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SUPERINTENDENCIA Y COMERCIO
Radicacion : 01063854 0.858532
Fecha (dd/mm/aa): 2001-12-07 16:44:48 Folios: 527
Tramite : 0.2 PATENTES D 1 REGISTRO/ 329 CAVELIER
Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

Señora Jefe de la
DIVISION DE NUEVAS CREACIONES
SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
E. S. D.

Referencia: Expediente No. 01.063 854

Solicitantes: **NEUROGEN CORPORATION Y PFIZER, INC.**

Asunto: Solicitud de patente para "**COMPUESTOS HETEROCÍCLICOS COMO LIGANDOS DE LOS RECEPTORES GABA$_A$**"

Fecha de solicitud : 8 de agosto de 2001

TRAMITE: 002 - EVENTO: 001 - ACTUACIÓN: 329

1. Yo, Emilio FERRERO, obrando como apoderado de las solicitantes en referencia, atentamente presento con este escrito la copia certificada de la solicitud de patente estadounidense No 60/223,669 del 07 de agosto de 2000, junto con su respectiva traducción de su descripción, reivindicaciones y certificaciones, de la cual se reclama prioridad en esta solicitud de patente

2. Ruego a la Señora Jefe se sirva aceptar este escrito con sus anexos, y se continúe con el trámite de la solicitud

Bogotá, -7 DIC 2001
Señora Jefe,

EMILIO FERRERO
T P A. No 31 929

COLO 12889-801-001-1
MRE-4

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SUPERINTENDENCIA Y COMERCIO

Radicacion : 01063854 00008002 Folios: 527

Fecha (AMD): 2001-12-07 16:44:38

Tramite : 002 PATENTES D 1 REGISTRO/ 329 COMPLEME

Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

PA 494066

THE UNITED STATES OF AMERICA

TO ALL TO WHOM THESE PRESENTS SHALL COME:

UNITED STATES DEPARTMENT OF COMMERCE

United States Patent and Trademark Office

November 19, 2001

THIS IS TO CERTIFY THAT ANNEXED HERETO IS A TRUE COPY FROM THE RECORDS OF THE UNITED STATES PATENT AND TRADEMARK OFFICE OF THOSE PAPERS OF THE BELOW IDENTIFIED PATENT APPLICATION THAT MET THE REQUIREMENTS TO BE GRANTED A FILING DATE UNDER 35 USC 111.

APPLICATION NUMBER: ***60/223,669***
FILING DATE: ***August 07, 2000***

By Authority of the
COMMISSIONER OF PATENTS AND TRADEMARKS

W. MONTGOMERY
Certifying Officer

08-08-00

PTO
08/07/00

Customer Number: 000959

PTO/SB/16 (8-98)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Attorney
In re the application of: George Maynard, et. al. Docket No. N2000.00

For:

Assistant Commissioner For Patents
Box Provisional patent Application
Washington, DC 20231

COVER SHEET FOR FILING PROVISIONAL PATENT APPLICATION

Dear Sir:

The accompanying application, entitled Heterocyclic Compounds as Ligands of the $GABA_A$ Receptor, is a provisional patent application under 37 C.F.R. § 1.51 (a)(2) and § 1.53 (b)(2).

1. ☒ The names and addresses of the inventors of this application are as follows:

	Last Name	First Name	Middle Initial	Residence
1.	Maynard	George		27 Glenwood Road Clinton, CT 06413
2	Yohannes	Daniel		393 Pequot Avenue New London, CT 06320
3.				
4.				
5.				
6.				

US Express Mailing No. EL074500423US

Attorney Docket: N2000.00[redacted]

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2. ☐ This invention was made by an agency of the United States Government or under contract with an agency of the United States Government. The name of the U.S. Government agency and the Government contract number are:

   Agency: _____

   Contract No.: _____

3. ☒ The following documents are enclosed:

   ☒ ___277___ pages of Specification and Claims

   ☒ ___1___ page of abstract

4. ☐ A verified statement to establish small entity status under 37 CFR 1.9 and 1.27 is enclosed.

5. ☐ An Assignment of the invention to _____ is enclosed. A check in the amount of $40.00 for recording this assignment and a recordation form cover sheet (Form PTO 1595) are also enclosed.

6. ☒ The fee for filing this provisional application, as set forth in 37 CFR 1.16(k), is $150.00.

   a. ☒ **A check for this filing is enclosed.**

   b. ☐ Charge the filing fee to Deposit Account No. 501116.

   c. ☐ The filing fee is not being paid at this time.

7. ☒ Please charge any fee deficiencies associated with this filing to Deposit Account No. 501116. ***A duplicate copy of this sheet is enclosed.***

Please address all future communications to:

Patent Department
Neurogen Corporation
35 Northeast Industrial Road
Branford, CT 06405

and direct telephone calls to: Leslie-Anne Horvath or Seth A. Fidel.

Respectfully submitted,

Leslie-Anne Horvath

8/9/00
Date

Leslie-Anne Horvath
Registration No. 44,778

Neurogen Corporation
35 Northeast Industrial Road
Branford, CT 06405
203-488-8201

US Express Mailing No. EL074500423US

[x] Attorney Docket No. : N2000.009 PATENT

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant : George Maynard, et al.

Serial No. : Not Yet Assigned

Filed : Herewith

For : Heterocyclic Compounds as Ligands of the $GABA_A$ Receptor

Box Provisional Application
Assistant Commissioner for Patents
Washington, D.C. 20231

EXPRESS MAIL INFORMATION

Attached hereto are the following papers which are to being sent by Express Mail Post Office To Addressee Service to : Box Provisional Application, Assistant Commissioner for Patents, Washington, D.C., 20231 on August 7, 2000:

1. Provisional Application for Patent Cover Sheet (2 sheets, 2 copies)
2. Specification and Claims for Patent Application: Heterocyclic Compounds as Ligands of the $GABA_A$ Receptor (277 pages)
3. Abstract for patent application (1 pages)
4. Check for Provisional Application Filing Fee (1 check, $150.00)

Express Mail Mailing Label No. EL074500423US

Respectfully submitted:
Leslie-Anne Horvath
Reg. No. 44,778
Neurogen Corp.
35 NE Industrial Rd.
Branford, CT 06405

August 7, 2000
Date Signed

Leslie-Anne Horvath

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APPLICATION FOR UNITED STATES LETTERS PATENT
IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

TITLE: Heterocyclic Compounds as Ligands of the $GABA_A$ Receptor

Inventors:

George Maynard
27 Glenwood Rd.
Clinton, CT 06413

Daniel Yohannes
393 Pequot Avenue
New London, CT 06320

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Heterocyclic Compounds as Ligands of the $GABA_A$ Receptor

Field of the Invention

This invention relates to heterocyclic compounds such as 5,6-Dihydro-4H-1,3a,6-triaza-as-indacenes,3-thia-1,7-diaza-cyclopenta[e]azulene-9-carboxylic acids, 4,5,6,7-tetrahydro-1-oxa-2,7-diaza-cyclopenta[e]azulene -9-carboxylic acids, 3,8,10-triaza-benzo[e]azulene-1-carboxylic acids, 1-oxa-2,7-diaza-cyclopenta[e]azulene-9-carboxylic acids, 1,3,7-triaza-cyclopenta[e]azulene-9-carboxylic acid phenyl amide and related compounds, and more specifically to such compounds that bind with high selectivity and high affinity to the benzodiazepine site of $GABA_A$ receptors. This invention also relates to pharmaceutical compositions comprising such compounds and to the use of such compounds in treatment of certain central nervous system (CNS) diseases. This invention also relates to the use of these heterocyclic compounds in combination with one or more other CNS agents to potentiate the effects of the other CNS agents. Additionally this invention relates to the use such compounds as probes for the localization of $GABA_A$ receptors in tissue sections.

WO 93/23397 PCT/US93/04500

Background

The $GABA_A$ receptor superfamily represents one of the classes of receptors through which the major inhibitory neurotransmitter, γ-aminobutyric acid, or GABA, acts. Widely, although unequally, distributed through the mammalian brain, GABA mediates many of its actions through a complex of proteins called the $GABA_A$ receptor, which causes alteration in chloride conductance and membrane polarization.

A number of cDNAs for $GABA_A$ receptor subunits have been characterized. To date at least 6α, 3β, 3γ, 1ε, 1δ and 2ρ subunits have been identified. It is generally accepted that native $GABA_A$ receptors are typically composed of 2α, 2β, and 1γ subunits (Pritchett & Seeburg *Science* 1989; 245:1389-1392 and Knight et. al., *Recept. Channels* 1998; 6:1-18). Evidence such as message distribution, genome localization and biochemical study results suggest that the major naturally occurring receptor combinations are $\alpha_1\beta_2\gamma_2$, $\alpha_2\beta_3\gamma_2$, $\alpha_3\beta_3\gamma_2$, and $\alpha_5\beta_3\gamma_2$ (Mohler et. al. Neuroch. Res. 1995; 20(5): 631 - 636).

Benzodiazepines exert their pharmacological actions by interacting with the benzodiazepine binding sites associated with the $GABA_A$ receptor. In addition to the benzodiazepine site, the $GABA_A$ receptor contains sites of interaction for several other classes of drugs. These include a steroid binding site, a picrotoxin site, and the barbiturate site. The benzodiazepine

site of the $GABA_A$ receptor is a distinct site on the receptor complex that does not overlap with the site of interaction for GABA or for other classes of drugs that bind to the receptor (see, e.g., Cooper, et al., The Biochemical Basis of Neuropharmacology, 6th ed., 1991, pp. 145-148, Oxford University Press, New York). Early electrophysiological studies indicated that a major action of the benzodiazepines was enhancement of GABAergic inhibition. Compounds that selectively bind to the benzodiazepine site and enhance the ability of GABA to open $GABA_A$ receptor channels are agonists of GABA receptors. Other compounds that interact with the same site but negatively modulate the action of GABA are called inverse agonists. Compounds belonging to a third class bind selectively to the benzodiazepine site and yet have little or no effect on GABA activity, but can block the action of $GABA_A$ receptor agonists or inverse agonists that act at this site. These compounds are referred to as antagonists.

The important allosteric modulatory effects of drugs acting at the benzodiazepine site were recognized early and the distribution of activities at different receptor subtypes has been an area of intense pharmacological discovery. Agonists that act at the benzodiazepine site are known to exhibit anxiolytic, sedative, and hypnotic effects, while compounds that act as inverse agonists at this site elicit anxiogenic,

cognition enhancing, and proconvulsant effects. While benzodiazepines have a long history of pharmaceutical use as anxiolytics, these compounds often exhibit a number of unwanted side effects. These may include cognitive impairment, sedation, ataxia, potentiation of ethanol effects, and a tendency for tolerance and drug dependence.

$GABA_A$ selective ligands may also act to potentiate the effects of certain other CNS active compounds. For example, there is evidence that selective serotonin reuptake inhibitors (SSRIs) may show greater antidepressant activity when used in combination with $GABA_A$ selective ligands than when used alone.

Description of related art

List any highly relevant references here and briefly describe providing structures where helpful

SUMMARY OF THE INVENTION

This invention provides heterocyclic compounds, such as 5,6-Dihydro-4H-1,3a,6-triaza-as-indacenes and related compounds, that bind with high affinity and high selectivity to the benzodiazepine site of the $GABA_A$ receptor, including human $GABA_A$ receptors.

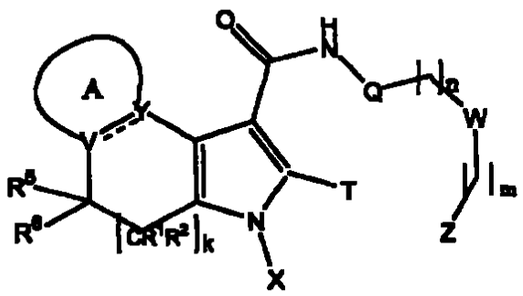
Thus, the invention provides novel compounds of Formula I (shown below), and pharmaceutical compositions comprising compounds of Formula I.

The invention further comprises methods of treating patients suffering from certain CNS disorders with an effective amount of a compound of the invention. The patient may be a human or other mammal. Treatment of humans, domesticated companion animals (pets) or livestock animals suffering from certain CNS disorders with an effective amount of a compound of the invention is encompassed by the invention.

In a separate aspect, the invention provides a method of potentiating the actions of other CNS active compounds. This method comprises administering an effective amount of a compound of the invention with another CNS active compound.

Additionally this invention relates to the use of the compounds of the invention as probes for the localization of $GABA_A$ receptors in tissue sections.

Accordingly, a broad aspect of the invention is directed to compounds of Formula A:



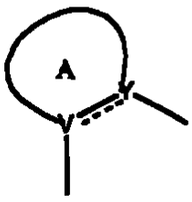
Formula A

or a pharmaceutically acceptable salt thereof, wherein:

R^1 and R^2 are independently chosen at each occurrence from hydrogen, halogen, hydroxy, cyano, nitro, amino, alkyl, alkenyl, alkynyl, haloalkyl, mono or diaminoalkyl, alkoxy, and k is 0, 1, 2, or 3;

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the group



represents an optionally substituted saturated, unsaturated or aromatic heterocyclic ring containing at least one nitrogen, oxygen or sulfur atom, wherein the V----Y bond is a single, double, or aromatic bond;

V is nitrogen, carbon, or CH;

Y is carbon, or CH;

R^5 and R^6 may be taken together to form a carbonyl group; or

R^5 and R^6 are independently chosen from hydrogen, halogen, hydroxy, nitro, cyano, $alkyl_1$, amino, -COOH, $-O(alkyl_1)$, $-SO_2NH_2$, $-SO_2NH(alkyl_1)$, $-SO_2N(alkyl_1)(alkyl_1)$, $-N(alkyl_1)CO(alkyl_1)$, $N(alkyl_1)CO_2(alkyl_1)$, $-NHSO_2(alkyl_1)$, $-N(alkyl_1)SO_2(alkyl_1)$, $-SO_2NHCO(alkyl_1)$, $-CONHSO_2(alkyl_1)$, $-CONH(alkyl_1)$, $-CON(alkyl_1)(alkyl_1)$, $-CO_2(alkyl_1)$, $-CO(alkyl_1)$ $-SO_{0-2}(alkyl_1)$, and optionally substituted carbocyclic aryl

or optionally substituted heteroaryl group having from 1 to 3 rings, 3 to 8 members in each ring and from 1 to 3 heteroatoms;

wherein $alkyl_1$ is independently chosen at each occurrence and is straight branched or cyclic, may contain one or two double or triple bonds, and is unsubstituted or substituted with one or more substituents selected from: hydroxy, oxo, halogen, amino, cyano, nitro, alkoxy, -COOH, $-SO_2NH_2$, $-SO_2NH(alkyl)$, $-SO_2N(alkyl)(alkyl)$, $-N(alkyl)CO(alkyl)$, $N(alkyl)CO_2(alkyl)$, $-NHSO_2(alkyl)$, $-N(alkyl)SO_2(alkyl)$, $-SO_2NHCO(alkyl)$, $-CONHSO_2(alkyl)$, $-CONH(alkyl)$, $-CON(alkyl)(alkyl)$, $-CO_2(alkyl)$, $-CO(alkyl)$ $-SO_{0-2}(alkyl)$;

X is chosen from hydrogen, hydroxy, amino, alkyl, and alkoxy;

T is chosen from hydrogen, halogen, hydroxy, amino, alkyl, and alkoxy;

Q is an optionally substituted carbocyclic aryl or optionally substituted heteroaryl group having from 1 to 3 rings, 3 to 8 members in each ring and from 1 to 3 heteroatoms;

W is hydrogen, 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 alkyl, or R^7 and R^8 may be taken together to represent a cyclic moiety having 3-7 carbon atoms;

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Z is hydrogen, hydroxy, straight or branched chain alkoxy, cycloalkyl, cycloalkyl(alkoxy), amino, mono or dialkylamino, or NR^9COR^{10} where R^9 and R^{10} are the same or different and represent hydrogen or straight or branched chain alkyl, or R^9 and R^{10} may be joined to from a cycloalkyl ring, or

Z is optionally substituted carbocyclic aryl or optionally substituted heteroaryl group having from 1 to 3 rings, 3 to 8 members in each ring and from 1 to 3 heteroatoms;

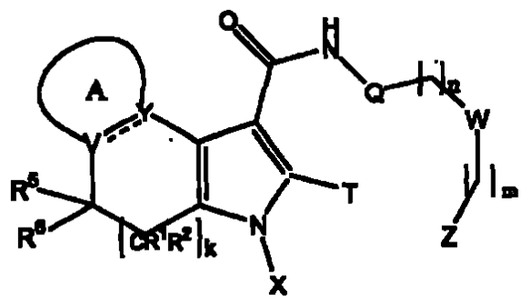
 and  represent carbon chains which may be substituted with hydrogen, halogen, cyano, nitro, amino, mono or dialkylamino, alkenyl, alkynyl, alkoxy, trifluoromethyl, trifluoromethoxy, straight or branched chain alkyl, or cycloalkyl, and

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

n is 0, 1, 2, or 3.

DETAILED DESCRIPTION OF THE INVENTION

In addition to compounds of Formula A, the invention also provides compounds of Formula I

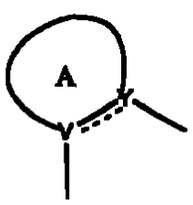


Formula I

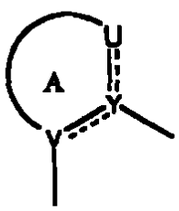
and the pharmaceutically acceptable salts thereof, wherein:

R^1 and R^2 are independently chosen at each occurrence from hydrogen, halogen, hydroxy, cyano, nitro, amino, haloalkyl, mono or diamino(C_{1-6})alkyl, C_{1-6} alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl and C_{1-6} alkoxy, and k is 0, 1, 2, or 3;

the group



is a group of the formula:



represents a saturated, unsaturated or aromatic heterocyclic ring containing at least one nitrogen, oxygen or sulfur atom,

wherein the and bonds may be single, double or aromatic bonds,

U is nitrogen, NR^A, S, or O;

V is nitrogen, carbon or CH;

Y is carbon, or CH;

and said saturated, unsaturated or aromatic heterocyclic ring is chosen from:

thienyl, thiazolyl, pyridyl, pyrimidinyl, imidazolyl, pyrazolyl, pyrazinyl, pyridizinyl, piperidinyl, oxazolyl, isoxazolyl, symmetrical and unsymmetrical triazolyl, pyrrolyl, furanyl, diazenyl, triazenyl, 1, 2, 4-triazolone, 4,5-dihydroimidazolyl, and 1,4,5,6-tetrahydropyrimidinyl, each of which is optionally substituted at any available nitrogen by R^A and optionally substituted at any available carbon by R^3 and R^4, wherein:

R^A is chosen from hydrogen, $C_{1-6}alkyl_1$, optionally substituted carbocyclic aryl and optionally substituted heteroaryl groups having from 1 to 3 rings, 3 to 8 members in each ring and from 1 to 3 heteroatoms;

R^5 and R^6 are independently chosen from hydrogen, halogen, hydroxy, nitro, cyano, $C_{1-6}alkyl_1$, amino, -COOH, $-O(C_{1-6}alkyl_1)$, $-NH(C_{1-6}alkyl_1)$, $-N(C_{1-6}alkyl_1)(C_{1-6}alkyl_1)$, $-SO_2NH_2$, $-SO_2NH(C_{1-6}alkyl_1)$, $-SO_2N(C_{1-6}alkyl_1)(C_{1-6}alkyl_1)$, $-N(C_{1-6}alkyl_1)CO(C_{1-6}alkyl_1)$, $N(C_{1-6}alkyl_1)CO_2(C_{1-6}alkyl_1)$, $-NHSO_2(C_{1-}$

$_6$alkyl$_1$), -N(C_{1-6}alkyl$_1$)SO_2(C_{1-6}alkyl$_1$), -SO_2NHCO(C_{1-6}alkyl$_1$), -CONHSO_2(C_{1-6}alkyl$_1$), -CONH(C_{1-6}alkyl$_1$), -CON(C_{1-6}alkyl$_1$)(C_{1-6}alkyl$_1$),-CO_2(C_{1-6}alkyl$_1$), -CO(C_{1-6}alkyl$_1$) and -SO_{0-2}(C_{1-6}alkyl$_1$),

wherein C_{1-6}alkyl$_1$ is independently chosen at each occurrence and is straight branched or cyclic, may contain one or two double or triple bonds, and is unsubstituted or substituted with one or more substituents selected from: hydroxy, oxo, halogen, amino, cyano, nitro, alkoxy, carbocylic or heterocyclic group, -COOH, -SO_2NH_2, -SO_2NH(C_{1-4}alkyl), -SO_2N(C_{1-4}alkyl)(C_{1-4}alkyl), -N(C_{1-4}alkyl)CO(C_{1-4}alkyl), N(C_{1-4}alkyl)CO_2(C_{1-4}alkyl), -NHSO_2(alkyl), -N(C_{1-4}alkyl)SO_2(C_{1-4}alkyl), -SO_2NHCO(C_{1-4}alkyl), -CONHSO_2(C_{1-4}alkyl), -CONH(C_{1-4}alkyl), -CON(C_{1-4}alkyl)(C_{1-4}alkyl), -CO_2(C_{1-4}alkyl), -CO(C_{1-4}alkyl), and -SO_{0-2}(C_{1-4}alkyl);

R^3 and R^4 are independently chosen at each occurrence, and are defined the same as R^3 and R^6;

X is chosen from hydrogen, hydroxy, amino, C_{1-6} alkyl, and C_{1-6}alkoxy;

T is chosen from hydrogen, halogen, hydroxy, amino, C_{1-6} alkyl, and C_{1-6} alkoxy;

Q is a phenyl, naphthyl, quinolinyl, thienyl, pyridyl, pyrimidinyl, pyrazinyl, oxazolyl, isoxazolyl, symmetrical

WO 93/22293 PCT/US93/03805

or unsymmetrical oxadiazolyl, symmetrical or unsymmetrical thiadiazolyl, symmetrical or unsymmetrical triazolyl, pyrazolyl, furanyl, diazenyl, triazenyl, or triazolopyrazinyl group;

each of which may be unsubstituted or substituted with up to three substituents independently selected from i) and ii) wherein

i) represents hydroxy, cyano, halogen, nitro, amino, mono or di(C_{1-6})alkylamino, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}alkoxy, trifluoromethyl, or trifluoromethoxy;

ii) represents straight or branched chain C_{1-6}alkyl optionally containing heteroatoms and optionally substituted with one or more carbocyclic or heterocyclic group;

W is hydrogen, 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 C_{1-6}alkyl, or R^7 and R^8 may be taken together to represent a cyclic moiety having 3-7 carbon atoms;

Z is hydrogen, hydroxy, straight or branched chain C_{1-6}alkoxy, C_{3-7}cycloalkyl, C_{3-7}cycloalkyl(C_{1-3}alkoxy), amino, mono or di C_{1-6}alkylamino, a carbocyclic or heterocylic group, or NR^9COR^{10} where R^9 and R^{10} are the same or different and

represent hydrogen or straight or branched chain C_{1-6}alkyl, or R^9 and R^{10} may be joined to from a C_{3-7} cycloalkyl ring, or

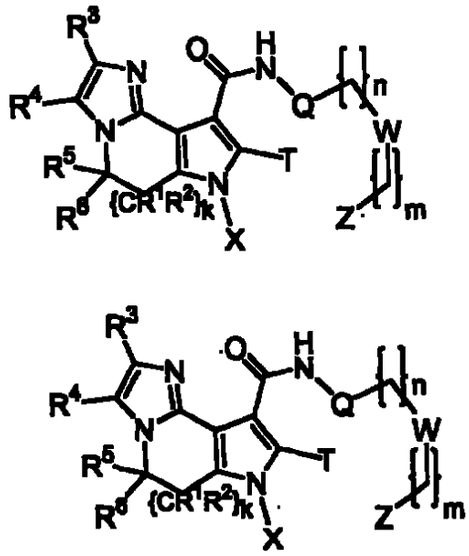
Z is a phenyl, napthyl, quinolinyl, thienyl, thiazolyl, pyridyl, pyrimidinyl, imidazolyl, pyrazolyl, pyrazinyl, pyridizinyl, piperidinyl, oxazolyl, isoxazolyl, symmetrical or unsymmetrical thiadiazolyl, symmetrical or unsymmetrical triazolyl, symmetrical or unsymmetrical oxadiazolyl, pyrrolyl, furanyl, pyrimidinyl, diazenyl, triazenyl, 1, 2, 4-triazolone, 4,5-dihydroimidazolyl, or 1,4,5,6-tetrahydropyrimidinyl group;

 , and  represent a carbon chain which may be substituted with hydrogen, halogen, cyano, nitro, amino, mono or di C_{1-6}alkylamino, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}alkoxy, trifluoromethyl, trifluoromethoxy, straight or branched chain C_{1-6}alkyl, or C_{3-7}cycloalkyl, and

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

n is 0, 1, 2, or 3.

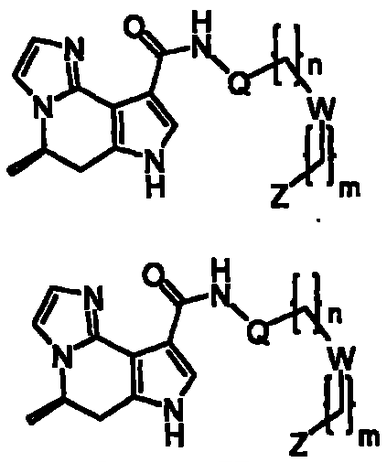
Further provided are compounds of Formula II



Formula II

and the pharmaceutically acceptable salts thereof,

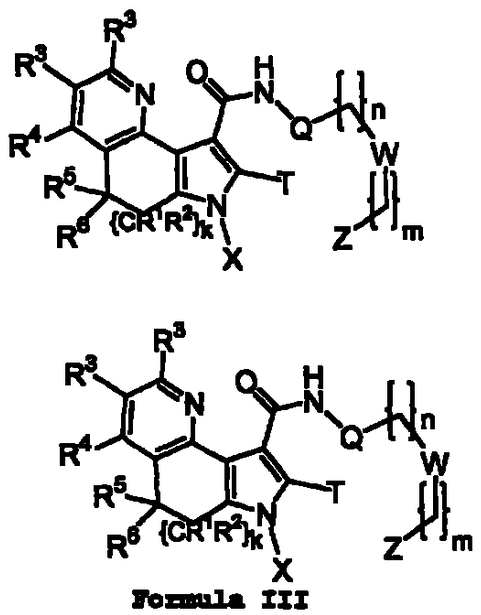
wherein the variables R^1, R^2, R^3, R^4, R^5, R^6, k, n, m, T, X, Q, W, and Z are as defined for Formula I. Compounds of Formula II include compounds where R^1 and R^2 are hydrogen, k is 1 or 2; R^3, R^4, R^5, and R^6, are independently chosen from hydrogen, halogen, amino, hydroxy, methyl, ethyl, methoxy, and ethoxy; and X and T are independently chosen from hydrogen, methyl, and ethyl (compounds of **Formula IIa**). Also includes as compounds of Formula II are compounds wherein R^1, R^2, R^3, R^4, R^5, and R^6 are hydrogen, and k is 1 (compounds of **Formula IIb**). Particularly included as compounds of Formula II are compounds of Formula IIc



Formula IIc.

In Formula IIc (above) the conformation of the methyl group at the 4-position of the indacene ring structure denotes (S) stereochemistry.

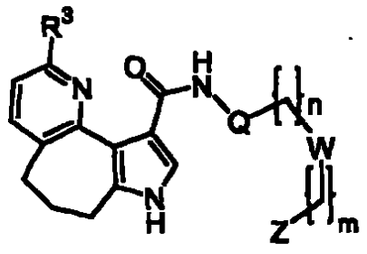
In another embodiment the invention includes compounds of Formula III



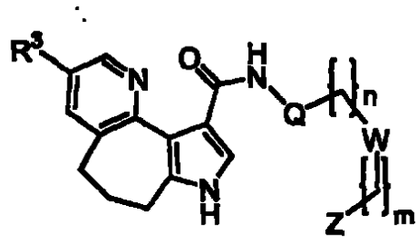
Formula III

and the pharmaceutically acceptable salts thereof, wherein the variables R^1, R^2, R^3, R^4, R^5, R^6, k, n, m, T, X, Q, W, and Z are as defined for Formula I. The definition of the variable R^3 at the 2- position of the pyridyl ring is independent of it definition at the 3- position. Included as compounds of Formula III are those compounds where k is 2 and R^1 and R^2 are hydrogen (compounds of **Formula IIIa**). Other compounds of Formula III are compounds k is 2; R^1 and R^2 are hydrogen; R^3, R^4, R^5, and R^6, are independently chosen at each occurrence from hydrogen, halogen, amino, hydroxy, methyl, ethyl, methoxy, and ethoxy; and X and T are independently chosen from hydrogen, methyl, and ethyl (compounds of **Formula IIIb**). Also particularly included as compounds of Formula III are compounds of Formula IIIc and Formula IIId

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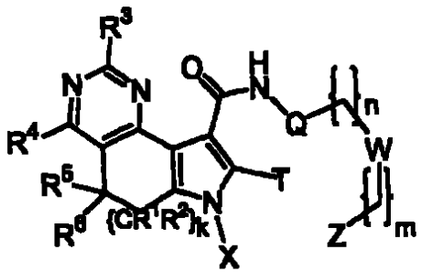
Formula IIIc

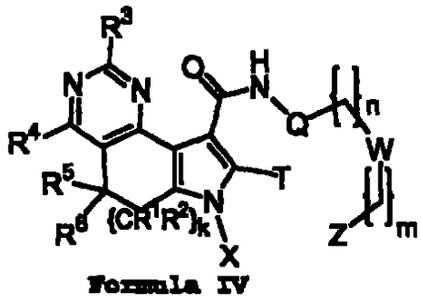


Formula IIId

wherein R^3 is hydrogen or methyl.

The invention also includes compounds of Formula IV

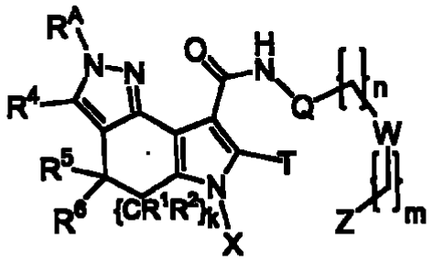




Formula IV

and the pharmaceutically acceptable salts thereof, wherein the variables R^1, R^2, R^3, R^4, R^5, R^6, k, n, m, T, X, Q, W, and Z are asdefined for Formula I. Particular compounds of Formula IV are those compounds where k is 2 and R^1 and R^2 are hydrogen (compounds of Formula IVa). Other compounds of Formula IV are those compounds were k is 2; R^1 and R^2 are hydrogen; R^3, R^4, R^5, and R^6, are independently chosen at each occurrence from hydrogen, halogen, amino, hydroxy, methyl, ethyl, methoxy, and ethoxy; and X and T are independently chosen from hydrogen, methyl, and ethyl (compounds of Formula IVb). Compounds of Formula IV particularly include compounds where k is 2 and R^1, R^2 R^3, R^4, R^5, and R^6 are all hydrogen (compounds of Formula IVc).

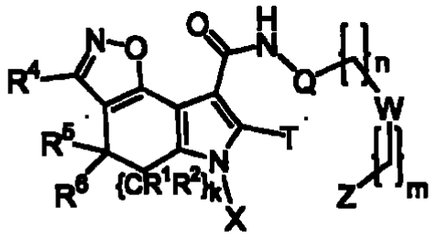
In another embodiment the invention includes compounds of Formula V



Formula V

and the pharmaceutically acceptable salts thereof wherein the variables R^1, R^2, R^A, R^4, R^5, R^6, k, n, m, T, X, Q, W, and Z are as for Formula I. In a more specific embodiment, the invention includes compounds of Formula V where k is 2 and R^1 and R^2 are hydrogen (compounds of **Formula Va**). Still other compounds of Formula V are those compounds where k is 2; R^1 and R^2 are hydrogen; R^A is C_{1-6}alkyl, phenyl, thienyl, pyridyl, pyrimidinyl, pyrrolyl, or imidazolyl; R^3, R^4, R^5, and R^6, are independently chosen from hydrogen, halogen, amino, hydroxy, methyl, ethyl, methoxy, and ethoxy; and X and T are independently chosen from hydrogen, methyl, and ethyl (compounds of **Formula Vb**). In a still more specific embodiment the invention includes compounds of Formula V where k is 2, R^1, R^2, R^3, R^4, R^5, and R^6 are all hydrogen; and R^A is methyl, ethyl, or pyridyl.

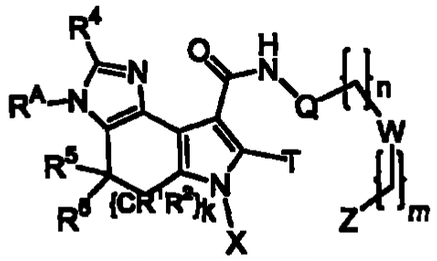
Yet another embodiment of the invention includes compounds of Formula VI



Formula VI

and the pharmaceutically acceptable salts thereof, wherein the variables R^1, R^2, R^4, R^5, R^6, k, n, m, T, X, Q, W, and Z are as defined for Formula I. Particular compounds of Formula VI are compounds where k is 2 and R^1 and R^2 are both hydrogen (compounds of **Formula VIa**). Other compounds of Formula VI are compounds where k is 2; and R^1 and R^2 are both hydrogen; R^4, R^5, and R^6, are independently chosen from hydrogen, halogen, amino, hydroxy, methyl, ethyl, methoxy, and ethoxy; and X and T are independently chosen from hydrogen, methyl, and ethyl (compounds of **Formula VIb**). A particular embodiment of the invention includes compounds of Formula VI where where k is 2; and R^1, R^2, R^5, R^6, X and T are all hydrogen; and R^4 is methyl (compounds of **Formula VIc**).

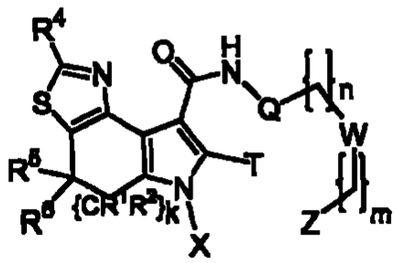
In still another embodiment, the invention provides compounds of Formula VII



Formula VII

and the pharmaceutically acceptable salts thereof, wherein the variables R^1, R^2, R^A, R^4, R^5, R^6, k, n, m, T, X, Q, W, and Z are as defined for Formula I. Included as compounds of Formula VII are compounds where k is 2 and R^1 and R^2 are hydrogen (compounds of **Formula VIIa**). More particularly, the invention includes compounds of Formula VII where k is 2; R^1 and R^2 are hydrogen; R^A is methyl, ethyl, or pyridyl; R^4, R^5, and R^6, are independently chosen from hydrogen, halogen, amino, hydroxy, methyl, ethyl, methoxy, and ethoxy; and X and T are independently chosen from hydrogen, methyl, and ethyl (compounds of **Formula VIIb**). The invention also particularly includes compounds of Formula VII where k is 2; R^1, R^2, R^4, R^5, R^6, X and T are all hydrogen; and R^A is methyl (compounds of **Formula VIIc**).

Further included as compounds of the invention are compounds of Formula VIII

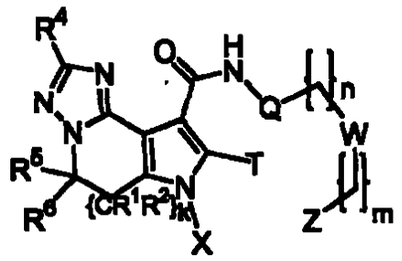


Formula VIII

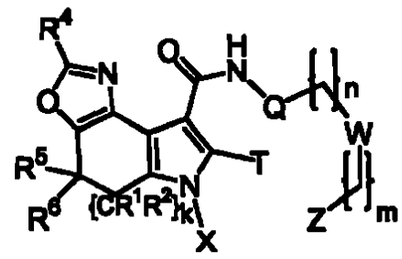
and the pharmaceutically acceptable salts thereof wherein the variables R^1, R^2, R^4, R^5, R^6, k, n, m, T, X, Q, W, and Z are as defined as for Formula I. Such compounds of Formula VIII include compounds where k is 2 and R^1 and R^2 are both hydrogen (compounds of **Formula VIIIa**). In yet another embodiment the invention provides compounds of Formula VIII where k is 2; R^1 and R^2 are both hydrogen; R^4, R^5, and R^6, are independently chosen from hydrogen, halogen, amino, hydroxy, methyl, ethyl, methoxy, and ethoxy; and X and T are independently chosen from hydrogen, methyl, and ethyl (compounds of **Formula VIIIb**). More particularly, the invention provides compounds of Formula VIII where k is 2; R^1, R^2, R^5, R^6, X, and T are all hydrogen; and R^4 is methyl (compounds of **Formula VIIIc**).

For each of Formula IIa, IIb, IIc, IIIa, IIIb, IIIc, IIId, IVa, IVb, IVc, Va, Vb, Vc, VIa, VIb, Vic, VIIa, VIIb, VIIc, VIIIa, VIIIb, and VIIIc the variables n, m, Q, W, and Z are as defined for Formula I.

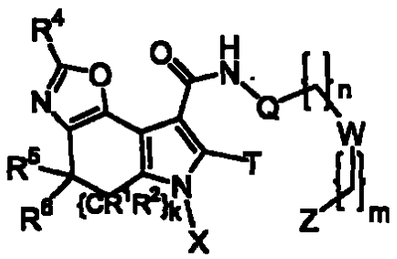
Alternate embodiments of the invention include compounds of Formula IX, Formula X, Formula XI, and Formula XII (shown below) and the pharmaceutically acceptable salts thereof wherein variables R^1, R^2, R^3, R^4, R^5, R^6, k, n, m, T, X, Q, W, and Z are as defined for Formula I.



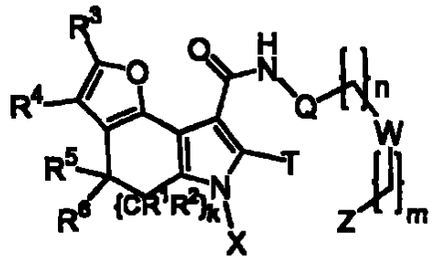
Formula IX



Formula X

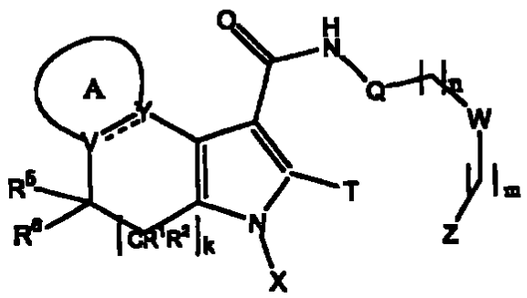


Formula XI



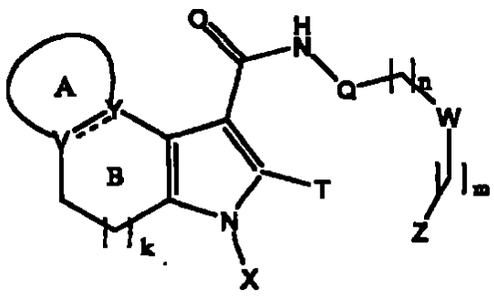
Formula XII

Other compounds provided by the invention, but outside definition of general Formula I include compounds of the formula



where Y is nitrogen, and all other variables are as defined for Formula I.

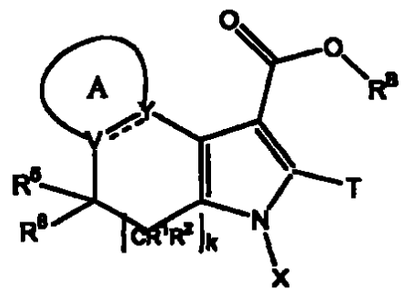
The invention also provides compounds of the formula:



where the "B-ring" would contain up to 4 heteroatoms selected from nitrogen, NR^A, S, and O and would be saturated, unsaturated or aromatic. All other variables are as defined for Formula I.

Further provided by the invention are novel intermediates useful in synthesizing compounds of the invention.

The final step in each of the synthetic schemes provided in the "Preparation of Compounds" section (below) involves the reaction of a novel ether compound to form an amide. For example, see step 11 of Scheme 1. Thus, the invention provides novel ether intermediates of Formula XX

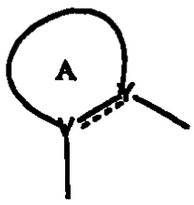


Formula XX

wherein

R^1 and R^2 are independently chosen at each occurrence from hydrogen, halogen, hydroxy, cyano, nitro, amino, alkyl, alkenyl, alkynyl, haloalkyl, and mono or diaminoalkyl, alkoxy, and k is 0, 1, 2, or 3;

the group



referred to as the "A-ring" represents an optionally substituted saturated, unsaturated or aromatic heterocyclic ring containing at least one nitrogen, oxygen or sulfur atom, wherein the $V\!=\!\!=\!\!=\!Y$ bond is a single, double, or aromatic bond;

V is nitrogen, carbon, or CH;

Y is carbon, or CH;

R^5 and R^6 may be taken together to form a carbonyl group; or

R^5 and R^6 are independently chosen from hydrogen, halogen, hydroxy, nitro, cyano, $alkyl_1$, amino, -COOH, $-O(alkyl_1)$, $-SO_2NH_2$, $-SO_2NH(alkyl_1)$, $-SO_2N(alkyl_1)(alkyl_1)$, $-N(alkyl_1)CO(alkyl_1)$, $N(alkyl_1)CO_2(alkyl_1)$, $-NHSO_2(alkyl_1)$, $-N(alkyl_1)SO_2(alkyl_1)$, $-SO_2NHCO(alkyl_1)$, $-CONHSO_2(alkyl_1)$, $-CONH(alkyl_1)$, $-CON(alkyl_1)(alkyl_1)$, $-CO_2(alkyl_1)$, $-CO(alkyl_1)$, $-SO_{0-2}(alkyl_1)$, optionally substituted carbocyclic aryl and optionally substituted heteroaryl groups having from 1 to 3 rings, 3 to 8 members in each ring and from 1 to 3 heteroatoms;

wherein $alkyl_1$ is independently chosen at each occurrence and is straight branched or cyclic, may contain one or two double or triple bonds, and is unsubstituted or substituted with one or more substituents selected from: hydroxy, oxo, halogen, amino, cyano, nitro, alkoxy, -COOH, $-SO_2NH_2$, - $SO_2NH(alkyl)$, $-SO_2N(alkyl)(alkyl)$, $-N(alkyl)CO(alkyl)$, $N(alkyl)CO_2(alkyl)$, $-NHSO_2(alkyl)$, $-N(alkyl)SO_2(alkyl)$, - $SO_2NHCO(alkyl)$, $-CONHSO_2(alkyl)$, $-CONH(alkyl)$, - $CON(alkyl)(alkyl)$, $-CO_2(alkyl)$, $-CO(alkyl)$ $-SO_{0-2}(alkyl)$;

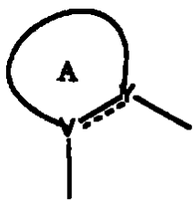
X is chosen from hydrogen, hydroxy, amino, alkyl, and alkoxy;

T is chosen from hydrogen, halogen, hydroxy, amino, alkyl, and alkoxy; and

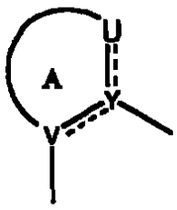
R^a is chosen from hydrogen, methyl, ethyl and benzyl.

Preferred compounds of Formula XX include compounds wherein R^1 and R^2 are independently chosen at each occurrence from hydrogen, halogen, hydroxy, cyano, nitro, amino, haloalkyl, mono or diamino(C_{1-6})alkyl, C_{1-6} alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl and C_{1-6} alkoxy, and k is 0, 1, 2, or 3;

the group



or the "A-ring" is a group of the formula:



which is a saturated, unsaturated or aromatic heterocyclic ring containing at least one nitrogen, oxygen or sulfur atom, wherein the U----Y and V----Y bonds may be single, double or aromatic bonds,

U is nitrogen, NR^A, S, or O;

V is nitrogen, carbon or CH;

Y is carbon, or CH;

and said saturated, unsaturated or aromatic heterocyclic ring is chosen from:

thienyl, thiazolyl, pyridyl, pyrimidinyl, imidazolyl, pyrazolyl, pyrazinyl, pyridizinyl, piperidinyl, oxazolyl, isoxazolyl, symmetrical and unsymmetrical triazolyl, pyrrolyl, furanyl, diazenyl, triazenyl, 1, 2, 4-triazolone, 4,5-dihydroimidazolyl, and 1,4,5,6-tetrahydropyrimidinyl, each of which is optionally substituted at any available nitrogen by R^A and optionally substituted at any available carbon by R^3 and R^4, wherein:

R^A is chosen from hydrogen, $C_{1-6}alkyl_1$, optionally substituted carbocyclic aryl and optionally substituted heteroaryl

groups having from 1 to 3 rings, 3 to 8 members in each ring and from 1 to 3 heteroatoms;

R^5 and R^6 are independently chosen from hydrogen, halogen, hydroxy, nitro, cyano, $C_{1-6}alkyl_1$, amino, -COOH, $-O(C_{1-6}alkyl_1)$, $-NH(C_{1-6}alkyl_1)$, $-N(C_{1-6}alkyl_1)(C_{1-6}alkyl_1)$, $-SO_2NH_2$, $-SO_2NH(C_{1-6}alkyl_1)$, $-SO_2N(C_{1-6}alkyl_1)(C_{1-6}alkyl_1)$, $-N(C_{1-6}alkyl_1)CO(C_{1-6}alkyl_1)$, $N(C_{1-6}alkyl_1)CO_2(C_{1-6}alkyl_1)$, $-NHSO_2(C_{1-6}alkyl_1)$, $-N(C_{1-6}alkyl_1)SO_2(C_{1-6}alkyl_1)$, $-SO_2NHCO(C_{1-6}alkyl_1)$, $-CONHSO_2(C_{1-6}alkyl_1)$, $-CONH(C_{1-6}alkyl_1)$, $-CON(C_{1-6}alkyl_1)(C_{1-6}alkyl_1)$, $-CO_2(C_{1-6}alkyl_1)$, $-CO(C_{1-6}alkyl_1)$ and $-SO_{0-2}(C_{1-6}alkyl_1)$,

wherein $C_{1-6}alkyl_1$ is independently chosen at each occurrence and is straight branched or cyclic, may contain one or two double or triple bonds, and is unsubstituted or substituted with one or more substituents selected from: hydroxy, oxo, halogen, amino, cyano, nitro, alkoxy, carbocylic or heterocyclic group, -COOH, $-SO_2NH_2$, $-SO_2NH(C_{1-4}alkyl)$, $-SO_2N(C_{1-4}alkyl)(C_{1-4}alkyl)$, $-N(C_{1-4}alkyl)CO(C_{1-4}alkyl)$, $N(C_{1-4}alkyl)CO_2(C_{1-4}alkyl)$, $-NHSO_2(alkyl)$, $-N(C_{1-4}alkyl)SO_2(C_{1-4}alkyl)$, $-SO_2NHCO(C_{1-4}alkyl)$, $-CONHSO_2(C_{1-4}alkyl)$, $-CONH(C_{1-4}alkyl)$, $-CON(C_{1-4}alkyl)(C_{1-4}alkyl)$, $-CO_2(C_{1-4}alkyl)$, $-CO(C_{1-4}alkyl)$, and $-SO_{0-2}(C_{1-4}alkyl)$;

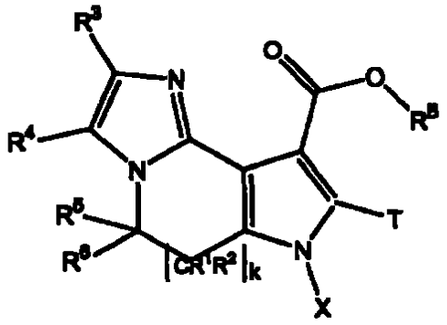
R^3 and R^4 are independently chosen at each occurrence, and are defined the same as R^5 and R^6;

X is chosen from hydrogen, hydroxy, amino, C_{1-6} alkyl, and C_{1-6}alkoxy;

T is chosen from hydrogen, halogen, hydroxy, amino, C_{1-6} alkyl, and C_{1-6} alkoxy; and

R^B is chosen from hydrogen, methyl, ethyl and benzyl. Such compounds will be referred to as compounds of Formula XXa.

The novel ether intermediates of this invention differ primarily in the type of "A-ring" present although other differences may be present. One class of intermediates provided by this invention is represented by Formula XXI

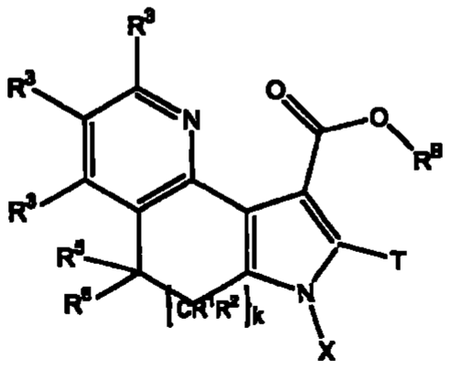


Formula XXI

wherein R^1, R^2, R^3, R^4, R^5, R^6, k, X, T, and R^B are as defined for Formula XXa. Preferred intermediates of Formula XXI are those compounds wherein R^B is defined as defined for Formula XXa; k is 1 or 2; R^1 and R^2 are both hydrogen; and R^3, R^4, R^5, and R^6, are

independently chosen from hydrogen, halogen, amino, hydroxy, methyl, ethyl, methoxy, and ethoxy (compounds of **Formula XXIIa**).

The invention further provides ether intermediates having a pyridyl "A-ring" such as compounds of Formula XXII

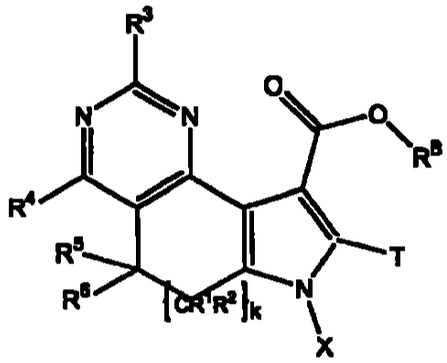


Formula XXII

wherein R^3 is independently selected at each occurrence and is as defined as for Formula XXa and R^1, R^2, R^3, R^5, R^6, k, X, T, and R^B are also defined as for Formula XXa. Particularly, the invention provides as compounds of Formula XXII, compounds where R^B is defined as for Formula XXa; R^1, R^2, R^3, R^5, R^6, k, X, and T are all hydrogen; R^3 is hydrogen at the 3- and 4- positions of the "A-ring" pyridyl group, and is chosen from hydrogen, halogen, amino, hydroxy, methyl, ethyl, methoxy, and ethoxy at the 2- position of this "A-ring" pyridyl group (compounds of **Formula XXIIa**). Also provided as compounds of Formula XXII, are compounds where R^B is defined as for Formula XXa; R^1, R^2, R^3, R^5, R^6, k, X, and T are all hydrogen; R^3 is hydrogen at the 2- and 4-

positions of the "A-ring" pyridyl group, and is chosen from hydrogen, halogen, amino, hydroxy, methyl, ethyl, methoxy, and ethoxy at the 3- position of this "A-ring" pyridyl group (compounds of **Formula XXIIb**).

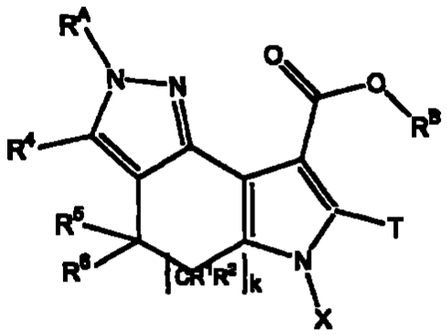
The invention provides ether intermediates of Formula XXIII having a pyrimidinyl "A-ring"



Formula XXIII

wherein R^1, R^2, R^3, R^4, R^5, R^6, k, X, T, and R^8 are as defined in Claim XXa. Preferred compounds of Formula XXIII include compounds where k is 2; R^1, R^2, R^3, R^5, R^6, X, and T are all hydrogen; R^8 is defined as for Formula XXa; and R^4 is chosen from hydrogen, halogen, amino, hydroxy, methyl, ethyl, methoxy, and ethoxy (compounds of Formula XXIIIa).

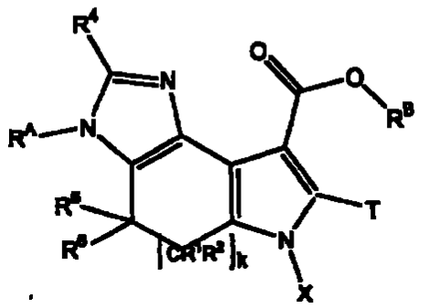
In one embodiment the invention provides compounds of Formula XIV where the "A-ring" is a pyrrole



Formula XIV

wherein R^A, R^1, R^2, R^4, R^5, R^6, k, X, T, and R^B are as defined in Formula XXa. Preferred compounds of Formula XIV include compounds where k is 2; R^A is chosen from hydrogen, methyl, ethyl, and phenyl; R^B is as defined in Formula XXa; and R^1, R^2, R^4, R^5, R^6, X, and T are all hydrogen (compounds of **Formula XIVa**).

The invention further includes compounds of Formula XV

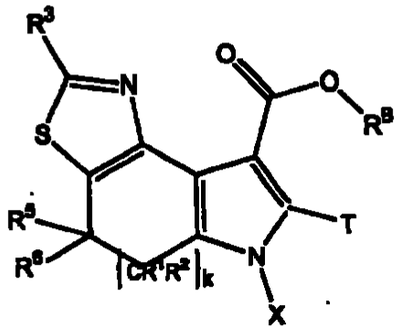


Formula XV

wherein R^A, R^1, R^2, R^3, R^4, R^5, R^6, k, X, T, and R^B are as defined for Formula XXa. Also included as compounds of Formula XV are compounds wherein k is 2; R^A, R^1, R^2, R^4, R^5, R^6, k, X, and T are

all hydrogen; R^B is as defined for Formula XXa; and R^4 is from chosen hydrogen, halogen, amino, hydroxy, methyl, ethyl, methoxy, and ethoxy (compounds of **Formula XVa**).

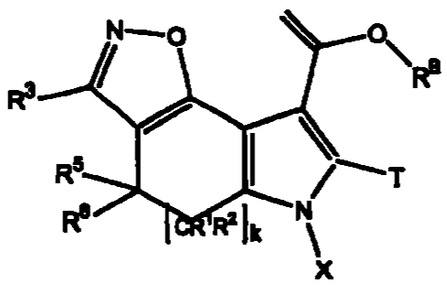
In yet another embodiment the invention provides novel ether intermediates of Formula XVI having thiazole "A-rings"



Formula XVI

wherein R^1, R^2, R^3, R^5, R^6, k, X, T, and R^B are as defined for Formula XXa. Preferably compounds of this class are those compounds where k is 2; R^1, R^2, R^5, R^6, X, and T are hydrogen; R^B is as defined for Formula XXa; and R^3 is chosen from R^3 is chosen from hydrogen, halogen, amino, hydroxy, methyl, ethyl, methoxy, and ethoxy (compounds of **Formula XVIa**).

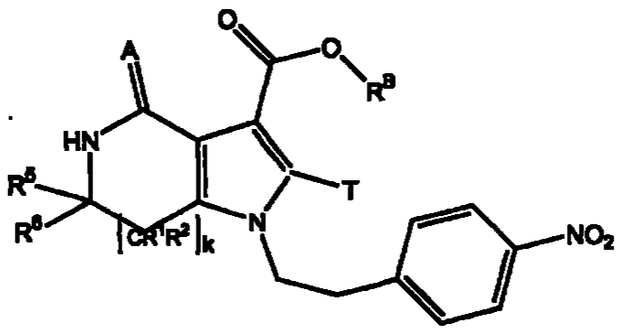
Another class of ether intermediates of the invention is represented by compounds of Formula XXVII having and isoxazole "A-ring"



Formula XXVII

wherein R^1, R^2, R^3, R^5, R^6, k, X, T, and R^8 are as defined in for Formula XXa. Preferably compounds of this class are those compounds where k is 2; R^1, R^2, R^5, R^6, X, and T are hydrogen; R^8 is as defined for Formula XXa; and R^3 is chosen from R^3 is chosen from hydrogen, halogen, amino, hydroxy, methyl, ethyl, methoxy, and ethoxy (compounds of **Formula XVIIa**).

In a number of the synthetic steps used to generate compounds of the invention novel protected intermediates are used. Such protected intermediates include compounds of Formula XXX useful in the synthesis of compounds of the invention having an imidazole "A-ring"



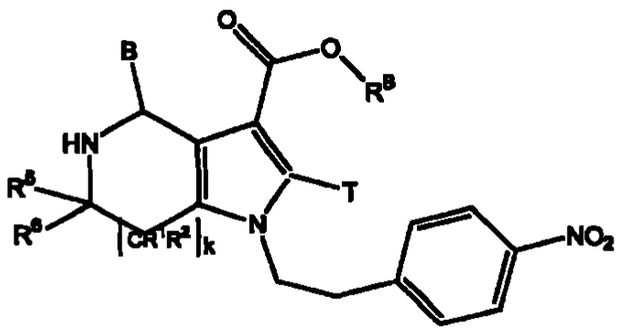
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Formula XXX

wherein A is oxygen or sulfur; k, R^1, R^2, R^5, R^6, R^8 and T are as defined for Formula XXa.

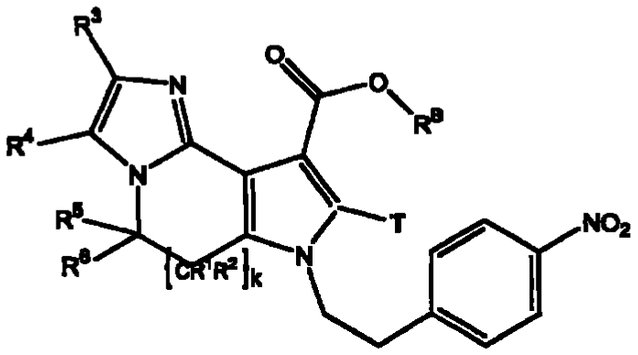
Another class of protected intermediates useful in the synthesis of compounds of the invention having an imidazole "A-ring" are compounds of Formula XXXI



Formula XXXI

Wherein B is $-SCH_3$ or $-NH(CH_2)CH(OCH_3)_2$ and k, R^1, R^2, R^5, R^6, R^8 and T are as defined for Formula XXa.

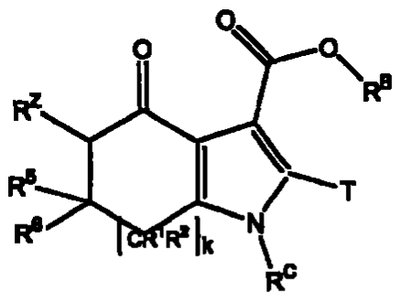
Also provided are compounds of Formula XXXII



Formula XXXII

wherein all variables present in compounds of Formula XXXII are defined as for compounds of Formula XXa.

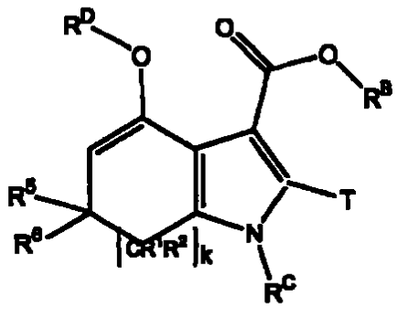
Other classes of novel intermediates provided by the invention are intermediates have BOC and TMS protecting groups (or analogues of such groups) such as compounds of Formula XXXIII



Formula XXXIII

Wherein R^C is chosen from t-butoxycarbonyl, phenyl, alkylsulfonyl, and ethylcarbamoyl; R^Z is hydrogen or bromo; and k, R^B, R^1, R^2, R^5, R^6, and T are defined as for compounds of Formula XXa.

Further provided are compounds of Formula XXXIV



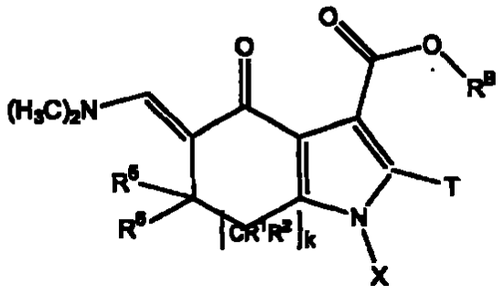
Formula XXXIV

R^C is chosen from t-butoxycarbonyl, phenyl, phenylsulfonyl, alkylsulfonyl, and ethylcarbamoyl;

R^D is chosen from trimethylsilyl, silylmethyl ether, and t-butyldimethylsilyl; and

k, R^B, R^1, R^2, R^5, R^6, and T are defined as for Formula XXa.

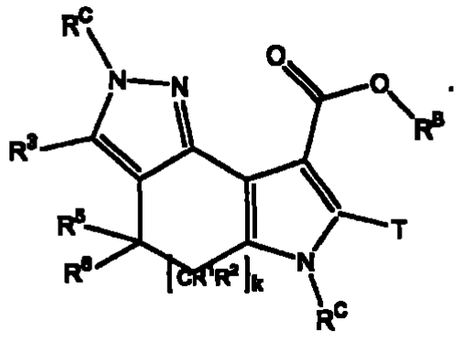
Further, the invention provides as intermediates compounds of Formula XXXV



Formula XXXV

wherein k, R^B, R^1, R^2, R^5, R^6, X and T are as defined for Formula XXa.

Finally, the invention provides compounds of Formula XXXVI as intermediates



Formula XXXVI

R^C is independently chosen at each occurrence from t-butoxycarbonyl, phenyl, phenylsulfonyl, alkylsulfonyl, and ethylcarbamoyl and all other variables are as defined for compounds of Formula XXa.

This invention relates to heterocyclic compounds, such as 5,6-Dihydro-4H-1,3a,6-triaza-as-indacenes,3-thia-1,7-diaza-cyclopenta[e]azulene-9-carboxylic acids, 4,5,6,7-tetrahydro-1-oxa-2,7-diaza-cyclopenta[e]azulene -9-carboxylic acids, 3,8,10-triaza-benzo[e]azulene-1-carboxylic acids, 1-oxa-2,7-diaza-cyclopenta[e]azulene-9-carboxylic acids, 1,3,7-triaza-cyclopenta[e]azulene-9-carboxylic acid phenyl amide and related compounds, that bind with high affinity to the benzodiazepine site of $GABA_A$ receptors, including human $GABA_A$ receptors. This

invention also includes such compounds that bind with high selectivity to the benzodiazepine site of $GABA_A$ receptors, including human $GABA_A$ receptors. Without wishing to be bound to any particular theory, it is believed that the interaction of the compounds of Formula I with the benzodiazepine site results in the pharmaceutical utility of these compounds.

The invention further comprises methods of treating patients in need of such treatment with an amount of a compound of the invention sufficient to alter the symptoms of a CNS disorder. Compounds of the inventions that act as agonists at $\alpha_2\beta_3\gamma_2$ and $\alpha_3\beta_3\gamma_2$ receptor subtypes are useful in treating anxiety disorders such as panic disorder, obsessive compulsive disorder and generalized anxiety disorder; stress disorders including post-traumatic stress, and acute stress disorders. Compounds of the inventions that act as agonists at $\alpha_2\beta_3\gamma_2$ and $\alpha_3\beta_3\beta_2$ receptor subtypes are also useful in treating depressive or bipolar disorders and in treating sleep disorders. Compounds of the invention that act as inverse agonists at the $\alpha_5\beta_3\gamma_2$ receptor subtype or $\alpha_1\beta_2\gamma_2$ and $\alpha_5\beta_3\gamma_2$ receptor subtypes are useful in treating cognitive disorders including those resulting from Down Syndrome, neurodegenerative diseases such as Alzheimer's disease and Parkinson's disease, and stroke related dementia. Compounds of the invention that act as agonists at the $\alpha_1\beta_2\gamma_2$ receptor

subtype are useful in treating convulsive disorders such as epilepsy. Compounds that act as antagonists at the benzodiazepine site are useful in reversing the effect of benzodiazepine overdose and in treating drug and alcohol addiction.

The diseases and/ or disorders that can also be treated using compounds and compositions according to the invention include:

Depression, e.g. depression, atypical depression, bipolar disorder, depressed phase of bipolar disorder.

Anxiety, e.g. general anxiety disorder (GAD), agoraphobia, panic disorder +/- agoraphobia, social phobia, specific phobia, Post traumatic stress disorder, obsessive compulsive disorder (OCD), dysthymia, adjustment disorders with disturbance of mood and anxiety, separation anxiety disorder, anticipatory anxiety acute stress disorder, adjustment disorders, cyclothymia.

Sleep disorders, e.g. sleep disorders including primary insomnia, circadian rhythm sleep disorder, dyssomnia NOS, parasomnias, including nightmare disorder, sleep terror disorder, sleep disorders secondary to depression and/or anxiety or other mental disorders, substance induced sleep disorder.

Cognition Impairment, e.g. cognition impairment, Alzheimer's disease, Parkinson's disease, mild cognitive impairment (MCI), age-related cognitive decline (ARCD), stroke, traumatic brain

injury, AIDS associated dementia, and dementia associated with depression, anxiety or psychosis.

Attention Deficit Disorder, e.g. Attention Deficit Disorder (ADD), Attnetion Deficit Hyperactivity Disorder (ADHD)

The invention also provides pharmaceutical compositions comprising one or more compounds of the invention together with at least one pharmaceutically acceptable carrier. Pharmaceutical compositions include packaged pharmaceutical compositions for treating disorders responsive to $GABA_A$ receptor modulation, e.g., treatment of anxiety, depression, sleep disorders or cognitive impairment by $GABA_A$ receptor modulation. The packaged pharmaceutical compositions include a container holding a therapeutically effective amount of at least one $GABA_A$ receptor modulator as described supra and instructions (e.g., labeling) indicating the contained $GABA_A$ receptor ligand is to be used for treating a disorder responsive to $GABA_A$ receptor modulation in the patient.

In a separate aspect, the invention provides a method of potentiating the actions of other CNS active compounds, which comprises administering an effective amount of a compound of the invention in combination with another CNS active compound. Such CNS active compounds include, but are not limited to the following: for anxiety, serotonin receptor (e.g. $5\text{-}HT_{1A}$) agonists and antagonists; for anxiety and depression, neurokinin receptor

antagonists or corticotropin releasing factor receptor (CRF_1) antagonists; for sleep disorders, melatonin receptor agonists; and for neurodegenerative disorders, such as Alzheimer's dementia, nicotinic agonists, muscarinic agents, acetylcholinesterase inhibitors and dopamine receptor agonists. Particularly the invention provides a method of potentiating the antidepressant activity of selective serotonin reuptake inhibitors (SSRIs) by administering an effective amount of a GABA agonist compound of the invention in combination with an SSRI.

Combination administration can be carried out in a fashion analogous to that disclosed in Da-Rocha, et al., *J. Psychopharmacology* (1997) 11(3) 211-218; Smith, et al., *Am. J. Psychiatry* (1998) 155(10) 1339-45; or Le, et al., *Alcohol and Alcoholism* (1996) 31 Suppl. 127-132. Also see, the discussion of the use of the $GABA_A$ receptor ligand 3-(5-methylisoxazol-3-yl)-6-(1-methyl-1,2,3-triazol-4-yl) methyloxy-1,2,4-triazolo [3,4-a]phthalzine in combination with nicotinic agonists, muscarinic agonists, and acetylcholinesterase inhibitors, in PCT International publications Nos. WO 99/47142, WO 99/47171, and WO 99/47131, respectively. Also see in this regard PCT International publication No. WO 99/37303 for its discussion of the use of a class of $GABA_A$ receptor ligands, 1,2,4-triazolo[4,3-b]pyridazines, in combination with SSRIs.

The present invention also pertains to methods of inhibiting the binding of benzodiazepine compounds, such as Ro15-1788, to the $GABA_A$ receptors which methods involve contacting a compound of the invention with cells expressing $GABA_A$ receptors, wherein the compound is present at a concentration sufficient to inhibit benzodiazepine binding to $GABA_A$ receptors *in vitro*. This method includes inhibiting the binding of benzodiazepine compounds to $GABA_A$ receptors *in vivo*, e.g., in a patient given an amount of a compound of Formula A or Formula I that would be sufficient to inhibit the binding of benzodiazepine compounds to $GABA_A$ receptors *in vitro*. In one embodiment, such methods are useful in treating benzodiazepine drug overdose. The amount of a compound that would be sufficient to inhibit the binding of a benzodiazepine compound to the $GABA_A$ receptor may be readily determined via a $GABA_A$ receptor binding assay, such as the assay described in Example 24. The $GABA_A$ receptors used to determine *in vitro* binding may be obtained from a variety of sources, for example from preparations of rat cortex or from cells expressing cloned human $GABA_A$ receptors.

The present invention also pertains to methods for altering the signal-transducing activity, particulary the chloride ion conductanc of $GABA_A$ receptors, said method comprising exposing cells expressing such receptors to an effective amount of a compound of the invention. This method includes altering the

signal-transducing activity of $GABA_A$ receptors *in vivo*, e.g., in a patient given an amount of a compound of Formula A or Formula I that would be sufficient to alter the signal-transducing activity of $GABA_A$ receptors *in vitro*. The amount of a compound that would be sufficient to alter the signal-transducing activity of $GABA_A$ receptors may be determined via a $GABA_A$ receptor signal transduction assay, such as the assay described in Example 25.

The $GABA_A$ receptor ligands provided by this invention and labeled derivatives thereof are also useful as standards and reagents in determining the ability of a potential pharmaceutical to bind to the $GABA_A$ receptor.

Labeled derivatives the $GABA_A$ receptor ligands provided by this invention are also useful as radiotracers for positron emission tomography (PET) imaging or for single photon emission computerized tomography (SPECT).

Definitions

For compounds of the present invention that have asymmetric centers, this invention includes all of the optical isomers or enantiomers and mixtures thereof as well as the racemic mixtures of the enantiomers.

In addition, compounds with carbon-carbon double bonds may occur in Z- and E- forms, with all isomeric forms of the compounds being included in the present invention. 491

When any variable (e.g. C_{1-6} alkyl, alkyl, alkyl$_1$ R^1-R^{10}) occurs more than one time in Formula I, its definition on each occurrence is independent of its definition at every other occurrence.

As used herein, the terms "alkyl" "C_{y-x} alkyl" in the present invention is meant straight or branched chain alkyl groups of generally up to 6 or 8 carbon atoms, or for C_{y-x} alkyl the number of carbon atoms specified, for example, C_{1-6} alkyl indicates straight or branched chain alkyl groups having from 1 to 6 carbon atoms. Examples of alkyl groups include methyl, ethyl, propyl, isopropyl, n-butyl, sec-butyl, tert-butyl, pentyl, 2-pentyl, isopentyl, neopentyl, hexyl, 2-hexyl, 3-hexyl, and 3-methylpentyl. Preferred C_{1-8} alkyl groups are methyl, ethyl, propyl, butyl, pentyl and cyclopentyl.

The term "alkoxy" represents an alkyl group, as described above, attached through an oxygen bridge, such as methoxy, ethoxy, propoxy and isopropoxy.

The term "alkenyl" is intended to include hydrocarbon chains of either a straight or branched configuration comprising one or more unsaturated carbon-carbon bonds which may occur in any stable point along the chain, such as ethenyl and propenyl.

The term "alkynyl" is intended to include hydrocarbon chains of either a straight or branched configuration comprising one or more triple carbon-carbon bonds which may occur in any stable point along the chain, such as ethynyl and propynyl.

The term "carbocylic aryl" is used to indicate aromatic groups that contain only carbon atoms in the ring structure. Such groups are optionally substituted.

The term "cycloalkyl" is intended to include saturated ring groups, having the specified number of carbon atoms, such as cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl.

In the term "(C_{3-x} cycloalkyl)C_{1-y} alkyl the point of attachment is on the alkyl group. This term encompasses, but is not limited to, cyclopropylmethyl, cyclohexylmethyl, cyclohexylmethyl.

The term "haloalkyl" is intended to include both branched and straight-chain saturated aliphatic hydrocarbon groups having the specified number of carbon atoms, substituted with 1 or more halogen (for example $-C_vF_w$ where v = 1 to 3 and w = 1 to (2v+1). Examples of haloalkyl include, but are not limited to, trifluoromethyl, trichloromethyl, pentafluoroethyl, and pentachloroethyl.

As used herein, the terms "heterocyclic group" or "heterocycloalkyl" is intended to mean a stable 5-to 7-membered monocyclic or bicyclic or 7-to 10-membered bicyclic heterocyclic

492

493

ring which is saturated partially unsaturated or unsaturated (aromatic), and which consists of carbon atoms and from 1 to 4 heteroatoms independently selected from N, O and S and including any bicyclic group in which any of the above-defined heterocyclic rings is fused to a benzene ring. The nitrogen and sulfur heteroatoms may optionally be oxidized. The term "heteroaryl" is used to specifically indicate aromatic heterocyclic groups.

The heterocyclic ring may be attached to its pendant group at any heteroatom or carbon atom that results in a stable structure. The heterocyclic rings described herein may be substituted on carbon or on a nitrogen atom if the resulting compound is stable. A nitrogen in the heterocycle may optionally be quaternized. It is preferred that when the total number of S and O atoms in the heterocycle exceeds 1, then these heteroatoms are not adjacent to one another. It is preferred that the total number of S and O atoms in the heterocycle is not more than 1. As used herein, the term "aromatic heterocyclic system" is intended to mean a stable 5-to 7-membered monocyclic or bicyclic or 7- to 10-membered bicyclic heterocyclic aromatic ring which consists of carbon atoms and from 1 to 4 heteroatoms independently selected from N, O and S. It is preferred that the total number of S and O atoms in the aromatic heterocycle is not more than 1.

Examples of heterocycles include, but are not limited to, acridinyl, azocinyl, benzimidazolyl, benzofuranyl, benzothiofuranyl, benzothiophenyl, benzoxazolyl, benzothiazolyl, benzotriazolyl, benoztetrazolyl, benzisoxazolyl, benzisothiazolyl, benzimidazolinyl, carbazolyl, NH-carbazolyl, carbolinyl, chromanyl, chromenyl, cinnolinyl, decahydroquinolinyl, 2*H*,6*H*-1,5,2-dithiazinyl, dihydrofuro[2,3-*b*]tetrahydrofuran, furanyl, furazanyl, imidazolidinyl, imidazolinyl, imidazolyl, 1H-indazolyl, indolenyl, indolinyl, indolizinyl, indolyl, 3*H*-indolyl, isobenzofuranyl, isochromanyl, isoindazolyl, isoindolinyl, isoindolyl, isoquinolinyl, isothiazolyl, isoxazolyl, morpholinyl, naphthyridinyl, octahydroisoquinolinyl, oxadiazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl;- 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, oxazolidinyl, oxazolyl, oxazolidinyl, pyrimidinyl, phenanthridinyl, phenanthrolinyl, phenazinyl, phenothiazinyl, phenoxathiinyl, phenoxazinyl, phthalazinyl, piperazinyl, piperidinyl, pteridinyl, purinyl, pyranyl, pyrazinyl, pyrazolidinyl, pyrazolinyl, pyrazolyl, pyridazinyl, pyridooxazole, pyridoimidazole, pyridothiazole, pyridinyl, pyridyl, pyrimidinyl, pyrrolidinyl, pyrrolinyl, 2*H*-pyrrolyl, pyrrolyl, quinazolinyl, quinolinyl, 4H-quinolizinyl, quinoxalinyl, quinuclidinyl, tetrahydrofuranyl, tetrahydroisoquinolinyl, tetrahydroquinolinyl,

6*H*-1,2,5-thiadiazinyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,2,5-thiadiazolyl, 1,3,4thiadiazolyl, thianthrenyl, thiazolyl, thienyl, thienothiazolyl, thienooxazolyl, thienoimidazolyl, thiophenyl, triazinyl, 1,2,3-triazolyl, 1,2,4-triazolyl, 1,2,5-triazolyl, 1,3,4-triazolyl, and xanthenyl.

The term "halogen" indicates fluorine, chlorine, bromine, and iodine.

Non-toxic "pharmaceutically acceptable salts" include, but are not limited to salts with inorganic acids such as hydrochloride, sulfate, phosphate, diphosphate, hydrobromide, and nitrite or salts with an organic acid such as malate, maleate, fumarate, tartrate, succinate, citrate, acetate, lactate, methanesulfonate, p-toluenesulfonate, 2-hydroxyethylsulfonate, salicylate and stearate. Similarly, pharmaceutically acceptable cations include, but are not limited to sodium, potassium, calcium, aluminum, lithium and ammonium. The present invention also encompasses the prodrugs of the compounds of Formula I.

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Pharmaceutical Preparations

Those skilled in the art will recognize various synthetic methodologies that may be employed to prepare non-toxic pharmaceutically acceptable prodrugs of the compounds encompassed by Formula I. Those skilled in the art will

recognize a wide variety of non-toxic pharmaceutically acceptable solvents that may be used to prepare solvates of the compounds of the invention, such as water, ethanol, mineral oil, vegetable oil, and dimethylsulfoxide.

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. Oral administration in the form of a pill, capsule, elixir, syrup, lozenge, troche, or the like is particularly preferred. The term parenteral as used herein includes subcutaneous injections, intradermal, intravascular (e.g., intravenous), intramuscular, spinal, intrathecal injection or like 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 that 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 monosterate 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 monoleate, and condensation products of the

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said partial esters with ethylene oxide, for example polyoxyethylene sorbitan monoleate. The emulsions may also contain sweetening and flavoring agents.

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

The compounds of general Formula I may also be administered in the form of suppositories, e.g., for rectal administration of

the drug. These compositions can be prepared by mixing the drug with a suitable non-irritating excipient that is solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum to release the drug. Such materials are cocoa butter and polyethylene glycols.

Compounds of general Formula I may be administered parenterally in a sterile medium. The drug, depending on the vehicle and concentration used, can either be suspended or dissolved in the vehicle. Advantageously, adjuvants such as local anesthetics, preservatives and buffering agents can be dissolved in the vehicle.

For administration to non-human animals, the composition may also be added to the animal feed or drinking water. It will be convenient to formulate these animal feed and drinking water compositions so that the animal takes in an appropriate quantity of the composition along with its diet. It will also be convenient to present the composition as a premix for addition to the feed or drinking water.

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.

Frequency of dosage may also vary depending on the compound used and the particular disease treated. However, for treatment of most disorders, a dosage regimen of 4 times daily or less is preferred. For the treatment of anxiety, depression, or cognitive impairment a dosage regimen of 1 or 2 times daily is particularly preferred. For the treatment of sleep disorders a single dose that rapidly reaches effective concentrations is desirable.

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

Preferred compounds of the invention will have certain pharmacological properties. Such properties include, but are not limited to oral bioavailability, low toxicity, low serum protein binding and desirable *in vitro* and *in vivo* half-lifes. Penetration of the blood brain barrier for compounds used to treat CNS disorders is necessary, while low brain levels of

502
503

compounds used to treat peripheral disorders are often preferred.

Assays may be used to predict these desirable pharmacological properties. Assays used to predict bioavailability include transport across human intestinal cell monolayers, including Caco-2 cell monolayers. Toxicity to cultured hepatocyctes may be used to predict compound toxicity. Penetration of the blood brain barrier of a compound in humans may be predicted from the brain levels of the compound in laboratory animals given the compound intravenously.

Serum protein binding may be predicted from albumin binding assays. Such assays are described in a review by Oravcová, et al. (Journal of Chromatography B (1996) volume 677, pages 1-27).

Compound half-life is inversely proportional to the frequency of dosage of a compound. *In vitro* half-lifes of compounds may be predicted from assays of microsomal half-life as described by Kuhnz and Gieschen (Drug Metabolism and Disposition, (1998) volume 26, pages 1120-1127).

Preparation of compounds

A general illustration of the preparation of compounds of Formula I in the present invention is given in Schemes 1-4. In the reaction schemes and discussions that follow, unless otherwise indicated, k, R^A, R^1, R^2, R^3, R^4, R^5, R^6 are as defined

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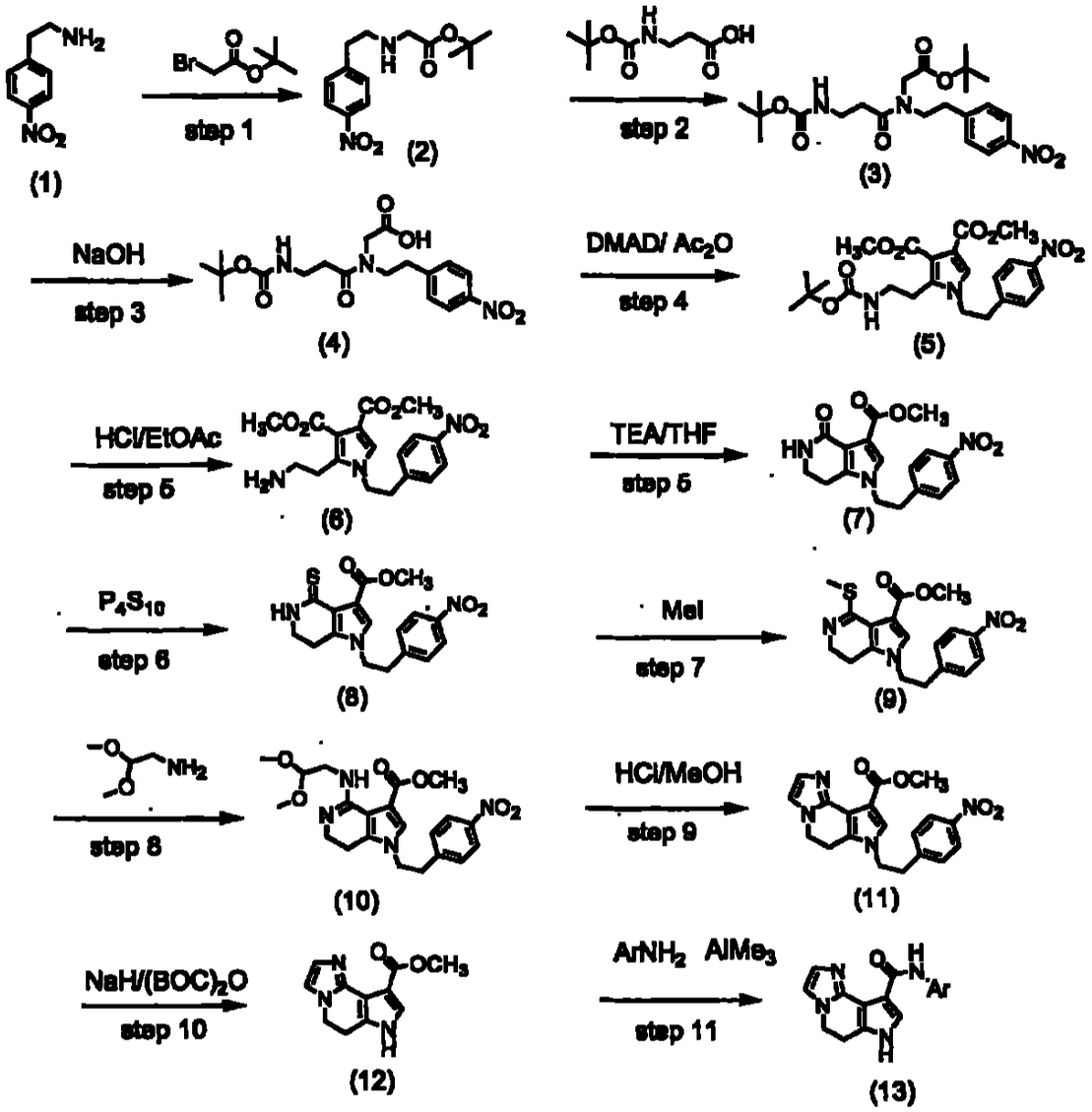
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above. Within the schemes and tables that follow, Ar is intended to represent $Q-(CH_2)_n-W-(CH_2)_n-Z$ as defined in Formula I or a suitably protected form thereof. When a protecting group is required, an optional deprotection step may be employed. Suitable protecting groups and methodology for protection and deprotection such as those described in *Protecting Groups in Organic Synthesis* by T. Greene are well known and appreciated in the art. Examples requiring protection/deprotection will be readily apparent to those skilled in the art.

WO 96/07639 PCT/US95/11205

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Scheme 1



In Scheme 1 step 1, *p*-nitrophenethylamine is alkylated with tert-butyl bromo acetate to form compound (2). In general, excess *p*-nitrophenethylamine is used in this reaction to minimize bis-alkylation. In step 2, the secondary amine in

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compound (2) is coupled with BOC-protected 3-aminopropanoic acid to form compound (3). This coupling may be efficiently accomplished by treating a mixture of compound (2) in pyridine with N-Boc 3-aminopropanoic with a coupling agent such as EDCI with stirring at ambient temperature. In step 3, the *tert*-butyl ester in compound (3) is cleaved under basic conditions to form the carboxylic acid (4). Compound (4) is reacted with dimethyl acetylene dicarboxylate in the presence of acetic anyhydride in step 4 to form the pyrrole (5). Pyrrole (5) is sequentually deprotected using hydrogen chloride in step 5 to expose the primary amine in compound (6) and cyclized in the presence of base to form lactam (7). In step 6, lactam (7) is converted to the thiolactam (8) by reaction under appropriate sulfur transfer conditions such as heating with P_4S_{10} in pyridine. In steps 7 and 8, thiolactam (8) is alkylated with methyl iodide in acetone to form the methylsulfanyl compound (9) which is reacted with aminoacetaldehyde dimethyl acetal in methanol to form compound (10). Cyclization of the dimethyl acetal derivative (10) is accomplished in step 9 by heating (10) with concentrated hydrochloric acid in methanol to form compound (11). Removal of the *p*-nitrophenethyl protecting group is accomplished in step 10 by treatment of (11) with sodium hydride in the presence of di-*tert*-butyl dicarbonate in dimethylformamide. Quenching of excess sodium hydride with acetic acid followed by hydrolysis of

the BOC group from the pyrrole nitrogen using aqueous potassium bicarbonate provides the desired deprotected material (12). As indicated by step 11 in Scheme 1, ester (12) serves as a versatile acylating agent for a variety of aluminum complexes of aryl and heteroaryl amines to form the corresponding amides (13).

Another procedure for forming amide derivatives (13) is provided in Example 2a and involves hydrolysis of ester (12) by heating in the presence of 48% hydrobromic acid. The resulting carboxylic acid is then reacted with various aryl amines in the presence of an appropriate coupling reagent such as O-(1H-benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate. Alternatively, the carboxylic acid may be converted to the mixed anhydride by reaction with ethyl or isobutyl chloroformate in the presence of triethylamine. The resulting mixed anhydride is then reacted with aryl amines.

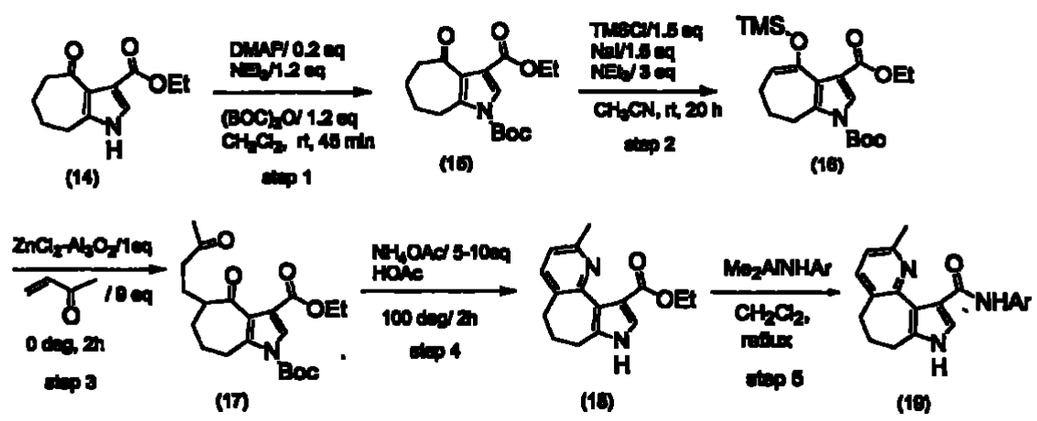
Compounds of Formula II where R^5 or R^6 is methyl are formed as illustrated in Scheme 1 by reaction of compound (2) with 3-aminobutyric acid in step 2. Optically pure or optically enriched material is obtained by separation of advanced intermediates on a suitable chiral HPLC column such as Chiralpak AD. For material resolved by this method, the absolute stereochemistry is correlated to a X-ray crystal structure of a chiral amide derivative. Alternatively, optically pure 3-

aminobutyric acid may be employed in step 2. Compounds of Formula II wherein both R^5 and R^6 are methyl are obtained as illustrated in Scheme 1 by use of 3-amino-3-methylbutyric acid in step 2.

Compounds of Formula II wherein R^3 is methyl may be formed as illustrated by Scheme 1 by employing 2-aminopropionaldehyde dimethyl acetal in step 8.

Those skilled in the art will realize that the synthetic transformations described by Scheme 1 may be accomplished using a variety of alternate reagents and reaction conditions. Further, it is readily apparent that additional compounds within the scope of Formula II but not specifically described within the experimental section may be prepared in analogous fashion.

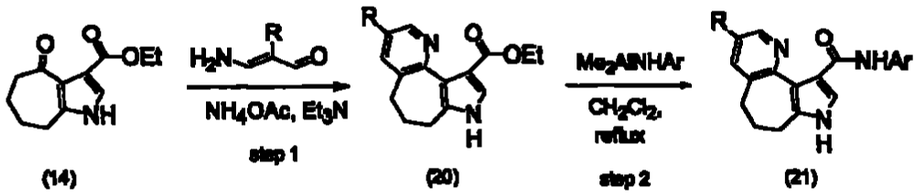
Scheme 2



Scheme 2 reveals a method for converting known ketone (14) (US patent no. 5,723,462, col.23-31 is hereby incorporated by reference for its teachings regarding the synthesis of such ketones) to compounds of Formula III with R^3 as methyl. Step 1 describes formation of the BOC-protected derivative (15). Typically this transformation is carried out by treating pyrrole (14) with di-tert-butyl dicarbonate in a suitable solvent such as dichloromethane or 1,4-dioxane at temperatures ranging from 0 °C to ambient temperature in the presence of an organic base such as triethylamine. Additives such as 4-N,N-dimethylaminopyridine may be used to facilitate this transformation. In step 2, the BOC-protected material (15) is efficiently converted to silyl enol ether (16) by treatment with a mixture of trimethylsilyl chloride, sodium iodide and triethylamine at ambient temperature. Lewis acid-facilitated 1,4-addition is accomplished in step 3 by treatment with excess methyl vinyl ketone at 0 °C in the presence of zinc chloride-alumina to yield the diketone (17). Treatment of the diketone (17) with ammonium acetate at elevated temperature in step 4 provides the desired methyl-substituted pyridyl derivative (18) which is aminated in step 5 using amination conditions previously described for Scheme 1.

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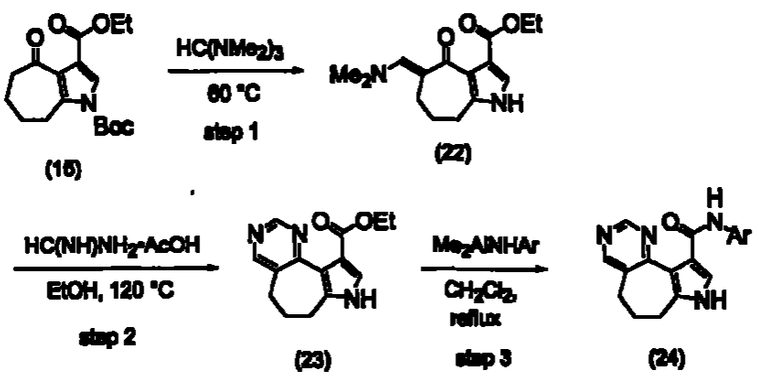
Scheme 3



Scheme 3 shows a method for converting known ketone (14) [US5723462] to compounds of Formula III with R^3 as hydrogen. In step 1, pyridine ring formation is accomplished by treatment of ketone (14) with 3-aminoacrolein (R = H) and catalytic ammonium acetate in triethylamine at elevated temperature. Conversion of (14) to (20) can also be accomplished by heating (14) in triethylamine with 3-dimethylaminoacrolein in the presence of excess ammonium acetate. If 3-amino-2-methylacrolein (R = CH_3) is used in step 1, a 3-methylpyridine ring is formed. Amination is accomplished in step 2 as previously described.

Those skilled in the art will recognize that the reactions described in Scheme 3 may also be applied to synthesize compounds of Formula III wherein k=1 by starting with the appropriate known ketone.

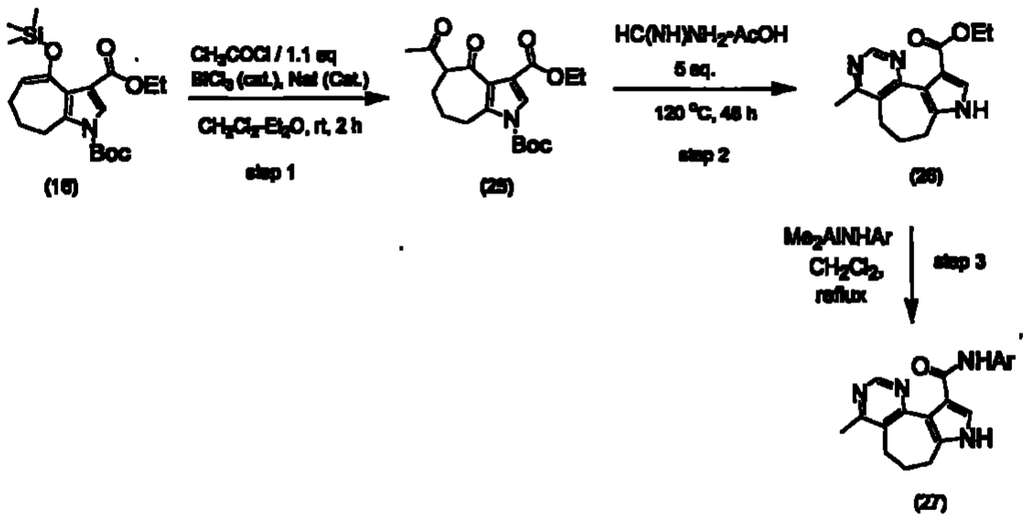
Scheme 4



Scheme 4 outlines conditions for conversion of ketone (15) to compounds of Formula IV. In step 1, ketone (15) is reacted with tris(dimethylamino)methane with heating in a sealed tube to afford compound (22). In step 2, compound (22) undergoes reaction with formamidine acetate in ethanol at 120 °C to yield the pyrimidine derivitive (23). As shown in step 3, compound (23) serves as a versatile intermediate for reaction with aluminum complexes of a variety of aryl amines under conditions previously described.

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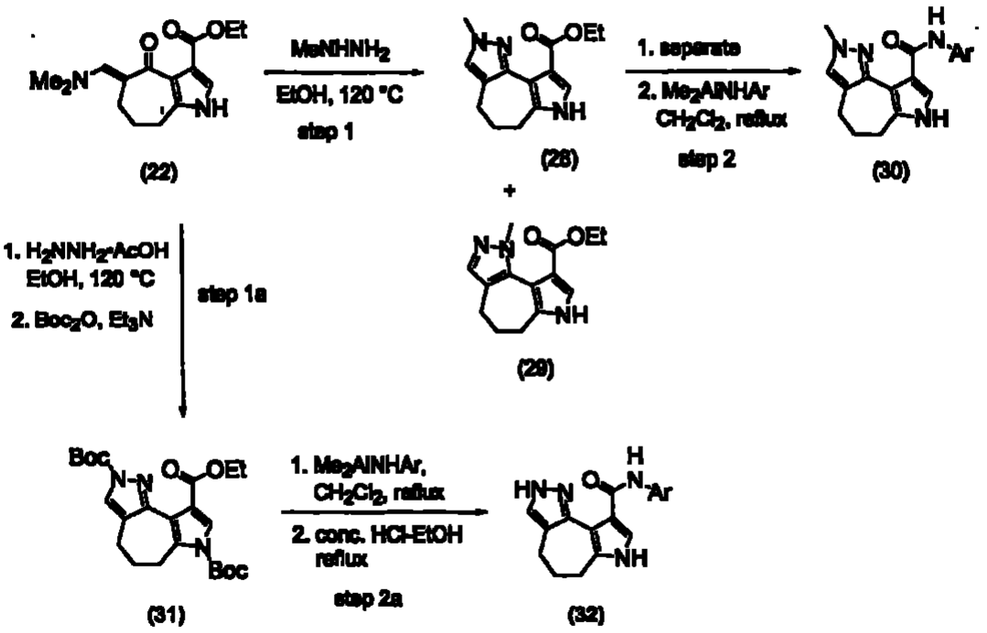
Scheme 5



Scheme 5 describes a method for producing compounds of Formula IV wherein R^4 is methyl. Reaction of compound (16) from Scheme 2 with acetyl chloride in the presence of catalytic sodium iodide and a suitable Lewis acid such as bismuth trichloride gives diketone (25). Subsequent reaction with formamidine acetate as per Scheme 4, provides methyl pyrimidine (26) which is aminated in step 3 as previously described.

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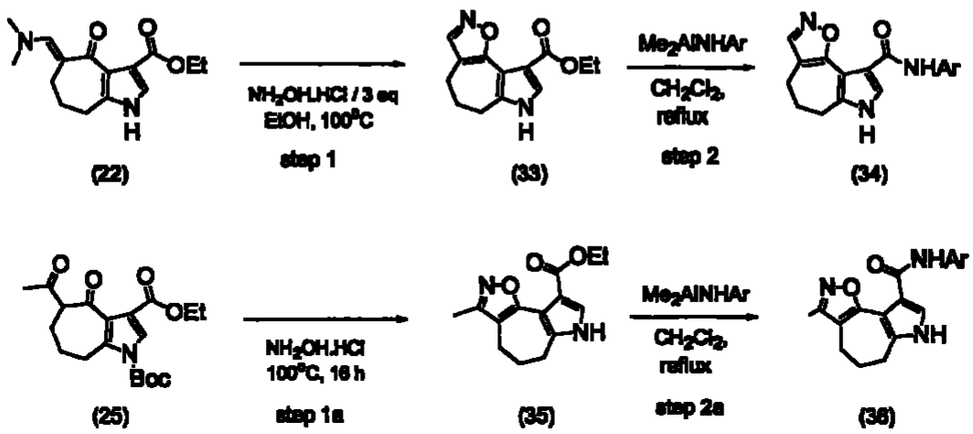
Scheme 6



Scheme 6 provides a means of obtaining compounds of Formula V. In step 1, compound (22) from Scheme 4 is reacted with methylhydrazine in ethanol at 120 °C to obtain approximately a 3:1 mixture of compounds (28) and (29). The structure of compound (28) is assigned based on X-ray crystal analysis. After separation by chromatography on silica gel, compound (28) is converted to amide derivatives in step 2 as previously described. Compound (29) may likewise be reacted. Reaction of (22) with hydrazine acetate as shown in step 1a provides a pyrazole ring with a free NH. To improve the handling characteristics of this material, it is BOC-protected by means

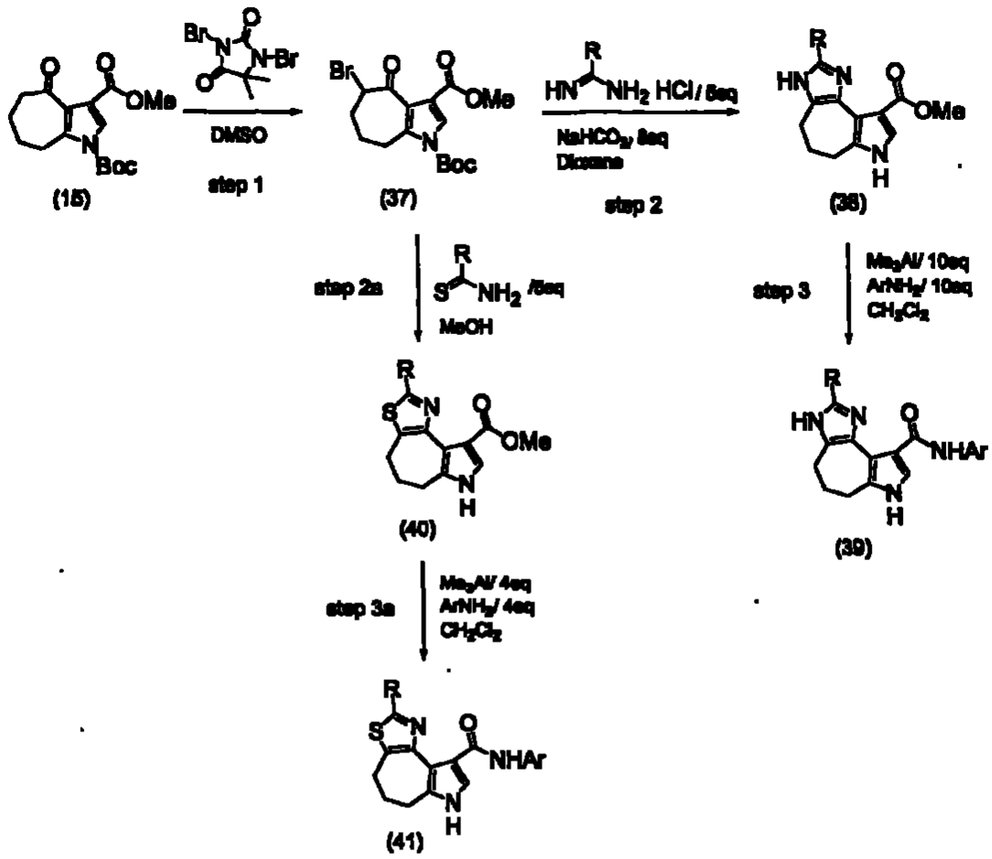
of reaction with di-*tert*-butyl dicarbonate in the presence of triethylamine to give compound (31). Compound (31) can be converted to amide derivatives (32) as shown in step 2a using previously described conditions.

