text{O} \cdot 2\text{HCl} \cdot 3\text{H}_2\text{O}$: C 55.00, H 8.18, N 8.75. Found: C 55.29, H 8.25, N 8.57.

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EXAMPLE 406-[4-(2-Diisopropylamino-ethoxy)-5,6,7,8-tetrahydro-naphthalen-1-yl]-pyridin-2-ylamine

Prepared as in Example 37, in 83% yield, mp 50-60°C, as the hydrochloride salt.

¹H-NMR (δ, CDCl₃): 1.04 (d, J=7, 6H), 1.85 (m, 2H), 1.75 (m, 2H), 2.89 (m, 4H), 2.83 (t, J=7, 2H), 3.05 (septet, J=7, 1H), 3.90 (t, J=7, 2H), 4.55 (bs, 2H), 6.38 (d, J=8, 1H), 6.65 (d, J=8, 1H), 6.70 (d, J=8, 1H), 7.09 (d, J=8, 1H), 7.42 (t, J=8, 1H).

¹³C-NMR (δ, CDCl₃): 20.79, 22.37, 22.81, 23.63, 28.16, 44.51, 49.42, 69.26, 105.99, 107.53, 114.39, 126.14, 126.79, 133.18, 136.12, 137.67, 156.51, 157.60, 158.88.

MS (%): 368 (parent+1, 100).

Anal. Calc'd. for C₂₃H₃₃N₃O•2HCl•5/2H₂O•(C₄H₁₀O): C 57.95, H 9.01, N 7.51. Found:
15 C 57.74, H 8.62, N 7.25.

EXAMPLE 416-[4-(2-Diethylamino-ethoxy)-5,6,7,8-tetrahydro-naphthalen-1-yl]-pyridin-2-ylamine

Prepared as in Example 37, in 42% yield, as a hygroscopic solid as the hydrochloride salt.

¹H-NMR (δ, CDCl₃): 1.07 (t, J=7, 6H), 1.66 (m, 2H), 1.735 (m, 2H), 2.6-2.8 (m, 8H), 2.91 (t, J=6, 2H), 4.05 (t, J=6, 2H), 4.49 (bs, 2H), 6.39 (d, J=8, 1H), 6.65 (d, J=8, 1H), 6.69 (d, J=8, 1H), 7.09 (d, J=8, 1H), 7.43 (t, J=8, 1H).

¹³C-NMR (δ, CDCl₃): 11.92, 22.35, 22.80, 23.60, 25.28, 28.11, 47.78, 51.67, 66.62, 105.96, 107.43, 114.43, 126.20, 126.77, 133.39, 136.20, 137.64, 156.43, 157.54, 158.91.

25 MS (%): 340 (parent+1, 100).

EXAMPLE 426-[4-[2-(3,4-Dihydro-1H-isoquinolin-2-yl)-ethoxy]-5,6,7,8-tetrahydro-naphthalen-1-yl]-pyridin-2-ylamine

Prepared as in Example 37, in 67% yield, as an amorphous solid, as the hydrochloride salt.

¹H-NMR (δ, CDCl₃): 1.67 (m, 2H), 1.79 (m, 2H), 2.73 (m, 4H), 2.94 (m, 4H), 3.03 (t, J=6, 2H), 3.83 (s, 2H), 4.24 (t, J=6, 2H), 4.87 (bs, 2H), 6.37 (d, J=8, 1H), 6.65 (d, J=8, 1H), 6.74 (d, J=8, 1H), 7.0-7.2 (m, 5H), 7.43 (t, J=8, 1H).

¹³C-NMR (δ, CDCl₃): 22.39, 22.81, 23.73, 28.17, 28.82, 32.46, 51.37, 56.38, 56.86, 66.47, 106.29, 107.47, 114.25, 125.56, 126.10, 126.14, 126.53, 126.95, 128.61, 133.25, 133.98, 134.47, 136.30, 137.84, 156.31, 157.79, 158.46.

MS (%): 400 (parent+1, 100).

HRMS Calc'd. for C₂₈H₃₀N₃O: 400.2383. Found: 400.2389.

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EXAMPLE 436-[4-(2-Piperidin-1-yl-ethoxy)-5,6,7,8-tetrahydro-naphthalen-1-yl]-pyridin-2-ylamine

Prepared as in Example 37, in 93% yield, as a foam, as the hydrochloride salt.

¹H-NMR (δ, CDCl₃): 1.42 (m, 2H), 1.58 (m, 6H), 1.74 (m, 2H), 2.51 (m, 4H), 2.67 (m, 4H), 2.79 (t, J=6, 2H), 4.10 (t, J=6, 2H), 4.535 (bs, 2H), 6.34 (d, J=8, 1H), 6.63 (d, J=8, 1H), 6.67 (d, J=8, 1H), 7.08 (d, J=8, 1H), 7.39 (t, J=8, 1H).

¹³C-NMR (δ, CDCl₃): 22.43, 22.87, 23.71, 24.18, 26.04, 28.23, 55.04, 58.01, 66.24, 106.05, 107.56, 114.37, 126.26, 126.88, 133.55, 136.26, 137.70, 156.38, 157.72, 158.90.

MS (%): 352 (parent+1, 100).

Anal. Calc'd. for C₂₂H₂₃N₃O•2HCl•2H₂O•1/2(C₄H₁₀O): C 57.94, H 8.10, N 8.45. Found: C 58.25, H 7.78, N 8.69.

EXAMPLE 446-[4-(2-Morpholin-4-yl-ethoxy)-5,6,7,8-tetrahydro-naphthalen-1-yl]-pyridin-2-ylamine:

Prepared as in Example 37, in 67% yield, as a white amorphous solid.

¹H-NMR (d, CDCl₃): 1.64 (m, 2H), 1.74 (m, 2H), 2.58 (m, 4H), 2.68 (m, 4H), 2.81 (t, J=6, 2H), 3.71 (m, 4H), 4.11 (t, J=6, 2H), 4.45 (bs, 2H), 6.39 (d, J=8, 1H), 6.66 (m, 2H), 7.09 (d, J=8, 1H), 7.43 (t, J=8, 1H).

¹³C-NMR (d, CDCl₃): 22.39, 22.85, 23.72, 28.21, 54.16, 57.73, 66.26, 67.03, 106.12, 107.61, 114.53, 126.36, 126.88, 136.39, 137.80, 156.30, 157.57, 158.83.

MS (%): 354 (parent+1, 100).

Anal. Calc'd. for C₂₁H₂₇N₃O₂•1/2H₂O: C 69.59, H 7.79, N 11.59. Found: C 69.61, H 7.51, N 11.56.

EXAMPLE 456-[4-[2-(7,8-Dihydro-5H-[1,3]dioxolo[4,5-g]isoquinolin-6-yl)-ethoxy]-5,6,7,8-tetrahydro-naphthalen-1-yl]-pyridin-2-ylamine

Prepared as in Example 37, in 82% yield, as a white, amorphous solid, as the hydrochloride salt.

¹H-NMR (d, CDCl₃): 1.65 (m, 2H), 1.76 (m, 2H), 2.72 (m, 4H), 2.84 (m, 4H), 2.98 (t, J=6, 2H), 3.69 (s, 2H), 4.20 (t, J=6, 2H), 4.52 (bs, 2H), 5.86 (s, 2H), 6.37 (d, J=8, 1H), 6.47 (s, 1H), 6.55 (s, 1H), 6.65 (d, J=8, 1H), 6.88 (d, J=8, 1H), 7.11 (d, J=8, 1H), 7.42 (t, J=8, 1H).

¹³C-NMR (d, CDCl₃): 22.44, 22.89, 23.79, 28.25, 29.09, 51.47, 56.57, 56.87, 66.69, 100.59, 106.11, 106.47, 107.57, 108.43, 114.46, 126.31, 126.92, 127.04, 127.51, 133.65, 136.38, 137.76, 145.67, 146.03, 156.35, 157.68, 158.87.

MS (%): 444 (parent+1, 100).

Anal. Calc'd. for C₂₇H₂₉N₃O₃: C 73.11, H 6.59, N 9.47. Found: C 73.37, H 7.19, N 8.96.

5 HRMS Calc'd. for $C_{27}H_{30}N_3O_3$: 444.2287. Found: 444.2287.

EXAMPLE 46

6-[4-[2-(4-Methyl-piperazin-1-yl)-ethoxy]-5,6,7,8-tetrahydro-naphthalen-1-yl]-pyridin-2-ylamine

10 Prepared as in Example 37, in 100% yield, as an amorphous solid, as the hydrochloride salt.

$^1\text{H-NMR}$ (d, CDCl_3): 1.62 (m, 2H), 1.72 (m, 2H), 2.26 (s, 3H), 2.4-2.8 (m, 12H), 2.81 (t, $J=6$, 2H), 4.09 (t, $J=6$, 2H), 4.50 (bs, 2H), 6.35 (d, $J=8$, 1H), 6.63 (m, 2H), 7.07 (d, $J=8$, 1H), 7.39 (t, $J=8$, 1H).

15 $^{13}\text{C-NMR}$ (d, CDCl_3): 22.4, 22.9, 23.37, 28.2, 46.1, 53.37, 55.2, 57.3, 66.3, 106.1, 107.6, 114.4, 126.3, 126.9, 133.6, 136.3, 137.7, 156.3, 157.7, 158.9.

MS (%): 367 (parent+1, 100).

Anal. Calc'd. for $C_{27}H_{30}N_4O \cdot 3\text{HCl} \cdot \text{H}_2\text{O} \cdot 1/2(\text{C}_4\text{H}_{10}\text{O})$: C 54.29, H 7.59, N 10.55. Found: C 54.20, H 7.59, N 10.50.

EXAMPLE 47

20 6-[4-[2-(4-Dimethylamino-piperidin-1-yl)-ethoxy]-5,6,7,8-tetrahydro-naphthalen-1-yl]-pyridin-2-ylamine

Prepared as in Example 37, in 92% yield, as an amorphous solid, as the hydrochloride salt.

25 $^1\text{H-NMR}$ (d, CDCl_3): 1.54 (m, 2H), 1.64 (m, 2H), 1.77 (m, 4H), 2.12 (m, 3H), 2.26 (s, 6H), 2.66 (m, 4H), 2.80 (t, $J=6$, 2H), 3.03 (m, 2H), 4.09 (t, $J=6$, 2H), 4.48 (bs, 2H), 6.37 (d, $J=8$, 1H), 6.64 (d, $J=8$, 1H), 6.67 (d, $J=8$, 1H), 7.07 (d, $J=8$, 1H), 7.41 (t, $J=8$, 1H).

$^{13}\text{C-NMR}$ (d, CDCl_3): 22.32, 22.78, 23.61, 28.27, 41.56, 53.55, 57.15, 62.04, 66.31, 105.96, 107.51, 114.36, 126.23, 126.79, 133.52, 136.22, 137.62, 149.63, 156.25, 157.56, 158.85.

30 MS (%): 395 (parent+1, 100).

HRMS Calc'd. for $C_{24}H_{35}N_4O$: C 395.2807. Found: 395.2811.

EXAMPLE 48

6-[4-(Piperidin-3-ylmethoxy)-5,6,7,8-tetrahydro-naphthalen-1-yl]-pyridin-2-ylamine

35 A. 2-(2,5-Dimethylpyrrolyl)-6-[4-N-(4-toluenesulfonyl)-(piperidin-3-ylmethoxy)-5,6,7,8-tetrahydro-naphthalen-1-yl]-pyridine

To a 125 mL round-bottomed flask equipped with condenser and N_2 inlet were added 2.0 g (6.3 mmol) 2-(2,5-dimethylpyrrolyl)-6-(4-hydroxy-5,6,7,8-tetrahydro-naphthalen-1-yl)-pyridine, 4.0 g (9.4 mmol) 3-(hydroxymethyl)-piperidine-di-p-toluenesulfonate, 3.5 g (25.2 mol) potassium carbonate, and 60 mL dry dimethylformamide. The reaction was heated at 140°C for 40 14 hours, cooled, and poured into water. The mixture was extracted with ethyl acetate, and the

5 organic layer washed thoroughly with water and brine, dried over sodium sulfate, and evaporated. The residue was chromatographed on silica gel using hexane/ethyl acetate as eluant to afford 3.1 g (86%) of a white solid.

¹H-NMR (δ, CDCl₃): 1.25 (m, 2H), 1.67 (m, 4H), 1.77 (m, 4H), 2.15 (s, 6H), 2.42 (s, 3H), 2.66 (m, 2H), 2.76 (m, 2H), 3.6-3.9 (m, 5H), 5.87 (s, 2H), 6.66 (d, J=8, 1H), 7.12 (d, J=8, 1H), 7.18 (d, J=8, 1H), 7.3-7.4 (m, 3H), 7.63 (m, 2H), 7.82 (t, J=8, 1H).

¹³C-NMR (δ, CDCl₃): 21.43, 22.19, 22.74, 23.53, 23.97, 26.44, 28.53, 35.74, 46.60, 49.30, 69.59, 106.48, 107.31, 119.42, 122.83, 126.39, 127.63, 128.55, 129.51, 132.52, 133.17, 136.62, 137.77, 143.34, 151.14, 156.50, 160.11.

MS (%): 570 (parent+1, 100).

15 B. 6-[4-N-(4-toluenesulfonyl)-(piperidin-3-ylmethoxy)-5,6,7,8-tetrahydro-naphthalen-1-yl]-pyridin-2-ylamine

To a 500 mL round-bottomed flask equipped with condenser and N₂ inlet were added 3.1 g (5.4 mmol) 2-(2,5-dimethylpyrrolyl)-6-[4-N-(4-toluenesulfonyl)-(piperidin-3-ylmethoxy)-5,6,7,8-tetrahydro-naphthalen-1-yl]-pyridine, 7.6 g (109 mmol) hydroxylamine hydrochloride, 20 250 mL ethanol, and 25 mL water. The reaction was refluxed 5 days, cooled, and evaporated. The residue was taken up in ethyl acetate and 1 N hydrochloric acid, and the organic layer washed with additional ethyl acetate and adjusted to pH 12 with 6 N sodium hydroxide solution, then extracted with ethyl acetate. The organic layer was washed with brine, dried over sodium sulfate, and evaporated to afford 2.87 g (100%) of a light brown foam.

25 ¹H-NMR (δ, CDCl₃): 1.16 (m, 1H), 1.6-1.8 (m, 7H), 2.2-2.4 (m, 3H), 2.41 (s, 3H), 2.7 (m, 4H), 3.7-3.9 (m, 4H), 4.51 (bs, 2H), 6.395 (d, J=8, 1H), 6.61 (d, J=8, 1H), 6.64 (d, J=8, 1H), 7.08 (d, J=8, 1H), 7.29 (m, 2H), 7.42 (t, J=8, 1H), 7.62 (m, 2H).

¹³C-NMR (δ, CDCl₃): 21.53, 22.39, 22.85, 23.62, 24.09, 26.52, 28.23, 35.84, 46.70, 49.43, 69.70, 106.19, 107.36, 114.43, 126.35, 126.87, 127.73, 129.61, 133.16, 133.71, 136.44, 30 137.80, 143.42, 156.18, 157.67, 158.73.

MS (%): 492 (parent+1, 100).

C. 6-[4-(Piperidin-3-ylmethoxy)-5,6,7,8-tetrahydro-naphthalen-1-yl]-pyridin-2-ylamine

To a three-necked round-bottomed flask equipped with condenser, septum and N₂ inlet were added 4.5 g (33.6 mmol) aluminum chloride and 150 mL dry 1,2-dimethoxyethane. The reaction was cooled to 0°C, and 79 mL (79 mmol) of a 1.0 M solution of lithium aluminum hydride in tetrahydrofuran was added. The reaction was stirred at room temperature for 30 35 min, then cooled to -70°C, and a solution of 2.77 g (5.6 mmol) 6-[4-N-(4-toluenesulfonyl)-(piperidin-3-ylmethoxy)-5,6,7,8-tetrahydro-naphthalen-1-yl]-pyridin-2-ylamine in 150 mL dry 1,2-dimethoxyethane was added over 10 min. The reaction was stirred and warmed to room 40 temperature, then heated at reflux for 3 days. The reaction was cooled, quenched carefully with

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5 1 N hydrochloric acid, then adjusted to pH 12 with 6 N sodium hydroxide solution. The mixture was extracted with several portions of methylene chloride, and the organic layer washed with aqueous sodium bicarbonate solution and brine, dried over sodium sulfate, and evaporated. The residue was chromatographed using methanol/methylene chloride/triethylamine as eluant to afford 784 mg (41.5%) of an off-white solid, which was converted to the hydrochloride salt.

10 $^1\text{H-NMR}$ (δ , CDCl_3): 1.21 (m, 1H), 1.46 (m, 1H), 1.6-2.0 (m, 8H), 2.4-2.6 (m, 2H), 2.66 (m, 3H), 3.1 (m, 2H), 3.76 (m, 2H), 4.57 (bs, 2H), 6.35 (d, $J=8$, 1H), 6.60 (d, $J=8$, 1H), 6.63 (d, $J=8$, 1H), 7.39 (t, $J=8$, 1H).

$^{13}\text{C-NMR}$ (δ , CDCl_3): 22.4, 22.9, 23.6, 25.3, 27.6, 28.2, 36.6, 46.2, 49.3, 70.7, 106.2, 107.3, 114.4, 126.4, 126.8, 133.5, 135.3, 137.8, 156.5, 157.8, 158.7.

15 MS (%): 338 (parent+1, 100).

Anal. Calc'd. for $\text{C}_{21}\text{H}_{27}\text{N}_3\text{O} \cdot 1/2\text{H}_2\text{O}$: C 72.80, H 8.15, N 12.13. Found: C 73.11, H 8.29, N 11.89.

EXAMPLE 49

20 6-[4-(1-Methyl-piperidin-3-ylmethoxy)-5,6,7,8-tetrahydro-naphthalen-1-yl]-pyridin-2-ylamine

Prepared from Example 48 by reductive amination with formaldehyde in formic acid, in 84.5% yield, as a yellow amorphous solid, as the hydrochloride salt.

$^1\text{H-NMR}$ (δ , CDCl_3): 1.12 (m, 2H), 1.6-2.0 (m, 8H), 2.18 (m, 1H), 2.29 (s, 3H), 2.69 (m, 4H), 2.79 (m, 1H), 3.00 (m, 1H), 3.81 (m, 2H), 4.44 (bs, 2H), 6.40 (d, $J=8$, 1H), 6.65 (m, 2H), 25 7.08 (d, $J=8$, 1H), 7.43 (t, $J=8$, 1H).

$^{13}\text{C-NMR}$ (δ , CDCl_3): 22.32, 22.80, 23.54, 24.83, 26.71, 28.16, 36.45, 46.60, 56.13, 59.30, 70.68, 105.98, 107.24, 114.49, 126.26, 126.74, 127.83, 133.29, 136.16, 137.68, 156.44, 157.49, 158.89.

MS (%): 352 (parent+1, 100).

30 HRMS Calc'd. for $\text{C}_{22}\text{H}_{30}\text{N}_3\text{O}$: 352.2389. Found: 352.2365.

EXAMPLE 50

6-[4-(1-Isobutyl-piperidin-3-ylmethoxy)-5,6,7,8-tetrahydro-naphthalen-1-yl]-pyridin-2-ylamine

35 Prepared from Example 48 by reductive amination with isobutyraldehyde, in 5.7% yield, as a light tan amorphous solid, as the hydrochloride salt.

$^1\text{H-NMR}$ (δ , CDCl_3): 0.90 (d, $J=6$, 6H), 1.19 (m, 1H), 1.6-2.0 (m, 10H), 2.15 (m, 3H), 2.68 (m, 4H), 2.83 (m, 1H), 2.98 (m, 1H), 3.83 (m, 2H), 4.54 (bs, 2H), 6.41 (d, $J=8$, 1H), 6.65 (m, 2H), 7.08 (d, $J=8$, 1H), 7.435 (t, $J=8$, 1H).

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5 ^{13}C -NMR (δ , CDCl_3): 20.99, 21.06, 22.42, 22.87, 23.61, 24.44, 25.36, 27.34, 28.22, 35.98, 54.48, 57.44, 67.05, 70.71, 106.19, 107.36, 114.54, 126.33, 126.86, 133.14, 136.24, 137.86, 156.58, 157.59, 158.82.

MS (%): 394 (parent+1, 100).

HRMS Calc'd. for $\text{C}_{25}\text{H}_{30}\text{N}_3\text{O}$: C 394.2858. Found: 394.2893.

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EXAMPLE 51

6-[4-[2-(7,8-Dihydro-5H-[1,3]dioxolo[4,5-g]isoquinolin-6-yl)-ethoxy]-naphthalen-1-yl]-pyridin-2-ylamine

Prepared as in Example 12, in 65% yield, as an amorphous solid.

15 ^1H -NMR (d, CDCl_3): 2.85 (m, 2H), 2.93 (m, 2H), 3.15 (t, J=6, 2H), 3.77 (s, 2H), 4.415 (t, J=6, 2H), 4.56 (bs, 2H), 5.87 (s, 2H), 6.48 (s, 1H), 6.51 (d, J=8, 1H), 6.56 (s, 1H), 6.88 (m, 2H), 7.4-7.6 (m, 4H), 8.10 (m, 1H), 8.31 (m, 1H).

^{13}C -NMR (d, CDCl_3): 28.9, 51.4, 56.4, 56.6, 66.8, 100.5, 104.3, 106.4, 106.5, 108.3, 115.3, 122.1, 125.1, 125.6, 125.8, 126.6, 126.8, 127.2, 131.3, 132.1, 138.0, 145.7, 146.0, 154.6, 157.6, 157.8.

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MS (%): 440 (parent+1, 100).

HRMS Calc'd. for $\text{C}_{27}\text{H}_{28}\text{N}_3\text{O}_3$: 440.1974. Found: 440.1971.

EXAMPLE 52

6-[7-(2-Dimethylamino-ethoxy)-indan-4-yl]-pyridin-2-ylamine

25 Prepared as in Example 37, starting with 1-indanol, in 57% yield, mp 215-218°C, as the hydrochloride salt.

^1H -NMR (d, CDCl_3): 2.00 (quin, J=6, 2H), 2.32 (s, 6H), 2.72 (t, J=6, 2H), 2.86 (t, J=7, 2H), 3.06 (t, J=7, 2H), 4.10 (t, J=6, 2H), 4.63 (bs, 2H), 6.32 (d, J=8, 1H), 6.71 (d, J=8, 1H), 6.76 (d, J=8, 1H), 7.39 (m, 2H).

30 ^{13}C -NMR (d, CDCl_3): 25.31, 29.56, 33.78, 46.07, 58.24, 66.46, 106.02, 109.34, 112.88, 127.97, 129.99, 132.66, 137.80, 144.30, 155.24, 157.34, 158.08.

MS (%): 298 (parent+1, 100).

Anal. Calc'd. for $\text{C}_{18}\text{H}_{23}\text{N}_3\text{O} \cdot 2\text{HCl} \cdot 1/2\text{H}_2\text{O}$: C 56.99, H 6.91, N 11.08. Found: C 56.59, H 6.93, N 11.01.

EXAMPLE 53

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6-[7-(2-Diisopropylamino-ethoxy)-indan-4-yl]-pyridin-2-ylamine

Prepared as in Example 37, in 63% yield, as a tan amorphous solid, as the hydrochloride salt.

40 ^1H -NMR (d, CDCl_3): 1.06 (d, J=6, 12H), 2.02 (quin, J=7, 2H), 2.875 (m, 4H), 3.10 (m, 4H), 3.98 (m, 2H), 4.52 (bs, 2H), 6.35 (d, J=8, 1H), 6.74 (d, J=8, 1H), 6.80 (d, J=8, 1H), 7.41 (m, 2H).

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5 ^{13}C -NMR (d, CDCl_3): 20.71, 25.33, 29.56, 33.81, 44.65, 49.86, 68.95, 105.94, 109.31, 112.99, 127.99, 129.76, 132.48, 137.83, 144.27, 155.39, 157.45, 157.94.

MS (%): 354 (parent+1, 100).

Anal. Calc'd. for $\text{C}_{22}\text{H}_{31}\text{N}_3\text{O} \cdot 2\text{HCl} \cdot \text{H}_2\text{O} \cdot 1/2(\text{C}_4\text{H}_9\text{O})$: C 59.87, H 8.37, N 8.73. Found: C 59.69, H 8.19, N 8.75.

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EXAMPLE 546-[7-(2-Morpholin-4-yl-ethoxy)-indan-4-yl]-pyridin-2-ylamine

Prepared as in Example 37, in 93% yield, as a tan amorphous solid.

^1H -NMR (d, CDCl_3): 2.01 (quin, J=7, 2H), 2.58 (m, 4H), 2.79 (t, J=6, 2H), 2.86 (t, J=7, 2H), 3.09 (t, J=7, 2H), 3.71 (m, 4H), 4.14 (t, J=6, 2H), 4.57 (bs, 2H), 6.33 (d, J=8, 1H), 6.72 (d, J=8, 1H), 6.79 (d, J=8, 1H), 7.40 (m, 2H).

15 ^{13}C -NMR (d, CDCl_3): 25.20, 29.50, 33.73, 54.10, 57.56, 66.18, 66.92, 105.89, 109.33, 112.81, 127.91, 130.07, 132.59, 137.71, 144.29, 155.04, 157.26, 157.95.

MS (%): 340 (parent+1, 100).

Anal. Calc'd. for $\text{C}_{20}\text{H}_{25}\text{N}_3\text{O}_2$: C 70.77, H 7.42, N 12.38. Found: C 70.49, H 7.58, N 12.02.

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EXAMPLE 556-[7-[2-(7,8-Dihydro-5H-[1,3]dioxolo[4,5-g]isoquinolin-6-yl)-ethoxy]-indan-4-yl]-pyridin-2-ylamine

Prepared as in Example 37, in 81% yield, as a foam.

25 ^1H -NMR (d, CDCl_3): 2.04 (quin, J=7, 2H), 2.8-3.0 (m, 8H), 3.11 (t, J=7, 2H), 3.70 (s, 2H), 4.24 (t, J=6, 2H), 4.63 (bs, 2H), 5.86 (s, 2H), 6.35 (d, J=8, 1H), 6.48 (s, 1H), 6.55 (s, 1H), 6.76 (d, J=8, 1H), 6.81 (d, J=8, 1H), 7.4-7.5 (m, 2H).

^{13}C -NMR (d, CDCl_3): 25.25, 28.83, 29.56, 33.75, 51.24, 56.29, 56.46, 66.49, 100.52, 105.99, 106.39, 108.34, 109.30, 112.86, 126.89, 127.28, 127.98, 129.88, 132.59, 137.82, 144.32, 145.63, 145.99, 155.12, 157.13, 157.87.

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MS (%): 430 (parent+1, 100).

HRMS Calc'd. for $\text{C}_{28}\text{H}_{29}\text{N}_3\text{O}_3$: 430.2160. Found: 430.2131.

EXAMPLE 566-[7-[2-(4-Methyl-piperazin-1-yl)-ethoxy]-indan-4-yl]-pyridin-2-ylamine

35 Prepared as in Example 37, in 81% yield, as a tan solid, mp > 205°C, as the hydrochloride salt.

^1H -NMR (d, CDCl_3): 2.00 (quin, J=7, 2H), 2.26 (s, 3H), 2.4-2.7 (m, 8H), 2.8-2.9 (m, 4H), 3.08 (t, J=7, 2H), 4.13 (t, J=6, 2H), 4.49 (bs, 2H), 6.34 (d, J=8, 1H), 6.71 (d, J=8, 1H), 6.79 (d, J=8, 1H), 7.40 (t, J=8, 1H).

5 ^{13}C -NMR (d, CDCl_3): 25.20, 29.46, 33.72, 45.96, 53.55, 55.04, 57.08, 66.24, 105.85, 109.32, 112.86, 127.86, 129.97, 132.61, 137.69, 144.23, 155.08, 157.31, 157.87.

MS (%): 353 (parent+1, 100).

HRMS Calc'd. for $\text{C}_{21}\text{H}_{29}\text{N}_4\text{O}$: 353.2345. Found: 353.2341.

EXAMPLE 57

10 6-[7-[2-(tert-Butyl-methyl-amino)-ethoxy]-indan-4-yl]-pyridin-2-ylamine

Prepared as in Example 37, in 96% yield, mp foams at 110°C, as the hydrochloride salt.

^1H -NMR (d, CDCl_3): 1.10 (s, 9H), 2.005 (quin, J=7, 2H), 2.34 (s, 3H), 2.81 (t, J=7, 2H), 2.87 (t, J=7, 2H), 3.07 (t, J=7, 2H), 4.09 (t, J=7, 2H), 4.79 (bs, 2H), 6.34 (d, J=8, 1H), 6.75 (m, 2H), 7.40 (m, 2H).

15 ^{13}C -NMR (d, CDCl_3): 14.11, 25.26, 25.89, 29.47, 32.51, 33.65, 36.50, 50.31, 67.47, 106.04, 109.13, 112.84, 128.01, 129.50, 132.33, 137.81, 144.07, 155.34, 156.10, 157.24, 158.05.

MS (%): 340 (parent+1, 100).

20 HRMS Calc'd. for $\text{C}_{21}\text{H}_{30}\text{N}_3\text{O}$: 340.2381. Found: 340.2389.

EXAMPLE 58

6-[7-[2-(4-Dimethylamino-piperidin-1-yl)-ethoxy]-indan-4-yl]-pyridin-2-ylamine

Prepared as in Example 37, in 100% yield, as an amorphous solid, as the hydrochloride salt.

25 ^1H -NMR (d, CDCl_3): 1.60 (m, 2H), 1.82 (m, 3H), 2.00 (quin, J=7, 2H), 2.13 (m, 2H), 2.27 (s, 6H), 2.80 (t, J=6, 2H), 2.85 (t, J=7, 2H), 3.06 (t, J=7, 2H), 4.15 (t, J=6, 2H), 4.75 (bs, 2H), 6.35 (d, J=8, 1H), 6.72 (d, J=8, 1H), 6.76 (d, J=8, 1H), 7.405 (m, 2H).

30 ^{13}C -NMR (d, CDCl_3): 25.22, 27.83, 29.47, 32.47, 33.63, 41.37, 53.51, 56.96, 61.98, 66.14, 106.04, 109.30, 112.86, 127.99, 129.77, 132.49, 137.81, 144.16, 155.09, 155.91, 157.20, 158.00.

MS (%): 381 (parent+1, 100).

HRMS Calc'd. for $\text{C}_{23}\text{H}_{33}\text{N}_4\text{O}$: 381.2669. Found: 381.2654.

EXAMPLE 59

6-[7-(2-Pyrrolidin-1-yl-ethoxy)-indan-4-yl]-pyridin-2-ylamine

35 Prepared as in Example 37, in 72% yield, mp 113-117°C, as the hydrochloride salt.

^1H -NMR (d, CDCl_3): 1.77 (m, 4H), 2.01 (uquin, J=7, 2H), 2.62 (m, 4H), 2.89 (m, 4H), 3.08 (t, J=7, 2H), 4.15 (t, J=6, 2H), 4.52 (bs, 2H), 6.34 (d, J=8, 1H), 6.73 (d, J=8, 1H), 6.79 (d, J=8, 1H), 7.40 (m, 4H).

40 ^{13}C -NMR (d, CDCl_3): 23.53, 25.30, 29.57, 33.78, 54.88, 54.98, 67.37, 105.94, 109.36, 112.99, 127.97, 129.94, 132.65, 137.80, 144.28, 155.27, 157.45, 157.95.

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5 MS (%): 324 (parent+1, 100).

Anal. Calc'd. for $C_{20}H_{25}N_3O \cdot 2HCl \cdot 3/2H_2O$: C 56.74, H 7.14, N 9.92. Found: C 56.40, H 7.07, N 9.84.

EXAMPLE 60

6-[7-[2-(N-Benzyl, N-methyl-amino)-ethoxy]]-indan-4-yl]-pyridin-2-ylamine

10 Prepared as in Example 37, in 48% yield, mp 110-130°C, as the hydrochloride salt.

1H -NMR (d, $CDCl_3$): 2.045 (quin, J=7, 2H), 2.37 (s, 3H), 2.87 (t, J=6, 2H), 2.92 (t, J=7, 2H), 3.13 (t, J=7, 2H), 3.65 (s, 2H), 4.16 (t, J=6, 2H), 4.65 (bs, 2H), 6.34 (d, J=8, 1H), 6.74 (d, J=8, 1H), 6.82 (d, J=8, 1H), 7.2-7.6 (m, 7H).

^{13}C -NMR (d, $CDCl_3$): 25.37, 29.67, 33.86, 43.04, 55.84, 62.74, 66.54, 106.04, 109.25,
15 112.94, 127.07, 128.04, 128.32, 129.06, 129.98, 132.62, 137.84, 139.06, 144.34, 155.34, 157.42, 158.13.

MS (%): 374 (parent+1, 100).

Anal. Calc'd. for $C_{24}H_{27}N_3O \cdot 2HCl$: C 64.57, H 6.55, N 9.41. Found: C 64.52, H 6.88, N 9.38.

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EXAMPLE 61

6-[7-[(4-Phenethylpiperazin-1-yl)-ethoxy]]-indan-4-yl]-pyridin-2-ylamine

Prepared as in Example 37, in 41% yield, mp 105-130°C, as the hydrochloride salt.

1H -NMR (d, $CDCl_3$): 1.995 (quin, J=7, 2H), 2.5-2.9 (m, 16H), 3.08 (t, J=7, 2H), 4.13 (t, J=6, 2H), 4.61 (bs, 2H), 6.30 (d, J=8, 1H), 6.70 (d, J=8, 1H), 6.76 (d, J=8, 1H), 7.2-7.5 (m, 7H).

25 ^{13}C -NMR (d, $CDCl_3$): 25.31, 29.57, 33.60, 33.82, 53.20, 53.69, 57.22, 60.55, 66.27, 7 105.95, 109.35, 112.82, 126.02, 128.00, 128.37, 128.66, 128.69, 130.07, 132.62, 137.76, 140.29, 144.30, 155.17, 157.34, 158.10.

MS (%): 443 (parent+1, 100).

Anal. Calc'd. for $C_{28}H_{34}N_4O \cdot 2HCl$: C 65.24, H 7.04, N 10.87. Found: C 65.03, H 7.23,
30 N 10.81.

EXAMPLE 62

6-[7-[(4-Isobutyl)piperazin-1-yl)-ethoxy]]-indan-4-yl]-pyridin-2-ylamine

Prepared as in Example 37, in 92% yield, mp 170-190°C, as the hydrochloride salt.

35 1H -NMR (d, $CDCl_3$): 0.85 (d, J=6, 6H), 1.73 (m, 1H), 2.0 (m, 2H), 2.04 (d, J=7, 2H), 2.40 (m, 4H), 2.60 (m, 4H), 2.79 (t, J=7, 2H), 2.84 (t, J=7, 2H), 3.07 (t, J=7, 2H), 4.13 (t, J=6, 2H), 4.57 (bs, 2H), 6.32 (d, J=8, 1H), 6.70 (d, J=8, 1H), 6.76 (d, J=8, 1H), 7.38 (m, 2H).

^{13}C -NMR (d, $CDCl_3$): 25.16, 25.28, 29.45, 33.69, 53.47, 53.70, 57.16, 66.22, 66.84, 105.82, 109.32, 112.79, 127.88, 129.96, 132.56, 137.85, 144.20, 155.12, 157.33, 157.92.

MS (%): 395 (parent+1, 100).

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- 5 Anal. Calc'd. for $C_{24}H_{34}N_4O \cdot 3HCl \cdot H_2O$: C 55.23, H 7.53, N 10.73. Found: C 55.51, H 7.72, N 10.46.

EXAMPLE 63

6-[4-(2-Amino-cyclohexyloxy)-naphthalen-1-yl]-pyridin-2-ylamine

Prepared as in Example 24, in 96% yield, mp 218-230°C, as the hydrochloride salt.

- 10 1H -NMR (d, $CDCl_3$): 1.36 (m, 4H), 1.76 (m, 2H), 2.0-2.4 (m, 2H), 3.05 (m, 1H), 4.10 (m, 1H), 4.62 (bs, 2H), 6.45 (d, J=8, 1H), 6.84 (d, J=8, 1H), 6.93 (d, J=8, 1H), 7.4-7.6 (m, 4H), 8.08 (m, 1H), 8.32 (m, 1H).

- ^{13}C -NMR (d, $CDCl_3$): 24.30, 24.49, 29.60, 33.36, 54.87, 83.58, 106.14, 106.51, 115.12, 122.07, 125.00, 125.71, 126.50, 126.57, 127.12, 131.32, 132.28, 137.94, 153.86, 157.64,
15 158.05.

MS (%): 334 (parent+1, 100).

 Anal. Calc'd. for $C_{21}H_{23}N_3O \cdot 2HCl \cdot 1/4H_2O \cdot 1/2(C_6H_8O)$: C 60.73, H 6.54, N 9.24.
Found: C 60.63, H 6.58, N 9.10.

EXAMPLE 64

- 20 6-[4-(Piperidin-3-ylmethoxy)-naphthalen-1-yl]-pyridin-2-ylamine

Prepared as in Example 24, in 38% yield, mp 164-185°C, as the hydrochloride salt.

- 1H -NMR (d, $CDCl_3$): 1.2-1.4 (m, 1H), 1.54 (m, 1H), 1.69 (m, 1H), 1.91 (m, 1H), 2.07 (m, 1H), 2.45 (m, 1H), 2.55 (m, 1H), 2.8-3.0 (m, 1H), 3.04 (m, 1H), 3.25 (m, 1H), 3.92 (m, 2H), 4.71 (bs, 2H), 6.43 (d, J=8, 1H), 6.78 (d, J=8, 1H), 6.82 (d, J=8, 1H), 7.4-7.6 (m, 4H), 8.08 (m, 1H),
25 8.29 (m, 1H).

- ^{13}C -NMR (d, $CDCl_3$): 25.72, 27.81, 36.93, 46.67, 49.84, 71.04, 103.97, 106.55, 115.05, 122.04, 125.02, 125.60, 125.73, 126.60, 127.17, 131.17, 132.05, 137.95, 154.79, 157.60, 158.13.

MS (%): 334 (parent+1, 100).

- 30 Anal. Calc'd. for $C_{21}H_{23}N_3O \cdot 2HCl \cdot 1/2H_2O \cdot 1/4(C_6H_8O)$: C 60.41, H 6.45, N 9.61.
Found: C 60.33, H 6.50, N 9.28.

EXAMPLE 65

6-[4-(1-Isobutyl-azetidin-3-yloxy)-naphthalen-1-yl]-pyridin-2-ylamine

Prepared as in Example 24, in 57% yield, mp 133-148°C, as the hydrochloride salt.

- 35 1H -NMR (d, $CDCl_3$): 0.91 (d, J=6, 6H), 1.65 (septet, J=6, 1H), 2.37 (d, J=7, 2H), 3.18 (m, 2H), 3.98 (m, 2H), 4.58 (bs, 2H), 5.01 (m, 1H), 6.47 (d, J=8, 1H), 6.59 (d, J=8, 1H), 6.84 (d, J=8, 1H), 7.3-7.5 (m, 4H), 8.09 (m, 1H), 8.30 (m, 1H).

- ^{13}C -NMR (d, $CDCl_3$): 20.89, 27.19, 62.17, 67.03, 68.54, 104.60, 106.61, 115.26, 122.16, 125.20, 125.66, 125.73, 126.78, 127.05, 131.87, 132.25, 138.04, 152.89, 157.70,
40 158.04.

5 MS (%): 348 (parent+1, 100).

Anal. Calc'd. for $C_{22}H_{23}N_3O \cdot 2HCl \cdot 1/2H_2O \cdot (C_4H_8O)$: C 60.35, H 7.01, N 8.12. Found: C 60.50, H 7.05, N 8.00.

EXAMPLE 66

6-[4-(8-Methyl-8-aza-bicyclo[3.2.1]oct-3-yloxy)-naphthalen-1-yl]-pyridin-2-ylamine

10 Prepared as in Example 24, in 93% yield, mp 260-275°C, as the hydrochloride salt.

1H -NMR (d, $CDCl_3$): 2.0-2.3 (m, 8H), 2.305 (s, 3H), 3.15 (m, 2H), 4.59 (bs, 2H), 4.75 (m, 1H), 6.43 (d, J=8, 1H), 6.79 (d, J=8, 1H), 6.84 (d, J=7, 1H), 7.4-7.6 (m, 4H), 8.09 (m, 1H), 8.29 (m, 1H).

^{13}C -NMR (d, $CDCl_3$): 25.81, 35.97, 40.52, 59.84, 69.09, 104.46, 106.38, 115.09,
15 122.16, 125.00, 125.70, 126.31, 126.47, 127.12, 130.74, 132.39, 137.89, 153.06, 157.79, 158.00.

MS (%): 360 (parent+1, 100).

Anal. Calc'd. for $C_{23}H_{23}N_3O \cdot 1/2(CO_2)$ (i.e., $\frac{1}{2}$ carboxylate): C 73.99, H 6.61, N 11.02. Found: C 74.00, H 6.65, N 10.85.

20

EXAMPLE 67

6-[4-(1-Furan-2-ylmethyl-azetidin-3-yloxy)-naphthalen-1-yl]-pyridin-2-ylamine

Prepared as in Example 24, in 50% yield, mp 75-90°C, as the hydrochloride salt.

1H -NMR (δ , $CDCl_3$): 3.34 (m, 2H), 3.71 (s, 2H), 3.97 (m, 2H), 4.58 (bs, 2H), 5.01 (m, 1H), 6.20 (m, 1H), 6.30 (m, 1H), 6.48 (d, J=8, 1H), 6.57 (d, J=8, 1H), 6.84 (d, J=7, 1H), 7.3-7.5
25 (m, 5H), 8.09 (m, 1H), 8.30 (m, 1H).

^{13}C -NMR (δ , $CDCl_3$): 54.89, 61.12, 66.84, 104.54, 106.57, 107.86, 110.06, 115.18, 122.07, 125.15, 125.63, 126.72, 126.95, 131.79, 132.16, 138.01, 142.28, 151.47, 152.74, 157.49, 157.90.

MS (%): 372 (parent+1, 100).

30 HRMS Calc'd. for $C_{22}H_{22}N_4O_2$: 372.1712. Found: 372.1690.

EXAMPLE 68

6-[4-(Pyrrolidin-2-ylmethoxy)-5,6,7,8-tetrahydro-naphthalen-1-yl]-pyridin-2-ylamine

Prepared as in Example 48, using R-N-t-BOC-pyrrolidine-2-methanol, followed by conversion to the tosylate and alkylation with 2-(2,5-dimethylpyrrolyl)-6-(4-hydroxy-5,6,7,8-tetrahydro-naphthalen-1-yl)-pyridine, then deblocking to afford a tan, amorphous solid, in 95%
35 yield, as the hydrochloride salt.

1H -NMR (δ , $CDCl_3$): 1.63 (m, 3H), 1.74 (m, 4H), 1.90 (m, 1H), 2.88 (m, 4H), 2.96 (AB, 2H), 3.50 (m, 1H), 3.90 (m, 2H), 4.58 (bs, 2H), 6.37 (d, J=8, 1H), 6.63 (d, J=7, 1H), 6.67 (d, J=8, 1H), 7.07 (d, J=8, 1H), 7.40 (t, J=8, 1H).

- 5 ^{13}C -NMR (δ , CDCl_3): 22.31, 22.77, 23.57, 25.28, 27.91, 28.13, 46.50, 57.42, 70.65, 106.06, 107.50, 114.32, 126.16, 126.80, 133.51, 136.22, 137.67, 156.28, 157.63, 158.72.
MS (%): 324 (parent+1, 100).
HRMS Calc'd. for $\text{C}_{20}\text{H}_{28}\text{N}_3\text{O}$: 324.2076. Found: 324.2055.

EXAMPLE 69

10 6-[4-(1-Methyl-pyrrolidin-2-ylmethoxy)-naphthalen-1-yl]-pyridin-2-ylamine

Prepared as in Example 24, using S-(-)-1-methyl-2-pyrrolidine methanol to afford, after deblocking in 88% yield, a tan solid, mp 80-95°C, $\alpha_D = -36.47^\circ$ ($c=1$, CH_2Cl_2).

- ^1H -NMR (δ , CDCl_3): 1.8 (m, 2H), 1.9 (m, 1H), 2.12 (m, 1H), 2.34 (m, 1H), 2.56 (s, 3H), 2.83 (m, 1H), 3.13 (m, 1H), 4.13 (AB, 2H), 4.63 (bs, 2H), 6.41 (d, $J=8$, 1H), 6.83 (m, 2H), 7.46
15 (m, 4H), 8.10 (m, 1H), 8.31 (m, 1H).

^{13}C -NMR (δ , CDCl_3): 23.00, 28.92, 41.87, 57.79, 64.27, 71.57, 104.06, 106.45, 115.09, 122.07, 124.97, 125.64, 125.73, 126.01, 126.53, 127.20, 131.29, 132.06, 137.89, 154.78, 157.69, 158.07.

MS (%): 334 (parent+1, 100).

- 20 Anal. Calc'd. for $\text{C}_{21}\text{H}_{23}\text{N}_3\text{O} \cdot 1/3\text{H}_2\text{O}$: C 74.31, H 7.03, N 12.38. Found: C 74.11, H 7.19, N 12.22.

EXAMPLE 70

6-[4-(2-Amino-cyclohexyloxy)-5,6,7,8-tetrahydro-naphthalen-1-yl]-pyridin-2-ylamine

- Prepared as in Example 48, via the following four-step sequence: 2-(2,5-
25 dimethylpyrrolyl)-6-[4-hydroxy-5,6,7,8-tetrahydro-naphthalen-1-yl]-pyridine was first alkylated with 2-chlorocyclohexanone, using potassium carbonate as the base and a catalytic amount of sodium iodide, in dimethylformamide at 80°C for 24 hours, in 92% yield. The resulting ketone was converted to the oxime methyl ether using O-methylhydroxylamine hydrochloride and triethylamine in methanol at reflux for 16 h in 81% yield. The oxime ether was then reduced to
30 the amine using borane methyl sulfide in tetrahydrofuran at reflux for 2 days, followed by refluxing in ethanol with sodium carbonate and cesium fluoride for 16 hours, in 12% yield. The amine was then deblocked with hydroxylamine hydrochloride in refluxing aqueous ethanol to afford the desired final product in 89% yield as a tan solid after conversion to the hydrochloride salt.

- 35 ^1H -NMR (δ , CDCl_3): 1.2-1.5 (m, 6H), 1.6-1.9 (m, 6H), 2.70 (m, 4H), 2.94 (m, 1H), 4.49 (m, 1H), 4.55 (bs, 2H), 6.39 (d, $J=8$, 1H), 6.65 (d, $J=8$, 1H), 6.72 (d, $J=8$, 1H), 7.07 (d, $J=8$, 1H), 7.43 (t, $J=8$, 1H).

^{13}C -NMR (δ , CDCl_3): 20.3, 22.4, 22.37, 23.7, 23.9, 27.4, 28.2, 30.9, 52.1, 75.8, 106.1, 108.6, 114.4, 126.8, 127.0, 133.1, 136.5, 137.7, 154.9, 157.6, 158.7.

5 MS (%): 338 (parent+1, 100).

HRMS Calc'd. for $C_{21}H_{28}N_3O$: 338.2232. Found: 338.2256.

