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SUPERINDUSTRIA Y COMERCIO
Radicacion : 00065554 00000004 Folios: 1
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Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

Señora Jefe de la
DIVISION DE NUEVAS CREACIONES
Superintendencia de Industria y Comercio
E. S. D.

Trámite :002
Evento :001
Actuación :593

Referencia	:	Expediente No. **00.065.554**
Asunto	:	Solicitud de patente para **"PIRROLCARBOXAMIDAS FUSIONADAS; UNA NUEVA CLASE DE LIGANDOS DE RECEPTORES CEREBRALES DE GABA"**
Solicitante	:	**NEUROGEN CORPORATION**
Fecha de Solicitud	:	31 de agosto de 2000

Yo, Emilio FERRERO, obrando como apoderado de la solicitante en referencia, atentamente, solicito a Usted se sirva ordenar la agilización del trámite de esta solicitud de patente y se sirva realizar el examen de patentabilidad de la misma. La última actuación que obra en el expediente es mi memorial número 00065554 00000003 radicado el 23 de enero de 2003, mediante el cual solicité se efectuara el examen de patentabilidad de la solictud en referencia.

Bogotá, 27 ENE. 2005
Señora Jefe,

Fondo 04

EMILIO FERRERO
T.P.A. No. 31.929

COLO 10611-801-005-2
DLM/DLM/ID-000071/WPC10611

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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISIÓN DE NUEVAS CREACI NES

2020
Bogotá, D.C., 01 de diciembre de 2005

Apoderado:Emilio Ferrero Oficio: 11704

ASUNTO Radicación: 00-65554
Trámite 002
Evento 001
Actuación 430
Folios

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

Documentos estudiados:

◆capitulo descriptivo, folios 2 a 106;
◆capitulo reivindicatorio, folios 339 a 406;
◆1° examen de forma, folios 189 y 190;
◆respuesta técnica al 1° examen de forma, folios 336 a 338;
◆2° examen de forma, folio 412;
◆solicitud de la cual se reivindica prioridad y la traducción exigida, folios 193 a 335;
◆ solicitud del examen de patentabilidad, folios 414 y 415.

Objeto de la invención:

El título de la invención "PIRROLCARBOXAMIDAS FUSIONADAS; UNA NUEVA CLASE DE LIGANDOS DE RECEPTORES CEREBRALES DE GABA".

Su objeto son los compuestos derivados de 4-oxo-4,5,6,7-tetrahidro-1*H*-indol-3-carboxamida y derivados 4-oxo-1,4,5,6,7,8-hexahidrociclohepta[*b*]pirrol-3-carboxamida y medicamentos que los comprenden como sustancia activa y sus sales fisiológicamente tolerables.

El campo de la invención, según la Clasificación Internacional de Patentes: A61K 31/40, 31/16

Claridad de la s licitud:

En el artículo 30 de la decisión 486 de la Comisión de la Comunidad Andina se establece: *"Las reivindicaciones definirán la materia que se desea proteger mediante la patente. Deben ser claras y concisas y estar enteramente sustentadas por la descripción"*.
-La reivindicación 66 que es una mezcla de compuesto, uso y método de tratamiento, lo cual es inaceptable en las reivindicaciones; la composición se debe caracterizar por sus elementos constitutivos, no por su uso o por el método de tratamiento.

-Las reivindicaciones 77 a 79 no son claras, puesto que el encabezado no es consecuente con el resto del texto de las reivindicaciones, se encabeza como un compuesto y se pretende caracterizar por los ensayos que se realizaron con dicho compuesto, lo cual es inaceptable, porque los compuestos secaracterizan técnicamente por su estructura química especifica, o su nombre químico, no por los ensayos que se hayan realizado con ellos.

-Las reivindicaciones 75 y 76, no es claras, puesto que el encabezado no es consecuente con el resto del texto de la reivindicación, se encabeza como un compuesto y se pretende caracterizar por un envazado, lo cual es inadmisible en las reivindicaciones; los compuestos se deben caracterizar por su estructura química definida, no en donde esten contenidos o cual sea la patologia que se va atratar, porque los compuestos esten envasados o sin enavasar son la misma materia.

Excepciones de Patentabilidad:

El artículo 20 de la Decisión 486 de la Comisión de la Comunidad Andina establece en su inciso d) que no serán patentables: *"los métodos terapéuticos o quirúrgicos para el tratamiento humano o animal, así como los métodos de diagnóstico aplicados a los seres humanos o a animales"*.

Las reivindicaciones 68, 69, 72, 73 y 74 reclaman un método para tratamiento del cuerpo animal, el cual incluye la administración de una composición farmacéutica que contiene alguno de los derivados de la solicitud, por lo tanto está inmersa bajo el alcance del artículo 20 de la Decisión 486.

Reivindicaciones de uso

Las reivindicaciones 70 y 71 reclaman el uso, y de acuerdo con la legislación colombiana el uso que se reclama en la reivindicación 18 no se considera para protección por patente, como se lee en el artículo 14 de la Decisión 486 de la

Comisión de la Comunidad Andina"... Los Países Miembros otorgarán patentes para las invenciones sean de **productos o procedimientos** en todos los campos de la tecnología..."; AQUÍ NO se hace alusión al uso.

Continuando con la última parte del Artículo 14"... (Los Países Miembros otorgarán patentes para las invenciones sean de **productos o procedimientos** en todos los campos de la tecnología, siempre que sean nuevas, tengan nivel inventivo y sean susceptibles de aplicación industrial." El hecho que se diga que el producto o el procedimiento tengan aplicación industrial no quiere decir que la aplicación industrial sea susceptible de patente.

Así mismo, citando **completamente** el artículo 19 este reza: " Se considerará que una **invención** *(léase producto o procedimiento)* es susceptible de aplicación industrial *(una característica de la invención)* cuando su objeto puede ser producido o utilizado en cualquier clase de industria, entendiéndose por industria la referida a cualquier actividad productiva, incluidos los servicios." Esta diciendo que una invención, producto o procedimiento, debe servir para algo. En ningún momento se dice que un uso pueda ser protegido como patente.

El artículo 16 dice: " Los productos o procedimientos *(o sea, los inventos, nótese que nunca se refieren a nada diferente)* ya patentados comprendidos en el estado de la técnica de conformidad con el Artículo 21 de la presente Decisión, no serán objeto de nueva patente por el simple hecho de atribuirse un uso distinto al originalmente comprendido por la patente inicial." Nunca se refieren a una protección para el uso, como erróneamente se podría interpretar. Se trata de no conceder nueva patente a un invento (exclusivamente productos o procedimientos) al que se le ha encontrado nueva función, pero que se trata exactamente del mismo producto o procedimiento. Es decir, sí el compuesto, aparato, etc. o método ya esta dentro del estado de la técnica, el hecho que se haya descubierto una nueva aplicación para el mismo compuesto, aparato, etc. o método, implica que no es merecedor de nueva patente, o que el nuevo uso le reestablezca la novedad. En ningún caso se dice que se esta protegiendo el uso. Simplemente se dice que el producto o procedimiento ya esta dentro del estado de la técnica y una utilización diferente no esta contemplada para permitir conceder patente al producto o al procedimiento nuevamente.

Los usos o segundos usos no son patentables, de conformidad con la sentencia del TJAC 89-AI-2000, los usos en general no son patentables.

Determinación del estado de la técnica:

El artículo 16 de la Decisión 486 de la Comisión establece: "*El estado de la técnica comprenderá todo lo que haya sido accesible al público por una descripción escrita u oral, utilización, comercialización o cualquier otro medio antes de la fecha de presentación de la solicitud de patente o, en su caso, de la prioridad reconocida.*
Sólo para el efecto de la determinación de la novedad, también se considerará dentro del estado de la técnica, el contenido de una solicitud de patente en trámite ante la oficina nacional competente, cuya fecha de presentación o de prioridad fuese anterior a la fecha de presentación o de prioridad de la solicitud de patente que se estuviese examinando, siempre que dicho contenido esté incluido en la solicitud de fecha anterior cuando ella se publique o hubiese transcurrido el plazo previsto en el artículo 40."

Se realizo la búsqueda del estado de la técnica con fecha anterior a la fecha de presentación de la primera solictud, de la cual se reivindica prioridad, 31de agosto-1999. Consultada la fuente de información con que cuenta este despacho se encontró muchos documentos documentos solo se adjuntaran algunos:

No.	Documento No.	Título	*Fecha de Publicación
D1	W0 9511885	Certain fused pyrrolecarboxanilides; a new class of gaba brain receptor ligands	04-may-1995
D2	US 5608079	Certain fused pyrrolecarboxanilides a new class of gaba brain receptor ligands	04-mar-1997
D3	WO 9726243	Novel fused pyrrolecarboxanilides; a new class of gaba brain receptor ligands	24-jul-1997
D4	WO 9734870	Certain fused pyrrolecarboxanilides as new gaba brain receptor ligands	25-sep-1997
D5	WO 9802420	Certain fused pyrrolecarboxanilides a new class of gaba brain receptor ligands	22-ene-1998
D6	US 5723462	Certain fused pyrrolecarboxanilides a new class of gaba brain receptor ligands	03-mar-1998|

Evaluación de los requisitos de patentabilidad:

El artículo 14 de la Decisión 486 de la Comisión de la Comunidad Andina establece: *"Los Países Miembros otorgarán patentes para las invenciones, sean de producto o de procedimiento, en todos los campos de la tecnología, siempre que sean nuevas, tengan nivel inventivo y sean susceptibles de aplicación industrial."*

En cumplimiento con este artículo, se procedió a evaluar los requisitos de novedad, nivel inventivo y aplicación industrial con el fin de establecer la patentabilidad de la invención reivindicada en la solicitud en estudio.

Evaluación de la Novedad:

El art.16 de la Decisión 486 de la Comisión de la Comunidad Andina establece: *"Una invención se considerará nueva cuando no está comprendida en el estado de la técnica." "El estado de la técnica comprenderá todo lo que haya sido accesible al público por una descripción escrita u oral, utilización, comercialización o cualquier otro medio antes de la fecha de presentación de la solicitud de patente o, en su caso, de la prioridad reconocida.*

Sólo para el efecto de la determinación de la novedad, también se considerará dentro del estado de la técnica, el contenido de una solicitud de patente en trámite ante la oficina nacional competente, cuya fecha de presentación o de prioridad fuese anterior a la fecha de presentación o de prioridad de la solicitud de patente que se estuviese examinando, siempre que dicho contenido esté incluido en la solicitud de fecha anterior cuando ella se publique o hubiese transcurrido el plazo previsto en el artículo 40."

La solicitud en estudio reclama como nuevo derivados de de 4-oxo-4,5,6,7-tetrahidro-1*H*-indol-3-carboxamida y derivados 4-oxo-1,4,5,6,7,8-hexahidrociclohepta[*b*]pirrol-3-carboxamida y medicamentos que los contienen.

-La anterioridad D1, comprende de 4-oxo-4,5,6,7-tetrahidro-1*H*-indol-3-carboxamida y derivados 4-oxo-1,4,5,6,7,8-hexahidrociclohepta[*b*]pirrol-3-carboxamida, N-(4-etoxifenil)-4-oxo-4,5,5,7-tetrahidro-1H-indol-3-carboxamida, donde por ejemplo estan los compuestos específicos del ejemplo 8 (a), (h-k), (m-q), (s-z), (u-(bo)), o del D3 el ejemplo 3 los compuestos (a-(ss)), ademas puede ver las estructuras especificas 72 a 78 y los medicamentos que los contienen, además de la descripción, demuestran claramente que los compuestos reclamados en la solicitud en estudio no son nuevos.

-Los documentos que citaron como D2, D4 a D6, contienen de 4-oxo-4,5,6,7-tetrahidro-1*H*-indol-3-carboxamida y derivados 4-oxo-1,4,5,6,7,8-hexahidrociclohepta[*b*]pirrol-3-carboxamida y medicamentos que los contienen, compuestos específicos de cada uno se pueden encontrar D2, ejemplo 8, y descripción; D4 en el ejmplo 3 y la descripción; D5 ejemplos 4, 5 y 6, y la descripción; D6 ver los ejemplos 3, 4, 5 y la tabla 1, al igual que la descripción; al igual que los procesos de síntesis y los medicamentos que los comprenden. Por lo cual se observa que la presente solicitud no tiene novedad.

Cuando una solicitud esta afectada su novedad, obviamente no posee nivel inventivo. En conclusión los requisitos de Patentabilidad de la presente solicitud **están** afectadas así:

Documento	Reivindicalones	Requisito que afecta
D1	1 a 93	Novedad
D2	1 a 93	Novedad
D3	1 a 93	Novedad
D4	1 a 93	Novedad
D5	1 a 93	Novedad
D6	1 a 93	Novedad
D7	1 a 93	Novedad
D8	1 a 93	Novedad

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

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2,literal e), del capítulo quinto del título primero de la circular única No. 10 de 2001.

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ALIX CARMENZA CESPEDES DE VERGEL
Jefe de División de Nuevas Creaciones

El anterior requerimiento fue notificado por fijación en lista, de fecha
09 DIC. 2005

CONCEPTO TÉCNICO No. 1944	EXAMINADOR TÉCNICOCódigo No.202012

D1

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PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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US 08/144,138 (CIP)
Filed on 27 October 1994 (27.10.94)

(71) Applicant (*for all designated States except US*): NEUROGEN CORPORATION [US/US]; 35 N.E. Industrial Road, Branford, CT 06405 (US).

(72) Inventors; and
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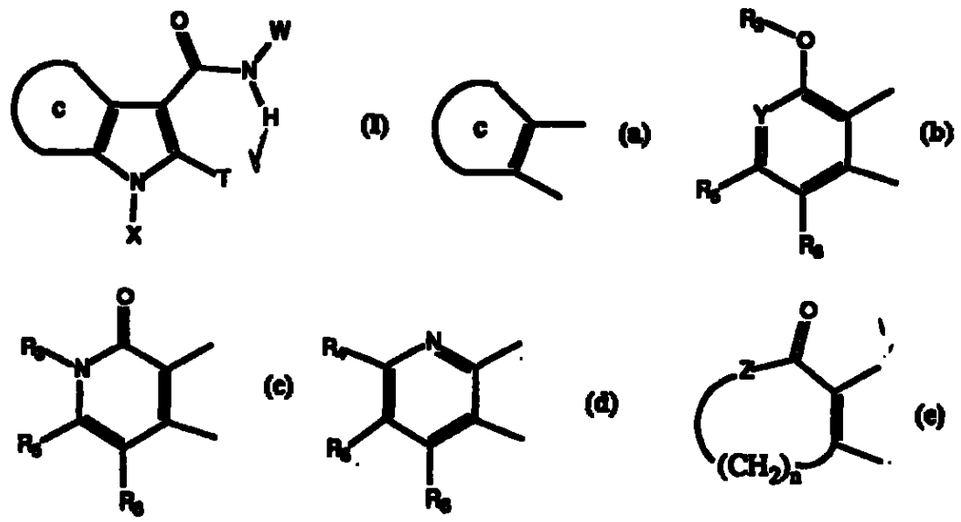
(74) Agent: SARUSSI, Steven, J.; Allegretti & Witcoff, Ltd., Ten South Wacker Drive, Chicago, IL 60606 (US).

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

Published
With international search report.

(54) Title: CERTAIN FUSED PYRROLECARBOXANILIDES; A NEW CLASS OF GABA BRAIN RECEPTOR LIGANDS



(57) Abstract

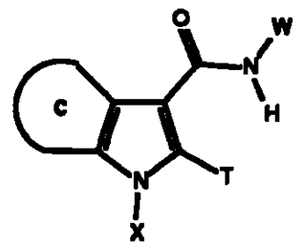
The present invention encompasses structures of formula (I) and the pharmaceutically acceptable non-toxic salts thereof wherein (a) represents (b), (c), (d) or (e), wherein W represents substituted or unsubstituted aryl groups; X is hydrogen, hydroxy or lower alkyl; T is hydrogen, halogen, hydroxyl, amino or alkyl; R_3 is hydrogen or an organic group; R_4 is hydrogen or substituted or unsubstituted organic substituent; R_5 and R_6 represent organic, and inorganic substituents; and n is 1, 2, 3, or 4. These compounds are highly selective agonists, antagonists or inverse agonists for GABAa brain receptors or prodrugs of agonists, antagonists or inverse agonists for GABAa brain receptors. These compounds are useful in the diagnosis and treatment of anxiety, sleep and seizure disorders, overdose with benzodiazepine drugs and for enhancement of memory.

D-65554

SUMMARY OF THE INVENTION

This invention provides novel compounds of Formula I which interact with a GABAa binding site, the benzodiazepine receptor.

The invention provides pharmaceutical compositions comprising compounds of Formula I. The invention also provides compounds useful in the diagnosis and treatment of anxiety, sleep and seizure disorders, overdose with benzodiazepine drugs and for enhancement of memory. Accordingly, a broad embodiment of the invention is directed to compounds of general Formula I:



I

or the pharmaceutically acceptable non-toxic salts thereof wherein:

T is

halogen, hydrogen, hydroxyl, amino or straight or branched chain lower alkoxy having 1-6 carbon atoms;

X is

hydrogen, hydroxyl or straight or branched chain lower alkyl having 1-6 carbon atoms;

W is

phenyl, 2 or 3-thienyl, 2, 3, or 4-pyridyl or 6-quinolinyl, each of which may be mono or disubstituted with halogen ,cyano, hydroxy, straight or branched chain lower alkyl having 1-6 carbon atoms, amino, mono or dialkylamino where each alkyl is independently straight or branched chain lower alkyl having 1-6 carbon atoms, straight or branched chain lower alkoxy having 1-6 carbon atoms, or NR_1COR_2, COR_2, $CONR_1R_2$ or CO_2R_2 where R_1 and R_2 are the same or different and represent hydrogen or straight or branched chain lower alkyl having 1-6 carbon atoms; and

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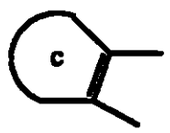
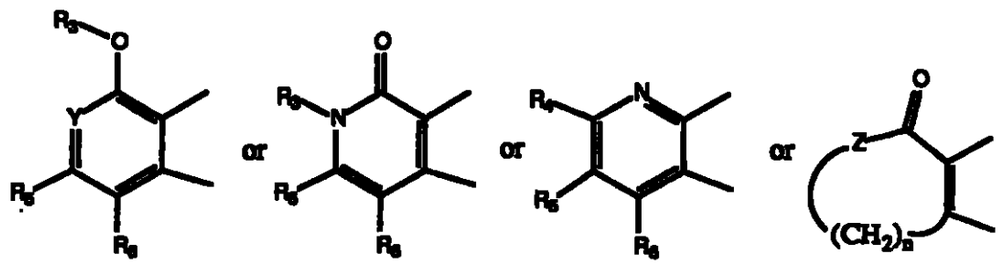


represents



wherein:

Y represents nitrogen or C-R_4;

Z represents N-R_7 or a carbon atom substituted with R_8 and R_9, i.e., $C(R_8)(R_9)$;

n is 1, 2, 3, or 4;

R_3 is

hydrogen, phenyl, 2, 3 or 4-pyridyl, straight or branched chain lower alkyl having 1-6 carbon atoms, or phenylalkyl or 2, 3 or 4-pyridylalkyl where each alkyl is straight or branched chain lower alkyl having 1-6 carbon atoms;

R_4 is

halogen or trifluoromethyl; or

$-OR_{10}$, $-COR_{10}$, $-CO_2R_{10}$, $-OCOR_{10}$, or $-R_{10}$, where R_{10} is hydrogen, phenyl, 2, 3 or 4-pyridyl, straight or branched chain lower alkyl having 1-6 carbon atoms, or phenylalkyl or 2, 3 or 4-pyridylalkyl where each alkyl is straight or branched chain lower alkyl having 1-6 carbon atoms; or

$-CONR_{11}R_{12}$ or $-(CH_2)_mNR_{11}R_{12}$, where m is 0, 1, or 2; R_{11} represents hydrogen, straight or branched chain lower alkyl having 1-6 carbon atoms; and R_{12} is hydrogen, phenyl, 2, 3 or 4-pyridyl, straight or branched chain lower alkyl

having 1-6 carbon atoms, or phenylalkyl or 2, 3 or 4-pyridylalkyl where each alkyl is straight or branched chain lower alkyl having 1-6 carbon atoms; or $NR_{11}R_{12}$ forms a heterocyclic group which is morpholyl, piperidyl, pyrrolidyl, or N-alkyl piperazyl;

R_5 and R_6 are the same or different and represent

hydrogen, halogen, straight or branched chain lower alkyl having 1-6 carbon atoms, or straight or branched chain lower alkoxy having 1-6 carbon atoms;

R_7 is

hydrogen, phenyl, 2, 3 or 4-pyridyl, straight or branched chain lower alkyl having 1-6 carbon atoms, or phenylalkyl or 2,3, or 4-pyridylalkyl where each alkyl is straight or branched chain lower alkyl having 1-6 carbon atoms;

R_8 is

hydrogen or straight or branched chain lower alkyl having 1-6 carbon atoms; and

R_9 is

$-COR_{13}$, $-CO_2R_{13}$ or $-R_{13}$, where R_{13} is hydrogen, phenyl, 2, 3 or 4-pyridyl, straight or branched chain lower alkyl having 1-6 carbon atoms, or phenylalkyl or 2, 3, or 4-pyridylalkyl where each alkyl is straight or branched chain lower alkyl having 1-6 carbon atoms; or

$-CONR_{14}R_{15}$ or $-(CH_2)_kNR_{14}R_{15}$, where k is 0, 1, or 2; R_{14} represents hydrogen, straight or branched chain lower alkyl having 1-6 carbon atoms; and R_{15} is hydrogen, phenyl, 2, 3, or 4-pyridyl, straight or branched chain lower alkyl having 1-6 carbon atoms, or phenylalkyl or 2, 3 or 4-pyridylalkyl where each alkyl is straight or branched chain lower alkyl having 1-6 carbon atoms; or $NR_{14}R_{15}$ forms a heterocyclic group which is morpholyl, piperidyl, pyrrolidyl, or N-alkyl piperazyl.

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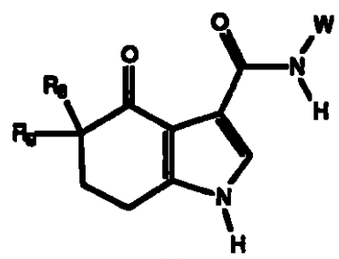
These compounds are highly selective agonists, antagonists or inverse agonists for GABAa brain receptors or prodrugs of agonists, antagonists or inverse agonists for GABAa brain receptors. In other words, while the compounds of the invention all interact with GABAa brain receptors, they do display identical physiologic activity. Thus, these compounds are useful in the diagnosis and treatment of anxiety, sleep and seizure disorders, overdose with benzodiazepine drugs and for enhancement of memory. For example, these compounds can easily be used to treat overdoses of benzodiazepine-type drugs as they would competitively bind to the benzodiazepine receptor.

DETAILED DESCRIPTION OF THE INVENTION

The novel compounds encompassed by the instant invention can be described by general formula I set forth above or the pharmaceutically acceptable non-toxic salts thereof.

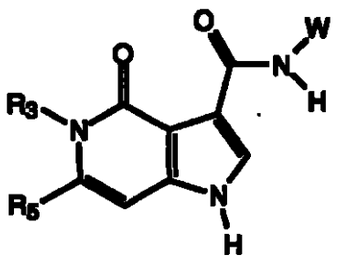
In addition, the present invention encompasses compounds of Formula II.



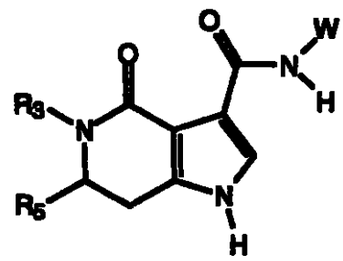
II

or the pharmaceutically acceptable non-toxic salts thereof wherein W, R8 and R9 are as defined above.

The present invention also encompasses compounds of Formula IIIa and IIIb:



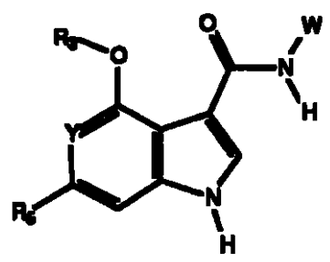
IIIa



IIIb

or the pharmaceutically acceptable non-toxic salts thereof wherein W, R3, and R5 are as defined above.

The present invention also encompasses compounds of Formula IV:



IV

or the pharmaceutically acceptable non-toxic salts thereof wherein W, Y, R3, and R5 are defined above.

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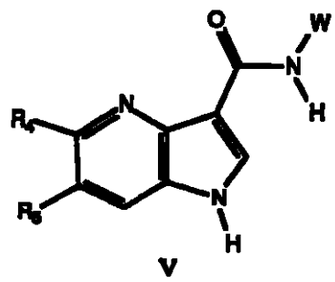
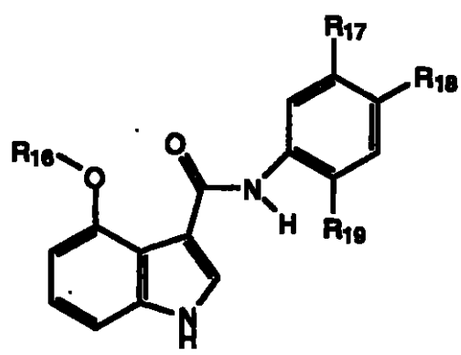
The present invention also encompasses compounds of Formula V:



V

or the pharmaceutically acceptable non-toxic salts thereof wherein W, R_4, and R_5 are defined above.

The invention further encompasses compounds of Formula VI:



VI

or the pharmaceutically acceptable non-toxic salts thereof where R_{16} is hydrogen, benzyl or straight or branched chain lower alkyl having 1-6 carbon atoms;

R_{17} is hydrogen or straight or branched chain lower alkoxy having 1-6 carbon atoms;

R_{18} is hydrogen, straight or branched chain lower alkozy having 1-6 carbon atoms, NR_1COR_2, COR_2, CO_2R_2 where R_1 and R_2 are as defined above, cyano, or halogen; and

R_{19} is hydrogen or 42
halogen.

The invention additionally encompasses compounds of formula VII:

heterocyclic group which is morpholyl, piperidyl, pyrrolidyl, or N-alkyl piperazyl;

R_5 and R_6 are the same or different and represent

hydrogen, halogen, straight or branched chain lower alkyl having 1-6 carbon atoms, or straight or branched chain lower alkoxy having 1-6 carbon atoms;

R_7 is

hydrogen, phenyl, 2, 3 or 4-pyridyl, straight or branched chain lower alkyl having 1-6 carbon atoms, or phenylalkyl or 2,3, or 4-pyridylalkyl where each alkyl is straight or branched chain lower alkyl having 1-6 carbon atoms;

R_8 is

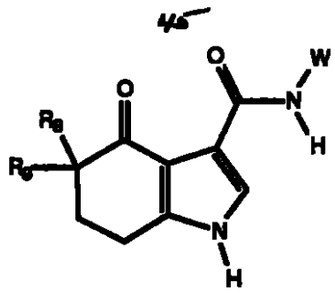
hydrogen or straight or branched chain lower alkyl having 1-6 carbon atoms; and

R_9 is

$-COR_{13}$, $-CO_2R_{13}$ or $-R_{13}$, where R_{13} is hydrogen, phenyl, 2, 3 or 4-pyridyl, straight or branched chain lower alkyl having 1-6 carbon atoms, or phenylalkyl or 2, 3, or 4-pyridylalkyl where each alkyl is straight or branched chain lower alkyl having 1-6 carbon atoms; or

$-CONR_{14}R_{15}$ or $-(CH_2)_kNR_{14}R_{15}$, where k is 0, 1, or 2; R_{14} represents hydrogen, straight or branched chain lower alkyl having 1-6 carbon atoms; and R_{15} is hydrogen, phenyl, 2, 3, or 4-pyridyl, straight or branched chain lower alkyl having 1-6 carbon atoms, or phenylalkyl or 2, 3 or 4-pyridylalkyl where each alkyl is straight or branched chain lower alkyl having 1-6 carbon atoms; or $NR_{14}R_{15}$ forms a heterocyclic group which is morpholyl, piperidyl, pyrrolidyl, or N-alkyl piperazyl.

2. A compound of the formula:



or the pharmaceutically acceptable non-toxic salts thereof wherein:

W is

phenyl, 2 or 3-thienyl, 2, 3, or 4-pyridyl or 6-quinolinyl, each of which may be mono or disubstituted with halogen, cyano, hydroxy, straight or branched chain lower alkyl having 1-6 carbon atoms, amino, mono or dialkylamino where each alkyl is independently straight or branched chain lower alkyl having 1-6 carbon atoms, straight or branched chain lower alkoxy having 1-6 carbon atoms, or NR_1COR_2, COR_2, $CONR_1R_2$ or CO_2R_2 where R_1 and R_2 are the same or different and represent hydrogen or straight or branched chain lower alkyl having 1-6 carbon atoms; and

R_8 is

hydrogen or straight or branched chain lower alkyl having 1-6 carbon atoms; and

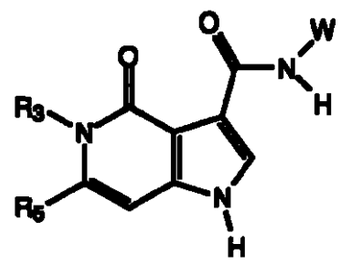
R_9 is

$-COR_{13}$, $-CO_2R_{13}$ or $-R_{13}$, where R_{13} is hydrogen, phenyl, 2, 3 or 4-pyridyl, straight or branched chain lower alkyl having 1-6 carbon atoms, or phenylalkyl or 2, 3, or 4-pyridylalkyl where each alkyl is straight or branched chain lower alkyl having 1-6 carbon atoms; or

$-CONR_{14}R_{15}$ or $-(CH_2)_kNR_{14}R_{15}$, where k is 0, 1, or 2; R_{14} represents hydrogen, straight or branched chain lower alkyl having 1-6 carbon atoms; and R_{15} is hydrogen, phenyl, 2, 3, or 4-pyridyl, straight or branched chain lower alkyl having 1-6 carbon atoms, or phenylalkyl or 2, 3 or 4-pyridylalkyl where each alkyl is straight or branched chain lower alkyl having 1-6 carbon atoms; or $NR_{14}R_{15}$ forms a

heterocyclic group which is morpholyl, piperidyl, pyrrolidyl, or N-alkyl piperazyl.