Scheme 7



Scheme 7 illustrates the synthesis of isoxazole derivatives of Formula VI. In step 1, compound (22) from Scheme 4 is reacted with hydroxylamine hydrochloride in ethanol at 100 °C to provide isoxazole (33). Analogous reaction of diketone (25) with hydroxylamine hydrochloride affords the methyl isoxazole (35). Amination of (33) and (35) is accomplished in steps 2 and 2a using previously described conditions.

Scheme 8



The synthesis of compounds of Formula VII and Formula VIII is outlined in Scheme 8. In Scheme 8 step 1, ketone (15) from Scheme 2 is brominated with a suitable brominating agent such as 1,3-dibromo-4,4-dimethylhydantoin. The resulting bromoketone (37) is reacted with various amidines in step 2 to give the corresponding imidazoles (38). Typically, the amidine hydrochloride is used in the presence of excess base in 1,4-

dioxane as solvent. Alternatively, bromoketone (37) can be reacted with thioamides to form thiazole derivatives (40). The esters (38) and (40) react to form amides as in steps 3 and 3a as previously described. Examples in the present invention of Formula VII and VIII with k=1 are formed using entirely analogous procedures.

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.

The invention is illustrated further by the following examples, which are not to be construed as limiting the invention in scope or spirit to the specific procedures described in them.

EXAMPLES

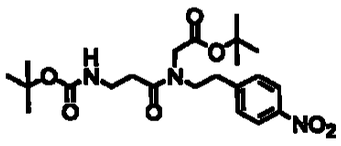
Example 1

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Preparation of 5,6-dihydro-4H-1,3a,6-triaza-as-indacene-8-carboxylic acid methyl ester

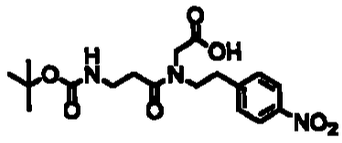
Step 1:

To a solution of p-nitro phenethylamine (45.3mmol) in 75 ml water is enough 30% NaOH in water added to achieve a pH of 12. The water layer is extracted with Dichloromethane. The organic layers were collected, dried over Na_2SO_4, and evaporated *in vacuo* yielding 7.4g yellow brown oil (98%). To a partialy dissolved mixture of free base (44.58 mmol) in ether is Bromo acetic acid t-butyl ester (22.29 mmol) slowly added over 15 min. Using an overhead stirring apparatus it stirred for 3 ½ days under a nitrogen atmosphere. Water is added to the reaction mixture, and the ether layer is washed 3 times with water and once with brine. The water layers were collected and back-extracted with a 50/50 ether/EtOAc mix. All the organic layers were collected, dried over Na_2SO_4, and evaporated *in vacuo*. The dark orange solid is chromatographed using Hexane 3: EtOAc 1 as mobile phase to yield 3.48g yellow solid (56%). 1HNMR (CDCl3) 1.42 (s, 9H), 2.90 (s, 4H), 3.29 (s, 2H), 7.35 (d, 2H), 8.13 (d, 2H) LRMS calcd 280.33 found [M+H] 281.1



Step 2:

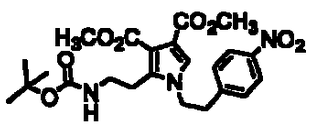
To a mixture of 2-(4-Nitro-phenyl)-ethylamino- acetic acid tert-butyl ester in 1ml pyridine is N-Boc B alanine (0.178mmol), and EDCI (0.214mmol) added. After stirring at RT for 3 ½ hours the pyridine is evaporated off. The remaining oil is taken up in EtOAc and washed with dilute acid. The organic layers were combined, dried over Na_2SO_4, and evaporated *in vacuo* yielding (3-tert-Butoxycarbonylamino-propionyl)-[2-(4-nitro-phenyl)-ethyl]-α-amino-acetic acid tert-butyl ester, 78mg yellow oil. ^{1}HNMR (CD_3OD) 1.45 (d, 9H), 1.50 (d, 9h), 2.46-2.48 (m, 2H), 2.98-3.08 (m, 2H), 3.27-3.35 (m, 2H), 3.62-3.75 (m, 2H), [4.03, 4.11] (s, 2H), 7.56-7.59 (m, 2H), 8.20-8.23 (m, 2H) LRMS calcd 451.52 found [M] 451.2



Step 3:

To a mixture of {(3-tert-Butoxycarbonylamino-propionyl)-[2-(4-nitro-phenyl)-ethyl]-amino}-acetic acid tert-butyl ester (2.5mmol) in .11 ml THF is 22 ml water added, followed by NaOH (17.5mmol). After heating at 60°C for 5 ½ hours it is quenched with acetic acid (20mmol). It is placed in the refrigerator

for 2 ½ days. The THF is evaporated off, and the remaining water is extracted several times with EtOAc. The organic layers were combined, dried over Na_2SO_4 and evaporated *in vacuo* yielding {(3-tert-Butoxycarbonylamino-propionyl)-[2-(4-nitro-phenyl)-ethyl]-amino}-acetic acid, 983mg, as a dark yellow/brown oil/foam (99%). ^{1}HNMR (CD_3OD) 1.40 (d, 9H), 2.44-2.45 (m, 2H), [2.98, 3.03] (t, 2H), 3.22-3.30 (m, 2H), [3.60, 3.65] (t, 2H), 4.06 (s, 2H), [7.52, 7.54] (d, 2h), 8.16 (t, 2H) LRMS calcd 395.42 found. [M-H] 394.0



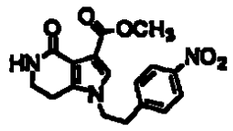
Step 4:

To a mixture of {(3-tert-Butoxycarbonylamino-propionyl)-[2-(4-nitro-phenyl)-ethyl]-amino}-acetic acid (0.253mmol) in 1ml acetic anhydride is dimethyl acetylene dicarboxylate (0.278mmol) added. After stirring at 85°C for 4 ½ hours the solvent is evaporated *in vacuo*. The dark brown oil is chromatographed using EtOAc 2: Hexane 3 as a mobile phase to yield 2-(2-tert-Butoxycarbonylamino-ethyl)-1-[2-(4-nitro-phenyl)-ethyl]-1H-pyrrole-3,4-dicarboxylic acid dimethyl ester, 79mg, as a yellow oil (66%). ^{1}HNMR (CD_3OD) 1.50 (s, 9H), 2.84 (t, 2H), 3.14-3.34

(m, 4H), 3.77 (s, 3H), 3.82 (s, 3H), 4.33 (t, 2H), 6.74 (t, 1H), 7.29 (s, 1H), 7.44 (d, 2H), 8.16 (d, 2H) LRMS calcd 475.50 found [M] 475.1

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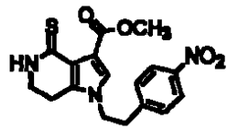
Step 5:

A solution of 2-(2-tert-Butoxycarbonylamino-ethyl)-1-[2-(4-nitro-phenyl)-ethyl]-1H-pyrrole-3,4-dicarboxylic acid dimethyl ester (0.292mmol) in 10 HCl/EtOAc is stirred at RT for ½ hour. The solvent is evaporated *in vacuo* and placed on the high vacuum pump for several hours yielding 139mg white solid ^{1}HNMR (CD_3OD) 2.92-2.94 (m, 2H), 2.97-2.99 (m, 2H), 3.20 (t, 3H), 3.75 (s, 3H), 3.79 (s, 3H), 4.26 (t, 2H), 7.33 (d, 3H), 8.15 (d, 2H) LRMS calcd 375.38 found [M+H] 376.2) which is stirred in 7ml THF with TEA (1.168mmol) at 60°C for 16 hours. The solvent is evaporated *in vacuo* and chromatographed using EtOAc 9: MeOH 1 as mobile phase to yield 1-[2-(4-Nitro-phenyl)-ethyl]-4-oxo-4,5,6,7-tetrahydro-1H-pyrrolo[3,2-c]pyridine-3-carboxylic acid methyl ester, 73mg, as a white solid (73%). ^{1}HNMR (CD_3OD) 2.47 (t, 2H), 3.16 (t, 2H), 3.23-3.33 (m, 2H), 3.74 (s, 3H),

4.23 (t,2H), 7.30 (t, 3H), 8.11 (d, 2H) LRMS calcd 343.33 found [M+H] 344.2

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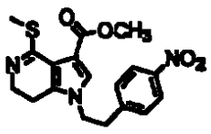
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Step 6:

In a round bottom flask under N_2 atm. were the 1-[2-(4-Nitro-phenyl)-ethyl]-4-oxo-4,5,6,7-tetrahydro-1H-pyrrolo[3,2-c]pyridine-3-carboxylic acid methyl ester (48.64mmol), P_4S_{10} (24.32mmol) and 240ml pyridine combined and heated at 65°C for 8 hours. After cooling to RT it is poured over ~600 ml ice and stirred for 2 hours. The yellow solid is filtered off, washed (2x) with water and dried on the high vacuum for 18h to yield 1-[2-(4-Nitro-phenyl)-ethyl]-4-thioxo-4,5,6,7-tetrahydro-1H-pyrrolo[3,2-c]pyridine-3-carboxylic acid methyl ester, 10.24g, as a yellow solid (65%). ^{1}HNMR (CD_3OD) 2.43 (t, 2H), 3.16 (t, 2H), 3.28-3.33 (m, 2H), 3.75 (s, 3H), 4.21 (t, 2H), 7.16 (s, 1H), 7.30 (d, 2H), 8.13 (d, 2H) LRMS calcd 359.41 found [M+H] 360.2

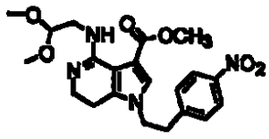
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Step 7:

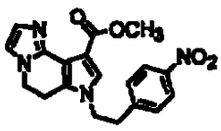
To a solution of 1-[2-(4-Nitro-phenyl)-ethyl]-4-thioxo-4,5,6,7-tetrahydro-1H-pyrrolo[3,2-c]pyridine-3-carboxylic acid methyl ester (28.16mmol) in 130ml acetone is MeI (56.32mmol) and K_2CO_3 (84.48mmol) added. The reaction mixture is stirred at RT for 2 ½ hours whereby the acetone is evaporated *in vacuo*. The remaining oil is taken up in Dichloromethane and washed two times with water. The organic solvents were collected, dried over Na_2SO_4 and evaporated *in vacuo* to yield 4-Methylsulfanyl-1-[2-(4-nitro-phenyl)-ethyl]-6,7-dihydro-1H-pyrrolo[3,2-c]pyridine-3-carboxylic acid methyl ester, 9.46g, as a yellow foam (90%). ^{1}HNMR (CD_3OD) 2.34-2.39 (m, 5H), 3.21 (t, 2H), 3.56 (t, 2H), 3.80 (s, 3H), 4.29 (t, 2H), 7.32-7.38 (m, 3H), 8.17 (d, 2H) LRMS calcd 373.43 found [M+H] 374.2

522
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Step 8:

In a round bottom flask were 4-Methylsulfanyl-1-[2-(4-nitro-phenyl)-ethyl]-6,7-dihydro-1H-pyrrolo[3,2-c]pyridine-3-carboxylic acid methyl ester (25.33mmol), amino acetaldhyde dimethyl acetal (63.32mmol) and 125ml MeOH combined (a part "oiled-out" that later went into solution) and stirred at RT for 20 hours. The solvent is evaporated *in vacuo* yielding 4-(2,2-Dimethoxy-ethylamino)-1-[2-(4-nitro-phenyl)-ethyl]-6,7-dihydro-1H-pyrrolo[3,2-c]pyridine-3-carboxylic acid methyl ester, 11.56g, as a yellow oil/solid that is taken on crude.

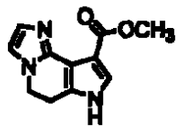


Step 9:

To a solution of 4-(2,2-Dimethoxy-ethylamino)-1-[2-(4-nitro-phenyl)-ethyl]-6,7-dihydro-1H-pyrrolo[3,2-c]pyridine-3-carboxylic acid methyl ester (25.33mmol) in 125ml MeOH is 10ml HCl conc. added. It is heated at 63°C for 15 hours. Since the reaction is not complete another 5ml HCl conc. is added, and it is heated again at 63°C for 10 hours. The solvent is evaporated in vacuo, and the remaining oil is dissolved in MeOH whereby

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K_2CO_3 (1.2eq.) is added. After stirred at RT for 1h the solid is filtered off, washed with MeOH and the filtrate is evaporated *in vacuo* yielding a yellow solid that is protonated. The protonated product is stirred in Dichloromethane and saturated $NaCO_3$ sol. until everything dissolved. The two layers were separated and the water layer is extracted two times with dichloromethane. The organic layers were collected, dried and evaporated *in vacuo* yielding a free base which is tritrated in EtOAc yielding 6-[2-(4-Nitro-phenyl)-ethyl]-5,6-dihydro-4H-1,3a,6-triaza-as-indacene-8-carboxylic acid methyl ester, 9.11g, as a yellow solid (77%). ^{1}HNMR (CD_3OD) 2.76 (t, 2H), 3.18 (t, 2H), 3.78 (s, 3H), 4.07 (t, 2H), 4.28 (t, 2H), 6.94 (s, 1H), 7.01 (s, 1H), 7.31 (d, 3H), 8.10 (d, 2H) LRMS calcd 366.38 found [M+H] 367.2



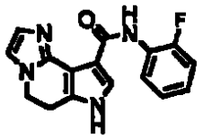
Step 10:

To a solution of 6-[2-(4-Nitro-phenyl)-ethyl]-5,6-dihydro-4H-1,3a,6-triaza-as-indacene-8-carboxylic acid methyl ester (19.67mmol) in 100ml DMF is treated with sodium hydride (60%, 1.97g, 49.18 mmol) portionwise. The reaction is complete in about 2h at 20oC. Chloroform is added and the reaction mixture is cooled to 5 oC before the dropwise addition of acetic acid

(3.15 ml, 55.08 mmol) until pH of 1-3. A saturated solution of aqueous KHCO3 (150ml) is added, stirred and separated. The separated organic phase is washed with water twice. The filtrate is concentrated directly. Most of the DMF is removed by high vacuum to give a brown wet solid. The wet solid is cooled to room temp. Ether is added, stirred, and filtered to give a brown solid which is dried in air overnight to give 5,6-dihydro-4H-1,3a,6-triaza-as-indacene-8-carboxylic acid methyl ester, 9.11g, (77%). ^{1}HNMR (CD_3OD) 3.05 (t, 2H), 3.86 (s, 3H), 4.25 (t, 2H), 6.97 (s, 1H), 7.05 (s, 1H), 7.40 (s, 1H) LRMS calcd 217.23 found [M-H] 216.1

Example 2

Preparation of 5,6-Dihydro-4H-1,3a,6-triaza-as-indacene-8-carboxylic acid (2-fluoro-phenyl)-amide



To a solution of 2-fluoroaniline (84uL, 0.829 mmol) in 2 mL dichloromethane at room temperature is added a 2M solution of trimethylaluminum in toluene (414 uL, 0.829 mmol) and the reaction is stirred at r.t. for 0.5 h. This solution is then

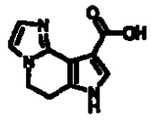
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syringed into the neat give 5,6-dihydro-4H-1,3a,6-triaza-as-indacene-8-carboxylic acid methyl ester (90 mg, 0.415 mmol) and stirred at reflux for 10 h. The reaction mixture is diluted with dichloromethane and poured onto water (30 mL). The whole mixture is filtered through celite and then separated. The aqueous phase is washed with dichloromethane and the combined organics were dried (Na2SO4) and concentrated in vacuo. The residue is purified by Flash-40 chromatography (EtOAc) to afford the product, 5,6-Dihydro-4H-1,3a,6-triaza-as-indacene-8-carboxylic acid (2-fluoro-phenyl)-amide, 63mg, as an glassy oil (48%). ^{1}HNMR (DMSO) 3.25 (t, 2H), 4.44 (t, 2H), 7.23-7.42 (m, 4H)., 7.57-7.63 (m, 2H), 7.96 (s, 1H) LRMS calcd 296.30 found (M-H) 295.0

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Example 2a

5,6-Dihydro-4H-1,3a,6-triaza-as-indacene-8-carboxylic acid hydrobromide

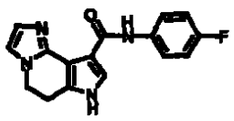


A solution of 5,6-dihydro-4H-1,3a,6-triaza-as-indacene-8-carboxylic acid methyl ester (516mg) and 48% hydrobromic acid (5mL) is heated at 60° for 60 hours. The mixture is cooled to room temperature and concentrated *in vacuo*. The residue is

slurried with diethyl ether and the ether is decanted off. This is repeated until no more color is visible in the ether layer. The remaining solid is dried *in vacuo* to give 5,6-dihydro-4H-1,3a,6-triaza-as-indacene-8-carboxylic acid hydrobromide, 350mg, brown solid 1H NMR(d6DMSO) 3.17 (2H, t), 4.40 (2H, t), 7.35 (1H, d), 7.57 (1H, d), 7.63 (1H, s), 12.34 (1H, s), 12.45 (1H, s).

Example 2b

5,6-Dihydro-4H-1,3a,6-triaza-as-indacene-8-carboxylic acid (4-fluorophenyl)amide



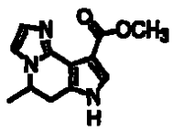
A mixture of 5,6-dihydro-4H-1,3a,6-triaza-as-indacene-8-carboxylic acid hydrobromide (58mg), O-(1H-benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (181mg), triethylamine (0.07mL), 4-fluoroaniline (30mg), and N,N-dimethylformamide (4mL) is heated at 40° for 18 hours. The mixture is cooled to room temperature, treated with water (15mL), and extracted with ethyl acetate (3 x 50mL). The combined organic layers were washed with water (2 x 15mL) and brine (1 x 15mL), dried over magnesium sulfate, and concentrated *in vacuo*. The residue is purified by preparative thin layer chromatography on silica gel, eluting with 5% methanol in

527

dichloromethane, to give 5,6-dihydro-4H-1,3a,6-triaza-as-indacene-8-carboxylic acid (4-fluorophenyl)amide, pale brown solid, 18mg, LRMS calcd 296.30, found [M+H] 297.2. 528

Example 2c

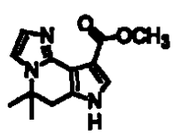
4-Methyl-5,6-dihydro-4H-1,3a,6-triaza-as-indacene-8-carboxylic methyl ester



The title compound is prepared following the procedure outlined in Example 1 starting with 3-aminobutyric acid. Electrospray MS *m/z* 232 [M+1]; ^{1}H NMR (DMSO-d6, 300 MHz) δ 11.62 (s, 1H), 7.38 (s, 1H), 7.08 (s, 1H), 6.81 (s, 1H), 4.43 (m, 1H), 3.68 (s, 3H), 3.05 (dd, 1H), 2.67 (dd, 1H), 1.38 (d, 3H).

Example 2d

4,4-Dimethyl-5,6-dihydro-4H-1,3a,6-triaza-as-indacene-8-carboxylic methyl ester

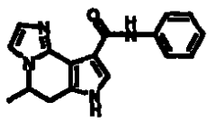


The title compound is prepared following the procedure outlined in Example 1 starting with 3-amino-3-methylbutyric acid. Electrospray MS *m/z* 246 [M+1]; ^{1}H NMR (DMSO-d6, 300 MHz) δ 11.70

(s, 1H), 7.39 (s, 1H), 7.18 (s, 1H), 6.82 (s, 1H), 3.68 (s, 3H), 2.85 (s, 2H), 1.40 (s, 6H).

Example 2e

4-Methyl-5,6-dihydro-4H-1,3a,6-triaza-as-indacene-8-carboxylic acid phenyl amide



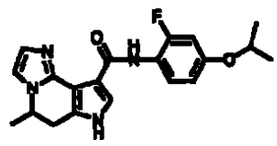
A mixture of 4-methyl-5,6-dihydro-4H-1,3a,6-triaza-as-indacene-8-carboxylic acid hydrobromide (25mg), aniline (12mg), 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (23mg), 1,4-dioxane (1.5mL), and water (1.5mL) is stirred at room temperature for 4 days. 0.5N sodium hydroxide solution (3mL) is added and the mixture is extracted with dichloromethane (3 x 50mL). The combined organic layers were washed with brine (1 x 10mL), dried over magnesium sulfate and concentrated *in vacuo*. The residue is purified by preparative thin layer chromatography on silica gel, eluting with 5% methanol in dichloromethane, to give 4-methyl-5,6-dihydro-4H-1,3a,6-triaza-as-indacene-8-carboxylic acid phenyl amide, cream solid, 7mg, LRMS calcd 292.34, found [M+H] 293.2.

529

530

Example 3

4-Methyl-5,6-dihydro-4H-1,3a,6-triaza-as-indacene-8-carboxylic acid (2-fluoro-4-isopropoxyphenyl)amide



Ethyl chloroformate (66μL) is added dropwise to an ice-cold mixture of 4-methyl-5,6-dihydro-4H-1,3a,6-triaza-as-indacene-8-carboxylic acid hydrobromide (192mg), triethylamine (0.33mL), and N,N-dimethylformamide (5mL). The mixture is stirred at 0° for 1 hour then at room temperature for 30 minutes. 2-Fluoro-4-isopropoxyaniline (66mg) is added and the mixture is stirred at room temperature for 18 hours. The mixture is diluted with ethyl acetate (50mL) then treated with water (25mL), and extracted with ethyl acetate (3 x 50mL). The combined organic layers were washed with water (2 x 20mL) and brine (1 x 20mL), dried over magnesium sulfate, and concentrated *in vacuo*. The residue is purified by preparative thin layer chromatography on silica gel, eluting with diethyl ether, to give a brown solid. This is treated with ethanol (2mL) and saturated aqueous potassium carbonate solution (1mL) and the mixture is heated at 60° for 30 minutes. The mixture is cooled to room temperature and diluted with water (3mL) and extracted with ethyl acetate (3 x 30mL). The combined organic layers were washed with brine (1

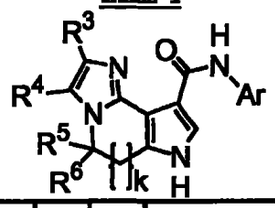
x 10mL), dried over magnesium sulfate, and concentrated *in vacuo*. The oily residue is purified by preparative thin layer chromatography on silica gel, eluting with 10% methanol in dichloromethane, to give 4-methyl-5,6-dihydro-4H-1,3a,6-triaza-as-indacene-8-carboxylic acid (2-fluoro-4-isopropoxyphenyl)amide, pale yellow solid, 10mg, LRMS calcd 368.40, found [M+H] 369.2.

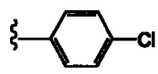
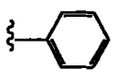
Example 4

Additional 1,3a,6-triaza-as-indacene-8-carboxylic acid compounds

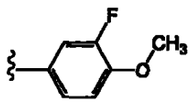
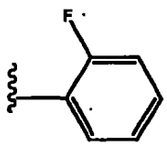
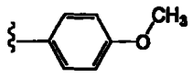
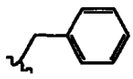
Using the methods shown in Scheme 1 and further illustrated in Examples 1, 2-2e, and 3 the compounds shown in Table 1 were synthesized.

TABLE 1

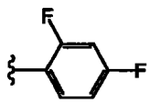
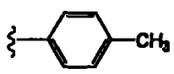
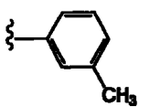


Cpd #	Name	R3	R4	R5	R6	n	Ar	Spectral Data
1.	5,6-Dihydro-4H-1,3a,6-triaza-as-indacene-8-carboxylic acid (4-chloro-phenyl)-amide	H	H	H	H	1		1HNMR (DMSO) 3.24 (t, 2H), 4.44 (t, 2H), 7.37 (s, 1H), 7.45 (d, 2H), 7.65 (s, 1H), 7.82 (d, 2H), 8.01 (m, 1H) LRMS calcd 312.76 found (M-H) 311.0
2.	5,6-Dihydro-4H-1,3a,6-triaza-as-indacene-8-carboxylic acid phenylamide	H	H	H	H	1		^{1}HNMR (DMSO) 3.24 (t, 2H), 4.44 (t, 2H), 7.14 (t, 1H), 7.37-7.42 (m, 3H), 7.65 (s, 1H), 7.77 (d, 2H), 8.00 (s, 1H) LRMS calcd 278.31 found (M-H) 277.0

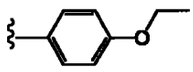
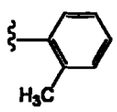
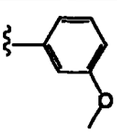
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3.	5,6-Dihydro-4H-1,3a,6-triaza-as-indacene-8-carboxylic acid (3-fluoro-4-methoxy-phenyl)-amide	H	H	H	H	1		1HNMR (DMSO) 3.23 (t, 2H), 3.84 (s, 3H), 4.44 (t, 2H), 7.19 (t, 1H), 7.37-7.44 (m, 2H), 7.64 (s, 1H), 7.79 (d, 1H), 7.95 (s, 1H) LRMS calcd 326.33 found (M-H) 325.2
4.	5,6-Dihydro-4H-1,3a,6-triaza-as-indacene-8-carboxylic acid 2-fluoro-benzylamide	H	H	H	H	1		1HNMR (DMSO) 3.21 (t, 2H), 4.41 (t, 2H), [4.52, 4.58] (d, 2H), 7.17-7.24 (m, 2H), 7.31-7.41 (m, 3H), 7.60 (s, 1H), 7.78 (s, 1H) LRMS calcd 310.33 found [M-H] 309.0
5.	5,6-Dihydro-4H-1,3a,6-triaza-as-indacene-8-carboxylic acid (4-methoxy-phenyl)-amide	H	H	H	H	1		1HNMR (DMSO) 3.19 (t, 2H), 3.72 (s, 3H), 4.39 (t, 2H), 6.92 (d, 2H), 7.31 (s, 1H), 7.60 (d, 3H), 7.92 (s, 1H) LRMS calcd 308.34 found [M+H] 309.0
6.	5,6-Dihydro-4H-1,3a,6-triaza-as-indacene-8-carboxylic acid	H	H	H	H	1		1HNMR (DMSO) 3.18 (t, 2H), 4.37 (t, 2H), 4.49 (d, 2H), 7.22-7.24 (m, 1H),

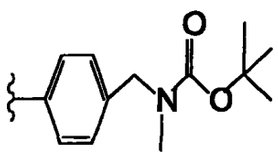
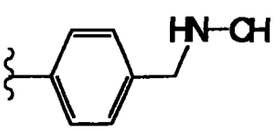
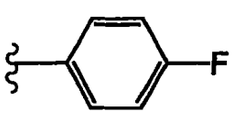
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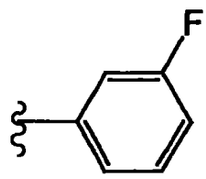
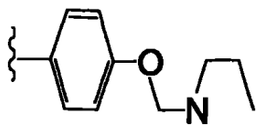
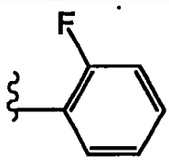
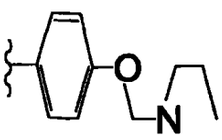
	benzylamide							7.27-7.33 (m, 5H), 7.56 (s, 1H), 7.72 (s, 1H), 9.03 (m, 1H) LRMS calcd 292.34 found [M+H] 293.4
7.	5,6-Dihydro-4H-1,3a,6-triaza-as-indacene-8-carboxylic acid (2,4-difluoro-phenyl)-amide	H	H	H	H	1		1HNMR (CD3OD) 3.28-3.31 (m, 2H), 4.7 (t, 2H), 6.95-7.04 (m, 1H), 7.05-7.09 (m, 1H), 7.31 (s, 1H), 7.43 (s, 1H), 7.69-7.74 (m, 1H), 7.79 (s, 1H), 9.80 (s, 1H) LRMS calcd found [M+]
8.	5,6-Dihydro-4H-1,3a,6-triaza-as-indacene-8-carboxylic acid p-tolylamide	H	H	H	H	1		1HNMR (CD3OD) 2.30 (s, 3H), 3.10 (t, 2H), 4.24 (t, 2H), 7.03-7.04 (m, 2H), 7.14 (d, 2H), 7.42 (s, 1H), 7.69 (d, 2H) LRMS calcd 292.34 found [M+H] 293.3
9.	5,6-Dihydro-4H-1,3a,6-triaza-as-indacene-8-carboxylic acid m-tolylamide	H	H	H	H	1		1HNMR (CD3OD) 2.34 (s, 3H), 3.11 (t, 2H), 4.24 (t, 2H), 6.89 (d, 1H), 7.04 (s, 2H), 7.20 (t, 1H), 7.42 (s,

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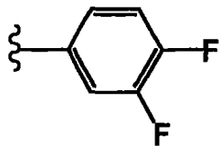
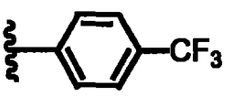
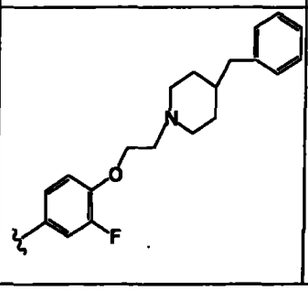
								(t, 1H), 7.42 (s, 1H), 7.60 (d, 1H), 7.65 (s, 1H) LRMS calcd 292.34 found [M+H] 293.2
10.	5,6-Dihydro-4H-1,3a,6-triaza-as-indacene-8-carboxylic acid (4-ethoxy-phenyl)-amide	H	H	H	H	1		1HNMR (CD3OD) 1.37 (t, 3H), 3.10 (t, 2H), 4.01 (q, 2H), 4.23 (t, 2H), 6.90 (d, 2H), 7.02 (d, 2H), 7.41 (s, 1H), 7.69 (d, 2H) LRMS calcd 322.37 found [M+H] 323.3
11.	5,6-Dihydro-4H-1,3a,6-triaza-as-indacene-8-carboxylic acid o-tolylamide	H	H	H	H	1		1HNMR (CD3OD) 2.37 (s, 3H), 3.12 (t, 2H), 4.24 (t, 2H), 6.91 (s, 1H), 7.01 (s, 1H), 7.09 (t, 1H), 7.18 (t, 1H), 7.24 (d, 1H), 7.44 (s, 1H), 7.50 (d, 1H) LRMS calcd 292.34 found [M+H] 293.3
12.	5,6-Dihydro-4H-1,3a,6-triaza-as-indacene-8-carboxylic acid (3-methoxy-phenyl)-amide	H	H	H	H	1		1HNMR (CD3OD) 3.11 (t, 2H), 3.80 (s, 3H), 4.24 (t, 2H), 6.64 (d, 1H), 7.04 (s, 2H), 7.23 (t, 1H), 7.31 (d, 1H), 7.43 (s, 1H), 7.57

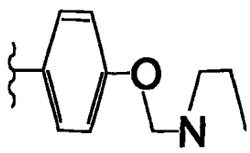
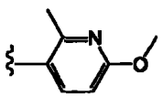
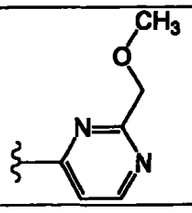
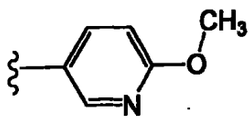
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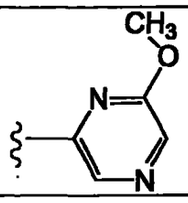
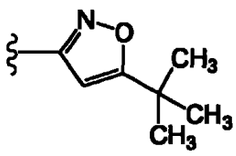
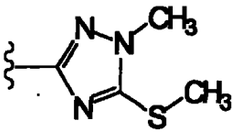
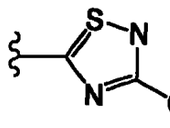
								7.43 (s, 1H), 7.57 (s, 1H) LRMS calcd 308.33 found [M+H] 309.2
13.	{4-[(5,6-Dihydro-4H-1,3a,6-triaza-as-indacene-8-carbonyl)-amino]-benzyl}-methyl-carbamic acid tert-butyl ester	H	H	H	H	1		
14.	5,6-Dihydro-4H-1,3a,6-triaza-as-indacene-8-carboxylic acid (4-methylaminomethyl-phenyl)-amide	H	H	H	H	1		1HNMR (CD3OD) 2.70 (s, 1H), 3.28-3.31 (m, 2H), 4.15 (s, 2H), 4.46 (t, 2H), 7.35 (s, 1H), 7.45-7.49 (m, 3H), 7.81 (s, 1H), 7.87-7.90 (m, 2H) LRMS calcd 321.38 found [M+H] 322.3
15.	5,6-Dihydro-4H-1,3a,6-triaza-as-indacene-8-carboxylic acid (4-fluoro-phenyl)-amide	H	H	H	H	1		

16.	5,6-Dihydro-4H-1,3a,6-triaza-as-indacene-8-carboxylic acid (3-fluoro-phenyl)-amide	H	H	H	H	1		
17.	4-Methyl-5,6-dihydro-4H-1,3a,6-triaza-as-indacene-8-carboxylic acid [4-(2-propylamino-ethoxy)-phenyl]-amide	H	H	H	CH3	1		
18.	4-Methyl-5,6-dihydro-4H-1,3a,6-triaza-as-indacene-8-carboxylic acid (2-fluoro-phenyl)-amide	H	H	H	CH3	1		LRMS calcd 310.33, found[M+H] 311.1
19.	5,6-Dihydro-4H-1,3a,6-triaza-as-indacene-8-carboxylic acid [4-(2-propylamino-ethoxy)-phenyl]-	H	H	H	H	1		LRMS calcd 379.46, found[M+H] 380.3

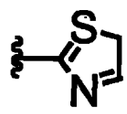
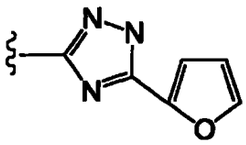
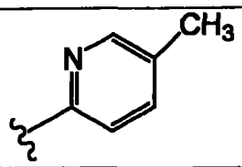
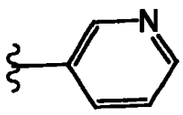
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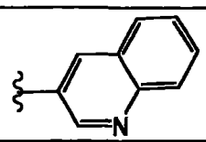
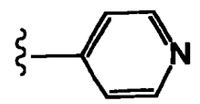
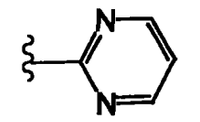
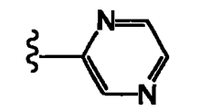
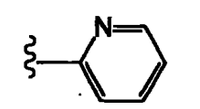
	amide							
20.	5,6-Dihydro-4H-1,3a,6-triaza-as-indacene-8-carboxylic acid (3,4-difluoro-phenyl)-amide	H	H	H	H	1		1HNMR (CD3OD) 3.16 (t, 2H), 4.30 (t, 2H), 7.10 (s, 2H), 7.21-7.29 (m, 1H), 7.49-7.55 (m, 2H), 7.93-8.02 (m, 1H) LRMS calcd 314.29 found [M+H] 315.1
21.	5,6-Dihydro-4H-1,3a,6-triaza-as-indacene-8-carboxylic acid (4-trifluoromethyl-phenyl)-amide	H	H	H	H	1		1HNMR (CD3OD) 3.12 (t, 2H), 4.25 (t, 2H), 7.06-7.07 (m, 2H), 7.46 (s, 1H), 7.62 (d, 2H), 8.04 (d, 2H) LRMS calcd 346.31 found [M+H] 347.1
22.	5,6-Dihydro-4H-1,3a,6-triaza-as-indacene-8-carboxylic acid {4-[2-(4-benzyl-piperidin-1-yl)-ethoxy]-3-fluoro-phenyl}-amide	H	H	H	H	1		LRMS calcd 513.61, found[M+H] 514.4

23.	5,6-Dihydro-4H-1,3a,6-triaza-as-indacene-8-carboxylic acid [4-(2-propylamino-ethoxy)-phenyl]-amide	H	H	H	H	1		
24.	5,6-Dihydro-4H-1,3a,6-triaza-as-indacene-8-carboxylic acid (6-methoxy-2-methyl-pyridin-3-yl)-amide	H	H	H	H	1		
25.	5,6-Dihydro-4H-1,3a,6-triaza-as-indacene-8-carboxylic acid (2-methoxymethyl-pyrimidin-4-yl)-amide	H	H	H	H	1		
26.	5,6-Dihydro-4H-1,3a,6-triaza-as-indacene-8-carboxylic acid (6-methoxy-pyridin-3-yl)-amide	H	H	H	H	1		[DMSO-d6] 3.1 (t, 1H), 3.9 (s, 3H), 4.3 (t, 2H), 6.9 (d, 1H), 7.0 (s, 1H), 7.2 (s, 1H), 7.5 (s, 2H), 8.2 (d, 1H), 8.6 (s, 1H), 11.8 (s, 1H), 13.2 (s, 1H)

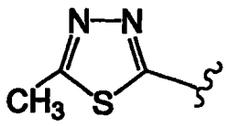
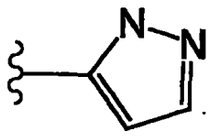
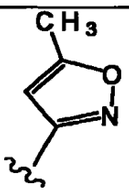
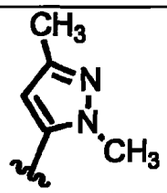
27.	5,6-Dihydro-4H-1,3a,6-triaza-as-indacene-8-carboxylic acid (6-methoxy-pyrazin-2-yl)-amide	H	H	H	H	1		
28.	5,6-Dihydro-4H-1,3a,6-triaza-as-indacene-8-carboxylic acid (5-tert-butyl-isoxazol-3-yl)-amide	H	H	H	H	1		
29.	5,6-Dihydro-4H-1,3a,6-triaza-as-indacene-8-carboxylic acid (1-methyl-5-methylsulfanyl-1H-[1,2,4]triazol-3-yl)-amide	H	H	H	H	1		
30.	5,6-Dihydro-4H-1,3a,6-triaza-as-indacene-8-carboxylic acid (3-methyl-[1,2,4]thiadiazo	H	H	H	H	1		

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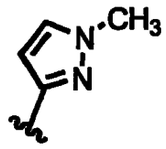
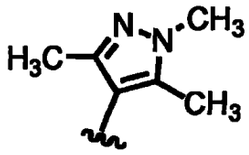
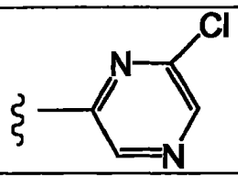
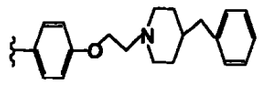
	1-5-yl)-amide							
31.	5,6-Dihydro-4H-1,3a,6-triaza-as-indacene-8-carboxylic acid thiazol-2-ylamide	H	H	H	H	1		[DMSO-d6] 3.1 (t, 1H), 4.3 (t, 2H), 7.0 (s, 1H), 7.2 (s, 1H), 7.3 (s, 1H), 7.5 (s, 2H), 7.6 (s, 1H), 12.0 (br s, 1H), >15 (s, 1H)
32.	5,6-Dihydro-4H-1,3a,6-triaza-as-indacene-8-carboxylic acid (5-furan-2-yl-1H-pyrazol-3-yl)-amide	H	H	H	H	1		
33.	5,6-Dihydro-4H-1,3a,6-triaza-as-indacene-8-carboxylic acid (5-methyl-pyridin-2-yl)-amide	H	H	H	H	1		
34.	5,6-Dihydro-4H-1,3a,6-triaza-as-indacene-8-carboxylic acid pyridin-3-ylamide	H	H	H	H	1		

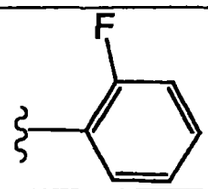
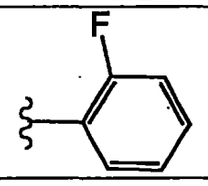
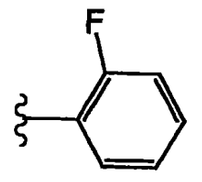
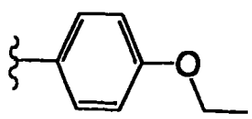
35.	5,6-Dihydro-4H-1,3a,6-triaza-as-indacene-8-carboxylic acid quinolin-3-ylamide	H	H	H	H	1		
36.	5,6-Dihydro-4H-1,3a,6-triaza-as-indacene-8-carboxylic acid pyridin-4-ylamide	H	H	H	H	1		
37.	5,6-Dihydro-4H-1,3a,6-triaza-as-indacene-8-carboxylic acid pyrimidin-2-ylamide	H	H	H	H	1		
38.	5,6-Dihydro-4H-1,3a,6-triaza-as-indacene-8-carboxylic acid pyrazin-2-ylamide	H	H	H	H	1		
39.	5,6-Dihydro-4H-1,3a,6-triaza-as-indacene-8-carboxylic acid pyridin-2-ylamide	H	H	H	H	1		[DMSO-d6] 3.1 (t, 1H), 4.3 (t, 2H), 7.0 (s, 1H), 7.1 (t, 1H), 7.2 (s, 1H), 7.5 (s, 2H), 7.8 (t,1H), 8.3 (d, 1H), 8.4 (s, 1H), 11.8 (s, 1H), 13.3 (s, 1H)

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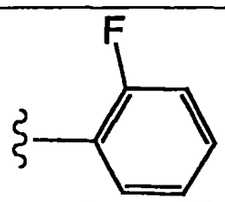
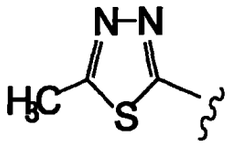
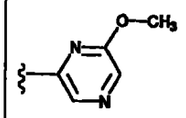
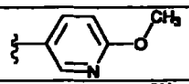
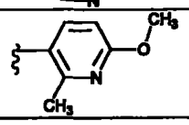
40.	5,6-Dihydro-4H-1,3a,6-triaza-as-indacene-8-carboxylic acid (5-methyl-[1,3,4]thiadiazol-2-yl)-amide	H	H	H	H	1		
41.	5,6-Dihydro-4H-1,3a,6-triaza-as-indacene-8-carboxylic acid (1H-pyrazol-3-yl)-amide	H	H	H	H	1		
42.	5,6-Dihydro-4H-1,3a,6-triaza-as-indacene-8-carboxylic acid (5-methyl-isoxazol-3-yl)-amide	H	H	H	H	1		
43.	5,6-Dihydro-4H-1,3a,6-triaza-as-indacene-8-carboxylic acid (2,5-dimethyl-2H-pyrazol-3-yl)-amide	H	H	H	H	1		

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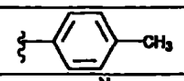
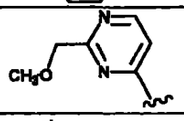
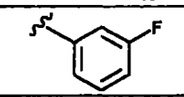
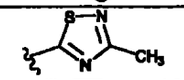
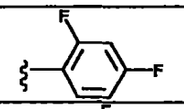
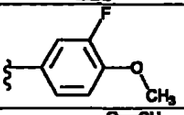
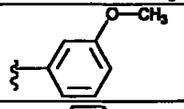
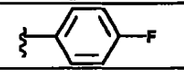
44.	5,6-Dihydro-4H-1,3a,6-triaza-as-indacene-8-carboxylic acid (1-methyl-1H-pyrazol-3-yl)-amide	H	H	H	H	1		
45.	5,6-Dihydro-4H-1,3a,6-triaza-as-indacene-8-carboxylic acid (1,3,5-trimethyl-1H-pyrazol-4-yl)-amide	H	H	H	H	1		
46.	5,6-Dihydro-4H-1,3a,6-triaza-as-indacene-8-carboxylic acid (6-chloro-pyrazin-2-yl)-amide	H	H	H	H	1		
47.	4-Methyl-5,6-dihydro-4H-1,3a,6-triaza-as-indacene-8-carboxylic acid {4-[2-(4-benzyl-piperidin-1-yl)-ethoxy]-phenyl}-amide	H	H	H	CH3	1		

48.	(R)-4-Methyl-5,6-dihydro-4H-1,3a,6-triaza-as-indacene-8-carboxylic acid (2-fluoro-phenyl)-amide	H	H	H	CH3	1		
49.	(S)-4-Methyl-5,6-dihydro-4H-1,3a,6-triaza-as-indacene-8-carboxylic acid (2-fluoro-phenyl)-amide	H	H	H	CH3	1		
50.	3-Dimethylaminomethyl-5,6-dihydro-4H-1,3a,6-triaza-as-indacene-8-carboxylic acid (2-fluoro-phenyl)-amide	$CH_2N(CH_3)_2$	H	H	H	1		
51.	4-Methyl-5,6-dihydro-4H-1,3a,6-triaza-as-indacene-8-carboxylic acid (4-ethoxy-phenyl)-amide	H	H	H	CH3	1		

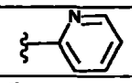
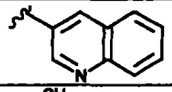
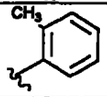
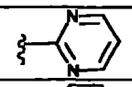
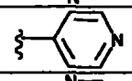
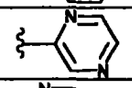
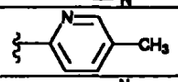
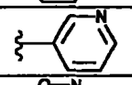
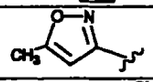
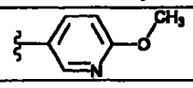
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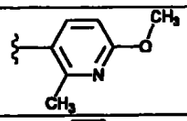
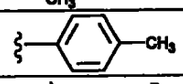
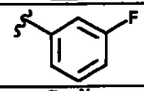
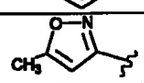
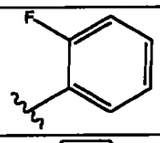
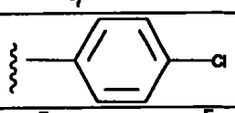
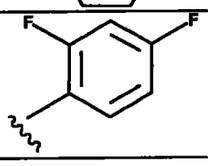
52.	3-Diethylaminomethyl-5,6-dihydro-4H-1,3a,6-triaza-as-indacene-8-carboxylic acid (2-fluoro-phenyl)-amide	$CH_2N(Et)_2$	H	H	H	1		
53.	4-Methyl-5,6-dihydro-4H-1,3a,6-triaza-as-indacene-8-carboxylic acid (5-methyl-[1,3,4]thiadiazol-2-yl)-amide	H	H	H	H	1		
54.		H	H	CH_3	H	1		
55.		H	H	CH_3	H	1		
56.		H	H	CH_3	H	1		

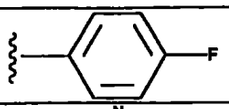
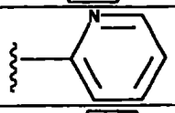
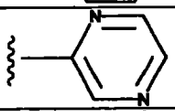
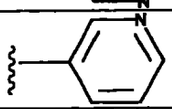
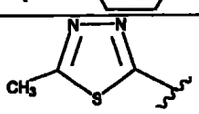
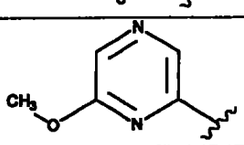
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57.		H	H	CH_3	H	1		
58.		H	H	CH_3	H	1		
59.		H	H	CH_3	H	1		
60.		H	H	CH_3	H	1		
61.		H	H	CH_3	H	1		
62.		H	H	CH_3	H	1		
63.		H	H	CH_3	H	1		
64.		H	H	CH_3	H	1		

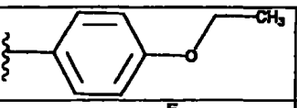
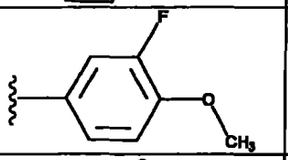
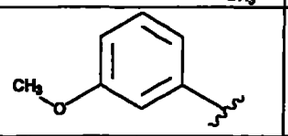
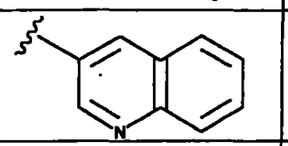
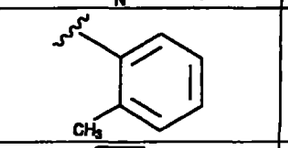
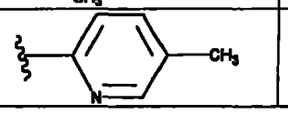
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65.		H	H	CH_3	H	1		
66.		H	H	CH_3	H	1		
67.		H	H	CH_3	H	1		
68.		H	H	CH_3	H	1		
69.		H	H	CH_3	H	1		
70.		H	H	CH_3	H	1		
71.		H	H	CH_3	H	1		
72.		H	H	CH_3	H	1		
73.		H	H	CH_3	H	1		
74.		H	H	H	CH_3	1		

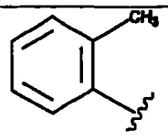
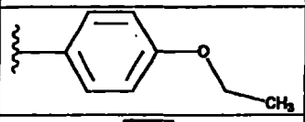
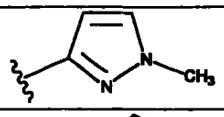
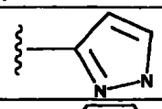
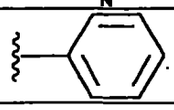
75.		H	H	H	CH_3	1		
76.		H	H	H	CH_3	1		
77.		H	H	H	CH_3	1		
78.		H	H	H	CH_3	1		
79.		H	H	CH_3	CH_3	1		
80.		H	H	H	CH_3	1		
81.		H	H	H	CH_3	1		

82.		H	H	H	CH_3	1		
83.		H	H	CH_3	H	1		
84.		H	H	H	CH_3	1		
85.		H	H	H	CH_3	1		
86.		H	H	H	CH_3	1		
87.		H	H	H	CH_3	1		
88.		H	H	H	CH_3	1		

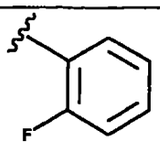
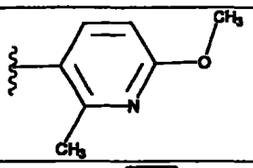
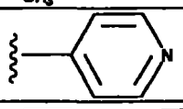
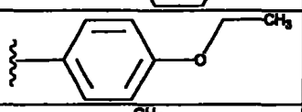
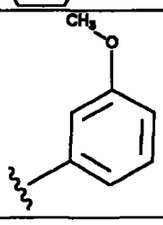
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89.		H	H	H	CH_3	1		
90.		H	H	H	CH_3	1		
91.		H	H	H	CH_3	1		
92.		H	H	H	CH_3	1		
93.		H	H	H	CH_3	1		
94.		H	H	H	CH_3	1		

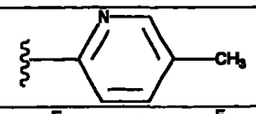
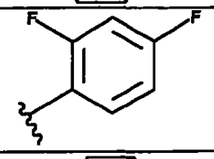
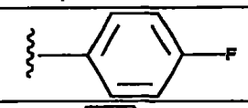
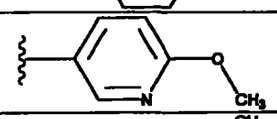
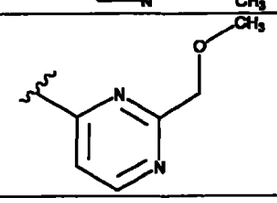
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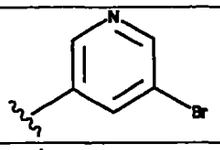
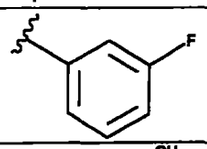
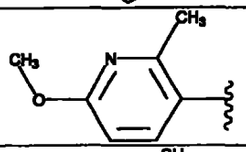
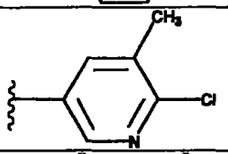
95.		H	H	H	CH_3	1		
96.		H	H	CH_3	CH_3	1		
97.		H	H	CH_3	CH_3	1		
98.		H	H	CH_3	CH_3	1		
99.		H	H	CH_3	CH_3	1		
100.		H	H	H	CH_3	1		

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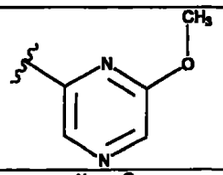
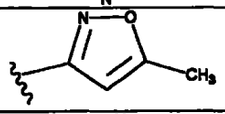
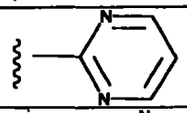
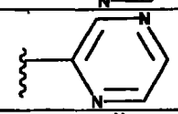
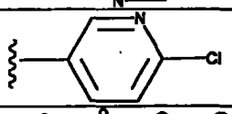
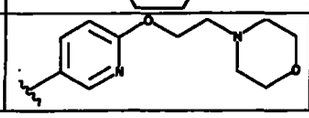
101.	2-Methyl-5,6-dihydro-4H-1,3a,6-triaza-as-indacene-8-carboxylic acid (2-fluoro-phenyl)-amide	CH_3	H	H	H	1		LRMS calcd 310.12, found[M+H] 311.1
102.		H	H	H	CH_3	1		
103.		H	H	H	CH_3	1		
104.		H	H	H	CH_3	1		
105.		H	H	CH_3	CH_3	1		

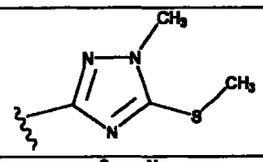
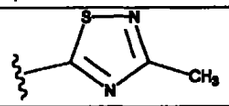
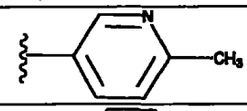
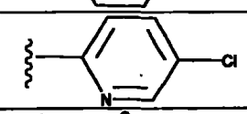
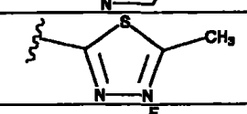
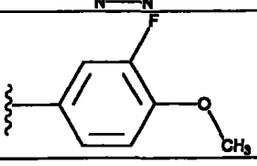
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106.		H	H	CH_3	CH_3	1		
107.		H	H	CH_3	CH_3	1		
108.		H	H	CH_3	CH_3	1		
109.		H	H	CH_3	CH_3	1		
110.		H	H	CH_3	CH_3	1		

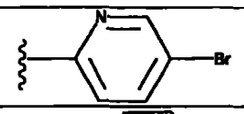
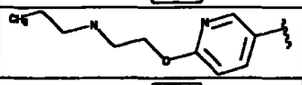
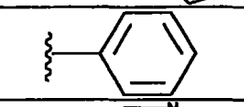
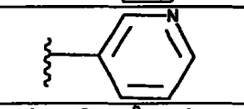
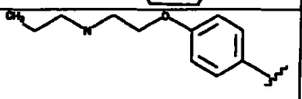
111.		H	H	CH_3	CH_3	1		
112.		H	H	CH_3	CH_3	1		
113.		H	H	CH_3	CH_3	1		
114.		H	H	CH_3	CH_3	1		
115.		H	H	CH_3	CH_3	1		

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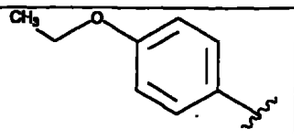
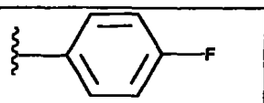
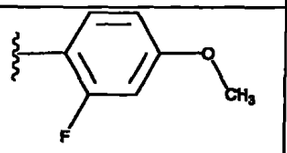
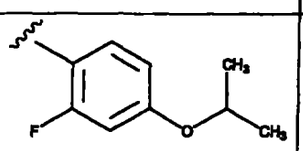
116.		H	H	CH_3	CH_3	1		
117.		H	H	CH_3	CH_3	1		
118.		H	H	CH_3	CH_3	1		
119.		H	H	CH_3	CH_3	1		
120.		H	H	CH_3	CH_3	1		
121.		H	H	CH_3	CH_3	1		

122.		H	H	CH_3	CH_3	1		
123.		H	H	CH_3	CH_3	1		
124.		H	H	CH_3	CH_3	1		
125.		H	H	CH_3	CH_3	1		
126.		H	H	CH_3	CH_3	1		
127.		H	H	CH_3	CH_3	1		

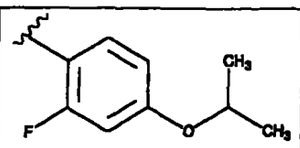
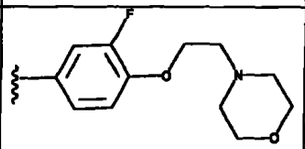
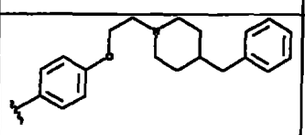
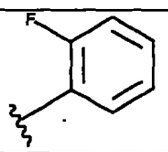
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128.		H	H	CH_3	CH_3	1		
129.		H	H	CH_3	CH_3	1		
130.		H	H	CH_3	CH_3	1		
131.		H	H	CH_3	CH_3	1		
132.		H	H	CH_3	CH_3	1		
133.	4-Methyl-5,6-dihydro-4H-1,3a,6-triaza-as-indacene-8-carboxylic acid [4-(2-propylaminoethoxy)phenyl] amide	H	H	H	CH_3	1		LRMS calcd 393.48, found[M+H] 394.4

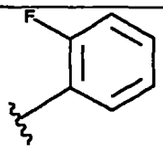
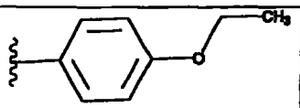
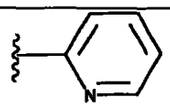
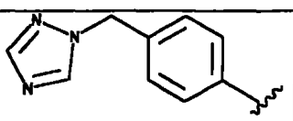
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134.	4-Methyl-5,6-dihydro-4H-1,3a,6-triaza-as-indacene-8-carboxylic acid (4-ethoxyphenyl)amide	H	H	H	CH_3	1		LRMS calcd 336.39, found[M+H] 337.2
135.	5,6-dihydro-4H-1,3a,6-triaza-as-indacene-8-carboxylic acid (4-fluorophenyl)amide	H	H	H	H	1		LRMS calcd 296.30, found[M+H] 297.2
136.	5,6-dihydro-4H-1,3a,6-triaza-as-indacene-8-carboxylic acid (2-fluoro-4-methoxyphenyl) amide	H	H	H	H	1		LRMS calcd 326.33, found[M+H] 327.2
137.	4-Methyl-5,6-dihydro-4H-1,3a,6-triaza-as-indacene-8-carboxylic acid (2-fluoro-4-isopropoxyphenyl)amide	H	H	H	CH3	1		LRMS calcd 368.40, found[M+H] 369.2

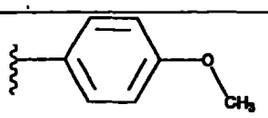
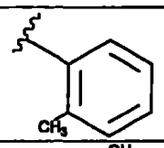
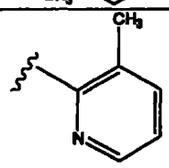
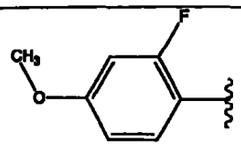
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138.	5,6-dihydro-4H-1,3a,6-triaza-as-indacene-8-carboxylic acid (2-fluoro-4-isopropoxyphenyl)amide	H	H	H	H	1		LRMS calcd 354.38, found[M+H] 355.2
139.	4-Methyl-5,6-dihydro-4H-1,3a,6-triaza-as-indacene-8-carboxylic acid [4-(2-propylaminoethoxy)phenyl] amide	H	H	H	CH3	1		LRMS calcd 393.48, found[M+H] 394.4
140.	4-methyl-5,6-dihydro-4H-1,3a,6-triaza-as-indacene-8-carboxylic acid {4-[2-(4-benzylpiperidinyl)ethoxy]phenyl} amide	H	H	H	CH3	1		LRMS calcd 509.64, found[M+H] 510.5
141.		$CH_2N(CH_3)_2$	$CH_2N(CH_3)_2$	H	H	1		

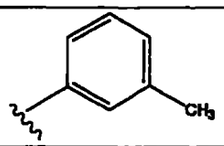
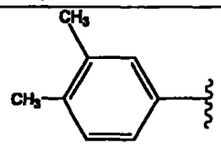
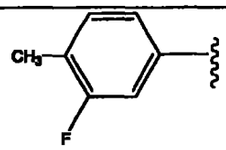
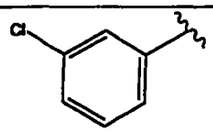
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142.	4,4-Dimethyl-5,6-dihydro-4H-1,3a,6-triaza-as-indacene-8-carboxylic acid (2-fluoro-phenyl)-amide	H	H	CH3	CH3	1		LRMS calcd 324 found [M+1] 325
143.	4,4-Dimethyl-5,6-dihydro-4H-1,3a,6-triaza-as-indacene-8-carboxylic acid (4-ethoxy-phenyl)-amide	H	H	CH3	CH3	1		LRMS calcd 350 found [M+1] 351
144.	4,4-Dimethyl-5,6-dihydro-4H-1,3a,6-triaza-as-indacene-8-carboxylic acid pyridin-2-ylamide	H	H	CH3	CH3	1		LRMS calcd 307 found [M+1] 308
145.	4,4-Dimethyl-5,6-dihydro-4H-1,3a,6-triaza-as-indacene-8-carboxylic acid (4-[1,2,4]triazol-1-ylmethyl-phenyl)-amide	H	H	CH3	CH3	1		LRMS calcd 387 found [M+1] 388

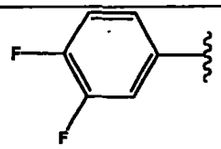
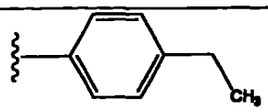
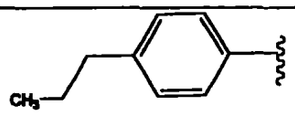
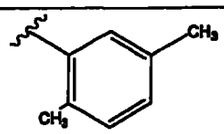
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146.	4,4-Dimethyl-5,6-dihydro-4H-1,3a,6-triaza-as-indacene-8-carboxylic acid (4-methoxy-phenyl)-amide	H	H	CH3	CH3	1		LRMS calcd 336 found [M+1] 337
147.	4,4-Dimethyl-5,6-dihydro-4H-1,3a,6-triaza-as-indacene-8-carboxylic acid o-tolylamide	H	H	CH3	CH3	1		LRMS calcd 320 found [M+1] 321
148.	4,4-Dimethyl-5,6-dihydro-4H-1,3a,6-triaza-as-indacene-8-carboxylic acid (3-methyl-pyridin-2-yl)-amide	H	H	CH3	CH3	1		LRMS calcd 321 found [M+1] 322
149.	4,4-Dimethyl-5,6-dihydro-4H-1,3a,6-triaza-as-indacene-8-carboxylic acid (2-fluoro-4-methoxy-phenyl)-amide	H	H	CH3	CH3	1		LRMS calcd 354 found [M+1]

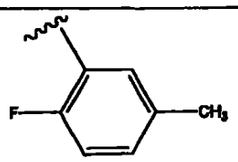
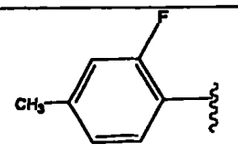
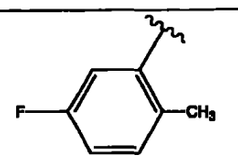
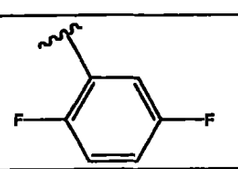
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150.	(R)-4-Methyl-5,6-dihydro-4H-1,3a,6-triaza-as-indacene-8-carboxylic acid m-tolylamide	H	H	H	CH3	1		MS m/z 307
151.	(R)-4-Methyl-5,6-dihydro-4H-1,3a,6-triaza-as-indacene-8-carboxylic acid (3,4-dimethyl-phenyl)-amide	H	H	H	CH3	1		MS m/z 321
152.	(R)-4-Methyl-5,6-dihydro-4H-1,3a,6-triaza-as-indacene-8-carboxylic acid (3-fluoro-4-methyl-phenyl)-amide	H	H	H	CH3	1		MS m/z 325
153.	(R)-4-Methyl-5,6-dihydro-4H-1,3a,6-triaza-as-indacene-8-carboxylic acid (3-chloro-phenyl)-amide	H	H	H	CH3	1		MS m/z 327

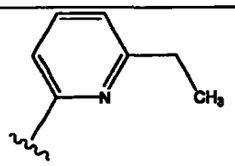
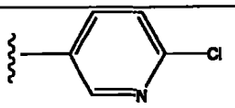
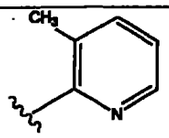
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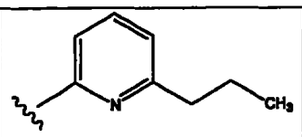
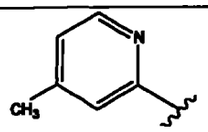
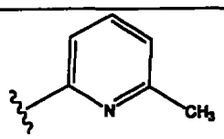
154.	(R)-4-Methyl-5,6-dihydro-4H-1,3a,6-triaza-as-indacene-8-carboxylic acid (3,4-difluoro-phenyl)-amide	H	H	H	CH3	1		MS m/z 329
155.	(R)-4-Methyl-5,6-dihydro-4H-1,3a,6-triaza-as-indacene-8-carboxylic acid (4-ethyl-phenyl)-amide	H	H	H	CH3	1		MS m/z 321
156.	(R)-4-Methyl-5,6-dihydro-4H-1,3a,6-triaza-as-indacene-8-carboxylic acid (4-propyl-phenyl)-amide	H	H	H	CH3	1		
157.	(R)-4-Methyl-5,6-dihydro-4H-1,3a,6-triaza-as-indacene-8-carboxylic acid (2,5-dimethyl-phenyl)-amide	H	H	H	CH3	1		MS m/z 321

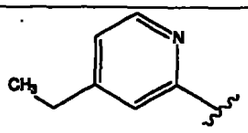
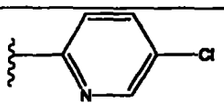
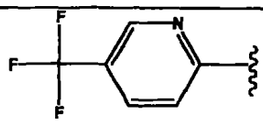
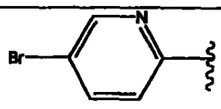
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158.	(R)-4-Methyl-5,6-dihydro-4H-1,3a,6-triaza-as-indacene-8-carboxylic acid (2-fluoro-5-methyl-phenyl)-amide	H	H	H	CH3	1		[CDCl3] 1.5 (d, 3H), 2.8 (dd, 1H), 3.1 (dd, 1H), 4.3 (q, 1H), 6.9 (app s, 2H), 7.0 (app s, 2H), 7.5 (s, 1H), 8.0 (d, 1H), 11.8 (s, 1H), 13.1 (s, 1H)
159.	(R)-4-Methyl-5,6-dihydro-4H-1,3a,6-triaza-as-indacene-8-carboxylic acid (2-fluoro-4-methyl-phenyl)-amide	H	H	H	CH3	1		[CDCl3] 1.5 (d, 3H), 2.8 (dd, 1H), 3.1 (dd, 1H), 4.3 (q, 1H), 6.9 (s, 1H), 6.95 (m, 2H), 7.0 (s, 1H), 7.5 (s, 1H), 8.0 (t, 1H), 10.8 (s, 1H), 13.1 (s, 1H)
160.	(R)-4-Methyl-5,6-dihydro-4H-1,3a,6-triaza-as-indacene-8-carboxylic acid (5-fluoro-2-methyl-phenyl)-amide	H	H	H	CH3	1		[CD3OD] 1.2 (d, 3H), 2.1 (s, 3H), 2.55 (dd, 1H), 2.95 (dd, 1H), 4.2 (q, 1H), 6.5 (t, 1H), 6.6 (s, 1H), 6.8 (s, 1H), 6.9 (t, 1H), 7.2 (m, 2H)
161.	(R)-4-Methyl-5,6-dihydro-4H-1,3a,6-triaza-as-indacene-8-carboxylic acid (2,5-difluoro-phenyl)-amide	H	H	H	CH3	1		[CD3OD] 1.2 (d, 3H), 2.55 (dd, 1H), 2.95 (dd, 1H), 4.2 (q, 1H), 6.55 (m, 1H), 6.6 (s, 1H), , 6.8 (s, 1H), 6.85 (m, 1H),

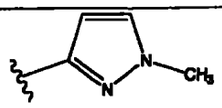
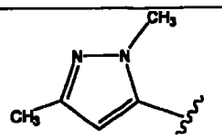
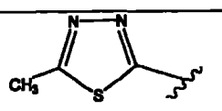
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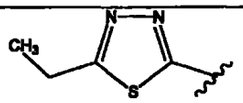
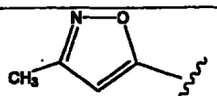
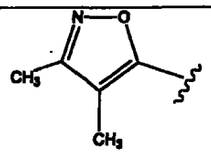
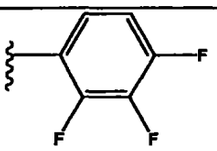
								7.2 (s, 1H), 7.8 (m, 1H)
162.	(R)-4-Methyl-5,6-dihydro-4H-1,3a,6-triaza-as-indacene-8-carboxylic acid (6-ethyl-pyridin-2-yl)-amide	H	H	H	CH3	1		[CD3OD] 1.0 (t, 3H), 1.2 (d, 3H), 2.45 (q, 2H), 2.5 (dd, 1H), 2.9 (dd, 1H), 4.2 (q, 1H), 6.65 (d, 1H), 6.7 (s, 1H), 6.8 (s, 1H), 7.2 (s, 1H), 7.4 (t, 1H), 7.8 (d, 1H)
163.	(R)-4-Methyl-5,6-dihydro-4H-1,3a,6-triaza-as-indacene-8-carboxylic acid (6-chloro-pyridin-3-yl)-amide	H	H	H	CH3	1		[CD3OD] 1.2 (d, 3H), 2.55 (dd, 1H), 2.95 (dd, 1H), 3.0 (s, 3H), 4.2 (q, 1H), 6.6 (s, 1H), , 6.8 (s, 1H), 7.1 (d, 1H), 7.2 (s, 1H), 8.0 (d, 1H), 8.6 (s, 1H)
164.	(R)-4-Methyl-5,6-dihydro-4H-1,3a,6-triaza-as-indacene-8-carboxylic acid (3-methyl-pyridin-2-yl)-amide	H	H	H	CH3	1		[CD3OD] 1.2 (d, 3H), 2.1 (s, 3H), 2.55 (dd, 1H), 2.95 (dd, 1H), 4.2 (q, 1H), 6.6 (s, 1H), 6.8 (s, 1H), 6.95 (dd, 1H), 7.2 (s, 1H), 7.45 (d, 1H), 8.0 (d, 1H)

165.	(R)-4-Methyl-5,6-dihydro-4H-1,3a,6-triaza-as-indacene-8-carboxylic acid (6-propyl-pyridin-2-yl)-amide	H	H	H	CH3	1		[CD3OD] 0.7 (t, 3H), 1.2 (d, 3H), 1.6 (sextet, 2H), 2.4 (t, 2H), 2.5 (dd, 1H), 2.9 (dd, 1H), 4.2 (q, 1H), 6.6 (d, 1H), 6.7 (s, 1H), 6.8 (s, 1H), 7.2 (s, 1H), 7.4 (t, 1H), 7.7 (d, 1H)
166.	(R)-4-Methyl-5,6-dihydro-4H-1,3a,6-triaza-as-indacene-8-carboxylic acid (4-methyl-pyridin-2-yl)-amide	H	H	H	CH3	1		[CDCl3] 1.4 (d, 3H), 2.4 (s, 3H), 2.75 (dd, 1H), 3.1 (dd, 1H), 4.3 (q, 1H), 6.8 (app s, 2H), 7.0 (s, 1H), 7.6 (s, 1H), 8.2 (s, 1H), 8.25 (d, 1H), 10.8 (s, 1H), 13.55 (s, 1H)
167.	(R)-4-Methyl-5,6-dihydro-4H-1,3a,6-triaza-as-indacene-8-carboxylic acid (6-methyl-pyridin-2-yl)-amide	H	H	H	CH3	1		[CDCl3] 1.4 (d, 3H), 2.6 (s, 3H), 2.75 (dd, 1H), 3.1 (dd, 1H), 4.3 (q, 1H), 6.9 (m, 2H), 7.1 (s, 1H), 7.55 (s, 1H), 7.6 (t, 1H), 8.2 (d, 1H), 10.7 (s, 1H), 13.6 (s, 1H)

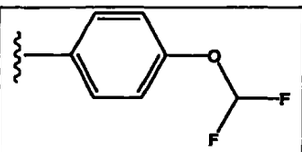
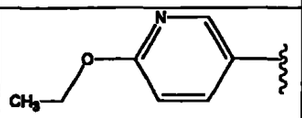
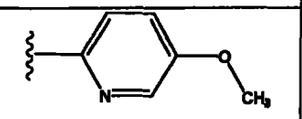
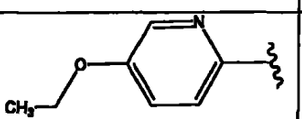
168.	(R)-4-Methyl-5,6-dihydro-4H-1,3a,6-triaza-as-indacene-8-carboxylic acid (4-ethyl-pyridin-2-yl)-amide	H	H	H	CH3	1		[CDCl3] 1.3 (t, 3H), 1.4 (d, 3H), 2.7 (q, 2H), 2.75 (dd, 1H(, 3.1 (dd, 1H), 4.3 (q, 1H), 6.8 (s, 1H), 6.85 (d, 1H), 7.0 (s, 1H), 7.6 (s, 1H), 8.3 (m, 2H), 10.8 (s, 1H), 13.55 (s, 1H)
169.	(R)-4-Methyl-5,6-dihydro-4H-1,3a,6-triaza-as-indacene-8-carboxylic acid (5-chloro-pyridin-2-yl)-amide	H	H	H	CH3	1		[DMSO-d6] 1.5 (d, 3H), 2.8 (dd, 1H), 3.2 (dd, 1H), 4.5 (q, 1H), 7.0 (s, 1H), 7.3 (s, 1H), 7.6 (s, 1H), 7.9 (d, 1H), 8.4 (d, 1H), 8.5 (s, 1H)
170.	(R)-4-Methyl-5,6-dihydro-4H-1,3a,6-triaza-as-indacene-8-carboxylic acid (5-trifluoromethyl-pyridin-2-yl)-amide	H	H	H	CH3	1		[DMSO-d6] 1.5 (d, 3H), 2.8 (dd, 1H), 3.2 (dd, 1H), 4.5 (q, 1H), 7.0 (s, 1H), 7.3 (s, 1H), 7.6 (s, 1H), 8.2 (d, 1H), 8.6 (d, 1H), 8.8 (s, 1H)
171.	(R)-4-Methyl-5,6-dihydro-4H-1,3a,6-triaza-as-indacene-8-carboxylic acid (5-bromo-	H	H	H	CH3	1		[DMSO-d6] 1.5 (d, 3H), 2.8 (dd, 1H), 3.2 (dd, 1H), 4.5 (q, 1H), 7.0 (s, 1H), 7.3 (s, 1H), 7.6 (s, 1H), 8.0

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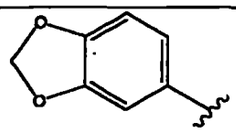
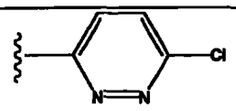
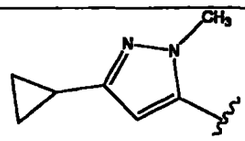
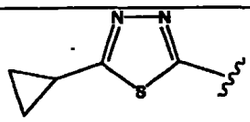
	pyridin-2-yl)-amide							(d, 1H), 8.4 (d, 1H), 8.5 (s, 1H)
172.	(R)-4-Methyl-5,6-dihydro-4H-1,3a,6-triaza-as-indacene-8-carboxylic acid (1-methyl-1H-pyrazol-3-yl)-amide	H	H	H	CH3	1		[DMSO-d6] 1.5 (d, 3H), 2.8 (dd, 1H), 3.2 (dd, 1H), 3.8 (s, 3H), 4.5 (1, 1H), 6.6 (s, 1H), 7.0 (s, 1H), 7.3 (s, 1H), 7.4 (s, 1H), 7.6 (s, 1H), 11.8 (s, 1H), 13.1 (s, 1H),
173.	(R)-4-Methyl-5,6-dihydro-4H-1,3a,6-triaza-as-indacene-8-carboxylic acid (2,5-dimethyl-2H-pyrazol-3-yl)-amide	H	H	H	CH3	1		[DMSO-d6] 1.5 (d, 3H), 2.1 (s, 3H), 2.8 (dd, 1H), 3.2 (dd, 1H), 3.8 (s, 3H), 4.5 (q, 1H), 6.5 (s, 1H), 7.0 (s, 1H), 7.3 (s, 1H), 7.5 (s, 1H), 11.8 (s, 1H), 13.2 (s, 1H)
174.	(R)-4-Methyl-5,6-dihydro-4H-1,3a,6-triaza-as-indacene-8-carboxylic acid (5-methyl-[1,3,4]thiadiazol-2-yl)-amide	H	H	H	CH3	1		[DMSO-d6] 1.5 (d, 3H), 2.7 (s, 3H), 2.9 (dd, 1H), 3.3 (dd, 1H), 4.6 (q, 1H), 7.1 (s, 1H), 7.4 (s, 1H), 7.6 (s, 1H), 12.0 (s, 1H), >14 (s, 1H)

175.	(R)-4-Methyl-5,6-dihydro-4H-1,3a,6-triaza-as-indacene-8-carboxylic acid (5-ethyl-[1,3,4]thiadiazol-2-yl)-amide	H	H	H	CH3	1		[DMSO-d6] 1.3 (t, 3H), 1.5 (d, 3H), 2.9 (dd, 1H), 3.0 (q, 2H), 3.3 (dd, 1H), 4.6 (q, 1H), 7.1 (s, 1H), 7.4 (s, 1H), 7.6 (s, 1H), 12.0 (s, 1H), >14 (s, 1H)
176.	(R)-4-Methyl-5,6-dihydro-4H-1,3a,6-triaza-as-indacene-8-carboxylic acid (3-methyl-isoxazol-5-yl)-amide	H	H	H	CH3	1		MS m/z 298
177.	(R)-4-Methyl-5,6-dihydro-4H-1,3a,6-triaza-as-indacene-8-carboxylic acid (3,4-dimethyl-isoxazol-5-yl)-amide	H	H	H	CH3	1		MS m/z 312
178.	(R)-4-Methyl-5,6-dihydro-4H-1,3a,6-triaza-as-indacene-8-carboxylic acid (2,3,4-trifluoro-phenyl)-amide	H	H	H	CH3	1		MS m/z 347

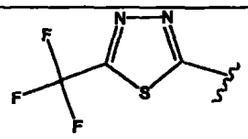
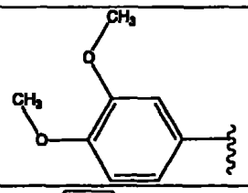
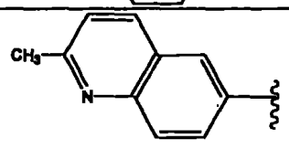
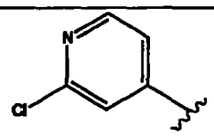
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179.	(R)-4-Methyl-5,6-dihydro-4H-1,3a,6-triaza-as-indacene-8-carboxylic acid (4-difluoromethoxy-phenyl)-amide	H	H	H	CH3	1		MS *m/z* 359
180.	(S)-4-Methyl-5,6-dihydro-4H-1,3a,6-triaza-as-indacene-8-carboxylic acid (6-ethoxy-pyridin-3-yl)-amide	H	H	H	CH3	1		LRMS 337.38 found (M+1) 338.2
181.	(S)-4-Methyl-5,6-dihydro-4H-1,3a,6-triaza-as-indacene-8-carboxylic acid (5-methoxy-pyridin-2-yl)-amide	H	H	H	CH3	1		LRMS calcd 323 found [M+1] 324
182.	(S)-4-Methyl-5,6-dihydro-4H-1,3a,6-triaza-as-indacene-8-carboxylic acid (5-ethoxy-pyridin-2-yl)-amide	H	H	H	CH3	1		LRMS calcd 337 found [M+1] 338

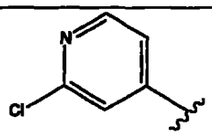
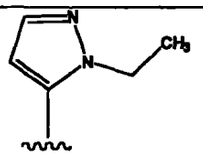
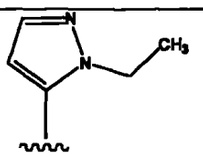
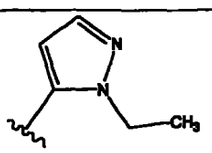
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183.	(R)-4-Methyl-5,6-dihydro-4H-1,3a,6-triaza-as-indacene-8-carboxylic acid benzo[1,3]dioxol-5-ylamide	H	H	H	CH3	1		MS m/z 337
184.	(R)-4-Methyl-5,6-dihydro-4H-1,3a,6-triaza-as-indacene-8-carboxylic acid (6-chloro-pyridazin-3-yl)-amide	H	H	H	CH3	1		MS m/z 329
185.	(R)-4-Methyl-5,6-dihydro-4H-1,3a,6-triaza-as-indacene-8-carboxylic acid (5-cyclopropyl-2-methyl-2H-pyrazol-3-yl)-amide	H	H	H	CH3	1		MS m/z 337
186.	(R)-4-Methyl-5,6-dihydro-4H-1,3a,6-triaza-as-indacene-8-carboxylic acid (5-cyclopropyl-[1,3,4]thiadiazol-2-yl)-amide	H	H	H	CH3	1		MS m/z 341

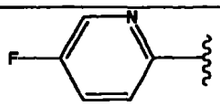
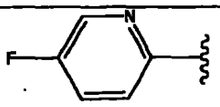
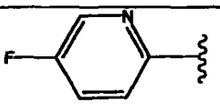
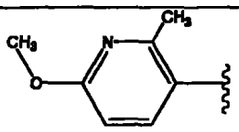
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187.	(R)-4-Methyl-5,6-dihydro-4H-1,3a,6-triaza-as-indacene-8-carboxylic acid (5-trifluoromethyl-[1,3,4]thiadiazol-2-yl)-amide	H	H	H	CH3	1		MS *m/z* 369
188.	(R)-4-Methyl-5,6-dihydro-4H-1,3a,6-triaza-as-indacene-8-carboxylic acid (3,4-dimethoxy-phenyl)-amide	H	H	H	CH3	1		MS *m/z* 353
189.	(R)-4-Methyl-5,6-dihydro-4H-1,3a,6-triaza-as-indacene-8-carboxylic acid (2-methyl-quinolin-6-yl)-amide	H	H	H	CH3	1		MS *m/z* 358
190.	5,6-Dihydro-4H-1,3a,6-triaza-as-indacene-8-carboxylic acid (2-chloro-pyridin-4-yl)-amide	H	H	H	H	1		MS *m/z* 314

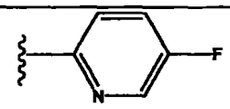
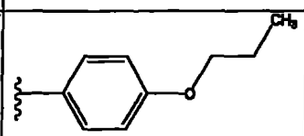
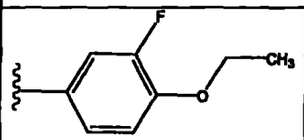
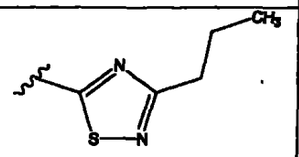
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191.	(R)-4-Methyl-5,6-dihydro-4H-1,3a,6-triaza-as-indacene-8-carboxylic acid (2-chloro-pyridin-4-yl)-amide	H	H	H	CH3			MS m/z 328
192.	(S)-4-Methyl-5,6-dihydro-4H-1,3a,6-triaza-as-indacene-8-carboxylic acid (2-ethyl-2H-pyrazol-3-yl)-amide	H	H	H	CH3	1		LCMS found (M+H) 312
193.	(R)-4-Methyl-5,6-dihydro-4H-1,3a,6-triaza-as-indacene-8-carboxylic acid (2-ethyl-2H-pyrazol-3-yl)-amide	H	H	H	CH3	1		LCMS found (M+H) 312
194.	4,4-Dimethyl-5,6-dihydro-4H-1,3a,6-triaza-as-indacene-8-carboxylic acid (2-ethyl-2H-pyrazol-3-yl)-amide	H	H	CH3	CH3	1		LCMS found (M+H) 326

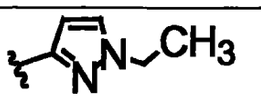
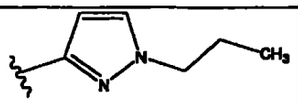
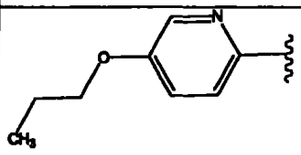
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195.	4,4-Dimethyl-5,6-dihydro-4H-1,3a,6-triaza-as-indacene-8-carboxylic acid (5-fluoro-pyridin-2-yl)-amide	H	H	CH3	CH3	1		LCMS found (M+H) 326
196.	(R)-4-Methyl-5,6-dihydro-4H-1,3a,6-triaza-as-indacene-8-carboxylic acid (5-fluoro-pyridin-2-yl)-amide	H	H	H	CH3	1		LCMS found (M+H) 312
197.	5,6-Dihydro-4H-1,3a,6-triaza-as-indacene-8-carboxylic acid (5-fluoro-pyridin-2-yl)-amide	H	H	H	H	1		LCMS found (M+H) 297
198.	(S)-4-Methyl-5,6-dihydro-4H-1,3a,6-triaza-as-indacene-8-carboxylic acid (6-methoxy-2-methyl-pyridin-3-yl)-amide	H	H	H	CH3	1		LRMS 337.38 found (M+1) 338.2

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199.	(S)- 4-Methyl-5,6-dihydro-4H-1,3a,6-triaza-as-indacene-8-carboxylic acid (5-fluoro-pyridin-2-yl)-amide	H	H	H	CH3	1		LRMS 311.11 found (M+1) 312.2
200.	(S)-4-Methyl-5,6-dihydro-4H-1,3a,6-triaza-as-indacene-8-carboxylic acid (4-propoxy-phenyl)-amide	H	H	H	CH3	1		LRMS 350.42 found (M-1) 349.2
201.	(S)-4-Methyl-5,6-dihydro-4H-1,3a,6-triaza-as-indacene-8-carboxylic acid (4-ethoxy-3-fluoro-phenyl)-amide	H	H	H	CH3	1		LRMS 354.38 found (M-1) 353.2
202.	(R)- 4-Methyl-5,6-dihydro-4H-1,3a,6-triaza-as-indacene-8-carboxylic acid (3-propyl-[1,2,4]thiadiazol-5-yl)-amide	H	H	H	CH3	1		LCMS found (M+H) 343

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203.	(R)-3,4,5,6-Tetrahydro-3,8,10-triaza-benzo[e]azulene-1-carboxylic acid (1-ethyl-1H-pyrazol-3-yl)-amide	H	H	H	CH3	1		LCMS found (M+H) 311
204.	(R)-3,4,5,6-Tetrahydro-3,8,10-triaza-benzo[e]azulene-1-carboxylic acid (1-propyl-1H-pyrazol-3-yl)-amide	H	H	H	CH3	1		LCMS found (M+H) 337
205.	(S)-4-Methyl-5,6-dihydro-4H-1,3a,6-triaza-as-indacene-8-carboxylic acid (5-propoxy-pyridin-2-yl)-amide	H	H	H	CH3	1		LRMS calcd 351 found [M+1] 352

577
578

Example 5

Additional 3,10-diaza-benzo[e]azulene-1-carboxylic acid compounds

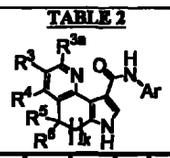
Using the methods shown in Schemes 2 and 3 the compounds shown in Table 2 were prepared.