EXAMPLE 71

6-[4-(Azetidin-2-ylmethoxy)-naphthalen-1-yl]-pyridin-2-ylamine

Prepared as in Example 24 using L-azetidine-2-carboxylic acid as the precursor to N-t-
10 BOC-azetidine-2-methanol as the reagent to add to 2-(2,5-dimethylpyrrolyl)-6-(4-fluoro-naphth-
1-yl)pyridine, followed by removal of blocking groups to afford 45% yield of a solid, mp 135-
150°C.

$^1\text{H-NMR}$ (δ , CDCl_3): 2.33 (m, 1H), 2.43 (m, 1H), 3.4 (bs, 1H), 3.54 (m, 1H), 3.67 (m,
1H), 4.20 (m, 2H), 4.37 (m, 1H), 4.625 (bs, 2H), 6.45 (d, J=8, 1H), 6.84 (m, 2H), 7.45 (m, 4H),
15 8.10 (m, 1H), 8.31 (m, 1H).

$^{13}\text{C-NMR}$ (δ , CDCl_3): 23.93, 44.25, 57.45, 72.10, 104.39, 106.54, 115.15, 122.00,
125.04, 125.63, 125.73, 126.63, 127.15, 131.50, 132.06, 137.95, 154.59, 157.62, 158.03.

MS (%): 306 (parent+1, 100).

Anal. Calc'd. for $C_{19}H_{19}N_3O \cdot 2\text{HCl} \cdot 3/2\text{H}_2\text{O} \cdot 1/2(\text{C}_4\text{H}_8\text{O})$: C 56.13, H 6.28, N 9.35.

20 Found: C 56.24, H 6.52, N 9.05.

EXAMPLE 72

6-[4-(1-Pyridin-3-ylmethyl-azetidin-3-yloxy)-naphthalen-1-yl]-pyridin-2-ylamine:

Prepared as in Example 24, in 24% yield, mp 150-180°C, as the hydrochloride salt.

$^1\text{H-NMR}$ (δ , CDCl_3): 3.29 (m, 2H), 3.71 (s, 2H), 3.92 (m, 2H), 4.57 (bs, 2H), 5.005 (m,
25 1H), 6.47 (d, J=8, 1H), 6.56 (d, J=8, 1H), 6.83 (d, J=7, 1H), 7.24 (m, 1H), 7.39 (d, J=8, 1H), 7.5-
7.6 (m, 4H), 7.63 (m, 1H), 8.09 (m, 1H), 8.29 (m, 1H), 8.50 (m, 1H), 8.54 (s, 1H).

$^{13}\text{C-NMR}$ (δ , CDCl_3): 60.9, 61.4, 66.8, 104.5, 106.6, 115.1, 122.0, 123.4, 125.5, 125.7,
126.7, 126.9, 132.0, 132.2, 133.3, 136.0, 138.0, 148.7, 149.8, 152.7, 157.5, 158.0.

MS (%): 383 (parent+1, 100).

30 Anal. Calc'd. for $C_{24}H_{22}N_4O \cdot 3\text{HCl} \cdot 3\text{H}_2\text{O} \cdot 1/3(\text{C}_4\text{H}_8\text{O})$: C 53.39, H 5.95, N 9.83. Found:
C 53.22, H 6.18, N 9.43.

EXAMPLE 73

6-[4-(Azetidin-3-ylmethoxy)-naphthalen-1-yl]-pyridin-2-ylamine

Prepared as in Example 24, in which N-BOC azetidine-3-methanol was added to 2-
35 (2,5-dimethylpyrrolyl)-6-(4-fluoro-naphth-1-yl)pyridine as in Example 24D followed by sequential
removal of the BOC and pyrrolyl protecting groups, with the final step proceeding in 75% yield,
in 75% yield, mp 88-110°C, as the hydrochloride salt.

$^1\text{H-NMR}$ (δ , CDCl_3): 3.27 (m, 1H), 3.64 (m, 2H), 3.78 (m, 2H), 4.25 (d, J=6, 2H), 4.63
(bs, 2H), 6.45 (d, J=8, 1H), 6.83 (m, 2H), 7.4-7.6 (m, 4H), 8.09 (m, 1H), 8.29 (m, 1H).

5 ^{13}C -NMR (δ , CDCl_3): 34.2, 49.8, 69.8, 104.2, 106.5, 115.1, 122.0, 125.0, 125.4, 125.6, 125.7, 126.6, 127.1, 131.4, 132.0, 138.0, 154.7, 157.6, 158.1.

MS (%): 306 (parent+1, 100).

Anal. Calc'd. for $\text{C}_{19}\text{H}_{19}\text{N}_3\text{O} \cdot 2\text{HCl} \cdot 2\text{H}_2\text{O} \cdot 3/2(\text{C}_4\text{H}_8\text{O})$: C 57.25, H 7.00, N 8.04. Found: C 57.47, H 7.14, N 8.21.

10

EXAMPLE 746-[4-(1-Pyridin-2-ylmethyl-azetidin-3-yloxy)-naphthalen-1-yl]-pyridin-2-ylamine:

Prepared as in Example 24, in 24% yield, mp 97-120°C, as the hydrochloride salt from tetrahydrofuran.

^1H -NMR (δ , CDCl_3): 3.42 (m, 2H), 3.89 (s, 2H), 4.015 (m, 2H), 4.62 (bs, 2H), 5.045 (m, 1H), 6.47 (d, J=8, 1H), 6.57 (d, J=8, 1H), 6.82 (d, J=7, 1H), 7.16 (m, 1H), 7.3-7.5 (m, 5H), 7.64 (t, J=8, 1H), 8.07 (m, 1H), 8.30 (m, 1H), 8.55 (m, 1H).

15

^{13}C -NMR (δ , CDCl_3): 61.62, 64.89, 67.10, 104.52, 106.64, 115.14, 122.09, 122.13, 122.42, 125.18, 125.60, 126.73, 126.92, 131.75, 132.16, 136.58, 138.04, 149.30, 152.77, 157.41, 157.76, 157.96.

20

MS (%): 383 (parent+1, 100).

Anal. Calc'd. for $\text{C}_{24}\text{H}_{22}\text{N}_4\text{O} \cdot 3\text{HCl} \cdot 7/4\text{H}_2\text{O}$: C 55.08, H 5.49, N 10.70. Found: C 55.44, H 5.61, N 10.31.

EXAMPLE 756-[4-(N-methyl-azetidin-3-yloxy)-naphthalen-1-yl]-pyridin-2-ylamine: Prepared as in

25 Example 24, using formaldehyde in methanol with sodium cyanoborohydride at room temperature, in 30% yield, mp 240-255°C, as the hydrochloride salt from tetrahydrofuran.

^1H -NMR (δ , CDCl_3): 2.45 (s, 3H), 2.75 (bs, 2H), 3.30 (m, 2H), 3.99 (m, 2H), 4.96 (m, 1H), 6.47 (d, J=8, 1H), 6.55 (d, J=8, 1H), 6.80 (d, J=7, 1H), 7.3-7.5 (m, 4H), 8.03 (m, 1H), 8.28 (m, 1H).

30

^{13}C -NMR (δ , CDCl_3): 45.81, 63.07, 66.19, 104.44, 106.84, 115.08, 121.97, 125.23, 125.43, 125.57, 126.76, 126.87, 131.82, 132.15, 138.14, 152.56, 157.13, 158.05.

MS (%): 306 (parent+1, 100).

Anal. Calc'd. for $\text{C}_{19}\text{H}_{19}\text{N}_3\text{O} \cdot 2\text{HCl} \cdot 2\text{H}_2\text{O}$: C 55.08, H 6.08, N 10.14. Found: C 55.34, H 6.01, N 9.82.

35

EXAMPLE 766-[4-(N-Isopropyl-azetidin-3-yloxy)-naphthalen-1-yl]-pyridin-2-ylamine

Prepared as in Example 24, as a byproduct of the reaction used for preparation of Example 75, from acetone in the methanol, in 19% yield, mp 120-135°C, as the hydrochloride salt from tetrahydrofuran.

5 $^1\text{H-NMR}$ (δ , CDCl_3): 0.99 (d, $J=6$, 6H), 2.49 (septet, $J=6$, 1H), 3.25 (m, 2H), 3.96 (m, 2H), 4.65 (bs, 2H), 4.97 (m, 1H), 6.48 (d, $J=8$, 1H), 6.60 (d, $J=8$, 1H), 6.81 (d, $J=6$, 1H), 7.4-7.5 (m, 4H), 8.03 (m, 1H), 8.27 (m, 1H).

$^{13}\text{C-NMR}$ (δ , CDCl_3): 19.30, 50.44, 58.78, 65.40, 104.52, 106.81, 115.12, 122.00, 125.20, 125.45, 125.56, 126.73, 126.89, 131.78, 132.15, 138.15, 152.66, 157.21, 158.02.

10 MS (%): 332 (parent+1, 100).

Anal. Calc'd. for $\text{C}_{21}\text{H}_{23}\text{N}_3\text{O}\cdot 2\text{HCl}\cdot 2\text{H}_2\text{O}$: C 57.02, H 6.61, N 9.50. Found: C 57.04, H 6.51, N 9.29.

EXAMPLE 77

15 6-[4-(2-Dimethylamino-ethoxy)-6,7,8,9-tetrahydro-5H-benzocyclohepten-1-yl]-pyridin-2-ylamine

Prepared as in Example 37, using 4-hydroxy-6,7,8,9-tetrahydro-5H-benzocycloheptene as the starting material, which was prepared as follows: 8 g (71.4 mmol) 2-hydroxypyrrone (Syn. Commun., 5, 461, (1975)) and 20 mL cycloheptene were reacted in a sealed tube at 150°C for 24 h to give 1-oxo-3,4,6,7,8,9-hexahydro-5H-benzocycloheptene in 49.5% yield, 20 followed by reaction with isopropenyl acetate to afford the enol acetate and treatment with 2,3-dichloro-5,6-dicyanobenzoquinone at 90°C for 1.5 h (see J. Med. Chem., 37, 3803 (1994)) to afford 4-acetoxy-6,7,8,9-tetrahydro-5H-benzocycloheptene in 69% yield as an oil. Hydrolysis with 3.7 equivalents of powdered potassium hydroxide in ethanol at room temperature for 2 h gave a 44% yield of the desired 4-hydroxy-6,7,8,9-tetrahydro-5H-benzocycloheptene after 25 purification by column chromatography as a white solid. The remaining steps in the sequence then followed Example 48. The final step proceeded in 89% yield to give the product as an amorphous solid as the hydrochloride salt from ether.

30 $^1\text{H-NMR}$ (δ , CDCl_3): 1.58 (m, 4H), 1.79 (m, 2H), 2.34 (s, 6H), 2.75 (m, 4H), 2.93 (m, 2H), 4.06 (t, $J=6$, 2H), 4.48 (bs, 2H), 6.39 (d, $J=8$, 1H), 6.62 (d, $J=8$, 1H), 6.74 (d, $J=8$, 1H), 7.10 (d, $J=8$, 1H), 7.41 (d, $J=8$, 1H).

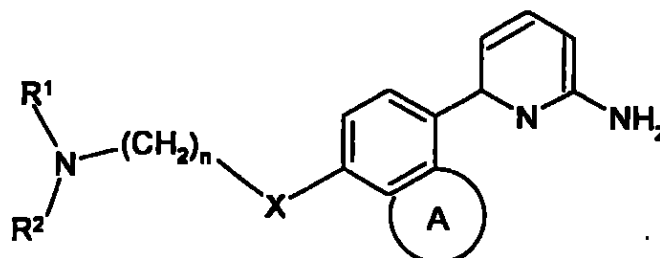
$^{13}\text{C-NMR}$ (δ , CDCl_3): 25.51, 27.36, 27.75, 31.21, 32.46, 46.03, 58.35, 67.43, 105.94, 109.95, 114.72, 127.58, 132.85, 133.74, 137.54, 142.88, 155.43, 157.74, 159.32.

MS (%): 326 (parent+1, 100).

5

CLAIMS

1. A compound of the formula



wherein ring A is a fused 5-7 membered saturated or unsaturated ring wherein from zero to two of the ring members are heteroatoms selected, independently, from nitrogen, oxygen and sulfur, with the proviso that no two adjacent ring members can both be heteroatoms;

X is oxygen or a bond;

n is an integer from two to six; and

R^1 and R^2 are selected, independently, from (C_1-C_6) alkyl, aryl, tetrahydronaphthalene and aralkyl, wherein said aryl and the aryl moiety of said aralkyl is phenyl or naphthyl and the alkyl moiety is straight or branched and contains from 1 to 6 carbon atoms, and wherein said (C_1-C_6) alkyl, said aryl, said tetrahydronaphthalene and the aryl moiety of said aralkyl may optionally be substituted with from one to three substituents, preferably from zero to two substituents, that are selected, independently, from halo (e.g., chloro, fluoro, bromo, iodo), nitro, hydroxy, cyano, amino, (C_1-C_4) alkoxy, and (C_1-C_4) alkylamino;

or R^1 and R^2 form, together with the nitrogen to which they are attached, a piperazine, piperidine or pyrrolidine ring or an azabicyclic ring containing from 6 to 14 ring members, from 1 to 3 of which are nitrogen and the rest of which are carbon;

and wherein said piperazine, azetidine, piperidine and pyrrolidine rings may optionally be substituted with one or more substituents, preferably with from zero to two substituents that are selected, independently, from (C_1-C_6) alkyl, amino, (C_1-C_6) alkylamino, [di-(C_1-C_6) alkyl]amino, phenyl substituted 5 to 6 membered heterocyclic rings containing from 1 to 4 rings nitrogen atoms, benzoyl, benzoylmethyl, benzylcarbonyl, phenylaminocarbonyl, phenylethyl and phenoxy carbonyl, and wherein the phenyl moieties of any of the foregoing substituents may optionally be substituted with one or more substituents, preferably with from zero to two substituents, that are selected, independently, from halo, (C_1-C_3) alkyl, (C_1-C_3) alkoxy, nitro, amino, cyano, CF_3 and OCF_3 ;

also R^1 or R^2 may be connected onto the $(CH_2)_n$ group to form a ring of from 4 to 7 members;

and the pharmaceutically acceptable salt of such compounds.

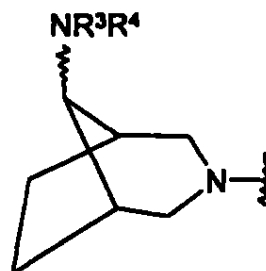
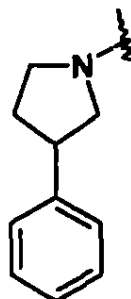
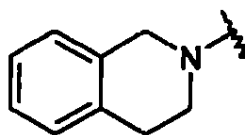
2. A compound according to claim 1, wherein NR^1R^2 is an optionally substituted piperidine, azetidine, piperazine or pyrrolidine ring or a 3-aza-bicyclo[3.1.0]hex-6-ylamine ring;

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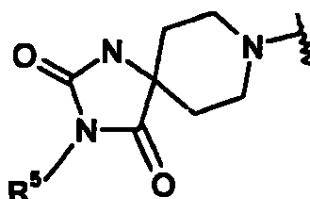
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- 5 and wherein said piperazine, azetidine, piperidine and pyrrolidine rings may optionally be substituted with one or more substituents, preferably with from zero to two substituents that are selected, independently, from (C₁-C₈)alkyl, amino, (C₁-C₈) alkylamino, [di-(C₁-C₈)alkyl]amino, phenyl substituted 5 to 6 membered heterocyclic rings containing from 1 to 4 rings nitrogen atoms, benzoyl, benzoylmethyl, benzylcarbonyl, phenylaminocarbonyl, phenylethyl and phenoxycarbonyl,
- 10 and wherein the phenyl moieties of any of the foregoing substituents may optionally be substituted with one or more substituents, preferably with from zero to two substituents, that are selected, independently, from halo, (C₁-C₃)alkyl, (C₁-C₃)alkoxy, nitro, amino, cyano, CF₃ and OCF₃.

3. A compound according to claim 1 wherein NR¹R² forms an azabicyclic ring having the formula



and



5

wherein R^3 and R^4 are selected from hydrogen, (C_1-C_6) alkyl, phenyl, naphthyl, (C_1-C_6) alkyl- $C(=O)-$, $HC(=O)-$, (C_1-C_6) alkoxy- $C(=O)-$, phenyl- $C(=O)-$, naphthyl- $C(=O)-$, and $R^6R^7NC(=O)-$ wherein R^6 and R^7 are selected, independently, from hydrogen and (C_1-C_6) alkyl; and

10

R^5 is selected from hydrogen, (C_1-C_6) alkyl, phenyl, naphthyl, phenyl- (C_1-C_6) alkyl- and naphthyl- (C_1-C_6) alkyl-.

5 4. A pharmaceutical composition for treating or preventing a condition selected from
the group consisting of migraine inflammatory diseases, stroke, acute and chronic pain,
hypovolemic shock, traumatic shock, reperfusion injury, Crohn's disease, ulcerative colitis, septic
shock, depression, Parkinson's disease, multiple sclerosis, AIDS associated dementia,
neurodegenerative diseases, neuron toxicity, Alzheimer's disease, chemical dependencies and
10 addictions, emesis, epilepsy, anxiety, psychosis, head trauma, adult respiratory distress syndrome
(ARDS), morphine induced tolerance and withdrawal symptoms, inflammatory bowel disease,
osteoarthritis, rheumatoid arthritis, ovulation, dilated cardiomyopathy, acute spinal cord injury,
Huntington's disease, glaucoma, macular degeneration, diabetic neuropathy, diabetic
nephropathy and cancer in a mammal, comprising an amount of a compound according to claim 1
15 that is effective in treating or preventing such condition and a pharmaceutically acceptable carrier.

 5. A method of treating or preventing a condition selected from the group consisting
of migraine inflammatory diseases, stroke, acute and chronic pain, hypovolemic shock, traumatic
shock, reperfusion injury, Crohn's disease, ulcerative colitis, septic shock, multiple sclerosis, AIDS
associated dementia, neurodegenerative diseases, neuron toxicity, depression, Parkinson's
20 disease, Alzheimer's disease, chemical dependencies and addictions, emesis, epilepsy, anxiety,
psychosis, head trauma, adult respiratory distress syndrome (ARDS), morphine induced tolerance
and withdrawal symptoms, inflammatory bowel disease, osteoarthritis, rheumatoid arthritis,
ovulation, dilated cardiomyopathy, acute spinal cord injury, Huntington's disease, glaucoma,
macular degeneration, diabetic neuropathy, diabetic nephropathy and cancer in a mammal,
25 comprising administering to said mammal an amount of a compound according to claim 1, that is
effective in treating or preventing such condition.

 6. A pharmaceutical composition for inhibiting nitric oxide synthase (NOS) in a
mammal, according to claim 1, comprising a NOS inhibiting effective amount of a compound
according to claim 1, and a pharmaceutically acceptable carrier.

30 7. A method of inhibiting NOS in a mammal, comprising administering to said
mammal a NOS inhibiting effective amount of a compound according to claim 1.

 8. A pharmaceutical composition for treating or preventing a condition selected from
the group consisting of migraine, inflammatory diseases, stroke, acute and chronic pain,
hypovolemic shock, traumatic shock, reperfusion injury, Crohn's disease, ulcerative colitis, septic
35 shock, multiple sclerosis, AIDS associated dementia, neurodegenerative diseases, neuron
toxicity, depression, Parkinson's disease, Alzheimer's disease, chemical dependencies and
addictions, emesis, epilepsy, anxiety, psychosis, head trauma, adult respiratory distress syndrome
(ARDS), morphine induced tolerance and withdrawal symptoms, inflammatory bowel disease,
osteoarthritis, rheumatoid arthritis, ovulation, dilated cardiomyopathy, acute spinal cord injury,
40 Huntington's disease, glaucoma, macular degeneration, diabetic neuropathy, diabetic

5 nephropathy and cancer in a mammal, comprising a NOS inhibiting effective amount of a compound according to claim 1 and a pharmaceutically acceptable carrier.

9. A method of treating or preventing a condition selected from the group consisting of migraine, inflammatory diseases, stroke, acute and chronic pain, hypovolemic shock, traumatic shock, reperfusion injury, Crohn's disease, ulcerative colitis, septic shock, multiple sclerosis, AIDS
10 associated dementia, neurodegenerative diseases, neuron toxicity, depression, Parkinson's disease, Alzheimer's disease, chemical dependencies and addictions, emesis, epilepsy, anxiety, psychosis, head trauma, adult respiratory distress syndrome (ARDS), morphine induced tolerance and withdrawal symptoms, inflammatory bowel disease, osteoarthritis, rheumatoid arthritis, ovulation, dilated cardiomyopathy, acute spinal cord injury, Huntington's disease, glaucoma,
15 macular degeneration, diabetic neuropathy, diabetic nephropathy and cancer in a mammal, comprising administering to said mammal a NOS inhibiting effective amount of a compound according to claim 1.

INTERNATIONAL SEARCH REPORT

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Intern. Appl. No. PCT/IB 98/01229	
A. CLASSIFICATION OF SUBJECT MATTER IPC 6 C07D401/10 A61K31/495 A61K31/44 A61K31/445 A61K31/47 C07D405/10 C07D213/73 C07D413/10 A61K31/535 C07D401/12 C07D405/12 C07D405/14 C07D453/02 C07D491/04	
According to International Patent Classification (IPC) or to both national classification and IPC	
B. FIELDS SEARCHED Minimum documentation searched (classification system followed by classification symbols) IPC 6 C07D A61K	
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched	
Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)	
C. DOCUMENTS CONSIDERED TO BE RELEVANT	
Category *	Citation of document, with indication, where appropriate, of the relevant passages Relevant to claim No
P,A	WO 98 24766 A (LOWE JOHN ADAMS III ; PFIZER (US)) 11 June 1998 see claim 1
P,A	WO 97 36871 A (WHITTLE PETER JOHN ; LOWE JOHN ADAMS III (US); PFIZER (US)) 9 October 1997 see claim 1
	--- -/--
☒ Further documents are listed in the continuation of box C ☒ Patent family members are listed in annex	
* Special categories of cited documents "A" document defining the general state of the art which is not considered to be of particular relevance "E" earlier document but published on or after the international filing date "L" document which may throw doubt on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) "O" document referring to an oral disclosure, use, exhibition or other means "P" document published prior to the international filing date but later than the priority date claimed "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention "X" document of particular relevance, the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone "Y" document of particular relevance, the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art "Z" document member of the same patent family	
Date of the actual completion of the international search	Date of mailing of the international search report
15 September 1998	23.09.98
Name and mailing address of the ISA European Patent Office, P. B. 5818 Patentkanal 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx 31 851 epo nl Fax (+31-70) 340-3015	Authorized officer Gettins, M

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INTERNATIONAL SEARCH REPORT

Int. Appl. No.
PCT/IB 98/01229

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No
A	PATENT ABSTRACTS OF JAPAN vol. 97, no. 9, 30 September 1997 & JP 09 132529 A (ONO PHARMACEUTICAL CO. LTD.), 20 May 1997, see abstract	1-9
A	& DATABASE WPI Week 9730 Derwent Publications Ltd., London, GB; AN 328451 see abstract	1-9
A	--- PATENT ABSTRACTS OF JAPAN vol. 97, no. 3, 31 March 1997 & JP 08 311028 A (JAPAN TOBACCO INC), 26 November 1996, see abstract	1-9
A	--- WO 96 18616 A (MERCK & CO INC ;ESSER CRAIG K (US); HAGMANN WILLIAM K (US); HOFFMA) 20 June 1996 see claim 1	1-9
A	--- EP 0 657 459 A (CHEM PHARM FORSCH GMBH) 14 June 1995 Compounds (II) see claim 5 -----	1-9

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215

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB 98/01229

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

- ☒ Claims Nos.:
because they relate to subject matter not required to be searched by the Authority, namely:
Although claims 5, 7 and 9 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
- ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
- ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

- ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
- ☐ As all searchable claims could be searched without effort justifying an additional fee, the Authority did not make payment of any additional fee.
- ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
- ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
☐ No protest accompanied the payment of additional search fees

Form PCT/ISA/210 (continuation of first sheet (1)) (July 1992)

INTERNATIONAL SEARCH REPORT

Information on patent family members

Intern. Appl. No.

PCT/IB 98/01229

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9824766 A	11-06-1998	NONE	
WO 9736871 A	09-10-1997	AU 1554897 A	22-10-1997
WO 9618616 A	20-06-1996	AU 4515696 A	03-07-1996
EP 0657459 A	14-06-1995	AT 400845 B	25-03-1996
		AT 246193 A	15-08-1995
		CA 2137443 A	07-06-1995
		CN 1111634 A	15-11-1995
		JP 7252260 A	03-10-1995
		NO 944680 A	07-06-1995

Form PCT/ISA/210 (patent family annex) (July 1992)



Analysis of D₂ and D₃ Receptor-Selective Ligands in Rats Trained to Discriminate Cocaine from Saline

K. J. GARNER AND L. E. BAKER

Department of Psychology, Western Michigan University, Kalamazoo, MI 49008

GARNER, K. J. AND L. E. BAKER. *Analysis of D₂ and D₃ receptor-selective ligands in rats trained to discriminate cocaine from saline.* PHARMACOL BIOCHEM BEHAV 64(2) 373-378, 1999.—This study examined the role of dopamine D₂ receptors in the stimulus generalization produced by 7-OH-DPAT and PD 128907 in rats trained to discriminate cocaine from saline. Twelve male Sprague-Dawley rats were trained to discriminate cocaine (10 mg/kg) from saline in a two-choice operant procedure using a FR20 schedule of water reinforcement. Stimulus generalization tests were administered with the D₂-preferring agonists (±)-7-OH-DPAT (0.01–0.3 mg/kg), (+)-7-OH-DPAT (0.01–0.3 mg/kg), and PD 128907 (0.01–0.3 mg/kg), and the selective D₂ agonist PNU-39156 (0.01–0.3 mg/kg). Complete generalization to cocaine was observed with (±)-7-OH-DPAT at doses that markedly suppressed response rate. Only partial stimulus generalization was observed with (+)-7-OH-DPAT and PD 128907 when these compounds were administered intraperitoneally, although subcutaneous injections of these compounds produced complete substitution. Response rate was also significantly reduced by these compounds. The selective D₂ agonist, PNU-91356 also fully substituted for the cocaine cue and suppressed response rate in a dose-dependent manner. To ascertain the importance of D₂ receptor actions in the stimulus generalization produced by (±)-7-OH-DPAT (0.1 mg/kg) and PD-128907 (0.3 mg/kg), the fairly selective D₂ antagonist, PNU-99194A (2.5–20 mg/kg) was also tested in combination with these compounds. Although PNU-99194A partially attenuated the stimulus generalization produced by (±)-7-OH-DPAT, it failed to block PD-128907 substitution for cocaine. These results indicate at least some involvement of D₂ receptors in the stimulus effects of (±)-7-OH-DPAT, although further investigations are clearly warranted. The present results also suggest that the cue properties of cocaine may be dissociated from the locomotor activating effects of this drug, because D₂/D₃ receptor agonists suppress locomotor activity but produce stimulus generalization to cocaine. © 1999 Elsevier Science Inc.

Cocaine D₂ Receptors D₂ Receptors 7-OH-DPAT PD 128907 PNU-91356 Drug discrimination

THE dopamine D₂ receptor has received considerable attention in recent investigations of the reinforcing and discriminative stimulus properties of cocaine. For example, the putative D₂ agonist, 7-hydroxy-N,N-di-n-propyl-2-aminotetralin (7-OH-DPAT) has been reported to shift the cocaine dose-response function to the left in animals trained to self-administer cocaine (8,22). Other researchers have noted that D₂-preferring antagonists reduce the breaking point in animals maintained on a progressive ratio of cocaine self-administration (25–27). These data suggest a potential modulatory role of the D₂ receptor in the reinforcing properties, and thereby, abuse liability of cocaine.

Presently, the role of D₂ receptors in cocaine's abuse potential remains highly speculative because D₂ receptor functions are not well understood. This is largely due to the lack

of highly selective D₂ receptor ligands for investigation. However, several compounds have been reported to bind with moderate selectivity to D₂ over D₃ receptors. For instance, 7-OH-DPAT has been reported to have as much as a 100-fold greater affinity for D₂ over D₃ receptors (7,20), and PD 128907 has been reported to exhibit a 300-fold or greater D₂:D₃ selectivity (15,24).

Drug discrimination procedures are frequently employed to characterize novel compounds and investigate their receptor mechanisms. It is generally well established that drugs with similar pharmacological mechanisms exhibit generalization to one another in drug discrimination investigations. In an attempt to characterize the role of D₂ receptor mechanisms in the discriminative stimulus effects of psychostimulant drugs, a number of recent studies have examined the ef-

Requests for reprints should be addressed to Lisa E. Baker, Department of Psychology, Western Michigan University, Kalamazoo, MI 49008.

feets of putative D₁ agonists in rats or monkeys trained to discriminate cocaine or *d*-amphetamine (1,4,6,19,28,30).

Several investigators have shown either complete or partial generalization to D₂-preferring agonists in rats trained to discriminate cocaine (1,19,28) or *d*-amphetamine (4,6). However, D₂-preferring antagonists [$(+)$ -A376, $(-)$ -11H232, $(-)$ -DS121] have been reported to only partially attenuate the discrimination of cocaine (10,11) and the more selective D₂ antagonist PN11-99194A [5,6-di-methoxy-2-(di-propylamino)indan-hydrochloride] does not block cocaine discrimination (3,4). In a recent study, we reported that PN11-99194A also does not block the stimulus generalization produced by $(+)$ -7-OH-DPAT in rats trained to discriminate *d*-amphetamine (4). These data question the importance of D₂ receptor modulation of the discriminative stimulus effects of $(-)$ -7-OH-DPAT. Moreover, $(-)$ -7-OH-DPAT failed to produce complete generalization for cocaine, indicating that D₂ receptors may also be important in mediating the cocaine cue (4). However, the training dose of cocaine is clearly an important determinant of stimulus generalization. Although we observed only partial substitution for 5 mg/kg cocaine (4), Acri et al. (1) reported complete substitution with $(-)$ -7-OH-DPAT in rats trained to discriminate 10 mg/kg cocaine. The present study further evaluated D₂ agonists for stimulus generalization to 10 mg/kg cocaine.

Several researchers have investigated the role of D₂ receptors in the discriminative stimulus effects of cocaine in tests of substitution with a variety of agonists (5,9,17,29,32) and in combination tests with antagonists (2,5,9,12,13,17,21,32). The results of these studies have led to the general conclusion that D₂ receptor activation alone is not sufficient to produce cocaine-like discriminative stimulus effects (17,32). The development of more selective ligands for both D₂ and D₁ receptors may differentiate the functional roles of these receptors in the behavioral effects of cocaine. PN11-91356 [(R)-5,6-Dihydro-5-(propylamino)-4h-imidazo[4,5-f]quinolin-2-(1H)-one, monohydrochloride] is a highly selective D₂ agonist (23). One aim of the present study was to examine this compound for stimulus generalization to cocaine and to compare its effects to those of the moderately selective D₂ agonists 7-OH-DPAT and PD 128907. In addition, this study further examined the ability of the highly selective D₁ antagonist PN11-99194A to block the stimulus generalization produced by $(-)$ -7-OH-DPAT and PD 128907.

MATERIALS

Subjects

The subjects were 12 male Sprague-Dawley rats (Harlan Breeding Laboratories, Indianapolis, IN) aged 60–90 days and weighing 250–300 g at the beginning of the study. For the duration of the study, rats were housed individually in wire mesh cages, in a colony maintained on a 12 L:12 D cycle (0700 to 1900 h) and at a relatively constant temperature (20–22°C) and humidity (50–65%). Commercial rat feed was provided *ad lib*, and water was restricted to amounts received during 20-min training sessions and an additional 15 min per day. In addition, free access to water was given for 24 h approximately every 7 days. The animals were maintained in accordance with the general principles of animal husbandry outlined by the National Institutes of Health, and the experimental protocol was reviewed and approved by the Institutional Animal Care and Use Committee of Western Michigan University.

Apparatus

Training and testing sessions were conducted in eight standard operant chambers (MED Associates Inc., St. Albans, VT; ENV-001), housed in sound- and light-attenuating shells to provide ventilation and masking noise. Each chamber contained an overhead 28-V houselight and a liquid reinforcer delivery mechanism (0.1 ml) that was mounted equidistant between two levers on the front panel of the chamber. A Zenith 320-SX microcomputer programmed with MED-PC instrumentation and software (MED Associates Inc., St. Albans, VT; version 2.0) was used to control experimental events and data collection.

Drugs

$(-)$ -7-OH-DPAT, PN11-91356, and PN11-99194A were generously provided by Pharmacia and Upjohn, Inc. (Kalamazoo, MI). Cocaine hydrochloride was provided by the National Institute on Drug Abuse (Rockville, MD). $(+)$ -7-OH-DPAT and PD 128907 were purchased from Research Biochemicals International (Natick, MA). All drugs were dissolved in sterile bacteriostatic (0.9%) saline. Cocaine was administered intraperitoneally (IP). $(-)$ -7-OH-DPAT and PN11-99194A were administered subcutaneously (SC). $(+)$ -7-OH-DPAT, PD 128907 and PN11-91356 were administered by both IP and SC injection. All doses of each drug were calculated based on the salt.

Training Procedures

Twelve rats were trained to discriminate cocaine (10.0 mg/kg, IP) from saline using a two-lever operant task under a fixed-ratio 20 (FR20) schedule of water reinforcement. Drug or saline injections were administered 15 min prior to the beginning of training sessions. Half the animals in each training group were reinforced with water (0.1 ml) for responding on the right lever after drug injections and on the left lever after saline injections. Conditions were reversed for the remaining animals. Levers were wiped with isopropyl alcohol before each session to reduce the influence of olfactory stimuli on lever pressing (16).

Training sessions lasted for 20 min, and were conducted 6 days per week. Drug and saline injections were given in a pseudorandom order, with the limitation that no more than two consecutive sessions occurred under the same condition. Training under each condition began on a FR1 schedule. Once responding was stable, the number of consecutive correct responses required for reinforcement was gradually increased until the final FR20 was reached. The criterion for discrimination was set at a minimum of 80% correct-lever selection prior to the delivery of the first reinforcer for 10 consecutive training sessions. Each subject was required to meet this criterion before testing began.

Testing Procedures

Stimulus generalization tests were conducted with several doses of cocaine (0, 2.5, 5.0, and 10.0 mg/kg), the D₂-preferring agonists, $(+)$ -7-OH-DPAT (0.01, 0.03, 0.10, and 0.30 mg/kg), $(-)$ -7-OH-DPAT (0.01, 0.03, 0.10, and 0.30 mg/kg), and PD 128907 (0.01, 0.03, 0.10, and 0.30 mg/kg), and the D₂-selective agonist, PN11-91356 (0.01, 0.03, 0.10, and 0.30 mg/kg). For stimulus generalization tests, all injections were administered 15 min prior to test sessions. Additionally, the D₂-preferring antagonist PN11-99194A (2.5, 5.0, 10.0, and 20.0 mg/kg, SC, 30 min) was administered in combination with $(-)$ -7-OH-DPAT (0.1 mg/kg SC, 15 min) and in combination PD-128907 (0.3

mg/kg SC, 15 min). Test sessions were conducted in a similar manner to training session with the exception that no reinforcers were delivered and each animal was removed from the chamber upon completion of 20 consecutive responses on either lever or when 20 min elapsed, whichever occurred first. For each drug tested, the order of doses was counterbalanced among subjects, and half the animals received tests after drug maintenance sessions while the other half received tests after saline maintenance sessions. Subjects were administered at least two training sessions between test sessions, and were required to maintain the 80% criterion under both training conditions before each test.

Data Analysis

Dose-response data were presented as the percent of total responses made on the drug-appropriate lever during test sessions. Response rate was presented as the number of responses made (on either lever) per second during test sessions. For each dose tested, the mean and SEM were calculated for each of these dependent measures. In the event that an animal did not complete at least 15 total responses during a test session, the percentage of drug-lever responses for that test was not included in the statistical analyses. Drug-lever selection that was 80% or greater was considered evidence for stimulus generalization. Drug-appropriate responding between 20 and 80% was considered evidence for partial substitution. For drugs that produced stimulus generalization, the dose-response curve was also analyzed using a nonlinear regression, and ED₅₀s and confidence intervals were calculated. One-way analyses of variance were conducted on response rate data. Statistical analyses were conducted using the software GraphPad Prism (GraphPad, Inc., San Diego, CA).

RESULTS

All subjects met the discrimination criterion stated above. The mean number of sessions to criterion was 54.67 (SEM = 4.11, range: 37-79). After meeting the initial criterion for discrimination, four animals began to exhibit poor stimulus control due to equipment failure. After the equipment problem was fixed, these animals were required to meet the discrimination criterion (10 consecutive sessions above 80% correct lever selection prior to first reinforcer) again before they were administered test sessions.

The cocaine dose-response curve and results of stimulus generalization tests are displayed in Fig. 1. The ED₅₀ for cocaine was 1.34 mg/kg (95% confidence intervals: 0.36-4.93 mg/kg). (+)-7-OH-DPAT substituted for cocaine in a dose-dependent manner (ED₅₀ = 0.02 mg/kg; 95% confidence intervals: 0.006-0.09 mg/kg). This compound also dose dependently reduced response rate, and this effect was statistically significant, $F(3, 47) = 6.11$, $p < 0.05$. Both 0.1 and 0.3 mg/kg produced complete stimulus generalization and reduced response rate significantly below saline control levels ($p < 0.01$). Eight of the 12 animals tested at 0.1 mg/kg completed the response requirement, and all eight exhibited complete stimulus generalization. Seven of the 12 animals tested at 0.3 mg/kg completed the response requirement, and six of these animals exhibited complete stimulus generalization.

(+)-7-OH-DPAT (IP) also produced dose-dependent increases in drug-appropriate responding; however, this compound produced only partial substitution at 0.3 mg/kg. Higher doses were not examined because eight of the 12 animals produced six or fewer responses when tested at this dose. Of the four animals that did complete the FR requirement, three ex-

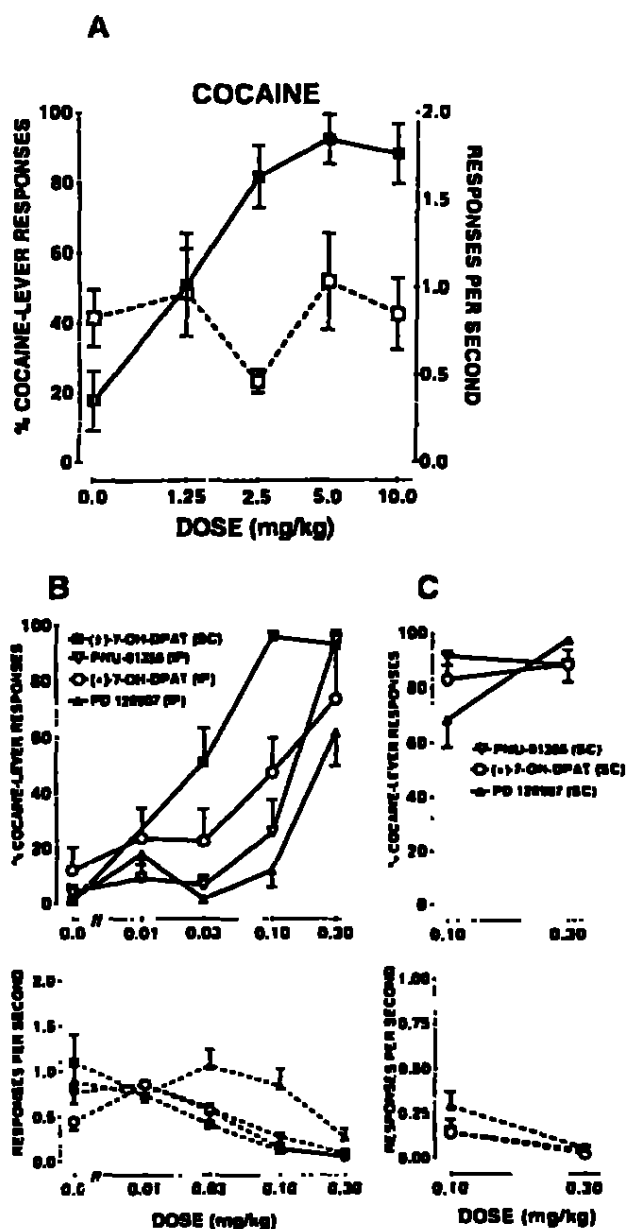


FIG. 1 (A) Cocaine dose response curve: percent cocaine lever responses and response rate ($n = 12$). (B) Results of stimulus generalization tests with (+)-7-OH-DPAT, (+)-7-OH-DPAT (IP), PN110919, and PN110919 + (+)-7-OH-DPAT in rats trained to discriminate cocaine (10 mg/kg) from saline ($n = 12$). (C) Results of stimulus generalization tests with (+)-7-OH-DPAT ($n = 12$), PN110919 ($n = 11$), and PN110919 + (+)-7-OH-DPAT ($n = 11$) following SC injection. In B and C, the percentage of cocaine lever responses is indicated in the top graph, and response rate is indicated in the bottom graph. See text for details regarding the number of animals that completed the response requirements during tests.

hibited complete stimulus generalization. The response rate suppression produced by (+)-7-OH-DPAT was statistically significant, $F(4, 59) = 6.72$, $p < 0.001$. Subjects were also tested with two doses of this compound (0.1 and 0.3 mg/kg) following SC injection (see Fig. 1C). Of the 10 animals that

completed the FR requirement, nine exhibited complete stimulus generalization following administration of the 0.1 mg/kg dose of (+)-7-OH-DPAT. Five animals completed the FR requirement following SC administration of 0.3 mg/kg, and four of these animals exhibited complete stimulus generalization.

When administered IP, PD 128907 also produced only partial substitution for cocaine. Ten animals completed at least 20 responses during substitution tests with 0.3 mg/kg. Two of these animals emitted 0% drug-appropriate responses, four animals emitted between 45 and 70% drug-appropriate responses, and four animals emitted greater than 90% drug-appropriate responses. Ten animals were also administered SC injections of PD 128907 (0.1 and 0.3 mg/kg). Nine animals completed the response requirement following the 0.3 mg/kg dose, and all nine exhibited complete generalization. This compound also significantly reduced response rate, $F(4, 59) = 3.75, p < 0.01$.

The selective D_2 agonist, PNU-99194A, produced dose-dependent increases in drug-appropriate responding and produced complete substitution for cocaine when administered IP (1.12, $\pm$ 0.16 mg/kg). Nine animals completed the response requirement following 0.3 mg/kg, and all nine exhibited complete stimulus generalization at this dose. Subcutaneous injections of this compound also produced complete substitution at both 0.1 and 0.3 mg/kg, although only five animals completed the response requirement following 0.3 mg/kg (SC). This compound also produced statistically significant response rate suppression, $F(4, 59) = 6.47, p < 0.001$.

Figure 2 depicts the effects of PNU-99194A on the stimulus generalization produced by (+)-7-OH-DPAT (0.1 mg/kg) and PD 128907 (0.3 mg/kg); this D_2 -preferring antagonist did not block the substitution of PD 128907, and only partially blocked the substitution of (+)-7-OH-DPAT. This partial antagonism only occurred at the highest dose of PNU-99194A. Of the six animals that completed the response requirement during tests with 20 mg/kg PNU-99194A and (+)-7-OH-DPAT, four emitted between 25 and 70% of their responses on the cocaine-appropriate lever, and two exhibited greater than 90% drug-appropriate responding. Three of the six animals administered 20 mg/kg PNU-99194A with PD 128907 were severely disrupted and made no responses. Thus, higher doses of PNU-99194A were not examined in combination with PD 128907.

DISCUSSION

The results of this study support previous findings that moderately selective dopamine D_2 receptor agonists produce stimulus generalization in rats trained to discriminate cocaine. As noted by Acri et al. (1), complete substitution occurs at doses that severely disrupt responding. The present results demonstrated only partial substitution for cocaine with PD 128907 and (+)-7-OH-DPAT when these compounds were administered by IP injection. However, the two highest doses (0.1 and 0.3 mg/kg) were also tested following SC injection, and evidence for complete stimulus generalization was observed. This is likely due to better drug absorption via the SC route. The racemic mixture of 7-OH-DPAT was also administered by SC injection, and produced full substitution for cocaine.

The present results suggest that the stimulus properties of cocaine may be dissociated from the locomotor activation produced by this drug. As mentioned above, the D_2/D_3 agonists markedly reduced response rates in the present study. Observations of the animals following administration of higher doses indicated sedative effects and a general decline

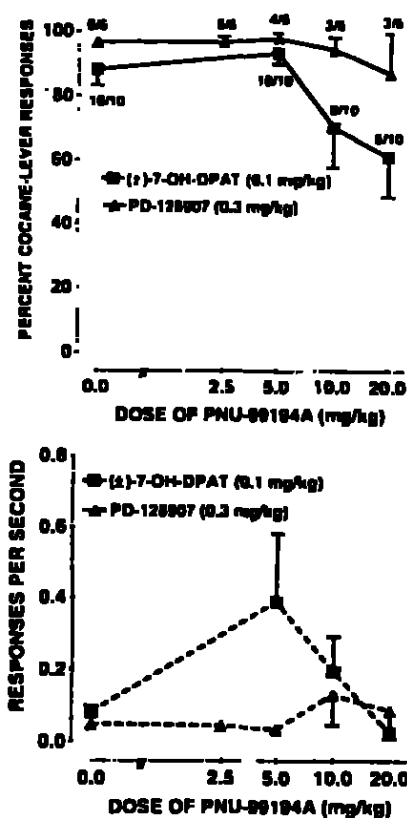


FIG. 2. Effects of PNU-99194A on the stimulus generalization produced by (+)-7-OH-DPAT (0.1 mg/kg SC; $n = 10$) or PD 128907 (0.3 mg/kg SC; $n = 6$) in rats trained to discriminate cocaine (10 mg/kg) from saline. The percentage of cocaine-lever responses is indicated in the top graph, and response rate is indicated in the bottom graph. The number of animals that completed the response requirement and the number of animals that were tested at each dose are represented in the figure as n/N .

in activity. This is consistent with previous reports that both 7-OH-DPAT and PD 128907 reduce locomotor activity in rats (14). In contrast, D_2 antagonists have been noted to produce locomotor activation, especially in rats habituated to their surroundings (18,31). Previous studies clearly indicate that D_2 antagonists do not mimic cocaine's discriminative stimulus effects (3,4,10,11).

The highly selective D_2 agonist, PNU-99194A also exhibited full substitution for cocaine in the present study. Following IP administration, this compound exhibited more complete substitution than either (+)-7-OH-DPAT or PD 128907 at an equivalent dose. Former research with other D_2 receptor agonists in tests of stimulus generalization to cocaine have provided inconsistent findings. For example, some investigators reported complete substitution with quinpirole in rats (5,9), while others reported only partial substitution with this compound and a variety of other D_2 selective agonists (32). Additionally, quinpirole did not substitute for cocaine in monkeys (17). Investigations of D_2 antagonists on cocaine discrimination have also produced some inconsistent findings. Although several researchers have reported that the D_2 antagonist haloperidol fails to completely block the discriminative stimulus

effects of cocaine (2,5,12,13,21,32), others have observed haloperidol to block the cocaine cue (9,17).

Despite these somewhat equivocal results, it has been suggested that D₁ receptor activation alone is insufficient to produce cocaine-like discriminative stimulus effects (17,32). However, with the development of more selective D₁ receptor ligands, the role of D₁ receptor actions in cocaine's discriminative stimulus effects warrants further investigation. Although previously considered a relatively selective D₁ agonist, quinpirole has an equivalent binding affinity for D₁ and D₂ receptors (23). Furthermore, although the agonists 7-OH-DPAT and PD 128907 bind with moderate selectivity to D₁ receptors, they also have relatively high affinities for D₂ receptors. Thus, the specific role of D₁ vs. D₂ receptors in the cocaine-like discriminative stimulus effects observed with these compounds (1) are still unclear.