3. A compound of the formula:



or the pharmaceutically acceptable non-toxic salts thereof wherein:

W is

phenyl, 2 or 3-thienyl, 2, 3, or 4-pyridyl or 6-quinolinyl, each of which may be mono or disubstituted with halogen, cyano, hydroxy, straight or branched chain lower alkyl having 1-6 carbon atoms, amino, mono or dialkylamino where each alkyl is independently straight or branched chain lower alkyl having 1-6 carbon atoms, straight or branched chain lower alkoxy having 1-6 carbon atoms, or NR_1COR_2, COR_2, $CONR_1R_2$ or CO_2R_2 where R_1 and R_2 are the same or different and represent hydrogen or straight or branched chain lower alkyl having 1-6 carbon atoms; and

R_3 is

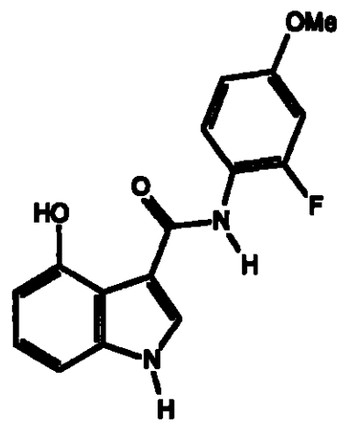
hydrogen, phenyl, 2, 3 or 4-pyridyl, straight or branched chain lower alkyl having 1-6 carbon atoms, or phenylalkyl or 2, 3 or 4-pyridylalkyl where each alkyl is straight or branched chain lower alkyl having 1-6 carbon atoms; and

R_5 is

hydrogen, halogen, straight or branched chain lower alkyl having 1-6 carbon atoms, or straight or branched chain lower alkoxy having 1-6 carbon atoms.

4. A compound of the formula:

Example 7



(Compound 2)

N-(2-Fluoro-4-methoxyphenyl)-4-benzyloxy-1H-indole-3-carboxamide (1.34 g, 3.4 mmol), prepared using the method above, was slurried with 10% Palladium on Carbon (134 mg) in ethanol (35 mL) in a Parr bottle and placed under a Hydrogen atmosphere (50 psi) for 5 h. Methanol (5 ml) was added and the mixture returned to the Hydrogen atmosphere for an additional 18 h. The solution was filtered through Celite, concentrated *in vacuo*, and the residue purified by flash chromatography to afford N-(2-fluoro-4-methoxyphenyl)-4-hydroxy-1H-indole-3-carboxamide (Compound 2) as a beige solid; mp 259-261°C (d).

Example 8

The following compounds were prepared essentially according to the procedures described in Examples 1-6:

(a) N-(4-Ethoxyphenyl)-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxamide (Compound 3); mp 217-218°C.

(b) N-(4-Ethoxyphenyl)-4-methoxy-1H-indole-3-carboxamide (Compound 4); mp 259-261°C (d).

(c) N-(3-Ethoxyphenyl)-4-methoxy-1H-indole-3-carboxamide (Compound 5).

(d) N-(2-Fluoro-4-methoxyphenyl)-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxamide (Compound 6).

(e) N-(2-Fluoro-4-ethoxyphenyl)-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxamide (Compound 7).

(f) N-(4-Methoxyphenyl)-4-methoxy-1H-indole-3-carboxamide (Compound 8).

(g) N-(2-Fluoro-4-ethoxyphenyl)-4-methoxy-1H-indole-3-carboxamide (Compound 9).

(h) N-(4-Cyanophenyl)-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxamide (Compound 10); mp 287-288°C.

(i) N-(3-Methoxyphenyl)-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxamide (Compound 11); mp 220-223°C.

(j) N-(4-Acetamidophenyl)-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxamide (Compound 12); mp 339-341°C.

(k) N-(4-Chlorophenyl)-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxamide (Compound 13).

(l) N-(2-Fluoro-4-methoxyphenyl)-4-benzyloxy-1H-indole-3-carboxamide (Compound 14).

(m) N-(4-acetylphenyl)-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxamide (Compound 15).

(n) N-(2-Fluoro-5-methoxyphenyl)-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxamide (Compound 16).

(o) N-(6-quinolinyl)-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxamide (Compound 17); mp 319-321°C.

(p) N-(4-Carbomethoxyphenyl)-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxamide (Compound 18); mp 261-262°C.

(q) N-(4-Carboxyphenyl)-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxamide (Compound 19).

(r) N-(4-Ethoxyphenyl)-4-hydroxy-1H-indole-3-carboxamide (Compound 20).

(s) N-(3-ethoxyphenyl)-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxamide (Compound 21).

(t) N-(2-fluoro-4-methoxyphenyl)-4-benzyloxy-1H-indole-3-carboxamide (Compound 22).

(u) N-(4-isopropoxyphenyl)-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxamide (Compound 23).

(v) N-(4-fluorophenyl)-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxamide (Compound 24).

(w) N-(4-pyridyl)-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxamide (Compound 25).

(x) N-(4-hydroxyphenyl)-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxamide (Compound 26).

(y) N-(4-aminophenyl)-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxamide (Compound 27).

(z) N-(3-pyridyl)-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxamide (Compound 28).

(aa) N-(4-(methoxymethyl)phenyl)-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxamide (Compound 29).

(ab) N-(3-fluoro-4-methoxyphenyl)-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxamide (Compound 30).

(ac) (compound 31 (ad) (compound 32)

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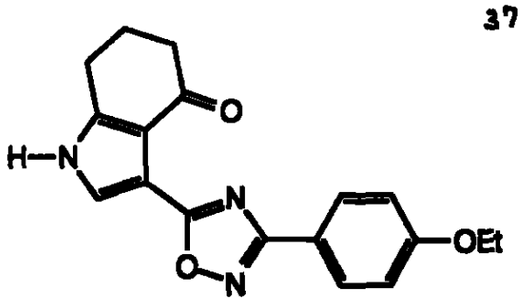
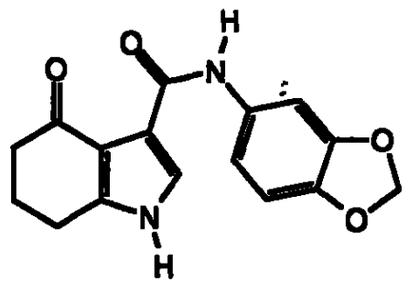
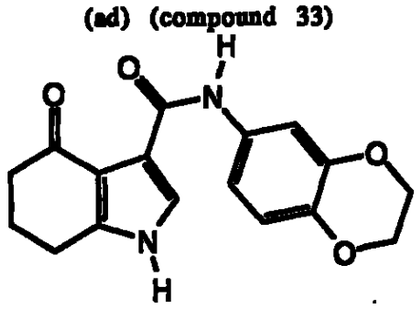
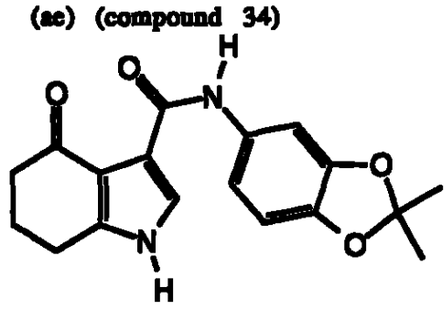




(ad) (compound 33)



(ae) (compound 34)



(af) N-(2-fluoro-4-isopropoxyphenyl)-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxamide (Compound 35).

(ag) N-(4-fluorophenyl)-4-oxo-5,5-dimethyl-4,5,6,7-tetrahydro-1H-indole-3-carboxamide (Compound 36).

(ah) N-(2-fluoro-4-methoxyphenyl)-4-oxo-5,5-dimethyl-4,5,6,7-tetrahydro-1H-indole-3-carboxamide (Compound 37).

(ai) N-(4-ethoxyphenyl)-4-oxo-5,5-dimethyl-4,5,6,7-tetrahydro-1H-indole-3-carboxamide (Compound 38).

(aj) N-(4-(methoxymethyl)phenyl)-4-oxo-5,5-dimethyl-4,5,6,7-tetrahydro-1H-indole-3-carboxamide (Compound 39).

(ak) N-(4-methoxyphenyl)-4-oxo-5,5-dimethyl-4,5,6,7-tetrahydro-1H-indole-3-carboxamide (Compound 40).

(al) N-(2-methoxy-5-pyridyl)-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxamide (Compound 41).

(am) N-(3,4-dihydroxyphenyl)-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxamide (Compound 42).

(an) N-phenyl-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxamide (Compound 43).

(ao) N-(2-pyridyl)-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxamide (Compound 44).

(ap) N-(2-fluoro-4-hydroxyphenyl)-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxamide (Compound 45).

(aq) N-(2-fluoro-4-methoxyphenyl)-4-oxo-6,6-dimethyl-4,5,6,7-tetrahydro-1H-indole-3-carboxamide (Compound 46).

(ar) N-(2-fluoro-4-ethoxyphenyl)-4-oxo-6,6-dimethyl-4,5,6,7-tetrahydro-1H-indole-3-carboxamide (Compound 47).

(as) N-(4-ethoxyphenyl)-4-oxo-6,6-dimethyl-4,5,6,7-tetrahydro-1H-indole-3-carboxamide (Compound 48).

(at) N-(2-amino-3-pyridyl)-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxamide (Compound 49).

(au) N-(4-methylphenyl)-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxamide (Compound 50).

(av) N-(3-methylphenyl)-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxamide (Compound 51).

(aw) N-(2-amino-4-methylphenyl)-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxamide (Compound 52).

(ax) N-(4-methylaminophenyl)-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxamide (Compound 53).

(ay) N-phenyl-4-oxo-6,6-dimethyl-4,5,6,7-tetrahydro-1H-indole-3-carboxamide (Compound 54).

(az) N-(3-hydroxy-4-methoxyphenyl)-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxamide (Compound 55).

(ba) N-(2-fluorophenyl)-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxamide (Compound 56).

(bb) N-(3-fluorophenyl)-4-oxo-6,6-dimethyl-4,5,6,7-tetrahydro-1H-indole-3-carboxamide (Compound 57).

(bc) N-(4-(2-hydroxyethoxy)phenyl)-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxamide (Compound 58).

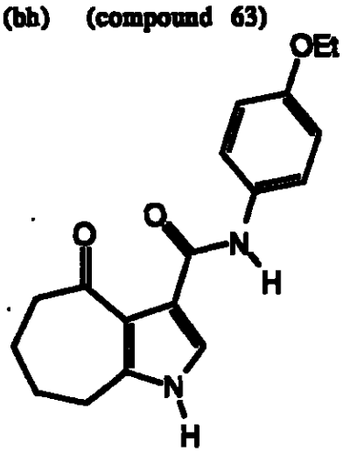
(bd) N-(2-thienyl)-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxamide (Compound 59).

(be) N-(4-(2-methoxyethoxy)phenyl)-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxamide (Compound 60).

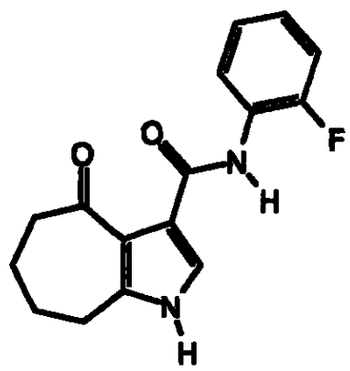
(bf) N-(2-(4-hydroxyphenyl)ethyl)-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxamide (Compound 61).

(bg) N-(2-(4-ethoxyphenyl)ethyl)-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxamide (Compound 62).

(bh) (compound 63)

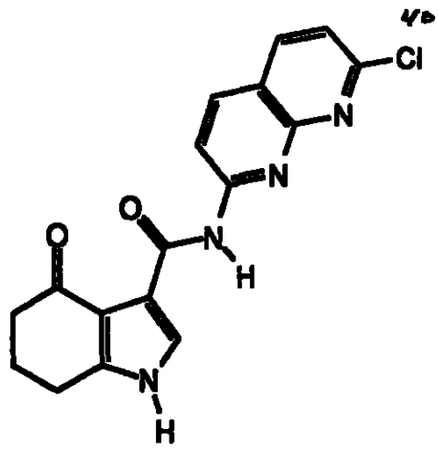


(bi) (compound 64)

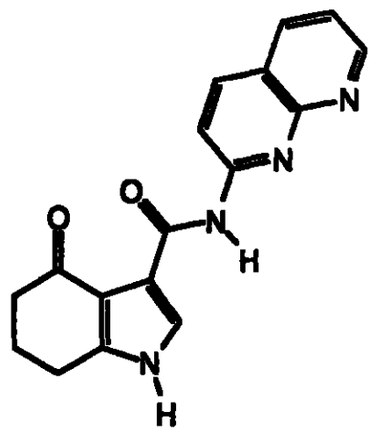


(bj) (compound 65)

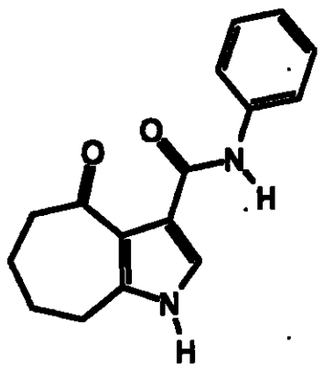
(bk) (compound 66)



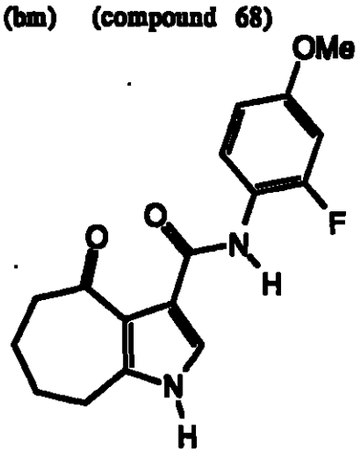
(bl) (compound 67)

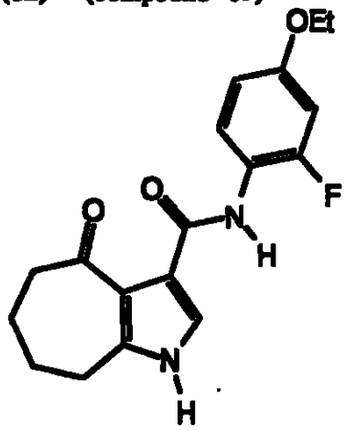


(bm) (compound 68)



(bn) (compound 69)





(bo) N-(4-fluoro-2-hydroxyphenyl)-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxamide (Compound 70).

D2 44

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US005608079A

United States Patent [19]

Albaugh et al.

[11] Patent Number: 5,608,079

[45] Date of Patent: Mar. 4, 1997

[54] **CERTAIN FUSED PYRROLECARBOXANILIDES; A NEW CLASS OF GABA BRAIN RECEPTOR LIGANDS**

[75] Inventors: **Pamela Albaugh**, Clinton; **Alan Hutchison**, Madison, both of Conn.

[73] Assignee: **Neurogen Corporation**, Branford, Conn.

[21] Appl. No.: 473,509

[22] Filed: Jun. 7, 1995

Related U.S. Application Data

[63] Continuation of Ser. No. 144,138, Oct. 27, 1993.

[51] Int. Cl.[6] C07D 209/18

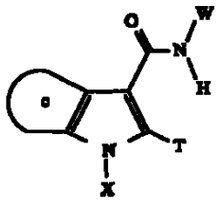
[52] U.S. Cl. 548/492

[58] Field of Search 548/492

Primary Examiner—David B. Springer
Attorney, Agent, or Firm—McDonnell Boehnen Hulbert & Berghoff, Ltd.

[57] **ABSTRACT**

The present invention encompasses structures of the formula I:

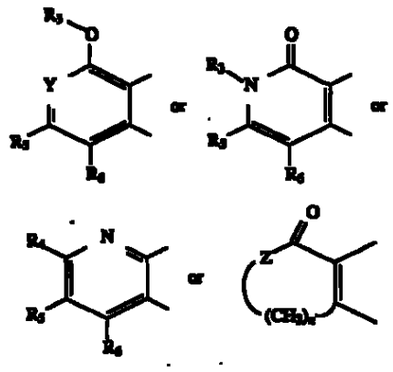


I

and the pharmaceutically acceptable non-toxic salts thereof wherein:

represents

-continued



wherein:

W represents substituted or unsubstituted aryl groups;

X is hydrogen, hydroxy or lower alkyl;

T is hydrogen, halogen, hydroxyl, amino or alkyl;

R_3 is hydrogen or an organic group;

R_4 is hydrogen or substituted or unsubstituted organic substituent;

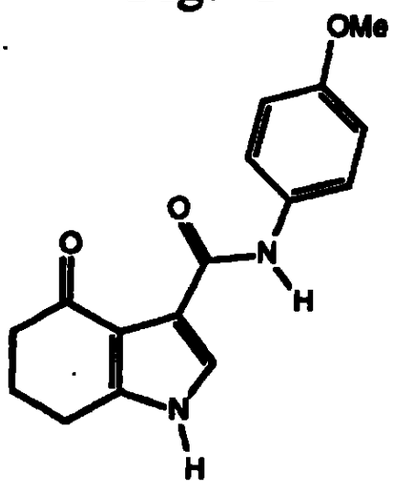
R_5 and R_6 represent organic, and inorganic substituents; and

n is 1, 2, 3, or 4.

These compounds are highly selective agonists, antagonists or inverse agonists for GABAa brain receptors or prodrugs of agonists, antagonists or inverse agonists for GABAa brain receptors. These compounds are useful in the diagnosis and treatment of anxiety, sleep and seizure disorders, overdose with benzodiazepine drugs and for enhancement of memory.

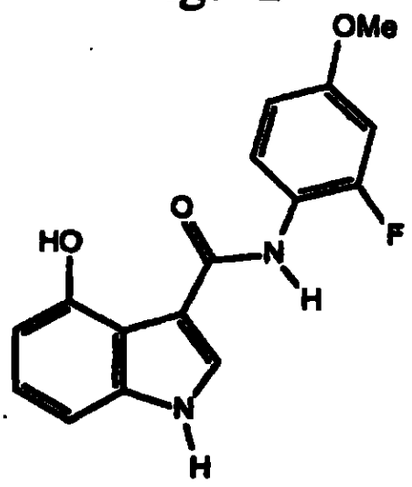
3 Claims, 5 Drawing Sheets

Fig. 1



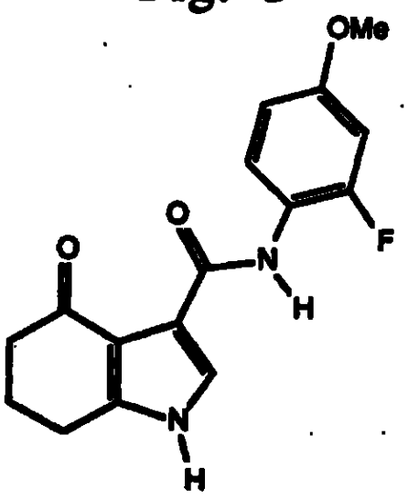
Compound 1

Fig. 2



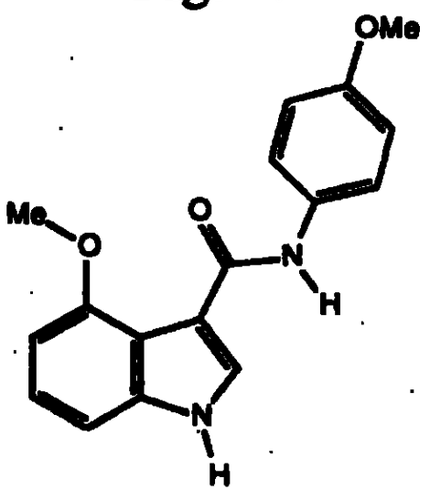
Compound 2

Fig. 3



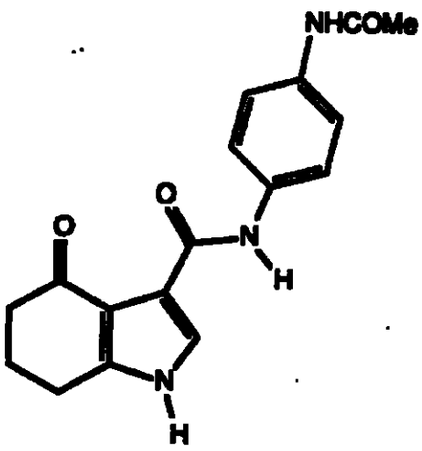
Compound 6

Fig. 4



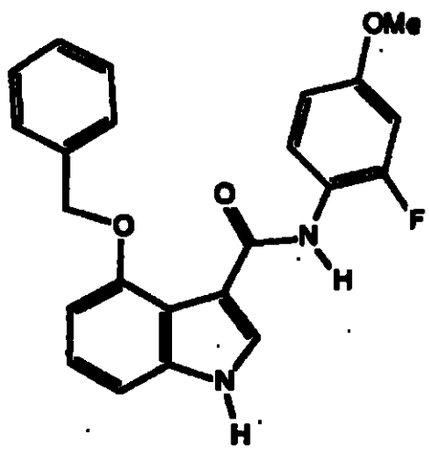
Compound 8

Fig. 5



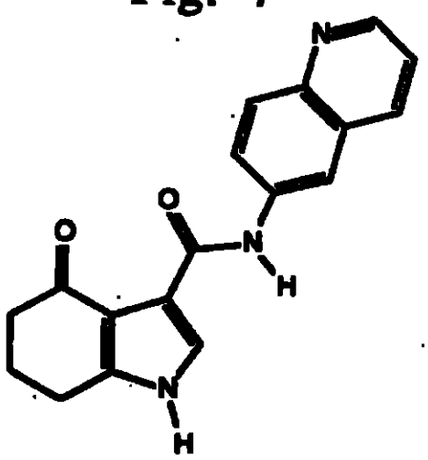
Compound 12

Fig. 6



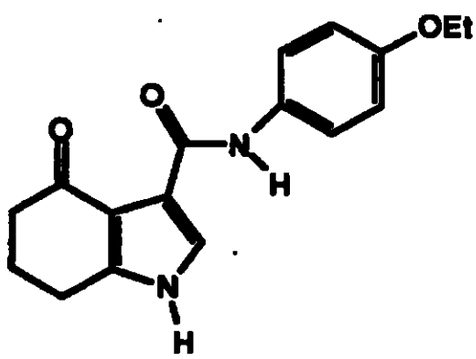
Compound 14

Fig. 7



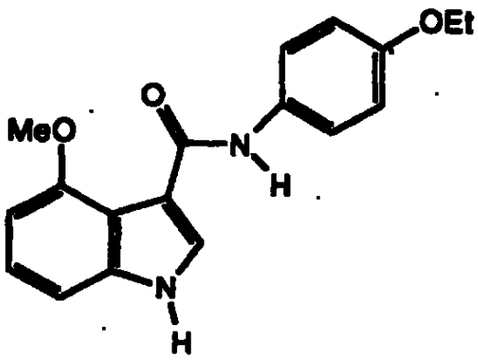
Compound 17

Fig. 8



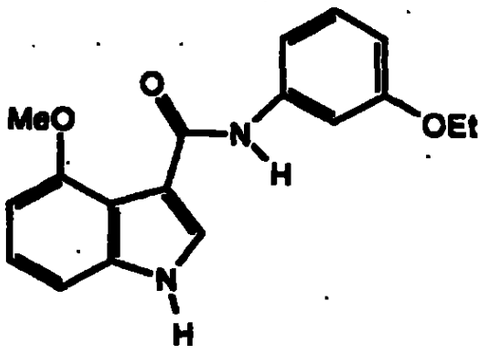
Compound 3

Fig. 9



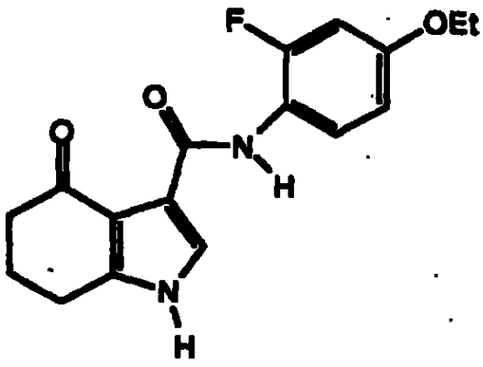
Compound 4

Fig. 10



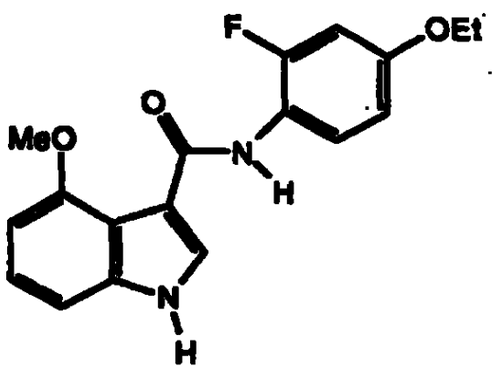
Compound 5

Fig. 11



Compound 7

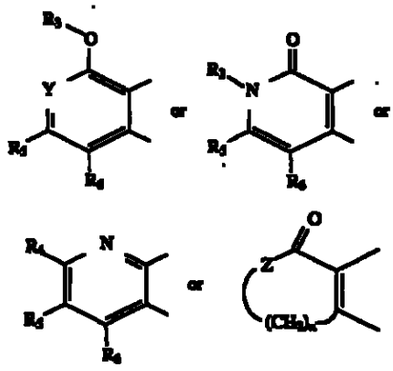
Fig. 12



Compound 9

1–6 carbon atoms, straight or branched chain lower alkoxy having 1–6 carbon atoms, or NR_1COR_2, COR_2, $CONR_1R_2$ or CO_2R_2 where R_1 and R_2 are the same or different and represent hydrogen or straight or branched chain lower alkyl having 1–6 carbon atoms; and

represents



wherein:

Y represents nitrogen or C—R_4;

Z represents N—R_7 or a carbon atom substituted with R_8 and R_9, i.e., $C(R_8)(R_9)$;

n is 1, 2, 3, or 4;

R_3 is

hydrogen, phenyl, 2, 3 or 4-pyridyl, straight or branched chain lower alkyl having 1–6 carbon atoms, or phenylalkyl or 2, 3 or 4-pyridylalkyl where each alkyl is straight or branched chain lower alkyl having 1–6 carbon atoms;

R_4 is

halogen or trifluoromethyl; or

—OR_{10}, —COR_{10}, —CO_2R_{10}, —$OCOR_{10}$, or —R_{10}, where R_{10} is hydrogen, phenyl, 2, 3 or 4-pyridyl, straight or branched chain lower alkyl having 1–6 carbon atoms, or phenylalkyl or 2, 3 or 4-pyridylalkyl where each alkyl is straight or branched chain lower alkyl having 1–6 carbon atoms; or

—$CONR_{11}R_{12}$ or —$(CH_2)_mNR_{11}R_{12}$, where m is 0, 1, or 2; R_{11} represents hydrogen, straight or branched chain lower alkyl having 1–6 carbon atoms; and R_{12} is hydrogen, phenyl, 2, 3 or 4-pyridyl, straight or branched chain lower alkyl having 1–6 carbon atoms, or phenylalkyl or 2, 3 or 4-pyridylalkyl where each alkyl is straight or branched chain lower alkyl having 1–6 carbon atoms; or $NR_{11}R_{12}$ forms a heterocyclic group which is morpholyl, piperidyl, pyrrolidyl, or N-alkyl piperazyl;

R_5 and R_6 are the same or different and represent

hydrogen, halogen, straight or branched chain lower alkyl having 1–6 carbon atoms, or straight or branched chain lower alkoxy having 1–6 carbon atoms;

R_7 is

hydrogen, phenyl, 2, 3 or 4-pyridyl, straight or branched chain lower alkyl having 1–6 carbon atoms, or phenylalkyl or 2, 3, or 4-pyridylalkyl where each alkyl is straight or branched chain lower alkyl having 1–6 carbon atoms;

R_8 is

hydrogen or straight or branched chain lower alkyl having 1–6 carbon atoms; and

R_9 is

—COR_{13}, —CO_2R_{13} or —R_{13}, where R_{13} is hydrogen, phenyl, 2, 3 or 4-pyridyl, straight or branched chain lower alkyl having 1–6 carbon atoms, or phenylalkyl or 2, 3, or 4-pyridylalkyl where each alkyl is straight or branched chain lower alkyl having 1–6 carbon atoms: or

—$CONR_{14}R_{15}$ or —$(CH_2)_kNR_{14}R_{15}$, where k is 0, 1, or 2; R_{14} represents hydrogen, straight or branched chain lower alkyl having 1–6 carbon atoms: and R_{15} is hydrogen, phenyl, 2, 3, or 4-pyridyl, straight or branched chain lower alkyl having 1–6 carbon atoms, or phenylalkyl or 2, 3 or 4-pyridylalkyl where each alkyl is straight or branched chain lower alkyl having 1–6 carbon atoms; or $NR_{14}R_{15}$ forms a heterocyclic group which is morpholyl, piperidyl, pyrrolidyl, or N-alkyl piperazyl.

These compounds are highly selective agonists, antagonists or inverse agonists for GABAa brain receptors or prodrugs of agonists, antagonists or inverse agonists for GABAa brain receptors. In other words, while the compounds of the invention all interact with GABAa brain receptors, they do display identical physiologic activity. Thus, these compounds are useful in the diagnosis and treatment of anxiety, sleep and seizure disorders, overdose with benzodiazepine drugs and for enhancement of memory. For example, these compounds can easily be used to treat overdoses of benzodiazepine-type drugs as they would competitively bind to the benzodiazepine receptor.