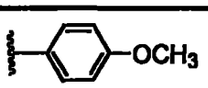
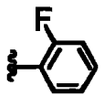
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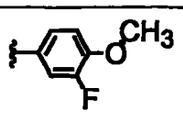
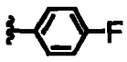
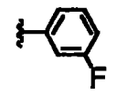
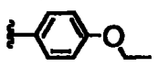
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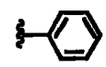
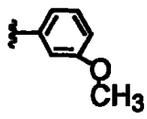
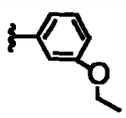
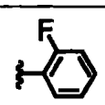
TABLE 2



Cmp. #	Name	R^{3a}	R^3	R^4	R^5	R^6	k	Ar	Spectral Data
1	9-Methyl-3,4,5,6-tetrahydro-3,10-diaza-benzo[e]azulene-1-carboxylic acid (4-methoxy-phenyl)-amide	CH_3	H	H	H	H	2		
2	9-Methyl-3,4,5,6-tetrahydro-3,10-diaza-benzo[e]azulene-1-carboxylic acid (2-fluoro-phenyl)-amide	CH_3	H	H	H	H	2		

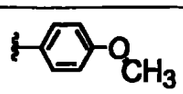
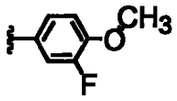
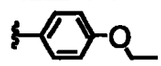
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3	9-Methyl-3,4,5,6-tetrahydro-3,10-diaza-benzo[e]azulene-1-carboxylic acid (3-fluoro-4-methoxy-phenyl)-amide	CH_3	H	H	H	H	2		
4	9-Methyl-3,4,5,6-tetrahydro-3,10-diaza-benzo[e]azulene-1-carboxylic acid (4-fluoro-phenyl)-amide	CH_3	H	H	H	H	2		
5	9-Methyl-3,4,5,6-tetrahydro-3,10-diaza-benzo[e]azulene-1-carboxylic acid (3-fluoro-phenyl)-amide	CH_3	H	H	H	H	2		
6	9-Methyl-3,4,5,6-tetrahydro-3,10-diaza-benzo[e]azulene-1-carboxylic acid (4-ethoxy-phenyl)-amide	CH_3	H	H	H	H	2		

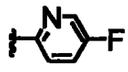
7	9-Methyl-3,4,5,6-tetrahydro-3,10-diaza-benzo[e]azulene-1-carboxylic acid phenylamide	CH_3	H	H	H	H	2		
8	9-Methyl-3,4,5,6-tetrahydro-3,10-diaza-benzo[e]azulene-1-carboxylic acid (3-methoxy-phenyl)-amide	CH_3	H	H	H	H	2		
9	9-Methyl-3,4,5,6-tetrahydro-3,10-diaza-benzo[e]azulene-1-carboxylic acid (3-ethoxy-phenyl)-amide	CH_3	H	H	H	H	2		
10	3,4,5,6-Tetrahydro-3,10-diaza-benzo[e]azulene-1-carboxylic acid (2-fluoro-phenyl)-amide	H	H	H	H	H	2		

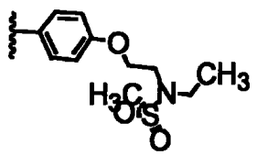
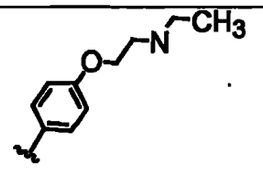
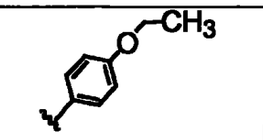
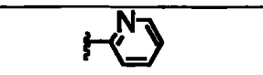
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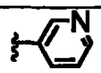
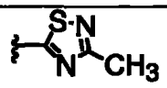
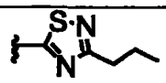
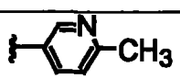
582

11	3,4,5,6-Tetrahydro-3,10-diaza-benzo[e]azulene-1-carboxylic acid (4-methoxy-phenyl)-amide	H	H	H	H	H	2		
12	3,4,5,6-Tetrahydro-3,10-diaza-benzo[e]azulene-1-carboxylic acid (3-fluoro-4-methoxy-phenyl)-amide	H	H	H	H	H	2		
13	3,4,5,6-Tetrahydro-3,10-diaza-benzo[e]azulene-1-carboxylic acid (4-ethoxy-phenyl)-amide	H	H	H	H	H	2		
14	3,4,5,6-Tetrahydro-3,10-diaza-benzo[e]azulene-1-carboxylic acid pyridin-2-ylamide	H	H	H	H	H	2		

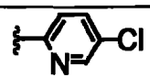
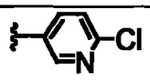
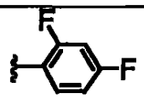
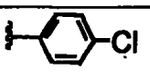
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15	3,4,5,6-Tetrahydro-3,10-diaza-benzo[e]azulene-1-carboxylic acid (1-methyl-1H-pyrazol-3-yl)-amide	H	H	H	H	H	2		
16	3,4,5,6-Tetrahydro-3,10-diaza-benzo[e]azulene-1-carboxylic acid (5-methyl-[1,3,4]thiadiazol-2-yl)-amide	H	H	H	H	H	2		
17	3,4,5,6-Tetrahydro-3,10-diaza-benzo[e]azulene-1-carboxylic acid (5-fluoro-pyridin-2-yl)-amide	H	H	H	H	H	2		

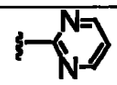
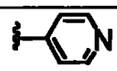
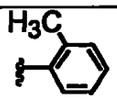
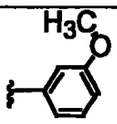
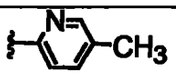
18	3,4,5,6-Tetrahydro-3,10-diaza-benzo[e]azulene-1-carboxylic acid {4-[2-(ethyl-methanesulfonyl-amino)-ethoxy]-phenyl}-amide	H	H	H	H	H	2		LRMS calcd 468 found [M+1] 469
19	3,4,5,6-Tetrahydro-3,10-diaza-benzo[e]azulene-1-carboxylic acid [4-(2-ethylamino-ethoxy)-phenyl]-amide	H	H	H	H	H	2		LRMS calcd 390 found [M+1] 391
20	8-Methyl-3,4,5,6-tetrahydro-3,10-diaza-benzo[e]azulene-1-carboxylic acid (4-ethoxy-phenyl)-amide	H	CH_3	H	H	H	2		
21	8-Methyl-3,4,5,6-tetrahydro-3,10-diaza-benzo[e]azulene-1-carboxylic acid pyridin-2-ylamide	H	CH_3	H	H	H	2		

22	3,4,5,6-Tetrahydro-3,10-diaza-benzo[e]azulene-1-carboxylic acid pyridin-3-ylamide	H	H	H	H	H	2		
23	3,4,5,6-Tetrahydro-3,10-diaza-benzo[e]azulene-1-carboxylic acid (3-methyl-[1,2,4]thiadiazol-5-yl)-amide	H	H	H	H	H	2		
24	3,4,5,6-Tetrahydro-3,10-diaza-benzo[e]azulene-1-carboxylic acid (3-propyl-[1,2,4]thiadiazol-5-yl)-amide	H	H	H	H	H	2		LCMS found (M+H) 354
25	3,4,5,6-Tetrahydro-3,10-diaza-benzo[e]azulene-1-carboxylic acid (6-methyl-pyridin-3-yl)-amide	H	H	H	H	H	2		

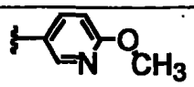
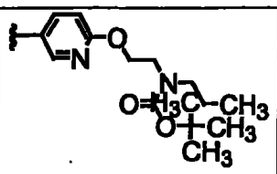
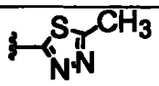
586

26	3,4,5,6-Tetrahydro-3,10-diaza-benzo[e]azulene-1-carboxylic acid (5-chloro-pyridin-2-yl)-amide	H	H	H	H	H	2		
27	3,4,5,6-Tetrahydro-3,10-diaza-benzo[e]azulene-1-carboxylic acid (6-chloro-pyridin-3-yl)-amide	H	H	H	H	H	2		
28	3,4,5,6-Tetrahydro-3,10-diaza-benzo[e]azulene-1-carboxylic acid (2,4-difluoro-phenyl)-amide	H	H	H	H	H	2		
29	3,4,5,6-Tetrahydro-3,10-diaza-benzo[e]azulene-1-carboxylic acid (4-chloro-phenyl)-amide	H	H	H	H	H	2		

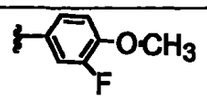
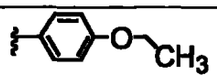
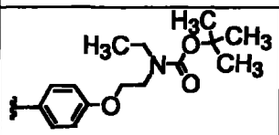
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30	3,4,5,6-Tetrahydro-3,10-diaza-benzo[e]azulene-1-carboxylic acid pyrimidin-2-ylamide	H	H	H	H	H	2		
31	3,4,5,6-Tetrahydro-3,10-diaza-benzo[e]azulene-1-carboxylic acid pyridin-4-ylamide	H	H	H	H	H	2		
32	3,4,5,6-Tetrahydro-3,10-diaza-benzo[e]azulene-1-carboxylic acid o-tolyl-amide	H	H	H	H	H	2		
33	3,4,5,6-Tetrahydro-3,10-diaza-benzo[e]azulene-1-carboxylic acid (5-bromo-pyridin-2-yl)-amide	H	H	H	H	H	2		
34	3,4,5,6-Tetrahydro-3,10-diaza-benzo[e]azulene-1-carboxylic acid (5-methyl-pyridin-2-yl)-amide	H	H	H	H	H	2		

588

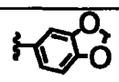
35	3,4,5,6-Tetrahydro-3,10-diaza-benzo[e]azulene-1-carboxylic acid (6-methoxy-pyridin-3-yl)-amide	H	H	H	H	H	2		
36	Propyl-(2-{5-[(3,4,5,6-tetrahydro-3,10-diaza-benzo[e]azulene-1-carbonyl)-amino]-pyridin-2-yloxy}-ethyl)-carbamic acid tert- butyl ester	H	H	H	H	H	2		
37	8-Methyl-3,4,5,6-tetrahydro-3,10-diaza-benzo[e]azulene-1-carboxylic acid (5-methyl-[1,3,4]thiadiazol-2-yl)-amide	H	CH_3	H	H	H	2		

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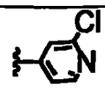
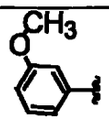
38	8-Methyl-3,4,5,6-tetrahydro-3,10-diaza-benzo[e]azulene-1-carboxylic acid (3-fluoro-4-methoxy-phenyl)-amide	H	CH_3	H	H	H	2		
39	3,4,5,6-Tetrahydro-3,10-diaza-benzo[e]azulene-1-carboxylic acid (4-ethoxy-phenyl)-amide	H	H	H	H	H	2		
40	Ethyl-(2-{4-[(3,4,5,6-tetrahydro-3,10-diaza-benzo[e]azulene-1-carbonyl)-amino]-phenoxy}-ethyl)-carbamic acid tert-butyl ester	H	H	H	H	H	2		

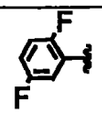
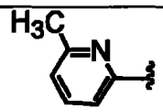
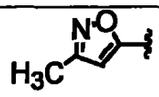
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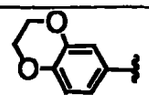
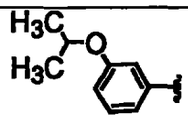
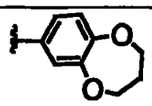
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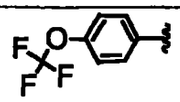
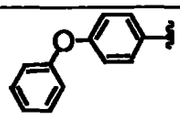
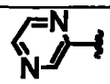
41	3,4,5,6-Tetrahydro-3,10-diaza-benzo[e]azulene-1-carboxylic acid (6-ethyl-pyridin-2-yl)-amide	H	H	H	H	H	2		[CDCl3] 1.35 (t, 3H), 2.3 ,(quint, 2H), 2.6 (t, 2H), 2.7 (t, 2H), 2.8 (q, 2H), 6.8 (d, 1H), 7.2 (dd, 1H), 7.55 (t, 1H), 7.6 (dd, 1H), 7.65 (s, 1H), 8.2 (d, 1H), 8.75 (d, 1H), 9.2 (br s, 1H)
42	3,4,5,6-Tetrahydro-3,10-diaza-benzo[e]azulene-1-carboxylic acid benzo[1,3]dioxol-5-ylamide	H	H	H	H	H	2		[CDCl3] 2.3 (quint, 2H), 2.6 (t, 2H), 2.7 (t, 2H), 6.8 (d, 1H), 7.1 (d, 1H), 7.2 (dd, 1H), 7.5 (s, 1H), 7.6 (s, 1H), 7.65 (d, 1H), 8.6 (d, 1H), 9.7 (br s, 1H)

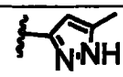
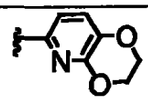
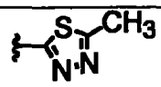
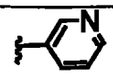
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43	3,4,5,6-Tetrahydro-3,10-diaza-benzo[e]azulene-1-carboxylic acid (2-chloro-pyridin-4-yl)-amide	H	H	H	H	H	2		[CDCl3] 2.3 (quint, 2H), 2.6 (t, 2H), 2.7 (t, 2H), 7.2 (dd, 1H), 7.5 (d, 1H), 7.6 (s, 1H), 7.65 (d, 1H), 7.8 (s, 1H), 8.2 (d, 1H), 8.6 (d, 1H), 9.0 (br s, 1H)
44	3,4,5,6-Tetrahydro-3,10-diaza-benzo[e]azulene-1-carboxylic acid (3-methoxy-phenyl)-amide	H	H	H	H	H	2		[CDCl3] 2.3 (quint, 2H), 2.6 (t, 2H), 2.7 (t, 2H), 3.8 (s, 3H), 6.6 (app s, 1H), 7.2 (dd, 1H), 7.25 (app s, 2H), 7.6 (m, 2H), 8.6 (d, 1H), 9.9 (br s, 1H)

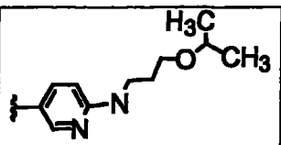
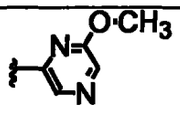
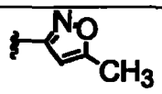
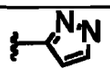
45	3,4,5,6-Tetrahydro-3,10-diaza-benzo[e]azulene-1-carboxylic acid (2,5-difluoro-phenyl)-amide	H	H	H	H	H	2		[CDCl3] 2.3 (quint, 2H), 2.6 (t, 2H), 2.7 (t, 2H), 6.7 (m, 1H), 7.0 (m, 1H), 7.2 (dd, 1H), 7.6 (dd, 1H), 7.65 (s, 1H), 8.5 (m, 1H), 8.6 (d, 1H), 9.2 (br s, 1H)
46	3,4,5,6-Tetrahydro-3,10-diaza-benzo[e]azulene-1-carboxylic acid (6-methyl-pyridin-2-yl)-amide	H	H	H	H	H	2		[CDCl3] 2.3 (quint, 2H), 2.4 (s, 3H), 2.6 (t, 2H), 2.7 (t, 2H), 6.8 (d, 1H), 7.2 (dd, 1H), 7.5 (t, 1H), 7.6 (dd, 1H), 7.65 (s, 1H), 8.2 (d, 1H), 8.7 (d, 1H), 9.8 (br s, 1H)
47	3,4,5,6-Tetrahydro-3,10-diaza-benzo[e]azulene-1-carboxylic acid (3-methyl-isoxazol-5-	H	H	H	H	H	2		[CDCl3] 2.25 (s, 3H), 2.3 (quint, 2H), 2.6 (t, 2H), 2.7 (t, 2H), 6.3 (s, 1H), 7.2 (dd, 1H),

	yl)-amide								7.6 (m, 2H), 8.6 (d, 1H), 8.8 (br s, 1H)
48	3,4,5,6-Tetrahydro-3,10-diaza-benzo[e]azulene-1-carboxylic acid (2,3-dihydro-benzo[1,4]dioxin-6-yl)-amide	H	H	H	H	H	2		LRMS *m/z* 362
49	3,4,5,6-Tetrahydro-3,10-diaza-benzo[e]azulene-1-carboxylic acid (3-isopropoxy-phenyl)-amide	H	H	H	H	H	2		LRMS *m/z* 362
50	3,4,5,6-Tetrahydro-3,10-diaza-benzo[e]azulene-1-carboxylic acid (3,4-dihydro-2H-benzo[b][1,4]dioxepin-7-yl)-amide	H	H	H	H	H	2		LRMS *m/z* 376

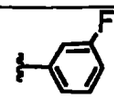
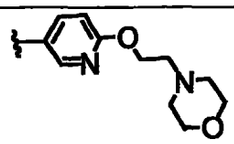
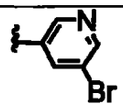
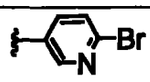
51	3,4,5,6-Tetrahydro-3,10-diaza-benzo[e]azulene-1-carboxylic acid (4-trifluoromethoxy-phenyl)-amide	H	H	H	H	H	2		LRMS m/z 388
52	3,4,5,6-Tetrahydro-3,10-diaza-benzo[e]azulene-1-carboxylic acid (4-phenoxy-phenyl)-amide	H	H	H	H	H	2		LRMS m/z 396
53	3,4,5,6-Tetrahydro-3,10-diaza-benzo[e]azulene-1-carboxylic acid pyrazin-2-ylamide	H	H	H	H	H	2		LRMS m/z 306
54	3,4,5,6-Tetrahydro-3,10-diaza-benzo[e]azulene-1-carboxylic acid (1-ethyl-1H-pyrazol-3-yl)-amide	H	H	H	H	H	2		LCMS found (M+H) 322

55	3,4,5,6-Tetrahydro-3,10-diaza-benzo[e]azulene-1-carboxylic acid (5-methyl-1H-pyrazol-3-yl)-amide	H	H	H	H	H	2		LCMS found (M+H) 309
56	3,4,5,6-Tetrahydro-3,10-diaza-benzo[e]azulene-1-carboxylic acid (2,3-dihydro-[1,4]dioxino[2,3-b]pyridin-6-yl)-amide	H	H	H	H	H	2		LCMS found (M+H) 363
57	3,4,5,6-Tetrahydro-3,10-diaza-benzo[e]azulene-1-carboxylic acid (5-methyl-[1,3,4]thiadiazol-2-yl)-amide	H	H	H	H	H	2		
58	3,4,5,6-Tetrahydro-3,10-diaza-benzo[e]azulene-1-carboxylic acid pyridin-3-ylamide	H	H	H	H	H	2		

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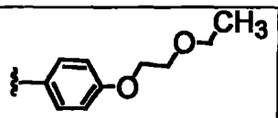
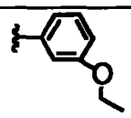
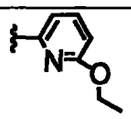
59	3,4,5,6-Tetrahydro-3,10-diaza-benzo[e]azulene-1-carboxylic acid [6-(3-isopropoxy-propylamino)-pyridin-3-yl]-amide	H	H	H	H	H	2		
60	3,4,5,6-Tetrahydro-3,10-diaza-benzo[e]azulene-1-carboxylic acid (6-methoxy-pyrazin-2-yl)-amide	H	H	H	H	H	2		
61	3,4,5,6-Tetrahydro-3,10-diaza-benzo[e]azulene-1-carboxylic acid (5-methyl-isoxazol-3-yl)-amide	H	H	H	H	H	2		
62	3,4,5,6-Tetrahydro-3,10-diaza-benzo[e]azulene-1-carboxylic acid (1H-pyrazol-3-yl)-amide	H	H	H	H	H	2		

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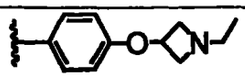
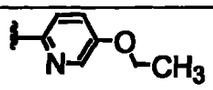
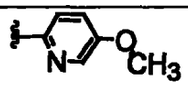
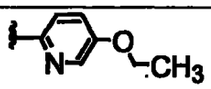
63	3,4,5,6-Tetrahydro-3,10-diaza-benzo[e]azulene-1-carboxylic acid (3-fluoro-phenyl)-amide	H	H	H	H	H	2		
64	3,4,5,6-Tetrahydro-3,10-diaza-benzo[e]azulene-1-carboxylic acid [6-(2-morpholin-4-yl-ethoxy)-pyridin-3-yl]-amide	H	H	H	H	H	2		
65	3,4,5,6-Tetrahydro-3,10-diaza-benzo[e]azulene-1-carboxylic acid (5-bromo-pyridin-3-yl)-amide	H	H	H	H	H	2		
66	3,4,5,6-Tetrahydro-3,10-diaza-benzo[e]azulene-1-carboxylic acid (6-bromo-pyridin-3-yl)-amide	H	H	H	H	H	2		

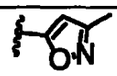
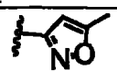
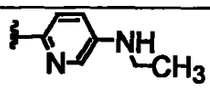
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67	3,4,5,6-Tetrahydro-3,10-diaza-benzo[e]azulene-1-carboxylic acid [4-(2-ethoxy-ethoxy)-phenyl]-amide	H	H	H	H	H	2		1HNMR (DMSO) 1.11(t, 3H), 2.15 (t, 2H), 2.49 (t, 2H), 2.73 (t, 2H), 3.46-3.49 (m, 2H), 3.67 (t, 2H), 4.0 (t, 2H), 6.90-6.92 (m, 2H), 7.58-8.41 (m, 5H), 8.69 (brs, 1H) LCMS found (M+H) 392.3
68	3,4,5,6-Tetrahydro-3,10-diaza-benzo[e]azulene-1-carboxylic acid (3-ethoxy-phenyl)-amide	H	H	H	H	H	2		LCMS found (M+H) 348
69	3,4,5,6-Tetrahydro-3,10-diaza-benzo[e]azulene-1-carboxylic acid (6-ethoxy-pyridin-2-yl)-amide	H	H	H	H	H	2		LCMS found (M+H) 349

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70	3,4,5,6-Tetrahydro-3,10-diaza-benzo[e]azulene-1-carboxylic acid [4-(1-ethyl-azetidin-3-yloxy)-phenyl]-amide	H	H	H	H	H	2		Electrospray mass spectrum: m/z 401 [M-1]
71	3,4,5,6-tetrahydro-3,10-diaza-benzo[e]azulene-1-carboxylic acid (5-ethoxy-pyridin-2-yl)-amide	H	H	H	H	H	2		LRMS calcd 348 found [M+1] 349
72	8-Methyl-3,4,5,6-tetrahydro-3,10-diaza-benzo[e]azulene-1-carboxylic acid (5-methoxy-pyridin-2-yl)-amide	H	CH_3	H	H	H	2		LRMS calcd 348 found [M+1] 349
73	8-Methyl-3,4,5,6-tetrahydro-3,10-diaza-benzo[e]azulene-1-carboxylic acid (5-ethoxy-pyridin-2-yl)-amide	H	CH_3	H	H	H	2		LRMS calcd 362 found [M+1] 363

74	8-Methyl-3,4,5,6-tetrahydro-3,10-diaza-benzo[e]azulene-1-carboxylic acid pyridazin-3-ylamide	H	CH_3	H	H	H	2		LRMS calcd 319 found [M+1] 320
75	8-Methyl-3,4,5,6-tetrahydro-3,10-diaza-benzo[e]azulene-1-carboxylic acid (3-methyl-isoxazol-5-yl)-amide	H	CH_3	H	H	H	2		LRMS calcd 322 found [M+1] 323
76	8-Methyl-3,4,5,6-tetrahydro-3,10-diaza-benzo[e]azulene-1-carboxylic acid (5-methyl-isoxazol-3-yl)-amide	H	CH_3	H	H	H	2		LRMS calcd 322 found [M+1] 323
77	3,4,5,6-Tetrahydro-3,10-diaza-benzo[e]azulene-1-carboxylic acid (6-ethylamino-pyridin-3-yl)-amide	H	H	H	H	H	2		LRMS calcd 347 found [M+1] 348

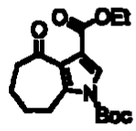
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Example 6

3-Methyl-3,4,5,6-tetrahydro-3,10-diaza-benzo[e]azulene-1-carboxylic acid ethyl ester

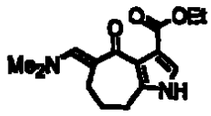


Step 1:

To a solution of 4-oxo-1,4,5,6,7,8-hexahydro-cyclohepta[*b*]pyrrole-3-carboxylic acid ethyl ester (4.80 g, 21.7 mmol) and Et_3N (3.93 mL, 28.2 mmol) in CH_2Cl_2 (40 mL) at 0 °C is added Boc_2O (5.68 g, 26.0 mmol) in one portion. The reaction mixture is allowed to stir at 0 °C for 10 min. and then at rt for 18 h. The reaction mixture is then diluted with half saturated aq NH_4Cl (70 mL) and extracted with EtOAc. The organic layer is then washed with H_2O (50 mL) and brine (50 mL). The aqueous washes were reextracted once with EtOAc, and the combined extracts were dried over Na_2SO_4 and concentrated. The crude material is purified by flash chromatography on silica gel. Elution with 4:1 hexanes-EtOAc followed by 3:1 hexanes-EtOAc afforded 7.00 g (quant) of 4-oxo-5,6,7,8-tetrahydro-4*H*-cyclohepta[*b*]pyrrole-1,3-dicarboxylic acid 1-tert-butyl ester 3-ethyl ester as a light yellow solid. ^1H NMR ($CDCl_3$, 300 MHz) δ 7.62 (s, 1H), 4.27 (q, J = 7.2 Hz, 2H), 3.22 (m, 2H), 2.78 (m, 2H), 1.86 (m, 4H), 1.60 (s, 9H), 1.31 (t, J = 7.2 Hz)

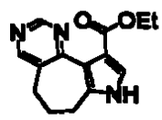
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Step 2:

A mixture of 4-oxo-5,6,7,8-tetrahydro-4*H*-cyclohepta[*b*]pyrrole-1,3-dicarboxylic acid 1-tert-butyl ester 3-ethyl ester (1.13 g, 3.52 mmol) and tris(dimethylamino)methane (1.02 g, 7.04 mmol) is stirred at 60 °C in a sealed tube for 4.5 h. After cooling, the thick slurry is taken up in Et_2O and filtered. The solid is washed with Et_2O and dried, affording 847 mg (87%) of 5-dimethylaminomethylene-4-oxo-1,4,5,6,7,8-hexahydro-cyclohepta[*b*]pyrrole-3-carboxylic acid ethyl ester as a light yellow-orange solid. ^1H NMR ($CDCl_3$, 300 MHz) δ 9.93 (br s, 1H), 7.58 (s, 1H), 7.12 (d, J = 2.7 Hz, 1H), 4.21 (q, J = 7.2 Hz, 2H), 3.06 (s, 6H), 2.68 (m, 2H), 2.47 (m, 2H), 1.80 (m, 2H), 1.26 (t, J = 7.2 Hz, 3H).



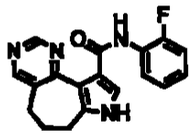
Step 3:

A mixture of 5-dimethylaminomethylene-4-oxo-1,4,5,6,7,8-hexahydro-cyclohepta[*b*]pyrrole-3-carboxylic acid ethyl ester (840 mg) and formamidine acetate (956 mg, 9.1 mmol) in EtOH (10 mL) is stirred at 120 °C for 4 h. After cooling, the reaction

mixture is diluted with CH_2Cl_2 and washed with half saturated aq $NaHCO_3$ (25 mL), H_2O (25 mL), and brine (25 mL). The aqueous washes were reextracted once with CH_2Cl_2, and the combined extracts were dried over K_2CO_3 and concentrated. The crude material is purified by flash chromatography on silica gel. Elution with 30:1 $CHCl_3$-MeOH followed by 20:1 $CHCl_3$-MeOH and finally 15:1 $CHCl_3$-MeOH afforded 606 mg (77%) of 3,4,5,6-tetrahydro-3,8,10-triaza-benzo[e]azulene-1-carboxylic acid ethyl ester as a light yellow solid. ^1H NMR ($CDCl_3$, 300 MHz) δ 9.30 (br s, 1H), 9.02 (s, 1H), 8.43 (s, 1H), 7.24 (d, J = 2.7 Hz, 1H), 4.26 (q, J = 7.2 Hz, 2H), 2.78 (t, J = 7.2 Hz, 2H), 2.70 (m, 2H), 2.12 (m, 2H), 1.26 (t, J = 7.2 Hz, 3H).

Example 7

3,4,5,6-Tetrahydro-3,8,10-triaza-benzo[e]azulene-1-carboxylic acid (2-fluoro-phenyl)-amide



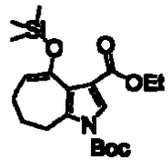
To a solution of 2-fluoroaniline (108 mg, 0.972 mmol) in CH_2Cl_2 (2.0 mL) at 0 °C under N_2 is slowly added $AlMe_3$ (0.49 mL, 2.0 *M* in toluene). The resulting solution is stirred at rt for 1 h. Next, 3,4,5,6-tetrahydro-3,8,10-triaza-benzo[e]azulene-1-carboxylic acid ethyl ester (50 mg, 0.194 mmol) is added in one

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portion. The resulting mixture is then stirred at reflux for 2 h. After cooling, the reaction mixture is carefully diluted with saturated aq NH_4Cl (~5 mL) and some H_2O. The mixture is stirred vigorously for 15 min. and then extracted three times with CH_2Cl_2. The combined extracts were dried over K_2CO_3 and concentrated. The crude material is purified by flash chromatography on silica gel. Elution with 40:1 $CHCl_3$-MeOH followed by 30:1 $CHCl_3$-MeOH and finally 20:1 $CHCl_3$-MeOH afforded 45 mg (72%) of 3,4,5,6-tetrahydro-3,8,10-triaza-benzo[e]azulene-1-carboxylic acid (2-fluoro-phenyl)-amide as a light yellow solid. Electrospray mass spectrum: *m/z* 321 [M-1].

Example 7a

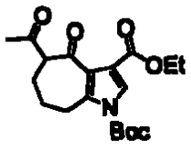
3-Methyl-4,5,6,7-tetrahydro-1-oxa-2,7-diaza-cyclopenta[e]azulene-9-carboxylic acid ethyl ester



Step 1:

To a mixture of 4-oxo-5,6,7,8-tetrahydro-4H-cyclohepta[b]pyrrole-1,3-dicarboxylic acid 1-tert-butyl ester 3-ethyl ester (4.6 mmol), sodium iodide (9.3 mmol), and triethylamine (13.9 mmol) in 15 ml acetonitrile is added

trimethylsylyl chloride (9.3 mmol). After stirring at RT for 2 hours it is quenched with 20 ml saturated $NaHCO_3$ solution and extracted several times with EtOAc. The combined organic layers were dried over Na_2SO_4 and evaporated in *vacuo* yielding 4-trimethylsilanyloxy-7,8-dihydro-6H-cyclohepta[b]pyrrole-1,3-dicarboxylic acid 1-tert-butyl ester 3-ethyl ester as a brown oil (95%). 1H NMR (CDCl3) 0.15 (s, 9H), 1.32 (t, 3H), 1.60 (s, 9H), 1.83-1.97 (m, 2H), 1.99-2.06 (m, 2H), 3.00 (t, 2H), 4.33 (q, 2H), 5.40 (t, 1H), 7.62 (s, 1H).



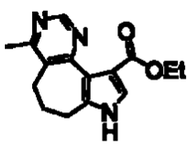
Step 2:

Bismuth (III) chloride (0.1 mmol) and sodium iodide (0.3 mmol) were transferred to a dried flask under nitrogen and 5 ml of a mixture of CH_2Cl_2/ether (9/1) is added by a syringe. This is followed by the addition of acetyl chloride (2.2 mmol) and the suspension is stirred for 5 min at RT. 4-trimethylsilanyloxy-7,8-dihydro-6H-cyclohepta[b]pyrrole-1,3-dicarboxylic acid 1-tert-butyl ester 3-ethyl ester (2 mmol) in 5 ml of the same solvent mixture is added. After 2 hours at RT, the mixture is quenched with 20 ml saturated $NaHCO_3$ solution and extracted several times with CH_2Cl_2. The organic layers were combined,

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dried over Na_2SO_4 and evaporated *in vacuo* yielding 5-acetyl-4-oxo-5,6,7,8-tetrahydro-4H-cyclohepta[b]pyrrole-1,3-dicarboxylic acid 1-tert-butyl ester 3-ethyl ester as an oil (86%). LRMS 363.4 found (M+1) 364.2



Step 3:

In a sealed tube were 5-acetyl-4-oxo-5,6,7,8-tetrahydro-4H-cyclohepta[b]pyrrole-1,3-dicarboxylic acid 1-tert-butyl ester 3-ethyl ester (1.1 mmol) and formamidine acetate (5.5 mmol) and 10 ml EtOH. The mixture is heated at 120°C for 48 hours. The solvent is evaporated in *vacuo* and the residue is taken up in CH_2Cl_2 and washed two times with $NaHCO_3$ (aq). The organic layer is dried over Na_2SO_4 and evaporated in *vacuo* and the residue chromatographed using 10% MeOH in CH_2Cl_2 as mobile phase to yield 7-Methyl-3,4,5,6-tetrahydro-3,8,10-triaza-benzo[e]azulene-1-carboxylic acid ethyl ester (36%). LRMS 271.1 found (M+1) 272

Example 7b

Additional 3,8,10-triaza-benzo[e]azulene-1-carboxylic acid compounds

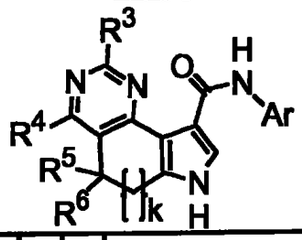
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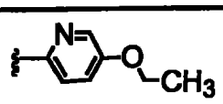
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Using the methods shown in Scheme 4 and further illustrated in Examples 6 and 7-7a the following compounds shown in Table 3 were synthesized.

09/080,659 02/27/98

TABLE 3

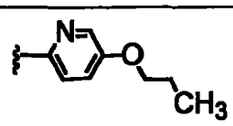
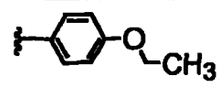
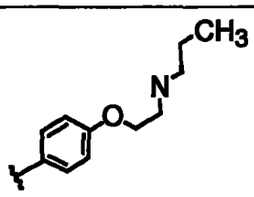


Cmp #	Name	R^3	R^4	R^5	R^6	k	Ar	Spectral Data
1	3,4,5,6-Tetrahydro-3,8,10-triaza-benzo[e]azulene-1-carboxylic acid (5-ethoxy-pyridin-2-yl)-amide	H	H	H	H	2		Electrospray mass spectrum: m/z 348 [M-1]

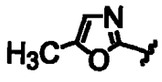
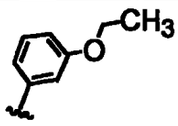
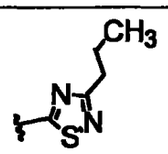
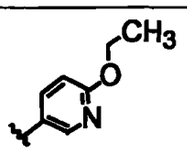
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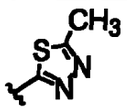
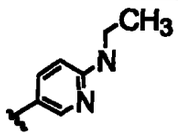
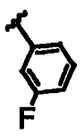
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2	3,4,5,6-Tetrahydro-3,8,10-triaza-benzo[e]azulene-1-carboxylic acid (5-*n*-propoxy-pyridin-2-yl)-amide	H	H	H	H	2		LRMS calcd 363 found [M+1] 364
3	3,4,5,6-Tetrahydro-3,8,10-triaza-benzo[e]azulene-1-carboxylic acid (4-ethoxy-phenyl)-amide	H	H	H	H	2		Electrospray mass spectrum: *m/z* 347 [M-1]
4	3,4,5,6-Tetrahydro-3,8,10-triaza-benzo[e]azulene-1-carboxylic acid [4-(2-propylamino-ethoxy)-phenyl]-amide	H	H	H	H	2		LRMS calcd 405 found [M+1] 406

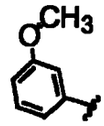
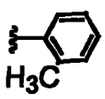
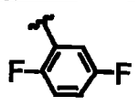
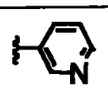
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5	3,4,5,6-Tetrahydro-3,8,10-triaza-benzo[e]azulene-1-carboxylic acid (5-methyl-oxazol-2-yl)-amide	H	H	H	H	2		LCMS found (M+H) 336
6	3,4,5,6-Tetrahydro-3,8,10-triaza-benzo[e]azulene-1-carboxylic acid (3-ethoxy-phenyl)-amide	H	H	H	H	2		LCMS found (M+H) 349
7	3,4,5,6-Tetrahydro-3,8,10-triaza-benzo[e]azulene-1-carboxylic acid (3-propyl-[1,2,4]thiadiazol-5-yl)-amide	H	H	H	H	2		LCMS found (M+H) 355
8	3,4,5,6-Tetrahydro-3,8,10-triaza-benzo[e]azulene-1-carboxylic acid (6-ethoxy-pyridin-3-yl)-amide	H	H	H	H	2		LRMS 349.39 found (M+1) 350.3

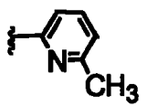
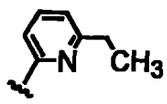
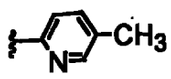
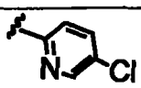
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9	3,4,5,6-Tetrahydro-3,8,10-triaza-benzo[e]azulene-1-carboxylic acid (5-methyl-[1,3,4]thiadiazol-2-yl)-amide	H	H	H	H	2		Electrospray mass spectrum: m/z 325 [M-1]
10	3,4,5,6-Tetrahydro-3,8,10-triaza-benzo[e]azulene-1-carboxylic acid (6-ethylamino-pyridin-3-yl)-amide	H	H	H	H	2		LRMS calcd 348 found [M+1] 349
11	3,4,5,6-Tetrahydro-3,8,10-triaza-benzo[e]azulene-1-carboxylic acid (3-fluoro-phenyl)-amide	H	H	H	H	2		[CDCl3] 2.3 (quint, 2H), 2.6 (t, 2H), 2.8 (t, 2H), 6.8 (app s, 1H), 7.3 (m, 2H), 7.7 (s, 1H), 7.8 (d, 1H), 8.6 (s, 1H), 9.2 (s, 1H), 10.4 (br s, 1H), 13.0 (s, 1H); LRMS calcd 322 found [M+1] 323

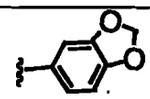
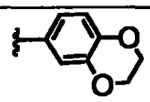
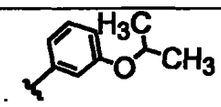
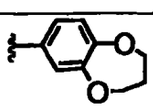
612

12	3,4,5,6-Tetrahydro-3,8,10-triaza-benzo[e]azulene-1-carboxylic acid (3-methoxy-phenyl)-amide	H	H	H	H	2		[CDCl3] 2.3 (quint, 2H), 2.6 (t, 2H), 2.8 (t, 2H), 3.8 (s, 3H), 6.6 (d, 1H), 7.2 (m, 2H), 7.6 (s, 1H), 7.7 (s, 1H), 8.6 (s, 1H), 9.2 (s, 1H), 10.4 (br s, 1H), 12.9 (s, 1H)
13	3,4,5,6-Tetrahydro-3,8,10-triaza-benzo[e]azulene-1-carboxylic acid o-tolyl-amide	H	H	H	H	2		[CDCl3] 2.3 (quint, 2H), 2.4 (s, 3H), 2.6 (app t, 4H), 7.1 (t, 1H), 7.2 (m, 2H), 7.65 (s, 1H), 7.75 (s, 1H), 8.6 (s, 1H), 9.0 (s, 1H), 10.5 (br s, 1H), 12.2 (s, 1H); LRMS calcd 318 found [M+1] 319
14	3,4,5,6-Tetrahydro-3,8,10-triaza-benzo[e]azulene-1-carboxylic acid (2,5-difluoro-phenyl)-amide	H	H	H	H	2		[CDCl3] 2.3 (quint, 2H), 2.6 (t, 2H), 2.8 (t, 2H), 6.7 (m, 1H), 7.05 (m, 1H), 7.75 (s, 1H), 8.45 (m, 1H), 8.6 (s, 1H), 9.2 (s, 1H), 10.0 (br s, 1H), 13.4 (s, 1H); Electrospray mass spectrum: m/z 339 [M-1
15	3,4,5,6-Tetrahydro-3,8,10-triaza-benzo[e]azulene-1-carboxylic acid pyridin-3-ylamide	H	H	H	H	2		[CDCl3 + CD3OD] 2.3 (quint, 2H), 2.6 (t, 2H), 2.8 (t, 2H), 7.3 (m, 2H), 7.6 (s, 1H), 8.3 (m, 2H), 8.6 (s, 1H), 8.8 (s, 1H), 9.2 (s, 1H)

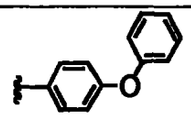
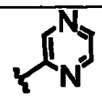
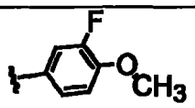
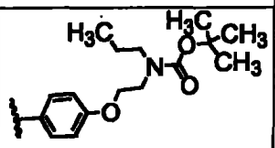
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16	3,4,5,6-Tetrahydro-3,8,10-triaza-benzo[e]azulene-1-carboxylic acid (6-methyl-pyridin-2-yl)-amide	H	H	H	H	2		[CDCl3] 2.3 (quint, 2H), 2.5 (s, 3H), 2.6 (t, 2H), 2.8 (t, 2H), 6.85 (d, 1H), 7.6 (t, 1H), 7.7 (s, 1H), 8.2 (d, 1H), 8.6 (s, 1H), 9.3 (s, 1H), 9.6 (br s, 1H)
17	3,4,5,6-Tetrahydro-3,8,10-triaza-benzo[e]azulene-1-carboxylic acid (6-ethyl-pyridin-2-yl)-amide	H	H	H	H	2		[CDCl3] 1.3 (t, 3H), 2.3 (quint, 2H), 2.6 (t, 2H), 2.8 (m, 4H), 6.8 (d, 1H), 7.5 (t, 1H), 7.6 (s, 1H), 8.1 (d, 1H), 8.5 (s, 1H), 9.2 (s, 1H)
18	3,4,5,6-Tetrahydro-3,8,10-triaza-benzo[e]azulene-1-carboxylic acid (5-methyl-pyridin-2-yl)-amide	H	H	H	H	2		[CDCl3] 2.2 (s, 3H), 2.3 (quint, 2H), 2.6 (t, 2H), 2.8 (t, 2H), 7.4 (d, 1H), 7.6 (s, 1H), 8.1 (s, 1H), 8.2 (d, 1H), 8.5 (s, 1H), 9.2 (s, 1H)
19	3,4,5,6-Tetrahydro-3,8,10-triaza-benzo[e]azulene-1-carboxylic acid (5-chloro-pyridin-2-yl)-amide	H	H	H	H	2		[CDCl3] 2.3 (quint, 2H), 2.6 (t, 2H), 2.8 (t, 2H), 7.6 (dd, 1H), 7.7 (s, 1H), 8.3 (d, 1H), 8.35 (d, 1H), 8.6 (s, 1H), 9.2 (s, 1H), 9.7 (br s, 1H)

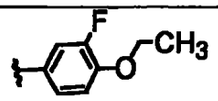
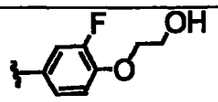
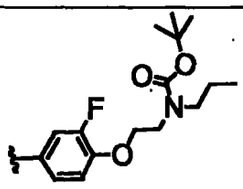
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20	3,4,5,6-Tetrahydro-3,8,10-triaza-benzo[e]azulene-1-carboxylic acid benzo[1,3]dioxol-5-ylamide	H	H	H	H	2		[CDCl3 + CD3OD] 2.3 (quint, 2H), 2.6 (t, 2H), 2.8 (t, 2H), 6.0 (s, 2H), 6.8 (d, 1H), 7.0 (dd, 1H), 7.4 (d, 1H), 7.6 (s, 1H), 8.6 (s, 1H), 9.1 (s, 1H)
21	3,4,5,6-Tetrahydro-3,8,10-triaza-benzo[e]azulene-1-carboxylic acid (2,3-dihydro-benzo[1,4]dioxin-6-yl)-amide	H	H	H	H	2		Electrospray mass spectrum: m/z 363 [M+1]
22	3,4,5,6-Tetrahydro-3,8,10-triaza-benzo[e]azulene-1-carboxylic acid (3-isopropoxy-phenyl)-amide	H	H	H	H	2		LRMS m/z 363
23	3,4,5,6-Tetrahydro-3,8,10-triaza-benzo[e]azulene-1-carboxylic acid (3,4-dihydro-2H-benzo[b][1,4]dioxepin-7-yl)-amide	H	H	H	H	2		LRMS m/z 377

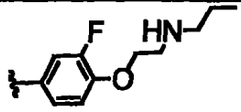
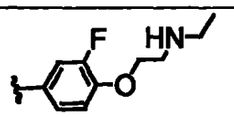
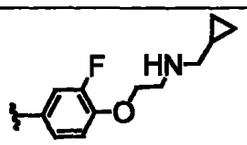
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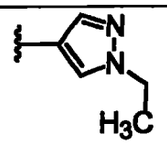
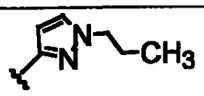
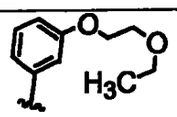
24	3,4,5,6-Tetrahydro-3,8,10-triaza-benzo[e]azulene-1-carboxylic acid (4-phenoxy-phenyl)-amide	H	H	H	H	2		LRMS m/z 397
25	3,4,5,6-Tetrahydro-3,8,10-triaza-benzo[e]azulene-1-carboxylic acid pyrazin-2-ylamide	H	H	H	H	2		LRMS calcd 306 found [M+1] 307; 1H NMR DMSO-d6, 2.14 (m, 2H), 2.62(m, 2H), 2.80(m, 2H), 7.64(s, 1H), 8.30(1H, d), 8.38(m, 1H), 8.66(s, 1H), 9.04(s, 1H), 9.48(s, 1H), 11.94(bs, 1H), 13.57(s, 1H)
26	3,4,5,6-Tetrahydro-3,8,10-triaza-benzo[e]azulene-1-carboxylic acid (3-fluoro-4-methoxy-phenyl)-amide	H	H	H	H	2		Electrospray mass spectrum: m/z 351 [M-1]
27	Propyl-(2-{4-[(3,4,5,6-tetrahydro-3,8,10-triaza-benzo[e]azulene-1-carbonyl)-amino]-phenoxy}-ethyl)-carbamic acid tert-butyl ester							LRMS calcd 505 found [M+1] 506

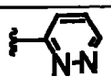
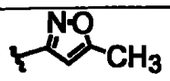
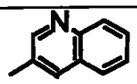
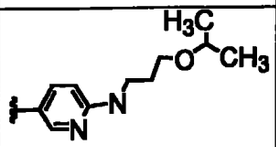
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28	3,4,5,6-Tetrahydro-3,8,10-triaza-benzo[e]azulene-1-carboxylic acid (4-ethoxy-3-fluoro-phenyl)-amide	H	H	H	H	2		LRMS 366.39 found (M+1) 367.3
29	3,4,5,6-Tetrahydro-3,8,10-triaza-benzo[e]azulene-1-carboxylic acid [3-fluoro-4-(2-hydroxy-ethoxy)-phenyl]-amide	H	H	H	H	2		LRMS calcd 382 found [M+1]
30	Propyl-(2-{4-[(3,4,5,6-tetrahydro-3,8,10-triaza-benzo[e]azulene-1-carbonyl)-amino]-phenoxy}-ethyl)-carbamic acid tert-butyl ester	H	H	H	H	2		LRMS calcd 505 found [M+1] 506

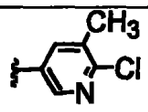
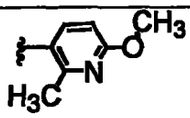
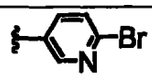
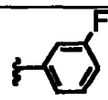
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31	3,4,5,6-Tetrahydro-3,8,10-triaza-benzo[e]azulene-1-carboxylic acid [3-fluoro-4-(2-propylamino-ethoxy)-phenyl]-amide	H	H	H	H	2		LRMS calcd 423 found [M-1] 422
32	3,4,5,6-Tetrahydro-3,8,10-triaza-benzo[e]azulene-1-carboxylic acid [4-(2-ethylamino-ethoxy)-3-fluoro-phenyl]-amide	H	H	H	H	2		LRMS calcd 409 found [M+1] 410
33	3,4,5,6-Tetrahydro-3,8,10-triaza-benzo[e]azulene-1-carboxylic acid {4-[2-(cyclopropylmethyl-amino)-ethoxy]-3-fluoro-phenyl}-amide	H	H	H	H	2		LRMS calcd 435 found [M+1] 436

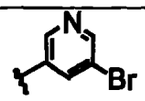
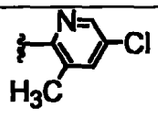
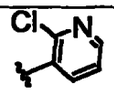
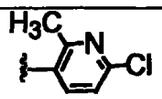
34	3,4,5,6-Tetrahydro-3,8,10-triaza-benzo[e]azulene-1-carboxylic acid (1-ethyl-1H-pyrazol-4-yl)-amide	H	H	H	H	2		^{1}HNMR (DMSO) 1.33 (t, 3H), 2.11-2.20 (m, 2H), 2.55-2.62 (m, 2H), 2.72-2.76 (m, 2H), 4.01 (q, 2H), 6.5 (s, 1H), 7.5 (s, 1H), 7.6 (s, 1H), 8.6 (s, 1H), 9.0 (S, 1H), 11.8 (brs, 1H), 12.7 (brs, 1H) LCMS found (M+H) 323
35	3,4,5,6-Tetrahydro-3,8,10-triaza-benzo[e]azulene-1-carboxylic acid (1-propyl-1H-pyrazol-3-yl)-amide	H	H	H	H	2		LCMS found (M+H) 337
36	3,4,5,6-Tetrahydro-3,8,10-triaza-benzo[e]azulene-1-carboxylic acid [3-(2-ethoxy-ethoxy)-phenyl]-amide	H	H	H	H	2		1HNMR (DMSO) 1.21-1.25 (m, 3H), 2.25 (t, 2H), 2.62 (t, 2H), 2.76 (t, 2H), 3.57-3.61 (m, 2H), 3.78-3.80 (m, 2H), 4.13-4.15 (m, 2H), 6.66-6.69 (m, 1H), 7.21-7.2 (m., 2H), 7.54 (brs, 1H), 7.66 (m, 1H), 8.56 (brs, 1H), 9.16 (brs, 1H), 12.9 (s, 1H) LCMS found (M+H) 393

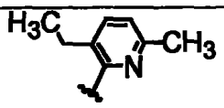
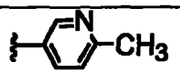
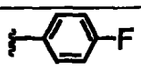
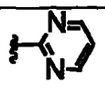
37	3,4,5,6-Tetrahydro-3,8,10-triaza-benzo[e]azulene-1-carboxylic acid pyridazin-3-ylamide	H	H	H	H	2		LRMS calcd 306 found [M+1] 307
38	3,4,5,6-Tetrahydro-3,8,10-triaza-benzo[e]azulene-1-carboxylic acid (5-methyl-isoxazol-3-yl)-amide	H	H	H	H	2		LCMS found (M+H) 310
39	3,4,5,6-Tetrahydro-3,8,10-triaza-benzo[e]azulene-1-carboxylic acid quinolin-3-ylamide	H	H	H	H	2		
40	3,4,5,6-Tetrahydro-3,8,10-triaza-benzo[e]azulene-1-carboxylic acid [6-(3-isopropoxy-propylamino)-pyridin-3-yl]-amide	H	H	H	H	2		

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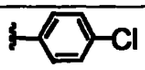
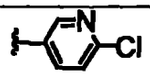
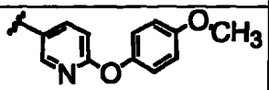
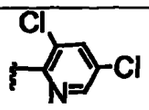
41	3,4,5,6-Tetrahydro-3,8,10-triaza-benzo[e]azulene-1-carboxylic acid (6-chloro-5-methyl-pyridin-3-yl)-amide	H	H	H	H	2		
42	3,4,5,6-Tetrahydro-3,8,10-triaza-benzo[e]azulene-1-carboxylic acid (6-methoxy-2-methyl-pyridin-3-yl)-amide	H	H	H	H	2		
43	3,4,5,6-Tetrahydro-3,8,10-triaza-benzo[e]azulene-1-carboxylic acid (6-bromo-pyridin-3-yl)-amide	H	H	H	H	2		
44	3,4,5,6-Tetrahydro-3,8,10-triaza-benzo[e]azulene-1-carboxylic acid (3-fluoro-phenyl)-amide	H	H	H	H	2		LRMS calcd 322 found [M+1] 323

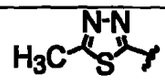
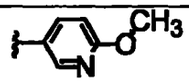
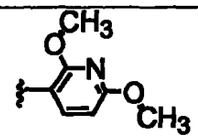
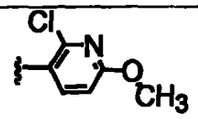
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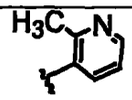
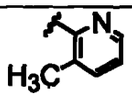
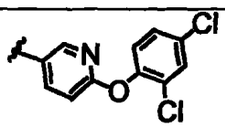
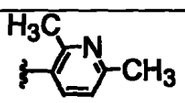
45	3,4,5,6-Tetrahydro-3,8,10-triaza-benzo[e]azulene-1-carboxylic acid (5-bromo-pyridin-3-yl)-amide	H	H	H	H	2		
46	3,4,5,6-Tetrahydro-3,8,10-triaza-benzo[e]azulene-1-carboxylic acid (5-chloro-3-methyl-pyridin-2-yl)-amide	H	H	H	H	2		
47	3,4,5,6-Tetrahydro-3,8,10-triaza-benzo[e]azulene-1-carboxylic acid (2-chloro-pyridin-3-yl)-amide	H	H	H	H	2		
48	3,4,5,6-Tetrahydro-3,8,10-triaza-benzo[e]azulene-1-carboxylic acid (6-chloro-2-methyl-pyridin-3-yl)-amide	H	H	H	H	2		

49	3,4,5,6-Tetrahydro-3,8,10-triaza-benzo[e]azulene-1-carboxylic acid (3-ethyl-6-methyl-pyridin-2-yl)-amide	H	H	H	H	2		
50	3,4,5,6-Tetrahydro-3,8,10-triaza-benzo[e]azulene-1-carboxylic acid (6-methyl-pyridin-3-yl)-amide	H	H	H	H	2		
51	3,4,5,6-Tetrahydro-3,8,10-triaza-benzo[e]azulene-1-carboxylic acid (4-fluoro-phenyl)-amide	H	H	H	H	2		
52	3,4,5,6-Tetrahydro-3,8,10-triaza-benzo[e]azulene-1-carboxylic acid pyrimidin-2-ylamide	H	H	H	H	2		

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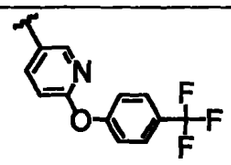
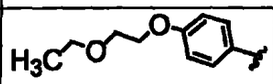
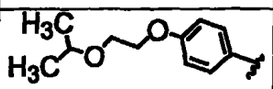
53	3,4,5,6-Tetrahydro-3,8,10-triaza-benzo[e]azulene-1-carboxylic acid (4-chloro-phenyl)-amide	H	H	H	H	2		
54	3,4,5,6-Tetrahydro-3,8,10-triaza-benzo[e]azulene-1-carboxylic acid (6-chloro-pyridin-3-yl)-amide	H	H	H	H	2		
55	3,4,5,6-Tetrahydro-3,8,10-triaza-benzo[e]azulene-1-carboxylic acid [6-(4-methoxy-phenoxy)-pyridin-3-yl]-amide	H	H	H	H	2		
56	3,4,5,6-Tetrahydro-3,8,10-triaza-benzo[e]azulene-1-carboxylic acid (3,5-dichloro-pyridin-2-yl)-amide	H	H	H	H	2		

57	3,4,5,6-Tetrahydro-3,8,10-triaza-benzo[e]azulene-1-carboxylic acid (5-methyl-[1,3,4]thiadiazol-2-yl)-amide	H	H	H	H	2		
58	3,4,5,6-Tetrahydro-3,8,10-triaza-benzo[e]azulene-1-carboxylic acid (6-methoxy-pyridin-3-yl)-amide	H	H	H	H	2		
59	3,4,5,6-Tetrahydro-3,8,10-triaza-benzo[e]azulene-1-carboxylic acid (2,6-dimethoxy-pyridin-3-yl)-amide	H	H	H	H	2		
60	3,4,5,6-Tetrahydro-3,8,10-triaza-benzo[e]azulene-1-carboxylic acid (2-chloro-6-methoxy-pyridin-3-yl)-amide	H	H	H	H	2		LRMS calcd 369 found [M+1] 370

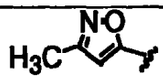
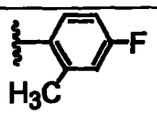
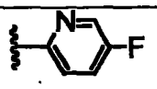
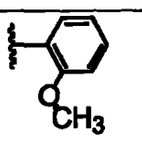
61	3,4,5,6-Tetrahydro-3,8,10-triaza-benzo[e]azulene-1-carboxylic acid (2-methyl-pyridin-3-yl)-amide	H	H	H	H	2		LRMS calcd 320 found [M+1] 321
62	3,4,5,6-Tetrahydro-3,8,10-triaza-benzo[e]azulene-1-carboxylic acid (3-methyl-pyridin-2-yl)-amide	H	H	H	H	2		Electrospray mass spectrum: *m/z* 320 [M+1]
63	3,4,5,6-Tetrahydro-3,8,10-triaza-benzo[e]azulene-1-carboxylic acid [6-(2,4-dichloro-phenoxy)-pyridin-3-yl]-amide	H	H	H	H	2		
64	3,4,5,6-Tetrahydro-3,8,10-triaza-benzo[e]azulene-1-carboxylic acid (2,6-dimethyl-pyridin-3-yl)-amide	H	H	H	H	2		

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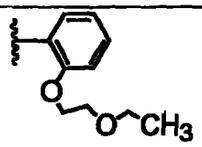
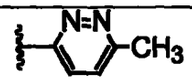
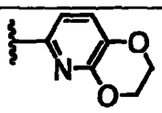
626

65	3,4,5,6-Tetrahydro-3,8,10-triaza-benzo[e]azulene-1-carboxylic acid [6-(4-trifluoromethyl-phenoxy)-pyridin-3-yl]-amide	H	H	H	H	2		
66	3,4,5,6-Tetrahydro-3,8,10-triaza-benzo[e]azulene-1-carboxylic acid [4-(2-ethoxy-ethoxy)-phenyl]-amide	H	H	H	H	2		1HNMR (DMSO) 1.09-1.13 (m, 3H), 2.15 (t, 2H), 2.6 (t, 2H), 2.74 (t, 2H), 3.46 - 3.51 (m, 2H), 3.65-3.67 (m, 2H), 4.01-4.04 (m, 2H), 6.66-6.69 (m, 2H), 7.54 (brs, 1H), 7.60-7.62 (m, 2H), 8.56-8.57 (brs, 1H), 11.7 (brs, 1H), 12.1 (s, 1H) LCMS found (M+H) 393
67	3,4,5,6-Tetrahydro-3,8,10-triaza-benzo[e]azulene-1-carboxylic acid [4-(2-isopropoxy-ethoxy)-phenyl]-amide	H	H	H	H	2		1HNMR (DMSO) 1.08-1.09 (m, 6H), 2.15 (t, 2H), 2.6 (t, 2H), 2.73 (t, 2H), 3.58 - 3.61 (m, 1H), 3.66 (t, 2H), 4.0 (t, 2H), 6.86-6.89 (m, 2H), 7.54 (brs, 1H), 7.60-7.62 (m, 2H), 8.64 (s, 1H), 9.16 (brs, 1H), 12.1 (s, 1H) LCMS found (M+H) 407

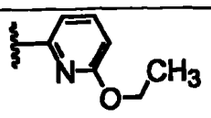
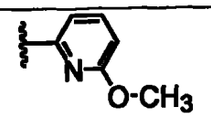
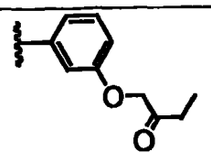
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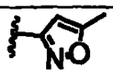
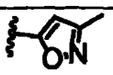
68	3,4,5,6-Tetrahydro-3,8,10-triaza-benzo[e]azulene-1-carboxylic acid (3-methyl-isoxazol-5-yl)-amide	H	H	H	H	2		LCMS found (M+H) 310
69	3,4,5,6-Tetrahydro-3,8,10-triaza-benzo[e]azulene-1-carboxylic acid (5-fluoro-2-methyl-phenyl)-amide	H	H	H	H	2		Electrospray mass spectrum: m/z 335 [M-1]
70	3,4,5,6-Tetrahydro-3,8,10-triaza-benzo[e]azulene-1-carboxylic acid (5-fluoro-2-methyl-phenyl)-amide	H	H	H	H	2		Electrospray mass spectrum: m/z 324 [M+1]
71	3,4,5,6-Tetrahydro-3,8,10-triaza-benzo[e]azulene-1-carboxylic acid (2-methoxy-phenyl)-amide	H	H	H	H	2		LRMS 334.38 found (M+1) 335.2

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72	3,4,5,6-Tetrahydro-3,8,10-triaza-benzo[e]azulene-1-carboxylic acid [2-(2-ethoxy-ethoxy)-phenyl]-amide	H	H	H	H	2		LRMS 392.46 found (M+1) 393.0
73	3,4,5,6-Tetrahydro-3,8,10-triaza-benzo[e]azulene-1-carboxylic acid 6-methyl-pyridazin-3-ylamide	H	H	H	H	2		LRMS 320.35 found (M+1) 321.0
74	3,4,5,6-Tetrahydro-3,10-diaza-benzo[e]azulene-1-carboxylic acid (2,3-dihydro-[1,4]dioxino[2,3-b]pyridin-6-yl)-amide	H	H	H	H	2		LCMS found (M+H) 363

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75	3,4,5,6-Tetrahydro-3,8,10-triaza-benzo[e]azulene-1-carboxylic acid (6-ethoxy-pyridin-2-yl)-amide	H	H	H	H	2		LCMS found (M+H) 350
76	3,4,5,6-Tetrahydro-3,8,10-triaza-benzo[e]azulene-1-carboxylic acid (6-methoxy-pyridin-2-yl)-amide	H	H	H	H	2		LCMS found (M+H) 336
77	3,4,5,6-Tetrahydro-3,8,10-triaza-benzo[e]azulene-1-carboxylic acid [3-(2-oxo-butoxy)-phenyl]-amide	H	H	H	H	2		LCMS found (M+H) 391

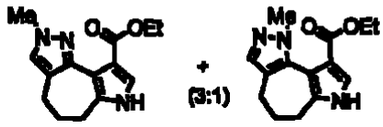
78	3,4,5,6-Tetrahydro-3,8,10-triaza-benzo[e]azulene-1-carboxylic acid (5-methyl-oxazol-2-yl)-amide	H	H	H	H	2		LCMS found (M+H) 310
79	7-Methyl-3,4,5,6-tetrahydro-3,8,10-triaza-benzo[e]azulene-1-carbo-xylic acid (5-methyl-isoxazol-3-yl)-amide	CH_3	H	H	H	2		LRMS 323.3 found (M+1) 324
80	7-Methyl-3,4,5,6-tetrahydro-3,8,10-triaza-benzo[e]azulene-1-carbo-xylic acid (3-methyl-isoxazol-5-yl)-amid	CH_3	H	H	H	2		LRMS 323.3 found (M+1) 324

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Example 8

1-methyl-4,5,6,7-tetrahydro-1*H*-1,2,7-triaza-cyclopenta[e]azulene -9-carboxylic acid ethyl ester and 2-methyl-4,5,6,7-tetrahydro-2*H*-1,2,7-triaza-cyclopenta[e]azulene -9-carboxylic acid ethyl ester



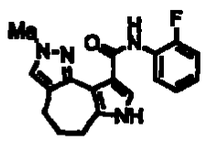
A mixture of ethyl 5-dimethylaminomethylene-4-oxo-1,4,5,6,7,8-hexahydro-cyclohepta[b]pyrrole-3-carboxylic acid ethyl ester (100 mg, 0.362 mmol) and methylhydrazine (83 mg, 1.81 mmol) in EtOH (2 mL) is stirred at 100 °C for 3h. After cooling, the reaction mixture is diluted with CH_2Cl_2 and washed with half saturated aq $NaHCO_3$ (10 mL), H_2O (10 mL), and brine (10 mL). The CH_2Cl_2 extract is dried over Na_2SO_4 and concentrated. The crude material is purified by flash chromatography on silica gel. Elution with 3:1 EtOAc-hexanes (+ 0.5% Et_3N) followed by 100% EtOAc (+ 0.5% Et_3N) separated the two regioisomers. Early fractions: 23 mg (25%) of 1-methyl-4,5,6,7-tetrahydro-1*H*-1,2,7-triaza-cyclopenta[e]azulene-9-carboxylic acid ethyl ester; electrospray mass spectrum: *m/z* 260 [M+1]; ^1H NMR ($CDCl_3$, 400 MHz) δ 9.32 (br s, 1H), 7.39 (d, J = 2.8 Hz, 1H), 7.37 (s, 1H), 4.27 (q, J = 7.2 Hz, 2H), 3.83 (s, 3H), 2.54 (m, 2H), 2.46 (m,

WO 00/39113 PCT/US99/30700

2H), 2.10 (m, 2H), 1.31 (t, J = 7.2 Hz, 3H). Later fractions: 69 mg (74%) of 2-methyl-4,5,6,7-tetrahydro-2*H*-1,2,7-triaza-cyclopenta[e]azulene-9-carboxylic acid ethyl ester; electrospray mass spectrum: *m/z* 260 [M+1]; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.42 (br s, 1H), 7.20 (d, J = 3.0 Hz, 1H), 7.05 (s, 1H), 4.29 (q, J = 7.2 Hz, 2H), 3.82 (s, 3H), 2.82 (m, 2H), 2.67 (m, 2H), 1.96 (m, 2H), 1.32 (t, J = 7.2 Hz, 3H).

Example 9

2-Methyl-4,5,6,7-tetrahydro-2*H*-1,2,7-triaza-cyclopenta[e]azulene-9-carboxylic acid (2-fluoro-phenyl)-amide



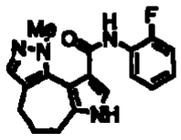
To a solution of 2-fluoroaniline (103 mg, 0.926 mmol) in CH_2Cl_2 (2.0 mL) at 0 °C under N_2 is slowly added $AlMe_3$ (0.46 mL, 2.0 *M* in toluene). The resulting solution is stirred at rt for 1 h. Next, 2-methyl-4,5,6,7-tetrahydro-2*H*-1,2,7-triaza-cyclopenta[e]azulene-9-carboxylic acid ethyl ester (60 mg, 0.231 mmol) is added in one portion. The resulting mixture is then stirred at reflux for 2 h. After cooling, the reaction mixture is carefully diluted with saturated aq NH_4Cl (~5 mL) and some H_2O. The mixture is stirred vigorously for 30 min. and then extracted three times with CH_2Cl_2 (containing some (~5%) MeOH).

The combined extracts were dried over K_2CO_3 and concentrated. The crude material is purified by flash chromatography on silica gel. Elution with 40:1 $CHCl_3$-MeOH followed by 30:1 $CHCl_3$-MeOH and finally 20:1 $CHCl_3$-MeOH afforded, after concentration of the fractions containing pure product, a residue, which is then granulated with Et_2O. The suspension is filtered, and the solid washed with Et_2O and dried, affording 45 mg (60%) of 2-methyl-4,5,6,7-tetrahydro-2*H*-1,2,7-triaza-cyclopenta[e]azulene-9-carboxylic acid (2-fluoro-phenyl)-amide as an off-white solid. Electrospray mass spectrum: *m/z* 325 [M+1].

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Example 10

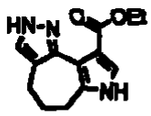
1-Methyl-4,5,6,7-tetrahydro-2*H*-1,2,7-triaza-cyclopenta[e]azulene-9-carboxylic acid (2-fluoro-phenyl)-amide



The title compound is prepared according to Example 9 using 2-fluoroaniline and 1-methyl-4,5,6,7-tetrahydro-1*H*-1,2,7-triaza-cyclopenta[e]azulene-9-carboxylic acid ethyl ester. Electrospray mass spectrum: *m/z* 325 [M+1].

Example 11

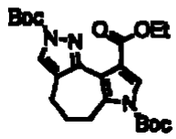
4,5,6,7-Tetrahydro-2*H*-1,2,7-triaza-cyclopenta[e]azulene-9-carboxylic acid ethyl ester



The title compound is prepared in analogous fashion to Example 8 using 5-dimethylaminomethylene-4-oxo-1,4,5,6,7,8-hexahydro-cyclohepta[*b*]pyrrole-3-carboxylic acid ethyl ester and hydrazine acetate. The crude product mixture is carried into the next step without purification. Electrospray mass spectrum: m/z 246 [M+1]; ^{1}H NMR (DMSO-d_6, 300 MHz) δ >13.0 (br s, 1H), 11.65 (br s, 1H), 7.49 (s, 1H), 7.20 (s, 1H), 4.25 (q, J = 7.2 Hz, 2H), 2.91 (m, 2H), 2.76 (m, 2H), 1.84 (m, 2H), 1.28 (t, J = 7.2 Hz, 3H).

Example 12

Preparation of 4,5,6,7-Tetrahydro-2*H*-1,2,7-triaza-cyclopenta[e]azulene-9-carboxylic acid (2-fluoro-phenyl)-amide

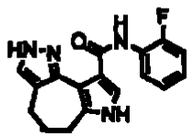


Step 1:

5,6-Dihydro-4*H*-1,2,7-triaza-cyclopenta[e]azulene-2,7,9-tricarboxylic acid 2,7-di-tert-butyl ester 9-ethyl ester is prepared by the procedure described in Example 8, using 4,5,6,7-tetrahydro-2*H*-1,2,7-triaza-cyclopenta[e]azulene-9-carboxylic

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634

acid ethyl ester, 2.3 eq of Boc_2O, and 2.5 eq of Et_3N. Electrospray mass spectrum: m/z 446 [M+1]; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.77 (s, 1H), 7.62 (s, 1H), 4.35 (q, J = 7.2 Hz, 2H), 3.26 (m, 2H), 2.68 (m, 2H), 1.99 (m, 2H), 1.61 (s, 9H), 1.59 (s, 9H), 1.33 (t, J = 7.2 Hz, 3H).



Step 2:

To a solution of 2-fluoroaniline (202 mg, 1.82 mmol) in CH_2Cl_2 (4.0 mL) at 0 °C under N_2 is slowly added $AlMe_3$ (0.91 mL, 2.0 *M* in toluene). The resulting solution is stirred at rt for 1 h. Next, 5,6-dihydro-4*H*-1,2,7-triaza-cyclopenta[e]azulene-2,7,9-tricarboxylic acid 2,7-di-tert-butyl ester 9-ethyl ester (162 mg, 0.364 mmol) is added in one portion. The resulting mixture is then stirred at reflux for 2 h. After cooling, the reaction mixture is carefully diluted with saturated aq NH_4Cl (~5 mL) and some H_2O. The mixture is stirred vigorously for 30 min. and then extracted three times with CH_2Cl_2 (containing some (~5%) MeOH). The combined extracts were dried over K_2CO_3 and concentrated. The crude material is purified by flash chromatography on silica gel, affording 102 mg (68%) of an amide product containing only one Boc group. ^1H NMR ($CDCl_3$, 300 MHz) δ 8.52 (td, J = 8.1, 1.4

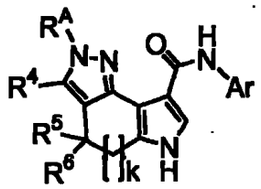
Hz, 1H), 8.06 (s, 1H), 7.36 (s, 1H), 7.18-7.03 (m, 3H), 3.37 (m, 2H), 2.79 (m, 2H), 2.03 (m, 2H), 1.62 (s, 9H). This product is then dissolved in 4 mL of EtOH and 1 mL of conc. aq HCl. The solution is stirred at rt overnight and at 90 °C for 3 h. The reaction mixture is then concentrated under a stream of N_2 to afford a solid, which is then suspended in H_2O and filtered. The solid is thoroughly washed with H_2O and Et_2O to afford, after drying, 34 mg (44%) of 4,5,6,7-tetrahydro-2*H*-1,2,7-triaza-cyclopenta[*e*]azulene-9-carboxylic acid (2-fluoro-phenyl)-amide as a light yellow/off-white solid. Electrospray mass spectrum: *m/z* 311 [M+1].

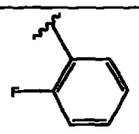
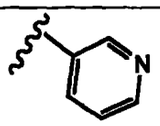
Example 12a

Additional 1,2,7-triaza-cyclopenta[*e*]azulene-9-carboxylic acid compounds

Using the method shown in Scheme 6 and further illustrated in Examples 8-12 the compounds shown in Table 4 were prepared.

TABLE 4

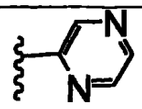
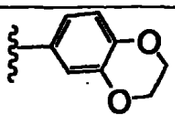
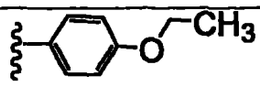
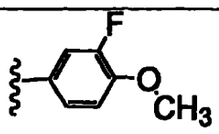


Cpd #	Name	R^A		R^5	R^6	n	Ar	Spectral Data
1	2-Methyl-4,5,6,7-tetrahydro-2H-1,2,7-triaza-cyclopenta[e]azulene-9-carboxylic acid (2-fluoro-phenyl)-amide	CH_3	H	H	H	2		MS m/z [M+1] 325
2	2-Methyl-4,5,6,7-tetrahydro-2H-1,2,7-triaza-cyclopenta[e]azulene-9-carboxylic acid pyridin-3-ylamide	CH_3	H	H	H	2		MS m/z [M+1] 308

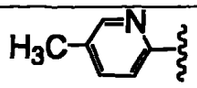
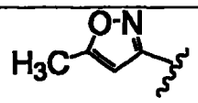
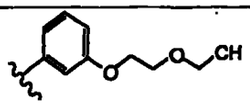
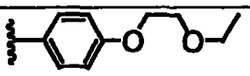
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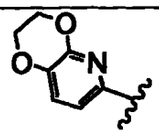
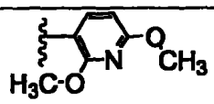
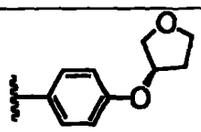
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3	2-Methyl-4,5,6,7-tetrahydro-2H-1,2,7-triaza-cyclopenta[e]azulene-9-carboxylic acid pyrazin-2-ylamide	CH_3	H	H	H	2		MS m/z [M+1] 309
4	2-Methyl-4,5,6,7-tetrahydro-2H-1,2,7-triaza-cyclopenta[e]azulene-9-carboxylic acid (2,3-dihydro-benzo[1,4]dioxin-6-yl)-amide	CH_3	H	H	H	2		MS m/z [M+1] 365
5	2-Methyl-4,5,6,7-tetrahydro-2H-1,2,7-triaza-cyclopenta[e]azulene-9-carboxylic acid (4-ethoxy-phenyl)-amide	CH_3	H	H	H	2		MS m/z [M-1] 349
6	2-Methyl-4,5,6,7-tetrahydro-2H-1,2,7-triaza-cyclopenta[e]azulene-9-carboxylic acid (3-fluoro-4-methoxy-phenyl)-amide	CH_3	H	H	H	2		MS m/z [M-1] 353

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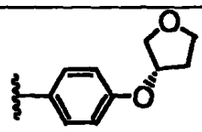
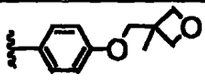
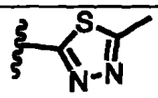
7	2-Methyl-4,5,6,7-tetrahydro-2H-1,2,7-triaza-cyclopenta[e]azulene-9-carboxylic acid (5-methyl-pyridin-2-yl)-amide	CH_3	H	H	H	2		MS m/z [M-1] 320
8	2-Methyl-4,5,6,7-tetrahydro-2H-1,2,7-triaza-cyclopenta[e]azulene-9-carboxylic acid (5-methyl-isoxazol-3-yl)-amide	CH_3	H	H	H	2		MS m/z [M-1] 310
9	2-Methyl-4,5,6,7-tetrahydro-2H-1,2,7-triaza-cyclopenta[e]azulene-9-carboxylic acid [3-(2-ethoxy-ethoxy)-phenyl]-amide	CH_3	H	H	H	2		MS m/z [M+1] 395
10	2-Methyl-4,5,6,7-tetrahydro-2H-1,2,7-triaza-cyclopenta[e]azulene-9-carboxylic acid [4-(2-ethoxy-	CH_3	H	H	H	2		MS m/z [M+1] 395

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	ethoxy)-phenyl]-amide							
11	2-Methyl-4,5,6,7-tetrahydro-2H-1,2,7-triaza-cyclopenta[e]azulene-9-carboxylic acid (2,3-dihydro-[1,4]dioxino[2,3-b]pyridin-6-yl)-amide	CH_3	H	H	H	2		MS m/z [M+1] 366
12	2-Methyl-4,5,6,7-tetrahydro-2H-1,2,7-triaza-cyclopenta[e]azulene-9-carboxylic acid (2,6-dimethoxy-pyridin-3-yl)-amide	CH_3	H	H	H	2		MS m/z [M+1] 368
13	(R)-2-Methyl-4,5,6,7-tetrahydro-2H-1,2,7-triaza-cyclopenta[e]azulene-9-carboxylic acid [4-(tetrahydro-furan-3-yloxy)-	CH_3	H	H	H	2		MS m/z [M+1] 393

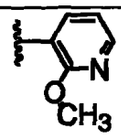
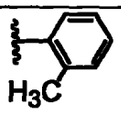
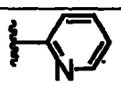
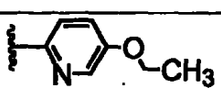
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	phenyl]-amide							
14	(S)-2-Methyl-4,5,6,7-tetrahydro-2H-1,2,7-triaza-cyclopenta[e]azulene-9-carboxylic acid [4-(tetrahydro-furan-3-yloxy)-phenyl]-amide	CH_3	H	H	H	2		MS m/z [M+1] 393
15	2-Methyl-4,5,6,7-tetrahydro-2H-1,2,7-triaza-cyclopenta[e]azulene-9-carboxylic acid [4-(3-methyl-oxetan-3-ylmethoxy)-phenyl]-amide	CH_3	H	H	H	2		MS m/z [M+1] 409
16	2-Methyl-4,5,6,7-tetrahydro-2H-1,2,7-triaza-cyclopenta[e]azulene-9-carboxylic acid [1,3,4]thiadiazol-2-ylamide	CH_3	H	H	H	2		MS m/z [M+1] 329

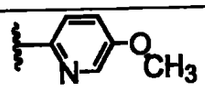
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17	2-Methyl-4,5,6,7-tetrahydro-2H-1,2,7-triaza-cyclopenta[e]azulene-9-carboxylic acid (2-methoxy-pyridin-3-yl)-amide	CH_3	H	H	H	2		MS m/z [M+1] 338
18	2-Methyl-4,5,6,7-tetrahydro-2H-1,2,7-triaza-cyclopenta[e]azulene-9-carboxylic acid o-tolylamide	CH_3	H	H	H	2		MS m/z [M+1] 321
19	2-Methyl-4,5,6,7-tetrahydro-2H-1,2,7-triaza-cyclopenta[e]azulene-9-carboxylic acid pyridin-2-ylamide	CH_3	H	H	H	2		MS m/z [M+1] 308
20	2-Methyl-4,5,6,7-tetrahydro-2H-1,2,7-triaza-cyclopenta[e]azulene-9-carboxylic acid (5-ethoxy-pyridin-2-yl)-amide	CH_3	H	H	H	2		MS m/z [M+1] 352

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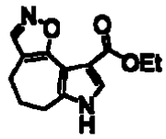
21	2-Methyl-4,5,6,7-tetrahydro-2H-1,2,7-triaza-cyclopenta[e]azulene-9-carboxylic acid (5-methoxy-pyridin-2-yl)-amide	CH_3	H	H	H	2		MS m/z [M+1] 338

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Example 13

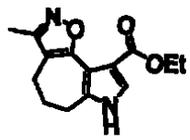
4,5,6,7-Tetrahydro-1-oxa-2,7-diaza-cyclopenta[e]azulene-9-carboxylic acid ethyl ester



In a sealed tube were 4-oxo-5,6,7,8-tetrahydro-4H-cyclohepta[b]pyrrole-1,3-dicarboxylic acid 1-tert-butyl ester 3-ethyl ester (2.6 mmol) and tris(dimethylamino)methane (5.2 mmol) combined and heated at 60°C for 3 hours. After cooling to RT the volatile material is removed in *vacuo*. To the residue were added hydroxylamine hydrochloride (7.8 mmol) and 7 ml EtOH. The mixture is heated at 100°C for 16 hours. The solvent is evaporated in *vacuo* and the residue is taken up in CH_2Cl_2 and washed two times with $NaHCO_3$ (aq). The organic layer is dried over Na_2SO_4 and evaporated in *vacuo* and the residue chromatographed using 10% MeOH in CH_2Cl_2 as mobile phase to yield 4,5,6,7-tetrahydro-1-oxa-2,7-diaza-cyclopenta[e]azulene-9-carboxylic acid ethyl ester as a white solid (76%). ^1H NMR ($CDCl_3$) 1.19 (t, 3H), 1.95-2.07 (m, 2H), 2.78 (t, 2H), 2.95 (t, 2H), 4.38 (q, 2H), 7.26 (s, 1H), 8.03 (s, 1H), 8.77 (s, 1H).

Example 14

3-Methyl-4,5,6,7-tetrahydro-1-oxa-2,7-diaza-cyclopenta[e]azulene -9-carboxylic acid ethyl ester



In a sealed tube were 5-acetyl-4-oxo-5,6,7,8-tetrahydro-4H-cyclohepta[b]pyrrole-1,3-dicarboxylic acid 1-tert-butyl ester 3-ethyl ester (1.1 mmol) and hydroxylamine hydrochloride (2.2 mmol) and 10 ml EtOH. The mixture is heated at 100°C for 16 hours. The solvent is evaporated in *vacuo* and the residue is taken up in CH_2Cl_2 and washed two times with $NaHCO_3$ (aq). The organic layer is dried over Na_2SO_4 and evaporated in *vacuo* and the residue chromatographed using 10% MeOH in CH_2Cl_2 as mobile phase to yield 3-methyl-4,5,6,7-tetrahydro-1-oxa-2,7-diaza-cyclopenta[e]azulene-9-carboxylic acid ethyl ester as a white solid (76%). ^1H NMR ($CDCl_3$ + CD_3OD) 1.3 (t, 3H), 1.90-1.98 (m, 2H), 2.10 (s, 3H), 2.35 (t, 2H), 2.75-2.82 (m, 2H), 4.21 (q, 2H), 7.15 (s, 1H).

Example 14a

Additional 1-oxa-2,7-diaza-cyclopenta[e]azulene-9-carboxylic acid compounds

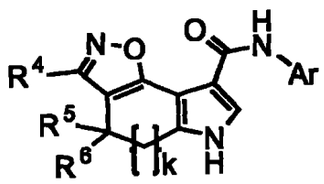
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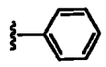
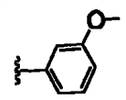
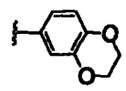
Using the method shown in Scheme 7 and further illustrated in Examples 13-14 the compounds shown in Table 5 were prepared. 646

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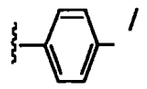
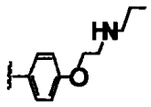
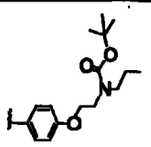
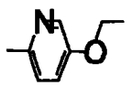
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TABLE 5

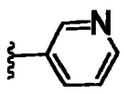
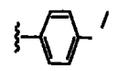
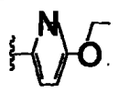
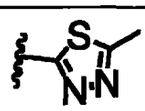


Cpd#	Name	R4	R5	R6	n	Ar	Spectral Data
1	4,5,6,7-Tetrahydro-1-oxa-2,7-diaza-cyclopenta[e]azulene-9-carboxylic acid phenyl-amide	H	H	H	2		LRMS calcd 293.32 found (M+1) 294
2	4,5,6,7-Tetrahydro-1-oxa-2,7-diaza-cyclopenta[e]azulene-9-carboxylic acid (3-methoxy-phenyl)-amide	H	H	H	2		LRMS calcd 323.3 found (M+1) 324
3	4,5,6,7-Tetrahydro-1-oxa-2,7-diaza-cyclopenta[e]azulene-9-carboxylic acid (2,3-dihydro-	H	H	H	2		LRMS calcd 351.3 found (M+1) 352.3

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	benzo[1,4]dioxin-6-yl)-amide						
4	4,5,6,7-Tetrahydro-1-oxa-2,7-diaza-cyclopenta[e]azulene-9-carboxylic acid (4-methoxy-phenyl)-amide	H	H	H	2		LRMS calcd 323.3 found (M-1) 322
5	4,5,6,7-Tetrahydro-1-oxa-2,7-diaza-cyclopenta[e]azulene-9-carboxylic acid [4-(2-propylamino-ethoxy)-phenyl]-amide	H	H	H	2		LRMS calcd 394.4 found (M+1) 395
6	Propyl-(2-{4-[(4,5,6,7-tetrahydro-1-oxa-2,7-diaza-cyclopenta[e]-azulene-9-carbonyl)-amino]-phenoxy}-ethyl)-carbamic acid tert-butyl ester	H	H	H	2		LRMS calcd 494.59 found (M-1) 493.3
7	4,5,6,7-Tetrahydro-1-oxa-2,7-diaza-cyclopenta[e]azulene-9-carboxylic acid (5-ethoxy-pyridin-2-yl)amide	H	H	H	2		LRMS calcd 338.36 found (M+1) 339

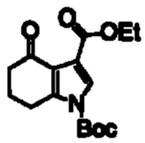
649

8	4,5,6,7-Tetrahydro-1-oxa-2,7-diaza-cyclopenta[e]azulene-9-carboxylic acid pyridin-3-ylamide	H	H	H	2		LRMS calcd 294.3 found (M+1) 295.3
9	3-Methyl-4,5,6,7-tetrahydro-1-oxa-2,7-diaza-cyclopenta[e]azulene-9-carboxylic acid (4-methoxy-phenyl)-amide	CH_3	H	H	2		LRMS calcd 337.4 found (M+1) 338
10	3-Methyl-4,5,6,7-tetrahydro-1-oxa-2,7-diaza-cyclopenta[e]azulene-9-carboxylic acid (5-ethoxy-pyridin-2-yl)-amide	CH_3	H	H	2		LRMS calcd 352.4 found (M+1) 353
11	3-Methyl-4,5,6,7-tetrahydro-1-oxa-2,7-diaza-cyclopenta[e]azulene-9-carboxylic acid 2-(5-methyl-[1,3,4]thiadiazol-2-yl)-amide	CH_3	H	H	2		LRMS calcd 329.4 found (M+1) 330

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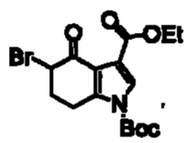
Example 15

2-methyl-5,6-dihydro-4H-thiazolo[4,5-e]indole-8-carboxylic acid ethyl ester



Step 1:

To a mixture of 4-Oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxylic acid ethyl ester (2.4 mmol) in 10 ml 1,4-dioxane is added di-t-butyl dicarbonate (2.9 mmol), followed by a solution of K_2CO_3 (2.9 mmol) in 5 ml H_2O. After stirring at RT for 16 hours 50 ml EtOAc and 50 ml H_2O were added to the mixture. The organic layer is separated and the aqueous layer is extracted several times with EtOAc. The organic layers were combined, dried over Na_2SO_4 and evaporated *in vacuo* yielding 4-Oxo-4,5,6,7-tetrahydro-indole-1,3-dicarboxylic acid 1-tert-butyl ester 3-ethyl ester, 700mg, as a dark yellow/brown oil (95%). ^1H NMR ($CDCl_3$) 1.38 (t, 3H), 1.62 (s, 9H), 2.11-2.19 (m, 2H), 2.50-2.58 (m, 2H), 3.17 (t, 2H), 4.37 (q, 2H), 7.70 (s, 1H).

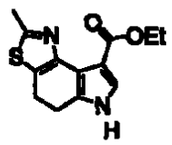


Step 2:

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To the solution of 4-oxo-4,5,6,7-tetrahydro-indole-1,3-dicarboxylic acid 1-tert-butyl ester 3-ethyl ester (33 mmol) in 140 ml THF is added dropwise a solution of phenyltrimethylammonium bromide (33 mmol) in 56 ml THF. After stirring at RT for an additional 11/2 hours the mixture is poured onto 200 ml 5% $NaHCO_3$ solution, and is then extracted several times with EtOAc. The organic layers were combined, dried over Na_2SO_4 and evaporated in *vacuo*. The dark brown oil is chromatographed using EtOAc 1: hexanes 10 as a mobile phase to yield 5-bromo-4-oxo-4,5,6,7-tetrahydro-indole-1,3-dicarboxylic acid 1-tert-butyl ester 3-ethyl ester, 5 g, as a white solid (40%). ^1H NMR ($CDCl_3$)1.39 (t, 3H), 1.62 (s, 9H), 2.42-2.51 (m, 2H), 3.20-3.38 (m, 2H), 4.35 (q, 2H), 4.58 (t, 1H), 7.79 (s, 1H).



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Step 3:

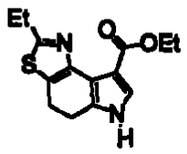
To a solution of 5-bromo-4-oxo-4,5,6,7-tetrahydro-indole 1,3-dicarboxylic acid 1-tert-butyl ester 3-ethyl ester (0.78 mmol) in 10 ml CH_3OH is added thioacetamide (1.55 mmol). After stirring under refluxing for 16 hours the solvent is removed in *vacuo*. The brown oil is chromatographed using EtOAC 1: hexane 1, followed by 5% MeOH in CH_2Cl_2 as mobile phases to yield 2-methyl-

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5,6-dihydro-4H-thiazolo[4,5-e]indole-8-carboxylic acid ethyl ester as a white solid (34%). ^{1}H NMR (DMSO-d_6) 1.27 (t, 3H), 2.60 (s, 3H), 2.78(t, 2H), 2.96 (t, 2H), 4.19 (q, 2H), 7.21 (s, 1H), 11.44 (s, 1H).

Example 16

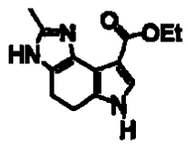
2-Ethyl-5,6-dihydro-4H-thiazolo[4,5-e]indole-8-carboxylic acid ethyl ester



The title compound is prepared by reacting 5-bromo-4-oxo-4,5,6,7-tetrahydro-indole 1,3-dicarboxylic acid 1-tert-butyl ester 3-ethyl ester with thiopropionamide essentially according to the procedures described in Example 15, Step 3. ^{1}H NMR ($CDCl_3$) 1.33-1.42 (m, 6H), 2.80-2.90 (m, 2H), 2.98-3.10 (m, 4H), 2.37 (q, 2H), 7.24 (s, 1H), 8.60 (s, 1H).

Example 17

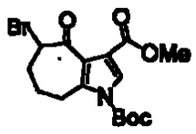
2-Methyl-3,4,5,6-tetrahydro-imidazo[4,5-e]indole-8-carboxylic acid ethyl ester



To a solution of 5-bromo-4-oxo-4,5,6,7-tetrahydro-indole 1,3-dicarboxylic acid 1-tert-butyl ester 3-ethyl ester (1.66 mmol) in 15 ml 1,4-dioxane is added acetamidine hydrochloride (3.32 mmol). After stirring under refluxing for 16 hours the solvent is removed in *vacuo*. To the residue is added 14 ml $CHCl_3$ and 2 ml MeOH and the mixture is stirred for 10 min. The solid is filtered off. The mother liquid is concentrated and is chromatographed using 10% MeOH in CH_2Cl_2 as mobile phase to yield 2-methyl-3,4,5,6-tetrahydro-imidazo[4,5-e]indole-8-carboxylic acid ethyl ester as a white solid (30 %). ^1H NMR (DMSO-d_6) 1.30 (t, 3H), 2.28 (s, 3H), 2.70 (t, 2H), 2.79 (t, 2H), 4.22 (q, 2H), 7.20 (s, 1H), 10.58 (s, 1H), 11.43 (s, 1H).

Example 18

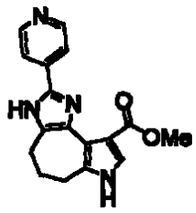
2-Pyridin-4-yl-4,5,6,7-tetrahydro-3H-1,3,7-triaza-cyclopenta-[e]azulene-9-carboxylic acid methyl ester



Step 1:

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To a solution of 4-Oxo-5,6,7,8-tetrahydro-4*H*-cyclohepta[b]pyrrole1,3-dicarboxylic acid 3-methyl ester 1-*tert*-butyl ester(1.1g, 3.6mmol) in DMSO(20ml) is added 1,3-dibromo-5,5-dimethylhydantoin(1.5g, 5.4mmol) portionwise with the aid of a cooling bath and the resulting mixture is stirred for 18h at RT. Water is added and the reaction mixture is extracted with ether . The combined ether layers were washed with saturated brine, dried over Na_2SO_4, and concentrated in vacuo. The residue is purified by flash chromatography(10%EtOAc/Hex to 25% EtOAc/Hex) to yield 915mg of 5-Bromo-4-oxo-5,6,7,8-tetrahydro-4*H*-cyclohepta[b]pyrrole-1,3-dicarboxylic acid 1-*tert*-butyl ester 3-methyl ester *as* a bright yellow oil (66%). ^1H NMR($CDCl_3$) 1.59 (s, 9H), 1.72-1.84 (m, 1H), 2.12-2.25 (m, 2H), 2.43-2.58 (m, 1H), 3.05-3.14 (m, 1H), 3.40-3.49 (m, 1H), 3.80 (s, 3H), 4.75 (m, 1H), 7.79 (s, 1H)



Step 2:

A mixture of 5-Bromo-4-oxo-5,6,7,8-tetrahydro-4*H*-cyclohepta[b]pyrrole-1,3-dicarboxylic acid 1-*tert*-butyl ester 3-methyl ester(467mg, 1.2mmol), 4-Amidinopyridine

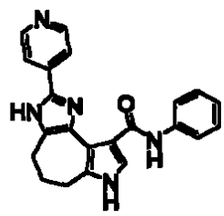
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hydrochloride(953mg, 6.1mmol), and $NaHCO_3$(813mg, 9.7mmol) in dioxane(20ml) is refluxed for 20h. After cooling to RT, MeOH(5ml) is added and the mixture is filtered. The filtrate is concentrated in vacuo and the brown residue is purified by flash chromatography (10% MeOH/ CH_2Cl_2) to yield 197 mg of 2-Pyridin-4-yl-4,5,6,7-tetrahydro-3*H*-1,3,7-triaza-cyclopenta[e]azulene-9-carboxylic acid methyl ester as a yellow solid (53%). ^{1}H NMR ($CDCl_3$) 2.06 (quint, 2H), 2.98 (t, 2H), 3.04 (t, 2H), 3.91 (s, 1H), 7.46 (s, 1H), 7.76 (d, 2H), 8.28 (br s, 1H)8.56 (d, 2H)

Example 19

2-Pyridin-4-yl-4,5,6,7-tetrahydrdo-3*H*-1,3,7-triaza-cyclopenta[e]-azulene-9-carboxylic acid phenyl amide



To a solution of Aniline(155□L, 1.7mmol) in CH_2Cl_2(5ml) at RT is added Trimethylaluminum(0.85ml of 2M solution in toluene, 1.7mmol) and the mixture is stirred for 30min. To this is added a solution of 2-Pyridin-4-yl-4,5,6,7-tetrahydro-3*H*-1,3,7-triaza-cyclopenta[e]azulene-9-carboxylic acid methyl ester(51mg, 0.17mmol) in CH_2Cl_2(2ml) and the mixture is refluxed for 18h and

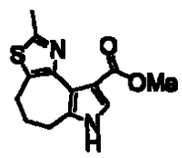
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diluted with CH_2Cl_2. MeOH(5ml) is added slowly with vigorous stirring. The mixture is filtered through celite, concentrated in vacuo, and purified by flash chromatography to yield 20mg of 2-Pyridin-4-yl-4,5,6,7-tetrahydrdo-3*H*-1,3,7-triaza-cyclopenta[e]azulene-9-carboxylic acid phenyl amide as a yellow solid(32%). LRMS calcd 369.43 found (M+H) 370.07

Example 20

2-Methyl-4,5,6,7-tetrahydro-3-thia-1,7-diaza-cyclopenta[e]azulene-9-carboxylic acid methyl ester



A mixture of 5-Bromo-4-oxo-5,6,7,8-tetrahydro-4-*H*-cyclohepta[b]pyrrole-1,3-dicarboxylic acid 1-tert-butyl ester 3-methyl ester(880mg, 2.27mmol) and Thioacetamide(426mg, 4.54mmol) in MeOH(20ml) is refluxed for 20h and concentrated in vacuo. The residue is purified by flash chromatography(50% EtOAc/ Hex to 10% MeOH/CH_2Cl_2) to yield 382mg of 2-Methyl-4,5,6,7-tetrahydro-3-thia-1,7-diaza-cyclopenta[e]azulene-9-carboxylic acid methyl ester as a yellow foam(64%).

^{1}H NMR (CD_3OD) 2.18 (quint, 2H), 2.61 (s, 3H), 2.70 (t, 2H), 2.78 (t, 2H), 3.73 (s, 3H), 7.29 (s, 1H)

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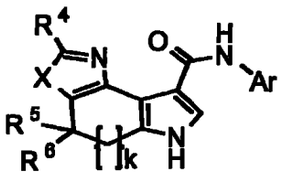
Example 21

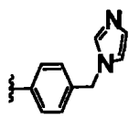
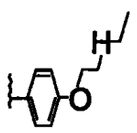
Additional 3-thia-1,7-diaza-cyclopenta[e]azulene-9-carboxylic acid and 1,3,7-triaza- cyclopenta[e]azulene-9-carboxylic acid phenyl amide compounds

Using the method shown in Scheme 8 and further illustrated in Examples 15-20 the compounds shown in Table 6 were prepared.

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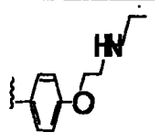
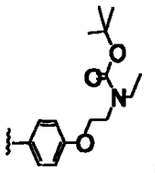
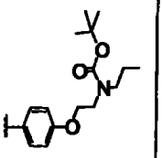
TABLE 6



Cpd#	Name	X	R4	R5	R6	n	Ar	Spectral Data
1	2-Methyl-4,5,6,7-tetrahydro-3-thia-1,7-diaza-cyclopenta[e]azulene-9-carboxylic acid (4-imidazol-1-ylmethyl-phenyl)-amide	S	CH_3	H	H	2		LRMS calcd 403.5 found (M+1) 404.1
2	2-Methyl-4,5,6,7-tetrahydro-3-thia-1,7-diaza-cyclopenta[e]azulene-9-carboxylic acid [4-(2-ethylamino-ethoxy)-phenyl]-amide	S	CH_3	H	H	2		LRMS calcd 410.54 found (M+1) 411.3

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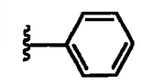
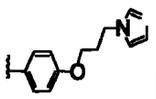
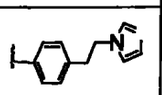
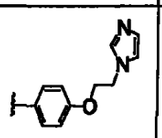
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3	2-Methyl-4,5,6,7-tetrahydro-3-thia-1,7-diaza-cyclopenta[e]azulene-9-carboxylic acid [4-(2-propylamino-ethoxy)-phenyl]-amide	S	CH_3	H	H	2		LRMS calcd 424.57 found (M-1) 423.2
4	Ethyl-(2-{4-[(2-methyl-4,5,6,7-tetrahydro-3-thia-1,7-diaza-cyclopenta[e]azulene-9-carbonyl)-amino]phenoxy}-ethyl)-carbamic acid tert-butyl ester	S	CH_3	H	H	2		LRMS calcd 510.66 found (M-1) 509.4
5	(2-{4-[(2-Methyl-4,5,6,7-tetrahydro-3-thia-1,7-diaza-cyclopenta[e]azulene-9-carbonyl)-amino]-phenoxy}-ethyl)-propyl-carbamic acid tert-butyl ester	S	CH_3	H	H	2		LRMS calcd 524.68 found (M-1) 523.2

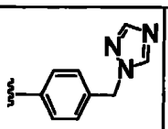
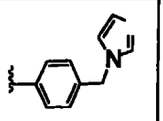
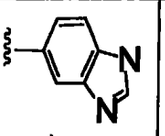
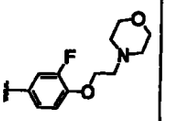
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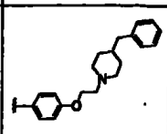
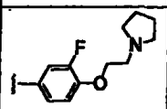
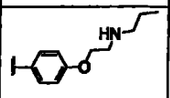
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6	2-Methyl-5,6-dihydro-4H-thiazolo[4,5-e]indole-8-carboxylic acid phenylamide	S	CH_3	H	H	1		LRMS calcd 309.39 found (M+1) 310.88
7	2-Methyl-5,6-dihydro-4H-thiazolo[4,5-e]indole-8-carboxylic acid [4-(3-imidazol-1-yl-propoxy)-phenyl]-amide	S	CH_3	H	H	1		LRMS calcd 433.53 found (M+1) 434.03
8	2-Methyl-5,6-dihydro-4H-thiazolo[4,5-e]indole-8-carboxylic acid [4-(2-imidazol-1-yl-ethyl)-phenyl]-amide	S	CH_3	H	H	1		LRMS calcd 403.51 found (M+1) 404.0
9	2-Methyl-5,6-dihydro-4H-thiazolo[4,5-e]indole-8-carboxylic acid [4-(2-imidazol-1-yl-ethoxy)-phenyl]-amide	S	CH_3	H	H	1		LRMS calcd 419.51 found (M+1) 420.0

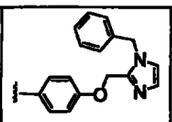
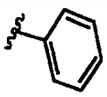
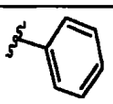
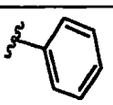
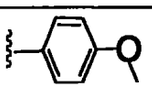
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10	2-Methyl-5,6-dihydro-4H-thiazolo[4,5-e]indole-8-carboxylic acid (4-[1,2,4]triazol-1-ylmethyl-phenyl)-amide	S	CH_3	H	H	1		LRMS calcd 390.47 found (M+1) 391.1
11	2-Methyl-5,6-dihydro-4H-thiazolo[4,5-e]indole-8-carboxylic acid (4-imidazol-1-ylmethyl-phenyl)-amide	S	CH_3	H	H	1		LRMS calcd 389.48 found (M+1) 390.1
12	2-Methyl-5,6-dihydro-4H-thiazolo[4,5-e]indole-8-carboxylic acid (1H-benzoimidazol-5-yl)-amide	S	CH_3	H	H	1		LRMS 349.42 found (M+1) 350.2
13	2-Methyl-5,6-dihydro-4H-thiazolo[4,5-e]indole-8-carboxylic acid [3-fluoro-4-(2-	S	CH_3	H	H	1		LRMS calcd 456.54 found 456.85

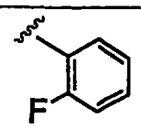
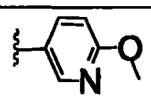
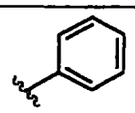
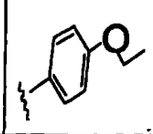
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	morpholin-4-yl-ethoxy)-phenyl]-amide							
14	2-Methyl-5,6-dihydro-4H-thiazolo[4,5-e]indole-8-carboxylic acid {4-[2-(4-benzyl-piperidin-1-yl)-ethoxy]-phenyl}-amide	S	CH_3	H	H	1		LRMS calcd 526.70 found 527.1
15	2-Methyl-5,6-dihydro-4H-thiazolo[4,5-e]indole-8-carboxylic acid [3-fluoro-4-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-amide	S	CH_3	H	H	1		LRMS calcd 440.54 found 440.9
16	2-Methyl-5,6-dihydro-4H-thiazolo[4,5-e]indole-8-carboxylic acid [4-(2-propylamino-ethoxy)-phenyl]-amide	S	CH_3	H	H	1		LRMS calcd 410.54 found (M+1) 411.0

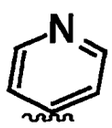
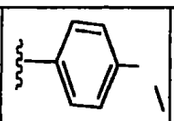
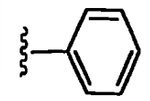
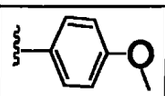
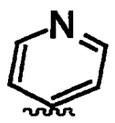
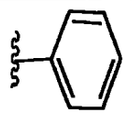
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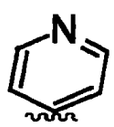
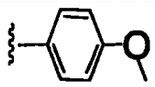
17	2-Methyl-5,6-dihydro-4H-thiazolo[4,5-e]indole-8-carboxylic acid [4-(1-benzyl-1H-imidazol-2-ylmethoxy)-phenyl]-amide	S	CH_3	H	H	1		LRMS calcd 496.59 found 497.03
18	2-Ethyl-5,6-dihydro-4H-thiazolo[4,5-e]indole-8-carboxylic acid phenylamide	S	Et	H	H	1		LRMS calcd 323.42 found 323.93
19	2-Methyl-3,4,5,6-tetrahydro-imidazo[4,5-e]indole-8-carboxylic acid phenylamide	NH	CH_3	H	H	1		LRMS calcd 292.34 found (M-1) 291.0
20	2-Methyl-4,5,6,7-tetrahydro-3*H*-1,3,7-triaza-cyclopenta[e]azulene-9-carboxylic acid phenylamide	NH	CH_3	H	H	2		LRMS calcd 306.37 found (M+H) 307.30
21	2-Methyl-4,5,6,7-tetrahydro-3*H*-1,3,7-triaza-cyclopenta[e]azulene-9-carboxylic acid(4-methoxy-phenyl)amide	NH	CH_3	H	H	2		LRMS calcd 336.39 found (M+H) 337.07

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22	2-Methyl-4,5,6,7-tetrahydro-3*H*-1,3,7-triaza-cyclopenta[e]azulene-9-carboxylic acid (2-fluoro-phenyl)-amide	NH	CH_3	H	H	2		LRMS calcd 324.35 found (M+H) 325.40
23	2-Methyl-4,5,6,7-tetrahydro-3*H*-1,3,7-triaza-cyclopenta[e]azulene-9-carboxylic acid (6-methoxy-pyridin-3-yl)-amide	NH	CH_3	H	H	2		LRMS calcd 337.38 found (M+H) 338.07
24	2-Cyclopropyl-4,5,6,7-tetrahydro-3*H*-1,3,7-triaza-cyclopenta[e] azulene-9-carboxylic acid phenylamide	NH		H	H	2		LRMS calcd 332.41 found (M+H) 333.06
25	2-Methyl-4,5,6,7-tetrahydro-3*H*-1,3,7-triaza-cyclopenta[e]azulene-9-carboxylic acid (4-ethoxy-phenyl)-amide	NH	CH_3	H	H	2		LRMS calcd 350.41 found (M+H) 351.08

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26	2-Pyridin-4-yl-4,5,6,7-tetrahydro-3*H*-1,3,7-triaza-cyclopenta[e] azulene-9-carboxylic acid (4-methoxy-phenyl)-amide	NH		H	H	2		LRMS calcd 399.39 found (M+H) 400.09
27	2-Methyl-4,5,6,7-tetrahydro-3-thia-1,7-diaza-cyclopenta[e]azulene-9-carboxylic acid phenylamide	S	CH_3	H	H	2		LRMS calcd 323.42 found (M+H) 324.30
28	2-Methyl-4,5,6,7-tetrahydro-3-thia-1,7-diaza-cyclopenta[e]azulene-9-carboxylic acid (4-methoxy-phenyl)-amide	S	CH_3	H	H	2		LRMS calcd 353.44, found (M+H) 354.02
29	2-Pyridin-4-yl-4,5,6,7-tetrahydro-3-thia-1,7-diaza-cyclopenta[e] azulene-9-carboxylic acid phenylamide	S		H	H	2		LRMS calcd 386.48 found (M+H) 387.03

30	2-Pyridin-4-yl-4,5,6,7-tetrahydro-3-thia-1,7-diaza-cyclopenta[e] azulene-9-carboxylic acid (4-methoxy-phenyl)-amide	S		H	H	2		LRMS calcd 416.50 found (M+H) 417.03

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Example 22

Preparation of radiolabeled probe compounds of the invention

The compounds of the invention are prepared as radiolabeled probes by carrying out their synthesis using precursors comprising at least one atom that is a radioisotope. The radioisotope is preferably selected from of at least one of carbon (preferably ^{14}C), hydrogen (preferably ^{3}H), sulfur (preferably ^{35}S), or iodine (preferably ^{125}I). Such radiolabeled probes are conveniently synthesized by a radioisotope supplier specializing in custom synthesis of radiolabeled probe compounds. Such suppliers include Amersham Corporation, Arlington Heights, IL; Cambridge Isotope Laboratories, Inc. Andover, MA; SRI International, Menlo Park, CA; Wizard Laboratories, West Sacramento, CA; ChemSyn Laboratories, Lexena, KS; American Radiolabeled Chemicals, Inc., St. Louis, MO; and Moravek Biochemicals Inc., Brea, CA.

Tritium labeled probe compounds are also conveniently prepared catalytically via platinum-catalyzed exchange in tritiated acetic acid, acid-catalyzed exchange in tritiated trifluoroacetic acid, or heterogeneous-catalyzed exchange with tritium gas. Such preparations are also conveniently carried out as a custom radiolabeling by any of the suppliers listed in the preceding paragraph using the compound of the invention as

substrate. In addition, certain precursors may be subjected to tritium-halogen exchange with tritium gas, tritium gas reduction of unsaturated bonds, or reduction using sodium borotritide, as appropriate.