The present study attempted to differentiate the relative importance of D₁ vs. D₂ receptors in the discriminative stimulus effects of cocaine by 1) comparing a highly selective D₁ agonist to moderately selective D₁ agonists, and 2) by challenging the substitution of (±)-7-OH-DPAT and PD 128907 for cocaine with a D₁ antagonist. PN11-91356 has an approximately 30-fold higher K_i for D₂ receptors than for D₁ receptors (23). Thus, the present results suggest that selective D₁ receptor activation may be sufficient to produce cocaine-like discriminative stimulus effects. However, investigations utilizing selective D₁ antagonists to challenge the substitution of D/D₁ agonists for cocaine are required to confirm this conclusion. Recent investigations by Spelman (28) examined the substitution of PD 128907 for cocaine in monkeys, then assessed three D₂ antagonists (nemonapride, eticlopride, and YM-43611) with differing affinities for D₂ receptors in combination with PD 128907. He reported that the order of potency with which these antagonists attenuated the substitution of PD 128907 for cocaine corresponded to the order of affinity of these compounds at cloned human D₂ receptors. Other researchers have also assessed the effects of eticlopride on the stimulus generalization produced by (±)-7-OH-DPAT in rats

trained to discriminate *d*-amphetamine, and reported that (±)-7-OH-DPAT substitution was partially blocked by this D₂/D₁ antagonist (6).

Previous investigations from our laboratory (4) indicated that the relatively selective D₁ antagonist PN11-99194A does not block (±)-7-OH-DPAT substitution for cocaine (5 mg/kg) or *d*-amphetamine (1 mg/kg). However, the present findings demonstrate partial antagonism of (±)-7-OH-DPAT substitution for cocaine (10 mg/kg). These results suggest at least some involvement of D₁ receptors in modulating the discriminative stimulus effects of (±)-7-OH-DPAT. It is intriguing, though, that PN11-99194A failed to block the substitution of PD-128907, which is reported to have a greater D₁ receptor affinity than (±)-7-OH-DPAT (15,24). Clearly, additional investigations are warranted. To investigate the importance of D₁ receptors in the stimulus effects of these D/D₁ agonists, we are also currently investigating the highly selective D₂ antagonist, remoxipride, for blockade of PD-128907 and (±)-7-OH-DPAT substitution. Preliminary data suggest that remoxipride (0.1-3.0 mg/kg) does not antagonize the stimulus generalization produced by these compounds. In addition, to further examine the role of D₁ receptors in mediating the discriminative stimulus effects of 7-OH-DPAT, we are also currently testing the effects of PN11-99194A in rats trained to discriminate the (+)-isomer of this compound. Preliminary findings also indicate partial antagonism of the (+)-7-OH-DPAT cue by PN11-99194A.

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REFERENCES

1. Acri, J. H.; Carter, S.; Alling, K.; Gietter-Dougliss, B.; Dijkstra, D.; Wikstrom, H.; Katz, J.; Witkin, J.: Assessment of cocaine-like discriminative stimulus effects of dopamine D₁ receptor ligands. *Eur. J. Pharmacol.* 281:R7-R9; 1995.
2. Baker, L. E.; Riddle, F. E.; Saunders, R. H.; Appel, J. B.: The role of monoamine uptake in the discriminative stimulus effects of cocaine and related compounds. *Behav. Pharmacol.* 4:69-79; 1993.
3. Baker, L. E.; Miller, M. E.; Svensson, K.: Assessment of the discriminative stimulus effects of the selective dopamine D₁ antagonist PN11-99194A in rats: Comparison to psychostimulants. *Behav. Pharmacol.* 8:243-252; 1997.
4. Baker, L. E.; Svensson, K. A.; Garner, K. J.; Goodwin, A. K.: The dopamine receptor antagonist PN11-99194A fails to block (+)-7-OH-DPAT substitution for *d*-amphetamine or cocaine. *Eur. J. Pharmacol.* 358:101-109; 1998.
5. Barrett, R. L.; Appel, J. B.: Effects of stimulation and blockade of dopamine receptor subtypes on the discriminative stimulus properties of cocaine. *Psychopharmacology (Berlin)* 92:13-16; 1989.
6. Bevens, R. A.; Klebaur, J. E.; Ward, M. T.: 7-OH-DPAT has *d*-amphetamine-like discriminative stimulus properties. *Pharmacol. Biochem. Behav.* 58:485-490; 1997.
7. Burris, K. D.; Pacheco, M. A.; Fritz, T. M.; Kung, M.-P.; Kung, H. F.; Molinoff, P. B.: Lack of discrimination by agonists for D₁ and D₂ dopamine receptors. *Neuropsychopharmacology* 12:333-345; 1995.
8. Caine, S. B.; Koob, G. F.: Pretreatment with the dopamine agonist 7-OH-DPAT shifts the cocaine self-administration dose-effect function to the left under different schedules in the rat. *Behav. Pharmacol.* 6:333-347; 1995.
9. Callahan, P. M.; Cunningham, K. A.: Discriminative stimulus properties of cocaine in relation to dopamine D₁ receptor function in rats. *J. Pharmacol. Exp. Ther.* 266:585-592; 1993.
10. Callahan, P. M.; Piercey, M. F.; Cunningham, K. A.: Effects of putative dopamine autoreceptor antagonists (+)-AJ 76 and (+)-UH 232 on the discriminative stimulus properties of cocaine. *Psychopharmacology (Berlin)* 107:73-77; 1992.
11. Clark, D.; Exner, M.; Furnidge, L. J.; Svensson, K.; Svensson, C.: Effects of the dopamine autoreceptor antagonist (-)-DS 121 on the discriminative stimulus properties of *d*-amphetamine and cocaine. *Eur. J. Pharmacol.* 274:67-74; 1995.
12. Colpaert, F. C.; Niemegeers, C. J. E.; Janssen, P. A. J.: Neuroleptic interference with the cocaine cue: Internal stimulus control of behavior and psychosis. *Psychopharmacology (Berlin)* 58:247-255; 1978.
13. Colpaert, F. C.; Niemegeers, C. J. E.; Janssen, P. A. J.: Discriminative stimulus properties of cocaine and *d*-amphetamine and antagonism by haloperidol: A comparative study. *Neuropharmacology* 17:937-942; 1978.
14. Daly, S. A.; Waddington, J. L.: Behavioural effects of the putative D₁ dopamine receptor agonist 7-OH-DPAT in relation to other "D₁-like" agonists. *Neuropharmacology* 32:509-510; 1993.

15. DeMattos, S. B.; Pugsley, T. A.; Shih, Y. S.; Whetzel, S. Z.; George, L. M.; VanLeeuwen, D. H.; MacKenzie, R. G.; Smith, S. J.; Gilase, S. A.; Wise, L. D.; Helfner, T. G. Identification and characterization of a dopamine D₂ selective compound, PD 128907. *Soc. Neurosci. Abstr.* 19:77; 1993.
16. Etance, K.; Goudie, A. J. Inter-animal olfactory cues in operant drug discrimination procedures in rat. *Psychopharmacology (Berlin)* 91:67-73; 1981.
17. Kleven, M. S.; Anthony, E. W.; Woolverton, W. L. Pharmacological characterization of the discriminative stimulus effects of cocaine in rhesus monkeys. *J. Pharmacol. Exp. Ther.* 254:312-317; 1990.
18. Kling-Petersen, T.; Ljung, E.; Wulter, L.; Svensson, K. Effects of the dopamine D₂- and autoreceptor preferring antagonist (+)-108 121 on locomotor activity, conditioned place preference and intracranial self-stimulation in the rat. *Behav. Pharmacol.* 6:107-115; 1995.
19. Lomas, X.; Negus, S. S.; Nader, M. A.; Mello, N. K. Effects of the putative dopamine D₂ receptor agonist 7-OH-DPAT in rhesus monkeys trained to discriminate cocaine from saline. *Psychopharmacology (Berlin)* 124:306-314; 1996.
20. Levesque, D.; Diaz, J.; Pilon, C.; Martres, M.; Giros, B.; Saud, E.; Schott, D.; Mogat, J.; Schwartz, J.; Sokoloff, P. Identification, characterization and localization of the dopamine D₂ receptor in rat brain using 7-[³H]-hydroxy-N,N-di-n-propyl-2-aminotetralin. *Proc. Natl. Acad. Sci. USA* 89:8155-8159; 1992.
21. McKenna, M. L.; Ho, B. T. The role of dopamine in the discriminative stimulus properties of cocaine. *Neuropharmacology* 19:297-303; 1980.
22. Parsons, L. H.; Caine, S. B.; Sokoloff, P.; Schwartz, J. C.; Koob, G. F.; Weiss, F. Neurochemical evidence that postsynaptic nucleus accumbens D₂ receptor stimulation enhances cocaine reinforcement. *J. Neurochem.* 3:1078-1089; 1996.
23. Piercey, M. F.; Camacho-Ochoa, M.; Smith, M. W. Functional roles for dopamine receptor subtypes. *Chin. Neuropharmacol.* 18:S34-S42; 1995.
24. Pugsley, T. A.; Davis, M. D.; Akumbe, H. C.; MacKenzie, R. G.; Shih, Y. H.; Damsma, G.; Wikstrom, H.; Whetzel, S. Z.; George, L. M.; Croke, L. W.; DeMattos, S. B.; Corbin, A. E.; Gilase, S. A.; Wise, L. D.; Dykstra, D.; Helfner, T. G. Neurochemical and functional characterization of the preferentially selective D₂ agonist PD 128907. *J. Pharmacol. Exp. Ther.* 275:1355-1366; 1995.
25. Richardson, N. R.; Piercey, M. F.; Svensson, K.; Collins, R. J.; Myers, J. E.; Roberts, D. C. S. Antagonism of cocaine self-administration by the preferential dopamine autoreceptor antagonist, (+)-AJ 76. *Brain Res.* 619:15-21; 1993.
26. Roberts, D. C. S.; Randall, R. Effect of dopaminergic drugs on cocaine reinforcement. *Chin. Neuropharmacol.* 18:S84-S95; 1995.
27. Smith, A.; Piercey, M. F.; Roberts, D. C. S. Effects of (+)-108 121 and (+)-UH 232 on cocaine self-administration in rats. *Psychopharmacology (Berlin)* 120:93-98; 1995.
28. Spearman, R. D. Dopamine D₂ receptor agonists partially reproduce the discriminative stimulus effects of cocaine in squirrel monkey. *J. Pharmacol. Exp. Ther.* 278:1128-1137; 1996.
29. Spearman, R. D.; Bergman, J.; Madras, B. K.; Meba, K. F. Discriminative stimulus effects of cocaine in squirrel monkeys. Involvement of dopamine receptor subtypes. *J. Pharmacol. Exp. Ther.* 259:945-953; 1991.
30. Varty, G. B.; Higgins, G. A. Investigations into the nature of a 7-OH-DPAT discriminative cue: Comparison with *D*-amphetamine. *Eur. J. Pharmacol.* 339:101-107; 1997.
31. Waters, N.; Svensson, K.; Haasma-Svensson, S. R.; Smith, M. W.; Carlsson, A. The dopamine D₂-receptor: A postsynaptic receptor inhibitory of rat locomotor activity. *J. Neural Transm.* 94:11-19; 1993.
32. Wilkin, J. M.; Nichols, D. E.; Terry, P.; Katz, J. L. Behavioral effects of selective dopaminergic compounds in rats discriminating cocaine injections. *J. Pharmacol. Exp. Ther.* 247:705-713; 1991.

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TI - D3-receptor test in vitro predicts decreased cocaine self-administration in rats

IN - Caine, S. Barak; Koob, George F.; Parsons, Loren H.; Everitt, Barry J.; Schwartz, Jean-Charles; Sokoloff, Pierre

CS - Department of Neuropharmacology, The Scripps Research Institute, La Jolla, CA, USA

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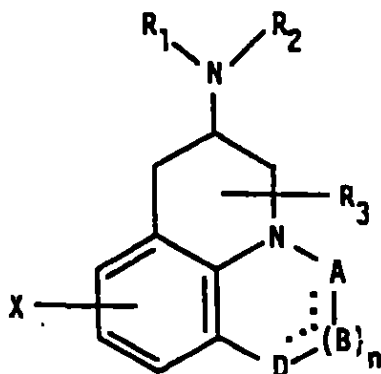
AB - The three dopamine agonists with highest reported D3 receptor selectivity in vitro, pramipexole, quinolorane and PD128,907, decreased self-administration of a high dose of cocaine in rats as a result of a leftward shift in the cocaine dose-effect function. In contrast the D3 preferring antagonist nafadotride increased cocaine self-administration. Moreover the relative potencies of these and other D2-like dopamine agonists (lisuride, 7-OH-DPAT, quinpirole, apomorphine, bromocriptine) to modulate cocaine self-administration were highly correlated with their relative potencies for increasing mitogenesis in vitro in cell lines expressing D3 but not D2 receptors. These results support the hypothesis that the D3 receptor may be an important target for pharmacotherapies for cocaine abuse and dependence.



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(54) Title: HETEROCYCLIC AMINES HAVING CENTRAL NERVOUS SYSTEM ACTIVITY



(I)

(57) Abstract

Tricyclic nitrogen containing compounds, having central nervous system activity of structural formula (I) and pharmaceutically acceptable salts thereof, wherein R_1 , R_2 , and R_3 are independently hydrogen, C_{1-6} alkyl, alkenyl, or alkynyl, C_{3-10} cycloalkyl, or R_1 and R_2 are joined to form a C_{2-7} cyclic amine which can contain additional heteroatoms; X is hydrogen, C_{1-6} alkyl, halogen, hydroxy, alkoxy, cyano, carboxamide, carboxyl, or carboalkoxyl; A is SO_2 , N , CH , CH_2 , $CHCH_3$, $C=O$, $C=S$, $C-SCH_3$, $C=NH$, $C-NH_2$, $C-NHCH_3$, $C-NHCOOCH_3$, or $C-NHCN$; B is CH_2 , CH , $C=O$, N , NH or $N-CH_3$; n is 0 or 1; and D is CH , CH_2 , $C=O$, O , N , NH or $N-CH_3$. These new compounds are suitable for treating schizophrenia, Parkinson's disease, anxiety, depression or as compounds for lowering blood pressure in animal or human hosts.

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HETEROCYCLIC AMINES HAVING CENTRAL NERVOUS SYSTEM ACTIVITY

Background of the Invention

The present invention is directed toward tricyclic nitrogen containing compounds, heterocyclic amines, having central nervous system activity. These new compounds are suitable for treating schizophrenia, Parkinson's disease, anxiety or as compounds for lowering blood pressure.

A series of dihydrophenalenes, tricyclic amine substituted compounds, and related compounds having central nervous system activity were described in PCT Int. Pub. No. WO87/04153 and in PCT Int. Pub. No. WO88/04292. A major difference between those compounds and the present invention is that the subject compounds have at least one nitrogen atom in the tricyclic ring structure which is shared by two of the ring structures. Generally, the subject compounds have exhibited antipsychotic activity and better oral bioavailability.

Information Disclosure Statement

PCT Int. Pub. No. WO87/04153 and PCT Int. Pub. No. WO88/04292 each describe tricyclic structures having central nervous system activity.

U.S. Patent 4,110,339 discloses 4-(di-n-propyl)amino-1,3,4,5-tetrahydrobenz(cd)indole compounds useful as prolactin inhibitors and in the treatment of Parkinsonism. European Patent Application 153,083 and German Patent 3,346,573 disclose methoxy substituted 4-(di-n-propyl)amino-1,3,4,5-tetrahydrobenz(cd)indole compounds. These publications disclose nitrogen containing tricyclic ring structures but the nitrogen is not shared by any of the rings.

Evans, D. D., Peters, D. J., J. Chem. Soc., Perkin Trans. 1, pp 285-88 (1974) discloses nitrogen containing tricyclic ring structures where the nitrogen is shared by two ring structures but additionally includes other substituents not common to the subject compounds.

Summary of the Invention

In one aspect, the present invention is directed toward tricyclic nitrogen containing compounds of Formula I, having central nervous system activity and pharmaceutically acceptable salts. R₁, R₂, and R₃ are independently hydrogen, C₁₋₆ alkyl, C₃₋₅ alkenyl, or C₃₋₅ alkynyl, C₃₋₇ cycloalkyl or C₄₋₁₀ cycloalkyl- or phenyl-substituted alkyl, or R₁ and R₂ are joined to form a C₃₋₇ cyclic amine which can contain additional heteroatoms and/or unsaturation. X is

hydrogen, C₁₋₆ alkyl, halogen, hydroxy, alkoxy, cyano, carboxamide, carboxyl, or carboalkoxyl. A is SO₂, N, CH, CH₂, CHCH₃, C-O, C-S, C-SCH₃, C-NH, C-NH₂, C-NHCH₃, C-NHCOOCH₃, or C-NHCN. B is CH₂, CH, C-O, N, NH or N-CH₃ and n is 0 or 1. D is CH, CH₂, C-O, O, N, NH or N-CH₃. These new compounds are suitable for treating schizophrenia, Parkinson's disease, anxiety, depression, or as compounds for lowering blood pressure.

In another aspect, the invention is a novel compound of the structural formula XXXV' where W is O or H₂ and R₁' and R₂ are independently hydrogen or a C₁₋₄ alkyl group. This compound is useful as an intermediate in the preparation of compounds of Formula I. Preferred compounds are where W is H₂ and R₁ and R₂ are the same such as CH₃ or C₃H₇ groups.

In yet another aspect, the present invention is a method for treating central nervous system (CNS) disorders such as anxiety, depression, hypertension and associated high blood pressure, Parkinson's disease and schizophrenia in animal or human hosts by administering a pharmaceutically effective amount of a compound of Formula I including pharmaceutically acceptable salts. Other uses for these compounds include panic attacks, eating disorders, obsessive-compulsive disturbances seen in dementia disorders. In addition, central 5-HT receptor activation are believed to be involved in mediating sexual behavior. These compounds would be useful to stimulate sexual activity and to alleviate impotence.

Detailed Description of the Invention

The present invention describes compounds having central nervous system activity. The compounds are identified by a tricyclic ring structure having a nitrogen atom shared by two rings to which an amine substituent (NR₁R₂) is attached as structurally depicted by Formula I on the Formula Sheet, below. Generally, these structures include a variety of fused tricyclic organic compounds; structures are shown in the Formula sheets. The systematic names for the ring systems in these compounds may be found by consulting the Ring Systems Handbook, 1988 edition, published by Chemical Abstracts Service. These names are derived by combining the names of benzene or a monocyclic heterocycle with the name of a bicyclic heterocycle to which it is fused. The atoms and bonds common to the fused rings are then specified to distinguish it from isomeric systems with

similar names.

Included in the invention are the 5-aminoimidazo-(4,5,1-ij)-quinolines and 5-aminoimidazo(4,5,1-ij)quinolinones of Structure I (compounds 6-71), compounds more simply referred to as imidazo-
5 quinolines and imidazoquinolinones or 5-aminoimidazoquinolines and 5-aminoimidazoquinolinones. These particular compounds have been found to be active in various central nervous system screens such as hypothermia and hypoxic stress tests and have been found to be dopamine and serotonin such as, 5HT_{1A} receptor binding assay
10 antagonists.

The subject compounds are typically represented by Formula I wherein R₁, R₂ and R₃ are independently hydrogen, C₁₋₆ alkyl, C₃₋₅ alkenyl, C₃₋₅ alkynyl, C₃₋₇ cycloalkyl, or C₄₋₁₀ cycloalkyl- or phenyl-substituted alkyl, or R₁ and R₂ are joined to form a C₃₋₇
15 cyclic amine which can contain additional heteroatoms and/or unsaturation; X is hydrogen, C₁₋₆ alkyl, halogen, hydroxy, alkoxy, cyano, carboxamide, carboxyl, or carboalkoxyl; n is 0 or 1; and A is SO₂, N, CH, CH₂, CH-halogen, CHCH₃, C=O, C=S, C-SCH₃, C-NH, C-NH₂, C-NHCH₃, C-NHCOOCH₃, or C-NHCN; B is CH₂, CH, CH-halogen, O, C=O, N, NH
20 or N-CH₃; n is 0 or 1; and D is CH, CH₂, CH-halogen, C=O, O, N, NH or N-CH₃.

Examples of "C₁₋₆ alkyl" are methyl, ethyl, propyl, butyl, pentyl and hexyl and isomeric forms thereof.

Examples of "alkenyl" groups are C₃₋₅ straight or branched unsaturated hydrocarbons having at least one double bond such as propenyl or butenyl.
25

Examples of "alkynyl" groups are C₃₋₅ straight or branched unsaturated hydrocarbons having at least one triple bond such as propynyl or butynyl.

30 Examples of "C₃₋₇ cycloalkyl" are cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, or cycloheptyl. Examples of cycloalkyl-substituted alkyl include (cyclopropyl)methyl, or (cyclobutyl)-methyl. Examples of phenyl-substituted alkyl include phenylmethyl (benzyl), 1-(phenyl)ethyl or 2-(phenyl)ethyl, or 4-(phenyl)butyl.

35 "C₃₋₇ cyclic amine" means where the R₁ and R₂ groups are joined to form a ring including the attached nitrogen atom, examples azetidine, pyrrolidine, piperidine, 2-methylpyrrolidine. This ring may also contain additional "hetero atoms" which are nitrogen, oxygen

or sulfur and/or unsaturation, eg piperazine, N-methylpiperazine, morpholine, imidazole.

"Halogen" is defined as being any of F, Cl, Br or I.

5 "Alkoxy" is defined as a C₁₋₆ alkyl group attached to an oxygen atom, such as methoxy, ethoxy, isopropoxy.

"Carboxamide" is defined as the group -CONH₂.

"Carboalkoxyl" is defined as the group -COOR, where R is lower alkyl, such as carbomethoxy, carboethoxy.

10 "Thiocarbonyl" is defined as the group C-S, that is a carbonyl group in which the oxygen atom is replaced by sulfur.

"Sulfonyl" is defined as SO₂ in which the sulfur atom is attached to the adjacent ring atom groups.

15 "Pharmaceutically acceptable salts" are hydrochloride, hydrobromide, hydroiodide, sulfate, phosphate, acetate, propionate, lactate, maleate, malate, succinate, tartrate, cyclohexanesulfamates, methane-sulfonates, ethanesulfonates, benzenesulfonates, toluenesulfonates and other pharmaceutically acceptable counter ions for amines. Additionally, the compounds of this invention may be administered in a suitable hydrated form.

20 The compounds of Formula I may be prepared from methyl-substituted heterocycles of Formula II and substituted 3-aminotetrahydroquinolines of Formula III following the general procedures described in Schemes 1-7. Schemes and Formulas are shown below.

25 In Formula II, m is 0 or 1; when m is 0 then a double bond joins N to A. In Formula III, W is O or H₂ and D' may be nitro, amino, hydroxy or alkoxy; the remaining groups in Formulas II and III are as defined for I.

30 Some of the methyl substituted heterocycle intermediates required for the work are described in the chemical literature as indicated. Literature procedures for the syntheses of 3-aminotetrahydroquinolines have been reported and can be used to build the 8-substituted compounds of Structure III required in this work; the compounds of Structure III where D' is nitro, amino, hydroxy or alkoxy are new compounds.

35 For the preparation of compounds III and for the conversion of compounds II to I, malonate intermediates of Formulas VI and VII are required. For the preparation of these compounds a malonic acid diester IV, preferably the dimethyl, diethyl or methyl benzyl

diester, is reacted with bromine in carbon tetrachloride to afford the bromomalononic acid diester V. This is reacted with the appropriate amine in a suitable solvent such as methylene chloride, ether, or tetrahydrofuran. After separating the amine hydrochloride by-product and removing any excess amine, the substituted aminomalonate of Formula VI may be used without further purification, or may be purified by chromatography before further use. Amines which have been used in this reaction include dimethylamine, pyrrolidine, piperidine, morpholine, imidazole, 4-methylpiperazine, propylamine, and (R)- and (S)- α -methylbenzylamine to give the intermediates VI listed in Table 1. The mixed esters of Table 1 (compounds VII through VIq) are particularly useful, as the carbobenzyloxy group can be removed by catalytic hydrogenation. Intermediates VI d-h give tertiary amine products which can be debenzylated by catalytic hydrogenation to the corresponding secondary amine derivatives.

Table 1. Structures of Aminomalonates of Formula VI

Compound	Amine	R'	R"
VIa	dimethylamine	ethyl	ethyl
VIb	dipropylamine	ethyl	ethyl
20 VIc	propylamine	ethyl	ethyl
VI d	(phenylmethyl)methylamine	ethyl	ethyl
VI e	(phenylmethyl)propylamine	ethyl	ethyl
VI f	benzylamine	ethyl	ethyl
VI g	α -(1-phenylethyl)amine	ethyl	ethyl
25 VI h	(R)- α -(1-phenylethyl)amine	ethyl	ethyl
VI i	dimethylamine	methyl	benzyl
VI j	dipropylamine	methyl	benzyl
VI k	pyrrolidine	methyl	benzyl
VI m	piperidine	methyl	benzyl
30 VI n	morpholine	methyl	benzyl
VI p	imidazole	methyl	benzyl
VI q	4-methylpiperazine	methyl	benzyl

When a primary amine is reacted with a compound of Formula V, the initially formed product VI may be reacted with an acyl chloride, an alkyl- or benzyl-chloroformate, or with di *t*-butyl dicarbonate to give the amides and carbamates of Formula VII. In Formula VII, R₁' is hydrogen, alkyl, alkoxycarbonyl, or benzyloxycarbonyl; compounds VII e-VII f (Table 2) have been prepared in this way from compound VI c.

Other aminomalonates of Formula VII may be prepared from dialkyl aminomalonates such as diethyl aminomalonate VIII. Compound VIII reacts with di *t*-butyl dicarbonate to give carbamate VIIc, a versatile intermediate in which the amine function is protected with the acid-labile *t*-butoxycarbonyl group. Reductive alkylation of VIII with propionaldehyde using sodium cyanoborohydride can be controlled so as to give secondary amine VIc or tertiary amine VIb as the major product. Compound VIc may be acylated with propionyl chloride to give VIIe or converted to the *t*-butoxycarbonyl derivative VIIf.

Table 2. Formulas of Aminomalonates of Formula VII

Compound	R ₁ '	R ₂	R'	R''
VIIa	H	H	ethyl	ethyl
VIIb	H	CH ₃	ethyl	ethyl
VIIc	OC(CH ₃) ₃	H	ethyl	ethyl
VIIId	C ₂ H ₅	H	ethyl	ethyl
VIIe	C ₂ H ₅	C ₃ H ₇	ethyl	ethyl
VIIIf	OC(CH ₃) ₃	C ₃ H ₇	ethyl	ethyl

The 2,3,6,7-tetrahydro-1*N*,5*N*-benzo(1*j*)quinolizin-2-amines of the invention, compounds of Formula I where A, B, and D are CH₂ may be prepared as shown in Scheme 1 for the preparation of compounds 1-5.

Bromination of 8-methylquinoline (IX) with *N*-bromosuccinimide afforded 8-(bromomethyl)quinoline (X) which was reacted with diethyl (formylamino)malonate (VIIa) to give XIa (R₁'=H). This was hydrogenated using a platinum catalyst to give XIIa which was hydrolyzed to XIIIa. This was hydrolyzed to XIV, methylated to XV, and reduced to give compound 1. Compound XIIIa was also reduced with lithium aluminum hydride to give a mixture of compounds 2 and 3. The propylamino analogues, compounds 4 and 5, were prepared as outlined in Scheme 1 from 8-(bromomethyl)quinoline and diethyl (1-oxopropyl)-malonate (VIIId).

Analogues may be prepared by substituting aminomalonates VIIi-VIIq for VIIa and VIIId in the above reaction sequence.

The 5,6-dihydro-*N,N*-dipropyl-4*H*-imidazo(4,5,1-*i*)quinolin-5-amines of the invention, compounds of Formula I where D is nitrogen, A is CH, n is 0 and D and A are joined by a double bond, may be prepared as illustrated in Scheme 2 for the preparation of compound 6. Catalytic hydrogenation of 2-methyl-6-nitroaniline (XVI) using a palladium catalyst afforded 3-methyl-1,2-benzenediamine (XVII) which

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was heated with formic acid to give 4-methylbenzimidazole (XVIII). This was heated in dioxane with di-*t*-butyl dicarbonate and the *t*-butyl 4-methylbenzimidazole-1-carboxylate (XIXa, R is OC(CH₃)₃) thus obtained was brominated with N-bromosuccinimide in carbon tetrachloride to give *t*-butyl 4-(bromomethyl)benzimidazole-1-carboxylate (XXa). Alkylation of XXa with the potassium salt of diethyl (dipropylamino)-malonate (VIb) in refluxing THF afforded XXIa which was hydrolyzed to XXII using sodium ethoxide in ethanol containing limited amounts of water. Compound XXII was reduced to the alcohol XXIII using lithium aluminum hydride. When XXIII was treated with carbon tetrabromide and triphenylphosphine in methylene chloride compound 6 was obtained directly.

Modifications may be made in this reaction sequence. The hydrolysis of XXIa to XXII may be carried out in two steps; under mild hydrolysis conditions, ethyl- α -(dipropylamino)-1H-benzimidazole-4-propanoate, formed by loss of the *t*-butoxycarbonyl group, can be obtained as the only reaction product, and this may be subsequently hydrolyzed to XXII. Compound XVIII was reacted with methyl chloroformate to give XIXb (R is OCH₃) which was converted in high yield to XXII as shown in Scheme 2. Acetylation of XVIII gave XIXc (R is CH₃) which was also converted to XXII, although the yield in this reaction was not as high as when the *t*-butoxycarbonyl or carbomethoxy protecting groups were used.

The reaction sequence of Scheme 2 may be used to prepare analogues in which the dipropylamine substituent is modified. Using the malonates VII - VIq in place of diethyl (dipropylamino)malonate (VIb), compounds 7-12 were obtained. In the preparation of these compounds the adduct formed by reacting the malonate with XXa was converted to the methyl α -(substituted amino)-1H-benzimidazole-4-propanoate by hydrogenolysis as described in Example 19.

The sequence may also be used to prepare compounds of Formula I which have a substituent (X) in the benzene ring. For example, using the substituted benzimidazoles, 5-methoxy-4-methylbenzimidazole, 6-methoxy-4-methylbenzimidazole, 4-methoxy-6-methylbenzimidazole and 5-chloro-4-methylbenzimidazole in place of 4-methylbenzimidazole (XVIII), compounds 14-18 were obtained. Compounds 14-16 were treated with hydrobromic acid to give the corresponding phenols 19-21 respectively.

An alternate synthesis of 5,6-dihydro-N,N-dipropyl-4*H*-imidazo(4,5,1-*ij*)quinolin-5-amines from 3-aminoquinoline (XXIV) is shown in Scheme 3. Compound XXIV was formylated to give XXV and this was hydrogenated using platinum oxide as catalyst and formylated to give XXVI in good yield. Bromination of XXVI gave the 6-bromo compound XXVII which was nitrated to give XXVIII. Hydrogenation of XXIX in presence of palladium charcoal gave the triamine XXX, which was treated with formic acid to give compound 22. The primary amine reacted with propionaldehyde and sodium cyanoborohydride to give the mono- and di-propylamine derivatives, compounds 23 and 6 respectively. Catalytic reduction of compound 22 in the presence of formaldehyde gave the previously described dimethylamine analogue (compound 7).

The sequence of Scheme 3 may also be used to prepare compounds of Formula I which have a substituent (X) in the benzene ring. For example, using 3-amino-6-methylquinoline in place of 3-aminoquinoline, compound 24 was obtained. The 3-amino-6-methylquinoline intermediate was prepared using literature procedures from *p*-toluidine and the sodium salt of nitromalonaldehyde. Other ring-substituted analogues can be prepared by this procedure.

The 5-amino-5,6-dihydro-4*H*-imidazo(4,5,1-*ij*)quinolin-2-ones of the invention, compounds where A is carbonyl, n is 0, and D is NH or N-(lower alkyl) may be prepared as shown in Scheme 4. Nitroquinoline XXIX, prepared as outlined in Scheme 3, was protected, reduced, and cyclized using phosgene to give the *t*-butoxycarbonyl-protected imidazoquinolinone XXXIII. This was hydrolyzed to the amine (compound 26) which was alkylated to give the dimethylamino analogue compound 27 and propylamino analogues, compounds 28 and 29. Further alkylation of compounds 27 and 29 using potassium hydride/methyl iodide gave compounds 30 and 31 respectively.

6-Bromo-1,2,3,4-tetrahydro-3-quinolinamine (compound XXIX) was alkylated with propyl iodide to give XXIVa and this was reduced to 1,2,3,4-tetrahydro-N³,N³-dipropyl-3,8-quinolinediamine, Formula XXXVa where R₁ and R₂ are C₃H₇. Alkylation of XXIX with formaldehyde/formic acid followed by catalytic reduction gave the corresponding dimethylamino compound Formula XXXVb where R₁ and R₂ are CH₃. Compound XXXVa has also been prepared from 2-nitrobenzylchloride in Example 67.

Intermediates XXXII, XXXVa and XXXVb may be used for the preparation of the 5-amino-5,6-dihydro-4*H*-imidazo(4,5,1-*ij*)quinolines and 5-amino-5,6-dihydro-4*H*-imidazo(4,5,1-*ij*)quinolin-2-ones of the invention and in the preparation of a variety of new heterocyclic analogues where the adjacent nitrogen atoms are joined to form a five or six membered heterocyclic ring as shown for compound XXXVa in Scheme 5. Compound XXXVa was reacted with thiophosgene or di-(2-pyridyl)thiocarbonate to give 5-(dipropylamino)-5,6-dihydro-4*H*-imidazo(4,5,1-*ij*)quinolin-2-thione (compound 33) which was further alkylated to 5,6-dihydro-2-methylthio-*N,N*-dipropyl-4*H*-imidazo(4,5,1-*ij*)quinoline-5-amine (compound 34). Compounds XXXVa reacted with cyanogen bromide to give compound 35 which was alkylated with methyl iodide to give compound 36. Compound XXXVa reacted with diphenyl cyanocarbonimidate to give compound 37 and with sulfamide to give compound 38.

Compounds with a six-membered heterocyclic ring were prepared by reacting compound XXXVa with ethyl bromoacetate to give compound 39, chloroacetic anhydride to give compound 40, butyl glyoxylate to give compound 41, ethyl oxalyl chloride or oxalyl chloride to give compound 42, ethyl bromopropionate to give compound 84, and *n*-chloropropionyl chloride to give compound 85.

A similar series of compounds (compounds 43-50) were prepared from 1,2,3,4-tetrahydro-*N*³,*N*³-dimethyl-3,8-quinolinediamine; other products may be obtained by substituting compound XXXII in these reactions.

The 5-amino-5,6-dihydro-4*H*-imidazo(4,5,1-*ij*)quinolin-2-ones of the invention may also be prepared by the route shown in Scheme 6. 3-Methyl-1,2-benzenediamine is reacted with carbonyl diimidazole or phosgene to give 4-methylbenzimidazolone (XXXVI). This is refluxed with phosphorus oxychloride to give XXXVII which is protected and reacted with *N*-bromosuccinimide to give compound XXXIX. This is coupled with VIIb and the resulting adduct LX is hydrolyzed to LI. Reduction with lithium aluminum hydride alcohol LXII which was treated with carbon tetrabromide/triphenylphosphine to give compound 51. Compound 51 was refluxed in acetic acid to effect conversion to compound 6.

Analogues of compounds 51 and 6 may be prepared by the procedure of Scheme 6. By using malonates VIk-q or VIg in place of VIIc,

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compounds 52-57 were prepared.

The sequence may also be used to prepare compounds of Formula I which have a substituent (X) in the benzene ring. For example, using the substituted benzimidazoles 2,5-dichloro-4-methylbenzimidazole, 2-chloro-5-methoxy-4-methylbenzimidazole, 2-chloro-6-methoxy-4-methylbenzimidazole and 2-chloro-4-methoxy-6-methylbenzimidazole in place of 2-chloro-4-methylbenzimidazole (XVIII) compounds 58-63 were obtained; these compounds have also been prepared from the ring substituted 1,2,3,4-tetrahydro-3,8-quinolinediamines as described in Examples 82-87.

Compounds with a methyl substituent at position 6 in the imidazoquinoline or imidazoquinolinone ring were prepared from 4-ethylbenzimidazole by the procedure of Scheme 2 (see Example 88) and by converting 2-ethylaniline to 1,2,3,4-tetrahydro-4-methyl-N³,N³-dimethyl-3,8-quinolinediamine using the procedure of Scheme 7 and 4. Compounds with an alkyl substituent at position 4 in the imidazoquinoline or imidazoquinolinone ring were prepared from intermediate XXIII and related primary alcohols by oxidation to the aldehyde, reacting the aldehyde with an alkyl magnesium bromide, and cyclizing the resulting alcohol (see Example 92). Following these procedures, compounds 64-71 were obtained.

The 5-amino-5,6-dihydro-4H-oxazolo(5,4,1-ij)quinolin-2-ones of the invention, compounds where A is carbonyl, n is 0 and D is 0, may be prepared as outlined in Scheme 7 for the preparation of compound 72. 3-Methyl-2-nitroanisole (XLIII) was reduced to XLIV and this was refluxed with acetic anhydride to give XLV. This product was brominated and coupled with VIb to give XLVII. Compound XLVII was refluxed with sodium ethoxide in ethanol to give XLVIII which was converted to the phenol XLIX and reduced with lithium aluminum hydride to L. Compound L was treated with carbonyl diimidazole to give compound 72.

The related compounds 73-79 were prepared by the procedure of Scheme 7 from compound XLVI and the appropriate malonate of Formula VI or VII. Compounds 80 and 82 were prepared by reacting phenol intermediate L with thiophosgene or ethyl bromoacetate.

Compounds 86-93, were prepared from the 4-methyl heterocycle of Formula II by the procedures described in Schemes 2 and 6.

Compounds 95-97 were prepared from 5-(propylamino)-5,6-dihydro-

4H-pyrrolo(3,2,1-ij)quinolin-2,3-dione (compound 94) which was prepared as described in Example 118.

6-(Dipropylamino)-2,3,6,7-tetrahydro-5H-pyrido(3,2,1-ij)quinazolin-3-one (compound 98) was prepared in nine steps from 3-methyl-2-nitrobenzoic acid as described in Example 122. Compounds 99-105 were prepared from the same starting material using the procedures described in Examples 123-129.

An alternative procedure for synthesizing the compounds of the invention is shown in Scheme 8. t-Butyl 1,2,3,4-Tetrahydro-5-(dipropylamino)quinoline-1-carboxylate prepared as described in Example 130 is converted to the anion LI which is further reacted as shown in Scheme 8 to yield compounds 87, 92, 95, 97 and 102. The compounds of the invention can be separated by conventional methods into R- and S- isomers; the invention includes both racemic and optically pure products. Resolution can be accomplished using resolving agents such as optically active dibenzoyltartaric acid, camphorsulfonic acid, bis-o-toluoyletartaric acid, tartaric acid, and diacetyl tartaric acid.

A second procedure useful in resolving primary and secondary amine compounds of Formula I involves their conversion to diastereomeric amides using an optically active acid. The diastereomeric amides are separated and the amide bond is cleaved to afford the optically pure Formula I compounds. This procedure is illustrated in Examples 49 and 50 for the preparation of the optical isomers of compound 29 using t-butoxycarbonyl-L-phenylalanine as the resolving agent. For the resolution, racemic compound 26 was coupled to t-butoxycarbonyl-L-phenylalanine and the diastereomeric amide products were separated by chromatography into the (+) and (-) forms; each isomer was carried forward as described in detail for the "(-) isomer" below. The (-) isomer was reacted with trifluoroacetic acid to give (-) N-(5,6-dihydro-2-oxo-4H-imidazo(4,5,1-ij)quinolin-5-yl)-L-phenylalanineamide. Edman degradation of this compound, by reaction with phenyl isothiocyanate followed by trifluoroacetic acid, removed the phenylalanine residue and afforded the (-) form of compound 26. Further reaction of this product with propionaldehyde and sodium cyanoborohydride gave the (-) form of compound 29, the more active isomer.

Compounds where the R₃ substituent is alkyl exist as dias-

tereomers in which the alkyl group and amine substituent (NR_1R_2) can be cis or trans to one another. The invention includes the use of such compounds as the isomer mixture (RR, RS, SR SS), the racemic diastereomers (R,R and S,S; or R,S and S,R) and the optically pure
5 diastereomer. The diastereomer mixture can be separated by conventional means, eg by silica gel chromatography. The racemic diastereomers thus obtained may be resolved into optically pure compounds using the procedures described above.

The compounds listed below were tested and found to have
10 possible useful antipsychotic activity properties as indicated by their having CNS activity (ED_{50} numbers of less than 50 mg/kg values) in the known hypothermia and/or hypoxic stress tests; several of the compounds have also shown analgesic activity. For these tests, groups of 4 male CF-1 mice are dosed ip (sc in the hypoxic stress and
15 HCl writhing tests) with suspensions or solutions in 0.25% aqueous methylcellulose. Doses of the compound under study began at 100 mg/kg and were decreased at a 0.3 log interval until no responders were obtained. The procedure described by Spearman and Karber, Finney, D.J. "Statistical Methods in Biological Assay", Chapter 20,
20 was used to calculate the ED_{50} and 95% confidence intervals.

In the hypothermia test, abdominal temperature was measured after 45 minutes. Mice with temperatures more than 2 standard deviations below the mean are hypothermic. This test is used to identify compounds which may be useful as antipsychotics or as
25 hypotensives.

In the hypoxic stress test, following compound administration the mice were placed individually in stoppered 125 ml Erlenmeyer flasks 30 min after receiving the test agent. The survival time is recorded. Mice surviving more than the mean + 2 standard deviations
30 in parallel run controls are scored as showing a drug effect. This test is used to identify compounds which may be useful as anxiolytics.

For determination of analgesic activity, thirty minutes after test compound injection, the mice were injected i.p with 0.15% HCl,
35 10 ml/kg. Mice were then placed in plastic boxes and observed for fifteen minutes to record the number of animals failing to writhe. If at least three of the mice receiving the test compound failed to writhe, the compound was retested at lower dose levels.

In the hypothermia and hypoxic stress tests, compounds of the invention have been found more potent than related compounds, showing ED₅₀'s values as low as 0.05 mg/kg. The compounds also had good activity in the hypothermia test when the animals were dosed orally with the drug.

The dosage regimen for treating patients with the compounds of this invention is selected in accordance with a variety of factors including the type, age, weight, sex, and medical condition of the patient, the severity of the psychosis, the route of administration and the particular compound employed. An ordinarily skilled physician or psychiatrist will readily determine and prescribe the effective amount of compound to prevent or arrest the progress of the condition. In so proceeding, the physician or psychiatrist could employ relatively low dosages at first, subsequently increasing the dose until a maximum response is obtained.

Initial dosages of the compounds of the invention are ordinarily in the area of at least 10 mg up to about 1200 mg per day orally, which may be given in a single dose or in multiple doses. When other forms of administration are employed equivalent doses are administered. When dosages beyond 600 mg are employed, care should be taken with each subsequent dose to monitor possible toxic effects.

The compounds of this invention are administered in oral unit dosage forms such as tablets, capsules, pills, powders, or granules. They may also be introduced parenterally, (e.g., subcutaneously, intravenously, or intramuscularly), using forms known to the pharmaceutical art. They also may be administered rectally or vaginally in such forms as suppositories or bougies. In general, the preferred route of administration is oral.

The compounds of this invention can also be administered as pharmaceutically or therapeutically acceptable salt such as hydrochloride, hydrobromide, hydroiodide, sulfate, phosphate, acetate, propionate, lactate, maleate, malate, succinate, tartrate, cyclohexanesulfamates, methanesulfonates, ethanesulfonates, benzenesulfonates, toluenesulfonates and the like. Additionally, the compounds of this invention may be administered in a suitable hydrated form.

Example 1. Benzyl methyl malonate

A mixture of dimethyl malonate (100 g, 0.75 mol) and benzyl alcohol (108 g, 1.0 mol) was heated for 2 h at 180°C under a distil-

lation head so as to remove the methanol generated in the reaction. The product was then distilled under reduced pressure to give a fore-run of 55 g (a mixture of dimethyl malonate and benzyl alcohol) followed by 63 g (40%) of benzyl methyl malonate, bp 105-115°C/0.2 mm
5 (98% pure by GC). The pot residue consisted of 71 g (33%) of dibenzyl malonate (90% pure by GC).

Example 2. Benzyl methyl bromomalonate

Bromine (17.6 g, 0.11 mol) was added to a stirred solution of benzyl methyl malonate (20.8 g, 0.10 mol) in carbon tetrachloride.
10 After 30 minutes the solvent was removed under reduced pressure to give 28 g of product (85% pure by gc, containing 7% benzyl methyl malonate) which was used without further purification.

Example 3. Diethyl (dipropylamino)malonate (compound VIb)

Dipropylamine (22.3 g, 0.22 mol) was added to a stirred solution
15 of diethyl bromomalonate (47.8 g, 0.20 mol) in THF (400 mL) and the solution was stirred for 18 hours at room temperature. The precipitate of dipropylamine hydrobromide was filtered off and washed with THF. The THF phase was evaporated and the residual oil was partitioned between ethyl acetate (200 mL) and sodium hydroxide solution
20 (10 mL of 4 N). The ethyl acetate phase was separated, washed with water (2 x 10 mL), and the solvent was removed under reduced pressure. The residual oil was dissolved in an equal volume of hexane and was applied to a silica gel column (420 g) which was eluted initially with ethyl acetate:hexane (1:20). The concentration of
25 ethyl acetate in the eluant was increased slowly until all the diethyl (dipropylamino)malonate was eluted from the column. Fractions containing the compound as determined by TLC and GC were pooled and the solvent was removed to give diethyl (dipropylamino)malonate as an oil in 80-90% yield.

30 Compounds VIa and VIc-VIh were obtained using this procedure, but substituting dimethylamine, propylamine, N-methylbenzylamine, N-propylbenzylamine, benzylamine, α -methylbenzylamine, (R)- α -methylbenzylamine for dipropylamine.

Compounds VII-VIp were obtained using this procedure, but
35 substituting benzyl methyl bromomalonate for diethyl bromomalonate and using dimethylamine, dipropylamine, pyrrolidine, piperidine, morpholine, 4-methylpiperazine and imidazole as the amine reaction component.

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Example 4. Diethyl (N-(1,1-dimethylethoxycarbonyl)propylamino)-malonate (compound VIIf)

Diethyl aminomalonate (21.1 g, 0.1 mol) was dissolved in ethanol and sodium ethoxide in ethanol (50 mL of 1 M) was added. Propionaldehyde (6.6 g, 0.11 mol) and sodium cyanoborohydride (3.6 g, 0.058 mol) were added to the stirred solution. After 30 minutes additional propionaldehyde (6.0 g) and sodium cyanoborohydride (2.6 g) were added to complete the reaction. The solution was evaporated, and the residue was partitioned between ethyl acetate and water. Evaporation of the ethyl acetate gave 25.1 g of diethyl (propylamino)malonate. This was mixed with di t-butyl dicarbonate (34 g, 0.156 mol) and the mixture was heated at 100°C for 1 hour. The crude product was chromatographed on silica gel using ethyl acetate:hexane as the eluant to give 21.2 g of diethyl (N-(1,1-dimethylethoxycarbonyl)propylamino)malonate as an oil.