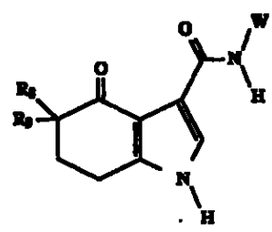
BRIEF DESCRIPTION OF THE DRAWINGS

FIGS. 1–20 show representative fused pyrrolecarboxamilides of the present invention.

DETAILED DESCRIPTION OF THE INVENTION

The novel compounds encompassed by the instant invention can be described by general formula I set forth above or the pharmaceutically acceptable non-toxic salts thereof.

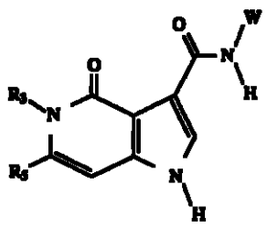
In addition, the present invention encompasses compounds of Formula II.



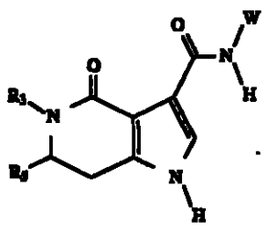
II

or the pharmaceutically acceptable non-toxic salts thereof wherein W, R_8 and R_9 are as defined above.

The present invention also encompasses compounds of Formula IIIa and IIIb:



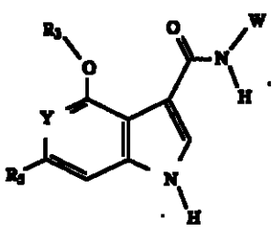
IIIa



IIIb

or the pharmaceutically acceptable non-toxic salts thereof wherein W, R_3, and R_5 are as defined above.

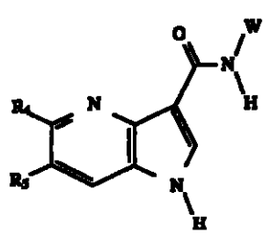
The present invention also encompasses compounds of Formula IV:



IV

or the pharmaceutically acceptable non-toxic salts thereof wherein W, Y, R_3, and R_5 are defined above.

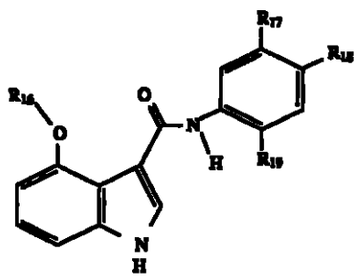
The present invention also encompasses compounds of Formula V:



V

or the pharmaceutically acceptable non-toxic salts thereof wherein W, R_4, and R_5 are defined above.

The invention further encompasses compounds of Formula VI:



VI

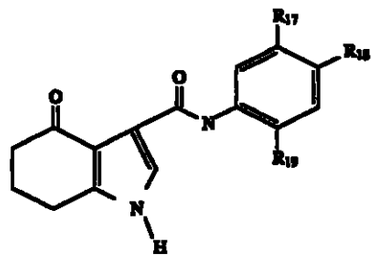
or the pharmaceutically acceptable non-toxic salts thereof where R_{16} is hydrogen, benzyl or straight or branched chain lower alkyl having 1–6 carbon atoms;

R_{17} is hydrogen or straight or branched chain lower alkoxy having 1–6 carbon atoms;

R_{18} is hydrogen, straight or branched chain lower alkoxy having 1–6 carbon atoms, NR_1COR_2, COR_2, CO_2R_2 where R_1 and R_2 are as defined above, cyano or halogen; and

R_{19} is hydrogen or halogen.

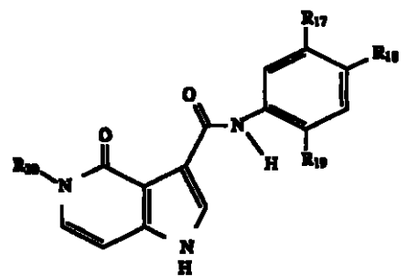
The invention additionally encompasses compounds of formula VII:



VII

or the pharmaceutically acceptable non-toxic salts thereof where R_{17}, R_{18} and R_{19} are defined above.

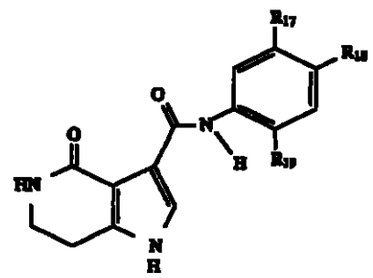
The invention further encompasses compounds of Formula VIII;



VIII

where R_{17}, R_{18}, and R_{19} are defined above and R_{20} is hydrogen or straight or branched chain alkyl having 1–6 carbon atoms.

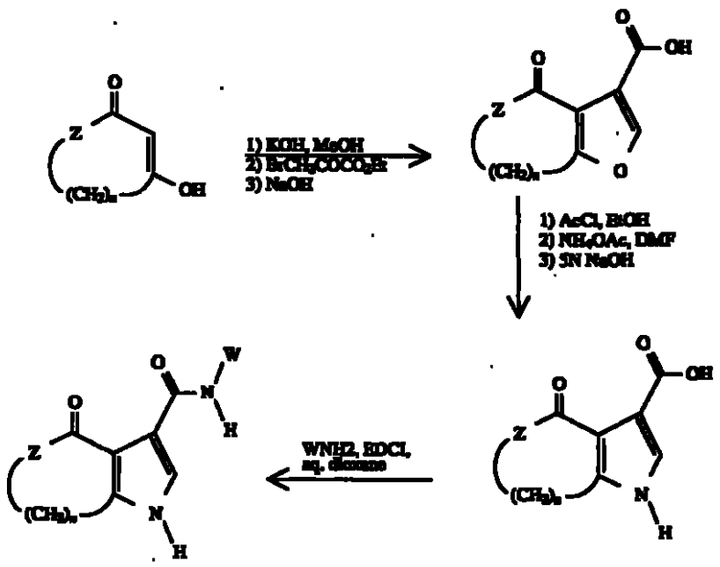
The invention further encompasses compounds of Formula IX;



IX

where R_{17}, R_{18}, and R_{19} are defined above.

Scheme I

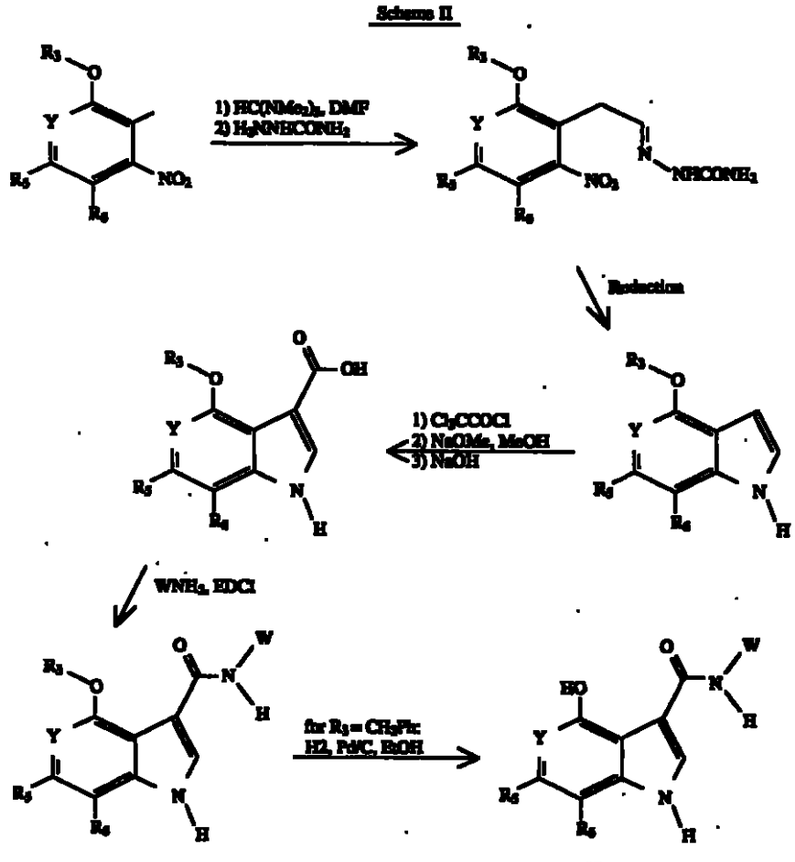


where:

W, Z, and n are as defined above.

Those having skill in the art will recognize that the starting materials may be varied and additional steps

Scheme II



W, R_3, Y, R_5, and R_6 are as defined above.

employed to produce compounds encompassed by the

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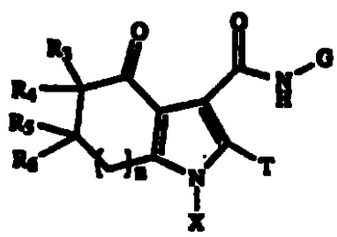


(I)

(1)

(2)

(3)

(4)

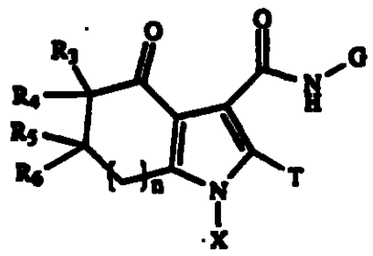
(57) Abstract

The present invention encompasses structures of formula (I) or the pharmaceutically acceptable non-toxic salts thereof wherein G represents (1) where Q is aryl substituents optionally mono or disubstituted with hydroxy or halogen; T is halogen, hydrogen, hydroxyl, amino or alkoxy having 1-6 carbon atoms; W is oxygen, nitrogen, sulfur, or optionally substituted methylene; X is hydrogen, hydroxyl, or alkyl; Z is an organic or inorganic substituent optionally forming a ring with substituents on Q; (2), (3) and (4) independently represent optionally substituted carbon chains; wherein k, m, and n are independently 0, or an integer of from 1-3; R_3, R_4, R_5, and R_6 are the same or different and represent organic or inorganic substituents. These compounds are highly selective agonists, antagonists or inverse agonists for GABAa brain receptors or prodrugs of agonists, antagonists or inverse agonists for GABAa brain receptors. These compounds are useful in the diagnosis and treatment of anxiety, sleep and seizure disorders, overdose with benzodiazepine drugs and for enhancement of memory.

SUMMARY OF THE INVENTION

This invention provides novel compounds of Formula I which interact with a GABAa binding site, the benzodiazepine receptor.

The invention provides pharmaceutical compositions comprising compounds of Formula I. The invention also provides compounds useful in the diagnosis and treatment of anxiety, sleep and seizure disorders, overdose with benzodiazepine drugs and for enhancement of memory. Accordingly, a broad embodiment of the invention is directed to compounds of general Formula I:



I

or the pharmaceutically acceptable non-toxic salts thereof wherein:

G represents

where

Q is phenyl, 2- or 3-thienyl, or 2-, 3-, or 4-pyridyl, all of which may be mono or disubstituted with hydroxy or halogen;

T is halogen, hydrogen, hydroxyl, amino or straight or branched chain lower alkoxy having 1-6 carbon atoms;

W is oxygen, nitrogen, sulfur, or CR_7R_8 where R_7 and R_8 are the same or different and represent hydrogen, straight or branched chain lower alkyl having 1-6 carbon atoms, or R_7-R_8 may be taken together to represent a cyclic moiety having 3-7 carbon atoms;

X is hydrogen, hydroxyl, or straight or branched chain lower alkyl having 1-6 carbon atoms;

Z is hydroxy, straight or branched chain lower alkoxy having 1-6 carbon atoms, cycloalkyl alkoxy having 3-7 carbon atoms, amino, mono, or dialkylamino where each alkyl is independently straight or branched chain lower alkyl having 1-6 carbon atoms or cycloalkyl having 3-7 carbon atoms, or NR_9COR_{10} where R_9 and R_{10} are the same or different and represent hydrogen or straight or branched chain lower alkyl having 1-6 carbon atoms or cycloalkyl having 3-7 carbon atoms; or

Z is connected, optionally through W, to Q to from a 1-6 membered ring;

 ,  , and  independently represent a carbon chain optionally substituted with hydrogen, halogen, or straight or branched chain lower alkyl having 1-6 carbon atoms;

wherein

k is 0, 1, 2, or 3;

m is 0, 1, 2, or 3; and

n is 0, 1, 2, or 3;

R_3, R_4, R_5, and R_6 are the same or different and are selected from hydrogen, straight or branched lower alkyl having 1-6 carbon atoms, $-COR_{11}$ or $-CO_2R_{11}$ where R_{11} is straight or branched lower alkyl having 1-6 carbon atoms or cycloalkyl having 3-7 carbon atoms; or $-CONR_{12}R_{13}$ where R_{12} and R_{13} are selected independently from hydrogen, straight or branched chain lower alkyl having 1-6 carbon atoms, cycloalkyl having 3-7 carbon atoms, phenyl, 2-, 3-, or 4-pyridyl, or $NR_{12}R_{13}$ forms a heterocyclic group which is morpholinyl, piperidinyl, pyrrolidinyl, or N-alkyl piperazinyl; or

R_3-R_4 taken together forms a cyclic moiety having 3-7 carbon atoms; or

R_5-R_6 may be taken together to form a cyclic moiety having 3-7 carbon atoms; and

where each alkyl group forming an R_3, R_4, R_5, or R_6 substituent or portion thereof may be substituted independently with hydroxy or mono- or dialkylamino where each alkyl is independently straight or branched chain

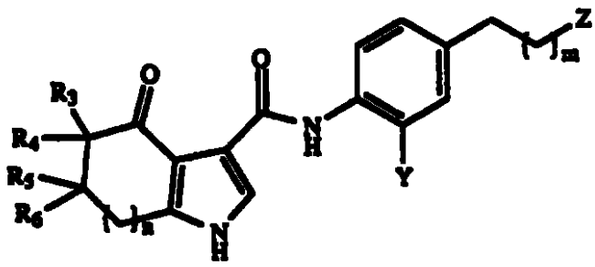
lower alkyl having 1-6 carbon atoms or cycloalkyl having 3-7 carbon atoms.

These compounds are highly selective agonists, antagonists or inverse agonists for GABAa brain receptors or prodrugs of agonists, antagonists or inverse agonists for GABAa brain receptors. In other words, while the compounds of the invention all interact with GABAa brain receptors, they do not display identical physiologic activity. Thus, these compounds are useful in the diagnosis and treatment of anxiety, sleep and seizure disorders, overdose with benzodiazepine drugs and for enhancement of memory. For example, these compounds can be used to treat overdoses of benzodiazepine-type drugs as they would competitively bind to the benzodiazepine receptor.

IV

wherein Y is hydrogen, halogen, or hydroxy; and W, Y, Z, k, m, n, R3, R4, R5, and R6 are defined as above.

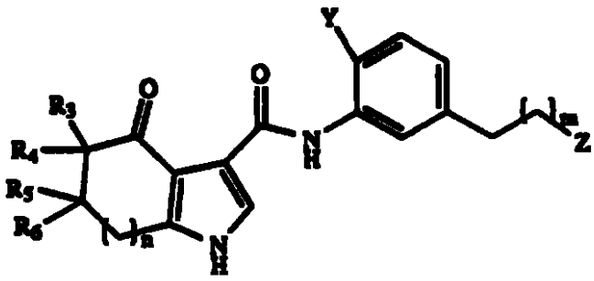
The present invention also encompasses compounds of Formula V.



V

wherein Y is hydrogen, halogen, or hydroxy; and W, Y, Z, k, m, n, R3, R4, R5, and R6 are defined as above.

The present invention also encompasses compounds of Formula VI.

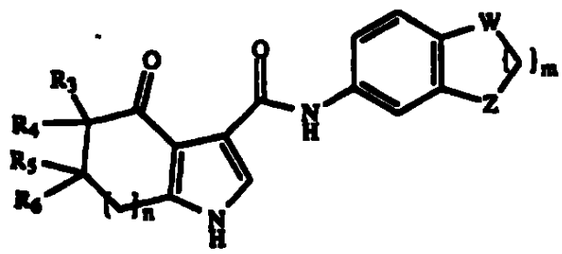


VI

wherein Y is hydrogen, halogen, or hydroxy; and W, Y, Z, k, m, n, R3, R4, R5, and R6 are defined as above.

The present invention also encompasses compounds of Formula VII.

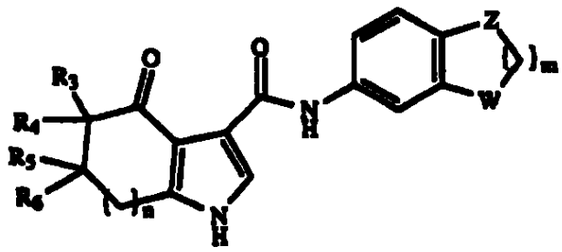
153
440



VII

wherein W, Z, m, n, R3, R4, R5, and R6 are defined as above.

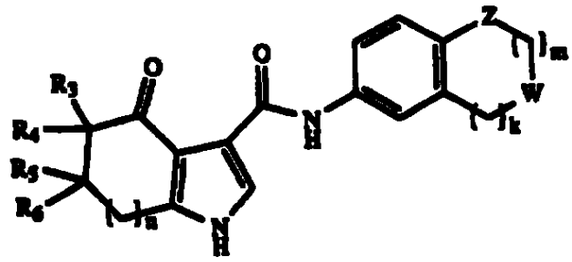
The present invention also encompasses compounds of Formula VIII.



VIII

wherein W, Z, m, n, R3, R4, R5, and R6 are defined as above.

The present invention also encompasses compounds of Formula IX.

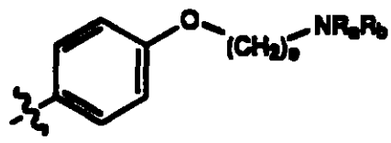


IX

wherein W, Z, k, m, n, R3, R4, R5, and R6 are defined as above.

The present invention also encompasses compounds of Formula X.

Another preferred G substituent is the following formula:



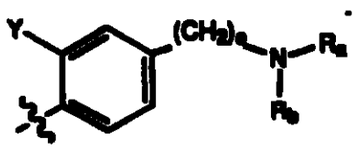
C

where R_a and R_b independently represent hydrogen or alkyl; and

e is an integer of 2-3.

More preferred G substituents of formula C include those where R_a is hydrogen, methyl or ethyl; and R_b is hydrogen. Particularly preferred G substituents of formula C include those where e is 2; R_a is hydrogen or methyl; and R_b is hydrogen.

Another preferred G substituent is the following formula:



D

where R_a represents hydrogen, alkyl, or C_{3-7} cycloalkyl;

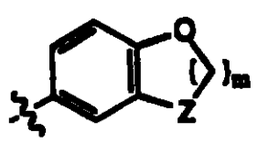
R_b represents hydrogen, alkyl, or acyl;

Y represents hydrogen or halogen; and

e is an integer of 1-3.

More preferred G substituents of formula D are those where Y is hydrogen or fluorine; and e is 1 or 2. Particularly preferred G substituents of formula D are those where Y is hydrogen or fluorine; e is 1 or 2; R_a is hydrogen, C_{1-3} alkyl, or cyclopropyl, and R_b is hydrogen, methyl, or acyl.

Another preferred G substituent is the following formula:

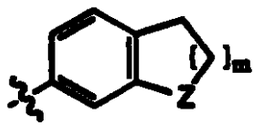


E

where Z is oxygen, nitrogen, or methylene; and m is 1 or 2.

Particularly preferred G substituents of formula E are those where Z is oxygen, and m is 1 or 2. Other particularly preferred G substituents of formula E are those where Z is nitrogen, and m is 1 or 2.

Another preferred G substituent is the following formula:

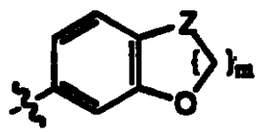


F

where Z is oxygen or nitrogen; and m is 1 or 2.

Particularly preferred G substituents of formula F are those where Z is nitrogen, and m is 1 or 2.

Another preferred G substituent is the following formula:

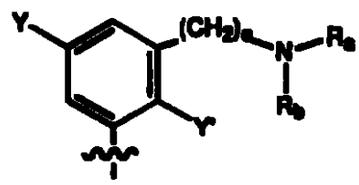


H

where Z is oxygen, nitrogen, or methylene; and m is 1 or 2.

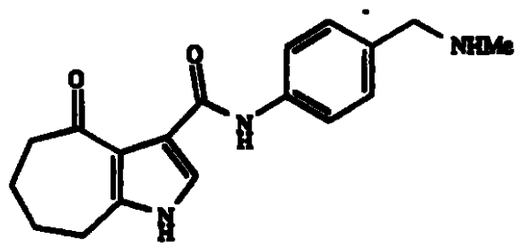
Particularly preferred G substituents of formula H are those where Z is nitrogen, and m is 1 or 2.

Another preferred G substituent is the following formula:

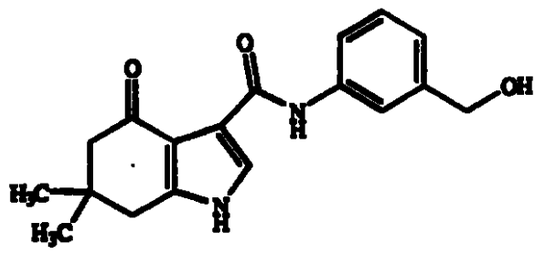


J

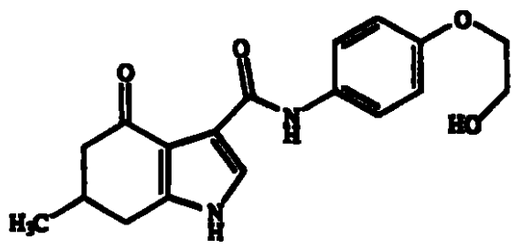
where R_a represents hydrogen, alkyl, or C_{3-7} cycloalkyl;



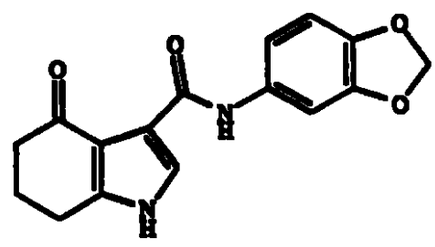
Compound 7



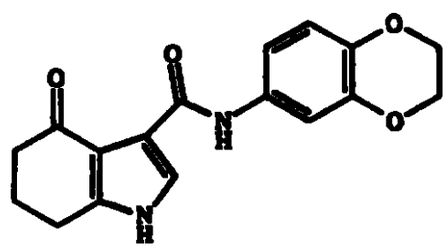
Compound 8



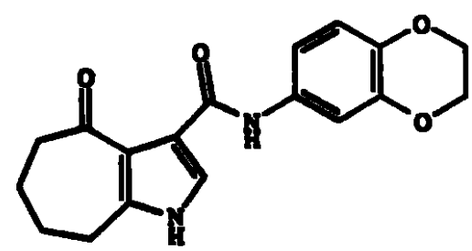
Compound 9



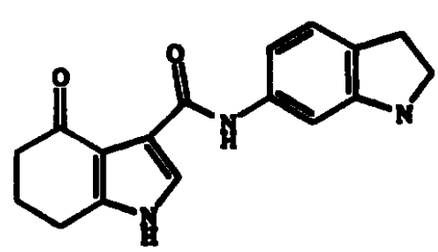
Compound 10



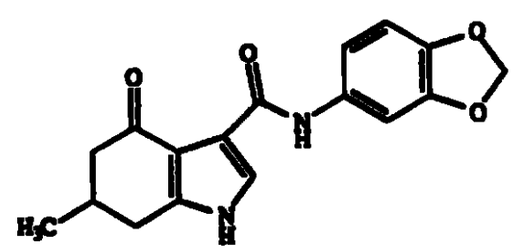
Compound 11



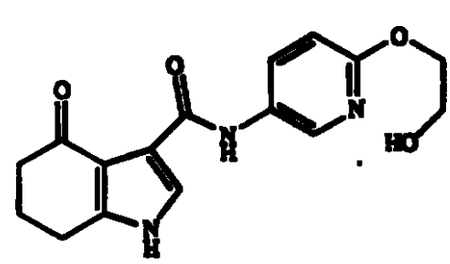
Compound 12



Compound 13



Compound 14

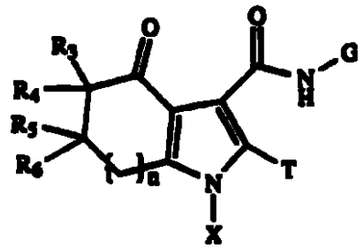


Compound 15

157
444

WHAT IS CLAIMED IS:

1. A compound of the formula:



or the pharmaceutically acceptable non-toxic salts thereof wherein:

G represents

where

Q is phenyl, 2- or 3-thienyl, or 2-, 3-, or 4-pyridyl, all of which may be mono or disubstituted with hydroxy or halogen;

T is halogen, hydrogen, hydroxyl, amino or alkoxy having 1-6 carbon atoms;

W is oxygen, nitrogen, sulfur, or CR_7R_8 where R_7 and R_8 are the same or different and represent hydrogen, alkyl, or R_7-R_8 taken together represents a cyclic moiety having 3-7 carbon atoms;

X is hydrogen, hydroxyl, or alkyl;

Z is hydroxy, alkoxy, cycloalkyl alkoxy having 3-7 carbon atoms, amino, mono, or dialkylamino where each alkyl is independently alkyl or cycloalkyl having 3-7 carbon atoms, or NR_9COR_{10} where R_9 and R_{10} are the same or different and represent hydrogen or alkyl or cycloalkyl having 3-7 carbon atoms; or

Z is connected, optionally through W, to Q to from a 1-6 membered ring;

 ,  , and  independently represent a carbon chain optionally substituted with hydrogen, halogen, or straight or branched chain lower alkyl having 1-6 carbon atoms;

wherein

k is 0, 1, 2, or 3;

m is 0, 1, 2, or 3; and

n is 0, 1, 2, or 3;

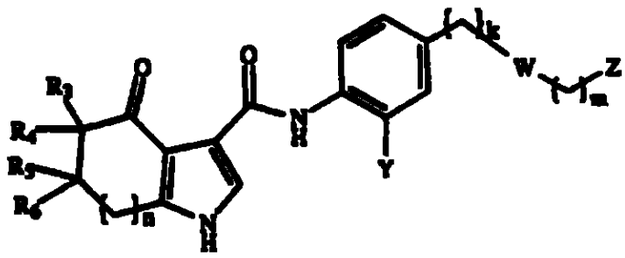
R_3, R_4, R_5, and R_6 are the same or different and are selected from hydrogen, alkyl , $-COR_{11}$ or $-CO_2R_{11}$ where R_{11} is alkyl or cycloalkyl having 3-7 carbon atoms; or $-CONR_{12}R_{13}$ where R_{12} and R_{13} are selected independently from hydrogen, alkyl, cycloalkyl having 3-7 carbon atoms, phenyl, 2-, 3-, or 4-pyridyl, or $NR_{12}R_{13}$ forms a heterocyclic group which is morpholinyl, piperidinyl, pyrrolidinyl, or N-alkyl piperazinyl; or

R_3-R_4 may be taken together to form a cyclic moiety having 3-7 carbon atoms; or

R_5-R_6 may be taken together to form a cyclic moiety having 3-7 carbon atoms; and

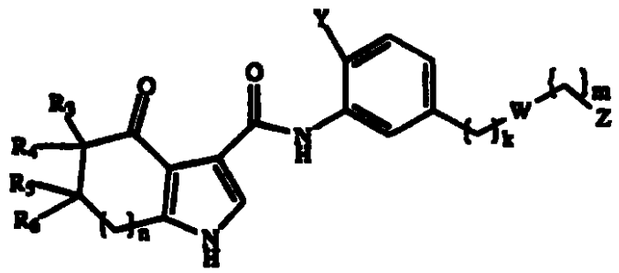
where each alkyl group forming an R_3, R_4, R_5, or R_6 substituent or portion thereof may be substituted independently with hydroxy or mono- or dialkylamino where each alkyl is independently alkyl or cycloalkyl having 3-7 carbon atoms.

2. A compound according to claim 1,which is:



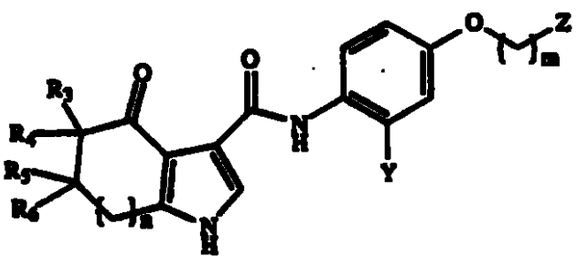
wherein Y is hydrogen, halogen, or hydroxy.

3. A compound according to claim 1,which is:



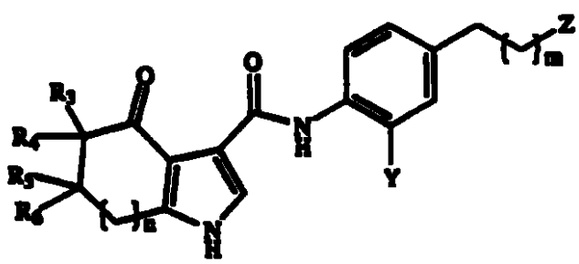
wherein Y is hydrogen, halogen, or hydroxy.

4. A compound according to claim 1,which is:



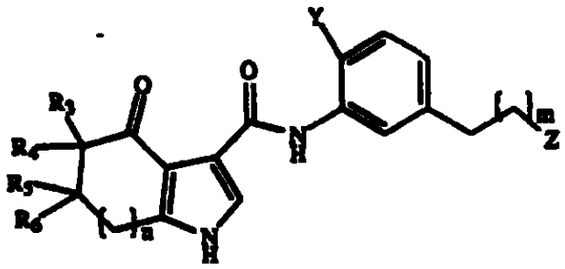
wherein Y is hydrogen, halogen, or hydroxy.