Example 23

Receptor autoradiography

Receptor autoradiography (receptor mapping) is carried out in vitro as described by Kuhar in sections 8.1.1 to 8.1.9 of Current Protocols in Pharmacology (1998) John Wiley & Sons, New York, using radiolabeled compounds of the invention prepared as described in the preceding Example.

Example 24

Binding Assay

This assay is a standard assay for $GABA_A$ binding affinity. The high affinity and high selectivity of compounds of this invention for the benzodiazepine site of the $GABA_A$ receptor is confirmed using the binding assay described in Thomas and Tallman (*J. Bio. Chem.* 1981; 156:9838-9842, and *J. Neurosci.* 1983; 3:433-440).

Rat cortical tissue is dissected and homogenized in 25 volumes (w/v) of Buffer A (0.05 M Tris HCl buffer, pH 7.4 at 4 °C). The tissue homogenate is centrifuged in the cold (4 °C) at

668

669

20,000 x g for 20 minutes. The supernatant is decanted, the pellet rehomogenized in the same volume of buffer, and centrifuged again at 20,000 x g. The supernatant of this centrifugation step is decanted and the pellet stored at -20 °C overnight. The pellet is then thawed and resuspended in 25 volumes of Buffer A (original wt/vol), centrifuged at 20,000 x g and the supernatant decanted. This wash step is repeated once. The pellet is finally resuspended in 50 volumes of Buffer A.

Incubations containi 100 µl of tissue homogenate, 100 µl of radioligand, (0.5 nM ^{3}H-Ro15-1788 [^{3}H-Flumazenil], specific activity 80 Ci/mmol), and test compound or control (see below), and are brought to a total volume of 500 µl with Buffer A. Incubations are carried for 30 min at 4°C and then rapidly filtered through Whatman GFB filters to separate free and bound ligand. Filters are washed twice with fresh Buffer A and counted in a liquid scintillation counter. Nonspecific binding (control) is determined by displacement of ^{3}H Ro15-1788 with 10 µM Diazepam (Research Biochemicals International, Natick, MA). Data were collected in triplicate, averaged, and percent inhibition of total specific binding (Total Specific Binding = Total - Nonspecific) was calculated for each compound.

A competition binding curve is obtained with up to 11 points spanning the compound concentration range from 10^{-12}M to

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10^{-5}M obtained per curve by the method described above for determining percent inhibition. K_i values are calculated according the Cheng-Prussof equation. When tested in this assay compounds of the invention exihibit K_i values of less than 1 uM, preferred compounds of the invention have K_i values of less than 500 nM and more preferred compounds of the invention have K_i values of less than 100 nM.

Example 25

Electrophysiology

The following assay is used to determine if a compound of the invention act as an agonist, an antagonist, or an inverse agonist at the benzodiazepine site of the $GABA_A$ receptor.

Assays are carried out as described in White and Gurley (NeuroReport 6: 1313-1316, 1995) and White, Gurley, Hartnett, Stirling, and Gregory (Receptors and Channels 3: 1-5, 1995) with modifications. Electrophysiological recordings are carried out using the two electrode voltage-clamp technique at a membrane holding potential of -70 mV. *Xenopus Laevis* oocytes are enzymatically isolated and injected with non-polyadenylated cRNA mixed in a ratio of 4:1:4 for α, β and γ subunits, respectively. Of the nine combinations of α, β and γ subunits described in the White et al. publications, preferred combinations are $\alpha_1\beta_2\gamma_2$,

$\alpha_2\beta_3\gamma_2$, $\alpha_3\beta_3\gamma_2$, and $\alpha_5\beta_3\gamma_2$. Preferably all of the subunit cRNAs in each combination are human clones or all are rat clones. The sequence of each of these cloned subunits is available from GENBANK, e.g., human α_1, GENBANK accession no. X14766, human α_2, GENBANK accession no. A28100; human α_3, GENBANK accession no. A28102; human α_5, GENBANK accession no. A28104; human β_2, GENBANK accession no. M82919; human β_3, GENBANK accession no. Z20136; human β_2, GENBANK accession no. X15376; rat α_1, GENBANK accession no. L08490, rat α_2, GENBANK accession no. L08491; rat α_3, GENBANK accession no. L08492; rat α_5, GENBANK accession no. L08494; rat β_2, GENBANK accession no. X15467; rat β_3, GENBANK accession no. X15468; and rat γ_2, GENBANK accession no. L08497. For each subunit combination, sufficient message for each constituent subunit is injected to provide current amplitudes of >10 nA when 1 μM GABA is applied.

Compounds are evaluated against a GABA concentration that evokes <10% of the maximal evokable GABA current (e.g. 1 μM - 9 μM). Each oocyte is exposed to increasing concentrations of compound in order to evaluate a concentration/effect relationship. Compound efficacy is calculated as a percent-change in current amplitude: $100*((Ic/I)-1)$, where Ic is the GABA evoked current amplitude observed in the presence of test

compound and I is the GABA evoked current amplitude observed in the absence of the test compound.

Specificity of a compound for the benzodiazepine site is determined following completion of a concentration/effect curve. After washing the oocyte sufficiently to remove previously applied compound, the oocyte is exposed to GABA + 1 μM RO15-1788, followed by exposure to GABA + 1 μM RO15-1788 + test compound. Percent change due to addition of compound is calculated as described above. Any percent change observed in the presence of RO15-1788 is subtracted from the percent changes in current amplitude observed in the absence of 1 μM RO15-1788. These net values are used for the calculation of average efficacy and EC_{50} values by standard methods. To evaluate average efficacy and EC_{50} values, the concentration/effect data are averaged across cells and fit to the logistic equation.

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

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and distinctly claim the subject matter regarded as invention, 673

the following claims conclude this specification.

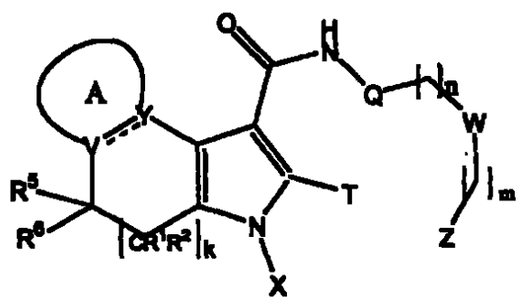
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What is claimed is:

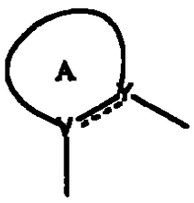
1. A compound of the formula



or a pharmaceutically acceptable salt thereof, wherein:

R^1 and R^2 are independently chosen at each occurrence from hydrogen, halogen, hydroxy, cyano, nitro, amino, alkyl, alkenyl, alkynyl, haloalkyl, mono or diaminoalkyl, alkoxy, and k is 0, 1, 2, or 3;

the group



represents an optionally substituted saturated, unsaturated or aromatic heterocyclic ring containing at least one nitrogen, oxygen or sulfur atom, wherein the V⁼⁼⁼⁼Y bond is a single, double, or aromatic bond;

V is nitrogen, carbon, or CH;

Y is carbon, or CH;

674
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R^5 and R^6 may be taken together to form a carbonyl group; or

R^5 and R^6 are independently chosen from hydrogen, halogen, hydroxy, nitro, cyano, $alkyl_1$, amino, -COOH, $-O(alkyl_1)$, $-SO_2NH_2$, $-SO_2NH(alkyl_1)$, $-SO_2N(alkyl_1)(alkyl_1)$, $-N(alkyl_1)CO(alkyl_1)$, $N(alkyl_1)CO_2(alkyl_1)$, $-NHSO_2(alkyl_1)$, $-N(alkyl_1)SO_2(alkyl_1)$, $-SO_2NHCO(alkyl_1)$, $-CONHSO_2(alkyl_1)$, $-CONH(alkyl_1)$, $-CON(alkyl_1)(alkyl_1)$, $-CO_2(alkyl_1)$, $-CO(alkyl_1)$ $-SO_{0-2}(alkyl_1)$, and optionally substituted carbocyclic aryl or optionally substituted heteroaryl group having from 1 to 3 rings, 3 to 8 members in each ring and from 1 to 3 heteroatoms;

wherein $alkyl_1$ is independently chosen at each occurrence and is straight branched or cyclic, may contain one or two double or triple bonds, and is unsubstituted or substituted with one or more substituents selected from: hydroxy, oxo, halogen, amino, cyano, nitro, alkoxy, -COOH, $-SO_2NH_2$, $-SO_2NH(alkyl)$, $-SO_2N(alkyl)(alkyl)$, $-N(alkyl)CO(alkyl)$, $N(alkyl)CO_2(alkyl)$, $-NHSO_2(alkyl)$, $-N(alkyl)SO_2(alkyl)$, $-SO_2NHCO(alkyl)$, $-CONHSO_2(alkyl)$, $-CONH(alkyl)$, $-CON(alkyl)(alkyl)$, $-CO_2(alkyl)$, $-CO(alkyl)$ $-SO_{0-2}(alkyl)$;

X is chosen from hydrogen, hydroxy, amino, alkyl, and alkoxy;

T is chosen from hydrogen, halogen, hydroxy, amino, alkyl, and alkoxy;

675

676

Q is an optionally substituted carbocyclic aryl or optionally substituted heteroaryl group having from 1 to 3 rings, 3 to 8 members in each ring and from 1 to 3 heteroatoms;

W is hydrogen, 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 alkyl, or R^7 and R^8 may be taken together to represent a cyclic moiety having 3-7 carbon atoms;

Z is hydrogen, hydroxy, straight or branched chain alkoxy, cycloalkyl, cycloalkyl(alkoxy), amino, mono or dialkylamino, or NR^9COR^{10} where R^9 and R^{10} are the same or different and represent hydrogen or straight or branched chain alkyl, or R^9 and R^{10} may be joined to from a cycloalkyl ring, or

Z is optionally substituted carbocyclic aryl or optionally substituted heteroaryl group having from 1 to 3 rings, 3 to 8 members in each ring and from 1 to 3 heteroatoms;

 and  represent carbon chains which may be substituted with hydrogen, halogen, cyano, nitro, amino, mono or dialkylamino, alkenyl, alkynyl, alkoxy, trifluoromethyl, trifluoromethoxy, straight or branched chain alkyl, or cycloalkyl, and

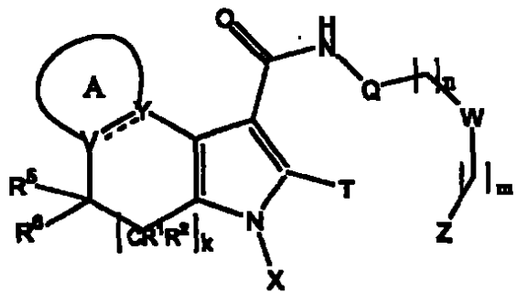
m is 0, 1, 2, or 3; and

n is 0, 1, 2, or 3.

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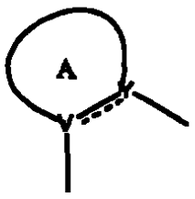
2. A compound according to Claim 1 of the formula



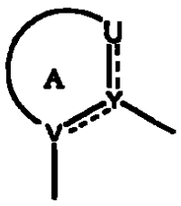
or a pharmaceutically acceptable salt thereof, wherein:

R^1 and R^2 are independently chosen at each occurrence from hydrogen, halogen, hydroxy, cyano, nitro, amino, haloalkyl, mono or diamino(C_{1-6})alkyl, C_{1-6} alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl and C_{1-6} alkoxy, and k is 0, 1, 2, or 3;

the group



is a group of the formula:



represents a saturated, unsaturated or aromatic heterocyclic ring containing at least one nitrogen, oxygen or sulfur atom,

wherein the U----Y and V----Y bonds may be single, double or aromatic bonds,

U is nitrogen, NR^A, S, or O;

V is nitrogen, carbon or CH;

Y is carbon, or CH;

and said saturated, unsaturated or aromatic heterocyclic ring is chosen from:

thienyl, thiazolyl, pyridyl, pyrimidinyl, imidazolyl, pyrazolyl, pyrazinyl, pyridizinyl, piperidinyl, oxazolyl, isoxazolyl, symmetrical and unsymmetrical triazolyl, pyrrolyl, furanyl, diazenyl, triazenyl, 1, 2, 4-triazolone, 4,5-dihydroimidazolyl, and 1,4,5,6-tetrahydropyrimidinyl, each of which is optionally substituted at any available nitrogen by R^A and optionally substituted at any available carbon by R^3 and R^4, wherein:

R^A is chosen from hydrogen, $C_{1-6}alkyl_1$, optionally substituted carbocyclic aryl and optionally substituted heteroaryl groups having from 1 to 3 rings, 3 to 8 members in each ring and from 1 to 3 heteroatoms;

R^3 and R^6 are independently chosen from hydrogen, halogen, hydroxy, nitro, cyano, $C_{1-6}alkyl_1$, amino, -COOH, $-O(C_{1-6}alkyl_1)$, $-NH(C_{1-6}alkyl_1)$, $-N(C_{1-6}alkyl_1)(C_{1-6}alkyl_1)$, $-SO_2NH_2$, $-SO_2NH(C_{1-6}alkyl_1)$, $-SO_2N(C_{1-6}alkyl_1)(C_{1-6}alkyl_1)$, $-N(C_{1-6}alkyl_1)CO(C_{1-6}alkyl_1)$, $N(C_{1-6}alkyl_1)CO_2(C_{1-6}alkyl_1)$, $-NHSO_2(C_{1-6}$

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$_{6}alkyl_1)$, $-N(C_{1-6}alkyl_1)SO_2(C_{1-6}alkyl_1)$, $-SO_2NHCO(C_{1-6}alkyl_1)$, $-CONHSO_2(C_{1-6}alkyl_1)$, $-CONH(C_{1-6}alkyl_1)$, $-CON(C_{1-6}alkyl_1)(C_{1-6}alkyl_1)$, $-CO_2(C_{1-6}alkyl_1)$, $-CO(C_{1-6}alkyl_1)$ and $-SO_{0-2}(C_{1-6}alkyl_1)$,

wherein $C_{1-6}alkyl_1$ is independently chosen at each occurrence and is straight branched or cyclic, may contain one or two double or triple bonds, and is unsubstituted or substituted with one or more substituents selected from: hydroxy, oxo, halogen, amino, cyano, nitro, alkoxy, carbocylic or heterocyclic group, $-COOH$, $-SO_2NH_2$, $-SO_2NH(C_{1-4}alkyl)$, $-SO_2N(C_{1-4}alkyl)(C_{1-4}alkyl)$, $-N(C_{1-4}alkyl)CO(C_{1-4}alkyl)$, $N(C_{1-4}alkyl)CO_2(C_{1-4}alkyl)$, $-NHSO_2(alkyl)$, $-N(C_{1-4}alkyl)SO_2(C_{1-4}alkyl)$, $-SO_2NHCO(C_{1-4}alkyl)$, $-CONHSO_2(C_{1-4}alkyl)$, $-CONH(C_{1-4}alkyl)$, $-CON(C_{1-4}alkyl)(C_{1-4}alkyl)$, $-CO_2(C_{1-4}alkyl)$, $-CO(C_{1-4}alkyl)$, and $-SO_{0-2}(C_{1-4}alkyl)$;

R^3 and R^4 are independently chosen at each occurrence, and are defined the same as R^5 and R^6;

X is chosen from hydrogen, hydroxy, amino, C_{1-6} alkyl, and C_{1-6}alkoxy;

T is chosen from hydrogen, halogen, hydroxy, amino, C_{1-6} alkyl, and C_{1-6} alkoxy;

Q is a phenyl, naphthyl, quinolinyl, thienyl, pyridyl, pyrimidinyl, pyrazinyl, oxazolyl, isoxazolyl, symmetrical

or unsymmetrical oxadiazolyl, symmetrical or unsymmetrical thiadiazolyl, symmetrical or unsymmetrical triazolyl, pyrazolyl, furanyl, diazenyl, triazenyl, or triazolopyrazinyl group;

each of which may be unsubstituted or substituted with up to three substituents independently selected from i) and ii) wherein

i) represents hydroxy, cyano, halogen, nitro, amino, mono or di(C_{1-6})alkylamino, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}alkoxy, trifluoromethyl, or trifluoromethoxy;

ii) represents straight or branched chain C_{1-6}alkyl optionally containing heteroatoms and optionally substituted with one or more carbocyclic or heterocyclic group;

W is hydrogen, 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 C_{1-6}alkyl, or R^7 and R^8 may be taken together to represent a cyclic moiety having 3-7 carbon atoms;

Z is hydrogen, hydroxy, straight or branched chain C_{1-6}alkoxy, C_{3-7}cycloalkyl, C_{3-7}cycloalkyl(C_{1-3}alkoxy), amino, mono or di C_{1-6}alkylamino, a carbocyclic or heterocylic group, or NR^9COR^{10} where R^9 and R^{10} are the same or different and

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represent hydrogen or straight or branched chain C_{1-6}alkyl, or R^9 and R^{10} may be joined to from a C_{3-7} cycloalkyl ring, or

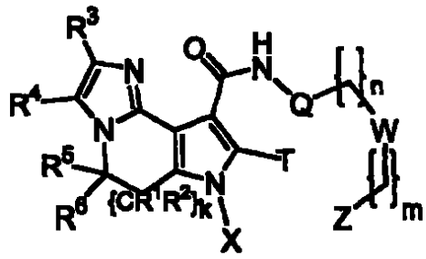
Z is a phenyl, napthyl, quinolinyl, thienyl, thiazolyl, pyridyl, pyrimidinyl, imidazolyl, pyrazolyl, pyrazinyl, pyridizinyl, piperidinyl, oxazolyl, isoxazolyl, symmetrical or unsymmetrical thiadiazolyl, symmetrical or unsymmetrical triazolyl, symmetrical or unsymmetrical oxadiazolyl, pyrrolyl, furanyl, pyrimidinyl, diazenyl, triazenyl, 1, 2, 4-triazolone, 4,5-dihydroimidazolyl, or 1,4,5,6-tetrahydropyrimidinyl group;

 , and  represent a carbon chain which may be substituted with hydrogen, halogen, cyano, nitro, amino, mono or di C_{1-6}alkylamino, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}alkoxy, trifluoromethyl, trifluoromethoxy, straight or branched chain C_{1-6}alkyl, or C_{3-7}cycloalkyl, and

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

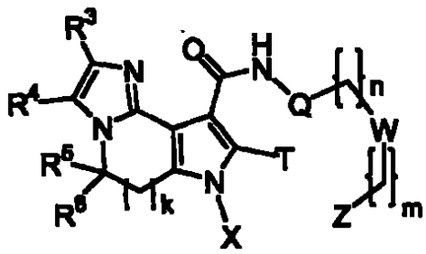
n is 0, 1, 2, or 3.

3. A compound according to Claim 2, of the formula:



wherein the variables R^1, R^2, R^3, R^4, R^5, R^6, k, n, m, T, X, Q, W, and Z are as defined in Claim 1.

4. A compound according to Claim 2, of the formula:



wherein the variables n, m, Q, W, and Z are as defined in Claim 2;

k is 1 or 2;

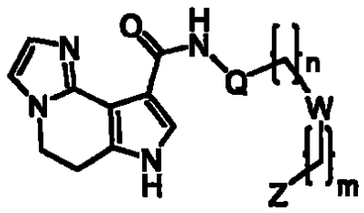
R^3, R^4, R^5, and R^6, are independently chosen from hydrogen, halogen, amino, hydroxy, methyl, ethyl, methoxy, and ethoxy; and

X and T are independently chosen from hydrogen, methyl, and ethyl.

5. A compound according to Claim 2, of the formula:

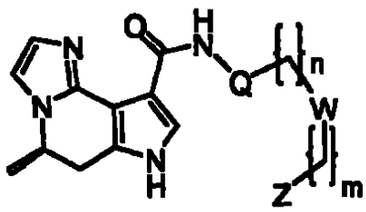
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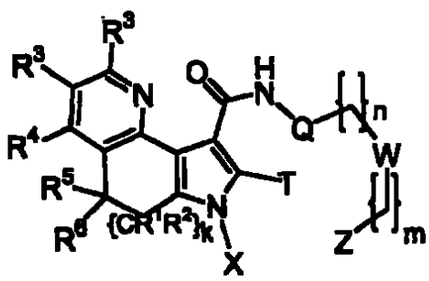
wherein the variables n, m, Q, W, and Z are as defined in Claim 2.

6. A compound according to Claim 2, of the formula:



wherein the variables n, m, Q, W, and Z are as defined in Claim 2.

7. A compound according to Claim 2, of the formula:

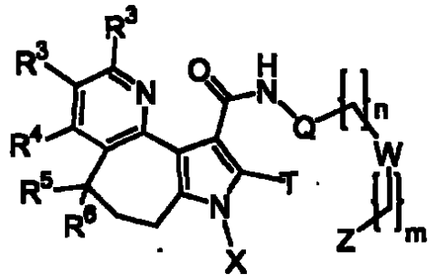


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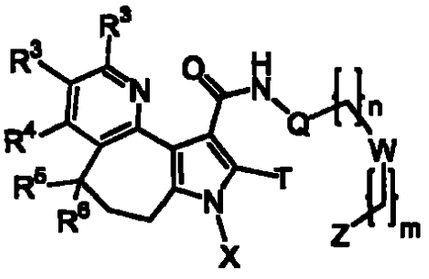
wherein the variables R^1, R^2, R^3, R^4, R^5, R^6, k, n, m, T, X, Q, W, and Z are as defined in Claim 2.

8. A compound according to Claim 2, of the formula:



wherein the variables R^3, R^4, R^5, R^6, n, m, T, X, Q, W, and Z are as defined in Claim 2.

9. A compound according to Claim 2, of the formula:

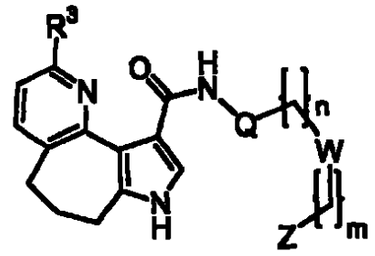


wherein the variables n, m, Q, W, and Z are as defined in Claim 2;

R^3, R^4, R^5, and R^6, are independently chosen at each occurrence from hydrogen, halogen, amino, hydroxy, methyl, ethyl, methoxy, and ethoxy; and

X and T are independently chosen from hydrogen, methyl, and ethyl.

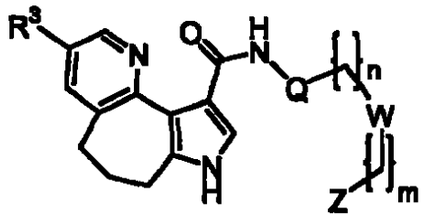
10. A compound according to Claim 2, of the formula:



wherein the variables n, m, T, X, Q, W, and Z are as defined in Claim 2; and

R^3 is hydrogen or methyl.

11. A compound according to Claim 2, of the formula:



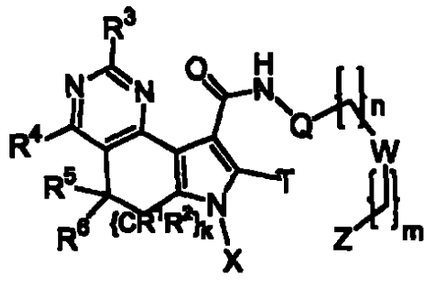
wherein the variables n, m, T, X, Q, W, and Z are as defined in Claim 2; and

R^3 is hydrogen or methyl.

12. A compound according to Claim 2, of the formula:

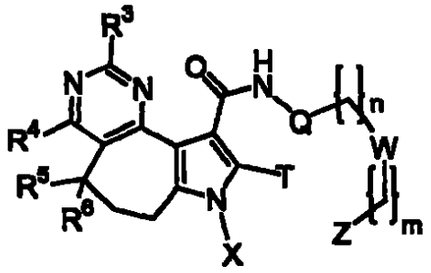
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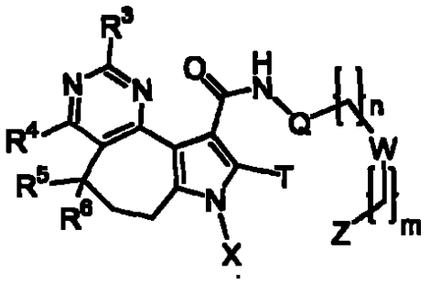
wherein the variables R^1, R^2, R^3, R^4, R^5, R^6, k, n, m, T, X, Q, W, and Z are as defined in Claim 2.

13. A compound according to Claim 2, of the formula:



wherein the variables R^3, R^4, R^5, R^6, n, m, T, X, Q, W, and Z are as defined in Claim 2.

14. A compound according to Claim 2, of the formula:

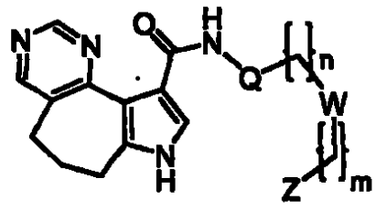


wherein the variables n, m, Q, W, and Z are as defined in Claim 2;

R^3, R^4, R^5, and R^6, are independently chosen at each occurrence from hydrogen, halogen, amino, hydroxy, methyl, ethyl, methoxy, and ethoxy; and

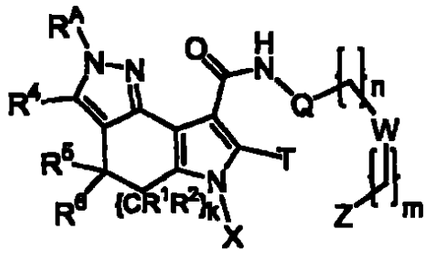
X and T are independently chosen from hydrogen, methyl, and ethyl.

15. A compound according to Claim 2, of the formula:



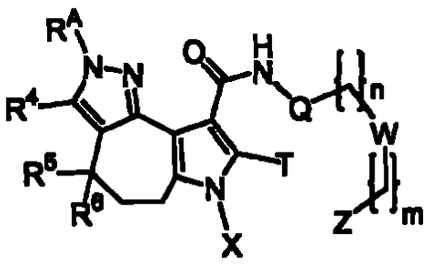
wherein the variables n, m, Q, W, and Z are as defined in Claim 2.

16. A compound according to Claim 2, of the formula



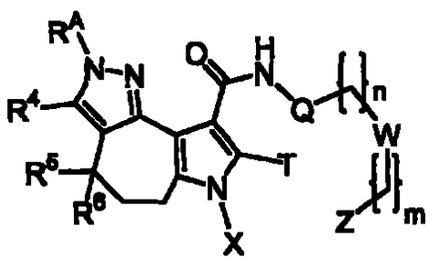
wherein the variables R^1, R^2, R^A, R^4, R^5, R^6, k, n, m, T, X, Q, W, and Z are as defined in Claim 2.

17. A compound according to Claim 2, of the formula



wherein the variables R^A, R^4, R^5, R^6, n, m, T, X, Q, W, and Z are as defined in Claim 2.

18. A compound according to Claim 2, of the formula



wherein the variables n, m, Q, W, and Z are as defined in Claim 2;

R^A is C_{1-6}alkyl, phenyl, thienyl, pyridyl, pyrimidinyl, pyrrolyl, or imidazolyl,

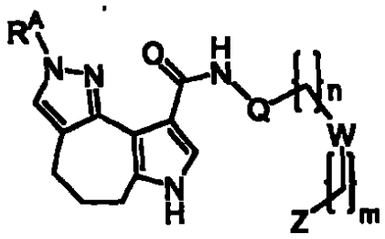
R^3, R^4, R^5, and R^6, are independently chosen from hydrogen, halogen, amino, hydroxy, methyl, ethyl, methoxy, and ethoxy; and

X and T are independently chosen from hydrogen, methyl, and ethyl.

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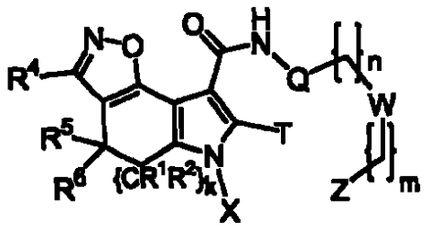
19. A compound according to Claim 2, of the formula



wherein the variables n, m, Q, W, and Z are as defined in Claim 2; and

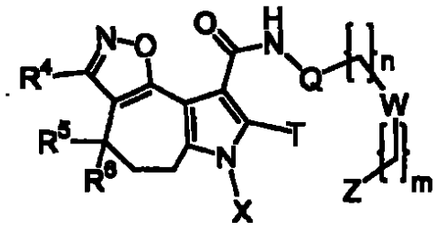
R^A is methyl, ethyl, or pyridyl.

20. A compound according to Claim 2, of the formula



wherein the variables R^1, R^2, R^4, R^5, R^6, k, n, m, T, X, Q, W, and Z are as defined in Claim 2.

21. A compound according to Claim 2, of the formula

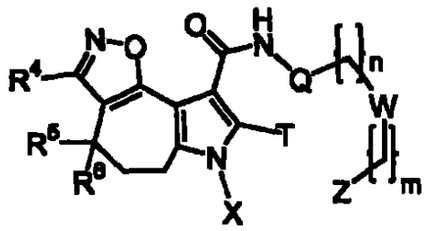


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wherein the variables R^4, R^5, R^6, n, m, T, X, Q, W, and Z are as defined in Claim 2.

22. A compound according to Claim 2, of the formula

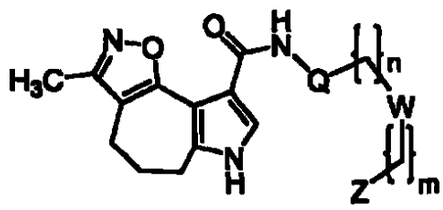


wherein the variables n, m, Q, W, and Z are as defined in Claim 2;

R^4, R^5, and R^6, are independently chosen from hydrogen, halogen, amino, hydroxy, methyl, ethyl, methoxy, and ethoxy; and

X and T are independently chosen from hydrogen, methyl, and ethyl.

23. A compound according to Claim 2, of the formula

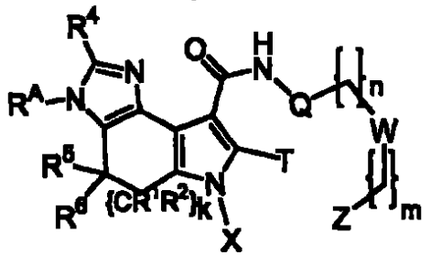


wherein the variables n, m, Q, W, and Z are as defined in Claim 2.

24. A compound according to Claim 2, of the formula

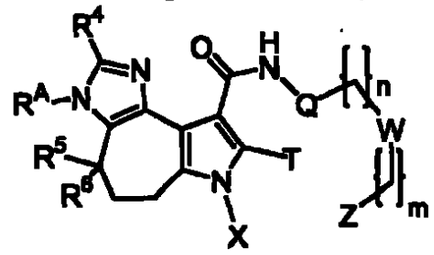
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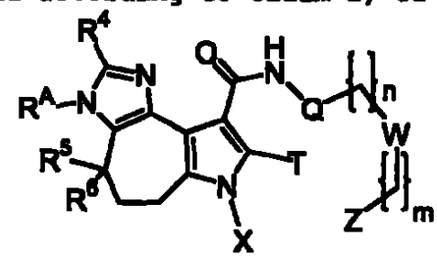
wherein the variables R^1, R^2, R^A, R^4, R^5, R^6, k, n, m, T, X, Q, W, and Z are as defined in Claim 2.

25. A compound according to Claim 2, of the formula



wherein the variables R^A, R^4, R^5, R^6, n, m, T, X, Q, W, and Z are as defined in Claim 2.

26. A compound according to Claim 2, of the formula



wherein the variables n, m, Q, W, and Z are as defined in Claim 2;

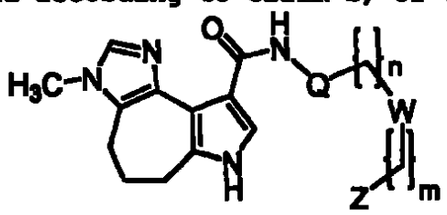
R^A is methyl, ethyl, or pyridyl;

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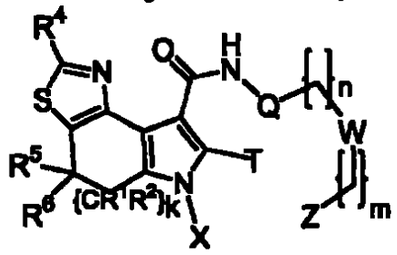
R^4, R^5, and R^6, are independently chosen from hydrogen, halogen, amino, hydroxy, methyl, ethyl, methoxy, and ethoxy; and X and T are independently chosen from hydrogen, methyl, and ethyl.

27. A compound according to Claim 2, of the formula



wherein the variables n, m, Q, W, and Z are as defined in Claim 2.

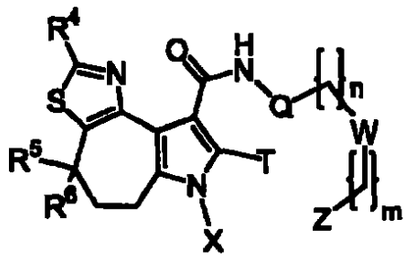
28. A compound according to Claim 2, of the formula



wherein the variables R^1, R^2, R^4, R^5, R^6, k, n, m, T, X, Q, W, and Z are as defined in Claim 2.

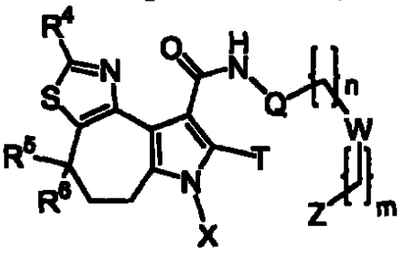
29. A compound according to Claim 2, of the formula

692
693



wherein the variables R^4, R^5, R^6, n, m, T, X, Q, W, and Z are as defined in Claim 2.

30. A compound according to Claim 2, of the formula

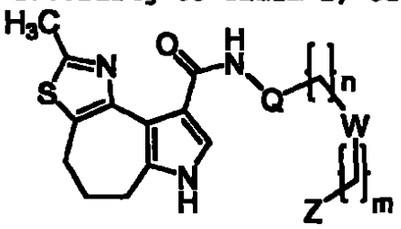


wherein the variables n, m, Q, W, and Z are as defined in Claim 2;

R^4, R^5, and R^6, are independently chosen from hydrogen, halogen, amino, hydroxy, methyl, ethyl, methoxy, and ethoxy; and

X and T are independently chosen from hydrogen, methyl, and ethyl.

31. A compound according to Claim 2, of the formula

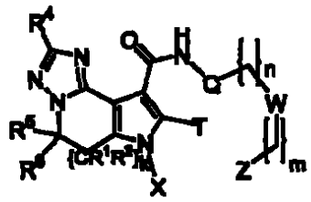


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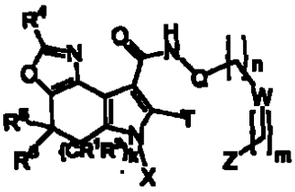
wherein the variables n, m, Q, W, and Z are as defined in Claim 2.

32. A compound according to Claim 2, of the formula



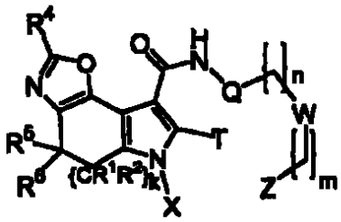
wherein the variables R^1, R^2, R^4, R^5, R^6, k, n, m, T, X, Q, W, and Z are as defined in Claim 2.

33. A compound according to Claim 2, of the formula



wherein the variables R^1, R^2, R^4, R^5, R^6, k, n, m, T, X, Q, W, and Z are as defined in Claim 2.

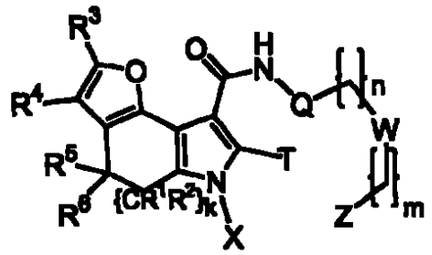
34. A compound according to Claim 2, of the formula:



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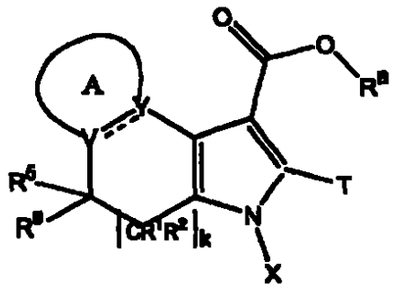
wherein the variables R^1, R^2, R^4, R^5, R^6, k, n, m, T, X, Q, W, and Z are as defined in Claim 2.

35. A compound according to Claim 2, of the formula



wherein the variables R^1, R^2, R^3, R^4, R^5, R^6, k, n, m, T, X, Q, W, and Z are as defined in Claim 2.

36. A compound of the formula:



wherein

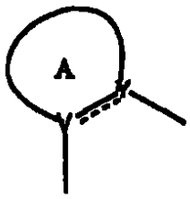
R^1 and R^2 are independently chosen at each occurrence from hydrogen, halogen, hydroxy, cyano, nitro, amino, alkyl,

695

alkenyl, alkynyl, haloalkyl, and mono or diaminoalkyl, alkoxy, and k is 0, 1, 2, or 3;

696

the group



which represents an optionally substituted saturated, unsaturated or aromatic heterocyclic ring containing at least one nitrogen, oxygen or sulfur atom, wherein the V----Y bond is a single, double, or aromatic bond;

V is nitrogen, carbon, or CH;

Y is carbon, or CH;

R^5 and R^6 may be taken together to form a carbonyl group; or

R^5 and R^6 are independently chosen from hydrogen, halogen, hydroxy, nitro, cyano, $alkyl_1$, amino, -COOH, $-O(alkyl_1)$, $-SO_2NH_2$, $-SO_2NH(alkyl_1)$, $-SO_2N(alkyl_1)(alkyl_1)$, $-N(alkyl_1)CO(alkyl_1)$, $N(alkyl_1)CO_2(alkyl_1)$, $-NHSO_2(alkyl_1)$, $-N(alkyl_1)SO_2(alkyl_1)$, $-SO_2NHCO(alkyl_1)$, $-CONHSO_2(alkyl_1)$, $-CONH(alkyl_1)$, $-CON(alkyl_1)(alkyl_1)$, $-CO_2(alkyl_1)$, $-CO(alkyl_1)$, $-SO_{0-2}(alkyl_1)$, optionally substituted carbocyclic aryl and optionally substituted heteroaryl groups having from 1 to 3

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rings, 3 to 8 members in each ring and from 1 to 3 heteroatoms;

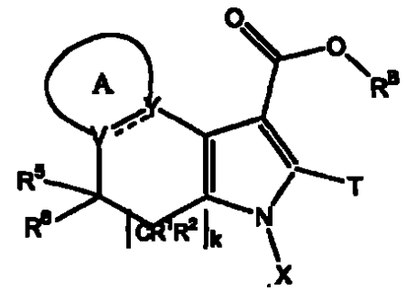
wherein $alkyl_1$ is independently chosen at each occurrence and is straight branched or cyclic, may contain one or two double or triple bonds, and is unsubstituted or substituted with one or more substituents selected from: hydroxy, oxo, halogen, amino, cyano, nitro, alkoxy, -COOH, $-SO_2NH_2$, -SO_2NH(alkyl), $-SO_2N$(alkyl)(alkyl), -N(alkyl)CO(alkyl), N(alkyl)CO_2(alkyl), $-NHSO_2$(alkyl), -N(alkyl)SO_2(alkyl), -SO_2NHCO(alkyl), $-CONHSO_2$(alkyl), -CONH(alkyl), -CON(alkyl)(alkyl), $-CO_2$(alkyl), -CO(alkyl) $-SO_{0-2}$(alkyl);

X is chosen from hydrogen, hydroxy, amino, alkyl, and alkoxy;

T is chosen from hydrogen, halogen, hydroxy, amino, alkyl, and alkoxy; and

R^3 is chosen from hydrogen, methyl, ethyl and benzyl.

37. A compound of the formula:

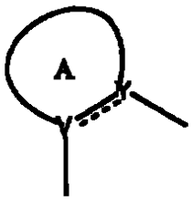


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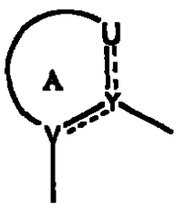
698

R^1 and R^2 are independently chosen at each occurrence from hydrogen, halogen, hydroxy, cyano, nitro, amino, haloalkyl, mono or diamino(C_{1-6})alkyl, C_{1-6} alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl and C_{1-6} alkoxy, and k is 0, 1, 2, or 3;

the group



is a group of the formula:



represents a saturated, unsaturated or aromatic heterocyclic ring containing at least one nitrogen, oxygen or sulfur atom, wherein the U----Y and V----Y bonds may be single, double or aromatic bonds,

U is nitrogen, NR^A, S, or O;

V is nitrogen, carbon or CH;

Y is carbon, or CH;

and said saturated, unsaturated or aromatic heterocyclic ring is chosen from:

thienyl, thiazolyl, pyridyl, pyrimidinyl, imidazolyl, pyrazolyl, pyrazinyl, pyridizinyl, piperidinyl, oxazolyl, isoxazolyl, symmetrical and unsymmetrical triazolyl, pyrrolyl, furanyl, diazenyl, triazenyl, 1, 2, 4-triazolone, 4,5-dihydroimidazolyl, and 1,4,5,6-tetrahydropyrimidinyl, each of which is optionally substituted at any available nitrogen by R^A and optionally substituted at any available carbon by R^3 and R^4, wherein:

R^A is chosen from hydrogen, $C_{1-6}alkyl_1$, optionally substituted carbocyclic aryl and optionally substituted heteroaryl groups having from 1 to 3 rings, 3 to 8 members in each ring and from 1 to 3 heteroatoms;

R^3 and R^4 are independently chosen at each occurrence, and are defined the same as R^5 and R^6;

R^5 and R^6 are independently chosen from hydrogen, halogen, hydroxy, nitro, cyano, $C_{1-6}alkyl_1$, amino, -COOH, $-O(C_{1-6}alkyl_1)$, $-NH(C_{1-6}alkyl_1)$, $-N(C_{1-6}alkyl_1)(C_{1-6}alkyl_1)$, $-SO_2NH_2$, $-SO_2NH(C_{1-6}alkyl_1)$, $-SO_2N(C_{1-6}alkyl_1)(C_{1-6}alkyl_1)$, $-N(C_{1-6}alkyl_1)CO(C_{1-6}alkyl_1)$, $N(C_{1-6}alkyl_1)CO_2(C_{1-6}alkyl_1)$, $-NHSO_2(C_{1-6}alkyl_1)$, $-N(C_{1-6}alkyl_1)SO_2(C_{1-6}alkyl_1)$, $-SO_2NHCO(C_{1-6}alkyl_1)$, $-CONHSO_2(C_{1-6}alkyl_1)$, $-CONH(C_{1-6}alkyl_1)$, $-CON(C_{1-6}alkyl_1)(C_{1-6}alkyl_1)$, $-CO_2(C_{1-6}alkyl_1)$, $-CO(C_{1-6}alkyl_1)$ and $-SO_{0-2}(C_{1-6}alkyl_1)$,

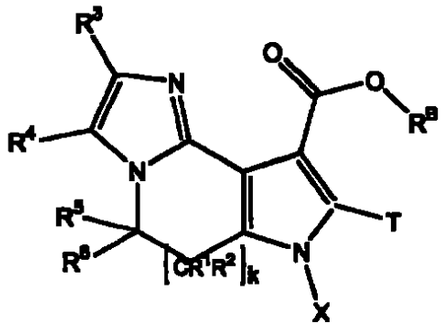
wherein $C_{1-6}alkyl_1$ is independently chosen at each occurrence and is straight branched or cyclic, may contain one or two double or triple bonds, and is unsubstituted or substituted with one or more substituents selected from: hydroxy, oxo, halogen, amino, cyano, nitro, alkoxy, carbocylic or heterocyclic group, $-COOH$, $-SO_2NH_2$, $-SO_2NH(C_{1-4}alkyl)$, $-SO_2N(C_{1-4}alkyl)(C_{1-4}alkyl)$, $-N(C_{1-4}alkyl)CO(C_{1-4}alkyl)$, $N(C_{1-4}alkyl)CO_2(C_{1-4}alkyl)$, $-NHSO_2(alkyl)$, $-N(C_{1-4}alkyl)SO_2(C_{1-4}alkyl)$, $-SO_2NHCO(C_{1-4}alkyl)$, $-CONHSO_2(C_{1-4}alkyl)$, $-CONH(C_{1-4}alkyl)$, $-CON(C_{1-4}alkyl)(C_{1-4}alkyl)$, $-CO_2(C_{1-4}alkyl)$, $-CO(C_{1-4}alkyl)$, and $-SO_{0-2}(C_{1-4}alkyl)$;

X is chosen from hydrogen, hydroxy, amino, C_{1-6} alkyl, and C_{1-6}alkoxy;

T is chosen from hydrogen, halogen, hydroxy, amino, C_{1-6} alkyl, and C_{1-6} alkoxy; and

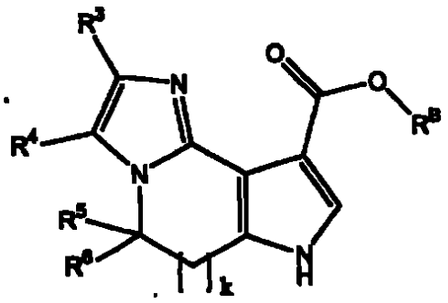
R^8 is chosen from hydrogen, methyl, ethyl and benzyl.

38. A compound according to Claim 37, which is:



wherein R^1, R^2, R^3, R^4, R^5, R^6, k, X, T, and R^8 are as defined in Claim 37.

39. A compound according to Claim 37, which is:



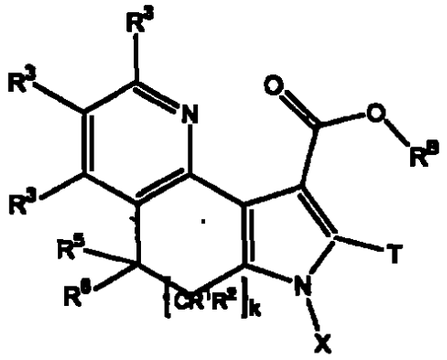
wherein:

R^8 is defined as in Claim 37;

k is 1 or 2;

R^3, R^4, R^5, and R^6, are independently chosen from hydrogen, halogen, amino, hydroxy, methyl, ethyl, methoxy, and ethoxy.

40. A compound according to Claim 37, which is:

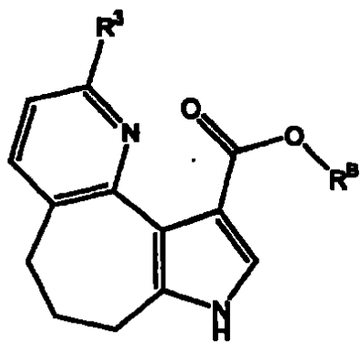


wherein:

R^3 is independently selected at each occurrence and is as defined in Claim 35; and

R^1, R^2, R^3, R^5, R^6, k, X, T, and R^B are as defined in Claim 37.

41. A compound according to Claim 37, which is:

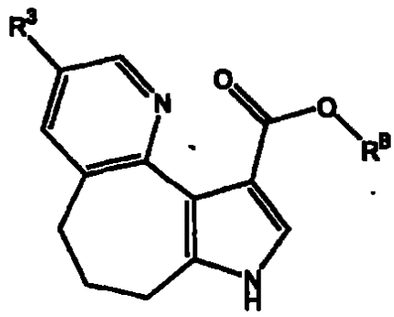


wherein:

R^B is defined as in Claim 37; and

R^3 is chosen from hydrogen, halogen, amino, hydroxy, methyl, ethyl, methoxy, and ethoxy.

42. A compound according to Claim 37, which is:

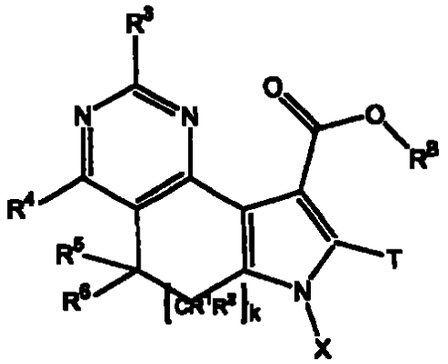


wherein:

R^8 is defined as in Claim 37; and

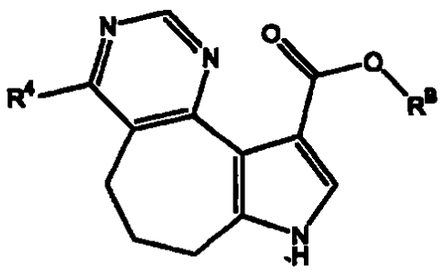
R^3 is chosen from hydrogen, halogen, amino, hydroxy, methyl, ethyl, methoxy, and ethoxy.

43. A compound according to Claim 37, which is:



wherein R^1, R^2, R^3, R^4, R^5, R^6, k, X, T, and R^8 are as defined in Claim 37.

44. A compound according to Claim 37, which is:



wherein:

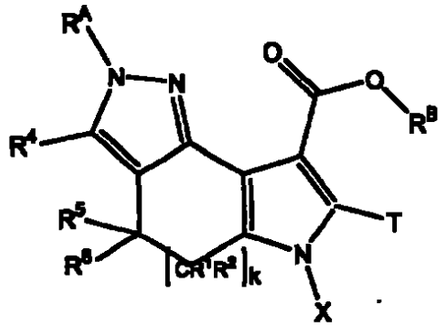
R^8 is defined as in Claim 37; and

R^4 is chosen from hydrogen, halogen, amino, hydroxy, methyl, ethyl, methoxy, and ethoxy.

203

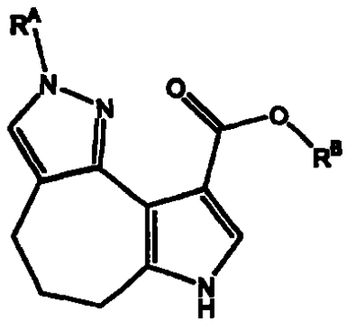
204

45. A compound according to Claim 37, which is:



wherein R^A, R^1, R^2, X, R^4, R^5, R^6, k, X, T, and R^B are as defined in Claim 37.

46. A compound according to Claim 37, which is:

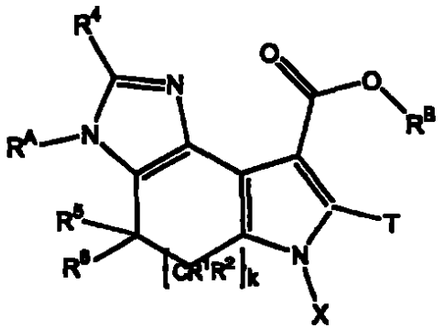


wherein:

R^A is chosen from hydrogen, methyl, ethyl, and phenyl; and

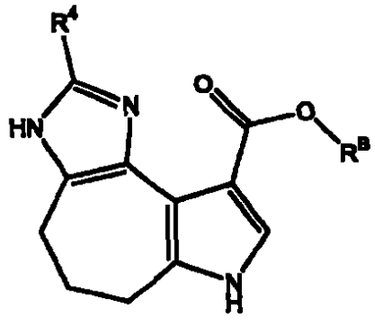
R^B is defined as in Claim 37.

47. A compound according to Claim 37, which is:



wherein R^A, R^1, R^2, R^3, R^4, R^5, R^6, k, X, T, and R^B are as defined in Claim 37.

48. A compound according to Claim 37, which is:

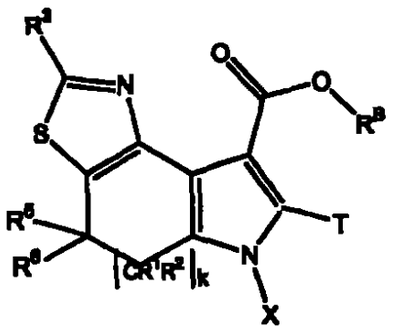


wherein:

R^B is defined as in Claim 37; and

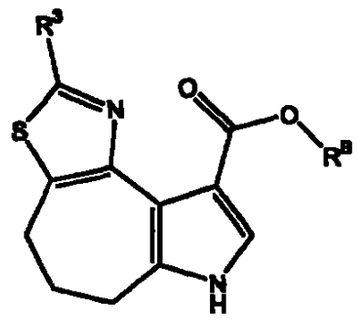
R^4 is from chosen hydrogen, halogen, amino, hydroxy, methyl, ethyl, methoxy, and ethoxy.

49. A compound according to Claim 37, which is:



wherein R^1, R^2, R^3, R^5, R^6, k, X, T, and R^8 are as defined in Claim 37.

50. A compound according to Claim 37, which is:

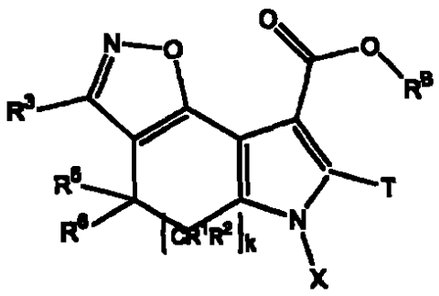


wherein:

R^8 is defined as in Claim 37; and

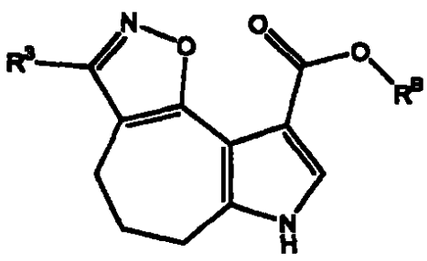
R^3 is chosen from hydrogen, halogen, amino, hydroxy, methyl, ethyl, methoxy, and ethoxy.

51. A compound according to Claim 37, which is:



wherein R^1, R^2, R^3, R^5, R^6, k, X, T, and R^8 are as defined in Claim 37.

52. A compound according to Claim 37, which is:

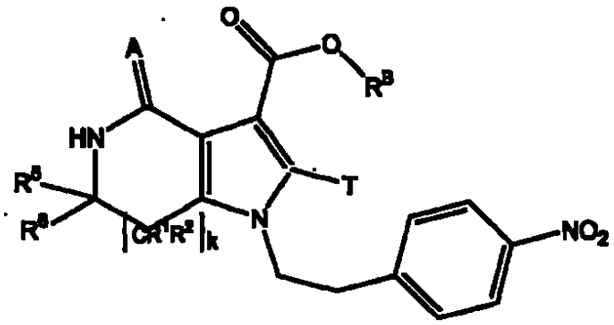


wherein:

R^8 is defined as in Claim 37; and

R^3 is chosen from hydrogen, halogen, amino, hydroxy, methyl, ethyl, methoxy, and ethoxy.

53. A compound of the formula:



wherein:

A is oxygen or sulfur;

R^1 and R^2 are independently chosen at each occurrence from hydrogen, halogen, hydroxy, cyano, nitro, amino, haloalkyl, mono or diamino(C_{1-6})alkyl, C_{1-6} alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl and C_{1-6} alkoxy, and k is 0, 1, 2, or 3;

R^5 and R^6 independently chosen from hydrogen, halogen, hydroxy, nitro, cyano, C_{1-6}alkyl$_1$, amino, -COOH, -O(C_{1-6}alkyl$_1$), -NH(C_{1-6}alkyl$_1$), -N(C_{1-6}alkyl$_1$)(C_{1-6}alkyl$_1$), $-SO_2NH_2$, $-SO_2NH(C_{1-6}$alkyl$_1$), $-SO_2N(C_{1-6}$alkyl$_1$)(C_{1-6}alkyl$_1$), -N(C_{1-6}alkyl$_1$)CO(C_{1-6}alkyl$_1$), N(C_{1-6}alkyl$_1$)CO_2(C_{1-6}alkyl$_1$), $-NHSO_2(C_{1-6}$alkyl$_1$), -N(C_{1-6}alkyl$_1$)SO_2(C_{1-6}alkyl$_1$), $-SO_2NHCO(C_{1-6}$alkyl$_1$), $-CONHSO_2(C_{1-6}$alkyl$_1$), -CONH(C_{1-6}alkyl$_1$), -CON(C_{1-6}alkyl$_1$)(C_{1-6}alkyl$_1$),-CO_2(C_{1-6}alkyl$_1$), -CO(C_{1-6}alkyl$_1$) and $-SO_{0-2}(C_{1-6}$alkyl$_1$),

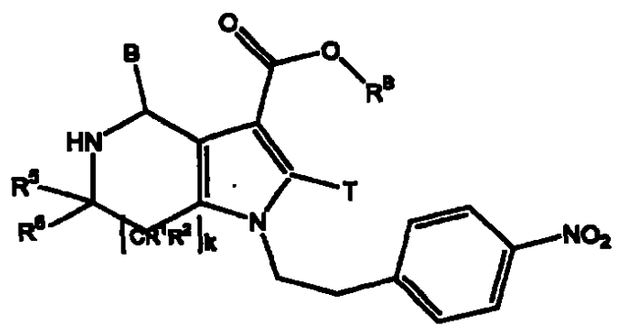
wherein C_{1-6}alkyl$_1$ is independently chosen at each occurrence and is straight branched or cyclic, may contain one or two

double or triple bonds, and is unsubstituted or substituted with one or more substituents selected from: hydroxy, oxo, halogen, amino, cyano, nitro, alkoxy, carbocylic or heterocyclic group, $-COOH$, $-SO_2NH_2$, $-SO_2NH(C_{1-4}alkyl)$, $-SO_2N(C_{1-4}alkyl)(C_{1-4}alkyl)$, $-N(C_{1-4}alkyl)CO(C_{1-4}alkyl)$, $N(C_{1-4}alkyl)CO_2(C_{1-4}alkyl)$, $-NHSO_2(alkyl)$, $-N(C_{1-4}alkyl)SO_2(C_{1-4}alkyl)$, $-SO_2NHCO(C_{1-4}alkyl)$, $-CONHSO_2(C_{1-4}alkyl)$, $-CONH(C_{1-4}alkyl)$, $-CON(C_{1-4}alkyl)(C_{1-4}alkyl)$, $-CO_2(C_{1-4}alkyl)$, $-CO(C_{1-4}alkyl)$, and $-SO_{0-2}(C_{1-4}alkyl)$;

T is chosen from hydrogen, halogen, hydroxy, amino, C_{1-6} alkyl, and C_{1-6} alkoxy; and

R^3 is chosen from hydrogen, methyl, ethyl and benzyl.

54. A compound of the formula:



wherein

B is $-SCH_3$ or $-NH(CH_2)CH(OCH_3)_2$;

R^1 and R^2 are independently chosen at each occurrence from hydrogen, halogen, hydroxy, cyano, nitro, amino, haloalkyl, mono or diamino(C_{1-6})alkyl, C_{1-6} alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl and C_{1-6} alkoxy, and k is 0, 1, 2, or 3;

R^5 and R^6 independently chosen from hydrogen, halogen, hydroxy, nitro, cyano, $C_{1-6}alkyl_1$, amino, -COOH, $-O(C_{1-6}alkyl_1)$, $-NH(C_{1-6}alkyl_1)$, $-N(C_{1-6}alkyl_1)(C_{1-6}alkyl_1)$, $-SO_2NH_2$, $-SO_2NH(C_{1-6}alkyl_1)$, $-SO_2N(C_{1-6}alkyl_1)(C_{1-6}alkyl_1)$, $-N(C_{1-6}alkyl_1)CO(C_{1-6}alkyl_1)$, $N(C_{1-6}alkyl_1)CO_2(C_{1-6}alkyl_1)$, $-NHSO_2(C_{1-6}alkyl_1)$, $-N(C_{1-6}alkyl_1)SO_2(C_{1-6}alkyl_1)$, $-SO_2NHCO(C_{1-6}alkyl_1)$, $-CONHSO_2(C_{1-6}alkyl_1)$, $-CONH(C_{1-6}alkyl_1)$, $-CON(C_{1-6}alkyl_1)(C_{1-6}alkyl_1)$, $-CO_2(C_{1-6}alkyl_1)$, $-CO(C_{1-6}alkyl_1)$ and $-SO_{0-2}(C_{1-6}alkyl_1)$,

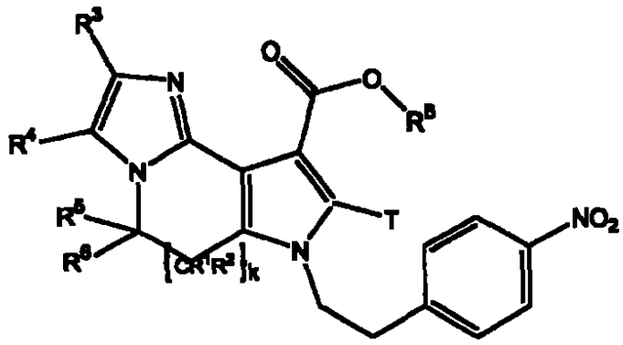
wherein $C_{1-6}alkyl_1$ is independently chosen at each occurrence and is straight branched or cyclic, may contain one or two double or triple bonds, and is unsubstituted or substituted with one or more substituents selected from: hydroxy, oxo, halogen, amino, cyano, nitro, alkoxy, carbocylic or heterocyclic group, -COOH, $-SO_2NH_2$, $-SO_2NH(C_{1-4}alkyl)$, $-SO_2N(C_{1-4}alkyl)(C_{1-4}alkyl)$, $-N(C_{1-4}alkyl)CO(C_{1-4}alkyl)$, $N(C_{1-4}alkyl)CO_2(C_{1-4}alkyl)$, $-NHSO_2(alkyl)$, $-N(C_{1-4}alkyl)SO_2(C_{1-4}alkyl)$, $-SO_2NHCO(C_{1-4}alkyl)$, $-CONHSO_2(C_{1-4}alkyl)$, $-CONH(C_{1-}$

$_4$alkyl), -CON(C_{1-6}alkyl)(C_{1-4}alkyl), -CO_2(C_{1-4}alkyl), -CO(C_{1-4}alkyl), and -SO_{0-2}(C_{1-6}alkyl);

T is chosen from hydrogen, halogen, hydroxy, amino, C_{1-6} alkyl, and C_{1-6} alkoxy; and

R^8 is chosen from hydrogen, methyl, ethyl and benzyl.

55. A compound of the formula:



wherein

R^1 and R^2 are independently chosen at each occurrence from hydrogen, halogen, hydroxy, cyano, nitro, amino, haloalkyl, mono or diamino(C_{1-6})alkyl, C_{1-6} alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl and C_{1-6} alkoxy, and k is 0, 1, 2, or 3;

R^5 and R^6 independently chosen from hydrogen, halogen, hydroxy, nitro, cyano, C_{1-6}alkyl$_1$, amino, -COOH, -O(C_{1-6}alkyl$_1$), -NH(C_{1-6}alkyl$_1$), -N(C_{1-6}alkyl$_1$)(C_{1-6}alkyl$_1$), -SO_2NH_2, -SO_2NH(C_{1-6}alkyl$_1$), -SO_2N(C_{1-6}alkyl$_1$)(C_{1-6}alkyl$_1$), -N(C_{1-6}alkyl$_1$)CO(C_{1-6}alkyl$_1$), N(C_{1-6}alkyl$_1$)CO_2(C_{1-6}alkyl$_1$), -NHSO_2(C_{1-6}alkyl$_1$), -N(C_{1-6}alkyl$_1$)SO_2(C_{1-6}alkyl$_1$), -SO_2NHCO(C_{1-6}alkyl$_1$), -CONHSO_2(C_{1-

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$_6$alkyl$_1$), -CONH(C_{1-6}alkyl$_1$), -CON(C_{1-6}alkyl$_1$)(C_{1-6}alkyl$_1$),-CO_2(C_{1-6}alkyl$_1$), -CO(C_{1-6}alkyl$_1$) and -SO_{0-2}(C_{1-6}alkyl$_1$),

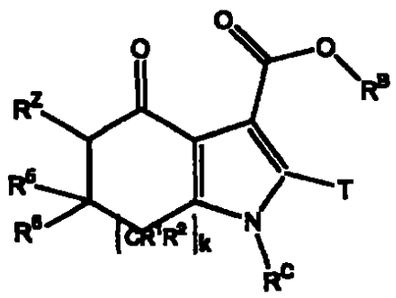
wherein C_{1-6}alkyl$_1$ is independently chosen at each occurrence and is straight branched or cyclic, may contain one or two double or triple bonds, and is unsubstituted or substituted with one or more substituents selected from: hydroxy, oxo, halogen, amino, cyano, nitro, alkoxy, carbocylic or heterocyclic group, -COOH, -SO_2NH_2, -SO_2NH(C_{1-4}alkyl), -SO_2N(C_{1-4}alkyl)(C_{1-4}alkyl), -N(C_{1-4}alkyl)CO(C_{1-4}alkyl), N(C_{1-4}alkyl)CO_2(C_{1-4}alkyl), -NHSO_2(alkyl), -N(C_{1-4}alkyl)SO_2(C_{1-4}alkyl), -SO_2NHCO(C_{1-4}alkyl), -CONHSO_2(C_{1-4}alkyl), -CONH(C_{1-4}alkyl), -CON(C_{1-4}alkyl)(C_{1-4}alkyl), -CO_2(C_{1-4}alkyl), -CO(C_{1-4}alkyl), and -SO_{0-2}(C_{1-4}alkyl);

T is chosen from hydrogen, halogen, hydroxy, amino, C_{1-6} alkyl, and C_{1-6} alkoxy; and

R^8 is chosen from hydrogen, methyl, ethyl and benzyl.

56. A compound of the formula

712 713



wherein:

k is 0, 1, 2, or 3;

R^B is chosen from hydrogen, methyl, ethyl and benzyl;

R^C is chosen from t-butoxycarbonyl, phenyl, alkylsulfonyl, and ethylcarbamoyl;

R^T is hydrogen or bromo;

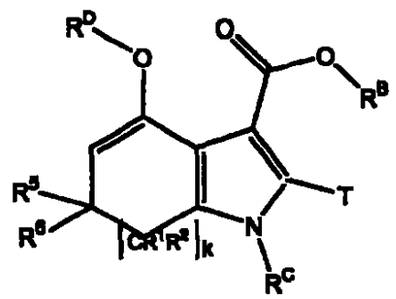
R^1 and R^2 are independently chosen at each occurrence from hydrogen, halogen, hydroxy, cyano, nitro, amino, haloalkyl, mono or diamino(C_{1-6})alkyl, C_{1-6} alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl and C_{1-6} alkoxy;

R^5 and R^6 independently chosen from hydrogen, halogen, hydroxy, nitro, cyano, $C_{1-6}alkyl_1$, amino, -COOH, $-O(C_{1-6}alkyl_1)$, $-NH(C_{1-6}alkyl_1)$, $-N(C_{1-6}alkyl_1)(C_{1-6}alkyl_1)$, $-SO_2NH_2$, $-SO_2NH(C_{1-6}alkyl_1)$, $-SO_2N(C_{1-6}alkyl_1)(C_{1-6}alkyl_1)$, $-N(C_{1-6}alkyl_1)CO(C_{1-6}alkyl_1)$, $N(C_{1-6}alkyl_1)CO_2(C_{1-6}alkyl_1)$, $-NHSO_2(C_{1-6}alkyl_1)$, $-N(C_{1-6}alkyl_1)SO_2(C_{1-6}alkyl_1)$, $-SO_2NHCO(C_{1-6}alkyl_1)$, $-CONHSO_2(C_{1-6}alkyl_1)$, $-CONH(C_{1-6}alkyl_1)$, $-CON(C_{1-6}alkyl_1)(C_{1-6}alkyl_1)$, $-CO_2(C_{1-6}alkyl_1)$, $-CO(C_{1-6}alkyl_1)$ and $-SO_{0-2}(C_{1-6}alkyl_1)$,

wherein $C_{1-6}alkyl_1$ is independently chosen at each occurrence and is straight branched or cyclic, may contain one or two double or triple bonds, and is unsubstituted or substituted with one or more substituents selected from: hydroxy, oxo, halogen, amino, cyano, nitro, alkoxy, carbocylic or heterocyclic group, $-COOH$, $-SO_2NH_2$, $-SO_2NH(C_{1-4}alkyl)$, $-SO_2N(C_{1-4}alkyl)(C_{1-4}alkyl)$, $-N(C_{1-4}alkyl)CO(C_{1-4}alkyl)$, $N(C_{1-4}alkyl)CO_2(C_{1-4}alkyl)$, $-NHSO_2(alkyl)$, $-N(C_{1-4}alkyl)SO_2(C_{1-4}alkyl)$, $-SO_2NHCO(C_{1-4}alkyl)$, $-CONHSO_2(C_{1-4}alkyl)$, $-CONH(C_{1-4}alkyl)$, $-CON(C_{1-4}alkyl)(C_{1-4}alkyl)$, $-CO_2(C_{1-4}alkyl)$, $-CO(C_{1-4}alkyl)$, and $-SO_{0-2}(C_{1-4}alkyl)$; and

T is chosen from hydrogen, halogen, hydroxy, amino, C_{1-6} alkyl, and C_{1-6} alkoxy.

57. A compound of the formula



wherein:

k is 0, 1, 2, or 3;

R^B is chosen from hydrogen, methyl, ethyl and benzyl;

R^c is chosen from t-butoxycarbonyl, phenyl, phenylsulfonyl, alkylsulfonyl, and ethylcarbamoyl;

R^D is chosen from trimethylsilyl, silylmethyl ether, and t-butyldimethylsilyl;

R^1 and R^2 are independently chosen at each occurrence from hydrogen, halogen, hydroxy, cyano, nitro, amino, haloalkyl, mono or diamino(C_{1-6})alkyl, C_{1-6} alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl and C_{1-6} alkoxy;

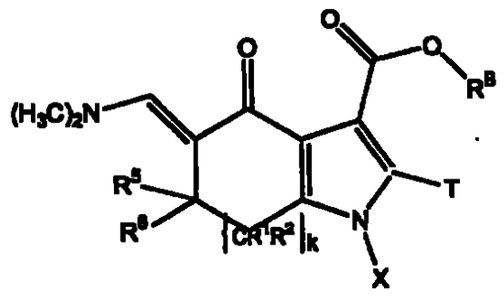
R^5 and R^6 independently chosen from hydrogen, halogen, hydroxy, nitro, cyano, $C_{1-6}alkyl_1$, amino, -COOH, $-O(C_{1-6}alkyl_1)$, $-NH(C_{1-6}alkyl_1)$, $-N(C_{1-6}alkyl_1)(C_{1-6}alkyl_1)$, $-SO_2NH_2$, $-SO_2NH(C_{1-6}alkyl_1)$, $-SO_2N(C_{1-6}alkyl_1)(C_{1-6}alkyl_1)$, $-N(C_{1-6}alkyl_1)CO(C_{1-6}alkyl_1)$, $N(C_{1-6}alkyl_1)CO_2(C_{1-6}alkyl_1)$, $-NHSO_2(C_{1-6}alkyl_1)$, $-N(C_{1-6}alkyl_1)SO_2(C_{1-6}alkyl_1)$, $-SO_2NHCO(C_{1-6}alkyl_1)$, $-CONHSO_2(C_{1-6}alkyl_1)$, $-CONH(C_{1-6}alkyl_1)$, $-CON(C_{1-6}alkyl_1)(C_{1-6}alkyl_1)$, $-CO_2(C_{1-6}alkyl_1)$, $-CO(C_{1-6}alkyl_1)$ and $-SO_{0-2}(C_{1-6}alkyl_1)$,

wherein $C_{1-6}alkyl_1$ is independently chosen at each occurrence and is straight branched or cyclic, may contain one or two double or triple bonds, and is unsubstituted or substituted with one or more substituents selected from: hydroxy, oxo, halogen, amino, cyano, nitro, alkoxy, carbocylic or heterocyclic group, -COOH, $-SO_2NH_2$, $-SO_2NH(C_{1-4}alkyl)$, -

$SO_2N(C_{1-4}alkyl)(C_{1-4}alkyl)$, $-N(C_{1-4}alkyl)CO(C_{1-4}alkyl)$, $N(C_{1-4}alkyl)CO_2(C_{1-4}alkyl)$, $-NHSO_2(alkyl)$, $-N(C_{1-4}alkyl)SO_2(C_{1-4}alkyl)$, $-SO_2NHCO(C_{1-4}alkyl)$, $-CONHSO_2(C_{1-4}alkyl)$, $-CONH(C_{1-4}alkyl)$, $-CON(C_{1-4}alkyl)(C_{1-4}alkyl)$, $-CO_2(C_{1-4}alkyl)$, $-CO(C_{1-4}alkyl)$, and $-SO_{0-2}(C_{1-4}alkyl)$; and

T is chosen from hydrogen, halogen, hydroxy, amino, C_{1-6} alkyl, and C_{1-6} alkoxy.

58. A compound of the formula



wherein:

k is 0, 1, 2, or 3;

R^3 is chosen from hydrogen, methyl, ethyl and benzyl;

X is chosen from hydrogen, hydroxy, amino, C_{1-6} alkyl, and C_{1-6}alkoxy;

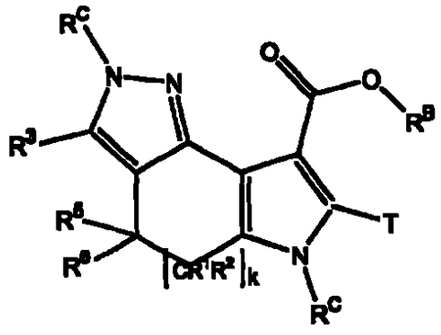
R^1 and R^2 are independently chosen at each occurrence from hydrogen, halogen, hydroxy, cyano, nitro, amino, haloalkyl, mono or diamino(C_{1-6})alkyl, C_{1-6} alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl and C_{1-6} alkoxy;

R^5 and R^6 independently chosen from hydrogen, halogen, hydroxy, nitro, cyano, $C_{1-6}alkyl_1$, amino, -COOH, $-O(C_{1-6}alkyl_1)$, $-NH(C_{1-6}alkyl_1)$, $-N(C_{1-6}alkyl_1)(C_{1-6}alkyl_1)$, $-SO_2NH_2$, $-SO_2NH(C_{1-6}alkyl_1)$, $-SO_2N(C_{1-6}alkyl_1)(C_{1-6}alkyl_1)$, $-N(C_{1-6}alkyl_1)CO(C_{1-6}alkyl_1)$, $N(C_{1-6}alkyl_1)CO_2(C_{1-6}alkyl_1)$, $-NHSO_2(C_{1-6}alkyl_1)$, $-N(C_{1-6}alkyl_1)SO_2(C_{1-6}alkyl_1)$, $-SO_2NHCO(C_{1-6}alkyl_1)$, $-CONHSO_2(C_{1-6}alkyl_1)$, $-CONH(C_{1-6}alkyl_1)$, $-CON(C_{1-6}alkyl_1)(C_{1-6}alkyl_1)$, $-CO_2(C_{1-6}alkyl_1)$, $-CO(C_{1-6}alkyl_1)$ and $-SO_{0-2}(C_{1-6}alkyl_1)$,

wherein $C_{1-6}alkyl_1$ is independently chosen at each occurrence and is straight branched or cyclic, may contain one or two double or triple bonds, and is unsubstituted or substituted with one or more substituents selected from: hydroxy, oxo, halogen, amino, cyano, nitro, alkoxy, carbocylic or heterocyclic group, -COOH, $-SO_2NH_2$, $-SO_2NH(C_{1-4}alkyl)$, $-SO_2N(C_{1-4}alkyl)(C_{1-4}alkyl)$, $-N(C_{1-4}alkyl)CO(C_{1-4}alkyl)$, $N(C_{1-4}alkyl)CO_2(C_{1-4}alkyl)$, $-NHSO_2(alkyl)$, $-N(C_{1-4}alkyl)SO_2(C_{1-4}alkyl)$, $-SO_2NHCO(C_{1-4}alkyl)$, $-CONHSO_2(C_{1-4}alkyl)$, $-CONH(C_{1-4}alkyl)$, $-CON(C_{1-4}alkyl)(C_{1-4}alkyl)$, $-CO_2(C_{1-4}alkyl)$, $-CO(C_{1-4}alkyl)$, and $-SO_{0-2}(C_{1-4}alkyl)$; and

T is chosen from hydrogen, halogen, hydroxy, amino, C_{1-6} alkyl, and C_{1-6} alkoxy.

59. A compound of the formula



wherein:

k is 0, 1, 2, or 3;

R^B is chosen from hydrogen, methyl, ethyl and benzyl;

R^C is independently chosen at each occurrence from t-butoxycarbonyl, phenyl, phenylsulfonyl, alkylsulfonyl, and ethylcarbamoyl;

R^1 and R^2 are independently chosen at each occurrence from hydrogen, halogen, hydroxy, cyano, nitro, amino, haloalkyl, mono or diamino(C_{1-6})alkyl, C_{1-6} alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl and C_{1-6} alkoxy;

R^3 is defined the same as R^5 and R^6;

R^5 and R^6 independently chosen from hydrogen, halogen, hydroxy, nitro, cyano, $C_{1-6}alkyl_1$, amino, -COOH, $-O(C_{1-6}alkyl_1)$, $-NH(C_{1-6}alkyl_1)$, $-N(C_{1-6}alkyl_1)(C_{1-6}alkyl_1)$, $-SO_2NH_2$, $-SO_2NH(C_{1-6}alkyl_1)$, $-SO_2N(C_{1-6}alkyl_1)(C_{1-6}alkyl_1)$, $-N(C_{1-6}alkyl_1)CO(C_{1-6}alkyl_1)$, $N(C_{1-6}alkyl_1)CO_2(C_{1-6}alkyl_1)$, $-NHSO_2(C_{1-6}alkyl_1)$, $-N(C_{1-6}alkyl_1)SO_2(C_{1-6}alkyl_1)$, $-SO_2NHCO(C_{1-6}alkyl_1)$, $-CONHSO_2(C_{1-}$

$_6$alkyl$_1$), -CONH(C_{1-6}alkyl$_1$), -CON(C_{1-6}alkyl$_1$)(C_{1-6}alkyl$_1$),-CO_2(C_{1-6}alkyl$_1$), -CO(C_{1-6}alkyl$_1$) and -SO_{0-2}(C_{1-6}alkyl$_1$),

wherein C_{1-6}alkyl$_1$ is independently chosen at each occurrence and is straight branched or cyclic, may contain one or two double or triple bonds, and is unsubstituted or substituted with one or more substituents selected from: hydroxy, oxo, halogen, amino, cyano, nitro, alkoxy, carbocylic or heterocyclic group, -COOH, -SO_2NH_2, -SO_2NH(C_{1-4}alkyl), -SO_2N(C_{1-4}alkyl)(C_{1-4}alkyl), -N(C_{1-4}alkyl)CO(C_{1-4}alkyl), N(C_{1-4}alkyl)CO_2(C_{1-4}alkyl), -NHSO_2(alkyl), -N(C_{1-4}alkyl)SO_2(C_{1-4}alkyl), -SO_2NHCO(C_{1-4}alkyl), -CONHSO_2(C_{1-4}alkyl), -CONH(C_{1-4}alkyl), -CON(C_{1-4}alkyl)(C_{1-4}alkyl), -CO_2(C_{1-4}alkyl), -CO(C_{1-4}alkyl), and -SO_{0-2}(C_{1-4}alkyl); and

T is chosen from hydrogen, halogen, hydroxy, amino, C_{1-6} alkyl, and C_{1-6} alkoxy.

60. A compound according to any one of Claims 1 to 36 for use in therapeutic treatment of a disease or disorder associated with pathogenic $GABA_A$ receptor signalling.

61. A pharmaceutical composition comprising a compound according to one of Claims 1 to 36 combined with at least one pharmaceutically acceptable carrier or excipient.

62. A method for the treatment of a disease or disorder associated with pathogenic $GABA_A$ receptor signalling, said method comprising administering to a patient in need of such treatment or prevention an effective amount of a compound according to any one of Claims 1 to 36.

63. A method according to Claim 62 wherein said disease or disorder associated with pathogenic $GABA_A$ receptor signalling is anxiety, depression, a sleep disorder, or cognitive impairment.

64. A method according to Claim 62 wherein the disease or disorder associated with pathogenic $GABA_A$ receptor signalling is Alzheimers disease, attention deficit disorder (ADD) or attention deficit hyperactivity disorder (ADHD).

65. The use of a compound according any one of Claims 1 to 36 for the manufacture of a medicament for the treatment of a disease or disorder associated with pathogenic $GABA_A$ receptor signalling.

WO 02/23599 PCT/GB01/04160

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66. The use of a compound according any one of Claims 1 to 36 for the manufacture of a medicament for the treatment of anxiety, depression, sleep disorders, or cognitive impairment.

67. A method for localizing $GABA_A$ receptors in a tissue sample comprising:
contacting with the sample a detectably-labeled compound according to any one of Claims 1 to 36 under conditions that permit binding of the compound to $GABA_A$ receptors, washing the sample to remove unbound compound, and detecting the bound compound.

68. A method of inhibiting the binding of a benzodiazepine compound to a $GABA_A$ receptor, said method comprising contacting a solution of a compound according to any one of Claims 1 to 36 with cells expressing such a receptor in the presence of the benzodiazepine, wherein the compound is present in the solution at a concentration sufficient to inhibit the binding a benzodiazepine compound to a $GABA_A$ receptor *in vitro*.

69. A method for altering the signal-transducing activity of $GABA_A$ receptors, said method comprising exposing cells expressing such receptors to a solution of a compound according

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to any one of Claims 1 to 36 at a concentration in the solution sufficient to inhibit RO15-1788 binding to cells expressing a cloned human $GABA_A$ receptor *in vitro*.

70. A packaged pharmaceutical composition comprising the pharmaceutical composition of Claim 24 in a container and instructions for using the composition to treat a patient suffering from a disorder responsive to agonism, inverse agonism or antagonism of the $GABA_A$ receptor.

71. The packaged pharmaceutical composition of claim 70, wherein said instructions indicate that said patient is suffering from one or more of anxiety, depression, a sleep disorder, and cognitive impairment.

72. A compound according to claim any one of Claims 1 to 36 wherein in a assay of $GABA_A$ receptor binding the compound exhibits a K_i at a $GABA_A$ receptor of 1 micromolar or less.

73. A compound according to claim 72 the compound exhibits a K_i of 100 nanomolar or less.

74. A compound according to claim 72 wherein compound exhibits a K_i of 10 nanomolar or less.

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ABSTRACT

Novel heterocyclic compounds such as 5,6-Dihydro-4H-1,3a,6-triaza-as-indacenes,3-thia-1,7-diaza-cyclopenta[e]azulene-9-carboxylic acids, 4,5,6,7-tetrahydro-1-oxa-2,7-diaza-cyclopenta[e]azulene -9-carboxylic acids, 3,8,10-triaza-benzo[e]azulene-1-carboxylic acids, 1-oxa-2,7-diaza-cyclopenta[e]azulene-9-carboxylic acids, 1,3,7-triaza-cyclopenta[e]azulene-9-carboxylic acid phenyl amides and related compounds are disclosed. These compounds are highly selective agonists, antagonists or inverse agonists for $GABA_A$ brain receptors or prodrugs of agonists, antagonists or inverse agonists for $GABA_A$ brain receptors and are therefore useful in the diagnosis and treatment of anxiety, depression, Down Syndrome, sleep and seizure disorders, overdose with benzodiazepine drugs and for enhancement of memory. Pharmaceutical compositions, including packaged pharmaceutical compositions, are further provided. Compounds of the invention are also useful as probes for the localization of $GABA_A$ receptors in tissue samples.

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LOS ESTADOS UNIDOS DE AMERICA

A TODO AQUEL A QUIEN CONCIERNA LO PRESENTE

DEPARTAMENTO DE COMERCIO DE LOS ESTADOS UNIDOS

Oficina de Patentes y Marcas de los Estados Unidos

19 de noviembre de 2001

LA PRESENTE ES PARA CERTIFICAR QUE ADJUNTA A LA MISMA HAY UNA COPIA FIEL DE LOS REGISTROS DE LA OFICINA DE PATENTES Y MARCAS DE LOS ESTADOS UNIDOS DE LOS DOCUMENTOS DE LA SOLICITUD DE PATENTE IDENTIFICADA EN LO QUE SIGUE, QUE CUMPLEN LOS REQUISITOS PARA OTORGARLE UNA FECHA DE PRESENTACIÓN BAJO 35 USC 111.

NÚMERO DE SOLICITUD: 60/223,669
FECHA DE PRESENTACIÓN: 07 de agosto de 2000

Por la Autoridad del
COMISARIO DE PATENTES Y MARCAS

W. MONTGOMERY

Oficial certificador

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Compuestos Heterocíclicos como Ligandos de los Receptores $GABA_A$

Campo de la Invención

Esta invención se refiere a compuestos heterocíclicos tales como 5,6-dihidro-4H-1,3a,6-triaza-as-indacenos, ácidos 3-tia-1,7-diaza- ciclopenta [e]azulen -9- carboxílicos, ácidos 4,5,6,7-tetrahidro-1-oxa- 2,7-diaza- ciclopenta [e]azulen-1-carboxílicos, ácidos 3,8,10- triaza- benzo [e] azulen -1-carboxílicos, ácidos 1-oxa-2,7-diaza-ciclopenta[e]azulen-9-carboxílicos, fenil amida de ácido 1,3,7-triaza-ciclopenta[e]azulen-9-carboxílico y compuestos relacionados, y más específicamente a aquellos compuestos que se enlazan con gran selectividad y gran afinidad al sitio benzodiazepina de los receptores GABAA. Esta invención también se refiere a las composiciones farmacéuticas que comprenden dichos compuestos y al uso de dichos compuestos en el tratamiento de ciertas enfermedades del sistema nervioso central (CNS). Esta invención también se relaciona con el uso de estos compuestos heterocíclicos en combinación con uno o más de otros gentes CNS para potenciar los efectos de los otros agentes CNS. Adicionalmente, esta invención se relaciona con el uso de dichos compuestos como exploratorios para la localización de receptores GABAA en secciones de tejido.

Antecedentes

La superfamilia de receptores $GABA_A$ representa una de las clases de receptores mediante la cual actúa el neurotransmisor inhibidor principal, ácido γ-aminobutírico, o GABA. Distribuido ampliamente aunque de manera no equitativa, a través del cerebro de los mamíferos, el GABA transmite muchas de sus acciones a través de un complejo de proteínas denominado receptor $GABA_A$, el cual causa alteración en la conductancia del cloruro y polarización de la membrana.

Se ha caracterizado un número de ADNcs de las subunidades de receptor $GABA_A$. Hasta el momento, se han identificado por lo

menos las subunidades 6α, 3β, 3γ, 1ε, 1δ y 2ρ. Por lo general, se acepta que los receptores $GABA_A$ nativos están típicamente compuestos por subunidades 2α, 2β, y 1γ (Pritchett & Seeburg *Science* 1989; 245:1389-1392 y Knight y otros, *Recept. Channels* 1998; 6:1-18). Los resultados de evidencias tales como distribución del mensaje, localización del genoma y estudio bioquímico sugieren que las combinaciones de receptor que ocurren naturalmente, de manera principal, son $\alpha_1\beta_2\gamma_2$, $\alpha_2\beta_3\gamma_2$, $\alpha_3\beta_3\gamma_2$, y $\alpha_5\beta_3\gamma_2$ (Mohler y otros, *Neuroch. Res.* 1995; 20(5):. 631 - 636).

Las benzodiazepinas ejercen sus acciones farmacológicas interactuando con los sitios de enlace de benzodiazepina asociados al receptor $GABA_A$. Además del sitio benzodiazepina, el receptor $GABA_A$ contiene sitios de interacción para diversas clases de fármacos. Estos incluyen un sitio de enlace de esteroide, un sitio picrotoxina y el sitio barbiturato. El sitio benzodiazepina del receptor $GABA_A$ es un sitio distinto del complejo receptor que no se superpone al sitio de interacción para GABA o para otras clases de fármacos que se enlazan con el receptor (véase, por ejemplo, Cooper, y otros, The Biochemical Basis of Neuropharmacology, 6ta ed., 1991, pp. 145-148, Oxford University Press, Nueva York). Estudios electrofisiológicos indicaron que la acción principal de las benzodiazepinas es el incremento de inhibición GABAérgica. Los compuestos que, selectivamente, se enlazan al sitio benzodiazepina e incrementan la capacidad de GABA para abrir canales de receptor $GABA_A$ son agonistas de los receptores GABA. Otros compuestos que interactúan con el mismo sitio pero que modulan negativamente la acción del GABA se denominan agonistas inversos. Los compuestos que pertenecen a una tercera clase se enlazan selectivamente al sitio benzodiazepina, e incluso tienen un pequeño efecto, o ninguno, en la actividad GABA, pero pueden bloquear la acción de los agonistas o agonistas inversos del receptor $GABA_A$ que actúan en este sitio. A estos compuestos se les denomina antagonistas.

Los efectos alostéricos modulatorios importantes de los fármacos que actúan en el sitio benzodiazepina se descubrieron al inicio y la distribución de actividades a subtipos de receptor diferente ha sido una zona de intenso descubrimiento

farmacológico. Los agonistas que actúan en el sitio benzodiazepina son conocidos por mostrar efectos ansiolíticos, sedantes e hipnóticos, mientras que los compuestos que actúan como agonistas inversos en este sitio provocan efectos ansiogénicos, incremento de la cognición y efectos proconvulsivos. Mientras que las benzodiazepinas tienen una larga historia de uso farmacéutico como ansiolíticos, estos compuestos a menudo muestran un número de efectos colaterales no deseados. Estos pueden incluir deficiencia cognitiva, sedación, ataxia, potenciación de los efectos del etanol y una tendencia a la tolerancia y dependencia al fármaco.

Los ligandos selectivos $GABA_A$ también pueden actuar para potenciar los efectos de ciertos otros compuestos CNS activos. Por ejemplo, existe evidencia que los inhibidores de reabsorción selectiva de serotonina (SSREs) pueden mostrar una actividad antidepresiva mayor cuando se usan en combinación con ligandos selectivos $GABA_A$ que cuando se usan solos.

Descripción de la técnica relacionada

Liste aquí cualquier referencia altamente relevante y describa brevemente proporcionando estructuras que sean de ayuda

RESUMEN DE LA INVENCIÓN

Esta invención proporciona compuestos heterocíclicos como 5,6-Dihidro- 4H-1,3a,6-triaza-as- indacenos y compuestos relativos, que enlazan con gran afinidad y gran selectividad al sitio de benzodiazepina del receptor $GABA_A$, incluyendo receptores $GABA_A$ humanos.

En consecuencia, la invención proporciona compuestos novedosos de la Fórmula I (que se muestran más adelante) y composiciones farmacéuticas que comprenden compuestos de Fórmula I.

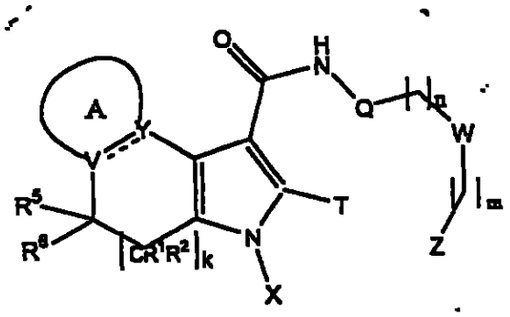
Asimismo, la invención comprende métodos para el tratamiento de pacientes que sufren ciertos desórdenes del CNS con una cantidad efectiva de un compuesto de la invención. El paciente puede ser un ser humano o un animal. El tratamiento de humanos, animales domésticos de compañía (mascotas) o ganado que sufren

ciertos desórdenes del CNS con una cantidad efectiva del compuesto de la invención está comprendido por la invención.

En un aspecto individual, la invención proporciona un método para potenciar las acciones de otros compuestos activos CNS. Este método comprende la administración de una cantidad efectiva del compuesto de la invención con otro compuesto activo en el CNS.

Adicionalmente, esta invención se refiere al uso de compuestos de la invención como ensayos para la localización de receptores $GABA_A$ en secciones de tejido.

En consecuencia, un amplio aspecto de la invención se refiere a compuestos de Fórmula A:



Fórmula A

O una sal farmacéuticamente aceptable de la misma, en donde:

R1 y R2 independientemente se seleccionan en cada ocasión de hidrógeno, halógeno, hidroxi, ciano, nitro, amino, alquilo, alquenilo, alquinilo, haloalquilo, mono- o dialquilamino, alcoxi, y k es 0, 1, 2, o 3;



El grupo representa un anillo heterocíclico opcionalmente aromático, insaturado o saturado que contiene al menos un átomo de nitrógeno, oxígeno o azufre, en donde el enlace V----Y es un enlace sencillo, doble o aromático;

V es nitrógeno, carbono, o CH;

Y es carbono o CH;

R5 y R6 pueden ser tomados juntos para formar un grupo carbonilo; o

R5 y R6 se seleccionan independientemente de hidrógeno, halógeno, hidroxi, nitro, ciano, alquil1, amino, -COOH, $-O(alquil_1)$, $-SO_2NH_2$, $-SO_2NH(alquil_1)$, $-SO_2N(alquil_1)(alquil_1)$, $-N(alquil_1)CO(alquil_1)$, $-N(alquil_1)CO_2(alquil_1)$, $-NHSO_2(alquil_1)$, $-N(alquil_1)SO_2(alquil_1)$, $-SO_2NHCO(alquil_1)$, $-CONHSO_2(alquil_1)$,

-CONH(alquil$_1$), -CON(alquil$_1$)(alquil$_1$), -CO_2(alquil$_1$), -CO(alquil$_1$), -SO_{0-2}(alquil$_1$), y opcionalmente un grupo arilo carbocíclico o heteroarilo opcionalmente sustituido que tiene de 1 a 3 anillos, 3 a 8 miembros en cada anillo y de 1 a 3 heteroátomos;

En donde alquil$_1$ es independientemente en cada ocasión cíclico, recto o ramificado, puede contener uno o dos enlaces dobles o triples, y es no sustituido o se sustituye con uno o más sustituyentes seleccionados a partir de hidroxi, oxo, halógeno, amino, ciano, nitro, alcoxi, -COOH, -SO_2NH_2, -SO_2NH(alquilo), -SO_2N(alquil)(alquilo), -N(alquil)CO(alquilo), -N(alquil) CO_2(alquilo), -$NHSO_2$ (alquilo), -N(alquil) SO_2(alquilo), -SO_2NHCO(alquilo), -$CONHSO_2$(alquilo), -CONH(alquilo), -CON(alquil) (alquilo), -CO_2(alquilo), -CO(alquilo), -SO_{0-2}(alquilo);

X es hidrógeno, hidroxi, amino, alquilo, o alcoxi;

T es hidrógeno, halógeno, hidroxi, amino, alquilo, y alcoxi;

Q es un grupo carbocíclico o heteroarilo opcionalmente sustituido que tiene de 1 a 3 anillos, de 3 a 8 miembros en cada anillo, y de 1 a 3 heteroátomos;

W es hidrógeno, oxígeno, nitrógeno, azufre, o CR^7R^8, en donde R^7 y R^8 son iguales o diferentes y representan hidrógeno, alquilo de cadena recta o ramificada, o R^7 y R^8 pueden tomarse juntos para representar una porción cíclica que tiene de 3 a 7 átomos de carbono;

Z es hidrógeno, hidroxi, alcoxi de cadena recta o ramificada, cicloalquilo, cicloalquil(alcoxi), amino, mono- o dialquilamino, o NR^9COR^{10} en donde R^9 y R^{10} son iguales o diferentes y representan hidrógeno o alquilo de cadena recta o ramificada, o R^9 y R^{10} se juntan para formar un anillo cicloalquilo, o

Z es un grupo arilo carbocíclico o heteroarilo opcionalmente sustituido, que tiene de 1 a 3 anillos, de 3 a 8 miembros en cada anillo y de 1 a 3 heteroátomos;

$(\ )_m$ y $(\ )_n$ independientemente representan cadenas de carbono que pueden estar sustituidas con hidrógeno, halógeno, ciano,

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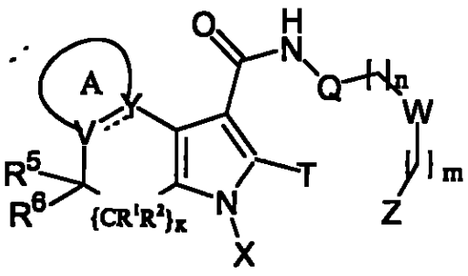
nitro, amino, mono- o dialquilamino, alquenilo, alquinilo, alcoxi, trifluorometilo, trifluorometoxi, alquilo de cadena recta o ramificada, o cicloalquilo; y

m es 0, 1, 2, ó 3; y

n es 0, 1, 2, ó 3.