Compound VIIa was obtained by following the same procedure, but substituting propionyl chloride for di t-butyl dicarbonate.

Example 5. Diethyl (1-oxopropyl)malonate (compound VIId)

Triethylamine (20 g, 0.2 mol) and propionic anhydride (12.54 g, 0.096 mol) were added to diethyl aminomalonate hydrochloride (20.40 g, 0.096 mol) in THF (300 mL) and the reaction was stirred at room temperature for 45 minutes. The solvent was removed under reduced pressure and the crude product was partitioned between ethyl acetate and water. The ethyl acetate phase was separated and evaporated to give 34.64 g of white solid. This was dissolved in hot ethyl acetate (60 mL), hexane (60 mL) was added, and the solution was filtered to remove insoluble material. The solution was cooled to -10°C and filtered to give 17.63 g (72%) of diethyl (1-oxopropyl)malonate, mp 89-93°C.

Compound VIIc was obtained by following the same procedure, but substituting di t-butyl dicarbonate for propionic anhydride.

Example 6. 8-(Bromomethyl)quinoline (compound X)

A mixture of 8-methylquinoline (45 g, 0.314 mol), N-bromosuccinimide (55 g, 0.309 mol) and benzoyl peroxide (1.5 g) in carbon tetrachloride (250 mL) was refluxed for 7 hours. The reaction was filtered and evaporated, and the crude product was crystallized from methanol (70 mL) to give 37.7 g of product. The mother liquors were chromatographed on silica gel in chloroform to give 17 g of material

which was crystallized from ethyl acetate:hexane to give an additional 12.0 g of product.

Example 7. Diethyl (formylamino)(8-quinolinylmethyl)propanedioate (compound XIa)

5 Diethyl (formylamino)malonate (22.0 g, 0.108 mol) was added to a stirred solution of sodium ethoxide in ethanol (prepared from 2.4 g of sodium and 250 mL of ethanol, 0.10 mol). After 5 min, 8-(bromomethyl)quinoline (22.0 g, 0.10 mol) was added and the solution was stirred for an additional 15 minutes. The solvent was removed under
10 reduced pressure and the product was partitioned between ethyl acetate and water. The ethyl acetate was removed and the residual oil was crystallized from ether to give 19.9 g (58%) of diethyl (formylamino)(8-quinolinylmethyl)propanedioate, mp 120-122°C. Anal. Calcd. for $C_{18}H_{20}N_2O_5$: C, 62.78; H, 5.85; N, 8.14. Found: C,
15 62.53; H, 6.03; N, 8.07.

Example 8. N-(2,3,6,7-Tetrahydro-3-oxo-1H,5H-benzo(1j)quinolizin-2-yl)-formamide (compound XIIIa)

Part A. Ethyl 2,3,6,7-tetrahydro-3-oxo-2-(formylamino)-1H,5H-benzo(1j)quinolizine-2-carboxylate (compound XIIa)

20 A mixture of diethyl (formylamino)(8-quinolinylmethyl)malonate (9.2 g, 26.7 mmol) and platinum oxide (0.7 g) in glacial acetic acid (150 mL) was hydrogenated (50 lb initial pressure) for 15 minutes (hydrogen uptake ca. 2 equiv). The mixture was filtered through celite and the solvent removed under reduced pressure. The product
25 was partitioned between ethyl acetate and sodium hydroxide solution. The ethyl acetate phase was washed with water, the ethyl acetate was evaporated, and the product was crystallized from ether to give 7.8 g (97%) of ethyl 2,3,6,7-tetrahydro-3-oxo-2-(formylamino)-1H,5H-benzo(1j)quinolizine-2-carboxylate, mp 103-106°C. Anal. Calcd. for
30 $C_{16}H_{18}N_2O_4$: C, 63.56; H, 6.00; N, 9.27. Found: C, 63.51; H, 6.09; N, 9.18.

Part B. N-(2,3,6,7-Tetrahydro-3-oxo-1H,5H-benzo(1j)quinolizin-2-yl)formamide (compound XIIIa)

Sodium hydroxide solution (5.0 mL of 4.0 N, 20 mmol) was slowly
35 added to ethyl 2,3,6,7-tetrahydro-3-oxo-2-(formylamino)-1H,5H-benzo(1j)quinolizine-2-carboxylate (3.04 g, 10.0 mmol) in methanol (25 mL). After stirring at room temperature for 30 min, hydrochloric acid (5.0 mL of 4.0 N) was added and the precipitate was filtered

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off, washed with water and air dried to give 2.4 g of N-(2,3,6,7-tetrahydro-3-oxo-1*H*,5*H*-benzo(1*j*)quinolizin-2-yl)formamide, mp 149-152°C. A portion of the product was recrystallized from ethyl acetate for analysis; mp 140-143°. Anal. Calcd. for C₁₃H₁₄N₂O₂: C, 67.81; H, 6.13; N, 12.17. Found: C, 67.67; H, 6.07; N, 11.94.

Example 9. 2,3,6,7-Tetrahydro-N,N-dimethyl-1*H*,5*H*-benzo(1*j*)quinolizin-2-amine (Compound 1)

Part A. 2,3,6,7-Tetrahydro-3-oxo-1*H*,5*H*-benzo(1*j*)quinolizin-2-amine (compound XIV)

10 A solution of N-(2,3,6,7-tetrahydro-3-oxo-1*H*,5*H*-benzo(1*j*)quinolizin-2-yl)-formamide (0.8 g, 3.4 mmol) in ethanolic hydrogen chloride (10 mL of 4.2 N) was heated at 50°C for 2 hours. The ethanol was cooled, an equal volume of ether was added, and the precipitate was filtered off and washed with ether to give 0.78 g of 2,3,6,7-tetra-
15 hydro-3-oxo-1*H*,5*H*-benzo(1*j*)quinolizin-2-amine hydrochloride, mp 216-221°C. The product was recrystallized for analysis; mp 219-222°C. Anal. Calcd. for C₁₂H₁₄N₂O·HCl: C, 60.37; H, 6.33; Cl, 14.85; N, 11.74. Found: C, 59.89; H, 6.42; Cl, 15.41; N, 11.68.

Part B. 2,3,6,7-Tetrahydro-N,N-dimethyl-1*H*,5*H*-benzo(1*j*)quinolizin-
20 2-amine (compound 1)

A mixture of 2,3,6,7-tetrahydro-3-oxo-1*H*,5*H*-benzo(1*j*)quinolizin-2-amine (2.0 g), 30% formaldehyde solution (1 mL) and 10% palladium/carbon (0.5 g) in ethanol (150 mL) was hydrogenated (50 lb initial hydrogen pressure) until uptake of hydrogen was complete (2
25 hours). The solution was filtered to remove the catalyst, evaporated, the crude product was dissolved in ether (300 mL) and lithium aluminum hydride (1.5 g) was added. After 1 hour, ethyl acetate was added, the solvents were removed under reduced pressure, and the product was partitioned between ethyl acetate and water. Evaporation
30 of the ethyl acetate gave an oil which was purified by chromatography on silica gel to give 1.03 g of 2,3,6,7-tetrahydro-N,N-dimethyl-1*H*,5*H*-benzo(1*j*)-quinolizin-2-amine.

The bulk of the product was converted to the maleate salt, mp 135-137°C from methanol:ether. A sample was recrystallized for
35 analysis; mp 135-137°C. Anal. Calcd. for C₁₄H₂₀N₂·C₄H₄O₄: C, 65.04; H, 7.28; N, 8.43. Found: C, 64.72; H, 7.43; N, 8.20.

Example 10. 2,3,6,7-Tetrahydro-N-methyl-1*H*,5*H*-benzo(1*j*)quinolizin-2-amine and N-Ethyl-2,3,6,7-tetrahydro-N-methyl-1*H*,5*H*-

benzo(1j)quinolizin-2-amine (Compounds 2 and 3)

N-(2,3,6,7-Tetrahydro-3-oxo-1*H*,5*H*-benzo(1j)quinolizin-2-yl)formamide (4 g, 0.017 mol) was added in 0.5 g aliquots every 10 min to a stirred solution of lithium aluminum hydride (2.77 g, 0.073 mol) in anhydrous ether (500 mL). After stirring overnight at room temperature the reaction was refluxed for 3 hours, cooled on ice and quenched with ethyl acetate and methanol. The solvent was evaporated under reduced pressure and the crude product was partitioned between ethyl acetate (800 mL) and water (40 mL). The ethyl acetate was separated, washed with water, and the ethyl acetate was evaporated to give 3.64 g of crude product. The products were separated by chromatography on silica gel in chloroform to give, as the first product eluted from the column, 1.4 g of N-ethyl-2,3,6,7-tetrahydro-N-methyl-1*H*,5*H*-benzo(1j)-quinolizin-2-amine. The compound was converted to the maleate salt, mp 90-100°C from methanol:ether. The product was recrystallized for analysis; mp 94-98°C. Anal. Calcd. for $C_{15}H_{22}N_2 \cdot C_4H_4O_4$: C, 65.87; H, 7.57; N, 8.09. Found: C, 65.53; H, 7.81; N, 8.08.

Continued elution of the column gave 1.3 g of 2,3,6,7-tetrahydro-N-methyl-1*H*,5*H*-benzo(1j)quinolizin-2-amine which was converted to the maleate salt, mp 151-155°C from methanol:ether. Anal. Calcd. for $C_{13}H_{18}N_2 \cdot C_4H_4O_4$: C, 64.13; H, 6.97; N, 8.80. Found: C, 63.79; H, 7.16; N, 8.62.

Example 11. Diethyl ((1-oxopropyl)amino)(8-quinolinylmethyl)propanedioate (compound XIb)

Diethyl (1-oxopropyl)malonate (15.14 g, 0.065 mol) was added to a stirred solution of sodium ethoxide in ethanol (165 mL of 0.4 M, 0.066 mol). After 5 minutes, 8-(bromomethyl)quinoline (13.15 g, 0.059 mol) was added and the solution was stirred for an additional 15 minutes. The solvent was removed under reduced pressure and the product was dissolved in ethyl acetate (300 mL) which was washed with water (3 x 10 mL). The ethyl acetate was removed and the residual solid (27.3 g) was crystallized from ethyl acetate:hexane to give 21.6 g of tan crystals, mp 80-100°C. Recrystallization of an aliquot (4 g) from ethyl acetate:hexane gave 2.87 g of tan crystals, mp 104-106°C. Anal. Calcd. for $C_{20}H_{24}N_2O_5$: C, 64.50; H, 6.50; N, 7.52. Found: C, 64.25; H, 6.51; N, 7.51.

Example 12. Ethyl 2,3,6,7-tetrahydro-3-oxo-2-((1-oxopropyl)amino)-

1*H*,5*H*-benzo(*ij*)quinoliz-ine-2-carboxylate (compound XIIb)

A mixture of diethyl ((1-oxopropyl)amino)(8-quinolinylmethyl)-propanedioate (17.47 g, 0.047 mol) and platinum oxide (0.72 g) in glacial acetic acid (150 mL) was hydrogenated (50 lb initial pressure) until hydrogen uptake ceased (1.8 equiv). The mixture was filtered through celite and the solvent removed under reduced pressure. The product was crystallized from ethyl acetate to give 12.08 g of crystals, mp 136-140°C. A sample was recrystallized from ethyl acetate for analysis; mp 137-141°C. Anal. Calcd. for C₁₈H₂₂N₂O₄: C, 65.44; H, 6.71; N, 8.48. Found: C, 65.66; H, 6.64; N, 8.43.

Example 13. N-(2,3,6,7-Tetrahydro-3-oxo-1*H*,5*H*-benzo(*ij*)quinolizin-2-yl)-propanamide (compound XIIb)

Sodium hydroxide solution (10 mL of 4.0 N, 0.04 mol) was slowly added to ethyl 2,3,6,7-tetrahydro-3-oxo-2-((1-oxopropyl)amino)-1*H*,5*H*-benzo(*ij*)quinolizine-2-carboxylate (3.33 g, 0.010 mol) in methanol (50 mL). After stirring at room temperature for 30 minutes, the solvent was removed under reduced pressure. The resulting solid was dissolved in water (20 mL) and methanol (trace), neutralized with 4N HCl (10 mL, 0.04 mol), cooled to -10°C, and the precipitate was filtered off and air dried to give 2.86 g of 2,3,6,7-tetrahydro-3-oxo-2-((1-oxopropyl)amino)-1*H*,5*H*-benzo(*ij*)quinolizine-2-carboxylic acid. This was refluxed in ethanol for 20 minutes to effect decarboxylation. The ethanol was removed under reduced pressure and the solid was crystallized from ethyl acetate:hexane to give 1.85 g of N-(2,3,6,7-tetrahydro-3-oxo-1*H*,5*H*-benzo(*ij*)quinolizin-2-yl)propanamide, mp 149-152°C. A sample was recrystallized for analysis; mp 152-154°C. Anal. Calcd. for C₁₅H₁₈N₂O₂: C, 69.74; H, 7.02; N, 10.85. Found: C, 69.33; H, 7.33; N, 10.68.

Example 14. 2,3,6,7-Tetrahydro-N-propyl-1*H*,5*H*-benzo(*ij*)quinolizin-2-amine (compound 4)

N-(2,3,6,7-Tetrahydro-3-oxo-1*H*,5*H*-benzo(*ij*)quinolizin-2-yl)propanamide (2.5 g, 0.01 mol) was dissolved in anhydrous ether (500 mL). The solution was cooled to 0°C, lithium aluminum hydride (1.46 g, 0.038 mol) was added and the reaction was refluxed for 4 hours. The reaction was quenched with ethyl acetate and methanol, the solvents were removed under reduced pressure and the material was partitioned

between ethyl acetate (400 mL) and water (50 mL). Evaporation of the ethyl acetate phase gave 2.35 g of yellow oil. The product was purified by chromatography on silica gel. Elution of the column with 1% and 2.5% methanol:chloroform gave 2.07 g of 2,3,6,7-tetrahydro-N-propyl-1*H*,5*H*-benzo(*ij*)quinolizin-2-amine.

The bulk of the product was converted to the hemifumarate salt which was recrystallized from methanol:ether; mp 190-194°C. Anal. Calcd. for $C_{15}H_{22}N_2 \cdot 1/2C_4H_4O_4$: C, 70.80; H, 8.39; N, 9.71. Found: C, 70.37; H, 8.26; N, 9.65.

10 Example 15. 2,3,6,7-Tetrahydro-N,N-dipropyl-1*H*,5*H*-benzo(*ij*)quinolizin-2-amine (compound 5)

A mixture of 2,3,6,7-tetrahydro-N-propyl-1*H*,5*H*-benzo(*ij*)quinolizin-2-amine (2.33 g, 0.01 mol), propyl iodide (5.16 g, 0.03 mol) and anhydrous potassium carbonate (3 g, 0.02 mol) in dimethylformamide
15 (75 mL) was stirred for 5 hours at 90°C. At this time additional propyl iodide (1.72 g, 0.01 mol) and potassium carbonate (0.5 g, 0.0036 mol) were added and the reaction was continued for an additional 2 hours. The reaction was cooled, filtered to remove inorganic material, and the solvent was removed under reduced pressure.
20 The product was partitioned between ethyl acetate (800 mL) and 4*N* sodium hydroxide (20 mL, 0.08 mol), the organic layer concentrated, filtered, and chromatographed on silica gel in 5-30% ethyl acetate:hexane to give 2.19 g of 2,3,6,7-tetrahydro-N,N-dipropyl-1*H*,5*H*-benzo(*ij*)quinolizin-2-amine.

25 A portion of the product was converted to the fumarate salt, mp 112.5-116°C. Recrystallization from methanol:ether gave light brown crystals, mp 112-116°C. Anal. Calcd. for $C_{18}H_{28}N_2 \cdot C_4H_4O_4$: C, 68.01; H, 8.30; N, 7.21. Found: C, 67.73; H, 8.47; N, 7.14.

Example 16. 4-Methyl-1*H*-benzimidazole (compound XVIII)

30 Part A. 3-Methyl-1,2-benzenediamine (compound XVII)

2-Methyl-6-nitroaniline (15.2 g, 0.1 mol) was dissolved by heating in ethanol (150 mL). The solution was cooled, 10% palladium on carbon (1.0 g) was added and the solution was hydrogenated (50 lb initial hydrogen pressure) until uptake of hydrogen ceased (1 hour).
35 The catalyst was filtered off and the ethanol was removed under reduced pressure to give 11.9 g (98%) of 3-methyl-1,2-benzenediamine as a solid which was used without purification.

Part B. 4-Methyl-1*H*-benzimidazole (Compound XVIII)

A mixture of 3-methyl-1,2-benzenediamine (11.9 g) and formic acid (150 mL) was heated at 70°C for 15 minutes. The solvent was removed under reduced pressure and the residual oil was stirred with water (100 mL) and sodium hydroxide solution (65 mL of 4.0 N) was added until the solution was just basic. The precipitate was filtered off, washed with water, and air dried to give 11.6 g (90%) of 4-methyl-1*H*-benzimidazole, mp 141-145°C.

Example 17. *t*-Butyl 4-(bromomethyl)-1*H*-benzimidazole-1-carboxylate (compound XXa)

10 Part A. *t*-Butyl 4-methyl-1*H*-benzimidazole-1-carboxylate (compound XIXa)

A mixture of 4-methyl-1*H*-benzimidazole (11.6 g, 0.088 mol) and di *t*-butyl dicarbonate (21.1 g, 0.097 mol) was heated at 80°C in dioxane (200 mL) for 1 hour. The solvent was removed under reduced pressure and the residual oil (24.3 g) was chromatographed on silica gel using ethyl acetate:hexane as the eluant to give 18.7 g (92%) of *t*-butyl 4-methyl-1*H*-benzimidazole-1-carboxylate as an oil.

Part B. *t*-Butyl 4-(bromomethyl)-1*H*-benzimidazole-1-carboxylate (compound XXa)

20 A mixture of *t*-butyl 4-methyl-1*H*-benzimidazole-1-carboxylate (11.6 g, 0.05 mol), *N*-bromosuccinimide (8.9 g, 0.05 mol) and benzoyl peroxide (0.25 g) in carbon tetrachloride (100 mL) was stirred at reflux for 1 hour. The solution was cooled and filtered to remove succinimide by-products and the solvent was removed. The crude product was chromatographed on silica gel using ethyl acetate:hexane (1:20) as the initial eluant to give, as the first major product eluted from the column, 1.6 g of *t*-butyl 4-(dibromomethyl)-1*H*-benzimidazole-1-carboxylate; recrystallization from hexane gave 1.04 g of product, mp 101-104°C. Anal. Calcd. for C₁₃H₁₄Br₂N₂O₂: C, 40.03; H, 3.62; Br, 40.92; N, 7.18. Found: C, 39.87; H, 3.83; Br, 41.18; N, 7.19.

Continued elution of the column gave 10.4 g of *t*-butyl 4-(bromomethyl)-1*H*-benzimidazole-1-carboxylate. The compound was recrystallized from hexane to give 9.6 g of product, mp 87-89°C. Anal. Calcd. for C₁₃H₁₅BrN₂O₂: C, 50.18; H, 4.86; Br, 25.68; N, 9.00. Found: C, 50.16; H, 5.04; Br, 25.71; N, 9.11.

Continued elution of the column gave 0.95 g of recovered *t*-butyl 4-(bromomethyl)-1*H*-benzimidazole-1-carboxylate.

Following the procedure of Example 17 part B but substituting methyl 4-methyl-1*H*-benzimidazole-1-carboxylate for *t*-butyl 4-methyl-1*H*-benzimidazole-1-carboxylate there was obtained methyl 4-(bromomethyl)-1*H*-benzimidazole-1-carboxylate (compound XXb).

- 5 Following the procedure of Example 17 part B but substituting 1-acetyl-4-methyl-1*H*-benzimidazole for *t*-butyl 4-methyl-1*H*-benzimidazole-1-carboxylate there was obtained 1-acetyl-4-(bromomethyl)benzimidazole (compound XXc), mp 109-112°C. Anal. Calcd. for C₁₀H₁₀BrN₂O: C, 47.45; H, 3.58; Br, 31.58; N, 11.07. Found: C, 47.47; H, 3.82; Br, 29.17; N, 11.21.

10 Example 18. 5,6-Dihydro-N,N-dipropyl-4*H*-imidazo(4,5,1-*i*)quinolin-5-amine (compound 6)

Part A. Diethyl (((1,1-dimethylethoxycarbonyl)-1*H*-benzimidazole-4-yl)methyl)-(dipropylamino)propanedioate (compound XXia)

- 15 Potassium hydride (3.3 g of 40% oil suspension, washed with ether to remove oil, 0.03 mol) was added to a stirred solution of diethyl (dipropylamino)-malonate (10.2 g, 0.039 mol) in dry THF (100 mL). After 5 minutes, *t*-butyl 4-(bromomethyl)-1*H*-benzimidazole-1-carboxylate (6.22 g, 0.02 mol) was added and the solution was
- 20 refluxed for 6 hours. The solvent was removed under reduced pressure and the residual oil was partitioned between ethyl acetate and water. After evaporation of the ethyl acetate, the crude product was chromatographed on silica gel using ethyl acetate:hexane as the eluant to give 7.9 g of diethyl (((1,1-dimethylethoxycarbonyl)-1*H*-
- 25 benzimidazole-4-yl)methyl)(dipropylamino)-propanedioate as an oil.

Part B. Ethyl α-(dipropylamino)-1*H*-benzimidazole-4-propanoate (compound XXII)

- A mixture of diethyl (((1,1-dimethylethoxycarbonyl)-1*H*-benzimidazole-4-yl)methyl)(dipropylamino)propanedioate (3.4 g, 6.9 mmol)
- 30 was dissolved in ethanol (50 mL) and treated with sodium ethoxide in ethanol (35 mL of 0.8 M, 4 equiv) and water (1.0 mL) and the reaction was refluxed for 4 hours. The solution was then cooled, neutralized by addition of 15 mL of 2.2 N HCl in ethanol, filtered to remove sodium chloride, and the solvent was removed under reduced pressure.
- 35 The product was partitioned between ethyl acetate and water, and the ethyl acetate was removed, and the crude product was chromatographed on silica gel using chloroform as the initial eluant. Elution of the column with 5% methanol chloroform gave 1.60 g of ethyl α-(dipropyla-

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mino)-1*H*-benzimidazole-4-propanoate. The product was crystallized from ethyl acetate:hexane; mp 78-80°C. Anal. Calcd. for C₁₈H₂₇N₃O₂: C, 68.11; H, 8.57; N, 13.24. Found: C, 68.41; H, 8.51; N, 13.22.

Part C. β -(Dipropylamino)-1*H*-benzimidazole-4-propanol (compound XXIII)

Lithium aluminum hydride (250 mg, 6.6 mmol) was added at 0°C to a stirred solution of ethyl α -(dipropylamino)-1*H*-benzimidazole-4-propanoate (1.5 g, 4.7 mmol) in dry THF (50 mL), and the solution was allowed to warm to room temperature. TLC in 10% methanol:chloroform showed that the reaction was complete in 15 minutes. Ethanol (5 mL) was added and the solvents were removed under reduced pressure. The residue was partitioned between ethyl acetate and water. Evaporation of the ethyl acetate gave 1.3 g of β -(dipropylamino)-1*H*-benzimidazole-4-propanol which was used without further purification.

Part D. 5,6-Dihydro-N,N-dipropyl-4*H*-imidazo(4,5,1-*ij*)quinolin-5-amine (compound 6)

Triphenylphosphine (625 mg, 2.4 mmol) was added to a stirred solution of β -(dipropylamino)-1*H*-benzimidazole-4-propanol (600 mg, 2.18 mmol) in methylene chloride (12 mL). After solution was complete, carbon tetrabromide (940 mg, 2.8 mmol) was added and the solution was stirred for 30 minutes. Methylene chloride (20 mL) was added and the solution was extracted with 25 mL 1.0 N hydrochloric acid. The methylene chloride was separated, reextracted with 10 mL 1.0 N HCl, and the combined aqueous extracts were basified (20 mL of 4.0 N NaOH) and extracted with ethyl acetate. After removing the ethyl acetate, the product was chromatographed on silica gel using chloroform as the initial eluant to give 380 mg of product. A sample was crystallized from hexane for analysis; mp 95-98°C. Anal. Calcd. for C₁₆H₂₃N₃: C, 74.66; H, 9.01; N, 16.33. Found: C, 74.28; H, 9.25; N, 16.36.

Example 19. 5,6-Dihydro-N,N-dimethyl-4*H*-imidazo(4,5,1-*ij*)quinolin-5-amine (compound 7)

Part A. (Dimethylamino)((1,1-dimethylethoxycarbonyl)-1*H*-benzimidazole-4-yl)methyl)-propanedioic acid methyl benzyl diester

This compound was obtained by following the procedure of Example 18 part A, but substituting (dimethylamino)propanedioic acid methyl benzyl diester (compound VII) for diethyl (dipropylamino)malonate.

Part B. Methyl α -(dimethylamino)-1*H*-benzimidazole-4-propanoate

A mixture of (dimethylamino)((1,1-dimethylethoxycarbonyl)-1*H*-benzimidazole-4-yl)methyl)propanedioic acid methyl benzyl diester (6.0 g) and 10% palladium charcoal (1 g) in ethanol (150 mL) was hydrogenated until hydrogen uptake ceased. The solution was filtered and evaporated to give 4.1 g of methyl α -(dimethylamino)-1*H*-benzimidazole-4-propanoate as an oil.

Part C. β -(Dimethylamino)-1*H*-benzimidazole-4-propanol

This compound was obtained by following the procedure of Example 18 part C, but substituting methyl α -(dimethylamino)-1*H*-benzimidazole-4-propanoate for ethyl α -(dipropylamino)-1*H*-benzimidazole-4-propanoate.

Part D. 5,6-Dihydro-N,N-dimethyl-4*H*-imidazo(4,5,1-*ij*)quinolin-3-amine

This compound was obtained by following the procedure of Example 18 part C but substituting β -(dimethylamino)-1*H*-benzimidazole-4-propanol for β -(dipropylamino)-1*H*-benzimidazole-4-propanol.

The bulk of the product was converted to the hydrochloride salt, mp 264-5°C from methanol:ether. Anal. Calcd. for C₁₂H₁₅N₃·2HCl: C, 52.56; H, 6.25; Cl, 25.86; N, 15.33. Found: C, 52.44; H, 6.53; Cl, 25.64; N, 15.18.

Example 20. 1-(5,6-Dihydro-4*H*-imidazo(4,5,1-*ij*)quinolin-5-yl)pyrrolidine (compound 8)

This compound was prepared by following the procedure of Example 19, but substituting (1-pyrrolidinyl)propanedioic acid methyl benzyl diester (compound VIk) for (dimethylamino)propanedioic acid methyl benzyl diester (compound VIIi). The bulk of the product was converted to the dihydrochloride salt, mp 291-294°C.

Example 21. 1-(5,6-Dihydro-4*H*-imidazo(4,5,1-*ij*)quinolin-5-yl)piperidine (compound 9)

This compound was prepared by following the procedure of Example 19, but substituting (1-piperidinyl)propanedioic acid methyl benzyl diester (compound VIIm) for (dimethylamino)propanedioic acid methyl benzyl diester (compound VIIi). The bulk of the product was converted to the dihydrochloride salt, mp 287-290°C.

Example 22. 4-(5,6-Dihydro-4*H*-imidazo(4,5,1-*ij*)quinolin-5-yl)morpholine (compound 10)

This compound was prepared by following the procedure of Example

19, but substituting (4-morpholinyl)propanedioic acid methyl benzyl diester (compound VIh) for (dimethylamino)propanedioic acid methyl benzyl diester (compound VII). The bulk of the product was converted to the dihydrochloride salt, mp 290-292°C.

- 5 Example 23. 1-(5,6-Dihydro-4H-imidazo(4,5,1-ij)quinolin-5-yl)-imidazole (compound 11)

This compound was prepared by following the procedure of Example 19, but substituting (1-imidazolyl)propanedioic acid methyl benzyl diester (compound VIp) for (dimethylamino)propanedioic acid methyl benzyl diester (compound VII). The bulk of the product was converted to the monohydrobromide salt, mp 239-242°C.

- 10 Example 24. 1-(5,6-Dihydro-4H-imidazo(4,5,1-ij)quinolin-5-yl)-4-methylpiperazine (compound 12)

This compound was prepared by following the procedure of Example 15 19, but substituting (4-methyl-1-piperazinyl)propanedioic acid methyl benzyl diester (compound VIq) for (dimethylamino)propanedioic acid methyl benzyl diester (compound VII).

- Example 25. N-(1-Phenylethyl)-5,6-Dihydro-4H-imidazo(4,5,1-ij)quinolin-5-amine (compound 13)

20 This compound was prepared by following the procedure of Example 18, but substituting diethyl (1-phenylethylamino)malonate (compound VIg) for diethyl (dipropylamino)malonate (compound VIb).

- Example 26. t-Butyl 4-(bromomethyl)-5-methoxy-1H-benzimidazole-1-carboxylate

- 25 Part A. 3-Chloro-2-methyl-6-nitrobenzenamine

A suspension of 2,6-dichloro-3-nitrotoluene (6.0 g, 29 mmol) in 50% methanolic ammonia (60 mL) was stirred at 130°C (340 lb pressure) for 18 hours. The autoclave was cooled to -30°C, opened, and the precipitate was filtered off and washed with methanol to give 4.14 g (76%) of 3-chloro-2-methyl-6-nitrobenzenamine.

- 30 Part B. 3-Methoxy-2-methyl-6-nitrobenzenamine

Sodium methoxide in methanol (110 mL of 25% solution, 0.49 mol, 20 equiv) was added to a stirred suspension of 3-chloro-2-methyl-6-nitrobenzenamine (4.0 g, 23.5 mmol) in methanol (250 mL) and the mixture was stirred at reflux for 18 hours. The solution was cooled, 35 neutralized with methanolic hydrogen chloride, filtered to remove sodium chloride, and the solvent was removed under reduced pressure. The residual solid was partitioned between ethyl acetate and water.

Evaporation of the ethyl acetate gave 3.7 g (86%) of 3-methoxy-2-methyl-6-nitrobenzenamine.

Part C. 4-Methoxy-3-methyl-1,2-benzenediamine

A mixture of 3-methoxy-2-methyl-4-nitrobenzenamine (3.5 g, 19.0 mmol) and 10% palladium on carbon (1.0 g) in absolute ethanol (150 mL) was hydrogenated (50 lb initial hydrogen pressure) until hydrogen uptake was complete (30 minutes). The solution was filtered through celite and the ethanol was removed to give 2.84 g (98%) of 4-methoxy-3-methyl-1,2-benzenediamine.

10 Part D. 5-Methoxy-4-methyl-1H-benzimidazole

A mixture of 4-methoxy-3-methyl-1,2-benzenediamine (2.8 g, 18.4 mmol) and formic acid (30 mL) was heated at 60°C for 30 minutes. The formic acid was removed under reduced pressure and the product was partitioned between chloroform and water containing sufficient sodium hydroxide to basify the solution. After evaporation of the solvent the crude product was chromatographed (methanol:chloroform) to give 2.55 g (84%) of 5-methoxy-4-methyl-1H-benzimidazole.

Part E. t-Butyl 5-methoxy-4-methyl-1H-benzimidazole-1-carboxylate

20 A mixture of 5-methoxy-4-methyl-1H-benzimidazole (2.5 g, 15.4 mmol) and di-t-butyl dicarbonate (4.2 g, 19.3 mmol) in dioxane (70 mL) was heated at 100°C for 1 hour. After evaporation of the solvent, the residue was chromatographed on silica gel to give 3.75 g (93%) of t-butyl 5-methoxy-4-methyl-1H-benzimidazole-1-carboxylate.

25 Part F. t-Butyl 4-(bromomethyl)-5-methoxy-1H-benzimidazole-1-carboxylate

A mixture of N-bromosuccinimide (2.66 g, 15.0 mmol), benzoyl peroxide (0.35 g) and t-butyl 5-methoxy-4-methyl-1H-benzimidazole-1-carboxylate (3.70 g, 14.1 mmol) in carbon tetrachloride (70 mL) was refluxed for 1 hour. The solution was cooled, filtered to remove succinimide by-products, evaporated, dissolved in ethyl acetate and chromatographed on silica gel using ethyl acetate:hexane as the eluent to give 4.8 g of product. This was crystallized from ethyl acetate:hexane to give 3.6 g (75%) of t-butyl 4-(bromomethyl)-5-methoxy-1H-benzimidazole-1-carboxylate, mp 127-129°C. Anal. Calcd. for $C_{14}H_{17}BrN_2O_3$: C, 49.28; H, 5.02; Br, 23.42; N, 8.21. Found: C, 49.27; H, 4.98; Br, 26.81; N, 7.71.

35 Example 27. 5,6-Dihydro-7-methoxy-N,N-dipropyl-4H-imidazo(4,5,1-i)quinolin-5-amine (compound 14)

This compound was prepared by following the procedure of Example 18, but substituting *t*-butyl 4-(bromomethyl)-5-methoxy-1*H*-benzimidazole-1-carboxylate for *t*-butyl 4-(bromomethyl)-1*H*-benzimidazole-1-carboxylate. The product was crystallized from pentane; mp 46-49°C. Anal. Calcd. for C₁₇H₂₅N₃O: C, 71.04; H, 8.77; N, 14.62. Found: C, 70.80; H, 8.89; N, 14.80.

The bulk of the product was converted to the dihydrochloride salt.

Example 28. 5,6-Dihydro-8-methoxy-*N,N*-dipropyl-4*H*-imidazo(4,5,1-*ij*)quinolin-5-amine (compound 15)

This compound was prepared by following the procedure of Example 18, but substituting *t*-butyl 4-(bromomethyl)-6-methoxy-1*H*-benzimidazole-1-carboxylate for *t*-butyl 4-(bromomethyl)-1*H*-benzimidazole-1-carboxylate.

Example 29. 5,6-Dihydro-9-methoxy-*N,N*-dipropyl-4*H*-imidazo(4,5,1-*ij*)quinolin-5-amine (compound 16)

This compound was prepared by following the procedure of Example 18, but substituting *t*-butyl 4-(bromomethyl)-7-methoxy-1*H*-benzimidazole-1-carboxylate for *t*-butyl 4-(bromomethyl)-1*H*-benzimidazole-1-carboxylate.

Example 30. 5,6-Dihydro-7-methoxy-*N,N*-dimethyl-4*H*-imidazo(4,5,1-*ij*)quinolin-5-amine (compound 17)

This compound was prepared by following the procedure of Example 18, but substituting *t*-butyl 4-(bromomethyl)-5-methoxy-1*H*-benzimidazole-1-carboxylate for *t*-butyl 4-(bromomethyl)-1*H*-benzimidazole-1-carboxylate and diethyl (dimethylamino)malonate for diethyl (dipropylamino)malonate.

Example 31. 7-Chloro-5,6-dihydro-*N,N*-dipropyl-4*H*-imidazo(4,5,1-*ij*)quinolin-5-amine (compound 18)

This compound was prepared by following the procedure of Example 18, but substituting *t*-butyl 5-chloro-4-(bromomethyl)-1*H*-benzimidazole-1-carboxylate for *t*-butyl 4-(bromomethyl)-1*H*-benzimidazole-1-carboxylate.

Example 32. 5-(Dipropylamino)-5,6-dihydro-4*H*-imidazo(4,5,1-*ij*)quinolin-7-ol (compound 19)

5,6-Dihydro-7-methoxy-*N,N*-dipropyl-4*H*-imidazo(4,5,1-*ij*)quinolin-5-amine (1.0 g) was heated at 130°C in 48% hydrobromic acid for 2 hours. The solution was cooled and was then evaporated under reduced

pressure. The solid thus obtained was crystallized from methanol:ether; mp 270°C.

Example 33. 5,6-Dihydro-5-(dipropylamino)-4*H*-imidazo(4,5,1-*ij*)quinolin-8-ol (compound 20)

- 5 This compound was prepared by following the procedure of Example 32, but substituting 5,6-dihydro-8-methoxy-*N,N*-dipropyl-4*H*-imidazo(4,5,1-*ij*)quinolin-5-amine for 5,6-dihydro-7-methoxy-*N,N*-dipropyl-4*H*-imidazo(4,5,1-*ij*)quinolin-5-amine.

10 Example 34. 5,6-Dihydro-5-(dipropylamino)-4*H*-imidazo(4,5,1-*ij*)quinolin-9-ol (compound 21)

This compound was prepared by following the procedure of Example 32, but substituting 5,6-dihydro-9-methoxy-*N,N*-dipropyl-4*H*-imidazo(4,5,1-*ij*)quinolin-5-amine for 5,6-dihydro-7-methoxy-*N,N*-dipropyl-4*H*-imidazo(4,5,1-*ij*)quinolin-5-amine.

15 Example 35. *N*-(3-quinolyl)formamide (compound XXV)

- A solution of acetic formic anhydride was prepared by slowly adding 95-97% formic acid (20.80 g, 17.05 mL, 0.45 mol) to acetic anhydride (40.84 g, 37.7 mL, 0.40 mol) at 0°C. The solution was stirred at room temperature for 2 hours, then added to a stirred
20 solution of 3-aminoquinoline (28.84 g, 0.20 mol) in dry tetrahydrofuran (300 mL). After 15 minutes, the solution was evaporated, methanol (50 mL) was added, and the solution stirred for an additional 30 minutes. The solution was then evaporated under reduced pressure and the residual oil was triturated with ether. The
25 resulting white solid was filtered to give 28.7 g (84%) of product, mp 157-160°C. Anal. Calcd. for C₁₀H₈N₂O: C, 69.75; H, 4.68; N, 16.27. Found: C, 69.45; H, 4.78; N, 16.31.

Example 36. *N*-(1-Formyl-1,2,3,4-tetrahydro-3-quinolyl)formamide (compound XXVI)

- 30 A mixture of *N*-(3-quinolyl)formamide (30.0 g, 0.175 mol), platinum oxide (2.0 g) and acetic acid (300 mL) was hydrogenated (50 lb. initial H₂ pressure) until 2 equivalents of H₂ were consumed (reaction time 3 hours). The mixture was filtered through celite and the acetic acid removed under reduced pressure. It was dissolved in
35 ethyl acetate and washed with NaOH solution and water. Evaporation of the ethyl acetate gave 29.4 g of crude material. This was dissolved in 200 mL THF and acetic formic anhydride (prepared from formic acid (27.2 g, 0.59 mol) and acetic anhydride (53.5 g,

0.52 mol) was added at 0°C. After 15 minutes, the solution was allowed to warm to room temperature, and after an additional 15 minutes, methanol (60 mL) was added. The solution was evaporated and the resulting oil was partitioned between ethyl acetate and 4N sodium hydroxide solution. The sodium hydroxide solution was repeatedly extracted with ethyl acetate. The combined ethyl acetate was evaporated, and the crude product was purified by chromatography on silica gel using 2.5% methanol:chloroform as eluant to give 22.55 g (69%) of product. An analytical sample was crystallized from methanol:ether (1:3); mp 125-128°C. Anal. Calcd. for $C_{11}H_{12}N_2O_2$: C, 64.69; H, 5.92; N, 13.72. Found: C, 64.60; H, 5.97; N, 13.66.

Example 37. N-(1-Formyl-6-bromo-1,2,3,4-tetrahydro-3-quinolyl)formamide (compound XXVII)

Bromine (10.2 g, 0.064 mol) was added to a stirred solution of N-(1-formyl-1,2,3,4-tetrahydro-3-quinolyl)formamide (14.0 g, 0.065 mol) in acetic acid (70 mL) containing anhydrous sodium acetate (10.2 g, 0.12 mol). The solution was stirred for 30 minutes and water (500 mL) was added. The precipitate was filtered off and air dried to give 15.8 g (86%) of N-(1-formyl-6-bromo-1,2,3,4-tetrahydro-3-quinolyl)formamide, mp 174-178°C. A sample was recrystallized from ethanol for analysis; mp 178-181°C.

Example 38. 6-Bromo-1,2,3,4-tetrahydro-8-nitro-3-quinolinamine (compound XXIX)

A mixture of N-(1-formyl-6-bromo-1,2,3,4-tetrahydro-3-quinolyl)formamide (12.8 g, 45.2 mmol) and sodium nitrate (12.8 g, 150 mmol) in trifluoroacetic acid (100 mL) was stirred at room temperature for 18 hours. The bulk of the solvent was removed under reduced pressure and the residue was partitioned between ethyl acetate and water. The ethyl acetate was washed with sodium hydroxide and water, and the ethyl acetate was removed to give 14.2 g of N-(1-formyl-6-bromo-1,2,3,4-tetrahydro-8-nitro-3-quinolyl)formamide (compound XXVIII) as a solid. This was dissolved in ethanolic hydrogen chloride (100 mL of 4.0 N), the mixture was refluxed for 1 hour, ether (200 mL) was added, and the precipitate was filtered off, washed with ether and dried to give 12.8 g (82%) of 6-bromo-1,2,3,4-tetrahydro-8-nitro-3-quinolinamine dihydrochloride, mp >300°C.

Example 39. 5,6-Dihydro-4H-imidazo(4,5,1-f)quinolin-5-amine dihydrochloride (compound 22)

A mixture of 6-bromo-1,2,3,4-tetra-8-nitrohydro-3-quinolinamine dihydrochloride (10.69 g, 0.031 mol), and 10% palladium on carbon (1.0 g) in absolute ethanol (175 mL) was hydrogenated (50 lb initial H₂ pressure) until the H₂ uptake had ceased (reaction time 1.5 hours). The mixture was filtered through celite and the solvent removed under reduced pressure. The residual foam was partitioned between ethyl acetate and 1 N sodium hydroxide solution. Evaporation of the ethyl acetate gave 5.41 g of 3,8-diamino-1,2,3,4-tetrahydro-quinoline (compound XXX) as a brown oil.

This oil was dissolved in formic acid (60 mL) and stirred at 55°C for 5 hours. The formic acid was then removed under high vacuum. The resulting oil was partitioned between ethyl acetate (400 mL) and 4 N sodium hydroxide (60 mL). The aqueous phase was extracted 5 times with ethyl acetate and the combined ethyl acetate extracts were washed with water (2 x 25 mL). The ethyl acetate was evaporated to give 5.5 g of material, a mixture of the desired product (80%) and its N-formyl derivative (20%). The crude product was dissolved in methanolic HCl (150 mL) to hydrolyze the N-formyl compound. After 1.5 hours at room temperature, the precipitate which formed was filtered and washed with methanol:ether (1:3) to give 6.33 g (82%) of 5,6-dihydro-4H-imidazo(4,5,1-ij)quinolin-5-amine dihydrochloride, mp >300°C. Anal. Calcd. for C₁₀H₁₁N₃·2HCl: C, 48.80; H, 5.32; Cl, 28.81; N, 17.07. Found: C, 48.68; H, 5.44; Cl, 28.60; N, 16.92.

Example 40. 5,6-Dihydro-N-propyl-4H-imidazo(4,5,1-ij)quinoline-5-amine (compound 23)

Propionaldehyde (11.0 g, 0.19 mol) and sodium cyanoborohydride (0.85 g, 0.014 mol) were added at 0°C to a stirred solution of 5,6-dihydro-4H-imidazo(4,5,1-ij)quinolin-5-amine dihydrochloride (3.0 g, 0.012 mol) in methanol (250 mL). After 20 minutes, methanolic ammonia (10 mL) was added and the solution was concentrated to an oil and partitioned between ethyl acetate and sodium hydroxide solution. The ethyl acetate phase was washed with water, evaporated, dissolved in chloroform and chromatographed on silica gel using 5% methanol:-chloroform as eluant to get, as the first product eluted from the column, 0.9 g (32%) of 5,6-dihydro-N,N-dipropyl-4H-imidazo(4,5,1-ij)quinoline-5-amine.

Continued elution of the column gave 1.65 g (65%) of the

monopropylamine derivative. This was dissolved in methanol and ethereal HCl and ether added. The precipitate was filtered off and recrystallized twice from methanol:ether to give 1.32 g of 5,6-dihydro-N-propyl-4H-imidazo(4,5,1-ij)quinoline-5-amine sesquihydrochloride, mp 294-297°C (dec). Anal. Calcd. for $C_{13}H_{17}N_3 \cdot 1.5HCl$: C, 57.83; H, 6.91; Cl, 19.70; N, 15.56. Found: C, 57.84; H, 7.04; Cl, 19.46; N, 15.26.

Example 41. 5,6-Dihydro-8-methyl-N,N-dipropyl-4H-imidazo(4,5,1-ij)quinolin-5-amine (Compound 24)

10 This compound was prepared by following the procedure of Example 40, but substituting 5,6-dihydro-8-methyl-4H-imidazo(4,5,1-ij)quinolin-5-amine dihydrochloride for 5,6-dihydro-4H-imidazo(4,5,1-ij)quinolin-5-amine dihydrochloride. The compound was crystallized from hexane; mp 91-94°C. Anal. Calcd. for $C_{17}H_{25}N_3O$: C, 75.23; H, 9.28; N, 15.48. Found: C, 75.08; H, 8.88; N, 15.67.

Example 42. 5,6-Dihydro-2-methyl-N,N-dipropyl-4H-imidazo(4,5,1-ij)quinolin-5-amine (Compound 25)

20 *t*-Butyl (8-amino-1,2,3,4-tetrahydro-3-quinolyl)carbamate (2.72 g) was treated with acetic anhydride (1.16 g) in THF (150 mL) for 2.5 hours. The reaction was evaporated and the crude product was dissolved in methanolic hydrogen chloride. After 5 hours, the solvent was removed to give 3.1 g of 5,6-dihydro-2-methyl-4H-imidazo(4,5,1-ij)quinolin-5-amine dihydrochloride.

25 This was converted to 5,6-dihydro-2-methyl-N,N-dipropyl-4H-imidazo(4,5,1-ij)quinolin-5-amine using the procedure of Example 40. The product was converted to the dihydrochloride salt, mp 202-205°C. Anal. Calcd. for $C_{13}H_{17}N_3 \cdot 2HCl$: C, 59.28; H, 7.91; Cl 20.59; N, 12.20. Found: C, 58.51; H, 8.02; Cl, 21.90; N, 11.41.

Example 43. *t*-Butyl (6-bromo-1,2,3,4-tetrahydro-8-nitro-3-quinol-30 inyl)carbamate (compound XXXI)

35 A mixture of 6-bromo-1,2,3,4-tetrahydro-8-nitro-3-quinolinamine (3.45 g, 0.01 mol), di *t*-butyl dicarbonate (3.0 g, 0.014 mol) and triethylamine (2.0 g, 0.02 mol) in DMF (50 mL) was stirred at room temperature for 1 hour. Water (7 mL) was slowly added to the stirred solution. The precipitate was filtered off and washed with water and air dried to give 3.7 g of bright orange solid, mp 193-195°C. Anal. Calcd. for $C_{14}H_{18}BrN_3O_4$: C, 45.17; H, 4.87; Br, 21.47; N, 11.29. Found: C, 45.25; H, 4.97; Br, 21.34; N, 11.38.

Example 44. *t*-Butyl (1,2,5,6-tetrahydro-2-oxo-4*H*-imidazo(4,5,1-*lj*)quinolin-5-yl)carbamate (compound XXXIII)

Part A. *t*-butyl (8-amino-1,2,3,4-tetrahydro-3-quinoliny)carbamate

A mixture of *t*-butyl (6-bromo-1,2,3,4-tetrahydro-8-nitro-3-quinoliny)carbamate (3.72 g, 0.01 mol), absolute ethanol (150 mL) and 10% palladium on carbon (0.60 g) was hydrogenated (50 lb hydrogen pressure) for 18 hours. The mixture was filtered through celite and the solvent removed. The residual foam was partitioned between ethyl acetate and 1 N sodium hydroxide, and the ethyl acetate phase was evaporated under reduced pressure to give 2.72 g of *t*-butyl (8-amino-1,2,3,4-tetrahydro-3-quinolyl)carbamate (compound XXXII) as an oil.