5. A compound according to claim 1,which is:



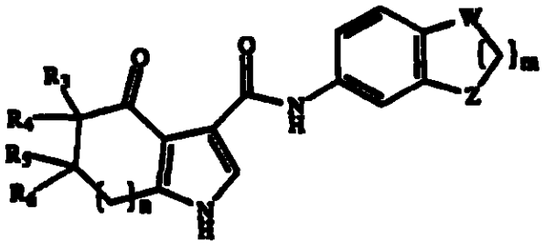
wherein Y is hydrogen, halogen, or hydroxy.

6. A compound according to claim 1,which is:

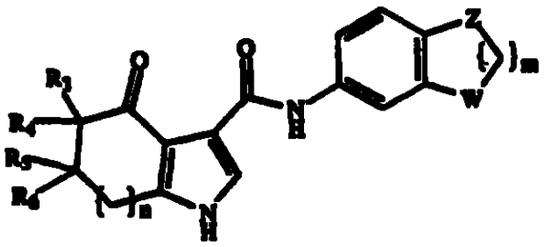


wherein Y is hydrogen, halogen, or hydroxy.

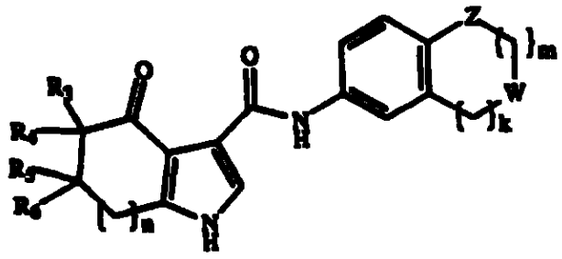
7. A compound according to claim 1,which is:



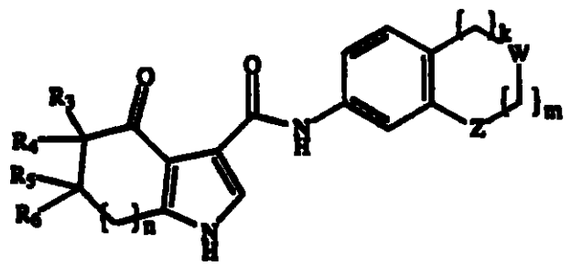
8. A compound of the formula:



9. A compound of the formula:



10. A compound of the formula:



11. A compound according to claim 1, which is N-[3-(Methylaminomethyl)phenyl]-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxamide .

12. A compound according to claim 1, which is N-[4-(Hydroxyethoxy)phenyl]-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxamide.

13. A compound according to claim 1, which is N-[4-(Methoxyethoxy)phenyl]-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxamide.

14. A compound according to claim 1, which is N-[-4-(3-Methylaminoethoxy)phenyl]-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxamide.

15. A compound according to claim 1, which is N-[4-(Methoxymethyl)phenyl]-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxamide.

16. A compound according to claim 1, which is N-[4-(Aminomethyl)phenyl]-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxamide.

17. A compound according to claim 1, which is N-[4-(Methylaminomethyl)phenyl]-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxamide.

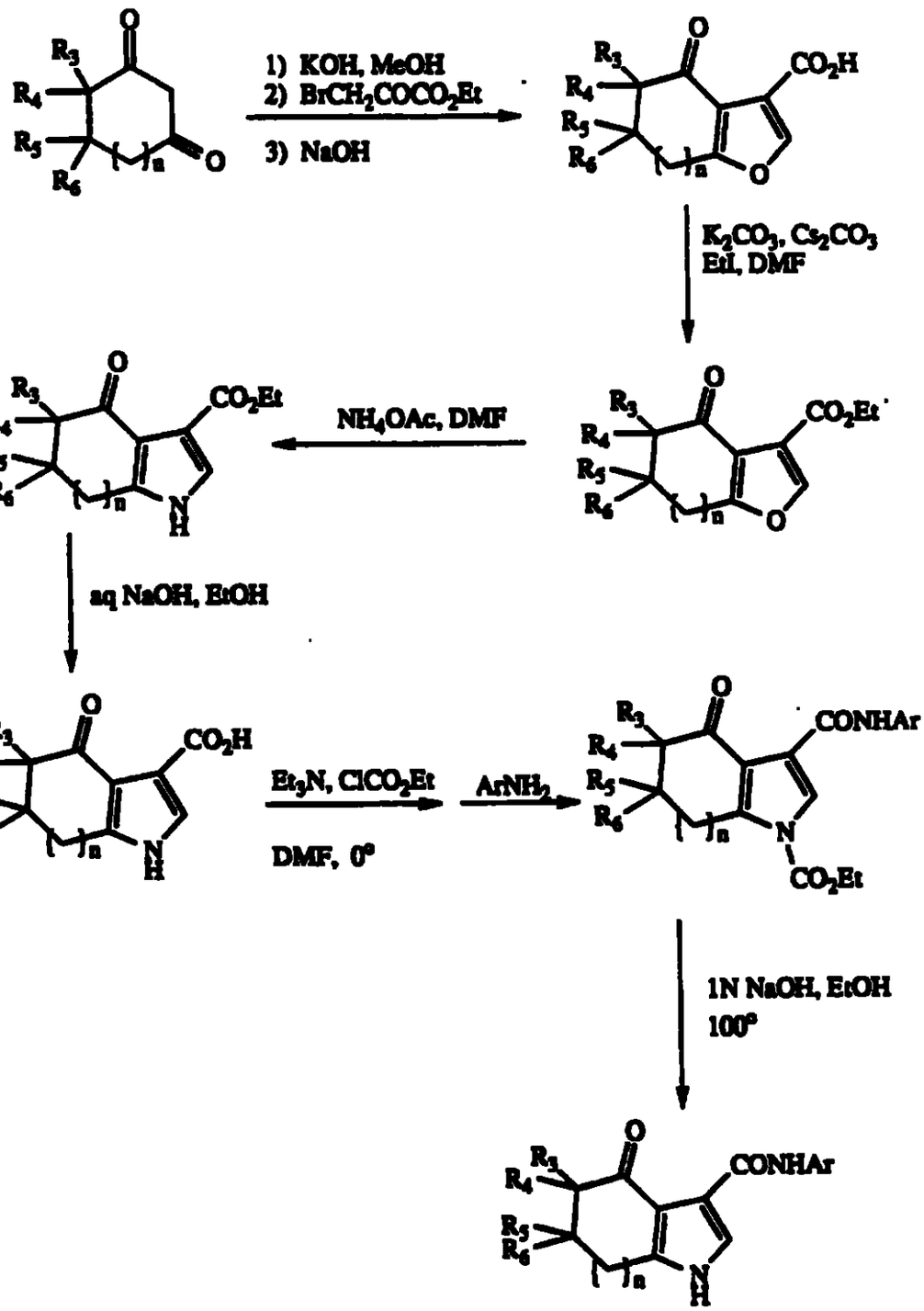
18. A compound according to claim 1, which is N-[2-Fluoro-4-(methylaminomethyl)phenyl]-4-oxo- 4,5,6,7-tetrahydro-1H-indole-3-carboxamide.

19. A compound according to claim 1, which is N-{4-[N-acetyl-(methylaminomethyl)phenyl]}-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxamide.

20. A compound according to claim 1, which is N-[4-(Ethylaminomethyl)phenyl]-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxamide.

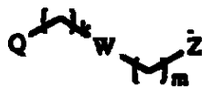
21. A compound according to claim 1, which is N-[4-(Isopropylaminomethyl)phenyl]-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxamide.

Scheme I



where:

Ar is



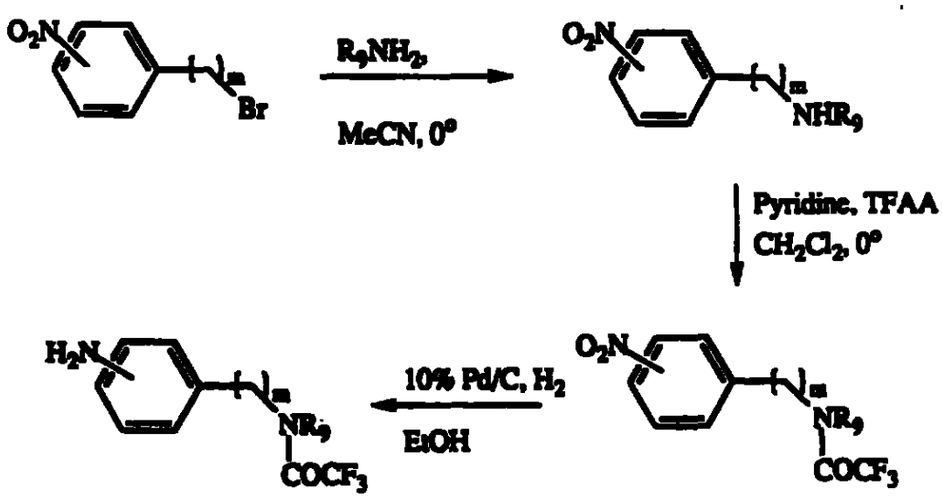
where Q, W, k, m,n, Z, R_3, R_4, R_5, and R_6 are as defined above.

Those having skill in the art will recognize that the starting materials may be varied and additional steps employed to produce compounds encompassed by the present invention, as demonstrated by the following examples.

In some cases protection of certain reactive functionalities may be necessary to achieve some of the above transformations. In general the need for such protecting groups will be apparent to those skilled in the art of organic synthesis as well as the conditions necessary to attach and remove such groups. Representative examples of the preparation of various protected aniline derivatives are shown in Schemes II (1), (2) and (3).

Scheme II

(1)



To a stirred solution of 4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxylic acid (100 mg, 0.6 mmol) and triethylamine (0.15 mL, 1.1 mmol) in N,N-dimethylformamide (5 mL) at 0° C is added ethyl chloroformate (0.1 mL, 1.1 mmol). After stirring an additional 1 hour, 3-(N-trifluoroacetyl-(methylaminomethyl)aniline (0.3 g, 1.3 mmol) is added. The reaction mixture is stirred for 4 hours, then poured into saturated aqueous ammonium chloride and extracted 2X with ethyl acetate. The combined organic layers are washed sequentially with brine, aqueous 2N hydrochloric acid, then brine, dried over sodium sulfate, filtered, and concentrated *in vacuo* . To the residue is added 15% aqueous potassium bicarbonate (5 mL) and methyl alcohol (3 mL), then heated at reflux for 3 hours. After cooling, the reaction mixture is extracted with ethyl acetate, the organic layer dried over sodium sulfate, filtered, and concentrated *in vacuo* to give N-[3-(methylaminomethyl)phenyl]-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxamide. m.p. 130-132°C.

Example 3

The following compounds are prepared essentially according to the procedures described in Examples 1-5:

(a) N-[3-(Methylaminomethyl)phenyl]-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxamide (Compound 1); mp 130-132° C.

(b) N-[4-(Hydroxyethoxy)phenyl]-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxamide; mp 245-247° C.

(c) N-[4-(Methoxyethoxy)phenyl]-4-oxo- 4,5,6,7-tetrahydro-1H-indole-3-carboxamide (Compound 2).

(d) N-[-4-(3-Methylaminoethoxy)phenyl]-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxamide; mp 233-236° C.

(e) N-[4-(Methoxymethyl)phenyl]-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxamide; mp 164-165° C.

(f) N-[4-(Aminomethyl)phenyl]-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxamide (Compound 6); mp >200° C (d).

(g) N-[4-(Methylaminomethyl)phenyl]-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxamide; mp 217-219° C.

(h) N-[2-Fluoro-4-(methylaminomethyl)phenyl]-4-oxo- 4,5,6,7-tetrahydro-1H-indole-3-carboxamide (Compound 3); mp 186-188°C.

(i) N-[4-[N-acetyl-(methylaminomethyl)phenyl]]-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxamide; mp 204-206° C.

(j) N-[4-(Ethylaminomethyl)phenyl]-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxamide; mp 194-195° C.

(k) N-[4-(Isopropylaminomethyl)phenyl]-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxamide; mp 164-166° C.

(l) N-[4-(Cyclopropylaminomethyl)phenyl]-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxamide (Compound 5); mp 171-173° C.

(m) N-[4-(Dimethylaminomethyl)phenyl]-4-oxo- 4,5,6,7-tetrahydro-1H-indole-3-carboxamide; mp 216-218°C.

(n) N-[4-(2-Aminoethyl)phenyl]-4-oxo- 4,5,6,7-tetrahydro-1H-ndole-3-carboxamide; mp 85-90° C.

(o) N-[4-(2-Methylaminoethyl)phenyl]-4-oxo- 4,5,6,7-tetrahydro-1H-indole-3-carboxamide (Compound 4); mp 197-200° C.

(p) N-[4-(Methoxymethyl)phenyl]-4-oxo-5,5-dimethyl-4,5,6,7-tetrahydro-1H-indole-3-carboxamide.

(q) N-[4-(Methylaminomethyl)phenyl-4-oxo-1,4,5,6,7,8-hexahydro-cyclohepta[b]pyrrole-3-carboxamide (Compound 7); mp 173-175° C.

(r) N-[4-[N-acetyl-(methylaminomethyl)phenyl]]-4-oxo-6-methyl-4,5,6,7-tetrahydro-1H-indole-3-carboxamide; mp 159-161° C.

(s) N-[4-(Methylaminomethyl)phenyl]-4-oxo-6-methyl-4,5,6,7-tetrahydro-1H-indole-3-carboxamide; mp 217-219° C.

(t) N-[4-(Hydroxymethyl)phenyl]-4-oxo-6-methyl-4,5,6,7-tetrahydro-1H-indole-3-carboxamide; mp 260-262° C.

(u) N-[4-(2-Hydroxyethoxy)phenyl]-4-oxo-6-methyl-4,5,6,7-tetrahydro-1H-indole-3-carboxamide (Compound 9); mp 245-247° C.

(v) N-[3-(Methylaminomethyl)phenyl]-4-oxo-6-methyl-4,5,6,7-tetrahydro-1H-indole-3-carboxamide; mp 172-174° C.

(w) N-[4-(2-Hydroxyethoxy)phenyl]-4-oxo-6,6-dimethyl-4,5,6,7-tetrahydro-1H-indole-3-carboxamide; mp 268-270° C.

(x) N-[3-(Hydroxymethyl)phenyl]-4-oxo-6,6-dimethyl-4,5,6,7-tetrahydro-1H-indole-3-carboxamide (Compound 8); mp 233-235°C.

(y) N-[4-(Hydroxymethyl)phenyl]-4-oxo-6,6-dimethyl-4,5,6,7-tetrahydro-1H-indole-3-carboxamide; mp 245-247°C.

(z) N-[4-(Methylaminomethyl)phenyl]-4-oxo-6,6-dimethyl-4,5,6,7-tetrahydro-1H-indole-3-carboxamide; mp 230-232°C.

(aa) N-(1,3-Benzodioxol-5-yl)-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxamide (Compound 10); mp 248-249° C.

(bb) N-(2,3-Dihydro-1,4-benzodioxin-6-yl)-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxamide (Compound 11); mp 254-256° C.

(cc) N-(3,4-Dihydro-2H-1,4-benzoxazin-6-yl)-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxamide; mp 216°C.

(dd) N-(2,2-Dimethyl-1,3-benzodioxol-5-yl)-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxamide.

(ee) N-(2,3-Dihydro-1H-indol-5-yl)-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxamide; mp 283-286°C.

(ff) N-(2,3-Dihydro-1H-indol-6-yl)-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxamide (Compound 13); mp 322-323°C.

(gg) N-(1,3-Benzodioxol-5-yl)-4-oxo-5,5-dimethyl-4,5,6,7-tetrahydro-1H-indole-3-carboxamide.

(hh) N-(2,3-Dihydro-1,4-benzodioxin-6-yl)-4-oxo-5,5-dimethyl-4,5,6,7-tetrahydro-1H-indole-3-carboxamide; mp 241-243°C.

(ii) N-(4H-1,3-Benzodioxin-7-yl)-4-oxo-5,5-dimethyl-4,5,6,7-tetrahydro-1H-indole-3-carboxamide; mp 251-252°C.

(jj) N-(1,3-Benzodioxol-5-yl)-4-oxo-1,4,5,6,7,8-hexahydro-cyclohepta[b]pyrrole-3-carboxamide; mp 210-212° C.

(kk) N-(2,3-Dihydro-1,4-benzodioxin-6-yl)-4-oxo-1,4,5,6,7,8-hexahydro-cyclohepta[b]pyrrole-3-carboxamide (Compond 12); mp 222-223° C.

(ll) N-(2,2-Dimethyl-1,3-benzodioxol-5-yl)-4-oxo-6-methyl-4,5,6,7-tetrahydro-1H-indole-3-carboxamide; mp 155-157°C.

(mm) N-(1,3-Benzodioxol-5-yl)-4-oxo-6-methyl-4,5,6,7-tetrahydro-1H-indole-3-carboxamide; mp 297-299°C.

(nn) N-(2,3-Dihydro-1,4-benzodioxin-6-yl)-4-oxo-6-methyl-4,5,6,7-tetrahydro-1H-indole-3-carboxamide; mp 290-292°C.

(oo) N-(1,3-Benzodioxol-5-yl)-4-oxo-6,6-dimethyl-4,5,6,7-tetrahydro-1H-indole-3-carboxamide; mp 245-246° C.

(pp) N-(2,3-Dihydro-1,4-benzodioxin-6-yl)-4-oxo-6,6-dimethyl-4,5,6,7-tetrahydro-1H-indole-3-carboxamide.

(qq) N-(4H-1,3-Benzodioxin-7-yl)-4-oxo-6,6-dimethyl-4,5,6,7-tetrahydro-1H-indole-3-carboxamide; mp 234-236° C.

(rr) N-[(2-Hydroxyethoxy)pyrid-5-yl]-4-oxo-6-methyl-4,5,6,7-tetrahydro-1H-indole-3-carboxamide (Compound 15); mp 221-223° C.

(ss) N-(3,4-Dihydro-2H-1,4-benzoxazin-7-yl)-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxamide.

D4 168 455

PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

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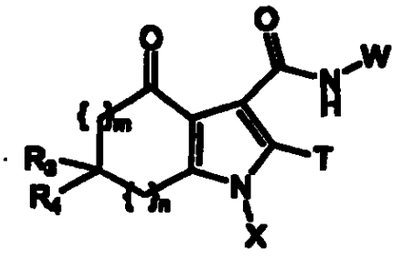
(54) Title: CERTAIN FUSED PYRROLECARBOXAMIDES AS GABA BRAIN RECEPTOR LIGANDS

(57) Abstract

Disclosed are compounds of formula (I), or the pharmaceutically acceptable non-toxic salts thereof, wherein W represents substituted or unsubstituted phenyl; T is hydrogen, halogen, hydroxyl, amino or alkyl; X is hydrogen, hydroxy, or lower alkyl; m is 0, 1, or 2; n is 0, 1, or 2; and R_3 and R_4 represent substituted or unsubstituted organic residues. These compounds are highly selective agonists, antagonists or inverse agonists for GABAa brain receptors or prodrugs of agonists, antagonists or inverse agonists for GABAa brain receptors. These compounds are useful in the diagnosis and treatment of anxiety, sleep and seizure disorders, overdose with benzodiazepine drugs and for enhancement of memory.

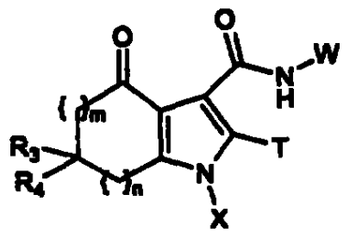


(I)

SUMMARY OF THE INVENTION

This invention provides novel compounds of Formula I which interact with a GABAa binding site, the benzodiazepine receptor.

The invention provides pharmaceutical compositions comprising compounds of Formula I. The invention also provides compounds useful in the diagnosis and treatment of anxiety, sleep and seizure disorders, overdose with benzodiazepine drugs and for enhancement of memory. Accordingly, a broad embodiment of the invention is directed to compounds of general Formula I:



I

or the pharmaceutically acceptable non-toxic salts thereof wherein:

W is aryl or heteroaryl; and

T is halogen, hydrogen, hydroxyl, amino or straight or branched chain lower alkoxy having 1-6 carbon atoms;

X is hydrogen, hydroxyl or straight or branched chain lower alkyl having 1-6 carbon atoms;

m is 0, 1, or 2;

n is 0, 1, or 2; and

R_3 and R_4 are the same or different and are selected from hydrogen, straight or branched lower alkyl having 1-6 carbon atoms, COR_5 or CO_2R_5 where R_5 is straight or branched lower alkyl having 1-6 carbon atoms or cycloalkyl having 3-7 carbon atoms, $CONR_6R_7$ where R_6 and R_7 are selected independently from hydrogen, straight or branched chain lower alkyl having 1-6 carbon atoms, cycloalkyl having 3-7 carbon atoms, phenyl, 2-,3-, or 4-pyridyl, or NR_6R_7 forms a heterocyclic group which is morpholinyl, piperidinyl, pyrrolidinyl, or N-alkyl piperazinyl; or

R_3-R_4 together represent a cyclic moiety having 3-7 carbon atoms; and

where each alkyl substituent in Formula I is optionally substituted with at least one group independently selected from hydroxy, mono- or dialkyl amino, phenyl or pyridyl.

These compounds are highly selective agonists, antagonists or inverse agonists for GABAa brain receptors or prodrugs of agonists, antagonists or inverse agonists for GABAa brain receptors. In other words, while the compounds of the invention all interact with GABAa brain receptors, they do not display identical physiologic activity. Thus, these compounds are useful in the diagnosis and treatment of anxiety, sleep and seizure disorders, overdose with benzodiazepine drugs and for enhancement of memory. For example, these compounds can be used to treat overdoses of benzodiazepine-type drugs as they would competitively bind to the benzodiazepine receptor.

DETAILED DESCRIPTION OF THE INVENTION

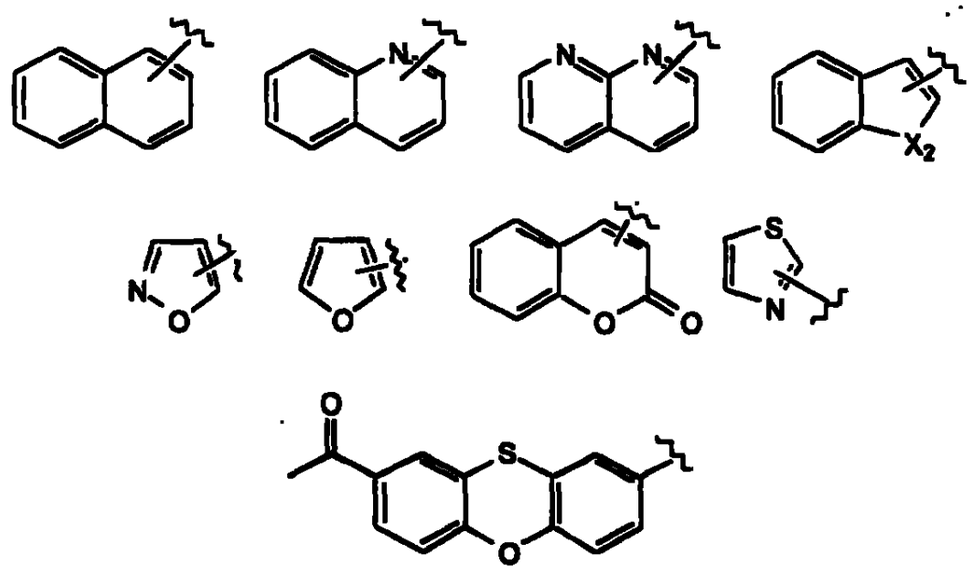
As used herein, the term "aryl" refers to aromatic carbocyclic groups having a single ring (e.g., phenyl), multiple rings (e.g., biphenyl), or multiple condensed rings in which at least one is aromatic. (e.g., 1,2,3,4-tetrahydronaphthyl, naphthyl, anthryl, or phenanthryl), which can optionally be substituted with e.g., halogen, lower alkyl, lower alkylthio, trifluoromethyl, lower acyloxy, aryl, and heteroaryl.

A preferred aryl group is phenyl optionally substituted with up to five groups selected independently from halogen, cyano, hydroxy, straight or branched chain lower alkyl having 1-6 carbon atoms or cycloalkyl having 3-7 carbon atoms, amino, mono or dialkylamino where each alkyl is independently straight or branched chain lower alkyl having 1-6 carbon atoms or cycloalkyl having 3-7 carbon atoms, straight or branched chain lower alkoxy having 1-6 carbon atoms, cycloalkyl alkoxy having 3-7 carbon atoms, or NR_1COR_2, COR_2, $CONR_1R_2$ or CO_2R_2 where R_1 and R_2 are the same or different and represent hydrogen or straight or branched chain lower alkyl having 1-6 carbon atoms or cycloalkyl having 3-7 carbon atoms

By heteroaryl is meant aromatic ring systems having at least one and up to four hetero atoms selected from the group consisting of nitrogen, oxygen and sulfur. Examples of heteroaryl groups are pyridyl, pyrimidinyl, pyrrolyl, pyrazolyl, pyrazinyl, pyridazinyl, oxazolyl, napthyridinyl, isoxazolyl, phthalazinyl, furanyl, quinolinyl, isoquinolinyl, thiazolyl, and thienyl, which can optionally be substituted with, e.g., halogen, lower alkyl, lower alkoxy, lower alkylthio, trifluoromethyl, lower acyloxy, aryl, heteroaryl, and hydroxy.

The aryl and heteroaryl groups herein are systems characterized by $4n+2$ π electrons, where n is an integer..

In addition to those mentioned above, other examples of the aryl and heteroaryl groups encompassed within the invention are the following:



As noted above, each of these groups can optionally be mono- or polysubstituted with groups selected independently from, for example, halogen, lower alkyl, lower alkoxy, lower alkylthio, trifluoromethyl, lower acyloxy, aryl, heteroaryl, and hydroxy.

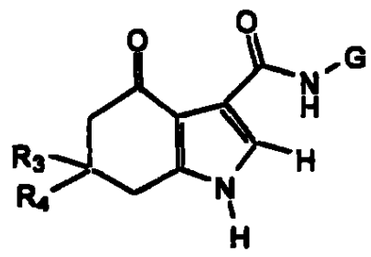
Still other examples of various aryl and heteroaryl groups are shown in Chart D of published International Application WO 93/17025.

By "alkyl" and "lower alkyl" in the present invention is meant straight or branched chain alkyl groups having 1-6 carbon atoms, such as, for example, methyl, ethyl, propyl, isopropyl, n-butyl, sec-butyl, tert-butyl, pentyl, 2-pentyl, isopentyl, neopentyl, hexyl, 2-hexyl, 3-hexyl, and 3-methylpentyl. Unless indicated otherwise, the alkyl group substituents herein are optionally substituted with at least one group independently selected from hydroxy, mono- or dialkyl amino, phenyl or pyridyl.

Where R_3 and R_4 are both alkyl, each alkyl is independently selected from lower alkyl.

By "alkoxy" and "lower alkoxy" in the present invention is meant straight or branched chain alkoxy groups having 1-6 carbon atoms, such as, for example, methoxy, ethoxy, propoxy, isopropoxy, n-butoxy, sec-butoxy, tert-butoxy, pentoxy, 2-pentyl, isopentoxy, neopentoxy, hexoxy, 2-hexoxy, 3-hexoxy, and 3-methylpentoxy.

As used herein "cycloalkyl alkoxy" refers to groups of the formula



VII

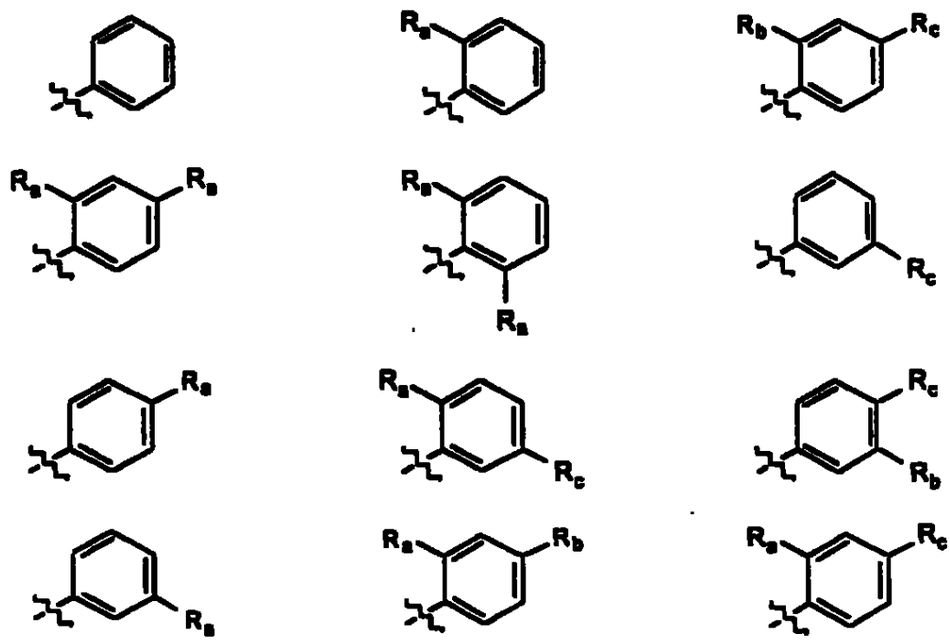
where

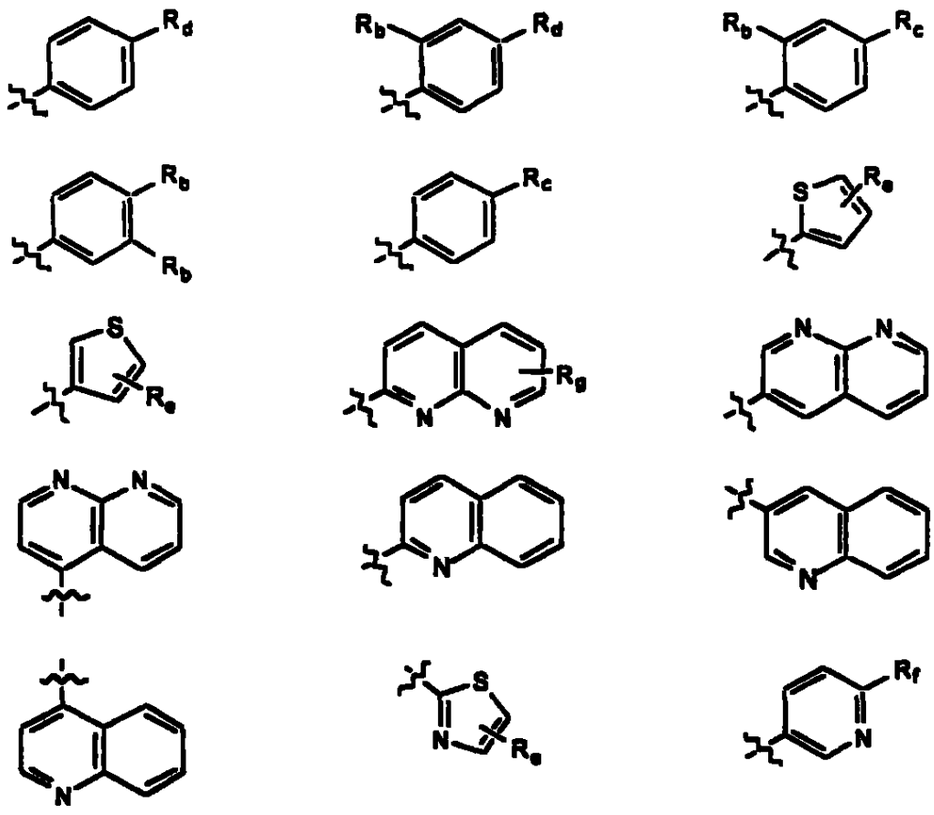
G represents aryl or heteroary such as, for example, thienyl, thiazolyl, pyridyl, napthyridinyl, quinolinyl, or phenyl, each of which is optionaly mono-, di- or trisubstituted with halogen alkyl alkoxy, or hydroxy; and

R_3 and R_4 are the same or different and represent hydrogen or alkyl, provided that not both R_3 and R_4 are hydrogen.