DESCRIPCIÓN DETALLADA DE LA INVENCIÓN

Además de los compuestos de Fórmula A, la invención también proporciona compuestos de Fórmula I

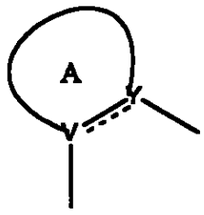


Fórmula I

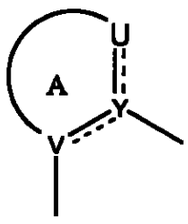
y las sales farmacéuticamente aceptables de los mismos, en donde:

R^1 y R^2 se eligen, independientemente, en cada caso, de hidrógeno, halógeno, hidroxi, ciano, nitro, amino, haloalquilo, mono o diamino(C_{1-6})alquilo, C_{1-6} alquilo, C_{2-6}alquenilo, C_{2-6}alquinilo y C_{1-6} alcoxi, y k es 0, 1, 2, ó 3;

El grupo



es un grupo de la fórmula:



que representa un anillo heterocíclico saturado, insaturado o aromático que contiene al menos un átomo de nitrógeno, oxígeno o

azufre, en donde los enlaces U----Y y V----Y pueden ser enlaces simples, dobles o aromáticos,

U es nitrógeno, NR^A, S, u O;

V es nitrógeno, carbono o CH;

Y es carbono, o CH;

Y el anillo heterocíclico saturado, insaturado o aromático se elige a partir de:

Tienilo, tiazolilo, piridilo, pirimidinilo, imidazolilo, pirazolilo, pirazinilo, piridizinilo, piperidinilo, oxazolilo, isoxazolilo, triazolilo simétrico y asimétrico, pirrolilo, furanilo, diazenilo, triazenilo, 1, 2, 4-triazolona, 4,5-dihidroimidazolilo, y 1,4,5,6-tetrahidropirimidinilo,

cada uno de los cuales se sustituye opcionalmente en cualquier nitrógeno disponible por R^A y opcionalmente se sustituye en cualquier carbono disponible por R^3 y R^4, en donde:

R^A se selecciona a partir de hidrógeno, $(C_1-C_6)alquil_1$, grupos arilo carbocíclico o heteroarilo opcionalmente sustituidos que tienen de 1 a 3 anillos, 3 a 8 miembros en cada anillo y de 1 a 3 heteroátomos;

R^5 y R^6 se eligen independientemente a partir de hidrógeno, halógeno, hidroxi, nitro, ciano, $C_{1-6}alquil_1$, amino, -COOH, $-O(C_{1-6}alquil_1)$, $-NH(C_{1-6}alquil_1)$, $-N(C_{1-6}alquil_1)(C_{1-6}alquil_1)$, $-SO_2NH_2$, $-SO_2NH(C_{1-6}alquil_1)$, $-SO_2N(C_{1-6}alquil_1)(C_{1-6}alquil_1)$, $-N(C_{1-6}alquil_1)CO(C_{1-6}alquil_1)$, $N(C_{1-6}alquil_1)CO_2(C_{1-6}alquil_1)$, $-NHSO_2(C_{1-6}alquil_1)$, $-N(C_{1-6}alquil_1)SO_2(C_{1-6}alquil_1)$, $-SO_2NHCO(C_{1-6}alquil_1)$, $-CONHSO_2(C_{1-6}alquil_1)$, $-CONH(C_{1-6}alquil_1)$, $-CON(C_{1-6}alquil_1)(C_{1-6}alquil_1)$, $-CO_2(C_{1-6}alquil_1)$, $-CO(C_{1-6}alquil_1)$ y $-SO_{0-2}(C_{1-6}alquil_1)$,

En donde $C_{1-6}alquil_1$ se elige independientemente en cada caso y es recto, ramificado o cíclico, puede contener uno o dos enlaces dobles o triples y es no sustituido o sustituido con uno o más sustituyentes seleccionados de: hidroxi, oxo, halógeno, amino, ciano, nitro, alcoxi, grupo carbocíclico o heterocíclico, -COOH, $-SO_2NH_2$, $-SO_2NH(C_{1-4}alquilo)$, $-SO_2N(C_{1-4}alquil)(C_{1-4}alquilo)$, $-N(C_{1-4}alquil)CO(C_{1-4}alquilo)$, $N(C_{1-4}alquil)CO_2(C_{1-4}alquilo)$, $-NHSO_2(alquilo)$, $-N(C_{1-4}alquil)SO_2(C_{1-4}alquilo)$, $-SO_2NHCO(C_{1-4}alquilo)$, $-CONHSO_2(C_{1-4}alquilo)$, $-CONH(C_{1-4}alquilo)$, $-CON(C_{1-4}$

$_4$alquil)(C_{1-4}alquilo), $-CO_2(C_{1-4}$alquilo), $-CO(C_{1-4}$alquilo), y $-SO_{0-2}(C_{1-4}$alquilo);

R^3 y R^4 se eligen, independientemente, en cada caso, y se definen igual que R^5 y R^6;

X se elige a partir de hidrógeno, hidroxi, amino, C_{1-6} alquilo, y C_{1-6}alcoxi;

T se elige a partir de hidrógeno, halógeno, hidroxi, amino, C_{1-6} alquilo, y C_{1-6} alcoxi;

Q es un fenilo, naftilo, quinolinilo, tienilo, piridilo, pirimidinilo, pirazinilo, oxazolilo, isoxazolilo, oxadiazolilo simétrico o asimétrico, tiadiazolilo simétrico o asimétrico, pirazolilo, furanilo, diazenilo, triazenilo, o triazolopirazinilo;

Cada uno de los cuales puede ser no sustituido o sustituido hasta con tres sustituyentes independientemente seleccionados de i) y ii), en donde

i) representa hidroxi, ciano, halógeno, nitro, amino, mono o di(C_{1-6})alquilamino, C_{2-6}alquenilo, C_{2-6}alquinilo, C_{1-6}alcoxi, trifluorometilo, o trifluorometoxi;

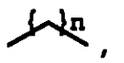
ii) representa cadena constante o ramificada C_{1-6}alquilo que opcionalmente contiene heteroátomos y opcionalmente se sustituye por uno o más grupos carbocíclicos o heterocíclicos;

W es hidrógeno, oxígeno, nitrógeno, azufre, o CR^7R^8, en donde R^7 y R^8 son iguales o diferentes, y representan hidrógeno, C_{1-6}alquilo de cadena recta o ramificada, o R^7 y R^8 se pueden tomar juntos para representar una porción cíclica que tiene 3-7 átomos de carbono;

Z es hidrógeno, hidroxi, C_{1-6}alcoxi de cadena recta o ramificada, C_{3-7}cicloalquil, C_{3-7}cicloalquil(C_{1-3}alcoxi), amino, mono o di C_{1-6}alquilamino, un grupo carbocíclico o heterocíclico, o NR^9CO^{10} en donde R^9 y R^{10} son iguales o diferentes y representan hidrógeno o C_{1-6}alquilo de cadena o ramificada, o R^9 y R^{10} se pueden unir para formar un anillo C_{3-7} cicloalquilo, o

Z es un fenilo, naftilo, quinolinilo, tienilo, tiazolilo, piridilo, pirimidinilo, imidazolilo, pirazolilo, pirazinilo,

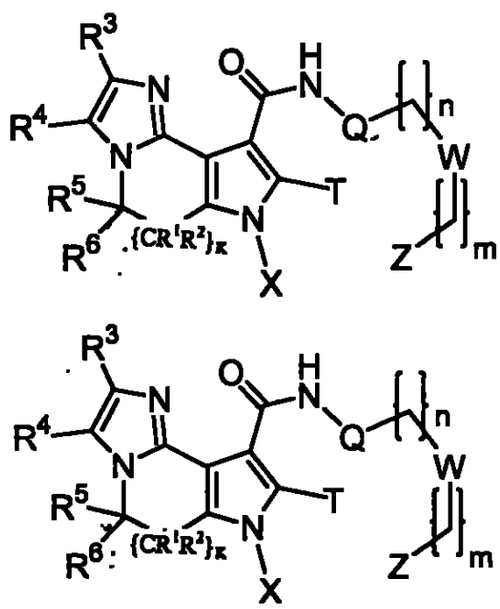
piridizinilo, piperidinilo, oxazolilo, isoxazolilo, tiadiazolilo simétrico o asimétrico, triazolilo simétrico o asimétrico, oxadiazolilo simétrico o asimétrico, pirrolilo, furanilo, pirimidinilo, diazenilo, triazenilo, 1, 2, 4-triazolona, 4,5-dihidroimidazolilo, o 1,4,5,6-grupo tetrahidropirimidinilo;

 y  representan una cadena de carbono opcionalmente sustituida por hidrógeno, halógeno, ciano, nitro, amino, mono o di C_{1-6}alquilamino, C_{2-6}alquenilo, C_{2-6}alquinilo, C_{1-6}alcoxi, trifluorometilo, trifluorometoxi, cadena recta o ramificada de C_{1-6}alquilo, o C_{3-7}cicloalquilo, y

m es 0, 1, 2, ó 3; y

n es 0, 1, 2, ó 3.

Además se proporciona compuestos de Fórmula II



Fórmula II

y las sales farmacéuticamente aceptables de los mismos,

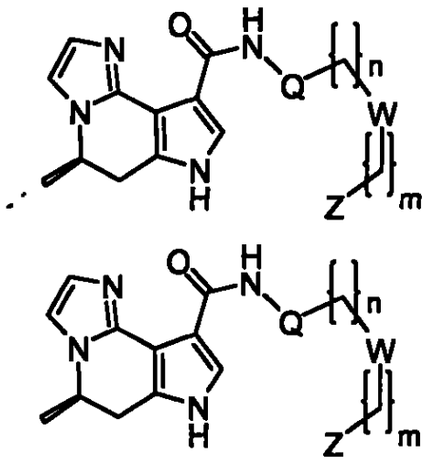
En donde las variables R^1, R^2, R^3, R^4, R^5, R^6, k, n, m, T, X, Q, W, y Z son como se definen para la Fórmula I.

Los compuestos de Fórmula II incluyen compuestos en donde R^1 y R^2 son hidrógeno; k es 1 ó 2;

R^3, R^4, R^5, y R^6, se eligen independientemente a partir de hidrógeno, halógeno, amino, hidroxi, metilo, etilo, metoxi y etoxi; y

X y T se seleccionan independientemente de hidrógeno, metilo, y etilo (compuestos de **Fórmula IIa**). También incluye compuestos de Fórmula II aquellos en donde R^1, R^2, R^3, R^4, R^5, y R^6 son hidrógeno, y k es 1 (compuestos de **Fórmula IIb**).

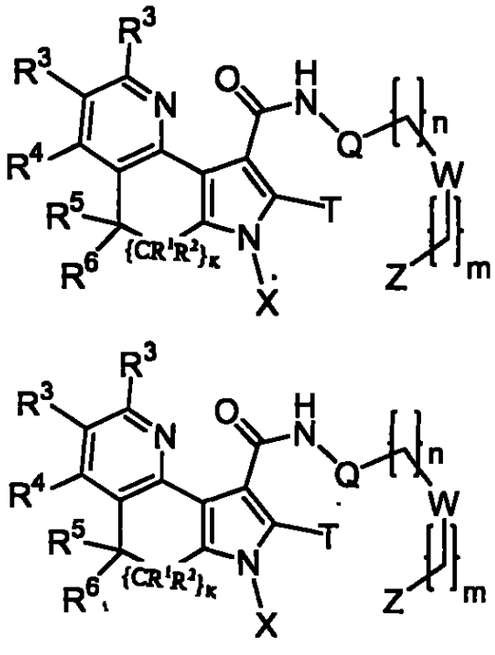
Los compuestos de Fórmula II particularmente recomendados son los compuestos de Fórmula IIc.



Fórmula IIc

En la Fórmula IIc (anterior) la conformación del grupo metilo en la posición 4 de la estructura de anillo indaceno denota (S) estereoquímica.

En otra materialización física, la invención incluye compuestos de Fórmula III.

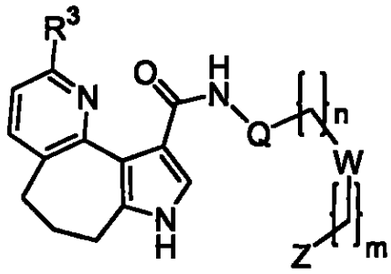


Fórmula III

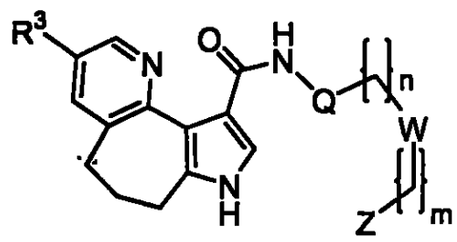
y las sales farmacéuticamente aceptables de los mismos, en donde las variables R^1, R^2, R^3, R^4, R^5, R^6, k, n, m, T, X, Q, W, y Z se definen como de Fórmula I.

La definición de la variable R^3 en la posición 2 del anillo piridilo es independiente de su definición en la posición 3.

Los compuestos específicos de Fórmula III son aquellos en donde k es 2 y R^1 y R^2 son hidrógeno (compuestos de **Fórmula IIIa**). Otros compuestos de Fórmula III son compuestos k es 2; R^1 y R^2 son hidrógeno; R^3, R^4, R^5, y R^6, se eligen independientemente en cada caso, de hidrógeno, halógeno, amino, hidroxi, metilo, etilo, metoxi y etoxi; y X y T se seleccionan independientemente de hidrógeno, metilo, y etilo (compuestos de **Fórmula IIIb**). Asimismo, se incluye en particular como compuestos de Fórmula III los compuestos de Fórmula IIIc y Fórmula IIId



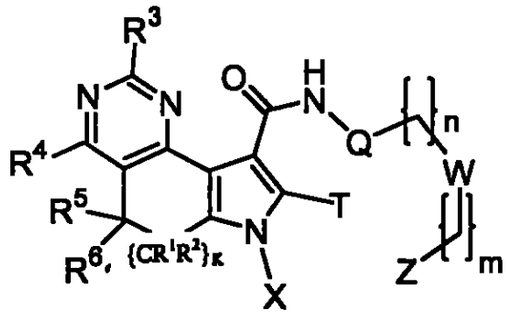
Formula IIIc

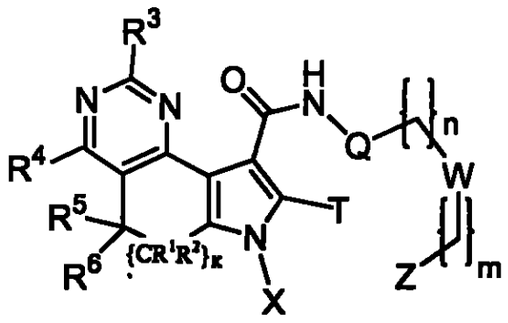


Formula IIId

En donde R^3 es hidrógeno o metilo.

La invención también incluye compuestos de Fórmula IV

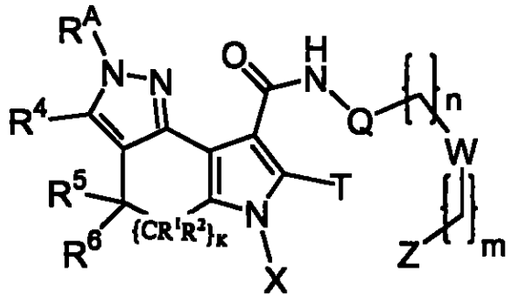




Fórmula IV

y las sales farmacéuticamente aceptables de los mismos, en donde las variables R^1, R^2, R^3, R^4, R^5, R^6, k, n, m, T, X, Q, W, y Z se encuentran como se define para la Fórmula I. Los compuestos particulares de Fórmula IV son aquellos compuestos en donde k es 2 y R^1 y R^2 son hidrógeno (compuestos de **Fórmula IVa**). Otros compuestos de Fórmula IV son aquellos compuestos en donde k es 2; R^1 y R^2 son hidrógeno; R^3, R^4, R^5, y R^6, se eligen independientemente, en cada caso, de hidrógeno, halógeno, amino, hidroxi, metilo, etilo, metoxi y etoxi; y X y T se seleccionan independientemente de hidrógeno, metilo y etilo (compuestos de **Fórmula IVb**). Los compuestos de Fórmula IV particularmente incluyen compuestos en donde k es 2 y R^1, R^2 R^3, R^4, R^5, y R^6 son todos hidrógeno (compuestos de **Fórmula IVc**).

En otra materialización física, el invento incluye compuestos de Fórmula V.

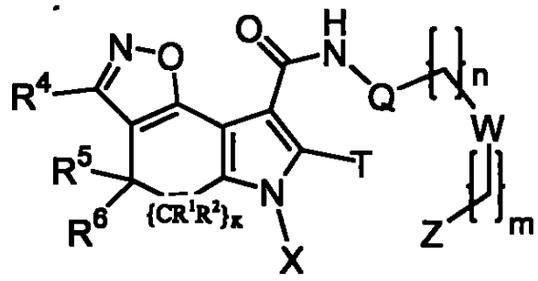


Fórmula V

y las sales farmacéuticamente aceptables de los mismos, en donde las variables R^1, R^2, R^A, R^4, R^5, R^6, k, n, m, T, X, Q, W, y Z son como en la Fórmula I. En una materialización física más específica, la invención incluye compuestos de Fórmula V en donde k es 2 y R^1 y R^2 son hidrógeno (compuestos de **Fórmula Va**). Inclusive otros compuestos de Fórmula V son aquellos compuestos en donde k es 2; R^1 y R^2 son hidrógeno; R^A es C_{1-6}alquilo, fenilo,

tienilo, piridilo, pirimidinilo, pirrolilo, o imidazolilo, R^3, R^4, R^5, y R^6, se eligen independientemente de hidrógeno, halógeno, amino, hidroxi, metilo, etilo, metoxi y etoxi; y X y T se seleccionan independientemente de hidrógeno, metilo y etilo (compuestos de **Fórmula Vb**). En una materialización física incluso más específica, la invención incluye compuestos de Fórmula V en donde k es 2, R^1, R^2, R^3, R^4, R^5, y R^6 son todos hidrógeno; y R^A es metilo, etilo, o piridilo.

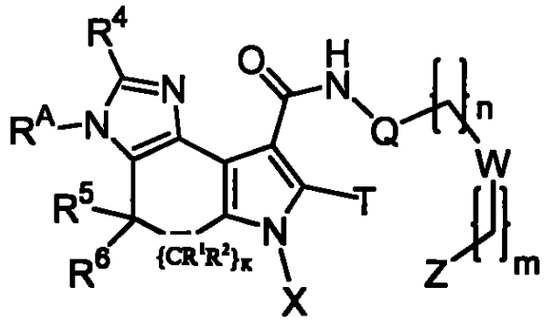
Aun otra materialización física de la invención incluye compuestos de Fórmula VI.



Fórmula VI

y las sales farmacéuticamente aceptables de los mismos, en donde las variables R^1, R^2, R^4, R^5, R^6, k, n, m, T, X, Q, W, y Z son como se define en la Fórmula I. Compuestos particulares de Fórmula VI son los compuestos en donde k es 2 y R^1 y R^2 son ambos hidrógeno (compuestos de **Fórmula VIa**). Otros compuestos de Fórmula VI son compuestos en donde k es 2; y R^1 y R^2 son ambos hidrógeno; R^4, R^5, y R^6, se eligen independientemente a partir de hidrógeno, halógeno, amino, hidroxi, metilo, etilo, metoxi y etoxi; y X y T se seleccionan independientemente de hidrógeno, metilo y etilo (compuestos de **Fórmula VIb**). Una materialización física en particular de la invención incluye compuestos de Fórmula VI en donde k es 2; y R^1, R^2, R^5, R^6, X y T son todos hidrógeno; y R^4 es metilo (compuestos de **Fórmula VIc**).

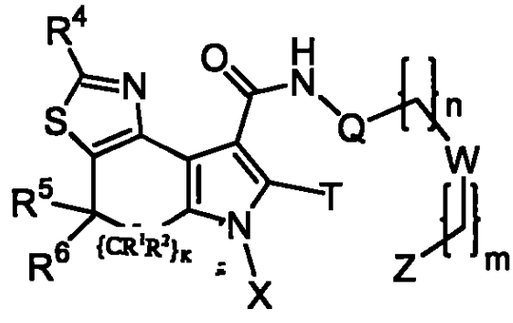
Incluso en otra materialización física, la invención proporciona compuestos de Fórmula VII



Fórmula VII

y las sales farmacéuticamente aceptables de los mismos, en donde las variables R^1, R^2, R^A, R^4, R^5, R^6, k, n, m, T, X, Q, W, y Z se definen como en la Fórmula I. Incluidos como compuestos de Fórmula VII se encuentran los compuestos en donde k es 2 y R^1 y R^2 son hidrógeno (compuestos de **Fórmula VIIa**). Más particularmente, la invención incluye compuestos de Fórmula VII en donde k es 2; R^1 y R^2 son hidrógeno; R^A es metilo, etilo, o piridilo; R^4, R^5, y R^6, se eligen independientemente a partir de hidrógeno, halógeno, amino, hidroxi, metilo, etilo, metoxi, y etoxi; y X y T se seleccionan independientemente de hidrógeno, metilo y etilo (compuestos de **Fórmula VIIb**). Asimismo, la invención incluye particularmente compuestos de Fórmula VII en donde k es 2; R^1, R^2, R^4, R^5, R^6, X y T son todos hidrógeno; y R^A es metilo (compuestos de **Fórmula VIIc**).

Asimismo, se incluye como compuestos de la invención los compuestos de Fórmula VIII.



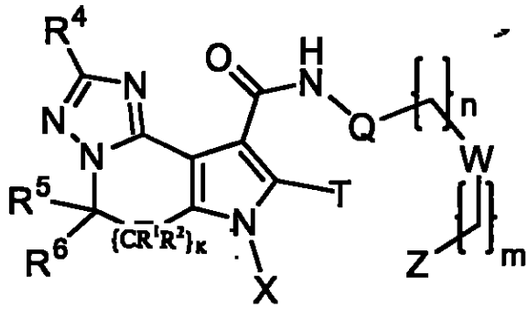
Fórmula VIII

y las sales farmacéuticamente aceptables de los mismos, en donde las variables R^1, R^2, R^4, R^5, R^6, k, n, m, T, X, Q, W, y Z son como se define para la Fórmula I. Dichos compuestos de Fórmula VIII incluyen compuestos en donde k es 2 y R^1 y R^2 son ambos hidrógeno (compuestos de **Fórmula VIIIa**). Incluso en otra

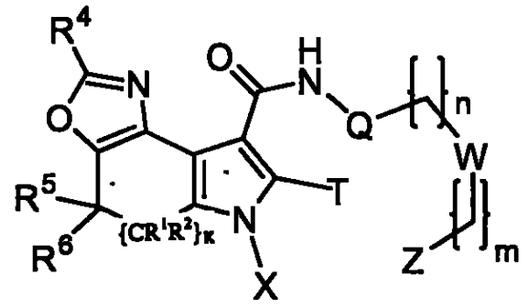
materialización física, la invención proporciona compuestos de Fórmula VIII en donde k es 2; R^1 y R^2 son ambos hidrógeno; R^4, R^5, y R^6, se eligen independientemente a partir de hidrógeno, halógeno, amino, hidroxi, metilo, etilo, metoxi y etoxi; y X y T se seleccionan independientemente de hidrógeno, metilo y etilo (compuestos de **Fórmula VIIIb**). Más particularmente, la invención proporciona compuestos de Fórmula VIII en donde k es 2; R^1, R^2, R^5, R^6, X, y T son todos hidrógeno; y R^4 es metilo (compuestos de **Fórmula VIIIc**).

Para cada una de las Fórmulas IIa, IIb, IIc, IIIa, IIIb, IIIc, IIId, IVa, IVb, IVc, Va, Vb, Vc, VIa, VIb, VIc, VIIa, VIIb, VIIc, VIIIa, VIIIb, y VIIIc las variables n, m, Q, W, y Z son como se definen para la Fórmula I.

Materializaciones físicas alternativas de la invención incluyen compuestos de Fórmula IX, Fórmula X, Fórmula XI, y Fórmula XII (que se muestran más adelante) y las sales farmacéuticamente aceptables de los mismos, en donde las variables R^1, R^2, R^3, R^4, R^5, R^6, k, n, m, T, X, Q, W, y Z son como se definen para la Fórmula I.

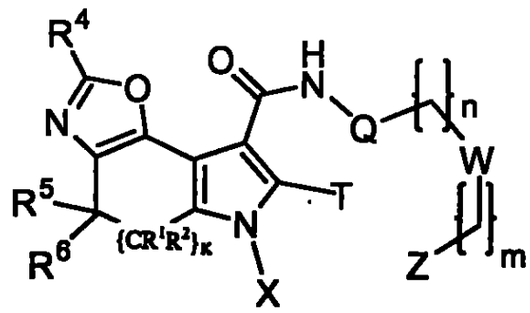


Formula IX

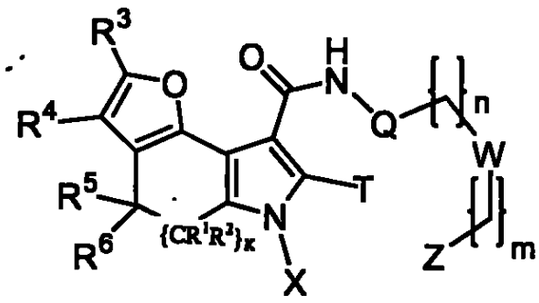


Formula X

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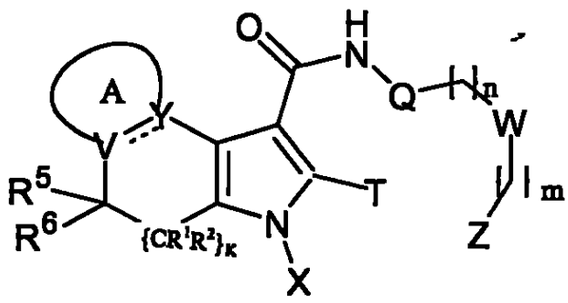


Formula XI



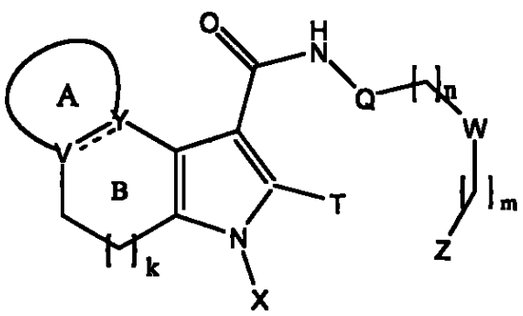
Formula XII

Otros compuestos que proporciona la invención, pero que se encuentran fuera de la definición de la Fórmula I general, incluyen compuestos de la Fórmula



En donde Y es nitrógeno, y todas las demás variables son como se definen para la Fórmula I.

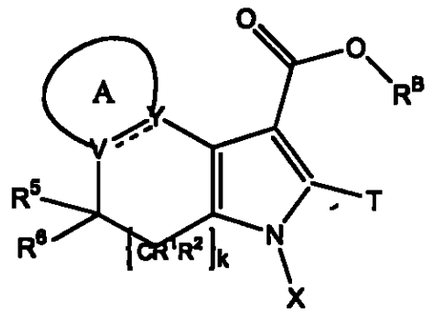
Asimismo, la invención proporciona compuestos de la Fórmula:



En donde el "anillo B" puede contener hasta 4 heteroátomos seleccionados de nitrógeno, NR^A, S, y O y puede ser saturado, insaturado o aromático. Todas las demás variables son como se define para la Fórmula I.

La invención proporciona además intermedios útiles en la síntesis de compuestos de la invención.

La etapa final en cada esquema sintético que se proporciona en la sección "Preparación de Compuestos" (más adelante) involucra la reacción de un compuesto éter novedoso para formar una amida. Por ejemplo, véase el paso 11 del Esquema 1. De esta forma, la invención proporciona intermedios éter novedosos de la Fórmula XX.

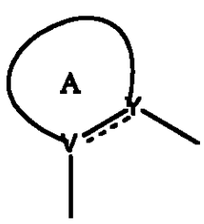


Fórmula XX

en donde

R^1 y R^2 se eligen independientemente en cada caso a partir de hidrógeno, halógeno, hidroxi, ciano, nitro, amino, alquilo, alquenilo, alquinilo, haloalquilo, y mono o dialquilamino, mono o dialquilaminoalquilo, alcoxi, y k es 0, 1, 2, ó 3;

El grupo



denominado "anillo A" representa un anillo heterocíclico sustituido, opcionalmente saturado, insaturado o aromático que contiene al menos un átomo de nitrógeno, oxígeno o

azufre, en donde el enlace $V\overset{\cdots}{=}Y$ es un enlace simple, doble o aromático;

V es nitrógeno, carbono, o CH;

Y es carbono, o CH;

R^5 y R^6 se pueden juntar para formar un grupo carbonilo; o

R^5 y R^6 se eligen independientemente a partir de hidrógeno, halógeno, hidroxi, nitro, ciano, $alquil_1$, amino, -COOH, -$O(alquil_1)$, -SO_2NH_2, -$SO_2NH(alquil_1)$, -$SO_2N(alquil_1)(alquil_1)$, -$N(alquil_1)CO(alquil_1)$, $N(alquil_1)CO_2(alquil_1)$, -$NHSO_2(alquil_1)$, -$N(alquil_1)SO_2(alquil_1)$, -$SO_2NHCO(alquil_1)$, -$CONHSO_2(alquil_1)$, -$CONH(alquil_1)$, -$CON(alquil_1)(alquil_1)$, -$CO_2(alquil_1)$, -$CO(alquil_1)$, -$SO_{0-2}(alquil_1)$, arilo carbocíclico sustituido opcionalmente y grupo heteroarilo sustituidos opcionalmente que tienen de 1 a 3 anillos, 3 a 8 miembros en cada anillo y de 1 a 3 heteroátomos;

En donde $alquil_1$ se elige independientemente en cada caso, y es recto, ramificado o cíclico, puede contener uno o dos enlaces dobles o triples y es no sustituido o sustituido por uno o más sustituyentes seleccionados a partir de: hidroxi, oxo, halógeno, amino, ciano, nitro, alcoxi, -COOH, -SO_2NH_2, -$SO_2NH(alquilo)$, -$SO_2N(alquil)(alquilo)$, -$N(alquil)CO(alquilo)$, $N(alquil)CO_2(alquilo)$, -$NHSO_2(alquilo)$, -$N(alquil)SO_2(alquilo)$, -$SO_2NHCO(alquilo)$, -$CONHSO_2(alquilo)$, -$CONH(alquilo)$, -$CON(alquil)(alquilo)$, -$CO_2(alquilo)$, -$CO(alquilo)$, -$SO_{0-2}(alquilo)$;

X se elige a partir de hidrógeno, hidroxi, amino, alquilo, y alcoxi;

T se elige a partir de hidrógeno, halógeno, hidroxi, amino, alquil, y alcoxi; y

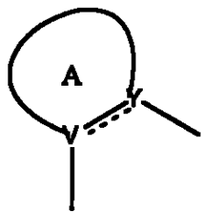
R^8 se elige a partir de hidrógeno, metilo, etilo y bencilo.

Compuestos recomendados de la Fórmula XX incluyen compuestos en donde

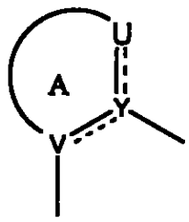
R^1 y R^2 se eligen independientemente en cada caso a partir de hidrógeno, halógeno, hidroxi, ciano, nitro, amino, haloalquilo,

mono o diamino(C_{1-6})alquilo, C_{1-6} alquilo, C_{2-6}alquenilo, C_{2-6}alquinilo y C_{1-6} alcoxi, y k es 0, 1, 2, ó 3;

El grupo



o el "anillo A" es un grupo de la Fórmula:



que es un anillo heterocícilico saturado, insaturado o aromático que contiene al menos un átomo de nitrógeno, oxígeno o azufre, en donde los enlaces U---Y y V---Y pueden ser enlaces simples, dobles o aromáticos,

U es nitrógeno, NR^A, S, u O;

V es nitrógeno, carbono o CH;

Y es carbono, o CH;

y dicho anillo heterocíclico saturado, insaturado o aromático se elige a partir de:

tienilo, tiazolilo, piridilo, pirimidinilo, imidazolilo, pirazolilo, pirazinilo, piridizinilo, piperidinilo, oxazolilo, isoxazolilo, triazolilo simétrico y asimétrico, pirrolilo, furanilo, diazenilo, triazenilo, 1, 2, 4-triazolona, 4,5-dihidroimidazolilo, y 1,4,5,6-tetrahidropirimidinilo,

Cada uno de los cuales se sustituye opcionalmente en cualquier nitrógeno disponible mediante R^A y sustituido opcionalmente en cualquier carbono disponible mediante R^3 y R^4, en donde:

R^A se elige a partir de hidrógeno, C_{1-6}alquil$_1$, arilo carbocíclico sustituido opcionalmente y grupos heteroarilo sustituidos opcionalmente que tienen de 1 a 3 anillos, 3 a 8 miembros en cada anillo y forman 1 a 3 heteroátomos;

R^5 y R^6 se eligen independientemente a partir de hidrógeno, halógeno, hidroxi, nitro, ciano, C_{1-6}alquil$_1$, amino, -COOH, -O(C_{1-6}alquil$_1$), -NH(C_{1-6}alquil$_1$), -N(C_{1-6}alquil$_1$)(C_{1-6}alquil$_1$), -

SO_2NH_2, $-SO_2NH(C_{1-6}alquil_1)$, $-SO_2N(C_{1-6}alquil_1)(C_{1-6}alquil_1)$, $-N(C_{1-6}alquil_1)CO(C_{1-6}alquil_1)$, $N(C_{1-6}alquil_1)CO_2(C_{1-6}alquil_1)$, $-NHSO_2(C_{1-6}alquil_1)$, $-N(C_{1-6}alquil_1)SO_2(C_{1-6}alquil_1)$, $-SO_2NHCO(C_{1-6}alquil_1)$, $-CONHSO_2(C_{1-6}alquil_1)$, $-CONH(C_{1-6}alquil_1)$, $-CON(C_{1-6}alquil_1)(C_{1-6}alquil_1)$, $-CO_2(C_{1-6}alquil_1)$, $-CO(C_{1-6}alquil_1)$ y $-SO_{0-2}(C_{1-6}alquil_1)$,

En donde $C_{1-6}alquil_1$ se elige independientemente en cada caso y es recto, ramificado o cíclico, puede contener uno o dos enlaces dobles o triples y es no sustituido o sustituido por uno o más sustituyentes seleccionados a partir de: hidroxi, oxo, halógeno, amino, ciano, nitro, alcoxi, grupo carbocíclico o heterocíclico, $-COOH$, $-SO_2NH_2$, $-SO_2NH(C_{1-4}alquil)$, $-SO_2N(C_{1-4}alquil)(C_{1-4}alquilo)$, $-N(C_{1-4}alquil)CO(C_{1-4}alquilo)$, $N(C_{1-4}alquil)CO_2(C_{1-4}alquilo)$, $-NHSO_2(alquilo)$, $-N(C_{1-4}alquil)SO_2(C_{1-4}alquilo)$, $-SO_2NHCO(C_{1-4}alquilo)$, $-CONHSO_2(C_{1-4}alquilo)$, $-CONH(C_{1-4}alquilo)$, $-CON(C_{1-4}alquil)(C_{1-4}alquilo)$, $-CO_2(C_{1-4}alquilo)$, $-CO(C_{1-4}alquilo)$, y $-SO_{0-2}(C_{1-4}alquilo)$;

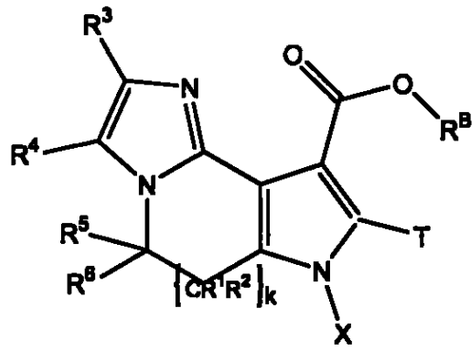
R^3 y R^4 se eligen independientemente en cada caso, y se definen igual que R^5 y R^6;

X se elige a partir de hidrógeno, hidroxi, amino, C_{1-6} alquilo, y C_{1-6}alcoxi;

T se elige a partir de hidrógeno, halógeno, hidroxi, amino, C_{1-6} alquilo, y C_{1-6} alcoxi; y

R^8 se elige a partir de hidrógeno, metilo, etilo y bencilo. Dichos compuestos se denominarán compuestos de la **Fórmula XXa**.

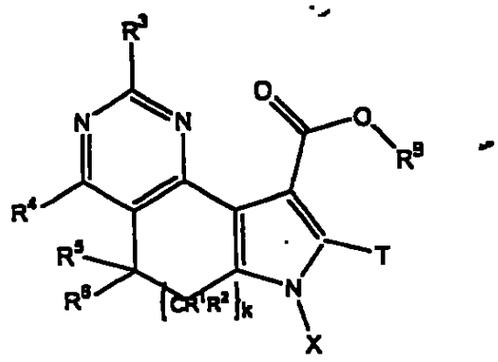
Los intermedios de éter nuevos de esta invención se diferencian principalmente del tipo de "anillo A" presente, aunque pueden presentarse otras diferencias. Una clase de intermedios que proporciona esta invención se representa mediante la Fórmula XXI.



Fórmula XXI

En donde R^1, R^2, R^3, R^4, R^5, R^6, k, X, T, y R^B son como se define para la Fórmula XXa. Intermedios recomendados de la Fórmula XXI son aquellos compuestos en donde R^B se define como se define para la Fórmula XXa; k es 1 ó 2; R^1 y R^2 son ambos hidrógeno; y R^3, R^4, R^5, y R^6, se eligen independientemente a partir de hidrógeno, halógeno, amino, hidroxi, metilo, etilo, metoxi, y etoxi (compuestos de **Fórmula XXIa**).

Asimismo, la invención proporciona intermedios de éter que tienen un "anillo A" de piridilo como los compuestos de Fórmula XXII



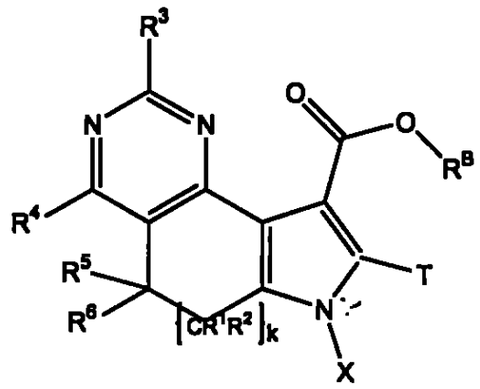
Fórmula XXII

En donde R^3 se selecciona independientemente en cada caso y es como se define para la Fórmula XXa y R^1, R^2, R^3, R^5, R^6, k, X, T; y R^B se define también como para la Fórmula XXa. Particularmente, la invención proporciona como compuestos de Fórmula XXII, compuestos en donde

R^B se define como para la Fórmula XXa; R^1, R^2, R^3, R^5, R^6, k, X, y T son todos hidrógeno; R^3 es hidrógeno en las posiciones 3- y 4- del grupo piridilo de "anillo A", y se elige a partir de hidrógeno, halógeno, amino, hidroxi, metilo, etilo, metoxi, y

etoxi en la posición 2- de este grupo piridilo de "anillo A" (compuestos de **Fórmula XXIIa**). También se proporciona como compuestos de Fórmula XXII, compuestos en donde R^B se define como para la Fórmula XXa; R^1, R^2, R^3, R^5, R^6, k, X, y T son todos hidrógeno; R^3 es hidrógeno en las posiciones 2- y 4- del grupo piridilo de "anillo A", y se elige a partir de hidrógeno, halógeno, amino, hidroxi, metilo, etilo, metoxi, y etoxi en la posición 3- de este grupo piridilo de "anillo A" (compuestos de **Fórmula XXIIb**).

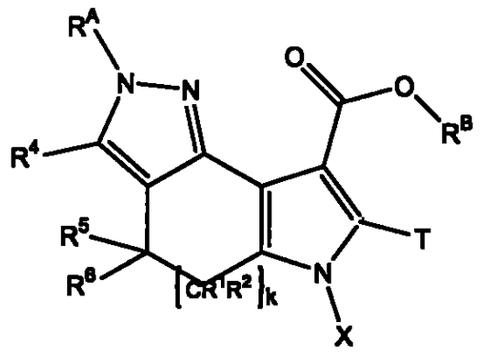
La invención proporciona intermedios de Fórmula XXIII que tienen un "anillo A" de pirimidinilo



Fórmula XXIII

En donde R^1, R^2, R^3, R^4, R^5, R^6, k, X, T, y R^B son como se define en la Reivindicación XXa. Compuestos recomendados de Fórmula XXIII incluyen compuestos en donde k es 2; R^1, R^2, R^3, R^5, R^6, X, y T son todos hidrógeno; R^B se define como para la Fórmula XXa; y R^4 se elige a partir de hidrógeno, halógeno, amino, hidroxi, metilo, etilo, metoxi, y etoxi (compuestos de Fórmula XXIIIa).

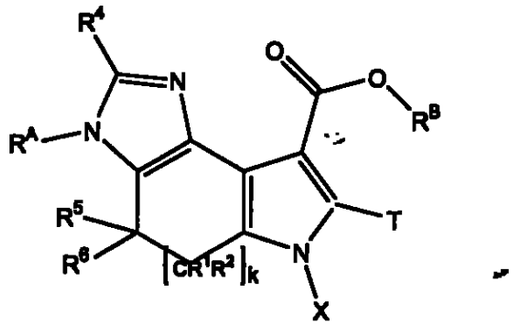
En una materialización física, la invención proporciona compuestos de Fórmula XIV en donde el "anillo A" es un pirrol



Fórmula XIV

En donde R^A, R^1, R^2, R^4, R^5, R^6, k, X, T, y R^B son como se define en la Fórmula XXa. Compuestos recomendados de la Fórmula XIV incluyen compuestos en donde k es 2; R^A se elige a partir de hidrógeno, metilo, etilo, y fenilo; R^B es como se define en la Fórmula XXa; y R^1, R^2, R^4, R^5, R^6, X, y T son todos hidrógeno (compuestos de **Fórmula XIVa**).

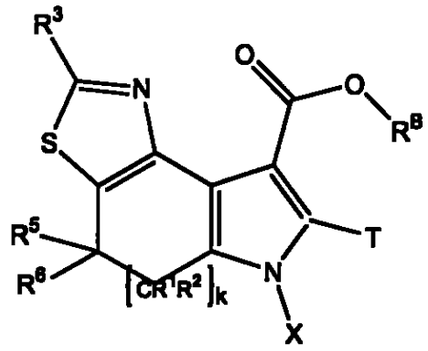
Además, la invención incluye compuestos de Fórmula XV



Fórmula XV

En donde R^A, R^1, R^2, R^3, R^4, R^5, R^6, k, X, T, y R^B son como se define para la Fórmula XXa. También se incluyen como compuestos de Fórmula XV los compuestos en donde k es 2; R^A, R^1, R^2, R^4, R^5, R^6, k, X, y T son todos hidrógeno; R^B es como se define para la Fórmula XXa; y R^4 se elige de hidrógeno, halógeno, amino, hidroxi, metilo, etilo, metoxi, y etoxi (compuestos de **Fórmula XVa**).

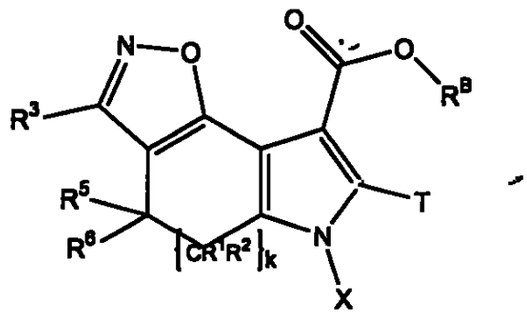
En otra materialización física, la invención proporciona intermedios de éter nuevos de Fórmula XVI que tienen "anillos A" de tiazol.



Fórmula XVI

En donde R^1, R^2, R^3, R^5, R^6, k, X, T, y R^B son como se definen para la Fórmula XXa. De preferencia, compuestos de esta clase son aquellos compuestos en donde k es 2; R^1, R^2, R^5, R^6, X, y T son hidrógeno; R^B es como se define para la Fórmula XXa; y R^3 se elige a partir de hidrógeno, halógeno, amino, hidroxi, metilo, etilo, metoxi, y etoxi (compuestos de **Fórmula XVIa**).

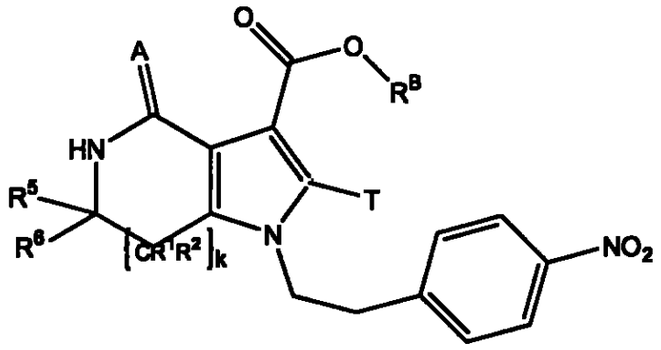
Otra clase de intermedios éter de la invención se representa mediante compuestos de Fórmula XXVII que tienen un "anillo A" de isoxazol.



Fórmula XXVII

En donde R^1, R^2, R^3, R^5, R^6, k, X, T, y R^B son como se define para la Fórmula XXa. De preferencia, compuestos de esta clase son aquellos compuestos en donde k es 2; R^1, R^2, R^5, R^6, X, y T son hidrógeno; R^B es como se define para la Fórmula XXa; y R^3 se elige a partir de hidrógeno, halógeno, amino, hidroxi, metilo, etilo, metoxi, y etoxi (compuestos de **Fórmula XVIIa**).

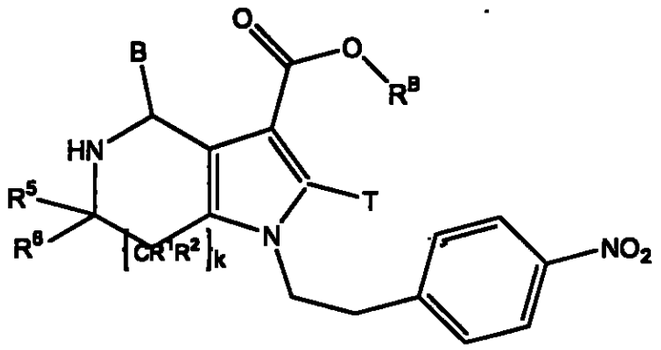
En un número de los pasos de síntesis utilizados para generar compuestos de la invención se utilizan intermedios protegidos nuevos. Estos intermedios protegidos incluyen compuestos de Fórmula XXX útiles en la síntesis de compuestos de la invención que tiene un "anillo A" de imidazol



Fórmula XXX

En donde A es oxígeno o azufre; k, R^1, R^2, R^5, R^6, R^8 y T son como se define para la Fórmula XXa.

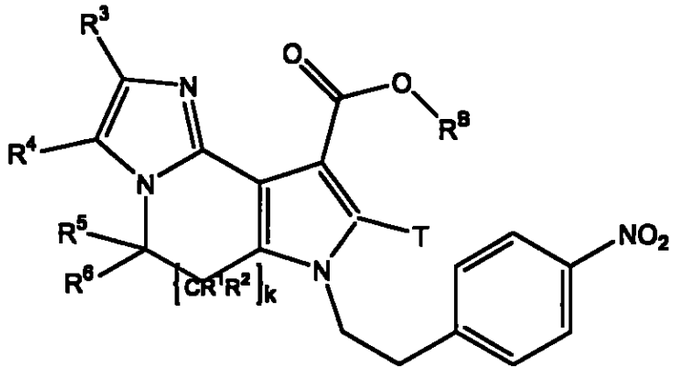
Otra clase de intermedios protegidos útiles en la síntesis de compuestos de la invención que tienen un "anillo A" de imidazol son compuestos de Fórmula XXXI.



Fórmula XXXI

En donde B es $-SCH_3$ o $-NH(CH_2)CH(OCH_3)_2$ y k, R^1, R^2, R^5, R^6, R^8 y T son como se define para la Fórmula XXa.

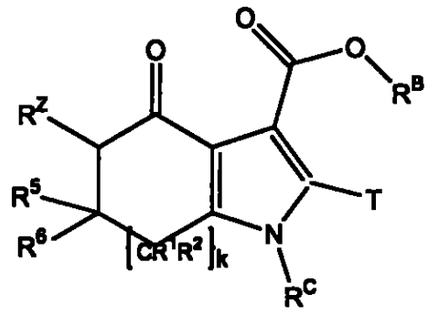
También se proporcionan compuestos de Fórmula XXXII



Fórmula XXXII

En donde todas las variables presentes en compuestos de Fórmula XXXII se definen como para los compuestos de Fórmula XXa.

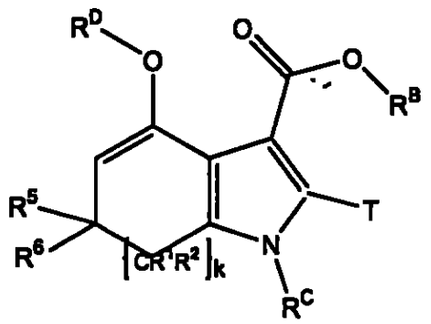
Otras clases de intermedios nuevos que proporciona la invención son intermedios que tienen grupos protectores BOC y TMS (o análogos de dichos grupos) como compuestos de Fórmula XXXIII.



Fórmula XXXIII

En donde R^C se elige a partir de t-butoxicarbonilo, fenilo, alquilsulfonilo, y etilcarbamoilo; R^Z es hidrógeno o bromo; y k, R^B, R^1, R^2, R^5, R^6, y T se definen como para compuestos de Fórmula XXa.

También se proporciona compuestos de Fórmula XXXIV.



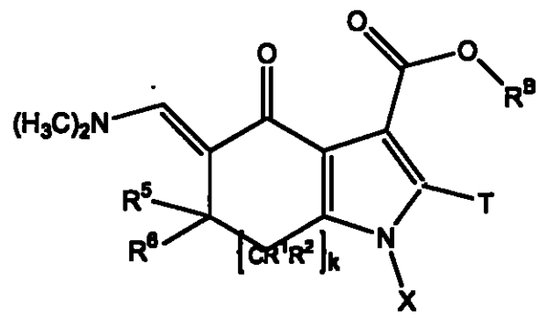
Fórmula XXXIV

R^C se elige a partir de t-butoxicarbonilo, fenilo, fenilsulfonilo, alquilsulfonilo, y etilcarbamoilo;

R^D se elige a partir de trimetilsililo, sililmetil éter, y t-butildimetilsililo; y

k, R^B, R^1, R^2, R^5, R^6, y T se definen como de Fórmula XXa.

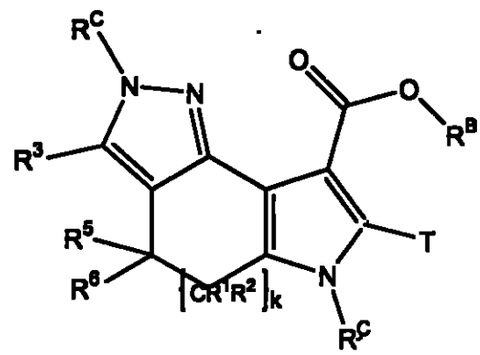
Asimismo, la invención proporciona como intermedios compuestos de Fórmula XXXV



Fórmula XXXV

En donde k, R^8, R^1, R^2, R^5, R^6, X y T se definen como para la Fórmula XXa.

Finalmente, la invención proporciona compuestos de Fórmula XXXVI como intermedios



Fórmula XXXVI

R^C se elige independientemente en cada caso a partir de t-butoxicarbonilo, fenilo, fenilsulfonilo, alquilsulfonilo, y etilcarbamoilo, y todas las demás variables son como se define para los compuestos de la Fórmula XXa.

Esta invención se refiere a compuestos heterocíclicos, como 5,6-Dihidro -4H-1,3a,6-triaza-as- indacenos, 3-tia-1,7-diaza-ciclopenta [e]azuleno-9-ácidos carboxílicos, 4,5,6,7-tetrahidro-1-oxa-2,7-diaza-ciclopenta [e]azuleno -9-ácidos carboxílicos, 3,8,10-triaza-benzo [e]azuleno-1-ácidos carboxílicos, 1-oxa-2,7-diaza-ciclopenta [e]azuleno-9-ácidos carboxílicos, 1,3,7-triaza-ciclopenta [e]azuleno-9-ácido carboxílico fenil amida y compuestos correspondientes, que enlazan mediante gran afinidad al sitio benzodiazepina de los receptores $GABA_A$, incluyendo receptores $GABA_A$ humanos. Esta invención también incluye los compuestos que enlazan o muestran gran selectividad al sitio benzodiazepina de los receptores $GABA_A$, incluyendo receptores

$GABA_A$ humanos. Sin pretender limitarse por ninguna teoría en particular, se cree que la interacción de los compuestos de la Fórmula I con el sitio benzodiazepina genera la utilidad farmacéutica de estos compuestos.

Asimismo, la invención comprende métodos de tratamiento a pacientes que necesitan dicho tratamiento mediante una cantidad del compuesto de la invención, suficiente para alterar los síntomas de un trastorno del CNS. Los compuestos de las invenciones que actúan como agonistas en subtipos de receptores $\alpha_2\beta_3\gamma_2$ y $\alpha_3\beta_3\gamma_2$ son útiles para el tratamiento de trastornos de ansiedad como trastorno de pánico, trastorno obsesivo-compulsivo y trastorno generalizado de ansiedad; trastornos por tensión incluyendo tensión postoperatoria, y trastornos por tensión aguda. Compuestos de la invención que actúan como agonistas en los subtipos de receptor $\alpha_2\beta_3\gamma_2$ y $\alpha_3\beta_3\beta_2$ son también útiles en el tratamiento de trastornos depresivos o bipolares y en el tratamiento de los trastornos del sueño. Los compuestos de la invención que actúan como agonistas inversos en el subtipo de receptor $\alpha_5\beta_3\gamma_2$ o subtipos de receptor $\alpha_1\beta_2\gamma_2$ y $\alpha_5\beta_3\gamma_2$ son útiles en el tratamiento de trastornos cognitivos incluyendo los que resultan del Síndrome Down, enfermedades neurodegenerativas como la enfermedad de Alzheimer y mal de Parkinson y demencia por hemorragia cerebral. Los compuestos de la invención que actúan como agonistas en el subtipo de receptor $\alpha_1\beta_2\gamma_2$ son útiles en el tratamiento de trastornos convulsivos como epilepsia. Compuestos que actúan como antagonistas en el sitio benzodiazepina son útiles en invertir el efecto de sobredosis de benzodiazepina y en el tratamiento de adicción a los fármacos y al alcohol.

Las enfermedades y/o desórdenes que se pueden tratar utilizando compuestos y composiciones de acuerdo con la invención incluyen:

Depresión, por ejemplo, depresión, depresión atípica, trastorno bipolar, fase depresiva de trastorno bipolar.

Ansiedad, por ejemplo, trastorno general de ansiedad (GAD), agorafobia, trastorno de pánico +/- agorafobia, fobia social, fobia específica, trastorno de tensión post-traumática, trastorno compulsivo obsesivo (OCD), distimia, desórdenes de ajuste con

perturbación anímica y ansiedad, trastorno de ansiedad por separación, trastorno de tensión aguda por ansiedad anticipada, trastorno de ajuste, ciclotimia.

Trastornos del sueño, por ejemplo, trastornos del sueño incluyendo insomnio primario, trastorno del sueño de ritmo circadiano, disomnio NOS, disomnio NOS, parasomnias, incluyendo trastorno de pesadillas, disgripnia por terror, trastornos del sueño secundarios a depresión y/o ansiedad u otros trastornos mentales, trastornos del sueño inducidos por sustancias.

Deficiencia Cognitiva, por ejemplo, deficiencia cognitiva, enfermedad de Alzheimer, mal de Parkinson, deficiencia cognitiva leve (MCI), disminución cognitiva asociada a la edad (ARCD), hemorragia cerebral, daño cerebral traumático, demencia asociada al SIDA y demencia asociada a la depresión, ansiedad o sicosis.

Trastorno de Déficit de Atención, por ejemplo, Trastorno de Déficit de la Atención (ADD), Trastorno de Hiperactividad y Déficit de la Atención (ADHD).

La invención también proporciiona composiciones farmacéuticas que comprenden uno o más compuestos de la invención junto con al menos un portador farmacéuticamente aceptable. Las composiciones farmacéuticas incluyen composiciones farmacéuticas envasadas para tratar trastornos que responden a la modulación del receptor $GABA_A$, por ejemplo, tratamiento de la ansiedad, depresión, trastornos del sueño o deficiencia cognitiva por modulación del receptor $GABA_A$. Las composiciones envasadas incluyen un envase que contiene una cantidad terapéuticamente efectiva de al menos un modulador del receptor $GABA_A$ como se ha descrito antes en instrucciones (por ejemplo, etiquetas) que indican el contenido de ligando de receptor $GABA_A$ que se debe usar para tratar un trastorno que responde a la modulación del receptor $GABA_A$ en el paciente.

En otro aspecto, la invención proporciona un método para potencializar las acciones de otros compuestos activos en el CNS, el cual comprende la administración de una cantidad efectiva de un compuesto de la invención en combinación con otro compuesto activo en el CNS. Dichos compuestos activos en el CNS incluyen, sin carácter limitativo, lo siguiente: para la ansiedad,

agonistas y antagonistas del receptor de serotonina (por ejemplo, 5-HT_{1A}); para la ansiedad y depresión, antagonistas del receptor de neuroquinina o antagonistas del receptor del factor de liberación de corticotropina (CRF_1); para trastornos del sueño, agonistas del receptor de melatonina; y para trastornos neurodegenerativos, tales como demencia por Alzheimer, agonistas nicotínicos, agentes muscarínicos, inhibidores de acetilcolinesterasa y agonistas del receptor de dopamina. Particularmente, la invención proporciona un método para potencializar la actividad antidepresiva de los inhibidores de recaptación de serotonina selectivos (SSRIs) al administrar una cantidad efectiva de un compuesto del agonista GABA de la invención en combinación con un SSRI.

La administración en combinación se puede realizar de una manera análoga a la que se divulga en Da-Rocha, y otros, *J. Psychopharmacology* (1997) 11(3) 211-218; Smith, y otros, *Am. J. Psychiatry* (1998) 155(10) 1339-45; o Le, y otros, *Alcohol and Alcoholism* (1996) 31 Suppl. 127-132. Véase también, la discusión sobre el uso del ligando del receptor $GABA_A$ 3-(5-metilisoxazol-3-il)-6-(1-metil-1,2,3-triazol-4-il) metiloxi-1,2,4-triazolo [3,4-a]ftalazina en combinación con agonistas nicotínicos, agonistas muscarínicoss, e inhibidores de acetilcolinesterasa, en las publicaciones internacionales PCT Nos. WO 99/47142, WO 99/47171, y WO 99/47131, respectivamente. También véase a este respecto la publicación Internacional PCT No. WO 99/37303 para tratar el uso de una clase de ligandos del receptor $GABA_A$, 1,2,4-triazolo[4,3-b]piridazinas, en combinación con SSRIs.

La presente invención también pertenece a métodos para inhibir el enlace de compuestos de benzodiazepina, tales como Ro15-1788, a receptores $GABA_A$ cuyos métodos implican hacer que un compuesto de la invención entre en contacto con células que expresan receptores $GABA_A$, en donde el compuesto está presente en una concentración suficiente para inhibir el enlace de benzodiazepina a receptores $GABA_A$ *in vitro*. Este método incluye inhibir el enlace de compuestos de benzodiazepina a receptores $GABA_A$ *in vivo*, por ejemplo, en un paciente que recibe una cantidad de un compuesto de la Fórmula A o Fórmula I que sería

suficiente para inhibir el enlace de compuestos de benzodiazepina a receptores $GABA_A$ *in vitro*. En una materialización física, dichos métodos son útiles para tratar sobredosis del fármaco de benzodiazepina. La cantidad de un compuesto que sería suficiente par inhibir el enlace de un compuesto de benzodiazepina al receptor $GABA_A$ se puede determinar fácilmente via un ensayo de enlace de receptor $GABA_A$, tal como el ensayo que se describe en el Ejemplo 24. Los receptores $GABA_A$ que se usan para determinar el enlace *in vitro* se pueden obtener de una variedad de fuentes, por ejemplo, de preparaciones de corteza de rata o de células que expresan receptores $GABA_A$ de humano clonados.

La presente invención también pertenece a métodos para alterar la actividad de transducción de señales, particularmente el conductor de iones de cloruro de receptores $GABA_A$, en donde el método comprende exponer células que expresan dichos receptores a una cantidad efectiva de un compuesto de la invención. Este método incluye la alteración de la actividad de transducción de señales de receptores $GABA_A$ *in vivo*, por ejemplo, en un paciente que recibe una cantidad de un compuesto de la Fórmula A o Fórmula I que sería suficiente para alterar la actividad de transducción de señales de receptores $GABA_A$ *in vitro*. La cantidad de un compuesto que sería suficiente para alterar la actividad de transducción de señales de receptores $GABA_A$ se puede determinar mediante un ensayo de transducción de señales de receptores $GABA_A$, tal como el ensayo que se describe en el Ejemplo 25.

Los ligandos de receptores $GABA_A$ proporcionados por esta invención y los derivados marcados de los mismos también son útiles como estándares y reactivos determinando la capacidad de enlace de un producto farmacéutico potencial a los receptores $GABA_A$.

Los derivados marcados de los ligandos de receptores $GABA_A$ proporcionados por esta invención también son útiles como radiotrazadores para generación de imágenes de tomografía de emisión de positrones (PET) o para tomografía computarizada de emisión de fotón único (SPECT).

Definiciones

Para los compuestos de la presente invención que tienen centros asimétricos, esta invención incluye todos los isómeros o enantiómeros ópticos y mezclas de los mismos así como las mezclas racémicas de los enantiómeros.

Además, los compuestos con enlaces de carbono-carbono pueden ocurrir en formas Z- y E-, con todas las formas isómeras de los compuestos que se incluyen en la presente invención.

Cuando cualquier variable (por ejemplo, C_{1-6} alquilo, alquilo, alquil$_1$ R^1-R^{10}) aparece más de una vez en la Fórmula I, su definición en cada caso es independiente.

Como se usa en el presente, los términos "alquilo" "C_{y-x} alquilo" en la presente invención significan grupos alquilo de cadena recta o ramificada generalmente de 6 a 8 átomos de carbono, o para C_{y-x} alquilo el número de átomos de carbono especificados, por ejemplo, C_{1-6} alquilo indica grupos alquilo de cadena recta o ramificada que tienen de 1 a 6 átomos de carbono. Ejemplos de grupos alquilo incluyen metilo, etilo, propilo, isopropilo, n-butilo, sec-butilo, ter-butilo, pentilo, 2-pentilo, isopentilo, neopentilo, hexilo, 2-hexilo, 3-hexilo, y 3-metilopentilo. Los grupos C_{1-8} alquilo recomendados son metilo, etilo, propilo, butilo, pentilo y ciclopentilo.

El término "alcoxi" representa un grupo alquilo, como se describre anteriormente, unido mediante un puente de oxígeno, tal como metoxi, etoxi, propoxi e isopropoxi.

El término "alquenilo" pretende incluir cadenas de hidrocarburo ya sea de configuración recta o ramificada que comprende uno o más enlaces carbono-carbono los cuales pueden aparecer en un punto estable a lo largo de la cadena, tales como etenilo y propenilo.

El término "alquinilo" pretende incluir cadenas de hidrocarburo ya sea de configuración recta o ramificada que comprenden uno o más enlaces triples de carbono-carbono que pueden aparecer en cualquier punto estable a lo largo de la cadena, tales como etinilo y propinilo.

El término "arilo carbocíclico" se usa para indicar grupos aromáticos, que tienen solamente átomos de carbono en la

estructura de anillo. Dichos grupos están opcionalmente sustituidos.

El término "cicloalquilo" se refiere a grupos de anillo saturado, que tienen un número específico de átomos de carbono, tales como ciclopropilo, ciclobutilo, ciclopentilo, o ciclohexilo.

En el término "(C_{3-x} cicloalquil)C_{1-y} alquilo el punto de unión está en el grupo alquilo. Ejemplos de dichos grupos son, pero no se limitan a, ciclopropilmetilo, ciclohexilmetilo, y ciclohexilmetilo.

El término "haloalquilo" pretende incluir grupos hidrocarburos alifáticos saturados de cadena ramificada y recta, los cuales tienen un número específico de átomos de carbono, sustituidos con 1 ó más halógenos (por ejemplo, $-C_vF_w$ en donde v = 1 a 3 y w = 1 a (2v+1). Ejemplos de haloalquilo incluyen, sin carácter limitativo, trifluorometilo, triclorometilo, pentafluoroetilo, y pentacloroetilo.

Como se usa en el presente, los términos "grupo heterocíclico" o "heterocicloalquilo" pretenden significar un anillo monocíclico o bicíclico con 5 a 7 miembros o heterocíclico bicíclico con 7 a 10 miembros el cual está saturado, parcialmente insaturado o insaturado (aromático), y el cual consiste de átomos de carbono y de 1 a 4 heteroátomos seleccionados independientemente de N, O y S y que incluyen cualquier grupo bicíclico en los que cualquiera de los anillos heterocíclicos definidos anteriormente se fusiona a un anillo de benceno. Los heteroátomos de nitrógeno y azufre se pueden oxidar opcionalmente. El término "heteroarilo" se usa para indicar específicamente grupos heterocíclicos aromáticos.

El anillo heterocíclico se puede unir a su grupo pendiente en cualquier heteroátomo o átomo de carbono que genera una estructura estable. Los anillos heterocíclicos que se describen en el presente se pueden sustituir por un átomo de carbono o nitrógeno si el compuesto resultante es estable. Un nitrógeno en el heterociclo puede ser opcionalmente cuaternizado. Se recomienda que cuando el número total de átomos S y O en el heterociclo excede 1, entonces estos heteroátomos no están unidos

entre sí. Se recomienda que el número total de átomos S y O en el heterociclo no sea mayor de 1. Como se usa en el presente, el término "sistema heterocíclico aromático" pretende significar un anillo heterocíclico estable monocíclico o bicíclico con 5 a 7 miembros o bicíclico con 7 a 10 miembros que consiste de átomos de carbono y de 1 a 4 heteroátomos seleccionados independientemente de N, O y S. Se recomienda que el número total de átomos S y O en el heterociclo aromático no sea mayor que 1.

Ejemplos de heterociclos incluyen, sin carácter limitativo, acridinilo, azocinilo, bencimidazolilo, benzofuranilo, benzotiofuranilo, benzotiofenilo, benzoxazolilo, benzotiazolilo, benzotriazolilo, benzotetrazolilo, bencisoxazolilo, bencisotiazolilo, bencimidazolinilo, carbazolilo, NH-carbazolilo, carbolinilo, cromanilo, cromenilo, cinolinilo, decahidroquinolinilo, 2*H*,6*H*-1,5,2-ditiazinilo, dihidrofuro[2,3-*b*]tetrahidrofurano, furanilo, furazanilo, iloidazolidinilo, imidazolinilo, imidazolilo, 1H-indazolilo, indolenilo, indolinilo, indolizinilo, indolilo, 3*H*-indolil , isobenzofuranilo, isocromanilo, isoindazolilo, isoindolinilo, isoindolilo, isoquinolinilo, isotiazolilo, isoxazolilo, morfolinilo, naftiridinilo, octahidroisoquinolinil , oxadiazolilo, 1,2,3-oxadiazolilo, 1,2,4-oxadiazolilo;- 1,2,5-oxadiazolilo, 1,3,4-oxadiazolilo, oxazolidinilo, oxazolilo, oxazolidinilo, pirimidinilo, fenantridinilo, fenantrolinilo, fenazinilo, fenotiazinilo, fenoxatiinilo, fenoxazinilo, ftalazinilo, piperazinilo, piperidinilo, pteridinilo, purinilo, piranilo, pirazinilo, pirazolidinilo, pirazolinilo, pirazolilo, piridazinilo, piridooxazola, piridoimidazol, piridotiazol, piridinilo, piridilo, pirimidinilo, pirrolidinilo, pirrolinilo, 2*H*-pirrolilo, pirrolilo, quinazolinilo, quinolinilo, 4H-quinolizinilo, quinoxalinilo, quinuclidinilo, tetrahidrofuranilo, tetrahidroisoquinolinilo, tetrahidroquinolinilo, 6*H*-1,2,5-tiadiazinilo, 1,2,3-tiadiazolilo, 1,2,4-tiadiazolilo, 1,2,5-tiadiazolilo, 1,3,4tiadiazolilo, tiantrenilo, tiazolilo, tienilo, tienotiazolilo, tienooxazolilo, tienoimidazolilo, tiofenilo, triazinilo, 1,2,3-triazolilo,

1,2,4-triazolilo, 1,2,5-triazolilo, 1,3,4-triazolilo, y xantenilo.

El término "halógeno" indica flúor, cloro, bromo, y yodo.

Las "sales farmacéuticamente aceptables" atóxicas incluyen, sin carácter limitativo, sales con ácido inorgánicos tales como clorhidrato, sulfato, fosfato, difosfato, bromhidrato, y nitrito o sales con un ácido orgánico tales como malato, maleato, fumarato, tartrato, succinato, citrato, acetato, lactato, metanosulfonato, p-toluenosulfonato, 2-hidroxietilsulfonato, salicilato y estearato. De manera similar, los cationes farmacéuticamente aceptables incluyen, sin carácter limitativo, sodio, potasio, calcio, aluminio, litio y amonio. La presente invención también comprende los profármacos de los compuestos de la Fórmula I.

Preparaciones Farmacéuticas

Los expertos en la técnica podrán reconocer diversas metodologías sintéticas que se pueden usar para preparar profármacos farmacéuticamente aceptables atóxicos de los compuestos comprendidos en la Fórmula I. Los expertos en la técnica podrán reconocer una amplia variedad de solventes farmacéuticamente aceptables atóxicos que se pueden usar para preparar solvatos de los compuestos de la invención, tales como agua, etanol, aceite mineral, aceite vegetal y dimetilsulfuro.

Los compuestos de la Fórmula I general se pueden administrar de manera oral, tópica, parenteral, mediante inhalación o aerosol o por vía rectal en formulaciones unitarias de dosis que contienen portadores, adyuvantes y vehículos atóxicos convencionales farmacéuticamente aceptables. La administración oral en la forma de píldora, cápsula, elíxir, jarabe, gragea, pastilla o similares se recomienda particularmente. El término parenteral como se usa en el presente incluye inyecciones subcutáneas, inyección intradérmica, intravascular (por ejemplo, intravenosa), intramuscular, espinal, intratecal o técnicas de inyección o infusión similares. Además, se proporciona una formulación farmacéutica que comprende un compuesto de la Fórmula I general y un portador farmacéuticamente aceptable. Uno o más

compuestos de la Fórmula I general pueden estar presentes en asociación con uno o más portadores atóxicos y/o diluyentes y/o adyuvantes farmacéuticamente aceptables y, si se desea, otros ingredientes activos. Las composiciones farmacéuticas que contienen compuestos de la Fórmula I general pueden estar en una forma adecuada para uso oral, por ejemplo, como tabletas, pastillas, grageas, suspensiones acuosas o aceitosas, polvos o gránulos dispersables, emulsión, cápsulas duras o blandas, o jarabes o elíxires.

Las composiciones para uso oral se pueden preparar de acuerdo con cualquier método conocido en la técnica para la fabricación de composiciones farmacéuticas, y dichas composiciones pueden contener uno o más agentes seleccionados del grupo que consiste en agentes edulcorantes, agentes saborizantes, agentes colorantes y agentes preservantes a fin de proporcionar preparaciones farmacéuticamente agradables a la vista y al paladar. Las tabletas contienen el ingrediente activo en la mezcla con excipientes atóxicos farmacéuticamente aceptables que son adecuados para la fabricación de tabletas. Estos excipientes pueden ser, por ejemplo, diluyentes inertes, tales como carbonato de calcio, carbonato de sodio, lactosa, fosfato de calcio o fosfato de sodio; agentes granulantes y desintegrantes, por ejemplo, almidón de maíz, o ácido algínico; agentes aglutinantes, por ejemplo, almidón, gelatina o acacia, y agentes lubricantes, por ejemplo, estearato de magnesio, ácido esteárico o talco. Las tabletas pueden estar no cubiertas o pueden estar cubiertas mediante técnicas conocidas para retrasar la desintegración y absorción en el tracto gastrointestinal y, por lo tanto, proporcionar una acción sostenida durante un período más prolongado. Por ejemplo, se puede emplear un material de retraso de tiempo tal como monoestearato de glicerol o diestearato de glicerol.

Las formulaciones para uso oral también se pueden presentar como cápsulas de gelatina dura en las que el ingrediente activo se mezcla con un diluyente sólido inerte, por ejemplo, carbonato de calcio, fosfato de calcio o caolín, o como cápsulas de gelatina blanda en las que el ingrediente activo se mezcla con

agua o un medio oleaginoso, por ejemplo aceite de cacahuate, parafina líquido o aceite de oliva.

Las suspensiones acuosas contienen los materiales activos en la mezcla con excipientes adecuados para la fabricación de suspensiones acuosas. Dichos excipientes son agentes de suspensión, por ejemplo, carboximetilocelulosa sódica, metilcelulosa, hidropropilmetilcelulosa, alginato de sodio, polivinilpirrolidona, goma de tragacanto y goma de acacia; los agentes dispersantes o humidificantes pueden ser fosfaturo natural, por ejemplo, lecitina, o productos de condensación de un óxido de alquileno con ácidos grasos, por ejemplo, estearato de polioxietileno, o productos de condensación de óxido de etileno con alcoholes alifáticos de cadena larga, por ejemplo, heptadecaetileneoxicetanol, o productos de condensación de óxido de etileno con ésteres parciales derivados de ácidos grasos y un hexitol tal como polioxietileno sorbitol monooleato, o productos de condensación de óxido de etileno con ésteres parciales derivados de ácidos grasos y anhidridos de hexitol, por ejemplo, polietileno sorbitan monooleato. Las suspensiones acuosas también pueden contener uno o más preservantes, por ejemplo, etilo, o n-propilo p-hidroxibenzoato, uno o más agentes colorantes, uno o más agentes edulcorantes, tales como sacarosa o sacarina.

Las suspensiones oleaginosas se pueden formular mediante la suspensión de los ingredientes activos en un aceite vegetal, por ejemplo, aceite de cacahuate, aceite de ajonjolí o aceite de coco, o en un aceite mineral tal como parafina líquida. Las suspensiones oleaginosas pueden contener un agente espesante, por ejemplo, cera de abejas, parafina dura o cetil alcohol. Los agentes edulcorantes tales como los que se mencionan anteriormente, y agentes saborizantes se pueden agregar para proporcionar preparaciones orales agradables al paladar. Estas composiciones se pueden preservar mediante la adición de un antioxidantes como el ácido ascórbico.

Los polvos y gránulos dispersables adecuados para la preparación de una suspensión acuosa mediante la adición de agua proporcionan el ingrediente activo en la mezcla con agente

dispersante humidificante, agente de suspensión y uno o más preservantes. Ejemplos de agentes dispersantes o humidificantes y agentes de suspensión se mencionan anteriormente. También pueden estar presentes excipientes adicionales, por ejemplo, agentes edulcorantes, saborizantes y colorantes.

Las composiciones farmacéuticas de la invención también pueden encontrarse en forma de emulsiones de aceite en agua. La fase aceitosa puede ser un aceite vegetal, por ejemplo aceite de oliva o aceite de cacahuate, o un aceite mineral, por ejemplo, parafina líquida o mezclas de los mismos. Los agentes emulsificantes adecuados puede ser gomas naturales, por ejemplo, goma de acacia o goma de tragacanto, fosfaturos naturales, por ejemplo, fríjol de soya, lecitina y ésteres o ésteres parciales derivados de ácidos grasos y hexitol, anhídridos, por ejemplo, monoleato de sorbitan, y productos de condensación de los ésteres parciales con óxido de etileno, por ejemplo, polioxietileno sorbitan monoleato. Las emulsiones también pueden contener agentes edulcorantes y saborizantes.

Los jarabes y elíxires se pueden formular con agentes edulcorantes, por ejemplo, glicerol, propilen glicol, sorbitol o sacarosa. Dichas formulaciones también pueden contener un demulcente, un preservante y agentes saborizantes y colorantes. Las composiciones farmacéuticas pueden estar en la forma de una suspensión acuosa u oleaginosa inyectable estéril. Esta suspensión se puede formular de acuerdo con la técnica conocida usando los agentes dispersantes o humidificantes adecuados y agentes de suspensión que se mencionaron anteriormente. La preparación inyectable estéril también puede ser una solución o suspensión inyectable estéril en un diluyente o solvente atóxico parenteralmente aceptable, por ejemplo como una solución en 1,3-butanodiol. Entre estos vehículos y solventes aceptables que se pueden usar se encuentran agua, solución de Ringer y solución de cloruro de sodio isotónico. Además, convencionalmente se usan aceites estériles fijos como un solvente o medio de suspensión. Para este propósito se puede utilizar cualquier aceite fijo blando incluyendo mono- o diglicéridos sintéticos.

Adicionalmente, los ácidos grasos tales como ácido oléico son útiles en la preparación de inyectables.

Los compuestos de la Fórmula I general también se pueden administrar en la forma de supositorios, por ejemplo, para administración rectal del fármaco. Estas composiciones se pueden preparar mezclando el fármaco con un excipiente no irritante adecuado que sea sólido a temperaturas normales pero líquido a temperatura rectal y que por lo tanto se derrite en el recto para liberar el fármaco. Dichos materiales son mantequilla de cacao y polietilen glicoles.

Los compuestos de la Fómula I general se pueden administrar de manera parenteraí en un medio estéril. El fármaco, dependiendo del vehículo y concentración usado, se puede suspender o disolver en el vehículo. De preferencia, los adyuvantes tales como anestésicos locales, preservantes y agentes amortiguadores se pueden disolver en el vehículo.

Para la administración a animales no humanos, la composición también se puede agregar al alimento o agua potable. Sería conveniente formular estas composiciones de alimento y agua potable de manera que el animal tome una cantidad adecuada de la composición junto con su dieta. También sería conveniente presentar la composición como una premezcla para la adición al alimento o agua potable.

Los niveles de dosificación del orden de alrededor de 0.1 mg a alrededor de 140 mg por kilogramo de peso corporal por día son útiles en el tratamiento de las condiciones indicadas anteriormente (alrededor de 0.5 mg a alrededor de 7 g por paciente por día). La cantidad de ingrediente activo que se puede combinar con los materiales del portador para producir una forma de dosificación única varían dependiendo del anfitrión tratado y el modo particular de administración. Las formas unitarias de dosificación generalmente contienen entre alrededor de 1 mg a alrededor de 500 mg de un ingrediente activo.

La frecuencia de la dosificación también puede variar dependiendo del compuesto usado y la enfermedad particular tratada. Sin embargo, se recomienda un régimen de dosificación de 4 veces al día para el tratamiento de la mayoría de los

trastornos. Para el tratamiento de la ansiedad, depresión o deficiencia cognitiva se recomienda particularmente un régimen de dosificación de 1 ó 2 veces al día. Para el tratamiento de trastornos del sueño se recomienda una dosis única que alcanza rápidamente concentraciones efectivas.

Sin embargo, se debe entender que el nivel de dosis específica para cualquier paciente particular depende de una variedad de factores que incluyen la actividad del compuesto específico que se utiliza, la edad, peso corporal, salud en general, sexo, dieta, tiempo de administración, ruta de administración y velocidad de excreción, combinación de fármaco y la severidad de la enfermedad particular sometida a terapia.

Los compuestos recomendados de la invención tendrán propiedades farmacológicas. Dichas propiedades incluyen, sin carácter limitativo, biodisponibilidad oral, baja toxicidad, enlace de proteína baja en suero y vida media deseada *in vitro* y en vivo. La penetración de la barrera cerebral sanguínea para los compuestos que se usan para tratar trastornos de CNS es necesaria, mientras que a menudo se recomiendan los niveles cerebrales bajos de los compuestos que se usan para tratar trastornos periféricos.

Los ensayos se pueden usar para pronosticar estas propiedades farmacológicas deseadas. Los ensayos que se usan para pronosticar la biodisponibilidad incluyen el transporte a través de monocapas celulares intestinales humanas, incluyendo monocapas de célula Caco-2. La toxicidad a los hepatocitos cultivados se puede usar para pronosticar la toxicidad del compuesto. La penetración de la barrera cerebral sanguínea de un compuesto en humanos se puede pronosticar a partir de los niveles cerebrales del compuesto en animales de laboratorio a los que se aplica el compuesto de manera intravenosa.

El enlace de proteína sérica se puede pronosticar a partir de los ensayos de enlace de albúmina. Dichos ensayos se describen en una revisión de Oravcová, y otros (Journal of Chromatography B (1996) volúmen 677, páginas 1-27).

La vida media del compuesto es proporcional de manera inversa a la frecuencia de la dosificación de un compuesto. Las

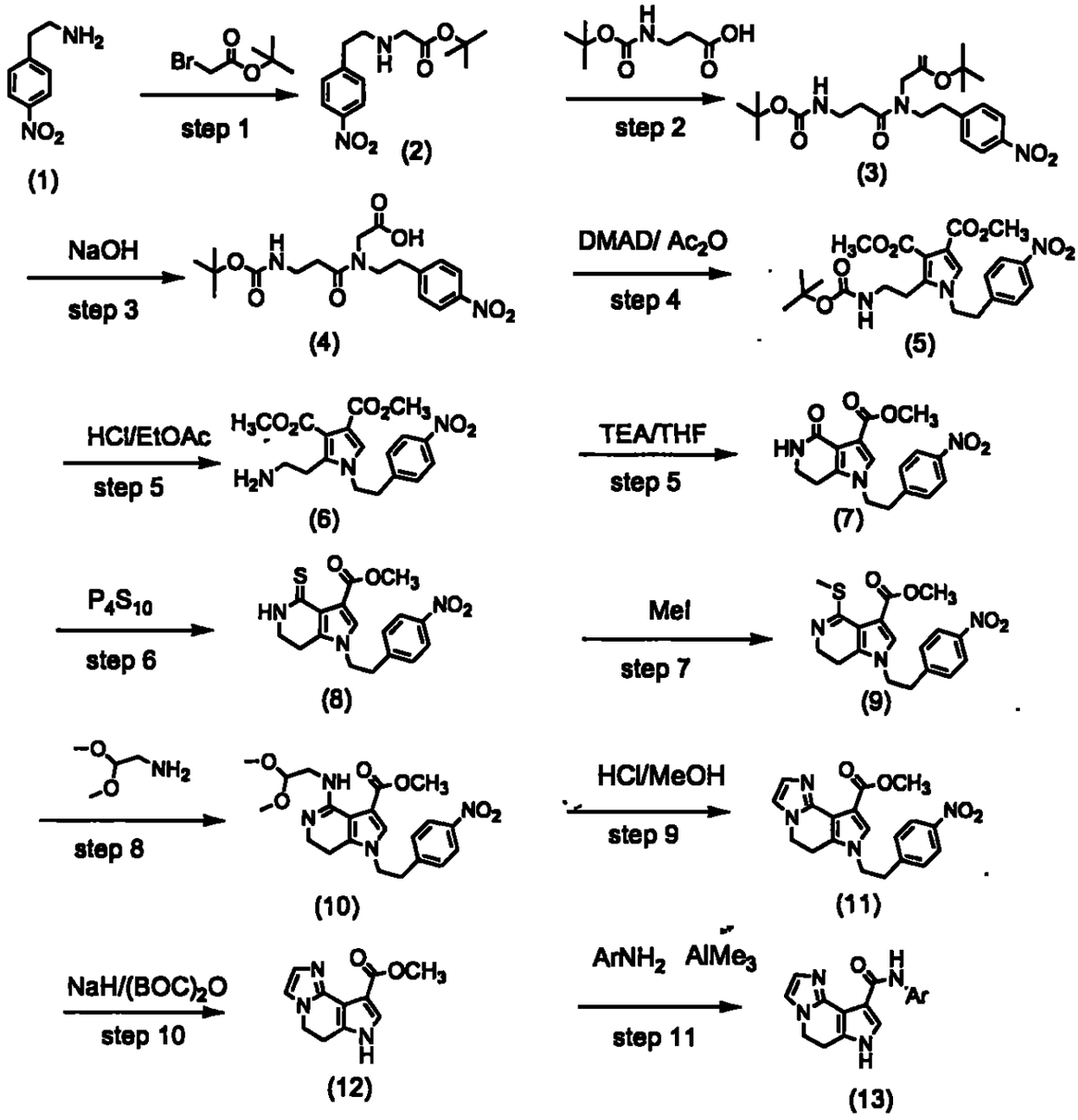
vidas medias *in vitro* de los compuestos se pueden pronosticar a partir de ensayos de vida media microsómica como lo describen Kuhnz y Gieschen (Drug Metabolism and Disposition, (1998) volúmen 26, páginas 1120-1127).

Preparación de compuestos

Una ilustración general de la preparación de compuestos de la Fórmula I en la presente invención se brinda en los Esquemas 1-4. En los esquemas de reacción y discusiones a continuación, a menos que se indique lo contrario, k, R^A, R^1, R^2, R^3, R^4, R^5, R^6 son como se definen anteriormente. Dentro de los esquemas y tablas a continuación, Ar pretende representar $Q-(CH_2)_n-W-(CH_2)_m-Z$ como se define en la Fórmula I o una forma protegida adecuada de la misma. Cuando se requiere un grupo protector, se puede usar un Paso de desprotección opcional. Los grupos protectores adecuados y metodología para la protección y desprotección tales como los que se describen en *Protecting Groups in Organic Synthesis* por T. Greene son bien conocidos y apreciados en la técnica. Los expertos en la materia podrán apreciar fácilmente los compuestos y productos intermedios que requieren protección/desprotección.

Esquema 1

Scheme 1



En el Esquema 1 Paso 1, *p*-nitrofenetilamina se alquiliza con *ter*-butilo bromo acetato para formar el compuesto (2). En general, el exceso de *p*-nitrofenetilamina se usa en esta reacción para minimizar la bis-alquilación. En el Paso 2, la amina secundaria en el compuesto (2) se acopla con ácido 3-aminopropanoico protegido con BOC para formar el compuesto (3). Este acoplamiento se puede lograr al tratar una mezcla del compuesto (2) en piridina con N-Boc 3-aminopropanoico con agente de acoplamiento tal como EDCI con agitación a temperatura ambiente. En el Paso 3, el *ter*-butilo éster en el compuesto (3)

se divide bajo condiciones básicas para formar el ácido carboxílico (4). El compuesto (4) se hace reaccionar con dimetil acetileno dicarboxilato en presencia del anhídrido acético en el Paso 4 para formar el pirrol (5). El pirrol (5) se desprotege de manera secuencial usando cloruro de hidrógeno en el Paso 5 para exponer la amina primaria en el compuesto (6) y se cicliza en presencia de base para formar lactama (7). En el Paso 6, el lactama (7) se convierte a tiolactama (8) mediante reacción bajo condiciones de transferencia de azufre adecuadas tales como calentar con P_4S_{10} en piridina. En los Pasos 7 y 8, el tiolactama (8) se alquiliza con yoduro de metilo en acetona para formar el compuesto tilosulfanilo (9), el cual se hace reaccionar con aminoacetaldehido dimetil acetal en metanol para formar el compuesto (10). La ciclización del derivado de dimetil acetal (10) se logra en el Paso 9 al calentar (10) con ácido clorhídrico concentrado en metanol para formar el compuesto (11). El retiro del grupo protector *p*-nitrofenetilo se logra en el Paso 10 mediante el tratamiento de (11) con hidruro de sodio en presencia de di-*ter*-butilo dicarbonato en dimetilformamida. La amortiguación del exceso de hidruro de sodio con ácido acético seguido de hidrólisis del grupo BOC del nitrógeno pirrol usando bicarbonato potásico acuoso proporciona el material desprotegido deseado (12). Como se indica en el Paso 11 en el Esquema 1, el éster (12) sirve como un agente de acilación versátil para una variedad de complejos de aril y heteroaril amina para formar las amidas correspondientes (13).

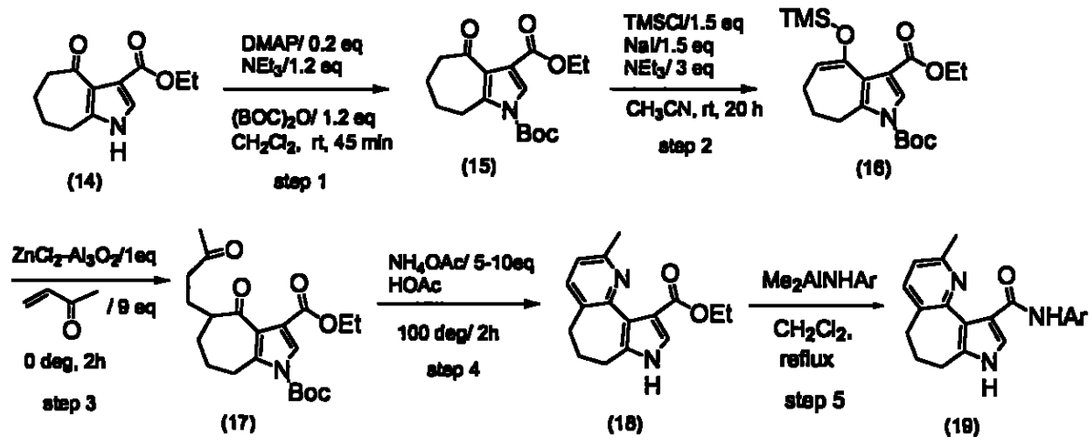
Otro procedimiento para formar derivados de amida (13) se proporciona en el Ejemplo 2ª, e implica hidrólisis del éster (12) mediante calentamiento en presencia de 48% de ácido bromhídrico. El ácido carboxílico resultante se hace reaccionar luego con varias aminas de arilo en presencia de un reagente de acoplamiento adecuado tal como O-(1H-benzotriazol-1-yl)-N,N,N',N'-tetrametilouronio hexafluorofosfato. Alternativamente, el ácido carboxílico puede convertirse al anhídrido mixto mediante reacción con etilo o isobutilo cloroformato en presencia de trietilamina. El anhídrido mixto resultante se hace reaccionar luego con aril aminas.

Los compuestos de la Fórmula II en los que R^5 o R^6 es metilo se forman como se ilustra en el Esquema 1 mediante reacción del compuesto (2) con ácido 3-aminobutírico en el Paso 2. El material ópticamente puro u ópticamente enriquecido se obtiene mediante la separación de intermedios avanzados en una columna HPLC quiral adecuada tal como Chiralpak AD. Para el material resuelto mediante este método, la estereoquímica absoluta es correlativa a una estructura de cristal de rayos x de un derivado de amida quiral. Alternativamente, el ácido 3- aminobutírico ópticamente puro se puede emplear en el Paso 2. Los compuestos de la Fórmula II en los que R^5 y R^6 son metilo se obtienen como se ilustra en el Esquema 1 mediante el uso de 3-amino-3-ácido metilobutírico en el Paso 2.

Los compuestos de la Fórmula II en los que R^3 es metilo se pueden formar como se ilustra en el Esquema 1 utilizando 2-aminopropionaldehído dimetil acetal en el Paso 8.

Los expertos en la técnica podrán observar que las transformaciones sintéticas que se describen mediante el Esquema 1 se pueden lograr usando una variedad de reactivos y condiciones de reacción alternos. Además, se puede observar que los compuestos adicionales dentro del alcance de la Fórmula II pero que no se describen específicamente dentro de la sección experimental se pueden preparar de manera análoga.

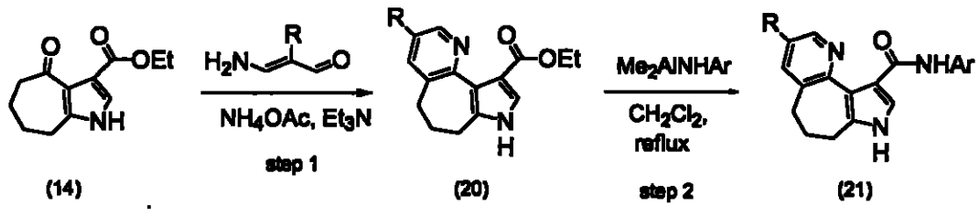
Scheme 2



El Esquema 2 revela un método para convertir la cetona conocida (14) (Patente de los Estados Unidos no. 5,723,462, col.23-31 se incorpora por referencia para su divulgación con

respecto a la síntesis de dichas cetonas) a compuestos de la Fórmula III con R^3 como metilo. El Paso 1 describe la formación del derivado protegido con BOC (15). Típicamente, esta transformación se lleva a cabo tratando el pirrol (14) con di-ter-butil dicarbonato en un solvente adecuado tal como diclorometano o 1,4-dioxano a temperaturas que oscilan entre 0°C a temperatura ambiente en presencia de una base orgáncia tal como trietilamina. Los aditivos tales como 4-N,N-dimetilaminopiridina se pueden usar para facilitar esta transformación. En el Paso 2, el material protegido con BOC (15) se convierte de manera eficiente a silil enol éter (16) mediante el tratamiento con una mezcla de cloruro de trimetilsililo, yoduro de sodio y trietilamina a temperatura ambiente. La adición 1,4- facilitada por ácido Lewis se logra en el Paso 3 mediante el tratamiento con exceso de metil vinil cetona a 0 °C en presencia de cloruro de zinc-alúmina para producir la dicetona (17). El tratamiento de la dicetona (17) con acetato de amonio a temperatura elevada en el Paso 4 proporciona el derivado de piridilo sustituido con metilo deseado (18), el cual se amina en el Paso 5 usando condiciones de aminación descritas anteriormente para el Esquema 1.

Scheme 3



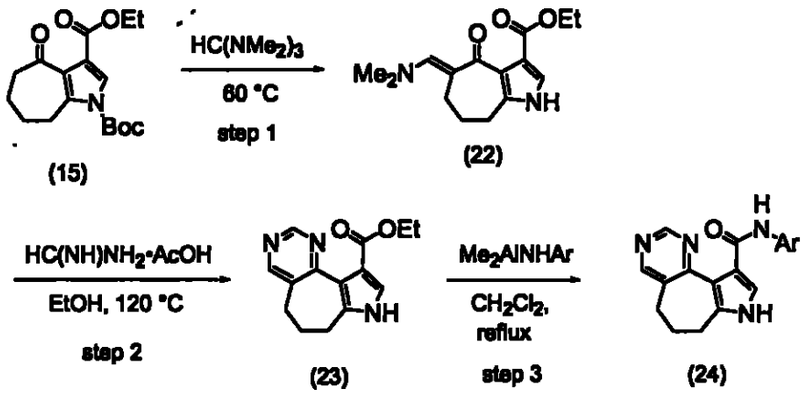
(14) (20) (21)

El Esquema 3 muestra un método para convertir la cetona conocida (14) [US5723462] a compuestos de la Fórmula III con R^3 como hidrógeno. En el Paso 1, la formación de anillo de piridina se logra mediante el tratamiento de cetona (14) con 3-aminoacroleina (R = H) y acetato de amonio catalítico en trietilamina a temperatura elevada. La conversión de (14) a (20) también se puede lograr al calentar (14) en trietilamina con 3-dimetilaminoacroleina en presencia de exceso de acetato de

amonio. Si se usa 3-amino-2-metilacroleina (R = CH_3) en el Paso 1, se forma un anillo de 3-metilpiridina. La aminación se logra en el Paso 2 como se describe anteriormente.

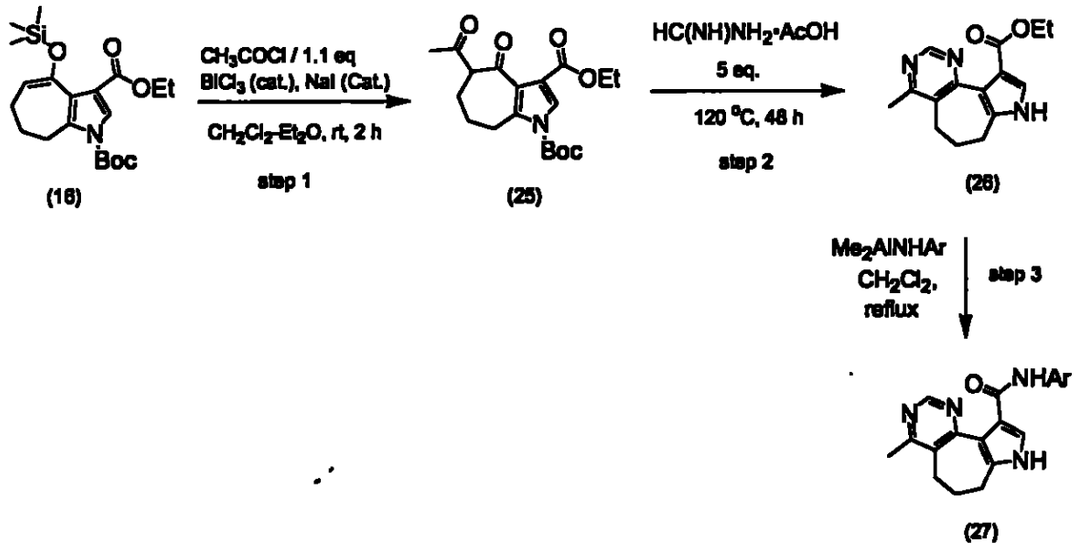
Los expertos en la técnica podrán reconocer que las reacciones que se describen en el Esquema 3 también se pueden aplicar a los compuestos sintetizados de la Fórmula III en los que k=1 teniendo material de inicio a la cetona conocida adecuada.

Scheme 4



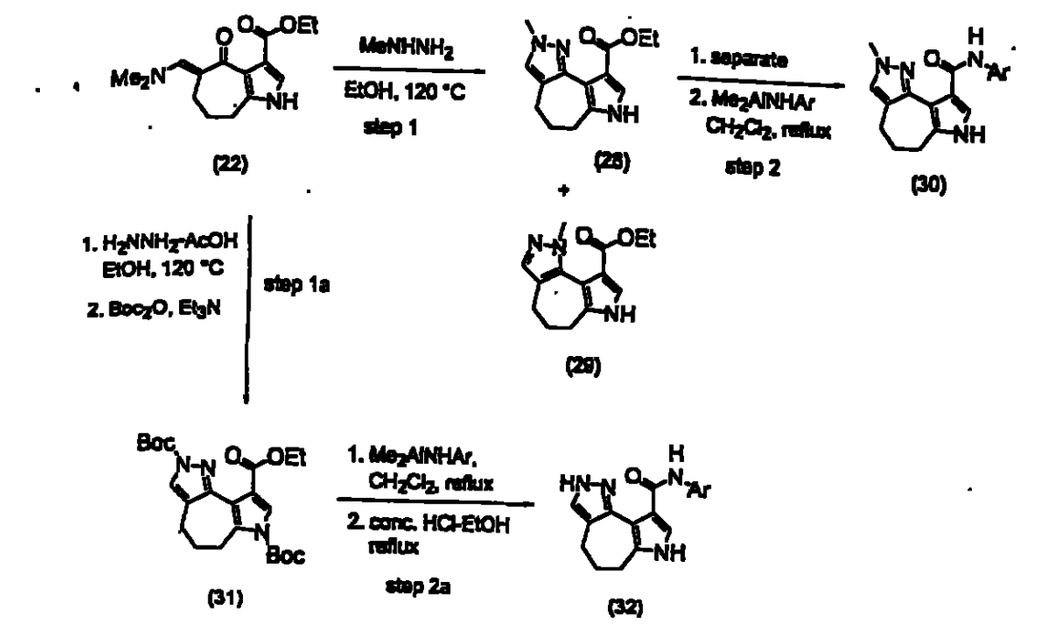
El Esquema 4 describe las condiciones para la conversión de cetona (15) a compuestos de la Fórmula IV. En el Paso 1, la cetona se hace reaccionar con tris(dimetilamino)metano con calentamiento en un tubo sellado para producir el compuesto (22). En el Paso 2, el compuesto (22) se somete a reacción con acetato de formamidina en etanol a 120 °C para producir el derivado de pirimidina (23). Como se muestra en el Paso 3, el compuesto (23) sirve como producto intermedio versátil para la reacción con complejos de aluminio de una variedad de aminas de arilo bajo condiciones descritas previamente.

Scheme 5



El Esquema 5 describe un método para producir compuestos de la Fórmula IV caracterizados porque R^4 es metilo. La reacción del compuesto (16) del Esquema 2 con cloruro de acetilo en presencia de yoduro de sodio catalítico y ácido Lewis adecuado tal como tricloruro de bismuto proporciona dicetona (25). La reacción subsiguiente con acetato de formamidina conforme al Esquema 4, proporciona metilpirimidina (26), la cual se amina en el Paso 3 como se describe previamente.

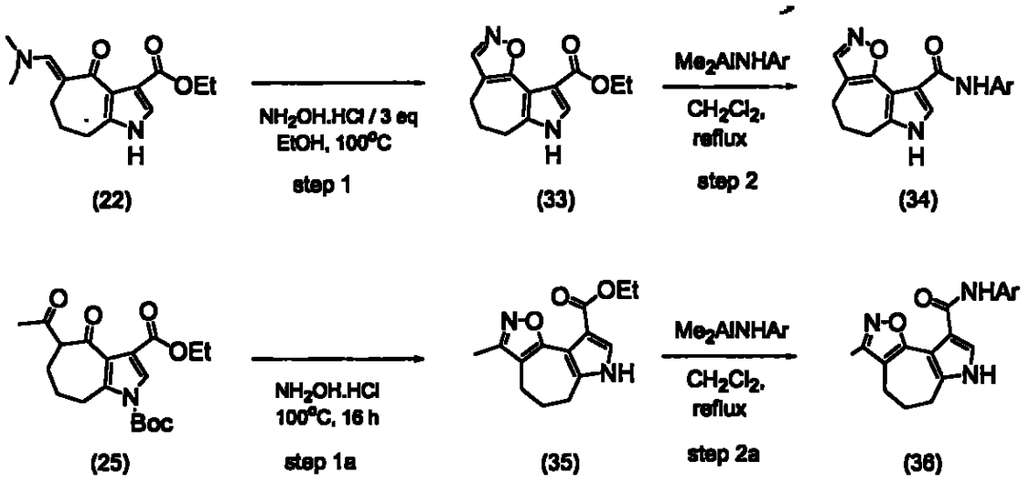
Scheme 6



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El Esquema 6 proporciona un medio para obtener compuestos de la Fórmula V. En el Paso 1, el compuesto (22) del Esquema 4 se hace reaccionar con metilhidrazina (R^A = CH_3) en etanol a 20°C para obtener aproximadamente una mezcla de 3:1 de los compuestos (28) y (29). La estructura del compuesto (28) se asigna basándose en el análisis de cristal de rayos X. Después de la separación por cromatografía en silica gel, el compuesto se convierte a derivados de amida en el Paso 2 como se describe anteriormente. El compuesto (29) se puede hace reaccionar de manera similar. La reacción de (22) con acetato de hidrazina como se muestra en el Paso 1a proporciona un anillo de pirazol con un NH libre. A fin de mejorar las características de manejo de este material, el mismo se encuentra protegido por medio de una reacción con di-ter-butil dicarbonato en presencia de trietilamina para producir el compuesto (31). El compuesto (31) se puede convertir a derivados de amida (32) como se muestra en el Paso 2a usando las condiciones descritas previamente.