Part B. *t*-Butyl (1,2,5,6-tetrahydro-2-oxo-4*H*-imidazo(4,5,1-*lj*)quinolin-5-yl)carbamate (compound XXXIII)

t-Butyl (8-amino-1,2,3,4-tetrahydro-3-quinolyl)carbamate (2.70 g) was dissolved in THF (100 mL) and stirred while a solution of phosgene in THF (20.7 mL of 0.40 M, 0.093 mol) was added. After 5 minutes, triethylamine (2.08 g, 0.020 mol) was added and the solution stirred for an additional 10 minutes. The THF was removed under reduced pressure and the material was partitioned between chloroform (250 mL) and water (20 mL). The chloroform was washed with 4N sodium hydroxide (5 mL) and evaporated. The crude material was combined with that of an earlier reaction (0.002 mol scale) and purified by chromatography on silica gel in 1% methanol:chloroform to give 2.28 g of product. Crystallization from methanol:ether (1:1) gave 1.60 g (54%) white solid, mp 235-36°C. Anal. Calcd. for C₁₅H₁₉N₃O₃: C, 62.26; H, 6.62; N, 14.52. Found: C, 61.65; H, 6.94; N, 14.23.

Example 45. 5-Amino-5,6-dihydro-4*H*-imidazo(4,5,1-*lj*)quinolin-2(1*H*)-one (compound 26)

t-Butyl (1,2,5,6-tetrahydro-2-oxo-4*H*-imidazo(4,5,1-*lj*)quinolin-5-yl)carbamate (1.65 g, 0.0057 mol) was dissolved in methanolic HCl (85 mL) and stirred at room temperature for 1 hour. The solvent was removed under reduced pressure to give 1.29 g of crude product. An analytical sample was recrystallized from methanol and ether to give a pink solid, mp >300°C. Anal. Calcd. for C₁₀H₁₁N₃O·HCl·1/2H₂O: C, 51.58; H, 5.58; Cl, 15.11; N, 17.90. Found: C, 51.04; H, 5.47; Cl, 15.10; N, 17.86.

Example 46. 5-(Dimethylamino)-5,6-dihydro-4*H*-imidazo(4,5,1-*lj*)quinolin-2(1*H*)-one hydrochloride (compound 27)

5-Amino-5,6-dihydro-4*H*-imidazo(4,5,1-*ij*)quinolin-2(1*H*)-one (0.73 g, 3.2 mmol) was dissolved in 1*N* sodium hydroxide solution (3.2 mL). To this was added absolute ethanol (100 mL), 37% formaldehyde solution (1.3 mL), 10% palladium on carbon (0.65 g), and the mixture was hydrogenated (50 lb. initial H₂ pressure) until H₂ uptake ceased (reaction time 5 hours). The mixture was filtered through celite and the solvent removed under reduced pressure to yield a clear oil. The crude material was combined with that of a previous reaction (2.5 mmol), dissolved in chloroform and gravity filtered to remove paraformaldehyde. The compound was purified by chromatographing on silica gel in 10% methanol:chloroform to give 0.88 g (71%) of 5-(dimethylamino)-5,6-dihydro-4*H*-imidazo(4,5,1-*ij*)quinolin-2(1*H*)-one an oil.

The bulk of the product was converted to the hydrochloride salt, mp 220-223°C. Anal. Calcd. for C₁₂H₁₅N₃O·HCl.1/2H₂O: C, 54.85; H, 6.52; Cl, 13.49; N, 15.99. Found: C, 54.97; H, 6.33; Cl, 13.08; N, 15.55.

Example 47. 5-(Propylamino)-5,6-dihydro-4*H*-imidazo(4,5,1-*ij*)quinolin-2(1*H*)-one (compound 28)

Sodium cyanoborohydride (0.17 g) was added in small portions over a 5-hour period to a stirred solution of 1.90 g (8.4 mmol) 5-amino-5,6-dihydro-4*H*-imidazo(4,5,1-*ij*)quinolin-2(1*H*)-one, 0.85 mL sodium methoxide and 1.5 g propionaldehyde in methanol (175 mL). Methanolic ammonia solution was added, and after 30 minutes, the solvent was evaporated. The residual oil was partitioned between ethyl acetate and water and the crude product obtained by evaporating the ethyl acetate was dissolved in chloroform and chromatographed on silica gel eluting with 2.5% methanol:chloroform to give 1.24 g (64% yield) of 5,6-dihydro-5-(propylamino)-4*H*-imidazo(4,5,1-*ij*)quinolin-2(1*H*)-one.

The bulk of the product was converted to the hydrochloride salt, mp >300°C from methanol:ether. Anal. Calcd. for C₁₃H₁₇N₃O·HCl: C, 58.31; H, 6.77; Cl, 13.24; N, 15.69. Found: C, 58.16; H, 6.92; Cl, 13.17; N, 15.18.

Example 48. 5-(Dipropylamino)-5,6-dihydro-4*H*-imidazo(4,5,1-*ij*)quinolin-2(1*H*)-one (compound 29)

Propionaldehyde (12.7 g, 0.21 mol) and sodium cyanoborohydride (2.22 g, 0.035 mol) were added at 0°C to a stirred solution of 5-

amino-5,6-dihydro-4*H*-imidazo(4,5,1-*ij*)quinolin-2(1*H*)-one (2.70 g, 0.012 mol) and sodium methoxide (1 mL of 3.8 M) in methanol (250 mL). The solution was allowed to warm to room temperature and, after 1 hour, methanolic ammonia (10 mL) was added. The solution was stirred
5 an additional 30 minutes and the solvent removed under reduced pressure. The mixture was dissolved in EtOAc (500 mL), washed with 4*N* NaOH (15 mL) and H₂O (2 x 10 mL) and evaporated. The crude product was dissolved in chloroform:methanol (2:1) and chromatographed on silica gel eluting with chloroform. The solid obtained
10 was triturated with ether:hexane (1:1, 40 mL) and filtered to give 2.12 g (65%) of product, mp 155-157°C. The analytical sample was recrystallized from ethyl acetate:hexane; mp 155-158°C. Anal. Calcd. for C₁₆H₂₃N₃O: C, 70.29; H, 8.48; N, 15.37. Found: C, 70.36; H, 8.78; N, 15.30.

15 The bulk of the product was converted to the hydrochloride salt, mp 221-224°C (dec). Anal. Calcd. for C₁₆H₂₃N₃O·HCl: C, 62.02; H, 7.81; Cl, 11.44; N, 13.56. Found: C, 61.88; H, 7.79; Cl, 11.50; N, 13.48.

20 Example 49. (-) 5-(Dipropylamino)-5,6-dihydro-4*H*-imidazo(4,5,1-*ij*)quinolin-2(1*H*)-one ((-) compound 29)

Part A. (+) and (-) *t*-Butoxycarbonyl N-(1-(1,2,5,6-tetrahydro-2-oxo-4*H*-imidazo(4,5,1-*ij*)quinolin-5-yl)-L-phenylalaninamide

A mixture of *t*-butoxycarbonyl-L-phenylalanine (2.9 g, 11 mmol), 5-amino-5,6-dihydro-4*H*-imidazo(4,5,1-*ij*)quinolin-2(1*H*)-one hydro-
25 chloride (2.25 g, 10 mmol), 1-hydroxybenzotriazole (1.65 g, 11 mmol), triethylamine (1.1 g, 11 mmol) and dicyclohexylcarbodiimide (3.09 g, 15 mmol) in dimethylformamide (50 mL) was stirred at room temperature for 2 hours. The solution was filtered to remove dicyclohexylurea, evaporated, and chromatographed to give, as the first product eluted
30 from the column, 1.8 g of (+) *t*-butoxycarbonyl N-(1,2,5,6-tetrahydro-2-oxo-4*H*-imidazo(4,5,1-*ij*)quinolin-5-yl)-L-phenylalaninamide. This was crystallized from methanol; mp 215-217°C; (α)_D^{NaOH} +26°. Anal. Calcd. for C₂₄H₂₈N₄O₄: C, 66.03; H, 6.47; N, 12.84. Found: C, 66.01; H, 6.54; N, 13.01.

35 Continued elution of the column gave 1.9 g of (-) *t*-butoxycarbonyl N-(1,2,5,6-tetrahydro-2-oxo-4*H*-imidazo(4,5,1-*ij*)quinolin-5-yl)-L-phenylalaninamide.

Part B. (-) 5-amino-5,6-dihydro-4*H*-imidazo(4,5,1-*ij*)quinolin-2(1*H*)-

one

- (-) *t*-Butoxycarbonyl N-(1,2,5,6-tetrahydro-2-oxo-4*H*-imidazo(4,5,1-*ij*)quinolin-5-yl)-L-phenylalaninamide (1.8 g) was stirred in ethanolic hydrogen chloride (50 mL of 4.0 N) for 1 hour. The solvent was removed and the residual oil was partitioned between chloroform and sodium hydroxide solution. Evaporation of the chloroform gave 1.4 g of (-) N-(1,2,5,6-tetrahydro-2-oxo-4*H*-imidazo(4,5,1-*ij*)quinolin-5-yl)phenylalaninamide. This was dissolved in acetonitrile:THF (30 mL of 1:1) and phenyl isothiocyanate (675 mg, 5 mmol) was added. After 1 hour, the solvents were removed and the residual oil was chromatographed on silica gel using chloroform as the initial eluant. Elution of the column with 5% methanol:chloroform gave 1.8 g of (-) N-((phenylamino)thiocarbonyl)-N-(1,2,5,6-tetrahydro-2-oxo-4*H*-imidazo(4,5,1-*ij*)quinolin-5-yl)phenylalaninamide. This was dissolved in trifluoroacetic acid (25 mL). After 1 hour the solvent was removed and the residue was dissolved in methanol (5 mL). Ether (50 mL) was added, the solution was cooled to -10°C, and the precipitate was filtered off, washed with ether, and air dried to give 1.2 g of (-) 5-amino-5,6-dihydro-4*H*-imidazo(4,5,1-*ij*)quinolin-2(1*H*)-one trifluoroacetate, mp 247°C (dec). (α)_D^{MeOH} -18°. Anal. Calcd. for C₁₀H₁₁N₃O·C₂HF₃O₂: C, 47.53; H, 3.99; F, 18.80; N, 13.97. Found: C, 47.31; H, 4.26; F, 17.37; N, 13.48.

Part C. (-) 5-(Dipropylamino)-5,6-dihydro-4*H*-imidazo(4,5,1-*ij*)quinolin-2(1*H*)-one

- This was prepared following the procedure of Example 47, but using (-) 5-amino-5,6-dihydro-4*H*-imidazo(4,5,1-*ij*)quinolin-2(1*H*)-one trifluoroacetate in place of 5-amino-5,6-dihydro-4*H*-imidazo(4,5,1-*ij*)quinolin-2(1*H*)-one. The hydrochloride salt of the product crystallized from methanol:ether as a hemihydrate (2.89% water content) with an indefinite melting point; (α)_D^{MeOH} -16.5°. Anal. Calcd. for C₁₆H₂₃N₃O·HCl·1/2H₂O: C, 62.02; H, 7.81; N, 13.56; Cl, 11.44. Found: C, 61.88; H, 7.79; N, 13.48; Cl, 11.50. The compound was also converted to the hydrobromide salt which was obtained as a monohydrate, mp 190-192°C from methanol/ether.

- Example 50. (+) 5-(Dipropylamino)-5,6-dihydro-4*H*-imidazo(4,5,1-*ij*)quinolin-2(1*H*)-one hydrochloride

This was prepared from (+) *t*-butoxycarbonyl N-(1,2,5,6-tetrahydro-2-oxo-4*H*-imidazo(4,5,1-*ij*)quinolin-5-yl)-L-phenylalaninamide using

the procedures described in Example 49, parts B and C. The hydrochloride salt of the product crystallized from methanol:ether as a hydrate (0.99% water content) with an indefinite melting point; (α)_D^{MeOH} +16.5°. Anal. Calcd. for C₁₆H₂₃N₃O·HCl·1/4H₂O: C, 61.13; H, 8.01; Cl, 11.28; N, 13.37. Found: C, 61.17; H, 8.08; Cl, 11.12; N, 13.35.

Example 51. 5-(Dipropylamino)-5,6-dihydro-1-methyl-4*H*-imidazo-(4,5,1-*ij*)quinolin-2(1*H*)-one (compound 30)

Potassium hydride (0.28 g of a 35% by wt. mineral oil dispersion, washed with ether to remove oil, 2.7 mmol) in dry THF was added to a stirred solution of 5-(dipropylamino)-5,6-dihydro-4*H*-imidazo-(4,5,1-*ij*)quinolin-2(1*H*)-one (0.60 g, 2.2 mmol) in dry THF (25 mL). Methyl iodide (0.31 g, 2.2 mmol) in dry THF was then added. After stirring at room temperature for 18 hours, methanol was slowly added to the solution. The solvent was then removed under reduced pressure and the material dissolved in methanol:chloroform (1:1) and chromatographed on silica gel using chloroform as eluant to give 0.50 g (79% yield) of a yellow solid. The product was recrystallized twice from hexane to give 0.28 g (44%) of 5-(dipropylamino)-5,6-dihydro-1-methyl-4*H*-imidazo(4,5,1-*ij*)quinolin-2(1*H*)-one, mp 83-85°C. Anal. Calcd. for C₁₇H₂₅N₃O: C, 71.04; H, 8.77; N, 14.62. Found: C, 71.25; H, 8.91; N, 14.74.

Example 52. 5-(Dimethylamino)-5,6-dihydro-1-methyl-4*H*-imidazo-(4,5,1-*ij*)quinolin-2(1*H*)-one (compound 31)

This compound was prepared by following the procedure of Example 51, but substituting 5-(dimethylamino)-5,6-dihydro-4*H*-imidazo(4,5,1-*ij*)quinolin-2(1*H*)-one for 5-(dipropylamino)-5,6-dihydro-4*H*-imidazo(4,5,1-*ij*)quinolin-2(1*H*)-one.

The product was converted to the hydrochloride salt which was crystallized from methanol:ether; mp 268-271°C. Anal. Calcd. for C₁₃H₁₇N₃O·HCl: C, 58.31; H, 6.77; Cl, 13.24; N, 15.69. Found: C, 58.40; H, 6.92; Cl, 13.05; N, 15.33.

Example 53. 5-(Dimethylamino)-5,6-dihydro-8-methyl-4*H*-imidazo-(4,5,1-*ij*)quinolin-2(1*H*)-one (compound 32)

This compound was prepared by following the procedure of Example 46, but substituting 5-amino-5,6-dihydro-6-methyl-4*H*-imidazo(4,5,1-*ij*)quinolin-2(1*H*)-one for 5-amino-5,6-dihydro-4*H*-imidazo(4,5,1-*ij*)quinolin-2(1*H*)-one.

The product was converted to the hydrochloride salt which was crystallized from methanol:ether; mp 281-284°C. Anal. Calcd. for $C_{13}H_{17}N_3O \cdot HCl$: C, 58.31; H, 6.77; Cl, 13.24; N, 15.69. Found: C, 58.00; H, 7.03; Cl, 12.94; N, 15.44.

5 Example 54. 6-Bromo-1,2,3,4-tetrahydro-8-nitro-N,N-dipropyl-3-quinolinamine (compound XXXIa)

A mixture of 6-bromo-1,2,3,4-tetrahydro-8-nitro-3-quinolinamine dihydrochloride (11.5 g, 0.033 mol), iodopropane (21 g, 0.12 mol) and anhydrous sodium carbonate (20 g, 0.19 mol) in dimethylformamide (100
10 mL) was stirred at 100°C for 5 hours. The solution was then evaporated, partitioned between ethyl acetate and water, and the ethyl acetate was evaporated to give a red oil. This was chromatographed on silica gel to give 8.2 g of 6-bromo-1,2,3,4-tetrahydro-8-nitro-N,N-dipropyl-3-quinolinamine. The product was crystallized from
15 ethyl acetate:hexane to give 7.6 g of product, mp 79-81°C. Anal. Calcd. for $C_{15}H_{22}BrN_3O_2$: C, 50.57; H, 6.23; Br, 22.43; N, 11.79. Found: C, 50.59; H, 6.27; Br, 22.53; N, 11.69.

Continued elution of the column afforded 1.5 g of 6-bromo-1,2,3,4-tetrahydro-8-nitro-N-propyl-3-quinolinamine as an oil.

20 Example 55. 6-Bromo-1,2,3,4-tetrahydro-N,N-dimethyl-8-nitro-3-quinolinamine (compound XXXIb)

A mixture of 6-bromo-1,2,3,4-tetrahydro-8-nitro-3-quinolinamine (1.5 g, 5.5 mmol), 37% aqueous formaldehyde (1.8 mL) and formic acid (10 mL) was heated at 100°C for 1 hour. The solution was then evaporated, partitioned between ethyl acetate (200 mL) and 4 N sodium hydroxide solution (10 mL), and the ethyl acetate was evaporated to
25 give a red oil. This was chromatographed on silica gel to give 1.58 g of 6-bromo-1,2,3,4-tetrahydro-N,N-dimethyl-8-nitro-3-quinolinamine. The product was crystallized from ethyl acetate:hexane; mp 88-91°C. Anal. Calcd. for $C_{11}H_{14}BrN_3O_2$: C, 44.01; H, 4.70; Br, 26.62; N,
30 14.00. Found: C, 44.04; H, 4.89; Br, 26.62; N, 13.97.

Example 56. 5-(Dipropylamino)-5,6-dihydro-4H-imidazo(4,5,1-1j)quinolin-2(1H)-thione (Compound 33)

Part A. 1,2,3,4-Tetrahydro-N³,N³-dipropyl-3,8-quinolinediamine
35 (compound XXXVb)

A mixture of 6-bromo-1,2,3,4-tetrahydro-8-nitro-N,N-dipropyl-3-quinolinamine (2.7 g) and 10% palladium charcoal (0.5 g) in ethanol (150 mL) was hydrogenated for 18 hours. The solution was filtered

and the ethanol evaporated to give 1.9 g of 1,2,3,4-tetrahydro-N³,N³-dipropyl-3,8-quinolinediamine as an oil.

Part B. 5-(Dipropylamino)-5,6-dihydro-4*H*-imidazo(4,5,1-*ij*)quinolin-2(1*H*)-thione

5 Di (2-pyridyl)thiocarbonate (1.6 g, 7.2 mmol) was added to a stirred solution of 1,2,3,4-tetrahydro-N³,N³-dipropyl-3,8-quinoline-diamine (1.6 g, 6.7 mmol) in THF (50 mL). The solution was stirred for 1 hour, evaporated, and partitioned between chloroform and water. The chloroform phase was evaporated and chromatographed on silica gel
10 using ethyl acetate:hexane (1:9) as the initial eluant to give 1.6 g of product. Crystallization from cyclohexane gave 1.3 g (67%) of 5-(dipropylamino)-5,6-dihydro-4*H*-imidazo(4,5,1-*ij*)quinolin-2(1*H*)-thione, mp 150-151°C. Anal. Calcd. for C₁₆H₂₃N₃S: C, 66.39; H, 8.01; N, 14.52; S, 11.08. Found: C, 66.50; H, 8.18; N, 14.56; S,
15 11.02.

Example 57. 5,6-Dihydro-2-methylthio-N,N-dipropyl-4*H*-imidazo(4,5,1-*ij*)quinolin-5-amine (compound 34)

This compound was prepared using the procedure of Example 51, but substituting 5-(dipropylamino)-5,6-dihydro-4*H*-imidazo(4,5,1-
20 *ij*)quinolin-2(1*H*)-thione for 5-(dipropylamino)-5,6-dihydro-4*H*-imidazo(4,5,1-*ij*)quinolin-2(1*H*)-one. The product was crystallized from pentane; mp 49-52°C. Anal. Calcd. for C₁₇H₂₅N₃S: C, 67.28; H, 8.30; N, 13.85; S, 10.57. Found: C, 67.57; H, 8.27; N, 14.00; S, 10.44.

25 Example 58. 5,6-Dihydro-N⁵,N⁵-dipropyl-4*H*-imidazo(4,5,1-*ij*)quinoline-2,5-diamine (compound 35)

This compound was prepared using the procedure of Example 56 part B, but substituting cyanogen bromide for di (2-pyridyl)thiocarbonate. The product was purified by chromatography and triturated
30 with ether; mp 160-170°C. Anal. Calcd. for C₁₆H₂₄N₄: C, 70.55; H, 8.88; N, 20.57. Found: C, 68.96; H, 9.03; N, 20.57.

Example 59. 5,6-Dihydro-N²-methyl-N⁵,N⁵-dipropyl-4*H*-imidazo(4,5,1-*ij*)quinoline-2,5-diamine (compound 36)

This compound was prepared using the procedure of Example 51,
35 but substituting 5,6-dihydro-N⁵,N⁵-dipropyl-4*H*-imidazo(4,5,1-*ij*)quinoline-2,5-diamine for 5-(dipropylamino)-5,6-dihydro-4*H*-imidazo(4,5,1-*ij*)quinolin-2(1*H*)-one. The product was separated by chromatography from the accompanying 5,6-dihydro-1-methyl-N⁵,N⁵-dipropyl-4*H*-

imidazo(4,5,1-*lj*)quinoline-2,5-diamine.

Example 60. 5-(Dipropylamino)-5,6-dihydro-4*H*-imidazo(4,5,1-*lj*)quinolin-2-yl)cyanamide (compound 37)

This compound was prepared using the procedure of Example 56
5 part B, but substituting diphenyl cyanocarbonimidate for di (2-pyridyl)thiocarbonate.

Example 61. 5,6-Dihydro-*N,N*-dipropyl-1*H*,4*H*-thiadiazolo(4,3,2-*lj*)quinoline-5-amine 2,2-dioxide (compound 38)

This compound was prepared using the procedure of Example 56
10 part B, but substituting sulfamide for di (2-pyridyl)thiocarbonate and carrying the reaction out at 150°C in absence of solvent.

Example 62. 1,2,6,7-Tetrahydro-6-(dipropylamino)-3*H*,5*H*-pyrido-(1,2,3-*de*)quinoxalin-3-one (compound 39)

This compound was prepared using the procedure of Example 56,
15 but substituting ethyl bromoacetate for di (2-pyridyl)thiocarbonate and carrying the reaction out at the reflux temperature. The crude product was chromatographed to give, as the major product and first compound eluted from the column, 1,2,6,7-tetrahydro-6-(dipropylamino)-3*H*,5*H*-pyrido(1,2,3-*de*)quinoxalin-3-one. The product was crystallized from ethyl acetate:hexane; mp 97-99°C. Anal. Calcd. for C₁₇H₂₅N₃O: C, 71.04; H, 8.77; N, 14.62. Found: C, 71.20; H, 8.90; N, 14.85.

Continued elution of the column gave a small amount of 1,2,6,7-tetrahydro-6-(dipropylamino)-3*H*,5*H*-pyrido(1,2,3-*de*)quinoxalin-2-one.

25 Example 63. 1,2,6,7-Tetrahydro-6-(dipropylamino)-3*H*,5*H*-pyrido-(1,2,3-*de*)quinoxalin-2-one (compound 40)

This compound was prepared using the procedure of Example 56, but substituting chloroacetic anhydride for di (2-pyridyl)thiocarbonate. The initially formed N⁸-(chloroacetyl)-1,2,3,4-tetrahydro-N³,N³-dipropyl-3,8-quinolinediamine was heated at 150°C in DMF to effect cyclization to 1,2,6,7-tetrahydro-6-(dipropylamino)-3*H*,5*H*-pyrido(1,2,3-*de*)quinoxalin-2-one which was thereby obtained as the hydrochloride salt which was crystallized from methanol:ether; mp 250-255°C (dec). Anal. Calcd. for C₁₇H₂₅N₃O·HCl: C, 63.04; H, 8.09; Cl, 10.95; N, 12.98. Found: C, 62.39; H, 8.34; Cl, 10.85; N, 12.84.

35 Example 64. 6,7-Dihydro-6-(dipropylamino)-3*H*,5*H*-pyrido(1,2,3-*de*)quinoxalin-3-one (compound 41)

This compound was prepared using the procedure of Example 56,

but substituting butyl glyoxylate for di (2-pyridyl)thiocarbonate and carrying the reaction out at the reflux temperature.

The bulk of the product was converted to the p-toluenesulfonate salt, mp 188-190°C from methanol:ether.

- 5 Example 65. 6,7-Dihydro-6-(dipropylamino)-1*H*,5*H*-pyrido(1,2,3-*de*)-quinoxalin-2,3-dione (compound 42)

This compound was prepared using the procedure of Example 56, but substituting ethyl oxalyl chloride for di (2-pyridyl)thiocarbonate and carrying the reaction out at the reflux temperature.

- 10 The product was crystallized from ethyl acetate:hexane; mp 166-168°C. Anal. Calcd. for C₁₇H₂₃N₃O₂: C, 67.75; H, 7.69; N, 13.94. Found: C, 67.66; H, 7.96; N, 13.80.

The bulk of the product was converted to the hydrochloride salt which was crystallized from methanol:ether; mp 250-255°C (dec).

- 15 Example 66. 5-(Dimethylamino)-5,6-dihydro-4*H*-imidazo(4,5,1-*ij*)quinolin-2(1*H*)-thione (compound 43)

Part A. 1,2,3,4-Tetrahydro-N³,N³-dimethyl-3,8-quinolinediamine (compound XXXVb)

- 20 A mixture of 6-bromo-1,2,3,4-tetrahydro-8-nitro-N,N-dimethyl-3-quinolinamine (1.15 g, 3.8 mmol) and 10% palladium charcoal (0.5 g) in ethanol (150 mL) was hydrogenated for 18 hours. The solution was filtered and the ethanol evaporated to give 0.73 g of 1,2,3,4-tetrahydro-N³,N³-dimethyl-3,8-quinolinediamine as an oil.

- Part B. 5-(Dimethylamino)-5,6-dihydro-4*H*-imidazo(4,5,1-*ij*)quinolin-2(1*H*)-thione
25

Di (2-pyridyl)thiocarbonate (0.92 g, 4.0 mmol) was added to a stirred solution of 1,2,3,4-tetrahydro-N³,N³-dimethyl-3,8-quinolinediamine (0.73 g, 3.8 mmol) in THF (50 mL). The solution was stirred for 1 hour, evaporated, and partitioned between chloroform and water.

- 30 The chloroform phase was evaporated and chromatographed on silica gel using ethyl acetate:hexane (1:9) as the initial eluant to give 0.68 g of product. Crystallization from cyclohexane gave 0.60 g of 5-(dimethylamino)-5,6-dihydro-4*H*-imidazo(4,5,1-*ij*)quinolin-2(1*H*)-thione, mp 203-205°C. Anal. Calcd. for C₁₂H₁₅N₃S: C, 61.77; H, 6.48; N, 18.01; S, 13.74. Found: C, 61.77; H, 6.53; N, 17.73; S, 35

Example 67. Alternate synthesis of 1,2,3,4-Tetrahydro-N³,N³-dimethyl-3,8-quinolinediamine (compound XXXVb)

Part A. Diethyl (formylamino)((2-nitrophenyl)methyl)propanedioate

Diethyl (formylamino)malonate (20.3 g, 0.1 mol) was added to a stirred solution of sodium ethoxide (250 mL of 0.4 M). 2-Nitrobenzyl chloride (17.2 g, 0.1 mol) was added, the mixture was refluxed for 2 hours and the solvent was then removed under reduced pressure. The material was partitioned between ethyl acetate and water, the ethyl acetate was separated and evaporated to give 40.3 g of crude product. The compound was crystallized from ethyl acetate:hexane to give 25.5 g of diethyl (formylamino)((2-nitrophenyl)methyl)propanedioate; mp 129-132°C.

10 Part B. Ethyl 3-(formylamino)-1,2,3,4-tetrahydro-2-oxo-3-quinolinecarboxylate

A mixture of diethyl (formylamino)((2-nitrophenyl)methyl)propanedioate (8.54 g, 0.025 mol) and 10% palladium on carbon (2.0 g) in absolute ethanol (200 mL) was hydrogenated (50 lb initial H₂ pressure) until hydrogen uptake ceased. The mixture was filtered through celite and refluxed for 2 hours to achieve cyclization. The solvent was removed under reduced pressure to give 6.6 g of product which was crystallized from methanol to give 5.0 g of white crystals, mp 187-190°C. Anal. Calcd. for C₁₃H₁₄N₂O₄: C, 59.53; H, 5.38; N, 10.68. Found: C, 59.77; H, 5.36; N, 10.75.

20 Part C. 3-(Formylamino)-3,4-dihydro-2(1H)quinolinone

Sodium hydroxide (50 mL of 4.0 N, 0.20 mol) was added to a stirred solution of ethyl 3-(formylamino)-1,2,3,4-tetrahydro-2-oxo-3-quinolinecarboxylate (11.3 g, 0.043 mol) in methanol (250 mL). After 30 minutes, a white precipitate appeared and, after 45 minutes water (50 mL) was added to the reaction. After refluxing overnight, hydrochloric acid (50 mL of 4.0 N, 0.20 mol) was added and the solvents were removed under reduced pressure. The residual solid was refluxed in ethanol (200 mL) for 1 hour, filtered to remove salt, and cooled to afford 6.8 g of product, mp 197-200°C. Anal. Calcd. for C₁₀H₁₀N₂O₂: C, 63.15; H, 5.30; N, 14.73. Found: C, 63.03; H, 5.37; N, 14.71.

30 Part D. 3-(Formylamino)-6-bromo-3,4-dihydro-8-nitro-2(1H)quinolinone

35 Bromine (16.0 g, 0.1 mol) was added to a stirred solution of 3-(formylamino)-3,4-dihydro-2(1H)quinolinone (19.0 g, 0.1 mol) and anhydrous sodium acetate (12.7 g, 0.2 mol) in acetic acid (500 mL). After 1 hour, water (1.5 L) was added and the precipitate was

filtered off and air dried to give 17.8 g of 3-(formylamino)-6-bromo-3,4-dihydro-2(1H)quinolinone, mp 275-282°C (dec). This was dissolved in trifluoroacetic acid (300 mL) and sodium nitrate (9.0 g) was added to the stirred solution. After 1 hour, water was added and the precipitate was filtered off and air dried to give 18.2 g of 3-(formylamino)-6-bromo-3,4-dihydro-8-nitro-2(1H)quinolinone, mp 232-235°C.

Part E. 3-(Amino)-6-bromo-3,4-dihydro-8-nitro-2(1H)quinolinone

This compound was prepared using the procedure of Example 9 part A, but substituting 3-(formylamino)-6-bromo-3,4-dihydro-8-nitro-2(1H)quinolinone for N-(2,3,6,7-tetrahydro-3-oxo-1H,5H-benzo(1j)quinolizin-2-yl)-formamide.

Part F. 3-(Dimethylamino)-6-bromo-3,4-dihydro-8-nitro-2(1H)quinolinone

This compound was prepared using the procedure of Example 55, but substituting 3-(formylamino)-6-bromo-3,4-dihydro-8-nitro-2(1H)quinolinone for 6-bromo-1,2,3,4-tetrahydro-8-nitro-3-quinolinamine. The product was crystallized from ethyl acetate; mp 162-165°C.

Part G. 3,8-Diamino-3,4-dihydro-N³,N³-dimethyl-2(1H)quinolinone

This compound was prepared using the procedure of Example 56 part A, but substituting 3-(dimethylamino)-6-bromo-3,4-dihydro-8-nitro-2(1H)quinolinone for 6-bromo-1,2,3,4-tetrahydro-8-nitro-N,N-dipropyl-3-quinolinamine.

Part H. 1,2,3,4-Tetrahydro-N³,N³-dimethyl-3,8-quinolinediamine

This compound was prepared using the procedure of Example 14, but substituting 3,8-diamino-3,4-dihydro-N³,N³-dimethyl-2(1H)quinolinone for N-(2,3,6,7-tetrahydro-3-oxo-1H,5H-benzo(1j)quinolizin-2-yl)propanamide.

Example 68. 5,6-Dihydro-N,N-dimethyl-2-methylthio-4H-imidazo(4,5,1-1j)quinoline-5-amine (compound 44)

This compound was prepared using the procedure of Example 51, but substituting 5-(dimethylamino)-5,6-dihydro-4H-imidazo(4,5,1-1j)quinolin-2(1H)-thione for 5-(dipropylamino)-5,6-dihydro-4H-imidazo(4,5,1-1j)quinolin-2(1H)-one. The product was crystallized from ethyl acetate:hexane; mp 84-86°C. Anal. Calcd. for C₁₃H₁₇N₃S: C, 63.12; H, 6.93; N, 16.99; S, 12.96. Found: C, 63.08; H, 7.02; N, 16.97; S, 12.82.

Example 69. 5,6-Dihydro-N⁵,N⁵-dimethyl-4H-imidazo(4,5,1-1j)quin-

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oline-2,5-diamine (compound 45)

This compound was prepared using the procedure of Example 66, but substituting cyanogen bromide for di (2-pyridyl)thiocarbonate.

Example 70. 5,6-Dihydro-N,N-dimethyl-4H-thiadiazolo(4,3,2-ij)quinoline-5-amine 2,2-dioxide (Compound 46)

This compound was prepared using the procedure of Example 66, but substituting sulfamide for di (2-pyridyl)thiocarbonate and carrying the reaction out at 150°C in absence of solvent.

Example 71. 1,2,6,7-Tetrahydro-6-(dimethylamino)-3H,5H-pyrido(1,2,3-de)quinoxalin-3-one (compound 47)

This compound was prepared using the procedure of Example 66, but substituting ethyl bromoacetate for di (2-pyridyl)thiocarbonate and carrying the reaction out at the reflux temperature.

Example 72. 1,2,6,7-Tetrahydro-6-(dimethylamino)-3H,5H-pyrido(1,2,3-de)quinoxalin-2-one (compound 48)

This compound was prepared using the procedure of Example 66, but substituting chloroacetic anhydride for di (2-pyridyl)thiocarbonate and cyclizing the initially formed N⁸-(chloroacetyl)-1,2,3,4-tetrahydro-N³,N³-dimethyl-3,8-quinolinediamine by heating at 150°C in DMF.

Example 73. 6,7-Dihydro-6-(dimethylamino)-3H,5H-pyrido(1,2,3-de)quinoxalin-3-one (compound 49)

This compound was prepared using the procedure of Example 66, but substituting butyl glyoxylate for di (2-pyridyl)thiocarbonate and carrying the reaction out at the reflux temperature.

Example 74. 6,7-Dihydro-6-(dimethylamino)-1H,5H-pyrido(1,2,3-de)quinoxalin-2,3-dione (compound 50)

This compound was prepared using the procedure of Example 66, but substituting ethyl oxalyl chloride for di (2-pyridyl)thiocarbonate and carrying the reaction out at the reflux temperature.

Example 75. Alternate synthesis of 5-(dipropylamino)-5,6-dihydro-4H-imidazo(4,5,1-ij)quinolin-2(1H)-one (compound 29)

Part A. 4-Methyl-1H-benzimidazolidinone

1,1-Carbonyldiimidazole (30.5 g, 0.19 mol) was added, with cooling, to a stirred solution of 3-methyl-1,2-benzenediamine (22.98 g, 0.19 mol) in dimethylformamide (200 mL) and the mixture was heated at 100°C for 1 hour. The solvent was removed under reduced pressure until solid began to appear. Water (200 mL) was slowly added, with

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stirring, to precipitate the desired product. The precipitate was filtered off and air-dried overnight to give 26.28 g brown solid, mp > 280°C, which was used without further purification.

Part B. 2-Chloro-4-methyl-1*H*-benzimidazole

- 5 Hydrogen chloride gas was bubbled through a stirred mixture of 4-methyl-1*H*-benzimidazolidinone (5 g, 0.034 mol) in phosphorus oxychloride (50 mL) for 1 hour at 120°C. The solvent was removed and the resulting solid was dissolved in water (50 mL). Ammonium hydroxide (20 mL) was carefully added until the mixture was basic.
- 10 The aqueous phase was then extracted with chloroform, filtered through celite, and evaporated to give 5.2 g of brown oil. The product was chromatographed on silica gel in chloroform, and was eluted with 14 methanol:chloroform to give 3.96 g of brown oil. Crystallization from ethyl acetate:hexane gave 2.72 g of brown
- 15 crystals, mp 137.5-139.5°C.

Part C. Methyl 2-chloro-4-methyl-1*H*-benzimidazole-1-carboxylate

- Potassium hydride (0.85 g of 35% in oil, washed with ether to remove oil, 7.4 mmol) was added to a stirred solution of 2-chloro-4-methyl-1*H*-benzimidazole (1.23 g, 7.4 mmol) in THF (25 mL). Methyl
- 20 chloroformate (0.7 g, 7.4 mmol) was added and the reaction was stirred 10 minutes. The solvent was removed and the material was partitioned between ethyl acetate and water. Evaporation of the organic layer gave 1.68 g of white solid. Crystallization from hexane gave 1.42 g of white crystals, mp 90-91°C. Anal. Calcd. for
- 25 C₁₀H₉ClN₂O₂: C, 53.47; H, 4.04; Cl, 15.78; N, 12.47. Found: C, 53.63; H, 4.11; Cl, 15.81; N, 12.45.

Part D. Methyl 4-(bromomethyl)-2-chloro-1*H*-benzimidazole-1-carboxylate

- A mixture of methyl 4-methyl-2-chloro-1*H*-benzimidazole-1-
- 30 carboxylate (17.5 g, 0.078 mol), N-bromosuccinimide (13.9 g, 0.078 mol) and benzoyl peroxide (2.0 g) in carbon tetrachloride (175 mL) was stirred at reflux for 2 hours. The solution was cooled, filtered to remove succinimide by-products, evaporated and crystallized from ethyl acetate:hexane to give 17.1 g of methyl-4-(bromomethyl)-2-
- 35 chloro-1*H*-benzimidazole-1-carboxylate as a pale yellow solid.

Part E. 2-Chloro-5,6-dihydro-*N,N*-dipropyl-4*H*-imidazo(4,5,1-*ij*)-quinolin-5-amine (compound 51)

This compound was prepared using the procedure of Example 18,

but substituting methyl-4-(bromomethyl)-2-chloro-1*H*-benzimidazole-1-carboxylate for methyl-4-(bromomethyl)-1*H*-benzimidazole-1-carboxylate. The bulk of the product was converted to the dihydrochloride salt, mp 165-170°C.

- 5 Part F. 5-(Dipropylamino)-5,6-dihydro-4*H*-imidazo(4,5,1-*ij*)quinolin-2(1*H*)-one (compound 29)

2-Chloro-5,6-dihydro-*N,N*-dipropyl-4*H*-imidazo(4,5,1-*ij*)quinolin-5-amine was refluxed in acetic acid for 1 hour. The solvent was removed and the residue was partitioned between ethyl acetate and
10 sodium hydroxide solution. Evaporation of the ethyl acetate afforded 5-(dipropylamino)-5,6-dihydro-4*H*-imidazo(4,5,1-*ij*)quinolin-2(1*H*)-one.

Example 76. 1-(1,2,5,6-Tetrahydro-2-oxo-4*H*-imidazo(4,5,1-*ij*)quinolin-5-yl)pyrrolidine (compound 52)

This compound was prepared by following the procedure of Example
15 44 part B, but substituting 1-(8-amino-1,2,3,4-tetrahydro-3-quinolyl)pyrrolidine for *t*-butyl (8-amino-1,2,3,4-tetrahydro-3-quinolyl)-carbamate.

Example 77. 1-(1,2,5,6-Tetrahydro-2-oxo-4*H*-imidazo(4,5,1-*ij*)quinolin-5-yl)piperidine (compound 53)

20 This compound was prepared by following the procedure of Example 44 part B, but substituting 1-(8-amino-1,2,3,4-tetrahydro-3-quinolyl)piperidine for *t*-butyl (8-amino-1,2,3,4-tetrahydro-3-quinolyl)carbamate.

Example 78. 4-(1,2,5,6-Tetrahydro-2-oxo-4*H*-imidazo(4,5,1-*ij*)quinolin-5-yl)morpholine (compound 54)

25 This compound was prepared by following the procedure of Example 44 part B, but substituting 1-(8-amino-1,2,3,4-tetrahydro-3-quinolyl)morpholine for *t*-butyl (8-amino-1,2,3,4-tetrahydro-3-quinolyl)carbamate.

30 Example 79. 1-(1,2,5,6-Tetrahydro-2-oxo-4*H*-imidazo(4,5,1-*ij*)quinolin-5-yl)imidazole (compound 55)

This compound was prepared by following the procedure of Example
44 part B, but substituting 1-(8-amino-1,2,3,4-tetrahydro-3-quinolyl)imidazole for *t*-butyl (8-amino-1,2,3,4-tetrahydro-3-quinolyl)carbamate.
35

Example 80. 1-(1,2,5,6-Tetrahydro-2-oxo-4*H*-imidazo(4,5,1-*ij*)quinolin-5-yl)-4-methylpiperazine (compound 56)

This compound was prepared by following the procedure of Example

44 part B, but substituting 1-(8-amino-1,2,3,4-tetrahydro-3-quinolyl)-4-methylpiperazine for *t*-butyl (8-amino-1,2,3,4-tetrahydro-3-quinolyl)carbamate.

5 Example 81. 5-((Phenylmethyl)methylamino)-5,6-dihydro-4*H*-imidazo(4,5,1-*ij*)quinolin-2(1*H*)-one (compound 57)

This compound was prepared by following the procedure of Example 44 part B, but substituting 1,2,3,4-tetrahydro-*N*³-methyl-*N*³-(phenylmethyl)quinoline-3,8-diamine for *t*-butyl (8-amino-1,2,3,4-tetrahydro-3-quinolyl)carbamate. The bulk of the product was converted to the
10 hydrochloride salt, mp 145-149°C from methanol/ether.

Example 82. 5-(Dipropylamino)-7-chloro-5,6-dihydro-4*H*-imidazo(4,5,1-*ij*)quinolin-2(1*H*)-one (compound 58)

This compound was prepared by following the procedure of Example 44 part B, but substituting 5-chloro-1,2,3,4-tetrahydro-*N*³,*N*³-dipropyl-3,8-quinolinediamine for *t*-butyl (8-amino-1,2,3,4-tetrahydro-3-quinolyl)carbamate.
15

Example 83. 5-(Dipropylamino)-5,6-dihydro-7-methoxy-4*H*-imidazo(4,5,1-*ij*)quinolin-2(1*H*)-one (compound 59)

This compound was prepared by following the procedure of Example 44 part B, but substituting 1,2,3,4-tetrahydro-5-methoxy-*N*³,*N*³-dipropyl-3,8-quinolinediamine for *t*-butyl (8-amino-1,2,3,4-tetrahydro-3-quinolyl)carbamate.
20

Example 84. 5-(Dipropylamino)-5,6-dihydro-8-methoxy-4*H*-imidazo(4,5,1-*ij*)quinolin-2(1*H*)-one (compound 60)

This compound was prepared by following the procedure of Example 44 part B, but substituting 1,2,3,4-tetrahydro-6-methoxy-*N*³,*N*³-dipropyl-3,8-quinolinediamine for *t*-butyl (8-amino-1,2,3,4-tetrahydro-3-quinolyl)carbamate.
25

Example 85. 5-(Dipropylamino)-5,6-dihydro-9-methoxy-4*H*-imidazo(4,5,1-*ij*)quinolin-2(1*H*)-one (compound 61)
30

This compound was prepared by following the procedure of Example 44 part B, but substituting 1,2,3,4-tetrahydro-7-methoxy-*N*³,*N*³-dipropyl-3,8-quinolinediamine for *t*-butyl (8-amino-1,2,3,4-tetrahydro-3-quinolyl)carbamate.

35 Example 86. 5-(Dimethylamino)-5,6-dihydro-8-methoxy-4*H*-imidazo(4,5,1-*ij*)quinolin-2(1*H*)-one (compound 62)

This compound was prepared by following the procedure of Example 44 part B, but substituting 1,2,3,4-tetrahydro-6-methoxy-*N*³,*N*³-

dimethyl-3,8-quinolinediamine for *t*-butyl (8-amino-1,2,3,4-tetrahydro-3-quinolyl)carbamate.

Example 87. 5-(Dimethylamino)-5,6-dihydro-4*H*-imidazo(4,5,1-*ij*)quinolin-8-ol (compound 63)

5 This compound was prepared by following the procedure of Example 32, but substituting 5-(dimethylamino)-5,6-dihydro-8-methoxy-4*H*-imidazo(4,5,1-*ij*)quinolin-2(1*H*)-one for 5,6-dihydro-7-methoxy-*N,N*-dipropyl-4*H*-imidazo(4,5,1-*ij*)quinolin-5-amine.

Example 88. 5,6-Dihydro-6-methyl-*N,N*-dimethyl-4*H*-imidazo(4,5,1-*ij*)quinolin-5-amine (compound 64)

Part A. 4-Ethyl-1*H*-benzimidazole

This compound was prepared following the procedure of Example 16, but substituting 4-bromo-2-ethyl-6-nitroaniline for 2-methyl-6-nitroaniline.

15 Part B. *t*-Butyl 4-(1-bromoethyl)-1*H*-benzimidazole-1-carboxylate

This compound was prepared following the procedure of Example 17, but substituting 4-ethyl-1*H*-benzimidazole for 4-methyl-1*H*-benzimidazole.

Part C. 5,6-Dihydro-6-methyl-*N,N*-dimethyl-4*H*-imidazo(4,5,1-*ij*)quinolin-5-amine

20 This compound, a mixture of diastereomers, was prepared following the procedure of Example 19, but substituting *t*-butyl 4-(1-bromoethyl)-1*H*-benzimidazole-1-carboxylate for *t*-butyl 4-(1-bromoethyl)-1*H*-benzimidazole-1-carboxylate.

25 Example 89. 5,6-Dihydro-6-methyl-*N,N*-dipropyl-4*H*-imidazo(4,5,1-*ij*)quinolin-5-amine (compound 65)

This compound, a mixture of diastereomers, was prepared following the procedure of Example 88 part C, but substituting methyl benzyl (dipropylamino)malonate for methyl benzyl (dimethylamino)malonate. The product was crystallized from hexane; mp 78-84°C. Anal. Calcd. for C₁₇H₂₃N₃O: C, 75.23; H, 9.28; N, 15.48. Found: C, 75.00; H, 9.47; N, 15.54.

Example 90. 5-(Dimethylamino)-5,6-dihydro-6-methyl-4*H*-imidazo(4,5,1-*ij*)quinolin-2(1*H*)-one hydrochloride (compound 66)

35 This compound, a mixture of diastereomers, was prepared following the procedure of Example 44 part B, but substituting 1,2,3,4-tetrahydro-4-methyl-*N*³,*N*³-dimethyl-3,8-quinolinediamine for *t*-butyl

(8-amino-1,2,3,4-tetrahydro-3-quinolyl)carbamate.

Example 91. 5-(Dipropylamino)-5,6-dihydro-6-methyl-4H-imidazo-(4,5,1-ij)quinolin-2(1H)-one hydrochloride (compound 67)

5 This compound, a mixture of diastereomers, was prepared following the procedure of Example 44 part B, but substituting 1,2,3,4-tetrahydro-4-methyl-N³,N³-dipropyl-3,8-quinolinediamine for *n*-butyl (8-amino-1,2,3,4-tetrahydro-3-quinolyl)carbamate.