Preferred compounds of Formula VII are those where R_3 and R_4 are C_{1-3} alkyl, and more preferably methyl. Other preferred compounds of Formula VII are those where R_3 is hydrogen and R_4 is C_{1-3} alkyl, and more preferably R_4 is methyl.

Preferred compounds of Formula VII include a G group selected from the following:





In the above G groups, the following definitions apply:

R_a is halogen;

R_b is hydroxy;

R_c represents alkoxy;

R_d represents alkyl;

R_e represents hydrogen or R_d;

R_f represents hydrogen, or R_c; and

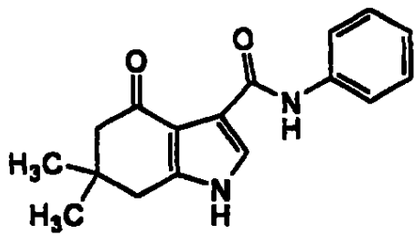
R_g represents hydrogen, R_a or R_c.

In those formulas where more than one of the same substituent appears, those substituents are the same or different.

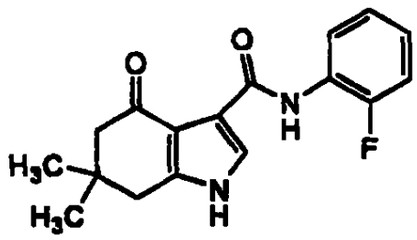
Particularly preffered R_a groups in G are fluorine. Particularly preferred R_c groups in G are methoxy and ethoxy. Particularly preferred R_d groups in G are methyl and ethyl.

Representative compounds of the invention are shown below in Table 1.

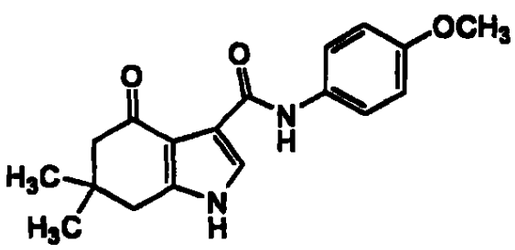
Table 1



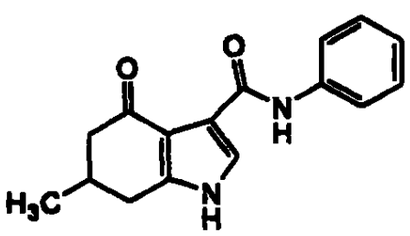
Compound 1



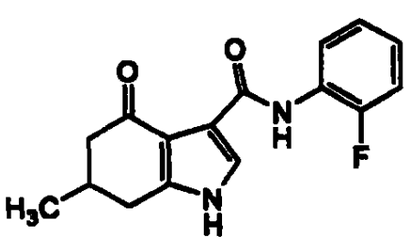
Compound 2



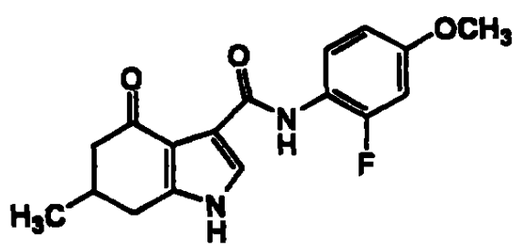
Compound 3



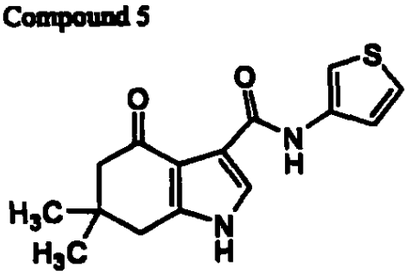
Compound 4



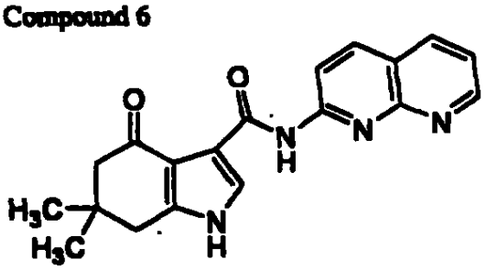
Compound 5



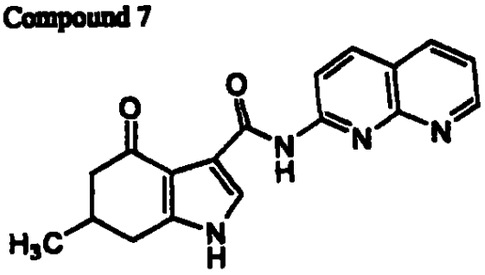
Compound 6



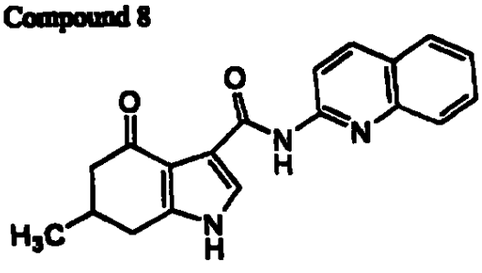
Compound 7



Compound 8

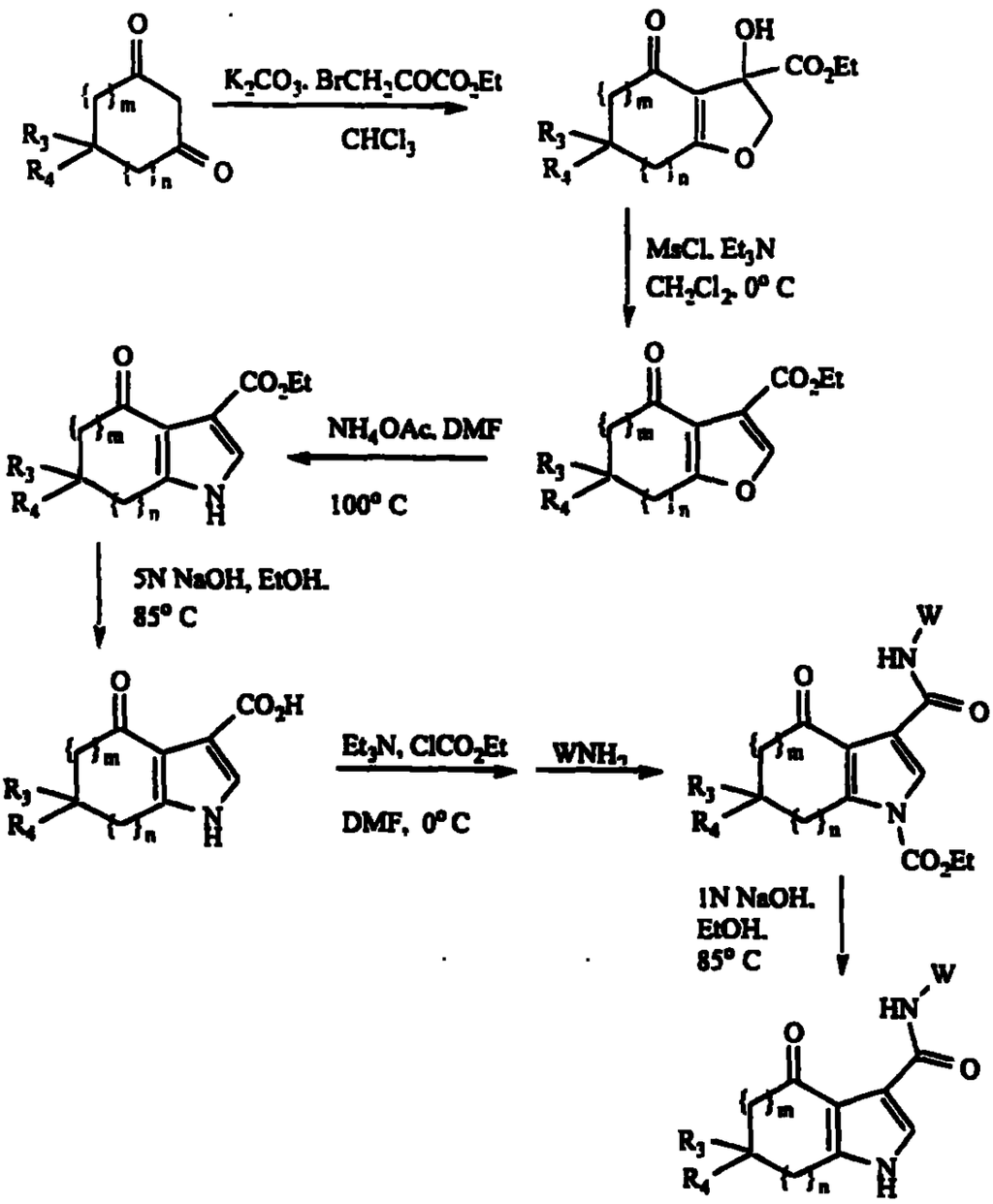


Compound 9



Compound 10

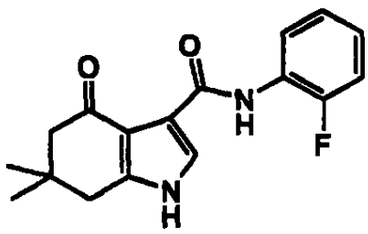
Scheme I



where W, m, n, R_3, and R_4 are defined as above.

Those having skill in the art will recognize that the starting materials may be varied and additional steps employed to produce compounds encompassed by the present invention, as demonstrated by the following examples. In some cases protection of certain reactive functionalities may be necessary to achieve some of the above transformations. In general the

Example 2



To a stirred solution of 4-oxo-6,6-dimethyl-4,5,6,7-tetrahydro-1H-indole-3-carboxylic acid (155 mg, 0.75 mmol) and triethylamine (209 µL, 1.5 mmol) in dimethylformamide (4 mL) at 0°C was added ethyl chloroformate (143 µL, 1.5 mmol). After stirring an additional 45 minutes, 2-fluoroaniline (145 µL, 1.5 mmol) was added. The reaction mixture was stirred for 30 minutes, then poured into aqueous 3.6N hydrochloric acid and extracted 2X with ethyl acetate. The combined organic layers were washed with water, dried over magnesium sulfate, filtered, and concentrated *in vacuo* . To the residue was added aqueous 5N sodium hydroxide (5 mL) and ethyl alcohol (1 mL), and the mixture was heated at reflux for 30 minutes. After cooling in an ice water bath, the reaction mixture was acidified with hydrochloric acid, the precipitate was collected, rinsed with water, and dried to give 55 mg of N-(2-fluorophenyl)-4-oxo-6,6-dimethyl-4,5,6,7-tetrahydro-1H-indole-3-carboxamide (Compound 2).

Example 3

The following compounds are prepared essentially according to the procedures described in Examples 1 and 2.

(a) N-Phenyl-4-oxo-6,6-dimethyl-4,5,6,7-tetrahydro-1H-indole-3-carboxamide (Compound 1).

(b) N-(2-Fluorophenyl)-4-oxo-6,6-dimethyl-4,5,6,7-tetrahydro-1H-indole-3-carboxamide; mp 259-261°C.

(c) N-(3-Fluorophenyl)-4-oxo-6,6-dimethyl-4,5,6,7-tetrahydro-1H-indole-3-carboxamide: mp 268-270°C.

(d) N-(2, 4- Diflurophenyl)-4-oxo-6.6-dimethyl-4,5,6,7-tetrahydro-1H-indole-3-carboxamide.

(e) N-(2,4-Difluorophenyl)-4-oxo-6.6-dimethyl-4,5.6,7-tetrahydro-1H-indole-3-carboxamide .

(f) N-(3Methoxyphenyl)-4-oxo-6,6-dimethyl-4,5,6,7-tetrahydro-1H-indole-3-carboxamide.

(g) N-(2-Hydroxy-4-methoxyphenyl)-4-oxo-6,6-dimethyl-4,5,6,7-tetrahydro-1H-indole-3-carboxamide; mp 190-192°C.

(h) N-(3-Hydroxy-4-methoxyphenyl)-4-oxo-6,6-dimethyl-4,5,6,7-tetrahydro-1H-indole-3-carboxamide; mp 282-284°C.

(i) N-(2-Fluoro-4-methoxyphenyl)-4-oxo-6,6-dimethyl-4,5,6,7-tetrahydro-1H-indole-3-carboxamide; mp 213-215°C.

(j) N-(2-Fluoro-4-methoxyphenyl)-4-oxo-6,6-dimethyl-4,5,6,7-tetrahydro-1H-indole-3-carboxamide.

(k) N-(2-Fluoro-5-methoxyphenyl)-4-oxo-6,6-dimethyl-4,5,6,7-tetrahydro-1H-indole-3-carboxamide.

(l) N-(2-Fluoro-4-methoxyphenyl)-4-oxo-6,6-dimethyl-4,5,6,7-tetrahydro-1H-indole-3-carboxamide; mp 225-227°C.

(m) N-(2-Methoxphenyl)-4-oxo-6.6-dimethyl-4.5.6.7-tetrahydro-1H-indole-3-carboxamide (Compound 3).

(n) N-(4-Ethoxyphenyl)-4-oxo-6.6-dimethyl-4,5,6,7-tetrahydro-1H-indole-3-carboxamide.

(o) N-(4-Methoxyphenyl)-4-oxo-6.6-dimethyl-4,5,6,7-tetrahydro-1H-indole-3-carboxamide.

(p) N-(2-Hydroxy-4-methylphenyl)-4-oxo-6,6-dimethyl-4,5,6,7-tetrahydro-1H-indole-3-carboxamide; mp 201-203°C.

(q) N-Phenyl-4-oxo-6-methyl-4,5,6,7-tetrahydro-1H-indole-3-carboxamide (Compound 4); mp 278-279°C.

(r) N-(2-Fluorophenyl)-4-oxo-6-methyl-4,5,6,7-tetrahydro-1H-indole-3-carboxamide (Compound 5); mp 264-265°C.

(s) N-(3-Fluorophenyl)-4-oxo-6-methyl-4.5,6,7-tetrahydro-1H-indole-3-carboxamide; mp 302-303°C.

(t) N-(4-Fluorophenyl)-4-oxo-6-methyl-4,5,6,7-tetrahydro-1H-indole-3-carboxamide; mp 262-264°C.

(u) N-(3-Methoxyphenyl)-4-oxo-6-methyl-4,5,6,7-tetrahydro-1H-indole-3-carboxamide; mp 234-235°C.

(v) N-(4-Hydroxyphenyl)-4-oxo-6-methyl-4,5,6,7-tetrahydro-1H-indole-3-carboxamide: mp 320°C.

(w) N-(2-Fluoro-4-hydroxyphenyl)-4-oxo-6-methyl-4.5,6,7-tetrahydro-1H-indole-3-carboxamide: mp 330°C.

(x) N-(2-Hydroxy-4-methoxyphenyl)-4-oxo-6-methyl-4.5,6,7-tetrahydro-1H-indole-3-carboxamide; mp 236-238°C.

(y) N-(4-Methoxyphenyl)-4-oxo-6-methyl-4,5,6,7-tetrahydro-1H-indole-3-carboxamide; mp 260-261°C.

(z) N-(2-Fluoro-4-methoxyphenyl)-4-oxo-6-methyl-4,5,6,7-tetrahydro-1H-indole-3-carboxamide (Compound 6); mp 217-219°C.

(aa) N-(4-Ethoxyphenyl)-4-oxo-6-methyl-4,5,6,7-tetrahydro-1H-indole-3-carboxamide; mp 269°C.

(bb) N-(2-Fluoro-4-ethoxyphenyl)-4-oxo-6-methyl-4,5,6,7-tetrahydro-1H-indole-3-carboxamide; mp 224-225°C.

(cc) N-(3,4-Dihydroxyphenyl)-4-oxo-6-methyl-4,5,6,7-tetrahydro-1H-indole-3-carboxamide; mp 267-269°C.

(dd) N-(2-Hydroxy-4-methylphenyl)-4-oxo-6-methyl-4,5,6,7-tetrahydro-1H-indole-3-carboxamide; mp 258-260°C.

(ee) N-(3-Thienyl)-4-oxo-6,6-dimethyl-4,5,6,7-tetrahydro-1H-indole-3-carboxamide (Compound 7).

(ff) N-(2-Thiazoyl)-4-oxo-6,6-dimethyl-4,5,6,7-tetrahydro-1H-indole-3-carboxamide.

(gg) N-(5-Methyl-2-thiazolyl)-4-oxo-6.6-dimethyl-4.5.6.7-tetrahydro-1H-indole-3-carboxamide.

(hh) N-(3-Pyridyl)-4-oxo-6.6-dimethyl-4.5.6,7-tetrahydro-1H-indole-3-carboxamide; mp 237-239°C.

(ii) N-(4-Methoxy-3-pyridyl)-4-oxo-6.6-dimethyl-4,5,6,7-tetrahydro-1H-indole-3-carboxamide; mp 217-218°C.

(jj) N-(2-Chloro-1,8-napthyridin-7-yl)-4-oxo-6,6-dimethyl-4,5,6,7-tetrahydro-1H-indole-3-carboxamide; mp 278-280°C.

(kk) N-(1,8-Napthyridin-2yl)-4-oxo-6,6-dimethyl-4,5,6,7-tetrahydro-1H-indole-3-carboxamide (compound 8); mp 389-390°C.

(ll) N-(3-Pyridyl)-4-oxo-6-methyl-4,5,6,7-tetrahydro-1H-indole-3-carboxamide; mp 225-227°C.

(mm) N-(4-Pyridyl)-4-oxo-6-methyl-4,5,6,7-tetrahydro-1H-indole-3-carboxamide; mp 280-290°C.

(nn) N-(1,8-Napthyridin-2-yl)-4-oxo-6-methyl-4,5,6,7-tetrahydro-1H-indole-3-carboxamide (Compound 9).

(oo) N-(6-Methyl-1,8-napthridin-2-yl)-4-oxo-6-methyl-4,5,6,7-tetrahydro-1H-indole-3-carboxamide; mp 338-340°C(d).

(pp) N-(2-Quinolinyl)-4-oxo-6-methyl-4,5,6,7-tetrahydro-1H-indole-3-carboxamide (Compound 10); mp 273-275°C.

(qq) N-(4-Pyridyl)-4-oxo-6,6-dimethyl-4,5,6,7-tetrahydro-1H-indole-3-carboxmide.

The invention and the manner and process of making and using it, are now described in such full, clear, concise and exact terms as to enable any person skilled in the art to which it pertains, to make and use the same. It is to be understood that the foregoing describes preferred embodiments of the present invention and that modifications may be made therein without departing from the spirit or scope of the present invention as set forth in the claims. To particularly point out and distinctly claim the subject matter regarded as invention, the following claims conclude this specification.

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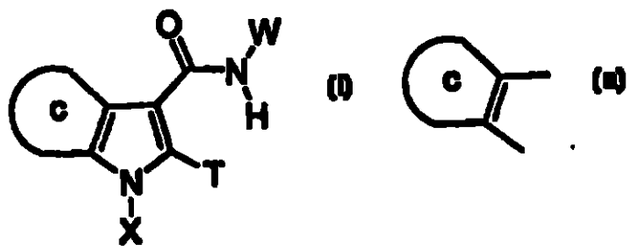
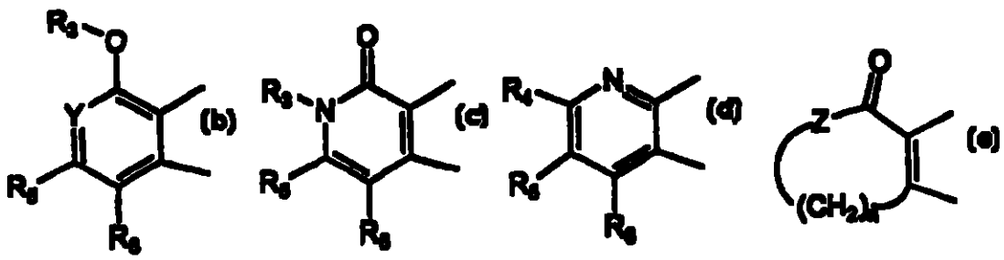
(54) Title: CERTAIN FUSED PYRROLECARBOXANILIDES; A NEW CLASS OF GABA BRAIN RECEPTOR LIGANDS





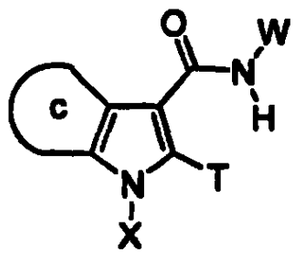
(57) Abstract

The present invention encompasses structures of formula (I) or the pharmaceutically acceptable non-toxic salts thereof wherein (a) represents (b) or (c) or (d) or (e) wherein: W represents substituted or unsubstituted phenyl; X is hydrogen, hydroxy or lower alkyl; T is hydrogen, halogen, hydroxy, nitro, amino or alkyl; R_3 is hydrogen or an organic group; R_4 is hydrogen or substituted or unsubstituted organic substituent; R_5 and R_6 represent organic, and inorganic substituents; and n is 1, 2, 3, or 4, which compounds are highly selective agonists, antagonists or inverse agonists for GABAa brain receptors or prodrugs of agonists, antagonists or inverse agonists for GABAa brain receptors. These compounds are useful in the diagnosis and treatment of anxiety, sleep and seizure disorders, overdose with benzodiazepine drugs and for enhancement of memory.

SUMMARY OF THE INVENTION

This invention provides novel compounds of Formula I which interact with a GABAa binding site, the benzodiazepine receptor.

The invention provides pharmaceutical compositions comprising compounds of Formula I. The invention also provides compounds useful in the diagnosis and treatment of anxiety, sleep and seizure disorders, overdose with benzodiazepine drugs and for enhancement of memory. Accordingly, a broad embodiment of the invention is directed to compounds of general Formula I:



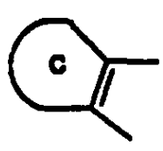
I

or the pharmaceutically acceptable non-toxic salts thereof wherein:

T is halogen, hydrogen, hydroxy, nitro, amino or lower alkoxy;

X is hydrogen, hydroxyl or lower alkyl;

W is phenyl or phenylalkyl where each phenyl is optionally substututed with up to 5 groups independently selected from halogen, hydroxy, lower alkyl, cycloalkyl having 3-7 carbon atoms, amino, mono- or dialkylamino where each alkyl is independently lower alkyl or cycloalkyl having 3-7 carbon atoms, lower alkoxy, cycloalkyl alkoxy having 3-7 carbon atoms, alkylenedioxy, or NR_1COR_2, COR_2, or $CONR_1R_2$ where R_1 and R_2 are the same or different and represent hydrogen, lower alkyl or cycloalkyl having 3-7 carbon atoms; and



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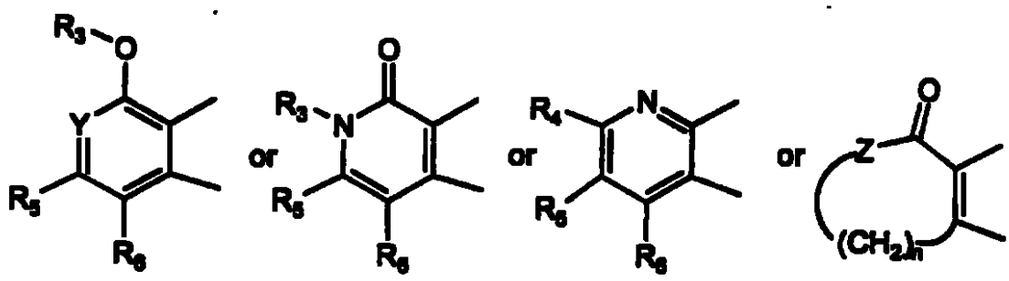


wherein:

Y represents nitrogen or C-R_4;

Z represents N-R_7 or a carbon atom substituted with R_8 and R_9, i.e., C(R_8)(R_9);

n is 1, 2, 3, or 4;

R_3 is hydrogen, phenyl, 2-, 3-, or 4-pyridyl, lower alkyl, or phenylalkyl or 2-, 3-, or 4-pyridylalkyl where each alkyl is lower alkyl;

R_4 is halogen or trifluoromethyl; or

-OR_{10}, -COR_{10}, -CO_2R_{10}, -$OCOR_{10}$, or -R_{10}, where R_{10} is hydrogen, phenyl, 2-, 3-, or 4-pyridyl, lower alkyl, or phenylalkyl or 2-, 3-, or 4-pyridylalkyl where each alkyl is lower alkyl; or

-$CONR_{11}R_{12}$ or -$(CH_2)_mNR_{11}R_{12}$, where m is 0, 1, or 2; R_{11} represents hydrogen, lower alkyl; and R_{12} is hydrogen, phenyl, 2-, 3-, or 4-pyridyl, lower alkyl, or phenylalkyl or 2-, 3-, or 4-pyridylalkyl where each alkyl is lower alkyl; or $NR_{11}R_{12}$ forms a heterocyclic group which is morpholinyl, piperidinyl, pyrrolidinyl, or N-alkyl piperazinyl;

R_5 and R_6 are the same or different and represent hydrogen, halogen, lower alkyl, or lower alkoxy;

R_7 is hydrogen, phenyl, 2-, 3-, or 4-pyridyl, lower alkyl, or phenylalkyl or 2-, 3-, or 4-pyridylalkyl where each alkyl is lower alkyl;

R_8 is hydrogen or lower alkyl; and

R_9 is -COR_{13}, -CO_2R_{13} or -R_{13}, where R_{13} is hydrogen, phenyl, 2-, 3-, or 4-pyridyl, lower alkyl, or phenylalkyl or 2-, 3-, or 4-pyridylalkyl where each alkyl is lower alkyl; or

R_9 is -$CONR_{14}R_{15}$ or -$(CH_2)_kNR_{14}R_{15}$, where k is 0, 1, or 2; R_{14} represents hydrogen, lower alkyl; and R_{15} is hydrogen, phenyl, 2-, 3-, or 4-pyridyl, lower alkyl, or phenylalkyl or 2-, 3-, or 4-pyridylalkyl where each alkyl is

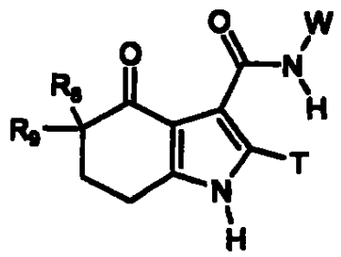
lower alkyl; or $NR_{14}R_{15}$ forms a heterocyclic group which is morpholinyl, piperidinyl, pyrrolidinyl, or N-alkyl piperazinyl.

These compounds are highly selective agonists, antagonists or inverse agonists for GABAa brain receptors or prodrugs of agonists, antagonists or inverse agonists for GABAa brain receptors. In other words, while the compounds of the invention all interact with GABAa brain receptors, they do not display identical physiologic activity. Thus, these compounds are useful in the diagnosis and treatment of anxiety, sleep and seizure disorders, overdose with benzodiazepine drugs and for enhancement of memory. For example, these compounds can easily be used to treat overdoses of benzodiazepine-type drugs as they would competitively bind to the benzodiazepine receptor.

DETAILED DESCRIPTION OF THE INVENTION

The novel compounds encompassed by the instant invention can be described by general formula I set forth above or the pharmaceutically acceptable non-toxic salts thereof.

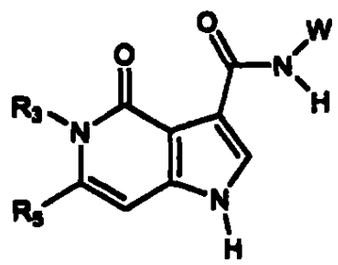
In addition, the present invention encompasses compounds of Formula II.



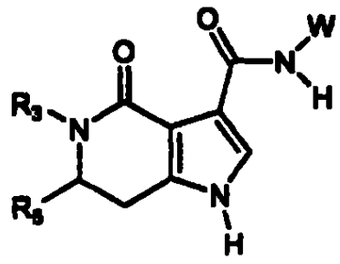
II

or the pharmaceutically acceptable non-toxic salts thereof wherein W, T, R8 and R9 are as defined above.