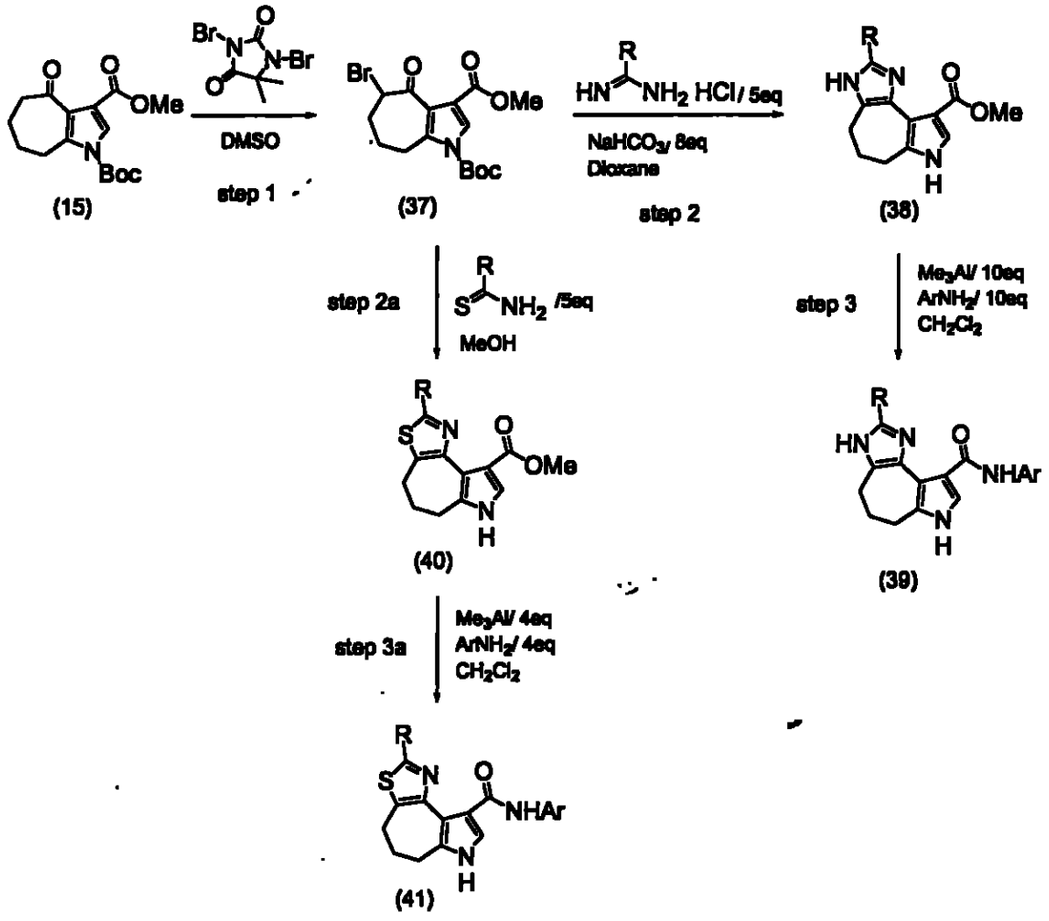
Scheme 7



El Esquema 7 ilustra la síntesis de derivados de isoxazol de la Fórmula VI. En el Paso 1, el compuesto (22) del Esquema 4 se hace reaccionar con clorhidrato de hidroxilamina en etanol a 100

°C para obtener isoxazol (33). La reacción análoga de dicetona (25) con clorhidrato de hidroxilamina produce el isoxazol de metilo (35). La aminación de (33) y (35) se logra en los Pasos 2 y 2a usando condiciones descritas anteriormente.

Scheme 8



La síntesis de los compuestos de la Fórmula VII y la Fórmula VIII se señala en el Esquema 8. En el Esquema 8, Paso 1, la cetona (15) del Esquema 2 se bromina con un agente brominante adecuado tal como 1,3-dibromo- 4,4-dimetil hidantoína. La bromocetona resultante (37) se hace reaccionar con varias amidinas en el Paso 2 para producir los imidazoles correspondientes (38). Típicamente, el clorhidrato de amidina se usa en presencia de base en exceso en 1,4-dioxano como solvente. Alternativamente, la bromocetona (37) se puede hacer reaccionar

con tioamidas para formar derivados de tiazol (40). Los ésteres (38) y (40) reaccionan para formar amidas como en los Pasos 3 y 3a como se describe previamente. Ejemplos en la presente invención de la Fórmula VII y VIII con k=1 se forman usando procedimientos totalmente análogos.

Los expertos en la técnica podrán reconocer que los materiales de inicio se pueden variar y que se pueden usar pasos adicionales para producir compuestos comprendidos por la presente invención, como se demuestra mediante los siguientes ejemplos. En algunos casos, la protección de ciertas funcionalidades reactivas puede ser necesaria para lograr algunas de las transformaciones. En general, los expertos en la materia de la síntesis orgánica podrán apreciar la necesidad de dichos grupos protectores así como las condiciones necesarias para unir y retirar dichos grupos.

La invención se ilustra además mediante los siguientes ejemplos, los cuales no se deben considerar como limitantes de la invención en cuanto al alcance o al espíritu de los procedimientos específicos descritos en los mismos.

EJEMPLOS

Ejemplo 1

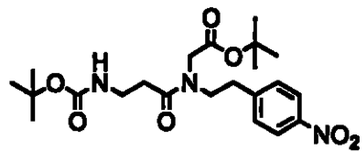
Preparación de 5,6-dihidro-4H-1,3a,6-triaza-as-indaceno-8-ácido carboxílico metil éster

Paso 1:

A una solución de p-nitro fenotilamina (45.3mmol) en 75 ml de agua es suficiente agregar 30% de NaOH en agua para lograr un pH de 12. La capa de agua se extrae con Diclorometano. Las capas orgánicas se recolectaron, se secaron sobre Na_2SO_4, y se evaporaron al vacío produciendo 7.4 g de aceite marrón amarillento (98%). A una mezcla disuelta parcialmente de base libre (44.58mmol) en éter se agrega lentamente ácido bromo acético t-butil éster (22.29 mmol) durante 15 min. Usando un aparato de agitación elevado se agitó por 3 ½ días bajo una atmósfera de nitrógeno. Se agrega agua a la mezcla de la

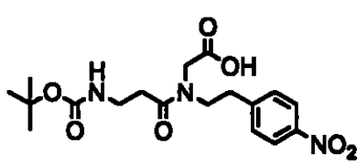
reacción, y la capa de éter se lava 3 veces con agua y una vez con salmuera. Las capas de agua se recolectaron y volvieron a extraer con mezcla 50/50 de éter/acetato de etilo. Todas las capas orgánicas se recolectaron, secaron sobre Na_2SO_4, y se evaporaron al vacío. El sólido anaranjado oscuro se sometió a cromatografía usando Hexano 3: acetato de etilo 1 como fase móvil para producir 3.48g de sólido amarillo (56%). 1HNMR (CDCl3) 1.42 (s, 9H), 2.90 (s, 4H), 3.29 (s, 2H), 7.35 (d, 2H), 8.13 (d, 2H) LRMS calculado 280.33; se encontró [M+H] 281.1

Paso 2:



A una mezcla de 2-(4-Nitro-fenil)-etilamino-ácido acético ter-butil éster en 1ml piridina se agregó N-Boc B alanina (0.178mmol) y EDCI (0.214mmol). Después de agitar a temperatura ambiente por 3½ horas, la piridina se evaporó. El aceite restante se vierte en acetato de etilo y se lava con ácido diluído. Las capas orgánicas se combinaron, se secaron sobre Na_2SO_4, y se evaporaron al vacío produciendo (3-ter-Butoxicarbonilamino-propionil)-[2-(4-nitro-fenil)-etil]-α-amino-ácido acético ter-butil éster, 78mg en forma de aceite amarillo. ^{1}HNMR (CD_3OD) 1.45 (d, 9H), 1.50 (d, 9h), 2.46-2.48 (m, 2H), 2.98-3.08 (m, 2H), 3.27-3.35 (m, 2H), 3.62-3.75 (m, 2H), [4.03, 4.11] (s, 2H), 7.56-7.59 (m, 2H), 8.20-8.23 (m, 2H) LRMS calculado 451.52; se encontró [M] 451.2

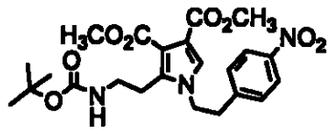
Paso 3:



A una mezcla de {(3-ter-Butoxicarbonilamino-propionil)-[2-(4-nitro-fenil)-etil]-amino}-ácido acético ter-butil éster 2.5mmol) en 11 ml THF se agrega 22 ml de agua, y luego NaOH (17.5mmol). Después de calentar a 60°C por 5 ½ horas, se amortigua con ácido

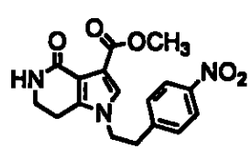
acético (20mmol). Se coloca en el refrigerador por 2½ días. El THF se evapora, y el agua restante se extrae varias veces con EtOAc. Las capas orgánicas se combinaron, se secaron sobre Na_2SO_4, y se evaporaron al vacío produciendo {(3-ter-Butoxicarbonilamino-propionil)-[2-(4-nitro-fenil)-etil]-amino}-ácido acético, 983mg, como un aceite/espuma amarillo/marrón oscuro (99%). ^{1}HNMR (CD_3OD) 1.40 (d, 9H), 2.44-2.45 (m, 2H), [2.98, 3.03] (t, 2H), 3.22-3.30 (m, 2H), [3.60, 3.65] (t, 2H), 4.06 (s, 2H), [7.52, 7.54] (d, 2h), 8.16 (t, 2H) LRMS calculado 395.42; se encontró [M-H] 394.0

Paso 4:



A una mezcla de {(3-ter-Butoxicarbonilamino-propionil)-[2-(4-nitro-fenil)-etil]-amino}-ácido acético (0.253mmol) en 1ml anhidruro acético se agrega dimetil acetileno dicarboxilato (0.278mmol). Después de agitación a 85°C por 4½ horas, el solvente se evapora al vacío. El aceite marrón oscuro se somete a cromatografía usando acetato de etilo 2: Hexano 3 como una fase móvil para producir 2-(2-ter-Butoxicarbonilamino-etil)- 1-[2-(4-nitro-fenil) -etil]-1H-pirrol-3,4-ácido dicarboxílico dimetil éster, 79mg, como un aceite amarillo (66%). ^{1}HNMR (CD_3OD) 1.50 (s, 9H), 2.84 (t, 2H), 3.14-3.34 (m, 4H), 3.77 (s, 3H), 3.82 (s, 3H), 4.33 (t, 2H), 6.74 (t, 1H), 7.29 (s, 1H), 7.44 (d, 2H), 8.16 (d, 2H) LRMS calculado 475.50; se encontró [M] 475.1

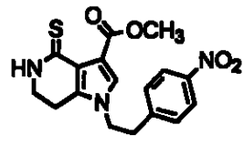
Paso 5:



Una solución de 2-(2-tert-Butoxicarbonilamino-etil)-1-[2-(4-nitro-fenil)-etil]-1H-pirrol-3,4-ácido dicarboxílico dimetil éster (0.292mmol) en 10 HCl/acetato de etilo se agita a temperatura ambiente por ½ hora. El solvente se evapora al vacío, y se coloca en la bomba de alto vacío por varias horas

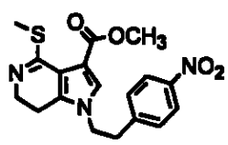
produciendo 139 mg de sólido blanco ^{1}HNMR (CD_3OD) 2.92-2.94 (m, 2H), 2.97-2.99 (m, 2H), 3.20 (t, 3H), 3.75 (s, 3H), 3.79 (s, 3H), 4.26 (t, 2H), 7.33 (d, 3H), 8.15 (d, 2H) LRMS calculado; 375.38 se encontró [M+H] 376.2), lo cual se agita en 7ml de THF con trietilamina (1.168mmol) a 60°C por 16 horas. El solvente se evapora al vacío, y se somete a cromatografía usando acetato de etilo 9: MeOH 1 como fase móvil para producir 1-[2-(4-Nitro-fenil)-etil]-4-oxo-4,5,6,7-tetrahidro-1H-pirrol[3,2-c]piridina-3-ácido carboxílico metil éster, 73mg, como un sólido blanco (73%). ^{1}HNMR (CD_3OD) 2.47 (t, 2H), 3.16 (t, 2H), 3.23-3.33 (m, 2H), 3.74 (s, 3H), 4.23 (t,2H), 7.30 (t, 3H), 8.11 (d, 2H) LRMS calculado 343.33; se encontró [M+H] 344.2

Paso 6:



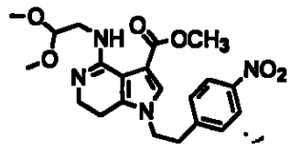
En un matraz de base redonda bajo atmósfera N_2 atm. se combinan 1-[2-(4-Nitro-fenil)-etil]-4-oxo-4,5,6,7-tetrahidro-1H-pirrolo[3,2-c]piridina-3-ácido carboxílico metil éster (48.64mmol), P_4S_{10} (24.32mmol) y 240ml piridina, y se calientan a 65°C por 8 horas. Después de enfriar a temperatura ambiente se vierte sobre ~600 ml de hielo y se agita por 2 horas. El sólido amarillo se filtra, se lava (2 veces) con agua, y se seca en la bomba de alto vacío por 18 horas para producir 1-[2-(4-Nitro-fenil) -etil]-4-tioxo- 4,5,6,7-tetrahidro-1H-pirrol[3,2-c]piridini-3-ácido carboxílico metil éster, 10.24g, como un sólido amarillo (65%). ^{1}HNMR (CD_3OD) 2.43 (t, 2H), 3.16 (t, 2H), 3.28-3.33 (m, 2H), 3.75 (s, 3H), 4.21 (t, 2H), 7.16 (s, 1H), 7.30 (d, 2H), 8.13 (d, 2H) LRMS calculado 359.41; se encontró [M+H] 360.2

Paso 7:



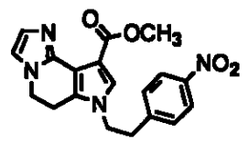
A una solución de 1-[2-(4-Nitro-fenil)-etil]-4-tioxo-4,5,6,7-tetrahidro-1H-pirrol[3,2-c]piridina-3-ácido carboxílico metil éster (28.16mmol) en 130ml acetona se agrega MeI (56.32mmol) y K_2CO_3 (84.48mmol). La mezcla de la reacción se agita a temperatura ambiente por 2½ horas en donde la acetona se evapora al vacío. El aceite restante se vierte en Diclorometano y se lava dos veces con agua. Los solventes orgánicos se recolectaron, se secaron sobre Na_2SO_4, y se evaporaron al vacío para producir 4-Metilosulfanil-1-[2-(4-nitro-fenil)-etil]-6,7-dihidro- 1H-pirrol[3,2-c]piridina-3-ácido carboxí metil éster, 9.46g, como una espuma amarilla (90%). ^{1}HNMR (CD_3OD) 2.34-2.39 (m, 5H), 3.21 (t, 2H), 3.56 (t, 2H), 3.80 (s, 3H), 4.29 (t, 2H), 7.32-7.38 (m, 3H), 8.17 (d, 2H) LRMS calculado 373.43, se encontró [M+H] 374.2

Paso 8:



En un matraz de base redonda se combinaron 4-Metilsulfanil-1-[2-(4-nitro-fenil)-etil]-6,7-dihidro-1H-pirrol[3,2-c]piridina-3-ácido carboxílico metil éster (25.33mmol), amino acetaldehído dimetil acetal (63.32mmol) y 125ml de MeOH (una parte "desgrasada" que más adelante se agregó a la solución), y se agitó a temperatura ambiente por 20 horas. El solvente se evapora al vacío produciendo 4-(2,2-Dimetoxi-etilamino)-1-[2-(4-nitro-fenil)-etil]-6,7-dihidro-1H-pirrol[3,2-c]piridina-3-ácido carboxílico metil éster, 11.56g, como un aceite/sólido amarillo que se toma en crudo.

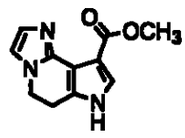
Paso 9:



A una solución de 4-(2,2-Dimetoxi-etilamino)-1-[2-(4-nitro-fenil)-etil]-6,7-dihidro-1H-pirrol[3,2-c]piridina-3-ácido carboxílico metil éster (25.33mmol) en 125ml MeOH se agrega 10ml

de HCl concentrado. Se calienta a 63°C por 15 horas. Debido a que la reacción no está completa se agrega otros 5ml de HCl concentrado, y se calienta nuevamente a 63°C por 10 horas. El solvente se evapora al vacío, y el aceite restante se disuelve en MeOH agregando K_2CO_3 (1.2eq.). Después de agitar a temperatura ambiente por 1 hora, el sólido se filtra, se lava con MeOH, y el filtrado se evapora al vacío produciendo un sólido amarillo que se protona. El producto protonado se agita en Diclorometano, y se satura con solución de $NaCO_3$ hasta que todo se disuelva. Las dos capas se separaron, y la capa de agua se extrajo dos veces con diclorometano. Las capas orgánicas se recolectaron, se secaron y se evaporaron al vacío produciendo una base libre que se tituló en acetato de etilo produciendo 6-[2-(4-Nitro-fenil)-etil]-5,6-dihidro- 4H-1,3a,6-triaza-as-indaceno -8-ácido carboxílico metil éster, 9.11g, como un sólido amarillo (77%). ^{1}HNMR (CD_3OD) 2.76 (t, 2H), 3.18 (t, 2H), 3.78 (s, 3H), 4.07 (t, 2H), 4.28 (t, 2H), 6.94 (s, 1H), 7.01 (s, 1H), 7.31 (d, 3H), 8.10 (d, 2H) LRMS calculado 366.38; se encontró [M+H] 367.2

Paso 10:

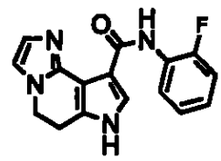


Una solución de 6-[2-(4-Nitro-fenil)-etil]-5,6-dihidro-4H-1,3a,6-triaza-as-indaceno-8-ácido carboxílico metil éster (19.67mmol) en 100ml DMF se trata con hidruro de sodio (60%, 1.97g, 49.18 mmol) por porciones. La reacción se completa en alrededor de 2 horas a 20°C. Se agrega cloroformo, y la mezcla de la reacción se enfría a 5°C antes de la adición por goteo de ácido acético (3.15 ml, 55.08 mmol) hasta un pH de 1-3. Se agrega una solución saturada de KHCO3 acuoso (150ml), se agita, y se separa. La fase orgánica separada se lava con agua dos veces. El filtrado se concentra directamente. La mayoría de la DMF se retira mediante alto vacío para proporcionar un sólido húmedo marrón. El sólido húmedo se enfría a temperatura ambiente. Se agrega el éter, se agita, y se filtra para producir un sólido marrón que se seca en aire durante toda la noche para brindar 5,6-dihidro-4H-1,3a,6-triaza-as-indaceno-8-ácido carboxílico metil éster, 9.11g, (77%). ^{1}HNMR

(CD_3OD) 3.05 (t, 2H), 3.86 (s, 3H), 4.25 (t, 2H), 6.97 (s, 1H), 7.05 (s, 1H), 7.40 (s, 1H) LRMS calculado 217.23; se encontró [M-H] 216.1

Ejemplo 2

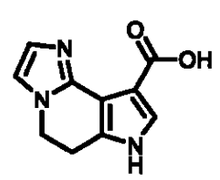
Preparación de 5,6-Dihidro-4H-1,3a,6-triaza-as-indaceno-8-ácido carboxílico (2-fluoro-fenil)-amida



A una solución de 2-fluoroanilina (84uL, 0.829 mmol) en 2 mL diclorometano a temperatura ambiente se agrega una solución 2M de trimetilaluminio en tolueno (414 uL, 0.829 mmol), y la reacción se agita a temperatura ambiente por 0.5 horas. Esta solución se aplica con jeringa al producto puro 5,6-dihidro-4H-1,3a,6-triaza-as-indaceno-8-ácido carboxílico metil éster (90 mg, 0.415 mmol), y se agita por reflujo durante 10 horas. La mezcla de la reacción se diluye con diclorometano, y se vierte en agua (30 mL). Toda la mezcla se filtra a través de celite, y luego se separa. La fase acuosa se lava con diclorometano, y las capas orgánicas combinadas se secaron (Na2SO4) y concentrarón al vacío. El residuo se purificó mediante cromatografía rápida-40 (EtOAc) para proporcionar el producto, 5,6-Dihidro-4H-1,3a,6-triaza-as-indaceno-8-ácido carboxílico (2-fluoro-fenil)-amida, 63mg, como un aceite vítreo (48%). ^{1}HNMR (DMSO) 3.25 (t, 2H), 4.44 (t, 2H), 7.23-7.42 (m, 4H), 7.57-7.63 (m, 2H), 7.96 (s, 1H) LRMS calculado 296.30; se encontró (M-H) 295.0

Ejemplo 2a

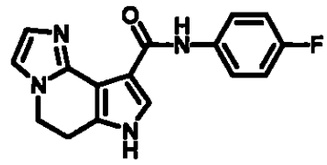
5,6-Dihidro-4H-1,3a,6-triaza-as-indaceno-8-ácido carboxílico bromhidrato



Una solución de 5,6-hidro-4H-1,3a,6-triaza-as-indaceno-8-ácido carboxílico metil éster (516mg) y 48% de ácido bromhídrico (5mL) se calienta a 60° por 60 horas. La mezcla se enfría a temperatura ambiente, y se concentra al vacío. El residuo se vuelve suspensión acuosa con éter de dietilo, y el éter se decanta. Esto se repite hasta que no hay más color visible en la capa de éter. El sólido restante se seca al vacío para proporcionar 5,6-dihidro-4H-1,3a,6-triaza-as-indaceno-8-ácido carboxílico bromhidrato, 350mg, como un sólido marrón 1H NMR(d6DMSO) 3.17 (2H, t), 4.40 (2H, t), 7.35 (1H, d), 7.57 (1H, d), 7.63 (1H, s), 12.34 (1H, s), 12.45 (1H, s).

Ejemplo 2b

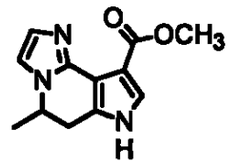
5,6-Dihidro-4H-1,3a,6-triaza-as-indaceno-8-ácido carboxílico (4-fluorofenil)amida



Una mezcla de 5,6-dihidro-4H-1,3a,6-triaza-as-indaceno-8-ácido carboxílico bromhidrato (58mg), O-(1H-benzotriazol-1-il)-N,N,N',N'-tetrametilouronio hexafluorofosfato (181mg), trietilamina (0.07mL), 4-fluoroanilina (30mg), y N,N-dimetilformamida (4mL) se calienta a 40° por 18 horas. La mezcla se enfría a temperatura ambiente, se trata con agua (15mL), y se extrae con acetato de etilo (3 x 50mL). Las capas orgánicas combinadas se lavaron con agua (2 x 15mL) y salmuera (1 x 15mL), se secaron sobre sulfato de magnesio, y se concentraron *al vacío*. El residuo se purifica mediante cromatografía en capa fina preparatoria sobre silica gel, eluyendo con metanol al 5% en diclorometano, para proporcionar 5,6-dihidro-4H-1,3a,6-triaza-as-indaceno-8-ácido carboxílico (4-fluorofenil)amida, como un sólido marrón claro, 18mg, LRMS calculado 296.30; se encontró [M+H] 297.2.

Ejemplo 2c

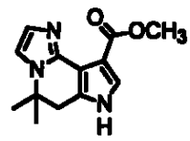
4-Metil-5,6-dihidro-4H-1,3a,6-triaza-as-indaceno-8-ácido carboxílico metil éster



El compuesto del título se prepara siguiendo el procedimiento señalado en el Ejemplo 1 empezando con 3-ácido aminobutírico. Electrorociador MS *m/z* 232 [M+1]; ^{1}H NMR (DMSO-d6, 300 MHz) δ 11.62 (s, 1H), 7.38 (s, 1H), 7.08 (s, 1H), 6.81 (s, 1H), 4.43 (m, 1H), 3.68 (s, 3H), 3.05 (dd, 1H), 2.67 (dd, 1H), 1.38 (d, 3H).

Ejemplo 2d

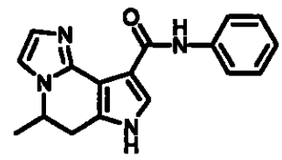
4,4-Dimetil-5,6-dihidro-4H-1,3a,6-triaza-as-indaceno-8-ácido carboxílico metil éster



El compuesto del título se prepara siguiendo el procedimiento señalado en el Ejemplo 1 empezando con 3-amino-3-ácido metilbutírico. Electrorociador MS *m/z* 246 [M+1]; ^{1}H NMR (DMSO-d6, 300 MHz) δ 11.70 (s, 1H), 7.39 (s, 1H), 7.18 (s, 1H), 6.82 (s, 1H), 3.68 (s, 3H), 2.85 (s, 2H), 1.40 (s, 6H).

Ejemplo 2e

4-Metil-5,6-dihidro-4H-1,3a,6-triaza-as-indaceno-8-ácido carboxílico fenil amida

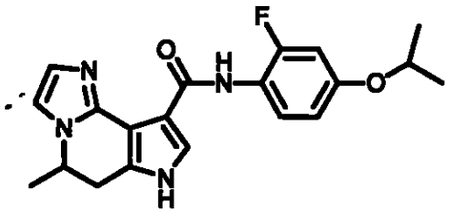


Una mezcla de 4-metil-5,6-dihidro-4H-1,3a,6-triaza-as-indaceno-8-ácido carboxílico bromhidrato (25mg), anilina (12mg), 1-[3-(dimetilamino)propil] -3-etil carbodiimida clorhidrato (23mg), 1,4-dioxano (1.5mL), y agua (1.5mL) se agita a temperatura ambiente por 4 días. Se agrega 0.5N de solución de hidróxido sódico (3mL) y la mezcla se extrae con diclorometano (3 x 50mL). Las capas combinadas se lavaron con salmuera (1 x 10mL), se secaron sobre sulfato de magnesio, y se concentraron al vacío. El residuo se purificó mediante cromatografía de capa fina

preparatoria sobre silica gel, eluyendo con metanol al 5% en diclorometano, para proporcionar 4-metilo-5,6-dihidro-4H-1,3a,6-triaza-as-indaceno-8-ácido carboxílico fenil amida, como un sólido crema, 7mg, LRMS calculado 292.34; se encontró [M+H] 293.2.

Ejemplo 3

4-Metil-5,6-dihidro-4H-1,3a,6-triaza-as-indaceno-8-ácido carboxílico (2-fluoro-4-isopropoxifenil)amida



Se agrega cloroformato de etilo (66µL) por goteo a una mezcla enfriada con hielo de 4-metil-5,6-dihidro-4H-1,3a,6-triaza-as-indaceno-8-ácido carboxílico bromhidrato (192mg), trietilamina (0.33mL), y N,N-dimetilformamida (5mL). La mezcla se agita a 0° por 1 hora, luego a temperatura ambiente por 30 minutos. Se agrega 2-Fluoro-4-isopropoxianilina (66mg), y la mezcla se agota a temperatura ambiente por 18 horas. La mezcla se diluye con acetato de etilo (50mL), luego se trata con agua (25mL), y se extrae con acetato de etilo (3 x 50mL). Las capas orgánicas combinadas se lavaron con agua (2 x 20mL) y salmuera (1 x 20mL), se secaron sobre sulfato de magnesio, y se concentraron al vacío. El residuo se purificó mediante cromatografía de capa fina preparatoria sobre silica gel, eluyendo con éter dietílico, para proporcionar un sólido marrón. Esto se trata con etanol (2mL), y se satura con solución de carbonato potásico acuoso saturado (1mL), y la mezcla se calienta a 60° por 30 minutos. La mezcla se deja enfriar a temperatura ambiente, se diluye con agua (3mL) y se extrae con acetato de etilo (3 x 30mL). Las capas orgánicas combinadas se lavaron con salmuera (1 x 10mL), se secaron sobre sulfato de magnesio, y se concentraron al vacío. El residuo aceitoso se purificó mediante cromatografía de capa fina preparatoria sobre silica gel, eluyendo con metanol al 10% en diclorometano, para proporcionar 4-metil-5,6-dihidro-4H-1,3a,6-triaza-as-indaceno-8-ácido carboxílico (2-fluoro-4-

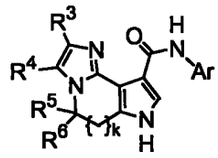
isopropoxifenil)amida, como un sólido amarillo claro, 10mg, LRMS calculado 368.40; se encontró [M+H] 369.2.

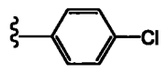
Ejemplo 4

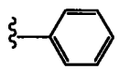
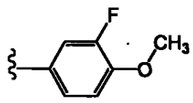
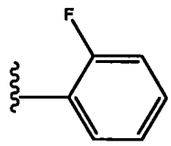
Compuestos adicionales de ácido 1,3a,6-triaza-as-indaceno-8-carboxílico

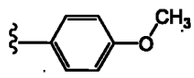
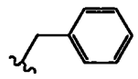
Usando métodos como se muestran de manera general en el Esquema 1 y que además se ilustran en los Ejemplos 1, 2-2e y 3, se sintetizaron los compuestos que se muestran en la Tabla 1.

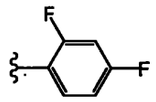
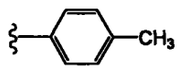
TABLA 1

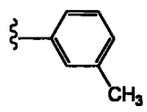
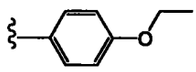


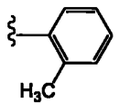
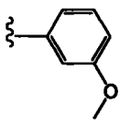
Com #	Nombre	R3	R4	R5	R6	k	Ar	Datos del Espectro
1.	5,6-Dihidro-4H-1,3a,6-triaza-as-indaceno-8-ácido carboxílico (4-cloro-fenil)-amida	H	H	H	H	1		1HNMR (DMSO) 3.24 (t, 2H), 4.44 (t, 2H), 7.37 (s, 1H), 7.45 (d, 2H), 7.65 (s, 1H), 7.82 (d, 2H), 8.01 (m, 1H) LRMS calculó 312.76 se encontró (M-H) 311.0

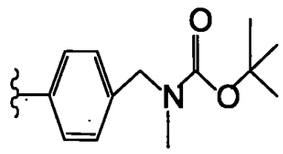
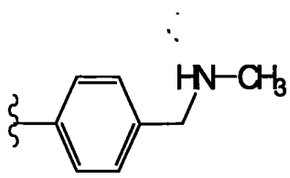
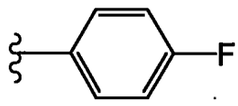
2.	5,6-Dihidro-4H-1,3a,6-triaza-as-indaceno-8-ácido carboxílico fenilamida	H	H	H	H	1		^{1}HNMR (DMSO) 3.24 (t, 2H), 4.44 (t, 2H), 7.14 (t, 1H), 7.37-7.42 (m, 3H), 7.65 (s, 1H), 7.77 (d, 2H), 8.00 (s, 1H) LRMS calculó 278.31 se encontró (M-H) 277.0
3.	5,6-Dihidro-4H-1,3a,6-triaza-as-indaceno-8-ácido carboxílico (3-fluoro-4-metoxi-fenil)-amida	H	H	H	H	1		1HNMR (DMSO) 3.23 (t, 2H), 3.84 (s, 3H), 4.44 (t, 2H), 7.19 (t, 1H), 7.37-7.44 (m, 2H), 7.64 (s, 1H), 7.79 (d, 1H), 7.95 (s, 1H) LRMS calculó 326.33 se encontró (M-H) 325.2
4.	5,6-Dihidro-4H-1,3a,6-triaza-as-indaceno-8-ácido carboxílico 2-fluoro-bencilamida	H	H	H	H	1		1HNMR (DMSO) 3.21 (t, 2H), 4.41 (t, 2H), [4.52, 4.58] (d, 2H), 7.17-7.24 (m, 2H), 7.31-7.41 (m, 3H), 7.60 (s, 1H), 7.78 (s, 1H) LRMS calculó 310.33 se encontró [M-H] 309.0

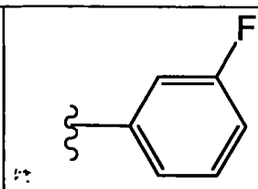
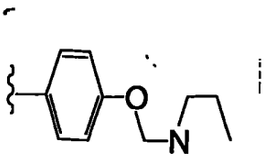
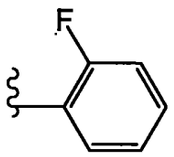
5.	5,6-Dihidro-4H-1,3a,6-triaza-as-indaceno-8-ácido carboxílico (4-metoxi-fenil)-amida	H	H	H	H	1		1HNMR (DMSO) 3.19 (t, 2H), 3.72 (s, 3H), 4.39 (t, 2H), 6.92 (d, 2H), 7.31 (s, 1H), 7.60 (d, 3H), 7.92 (s, 1H) LRMS calculó 308.34 se encontró [M+H] 309.0
6.	5,6-Dihidro-4H-1,3a,6-triaza-as-indaceno-8-ácido carboxílico benzilamida	H	H	H	H	1		1HNMR (DMSO) 3.18 (t, 2H), 4.37 (t, 2H), 4.49 (d, 2H), 7.22-7.24 (m, 1H), 7.27-7.33 (m, 5H), 7.56 (s, 1H), 7.72 (s, 1H), 9.03 (m, 1H) LRMS calculó 292.34 se encontró [M+H] 293.4

7.	5,6-Dihidro-4H-1,3a,6-triaza-as-indaceno-8-ácido carboxílico (2,4-difluoro-fenil)-amida	H	H	H	H	1		1HNMR (CD3OD) 3.28-3.31 (m, 2H), 4.7 (t, 2H), 6.95-7.04 (m, 1H), 7.05-7.09 (m, 1H), 7.31 (s, 1H), 7.43 (s, 1H), 7.69-7.74 (m, 1H), 7.79 (s, 1H), 9.80 (s, 1H) LRMS calculó se encontró [M+]
8.	5,6-Dihidro-4H-1,3a,6-triaza-as-indaceno-8-ácido carboxílico p-tolilamida	H	H	H	H	1		1HNMR (CD3OD) 2.30 (s, 3H), 3.10 (t, 2H), 4.24 (t, 2H), 7.03-7.04 (m, 2H), 7.14 (d, 2H), 7.42 (s, 1H), 7.69 (d, 2H) LRMS calculó 292.34 se encontró [M+H] 293.3

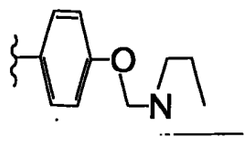
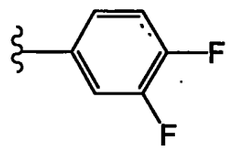
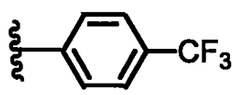
9.	5,6-Dihidro-4H-1,3a,6-triaza-as-indaceno-8-ácido carboxílico m-tolilamida	H	H	H	H	1		1HNMR (CD3OD) 2.34 (s, 3H), 3.11 (t, 2H), 4.24 (t, 2H), 6.89 (d, 1H), 7.04 (s, 2H), 7.20 (t, 1H), 7.42 (s, 1H), 7.60 (d, 1H), 7.65 (s, 1H) LRMS calculó 292.34 se encontró [M+H] 293.2
10.	5,6-Dihidro-4H-1,3a,6-triaza-as-indaceno-8-ácido carboxílico (4-etoxi-fenil)-amida	H	H	H	H	1		1HNMR (CD3OD) 1.37 (t, 3H), 3.10 (t, 2H), 4.01 (q, 2H), 4.23 (t, 2H), 6.90 (d, 2H), 7.02 (d, 2H), 7.41 (s, 1H), 7.69 (d, 2H) LRMS calculó 322.37 se encontró [M+H] 323.3

11.	5,6-Dihidro-4H-1,3a,6-triaza-as-indaceno-8-ácido carboxílico o-tolilamida	H	H	H	H	1		1HNMR (CD3OD) 2.37 (s, 3H), 3.12 (t, 2H), 4.24 (t, 2H), 6.91 (s, 1H), 7.01 (s, 1H), 7.09 (t, 1H), 7.18 (t, 1H), 7.24 (d, 1H), 7.44 (s, 1H), 7.50 (d, 1H) LRMS calculó 292.34 se encontró [M+H] 293.3
12.	5,6-Dihidro-4H-1,3a,6-triaza-as-indaceno-8-ácido carboxílico (3-metoxi-fenil)-amida	H	H	H	H	1		1HNMR (CD3OD) 3.11 (t, 2H), 3.80 (s, 3H), 4.24 (t, 2H), 6.64 (d, 1H), 7.04 (s, 2H), 7.23 (t, 1H), 7.31 (d, 1H), 7.43 (s, 1H), 7.57 (s, 1H) LRMS calculó 308.33 se encontró [M+H] 309.2

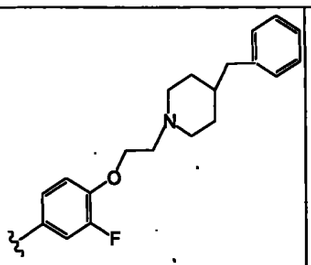
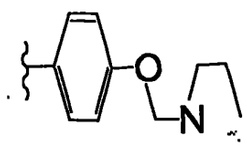
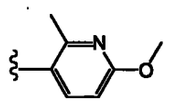
13.	{4-[(5,6-Dihidro-4H-1,3a,6-triaza-as-indaceno-8-carbonil)-amino]-bencil}-metil-ácido carbámico ter-butil éster	H	H	H	H	1		
14.	5,6-Dihidro-4H-1,3a,6-triaza-as-indaceno-8-ácido carboxílico (4-metilaminometil-fenil)-amida	H	H	H	H	1		1HNMR (CD3OD) 2.70 (s, 1H), 3.28-3.31 (m, 2H), 4.15 (s, 2H), 4.46 (t, 2H), 7.35 (s, 1H), 7.45-7.49 (m, 3H), 7.81 (s, 1H), 7.87-7.90 (m, 2H) LRMS calculó 321.38 se encontró [M+H] 322.3
15.	5,6-Dihidro-4H-1,3a,6-triaza-as-indaceno-8-ácido carboxílico (4-fluoro-fenil)-amida	H	H	H	H	1		

16.	5,6-Dihidro-4H-1,3a,6-triaza-as-indaceno-8-ácido carboxílico (3-fluoro-fenil)-amida	H	H	H	H	1		
17.	4-Metil-5,6-dihidro-4H-1,3a,6-triaza-as-indaceno-8-ácido carboxílico [4-(2-propilamino-etoxi)-fenil]-amida	H	H	H	CH3	1		
18.	4-Metil-5,6-dihidro-4H-1,3a,6-triaza-as-indaceno-8-ácido carboxílico (2-fluoro-fenil)-amida	H	H	H	CH3	1		LRMS calculó 310.33, se encontró [M+H] 311.1

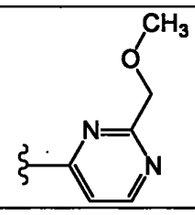
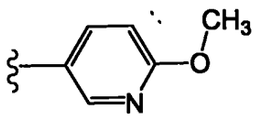
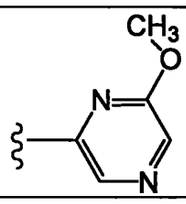
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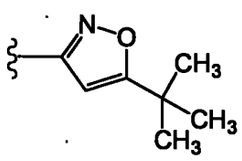
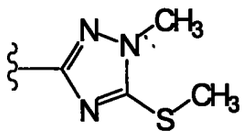
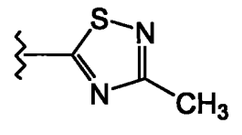
19.	5,6-Dihidro-4H-1,3a,6-triaza-as-indaceno-8-ácido carboxílico [4-(2-propilamino-etoxi)-fenil]-amida	H	H	H	H	1		LRMS calculó 379.46, se encontró [M+H] 380.3
20.	5,6-Dihidro-4H-1,3a,6-triaza-as-indaceno-8-ácido carboxílico (3,4-difluoro-fenil)-amida	H	H	H	H	1		1HNMR (CD3OD) 3.16 (t, 2H), 4.30 (t, 2H), 7.10 (s, 2H), 7.21-7.29 (m, 1H), 7.49-7.55 (m, 2H), 7.93-8.02 (m, 1H) LRMS calculó 314.29 se encontró [M+H] 315.1
21.	5,6-Dihidro-4H-1,3a,6-triaza-as-indaceno-8-ácido carboxílico (4-trifluorometil-fenil)-amida	H	H	H	H	1		1HNMR (CD3OD) 3.12 (t, 2H), 4.25 (t, 2H), 7.06-7.07 (m, 2H), 7.46 (s, 1H), 7.62 (d, 2H), 8.04 (d, 2H) LRMS calculó 346.31 se encontró [M+H] 347.1

793

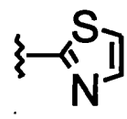
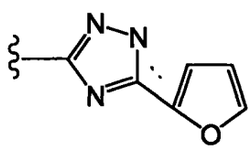
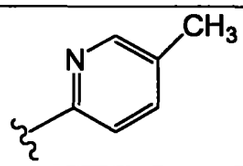
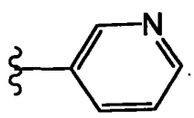
22.	5,6-Dihídro-4H-1,3a,6-triaza-as-indaceno-8-ácido carboxílico {4-[2-(4-bencil-piperidin-1-il)-etoxi]-3-fluoro-fenil}-amida	H	H	H	H	1		LRMS calculó 513.61, se encontró [M+H] 514.4
23.	5,6-Dihidro-4H-1,3a,6-triaza-as-indaceno-8-ácido carboxílico [4-(2-propilamino-etoxi)-fenil-amida	H	H	H	H	1		
24.	5,6-Dihidro-4H-1,3a,6-triaza-as-indaceno-8-ácido carboxílico (6-metoxi-2-metil-piridin-3-il)-amida	H	H	H	H	1		

794

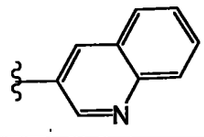
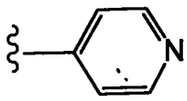
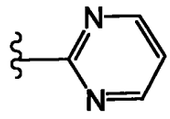
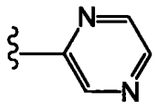
25.	5,6-Dihidro-4H-1,3a,6-triaza-as-indaceno-8-ácido carboxílico (2-metoximetil-pirimidin-4-il)-amida	H	H	H	H	1		
26.	5,6-Dihidro-4H-1,3a,6-triaza-as-indaceno-8-ácido carboxílico (6-metoxi-piridin-3-il)-amida	H	H	H	H	1		[DMSO-d6] 3.1 (t, 1H), 3.9 (s, 3H), 4.3 (t, 2H), 6.9 (d, 1H), 7.0 (s, 1H), 7.2 (s, 1H), 7.5 (s, 2H), 8.2 (d, 1H), 8.6 (s, 1H), 11.8 (s, 1H), 13.2 (s, 1H)
27.	5,6-Dihidro-4H-1,3a,6-triaza-as-indaceno-8-ácido carboxílico (6-metoxi-pirazin-2-il)-amida	H	H	H	H	1		

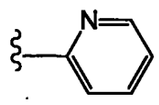
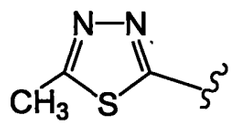
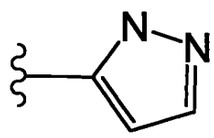
28.	5,6-Dihidro-4H-1,3a,6-triaza-as-indaceno-8-ácido carboxílico (5-ter-butil-isoxazol-3-il)-amida	H	H	H	H	1		
29.	5,6-Dihidro-4H-1,3a,6-triaza-as-indaceno-8-ácido carboxílico (1-metil-5-metilsulfanil-1H-[1,2,4]triazol-3-il)-amida	H	H	H	H	1		
30.	5,6-Dihidro-4H-1,3a,6-triaza-as-indaceno-8-ácido carboxílico (3-metil-[1,2,4]tiadiazol 1-5-il)-amida	H	H	H	H	1		

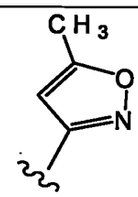
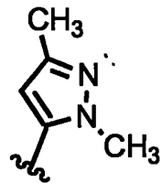
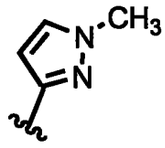
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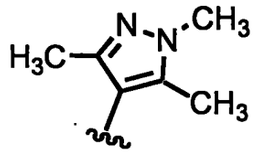
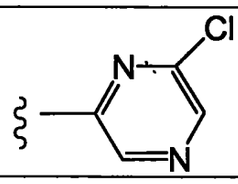
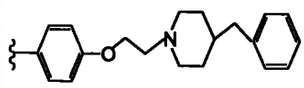
31.	5,6-Dihidro-4H-1,3a,6-triaza-as-indaceno-8-ácido carboxílico tiazol-2-ilamida	H	H	H	H	1		[DMSO-d6] 3.1 (t, 1H), 4.3 (t, 2H), 7.0 (s, 1H), 7.2 (s, 1H), 7.3 (s, 1H), 7.5 (s, 2H), 7.6 (s, 1H), 12.0 (br s, 1H), >15 (s, 1H)
32.	5,6-Dihidro-4H-1,3a,6-triaza-as-indaceno-8-ácido carboxílico (5-furan-2-il-1H-pirazol-3-il)-amida	H	H	H	H	1		
33.	5,6-Dihidro-4H-1,3a,6-triaza-as-indaceno-8-ácido carboxílico (5-metil-piridin-2-il)-amida	H	H	H	H	1		
34.	5,6-Dihidro-4H-1,3a,6-triaza-as-indaceno-8-ácido carboxílico piridin-3-ilamida	H	H	H	H	1		

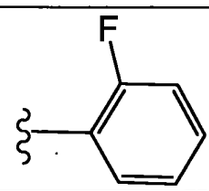
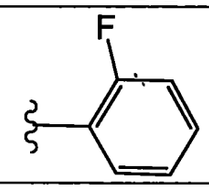
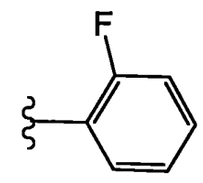
797

35.	5,6-Dihidro-4H-1,3a,6-triaza-as-indaceno-8-ácido carboxílico quinolin-3-ilamida	H	H	H	H	1		
36.	5,6-Dihidro-4H-1,3a,6-triaza-as-indaceno-8-ácido carboxílico piridin-4-ilamida	H	H	H	H	1		
37.	5,6-Dihidro-4H-1,3a,6-triaza-as-indaceno-8-ácido carboxílico pirimidin-2-ilamida	H	H	H	H	1		
38.	5,6-Dihidro-4H-1,3a,6-triaza-as-indaceno-8-ácido carboxílico pirazin-2-ilamida	H	H	H	H	1		

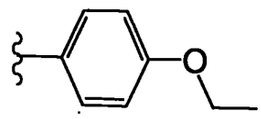
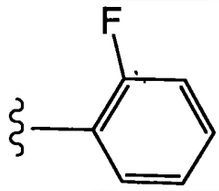
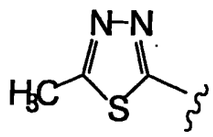
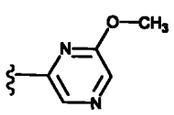
39.	5,6-Dihidro-4H-1,3a,6-triaza-as-indaceno-8-ácido carboxílico piridina-2-ilamida	H	H	H	H	1		[DMSO-d6] 3.1 (t, 1H), 4.3 (t, 2H), 7.0 (s, 1H), 7.1 (t, 1H), 7.2 (s, 1H), 7.5 (s, 2H), 7.8 (t,1H), 8.3 (d, 1H), 8.4 (s, 1H), 11.8 (s, 1H), 13.3 (s, 1H)
40.	5,6-Dihidro-4H-1,3a,6-triaza-as-indaceno-8-ácido carboxílico (5-metil-[1,3,4]tiadiazol-2-il)-amida	H	H	H	H	1		
41.	5,6-Dihidro-4H-1,3a,6-triaza-as-indaceno-8-ácido carboxílico (1H-pirazol-3-il)-amida	H	H	H	H	1		

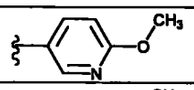
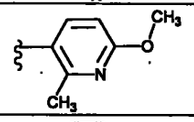
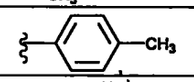
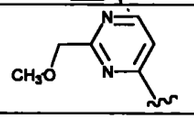
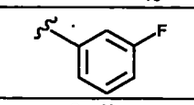
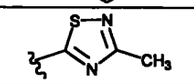
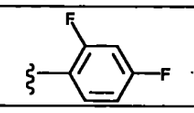
42.	5,6-Dihidro-4H-1,3a,6-triaza-as-indaceno-8-ácido carboxílico (5-metil-isoxazol-3-il)-amida	H	H	H	H	1		
43.	5,6-Dihidro-4H-1,3a,6-triaza-as-indaceno-8-ácido carboxílico (2,5-dimetil-2H-pirazol-3-il)-amida	H	H	H	H	1		
44.	5,6-Dihidro-4H-1,3a,6-triaza-as-indaceno-8-ácido carboxílico (1-metil-1H-pirazol-3-il)-amida	H	H	H	H	1		

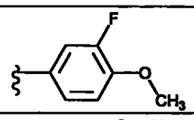
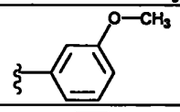
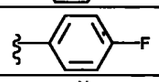
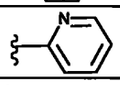
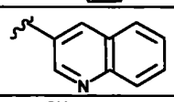
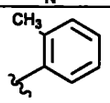
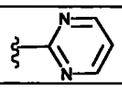
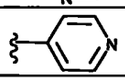
45.	5,6-Dihidro-4H-1,3a,6-triaza-as-indaceno-8-ácido carboxílico (1,3,5-trimetil-1H-pirazol-4-il)-amida	H	H	H	H	1		
46.	5,6-Dihidro-4H-1,3a,6-triaza-as-indaceno-8-ácido carboxílico (6-cloro-pirazin-2-il)-amida	H	H	H	H	1		
47.	4-Metil-5,6-dihidro-4H-1,3a,6-triaza-as-indaceno-8-ácido carboxílico {4-[2-(4-bencil-piperidin-1-il)-etoxi]-fenil}-amida	H	H	H	CH3	1		

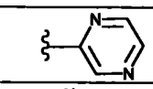
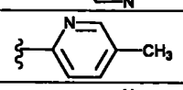
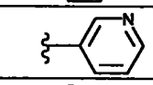
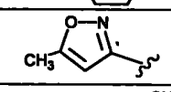
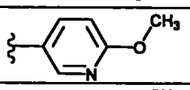
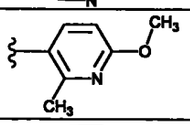
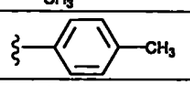
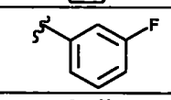
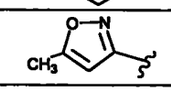
48.	(R)-4-Metil-5,6-dihidro-4H-1,3a,6-triaza-as-indaceno-8-ácido carboxílico (2-fluoro-fenil)-amida	H	H	H	CH3	1		
49.	(S)-4-Metil-5,6-dihidro-4H-1,3a,6-triaza-as-indaceno-8-ácido carboxílico (2-fluoro-fenil)-amida	H	H	H	CH3	1		
50.	3-Dimetilamino-metil-5,6-dihidro-4H-1,3a,6-triaza-as-andaceno-8-ácido carboxílico (2-fluoro-fenil)-amida	$CH_2N(CH_3)_2$	H	H	H	1		

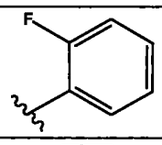
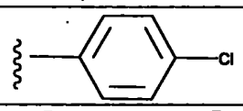
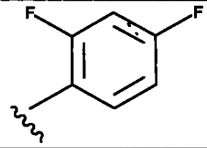
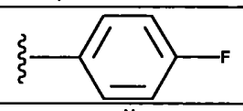
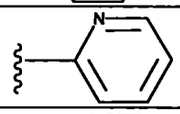
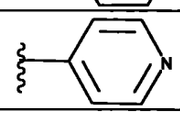
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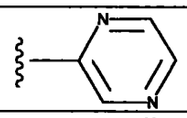
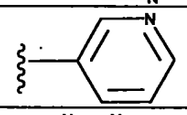
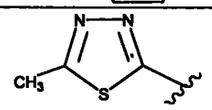
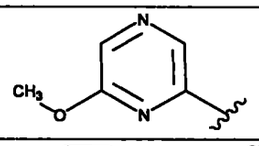
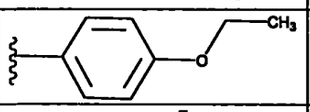
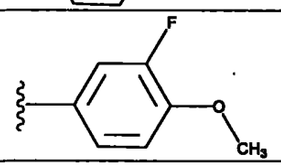
51.	4-Metil-5,6-dihidro-4H-1,3a,6-triaza-as-indaceno-8-ácido carboxílico (4-etoxi-fenil)-amida	H	H	H	CH3	1		
52.	3-Dietilamino-metil-5,6-dihidro-4H-1,3a,6-triaza-as-indaceno-8-ácido carboxílico (2-fluoro-fenil)-amida	$CH_2N(Et)_2$	H	H	H	1		
53.	4-Metil-5,6-dihidro-4H-1,3a,6-triaza-as-indaceno-8-ácido carboxílico (5-metil-[1,3,4] tiadiazol-2-il)-amida	H	H	H	H	1		
54.		H	H	CH_3	H	1		

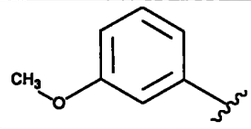
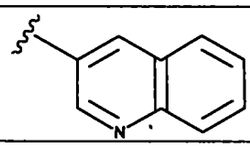
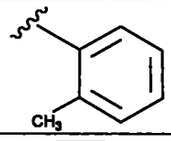
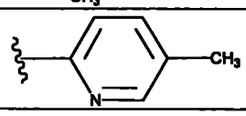
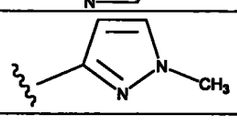
55.		H	H	CH_3	H	1		
56.		H	H	CH_3	H	1		
57.		H	H	CH_3	H	1		
58.		H	H	CH_3	H	1		
59.		H	H	CH_3	H	1		
60.		H	H	CH_3	H	1		
61.		H	H	CH_3	H	1		

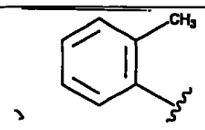
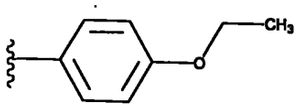
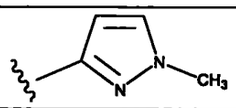
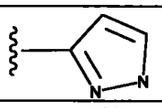
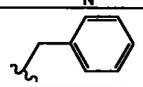
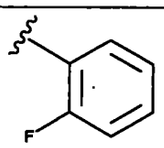
62		H	H	CH_3	H	1		
63		H	H	CH_3	H	1		
64		H	H	CH_3	H	1		
65		H	H	CH_3	H	1		
66		H	H	CH_3	H	1		
67		H	H	CH_3	H	1		
68		H	H	CH_3	H	1		
69		H	H	CH_3	H	1		

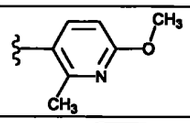
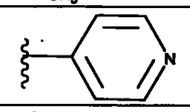
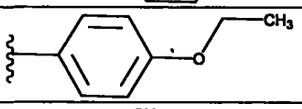
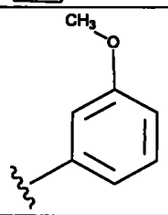
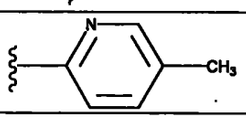
70		H	H	CH_3	H	1		
71		H	H	CH_3	H	1		
72		H	H	CH_3	H	1		
73		H	H	CH_3	H	1		
74		H	H	H	CH_3	1		
75		H	H	H	CH_3	1		
76.		H	H	H	CH_3	1		
77		H	H	H	CH_3	1		
78		H	H	H	CH_3	1		

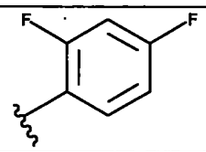
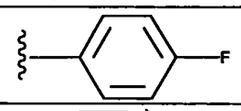
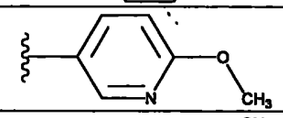
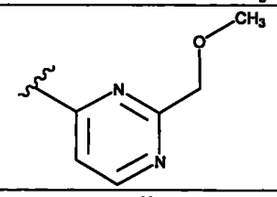
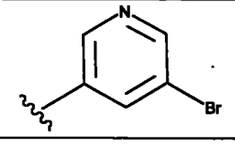
79.		H	H	CH_3	CH_3	1		
80.		H	H	H	CH_3	1		
81.		H	H	H	CH_3	1		
82.		H	H	H	CH_3	1		
83.		H	H	CH_3	H	1		
84.		H	H	H	CH_3	1		

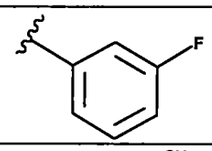
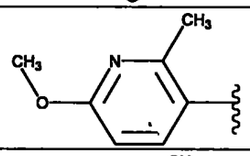
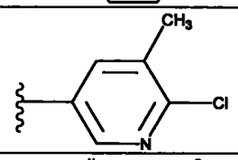
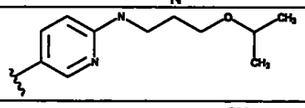
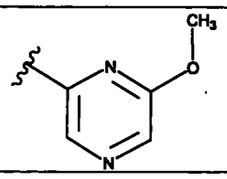
85.		H	H	H	CH_3	1		
86.		H	H	H	CH_3	1		
87.		H	H	H	CH_3	1		
88.		H	H	H	CH_3	1		
89.		H	H	H	CH_3	1		
90.		H	H	H	CH_3	1		

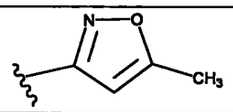
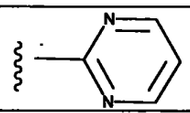
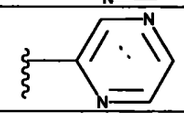
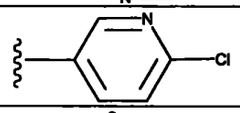
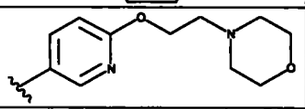
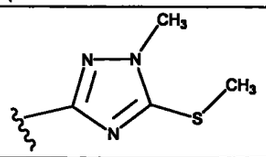
91		H	H	H	CH_3	1		
92		H	H	H	CH_3	1		
93		H	H	H	CH_3	1		
94		H	H	H	CH_3	1		
95		H	H	H	CH_3	1		

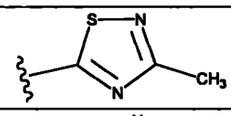
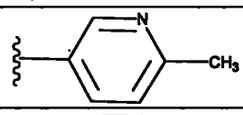
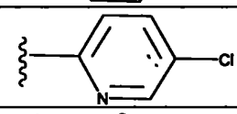
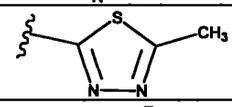
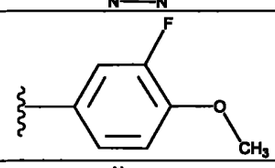
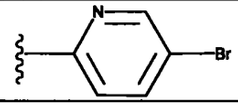
96.		H	H	CH_3	CH_3	1		
97.		H	H	CH_3	CH_3	1		
98.		H	H	CH_3	CH_3	1		
99.		H	H	CH_3	CH_3	1		
100.		H	H	H	CH_3	1		
101.	2-metil-5,6-dihidro-4H-1,3a,6-triaza-as-indaceno-8-carboxílico ácido (2-fluoro-fenil)-amida	CH_3	H	H	H	1		LRMS calculado 310.12, encontrado [M+H] 311.1

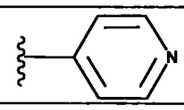
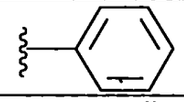
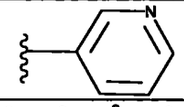
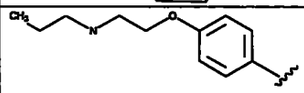
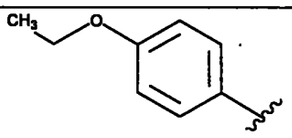
102.		H	H	H	CH_3	1		
103.		H	H	H	CH_3	1		
104.		H	H	H	CH_3	1		
105.		H	H	CH_3	CH_3	1		
106.		H	H	CH_3	CH_3	1		

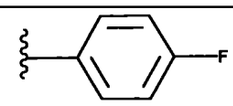
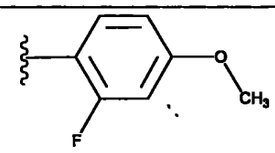
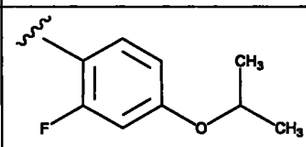
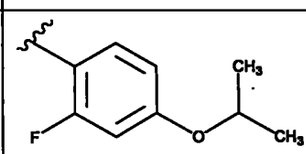
107.		H	H	CH_3	CH_3	1		
108.		H	H	CH_3	CH_3	1		
109.		H	H	CH_3	CH_3	1		
110.		H	H	CH_3	CH_3	1		
111.		H	H	CH_3	CH_3	1		

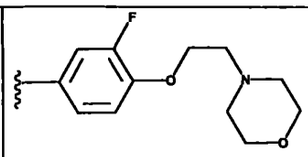
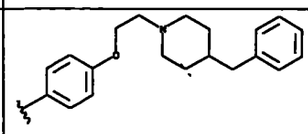
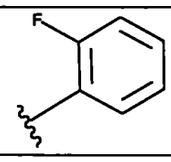
112.		H	H	CH_3	CH_3	1		
113.		H	H	CH_3	CH_3	1		
114.		H	H	CH_3	CH_3	1		
115.		H	H	CH_3	CH_3	1		
116.		H	H	CH_3	CH_3	1		

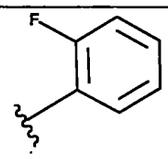
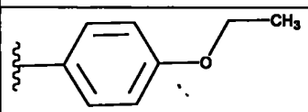
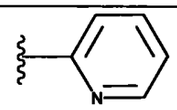
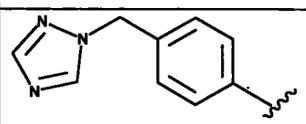
117.		H	H	CH_3	CH_3	1		
118.		H	H	CH_3	CH_3	1		
119.		H	H	CH_3	CH_3	1		
120.		H	H	CH_3	CH_3	1		
121.		H	H	CH_3	CH_3	1		
122.		H	H	CH_3	CH_3	1		

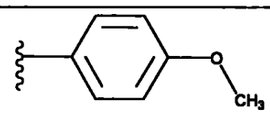
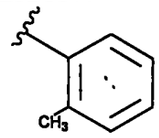
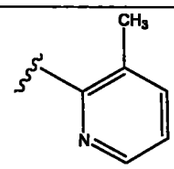
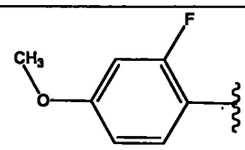
123.		H	H	CH_3	CH_3	1		
124.		H	H	CH_3	CH_3	1		
125.		H	H	CH_3	CH_3	1		
126.		H	H	CH_3	CH_3	1		
127.		H	H	CH_3	CH_3	1		
128.		H	H	CH_3	CH_3	1		

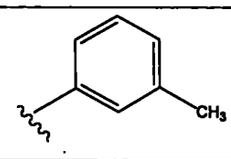
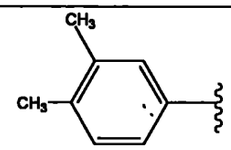
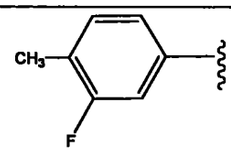
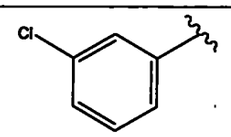
129.		H	H	CH_3	CH_3	1		
130.		H	H	CH_3	CH_3	1		
131.		H	H	CH_3	CH_3	1		
132.		H	H	CH_3	CH_3	1		
133.	4-Metil-5,6-Dihidro-4H-1,3a,6-triaza-as-indaceno-8-ácido carboxílico [4-(2-propil-amino-etoxi)fenil] amida	H	H	H	CH_3	1		LRMS calculó 393.48, se encontró [M+H] 394.4
134.	4-Metil-5,6-Dihidro-4H-1,3a,6-triaza-as-indaceno-8-ácido carboxílico (4-etoxifenil)amida	H	H	H	CH_3	1		LRMS calculó 336.39, se encontró [M+H] 337.2

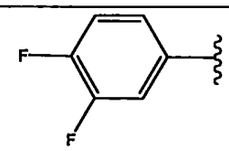
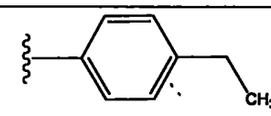
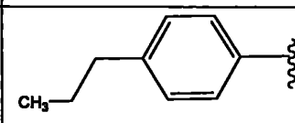
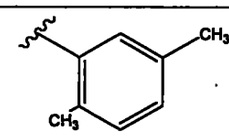
135.	5,6-Dihidro-4H-1,3a,6-triaza-as-indaceno-8-ácido carboxílico (4-fluorofenil) amida	H	H	H	H	1		LRMS calculó 296.30, se encontró [M+H] 297.2
136.	5,6-Dihidro-4H-1,3a,6-triaza-as-indaceno-8-ácido carboxílico (2-fluoro-4-metoxifenil) amida	H	H	H	H	1		LRMS calculó 326.33, se encontró [M+H] 327.2
137.	4-Metil-5,6-Dihidro-4H-1,3a,6-triaza-as-indaceno-8-ácido carboxílico (2-fluoro-4-isopropoxifenil) amida	H	H	H	CH3	1		LRMS calculó 368.40, se encontró [M+H] 369.2
138.	5,6-Dihidro-4H-1,3a,6-triaza-as-indaceno-8-ácido carboxílico (2-fluoro-4-isopropoxifenil) amida	H	H	H	H	1		LRMS calculó 354.38, se encontró [M+H] 355.2

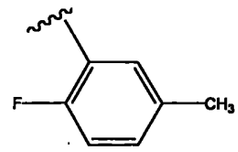
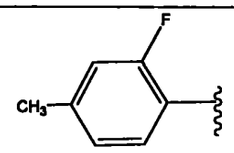
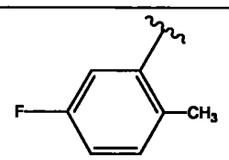
139.	4-Metil-5,6-Dihidro-4H-1,3a,6-triaza-as-indaceno-8-ácido carboxílico [4-(2-propilamino-etoxi)fenil] amida	H	H	H	CH3	1		LRMS calculó 393.48, se encontró [M+H] 394.4
140.	4-metil-5,6-Dihidro-4H-1,3a,6-triaza-as-indaceno-8-ácido carboxílico {4-[2-(4-bencil-piperidinil) etoxi] fenil} amida	H	H	H	CH3	1		LRMS calculó 509.64, se encontró [M+H] 510.5
141.		$CH_2N(CH_3)_2$	$CH_2N(CH_3)_2$	H	H	1		

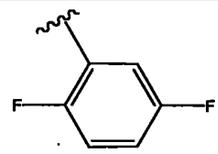
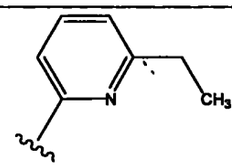
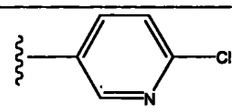
142.	4,4-Dimetil-5,6-Dihidro-4H-1,3a,6-triaza-as-indaceno-8-ácido carboxílico (2-fluoro-fenil)-amida	H	H	CH3	CH3	1		LRMS calculó 324 se encontró [M+1] 325
143.	4,4-Dimetil-5,6-Dihidro-4H-1,3a,6-triaza-as-indaceno-8-ácido carboxílico (4-etoxi-fenil)-amida	H	H	CH3	CH3	1		LRMS calculó 350 se encontró [M+1] 351
144.	4,4-Dimetil-5,6-Dihidro-4H-1,3a,6-triaza-as-indaceno-8-ácido carboxílico piridin-2-ilamida	H	H	CH3	CH3	1		LRMS calculó 307 se encontró [M+1] 308
145.	4,4-Dimetil-5,6-Dihidro-4H-1,3a,6-triaza-as-indaceno-8-ácido carboxílico (4-[1,2,4]triazol-1-ilmetil-fenil)-amida	H	H	CH3	CH3	1		LRMS calculó 387 se encontró [M+1] 388

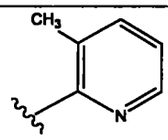
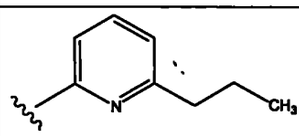
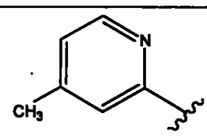
146.	4,4-Dimetil-5,6-Dihidro-4H-1,3a,6-triaza-as-indaceno-8-ácido carboxílico (4-metoxi-fenil)-amida	H	H	CH3	CH3	1		LRMS calculó 336 se encontró [M+1] 337
147.	4,4-Dimetil-5,6-Dihidro-4H-1,3a,6-triaza-as-indaceno-8-ácido carboxílico o-tolilamida	H	H	CH3	CH3	1		LRMS calculó 320 se encontró [M+1] 321
148.	4,4-Dimetil-5,6-Dihidro-4H-1,3a,6-triaza-as-indaceno-8-ácido carboxílico (3-metil-piridin-2-il)-amida	H	H	CH3	CH3	1		LRMS calculó 321 se encontró [M+1] 322
149.	4,4-Dimetil-5,6-Dihidro-4H-1,3a,6-triaza-as-indaceno-8-ácido carboxílico (2-fluoro-4-metoxi-fenil)-amida	H	H	CH3	CH3	1		LRMS calculó 354 se encontró [M+1]

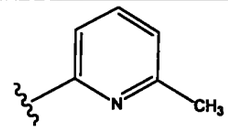
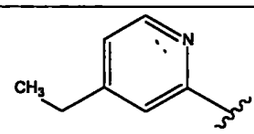
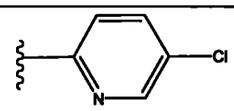
150.	(R)-4-Metil-5,6-Dihidro-4H-1,3a,6-triaza-as-indaceno-8-ácido carboxílico m-tolilamida	H	H	CH3	H	1		MS *m/z* 307
151.	(R)-4-Metil-5,6-Dihidro-4H-1,3a,6-triaza-as-indaceno-8-ácido carboxílico (3,4-dimetil-fenil)-amida	H	H	CH3	H	1		MS *m/z* 321
152.	(R)-4-Metil-5,6-Dihidro-4H-1,3a,6-triaza-as-indaceno-8-ácido carboxílico (3-fluoro-4-metil-fenil)-amida	H	H	CH3	H	1		MS *m/z* 325
153.	(R)-4-Metil-5,6-Dihidro-4H-1,3a,6-triaza-as-indaceno-8-ácido carboxílico (3-cloro-fenil)-amida	H	H	CH3	H	1		MS *m/z* 327

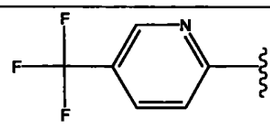
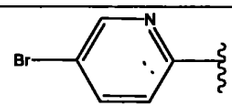
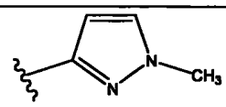
154.	(R)-4-Metil-5,6-Dihidro-4H-1,3a,6-triaza-as-indaceno-8-ácido carboxílico (3,4-difluoro-fenil)-amida	H	H	H	CH3	1		MS *m/z* 329
155.	(R)-4-Metil-5,6-Dihidro-4H-1,3a,6-triaza-as-indaceno-8-ácido carboxílico (4-etil-fenil)-amida	H	H	H	CH3	1		MS *m/z* 321
156.	(R)-4-Metil-5,6-Dihidro-4H-1,3a,6-triaza-as-indaceno-8-ácido carboxílico (4-propil-fenil)-amida	H	H	H	CH3	1		
157.	(R)-4-Metil-5,6-Dihidro-4H-1,3a,6-triaza-as-indaceno-8-ácido carboxílico (2,5-dimetil-fenil)-amida	H	H	H	CH3	1		MS *m/z* 321

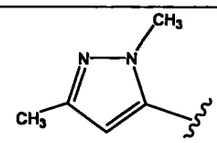
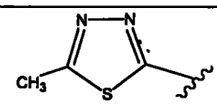
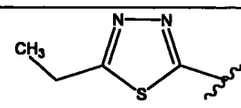
158.	(R)-4-Metil-5,6-Dihidro-4H-1,3a,6-triaza-as-indaceno-8-ácido carboxílico (2-fluoro-5-metil-fenil)-amida	H	H	H	CH3	1		[CDCl3] 1.5 (d, 3H), 2.8 (dd, 1H), 3.1 (dd, 1H), 4.3 (q, 1H), 6.9 (app s, 2H), 7.0 (app s, 2H), 7.5 (s, 1H), 8.0 (d, 1H), 11.8 (s, 1H), 13.1 (s, 1H)
159.	(R)-4-Metil-5,6-Dihidro-4H-1,3a,6-triaza-as-indaceno-8-ácido carboxílico (2-fluoro-4-metil-fenil)-amida	H	H	H	CH3	1		[CDCl3] 1.5 (d, 3H), 2.8 (dd, 1H), 3.1 (dd, 1H), 4.3 (q, 1H), 6.9 (s, 1H), 6.95 (m, 2H), 7.0 (s, 1H), 7.5 (s, 1H), 8.0 (t, 1H), 10.8 (s, 1H), 13.1 (s, 1H)
160.	(R)-4-Metil-5,6-Dihidro-4H-1,3a,6-triaza-as-indaceno-8-ácido carboxílico (5-fluoro-2-metil-fenil)-amida	H	H	H	CH3	1		[CD3OD] 1.2 (d, 3H), 2.1 (s, 3H), 2.55 (dd, 1H), 2.95 (dd, 1H), 4.2 (q, 1H), 6.5 (t, 1H), 6.6 (s, 1H), 6.8 (s, 1H), 6.9 (t, 1H), 7.2 (m, 2H)

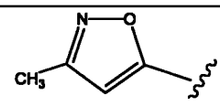
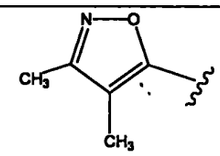
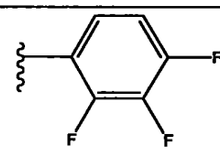
161.	(R)-4-Metil-5,6-Dihidro-4H-1,3a,6-triaza-as-indaceno-8-ácido carboxílico (2,5-difluoro-fenil)-amida	H	H	H	CH3	1		[CD3OD] 1.2 (d, 3H), 2.55 (dd, 1H), 2.95 (dd, 1H), 4.2 (q, 1H), 6.55 (m, 1H), 6.6 (s, 1H), , 6.8 (s, 1H), 6.85 (m, 1H), 7.2 (s, 1H), 7.8 (m, 1H)
162.	(R)-4-Metil-5,6-Dihidro-4H-1,3a,6-triaza-as-indaceno-8-ácido carboxílico (6-etil-piridin-2-il)-amida	H	H	H	CH3	1		[CD3OD] 1.0 (t, 3H), 1.2 (d, 3H), 2.45 (q, 2H), 2.5 (dd, 1H), 2.9 (dd, 1H), 4.2 (q, 1H), 6.65 (d, 1H), 6.7 (s, 1H), 6.8 (s, 1H), 7.2 (s, 1H), 7.4 (t, 1H), 7.8 (d, 1H)
163.	(R)-4-Metil-5,6-Dihidro-4H-1,3a,6-triaza-as-indaceno-8-ácido carboxílico (6-cloro-piridin-3-il)-amida	H	H	H	CH3	1		[CD3OD] 1.2 (d, 3H), 2.55 (dd, 1H), 2.95 (dd, 1H), 3.0 (s, 3H), 4.2 (q, 1H), 6.6 (s, 1H), , 6.8 (s, 1H), 7.1 (d, 1H), 7.2 (s, 1H), 8.0 (d, 1H), 8.6 (s, 1H)

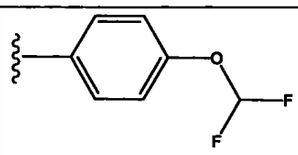
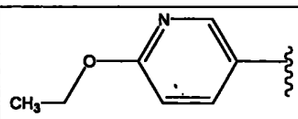
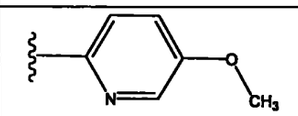
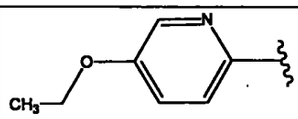
164.	(R)-4-Metil-5,6-Dihidro-4H-1,3a,6-triaza-as-indaceno-8-ácido carboxílico (3-metil-piridin-2-il)-amida	H	H	H	CH3	1		[CD3OD] 1.2 (d, 3H), 2.1 (s, 3H), 2.55 (dd, 1H), 2.95 (dd, 1H), 4.2 (q, 1H), 6.6 (s, 1H), 6.8 (s, 1H), 6.95 (dd, 1H), 7.2 (s, 1H), 7.45 (d, 1H), 8.0 (d, 1H)
165.	(R)-4-Metil-5,6-Dihidro-4H-1,3a,6-triaza-as-indaceno-8-ácido carboxílico (6-propil-piridin-2-il)-amida	H	H	H	CH3	1		[CD3OD] 0.7 (t, 3H), 1.2 (d, 3H), 1.6 (sextet, 2H), 2.4 (t, 2H), 2.5 (dd, 1H), 2.9 (dd, 1H), 4.2 (q, 1H), 6.6 (d, 1H), 6.7 (s, 1H), 6.8 (s, 1H), 7.2 (s, 1H), 7.4 (t, 1H), 7.7 (d, 1H)
166.	(R)-4-Metil-5,6-Dihidro-4H-1,3a,6-triaza-as-indaceno-8-ácido carboxílico (4-metil-piridin-2-il)-amida	H	H	H	CH3	1		[CDCl3] 1.4 (d, 3H), 2.4 (s, 3H), 2.75 (dd, 1H), 3.1 (dd, 1H), 4.3 (q, 1H), 6.8 (app s, 2H), 7.0 (s, 1H), 7.6 (s, 1H), 8.2 (s, 1H), 8.25 (d, 1H), 10.8 (s, 1H), 13.55 (s, 1H)

167.	(R)-4-Metil-5,6-Dihidro-4H-1,3a,6-triaza-as-indaceno-8-ácido carboxílico (6-metil-piridin-2-il)-amida	H	H	H	CH3	1		[CDCl3] 1.4 (d, 3H), 2.6 (s, 3H), 2.75 (dd, 1H), 3.1 (dd, 1H), 4.3 (q, 1H), 6.9 (m, 2H), 7.1 (s, 1H), 7.55 (s, 1H), 7.6 (t, 1H), 8.2 (d, 1H), 10.7 (s, 1H), 13.6 (s, 1H)
168.	(R)-4-Metil-5,6-Dihidro-4H-1,3a,6-triaza-as-indaceno-8-ácido carboxílico (4-etil-piridin-2-il)-amida	H	H	H	CH3	1		[CDCl3] 1.3 (t, 3H), 1.4 (d, 3H), 2.7 (q, 2H), 2.75 (dd, 1H(, 3.1 (dd, 1H), 4.3 (q, 1H), 6.8 (s, 1H), 6.85 (d, 1H), 7.0 (s, 1H), 7.6 (s, 1H), 8.3 (m, 2H), 10.8 (s, 1H), 13.55 (s, 1H)
169.	(R)-4-Metil-5,6-Dihidro-4H-1,3a,6-triaza-as-indaceno-8-ácido carboxílico (5-cloro-piridin-2-il)-amida	H	H	H	CH3	1		[DMSO-d6] 1.5 (d, 3H), 2.8 (dd, 1H), 3.2 (dd, 1H), 4.5 (q, 1H), 7.0 (s, 1H), 7.3 (s, 1H), 7.6 (s, 1H), 7.9 (d, 1H), 8.4 (d, 1H), 8.5 (s, 1H)

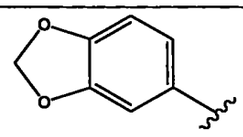
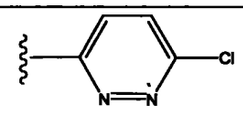
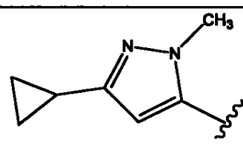
170.	(R)-4-Metil-5,6-Dihidro-4H-1,3a,6-triaza-as-indaceno-8-ácido carboxílico (5-trifluorometil-piridin-2-il)-amida	H	H	H	CH3	1		[DMSO-d6] 1.5 (d, 3H), 2.8 (dd, 1H), 3.2 (dd, 1H), 4.5 (q, 1H), 7.0 (s, 1H), 7.3 (s, 1H), 7.6 (s, 1H), 8.2 (d, 1H), 8.6 (d, 1H), 8.8 (s, 1H)
171.	(R)-4-Metil-5,6-Dihidro-4H-1,3a,6-triaza-as-indaceno-8-ácido carboxílico (5-bromo-piridin-2-il)-amida	H	H	H	CH3	1		[DMSO-d6] 1.5 (d, 3H), 2.8 (dd, 1H), 3.2 (dd, 1H), 4.5 (q, 1H), 7.0 (s, 1H), 7.3 (s, 1H), 7.6 (s, 1H), 8.0 (d, 1H), 8.4 (d, 1H), 8.5 (s, 1H)
172.	(R)-4-Metil-5,6-Dihidro-4H-1,3a,6-triaza-as-indaceno-8-ácido carboxílico (1-metil-1H-pirazol-3-il)-amida	H	H	H	CH3	1		[DMSO-d6] 1.5 (d, 3H), 2.8 (dd, 1H), 3.2 (dd, 1H), 3.8 (s, 3H), 4.5 (1, 1H), 6.6 (s, 1H), 7.0 (s, 1H), 7.3 (s, 1H), 7.4 (s, 1H), 7.6 (s, 1H), 11.8 (s, 1H), 13.1 (s, 1H),

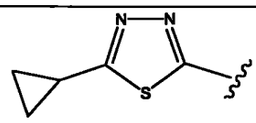
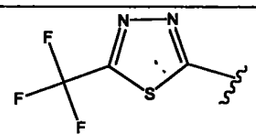
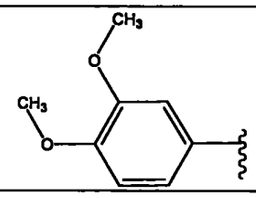
173.	(R)-4-Metil-5,6-Dihidro-4H-1,3a,6-triaza-as-indaceno-8-ácido carboxílico (2,5-dimetil-2H-pirazol-3-il)-amida	H	H	H	CH3	1		[DMSO-d6] 1.5 (d, 3H), 2.1 (s, 3H), 2.8 (dd, 1H), 3.2 (dd, 1H), 3.8 (s, 3H), 4.5 (q, 1H), 6.5 (s, 1H), 7.0 (s, 1H), 7.3 (s, 1H), 7.5 (s, 1H), 11.8 (s, 1H), 13.2 (s, 1H)
174.	(R)-4-Metil-5,6-Dihidro-4H-1,3a,6-triaza-as-indaceno-8-ácido carboxílico (5-metil-[1,3,4]tiadiazol-2-il)-amida	H	H	H	CH3	1		[DMSO-d6] 1.5 (d, 3H), 2.7 (s, 3H), 2.9 (dd, 1H), 3.3 (dd, 1H), 4.6 (q, 1H), 7.1 (s, 1H), 7.4 (s, 1H), 7.6 (s, 1H), 12.0 (s, 1H), >14 (s, 1H)
175.	(R)-4-Metil-5,6-Dihidro-4H-1,3a,6-triaza-as-indaceno-8-ácido carboxílico (5-etil-[1,3,4]tiadiazol-2-il)-amida	H	H	H	CH3	1		[DMSO-d6] 1.3 (t, 3H), 1.5 (d, 3H), 2.9 (dd, 1H), 3.0 (q, 2H), 3.3 (dd, 1H), 4.6 (q, 1H), 7.1 (s, 1H), 7.4 (s, 1H), 7.6 (s, 1H), 12.0 (s, 1H), >14 (s, 1H)

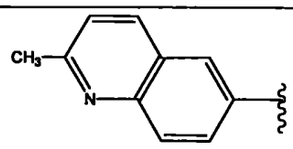
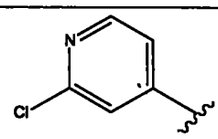
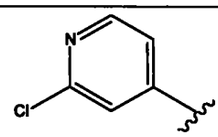
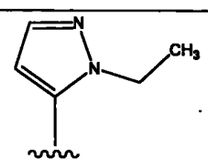
176.	(R)-4-Metil-5,6-Dihidro-4H-1,3a,6-triaza-as-indaceno-8-ácido carboxílico (3-metil-isoxazol-5-il)-amida	H	H	H	CH3	1		MS *m/z* 298
177.	(R)-4-Metil-5,6-Dihidro-4H-1,3a,6-triaza-as-indaceno-8-ácido carboxílico (3,4-dimetil-isoxazol-5-il)-amida	H	H	H	CH3	1		MS *m/z* 312
178.	(R)-4-Metil-5,6-Dihidro-4H-1,3a,6-triaza-as-indaceno-8-ácido carboxílico (2,3,4-trifluoro-fenil)-amida	H	H	H	CH3	1		MS *m/z* 347

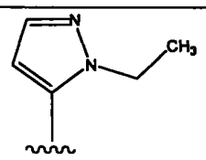
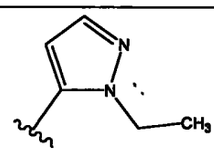
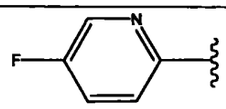
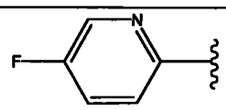
179.	(R)-4-Metil-5,6-Dihidro-4H-1,3a,6-triaza-as-indaceno-8-ácido carboxílico (4-difluorometoxi-fenil)-amida	H	H	H	CH3	1		MS *m/z* 359
180.	(S)-4-Metil-5,6-Dihidro-4H-1,3a,6-triaza-as-indaceno-8-ácido carboxílico (6-etoxi-piridin-3-il)-amida	H	H	H	CH3	1		LRMS 337.38 se encontró (M+1) 338.2
181.	(S)-4-Metil-5,6-Dihidro-4H-1,3a,6-triaza-as-indaceno-8-ácido carboxílico (5-metoxi-piridin-2-il)-amida.	H	H	H	CH3	1		LRMS calculó 323 se encontró [M+1] 324
182.	(S)-4-Metil-5,6-Dihidro-4H-1,3a,6-triaza-as-indaceno-8-ácido carboxílico (5-etoxi-piridin-2-il)-amida	H	H	H	CH3	1		LRMS calculó 337 se encontró [M+1] 338

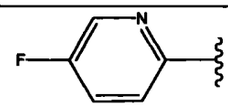
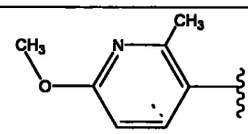
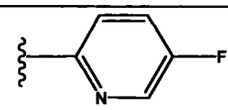
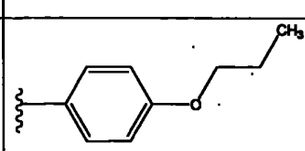
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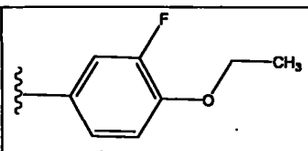
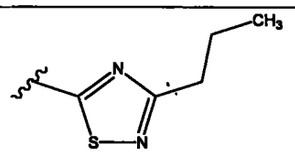
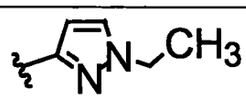
183.	(R)-4-Metil-5,6-Dihidro-4H-1,3a,6-triaza-as-indaceno-8-ácido carboxílico benzo[1,3]dioxol-5-ilamida	H	H	H	CH3	1		MS *m/z* 337
184.	(R)-4-Metil-5,6-Dihidro-4H-1,3a,6-triaza-as-indaceno-8-ácido carboxílico (6-cloro-piridazin-3-il)-amida	H	H	H	CH3	1		MS *m/z* 329
185.	(R)-4-Metil-5,6-Dihidro-4H-1,3a,6-triaza-as-indaceno-8-ácido carboxílico (5-ciclopropil-2-metil-2H-pirazol-3-il)-amida	H	H	H	CH3	1		MS *m/z* 337

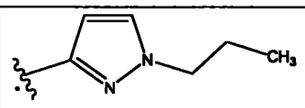
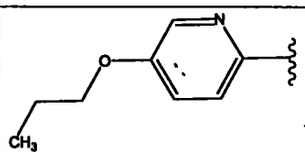
186.	(R)-4-Metil-5,6-Dihidro-4H-1,3a,6-triaza-as-indaceno-8-ácido carboxílico (5-ciclopropil-[1,3,4]tiadiazol-2-il)-amida	H	H	H	CH3	1		MS *m/z* 341
187.	(R)-4-Metil-5,6-Dihidro-4H-1,3a,6-triaza-as-indaceno-8-ácido carboxílico (5-trifluorometil-[1,3,4]tiadiazol-2-il)-amida	H	H	H	CH3	1		MS *m/z* 369
188.	(R)-4-Metil-5,6-Dihidro-4H-1,3a,6-triaza-as-indaceno-8-ácido carboxílico (3,4-dimetoxi-fenil)-amida	H	H	H	CH3	1		MS *m/z* 353

189.	(R)-4-Metil-5,6-Dihidro-4H-1,3a,6-triaza-as-indaceno-8-ácido carboxílico (2-metil-quinolin-6-il)-amida	H	H	H	CH3	1		MS *m/z* 358
190.	5,6-Dihidro-4H-1,3a,6-triaza-as-indaceno-8-ácido carboxílico (2-cloro-piridin-4-il)-amida	H	H	H	H	1		MS *m/z* 314
191.	(R)-4-Metil-5,6-Dihidro-4H-1,3a,6-triaza-as-indaceno-8-ácido carboxílico (2-cloro-piridin-4-il)-amida	H	H	H	CH3			MS *m/z* 328
192.	(S)-4-Metil-5,6-Dihidro-4H-1,3a,6-triaza-as-indaceno-8-ácido carboxílico (2-etil-2H-pirazol-3-il)-amida	H	H	H	CH3	1		LCSe encontró MS (M+H) 312

193.	(R)-4-Metil-5,6-Dihidro-4H-1,3a,6-triaza-as-indaceno-8-ácido carboxílico (2-etil-2H-pirazol-3-il)-amida	H	H	H	CH3	1		LCSe encontró MS (M+H) 312
194.	4,4-Dimetil-5,6-Dihidro-4H-1,3a,6-triaza-as-indaceno-8-ácido carboxílico (2-etil-2H-pirazol-3-il)-amida	H	H	CH3	CH3	1		LCSe encontró MS (M+H) 326
195.	4,4-Dimetil-5,6-Dihidro-4H-1,3a,6-triaza-as-indaceno-8-ácido carboxílico (5-fluoro-piridin-2-il)-amida	H	H	CH3	CH3	1		LCSe encontró MS (M+H) 326
196.	(R)-4-Metil-5,6-Dihidro-4H-1,3a,6-triaza-as-indaceno-8-ácido carboxílico (5-fluoro-piridin-2-il)-amida	H	H	H	CH3	1		LCSe encontró MS (M+H) 312

197.	5,6-Dihidro-4H-1,3a,6-triaza-as-indaceno-8-ácido carboxílico (5-fluoro-piridin-2-il)-amida	H	H	H	H	1		LCSe encontró MS (M+H) 297
198.	(S)-4-Metil-5,6-Dihidro-4H-1,3a,6-triaza-as-indaceno-8-ácido carboxílico (6-metoxi-2-metil-piridin-3-il)-amida	H	H	H	CH3	1		LRMS 337.38 se encontró (M+1) 338.2
199.	(S)- 4-Metil-5,6-Dihidro-4H-1,3a,6-triaza-as-indaceno-8-ácido carboxílico (5-fluoro-piridin-2-il)-amida	H	H	H	CH3	1		LRMS 311.11 se encontró (M+1) 312.2
200.	(S)-4-Metil-5,6-Dihidro-4H-1,3a,6-triaza-as-indaceno-8-ácido carboxílico (4-propoxi-fenil)-amida	H	H	H	CH3	1		LRMS 350.42 se encontró (M-1) 349.2

201.	(S)-4-Metil-5,6-Dihidro-4H-1,3a,6-triaza-as-indaceno-8-ácido carboxílico (4-etoxi-3-fluoro-fenil)-amida	H	H	H	CH3	1		LRMS 354.38 se encontró (M-1) 353.2
202.	(R)- 4-Metil-5,6-Dihidro-4H-1,3a,6-triaza-as-indaceno-8-ácido carboxílico (3-propil-[1,2,4]tiadiazol-5-il)-amida	H	H	CH3	H	1		LCSe encontró MS (M+H) 343
203.	(R)-3,4,5,6-Tetrahidro-3,8,10-triaza-benzo[e]azuleno-1-ácido carboxílico (1-etil-1H-pirazol-3-il)-amida	H	H	H	CH3	1		LCSe encontró MS (M+H) 311

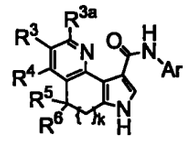
204.	(R)-3,4,5,6-Tetrahidro-3,8,10-triaza-benzo[e]azuleno-1-ácido carboxílico (1-propil-1H-pirazol-3-il)-amida	H	H	H	CH3	1		LCSe encontró MS (M+H) 337
205.	(S)-4-Metil-5,6-Dihidro-4H-1,3a,6-triaza-as-indaceno-8-ácido carboxílico (5-propoxi-piridin-2-il)-amida	H	H	H	CH3	1		LRMS calculó 351 se encontró [M+1] 352

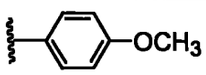
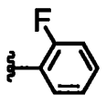
Ejemplo 5

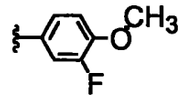
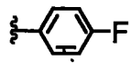
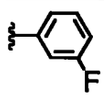
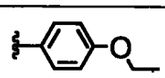
Compuestos adicionales de ácido 3,10-diaza-benzo[e]azuleno-1-carboxílico

Los compuestos que se muestran en la Tabla 2 se prepararon usando los métodos que se presentan en los Esquemas 2 y 3.