10 Example 92. 5,6-Dihydro-4-methyl-N,N-dipropyl-4H-imidazo(4,5,1-ij)quinolin-5-amine (compound 68)

Part A. β -(dipropylamino)-1H-benzimidazole-4-propanal

Oxalyl chloride (1.2 mL, 0.014 mol) was added with stirring to methylene chloride (20mL) at -78°C. Ten minutes after addition was complete, DMSO (2 mL) was added and stirring was continued for an
15 additional 10 minutes. β -Dipropylamino)-1H-benzimidazole-4-propanol (2.1 g, 7.5 mmol) in methylene chloride was added and, after 30 minutes, the solution was allowed to warm to room temperature. Water was added, the methylene chloride was separated and evaporated, and the residue was chromatographed on silica gel to give β -(dipropyl-
20 amino)-1H-benzimidazole-4-propanal as an oil.

Part B. β -(dipropylamino)- α -methyl-1H-benzimidazole-4-propanol

Methyl magnesium bromide (3.3 mL of 3.0 M in ether, 6 mmol) was added to a stirred solution of β -(dipropylamino)-1H-benzimidazole-4-propanal (1.45 g, 5 mmol) in THF (25 mL). The solution was stirred
25 for 1 hour, evaporated, and partitioned between ethyl acetate and water. The ethyl acetate was evaporated and the residue was chromatographed on silica gel to give β -(dipropylamino)- α -methyl-1H-benzimidazole-4-propanol as an oil.

30 Part C. 5,6-Dihydro-4-methyl-N,N-dipropyl-4H-imidazo(4,5,1-ij)quinolin-5-amine

This compound, a mixture of diastereomers, was prepared following the procedure of Example 18 part D, but substituting β -(dipropylamino)- α -methyl-1H-benzimidazole-4-propanol for β -(dipropylamino)-1H-benzimidazole-4-propanol.

35 Example 93. 5,6-Dihydro-4-methyl-N,N-dimethyl-4H-imidazo(4,5,1-ij)quinolin-5-amine (compound 69)

This compound, a mixture of diastereomers, was prepared following the procedure of Example 18 part D, but substituting β -(dimethyl-

amino)- α -methyl-1*H*-benzimidazole-4-propanol for β -(dipropylamino)-1*H*-benzimidazole-4-propanol.

Example 94. 5-(Dipropylamino)-5,6-dihydro-4-methyl-4*H*-imidazo-(4,5,1-*lj*)quinolin-2(1*H*)-one hydrochloride (compound 70)

This compound, a mixture of diastereomers, was prepared following the procedure of Example 44 part B, but substituting 1,2,3,4-tetrahydro-2-methyl-*N*³,*N*³-dipropyl-3,8-quinolinediamine for *t*-butyl (8-amino-1,2,3,4-tetrahydro-3-quinolyl)carbamate.

Example 95. 5-(Dimethylamino)-5,6-dihydro-4-methyl-4*H*-imidazo-(4,5,1-*lj*)quinolin-2(1*H*)-one hydrochloride (compound 71)

This compound, a mixture of diastereomers, was prepared following the procedure of Example 44 part B, but substituting 1,2,3,4-tetrahydro-2-methyl-*N*³,*N*³-dimethyl-3,8-quinolinediamine for *t*-butyl (8-amino-1,2,3,4-tetrahydro-3-quinolyl)carbamate.

Example 96. 5-(Dipropylamino)-5,6-dihydro-2*H*,4*H*-oxazolo(5,4,3-*lj*)quinolin-2-one (compound 72)

Part A. *N*-Acetyl-*N*-(2-methoxy-6-methylphenyl)acetamide (compound XLV)

Palladium charcoal (1.0 g of 10%) was added to a solution of 3-methyl-2-nitroanisole (16.8 g, 0.1 mol) in ethanol (150 mL) and the solution was hydrogenated (50 lb initial hydrogen pressure) until hydrogen uptake ceased (2 hours). The solution was filtered and evaporated to give 13.8 g of 2-methoxy-6-methylbenzenamine (compound XLIV) as an oil. The product was dissolved in acetic anhydride (100 mL) and the resulting solution was refluxed for 1 hour. Part of the solvent (50 mL) was slowly removed over a 1-hour period, after which time the solution was cooled and the remainder of the solvent was removed under reduced pressure. The residual oil was crystallized from ethyl acetate:hexane (200 mL of 1:2) to give 20.5 g of *N*-acetyl-*N*-(2-methoxy-6-methylphenyl)-acetamide, mp 116-119°C. Anal Calcd for C₁₂H₁₅NO₃: C, 65.14; H, 6.83; N, 6.33. Found: C, 65.44; H, 7.04; N, 6.39.

Part B. *N*-Acetyl-*N*-(2-(bromomethyl)-6-methoxyphenyl)acetamide (compound XLVI)

A mixture of *N*-acetyl-*N*-(2-methoxy-6-methylphenyl)acetamide (25.0 g, 0.11 mol), *N*-bromosuccinimide (20.1 g, 0.11 mol), and

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benzoyl peroxide (4.5 g, 0.019 mol) in carbon tetrachloride (300 mL) was stirred under reflux for 3 hours. The solution was cooled, filtered, and evaporated, and the residual solid was crystallized from ethyl acetate:hexane to give 21.0 g of N-acetyl-N-(2-(bromo-methyl)-6-methoxyphenyl)acetamide, 95% pure by GC analysis.

Part C. Diethyl ((2-(diacetylamino)-3-methoxyphenyl)-methyl)propanedioate (compound XLVII)

Potassium hydride (13.4 g of 35%, 117 mmol) was added to a stirred solution of diethyl dipropylaminomalonate (34.6 g, 133 mmol) in THF (200 mL). N-Acetyl-N-(2-(bromomethyl)-6-methoxyphenyl)-acetamide (10.0 g, 33 mmol) was added and the solution was heated under reflux for 1 hour. The solution was evaporated and the residual oil was partitioned between ethyl acetate and water. After evaporation of the ethyl acetate, the residue was chromatographed on silica gel using ethyl acetate:hexane (1:10 as the eluant to give 9.2 g of diethyl ((2-(diacetylamino)-3-methoxyphenyl)methyl)propanedioate. Crystallization from ethyl acetate:hexane gave 8.4 g of product, mp 72-75°C. Anal Calcd for $C_{25}H_{38}N_2O_7$: C, 62.74; H, 8.00; N, 5.85. Found: C, 62.59; H, 8.00; N, 5.87.

Part D. 3-(Dipropylamino)-3,4-dihydro-8-methoxy-2(1H)quinolinone (compound XLVIII)

Diethyl ((2-(diacetylamino)-3-methoxyphenyl)methyl)propanedioate (6.34 g) was dissolved in sodium ethoxide in ethanol (150 mL of 1.4 M). After 20 min, the solution was heated under reflux for 15 hours; water was added to the reaction after 1 hour (1 mL), 3 hours (2 mL), 4 hours (5 mL) and 5 hours (15 mL). The solution was filtered to remove precipitated inorganic material and the solvents were removed under reduced pressure, and the residue was partitioned between ethyl acetate and water. The oil obtained after evaporation of the ethyl acetate was chromatographed on silica gel to give 3.3 g of 3-(dipropylamino)-3,4-dihydro-8-methoxy-2(1H)quinolinone. The product was crystallized from pentane to give 2.0 g of product, mp 50-54°C. Anal Calcd for $C_{16}H_{24}N_2O_2$: C, 69.53; H, 8.75; N, 10.14. Found: C, 69.56; H, 8.98; N, 10.24.

Part E. 1,2,3,4-Tetrahydro-8-methoxy-N,N-dipropyl-3-quinolinamine (compound XLIX)

Lithium aluminum hydride (1.08 g, 27.7 mmol) was added to a stirred solution of 3-(dipropylamino)-3,4-dihydro-8-methoxy-2(1H)qui-

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nolinone (1.05 g, 3.8 mmol) in THF (50 mL) and the solution was heated at 50°C for 1 hour. After cooling, ethyl acetate followed by methanol were added to destroy excess hydride, and the solvent was evaporated. The residue was partitioned between ethyl acetate and water. Evaporation of the ethyl acetate gave 0.98 g of 1,2,3,4-tetrahydro-8-methoxy-N,N-dipropyl-3-quinolinamine as an oil.

Part F. 1,2,3,4-Tetrahydro-8-hydroxy-N,N-dipropyl-3-quinolinamine (compound L)

A solution of 1,2,3,4-tetrahydro-8-methoxy-N,N-dipropyl-3-quinolinamine (0.98 g) in hydrobromic acid (20 mL of 48%) was heated at 155°C for 6 hours. The solution was cooled, evaporated, and partitioned between ethyl acetate and saturated sodium bicarbonate solution. The aqueous phase was re-extracted with ethyl acetate and the combined organic phases were evaporated to give 0.88 g of 1,2,3,4-tetrahydro-8-hydroxy-N,N-dipropyl-3-quinolinamine as an oil.

Part G. 5-(Dipropylamino)-5,6-dihydro-2H,4H-oxazolo(5,4,3-ij)quinolin-2-one (compound 72)

Carbonyldiimidazole (0.46 g, 2.8 mmol) was added to a stirred solution of 1,2,3,4-tetrahydro-8-hydroxy-N,N-dipropyl-3-quinolinamine (0.59 g, 2.4 mmol) in THF (10 mL). After 5 minutes, the solvent was removed and the residue was dissolved in ethyl acetate and chromatographed on silica gel using 5% ethyl acetate in hexane as the initial eluant to give 0.57 g of 5-(dipropylamino)-5,6-dihydro-2H,4H-oxazolo(5,4,3-ij)quinolin-2-one as an oil.

The bulk of the product was converted to the p-toluenesulfonate salt, mp 192-194°C from methanol:ether. Anal Calcd for $C_{16}H_{22}N_2O_2 \cdot C_7H_8O_3S$: C, 61.86; H, 6.77; N, 6.28; S, 7.18. Found: C, 61.90; H, 6.97; N, 6.28; S, 7.18.

Example 97. 5-(Propylamino)-5,6-dihydro-2H,4H-oxazolo(5,4,3-ij)quinolin-2-one (compound 73)

Part A. 5-(N-(phenylmethyl)propylamino)-5,6-dihydro-2H,4H-oxazolo(5,4,3-ij)quinolin-2-one

This compound was obtained by following the procedure of Example 96, but substituting diethyl (N-(phenylmethyl)propylamino)malonate for diethyl (dipropylamino)malonate.

Part B. 5-(Propylamino)-5,6-dihydro-2H,4H-oxazolo(5,4,3-ij)quinolin-2-one

This compound was obtained by following the procedure of Example

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66 part A, but substituting 5-(N-(phenylmethyl)propylamino)-5,6-dihydro-2H,4H-oxazolo(5,4,3-ij)quinolin-2-one for 6-bromo-1,2,3,4-tetrahydro-8-nitro-N,N-dimethyl-3-quinolinamine.

5 Example 98. 5-(Dimethylamino)-5,6-dihydro-2H,4H-oxazolo(5,4,3-ij)quinolin-2-one (compound 74)

This compound was prepared following the procedure of Example 96, but substituting diethyl (dimethylamino)malonate for diethyl (dipropylamino)malonate.

10 Example 99. 5-(N-methyl-1-(phenyl)ethylamino)-5,6-dihydro-2H,4H-oxazolo(5,4,3-ij)quinolin-2-one (compound 75)

This compound was prepared following the procedure of Example 96, but substituting diethyl (N-methyl-2-(phenyl)ethylamino)malonate for diethyl (dipropylamino)malonate.

15 Example 100. 1-(5,6-Dihydro-2-oxo-2H,4H-oxazolo(5,4,3-ij)quinolin-5-yl)pyrrolidine (compound 76)

This compound was prepared by following the procedure of Example 96, but substituting (1-pyrrolidinyl)propanedioic acid methyl benzyl diester (compound VIk) for diethyl dipropylaminomalonate.

20 Example 101. 1-(5,6-Dihydro-2-oxo-2H,4H-oxazolo(5,4,3-ij)quinolin-5-yl)piperidine (compound 77)

This compound was prepared by following the procedure of Example 96, but substituting (1-piperidinyl)propanedioic acid methyl benzyl diester (compound VI_m) for diethyl dipropylaminomalonate.

25 Example 102. 4-(5,6-Dihydro-2-oxo-2H,4H-oxazolo(5,4,3-ij)quinolin-5-yl)morpholine (compound 78)

This compound was prepared by following the procedure of Example 96, but substituting (4-morpholinyl)propanedioic acid methyl benzyl diester (compound VI_n) for diethyl dipropylaminomalonate.

30 Example 103. 1-(5,6-Dihydro-2-oxo-2H,4H-oxazolo(5,4,3-ij)quinolin-5-yl)imidazole (compound 79)

This compound was prepared by following the procedure of Example 96, but substituting (1-imidazolyl)propanedioic acid methyl benzyl diester (compound VI_p) for diethyl dipropylaminomalonate.

35 Example 104. 5-(Dipropylamino)-5,6-dihydro-2H,4H-oxazolo(5,4,3-ij)quinolin-2-thione (compound 80)

This compound was prepared by following the procedure of Example 56 part B, but substituting 1,2,3,4-tetrahydro-8-hydroxy-N,N-dipropyl-3-quinolinamine for 1,2,3,4-tetrahydro-N³,N³-dipropyl-3,8-quinoli-

amine.

Example 105. 5-(Dimethylamino)-5,6-dihydro-2H,4H-oxazolo(5,4,3-1j)quinolin-2-thione (compound 81)

This compound was prepared by following the procedure of Example 56 part B, but substituting 1,2,3,4-tetrahydro-8-hydroxy-N,N-dimethyl-3-quinolinamine for 1,2,3,4-tetrahydro-N³,N³-dipropyl-3,8-quinolinediamine.

Example 106. 6-(Dipropylamino)-6,7-dihydro-5H-pyrido(1,2,3-de)-1,4-benzoxazin-3(H)-one (compound 82)

This compound was prepared by following the procedure of Example 56 part B, but substituting ethyl bromoacetate for di (2-pyridyl)thiocarbonate and the sodium salt of 1,2,3,4-tetrahydro-8-hydroxy-N,N-dipropyl-3-quinolinamine for 1,2,3,4-tetrahydro-N³,N³-dipropyl-3,8-quinolinediamine. The bulk of the product was converted to the maleate salt, mp 124-127°C.

Example 107. 6-(Dimethylamino)-6,7-dihydro-5H-pyrido(1,2,3-de)-1,4-benzoxazin-3(2H)-one (compound 83)

This compound was prepared by following the procedure of Example 56 part B, but substituting ethyl bromoacetate for di (2-pyridyl)thiocarbonate and the sodium salt of 1,2,3,4-tetrahydro-8-hydroxy-N,N-dimethyl-3-quinolinamine for 1,2,3,4-tetrahydro-N³,N³-dipropyl-3,8-quinolinediamine.

Example 108. 1,2,6,7-Tetrahydro-6-(dipropylamino)-2-methyl-3H,5H-pyrido(1,2,3-de)quinoxalin-3-one (compound 84)

This compound was prepared using the procedure of Example 56, but substituting ethyl α-bromopropionate for di (2-pyridyl)thiocarbonate and carrying the reaction out at the reflux temperature. The crude product was chromatographed to give, as the major product and first compound eluted from the column, 1,2,6,7-tetrahydro-6-(dipropylamino)-2-methyl-3H,5H-pyrido(1,2,3-de)quinoxalin-3-one.

Example 109. 1,2,6,7-Tetrahydro-6-(dipropylamino)-3-methyl-3H,5H-pyrido(1,2,3-de)quinoxalin-2-one (compound 85)

This compound was prepared using the procedure of Example 56, but substituting chloropropionyl chloride for di (2-pyridyl)thiocarbonate. The initially formed N⁸-(α-chloropropionyl)-1,2,3,4-tetrahydro-N³,N³-dipropyl-3,8-quinolinediamine was heated at 150°C in DMF to effect cyclization to 1,2,6,7-tetrahydro-6-(dipropylamino)-3-methyl-3H,5H-pyrido(1,2,3-de)quinoxalin-2-one.

Example 110. 5,6-Dihydro-N,N-dipropyl-4H-pyrrolo(3,2,1-ij)quinolin-5-amine (compound 86)

This compound was prepared by following the procedure of Example 18, but substituting methyl 7-(bromomethyl)-1H-indole-1-carboxylate for t-butyl 4-(bromomethyl)-1H-benzimidazole-1-carboxylate.

Example 111. 5,6-Dihydro-N,N-dimethyl-4H-pyrrolo(3,2,1-ij)quinolin-5-amine (compound 87)

This compound was prepared by following the procedure of Example 18, but substituting methyl 7-(bromomethyl)-1H-indole-1-carboxylate for t-butyl 4-(bromomethyl)-1H-benzimidazole-1-carboxylate and diethyl (dimethylamino)malonate for diethyl (dipropylamino)malonate. The bulk of the product was converted to the maleate salt, mp 114-115°C from THF/ether.

Example 112. 5,6-Dihydro-N,N-dipropyl-4H-pyrazolo(4,3,2-ij)quinolin-5-amine (compound 88)

This compound was prepared by following the procedure of Example 18, but substituting methyl 7-(bromomethyl)-1H-indazole-1-carboxylate for t-butyl 4-(bromomethyl)-1H-benzimidazole-1-carboxylate.

Example 113. 5,6-Dihydro-N,N-dimethyl-4H-pyrazolo(4,3,2-ij)quinolin-5-amine (compound 89)

This compound was prepared by following the procedure of Example 18, but substituting methyl 7-(bromomethyl)-1H-indazole-1-carboxylate for t-butyl 4-(bromomethyl)-1H-benzimidazole-1-carboxylate and diethyl (dimethylamino)malonate for diethyl (dipropylamino)malonate.

Example 114. 5,6-Dihydro-N,N-dipropyl-4H-triazolo(4,5,1-ij)quinolin-5-amine (compound 90)

This compound was prepared by following the procedure of Example 18, but substituting methyl 4-(bromomethyl)-1H-benzotriazole-1-carboxylate for t-butyl 4-(bromomethyl)-1H-benzimidazole-1-carboxylate.

Example 115. 5,6-Dihydro-N,N-dimethyl-4H-triazolo(4,5,1-ij)quinolin-5-amine (compound 91)

This compound was prepared by following the procedure of Example 18, but substituting methyl 4-(bromomethyl)-1H-benzotriazole-1-carboxylate for t-butyl 4-(bromomethyl)-1H-benzimidazole-1-carboxylate and diethyl (dimethylamino)-malonate for diethyl (dipropylamino)malonate.

Example 116. 1,2,5,6-Tetrahydro-N,N-dipropyl-4H-pyrrolo(3,2,1-

1j)quinolin-5-amine (compound 92)

This compound was prepared by following the procedure of Example 18, but substituting *t*-butyl 2,3-dihydro-7-(bromomethyl)-1*H*-indole-1-carboxylate for *t*-butyl 4-(bromomethyl)-1*H*-benzimidazole-1-carboxylate. The bulk of the product was converted to the maleate salt, mp 139-140°C from THF/ether.

Example 117. 1,2,5,6-Tetrahydro-*N,N*-dimethyl-4*H*-pyrrolo(3,2,1-*ij*)quinolin-5-amine (compound 93)

This compound was prepared by following the procedure of Example 18, but substituting *t*-butyl 2,3-dihydro-7-(bromomethyl)-1*H*-indole-1-carboxylate for *t*-butyl 4-(bromomethyl)-1*H*-benzimidazole-1-carboxylate and diethyl (dimethylamino)malonate for diethyl (dipropylamino)malonate.

Example 118. 5-(Propylamino)-5,6-dihydro-4*H*-pyrrolo(3,2,1-*ij*)quinolin-2,3*H*)-dione (compound 94)

Part A. *N*-Propyl-*N*-(6-bromo-1,2,3,4-tetrahydro-8-nitroquinolin-3-yl)formamide

This product was prepared by following the procedure of Example 35, but substituting 6-bromo-1,2,3,4-tetrahydro-8-nitro-*N*-propyl-3-quinolinamine for 3-aminoquinoline.

Part B. *N*-propyl-*N*-(8-amino-1,2,3,4-tetrahydro-3-quinolyl)formamide

This product was prepared by following the procedure of Example 56 part A, but substituting *N*-propyl-*N*-(6-bromo-1,2,3,4-tetrahydro-8-nitro-3-quinolyl for 6-bromo-1,2,3,4-tetrahydro-8-nitro-*N,N*-dipropyl-3-quinolinamine.

Part C. *N*-propyl-*N*-(5,6-dihydro-2,3-dioxo-4*H*-pyrrolo(3,2,1-*ij*)quinolin-5-yl)formamide

Oxalyl chloride (1.26 g, 0.01 mol) was added to a stirred solution of *N*-propyl-*N*-(6-bromo-1,2,3,4-tetrahydro-8-nitroquinolin-3-yl)formamide (3.14 g, 0.01 mol) in ether (100 mL). After 30 minutes, the ether was removed and the residue was heated at 100°C for 4 hours to effect cyclization. The crude product was partitioned between ethyl acetate and water, the ethyl acetate phase was evaporated, and the residual product was chromatographed on silica gel to give *N*-propyl-*N*-(5,6-dihydro-2,3-dioxo-4*H*-pyrrolo(3,2,1-*ij*)quinolin-5-yl)formamide.

Part D. 5-(Propylamino)-5,6-dihydro-4*H*-pyrrolo(3,2,1-*ij*)quinolin-2,3-dione (compound 94)

N-Propyl-N-(5,6-dihydro-2,3-dioxo-4H-pyrrolo(3,2,1-ij)quinolin-5-yl)formamide was refluxed for 1 hour with ethanolic hydrogen chloride to give the hydrochloride salt of 5-(propylamino)-5,6-dihydro-4H-pyrrolo(3,2,1-ij)quinolin-2,3-dione.

5 Example 119. 5-(Dipropylamino)-5,6-dihydro-4H-pyrrolo(3,2,1-ij)quinolin-1,3-dione (compound 95)

This product was prepared by following the procedure of Example 54, but substituting 5-(propylamino)-5,6-dihydro-4H-pyrrolo(3,2,1-ij)quinolin-2,3-dione hydrochloride for 6-bromo-1,2,3,4-tetrahydro-10 8-nitro-3-quinolinamine dihydrochloride.

Example 120. 5-(Propylamino)-5,6-dihydro-4H-pyrrolo(3,2,1-ij)quinolin-2(1H)-one (compound 96)

This product was prepared by following the procedure of Example 36, but substituting 5-(propylamino)-5,6-dihydro-4H-pyrrolo(3,2,1-ij)quinolin-2,3-dione for N-(3-quinolyl)formamide. 15

Example 121. 5-(Dipropylamino)-5,6-dihydro-4H-pyrrolo(3,2,1-ij)quinolin-2(1H)-one (compound 97)

This product was prepared by following the procedure of Example 36, but substituting 5-(dipropylamino)-5,6-dihydro-4H-pyrrolo(3,2,1-ij)quinolin-2,3-dione for N-(3-quinolyl)formamide. The product was 20 crystallized from hexane, mp 86-88°C.

Example 122. 6-(Dipropylamino)-2,3,6,7-tetrahydro-5H-pyrido(3,2,1-ij)quinazolin-3-one (compound 98)

Part A. Methyl 3-methyl-2-nitrobenzoate

25 3-Methyl 2-nitrobenzoic acid (15.0 g) was stirred overnight with methanolic hydrogen chloride (150 mL of 2.2 N). The reaction was then refluxed for 3 hours, cooled and filtered to give 9.0 g of methyl 3-methyl-2-nitrobenzoate, mp 72-75°C. The mother liquors of the filtration contained a mixture of the starting acid and ester 30 product.

Part B. Methyl 3-(bromomethyl)-2-nitrobenzoate

This product was prepared by following the procedure of Example 6, but substituting methyl 3-methyl-2-nitrobenzoate for 8-methylquinoline. The product was purified by chromatography on silica gel and 35 was crystallized from ethyl acetate:hexane; mp 91-95°C.

Part C. (Dipropylamino)((3-carbomethoxy-2-nitrophenyl)methyl)propanedioic acid methyl benzyl diester

This product was prepared by following the procedure of Example

19 part A, but substituting methyl 3-(bromomethyl)-2-nitrobenzoate for *t*-butyl 4-(bromomethyl)-1*H*-benzimidazole-1-carboxylate and (dipropylamino)propanedioic acid methyl benzyl diester for diethyl (dipropylamino)malonate.

5 Part D. Methyl 3-(dipropylamino)-1,2,3,4-tetrahydro-2-oxo-8-quinolinecarboxylate

A mixture of (dipropylamino)((3-carbomethoxy-2-nitrophenyl)methyl)propanedioic acid methyl benzyl diester (5.0 g), 10% palladium charcoal (0.5 g) in methanol (150 mL) was hydrogenated until hydrogen
10 uptake ceased. The solution was filtered and the solvent removed to give 3.0 g of methyl α -(dipropylamino)-(2-amino-3-carbomethoxyphenyl)propanoate as an oil. This was refluxed in DMF for 18 hours to effect cyclization. The solvent was removed and the residual oil was chromatographed on silica gel to give 2.4 g of methyl 3-(dipropylami-
15 no)-1,2,3,4-tetrahydro-2-oxo-8-quinolinecarboxylate.

Part E. 3-(Dipropylamino)-1,2,3,4-tetrahydro-2-oxo-8-quinolinecarboxylic acid

A mixture of methyl 3-(dipropylamino)-1,2,3,4-tetrahydro-2-oxo-8-quinolinecarboxylate (1.0 g), methanol (15 mL) and 4.0 N sodium
20 hydroxide solution (3.3 mL) was stirred at room temperature for 30 minutes. The methanol was removed and the residue was reconstituted in water (5 mL) and neutralized by addition of 4.0 N hydrochloric acid (3.3 mL). The precipitate was filtered off, washed with water and air dried to give 0.67 g of 3-(dipropylamino)-1,2,3,4-tetrahydro-
25 2-oxo-8-quinolinecarboxylic acid, mp 214-217°C. Anal Calcd for $C_{16}H_{22}N_2O_3$: C, 66.18; H, 7.64; N, 9.65. Found: C, 65.99; H, 7.67; N, 9.62.

Part F. 3-(Dipropylamino)-1,2,3,4-tetrahydro-2-oxo-8-quinolinecarboxamide

30 A mixture of 3-(dipropylamino)-1,2,3,4-tetrahydro-2-oxo-8-quinolinecarboxylic acid (1.0 g), 1-hydroxybenzotriazole (1.65 g, 11 mmol) and dicyclohexylcarbodiimide (3.09 g, 15 mmol) in dimethylformamide (25 mL) was stirred at room temperature for 15 minutes. Ammonia was then bubbled into the solution, and, after 15 minutes the
35 solution was filtered, evaporated and partitioned between ethyl acetate and sodium hydroxide solution. The ethyl acetate was evaporated and the residual solid was purified by chromatography on silica gel using ethyl acetate as the eluant to give 0.98 g of

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product. This was crystallized from methanol to give 0.78 g of 3-(dipropylamino)-1,2,3,4-tetrahydro-2-oxo-8-quinolinecarboxamide, mp 214-217°C. Anal Calcd for $C_{16}H_{23}N_3O_2$: C, 66.41; H, 8.01; N, 14.52. Found: C, 66.46; H, 8.30; N, 14.69.

5 Part G. 1,2,3,4-Tetrahydro-8-(aminomethyl)-N,N-dipropyl-3-quinolinamine

Lithium aluminum hydride (1.5 g) was added to a stirred solution of 3-(dipropylamino)-1,2,3,4-tetrahydro-2-oxo-8-quinolinecarboxamide (0.75 g) in THF (125 mL) and the solution was refluxed for 2 days.
10 The solution was cooled and excess hydride was destroyed by addition of methanol (20 mL) and the solvents were removed under reduced pressure. The residue was partitioned between ethyl acetate (400 mL) and water (15 mL). The ethyl acetate was decanted from the inorganic solids and the solvent removed under reduced pressure. The residual
15 oil was dissolved in chloroform and chromatographed on silica gel. Elution of the column with 5% methanol:chloroform gave 0.40 g of 1,2,3,4-tetrahydro-8-(aminomethyl)-N,N-dipropyl-3-quinolinamine.

Part H. 6-(Dipropylamino)-2,3,6,7-tetrahydro-5H-pyrido(3,2,1-ij)quinazolin-3-one (compound 98)

20 This compound was prepared by following the procedure of Example 96 part G, but substituting 1,2,3,4-tetrahydro-8-(aminomethyl)-N,N-dipropyl-3-quinolinamine for 1,2,3,4-tetrahydro-8-hydroxy-N,N-dipropyl-3-quinolinamine. The product was crystallized from hexane; mp 116-119°C.

25 Example 123. 6-(Dimethylamino)-2,3,6,7-tetrahydro-5H-pyrido(3,2,1-ij)quinazolin-3-one (compound 99)

This compound was prepared by following the procedure of Example 122, but substituting (dimethylamino)propanedioic acid methyl benzyl diester for (dipropylamino)propanedioic acid methyl benzyl diester in
30 part C of the reaction sequence.

Example 124. 6-(Dipropylamino)-6,7-dihydro-1H,5H-pyrido(1,2,3-de)-2,4-benzoxazine-3-one (compound 100)

Part A. 1,2,3,4-Tetrahydro-8-(hydroxymethyl)-N,N-dipropyl-3-quinolinamine

35 This compound was obtained by following the procedure of Example 122 part G, but substituting methyl 3-(dipropylamino)-1,2,3,4-tetrahydro-2-oxo-8-quinolinecarboxylate for 3-(dipropylamino)-1,2,3,4-tetrahydro-2-oxo-8-quinolineoxamide.

Part B. 6-(Dipropylamino)-6,7-dihydro-1*H*,5*H*-pyrido(1,2,3-*de*)-2,4-benzoxazine-3-one (compound 100)

This compound was prepared by following the procedure of Example 44 part B, but substituting 1,2,3,4-tetrahydro-8-(hydroxymethyl)-
5 N,N-dipropyl-3-quinolinamine for *t*-butyl(8-amino-1,2,3,4-tetrahydro-3-quinolyl)carbamate. The bulk of the product was converted to the hydrochloride salt, mp 192-195°C.

Example 125. 6-(Dimethylamino)-6,7-dihydro-1*H*,5*H*-pyrido(3,2,1-*ef*)-2,4-benzoxazine-3-one (compound 101)

10 This compound was obtained by following the procedure of Example 124, but substituting methyl 3-(dimethylamino)-1,2,3,4-tetrahydro-2-oxo-8-quinolinecarboxylate for methyl 3-(dipropylamino)-1,2,3,4-tetrahydro-2-oxo-8-quinolinecarboxylate.

Example 126. 6-(Dipropylamino)-6,7-dihydro-3*H*,5*H*-benzo(1*j*)quinolizin-3-one (compound 102)
15

Part A. 5-(Dipropylamino)-1,2,3,4-tetrahydro-8-quinolinecarboxaldehyde

This compound was obtained by following the procedure of Example 92 part A, but substituting 1,2,3,4-tetrahydro-8-(hydroxymethyl)-N,N-
20 dipropyl-3-quinolinamine for β -(dipropylamino)-1*H*-benzimidazole-4-propanol.

Part B. 6-(Dipropylamino)-6,7-dihydro-3*H*,5*H*-benzo(1*j*)quinolizin-3-one (compound 102)

A mixture of 5-(dipropylamino)-1,2,3,4-tetrahydro-8-quinoline-
25 carboxaldehyde (2.60 g, 0.01 mol), diethyl malonate (1.76 g, 0.011 mol), piperidine (0.3 g) and acetic acid (0.1 mL) in ethanol (20 mL) was refluxed for 6 hours. The solvents were removed and the residue was reconstituted in DMF and refluxed for 3 hours. The DMF was removed and the residue was chromatographed to give 6-(dipropyl-
30 amino)-6,7-dihydro-3-oxo-3*H*,5*H*-benzo(1*j*)quinolizin-2-carboxylate. This was dissolved in ethanol (50 mL) and treated with sodium hydroxide solution (10 mL of 4 N) for 1 hour. The solution was neutralized with hydrochloric acid to give 6-(dipropylamino)-6,7-dihydro-3*H*,5*H*-benzo(1*j*)quinolizin-3-one. The product was crystall-
35 ized from hexane, mp 82-84°C.

Example 127. 6-(Dimethylamino)-6,7-dihydro-3*H*,5*H*-benzo(1*j*)quinolizin-3-one (compound 103)

This compound was obtained by following the procedure of Example

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126, but substituting 1,2,3,4-tetrahydro-8-(hydroxymethyl)-N,N-dimethyl-3-quinolinamine for 1,2,3,4-tetrahydro-8-(hydroxymethyl)-N,N-dipropyl-3-quinolinamine.

5 Example 128. 6-(Dipropylamino)-2,3,6,7-tetrahydro-3H,5H-benzo(1j)quinolizin-3-one (compound 104)

This product was prepared by following the procedure of Example 36, but substituting 6-(dipropylamino)-6,7-dihydro-3H,5H-benzo(1j)quinolizin-3-one for N-(3-quinolyl)formamide. The product was crystallized from pentane, mp 44-46°C.

10 Example 129. 6-(Dimethylamino)-2,3,6,7-tetrahydro-3H,5H-benzo(1j)quinolizin-3-one (compound 105)

This product was prepared by following the procedure of Example 36, but substituting 6-(dipropylamino)-6,7-dihydro-3H,5H-benzo(1j)quinolizin-3-one for N-(3-quinolyl)formamide.

15 Example 130. t-Butyl 1,2,3,4-Tetrahydro-5-(dipropylamino)quinoline-1-carboxylate

A mixture of 1,2,3,4-tetrahydro-N³,N³-dipropylquinoline (31.4 g, 0.135 mol) and di t-butyl dicarbonate (32.5 g, 0.149 mol) was heated at 100°C for 1 hour. The product was chromatographed on silica gel
20 using ethyl acetate:hexane as the eluant to give 42.6 g of t-butyl 1,2,3,4-tetrahydro-5-(dipropylamino)quinoline-1-carboxylate, mp 40-42°C.

A portion of the product was converted to the hydrochloride salt, mp 168°C (dec) from methanol:ether.

25 Example 131. t-Butyl 1,2,3,4-Tetrahydro-8-methyl-5-(dipropylamino)-quinoline-1-carboxylate (LII)

s-Butyl lithium (17.7 mL of 1.3 M in hexane (0.045 mol) was added at -78°C to a stirred solution of t-butyl 1,2,3,4-tetrahydro-5-(dipropylamino)quinoline-1-carboxylate (10 g, 0.030 mol) in THF (200
30 mL). After 15 minutes, methyl iodide (17.1 g, 0.13 mol) was added and the solution was allowed to warm to room temperature. The THF was removed under reduced pressure, and the residual oil was parti-

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tioned between ethyl acetate and water. The ethyl acetate was evaporated and the residual oil was chromatographed on silica gel to afford 10.65 g of t-butyl 1,2,3,4-tetrahydro-8-methyl-5-(dipropylamino)quinoline-1-carboxylate as an oil.

- 5 Example 132. 5-(Dipropylamino)-5,6-dihydro-4H-pyrrolo[3,2,1-
1j]quinolin-2(1H)-one (compound 97)

Following the procedure of Example 131, but substituting t-butyl 1,2,3,4-tetrahydro-8-methyl-5-(dipropylamino)quinoline-1-carboxylate for t-butyl 1,2,3,4-tetrahydro-5-(dipropylamino)quinoline-1-carboxylate and carbon dioxide for methyl iodide there was obtained 1,2,3,4-tetrahydro-1-(t-butoxycarbonyl)-5-(dipropylamino)quinoline-8-propionic acid. The product was treated with trifluoroacetic acid to remove the t-butoxycarbonyl group and effect cyclization to 5-(dipropylamino)-5,6-dihydro-4H-pyrrolo[3,2,1-1j]quinolin-2(1H)-one, mp 84-86°C.

- 15 Example 133. Lithium aluminum hydride reduction of 5-(Dipropylamino)-5,6-dihydro-4H-pyrrolo[3,2,1-1j]quinolin-2(1H)-one (compound 97).

A mixture of 5-(dipropylamino)-5,6-dihydro-4H-pyrrolo[3,2,1-1j]quinolin-2(1H)-one (0.75 g) and lithium aluminum hydride (0.21 g) was stirred in ether (20 mL) for 45 minutes. The reaction was quenched with methanol, evaporated and partitioned between ethyl acetate and water. Evaporation of the ethyl acetate gave an oil which was chromatographed on silica gel using ethyl acetate:hexane (1:20) as eluant to give, as the first compound eluted from the column 0.27 g of 5,6-dihydro-N,N-dipropyl-4H-pyrrolo[3,2,1-1j]quinolin-5-amine (compound 87). Continued elution of the column gave 0.34 g of 1,2,5,6-tetrahydro-N,N-dipropyl-4H-pyrrolo[3,2,1-1j]quinolin-5-amine (compound 92).

Example 134. 5,6-dihydro-5-(dipropylamino)-4H-pyrrolo[3,2,1-
1j]quinolin-2,3-dione (compound 95).

Following the procedure of Example 131, but substituting ethyl oxalate for methyl iodide, there was obtained 1,2,3,4-tetrahydro-1-
5 (t-butoxycarbonyl)- α -oxo-5-(dipropylamino)quinoline-8-propionic acid (LIII). The product was treated with trifluoroacetic acid to effect cyclization to 5,6-dihydro-5-(dipropylamino)-4H-pyrrolo[3,2,1-
1j]quinolin-2,3-dione (compound 95)

Example 135. 6-(Dipropylamino)-6,7-dihydro-3H,5H-benzo[1j]quinoliz-
10 in-3-one (compound 102)

Following the procedure of Example 131, but substituting ethyl formate for methyl iodide there was obtained t-butyl 8-formyl-
1,2,3,4-tetrahydro-5-(dipropylamino)quinoline-1-carboxylate (LIV) as an oil. The product (3.6 g) was added to a stirred solution of
15 trimethyl phosphonoacetate (3.64 g) and sodium hydride (0.96 g) in acetonitrile (75 mL). The solution was evaporated, chromatographed to afford 3.6 g of methyl 1,2,3,4-tetrahydro-1-(t-butoxycarbonyl)- α -
oxo-5-(dipropylamino)quinoline-8-butenate (LV) as an oil. The product was treated with trifluoroacetic acid to remove the t-butoxy-
20 carbonyl protecting group and refluxed in ethanol to effect cyclization to 6-(dipropylamino)-6,7-dihydro-3H,5H-benzo[1j]quinolizin-3-one (compound 102).

Example 136. Allylation of 5-(amino)-5,6-dihydro-4H-imidazo[4,5,1-
1j]quinolin-2(1H)-one.

25 Following the procedure of Example 54, but substituting allyl bromide for iodopropane and 5-(amino)-5,6-dihydro-4H-imidazo[4,5,1-
1j]quinolin-2(1H)-one for 6-bromo-1,2,3,4-tetrahydro-8-nitro-3-quinolinamine dihydrochloride there were obtained 5-(diallylamino)-

5,6-dihydro-4*H*-imidazo[4,5,1-*ij*]quinolin-2(1*H*)-one, mp 150-152 from ethyl acetate and 5-(allylamino)-5,6-dihydro-4*H*-imidazo[4,5,1-*ij*]quinolin-2(1*H*)-one. The latter compound was converted to the hydrochloride salt, mp 260°C from methanol:ether.

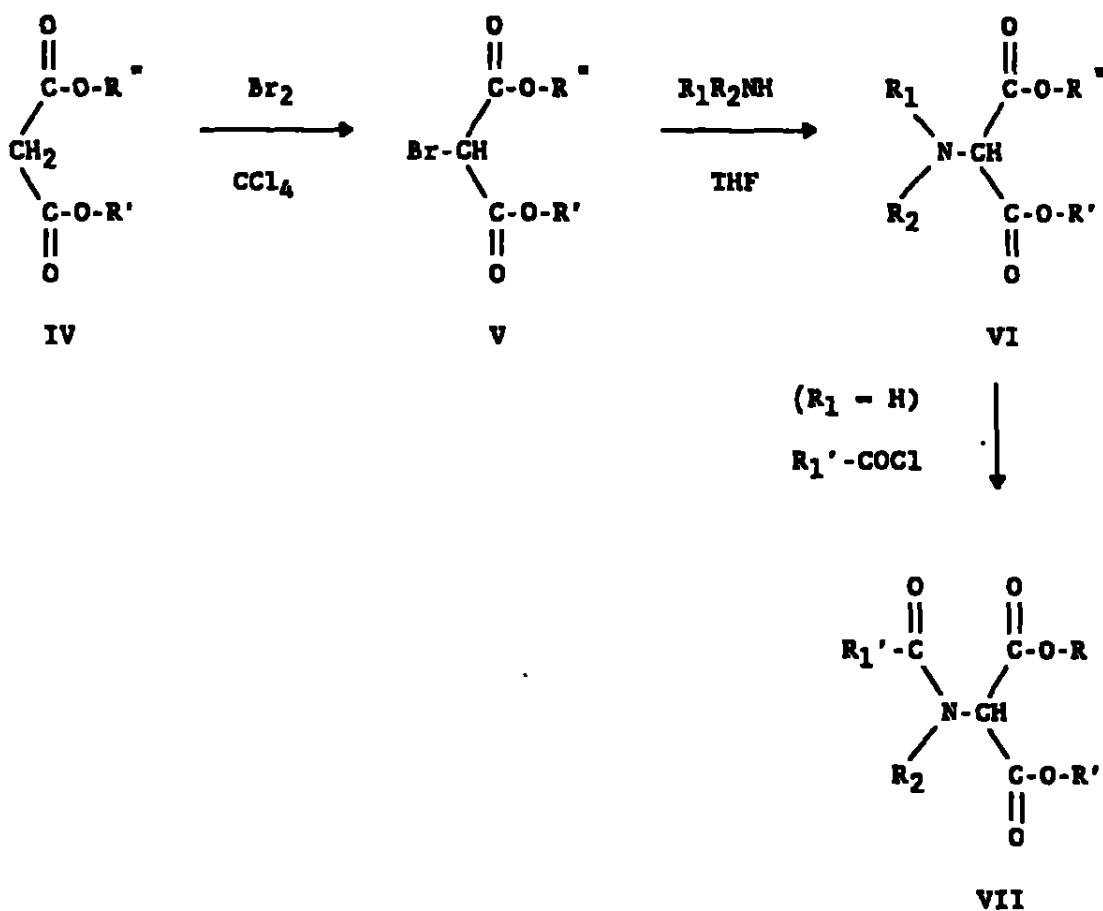
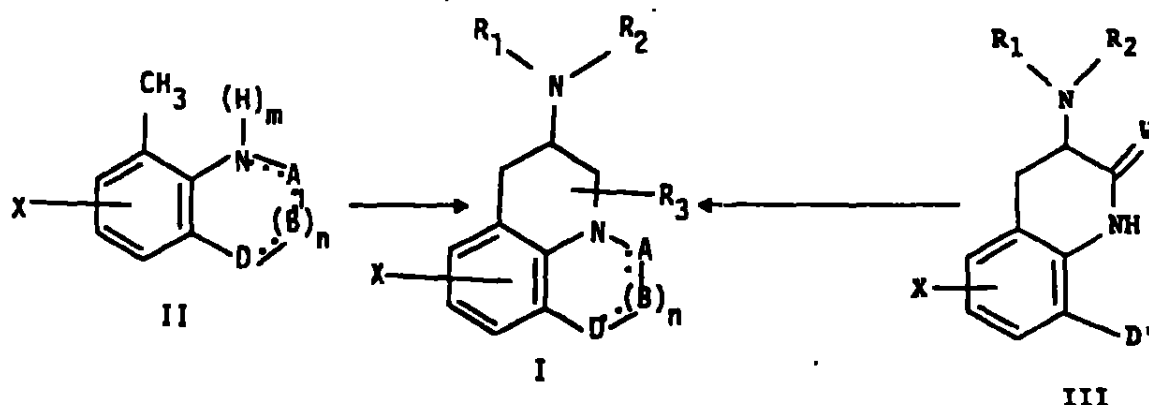
- 5 Example 137. Reaction of 5-(amino)-5,6-dihydro-4*H*-imidazo[4,5,1-*ij*]quinolin-2(1*H*)-one with cyclopropylmethyl bromide.

Following the procedure of Example 54, but substituting cyclopropylmethyl bromide for iodopropane and 5-(amino)-5,6-dihydro-4*H*-imidazo[4,5,1-*ij*]quinolin-2(1*H*)-one for 6-bromo-1,2,3,4-tetrahydro-8-nitro-3-quinolinamine dihydrochloride there were obtained 5-[bis(cyclopropylmethyl)amino]-5,6-dihydro-4*H*-imidazo[4,5,1-*ij*]quinolin-2(1*H*)-one, mp 152-154 from ethyl acetate:hexane and 5-(cyclopropylmethylamino)-5,6-dihydro-4*H*-imidazo[4,5,1-*ij*]quinolin-2(1*H*)-one. The latter compound was converted to the hydrochloride salt, mp 309°C (dec) from methanol:ether.