The present invention also encompasses compounds of Formula IIIa and IIIb:



IIIa

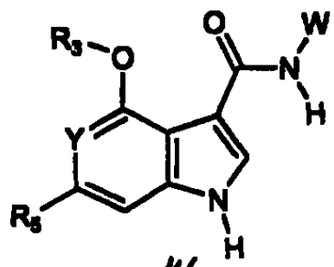


IIIb

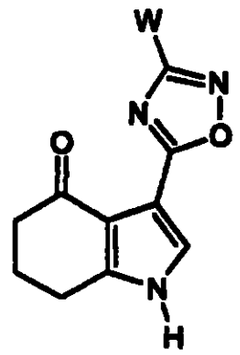
or the pharmaceutically acceptable non-toxic salts thereof wherein W, R3, and R5 are as defined above.

Preferred compounds of Formula IIIb are those where R3 is hydrogen or alkyl; and R5 is hydrogen.

The present invention also encompasses compounds of Formula IV:



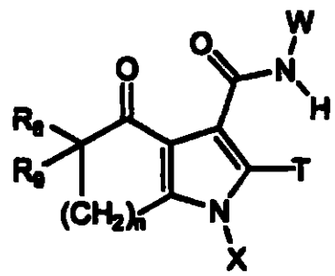
The invention further encompasses compounds of Formula XII:



XII

wherein W represents phenyl, 2- or 3-thienyl, 2-, 3-, or 4-pyridyl or 6-quinolinyl, each of which may be mono or disubstituted with halogen, cyano, hydroxy, lower alkyl, amino, mono or dialkylamino where each alkyl is independently lower alkyl, lower alkoxy, or NR_1COR_2, COR_2, $CONR_1R_2$ or CO_2R_2 where R_1 and R_2 are the same or different and represent hydrogen or lower alkyl.

Further, the present invention provides compounds of Formula XIII:



XIII

wherein W, R8 and R9 are as defined above;

T represents hydrogen, amino, or nitro;

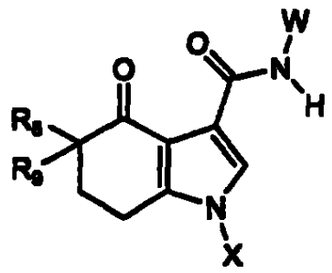
X is alkyl or hydrogen; and

n is 1 or 2.

A preferred group of compounds of Formula XIII are those where R8 and R9 are independently alkyl or hydrogen; and n is 1. Another preferred group of compounds of Formula XIII are those where R8 and R9 are independently alkyl or hydrogen; and n is 2.

Particularly preferred compounds of Formula XIII where n is 2 are those where R8 and R9 are hydrogen; and X and T are both hydrogen.

The invention also provides compounds of Formula XIV:



XIV

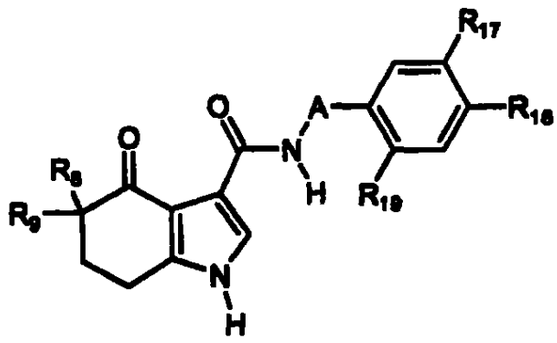
wherein W is as defined above;

R8 and R9 are independently alkyl or hydrogen; and

X is hydrogen, methyl, or ethyl.

Preferred compounds of Formula XIV are those where R8 and R9 are both hydrogen and X is hydrogen.

The present invention further provides compounds of Formula XV.



XV

R8 and R9 are as defined above;

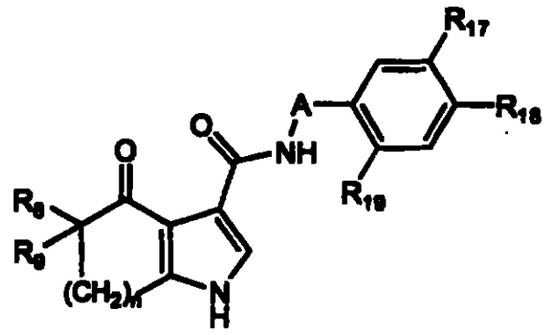
A represents an alkylene group of 1-6 carbon atoms optionally substituted with up to two alkyl groups independently having 1-3 carbon atoms;

R_{17} is hydrogen, halogen, hydroxyl, lower alkyl, lower alkoxy, amino, mono or dialkylamino where each alkyl is independently striaght or branched chain lower alkyl having 1-6 carbon atoms;

R_{18} is hydrogen, hydroxyl, lower alkyl, lower alkoxy, amino, mono or dialkylamino where each alkyl is independently striaght or branched chain lower alkyl, NR_1COR_2, COR_2, CO_2R_2 where R_1 and R_2 are as defined above, cyano, or halogen; and

R_{19} is hydrogen, hydroxyl, or halogen.

The present invention also encompasses compounds of Formula XVI.



XVI

R_8 and R_9 are as defined above;

A represents an alkylene group of 1-6 carbon atoms optionally substituted with up to two alkyl groups independently having 1-3 carbon atoms;

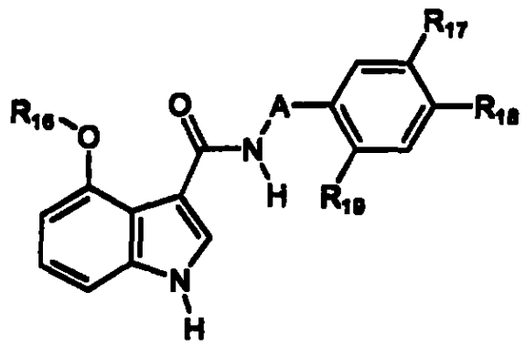
n is 1 or 2;

R_{17} is hydrogen, halogen, hydroxyl, lower alkyl, lower alkoxy, amino, mono or dialkylamino where each alkyl is independently striaght or branched chain lower alkyl having 1-6 carbon atoms;

R_{18} is hydrogen, hydroxyl, lower alkyl, lower alkoxy, amino, mono or dialkylamino where each alkyl is independently striaght or branched chain lower alkyl, NR_1COR_2, COR_2, CO_2R_2 where R_1 and R_2 are as defined above, cyano, or halogen; and

R_{19} is hydrogen, hydroxyl, or halogen.

Further, the present invention provides compounds of Formula XVII.



XVII

A represents an alkylene group of 1-6 carbon atoms optionally substituted with up to two alkyl groups independently having 1-3 carbon atoms;

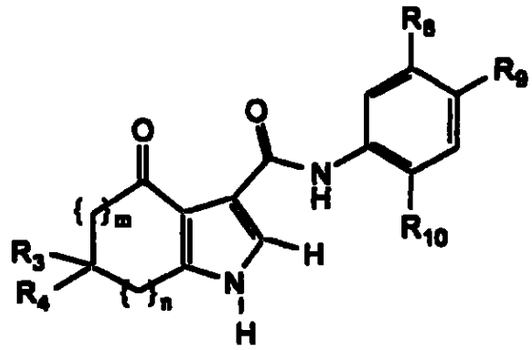
R_{16} is hydrogen, benzyl, or lower alkyl;

R_{17} is hydrogen, halogen, hydroxyl, lower alkyl, lower alkoxy, amino, mono or dialkylamino where each alkyl is independently striaght or branched chain lower alkyl having 1-6 carbon atoms;

R_{18} is hydrogen, hydroxyl, lower alkyl, lower alkoxy, amino, mono or dialkylamino where each alkyl is independently striaght or branched chain lower alkyl, NR_1COR_2, COR_2, CO_2R_2 where R_1 and R_2 are as defined above, cyano, or halogen; and

R_{19} is hydrogen, hydroxyl, or halogen.

In addition, the present invention encompasses compounds of Formula DII.



DII

wherein

R_3 and R_4 are the same or different and represent hydrogen, alkyl, COR_5 or CO_2R_5 where R_5 is alkyl or cycloalkyl having 3-7 carbon atoms, $CONR_6R_7$ where R_6 and R_7 are selected independently from hydrogen, alkyl, cycloalkyl having 3-7 carbon atoms,

phenyl, 2-,3-, or 4-pyridyl , or NR_6R_7 forms a heterocyclic group which is morpholinyl, piperidinyl, pyrrolidinyl, or N-alkyl piperazinyl; or

R_3-R_4 together represent a cyclic moiety having 3-7 carbon atoms;

R_8 is hydrogen, halogen, hydroxyl, alkyl, alkoxy, cycloalkyl alkoxy having 3-7 carbon atoms, amino, mono- or dialkylamino; and

R_9 is hydrogen, halogen, cyano, hydroxy, alkyl, alkoxy, cycloalkyl alkoxy having 3-7 carbon atoms, amino, mono- or dialkylamino, NR_1COR_2, COR_2, or CO_2R_2 where R_1 and R_2 are the same or different and represent hydrogen, alkyl, or cycloalkyl having 3-7 carbon atoms; and

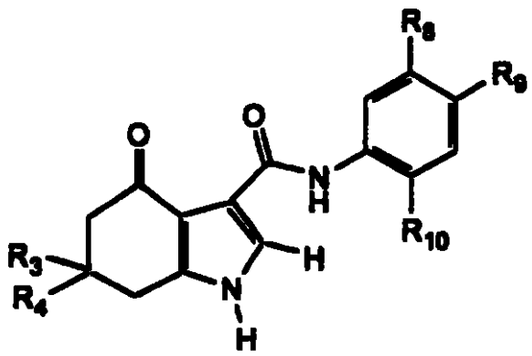
R_{10} is hydrogen, halogen, hydroxyl, alkyl, alkoxy, amino, mono- or dialkylamino;

m is 0, 1, or 2; and

n is 0, 1, or 2.

Preferred compounds of Formula DII are those where the phenyl group is mono-, di-, or trisubstituted in the 2,4, and/or5 positions relative to the point of attachment of the phenyl ringto the amide nitrogen.

In addition, the present invention encompasses compounds of Formula DIII.



DIII

wherein

R_3 and R_4 are the same or different and represent hydrogen or alkyl;

R_8 is hydrogen, halogen, hydroxyl, alkyl, alkoxy, cycloalkyl alkoxy having 3-7 carbon atoms, amino, mono- or dialkylamino; and

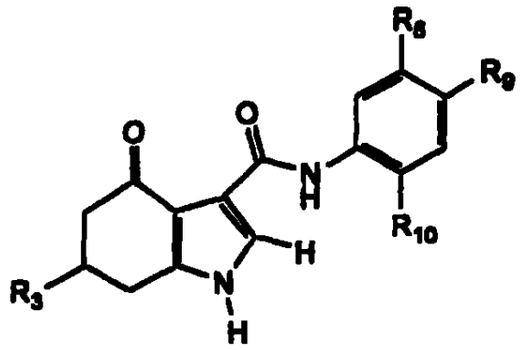
R_9 is hydrogen, halogen, cyano, hydroxy, alkyl, alkoxy, cycloalkyl alkoxy having 3-7 carbon atoms, amino, mono- or dialkylamino, NR_1COR_2, COR_2, or CO_2R_2 where R_1 and

R_2 are the same or different and represent hydrogen, alkyl, or cycloalkyl having 3-7 carbon atoms; and

R_{10} is hydrogen, halogen, hydroxyl, alkyl, alkoxy, amino, mono- or dialkylamino.

Preferred compounds of Formula DIII are those where the phenyl group is mono-, di-, or trisubstituted in the 2,4, and/or 5 positions relative to the point of attachment of the phenyl ring to the amide nitrogen. Particularly preferred compounds of Formula DIII are those where the phenyl group in trisubstituted in the 2,4, and 5 positions relative to the point of attachment of the phenyl ring to the amide nitrogen, and R_8, R_9, and R_{10} are independently selected from hyrogen, halogen, hydroxy, alkoxy, and alkyl, provided that not all of R_8, R_9, and R_{10} are hydrogen.

In addition, the present invention encompasses compounds of Formula DIV.



DIV

wherein

R_3 represents alkyl;

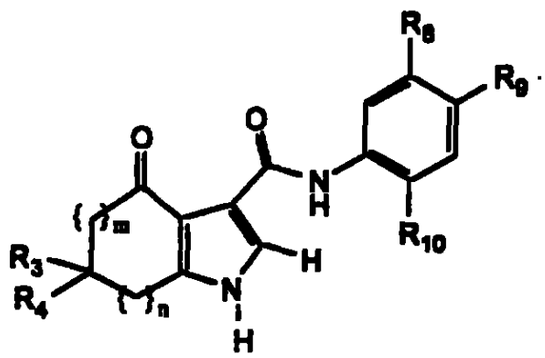
R_8 is hydrogen, halogen, hydroxyl, alkyl, alkoxy, cycloalkyl alkoxy having 3-7 carbon atoms, amino, mono- or dialkylamino; and

R_9 is hydrogen, halogen, cyano, hydroxy, alkyl, alkoxy, cycloalkyl alkoxy having 3-7 carbon atoms, amino, mono- or dialkylamino, NR_1COR_2, COR_2, or CO_2R_2 where R_1 and R_2 are the same or different and represent hydrogen, alkyl, or cycloalkyl having 3-7 carbon atoms; and

R_{10} is hydrogen, halogen, hydroxyl, alkyl, alkoxy, amino, mono- or dialkylamino.

Preferred compounds of Formula DIV are those where R_8, R_9, and R_{10} are independently selected from hydrogen, halogen, hydroxy, alkoxy, and alkyl, provided that not all of R_8, R_9, and R_{10} are hydrogen.

In addition, the present invention encompasses compounds of Formula DV.



DVI

wherein

q is an integer of from 2-6;

R8 is hydrogen, halogen, hydroxyl, alkyl, alkoxy, cycloalkyl alkoxy having 3-7 carbon atoms, amino, mono- or dialkylamino; and

R9 is hydrogen, halogen, cyano, hydroxy, alkyl, alkoxy, cycloalkyl alkoxy having 3-7 carbon atoms, amino, mono- or dialkylamino, NR_1COR_2, COR_2, or CO_2R_2 where R_1 and R_2 are the same or different and represent hydrogen, alkyl, or cycloalkyl having 3-7 carbon atoms; and

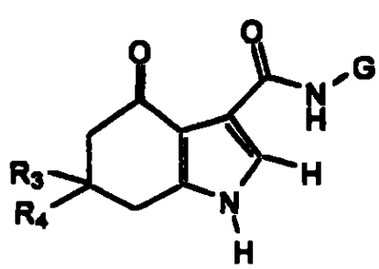
R_{10} is hydrogen, halogen, hydroxyl, alkyl, alkoxy, amino, mono- or dialkylamino;

m is 0, 1, or 2; and

n is 0, 1, or 2.

Preferred compounds of Formula DVI are those where R_8, R_9, and R_{10} are independently selected from hydrogen, halogen, hydroxy, alkoxy, and alkyl, provided that not all of R_8, R_9, and R_{10} are hydrogen.

In addition, the present invention encompasses compounds of Formula DVII.



DVII

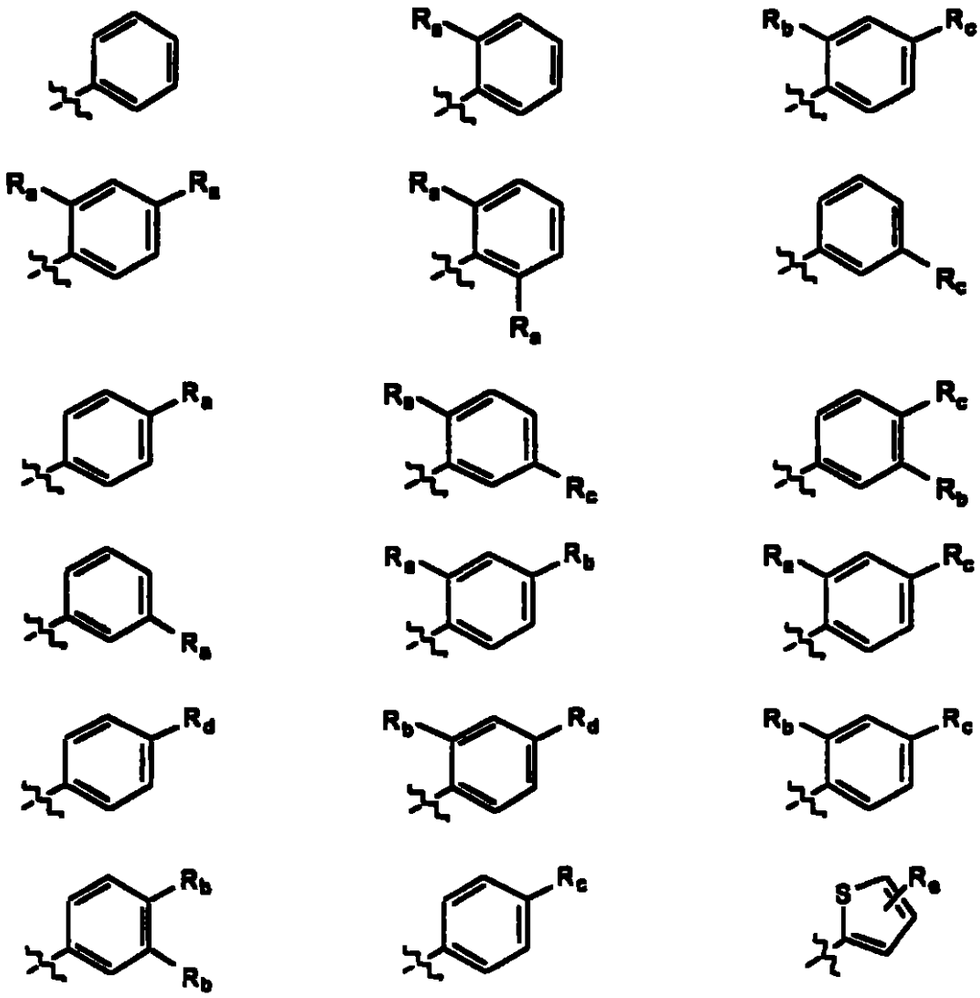
where

G represents aryl or heteroary such as, for example, thienyl, thiazolyl, pyridyl, napthyridinyl, quinolinyl, or phenyl, each of which is optionaly mono-, di- or trisubstituted with halogen alkyl alkoxy, or hydroxy; and

R3 and R4 are the same or different and represent hydrogen or alkyl, provided that not both R3 and R4 are hydrogen.

Preferred compounds of Formula DVII are those where R3 and R4 are C_{1-3} alkyl, and more preferably methyl. Other preferred compounds of Formula DVII are those where R3 is hydrogen and R4 is C_{1-3} alkyl, and more preferably R4 is methyl.

Preferred compounds of Formula DVII include a G group selected from the following:



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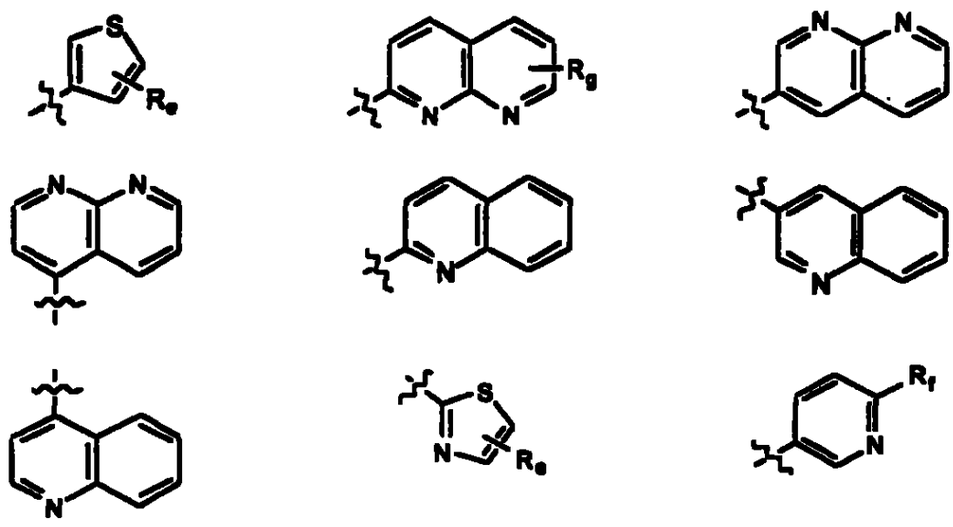
432



In the above G groups, the following definitions apply:

R_a is halogen;

R_b is hydroxy;

R_c represents alkoxy;

R_d represents alkyl;

R_e represents hydrogen or R_d;

R_f represents hydrogen, or R_c; and

R_g represents hydrogen, R_a or R_c.

In those formulas where more than one of the same substituent appears, those substituents are the same or different.

Particularly preffered R_a groups in G are fluorine. Particularly preferred R_c groups in G are methoxy and ethoxy. Particularly preferred R_d groups in G are methyl and ethyl.

Representative compounds of the invention are shown below in Table 1.

Table 1

methanesulfonic, nitric, benzoic, citric, tartaric, maleic, hydroiodic, alkanoic such as acetic, HOOC-$(CH_2)_n$-COOH where n is 0-4, and the like. Those skilled in the art will recognize a wide variety of non-toxic pharmaceutically acceptable addition salts.

The present invention also encompasses the prodrugs, preferably acylated prodrugs, of the compounds of Formula I. Those skilled in the art will recognize various synthetic methodologies which may be employed to prepare non-toxic pharmaceutically acceptable addition salts and acylated prodrugs of the compounds encompassed by Formula I.

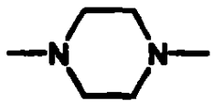
By "alkyl" and "lower alkyl" in the present invention is meant straight or branched chain alkyl groups having 1-6 carbon atoms, such as, for example, methyl, ethyl, propyl, isopropyl, n-butyl, sec-butyl, tert-butyl, pentyl, 2-pentyl, isopentyl, neopentyl, hexyl, 2-hexyl, 3-hexyl, and 3-methylpentyl.

By "phenylalkyl" as used herein is meant a phenyl group covalently bonded to an alkyl group as defined above and the alkyl group is covalently bonded to another moiety, such as, for example, a nitrogen atom.

By "alkoxy" and "lower alkoxy" in the present invention is meant straight or branched chain alkoxy groups having 1-6 carbon atoms, such as, for example, methoxy, ethoxy, propoxy, isopropoxy, n-butoxy, sec-butoxy, tert-butoxy, pentoxy, 2-pentyl, isopentoxy, neopentoxy, hexoxy, 2-hexoxy, 3-hexoxy, and 3-methylpentoxy.

By the term "halogen" in the present invention is meant fluorine, bromine, chlorine, and iodine.

By "N-alkylpiperazyl" in the invention is meant radicals of the formula:



where R is a lower alkyl as defined above.

By "monoalkylamino" as used herein is meant an amino substitutent substituted with one (1) alkyl group where the alkyl group is lower alkyl as defined above.

By "dialkylamino" as used herein is meant an amino substitutent substituted with two (2) alkyl groups where the alkyl groups are independently lower alkyl groups as defined above.

By "alkylenedioxy" as used herein is meant a group of the formula -O-A-O- where A represents C_1-C_3 alkylene optinally substituted with up to two C_1-C_2 alkyl groups and each oxygen atom is covalently bound to the aromatic ring, i.e., the phenyl group. The oxygen

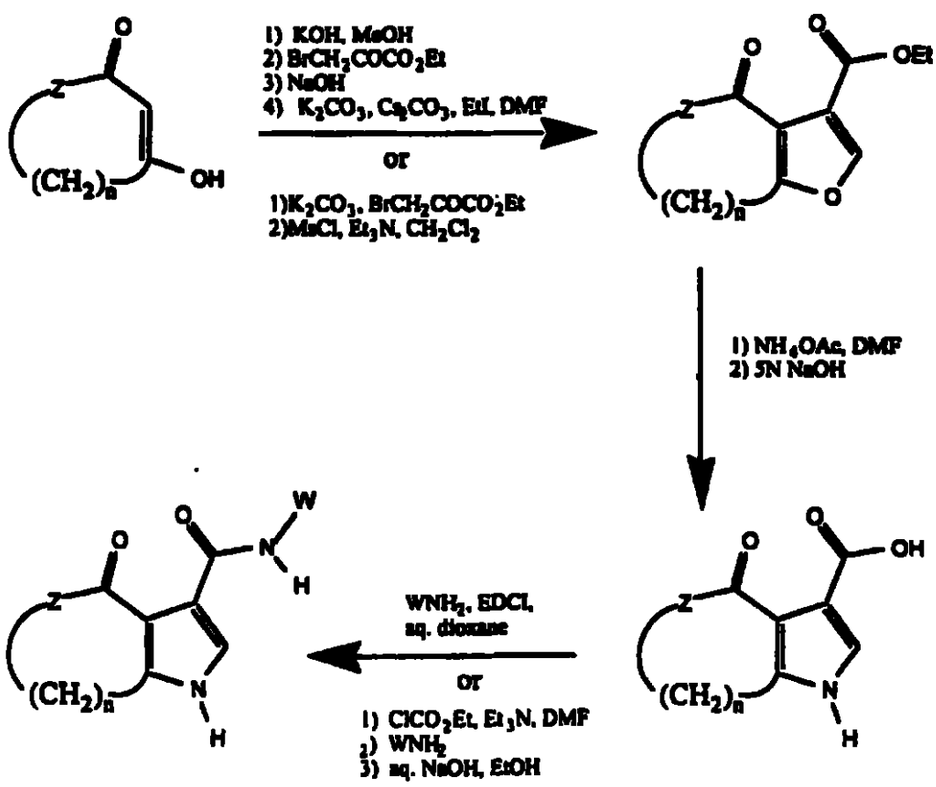
or dissolved in the vehicle. Advantageously, adjuvants such as local anaesthetics, preservatives and buffering agents can be dissolved in the vehicle.

Dosage levels of the order of from about 0.1 mg to about 140 mg per kilogram of body weight per day are useful in the treatment of the above-indicated conditions (about 0.5 mg to about 7 g per patient per day). The amount of active ingredient that may be combined with the carrier materials to produce a single dosage form will vary depending upon the host treated and the particular mode of administration. Dosage unit forms will generally contain between from about 1 mg to about 500 mg of an active ingredient.

It will be understood, however, that the specific dose level for any particular patient will depend upon a variety of factors including the activity of the specific compound employed, the age, body weight, general health, sex, diet, time of administration, route of administration, and rate of excretion, drug combination and the severity of the particular disease undergoing therapy.

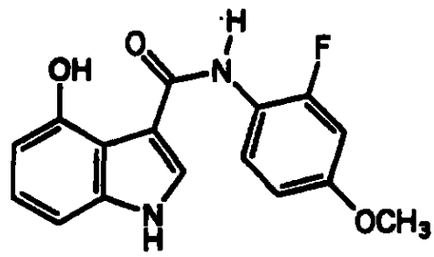
An illustration of the preparation of compounds of the present invention is given in Schemes I and II.

Scheme I



where W, Z, and n are as defined above.

Example 3



(Compound 2)

N-(2-Fluoro-4-methoxyphenyl)-4-benzyloxy-1H-indole-3-carboxamide (1.34 g, 3.4 mmol), prepared using the method above, was slurried with 10% palladium on carbon (134 mg) in ethanol (35 mL) in a Parr bottle and placed under a hydrogen atmosphere (50 psi) for 5 h. Methanol (5 ml) was added and the mixture returned to the Hydrogen atmosphere for an additional 18 h. The solution was filtered through Celite, concentrated *in vacuo*, and the residue purified by flash chromatography to afford N-(2-fluoro-4-methoxyphenyl)-4-hydroxy-1H-indole-3-carboxamide (Compound 2) as a beige solid; mp 259-261°C (d).

Example 4

The following compounds were prepared essentially according to the procedures described in Examples 1-3:

(a) N-(4-Ethoxyphenyl)-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxamide (Compound 3); mp 217-218°C.

(b) N-(4-Ethoxyphenyl)-4-methoxy-1H-indole-3-carboxamide (Compound 4); mp 259-261°C (d).

(c) N-(3-Ethoxyphenyl)-4-methoxy-1H-indole-3-carboxamide (Compound 5).

(d) N-(2-Fluoro-4-methoxyphenyl)-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxamide (Compound 6).

(e) N-(2-Fluoro-4-ethoxyphenyl)-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxamide (Compound 7).

(f) N-(4-Methoxyphenyl)-4-methoxy-1H-indole-3-carboxamide (Compound 8).

(g) N-(2-Fluoro-4-ethoxyphenyl)-4-methoxy-1H-indole-3-carboxamide (Compound 9).

(h) N-(4-Cyanophenyl)-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxamide (Compound 10); mp 287-288°C.

(i) N-(3-Methoxyphenyl)-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxamide (Compound 11); mp 220-223°C.

(j) N-(4-Acetamidophenyl)-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxamide (Compound 12); mp 339-341°C.

(k) N-(4-Chlorophenyl)-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxamide (Compound 13).

(l) N-(2-Fluoro-4-methoxyphenyl)-4-benzyloxy-1H-indole-3-carboxamide (Compound 14).

(m) N-(4-Acetylphenyl)-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxamide (Compound 15).

(n) N-(2-Fluoro-5-methoxyphenyl)-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxamide (Compound 16).

(o) N-(4-Carbomethoxyphenyl)-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxamide (Compound 17); mp 261-262°C.

(p) N-(4-Carboxyphenyl)-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxamide (Compound 18).

(q) N-(4-Ethoxyphenyl)-4-hydroxy-1H-indole-3-carboxamide (Compound 19).

(r) N-(3-Ethoxyphenyl)-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxamide (Compound 20).

(s) N-(2-Fluoro-4-methoxyphenyl)-4-benzyloxy-1H-indole-3-carboxamide (Compound 21).