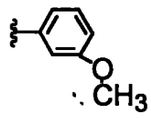
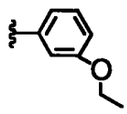
TABLA 2

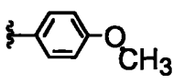
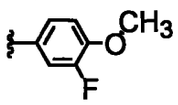
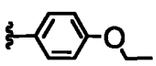


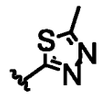
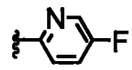
Com. #	Nombre	R^{3a}	R^3	R^4	R^5	R^6	k	Ar	Datos del Espectro
1	9-Metil-3,4,5,6-tetrahidro-3,10-diaza-benzo[e]azuleno-1-ácido carboxílico (4-metoxi-fenil)-amida	CH_3	H	H	H	H	2		
2	9-Metil-3,4,5,6-tetrahidro-3,10-diaza-benzo[e]azuleno-1-ácido carboxílico (2-fluoro-fenil)-amida	CH_3	H	H	H	H	2		

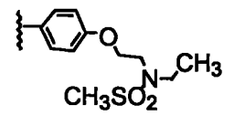
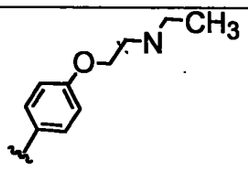
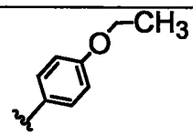
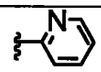
3	9-Metil-3,4,5,6-tetrahidro-3,10-diaza-benzo[e]azuleno-1-ácido carboxílico (3-fluoro-4-metoxi-fenil)-amida	CH_3	H	H	H	H	2		
4	9-Metil-3,4,5,6-tetrahidro-3,10-diaza-benzo[e]azuleno-1-ácido carboxílico (4-fluoro-fenil)-amida	CH_3	H	H	H	H	2		
5	9-Metil-3,4,5,6-tetrahidro-3,10-diaza-benzo[e]azuleno-1-ácido carboxílico (3-fluoro-fenil)-amida	CH_3	H	H	H	H	2		
6	9-Metil-3,4,5,6-tetrahidro-3,10-diaza-benzo[e]azuleno-1-ácido carboxílico (4-etoxi-fenil)-amida	CH_3	H	H	H	H	2		

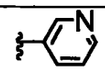
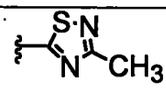
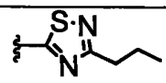
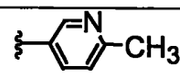
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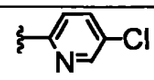
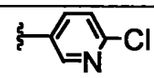
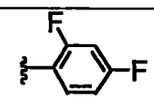
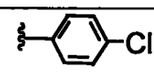
7	9-Metil-3,4,5,6-tetrahidro-3,10-diaza-benzo[e]azuleno-1-ácido carboxílico fenilamida	CH_3	H	H	H	H	2		
8	9-Metil-3,4,5,6-tetrahidro-3,10-diaza-benzo[e]azuleno-1-ácido carboxílico (3-metoxi-fenil)-amida	CH_3	H	H	H	H	2		
9	9-Metil-3,4,5,6-tetrahidro-3,10-diaza-benzo[e]azuleno-1-ácido carboxílico (3-etoxi-fenil)-amida	CH_3	H	H	H	H	2		
10	3,4,5,6-Tetrahidro-3,10-diaza-benzo[e]azuleno-1-ácido carboxílico (2-fluoro-fenil)-amida	H	H	H	H	H	2		

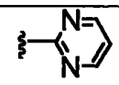
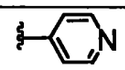
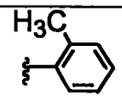
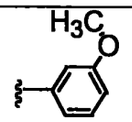
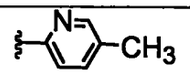
11	3,4,5,6-Tetrahidro-3,10-diaza-benzo[e]azuleno-1-ácido carboxílico (4-metoxi-fenil)-amida	H	H	H	H	H	2		
12	3,4,5,6-Tetrahidro-3,10-diaza-benzo[e]azuleno-1-ácido carboxílico (3-fluoro-4-metoxi-fenil)-amida	H	H	H	H	H	2		
13	3,4,5,6-Tetrahidro-3,10-diaza-benzo[e]azuleno-1-ácido carboxílico (4-etoxi-fenil)-amida	H	H	H	H	H	2		
14	3,4,5,6-Tetrahidro-3,10-diaza-benzo[e]azuleno-1-ácido carboxílico piridin-2-ilamida	H	H	H	H	H	2		

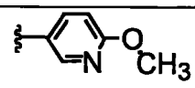
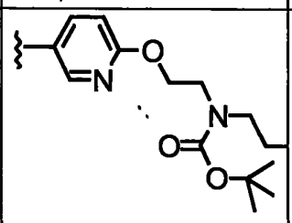
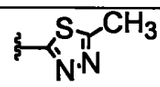
15	3,4,5,6-Tetrahidro-3,10-diaza-benzo[e]azuleno-1-ácido carboxílico (1-metil-1H-pirazol-3-il)-amida	H	H	H	H	H	2		
16	3,4,5,6-Tetrahidro-3,10-diaza-benzo[e]azuleno-1-ácido carboxílico (5-metil-[1,3,4]thiadiazol-2-il)-amida	H	H	H	H	H	2		
17	3,4,5,6-Tetrahidro-3,10-diaza-benzo[e]azuleno-1-ácido carboxílico (5-fluoro-piridin-2-il)-amida	H	H	H	H	H	2		

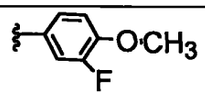
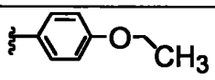
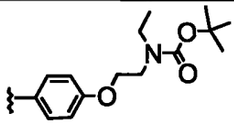
18	3,4,5,6-Tetrahidro-3,10-diaza-benzo[e]azuleno-1-ácido carboxílico {4-[2-(etil-metanosulfonil-amino)-etoxi]-fenil}-amida	H	H	H	H	H	2		LRMS calculó 468 se encontró [M+1] 469
19	3,4,5,6-Tetrahidro-3,10-diaza-benzo[e]azuleno-1-ácido carboxílico [4-(2-etilamino-etoxi)-fenil]-amida	H	H	H	H	H	2		LRMS calculó 390 se encontró [M+1] 391
20	8-Metil-3,4,5,6-tetrahidro-3,10-diaza-benzo[e]azuleno-1-ácido carboxílico (4-etoxi-fenil)-amida	H	CH_3	H	H	H	2		
21	8-Metil-3,4,5,6-tetrahidro-3,10-diaza-benzo[e]azuleno-1-ácido carboxílico piridin-2-ilamida	H	CH_3	H	H	H	2		

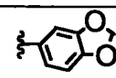
22	3,4,5,6-Tetrahidro-3,10-diaza-benzo[e]azuleno-1-ácido carboxílico piridin-3-ilamida	H	H	H	H	H	2		
23	3,4,5,6-Tetrahidro-3,10-diaza-benzo[e]azuleno-1-ácido carboxílico (3-metil-[1,2,4]tiadiazol-5-il)-amida	H	H	H	H	H	2		
24	3,4,5,6-Tetrahidro-3,10-diaza-benzo[e]azuleno-1-ácido carboxílico (3-propil-[1,2,4]tiadiazol-5-il)-amida	H	H	H	H	H	2		LCMS se encontró (M+H) 354
25	3,4,5,6-Tetrahidro-3,10-diaza-benzo[e]azuleno-1-ácido carboxílico (6-metil-piridin-3-il)-amida	H	H	H	H	H	2		

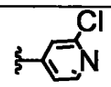
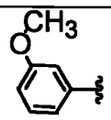
26	3,4,5,6-Tetrahidro-3,10-diaza-benzo[e]azuleno-1-ácido carboxílico (5-cloro-piridin-2-il)-amida	H	H	H	H	H	2		
27	3,4,5,6-Tetrahidro-3,10-diaza-benzo[e]azuleno-1-ácido carboxílico (6-cloro-piridin-3-il)-amida	H	H	H	H	H	2		
28	3,4,5,6-Tetrahidro-3,10-diaza-benzo[e]azuleno-1-ácido carboxílico (2,4-difluoro-fenil)-amida	H	H	H	H	H	2		
29	3,4,5,6-Tetrahidro-3,10-diaza-benzo[e]azuleno-1-ácido carboxílico (4-cloro-fenil)-amida	H	H	H	H	H	2		

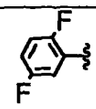
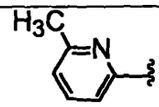
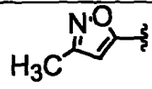
30	3,4,5,6-Tetrahidro-3,10-diaza-benzo[e]azuleno-1-ácido carboxílico pirimidin-2-ilamida	H	H	H	H	H	2		
31	3,4,5,6-Tetrahidro-3,10-diaza-benzo[e]azuleno-1-ácido carboxílico piridin-4-ilamida	H	H	H	H	H	2		
32	3,4,5,6-Tetrahidro-3,10-diaza-benzo[e]azuleno-1-ácido carboxílico o- tolil-amida	H	H	H	H	H	2		
33	3,4,5,6-Tetrahidro-3,10-diaza-benzo[e]azuleno-1-ácido carboxílico (5-bromo-piridin-2-il)-amida	H	H	H	H	H	2		
34	3,4,5,6-Tetrahidro-3,10-diaza-benzo[e]azuleno-1-ácido carboxílico (5-metil-piridin-2-il)-amida	H	H	H	H	H	2		

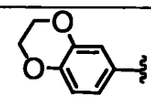
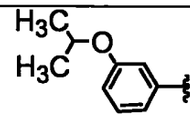
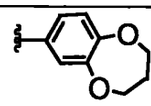
35	3,4,5,6-Tetrahidro-3,10-diaza-benzo[e]azuleno-1-ácido carboxílico (6-metoxi-piridin-3-il)-amida	H	H	H	H	H	2		
36	Propil-(2-{5-[(3,4,5,6-tetrahidro-3,10-diaza-benzo[e]azuleno-1-carbonil)-amino]-piridin-2-iloxi}-etil)-ácido carbámico ter-butil éster	H	H	H	H	H	2		
37	8-Metil-3,4,5,6-tetrahidro-3,10-diaza-benzo[e]azuleno-1-ácido carboxílico (5-metil-[1,3,4]tiadiazol-2-il)-amida	H	CH_3	H	H	H	2		

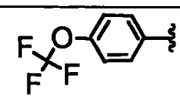
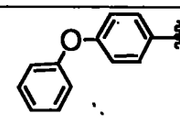
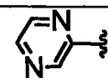
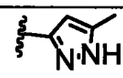
38	8-Metil-3,4,5,6-tetrahidro-3,10-diaza-benzo[e]azuleno-1-ácido carboxílico (3-fluoro-4-metoxi-fenil)-amida	H	CH_3	H	H	H	2		
39	3,4,5,6-Tetrahidro-3,10-diaza-benzo[e]azuleno-1-ácido carboxílico (4-etoxi-fenil)-amida	H	H	H	H	H	2		
40	Etil-(2-{4-[(3,4,5,6-tetrahidro-3,10-diaza-benzo[e]azuleno-1-carbonil)-amino]-fenoxi}-ethil)-ácido carbámico ter-butil éster	H	H	H	H	H	2		

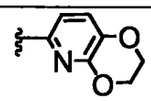
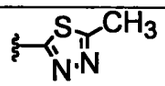
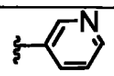
41	3,4,5,6-Tetrahidro-3,10-diaza-benzo[e]azuleno-1-ácido carboxílico (6-etil- piridin-2-il)-amida	H	H	H	H	H	2		[CDCl3] 1.35 (t, 3H), 2.3 (quint, 2H), 2.6 (t, 2H), 2.7 (t, 2H), 2.8 (q, 2H), 6.8 (d, 1H), 7.2 (dd, 1H), 7.55 (t, 1H), 7.6 (dd, 1H), 7.65 (s, 1H), 8.2 (d, 1H), 8.75 (d, 1H), 9.2 (br s, 1H)
42	3,4,5,6-Tetrahidro-3,10-diaza-benzo[e]azuleno-1-ácido carboxílico benzo[1,3]dioxol-5-ilamida	H	H	H	H	H	2		[CDCl3] 2.3 (quint, 2H), 2.6 (t, 2H), 2.7 (t, 2H), 6.8 (d, 1H), 7.1 (d, 1H), 7.2 (dd, 1H), 7.5 (s, 1H), 7.6 (s, 1H), 7.65 (d, 1H), 8.6 (d, 1H), 9.7 (br s, 1H)

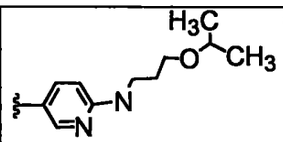
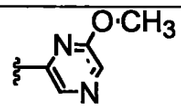
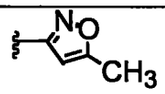
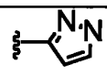
43	3,4,5,6-Tetrahidro-3,10-diaza-benzo[e]azuleno-1-ácido carboxílico (2-cloro- piridin-4-il)-amida	H	H	H	H	H	2		[CDCl3] 2.3 (quint, 2H), 2.6 (t, 2H), 2.7 (t, 2H), 7.2 (dd, 1H), 7.5 (d, 1H), 7.6 (s, 1H), 7.65 (d, 1H), 7.8 (s, 1H), 8.2 (d, 1H), 8.6 (d, 1H), 9.0 (br s, 1H)
44	3,4,5,6-Tetrahidro-3,10-diaza-benzo[e]azuleno-1-ácido carboxílico (3-metoxi- fenil)-amida	H	H	H	H	H	2		[CDCl3] 2.3 (quint, 2H), 2.6 (t, 2H), 2.7 (t, 2H), 3.8 (s, 3H), 6.6 (app s, 1H), 7.2 (dd, 1H), 7.25 (app s, 2H), 7.6 (m, 2H), 8.6 (d, 1H), 9.9 (br s, 1H)

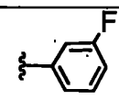
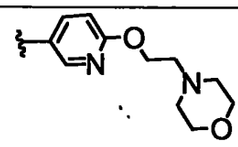
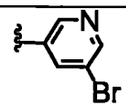
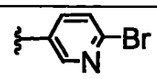
45	3,4,5,6-Tetrahidro-3,10-diaza-benzo[e] azuleno-1-ácido carboxílico (2,5-difluoro-fenil)-amida	H	H	H	H	H	2		[CDCl3] 2 3 (quint, 2H), 2.6 (t, 2H), 2.7 (t, 2H), 6 7 (m, 1H), 7.0 (m, 1H), 7 2 (dd, 1H), 7 6 (dd, 1H), 7 65 (s, 1H), 8 5 (m, 1H), 8 6 (d, 1H), 9 2 (br s, 1H)
46	3,4,5,6-Tetrahidro-3,10-diaza-benzo[e]azuleno-1-ácido carboxílico (6- metil-piridin -2-il)-amida	H	H	H	H	H	2		[CDCl3] 2.3 (quint, 2H), 2.4 (s, 3H), 2.6 (t, 2H), 2 7 (t, 2H), 6.8 (d, 1H), 7.2 (dd, 1H), 7.5 (t, 1H), 7.6 (dd, 1H), 7 65 (s, 1H), 8.2 (d, 1H), 8.7 (d, 1H), 9.8 (br s, 1H)
47	3,4,5,6-Tetrahidro-3,10-diaza-benzo[e]azuleno-1-ácido carboxílico (3- metil-isoxazol	H	H	H	H	H	2		[CDCl3] 2.25 (s, 3H), 2 3 (quint, 2H), 2.6 (t, 2H), 2.7 (t, 2H), 6.3 (s, 1H),

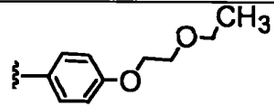
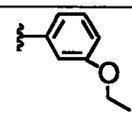
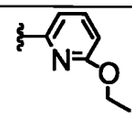
	-5-il)-amida								7.2 (dd, 1H), 7.6 (m, 2H), 8.6 (d, 1H), 8.8 (br s, 1H)
48	3,4,5,6-Tetrahidro-3,10-diaza-benzo[e]azuleno-1-ácido carboxílico (2,3-dihidro-benzo[1,4]dioxin-6-il)-amida	H	H	H	H	H	2		LRMS *m/z* 362
49	3,4,5,6-Tetrahidro-3,10-diaza-benzo[e] azuleno-1-ácido carboxílico (3-isopropoxi-fenil)-amida	H	H	H	H	H	2		LRMS *m/z* 362
50	3,4,5,6-Tetrahidro-3,10-diaza-benzo[e] azuleno-1-ácido carboxílico (3,4-dihidro-2H-benzo[b][1,4]dioxa pin-7-il)-amida	H	H	H	H	H	2		LRMS *m/z* 376

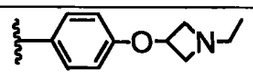
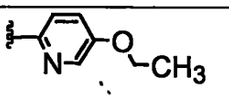
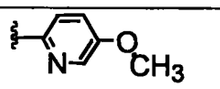
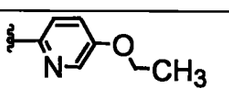
51	3,4,5,6-Tetrahidro-3,10-diaza-benzo[e] azuleno-1-ácido carboxílico (4-trifluoro-metoxi-fenil)-amida	H	H	H	H	H	2		LRMS *m/z* 388
52	3,4,5,6-Tetrahidro-3,10-diaza-benzo[e] azuleno-1-ácido carboxílico (4-fenoxi -fenil) -amida	H	H	H	H	H	2		LRMS *m/z* 396
53	3,4,5,6-Tetrahidro-3,10-diaza-benzo[e] azuleno-1-ácido carboxílico pirazin-2-ilamida	H	H	H	H	H	2		LRMS *m/z* 306
54	3,4,5,6-Tetrahidro-3,10-diaza-benzo[e] azuleno-1-ácido carboxílico (1-etil-1H-pirazol-3-il)-amida	H	H	H	H	H	2		LCMS se encontró (M+H) 322
55	3,4,5,6-Tetrahidro-3,10-diaza-benzo[e] azuleno-1-ácido carboxílico (5-metil-1H-pirazol-	H	H	H	H	H	2		LCMS se encontró (M+H) 309

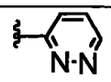
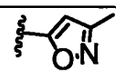
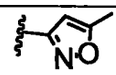
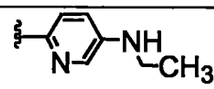
	3-il)-amida								
56	3,4,5,6-Tetrahidro-3,10-diaza-benzo[e] azuleno-1-ácido carboxílico (2,3-dihidro-[1,4] dioxino[2,3-b]piridin-6-il)-amida	H	H	H	H	H	2		LCMS se encontró (M+H) 363
57	3,4,5,6-Tetrahidro-3,10-diaza-benzo[e] azuleno-1-ácido carboxílico (5-metil-[1,3,4] tiadiazol-2-il)-amida	H	H	H	H	H	2		
58	3,4,5,6-Tetrahidro-3,10-diaza-benzo[e] azuleno-1-ácido carboxílico pridin-3-ilamida	H	H	H	H	H	2		

59	3,4,5,6-Tetrahidro-3,10-diaza-benzo[e] azuleno-1-ácido carboxílico [6-(3-isopropoxi-propilamino)-piridin-3-il]-amida	H	H	H	H	H	2		
60	3,4,5,6-Tetrahidro-3,10-diaza-benzo[e] azuleno-1-ácido carboxílico (6-metoxi-pirazin-2-il)-amida	H	H	H	H	H	2		
61	3,4,5,6-Tetrahidro-3,10-diaza-benzo[e] azuleno-1-ácido carboxílico (5-metil-isoxazol-3-il)-amida	H	H	H	H	H	2		
62	3,4,5,6-Tetrahidro-3,10-diaza-benzo[e] azuleno-1-ácido carboxílico (1H-pirazol-3-il)-amida	H	H	H	H	H	2		

63	3,4,5,6-Tetrahidro-3,10-diaza-benzo[e] azuleno-1-ácido carboxílico (3-fluoro-fenil)-amida	H	H	H	H	H	2		
64	3,4,5,6-Tetrahidro-3,10-diaza-benzo[e] azuleno-1-ácido carboxílico [6-(2-morfolin-4-il-etoxi)-piridin-3-il]-amida	H	H	H	H	H	2		
65	3,4,5,6-Tetrahidro-3,10-diaza-benzo[e] azuleno-1-ácido carboxílico (5-bromo-piridin-3-il)-amida	H	H	H	H	H	2		
66	3,4,5,6-Tetrahidro-3,10-diaza-benzo[e] azuleno-1-ácido carboxílico (6-bromo-piridin-3-il)-amida	H	H	H	H	H	2		

67	3,4,5,6-Tetrahidro-3,10-diaza-benzo[e] azuleno-1-ácido carboxílico [4-(2-etoxi-etoxi)-fenil]-amida	H	H	H	H	H	2		1HNMR (DMSO) 1 11(t, 3H), 2 15 (t, 2H), 2 49 (t, 2H), 2 73 (t, 2H), 3 46-3 49 (m, 2H), 3 67 (t, 2H), 4 0 (t, 2H), 6 90-6.92 (m, 2H), 7.58-8 41 (m, 5H), 8.69 (brs, 1H) LCMS se encontró (M+H) 392.3
68	3,4,5,6-Tetrahidro-3,10-diaza-benzo[e] azuleno-1-ácido carboxílico (3-etoxi-fenil)-amida	H	H	H	H	H	2		LCMS se encontró (M+H) 348
69	3,4,5,6-Tetrahidro-3,10-diaza-benzo[e] azuleno-1-ácido carboxílico (6-etoxi-piridin-2-il)-amida	H	H	H	H	H	2		LCMS se encontró (M+H) 349

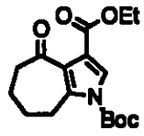
70	3,4,5,6-Tetrahidro-3,10-diaza-benzo[e] azuleno-1-ácido carboxílico [4-(1-etil-acetidin-3-iloxi)-fenil]-amida	H	H	H	H	H	2		Espectro de masa de Electrorociador: m/z 401.4 [M-1]
71	3,4,5,6-tetrahidro-3,10-diaza-benzo[e] azuleno-1- ácido carboxílico (5-etoxi-piridin-2-il)-amida	H	H	H	H	H	2		LRMS calculó 348 se encontró [M+1] 349
72	8-Metil-3,4,5,6-tetrahidro-3,10-diaza-benzo[e] azuleno-1-ácido carboxílico (5-metoxi-piridin-2-il)-amida	H	CH_3	H	H	H	2		LRMS calculó 348 se encontró [M+1] 349
73	8-Metil-3,4,5,6-tetrahidro-3,10-diaza-benzo[e] azuleno-1- ácido carboxílico (5-etoxi-piridin-2-il)-amida	H	CH_3	H	H	H	2		LRMS calculó 362 se encontró [M+1] 363

74	8-Metil-3,4,5,6-tetrahidro-3,10-diaza-benzo[e] azuleno-1-ácido carboxílico piridazin-3-ilamida	H	CH_3	H	H	H	2		LRMS calculó 319 se encontró [M+1] 320
75	8-Metil-3,4,5,6-tetrahidro-3,10-diaza-benzo[e] azuleno-1-ácido carboxílico (3-metil-isoxazol-5-il)-amida	H	CH_3	H	H	H	2		LRMS calculó 322 se encontró [M+1] 323
76	8-Metil-3,4,5,6-tetrahidro-3,10-diaza-benzo[e] azuleno-1-ácido carboxílico (5-metil-isoxazol-3-il)-amida	H	CH_3	H	H	H	2		LRMS calculó 322 se encontró [M+1] 323
77	3,4,5,6-Tetrahidro-3,10-diaza-benzo[e] azuleno-1-ácido carboxílico (6-etilamino-piridin-3-il)-amida	H	H	H	H	H	2		LRMS calculó 347 se encontró [M+1] 348

861

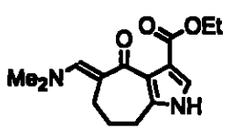
Ejemplo 6

3-Metil-3,4,5,6-tetrahidro-3,10-diaza-benzo[e]azuleno-1-ácido carboxilico etil éster



Paso 1:

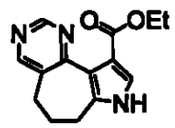
A una solución de 4-oxo-1,4,5,6,7,8-hexahidro-ciclohepta[*b*]pirrol-3-ácido carboxilico etil éster (4.80 g, 21.7 mmol) y Et_3N (3.93 mL, 28.2 mmol) en CH_2Cl_2 (40 mL) a 0 °C se agregó una porción de Boc_2O (5.68 g, 26.0 mmol). La mezcla de la reacción se dejó agitar a 0 °C durante 10 minutos y luego a temperatura ambiente durante 18 horas. La mezcla de la reacción luego se diluyó con una porción acuosa de NH_4Cl medio saturada (70 mL) y se extrajo con EtOAc. La capa orgánica se lavó luego con H_2O (50 mL) y salmuera (50 mL). Los lavados acuosos se volvieron a extraer una vez con EtOAc, y los extractos combinados se secaron sobre Na_2SO_4 y se concentraron. El material crudo se purificó por cromatografía rápida sobre silica gel. La elución con 4:1 hexanos-acetato de etilo a continuación de 3:1 hexanos-acetato de etilo produjeron 7.00 g (quant) de 4-oxo-5,6,7,8-tetrahidro-4*H*-ciclohepta[*b*]pirrol-1,3-ácido dicarboxilico 1-ter-butil éster 3-etil éster en la foma de un sólido amarillo claro. ^1H NMR ($CDCl_3$, 300 MHz) δ 7.62 (s, 1H), 4.27 (q, J = 7.2 Hz, 2H), 3.22 (m, 2H), 2.78 (m, 2H), 1.86 (m, 4H), 1.60 (s, 9H), 1.31 (t, J = 7.2 Hz)



Paso 2:

862

Una mezcla de 4-oxo-5,6,7,8-tetrahidro-4*H*-ciclohepta[*b*]pirrol-1,3-ácido dicarboxílico 1-ter-butil éster 3-etil éster (1.13 g, 3.52 mmol) y tris(dimetilamino)metano (1.02 g, 7.04 mmol) se agitó a 60°C dentro de un tubo con cierre hermético durante 4.5 horas. Luego de enfriarse, la pasta aguada delgada se colocó en Et_2O y se filtró. El compuesto sólido se lavó con Et_2O y se secó, produciendo 847 mg (87%) de 5-dimetilamino metileno-4-oxo-1,4,5,6,7,8- hexahidro-ciclohepta[*b*]pirrol-3-ácido carboxílico etil éster en la forma de un sólido amarillo-naranja claro. ^1H NMR ($CDCl_3$, 300 MHz) δ 9.93 (br s, 1H), 7.58 (s, 1H), 7.12 (d, J = 2.7 Hz, 1H), 4.21 (q, J = 7.2 Hz, 2H), 3.06 (s, 6H), 2.68 (m, 2H), 2.47 (m, 2H), 1.80 (m, 2H), 1.26 (t, J = 7.2 Hz, 3H).



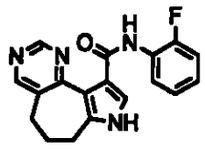
Paso 3:

Una mezcla de 5-dimetilaminometileno-4-oxo-1,4,5,6,7,8-hexahidro-ciclohepta[*b*]pirrol-3-ácido carboxílico etil éster (840 mg) y acetato de formamidina (956 mg, 9.1 mmol) en EtOH (10 mL) se agitó a 120 °C durante 4 horas. Después de que se haya enfriado, la mezcla de la reacción se diluye con CH_2Cl_2 y se lava con $NaHCO_3$ acuoso medio saturado (25 mL), H_2O (25 mL), y salmuera (25 mL). Los lavados acuosos se volvieron a extraer una vez con CH_2Cl_2, y los extractos combinados se secaron sobre K_2CO_3 y se concentraron. El material crudo se purificó mediante cromatografía rápida sobre silica gel. La elución con 30:1 $CHCl_3$-MeOH seguida por 20:1 $CHCl_3$-MeOH y finalmente 15:1 $CHCl_3$-

MeOH produjo 606 mg (77%) de 3,4,5,6-tetrahidro-3,8,10-triaza-benzo[e]azuleno-1-ácido carboxílico etil éster en la forma de un sólido amarillo claro. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.30 (br s, 1H), 9.02 (s, 1H), 8.43 (s, 1H), 7.24 (d, J = 2.7 Hz, 1H), 4.26 (q, J = 7.2 Hz, 2H), 2.78 (t, J = 7.2 Hz, 2H), 2.70 (m, 2H), 2.12 (m, 2H), 1.26 (t, J = 7.2 Hz, 3H).

Ejemplo 7

3,4,5,6-tetrahidro-3;8,10-triaza-benzo[e]azuleno-1-ácido carboxílico (2-fluoro-fenil)-amida

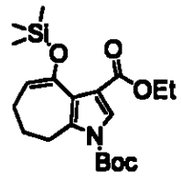


A una solución de 2-fluoroanilina (108 mg, 0.972 mmol) en CH_2Cl_2 (2.0 mL) a 0°C bajo N_2 se agregó lentamente $AlMe_3$ (0.49 mL, 2.0 *M* en tolueno). La solución resultante se agitó a temperatura ambiente durante 1 hora. Luego, se agregó una porción de 3,4,5,6-tetrahidro-3,8,10-triaza-benzo[e]azuleno-1-ácido carboxílico etil éster (50 mg, 0.194 mmol). La mezcla resultante se agitó luego por reflujo durante 2 horas. Después que se enfrió, la mezcla de la reacción se diluye cuidadosamente con NH_4Cl acuoso saturado (~5 mL) y algo de H_2O. La mezcla se agitó fuertemente durante 15 minutos, y luego se extrajo tres veces con CH_2Cl_2. Los extractos combinados se secaron sobre K_2CO_3 y se concentraron. El material crudo se purificó por cromatografía rápida sobre silica gel. La elución con 40:1 $CHCl_3$-MeOH seguido por 30:1 $CHCl_3$-MeOH y finalmente 20:1 $CHCl_3$-MeOH produjo 45 mg (72%) of 3,4,5,6-tetrahidro-3,8,10-triaza-benzo[e]azuleno-1-ácido

carboxílico (2-fluoro-fenil)-amida en la forma de un sólido amarillo claro. Espectro de masa del electrovaporizador: *m/z* 321 [M-1].

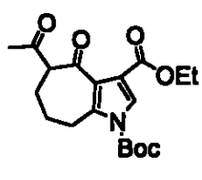
Ejemplo 7a

3-Metil-4,5,6,7-tetrahidro-1-oxa-2,7-diaza-ciclopenta[e]azuleno - 9-ácido carboxílico etil éster



Paso 1:

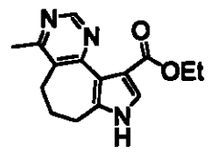
A una mezcla de 4-oxo-5,6,7,8-tetrahidro-4H-ciclohepta[b]pirrol-1,3-ácido dicarboxílico 1-ter-butil éster 3-etil éster (4.6 mmol), ioduro de sodio (9.3 mmol), y trietilamina (13.9 mmol) en 15 ml acetonitrilo se le agregó cloruro de trimetilsililo (9.3 mmol). Después de agitar a temperatura ambiente durante 2 horas se amortiguó con una solución de 20 ml $NaHCO_3$ saturado y se extrajo varias veces con EtOAc. Las capas orgánicas combinadas se secaron sobre Na_2SO_4 y se evaporaron al vacío produciendo 4-trimetilsilaniloxi-7,8-dihidro-6H-ciclohepta[b]pirrol-1,3-ácido dicarboxílico 1-ter-butil éster 3-etil éster en la forma de un aceite marrón (95%). 1H NMR (CDCl3) 0.15 (s, 9H), 1.32 (t, 3H), 1.60 (s, 9H), 1.83-1.97 (m, 2H), 1.99-2.06 (m, 2H), 3.00 (t, 2H), 4.33 (q, 2H), 5.40 (t, 1H), 7.62 (s, 1H).



Paso 2:

865

Bismuto (III) cloruro (0.1 mmol) y ioduro de sodio (0.3 mmol) se transfirieron a un matraz seco bajo nitrógeno y 5 ml de una mezcla de CH_2Cl_2/éter (9/1) se agregó utilizando una jeringa. Posteriormente se agregó cloruro de acetilo (2.2 mmol) y la suspensión se agitó durante 5 minutos a temperatura ambiente. Se agregó una solución de 4-trimetilsilaniloxi- 7,8-dihidro-6H-ciclohepta[b]pirrol-1,3-ácido dicarboxílico 1-ter-butil éster 3-etil éster (2 mmol) en 5 ml del mismo solvente. Después de dos horas a temperatura ambiente, la mezcla se amortiguó con una solución de 20 ml de $NaHCO_3$ saturado y se extrajo varias veces con CH_2Cl_2. Las capas orgánicas se combinaron, se secaron sobre Na_2SO_4 y se evaporaron al vacío produciendo 5-acetil-4-oxo-5,6,7,8-tetrahidro-4H-ciclohepta[b]pirrol-1,3-ácido dicarboxílico 1-ter-butil éster 3-etil éster en la forma de un aceite (86%). LRMS 363.4 se encontró (M+1) 364.2



Paso 3:

En un tubo con cierre hermético se encontró 5-acetil-4-oxo-5,6,7,8-tetrahidro-4H-ciclohepta[b]pirrol-1,3-ácido dicarboxílico 1-ter-butil éster 3-etil éster (1.1 mmol) y acetato de formamidina (5.5 mmol) y 10 ml de EtOH. La mezcla se calentó a 120°C durante 48 horas. El solvente se evaporó al vacío y el residuo se vertió en CH_2Cl_2 y se lavó dos veces con $NaHCO_3$ (acuoso). La capa orgánica se secó sobre Na_2SO_4 y se evaporó al

vacío y el residuo cromatografiado usó el 10% MeOH en CH_2Cl_2 en la forma de una capa móvil para producir 7-Metil-3,4,5,6-tetrahidro -3,8,10-triaza- benzo[e]azuleno-1-ácido carboxílico etil éster (36%). LRMS 271.1 se encontró (M+1) 272

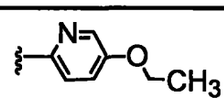
Ejemplo 7b

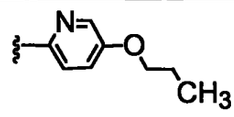
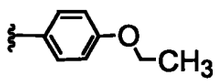
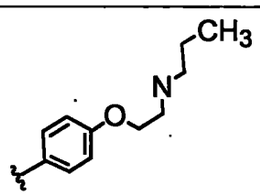
Compuestos adicionales de 3,8,10-triaza-benzo[e]azuleno-1-ácido carboxílico

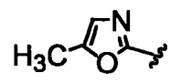
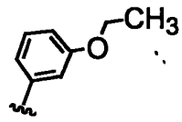
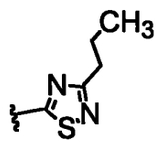
Utilizando los métodos mostrados en el Esquema 4 y aquellos ilustrados en los Ejemplos 6 y 7-7a se sintetizaron los siguientes compuestos que se muestran en la Tabla 3.

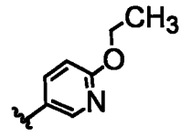
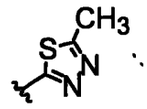
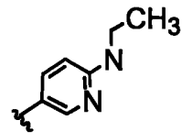
TABLA 3

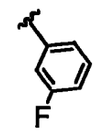
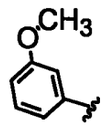
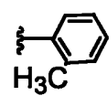
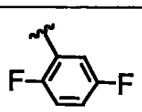


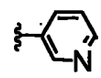
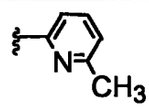
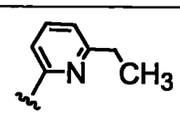
Com. #	Nombre	R^3	R^4	R^5	R^6	k	Ar	Datos del Espectro
1.	3,4,5,6-tetrahidro-3,8,10-triaza-benzo[e]azuleno-1-ácido carboxílico (5-etoxi-piridin-2-il)-amida	H	H	H	H	2		Espectro de Masa Electrovaporizador: *m/z* 348 [M-1]

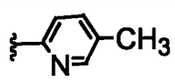
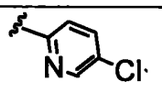
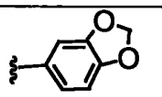
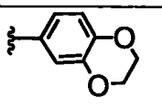
2.	3,4,5,6-tetrahidro-3,8,10-triaza-benzo[e]azuleno-1-ácido carboxílico (5-*n*-propoxi-piridin-2-il)-amida	H	H	H	H	2		LRMS calculado 363 se encontró [M+1] 364
3.	3,4,5,6-tetrahidro-3,8,10-triaza-benzo[e]azuleno-1-ácido carboxílico (4-etoxi-fenil)-amida	H	H	H	H	2		Espectro de masa Electrovaporizador: *m/z* 347 [M-1]
4.	3,4,5,6-tetrahidro-3,8,10-triaza-benzo[e]azuleno-1-ácido carboxílico [4-(2-propilamino-etoxi)-fenil]-amida	H	H	H	H	2		LRMS calculado 405 se encontró [M+1] 406

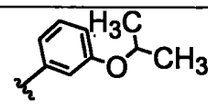
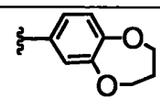
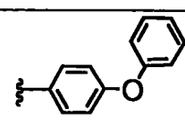
5.	3,4,5,6-tetrahidro-3,8,10-triaza-benzo[e]azuleno-1-ácido carboxílico (5-metil-oxazol-2-il)-amida	H	H	H	H	2		se encontró LCMS (M+H) 336
6.	3,4,5,6-tetrahidro-3,8,10-triaza-benzo[e]azuleno-1-ácido carboxílico (3-etoxi-fenil)-amida	H	H	H	H	2		se encontró LCMS (M+H) 349
7.	3,4,5,6-tetrahidro-3,8,10-triaza-benzo[e]azuleno-1-ácido carboxílico (3-propil-[1,2,4]tiadiazol-5-il)-amida	H	H	H	H	2		se encontró LCMS (M+H) 355

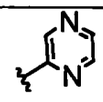
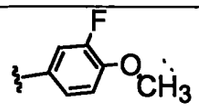
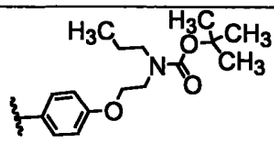
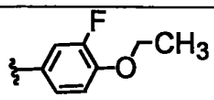
8.	3,4,5,6-tetrahidro-3,8,10-triaza-benzo[e]azuleno-1-ácido carboxílico (6-etoxi-piridin-3-il)-amida	H	H	H	H	2		LRMS 349.39 se encontró (M+1) 350.3
9.	3,4,5,6-tetrahidro-3,8,10-triaza-benzo[e]azuleno-1-ácido carboxílico (5-metil-[1,3,4]thiadiazol-2-il)-amida	H	H	H	H	2		Espectro de masa de electrorociador: *m/z* 325 [M-1]
10.	3,4,5,6-tetrahidro-3,8,10-triaza-benzo[e]azuleno-1-ácido carboxílico (6-etilamino-piridin-3-il)-amida	H	H	H	H	2		LRMS calculado 348 se encontró [M+1] 349

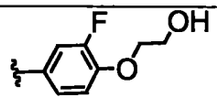
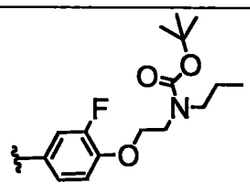
11.	3,4,5,6-tetrahidro-3,8,10-triaza-benzo[e]azuleno-1-ácido carboxílico (3-fluoro-fenil)-amida	H	H	H	H	2		[CDCl3] 2.3 (quint, 2H), 2.6 (t, 2H), 2.8 (t, 2H), 6.8 (ap s, 1H), 7.3 (m, 2H), 7.7 (s, 1H), 7.8 (d, 1H), 8.6 (s, 1H), 9.2 (s, 1H), 10.4 (br s, 1H), 13.0 (s, 1H); LRMS calculado 322 se encontró [M+1] 323
12.	3,4,5,6-tetrahidro-3,8,10-triaza-benzo[e]azuleno-1-ácido carboxílico (3-metoxi-fenil)-amida	H	H	H	H	2		[CDCl3] 2.3 (quint, 2H), 2.6 (t, 2H), 2.8 (t, 2H), 3.8 (s, 3H), 6.6 (d, 1H), 7.2 (m, 2H), 7.6 (s, 1H), 7.7 (s, 1H), 8.6 (s, 1H), 9.2 (s, 1H), 10.4 (br s, 1H), 12.9 (s, 1H)
13.	3,4,5,6-tetrahidro-3,8,10-triaza-benzo[e]azuleno-1-ácido carboxílico o-tolil-amida	H	H	H	H	2		[CDCl3] 2.3 (quint, 2H), 2.4 (s, 3H), 2.6 (app t, 4H), 7.1 (t, 1H), 7.2 (m, 2H), 7.65 (s, 1H), 7.75 (s, 1H), 8.6 (s, 1H), 9.0 (s, 1H), 10.5 (br s, 1H), 12.2 (s, 1H); LRMS calculado 318 se encontró [M+1] 319
14.	3,4,5,6-tetrahidro-3,8,10-triaza-benzo[e]azuleno-1-ácido	H	H	H	H	2		[CDCl3] 2.3 (quint, 2H), 2.6 (t, 2H), 2.8 (t, 2H), 6.7 (m, 1H), 7.05 (m, 1H), 7.75 (s, 1H), 8.45 (m, 1H), 8.6 (s, 1H), 9.2 (s,

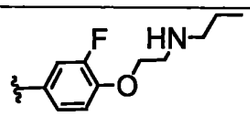
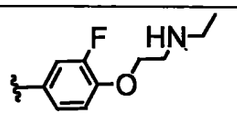
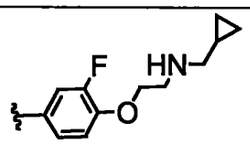
	carboxílico (2,5-difluoro-fenil)-amida							1H), 10.0 (br s, 1H), 13.4 (s, 1H); Espectro de masa de electrorociador: *m/z* 339 [M-1
15.	3,4,5,6-tetrahidro-3,8,10-triaza-benzo[e]azuleno-1-ácido carboxílico piridin-3-ilamida	H	H	H	H	2		[CDCl3 + CD3OD] 2.3 (quint, 2H), 2.6 (t, 2H), 2.8 (t, 2H), 7.3 (m, 2H), 7.6 (s, 1H), 8.3 (m, 2H), 8.6 (s, 1H), 8.8 (s, 1H), 9.2 (s, 1H)
16.	3,4,5,6-tetrahidro-3,8,10-triaza-benzo[e]azuleno-1-ácido carboxílico (6-metil-piridin-2-il)-amida	H	H	H	H	2		[CDCl3] 2.3 (quint, 2H), 2.5 (s, 3H), 2.6 (t, 2H), 2.8 (t, 2H), 6.85 (d, 1H), 7.6 (t, 1H), 7.7 (s, 1H), 8.2 (d, 1H), 8.6 (s, 1H), 9.3 (s, 1H), 9.6 (br s, 1H)
17.	3,4,5,6-tetrahidro-3,8,10-triaza-benzo[e]azuleno-1-ácido carboxílico (6-etil-piridin-2-il)-amida	H	H	H	H	2		[CDCl3] 1.3 (t, 3H), 2.3 (quint, 2H), 2.6 (t, 2H), 2.8 (m, 4H), 6.8 (d, 1H), 7.5 (t, 1H), 7.6 (s, 1H), 8.1 (d, 1H), 8.5 (s, 1H), 9.2 (s, 1H)

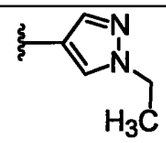
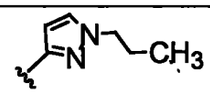
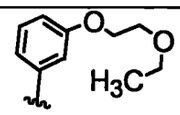
18.	3,4,5,6-tetrahidro-3,8,10-triaza-benzo[e]azuleno-1-ácido carboxílico (5-metil-piridin-2-il)-amida	H	H	H	H	2		[CDCl3] 2.2 (s, 3H), 2.3 (quint, 2H), 2.6 (t, 2H), 2.8 (t, 2H), 7.4 (d, 1H), 7.6 (s, 1H), 8.1 (s, 1H), 8.2 (d, 1H), 8.5 (s, 1H), 9.2 (s, 1H)
19.	3,4,5,6-tetrahidro-3,8,10-triaza-benzo[e]azuleno-1-ácido carboxílico (5-cloro-piridin-2-il)-amida	H	H	H	H	2		[CDCl3] 2.3 (quint, 2H), 2.6 (t, 2H), 2.8 (t, 2H), 7.6 (dd, 1H), 7.7 (s, 1H), 8.3 (d, 1H), 8.35 (d, 1H), 8.6 (s, 1H), 9.2 (s, 1H), 9.7 (br s, 1H)
20.	3,4,5,6-tetrahidro-3,8,10-triaza-benzo[e]azuleno-1-ácido carboxílico benzo[1,3]dioxol-5-ilamida	H	H	H	H	2		[CDCl3 + CD3OD] 2.3 (quint, 2H), 2.6 (t, 2H), 2.8 (t, 2H), 6.0 (s, 2H), 6.8 (d, 1H), 7.0 (dd, 1H), 7.4 (d, 1H), 7.6 (s, 1H), 8.6 (s, 1H), 9.1 (s, 1H)
21.	3,4,5,6-tetrahidro-3,8,10-triaza-benzo[e]azuleno-1-ácido carboxílico (2,3-dihidro-benzo[1,4]dioxin-	H	H	H	H	2		Espectro de masa de electrorociador: *m/z* 363 [M+1]

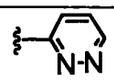
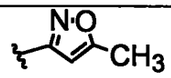
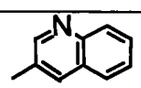
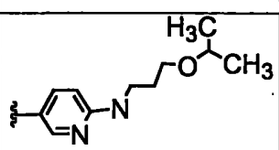
	6-il)-amida							
22.	3,4,5,6-tetrahidro-3,8,10-triaza-benzo[e]azuleno-1-ácido carboxílico (3-isopropoxi-fenil)-amida	H	H	H	H	2		LRMS *m/z* 363
23.	3,4,5,6-tetrahidro-3,8,10-triaza-benzo[e]azuleno-1-ácido carboxílico (3,4-dihidro-2H-benzo[b][1,4]dioxepin-7-il)-amida	H	H	H	H	2		LRMS *m/z* 377
24.	3,4,5,6-tetrahidro-3,8,10-triaza-benzo[e]azuleno-1-ácido carboxílico (4-fenoxi-fenil)-amida	H	H	H	H	2		LRMS *m/z* 397

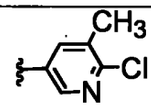
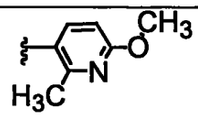
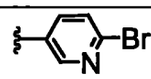
25.	3,4,5,6-tetrahidro-3,8,10-triaza-benzo[e]azuleno-1-ácido carboxílico pirazin-2-ilamida	H	H	H	H	2		LRMS calculado 306 se encontró [M+1] 307; 1H NMR DMSO-d6, 2.14 (m, 2H), 2.62(m, 2H), 2.80(m, 2H), 7.64(s, 1H), 8.30(1H, d), 8.38(m, 1H), 8.66(s, 1H), 9.04(s, 1H), 9.48(s, 1H), 11.94(bs, 1H), 13.57(s, 1H)
26.	3,4,5,6-tetrahidro-3,8,10-triaza-benzo[e]azuleno-1-ácido carboxílico (3-fluoro-4-metoxi-fenil)-amida	H	H	H	H	2		Espectro de masa de electrorociador: *m/z* 351 [M-1]
27.	Propil-(2-{4-[(3,4,5,6-tetrahidro-3,8,10-triaza-benzo[e]azuleno-1-Carbonil)-amino]-fenoxi}-etil)-ácido carbamico ter-butil éster							LRMS calculado 505 se encontró [M+1] 506
28.	3,4,5,6-tetrahidro-3,8,10-triaza-benzo[e]azuleno-1-ácido carboxílico (4-	H	H	H	H	2		LRMS 366.39 se encontró (M+1) 367.3

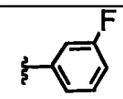
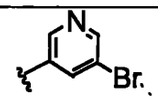
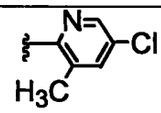
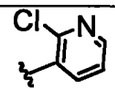
	etoxi-3-fluoro-fenil)-amida							
29.	3,4,5,6-tetrahidro-3,8,10-triaza-benzo[e]azuleno-1-ácido carboxílico [3-fluoro-4-(2-hidroxi-etoxi)-fenil]-amida	H	H	H	H	2		LRMS calculado 382 se encontró [M+1]
30.	Propil-(2-{4-[(3,4,5,6-tetrahidro-3,8,10-triaza-benzo[e]azuleno-1-carbonil)-amino]-fenoxi}-ethil)-ácido carbamico ter-butil éster	H	H	H	H	2		LRMS calculado 505 se encontró [M+1] 506

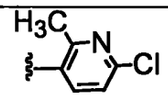
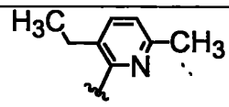
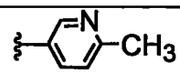
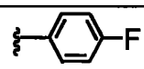
31.	3,4,5,6-tetrahidro-3,8,10-triaza-benzo[e]azuleno-1-ácido carboxílico [3-fluoro-4-(2-propilamino-etoxi)-fenil]-amida	H	H	H	H	2		LRMS calculado 423 se encontró [M-1] 422
32.	3,4,5,6-tetrahidro-3,8,10-triaza-benzo[e]azuleno-1-ácido carboxílico [4-(2-etilamino-etoxi)-3-fluoro-fenil]-amida	H	H	H	H	2		LRMS calculado 409 se encontró [M+1] 410
33.	3,4,5,6-tetrahidro-3,8,10-triaza-benzo[e]azuleno-1-ácido carboxílico {4-[2-(ciclopropilmetil-amino)-etoxi]-3-fluoro-fenil}-amida	H	H	H	H	2		LRMS calculado 435 se encontró [M+1] 436

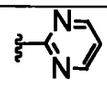
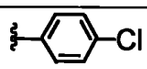
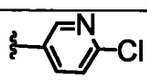
34.	3,4,5,6-tetrahidro-3,8,10-triaza-benzo[e]azuleno-1-ácido carboxílico (1-etil-1H-pirazol-4-il)-amida	H	H	H	H	2		^{1}HNMR (DMSO) 1.33 (t, 3H), 2.11-2.20 (m, 2H), 2.55-2.62 (m, 2H), 2.72-2.76 (m, 2H), 4.01 (q, 2H), 6.5 (s, 1H), 7.5 (s, 1H), 7.6 (s, 1H), 8.6 (s, 1H), 9.0 (S, 1H), 11.8 (brs, 1H), 12.7 (brs, 1H) se encontró LCMS (M+H) 323
35.	3,4,5,6-tetrahidro-3,8,10-triaza-benzo[e]azuleno-1-ácido carboxílico (1-propil-1H-pirazol-3-il)-amida	H	H	H	H	2		se encontró LCMS (M+H) 337
36.	3,4,5,6-tetrahidro-3,8,10-triaza-benzo[e]azuleno-1-ácido carboxílico [3-(2-etoxi-etoxi)-fenil]-amida	H	H	H	H	2		1HNMR (DMSO) 1.21-1.25 (m, 3H), 2.25 (t, 2H), 2.62 (t, 2H), 2.76 (t, 2H), 3.57-3.61 (m, 2H), 3.78-3.80 (m, 2H), 4.13-4.15 (m, 2H), 6.66-6.69 (m, 1H), 7.21-7.2 (m., 2H), 7.54 (brs, 1H), 7.66 (m, 1H), 8.56 (brs, 1H), 9.16 (brs, 1H), 12.9 (s, 1H) se encontró LCMS (M+H) 393

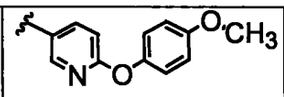
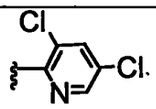
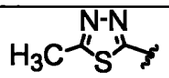
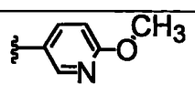
37.	3,4,5,6-tetrahidro-3,8,10-triaza-benzo[e]azuleno-1-ácido carboxílico piridazin-3-ilamida	H	H	H	H	2		LRMS calculado 306 se encontró [M+1] 307
38.	3,4,5,6-tetrahidro-3,8,10-triaza-benzo[e]azuleno-1-ácido carboxílico (5-metil-isoxazol-3-il)-amida	H	H	H	H	2		se encontró LCMS (M+H) 310
39.	3,4,5,6-tetrahidro-3,8,10-triaza-benzo[e]azuleno-1-ácido carboxílico quinolin-3-ilamida	H	H	H	H	2		
40.	3,4,5,6-tetrahidro-3,8,10-triaza-benzo[e]azuleno-1-ácido carboxílico [6-(3-isopropoxi-propilamino)-piridin-3-il]-	H	H	H	H	2		

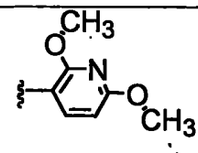
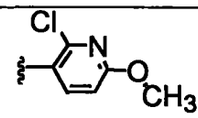
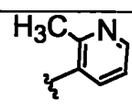
	amida							
41.	3,4,5,6-tetrahidro-3,8,10-triaza-benzo[e]azuleno-1-ácido carboxílico (6-cloro-5-metil-piridin-3-il)-amida	H	H	H	H	2		
42.	3,4,5,6-tetrahidro-3,8,10-triaza-benzo[e]azuleno-1-ácido carboxílico (6-metoxi-2-metil-piridin-3-il)-amida	H	H	H	H	2		
43.	3,4,5,6-tetrahidro-3,8,10-triaza-benzo[e]azuleno-1-ácido carboxílico (6-bromo-piridin-3-il)-amida	H	H	H	H	2		

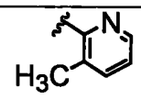
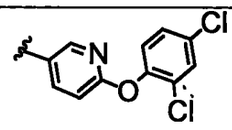
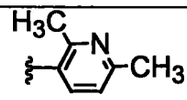
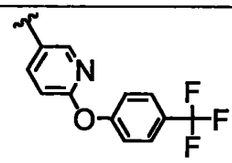
44.	3,4,5,6-tetrahidro-3,8,10-triaza-benzo[e]azuleno-1-ácido carboxílico (3-fluoro-fenil)-amida	H	H	H	H	2		LRMS calculado 322 se encontró [M+1] 323
45.	3,4,5,6-tetrahidro-3,8,10-triaza-benzo[e]azuleno-1-ácido carboxílico (5-bromo-piridin-3-il)-amida	H	H	H	H	2		
46.	3,4,5,6-tetrahidro-3,8,10-triaza-benzo[e]azuleno-1-ácido carboxílico (5-cloro-3-metil-piridin-2-il)-amida	H	H	H	H	2		
47.	3,4,5,6-tetrahidro-3,8,10-triaza-benzo[e]azuleno-1-ácido carboxílico (2-cloro-piridin-3-il)-amida	H	H	H	H	2		

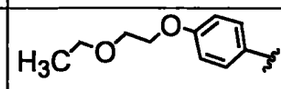
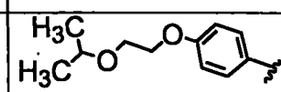
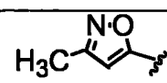
48.	3,4,5,6-tetrahidro-3,8,10-triaza-benzo[e]azuleno-1-ácido carboxílico (6-cloro-2-metil-piridin-3-il)-amida	H	H	H	H	2		
49.	3,4,5,6-tetrahidro-3,8,10-triaza-benzo[e]azuleno-1-ácido carboxílico (3-etil-6-metil-piridin-2-il)-amida	H	H	H	H	2		
50.	3,4,5,6-tetrahidro-3,8,10-triaza-benzo[e]azuleno-1-ácido carboxílico (6-metil-piridin-3-il)-amida	H	H	H	H	2		
51.	3,4,5,6-tetrahidro-3,8,10-triaza-benzo[e]azuleno-1-ácido carboxílico (4-fluoro-fenil)-	H	H	H	H	2		

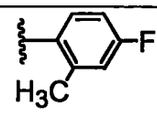
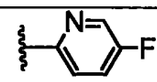
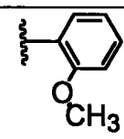
	amida							
52.	3,4,5,6-tetrahidro-3,8,10-triaza-benzo[e]azuleno-1-ácido carboxílico pirimidin-2-ilamida	H	H	H	H	2		
53.	3,4,5,6-tetrahidro-3,8,10-triaza-benzo[e]azuleno-1-ácido carboxílico (4-cloro-fenil)-amida	H	H	H	H	2		
54.	3,4,5,6-tetrahidro-3,8,10-triaza-benzo[e]azuleno-1-ácido carboxílico (6-cloro-piridin-3-il)-amida	H	H	H	H	2		

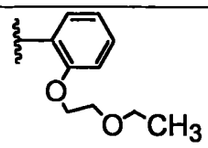
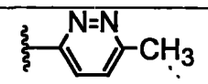
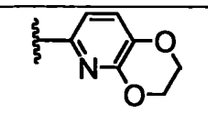
55.	3,4,5,6-tetrahidro-3,8,10-triaza-benzo[e]azuleno-1-ácido carboxílico [6-(4-metoxi-fenoxi)-piridin-3-il]-amida	H	H	H	H	2		
56.	3,4,5,6-tetrahidro-3,8,10-triaza-benzo[e]azuleno-1-ácido carboxílico (3,5-dicloro-piridin-2-il)-amida	H	H	H	H	2		
57.	3,4,5,6-tetrahidro-3,8,10-triaza-benzo[e]azuleno-1-ácido carboxílico (5-metil-[1,3,4]tiadiazol-2-il)-amida	H	H	H	H	2		
58.	3,4,5,6-tetrahidro-3,8,10-triaza-benzo[e]azuleno-1-ácido carboxílico (6-metoxi-piridin-3-	H	H	H	H	2		

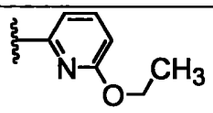
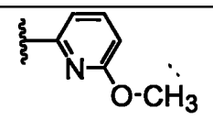
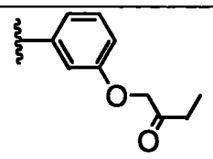
	il)-amida							
59.	3,4,5,6-tetrahidro-3,8,10-triaza-benzo[e]azuleno-1-ácido carboxílico (2,6-dimetoxi-piridin-3-il)-amida	H	H	H	H	2		
60.	3,4,5,6-tetrahidro-3,8,10-triaza-benzo[e]azuleno-1-ácido carboxílico (2-cloro-6-metoxi-piridin-3-il)-amida	H	H	H	H	2		LRMS calculado 369 se encontró [M+1] 370
61.	3,4,5,6-tetrahidro-3,8,10-triaza-benzo[e]azuleno-1-ácido carboxílico (2-metil-piridin-3-il)-amida	H	H	H	H	2		Se encontró MS [M+H] 320.2

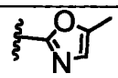
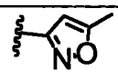
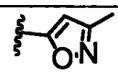
62.	3,4,5,6-tetrahidro-3,8,10-triaza-benzo[e]azuleno-1-ácido carboxílico (3-metil-piridin-2-il)-amida	H	H	H	H	2		Espectro de masa de electrorociador: *m/z* 320 [M+1]
63.	3,4,5,6-tetrahidro-3,8,10-triaza-benzo[e]azuleno-1-ácido carboxílico [6-(2,4-dicloro-fenoxi)-piridin-3-il]-amida	H	H	H	H	2		
64.	3,4,5,6-tetrahidro-3,8,10-triaza-benzo[e]azuleno-1-ácido carboxílico (2,6-dimetil-piridin-3-il)-amida	H	H	H	H	2		
65.	3,4,5,6-tetrahidro-3,8,10-triaza-benzo[e]azuleno-1-ácido carboxílico [6-(4-trifluorometil-	H	H	H	H	2		

	fenoxi)-piridin-3-il]-amida							
66.	3,4,5,6-tetrahidro-3,8,10-triaza-benzo[e]azuleno-1-ácido carboxílico [4-(2-etoxi-etoxi)-fenil]-amida	H	H	H	H	2		1HNMR (DMSO) 1.09-1.13 (m, 3H), 2.15 (t, 2H), 2.6 (t, 2H), 2.74 (t, 2H), 3.46 - 3.51 (m, 2H), 3.65-3.67 (m, 2H), 4.01-4.04 (m, 2H), 6.66-6.69 (m, 2H), 7.54 (brs, 1H), 7.60-7.62 (m, 2H), 8.56-8.57 (brs, 1H), 11.7 (brs, 1H), 12.1 (s, 1H) se encontró LCMS (M+H) 393
67.	3,4,5,6-tetrahidro-3,8,10-triaza-benzo[e]azuleno-1-ácido carboxílico [4-(2-isopropoxi-etoxi)-fenil]-amida	H	H	H	H	2		1HNMR (DMSO) 1.08-1.09 (m, 6H), 2.15 (t, 2H), 2.6 (t, 2H), 2.73 (t, 2H), 3.58 - 3.61 (m, 1H), 3.66 (t, 2H), 4.0 (t, 2H), 6.86-6.89 (m, 2H), 7.54 (brs, 1H), 7.60-7.62 (m, 2H), 8.64 (s, 1H), 9.16 (brs, 1H), 12.1 (s, 1H) se encontró LCMS (M+H) 407
68.	3,4,5,6-tetrahidro-3,8,10-triaza-benzo[e]azuleno-1-ácido carboxílico (3-	H	H	H	H	2		se encontró LCMS (M+H) 310

	metil-isoxazol-5-il)-amida							
69.	3,4,5,6-tetrahidro-3,8,10-triaza-benzo[e]azuleno-1-ácido carboxílico (5-fluoro-2-metil-fenil)-amida	H	H	H	H	2		Espectro de masa de electrorociador: *m/z* 335 [M-1]
70.	3,4,5,6-tetrahidro-3,8,10-triaza-benzo[e]azuleno-1-ácido carboxílico (5-fluoro-2-metil-fenil)-amida	H	H	H	H	2		Espectro de masa de electrorociador: *m/z* 324 [M+1]
71.	3,4,5,6-tetrahidro-3,8,10-triaza-benzo[e]azuleno-1-ácido carboxílico (2-metoxi-fenil)-amida	H	H	H	H	2		LRMS 334.38 se encontró (M+1) 335.2

72.	3,4,5,6-tetrahidro-3,8,10-triaza-benzo[e]azuleno-1-ácido carboxílico [2-(2-etoxi-etoxi)-fenil]-amida	H	H	H	H	2		LRMS 392.46 se encontró (M+1) 393.0
73.	3,4,5,6-tetrahidro-3,8,10-triaza-benzo[e]azuleno-1-ácido carboxílico 6-metil-piridazin-3-ilamida	H	H	H	H	2		LRMS 320.35 se encontró (M+1) 321.0
74.	3,4,5,6-tetrahidro-3,10-diaza-benzo[e]azuleno-1-ácido carboxílico (2,3-dihidro-[1,4]dioxino[2,3-b]piridin-6-il)-amida	H	H	H	H	2		se encontró LCMS (M+H) 363

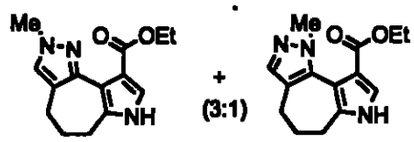
75.	3,4,5,6-tetrahidro-3,8,10-triaza-benzo[e]azuleno-1-ácido carboxílico (6-etoxi-piridin-2-il)-amida	H	H	H	H	2		Se encontró LCMS (M+H) 350
76.	3,4,5,6-tetrahidro-3,8,10-triaza-benzo[e]azuleno-1-ácido carboxílico (6-metoxi-piridin-2-il)-amida	H	H	H	H	2		Se encontró LCMS (M+H) 336
77.	3,4,5,6-tetrahidro-3,8,10-triaza-benzo[e]azuleno-1-ácido carboxílico [3-(2-oxo-butoxi)-fenil]-amida	H	H	H	H	2		se encontró LCMS (M+H) 391

78.	3,4,5,6-tetrahidro-3,8,10-triaza-benzo[e]azuleno-1-ácido carboxílico (5-metil-oxazol-2-il)-amida	H	H	H	H	2		Se encontró LCMS (M+H) 310
79.	7-metil-3,4,5,6-tetrahidro-3,8,10-triaza-benzo[e]azuleno-1-ácido carboxílico (5-metil-isoxazol-3-il)-amida	CH_3	H	H	H	2		LRMS 323 se encontró (M+1) 324
80.	7-metil-3,4,5,6-tetrahidro-3,8,10-triaza-benzo[e]azuleno-1-ácido carboxílico (3-metil-isoxazol-5-il)-amida	CH_3	H	H	H	2		LRMS 323 se encontró (M+1) 324

892

Ejemplo 8

1-metil-4,5,6,7-tetrahidro-1*H*-1,2,7-triaza-ciclopenta[e]azuleno -9-ácido carboxílico etil éster y 2-metil-4,5,6,7-tetrahidro-2*H*-1,2,7-triaza-ciclopenta[e]azuleno -9-ácido carboxílico etil éster

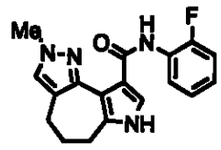


Una mezcla de etil 5-dimetilaminometileno-4-oxo-1,4,5,6,7,8-hexahidro-ciclohepta[*b*]pirrol-3-ácido carboxílico etil éster (100 mg, 0.362 mmol) y metilhidrazina (83 mg, 1.81 mmol) en EtOH (2 mL) se agitó a 100°C durante 3 horas. Después de enfriarse, la mezcla de la reacción se diluyó con CH_2Cl_2 y se lavó con $NaHCO_3$ acuoso medio saturado (10 mL), H_2O (10 mL), y salmuera (10 mL). El extracto CH_2Cl_2 se secó sobre Na_2SO_4 y se concentró. El material crudo se purificó por cromatografía rápida sobre silica gel. La elución con 3:1 EtOAc-hexanos (+ 0.5% Et_3N) seguido por acetato de etilo al 100% (+ 0.5% Et_3N) se separó en dos regioisómeros. Primeras fracciones: 23 mg (25%) de 1-metil-4,5,6,7 -tetrahidro-1*H*- 1,2,7-triaza-ciclopenta[e] azuleno-9-ácido carboxílico etil éster; espectro de masa del electrovaporizador: *m/z* 260 [M+1]; ^1H NMR ($CDCl_3$, 400 MHz) δ 9.32 (br s, 1H), 7.39 (d, J = 2.8 Hz, 1H), 7.37 (s, 1H), 4.27 (q, J = 7.2 Hz, 2H), 3.83 (s, 3H), 2.54 (m, 2H), 2.46 (m, 2H), 2.10 (m, 2H), 1.31 (t, J = 7.2 Hz, 3H). Ultimas fracciones: 69 mg (74%) de 2-metil-4,5,6,7-tetrahidro-2*H*-1,2,7-triaza-ciclopenta[e]azuleno-9-ácido carboxílico etil éster; espectro de masa de electrovaporizador: *m/z* 260 [M+1]; ^1H NMR ($CDCl_3$, 300 MHz) δ 8.42 (br s, 1H), 7.20 (d, J = 3.0 Hz, 1H), 7.05 (s, 1H),

4.29 (q, J = 7.2 Hz, 2H), 3.82 (s, 3H), 2.82 (m, 2H), 2.67 (m, 2H), 1.96 (m, 2H), 1.32 (t, J = 7.2 Hz, 3H).

Ejemplo 9

2-Metil- 4,5,6,7- tetrahidro-2*H*- 1,2,7-triaza -ciclopenta [e]azuleno -9-ácido carboxílico (2-fluoro-fenil)-amida

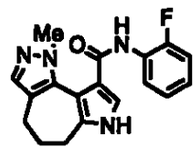


A una solución de 2-fluoroanilina (103 mg, 0.926 mmol) en CH_2Cl_2 (2.0 mL) a 0 °C bajo N_2 se le agregó lentamente $AlMe_3$ (0.46 mL, 2.0 *M* en tolueno). La solución resultante se agitó a temperatura ambiente durante 1 hora. Luego se agregó una porción de 2-metil- 4,5,6,7- tetrahidro-2*H*-1,2,7-triaza-ciclopenta[e]azuleno-9-ácido carboxílico etil éster (60 mg, 0.231 mmol). La mezcla resultante se agitó luego por reflujo durante 2 horas. Después de enfriarse, la mezcla de la reacción se diluyó cuidadosamente con NH_4Cl acuoso saturado (~5 mL) y algo de H_2O. La mezcla se agitó fuertemente durante 30 minutos y luego se extrajo tres veces con CH_2Cl_2 (conteniendo algo (~5%) MeOH). Los extractos combinados se secaron sobre K_2CO_3 y se concentraron. El material crudo se purificó mediante cromatografía rápida sobre silica gel. La elución con 40:1 $CHCl_3$-MeOH seguida por 30:1 $CHCl_3$-MeOH y finalmente 20:1 $CHCl_3$-MeOH produjo, después de la concentración de las fracciones que contenían el producto puro, un residuo, el cual luego se granuló con Et_2O. La suspensión se filtró, y el sólido se lavó con Et_2O y se secó, produciendo 45 mg (60%) de 2-metil-4,5,6,7-tetrahidro- 2*H*-1,2,7-triaza-

ciclopenta[e]azuleno-9-ácido carboxílico (2-fluoro-fenil)-amida en la forma de un sólido blancuzco. Espectro de masa del electrovaporizador: *m/z* 325 [M+1].

Ejemplo 10

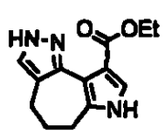
1-metil- 4,5,6,7-tetrahidro -2*H*- 1,2,7-triaza -ciclopenta [e]azuleno -9-ácido carboxílico (2-fluoro-fenil)-amida



El compuesto del título se preparó de acuerdo al Ejemplo 9 usando 2-fluoroanilina y 1-metil-4,5,6,7-tetrahidro-1*H*-1,2,7-triaza-ciclopenta[e]azuleno-9-ácido carboxílico etil éster. Espectro de masa del electrovaporizador: *m/z* 325 [M+1].

Ejemplo 11

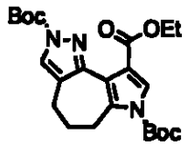
4,5,6,7- tetrahidro-2*H*- 1,2,7-triaza-ciclopenta [e]azuleno-9-ácido carboxílico etil éster



El compuesto del título se preparó en forma analógica al Ejemplo 8 usando 5-dimetilaminometileno-4-oxo-1,4,5,6,7,8-hexahidro-ciclohepta[*b*]pirrol-3-ácido carboxílico etil éster y acetato de hidrazina. La mezcla del producto crudo se llevó a cabo en el próximo paso sin purificación. Espectro de masa del electrovaporizador: *m/z* 246 [M+1]; ^{1}H NMR (DMSO-d_6, 300 MHz) δ >13.0 (br s, 1H), 11.65 (br s, 1H), 7.49 (s, 1H), 7.20 (s, 1H), 4.25 (q, J = 7.2 Hz, 2H), 2.91 (m, 2H), 2.76 (m, 2H), 1.84 (m, 2H), 1.28 (t, J = 7.2 Hz, 3H).

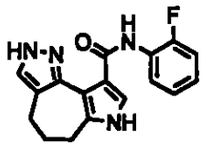
Ejemplo 12

Preparación de 4,5,6,7-tetrahidro-2*H*-1,2,7-triaza-ciclopenta[e]azuleno-9-ácido carboxílico (2-fluoro-fenil)-amida



Paso 1:

5,6-dihidro-4*H*-1,2,7-triaza-ciclopenta[e] azuleno-2,7,9-ácido tricarboxílico 2,7-di-ter-butil éster 9-etil éster se preparó a través del procedimiento descrito en el Ejemplo 8, usando 4,5,6,7-tetrahidro-2*H*- 1,2,7-triaza-ciclopenta[e] azuleno-9-ácido carboxílico etil éster, 2.3 equivalente a Boc_2O, y 2.5 eq de Et_3N. Espectro de masa del electrovaporizador: *m/z* 446 [M+1]; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.77 (s, 1H), 7.62 (s, 1H), 4.35 (q, J = 7.2 Hz, 2H), 3.26 (m, 2H), 2.68 (m, 2H), 1.99 (m, 2H), 1.61 (s, 9H), 1.59 (s, 9H), 1.33 (t, J = 7.2 Hz, 3H).



Paso 2:

A una solución de 2-fluoroanilina (202 mg, 1.82 mmol) en CH_2Cl_2 (4.0 mL) a 0°C bajo N_2 se le agregó lentamente $AlMe_3$ (0.91 mL, 2.0 *M* en tolueno). La solución resultante se agitó a temperatura ambiente durante 1 hora. Luego, se agregó una porción de 5,6-dihidro-4*H*-1,2,7-triaza-ciclopenta[e]azuleno-2,7,9-ácido tricarboxílico 2,7-di-ter-butil éster 9-etil éster

(162 mg, 0.364 mmol). La mezcla resultante se agitó luego por reflujo durante 2 horas. Después de enfriarse, la mezcla de la reacción se diluyó cuidadosamente con NH_4Cl acuoso saturado (~5 mL) y algo de H_2O. La mezcla se agitó fuertemente durante 30 minutos y luego se extrajo tres veces con CH_2Cl_2 (conteniendo algo de (~5%) MeOH). Los extractos combinados se secaron sobre K_2CO_3 y se concentraron. El material crudo se purificó mediante cromatografía rápida sobre silica gel, produciendo 102 mg (68%) de un producto de amida conteniendo solamente un grupo Boc. ^1H NMR ($CDCl_3$, 300 MHz) δ 8.52 (td, J = 8.1, 1.4 Hz, 1H), 8.06 (s, 1H), 7.36 (s, 1H), 7.18-7.03 (m, 3H), 3.37 (m, 2H), 2.79 (m, 2H), 2.03 (m, 2H), 1.62 (s, 9H). Luego este producto se disolvió en 4 mL de EtOH y 1 mL de HCl acuoso concentrado. La solución se agitó a temperatura ambiente durante toda la noche y a 90°C durante 3 horas. La mezcla de la reacción luego se concentró bajo un flujo de N_2 para producir un solido, el cual luego se suspendió en H_2O y se filtró. El sólido se lavó minuciosamente con H_2O y Et_2O para producir, después de secarse, 34 mg (44%) de 4,5,6,7-tetrahidro-2*H*- 1,2,7-triaza-ciclopenta [e]azuleno-9-ácido carboxílico (2-fluoro-fenil)-amida en la foma de un sólido amarillo claro/blancuzco. Espectro de masa del electrovaporizador: *m/z* 311 [M+1].

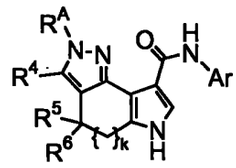
Ejemplo 12a

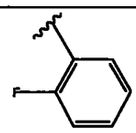
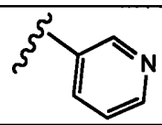
Compuestos adicionales de 1,2,7-triaza-ciclopenta[e]azuleno-9-ácido carboxílico [1,3,4]thiadiazol-2-ilamida

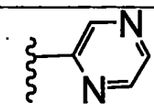
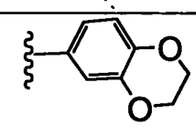
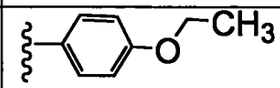
Usando el método mostrado en el Esquema 6 y otros métodos ilustrados en los Ejemplos 8-12 se prepararon los compuestos mostrados en la Tabla 4.

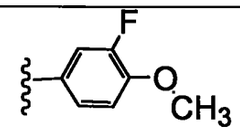
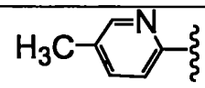
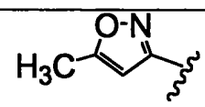
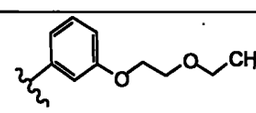
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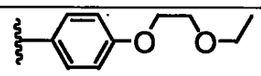
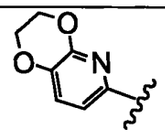
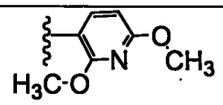
TABLA 4

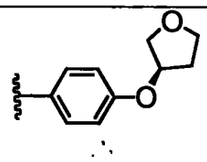
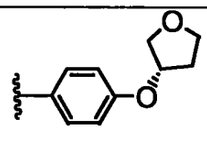
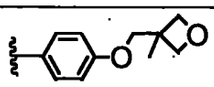


Com #	Nombre	R^A	R^4	R^5	R^6	k	Ar	Datos del Espectro
1	2-metil-4,5,6,7-tetrahidro-2H-1,2,7-triaza-ciclopenta[e]azuleno-9-ácido carboxílico (2-fluoro-fenil)-amida	CH_3	H	H	H	2		MS *m/z* [M+1] 325
2	2-metil-4,5,6,7-tetrahidro-2H-1,2,7-triaza-ciclopenta[e]azuleno-9-	CH_3	H	H	H	2		MS *m/z* [M+1] 308

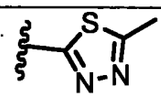
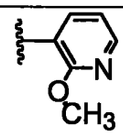
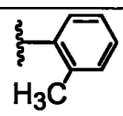
	ácido carboxílico piridina-3-ilamida							
3	2-metil-4,5,6,7-tetrahidro-2H-1,2,7-triaza-ciclopenta[e]azuleno-9-ácido carboxílico pirazin-2-ilamida	CH_3	H	H	H	2		MS *m/z* [M+1] 309
4	2-metil-4,5,6,7-tetrahidro-2H-1,2,7-triazà-ciclopenta[e]azuleno-9-ácido carboxílico (2,3-dihidro-benzo[1,4]dioxin-6-il)-amida	CH_3	H	H	H	2		MS *m/z* [M+1] 365
5	2-metil-4,5,6,7-tetrahidro-2H-1,2,7-triaza-ciclopenta[e]azuleno-9-ácido carboxílico (4-etoxi-fenil)-amida	CH_3	H	H	H	2		MS *m/z* [M-1] 349

6	2-Metil-4,5,6,7-tetrahidro-2H-1,2,7-triaza-ciclopenta[e]azuleno-9-ácido carboxílico (3-fluoro-4-metoxi-fenil)-amida	CH_3	H	H	H	2		MS *m/z* [M-1] 353
7	2-Metil-4,5,6,7-tetrahidro-2H-1,2,7-triaza-ciclopenta[e]azuleno-9-ácido carboxílico (5-metil-piridina-2-il)-amida	CH_3	H	H	H	2		MS *m/z* [M-1] 320
8	2-Metil-4,5,6,7-tetrahidro-2H-1,2,7-triaza-ciclopenta[e]azuleno-9-ácido carboxílico (5-metil-isoxazol-3-il)-amida	CH_3	H	H	H	2		MS *m/z* [M-1] 310
9	2-Metil-4,5,6,7-tetrahidro-2H-1,2,7-triaza-ciclopenta[e]azuleno-9-ácido carboxílico	CH_3	H	H	H	2		MS *m/z* [M+1] 395

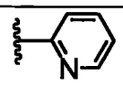
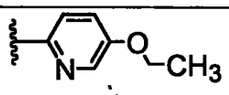
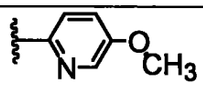
	[3-(2-etoxi-etoxi)-fenil]-amida							
10	2-Metil-4,5,6,7-tetrahidro-2H-1,2,7-triaza-ciclopenta[e]azuleno-9-ácido carboxílico [4-(2-etoxi-etoxi)-fenil]-amida	CH_3	H	H	H	2		MS *m/z* [M+1] 395
11	2-Metil-4,5,6,7-tetrahidro-2H-1,2,7-triaza-ciclopenta[e]azuleno-9-ácido carboxílico (2,3-dihidro-[1,4]dioxino[2,3-b]piridina-6-il)-amida	CH_3	H	H	H	2		MS *m/z* [M+1] 366
12	2-Metil-4,5,6,7-tetrahidro-2H-1,2,7-triaza-ciclopenta[e]azuleno-9-ácido carboxílico (2,6-dimetoxi-piridina-3-il)-	CH_3	H	H	H	2		MS *m/z* [M+1] 368

	amida							
13	(R)-2-Metil-4,5,6,7-tetrahidro-2H-1,2,7-triaza-ciclopenta[e]azuleno-9-ácido carboxílico [4-(tetrahidro-furan-3-iloxi)-fenil]-amida	CH_3	H	H	H	2		MS *m/z* [M+1] 393
14	(S)-2-Metil-4,5,6,7-tetrahidro-2H-1,2,7-triaza-ciclopenta[e]azuleno-9-ácido carboxílico [4-(tetrahidro-furan-3-iloxi)-fenil]-amida	CH_3	H	H	H	2		MS *m/z* [M+1] 393
15	2-Metil-4,5,6,7-tetrahidro-2H-1,2,7-triaza-ciclopenta[e]azuleno-9-ácido carboxílico [4-(3-metil-oxetan-	CH_3	H	H	H	2		MS *m/z* [M+1] 409

902

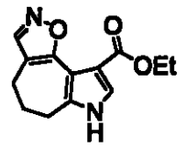
	3-ilmetoxi)-fenil]-amida							
16	2-Metil-4,5,6,7-tetrahidro-2H-1,2,7-triaza-ciclopenta[e]azuleno-9-ácido carboxílico [1,3,4]tiadiazol-2-ilamida	CH_3	H	H	H	2		MS *m/z* [M+1] 329
17	2-Metil-4,5,6,7-tetrahidro-2H-1,2,7-triaza-ciclopenta[e]azuleno-9-ácido carboxílico (2-metoxi-piridina-3-il)-amida	CH_3	H	H	H	2		MS *m/z* [M+1] 338
18	2-Metil-4,5,6,7-tetrahidro-2H-1,2,7-triaza-ciclopenta[e]azuleno-9-ácido carboxílico o-tolilamida	CH_3	H	H	H	2		MS *m/z* [M+1] 321

903

19	2-Metil-4,5,6,7-tetrahidro-2H-1,2,7-triaza-ciclopenta[e]azu-leno-9-ácido carboxílico piridina-2-ilamida	CH_3	H	H	H	2		MS *m/z* [M+1] 308
20	2-Metil-4,5,6,7-tetrahidro-2H-1,2,7-triaza-ciclopenta[e]azul eno-9-ácido carboxílico (5-etoxi-piridina-2-il)-amida	CH_3	H	H	H	2		MS *m/z* [M+1] 352
21	2-Metil-4,5,6,7-tetrahidro-2H-1,2,7-triaza-ciclopenta[e]azu-leno-9-ácido carboxílico (5-metoxi-piridina-2-il)-amida	CH_3	H	H	H	2		MS *m/z* [M+1] 338

Ejemplo 13

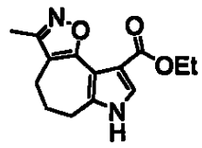
4,5,6,7-tetrahidro-1-oxa-2,7-diaza-ciclopenta[e]azuleno-9-ácido carboxílico etil éster



En un tubo con cierre hermético 4-oxo-5,6,7,8-tetrahidro-4H-ciclohepta[b]pirrol-1,3-ácido dicarboxílico 1-ter-butil éster 3-etil éster (2.6 mmol) y tris(dimetilamino)metano (5.2 mmol) se combinaron y calentaron a 60°C durante 3 horas. Después de enfriarse a temperatura ambiente el material volátil se retiró al vacío. Se añadió al residuo clorhidrato de hidroxilamina (7.8 mmol) y 7 ml EtOH. La mezcla se calentó a 100°C durante 16 horas. El solvente se evaporó al vacío y el residuo se recogió en CH_2Cl_2 y se lavó dos veces con $NaHCO_3$ (acuoso). La capa orgánica se secó sobre Na_2SO_4 y se evaporó al vacío y el residuo se cromatografió usando MeOH al 10% en CH_2Cl_2 en la forma de una fase móvil para producir 4,5,6,7-tetrahidro -1-oxa-2,7-diaza-ciclopenta [e]azuleno-9-ácido carboxílico etil éster en la foma de un sólido blanco (76%). ^1H NMR ($CDCl_3$) 1.19 (t, 3H), 1.95-2.07 (m, 2H), 2.78 (t, 2H), 2.95 (t, 2H), 4.38 (q, 2H), 7.26 (s, 1H), 8.03 (s, 1H), 8.77 (s, 1H).

Ejemplo 14

3-Metil-4,5,6,7-tetrahidro-1-oxa-2,7-diaza-ciclopenta[e]azuleno -9-ácido carboxílico etil éster



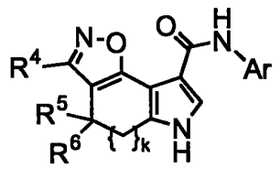
En un tubo con cierre hermético se concentraron 5-acetil-4-oxo-5,6,7,8- tetrahidro-4H-ciclohepta [b]pirrol -1,3-ácido dicarboxílico 1-ter-butil éster 3-etil éster (1.1 mmol) y clorhidrato de hidroxilamina (2.2 mmol) y 10 ml EtOH. La mezcla se calentó a 100°C durante 16 horas. El solvente se evaporó al vacío y el residuo se recogió en CH_2Cl_2 y se lavó dos veces con $NaHCO_3$ (aq). La capa orgánica se secó sobre Na_2SO_4 y se evaporó al vacío y el residuo se sometió a cromatografía usando MeOH al 10% en CH_2Cl_2 en forma de fase móvil para producir 3-metil-4,5,6,7-tetrahidro-1-oxa-2,7-diaza-ciclopenta[e]azuleno-9-ácido carboxílico etil éster en la forma de un sólido blanco (76%). ^1H NMR ($CDCl_3$ + CD_3OD) 1.3 (t, 3H), 1.90-1.98 (m, 2H), 2.10 (s, 3H), 2.35 (t, 2H), 2.75-2.82 (m, 2H), 4.21 (q, 2H), 7.15 (s, 1H).

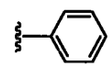
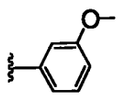
Ejemplo 14a

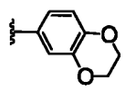
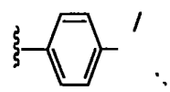
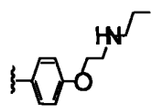
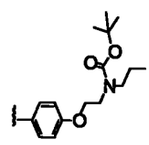
Compuestos adicionales de 1-oxa-2,7-diaza-ciclopenta[e]azuleno -9-ácido carboxílico

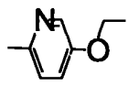
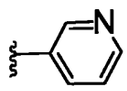
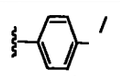
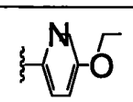
Usando el método mostrado en el Esquema 7 y otros métodos ilustrados en los Ejemplos 13-14 se prepararon los compuestos que se muestran en la Tabla 5.

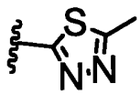
TABLA 5



Com#	Nombre	R4	R5	R6	k	Ar	Datos del Espectro
1	4,5,6,7-tetrahidro-1-oxa-2,7-diaza-ciclopenta[e]azuleno-9-ácido carboxílico fenil-amida	H	H	H	2		LRMS calculado 293.32 se encontró (M+1) 294
2	4,5,6,7-tetrahidro-1-oxa-2,7-diaza-ciclopenta[e]azuleno-9-ácido carboxílico (3-metoxi-fenil)-amida	H	H	H	2		LRMS calculado 323.3 se encontró (M+1) 324

3	4,5,6,7-tetrahidro-1-oxa-2,7-diaza-ciclopenta[e]azuleno-9-ácido carboxílico (2,3-dihidro-benzo[1,4]dioxin-6-il)-amida	H	H	H	2		LRMS calculado 351.3 se encontró (M+1) 352.3
4	4,5,6,7-tetrahidro-1-oxa-2,7-diaza-ciclopenta[e]azuleno-9-ácido carboxílico (4-metoxi-fenil)-amida	H	H	H	2		LRMS calculado 323.3 se encontró (M-1) 322
5	4,5,6,7-tetrahidro-1-oxa-2,7-diaza-ciclopenta[e]azuleno-9-ácido carboxílico [4-(2-propilamino-etoxi)-fenil]-amida	H	H	H	2		LRMS calculado 394.4 se encontró (M+1) 395
6	Propil-(2-{4-[(4,5,6,7-tetrahidro-1-oxa-2,7-diaza-ciclopenta[e]-azul-ene-9-carbonil)-amino]-fenoxi}-etil)-ácido carbámico ter-butil éster	H	H	H	2		LRMS calculado 494.59 se encontró (M-1) 493.3

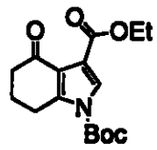
7	4,5,6,7-tetrahidro-1-oxa-2,7-diaza-ciclopenta[e]azuleno-9-ácido carboxílico (5-etoxi-piridina-2-il)amida	H	H	H	2		LRMS calculado 338.36 se encontró (M+1) 339
8	4,5,6,7-tetrahidro-1-oxa-2,7-diaza-ciclopenta[e]azuleno-9-ácido carboxílico piridina-3-ilamida	H	H	H	2		LRMS calculado 294.3 se encontró (M+1) 295.3
9	3-Metil-4,5,6,7-tetrahidro-1-oxa-2,7-diaza-ciclopenta[e]azuleno-9-ácido carboxílico (4-metoxi-fenil)-amida	CH_3	H	H	2		LRMS calculado 337.4 se encontró (M+1) 338
10	3-Metil-4,5,6,7-tetrahidro-1-oxa-2,7-diaza-ciclopenta[e]azuleno-9-ácido carboxílico (5-etoxi-piridina-2-il)-amida	CH_3	H	H	2		LRMS calculado 352.4 se encontró (M+1) 353

11	3-Metil-4,5,6,7-tetrahidro-1-oxa-2,7-diaza-ciclopenta[e]azuleno-9-ácido carboxílico 2-(5-metil-[1,3,4]thiadiazol-2-il)-amida	CH_3	H	H	2		LRMS calculado 329.4 se encontró (M+1) 330

911

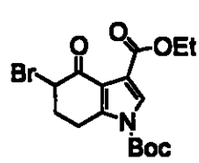
Ejemplo 15

2-metil-5,6-dihidro-4H-tiazol[4,5-e]indol-8-ácido carboxílico etil éster



Paso 1:

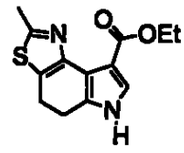
A una mezcla de 4-oxo-4,5,6,7-tetrahidro-1H-indol-3-ácido carboxílico etil éster (2.4 mmol) en 10 ml 1,4-dioxano se le agregó di-t-butil dicarbonato (2.9 mmol), seguido por una solución de K_2CO_3 (2.9 mmol) en 5 ml H_2O. Después de agitar a temperatura ambiente durante 16 horas se añadió a la mezcla 50 ml acetato de etilo y 50 ml H_2O. La capa orgánica se separó y la capa acuosa se extrajo varias veces con EtOAc. Las capas orgánicas se combinaron, se secaron sobre Na_2SO_4 y se evaporó al vacío produciendo 4-oxo-4,5,6,7-tetrahidro-indol-1,3-ácido dicarboxílico 1-ter-butil éster 3-etil éster, 700mg, en forma de un aceite amarillo oscuro/marrón (95%). ^1H NMR ($CDCl_3$) 1.38 (t, 3H), 1.62 (s, 9H), 2.11-2.19 (m, 2H), 2.50-2.58 (m, 2H), 3.17 (t, 2H), 4.37 (q, 2H), 7.70 (s, 1H).



Paso 2:

A la solución de 4-oxo-4,5,6,7-tetrahidro-indol-1,3-ácido dicarboxílico 1-ter-butil éster 3-etil éster (33 mmol) en 140 ml THF se agregó por goteo una solución de bromuro de

feniltrimetilamonio (33 mmol) en 56 ml THF. Luego de agitar a temperatura ambiente durante un período adicional de hora y media la mezcla se vertió sobre una solución de 200 ml 5% $NaHCO_3$, y luego se extrajo varias veces con EtOAc. Las capas orgánicas se combinaron, se secaron sobre Na_2SO_4 y se evaporaron al vacío. El aceite marrón oscuro se sometió a cromatografía usando acetato de etilo 1:hexanos 10 en forma de una fase móvil para producir 5-bromo-4-oxo-4,5,6,7-tetrahidro-indol-1,3-ácido dicarboxílico 1-ter-butil éster 3-etil éster, 5 g, en forma de un sólido blanco (40%). ^1H NMR ($CDCl_3$)1.39 (t, 3H), 1.62 (s, 9H), 2.42-2.51 (m, 2H), 3.20-3.38 (m, 2H), 4.35 (q, 2H), 4.58 (t, 1H), 7.79 (s, 1H).

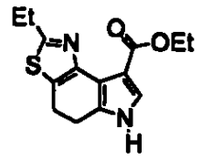


Paso 3:

A una solución de 5-bromo-4-oxo-4,5,6,7-tetrahidro-indol 1,3-ácido dicarboxílico 1-ter-butil éster 3-etil éster (0.78 mmol) en 10 ml CH_3OH se agregó tioacetamida (1.55 mmol). Luego de agitar bajo reflujo durante 16 horas el solvente se retiró al vacío. El aceite marrón se sometió a cromatografía usando EtOAC 1:hexano 1, seguido por 5% MeOH en CH_2Cl_2 en forma de fases móviles para producir 2-metil-5,6-dihidro-4H-tiazol[4,5-e]indol-8-ácido carboxílico etil éster en la forma de un sólido blanco (34%). ^1H NMR (DMSO-d_6) 1.27 (t, 3H), 2.60 (s, 3H), 2.78(t, 2H), 2.96 (t, 2H), 4.19 (q, 2H), 7.21 (s, 1H), 11.44 (s, 1H).

Ejemplo 16

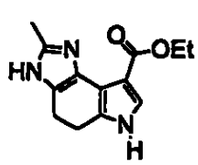
2-Etil-5,6-dihidro-4H-tiazol[4,5-e]indol-8-ácido carboxílico etil éster



El compuesto del título se preparó por reacción de 5-bromo-4-oxo-4,5,6,7-tetrahidro-indol 1,3-ácido dicarboxílico 1-ter-butil éster 3-etil éster con tiopropionamida esencialmente de acuerdo a los procedimientos descritos en el Ejemplo 15, Paso 3. ^{1}H NMR ($CDCl_3$) 1.33-1.42 (m, 6H), 2.80-2.90 (m, 2H), 2.98-3.10 (m, 4H), 2.37 (q, 2H), 7.24 (s, 1H), 8.60 (s, 1H).

Ejemplo 17

2-Metil- 3,4,5,6- tetrahidro- imidazo [4,5-e] indol -8- ácido carboxílico etil éster

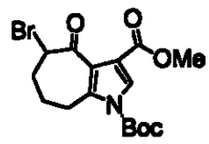


A una solución de 5-bromo-4-oxo-4,5,6,7-tetrahidro-indol 1,3-ácido dicarboxílico 1-ter-butil éster 3-etil éster (1.66 mmol) en 15 ml 1,4-dioxano se le agregó clorhidrato de acetamidina (3.32 mmol). Después de agitar bajo reflujo durante 16 horas el solvente se retiró al vacío. Al residuo se le añadió 14 ml $CHCl_3$ y 2 ml MeOH y la mezcla se agitó durante 10 minutos. El sólido se filtró. El líquido madre se concentró y se sometió a cromatografía usando 10% MeOH en CH_2Cl_2 en forma de una fase móvil para producir 2-metil-3,4,5,6-tetrahidro-imidazo[4,5-e]indol-8-ácido carboxílico etil éster en la foma de un sólido blanco (30 %). ^{1}H NMR (DMSO-d_6) 1.30 (t, 3H), 2.28 (s, 3H), 2.70

(t, 2H), 2.79 (t, 2H), 4.22 (q, 2H), 7.20 (s, 1H), 10.58 (s, 1H), 11.43 (s, 1H).

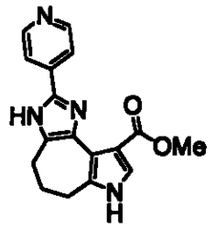
Ejemplo 18

2-Piridin- 4-il-4,5,6,7- tetrahidro-3*H*-1,3,7-triaza-ciclopenta-[e]azuleno-9-ácido carboxílico metil éster



Paso 1:

A una solución de 4-Oxo-5,6,7,8-tetrahidro-4*H*-ciclohepta[b]pirrol-1,3-ácido dicarboxílico 3-metil éster 1-ter-butil éster(1.1g, 3.6mmol) en DMSO(20ml) se agregó 1,3-dibromo-5,5-dimetilhidantoin(1.5g, 5.4mmol) en porciones con la ayuda de un baño frío y la mezcla de la reacción se agitó duante 18 horas a temperatura ambiente. Se agregó agua y la mezcla de la reacción se extrajo con éter. Las capas de éter combinado se lavaron con salmuera saturada, se secaron sobre Na_2SO_4, y se concentraron al vacío. El residuo se purificó mediante cromatografía rápida(10%EtOAc/Hex para 25% EtOAc/Hex) para producir 915mg de 5-Bromo-4-oxo-5,6,7,8-tetrahidro-4*H*-ciclohepta[b]pirrol-1,3-ácido dicarboxílico 1-ter-butil éster 3-metil éster en la forma de un aceite color amarillo brillante (66%). ^1H NMR($CDCl_3$) 1.59 (s, 9H), 1.72-1.84 (m, 1H), 2.12-2.25 (m, 2H), 2.43-2.58 (m, 1H), 3.05-3.14 (m, 1H), 3.40-3.49 (m, 1H), 3.80 (s, 3H), 4.75 (m, 1H), 7.79 (s, 1H)

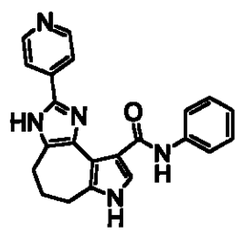


Paso 2:

Una mezcla de 5-Bromo-4-oxo-5,6,7,8-tetrahidro-4*H*-ciclohepta[b]pirrol-1,3-ácido dicarboxílico 1-*ter*-butil éster 3-metil éster(467mg, 1.2mmol), 4-amidinopiridina clorhidrato (953mg, 6.1mmol), y $NaHCO_3$(813mg, 9.7mmol) en dioxano(20ml) se sometió a reflujo durante 20 horas. Después de que se enfrió a temperatura ambiente, se agregó MeOH(5ml) y la mezcla se filtró. El filtrado se concentró al vacío y el residuo marrón se purificó mediante cromatografía rápida (10% MeOH/ CH_2Cl_2) para producir 197 mg de 2-Piridina-4-il-4,5,6,7-tetrahidro-3*H*-1,3,7-triaza-ciclopenta[e]azuleno-9-ácido carboxílico metil éster en la forma de un sólido amarillo (53%). ^{1}H NMR ($CDCl_3$) 2.06 (quint, 2H), 2.98 (t, 2H), 3.04 (t, 2H), 3.91 (s, 1H), 7.46 (s, 1H), 7.76 (d, 2H), 8.28 (br s, 1H)8.56 (d, 2H)

Ejemplo 19

2-Piridin-4-il-4,5,6,7- tetrahidro-3*H*-1,3,7-triaza- ciclopenta [e]-azuleno-9-ácido carboxílico fenil amida

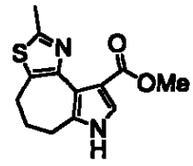


A una solución de Anilina(155 L, 1.7mmol) en CH_2Cl_2(5ml) a temperatura ambiente se añadió Trimetilaluminio (0.85ml de una

solución 2M en tolueno, 1.7mmol) y la mezcla se agitó durante 30 minutos. A esta mezcla se le añadió una solución de 2-Piridina-4-il- 4,5,6,7-tetrahidro -*3H*-1,3,7-triaza-ciclopenta [e]azuleno-9-ácido carboxílico metil éster(51mg, 0.17mmol) en CH_2Cl_2(2ml) y la mezcla se sometió a reflujo durante 18 horas y se diluyó con CH_2Cl_2. Se agregó MeOH(5ml) lentamente agitando fuertemente. La mezcla se filtró a través de Celita, se concentró al vacío, y se purificó mediante cromatografía rápida para producir 20mg de 2-Piridina-4-il-4,5,6,7-tetrahido-3*H*-1,3,7-triaza-ciclopenta[e]azuleno-9-ácido carboxílico fenil amida en la forma de un sólido amarillo (32%). El LRMS calculado 369.43 se encontró (M+H) 370.07

Ejemplo 20

2-Metil-4,5,6,7-tetrahidro-3-tia-1,7-diaza-ciclopenta[e]azuleno-9-ácido carboxílico metil éster



Una mezcla de 5-Bromo-4-oxo-5,6,7,8-tetrahidro-4-*H*-ciclohepta[b]pirrol-1,3-ácido dicarboxílico 1-ter-butil éster 3-metil éster(880mg, 2.27mmol) y tioacetamida (426mg, 4.54mmol) en MeOH(20ml) se sometió a reflujo durante 20 horas y se concentró al vacío. El residuo se purificó mediante cromatografía rápida (50% EtOAc/Hex para MeOH/CH_2Cl_2 al 10%) para producir 382mg de 2-Metil-4,5,6,7-tetrahidro-3-tia-1,7-diaza-ciclopenta[e]azuleno-9-ácido carboxílico metil éster en la forma de una espuma amarilla (64%).

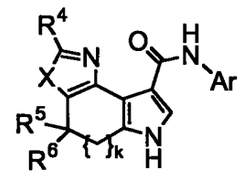
^{1}H NMR (CD_3OD) 2.18 (quint, 2H), 2.61 (s, 3H), 2.70 (t, 2H), 2.78 (t, 2H), 3.73 (s, 3H), 7.29 (s, 1H)

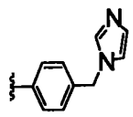
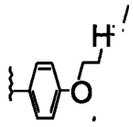
Ejemplo 21

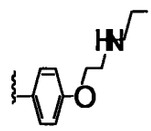
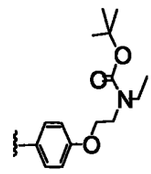
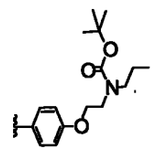
Compuestos adicionales de ácido 3-tia-1,7-diaza-ciclopenta [e]azulen-9-carboxílico y fenil amida de ácido 1,3,7-triaza-ciclopenta [e]azulen-9-carboxílico

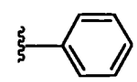
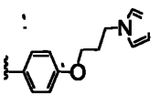
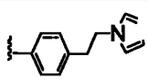
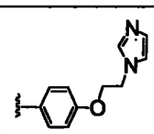
Usando el método mostrado en el Esquema 8 otros métodos ilustrados en los Ejemplos 15-20 se prepararon los compuestos mostrados en la Tabla 6.