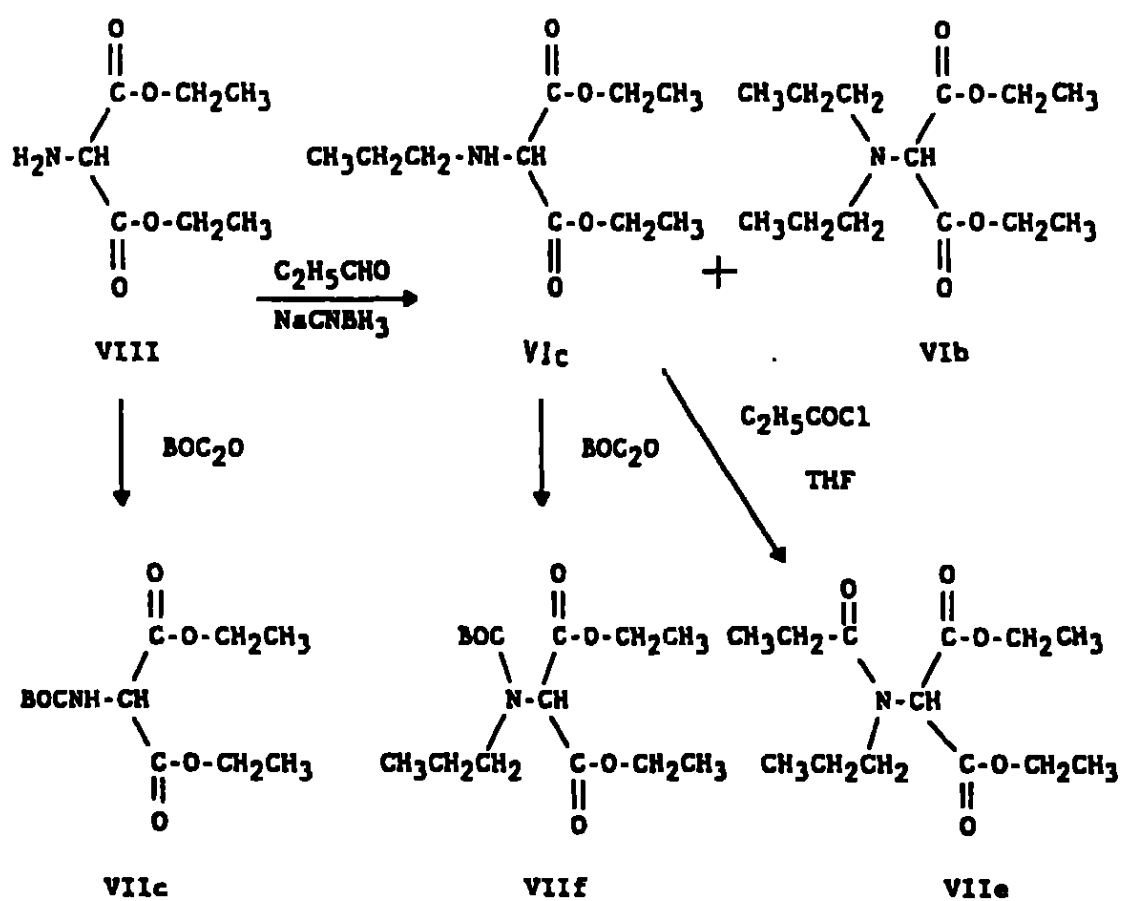
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FORMULAS

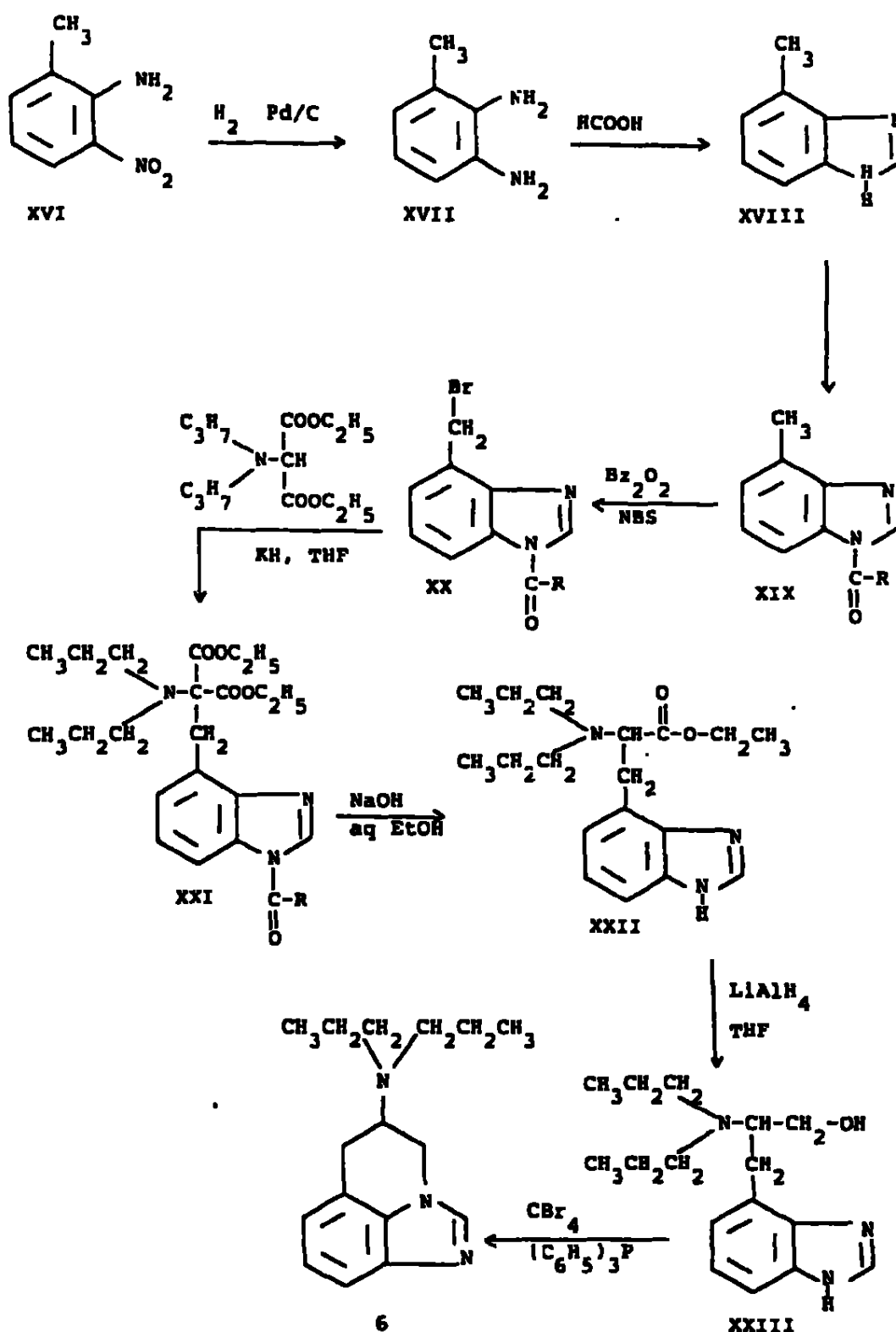


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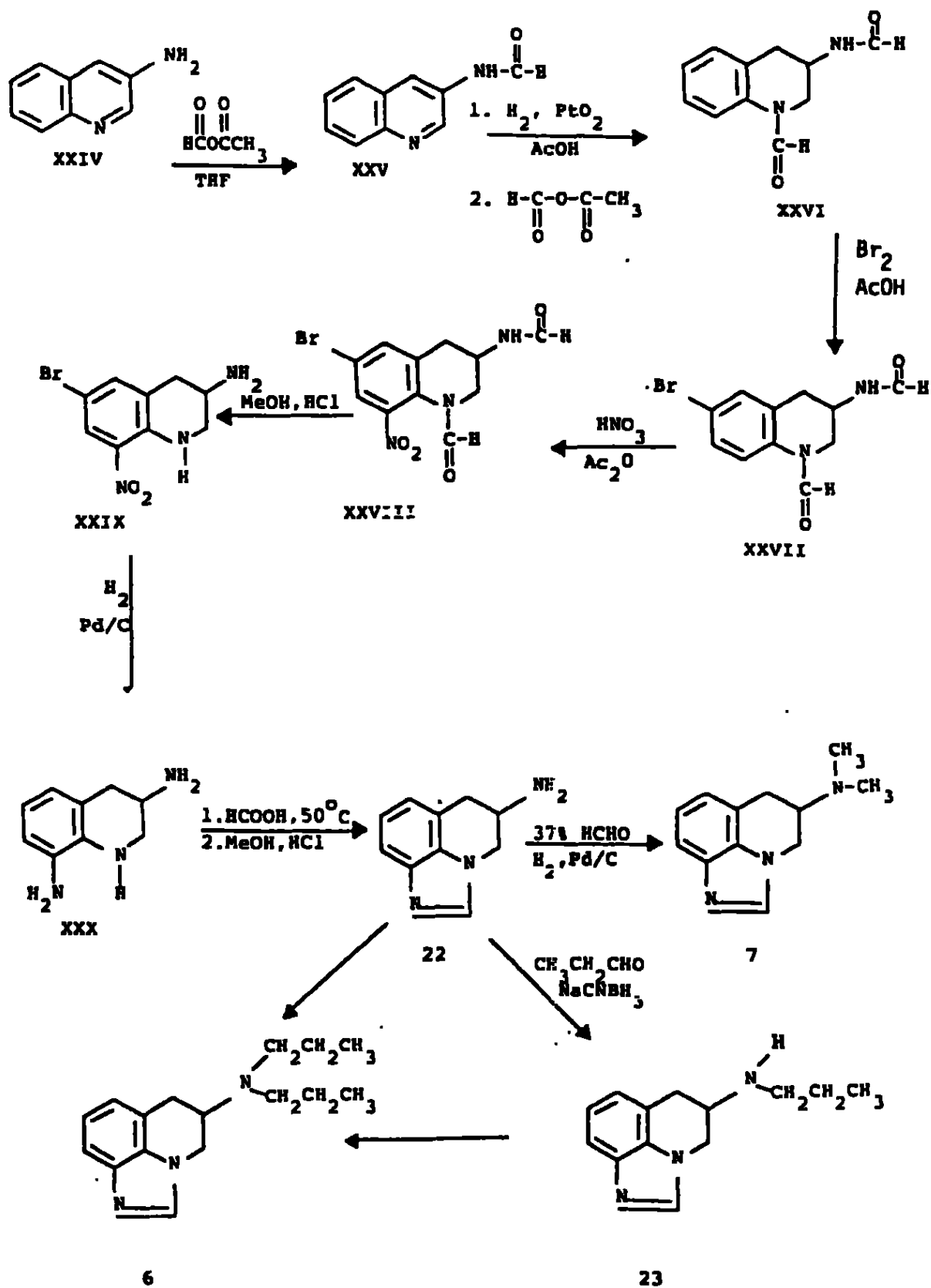
SCHEME 2

Synthesis of 5,6-Dihydro-N,N-dipropyl-4H-imidazo(4,5,1-i)quinolin-5-amine



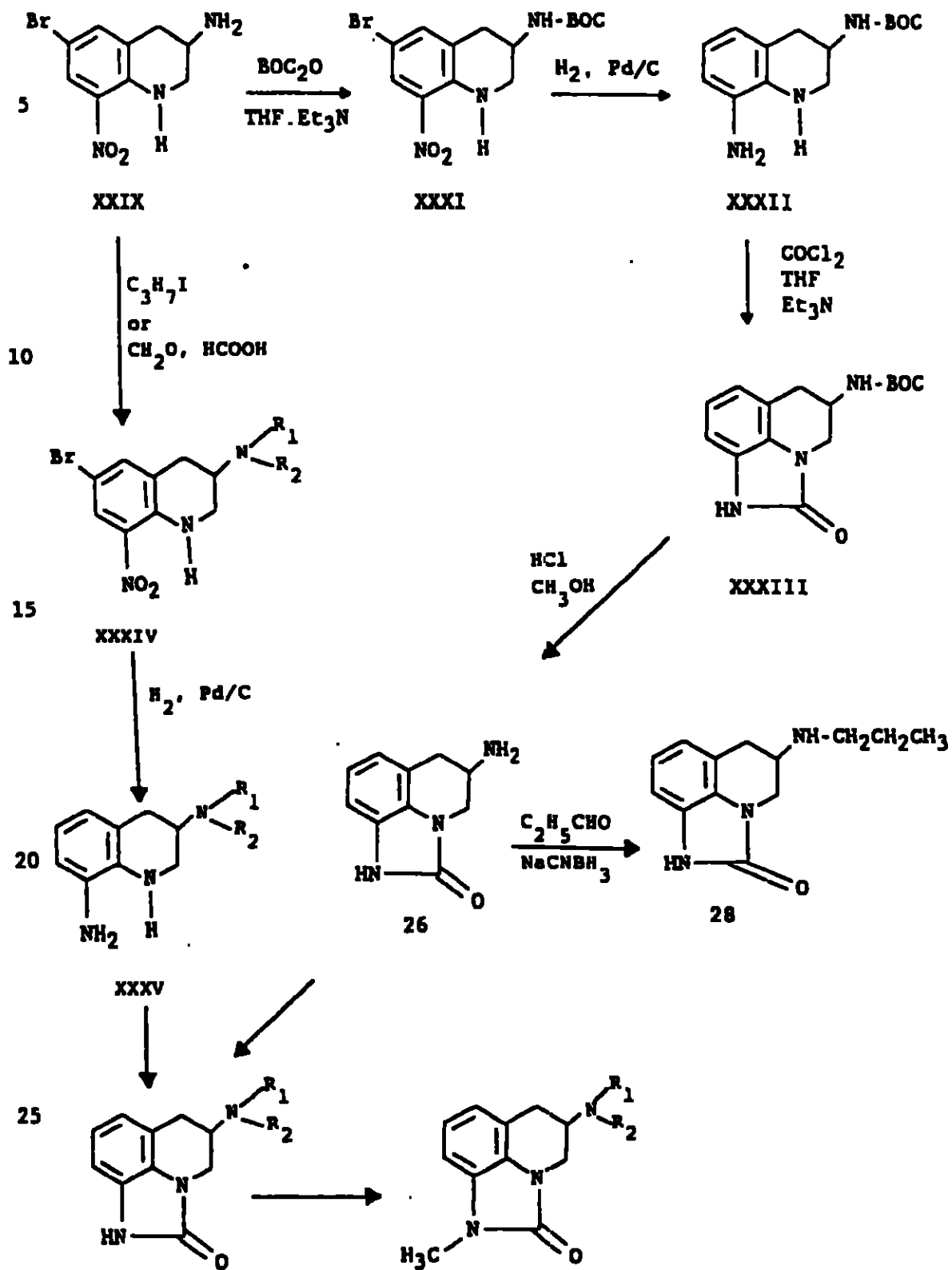
SCHEME 3

Synthesis of 5,6-Dihydro-4H-imidazo(4,5,1-j)quinolin-5-amines

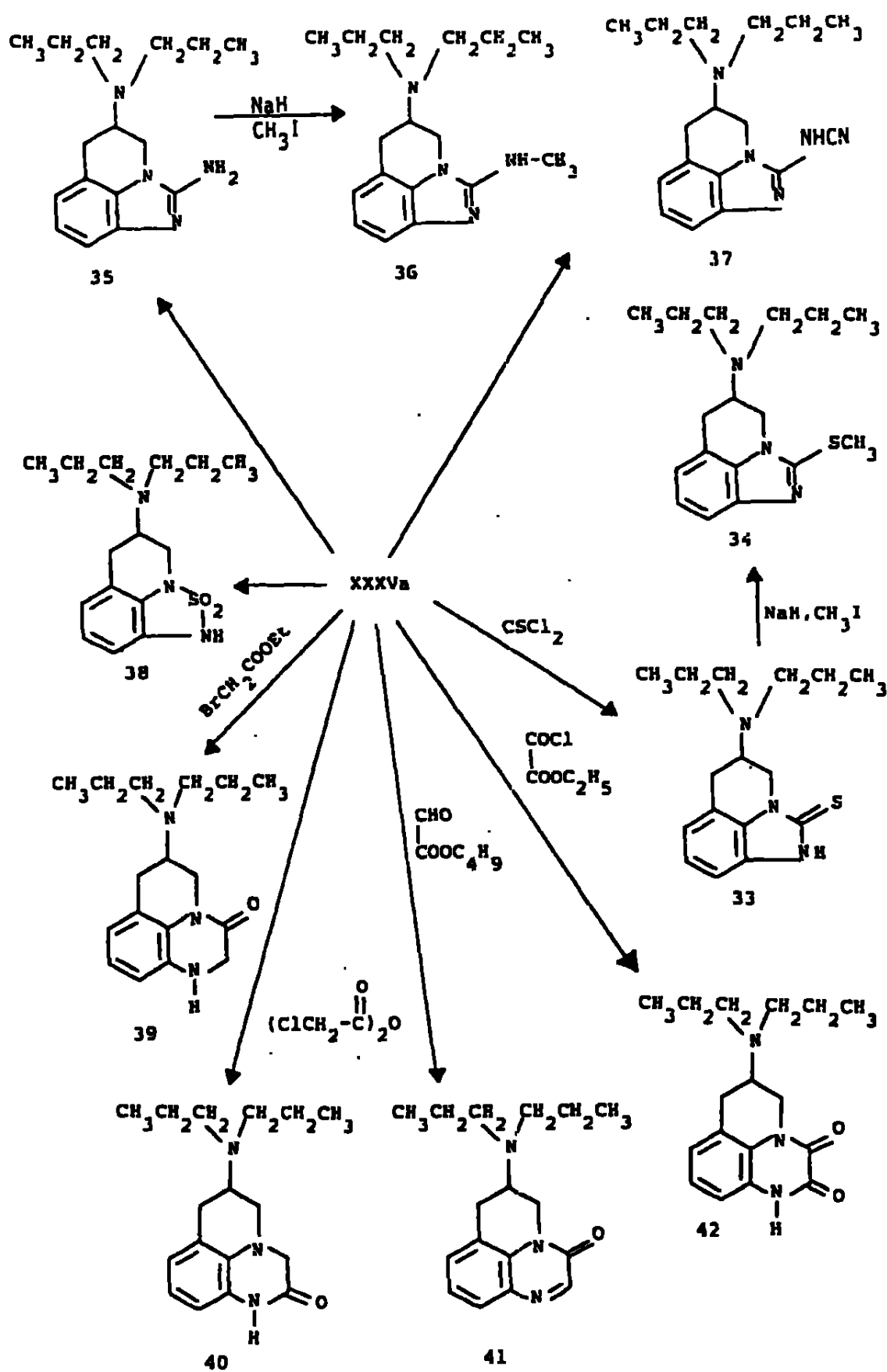


SCHEME 4

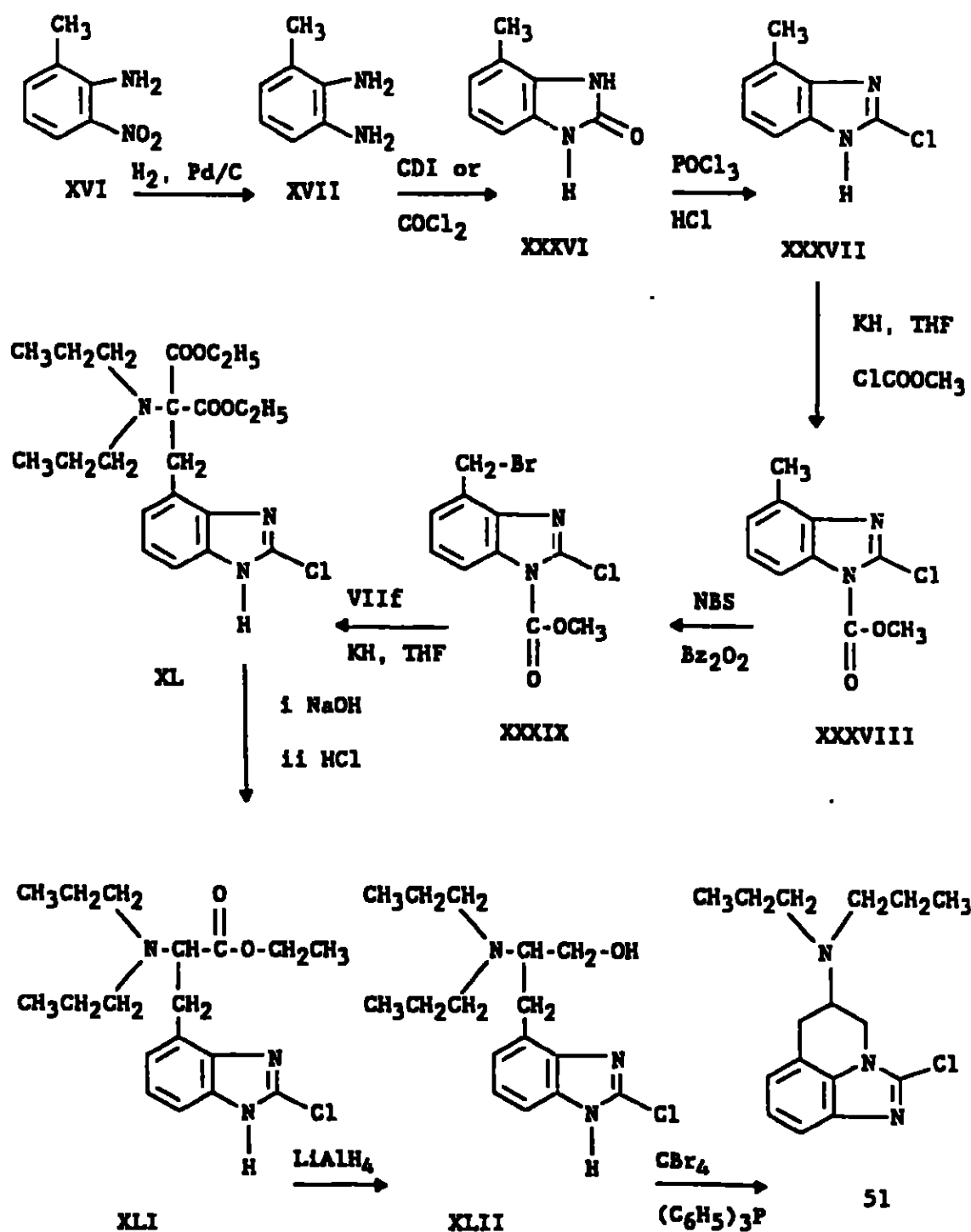
Synthesis of 5-Amino-5,6-dihydro-4H-imidazo(4,5,1-f)quinolin-2-ones

R₁ and R₂ are both (a) C₃H₇ or (b) CH₃

SCHEME 5

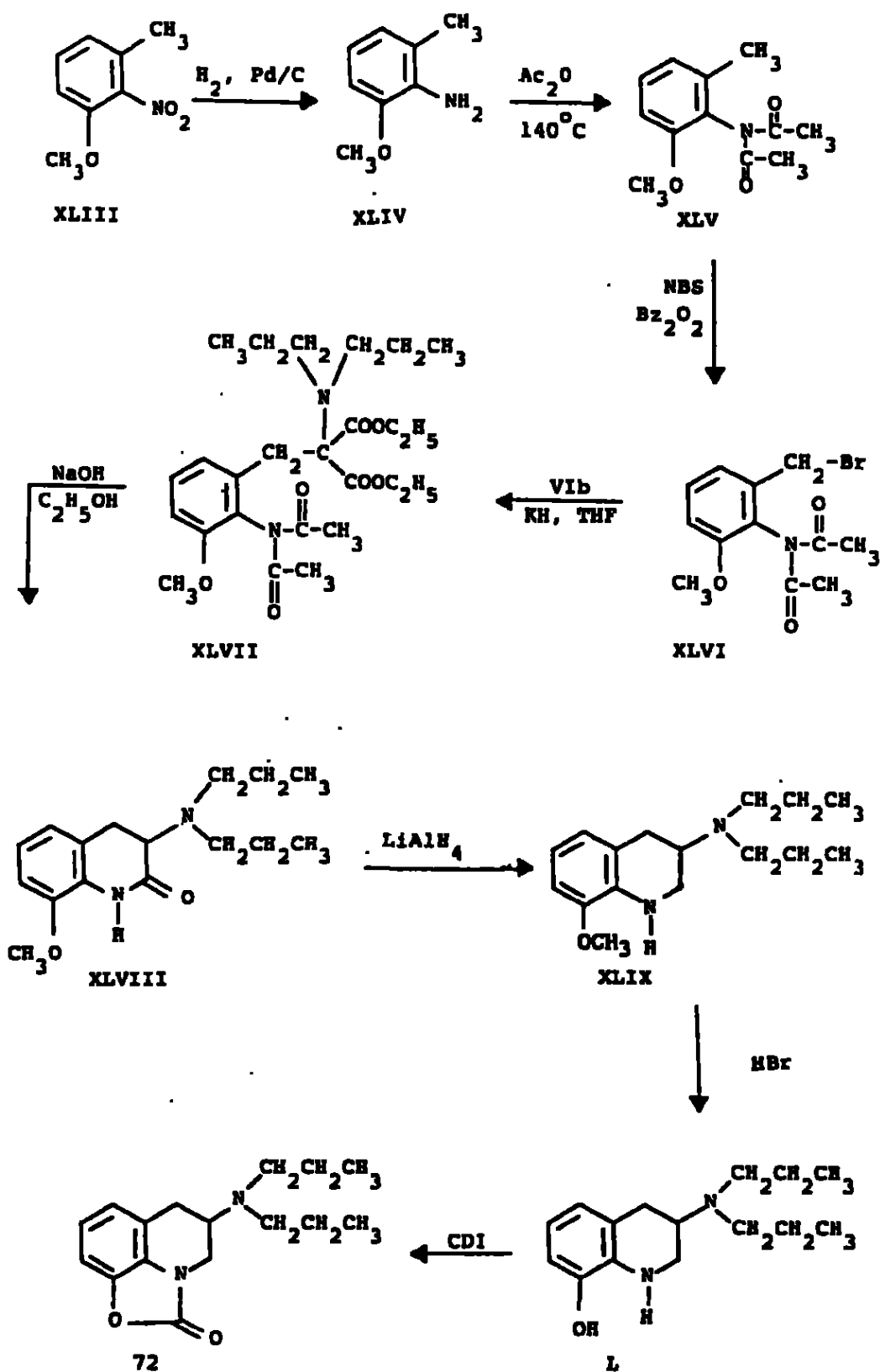


SCHEME 6



SCHEME 7

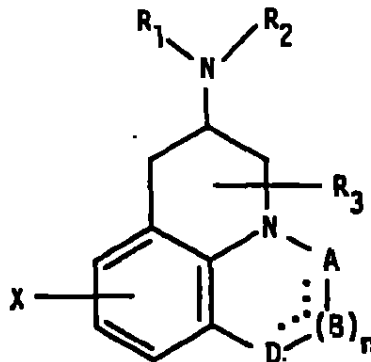
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WHAT IS CLAIMED:

1. A compound of the following structural formula:



and pharmaceutically acceptable salts thereof wherein,

R₁, R₂, and R₃ are independently

a) hydrogen,

b) C₁₋₆ alkyl, C₃₋₅ alkenyl, or C₃₋₅ alkynyl,

c) C₃₋₇ cycloalkyl, C₆₋₁₀ cycloalkyl- or phenyl- substituted C₁₋₆ alkyl, or

d) R₁ and R₂ are joined to form a C₃₋₇ cyclic amine which can contain additional heteroatoms and/or unsaturation;

25 X is

a) hydrogen,

b) C₁₋₆ alkyl,

c) halogen,

d) hydroxy,

30 e) alkoxy,

f) cyano,

g) carboxamide,

h) carboxyl, or

i) carboalkoxyl;

35 A is

a) CH, CH₂, CH-halogen, CHCH₃, C=O, C=S, C-SCH₃, C-NH, C-NH₂, C-NHCH₃, C-NHCOOCH₃, or C-NHCN;

b) SO₂, or

c) N;

40 B is

a) CH₂, CH, CH-halogen, or C=O, or

300
0036b) N, NH or N-CH₃;

c) O

n is 0 or 1; and

D is

5 a) CH, CH₂, CH-halogen or C=O,

b) O,

c) N, NH or N-CH₃.

2. The compound of Claim 1 wherein D is N or NH, and n is 0.

10

3. The compound of Claim 2 wherein A is CH, CH₂, CHCH₃, C=O, C=S, C-SCH₃, C-NH, C-NH₂, C-NHCH₃, C-NHCOOCH₃, or C-NHCN.

4. The compound of Claim 3 wherein A is CH or C=O.

15

5. The compound of Claim 4 which is

a) 5-(Dimethylamino)-5,6-dihydro-4H-imidazo(4,5,1-ij)quinolin-2(1H)-one hydrochloride

b) 5-(Propylamino)-5,6-dihydro-4H-imidazo(4,5,1-ij)quinolin-2(1H)-one

20

c) 5-(Dipropylamino)-5,6-dihydro-4H-imidazo(4,5,1-ij)quinolin-2(1H)-one

d) (-)5-(Dipropylamino)-5,6-dihydro-4H-imidazo(4,5,1-ij)quinolin-2(1H)-one

25

e) 5,6-Dihydro-N,N-dipropyl-4H-imidazo(4,5,1-ij)quinolin-5-amine

f) 5,6-Dihydro-N-propyl-4H-imidazo(4,5,1-ij)quinoline-5-amine

g) 5,6-Dihydro-5-(dipropylamino)-4H-imidazo(4,5,1-ij)quinolin-8-ol

30

6. The compound of Claim 1 wherein D is N and n is 1.

7. The compound of Claim 6 which is

a) 1,2,6,7-Tetrahydro-6-(dipropylamino)-3H,5H-pyrido(1,2,3-de)quinoxalin-3-one

35

b) 1,2,6,7-Tetrahydro-6-(dipropylamino)-3H,5H-pyrido(1,2,3-de)quinoxalin-2-one

c) 6,7-Dihydro-6-(dipropylamino)-3H,5H-pyrido(1,2,3-de)-

quinoxalin-3-one

- d) 6,7-Dihydro-6-(dipropylamino)-3H,5H-pyrido(1,2,3-de)-
quinoxalin-2,3-dione

5 8. The compound of Claim 1 wherein D is O, n is 0 and A is CH, CH₂,
CHCH₃, C=O, C-S, C-SCH₃, C-NH, C-NH₂, C-NHCH₃, C-NHCOOCH₃, or
C-NHCN.

9. The compound of Claim 8 wherein A is C=O or C-S.

10

10. The compound of Claim 9 which is

- a) 5-(Dipropylamino)-5,6-dihydro-2H,4H-oxazolo(5,4,3-ij)quino-
lin-2-one
b) 5-(Propylamino)-5,6-dihydro-2H,4H-oxazolo(5,4,3-ij)quinol-
in-2-one
15 c) 5-(Dimethylamino)-5,6-dihydro-2H,4H-oxazolo(5,4,3-ij)quino-
lin-2-one.

11. The compound of Claim 1 wherein D is CH, CH₂ or C=O and n is 0.

20

12. The compound of Claim 11 which is

- a) 5,6-Dihydro-N,N-dipropyl-4H-pyrrolo(3,2,1-ij)quinolin-5-
amine
b) 5,6-Dihydro-N,N-dimethyl-4H-pyrrolo(3,2,1-ij)quinolin-5-
amine
25 c) 5,6-Dihydro-N,N-dipropyl-4H-pyrazolo(4,3,2-ij)quinolin-5-
amine
d) 5,6-Dihydro-N,N-dimethyl-4H-pyrazolo(4,3,2-ij)quinolin-5-
amine
30 e) 1,2,5,6-Tetrahydro-N,N-dipropyl-4H-pyrrolo(3,2,1-ij)quinol-
in-5-amine
f) 1,2,5,6-Tetrahydro-N,N-dimethyl-4H-pyrrolo(3,2,1-ij)quinol-
in-5-amine
g) 5-(Propylamino)-5,6-dihydro-4H-pyrrolo(3,2,1-ij)quinolin-
2,3-dione
35 h) 5-(Dipropylamino)-5,6-dihydro-4H-pyrrolo(3,2,1-ij)quinolin-
2,3-dione
i) 5-(Propylamino)-5,6-dihydro-4H-pyrrolo(3,2,1-ij)quinolin-

2(1H)-one

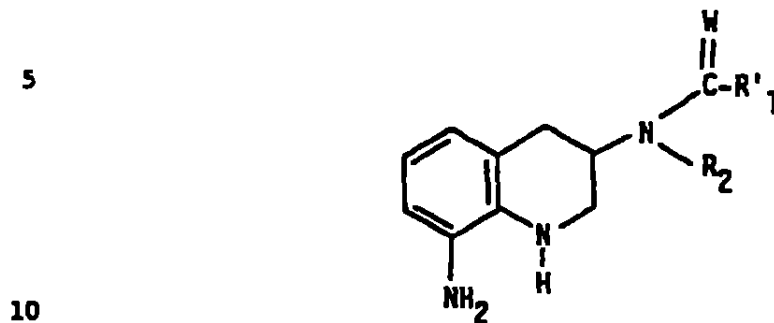
- j) 5-(Dipropylamino)-5,6-dihydro-4H-pyrrolo(3,2,1-ij)quinolin-2(1H)-one

5 13. The compound of Claim 1 wherein D is CH, CH₂, or C=O and n is 1.

14. The compound of Claim 13 which is

- a) 2,3,6,7-Tetrahydro-N,N-dimethyl-1H,5H-benzo(ij)quinolizin-2-amine
- 10 b) 2,3,6,7-Tetrahydro-N-methyl-1H,5H-benzo(ij)quinolizin-2-amine
- c) N-Ethyl-2,3,6,7-tetrahydro-N-methyl-1H,5H-benzo(ij)quinolizin-2-amine
- 15 d) 2,3,6,7-Tetrahydro-N-propyl-1H,5H-benzo(ij)quinolizin-2-amine
- e) 2,3,6,7-Tetrahydro-N,N-dipropyl-1H,5H-benzo(ij)quinolizin-2-amine
- f) 6-(Dipropylamino)-2,3,6,7-tetrahydro-5H-pyrido(3,2,1-ij)quinazolin-3-one
- 20 g) 6-(Dimethylamino)-2,3,6,7-tetrahydro-5H-pyrido(3,2,1-ij)quinazolin-3-one
- h) 6-(Dipropylamino)-6,7-dihydro-1H,5H-pyrido(1,2,3-de)-2,4-benzoxazine-3-one
- i) 6-(Dimethylamino)-6,7-dihydro-1H,5H-pyrido(1,2,3-de)-2,4-benzoxazine-3-one
- 25 j) 6-(Dipropylamino)-6,7-dihydro-3H,5H-benzo(ij)quinolizin-3-one
- k) 6-(Dimethylamino)-6,7-dihydro-3H,5H-benzo(ij)quinolizin-3-one
- 30 l) 6-(Dipropylamino)-2,3,6,7-tetrahydro-3H,5H-benzo(ij)quinolizin-3-one
- m) 6-(Dimethylamino)-2,3,6,7-tetrahydro-3H,5H-benzo(ij)quinolizin-3-one

35 15. A compound of the following structural formula XXXV

00804
353

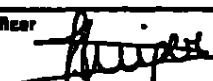
15 where W is O or H₂; and R'₁ and R₂ are independently hydrogen or a C₁₋₄ alkyl group.

16. The compounds according to Claim 15 which are
- a) 1,2,3,4-tetrahydro-N³,N³-dimethyl-3,8-quinolinediamine
 - b) 1,2,3,4-tetrahydro-N³,N³-dipropyl-3,8-quinolinediamine
 - 20 c) t-butyl(8-amino-1,2,3,4-tetrahydro-3-quinoliny)l)carbamate
 - d) N-propyl-N-(8-amino-1,2,3,4-tetrahydro-3-quinolyl)formamide.

17. A use of a compound of Formula I for the manufacture of a
medicament for treating central nervous system disorders in animal or
25 human hosts comprising the administration of a pharmaceutically
effective amount of a compound of Formula I.

INTERNATI NAL SEARCH REP RT

International Application No PCT/US 90/02621 00305

I. CLASSIFICATION OF SUBJECT MATTER (If several classification symbols apply, indicate all) *		
According to International Patent Classification (IPC) or to both National Classification and IPC		
IPC ⁵ : C 07 D 455/04, C 07 D 471/06, C 07 D 498/06, C 07 D 513/06, A 61 K 31/435, A 61 K 31/495, A 61 K 31/535, A 61 K 31/54		
II. FIELDS SEARCHED		
Minimum Documentation Searched *		
Classification System	Classification Symbols	
IPC ⁵	C 07 D 455/00, C 07 D 471/00, C 07 D 498/00, C 07 D 513/00, A 61 K 31/00, C 07 D 215/00	
Documentation Searched other than Minimum Documentation to the Extent that such Documents are included in the Fields Searched *		
III. DOCUMENTS CONSIDERED TO BE RELEVANT *		
Category *	Citation of Document, " with indication, where appropriate, of the relevant passages **	Relevant to Claim No. **
A	Chemical Abstracts, vol. 95, no. 7, 17 August 1981, (Columbus, Ohio, US), see page 726, abstract 62240y, & JP, A, 8125182 (YOSHITOMI PHARMA- CEUTICAL INDUSTRIES, LTD) 10 March 1981 -----	1,17
* Special categories of cited documents: ** "A" document defining the general state of the art which is not considered to be of particular relevance "E" earlier document but published on or after the international filing date "L" document which may throw doubt on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) "O" document referring to an oral disclosure, use, exhibition or other means "P" document published prior to the international filing date but later than the priority date claimed "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention "X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step "Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art "A" document member of the same patent family		
IV. CERTIFICATION		
Date of the Actual Completion of the International Search		Date of Mailing of this International Search Report
8th September 1990		27 SEP 1990
International Searching Authority		Signature of Authorized Officer
EUROPEAN PATENT OFFICE		Mme N. KUIPER 

Form PCT/ISA/210 (second sheet) (January 1985)

INTERNATIONAL SEARCH REPORT

International Application No. PCT/US 90/02621-2-

I. CLASSIFICATION OF SUBJECT MATTER (If several classification symbols apply, indicate all) ¹ According to International Patent Classification (IPC) or to both National Classification and IPC IPC ⁵ : C 07 D 215/40, // (C 07 D 471/06, 235:00, 221:00), (C 07 D 471/06, 241:00, 221:00), (C 07 D 498/06, 263:00, 221:00), . /		
II. FIELDS SEARCHED Minimum Documentation Searched ²		
Classification System	Classification Symbols	
IPC ⁵		
Documentation Searched other than Minimum Documentation to the Extent that such Documents are included in the Fields Searched ³		
III. DOCUMENTS CONSIDERED TO BE RELEVANT ⁴		
Category ⁵	Citation of Document, ⁶ with indication, where appropriate, of the relevant passages ⁷	Relevant to Claim No. ⁸
⁹ Special categories of cited documents: ¹⁰ "A" document defining the general state of the art which is not considered to be of particular relevance "E" earlier document but published on or after the international filing date "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) "O" document referring to an oral disclosure, use, exhibition or other means "P" document published prior to the international filing date but later than the priority date claimed "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art. "A" document member of the same patent family		
IV. CERTIFICATION		
Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report	
International Searching Authority	Signature of Authorized Officer	
EUROPEAN PATENT OFFICE		

Form PCT/ISA/16 (second sheet) (January 1983)

INTERNATIONAL SEARCH REPORT

International Application No PCT/US 90/02621

I. CLASSIFICATION OF SUBJECT MATTER (If several classification symbols apply, indicate all) ¹ According to International Patent Classification (IPC) or to both National Classification and IPC (C 07 D 471/06, 221:00, 209:00), (C 07 D 471/06, 231:00, IPC ⁵ : 221:00), (C 07 D 513/06, 285:00, 221:00), ./.		
II. FIELDS SEARCHED Minimum Documentation Searched ⁷		
Classification System	Classification Symbols	
IPC ⁵		
Documentation Searched other than Minimum Documentation to the extent that such Documents are included in the Fields Searched ⁸		
III. DOCUMENTS CONSIDERED TO BE RELEVANT ⁹		
Category ⁹	Citation of Document, ¹¹ with indication, where appropriate, of the relevant passages ¹²	Relevant to Claim No. ¹³
¹⁰ Special categories of cited documents: ¹⁴ "A" document defining the general state of the art which is not considered to be of particular relevance "E" earlier document but published on or after the international filing date "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) "O" document referring to an oral disclosure, use, exhibition or other means "P" document published prior to the international filing date but later than the priority date claimed "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combinations being obvious to a person skilled in the art. "A" document member of the same patent family		
IV. CERTIFICATION		
Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report	
International Searching Authority	Signature of Authorized Officer	
EUROPEAN PATENT OFFICE		

Form PCT/ISA/210 (second sheet) (January 1983)

INTERNATIONAL SEARCH REPORT

International Application No PCT/US 90/02621⁻⁴⁻

I. CLASSIFICATION OF SUBJECT MATTER (If several classification symbols apply, indicate all) ⁶ According to International Patent Classification (IPC) or to both National Classification and IPC IPC ⁵ : (C 07 D 498/06, 265:00, 221:00), (C 07 D 471/06, 249:00, 221:00)								
II. FIELDS SEARCHED Minimum Documentation Searched⁷ <table style="width: 100%; border-collapse: collapse;"> <tr> <th style="width: 15%; border: 1px solid black; padding: 2px;">Classification System</th> <th style="border: 1px solid black; padding: 2px;">Classification Symbols</th> </tr> <tr> <td style="border: 1px solid black; padding: 10px; vertical-align: top;">IPC⁵</td> <td style="border: 1px solid black; height: 50px;"></td> </tr> </table> Documentation Searched other than Minimum Documentation to the extent that such Documents are included in the Fields Searched⁸			Classification System	Classification Symbols	IPC ⁵			
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III. DOCUMENTS CONSIDERED TO BE RELEVANT⁹ <table border="1" style="width: 100%; border-collapse: collapse;"> <thead> <tr> <th style="width: 5%; padding: 2px;">Category⁹</th> <th style="width: 85%; padding: 2px;">Citation of Document,¹¹ with indication, where appropriate, of the relevant passages¹²</th> <th style="width: 10%; padding: 2px;">Relevant to Claim No.¹³</th> </tr> </thead> <tbody> <tr style="height: 300px;"> <td style="border: 1px solid black;"></td> <td style="border: 1px solid black;"></td> <td style="border: 1px solid black;"></td> </tr> </tbody> </table>			Category ⁹	Citation of Document, ¹¹ with indication, where appropriate, of the relevant passages ¹²	Relevant to Claim No. ¹³			
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⁵ Special categories of cited documents: "A" document defining the general state of the art which is not considered to be of particular relevance "G" earlier document but published on or after the international filing date "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) "O" document referring to an oral disclosure, use, exhibition or other means "P" documents published prior to the international filing date but later than the priority date claimed "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art. "Z" document member of the same patent family								
IV. CERTIFICATION <table style="width: 100%; border-collapse: collapse;"> <tr> <td style="width: 50%; border: 1px solid black; padding: 5px; vertical-align: top;"> Date of the Actual Completion of the International Search </td> <td style="width: 50%; border: 1px solid black; padding: 5px; vertical-align: top;"> Date of Mailing of this International Search Report </td> </tr> <tr> <td style="border: 1px solid black; padding: 5px; vertical-align: top;"> International Searching Authority EUROPEAN PATENT OFFICE </td> <td style="border: 1px solid black; padding: 5px; vertical-align: top;"> Signature of Authorized Officer </td> </tr> </table>			Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report	International Searching Authority EUROPEAN PATENT OFFICE	Signature of Authorized Officer		
Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report							
International Searching Authority EUROPEAN PATENT OFFICE	Signature of Authorized Officer							

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Research report

Levodopa or D2 agonist induced dyskinesia in MPTP monkeys: correlation with changes in dopaminic and GABA_A receptors in the striatopallidal complex.

F. Calon ^a, M. Goulet ^a, P.J. Blanchet ^b, J.C. Martel ^{a,b}, M.F. Piercey ^c, P.J. Bédard ^b,
T. Di Paolo ^{a,*}

^a School of Pharmacy, Laval University and Centre de recherche en endocrinologie moléculaire, Le Centre Hospitalier de l'Université Laval,
Québec, Canada G1V 4G2

^b Department of Pharmacology, Faculty of Medicine, Laval University and Neurobiology Research Center, Hôpital de l'Enfant-Jésus, Québec, Canada
^c CNS Research Division, The Upjohn Co., Kalamazoo, MI, U.S.A

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Abstract

Dopamine D1 and D2 receptors as well as the GABA/benzodiazepine receptor complex in the striatum and the globus pallidus (internal: GPi and external: GPe) were studied by autoradiography using [³H]SCH 23390, [³H]piperone, and [³H]flunitrazepam ([³H]FNZ) respectively, in five groups of cynomolgus monkeys. These included (i) untreated 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-monkeys; (ii) MPTP monkeys treated chronically with levodopa injections; (iii) MPTP monkeys treated chronically with injections of the novel D2 agonist U91356A; (iv) MPTP monkeys treated chronically with U91356A delivered through an osmotic mini-pump; and (5) naïve controls. Animals treated in a pulsatile mode with U91356A or levodopa injections showed progressive sensitization to their respective drug and developed choreic dyskinesia. In contrast, animals treated in a continuous mode with U91356A showed behavioral tolerance but did not develop dyskinesia. A trend for a down-regulation of putaminal D2 receptors was observed following D2 agonist stimulation with U91356A. Striatal [³H]FNZ binding was significantly decreased only in animals treated in a continuous mode with U91356A. The dopamine receptor decrease in the striatum could be implicated with the development of tolerance but cannot explain the appearance of dyskinesia. Denervation by MPTP was associated with a decrease of the GPe/GPi [³H]FNZ binding ratio which reflects an imbalance of striatal output pathways: this ratio was not reversed by any of the treatments although changes were observed in the GPe and GPi. Indeed, pulsatile U91356A treatment restored the decreased [³H]FNZ binding in the GPe near control values and levodopa showed a similar tendency. A significant increase of [³H]FNZ binding in the GPi only of dyskinetic monkeys, namely those treated with pulsatile U91356A or levodopa was seen compared to untreated MPTP or naïve controls. This GABA_A receptor up-regulation might lead to a supersensitive state of the GPi to gabaergic input which may be involved in the mechanism underlying the development of dopaminomimetic-induced dyskinesia.

Keywords: Parkinson's disease; Basal ganglia; Dyskinesia; GABA_A receptor; Dopamine receptor; Globus Pallidus; 1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine

1. Introduction

Dyskinesia is one of the main side-effects following chronic levodopa treatment of Parkinson's disease [52]. Moreover, dyskinesia usually accompanies other long term complications such as a gradual shortening of the

anti-parkinsonian response to levodopa, a progressive narrowing of the levodopa therapeutic window and even unpredictable 'on-off' phenomenon [51,52]. Chronic dopaminomimetic treatment, normal striatal outflow and severe dopaminergic denervation seem to be required for the development of dyskinesia [52]. However, the precise neurochemical mechanisms underlying the development of dopaminomimetic-induced dyskinesia still remain unknown.

Supersensitivity of striatal dopamine (DA) receptors resulting from postsynaptic adaptation following ni-

* Corresponding author. Fax: (11418) 654 2761

gastrostriatal denervation and dopaminergic treatment has been hypothesized to be a crucial factor in the induction of dyskinesia [16,42]. Indeed, D2 receptors have been shown to be increased in the brain of 1-methyl-4-phenyl 1,2,3,6-tetrahydropyridine (MPTP) monkeys, [27–29,37] 6-hydroxydopamine (6-OHDA)-lesioned rats [39] and human Parkinsonians [40,56]. However, no dyskinesia is usually seen at the beginning of dopaminomimetic treatment when DA receptors would be expected to be supersensitive.

A disequilibrium in the relative proportion of D1 versus D2 DA receptors following dopaminomimetic treatment has been postulated to be associated with susceptibility to develop dyskinesia [30,50].

It has been suggested that the development of dyskinesia is associated with preferential activation of D1 receptors [12,37,50] whereas other authors have implicated rather the D2 receptor subtype [8,18]. However, studies in MPTP monkeys have clearly shown that chronic treatment with either D1 or D2 agonists can induce dyskinesia similar to those observed following levodopa administration [7,35,45]. This suggests that the neurochemical mechanisms involved in the development of dyskinesia are not strictly related to the specific stimulation of one DA receptor subtype.

Although most of the work to date has focused on striatal DA receptors, basal ganglia components downstream from these receptors are also altered by nigral denervation or dopaminomimetic treatments and appear to be involved in the process of dyskinesia [2,18,20,41,46,47,57,58].

Fluctuation of plasma concentrations of a dopaminomimetic seem to be relevant to the onset of dyskinesia. Indeed, the mode of administration of dopaminomimetics in a pulsatile or continuous fashion induces a different basal ganglia functional state in 6-OHDA-lesioned rats [23–26,32,41]. Moreover, it is generally agreed that continuous steady-state administration of levodopa in human Parkinsonians reduces the fluctuations in motor performance such as dyskinesia but can induce tolerance to levodopa [15,49].

In the present report, we studied biochemical markers of basal ganglia function such as striatal D1 and D2 receptors as well as pallidal and striatal GABA_A receptors in groups of MPTP monkeys after different chronic dopaminergic treatment regimens, some of which led to the development of dyskinesia and others which did not, the purpose being to find changes that could be correlated.