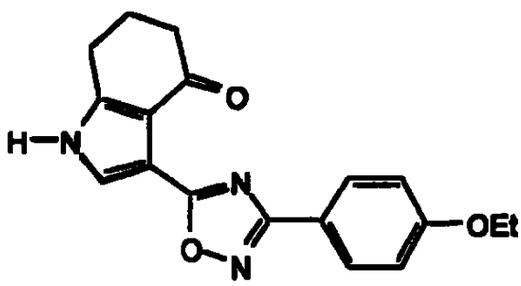
(t) N-(4-Isopropoxyphenyl)-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxamide (Compound 22).

(u) N-(4-Fluorophenyl)-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxamide (Compound 23).

(v) N-(4-Hydroxyphenyl)-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxamide (Compound 24).

(w) N-(4-Aminophenyl)-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxamide (Compound 25).

(x) N-(3-Fluoro-4-methoxyphenyl)-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxamide (Compound 26); mp: 230-232°C.



(y) (compound 27)

(z) N-(2-Fluoro-4-isopropoxyphenyl)-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxamide (Compound 28).

(aa) N-(4-Fluorophenyl)-4-oxo-5,5-dimethyl-4,5,6,7-tetrahydro-1H-indole-3-carboxamide (Compound 29).

(ab) N-(2-Fluoro-4-methoxyphenyl)-4-oxo-5,5-dimethyl-4,5,6,7-tetrahydro-1H-indole-3-carboxamide (Compound 30); mp 193-194°C.

(ac) N-(4-Ethoxyphenyl)-4-oxo-5,5-dimethyl-4,5,6,7-tetrahydro-1H-indole-3-carboxamide (Compound 31).

(ad) N-(4-Methoxyphenyl)-4-oxo-5,5-dimethyl-4,5,6,7-tetrahydro-1H-indole-3-carboxamide (Compound 32).

(ae) N-(2-Methoxy-5-bromophenyl)-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxamide (Compound 33).

(af) N-(3,4-Dihydroxyphenyl)-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxamide (Compound 34).

(ag) N-Phenyl-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxamide (Compound 35) (Also, see Example 5).

(ah) N-(2-Fluoro-4-hydroxyphenyl)-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxamide (Compound 36).

(ai) N-(2-Fluoro-4-methoxyphenyl)-4-oxo-6,6-dimethyl-4,5,6,7-tetrahydro-1H-indole-3-carboxamide (Compound 37), mp 213-215°C.

(aj) N-(2-Fluoro-4-ethoxyphenyl)-4-oxo-6,6-dimethyl-4,5,6,7-tetrahydro-1H-indole-3-carboxamide (Compound 38).

(ak) N-(4-Ethoxyphenyl)-4-oxo-6,6-dimethyl-4,5,6,7-tetrahydro-1H-indole-3-carboxamide (Compound 39).

(al) N-(4-Methylphenyl)-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxamide (Compound 40).

(am) N-(3-Methylphenyl)-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxamide (Compound 41).

(an) N-(2-Amino-4-methylphenyl)-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxamide (Compound 42).

(ao) N-(4-Methylaminophenyl)-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxamide (Compound 43).

(ap) N-Phenyl-4-oxo-6,6-dimethyl-4,5,6,7-tetrahydro-1H-indole-3-carboxamide (Compound 44).

(aq) N-(3-Hydroxy-4-methoxyphenyl)-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxamide (Compound 45).

(ar) N-(2-Fluorophenyl)-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxamide (Compound 46).

(as) N-(3-Fluorophenyl)-4-oxo-6,6-dimethyl-4,5,6,7-tetrahydro-1H-indole-3-carboxamide (Compound 47).

(at) N-(2-(4-Hydroxyphenyl)ethyl)-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxamide (Compound 48).

(au) N-(2-(4-Ethoxyphenyl)ethyl)-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxamide (Compound 49).

(av) N-(4-Ethoxyphenyl)-4-oxo-1,4,5,6,7,8-hexahydro-cyclohepta[b]pyrrole-3-carboxamide (Compound 50) (alternate name: (10-aza-6-oxobicyclo[5.3.0]deca-1(7),8-dien-8-yl)-N-(4-ethoxyphenyl)formamide).

(aw) N-(2-Fluorophenyl)-4-oxo-1,4,5,6,7,8-hexahydro-cyclohepta[b]pyrrole-3-carboxamide (Compound 51) (alternate name: (10-aza-6-oxobicyclo[5.3.0]deca-1(7),8-dien-8-yl)-N-(2-fluorophenyl)formamide).

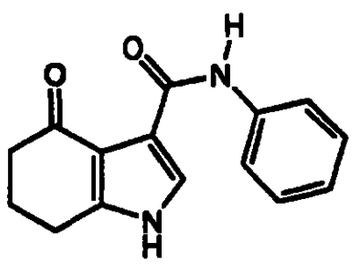
(ax) N-Phenyl-4-oxo-1,4,5,6,7,8-hexahydro-cyclohepta[b]pyrrole-3-carboxamide (Compound 52) (alternate name: (10-aza-6-oxobicyclo[5.3.0]deca-1(7),8-dien-8-yl)-N-phenylformamide).

(ay) N-(2-Fluoro-4-methoxyphenyl)-4-oxo-1,4,5,6,7,8-hexahydro-cyclohepta[b]pyrrole-3-carboxamide (Compound 53) (alternate name: (10-aza-6-oxobicyclo[5.3.0]deca-1(7),8-dien-8-yl)-N-(2-fluoro-4-methoxyphenyl)formamide).

(az) N-(2-Fluoro-4-ethoxyphenyl)-4-oxo-1,4,5,6,7,8-hexahydro-cyclohepta[b]pyrrole-3-carboxamide (Compound 54) (alternate name: (10-aza-6-oxobicyclo[5.3.0]deca-1(7),8-dien-8-yl)-N-(2-fluoro-4-ethoxyphenyl)formamide).

(ba) N-(4-Fluoro-2-hydroxyphenyl)-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxamide (Compound 55).

Example 5



Compound 35

A mixture of 4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxylic acid (179 mg, 1 mmol), aniline (0.46 mL, 5 mmol), and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide

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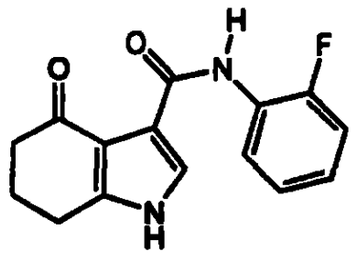
hydrochloride (959 mg, 5 mmol) in 50% aqueous dioxane (10 mL) was allowed to stir at ambient temperature for 17.5 hours, then concentrated *in vacuo* . The residue was cooled in an ice water bath, aqueous 3.6 N hydrochloric acid was added, and the precipitate collected, rinsed with aqueous 3.6 N hydrochloric acid then water and dried. Recrystallization from ethyl alcohol afforded N-phenyl-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxamide (Compound 35) (164 mg). mp 225-226° C.

Example 6



Compound 46

To a solution of 4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxylic acid (538 mg, 3 mmol) and triethylamine (0.88 mL, 6.3 mmol) in N,N-dimethylformamide (15 mL) at 0° C was added ethyl chloroformate (0.57 mL, 6 mmol). After stirring at 0° C for 45 minutes, 2-fluoroaniline (0.58 mL, 6 mmol) wad added. The mixture was stirred for an additional 45 minutes, then allowed to stir at ambient temperature for 14 hours. The mixture was poured into aqueous 1.2 N hydrochloric acid and extracted 2X with ethyl acetate. The combined organic layers were washed with water, dried over magnesium sulfate, filtered, and concentrated *in vacuo* . To the residue was added aqueous 1N sodium hydroxide (10 mL) and ethyl alcohol (2 mL) and the mixture heated at reflux for 4.5 hours. After cooling in an ice water bath, the mixture was acidified with aqueous hydrochloric acid, the precipitate collected, rinsed with water and dried. Recrystallization from ethyl alcohol afforded N-(2-fluorophenyl)-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxamide (Compound 46) (530 mg). mp 238-240° C.

DG 204

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US005723462A

United States Patent [19]

Albaugh et al.

[11] Patent Number: 5,723,462

[45] Date of Patent: Mar. 3, 1998

[54] CERTAIN FUSED PYRROLECARBOXAMIDES A NEW CLASS OF GABA BRAIN RECEPTOR LIGANDS

[75] Inventors: Pamela Albaugh, Clinton; Gang Liu, Branford; Alan Hutchison, Madison, all of Conn.

[73] Assignee: Neurogen Corporation, Branford, Conn.

[21] Appl. No.: 639,166

[22] Filed: Apr. 26, 1996

[51] Int. Cl.[6] C07D 239/70; C07D 209/18; C07D 275/02; A61K 31/425

[52] U.S. Cl. 514/249; 514/365; 514/371; 544/349; 544/353; 544/356; 544/372; 544/373; 544/144; 548/146; 548/190; 548/195; 546/192; 546/201; 546/277.4; 546/278.1

[58] Field of Search 544/144, 349, 544/353, 356, 373; 546/192, 201, 277.4, 278.1; 548/146, 190, 195, 492; 514/249, 365, 371

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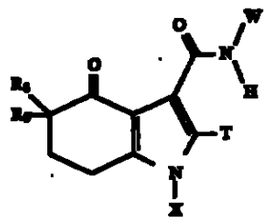
Primary Examiner—John M. Ford
Assistant Examiner—Sabiha N. Qazi
Attorney, Agent, or Firm—McDonnell Boehnen Hulbert & Berghoff

[57] ABSTRACT

Disclosed are compounds of formula I:



I

wherein

R_a and R_b independently represent hydrogen or organic substituents;

W represents optionally substituted thiazolyl or quinoxalinyl;

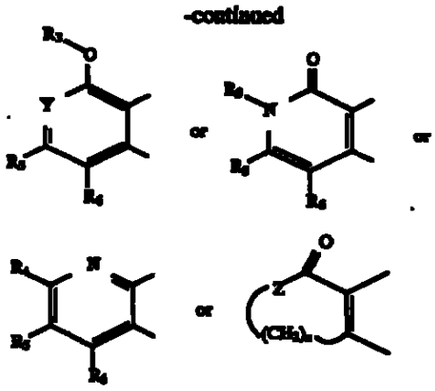
X is hydrogen, hydroxy or lower alkyl; and

T is hydrogen, halogen, hydroxy, nitro, amino or alkyl.

which compounds are highly selective agonists, antagonists or inverse agonists for GABAa brain receptors or prodrugs of agonists, antagonists or inverse agonists for GABAa brain receptor. These compounds are useful in the diagnosis and treatment of anxiety, sleep and seizure disorders, overdose with benzodiazepine drugs and for enhancement of memory.

11 Claims, No Drawings

-continued



wherein:

Y represents nitrogen or C—R_4;

Z represents N—R_7 or a carbon atom substituted with R_8 and R_9, i.e., C(R_8)(R_9); n is 1, 2, 3, or 4;

R_3 is hydrogen, phenyl, 2-, 3-, or 4-pyridyl, straight or branched chain lower alkyl having 1–6 carbon atoms, or phenylalkyl or 2-, 3, or 4-pyridylalkyl where each alkyl is straight or branched chain lower alkyl having 1–6 carbon atoms;

R_4 is halogen or trifluoromethyl; or

—OR_{10}, —COR_{10}, —CO_2R_{10}, —$OCOR_{10}$, or —R_{10}, where R_{10} is hydrogen, phenyl, 2-,3, or 4-pyridyl, straight or branched chain lower alkyl having 1–6 carbon atoms, or phenylalkyl or 2-, 3-, or 4-pyridylalkyl where each alkyl is straight or branched chain lower alkyl having 1–6 carbon atoms; or

—$CONR_{11}R_{12}$ or —$(CH_2)_mNR_{11}R_{12}$, where m is 0, 1, or 2; R_{11} represents hydrogen, straight or branched chain lower alkyl having 1–6 carbon atoms; and R_{12} is hydrogen, phenyl, 2-, 3-, or 4-pyridyl, straight or branched chain lower alkyl having 1–6 carbon atoms, or phenylalkyl or 2-, 3-, or 4-pyridylalkyl where each alkyl is straight or branched chain lower alkyl having 1–6 carbon atoms; or $NR_{11}R_{12}$ forms a heterocyclic group which is morpholinyl, piperidinyl, pyrrolidinyl, or N-alkyl piperazinyl;

R_5 and R_6 are the same or different and represent hydrogen, halogen, straight or branched chain lower alkyl having 1–6 carbon atoms, or straight or branched chain lower alkoxy having 1–6 carbon atoms;

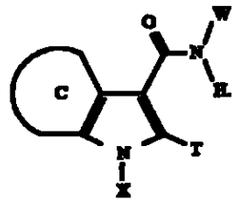
R_7 is hydrogen, phenyl, 2-, 3-, or 4-pyridyl, straight or branched chain lower alkyl having 1–6 carbon atoms, or phenylalkyl or 2-, 3-, or 4-pyridylalkyl where each alkyl is straight or branched chain lower alkyl having 1–6 carbon atoms;

R_8 is hydrogen or straight or branched chain lower alkyl having 1–6 carbon atoms; and

R_9 is —COR_{13}, —CO_2R_{13} or —R_{13}, where R_{13} is hydrogen, phenyl, 2-, 3-, or 4-pyridyl, straight or branched chain lower alkyl having 1–6 carbon atoms, or phenylalkyl or 2-, 3-, or 4-pyridylalkyl where each alkyl is straight or branched chain lower alkyl having 1–6 carbon atoms; or

—$CONR_{14}R_{15}$ or —$(CH_2)_kNR_{14}R_{15}$, where k is 0, 1, or 2; R_{14} represents hydrogen, straight or branched chain lower alkyl having 1–6 carbon atoms; and R_{15} is hydrogen, phenyl, 2-, 3-, or 4-pyridyl, straight or branched chain lower alkyl having 1–6 carbon atoms, or phenylalkyl or 2-, 3-, or 4-pyridylalkyl where each alkyl is straight or branched chain lower alkyl having 1–6 carbon atoms; or $NR_{14}R_{15}$ forms a heterocyclic group which is morpholinyl, piperidinyl, pyrrolidinyl, or N-alkyl piperazinyl.

International Application No. PCT/US94/12300, filed Oct. 26, 1994 and published May 4, 1995, the disclosure of which is incorporated herein in its entirety, also discloses pyrrole derivatives of the general formula described in U.S. Pat. No. 5,484,944, i.e.,

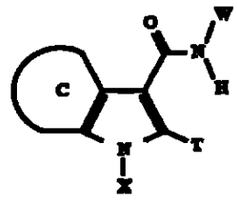


The substituents on this general formula are as defined in U.S. Pat. No. 5,484,944. In addition, U.S. Application Ser. No. 08/473,509, filed Jun. 7, 1995, the disclosure of which is incorporated herein in its entirety, discloses compounds of the general formula set forth in U.S. Pat. No. 5,484,944.

SUMMARY OF THE INVENTION

This invention provides novel compounds of Formula I which interact with a $GABA_A$ binding site, the benzodiazepine receptor.

The invention provides pharmaceutical compositions comprising compounds of Formula I. The invention also provides compounds useful in the diagnosis and treatment of anxiety, sleep and seizure disorders, overdose with benzodiazepine drugs and for enhancement of memory. Accordingly, a broad embodiment of the invention is directed to compounds of general Formula I:



I

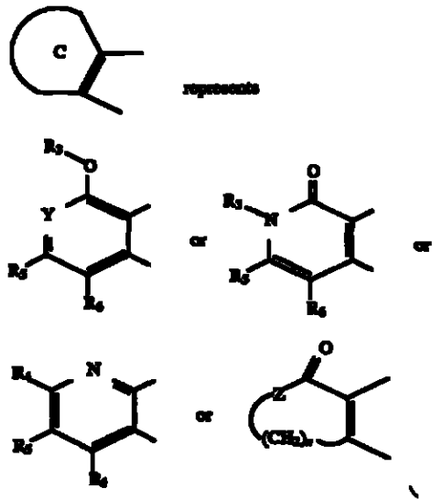
or the pharmaceutically acceptable non-toxic salts thereof wherein:

T is halogen, hydrogen, hydroxy, nitro, amino or straight or branched chain lower alkoxy having 1–6 carbon atoms;

X is hydrogen, hydroxyl or straight or branched chain lower alkyl having 1–6 carbon atoms;

W is an heteroaryl which may be mono or multi-substituted independently with halogen, cyano, hydroxy, straight or branched chain lower alkyl having 1–6 carbon atoms or cycloalkyl having 3–7 carbon atoms, amino, mono or dialkylamino where each alkyl is independently straight or branched chain lower alkyl having 1–6 carbon atoms or cycloalkyl having 3–7 carbon atoms, straight or branched chain lower alkoxy having 1–6 carbon atoms, cycloalkyl alkoxy having 3–7 carbon atoms, or NR_1COR_2, COR_2, $CONR_1R_2$ or CO_2R_2 where R_1 and R_2 are the same or different and represent hydrogen or straight or branched chain lower

alkyl having 1–6 carbon atoms or cycloalkyl having 3–7 carbon atoms; and



wherein:

Y represents nitrogen or C—R_4;

Z represents N—R_7 or a carbon atom substituted with R_8 and R_9, i.e., $C(R_8)(R_9)$;

n is 1, 2, 3, or 4;

R_3 is hydrogen, phenyl, 2-, 3- or 4-pyridyl, straight or branched chain lower alkyl having 1–6 carbon atoms, or phenylalkyl or 2-, 3- or 4-pyridylalkyl where each alkyl is straight or branched chain lower alkyl having 1–6 carbon atoms;

R_4 is hydrogen, halogen or trifluoromethyl; or —OR_{10}, —COR_{10}, —CO_2R_{10}, —$OCOR_{10}$, or —R_{10}, where R_{10} is hydrogen, phenyl, 2-, 3- or 4-pyridyl, straight or branched chain lower alkyl having 1–6 carbon atoms, or phenylalkyl or 2-, 3- or 4-pyridylalkyl where each alkyl is straight or branched chain lower alkyl having 1–6 carbon atoms; or

—$CONR_{11}R_{12}$ or —$(CH_2)_mNR_{11}R_{12}$, where m is 0, 1, or 2; R_{11} represents hydrogen, straight or branched chain lower alkyl having 1–6 carbon atoms; and R_{12} is hydrogen, phenyl, 2-, 3- or 4-pyridyl, straight or branched chain lower alkyl having 1–6 carbon atoms, or phenylalkyl or 2-, 3- or 4-pyridylalkyl where each alkyl is straight or branched chain lower alkyl having 1–6 carbon atoms; or $NR_{11}R_{12}$ forms a heterocyclic group which is morpholinyl, piperidinyl, pyrrolidinyl, or N-alkyl piperazinyl;

R_5 and R_6 are the same or different and represent hydrogen, halogen, straight or branched chain lower alkyl having 1–6 carbon atoms, or straight or branched chain lower alkoxy having 1–6 carbon atoms;

R_7 is hydrogen, phenyl, 2-, 3- or 4-pyridyl, straight or branched chain lower alkyl having 1–6 carbon atoms, or phenylalkyl or 2-3-, or 4-pyridylalkyl where each alkyl is straight or branched chain lower alkyl having 1–6 carbon atoms;

R_8 is hydrogen or straight or branched chain lower alkyl having 1–6 carbon atoms; and

R_9 is —COR_{13}, —CO_2R_{13} or —R_{13}, where R_{13} is hydrogen, phenyl, 2-, 3- or 4-pyridyl, straight or branched chain lower alkyl having 1–6 carbon atoms, or phenylalkyl or 2-, 3-, or 4-pyridylalkyl where each alkyl is straight or branched chain lower alkyl having 1-6 carbon atoms; or

R_9 is —$CONR_{14}R_{15}$ or —$(CH_2)_kNR_{14}R_{15}$, where k is 0, 1, or 2; R_{14} represents hydrogen, straight or branched chain lower alkyl having 1–6 carbon atoms; and R_{15} is hydrogen, phenyl, 2-, 3-, or 4-pyridyl, straight or branched chain lower alkyl having 1–6 carbon atoms, or phenylalkyl or 2-, 3- or 4-pyridylalkyl where each alkyl is straight or branched chain lower alkyl having 1–6 carbon atoms; or $NR_{14}R_{15}$ forms a heterocyclic group which is morpholinyl, piperidinyl, pyrrolidinyl, or N-alkyl piperazinyl.

These compounds are highly selective agonists, antagonists or inverse agonists for GABAa brain receptors or prodrugs of agonists, antagonists or inverse agonists for GABAa brain receptors. In other words, while the compounds of the invention all interact with GABAa brain receptors, they do not display identical physiological activity. Thus, these compounds are useful in the diagnosis and treatment of anxiety, sleep and seizure disorders, overdose with benzodiazepine drugs and for enhancement of memory. For example, these compounds can easily be used to treat overdoses of benzodiazepine-type drugs as they would competitively bind to the benzodiazepine receptor.

DETAILED DESCRIPTION OF THE INVENTION

By heteroaryl herein is meant aromatic ring systems comprising one or more 5-, 6-, or 7-membered rings containing at least one and up to four heteroatoms selected from nitrogen, oxygen, or sulfur. Such heteroaryl groups include, for example, thiazyl, furanyl, thiazolyl, imidazolyl, (is) oxazolyl, pyridyl, pyrimidinyl, (iso)quinolinyl, napthyridinyl, benzimidazolyl, benzoxazolyl. Other examples of heteroaryl groups are pyrrolyl, pyrazolyl, pyrazinyl, pyridazinyl, and phthalazinyl.

The heteroaryl groups herein are systems characterized by $4n+2\pi$ electrons, where n is an integer.

Each of these heteroaryl groups can optionally be mono- or polysubstituted with groups selected independently from, for example, halogen, lower alkyl, lower alkoxy, lower alkylthio, trifluoromethyl, lower acyloxy, aryl, heteroaryl, and hydroxy.

By "alkyl" and "lower alkyl" in the present invention is meant straight or branched chain alkyl groups having 1–6 carbon atoms, such as, for example, methyl, ethyl, propyl, isopropyl, n-butyl, sec-butyl, tert-butyl, pentyl, 2-pentyl, isopentyl, neopentyl, hexyl, 2-hexyl, 3-hexyl, and 3-methylpentyl. Unless indicated otherwise, the alkyl group substituents herein are optionally substituted with at least one group independently selected from hydroxy, mono- or dialkyl amino, phenyl or pyridyl.

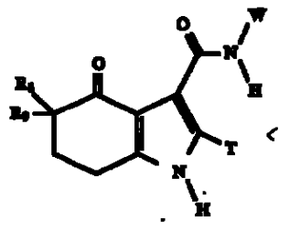
By "alkoxy" and "lower alkoxy" in the present invention is meant straight or branched chain alkoxy groups having 1–6 carbon atoms, such as, for example, methoxy, ethoxy, propoxy, isopropoxy, n-butoxy, sec-butoxy, tert-butoxy, pentoxy, 2-pentoxy, isopentoxy, neopentoxy, hexoxy, 2-hexoxy, 3-hexoxy, and 3-methylpentoxy.

Still other examples of various aryl and heteroaryl groups are shown in Chart D of published International Application WO 93/17025.

By the term "halogen" or "Hal" in the present invention is meant fluorine, bromine, chlorine, and iodine.

The novel compounds encompassed by the instant invention can be described by general Formula I set forth above or the pharmaceutically acceptable non-toxic salts thereof.

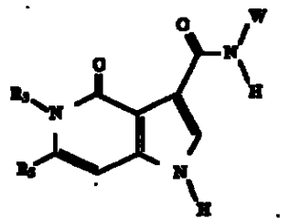
In addition, the present invention encompasses compounds of Formula II.



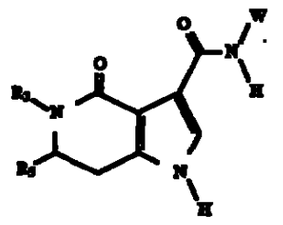
II

or the pharmaceutically acceptable non-toxic salts thereof wherein W, T, R_4 and R_5 are as defined above.

The present invention also encompasses compounds of Formula IIIa and IIIb:



IIIa

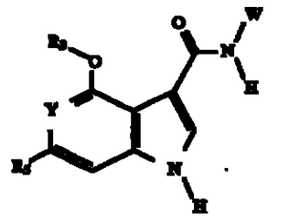


IIIb

or the pharmaceutically acceptable non-toxic salts thereof wherein W, R_5, and R_5 are as defined above.

Preferred compounds of Formula IIIb are those where R_5 is hydrogen or alkyl; and R_5 is hydrogen.

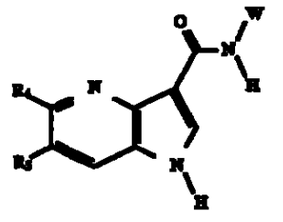
The present invention also encompasses compounds of Formula IV:



IV

or the pharmaceutically acceptable non-toxic salts thereof wherein W, Y, R_5, and R_5 are defined above.

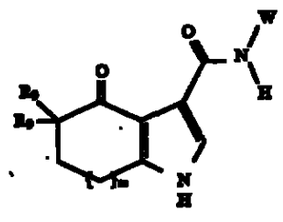
The present invention also encompasses compounds of Formula V:



V

or the pharmaceutically acceptable non-toxic salts thereof wherein W, R_4, and R_5 are defined above.

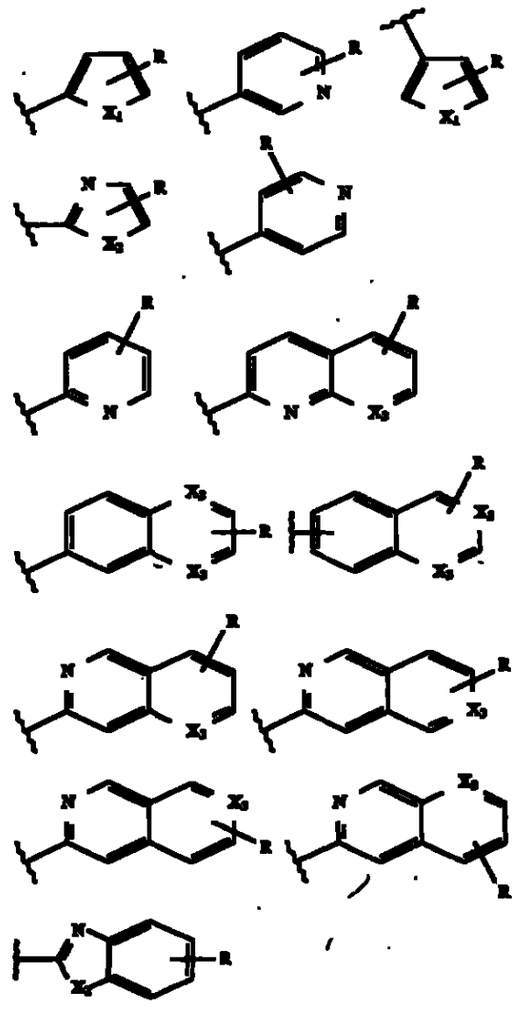
The invention further encompasses compounds of Formula VI:



VI

or the pharmaceutically acceptable non-toxic salts thereof wherein W and R_5 are defined above, and each R_5 is is the same or different and is as defined above; and m is 1,2, or 3.

Preferred compounds of Formulas I–VI include a W group selected from the following:



In the above W groups, the following definitions apply:

X_1 is oxygen or sulfur;

X_2 is oxygen, sulfur, or NR;

each X_3 is independently nitrogen or CR; and

R is hydrogen, alkyl, alkoxy, and halogen.

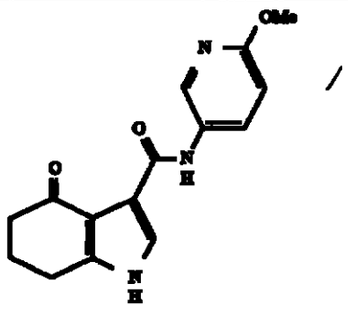
Those skilled in the art will recognize that the above W groups may have different substitution patterns that are encompassed within the invention.

Particularly preferred W groups of the invention are the following: 4-methoxy-3-pyridyl; 3-thienyl; 2-methoxy-1,8-napthyridin-7-yl; 6-methyl-1,8-napthyridin-7-yl; 2-chloro-1,8napthyridin-7-yl; 2-pyridyl; 3-pyridyl; 5-methyl-2-thiazolyl; 2-thienyl; 2-thiazolyl; 2-quinolinyl; and 2-quinoxalinyl.

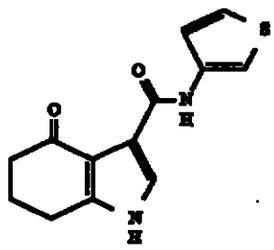
Representative compounds of the invention are shown below in Table 1.