TABLA 6

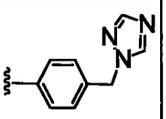
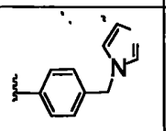
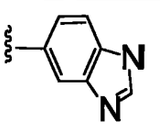


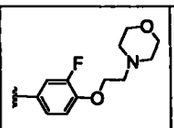
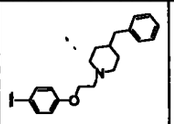
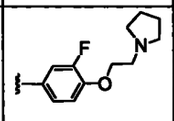
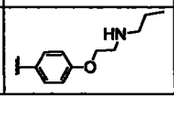
Com#	Nombre	X	R4	R5	R6	k	Ar	Datos del Espectro
1	2-Metil-4,5,6,7-tetrahidro-3-tia-1,7-diaza-ciclopenta[e]azuleno-9-ácido carboxílico (4-imidazol-1-ilmetil-fenil)-amida	S	CH_3	H	H	2		LRMS calculado 403.5 se encontró (M+1) 404.1
2	2-Metil-4,5,6,7-tetrahidro-3-tia-1,7-diaza-ciclopenta[e]azuleno-9-ácido carboxílico [4-(2-etilamino-	S	CH_3	H	H	2		LRMS calculado 410.54 se encontró (M+1) 411.3

	etoxi)-fenil]-amida							
3	2-Metil-4,5,6,7-tetrahidro-3-tia-1,7-diaza-ciclopenta[e]azuleno-9-ácido carboxílico [4-(2-propilamino-etoxi)-fenil]-amida	S	CH_3	H	H	2		LRMS calculado 424.57 se encontró (M-1) 423.2
4	Etil-(2-{4-[(2-metil-4,5,6,7-tetrahidro-3-tia-1,7-diaza-ciclopenta[e]azuleno-9-carbonil)-amino]fenoxi}-etil)-ácido carbámico terbutil éster	S	CH_3	H	H	2		LRMS calculado 510.66 se encontró (M-1) 509.4
5	(2-{4-[(2-Metil-4,5,6,7-tetrahidro-3-tia-1,7-diaza-ciclopenta[e]azuleno-9-carbonil)-amino]-fenoxi}-etil)-propil-ácido carbámico	S	CH_3	H	H	2		LRMS calculado 524.68 se encontró (M-1) 523.2

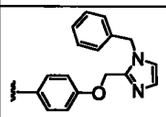
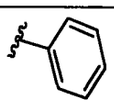
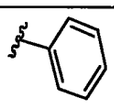
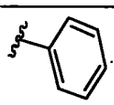
	ter-butil éster							
6	2-Metil-5,6-dihidro-4H-tiazol[4,5-e]indol-8-ácido carboxílico fenilamida	S	CH_3	H	H	1		LRMS calculado 309.39 se encontró (M+1) 310.88
7	2-Metil-5,6-dihidro-4H-tiazol[4,5-e]indol-8-ácido carboxílico [4-(3-imidazol-1-il-propoxi)-fenil]-amida	S	CH_3	H	H	1		LRMS calculado 433.53 se encontró (M+1) 434.03
8	2-Metil-5,6-dihidro-4H-tiazol[4,5-e]indol-8-ácido carboxílico [4-(2-imidazol-1-il-etil)-fenil]-amida	S	CH_3	H	H	1		LRMS calculado 403.51 se encontró (M+1) 404.0
9	2-Metil-5,6-dihidro-4H-tiazol[4,5-e]indol-8-ácido carboxílico [4-(2-imidazol-1-il-	S	CH_3	H	H	1		LRMS calculado 419.51 se encontró (M+1) 420.0

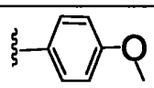
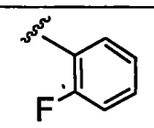
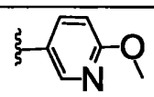
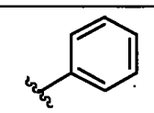
920

	etoxi)-fenil]-amida							
10	2-Metil-5,6-dihidro-4H-tiazol[4,5-e]indol-8-ácido carboxílico (4-[1,2,4]triazol-1-ilmetil-fenil)-amida	S	CH_3	H	H	1		LRMS calculado 390.47 se encontró (M+1) 391.1
11	2-Metil-5,6-dihidro-4H-tiazol[4,5-e]indol-8-ácido carboxílico (4-imidazol-1-ilmetil-fenil)-amida	S	CH_3	H	H	1		LRMS calculado 389.48 se encontró (M+1) 390.1
12	2-Metil-5,6-dihidro-4H-tiazol[4,5-e]indol-8-ácido carboxílico (1H-benzoimidazol-5-il)-amida	S	CH_3	H	H	1		LRMS 349.42 se encontró (M+1) 350.2

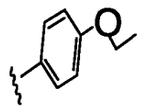
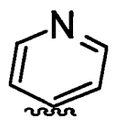
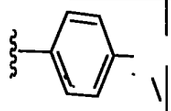
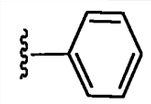
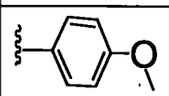
13	2-Metil-5,6-dihidro-4H-tiazol[4,5-e]indol-8-ácido carboxílico [3-fluoro-4-(2-morfolin-4-il-etoxi)-fenil]-amida	S	CH_3	H	H	1		LRMS calculado 456.54 se encontró 456.85
14	2-Metil-5,6-dihidro-4H-tiazol[4,5-e]indol-8-ácido carboxílico {4-[2-(4-benzil-piperidin-1-il)-etoxi]-fenil}-amida	S	CH_3	H	H	1		LRMS calculado 526.70 se encontró 527.1
15	2-Metil-5,6-dihidro-4H-tiazol[4,5-e]indol-8-ácido carboxílico [3-fluoro-4-(2-pirrolidin-1-il-etoxi)-fenil]-amida	S	CH_3	H	H	1		LRMS calculado 440.54 se encontró 440.9
16	2-Metil-5,6-dihidro-4H-tiazol[4,5-e]indol-8-ácido	S	CH_3	H	H	1		LRMS calculado 410.54 se encontró (M+1) 411.0

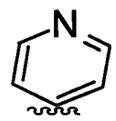
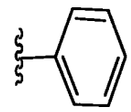
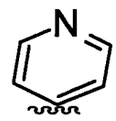
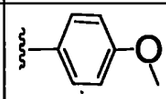
922

	carboxílico [4-(2-propilamino-etoxi)-fenil]-amida							
17	2-Metil-5,6-dihidro-4H-tiazol[4,5-e]indol-8-ácido carboxílico [4-(1-benzil-1H-imidazol-2-ilmetoxi)-fenil]-amida	S	CH_3	H	H	1		LRMS calculado 496.59 se encontró 497.03
18	2-Etil-5,6-dihidro-4H-tiazol[4,5-e]indol-8-ácido carboxílico fenilamida	S	Et	H	H	1		LRMS calculado 323.42 se encontró 323.93
19	2-Metil-3,4,5,6-tetrahidro-imidazo[4,5-e]indol-8-ácido carboxílico fenilamida	NH	CH_3	H	H	1		LRMS calculado 292.34 se encontró (M-1) 291.0
20	2-Metil-4,5,6,7-tetrahidro-3*H*-1,3,7-triaza-ciclopenta[e]azu-leno-9-ácido carboxílico fenilamida	NH	CH_3	H	H	2		LRMS calculado 306.37 se encontró (M+H)307.30

21	2-Metil-4,5,6,7-tetrahidro-3*H*-1,3,7-triaza-ciclopenta[e]azu-leno-9-ácido carboxílico(4-metoxi-fenil)amida	NH	CH_3	H	H	2		LRMS calculado 336.39 se encontró (M+H)337.07
22	2-Metil-4,5,6,7-tetrahidro-3*H*-1,3,7-triaza-ciclopenta[e]azul eno-9-ácido carboxílico (2-fluoro-fenil)-amida	NH	CH_3	H	H	2		LRMS calculad 324.35 se encontró (M+H)325.40
23	2-Metil-4,5,6,7-tetrahidro-3*H*-1,3,7-triaza-ciclopenta[e]azul eno-9-ácido carboxílico (6-metoxi-piridina-3-il)-amida	NH	CH_3	H	H	2		LRMS calculado 337.38 se encontró (M+H)338.07
24	2-ciclopropil-4,5,6,7-tetrahidro-3*H*-1,3,7-triaza-ciclopenta[e] azuleno-9-ácido carboxílico fenilamida	NH		H	H	2		LRMS calculado 332.41 se encontró (M+H)333.06

924

25	2-Metil-4,5,6,7-tetrahidro-3*H*-1,3,7-triaza-ciclopenta[e]azu-leno-9-ácido carboxílico (4-etoxi-fenil)-amida	NH	CH_3	H	H	2		LRMS calculado 350.41 se encontró (M+H) 351.08
26	2-piridina-4-il-4,5,6,7-tetrahidro-3*H*-1,3,7-triaza-ciclopenta[e] azuleno-9-ácido carboxílico (4-metoxi-fenil)-amida	NH		H	H	2		LRMS calculado 399.39 se encontró (M+H) 400.09
27	2-Metil-4,5,6,7-tetrahidro-3-tia-1,7-diaza-ciclopenta[e]azu-leno-9-ácido carboxílico fenilamida	S	CH_3	H	H	2		LRMS calculado 323.42 se encontró (M+H) 324.30
28	2-Metil-4,5,6,7-tetrahidro-3-tia-1,7-diaza-ciclopenta[e]azu-leno-9-ácido carboxílico (4-metoxi-fenil)-amida	S	CH_3	H	H	2		LRMS calculado 353.44, se encontró (M+H) 354.02

29	2-Piridina-4-il-4,5,6,7-tetrahidro-3-tia-1,7-diaza-ciclopenta[e] azuleno-9-ácido carboxílico fenilamida	S		H	H	2		LRMS calculado 386.48 se encontró (M+H) 387.03
30	2-Piridina-4-il-4,5,6,7-tetrahidro-3-tia-1,7-diaza-ciclopenta[e] azuleno-9-ácido carboxílico (4-metoxi-fenil)-amida	S		H	H	2		LRMS calculado 416.50 se encontró (M+H) 417.03

926

Ejemplo 22

Preparación de compuestos de prueba radioetiquetados de la invención

Los compuestos de la invención se preparan como pruebas radioetiquetadas realizando sus síntesis usando precursores que comprenden al menos un átomo que es un radioisótopo. El radioisótopo se selecciona preferentemente de al menos un carbono (preferentemente ^{14}C), hidrógeno (preferentemente ^{3}H), azufre (preferentemente ^{35}S), o yodo (preferentemente ^{125}I). Dichas pruebas radioetiquetadas se sintetizan convenientemente por un proveedor de radioisótopo especializado en síntesis acostumbradas de compuestos de prueba radioetiquetados. Dichos proveedores son Amersham Corporation, Arlington Heights, IL; Cambridge Isotope Laboratories, Inc. Yover, MA; SRI International, Menlo Park, CA; Wizard Laboratories, West Sacramento, CA; ChemSyn Laboratories, Lexena, KS; American Radiolabeled Chemicals, Inc., St. Louis, MO; y Moravek Biochemicals Inc., Brea, CA.

Los compuestos de prueba etiquetados de tritio también se preparan convenientemente de modo catalítico a través de un intercambio catalizado con platino en ácido acético tritiado, intercambio catalizado con ácido en ácido trifluoroacético tritiado, o intercambio catalizado de manera heterogénea con gas de tritio. Dichas preparaciones también se realizan convenientemente como un etiquetado de costumbre por medio de algunos de los proveedores mencionados en el párrafo anterior usando el compuesto de la invención como substrato. Asimismo, algunos precursores se pueden ajustar al intercambio de tritio-halógeno con gas de tritio, reducción de gas de tritio de enlaces no saturados, o reducción usando borotrituro de sodio, según sea conveniente.

Ejemplo 23

Autoradiografía del receptor

La autoradiografía del receptor (mapeo del receptor) se realiza in vitro como lo describe Kuhar en las secciones 8.1.1 a 8.1.9 de los Protocolos Actuales en Farmacología (1998) John Wiley & Sons, New York, usando compuestos radioetiquetados de la invención preparados como se describe en el presente Ejemplo.

Ejemplo 24

Ensayo de Enlace

Esta ensayo es un ensayo estándar para la afinidad de enlace $GABA_A$. La alta afinidad y alta selectividad de los compuestos de esta invención para los lugares de benzodiazepina del receptor $GABA_A$ se confirma usando el ensayo de enlace que se describe en Thomas y Tallman (*J. Bio. Chem.* 1981; 156:9838-9842, y *J. Neurosci.* 1983; 3:433-440).

El tejido cortical de rata se diseca y homogeniza en 25 volúmenes (p/v) del Amortiguador A (0.05 M Tris HCl amortiguador, pH 7.4 a 4 °C). El tejido homogenizado se somete a centrifugación en frío (4 °C) a 20,000 x g durante 20 minutos. El sobrenadante se decanta, la gragea se vuelve a homogenizar en el mismo volumen de amortiguador, y se somete a centrifugación nuevamente a 20,000 x g. El sobrenadante de este paso de centrifugación se decanta y la gragea se almacena a -20 °C durante toda la noche. Luego, la gragea se descongela y se vuelve a suspender en 25 volúmenes de Amortiguador A (original p/v), se centrifuga a 20,000 x g y el sobrenadante se decanta. Este paso de lavado se vuelve a repetir una vez más. La gragea finalmente se vuelve a suspender en 50 volúmenes de Amortiguador

A.

Las incubaciones contienen 100 µl de tejido homogenizado, 100 µl de radioligando, (0.5 nM ^{3}H-Ro15-1788 [^{3}H-Flumazenil], actividad específica 80 Ci/mmol), y el compuesto de prueba o control (véase lo que se menciona líneas abajo), y se detienen a un volumen total de 500 µl con Amortiguador A. Las incubaciones se realizan por 30 minutos a 4°C y luego se filtran rápidamente a través de filtros Whatman GFB para separarlas libremente y enlazar el ligando. Los filtros se lavan dos veces con Amortiguador A fresco y se cuentan en un contador líquido intermitente. El enlace no específico (control) se determina al reemplazar el ^{3}H Ro15-1788 con 10 µM Diazepam (Research Biochemicals International, Natick, MA). Los datos se obtienen por triplicado, en promedio, y la inhibición porcentual del enlace específico total (Enlace Específico Total = Total - No específico) se calcula para cada compuesto.

Una curva de competencia de enlace se obtiene con más de 11 puntos que abarca el rango de concentración del compuesto de 10^{-12}M a 10^{-5}M obtenido por curva a través del método descrito líneas arriba para determinar la inhibición porcentual. Los valores K_i se calculan de conformidad con la ecuación Cheng-Prussof. Cuando se examina en esta prueba los compuestos de las Fórmulas A e I, los valores K_i presentan menos del 1 uM, los compuestos recomendados de la invención tienen valores K_i menores que 500 nM y la mayoría de compuestos recomendados tienen valores K_i menores que 100 nM.

Ejemplo 25

Electrofisiología

El siguiente ensayo se usa para determinar si un compuesto de la invención actúa como agonista, antagonista, o agonista invertido en el lugar de la benzodiazepina del receptor $GABA_A$.

Las pruebas se llevan acabo como se describe en White y Gurley (NeuroReport 6: 1313-1316, 1995) y White, Gurley, Hartnett, Stirling, y Gregory (Receptors and Channels 3: 1-5, 1995) con modificaciones. Los registros electrofisiológicos se realizan usando la técnica de pinza de voltaje con electrodo doble en una membrana que mantiene un potencial de -70 mV. Los oocitos *Xenopus Laevis* se aislan enzimáticamente e inyectan con ARNc non-poliadenilatado mezclado en una proporción de 4:1:4 para las subunidades a, β y γ, respectivamente. De las nueve combinaciones de las subunidades a, β y γ que se describen en las publicaciones White y otros, las combinaciones recomendadas son $a_1\beta_2\gamma_2$, $a_2\beta_3\gamma_2$, $a_3\beta_3\gamma_2$, y $a_5\beta_3\gamma_2$. Preferentemente, todas las unidades ARNc en cada combinación son clones humanos o todas son clones de rata. La secuencia de cada una de estas subunidades clonadas está disponible en GENBANK, por ejemplo, a_1 humano, GENBANK acceso No. X14766, a_2 humano, GENBANK acceso No. A28100; a_3 humano, GENBANK acceso No. A28102; a_5 humano, GENBANK acceso No. A28104; β_2 humano, GENBANK acceso No. M82919; β_3 humano, GENBANK acceso No. Z20136; β_2 humano, GENBANK acceso No. X15376; a_1 rata, GENBANK acceso No. L08490, a_2 rata, GENBANK acceso No. L08491; a_3 rata, GENBANK acceso No. L08492; a_5 rata, GENBANK acceso No. L08494; β_2 rata, GENBANK acceso No. X15467; $ß_3$ rata, GENBANK acceso No. X15468; y γ_2 rata, GENBANK acceso No. L08497. Para cada combinación de las subunidades, un mensaje suficiente para cada subunidad constituyente se inyecta para proporcionar amplitudes actuales de >10 nA cuando se aplica 1 μM GABA.

Los compuestos se evalúan contra una concentración GABA que evoca <10% del GABA actual evocable máximo (por ejemplo, 1 μM - 9 μM). Cada oocito se expone para incrementar las concentraciones del compuesto a fin de evaluar una relación de concentración/efecto. La eficacia del compuesto se calcula como un cambio porcentual en la amplitud actual: 100*((Ic/I)-1), donde Ic es el GABA obtenido en la amplitud actual observado en presencia del compuesto de prueba e I es la amplitud actual evocada de GABA observada en ausencia del compuesto de prueba.

El carácter específico de un compuesto para el lugar de benzodiazepina se determina después de completar una curva de concentración/efecto. Después de lavar el oocito suficientemente para retirar el compuesto previamente aplicado, el oocito se expone al GABA + 1 μM RO15-1788, seguido por la exposición al GABA + 1 μM RO15-1788 + compuesto de prueba. El cambio porcentual debido a la adición del compuesto se calcula como se describe líneas arriba. Cualquier cambio porcentual observado en presencia de RO15-1788 se sustrae de los cambios porcentuales en la amplitud actual observada en ausencia de 1 μM RO15-1788. Estos valores netos se usan para el cálculo de la eficacia promedio y los valores EC_{50} mediante los métodos estándar. Para evaluar la eficacia promedio y valores EC_{50}, los datos de concentración/efecto se promedian a través de las células y se adaptan a la ecuación logística.

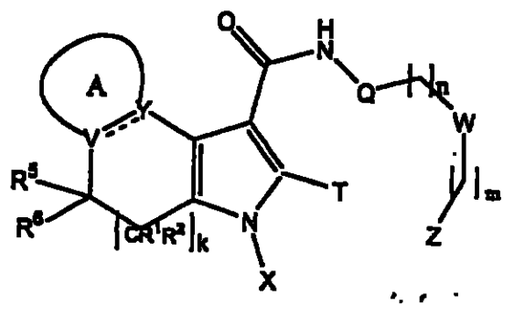
La invención y la manera y el proceso de hacer y usar la misma, se describen en términos totales, claros, concisos y exactos para permitir que los expertos en la técnica a los cuales pertenece esta invención, puedan hacer y usar la misma. Se debe entender que lo antedicho describe las materializaciones físicas recomendadas de la presente invención y que se pueden efectuar

modificaciones en la misma sin apartarse del espíritu o alcance de la presente invención como se establece en las reivindicaciones. Para señalar particularmente y reivindicar claramente el asunto materia que se relaciona con la invención, las siguientes reivindicaciones concluyen esta especificación.

933

Reivindicaciones:

1. Un compuesto de la fórmula



o una sal farmacéuticamente aceptable de la misma que se caracteriza porque:

R^1 y R^2 representan independientemente en cada ocasión hidrógeno, halógeno, hidroxi, ciano, nitro, amino, alquilo, alquenilo, alquinilo, haloalquilo, mono- o di-alquilamino, alcoxi, y k es 0, 1, 2, o 3;

el grupo  representa un anillo opcionalmente substituido saturado, insaturado, o aromático heterocíclico que contiene al menos un átomo de nitrógeno, oxígeno, o azufre, en donde el enlace es un enlace sencillo, doble o aromático;

V es nitrógeno, carbono, o CH;

Y es carbono o CH;

R^5 y R^6 pueden tomarse en forma conjunta para formar un grupo de carbonilo; o

R^5 y R^6 son independientemente hidrógeno, halógeno, hidroxi, nitro, ciano, $alquil_1$, amino, -COOH, $-O(alquil_1)$, $-SO_2NH_2$, $-SO_2NH(alquil_1)$, $-SO_2N(alquil_1)(alquil_1)$, $-N(alquil_1)CO(alquil_1)$, $-N(alquil_1)CO_2(alquil_1)$, $-NHSO_2(alquil_1)$, $-N(alquil_1)SO_2(alquil_1)$, $-SO_2NHCO(alquil_1)$, $-CONHSO_2(alquil_1)$, $-CONH(alquil_1)$, $-CON(alquil_1)(alquil_1)$, $-CO_2(alquil_1)$, $-CO(alquil_1)$, $-SO_{0-2}(alquil_1)$, y un grupo heteroarilo o carbocíclico arilo opcionalmente sustituido que tiene de 1 a 3 anillos, de 3 a 8 miembros en cada anillo y de 1 a 3 heteroátomos;

En donde $alquil_1$ es independientemente en cada ocasión recto, ramificado, o cíclico, puede contener uno o dos enlaces dobles o triples, y es no sustituido o se sustituye con uno o más sustituyentes independientemente

seleccionados de hidroxi, oxo, halógeno, amino, ciano, nitro, alcoxi, -COOH, $-SO_2NH_2$, $-SO_2NH$(alquil), $-SO_2N$(alquil)(alquil), -N(alquil)CO(alquil), $-N(alquil)CO_2$(alquil), $-NHSO_2$(alquil), $-N(alquil)SO_2$(alquil), $-SO_2NHCO$(alquil), $-CONHSO_2$(alquil), -CONH(alquil), -CON(alquil)(alquil), $-CO_2$(alquil), -CO(alquil), $-SO_{0-2}$(alquil);

X es hidrógeno, hidroxi, amino, alquilo, y alcoxi;

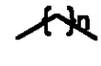
T es hidrógeno, halógeno, hidroxi, amino, alquilo, y alcoxi;

Q es un grupo carbocíclico arilo o heteroarilo opcionalmente sustituido que tiene de 1 a 3 anillos, de 3 a 8 miembros en cada anillo, y de 1 a 3 heteroátomos;

W es hidrógeno, oxígeno, nitrógeno, azufre, o CR^7R^8 donde R^7 y R^8 son los mismos o diferentes y representan hidrógeno, alquilo de cadena recta o ramificada, o R^7 y R^8 pueden tomarse juntos para representar una porción cíclica que tiene de 3 a 7 átomos de carbono;

Z es hidrógeno, hidroxi, alcoxi de cadena recta o ramificada, cicloalquilo, cicloalquil(alcoxi), amino, mono- o dialquilamina, o NR^9COR^{10} donde R^9 y R^{10} son los mismos o diferentes y representan hidrógeno o alquilo de cadena recta o ramificada, o R^9 y R^{10} pueden unirse para formar un anillo cicloalquilo, o

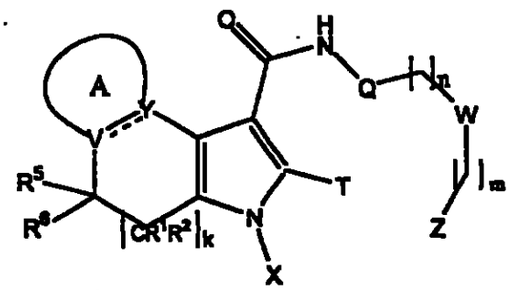
Z es un grupo carbocíclico arilo o heteroarilo opcionalmente sustituido que tiene de 1 a 3 anillos, de 3 a 8 miembros en cada anillo y de 1 a 3 heteroátomos; y

 y  representan cadenas de carbono opcionalmente sustituidas con hidrógeno, halógeno, ciano, nitro, amino, mono- o dialquilamino, alquenilo, alquinilo, alcoxi, trifluorometilo, trifluorometoxi, alquilo de cadena recta o ramificada, o cicloalquilo; y

m es 0, 1, 2, o 3; y

n es 0, 1, 2, o 3.

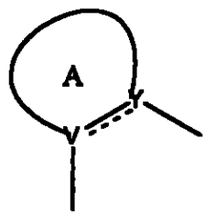
2. Un compuesto conformidad con la reivindicación 1, de fórmula



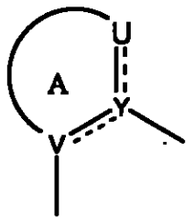
O una sal farmacéuticamente aceptable del mismo, en donde:

R^1 y R^2 se eligen, independientemente, en cada caso, de hidrógeno, halógeno, hidroxi, ciano, nitro, amino, haloalquilo, mono o diamino(C_{1-6})alquilo, C_{1-6} alquilo, C_{2-6}alquenilo, C_{2-6}alquinilo y C_{1-6} alcoxi, y k es 0, 1, 2, ó 3;

El grupo



es un grupo de la fórmula:



que representa un anillo heterocíclico saturado, insaturado o aromático que contiene al menos un átomo de nitrógeno, oxígeno o azufre, en donde los enlaces U----Y y V----Y pueden ser enlaces simples, dobles o aromáticos,

U es nitrógeno, NR^A, S, u O;

V es nitrógeno, carbono o CH;

Y es carbono, o CH;

Y el anillo heterocíclico saturado, insaturado o aromático se elige a partir de:

Tienilo, tiazolilo, piridilo, pirimidinilo, imidazolilo, pirazolilo, pirazinilo, piridizinilo, piperidinilo, oxazolilo, isoxazolilo, triazolilo simétrico y asimétrico, pirrolilo, furanilo, diazenilo, triazenilo, 1, 2, 4-triazolona, 4,5-dihidroimidazolilo, y 1,4,5,6-tetrahidropirimidinilo,

cada uno de los cuales se sustituye opcionalmente en cualquier nitrógeno disponible por R^A y opcionalmente se sustituye en cualquier carbono disponible por R^3 y R^4, en donde:

R^A se selecciona a partir de hidrógeno, (C_1-C_6)alquil$_1$,

grupos arilo carbocíclico o heteroarilo opcionalmente sustituidos que tienen de 1 a 3 anillos, 3 a 8 miembros en cada anillo y de 1 a 3 heteroátomos;

R^5 y R^6 se eligen independientemente a partir de hidrógeno, halógeno, hidroxi, nitro, ciano, C_{1-6}alquil$_1$, amino, -COOH, -O(C_{1-6}alquil$_1$), -NH(C_{1-6}alquil$_1$), -N(C_{1-6}alquil$_1$)(C_{1-6}alquil$_1$), $-SO_2NH_2$, $-SO_2NH(C_{1-6}$alquil$_1)$, $-SO_2N(C_{1-6}$alquil$_1)(C_{1-6}$alquil$_1)$, -N(C_{1-6}alquil$_1$)CO(C_{1-6}alquil$_1$), N(C_{1-6}alquil$_1$)$CO_2(C_{1-6}$alquil$_1)$, $-NHSO_2(C_{1-6}$alquil$_1)$, $-N(C_{1-6}$alquil$_1)SO_2(C_{1-6}$alquil$_1)$, $-SO_2NHCO(C_{1-6}$alquil$_1)$, $-CONHSO_2(C_{1-6}$alquil$_1)$, -CONH(C_{1-6}alquil$_1$), -CON(C_{1-6}alquil$_1$)(C_{1-6}alquil$_1$), $-CO_2(C_{1-6}$alquil$_1)$, -CO(C_{1-6}alquil$_1$) y $-SO_{0-2}(C_{1-6}$alquil$_1)$,

En donde C_{1-6}alquil$_1$ se elige independientemente en cada caso y es recto, ramificado o cíclico, puede contener uno o dos enlaces dobles o triples y es no sustituido o sustituido con uno o más sustituyentes seleccionados de: hidroxi, oxo, halógeno, amino, ciano, nitro, alcoxi, grupo carbocíclico o heterocíclico, -COOH, $-SO_2NH_2$, $-SO_2NH(C_{1-4}$alquilo), $-SO_2N(C_{1-4}$alquil$)(C_{1-4}$alquilo), -N(C_{1-4}alquil)CO(C_{1-4}alquilo), N(C_{1-4}alquil)$CO_2(C_{1-4}$alquilo), $-NHSO_2$(alquilo), -N(C_{1-4}alquil)$SO_2(C_{1-4}$alquilo), $-SO_2NHCO(C_{1-4}$alquilo), $-CONHSO_2(C_{1-4}$alquilo), -CONH(C_{1-4}alquilo), -CON(C_{1-4}alquil)(C_{1-4}alquilo), $-CO_2(C_{1-4}$alquilo), -CO(C_{1-4}alquilo), y $-SO_{0-2}(C_{1-4}$alquilo);

R^3 y R^4 se eligen, independientemente, en cada caso, y se definen igual que R^5 y R^6;

X se elige a partir de hidrógeno, hidroxi, amino, C_{1-6} alquilo, y C_{1-6}alcoxi;

T se elige a partir de hidrógeno, halógeno, hidroxi, amino, C_{1-6} alquilo, y C_{1-6} alcoxi;

Q es un fenilo, naftilo, quinolinilo, tienilo, piridilo, pirimidinilo, pirazinilo, oxazolilo, isoxazolilo, oxadiazolilo simétrico o asimétrico, tiadiazolilo simétrico o asimétrico, pirazolilo, furanilo, diazenilo, triazenilo, o triazolopirazinilo;

Cada uno de los cuales puede ser no sustituido o sustituido hasta con tres sustituyentes independientemente seleccionados de i) y ii), en donde

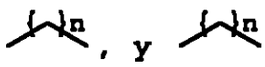
i) representa hidroxi, ciano, halógeno, nitro, amino, mono o di(C_{1-6})alquilamino, C_{2-6}alquenilo, C_{2-6}alquinilo, C_{1-6}alcoxi, trifluorometilo, o trifluorometoxi;

ii) representa cadena constante o ramificada C_{1-6}alquilo que opcionalmente contiene heteroátomos y opcionalmente se sustituye por uno o más grupos carbocíclicos o heterocíclicos;

W es hidrógeno, oxígeno, nitrógeno, azufre, o CR^7R^8, en donde R^7 y R^8 son iguales o diferentes, y representan hidrógeno, C_{1-6}alquilo de cadena recta o ramificada, o R^7 y R^8 se pueden tomar juntos para representar una porción cíclica que tiene 3-7 átomos de carbono;

Z es hidrógeno, hidroxi, C_{1-6}alcoxi de cadena recta o ramificada, C_{3-7}cicloalquil, C_{3-7}cicloalquil(C_{1-3}alcoxi), amino, mono o di C_{1-6}alquilamino, un grupo carbocíclico o heterocíclico, o NR^9CO^{10} en donde R^9 y R^{10} son iguales o diferentes y representan hidrógeno o C_{1-6}alquilo de cadena o ramificada, o R^9 y R^{10} se pueden unir para formar un anillo C_{3-7} cicloalquilo, o

Z es un fenilo, naftilo, quinolinilo, tienilo, tiazolilo, piridilo, pirimidinilo, imidazolilo, pirazolilo, pirazinilo, piridizinilo, piperidinilo, oxazolilo, isoxazolilo, tiadiazolilo simétrico o asimétrico, triazolilo simétrico o asimétrico, oxadiazolilo simétrico o asimétrico, pirrolilo, furanilo, pirimidinilo, diazenilo, triazenilo, 1, 2, 4-triazolona, 4,5-dihidroimidazolilo, o 1,4,5,6-grupo tetrahidropirimidinilo;

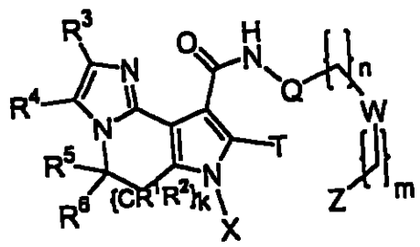

, y

representan una cadena de carbono opcionalmente sustituida por hidrógeno, halógeno, ciano, nitro, amino, mono o di C_{1-6}alquilamino, C_{2-6}alquenilo, C_{2-6}alquinilo, C_{1-6}alcoxi, trifluorometilo, trifluorometoxi, cadena recta o ramificada de C_{1-6}alquilo, o C_{3-7}cicloalquilo, y

m es 0, 1, 2, ó 3; y

n es 0, 1, 2, ó 3.

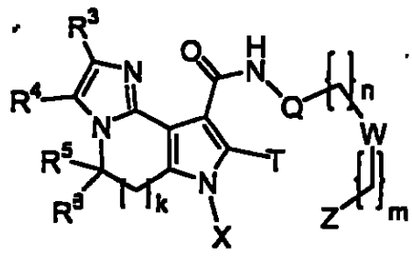
3. Un compuesto de acuerdo con la reivindicación 2, de la fórmula:



938

En donde las variables R^1, R^2, R^3, R^4, R^5, R^6, k, n, m, T, X, Q, W, y Z son como se definieron en la reivindicación 1.

4. Un compuesto de acuerdo con la reivindicación 2, de la fórmula

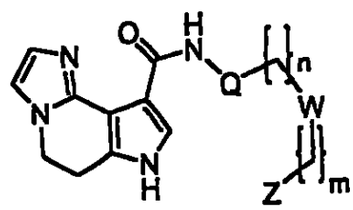


En donde las variables n, m, Q, W, y Z son como se definieron en la reivindicación 2;

k es 1 o 2;

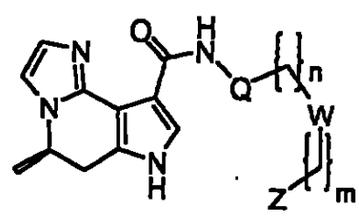
R^3, R^4, R^5, y R^6, son escogidos independientemente de hidrógeno, halógeno, amino, hidroxi, metilo, etilo, metoxi, y etoxi y X y T se escogen independientemente de hidrógeno, metilo, y etilo.

5. Un compuesto de acuerdo con la reivindicación 2, de la fórmula



En donde las variables n, m, Q, W, y Z son como se definieron en la reivindicación 2.

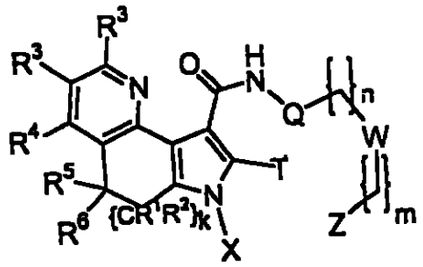
6. Un compuesto de acuerdo con la reivindicación 2, de la fórmula



En donde las variables n, m, Q, W, y Z son como se definieron en la reivindicación 2.

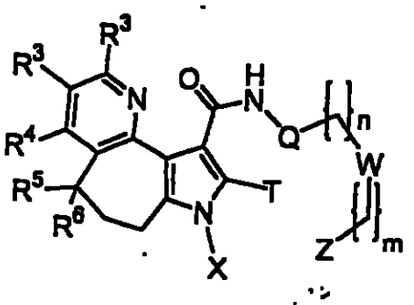
939

7. Un compuesto de acuerdo con la reivindicación 2, de la fórmula



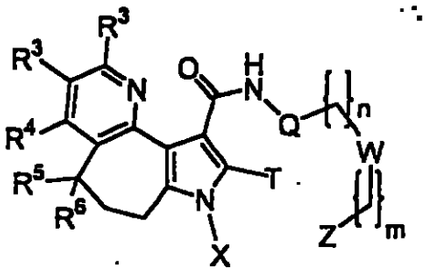
En donde las variables R^1, R^2, R^3, R^4, R^5, R^6, k, n, m, T, X, Q, W, y Z son como se definieron en la reivindicación 2.

8. Un compuesto de acuerdo con la reivindicación 2, de la fórmula



En donde las variables R^3, R^4, R^5, R^6, n, m, T, X, Q, W, y Z son como se definieron en la reivindicación 2.

9. Un compuesto de acuerdo con la reivindicación 2, de la fórmula:



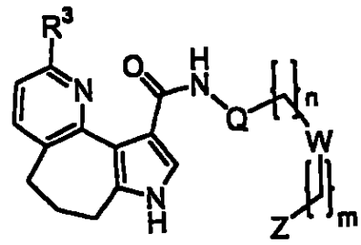
En donde las variables n, m, Q, W, y Z son como se definieron en la reivindicación 2;

k es 1 o 2;

R^3, R^4, R^5, y R^6, son escogidos independientemente de hidrógeno, halógeno, amino, hidroxi, metilo, etilo, metoxi, y etoxi; y X y T se escogen independientemente de hidrógeno, metilo, y etilo.

940

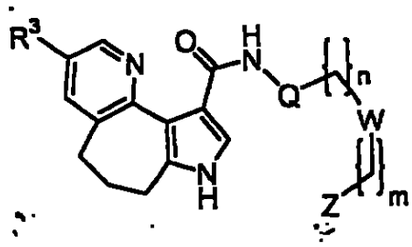
10. Un compuesto de acuerdo con la reivindicación 2, de la fórmula:



En donde las variables n, m, T, X, Q, W, y Z son como se definieron en la reivindicación 2; y

R^3 es hidrógeno o metilo.

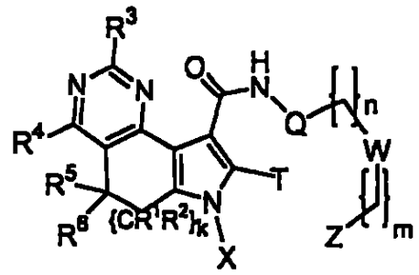
11. Un compuesto de acuerdo con la reivindicación 2, de la fórmula:



En donde las variables n, m, T, X, Q, W, y Z son como se definieron en la reivindicación 2; y

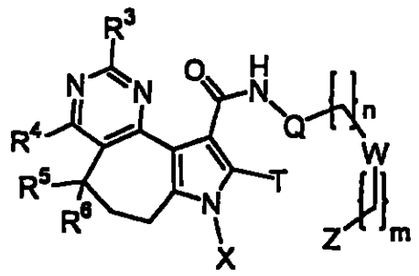
R^3 es hidrógeno o metilo.

12. Un compuesto de acuerdo con la reivindicación 2, de la fórmula



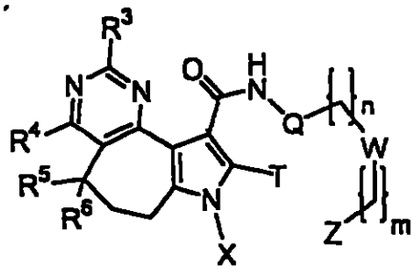
En donde las variables R^1, R^2, R^3, R^4, R^5, R^6, k, n, m, T, X, Q, W, y Z son como se definieron en la reivindicación 2.

13. Un compuesto de acuerdo con la reivindicación 2, de la fórmula



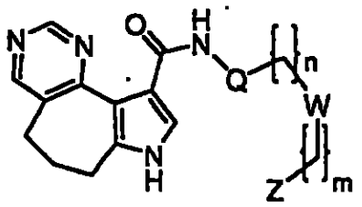
En donde las variables R^3, R^4, R^5, R^6, n, m, T, X, Q, W, y Z son como se definieron en la reivindicación 2.

14. Un compuesto de acuerdo con la reivindicación 2, de la fórmula:



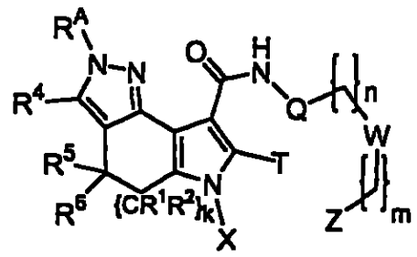
En donde las variables n, m, Q, W, y Z son como se definieron en la reivindicación 2;
R^3, R^4, R^5, y R^6, son escogidos independientemente de hidrógeno, halógeno, amino, hidroxi, metilo, etilo, metoxi, y etoxi; y
X y T se escogen independientemente de hidrógeno, metilo, y etilo.

15. Un compuesto de acuerdo con la reivindicación 2, de la fórmula:



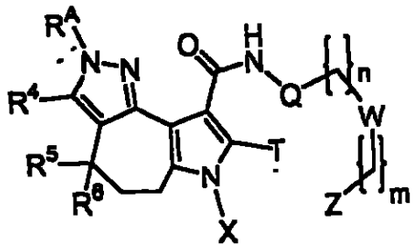
En donde las variables n, m, Q, W, y Z son como se definieron en la reivindicación 2.

16. Un compuesto de acuerdo con la reivindicación 2, de la fórmula



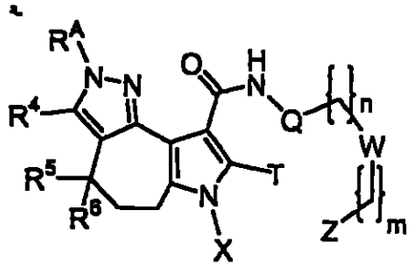
En donde las variables R^1, R^2, R^A, R^4, R^5, R^6, k, n, m, T, X, Q, W, y Z son como se definieron en la reivindicación 2.

17. Un compuesto de acuerdo con la reivindicación 2, de la fórmula



En donde las variables R^A, R^4, R^5, R^6, n, m, T, X, Q, W, y Z son como se definieron en la reivindicación 2.

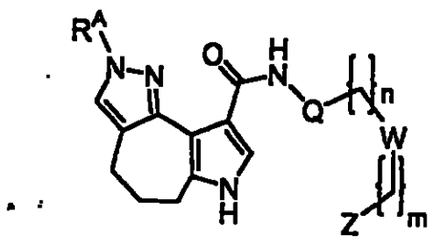
18. Un compuesto de acuerdo con la reivindicación 2, de la fórmula:



En donde las variables n, m, Q, W, y Z son como se definieron en la reivindicación 2;
R^A es C_1-C_6 alquilo, fenilo, tienilo, piridilo, pirimidinilo, pirrolilo, o imidazolilo,
R^3, R^4, R^5, y R^6, son escogidos independientemente de hidrógeno, halógeno, amino, hidroxi, metilo, etilo, metoxi, y etoxi; y
X y T se escogen independientemente de hidrógeno, metilo, y etilo.

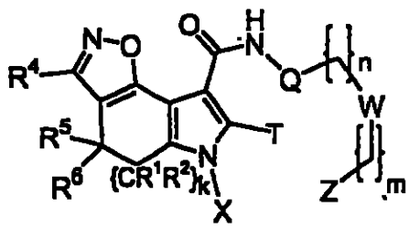
19. Un compuesto de acuerdo con la reivindicación 2, de la

fórmula:



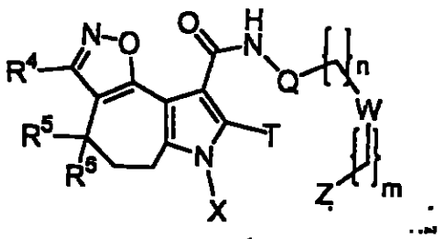
En donde las variables n, m, Q, W, y Z son como se definieron en la reivindicación 2; y
R^A es metilo, etilo, o piridilo.

20. Un compuesto de acuerdo con la reivindicación 2, de la fórmula



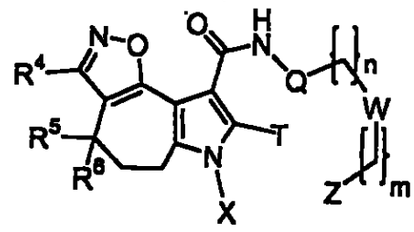
En donde las variables R^1, R^2, R^4, R^5, R^6, k, n, m, T, X, Q, W, y Z son como se definieron en la reivindicación 2.

21. Un compuesto de acuerdo con la reivindicación 2, de la fórmula



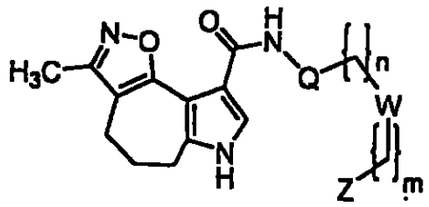
En donde las variables R^4, R^5, R^6, n, m, T, X, Q, W, y Z son como se definieron en la reivindicación 2.

22. Un compuesto de acuerdo con la reivindicación 2, de la fórmula:



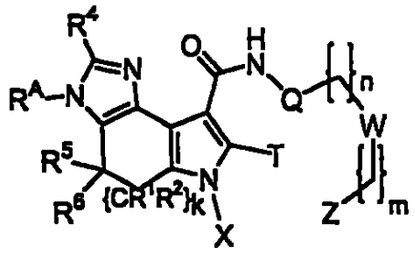
En donde las variables n, m, Q, W, y Z son como se definieron en la reivindicación 2;
R^4, R^5, y R^6, son escogidos independientemente de hidrógeno, halógeno, amino, hidroxi, metilo, etilo, metoxi, y etoxi; y
X y T se escogen independientemente de hidrógeno, metilo, y etilo.

23. Un compuesto de acuerdo con la reivindicación 2, de la fórmula:



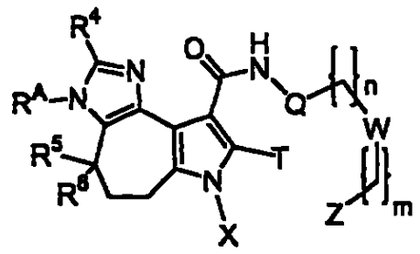
En donde las variables n, m, Q, W, y Z son como se definieron en la reivindicación 2.

24. Un compuesto de acuerdo con la reivindicación 2, de la fórmula



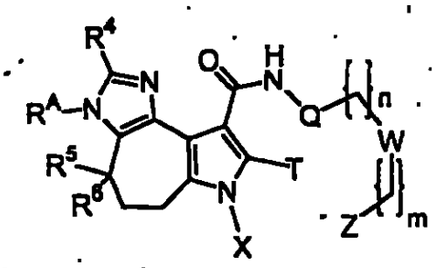
En donde las variables R^1, R^2, R^A, R^4, R^5, R^6, k, n, m, T, X, Q, W, y Z son como se definieron en la reivindicación 2.

25. Un compuesto de acuerdo con la reivindicación 2, de la fórmula



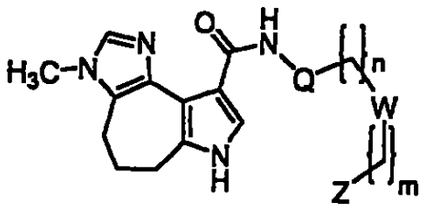
En donde las variables R^A, R^4, R^5, R^6, n, m, T, X, Q, W, y Z son como se definieron en la reivindicación 2.

26. Un compuesto de acuerdo con la reivindicación 2, de la fórmula:



En donde las variables n, m, Q, W, y Z son como se definieron en la reivindicación 2;
R^A es metilo, etilo o piridilo;
R^4, R^5, y R^6, son escogidos independientemente de hidrógeno, halógeno, amino, hidroxi, metilo, etilo, metoxi, y etoxi; y
X y T se escogen independientemente de hidrógeno, metilo, y etilo.

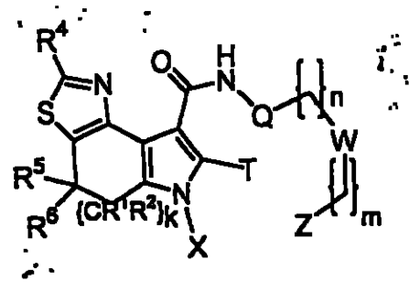
27. Un compuesto de acuerdo con la reivindicación 2, de la fórmula:



En donde las variables n, m, Q, W, y Z son como se definieron en la reivindicación 2.

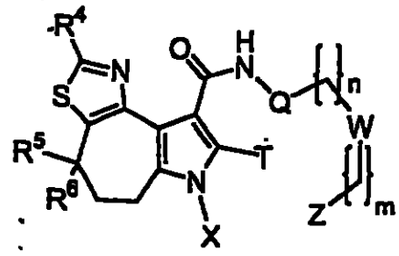
28. Un compuesto de acuerdo con la reivindicación 2, de la fórmula

946



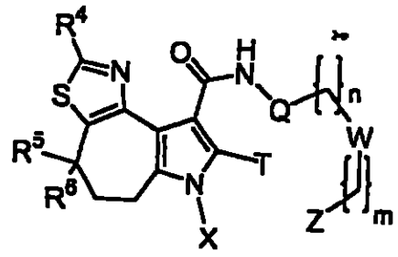
En donde las variables R^1, R^2, R^4, R^5, R^6, k, n, m, T, X, Q, W, y Z son como se definieron en la reivindicación 2.

29. Un compuesto de acuerdo con la reivindicación 2, de la fórmula



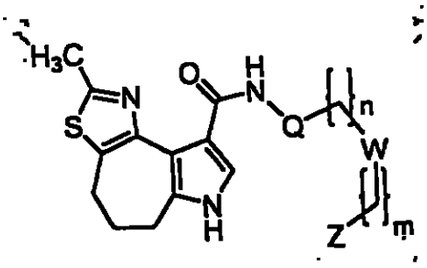
En donde las variables R^4, R^5, R^6, k, n, m, T, X, Q, W, y Z son como se definieron en la reivindicación 2.

30. Un compuesto de acuerdo con la reivindicación 2, de la fórmula:



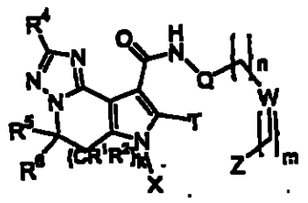
En donde las variables n, m, Q, W, y Z son como se definieron en la reivindicación 2;
R^4, R^5, y R^6, son escogidos independientemente de hidrógeno, halógeno, amino, hidroxi, metilo, etilo, metoxi, y etoxi; y
X y T se escogen independientemente de hidrógeno, metilo, y etilo.

31. Un compuesto de acuerdo con la reivindicación 2, de la fórmula:



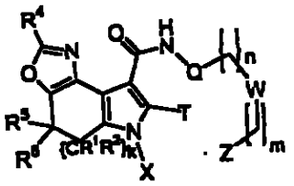
En donde las variables n, m, Q, W, y Z son como se definieron en la reivindicación 2.

32. Un compuesto de acuerdo con la reivindicación 2, de la fórmula



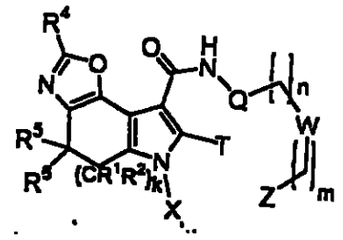
En donde las variables R^1, R^2, R^4, R^5, R^6, k, n, m, T, X, Q, W, y Z son como se definieron en la reivindicación 2.

33. Un compuesto de acuerdo con la reivindicación 2, de la fórmula



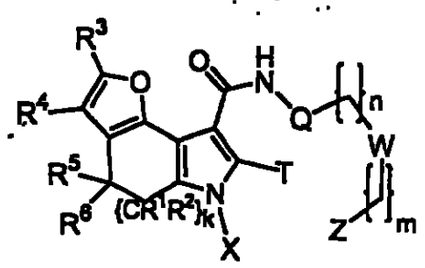
En donde las variables R^1, R^2, R^4, R^5, R^6, k, n, m, T, X, Q, W, y Z son como se definieron en la reivindicación 2.

34. Un compuesto de acuerdo con la reivindicación 2, de la fórmula



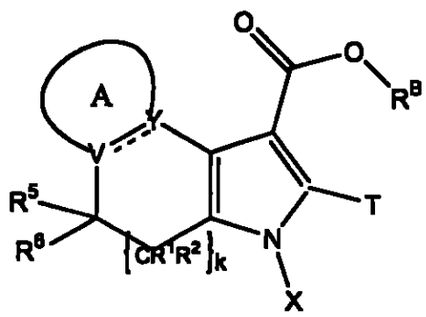
En donde las variables R^1, R^2, R^4, R^5, R^6, k, n, m, T, X, Q, W, y Z son como se definieron en la reivindicación 2.

35. Un compuesto de acuerdo con la reivindicación 2, de la fórmula



En donde las variables R^1, R^2, R^3, R^4, R^5, R^6, k, n, m, T, X, Q, W, y Z son como se definieron en la reivindicación 2.

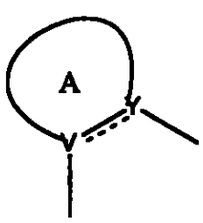
36. Un compuesto de la fórmula:



en donde

R^1 y R^2 se eligen independientemente en cada caso a partir de hidrógeno, halógeno, hidroxi, ciano, nitro, amino, alquilo, alquenilo, alquinilo, haloalquilo, y mono o dialquilamino, mono o dialquilaminoalquilo, alcoxi, y k es 0, 1, 2, ó 3;

El grupo



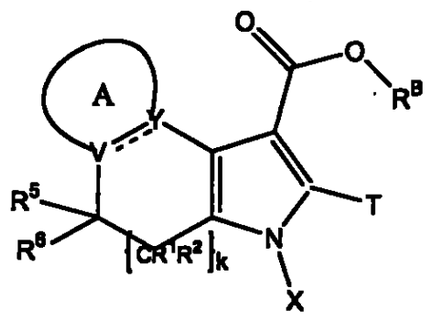
el cual representa un anillo heterocíclico

opcionalmente sustituido, saturado, insaturado o aromático que contiene al menos un átomo de nitrógeno, oxígeno o azufre, en donde el enlace $^{V\text{----}Y}$ es un enlace simple, doble o aromático;
V es nitrógeno, carbono, o CH;
Y es carbono, o CH;

R^5 y R^6 se pueden juntar para formar un grupo carbonilo; o
R^5 y R^6 se eligen independientemente a partir de hidrógeno, halógeno, hidroxi, nitro, ciano, alquil$_1$, amino, -COOH, -O(alquil$_1$), -SO_2NH_2, -SO_2NH(alquil$_1$), -SO_2N(alquil$_1$) (alquil$_1$), -N(alquil$_1$)CO(alquil$_1$), N(alquil$_1$)CO_2(alquil$_1$), -$NHSO_2$(alquil$_1$), -N(alquil$_1$)SO_2(alquil$_1$), -SO_2NHCO(alquil$_1$), -CONHSO_2(alquil$_1$), -CONH(alquil$_1$), -CON(alquil$_1$) (alquil$_1$), -CO_2(alquil$_1$), -CO(alquil$_1$), -SO_{0-2}(alquil$_1$), arilo carbocíclico sustituido opcionalmente y grupo heteroarilo sustituidos opcionalmente que tienen de 1 a 3 anillos, 3 a 8 miembros en cada anillo y de 1 a 3 heteroátomos;

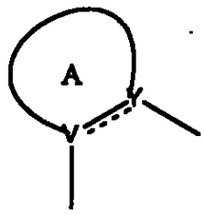
En donde alquil$_1$ se elige independientemente en cada caso, y es recto, ramificado o cíclico, puede contener uno o dos enlaces dobles o triples y es no sustituido o sustituido por uno o más sustituyentes seleccionados a partir de: hidroxi, oxo, halógeno, amino, ciano, nitro, alcoxi, -COOH, -SO_2NH_2, -SO_2NH(alquilo), -SO_2N(alquil)(alquilo), -N(alquil)CO(alquilo), N(alquil) CO_2(alquilo), -$NHSO_2$(alquilo), -N(alquil)SO_2(alquilo), -SO_2NHCO(alquilo), -CONHSO_2(alquilo), -CONH(alquilo), -CON(alquil)(alquilo), -CO_2(alquilo), -CO(alquilo), -SO_{0-2}(alquilo);
X se elige a partir de hidrógeno, hidroxi, amino, alquilo, y alcoxi;
T se elige a partir de hidrógeno, halógeno, hidroxi, amino, alquil, y alcoxi; y
R^8 se elige a partir de hidrógeno, metilo, etilo y bencilo.

37. Un compuesto de la fórmula:

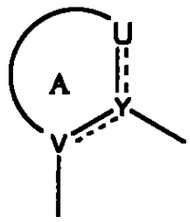


R^1 y R^2 se eligen independientemente en cada caso a partir de hidrógeno, halógeno, hidroxi, ciano, nitro, amino, haloalquilo, mono o diamino(C_{1-6})alquilo, C_{1-6} alquilo, C_{2-6}alquenilo, C_{2-6}alquinilo y C_{1-6} alcóxi, y k es 0, 1, 2, ó 3;

El grupo



es un grupo de la Fórmula:



representa un anillo heterocícilico saturado, insaturado o aromático que contiene al menos un átomo de nitrógeno, oxígeno o azufre, en donde los enlaces U----Y y V----Y pueden ser enlaces simples, dobles o aromáticos,

U es nitrógeno, NR^A, S, u O;

V es nitrógeno, carbono o CH;

Y es carbono, o CH;

y dicho anillo heterocíclico saturado, insaturado o aromático se elige a partir de:

tienilo, tiazolilo, piridilo, pirimidinilo, imidazolilo, pirazolilo, pirazinilo, piridizinilo, piperidinilo, oxazolilo, isoxazolilo, triazolilo simétrico y asimétrico, pirrolilo, furanilo, diazenilo, triazenilo, 1, 2, 4-triazolona, 4,5-dihidroimidazolilo, y 1,4,5,6-tetrahidropirimidinilo,

Cada uno de los cuales se sustituye opcionalmente en cualquier

nitrógeno disponible mediante R^A y sustituido opcionalmente en cualquier carbono disponible mediante R^3 y R^4, en donde:

R^A se elige a partir de hidrógeno, C_{1-6}alquil$_1$, arilo carbocíclico sustituido opcionalmente y grupos heteroarilo sustituidos opcionalmente que tienen de 1 a 3 anillos, 3 a 8 miembros en cada anillo y de 1 a 3 heteroátomos;

R^5 y R^6 se eligen independientemente a partir de hidrógeno, halógeno, hidroxi, nitro, ciano, C_{1-6}alquil$_1$, amino, -COOH, -O(C_{1-6}alquil$_1$), -NH(C_{1-6}alquil$_1$), -N(C_{1-6}alquil$_1$)(C_{1-6}alquil$_1$), -SO_2NH_2, -SO_2NH(C_{1-6}alquil$_1$), -SO_2N(C_{1-6}alquil$_1$)(C_{1-6}alquil$_1$), -N(C_{1-6}alquil$_1$)CO(C_{1-6}alquil$_1$), N(C_{1-6}alquil$_1$)CO_2(C_{1-6}alquil$_1$), -NHSO_2(C_{1-6}alquil$_1$), -N(C_{1-6}alquil$_1$)SO_2(C_{1-6}alquil$_1$), -SO_2NHCO(C_{1-6}alquil$_1$), -CONHSO_2(C_{1-6}alquil$_1$), -CONH(C_{1-6}alquil$_1$), -CON(C_{1-6}alquil$_1$)(C_{1-6}alquil$_1$), -CO_2(C_{1-6}alquil$_1$), -CO(C_{1-6}alquil$_1$) y -SO_{0-2}(C_{1-6}alquil$_1$),

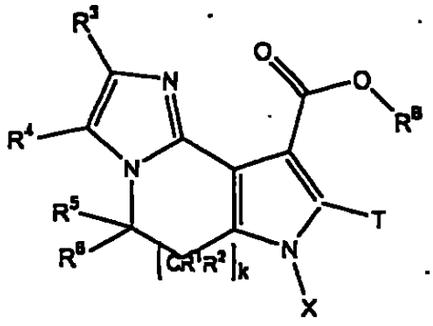
En donde C_{1-6}alquil$_1$ se elige independientemente en cada caso y es recto, ramificado o cíclico, puede contener uno o dos enlaces dobles o triples y es no sustituido o sustituido por uno o más sustituyentes seleccionados a partir de: hidroxi, oxo, halógeno, amino, ciano, nitro, alcoxi, grupo carbocíclico o heterocíclico, -COOH, -SO_2NH_2, -SO_2NH(C_{1-4}alquil), -SO_2N(C_{1-4}alquil)(C_{1-4}alquilo), -N(C_{1-4}alquil)CO(C_{1-4}alquilo), N(C_{1-4}alquil)CO_2(C_{1-4}alquilo), -NHSO_2(alquilo), -N(C_{1-4}alquil)SO_2(C_{1-4}alquilo), -SO_2NHCO(C_{1-4}alquilo), -CONHSO_2(C_{1-4}alquilo), -CONH(C_{1-4}alquilo), -CON(C_{1-4}alquil)(C_{1-4}alquilo), -CO_2(C_{1-4}alquilo), -CO(C_{1-4}alquilo), y -SO_{0-2}(C_{1-4}alquilo);

X se elige a partir de hidrógeno, hidroxi, amino, C_{1-6} alquilo, y C_{1-6}alcoxi;

T se elige a partir de hidrógeno, halógeno, hidroxi, amino, C_{1-6} alquilo, y C_{1-6} alcoxi; y

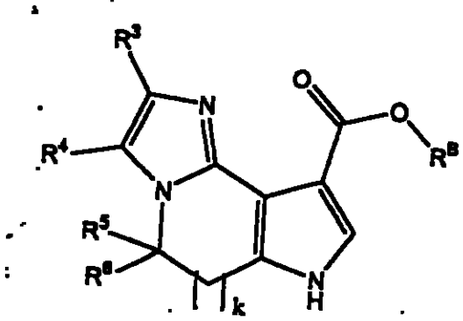
R^8 se elige a partir de hidrógeno, metilo, etilo y bencilo.

38. Un compuesto de acuerdo con la reivindicación 37, de la fórmula



En donde las variables R^1, R^2, R^3, R^4, R^5, R^6, k, T, X, y R^B son como se definieron en la reivindicación 37.

39. Un compuesto de acuerdo con la reivindicación 37, el cual es:



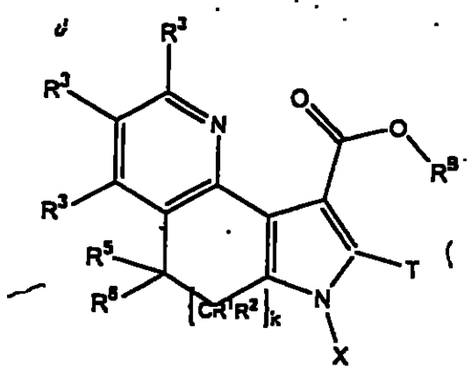
En donde:

R^B se define como en la reivindicación 37;

K es 1 o 2;

R^3, R^4, R^5, R^6, se seleccionan independientemente de hidrógeno, halógeno, amino, hidroxi, metilo, etilo, metoxi, y etoxi.

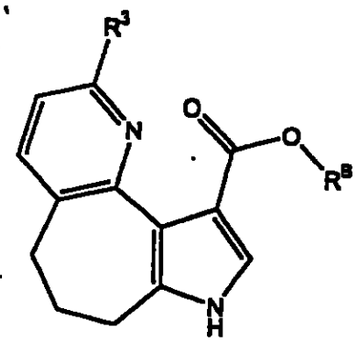
40. Un compuesto de acuerdo con la reivindicación 37, el cual es:



En donde R^3 se selecciona en cada ocasión independientemente y es como se define en la reivindicación 35; y

R^1, R^2, R^3, R^5, R^6, k, T, X, y R^B son como se definieron en la reivindicación 37.

41. Un compuesto de acuerdo con la reivindicación 37, el cual es:

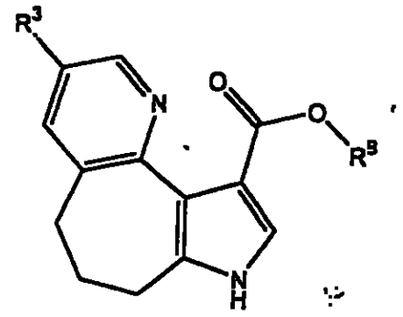


En donde:

R^B se define como en la reivindicación 37; y

R^3 se selecciona de hidrógeno, halógeno, amino, hidroxi, metilo, etilo, metoxi, y etoxi.

42. Un compuesto de acuerdo con la reivindicación 37, el cual es:

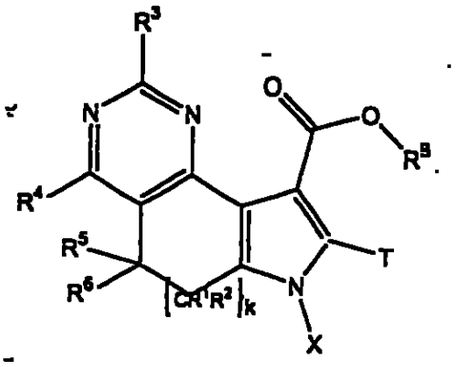


En donde:

R^B se define como en la reivindicación 37; y

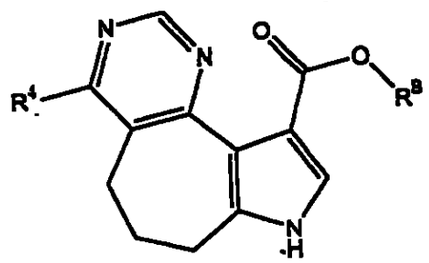
R^3 se selecciona de hidrógeno, halógeno, amino, hidroxi, metilo, etilo, metoxi, y etoxi.

43. Un compuesto de acuerdo con la reivindicación 37, el cual es:



En donde R^1, R^2, R^3, R^4, R^5, R^6, k, T, X, y R^B son como se definieron en la reivindicación 37.

44. Un compuesto de acuerdo con la reivindicación 37, el cual es:

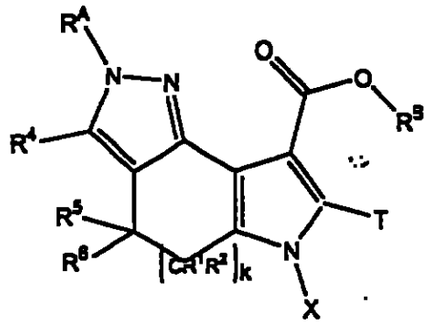


En donde:

R^B se define como en la reivindicación 37; y

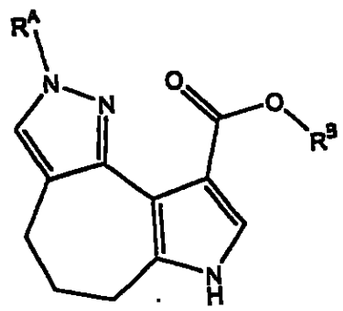
R^4 se selecciona de hidrógeno, halógeno, amino, hidroxi, metilo, etilo, metoxi, y etoxi.

45. Un compuesto de acuerdo con la reivindicación 37, el cual es:



En donde R^A, R^1, R^2, X, R^4, R^5, R^6, k, T, X, y R^B son como se definieron en la reivindicación 37.

46. Un compuesto de acuerdo con la reivindicación 37, el cual es:

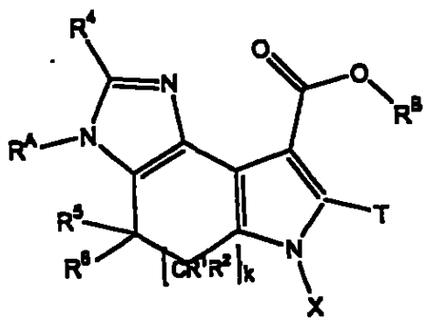


En donde:

R^A se selecciona de hidrógeno, metilo, etilo y fenilo; y

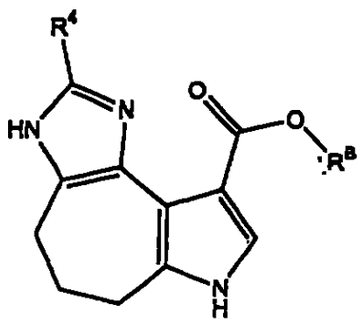
R^B se define como en la reivindicación 37.

47. Un compuesto de acuerdo con la reivindicación 37, el cual es:



En donde R^A, R^1, R^2, R^3, R^4, R^5, R^6, k, T, X, y R^B son como se definieron en la reivindicación 37.

48. Un compuesto de acuerdo con la reivindicación 37, el cual es:

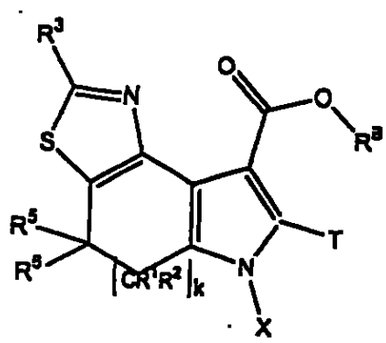


En donde:

R^B se define como en la reivindicación 37; y

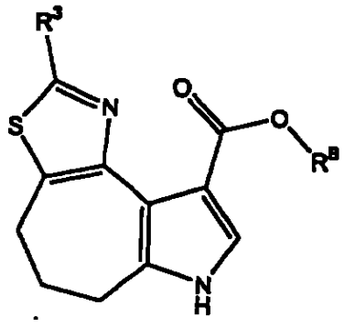
R^4 se selecciona de hidrógeno, halógeno, amino, hidroxi, metilo, etilo, metoxi, y etoxi.

49. Un compuesto de acuerdo con la reivindicación 37, el cual es:



En donde R^1, R^2, R^3, R^5, R^6, k, T, X, y R^B son como se definieron en la reivindicación 37.

50. Un compuesto de acuerdo con la reivindicación 37, el cual es:

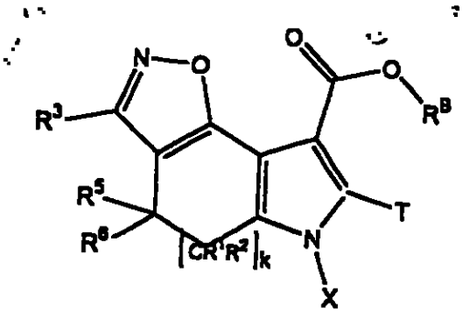


En donde:

R^B se define como en la reivindicación 37; y

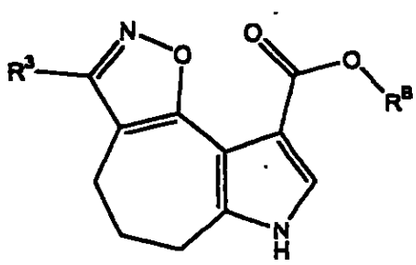
R^3 se selecciona de hidrógeno, halógeno, amino, hidroxi, metilo, etilo, metoxi, y etoxi.

51. Un compuesto de acuerdo con la reivindicación 37, el cual es:



En donde R^1, R^2, R^3, R^5, R^6, k, T, X, y R^B son como se definieron en la reivindicación 37.

52. Un compuesto de acuerdo con la reivindicación 37, el cual es:

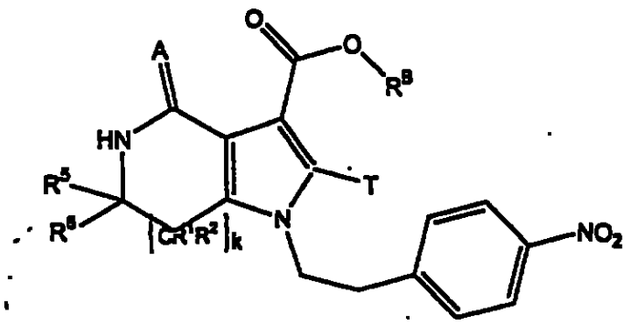


En donde:

R^B se define como en la reivindicación 37; y

R^3 se selecciona de hidrógeno, halógeno, amino, hidroxi, metilo, etilo, metoxi, y etoxi.

53. Un compuesto de la fórmula



A es oxígeno o azufre;

R^1 y R^2 se seleccionan independientemente en cada ocasión de hidrógeno, halógeno, hidroxi, ciano, nitro, amino, haloalquilo, mono- o diamino(C_1-C_6)alquilo, C_1-C_6 alquilo, C_2-C_6alquenilo, C_2-C_6alquinilo, y C_1-C_6 alcoxi, y k es 0, 1, 2, o 3;

R^5 y R^6 se escogen independientemente de hidrógeno, halógeno, hidroxi, nitro, ciano, C_1-C_6 alquil$_1$, amino, -COOH, -O(C_1-C_6 alquil$_1$), -NH(C_1-C_6 alquil$_1$), -N(C_1-C_6 alquil$_1$)(C_1-C_6 alquil$_1$), , $-SO_2NH_2$, $-SO_2NH$(C_1-C_6 alquil$_1$), $-SO_2N$(C_1-C_6 alquil$_1$)(C_1-C_6 alquil$_1$), -N(C_1-C_6 alquil$_1$)CO(C_1-C_6 alquil$_1$), -N(C_1-C_6 alquil$_1$)CO_2(C_1-C_6 alquil$_1$), $-NHSO_2$(C_1-C_6 alquil$_1$), -N(C_1-C_6 alquil$_1$)SO_2(C_1-C_6 alquil$_1$), $-SO_2NHCO$(C_1-C_6 alquil$_1$), $-CONHSO_2$(C_1-C_6 alquil$_1$), -CONH(C_1-C_6 alquil$_1$), -CON(C_1-C_6 alquil$_1$)(C_1-C_6 alquil$_1$), $-CO_2$(C_1-C_6 alquil$_1$), -CO(C_1-C_6 alquil$_1$), $-SO_{0-2}$(C_1-C_6 alquil$_1$),

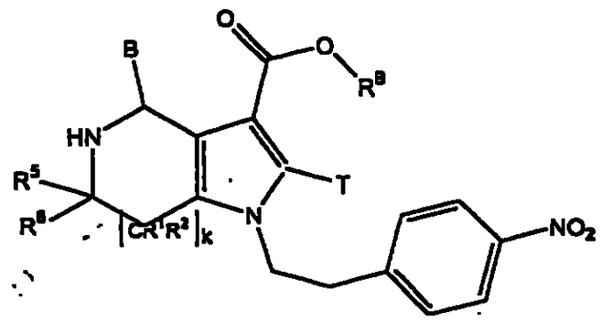
En donde C_1-C_6 alquil$_1$ se selecciona independientemente en cada ocasión y es recto, ramificado, o cíclico, puede contener 1 o dos enlaces dobles o triples, y es no sustituido o se sustituye con uno o más sustituyentes escogidos de hidroxi, oxo, halógeno, amino, ciano, nitro, alcoxi, grupo carbocíclico o heterocíclico, -COOH, $-SO_2NH_2$, $-SO_2NH$(C_1-C_4alquil), $-SO_2N$(C_1-C_4alquil)(C_1-C_4alquil), -N(C_1-C_4alquil)CO(C_1-C_4alquil), -N(C_1-C_4alquil)CO_2(C_1-C_4alquil), $-NHSO_2$(alquil), -N(C_1-C_4alquil)SO_2(C_1-C_4alquil), $-SO_2NHCO$(C_1-C_4alquil), $-CONHSO_2$(C_1-C_4alquil), -CONH(C_1-C_4alquil), -CON(C_1-

C_4alquil) (C_1-C_4alquil), -CO_2(C_1-C_4alquil), -CO(C_1-C_4alquil), y -SO_{0-2}(C_1-C_4alquil);

T se escoge de hidrógeno, halógeno, hidroxi, amina, (C_1-C_6)alquilo, y (C_1-C_6)alcoxi; y

R^B es hidrógeno, metilo, etilo y bencilo.

54. Un compuesto de la fórmula:



En donde

B es -SCH_3 o -$NH(CH_2)CH(OCH_3)_2$;

R^1 y R^2 se seleccionan independientemente en cada ocasión de hidrógeno, halógeno, hidroxi, ciano, nitro, amino, haloalquilo, mono- o diamino(C_1-C_6)alquilo, C_1-C_6 alquilo, C_2-C_6alquenilo, C_2-C_6alquinilo, y C_1-C_6 alcoxi, y k es 0, 1, 2, o 3;

R^5 y R^6 se escogen independientemente de hidrógeno, halógeno, hidroxi, nitro, ciano, C_1-C_6 alquil$_1$, amino, -COOH, -O(C_1-C_6 alquil$_1$), -NH(C_1-C_6 alquil$_1$), -N(C_1-C_6 alquil$_1$)(C_1-C_6 alquil$_1$), , -SO_2NH_2, -SO_2NH(C_1-C_6 alquil$_1$), -SO_2N(C_1-C_6 alquil$_1$)(C_1-C_6 alquil$_1$), -N(C_1-C_6 alquil$_1$)CO(C_1-C_6 alquil$_1$), -N(C_1-C_6 alquil$_1$)CO_2(C_1-C_6 alquil$_1$), -NHSO_2(C_1-C_6 alquil$_1$), -N(C_1-C_6 alquil$_1$)SO_2(C_1-C_6 alquil$_1$), -SO_2NHCO(C_1-C_6 alquil$_1$), -CONHSO_2(C_1-C_6 alquil$_1$), -CONH(C_1-C_6 alquil$_1$), -CON(C_1-C_6 alquil$_1$)(C_1-C_6 alquil$_1$), -CO_2(C_1-C_6 alquil$_1$), -CO(C_1-C_6 alquil$_1$), -SO_{0-2}(C_1-C_6 alquil$_1$),

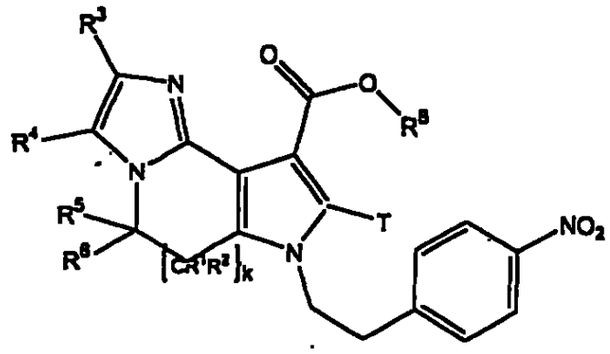
En donde C_1-C_6 alquil$_1$ se selecciona independientemente en cada ocasión y es recto, ramificado, o cíclico, puede contener 1 o dos enlaces dobles o triples, y es no sustituido o se sustituye con uno o más sustituyentes escogidos de hidroxi, oxo, halógeno, amino, ciano, nitro, alcoxi, grupo carbocíclico o heterocíclico, -COOH, -SO_2NH_2, -SO_2NH(C_1-C_4alquil), -SO_2N(C_1-C_4alquil)(C_1-C_4alquil), -N(C_1-C_4alquil)CO(C_1-C_4alquil), -N(C_1-C_4alquil)CO_2(C_1-C_4alquil), -NHSO_2(alquil), -N(C_1-C_4alquil)SO_2(C_1-C_4alquil), -SO_2NHCO(C_1-

C_4alquil), -$CONHSO_2$(C_1-C_4alquil), -CONH(C_1-C_4alquil), -CON(C_1-C_4alquil) (C_1-C_4alquil), -CO_2(C_1-C_4alquil), -CO(C_1-C_4alquil), y -SO_{0-2}(C_1-C_4alquil);

T se escoge de hidrógeno, halógeno, hidroxi, amino, (C_1-C_6)alquilo, y (C_1-C_6)alcoxi; y

R^B es hidrógeno, metilo, etilo y bencilo.

55. Un compuesto de la fórmula:



En donde

R^1 y R^2 se seleccionan independientemente en cada ocasión de hidrógeno, halógeno, hidroxi, ciano, nitro, amino, haloalquilo, mono- o diamino(C_1-C_6)alquilo, C_1-C_6 alquilo, C_2-C_6alquenilo, C_2-C_6alquinilo, y C_1-C_6 alcoxi, y k es 0, 1, 2, o 3;

R^5 y R^6 se escogen independientemente de hidrógeno, halógeno, hidroxi, nitro, ciano, C_1-C_6 alquil$_1$, amino, -COOH, -O(C_1-C_6 alquil$_1$), -NH(C_1-C_6 alquil$_1$), -N(C_1-C_6 alquil$_1$)(C_1-C_6 alquil$_1$), , -SO_2NH_2, -SO_2NH(C_1-C_6 alquil$_1$), -SO_2N(C_1-C_6 alquil$_1$)(C_1-C_6 alquil$_1$), -N(C_1-C_6 alquil$_1$)CO(C_1-C_6 alquil$_1$), -N(C_1-C_6 alquil$_1$)CO_2(C_1-C_6 alquil$_1$), -$NHSO_2$(C_1-C_6 alquil$_1$), -N(C_1-C_6 alquil$_1$)SO_2(C_1-C_6 alquil$_1$), -SO_2NHCO(C_1-C_6 alquil$_1$), -$CONHSO_2$(C_1-C_6 alquil$_1$), -CONH(C_1-C_6 alquil$_1$), -CON(C_1-C_6 alquil$_1$)(C_1-C_6 alquil$_1$), -CO_2(C_1-C_6 alquil$_1$), -CO(C_1-C_6 alquil$_1$), -SO_{0-2}(C_1-C_6 alquil$_1$),

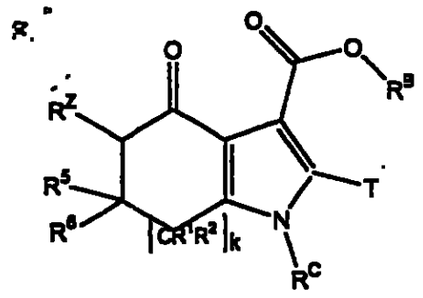
En donde C_1-C_6 alquil$_1$ se selecciona independientemente en cada ocasión y es recto, ramificado, o cíclico, puede contener 1 o dos enlaces dobles o triples, y es no sustituido o se sustituye con uno o más sustituyentes escogidos de hidroxi, oxo, halógeno, amino, ciano, nitro, alcoxi, grupo carbocíclico o heterocíclico, -COOH, -SO_2NH_2, -SO_2NH(C_1-C_4alquil), -SO_2N(C_1-C_4alquil)(C_1-C_4alquil), -N(C_1-

C_4alquil)CO(C_1-C_4alquil), -N(C_1-C_4alquil)CO_2(C_1-C_4alquil), -$NHSO_2$(alquil), -N(C_1-C_4alquil)SO_2(C_1-C_4alquil), -SO_2NHCO(C_1-C_4alquil), -$CONHSO_2$(C_1-C_4alquil), -CONH(C_1-C_4alquil), -CON(C_1-C_4alquil) (C_1-C_4alquil), -CO_2(C_1-C_4alquil), -CO(C_1-C_4alquil), y -SO_{0-2}(C_1-C_4alquil);

T se escoge de hidrógeno, halógeno, hidroxi, amino, (C_1-C_6)alquilo, y (C_1-C_6)alcoxi; y

R^B es hidrógeno, metilo, etilo y bencilo.

56. Un compuesto de la fórmula



k es 0, 1, 2, o 3;

R^B se escoge de hidrógeno, metilo, etilo y bencilo;

R^C se escoge independientemente en cada caso de t-butoxicarbonilo, fenilo, alquilsulfonilo, y etilcarbamoilo;

R^Z es hidrógeno o bromo;

R^1 y R^2 se seleccionan independientemente en cada ocasión de hidrógeno, halógeno, hidroxi, ciano, nitro, amino, haloalquilo, mono- o diamino(C_1-C_6)alquilo, C_1-C_6 alquilo, C_2-C_6alquenilo, C_2-C_6alquinilo, y C_1-C_6 alcoxi; y

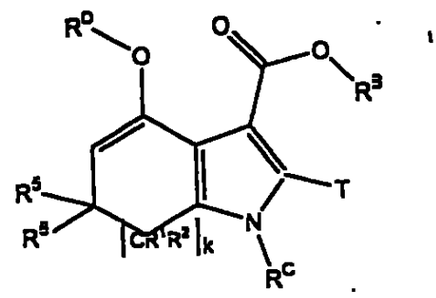
R^5 y R^6 se escogen independientemente de hidrógeno, halógeno, hidroxi, nitro, ciano, C_1-C_6 alquil$_1$, amino, -COOH, -O(C_1-C_6 alquil$_1$), -NH(C_1-C_6 alquil$_1$), -N(C_1-C_6 alquil$_1$)(C_1-C_6 alquil$_1$), , -SO_2NH_2, -SO_2NH(C_1-C_6 alquil$_1$), -SO_2N(C_1-C_6 alquil$_1$)(C_1-C_6 alquil$_1$), -N(C_1-C_6 alquil$_1$)CO(C_1-C_6 alquil$_1$), -N(C_1-C_6 alquil$_1$)CO_2(C_1-C_6 alquil$_1$), -$NHSO_2$(C_1-C_6 alquil$_1$), -N(C_1-C_6 alquil$_1$)SO_2(C_1-C_6 alquil$_1$), -SO_2NHCO(C_1-C_6 alquil$_1$), -$CONHSO_2$(C_1-C_6 alquil$_1$), -CONH(C_1-C_6 alquil$_1$), -CON(C_1-C_6 alquil$_1$)(C_1-C_6 alquil$_1$), -CO_2(C_1-C_6 alquil$_1$), -CO(C_1-C_6 alquil$_1$), -SO_{0-2}(C_1-C_6 alquil$_1$),

En donde C_1-C_6 alquil$_1$ se selecciona independientemente en cada ocasión y es recto, ramificado, o cíclico, puede contener 1 o dos enlaces dobles o triples, y es no sustituido o se sustituye con uno o más sustituyentes escogidos de hidroxi,

oxo, halógeno, amino, ciano, nitro, alcoxi, grupo carbocíclico o heterocíclico, -COOH, $-SO_2NH_2$, $-SO_2NH(C_1-C_4alquil)$, $-SO_2N(C_1-C_4alquil)(C_1-C_4alquil)$, $-N(C_1-C_4alquil)CO(C_1-C_4alquil)$, $-N(C_1-C_4alquil)CO_2(C_1-C_4alquil)$, $-NHSO_2(alquil)$, $-N(C_1-C_4alquil)SO_2(C_1-C_4alquil)$, $-SO_2NHCO(C_1-C_4alquil)$, $-CONHSO_2(C_1-C_4alquil)$, $-CONH(C_1-C_4alquil)$, $-CON(C_1-C_4alquil)(C_1-C_4alquil)$, $-CO_2(C_1-C_4alquil)$, $-CO(C_1-C_4alquil)$, y $-SO_{0-2}(C_1-C_4alquil)$; y

T se escoge de hidrógeno, halógeno, hidroxi, amina, (C_1-C_6)alquilo, y C_1-C_6 alcoxi.

57. Un compuesto de la fórmula



En donde:

k es 0, 1, 2, o 3;

R^B se escoge de hidrógeno, metilo, etilo y bencilo;

R^C se escoge independientemente en cada caso de t-butoxicarbonilo, fenilo, fenilsulfonilo, alquilsulfonilo, y etilcarbamoilo;

R^D se escoge de trimetilsililo, sililmetil éter, y t-butildimetilsililo;

R^1 y R^2 se seleccionan independientemente en cada ocasión de hidrógeno, halógeno, hidroxi, ciano, nitro, amino, haloalquilo, mono- o diamino(C_1-C_6)alquilo, C_1-C_6 alquilo, C_2-C_6alquenilo, C_2-C_6alquinilo, y C_1-C_6 alcoxi;

R^5 y R^6 se escogen independientemente de hidrógeno, halógeno, hidroxi, nitro, ciano, C_1-C_6 $alquil_1$, amino, -COOH, $-O(C_1-C_6$ $alquil_1)$, $-NH(C_1-C_6$ $alquil_1)$, $-N(C_1-C_6$ $alquil_1)(C_1-C_6$ $alquil_1)$, , $-SO_2NH_2$, $-SO_2NH(C_1-C_6$ $alquil_1)$, $-SO_2N(C_1-C_6$ $alquil_1)(C_1-C_6$ $alquil_1)$, $-N(C_1-C_6$ $alquil_1)CO(C_1-C_6$ $alquil_1)$, $-N(C_1-C_6$ $alquil_1)CO_2(C_1-C_6$ $alquil_1)$, $-NHSO_2(C_1-C_6$ $alquil_1)$, $-N(C_1-C_6$ $alquil_1)SO_2(C_1-C_6$ $alquil_1)$, $-SO_2NHCO(C_1-C_6$ $alquil_1)$, $-CONHSO_2(C_1-C_6$ $alquil_1)$, $-CONH(C_1-C_6$ $alquil_1)$, $-CON(C_1-C_6$

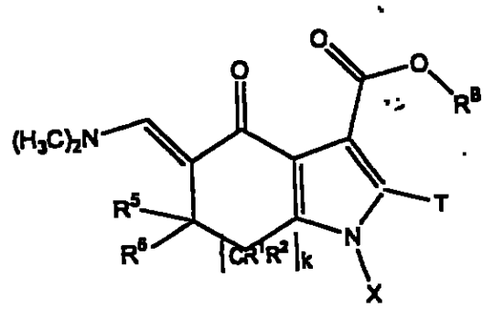
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alquil$_1$)(C_1-C_6 alquil$_1$), -CO_2(C_1-C_6 alquil$_1$), -CO(C_1-C_6 alquil$_1$), -SO_{0-2}(C_1-C_6 alquil$_1$),

En donde C_1-C_6 alquil$_1$ se selecciona independientemente en cada ocasión y es recto, ramificado, o cíclico, puede contener 1 o dos enlaces dobles o triples, y es no sustituido o se sustituye con uno o más sustituyentes escogidos de hidroxi, oxo, halógeno, amino, ciano, nitro, alcoxi, grupo carbocíclico o heterocíclico, -COOH, -SO_2NH_2, -SO_2NH(C_1-C_4alquil), -SO_2N(C_1-C_4alquil)(C_1-C_4alquil), -N(C_1-C_4alquil)CO(C_1-C_4alquil), -N(C_1-C_4alquil)CO_2(C_1-C_4alquil), -$NHSO_2$(alquil), -N(C_1-C_4alquil)SO_2(C_1-C_4alquil), -SO_2NHCO(C_1-C_4alquil), -$CONHSO_2$(C_1-C_4alquil), -CONH(C_1-C_4alquil), -CON(C_1-C_4alquil) (C_1-C_4alquil), -CO_2(C_1-C_4alquil), -CO(C_1-C_4alquil), y -SO_{0-2}(C_1-C_4alquil); y

T se escoge de hidrógeno, halógeno, hidroxi, amino, (C_1-C_6)alquilo, y C_1-C_6 alcoxi.

58. Un compuesto de fórmula



En donde:

k es 0, 1, 2, o 3;

R^B se escoge de hidrógeno, metilo, etilo y bencilo;

X se escoge de hidrógeno, hidroxi, amino, C_1-C_6 alquilo, y C_1-C_6 alcoxi;

R^1 y R^2 se seleccionan independientemente en cada ocasión de hidrógeno, halógeno, hidroxi, ciano, nitro, amino, haloalquilo, mono- o diamino(C_1-C_6)alquilo, C_1-C_6 alquilo, C_2-C_6alquenilo, C_2-C_6alquinilo, y C_1-C_6 alcoxi;

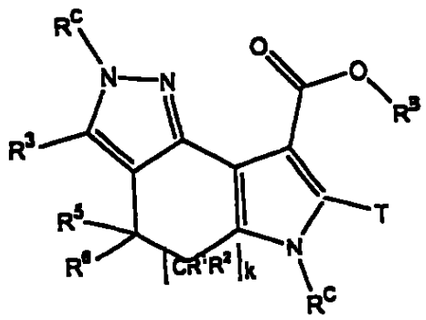
R^5 y R^6 se escogen independientemente de hidrógeno, halógeno, hidroxi, nitro, ciano, C_1-C_6 alquil$_1$, amino, -COOH, -O(C_1-C_6 alquil$_1$), -NH(C_1-C_6 alquil$_1$), -N(C_1-C_6 alquil$_1$)(C_1-C_6 alquil$_1$), , -SO_2NH_2, -SO_2NH(C_1-C_6 alquil$_1$), -SO_2N(C_1-C_6 alquil$_1$)(C_1-C_6 alquil$_1$), -N(C_1-C_6 alquil$_1$)CO(C_1-C_6 alquil$_1$),

$-N(C_1-C_6$ alquil$_1)CO_2(C_1-C_6$ alquil$_1)$, $-NHSO_2(C_1-C_6$ alquil$_1)$, $-N(C_1-C_6$ alquil$_1)SO_2(C_1-C_6$ alquil$_1)$, $-SO_2NHCO(C_1-C_6$ alquil$_1)$, $-CONHSO_2(C_1-C_6$ alquil$_1)$, $-CONH(C_1-C_6$ alquil$_1)$, $-CON(C_1-C_6$ alquil$_1)(C_1-C_6$ alquil$_1)$, $-CO_2(C_1-C_6$ alquil$_1)$, $-CO(C_1-C_6$ alquil$_1)$, $-SO_{0-2}(C_1-C_6$ alquil$_1)$,

En donde C_1-C_6 alquil$_1$ se selecciona independientemente en cada ocasión y es recto, ramificado, o cíclico, puede contener 1 o dos enlaces dobles o triples, y es no sustituido o se sustituye con uno o más sustituyentes escogidos de hidroxi, oxo, halógeno, amino, ciano, nitro, alcoxi, grupo carbocíclico o heterocíclico, -COOH, $-SO_2NH_2$, $-SO_2NH(C_1-C_4$alquil), $-SO_2N(C_1-C_4$alquil$)(C_1-C_4$alquil), $-N(C_1-C_4$alquil$)CO(C_1-C_4$alquil), $-N(C_1-C_4$alquil$)CO_2(C_1-C_4$alquil), $-NHSO_2$(alquil), $-N(C_1-C_4$alquil$)SO_2(C_1-C_4$alquil), $-SO_2NHCO(C_1-C_4$alquil), $-CONHSO_2(C_1-C_4$alquil), $-CONH(C_1-C_4$alquil), $-CON(C_1-C_4$alquil$)(C_1-C_4$alquil), $-CO_2(C_1-C_4$alquil), $-CO(C_1-C_4$alquil), y $-SO_{0-2}(C_1-C_4$alquil); y

T se escoge de hidrógeno, halógeno, hidroxi, amino, (C_1-C_6)alquilo, y C_1-C_6 alcoxi.

59. Un compuesto de la fórmula



En donde:

k es 0, 1, 2, o 3;

R^B se escoge de hidrógeno, metilo, etilo y bencilo;

R^C se escoge independientemente en cada caso de t-butoxicarbonilo, fenilo, fenilsulfonilo, alquilsulfonilo, y etilcarbamoilo;

R^1 y R^2 se seleccionan independientemente en cada ocasión de hidrógeno, halógeno, hidroxi, ciano, nitro, amino, haloalquilo, mono- o diamino(C_1-C_6)alquilo, C_1-C_6 alquilo, C_2-C_6alquenilo, C_2-C_6alquinilo, y C_1-C_6 alcoxi;

R^3 se define igual que R^5 y R^6;

R^5 y R^6 se escogen independientemente de hidrógeno, halógeno, hidroxi, nitro, ciano, C_1-C_6 alquil$_1$, amino, -COOH, -O(C_1-C_6 alquil$_1$), -NH(C_1-C_6 alquil$_1$), -N(C_1-C_6 alquil$_1$)(C_1-C_6 alquil$_1$), , $-SO_2NH_2$, $-SO_2NH(C_1$-C_6 alquil$_1$), $-SO_2N(C_1$-C_6 alquil$_1$)(C_1-C_6 alquil$_1$), -N(C_1-C_6 alquil$_1$)CO(C_1-C_6 alquil$_1$), -N(C_1-C_6 alquil$_1$)CO_2(C_1-C_6 alquil$_1$), $-NHSO_2(C_1$-C_6 alquil$_1$), -N(C_1-C_6 alquil$_1$)SO_2(C_1-C_6 alquil$_1$), $-SO_2NHCO(C_1$-C_6 alquil$_1$), $-CONHSO_2(C_1$-C_6 alquil$_1$), -CONH(C_1-C_6 alquil$_1$), -CON(C_1-C_6 alquil$_1$)(C_1-C_6 alquil$_1$), $-CO_2(C_1$-C_6 alquil$_1$), -CO(C_1-C_6 alquil$_1$), $-SO_{0-2}(C_1$-C_6 alquil$_1$),

En donde C_1-C_6 alquil$_1$ se selecciona independientemente en cada ocasión y es recto, ramificado, o cíclico, puede contener 1 o dos enlaces dobles o triples, y es no sustituido o se sustituye con uno o más sustituyentes escogidos de hidroxi, oxo, halógeno, amino, ciano, nitro, alcoxi, grupo carbocíclico o heterocíclico, -COOH, $-SO_2NH_2$, $-SO_2NH(C_1$-C_4alquil), $-SO_2N(C_1$-C_4alquil)(C_1-C_4alquil), -N(C_1-C_4alquil)CO(C_1-C_4alquil), -N(C_1-C_4alquil)CO_2(C_1-C_4alquil), $-NHSO_2$(alquil), -N(C_1-C_4alquil)SO_2(C_1-C_4alquil), $-SO_2NHCO(C_1$-C_4alquil), $-CONHSO_2(C_1$-C_4alquil), -CONH(C_1-C_4alquil), -CON(C_1-C_4alquil) (C_1-C_4alquil), $-CO_2(C_1$-C_4alquil), -CO(C_1-C_4alquil), y $-SO_{0-2}(C_1$-C_4alquil); y

T se escoge de hidrógeno, halógeno, hidroxi, amino, (C_1-C_6)alquilo, y C_1-C_6 alcoxi.

60. Un compuesto de conformidad con cualquiera de las reivindicaciones 1 a 36 para uso en el tratamiento terapéutico de una enfermedad o desorden asociado con la señalización de receptores $GABA_A$ patogénicos.

61. Una composición farmacéutica que comprende un compuesto de conformidad con una de las reivindicaciones 1 a 36 combinado con por lo menos un portador o excipiente farmacéuticamente aceptable.

62. Un método para el tratamiento de una enfermedad o desorden asociado con la señalización de receptores $GABA_A$ patogénicos, donde dicho método comprende la administración a un paciente en necesidad de dicho tratamiento o prevención de una cantidad efectiva de un compuesto de acuerdo con una de las

reivindicaciones 1 a 36.

63. Un método de acuerdo con la reivindicación 62 en donde dicha enfermedad o desorden asociado con la señalización de receptores $GABA_A$ patogénicos es ansiedad, depresión, desorden del sueño o deterioro cognitivo.

64. Un método de acuerdo con la reivindicación 62 en donde dicha enfermedad o desorden asociado con la señalización de receptores $GABA_A$ patogénicos es la enfermedad de Alzheimer, desorden de déficit de atención (ADD) o desorden de déficit de atención hiperactivo (ADHD).

65. El uso de un compuesto de acuerdo con una de las reivindicaciones 1 a 36 para la manufactura de un medicamento para el tratamiento de una enfermedad o desorden asociado con la señalización de receptores $GABA_A$ patogénicos.

66. El uso de un compuesto de acuerdo con una de las reivindicaciones 1 a 36 para la manufactura de un medicamento para el tratamiento de la ansiedad, depresión, desorden del sueño o deterioro cognitivo.

67. Un método para localizar receptores $GABA_A$ en una muestra de tejido que comprende:

Poner en contacto con la muestra un compuesto de acuerdo con una de las reivindicaciones 1 a 36, marcado de forma detectable, bajo condiciones que permitan la unión del compuesto con los receptores $GABA_A$, lavar la muestra para remover compuesto sin ligarse, y detectar el compuesto ligado.

68. Un método para inhibir la unión de un compuesto de benzodiazepina a un receptor $GABA_A$, dicho método comprende poner en contacto una solución de un compuesto de acuerdo con una de las reivindicaciones 1 a 36, con células que expresan dicho receptor en presencia de una benzodiazepina, en donde el compuesto está presente en la solución a una concentración suficiente para inhibir la unión de un compuesto de benzodiazepina a un receptor $GABA_A$ *in vitro*.

69. Un método para alterar la actividad transductora de señales de receptores $GABA_A$, dicho método comprende exponer las células que expresan dichos receptores a una solución de un compuesto de acuerdo con una de las reivindicaciones 1 a 36 a una concentración suficiente en la solución para inhibir la unión RO15-1788 a células que expresan receptores $GABA_A$ clonados humanos *in vitro*.

70. Una composición farmacéutica empacada que comprende la composición farmacéutica de la reivindicación 24 en un contenedor e instrucciones para usar la composición para tratar un paciente que sufra de un desorden que responda al agonismo, agonismo inverso o antagonismo del receptor $GABA_A$.

71. La composición farmacéutica empacada de la reivindicación 70 en donde dichas instrucciones indican que dicho paciente sufre de una o más de ansiedad, depresión, desordenes de sueño o deterioro cognitivo.

72. Un compuesto de acuerdo con una de las reivindicaciones 1 a 36 en donde en un ensayo de unión de receptor $GABA_A$, el compuesto exhibe un K_i en un receptor $GABA_A$ de 1 micromolar o menos.

73. Un compuesto de acuerdo con la reivindicación 72 en donde el compuesto exhibe un K_i de 100 nanomolar o menos.

74. Un compuesto de acuerdo con la reivindicación 72 en donde el compuesto exhibe un K_i de 10 nanomolar o menos.

967

RESUMEN DE LA DIVULGACIÓN

Se describen nuevos compuestos heterocíclicos como 5,6-dihidro-4H-1,3a,6-triaza-as-indacenos, ácidos 3-tia- 1,7-diaza-ciclopenta [e]azulen -9- carboxílicos, ácidos 4,5,6,7-tetrahidro-1-oxa- 2,7-diaza- ciclopenta [e]azulen-1-carboxílicos, ácidos 3,8,10- triaza- benzo [e] azulen -1-carboxílicos, ácidos 1-oxa-2,7-diaza-ciclopenta[e]azulen-9-carboxílicos, fenil amidas de ácido 1,3,7-triaza-ciclopenta[e] azulen-9-carboxílico y compuestos relacionados. Dichos compuestos son agonistas, agonistas inversos o antagonistas altamente selectivos para los receptores $GABA_A$ del cerebro o prodrogas de agonistas, agonistas inversos o antagonistas altamente selectivos para los receptores $GABA_A$ del cerebro y por lo tanto son útiles en el diagnóstico y tratamiento de la ansiedad, depresión, síndrome de Down, desordenes y ataques del sueño, sobredosis con drogas de benzodiazepina y para el mejoramiento de la memoria. También se proporcionan composiciones farmacéuticas que incluyen composiciones farmacéuticas empacadas. Los compuestos de la invención también son útiles como pruebas para la localización de receptores $GABA_A$ en muestras de tejido.