2. Materials and methods

2.1. Animals and treatments

Sixteen ovariectomized female cynomolgous monkeys (*Macaca fascicularis*; 2.34–3.05 kg) were housed individually and exposed to a 12 h light/dark cycle. They were fed once per day and had free access to water. Three ovariectomized animals received no treatment and served as normal controls. Thirteen monkeys received repeated standard 2 mg subcutaneous doses of MPTP until a satisfactory and stable parkinsonian syndrome developed (Table 1). Nine of these animals received experimental drugs whereas four served as untreated MPTP controls. Dopaminergic treatments were initiated after a drug-free observation period of at least one month following the last MPTP injection. U91356A ((R)-5-(propylamino)-5,6-dihydro-4H-imidazo[4,5,1-ij]-quinolin-2(1H)-one hydrochloride, The Upjohn Co., Kalamazoo, MI) [48] which has high affinity for the D2 receptor ($K_i = 1.3$ nM) and moderate affinity to the 5-HT_{1A} site ($K_i = 58$ nM) was administered in a continuous ($n = 3$; PUMP group) or pulsatile ($n = 3$; PULSE group) mode for one month. Continuous infusion of U91356A (50–63 µg/kg/h) was given by an osmotic minipump (Alza Co., Palo Alto, CA, Model 2004) implanted intramuscularly under a light ketamine anesthesia. The PULSE group received twice daily s.c. injections of U91356A (600 mg/kg each time) at 7–8 h intervals, for a total a daily dose roughly equivalent to the PUMP group. Concurrently, Lev-

Table 1

General evaluation of parkinsonian syndrome in monkeys following injection of MPTP and subsequent behavioral effect of treatment with the D2 agonist U91356A (U91) or levodopa as well as striatal catecholamine levels

Group	n	MPTP dose (mg/kg)	Final parkinsonian score	Parkinsonian symptoms relief	Dyskinesia	Striatal catecholamine level (ng/mg of protein)		
						DA	DOPAC	HVA
Control	1	–	–	–	–	157.5 ± 19.1	20.2 ± 0.5	153.0 ± 38.7
MPTP Untreated	4	5.0 ± 1.0	4.8 ± 0.3	–	–	50 ± 0.8 ^a	1.5 ± 0.5 ^a	30.8 ± 13.4 ^a
MPTP + L-Dopa	3	3.3 ± 1.3	6.3 ± 1.2	++	yes	27 ± 0.9 ^a	1.5 ± 0.6 ^a	20.2 ± 9.8 ^a
MPTP + U91 Pulse	3	8.2 ± 4.2	5.0 ± 0.6	++	yes	36 ± 1.2 ^a	1.7 ± 0.4 ^a	31.1 ± 12.9 ^a
MPTP + U91 Pump	3	5.5 ± 1.5	5.3 ± 0.7	++	no	51 ± 1.3 ^a	1.2 ± 0.4 ^a	33.3 ± 7.7 ^a

^a Animals treated continuously with U91356A developed behavioral tolerance

^b $P < 0.001$ vs. control (Scheffé F test following one factor ANOVA)

^c $P < 0.005$ vs. control (Fisher PLSD test following one factor ANOVA) Values shown are the mean ± S.E.M

odopa (100 mg/kg/day) as well as a peripheral dopa decarboxylase inhibitor Benserazide (25 mg/kg/day) were given to three other MPTP monkeys (1-DOPA group) during 1 month.

2.2. Behavioral measures

Monkeys were observed at least 6 h daily through a one-way screen and scored every 30 min to obtain a quantitative assessment of the antiparkinsonian response as described before [36]. The normal status is rated 0, and maximal disability 10. Monkeys had a baseline parkinsonian syndrome of variable intensity with scores from 5 to 7. Relief of parkinsonism from drug treatment was considered definite when this score improved by at least 2 points.

Home cages equipped with photoelectric cells were used in order to record the mobility of animals continuously throughout the experiment. A light beam is interrupted by the movements of the animal and signals are cumulated by a computer which provides a mobility count every 15 min.

Dopamine agonist-induced dyskinesia was also evaluated according to a modified Abnormal Involuntary Movements Scale for MPTP monkeys. The intensity was rated as follows: absent = 0; mild, occasional = 1; moderate, intermittent = 2; severe, frequent = 3. Intermediate scores (0.5, 1.5, 2.5) were allowed to reflect slight bodily asymmetries. Each body segment was scored individually (each limb, face, neck, trunk) every 30 min. We also distinguished chorea from dystonia, as defined by the Research Group on Extrapyrarnidal Disorders of the World Federation of Neurology [43]. The dyskinesia score provided at a given time is the sum of the scores for all segments.

2.3. Biochemical studies

After the end of the chronic dopaminomimetic treatment and after a 3 day drug washout, all monkeys were sacrificed by an overdose of pentobarbital. The brains were removed and placed in isopentane (-40°C) and kept frozen at -80°C . Coronal sections (20 μm) were cut on a cryostat (-18°C) and slices were thaw-mounted onto gelatin and chrome alum coated slides for autoradiographic studies. Small tissue pieces were taken and kept frozen in perchloric acid for catecholamine contents determination. Caudate and putamen concentrations of DA and its metabolites, dihydroxyphenylacetic acid (DOPAC) and homovanillic acid (HVA) were quantified by HPLC with electrochemical detection as previously described [21].

Density of D1 and D2 antagonist sites as well as D2 agonist sites, was measured by autoradiography of [^3H]SCH 23390 (Amersham; 72.8 Ci/mmol), [^3H]piperone (Amersham; 108 Ci/mmol), and [^3H]N-

n-propylnorapomorphine ([^3H]NPA; NEN-Dupont, 53.4 Ci/mmol) binding, respectively, essentially as previously described [29]. GABA_A receptor density was evaluated with [^3H]flunitrazepam (Amersham; 84 Ci/mmol) binding to the benzodiazepine site of the GABA_A/benzodiazepine receptor complex. [^3H]flunitrazepam binding experiments were performed with slight modifications of previous assays [59]. Sections were preincubated for 15 min. in a Tris-HCl buffer (pH = 7.3–7.4). Then, they were incubated 45 min. at room temperature with 10 nM of [^3H]flunitrazepam. Non-specific binding was determined in presence of 1 mM clonazepam. Sections were washed twice for 10 min. in cold buffer (4°C) and then rinsed 10 s in cold distilled water. After this step for all ligands, the slide-mounted tissue sections were dried overnight at room temperature and then exposed to [^3H] sensitive films (Hyperfilm, Amersham) along with tritium standards (microscales Amersham) during 3 weeks for [^3H]NPA and 2 weeks for the other ligands. Films were developed and autoradiograms analysed as previously described [29]. Specific binding to DA and GABA_A receptors was measured at three rostrocaudal coordinates: anterior (A19.0–A22.0); medial (A17.0–A19.0) and posterior (A17.0–A14.0) [61]. Caudate and putamen were each divided in two sub-regions along a medial-lateral axis. The external segment of the globus pallidus (GPe) was divided into a rostral and a caudal part with respect to the anterior margin of the internal segment globus pallidus (GPi). Data were computed separately for each sub-region and were grouped when regional effects were similar. In total, at least 60 slices were quantified for each animal for each ligand.

2.4. Statistics

[^3H]SCH 23390 and [^3H]piperone binding data were statistically compared using a two-factor ANOVA including treatment and assay batch as the two dependent variables to account for interassay variability. The D1/D2 receptor ratios, catecholamine concentrations and [^3H]flunitrazepam binding data were statistically compared with a Fisher probability of least significant difference (PLSD) test and/or Sheffe's *F*-test following a one factor ANOVA.

3. Results

Striatal catecholamine levels and Parkinsonian scores were comparable between each group of MPTP monkeys (Table 1). Therefore, the extent of denervation was considered to be roughly equivalent for all MPTP monkeys.

Continuous infusion of U91356A induced a good relief of Parkinsonian symptoms less than two days

after the pump implant. Thereafter, the response gradually decreased, suggesting behavioral tolerance (Fig. 1 and Table 1). Levodopa or U91356A given in a pulsatile schedule produced very good motor recovery with a progressive increase in locomotion counts throughout the trial and induced dyskinesia (Fig. 1 and Table 1). A detailed report of the behavioral assessment of these monkeys is described elsewhere [9].

3.1. Autoradiography of D1 and D2 receptors

No significant variation of striatal D1 or D2 receptors was seen between the various treatment groups. Nevertheless, D2 receptors tended to decrease in the striatum of monkeys of the PUMP and PULSE groups. Indeed, [³H]spiperone binding tended to decrease more specifically in the putamen and more so in the PUMP group (Table 2). The D1/D2 ratios, however, underwent slight but significant changes mostly in the putamen. The ratios decreased in untreated MPTP monkeys, and increased in all the U91-treated animals. These changes are mainly due to D2 receptor variations rather than changes of the D1 receptor subtype. No significant change of [³H]SCH 23390 and [³H]spiperone binding was seen in GPe, GPi and nucleus accumbens (data not shown). [³H]NPA binding to

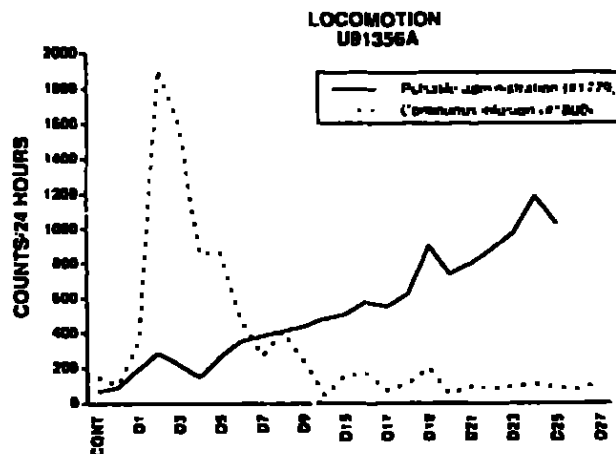


Fig. 1. Linear representation of the total daily counts of locomotion activity recorded for two monkeys treated chronically with the D2 agonist U91356A, one in a continuous manner with a minipump (broken line) and another by injections twice daily (solid line). Note the progressive increase in response after pulsatile administration and the initial strong response followed by loss of efficacy after continuous administration. (CONT: saline control; D1, D3, etc., day one, day three, etc. of drug treatment).

the agonist site of D2 receptors showed changes similar to [³H]spiperone binding following MPTP and drug treatments (data not shown).

Table 2

Effect of chronic treatment of MPTP monkeys with the D2 agonist U91356A (U91) or levodopa on caudate and putamen D1 and D2 receptor density as measured by autoradiography

Group	n	[³ H]SCH 23390 binding		[³ H]spiperone binding		[³ H]SCH 23390/[³ H]spiperone binding ratio	
		Caudate	Putamen	Caudate	Putamen	Caudate	Putamen
Control	3	448.0 ± 13.7	344.7 ± 19.1	229.7 ± 8.7	183.1 ± 7.0	1.98 ± 0.03	1.88 ± 0.02
MPTP Untreated	4	428.4 ± 12.9	367.7 ± 13.8	218.1 ± 6.2	197.1 ± 7.1	1.98 ± 0.06	1.80 ± 0.03 *
MPTP + (-)-Dopa	3	435.0 ± 22.2	364.0 ± 28.9	229.8 ± 10.4	196.6 ± 11.3	1.91 ± 0.04	1.90 ± 0.01
MPTP + U91 Pulse	3	448.4 ± 14.7	353.1 ± 27.3	202.1 ± 13.0	174.5 ± 8.1	2.19 ± 0.12 *	2.00 ± 0.01 **d
MPTP + U91 Pump	3	418.2 ± 21.1	329.1 ± 29.8	234.9 ± 14.3	166.4 ± 9.3	2.09 ± 0.11	2.00 ± 0.03 **d

Values shown are mean ± S.E.M. expressed in fmol/mg of tissue. Statistical comparisons were made using a Fisher PLSD test following one factor ANOVA.

* $P < 0.05$, and ** $P < 0.01$ vs. Control, * $P < 0.05$ vs. MPTP + (-)-Dopa, ^d $P < 0.001$ vs. MPTP untreated.

Table 3

Effect of chronic treatment of MPTP monkeys with the D2 agonist U91356A (U91) or levodopa on caudate and putamen GABA_A receptor density as measured by autoradiography

Group	n	[³ H]Flunitrazepam binding			
		Caudate		Putamen	
		Medial	Lateral	Medial	Lateral
Control	3	441.9 ± 9.0	433.8 ± 16.7	417.4 ± 42.2	462.7 ± 31.8
MPTP Untreated	4	415.6 ± 19.2	360.7 ± 32.0	380.9 ± 26.1	432.4 ± 42.6
MPTP + (-)-Dopa	3	444.3 ± 1.4	450.5 ± 23.8 *	423.8 ± 14.0	515.0 ± 43.2
MPTP + U91 Pulse	3	379.3 ± 21.8 **	361.0 ± 30.9 *	373.1 ± 18.9	433.8 ± 24.2
MPTP + U91 Pump	3	342.9 ± 16.6 ***	319.6 ± 17.3 **d	332.9 ± 14.7 *	382.6 ± 20.6 *

* $P < 0.05$, * $P < 0.005$ vs. Control, * $P < 0.05$, ^d $P < 0.01$, * $P < 0.005$ vs. MPTP + (-)-Dopa, ¹ $P < 0.05$, ² $P < 0.01$ vs. MPTP untreated. Statistical comparisons were made using a Fisher PLSD test following one factor ANOVA. Values shown are mean ± S.E.M. expressed in fmol/mg of tissue.

[³H] Flunitrazepam autoradiography

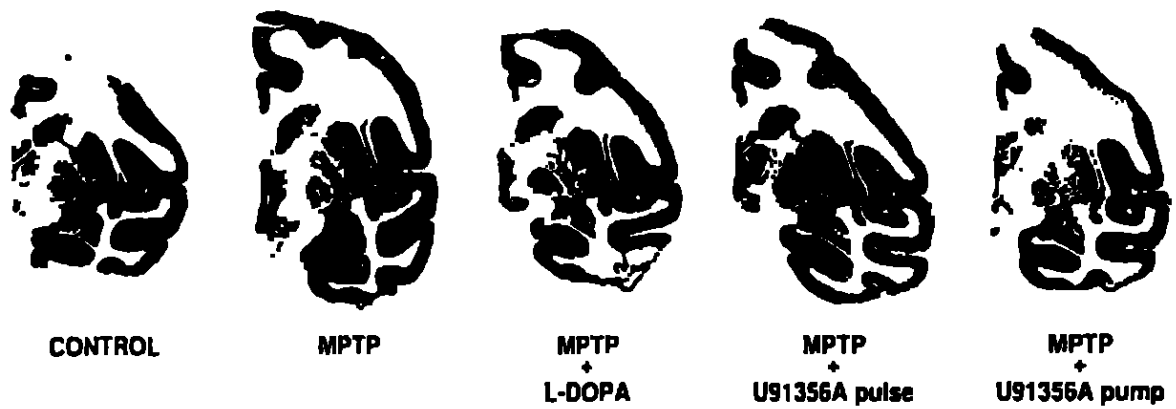


Fig. 2. Autoradiograms of [³H]flunitrazepam binding in brain slices (including GPe, GPi, caudate, putamen) of a control monkey (control), an untreated MPTP monkey (MPTP), a MPTP monkey treated chronically with L-DOPA injections (MPTP + L-DOPA), a MPTP monkey treated chronically with U91356A injections (MPTP-U91356A pulse) or with U91356A delivered through an osmotic mini-pump (MPTP + U91356A pump).

3.2. Autoradiography: GABA_A receptors

The GABA_A/benzodiazepine receptor complex as quantified with [³H]FNZ binding tended to decrease in the GPe but increased in the GPi in untreated MPTP monkeys without reaching statistical significance in either area (Figs. 2 and 3). However, in the rostral part of the GPe this decrease of [³H]FNZ binding was statistically significant (–26%; $P < 0.05$ vs. control; data not shown). Nevertheless, [³H]FNZ binding in the GPe generally showed a very similar pattern of variation along the rostrocaudal axis.

Treatment with U91356A in a pulsatile regimen reestablished [³H]FNZ binding in the GPe near control values (+32%; $P < 0.05$ vs. MPTP) and the levodopa group showed a similar tendency. In the GPi of monkeys from the L-DOPA and PULSE groups, [³H]FNZ binding was significantly elevated (+55% and +58% vs. control, +36% and +38% vs. untreated MPTP monkeys, respectively; $P < 0.05$) (Figs. 2 and 3). In animals of the PUMP group, GABA_A receptors in the GPe and GPi were less affected by treatment with values close to untreated-MPTP monkeys. Denervation induced by MPTP led to a decrease of GPe/GPi [³H]FNZ binding ratio (–31% vs. control, $n = 13$, $P < 0.001$) in all MPTP-treated animals whatever the subsequent treatment (Figs. 2 and 3).

In the caudate and the putamen, [³H]FNZ binding was significantly decreased in monkeys of the PUMP group (–13% vs. MPTP, –21% vs. control ($P < 0.05$; total striatum) but less strikingly in the animals of the PULSE group (–3% vs. MPTP, –12% vs. control; total striatum). These changes appeared more pronounced in the caudate than in the putamen (Table 3).

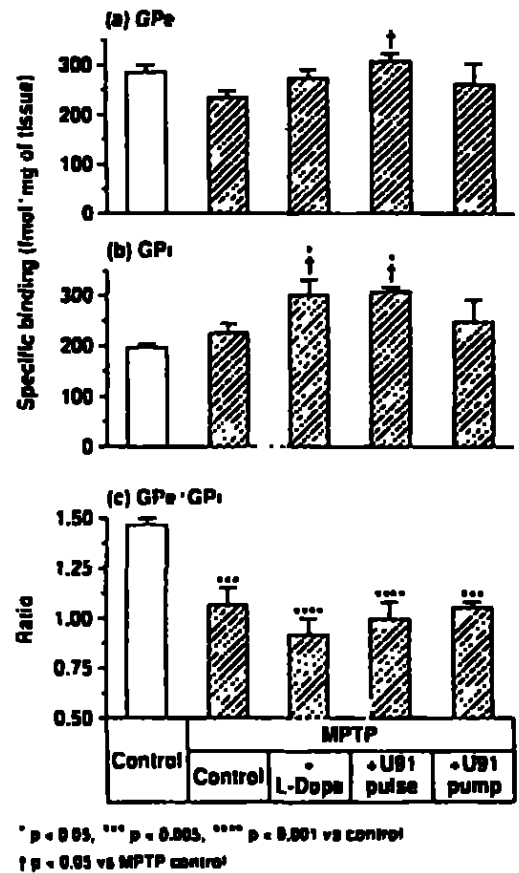


Fig. 3. Effect of chronic treatment of MPTP monkeys with the D2 agonist U91356A (U91) by injections (pulse) or through osmotic mini-pumps (pump) or levodopa injections on [³H]flunitrazepam specific binding in the (a) GPe, (b) GPi, and on the (c) GPe/GPi binding ratio as compared to intact controls. Results shown are the mean $\pm$ S.E.M. of 3–4 animals per group. Statistical comparisons were performed using a Fisher PLSD following one factor ANOVA.

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No change was observed in the nucleus accumbens (data not shown).

4. Discussion

Dyskinetogenic properties of selective D2 agonists similar to those we have observed have been reported previously in MPTP-treated primates [6,7,35,45]. Indeed, with the notable exception of bromocriptine, all dopaminomimetics tested to date chronically which show good antiparkinsonian efficacy also induce similar dyskinesia in animals and humans [6,7]. Therefore, the relative specificity for either the D1 or D2 receptor subtype of a DA agonist is probably not a major indication of its dyskinetogenic potentiality.

4.1. Striatal D1, D2 and GABA_A receptors

It is generally agreed that MPTP-induced denervation in monkeys causes an up-regulation of striatal D2 receptors mostly in the lateral putamen whilst the D1 receptor density is less or not at all affected [3,4,27–30,37]. In the putamen, the decrease of the D1/D2 ratio observed here reflects a greater increase for D2 than D1 receptors following nigral denervation which is in accordance with previous observations. Moreover, also in the putamen, chronic D2 receptor stimulation in MPTP monkeys led to an increase of the D1/D2 ratio in monkeys of the PUMP and PULSE groups due to a greater decrease of D2 than D1 receptors. However in the present experiment, levodopa treatment did not alter striatal D1 nor D2 receptor densities as reported previously [4,6,27,37]. The fact that slight D1/D2 ratio changes have reached statistical significance, whereas D1 and D2 receptor variations separately did not, can mostly be explained by a critical decrease of interindividual variability resulting from computing ratio. The use of D1/D2 ratios gives also a better indication of the balance of the two DA receptor subtypes in a specific animal.

Behavioral tolerance observed in the present experiment in monkeys treated continuously with U91356A is in agreement with previous studies with other D2 agonists given in a continuous fashion in humans [14] or MPTP monkeys [3] which reported a marked loss of efficacy with time but an improvement of dyskinesia. A study with another D2 agonist, lisuride, reported no behavioral tolerance but patients undergoing the treatment were given lower doses at night [5]. Behavioral tolerance has been associated with a decrease of striatal [³H]piperone binding following treatment of MPTP monkeys [3] or 6-OHDA mice [63] with continuous infusion of a D2 agonist. Moreover, the D2 agonist quinpirole given continuously to normal mice induces a decrease of striatal [³H]piperone binding and D2 receptor mRNA [17]. In contrast, studies in 6-OHDA

rats report no change of D2 receptors following continuous administration of the D2 agonist quinpirole [24] or levodopa [41]. Our results, however, show a trend for putaminal [³H]piperone binding to decrease in monkeys of the PUMP or the PULSE groups. These autoradiographic results are consistent with saturation binding data performed on striatal homogenates from the other cerebral hemisphere of the same animals [8]. This tendency of [³H]piperone binding to decrease seems to be caused mostly by the specific D2 receptor stimulation rather than the mode of administration in a pulsatile or continuous regimen. Hence, the decrease of sensitivity to U91356A observed in the PUMP group could be explained in part by a down-regulation phenomenon. Changes in cellular response mechanisms downstream from the receptor–ligand interaction such as transduction processes could also be involved. Furthermore, DA receptor autoradiography strongly suggests that dyskinesia observed in animals of PULSE and L-DOPA groups cannot be attributed to supersensitivity of D2 receptors.

MPTP-induced denervation did not alter striatal GABA_A receptor density levels as previously reported in MPTP monkeys [59]. Moreover, levodopa treatment also had no effect which is in accordance with results in 6-OHDA rats reporting that levodopa given in an intermittent or continuous fashion does not change striatal [³H]FNZ binding [34]. The decrease of [³H]FNZ binding in monkeys of the PUMP group was more intense in the medial part of the caudate, and less in the lateral side of the putamen. The caudate especially in the medial part receives a prominent input from the associative cortex in contrast with the putamen which receives innervation mostly from the sensorimotor cortex [54]. Hence, the changes observed might be related to an alteration of the input from associative areas of the cerebral cortex.

Striatal GABA_A receptors are thought to respond mainly to collateral of striatopallidal and striatonigral neurons [2,10,33]. Hence, changes of GABA_A receptor density could reflect general changes of the total striatal outflow but have no specific relationship with either of the two major efferent pathways of the striatum. Therefore, stimulation of D2 receptors in a continuous fashion would enhance the overall striatal gabaergic activity though the exact location of these responding D2 receptors is unclear. Further investigation are needed to understand these results.

4.2. GABA_A receptors in the globus pallidus and dyskinesia

Dyskinesia occurring after chronic dopaminergic treatment could be explained by an exaggerated reversal of neural function patterns ensuing a transient 'overresponse' to dopaminergic stimulation since dyskinesia is commonly seen at peak-dose of levodopa. Other patho-

logical states such as ballism, Huntington disease, and tardive dyskinesia producing abnormal basal ganglia function are known to induce choreic dyskinesia similar to dopaminomimetic-induced dyskinesia. Most of the work on these motor disorders suggests that all forms of choreic dyskinesia whatever their origin share a common underlying neural mechanism involving loss of activity of the glutamatergic subthalamicopallidal pathway [2,18,20]. Moreover, direct ablation of the STN [13,62], direct GABA antagonist injection in the GPe or the STN [19], and direct glutamatergic antagonist injection in the GPi [60] elicit dyskinesia in normal primates. These experimental procedures are thought to induce dyskinesia in normal subjects by decreasing the STN-GPi glutamatergic activity.

Most of the experimental evidence suggests that all forms of choreic dyskinesia including dopaminomimetic-induced dyskinesia imply a (transient) lowered gabaergic output from the GPi to the thalamus [2,18,20]. This loss of GPi activity can be in response to (i) an hypoexcitation from subthalamic glutamatergic neurons (indirect output pathway from the striatum) and/or (ii) an hyperinhibition of the GPi by striatonigral gabaergic neurons (direct output pathway from the striatum) and/or (iii) an hyperinhibition of the GPi by the GPe-GPi pathway recently characterized by Parent and Hazrati [55]. Glutamatergic receptor desensitization or gabaergic receptor (GABA_A and/or GABA_B) supersensitization in the GPi following long term dopaminergic treatment might therefore be involved in the triggering of dyskinesia.

The GABA_A receptor changes after MPTP-induced denervation observed in this study are consistent with the general pattern of neural changes underlying the parkinsonian syndrome. It is expected that nigral denervation causes the striatopallidal pathway to be overactive and thus down-regulate GABA_A receptors in the GPe whereas it has the opposite effect in the GPi. To support this, in the ipsilateral hemisphere of rats with a unilateral 6-OHDA lesion, [^3H]FNZ binding to GABA_A receptors was shown to be decreased in the globus pallidus and increased in the SNr and in the entopeduncular nucleus (EP) which is the rodent equivalent of GPi [34,53]. Studies in monkeys following systemic MPTP administration [59] and in patients suffering from idiopathic Parkinson's disease [38] report a decrease of [^3H]FNZ binding in the GPe but no change was seen in the GPi. However, in hemiparkinsonian monkeys a significant elevation of [^3H]FNZ binding in the GPi has also been demonstrated [59]. In the present study we observed a down-regulation of [^3H]FNZ binding in the GPe although statistically significant only in the more rostral part whereas an opposite trend is observed in the GPi.

Assuming that a change of receptor density is dependent of the level of afferent activity, the differential

output drive of the two major striatal efferents can be correlated or visualized with the GABA_A receptor density ratio between the GPe and the GPi. The important decrease of the GPe/GPi ratio of [^3H]FNZ binding reported here in all MPTP-exposed primates further supports the idea of a disequilibrium between the two striatal efferent pathways generated by loss of sufficient dopaminergic activity. Surprisingly, the decrease of GPe/GPi [^3H]FNZ binding ratio was not corrected by any of the present treatments. Indeed, it seems that whatever the GABA_A receptor variation in one segment of the globus pallidus there is a concomitant change in the other segment which keeps the ratio decreased compared to unlesioned animals.

By contrast to the intermittent treatment with levodopa or U91356A, continuous stimulation of D2 receptors had no effect on [^3H]FNZ binding in either segments of the globus pallidus. Hence, striatal outflow as estimated with GPe and GPi [^3H]FNZ binding appears very similar to untreated MPTP monkeys. This suggests that the desensitization mediating the decrease in response to continuous D2 agonist stimulation is related to the D2 receptor site.

Gnanalingham et al. [34] have shown that intermittent treatment with levodopa in 6-OHDA rats does not reverse the lowered [^3H]FNZ binding in the GP induced by the lesion but restores the [^3H]FNZ binding increase in the EP and SNr to normal levels. Assuming that [^3H]FNZ binding changes reflect the gabaergic output activity level of the striatum, these authors suggest that levodopa treatment may alleviate the dysfunction of the striatonigral but not the striatopallidal output in rodents. In contrast, our results in primates show that intermittent treatment with levodopa or a D2 agonist restores the [^3H]FNZ binding in GPe to normal values but further enhances the elevation seen in the GPi. Indeed, these findings suggest that levodopa treatment in MPTP monkeys tends to rectify the enhanced inhibitory drive from the striatopallidal medium spiny output neurons to the GPe while it does not seem to correct the abnormal striatonigral activity. Moreover, levodopa and U91356A intermittent treatments induced similar effects on [^3H]FNZ binding suggesting a D2-like activity of levodopa in primates. In rodents, however, the levodopa activity which is more prominent on the striatonigral pathway could imply a D1-like action. Neurophysiological differences between rodents and primates could account for these discrepancies. Indeed, rodents do not develop dyskinesia, thus implying important differences in their basal ganglia function as compared to primates.

Of prime interest is the significant elevation observed in monkeys of the two dyskinetic groups (L-DOPA and PULSE) of [^3H]FNZ binding in the GPi. With the striatal DA receptor segregation hypothesis in mind, D2 specific stimulation could have been ex-

pected to have no modulatory effect on gabaergic GPi receptors located postsynaptically from striatonigral medium spiny output neurons which are more sensitive to D1 stimulation. Most surprisingly, levodopa, a D1/D2 mixed agonist induced [^3H]FNZ binding changes similar to those of a D2 agonist. This suggests that a mechanism more related to the D2 stimulation is responsible for the up-regulation of the GABA_A/benzodiazepine receptor complex in the GPi. A fraction of D2 receptors located on striatonigral medium spiny output neurons [31,44] could account at least in part for these effects. [^3H]FNZ binding studies in the two segments of the globus pallidus following chronic treatment with a full D1 agonist could help to elucidate these questions.

It can be postulated that the high [^3H]FNZ binding observed in the GPi indicates an up-regulation of GABA_A receptors reflecting long term compensatory mechanisms to either a very low activity level or even a 'disturbed' (fluctuating) gabaergic input. This up-regulation of [^3H]FNZ binding could reflect a supersensitive state of the GABA_A/benzodiazepine receptor complex in the GPi. Thus, striatal or GPe gabaergic projections to the GPi could generate an exaggerated inhibitory response. An ensuing underactivity of the GPi-Thalamus gabaergic pathway might produce an amplified thalamo-cortical transmission to the motor cortex that could be involved in the generation of abnormal movement patterns such as choreic dyskinesia.

Indeed, 2-deoxyglucose uptake studies have shown a high level of glucose consumption in the GPi of MPTP monkeys 45 min after levodopa or apomorphine treatment [46,58]. This elevation, reflecting changes in overall level of intrinsic synaptic activity, is most likely due to increased terminal activity of an afferent input [46,47]. The three main projections to the GPi come from the STN, the striatum and the GPe [31,54,55]. Since the STN-GPi pathway has been shown to be concomitantly underactive [46,58], this would suggest that the GPe-GPi and/or the striatonigral gabaergic inputs mediate an overinhibition of the GPi during the dyskinetic process.

It is important to note however that besides the GABA_A/benzodiazepine receptor complex, GABA_B receptors are also present in the globus pallidus of rats [11]. Furthermore, excitatory amino acid receptors are also found in the EP as well as in all basal ganglia nuclei in rats [1]. The overactivity of the STN-GPi pathway which has been shown to be a consequence of nigral denervation could generate down-regulation of glutamatergic receptors in the GPi which has been already found in the SNr of human parkinsonians [22]. Such a down-regulation of glutamate receptors could be hypothesized to also account for the overinhibition of GPi neurons. Hence, further studies of these recep-

tor systems will be necessary to draw any conclusion on the state of sensitivity of the GPi associated with dyskinesia.

5. Conclusion

The present results show that D2 receptors remained unchanged or tended to decrease in response to chronic stimulation of D2 receptors. Thus, clearly dyskinesia cannot be ascribed to supersensitivity of DA receptors at least in term of density.

However, our results show for the first time that GABA_A receptors located downstream from DA receptors in the GPi are significantly up-regulated in dyskinetic monkeys after chronic levodopa or D2 agonist administration in a pulsatile regimen. This suggests that GPi GABA_A receptor supersensitivity rather than the long postulated DA receptor supersensitivity might be involved in the neurochemical mechanism underlying the development of dyskinesia after long-term chronic dopaminergic treatment.

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References

- [1] Albin, R.L., Makiniewicz, R.L., Hollingworth, Z., Dure, L.S., Young, A.B. and Penney, J.B., Excitatory amino acid receptors in rat basal ganglia, *Neuroscience*, 46 (1992) 35–48.
- [2] Albin, R.L., Young, A.B. and Penney, J.B., The functional anatomy of basal ganglia disorders, *Trends Neurosci.*, 12 (1989) 366–375.
- [3] Alexander, G.M., Brainard, L., Gordon, S.W., Hichens, M., Grothusen, J.R. and Schwartzman, R.J., Dopamine receptor changes in untreated and (+)-PIBO-treated MPTP parkinsonian primates, *Brain Res.*, 547 (1991) 181–189.
- [4] Alexander, G.M., Schwartzman, R.J., Grothusen, J.R., Brainard, L. and Gordon, S.W., Change in brain dopamine receptor in MPTP parkinsonian monkeys following L-Dopa treatment, *Brain Res.*, 525 (1993) 276–282.
- [5] Banati, F., Mouradian, M., Davis, T.L., Giuffra, M., Brughitta, G., Conant, K.E. and Chase, T.N., Continuous fluoxetine effects on central dopaminergic mechanisms in Parkinson's disease, *Ann. Neurol.*, 32 (1992) 776–781.
- [6] Bédard, P.J., Di Paolo, T., Falardeau, P. and Roucher, R., Chronic treatment with levodopa, but not bromocriptine induces dyskinesia in MPTP-parkinsonian monkeys. Correlation with [^3H]spiperone binding, *Brain Res.*, 379 (1986) 294–299.
- [7] Bédard, P.J., Gomez-Mancilla, B., Blanchette, P., Gagnon, C., Falardeau, P. and Di Paolo, T., Role of selective D1 and D2 agonists in inducing dyskinesia in drug-naïve MPTP monkeys, *Adv. Neurol.*, 60 (1993) 113–118.

- [8] Blanchet, P., Bédard, P.J., Britton, D.R. and Kebabian, J.W., Differential effect of selective D1 and D2 dopamine receptor agonists on Levodopa-induced dyskinesia in 1-methyl-4-phenyl-1,2,3,4-tetrahydropyridine-exposed monkeys, *J. Pharmacol. Exp. Ther.*, 267 (1993) 275-279.
- [9] Blanchet, P.J., Calon, F., Martel, J.C., Bédard, P.J., Di Paolo, T., Walter, R.R. and Piercey, M.F., Continuous administration decreases and pulsatile administration increases behavioral sensitivity to a novel dopamine D2 agonist (U-91356A) in MPTP monkeys, *J. Pharmacol. Exp. Ther.*, 272 (1995) 854-859.
- [10] Bolam, J.P., Powell, J.F., Wu, J.Y. and Smith, A.D., Glutamate decarboxylase immunoreactive structures in the rat neostriatum: A correlated light and electron microscopic study including a combination of Golgi impregnation with immunocytochemistry, *J. Comp. Neurol.*, 237 (1985) 1-20.
- [11] Bowerly, N.G., Huuhun, A.L. and Price, G.W., GABA and GABAB receptor site distribution in the rat central nervous system, *Neuroscience*, 20 (1987) 365-383.
- [12] Bryce, S., Rupniak, N.M.J., Stevenson, M.J. and Iversen, S.D., Differential effects of D1 or D2 agonist in MPTP-treated primates: functional implication for Parkinson disease, *Neurology*, 40 (1990) 927-933.
- [13] Carpenter, M.D., Whittier, J.R. and Mettler, F.A., Analysis of choreoid hyperkinesia in the rhesus monkey. Surgical and pharmacological analysis of hyperkinesia resulting from lesions of the subthalamic nucleus of Luys, *J. Comp. Neurol.*, 92 (1950) 293-332.
- [14] Cedarbaum, J.M., Clark, M., Toy, L.H. and Ciren-Parsons, A., Sustained-release (+)-PHNO (MK-458 (HPMC)) in the treatment of Parkinson's disease: evidence for tolerance to a selective D2-receptor agonist administered as a long-acting formulation, *Mov. Dis.*, 5 (1990) 298-303.
- [15] Cedarbaum, J.M., Silvestri, R.N. and Kutt, H., Sustained enteral administration of levodopa increases and interrupted infusion decreases levodopa dose requirement, *Neurology*, 40 (1990) 995-997.
- [16] Chase, T.N., Holden, E.M. and Brady, J.A., Levodopa-induced dyskinesia, *Arch. Neurol.*, 29 (1973) 328-330.
- [17] Chen, J.F., Aloyo, V.J. and Weiss, B., Continuous treatment with the D2 agonist dopamine receptor agonist quinpirole decreases D2 dopamine receptors, D2 dopamine receptor messenger RNA and prenekephalin messenger RNA, and increases muscarinic receptors in mouse striatum, *Neuroscience*, 54 (1993) 669-681.
- [18] Crossman, A.R., A hypothesis on the pathological mechanism that underlie levodopa- or dopamine agonist-induced dyskinesia in Parkinson's disease: implications for future strategies in treatment, *Movement Dis.*, 5 (1990) 100-108.
- [19] Crossman, A.R., Sambrink, M.A. and Jackson, A., Experimental hemichorea/hemiballismus in the monkey, *Brain*, 107 (1984) 579-596.
- [20] DeLong, M.R., Primate models of movement disorder of basal ganglia origin, *Trends Neurosci.*, 13 (1990) 281-285.
- [21] Di Paolo, T., Bédard, P.J., Dangle, M. and Boucher, R., Long-term effects of MPTP on central and peripheral catecholamine and indolamine concentrations in monkeys, *Brain Res.*, 379 (1986) 286-293.
- [22] DiLazari, M.C., Hollingsworth, Z., Young, A.H. and Penney, J.B., Glutamate receptors in the substantia nigra of Parkinson's disease brains, *Neurology*, 42 (1992) 402-406.
- [23] Engber, T.M., Boldry, S., Kuo, C.R. and Chase, T.N., Dopaminergic modulation of striatal neuropeptides: differential effect of D1 and D2 receptor stimulation on somatostatin, neuropeptide Y, neurotensin, dynorphin and enkephalin, *Brain Res.*, 581 (1992) 261-266.
- [24] Engber, T.M., Marin, C., Susel, Z. and Chase, T.N., Differential effects of chronic dopamine D1 and D2 receptor agonists on rotational behavior and dopamine receptor binding, *Eur. J. Pharmacol.*, 219 (1993) 385-393.
- [25] Engber, T.M., Susel, Z., Juncos, J.L. and Chase, T.N., Continuous and intermittent levodopa differentially affect rotation induced by D1 and D2 dopamine agonists, *Eur. J. Pharmacol.*, 164 (1989) 291-298.
- [26] Engber, T.M., Susel, Z., Kuo, S., Gerfen, C.R. and Chase, T.N., Levodopa replacement therapy alters enzyme activities in striatum and neuropeptide content in striatal output regions of 6-hydroxydopamine lesioned rats, *Brain Res.*, 552 (1991) 113-118.
- [27] Falardeau, P., Bédard, P.J. and Di Paolo, T., Relation between basal dopamine K_{m} and D2 dopamine receptor density in MPTP monkeys, *Neurosci. Lett.*, 86 (1988) 225-229.
- [28] Falardeau, P., Bouchard, S., Bédard, P.J., Brucher, R. and Di Paolo, T., Behavioral and biochemical effect of chronic treatment with D-1 and/or D-2 dopamine agonists in MPTP monkeys, *Eur. J. Pharmacol.*, 150 (1988) 59-66.
- [29] Gagnon, C., Bédard, P.J. and Di Paolo, T., Effect of chronic treatment of MPTP monkeys with dopamine D-1 and/or D-2 receptor agonists, *Eur. J. Pharmacol.*, 178 (1990) 115-120.
- [30] Gagnon, C., Gomez-Mancilla, B., Bédard, P.J. and Di Paolo, T., Chronic CY 208-243 treatment of MPTP-monkeys causes regional changes of dopamine and GABA_A receptors, *Neurosci. Lett.*, 163 (1993) 31-35.
- [31] Gerfen, C.R., The neostriatal mosaic: multiple levels of compartmental organization in the basal ganglia, *Annu. Rev. Neurosci.*, 15 (1992) 285-320.
- [32] Gerfen, C.R., Engber, T.M., Mahan, L.C., Susel, Z., Chase, T.N., Monetta, P.J. and Sibley, D.R., D1 and D2 dopamine receptor-regulated gene expression of striatonigral and striatopallidal neurons, *Science*, 250 (1990) 1429-1432.
- [33] Girault, J.A., Spampinato, U., Glowinski, J. and Besson, M.J., In vivo release of [³H]-aminobutyric acid in the rat neostriatum. II. Opposing effects of D1 and D2 dopamine receptor stimulation in the dorsal caudate putamen, *Neuroscience*, 19 (1986) 1109-1117.
- [34] Gnanalingham, K.K. and Robertson, R.G., Chronic continuous and intermittent 1-3,4-dihydroxyphenylalanine treatments differentially affect basal ganglia function in 6-hydroxydopamine lesioned rats: an autoradiographic study using [³H]flunitrazepam, *Neuroscience*, 57 (1993) 673-681.
- [35] Gomez-Mancilla, B. and Bédard, P.J., Effect of chronic treatment with (+)-PHNO, a D2 agonist in MPTP-treated monkeys, *Exp. Neurol.*, 117 (1992) 185-189.
- [36] Gomez-Mancilla, B., Brucher, R., Gagnon, C., Di Paolo, T., Markstein, R. and Bédard, P.J., Effect of adding the D-1 agonist CY 208-243 to chronic bromocriptine treatment I. Evaluation of motor parameters in relation to striatal catecholamine content and dopamine receptors, *Mov. Disord.*, 8 (1993) 144-150.
- [37] Graham, W.C., Sambrink, M.A. and Crossman, A.R., Differential effect of chronic dopaminergic treatment on dopamine D1 and D2 receptors in the monkey brain in MPTP-induced parkinsonism, *Brain Res.*, 602 (1993) 290-303.
- [38] Grilliths, P.D., Sambrink, M.A., Perry, R. and Crossman, A.R., Changes in benzodiazepine and acetylcholine receptors in the globus pallidus in Parkinson's disease, *J. Neurol. Sci.*, 100 (1990) 131-136.
- [39] Guérin, H., Sillet, C. and Mouchet, P., Changes of the striatal [³H]-spiperone binding at 3-6 week after nigrostriatal denervation and after two years, *Life Sci.*, 37 (1985) 953-961.
- [40] Guttman, M. and Seeman, P., 1-DXPA reverses the elevated density of D2 dopamine receptor in Parkinson's diseased striatum, *J. Neural Transm.*, 64 (1985) 93-104.
- [41] Juncos, J.L., Engber, T.M., Rasmussen, R., Susel, Z., Thibaut, F.,

- Phiska, A., Agid, Y. and Chase, T.N., Continuous and intermittent levodopa differentially affect basal ganglia function, *Ann Neurol.*, 25 (1989) 473-478.
- [42] Klawans, H.L., Goetz, C., Nausieda, P.A. and Weiner, W.J., Levodopa-induced dopamine receptor hypersensitivity, *Ann Neurol.*, 2 (1977) 125-129.
- [43] Lakke, J.P.W.F., Classification of extrapyramidal disorder, *J. Neurol. Sci.*, 51 (1981) 311-327.
- [44] Lester, J., Fink, S., Aronin, N. and DiFiglia, M., Colocalization of D1 and D2 dopamine receptor messenger RNAs in striatal neurons, *Brain Res.*, 621 (1993) 71-78.
- [45] Luquin, M.R., Laguna, J. and Ojoso, J.A., Selective D2 receptor stimulation induces dyskinesia in parkinsonian monkeys, *Ann. Neurol.*, 31 (1992) 551-554.
- [46] Mitchell, J.J., Boyce, S., Sambrook, M.A. and Crossman, A.R., A 2-deoxyglucose study of the effects of dopamine agonist on the parkinsonian brain, *Brain*, 115 (1992) 819-824.
- [47] Mitchell, J.J., Clarke, C.E., Boyce, S., Robertson, R.G., Peggs, D., Sambrook, M.A. and Crossman, A.R., Neural mechanism underlying parkinsonian symptoms based upon regional uptake of 2-deoxyglucose in monkeys exposed to 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine, *Neuroscience*, 32 (1989) 213-226.
- [48] Moon, M.W., Morris, J.K., Heier, R.F., Hsi, R.S.P., Mann, M.C., Royer, M.E., Walters, R.R., Lawson, C.F., Smith, M.W., Lahti, R.A., Piercey, M.F. and Sethy, V.H., Medicinal chemistry of imidazoquinoline dopamine receptor agonists, *Drug Des. Discov.*, 9 (1993) 313-322.
- [49] Mouradian, M.M., Heuser, I.J.E., Baronti, F. and Chase, T.N., Modification of central dopaminergic mechanism by continuous levodopa therapy for advanced Parkinson's disease, *Ann. Neurol.*, 27 (1990) 18-23.
- [50] Mouradian, M.M., Heuser, I.J.E., Baronti, F., Fabbrini, G., Juncos, J.L. and Chase, T.N., Pathogenesis of dyskinesia in Parkinson's disease, *Ann. Neurol.*, 25 (1989) 523-526.
- [51] Mouradian, M.M., Juncos, J.L., Fabbrini, G., Schlegel, J., Hartke, J.J. and Chase, T.N., Motor fluctuation in Parkinson's disease: central pathophysiological mechanism. Part II, *Ann. Neurol.*, 24 (1988) 372-378.
- [52] Nutt, J.G., Levodopa induced dyskinesia: review, observations, and speculation, *Neurology*, 40 (1990) 340-345.
- [53] Pan, H.S., Penney, J.B. and Young, A.D., Gamma-aminobutyric acid and benzodiazepine receptor changes induced by unilateral 6-hydroxydopamine lesions of the medial forebrain, *Mol. J. Neurochem.*, 45 (1985) 1396-1404.
- [54] Parent, A., Estrinsic connection of the basal ganglia, *Trends Neurosci.*, 13 (1990) 254-258.
- [55] Parent, A. and Hazrati, L.N., Anatomical aspects of information processing in primate basal ganglia, *Trends Neurosci.*, 16 (1993) 111-116.
- [56] Playford, E.D. and Brooks, D.J., In vivo and in vitro studies of the dopaminergic system in movement disorders, *Cerebr. Metab. Brain Metab.*, 4 (1992) 144-170.
- [57] Porrino, L.J., Burns, R.S., Crane, A.M., Palombo, E., Kopin, I.J. and Sokoloff, L., Changes in local cerebral glucose utilization associated with parkinson syndrome induced by MPTP in the primate, *Life Sci.*, 40 (1987) 1657-1664.
- [58] Porrino, L.J., Burns, R.S., Crane, A.M., Palombo, E., Kopin, I.J. and Sokoloff, L., Local cerebral metabolic effects of L-DOPA therapy in 1-methyl-4-phenyl-1,2,3,4-tetrahydropyridine-induced parkinsonism in monkey, *Proc. Natl. Acad. Sci.*, 84 (1987) 5995-5999.
- [59] Robertson, R.G., Clarke, C.A., Boyce, S., Sambrook, M.A. and Crossman, A.R., The role of striatopallidal neurones utilizing gamma-aminobutyric acid in pathophysiology of MPTP-induced parkinsonism in the primate: evidence from [³H]flunitrazepam autoradiography, *Brain Res.*, 531 (1990) 95-104.
- [60] Robertson, R.G., Farmery, M.A., Sambrook, M.A. and Crossman, A.R., Dyskinesia in the primate following injection of an excitatory amino acid antagonist into the medial segment of the globus pallidus, *Brain Res.*, 476 (1989) 317-322.
- [61] Szabo, J. and Cowan, W.M., A stereotaxic Atlas of the brain of the cynomolgus monkey (*Macaca fascicularis*), *J. Comp. Neurol.*, 222 (1984) 265-310.
- [62] Whittier, J.W., Hallism and the subthalamic nucleus (nucleus hypothalamicus: corpus Luysi), *Arch. Neurol. Psychol.*, 58 (1947) 672-692.
- [63] Winkler, J.D. and Weiss, H., Effect of continuous exposure to selective D1 and D2 dopaminergic agonist on rotational behavior in supersensitive mice, *J. Pharmacol. Exp. Ther.*, 249 (1989) 507-516.