TABLE 1

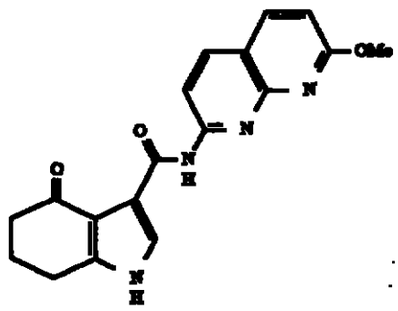
Compound 1



Compound 2



Compound 3



Compound 4

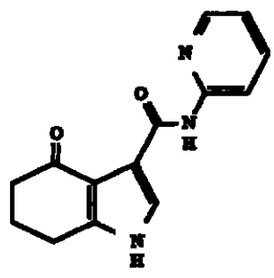
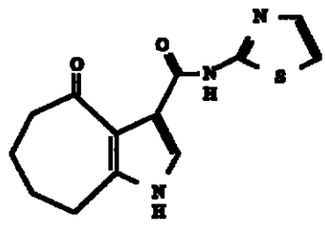
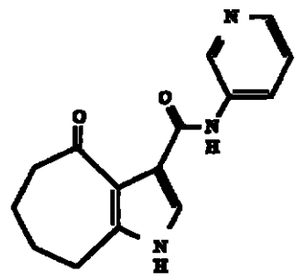


TABLE 1-continued

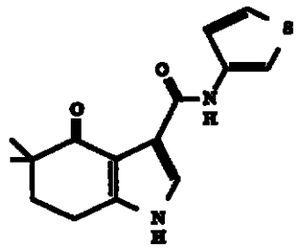
Compound 5



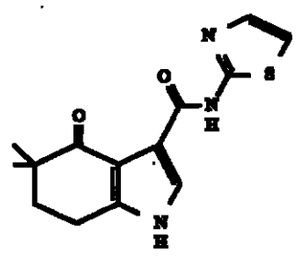
Compound 6



Compound 7



Compound 8



Compound 9

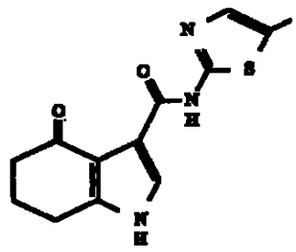
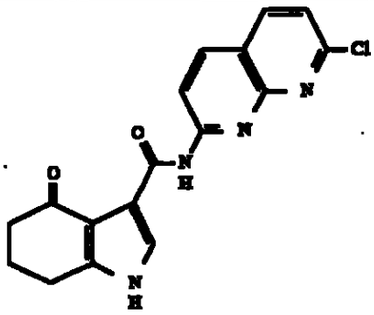
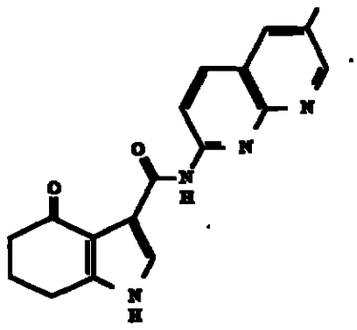


TABLE 1-continued

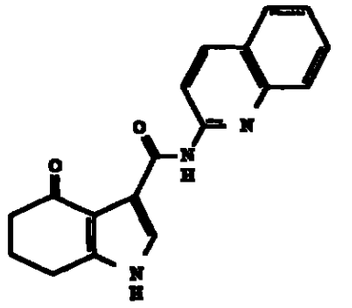
Compound 10



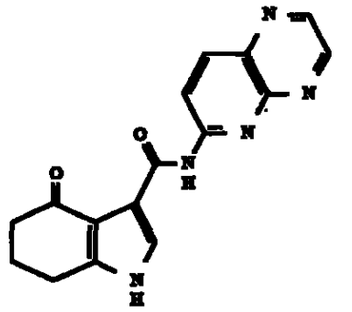
Compound 11



Compound 12



Compound 13



Representative compounds of the present invention, which are encompassed by Formula I, include, but are not limited to the compounds in Table I and their pharmaceutically acceptable salts. Non-toxic pharmaceutically acceptable salts include salts of acids such as hydrochloric, phosphoric, hydrobromic, sulfuric, sulfinic, formic, toluenesulfonic, methanesulfonic, nitric, benzoic, citric, tartaric, maleic, hydroiodic, alkanoic such as acetic, HOOC—$(CH_2)_n$—COOH where n is 0–4, and the like. Those skilled in the an will recognize a wide variety of non-toxic pharmaceutically acceptable addition salts.

The present invention also encompasses the prodrugs, preferably acylated prodrugs, of the compounds of Formula I. Those skilled in the art will recognize various synthetic methodologies which may be employed to prepare non-toxic pharmaceutically acceptable addition salts and acylated prodrugs of the compounds encompassed by Formula I.

By "alkyl" and "lower alkyl" in the present invention is meant straight or branched chain alkyl groups having 1–6 carbon atoms, such as, for example, methyl, ethyl, propyl, isopropyl, n-butyl, sec-butyl, tert-butyl, pentyl, 2-pentyl, isopentyl, neopentyl, hexyl, 2-hexyl, 3-hexyl, and 3-methylpentyl.

By "alkoxy" and "lower alkoxy" in the present invention is meant straight or branched chain alkoxy groups having 1–6 carbon atoms, such as, for example, methoxy, ethoxy, propoxy, isopropoxy, n-butoxy, sec-butoxy, tert-butoxy, pentoxy, 2-pentyl, isopentoxy, neopentoxy, hexoxy, 2-hexoxy, 3-hexoxy, and 3-methylpentoxy.

By the term "halogen" in the present invention is meant fluorine, bromine, chlorine, and iodine.

By "N-alkylpiperazyl" in the invention is meant radicals of the formula:

where R is a straight or branched chain lower alkyl as defined above.

By "monoalkylamino" as used herein is meant an amino substituent substituted with one (1) alkyl group where the alkyl group is lower alkyl as defined above.

By "dialkylamino" as used herein is meant an amino substituent substituted with two (2) alkyl groups where the alkyl groups are independently lower alkyl groups as defined above.

The pharmaceutical utility of compounds of this invention are indicated by the following assay for GABAa receptor binding activity.

Assays are carried out as described in Thomas and Tallman (J. Bio. Chem. 156: 9838–9842, J. Neurosci. 3: 433–440, 1983). Rat cortical tissue is dissected and homogenized in 25 volumes (w/v) of 0.05M Tris HCl buffer (pH 7.4 at 4° C.). The tissue homogenate is centrifuged in the cold (4°) at 20,000×g for 20'. The supernatant is decanted and the pellet is rehomogenized in the same volume of buffer and again centrifuged at 20,000×g. The supernatant is decanted and the pellet is frozen at –20° C. overnight. The pellet is then thawed and rehomogenized in 25 volume (original wt/vol) of buffer and the procedure is carried out twice. The pellet is finally resuspended in 50 volumes (w/vol of 0.05M Tris HCl buffer (pH 7.4 at 40° C.).

Incubations contain 100 ml of tissue homogenate, 100 ml of radioligand 0.5 nM (^{3}H-RO15-1788 [^{3}H-Flumazenil] specific activity 80 Ci/mmol), drug or blocker and buffer to a total volume of 500 ml. Incubations are carried for 30 min at 4° C. then are rapidly filtered through GFB filters to separate free and bound ligand. Filters are washed twice with fresh 0.05M Tris HCl buffer (pH 7.4 at 4° C.) and counted in a liquid scintillation counter. 1.0 mM diazepam is added to some tubes to determine nonspecific binding. Data are collected in triplicate determinations, averaged and % inhibition of total specific binding is calculated. Total Specific Binding=Total–Nonspecific. In some cases, the amounts of unlabeled drugs is varied and total displacement curves of binding are carried out. Data are converted to IC_{50}

or K_i. Representative data for compounds of this invention are listed in Table 2.

TABLE 2

Compound Number	K_i(nM)
1	11
2	3
3	66
4	3
5	2
6	25
7	15
8	2
9	9
10	83
11	3
12	50
13	64

The compounds of general Formula I may be administered orally, topically, parenterally, by inhalation or spray or rectally in dosage unit formulations containing conventional non-toxic pharmaceutically acceptable carriers, adjuvants and vehicles. The term parenteral as used herein includes subcutaneous injections, intravenous, intramuscular, intrasternal injection or infusion techniques. In addition, there is provided a pharmaceutical formulation comprising a compound of general Formula I and a pharmaceutically acceptable carrier. One or more compounds of general Formula I may be present in association with one or more non-toxic pharmaceutically acceptable carriers and/or diluents and/or adjuvants and if desired other active ingredients. The pharmaceutical compositions containing compounds of general Formula I may be in a form suitable for oral use, for example, as tablets, troches, lozenges, aqueous or oily suspensions, dispersible powders or granules, emulsion, hard or soft capsules, or syrups or elixirs.

Compositions intended for oral use may be prepared according to any method known to the art for the manufacture of pharmaceutical compositions and such compositions may contain one or more agents selected from the group consisting of sweetening agents, flavoring agents, coloring agents and preserving agents in order to provide pharmaceutically elegant and palatable preparations. Tablets contain the active ingredient in admixture with non-toxic pharmaceutically acceptable excipients which are suitable for the manufacture of tablets. These excipients may be for example, inert diluents, such as calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate; granulating and disintegrating agents, for example, corn starch, or alginic acid; binding agents, for example starch, gelatin or acacia, and lubricating agents, for example magnesium stearate, stearic acid or talc. The tablets may be uncoated or they may be coated by known techniques to delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monostearate or glyceryl distearate may be employed.

Formulations for oral use may also be presented as hard gelatin capsules wherein the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules wherein the active ingredient is mixed with water or an oil medium, for example peanut oil, liquid paraffin or olive oil.

Aqueous suspensions contain the active materials in admixture with excipients suitable for the manufacture of aqueous suspensions. Such excipients are suspending agents, for example sodium carboxymethylcellulose, methylcellulose, hydropropylmethylcellulose, sodium alginate, polyvinylpyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents may be a naturally-occurring phosphatide, for example, lecithin, or condensation products of an alkylene oxide with fatty acids, for example polyoxyethylene stearate, or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethyleneoxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, for example polyethylene sorbitan monooleate. The aqueous suspensions may also contain one or more preservatives, for example ethyl, or n-propyl p-hydroxybenzoate, one or more coloring agents, one or more flavoring agents, and one or more sweetening agents, such as sucrose or saccharin.

Oily suspensions may be formulated by suspending the active ingredients in a vegetable oil, for example arachis oil, olive oil, sesame oil or coconut oil, or in a mineral oil such as liquid paraffin. The oily suspensions may contain a thickening agent, for example beeswax, hard paraffin or cetyl alcohol. Sweetening agents such as those set forth above, and flavoring agents may be added to provide palatable oral preparations. These compositions may be preserved by the addition of an anti-oxidant such as ascorbic acid.

Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water provide the active ingredient in admixture with a dispersing or wetting agent, suspending agent and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those already mentioned above. Additional excipients, for example sweetening, flavoring and coloring agents, may also be present.

Pharmaceutical compositions of the invention may also be in the form of oil-in-water emulsions. The oily phase may be a vegetable oil, for example olive oil or arachis oil, or a mineral oil, for example liquid paraffin or mixtures of these. Suitable emulsifying agents may be naturally-occurring gums, for example gum acacia or gum tragacanth, naturally-occurring phosphatides, for example soy bean, lecithin, and esters or partial esters derived from fatty acids and hexitol, anhydrides, for example sorbitan monooleate, and condensation products of the said partial esters with ethylene oxide, for example polyoxyethylene sorbitan monooleate. The emulsions may also contain sweetening and flavoring agents.

Syrups and elixirs may be formulated with sweetening agents, for example glycerol, propylene glycol, sorbitor or sucrose. Such formulations may also contain a demulcent, a preservative and flavoring and coloring agents. The pharmaceutical compositions may be in the form of a sterile injectable aqueous or oleaginous suspension. This suspension may be formulated according to the known art using those suitable dispersing or wetting agents and suspending agents which have been mentioned above. The sterile injectable preparation may also be sterile injectable solution or suspension in a non-toxic parentally acceptable diluent or solvent, for example as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed including synthetic mono-or diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectables.

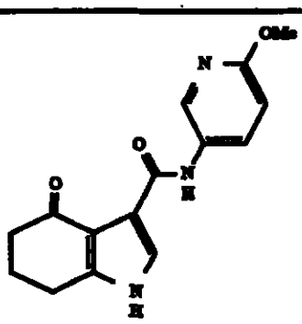
Those skilled in the art will recognize that the above W groups may have different substitution patterns that are encompassed within the invention.

Particularly preferred W groups of the invention are the following: 4-methoxy-3-pyridyl; 3-thienyl; 2-methoxy-1,8-napthyridin-7-yl; 6-methyl-1,8-napthyridin-7-yl; 2-chloro-1,8napthyridin-7-yl; 2-pyridyl; 3-pyridyl; 5-methyl-2-thiazolyl; 2-thienyl; 2-thiazolyl; 2-quinolinyl; and 2-quinoxalinyl.

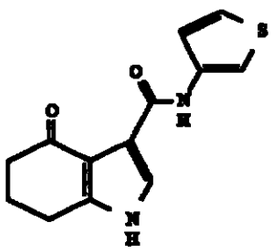
Representative compounds of the invention are shown below in Table 1.

TABLE 1

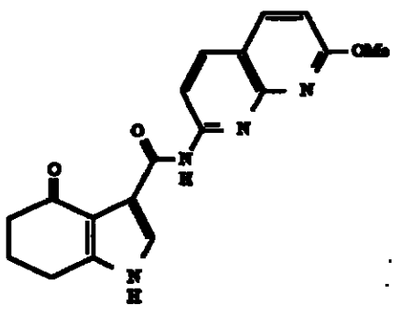
Compound 1



Compound 2



Compound 3



Compound 4

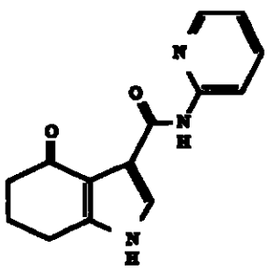
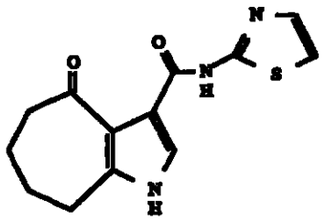
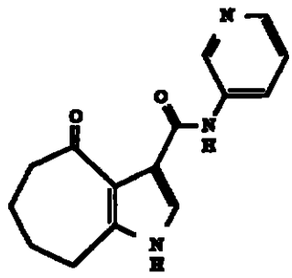


TABLE 1-continued

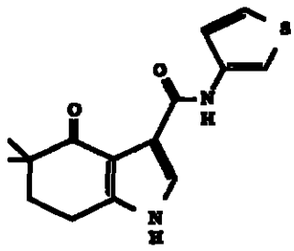
Compound 5



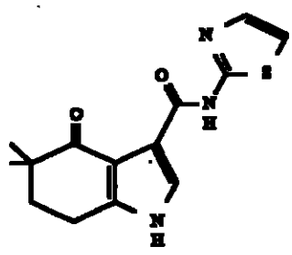
Compound 6



Compound 7



Compound 8



Compound 9

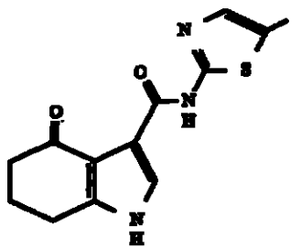
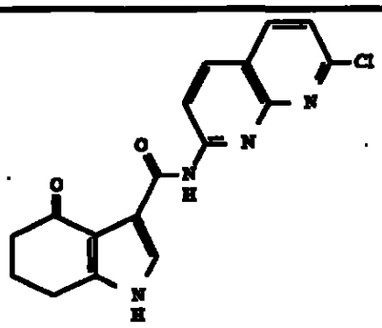
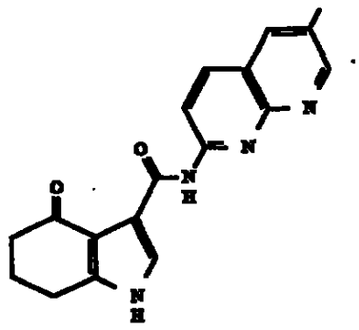
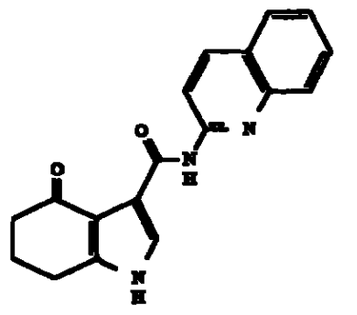
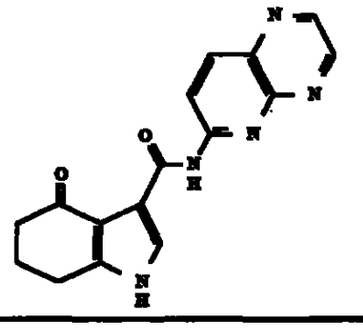


TABLE 1-continued

Compound 10	
Compound 11	
Compound 12	
Compound 13	

Representative compounds of the present invention, which are encompassed by Formula I, include, but are not limited to the compounds in Table I and their pharmaceutically acceptable salts. Non-toxic pharmaceutically acceptable salts include salts of acids such as hydrochloric, phosphoric, hydrobromic, sulfuric, sulfinic, formic, toluenesulfonic, methanesulfonic, nitric, benzoic, citric, tartaric, maleic, hydroiodic, alkanoic such as acetic, HOOC—$(CH_2)_n$—COOH where n is 0–4, and the like. Those skilled in the an will recognize a wide variety of non-toxic pharmaceutically acceptable addition salts.

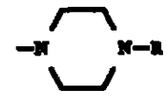
The present invention also encompasses the prodrugs, preferably acylated prodrugs, of the compounds of Formula I. Those skilled in the art will recognize various synthetic methodologies which may be employed to prepare non-toxic pharmaceutically acceptable addition salts and acylated prodrugs of the compounds encompassed by Formula I.

By "alkyl" and "lower alkyl" in the present invention is meant straight or branched chain alkyl groups having 1–6 carbon atoms, such as, for example, methyl, ethyl, propyl, isopropyl, n-butyl, sec-butyl, tert-butyl, pentyl, 2-pentyl, isopentyl, neopentyl, hexyl, 2-hexyl, 3-hexyl, and 3-methylpentyl.

By "alkoxy" and "lower alkoxy" in the present invention is meant straight or branched chain alkoxy groups having 1–6 carbon atoms, such as, for example, methoxy, ethoxy, propoxy, isopropoxy, n-butoxy, sec-butoxy, tert-butoxy, pentoxy, 2-pentyl, isopentoxy, neopentoxy, hexoxy, 2-hexoxy, 3-hexoxy, and 3-methylpentoxy.

By the term "halogen" in the present invention is meant fluorine, bromine, chlorine, and iodine.

By "N-alkylpiperazyl" in the invention is meant radicals of the formula:



where R is a straight or branched chain lower alkyl as defined above.

By "monoalkylamino" as used herein is meant an amino substituent substituted with one (1) alkyl group where the alkyl group is lower alkyl as defined above.

By "dialkylamino" as used herein is meant an amino substituent substituted with two (2) alkyl groups where the alkyl groups are independently lower alkyl groups as defined above.

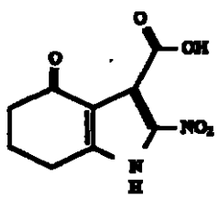
The pharmaceutical utility of compounds of this invention are indicated by the following assay for GABAa receptor binding activity.

Assays are carried out as described in Thomas and Tallman (J. Bio. Chem. 156: 9838–9842, J. Neurosci. 3: 433–440, 1983). Rat cortical tissue is dissected and homogenized in 25 volumes (w/v) of 0.05M Tris HCl buffer (pH 7.4 at 4° C.). The tissue homogenate is centrifuged in the cold (4°) at 20,000×g for 20'. The supernatant is decanted and the pellet is rehomogenized in the same volume of buffer and again centrifuged at 20,000×g. The supernatant is decanted and the pellet is frozen at −20° C. overnight. The pellet is then thawed and rehomogenized in 25 volume (original wt/vol) of buffer and the procedure is carried out twice. The pellet is finally resuspended in 50 volumes (w/vol of 0.05M Tris HCl buffer (pH 7.4 at 40° C.).

Incubations contain 100 ml of tissue homogenate, 100 ml of radioligand 0.5 nM (^{3}H-RO15-1788 [^{3}H-Flumazenil] specific activity 80 Ci/mmol), drug or blocker and buffer to a total volume of 500 mL. Incubations are carried for 30 min at 4° C. then are rapidly filtered through GFB filters to separate free and bound ligand. Filters are washed twice with fresh 0.05M Tris HCl buffer (pH 7.4 at 4° C.) and counted in a liquid scintillation counter. 1.0 mM diazepam is added to some tubes to determine nonspecific binding. Data are collected in triplicate determinations, averaged and % inhibition of total specific binding is calculated. Total Specific Binding=Total−Nonspecific. In some cases, the amounts of unlabeled drugs is varied and total displacement curves of binding are carried out. Data are converted to IC_{50}

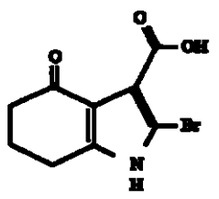
(180 mg, 1 mmol) and a methanolic solution of sodium methoxide (458 μL, 25 wt. %) in methyl alcohol (2 mL) was heated at 50° C. for 19 hours. The reaction mixture was allowed to cool, filtered through Celite using dichloromethane, concentrated in vacuo and the residue purified on Silica gel (1:9:0.2 methyl alcohol/dichloromethane/ammonium hydroxide) to afford 2-methoxy-7-amino-1,8-naphthyridine as a pale yellow solid.

18. 2-Nitro-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxylic acid



4-Oxo-4,5,6,7-tetrahydro-1 H-indole-3-carboxylic acid (179 mg, 1 mmol) was added in portions over 30 minutes to fuming nitric acid (2 mL) at 0° C. The mixture was stirred an additional 1.25 hours, then allowed to stir at ambient temperature for 1.25 hours. The mixture was poured into ice water and extracted 2× with ethyl acetate. The combined organic layers were dried over magnesium sulfate, filtered, and concentrated in vacuo to give the title compound (0.19 g).

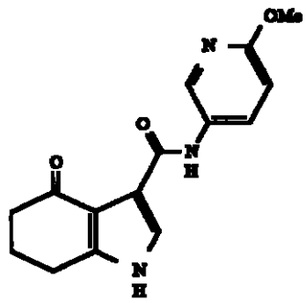
19. 2-Bromo-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxylic acid



To a solution of 4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxylic acid (886 mg, 5 mmol) and catalytic benzoyl peroxide in N,N-dimethylformamide (5 mL) at 0° C. was added N-bromosuccinimide (1.869 g, 10.5 mmol)in four equal portions over 1 hour. The mixture was stirred an additional hour, then poured into ice water, the precipitate collected and rinsed with water then diethyl ether and dried. Purification on Silica gel (5% methyl alcohol in 1:1:1 dichloromethane/ethyl acetate/hexanes) gave 2-bromo-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxylic acid (376 mg).

EXAMPLE 2

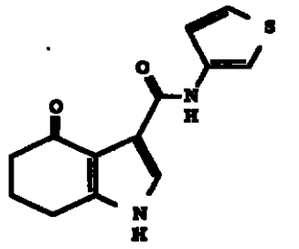
Compound 1



To a stirring solution of 4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxylic acid (179 mg, 1 mmol) and triethylamine (293 μl, 2.1 mmol) in N,N-dimethylformamide (3 mL) at 0° C. was added ethyl chloroformate (191 μl, 2 mmol). After stirring an additional 30 minutes, a solution of 2-methoxy-5-amino-pyridine (216 mg, 2 mmol) in N,N-dimethylformamide (3 mL) was added. The reaction mixture was allowed to stir for an additional 75 minutes, then poured into saturated aqueous ammonium chloride and extracted 2× with ethyl acetate. The combined organic layers were washed with water, dried over magnesium sulfate, filtered, and concentrated in vacuo. To the residue was added aqueous 5N sodium hydroxide (5 mL) and ethyl alcohol (1 mL), then heated at reflux for 1 hour. After cooling in an ice water bath, the reaction mixture was poured into saturated aqueous ammonium chloride and extracted 2× with ethyl acetate. The combined organic layers were dried over magnesium sulfate, filtered, concentrated in vacuo, and the residue recrystallized from ethyl acetate to give N-(4-methoxy-3-pyridyl)-4-oxo-4,5,6,7-tetrahydro-1H-indole 3-carboxamide (56 mg); m.p. 209°–210° C. (Compound 1).

EXAMPLE 3

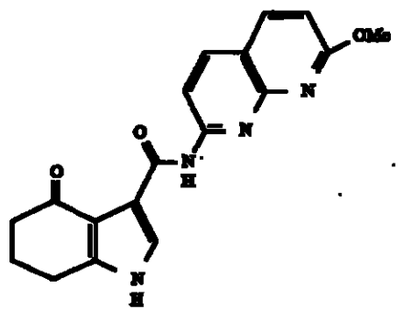
Compound 2



A mixture of 4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxylic acid (358 mg, 2 mmol), methyl 3-amino-2-thiophenecarboxylate (1.57 g, 10 mmol), and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (1.92 g, 10 mmol) in 1:1 dioxane/water (20 mL) was stirred at ambient temperature for 7 days. The reaction mixture was poured into saturated aqueous ammonium chloride and extracted 2× with ethyl acetate. The combined organic layers were dried over magnesium sulfate, filtered, concentrated in vacuo, triturated with diethyl ether, and purified on Silica gel (5:32:32:32 methyl alcohol/dichloromethane/ethyl acetate/hexanes) to give methyl N-(3-thiophene-2-carboxylate)-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxamide. Aqueous 1N sodium hydroxide (5 mL) and ethyl alcohol (1 mL) was

added and heated at reflux for 45 minutes. The reaction mixture was cooled in an ice water bath, acidified with aqueous hydrochloric acid, and the precipitate collected, rinsed with water and dried. The solid was suspended in toluene (3 mL), a catalytic amount of p-toluenesulfonic acid was added, and the mixture heated at reflux for 21 hours. The reaction mixture was concentrated in vacuo, the product triturated with diethyl ether and recrystallized from ethyl acetate to afford N-(3-thienyl)-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxamide (Compound 2).

EXAMPLE 4



Compound 3

To a stirring solution of N-(tert-butoxycarbonyl)-4-oxo-4,5,6,7-1H-indole-3-carboxylic acid (140 mg, 0.5 mmol) and triethylamine (146 µl, 1.1 mmol) in N,N-dimethylformamide (2 mL) at 0° C. was added ethyl chloroformate (50 µl, 0.5 mmol). After stirring an additional 30 minutes, 2-methoxy-7-amino-1,8-napthyridine (96 mg, 0.6 mmol) was added. The reaction mixture was allowed to stir at ambient temperature for 69 hours, then poured into saturated aqueous ammonium chloride. The precipitate was collected, rinsed with water then diethyl ether, and dried. The solid was then suspended in dichloromethane (2 mL) and trifluoroacetic acid (2 mL) was added dropwise. After stirring for one hour, the reaction mixture was concentrated in vacuo, the residue cooled in an ice water bath, and saturated aqueous sodium bicarbonate was added. The precipitate was collected, rinsed with water then diethyl ether, and dried to give N-(2-methoxy-1,8-napthyridin-7-yl)-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxamide (92 mg) (Compound 3); mp 173°–181° C.

EXAMPLE 5

The following compounds are prepared essentially according to the procedures described above in Examples 1–4:

(a) N-(2-Pyridyl)-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxamide (Compound 4).

(b) N-(3-Pyridyl)-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxamide.

(c) N-(4-Ethoxy-3-pyridyl)-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxamide; mp 224°–225° C.

(d) N-(4-Pyridyl)-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxamide; mp 319°–320° C. (d).

(e) N-(5-Methyl-2-thiazolyl)-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxamide (Compound 9).

(f) N-(3-Thienyl)-4-oxo-5,5-dimethyl-4,5,6,7-tetrahydro-1H-indole-3-carboxamide (Compound 7); mp 242°–243° C.

(g) N-(2-Thiazolyl)-4-oxo-5,5-dimethyl-4,5,6,7-tetrahydro-1H-indole-3-carboxamide (Compound 8).

(h) N-(3-Pyridyl)-4-oxo-5,5-dimethyl-4,5,6,7-tetrahydro-1H-indole-3-carboxamide; mp 225°–227° C.

(i) N-(4-Methoxy-3-pyridyl)-4-oxo-5,5-dimethyl-4,5,6,7-tetrahydro-1H-indole-3-carboxamide.

(j) N-(4-Pyridyl)-4-oxo-5,5-dimethyl-4,5,6,7-tetrahydro-1H-indole-3-carboxamide; mp 342°–344° C.

(k) N-(2-Thiazolyl)-4-oxo-1,4,5,6,7,8-hexahydro-cyclohepta[b]pyrrole-3-carboxamide (Compound 5); mp 279°–280° C.

(l) N-(3-Pyridyl)-4-oxo-1,4,5,6,7,8-hexahydro-cyclohepta[b]pyrrole-3-carboxamide (Compound 6); mp 224°–225° C.

(m) N-(4-Pyridyl)-4-oxo-1,4,5,6,7,8-hexahydro-cyclohepta[b]pyrrole-3-carboxamide; mp 205° C.

(n) N-(4-Methoxy-3-pyridyl)-4-oxo-1,4,5,6,7,8-hexahydro-cyclohepta[b]pyrrole-3-carboxamide; mp 180°–182° C.

(o) N-(4-Methyl-3-pyridyl)-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxamide.

(p) N-(2-Chloro-1,8-napthyridin-7-yl)-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxamide (Compound 10).

(q) N-(1,8-Napthyridin-2-yl)-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxamide; mp 305°–310° C. (d).

(r) N-(6-Methyl-1,8-napthyridin-2-yl))-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxamide (Compound 11); mp 345° C. (d).

(s) N-(2,4-Dimethyl-1,8-napthyridin-7-yl)-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxamide; mp 345°–347° C.

(t) N-(2-Quinolinyl)-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxamide (Compound 12); mp 335°–338° C.

(u) N-(3-Quinolinyl)-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxamide; mp 262°–269° C.

(v) N-(6-Quinolinyl)-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxamide; mp 319°–321° C.

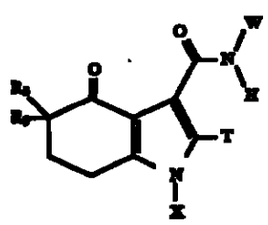
(w) N-(2-Quinoxalinyl)-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxamide; mp 296°–298° C.

(x) N-(6-Quinoxalinyl)-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxamide (Compound 13); mp >300° C.

The invention and the manner and process of making and using it, are now described in such full, clear, concise and exact terms as to enable any person skilled in the art to which it pertains, to make and use the same. It is to be understood that the foregoing describes preferred embodiments of the present invention and that modifications may be made therein without departing from the spirit or scope of the present invention as set forth in the claims. To particularly point out and distinctly claim the subject matter regarded as invention, the following claims conclude this specification.

What is claimed is:

1. A compound of the formula:



or the pharmaceutically acceptable non-toxic salts thereof wherein: