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ART
44

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RINTENDENCIA

01-84452

DELEGATURA DE PROPIEDAD INDUSTRIAL

DIVISIÓN DE NUEVAS CREACIONES

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
INVENTARIO

SOLICITUD DE PATENTE DE INVENCIÓN

TITULO: AGONISTAS DE ADRENORECEPTORES ALFA2C

SOLICITANTE: SCHERING CORPORATION and PHARMACOPEIA, LLC

DIRECCIÓN: 2000 Galloping Hill Road, Kenilworth, NJ 07033-0530 E.U.A. y 10275 Science Center Drive, San Diego, California 92121 E.UA.

APODERADO: CARLOS R. OLARTE

BOGOTÁ 12 de Agosto de 2009

P2009/80014

FN. 13-04-2004

OLARTERAISBECK
OLARTE RAISBECK MOURE

Industria y Comercio
SUPERINTENDENCIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 09-084452- -00000-0000
Fecha: 2009-08-12 17:47:12 Dep. 2020 NUECREACIONI
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 380

PETITORIO - FORMULARIO ÚNICO DE SOLICITUD
PATENTE PCT
ENTRADA EN FASE NACIONAL **P2009/000149**

SOLICITUD DE:

(1) [X] Patente de Invención. [ ] Patente de Modelo de Utilidad.

[X] Capítulo I. [ ] Capítulo II.

(2) **SOLICITANTE (71)**

Nombre: SCHERING CORPORATION y PHARMACOPEIA, LLC
Dirección: 2000 Galloping Hill Road, Kenilworth, NJ 07033-0530 E.U.A. y 10275 Science Center Drive, San Diego, California 92121 E.U.A
Nacionalidad o Domicilio: Estadounidenses
Lugar de Constitución: Estados Unidos
Teléfono: _____ **Fax:** _____
E-mail: _____

IDENTIFICACIÓN
C.C. [ ] **NIT** [ ]
C.E. [ ] **Otro** [ ]
Cual _____
Número _____

REPRESENTANTE O APODERADO

Nombre: CARLOS R. OLARTE
Dirección: World Trade Center, Torre A, Calle 100 No. 8A-37 Piso 10.
Teléfono: 601-7700 **Fax:** 601-7799
E-mail: office@olarteraisbeck.com

IDENTIFICACIÓN
C.C. [x] **NIT** [ ]
C.E. [ ] **Otro** [ ]
Cual _____
Número 79.782.747 Btá
TP 74.295

INVENTOR (ES) (72)

Nombre: VER PAGINA ADJUNTA
Dirección: VER PAGINA ADJUNTA
Nacionalidad o Domicilio: VER PAGINA ADJUNTA

(5) **PCT (86)**

Solicitud Internacional No. PCT/US2008/001776 Fecha Febrero 11, 2008

Publicación Internacional No. WO 2008/100463 Fecha Agosto 21, 2008

(6) **Título (54 DERIVADOS DE 3,4-DIHIDRO-1,4-BENZOXAZINA, 3,4-DIHIDRO-1, 4-BENZOTIAZINA Y 1,2,3,4-TETRAHIDRO-QUINOXALINA COMO AGONISTAS DE LOS ADRENORECEPTORES ALPHA2C**

Clasificación Internacional (51) A61K 31/4985, A61K 31/5383, A61K 31/42, C07D 403/06, C07D 413/06, C07D 143/14, C07D 417/06, C07D 471/04, C07D 498/04, A61P 11/02, A61P 29/00, A61P 25/24, A61P 27/04

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SI [X] **NO** [ ]

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US	Febrero 13, 2007	11/705,673

(9) **Comprobante de pago No.** 09-59,432 **Fecha** Agosto 11 de 2009

ANEXOS

2

- [x] Comprobante de pago de la tasa de presentación de la solicitud.
- [x] Documento que acredita la existencia y representación legal cuando el solicitante sea persona jurídica.
- [x] Poderes, si fuere el caso. Adjunto copia simple ver expediente No. 07-003.682
- [ ] Documento de cesión del inventor al solicitante o a su causante.
- [ ] Declaraciones
- [x] Copia de la solicitud internacional. (Resumen, descripción, reivindicaciones, dibujos).
- [x] Traducción de la solicitud internacional al castellano. (Resumen, descripción, reivindicaciones, dibujos).
- [ ] Copia del examen preliminar internacional efectuado por la Autoridad Internacional de Examen Preliminar (IPEA).
- [ ] Traducción del examen preliminar internacional efectuado por la IPEA.
- [ ] De ser el caso, copia del contrato de acceso.
- [ ] De ser el caso, documento que acredite la licencia o autorización de uso de conocimientos tradicionales de las comunidades indígenas.
- [ ] De ser el caso, certificado de depósito del material biológico.
- [ ] Arte final 12 x 12.
- [ ] De ser el caso, información sobre otras solicitudes de patente o títulos obtenidos en el extranjero por el mismo titular o su causante, relacionadas parcial o totalmente con la invención de esta solicitud.
- [x] De ser el caso, modificaciones efectuadas a la solicitud internacional.
- [x] Otros. Búsqueda Internacional

(11) **FIGURA CARACTERÍSTICA:**

(12) Solicito la concesión de la patente,

NOMBRE: CARLOS R. OLARTE FIRMA:

C.C. 79.782.747 Btá T.P. 74.295

Instrucciones para el diligenciamiento del presente formulario, ver reverso de esta página.

LISTA DE INVENTORES

PCT/US2008/001776

1. Kevin D. MCCORMICK,
15 Brookfield Drive, Basking Ridge,
New Jersey 07920
Estados Unidos
Nacionalidad: Estadounidense

2. Christopher W. BOYCE,
71 Bonnell Street, Flemington,
New Jersey 08822
Estados Unidos
Nacionalidad: Estadounidense

3. Neng-yang SHIH,
2 Tyler Road, Lexington,
Massachusetts 02420
Estados Unidos
Nacionalidad: Estadounidense

4. Robert G. ASLANIAN,
144 Phillip Drive, Rockaway,
New Jersey 07866
Estados Unidos
Nacionalidad: Estadounidense

5. Salem FEVRIER,
8 Washington Place, Cranford,
New Jersey 07016
Estados Unidos
Nacionalidad: Estadounidense

6. Pietro MANGIARACINA,
4 Montclair Avenue, Monsey,
New York 10952
Estados Unidos
Nacionalidad: Estadounidense

7. Manuel DE LERA RUIZ,
1236 Magnolia Lane;
Branchburg, New Jersey 08876
Estados Unidos
Nacionalidad: Española

8. Younong YU,
280 Bromley Place,
East Brunswick,
New Jersey 08816
Estados Unidos
Nacionalidad: China

LISTA DE INVENTORES

PCT/US2008/001776

9. Junying ZHENG,
49 Wexford Way, Bridgewater,
New Jersey 08807
Estados Unidos
Nacionalidad: Estadounidense

10. Chia-yu HUANG,
319 Oak Lane, Princeton Junction,
New Jersey 08550
Estados Unidos
Nacionalidad: Estadounidense

11. Bo LIANG,
239 Bromley Place,
East Brunswick, New Jersey 08816
Estados Unidos
Nacionalidad: China

12. Rong-Qiang LIU,
15 Shepherd Way, Kendall Park,
New Jersey 08824
Estados Unidos
Nacionalidad: Estadounidense

13. Ruiyan LIU,
496 Kings Road, Yardley,
Pennsylvania 19067
Estados Unidos
Nacionalidad: Estadounidense

14. Lisa GUISE ZAWACKI,
1226 Pebble Court, Yardley,
Pennsylvania 19067
Estados Unidos
Nacionalidad: Estadounidense

5

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 09 - 59,432
FECHA : AGOSTO 11 DE 2009

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Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 380

***** C O N S I G N A C I O N *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
OLARTE RAISBEK	CONSIGNACION	BANCO DE BOGOTA	062754387	105797716	11/08/2009	9,384,000.00

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

CANT.	RENTISTICO	CONCEPTO		TOTAL CONCEPTO
1	50005-01-01 SOLICITUDES	1	TRAMITES DE SOL. DE PATENTE DE IN	540,000.00
			TOTAL : $	540,000.00

SON: QUINIENTOS CUARENTA MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No._____

Traducción oficial del Inglés por Marlén Neira Castro, resolución 2117 del Ministerio de Justicia de Colombia

APOSTILLA EN PODER DE REPRESENTACIÓN DE

SCHERING CORPORATION

APOSTILLA

(Convención de la Haya del 5 de octubre de 1961)

1. País: Estados Unidos de América
   - Este documento Público
2. ha sido firmado por Marguerite La Corte
3. Quien ejerce funciones de Notario público de Nueva Jersey
4. Lleva el sello de Marguertie La Corte Notario

CERTIFICADO

5. En Trenton, Nueva Jersey
6. El 29 de agosto 2003
7. Por John E. McCormac Contador Publico- Tesorero de Nueva Jersey 8. No. A 180345
9. Gran Sello del Estado de Nueva Jersey
10. Firma legible de John M.

PODER DE REPRESENTACIÓN

Bilingüe inglés- español otorgado en Kenilworth, Nueva Jersey, Estados Unidos, el 7 de agosto de 2003 y firmado por Edward H. Mazer - Director Juridico senior.

CERTIFICADO NOTARIAL

Bilingüe inglés- español, fechado el 7 de agosto, 2003 certificando las funciones de Edward H. Mazer - Director Juridico senior, de Schering Corporation.

Las certificaciones anteriores se basan en el Poder de representación fechado el 4 noviembre de 2002.

Sello: Marguerite La Corte- Notario público,
Estado de Nueva Jersey
Su comisión vence el 7 de octubre de 2003.
Sello en alto relieve del Notario Público

Es traducción fiel del inglés, con copia archivo, para confrontación. Bogotá 5 septiembre, 2003.

MARLEN NEIRA CASTRO
Traductor e Intérprete Oficial
Inglés - Español - Inglés
Resolución No. 2117 del 7 Oct 1987

APOSTILLE

(CONVENTION DE LA HAYE DU 5 OCTOBRE 1961)

1. COUNTRY: UNITED STATES OF AMERICA

2. THIS PUBLIC DOCUMENT HAS BEEN SIGNED BY:
MARGUERITE LA CORTE

3. ACTING IN THE CAPACITY OF:
NOTARY PUBLIC OF NEW JERSEY

4. BEARS THE SEAL/STAMP OF:
MARGUERITE LA CORTE, NOTARY

CERTIFIED

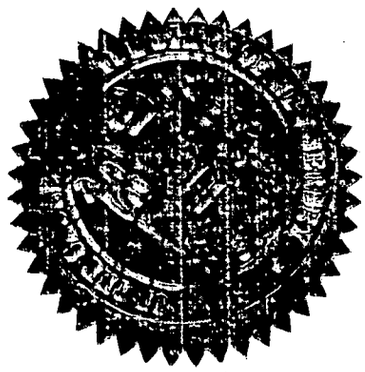
5. AT TRENTON, NEW JERSEY

6. THE 29TH DAY OF AUGUST 2003

7. BY: John E McCormac, CPA, NEW JERSEY TREASURER

8. NO. A180345

9. SEAL/STAMP:



10. SIGNATURE

OLARTERAISBECK

OLARTE RAISBECK & FRIERI, LTDA.
LEGAL & PROFESSIONAL SERVICES

WORLD TRADE CENTER – TORRE C
CALLE 100 NO. 8A-55 PISO 10
BOGOTA, COLOMBIA
TELEPHONE: +57-1 638-6200
FAX: +57-1 638-6201

www.olarteraisbeck.com

Power of Attorney

The undersigned,
SCHERING CORPORATION
domiciled in
2000 Galloping Hill Road, Kenilworth, New Jersey 07033–0532, U.S.A.

by means of these presents hereby grants to **Carlos R. Olarte and/or Ana María Frieri** full and sufficient Power of Attorney to file, prosecute, obtain, defend and enforce any and all of the company's **Patents, Utility Models and Industrial Designs** in the Republic of Colombia, to which end it empowers them to take all steps necessary before any administrative or judicial authority of any class for the objects stated, to file petitions, appeals, replies and oppositions, pay taxes and annuities, request testimonies, receive documents and securities, abandon applications and collect refunds. Sufficient power is hereby granted to receive notifications on behalf of the Company, to confer powers on those who are to represent the company judicially and extrajudicially, to answer in court in the matter of all claims and demands that may be presented in connection with the objects stated, giving them likewise power to substitute these presents and revoke such substitutions.

Poder

El suscrito,

domiciliado en
2000 Galloping Hill Road, Kenilworth, New Jersey 07033–0532, U.S.A.

por medio del presente otorga a **Carlos R. Olarte y/o Ana María Frieri** poder especial, amplio y suficiente para presentar, tramitar, obtener, defender y hacer respetar todas y cualquiera de **Patentes, Modelos de Utilidad y Diseños Industriales** de la compañía en la República de Colombia, a cuyo efecto los faculta para dar todos los pasos necesarios ante cualquier autoridad administrativa o judicial de cualquier jerarquía para cumplir con lo encomendado, elevar solicitudes, apelaciones, respuestas y oposiciones, pagar impuestos y anualidades, solicitar testimonios, recibir documentos y valores, desistir y percibir. Se concede poder bastante para recibir notificaciones a nombre de la compañía, otorgar poderes a quienes vayan a representar a la compañía judicial y extrajudicialmente, responder en juicio a todas las reclamaciones o demandas que por motivo de lo encomendado se presentaren, dándoles asimismo facultad para sustituir el presente y revocar dichas sustituciones.

Signature/Firma: _____
Edward H. Mazer, Senior Legal Director

Date/Fecha: **August 7, 2003**

City,Country/Ciudad,Pais: **Kenilworth, New Jersey, U.S.A.**

OLARTERAISBECK

OLARTE RAISBECK & FRIERI, LTDA.
LEGAL & PROFESSIONAL SERVICES

WORLD TRADE CENTER – TORRE C
CALLE 100 NO. 8A-55 PISO 10
BOGOTA, COLOMBIA
TELEPHONE: +57-1 638-6200
Fax: +57-1 638-6201

www.olarteraisbeck.com

Notarial Certification

On this date, August 7, 2003

The undersigned Notary Public certifies:

1. That Edward H. Mazer

of legal age and domiciled in 119 Greenwood Drive, Millburn, New Jersey 07041, U.S.A. signed the foregoing document.

2. That the grantor has executed the foregoing document as Senior Legal Director of SCHERING CORPORATION

3. That SCHERING CORPORATION having its principal place of business located in 2000 Galloping Hill Road, Kenilworth, New Jersey 07033-0530, U.SA.. is duly incorporated, is currently in existence, and that the purposes for which the Power of Attorney is granted are within the scope of its corporate purposes.

4. That the grantor has the authority to execute the Power of Attorney and that his/her representation is legal.

5. The foundation for my certifications contained in points 2, 3 and 4 was the exhibition of the following authentic document(s):

Power of Attorney, dated November 4, 2002.

Certificación Notarial

En esta fecha,

el Notario Público suscrito certifica:

1. Que

mayor de edad y domiciliado

suscribió el documento que antecede.

2. Que el otorgante ha suscrito el referido documento en su carácter de

de

4. Que

con sede principal ubicada en

está legalmente constituida, que tiene existencia legal vigente y que los propósitos para los cuales se otorga el poder se encuentra dentro de los que comprenden su objeto social.

4. Que el otorgante tiene la representación para suscribir el poder, y que ésta es legítima.

5. El fundamento de mis certificaciones contenidas en los puntos 2, 3 y 4 fue la exhibición de los (del) siguiente(s) documento(s) auténtico(s):

NOTARY PUBLIC (Signature):

Marguerite La Corte

Marguerite La Corte
Notary Public of New Jersey
My Commission Expires October 7, 2003

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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A61K 31/42 (2006.01) *A61P 11/02* (2006.01)
C07D 403/06 (2006.01) *A61P 29/00* (2006.01)
C07D 413/06 (2006.01) *A61P 25/24* (2006.01)
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(71) Applicants *(for all designated States except US)*: **SCHERING CORPORATION** [US/US]; 2000 Galloping Hill Road, Kenilworth, New Jersey 07033-0530 (US). **PHARMACOPEIA, INC.** [US/US]; 3000 Eastpark Boulevard, Cranbury, New Jersey 08512 (US).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: **MCCORMICK, Kevin, D.** [US/US]; 15 Brookfield Drive, Basking Ridge, New Jersey 07920 (US). **BOYCE, Christopher, W.** [US/US]; 71 Bonnell Street, Flemington, New Jersey 08822 (US). **SHIH, Neng-yang** [US/US]; 2 Tyler Road, Lexington, Massachusetts 02420 (US). **ASLANIAN, Robert, G.** [US/US]; 144 Philip Drive, Rockaway, New Jersey 07866 (US). **FEVRIER, Salem** [US/US]; 8 Washington Place, Cranford, New Jersey 07016 (US). **MANGIARACINA, Pietro** [US/US]; 4 Montclair Avenue, Monsey, New York 10952 (US). **DE LERA RUIZ, Manuel** [ES/US]; 1236 Magnolia Lane, Branchburg, New Jersey 08876 (US). **YU, Younong** [CN/US]; 280 Bromley Place, East Brunswick, New Jersey 08816 (US). **ZHENG, Junying** [CN/US]; 49 Wexford Way, Bridgewater, New Jersey 08807 (US). **HUANG, Chia-yu** [US/US]; 319 Oak Lane, Princeton Junction, New Jersey 08550 (US). **LIANG, Bo** [CN/US]; 239 Bromley Place, East Brunswick, New Jersey 08816 (US). **LIU, Rong-Qiang** [US/US]; 15 Shepherd Way, Kendall Park, New Jersey 08824 (US). **LIU, Ruiyan** [US/US]; 496 Kings Road, Yardley, Pennsylvania 19067 (US). **GUISE ZAWACKI, Lisa** [US/US]; 1226 Pebble Court, Yardley, Pennsylvania 19067 (US).

(74) Agent: **RUSSELL, Mark, W.**; Schering-Plough Corporation, Patent Department, K-6-1 1990, 2000 Galloping Hill Road, Kenilworth, New Jersey 07033-0530 (US).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MT, NL, NO, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*
— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

(54) Title: 3,4-DIHYDR0-L,4-BENZ0XAZINE, 3, 4-DIHYDR0-1, 4-BENZOTHIAZINE AND 1,2,3,4-TETRAHYDRO-QUINOXALINE DERIVATIVES AS ALPHA2C ADRENORECEPTOR AGONISTS

(57) Abstract: The present invention relates to a novel class of phenylmorpholine and phenyl thiomorpholine compounds useful as alpha2C adrenergic receptor agonists, pharmaceutical compositions containing the compounds, and methods of treatment, prevention, inhibition,- or amelioration of one or more diseases associated with the alpha2C adrenergic receptor agonists, such as allergic rhinitis, congestion, pain, diarrhea, glaucoma, congestive heart failure, cardiac ischemia, manic disorders, depression, anxiety and schizophrenia.

WO 2008/100463 A1

3,4-DIHYDRO-1,4-BENZOXAZINE, 3,4-DIHYDRO-1,4-BENZOTHIAZINE AND 1,2,3,4-TETRAHYDRO-QUINOXALINE DERIVATIVES AS ALPHA2C ADRENORECEPTOR AGONISTS

Field of the Invention

The present invention relates to phenylmorpholine and phenylthiomorpholine compounds useful as α2C adrenergic receptor agonists, pharmaceutical compositions containing the compounds, and methods of treatment and prevention using the compounds and compositions to treat disease states such as congestion (including nasal congestion), migraine, congestive heart failure, cardiac ischemia, pain, glaucoma, and psychotic disorders without substantial adverse side effects associated with α2A receptor agonist treatments.

Background of the Invention

The initial classification of adrenergic receptors into α- and β-families was first described by Ahlquist in 1948 (Ahlquist RP, "A Study of the Adrenergic Receptors," Am. J. Physiol. 153:586-600 (1948)). Functionally, the α-adrenergic receptors were shown to be associated with most of the excitatory functions (vasoconstriction, stimulation of the uterus and pupil dilation) and B-adrenergic receptors were implicated in vasodilation, bronchodilation and myocardial stimulation (Lands et al., "Differentiation of Receptor Systems Activated by Sympathomimetic amines," Nature 214:597-598 (1967)). Since this early work, α-adrenergic receptors have been subdivided into α1 - and α2-adrenergic receptors. Cloning and expression of α-adrenergic receptors have confirmed the presence of multiple subtypes of both α1 - (α1A, α1B, α1D) and α2-(α2A, α2B, α2C) adrenergic receptors (Michel et al., "Classification of α_1 -Adrenoceptor Subtypes," Naunyn-Schmiedeberg's Arch. Pharmacol, 352:1-10 (1995); Macdonald et al., "Gene Targeting--Homing in on α_2 -Adrenoceptor-Subtype Function," TIPS, 18:211-219 (1997)).

Current therapeutic uses of α2 adrenergic receptor drugs involve the ability of those drugs to mediate many of the physiological actions of the endogenous catecholamines. There are many drugs that act on these receptors to control hypertension, intraocular pressure, eye reddening and nasal congestion and induce analgesia and anesthesia.

α2 adrenergic receptors can be found in the rostral ventrolateral medulla, and are known to respond to the neurotransmitter norepinephrine and the antihypertensive

drug clonidine to decrease sympathetic outflow and reduce arterial blood pressure (Bousquet et al., "Role of the Ventral Surface of the Brain Stem in the Hypothesive Action of Clonidine," Eur. J. Pharmacol., 34:151-156 (1975); Bousquet et al., "Imidazoline Receptors: From Basic Concepts to Recent Developments," 26:S1-S6 (1995)). Clonidine and other imidazolines also bind to imidazoline receptors (formerly called imidazoline-guanidinium receptive sites or IGRS) (Bousquet et al., "Imidazoline Receptors: From Basic Concepts to Recent Developments," 26:S1-S6 (1995)). Some researchers have speculated that the central and peripheral effects of imidazolines as hypotensive agents may be related to imidazoline receptors (Bousquet et al., "Imidazoline Receptors: From Basic Concepts to Recent Developments," 26:S1-S6 (1995); Reis et al., "The Imidazoline Receptor: Pharmacology, Functions, Ligands, and Relevance to Biology and Medicine," Ann. N.Y. Acad. Sci., 763:1-703 (1995).

Compounds which have adrenergic activity are well known in the art, and are described in numerous patents and scientific publications. The two main families of adrenergic receptor are termed alpha adrenergic receptors and beta adrenergic receptors in the art, and each of these two families is known to have subtypes, which are designated by letters of the alphabet, such as α2A, α2B, and α2C. It is generally known that adrenergic activity is useful for treating animals of the mammalian species, including humans, for curing or alleviating the symptoms and conditions of numerous diseases and conditions. In other words, it is generally accepted in the art that pharmaceutical compositions having an adrenergic compound or compounds as the active ingredient are useful for treating, among other things, glaucoma, chronic pain, migraines, heart failure, and psychotic disorders. It is also known that compounds having adrenergic activity, such as α2A agonists, may be associated with undesirable side effects. Examples of such side effects include hyper-and hypotension, sedation, locomotor activity, and body temperature variations.

It has been discovered in accordance with the present invention that adrenergic compounds that act selectively, and preferably even specifically, as agonists of the α2C or the α2B/α2C (hereinafter referred to as α2C or α2B/2C) receptor subtypes in preference over the α2A receptor subtype, with adrenergic compounds that are functionally selective agonists of the α2C receptor subtype in preference over the α2A receptor subtype and α2B/2C receptor subtype, possess desirable therapeutic properties associated with adrenergic receptors but without having one or more

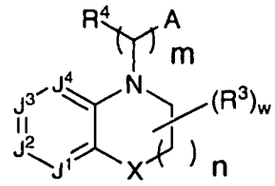
undesirable side effects such as changes in blood pressure (e.g., a hypertensive or hypotensive effect) or sedation. For the purposes of this present invention, a compound is defined to be an active agonist of the α2C receptor subtype if the compound's efficacy at the α2C receptor is ≥ 30% E_{max} (GTPγS assay). A compound is a functionally selective agonist of the α2C receptor subtype over the α2A receptor subtype if the compound's efficacy at the α2C receptor is ≥ 30% E_{max} (GTPγS assay) and its efficacy at the α2A receptor is ≤ 30% E_{max} (GTPγS assay).

There is a need for new compounds, formulations, treatments and therapies to treat diseases and disorders associated with α2C adrenergic receptors. Furthermore , there is a need to develop compounds that are functionally selective for the α2C receptor subtype with respect to the α2A receptor subtype or the α2B/α2C receptor subtype. It is, therefore, an object of this invention to provide compounds useful in the treatment or prevention or amelioration of such diseases and disorders.

Summary of the Invention

In its many embodiments, the present invention provides a novel class of heterocyclic compounds as active or functionally selective α2C adrenergic receptor agonists or metabolites, stereoisomers (e.g., enantiomers or diasteromers) salts, solvates or polymorphs thereof, methods of preparing such compounds, pharmaceutical compositions comprising one or more such compounds, methods of preparing pharmaceutical formulations comprising one or more such compounds, and methods of treatment, prevention, inhibition or amelioration of one or more conditions associated with α2C receptors using such compounds or pharmaceutical compositions.

In one aspect, the present application discloses a compound, or pharmaceutically acceptable salts or metabolites, solvates or polymorphs of said compound, said compound having the general structure shown in Formula I:



Formula I

wherein:

A is a 5-membered heterocyclic ring containing 1-3 heteroatoms, and is optionally substituted with at least one R^5 and/or 1 or 2 (=O) (carbonyl) groups;

X is -O-, $-S(O)_p-$, or $-N(R^6)-$;

J^1, J^2, J^3, and J^4 are independently -N-, -N(O)- or $-C(R^2)-$, provided that 0-3 of J^1, J^2, J^3 and J^4 are –N-;

R^2 is independently selected from the group consisting of H, -OH, halo, -CN, $-NO_2$, $-S(O)_pR^7$, $-NR^7R^{7'}$ $-[C(R^a)(R^b)]_qYR^{7'}$, $-[C(R^a)(R^b)]_qN(R^7)YR^{7'}$, $C(R^a)(R^b)]_qOYR^{7'}$, $-[C(R^a)(R^b)]_qON=CR^7R^{7'}$, $-P(=O)(OR^7)(OR^{7'})$, $-P(=O)NR^7R^{7'}$, and $-P(=O)R^8{}_2$, and alkyl, alkoxy, alkenyl, alkenyloxy, alkynyl, cycloalkyl, cycloalkoxy, aryl, aryloxy, arylalkyl, heteroaryl, heteroarylalkyl, heterocyclyl, and heterocyclylalkyl groups optionally substituted with at least one R^5;

Y is selected from the group consisting of a bond, -C(=O)-, $-C(=O)NR^7-$, $-C(=O)O-$, $-C(=NR^7)-$, $-C(=O)-[C(R^a)(R^b)]_{n'}-O-C(=O)-$, $-C(=O)N(R^c)-O-$, $-C(=NOR^7)-$, $-C(=NR^7)NR^7-$, $-C(=NR^7)N(R^c)O-$, $-S(O)_p-$, $-SO_2NR^7-$, and $-C(S)NR^7-$;

wherein R^a and R^b are independently selected from the group consisting of H, alkyl, alkoxy, and halo,

R^c is H or alkyl;

R^3 is independently selected from the group consisting of H, (=O), AND halo, and alkyl, alkoxy, alkenyl, alkenyloxy, alkynyl, cycloalkyl, cycloalkoxy, aryl, aryloxy, arylalkyl, heteroaryl, heteroarylalkyl, heterocyclyl, and heterocyclylalkyl groups optionally substituted with at least one R^5, provided that when n is 3 or 4, no more than 2 of the R^3 groups may be (=O);

R^4 is independently selected from the group consisting of H, -CN, and halo, and alkyl, alkoxy, alkenyl, alkenyloxy, alkynyl, cycloalkyl, cycloalkoxy, aryl, aryloxy, arylalkyl, heteroaryl, heteroarylalkyl, heterocyclyl, and heterocyclylalkyl groups optionally substituted with at least one R^5;

R^5 is independently selected from the group consisting of H, halo, -OH, -CN, $-NO_2$, $-NR^7R^{7'}$, and $-S(O)_pR^7$, and alkyl, alkoxy, alkenyl, alkenyloxy, alkynyl, cycloalkyl, cycloalkoxy, aryl, aryloxy, arylalkyl, heteroaryl, heteroarylalkyl, heterocyclyl, and heterocyclylalkyl groups, each of which is optionally substituted with at least one of halo, -OH, -CN, $-NO_2$, $-NR^7R^{7'}$, and $-S(O)_pR^7$ substituents and/or 1 or 2 (=O) groups;

R^6 is independently selected from the group consisting of H and alkyl, alkoxy, alkenyl, alkenyloxy, alkynyl, cycloalkyl, cycloalkoxy, aryl, aryloxy, arylalkyl, heteroaryl,

heteroarylalkyl, heterocyclyl, and heterocyclylalkyl groups, each of which is optionally substituted with at least one of halo, -OH, -CN, $-NO_2$, $-NR^7R^{7'}$, and $-S(O)_pR^7$ substituents and/or 1 or 2 (=O) groups, and $-C(=O)R^7$, $-C(=O)OR^7$, $-C(=O)NR^7R^{7'}$, $-SO_2R^7$ and $-SO_2NR^7R^{7'}$;

R^7 is independently selected from the group consisting of H and alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, cyclocyclenyl, cyclocyclenylalkyl, aryl, arylalkyl, heterocyclyl, heterocyclylalkyl, heterocyclenyl, heterocyclenylalkyl, heteroaryl, and heteroarylalkyl, groups, each of which is optionally substituted one or more times (preferably 1 to 5, more preferably 1 to 3) by R^{12};

$R^{7'}$ is independently selected from the group consisting of H and alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, cyclocyclenyl, cyclocyclenylalkyl, aryl, arylalkyl, heterocyclyl, heterocyclylalkyl, heterocyclenyl, heterocyclenylalkyl, heteroaryl, and heteroarylalkyl, groups, each of which is optionally substituted one or more times (preferably 1 to 5, more preferably 1 to 3) by R^{12}; or

R^7 and $R^{7'}$ together with the nitrogen atom to which they are attached form a 3- to 8-membered heterocyclyl, heterocyclenyl or heteroaryl ring having, in addition to the N atom, 1 or 2 additional hetero atoms selected from the group consisting of O, N, $-N(R^9)-$ and S, wherein said rings are optionally substituted by 1 to 5 independently selected R^5 moieties and/or 1 or 2 (=O) groups,

R^8 is independently selected from the group consisting of alkyl, alkenyl, alkynyl, cycloalkyl, aryl, arylalkyl, heteroaryl, and heteroarylalkyl groups, each of which is optionally substituted with at least one of halo, -OH, -CN, $-NO_2$, $-N(R^{11})_2$, and $-S(O)_pR^{11}$ substituents and/or 1 or 2 (=O) groups;

R^9 is independently selected from the group consisting of H, $-C(O)-R^{10}$, $-C(O)-OR^{10}$, and $-S(O)_p-OR^{10}$ and alkyl, alkenyl, alkynyl, cycloalkyl, aryl, arylalkyl, heteroaryl, and heteroarylalkyl groups, each of which is optionally substituted with at least one of halo, -OH, -CN, $-NO_2$, $-N(R^{11})_2$, and $-S(O)_pR^{11}$ substituents and/or 1 or 2 (=O) groups; and

R^{10} is selected from the group consisting of alkyl, alkenyl, alkynyl, cycloalkyl, aryl, arylalkyl, heteroaryl, and heteroarylalkyl groups, each of which is optionally substituted with at least one of halo, -OH, -CN, $-NO_2$, $-N(R^{11})_2$, and $-S(O)_pR^{11}$ substituents and/or 1 or 2 (=O) groups;

R^{11} is a moiety independently selected from the group consisting of H and alkyl, alkoxy, alkenyl, alkenyloxy, alkynyl, cycloalkyl, cycloalkoxy, aryl, aryloxy, arylalkyl, heteroaryl, heteroarylalkyl, heterocyclyl, and heterocyclylalkyl, each of which is optionally substituted by at least one substituent independently selected from the group consisting of halo, -OH, -CN, $-NO_2$, $-N(R^{11'})_2$, and $-S(O)_pR^{11'}$ and/or 1 or 2 (=O) groups;

$R^{11'}$ is independently selected from the group consisting of H, alkyl, alkoxy, alkenyl, alkenyloxy, alkynyl, cycloalkyl, cycloalkoxy, aryl, aryloxy, arylalkyl, heteroaryl, heteroarylalkyl, heterocyclyl, and heterocyclylalkyl;

R^{12} is independently selected from selected from the group consisting of H, halo, -OH, -CN, $-NO_2$, $-N(R^{11})_2$, and $-S(O)_pR^{11}$ and/or 1 or 2 (=O) groups, and alkyl, alkoxy, alkenyl, alkenyloxy, alkynyl, cycloalkyl, cycloalkenyl, cycloalkoxy, aryl, aryloxy, arylalkyl, heteroaryl, heteroaryloxy, heteroarylalkyl, heterocyclyl, heterocyclenyl, heterocyclenyloxy, heterocyclylalkyl, heterocyclenylalkyl, arylalkoxy, heteroarylalkoxy, heterocyclylalkoxy, and heterocyclenylalkoxy groups, each of which in turn is optionally substituted by at least once (preferably 1 to 5, more preferably 1 to 3) by a substituent selected from the group consisting of H, alkyl, haloalkyl, halo, -OH, optionally substituted alkoxy, optionally substituted aryloxy, optionally substituted cycloalkoxy, optionally substituted heteroaryloxy, optionally substituted heterocyclenyloxy, -CN, $-NO_2$, $-N(R^{11})_2$, and $-S(O)_pR^{11}$ and/or 1 or 2 (=O) groups, wherein said optionally substituted alkoxy, aryloxy, optionally substituted cycloalkoxy, optionally substituted heteroaryloxy, and heterocyclenyloxy when substituted are substituted one or more (preferably 1 to 5, more preferably 1 to 3) times by R^{11};

m is 1-5;

n is independently1-3;

n' is independently 1-3

p is independently 0-2;

q is independently 0-6; and

w is 0-4

with the following provisos:

(a) if J^1-J^4 are each -C(H)-, n is 1, m is 1, R^4 is H, A is 3H-imidazol-4-yl, and X is $-N(R^6)-$, then R^6 is not -C(=O)-naphthyl;

(b) if J^1-J^4 are each -C(H)-, n is 1, m is 1, R^4 is H, A is 1H-imidazol-4-yl, and X is -N(R^6)-, then R^6 is not -S(O_2)-naphthyl; and

(c) if J^1, J^2, and J^4 are each -C(H)-, J^3 is -C(Br)-, n is 2, m is 1, R^3 is 3-benzyl, R^4 is H, A is 1H-imidazol-4-yl, and X is -N(R^6)-, then R^6 is not -C(O_2)benzyl.

The compounds of Formula I can be useful as α2C adrenergic receptor agonists, and can be useful in the treatment and prevention of allergic rhinitis, all types of congestion (including, but not limited to nasal congestion), migraine, congestive heart failure, cardiac ischemia, glaucoma, and psychotic disorders. Further, the compounds of Formula I can be useful in the treatment of pain (both chronic and acute), such as pain that is caused by inflammation, neuropathy, arthritis (including osteo and rheumatoid arthritis), diabetes (e.g., diabetes mellitus or diabetes insipidus) or pain of an unknown origin. Examples of neuropathic pain may include but not limited to; diabetic neuropathy, neuralgia of any etiology (e.g. post-herpetic, trigeminal), chemotherapy-induced neuropathy, HIV, lower back pain of neuropathic origin (e.g. sciatica), traumatic peripheral nerve injury of any etiology, central pain (e.g. post-stroke, thalamic, spinal nerve injury). Other pain that can be treated is nociceptive pain and pain that is visceral in origin or pain that is secondary to inflammation or nerve damage in other diseases. Other utilities for the inventive compounds could include stress-induced urinary incontinence and neuronal damage from ischemia.

Alternatively, the present invention provides for a method for the treatment of congestion in a mammal in need thereof which comprises administering to a mammal an effective dose of at least one compound having adrenergic activity wherein said compound is a functionally selective agonist of the α2c receptor.

A further embodiment of the present invention is a method for the treatment of congestion in a mammal in need thereof which comprises administering to a mammal an effective dose of at least one compound having adrenergic activity wherein said compound is a selective agonist of the α2c adrenergic receptor, wherein the functional selective agonist of the α2c receptor has an efficacy that is greater than or equal to 30% E_{max} when assayed in the GTPγS assay .

Another embodiment of the present invention is a method for the treatment of congestion in a mammal in need thereof without modifying the systemic blood pressure at therapeutic doses which comprises administering to the mammal an

effective dose of at least one compound having adrenergic activity wherein said compound is a functionally selective agonist of the α2c receptor.

Detailed Description

In an embodiment, the present invention discloses certain heterocyclic compounds which are represented by structural Formula I, or a pharmaceutically acceptable salt or solvate thereof, wherein the various moieties are as described above.

In another embodiment, if J^1-J^4 are each -C(H)-, n is 1, m is 1, R^4 is H, A is 1H-imidazol-4-yl, and X is -N(R^6)-, then R^6 is not -C(=O)-naphthyl.

In another embodiment, if J^1-J^4 are each -C(H)-, n is 1, m is 1, R^4 is H, A is 1H-imidazol-4-yl, and X is -N(R^6)-, then R^6 is not -S(O_2)-naphthyl.

In another embodiment, if J^1, J^2, and J^4 are each -C(H)-, J^3 is -C(Br)-, n is 2, m is 1, R^3 is 3-benzyl, R^4 is H, A is 1H-imidazol-4-yl, and X is -N(R^6)-, then R^6 is not -C(O_2)benzyl.

In another embodiment, J^1-J^4 are each -C(R^2)-, n is 1, A is imidazolyl, and X is -O-.

In another embodiment, J^1-J^4 are each -C(H)-, n is 1, A is imidazolyl, and X is -O-.

In another embodiment, J^1-J^4 are each -C(R^2)-, n is 1, A is imidazolyl, and X is -N(R^6)-.

In another embodiment, J^1-J^4 are each -C(R^2)-, n is 1, A is imidazolyl, and X is -$S(O)_p$-.

In another embodiment, J^1-J^3 are each -C(R^2)-, preferably -CH-;

In another embodiment, J^1 is -N-.

In another embodiment, J^2 is -N-.

In another embodiment, J^3 is -N-.

In another embodiment, J^4 is -N-.

In another embodiment, A is a 5-membered heterocyclic ring containing at least one ring nitrogen.

In another embodiment, A is a 5-membered heteroaryl, heterocyclyl or heterocyclenyl ring containing at least one ring nitrogen.

In another embodiment A is an optionally substituted 5-membered heteroaryl, heterocyclenyl or heterocyclyl ring. Preferred optionally substituted heteroaryl, heterocyclenyl or heterocyclyl 5-membered rings include, for example, imidazole, thiazole, pyrrole, isoxazole, oxazole, isothiazole, pyrazole, imadazoline, imidazol-2-one, imidazol-2-thione, 2-aminoimidazoline, oxazoline, oxazol-2-one, oxazol-2-thione, 2-aminooxazoline, thiazoline, thiazol-2-one, thiazol-2-thione, 2-aminothiazoline, pyrroline, pyrazoline, pyrrolidine, imidazolidine, and pyrazolidine. A more preferred set of 5-membered rings includes: imidazole, imadazoline, imidazol-2-one, imidazol-2-thione, 2-aminoimidazoline, oxazoline, oxazol-2-one, oxazol-2-thione, and 2-aminooxazoline. A most preferred set of 5-memebered rings includes imidazole. Optionally substituents include any of the "ring system substituents" identified below.

In another embodiment, R^2 is independently selected from H, -OH, halo, -CN, $-NO_2$, $-(CH_2)_qYR^7$, $-(CH_2)_qN(R^7)YR^{7'}$, $-(CH_2)_qOYR^{7'}$, $-(CH_2)_qON=CR^7R^{7'}$, $-P(=O)(OR^7)(OR^{7'})$, $-P(=O)(NR^7R^{7'})_2$, $-P(=O)R^8{}_2$, alkyl, alkoxy and polyhaloalkoxy.

In another embodiment R^2 is $-(CH_2)_qYR^7$, $-(CH_2)_qN(R^7)YR^{7'}$ and Y is $-C(=O)-[C(R^a)(R^b)]_{n'}-O-C(=O)-$ or $-C(=O)N(R^c)-O-$.

In another embodiment, J^3 is $-C(R^2)-$, R^2 is $-(CH_2)_qN(R^7)YR^{7'}$, q = 0, Y is $-C(=O)-$, $-C(=O)NR^7-$,or $-C(=O)O-$, and R^7 is Me or Et.

In another embodiment, R^3 is independently selected from H, alkyl, alkoxy, alkenyl, alkenyloxy, alkynyl, cycloalkyl, cycloalkoxy, aryl, aryloxy, arylalkyl, heteroaryl, heteroarylalkyl, heterocyclyl, and heterocyclylalkyl groups optionally substituted with at least one R^5.

In another embodiment, R^3 is independently selected from H, alkyl and haloalkyl.

In another embodiment, R^4 is independently selected from H, alkyl, alkoxy, alkenyl, alkenyloxy, alkynyl, cycloalkyl, cycloalkoxy, aryl, aryloxy, arylalkyl, heteroaryl, heteroarylalkyl, heterocyclyl, and heterocyclylalkyl groups optionally substituted with at least one R^5.

In another embodiment, R^4 is independently selected from H, alkyl, allyl, and haloalkyl.

In another embodiment, R^4 is independently selected from H and alkyl.

In another embodiment, R^5 is independently selected from H, halo, $-NR^7R^{7'}$, –

$S(O)_pR^7$, alkyl, and alkoxy.

In another embodiment, R^6 is independently selected from H, alkyl, haloalkyl, cycloalkyl, $-C(=O)R^7$, $-C(=O)OR^7$, $-C(=O)NR^7R^{7'}$, $-SO_2R^7$ and $-SO_2NR^7R^{7'}$.

In another embodiment, R^7 is independently chosen from H, alkyl, haloalkyl, cycloalkyl, aryl, and heteroaryl.

In another embodiment, R^7 is independently selected from the group consisting of H and alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, cyclocyclenyl, cyclocyclenylalkyl, aryl, arylalkyl, heterocyclyl, heterocyclylalkyl, heterocyclenyl, heterocyclenylalkyl, heteroaryl, and heteroarylalkyl groups, each of which is optionally substituted one or more times (preferably 1 to 5, more preferably 1 to 3) by R^{12}.

In another embodiment, $R^{7'}$ is independently chosen from H, alkyl, haloalkyl, cycloalkyl, aryl, and heteroaryl.

In another embodiment, $R^{7'}$ is independently selected from the group consisting of H and alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, cyclocyclenyl, cyclocyclenylalkyl, aryl, arylalkyl, heterocyclyl, heterocyclylalkyl, heterocyclenyl, heterocyclenylalkyl, heteroaryl, and heteroarylalkyl groups, each of which is optionally substituted one or more times (preferably 1 to 5, more preferably 1 to 3) by R^{12}.

In another embodiment, R^7 and $R^{7'}$ together with the N atom to which they are attached form a aziridine, azetidine, pyrrole, pyrrolidine, piperidine, piperazine or morpholine ring, each of which are optionally substituted by R^5.

In another embodiment, R^8 is independently chosen from alkyl, haloalkyl, cycloalkyl, aryl, and heteroaryl.

In another embodiment R^{12} is independently an arylalkoxy, heteroarylalkoxy, heterocyclylalkoxy, and heterocyclenylalkoxy group, each of which in turn is optionally substituted by at least once (preferably 1 to 5, more preferably 1 to 3) by a substituent selected from the group consisting of H, alkyl, haloalkyl, halo, -OH, optionally substituted alkoxy, optionally substituted aryloxy, optionally substituted cycloalkoxy, optionally substituted heteroaryloxy, optionally substituted heterocyclenyloxy, -CN, $-NO_2$, $-N(R^{11})_2$, and $-S(O)_pR^{11}$, wherein said optionally substituted alkoxy, aryloxy, optionally substituted cycloalkoxy, optionally substituted heteroaryloxy, and heterocyclenyloxy when substituted are substituted one or more (preferably 1 to 5, more preferably 1 to 3) times by R^{11}.

In another embodiment R^{12} is independently selected from the group consisting of H, halo, -OH, -CN, $-NO_2$, $-N(R^{11})_2$, and $-S(O)_pR^{11}$, and alkyl, alkoxy, alkenyl, alkenyloxy, alkynyl, cycloalkyl, cycloalkenyl, cycloalkoxy, aryl, aryloxy, arylalkyl, heteroaryl, heteroaryloxy, heteroarylalkyl, heterocyclyl, heterocyclenyl, heterocyclenyloxy, heterocyclylalkyl, heterocyclenylalkyl, groups, each of which in turn is optionally substituted by at least once (preferably 1 to 5, more preferably 1 to 3) by a substituent selected from the group consisting of H, alkyl, haloalkyl, halo, -OH, optionally substituted alkoxy, optionally substituted aryloxy, optionally substituted cycloalkoxy, optionally substituted heteroaryloxy, optionally substituted heterocyclenyloxy, -CN, $-NO_2$, $-N(R^{11})_2$, and $-S(O)_pR^{11}$, wherein said optionally substituted alkoxy, aryloxy, optionally substituted cycloalkoxy, optionally substituted heteroaryloxy, and heterocyclenyloxy when substituted are substituted one or more (preferably 1 to 5, more preferably 1 to 3) times by R^{11}.

In another embodiment J^1, J^2 and J^4 are –CH-; X is –O- or –S-; m is 1 and n is 1 or 2.

In another embodiment R^2 is $-(CH_2)_qYR^7$, or $-(CH_2)_qN(R^7)YR^{7'}$, Y is -C(=O)-$[C(R^a)(R^b)]_n$-O-C(=O)-, n is 1 or 2, and R^a and R^b are independently H or alkyl (preferably methyl or ethyl).

In another embodiment, A is an optionally substituted imidazole;

R^2 is $-(CH)_qN(R^7)Y(R^{7'})$;

Y is -C(=O)O-, -(C=O)N(R^c)-O- or $-C(O)NR^7$; and

R^7 is independently selected from the group consisting of H, alkyl, cycloalkyl, alkenyl, alkynyl, aryl, heteroaryl, arylalkyl, and heteroarylalkyl, said groups being optionally substituted one or more times by a substituent independently selected from the group consisting of H, alkyl, cycloalkyl, alkoxy, halo, -OH, -CN, $-NO_2$, $-N(R^{11})_2$, $-S(O)_pR^{11}$, optionally substituted aryl, optionally substituted aryloxy and optionally substituted heteroaryloxy, said optionally substituted optionally substituted aryl, optionally substituted aryloxy and optionally substituted heteroaryloxy when substituted are independently substituted one or more times by a substituent selected from the group consisting of H, alkyl, cycloalkyl, alkoxy, halo, -OH, NO_2, $-N(R^{11})_2$ and $-S(O)_pR^{11}$.

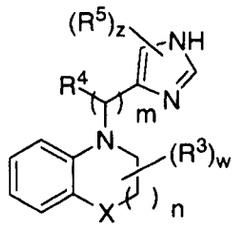
In another embodiment, m is 1 or 2.

In another embodiment, n is 1 or 2.

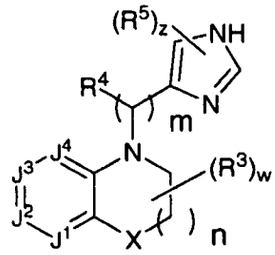
In another embodiment, n is 1.

In another embodiment, q is 0, 1, 2, or 3.

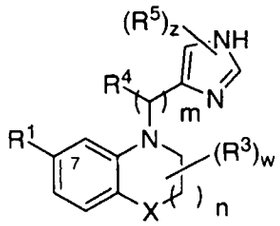
In another embodiment, the present invention discloses compounds which are represented by structural formulae **II-V** or a pharmaceutically acceptable salt, solvate or ester thereof, wherein the various moieties are as described above:



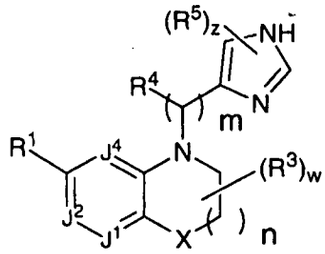
Formula **II**



Formula **III**



Formula **IV**



Formula **V**

wherein z is 0-3 and R^1 is selected from the group consisting of H, -OH, halo, -CN, $-NO_2$, ~~$-SR^7$~~ $-S(O)_pR^7$, $-(CH_2)_qYR^7$, $-(CH_2)_qN(R^7)YR^{7'}$, $-(CH_2)_qOYR^7$, $-(CH_2)_qON{=}C\ NR^7R^{7'}$, $-P(=O)(OR^7)(OR^{7'})$, $-P(=O)(NR^7R^{7'})_2$, $-P(=O)R^8{}_2$ and alkyl, alkoxy, alkenyl, alkenyloxy, alkynyl, cycloalkyl, cycloalkoxy, aryl, aryloxy, arylalkyl, heteroaryl, heteroarylalkyl, heterocyclyl, and heterocyclylalkyl groups optionally substituted with at least one R^5.

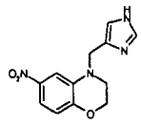
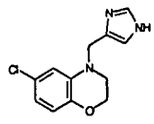
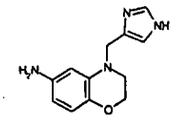
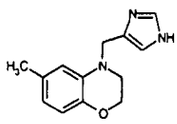
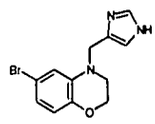
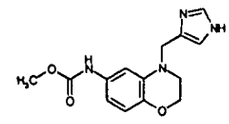
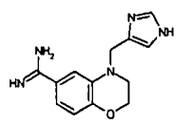
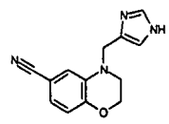
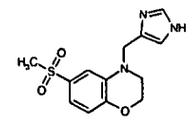
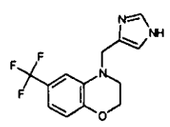
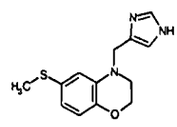
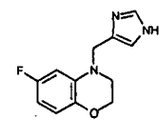
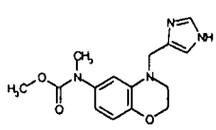
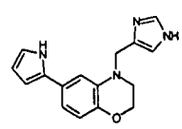
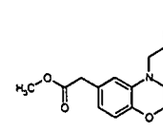
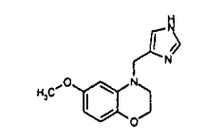
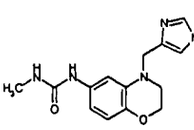
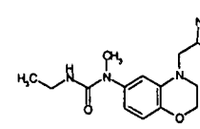
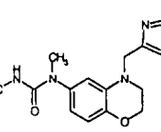
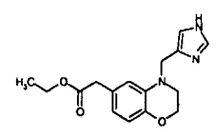
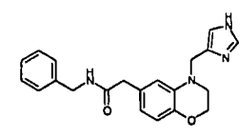
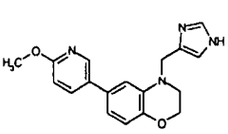
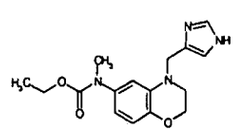
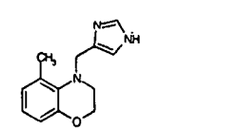
In another embodiment in the above formulae R^1 is $-(CH_2)_qYR^7$, or $-(CH_2)_qN(R^7)YR^{7'}$.

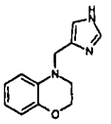
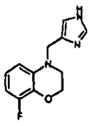
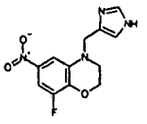
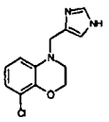
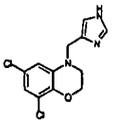
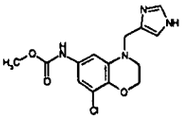
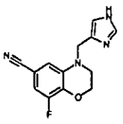
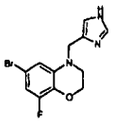
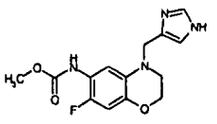
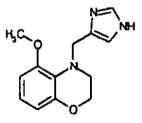
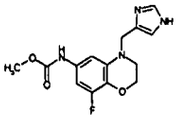
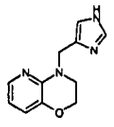
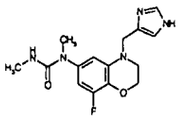
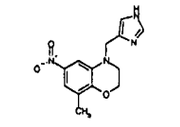
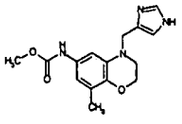
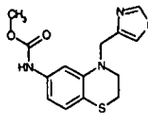
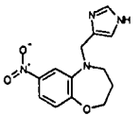
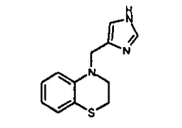
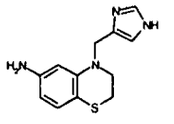
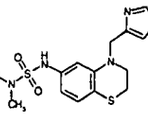
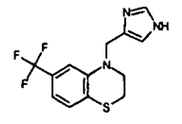
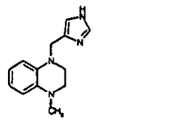
In another embodiment in the above formulae, Y is $-(=O)O-$ or $-(C=O)NR^7$.

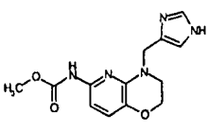
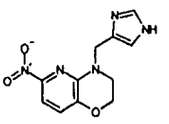
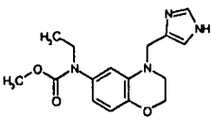
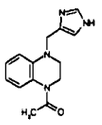
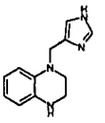
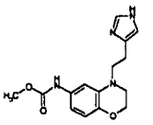
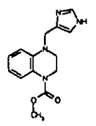
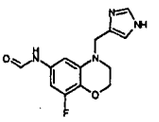
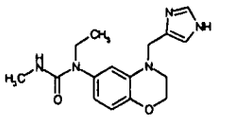
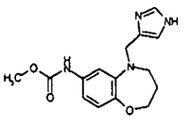
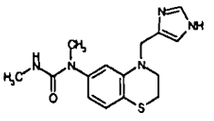
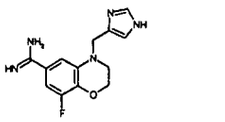
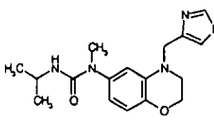
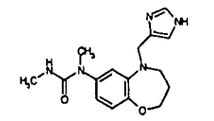
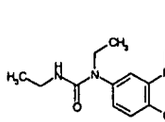
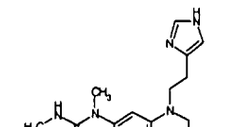
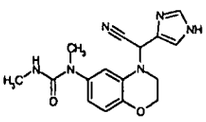
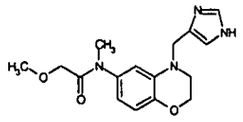
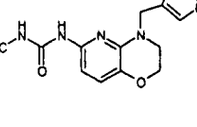
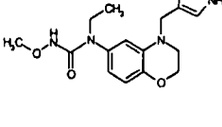
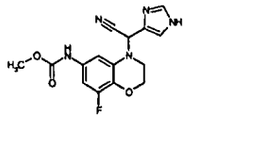
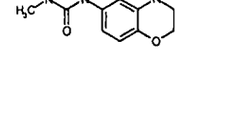
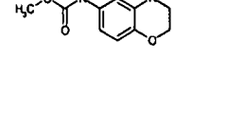
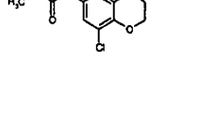
In another embodiment in the above formulae, Y is $-C(=O)-[C(R^a)(R^b)]_n-O-C(=O)-$.

In another embodiment in the above formulae R^1 is $-(CH_2)_qN(R^7)YR^{7'}$ and Y is $-C(=O)N(R^c)-O-$.

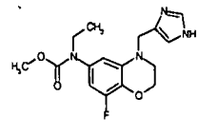
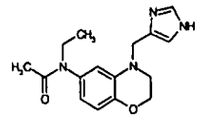
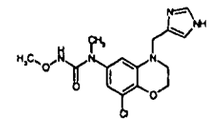
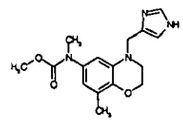
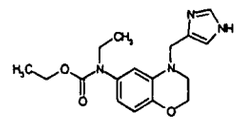
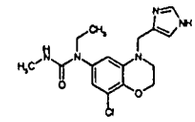
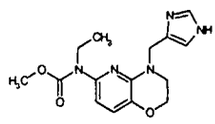
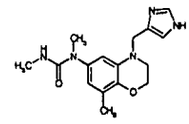
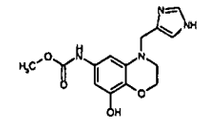
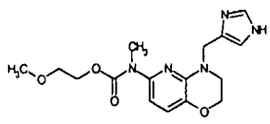
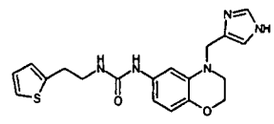
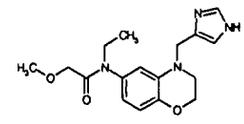
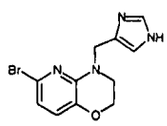
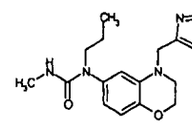
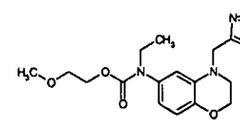
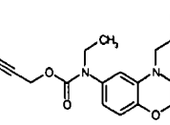
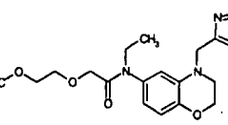
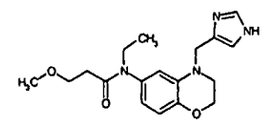
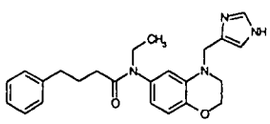
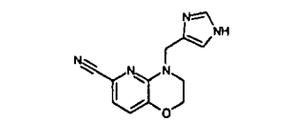
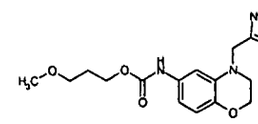
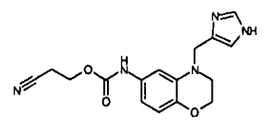
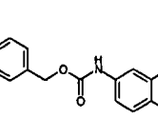
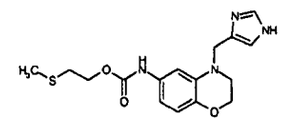
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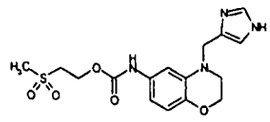

























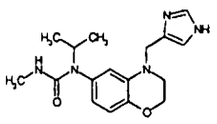
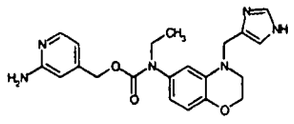
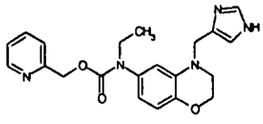
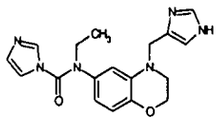
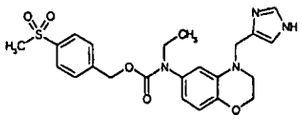
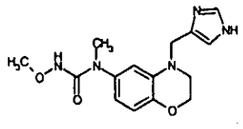
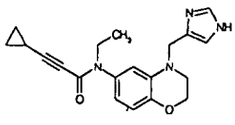
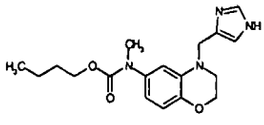
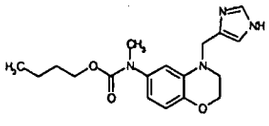
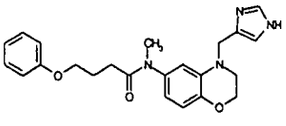
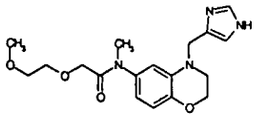
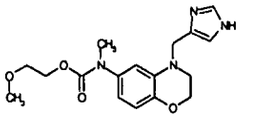
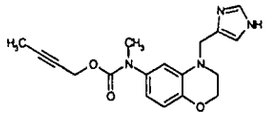
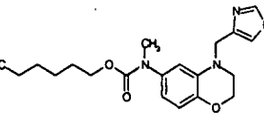
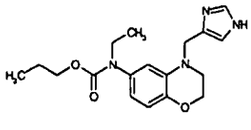
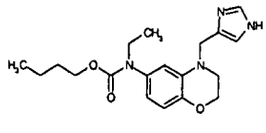
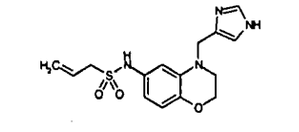
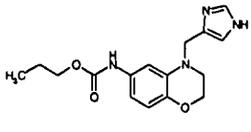
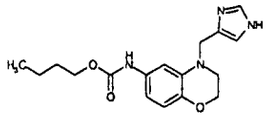
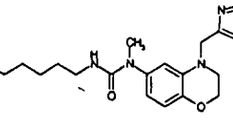
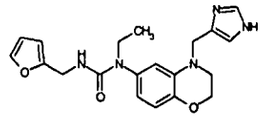

























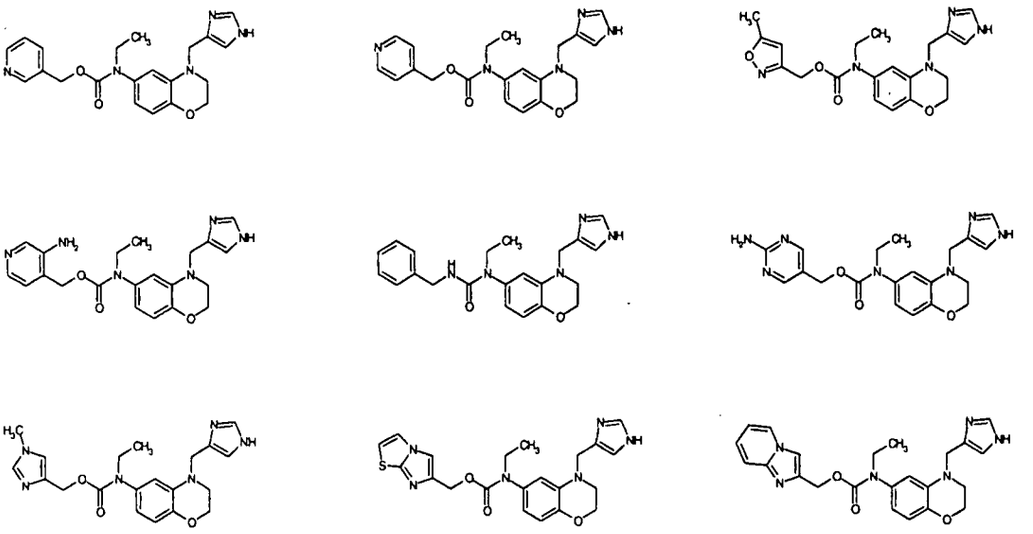
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Another group of inventive compounds is as follows:

As used above, and throughout this disclosure, the following terms, unless otherwise indicated, shall be understood to have the following meanings:

"Patient" includes both human and animals.

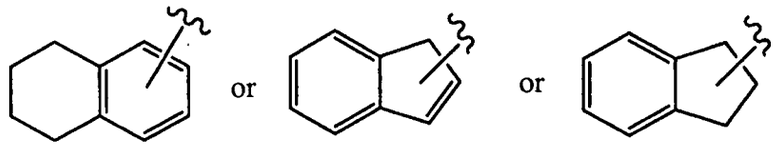
"Mammal" means humans and other mammalian animals.

"Congestion" refers to all type of congestion including, but not limited to, congestion associated with perennial allergic rhinitis, seasonal allergic rhinitis, non-allergic rhinitis, vasomotor rhinitis, rhinitis medicamentosa, sinusitis, acute rhinosinusitis, or chronic rhinosinusitis or when the congestion is caused by polyps or is virally induced, such as congestion associated with the common cold.

"Alkyl" means an aliphatic hydrocarbon group which may be straight or branched and comprising about 1 to about 20 carbon atoms in the chain. Preferred alkyl groups contain about 1 to about 12 carbon atoms in the chain. More preferred alkyl groups contain about 1 to about 6 carbon atoms in the chain. Branched means that one or more lower alkyl groups such as methyl, ethyl or propyl, are attached to a linear alkyl chain. "Lower alkyl" means a group having about 1 to about 6 carbon atoms in the chain which may be straight or branched. The term "substituted alkyl" means that the alkyl group may be substituted by one or more substituents which may be the same or different, each substituent being independently selected from the group consisting of halo, alkyl, aryl, cycloalkyl, cyano, hydroxy, alkoxy, alkylthio, amino, -NH(alkyl), -NH(cycloalkyl), -N(alkyl)$_2$, carboxy and –C(O)O-alkyl. Non-limiting examples of suitable alkyl groups include methyl, ethyl, n-propyl, isopropyl and t-butyl.

"Alkynyl" means an aliphatic hydrocarbon group containing at least one carbon-carbon triple bond and which may be straight or branched and comprising about 2 to about 15 carbon atoms in the chain. Preferred alkynyl groups have about 2 to about 12 carbon atoms in the chain; and more preferably about 2 to about 4 carbon atoms in the chain. Branched means that one or more lower alkyl groups such as methyl, ethyl or propyl, are attached to a linear alkynyl chain. "Lower alkynyl" means about 2 to about 6 carbon atoms in the chain which may be straight or branched. Non-limiting examples of suitable alkynyl groups include ethynyl, propynyl, 2-butynyl and 3-methylbutynyl. The term "substituted alkynyl" means that the alkynyl group may be substituted by one or more substituents which may be the same or different, each substituent being independently selected from the group consisting of alkyl, aryl and cycloalkyl.

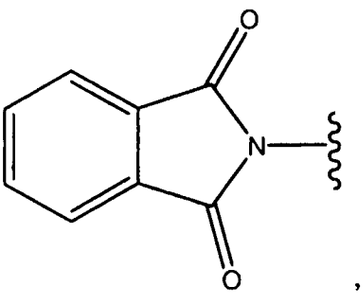
"Aryl" means an aromatic monocyclic or multicyclic ring system, in which at least one of the multicyclic rings is an aryl ring, comprising about 6 to about 14 carbon atoms, preferably about 6 to about 10 carbon atoms. The aryl group can be optionally substituted with one or more "ring system substituents" which may be the same or different, and are as defined herein. Non-limiting examples of suitable aryl groups include phenyl and naphthyl. Non-limiting examples of aryl multicyclic ring systems include:



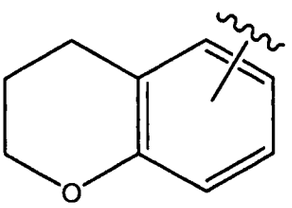
"Heteroaryl" means an aromatic monocyclic or multicyclic ring system, in which at least one of the multicyclic rings is aromatic, comprising about 5 to about 14 ring atoms, preferably about 5 to about 10 ring atoms, in which one or more of the ring atoms is an element other than carbon, for example nitrogen, oxygen or sulfur, alone or in combination. Preferred heteroaryls contain about 5 to about 6 ring atoms. The "heteroaryl" can be optionally substituted by one or more "ring system substituents" which may be the same or different, and are as defined herein. The prefix aza, oxa or thia before the heteroaryl root name means that at least a nitrogen, oxygen or sulfur atom respectively, is present as a ring atom. A nitrogen atom of a heteroaryl can be optionally oxidized to the corresponding N-oxide. Non-limiting examples of suitable heteroaryls include pyridyl, pyrazinyl, furanyl, thienyl, pyrimidinyl, isoxazolyl,

isothiazolyl, oxazolyl, thiazolyl, pyrazolyl, furazanyl, pyrrolyl, pyrazolyl, triazolyl, 1,2,4-thiadiazolyl, pyrazinyl, pyridazinyl, quinoxalinyl, phthalazinyl, imidazo[1,2-a]pyridinyl, imidazo[2,1-b]thiazolyl, benzofurazanyl, indolyl, azaindolyl, benzimidazolyl, benzothienyl, quinolinyl, imidazolyl, thienopyridyl, quinazolinyl, thienopyrimidyl, pyrrolopyridyl, imidazopyridyl, isoquinolinyl, benzoazaindolyl, 1,2,4-triazinyl, benzothiazolyl and the like.

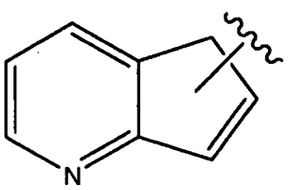
Non-limiting examples of hetreroaryl multicyclic ring systems include:



,



or



"Aralkyl" or "arylalkyl" means an aryl-alkyl- group in which the aryl and alkyl are as previously described. Preferred aralkyls comprise a lower alkyl group. Non-limiting examples of suitable aralkyl groups include benzyl, 2-phenethyl and naphthalenylmethyl. The bond to the parent moiety is through the alkyl.

"Alkylaryl" means an alkyl-aryl- group in which the alkyl and aryl are as previously described. Preferred alkylaryls comprise a lower alkyl group. Non-limiting example of a suitable alkylaryl group is tolyl. The bond to the parent moiety is through the aryl.

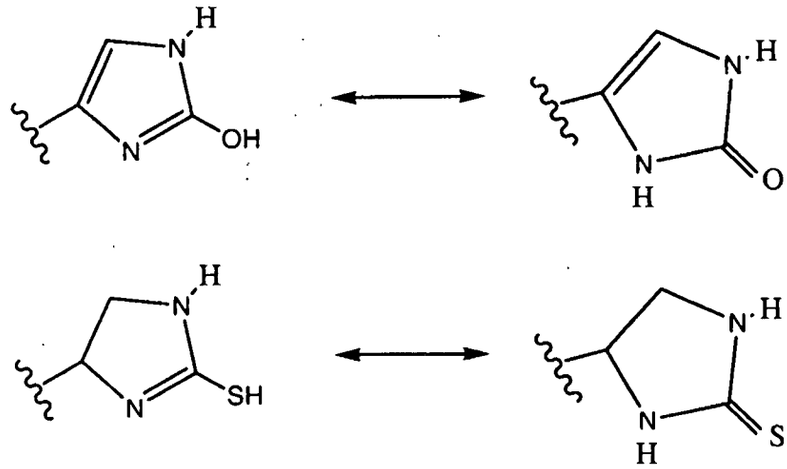
"Cycloalkyl" means a non-aromatic mono- or multicyclic ring system comprising about 3 to about 10 carbon atoms, preferably about 5 to about 10 carbon atoms. Preferred cycloalkyl rings contain about 5 to about 7 ring atoms. The cycloalkyl can be optionally substituted with one or more "ring system substituents" which may be the same or different, and are as defined above. Non-limiting examples of suitable monocyclic cycloalkyls include cyclopropyl, cyclopentyl, cyclohexyl, cycloheptyl and the like. Non-limiting examples of suitable multicyclic cycloalkyls include 1-decalinyl, norbornyl, adamantyl and the like.

"Halogen" and "Halo" mean fluorine, chlorine, bromine, or iodine. Preferred are fluorine, chlorine or bromine, and more preferred are fluorine and chlorine.

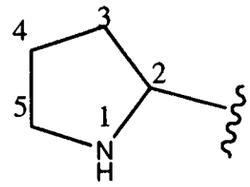
"Ring system substituent" means a substituent attached to an aromatic or non-aromatic ring system which, for example, replaces an available hydrogen on the ring system. Ring system substituents may be the same or different, each being independently selected from the group consisting of aryl, heteroaryl, aralkyl, alkylaryl, heteroaralkyl, alkylheteroaryl, hydroxy, hydroxyalkyl, alkoxy, aryloxy, aralkoxy, acyl, aroyl, halo, nitro, cyano, carboxy, alkoxycarbonyl, aryloxycarbonyl, aralkoxycarbonyl, alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, alkylthio, arylthio, heteroarylthio, aralkylthio, heteroaralkylthio, cycloalkyl, heterocyclyl, Y_1Y_2N-, Y_1Y_2N-alkyl-, $Y_1Y_2NC(O)$- and $Y_1Y_2NSO_2$-, wherein Y_1 and Y_2 may be the same or different and are independently selected from the group consisting of hydrogen, alkyl, aryl, and aralkyl.

"Heterocyclyl" means a non-aromatic saturated monocyclic or multicyclic ring system comprising about 3 to about 10 ring atoms, preferably about 5 to about 10 ring atoms, in which one or more of the atoms in the ring system is an element other than carbon, for example nitrogen, oxygen or sulfur, alone or in combination. There are no adjacent oxygen and/or sulfur atoms present in the ring system. Preferred heterocyclyls contain about 5 to about 6 ring atoms. The prefix aza, oxa or thia before the heterocyclyl root name means that at least a nitrogen, oxygen or sulfur atom respectively is present as a ring atom. Any –NH in a heterocyclyl ring may exist protected such as, for example, as an -N(Boc), -N(CBz), -N(Tos) group and the like; such protected moieties are also considered part of this invention. The heterocyclyl can be optionally substituted by one or more "ring system substituents" which may be the same or different, and are as defined herein. The nitrogen or sulfur atom of the heterocyclyl can be optionally oxidized to the corresponding N-oxide, S-oxide or S,S-dioxide. Non-limiting examples of suitable monocyclic heterocyclyl rings include piperidyl, pyrrolidinyl, piperazinyl, morpholinyl, thiomorpholinyl, thiazolidinyl, 1,4-dioxanyl, tetrahydrofuranyl, tetrahydrothiophenyl, and the like.

Compounds of Formula I and salts, esters, solvates and prodrugs thereof, may exist in their tautomeric form (for example, as an amide or imino ether). All such tautomeric forms are contemplated herein as part of the present invention. Non-limiting examples of tautomeric forms that are part of this invention are as follows:

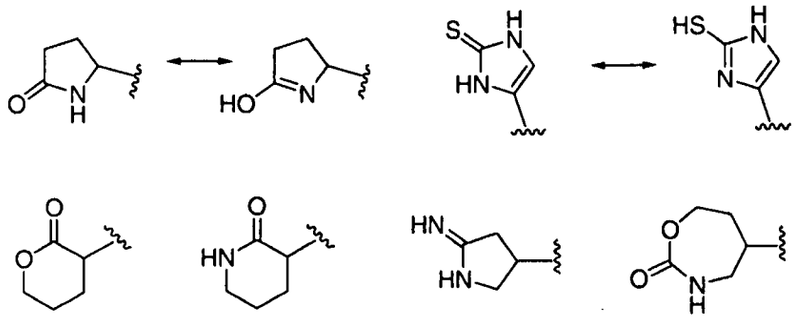


It should be noted that in saturated heterocyclyl containing systems of this invention, there are no hydroxyl, amino, or thiol groups on carbon atoms adjacent to a N, O or S atom. Thus, for example, in the ring:

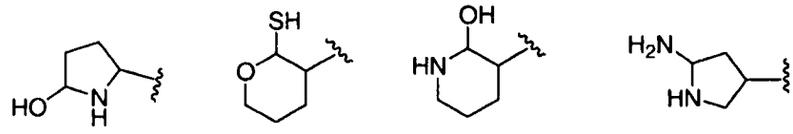


there is no -OH attached directly to carbons marked 2 and 5. It should also be noted that this definition does not preclude (=O), (=S), or (=N) substitutions, or their tautomeric forms, on C atoms adjacent to a N, O or S. Thus, for example, in the above ring, (=O) substitution on carbon 5, or its imino ether tautomer is allowed.

Non-limiting examples which illustrate the present invention are as follows:



The following non-limiting examples serve to illustrate radicals not contemplated by the present invention:



"Alkynylalkyl" means an alkynyl-alkyl- group in which the alkynyl and alkyl are as previously described. Preferred alkynylalkyls contain a lower alkynyl and a lower alkyl group. The bond to the parent moiety is through the alkyl. Non-limiting examples of suitable alkynylalkyl groups include propargylmethyl.

"Heteroaralkyl" or "heteroarylalkyl" means a heteroaryl-alkyl- group in which the heteroaryl and alkyl are as previously described. Preferred heteroaralkyls contain a lower alkyl group. Non-limiting examples of suitable aralkyl groups include pyridylmethyl, and quinolin-3-ylmethyl. The bond to the parent moiety is through the alkyl.

"Heterocyclylalkyl" means a heterocyclyl-alkyl group in which the heterocyclyl and the alkyl are as previously described. Preferred heterocyclylalkyls contain a lower alkyl group, Non-limiting examples of suitable heterocyclylalkyl groups include piperidylmethyl, piperidylethyl, pyrrolidylmethyl, morpholinylpropyl, piperazinylethyl, azindylmethyl, azetidylethyl, oxiranylpropyl and the like. The bond to the parent moiety is through the alkyl group.

"Heterocyclenyl" (or "heterocycloalkeneyl") means a non-aromatic monocyclic or multicyclic ring system comprising about 3 to about 10 ring atoms, preferably about 5 to about 10 ring atoms, in which one or more of the atoms in the ring system is an element other than carbon, for example nitrogen, oxygen or sulfur atom, alone or in combination, and which contains at least one carbon-carbon double bond or carbon-nitrogen double bond. There are no adjacent oxygen and/or sulfur atoms present in the ring system. Preferred heterocyclenyl rings contain about 5 to about 6 ring atoms. The prefix aza, oxa or thia before the heterocyclenyl root name means that at least a nitrogen, oxygen or sulfur atom respectively is present as a ring atom. The heterocyclenyl can be optionally substituted by one or more ring system substituents, wherein "ring system substituent" is as defined above. The nitrogen or sulfur atom of the heterocyclenyl can be optionally oxidized to the corresponding N-oxide, S-oxide or S,S-dioxide. Non-limiting examples of suitable monocyclic azaheterocyclenyl groups include 1,2,3,4- tetrahydropyridyl, 1,2-dihydropyridyl, 1,4-dihydropyridyl, 1,2,3,6-tetrahydropyridyl, 1,4,5,6-tetrahydropyrimidyl, 2-pyrrolinyl, 3-pyrrolinyl, 2-imidazolinyl, 2-pyrazolinyl, and the like. Non-limiting examples of suitable oxaheterocyclenyl groups include 3,4-dihydro-2H-pyran, dihydrofuranyl, fluorodihydrofuranyl, and the like. Non-limiting example of a suitable multicyclic oxaheterocyclenyl group is 7-

oxabicyclo[2.2.1]heptenyl. Non-limiting examples of suitable monocyclic thiaheterocyclenyl rings include dihydrothiophenyl, dihydrothiopyranyl, and the like.

"Hydroxyalkyl" means a HO-alkyl- group in which alkyl is as previously defined. Preferred hydroxyalkyls contain lower alkyl. Non-limiting examples of suitable hydroxyalkyl groups include hydroxymethyl and 2-hydroxyethyl.

"Heterocyclenylalkyl" means a heterocyclenyl-alkyl group in which the heterocyclenyl and the alkyl are as previously described.

"Acyl" means an organic acid group in which the -OH of the carboxyl group is replaced by some other substituent. Suitable non-limiting examples include H-C(O)-, alkyl-C(O)- , cycloalkyl-C(O)-, heterocyclyl-C(O)-, and heteroaryl-C(O)- groups in which the various groups are as previously described. The bond to the parent moiety is through the carbonyl. Preferred acyls contain a lower alkyl. Non-limiting examples of suitable acyl groups include formyl, acetyl and propanoyl.

"Aroyl" means an aryl-C(O)- group in which the aryl group is as previously described. The bond to the parent moiety is through the carbonyl. Non-limiting examples of suitable groups include benzoyl and 1-naphthoyl.

"Alkoxy" means an alkyl-O- group in which the alkyl group is as previously described. Non-limiting examples of suitable alkoxy groups include methoxy, ethoxy, n-propoxy, isopropoxy and n-butoxy. The bond to the parent moiety is through the ether oxygen.

"Aryloxy" means an aryl-O- group in which the aryl group is as previously described. Non-limiting examples of suitable aryloxy groups include phenoxy and naphthoxy. The bond to the parent moiety is through the ether oxygen.

"Aralkyloxy" or "arylalkyloxy" means an aralkyl-O- group in which the aralkyl group is as previously described. Non-limiting examples of suitable aralkyloxy groups include benzyloxy and 1- or 2-naphthalenemethoxy. The bond to the parent moiety is through the ether oxygen.

"Heteroarylalkoxy" means a heteroarylalkyl-O-group in which the heteroarylalkyl group is as previously described.

"Heterocyclylalkoxy" means a heterocyclylalkyl-O group in which the hetrocyclylalkyl group is as previously described.

"Heterocyclenylalkoxy" means a heterocyclenylalkyl-O group in which the heterocyclenylalkyl group is as previously described.

"Alkylthio" means an alkyl-S- group in which the alkyl group is as previously described. Non-limiting examples of suitable alkylthio groups include methylthio and ethylthio. The bond to the parent moiety is through the sulfur.

"Arylthio" means an aryl-S- group in which the aryl group is as previously described. Non-limiting examples of suitable arylthio groups include phenylthio and naphthylthio. The bond to the parent moiety is through the sulfur.

"Aralkylthio" means an aralkyl-S- group in which the aralkyl group is as previously described. Non-limiting example of a suitable aralkylthio group is benzylthio. The bond to the parent moiety is through the sulfur.

"Alkoxycarbonyl" means an alkyl-O-CO- group. Non-limiting examples of suitable alkoxycarbonyl groups include methoxycarbonyl and ethoxycarbonyl. The bond to the parent moiety is through the carbonyl.

"Aryloxycarbonyl" means an aryl-O-C(O)- group. Non-limiting examples of suitable aryloxycarbonyl groups include phenoxycarbonyl and naphthoxycarbonyl. The bond to the parent moiety is through the carbonyl.

"Aralkoxycarbonyl" means an aralkyl-O-C(O)- group. Non-limiting example of a suitable aralkoxycarbonyl group is benzyloxycarbonyl. The bond to the parent moiety is through the carbonyl.

"Alkylsulfonyl" means an alkyl-$S(O_2)$- group. Preferred groups are those in which the alkyl group is lower alkyl. The bond to the parent moiety is through the sulfonyl.

"Arylsulfonyl" means an aryl-$S(O_2)$- group. The bond to the parent moiety is through the sulfonyl.

The term "substituted" means that one or more hydrogens on the designated atom is replaced with a selection from the indicated group, provided that the designated atom's normal valency under the existing circumstances is not exceeded, and that the substitution results in a stable compound. Combinations of substituents and/or variables are permissible only if such combinations result in stable compounds. By "stable compound' or "stable structure" is meant a compound that is sufficiently robust to survive isolation to a useful degree of purity from a reaction mixture, and formulation into an efficacious therapeutic agent.

It is noted that carbons of formula I can be replaced with 1-3 silicon atoms, provided all valency requirements are satisfied.

The term "optionally substituted" means optional substitution with the specified groups, radicals or moieties.

It should also be noted that any heteroatom with unsatisfied valences in the text, schemes, examples and Tables herein is assumed to have the hydrogen atom to satisfy the valences.

When a functional group in a compound is termed "protected", this means that the group is in modified form to preclude undesired side reactions at the protected site when the compound is subjected to a reaction. Suitable protecting groups will be recognized by those with ordinary skill in the art as well as by reference to standard textbooks such as, for example, T. W. Greene *et al*, *Protective Groups in organic Synthesis* (1991), Wiley, New York.

When any variable (e.g., aryl, heterocycle, R^2, etc.) occurs more than one time in any constituent or formula, its definition on each occurrence is independent of its definition at every other occurrence.

Unless defined otherwise, all definitions for the variables follow the convention that the group to the right forms the point of attachement to the molecule; i.e., if a definition is arylalkyl, this means that the alkyl portion of the definition is attached to the molecule.

Further, all divalent variable are attached from left to right. For example when R^2 is $-(CH_2)_qN(R^7)YR^{7'}$, and Y is $-C(=O)-[C(R^a)(R^b)]_n-O-C(=O)-$, then R^2 forms the group $-(CH_2)_qN(R^7)-C(=O)-[C(R^a)(R^b)]_n-O-C(=O)-R^{7'}$.

As used herein, the term "composition" is intended to encompass a product comprising the specified ingredients in the specified amounts, as well as any product which results, directly or indirectly, from combination of the specified ingredients in the specified amounts.

Prodrugs and solvates of the compounds of the invention are also contemplated herein. The term "prodrug", as employed herein, denotes a compound that is a drug precursor which, upon administration to a subject, undergoes chemical conversion by metabolic or chemical processes to yield a compound of formula I or a salt and/or solvate thereof. A discussion of prodrugs is provided in T. Higuchi and V. Stella, *Pro-drugs as Novel Delivery Systems* (1987) Volume 14 of the A.C.S. Symposium Series, and in *Bioreversible Carriers in Drug Design,* (1987) Edward B.

Roche, ed., American Pharmaceutical Association and Pergamon Press, both of which are incorporated herein by reference thereto.

For example, if a compound of Formula (I) or a pharmaceutically acceptable salt, hydrate or solvate of the compound contains a carboxylic acid functional group, a prodrug can comprise an ester formed by the replacement of the hydrogen atom of the acid group with a group such as, for example, (C_1–C_8)alkyl, (C_2-C_{12})alkanoyloxymethyl, 1-(alkanoyloxy)ethyl having from 4 to 9 carbon atoms, 1-methyl-1-(alkanoyloxy)-ethyl having from 5 to 10 carbon atoms, alkoxycarbonyloxymethyl having from 3 to 6 carbon atoms, 1-(alkoxycarbonyloxy)ethyl having from 4 to 7 carbon atoms, 1-methyl-1-(alkoxycarbonyloxy)ethyl having from 5 to 8 carbon atoms, N-(alkoxycarbonyl)aminomethyl having from 3 to 9 carbon atoms, 1-(N-(alkoxycarbonyl)amino)ethyl having from 4 to 10 carbon atoms, 3-phthalidyl, 4-crotonolactonyl, gamma-butyrolacton-4-yl, di-N,N-(C_1-C_2)alkylamino(C_2-C_3)alkyl (such as β-dimethylaminoethyl), carbamoyl-(C_1-C_2)alkyl, N,N-di (C_1-C_2)alkylcarbamoyl-(C1-C2)alkyl and piperidino-, pyrrolidino- or morpholino(C_2-C_3)alkyl, and the like.

Similarly, if a compound of Formula (I) contains an alcohol functional group, a prodrug can be formed by the replacement of the hydrogen atom of the alcohol group with a group such as, for example, (C_1-C_6)alkanoyloxymethyl, 1-((C_1-C_6)alkanoyloxy)ethyl, 1-methyl-1-((C_1-C_6)alkanoyloxy)ethyl, (C_1-C_6)alkoxycarbonyloxymethyl, N-(C_1-C_6)alkoxycarbonylaminomethyl, succinoyl, (C_1-C_6)alkanoyl, α-amino(C_1-C_4)alkanyl, arylacyl and α-aminoacyl, or α-aminoacyl-α-aminoacyl, where each α-aminoacyl group is independently selected from the naturally occurring L-amino acids, -P(O)(OH)$_2$, -P(O)(O(C_1-C_6)alkyl)$_2$ or glycosyl (the radical resulting from the removal of a hydroxyl group of the hemiacetal form of a carbohydrate), and the like.

If a compound of Formula I incorporates a -NH- functional group, such as a in a primary or secondary amine or in a nitrogen-containing heterocycle, such as imidazole or piperazine ring, a prodrug can be formed by the replacement of a hydrogen atom in the amine group with a group such as, for example, R-carbonyl, RO-carbonyl, NRR'-carbonyl where R and R' are each independently (C_1-C_{10})alkyl, (C_3-C_7) cycloalkyl, benzyl, or R-carbonyl is a natural α-aminoacyl or natural α-aminoacyl, -C(OH)C(O)OY^1 wherein Y^1 is H, (C_1-C_6)alkyl or benzyl, -C(OY^2)Y^3 wherein Y^2 is (C_1-C_4) alkyl and Y^3 is (C_1-C_6)alkyl, carboxy (C_1-C_6)alkyl, amino(C_1-C_4)alkyl or mono-N- or di-N,N-(C_1-

C_6)alkylaminoalkyl, -C(Y^4)Y^5 wherein Y^4 is H or methyl and Y^5 is mono-N- or di-N,N-(C_1-C_6)alkylamino morpholino, piperidin-1-yl or pyrrolidin-1-yl, and the like.

"Effective amount" or "therapeutically effective amount" is meant to describe an amount of compound or a composition of the present invention effective in producing the desired therapeutic, ameliorative, inhibitory or preventative effect.

"Capsule" is meant to describe a special container or enclosure made of methyl cellulose, polyvinyl alcohols, or denatured gelatins or starch for holding or containing compositions comprising the active ingredients. Hard shell capsules are typically made of blends of relatively high gel strength bone and pork skin gelatins. The capsule itself may contain small amounts of dyes, opaquing agents, plasticizers and preservatives.

"Tablet" is meant to describe a compressed or molded solid dosage form containing the active ingredients with suitable diluents. The tablet can be prepared by compression of mixtures or granulations obtained by wet granulation, dry granulation or by compaction.

"Oral gels" is meant to describe to the active ingredients dispersed or solubilized in a hydrophillic semi-solid matrix.

"Powders for constitution" refers to powder blends containing the active ingredients and suitable diluents which can be suspended in water or juices.

"Diluent" refers to substances that usually make up the major portion of the composition or dosage form. Suitable diluents include sugars such as lactose, sucrose, mannitol and sorbitol; starches derived from wheat, corn, rice and potato; and celluloses such as microcrystalline cellulose. The amount of diluent in the composition can range from about 10 to about 90% by weight of the total composition, preferably from about 25 to about 75%, more preferably from about 30 to about 60% by weight, even more preferably from about 12 to about 60%.

"Disintegrants" refers to materials added to the composition to help it break apart (disintegrate) and release the medicaments. Suitable disintegrants include starches; "cold water soluble" modified starches such as sodium carboxymethyl starch; natural and synthetic gums such as locust bean, karaya, guar, tragacanth and agar; cellulose derivatives such as methylcellulose and sodium carboxymethylcellulose; microcrystalline celluloses and cross-linked microcrystalline celluloses such as sodium croscarmellose; alginates such as alginic acid and sodium

alginate; clays such as bentonites; and effervescent mixtures. The amount of disintegrant in the composition can range from about 2 to about 15% by weight of the composition, more preferably from about 4 to about 10% by weight.

"Binders" refers to substances that bind or "glue" powders together and make them cohesive by forming granules, thus serving as the "adhesive" in the formulation. Binders add cohesive strength already available in the diluent or bulking agent. Suitable binders include sugars such as sucrose; starches derived from wheat, corn rice and potato; natural gums such as acacia, gelatin and tragacanth; derivatives of seaweed such as alginic acid, sodium alginate and ammonium calcium alginate; cellulosic materials such as methylcellulose and sodium carboxymethylcellulose and hydroxypropylmethylcellulose; polyvinylpyrrolidone; and inorganics such as magnesium aluminum silicate. The amount of binder in the composition can range from about 2 to about 20% by weight of the composition, more preferably from about 3 to about 10% by weight, even more preferably from about 3 to about 6% by weight.

"Lubricant" is meant to describe a substance added to the dosage form to enable the tablet, granules, etc. after it has been compressed, to release from the mold or die by reducing friction or wear. Suitable lubricants include metallic stearates such as magnesium stearate, calcium stearate or potassium stearate; stearic acid; high melting point waxes; and water soluble lubricants such as sodium chloride, sodium benzoate, sodium acetate, sodium oleate, polyethylene glycols and d'l-leucine. Lubricants are usually added at the very last step before compression, since they must be present on the surfaces of the granules and in between them and the parts of the tablet press. The amount of lubricant in the composition can range from about 0.2 to about 5% by weight of the composition, preferably from about 0.5 to about 2%, more preferably from about 0.3 to about 1.5% by weight.

"Glidents" means materials that prevent caking and improve the flow characteristics of granulations, so that flow is smooth and uniform. Suitable glidents include silicon dioxide and talc. The amount of glident in the composition can range from about 0.1% to about 5% by weight of the total composition, preferably from about 0.5 to about 2% by weight.

"Coloring agents" refers to excipients that provide coloration to the composition or the dosage form. Such excipients can include food grade dyes and food grade dyes adsorbed onto a suitable adsorbent such as clay or aluminum oxide. The

amount of the coloring agent can vary from about 0.1 to about 5% by weight of the composition, preferably from about 0.1 to about 1%.

"Bioavailability" refers to the rate and extent to which the active drug ingredient or therapeutic moiety is absorbed into the systemic circulation from an administered dosage form as compared to a standard or control. Conventional methods for preparing tablets are known. Such methods include dry methods such as direct compression and compression of granulation produced by compaction, or wet methods or other special procedures. Conventional methods for making other forms for administration such as, for example, capsules, suppositories and the like are also well known.

The compounds of Formula I can form salts which are also within the scope of this invention. Reference to a compound of Formula I herein is understood to include reference to salts thereof, unless otherwise indicated. The term "salt(s)", as employed herein, denotes acidic salts formed with inorganic and/or organic acids, as well as basic salts formed with inorganic and/or organic bases. In addition, when a compound of Formula III contains both a basic moiety, such as, but not limited to a pyridine or imidazole, and an acidic moiety, such as, but not limited to a carboxylic acid, zwitterions ("inner salts") may be formed and are included within the term "salt(s)" as used herein. Pharmaceutically acceptable (i.e., non-toxic, physiologically acceptable) salts are preferred, although other salts are also useful. Salts of the compounds of the Formula I may be formed, for example, by reacting a compound of Formula I with an amount of acid or base, such as an equivalent amount, in a medium such as one in which the salt precipitates or in an aqueous medium followed by lyophilization.

Exemplary acid addition salts include acetates, ascorbates, benzoates, benzenesulfonates, bisulfates, borates, butyrates, citrates, camphorates, camphorsulfonates, fumarates, hydrochlorides, hydrobromides, hydroiodides, lactates, maleates, methanesulfonates, naphthalenesulfonates, nitrates, oxalates, phosphates, propionates, salicylates, succinates, sulfates, tartarates, thiocyanates, toluenesulfonates (also known as tosylates,) and the like. Additionally, acids which are generally considered suitable for the formation of pharmaceutically useful salts from basic pharmaceutical compounds are discussed, for example, by S. Berge *et al*, *Journal of Pharmaceutical Sciences* (1977) 66(1) 1-19; P. Gould, *International J. of*

Pharmaceutics (1986) 33 201-217; Anderson *et al, The Practice of Medicinal Chemistry* (1996), Academic Press, New York; and in *The Orange Book* (Food & Drug Administration, Washington, D.C. on their website). These disclosures are incorporated herein by reference thereto.

Exemplary basic salts include ammonium salts, alkali metal salts such as sodium, lithium, and potassium salts, alkaline earth metal salts such as calcium and magnesium salts, salts with organic bases (for example, organic amines) such as dicyclohexylamines, t-butyl amines, and salts with amino acids such as arginine, lysine and the like. Basic nitrogen-containing groups may be quarternized with agents such as lower alkyl halides (e.g. methyl, ethyl, and butyl chlorides, bromides and iodides), dialkyl sulfates (e.g. dimethyl, diethyl, and dibutyl sulfates), long chain halides (e.g. decyl, lauryl, and stearyl chlorides, bromides and iodides), aralkyl halides (e.g. benzyl and phenethyl bromides), and others.

All such acid salts and base salts are intended to be pharmaceutically acceptable salts within the scope of the invention and all acid and base salts are considered equivalent to the free forms of the corresponding compounds for purposes of the invention.

Compounds of Formula I, and salts, solvates and prodrugs thereof, may exist in their tautomeric form (for example, as an amide or imino ether). All such tautomeric forms are contemplated herein as part of the present invention.

All stereoisomers (for example, geometric isomers, optical isomers and the like) of the present compounds (including those of the salts, solvates and prodrugs of the compounds as well as the salts and solvates of the prodrugs), such as those which may exist due to asymmetric carbons or sulfurs on various substituents, including enantiomeric forms (which may exist even in the absence of asymmetric carbons), rotameric forms, atropisomers, and diastereomeric forms, are contemplated within the scope of this invention. For example, if a compound of Formula (I) incorporates a double bond or a fused ring, both the cis- and trans-forms, as well as mixtures, are embraced within the scope of the invention. Individual stereoisomers of the compounds of the invention may, for example, be substantially free of other isomers, or may be admixed, for example, as racemates or with all other, or other selected, stereoisomers. The chiral centers of the present invention can have the S or R configuration as defined by the *IUPAC* 1974 Recommendations. The use of the terms

"salt", "solvate" "prodrug" and the like, is intended to equally apply to the salt, solvate and prodrug of enantiomers, stereoisomers, rotamers, tautomers, racemates or prodrugs of the inventive compounds.

Diasteromeric mixtures can be separated into their individual diastereomers on the basis of their physical chemical differences by methods well known to those skilled in the art, such as, for example, by chromatography and/or fractional crystallization. Enantiomers can be separated by converting the enantiomeric mixture into a diasteromeric mixture by reaction with an appropriate optically active compound (e.g., chiral auxiliary such as a chiral alcohol or Mosher's acid chloride), separating the diastereomers and converting (e.g., hydrolyzing) the individual diastereomers to the corresponding pure enantiomers. Also, some of the compounds of Formula (I) may be atropisomers (e.g., substituted biaryls) and are considered as part of this invention. Enantiomers can also be separated by use of chiral HPLC column.

Polymorphic forms of the compounds of formula I, and of the salts, solvates and prodrugs of the compounds of formula I, are intended to be included in the present invention

The present invention also embraces isotopically-labelled compounds of the present invention which are identical to those recited herein, but for the fact that one or more atoms are replaced by an atom having an atomic mass or mass number different from the atomic mass or mass number usually found in nature. Examples of isotopes that can be incorporated into compounds of the invention include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorus, fluorine and chlorine, such as ^{2}H, ^{3}H, ^{13}C, ^{14}C, ^{15}N, ^{18}O, ^{17}O, ^{31}P, ^{32}P, ^{35}S, ^{18}F, and ^{36}Cl, respectively.

Certain isotopically-labelled compounds of Formula (I) (e.g., those labeled with ^{3}H , ^{11}C and ^{14}C) are useful in compound and/or substrate tissue distribution assays. Tritiated (i.e., ^{3}H) and carbon-14 (i.e., ^{14}C) isotopes are particularly preferred for their ease of preparation and detectability. Further, substitution with heavier isotopes such as deuterium (i.e., ^{2}H) may afford certain therapeutic advantages resulting from greater metabolic stability (e.g., increased in vivo half-life or reduced dosage requirements) and hence may be preferred in some circumstances. Isotopically labelled compounds of Formula (I) can generally be prepared by following procedures analogous to those disclosed in the Schemes and/or in the Examples hereinbelow, by

substituting an appropriate isotopically labelled reagent for a non-isotopically labelled reagent.

The compounds according to the invention have pharmacological properties; in particular, the compounds of Formula I can be useful as α2C adrenoreceptor agonists.

A preferred dosage is about 0.001 to 500 mg/kg of body weight/day of the compound of Formula I. An especially preferred dosage is about 0.01 to 25 mg/kg of body weight/day of a compound of Formula I, or a pharmaceutically acceptable salt or solvate of said compound.

The compounds of this invention may also be useful in combination (administered together or sequentially) with one or more therapeutic agents such as, for example, glucocorticosteroids, PDE-4 inhibitors, anti-muscarinic agents, cromolyn sodium, H_1 receptor antagonists, 5-HT_1 agonists, NSAIDs, angiotensin-converting enzyme inhibitors, angiotensin II receptor agonists, β-blockers, β-agonists (including both short and long acting), leukotriene antagonists, diuretics, aldosterone antagonists; ionotropic agents, natriuretic peptides, pain management/analgesic agents, anti-anxiety agents, anti-migraine agents, and therapeutic agents suitable for treating heart conditions, psychotic disorders, and glaucoma.

Suitable steroids include prednisolone, fluticasone (including all esters such as the propionate or furoate esters), triamcinolone, beclomethasone, mometasone (including any ester form such as mometasone furoate), budasamine, ciclesonide, betamethasone, dexamethasone, prednisone, flunisolide, and cortisone.

Suitable PDE-4 inhibitors include roflumilast, theophylline, rolipram, piclamilast, cilomilast, and CDP-840.

Suitable antiimuscarinic agents include ipratropium bromide and tiatropium bromide.

Suitable H_1 antagonists include astemizole, azatadine, azelastine, acrivastine, brompheniramine, cetirizine, chlorpheniramine, clemastine, cyclizine, carebastine, cyproheptadine, carbinoxamine, descarboethoxyloratidine, diphenhydramine, doxylamine, dimethindene, ebastine, epinastine, efletirizeine, fexofenadine, hydroxyzine, ketotifen, loratidine, levocabastine, meclizine, fexofenadine, hydroxyzine, ketotifen, loratadine, levocabastine, meclizine, mizolastine, mequitazine, mianserin, noberastine, norastemizole, picumast, pyrilamine, promethazine, terfenadine, tripelennamine, temelastine, trimeprazine or triprolidine.

Suitable anti-inflammatory agents include aspirin, diclofenac, diflunisal, etodolac, flurbiprofen, ibuprofen, indomethacin, ketoprofen, ketorolac, nabumetone, naproxen, oxaprozin, piroxicam, sulindac, and tolmetin.

Suitable aldosterone antagonists include spironolactone.

Suitable ionotropic agents include digitalis.

Suitable angiotensin II receptor agonists include irbesartan and losartan.

Suitable diuretics include spironolactone, methyclothiazide, bumetanide, torsemide, hydroflumethiazide, trichlormethiazide, hydroclorothiazide, triamterene, ethacrynic acid, methyclothiazide, hydrochlorothiazide, benzthiazide, hydrochlorothiazide, quinethazone, hydrochlorothiazide, chlorthalidone, furosemide, indapamide, hydroclorothiazide, triamterene, trichlormethiazide, hydrochlorothiazide, amiloride HCl, amiloride HCl, metolazone, trichlormethiazide, bendroflumethiazide, hydrochlorothiazide, polythiazide, hydroflumethiazide, chlorthalidone, and metolazone.

Suitable pain management/analgesic agents include; Celecoxib, amitriptyline, ibuprofen, naproxen, tramadol, rofecoxib, oxycodone HCl, acetaminophenoxycodone HCl, carbamazepine, amitriptyline, diclofenac, diclofenac, etodolac, fenoprofen calcium, flurbiprofen, ibuprofen, indomethacin, ketoprofen, ketorolac tromethamine, mefenamic acid, meloxicam, nabumetone, naproxen, oxaprozin, piroxicam, sulindac, tolmetin sodium, valdecoxib, diclofenac/ misoprostol, oxycontin, vicodin, darvocet, percocet, morphine sulfate, dilaudid, stadol, stadol NS, nalbuphine, acetaminophen with codeine, acetaminophen with codeine #4, Lidoderm® patches, ziconotide, duloxetine, roboxetine, gabapentin and pregabalin.

Suitable β-blockers include acebutolol, atenolol, atenolol/chlorthalidone, betaxolol, bisoprolol fumarate, bisoprolol/HCTZ, labetolol, metoprolol tartrate, nadolol, pindolol, propranolol, propranolol/HCTZ, sotalol, and timolol.

Suitable β-agonists include dobutamine, ritodrine, salbutamol, levalbuterol, metaproternol, formoterol, fenoterol, bambuterol, brocaterol, clenbuterol, terbutaline, tulobuterol, epinephrine, isoprenalin, and hexoprenalin.

Suitable leukotriene antagonists include levamisole.

Suitable anti-migraine agents include rovatriptan succinate, naratriptan HCl, rizatriptan benzoate, sumatriptan succinate, zolmitriptan, almotriptan malate, methysergide maleate, dihydroergotamine mesylate, ergotamine tartrate, ergotamine

tartrate/caffeine, Fioricet®, Fiorninal®, Depakene®, and Depakote®.

Suitable anti-anxiety and anti-depressant agents include amitriptyline HCl, bupropion HCl, citalopram hydrobromide, clomipramine HCl, desipramine, fluoxetine, fluvoxamine maleate, maprotiline HCl, mirtazapine, nefazodone HCl, nortriptyline, paroxetine HCl, protriptyline HCl, sertraline HCl, doxepin, and trimipramine maleate.

Suitable angiotensin converting enzyme inhibitors include Captopril, enalapril, enalapril/HCTZ , lisinopril, lisinopril/HCTZ, and Aceon®.

The pharmacological properties of the compounds of this invention may be confirmed by a number of pharmacological assays. The exemplified pharmacological assays which are described later have been carried out with the compounds according to the invention and their salts.

This invention is also directed to pharmaceutical compositions which comprise at least one compound of Formula I, or a pharmaceutically acceptable salt or solvate of said compound and at least one pharmaceutically acceptable carrier.

For preparing pharmaceutical compositions from the compounds described by this invention, inert, pharmaceutically acceptable carriers can be either solid or liquid. Solid form preparations include powders, tablets, dispersible granules, capsules, cachets and suppositories. The powders and tablets may be comprised of from about 5 to about 95 percent active ingredient. Suitable solid carriers are known in the art, e.g., magnesium carbonate, magnesium stearate, talc, sugar or lactose. Tablets, powders, cachets and capsules can be used as solid dosage forms suitable for oral administration. Examples of pharmaceutically acceptable carriers and methods of manufacture for various compositions may be found in A. Gennaro (ed.), *Remington's Pharmaceutical Sciences,* 18th Edition, (1990), Mack Publishing Co., Easton, Pennsylvania.

Liquid form preparations include solutions, suspensions and emulsions. As an example may be mentioned water or water-propylene glycol solutions for parenteral injection or addition of sweeteners and opacifiers for oral solutions, suspensions and emulsions. Liquid form preparations may also include solutions for intranasal administration.

Aerosol preparations suitable for inhalation may include solutions and solids in powder form, which may be in combination with a pharmaceutically acceptable carrier, such as an inert compressed gas, e.g. nitrogen.

Also included are solid form preparations that are intended to be converted, shortly before use, to liquid form preparations for either oral or parenteral administration. Such liquid forms include solutions, suspensions and emulsions.

The compounds of the invention may also be deliverable transdermally. The transdermal compositions can take the form of creams, lotions, aerosols and/or emulsions and can be included in a transdermal patch of the matrix or reservoir type as are conventional in the art for this purpose.

The compounds of this invention may also be delivered subcutaneously.

Preferably the compound is administered orally.

Preferably, the pharmaceutical preparation is in a unit dosage form. In such form, the preparation is subdivided into suitably sized unit doses containing appropriate quantities of the active component, e.g., an effective amount to achieve the desired purpose.

The quantity of active compound in a unit dose of preparation may be varied or adjusted from about 1 mg to about 100 mg, preferably from about 1 mg to about 50 mg, more preferably from about 1 mg to about 25 mg, according to the particular application.

The actual dosage employed may be varied depending upon the requirements of the patient and the severity of the condition being treated. Determination of the proper dosage regimen for a particular situation is within the skill of the art. For convenience, the total daily dosage may be divided and administered in portions during the day as required.

The amount and frequency of administration of the compounds of the invention and/or the pharmaceutically acceptable salts thereof will be regulated according to the judgment of the attending clinician considering such factors as age, condition and size of the patient as well as severity of the symptoms being treated. A typical recommended daily dosage regimen for oral administration can range from about 1 mg/day to about 500 mg/day, preferably 1 mg/day to 200 mg/day, in two to four divided doses.

Another aspect of this invention is a kit comprising a therapeutically effective amount of at least one compound of Formula I, or a pharmaceutically acceptable salt or solvate of said compound and a pharmaceutically acceptable carrier, vehicle or diluent.

Yet another aspect of this invention is a kit comprising an amount of at least one compound of Formula I, or a pharmaceutically acceptable salt or solvate of said compound and an amount of at least one therapeutic agent listed above, wherein the amounts of the two or more ingredients result in desired therapeutic effect.

The invention disclosed herein is exemplified by the following preparations and examples which should not be construed to limit the scope of the disclosure. Alternative mechanistic pathways and analogous structures will be apparent to those skilled in the art.

Where NMR data are presented, ^1H spectra were obtained on either a Varian VXR-200 (200 MHz, ^1H), Varian Gemini-300 (300 MHz), Varian Mercury VX-400 (400MHz), or Bruker-Biospin AV-500 (500MHz), and are reported as ppm with number of protons and multiplicities indicated parenthetically. Where LC/MS data are presented, analyses was performed using an Applied Biosystems API-100 mass spectrometer and C18 column, 10-95% CH_3CN-H_2O (with 0.05% TFA) gradient. The observed parent ion is given.

The following solvents and reagents may be referred to by their abbreviations in parenthesis:

Me = methyl; Et = ethyl; Pr = propyl; Bu = butyl; Ph = phenyl, and Ac = acetyl

µl = microliters

AcOEt or EtOAc = ethyl acetate

AcOH or HOAc = acetic acid

ACN = acetonitrile

atm = atmosphere

Boc or BOC = tert-butoxycarbonyl

DCE = dichloroethane

DCM or CH_2Cl_2: dichloromethane:

DIPEA = diisopropylethylamine

DMAP = 4-dimethylaminopyridine

DMF = dimethylformamide

DMS = dimethylsulfide

DMSO = dimethyl sulfoxide

EDCI = 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide

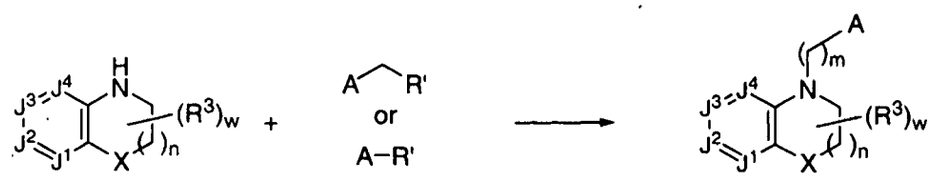
Fmoc = 9-fluorenylmethoxycarbonyl

g = grams
h = hour
hal = halogen
HOBt = 1-hydroxybenzotriazole
LAH = lithium aluminum hydride
LCMS = liquid chromatography mass spectrometry
min = minute
mg = milligrams
mL = milliliters
mmol = millimoles
MCPBA = 3-chloroperoxybenzoic acid
MeOH = methanol
MS = mass spectrometry
NMR = nuclear magnetic resonance spectroscopy
RT or rt = room temperature (ambient, about 25ºC)
TEA or Et_3N = triethylamine
TFA = trifluoroacetic acid
THF = tetrahydrofuran
TLC = thin layer chromatography
TMS = trimethylsilyl
Tr = triphenylmethyl

Examples

The compounds of this invention can be prepared as generally described in Schemes 1 and 2, and the following examples. Scheme 1 shows an approach in which **S1** and **S2** are joined together. Examples of these approaches include reaction of **S1** with an electrophilic **S2** compound, where **R'** is a carboxaldehyde (coupling by reductive amination), carboxylic acid (amide coupling) or halide (coupling by alkylation).

Scheme 1



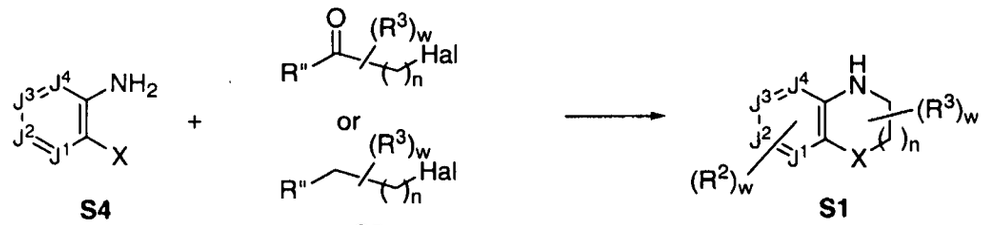
S1
X = N, O, or S

S2a R' = CHO
S2b R' = CO_2H
S2c R' = CH_2(Hal)

S3

Scheme 2 discloses a general approach for synthesizing **S1**, whereby an appropriately substituted aniline **S4** can be converted to **S1** through a single or multistep ring cyclization approach.

Scheme 2



S4

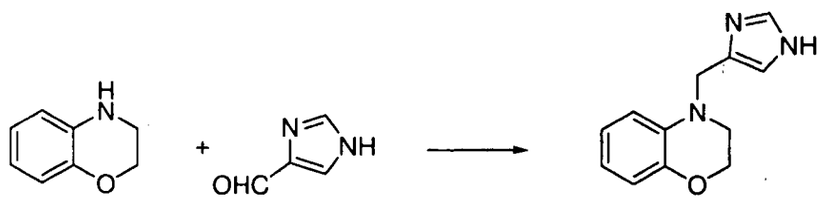
S5
R" = H, OR or Hal

S1

Compounds of formula **S3** can be prepared by the general methods outlined above. Specifically exemplified compounds were prepared from **S4** or **S1** fragments as described in the examples below or from starting materials known in the art.

The starting materials and reagents used in preparing compounds described are either available from commercial suppliers such as Aldrich Chemical Co. (Wisconsin, USA) and Acros Organics Co. (New Jersey, USA) or were prepared by literature methods known to those skilled in the art. These examples are being provided to further illustrate the present invention. They are for illustrative purposes only; the scope of the invention is not to be considered limited in any way thereby.

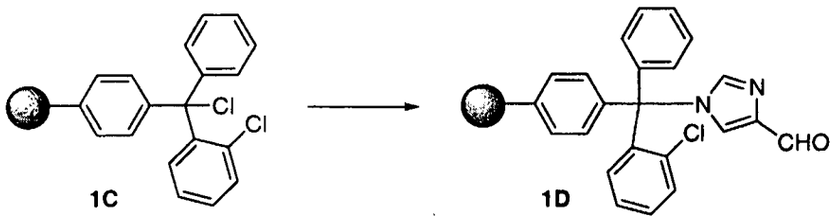
PREPARATIVE EXAMPLE 1



1A **1B** **1**

A solution of 3,4-dihydro-2H-1,4-benzoxazine **1A** (0.1 g, 0.75 mmol) in DCE (10 mL) was treated with imidazole-4-carboxaldehye **1B** (0.11 g, 1.1 mmol), $NaBH(OAc)_3$ (0.47 g, 2.2 mmol), and AcOH (one drop) and stirred at 60 °C overnight. The reaction was then diluted with CH_2Cl_2, washed with saturated aqueous $NaHCO_3$, dried over Na_2SO_4, and concentrated. Chromatography (0-4% 7 N NH_3-MeOH/CH_2Cl_2) provided **1** as a beige solid (0.08 g, 50%). LMCS m/z 216 (MH+).

Alternatively, the title compound **1** can be synthesized by the reaction of **1A** and resin bound imidazole-4-carboxaldehye **1D** as described below:

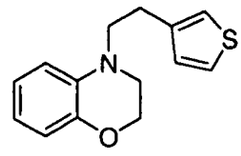


1C **1D**

Novabiochem Resin **1C** (100-200 mesh, 1% DVB, 1.4 mmol/g, 5g) was suspended in anhydrous DMF (25 mL) and DCE (25 mL) and treated sequentially with **1B** (2 g, 21 mmol) and TEA (2.96 mL, 21 mmol). The resin was shaken overnight and washed with DMF (3x), MeOH (3x), and DCM (4x) then dried in vacuo overnight. The resulting resin **1D** (100 mg, 1.4 mmol/g, 0.14 mmol) was suspended in DCE (4 mL) and treated with **1A** (94.5mg, 0.7 mmol) and $NaBH(OAc)_3$ (148mg, 0.7 mmol). The reaction was shaken overnight and washed with DMF (3x), MeOH (3x), and DCM (4x), then dried in vacuo. The resulting resin was subjected to 30%TFA/DCM, stirred at RT for 2 h and the mixture was concentrated under vacuum. The residue was purified by Gilson prep-HPLC to afford compound **1** (12.3 mg).

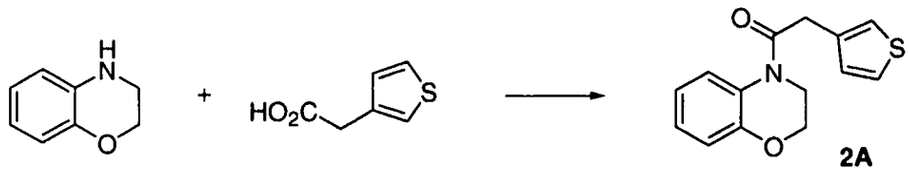
52

PREPARATIVE EXAMPLE 2



2

Step 1



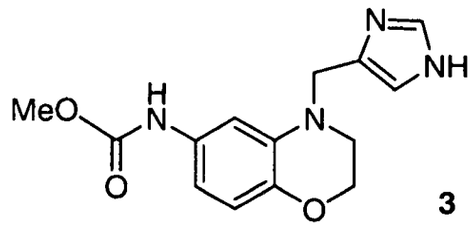
2A

A solution of 3,4-dihydro-2H-1,4-benzoxazine (0.52 g, 3.8 mmol) and thiophene-3-acetic acid (0.82 g, 5.7 mmol) in 1:1 CH_2Cl_2:DMF (20 mL) was treated with DIPEA (2.6 ml, 15 mmol), HOBt (1.29 g, 9.5 mmol), and EDCI (1.83 g, 9.5 mmol) and stirred at 70 °C overnight. The reaction was then diluted with CH_2Cl_2, washed with saturated aqueous $NaHCO_3$, dried over Na_2SO_4, and concentrated. Chromatography (0-10% 1 N NH_3-MeOH/EtOAc) provided **2A** as a red solid (0.54g, 55%)

Step 2

A solution of **2A** (0.094 g, 0.36 mmol) in THF (10 mL) was treated with BH_3-SMe_2 (2M/THF, 0.27 mL, 0.54 mmol) and stirred at reflux for 2h. The reaction was concentrated and subjected to chromatography (EtOAc) to provide **2** as a white solid (0.040 g, 45%). LMCS m/z 246 (MH+).

PREPARATIVE EXAMPLE 3



3

Step 1



3A **3B**

A mixture of 2-amino-4-nitrophenol (**3A**, 25.03 g, 0.16 mol) in 4-methyl-2-pentanone and water (420 mL, 1:1) was treated with sodium bicarbonate (32.74g, 0.39mol), cooled to 0 °C, and treated then with chloroacetyl chloride (15.52 mL, 0.19 mol). The reaction mixture was heated to reflux overnight. After cooling to RT, the mixture was concentrated under vacuum. The residue was diluted with water (200 mL) and EtOAc (100 mL), and filtered to give the pale gray solid **3B** (26.05 g). The filtrate was separated and the aqueous was extracted with EtOAc (3 x 100 mL). The combined organic layers were washed with water, and dried ($MgSO_4$), filtered, and concentrated under vacuum to give additional light gray solid **3B** (7.7 g). The resulting solid (quantitative yield) was used for next reaction without further purification.

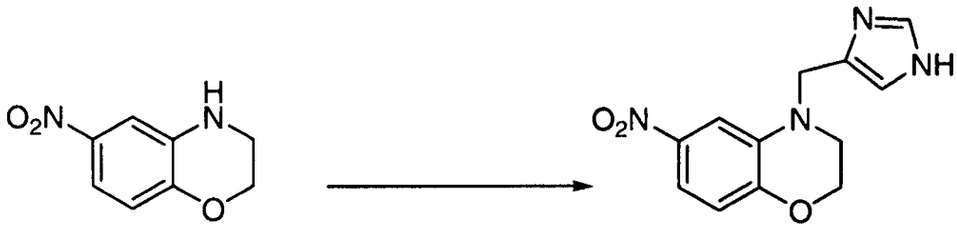
Step 2



3B **3C**

To compound **3B** (6.76 g, 34.84 mmol) in anhydrous THF (200 mL) was added BH_3-SMe_2 (2.0M/THF, 35 mL, 69.68 mmol). The mixture was heated to reflux for 2 h. After cooling to RT, the mixture was quenched with MeOH (10 ml) and heated to reflux for another 10 minutes. The reaction mixture was concentrated under vacuum. Chromatography (10%-30% EtOAc/hexanes) provided **3C** (6.1 g, 97% for two steps).

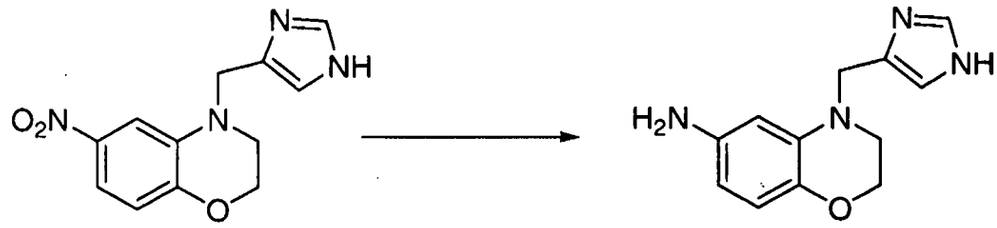
Step 3



3C **3D**

A mixture of **3C** (4.35 g, 21.16 mmol) in anhydrous dichloroethane (60 mL) was treated with imidazole-4-carboxaldehye (**1B**, 2.79 g, 28.99 mmol) and AcOH (0.35 mL, 6 mmol). The mixture was stirred at RT for 10 min and then treated with $NaBH(OAc)_3$ (15.36 g, 72.48 mmol). The reaction mixture was stirred at RT overnight, and quenched with 2N NaOH solution, concentrated under vacuum. The residue was diluted with water (50 mL) and extracted with EtOAc (4 x 100 mL). The organic layer was dried ($MgSO_4$), filtered, and concentrated under vacuum. Chromatography (DCM containing 1 to 5% of 7N NH_3 in MeOH) provided **3D** (5.56g, 89%). MS m/z 261 (MH+).

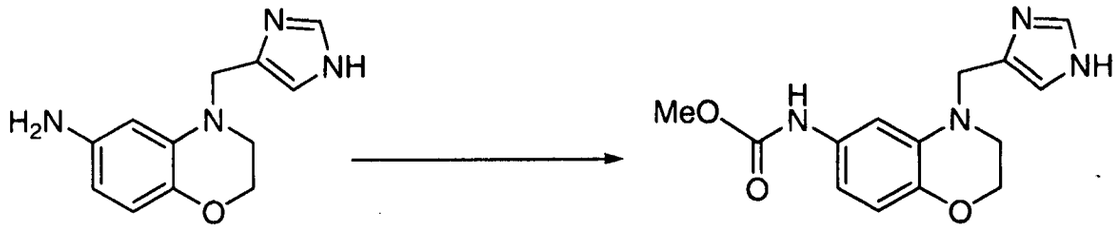
Step 4



3D **3E**

Compound **3D** (5.56 g, 21.38 mmol) was dissolved in MeOH/EtOAc (300 mL, 1:1), 10% Pd/C (1.11 g, 20% by weight) was carefully added. The mixture was stirred at RT under a hydrogen balloon overnight and filtered. The solvent was evaporated off under vacuum to give a white solid **3E** (5.46 g, 100%). MS m/z 231 (MH+).

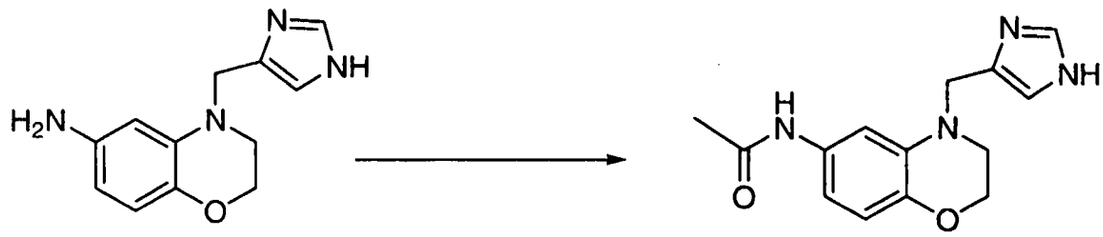
Step 5



3E **3**

A mixture of amine **3E** (2.14 g, 9.30 mmol) in anhydrous DCM (40 mL) was sequentially treated with TEA (3.24 mL, 23.3 mmol) and $ClCO_2Me$ (1.43 mL, 18.6 mmol). The mixture was stirred at RT for 2 h, and then quenched with 2N NaOH solution. The resulting mixture was stirred for another 2 h and separated. The aqueous layer was extracted with DCM (3 x 50 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated under vacuum. Chromatography (DCM containing 1 to 4% of 7N NH_3/MeOH) provided **3** as a white solid (1.64 g, 61%). MS m/z 289 (MH+).

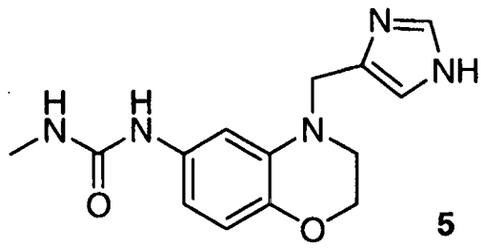
PREPARATIVE EXAMPLE 4



3E **4**

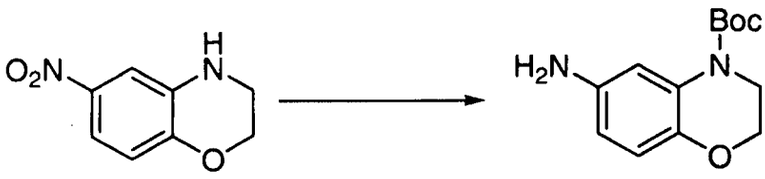
In a manner similar to Example 3, Step 5, amine **3E** was treated with TEA and AcCl to provide the compound **4**. MS m/z 273 (MH+).

PREPARATIVE EXAMPLE 5



5

Steps 1-2

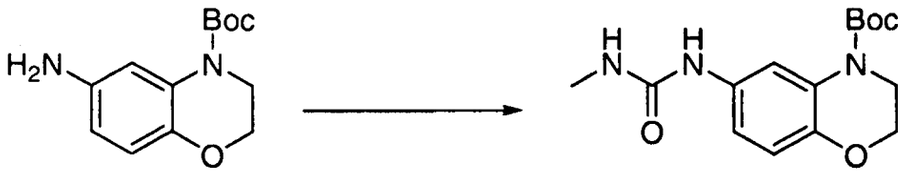


3C **5A**

A solution of **3C** (3 g, 16.7 mmol) in anhydrous DCM (100 mL) was treated with Boc_2O (7.27g, 33.3 mmol), pyridine (5.39 mL, 66.7 mmol), and catalytic DMAP. The mixture was stirred at RT overnight and concentrated under vacuum. The residue was diluted with water (50 mL) and extracted with EtOAc (3 x 100 mL). The combined organic layers were dried ($MgSO_4$), concentrated and subjected to chromatography (5-5% EtOAc/hexanes, yield: 3g, 64%).

The resulting product was hydrogenated in a manner similar to that found in Example 3, Step 4 to provide **5A.**

Step 3



5A **5B**

To amine **5A** (1.1 g, 4.4 mmol) in anhydrous THF (15 mL) was added MeNCO (215 mg, 4.4 mmol). The mixture was stirred at RT overnight and then concentrated. Chromatography (DCM containing 1 to 5% of 7N NH_3/MeOH) provided **5B** (890 mg, 66%).

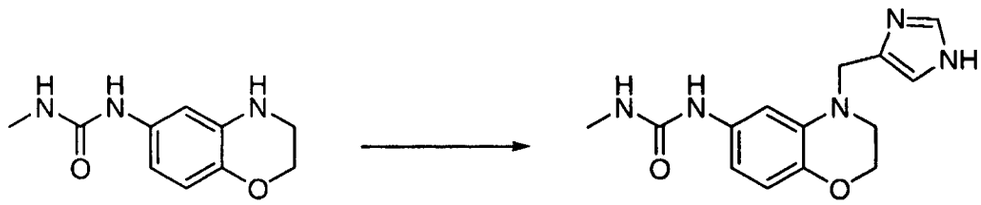
Step 4



5B **5C**

Compound **5B** (890 mg, 2.9 mmol) was stirred at RT in 30% TFA/DCM (14 mL) containing three drops of Et_3SiH for 1 h, and then quenched with 2N NaOH solution. The mixture was extracted with EtOAc (3 x 50 mL). The organic layer was dried ($MgSO_4$), filtered and concentrated under vacuum. The residue (**5C**, 600mg) was used in the next reaction without further purification.

Step 5

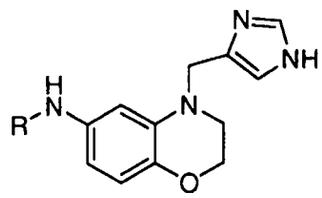


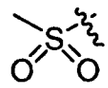
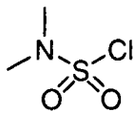
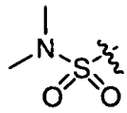
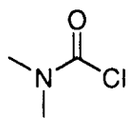
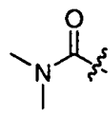
5C **5**

In a manner similar to that described in Example 3 (Step 3), compound **5C** was treated with imidazole-4-carboxaldehyde (**1B**) to provide title compound **5** (56% for two steps). MS m/z 288 (MH+).

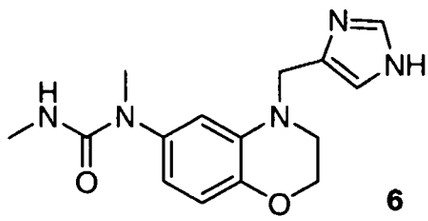
Compounds **5D-5F** in **Table 1** below can be prepared from compound **5A** using various capping reagents as shown, followed by Boc-deprotection and reductive alkylation as described above.

Table 1



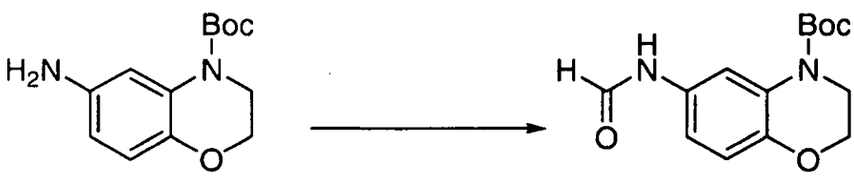
Cpd	Reagent	R	MS (MH+)
5D	Methanesulfonic anhydride/pyridine		309
5E	 and pyridine		338
5F	 and pyridine		302

PREPARATIVE EXAMPLE 6



6

Step 1



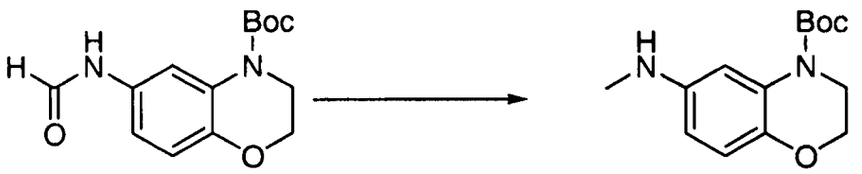
5A **6A**

To a flask with Ac_2O (2.02 mL, 21.4 mmol) at 0 °C was added HCO_2H (0.82 mL, 21.4 mmol) by syringe. After stirring at 0 °C for 5 min, the mixture was heated up to 55 °C for 2h, and then was cooled to 0 °C again. Amine **5A** (2g, 8.0 mmol) in anhydrous THF (100 mL) was added and the mixture was stirred at 0 °C for 30 min. The reaction mixture was concentrated under vacuum and diluted with 2 N NaOH solution to pH 9, extracted with EtOAc (3 x 50 mL). The organic layer was dried

($MgSO_4$), filtered, and concentrated under vacuum to give a foam **6A** (quantitative yield).

Alternatively, a mixture of compound **5A** (17.5 g, 69.9 mmol) in butyl formate (700 ml) was heated at 50°C for 3h and then left at RT overnight. The reaction mixture was then concentrated, added to 100 ml of 0.5N NaOH, extracted with CH_2Cl_2 (4X), dried with Na_2SO_4, and concentrated. Chromatography (10%-50% EtOAc/hexane) gave **6A** (9.19 g, 47 %) as a light brown sticky foam.

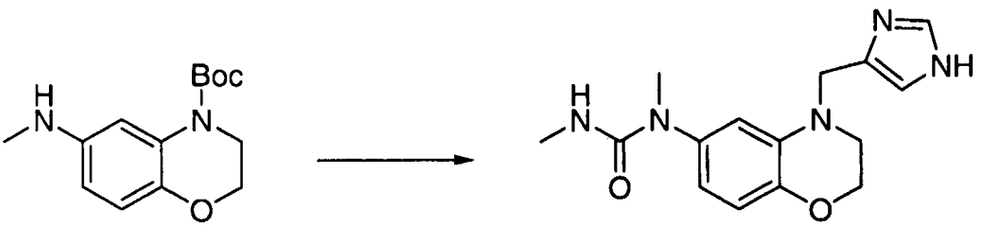
Step 2



6A **6B**

A mixture of compound **6A** (2.75 g, 9.88 mmol) in THF (30 ml) was treated slowly with BH_3-DMS (2.0 M/THF, 7.8 ml) and then heated at reflux for 3h. The reaction mixture was concentrated, treated with K_2CO_3 (1.5 g) and EtOH, and then stirred overnight at RT. The reaction mixture was filtered, concentrated, added to H_2O and extracted with CH_2Cl_2 (4X). The combined organic layers were dried with Na_2SO_4, filtered and concentrated to provide **6B** as a clear oil (2.76 g).

Steps 3-5



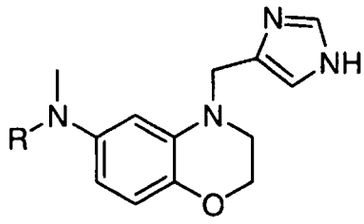
6B **6**

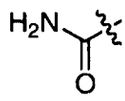
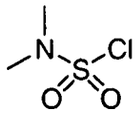
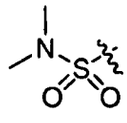
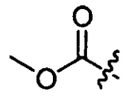
A solution of **6B** (2.76 g, crude) in CH_2Cl_2 (20 ml) was treated slowly with MeNCO (1.0 g, 12.5 mmol) and stirred at RT overnight. The reaction mixture was concentrated and chromatographed (50% to 80% EtOAc/hex, 3.10 g, 98% yield from **6A**). This product (3.10 g, 9.65 mmol) was taken up in of CH_2Cl_2 (80 ml) and deprotected with of TFA (11.5 ml) as described in Example 5, Step 4 (95% yield). A

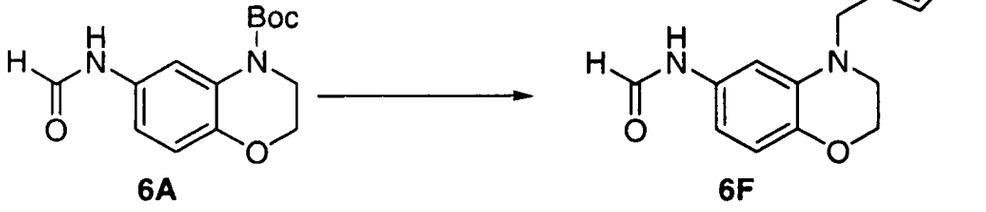
mixture of the resulting amine and aldehyde **1B** (1 eq) in a minimal amount of CH_2Cl_2 was treated with $Ti(OiPr)_4$ (1.3 eq). After stirring for 2h at RT, $NaBH_4$ (1.2 eq) and EtOH were added. The reaction mixture was then stirred overnight, concentrated, treated with H_2O and extracted with CH_2Cl_2 (4X). The combined organic layers were dried with Na_2SO_4, filtered, concentrated and chromatographed (silica gel, 5% MeOH/ CH_2Cl_2 w/ NH_3) to provide the title compound **6** (74% yield). MS m/z 302 (MH+).

Compounds in **Table 2** below can be prepared from compound **6B** using the various capping reagents as shown, followed by Boc-deprotection and reductive alkylation as shown in Example 5.

Table 2

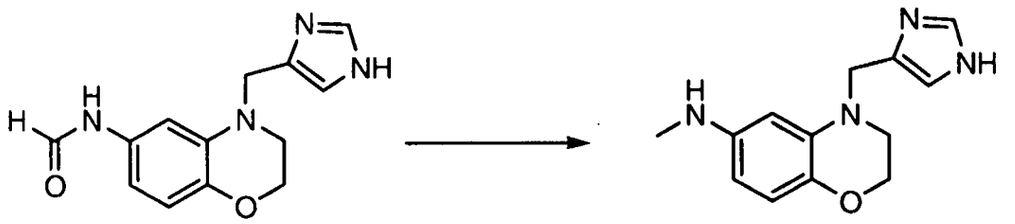


Cpd	Reagent	R	MS (MH+)
6C	TMSNCO		288
6D	 /pyridine		352
6E	MeCOCl /pyridine		303



6A **6F**

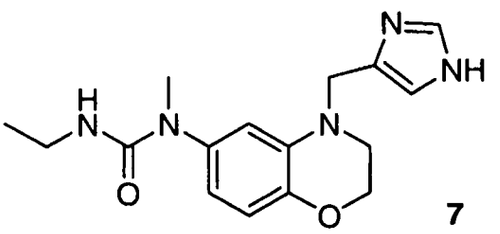
Compound **6F** was prepared as follows: **6A** was treated with TFA, followed by reductive alkylation with imidazole-4-carboxaldehyde (**1B**) as described previously in Example 5 (Step 4) and Example 3 (Step 3). MS m/z 259 (MH+).



6F **6G**

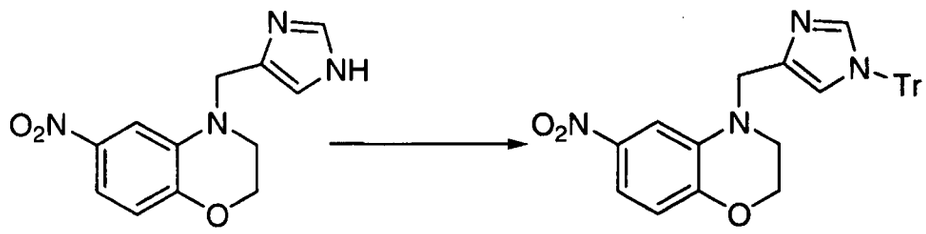
In a manner similar to Example 3, Step 2, compound **6F** was reduced with BH_3-SMe_2 to provide **6G**. MS m/z 245 (MH+).

PREPARATIVE EXAMPLE 7



7

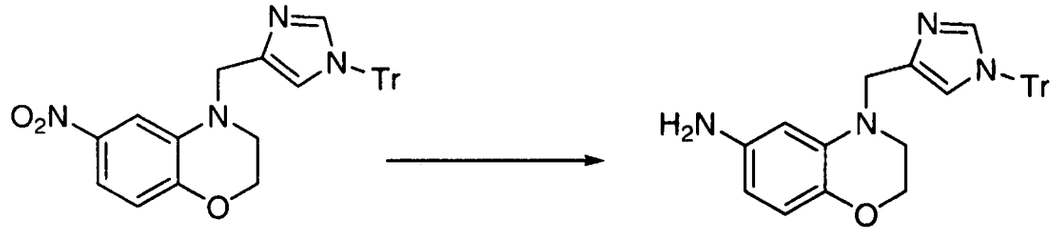
Step 1



3D **7A**

To a suspension of compound **3D** (4.8 g, 18.46 mmol) in anhydrous DCM (200 mL) was sequentially added TrCl (5.15 g, 18.46 mmol) and TEA (7.7 mL, 55.37 mmol). The mixture was stirred at RT overnight, and quenched with saturated NH_4Cl solution. The solution was separated and the aqueous was extracted with DCM (3 x 100 mL). The combined organic layers were washed with water, dried ($MgSO_4$), filtered, and concentrated under vacuum to give red yellowish solid **7A** (9.13g, yield: 98%).

Step 2

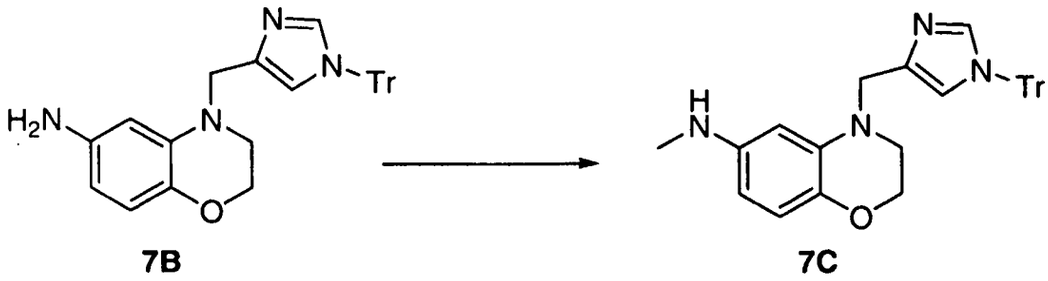


7A **7B**

To compound **7A** (4.55g, 9.06 mmol) in MeOH/EtOAc (400 mL, 1:1) in a hydrogenation bottle was added 10% Pd-C (1 g). The reaction vessel was shaken in the Parr shaker under 50 psi hydrogen for 4h. Then the catalyst was filtered off through a celite bed and washed with MeOH and EtOAc. The filtrate was concentrated under vacuum to give white solid **7B** (3.81 g, 89%).

63

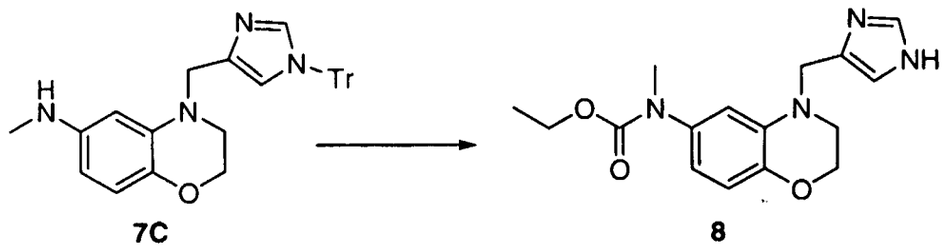
Steps 3-6



7B **7C**

Following the approach outlined in Example 6 (Steps 1-2), **7B** was treated with Ac_2O/HCO_2H and then reduced with BH_3-SMe_2 to afford **7C.** In a manner similar to that found in Example 5 (Steps 3-4), **7C** was further elaborated by treatment with EtNCO and deprotection with TFA to provide the title compound **7**. MS m/z 316 (MH+).

PREPARATIVE EXAMPLE 8

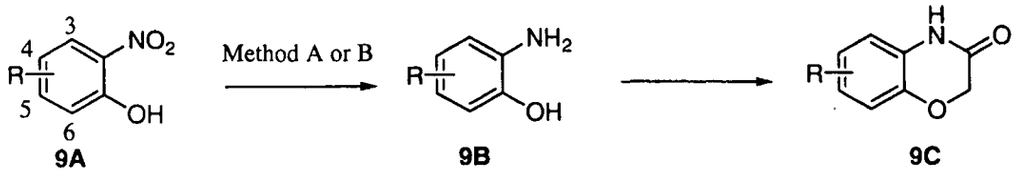


7C **8**

To compound **7C** (1.5 g, 3.09 mmol) in anhydrous DCM (10 mL) was added pyridine (0.5 mL, 6.18 mmol) and $ClCO_2Et$ (0.59 mL, 6.18 mmol) sequentially. The mixture was stirred at RT overnight, and then quenched with saturated NH_4Cl solution. The solution was concentrated and the aqueous was extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with brine, dried ($MgSO_4$), filtered, and concentrated under vacuum.

The residue was then deprotected with TFA, in a manner described in Example 5, Step 4, to afford compound **8** (145 mg, 15% for two steps). MS m/z 317 (MH+).

PREPARATIVE EXAMPLE 9

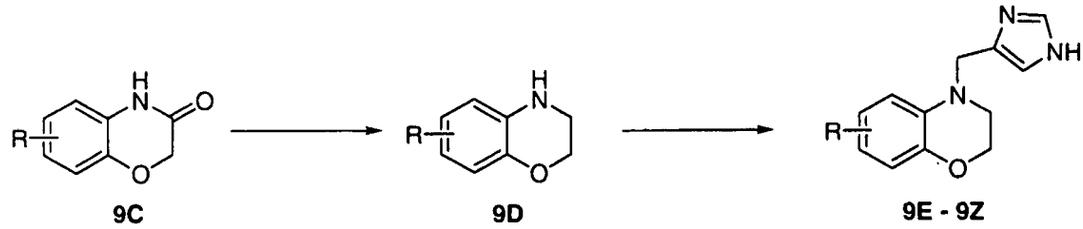


9A 9B 9C

The synthesis in Example 9 used starting materials **9A**, **9B** or **9C**. Compound **9B** can be synthesized from **9A** by using reduction method A or B:

Method A: To compound **9A** in MeOH was added 10% Pd/C and the mixture was stirred at RT under hydrogen balloon overnight. Then the catalyst was filtered off through a celite bed and washed with MeOH. The filtrate was concentrated to give compound **9B** for next reaction without further purification.

Method B: To compound **9A** in EtOH was added $SnCl_2$-$2H_2O$ (4eq.), and the mixture was heated to reflux for 2 h. The mixture was concentrated and poured into ice, neutralized to pH 7 with sat. $NaHCO_3$. Then the solid was filter off and washed extensively with EtOAc. The filtrate was separated and the aqueous was extracted with (3x). The organic layer was dried ($MgSO_4$), filtered and concentrated to give compound **9B**.



9C 9D 9E - 9Z

Compounds **9E-9Z** (shown in **Table 3**) were synthesized starting from **9A, 9B** or **9C** by following the procedures described in Example 3. The selective single-nitro reduction of starting material **9A13** (2,6-dinitrophenol) using Method A provided 2-amino-6-nitrophenol.

Table 3

Starting Material	R	Reduction method from 9A	Cpd	Spectral data MS (MH+) unless noted
9A1	4-F	A	**9E**	234
9A2	5-F	A	**9F**	234
9A3	6-F	A	**9G**	234
9A4	5,6-diF	A	**9H**	252
9B1	4-Cl	N.A.	**9I**	^{1}H NMR ($CDCl_3$): 7.60 (s, 1H), 6.90 (s, 1H), 6.75 (d, 1H), 6.66 (d, 1H), 6.55 (dd, 1H), 4.40 (s, 2H), 4.20 (t, 2H), 3.40 (t, 2H)
9B2	5-Cl	N. A.	**9J**	250
9A5	6-Cl	B	**9K**	250
9A6	4,6-diCl	B	**9L**	284
9C1	4-Me	N.A.	**9M**	230
9A7	3-Me	A	**9N**	230
9B3	4-Ph	N.A.	**9O**	292
9A8	4-Br	B	**9P**	294
9A9	4-CF_3	A	**9Q**	284
9A10	3-OMe	A	**9R**	246
9A11	4-OMe	A	**9S**	246
9B4	5-OMe	N.A.	**9T**	246
9A12	6-OMe	A	**9U**	246
9B5	4-SO_2NH_2	N.A.	**9V**	295
9B6	4-SO_2Et	N.A.	**9W**	308
9B7	5-NO_2	N.A.	**9X**	261
9A13	6-NO_2	A	**9Y**	261
9A14	4-CO_2CH_3	B	**9Z**	274

Starting material **9A10** in **Table 3** was prepared as follows:

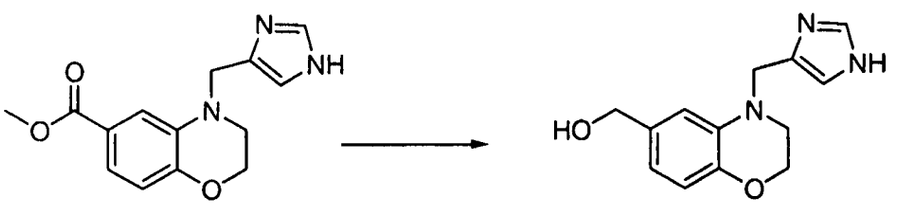
Dimethylsulfate (2.7 mL, 0.058 mmol) was added carefully to 2-nitrobenzene-1,3-diol (2.5 g, 0.232 mmol) and the mixture was stirred vigorously while 10% NaOH solution (21 mL) was added and the temperature was kept below 40 °C. After about

15 min, the mixture was cooled and then filtered. The filtrate was collected and acidified with 10% HCl, and extracted with ether (3 x 25 mL). The organic layer was dried ($MgSO_4$), filtered, and concentrated under vacuum. Chromatography (10-30% EtOAc/hexanes) provided **9A10** (1 g, 37%).

Starting material **9A12** in **Table 3** was prepared as follows:

Fuming HNO_3 (0.34 mL, 0.008 mmol) was carefully added to a mixture of 2-methoxyphenol (0.886 mL, 0.008 mmol) in anhydrous DCM (10 mL) at -20 °C. After stirring for 2 h at RT, the mixture was concentrated under vacuum. Chromatography (10-30% EtOAc/ hexanes) provided **9A12** (400 mg, 29%) and 2-methoxy-3-nitrophenol (400 mg, 29%).

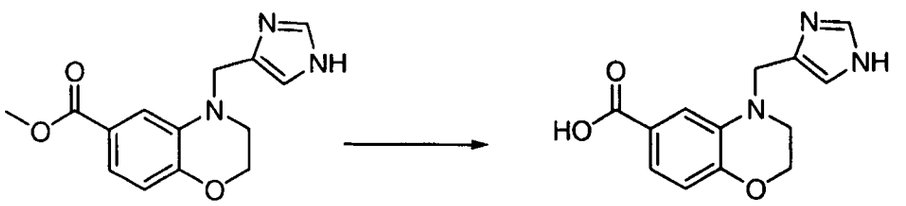
PREPARATIVE EXAMPLE 10



9Z **10**

A mixture of compound **9Z** (46 mg, 0.24 mmol) in anhydrous THF (10 mL) at 0 °C was carefully treated with LAH powder (18 mg, 0.48 mmol) and then stirred for 2 h at RT. The reaction was quenched with 1N NaOH solution (2 mL), filtered and concentrated under vacuum. Chromatography (DCM with 3 to 5% of 7N NH_3-MeOH) provided **10** (47 mg, 80%). MS m/z 246(MH+).

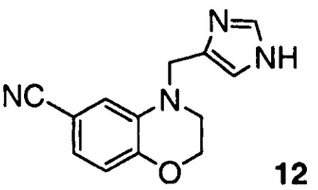
PREPARATIVE EXAMPLE 11



9Z 11

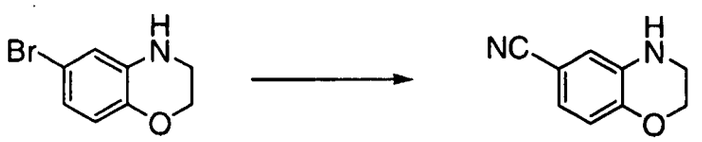
A mixture of **9Z** (67 mg, 0.24 mmol) in MeOH (5 mL) was treated with NaOH (15 mg, 0.38 mmol) and stirred at RT overnight. The reaction was then neutralized with 10% HCl and concentrated under vacuum. The residue was taken up in MeOH, stirred for 1 h, filtered, and concentrated. Chromatography (Prep-HPLC) provided compound **11** (21 mg, 32%). MS m/z 260(MH+).

PREPARATIVE EXAMPLE 12



12

Steps 1



9D 12A

A mixture of 6-bromo-3,4-dihydro-2H-benzo[1,4]oxazine (**9D**, 1.5 g, 7.05 mmol) and CuCN (1.58 g, 17.61 mmol) in anhydrous DMF (15 mL) was stirred at 130 °C for 3 h and then at 150 °C overnight. Then the mixture was cooled to RT, quenched with water and concentrated under vacuum. The residue was taken up in 2N NaOH and EtOAc (100 mL) and then agitated in a sonicator for 1 h. The precipitate was filtered off and washed with EtOAc. The filtrate and washings were combined and extracted with EtOAc (2 x 80 mL). The organic layer was dried ($MgSO_4$), filtered and concentrated under vacuum to give compound **12A** (1.062 g, 94%).

Step 2

In a manner similar to that found in Example 3, Step 3, **12A** was converted to the title compound **12**. MS m/z 241 (MH+).

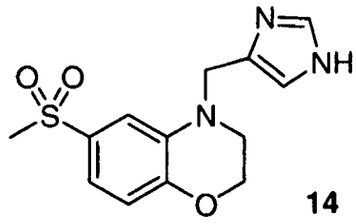
EXAMPLE 13



12 **13**

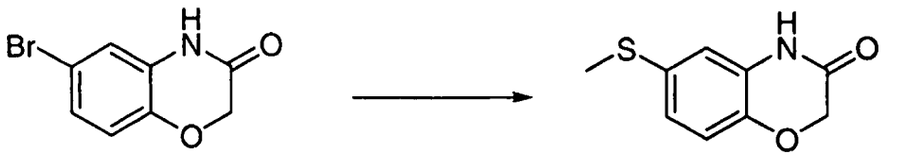
A solution of **12** (0.179 g, 0.75 mmol) in anhydrous EtOH (10 mL) was cooled to 0 °C and treated with bubbling HCl gas for 15 min. The mixture was stirred at 0 °C for 30 min, warmed to RT overnight, and concentrated. The residue was dissolved in 2.0 M NH_3-MeOH (5 mL), stirred at RT for 4 h, and then concentrated under vacuum. Chromatography (Ranin-Prep HPLC, Waters SunFire™ Prep C18 5 µM, 19-100 mm column, 5-90% CH_3CN/H_2O gradient) gave the compound **13** (36 mg: 19%). MS m/z 258 (MH+).

PREPARATIVE EXAMPLE 14



14

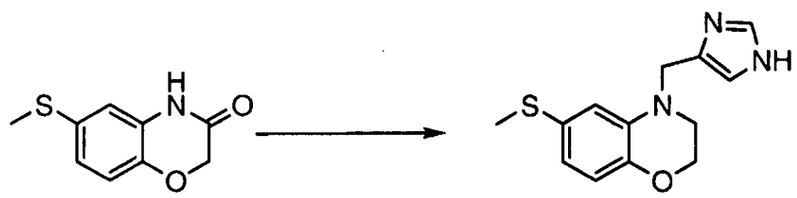
Step 1



9C **14A**

To a suspension of KH (30% in mineral oil, washed with hexanes, 1.2 g, 8.98 mmol) in anhydrous THF (20 mL) at 0 °C under argon was added a solution of 6-bromo-4H-benzo[1,4]oxazin-3-one (**9C**, 1.02 g, 4.49 mmol) in THF (20 mL). After 15 min, the solution was cooled to -78 °C, and *t*-BuLi (1.7 M in pentane, 5.18 mL, 8.8 mmol) was added dropwise. The mixture was stirred for 15 min at -78 °C, and then treated with dimethyl disulfide dropwise. The solution was warmed gradually to RT and stirred overnight. The reaction was then quenched by sat. NH_4Cl (15 mL) carefully, and filtered. The filtrate was diluted with water and extracted with EtOAc (3 x 50 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated. Chromatography (5-25% EtOAc/ hexanes) provided **14A** (0.483 g, 55%).

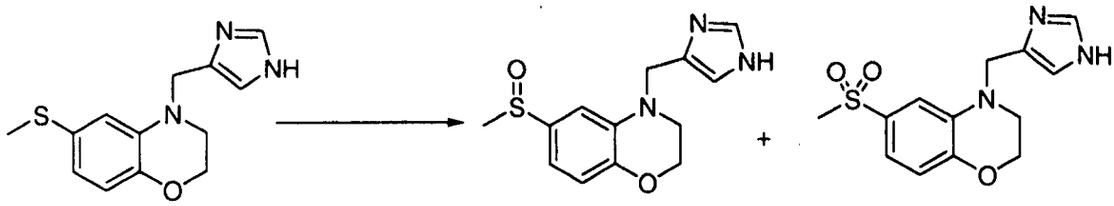
Steps 2-3



14A **14B**

In a manner similar to that found in Example 3, Steps 2-3, **14A** was reduced with BH_3-SMe_2 and treated with imidazole-4-carboxaldehyde to provide **14B**. MS m/z 262(MH+).

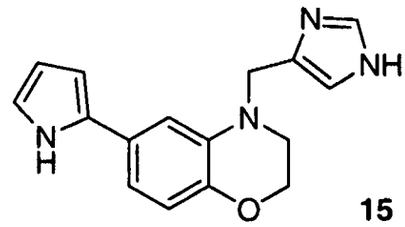
Step 4



14B **14C** **14**

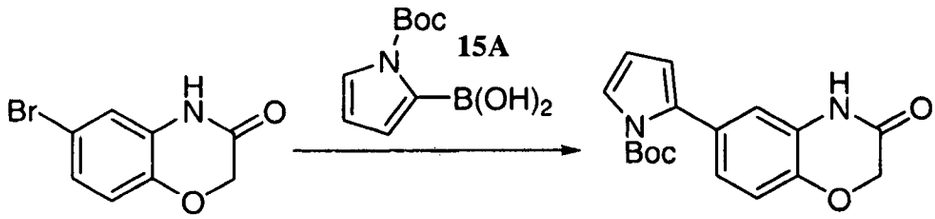
To compound **14B** (0.447 g, 1.71 mmol) in anhydrous DCM (10 mL) was added MCPBA (77%, 0.85g, 3.77 mmol), and the mixture was stirred at RT overnight. The reaction was quenched with sat. Na_2CO_3 solution and the solvent was removed under vacuum. The concentrated solution was extracted with EtOAc (3 x 10 mL). The organic layer was dried ($MgSO_4$), filtered, and concentrated under vacuum. Chromatography (DCM containing 1-7% of 7N NH_3-MeOH) provided the title compound **14** (67 mg, 13%, MS m/z 294 MH+) and a mixture of **14C** and **14**, which was purified by Ranin-preparative HPLC to provided **14C** (39 mg, 8%, MS m/z 278 MH+).

PREPARATIVE EXAMPLE 15



15

Steps 1

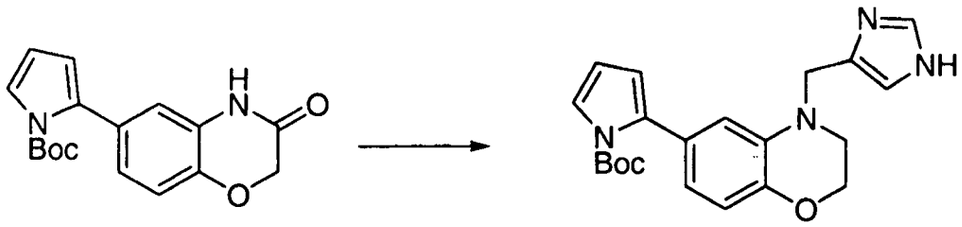


9C **15B**

To compound 6-bromo-4H-benzo[1,4]oxazin-3-one (**9C**, 500 mg, 2.2 mmol) in toluene (44 mL) was added $Pd(PPh_3)_4$ (127 mg, 0.11 mmol). After stirring at RT for 30 min, boronic acid **15A** (697 mg, 3.3 mmol) in EtOH (13 mL, 0.25 M) and saturated $NaHCO_3$ solution (22 mL) were added and the solution was heated to reflux overnight.

Then the mixture was cooled to RT, and poured into saturated NaCl solution, and concentrated under vacuum. The residue was diluted with water and extracted with EtOAc (3 x 25 mL). The organic layer was dried ($MgSO_4$), filtered, and concentrated under vacuum. Chromatography (10 to 30% EtOAc/ hexanes) provided **15B** (320 mg, 46%).

Steps 2-3



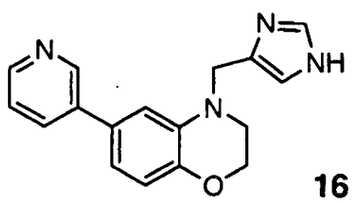
15B **15C**

In a manner similar to that found in Example 3, Steps 2-3, **15B** was reduced with BH_3-SMe_2 and treated with imidazole-4-carboxaldehyde to provide **15C**. MS m/z 381 (MH+).

Step 4

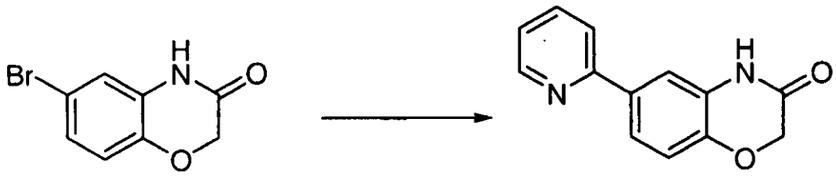
A mixture of **15C** (143 mg, 0.37 mmol) in 4.0M HCl-dioxane (1.5 mL, 0.56 mmol) was stirred at RT overnight. The reaction was neutralized with 7N NH_3-MeOH and concentrated. The residue was purified by preparative TLC (DCM containing 10% of 7N NH_3-MeOH) to provide the title compound **15** (28 mg, 26%). MS m/z 281 (MH+).

PREPARATIVE EXAMPLE 16



16

Step 1



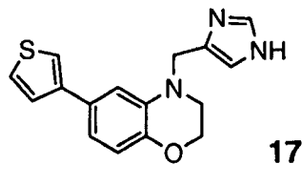
9C **16A**

To a stirred solution of Pd $(OAc)_2$ (3 mg, 0.0125 mmol) and PPh_3 (13 mg, 0.05 mmol) in anhydrous THF (2 mL) under argon was added 6-bromo-4H-benzo[1,4]oxazin-3-one (**9C**, 57 mg, 0.25 mmol). The mixture was stirred at RT for 10 min and treated sequentially with a solution of 3-pyridine boronic acid (62 mg, 0.5 mmol) in EtOH (1 mL) and aqueous $NaHCO_3$ solution (2 M, 2 mL). The mixture was heated to reflux for 2 h and then cooled to RT. The solution was poured into saturated NaCl solution, and then concentrated under vacuum. The residue was diluted with water (5 mL) and extracted with EtOAC (3 x 10 mL). The organic layer was dried ($MgSO_4$), filtered, and concentrated under vacuum. Chromatography (10-30% EtOAc/hexanes) provided **16A** (21mg, 37%).

Steps 2-3

Compound **16A** was converted to compound **16** by reduction with BH_3-SMe_2 and reductive alkylation with imidazole-4-carboxaldehyde as described in Example 3, Steps 2-3. MS m/z 293(MH+).

PREPARATIVE EXAMPLE 17



17

Step 1



9C **17A**

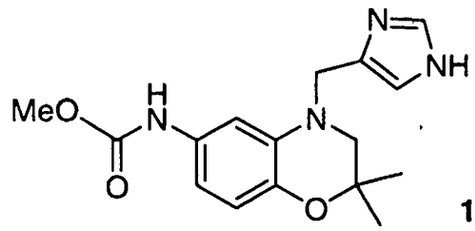
A Smith process vial (2-5 mL) was charged with a stir bar, 6-bromo-4H-benzo[1,4]oxazin-3-one (**9C**, 23 mg, 0.1 mmol), thiophen-3-ylboronic acid (17mg, 0.13

mmol) and EtOH (2 mL). Aqueous K_2CO_3 (1 M, 0.12 mL) and polymer-supported Pd (40 mg, 3 mol% Pd, FiberCat. 1000-D32, Pd% 4.26) were then added sequentially. The reaction vessel was sealed and heated to 110 °C for 1 h under microwave irradiation. After cooling, the reaction mixture was transferred to a prepacked column of Si-carbonate (2 g, 0.79 mmol/g), which had been conditioned with MeOH/DCM (1:1). The product was eluted with MeOH/DCM (1:1, 3 x 3 mL, gravity filtration) and concentrated to give compound **17A** (18 mg, 80%).

Steps 2-3

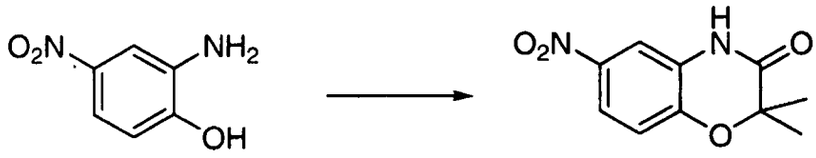
Compound **17A** was converted to **17** in a manner similar to that found in Example 3, Steps 2-3. MS m/z 298 (MH+).

PREPARATIVE EXAMPLE 18



18

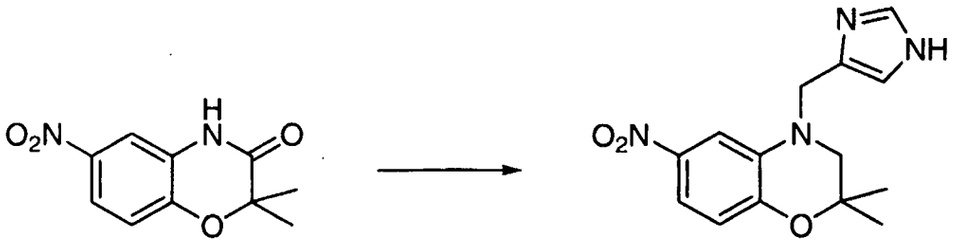
Step 1



3A **18A**

A Smith process vial (20 mL) was charged with a stir bar, compound **3A** (1 g, 6.49 mmol), ethyl 2-bromo-2-methylpropanoate (1 mL, 6.81 mmol), KF (1.13 g, 19.5 mmol) and DMF (10 mL). The reaction vessel was sealed and heated to 160 °C for 1 h under microwave irradiation. After cooling, the reaction mixture was poured into ice-water and extracted with EtOAc (3 x 50 mL). The organic layer was dried ($MgSO_4$), filtered, and concentrated under vacuum. Chromatography (10-30% EtOAc/hexanes) gave **18A** (0.245 g, 17%).

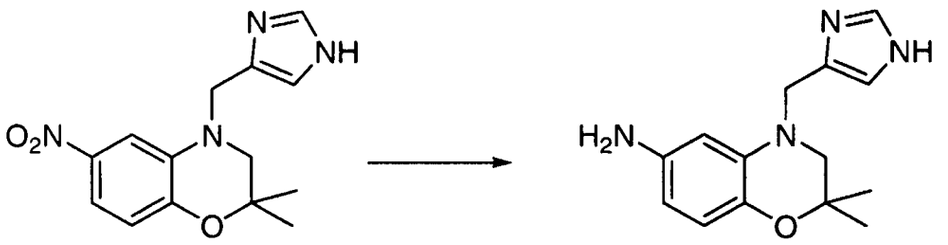
Step 2-3



18A **18B**

In a manner similar to that found in Example 3, Steps 2-3, **18A** was reduced with BH_3-SMe_2 and reacted with imidazole-4-carboxaldehyde to provide **18B**. MS m/z 289 (MH+).

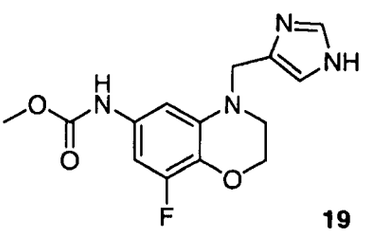
Step 4-5



18B **18C**

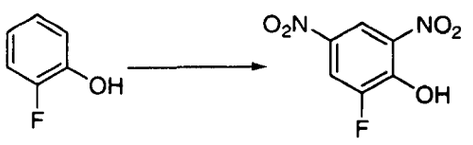
Following the procedure found in Example 3, Step 4, **18B** was hydrogenated to give compound **18C.** In a manner similar to that found in Example 3, Step 5, **18C** was further reacted with $ClCO_2Me$ to provide the title compound **18**. MS m/z 317 (MH+).

PREPARATIVE EXAMPLE 19



19

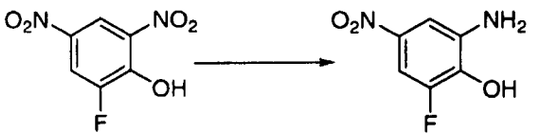
Step 1



19A **19B**

To 2-fluorophenol (**19A**, 8 mL, 86.4 mmol) in anhydrous DCM (70 mL) at 0 °C was added fuming HNO_3 (0.34 mL, 0.008 mmol) dropwise through an addition funnel. The mixture was warmed to RT and stirred for 2 h, then cooled to 0 °C again and quenched with 2N NaOH solution to pH 5. The mixture was concentrated under vacuum, diluted with water, extracted with EtOAc (3 x 100 mL). The combined organic layer was dried ($MgSO_4$), filtered, and concentrated under vacuum to give compound **19B** (15.07 g, yield: 86.4%).

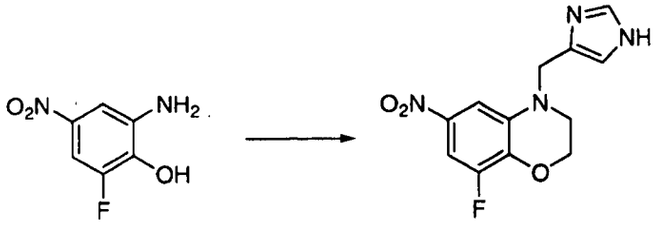
Step 2



19B **19C**

A solution of **19B** (15.07g, 74.6 mmol) in EtOH (300 mL) was treated with $SnCl_2$-$2H_2O$ (50.5 g, 224 mmol) and heated to reflux for 2 h. The mixture was concentrated, poured into ice, and neutralized to pH 7 with 2N NaOH solution. The solid was filtered off and washed with EtOAc (5 x 500 mL). The filtrate was separated and the aqueous was extracted with EtOAc (3 x 100 mL). The organic layer was dried ($MgSO_4$), filtered and concentrated under afford **19C** (12.59 g, 98%).

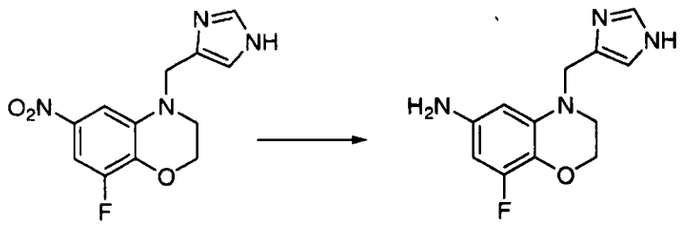
Steps 3-5



19C **19D**

In a manner similar to that found in Example 3, Steps 1-3, **19C** was reacted with chloroacetyl chloride, reduced with BH_3-SMe_2, and treated with imidazole-4-carboxaldehyde to provide compound **19D.** MS m/z 279 (MH+).

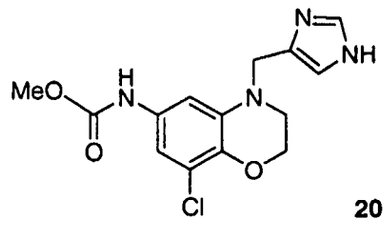
Steps 6-7



19D **19E**

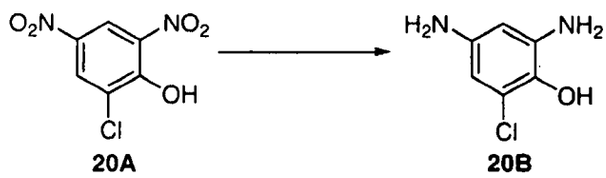
In a manner similar to that found in Example 3, Step 4, **19D** was hydrogenated to afford compound **19E.** MS m/z 249 (MH+). Compound **19E** was further reacted with $ClCO_2Me$ as described in Example 3, Step 5, to provide the title compound **19.** MS m/z 307 (MH+).

PREPARATIVE EXAMPLE 20



20

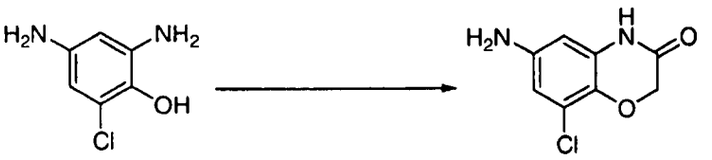
Step 1



20A **20B**

To 2-chloro-4,6-dinitrophenol (**20A**, 2 g, 9.18 mmol) in EtOH (100 mL) was added a scoop of Raney nickel (20% by weight) carefully. The mixture was stirred at RT under hydrogen balloon overnight and then filtered. The solvent was evaporated off under vacuum to give white solid **20B** (1.3 g, 89%) and used directly in the next reaction.

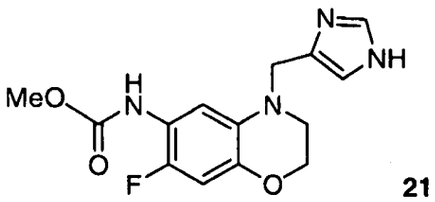
Steps 2-5



20B **20C**

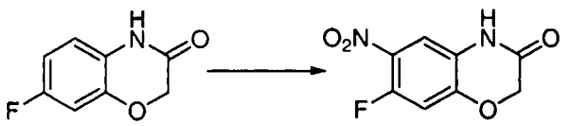
Following the procedure described in example 3, Step 1, **20B** was reacted with chloroacetyl chloride to provide **20C** (5%). Compound **20C** was treated with $ClCO_2Me$, reduced with BH_3-SMe_2, and reductively alklyated in a manner similar to that found in Example 8 and Example 3 (Steps 2-3) to afford the title compound **20.** MS m/z 323 (MH+).

PREPARATIVE EXAMPLE 21



21

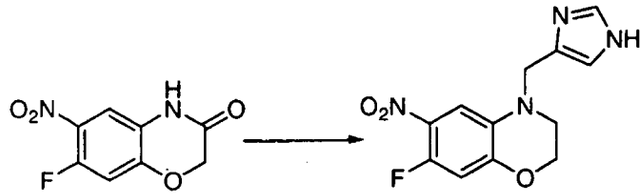
Step 1



21A **21B**

To compound **21A** (5 g, 30 mmol) in concentrated H_2SO_4 (17 mL) was added a 1:1 mixture of fuming HNO_3 and conc. H_2SO_4 (7 mL) over 15 min. The mixture was stirred for additional 30 min at RT and was slowly poured into ice water (500 mL). The mixture was filtered to collect solid and washed with water (4x). The solid was placed under high vacuum in an 80 °C oil bath for 5 h to provide **21B** (3.82 g, 60%).

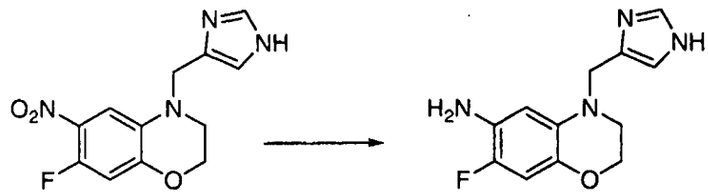
Steps 2-3



21B **21C**

In a manner similar to that found in Example 3, Steps 2-3, **21B** was reduced with BH_3-SMe_2 and then treated with imidazole-4-carboxaldehye to afford compound **21C.** MS m/z 279 (MH+).

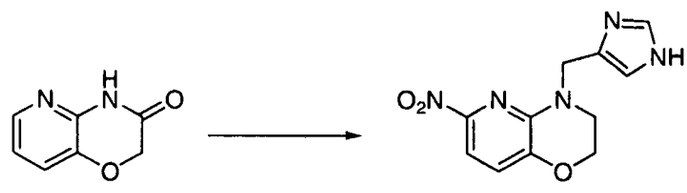
Steps 4-5



21C **21D**

In a manner similar to that found in Example 3, Steps 4, **21C** was hydrogenated to provide compound **21D**. Compound **21D** was then converted to the title compound **21** as described in Example 3, Step 5. MS m/z 307 (MH+).

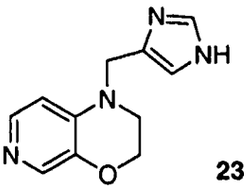
PREPARATIVE EXAMPLE 22



22A **22**

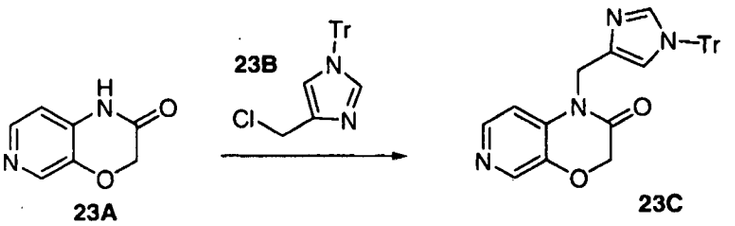
Following the procedures described in Example 21 (Step 1) and Example 3 (Steps 2-3), **22A** was nitrated with HNO_3, reduced with BH_3-SMe_2, and reacted with imidazle-4-carboxaldehyde to provide compound **22.** MS m/z 262 (MH+).

PREPARATIVE EXAMPLE 23



23

Step 1



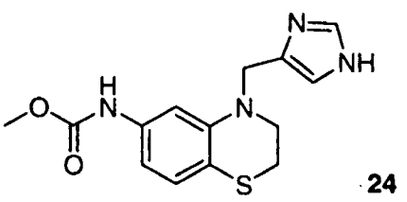
23A 23C

A solution of compound **23A** (330 mg, 2.2 mmol, U.S. Patent No. 5,652,363) in DMF (4 mL) was treated with NaH (60% in mineral oil, 88 mg, 2.2 mmol) at RT. The mixture was stirred for 20 min, followed by addition of a solution of compound **23B** (0.79 g, 2.2 mmol, J. Med. Chem., 2002, 45, 533) in DMF (4 mL). The mixture was stirred at 45 °C for 3 days, and then quenched with water and concentrated under vacuum. The residue was dissolved in EtOAc (50 mL), washed with water (2 x 10 mL). The organic layer was dried (Na_2SO_4), filtered, and concentrated under vacuum. Chromatography (DCM with 2-3% 7 N NH_3-MeOH) provided **23C** (519 mg, 50%). MS m/z 473 (MH+).

Steps 2-3

In a manner similar to that found in Example 2 (Step 2) and Example 15 (Step 4), **23C** was reduced with BH_2-SMe_2 (18 h at reflux) and then deprotected with HCl-dioxane (1 h at 60 °C) to provide the title compound **23**. MS m/z 217 (MH+).

PREPARATIVE EXAMPLE 24



24

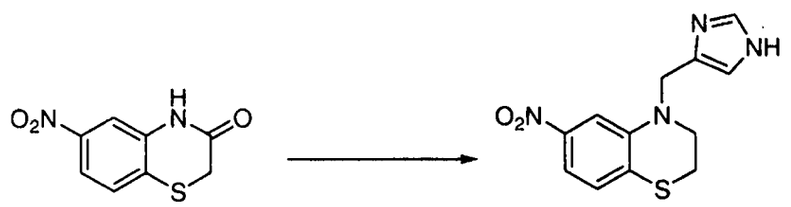
Step 1



24A **24B**

A stirred solution of 2-chloro-5-nitroaniline **24A** (34.4 g, 0.2 mol) in absolute EtOH (200 mL) at 70 °C was treated gradually with a solution of sodium sulfide nonahydrate (48 g, 0.2 mol) and sulfur (9.6 g, 0.3 mol), which had been preheated to melting. The mixture was refluxed for 30 min and cooled to RT. The mixture was filtered to collect the solid, wash with water. The solid was dried under vacuum at 100 °C for 5 h. The resulting solid was taken up in water (200 mL) and treated with NaOH (8 g, 0.2 mol) and $ClCH_2COOH$ (18.9g, 0.2 mol). The mixture was then heated to reflux for 1.5 h. After cooling down, the mixture was acidified with 10% HCl solution and filtered to collect brown-yellow solid, and washed with water to give compound **24B** (25 g, 60%).

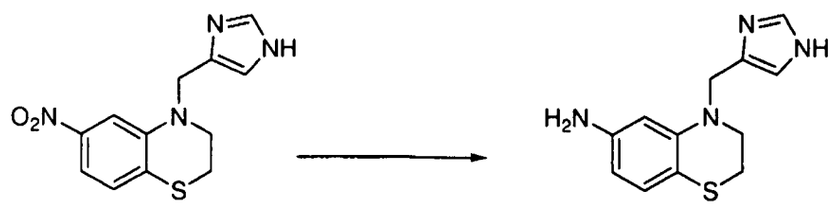
Steps 2-3



24B **24C**

Following the procedure described in Example 3, Steps 2-3, **24B** was reduced with BH_3-SMe_2 and treated with imidazole-4-carboxaldehyde to provide **24C.** MS m/z 277 (MH+).

Steps 4-5

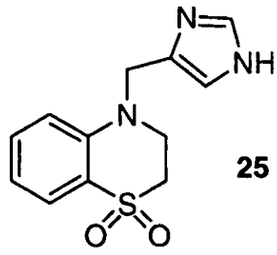


24C **24D**

In a manner similar to that found in Example 3, Step 4, **24C** was hydrogenated to provide **24D**. MS m/z 247 (MH+). Compound **24D** was further treated with

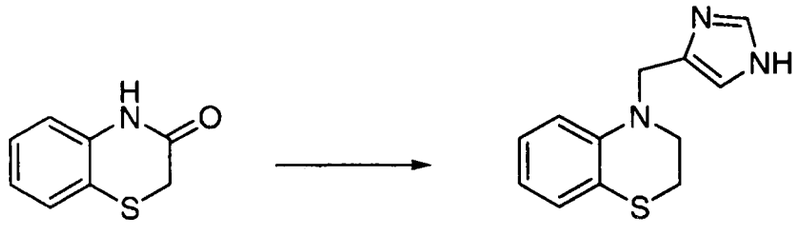
$ClCO_2Me$ as described in Example 3, Step 5, to provide the title compound **24.** MS m/z 305 (MH+).

PREPARATIVE EXAMPLE 25



25

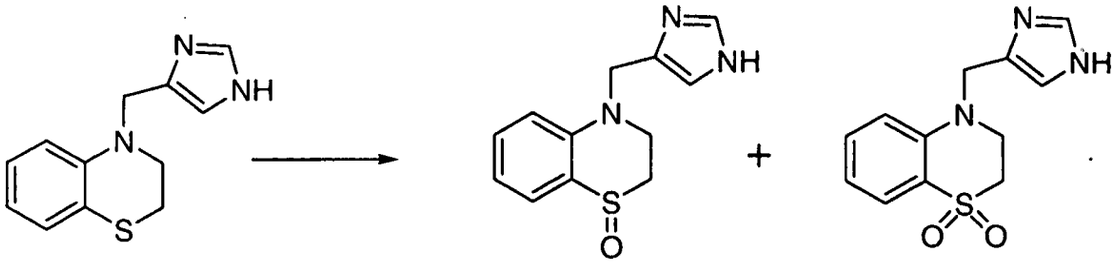
Steps 1-2



25A **25B**

Following procedures described in Example 3 (Steps 2-3), compound **25A** was subjected to reduction with BH_3-SMe_2 and then reductive amination with imidazole-4-carboxaldehyde to provide compound **25B**. MS m/z 232 (MH+).

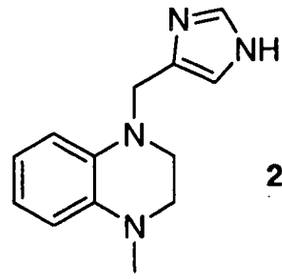
Step 3



25B **25C** **25**

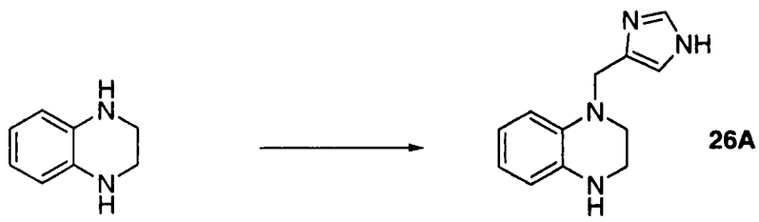
In a manner similar to that found in Example 14, Step 4, **25B** was oxidized with MCPBA to the afford compounds **25C** (MS m/z 248 MH+) and **25** (MS m/z 264 MH+).

PREPARATIVE EXAMPLE 26



26

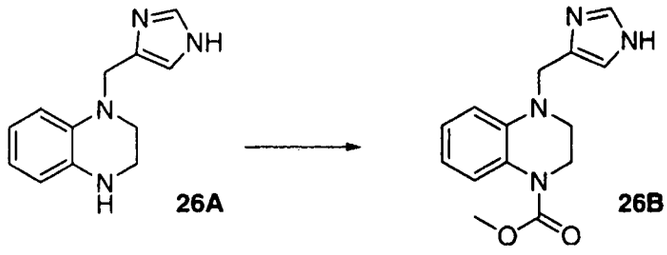
Step 1



26A

In a manner similar to that found in Example 1, 1,2,3,4-tetrahydro-quinoxaline and imidazole-4-carboxaldehye **1B** underwent reductive amination to provide **26A.** LMCS m/z 215 (MH+).

Step 2



26A **26B**

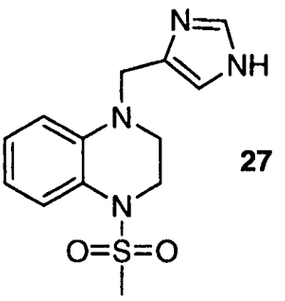
In a manner similar to that found in Example 3, Step 5, **26A** was converted to **26B.** LMCS m/z 273 (MH+).

Step 3

Compound **26B** (120 mg) was added portionwise to a stirred slurry of LAH powder (500 mg) in Et_2O (15 mL) at 0 °C. The mixture was refluxed for 1 h and then cooled to 0 °C. The reaction was treated sequentially with H_2O (0.5 mL), 1 N NaOH (0.5 mL), and H_2O (1.5 mL). and then concentrated. Chromatography (DCM with 2 to 5% of 7N NH_3-MeOH) provided the title compound **26.** MS m/z 229(MH+).

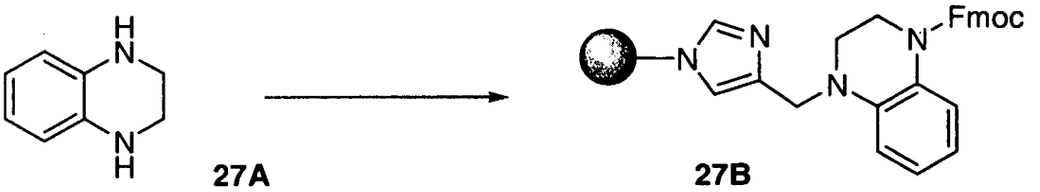
Alternatively, compounds in this class may be synthesized by a solid phase approach as described in the following Example 27.

PREPARATIVE EXAMPLE 27



27

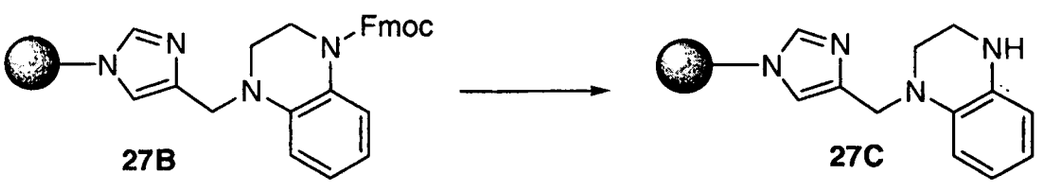
Steps 1-2



27A 27B

A mixture of 1,2,3,4-tetrahydroquinoxaline (**27A**, 2 g, 14.9 mmol) in dioxane (15 mL) and water (24 mL) at 0 °C was sequentially treated with Na_2CO_3 (1.58 g, 14.9 mmol) and FmocCl (3.84g, 14.9 mmol) in dioxane (20 mL, added dropwise). The mixture was warmed to RT gradually and stirred overnight. The reaction mixture was diluted with water (50 mL) and extracted with DCM (2 x 70 mL). The combined organic layers were dried (Na_2SO_4), concentrated, and subjected to chromatography (30-40% EtOAc/hexanes, yields 0.75g, 14%). Subsequent reaction with resin **1D** as described in Example 1 provided **27B.**

Steps 3-5



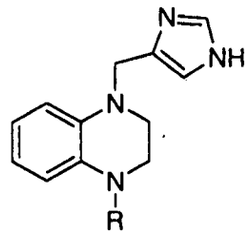
27B 27C

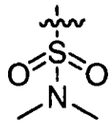
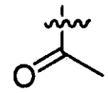
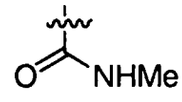
Compound **27B** (0.5 g, 1.4 mmol/g) was stirred in 30% piperidine/DMF overnight. The resin was washed with DMF (3x), MeOH (3x) and DCM and then dried in vacuo to provide **27C**. Resin **27C** (125mg, 1.4 mmol/g) was suspended in DCM (5

mL) and treated with pyridine (0.283 mL, 3.5 mmol) and $MeSO_2Cl$ (0.135 mL, 1.75 mmol). The reaction was shaken overnight, then washed with MeOH (2x), DMF (2x), DCM (2x), MeOH (2x) and DCM (3x). Subsequent cleavage from the resin with TFA, as described in Example 1, provided the title compound **27**. MS m/z 293 (MH+).

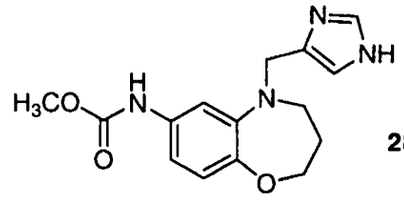
Compounds in **Table 4** can be prepared from Resin **27C** by reaction with the various reagents shown followed by TFA cleavage.

Table 4



Cpd	Reagent	R	MS (MH+)
27D	Me_2NSO_2Cl/ pyridine		322
27E	Ac_2O/ pyridine		257
27F	MeNCO		272

PREPARATIVE EXAMPLE 28



28

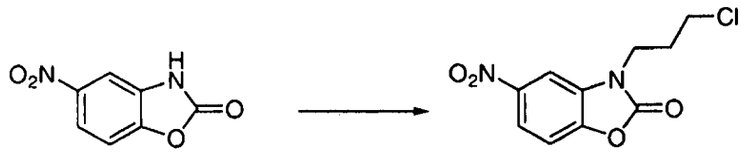
Step 1



3A **28A**

To 6-nitro-2-aminophenol (**3A**, 3.03g, 19.7 mmol) in anhydrous DCM (50 mL) was added dipyridylcarbonate (4.25 g, 19.7 mmol). The mixture was stirred at RT overnight, and then concentrated under vacuum. Chromatography (1-6% MeOH/DCM) afforded the solid **28A** (2.77 g, 78%).

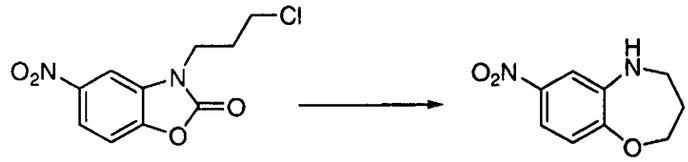
Step 2



28A **28B**

A solution of **28A** (0.69 g, 3.83 mmol) in 2-ethoxyethanol (10 mL) was treated with KOH (0.22 g, 3.83 mmol) and stirred at RT for 1 h. The mixture was then heated to reflux and treated with 1-bromo-3-chloropropane (0.75 mL, 7.67 mmol). After refluxing for 4 h, the solution was filtered and concentrated to provide **28B**, which was taken on to Step 3 without further purification.

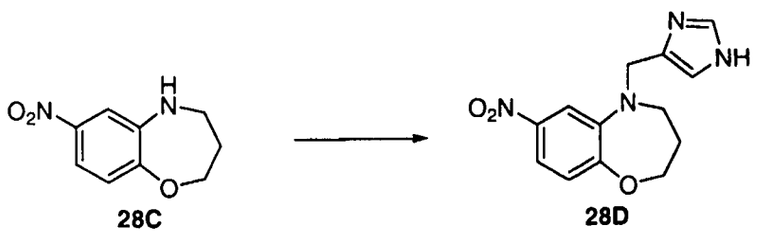
Step 3



28B **28C**

A solution of **28B** in 2-ethoxyethanol and DMF (10 mL, 1:1) was transferred into a Smith process vial (20 mL) with a stir bar, and treated with KOH (0.86g, 15.32 mmol). The reaction vessel was sealed and heated to 220 °C for 1 h under microwave irradiation. After cooling, the reaction mixture was filtered and concentrated. The residue was diluted with water and extracted with EtOAc (3 x 10 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated under vacuum. Chromatography (DCM containing 1-5% 7N NH_3-MeOH) provided **28C** (124 mg, 17% for 2 steps).

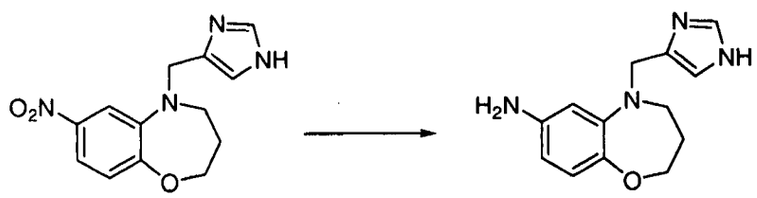
Step 4



28C **28D**

In a manner similar to that found in Example 3 (Step 3), **28C** was reacted with imidazole-4-carboxyaldehyde to provide compound **28D.** MS m/z 275 (MH+).

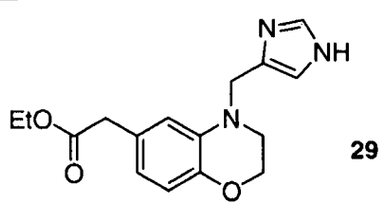
Steps 5-6



28D **28E**

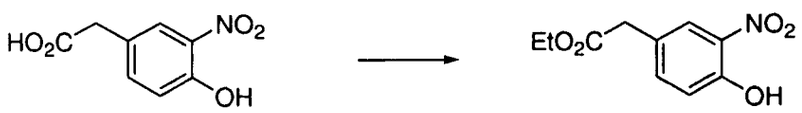
In a manner similar to that found in Example 3 (Step 4), **28D** was hydrogenated to afford compound **28E.** MS m/z 245 (MH+). Following the procedure found in Example 3 (Step 5), **28E** was further reacted with $ClCO_2Me$ to provide the title compound **28**. MS m/z 303 (MH+).

PREPARATIVE EXAMPLE 29



29

Step 1

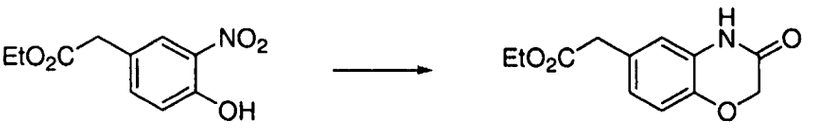


29A

A mixture of 4-hydroxy-3-nitrophenylacetic acid (10 g, 51 mmol) and 4M HCl-dioxane (40 mL) in EtOH (150 mL) was refluxed for 2 h and concentrated. The residue was then taken up in1 N NaOH (50 mL) and extracted with CH_2Cl_2 (8x). The

combined organic layers were dried over Na_2SO_4, and concentrated to provide **29A** (8.39 g, 73%) as a yellow oil.

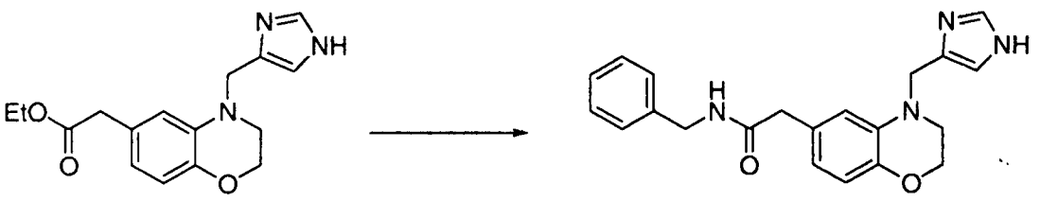
Steps 2-5



29A **29B**

In a manner similar to that described in Example 20 (Step 1) and Example 3 (Step 1), **29A** was hydrogenated with Raney Ni (50 psi H_2) and then cyclized with chloroacetyl chloride to provide **29B**. Compound **29B** could be further elaborated to the title compound **29** following the procedure detailed in Example 3 (Steps 2-3). LMCS m/z 302 (MH+).

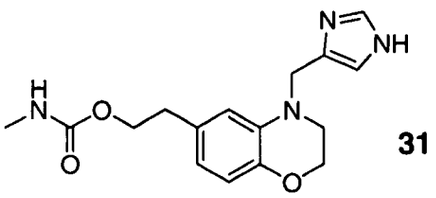
PREPARATIVE EXAMPLE 30



29 **30**

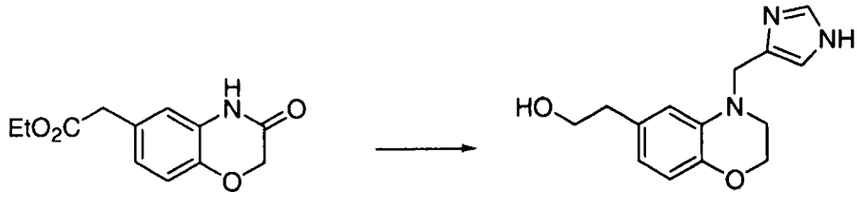
A stirred solution of benyzlamine (0.070 mL, 0.66 mmol) in CH_2Cl_2 (10 mL) was treated dropwise with $AlMe_3$ (2M/toluene, 0.33 mL, 0.66 mmol) at 20 °C. After 20 min, a solution of **29** (0.10 g, 0.33 mmol) in CH_2Cl_2 (3 mL) was added slowly. The mixture was then heated at reflux overnight and cooled to 20 °C. The reaction was quenched with H_2O (0.5 mL), and stirred 1h. The mixture was then dried with Na_2SO_4, filtered, and concentrated. Chromatography (2-5% 1 N NH_3-MeOH/CH_2Cl_2) provided **30** as a white film (0.115 g, 96%). LMCS m/z 363 (MH+).

PREPARATIVE EXAMPLE 31



31

Steps 1-2



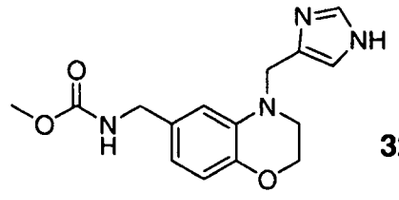
29B **31A**

In a manner similar to that found in Example 26 (Step 3) and Example 1, **29B** was reduced with LAH and then treated with imidazole-4-carboxaldehyde to provide **31A.** LMCS m/z 260 (MH+).

Step 3

A solution of **31A** (0.20 g, 77 mmol) in 1,2-dichloroethane (10 mL) was treated with Et_3N (0.20 mL, 1.5 mmol) and MeNCO (0.050 mL, 0.85 mmol) and stirred for 3h at 20 °C. The mixture was treated with H_2O (10 mL), extracted with CH_2Cl_2 (2x), and concentrated. The residue was subjected to chromatography (2-5% MeOH/ CH_2Cl_2) and then stirred in Et_2NH (5 mL) at 20 °C overnight. The mixture was concentrated, treated with 1 N NaOH, and extracted with CH_2Cl_2 (3x). The combined organic extracts were dried with Na_2SO_4, and concentrated. Chromatography (5% MeOH/CH_2Cl_2) provided **31** as a white film (0.080 g, 33%). LMCS m/z 317 (MH+).

PREPARATIVE EXAMPLE 32



32

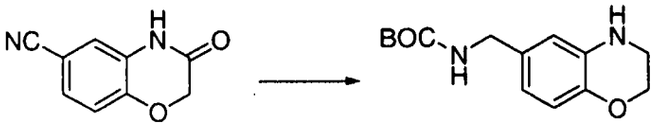
Step 1-2



32A **32B**

Following the procedures found in Example 20 (Step 1) and Example 3 (Step 1), **32A** was hydrogenated with Raney Ni (50 psi H_2) and then cyclized with chloroacetyl chloride to provide **32B**.

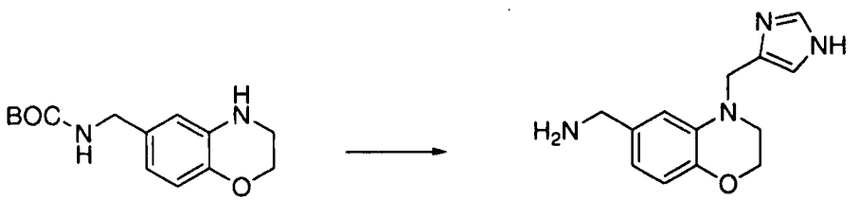
Steps 3-4



32B **32C**

Following the procedure found in Example 26 (Step 3), the nitrile and amide found in compound **32B** were concomitantly reduced with LAH. The resultant product (0.83 g, 5.1 mmol) in CH_2Cl_2 (50 mL) was treated with BOC_2O (1.07 g, 5.1 mmol), stirred at 20 °C for 0.5 h and then concentrated. Chromatography (20-50% EtOAc/hexanes) provided **32C** as a white sticky foam (1.19 g, 89%)

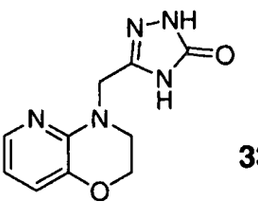
Steps 5-6



32C **32D**

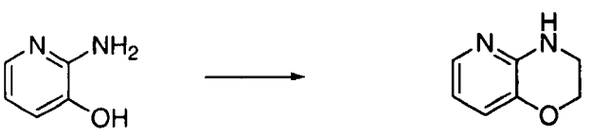
In a manner similar to that found in Example 1 and Example 15 (Step 4), **32C** was treated with imidazole-4-carboxaldehyde and then deprotected to afford **32D.** LMCS m/z 245 (MH+). Following the procedure described Example 3, Step 5, **32D** was treated with $ClCO_2Me$ and converted to the title compound **32.** LMCS m/z 303 (MH+).

PREPARATIVE EXAMPLE 33



33

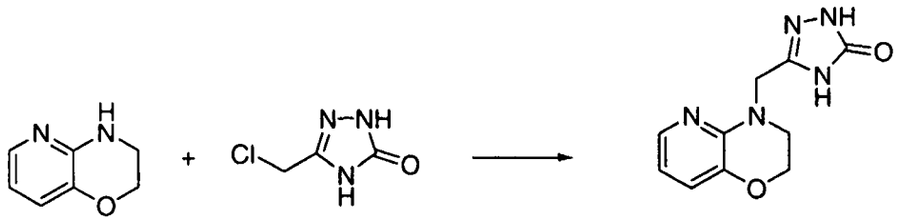
Step 1-2



33A

In a manner similar to that found in Example 3 (Step 1) and Example 26 (Step 3), 2-amino-3-hydroxypyridine was cyclized with chloroacetyl chloride and then reduced with LAH to afford **33A.**

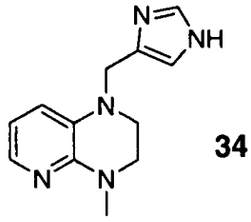
Step 3



33A **33B** **33**

A solution of **33A** (0.105 g 0.77 mmol) in DMF (5 mL) was treated with $KN(SiMe_3)_2$ (0.5 M/toluene, 1.8 mL, 0.93 mmol), stirred at 0 °C for 20 min, and then treated with **33B** (0.155 g 1.16 mmol, Tetrahedron Letters **2000**, 41, 8661). The reaction was warmed to 20 °C, stirred 2h, and concentrated. The residue was then treated with 0.5 N NaOH (10 mL) and washed with CH_2Cl_2 (3x). The aqueous layer was concentrated and subjected to chromatography (20-80% EtOAc/hexanes) to provide **33** as a white solid (0.065 g, 36%). LMCS m/z 234 (MH+).

PREPARATIVE EXAMPLE 34



34

Step 1



34A

A mixture of 2-chloro-3-nitropyridine (9.4 g, 59 mmol), glycine ethyl ester hydrochloride (10.8 g, 77 mmol), and K_2CO_3 (21.3 g, 154 mmol) in toluene (100mL) was refluxed overnight. The mixture was then filtered, concentrated, and subjected to chromatography (20% EtOAc/hexanes). The resulting yellow solid was dissolved in

EtOH (300 mL), treated with Raney Ni (2 g) and hydrogenated at 40 psi H_2 overnight. The mixture was filtered, concentrated and chromatographed (2-5% MeOH/CH_2Cl_2) to provide **34A** (1.25 g, 14%) and N-(3-amino-2-pyridinyl)glycine ethyl ester (8.2 g, 71%).

Step 2



34A **34B**

In a manner similar to that found in Example 5 (Step 1), **34A** was converted to **34B** (BOC_2O, DMAP and Et_3N in refluxing DCM).

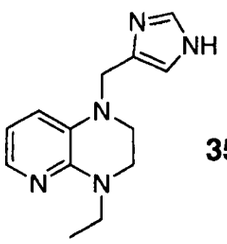
Step 3-4



34B **34C**

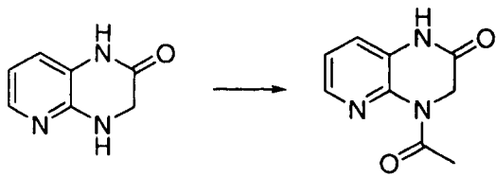
In a manner similar to that found in Example 26 (Step 3), **34B** was treated with LAH to provide **34C** as a white solid (0.040 g, 48%). Following the procedure found in Example 1, **34C** was then treated with imidazole-4-carboxaldehyde to provide the title compound **34.** LMCS m/z 230 (MH+).

PREPARATIVE EXAMPLE 35



35

Steps 1-3

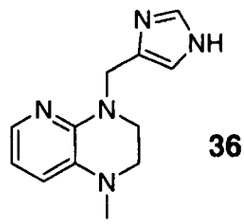


34A **35A**

A solution of **34A** (0.260 g, 1.74 mmol) in THF (15 mL) was treated with Et_3N (1.2 mL, 8.7 mmol) and Ac_2O (0.33 mL, 3.5 mmol) and stirred overnight at 20 °C. The reaction was treated diluted with H_2O (10 mL) and extracted with 10% MeOH/CH_2Cl_2 (3x). The combined organic extracts were dried with Na_2SO_4 and concentrated. Chromatography (20-50% EtOAc/hexanes) provided **35A** as a white solid (0.140 g, 42%).

In a manner similar to that found in Example 26 (Step 3) and Example 1, **35A** was reduced with LAH and then treated with imidazole-4-carboxaldehyde to provide the title compound **35.** LMCS m/z 244 (MH+).

PREPARATIVE EXAMPLE 36



36

Steps 1-3

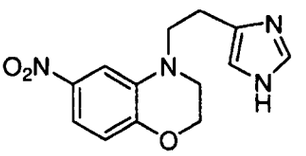


34A **36A**

A solution of **34A** (0.200 g 1.33 mmol) in DMF (15 mL) was treated with $KN(SiMe_3)_2$ (0.5M/toluene, 3.2 mL, 0.93 mmol), stirred at 0 °C for 30 min, and then treated with CH_3I (0.12 mL, 2.00 mmol). The reaction was warmed to 20 °C, stirred overnight, and concentrated. The residue was then treated with 0.5 N NaOH (10 mL) and extracted with CH_2Cl_2 (3x). The combined organic layers were concentrated and subjected to chromatography (2-5% MeOH/CH_2Cl_2) to provide **36A** (0.120 g, 55%).

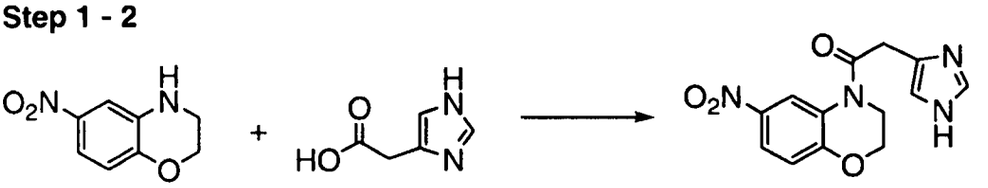
In a manner similar to that found in Example 26 (Step 3) and Example 1, **36A** was reduced with LAH and then reacted with imidazole-4-carboxaldehyde to provide **36.** LMCS m/z 230 (MH+).

PREPARATIVE EXAMPLE 37



37

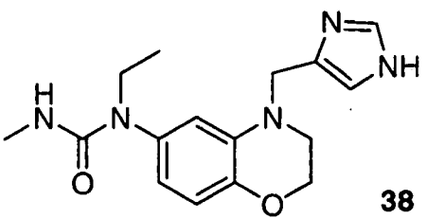
Step 1 - 2



3C **37A**

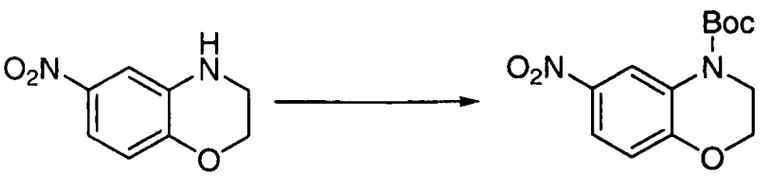
A mixture of **3C** (2g, 11.1 mmol) in anhydrous DMF (20 mL) was treated with 2-(1*H*-imidazol-4-yl)acetic acid (2g, 17.5 mmol), HATU (6.2g, 16.3 mmol) and DIEA (0.4 mL, 2.3 mmol) at 25 °C. The mixture was stirred at room temperature overnight and then concentrated under vacuum. Column chromatography (DCM containing 1 - 6% of 7N NH_3/MeOH) provided **37A** (1.2g, yield: 38%). In a manner similar to Example 2, Step 2, compound **37A** was reduced with BH_3-SMe_2 to provide compound **37**. MS m/z 275 (MH+).

PREPARATIVE EXAMPLE 38



38

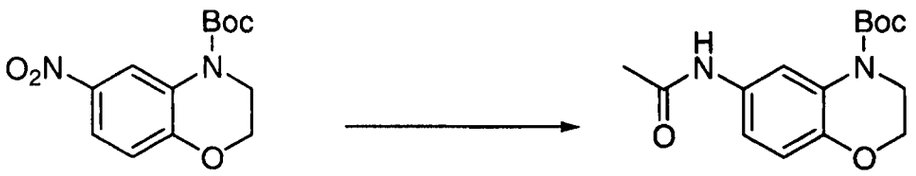
Step 1



3C **38A**

A solution of compound **3C** (14.1 g, 78 mmol) in MeCN (200 mL) was treated with $(BOC)_2O$ (20.5 g, 94 mmol) and DMAP (0.5 g) and then refluxed overnight. The reaction mixture was concentrated and chromatographed (10% -50% EtOAc/hexanes) to give compound **38A** (16.1 g, 74%, typically 70-90%) and recovered starting material **3C**.

Steps 2-3

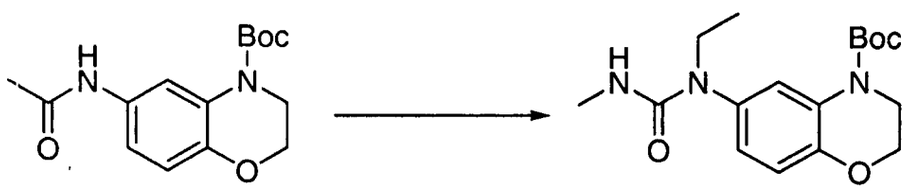


38A **38B**

A mixture of compound **38A** (16.1 g, 58 mmol) in EtOH (300 ml) was treated with Raney Ni (~5 g) and hydrogenated (40 psi H_2) overnight. The reaction mixture was filtered and concentrated.

The resulting white solid (~15.3 g, 61 mmol) was suspended in anhydrous THF (200mL) and treated slowly with Ac_2O (~18mL, 173 mmol). After stirring for 2 h at 20 °C, the reaction mixture was concentrated in vacuo and taken up in 25% aqueous NaOH (100mL) and CH_2Cl_2. The layers were separated. The aqueous layer was further extracted with CH_2Cl_2 (3x). The organic layers were combined, dried with Na_2SO_4, and filtered to give **38B** as a gray solid (17.6 g, quantitative yield).

Steps 4-5



38B **38C**

A solution of compound **38B** (21 g, 72 mmol) in THF (300 ml) at 0 °C was slowly treated with BH_3-DMS (60 ml, 2M/THF) and then heated to reflux overnight. The mixture was concentrated, treated with K_2CO_3 (9.9 g) and EtOH (300 mL) and then refluxed for 45 min. The reaction mixture was filtered, concentrated, added to H_2O and extracted with CH_2Cl_2 (4x). The combined organic layers were dried with Na_2SO_4, filtered and concentrated.

The resulting clear oil (21.9 g) was dissolved in anhydrous CH_2Cl_2 (300 ml), treated slowly with MeNCO (~5 g, 86 mmol), and then stirred at RT for 30 min. The

reaction mixture was concentrated and chromatographed (50%-80% EtOAc/hexanes) to give the product **38C** as a white solid (21.65 g, 90% yield for two steps).

Steps 6-7

A solution of compound **38C** (21.65 g, 65 mmol) in of CH_2Cl_2 (300 ml) was treated with TFA (100 mL) and refluxed for 0.5 h. The reaction mixture was concentrated, treated with 20% NaOH (150mL) and extracted with CH_2Cl_2 (4X). The combined organic layers were dried with Na_2SO_4, filtered and concentrated to give a white solid (14.23 g, ~93%).

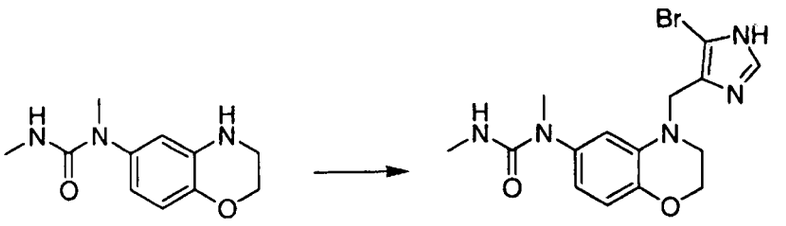
The crude product (16.2 g, 68.9 mmol) was combined with 4-imidazolecarboxaldehyde (**1B**, 6.6 g, 68.9 mmol) and $Ti(OiPr)_4$ (25 mL, 86 mmol) in CH_2Cl_2 (15 ml) and stirred at RT until the reaction mixture became clear (~1 h). Following the addition of $NaBH_4$ (3.3 g, 86 mmol) and EtOH (200 mL), the reaction was stirred at RT overnight and concentrated. The residue was taken up in 0.5 N NaOH and extracted with CH_2Cl_2 (4x). The combined organic layers were dried with Na_2SO_4, filtered, and concentrated. Chromatography (5-10% of 7N NH_3-MeOH in CH_2Cl_2) provided compound **38** (14.13 g, 68%) as a white solid.

PREPARATIVE EXAMPLE 39



1B **39A**

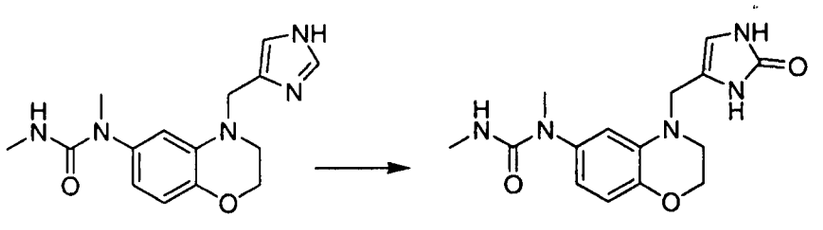
Bromine (8.0 g, 50 mmol, 2.3 eq) in anhydrous Ac_2O (40 mL) was added dropwise to a solution of **1B** (2.08 g, 21.7 mmol) and NaOAc (18.7 g, 228 mmol, 10.5 eq) in anhydrous HOAc (200 mL) over a period of 1 h at RT. The resulting mixture was stirred at RT for 2.5 h and then concentrated. The residue was partitioned between Et_2O (200 mL) and water (200 mL), the layers were separated and the aqueous layer was extracted with Et_2O (200 mL). The combined organic phase was dried, concentrated and chromatographed (EtOAc) to afford 5-bromo-4-formyl imidazole **39A** (1.00 g, 26%) as white crystals.



39B **39**

In a manner similar to that found in Example 1, **39A** was treated with **39B** (Example 6) to afford the title compound **39.** LCMS m/z 280 (MH+).

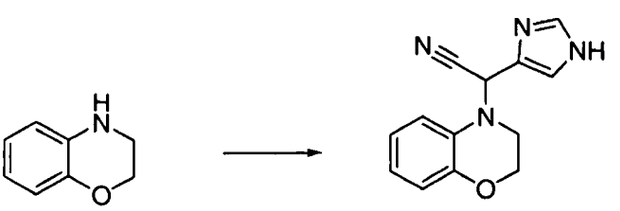
PREPARATIVE EXAMPLE 40



6 **40**

A mixture of **6** (0.25 g, 0.83 mmol) and $NaHCO_3$ (0.7g, 8.3 mmol) in 1:1 THF-H_2O (20 mL) was stirred vigorously for 10 min and then treated with phenyl chloroformate (PhOCOCl, 0.26 mL, 2.1 mmol). The reaction was stirred at RT for 2 h and then diluted with EtOAc. The organic layer was isolated, dried over Na_2SO_4 and concentrated. The resulting residue was dissolved in MeOH, treated with Et_3N (0.6 mL, 4.3 mmol) and stirred overnight. The solution was concentrated and subjected to chromatography (5-10% NH_3-MeOH/EtOAc) to provide the title compound **40** as a light yellow foam (0.2 g, 76%).

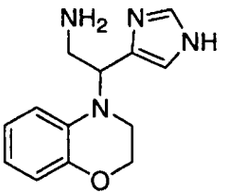
PREPARATIVE EXAMPLE 41



1A **41**

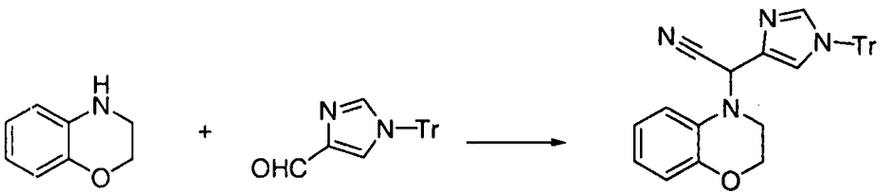
A mixture of **1A** (0.2 g, 1.5 mmol) and imidazole-4-carboxaldehyde (**1B**, 0.16 g, 1.6 mmol) in CH_2Cl_2 (5 mL) was treated with $Ti(OiPr)_4$ (0.55 mL, 1.88 mmol), stirred at RT overnight, and then treated with Et_2AlCN (2 mL, 1M/toluene). After 18 h, EtOAc, H_2O, and celite were added. Filtration and subsequent chromatography (0-10% of 7N NH_3–MeOH in CH_2Cl_2) provided **41** as a yellow solid (0.178 g, 50%). LCMS m/z 241 (MH+).

PREPARATIVE EXAMPLE 42



41

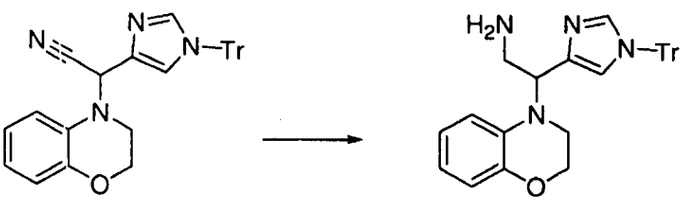
Step 1



1A **42A** **42B**

In a manner similar to that found in Example 41, a mixture of **1A** and **42A** (Journal of Medicinal Chemistry, **1971**, *14*, 883) was treated sequentially with $Ti(OiPr)_4$ and Et_2AlCN to provide the compound **42B.**

Steps 2-3



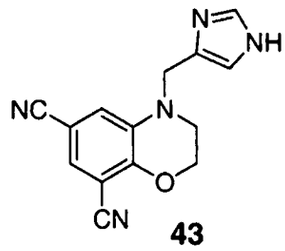
42B **42C**

A solution of **42B** (0.2 g, 0.41 mmol) in 1N NH_3-MeOH (50 mL) was treated with Raney Ni and hydrogenated (50 psi H_2) overnight at RT. Filtration and subsequent

chromatography (0-7% of 7N NH_3–MeOH in CH_2Cl_2) provided **42C** as a yellow film (0.15 g, 74%).

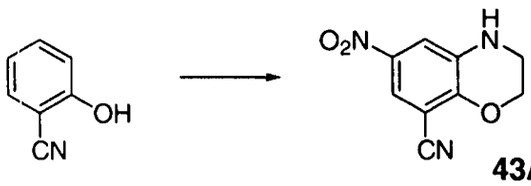
A mixture of **42C** (145 mg, 0.3 mmol) in CH_2Cl_2 (2 mL) was treated with TFA (0.5 mL) and Et_3SiH (0.05 mL). The reaction mixture was stirred at RT overnight and then concentrated. Chromatography (2-15% of 7 N NH_3-MeOH in CH_2Cl_2) provided the title compound **42** (69 mg, 95%) as a yellow oil. LCMS m/z 245 (MH+).

PREPARATIVE EXAMPLE 43



43

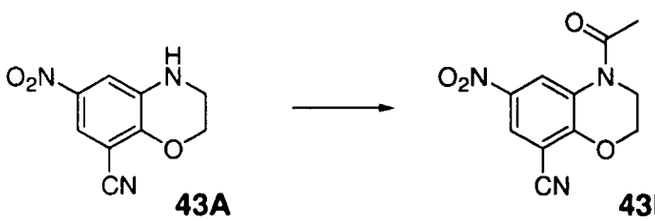
Steps 1-4



43A

In a manner similar to that described in Examples 19 and 3, 2-cyanophenol was subjected to bis-nitration with HNO_3, selective reduction with $SnCl_2$, cyclization with chloroacetyl chloride, and reduction with BH_3-SMe_2 to provide **43A**.

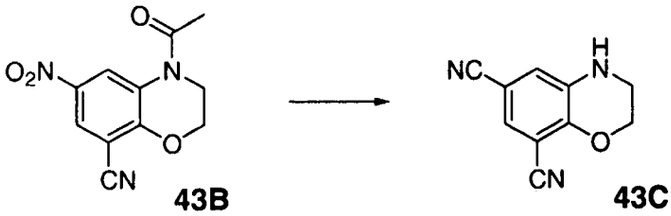
Step 5



43A **43B**

A mixture of **43A** (0.65 g, 3.2 mmol) and Et_3N (0.9 mL, 6.3 mmol) in CH_2Cl_2 (60 mL) was treated with Ac_2O (6 mL) and DMAP (0.15 g) and then refluxed for 2 d. The reaction was then cooled, washed with 1N HCl (2x), washed with brine, dried over Na_2SO_4, and concentrated. Chromatography (10-100% of EtOAc/hexanes) provided **43B** as a yellow solid (0.688 g, 88%).

Steps 5-8



43B 43C

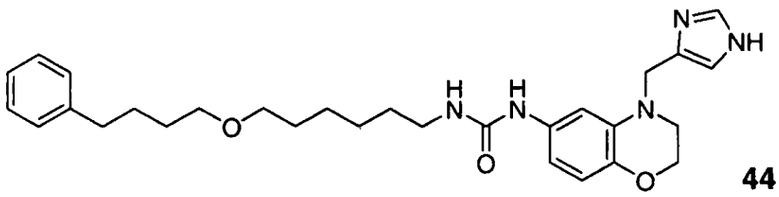
In a manner similar to that described in Example 3 (Step 4), **43B** was hydrogenated with Pd/C.

A mixture of the aniline product (0.080 g, 0.38 mmol) in 6M HCl (0.5 mL) was treated with a solution of $NaNO_2$ (27 mg, 0.39 mmol) at 0 °C. After 0.5 h, the solution was neutralized with sat. aq. Na_2CO_3 and then added dropwise to solution of CuCN (37 mg, 0.41 mmol) and NaCN (40 mg, 0.82 mmol). The resulting mixture was stirred at 60 °C overnight and then filtered.

The brown precipitate (44 mg) was collected and then treated with 10% aq. NaOH (0.5 mL) for 2h at RT. The reaction was then diluted with H_2O and extracted with CH_2Cl_2 (3x). The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated. Chromatography (20-100% of EtOAc/hexanes) provided **43C** as a beige solid (0.0.15 g).

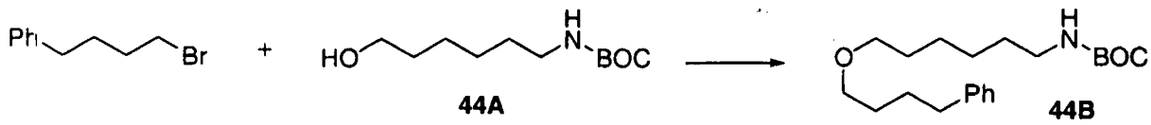
In a manner similar to that described in Example 3 (Step 3), **43C** was converted to the title compound **43.** LCMS m/z 266 (MH+).

PREPARATIVE EXAMPLE 44



44

Step 1

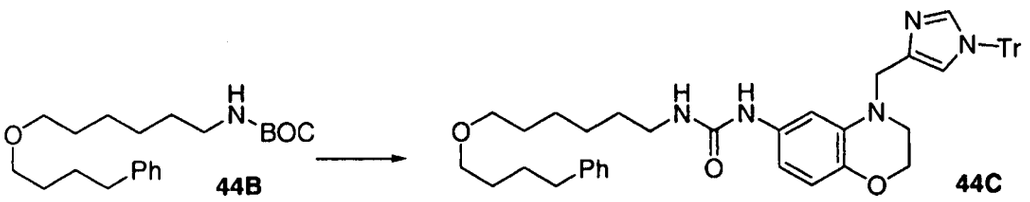


44A 44B

A solution of 4-phenylbutyl bromide (0.98 g, 4.6 mmol) and **44A** (1.0 g, 4.6 mmol) in 10 mL of benzene was treated sequentially with Bu_4NHSO_4 (0.16 g, 0.46 mmol) and 50% aqueous NaOH (2.4 mL, 46 mmol, added slowly). After stirring at RT under N_2 for 20 h, the solvent was removed. The reaction mixture was then diluted with H_2O, extracted with EtOAc, washed with H_2O (3x) and brine, dried over Na_2SO_4,

and filtered. The filtrate was concentrated and chromatographed (5-10% EtOAc/hexanes) to provide **44B** (0.7 g, 44%).

Steps 2-3

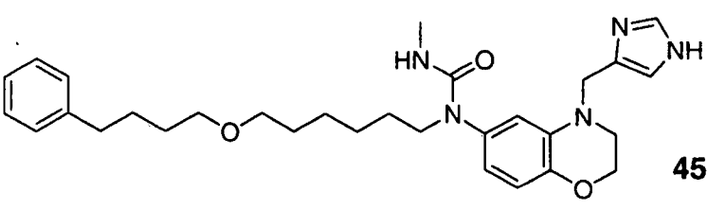


To a solution of **44B** (0.2 g, 0.57 mmol) in 5 mL of CH_2Cl_2 (5 mL) was added TFA (1.5mL). After stirring at RT for 1.5 h, the solution was cooled to 0 °C and treated with concentrated aqueous NH_3 (until pH = 10-11). The mixture was extracted with CH_2Cl_2, dried over Na_2SO_4, and filtered. The filtrate was concentrated to give an unstable amine (0.12 g, 84%) which was immediately taken up in CH_2Cl_2 (8 mL) and treated with compound **7B** (0.21g, 0.44mmol) and Et_3N (0.17 mL, 1.2mmol). After the mixture was cooled to -50 °C, triphosgene (0.04 g, 0.13 mmol) was added to the solution. The mixture was stirred at -50 °C under N_2 for 1h, then slowly warmed up to RT, and stirred under N_2 overnight. After adding 5% aqueous NaOH (10 mL), the products were extracted with CH_2Cl_2, dried over Na_2SO_4, and filtered. Chromatography (2% MeOH/EtOAc) provided **44C** (0.2 g, 67%).

Step 4

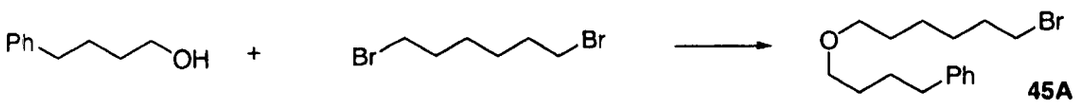
A mixture of **44C** (0.13 g) in 3N HCl-MeOH (8 mL) was heated at 60 °C under N_2 for 1.5 h, cooled to 0 °C and neutralized with concentrated aqueous NH_3. The solution was concentrated, taken up in H_2O and extracted with CH_2Cl_2. The organic extract was dried over Na_2SO_4, filtered and chromatographed (5% NH_3-MeOH in CH_2Cl_2) to give the title compound **44** (0.05 g, 62%). LCMS m/z 506 (MH+).

PREPARATIVE EXAMPLE 45



101

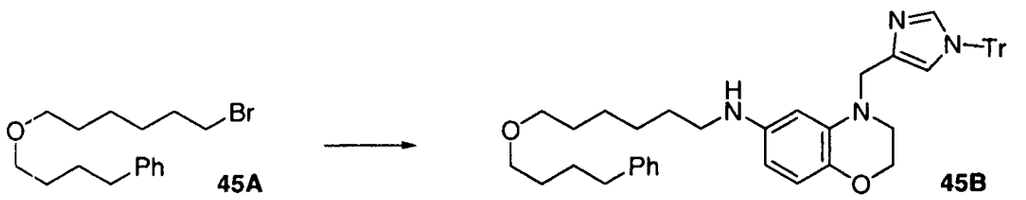
Step 1



45A

A solution of 4-phenylbutanol (2.50 g, 16.6 mmol) and 1,6-dibromohexane (8.12 g, 33.2 mmol) in anhydrous THF (30 mL) was treated slowly with NaH (1.0 g, 24.9 mmol) at RT. After refluxing under N_2 for 20 h, the mixture was cooled to RT, and quenched with H_2O. The products were extracted with ether, washed with brine, dried over Na_2SO_4, and filtered. The filtrate was concentrated and chromatographed (2% EtOAc/hexanes) to give **45A** (3.3 g, 63%).

Steps 2-4

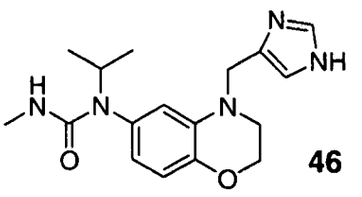


45A **45B**

To a solution of **45A** (0.07 g, 0.21 mmol) and **7B** (0.1 g, 0.21 mmol) in toluene (3 mL) and DMF (0.5 mL) was added DIPEA (0.07 mL, 0.42 mmol) at RT. After heating at 80 °C under N_2 for 20 h, the mixture was concentrated, taken up in CH_2Cl_2, washed with H_2O (3x) and brine, dried over Na_2SO_4, and filtered. Chromatography (60% EtOAc/hexanes) provided **45B** (0.04 g, 27%).

In a manner similar to that described in Example 5 (Step 3) and Example 44 (Step 4), **45B** was sequentially treated with MeNCO and HCl to provide the title compound **45.** LCMS m/z 520 (MH+).

PREPARATIVE EXAMPLE 46



46

Steps 1-2



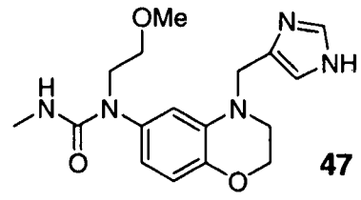
46A **46B**

Compound **46A** (from Example 38, Step 2, 250 mg, 1 mmol) was taken up in DCE (10 mL) and treated sequentially with 2-methoxypropene (0.14 mL, 1.5 mmol), HOAc (0.06 mL, 1.1 mmol), and $NaBH(OAc)_3$ (424 mg, 2.0 mmol). The reaction mixture was stirred at RT overnight, quenched with 1.0 N NaOH and extracted with CH_2Cl_2 (3 x 20 mL). The combined organic layers were washed with brine, dried, and then concentrated. Chromatography (EtOAc/hexanes) afforded **46B** (190 mg, 65%).

Steps 3-5

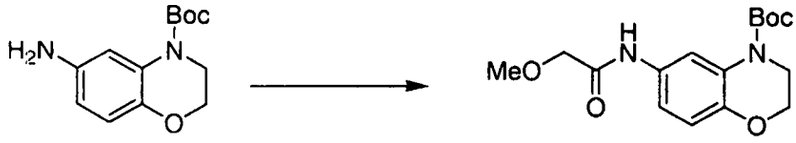
In a manner similar to that described in Example 38 (Steps 5-7), **46B** was sequentially treated with MeNCO, deprotected with TFA, and treated with 4-imdazolecarboxaldehyde to provide the title compound **46**. LCMS m/z 330 (MH+).

PREPARATIVE EXAMPLE 47



47

Step 1



46A **47A**

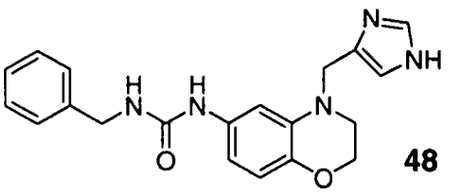
A mixture of **46A** (500 mg, 2 mmol) in CH_2Cl_2 (10 mL) was sequentially treated with methoxyacetyl chloride (0.22 mL, 2.4 mmol) and TEA (0.56 mL, 4.0 mmol). The reaction mixture was stirred at RT overnight, quenched with sat. $NaHCO_3$, and extracted with CH_2Cl_2 (2 x 20 mL). The combined organic layers were washed with

brine, dried, and concentrated. Chromatography (EtOAc/hexanes) afforded **47A** (610 mg, 95%).

Steps 2-5

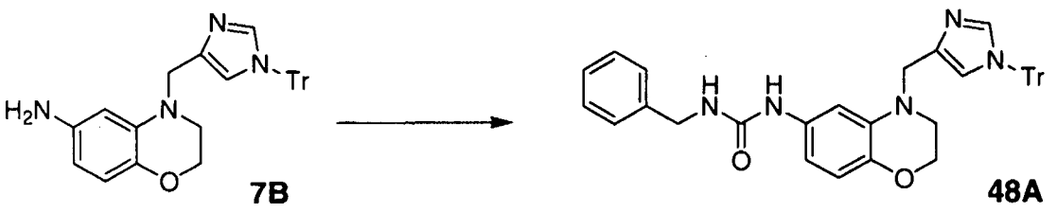
In a manner similar to that described in Example 38 (Steps 4-7), **47A** was reduced with BH_3-SMe_e, treated with MeNCO, deprotected with TFA, and treated with 4-imdazolecarboxaldehyde to provide the title compound **47**. LCMS m/z 346 (MH+)

PREPARATIVE EXAMPLE 48



48

Steps 1-2

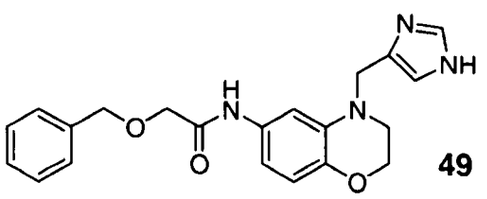


7B **48A**

A solution of **7B** (140 mg, 0.3 mmol) in anhydrous CH_2Cl_2 (5 mL) was treated with benzyl isocyanate (48 mg, 0.36 mmol). The reaction mixture was stirred at RT overnight and then concentrated. Chromatography afforded **48A** (130 mg, 72%).

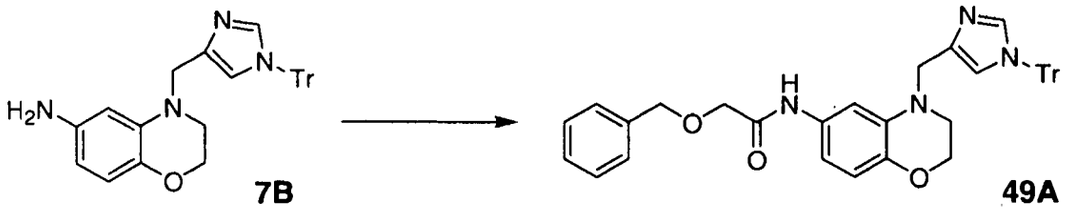
In a manner similar to that described in Example 42 (Step 3), **48A** was deprotected with with TFA and Et_3SiH to provide the title compound **48**. LCMS m/z 364 (MH+).

PREPARATIVE EXAMPLE 49



49

Steps 1-2

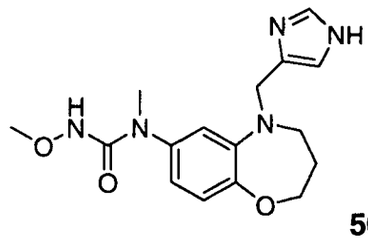


7B **49A**

A mixture of **7B** (1.0 g, 2.12 mmol), benzyloxyacetic acid (0.46 g, 2.75 mmol), EDCI (0.61 g, 3.18 mmol) and HOBt (0.42 g, 3.18 mmol) in DMF were stirred at RT for 1 d. The reaction was quenched with 0.5 N aq. NaOH (50 mL) and extracted with CH_2Cl_2. The combined extracts were washed with brine, dried (Na_2SO_4) and concentrated. Preparative TLC chromatography (5% NH_3-MeOH in CH_2Cl_2) provided **49A** (0.52 g).

In a manner similar to that described in Example 42 (Step 3), **49A** was deprotected with TFA and Et_3SiH to provide the title compound **49**. LCMS m/z 379 (MH+).

PREPARATIVE EXAMPLE 50



50

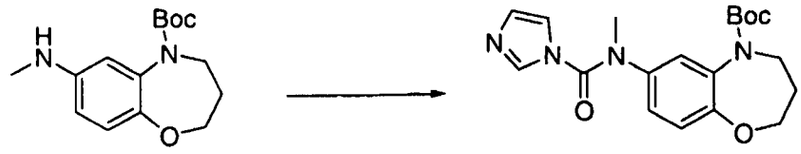
Steps 1-4



28C **50A**

In a manner similar to that described in Example 5 (Steps 1-2) and Example 6 (Steps 1-2), compound **28C** was converted to **50A.**

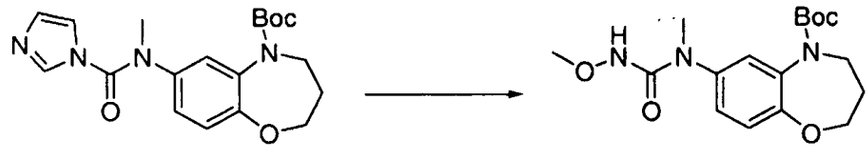
Step 5



50A **50B**

A mixture of **50A** (0.247 g, 0.99 mmol) in anhydrous DCM (5 mL) was treated with carbonyldiimidazole (0.32 g, 1.97 mmol) and Et_3N (0.28 mL, 1.97 mmol) and then stirred at RT overnight. The reaction was washed with water and extracted with DCM (3 x 10 mL). The combined organic layer was dried ($MgSO_4$), filtered, and concentrated under vacuum to give compound **50B.**

Steps 6-8

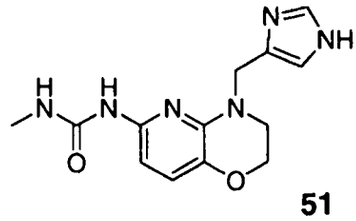


50B **50C**

A solution of **50B** was in anhydrous MeCN (5 mL) in a sealed tube was treated with MeI (2 mL). The sealed reaction mixture was heated to 55 °C for 3 h, cooled to RT and concentrated. The residue was dissolved in anhydrous THF (5 mL) and then treated with $MeONH_2$-HCl (0.25 g, 2.97 mmol) and DIEA (0.53 mL, 2.97 mmol). After stirring at RT overnight, the reaction was quenched with saturated NH_4Cl solution and concentrated under vacuum. The residue was diluted with water and extracted with EtOAc (3 x 10 mL). The combined organic layer was dried ($MgSO_4$), filtered, and concentrated under vacuum to afford crude compound **50C** (279 mg, 80% for 3 steps).

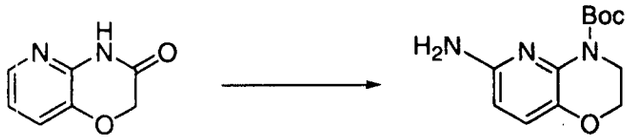
In a manner similar to that found in Example 5 (Step 4) and Example 3 (Step 3), compound **50C** was deprotected and converted to the title compound **50**. MS m/z = 332 (MH+).

PREPARATIVE EXAMPLE 51



51

Steps 1-4



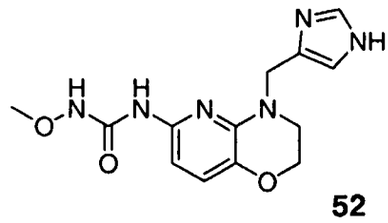
22A **51A**

In a manner similar to that described in Example 21 (Step 1), Example 3 (Step 2), Example 5 (Step 1) and Example 3 (Step 4), compound **22A** was sequentially nitrated, reduced with BH_3-SMe_2, treated with Boc_2O, and hydrogenated to yield compound **51A**.

Steps 5-7

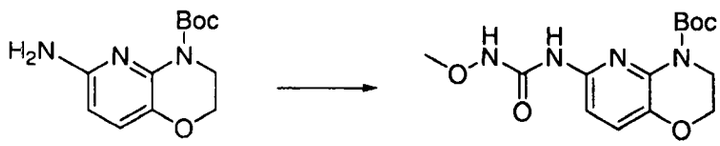
In a manner similar to that described in Example 5 (Steps 3-5), **51A** was treated with MeNCO, deprotected with TFA, and converted to the title compound **51**. MS m/z = 289 (MH+).

PREPARATIVE EXAMPLE 52



52

Steps 1-3

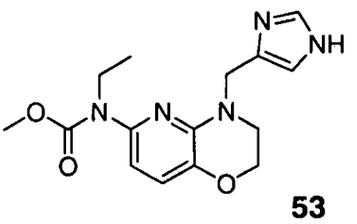


51A **52A**

To a solution of **51A** (740 mg, 2.95 mmol) in DCM (30 ml) was added 4-nitrophenylchloroformate (891 mg, 4.42 mmol) and pyridine (0.48 ml, 5.90 mmol). After stirring overnight at RT, TLC indicated consumption of the starting material. $MeONH_2$-HCl salt (739 mg, 8.84 mmol) in anhydrous THF (10 ml) and DIEA (1.57 mL, 8.84 mmol) were then sequentially added. After stirring at RT overnight, the reaction was quenched by water, concentrated, diluted with water and extracted with EtOAc. The organic phase was dried ($MgSO_4$), filtered, and concentrated. Flash chromatography (20-50% of EtOAc/hexanes) provided **52A** (650 mg, 68%).

In a manner similar to that found in Example 5 (Step 4) and Example 3 (Step 3), **52A** was converted to **52**. MS m/z = 305 (MH+).

PREPARATIVE EXAMPLE 53



53

Steps 1-3

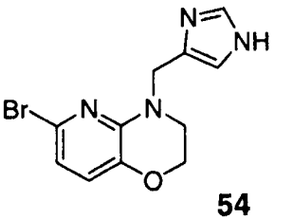


51A **53A**

To compound **51A** (100 mg, 0.40 mmol) in DCE (5 mL) was added acetaldehyde (0.045 mL, 0.80 mmol). The mixture was stirred at RT for 1 h and then treated with MeOH (3 mL) and $NaBH_4$ (45.5 mg, 1.2 mmol). After stirring at RT overnight, the reaction was quenched by 2N NaOH solution, concentrated, diluted with water and extracted with EtOAc. The organic phase was dried (MgSO4), filtered, and concentrated under vacuum to give a residue **53A** (40 mg, 36%).

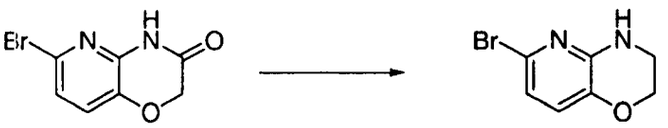
In a manner similar to that found in Example 3 (Step 5), Example 5 (Step 4) and Example 3 (Step 3), **53A** was treated with $ClCO_2Me$/pyridine, deprotected with TFA and converted to the title compound **53**. MS m/z = 318 (MH+).

PREPARATIVE EXAMPLE 54



54

Steps 1-2

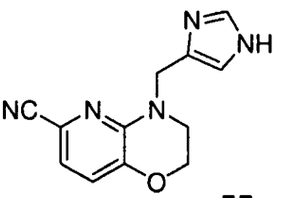


54A **54B**

In a manner similar to that found in Example 3 (Step 2), compound **54A** (see WO 2006/020561) was reduced with BH_3-SMe_2 to provide **54B**.

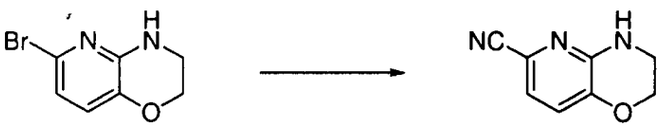
Compound **54B** was then elaborated into **54** (MS m/z = 295, MH+) as previously described in Example 3 (Step 3).

PREPARATIVE EXAMPLE 55



55

Steps 1-2

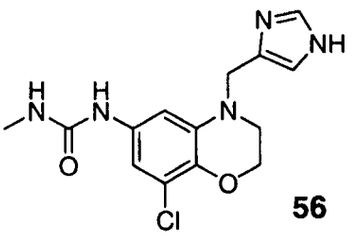


54B **55A**

A Smith process vial was charged with a stir bar, compound **54B** (0.33 g, 1.54 mmol), CuCN (0.276 g, 3.08 mmol) and DMF (3 mL). The reaction vessel was sealed and heated to 120 °C for 3 h under microwave irradiation. After cooling, the reaction mixture was transferred to a round bottom flask and concentrated under vacuum. Compound **55A** was obtained quantitatively by continuous extraction with EtOAc in a Soxlet apparatus.

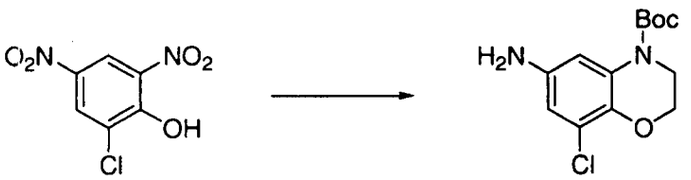
Compound **55A** was then elaborated into **55** (MS m/z = 242, MH+) as previously described in Example 3 (Step 3).

PREPARATIVE EXAMPLE 56



56

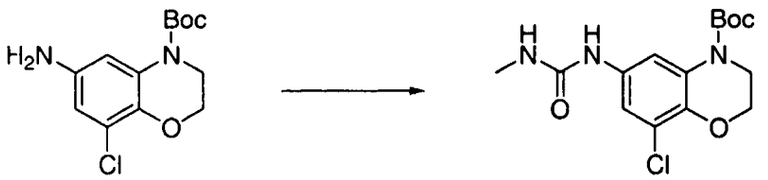
Steps 1-5



56A

In a manner similar to that previously described, 2-chloro-4,6-dinitrophenol was sequentially reduced with $SnCl_2$ (Example 19, Step 2), treated with chloroacetyl chloride, reduced with BH_3-SMe_2 (Example 3, Steps 1-2), protected with Boc_2O (Example 5, Step 1), and reduced again with $SnCl_2$ to yield compound **56A**.

Steps 6-8



56A **56B**

To a solution of compound **56A** (0.29 g, 1 mmol) in anhydrous DCM (3 ml) was added 4-nitrophenylchloroformate (0.24 g, 1.2 mmol) and pyridine (0.13 ml, 1.57 mmol). After stirring overnight at RT, the reaction was quenched with sat. NH_4Cl solution and extracted with DCM. The organic phase was then concentrated. A solution of this residue in CH_3CN (5 mL) was treated with 40% $MeNH_2$ in H_2O (20 mL) and heated in a sealed tube at 90 °C overnight. The mixture was cooled, stirred at RT overnight, and then quenched with water. The reaction was concentrated, diluted with

water and extracted with EtOAc. The organic phase was dried ($MgSO_4$), filtered, and concentrated to give **56B**.

As described previously in Example 5 (Step 4) and Example 3 (Step 3), **56B** was deprotected and converted to **56**. MS m/z = 322 (MH+).

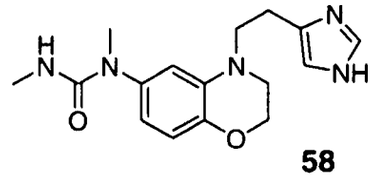
PREPARATIVE EXAMPLE 57



127 **57**

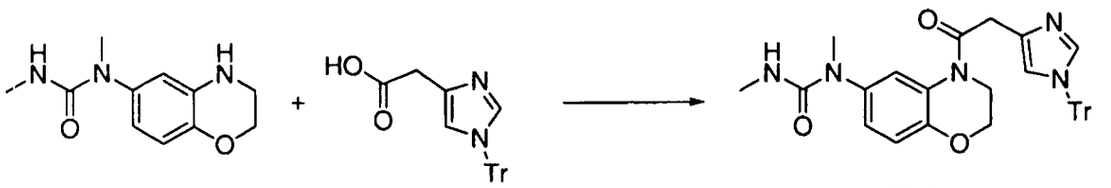
Compound **127** (0.388 g, 1.22 mmol) was dissolved in anhydrous DCM (10 mL) and cooled to -78 °C. To this solution was added 1.0M BBr_3 in DCM (6.1 mL) dropwise. The reaction mixture was stirred at -78 °C for 30 min and then at RT for 3 h. The reaction was quenched with water and neutralized with 2N NaOH solution. The mixture was separated and the aqueous phase was extracted with DCM (3 x 10 mL). The organic phase was dried ($MgSO_4$), filtered, and concentrated under vacuum. The residue was purified by flash column chromatography (DCM containing 2 to 8% of 7N NH_3 in MeOH) to afford compound **57** in 30% yield. MS m/z = 305 (MH+).

PREPARATIVE EXAMPLE 58



58

Step 1



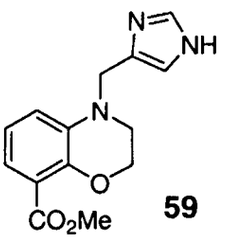
58A **58B** **58C**

In a manner similar to that described in Example 37, compound **58A** (prepared in Example 6) and **58B** (Bioconjugate Chemistry, *13*, 333-350, 2002) were reacted with HATU to provide **58C**. MS m/z = 572 (MH+)

Steps 2-3

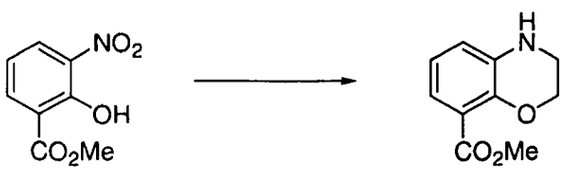
A solution of **58C** (720 mg, 1.3 mmol) in THF (50 mL) was treated with BH_3-SMe_2 (5 mL, 2 M in THF) and heated at 80 °C for 12 h. After it was cooled to 25 °C, MeOH (15 mL) was added dropwise until bubbling ceased. The solvent was removed and partitioned between EtOAc and water. The organic phase was dried over Na_2SO_4 and concentrated. The crude residue was stirred in DCM/TFA (1:3, 5 mL) at 25 °C for 4 h. Solvent was removed and the residue was partitioned between EtOAc and water. The organic phase was dried and concentrated. Column chromatography and preparative TLC (DCM containing 5% of 7N NH_3/MeOH) gave **58**. MS m/z = 316 (MH+).

PREPARATIVE EXAMPLE 59



59

Steps 1-3



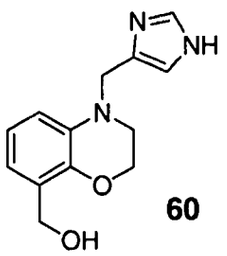
59A

In a manner similar to that described in Example 3 (Step 4 then Steps 1-2), methyl 2-hydroxy-3-nitrobenzoate was sequentially hydrogenated, treated with chloroacetylchloride, and reduced with BH_3-SMe_2 to yield compound **59A**.

Step 4

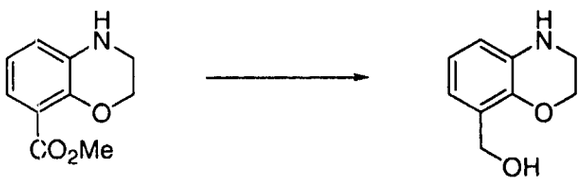
Compound **59A** was treated with 4-imidazolecarboxaldehyde to afford the title compound **59** in a manner similar to that described in Example 3 (Step 3). MS m/z = 274 (MH+).

PREPARATIVE EXAMPLE 60



60

Steps 1-2

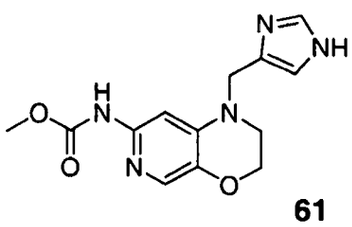


59A **60A**

A mixture of $LiBH_4$ (44 mg, 2 mmol) and **59A** (400 mg, 2 mmol) in THF (50 mL) was stirred at RT for 4 h and then concentrated. The residue was partitioned between EtOAc and water. The organic phase was dried and concentrated to give **60A** (300 mg, 91%).

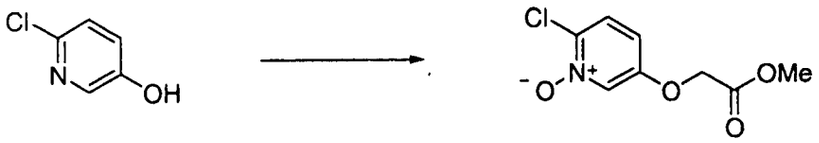
Compound **60A** was converted to **60** in a manner similar to that described in Example 3 (Step 3). MS m/z = 246 (MH+).

PREPARATIVE EXAMPLE 61



61

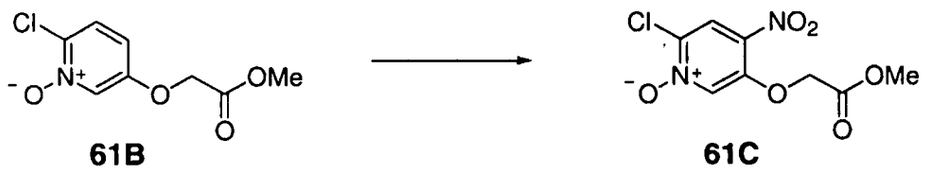
Steps 1-2



61A **61B**

To 2-chloro-5-hydroxypyridine (**61A**) in acetone (80 mL) was added K_2CO_3 (8.96 g, 65 mmol) and methylchloroacetate (2.54 mL, 29 mmol). The mixture was heated at 60 °C for 4 h. After cooling to RT, the mixture was filtered, and the solids were washed with acetone (50 mL). The filtrate was concentrated *in vacuo* to give 4.3 g intermediate (92% yield). The intermediate (4.3 g, 21.3 mmol) was dissolved in $CHCl_3$ (75 mL) and treated with m-chloroperbenzoic acid (4.78 g, 27.7 mmol). The resulting solution was heated at 50 °C for 4 h, then stirred at RT overnight. The mixture was treated with sodium sulfate, filtered and concentrated *in vacuo*. Flash column chromatography (5%-10% MeOH in DCM) provided **61B** (3.46 g, 75%).

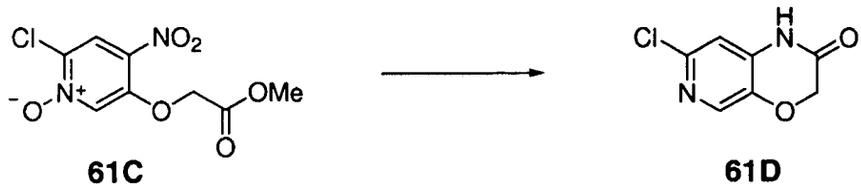
Steps 3-4



61B **61C**

The N-oxide **61B** (1.0 g, 4.61 mmol) was dissolved in H_2SO_4 (2 mL) at 0 °C. HNO_3 (1 mL) was added slowly over several minutes. The reaction mixture was then placed in an oil bath heated to 40 °C. The temperature was slowly raised to 75 °C over 1 h and then maintained there for 2 h. The mixture was then poured over ice and adjusted to pH 9 by the addition of 50% NaOH. Water was removed *in vacuo*, and the resultant solids were washed with MeOH to yield crude nitro pyridine N-oxide intermediate (2.6 g). A portion of this intermediate (1.33 g, 5.3 mmol) was dissolved in MeOH (50 mL) and treated with H_2SO_4 (1 mL). The mixture was heated at 70 °C for 2 h and then concentrated. The residue was treated with 1N NaOH (20 mL) and EtOAc (50 mL). The solution was extracted with EtOAc (2 x 50 mL). The combined organic extracts were dried over sodium sulfate, filtered and concentrated *in vacuo* to give compound **61C** (1.4 g, 100%).

Steps 5-6



61C **61D**

A mixture of **61C** (0.06 g, 0.23 mmol) in MeOH (2 mL) was treated with iron powder (0.09 g, 1.61 mmol) and HOAc (0.08 mL). The resulting solution was heated at 70 °C for 4 h. The hot solution was filtered through a pad of celite and concentrated. The residue was taken up in MeOH (2 mL) and treated with K_2CO_3 (0.073 g, 0.53 mmol). After heating at 65 °C for 2 h, the solvent was removed *in vacuo* and the product purified by preparative TLC (5% MeOH in DCM) to give compound **61D** (0.032 g, 76%).

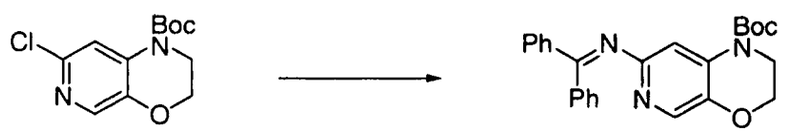
Steps 7-8



61D **61E**

In a manner similar to that found in Example 3 (Step 2) and Example 5 (Step 1), compound **61D** was reduced and protected to give compound **61E**.

Step 9



61E **61F**

A mixture of **61E** (0.250 g, 0.91 mmol), benzophenoneimine (0.152 mL, 0.91 mmol), tris(dibenzylideneacetone dipalladium(0) (0.004 g, 0.0045 mmol), rac-2,2'-Bis(diphenylphosphino)-1,1'-binaphthalene (0.004 g, 0.007 mmol), and NaO*t*Bu (0.088g, 0.91 mmol) in toluene (8 mL) in a culture tube was heated in a rotating oven at 80 °C overnight. After cooling to RT, the contents were transferred to a round-

bottomed flask and treated with several scoops of silica gel. The solvent was removed *in vacuo* and the product purified by flash column chromatography (10% to 50% EtOAc-hexanes) to give **61F** (0.205 g, 54%).

Steps 10-13

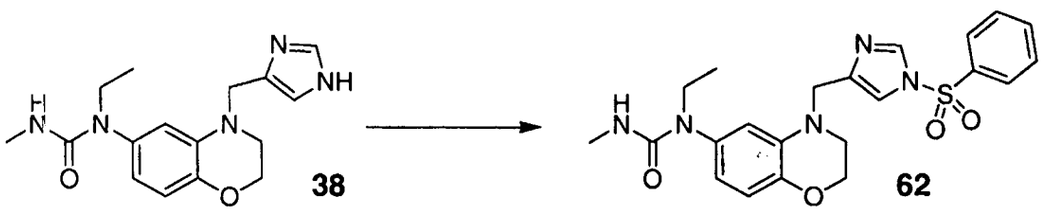


61F **61G**

A mixture of **61F** (0.205 g, 0.5 mmol) in THF (4 mL) was treated with 15% aqueous citric acid solution (4 mL). The resulting solution was stirred at RT overnight. Saturated aqueous $NaHCO_3$ (5 mL) was added and the solution was extracted with EtOAc (2 x 25mL). The organic extracts were dried over sodium sulfate, filtered and concentrated *in vacuo*. The product was purified by flash column chromatography (10% to 50% EtOAc-hexanes) to give **61G** (0.114g, 91%).

In a manner similar to that found in Example 3 (Step 5), Example 5 (Step 4) and Example 3 (Step 3), compound **61G** was sequentially treated with $ClCO_2Me$, deprotected and converted the title compound **61**. MS m/z = 290 (MH+).

PREPARATIVE EXAMPLE 62

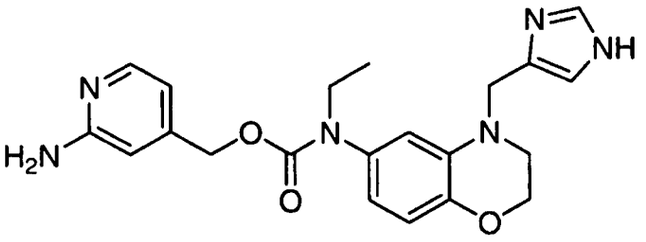


38 **62**

A slurry of **38** in anhydrous DCE (4 ml) and anhydrous THF (4 ml) was treated with anhydrous TEA (0.2 ml) followed by benzenesulfonyl chloride (0.070 mL). After 2 h at RT, additional benzenesulfonyl (0.2 mL) was added. The mixture was stirred for 1 h, then diluted with CH_2Cl_2, washed with brine, dried (Na_2SO_4), and concentrated. Preparative TLC chromatography (9% MeOH/CH_2Cl_2) afforded **62** (43 mg).

116

PREPARATIVE EXAMPLE 63



63

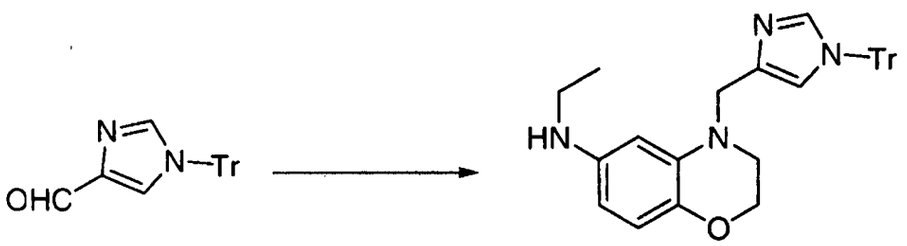
Step 1



38B 63A

In a manner similar to that found in Example 38 (Step 6), **38B** was sequentially deprotected with TFA to provide **63A.**

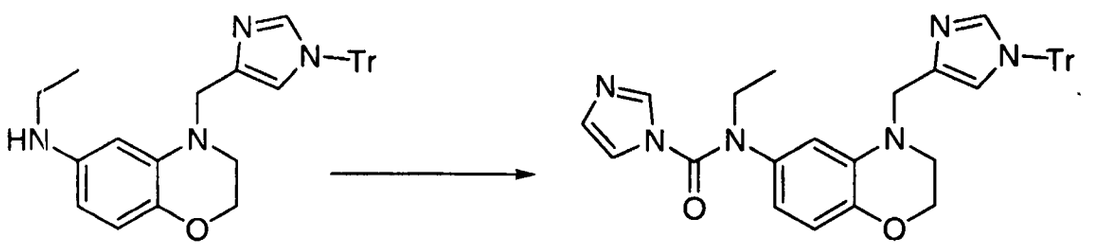
Steps 2-3



42A 63B

In a manner similar to that found in Example 3 (Step 3) and Example 26 (Step 3), **42A** (Journal of Medicinal Chemistry, **1971**, *14*, 883) was sequentially treated with **63A**/$NaBH(OAc)_3$, and then reduced with LAH in THF to provide **63B.**

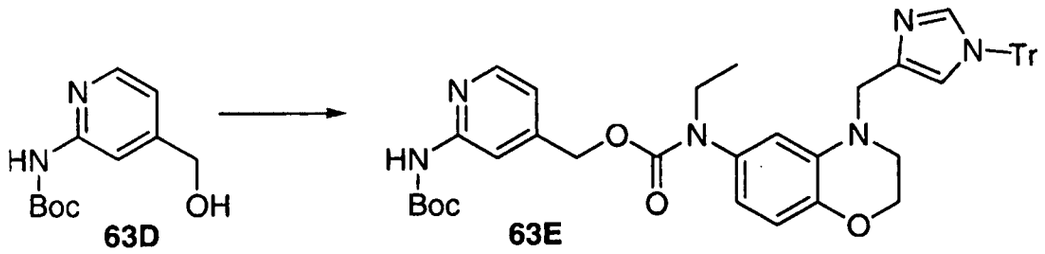
Step 4



63B 63C

In a manner similar to that found in Example 50 (Step 5), **63B** was reacted with carbonyldiimidazole to provide **63C.**

Steps 5-6

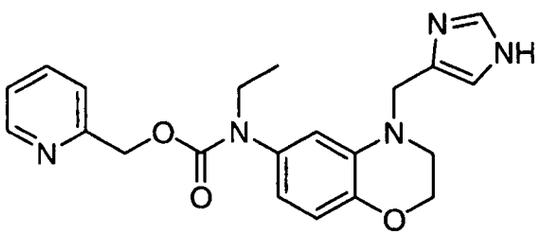


63D **63E**

A solution of **63D** (188 mg, 0.84 mmol, PCT WO2002032893) in THF (4 mL) at 20 °C was treated with NaHMDS (340 µL, 1.68 mmol), stirred for 1h, and then treated with **63C** (100 mg, 0.17 mmol). After stirring overnight, the solution was diluted with $NaHCO_3$ (10 mL) and extracted with CH_2Cl_2 (3 x 10 mL). The combined organic phase was concentrated in vacuo to provide **63E.**

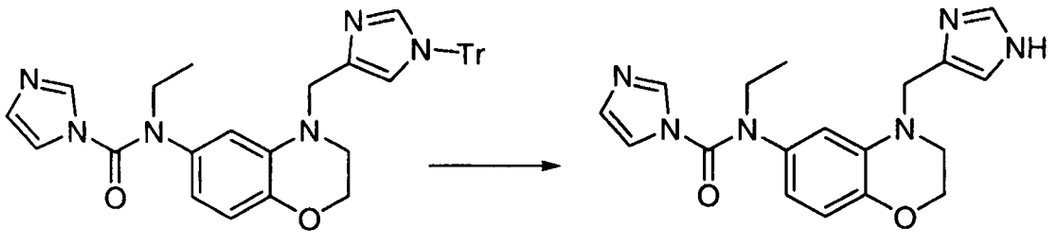
This product was then treated with TFA/Et_3SiH to provide the title compound **63** in a manner similar to that found in Example 42 (Step 3). LCMS m/z 409 (MH+).

PREPARATIVE EXAMPLE 64



64

Steps 1-2

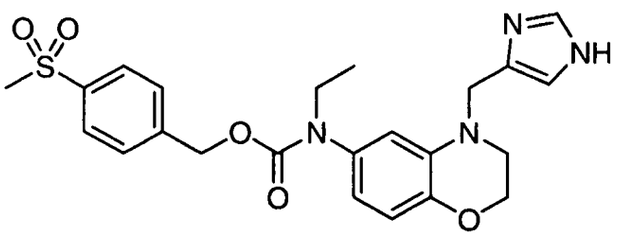


63B **64A**

In a manner similar to that found in Example 42 (Step 3), **63C** was treated with TFA/Et_3SiH to provide **64A.** LCMS m/z 353 (MH+).

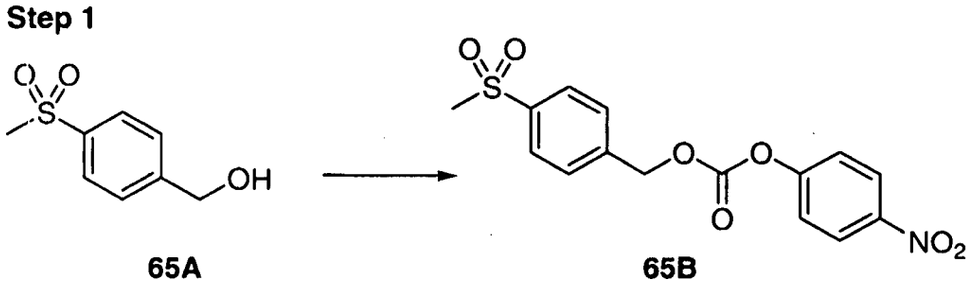
This product was then treated with NaHMDS and pyridine-2-methanol, as described in Example 63 (Step 5) to provide the title compound **64**. LCMS m/z 394 (MH+).

PREPARATIVE EXAMPLE 65



65

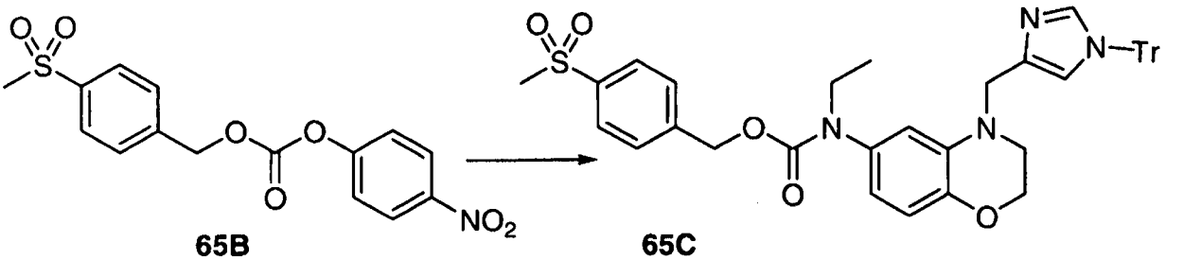
Step 1



65A **65B**

A solution of 4-(methylsulfonyl)benzyl alcohol (**65A**, 150 mg, 0.81 mmol) in THF (3 mL) at 20 °C was treated with 4-nitrophenyl chloroformate (162 mg, 0.81 mmol) and pyridine (66 µL, 0.81 mmol). The mixture was stirred overnight and then partitioned between EtOAc and water. The organic layer was washed with brine, dried over Na_2SO_4 and concentrated to provide **65B**.

Steps 2-3

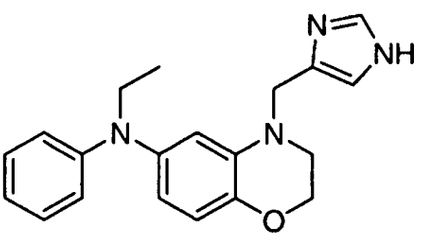


65B **65C**

A solution of **65B** (crude material from previous step) in THF (3 mL) was treated with **63B** (160 mg, 0.34 mmol) and pyridine (66 mL, 0.81 mmol). After stirring for 2d at 20 °C, the mixture was diluted with CH_2Cl_2, washed with saturated aqueous $NaHCO_3$, and concentrated to provide **65C**.

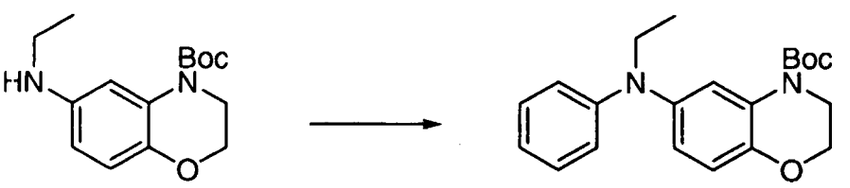
This product was then deprotected with TFA to provide the title compound **65** in a manner similar to that found in Example 42 (Step 3). LCMS m/z 471 (MH+).

PREPARATIVE EXAMPLE 66



66

Steps 1-3

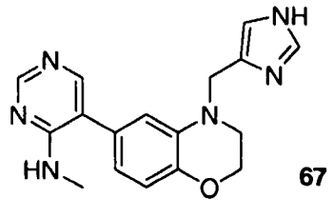


66A **66B**

A solution of bromobenzene (135 mg, 0.863 mmol), **66A** (200 mg, 0.719 mmol, product of Example 38, Step 4) was treated with $Pd_2(dba)_3$ (33 mg, 0.036 mmol), Ligand S-Phos (30 mg, 0.076 mmol), and NaOtBu (90 mg, 0.934 mmol). The mixture was stirred at 100°C for 12 h under N_2, filtered. Chromatography (50% EtOAc/Hexane) afforded **66B** as an oil.

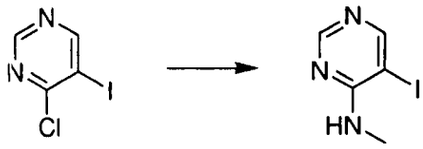
In a manner similar to that found in Example 38 (Step 6) and Example 3 (Step 3), **66B** was then deprotected with TFA and then converted to the title compound **66**. LCMS m/z 335 (MH+).

PREPARATIVE EXAMPLE 67



67

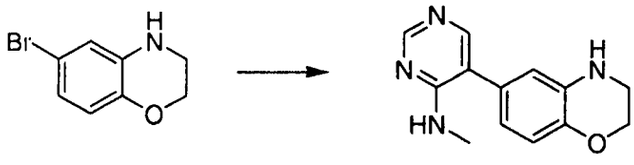
Step 1



67A **67B**

A solution of 4-chloro-5-iodopyrimidine **67A** (2.03 g, 8.44 mmol) in 40% aqueous $MeNH_2$ solution was stirred at RT for 17h. The mixture was then extracted with DCM (2 x 150 ml). The combined organic phase were dried concentrated to give 5-iodo-4-methylaminopyrimidine **67B** (1.55 g, 78%) as an orange solid which was used for the next step without further purification.

Steps 2-3



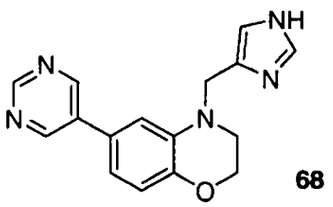
67C **67D**

A 15 mL-sealed tube was charged with 6-bromophenyl morpholine (**67C**, 0.431 g, 2.013 mmol), bis(pinacolato)diboron (1.02 g, 4.03 mmol), KOAc (0.592 g, 6.04 mmol), $Pd(dppf)Cl_2$.DCM (0.164 g, 0.20 mmol) and dry 1,4-dioxane (8 ml). The resulting mixture was heated at 100 °C for 1.5h. The mixture was then cooled to RT

and treated sequentially with 5-iodo-4-methylaminopyrimidine (**67B**, 0.66 g, 4.03 mmol, 2.0 eq) and 1 M aqueous K_2CO_3 (5 mL). The resulting mixture was heated again at 100 °C for 13h, cooled to RT, diluted with water and extracted with DCM to give a brown oil. Chromatography (0-10% of (9:1 MeOH/NH_3) in DCM) provided **67D** (0.198 g, 41%) as a pale brown foam.

In a manner similar to that described in Example 3 (Step 3), compound **67D** converted to the title compound **67**. MS m/z 323 (MH+).

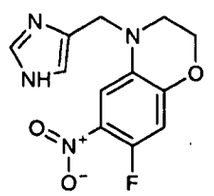
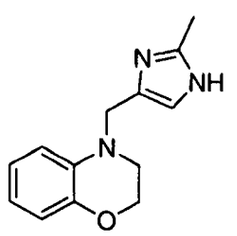
PREPARATIVE EXAMPLE 68

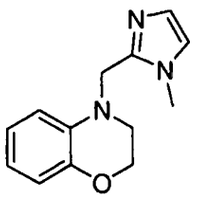
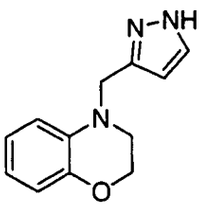
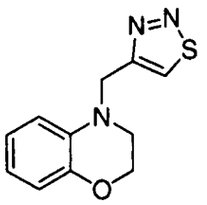
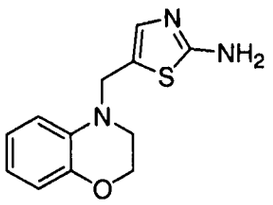
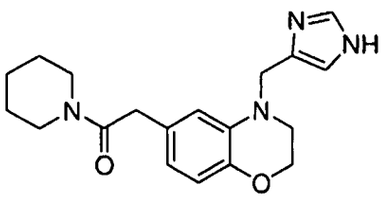
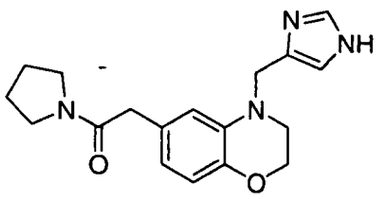
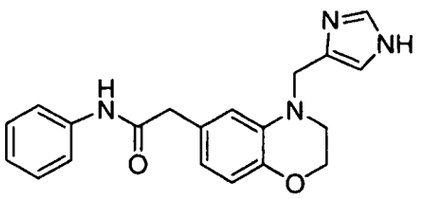
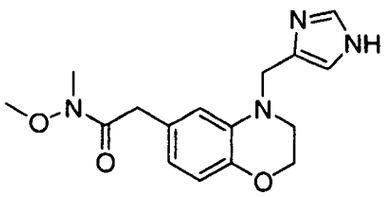


68

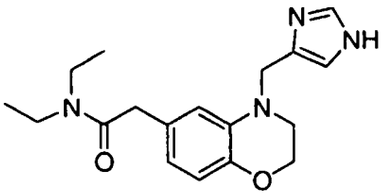
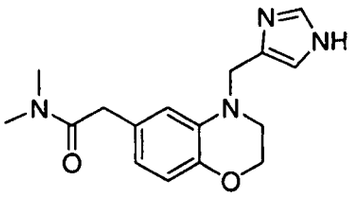
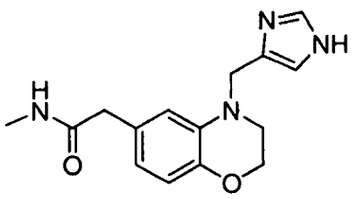
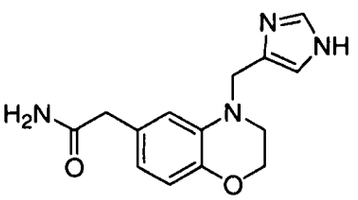
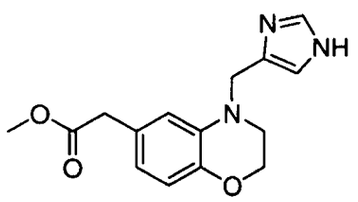
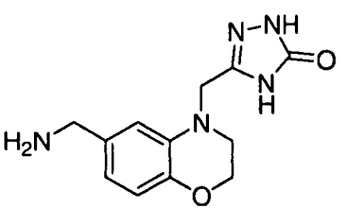
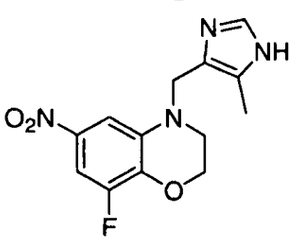
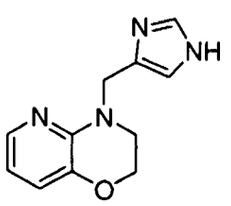
In a manner similar to those previously described (Examples 15-17, 67), 6-bromophenyl morpholine (**67C**) was treated with pyrimidine-5-boronic acid, $PdCl_2(dppf)$, and K_2CO_3, to provide compound 6-(pyrimidin-5-yl)-benzomorpholine, which was further converted to the title compound **68**. MS m/z 294 (MH+).

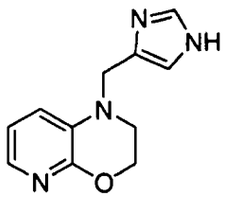
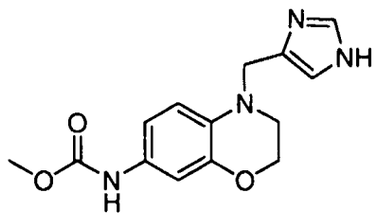
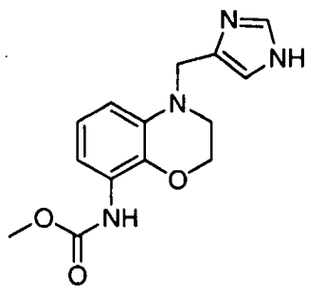
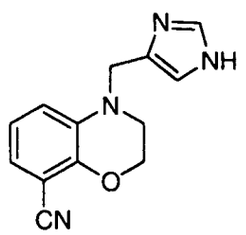
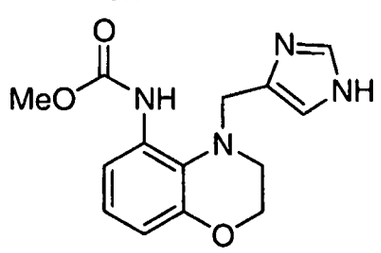
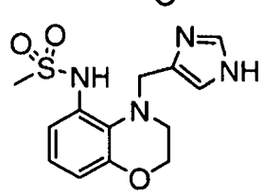
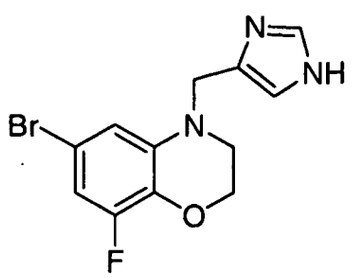
The following compounds were prepared following essentially the same procedure as described above.

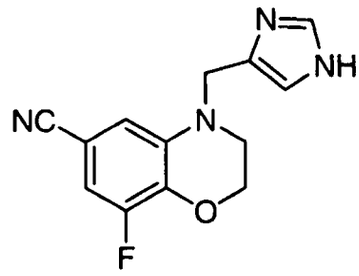
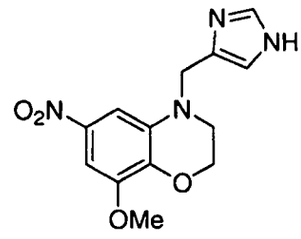
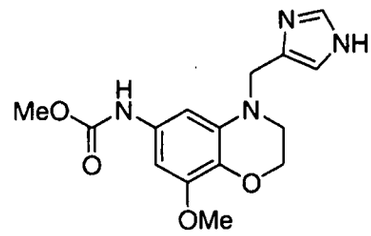
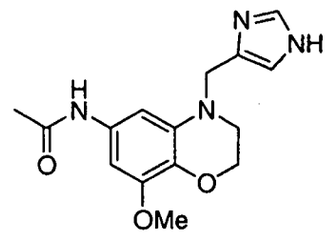
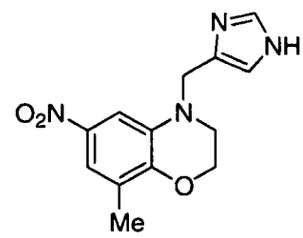
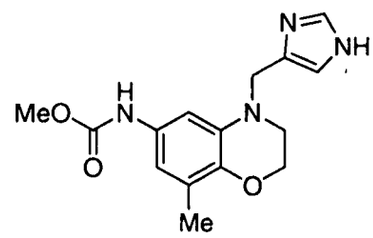
Cpd	Structure	MS (MH+)
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101		230

102		230
103		216
104		234
105		248
106		341
107		327
108		349
109		317

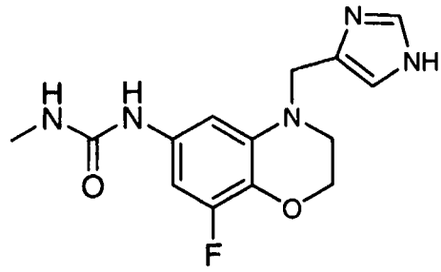
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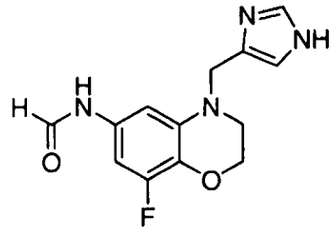
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116		293
117		217

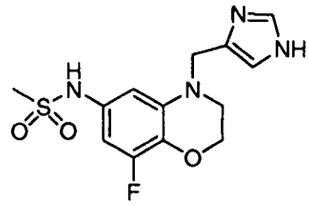
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124		312

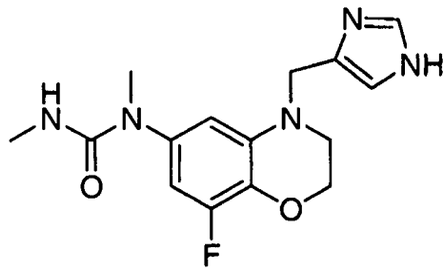
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126		291
127		319
128		303
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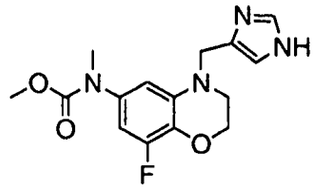
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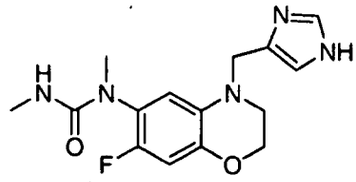
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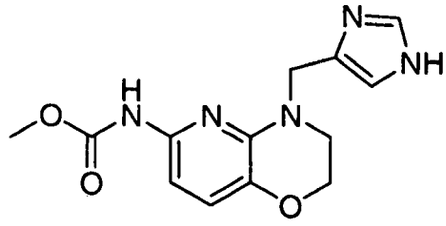
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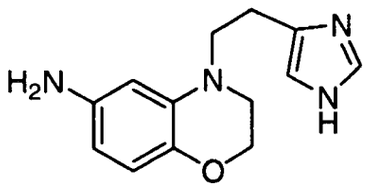
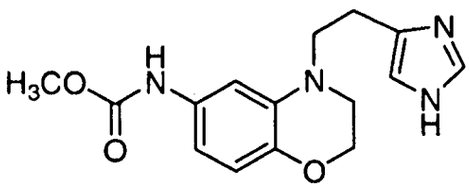
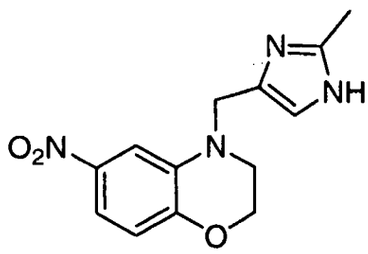
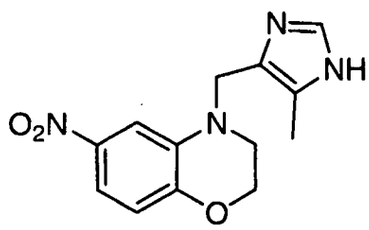
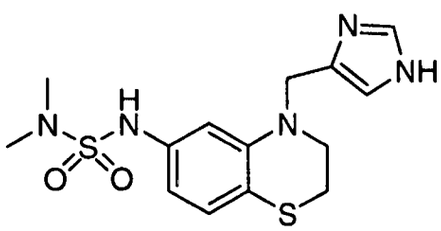
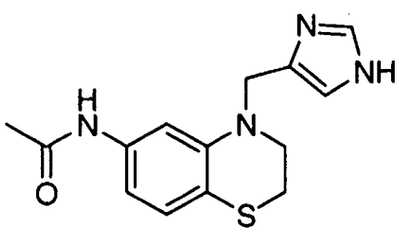
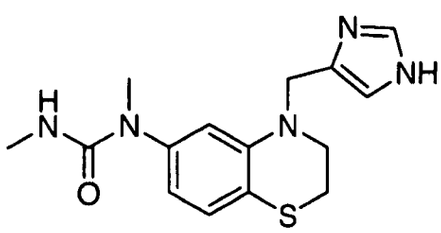
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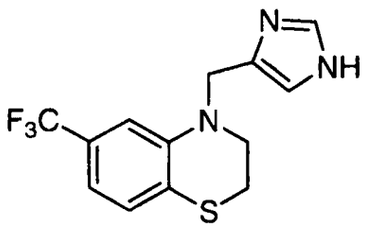
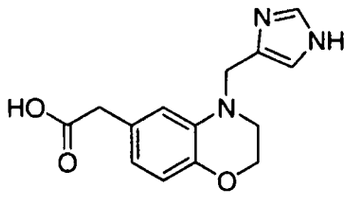
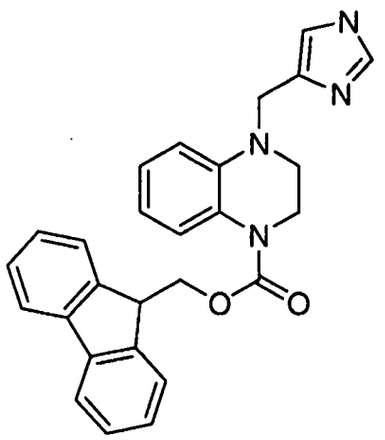
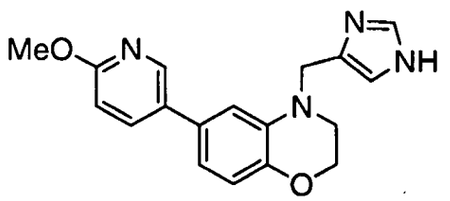
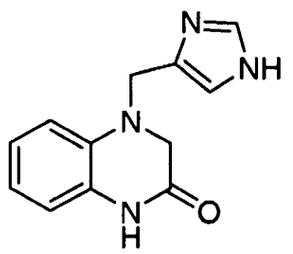
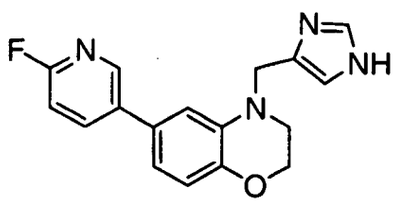
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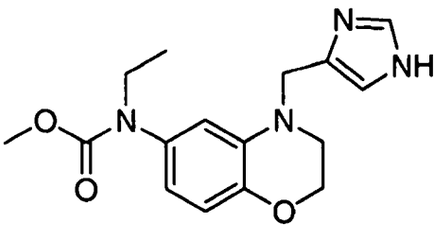
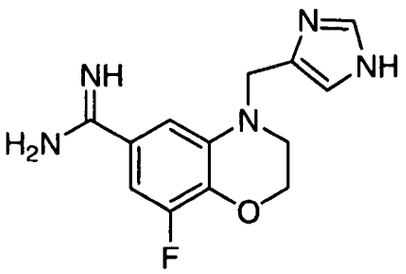
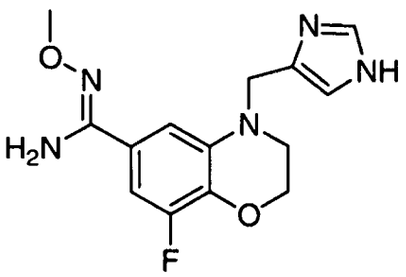
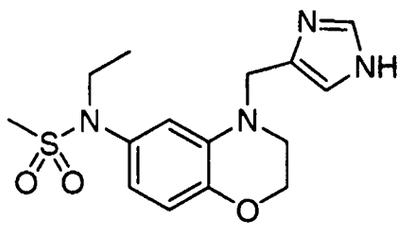
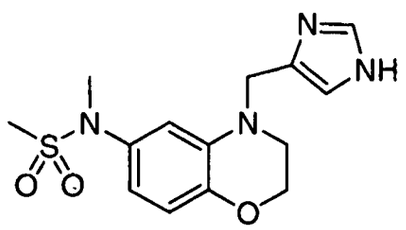
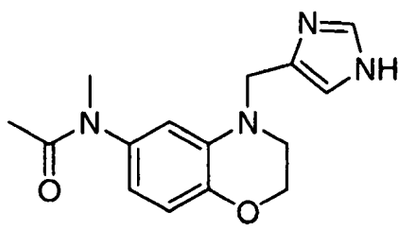
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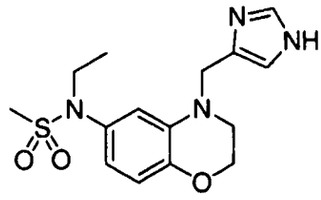
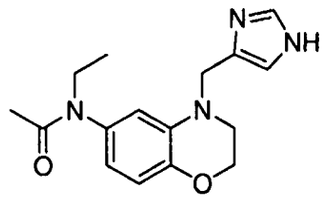
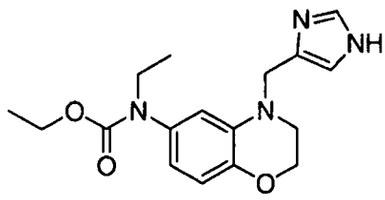
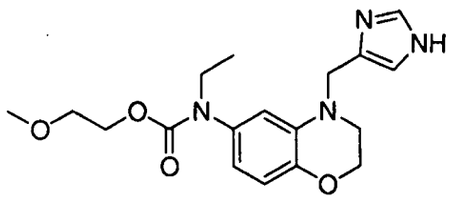
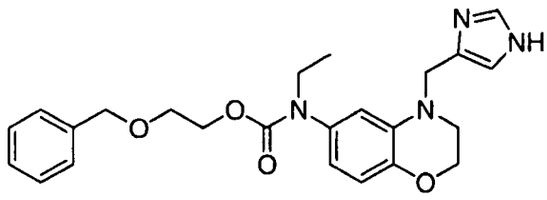
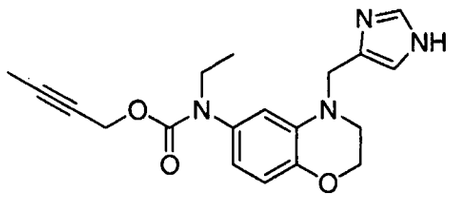
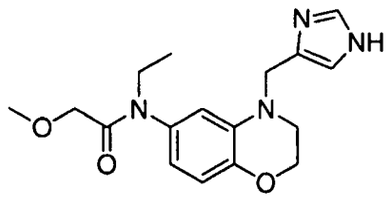
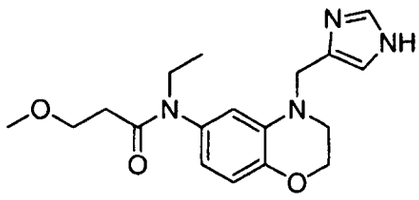
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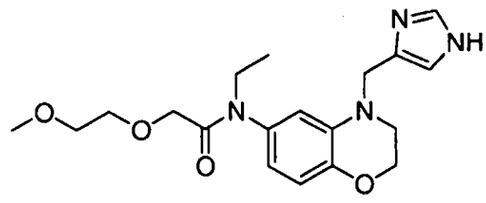
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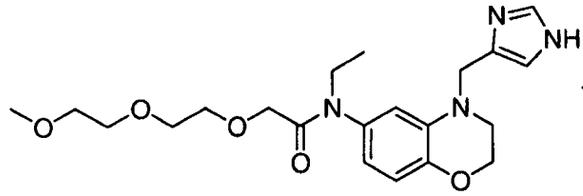
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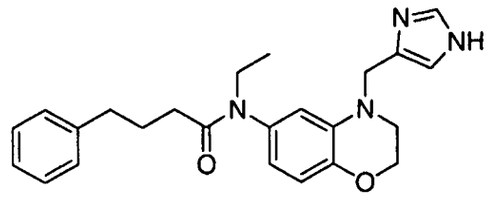
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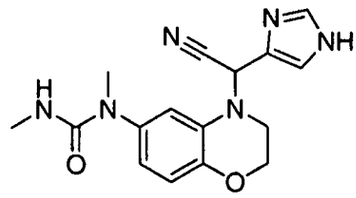
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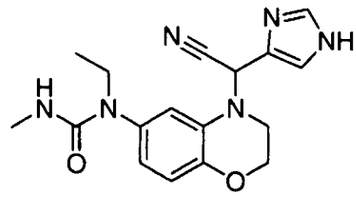
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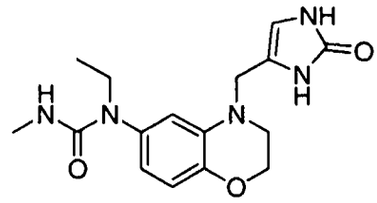
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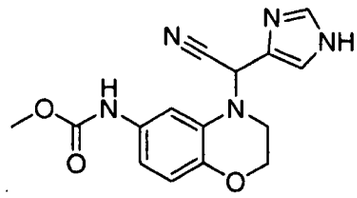
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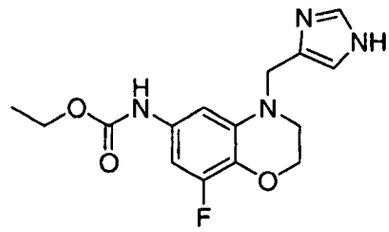
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168  327

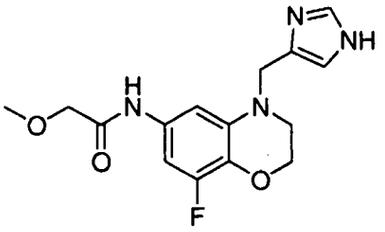
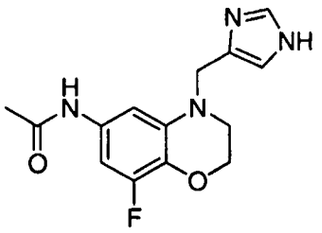
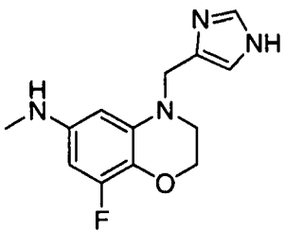
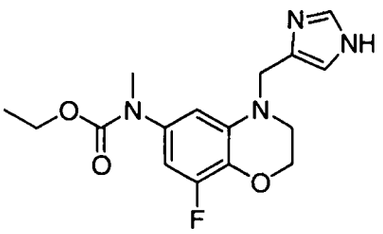
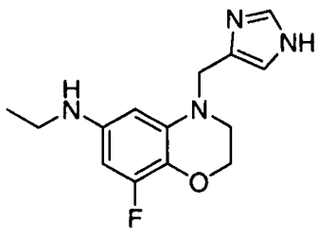
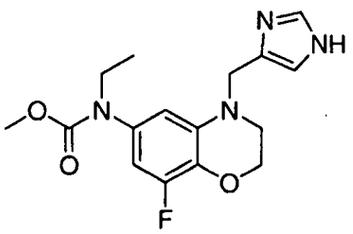
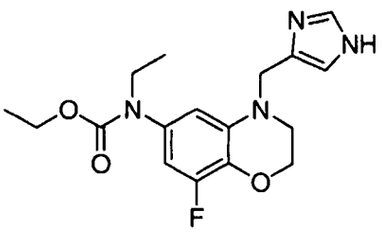
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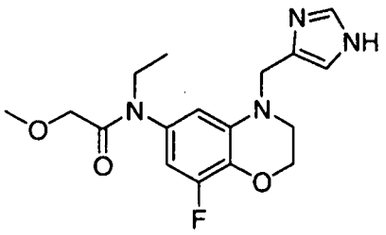
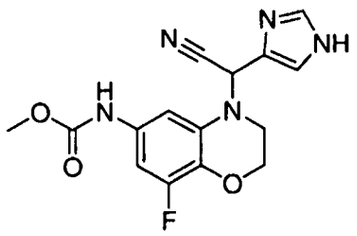
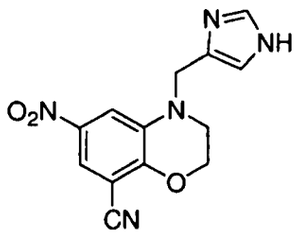
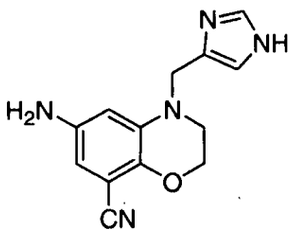
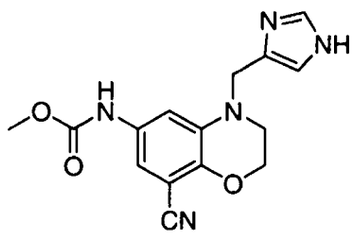
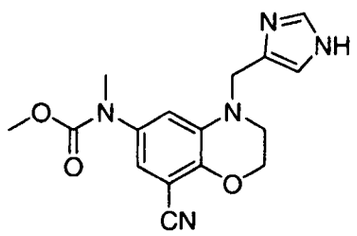
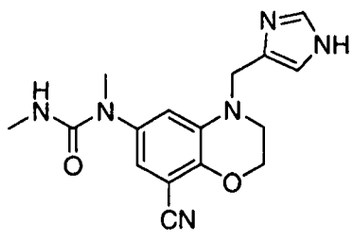
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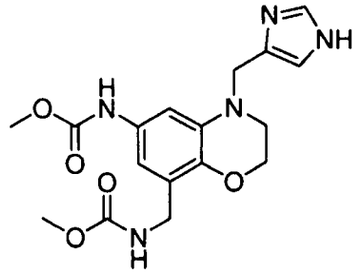
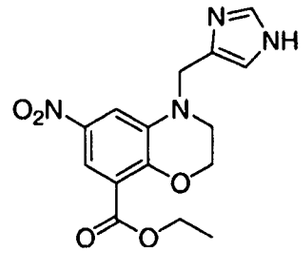
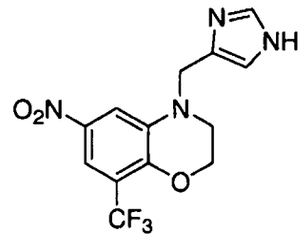
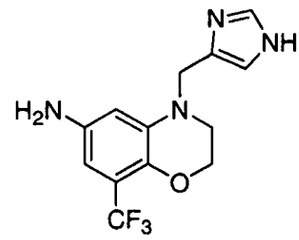
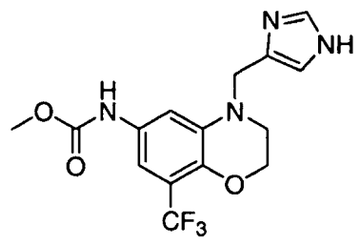
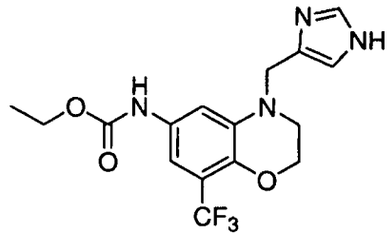
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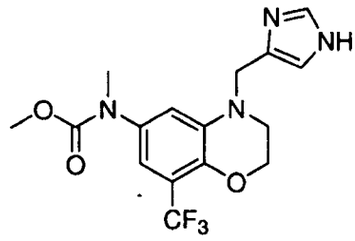
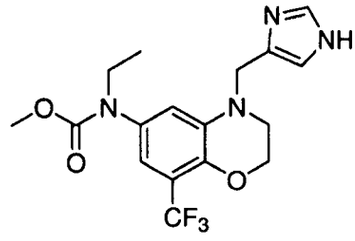
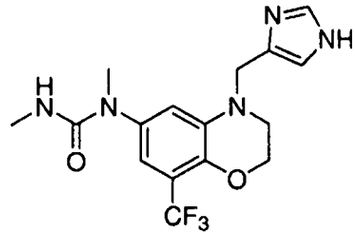
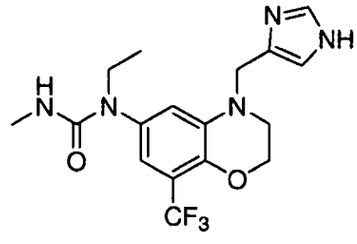
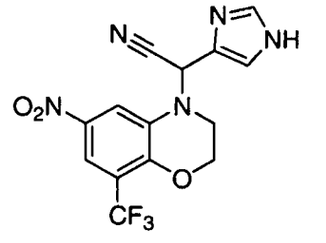
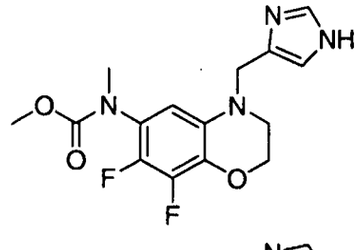
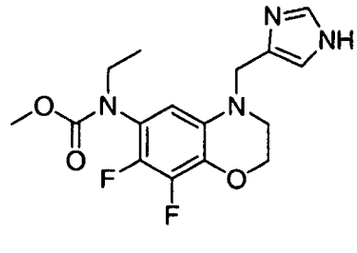
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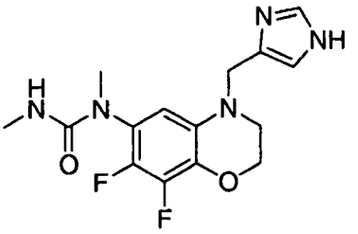
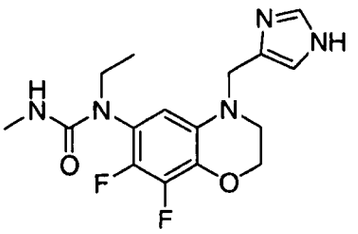
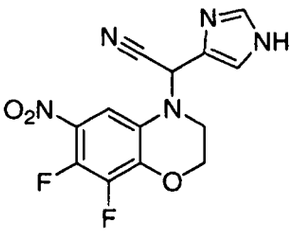
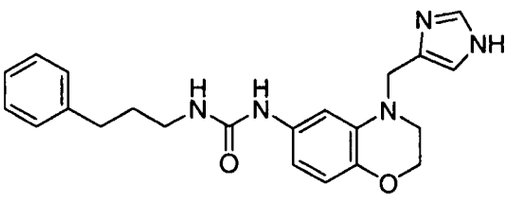
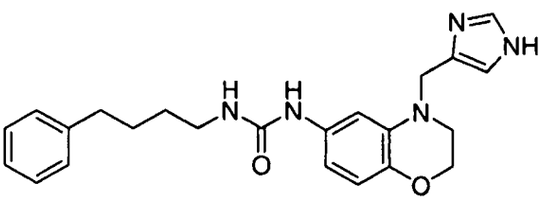
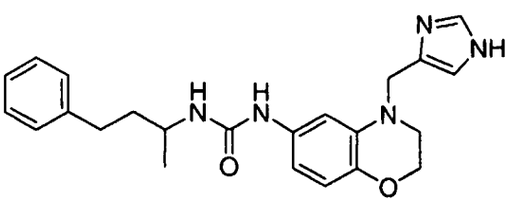
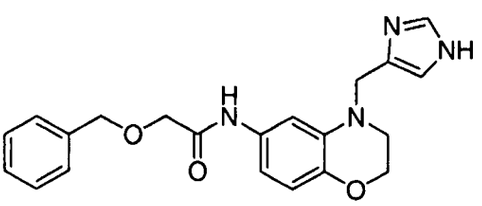
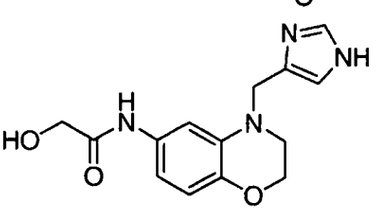
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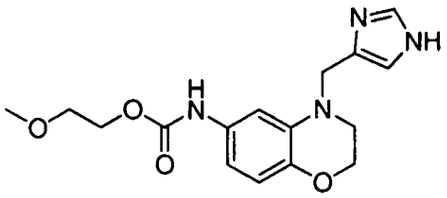
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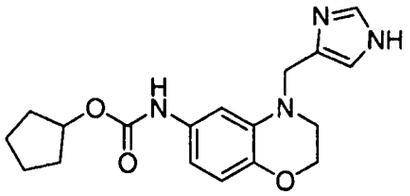
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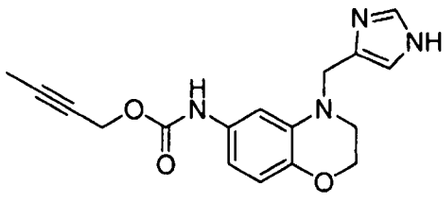
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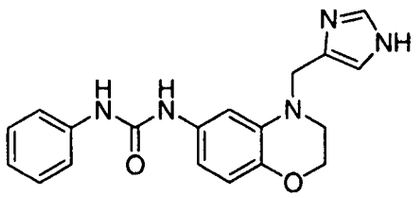
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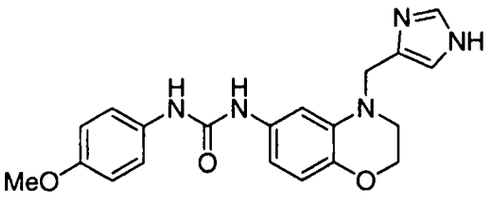
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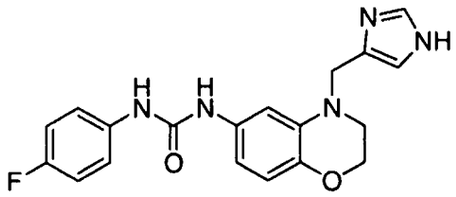
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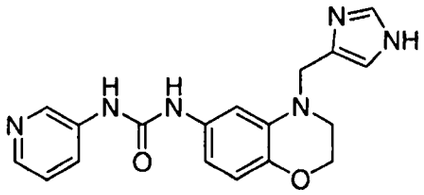
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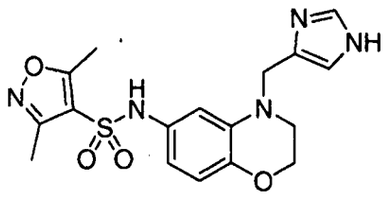
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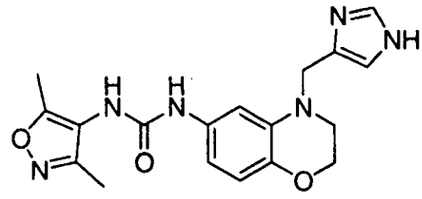
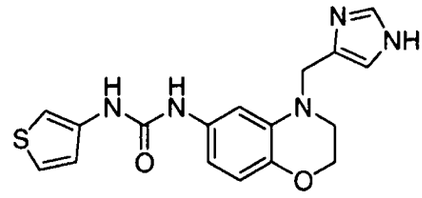
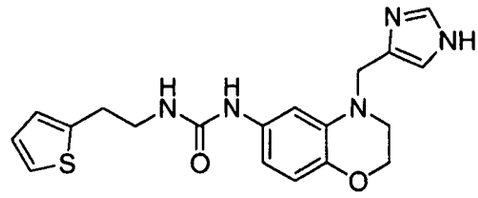
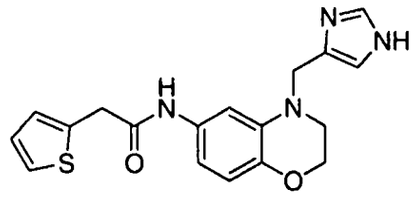
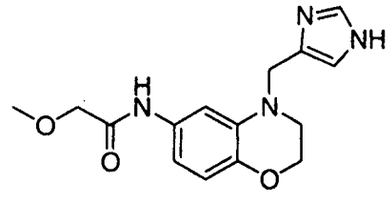
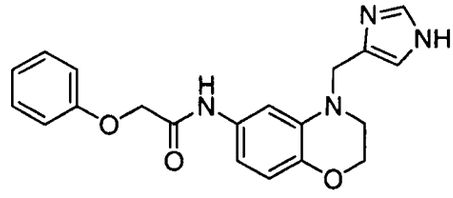
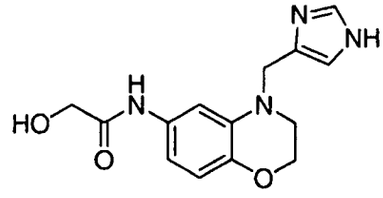
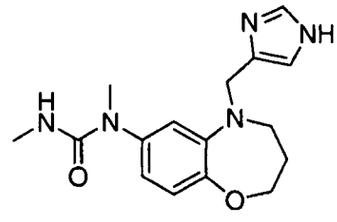
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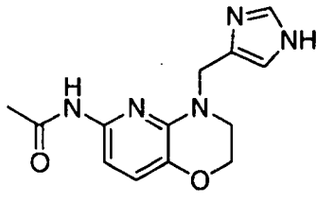
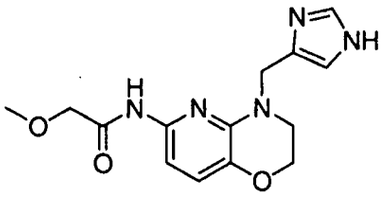
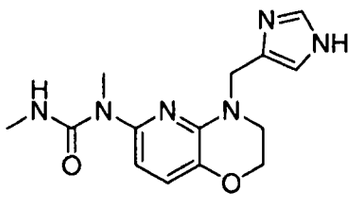
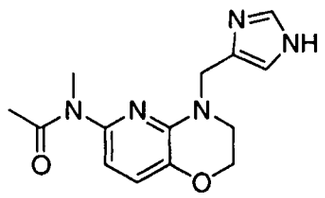
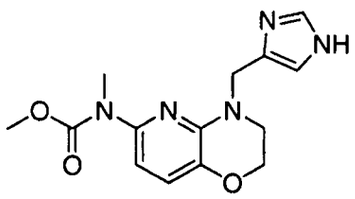
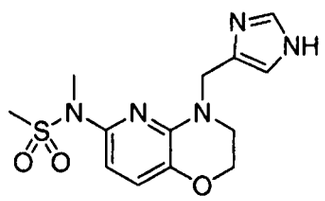
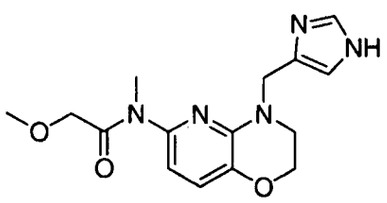
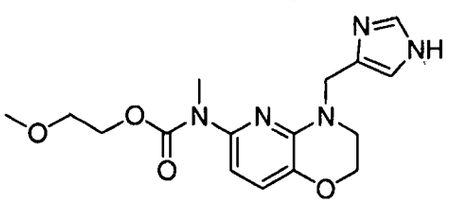
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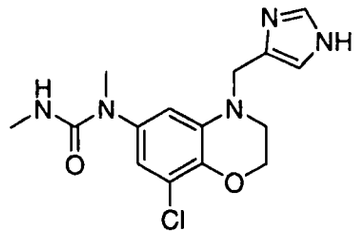
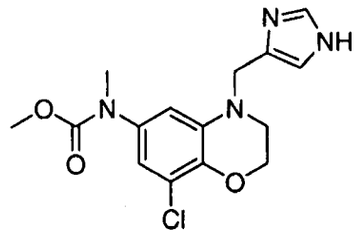
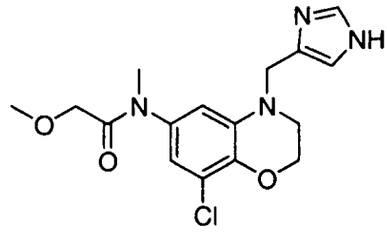
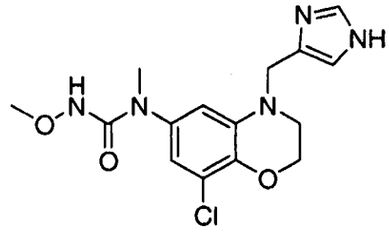
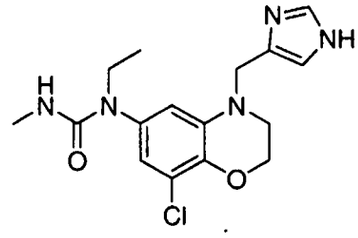
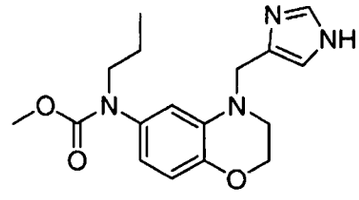
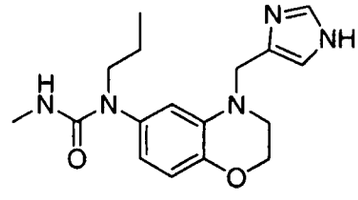
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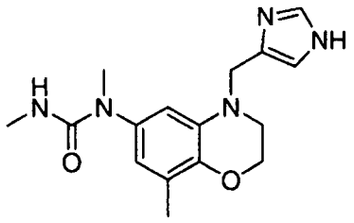
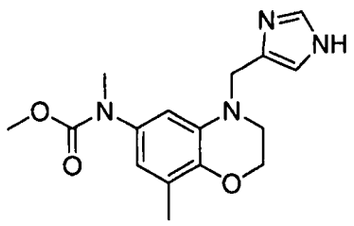
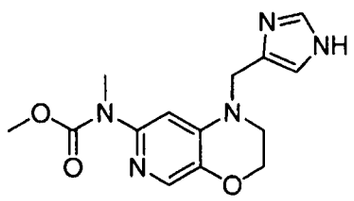
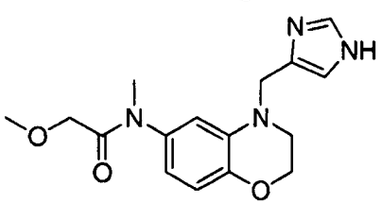
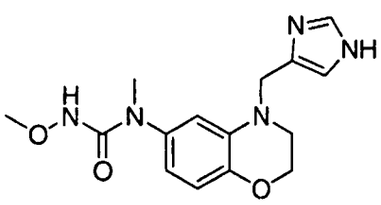
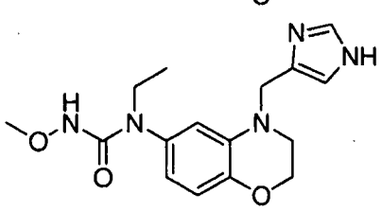
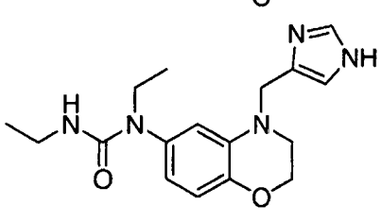
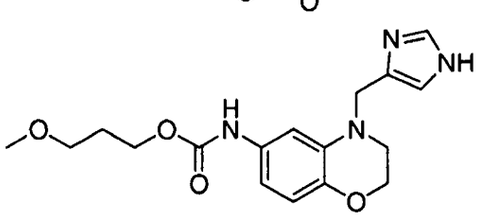
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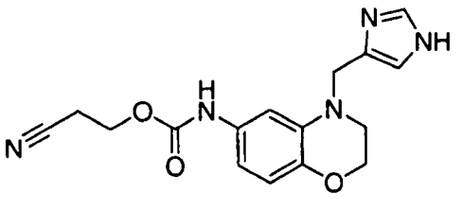
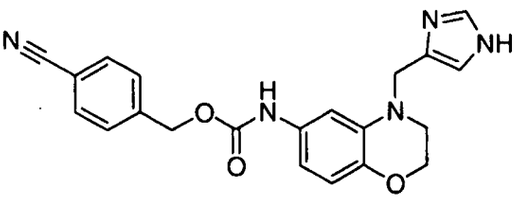
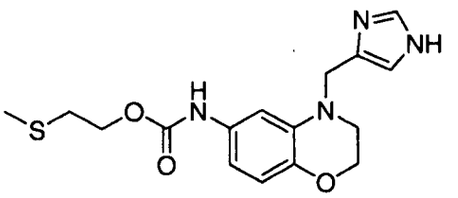
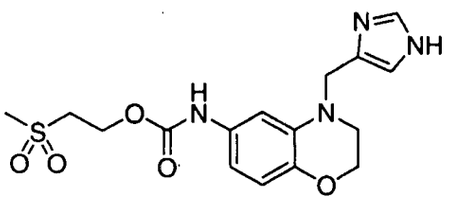
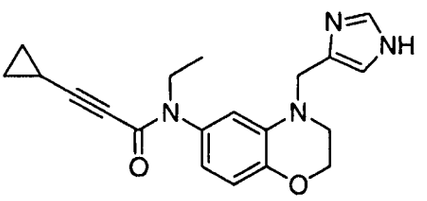
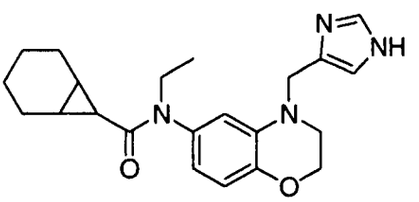
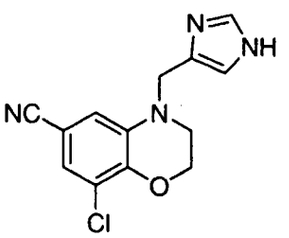
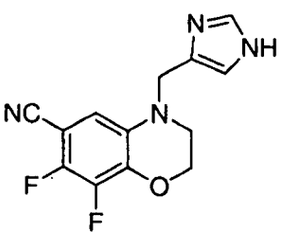
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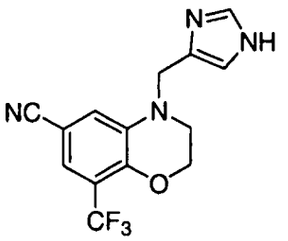
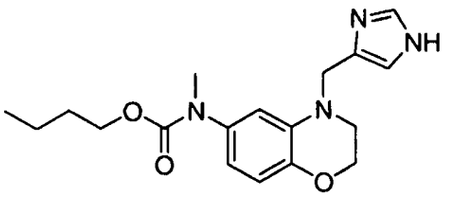
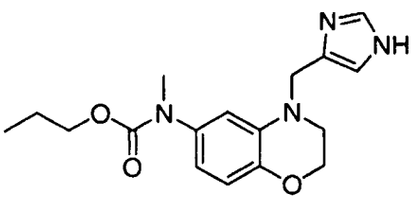
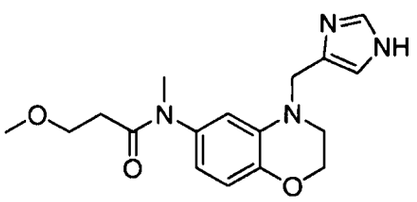
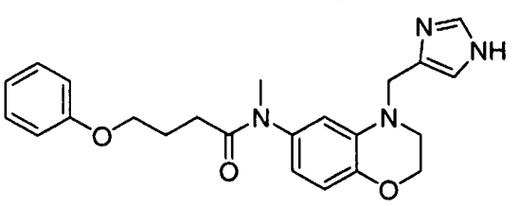
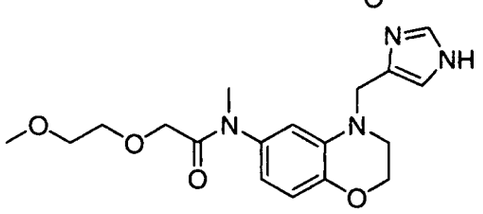
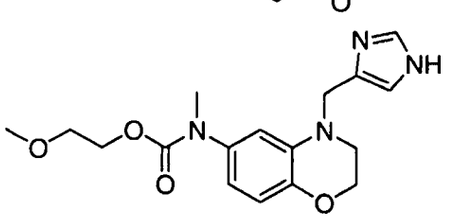
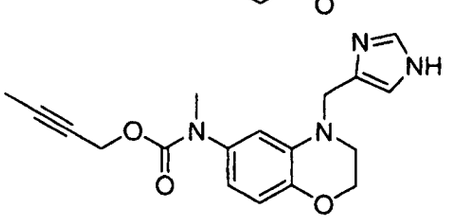
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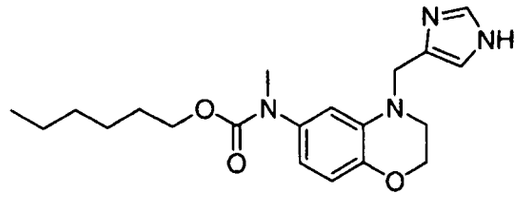
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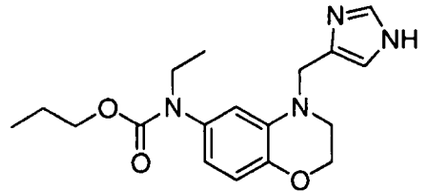
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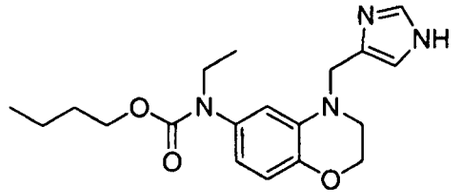
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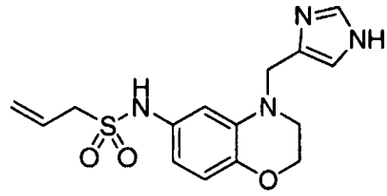
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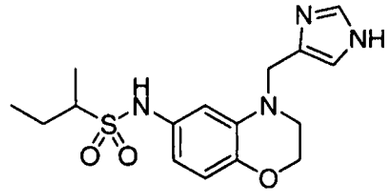
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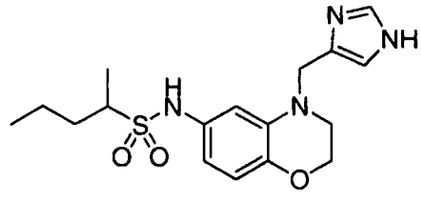
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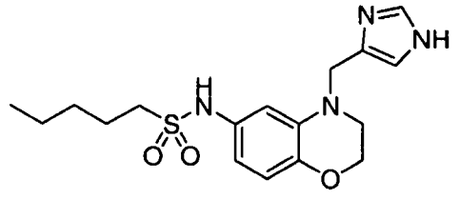
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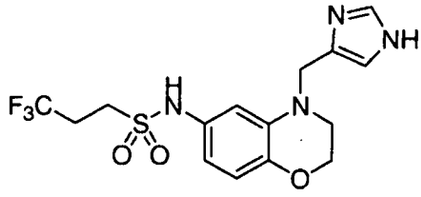
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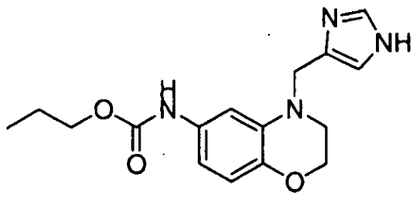
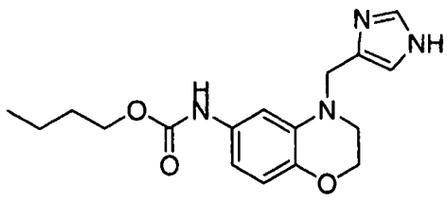
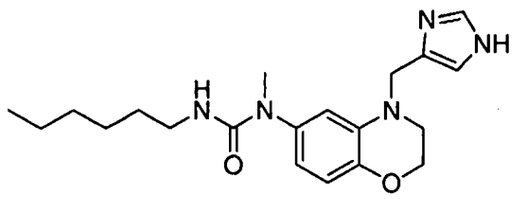
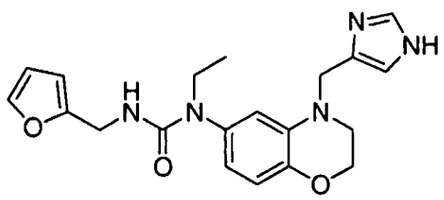
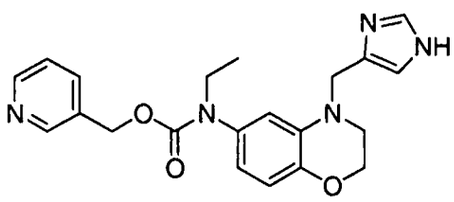
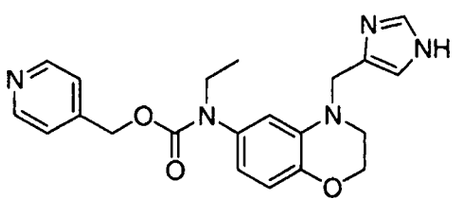
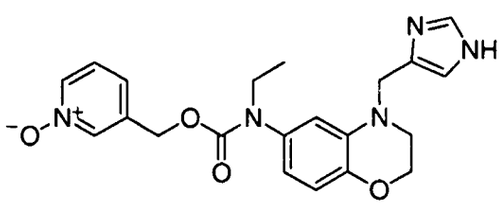
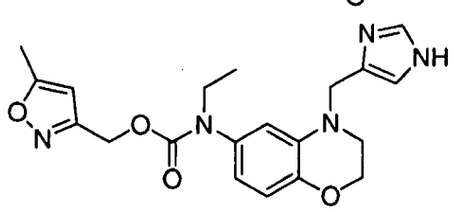
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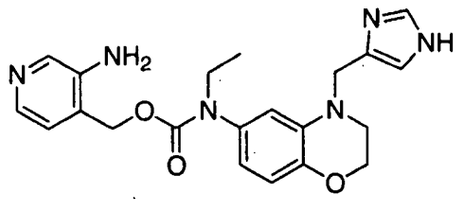
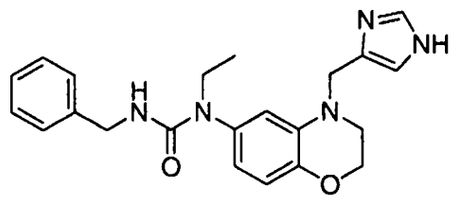
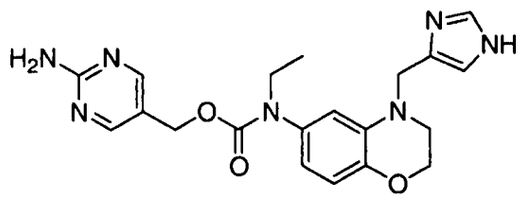
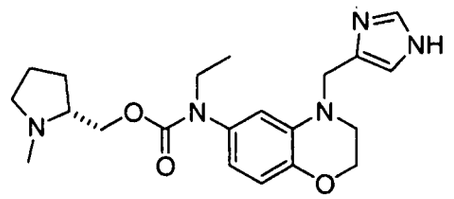
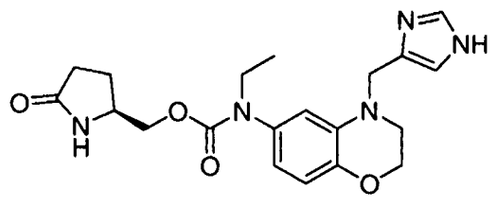
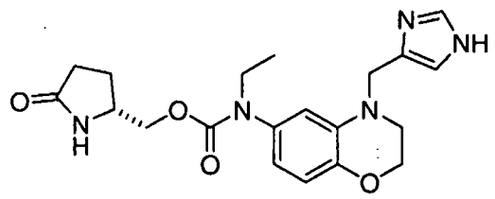
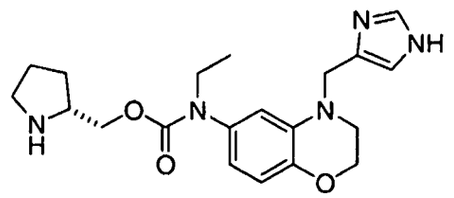
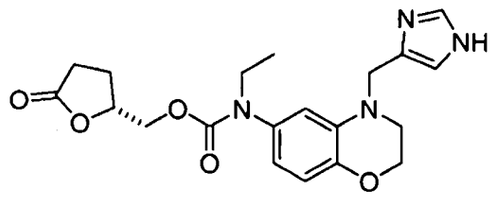
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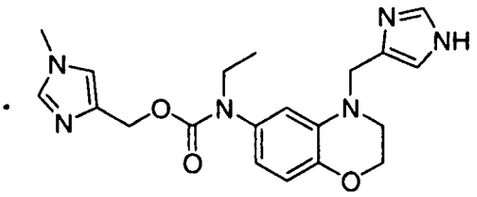
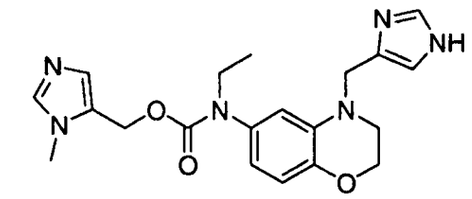
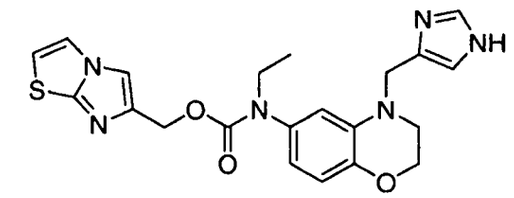
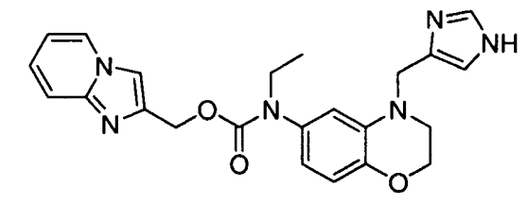
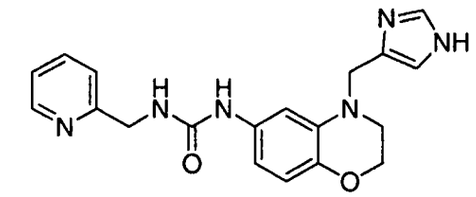
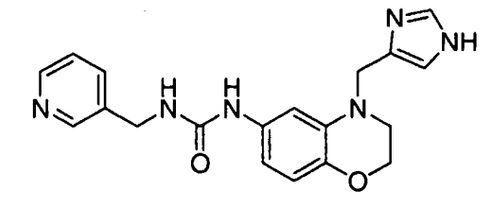
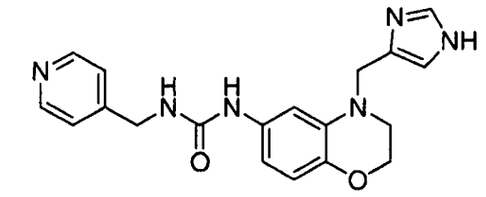
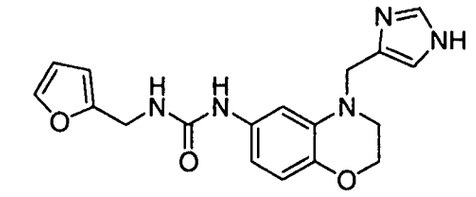
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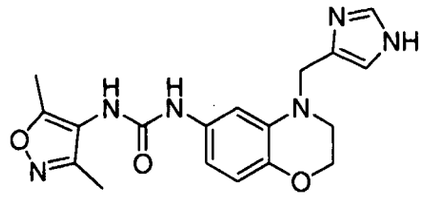
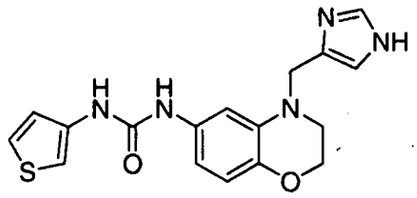
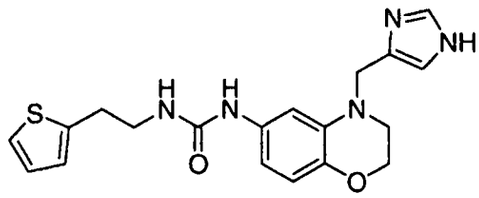
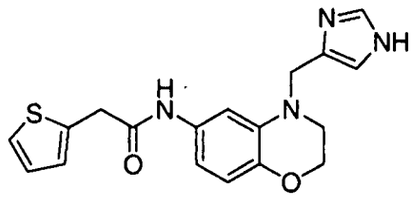
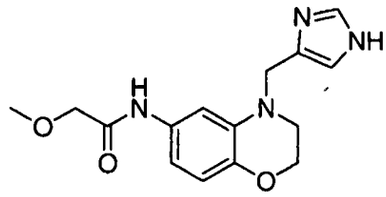
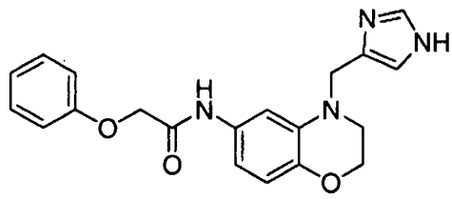
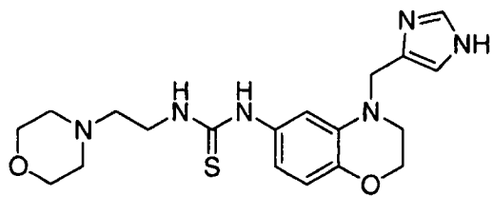
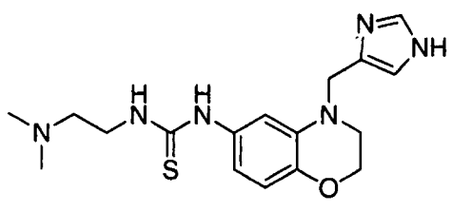
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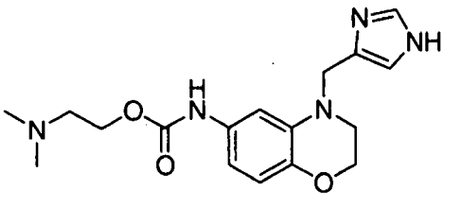
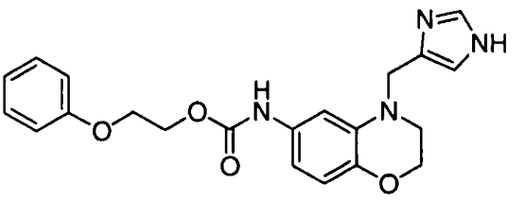
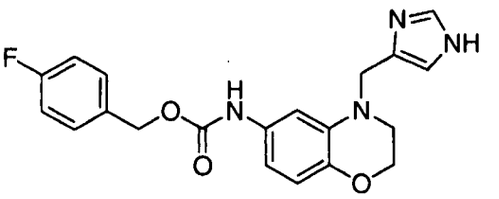
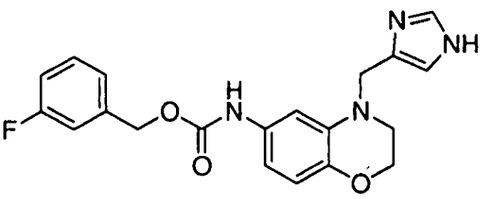
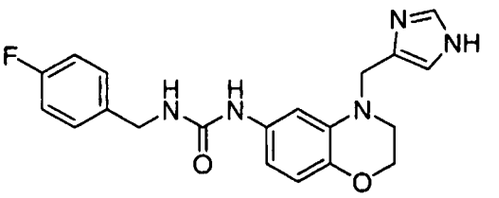
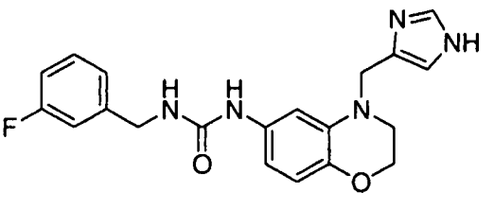
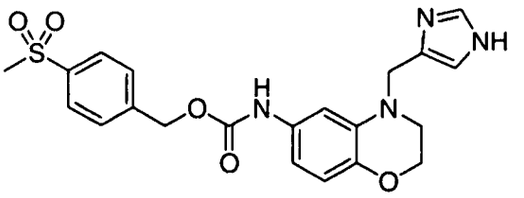
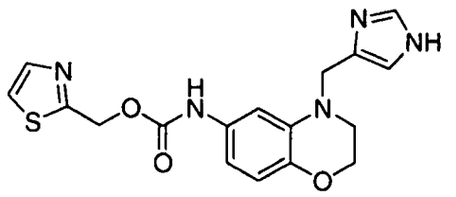
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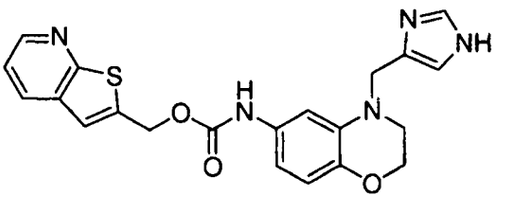
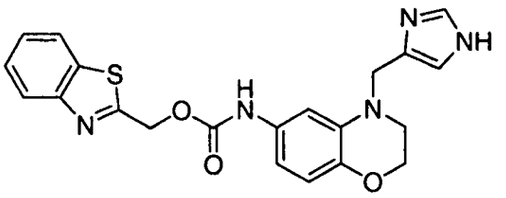
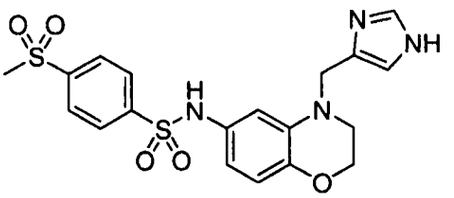
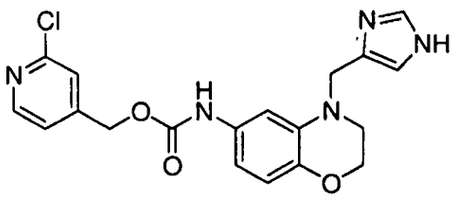
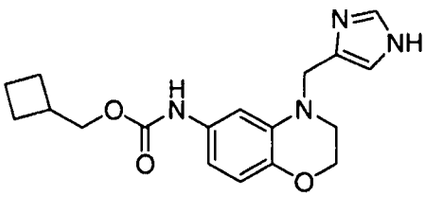
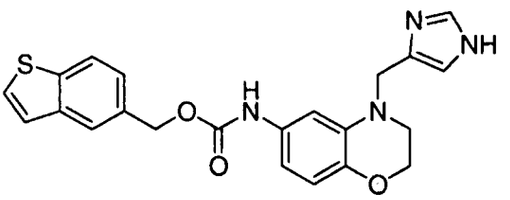
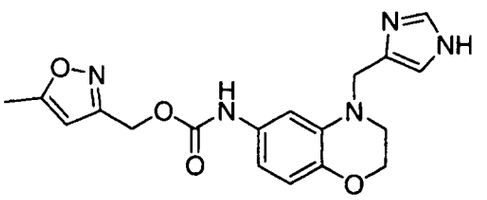
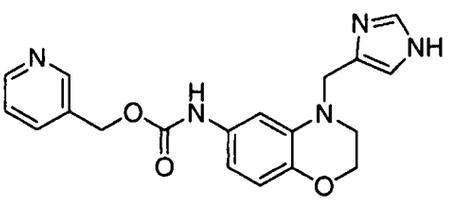
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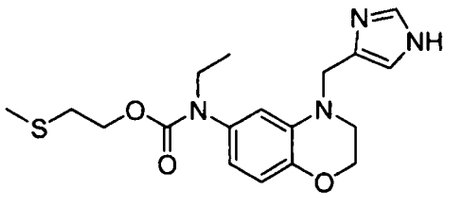
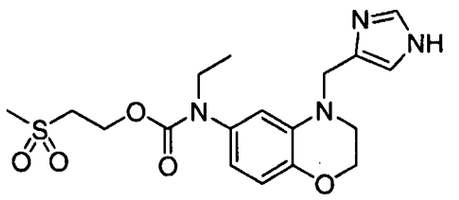
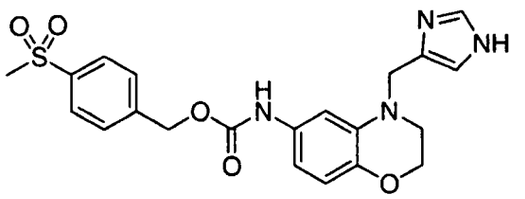
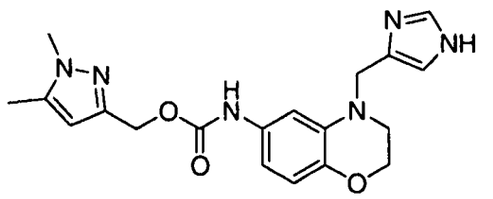
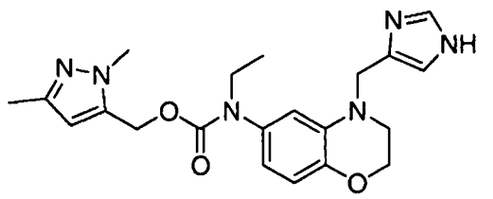
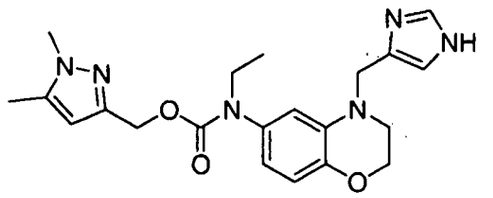
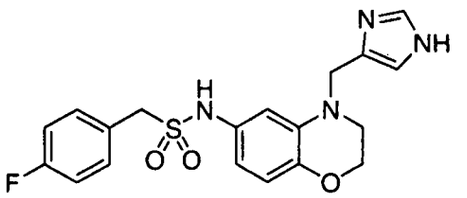
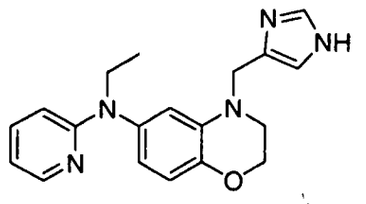
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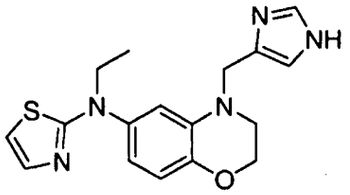
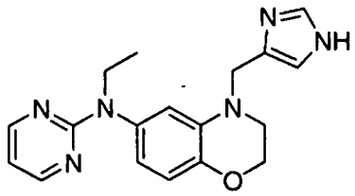
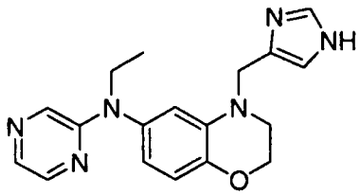
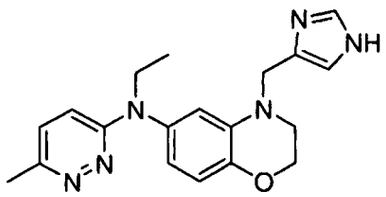
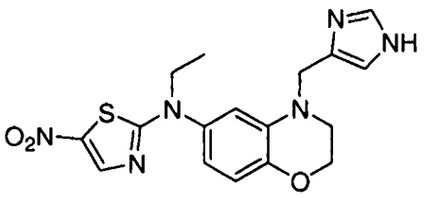
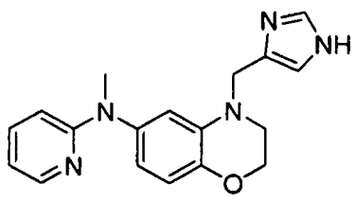
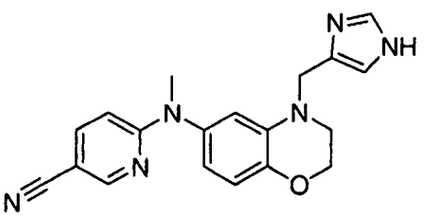
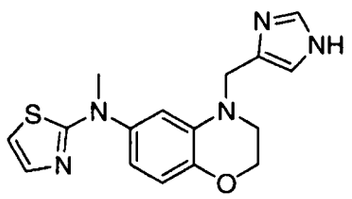
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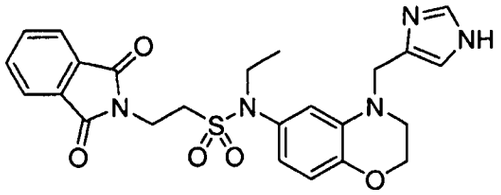
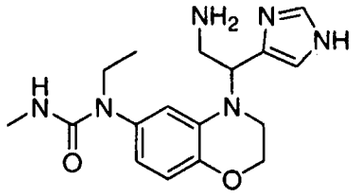
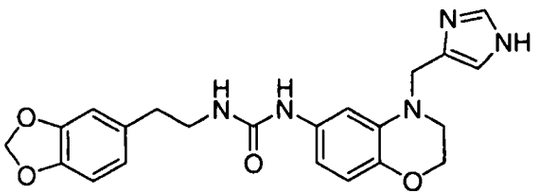
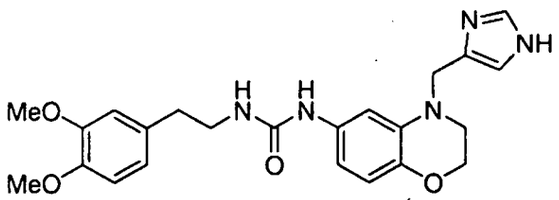
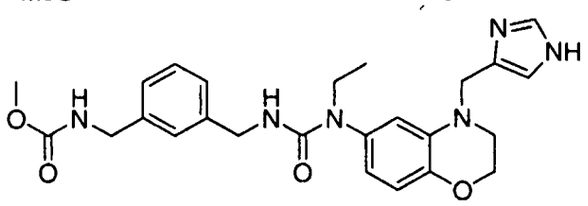
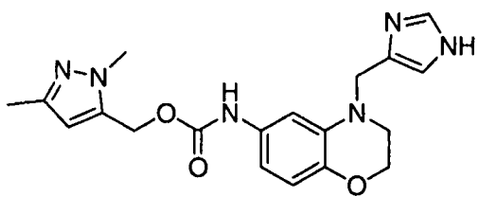
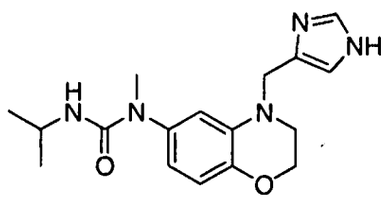
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151

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331		387
332		322
333		347
334		328

335		496
336		345
337		422
338		438
339		479
340		383
341		330

ASSAY:

Efficacy agonist activity values (E_{max}, GTPγS assay) for α2C were determined by following the general procedure detailed by Umland *et. al* ("Receptor reserve analysis of the human α_{2c}-adrenoceptor using [^{35}S]GTPγS and cAMP functional assays" European Journal of Pharmacology **2001**, 411, 211-221). For the purposes of the present invention, a compound is defined to be an active agonist of the α2C receptor subtype if the compound's efficacy at the α2C receptor is ≥ 30% E_{max} (GTPγS assay). A compound is a functionally selective agonist of the α2C receptor subtype over the α2A receptor subtype if the compound's efficacy at the α2C receptor is ≥ 30% E_{max} (GTPγS assay) and its efficacy at the α2A receptor is ≤ 30% E_{max} (GTPγS assay).

The following compounds were evaluated to be active or functionally selective agonists of the α2C receptor subtype based on the previously defined definition: **1, 3, 3D, 3E, 5, 6, 6E, 7, 8, 9E, 9G, 9I, 9K, 9L, 9M, 9N, 9P, 9Q, 9R, 9S, 12, 13, 14, 14B, 15, 19, 19D, 20, 21, 22, 24, 24D, 25B, 26, 26A, 26B, 27E, 28, 28D, 29, 30, 37, 38, 46, 51, 53, 54, 55, 57, 58, 63, 64, 64A, 65, 114, 117, 124, 125, 129, 130, 132, 134, 135, 137, 139, 142, 144, 145, 148, 151, 152, 158, 159, 160, 162, 163, 164, 165, 167, 168, 169, 171, 178, 181, 218, 223, 231, 232, 235, 236, 238, 239, 240, 242, 243, 244, 245, 246, 247, 248, 249, 250, 251, 253, 256, 257, 259, 260, 261, 262, 263, 264, 265, 266, 271, 272, 273, 274, 275, 276, 278, 279, 280, 281, 287, 289, 290, 291, 297, 304, 305, 306, 307, 308, 309, 310, 311, 312, 314, 315, 316, 317, 318, 319, 321, 323, 324, 326, 327, 329, 331, 332, 335,** and **340.**

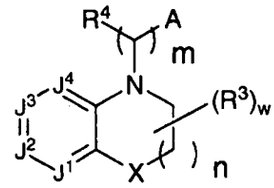
While the present invention has been described with in conjunction with the specific embodiments set forth above, many alternatives, modifications and other variations thereof will be apparent to those of ordinary skill in the art. All such alternatives, modifications and variations are intended to fall within the spirit and scope of the present invention.

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CLAIMS

What is claimed is:

1. A compound having the general structure shown in Formula I:



Formula I

or a pharmaceutically acceptable salt, ester, solvate or prodrug of said compound, wherein:

A is a 5-membered heterocyclic ring containing 1-3 heteroatoms, and is optionally substituted with at least one R^5 and/or 1 or 2 (=O) (carbonyl) groups;

X is -O-, -$S(O)_p$-, or -$N(R^6)$-;

J^1, J^2, J^3, and J^4 are independently -N-, -N(O)- or -$C(R^2)$-, provided that 0-3 of J^1, J^2, J^3 and J^4 are –N-;

R^2 is independently selected from the group consisting of H, -OH, halo, -CN, -NO_2, -$S(O)_pR^7$, -$NR^7R^{7'}$, -$[C(R^a)(R^b)]_qYR^{7'}$, -$[C(R^a)(R^b)]_qN(R^7)YR^{7'}$, $C(R^a)(R^b)]_qOYR^{7'}$, -$[C(R^a)(R^b)]_qON{=}CR^7R^{7'}$, -$P(=O)(OR^7)(OR^{7'})$, -$P(=O)NR^7R^{7'}$, and -$P(=O)R^8{}_2$, and alkyl, alkoxy, alkenyl, alkenyloxy, alkynyl, cycloalkyl, cycloalkoxy, aryl, aryloxy, arylalkyl, heteroaryl, heteroarylalkyl, heterocyclyl, and heterocyclylalkyl groups optionally substituted with at least one R^5;

Y is selected from the group consisting of a bond, -C(=O)-, -$C(=O)NR^7$-, -$C(=O)O$-, -$C(=NR^7)$-, -$C(=O)$-$[C(R^a)(R^b)]_{n'}$-O-C(=O)-, -$C(=O)N(R^c)$-O-, -$C(=NOR^7)$-, -$C(=NR^7)NR^7$-, -$C(=NR^7)N(R^c)O$-, -$S(O)_p$-, -SO_2NR^7-, and -$C(S)NR^7$-;

wherein R^a and R^b are independently selected from the group consisting of H, alkyl, alkoxy, and halo,

R^c is H or alkyl;

R^3 is independently selected from the group consisting of H, halo, and (=O), and alkyl, alkoxy, alkenyl, alkenyloxy, alkynyl, cycloalkyl, cycloalkoxy, aryl, aryloxy, arylalkyl, heteroaryl, heteroarylalkyl, heterocyclyl, and heterocyclylalkyl groups optionally substituted with at least one R^5, provided that when n is 3 or 4, no more than 2 of the R^3 groups may be (=O);

R^4 is independently selected from the group consisting of H, -CN, and halo, and alkyl, alkoxy, alkenyl, alkenyloxy, alkynyl, cycloalkyl, cycloalkoxy, aryl, aryloxy, arylalkyl, heteroaryl, heteroarylalkyl, heterocyclyl, and heterocyclylalkyl groups optionally substituted with at least one R^5;

R^5 is independently selected from the group consisting of H, halo, -OH, -CN, $-NO_2$, $-NR^7R^{7'}$, and $-S(O)_pR^7$, and alkyl, alkoxy, alkenyl, alkenyloxy, alkynyl, cycloalkyl, cycloalkoxy, aryl, aryloxy, arylalkyl, heteroaryl, heteroarylalkyl, heterocyclyl, and heterocyclylalkyl groups, each of which is optionally substituted with at least one of halo, -OH, -CN, $-NO_2$, $-NR^7R^{7'}$, and $-S(O)_pR^7$ substituents and/or 1 or 2 (=O) groups;

R^6 is independently selected from the group consisting of H and alkyl, alkoxy, alkenyl, alkenyloxy, alkynyl, cycloalkyl, cycloalkoxy, aryl, aryloxy, arylalkyl, heteroaryl, heteroarylalkyl, heterocyclyl, and heterocyclylalkyl groups, each of which is optionally substituted with at least one of halo, -OH, -CN, $-NO_2$, $-NR^7R^{7'}$, and $-S(O)_pR^7$ substituents and/or 1 or 2 (=O) groups, and $-C(=O)R^7$, $-C(=O)OR^7$, $-C(=O)NR^7R^{7'}$, $-SO_2R^7$ and $-SO_2NR^7R^{7'}$;

R^7 is independently selected from the group consisting of H and alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, cyclocyclenyl, cyclocyclenylalkyl, aryl, arylalkyl, heterocyclyl, heterocyclylalkyl, heterocyclenyl, heterocyclenylalkyl, heteroaryl, and heteroarylalkyl, groups, each of which is optionally substituted one or more times (preferably 1 to 5, more preferably 1 to 3) by R^{12};

$R^{7'}$ is independently selected from the group consisting of H and alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, cyclocyclenyl, cyclocyclenylalkyl, aryl, arylalkyl, heterocyclyl, heterocyclylalkyl, heterocyclenyl, heterocyclenylalkyl, heteroaryl, and heteroarylalkyl, groups, each of which is optionally substituted one or more times (preferably 1 to 5, more preferably 1 to 3) by R^{12}; or

R^7 and $R^{7'}$ together with the nitrogen atom to which they are attached form a 3- to 8-membered heterocyclyl, heterocyclenyl or heteroaryl ring having, in addition to the N atom, 1 or 2 additional hetero atoms selected from the group consisting of O, N, $-N(R^9)-$ and S, wherein said rings are optionally substituted by 1 to 5 independently selected R^5 moieties and/or 1 or 2 (=O) groups,

R^8 is independently selected from the group consisting of alkyl, alkenyl, alkynyl, cycloalkyl, aryl, arylalkyl, heteroaryl, and heteroarylalkyl groups, each of which is

optionally substituted with at least one of halo, -OH, -CN, -NO_2, -$N(R^{11})_2$, and –$S(O)_pR^{11}$ substituents and/or 1 or 2 (=O) groups;

R^9 is independently selected from the group consisting of H, -C(O)-R^{10}, -C(O)-OR^{10}, and –$S(O)_p$-OR^{10} and alkyl, alkenyl, alkynyl, cycloalkyl, aryl, arylalkyl, heteroaryl, and heteroarylalkyl groups, each of which is optionally substituted with at least one of halo, -OH, -CN, -NO_2, -$N(R^{11})_2$, and –$S(O)_pR^{11}$ substituents and/or 1 or 2 (=O) groups; and

R^{10} is selected from the group consisting of alkyl, alkenyl, alkynyl, cycloalkyl, aryl, arylalkyl, heteroaryl, and heteroarylalkyl groups, each of which is optionally substituted with at least one of halo, -OH, -CN, -NO_2, -$N(R^{11})_2$, and –$S(O)_pR^{11}$ substituents and/or 1 or 2 (=O) groups;

R^{11} is a moiety independently selected from the group consisting of H and alkyl, alkoxy, alkenyl, alkenyloxy, alkynyl, cycloalkyl, cycloalkoxy, aryl, aryloxy, arylalkyl, heteroaryl, heteroarylalkyl, heterocyclyl, and heterocyclylalkyl, each of which is optionally substituted by at least one substituent independently selected from the group consisting of halo, -OH, -CN, -NO_2, -$N(R^{11'})_2$, and –$S(O)_pR^{11'}$ and/or 1 or 2 (=O) groups;

$R^{11'}$ is independently selected from the group consisting of H, alkyl, alkoxy, alkenyl, alkenyloxy, alkynyl, cycloalkyl, cycloalkoxy, aryl, aryloxy, arylalkyl, heteroaryl, heteroarylalkyl, heterocyclyl, and heterocyclylalkyl;

R^{12} is independently selected from selected from the group consisting of H, halo, -OH, -CN, -NO_2, -$N(R^{11})_2$, and –$S(O)_pR^{11}$ and/or 1 or 2 (=O) groups, and alkyl, alkoxy, alkenyl, alkenyloxy, alkynyl, cycloalkyl, cycloalkenyl, cycloalkoxy, aryl, aryloxy, arylalkyl, heteroaryl, heteroaryloxy, heteroarylalkyl, heterocyclyl, heterocyclenyl, heterocyclenyloxy, heterocyclylalkyl, heterocyclenylalkyl, arylalkoxy, heteroarylalkoxy, heterocyclylalkoxy, and heterocyclenylalkoxy groups, each of which in turn is optionally substituted by at least once by a substituent selected from the group consisting of H, alkyl, haloalkyl, halo, -OH, optionally substituted alkoxy, optionally substituted aryloxy, optionally substituted cycloalkoxy, optionally substituted heteroaryloxy, optionally substituted heterocyclenyloxy, -CN, -NO_2, -$N(R^{11})_2$, and –$S(O)_pR^{11}$ and/or 1 or 2 (=O) groups, wherein said optionally substituted alkoxy, aryloxy, optionally substituted cycloalkoxy, optionally substituted heteroaryloxy, and heterocyclenyloxy when substituted are substituted one or more times by R^{11};

m is 1-5;

n is independently1-3;

n' is independently 1-3

p is independently 0-2;

q is independently 0-6; and

w is 0-4

with the following provisos:

(a) if J^1-J^4 are each -C(H)-, n is 1, m is 1, R^4 is H, A is 3H-imidazol-4-yl, and X is -N(R^6)-, then R^6 is not -C(=O)-naphthyl;

(b) if J^1-J^4 are each -C(H)-, n is 1, m is 1, R^4 is H, A is 1H-imidazol-4-yl, and X is -N(R^6)-, then R^6 is not -S(O_2)-naphthyl; and

(c) if J^1, J^2, and J^4 are each -C(H)-, J^3 is -C(Br)-, n is 2, m is 1, R^3 is 3-benzyl, R^4 is H, A is 1H-imidazol-4-yl, and X is -N(R^6)-, then R^6 is not -C(O_2)benzyl.

2. The compound of claim 1, wherein:

J^1-J^4 are each -C(R^2)-;

A is a 5-membered heteroaryl or heterocyclenyl ring selected from the group consisting of imidazole, imadazoline, and oxazoline, which is optionally substituted with at least one R^5;

X is -O-, -S(O)$_p$-, or -N(R^6)-;

R^2 is independently selected from the group consisting of H, -OH, halo, -CN, -NO_2, -(CH_2)$_q$YR^7, -(CH_2)$_q$N(R^7)Y$R^{7'}$, -(CH_2)$_q$O$R^{7'}$ and -(CH_2)$_q$ON=C$R^7R^{7'}$, and alkyl, alkoxy, alkenyl, alkynyl, cycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, and heterocyclyl groups optionally substituted with at least one R^5;

Y is selected from the group consisting of a bond, –C(=O)-, -C(=O)NR^7-, -C(=O)O-, -C(=NR^7)-, -C(=O)-[C(R^a)(R^b)]$_{n'}$-O-C(=O)-, -C(=O)N(R^c)-O-, -C(=NOR^7)-, -C(=NR^7)NR^7-, -C(=NR^7)NR^7O-, -S(O)$_p$-, -SO_2NR^7-, -C(S)NR^7-;

R^3 is independently selected from the group consisting of H and alkyl, alkoxy, alkenyl, alkenyloxy, alkynyl, cycloalkyl, cycloalkoxy, aryl, aryloxy, arylalkyl, heteroaryl, heteroarylalkyl, heterocyclyl, and heterocyclylalkyl groups optionally substituted with at least one R^5;

R^4 is independently selected from the group consisting of H and alkyl, alkoxy, alkenyl, alkenyloxy, alkynyl, cycloalkyl, cycloalkoxy, aryl, aryloxy, arylalkyl, heteroaryl,

heteroarylalkyl, heterocyclyl, and heterocyclylalkyl groups optionally substituted with at least one R^5;

R^5 is independently selected from the group consisting of H, halo, -OH, -CN, $-NO_2$, $-NR^7R^{7'}$, $-SR^7$, and alkyl, alkoxy, alkenyl, alkenyloxy, alkynyl, cycloalkyl, cycloalkoxy, aryl, aryloxy, arylalkyl, heteroaryl, heteroarylalkyl, heterocyclyl, and heterocyclylalkyl groups, each of which is optionally substituted with at least one of halo, -OH, -CN, $-NO_2$, $-NR^7R^{7'}$, and $-S(O)_pR^7$ substituents;

R^6 is independently selected from the group consisting of H and alkyl, alkoxy, alkenyl, alkenyloxy, alkynyl, cycloalkyl, cycloalkoxy, aryl, aryloxy, arylalkyl, heteroaryl, heteroarylalkyl, heterocyclyl, and heterocyclylalkyl groups, each of which is optionally substituted with at least one of halo, -OH, -CN, $-NO_2$, $-NR^7R^{7'}$, and $-SR^7$ substituents, and $-C(=O)R^7$, $-C(=O)OR^7$, $-C(=O)NR^7R^{7'}$, $-SO_2R^7$ and $-SO_2NR^7R^{7'}$;

R^7 is independently selected from the group consisting of H and alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, cyclocyclenyl, cyclocyclenylalkyl, aryl, arylalkyl, heterocyclyl, heterocyclylalkyl, heterocyclenyl, heterocyclenylalkyl, heteroaryl, and heteroarylalkyl, groups, each of which is optionally substituted one or more times by R^{12};

$R^{7'}$ is independently selected from the group consisting of H and alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, cyclocyclenyl, cyclocyclenylalkyl, aryl, arylalkyl, heterocyclyl, heterocyclylalkyl, heterocyclenyl, heterocyclenylalkyl, heteroaryl, and heteroarylalkyl, groups, each of which is optionally substituted one or more times by R^{12}; or

R^7 and $R^{7'}$ together with the nitrogen atom together form a 3- to 8-membered heterocyclyl, heterocyclenyl or heteroaryl ring having, in addition to the N atom, 1 or 2 additional hetero atoms selected from the group consisting of O, N, $-N(R^9)-$ and S, wherein said rings are optionally substituted by 1 to 5 independently selected R^5 moieties,

R^8 is independently selected from the group consisting of alkyl, alkenyl, alkynyl, cycloalkyl, aryl, arylalkyl, heteroaryl, and heteroarylalkyl groups, each of which is optionally substituted with at least one of halo, -OH, -CN, $-NO_2$, $-N(R^{11})_2$, and $-SR^{11}$ substituents;

R^9 is independently selected from the group consisting of H, $-C(O)-R^{10}$, $-C(O)-OR^{10}$, and $-S(O)_p-OR^{10}$ and alkyl, alkenyl, alkynyl, cycloalkyl, aryl, arylalkyl,

heteroaryl, and heteroarylalkyl groups, each of which is optionally substituted with at least one of halo, -OH, -CN, $-NO_2$, $-N(R^{11})_2$, and $-SR^{11}$ substituents; and

R^{10} is selected from the group consisting of alkyl, alkenyl, alkynyl, cycloalkyl, aryl, arylalkyl, heteroaryl, and heteroarylalkyl groups, each of which is optionally substituted with at least one of halo, -OH, -CN, $-NO_2$, $-N(R^{11})_2$, and $-SR^{11}$ substituents;

R^{11} is a moiety independently selected from the group consisting of H and alkyl, alkoxy, alkenyl, alkenyloxy, alkynyl, cycloalkyl, cycloalkoxy, aryl, aryloxy, arylalkyl, heteroaryl, heteroarylalkyl, heterocyclyl, and heterocyclylalkyl, each of which is optionally substituted by at least one substituent independently selected from the group consisting of halo, -OH, -CN, $-NO_2$, $-N(R^{11'})_2$, and $-S(O)_pR^{11'}$;

$R^{11'}$ is independently selected from the group consisting of H, alkyl, alkoxy, alkenyl, alkenyloxy, alkynyl, cycloalkyl, cycloalkoxy, aryl, aryloxy, arylalkyl, heteroaryl, heteroarylalkyl, heterocyclyl, and heterocyclylalkyl;

R^{12} is independently selected from selected from the group consisting of H, halo, -OH, -CN, $-NO_2$, $-N(R^{11})_2$, and $-S(O)_pR^{11}$, and alkyl, alkoxy, alkenyl, alkenyloxy, alkynyl, cycloalkyl, cycloalkenyl, cycloalkoxy, aryl, aryloxy, arylalkyl, heteroaryl, heteroaryloxy, heteroarylalkyl, heterocyclyl, heterocyclenyl, heterocyclenyloxy, heterocyclylalkyl, heterocyclenylalkyl, arylalkyloxy, heteroarylalkyloxy, heterocyclylalkyloxy, and heterocyclenylalkoxy groups, each of which in turn is optionally substituted by at least once by a substituent selected from the group consisting of H, alkyl, haloalkyl, halo, -OH, optionally substituted alkoxy, optionally substituted aryloxy, optionally substituted cycloalkoxy, optionally substituted heteroaryloxy, optionally substituted heterocyclenyloxy, -CN, $-NO_2$, $-N(R^{11})_2$, and $-S(O)_pR^{11}$, wherein said optionally substituted alkoxy, aryloxy, optionally substituted cycloalkoxy, optionally substituted heteroaryloxy, and heterocyclenyloxy when substituted are substituted one or more times by R^{11};

m is 1 or 2;

n is independently1 or 2;

p is independently 0-2;

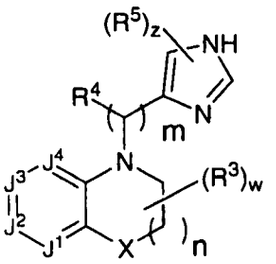
q is independently 0-3; and

w is 0-4.

3. The compound of claim 2 wherein A is optionally substituted imidazole.

4. The compound of claim 2 wherein X is –O- or $-S(O)_p-$.

5. A compound represented by the structural formula:



Formula **III**

or a pharmaceutically acceptable salt, ester, solvate, or prodrug of said compound, wherein:

X is -O-, $-S(O)_p-$, or $-N(R^6)-$;

J^1, J^2, J^3, and J^4 are independently –N- or $-C(R^2)-$, provided that 0-3 of J^1, J^2, J^3 and J^4 are -N-;

R^2 is independently selected from the group consisting of H, -OH, halo, -CN, $-NO_2$, $-(CH_2)_qYR^7$, $-(CH_2)_qN(R^7)YR^{7'}$, $-(CH_2)_qOYR^7$, $-(CH_2)_qON=CR^7R^{7'}$, $-P(=O)(OR^7)(OR^{7'})$, $-P(=O)(NR^7R^{7'})_2$, $-P(=O)R^8{}_2$, and alkyl, alkoxy, alkenyl, alkynyl, cycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, and heterocyclyl groups optionally substituted with at least one R^5;

Y is selected from the group consisting of a bond, -C(=O)-, $-C(=O)NR^7-$, -C(=O)O-, $-C(=O)-[C(R^a)(R^b)]_n-O-C(=O)-$, $-C(=O)N(R^c)-O-$, $-S(O)_p-$, $-SO_2NR^7-$, and $-C(S)NR^7-$;

wherein R^a and R^b are independently selected from the group consisting of H, alkyl, alkoxy, and halo, and

R^c is H or alkyl;

R^3 is independently selected from the group consisting of H and alkyl, alkoxy, alkenyl, alkenyloxy, alkynyl, cycloalkyl, cycloalkoxy, aryl, aryloxy, arylalkyl, heteroaryl, heteroarylalkyl, heterocyclyl, and heterocyclylalkyl groups optionally substituted with at least one R^5;

R^4 is independently selected from the group consisting of H –CN and halo, and alkyl, alkoxy, alkenyl, alkenyloxy, alkynyl, cycloalkyl, cycloalkoxy, aryl, aryloxy,

arylalkyl, heteroaryl, heteroarylalkyl, heterocyclyl, and heterocyclylalkyl groups optionally substituted with at least one R^5;

R^5 is independently selected from the group consisting of H, halo, -OH, -CN, $-NO_2$, $-NR^7R^{7'}$, and $-S(O)_pR^7$, and alkyl, alkoxy, alkenyl, alkenyloxy, alkynyl, cycloalkyl, cycloalkoxy, aryl, aryloxy, arylalkyl, heteroaryl, heteroarylalkyl, heterocyclyl, and heterocyclylalkyl groups, each of which is optionally substituted with at least one of halo, -OH, -CN, $-NO_2$, $-NR^7R^{7'}$, and $-S(O)_pR^7$ substituents and/or 1 or 2 (=O) groups;

R^6 is independently selected from the group consisting of H and alkyl, alkoxy, alkenyl, alkenyloxy, alkynyl, cycloalkyl, cycloalkoxy, aryl, aryloxy, arylalkyl, heteroaryl, heteroarylalkyl, heterocyclyl, and heterocyclylalkyl groups, each of which is optionally substituted with at least one of halo, -OH, -CN, $-NO_2$, $-NR^7R^{7'}$, and $-S(O)_pR^7$ substituents and/or 1 or 2 (=O) groups, and $-C(=O)R^7$, $-C(=O)OR^7$, $-C(=O)NR^7R^{7'}$, $-SO_2R^7$ and $-SO_2NR^7R^{7'}$;

R^7 is independently selected from the group consisting of H and alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, cyclocyclenyl, cyclocyclenylalkyl, aryl, arylalkyl, heterocyclyl, heterocyclylalkyl, heterocyclenyl, heterocyclenylalkyl, heteroaryl, and heteroarylalkyl, groups, each of which is optionally substituted one or more times by R^{12};

$R^{7'}$ is independently selected from the group consisting of H and alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, cyclocyclenyl, cyclocyclenylalkyl, aryl, arylalkyl, heterocyclyl, heterocyclylalkyl, heterocyclenyl, heterocyclenylalkyl, heteroaryl, and heteroarylalkyl, groups, each of which is optionally substituted one or more times by R^{12}; or

R^7 and $R^{7'}$ together with the nitrogen atom to which they are attached form a 3- to 8-membered heterocyclyl, heterocyclenyl or heteroaryl ring having, in addition to the N atom, 1 or 2 additional hetero atoms selected from the group consisting of O, N, $-N(R^9)-$ and S, wherein said rings are optionally substituted by 1 to 5 independently selected R^5 moieties,

R^8 is independently selected from the group consisting of alkyl, alkenyl, alkynyl, cycloalkyl, aryl, arylalkyl, heteroaryl, and heteroarylalkyl groups, each of which is optionally substituted with at least one of halo, -OH, -CN, $-NO_2$, $-N(R^{11})_2$, and $-S(O)_pR^{11}$ substituents;

R^9 is independently selected from the group consisting of H, -C(O)-R^{10}, -C(O)-OR^{10}, and $-S(O)_p$-OR^{10} and alkyl, alkenyl, alkynyl, cycloalkyl, aryl, arylalkyl, heteroaryl, and heteroarylalkyl groups, each of which is optionally substituted with at least one of halo, -OH, -CN, $-NO_2$, $-N(R^{11})_2$, and $-S(O)_pR^{11}$ substituents; and

R^{10} is selected from the group consisting of alkyl, alkenyl, alkynyl, cycloalkyl, aryl, arylalkyl, heteroaryl, and heteroarylalkyl groups, each of which is optionally substituted with at least one of halo, -OH, -CN, $-NO_2$, $-N(R^{11})_2$, and $-S(O)_pR^{11}$ substituents;

R^{11} is a moiety independently selected from the group consisting of H and alkyl, alkoxy, alkenyl, alkenyloxy, alkynyl, cycloalkyl, cycloalkoxy, aryl, aryloxy, arylalkyl, heteroaryl, heteroarylalkyl, heterocyclyl, and heterocyclylalkyl, each of which is optionally substituted by at least one substituent independently selected from the group consisting of halo, -OH, -CN, $-NO_2$, $-N(R^{11'})_2$, and $-S(O)_pR^{11'}$;

$R^{11'}$ is independently selected from the group consisting of H, alkyl, alkoxy, alkenyl, alkenyloxy, alkynyl, cycloalkyl, cycloalkoxy, aryl, aryloxy, arylalkyl, heteroaryl, heteroarylalkyl, heterocyclyl, and heterocyclylalkyl;

R^{12} is independently selected from selected from the group consisting of H, halo, -OH, -CN, $-NO_2$, $-N(R^{11})_2$, and $-S(O)_pR^{11}$, and alkyl, alkoxy, alkenyl, alkenyloxy, alkynyl, cycloalkyl, cycloalkenyl, cycloalkoxy, aryl, aryloxy, arylalkyl, heteroaryl, heteroaryloxy, heteroarylalkyl, heterocyclyl, heterocyclenyl, heterocyclenyloxy, heterocyclylalkyl, heterocyclenylalkyl, arylalkyloxy, heteroarylalkyloxy, heterocyclylalkyloxy, and heterocyclenylalkoxy groups, each of which in turn is optionally substituted by at least once by a substituent selected from the group consisting of H, alkyl, haloalkyl, halo, -OH, optionally substituted alkoxy, optionally substituted aryloxy, optionally substituted cycloalkoxy, optionally substituted heteroaryloxy, optionally substituted heterocyclenyloxy, -CN, $-NO_2$, $-N(R^{11})_2$, and $-S(O)_pR^{11}$, wherein said optionally substituted alkoxy, aryloxy, optionally substituted cycloalkoxy, optionally substituted heteroaryloxy, and heterocyclenyloxy when substituted are substituted one or more times by R^{11};

m is 1-5;

n is independently 1-3;

p is independently 0-2;

q is independently 0-6;

z is 0-3; and

w is 0-4,

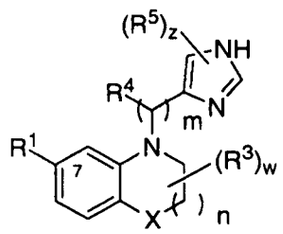
with the following provisos:

(a) if J^1-J^4 are each -C(H)-, n is 1, m is 1, R^4 is H, A is 3H-imidazol-4-yl, and X is -N(R^6)-, then R^6 is not -C(=O)-naphthyl;

(b) if J^1-J^4 are each -C(H)-, n is 1, m is 1, R^4 is H, A is 1H-imidazol-4-yl, and X is -N(R^6)-, then R^6 is not -S(O_2)-naphthyl; and

(c) if J^1, J^2, and J^4 are each -C(H)-, J^3 is -C(Br)-, n is 2, m is 1, R^3 is 3-benzyl, R^4 is H, and X is -N(R^6)-, then R^6 is not -C(O_2)benzyl.

6. A compound represented by the structural formula:



Formula **IV**

or a pharmaceutically acceptable salt, ester, solvate or prodrug of said compound, wherein:

R^1 is selected from the group consisting of H, -OH, halo, -CN, -NO_2, -SR^7-$(CH_2)_qYR^7$, -$(CH_2)_qN(R^7)YR^{7'}$, -$(CH_2)_qOYR^7$, -$(CH_2)_qON{=}CR^7R^{7'}$, -P(=O)(OR^7)($OR^{7'}$), -P(=O)($NR^7R^{7'}$)$_2$, -P(=O)$R^8{}_2$, and alkyl, alkoxy, alkenyl, alkenyloxy, alkynyl, cycloalkyl, cycloalkoxy, aryl, aryloxy, arylalkyl, heteroaryl, heteroarylalkyl, heterocyclyl, and heterocyclylalkyl groups optionally substituted with at least one R^5;

X is -O-, or -S($O)_p$-;

Y is selected from the group consisting of a bond, -C(=O)-, -C(=O)NR^7-, -C(=O)O-, -C(=O)-[$C(R^a)(R^b)]_n$-O-C(=O)-, -C(=O)N(R^c)-O-,

wherein R^a and R^b are independently selected from the group consisting of H, alkyl, alkoxy, and halo, and

R^c is H or alkyl;

R^3 is independently selected from the group consisting of H and alkyl, alkoxy, alkenyl, alkenyloxy, alkynyl, cycloalkyl, cycloalkoxy, aryl, aryloxy, arylalkyl, heteroaryl, heteroarylalkyl, heterocyclyl, and heterocyclylalkyl groups optionally substituted with at least one R^5;

R^4 is independently selected from the group consisting of H –CN and halo, and alkyl, alkoxy, alkenyl, alkenyloxy, alkynyl, cycloalkyl, cycloalkoxy, aryl, aryloxy, arylalkyl, heteroaryl, heteroarylalkyl, heterocyclyl, and heterocyclylalkyl groups optionally substituted with at least one R^5;

R^5 is independently selected from the group consisting of H, halo, -OH, -CN, $-NO_2$, $-NR^7R^{7'}$, and $-S(O)_pR^7$, and alkyl, alkoxy, alkenyl, alkenyloxy, alkynyl, cycloalkyl, cycloalkoxy, aryl, aryloxy, arylalkyl, heteroaryl, heteroarylalkyl, heterocyclyl, and heterocyclylalkyl groups, each of which is optionally substituted with at least one of halo, -OH, -CN, $-NO_2$, $-NR^7R^{7'}$, and $-S(O)_pR^7$ substituents and/or 1 (=O) group;

R^6 is independently selected from the group consisting of H and alkyl, alkoxy, alkenyl, alkenyloxy, alkynyl, cycloalkyl, cycloalkoxy, aryl, aryloxy, arylalkyl, heteroaryl, heteroarylalkyl, heterocyclyl, and heterocyclylalkyl groups, each of which is optionally substituted with at least one of halo, -OH, -CN, $-NO_2$, $-NR^7R^{7'}$, and $-S(O)_pR^7$ substituents and/or 1 or 2 (=O) groups, and $-C(=O)R^7$, $-C(=O)OR^7$, $-C(=O)NR^7R^{7'}$, $-SO_2R^7$ and $-SO_2NR^7R^{7'}$;

R^7 is independently selected from the group consisting of H and alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, cyclocyclenyl, cyclocyclenylalkyl, aryl, arylalkyl, heterocyclyl, heterocyclylalkyl, heterocyclenyl, heterocyclenylalkyl, heteroaryl, and heteroarylalkyl, groups, each of which is optionally substituted one or more times by R^{12};

$R^{7'}$ is independently selected from the group consisting of H and alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, cyclocyclenyl, cyclocyclenylalkyl, aryl, arylalkyl, heterocyclyl, heterocyclylalkyl, heterocyclenyl, heterocyclenylalkyl, heteroaryl, and heteroarylalkyl, groups, each of which is optionally substituted one or more times by R^{12}; or

R^7 and $R^{7'}$ together with the nitrogen atom to which they are attached form a 3- to 8-membered heterocyclyl, heterocyclenyl or heteroaryl ring having, in addition to the N atom, 1 or 2 additional hetero atoms selected from the group consisting of O, N,

-N(R^9)- and S, wherein said rings are optionally substituted by 1 to 5 independently selected R^5 moieties,

R^8 is independently selected from the group consisting of alkyl, alkenyl, alkynyl, cycloalkyl, aryl, arylalkyl, heteroaryl, and heteroarylalkyl groups, each of which is optionally substituted with at least one of halo, -OH, -CN, -NO_2, -N(R^{11})$_2$, and –S(O)$_p$$R^{11}$ substituents;

R^9 is independently selected from the group consisting of H, -C(O)-R^{10}, -C(O)-OR^{10}, and –S(O)$_p$-OR^{10} and alkyl, alkenyl, alkynyl, cycloalkyl, aryl, arylalkyl, heteroaryl, and heteroarylalkyl groups, each of which is optionally substituted with at least one of halo, -OH, -CN, -NO_2, -N(R^{11})$_2$, and –S(O)$_p$$R^{11}$ substituents; and

R^{10} is selected from the group consisting of alkyl, alkenyl, alkynyl, cycloalkyl, aryl, arylalkyl, heteroaryl, and heteroarylalkyl groups, each of which is optionally substituted with at least one of halo, -OH, -CN, -NO_2, -N(R^{11})$_2$, and –S(O)$_p$$R^{11}$ substituents;

R^{11} is a moiety independently selected from the group consisting of H and alkyl, alkoxy, alkenyl, alkenyloxy, alkynyl, cycloalkyl, cycloalkoxy, aryl, aryloxy, arylalkyl, heteroaryl, heteroarylalkyl, heterocyclyl, and heterocyclylalkyl, each of which is optionally substituted by at least one substituent independently selected from the group consisting of halo, -OH, -CN, -NO_2, -N($R^{11'}$)$_2$, and –S(O)$_p$$R^{11'}$;

$R^{11'}$ is independently selected from the group consisting of H, alkyl, alkoxy, alkenyl, alkenyloxy, alkynyl, cycloalkyl, cycloalkoxy, aryl, aryloxy, arylalkyl, heteroaryl, heteroarylalkyl, heterocyclyl, and heterocyclylalkyl;

R^{12} is independently selected from selected from the group consisting of H, halo, -OH, -CN, -NO_2, -N(R^{11})$_2$, and –S(O)$_p$$R^{11}$, and alkyl, alkoxy, alkenyl, alkenyloxy, alkynyl, cycloalkyl, cycloalkenyl, cycloalkoxy, aryl, aryloxy, arylalkyl, heteroaryl, heteroaryloxy, heteroarylalkyl, heterocyclyl, heterocyclenyl, heterocyclenyloxy, heterocyclylalkyl, heterocyclenylalkyl, arylalkyloxy, heteroarylalkyloxy, heterocyclylalkyloxy, and heterocyclenylalkoxy groups, each of which in turn is optionally substituted by at least once by a substituent selected from the group consisting of H, alkyl, haloalkyl, halo, -OH, optionally substituted alkoxy, optionally substituted aryloxy, optionally substituted cycloalkoxy, optionally substituted heteroaryloxy, optionally substituted heterocyclenyloxy, -CN, -NO_2, -N(R^{11})$_2$, and –S(O)$_p$$R^{11}$, wherein said optionally substituted alkoxy, aryloxy, optionally substituted

cycloalkoxy, optionally substituted heteroaryloxy, and heterocyclenyloxy when substituted are substituted one or more times by R^{11};

m is 1-5;

n is independently 1-3;

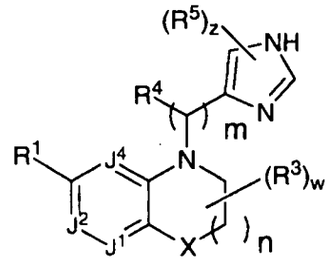
p is independently 0-2;

q is independently 0-6;

z is 0-3; and

w is 0-4.

7. A compound represented by the structural formula:



Formula **V**

or a pharmaceutically acceptable salt or solvate of said compound, wherein:

R^1 is $-(CH_2)_qN(R^7)YR^{7'}$;

X is -O-, or $-S(O)_p-$;

J^1, J^2, and J^4 are independently -N- or $-C(R^2)-$, provided that 0-3 of J^1, J^2, and J^4 are -N-;

R^2 is independently selected from the group consisting of H, -OH, halo, -CN, $-NO_2$, and alkyl, alkoxy, alkenyl, alkynyl, cycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, and heterocyclyl groups optionally substituted with at least one R^5;

Y is C(=O)-, $-C(=O)NR^7-$, -C(=O)O-, $-C(=O)-[C(R^a)(R^b)]_n-O-C(=O)-$, or $-C(=O)N(R^c)-O-$,

wherein R^a and R^b are independently selected from the group consisting of H, alkyl, alkoxy, and halo, and

R^c is H or alkyl;

R^3 is independently selected from the group consisting of H and alkyl, alkoxy, alkenyl, alkenyloxy, alkynyl, cycloalkyl, cycloalkoxy, aryl, aryloxy, arylalkyl, heteroaryl, heteroarylalkyl, heterocyclyl, and heterocyclylalkyl groups optionally substituted with at least one R^5;

R^4 is independently selected from the group consisting of H –CN and halo, and alkyl, alkoxy, alkenyl, alkenyloxy, alkynyl, cycloalkyl, cycloalkoxy, aryl, aryloxy, arylalkyl, heteroaryl, heteroarylalkyl, heterocyclyl, and heterocyclylalkyl groups optionally substituted with at least one R^5;

R^5 is independently selected from the group consisting of H, halo, -OH, -CN, $-NO_2$, $-NR^7R^{7'}$, and $-S(O)_pR^7$, and alkyl, alkoxy, alkenyl, alkenyloxy, alkynyl, cycloalkyl, cycloalkoxy, aryl, aryloxy, arylalkyl, heteroaryl, heteroarylalkyl, heterocyclyl, and heterocyclylalkyl groups, each of which is optionally substituted with at least one of halo, -OH, -CN, $-NO_2$, $-NR^7R^{7'}$, and $-S(O)_pR^7$ substituents and/or 1 (=O) group;

R^6 is independently selected from the group consisting of H and alkyl, alkoxy, alkenyl, alkenyloxy, alkynyl, cycloalkyl, cycloalkoxy, aryl, aryloxy, arylalkyl, heteroaryl, heteroarylalkyl, heterocyclyl, and heterocyclylalkyl groups, each of which is optionally substituted with at least one of halo, -OH, -CN, $-NO_2$, $-NR^7R^{7'}$, and $-S(O)_pR^7$ substituents and/or 1 or 2 (=O) groups, and $-C(=O)R^7$, $-C(=O)OR^7$, $-C(=O)NR^7R^{7'}$, $-SO_2R^7$ and $-SO_2NR^7R^{7'}$;

R^7 is independently selected from the group consisting of H and alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, cyclocyclenyl, cyclocyclenylalkyl, aryl, arylalkyl, heterocyclyl, heterocyclylalkyl, heterocyclenyl, heterocyclenylalkyl, heteroaryl, and heteroarylalkyl, groups, each of which is optionally substituted one or more times by R^{12};

$R^{7'}$ is independently selected from the group consisting of H and alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, cyclocyclenyl, cyclocyclenylalkyl, aryl, arylalkyl, heterocyclyl, heterocyclylalkyl, heterocyclenyl, heterocyclenylalkyl, heteroaryl, and heteroarylalkyl, groups, each of which is optionally substituted one or more times by R^{12} or

R^7 and $R^{7'}$ together with the nitrogen atom together form a 3- to 8-membered heterocyclyl, heterocyclenyl or heteroaryl ring having, in addition to the N atom, 1 or 2 additional hetero atoms selected from the group consisting of O, N, $-N(R^9)-$ and S, wherein said rings are optionally substituted by 1 to 5 independently selected R^5 moieties,

R^8 is independently selected from the group consisting of alkyl, alkenyl, alkynyl, cycloalkyl, aryl, arylalkyl, heteroaryl, and heteroarylalkyl groups, each of which is

optionally substituted with at least one of halo, -OH, -CN, -NO_2, -$N(R^{11})_2$, and –$S(O)_pR^{11}$ substituents;

R^9 is independently selected from the group consisting of H, -C(O)-R^{10}, -C(O)-OR^{10}, and –$S(O)_p$-OR^{10} and alkyl, alkenyl, alkynyl, cycloalkyl, aryl, arylalkyl, heteroaryl, and heteroarylalkyl groups, each of which is optionally substituted with at least one of halo, -OH, -CN, -NO_2, -$N(R^{11})_2$, and –$S(O)_pR^{11}$substituents; and

R^{10} is selected from the group consisting of alkyl, alkenyl, alkynyl, cycloalkyl, aryl, arylalkyl, heteroaryl, and heteroarylalkyl groups, each of which is optionally substituted with at least one of halo, -OH, -CN, -NO_2, -$N(R^{11})_2$, and –$S(O)_pR^{11}$ substituents;

R^{11} is a moiety independently selected from the group consisting of H and alkyl, alkoxy, alkenyl, alkenyloxy, alkynyl, cycloalkyl, cycloalkoxy, aryl, aryloxy, arylalkyl, heteroaryl, heteroarylalkyl, heterocyclyl, and heterocyclylalkyl, each of which is optionally substituted by at least one substituent independently selected from the group consisting of halo, -OH, -CN, -NO_2, -$N(R^{11'})_2$, and –$S(O)_pR^{11'}$;

$R^{11'}$ is independently selected from the group consisting of H, alkyl, alkoxy, alkenyl, alkenyloxy, alkynyl, cycloalkyl, cycloalkoxy, aryl, aryloxy, arylalkyl, heteroaryl, heteroarylalkyl, heterocyclyl, and heterocyclylalkyl;

R^{12} is independently selected from selected from the group consisting of H, halo, -OH, -CN, -NO_2, -$N(R^{11})_2$, and –$S(O)_pR^{11}$, and alkyl, alkoxy, alkenyl, alkenyloxy, alkynyl, cycloalkyl, cycloalkenyl, cycloalkoxy, aryl, aryloxy, arylalkyl, heteroaryl, heteroaryloxy, heteroarylalkyl, heterocyclyl, heterocyclenyl, heterocyclenyloxy, heterocyclylalkyl, heterocyclenylalkyl, arylalkyloxy, heteroarylalkyloxy, heterocyclylalkyloxy, and heterocyclenylalkoxy groups, each of which in turn is optionally substituted by at least once by a substituent selected from the group consisting of H, alkyl, haloalkyl, halo, -OH, optionally substituted alkoxy, optionally substituted aryloxy, optionally substituted cycloalkoxy, optionally substituted heteroaryloxy, optionally substituted heterocyclenyloxy, -CN, -NO_2, -$N(R^{11})_2$, and –$S(O)_pR^{11}$, wherein said optionally substituted alkoxy, aryloxy, optionally substituted cycloalkoxy, optionally substituted heteroaryloxy, and heterocyclenyloxy when substituted are substituted one or more times by R^{11}

m is 1-5;

n is independently1-3;

p is independently 0-2;

q is independently 0-6;

z is 0-3; and

w is 0-4.

8. The compound of claim 7, wherein:

J^1 and J^2 are $-C(R^2)-$

J^3 is $-C(R^2)-$ or $-N-$;

X is $-O-$;

R^2 is H, halo, or alkyl groups optionally substituted with at least one R^5;

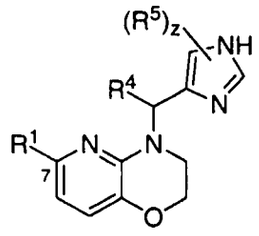
R^3 is H;

R^4 is H, alkyl or CN;

R^5 is H or halo

or a pharmaceutically acceptable salt, ester, solvate or prodrug thereof.

9. A compound represented by the structural formula:



Formula **IV**

or a pharmaceutically acceptable salt, ester, solvate or rodrug thereof wherein:

R^1 is selected from the group consisting of H, -OH, halo, -CN, $-NO_2$, $-SR^7-(CH_2)_qYR^{7'}$, $-(CH_2)_qN(R^7)YR^{7'}$, $-(CH_2)_qOYR^7$, $-(CH_2)_qON{=}CR^7R^{7'}$and alkyl, alkoxy, alkenyl, alkenyloxy, alkynyl, cycloalkyl, cycloalkoxy, aryl, aryloxy, arylalkyl, heteroaryl, heteroarylalkyl, heterocyclyl, and heterocyclylalkyl groups optionally substituted with at least one R^5;

Y is selected from the group consisting of a bond, $-C(=O)-$, $-C(=O)NR^7-$, $-C(=O)O-$, $-C(=O)-[C(R^a)(R^b)]_n-O-C(=O)-$, $-C(=O)N(R^c)-O-$,

wherein R^a and R^b are independently selected from the group consisting of H, alkyl, alkoxy, and halo, and

R^c is H or alkyl;

R^4 is independently selected from the group consisting of H, - CN and alkyl optionally substituted with at least one R^5;

R^5 is independently selected from the group consisting of H, halo, -OH, -CN, $-NO_2$, $-NR^7R^{7'}$, $-S(O)_pR^7$, and alkyl, alkoxy, alkenyl, alkenyloxy, alkynyl, cycloalkyl, cycloalkoxy, aryl, aryloxy, arylalkyl, heteroaryl, heteroarylalkyl, heterocyclyl, and heterocyclylalkyl groups, each of which is optionally substituted with at least one of halo, -OH, -CN, $-NO_2$, $-NR^7R^{7'}$, and $-S(O)_pR^7$ substituents;

R^7 is independently selected from the group consisting of H and alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, cyclocyclenyl, cyclocyclenylalkyl, aryl, arylalkyl, heterocyclyl, heterocyclylalkyl, heterocyclenyl, heterocyclenylalkyl, heteroaryl, and heteroarylalkyl, groups, each of which is optionally substituted one or more times by R^{12};

$R^{7'}$ is independently selected from the group consisting of H and alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, cyclocyclenyl, cyclocyclenylalkyl, aryl, arylalkyl, heterocyclyl, heterocyclylalkyl, heterocyclenyl, heterocyclenylalkyl, heteroaryl, and heteroarylalkyl, groups, each of which is optionally substituted one or more times by R^{12}; or

R^7 and $R^{7'}$ together with the nitrogen atom to which they are attached form a 3- to 8-membered heterocyclyl, heterocyclenyl or heteroaryl ring having, in addition to the N atom, 1 or 2 additional hetero atoms selected from the group consisting of O, N, $-N(R^9)-$ and S, wherein said rings are optionally substituted by 1 to 5 independently selected R^5 moieties,

R^9 is independently selected from the group consisting of H, $-C(O)-R^{10}$, $-C(O)-OR^{10}$, and $-S(O)_p-OR^{10}$ and alkyl, alkenyl, alkynyl, cycloalkyl, aryl, arylalkyl, heteroaryl, and heteroarylalkyl groups, each of which is optionally substituted with at least one of halo, -OH, -CN, $-NO_2$, $-N(R^{11})_2$, and $-S(O)_pR^{11}$ substituents; and

R^{10} is selected from the group consisting of alkyl, alkenyl, alkynyl, cycloalkyl, aryl, arylalkyl, heteroaryl, and heteroarylalkyl groups, each of which is optionally substituted with at least one of halo, -OH, -CN, $-NO_2$, $-N(R^{11})_2$, and $-S(O)_pR^{11}$ substituents;

R^{11} is a moiety independently selected from the group consisting of H and alkyl, alkoxy, alkenyl, alkenyloxy, alkynyl, cycloalkyl, cycloalkoxy, aryl, aryloxy, arylalkyl, heteroaryl, heteroarylalkyl, heterocyclyl, and heterocyclylalkyl, each of which is optionally substituted by at least one substituent independently selected from the group consisting of halo, -OH, -CN, $-NO_2$, $-N(R^{11'})_2$, and $-S(O)_pR^{11'}$;

$R^{11'}$ is independently selected from the group consisting of H, alkyl, alkoxy, alkenyl, alkenyloxy, alkynyl, cycloalkyl, cycloalkoxy, aryl, aryloxy, arylalkyl, heteroaryl, heteroarylalkyl, heterocyclyl, and heterocyclylalkyl;

R^{12} is independently selected from selected from the group consisting of H, halo, -OH, -CN, $-NO_2$, $-N(R^{11})_2$, and $-S(O)_pR^{11}$, and alkyl, alkoxy, alkenyl, alkenyloxy, alkynyl, cycloalkyl, cycloalkenyl, cycloalkoxy, aryl, aryloxy, arylalkyl, heteroaryl, heteroaryloxy, heteroarylalkyl, heterocyclyl, heterocyclenyl, heterocyclenyloxy, heterocyclylalkyl, heterocyclenylalkyl, arylalkyloxy, heteroarylalkyloxy, heterocyclylalkyloxy, and heterocyclenylalkoxy groups, each of which in turn is optionally substituted by at least once by a substituent selected from the group consisting of H, alkyl, haloalkyl, halo, -OH, optionally substituted alkoxy, optionally substituted aryloxy, optionally substituted cycloalkoxy, optionally substituted heteroaryloxy, optionally substituted heterocyclenyloxy, -CN, $-NO_2$, $-N(R^{11})_2$, and $-S(O)_pR^{11}$, wherein said optionally substituted alkoxy, aryloxy, optionally substituted cycloalkoxy, optionally substituted heteroaryloxy, and heterocyclenyloxy when substituted are substituted one or more times by R^{11};

p is 0-2;

q is 0-6; and

z is 0-3.

10. The compound of claim 2, wherein:

J^1 and J^2 are $-C(R^2)-$

J^3 is $-C(R^2)-$ or $-N-$;

X is $-O-$;

R^2 is H, halo, or alkyl groups optionally substituted with at least one R^5;

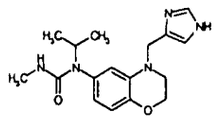
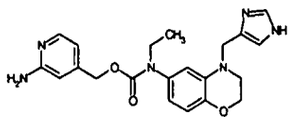
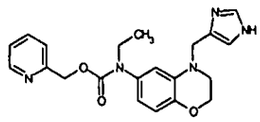
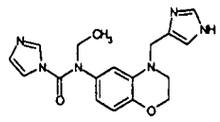
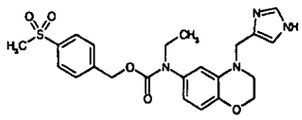
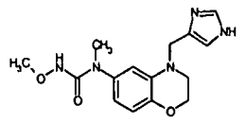
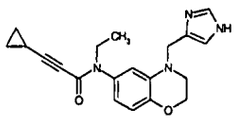
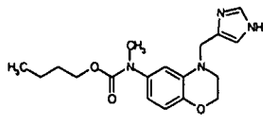
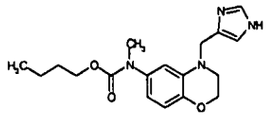
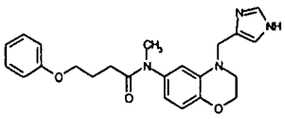
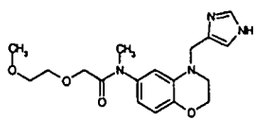
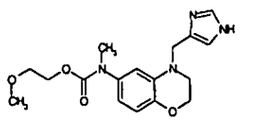
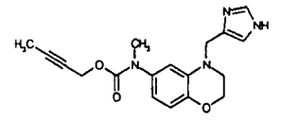
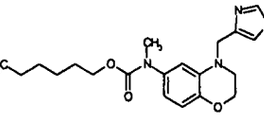
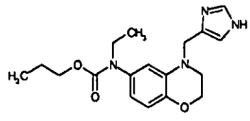
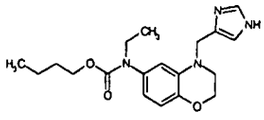
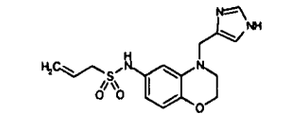
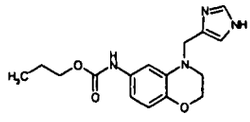
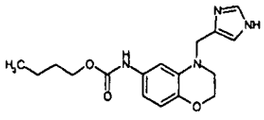
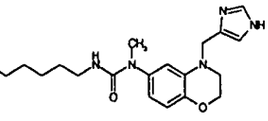
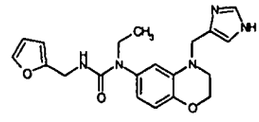
R^3 is H;

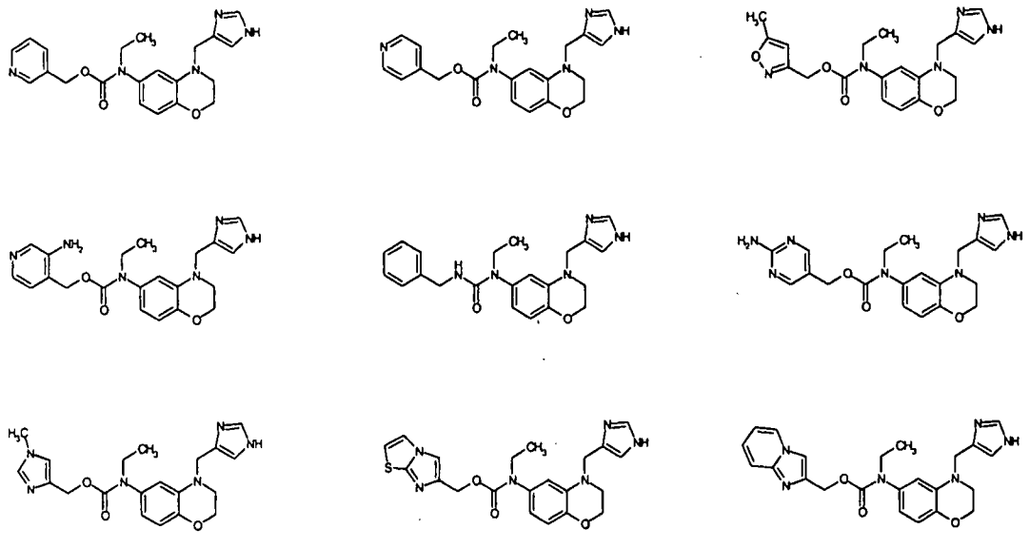
R^4 is H, alkyl or CN;

R^5 is H or halo

or a pharmaceutically acceptable salt, ester, solvate or prodrug thereof.

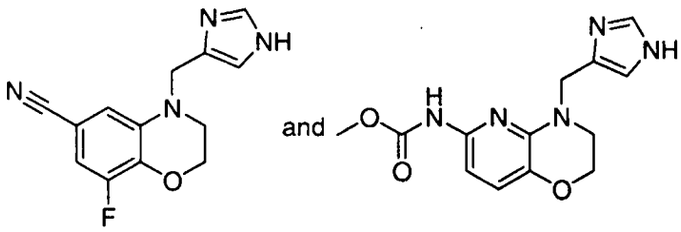
11. A compound selected from the group consisting of



or a pharmaceutically acceptable salt or solvate thereof.

12. A compound selected from the group consisting of:



or a pharmaceutically acceptable salt thereof.

13. A pharmaceutical composition comprising at least one compound of claim 12, or a pharmaceutically acceptable salt or solvate thereof and at least one pharmaceutically acceptable carrier, adjuvant or vehicle

14. A method for treating one or more conditions associated with α2C adrenergic receptors, comprising administering to a mammal in need of such treatment the compound of claim 12 or a pharmaceutically acceptable salt or solvate thereof.

15. A pharmaceutical composition comprising at least one compound of claim 1, or a pharmaceutically acceptable salt or solvate thereof and at least one pharmaceutically acceptable carrier, adjuvant or vehicle.

16. A pharmaceutical composition comprising at least one compound of claim 11, or a pharmaceutically acceptable salt or solvate thereof and at least one pharmaceutically acceptable carrier, adjuvant or vehicle.

17. The pharmaceutical composition of claim 15, further comprising one or more additional therapeutic agents.

18. The pharmaceutical composition of claim 16, further comprising one or more additional therapeutic agents.

19. The pharmaceutical composition of claim 17, wherein said additional therapeutic agents are selected from the group consisting of anti-inflammatory steroids, PDE-4 inhibitors, anti-muscarinic agents, cromolyn sodium, H_1 receptor antagonists, 5-HT_1 agonists, NSAIDs, angiotensin-converting enzyme inhibitors, angiotensin II receptor agonists, β-blockers, β-agonists, leukotriene antagonists, diuretics, aldosterone antagonists, ionotropic agents, natriuretic peptides, pain management agents, anti-anxiety agents, anti-migraine agents, and therapeutic agents suitable for treating heart conditions, psychotic disorders, and glaucoma.

20. The pharmaceutical composition of claim 18, wherein said additional therapeutic agents are selected from the group consisting of steroids, PDE-4 inhibitors, anti-muscarinic agents, cromolyn sodium, H_1 receptor antagonists, 5-HT_1 agonists, NSAIDs, angiotensin-converting enzyme inhibitors, angiotensin II receptor agonists, β-blockers, β-agonists, leukotriene antagonists, diuretics, aldosterone antagonists, ionotropic agents, natriuretic peptides, pain management agents, anti-anxiety agents, anti-migraine agents, and therapeutic agents suitable for treating heart conditions, psychotic disorders, and glaucoma.

21. A method for selectively stimulating α2C adrenergic receptors in a cell in need thereof, comprising contacting said cell with a therapeutically effective amount of at least one compound according to claim 1 or a salt or solvate thereof.

22. A method for treating one or more conditions associated with α2C adrenergic receptors, comprising administering to a mammal in need of such treatment at least one compound according to claim 1 or a salt or solvate thereof.

23. A method for treating one or more conditions associated with α2C adrenergic receptors, comprising administering to a mammal in need of such treatment the compound of claim 11 or a pharmaceutically acceptable salt or solvate thereof.

24. The method of claim 22, wherein the conditions are selected from the group consisting of allergic rhinitis, congestion, pain, diarrhea, glaucoma, congestive heart failure, cardiac ischemia, manic disorders, depression, anxiety, migraine, stress-induced urinary incontinence, neuronal damage from ischemia and schizophrenia.

25. The method of claim 23, wherein the conditions are selected from the group consisting of allergic rhinitis, congestion, pain, diarrhea, glaucoma, congestive heart failure, cardiac ischemia, manic disorders, depression, anxiety, and schizophrenia.

26. The method of claim 24, wherein the condition is congestion.

27. The method of claim 25, wherein the condition is congestion.

28. The method of claim 26, wherein the congestion is associated with perennial allergic rhinitis, seasonal allergic rhinitis, non-allergic rhinitis, vasomotor rhinitis, rhinitis medicamentosa, sinusitis, acute rhinosinusitis, or chronic rhinosinusitis.

29. The method of claim 26, wherein the congestion is caused by polyps or is virally induced.

30. The method of claim 27, wherein the congestion is associated with perennial allergic rhinitis, seasonal allergic rhinitis, non-allergic rhinitis, vasomotor rhinitis, rhinitis medicamentosa, sinusitis, acute rhinosinusitis, or chronic rhinosinusitis.

31. The method of claim 27, wherein the congestion is caused by polyps or is virally induced.

32. The method of claim 24, wherein the condition is pain.

33. The method of claim 32, wherein the pain is associated with neuropathy, inflammation, arthritis or diabetes.

34. The method of claim 25, wherein the condition is pain.

35. The method of claim 34, wherein the pain is associated with neuropathy, inflammation, arthritis or diabetes.

36. A compound of claim 1, in isolated and purified form.

AGONISTAS DE ADRENORECEPTORES ALFA2C

Campo de la Invención

La presente invención se refiere a compuestos fenilmorfolina y feniltiomorfolina útiles como agonistas de receptores adrenérgicos α2C, composiciones farmacéuticas que contienen los compuestos y métodos de tratamiento y prevención, usando los compuestos y composiciones para tratar enfermedades tales como congestión (incluyendo congestión nasal), migraña, insuficiencia cardíaca congestiva, isquemia cardíaca, dolor, glaucoma, y trastornos psicóticos sin efectos secundarios sustancialmente adversos asociados con los tratamientos con agonista del receptor α2A.

Antecedentes de la Invención

La clasificación inicial de receptores adrenérgicos en familias α y ß fue descrita primero por Ahlquist en 1948 (Ahlquist RP, "A Study of the Adrenergic Receptors," Am. J. Phisiol. 153:586-600 (1948)). Funcionalmente, se demostró que los receptores α-adrenérgicos estaban asociados con la mayoría de las funciones excitatorias (vasoconstricción, estimulación del útero y dilatación de la pupila) y los receptores β-adrenérgicos estaban implicados en la vasodilatación, broncodilatación y estimulación del miocardio (Lands et al., "Differentiation of Receptor Systems Activated by Sympathomimetic amines," Nature 214:597-598 (1967)). Debido a este trabajo previo, los receptores α-adrenérgicos han sido subdivididos en receptores adrenérgicos α1 y α2. La clonación y expresión de receptores α-adrenérgicos ha confirmado la presencia de múltipes subtipos tanto de receptores adrenérgicos α1 (α1A, α1B, α1D) como de α2 (α2A, α2B, α2C) (Michel et al., "Classification of α_1-Adrenoceptor Subtypes," Naunyn-Schmiedeberg's Arch. Pharmacol, 352:1-10 (1995); Macdonald et al., "Gene Targeting--Homing en on α_2 -Adrenoceptor-Subtype Function," TIPS, 18:211-219 (1997)).

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Los usos terapéuticos corrientes de drogas receptores adrenérgicos α-2 involucran la capacidad de dichos drogas para intermediar en muchas de las acciones fisiológicas de las catecolaminas endógenas. Existen muchos drogas que actúan sobre estos receptores para controlar la hipertensión, la presión intraocular,

el enrojecimiento de los ojos y la congestión nasal, que inducen a analgesia y anestesia.

Pueden hallarse receptores adrenérgicos α2 en la médula rostral ventrolateral, de los cuales se sabe que responden a la norepinefrina neurotransmisora, y al droga antihipertensor clonidina, para disminuir el sobre-flujo del simpático y reducir la presión arterial de la sangre (Bousquet et al., "Role of the Ventral Surface of the Brain Stem en the Hipothesive Action of Clonidine," Eur. J. Pharmacol., 34:151-156 (1975); Bousquet et al., "Imidazoline Receptors: From Basic Concepts to Recent Developments," 26:S1-S6 (1995)). La clonidina y otras imidazolinas se adhieren también a los receptores imidazolina (denominados anteriormente sitios receptores de imidazolina- guanidinio o IGRS) (Bousquet et al., "Imidazoline Receptors: From Basic Concepts to Recent Developments," 26:S1-S6 (1995)). Algunos investigadores han especulado que los efectos centrales y periféricos de las imidazolinas como agentes hipotensores pueden estar relacionados con los receptores imidazolina (Bousquet et al., "Imidazoline Receptors: From Basic Concepts to Recent Developments," 26:S1-S6 (1995); Reis et al., "The Imidazoline Receptor: Pharmacology, Functions, Ligands, and Relevance to Biology and Medicine," Ann. N.Y. Acad. Sci., 763:1-703 (1995).

Los compuestos que tienen actividad adrenérgica son bien conocidos en la materia y han sido descritos en numerosas patentes y publicaciones científicas. Las dos familias principales de receptores adrenérgicos se denominan receptores adrenérgicos alfa y receptores adrenérgicos beta, en la materia, y se sabe que cada una de estas dos familias tiene subtipos, que están designados con letras del alfabeto, tales como α2A, α2B y α2C. Se sabe en general que la actividad adrenérgica es útil para tratar especies animales de la especie de los mamíferos, incluyendo seres humanos, para curar o aliviar los síntomas y alteraciones de numerosas enfermedades y trastornos. En otras palabras, es generalmente aceptado en la materia que las composiciones farmacéuticas que tienen un compuesto o compuestos adrenérgicos como ingrediente activo son útiles para el tratamiento, entre otras cosas, de glaucoma, dolor crónico, migrañas, insuficiencia cardiaca, y trastornos psicóticos. También se sabe que los compuestos que tienen actividad adrenérgica, tales como los agonistas α2A, pueden estar asociados con

efectos secundarios indeseables. Efectos de dichos efectos incluyen hiper e hipotensión, sedación, actividad locomotora y variaciones de la temperatura corporal.

Se ha descubierto de acuerdo con la presente invención, que los compuestos adrenérgicos que actúan selectivamente y preferiblemente, incluso específicamente, como agonistas de los subtipos receptores α2C o de α2B/α2C (denominados a continuación α2C o α2B/2C) con preferencia sobre el subtipo receptor α2A, con compuestos adrenérgicos que son agonistas funcionalmente selectivos del subtipo receptor α2C con preferencia sobre el subtipo receptor α2A y el subtipo receptor α2B/2C, poseen propiedades terapéuticas deseables, asociadas con los receptores adrenérgicos, pero sin que tengan uno o más efectos secundarios indeseables, tales como cambios en la presión sanguínea (por ejemplo un efecto de hipertensión o hipotensión) o sedación. Para los propósitos de la presente invención, un compuesto se define como un agonista activo del subtipo receptor α2C si la eficacia del compuesto en el receptor α2C es de ≥ del 30% E_{max} (ensayo GTPγS). Un compuesto es un agonista funcionalmente selectivo del subtipo receptor α2C sobre el subtipo receptor α2A, si la eficacia del compuesto en el receptor α2C es de ≥ del 30% E_{max} (ensayo GTPγS) y su eficacia en el receptor α2A es de ≤ del 30% E_{max} (ensayo GTPγS).

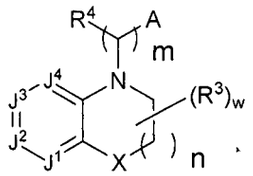
Existe la necesidad de nuevos compuestos, formulaciones, tratamientos y terapias para tratar enfermedades y trastornos asociados con receptores adrenérgicos α2C. Además, existe la necesidad de desarrollar compuestos que sean funcionalmente selectivos para el subtipo receptor α2C con respecto al subtipo receptor α2A o el subtipo receptor α2B/2C. Por lo tanto, un objeto de esta invención es el de proveer compuestos útiles en el tratamiento o prevención o mejoramiento de dichas enfermedades y trastornos.

Compendio de la Invención

En sus muchas realizaciones, la presente invención provee una nueva clase de compuestos heterocíclicos como agonistas de receptores adrenérgicos α2C activos o funcionalmente selectivos, o metabolitos, estereoisómeros, (por ejemplo enantiómeros o diastereómeros), sales, solvatos o polimorfos de éstos,

métodos de preparación de dichos compuestos, composiciones farmacéuticas que comprenden uno o más de dichos compuestos, métodos de preparación de formulaciones farmacéuticas que comprenden uno o más de dichos compuestos y métodos de tratamiento, prevención, inhibición o mejoramiento de uno o más trastornos asociados con receptores α2C usando dichos compuestos o composiciones farmacéuticas.

En un aspecto, la presente solicitud describe un compuesto, o sales, o metabolitos, solvatos, o polimorfos farmacéuticamente aceptables de dicho compuesto, donde dicho compuesto tiene la estructura general que se muestra en la Fórmula I:



Fórmula I

donde:

A es un anillo heterociclico de 5 miembros que contiene 1-3 heteroátomos, y está opcionalmente sustituido con por lo menos un R^5 y/o 1 o 2 grupos (=O) (carbonilo);

X es -O-, -$S(O)_p$-, o -$N(R^6)$-;

J^1, J^2, J^3, y J^4 son independientemente -N-, -N(O)- or -$C(R^2)$-, con la condición de que 0-3 de J^1, J^2, J^3 y J^4 sean –N-;

R^2 está independientemente seleccionado del grupo que consiste en H, -OH, halo, -CN, -NO_2, -$S(O)_pR^7$, -$NR^7R^{7'}$ -$[C(R^a)(R^b)]_qYR^{7'}$, -$[C(R^a)(R^b)]_qN(R^7)YR^{7'}$, $C(R^a)(R^b)]_qOYR^{7'}$, -$[C(R^a)(R^b)]_qON=CR^7R^{7'}$, -$P(=O)(OR^7)(OR^{7'})$, -$P(=O)NR^7R^{7'}$, y -$P(=O)R^8{}_2$, y grupos alquilo, alcoxi, alquenilo, alqueniloxi, alquinilo, cicloalquilo, cicloalcoxi, arilo, ariloxi, arilalquilo, heteroarilo, heteroarilalquilo, heterociclilo, y heterociclilalquilo, opcionalmente sustituido con por lo menos un R^5;

Y está seleccionado del grupo que consiste en un enlace, -C(=O)-, -$C(=O)NR^7$-, -C(=O)O-, -$C(=NR^7)$-, -C(=O)-$[C(R^a)(R^b)]_n$-O-C(=O)-, -$C(=O)N(R^c)$-O-, -$C(=NOR^7)$-, -$C(=NR^7)NR^7$-, -$C(=NR^7)N(R^c)$O-, -$S(O)_p$-, -SO_2NR^7-, y -$C(S)NR^7$-;

donde R^a y R^b están independientemente seleccionados del grupo que consiste en H, alquilo, alcoxi, y halo,

R^c es H o alquilo;

R^3 está independientemente seleccionado del grupo que consiste en H, (=O), Y halo, y grupos alquilo, alcoxi, alquenilo, alqueniloxi, alquinilo, cicloalquilo, cicloalcoxi, arilo, ariloxi, arilalquilo, heteroarilo, heteroarilalquilo, heterociclilo, y heterociclilalquilo, opcionalmente sustituidos con por lo menos un R^5, con la condición de que cuando n es 3 o 4, no más de 2 de los grupos R^3 puede ser (=O);

R^4 está independientemente seleccionado del grupo que consiste en H, -CN, y halo, y grupos alquilo, alcoxi, alquenilo, alqueniloxi, alquinilo, cicloalquilo, cicloalcoxi, arilo, ariloxi, arilalquilo, heteroarilo, heteroarilalquilo, heterociclilo, y heterociclilalquilo, opcionalmente sustituidos con por lo menos un R^5;

R^5 está independientemente seleccionado del grupo que consiste en H, halo, -OH, -CN, $-NO_2$, $-NR^7R^{7'}$, y $-S(O)_pR^7$, y grupos alquilo, alcoxi, alquenilo, alqueniloxi, alquinilo, cicloalquilo, cicloalcoxi, arilo, ariloxi, arilalquilo, heteroarilo, heteroarilalquilo, heterociclilo, y heterociclilalquilo, cada uno de los cuales está opcionalmente sustituido con por lo menos un de los sustituyentes halo, -OH, -CN, $-NO_2$, $-NR^7R^{7'}$, y $-S(O)_pR^7$ y/o 1 o 2 grupos (=O);

R^6 está independientemente seleccionado del grupo que consiste en H y grupos alquilo, alcoxi, alquenilo, alqueniloxi, alquinilo, cicloalquilo, cicloalcoxi, arilo, ariloxi, arilalquilo, heteroarilo, heteroarilalquilo, heterociclilo, y heterociclilalquilo, cada uno de los cuales está opcionalmente sustituido con por lo menos uno de los sustituyentes halo, -OH, -CN, $-NO_2$, $-NR^7R^{7'}$, y $-S(O)_pR^7$ y/o 1 o 2 grupos (=O), y $-C(=O)R^7$, $-C(=O)OR^7$, $-C(=O)NR^7R^{7'}$, $-SO_2R^7$ y $-SO_2NR^7R^{7'}$;

R^7 está independientemente seleccionado del grupo que consiste en H y grupos alquilo, alquenilo, alquinilo, cicloalquilo, cicloalquilalquilo, ciclociclenilo, ciclociclenilalquilo, arilo, arilalquilo, heterociclilo, heterociclilalquilo, heterociclenilo, heterociclenilalquilo, heteroarilo, y heteroarilalquilo, cada uno de los cuales está opcionalmente sustituido una o más veces (preferiblemente 1 a 5, más preferiblemente 1 a 3) con R^{12};

$R^{7'}$ está independientemente seleccionado del grupo que consiste en H y grupos alquilo, alquenilo, alquinilo, cicloalquilo, cicloalquilalquilo, ciclociclenilo, ciclociclenilalquilo, arilo, arilalquilo, heterociclilo, heterociclilalquilo, heterociclenilo, heterociclenilalquilo, heteroarilo, y heteroarilalquilo, cada uno de los cuales está opcionalmente sustituido una o más veces (preferiblemente 1 a 5, más preferiblemente 1 a 3) con R^{12}; o

R^7 y $R^{7'}$ conjuntamente con el átomo de nitrógeno al cual están unidos forman un anillo heterociclilo, heterociclenilo o heteroarilo de 3 a 8 miembros que tiene, además del átomo N, 1 o 2 heteroátomos adicionales seleccionados del grupo que consiste en O, N, -N(R^9)- y S, donde dichos anillos están opcionalmente sustituidos con 1 a 5 restos R^5 independientemente seleccionados y/o 1 o 2 grupos (=O),

R^8 está independientemente seleccionado del grupo que consiste en grupos alquilo, alquenilo, alquinilo, cicloalquilo, arilo, arilalquilo, heteroarilo, y heteroarilalquilo, cada uno de los cuales está opcionalmente sustituido con por lo menos un de los sustituyentes halo, -OH, -CN, -NO_2, -N(R^{11})$_2$, y –S(O)$_p$$R^{11}$ y/o 1 o 2 grupos (=O);

R^9 está independientemente seleccionado del grupo que consiste en H, -C(O)-R^{10}, -C(O)-OR^{10}, y –S(O)$_p$-OR^{10} y grupos alquilo, alquenilo, alquinilo, cicloalquilo, arilo, arilalquilo, heteroarilo, y heteroarilalquilo, cada uno de los cuales está opcionalmente sustituido con por lo menos uno de los sustituyentes halo, -OH, -CN, -NO_2, -N(R^{11})$_2$, y –S(O)$_p$$R^{11}$ y/o 1 o 2 grupos (=O); y

R^{10} está seleccionado del grupo que consiste en grupos alquilo, alquenilo, alquinilo, cicloalquilo, arilo, arilalquilo, heteroarilo, y heteroarilalquilo, cada uno de los cuales está opcionalmente sustituido con por lo menos uno de los sustituyentes halo, -OH, -CN, -NO_2, -N(R^{11})$_2$, y –S(O)$_p$$R^{11}$ y/o 1 o 2 grupos (=O);

R^{11} es un resto independientemente seleccionado del grupo que consiste en H y alquilo, alcoxi, alquenilo, alqueniloxi, alquinilo, cicloalquilo, cicloalcoxi, arilo, ariloxi, arilalquilo, heteroarilo, heteroarilalquilo, heterociclilo, y heterociclilalquilo, cada uno de los cuales está opcionalmente sustituido con por lo menos un sustituyente independientemente seleccionado del grupo que consiste en halo, -OH, -CN, -NO_2, -N($R^{11'}$)$_2$, y –S(O)$_p$$R^{11'}$ y/o 1 o 2 grupos (=O);

Industria y Comercio
SUPERINTENDENCIA

DIVISIÓN DE NUEVAS CREACIONES

RADICACIÓN EXPEDIENTE No. 09-084452

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

FUE PUBLICADO EN LA GACETA DE PROPIEDAD INDUSTRIAL No **623** DE

FECHA **20** DE **DICIEMBRE DE 2010** EL TÉRMINO HÁBIL SEÑALADO POR LA

LEY EXPIRA EL **15** DE **MARZO** DEL **2011**

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

SE PRESENTARON OPOSICIONES POR PARTE DE TERCEROS.

SI _ _ NO___ ___ **X** _ _ _

Solicitud de Patente de Invención PCT

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$R^{11'}$ está independientemente seleccionado del grupo que consiste en H, alquilo, alcoxi, alquenilo, alqueniloxi, alquinilo, cicloalquilo, cicloalcoxi, arilo, ariloxi, arilalquilo, heteroarilo, heteroarilalquilo, heterociclilo, y heterociclilalquilo;

R^{12} está independientemente seleccionado del grupo que consiste en H, halo, -OH, -CN, $-NO_2$, $-N(R^{11})_2$, y $-S(O)_pR^{11}$ y/o 1 o 2 grupos (=O), y grupos alquilo, alcoxi, alquenilo, alqueniloxi, alquinilo, cicloalquilo, cicloalquenilo, cicloalcoxi, arilo, ariloxi, arilalquilo, heteroarilo, heteroariloxi, heteroarilalquilo, heterociclilo, heterociclenilo, heterocicleniloxi, heterociclilalquilo, heterociclenilalquilo, arilalcoxi, heteroarilalcoxi, heterociclilalcoxi, y heterociclenilalcoxi, cada uno de los cuales a su vez está opcionalmente sustituido con por lo menos una vez (preferiblemente 1 a 5, más preferiblemente 1 a 3) con un sustituyente seleccionado del grupo que consiste en H, alquilo, haloalquilo, halo, -OH, alcoxi opcionalmente sustituido, ariloxi opcionalmente sustituido, cicloalcoxi opcionalmente sustituido, heteroariloxi opcionalmente sustituido, heterocicleniloxi opcionalmente sustituido, -CN, $-NO_2$, $-N(R^{11})_2$, y $-S(O)_pR^{11}$ y/o 1 o 2 grupos (=O), donde dicho alcoxi opcionalmente sustituido, ariloxi, cicloalcoxi opcionalmente sustituido, heteroariloxi opcionalmente sustituido, y heterocicleniloxi cuando están sustituidos, lo están una o más (preferiblemente 1 a 5, más preferiblemente 1 a 3) veces con R^{11};

m es 1-5;

n es independientemente 1-3;

n' es independientemente 1-3

p es independientemente 0-2;

q es independientemente 0-6; y

w es 0-4

con las siguientes condiciones:

(a) si J^1-J^4 son cada uno -C(H)-, n es 1, m es 1, R^4 es H, A es 3H-imidazol-4-ilo, y X es $-N(R^6)-$, entonces R^6 no es -C(=O)-naftilo;

(b) si J^1-J^4 son cada uno -C(H)-, n es 1, m es 1, R^4 es H, A es 1H-imidazol-4-ilo, y X es $-N(R^6)-$, entonces R^6 no es $-S(O_2)$-naftilo; y

(c) si J^1, J^2, y J^4 son cada uno -C(H)-, J^3 es -C(Br)-, n es 2, m es 1, R^3 es 3-bencilo, R^4 es H, A es 1H-imidazol-4-ilo, y X es -N(R^6)-, entonces R^6 no es -C(O_2)bencilo.

Los compuestos de Fórmula I pueden ser como agonistas receptores adrenérgicos α2C, y pueden ser útiles en el tratamiento y prevención de rinitis alérgica, todo tipo de congestión (que incluye, pero no está limitado a congestión nasal), migraña, insuficiencia cardíaca congestiva, isquemia cardíaca, glaucoma, y trastornos psicóticos. Además, los compuestos de Fórmula I pueden ser útiles en el tratamiento del dolor (tanto dolor crónico como dolor agudo), tal como dolor causado por inflamación, neuropatía, artritis (que incluye osteartritis y artritis reumatoidea), diabetes (por ejemplo, diabetes mellitus o diabetes insipidus) o dolor de origen desconocido. Ejemplos de dolor neuropático pueden incluir, pero no están llimitados a; neuropatía diabética, neuralgia de cualquier etiología (por ejemplo, post-herpética, trigeminal), neuropatía inducida por quimioterapia, HIV, lumbalgia de origen neuropático (por ejemplo, ciática), lesión traumática de nervios periféricos de cualquier etiología, dolor central (por ejemplo, post-apoplejía, talámico, lesión del nervio espinal). Otro dolor que puede ser tratado es dolor nocireceptor y dolor que es de origen visceral o dolor que es secundario a inflamación o daño neuronal en otras enfermedades. Otros usos para los compuestos de la invención pueden incluir estrés inducido por incontinencia urinaria y daño neuronal causado por isquemia.

Alternativamente, la presente invención provee un método para el tratamiento de congestión en un mamífero que necesita dicho tratamiento que comprende administrar a un mamífero una dosis eficaz de por lo menos un compuesto que tiene actividad adrenérgica donde dicho compuesto es un agonista funcionalmente selectivo del receptor α2c.

Una realización adicional de la presente invención es un método para el tratamiento de congestión en un mamífero que lo necesita que comprende administrar a un mamífero una dosis eficaz de por lo menos un compuesto que tiene actividad adrenérgica donde dicho compuesto es un agonista funcionalmente selectivo del receptor α2C, donde el agonista selectivo del receptor α2c tiene una

eficacia que es mayor o igual al 30% E_{max} cuando es ensayada en el ensayo GTPγS.

Otra realización de la presente invención es un método para el tratamiento de la congestión en un mamífero que lo necesita sin modificar la presión sanguínea sistémica a dosis terapéuticas que comprende administrar al mamífero una dosis eficaz de por lo menos un compuesto que tiene actividad adrenérgica donde dicho compuesto es un agonista selectivo del receptor α2C.

Descripción Detallada

En una realización, la presente invención describe ciertos compuestos heterociclilo que están representados por la Fórmula estructural I, o una sal o solvato del mismo farmacéuticamente aceptable, donde los varios restos son tal como se han definido anteriormente

En otra realización, si J^1-J^4 son cada uno -C(H)-, n es 1, m es 1, R^4 es H, A es 1H-imidazol-4-ilo, y X es -N(R^6)-, entonces R^6 no es -C(=O)-naftilo.

En otra realización, si J^1-J^4 son cada uno -C(H)-, n es 1, m es 1, R^4 es H, A es 1H-imidazol-4-ilo, y X es -N(R^6)-, entonces R^6 no es -S(O_2)-naftilo.

En otra realización, si J^1, J^2, y J^4 son cada uno -C(H)-, J^3 es -C(Br)-, n es 2, m es 1, R^3 es 3-bencilo, R^4 es H, A es 1H-imidazol-4-ilo, y X es -N(R^6)-, entonces R^6 no es -C(O_2)bencilo.

En otra realización, J^1-J^4 son cada uno -C(R^2)-, n es 1, A es imidazolilo, y X es -O-.

En otra realización, J^1-J^4 son cada uno -C(H)-, n es 1, A es imidazolilo, y X es -O-.

En otra realización, J^1-J^4 son cada uno -C(R^2)-, n es 1, A es imidazolilo, y X es -N(R^6)-.

En otra realización, J^1-J^4 son cada uno -C(R^2)-, n es 1, A es imidazolilo, y X es -S(O)$_p$-.

En otra realización, J^1-J^3 son cada uno -C(R^2)-, preferiblemente -CH-;

En otra realización, J^1 es -N-.

En otra realización, J^2 es -N-.

En otra realización, J^3 es -N-.

En otra realización, J^4 es -N-.

En otra realización, A es un anillo heterocíclico de 5 miembros que contiene por lo menos un anillo de nitrógeno.

En otra realización, A es un anillo heteroarilo, heterociclilo o heterociclenilo de 5 miembros que contiene por lo menos un anillo de nitrógeno.

En otra realización A es un anillo heteroarilo, heterociclenilo o heterociclilo de 5 miembros opcionalmente sustituido. Anillos heteroarilo, heterociclenilo o heterociclilo opcionalmente sustituidos de 5 miembros incluyen, por ejemplo, imidazol, tiazol, pirrol, isoxazol, oxazol, isotiazol, pirazol, imadazolina, imidazol-2-ona, imidazol-2-tiona, 2-aminoimidazolina, oxazolina, oxazol-2-ona, oxazol-2-tiona, 2-aminooxazolina, tiazolina, tiazol-2-ona, tiazol-2-tiona, 2-aminotiazolina, pirrolina, pirazolina, pirrolidina, imidazolidina, y pirazolidina. Un grupo más preferido de anillos de 5 miembros incluye: imidazol, imadazolina, imidazol-2-ona, imidazol-2-tiona, 2-aminoimidazolina, oxazolina, oxazol-2-ona, oxazol-2-tiona, y 2-aminooxazolina. Un grupo aún más preferido de anillos de 5 miembros incluye imidazol. Sustituyentes opcionalmente sustituidos incluyen cualquiera de los "sustituyentes del sistema de anillo" identificados a continuación.

En otra realización, R^2 está independientemente seleccionado de H, -OH, halo, -CN, $-NO_2$, $-(CH_2)_qYR^7$, $-(CH_2)_qN(R^7)YR^{7'}$, $-(CH_2)_qOYR^{7'}$, $-(CH_2)_qON=CR^7R^{7'}$, $-P(=O)(OR^7)(OR^{7'})$, $-P(=O)(NR^7R^{7'})_2$, $-P(=O)R^8{}_2$, alquilo, alcoxi y polihaloalcoxi.

En otra realización R^2 es $-(CH_2)_qYR^7$, $-(CH_2)_qN(R^7)YR^{7'}$ e Y es $-C(=O)-[C(R^a)(R^b)]_{n'}-O-C(=O)-$ o $-C(=O)N(R^c)-O-$.

En otra realización, J^3 es $-C(R^2)-$, R^2 es $-(CH_2)_qN(R^7)YR^{7'}$, q = 0, Y es -C(=O)-, $-C(=O)NR^7-$,o -C(=O)O-, y R^7 es Me o Et.

En otra realización, R^3 está independientemente seleccionado de grupos H, alquilo, alcoxi, alquenilo, alqueniloxi, alquinilo, cicloalquilo, cicloalcoxi, arilo, ariloxi, arilalquilo, heteroarilo, heteroarilalquilo, heterociclilo, y heterociclilalquilo, opcionalmente sustituidos con por lo menos un R^5.

En otra realización, R^3 está independientemente seleccionado de H, alquilo y haloalquilo.

En otra realización, R^4 está independientemente seleccionado de grupos H, alquilo, alcoxi, alquenilo, alqueniloxi, alquinilo, cicloalquilo, cicloalcoxi, arilo, ariloxi,

arilalquilo, heteroarilo, heteroarilalquilo, heterociclilo, y heterociclilalquilo opcionalmente sustituidos con por lo menos un R^5.

En otra realización, R^4 está independientemente seleccionado de H, alquilo, alilo, y haloalquilo.

En otra realización, R^4 está independientemente seleccionado de H y alquilo.

En otra realización, R^5 está independientemente seleccionado de H, halo, - $NR^7R^{7'}$, $-S(O)_pR^7$, alquilo, y alcoxi.

En otra realización, R^6 está independientemente seleccionado de H, alquilo, haloalquilo, cicloalquilo, $-C(=O)R^7$, $-C(=O)OR^7$, $-C(=O)NR^7R^{7'}$, $-SO_2R^7$ y $-SO_2NR^7R^{7'}$.

En otra realización, R^7 está independientemente elegido de H, alquilo, haloalquilo, cicloalquilo, arilo, y heteroarilo.

En otra realización, R^7 está independientemente seleccionado del grupo que consiste en H y grupos alquilo, alquenilo, alquinilo, cicloalquilo, cicloalquilalquilo, ciclociclenilo, ciclociclenilalquilo, arilo, arilalquilo, heterociclilo, heterociclilalquilo, heterociclenilo, heterociclenilalquilo, heteroarilo, y heteroarilalquilo, cada uno de los cuales está opcionalmente sustituido una o más veces (preferiblemente 1 a 5, más preferiblemente 1 a 3) con R^{12}.

En otra realización, $R^{7'}$ está independientemente elegido de H, alquilo, haloalquilo, cicloalquilo, arilo, y heteroarilo.

En otra realización, $R^{7'}$ está independientemente seleccionado del grupo que consiste en H y grupos alquilo, alquenilo, alquinilo, cicloalquilo, cicloalquilalquilo, ciclociclenilo, ciclociclenilalquilo, arilo, arilalquilo, heterociclilo, heterociclilalquilo, heterociclenilo, heterociclenilalquilo, heteroarilo, y heteroarilalquil, cada uno de los cuales está opcionalmente sustituido una o más veces (preferiblemente 1 a 5, más preferiblemente 1 a 3) con R^{12}.

En otra realización, R^7 y $R^{7'}$ conjuntamente con el átomo N al cual están unidos forman un anillo aziridina, azetidina, pirrol, pirrolidina, piperidina, piperazina o morfolina, cada uno de los cuales están opcionalmene sustituidos con R^5.

En otra realización, R^8 está independientemente elegido entre alquilo, haloalquilo, cicloalquilo, arilo, y heteroarilo.

En otra realización R^{12} es independientemente un grupo arilalcoxi, heteroarilalcoxi, heterociclilalcoxi, y heterociclenilalcoxi, cada uno de los cuales a su vez está opcionalmente sustituido con por lo menos una vez (preferiblemente 1 a 5, más preferiblemente 1 a 3) con un sustituyente seleccionado del grupo que consiste en H, alquilo, haloalquilo, halo, -OH, alcoxi opcionalmente sustituido, ariloxi opcionalmente sustituido, cicloalcoxi opcionalmente sustituido, heteroariloxi opcionalmente sustituido, heterocicleniloxi opcionalmente sustituido, -CN, $-NO_2$, $-N(R^{11})_2$, y $-S(O)_pR^{11}$, donde dichos alcoxi opcionalmente sustituido, ariloxi, cicloalcoxi opcionalmente sustituido, heteroariloxi opcionalmente sustituido, y heterocicleniloxi cuando están sustituidos lo están una o más (preferiblemente 1 a 5, más preferiblemente 1 a 3) veces con R^{11}.

En otra realización R^{12} está independientemente seleccionado del grupo que consiste en H, halo, -OH, -CN, $-NO_2$, $-N(R^{11})_2$, y $-S(O)_pR^{11}$, y grupos alquilo, alcoxi, alquenilo, alqueniloxi, alquinilo, cicloalquilo, cicloalquenilo, cicloalcoxi, arilo, ariloxi, arilalquilo, heteroarilo, heteroariloxi, heteroarilalquilo, heterociclilo, heterociclenilo, heterocicleniloxi, heterociclilalquilo, heterociclenilalquilo, cada uno de los cuales a su vez está opcionalmente sustituido con por lo menos una vez (preferiblemente 1 a 5, más preferiblemente 1 a 3) con un sustituyente seleccionado del grupo que consiste en H, alquilo, haloalquilo, halo, -OH, alcoxi opcionalmente sustituido, ariloxi opcionalmente sustituido, cicloalcoxi opcionalmente sustituido, heteroariloxi opcionalmente sustituido, heterocicleniloxi opcionalmente sustituido, -CN, $-NO_2$, $-N(R^{11})_2$, y $-S(O)_pR^{11}$, donde dichos alcoxi opcionalmente sustituido, ariloxi, cicloalcoxi opcionalmente sustituido, heteroariloxi opcionalmente sustituido, y heterocicleniloxi cuando están sustituidos lo están una o más (preferiblemente 1 a 5, más preferiblemente 1 a 3) veces con R^{11}.

En otra realización J^1, J^2 y J^4 son –CH-; X es –O- o –S-; m es 1 y n es 1 o 2.

En otra realización R^2 es $-(CH_2)_qYR^7$, o $-(CH_2)_qN(R^7)YR^{7'}$, Y es $-C(=O)-[C(R^a)(R^b)]_n-O-C(=O)-$, n es 1 o 2, y R^a y R^b son independientemente H o alquilo (preferiblemente metilo o etilo).

En otra realización, A es un imidazol opcionalmente sustituido;

R^2 es $-(CH)_qN(R^7)Y(R^{7'})$;

Y es -C(=O)O-, -(C=O)N(R^c)-O- o $-C(O)NR^7$; y

R^7 está independientemente seleccionado del grupo que consiste en H, alquilo, cicloalquilo, alquenilo, alquinilo, arilo, heteroarilo, arilalquilo, y heteroarilalquilo, están dichos grupos opcionalmente sustituidos una o más veces con un sustituyente independientemente seleccionado del grupo que consiste en H, alquilo, cicloalquilo, alcoxi, halo, -OH, -CN, $-NO_2$, $-N(R^{11})_2$, $-S(O)_pR^{11}$, arilo opcionalmente sustituido, ariloxi opcionalmente sustituido y heteroariloxi opcionalmente sustituido, dicho arilo opcionalmente sustituido, ariloxi opcionalmente sustituido y heteroariloxi opcionalmente sustituido cuando están sustituidos están independientemente sustituidos una o más veces con un sustituyente seleccionado del grupo que consiste en H, alquilo, cicloalquilo, alcoxi, halo, -OH, NO_2, $-N(R^{11})_2$ y $-S(O)_pR^{11}$.

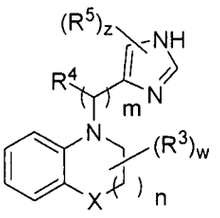
En otra realización, m es 1 o 2.

En otra realización, n es 1 o 2.

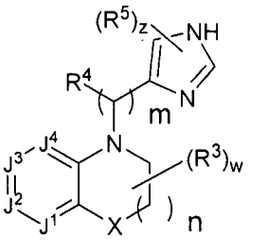
En otra realización, n es 1.

En otra realización, q es 0, 1, 2, o 3.

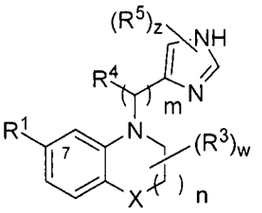
En otra realización, la presente invención describe compuestos que están representados por las fórmulas estructurales **II-V** o una sal, solvato o éster del mismo farmacéuticamente aceptable, donde los varios restos son tal como se describieron anteriormente:



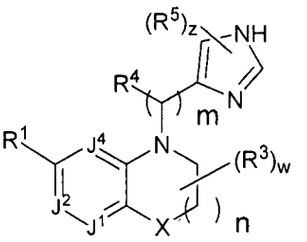
Formula **II**



Formula **III**



Formula **IV**



Formula **V**

donde z es 0-3 y R^1 está seleccionado del grupo que consiste en H, -OH, halo, -CN, $-NO_2$, ~~$-SR^7$~~ $-S(O)_pR^7$, $-(CH_2)_qYR^7$, $-(CH_2)_qN(R^7)YR^{7'}$, $-(CH_2)_qOYR^7$, $-(CH_2)_qON{=}C\ NR^7R^{7'}$, $-P(=O)(OR^7)(OR^{7'})$, $-P(=O)(NR^7R^{7'})_2$, $-P(=O)R^8{}_2$ y grupos alquilo, alcoxi, alquenilo, alqueniloxi, alquinilo, cicloalquilo, cicloalcoxi, arilo, ariloxi, arilalquilo, heteroarilo, heteroarilalquilo, heterociclilo, y heterociclilalquilo, opcionalmente sustituidos con por lo menos un R^5.

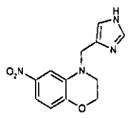
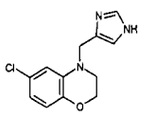
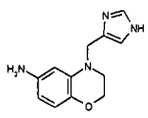
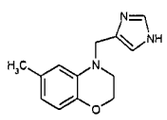
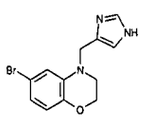
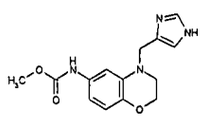
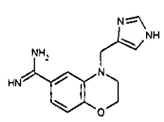
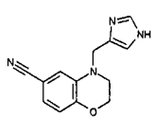
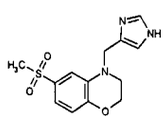
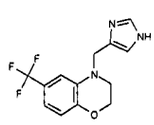
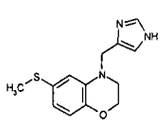
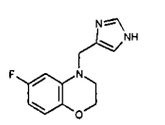
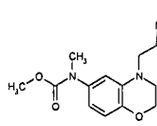
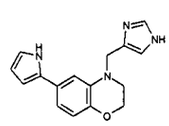
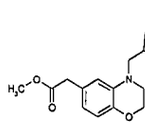
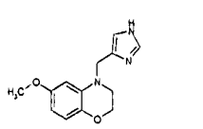
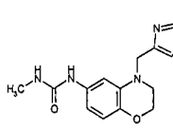
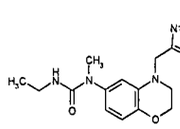
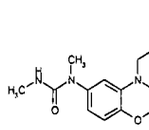
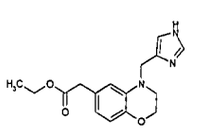
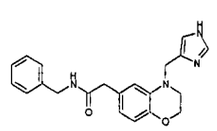
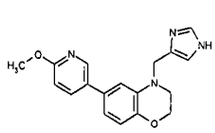
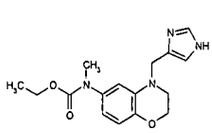
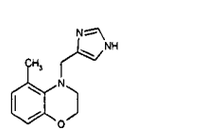
En otra realización en las fórmulas anteriores R^1 es $-(CH_2)_qYR^7$, o $-(CH_2)_qN(R^7)YR^{7'}$.

En otra realización en las fórmulas anteriores, Y es –(=O)O- o $-(C{=}O)NR^7$.

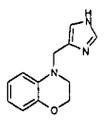
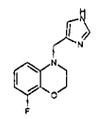
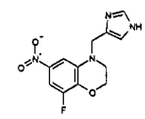
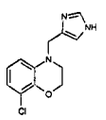
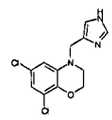
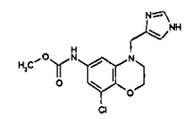
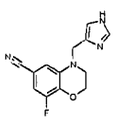
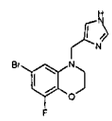
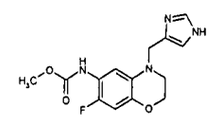
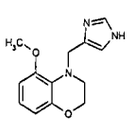
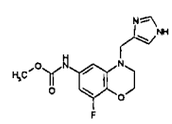
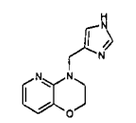
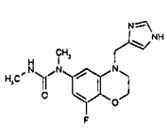
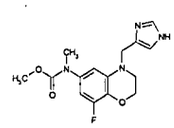
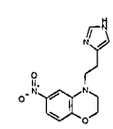
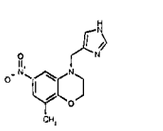
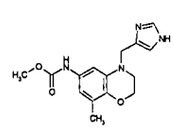
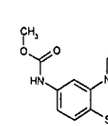
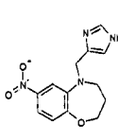
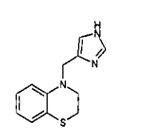
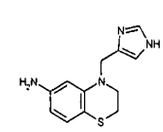
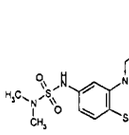
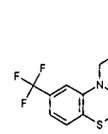
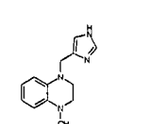
En otra realización en las fórmulas anteriores, Y es $-C(=O)-[C(R^a)(R^b)]_n-O-C(=O)-$.

En otra realización en las fórmulas anteriores R^1 es $-(CH_2)_qN(R^7)YR^{7'}$ e Y es $-C(=O)N(R^c)-O-$.

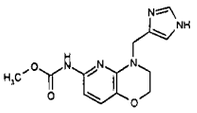
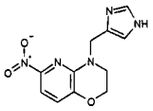
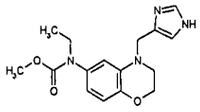
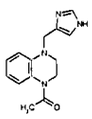
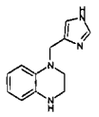
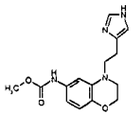
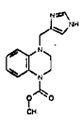
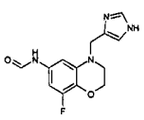
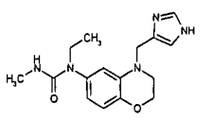
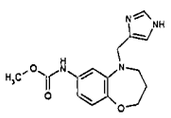
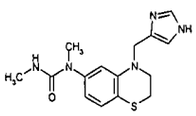
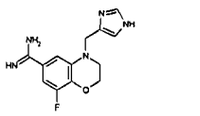
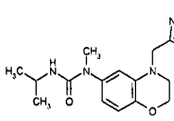
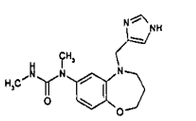
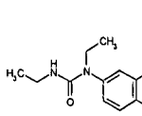
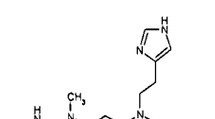
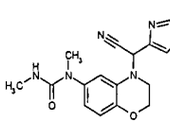
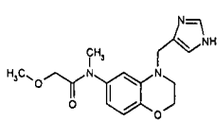
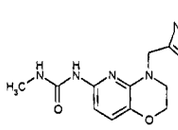
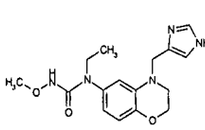
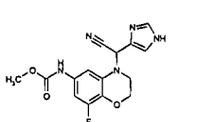
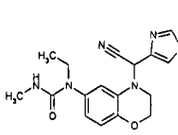
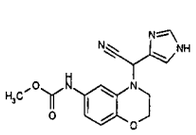
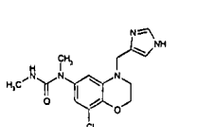
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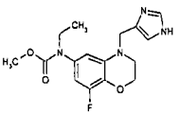
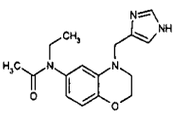
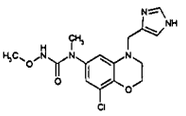
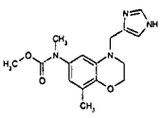
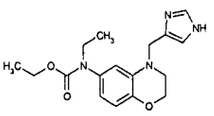
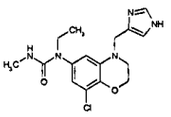
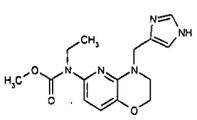
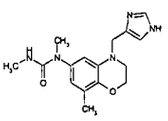
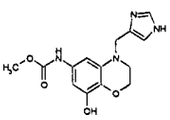
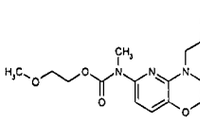
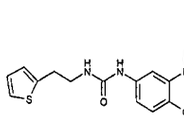
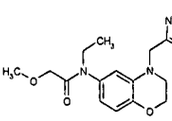
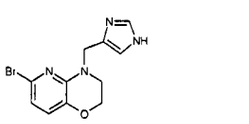
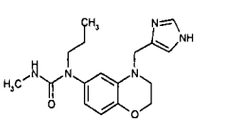
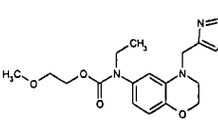
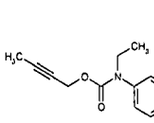
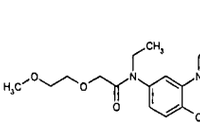
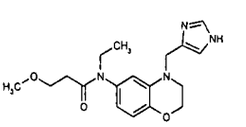
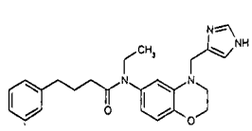
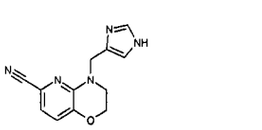
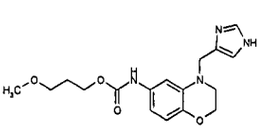
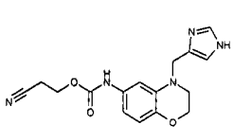
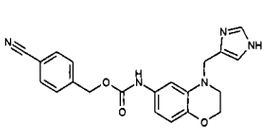
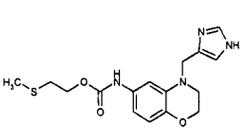

























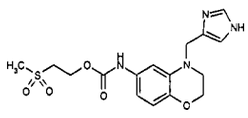
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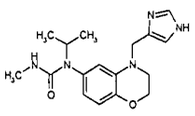
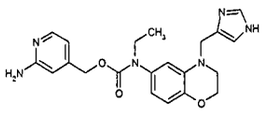
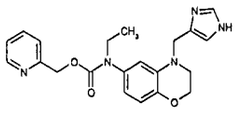
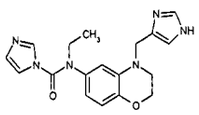
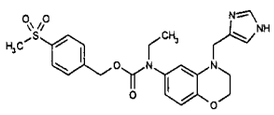
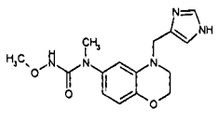
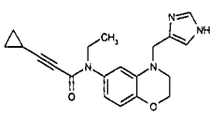
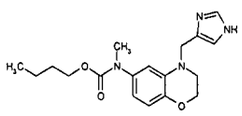
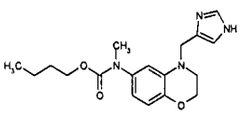
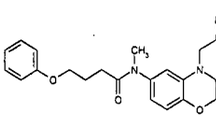
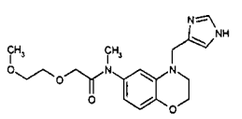
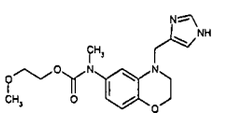
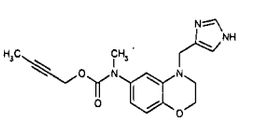
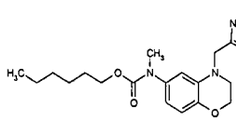
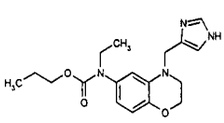
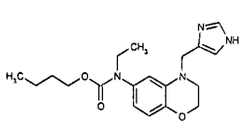
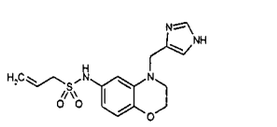
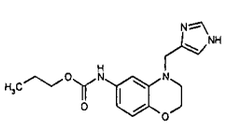
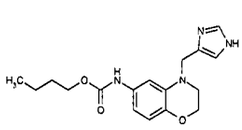
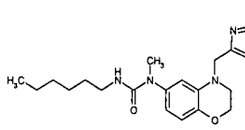
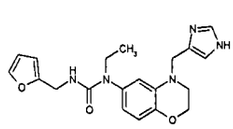

























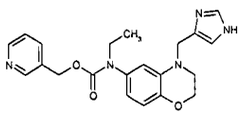
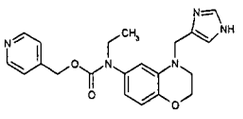
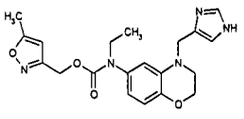
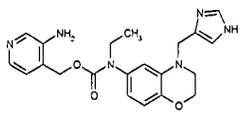
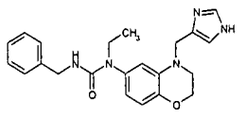
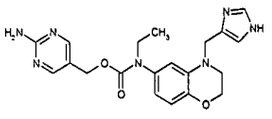
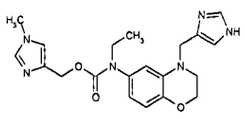
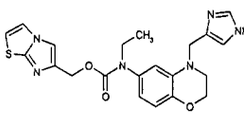
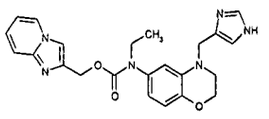



























Otro grupo de compuestos de la invención es el siguiente:

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Tal como se usó anteriormente y a través de esta descripción, los términos siguientes, a menos que se indique lo contrario, se interpretarán con los significados siguientes:

"Paciente" incluye tanto seres humanos como animales.

"Mamífero" significa seres humanos y otros animales mamíferos.

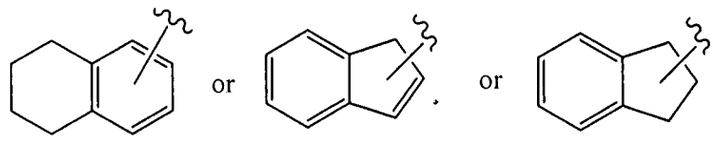
"Congestión" se refiere a todos los tipos de congestión incluyendo, pero sin limitarlo a congestión asociada con rinitis alérgica perenne, rinitis, rinitis alérgica estacional, rinitis no alérgica, rinitis vasomotora, rinitis medicamentosa, sinusitis, rinosinusitis aguda o rinosinusitis crónica o cuando la congestión es causada por pólipos, o es inducida viralmente, tal como congestión asociada con un resfrío común.

"Alquilo" significa un grupo hidrocarbonado alifático que puede ser de cadena recta o ramificada y que comprende aproximadamente 1 hasta aproximadamente 20 átomos de carbono en la cadena. Los grupos alquilo preferidos contienen aproximadamente 1 hasta aproximadamente 12 átomos de carbono en la cadena. Grupos alquilo más preferidos contienen aproximadamente 1 hasta aproximadamente 6 átomos de carbono en la cadena. Ramificado significa que uno o más grupos alquilo inferior, tales como metilo, etilo o propilo, están unidos a una cadena alquilo lineal. "Alquilo inferior" significa un grupo que tiene aproximadamente 1 hasta aproximadamente 6 átomos de carbono en la

cadena, la cual puede ser recta o ramificada. El término "alquilo sustituido" significa que el grupo alquilo puede estar sustituido con uno o mas sustituyentes que pueden ser iguales o diferentes, donde cada sustituyente está seleccionado independientemente del grupo que consiste en halo, alquilo, arilo, cicloalquilo, ciano, hidroxi, alcoxi, alquiltio, amino, -NH(alquilo), -NH(cicloalquilo), -$N(alquilo)_2$, carboxi y –C(O)O-alquilo. Ejemplos no limitativos de grupos alquilo apropiados incluyen metilo, etilo, n-propilo, isopropilo y t-butilo.

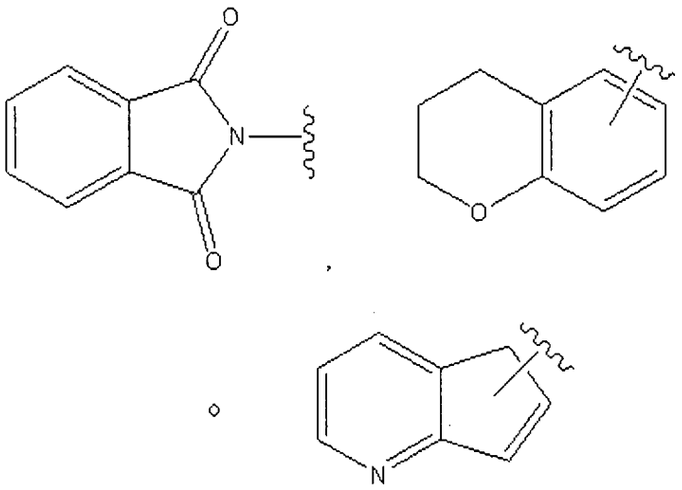
"Alquinilo" significa un grupo hidrocarbonado alifático que contiene por lo menos un enlace triple de carbono a carbono y que puede ser recto o ramificado y que comprende aproximadamente 2 hasta aproximadamente 15 átomos de carbono en la cadena. Los grupos alquinilo preferidos tienen aproximadamente 2 hasta aproximadamente 12 átomos de carbono en la cadena; y más preferiblemente aproximadamente 2 hasta aproximadamente 4 átomos de carbono en la cadena. Ramificado significa que uno o más grupos alquilo inferior tales como metilo, etilo o propilo, están unidos a una cadena alquinilo lineal. "Alquinilo inferior" significa aproximadamente 2 hasta aproximadamente 6 átomos de carbono en la cadena, la cual puede ser recta o ramificada. Ejemplos no limitativos de grupos alquinilo apropiados incluyen etinilo, propinilo, 2-butinilo y 3-metilbutinilo. El término "alquinilo sustituido" significa que el grupo alquinilo puede estar sustituido con uno o más sustituyentes que pueden ser iguales o diferentes, donde cada sustituyente está independientemente seleccionado del grupo que consiste en alquilo, arilo y cicloalquilo.

"Arilo" significa un sistema de anillo aromático monocíclico o multicíclico, en el cual por lo menos uno de los anillos multicíclicos es un anillo arilo, que comprende desde aproximadamente 6 hasta aproximadamente 14 átomos de carbono, preferiblemente aproximadamente 6 hasta aproximadamente 10 átomos de carbono. El grupo arilo puede estar sustituido opcionalmente con uno o más "sustituyentes del sistema de anillo" que pueden ser iguales o diferentes y que son tal como se definen aquí. Ejemplos no limitativos de grupos arilo apropiados incluyen fenilo y naftilo. Ejemplos no limitativos de sistemas de anillo multicíclicos de arilo incluyen:



"Heteroarilo" significa un sistema de anillo monocíclico o multicíclico, aromático en el cual por lo menos uno de los anillos multicíclicos es aromático, que comprende aproximadamente 5 hasta aproximadamente 14 átomos en el anillo, preferiblemente aproximadamente 5 hasta aproximadamente 10 átomos en el anillo, en el cual uno o más de los átomos del anillo son un elemento distinto del carbono, por ejemplo nitrógeno, oxígeno o azufre, solo o en combinación. Los heteroarilos preferidos contienen aproximadamente 5 hasta aproximadamente 6 átomos en el anillo. El "heteroarilo" puede estar opcionalmente sustituido con uno o más "sustituyentes del sistema de anillo" que pueden ser iguales o diferentes y son tal como se definen aquí. El prefijo aza, oxa o tia antes del nombre de raíz heteroarilo significa que por lo menos un átomo de nitrógeno, oxígeno o azufre respectivamente, está presente como un átomo del anillo. Un átomo de nitrógeno de un heteroarilo puede estar opcionalmente oxidado al N-óxido correspondiente. Ejemplos no limitativos de heteroarilos apropiados incluyen piridilo, piracinilo, furanilo, tienilo, pirimidinilo, isoxazolilo, isotiazolilo, oxazolilo, tiazolilo, pirazolilo, furazanilo, pirrolilo, pirazolilo, triazolilo, 1,2,4-tiadiazolilo, piracinilo, piridacinilo, quinoxalinilo, ftalacinilo, imidazo[1,2-a]piridinilo, imidazo[2,1-b]tiazolilo, benzofurazanilo, indolilo, azaindolilo, benzimidazolilo, benzotienilo, quinolinilo, imidazolilo, tienopiridilo, quinazolinilo, tienopirimidilo, pirrolopiridilo, imidazopiridilo, isoquinolinilo, benzoazaindolilo, 1,2,4-triacinilo, benzotiazolilo y similares.

Ejemplos no limitativos de sistemas de anillo multicíclicos de heteroarilo incluyen:



"Aralquilo" o "arilalquilo" significa un grupo aril-alquilo en el cual el arilo y el alquilo son tal como se han descrito previamente. Los aralquilos preferidos comprenden un grupo alquilo inferior. Ejemplos no limitativos de grupos aralquilo apropiados incluyen bencilo, 2-fenetilo y naftalenilmetilo. El enlace con el resto principal es a través del alquilo.

"Alquilarilo" significa un grupo alquil-arilo en el cual el alquilo y el arilo son tal como se han descrito previamente. Alquilarilos preferidos comprenden un grupo alquilo inferior. Un ejemplo no limitativo de un grupo alquilarilo apropiado es tolilo. El enlace con el resto principal es a través del arilo.

"Cicloalquilo" significa un sistema de anillo mono- o multicíclico no aromático que comprende aproximadamente 3 hasta aproximadamente10 átomos de carbono, preferiblemente aproximadamente 5 hasta aproximadamente 10 átomos de carbono. Los anillos cicloalquilo preferidos contienen aproximadamente 5 hasta aproximadamente 7 átomos en el anillo. El cicloalquilo puede estar opcionalmente sustituido con uno o más "sustituyentes del sistema de anillo" que pueden ser iguales o diferentes, y son tal como se han definido previamente. Ejemplos no limitativos de cicloalquilos monocíclicos apropiados incluyen ciclopropilo, ciclopentilo, ciclohexilo, cicloheptilo y similares. Ejemplos no limitativos de cicloalquilos multicíclicos apropiados incluyen 1-decalinilo, norbornilo, adamantilo y similares.

"Halógeno" y "Halo" significan fluor, cloro, bromo, o yodo. Se prefiere fluor, cloro o bromo, y los más preferidos son fluor y cloro.

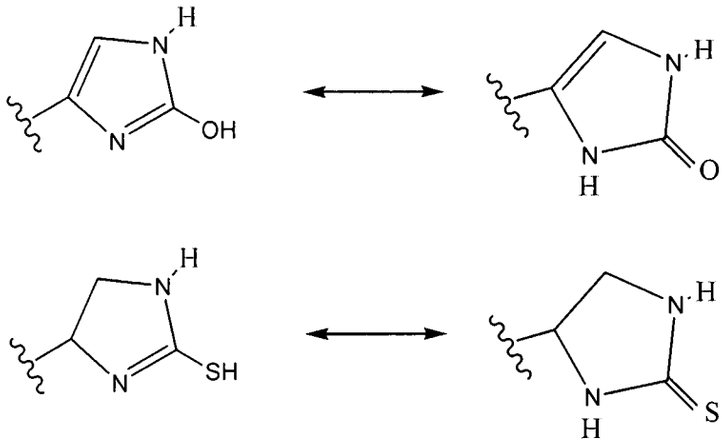
"Sustituyente del sistema de anillo" significa un sustituyente unido a un sistema de anillo aromático o no aromático el cual, por ejemplo, reemplaza un hidrógeno disponible en el sistema de anillo. Los sustituyentes del sistema de anillo puede ser iguales o diferentes y cada uno está independientemente seleccionado del grupo que consiste en arilo, heteroarilo, aralquilo, alquilarilo, heteroaralquilo, alquilheteroarilo, hidroxi, hidroxialquilo, alcoxi, ariloxi, aralcoxi, acilo, aroilo, halo, nitro, ciano, carboxi, alcoxicarbonilo, ariloxicarbonilo, aralcoxicarbonilo, alquilsulfonilo, arilsulfonilo, heteroarilsulfonilo, alquiltio, ariltio, heteroariltio, aralquiltio, heteroaralquiltio, cicloalquilo, heterociclilo, Y_1Y_2N-, Y_1Y_2N-alquilo-, $Y_1Y_2NC(O)$- y $Y_1Y_2NSO_2$-, donde Y_1 e Y_2 pueden ser iguales o diferentes y están seleccionados independientemente del grupo que consiste en hidrógeno, alquilo, arilo y aralquilo.

"Heterociclilo" significa un sistema de anillo monocíclico o multicíclico no aromático que comprende aproximadamente 3 hasta aproximadamente 10 átomos en el anillo, preferiblemente aproximadamente 5 hasta aproximadamente10 átomos en el anillo, en el cual uno o más de los átomos en el sistema de anillo son un elemento distinto de carbono, por ejemplo nitrógeno, oxígeno o azufre, solos o en combinación. No hay átomos de oxígeno y/o azufre adyacentes presentes en el sistema de anillo. Los heterociclilos preferidos contienen aproximadamente 5 hasta aproximadamente 6 átomos en el anillo. El prefijo aza, oxa o tia antes del nombre de raíz heterociclilo significa que por lo menos un átomo de nitrógeno, oxígeno o azufre respectivamente están presentes como átomo del anillo. Cualquier –NH en un anillo heterociclilo puede existir, protegido, tal como, por ejemplo, un grupo -N(Boc), -N(CBz), -N(Tos) y similares; dichos restos protegidos se consideran también parte de esta invención. El heterociclilo puede estar opcionalmente sustituido con uno o más "sustituyentes del sistema de anillo" que pueden ser iguales o diferentes, y son tal como se definen aquí. El átomo de de nitrógeno o azufre del heterociclilo puede ser opcionalmente oxidado al N-óxido, S- óxido o S,S-dióxido. Ejemplos no limitativos de anillos heterociclilo monocíclicos incluyen, piperidilo, pirrolidinilo, piperacinilo,

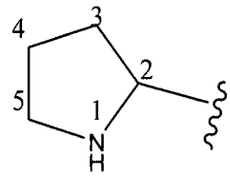
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morfolinilo, tiomorfolinilo, tiazolidinilo, 1,4-dioxanilo, tetrahidrofuranilo, tetrahidrotiofenilo, y similares.

Los compuestos de Fórmula I y sales, ésteres, solvatos y prodrogas de éstos, pueden existir en su forma tautomérica (por ejemplo, como una amida o imino éter). Todas dichas formas tautoméricas están contempladas aquí como parte de la presente invención. Ejemplos no limitativos de formas tautoméricas que son parte de esta invención son los siguientes:

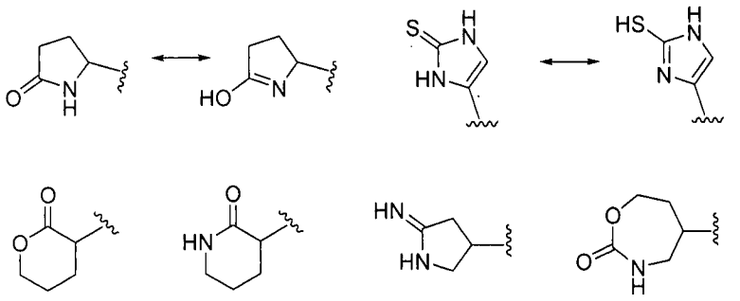


Cabe observar que en los sistemas que contienen heterociclilo saturado, de esta invención, no hay grupos hidroxilo, amino, o tiol en los átomos de carbono adyacentes a un átomo de N, O o S. Por lo tanto, por ejemplo, en el anillo:

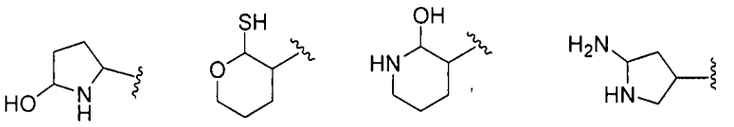


no hay ningún –OH unido directamente a los carbonos marcados con 2 y 5. Cabe observar también que esta definición no excluye las sustituciones (=O), (=S), o (=N), o sus formas tautoméricas en los átomos de C adyacentes a N, O u S. Por lo tanto, por ejemplo, en el anillo anterior, la sustitución (=O) en el carbono 5, o su tautómero imino éter está permitida.

Ejemplos no limitativos que ilustran la presente invención son los siguientes:



Los ejemplos no limitativos siguientes sirven para ilustrar radicales no contemplados por la presente invención:



"Alquinilalquilo" significa un grupo alquinil-alquilo- en el cual el alquinilo y el alquilo son tal como se han descrito previamente. Los alquinil alquilos preferidos contienen un grupo alquinilo inferior y un grupo alquilo inferior. El enlace con el resto principal es a través del alquilo. Ejemplos no limitativos de grupos alquinil alquilo apropiados incluyen propargil metilo.

"Heteroaralquilo" o "heteroarilalquilo" significa un grupo heteroaril-alquilo- en el cual el heteroarilo y el alquilo son tal como se han descrito previamente. Los heteroaralquilos preferidos contienen un grupo alquilo inferior. Ejemplos no limitativos de grupos aralquilo apropiados incluyen piridilmetilo, y quinolin-3-ilmetilo. El enlace con el resto principal es a través del alquilo.

"Heterociclilalquilo" significa un grupo heterociclil-alquilo en el cual el heterociclilo y el alquilo son tal como se han descrito previamente. Los heterociclilalquilos preferidos contienen un grupo alquilo inferior. Ejemplos no limitativos de grupos heterociclilalquilo apropiados incluyen piperidilmetilo, piperidiletilo, pirrolidilmetilo, morfolinilpropilo, piperaciniletilo, acindilmetilo,

acetidiletilo, oxiranilpropilo y similares. El enlace con el resto principal es a través del grupo alquilo.

"Heterociclenilo" (o "heterocicloalquenilo") significa un sistema de anillo monocíclico o multicíclico no aromático que comprende aproximadamente 3 hasta aproximadamente 10 átomos en el anillo, preferiblemente aproximadamente 5 hasta aproximadamente 10 átomos en el anillo, donde uno o más de los átomos en el sistema de anillo son un elemento distinto del carbono, por ejemplo un átomo de nitrógeno, oxígeno o azufre, solo o en combinación, y que contiene por lo menos un enlace doble de carbono a carbono, o un enlace doble de carbono a nitrógeno. No hay átomos adyacentes de oxígeno y/o azufre presentes en el sistema de anillo. Los anillos heterociclenilo preferidos contienen aproximadamente 5 hasta aproximadamente 6 átomos en el anillo. El prefijo aza, oxa o tia antes del nombre de raíz heterociclenilo significa que por lo menos un átomo de nitrógeno, oxigeno o azufre respectivamente, está presente como átomo del anillo. El heterociclenilo puede estar opcionalmente sustituido con uno o más sustituyentes del sistema de anillo, donde "sustituyente del sistema de anillo" es tal como se ha definido previamente. El átomo de nitrógeno o azufre del heterociclenilo puede estar opcionalmente oxidado al N-óxido, S-óxido o S,S-dióxido correspondiente. Ejemplos no limitativos de grupos aza heterociclenilo monocíclicos apropiados incluyen 1,2,3,4- tetrahidropiridilo, 1,2-dihidropiridilo, 1,4-dihidropiridilo, 1,2,3,6-tetrahidropiridilo, 1,4,5,6-tetrahidropirimidilo, 2-pirrolinilo, 3-pirrolinilo, 2-imidazolinilo, 2-pirazolinilo, 2-oxazolinilo, 2-tiazolinilo y similares. Ejemplos no limitativos de grupos oxa heterociclenilo apropiados incluyen 3,4-dihidro-2H-pirano, dihidrofuranilo, fluordihidrofuranilo, y similares. Un ejemplo no limitativo de un grupo oxa heterociclenilo multicíclico apropiado es 7-oxabiciclo[2.2.1]heptenilo. Ejemplos no limitativos de anillos tiaheterociclenilo apropiados incluyen dihidrotiofenilo, dihidrotiopiranilo y similares.

"Hidroxialquilo" significa un grupo HO-alquilo- en el cual el alquilo es tal como se ha definido previamente. Los hidroxialquilos preferidos contienen alquilo inferior. Ejemplos no limitativos de grupos hidroxialquilo apropiados incluyen hidroximetilo y 2-hidroxietilo.

"Heterociclenilalquilo" significa un grupo heterociclenil- alquilo en el cual el heterociclenilo y el alquilo son tal como se han descrito previamente.

"Acilo" significa un grupo de ácido orgánico en el cual el -OH del grupo carboxilo es reemplazado con cualquier otro sustituyente. Ejemplos no limitativos apropiados incluyen grupos H-C(O)-, alquilo-C(O)-, cicloalquilo-C(O)-, heterociclilo-C(O)-, y heteroarilo-C(O)- donde los varios grupos son tal como los descritos previamente. El enlace con el resto principal es a través del carbonilo. Los acilos preferidos contienen un alquilo inferior. Ejemplos no limitativos de grupos acilo apropiados incluyen formilo, acetilo y propanoilo.

"Aroilo" significa un grupo aril-C(O)- en el cual el grupo arilo es tal como se ha descrito previamente. El enlace con el resto principal es a través del carbonilo. Ejemplos no limitativos de grupos apropiados incluyen benzoilo y 1-naftoilo.

"Alcoxi" significa un grupo alquilo-O- en el cual el grupo alquilo es tal como se ha descrito previamente. Ejemplos no limitativos de grupos alcoxi apropiados incluyen metoxi, etoxi, n-propoxi, isopropoxi y n-butoxi. El enlace con el resto principal es a través del oxígeno del éter.

"Ariloxi" significa un grupo aril-O- en el cual el grupo arilo es tal como se ha descrito previamente. Ejemplos no limitativos de grupos ariloxi incluyen fenoxi y naftoxi. El enlace con el resto principal es a través del oxígeno del éter.

"Aralquiloxi" o "arilalquiloxi" significa un grupo aralquil-O- en el cual el grupo aralquilo es tal como se ha descrito previamente. Ejemplos no limitativos de grupos aralquiloxi apropiados incluyen benciloxi y 1- o 2-naftalenmetoxi. El enlace con el resto principal es a través del oxígeno del éter.

"Heteroarilalcoxi" significa un grupo heteroarilalquil-O- en el cual el grupo heteroarilalquilo es tal como se ha descrito previamente.

"Heterociclilalcoxi" significa un grupo heterocicliloalquil-O en el cual el grupo heterocililalquilo es tal como se ha descrito previamente.

"Heterociclenilalcoxi" significa un grupo heterociclenilalquil-O en el cual el grupo heterociclenilalquilo es tal como se ha descrito previamente.

"Alquiltio" significa un grupo alquil-S- en el cual el grupo alquilo es tal como se ha descrito previamente. Ejemplos no limitativos de grupos alquiltio apropiados incluyen metiltio y etiltio. El enlace con el resto principal es a través del azufre.

"Ariltio" significa un grupo aril-S- en el cual el grupo arilo es tal como se ha descrito previamente. Ejemplos no limitativos de grupos ariltio incluyen feniltio y naftiltio. El enlace con el resto principal es a través del azufre.

"Aralquiltio" significa un grupo aralquil-S- en el cual el grupo aralquilo es tal como se ha descrito previamente. Un ejemplo no limitativo de un grupo aralquiltio apropiado es benciltio. El enlace con el resto principal es a través del azufre.

"Alcoxicarbonilo" significa un grupo alquil-O-CO-. Ejemplos no limitativos de grupos alcoxicarbonilo incluyen metoxicarbonilo y etoxicarbonilo. El enlace con el resto principal es a través del carbonilo.

"Ariloxicarbonilo" significa un grupo aril-O-C(O)-. Ejemplos no limitativos de grupos ariloxicarbonilo apropiados, incluyen fenoxicarbonilo y naftoxicarbonilo. El enlace con el resto principal es a través del carbonilo.

"Aralcoxicarbonilo" significa un grupo aralquil-O-C(O)-. Un ejemplo no limitativo de un grupo aralcoxicarbonilo es benciloxicarbonilo. El enlace con el resto principal es a través del carbonilo.

"Alquilsulfonilo" significa un grupo alquil-$S(O_2)$-. Son grupos preferidos aquellos en los cuales el grupo alquilo es alquilo inferior. El enlace con el resto principal es a través del sulfonilo.

"Arilsulfonilo" significa un grupo aril-$S(O_2)$-. El enlace con el resto principal es a través del sulfonilo.

El término "sustituido" significa que uno o más hidrógenos en el átomo designado son reemplazados con una selección del grupo indicado, con la condición de no exceder la valencia normal del átomo designado bajo las circunstancias existentes, y que la sustitución dé como resultado un compuesto. estable. Únicamente se permiten combinaciones de sustituyentes y/ o variables, si dichas combinaciones dan como resultado compuestos estables. Mediante "compuesto estable" o estructura estable" se hace referencia a un compuesto que es suficientemente robusto para sobrevivir a la aislación hasta un grado útil de pureza desde su mezcla de reacción, y puede ser formulado como un agente terapéutico eficaz.

Cabe observar que los carbonos de la fórmula I pueden ser reemplazados con 1-3 átomos de silicio, con la condición de satisfacer todos los requisitos de la valencia.

El término "opcionalmente sustituido" significa sustitución opcional con los grupos, radicales o restos especificados.

Cabe observar que se asume que cualquier heteroátomo con valencias no satisfechas en el texto, esquemas, ejemplos y Tablas que se dan aquí, tiene el átomo de hidrógeno para satisfacer las valencias.

Cuando un grupo funcional en un compuesto se denomina "protegido", significa que el grupo está en forma modificada para evitar reacciones secundarias indeseables en el sitio protegido cuando un compuesto es sometido a una reacción. Los grupos protectores apropiados serán reconocidos por los expertos en la materia, así como también con referencia a los libros de texto convencionales tales como por ejemplo T. W. Greene *et al*, *Protective Groups in organic Synthesis* (1991), Wiley, New York.

Cuando ocurre cualquier variable (por ejemplo, arilo, heterociclo, R^2, etc.) más de una vez en cualquier constituyente de la fórmula, su definición cada vez que ocurre es independiente de su definición cada vez que vuelve a ocurrir.

A menos que se defina de otra manera, todas las definiciones para las variables siguen la convención de que el grupo a la derecha forma el punto de unión a la molécula; es decir, si una definición es arilalquilo, esto significa que el resto alquilo de la definición está unido a la molécula.

Además, todas las variables divalentes están unidas de izquierda a derecha. Por ejemplo, cuando R^2 es $-(CH_2)_qN(R^7)YR^{7'}$, e Y es $-C(=O)-[C(R^a)(R^b)]_n-O-C(=O)-$, entonces R^2 forma el grupo $-(CH_2)_qN(R^7)-C(=O)-[C(R^a)(R^b)]_n-O-C(=O)-R^{7'}$.

Tal como se usa aquí, el término "composición abarca un producto que comprende los ingredientes especificados en las cantidades especificadas, así como también cualquier producto que es el resultado, directo o indirecto, de la combinación de los ingredientes especificados en las cantidades especificadas.

También se contemplan aquí las prodrogas y solvatos de los compuestos de la invención. El término "prodroga", tal como se emplea aquí, denota un

compuesto que es un precursor de una droga, que, por administración a un sujeto, sufre conversión química causada por procesos metabólicos o químicos para proporcionar un compuesto de fórmula I o una sal y/o solvato de éste. Una discusión de prodrogas está provista en T. Higuchi y V. Stella, *Pro-drugs as Novel Delivery Systems* (1987) Volumen 14 de A.C.S. Symposium Series, y en *Bioreversible Carriers in Drug Design,* (1987) Edward B. Roche, ed., American Pharmaceutical Association and Pergamon Press, los cuales se incorporan aquí como referencia a los mismos.

Por ejemplo, si un compuesto de Fórmula (I) o una sal, hidrato o solvato farmacéuticamente aceptable del compuesto contiene un grupo funcional de ácido carboxílico, una prodroga puede comprender un éster formado por el reemplazo del átomo de hidrógeno del grupo ácido con un grupo tal como por ejemplo alquilo C_1–C_8, alcanoiloximetilo C_2-C_{12}, 1-(alcanoiloxi) etilo que tiene de 4 a 9 átomos de carbono, 1-metil-1-(alcanoiloxi)-etilo que tiene de 5 a 10 átomos de carbono, alcoxi carboniloximetilo que tiene de 3 a 6 átomos de carbono, 1-(alcoxicarboniloxi) etilo que tiene de 4 a 7 átomos de carbono, 1-metil-1-(alcoxi carboniloxi) etilo que tiene de 5 a 8 átomos de carbono, N-(alcoxicarbonil) aminometilo que tiene de 3 a 9 átomos de carbono, 1-(N-(alcoxicarbonilo)amino)etilo que tiene de 4 a 10 átomos de carbono, 3-ftalidilo, 4-crotonolactonilo, gamma-butirolacton-4-ilo, di-N,N-(C_1-C_2)alquilamino alquilo C_2-C_3 (tal como β-dimetilaminoetilo), carbamoil- alquilo C_1-C_2, N,N-di alquilcarbamoilo C_1-C_2 –alquilo C_1-C_2 y piperidino-, pirrolidino- o morfolino alquilo C_2-C_3 y similares.

De manera similar, si un compuesto de Fórmula (I) contiene un grupo funcional alcohol puede formarse una prodroga por reemplazo del átomo de hidrógeno del grupo alcohol con un grupo tal como, por ejemplo, alcanoiloximetilo C_1-C_6, 1-(alcanoiloxi C_1-C_6) etilo, 1-metil-1-(alcanoiloxi C_1-C_6) etilo, alcoxi carboniloximetilo C_1-C_6, N-alcoxicarbonilaminometilo C_1-C_6, succinoilo, alcanoilo C_1-C_6, α-amino alcanilo C_1-C_4, arilacilo y α-aminoacilo, o α-aminoacil-α-aminoacilo, donde cada grupo α-aminoacilo está seleccionado independientemente del grupo de L-amino ácidos naturales, -P(O)$(OH)_2$, -P(O)(O alquilo C_1-$C_6)_2$ o glicosilo (el radical resultante de la remoción de un grupo hidroxilo de la forma hemiacetal de un carbohidrato), y similares.

Si un compuesto de Fórmula I incorpora un grupo funcional -NH-, tal como en una amina primaria o secundaria o en un heterociclo que contiene nitrógeno, tal como un anillo imidazol o piperacina, puede formarse una prodroga por el reemplazo de un átomo de hidrógeno en el grupo amino con un grupo tal como por ejemplo, R-carbonilo, RO- carbonilo, NRR'-carbonilo donde R y R' son cada uno independientemente alquilo C_1-C_{10}, cicloalquilo C_3-C_7, bencilo, o R-carbonilo es un α-aminoacilo natural o α-aminoacilo natural, -C(OH)C(O)OY^1 donde Y^1 es H, alquilo C_1-C_6 o bencilo, -$C(OY^2)Y^3$ donde Y^2 es alquilo C_1-C_4 e Y^3 es alquilo C_1-C_6, carboxi alquilo C_1-C_6, amino alquilo C_1-C_4 o mono-N- o di-N,N-alquilaminoalquilo C_1-C_6, -$C(Y^4)Y^5$ donde Y^4 es H o metilo e Y^5 es mono-N- o di-N,N- alquilamino C_1-C_6 morfolino, piperidin-1-ilo o pirrolidin-1-ilo, y similares.

"Cantidad eficaz" o "cantidad terapéuticamente eficaz" tiene el significado de una cantidad de un compuesto o una composición de la presente invención, que es eficaz para producir el efecto terapéutico, mejorador inhibidor o preventivo deseado.

"Cápsula" tiene el significado de un recipiente especial o un receptáculo de metil celulosa, de alcoholes de polivinilo, o gelatinas desnaturalizadas o almidón, destinado a contener composiciones que comprenden ingredientes activos. Las cápsulas de cáscara dura están típicamente hechas con mezclas de gelatinas de hueso y piel de cerdo de un gel de resistencia relativamente alta. La cápsula misma puede contener pequeñas cantidades de colorantes, agentes opacantes, plastificantes y preservadores.

"Tableta" tiene el significado de una forma de dosificación sólida comprimida o moldeada que contiene los ingredientes activos con diluyentes apropiados. La tableta puede prepararse por compresión de mezclas o granulados obtenidos por granulación en húmedo, granulación en seco o por compactación.

"Geles orales" se refiere a los ingredientes activos dispersados o solubilizados en una matriz hidrofílica semi-sólida.

"Polvos para reconstitución" se refiere a mezclas en polvo que contienen los ingredientes activos y diluyentes apropiados que pueden suspenderse en agua o jugos.

"Diluyente" se refiere a sustancias que usualmente constituyen el resto principal de la composición o forma de dosificación. Diluyentes apropiados incluyen azúcares tales como lactosa, sucrosa, mannitol y sorbitol; almidones derivados de trigo, maíz, arroz y patata; y celulosas tales como celulosa microcristalina. La cantidad de diluyente en la composición puede estar en un rango de desde aproximadamente 10 hasta aproximadamente 90% en peso de la composición total, preferiblemente desde aproximadamente 25 hasta aproximadamente 75%, más preferiblemente desde aproximadamente 30 hasta aproximadamente 60% en peso, aún más preferiblemente desde aproximadamente 12 hasta aproximadamente 60%.

"Desintegrantes" se refiere a materiales agregados a la composición para ayudar a separar (desintegrar) y liberar los medicamentos. Desintegrantes apropiados incluyen almidones; almidones modificados "solubles en agua fría" tales como almidón de carboximetilo de sodio; gomas naturales y sintéticas tales como de semilla de algarrobo, karaya, guar, tragacanto y agar; derivados de celulosa tales como metilcelulosa y carboximetilcelulosa de sodio; celulosas microcristalinas y celulosas microcristalinas entrecruzadas tales como croscarmelosa de sodio; alginatos tales como ácido algínico y alginato de sodio; arcillas tales como bentonitas; y mezclas efervescentes. La cantidad de desintegrante en la composición puede estar en un rango de desde aproximadamente 2 hasta aproximadamente 15% en peso de la composición, más preferiblemente desde aproximadamente 4 hasta aproximadamente 10% en peso.

"Aglutinantes" se refiere a sustancias que se adhieren o "pegan" polvos entre sí, y los convierten en cohesivos formando gránulos, los cuales sirven como "adhesivos" en la formulación. Los aglutinantes agregan resistencia cohesiva ya disponible en el diluyente o agente dador de volumen. Aglutinantes apropiados incluyen azúcares tales como sucrosa; almidones derivados de trigo, maíz, arroz y patata; gomas naturales tales como goma acacia, gelatina, tragacanto; derivados de algas tales como ácido algínico, alginato de sodio y alginato de calcio y amonio; materiales celulósicos tales como metilcelulosa y carboxi metilcelulosa de sodio e hidroxi propil metilcelulosas; polivinilpirrolidona; e inorgánicos tales como

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silicato de magnesio aluminio. La cantidad de aglutinante en la composición puede estar en un rango de desde aproximadamente 2 hasta aproximadamente 20% en peso de la composición, más preferiblemente desde aproximadamente 3 hasta aproximadamente 10% en peso, aún más preferiblemente desde aproximadamente 3 hasta aproximadamente 6% en peso.

"Lubricante" tiene el significado de una sustancia agregada a la forma de dosificación para permitir que la tableta, gránulos etc. después de haber sido comprimidos, se liberen desde el molde o matriz, por reducción, por fricción o desgaste. Entre los lubricantes apropiados se incluyen estearatos metálicos tales como estearato de magnesio, estearato de calcio o estearato de potasio; ácido esteárico; ceras de alto punto de fusión; y lubricantes solubles en agua tales como cloruro de sodio, benzoato de sodio, acetato de sodio, oleato de sodio, polietilen glicoles y d'l-leucina. Los lubricantes se agregan usualmente en la última etapa antes de la compresión, debido a que deben estar presentes en las superficies de los gránulos y entre los mismos y las partes de la prensa- tabletas. La cantidad de lubricante en la composición puede estar en un rango de desde aproximadamente 0,2 hasta aproximadamente 5% en peso de la composición, preferiblemente desde aproximadamente 0,5 hasta aproximadamente 2%, más preferiblemente desde aproximadamente 0,3 hasta aproximadamente 1,5% en peso.

"Deslizantes" se refiere a materiales que evitan el aterronamiento y mejoran las características de fluidez de las granulaciones, de manera que el flujo sea liso y uniforme. Deslizantes apropiados incluyen dióxido de silicio y talco. La cantidad de deslizante en la composición está en un rango de desde aproximadamente 0,1% hasta aproximadamente 5% en peso de la composición total, preferiblemente desde 0,5 hasta aproximadamente 2% en peso.

"Agentes colorantes" se refiere a excipientes que proveen coloración para la composición o forma de dosificación. Dichos excipientes pueden incluir colorantes de calidad comestible y colorantes de calidad comestible adsorbidos sobre un adsorbente apropiado tales como arcilla u óxido de aluminio. La cantidad de agente colorante puede variar desde aproximadamente 0,1 hasta aproximadamente 5% en peso de la composición, preferiblemente desde aproximadamente 0,1 hasta aproximadamente 1%.

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"Biodisponibilidad" se refiere al régimen y grado hasta el cual el ingrediente farmacológico activo o resto terapéutico es absorbido dentro de la circulación sistémica desde una forma de dosificación administrada, en comparación con un modelo o control. Se conocen métodos convencionales para preparar tabletas. Dichos métodos incluyen métodos secos tales como los de compresión directa y compresión de granulación producida por compactación, o métodos húmedos u otros procedimientos especiales. Los métodos convencionales para preparar otras formas para administración, tales como por ejemplo, cápsulas, supositorios y similares son asimismo bien conocidos.

Los compuestos de fórmula I pueden formar sales que están también dentro del alcance de esta invención. La referencia que se hace aquí a un compuesto de fórmulas I se interpreta como incluyendo referencia a las sales de éstos, a menos que se indique lo contrario. El termino "sal(es)", tal como se emplea aquí, denota sales ácidas formadas con ácidos inorgánicos u orgánicos, así como también sales básicas formadas con bases inorgánicas y/u orgánicas. Además, cuando un compuesto de fórmula III contiene a ambos, un resto básico, tal como, pero sin limitarlo a una piridina o imidazol, y un resto ácido, tal como pero sin limitarlo a un ácido carboxílico, pueden formarse zwiteriones ("sales internas") y se incluyen dentro del término "sal(es)" tal como se usa aquí. Se prefieren sales farmacéuticamente aceptables (es decir no tóxicas, fisiológicamente aceptables) aunque otras sales son también útiles. Las sales de los compuestos de la fórmula I pueden formarse, por ejemplo, por reacción de un compuesto de fórmulas I con una cantidad de ácido o base, tal como una cantidad equivalente, en un medio tal como aquel en el cual la sal precipita o en un medio acuoso seguido de liofilización.

Ejemplos de sales de adición de ácido incluyen acetatos, ascorbatos, benzoatos, bencensulfonatos, bisulfatos, boratos, butiratos, citratos, alcanforatos, alcanforsulfonatos, fumaratos, clorhidratos, bromhidratos, yodhidratos, lactatos, maleatos, metansulfonatos, naftalensulfonatos, nitratos, oxalatos, fosfatos, propionatos, salicilatos, succinatos, sulfatos, tartratos, tiocianatos, toluensulfonatos (conocidos también como tosilatos,) y similares. Adicionalmente, ácidos que son considerados generalmente apropiados para la formación de sales

farmacéuticamente útiles a partir de compuestos farmacéuticos, han sido estudiados por ejemplo, por S. Berge *et al*, *Journal of Pharmaceutical Sciences* (1977) 66(1) 1-19; P. Gould, *International J. of Pharmaceutics* (1986) 33 201-217; Anderson *et al*, *The Practice of Medicinal Chemistry* (1996), Academic Press, New York; y en *The Orange Book* (Food & Drug Administration, Washington, D.C. en su sitio de la red). Estas descripciones se incorporan aquí como referencia.

Ejemplos de sales básicas incluyen sales de amonio, sales de metales alcalinos tales como sales de sodio, litio y potasio, sales de metales alcalino térreos tales como sales de calcio y magnesio, sales con bases orgánicas (por ejemplo, aminas orgánicas) tales como diciclohexilaminas, t-butil aminas, y sales con amino ácidos tales como arginina, lisina y similares. Grupos básicos que contienen nitrógeno puede ser cuaternizados con agentes tales como haluros de alquilo inferior (por ejemplo, cloruros, bromuros y yoduros de metilo, etilo, y butilo), sulfatos de dialquilo (por ejemplo, sulfatos de dimetilo, dietilo y dibutilo), haluros de cadena larga (por ejemplo cloruros, bromuros y yoduros de decilo, laurilo y estearilo), haluros de aralquilo (por ejemplo bromuros de bencilo y fenetilo), y otros.

Todas dichas sales ácidas y sales básicas se consideran sales farmacéuticamente aceptables dentro del alcance de la invención y todas dichas sales ácidas y básicas se consideran equivalentes a las formas libres de los compuestos correspondientes para los propósitos de la invención.

Los compuestos de Fórmula I y las sales, solvatos y prodrogas de éstos, pueden existir en su forma tautomérica (por ejemplo, como amida o imino éter). Todas dichas formas tautoméricas están contempladas aquí como parte de la presente invención.

Todos los estereoisómeros (por ejemplo, isómeros geométricos, isómeros ópticos y similares) de los presentes compuestos (incluyendo aquellos de las sales, solvatos y prodrogas de los compuestos así como también las sales y solvatos de las prodrogas), tal como aquellos que pueden existir debido a carbonos o sulfuros asimétricos en varios sustituyentes, incluyendo las formas enantioméricas (que pueden existir incluso en ausencia de carbonos asimétricos), formas rotaméricas, atropisómeros y formas diastereoméricas, están

contemplados dentro del alcance de esta invención. Por ejemplo, si un compuesto de Fórmula I incorpora un enlace doble o un anillo fusionado, ambas formas, la forma cis y la forma trans, así como también mezclas, están abarcadas dentro del alcance de la invención. Los estereoisómeros individuales de los compuestos de la invención, pueden, por ejemplo, estar sustancialmente libres de otros isómeros, o pueden mezclarse, por ejemplo, como racematos o con todos los otros, u otros estereoisómeros seleccionados. Los centros quirales de la presente invención pueden tener la configuración S o R tal como ha sido definida por Recomendaciones *IUPAC* 1974. El uso de los términos "sal", "solvato" "prodroga" y similares, puede aplicarse igualmente a la sal, solvato y prodroga de los enantiómeros, estereoisómeros, rotámeros, tautómeros, racematos o prodrogas de los compuestos de la invención.

Pueden separarse mezclas diastereoméricas en sus diastereómeros individuales en base a sus diferencia fisico- químicas, por métodos bien conocidos por los expertos en la materia, tales como, por ejemplo por cromatografía y/o cristalización fraccionadas. Pueden separarse enantiómeros por conversión de la mezcla enantiomérica en una mezcla diastereomérica por reacción con un compuesto ópticamente activo apropiado (por ejemplo, un auxiliar quiral tal como un alcohol quiral o cloruro ácido de Mosher), separando los diastereómeros y convirtiendo (por ejemplo, hidrolizando) los diastereómeros individuales a los enantiómeros puros correspondientes. Asimismo, algunos de los compuestos de las Fórmulas Ia y Ib pueden ser atropisómeros (por ejemplo, biarilos sustituidos) y se consideran parte de esta invención. También pueden separarse enantiómeros mediante el uso de una columna de HPLC.

Las formas polimórficas de los compuestos de Fórmula I, y de las sales, solvatos y prodrogas de los compuestos de Fórmula I, se desea incluirlos en la presente invención.

La presente invención abarca también compuestos rotulados isotópicamente de la presente invención, los cuales son idénticos a los que se mencionan aquí, excepto por el hecho de que uno o más átomos son reemplazados con un átomo que tiene una masa atómica o un número de masa diferente de la masa atómica o número de masa que se encuentra usualmente en

la naturaleza. Ejemplos de isótopos que pueden incorporarse a los compuestos de la invención incluyen isótopos de hidrógeno, carbono, nitrógeno, oxígeno, fósforo, fluor y cloro tales como ^{2}H, ^{3}H, ^{13}C, ^{14}C, ^{15}N, ^{18}O, ^{17}O, ^{31}P, ^{32}P, ^{35}S, ^{18}F, y ^{36}Cl, respectivamente.

Ciertos compuestos de Fórmula I rotulados isotópicamente (por ejemplo, aquellos rotulados con ^{3}H y ^{14}C) son útiles en ensayos de compuestos y/ o distribución de tejido de sustratos. Los isótopos tritiados (es decir, ^{3}H) y de carbono-14 (es decir, ^{14}C) son particularmente preferidos debido a su facilidad de preparación y detectabilidad. Además, la sustitución con isótopos más pesados tales como deuterio (es decir, ^{2}H) pueden proporcionar ciertas ventajas terapéuticas que son el resultado de una mayor estabilidad metabólica (por ejemplo aumento de la semivida *in vivo* o reducción de los requisitos de dosificación) y por consiguiente, pueden ser preferibles en ciertas circunstancias. Los compuestos rotulados isotópicamente de Fórmula I pueden prepararse generalmente siguiendo procedimientos análogos a los descritos en los Esquemas y/ o en los Ejemplos que se dan a continuación, sustituyendo un reactivo rotulado isotópicamente apropiado, con un reactivo no rotulado isotópicamente.

Los compuestos de acuerdo con la invención tienen propiedades farmacológicas; en particular, los compuestos de Fórmula I pueden ser útiles como agonistas de adrenoreceptores α2C.

Una dosis preferida es de aproximadamente 0,001 a 500 mg/kg de peso corporal por día, del compuesto de Fórmula I. Una dosis especialmente preferida es de aproximadamente 0,01 a 25 mg/kg de peso corporal por día de un compuesto de Fórmula I, o una sal o solvato de dicho compuesto farmacéuticamente aceptables.

Los compuestos de esta invención, pueden ser también útiles en combinación (administrados conjuntamente o consecutivamente) con uno o más agentes terapéuticos, tales como, por ejemplo, glucoesteroides, inhibidores de PDE-4, agentes anti-muscarínicos, cromolin sodio, antagonistas del receptor H_1, agonistas de 5-HT_1, NSAIDs, inhibidores de la enzima conversora de angiotensina, agonistas del receptor angiotensina II, bloqueadores β, agonistas β (incluyendo

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acción prolongada y corta), antagonistas de leucotrieno, diuréticos, antagonistas de aldosterona, agentes ionotrópicos, péptidos natriuréticos, agentes analgésicos/ controladores de dolor, agentes anti- ansiolíticos, agentes anti- migraña y agentes terapéuticos apropiados para tratar afecciones cardíacas, trastornos psicóticos y glaucoma.

Esteroides apropiados incluyen prednisolona, fluticasona (incluyendo todos los ésteres tales como ésteres de propionato o furoato), triamcinolona, beclometasona, mometasona (incluyendo cualquier forma de éster tal como furoato de mometasona), budasamina, ciclesonida, betametasona, dexametasona, prednisona, flunisolida y cortisona.

Inhibidores de PDE-4 apropiados incluyen roflumilast, teofilina, rolipram, piclamilast, cilomilast y CDP-840.

Agentes anti muscarínicos apropiados incluyen bromuro de ipratropio y bromuro de tiatropio.

Antagonistas de H_1 apropiados incluyen astemizol, azatadina, azelastina, acrivastina, bromfeniramina, cetirizina, clorfeniramina, clemastina, ciclicina, carebastina, ciproheptadina, carbinoxamina, descarboetoxiloratidina, difenhidramina, doxilamina, dimetindeno, ebastina, epinastina, efletirizeina, fexofenadina, hidroxizina, cetotifen, loratidina, levocabastina, meclizina, fexofenadina, hidroxicina, cetotifen, loratadina, levocabastina, meclicina, mizolastina, mequitacina, mianserina, noberastina, norastemizol, picumast, pirilamina, prometazina, terfenadina, tripelennamina, temelastina, trimeprazina o triprolidina.

Agentes anti- inflamatorios apropiados incluyen aspirina, diclofenac, diflunisal, etodolac, flurbiprofeno, ibuprofeno, indometacina, cetoprofeno, cetorolac, nabumetona, naproxeno, oxaprozina, piroxicam, sulindac, y tolmetina.

Antagonistas de aldosterona apropiados incluyen espironolactona.

Agentes ionotrópicos apropiados incluyen digitalis.

Agonistas apropiados del receptor de angiotensina II incluyen irbesartan y losartan.

Diuréticos apropiados incluyen espironolactona, meticlotiazida, bumetanida, torsemida, hidroflumetiazida, triclormetiazida, hidroclorotiazida,

triamtereno, ácido etacrínico meticlotiazida, hidroclorotiazida, benztiazida, hidroclorotiazida, quinetazona, hidroclorotiazida, clortalidona, furosemida, indapamida, hidroclorotiazida, triamtereno, triclormetiazida, hidroclorotiazida, HCl de amilorida, HCl de amilorida, metolazona, triclormethiazide, bendroflumetiazida, hidrochlorotiazida, politiazida, hidroflumetiazida, clortalidona, y metolazona.

Agentes analgésicos/ controladores del dolor apropiados, incluyen Celecoxib, amitriptilina, ibuprofeno, naproxeno, gabapentina, tramadol, rofecoxib, HCl de oxicodona, HCl de acetaminofenoxicodona, carbamazepina, amitriptilina, diclofenac, diclofenac, etodolac, fenoprofeno calcio, flurbiprofeno, ibuprofeno, indometacina, cetoprofeno, cetorolac trometamina, ácido mefenámico, meloxicam, nabumetona, naproxeno, oxaprozina, piroxicam, sulindac, tolmetina sodio, valdecoxib, diclofenac/misoprostol, oxicontina, vicodina, darvocet, percocet, sulfato de morfina, dilaudid, estadol, estadol NS, acetaminofeno con codeína, acetaminofeno con codeína #4, parches Lidoderm®, ziconotida, duloxetina, roboxetina, gabapentina y pregabalina.

Bloqueadores β apropiados incluyen acebutolol, atenolol, atenolol/ clortalidona, betaxolol, fumarato de bisoprolol, bisoprolol/HCTZ, labetolol, tartrato de metoprolol, nadolol, pindolol, propranolol, propranolol/ HCTZ, sotalol, y timolol.

Agonistas β apropiados incluyen dobutamina, ritodrina, salbutamol, levalbuterol, metaproternol, formoterol, fenoterol, bambuterol, brocaterol, clenbuterol, terbutalina, tulobuterol, epinefrina, isoprenalina, y hexoprenalina.

Antagonistas de leucotrieno apropiados incluyen levamisol.

Agentes anti- migraña apropiados incluyen succinato de rovatriptano, HCl de naratriptano, benzoato de rizatriptano, succinato de sumatriptano, zolmitriptano, malato de almotriptano, maleato de etisergida, mesilato de dihidroergotamina, tartrato de ergotamina, tartrato de ergotamina/ cafeína, Fioricet®, Fiorninal®, Depakene®, y Depakote®.

Agentes anti- ansiolíticos y anti- depresivos incluyen HCl de amitriptilina HCl de bupropion, bromhidrato de citalopram, HCl de clomipramina, desipramina, fluoxetina, maleato de fluvoxamina, HCl de maprotilina, mirtazapina, HCl de

nefazodona, nortriptilina, HCl de paroxetina, HCl de protriptilina, HCl de sertralina, doxepina, y maleato de trimipramina.

Inhibidores de la enzima conversora de angiotensina apropiados incluyen Captopril, enalapril, enalapril/HCTZ, lisinopril, lisinopril/HCTZ, y Aceon®.

Las propiedades farmacológicas de los compuestos de esta invención pueden ser confirmadas por una variedad de ensayos farmacológicos. Los ensayos farmacológicos ejemplificados que se describen a continuación han sido llevados a cabo con compuestos de acuerdo con la invención y sus sales.

Esta invención está también dirigida a composiciones farmacéuticas que comprenden por lo menos un compuesto de Fórmula I o una sal o solvato de dicho compuesto farmacéuticamente aceptable y por lo menos un portador farmacéuticamente aceptable.

Para preparar composiciones farmacéuticas a partir de los compuestos descritos por esta invención, los portadores inertes, farmacéuticamente aceptables pueden ser sólidos o líquidos. Las preparaciones de forma sólida incluyen polvos, tabletas, gránulos dispersables, as, sellos y supositorios. Los polvos y tabletas pueden estar constituidos por desde aproximadamente 5 hasta aproximadamente 95 por ciento de ingrediente activo. Los portadores sólidos apropiados son conocidos en la materia, por ejemplo carbonato de magnesio, estearato de magnesio, talco, azúcar o lactosa. Pueden usarse tabletas, polvos, sellos y cápsulas como formas de administración oral apropiadas. Ejemplos de portadores farmacéuticamente aceptables y métodos de manufactura para varias composiciones pueden hallarse en A. Gennaro (ed.), *Remington's Pharmaceutical Sciences,* 18ª Edición, (1990), Mack Publishing Co., Easton, Pennsylvania.

Las preparaciones de forma líquida incluyen soluciones, suspensiones y emulsiones. Como ejemplo, pueden mencionarse agua o soluciones de agua y propilen glicol para inyección parenteral o adición de edulcorantes y opacantes para soluciones, suspensiones y emulsiones Las preparaciones de forma líquida pueden incluir también soluciones o suspensiones para administración intranasal.

Las preparaciones en aerosol apropiadas para inhalación incluyen soluciones y sólidos en forma de polvo, que pueden estar en combinación con un

portador farmacéuticamente aceptable, tal como gas comprimido inerte, por ejemplo nitrógeno.

También se incluyen preparaciones en forma sólida, que están destinadas a ser convertidas, poco tiempo antes de su uso, a preparaciones en forma líquida para administración oral o bien parenteral. Dichas formas líquidas incluyen soluciones, suspensiones y emulsiones.

Los compuestos de la invención pueden ser también liberables transdérmicamente. Las composiciones transdérmicas pueden tener la forma de cremas, lociones, aerosoles y/o emulsiones y pueden incluirse en un parche transdérmico del tipo de matriz o reservorio que son convencionales en la materia, para este propósito.

Los compuestos de esta invención pueden ser liberados subcutáneamente.

Preferiblemente los compuestos se administran por via oral.

Preferiblemente, la preparación farmacéutica está en forma de una forma de dosificación unitaria. De tal forma, la preparación puede subdividirse en dosis unitarias del tamaño conveniente que contienen las cantidades apropiadas de componente activo, por ejemplo una cantidad eficaz para lograr el propósito deseado.

La cantidad de compuesto activo en una dosis de preparación unitaria puede variar o ajustarse desde aproximadamente 1 mg hasta aproximadamente 100 mg, preferiblemente desde aproximadamente 1 mg hasta aproximadamente 50 mg, más preferiblemente desde aproximadamente 1 mg hasta aproximadamente 25 mg, de acuerdo con la aplicación particular.

La dosis real empleada puede variar dependiendo de los requisitos del paciente y de la gravedad de la afección que se está tratando. La determinación del régimen de dosificación para una situación particular está dentro de la experiencia en la materia. Por razones de conveniencia, la dosis diaria total puede dividirse y administrarse en porciones durante el día, si es necesario.

La cantidad y frecuencia de administración de los compuestos de la invención y/o de sus sales farmacéuticamente aceptables, se regulará de acuerdo con la opinión del médico de cabecera considerando factores tales como la edad, estado y peso del paciente, así como también la gravedad de los síntomas que se

están tratando. Un régimen de dosificación diario típico recomendado para administración oral puede estar en un rango de desde aproximadamente 500 mg/día, preferiblemente 1 mg/día a 200 mg/día, en dos o más dosis divididas.

Otro aspecto de esta invención es un equipo que comprende una cantidad terapéuticamente eficaz de por lo menos un compuesto de Fórmula I o una sal farmacéuticamente aceptable o solvato de dicho compuesto y un portador vehículo o diluyente farmacéuticamente aceptable.

Un aspecto más de esta invención es un equipo que comprende por lo menos un compuesto de Fórmula I, o una sal farmacéuticamente aceptable o un solvato de dicho compuesto y una cantidad de por lo menos un agente terapéutico enumerado previamente, donde las cantidades de dos o más ingredientes dan como resultado el efecto terapéutico deseado.

La invención descrita aquí se ejemplifica mediante las preparaciones y ejemplos siguientes que no deben considerarse limitativos del alcance de la descripción. Vías mecanísticas alternativas y estructuras análogas resultarán aparentes para los expertos en la materia.

Cuando se presentan datos de RMN, se obtuvo la espectrografía ^1H en cualquiera de un Varian VXR-200 (200 MHz, ^1H), Varian Gemini-300 (300 MHz), Varian Mercury VX-400 (400MHz), o Bruker-Biospin AV-500 (500MHz), y se informaron como ppm con el número de protones y las multiplicidades indicadas entre paréntesis. Los datos que se presentan de LC/MS, son el resultado de los análisis que se efectuaron usando un espectrógrafo de masa de Applied Biosystems API-100 y una columna C18, 10-95% CH_3CN-H_2O (con 0,05% TFA) gradiente. Se da el ion parental observado.

Los siguientes solventes y reactivos pueden citarse mediante sus abreviaturas entre paréntesis.

Me = metilo; Et = etilo; Pr = propilo; Bu = butilo; Ph = fenilo y Ac = acetilo

µl = microlitros

AcOEt o EtOAc = acetato de etilo

AcOH o HOAc = ácido acético

ACN = acetonitrilo

atm = atmósfera

Boc o BOC = ter-butoxicarbonilo

DCE = dicloroetano

DCM o CH_2Cl_2: diclorometano

DIPEA = diisopropiletilamina

DMAP = 4-dimetilaminopiridina

DMF = dimetilformamida

DMS = sulfuro de dimetilo

DMSO = sulfóxido de dimetilo

EDCI = 1-(3-dimetilaminopropil)-3-etilcarbodiimida

Fmoc = 9-fluiorenil metoxi carbonilo

g = gramos

h = hora

hal = halógeno

HOBt = 1-hidroxibenzotirazol

LAH = hidruro de litio aluminio

LCMS = espectrometría de masa de cromatografía líquida

min = minuto

mg = miligramos

mL = mililitros

mmol = milimoles

MCPBA = ácido 3-cloroperoxibenzoico

MeOH: metanol

MS = espectrometría de masa

NMR = espectroscopia de resonancia magnética nuclear

RT o rt = temperatura ambiente (aproximadamente 25° C).

TEA o Et_3N = trietilamina

TFA = ácido trifluoracético

THF = tetrahidrofurano

TLC = cromatografía de capa delgada

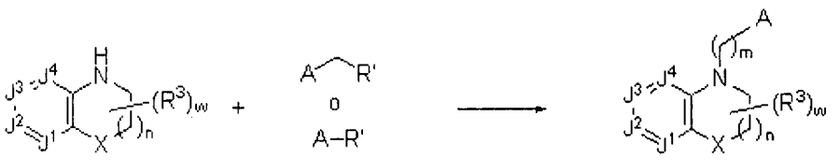
TMS = trimetilsililo

Tr = trifenilmetilo

Ejemplos

Los compuestos de esta invención pueden prepararse tal como se ha descrito en general en los esquemas 1 y 2, y los ejemplos siguientes. El esquema 1 muestra una realización en la cual **S1** y **S2** están unidos conjuntamente. Ejemplos de estas realizaciones incluyen la reacción de **S1** con un compuesto elecrofílico **S2**, donde **R'** es un carboxaldehído (acoplamiento por aminación reductiva), ácido carboxílico (acoplamiento de amida) o haluro (acoplamiento por alquilación).

Esquema 1



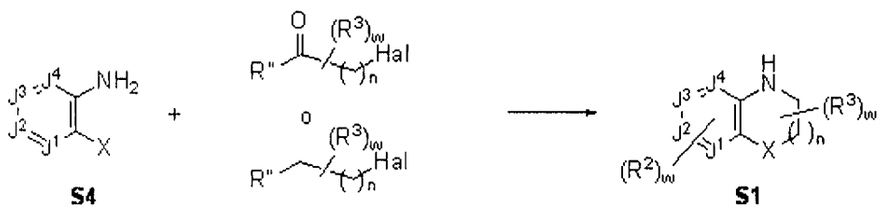
S1
X = N, O, o S

S2a R' = CHO
S2b R' = CO_2H
S2c R' = CH_2(Hal)

S3

El esquema 2 describe una realización general para sintetizar **S1**, mediante lo cual una anilina apropiadamente sustituida **S4** puede convertirse a **S1** a través de una realización de ciclación de anillo único o de etapas múltiples.

Esquema 2



S4

S5
R" = H, OR o Hal

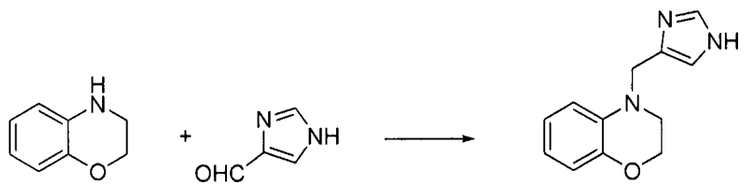
S1

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Los compuestos de fórmula **S3** pueden prepararse por los métodos generales señalados anteriormente. Los compuestos ejemplificados específicamente fueron preparados a partir de los restos **S4** o **S1** tal como se describieron en los ejemplos siguientes o a partir de los materiales de partida conocidos en la materia.

Los materiales de partida y los reactivos usados para preparar los compuestos descritos, son asequibles en proveedores comerciales tales como Aldrich Chemical Co. (Wisconsin, USA) y Acros Organics Co. (New Jersey, USA) o bien se preparan por métodos de la literatura conocidos por los expertos en la materia. Estos ejemplos se proveen para ilustrar adicionalmente la presente invención. Dichos ejemplos se proveen con propósitos ilustrativos solamente, y el alcance de la invención no debe considerarse limitado en ninguna de sus formas.

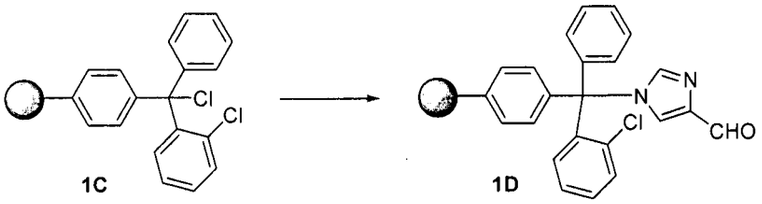
EJEMPLO PREPARATIVO 1



1A **1B** **1**

Una solución de 3,4-dihidro-2H-1,4-benzoxazina **1A** (0.1 g, 0.75 mmol) en DCE (10 mL) se trató con imidazol-4-carboxaldehído **1B** (0.11 g, 1.1 mmol), $NaBH(OAc)_3$ (0.47 g, 2.2 mmol), y AcOH (una gota) y se agitó a 60 °C durante la noche. La reacción se diluyó luego con CH_2Cl_2, se lavó con $NaHCO_3$ acuoso saturado, se secó sobre Na_2SO_4, y se concentró. La cromatografía (0-4% 7 N NH_3-MeOH/CH_2Cl_2) proporcionó **1** en forma de un sólido beige (0.08 g, 50%). LMCS m/z 216 (MH+).

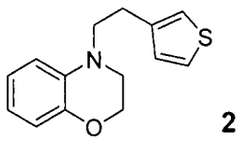
Alternativamente, el compuesto del título **1** puede ser sintetizado mediante la reacción de **1A** e imidazol-4-carboxaldehído **1D** unido por resina, tal como se describe a continuación:



1C 1D

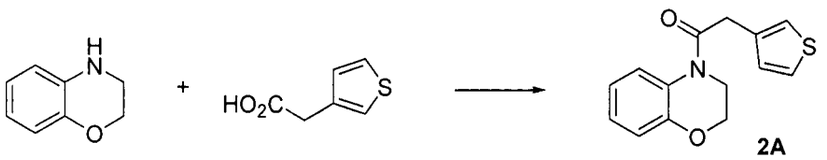
Resina Novabiochem **1C** (malla 100-200, 1% DVB, 1.4 mmol/g, 5g) se suspendió en DMF anhidro (25 mL) y DCE (25 mL) y se trató consecutivamente con **1B** (2 g, 21 mmol) y TEA (2.96 mL, 21 mmol). La resina se dejó bajo agitación durante la noche y se lavó con DMF (3x), MeOH (3x), y DCM (4x) y luego se secó al vacío durante la noche. La resina resultante **1D** (100 mg, 1.4 mmol/g, 0.14 mmol) se suspendió en DCE (4 mL) y se trató con **1A** (94.5mg, 0.7 mmol) y $NaBH(OAc)_3$ (148mg, 0.7 mmol). La reacción se agitó durante la noche y se lavó con DMF (3x), MeOH (3x), y DCM (4x), y luego se secó al vacío. La resina resultante se sometió a 30% de TFA/DCM, se agitó a temperatura ambiente durante 2 h y la mezcla se concentró al vacío. El residuo se purificó por -HPLC preparativa Gilson para proporcionar el compuesto **1** (12.3 mg).

EJEMPLO PREPARATIVO 2



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Etapa 1



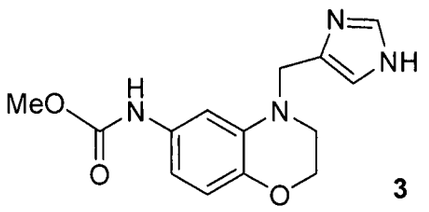
2A

Una solución de 3,4-dihidro-2H-1,4-benzoxazina (0.52 g, 3.8 mmol) y ácido tiofen-3-acético (0.82 g, 5.7 mmol) en 1:1 CH_2Cl_2:DMF (20 mL) se trató con DIPEA (2.6 ml, 15 mmol), HOBt (1.29 g, 9.5 mmol), y EDCI (1.83 g, 9.5 mmol) y se agitó a 70 °C durante la noche. La reacción se diluyó luego con CH_2Cl_2, se lavó con $NaHCO_3$ acuoso saturado, se secó sobre Na_2SO_4, y se concentró. La cromatografía (0-10% NH_3-MeOH/EtOAc 1N) proporcionó **2A** en forma de un sólido rojo (0.54g, 55%)

Etapa 2

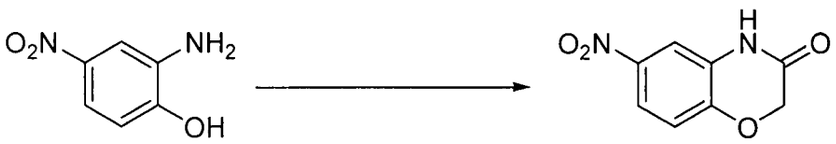
Una solución de **2A** (0.094 g, 0.36 mmol) en THF (10 mL) se trató con BH_3-SMe_2 (2M/THF, 0.27 mL, 0.54 mmol) y se agitó a reflujo durante 2h. La reacción se concentró y se sometió a cromatografía (EtOAc) para proporcionar **2** en forma de un sólido blanco (0.040 g, 45%). LMCS m/z 246 (MH+).

EJEMPLO PREPARATIVO 3



3

Etapa 1



3A **3B**

Una mezcla de 2-amino-4-nitrofenol (**3A**, 25.03 g, 0.16 mol) en 4-metil-2-pentanona y agua (420 mL, 1:1) se trató con bicarbonato de sodio (32.74 g, 0.39 mol), se enfrió a 0 °C, y se trató luego con cloruro de cloroacetilo (15.52 mL, 0.19 mol). La mezcla de reacción se calentó a reflujo durante la noche. Después de enfriar a temperatura ambiente, la mezcla se concentró bajo vacío. El residuo se diluyó luego con agua (200 mL) y EtOAc (100 mL), y se filtró para proporcionar el sólido de color gris pálido **3B** (26.05 g). El filtrado se separó y el acuoso se extrajo con EtOAc (3 x 100 mL). Las capas orgánicas combinadas se lavaron con agua, y se secaron ($MgSO_4$), se filtraron y se concentraron bajo vacío para proporcionar sólido adicional de color gris claro **3B** (7.7 g). El sólido resultante (rendimiento cuantitativo) se usó para la siguiente reacción sin purificación adicional.

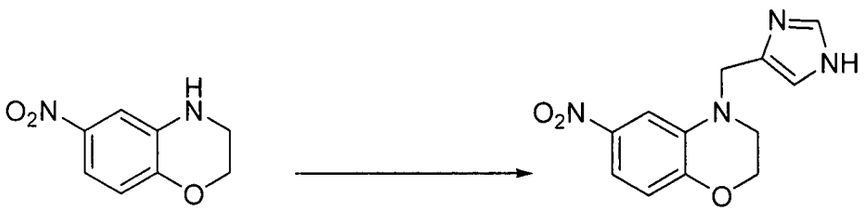
Etapa 2



3B **3C**

Al compuesto **3B** (6.76 g, 34.84 mmol) en THF anhidro (200 mL) se agregó BH_3-SMe_2 (2.0M/THF, 35 mL, 69.68 mmol). La mezcla se calentó a reflujo durante 2 h. Después de enfriar a temperatura ambiente, la mezcla se apagó con MeOH (10 ml) y se calentó a reflujo durante otros 10 minutos. La mezcla de reacción se concentró bajo vacío. La cromatografía (10%-30% EtOAc/hexanos) proporcionó **3C** (6.1 g, 97% para dos etapas).

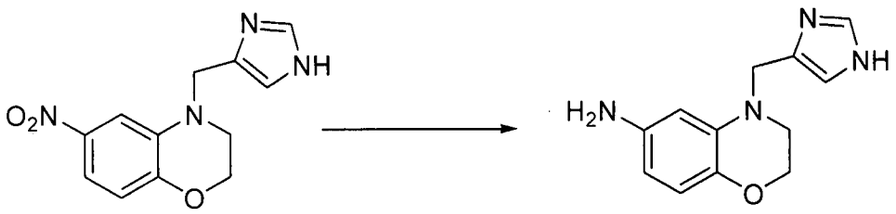
Etapa 3



3C **3D**

Una mezcla de **3C** (4.35 g, 21.16 mmol) en dicloroetano anhidro (60 mL) se trató con imidazol-4-carboxaldehido (**1B**, 2.79 g, 28.99 mmol) y AcOH (0.35 mL, 6 mmol). La mezcla se agitó a temperatura ambiente durante 10 min y luego se trató con $NaBH(OAc)_3$ (15.36 g, 72.48 mmol). La mezcla de reacción se agitó a temperatura ambiente durante la noche, y se apagó con una solución de NaOH 2N, y se concentró bajo vacío. El residuo se diluyó con agua (50 mL) y se extrajo con EtOAc (4 x 100 mL). La capa orgánica se secó ($MgSO_4$), se filtró, y se concentró bajo vacío. La cromatografía (DCM contenía 1 a 5% de NH_3 7N en MeOH) proporcionó **3D** (5.56g, 89%). EM m/z 261 (MH+).

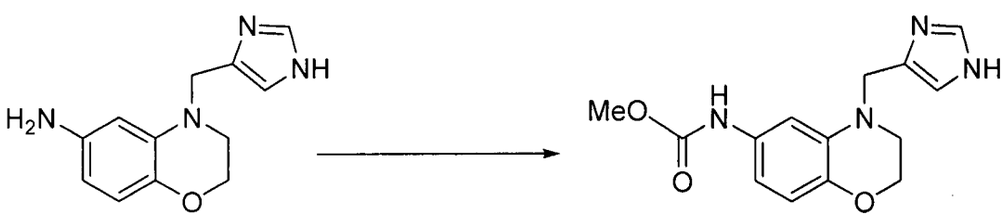
Etapa 4



3D **3E**

El compuesto **3D** (5.56 g, 21.38 mmol) se disolvió en MeOH/EtOAc (300 mL, 1:1), y se agregó cuidadosamente 10% de Pd/C (1.11 g, 20% por peso). La mezcla se agitó a temperatura ambiente bajo un balón de hidrógeno durante la noche y se filtró. El solvente se evaporó bajo vacío para proporcionar un sólido blanco **3E** (5.46 g, 100%). EM m/z 231 (MH+).

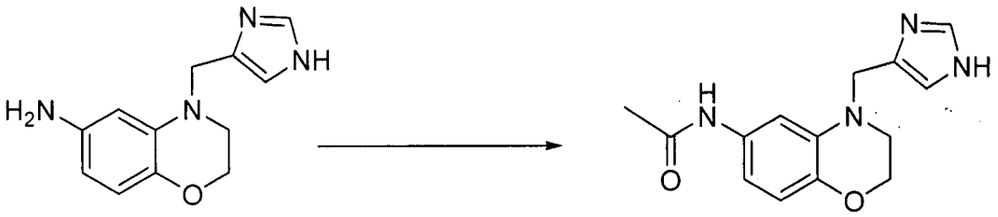
Etapa 5



3E **3**

Una mezcla de amina **3E** (2.14 g, 9.30 mmol) en DCM anhidro (40 mL) se trató consecutivamente con TEA (3.24 mL, 23.3 mmol) y $ClCO_2Me$ (1.43 mL, 18.6 mmol). La mezcla se agitó a temperatura ambiente durante 2 h, y luego se apagó con una solución NaOH 2N. La mezcla resultante se agitó durante otras 2 h y se separó. La capa acuosa se extrajo con DCM (3 x 50 mL). Las capas orgánicas combinadas se secaron ($MgSO_4$), se filtraron, y se concentraron bajo vacío. La cromatografía (DCM que contenía 1 a 4% de NH_3/MeOH 7N) proporcionó **3** en forma de un sólido blanco (1.64 g, 61%). EM m/z 289 (MH+).

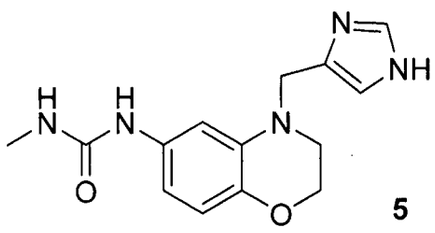
EJEMPLO PREPARATIVO 4



3E **4**

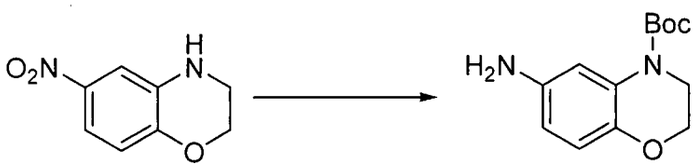
De manera similar al Ejemplo 3, Etapa 5, se trató la amina **3E** con TEA y AcCl para proporcionar el compuesto **4**. EM m/z 273 (MH+).

EJEMPLO PREPARATIVO 5



5

Etapas 1-2



3C **5A**

Una solución de **3C** (3 g, 16.7 mmol) en DCM anhidro (100 mL) se trató con Boc_2O (7.27g, 33.3 mmol), piridina (5.39 mL, 66.7 mmol), y DMAP catalítico. La mezcla se agitó a temperatura ambiente durante la noche y se concentró bajo vacío. El residuo se diluyó con agua (50 mL) y se extrajo con EtOAc (3 x 100 mL). Las capas orgánicas combinadas se secaron ($MgSO_4$), se concentraron y se sometieron a cromatografía (5-5% EtOAc/hexanos, rendimiento: 3g, 64%).

El producto resultante se hidrogenó de manera similar a la descrita en el Ejemplo 3, Etapa 4 para proporcionar **5A.**

Etapa 3



5A **5B**

A la amina **5A** (1.1 g, 4.4 mmol) en THF anhidro (15 mL) se agregó MeNCO (215 mg, 4.4 mmol). La mezcla se agitó a temperatura ambiente durante la noche y luego se concentró. La cromatografía (DCM que contenía 1 a 5% de NH_3/MeOH 7N) proporcionó **5B** (890 mg, 66%).

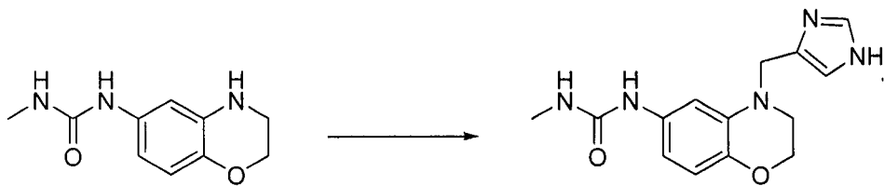
Etapa 4



5B **5C**

El compuesto **5B** (890 mg, 2.9 mmol) se agitó a temperatura ambiente en 30% de TFA/DCM (14 mL) que contenía 3 gotas de Et_3SiH durante 1 h, y luego se apagó con una solución de NaOH 2N. La mezcla se extrajo con EtOAc (3 x 50 mL). La capa orgánica se secó ($MgSO_4$), se filtró y se concentró bajo vacío. El residuo (**5C**, 600mg) se usó en la reacción siguiente sin purificación adicional.

Etapa 5

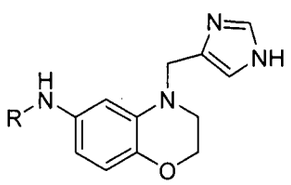


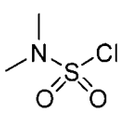
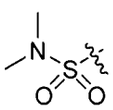
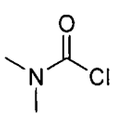
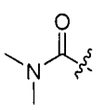
5C **5**

De manera similar a la descrita en el Ejemplo 3 (Etapa 3), se trató el compuesto **5C** con imidazol-4-carboxaldehído (**1B**) para proporcionar el compuesto del título **5** (56% durante dos etapas). EM m/z 288 (MH+).

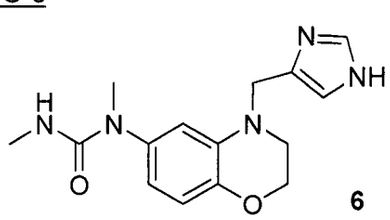
Los compuestos **5D-5F** en la **Tabla 1** siguiente pueden prepararse a partir del compuesto **5A** usando varios reactivos de acoplamiento tal como se muestra, seguido de desprotección Boc y alquilación reductiva tal como se describió anteriormente.

Tabla 1



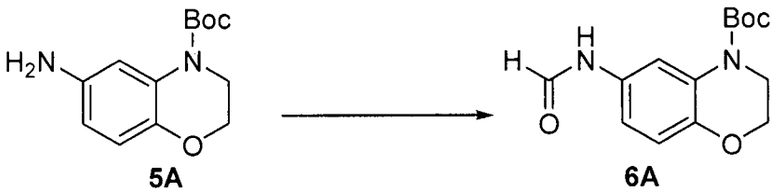
Comp.	Reactivo	R	EM (MH+)
5D	Anhídrido metansulfónico /piridina		309
5E	 y piridina		338
5F	 y piridina		302

EJEMPLO PREPARATIVO 6



6

Etapa 1

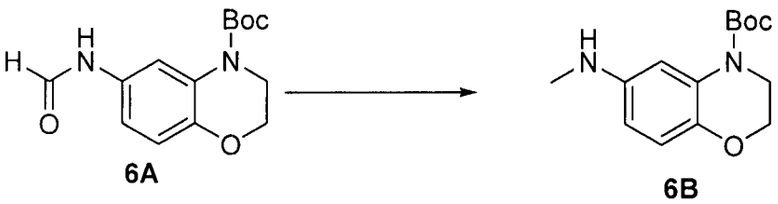


5A **6A**

A un frasco con Ac_2O (2.02 mL, 21.4 mmol) a 0 °C se agregó HCO_2H (0.82 mL, 21.4 mmol) a través de una jeringa. Después de agitar a 0 °C durante 5 min, la mezcla se calentó a 55 °C durante 2h, y luego se enfrió nuevamente a 0 °C. Se agregó la amina **5A** (2g, 8.0 mmol) en THF anhidro (100 mL) y la mezcla se agitó a 0 °C durante 30 min. La mezcla de reacción se concentró bajo vacío y se diluyó con una solución de NaOH 2N a pH 9, y se extrajo con EtOAc (3 x 50 mL). La capa orgánica se secó ($MgSO_4$), se filtró y se concentró bajo vacío para proporcionar una espuma **6A** (rendimiento cuantitativo).

Alternativamente, una mezcla del compuesto **5A** (17.5 g, 69.9 mmol) en formiato de butilo (700 ml) se calentó a 50°C durante 3h y luego se dejó a temperatura ambiente durante la noche. Luego se concentró la mezcla de reacción, se agregó a 100 ml de NaOH 0,5 N, y se extrajo con CH_2Cl_2 (4X), se secó con Na_2SO_4, y se concentró. La cromatografía (10%-50% EtOAc/hexano) proporcionó **6A** (9.19 g, 47 %) en forma de una espuma pegajosa de color marrón claro.

Etapa 2

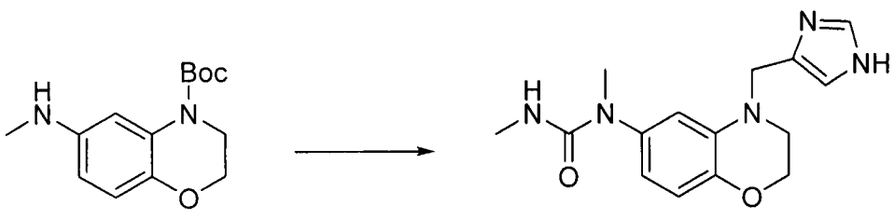


6A **6B**

Una mezcla del compuesto **6A** (2.75 g, 9.88 mmol) en THF (30 ml) se trató lentamente con BH_3-DMS (2.0 M/THF, 7.8 ml) y luego se calentó a reflujo durante 3h. La mezcla de reacción se concentró, se trató con K_2CO_3 (1.5 g) y EtOH, y luego se agitó durante la noche a temperatura ambiente. La mezcla de reacción se filtró, se concentró y se agregó a H_2O y se extrajo con CH_2Cl_2 (4X). Las capas

orgánicas combinadas se secaron con Na_2SO_4, se filtraron y se concentraron para proporcionar **6B** en forma de un aceite claro (2.76 g).

Etapas 3-5

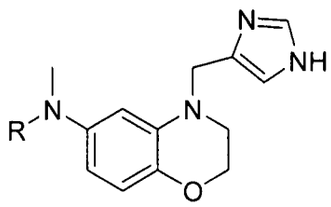


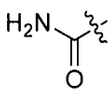
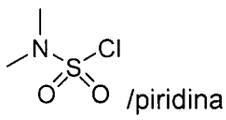
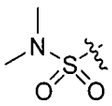
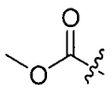
6B **6**

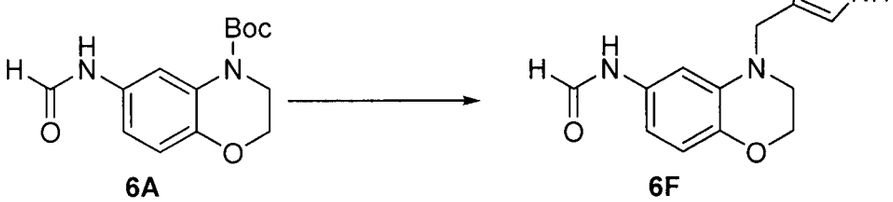
Una solución de **6B** (2.76 g, crudo) en CH_2Cl_2 (20 ml) se trató lentamente con MeNCO (1.0 g, 12.5 mmol) y se agitó a temperatura ambiente durante la noche. La mezcla de reacción se concentró y se cromatografió (50% a 80% de EtOAc/hex, 3.10 g, 98% rendimiento de **6A**). Este producto (3.10 g, 9.65 mmoles) se extrajo en CH_2Cl_2 (80 ml) y se desprotegió con TFA (11.5 ml) tal como se describió en el Ejemplo 5, Etapa 4 (95% de rendimiento). Una mezcla de la amina resultante y el aldehído **1B** (1 eq) en una cantidad mínima de CH_2Cl_2 se trató con $Ti(OiPr)_4$ (1.3 eq). Después de agitar durante 2h a temperatura ambiente, se agregaron $NaBH_4$ (1.2 eq) y EtOH. La mezcla de reacción se agitó luego durante la noche, se concentró, se trató con H_2O y se extrajo con CH_2Cl_2 (4X). Las capas orgánicas combinadas se secaron con Na_2SO_4, se filtraron, se concentraron y se cromatografiaron (gel de sílice, 5% de MeOH/ CH_2Cl_2 w/ NH_3) para proporcionar el compuesto del título **6** (74% de rendimiento). EM m/z 302 (MH+).

Los compuestos en la **Tabla 2** siguiente pueden prepararse a partir del compuesto **6B,** usando los varios reactivos de acoplamiento tal como se muestra, seguido de desprotección Boc y alquilación reductiva tal como se muestra en el Ejemplo 5.

Tabla 2

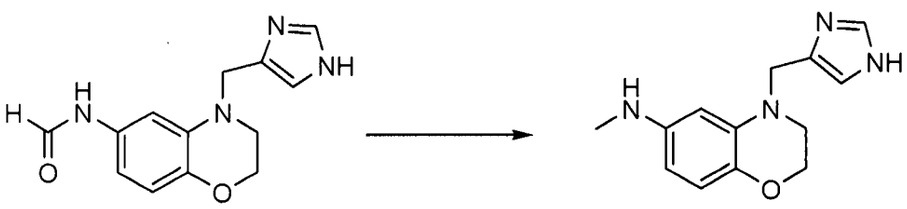


Comp.	Reactivo	R	EM (MH+)
6C	TMSNCO		288
6D	 /piridina		352
6E	MeCOCl /piridina		303



6A **6F**

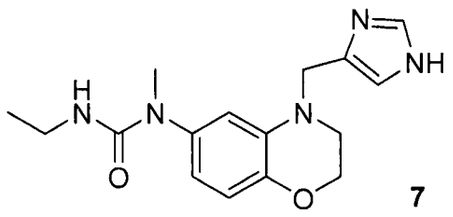
El compuesto **6F** se preparó de la manera siguiente: **6A** se trató con TFA, seguido de alquilación reductiva con imidazol-4-carboxaldehído (**1B**) tal como se ha descrito previamente en el Ejemplo 5 (Etapa 4) y en el Ejemplo 3 (Etapa 3). EM m/z 259 (MH+).



6F **6G**

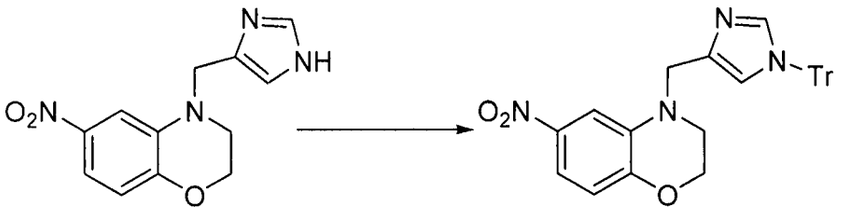
De manera similar al Ejemplo 3, Etapa 2, el compuesto **6F** se redujo con BH_3-SMe_2 para proporcionar **6G**. EM m/z 245 (MH+).

EJEMPLO PREPARATIVO 7



7

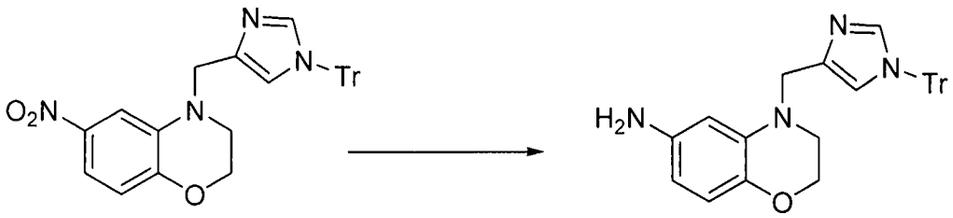
Etapa 1



3D **7A**

A una suspensión del compuesto **3D** (4.8 g, 18.46 mmol) en DCM anhidro (200 mL) se agregó consecutivamente TrCl (5.15 g, 18.46 mmol) y TEA (7.7 mL, 55.37 mmol). La mezcla se se agitó a temperatura ambiente durante la noche, y se apagó con una solución saturada de NH_4Cl. La solución se separó y el acuoso se extrajo con DCM (3 x 100 mL). Las capas orgánicas combinadas se lavaron con agua, se secaron ($MgSO_4$), se filtraron, y se concentraron bajo vacío para proporcionar un sólido rojo amarillento **7A** (9.13g, rendimiento: 98%).

Etapa 2

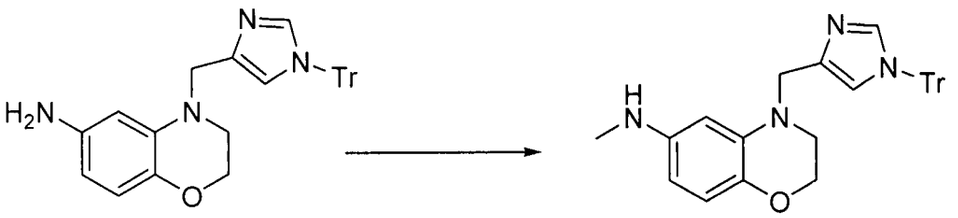


7A **7B**

A un compuesto **7A** (4.55g, 9.06 mmol) en MeOH/EtOAc (400 mL, 1:1) en una botella de hidrogenación se agregó 10% de Pd-C (1 g). El recipiente de reacción se agitó en el agitador Parr bajo 50 psi de hidrógeno durante 4h. Luego

el catalizador se filtró a través de una almohadilla de celite y se lavó con MeOH y EtOAc. El filtrado se concentró bajo vacío para proporcionar el sólido blanco **7B** (3.81 g, 89%).

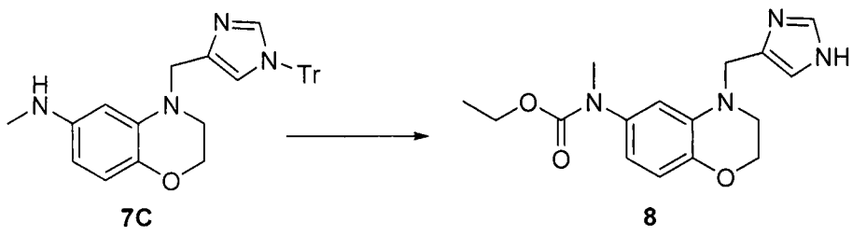
Etapas 3-6



7B **7C**

Siguiendo la realización mencionada en el Ejemplo 6 (Etapas 1-2), **7B** se trató con Ac_2O/HCO_2H y luego se redujo con BH_3-SMe_2 para proporcionar **7C.** De manera similar a la descrita en el Ejemplo 5 (Etapas 3-4), **7C** se elaboró adicionalmente mediante tratamiento con EtNCO y desprotección con TFA para proporcionar el compuesto del título **7**. EM m/z 316 (MH+).

EJEMPLO PREPARATIVO 8

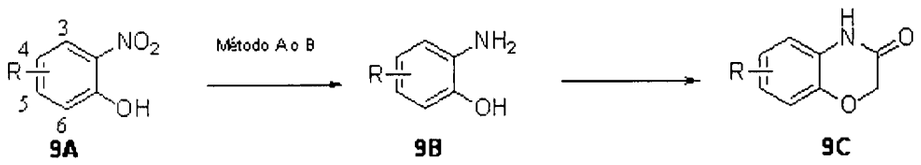


7C **8**

Al compuesto **7C** (1.5 g, 3.09 mmol) en DCM anhidro (10 mL) se agregó consecutivamente piridina (0.5 mL, 6.18 mmol) y $ClCO_2Et$ (0.59 mL, 6.18 mmol). La mezcla se agitó a temperatura ambiente durante la noche, y luego se apagó con una solución saturada de NH_4Cl. La solución se concentró y el acuoso se extrajo con EtOAc (3 x 50 mL). Las capas orgánicas combinadas se lavaron con salmuera, se secaron ($MgSO_4$), se filtraron y se concentraron bajo vacío.

El residuo se desprotegió luego con TFA, de la manera descrita en el Ejemplo 5, Etapa 4, para proporcionar el compuesto **8** (145 mg, 15% durante dos etapas). EM m/z 317 (MH+).

EJEMPLO PREPARATIVO 9

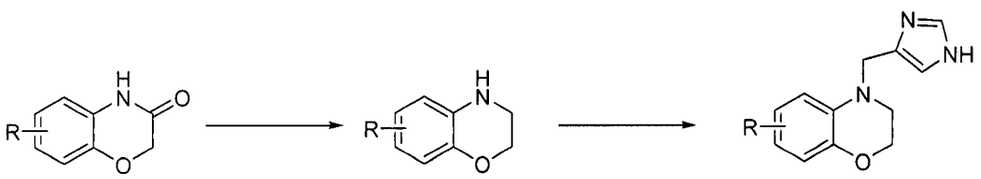


9A **9B** **9C**

En la síntesis del Ejemplo 9 usaron los materiales de partida **9A**, **9B** o **9C**. El compuesto **9B** puede ser sintetizado a partir de **9A** mediante el uso del método de reducción A o B:

Método A: Al compuesto **9A** en MeOH se agregó 10% de Pd/C y la mezcla se agitó a temperatura ambiente bajó un balón de hidrógeno durante la noche. Luego el catalizador se filtró a través de una almohadilla de celite y se lavó con MeOH. El filtrado se concentró para proporcionar el compuesto **9B** para la reacción siguiente sin purificación adicional.

Método B: Al compuesto **9A** en EtOH se agregó $SnCl_2$-$2H_2O$ (4eq.), y la mezcla se calentó a reflujo durante 2 h. La mezcla se concentó y se vertió en hielo, se neutralizó a pH 7 con $NaHCO_3$ saturado. Luego el sólido se filtró y se lavó concienzudamente con EtOAc. El filtrado se separó y el acuoso se extrajo con (3x). La capa orgánica se secó ($MgSO_4$), se filtró y se concentró para proporcionar el compuesto **9B**.



9C **9D** **9E - 9Z**

Los compuestos **9E-9Z** (mostrados en la **Tabla 3**) se sintetizaron a partir de **9A, 9B** o **9C** siguiendo los procedimientos descritos en el Ejemplo 3. La reducción selectiva de nitro únicamente del material de partida **9A13** (2,6-dinitrofenol) usando el Método A proporcionó 2-amino-6-nitrofenol.

Tabla 3

Material de partida	**R**	**Método de Reducción a partir de 9A**	**Comp.**	**Datos espectrales MS (MH+) a menos que se especifique**
9A1	4-F	A	**9E**	234
9A2	5-F	A	**9F**	234
9A3	6-F	A	**9G**	234
9A4	5,6-diF	A	**9H**	252
9B1	4-Cl	N.A.	**9I**	^{1}H RMN ($CDCl_3$): 7.60 (s, 1H), 6.90 (s, 1H), 6.75 (d, 1H), 6.66 (d, 1H), 6.55 (dd, 1H), 4.40 (s, 2H), 4.20 (t, 2H), 3.40 (t, 2H)
9B2	5-Cl	N. A.	**9J**	250
9A5	6-Cl	B	**9K**	250
9A6	4,6-diCl	B	**9L**	284
9C1	4-Me	N.A.	**9M**	230
9A7	3-Me	A	**9N**	230
9B3	4-Ph	N.A.	**9O**	292
9A8	4-Br	B	**9P**	294
9A9	4-CF_3	A	**9Q**	284
9A10	3-OMe	A	**9R**	246
9A11	4-OMe	A	**9S**	246
9B4	5-OMe	N.A.	**9T**	246
9A12	6-OMe	A	**9U**	246
9B5	4-SO_2NH_2	N.A.	**9V**	295

9B6	4-SO_2Et	N.A.	**9W**	308
9B7	5-NO_2	N.A.	**9X**	261
9A13	6-NO_2	A	**9Y**	261
9A14	4-CO_2CH_3	B	**9Z**	274

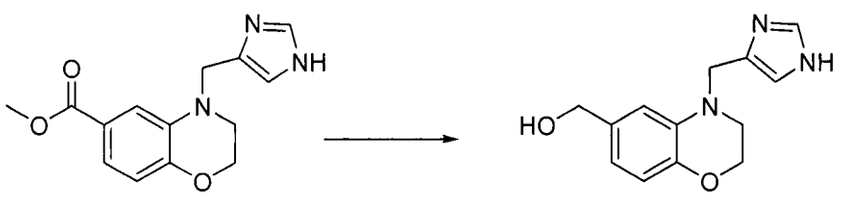
El material de partida **9A10** en la **Tabla 3** se preparó de la manera siguiente:

Se agregó cuidadosamene sulfato de dimetilo (2.7 mL, 0.058 mmol) a 2-nitrobencen-1,3-diol (2.5 g, 0.232 mmol) y la mezcla se agitó vigorosamente mientras se agregaba una solución NaOH al 10% (21 mL) y la temperatura se mantenía por debajo de los 40 °C. Después de aproximadamente 15 min, la mezcla se enfrió y luego se filtró. El filtrado se recogió y se acidificó con HCl al 10%, y se extrajo con éter (3 x 25 mL). La capa orgánica se secó ($MgSO_4$), se filtró y se concentró bajo vacío. La cromatografía (10-30% de EtOAc/hexanos) proporcionó **9A10** (1 g, 37%).

El material de partida **9A12** en la **Tabla 3** se preparó de la manera siguiente:

Se agregó cuidadosamente HNO_3 fumante (0.34 mL, 0.008 mmol) a una mezcla de 2-metoxifenol (0.886 mL, 0.008 mmol) en DCM anhidro (10 mL) a -20 °C. Después de agitar durante 2 h a temperatura ambiente, la mezcla se concentró bajo vacío. La cromatografía (10-30% EtOAc/ hexanos) proporcionó **9A12** (400 mg, 29%) y 2-metoxi-3-nitrofenol (400 mg, 29%).

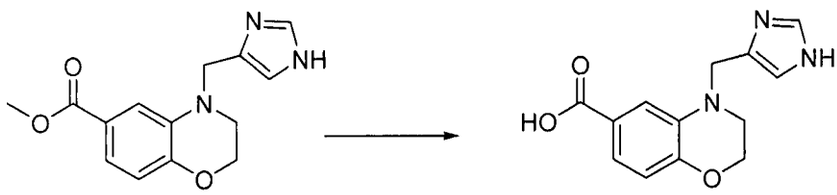
EJEMPLO PREPARATIVO 10



9Z **10**

Una mezcla del compuesto **9Z** (46 mg, 0.24 mmol) en THF anhidro (10 mL) a 0 °C se trató cuidadosamente con LAH en polvo (18 mg, 0.48 mmol) y luego se agitó durante 2 horas a temperatura ambiente. La reacción se apagó con una solución de NaOH 1N (2 mL), se filtró y se concentró bajo vacío. La cromatografía (DCM con 3 a 5% de NH_3-MeOH 7N) proporcionó **10** (47 mg, 80%). MS m/z 246(MH+).

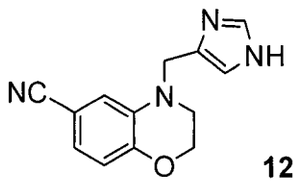
EJEMPLO PREPARATIVO 11



9Z **11**

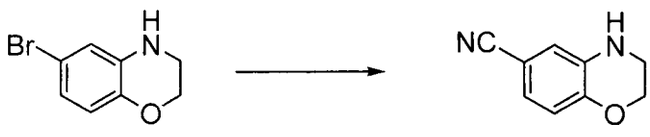
Una mezcla de **9Z** (67 mg, 0.24 mmol) en MeOH (5 mL) se trató con NaOH (15 mg, 0.38 mmol) y se agitó a temperatura ambiente durante la noche. La reacción se neutralizó luego con 10% de HCl y se concentró bajo vacío. El residuo se extrajo en MeOH, se agitó durante 1 h, se filtró y se concentró. La cromatografía (Prep-HPLC) proporcionó el compuesto **11** (21 mg, 32%). EM m/z 260(MH+).

EJEMPLO PREPARATIVO 12



12

Etapas 1



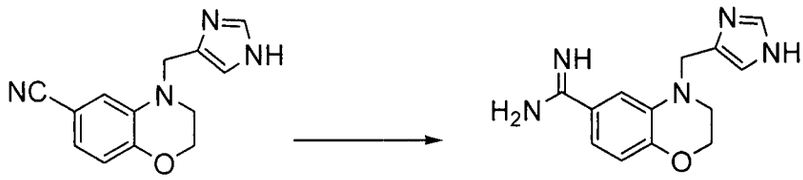
9D **12A**

Una mezcla de 6-bromo-3,4-dihidro-2H-benzo[1,4]oxazina (**9D**, 1.5 g, 7.05 mmol) y CuCN (1.58 g, 17.61 mmol) en DMF anhidro (15 mL) se agitó a 130°C durante 3 h y luego a 150°C durante la noche. Luego, la mezcla se enfrió a temperatura ambiente, se apagó con agua y se concentró bajo vacío. El residuo se extrajo en NaOH 2N y EtOAc (100 mL) y luego se agitó en un sonicador durante 1 h. El precipitado se filtró y se lavó con EtOAc. El filtrado y los lavados se combinaron y se extrajeron con EtOAc (2 x 80 mL). La capa orgánica se secó ($MgSO_4$), se filtró y se concentró para proporcionar el compuesto **12A** (1.062 g, 94%).

Etapa 2

De manera similar a la descrita en el Ejemplo 3, Etapa 3, **12A** se convirtió al compuesto del título **12**. MS m/z 241 (MH+).

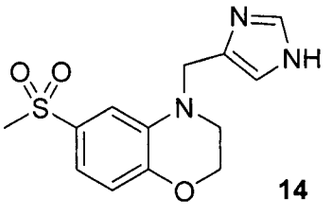
EJEMPLO 13



12 **13**

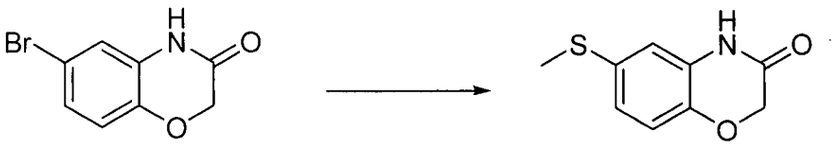
Una solución de **12** (0.179 g, 0.75 mmol) en EtOH anhidro (10 mL) se enfrió a 0 °C y se trató con un gas HCl burbujeante durante 15 min. La mezcla se agitó a 0 °C durante 30 min, se calentó a temperatura ambiente durante la noche, y se concentró. El residuo se disolvió en NH_3-MeOH 2,0 M (5 mL), se agitó a temperatura ambiente durante 4 h, y luego se concentró bajo vacío. La cromatografía (Ranin-Prep HPLC, Waters SunFire™ Prep C18 5 μM, columna 19-100 mm, gradiente 5-90% de CH_3CN/H_2O) proporcionó el compuesto **13** (36 mg: 19%). MS m/z 258 (MH+).

EJEMPLO PREPARATIVO 14



14

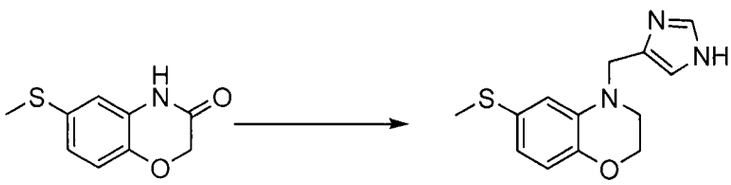
Etapa 1



9C **14A**

A una suspensión de KH (30% en aceite mineral, lavada con hexanos, 1.2 g, 8.98 mmol) en THF anhidro (20 mL) a 0 °C bajo argón se agregó una solución de 6-bromo-4H-benzo[1,4]oxazin-3-ona (**9C**, 1.02 g, 4.49 mmol) en THF (20 mL). Después de 15 min, la solución se enfrió a -78 °C, y se agregó por goteo *t*-BuLi (1.7 M en pentano, 5.18 mL, 8.8 mmol). La mezcla se agitó durante 15 min a -78 °C, y luego se trató por goteo con disulfuro de dimetilo. La solución se calentó gradualmente a temperatura ambiente y se agitó durante la noche. La reacción se apagó luego cuidadosamente con NH_4Cl sat. (15 mL) y se filtró. El filtrado se diluyó con agua y se extrajo con EtOAc (3 x 50 mL). Las capas orgánicas combinadas se secaron ($MgSO_4$), se filtraron y se concentraron. La cromatografía (5-25% EtOAc/ hexanos) proporcionó **14A** (0.483 g, 55%).

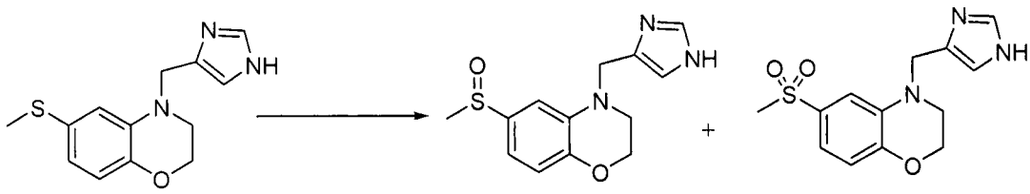
Etapas 2-3



14A **14B**

De manera similar a la descrita en el Ejemplo 3, Etapas 2-3, se redujo **14A** con BH_3-SMe_2 y se trató con imidazol-4-carboxaldehído para proporcionar **14B**. MS m/z 262(MH+).

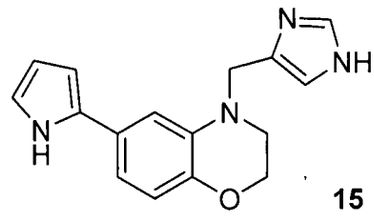
Etapa 4



14B **14C** **14**

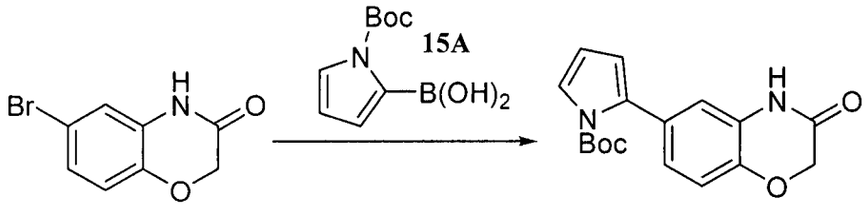
A un compuesto **14B** (0.447 g, 1.71 mmol) en DCM anhidro (10 mL) se agregó MCPBA (77%, 0.85g, 3.77 mmol), y la mezcla se agitó a temperatura ambiente durante la noche. La reacción se apagó con una solución Na_2CO_3 sat. y el solvente se removió bajo vacío. La solución concentrada se extrajo con EtOAc (3 x 10 mL). La capa orgánica se secó ($MgSO_4$), se filtró, y se concentró bajo vacío. La cromatografía (DCM que contenía 1-7% de NH_3-MeOH 7N) proporcionó el compuesto del título **14** (67 mg, 13%, MS m/z 294 MH+) y una mezcla de **14C** y **14**, que se purificó con HPLC preparativa Ranin para proporcinar **14C** (39 mg, 8%, MS m/z 278 MH+).

EJEMPLO PREPARATIVO 15



15

Etapas 1

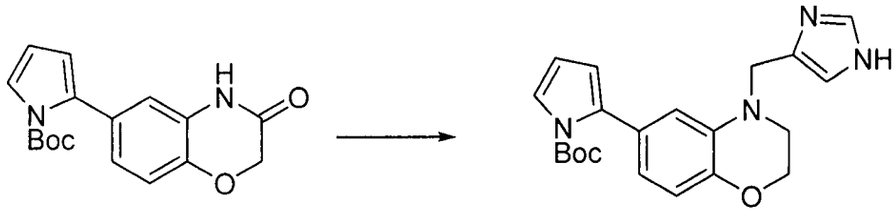


9C **15A** **15B**

A un compuesto 6-bromo-4H-benzo[1,4]oxazin-3-ona (**9C**, 500 mg, 2.2 mmol) en tolueno (44 mL) se agregó $Pd(PPh_3)_4$ (127 mg, 0.11 mmol). Después de agitar a temperatura ambiente durante 30 min, se agregaron ácido borónico **15A**

(697 mg, 3.3 mmol) en EtOH (13 mL, 0.25 M) y una solución $NaHCO_3$ saturada (22 mL) y la solución se calentó a reflujo durante la noche. Luego la mezcla se enfrió a temperatura ambiente, y se vertió en una solución NaCl saturada, y se concentró bajo vacío. El residuo se diluyó con agua y se extrajo con EtOAc (3 x 25 mL). La capa orgánica se secó ($MgSO_4$), se filtró, y se concentró bajo vacío. La cromatografía (10 a 30% de EtOAc/ hexanos) proporcionó **15B** (320 mg, 46%).

Etapas 2-3



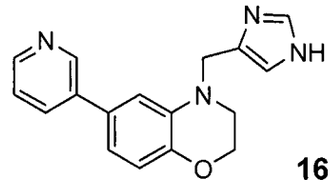
15B **15C**

De manera similar a la descrita en el EJEMPLO 3, Etapas 2-3, se redujo **15B con** BH_3-SMe_2 y se trató con imidazol-4-carboxaldehído para proporcionar **15C**. MS m/z 381 (MH+).

Etapa 4

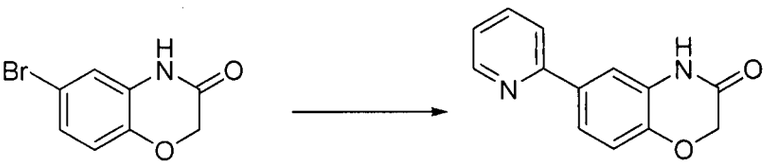
Una mezcla de **15C** (143 mg, 0.37 mmol) en HCl-dioxano 4.0 M (1.5 mL, 0.56 mmol) se agitó a temperatura ambiente durante la noche. La reacción se neutralizó con NH_3-MeOH 7N y se concentró. El residuo se purificó con TLC preparativa (DCM que contenía 10% de NH_3-MeOH 7N) para proporcionar el compuesto del título **15** (28 mg, 26%).MS m/z 281 (MH+).

EJEMPLO PREPARATIVO 16



16

Etapa 1



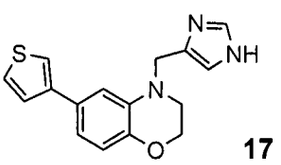
9C **16A**

A una solución agitada de Pd $(OAc)_2$ (3 mg, 0.0125 mmol) y PPh_3 (13 mg, 0.05 mmol) en THF anhidro (2 mL) bajo argón se agregó 6-bromo-4H-benzo[1,4]oxazin-3-ona (**9C**, 57 mg, 0.25 mmol). La mezcla se agitó a temperatura ambiente durante 10 min y se trató consecutivamente con una solución de ácido 3-piridin borónico (62 mg, 0.5 mmol) en EtOH (1 mL) y una solución $NaHCO_3$ acuosa (2 M, 2 mL). La mezcla se calentó a reflujo durante 2 h y luego se enfrió a temperatura ambiente. La solución se vertió en una solución de NaCl saturada, y luego se concentró al vacío. El residuo se diluyó con agua (5 mL) y se extrajo con EtOAC (3 x 10 mL). La capa orgánica se secó ($MgSO_4$), se filtró, y se concentró bajo vacío. La cromatografía (10-30% EtOAc/hexanos) proporcionó **16A** (21mg, 37%).

Etapas 2-3

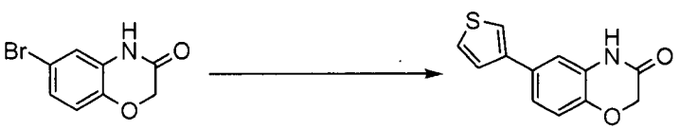
El compuesto **16A** se convirtió al compuesto **16** por reducción con BH_3-SMe_2 y alquilación reductiva con imidazol-4-carboxaldehído tal como se describió en el EJEMPLO 3, Etapas 2-3.MSm/z 293(MH+).

EJEMPLO PREPARATIVO 17



17

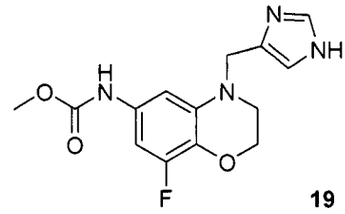
Etapa 1



9C **17A**

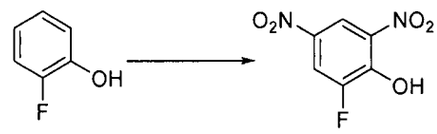
247

EJEMPLO PREPARATIVO 19



19

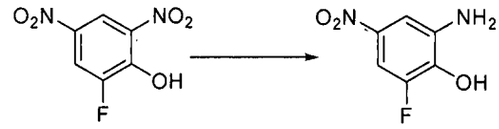
Etapa 1



19A 19B

A 2-fluorfenol (**19A**, 8 mL, 86.4 mmoles) en DCM anhidro (70 mL) a 0 °C se agregó HNO_3 fumante, (0.34 mL, 0.008 mmol) por goteo, a través de un recipiente de adición. La mezcla se calentó a temperatura ambiente y se agitó durante 2 h, luego se enfrió a 0 °C nuevamente y se apagó con una solución NaOH 2N a pH 5. La mezcla se concentró bajo vacío, se diluyó con agua, se extrajo con EtOAc (3 x 100 mL). La capa orgánica combinada se secó ($MgSO_4$), se filtró y se concentró bajo vacío para proporcionar el compuesto **19B** (15.07 g, rendimiento: 86.4%).

Etapa 2



19B 19C

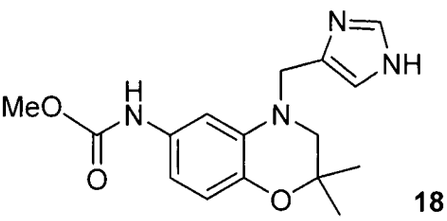
Una solución de **19B** (15.07g, 74.6 mmol) en EtOH (300 mL) se trató con $SnCl_2$-$2H_2O$ (50.5 g, 224 mmol) y se calentó a reflujo durante 2 h. La mezcla se concentró, se vertió en hielo, y se neutralizó a pH 7 con una solución NaOH 2N. El sólido se filtró y se lavó con EtOAc (5 x 500 mL). El filtrado se separó y el acuoso se extrajo con EtOAc (3 x 100 mL). La capa orgánica se secó ($MgSO_4$), se filtró y se concentró proporcionando **19C** (12.59 g, 98%).

Un frasco de procesamiento Smith (2-5 mL) se cargó con una barra agitadora, 6-bromo-4H-benzo[1,4]oxazin-3-ona (**9C**, 23 mg, 0.1 mmol), ácido tiofen-3-ilborónico (17mg, 0.13 mmol) y EtOH (2 mL). Luego se agregaron consecutivamente K_2CO_3 acuoso (1 M, 0.12 mL) y Pd soportado sobre polímero (40 mg, 3 mol % de Pd, Fiber Cat. 1000-D32, Pd% 4.26). El recipiente de reacción se selló y se calentó a 110 °C durante 1 h bajo irradiación por microondas. Después de enfriamiento, la mezcla de reacción se transfirió a una columna pre-empaquetada de carbonato Si (2 g, 0.79 mmol/g), que había sido acondicionado con MeOH/DCM (1:1). El producto se eluyó con MeOH/DCM (1:1, 3 x 3 mL, filtración gravitacional) y se concentró para proporcionar el compuesto **17A** (18 mg, 80%).

Etapas 2-3

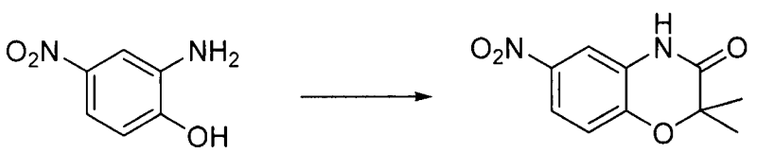
El compuesto **17A** se convirtió a **17** de manera similar a la descrita en el Ejemplo 3, Etapas 2-3. MS m/z 298 (MH+).

EJEMPLO PREPARATIVO 18



18

Etapa 1

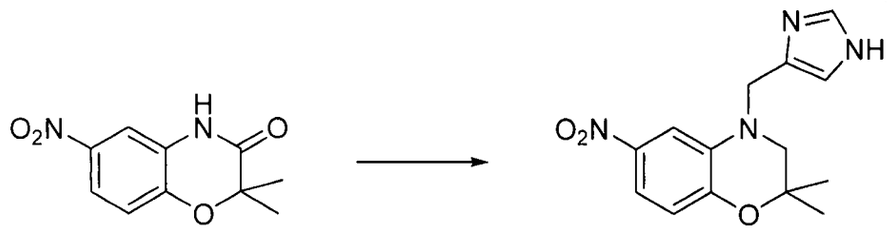


3A **18A**

Un frasco de procesamiento Smith (20 mL) se cargó con una barra agitadora, compuesto **3A** (1 g, 6.49 mmol), 2-bromo-2-metilpropanoato de etilo (1 mL, 6.81 mmol), KF (1.13 g, 19.5 mmol) y DMF (10 mL). El recipiente de reacción se selló y se calentó a 160 °C durante 1 h bajo irradiación por microondas.

Después de enfriar la mezcla de reacción se vertió en agua helada y se extrajo con EtOAc (3 x 50 mL). La capa orgánica se secó ($MgSO_4$), se filtró, y se concentró bajo vacío. La cromatografía (10-30% de EtOAc/hexanos) proporcionó **18A** (0.245 g, 17%).

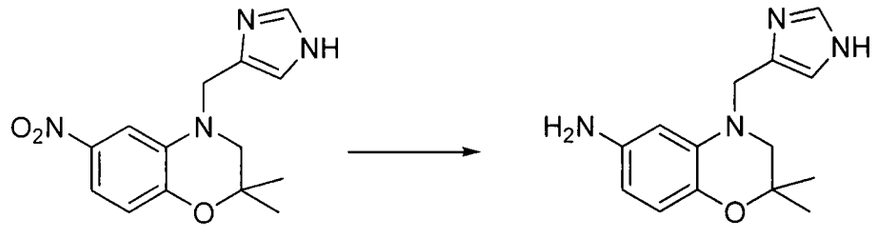
Etapa 2-3



18A **18B**

De manera similar a la descrita en el EJEMPLO 3, Etapas 2-3, se redujo **18A con** BH_3-SMe_2 y se hizo reaccionar con imidazol-4-carboxaldehído para proporcionar **18B**.MS m/z 289 (MH+).

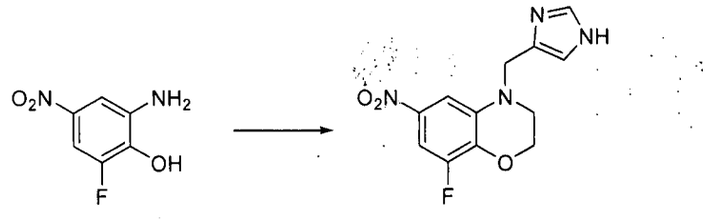
Etapa 4-5



18B **18C**

Siguiendo el procedimiento que se da en el EJEMPLO 3, Etapa 4, se hidrogenó **18B** para proporcionar el compuesto **18C.** De manera similar a la descrita en el EJEMPLO 3, Etapa 5, **18C** se hizo reaccionar adicionalmente con $ClCO_2Me$ para proporcionar el compuesto del título **18**.MS m/z 317 (MH+).

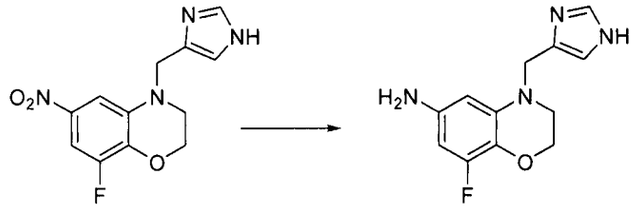
Etapas 3-5



19C **19D**

De manera similar a la descrita en el EJEMPLO 3, Etapas 1-3, se hizo reaccionar **19C** con cloruro de cloroacetilo, se redujo con BH_3-SMe_2, y se trató con imidazol-4-carboxaldehído para proporcionar el compuesto **19D.** MS m/z 279 (MH+).

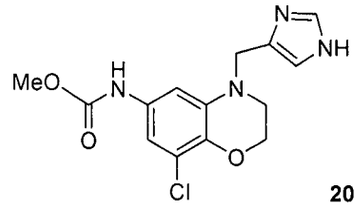
Etapas 6-7



19D **19E**

De manera similar a la descrita en el Ejemplo 3, Etapa 4, se hidrogenó **19D** para proporcionar el compuesto **19E.** MS m/z 249 (MH+). El compuesto **19E** se hizo reaccionar adicionalmente con $ClCO_2Me$ tal como se describió en el Ejemplo 3, Etapa 5, para proporcionar el compuesto del título **19**. MS m/z 307 (MH+).

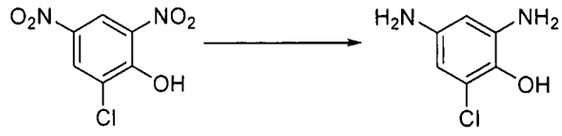
EJEMPLO PREPARATIVO 20



20

249

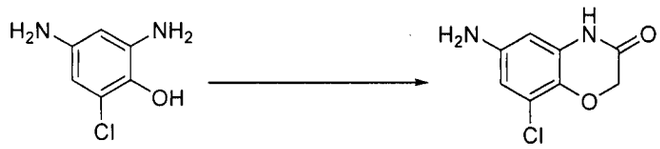
Etapa 1



20A **20B**

A 2-cloro-4,6-dinitrofenol (**20A**, 2 g, 9.18 mmol) en EtOH (100 mL) se agregó cuidadosamente una cucharada de níquel Raney (20% en peso). La mezcla se agitó a temperatura ambiente bajo un balón de hidrógeno durante la noche y luego se filtró. El solvente se evaporó bajo vacío para proporcionar un sólido blanco **20B** (1.3 g, 89%) y usar directamente en la reacción siguiente.

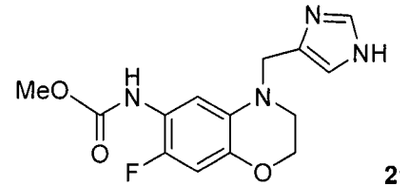
Etapas 2-5



20B **20C**

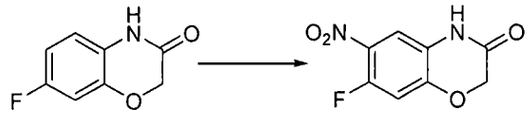
Siguiendo el procedimiento descrito en el Ejemplo 3, Etapa 1, se hizo reaccionar **20B** cloruro de cloroacetilo para proporcionar **20C** (5%). El compuesto **20C** se trató con $ClCO_2Me$, se redujo con BH_3-SMe_2, y alquilación reductiva de manera similar a la descrita en el Ejemplo 8 y en el Ejemplo 3 (Etapas 2-3) para proporcionar el compuesto del título **20.** MS m/z 323 (MH+).

EJEMPLO PREPARATIVO 21



21

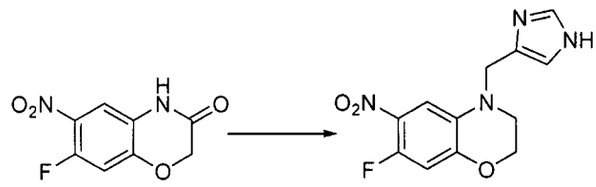
Etapa 1



21A **21B**

Al compuesto **21A** (5 g, 30 mmol) en H_2SO_4 concentrado (17 mL) se agregó una mezcla 1:1 de HNO_3 fumante y H_2SO_4 conc. (7 mL) durante 15 min. La mezcla se agitó durante 30 min adicionales a temperatura ambiente y se vertió lentamente en agua helada (500 mL). La mezcla se filtró hasta recoger el sólido y se lavó con agua (4x). El sólido se colocó bajo alto vacío en un baño de aceite a 80 °C durante 5 h para proporcionar **21B** (3.82 g, 60%).

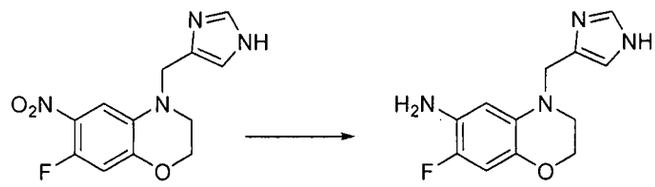
Etapas 2-3



21B **21C**

De manera similar a la descrita en el Ejemplo 3, Etapas 2-3, se redujo **21B** con BH_3-SMe_2 y luego se trató con imidazol-4-carboxaldehído para proporcionar el compuesto **21C.** MS m/z 279 (MH+).

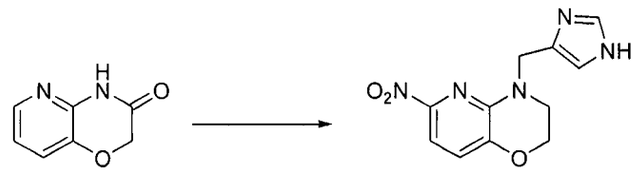
Etapas 4-5



21C **21D**

De manera similar a la descrita en el Ejemplo 3, Etapas 4, se hidrogenó **21C** para proporcionar el compuesto **21D**. El compuesto **21D** se convirtió luego al compuesto del título **21** tal como se describió en el Ejemplo 3, Etapa 5.MSm/z 307 (MH+).

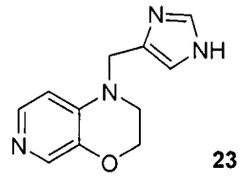
EJEMPLO PREPARATIVO 22



22A **22**

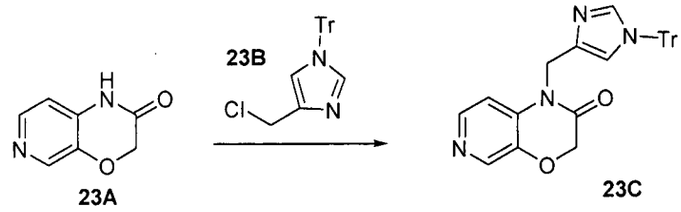
Siguiendo los procedimientos descritos en el Ejemplo 21 (Etapa 1) y Ejemplo 3 (Etapas 2-3), se nitritó **22A** con HNO_3, se redujo con BH_3-SMe_2, y se hizo reaccionar con imidazol-4-carboxaldehído para proporcionar el compuesto **22.** MS m/z 262 (MH+).

EJEMPLO PREPARATIVO 23



23

Etapa 1



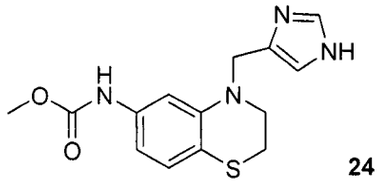
Una solución del compuesto **23A** (330 mg, 2.2 mmol, Patente Norteamericana No. 5.652.363) en DMF (4 mL) se trató con NaH (60% en aceite mineral, 88 mg, 2.2 mmol) a temperatura ambiente. La mezcla se agitó durante 20 min, seguido de adición de una solución del compuesto **23B** (0.79 g, 2.2 mmol, J. Med. Chem., 2002, 45, 533) en DMF (4 mL). La mezcla se se agitó a 45 °C durante 3 días, y luego se apagó con agua se concentró bajo vacío. El residuo se disolvió en EtOAc (50 mL), se lavó con agua (2 x 10 mL). La capa orgánica se secó (Na_2SO_4), se filtró y se concentró bajo vacío. La cromatografía (DCM con 2-3% NH_3-MeOH 7N) proporcionó **23C** (519 mg, 50%). MS m/z 473 (MH+).

Etapas 2-3

De manera similar a la descrita en el Ejemplo 2 (Etapa 2) y Ejemplo 15 (Etapa 4), se redujo **23C** con BH_2-SMe_2 (18 h a reflujo) y luego se desprotegió con HCl-dioxano (1 h a 60 °C) para proporcionar el compuesto del título **23**. MS m/z 217 (MH+).

252

EJEMPLO PREPARATIVO 24



24

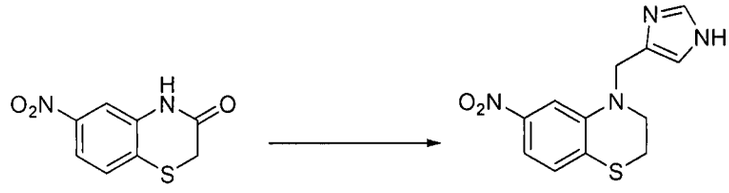
Etapa 1



24A **24B**

Una solución agitada de 2-cloro-5-nitroanilina **24A** (34.4 g, 0.2 mol) en EtOH absoluto (200 mL) a 70 °C se trató gradualmente con una solución de nonahidrato de sulfuro de sodio (48 g, 0.2 mol) y azufre (9.6 g, 0.3 mol), que había sido pre-calentada hasta fusión. La mezcla se reflujó durante 30 min y se enfrió a temperatura ambiente. La mezcla se filtró para recoger el sólido, y se lavó con agua. El sólido se secó bajo vacío a 100 °C durante 5 h. El sólido resultante se extrajo en agua (200 mL) y se trató con NaOH (8 g, 0.2 mol) y $ClCH_2COOH$ (18.9g, 0.2 mol). La mezcla se calentó luego a reflujo durante 1.5 h. Después de enfriar, la mezcla se acidificó con una solución de HCl al 10% y se filtró para recoger un sólido marrón-amarillento, y se lavó con agua para proporcionar el compuesto **24B** (25 g, 60%).

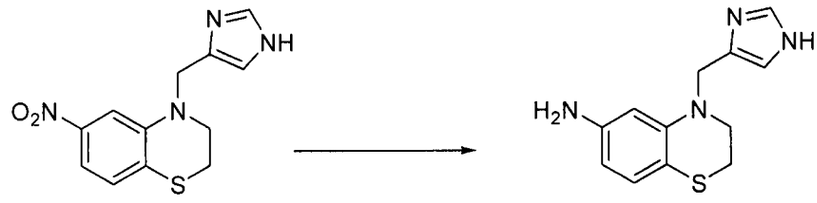
Etapas 2-3



24B **24C**

Siguiendo el procedimiento descrito en el Ejemplo 3, Etapas 2-3, se redujo **24B** con BH_3-SMe_2 y se trató con imidazol-4-carboxaldehído para proporcionar **24C.** MS m/z 277 (MH+).

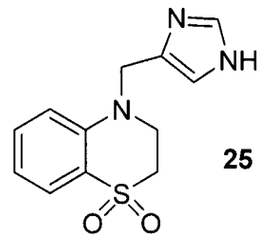
Etapas 4-5



24C **24D**

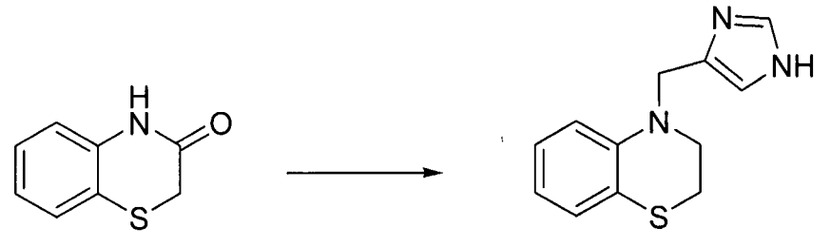
De manera similar a la descrita en el Ejemplo 3, Etapa 4, se hidrogenó **24C** para proporcionar **24D**. MS m/z 247 (MH+). El compuesto **24D** se trató adicionalmente con $ClCO_2Me$ tal como se describió en el Ejemplo 3, Etapa 5, para proporcionar el compuesto del título **24.** MS m/z 305 (MH+).

EJEMPLO PREPARATIVO 25



25

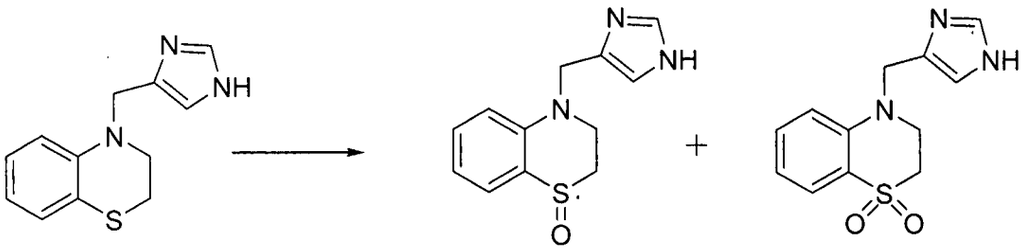
Etapas 1-2



25A **25B**

Siguiendo procedimientos descritos en el Ejemplo 3 (Etapas 2-3), el compuesto **25A** se sometió a reducción con BH_3-SMe_2 y luego a aminación reductiva con imidazol-4-carboxaldehído para proporcionar el compuesto **25B**. MS m/z 232 (MH+).

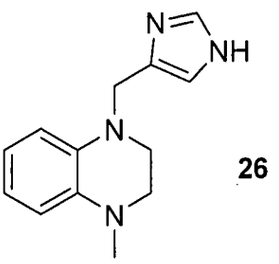
Etapa 3



25B **25C** **25**

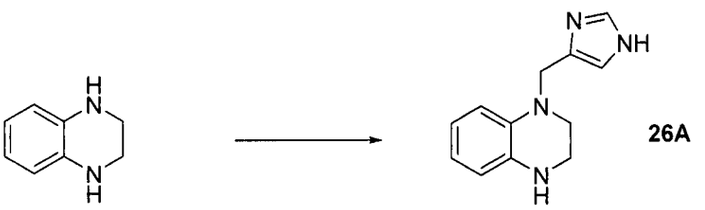
De manera similar a la descrita en el Ejemplo 14, Etapa 4, se oxidó **25B** con MCPBA para proporcionar los compuestos **25C** (ES m/z 248 MH+) y **25** (MS m/z 264 MH+).

EJEMPLO PREPARATIVO 26



26

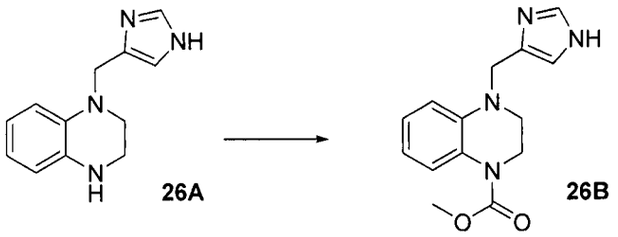
Etapa 1



26A

De manera similar a la descrita en el Ejemplo 1, 1,2,3,4-tetrahidro-quinoxalina y imidazol-4-carboxaldehído **1B** fueron sometidos a aminación reductiva para proporcionar **26A.** LMCS m/z 215 (MH+).

Etapa 2



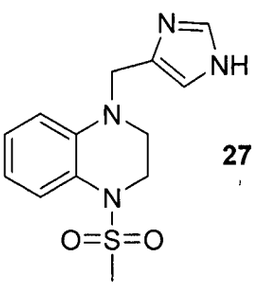
26A **26B**

De manera similar a la descrita en el Ejemplo 3, Etapa 5, **26A** se convirtió a **26B.** LMCS m/z 273 (MH+).

Etapa 3

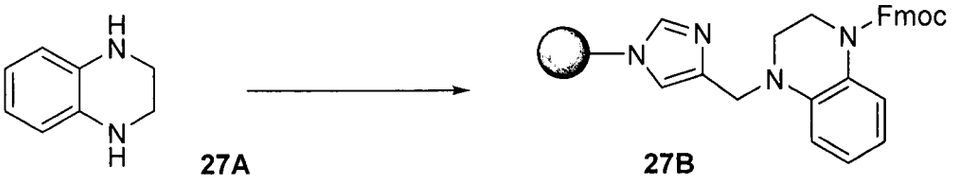
El compuesto **26B** (120 mg) se agregó en porciones a una suspensión agitada de LAH en polvo (500 mg) en Et_2O (15 mL) a 0 °C. La mezcla se reflujó durante 1 h y luego se enfrió a 0 °C. La reacción se trató consecutivamente con H_2O (0.5 mL), NaOH 1N (0.5 mL), y H_2O (1.5 mL). y luego se concentró. La cromatografía (DCM con 2 a 5% de NH_3-MeOH 7N) proporcionó el compuesto del título **26.** MS m/z 229(MH+). Alternativamente, los compuestos de ese tipo pueden ser sintetizados mediante un procedimiento de fase sólida tal como se ha descrito en el siguiente EJEMPLO 27.

EJEMPLO PREPARATIVO 27



27

Etapas 1-2



27A **27B**

256

Una mezcla de 1,2,3,4-tetrahidroquinoxalina (**27A**, 2 g, 14.9 mmol) en dioxano (15 mL) y agua (24 mL) a 0 °C se trató consecutivamente con Na_2CO_3 (1.58 g, 14.9 mmol) y FmocCl (3.84g, 14.9 mmol) en dioxano (20 mL, agregadp por goteo). La mezcla se calentó gradualmente a temperatura ambiente y se agitó durante la noche. La mezcla de reacción se diluyó con agua (50 mL) y se extrajo con DCM (2 x 70 mL). Las capas orgánicas combinadas se secaron (Na_2SO_4), se concentraron y sometieron a cromatografía (30-40% EtOAc/hexanos, rendimiento 0.75g, 14%). La reacción subsiguiente con resina **1D** tal como se ha descrito en el Ejemplo 1 proporcionó **27B.**

Etapas 3-5

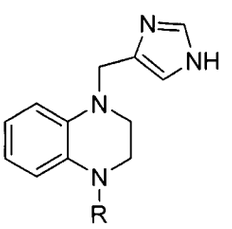


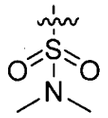
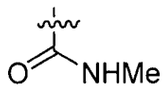
27B **27C**

El compuesto **27B** (0.5 g, 1.4 mmol/g) se agitó en 30% de piperidina/DMF durante la noche. La resina se lavó con DMF (3x), MeOH (3x) y DCM y luego se secó al vacío para proporcionar **27C**. La resina **27C** (125mg, 1.4 mmol/g) se suspendió en DCM (5 mL) y se trató con piridina (0.283 mL, 3.5 mmol) y $MeSO_2Cl$ (0.135 mL, 1.75 mmol). La reacción se agitó durante la noche, luego se lavó con MeOH (2x), DMF (2x), DCM (2x), MeOH (2x) y DCM (3x). La disociación subsiguiente de la resina con TFA, tal como ha sido descrito en el Ejemplo 1, proporcionó el compuesto del título **27**. MS m/z 293 (MH+).

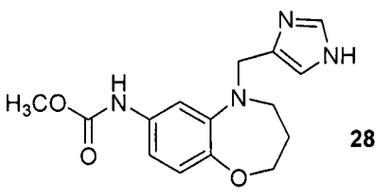
Los compuestos en la **Tabla 4** pueden ser preparados a partir de la resina **27C** mediante reacción con los varios reactivos mostrados seguido de disociación. con TFA.

Tabla 4



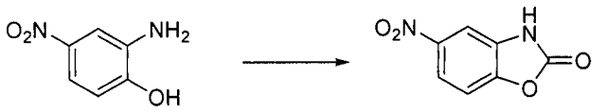
Comp	Reactivo	R	MS (MH+)
27D	Me_2NSO_2Cl/ piridina		322
27E	Ac_2O/ piridina		257
27F	MeNCO		272

EJEMPLO PREPARATIVO 28



28

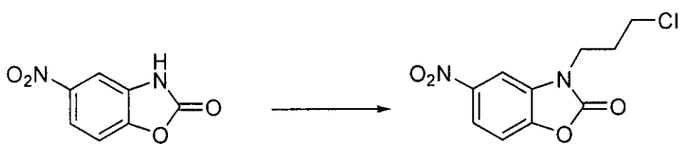
Etapa 1



3A **28A**

A 6-nitro-2-aminofenol (**3A**, 3.03g, 19.7 mmol) en DCM anhidro (50 mL) se agregó carbonato de dipiridilo (4.25 g, 19.7 mmol). La mezcla se agitó a temperatura ambiente durante la noche, y luego se concentró bajo vacío. La cromatografía (1-6% MeOH/DCM) proporcionó el sólido **28A** (2.77 g, 78%).

Etapa 2

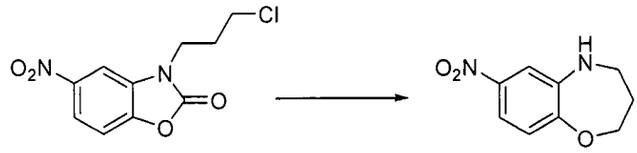


28A **28B**

Una solución de **28A** (0.69 g, 3.83 mmol) en 2-etoxietanol (10 mL) se trató con KOH (0.22 g, 3.83 mmol) y se agitó a temperatura ambiente durante 1 hora. La mezcla se calentó luego a reflujo y se trató con 1-bromo-3-cloropropano (0.75 mL, 7.67 mmol). Después de reflujar durante 4 h, la solución se filtró y se

concentró para proporcionar **28B**, que se extrajo en la Etapa 3 sin purificación adicional.

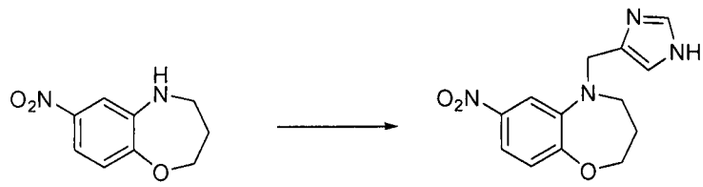
Etapa 3



28B **28C**

Una solución de **28B** en 2-etoxietanol y DMF (10 mL, 1:1) se transfirió a un frasco de procesamiento Smith (20 mL) con una barra agitadora, y se trató con KOH (0.86g, 15.32 mmol). El recipiente de reacción se selló y se calentó a 220 °C durante 1 h bajo irradiación por microondas. Después de enfriar, la mezcla de reacción se filtró y se concentró. El residuo se diluyó con agua y se extrajo con EtOAc (3 x 10 mL). Las capas orgánicas combinadas se secaron ($MgSO_4$), se filtraron y se concentraron bajo vacío. La cromatografía (DCM que contenía 1-5% NH_3-MeOH 7N) proporcionó **28C** (124 mg, 17% para dos etapas).

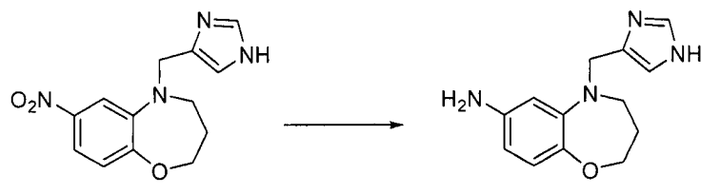
Etapa 4



28C **28D**

De manera similar a la descrita en el Ejemplo 3 (Etapa 3), se hizo reaccionar **28C** con imidazol-4-carboxialdehído para proporcionar el compuesto **28D.** MS m/z 275 (MH+).

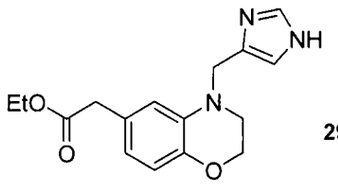
Etapas 5-6



28D **28E**

De manera similar a la descrita en el Ejemplo 3 (Etapa 4), **28D** se hidrogenó para proporcionar el compuesto **28E.** MS m/z 245 (MH+). Siguiendo el procedimiento descrito en el Ejemplo 3 (Etapa 5), **28E** se hizo reaccionar adicionalmente con $ClCO_2Me$ para proporcionar el compuesto del título **28**. MS m/z 303 (MH+).

EJEMPLO PREPARATIVO 29



29

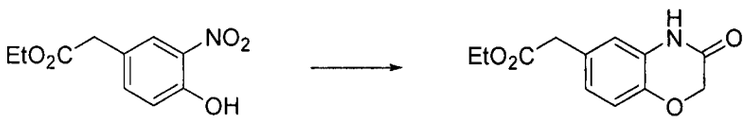
Etapa 1



29A

Una mezcla de ácido 4-hidroxi-3-nitrofenilacético (10 g, 51 mmol) y HCl-dioxano 4M (40 mL) en EtOH (150 mL) se reflujó durante 2 h y se concentró. El residuo se extrajo en NaOH 1N (50 mL) y se extrajo con CH_2Cl_2 (8x). Las capas orgánicas combinadas se secaron sobre Na_2SO_4, y se concentraron para proporcionar **29A** (8.39 g, 73%) en forma de un aceite amarillo.

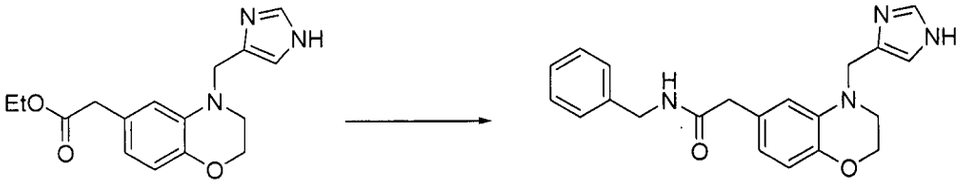
Etapas 2-5



29A **29B**

De manera similar a la descrita en el Ejemplo 20 (Etapa 1) y Ejemplo 3 (Etapa 1), se hidrogenó **29A** con níquel Raney (50 psi H_2) y luego se cicló con cloruro de cloroacetilo para proporcionar **29B**. El compuesto **29B** pudo ser adicionalmente elaborado al compuesto del título **29** siguiendo el procedimiento detallado en el Ejemplo 3 (Etapas 2-3). LMCS m/z 302 (MH+).

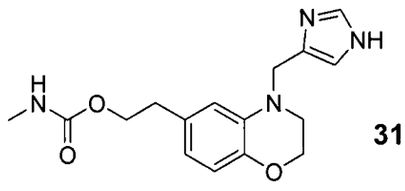
EJEMPLO PREPARATIVO 30



29 **30**

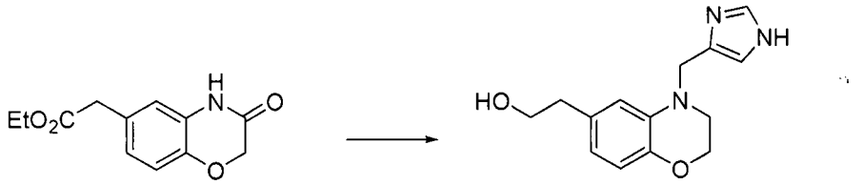
Una solución agitada de bencilamina (0.070 mL, 0.66 mmol) en CH_2Cl_2 (10 mL) se trató por goteo con $AlMe_3$ (2M/tolueno, 0.33 mL, 0.66 mmol) a 20 °C. Después de 20 min, se agregó lentamente una solución de **29** (0.10 g, 0.33 mmol) en CH_2Cl_2 (3 mL). La mezcla se calentó luego a reflujo durante la noche y se enfrió a 20 °C. La reacción se apagó con H_2O (0.5 mL), y se agitó durante 1h. La mezcla se secó luego con Na_2SO_4, se filtró y se concentró. La cromatografía (2-5% NH_3-MeOH/CH_2Cl_2 1N) proporcionó **30** en forma de una película blanca (0.115 g, 96%). LMCS m/z 363 (MH+).

EJEMPLO PREPARATIVO 31



31

Etapas 1-2



29B **31A**

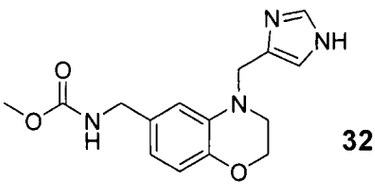
De manera similar a la descrita en el Ejemplo 26 (Etapa 3) y Ejemplo 1, **29B** se redujo con LAH y luego se trató con imidazol-4-carboxaldehído para proporcionar **31A.** LMCS m/z 260 (MH+).

Etapa 3

Una solución de **31A** (0.20 g, 77 mmol) en 1,2-dicloroetano (10 mL) se trató con Et_3N (0.20 mL, 1.5 mmol) y MeNCO (0.050 mL, 0.85 mmol) y se agitó durante

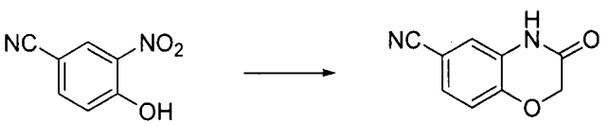
3h a 20 °C. La mezcla se trató con H_2O (10 mL), se extrajo con CH_2Cl_2 (2x), y se concentró. El residuo se sometió a cromatografía (2-5% MeOH/ CH_2Cl_2) y luego se agitó en Et_2NH (5 mL) a 20 °C durante la noche. La mezcla se concentró, y se trató con NaOH 1N, y se extrajo con CH_2Cl_2 (3x). Los extractos orgánicos combinados se secaron con Na_2SO_4, y se concentraron. La cromatografía (5% MeOH/CH_2Cl_2) proporcionó **31** en forma de una película blanca (0.080 g, 33%). LMCS m/z 317 (MH+).

EJEMPLO PREPARATIVO 32



32

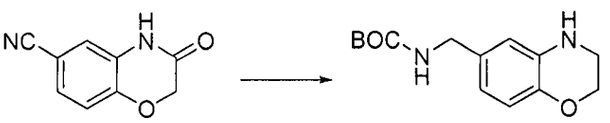
Etapa 1-2



32A **32B**

Siguiendo los procedimientos descritos en el Ejemplo 20 (Etapa 1) y Ejemplo 3 (Etapa 1), se hidrogenó **32A** con niquel Raney (50 psi H_2) y luego se cicló con cloruro de cloroacetilo para proporcionar **32B**.

Etapas 3-4

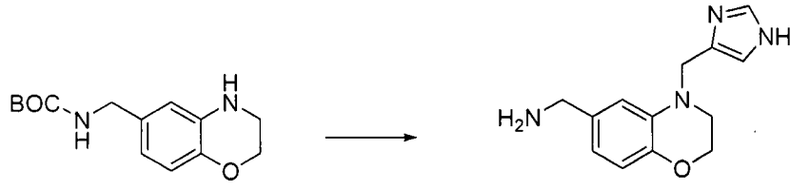


32B **32C**

Siguiendo el procedimiento descrito en el Ejemplo 26 (Etapa 3), el nitrilo y la amida que se encuentran en el compuesto **32B,** fueron concomitantemente reducidos con LAH. El producto resultante (0.83 g, 5.1 mmol) en CH_2Cl_2 (50 mL) se trató con BOC_2O (1.07 g, 5.1 mmol), se agitó a 20 °C durante 0.5 h y luego se concentró. La cromatografía (20-50% EtOAc/hexanos) proporcionó **32C** en forma de una espuma blanca pegajosa (1.19 g, 89%)

262

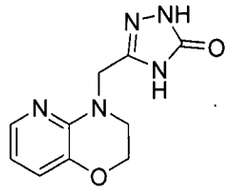
Etapas 5-6



32C **32D**

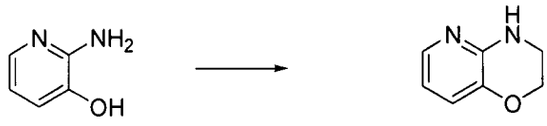
De manera similar a la descrita en el Ejemplo 1 y Ejemplo 15 (Etapa 4), **32C** se trató con imidazol-4-carboxaldehído y luego se desprotegió para proporcionar **32D.** LMCS m/z 245 (MH+). Siguiendo el procedimiento descrito en el Ejemplo 3, Etapa 5, **32D** se trató con $ClCO_2Me$ y se convirtió al compuesto del título **32.** LMCS m/z 303 (MH+).

EJEMPLO PREPARATIVO 33



33

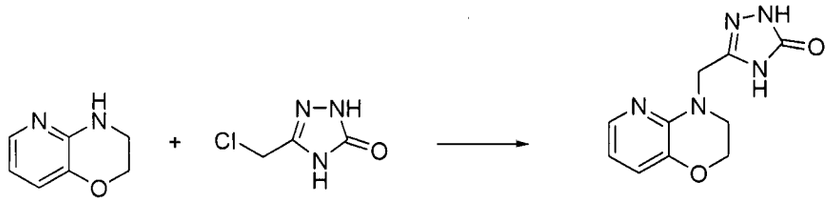
Etapa 1-2



33A

De manera similar a la descrita en el Ejemplo 3 (Etapa 1) y Ejemplo 26 (Etapa 3), 2-amino-3-hidroxipiridina se cicló con cloruro de cloroacetilo y luego se redujo con LAH para proporcionar **33A.**

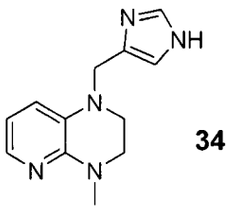
Etapa 3



33A **33B** **33**

Una solución de **33A** (0.105 g 0.77 mmol) en DMF (5 mL) se trató con $KN(SiMe_3)_2$ (0.5 M/tolueno, 1.8 mL, 0.93 mmol), se agitó a 0 °C durante 20 min, y luego se trató con **33B** (0.155 g 1.16 mmol, Tetrahedron Letters **2000**, 41, 8661). La reacción se calentó a 20 °C, se agitó durante 2h, y se concentró. El residuo se trató luego con NaOH 0,5 N (10 mL) y se lavó con CH_2Cl_2 (3x). La capa acuosa se concentró y se sometió a cromatografía (20-80% EtOAc/hexanos) para proporcionar **33** en forma de un sólido blanco (0.065 g, 36%). LMCS m/z 234 (MH+).

EJEMPLO PREPARATIVO 34



34

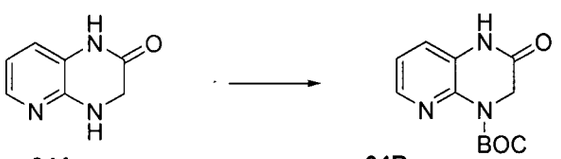
Etapa 1



34A

Una mezcla de 2-cloro-3-nitropiridina (9.4 g, 59 mmol), cloruro de éster etílico de glicina (10.8 g, 77 mmol), y K_2CO_3 (21.3 g, 154 mmol) en tolueno (100mL) se reflujo durante la noche. La mezcla se filtró luego, se concentró y se sometió a cromatografía (20% EtOAc/hexanos). El sólido amarillo resultante se disolvió en EtOH (300 mL), se trató con níquel Raney (2 g) y se hidrogenó a 40 psi H_2 durante la noche. La mezcla se filtró, se concentró y se cromatografió (2-5% MeOH/CH_2Cl_2) para proporcionar **34A** (1.25 g, 14%) y éster etilico de N-(3-amino-2-piridinil)glicina (8.2 g, 71%).

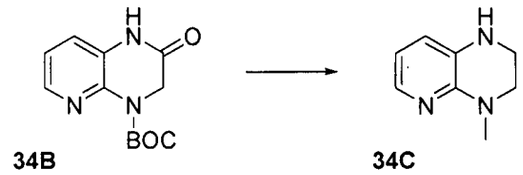
Etapa 2



34A **34B**

De manera similar a la descrita en el Ejemplo 5 (Etapa 1), **34A** se convirtió a **34B** (BOC_2O, DMAP y Et_3N en DCM reflujante).

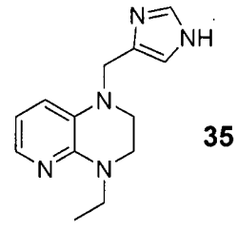
Etapa 3-4



34B **34C**

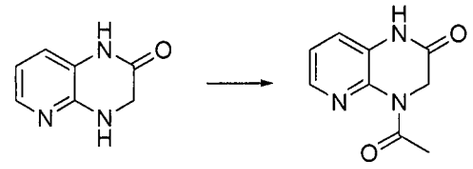
De manera similar a la descrita en el Ejemplo 26 (Etapa 3), **34B** se trató con LAH para proporcionar **34C** en forma de un sólido blanco (0.040 g, 48%). Siguiendo el procedimiento descrito en el Ejemplo 1, **34C** se trató luego con imidazol-4-carboxaldehído para proporcionar el compuesto del título **34.** LMCS m/z 230 (MH+).

EJEMPLO PREPARATIVO 35



35

Etapas 1-3

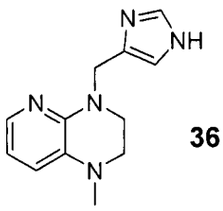


34A **35A**

Una solución de **34A** (0.260 g, 1.74 mmol) en THF (15 mL) se trató con Et_3N (1.2 mL, 8.7 mmol) y Ac_2O (0.33 mL, 3.5 mmol) y se agitó durante la noche a 20 °C. La reacción se trató, diluida, con H_2O (10 mL) y se extrajo con 10% $MeOH/CH_2Cl_2$ (3x). Los extractos orgánicos combinados se secaron con Na_2SO_4 y se concentraron. La cromatografía (20-50% EtOAc/hexanos) proporcionó **35A** en forma de un sólido blanco (0.140 g, 42%).

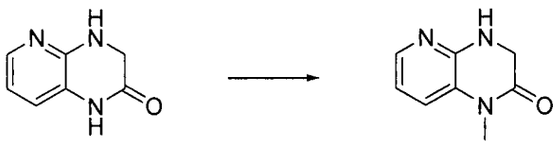
De manera similar a la descrita en el Ejemplo 26 (Etapa 3) y Ejemplo 1, **35A** se redujo con LAH y luego se trató con imidazol-4-carboxaldehído para proporcionar el compuesto del título **35.** LMCS m/z 244 (MH+).

EJEMPLO PREPARATIVO 36



36

Etapas 1-3

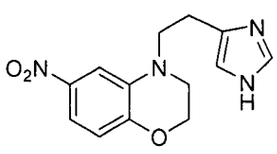


34A **36A**

Una solución de **34A** (0.200 g 1.33 mmol) en DMF (15 mL) se trató con $KN(SiMe_3)_2$ (0.5M /tolueno, 3.2 mL, 0.93 mmol), se agitó a 0 °C durante 30 min, y luego se trató con CH_3I (0.12 mL, 2.00 mmol). La reacción se calentó a 20 °C, se agitó durante la noche, y se concentró. El residuo se trató luego con NaOH 0,5 N (10 mL) y se extrajo con CH_2Cl_2 (3x). Las capas orgánicas combinadas se concentraron y se sometieron a cromatografía (2-5% $MeOH/CH_2Cl_2$) para proporcionar **36A** (0.120 g, 55%).

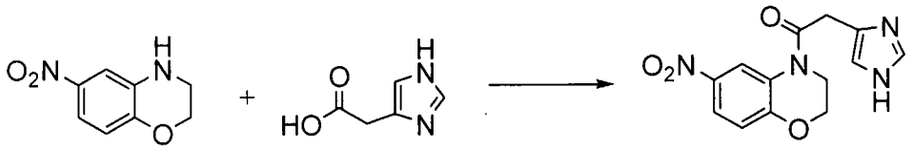
De manera similar a la descrita en el Ejemplo 26 (Etapa 3) y Ejemplo 1, se redujo **36A** con LAH y luego se hizo reaccionar con imidazol-4-carboxaldehído para proporcionar **36.** LMCS m/z 230 (MH+).

EJEMPLO PREPARATIVO 37



37

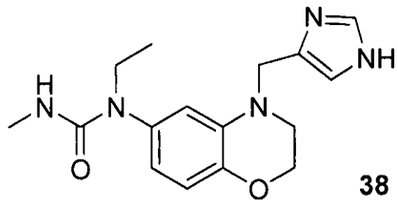
Etapa 1 - 2



3C **37A**

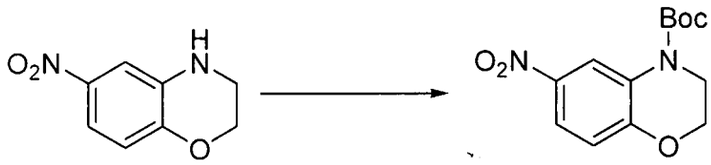
Una mezcla de **3C** (2g, 11.1 mmol) en DMF anhidro (20 mL) se trató con ácido 2-(1*H*-imidazol-4-il)acético (2g, 17.5 mmol), HATU (6.2g, 16.3 mmol) y DIEA (0.4 mL, 2.3 mmol) a 25 °C. La mezcla se agitó a temperatura ambiente durante la noche y luego se concentró bajo vacío. La cromatografía en columna (DCM que contenía 1 - 6% de NH_3/MeOH 7N) proporcionó **37A** (1.2g, rendimiento: 38%). De manera similar a la del Ejemplo 2, Etapa 2, se redujo el compuesto **37A** con BH_3-SMe_2 para proporcionar el compuesto **37**. MS m/z 275 (MH+).

EJEMPLO PREPARATIVO 38



38

Etapa 1



3C **38A**

Una solución del compuesto **3C** (14.1 g, 78 mmol) en MeCN (200 mL) se trató con $(BOC)_2O$ (20.5 g, 94 mmol) y DMAP (0.5 g) y luego se reflujo durante la noche. La mezcla de reacción se concentró y se cromatografió (10% -50% EtOAc/hexanos) para proporcionar el compuesto **38A** (16.1 g, 74%, típicamente 70-90%) y se recuperó el material de partida **3C**.

Etapas 2-3

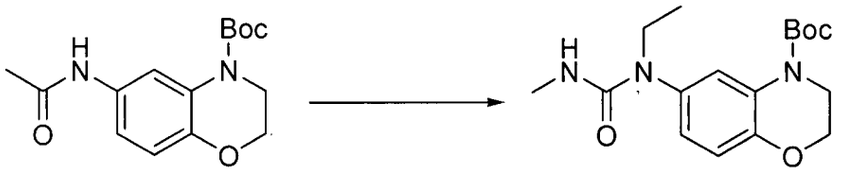


38A **38B**

Una mezcla del compuesto **38A** (16.1 g, 58 mmol) en EtOH (300 ml) se trató con níquel Raney (~5 g) y se hidrogenó (40 psi H_2) durante la noche. La mezcla de reacción se filtró y se concentró.

El sólido blanco resultante (~15.3 g, 61 mmol) se suspendió en THF anhidro (200mL) y se trató lentamente con Ac_2O (~18mL, 173 mmol). Después de agitar durante 2 h a 20 °C, la mezcla de reacción se concentró al vacío y se extrajo en NaOH acuoso al 25% (100mL) y CH_2Cl_2. Las capas se separaron. La capa acuosa se extrajo además con CH_2Cl_2 (3x). Las capas orgánicas se combinaron, se secaron con Na_2SO_4, y se filtraron para proporcionar **38B** en forma de un sólido gris (17.6 g, rendimiento cuantitativo).

Etapas 4-5



38B **38C**

Una solución del compuesto **38B** (21 g, 72 mmol) en THF (300 ml) a 0 °C se trató lentamente con BH_3-DMS (60 ml, 2M/THF) y luego se calentó a reflujo durante la noche. La mezcla se concentró, se trató con K_2CO_3 (9.9 g) y EtOH (300 mL) y luego se reflujó durante 45 min. La mezcla de reacción se filtró, se concentró, se agregó a H_2O y se extrajo con CH_2Cl_2 (4x). Las capas orgánicas combinadas se secaron con Na_2SO_4, se filtraron y se concentraron.

El aceite claro resultante (21.9 g) se disolvió en CH_2Cl_2 anhidro (300 ml), se trató lentamente con MeNCO (~5 g, 86 mmol), y luego se agitó a temperatura ambiente durante 30 min. La mezcla de reacción se concentró y se cromatografió

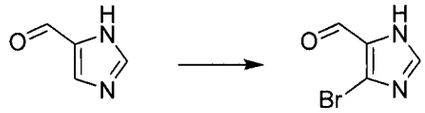
(50%-80% EtOAc/hexanos) para proporcionar el producto **38C** en forma de un sólido blanco (21.65 g, 90% rendimiento por dos etapas).

Etapas 6-7

Una solución del compuesto **38C** (21.65 g, 65 mmol) en CH_2Cl_2 (300 ml) se trató con TFA (100 mL) y se reflujó durante 0.5 h. La mezcla de reacción se concentró, se trató con NaOH al 20% (150mL) y se extrajo con CH_2Cl_2 (4X). Las capas orgánicas combinadas se secaron con Na_2SO_4, se filtraron y se concentraron para proporcionar un sólido blanco (14.23 g, ~93%).

El producto crudo (16.2 g, 68.9 mmol) se combinó con 4-imidazolcarboxaldehído (**1B**, 6.6 g, 68.9 mmol) y $Ti(OiPr)_4$ (25 mL, 86 mmol) en CH_2Cl_2 (15 ml) y se agitó a temperatura ambiente hasta que la mezcla de reacción se tornó clara (~1 h). Siguiendo la adición de $NaBH_4$ (3.3 g, 86 mmol) y EtOH (200 mL), la reacción se agitó a temperatura ambiente durante la noche y se concentró. El residuo se extrajo en NaOH 0,5 N y se extrajo con CH_2Cl_2 (4x). Las capas orgánicas combinadas se secaron con Na_2SO_4, se filtraron y se concentraron. La cromatografía (5-10% de NH_3-MeOH 7N en CH_2Cl_2) proporcionó el compuesto **38** (14.13 g, 68%) en forma de un sólido blanco.

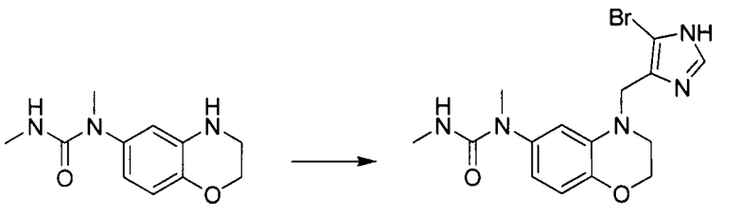
EJEMPLO PREPARATIVO 39



1B **39A**

Se agregó por goteo bromo (8.0 g, 50 mmol, 2.3 eq) en Ac_2O anhidro (40 mL) a una solución de **1B** (2.08 g, 21.7 mmol) y NaOAc (18.7 g, 228 mmol, 10.5 eq) en HOAc anhidro (200 mL) durante un período de 1 h a temperatura ambiente. La mezcla resultante se agitó a temperatura ambiente durante 2.5 h y luego se concentró. El residuo se dividió entre Et_2O (200 mL) y agua (200 mL), las capas se separaron y la capa acuosa se extrajo con Et_2O (200 mL). La fase

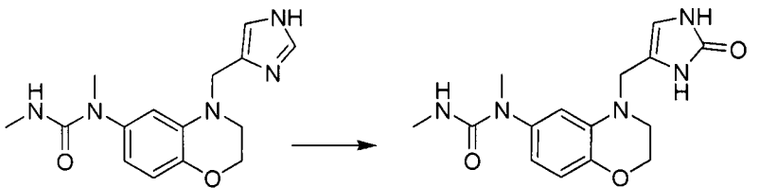
orgánica combinada se secó, se concentró, y se cromatografió (EtOAc) para proporcionar 5-bromo-4-formil imidazol **39A** (1.00 g, 26%) en forma de cristales blancos.



39B **39**

De manera similar a la descrita en el Ejemplo 1, **39A** se trató con **39B** (Ejemplo 6) para proporcionar el compuesto del título **39.** LCES m/z 280 (MH+).

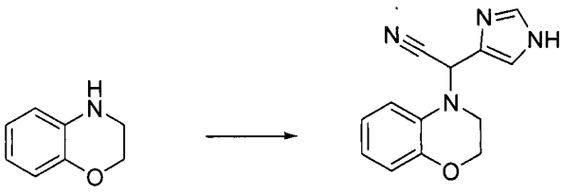
EJEMPLO PREPARATIVO 40



6 **40**

Una mezcla de **6** (0.25 g, 0.83 mmol) y $NaHCO_3$ (0.7g, 8.3 mmol) en 1:1 THF-H_2O (20 mL) se agitó vigorosamente durante 10 min y luego se trató con cloroformiato de fenilo (PhOCOCl, 0.26 mL, 2.1 mmol). La reacción se agitó a temperatura ambiente durante 2 h y luego se diluyó con EtOAc. La capa orgánica se aisló, se secó sobre Na_2SO_4 y se concentró. El residuo resultante se disolvió en MeOH, se trató con Et_3N (0.6 mL, 4.3 mmol) y se agitó durante la noche. La solución se concentró y se sometió a cromatografía (5-10% NH_3-MeOH/EtOAc) para proporcionar el compuesto del título **40** en forma de una espuma amarillo clara (0.2 g, 76%).

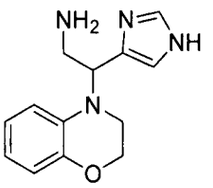
EJEMPLO PREPARATIVO 41



1A **41**

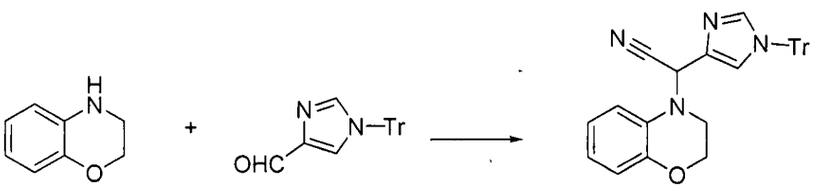
Una mezcla de **1A** (0.2 g, 1.5 mmol) e imidazol-4-carboxaldehído (**1B**, 0.16 g, 1.6 mmol) en CH_2Cl_2 (5 mL) se trató con $Ti(OiPr)_4$ (0.55 mL, 1.88 mmol), se agitó a temperatura ambiente durante la noche, y luego se trató con Et_2AlCN (2 mL, 1M/ tolueno). Después de 18 h, se agregaron EtOAc, H_2O, y celite. La filtración y subsiguiente cromatografía (0-10% de NH_3–MeOH 7N en CH_2Cl_2) proporcionó **41** en forma de un sólido amarillo (0.178 g, 50%). LCES m/z 241 (MH+).

EJEMPLO PREPARATIVO 42



41

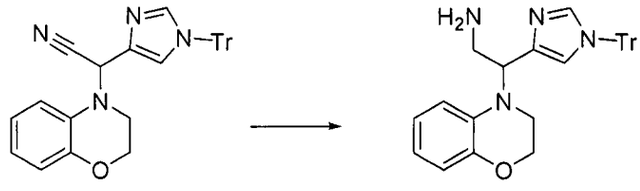
Etapa 1



1A **42A** **42B**

De manera similar a la descrita en el Ejemplo 41, una mezcla de **1A** y **42A** (Journal of Medicinal Chemistry, **1971**, *14*, 883) se trató consecutivamente con $Ti(OiPr)_4$ y Et_2AlCN para proporcionar el compuesto **42B.**

Etapas 2-3

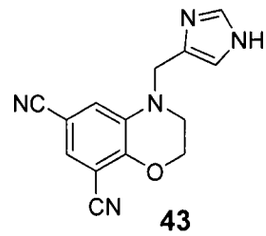


42B **42C**

Una solución de **42B** (0.2 g, 0.41 mmol) en NH_3-MeOH 1N (50 mL) se trató con níquel Raney Ni y se hidrogenó (50 psi H_2) durante la noche a temperatura ambiente. La filtración y subsiguiente cromatografía (0-7% de NH_3–MeOH 7N en CH_2Cl_2) proporcionó **42C** en forma de una película amarilla (0.15 g, 74%).

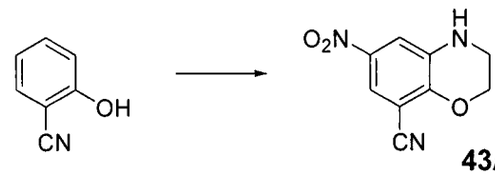
Una mezcla de **42C** (145 mg, 0.3 mmol) en CH_2Cl_2 (2 mL) se trató con TFA (0.5 mL) y Et_3SiH (0.05 mL). La mezcla de reacción se agitó a temperatura ambiente durante la noche y luego se concentró. La cromatografía (2-15% de NH_3-MeOH 7N en CH_2Cl_2) proporcionó el compuesto del título **42** (69 mg, 95%) en forma de un aceite amarillo. LCES m/z 245 (MH+).

EJEMPLO PREPARATIVO 43



43

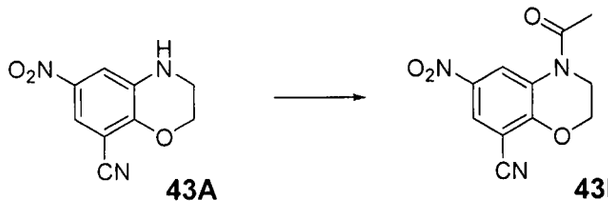
Etapas 1-4



43A

De manera similar a la descrita en los Ejemplos 19 y 3, se sometió 2-cianofenol a bis-nitración con HNO_3, reducción selectiva con $SnCl_2$, ciclación con cloruro de cloroacetilo y reducción con BH_3-SMe_2 para proporcionar **43A**.

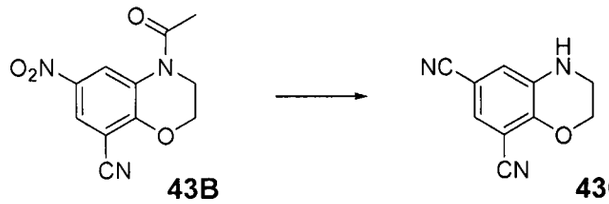
Etapa 5



43A **43B**

Una mezcla de **43A** (0.65 g, 3.2 mmol) y Et_3N (0.9 mL, 6.3 mmol) en CH_2Cl_2 (60 mL) se trató con Ac_2O (6 mL) y DMAP (0.15 g) y luego se reflujó durante 2 días. Luego se enfrió la reacción, se lavó con HCl 1N (2x), se lavó con salmuera, se secó sobre Na_2SO_4, y se concentró. La cromatografía (10-100% of EtOAc/hexanos) proporcionó **43B** en forma de un sólido amarillo (0.688 g, 88%).

Etapas 5-8



43B **43C**

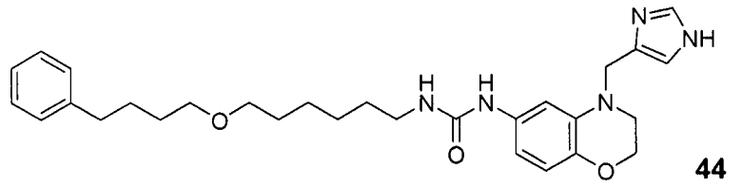
De manera similar a la descrita en el Ejemplo 3 (Etapa 4), se hidrogenó **43B** con Pd/C.

Una mezcla del producto de anilina (0.080 g, 0.38 mmol) en HCl 6M (0.5 mL) se trató con una solución de $NaNO_2$ (27 mg, 0.39 mmol) a 0 °C. Después de 0.5 h, la solución se neutralizó con Na_2CO_3 ac. sat. y luego se agregó por goteo a una solución de CuCN (37 mg, 0.41 mmol) y NaCN (40 mg, 0.82 mmol). La mezcla resultante se agitó luego a 60 °C durante la noche y luego se filtró.

El precipitado marrón (44 mg) se recogió y luego se trató con NaOH ac. al 10% (0.5 mL) durante 2h a temperatura ambiente. La reacción se diluyó luego con H_2O y se extrajo con CH_2Cl_2 (3x). Las capas orgánicas combinadas se lavaron con salmuera, se secaron sobre Na_2SO_4, y se concentraron. La cromatografía (20-100% de EtOAc/hexanos) proporcionó **43C** en forma de un sólido beige (0.0.15 g).

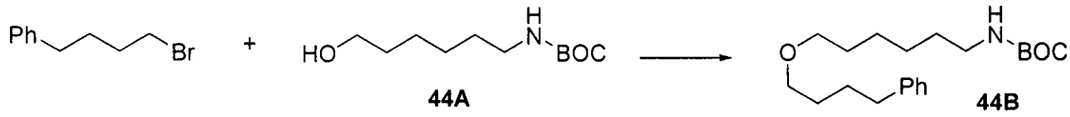
De manera similar a la descrita en el Ejemplo 3 (Etapa 3), se convirtió **43C** al compuesto del título **43.** LCMS m/z 266 (MH+).

EJEMPLO PREPARATIVO 44



44

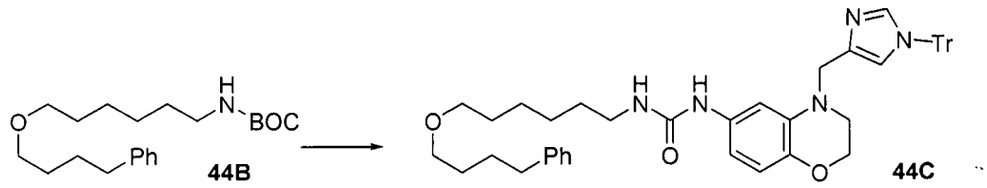
Etapa 1



44A **44B**

Una solución de bromuro de 4-fenilbutilo (0.98 g, 4.6 mmol) y **44A** (1.0 g, 4.6 mmol) en 10 mL de benceno se trató consecutivamente con Bu_4NHSO_4 (0.16 g, 0.46 mmol) y NaOH acuoso al 50% (2.4 mL, 46 mmol, se agregó lentamente). Después de agitar a temperatura ambiente bajo N_2 durante 20 h, el solvente se removió. La mezcla de reacción se diluyó luego con H_2O, se extrajo con EtOAc, se lavó con H_2O (3x) y salmuera, se secó sobre Na_2SO_4, y se filtró. El filtrado se concentró y se cromatografió (5-10% EtOAc/hexanos) para proporcionar **44B** (0.7 g, 44%).

Etapas 2-3



44B **44C**

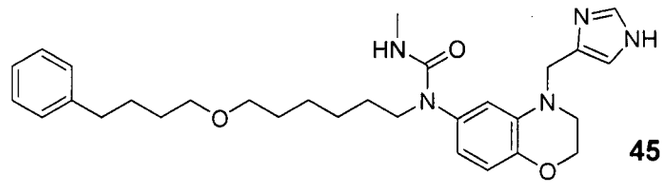
A una solución de **44B** (0.2 g, 0.57 mmol) en 5 mL de CH_2Cl_2 (5 mL) se agregó TFA (1.5mL). Después de agitar a temperatura ambiente durante 1.5 h, la solución se enfrió a 0 °C y se trató con NH_3 acuoso concentrado (hasta pH = 10-11). La mezcla se extrajo con CH_2Cl_2, se secó sobre Na_2SO_4, y se filtró. El filtrado se concentró para proporcionar una amina inestable (0.12 g, 84%) que se extrajo inmediatamente en CH_2Cl_2 (8 mL) y se trató con el compuesto **7B** (0.21g, 0.44mmol) y Et_3N (0.17 mL, 1.2mmol). Después de enfriar la mezcla a -50 °C, se agregó trifosgeno (0.04 g, 0.13 mmol) a la solución. La mezcla se agitó a -50 °C

bajo N_2 durante 1h, luego se calentó lentamente hasta temperatura ambiente, y se agitó bajo N_2 durante la noche. Después de agregar NaOH acuoso al 5% (10 mL), los productos se extrajeron con CH_2Cl_2, se secaron sobre Na_2SO_4, y se filtraron. La cromatografía (2% MeOH/EtOAc) proporcionó **44C** (0.2 g, 67%).

Etapa 4

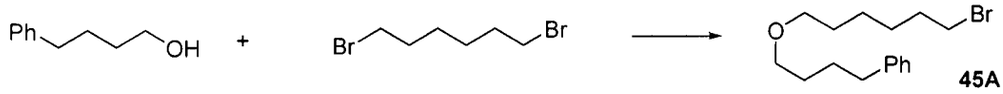
Una mezcla de **44C** (0.13 g) en HCl-MeOH 3n (8 mL) se calentó a 60 °C bajo N_2 durante 1.5 h, se enfrió a 0 °C y se neutralizó con NH_3 acuoso concentrado. La solución se concentró, se extrajo en H_2O y extrajo con CH_2Cl_2. Los extractos orgánicos se secaron sobre Na_2SO_4, se filtraron y se cromatografiaron (NH_3-MeOH al 5% en CH_2Cl_2) para proporcionar el compuesto del título **44** (0.05 g, 62%). LCMSm/z 506 (MH+).

EJEMPLO PREPARATIVO 45



45

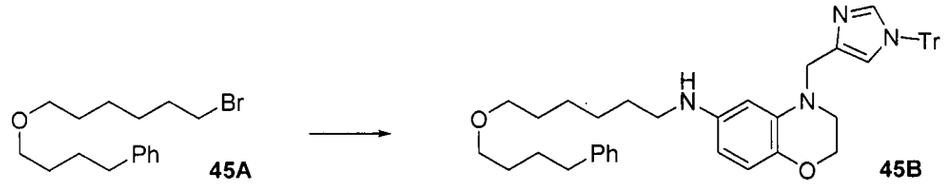
Etapa 1



45A

Una solución de 4-fenilbutanol (2.50 g, 16.6 mmol) y 1,6-dibromohexano (8.12 g, 33.2 mmol) en THF anhidro (30 mL) se trató lentamente con NaH (1.0 g, 24.9 mmol) a temperatura ambiente. Después de reflujo bajo N_2 durante 20 h, la mezcla se enfrió a temperatura ambiente, y se apagó con H_2O. Los productos se extrajeron con éter, se lavaron con salmuera, se secaron sobre Na_2SO_4, y se filtraron. El filtrado se concentró y se cromatografió (2% EtOAc/hexanos) para proporcionar **45A** (3.3 g, 63%).

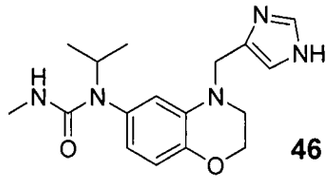
Etapas 2-4



A una solución de **45A** (0.07 g, 0.21 mmol) y **7B** (0.1 g, 0.21 mmol) en tolueno (3 mL) y DMF (0.5 mL) se agregó DIPEA (0.07 mL, 0.42 mmol) a temperatura ambiente. Después de calentar a 80 °C bajo N_2 durante 20 h, la mezcla se concentró, se extrajo en CH_2Cl_2, se lavó con H_2O (3x) y salmuera, se secó sobre Na_2SO_4, y se filtró. La cromatografía (60% EtOAc/hexanos) proporcinó **45B** (0.04 g, 27%).

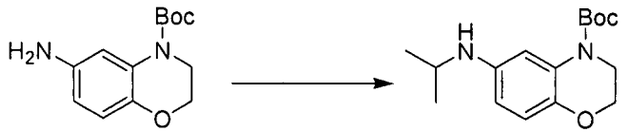
De manera similar a la descrita en el Ejemplo 5 (Etapa 3) y Ejemplo 44 (Etapa 4), se trató consecutivamente **45B** con MeNCO y HCl para proporcionar el compuesto del título **45.** LCMSm/z 520 (MH+).

EJEMPLO PREPARATIVO 46



46

Etapas 1-2



46A **46B**

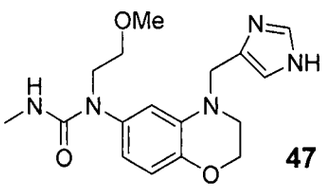
El compuesto **46A** (del Ejemplo 38, Etapa 2, 250 mg, 1 mmol) se extrajo en DCE (10 mL) y se trató consecutivamente con 2-metoxipropeno (0.14 mL, 1.5 mmol), HOAc (0.06 mL, 1.1 mmol), y $NaBH(OAc)_3$ (424 mg, 2.0 mmol). La mezcla de reacción se agitó a temperatura ambiente durante la noche, se apagó con NaOH 1,0 N y se extrajo con CH_2Cl_2 (3 x 20 mL). Las capas orgánicas

combinadas se lavaron con salmuera, se secaron y luego se concentraron. La cromatografía (EtOAc/hexanos) proporcionó **46B** (190 mg, 65%).

Etapas 3-5

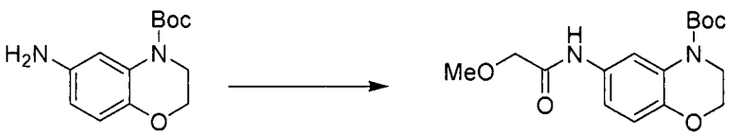
De manera similar a la descrita en el Ejemplo 38 (Etapas 5-7), se trató consecutivamente **46B** con MeNCO, se desprotegió con TFA, y se trató con 4-imidazol carboxaldehído para proporcionar el compuesto del título **46**.LCMSm/z 330 (MH+).

EJEMPLO PREPARATIVO 47



47

Etapa 1



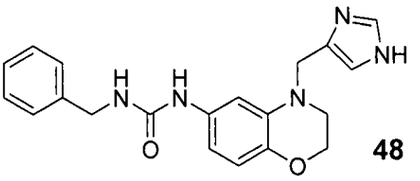
46A **47A**

Una mezcla de **46A** (500 mg, 2 mmol) en CH_2Cl_2 (10 mL) se trató consecutivamente con cloruro de metoxiacetilo (0.22 mL, 2.4 mmol) y TEA (0.56 mL, 4.0 mmol). La mezcla de reacción se agitó a temperatura ambiente durante la noche, se apagó con $NaHCO_3$ saturado, y se extrajo con CH_2Cl_2 (2 x 20 mL). Las capas orgánicas combinadas se lavaron con salmuera, se secaron y se concentraron. La cromatografía (EtOAc/hexanos) proporcionó **47A** (610 mg, 95%).

Etapas 2-5

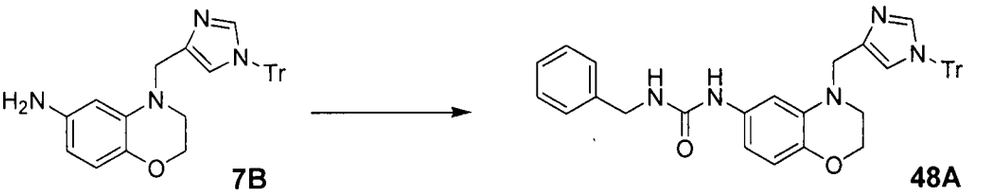
De manera similar a la descrita en el Ejemplo 38 (Etapas 4-7), se redujdo **47A** con BH_3-SMe_e, se trató con MeNCO, se desprotegió con TFA, y se trató con 4-imidazolcarboxaldehído para proporcionar el compuesto del título **47**. LCMS m/z 346 (MH+)

EJEMPLO PREPARATIVO 48



48

Etapas 1-2

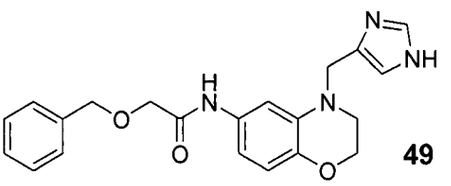


7B **48A**

Una solución de **7B** (140 mg, 0.3 mmol) en CH_2Cl_2 anhidro (5 mL) se trató con isocianato de bencilo (48 mg, 0.36 mmol). La mezcla de reacción se agitó a temperatura ambiente durante la noche y luego se concentró. La cromatografía proporcionó **48A** (130 mg, 72%).

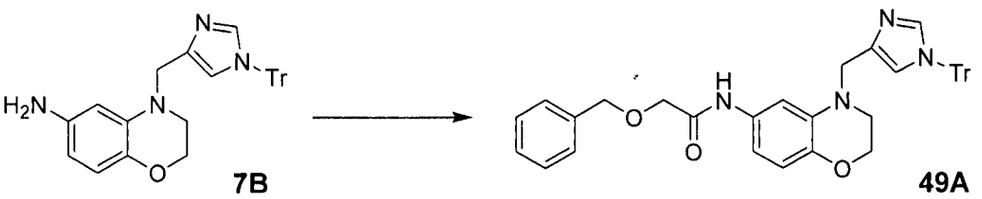
De manera similar a la descrita en el Ejemplo 42 (Etapa 3), **48A** se desprotegió con TFA y Et_3SiH para proporcionar el compuesto del título **48**. LCMSm/z 364 (MH+).

EJEMPLO PREPARATIVO 49



49

Etapas 1-2

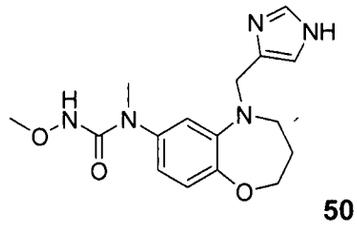


7B **49A**

Una mezcla de **7B** (1.0 g, 2.12 mmol), ácido benciloxiacético (0.46 g, 2.75 mmol), EDCI (0.61 g, 3.18 mmol) y HOBt (0.42 g, 3.18 mmol) en DMF se agitaron a temperatura ambiente durante 1 día. La reacción se apagó con NaOH ac. 0,5 N (50 mL) y se extrajo con CH_2Cl_2. Los extractos combinados se lavaron con salmuera, se secaron (Na_2SO_4) y se concentraron. La cromatografía por TLC preparativa (5% NH_3-MeOH en CH_2Cl_2) proporcionó **49A** (0.52 g).

De manera similar a la descrita en el Ejemplo 42 (Etapa 3), **49A** se desprotegió con TFA y Et_3SiH para proporcionar el compuesto del título **49**. LCMS m/z 379 (MH+).

EJEMPLO PREPARATIVO 50



50

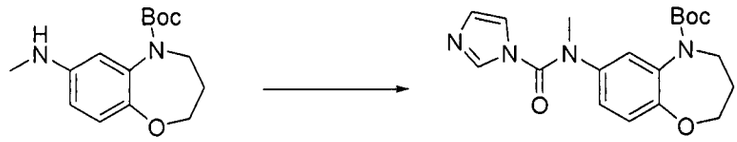
Etapas 1-4



28C **50A**

De manera similar a la descrita en el Ejemplo 5 (Etapas 1-2) y Ejemplo 6 (Etapas 1-2), el compuesto **28C** se convirtió al **50A.**

Etapa 5



50A **50B**

Una mezcla de **50A** (0.247 g, 0.99 mmol) en DCM anhidro (5 mL) se trató con carbonildiimidazol (0.32 g, 1.97 mmol) y Et_3N (0.28 mL, 1.97 mmol) y luego se

agitó a temperatura ambiente durante la noche. La reacción se lavó con agua y se extrajo con DCM (3 x 10 mL). La capa orgánica combinada se secó ($MgSO_4$), se filtró y se concentró bajo vacío para proporcionar el compuesto **50B.**

Etapas 6-8

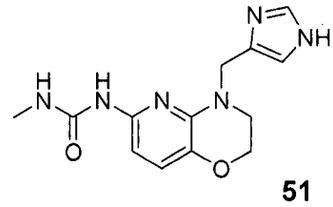


50B **50C**

Una solución de **50B** en MeCN anhidro (5 mL) en un tubo sellado se trató con MeI (2 mL). La mezcla de reacción sellada se calentó a 55 °C durante 3 h, se enfrió a temperatura ambiente y se concentró. El residuo se disolvió en THF anhidro (5 mL) y luego se trató con $MeONH_2$-HCl (0.25 g, 2.97 mmol) y DIEA (0.53 mL, 2.97 mmol). Después de agitar a temperatura ambiente durante la noche, la reacción se apagó con una solución de NH_4Cl saturada y se concentró bajo vacío. El residuo se diluyó con agua y se extrajo con EtOAc (3 x 10 mL). La capa orgánica combinada se secó ($MgSO_4$), se filtró y se concentró bajo vacío para proporcionar el compuesto crudo **50C** (279 mg, 80% para 3 etapas).

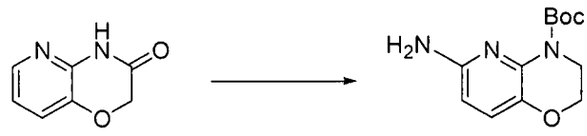
De manera similar a la descrita en el Ejemplo 5 (Etapa 4) y EJEMPLO 3 (Etapa 3), se desprotegió el compuesto **50C** y se convirtió al compuesto del título **50**. MS m/z = 332 (MH+).

EJEMPLO PREPARATIVO 51



51

Etapas 1-4



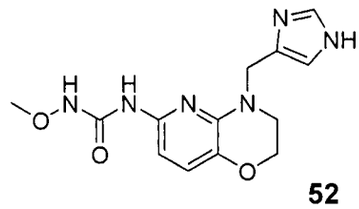
22A **51A**

De manera similar a la descrita en el Ejemplo 21 (Etapa 1), Ejemplo 3 (Etapa 2), Ejemplo 5 (Etapa 1) y Ejemplo 3 (Etapa 4), el compuesto **22A** fue consecutivamente nitrado, reducido con BH_3-SMe_2, tratado con Boc_2O, e hidrogenado, para obtener el compuesto **51A**.

Etapas 5-7

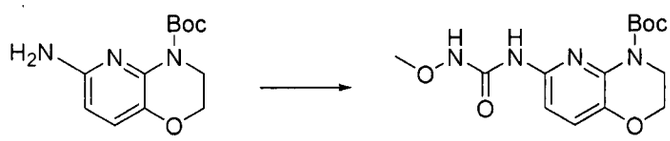
De manera similar a la descrita en el Ejemplo 5 (Etapas 3-5), **51A** se trató con MeNCO, se desprotegió con TFA, y se convirtió al compuesto del título **51**. MS m/z = 289 (MH+).

EJEMPLO PREPARATIVO 52



52

Etapas 1-3

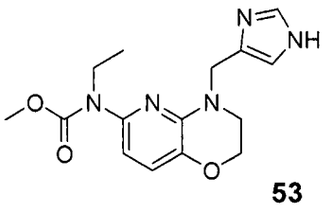


51A **52A**

A una solución de **51A** (740 mg, 2.95 mmol) en DCM (30 ml) se agregó cloroformiato de 4-nitrofenilo (891 mg, 4.42 mmol) y piridina (0.48 ml, 5.90 mmol). Después de agitar durante la noche a temperatura ambiente, la TLC indicó que el material de partida se había consumido. Luego se agregaron consecutivamente, sal de $MeONH_2$-HCl (739 mg, 8.84 mmol) en THF anhidro (10 ml) y DIEA (1.57 mL, 8.84 mmol). Después de agitar a temperatura ambiente durante la noche, la reacción se apagó con agua, se concentró, se diluyó con agua y se extrajo con EtOAc. La fase orgánica se secó ($MgSO_4$), se filtró y se concentró. La cromatografía evaporativa (20-50% de EtOAc/hexanos) proporcionó **52A** (650 mg, 68%).

De manera similar a la descrita en el Ejemplo 5 (Etapa 4) y Ejemplo 3 (Etapa 3), **52A** se convirtió a **52**. MS m/z = 305 (MH+).

EJEMPLO PREPARATIVO 53



53

Etapas 1-3

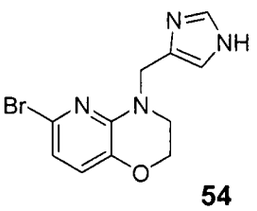


51A **53A**

Al compuesto **51A** (100 mg, 0.40 mmol) en DCE (5 mL) se agregó acetaldehído (0.045 mL, 0.80 mmol). La mezcla se agitó a temperatura ambiente durante 1 h y luego se trató con MeOH (3 mL) y $NaBH_4$ (45.5 mg, 1.2 mmol). Después de agitar a temperatura ambiente durante la noche, la reacción se apagó con una solución de NaOH 2N, se concentró, se diluyó con agua y se extrajo con EtOAc. La fase orgánica se secó (MgSO4), se filtró y se concentró bajo vacío para proporcionar un residuo **53A** (40 mg, 36%).

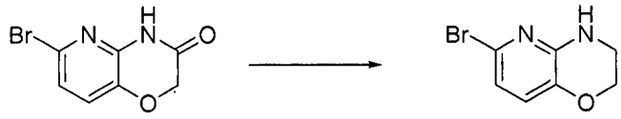
De manera similar a la descrita en el Ejemplo 3 (Etapa 5), Ejemplo 5 (Etapa 4) y Ejemplo 3 (Etapa 3), **53A** se trató con $ClCO_2Me$/piridina, se desprotegió con TFA y se convirtió al compuesto del título **53**. MS m/z = 318 (MH+).

EJEMPLO PREPARATIVO 54



54

Etapas 1-2

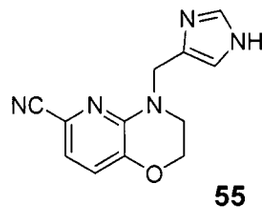


54A **54B**

De manera similar a la descrita en el Ejemplo 3 (Etapa 2), el compuesto **54A** (ver WO 2006/020561) se redujo con BH_3-SMe_2 para proporcionar **54B**.

El compuesto **54B** se elaboró luego con **54** (MS m/z = 295, MH+) tal como se ha descrito previamente en el Ejemplo 3 (Etapa 3).

EJEMPLO PREPARATIVO 55



55

Etapas 1-2

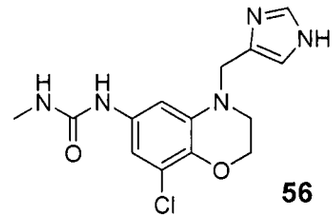


54B **55A**

Un frasco de procesamiento Smith se cargó con una barra agitadora, el compuesto **54B** (0.33 g, 1.54 mmoles), CuCN (0.276 g, 3.08 mmoles) y DMF (3 mL). El recipiente de reacción se selló y se calentó a 120 °C durante 3 h bajo irradiación en horno microondas. Después de enfriar, la mezcla de reacción se transfirió a un frasco de cuello redondo y se concentró bajo vació. El compuesto **55A** se obtuvo cuantitativamente mediante extracción continua con EtOAc en un aparato Soxlet.

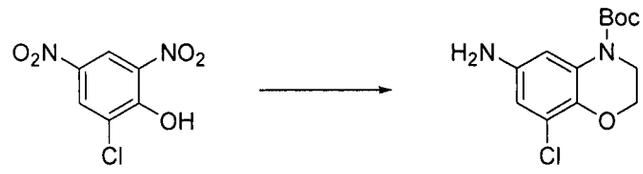
El compuesto **55A** se elaboró luego en **55** (MS m/z = 242, MH+) tal como se ha descrito previamente en el Ejemplo 3 (Etapa 3).

EJEMPLO PREPARATIVO 56



56

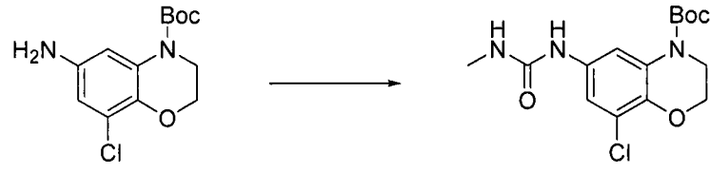
Etapas 1-5



56A

De manera similar a la descrita previamente, 2-cloro-4,6-dinitrofenol se redujo consecutivamente con $SnCl_2$ (EJEMPLO 19, Etapa 2), se trató con cloruro de cloroacetilo, se redujo con BH_3-SMe_2 (Ejemplo 3, Etapas 1-2), se protegió con Boc_2O (Ejemplo 5, Etapa 1), y se redujo nuevamente con $SnCl_2$ para proporcionar el compuesto **56A**.

Etapas 6-8



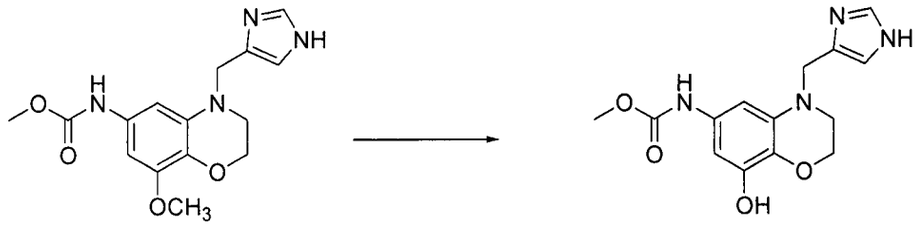
56A **56B**

A una solución del compuesto **56A** (0.29 g, 1 mmol) en DCM anhidro (3 ml) se agregó cloroformiato de 4-nitrofenilo (0.24 g, 1.2 mmol) y piridina (0.13 ml, 1.57 mmol). Después de agitar durante la noche a temperatura ambiente, la reacción se apagó con una solución de NH_4Cl sat. y se extrajo con DCM. Luego, la fase orgánica se concentró. Una solución de este residuo en CH_3CN (5 mL) se trató con 40% $MeNH_2$ en H_2O (20 mL) y se calentó en un tubo sellado a 90 °C durante la noche. La mezcla se enfrió, se agitó a temperatura ambiente durante la noche, y luego se apagó con agua. La reacción se concentró, se diluyó con agua y se

extrajo con EtOAc. La fase orgánica se secó ($MgSO_4$), se filtró y se concentró para proporcionar **56B**.

Tal como se ha descrito previamente en el Ejemplo 5 (Etapa 4) y Ejemplo 3 (Etapa 3), **56B** se desprotegió y se convirtió a **56**. MS m/z = 322 (MH+).

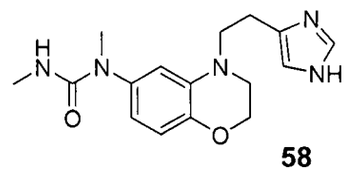
EJEMPLO PREPARATIVO 57



127 **57**

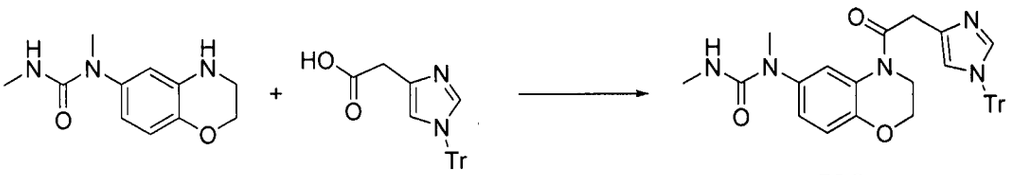
El compuesto **127** (0.388 g, 1.22 mmol) se disolvió en DCM anhidro (10 mL) y se enfrió a -78 °C. A esta solución se agregó BBr_3 1,0M en DCM (6.1 mL) por goteo. La mezcla de reacción se agitó a -78 °C durante 30 min y luego a temperatura ambiente durante 3 h. La reacción se apagó con agua y se neutralizó con una solución de NaOH 2N. La mezcla se separó y la fase acuosa se extrajo con DCM (3 x 10 mL). La fase orgánica se secó ($MgSO_4$), se filtró y se concentró bajo vacío. El residuo se purificó por cromatografía en columna evaporativa (DCM que contenía 2 a 8% de NH_3 7N en MeOH) para proporcionar el compuesto **57** en 30% de rendimiento. MS m/z = 305 (MH+).

EJEMPLO PREPARATIVO 58



58

Etapa 1



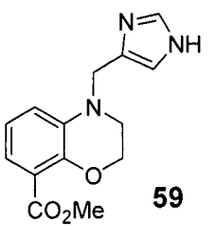
58A **58B** **58C**

De manera similar a la descrita en el Ejemplo 37, el compuesto **58A** (preparado en el Ejemplo 6) y **58B** (Bioconjugate Chemistry *13*, 333-350, 2002) se hicieron reaccionar con HATU para proporcionar **58C**. MS m/z = 572 (MH+)

Etapas 2-3

Una solución de **58C** (720 mg, 1.3 mmol) en THF (50 mL) se trató con BH_3-SMe_2 (5 mL, 2 M en THF) y se calentó a 80 °C durante 12 h. Después de enfriar a 25 °C, se agregó por goteo MeOH (15 mL) hasta que cesó el burbujeo. El solvente se removió y se dividió entre EtOAc y agua. La fase orgánica se secó sobre Na_2SO_4 y se concentró. El residuo crudo se agitó en DCM/TFA (1:3, 5 mL) a 25 °C durante 4 h. El solvente se removió y el residuo se dividió entre EtOAc y agua. La fase orgánica se secó y se concentró. La cromatografía en columna y la TLC preparativa (DCM que contenía 5% de NH_3/MeOH 7N) proporcionaron **58**. MS m/z = 316 (MH+).

EJEMPLO PREPARATIVO 59



59

Etapas 1-3



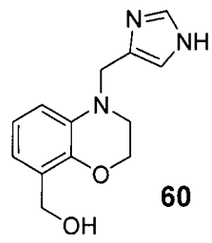
59A

De manera similar a la descrita en el Ejemplo 3 (Etapa 4 luego Etapas 1-2), se hidrogenó consecutivamente 2-hidroxi-3-nitrobenzoato de metilo, se trató con cloruro de cloroacetilo y se redujo con BH_3-SMe_2 para proporcionar el compuesto **59A**.

Etapa 4

Se trató el compuesto **59A** con 4-imidazolcarboxaldehído para proporcionar el compuesto del título **59** de manera similar a la descrita en el Ejemplo 3 (Etapa 3). MS m/z = 274 (MH+).

EJEMPLO PREPARATIVO 60



60

Etapas 1-2

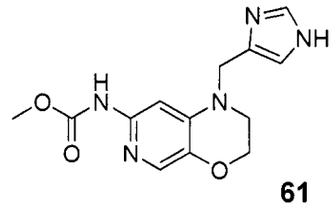


59A **60A**

Una mezcla de $LiBH_4$ (44 mg, 2 mmol) y **59A** (400 mg, 2 mmol) en THF (50 mL) se agitó a temperatura ambiente durante 4 h y luego se concentró. El residuo se dividió entre EtOAc y agua. La fase orgánica se secó y se concentró para proporcionar **60A** (300 mg, 91%).

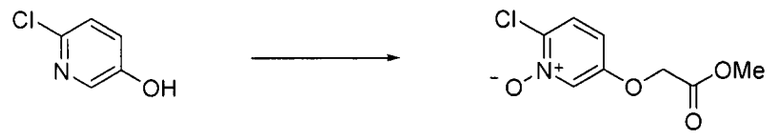
El compuesto **60A** se convirtió al **60** de manera similar a la descrita en el Ejemplo 3 (Etapa 3). MS m/z = 246 (MH+).

EJEMPLO PREPARATIVO 61



61

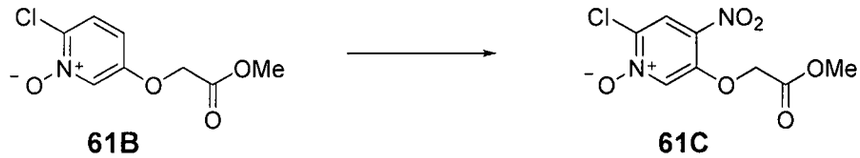
Etapas 1-2



61A **61B**

A 2-cloro-5-hidroxipiridina (**61A**) en acetona (80 mL) se agregó K_2CO_3 (8.96 g, 65 mmol) y cloroacetato de metilo (2.54 mL, 29 mmoles). La mezcla se calentó a 60 °C durante 4 h. Después de enfriar a temperatura ambiente, la mezcla se filtró y los sólidos se lavaron con acetona (50 mL). El filtrado se concentró al vacío para proporcionar 4.3 g del intermediario (92% de rendimiento). El intermediario (4.3 g, 21.3 mmol) se disolvió en $CHCl_3$ (75 mL) y se trató con ácido m-cloroperbenzoico (4.78 g, 27.7 mmol). La solución resultante se calentó a 50 °C durante 4 h, luego se agitó a temperatura ambiente durante la noche. La mezcla se trató con sulfato de sodio, se filtró y se concentró al vacío. La cromatografía en columna evaporativa (5%-10% MeOH en DCM) proporcionó **61B** (3.46 g, 75%).

Etapas 3-4

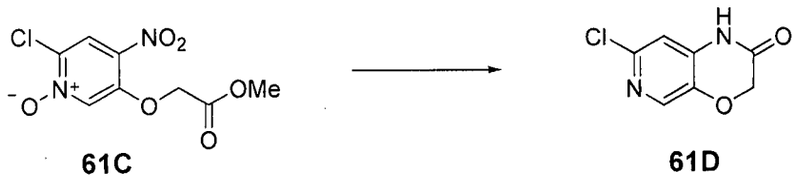


61B **61C**

Se disolvió N-óxido **61B** (1.0 g, 4.61 mmol) en H_2SO_4 (2 mL) a 0 °C. Se agregó lentamente HNO_3 (1 mL) durante varios minutos. La mezcla de reacción se colocó luego en un baño de aceite calentado a 40 °C. La temperatura se elevó lentamente hasta 75 °C durante 1 h y luego se mantuvo así durante 2 h. La mezcla se vertió luego en hielo y se ajustó el pH a 9 mediante la adición de 50%

de NaOH. Se removió el agua al vacío, y los sólidos resultantes se lavaron con MeOH para proporcionar el intermediario óxido de nitro piridina crudo (2.6 g). Una porción de este intermediario (1.33 g, 5.3 mmol) se disolvió en MeOH (50 mL) y se trató con H_2SO_4 (1 mL). La mezcla se calentó a 70 °C durante 2 h y luego se concentró. El residuo se trató con NaOH 1N (20 mL) y EtOAc (50 mL). La solución se extrajo con EtOAc (2 x 50 mL). Los extractos orgánicos combinados se secaron sobre sulfato de sodio, se filtraron y se concentraron al vacío para proporcionar el compuesto **61C** (1.4 g, 100%).

Etapas 5-6



61C **61D**

Una mezcla de **61C** (0.06 g, 0.23 mmol) en MeOH (2 mL) se trató con hierro en polvo (0.09 g, 1.61 mmol) y HOAc (0.08 mL). La solución resultante se calentó a 70 °C durante 4 h. La solución caliente se filtró a través de una almohadilla de celite y se concentró. El residuo se extrajo en MeOH (2 mL) y se trató con K_2CO_3 (0.073 g, 0.53 mmol). Después de calentar a 65 °C durante 2 h, el solvente se removió al vacío y el producto se purificó por TLC preparativa (5% MeOH en DCM) para proporcionar el compuesto **61D** (0.032 g, 76%).

Etapas 7-8



61D **61E**

De manera similar a la descrita en el Ejemplo 3 (Etapa 2) y Ejemplo 5 (Etapa 1), el compuesto **61D** se redujo y se protegió para proporcionar el compuesto **61E**.

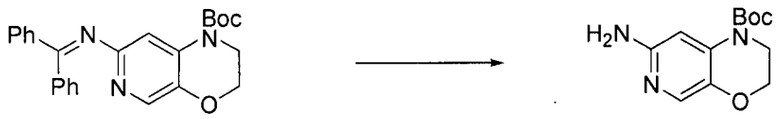
Etapa 9



61E **61F**

Una mezcla de **61E** (0.250 g, 0.91 mmol), benzofenonimina (0.152 mL, 0.91 mmol), tris(dibenzilidenacetona dipaladio(0) (0.004 g, 0.0045 mmol), rac-2,2'-Bis(difenilfosfino)-1,1'-binaftaleno (0.004 g, 0.007 mmol), y NaO*t*Bu (0.088g, 0.91 mmol) en tolueno (8 mL) en un tubo de cultivo se calentó en un horno giratorio a 80 °C durante la noche. Después de enfriar a temperatura ambiente, El contenido se transfirió a un frasco de cuello redondo y se trató con varias cucharadas de de gel de sílice. El solvente se removió al vacío y el producto se purificó por cromatografía en columna evaporativa (10% a 50% de EtOAc-hexanos) para proporcionar **61F** (0.205 g, 54%).

Etapas 10-13

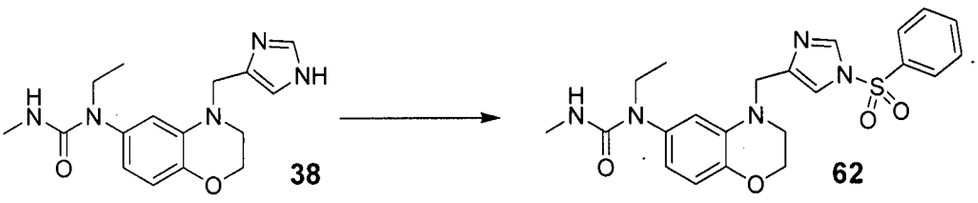


61F **61G**

Una mezcla de **61F** (0.205 g, 0.5 mmol) en THF (4 mL) se trató con 15% de una solución de ácido cítrico acuoso (4 mL). La solución resultante se agitó a temperatura ambiente durante la noche. Se agregó $NaHCO_3$ acuoso saturado (5 mL) y la solución se extrajo con EtOAc (2 x 25mL). Los extractos orgánicos se secaron sobre sulfato de sodio, se filtraron y se concentraron al vacío. El producto se purificó por cromatografía en columna evaporativa (10% a 50% de EtOAc-hexanos) para proporcionar **61G** (0.114g, 91%).

De manera similar a la descrita en el Ejemplo 3 (Etapa 5), Ejemplo 5 (Etapa 4) y Ejemplo 3 (Etapa 3), el compuesto **61G** se trató consecutivamente con $ClCO_2Me$, se desprotegió y se convirtió al compuesto del título **61**. MS m/z = 290 (MH+).

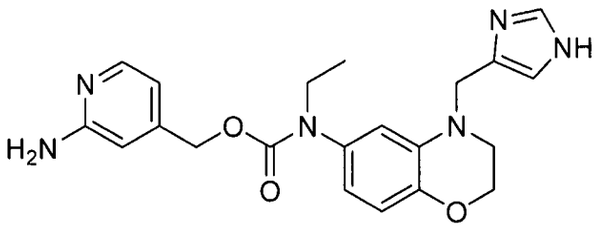
EJEMPLO PREPARATIVO 62



38 **62**

Una suspensión de **38** en DCE anhidro (4 ml) y THF anhidro (4 ml) se trató con TEA anhidro (0.2 ml) seguido de cloruro de bencensulfonilo (0.070 mL). Después de 2 h a temperatura ambiente, se agregó bencensulfonilo adicional (0.2 mL). La mezcla se agitó durante 1 h, luego se diluyó con CH_2Cl_2, se lavó con salmuera, se secó (Na_2SO_4), y se concentró. La cromatografía por TLC preparativa (9% de MeOH/CH_2Cl_2) proporcionó **62** (43 mg).

EJEMPLO PREPARATIVO 63



63

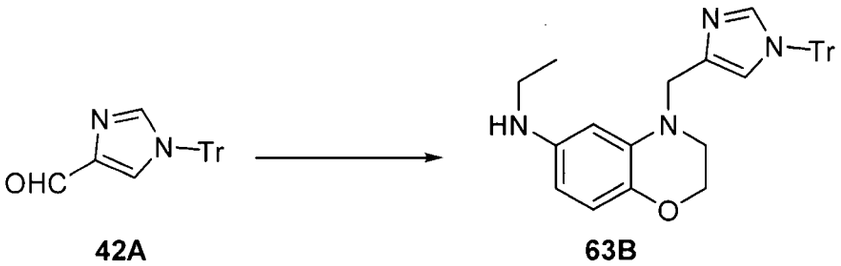
Etapa 1



38B **63A**

De manera similar a la descrita en el Ejemplo 38 (Etapa 6), **38B** se desprotegió consecutivamente con TFA para proporcionar **63A.**

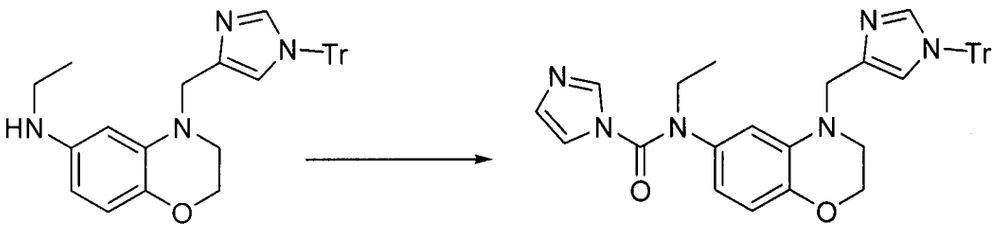
Etapas 2-3



42A **63B**

De manera similar a la descrita en el Ejemplo 3 (Etapa 3) y Ejemplo 26 (Etapa 3), **42A** (Journal of Medicinal Chemistry, **1971**, *14*, 883) se trató consecutivamente con **63A**/$NaBH(OAc)_3$, y luego se redujo con LAH en THF para proporcionar **63B.**

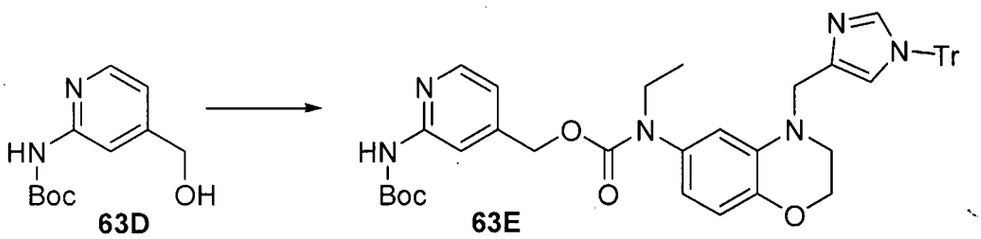
Etapa 4



63B **63C**

De manera similar a la descrita en el Ejemplo 50 (Etapa 5), **63B** se hizo reaccionar con carbonildiimidazol para proporcionar **63C.**

Etapas 5-6

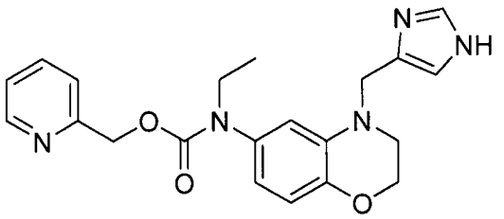


63D **63E**

Una solución de **63D** (188 mg, 0.84 mmol, PCT WO2002032893) en THF (4 mL) a 20 °C se trató con NaHMDS (340 µL, 1.68 mmol), se agitó durante 1h, y luego se trató con **63C** (100 mg, 0.17 mmol). Después de agitar durante la noche, la solución se diluyó con $NaHCO_3$ (10 mL) y se extrajo con CH_2Cl_2 (3 x 10 mL). La fase orgánica combinada se concentró al vacío para proporcionar **63E**.

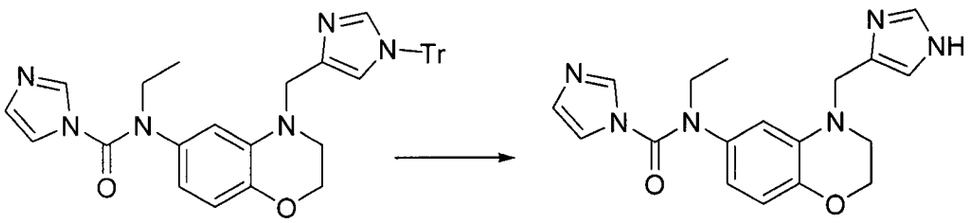
Este producto se trató luego con TFA/Et_3SiH para proporcionar el compuesto del título **63** de manera similar a la descrita en el Ejemplo 42 (Etapa 3). LCMS m/z 409 (MH+).

EJEMPLO PREPARATIVO 64



64

Etapas 1-2

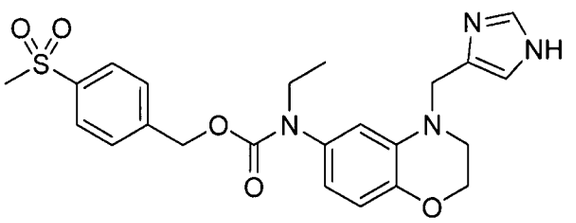


63B **64A**

De manera similar a la descrita en el Ejemplo 42 (Etapa 3), **63C** se trató con TFA/Et_3SiH para proporcionar **64A.** LCMS m/z 353 (MH+).

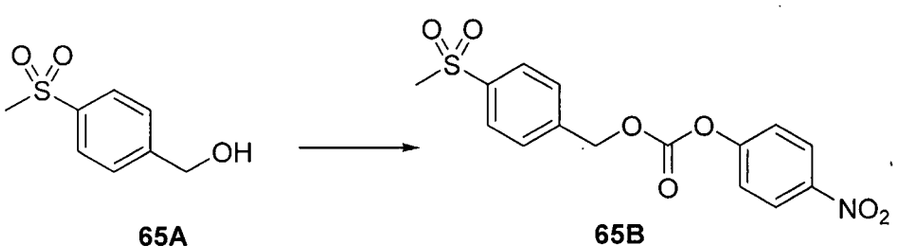
Este producto se trató luego con NaHMDS y piridin-2-metanol, tal como se describió en el Ejemplo 63 (Etapa 5) para proporcionar el compuesto del título **64**. LCMS m/z 394 (MH+).

EJEMPLO PREPARATIVO 65



65

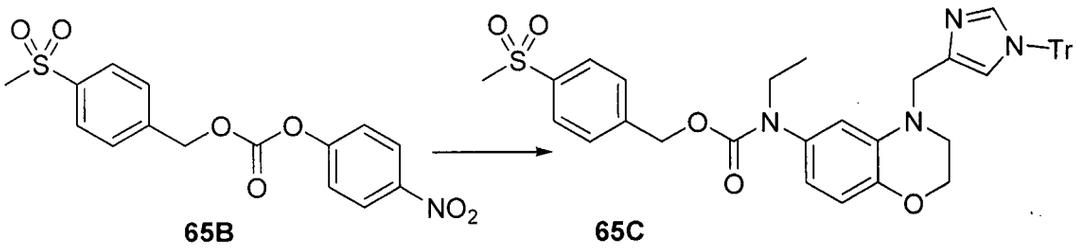
Etapa 1



65A **65B**

Una solución de alcohol 4-(metilsulfonil)bencílico (**65A**, 150 mg, 0.81 mmol) en THF (3 mL) a 20 °C se trató con cloroformiato 4-nitrofenilico (162 mg, 0.81 mmol) y piridina (66 μL, 0.81 mmol). La mezcla se agitó durante la noche y luego se dividió entre EtOAc y agua. La capa orgánica se lavó con salmuera, se secó sobre Na_2SO_4 y se concentró para proporcionar **65B**.

Etapas 2-3

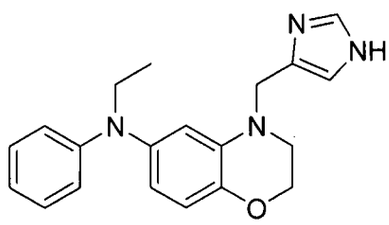


65B **65C**

Una solución de **65B** (material crudo de la etapa previa) en THF (3 mL) se trató con **63B** (160 mg, 0.34 mmol) y piridina (66 mL, 0.81 mmol). Después de agitar durante 2 días a 20 °C, la mezcla se diluyó con CH_2Cl_2, se lavó con $NaHCO_3$, acuoso saturado, y se concentró para proporcionar **65C**.

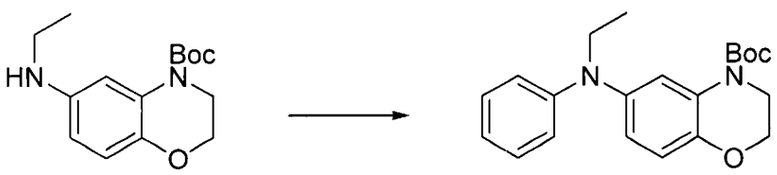
Este producto se desprotegió luego con TFA para proporcionar el compuesto del título **65** de manera similar a la descrita en el Ejemplo 42 (Etapa 3). LCMS m/z 471 (MH+).

EJEMPLO PREPARATIVO 66



66

Etapas 1-3

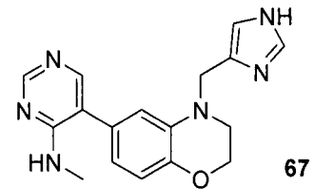


66A **66B**

Una solución de bromobenceno (135 mg, 0.863 mmol), **66A** (200 mg, 0.719 mmol, producto del Ejemplo 38, Etapa 4) se trató con $Pd_2(dba)_3$ (33 mg, 0.036 mmol), Ligy S-Phos (30 mg, 0.076 mmol), y NaOtBu (90 mg, 0.934 mmol). La mezcla se agitó a 100°C durante 12 h bajo N_2, se filtró. La cromatografía (50% EtOAc/Hexano) proporcionó **66B** en forma de un aceite.

De manera similar a la descrita en el Ejemplo 38 (Etapa 6) y Ejemplo 3 (Etapa 3), **66B** se desprotegió luego con TFA y luego se convirtió al compuesto del título **66**. LCMSm/z 335 (MH+).

EJEMPLO PREPARATIVO 67



67

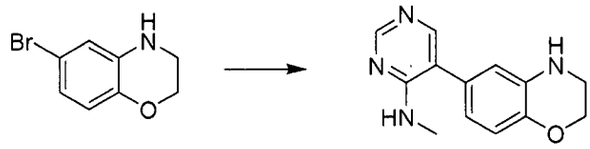
Etapa 1



67A **67B**

Una solución de 4-cloro-5-yodopirimidina **67A** (2.03 g, 8.44 mmol) en una solución de $MeNH_2$ acuosa al 40% se agitó a temperatura ambiente durante 17 horas. La mezcla se extrajo luego con DCM (2 x 150 ml). Las fases orgánicas combinadas se secaron y se concentraron para proporcionar 5-yodo-4-metilaminopirimidina **67B** (1.55 g, 78%) en forma de un sólido naranja que se usó en la etapa siguiente sin purificación adicional.

Etapas 2-3



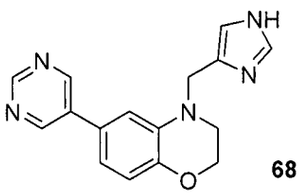
67C **67D**

295

Un tubo sellado de 15 mL se cargó con 6-bromofenil morfolina (**67C**, 0.431 g, 2.013 mmol), bis(pinacolato)diborónico (1.02 g, 4.03 mmol), KOAc (0.592 g, 6.04 mmol), $Pd(dppf)Cl_2$.DCM (0.164 g, 0.20 mmol) y 1,4-dioxano seco (8 ml). La mezcla resultante se calentó a 100 °C durante 1.5h. La mezcla se enfrió luego a temperatura ambiente y se trató consecutivamente con 5-yodo-4-metil amino pirimidina (**67B**, 0.66 g, 4.03 mmol, 2.0 eq) y K_2CO_3 acuoso 1M (5 mL). La mezcla resultante se calentó nuevamente a 100 °C durante 13h, se enfrió a temperatura ambiente, se diluyó con agua y se extrajo con DCM para proporcionar un aceite marrón. La cromatografía (0-10% de (9:1 $MeOH/NH_3$) en DCM) proporcionó **67D** (0.198 g, 41%) en forma de una espuma de color marrón pálido.

De manera similar a la descrita en el Ejemplo 3 (Etapa 3), el compuesto **67D** se convirtió al compuesto del título **67**.ES m/z 323 (MH+).

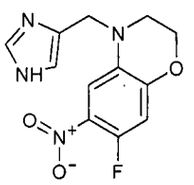
EJEMPLO PREPARATIVO 68



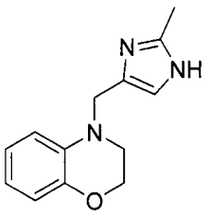
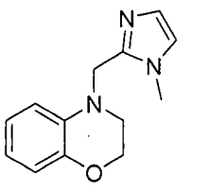
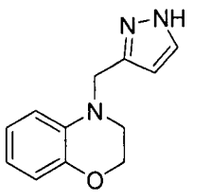
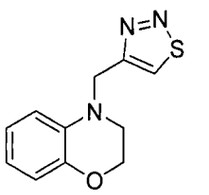
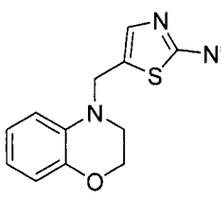
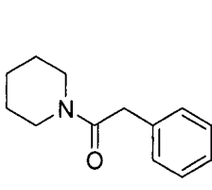
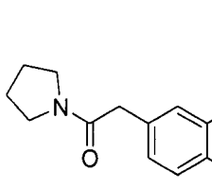
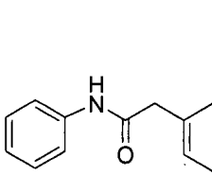
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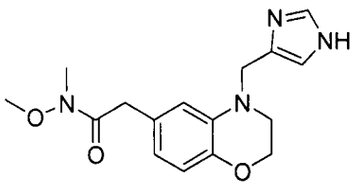
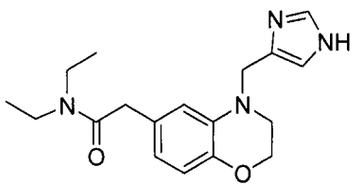
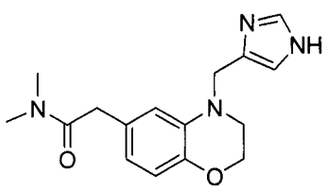
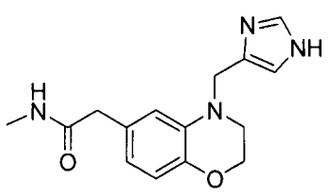
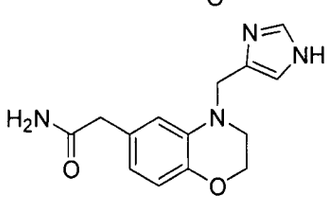
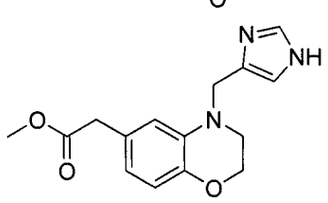
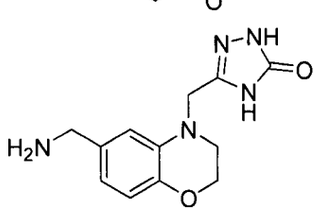
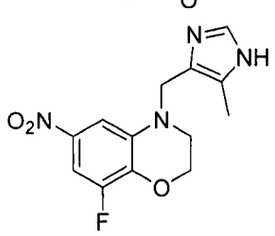
De manera similar a la descrita previamente (Ejemplos 15-17, 67), 6-bromofenil morfolina (**67C**) se trató con ácido pirimidin-5-borónico, $PdCl_2(dppf)$, y K_2CO_3, para proporcionar el compuesto 6-(pirimidin-5-il)-benzomorfolina, que se convirtió adicionalmente al compuesto del título **68**. MS m/z 294 (MH+).

Los siguientes compuestos se prepararon siguiendo esencialmente el mismo procedimiento tal como se describió anteriormente.

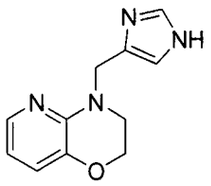
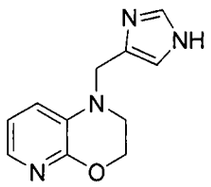
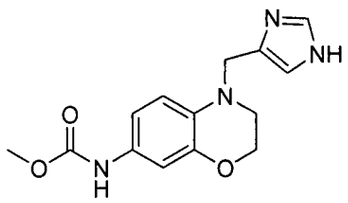
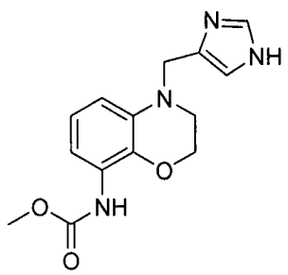
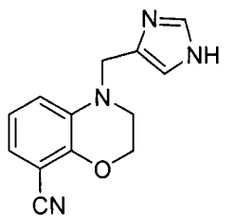
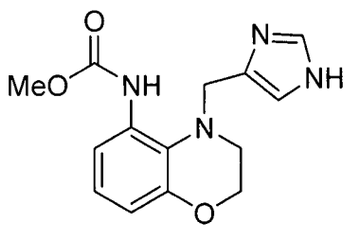
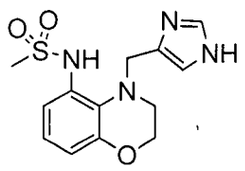
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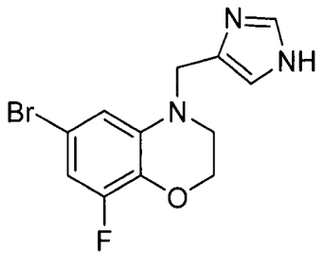
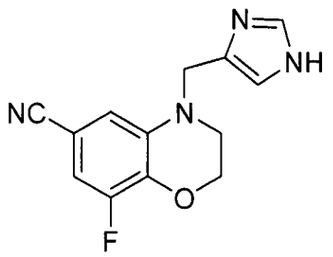
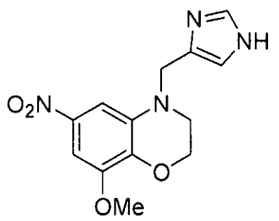
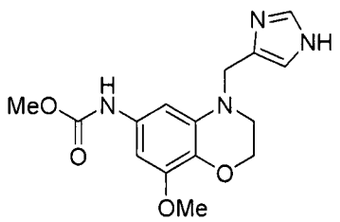
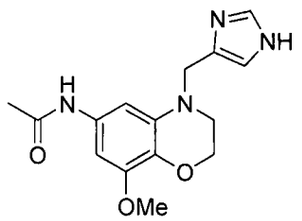
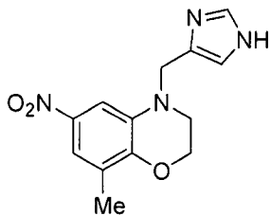
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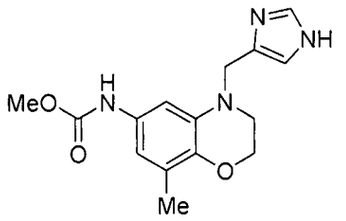
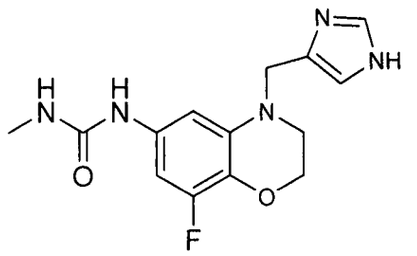
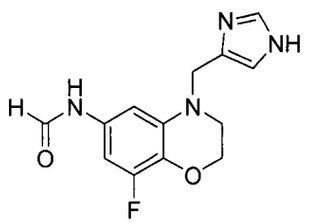
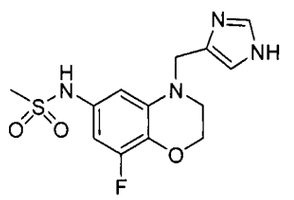
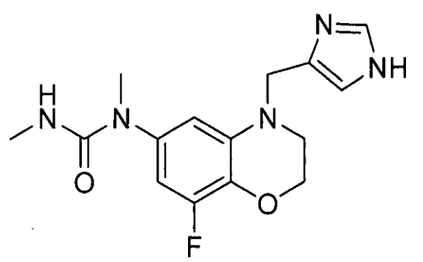
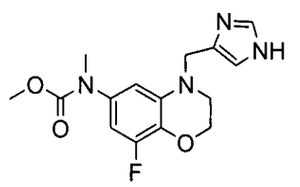
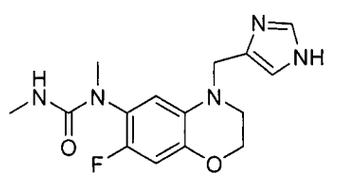
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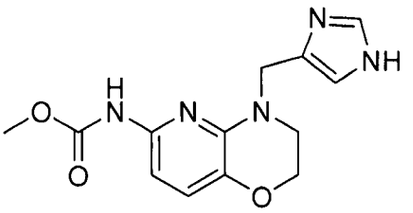
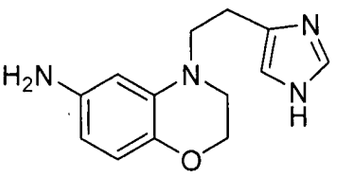
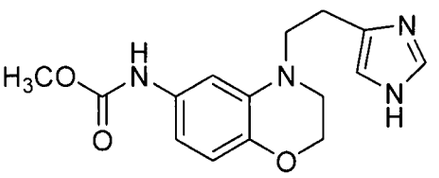
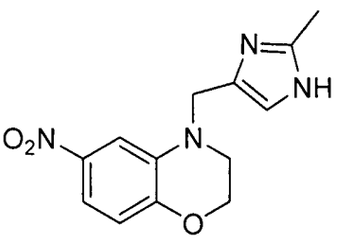
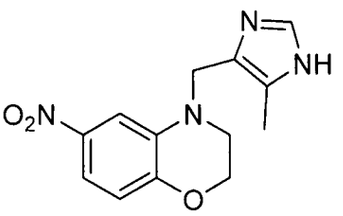
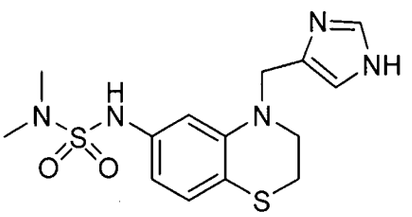
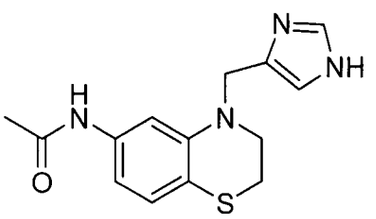
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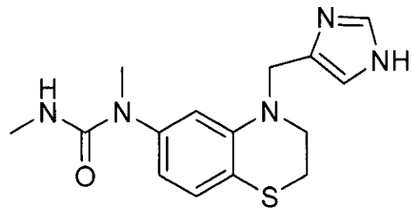
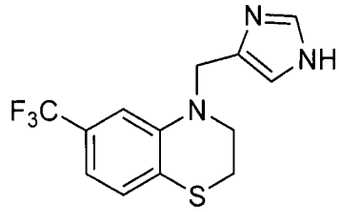
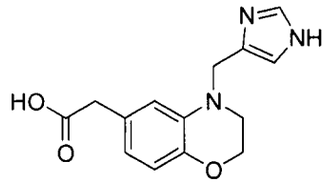
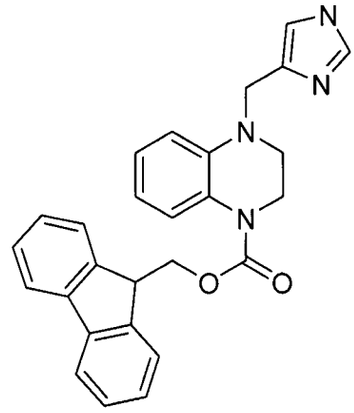
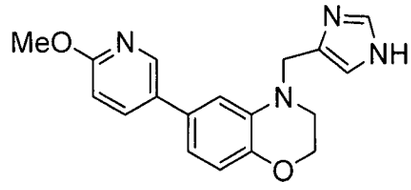
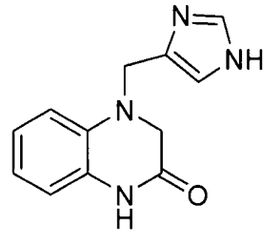
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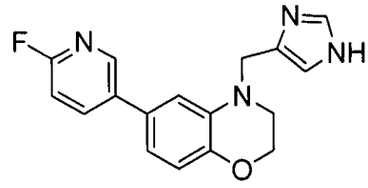
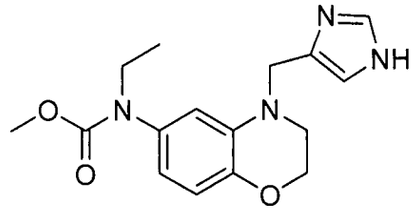
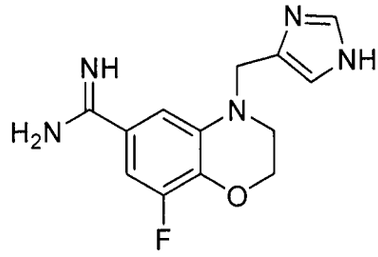
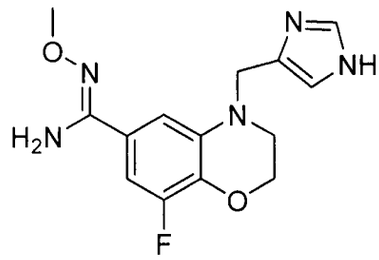
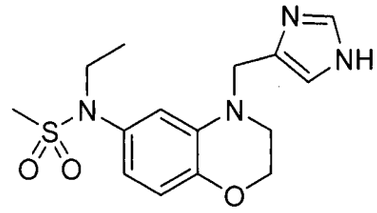
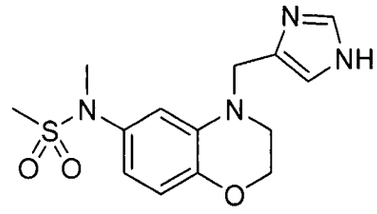
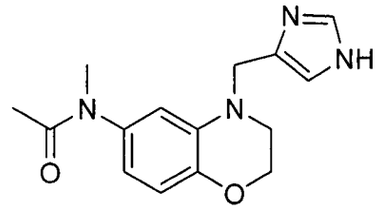
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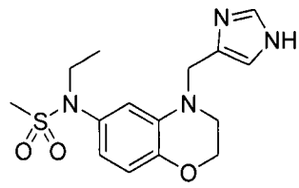
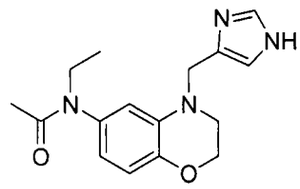
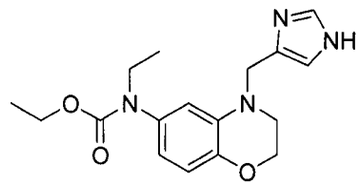
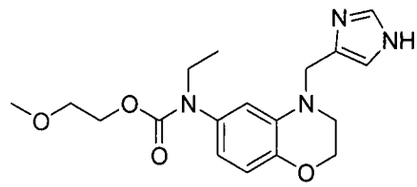
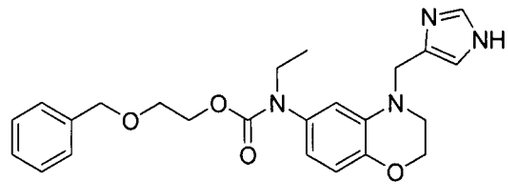
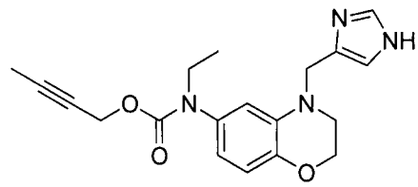
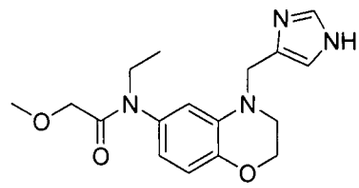
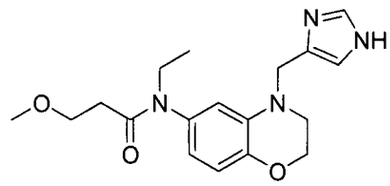
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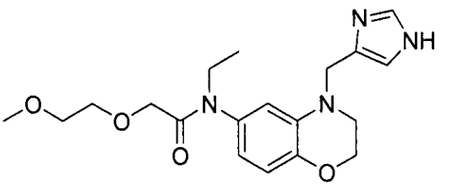
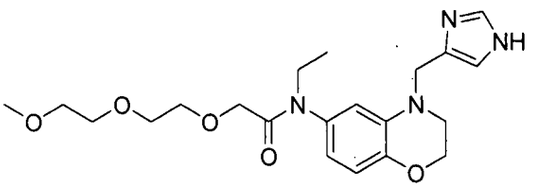
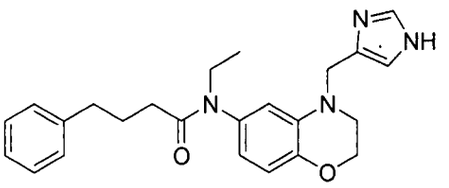
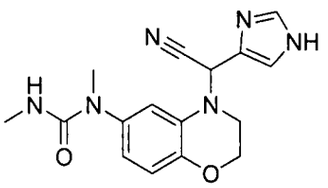
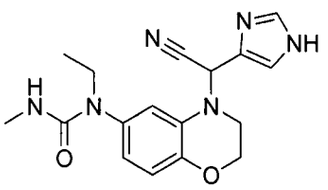
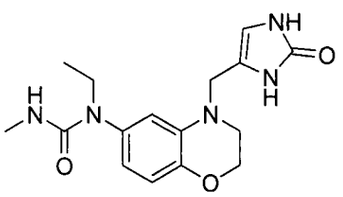
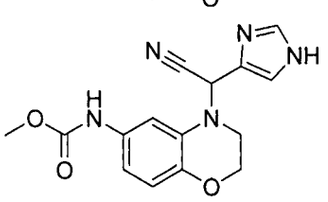
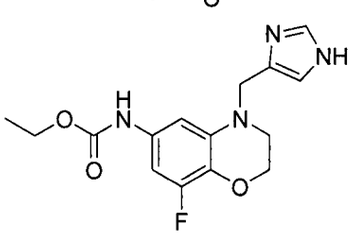
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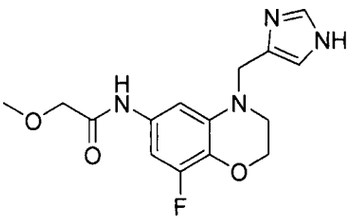
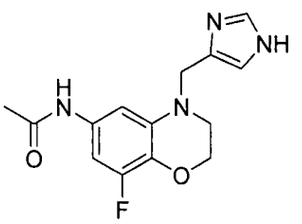
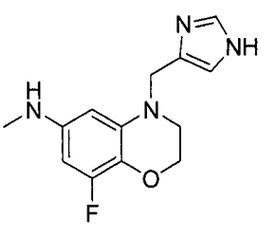
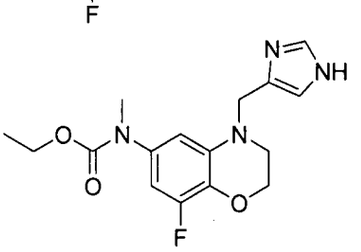
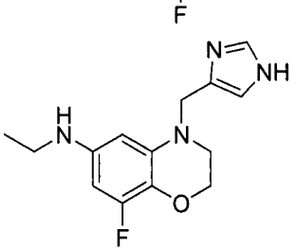
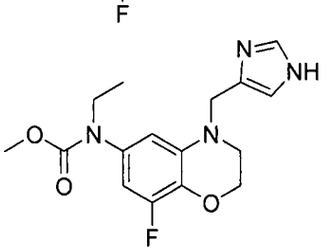
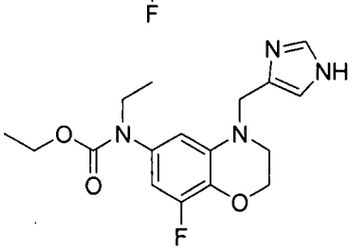
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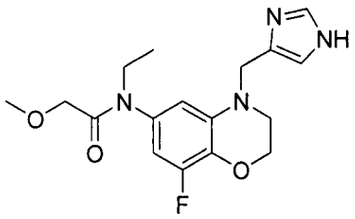
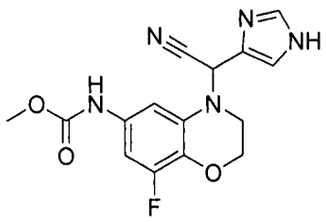
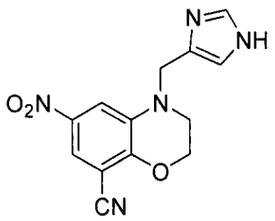
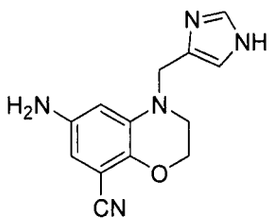
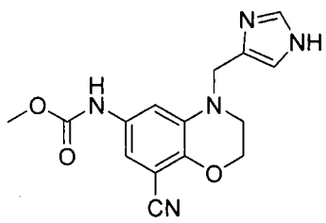
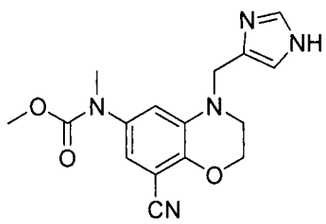
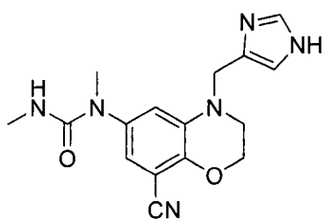
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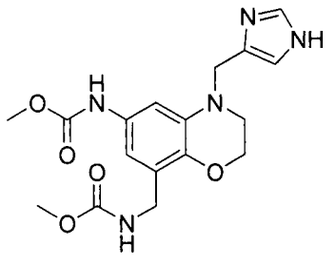
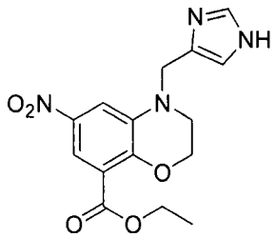
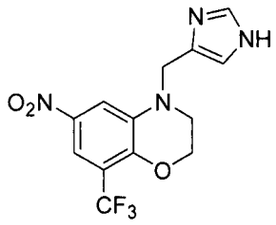
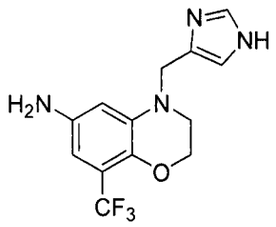
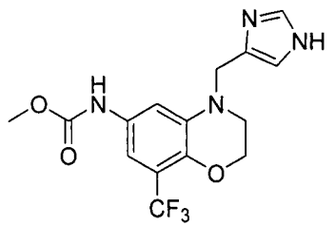
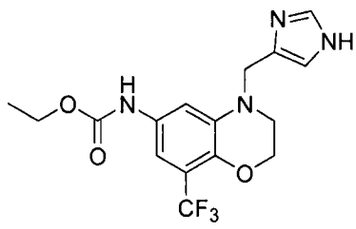
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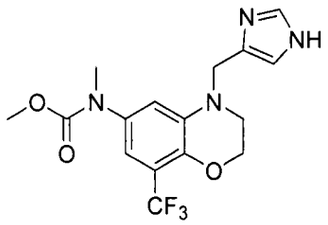
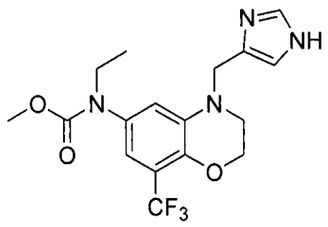
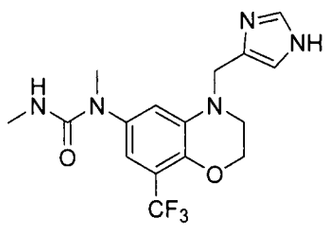
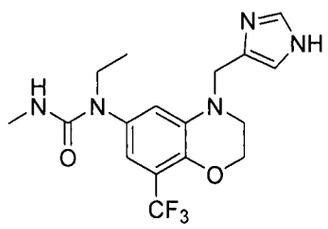
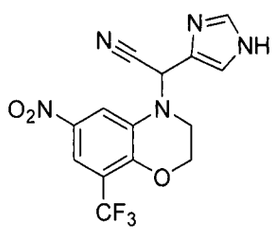
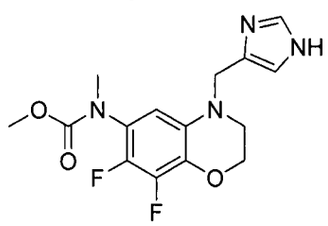
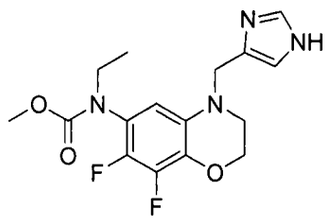
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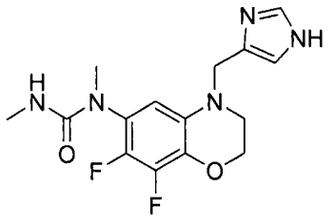
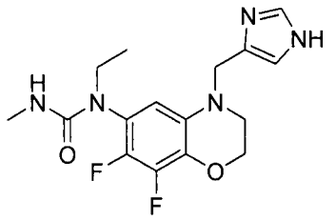
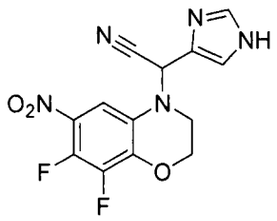
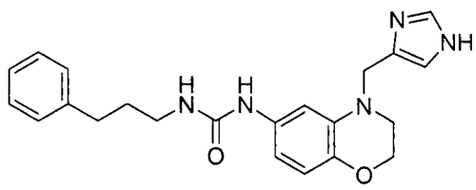
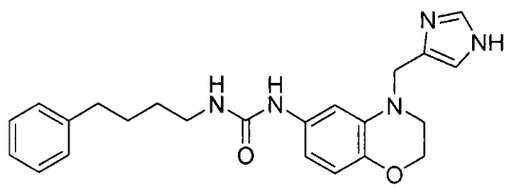
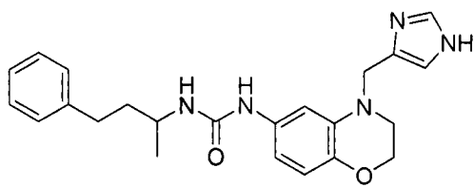
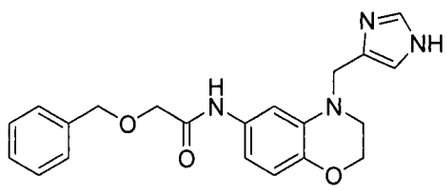
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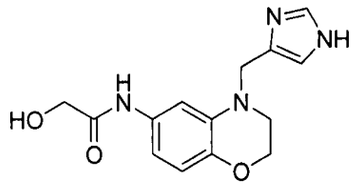
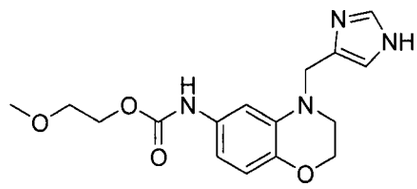
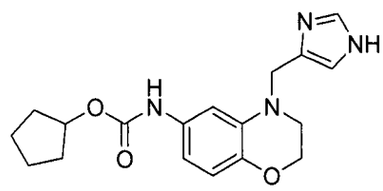
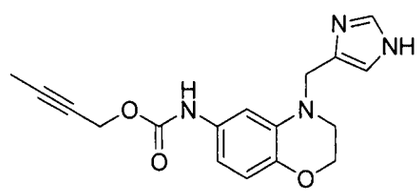
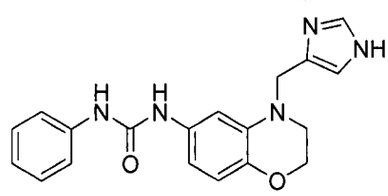
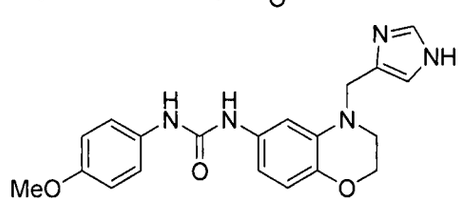
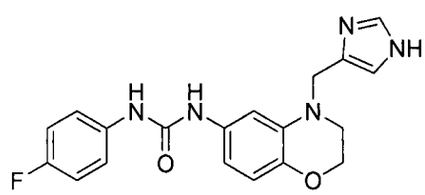
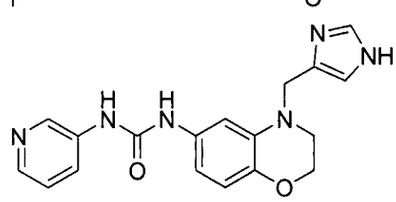
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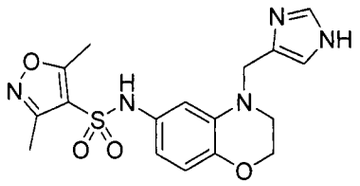
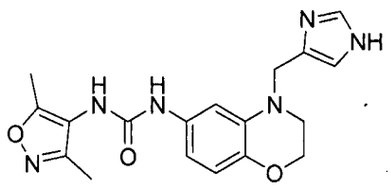
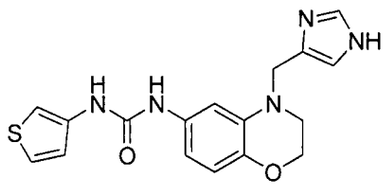
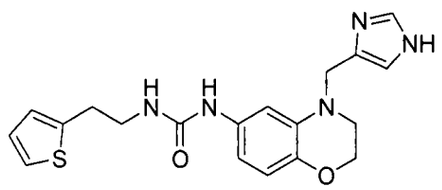
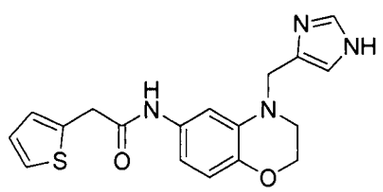
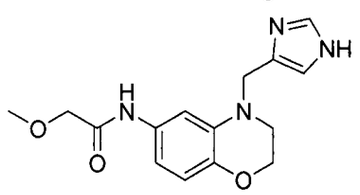
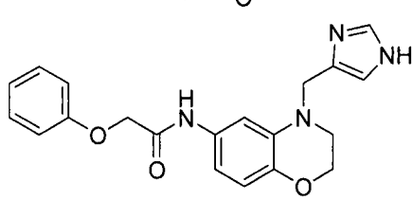
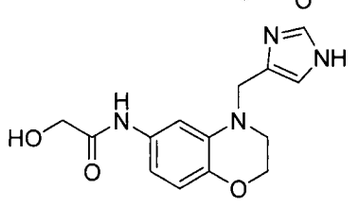
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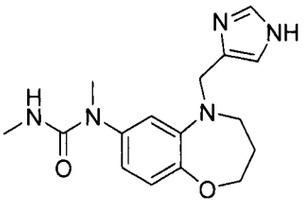
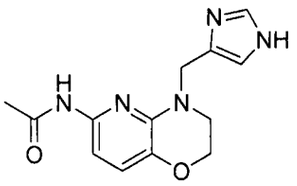
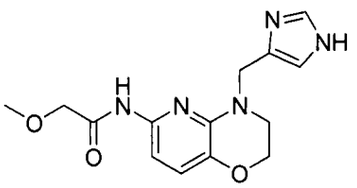
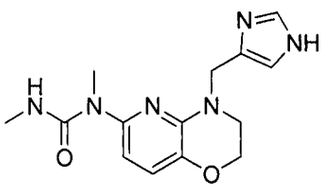
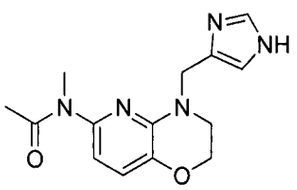
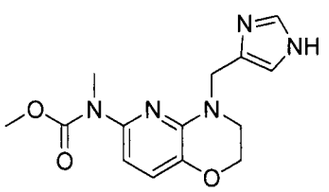
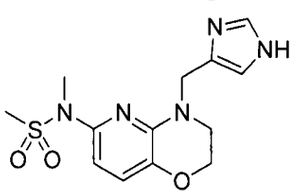
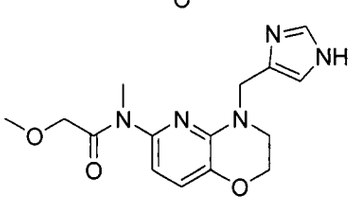
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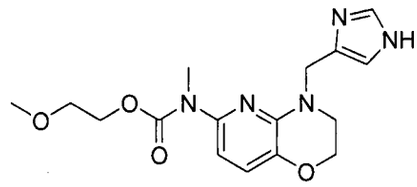
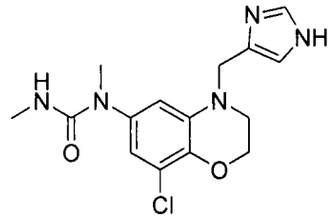
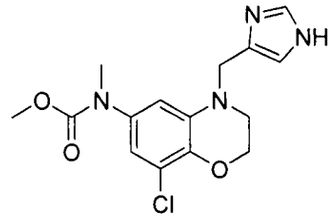
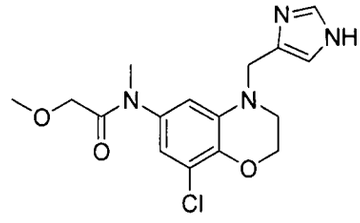
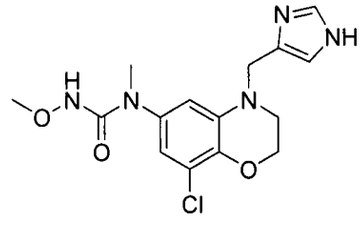
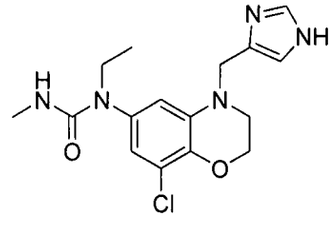
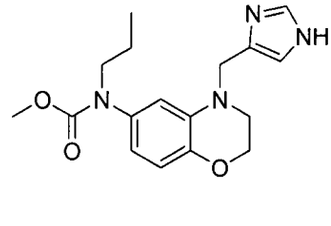
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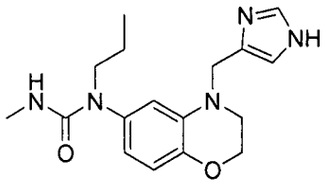
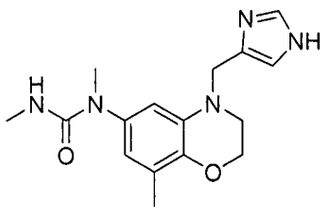
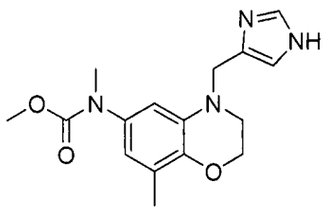
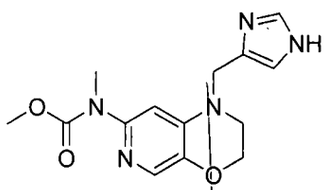
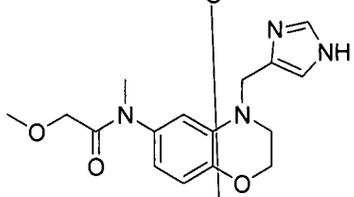
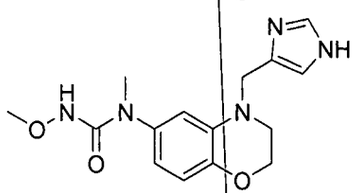
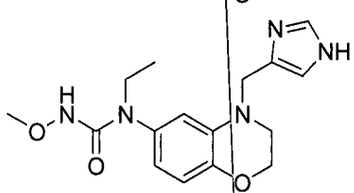
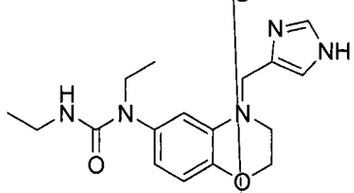
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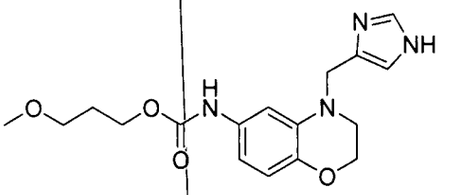
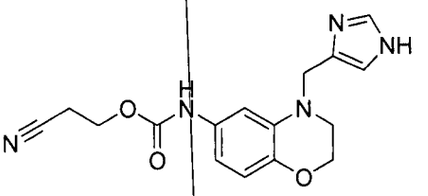
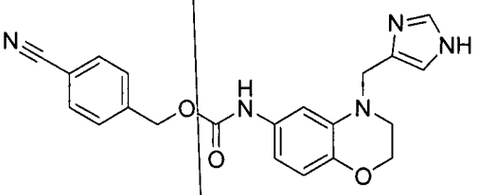
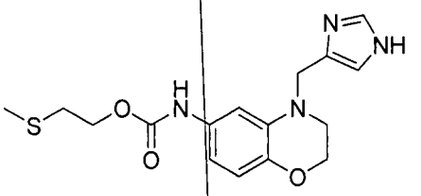
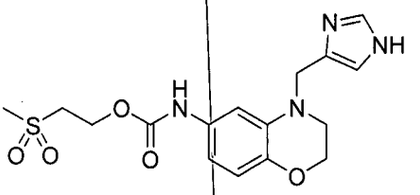
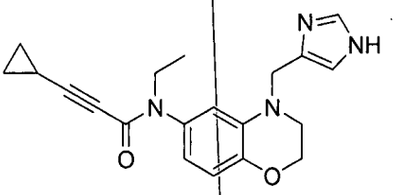
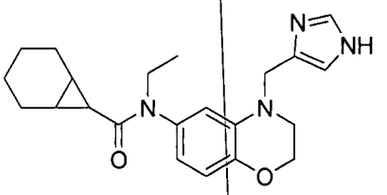
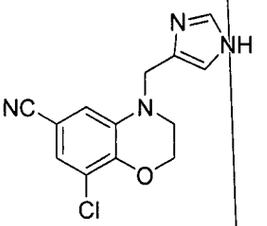
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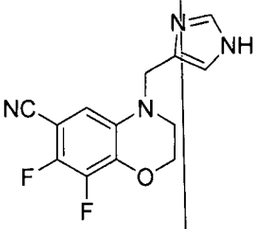
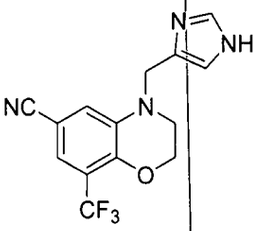
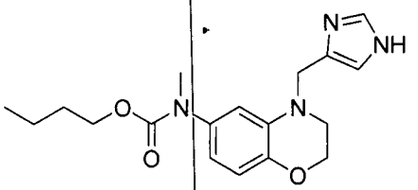
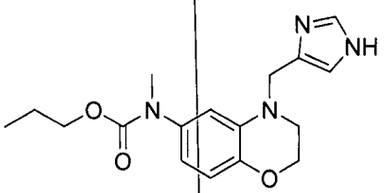
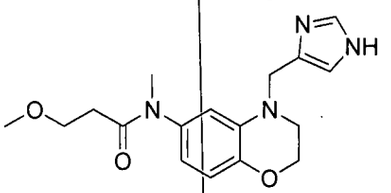
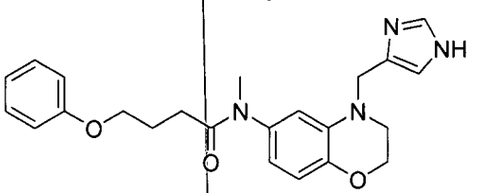
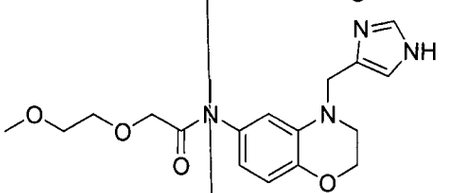
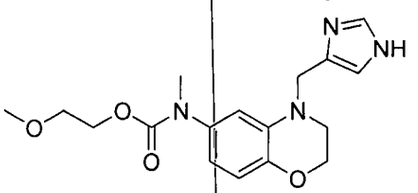
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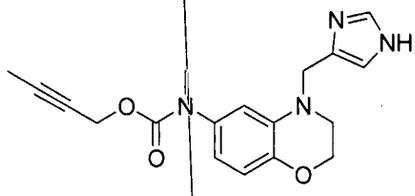
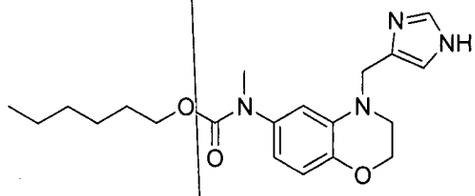
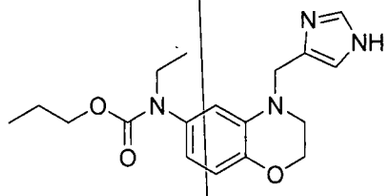
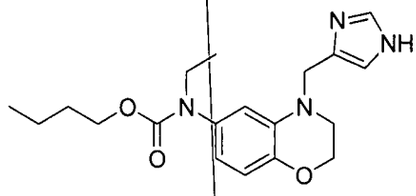
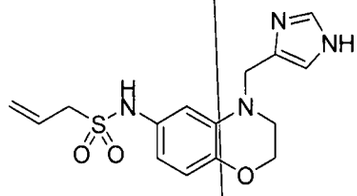
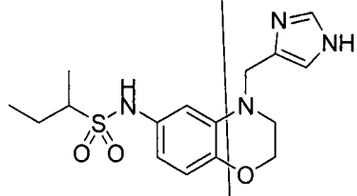
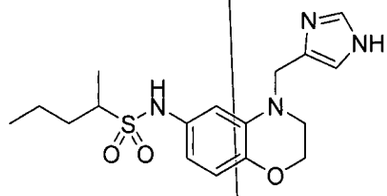
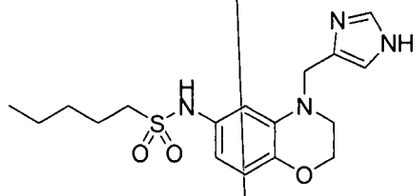
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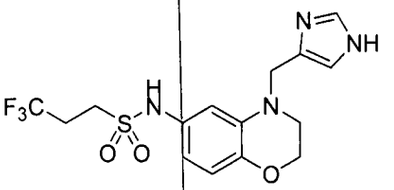
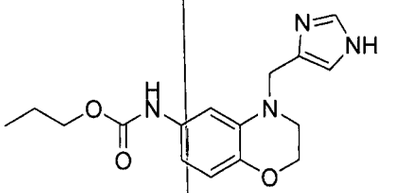
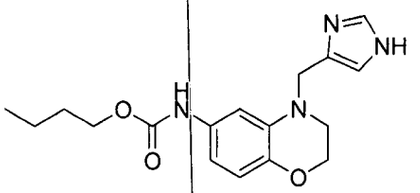
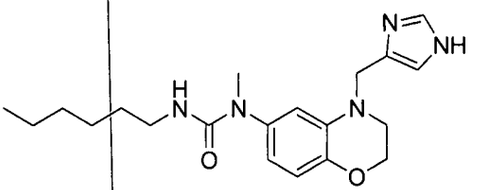
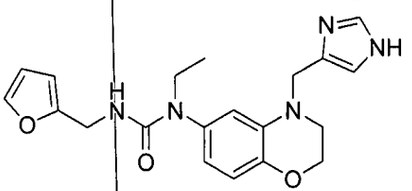
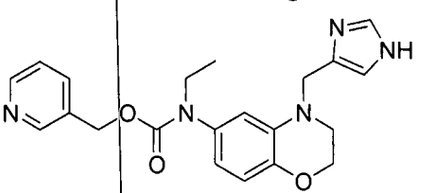
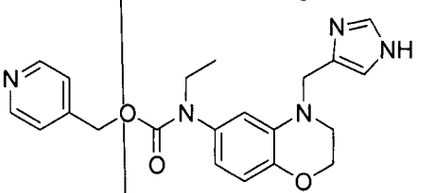
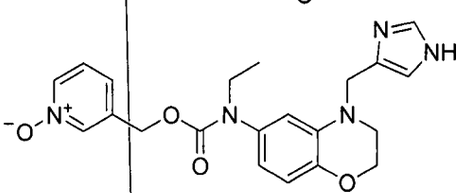
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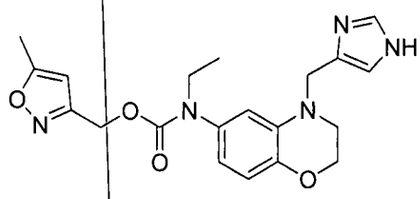
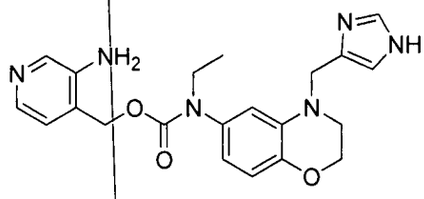
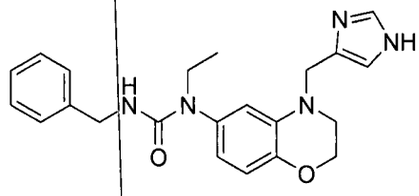
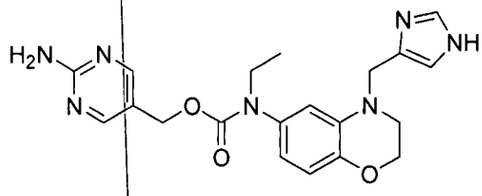
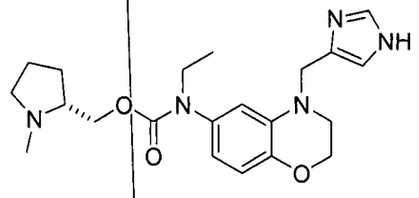
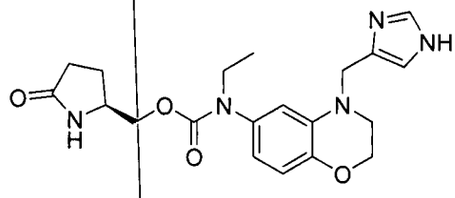
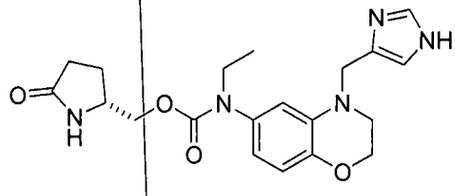
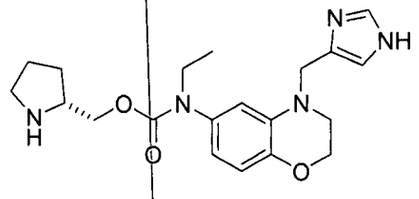
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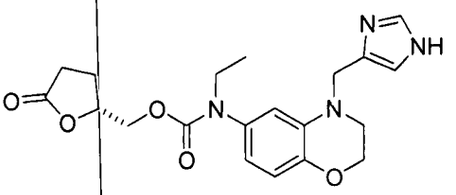
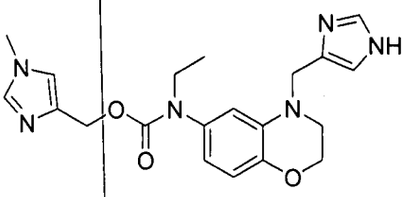
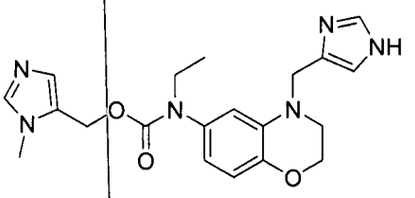
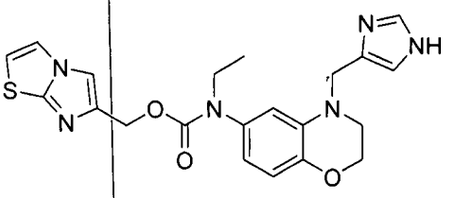
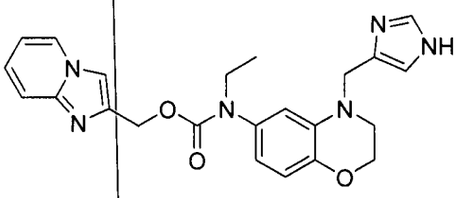
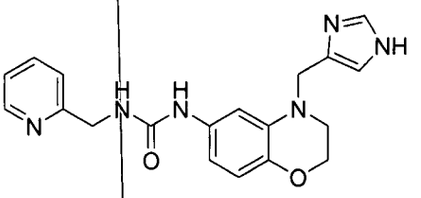
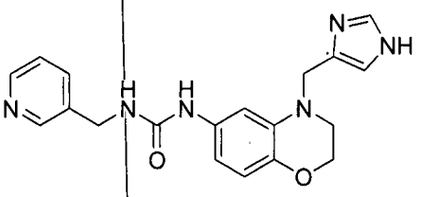
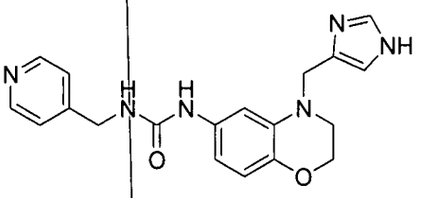
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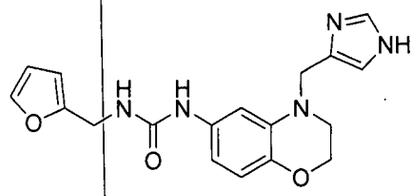
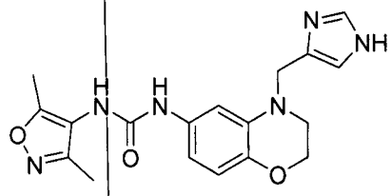
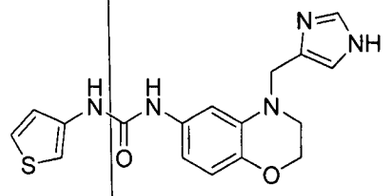
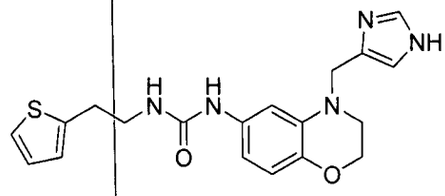
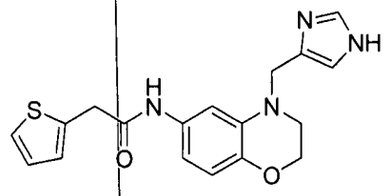
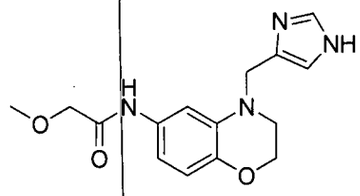
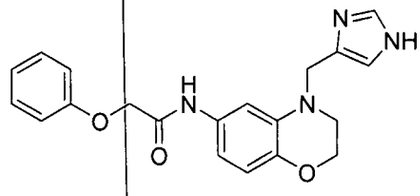
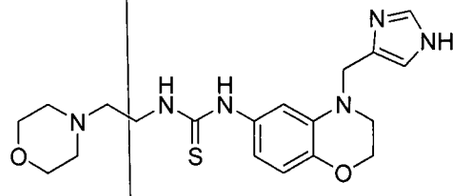
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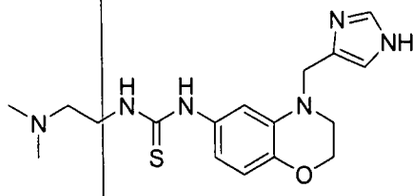
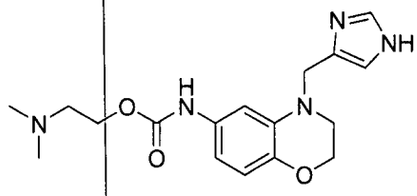
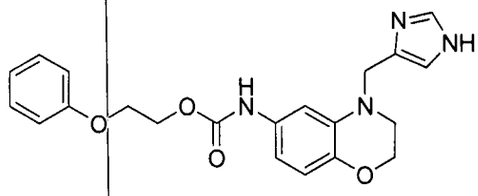
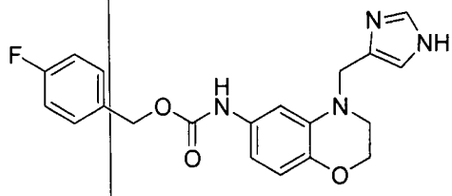
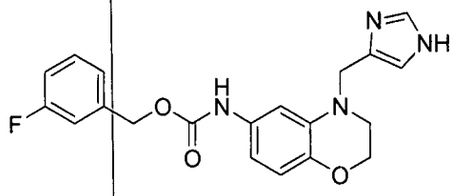
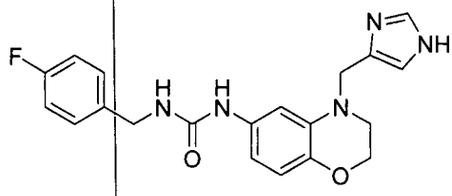
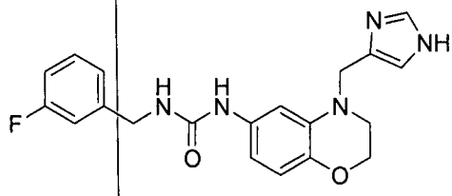
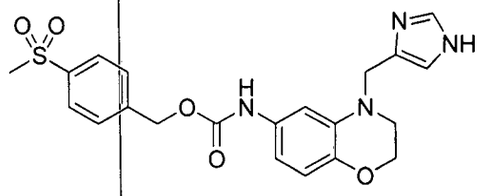
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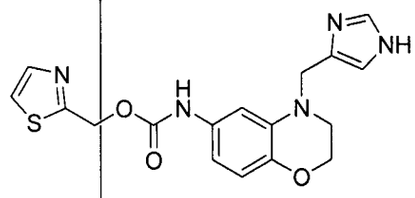
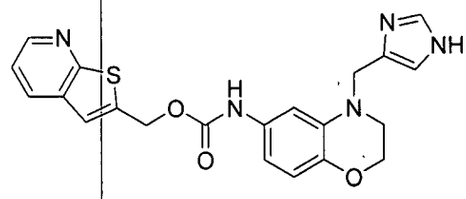
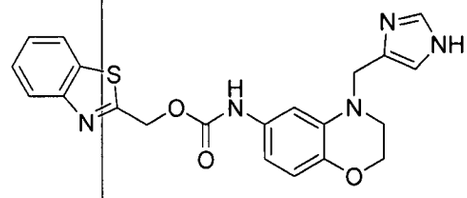
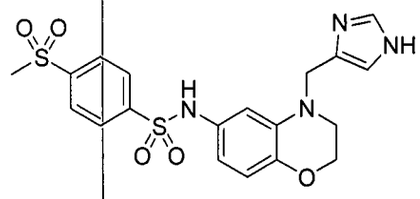
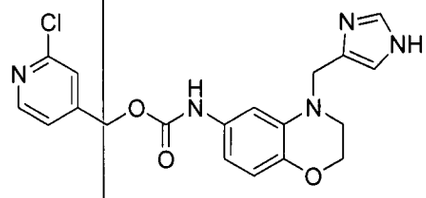
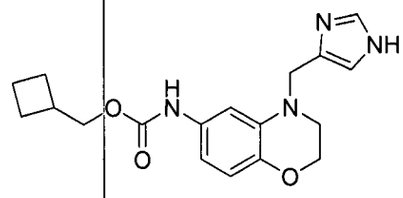
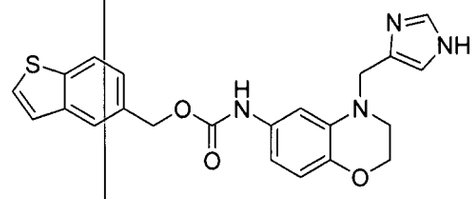
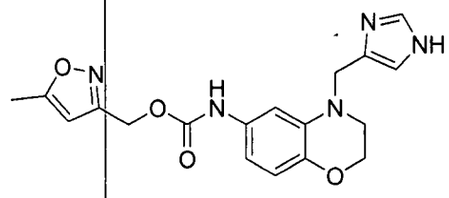
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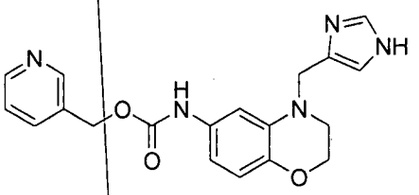
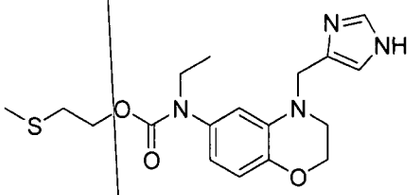
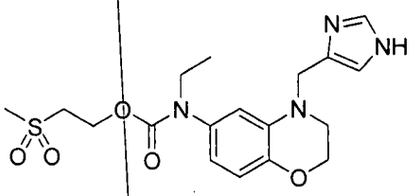
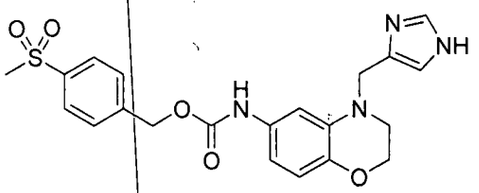
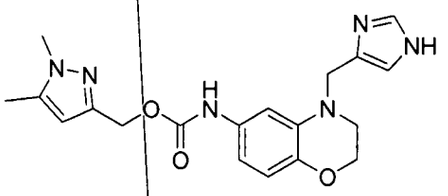
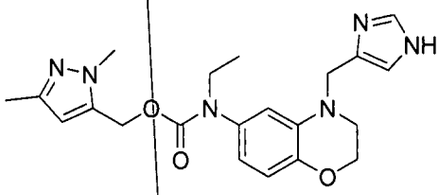
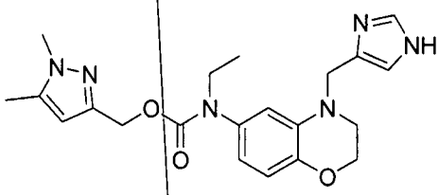
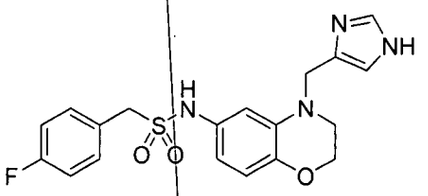
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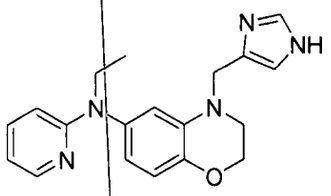
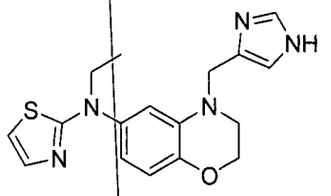
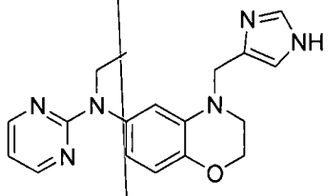
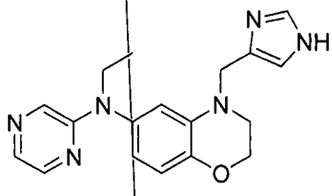
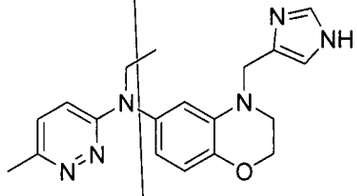
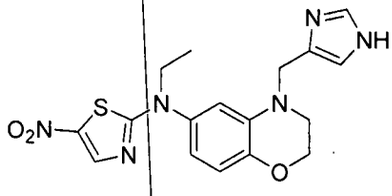
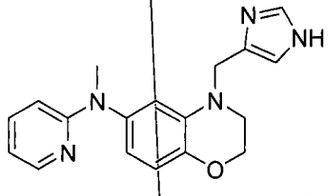
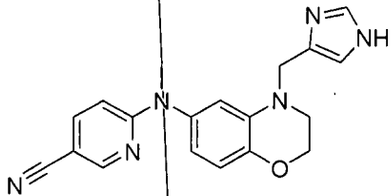
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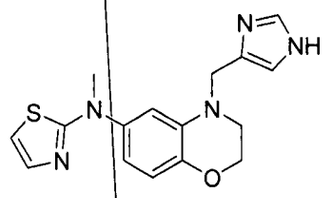
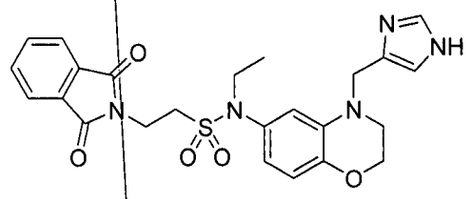
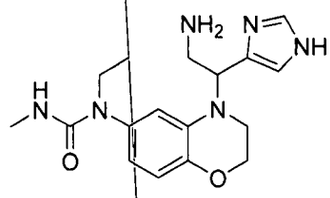
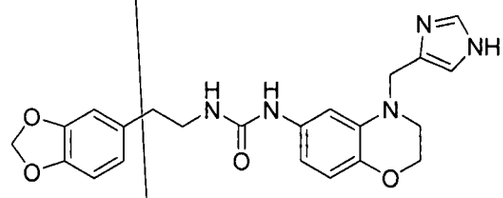
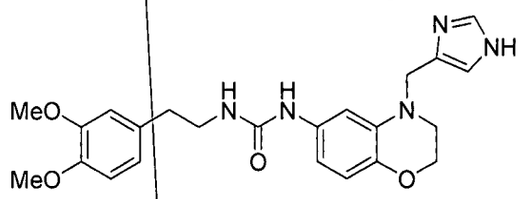
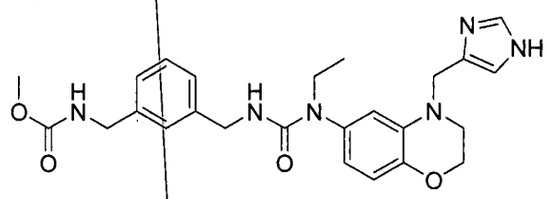
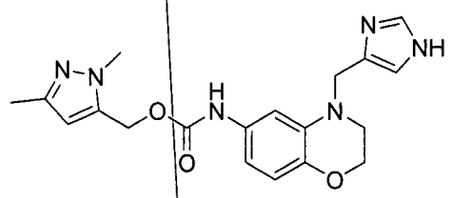
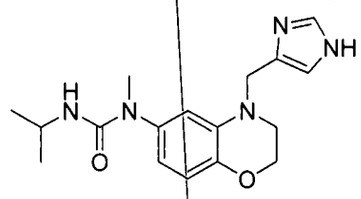
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325		403

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337		422
338		438
339		479
340		383
341		330

ENSAYO:

Los valores de la eficacia de actividad agonista (Emax, ensayo GTPγS) para α2C se determinaron siguiendo el procedimiento general de UmLand *et. al* ("Receptor reserve analysis of the human α_{2c}-adrenoceptor using [^{35}S]GTPγS y cAMP functional assays" European Journal of Pharmacology **2001**, 411, 211-221). Para los propósitos de la presente invención un compuesto se define como un agonista activo del sub-tipo receptor α2C si la eficacia del compuesto en el receptor α2C es de ≥ 30% Emax (ensayo GTPγS). Un compuesto es un agonista funcionalmente selectivo del sub-tipo receptor α2C sobre el sub-tipo receptor α2A si la eficacia del compuesto en el receptor α2C es ≥ 30% E_{max} (ensayo GTPγS) y su eficacia en el receptor α2A es ≤ 30% E_{max} (ensayo GTPγS).

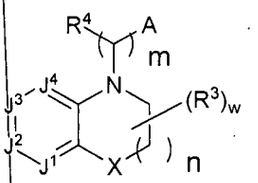
Los siguientes compuestos fueron evaluados como agonistas activos o funcionalmente selectivos del sub-tipo receptor α2C basados en la definición que se ha definido previamente: **1, 3, 3D, 3E, 5, 6, 6E, 7, 8, 9E, 9G, 9I, 9K, 9L, 9M, 9N, 9P, 9Q, 9R, 9S, 12, 13, 14, 14B, 15, 19, 19D, 20, 21, 22, 24, 24D, 25B, 26, 26A, 26B, 27E, 28, 28D, 29, 30, 37, 38, 46, 51, 53, 54, 55, 57, 58, 63, 64, 64A, 65, 114, 117, 124, 125, 129, 130, 132, 134, 135, 137, 139, 142, 144, 145, 148, 151, 152, 158, 159, 160, 162, 163, 164, 165, 167, 168, 169, 171, 178, 181, 218, 223, 231, 232, 235, 236, 238, 239, 240, 242, 243, 244, 245, 246, 247, 248, 249, 250, 251, 253, 256, 257, 259, 260, 261, 262, 263, 264, 265, 266, 271, 272, 273, 274, 275, 276, 278, 279, 280, 281, 287, 289, 290, 291, 297, 304, 305, 306, 307, 308, 309, 310, 311, 312, 314, 315, 316, 317, 318, 319, 321, 323, 324, 326, 327, 329, 331, 332, 335,** y **340.**

Si bien la presente invención ha sido descrita conjuntamente con las realizaciones específicas indicadas anteriormente, muchas alternativas, modificaciones y otras variaciones de la misma, resultarán aparentes para los expertos en la materia. Todas dichas alternativas, modificaciones y variaciones están abarcadas dentro del espíritu y alcance de la presente invención.

REIVINDICACIONES

Habiendo así especialmente descrito y determinado la naturaleza de la presente invención y la forma cómo la misma ha de ser llevada a la práctica se declara reivindicar como de propiedad y derecho exclusivo:

1. Un compuesto que tiene la estructura general que se muestra en la Fórmula I:



Formula I

o una sal, éster, solvato o prodroga farmacéuticamente aceptable de dicho compuesto donde:

A es un anillo heterocíclico de 5 miembros que contiene 1-3 heteroátomos, y está opcionalmente sustituido con por lo menos un R^5 y/o 1 o 2 grupos (=O) (carbonilo);

X es -O-, -$S(O)_p$-, o -$N(R^6)$-;

J^1, J^2, J^3, y J^4 son independientemente -N-, -N(O)- o -$C(R^2)$-, con la condición de que 0-3 de J^1, J^2, J^3 y J^4 sean –N-;

R^2 está independientemente seleccionado del grupo que consiste en H, -OH, halo, -CN, -NO_2, -$S(O)_pR^7$, -$NR^7R^{7'}$, -$[C(R^a)(R^b)]_qYR^{7'}$, -$[C(R^a)(R^b)]_qN(R^7)YR^{7'}$, $C(R^a)(R^b)]_qOYR^{7'}$, -$[C(R^a)(R^b)]_qON=CR^7R^{7'}$, -$P(=O)(OR^7)(OR^{7'})$, -$P(=O)NR^7R^{7'}$, y -$P(=O)R^8{}_2$, y grupos alquilo, alcoxi, alquenilo, alqueniloxi, alquinilo, cicloalquilo, cicloalcoxi, arilo, ariloxi, arilalquilo, heteroarilo, heteroarilalquilo, heterociclilo, y heterociclilalquilo, sustituidos opcionalmente con por lo menos un R^5;

Y está seleccionado del grupo que consiste en un enlace, -C(=O)-, -$C(=O)NR^7$-, -C(=O)O-, -$C(=NR^7)$-, -C(=O)-$[C(R^a)(R^b)]_{n'}$- O-C(=O)-,

-C(=O)N(R^c)-O-, -C(=NOR^7)-, -C(=NR^7)NR^7-, -C(=NR^7)N(R^c)O-, -S(O)$_p$-, -SO_2NR^7-, y -C(S)NR^7-;

donde R^a y R^b están independientemente seleccionados del grupo que consiste en H, alquilo, alcoxi, y halo,

R^c es H o alquilo;

R^3 está independientemente seleccionado del grupo que consiste en H, halo, y (=O), y grupos alquilo, alcoxi, alquenilo, alqueniloxi, alquinilo, cicloalquilo, cicloalcoxi, arilo, ariloxi, arilalquilo, heteroarilo, heteroarilalquilo, heterociclilo, y heterociclilalquilo, opcionalmente sustituidos con por lo menos un R^5, con la condición de que cuando n es 3 o 4, no más de 2 de los grupos R^3 pueden ser(=O);

R^4 está independientemente seleccionado del grupo que consiste en H, -CN, y halo, y grupos alquilo, alcoxi, alquenilo, alqueniloxi, alquinilo, cicloalquilo, cicloalcoxi, arilo, ariloxi, arilalquilo, heteroarilo, heteroarilalquilo, heterociclilo, y heterociclilalquilo, opcionalmente sustituidos con por lo menos un R^5;

R^5 está independientemente seleccionado del grupo que consiste en H, halo, -OH, -CN, -NO_2, -N$R^7R^{7'}$, y –S(O)$_p$$R^7$, y grupos alquilo, alcoxi, alquenilo, alqueniloxi, alquinilo, cicloalquilo, cicloalcoxi, arilo, ariloxi, arilalquilo, heteroarilo, heteroarilalquilo, heterociclilo, y heterociclilalquilo, cada uno de los cuales está opcionalmente sustituido con por lo menos uno de los sustituyentes halo, -OH, -CN, -NO_2, -N$R^7R^{7'}$, y –S(O)$_p$$R^7$ y/o 1 o 2 grupos (=O);

R^6 está independientemente seleccionado del grupo que consiste en H y grupos alquilo, alcoxi, alquenilo, alqueniloxi, alquinilo, cicloalquilo, cicloalcoxi, arilo, ariloxi, arilalquilo, heteroarilo, heteroarilalquilo, heterociclilo, y heterociclilalquilo, cada uno de los cuales está opcionalmente sustituido con por lo menos uno de los sustituyentes halo, -OH, -CN, -NO_2, -N$R^7R^{7'}$, y –S(O)$_p$$R^7$ y/o 1 o 2 grupos (=O), y -C(=O)R^7, -C(=O)OR^7, -C(=O)N$R^7R^{7'}$, -SO_2R^7 y -SO_2N$R^7R^{7'}$;

R^7 está independientemente seleccionado del grupo que consiste en H y grupos alquilo, alquenilo, alquinilo, cicloalquilo, cicloalquilalquilo, ciclociclenilo, ciclociclenilalquilo, arilo, arilalquilo, heterociclilo, heterociclilalquilo, heterociclenilo, heterociclenilalquilo, heteroarilo, y heteroarilalquilo, cada uno de los cuales está

opcionalmente sustituido una o más veces (preferiblemente 1 a 5, más preferiblemente 1 a 3) con R^{12};

$R^{7'}$ está independientemente seleccionado del grupo que consiste en H y grupos alquilo, alquenilo, alquinilo, cicloalquilo, cicloalquilalquilo, ciclociclenilo, ciclociclenilalquilo, arilo, arilalquilo, heterociclilo, heterociclilalquilo, heterociclenilo, heterociclenilalquilo, heteroarilo, y heteroarilalquilo, cada uno de los cuales está opcionalmente sustituido una o más veces (preferiblemente 1 a 5, más preferiblemente 1 a 3) con R^{12}; o

R^7 y $R^{7'}$ conjuntamente con el átomo de nitrógeno al cual están unidos forman un anillo heterociclilo, heterociclenilo o heteroarilo de 3 a 8 miembros que tiene, además del átomo N, 1 o 2 heteroátomos adicionales seleccionados del grupo que consiste en O, N, -N(R^9)- y S, donde dichos anillos están opcionalmente sustituidos con 1 a 5 restos seleccionados independientemente de los restos R^5 y/o 1 o 2 grupos (=O),

R^8 está independientemente seleccionado del grupo que consiste en grupos alquilo, alquenilo, alquinilo, cicloalquilo, arilo, arilalquilo, heteroarilo, y heteroarilalquilo, cada uno de los cuales está opcionalmente sustituido con por lo menos uno de los sustituyentes halo, -OH, -CN, $-NO_2$, -N(R^{11})$_2$, y $-S(O)_pR^{11}$ y/o 1 o 2 grupos (=O);

R^9 está independientemente seleccionado del grupo H, -C(O)-R^{10}, -C(O)-OR^{10}, y $-S(O)_p$-OR^{10} y grupos alquilo, alquenilo, alquinilo, cicloalquilo, arilo, arilalquilo, heteroarilo, y heteroarilalquilo, cada uno de los cuales está opcionalmente sustituido con por lo menos uno de los sustituyentes halo, -OH, -CN, $-NO_2$, -N(R^{11})$_2$, y $-S(O)_pR^{11}$ y/o 1 o 2 grupos(=O); y

R^{10} está seleccionado del grupo que consiste en grupos alquilo, alquenilo, alquinilo, cicloalquilo, arilo, arilalquilo, heteroarilo, y heteroarilalquilo, cada uno de los cuales está opcionalmente sustituido con por lo menos uno de los sustituyentes halo, -OH, -CN, $-NO_2$, -N(R^{11})$_2$, y $-S(O)_pR^{11}$ y/o 1 o 2 grupos (=O);

R^{11} es un resto independientemente seleccionado del grupo que consiste en H y alquilo, alcoxi, alquenilo, alqueniloxi, alquinilo, cicloalquilo, cicloalcoxi, arilo, ariloxi, arilalquilo, heteroarilo, heteroarilalquilo, heterociclilo, y heterociclilalquilo, cada uno de los cuales está opcionalmente sustituido con por lo menos un

sustituyente independientemente seleccionado del grupo que consiste en halo, -OH, -CN, $-NO_2$, $-N(R^{11'})_2$, y $-S(O)_pR^{11'}$ y/o 1 o 2 grupos (=O);

$R^{11'}$ está independientemente seleccionado del grupo que consiste en H, alquilo, alcoxi, alquenilo, alqueniloxi, alquinilo, cicloalquilo, cicloalcoxi, arilo, ariloxi, arilalquilo, heteroarilo, heteroarilalquilo, heterociclilo, y heterociclilalquilo;

R^{12} está independientemente seleccionado del grupo que consiste en grupos H, halo, -OH, -CN, $-NO_2$, $-N(R^{11})_2$, y $-S(O)_pR^{11}$ y/o 1 o 2 (=O), y grupos alquilo, alcoxi, alquenilo, alqueniloxi, alquinilo, cicloalquilo, cicloalquenilo, cicloalcoxi, arilo, ariloxi, arilalquilo, heteroarilo, heteroariloxi, heteroarilalquilo, heterociclilo, heterociclenilo, heterocicleniloxi, heterociclilalquilo, heterociclenilalquilo, arilalcoxi, heteroarilalcoxi, heterociclilalcoxi, y heterociclenilalcoxi, cada uno de los cuales a su vez está opcionalmente sustituido, por lo menos una vez, con un sustituyente seleccionado del grupo que consiste en H, alquilo, haloalquilo, halo, -OH, alcoxi opcionalmente sustituido, ariloxi opcionalmente sustituido, cicloalcoxi opcionalmente sustituido, heteroariloxi opcionalmente sustituido, heterocicleniloxi opcionalmente sustituido, -CN, $-NO_2$, $-N(R^{11})_2$, y $-S(O)_pR^{11}$ y/o 1 o 2 grupos (=O), donde dicho alcoxi opcionalmente sustituido, ariloxi, cicloalcoxi opcionalmente sustituido, heteroariloxi opcionalmente sustituido, y heterocicleniloxi cuando están sustituidos, lo están una o más veces con R^{11};

m es 1-5;

n es independientemente1-3;

n' es independientemente 1-3

p es independientemente 0-2;

q es independientemente 0-6; y

w es 0-4

con las condiciones siguientes:

(a) si J^1-J^4 son cada uno -C(H)-, n es 1, m es 1, R^4 es H, A es 3H-imidazol-4-ilo, y X es $-N(R^6)-$, entonces R^6 no es -C(=O)-naftilo;

(b) si J^1-J^4 son cada uno -C(H)-, n es 1, m es 1, R^4 es H, A es 1H-imidazol-4-ilo, y X es $-N(R^6)-$, entonces R^6 no es $-S(O_2)$-naftilo; y

(c) si J^1, J^2, y J^4 son cada uno -C(H)-, J^3 es -C(Br)-, n es 2, m es 1, R^3 es 3-bencilo, R^4 es H, A es 1H-imidazol-4-ilo, y X es -N(R^6)-, entonces R^6 no es -C(O_2) bencilo.

2. El compuesto de la reivindicación 1, donde:

J^1-J^4 son cada uno -C(R^2)-;

A es un anillo heteroarilo o heterociclenilo de 5 miembros seleccionado del grupo que consiste en imidazol, imadazolina, y oxazolina, que está opcionalmente sustituido con por lo menos un R^5;

X es -O-, -S(O)$_p$-, o -N(R^6)-;

R^2 está independientemente seleccionado del grupo que consiste en H, -OH, halo, -CN, -NO_2, -$(CH_2)_qYR^7$, -$(CH_2)_qN(R^7)YR^{7'}$, -$(CH_2)_qOYR^{7'}$ y -$(CH_2)_qON{=}CR^7R^{7'}$, y grupos alquilo, alcoxi, alquenilo, alquinilo, cicloalquilo, arilo, arilalquilo, heteroarilo, heteroarilalquilo, y heterociclilo opcionalmente sustituido con por lo menos un R^5;

Y está seleccionado del grupo que consiste en un enlace, –C(=O)-, -C(=O)NR^7-, -C(=O)O-, -C(=NR^7)-, -C(=O)-[C(R^a)(R^b)]$_n$-O-C(=O)-, -C(=O)N(R^c)-O-, -C(=NOR^7)-, -C(=NR^7)NR^7-, -C(=NR^7)NR^7O-, -S(O)$_p$-, -SO_2NR^7-, -C(S)NR^7-;

R^3 está independientemente seleccionado del grupo que consiste en H y grupos alquilo, alcoxi, alquenilo, alqueniloxi, alquinilo, cicloalquilo, cicloalcoxi, arilo, ariloxi, arilalquilo, heteroarilo, heteroarilalquilo, heterociclilo, y heterociclilalquilo opcionalmente sustituido con por lo menos un R^5;

R^4 está independientemente seleccionado del grupo que consiste en H y grupos alquilo, alcoxi, alquenilo, alqueniloxi, alquinilo, cicloalquilo, cicloalcoxi, arilo, ariloxi, arilalquilo, heteroarilo, heteroarilalquilo, heterociclilo, y heterociclilalquilo, opcionalmente sustituido con por lo menos un R^5;

R^5 está independientemente seleccionado del grupo que consiste en H, halo, -OH, -CN, -NO_2, -N$R^7R^{7'}$, -SR^7, y grupos alquilo, alcoxi, alquenilo, alqueniloxi, alquinilo, cicloalquilo, cicloalcoxi, arilo, ariloxi, arilalquilo, heteroarilo, heteroarilalquilo, heterociclilo, y heterociclilalquilo, cada uno de los cuales está opcionalmente sustituido con por lo menos uno de los sustituyentes halo, -OH, -CN, -NO_2, -N$R^7R^{7'}$, y –S(O)$_p$$R^7$;

R^6 está independientemente seleccionado del grupo que consiste en H y grupos alquilo, alcoxi, alquenilo, alqueniloxi, alquinilo, cicloalquilo, cicloalcoxi, arilo, ariloxi, arilalquilo, heteroarilo, heteroarilalquilo, heterociclilo, y heterociclilalquilo, cada uno de los cuales está opcionalmente sustituido con por lo menos uno de halo, -OH, -CN, $-NO_2$, $-NR^7R^{7'}$, y sustituyentes $-SR^7$, y $-C(=O)R^7$, $-C(=O)OR^7$, $-C(=O)NR^7R^{7'}$, $-SO_2R^7$ y $-SO_2NR^7R^{7'}$;

R^7 está independientemente seleccionado del grupo que consiste en H y grupos alquilo, alquenilo, alquinilo, cicloalquilo, cicloalquilalquilo, ciclociclenilo, ciclociclenilalquilo, arilo, arilalquilo, heterociclilo, heterociclilalquilo, heterociclenilo, heterociclenilalquilo, heteroarilo, y heteroarilalquilo, cada uno de los cuales está opcionalmente sustituido una o más veces con R^{12};

$R^{7'}$ está independientemente seleccionado del grupo que consiste en H y grupos alquilo, alquenilo, alquinilo, cicloalquilo, cicloalquilalquilo, ciclociclenilo, ciclociclenilalquilo, arilo, arilalquilo, heterociclilo, heterociclilalquilo, heterociclenilo, heterociclenilalquilo, heteroarilo, y heteroarilalquilo, cada uno de los cuales está opcionalmente sustituido una o más veces con R^{12}; o

R^7 y $R^{7'}$ conjuntamente con el átomo de nitrógeno forman un anillo heterociclilo, heterociclenilo o heteroarilo de 3 a 8 miembros que tiene, en adición al átomo de N, 1 o 2 hetero átomos adicionales seleccionados del grupo que consiste en O, N, $-N(R^9)-$ y S, donde dichos anillos están sustituidos opcionalmente con 1 a 5 restos seleccionados independientemente de restos R^5,

R^8 está independientemente seleccionado del grupo que consiste en grupos alquilo, alquenilo, alquinilo, cicloalquilo, arilo, arilalquilo, heteroarilo, y heteroarilalquilo, cada uno de los cuales está opcionalmente sustituido con por lo menos uno de los sustituyentes halo, -OH, -CN, $-NO_2$, $-N(R^{11})_2$, y $-SR^{11}$;

R^9 está independientemente seleccionado del grupo que consiste en H, $-C(O)-R^{10}$, $-C(O)-OR^{10}$, y $-S(O)_p-OR^{10}$ y grupos alquilo, alquenilo, alquinilo, cicloalquilo, arilo, arilalquilo, heteroarilo, y heteroarilalquilo, cada uno de los cuales está opcionalmente sustituido con por lo menos uno de los sustituyentes halo, -OH, -CN, $-NO_2$, $-N(R^{11})_2$, y $-SR^{11}$; y

R^{10} está seleccionado del grupo que consiste en grupos alquilo, alquenilo, alquinilo, cicloalquilo, arilo, arilalquilo, heteroarilo, y heteroarilalquilo, cada uno de los cuales está opcionalmente sustituido con por lo menos uno de los sustituyentes halo, -OH, -CN, $-NO_2$, $-N(R^{11})_2$, y $-SR^{11}$;

R^{11} es un resto independientemente seleccionado del grupo que consiste en H y alquilo, alcoxi, alquenilo, alqueniloxi, alquinilo, cicloalquilo, cicloalcoxi, arilo, ariloxi, arilalquilo, heteroarilo, heteroarilalquilo, heterociclilo, y heterociclilalquilo, cada uno de los cuales está opcionalmente sustituido con por lo menos un sustituyente independientemente seleccionado del grupo que consiste en halo, -OH, -CN, $-NO_2$, $-N(R^{11'})_2$, y $-S(O)_pR^{11'}$;

$R^{11'}$ está independientemente seleccionado del grupo que consiste en H, alquilo, alcoxi, alquenilo, alqueniloxi, alquinilo, cicloalquilo, cicloalcoxi, arilo, ariloxi, arilalquilo, heteroarilo, heteroarilalquilo, heterociclilo, y heterociclilalquilo;

R^{12} está independientemente seleccionado del grupo que consiste en H, halo, -OH, -CN, $-NO_2$, $-N(R^{11})_2$, y $-S(O)_pR^{11}$, y grupos alquilo, alcoxi, alquenilo, alqueniloxi, alquinilo, cicloalquilo, cicloalquenilo, cicloalcoxi, arilo, ariloxi, arilalquilo, heteroarilo, heteroariloxi, heteroarilalquilo, heterociclilo, heterociclenilo, heterocicleniloxi, heterociclilalquilo, heterociclenilalquilo, arilalquiloxi, heteroarilalquiloxi, heterociclilalquiloxi, y heterociclenilalcoxi, cada uno de los cuales a su vez está opcionalmente sustituido, por lo menos una vez, con un sustituyente seleccionado del grupo que consiste en H, alquilo, haloalquilo, halo, -OH, alcoxi opcionalmente sustituido, ariloxi opcionalmente sustituido, cicloalcoxi, opcionalmente sustituido, heteroariloxi opcionalmente sustituido, heterocicleniloxi opcionalmente sustituido, -CN, $-NO_2$, $-N(R^{11})_2$, y $-S(O)_pR^{11}$, donde dicho alcoxi opcionalmente sustituido, ariloxi, cicloalcoxi opcionalmente sustituido, heteroariloxi opcionalmente sustituido, y heterocicleniloxi cuando está sustituido, está sustituido una o más veces con R^{11};

m es 1 o 2;

n es independientemente 1 o 2;

p es independientemente 0-2;

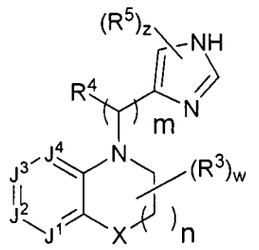
q es independientemente 0-3; y

w es 0-4.

3. El compuesto de la reivindicación 2, donde A es imidazol opcionalmente sustituido

4. El compuesto de la reivindicación 2, donde X es –O- u $-S(O)_p-$.

5. Un compuesto representado por la fórmula estructural:



Formula **III**

o una sal, solvato o prodroga farmacéuticamente aceptables de dicho compuesto, donde

X es -O-, $-S(O)_p-$, o $-N(R^6)-$;

J^1, J^2, J^3, y J^4 son independientemente –N- o $-C(R^2)-$, con la condición de que 0-3 de J^1, J^2, J^3 y J^4 sean -N-;

R^2 está independientemente seleccionado del grupo que consiste en H, -OH, halo, -CN, $-NO_2$, $-(CH_2)_qYR^7$, $-(CH_2)_qN(R^7)YR^{7'}$, $-(CH_2)_qOYR^7$, $-(CH_2)_qON=CR^7R^{7'}$, $-P(=O)(OR^7)(OR^{7'})$, $-P(=O)(NR^7R^{7'})_2$, $-P(=O)R^8{}_2$, y grupos alquilo, alcoxi, alquenilo, alquinilo, cicloalquilo, arilo, arilalquilo, heteroarilo, heteroarilalquilo, y heterociclilo opcionalmente sustituido con por lo menos un R^5;

Y está seleccionado del grupo que consiste en un enlace, -C(=O)-, $-C(=O)NR^7-$,-C(=O)O-, $-C(=O)-[C(R^a)(R^b)]_{n'}-O-C(=O)-$, $-C(=O)N(R^c)-O-$, $-S(O)_p-$, $-SO_2NR^7-$, y $-C(S)NR^7-$;

donde R^a y R^b están independientemente seleccionados del grupo que consiste en H, alquilo, alcoxi, y halo, y

R^c es H o alquilo;

R^3 está independientemente seleccionado del grupo que consiste en H y grupos alquilo, alcoxi, alquenilo, alqueniloxi, alquinilo, cicloalquilo, cicloalcoxi, arilo, ariloxi, arilalquilo, heteroarilo, heteroarilalquilo, heterociclilo, y heterociclilalquilo, opcionalmente sustituido con por lo menos un R^5;

R^4 está independientemente seleccionado del grupo que consiste en H – CN y halo, y grupos alquilo, alcoxi, alquenilo, alqueniloxi, alquinilo, cicloalquilo, cicloalcoxi, arilo, ariloxi, arilalquilo, heteroarilo, heteroarilalquilo, heterociclilo, y heterociclilalquilo, opcionalmente sustituido con por lo menos un R^5;

R^5 está independientemente seleccionado del grupo que consiste en H, halo, -OH, -CN, $-NO_2$, $-NR^7R^{7'}$, y $-S(O)_pR^7$, y grupos alquilo, alcoxi, alquenilo, alqueniloxi, alquinilo, cicloalquilo, cicloalcoxi, arilo, ariloxi, arilalquilo, heteroarilo, heteroarilalquilo, heterociclilo, y heterociclilalquilo, cada uno de los cuales está opcionalmente sustituido con por lo menos uno de los sustituyentes halo, -OH, -CN, $-NO_2$, $-NR^7R^{7'}$, y $-S(O)_pR^7$ y/o 1 o 2 grupos (=O);

R^6 está independientemente seleccionado del grupo que consiste en H y grupos alquilo, alcoxi, alquenilo, alqueniloxi, alquinilo, cicloalquilo, cicloalcoxi, arilo, ariloxi, arilalquilo, heteroarilo, heteroarilalquilo, heterociclilo, y heterociclilalquilo, cada uno de los cuales está opcionalmente sustituido con por lo menos uno de los sustituyentes halo, -OH, -CN, $-NO_2$, $-NR^7R^{7'}$, y $-S(O)_pR^7$ y/o 1 o 2 grupos (=O), y $-C(=O)R^7$, $-C(=O)OR^7$, $-C(=O)NR^7R^{7'}$, $-SO_2R^7$ y $-SO_2NR^7R^{7'}$;

R^7 está independientemente seleccionado del grupo que consiste en H y grupos alquilo, alquenilo, alquinilo, cicloalquilo, cicloalquilalquilo, ciclociclenilo, ciclociclenilalquilo, arilo, arilalquilo, heterociclilo, heterociclilalquilo, heterociclenilo, heterociclenilalquilo, heteroarilo, y heteroarilalquilo, cada uno de los cuales está opcionalmente sustituido una o más veces con R^{12};

$R^{7'}$ está independientemente seleccionado del grupo que consiste en H y grupos alquilo, alquenilo, alquinilo, cicloalquilo, cicloalquilalquilo, ciclociclenilo, ciclociclenilalquilo, arilo, arilalquilo, heterociclilo, heterociclilalquilo, heterociclenilo, heterociclenilalquilo, heteroarilo, y heteroarilalquilo, cada uno de los cuales está opcionalmente sustituido una o más veces con R^{12}; o

R^7 y $R^{7'}$ conjuntamente con el átomo de nitrógeno al cual están unidos forman un anillo heterociclilo, heterociclenilo o heteroarilo de 3 a 8

miembros que tiene, además del átomo N, 1 o 2 heteroátomos adicionales seleccionados del grupo que consiste en O, N, -N(R^9)- y S, donde dichos anillos están opcionalmente sustituidos con 1 a 5 restos R^5 independientemente seleccionados,

R^8 está independientemente seleccionado del grupo que consiste en grupos alquilo, alquenilo alquinilo, cicloalquilo, arilo, arilalquilo, heteroarilo, y heteroarilalquilo, cada uno de los cuales está opcionalmente sustituido con por lo menos uno de los sustituyentes halo, -OH, -CN, -NO_2, -N(R^{11})$_2$, y –S(O)$_p$$R^{11}$;

R^9 está independientemente seleccionado del grupo que consiste en H, -C(O)-R^{10}, -C(O)-OR^{10}, y –S(O)$_p$-OR^{10} y grupos alquilo, alquenilo, alquinilo, cicloalquilo, arilo, arilalquilo, heteroarilo, y heteroarilalquilo, cada uno de los cuales está opcionalmente sustituido con por lo menos uno de los sustituyentes halo, -OH, -CN, -NO_2, -N(R^{11})$_2$, y –S(O)$_p$$R^{11}$; y

R^{10} está seleccionado del grupo que consiste en grupos alquilo, alquenilo, alquinilo, cicloalquilo, arilo, arilalquilo, heteroarilo, y heteroarilalquilo, cada uno de los cuales está opcionalmente sustituido con por lo menos uno de los sustituyentes halo, -OH, -CN, -NO_2, -N(R^{11})$_2$, y –S(O)$_p$$R^{11}$;

R^{11} es un resto independientemente seleccionado del grupo que consiste en H y alquilo, alcoxi, alquenilo, alqueniloxi, alquinilo, cicloalquilo, cicloalcoxi, arilo, ariloxi, arilalquilo, heteroarilo, heteroarilalquilo, heterociclilo, y heterociclilalquilo, cada uno de los cuales está opcionalmente sustituido con por lo menos un sustituyente independientemente seleccionado del grupo que consiste en halo, -OH, -CN, -NO_2, -N($R^{11'}$)$_2$, y –S(O)$_p$$R^{11'}$;

$R^{11'}$ está independientemente seleccionado del grupo que consiste en H, alquilo, alcoxi, alquenilo, alqueniloxi, alquinilo, cicloalquilo, cicloalcoxi, arilo, ariloxi, arilalquilo, heteroarilo, heteroarilalquilo, heterociclilo, y heterociclilalquilo;

R^{12} está independientemente seleccionado del grupo que consiste en H, halo, -OH, -CN, -NO_2, -N(R^{11})$_2$, y –S(O)$_p$$R^{11}$, y grupos alquilo, alcoxi, alquenilo, alqueniloxi, alquinilo, cicloalquilo, cicloalquenilo, cicloalcoxi, arilo, ariloxi, arilalquilo, heteroarilo, heteroariloxi, heteroarilalquilo, heterociclilo, heterociclenilo, heterocicleniloxi, heterociclilalquilo, heterociclenilalquilo, arilalquiloxi, heteroarilalquiloxi, heterociclilalquiloxi, y heterociclenilalcoxi, cada uno de los

cuales a su vez está opcionalmente sustituido por lo menos una vez con un sustituyente seleccionado del grupo que consiste en H, alquilo, haloalquilo, halo, -OH, alcoxi opcionalmente sustituido, ariloxi opcionalmente sustituido, cicloalcoxi opcionalmente sustituido, heteroariloxi opcionalmente sustituido, heterocicleniloxi opcionalmente sustituido,-CN, $-NO_2$, $-N(R^{11})_2$, y $-S(O)_pR^{11}$, donde dicho alcoxi opcionalmente sustituido, ariloxi, cicloalcoxi opcionalmente sustituido, heteroariloxi opcionalmente sustituido, y heterocicleniloxi cuando están sustituidos, lo están una o más veces con R^{11};

m es 1-5;

n es independientemente 1-3;

p es independientemente 0-2;

q es independientemente 0-6;

z es 0-3; y

w es 0-4,

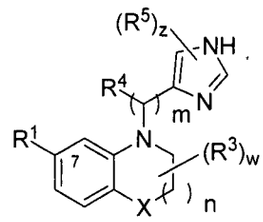
con las condiciones siguientes:

a) si J^1-J^4 son cada uno -C(H)-, n es 1, m es 1, R^4 es H, A es 3H-imidazol-4-ilo, y X es $-N(R^6)-$, entonces R^6 no es -C(=O)-naftilo;

(b) si J^1-J^4 son cada uno -C(H)-, n es 1, m es 1, R^4 es H, A es 1H-imidazol-4-ilo, y X es $-N(R^6)-$, entonces R^6 no es $S(O_2)$-naftilo; y

(c) si J^1, J^2, y J^4 son cada uno -C(H)-, J^3 es -C(Br)-, n es 2, m es 1, R^3 es 3-bencilo, R^4 es H, y X es $-N(R^6)-$, entonces R^6 no es $-C(O_2)$ bencilo.

6. Un compuesto representado por la fórmula estructural:



Formula **IV**

o una sal, éster, solvato o prodroga farmacéuticamente aceptables de dicho compuesto,

donde:

R^1 está seleccionado del grupo que consiste en H, -OH, halo, -CN, -NO_2, -SR^7-$(CH_2)_qYR^7$, -$(CH_2)_qN(R^7)YR^{7'}$, -$(CH_2)_qOYR^7$, -$(CH_2)_qON=CR^7R^{7'}$, -$P(=O)(OR^7)(OR^{7'})$, -$P(=O)(NR^7R^{7'})_2$, -$P(=O)R^8{}_2$., y grupos alquilo, alcoxi, alquenilo, alqueniloxi, alquinilo, cicloalquilo, cicloalcoxi, arilo, ariloxi, arilalquilo, heteroarilo, heteroarilalquilo, heterociclilo, y heterociclilalquilo, opcionalmente sustituidos con por lo menos un R^5;

X es -O-, o -$S(O)_p$-;

Y está seleccionado del grupo que consiste en un enlace, -C(=O)-, -$C(=O)NR^7$-, -C(=O)O-, -$C(=O)$-$[C(R^a)(R^b)]_n$-O-C(=O)-, -$C(=O)N(R^c)$-O-,

donde R^a y R^b están independientemente seleccionados del grupo que consiste en H, alquilo, alcoxi, y halo, y

R^c es H o alquilo;

R^3 está independientemente seleccionado del grupo que consiste en H y grupos alquilo, alcoxi, alquenilo, alqueniloxi, alquinilo, cicloalquilo, cicloalcoxi, arilo, ariloxi, arilalquilo, heteroarilo, heteroarilalquilo, heterociclilo y heterociclilalquilo, opcionalmente sustituidos con por lo menos un R^5;

R^4 está independientemente seleccionado del grupo que consiste en H – CN y halo, y grupos alquilo, alcoxi, alquenilo, alqueniloxi, alquinilo, cicloalquilo, cicloalcoxi, arilo, ariloxi, arilalquilo, heteroarilo, heteroarilalquilo, heterociclilo, y heterociclilalquilo opcionalmente sustituidos con por lo menos un R^5;

R^5 está independientemente seleccionado del grupo que consiste en H, halo, -OH, -CN, -NO_2, -$NR^7R^{7'}$, y –$S(O)_pR^7$, y grupos alquilo, alcoxi, alquenilo, alqueniloxi, alquinilo, cicloalquilo, cicloalcoxi, arilo, ariloxi, arilalquilo, heteroarilo, heteroarilalquilo, heterociclilo, y heterociclilalquilo, cada uno de los cuales está opcionalmente sustituido con por lo menos uno de los sustituyentes halo, -OH, -CN, -NO_2, -$NR^7R^{7'}$, y –$S(O)_pR^7$ y/o 1 grupo (=O);

R^6 está independientemente seleccionado del grupo que consiste en H y grupos alquilo, alcoxi, alquenilo, alqueniloxi, alquinilo, cicloalquilo, cicloalcoxi, arilo, ariloxi, arilalquilo, heteroarilo, heteroarilalquilo, heterociclilo, y heterociclilalquilo, cada uno de los cuales está opcionalmente sustituido con por lo

menos uno de los sustituyentes halo, -OH, -CN, $-NO_2$, $-NR^7R^{7'}$, y $-S(O)_pR^7$ y/o 1 o 2 grupos (=O) y $-C(=O)R^7$, $-C(=O)OR^7$, $-C(=O)NR^7R^{7'}$, $-SO_2R^7$ y $-SO_2NR^7R^{7'}$;

R^7 está independientemente seleccionado del grupo que consiste en H y grupos alquilo, alquenilo, alquinilo, cicloalquilo, cicloalquilalquilo, ciclociclenilo, ciclociclenilalquilo, arilo, arilalquilo, heterociclilo, heterociclilalquilo, heterociclenilo, heterociclenilalquilo, heteroarilo, y heteroarilalquilo, cada uno de los cuales está opcionalmente sustituido una o más veces con R^{12};

$R^{7'}$ está independientemente seleccionado del grupo que consiste en H y grupos alquilo, alquenilo, alquinilo, cicloalquilo, cicloalquilalquilo, ciclociclenilo, ciclociclenilalquilo, arilo, arilalquilo, heterociclilo, heterociclilalquilo, heterociclenilo, heterociclenilalquilo, heteroarilo, y heteroarilalquilo, cada uno de los cuales está opcionalmente sustituido una o más veces con R^{12}; o

R^7 y $R^{7'}$ conjuntamente con el átomo de nitrógeno al cual están unidos forman un anillo heterociclilo, heterociclenilo o heteroarilo de a 3 a 8 miembros que tiene, además del átomo N, 1 o 2 heteroátomos adicionales seleccionados del grupo que consiste en O, N, $-N(R^9)-$ y S, donde dichos anillos están opcionalmente sustituidos con 1 a 5 restos R^5, independientemente seleccionados

R^8 está independientemente seleccionado del grupo que consiste en grupos alquilo, alquenilo, alquinilo, cicloalquilo, arilo, arilalquilo, heteroarilo, y heteroarilalquilo, cada uno de los cuales está opcionalmente sustituido con por lo menos uno de los sustituyentes halo, -OH, -CN, $-NO_2$, $-N(R^{11})_2$, y $-S(O)_pR^{11}$;

R^9 está independientemente seleccionado del grupo que consiste en H, $-C(O)-R^{10}$, $-C(O)-OR^{10}$, y $-S(O)_p-OR^{10}$ y grupos alquilo, alquenilo, alquinilo, cicloalquilo, arilo, arilalquilo, heteroarilo, y heteroarilalquilo, cada uno de los cuales está opcionalmente sustituido con por lo menos uno de los sustituyentes halo, -OH, -CN, $-NO_2$, $-N(R^{11})_2$, y $-S(O)_pR^{11}$; y

R^{10} está seleccionado del grupo que consiste en grupos alquilo, alquenilo, alquinilo, cicloalquilo, arilo, arilalquilo, heteroarilo, y heteroarilalquilo, cada uno de los cuales está opcionalmente sustituido con por lo menos uno de los sustituyentes halo, -OH, -CN, $-NO_2$, $-N(R^{11})_2$, y $-S(O)_pR^{11}$;

R^{11} es un resto independientemente seleccionado del grupo que consiste en H y alquilo, alcoxi, alquenilo, alqueniloxi, alquinilo, cicloalquilo, cicloalcoxi, arilo,

ariloxi, arilalquilo, heteroarilo, heteroarilalquilo, heterociclilo, y heterociclilalquilo, cada uno de los cuales está opcionalmente sustituido con por lo menos un sustituyente independientemente seleccionado del grupo que consiste en halo, -OH, -CN, $-NO_2$, $-N(R^{11'})_2$, y $-S(O)_pR^{11'}$;

$R^{11'}$ está independientemente seleccionado del grupo que consiste en H, alquilo, alcoxi, alquenilo, alqueniloxi, alquinilo, cicloalquilo, cicloalcoxi, arilo, ariloxi, arilalquilo, heteroarilo, heteroarilalquilo, heterociclilo, y heterociclilalquilo;

R^{12} está independientemente seleccionado del grupo que consiste en H, halo, -OH, -CN, $-NO_2$, $-N(R^{11})_2$, y $-S(O)_pR^{11}$, y grupos alquilo, alcoxi, alquenilo, alqueniloxi, alquinilo, cicloalquilo, cicloalquenilo, cicloalcoxi, arilo, ariloxi, arilalquilo, heteroarilo, heteroariloxi, heteroarilalquilo, heterociclilo, heterociclenilo, heterocicleniloxi, heterociclilalquilo, heterociclenilalquilo, arilalquiloxi, heteroarilalquiloxi, heterociclilalquiloxi, y heterociclenilalcoxi, cada uno de los cuales a su vez está opcionalmente sustituido, por lo menos una vez, con un sustituyente seleccionado del grupo que consiste en H, alquilo, haloalquilo, halo, -OH, alcoxi opcionalmente sustituido, ariloxi opcionalmente sustituido, cicloalcoxi opcionalmente sustituido, heteroariloxi opcionalmente sustituido, heterocicleniloxi opcionalmente sustituido, -CN, $-NO_2$, $-N(R^{11})_2$, y $-S(O)_pR^{11}$, donde dichos alcoxi opcionalmente sustituido, ariloxi, cicloalcoxi opcionalmente sustituido, heteroariloxi opcionalmente sustituido, y heterocicleniloxi cuando están sustituidos, lo están una o más veces con R^{11};

m es 1-5;

n es independientemente 1-3;

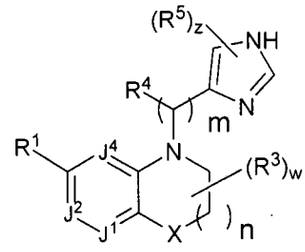
p es independientemente 0-2;

q es independientemente 0-6

z es 0-3; y

w es 0-4.

7. Un compuesto representado por la fórmula estructural:



Formula **V**

o una sal o solvato farmacéuticamente aceptable de dicho compuesto, donde:

R^1 es $-(CH_2)_qN(R^7)YR^{7'}$;

X es -O-, or $-S(O)_p-$;

J^1, J^2, y J^4 son independientemente -N- o $-C(R^2)-$, con la condición de que 0-3 de J^1, J^2, y J^4 sean -N-;

R^2 está independientemente seleccionado del grupo que consiste en H, -OH, halo, -CN, $-NO_2$, y grupos alquilo, alcoxi, alquenilo, alquinilo, cicloalquilo, arilo, arilalquilo, heteroarilo, heteroarilalquilo, y heterociclilo opcionalmente sustituido con por lo menos un R^5

Y es C(=O)-, $-C(=O)NR^7-$, -C(=O)O-, $-C(=O)-[C(R^a)(R^b)]_{n'}-O-C(=O)-$, o $-C(=O)N(R^c)-O-$,

donde R^a y R^b están independientemente seleccionados del grupo que consiste en H, alquilo, alcoxi, y halo, y

R^c es H o alquilo;

R^3 está independientemente seleccionado del grupo que consiste en H y grupos alquilo, alcoxi, alquenilo, alqueniloxi, alquinilo, cicloalquilo, cicloalcoxi, arilo, ariloxi, arilalquilo, heteroarilo, heteroarilalquilo, heterociclilo, y heterociclilalquilo, opcionalmente sustituido con por lo menos un R^5;

R^4 está independientemente seleccionado del grupo que consiste en H – CN y halo, y grupos alquilo, alcoxi, alquenilo, alqueniloxi, alquinilo, cicloalquilo, cicloalcoxi, arilo, ariloxi, arilalquilo, heteroarilo, heteroarilalquilo, heterociclilo, y heterociclilalquilo, opcionalmente sustituido con por lo menos un R^5;

R^5 está independientemente seleccionado del grupo que consiste en H, halo, -OH, -CN, $-NO_2$, $-NR^7R^{7'}$, y $-S(O)_pR^7$, y grupos alquilo, alcoxi, alquenilo, alqueniloxi, alquinilo, cicloalquilo, cicloalcoxi, arilo, ariloxi, arilalquilo, heteroarilo,

heteroarilalquilo, heterociclilo, y heterociclilalquilo, cada uno de los cuales está opcionalmente sustituido con por lo menos uno de los sustituyentes halo, -OH, -CN, $-NO_2$, $-NR^7R^{7'}$, y $-S(O)_pR^7$ y/o 1 grupo (=O);

R^6 está independientemente seleccionado del grupo que consiste en H y grupos alquilo, alcoxi, alquenilo, alqueniloxi, alquinilo, cicloalquilo, cicloalcoxi, arilo, ariloxi, arilalquilo, heteroarilo, heteroarilalquilo, heterociclilo, y heterociclilalquilo, cada uno de los cuales está opcionalmente sustituido con por lo menos uno de los sustituyentes halo, -OH, -CN, $-NO_2$, $-NR^7R^{7'}$, y $-S(O)_pR^7$ y/o 1 o 2 grupos (=O), y $-C(=O)R^7$, $-C(=O)OR^7$, $-C(=O)NR^7R^{7'}$, $-SO_2R^7$ y $-SO_2NR^7R^{7'}$;

R^7 está independientemente seleccionado del grupo que consiste en H y grupos alquilo, alquenilo, alquinilo, cicloalquilo, cicloalquilalquilo, ciclociclenilo, ciclociclenilalquilo, arilo, arilalquilo, heterociclilo, heterociclilalquilo, heterociclenilo, heterociclenilalquilo, heteroarilo, y heteroarilalquilo, cada uno de los cuales está opcionalmente sustituido una o más veces con R^{12};

$R^{7'}$ está independientemente seleccionado del grupo que consiste en H y grupos alquilo, alquenilo, alquinilo, cicloalquilo, cicloalquilalquilo, ciclociclenilo, ciclociclenilalquilo, arilo, arilalquilo, heterociclilo, heterociclilalquilo, heterociclenilo, heterociclenilalquilo, heteroarilo, y heteroarilalquilo, cada uno de los cuales está opcionalmente sustituido una o más veces con R^{12} o

R^7 y $R^{7'}$ conjuntamente con el átomo de nitrógeno forman un anillo heterociclilo, heterociclenilo o heteroarilo de 3 a 8 miembros que tiene, en adición al átomo de N, 1 o 2 hetero átomos adicionales seleccionados del grupo que consiste en O, N, $-N(R^9)-$ y S, donde dichos anillos están opcionalmente sustituidos con 1 a 5 restos R^5, independientemente seleccionadas,

R^8 está independientemente seleccionado del grupo que consiste en grupos alquilo, alquenilo, alquinilo, cicloalquilo, arilo, arilalquilo, heteroarilo, y heteroarilalquilo, cada uno de los cuales está opcionalmente sustituido con por lo menos uno de los sustituyentes halo, -OH, -CN, $-NO_2$, $-N(R^{11})_2$, y $-S(O)_pR^{11}$;

R^9 está independientemente seleccionado del grupo que consiste en H, $-C(O)-R^{10}$, $-C(O)-OR^{10}$, y $-S(O)_p-OR^{10}$ y grupos alquilo, alquenilo, alquinilo, cicloalquilo, arilo, arilalquilo, heteroarilo, y heteroarilalquilo, cada uno de los cuales

está opcionalmente sustituido con por lo menos uno de los sustituyentes halo, -OH, -CN, $-NO_2$, $-N(R^{11})_2$, y $-S(O)_pR^{11}$; y

R^{10} está seleccionado del grupo que consiste en grupos alquilo, alquenilo, alquinilo, cicloalquilo, arilo, arilalquilo, heteroarilo, y heteroarilalquilo cada uno de los cuales está opcionalmente sustituido con por lo menos uno de los sustituyentes halo, -OH, -CN, $-NO_2$, $-N(R^{11})_2$, y $-S(O)_pR^{11}$;

R^{11} es un resto independientemente seleccionado del grupo que consiste en H y alquilo, alcoxi, alquenilo, alqueniloxi, alquinilo, cicloalquilo, cicloalcoxi, arilo, ariloxi, arilalquilo, heteroarilo, heteroarilalquilo, heterociclilo, y heterociclilalquilo, cada uno de los cuales está opcionalmente sustituido con por lo menos un sustituyente independientemente seleccionado del grupo que consiste en halo, -OH, -CN, $-NO_2$, $-N(R^{11'})_2$, y $-S(O)_pR^{11'}$;

$R^{11'}$ está independientemente seleccionado del grupo que consiste en H, alquilo, alcoxi, alquenilo, alqueniloxi, alquinilo, cicloalquilo, cicloalcoxi, arilo, ariloxi, arilalquilo, heteroarilo, heteroarilalquilo, heterociclilo, y heterociclilalquilo;

R^{12} está independientemente seleccionado del grupo que consiste en H, halo, -OH, -CN, $-NO_2$, $-N(R^{11})_2$, y $-S(O)_pR^{11}$, y grupos alquilo, alcoxi, alquenilo, alqueniloxi, alquinilo, cicloalquilo, cicloalquenilo, cicloalcoxi, arilo, ariloxi, arilalquilo, heteroarilo, heteroariloxi, heteroarilalquilo, heterociclilo, heterociclenilo, heterocicleniloxi, heterociclilalquilo, heterociclenilalquilo, arilalquiloxi, heteroarilalquiloxi, heterociclilalquiloxi, y heterociclenilalcoxi, cada uno de los cuales a su vez está opcionalmente sustituido por lo menos una vez con un sustituyente seleccionado del grupo que consiste en H, alquilo, haloalquilo, halo, -OH, alcoxi opcionalmente sustituido, ariloxi opcionalmente sustituido, cicloalcoxi opcionalmente sustituido, heteroariloxi opcionalmente sustituido, heterocicleniloxi opcionalmente sustituido, -CN, $-NO_2$, $-N(R^{11})_2$, y $-S(O)_pR^{11}$, donde dicho alcoxi opcionalmente sustituido, ariloxi, cicloalcoxi opcionalmente sustituido, heteroariloxi opcionalmente sustituido, y heterocicleniloxi cuando están sustituidos, lo están una o más veces con R^{11}

m es 1-5;

n es independientemente1-3;

p es independientemente 0-2

q es independientemente 0-6;

z es 0-3; y

w es 0-4.

8. El compuesto de la reivindicación 7, donde:

J^1 y J^2 son $-C(R^2)-$

J^3 es $-C(R^2)-$ o $-N-$;

X es $-O-$;

R^2 es H, halo, o grupos alquilo opcionalmente sustituidos con por lo menos un R^5;

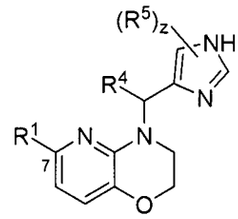
R^3 es H;

R^4 es H, alquilo o CN;

R^5 es H o halo

o una sal, éster, solvato o prodroga del mismo.

9. Un compuesto representado por la fórmula estructural:



Formula **IV**

o una sal, éster, solvato o prodroga farmacéuticamente aceptables de dicho compuesto, donde

R^1 está seleccionado del grupo que consiste en H, -OH, halo, -CN, $-NO_2$, $-SR^7-(CH_2)_qYR^{7'}$, $-(CH_2)_qN(R^7)YR^{7'}$, $-(CH_2)_qOYR^7$, $-(CH_2)_qON=CR^7R^{7'}$ y grupos alquilo, alcoxi, alquenilo, alqueniloxi, alquinilo, cicloalquilo, cicloalcoxi, arilo, ariloxi, arilalquilo, heteroarilo, heteroarilalquilo, heterociclilo, y heterociclilalquilo, opcionalmente sustituidos con por lo menos un R^5;

Y está seleccionado del grupo que consiste en un enlace, -C(=O)-, $-C(=O)NR^7-$, -C(=O)O-, $-C(=O)-[C(R^a)(R^b)]_{n'}-O-C(=O)-$, $-C(=O)N(R^c)-O-$,

donde R^a y R^b están independientemente seleccionados del grupo que consiste en H, alquilo, alcoxi, y halo, y

R^c es H o alquilo;

R^4 está independientemente seleccionado del grupo que consiste en H, -CN y alquilo opcionalmente sustituido con por lo menos un R^5;

R^5 está independientemente seleccionado del grupo que consiste en H, halo, -OH, -CN, $-NO_2$, $-NR^7R^{7'}$, $-S(O)_pR^7$, y grupos alquilo, alcoxi, alquenilo, alqueniloxi, alquinilo, cicloalquilo, cicloalcoxi, arilo, ariloxi, arilalquilo, heteroarilo, heteroarilalquilo, heterociclilo, y heterociclilalquilo, cada uno de los cuales está opcionalmente sustituido con por lo menos uno de los sustituyentes halo, -OH, -CN, $-NO_2$, $-NR^7R^{7'}$, y $-S(O)_pR^7$;

R^7 está independientemente seleccionado del grupo que consiste en H y grupos alquilo, alquenilo, alquinilo, cicloalquilo, cicloalquilalquilo, ciclociclenilo, ciclociclenilalquilo, arilo, arilalquilo, heterociclilo, heterociclilalquilo, heterociclenilo, heterociclenilalquilo, heteroarilo, y heteroarilalquilo, cada uno de los cuales está opcionalmente sustituido una o más veces con R^{12};

$R^{7'}$ está independientemente seleccionado del grupo que consiste en H y grupos alquilo, alquenilo, alquinilo, cicloalquilo, cicloalquilalquilo, ciclociclenilo, ciclociclenilalquilo, arilo, arilalquilo, heterociclilo, heterociclilalquilo, heterociclenilo, heterociclenilalquilo, heteroarilo, y heteroarilalquilo,, cada uno de los cuales está opcionalmente sustituido una o más veces con R^{12}; o

R^7 y $R^{7'}$ conjuntamente con el átomo de nitrógeno al cual están unidos forman un anillo heterociclilo, heterociclenilo o heteroarilo que tiene, además del átomo N, 1 o 2 heteroátomos adicionales seleccionados del grupo que consiste en O, N, $-N(R^9)-$ y S, donde dichos anillos están opcionalmente sustituidos con 1 a 5 restos R^5, independientemente seleccionados

R^9 está independientemente seleccionado del grupo que consiste en H, $-C(O)-R^{10}$, $-C(O)-OR^{10}$, y $-S(O)_p-OR^{10}$ y grupos alquilo, alquenilo, alquinilo, cicloalquilo, arilo, arilalquilo, heteroarilo, y heteroarilalquilo, cada uno de los cuales está opcionalmente sustituido con por lo menos uno de los sustituyentes halo, -OH, -CN, $-NO_2$, $-N(R^{11})_2$, y $-S(O)_pR^{11}$; y

R^{10} está seleccionado del grupo que consiste en grupos alquilo, alquenilo, alquinilo, cicloalquilo, arilo, arilalquilo, heteroarilo, y heteroarilalquilo, cada uno de

los cuales está opcionalmente sustituido con por lo menos uno de los sustituyentes halo, -OH, -CN, $-NO_2$, $-N(R^{11})_2$, y $-S(O)_pR^{11}$;

R^{11} es un resto independientemente seleccionado del grupo que consiste en H y alquilo, alcoxi, alquenilo, alqueniloxi, alquinilo, cicloalquilo, cicloalcoxi, arilo, ariloxi, arilalquilo, heteroarilo, heteroarilalquilo, heterociclilo, y heterociclilalquilo, cada uno de los cuales está opcionalmente sustituido con por lo menos un sustituyente independientemente seleccionado del grupo que consiste en halo, -OH, -CN, $-NO_2$, $-N(R^{11'})_2$, y $-S(O)_pR^{11'}$;

$R^{11'}$ está independientemente seleccionado del grupo que consiste en H, alquilo, alcoxi, alquenilo, alqueniloxi, alquinilo, cicloalquilo, cicloalcoxi, arilo, ariloxi, arilalquilo, heteroarilo, heteroarilalquilo, heterociclilo, y heterociclilalquilo;

R^{12} está independientemente seleccionado del grupo que consiste en H, halo, -OH, -CN, $-NO_2$, $-N(R^{11})_2$, y $-S(O)_pR^{11}$, y grupos alquilo, alcoxi, alquenilo, alqueniloxi, alquinilo, cicloalquilo, cicloalquenilo, cicloalcoxi, arilo, ariloxi, arilalquilo, heteroarilo, heteroariloxi, heteroarilalquilo, heterociclilo, heterociclenilo, heterocicleniloxi, heterociclilalquilo, heterociclenilalquilo, arilalquiloxi, heteroarilalquiloxi, heterociclilalquiloxi, y heterociclenilalcoxi, cada uno de los cuales a su vez, está opcionalmente sustituido por lo menos una vez con un sustituyente seleccionado del grupo que consiste en H, alquilo, haloalquilo, halo, -OH, alcoxi opcionalmente sustituido, ariloxi opcionalmente sustituido, cicloalcoxi opcionalmente sustituido, heteroariloxi opcionalmente sustituido, heterocicleniloxi opcionalmente sustituido, -CN, $-NO_2$, $-N(R^{11})_2$, y $-S(O)_pR^{11}$, donde dicho alcoxi opcionalmente sustituido, ariloxi, cicloalcoxi opcionalmente sustituido, heteroariloxi opcionalmente sustituido, y heterocicleniloxi, cuando están sustituidos, lo están una o más veces con R^{11};

p es 0-2;

q es 0-6; y

z es 0-3.

10. El compuesto de la reivindicación 2, donde:

J^1 y J^2 son $-C(R^2)-$

J^3 es $-C(R^2)-$ o $-N-$;

X es $-O-$;

R^2 es H, halo, o grupos alquilo opcionalmente sustituidos con por lo menos un R^5;

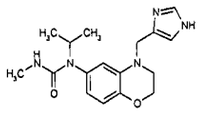
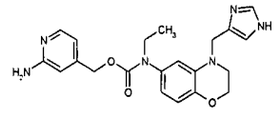
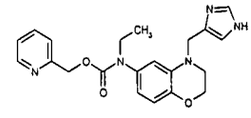
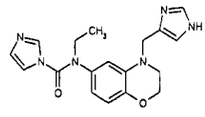
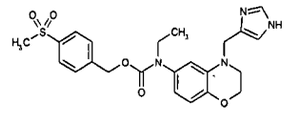
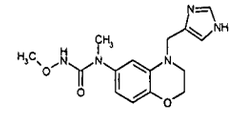
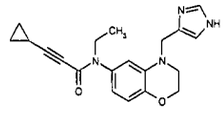
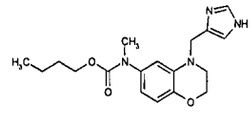
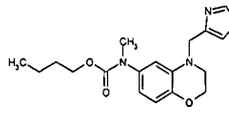
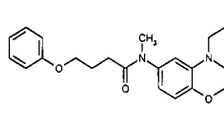
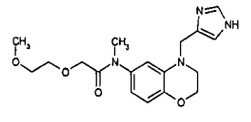
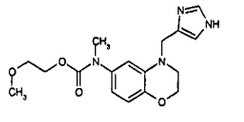
R^3 es H;

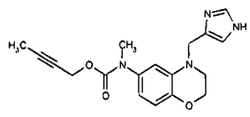
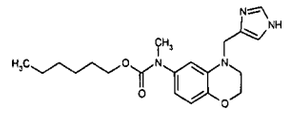
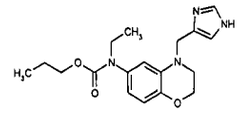
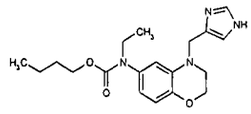
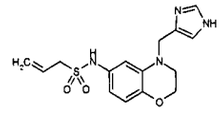
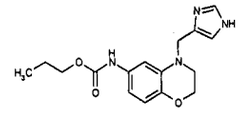
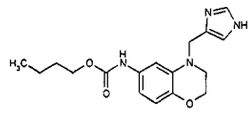
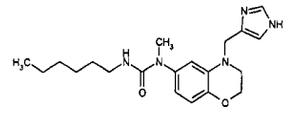
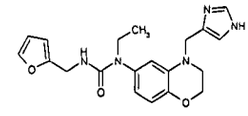
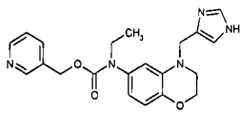
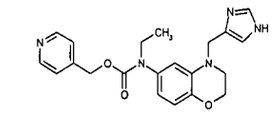
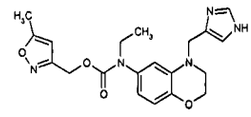
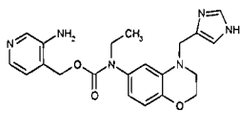
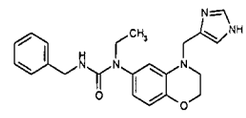
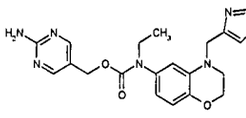
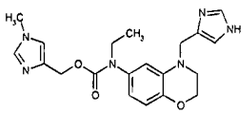
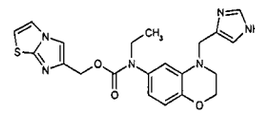
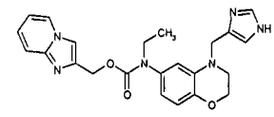
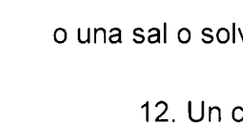
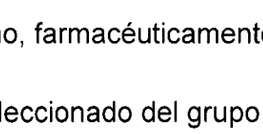
R^4 es H, alquilo o CN;

R^5 es H o halo

o una sal, éster, solvato o prodroga farmacéuticamente aceptables de dicho compuesto.

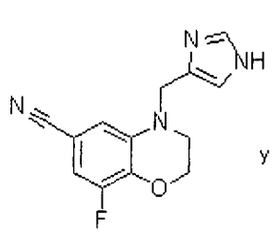
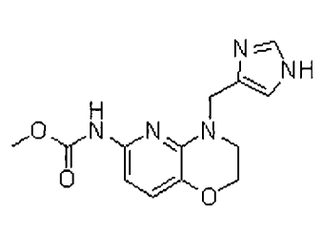
11. Un compuesto seleccionado del grupo que consiste en

o una sal o solvato del mismo, farmacéuticamente aceptable.

12. Un compuesto seleccionado del grupo que consiste en


y


o una sal del mismo, farmacéuticamente aceptable.

13. Una composición farmacéutica que comprende por lo menos un compuesto de la reivindicación 12, o una sal o solvato del mismo, farmacéuticamente aceptable y por lo menos un portador, coadyuvante o vehículo farmacéuticamente aceptable.

14. Un método para tratar una o más afecciones asociadas con receptores adrenérgicos α2C, que comprende administrar a un mamífero que necesita dicho tratamiento, el compuesto de la reivindicación 12 o una sal o solvato del mismo, farmacéuticamente aceptable.

15. Una composición farmacéutica que comprende por lo menos un compuesto de la reivindicación 1, o una sal o solvato del mismo, farmacéuticamente aceptable y por lo menos un portador, coadyuvante o vehículo farmacéuticamente aceptable.

16. Una composición farmacéutica que comprende por lo menos un compuesto de la reivindicación 11, o una sal o solvato del mismo, farmacéuticamente aceptable y por lo menos un portador, coadyuvante o vehículo farmacéuticamente aceptable.

17. La composición farmacéutica de la reivindicación 15, que comprende además, uno o más agentes terapéuticos adicionales.

18 La composición farmacéutica de la reivindicación 16, que comprende además, uno o más agentes terapéuticos adicionales.

19. La composición farmacéutica de la reivindicación 17, donde dichos, agentes terapéuticos adicionales están seleccionados del grupo que consiste en esteroides anti-inflamatorios, inhibidores de PDE-4, agentes anti-muscarínicos, cromolin sodio, antagonistas del receptor H_1, agonistas de 5-HT_1, NSAIDs, inhibidores de la enzima convertidora de angiotensina, agonistas del receptor angiotensina II, bloqueadores β, agonistas β, antagonistas de leucotrieno,

diuréticos, antagonistas de aldosterona, agentes ionotrópicos, péptidos natriureticos, péptidos, agentes para el control del dolor, agentes anti- ansiolíticos, agentes anti- migraña y agentes terapéuticos apropiados para tratar afecciones cardíacas, trastornos psicóticos y glaucoma.

20. La composición farmacéutica de la reivindicación 18, donde dichos agentes terapéuticos adicionales están seleccionados del grupo que consiste en esteroides, inhibidores de PDE-4, agentes anti-muscarínicos, cromolin sodio, antagonistas del receptor H_1, agonistas de 5-HT_1, NSAIDs, inhibidores de la enzima convertidora de angiotensina, agonistas del receptor angiotensina II, bloqueadores β, agonistas β, antagonistas de leucotrieno, diuréticos, antagonistas de aldosterona, agentes ionotrópicos, péptidos natriuréticos, agentes para el control del dolor, agentes anti- ansiolíticos, agentes anti- migraña y agentes terapéuticos apropiados para tratar afecciones cardíacas, trastornos psicóticos y glaucoma.

21. Un método para estimular selectivamente receptores adrenérgicos α2C en una célula que lo necesita, que comprende poner dicha célula en contacto con una cantidad terapéuticamente eficaz de por lo menos un compuesto de acuerdo con la reivindicación 1 o una sal o solvato del mismo.

22. Un método para tratar una o más afecciones que están asociadas con receptores adrenérgicos α2C, que comprende administrar a un mamífero que necesita dicho tratamiento, al menos un compuesto de acuerdo con la reivindicación 1 o una sal o solvato del mismo.

23. Un método para tratar una o más afecciones que están asociadas con receptores adrenérgicos α2C, que comprende administrar a un mamífero que necesita dicho tratamiento, el compuesto de la reivindicación 11 o una sal o solvato del mismo farmacéuticamente aceptable.

24. El método de la reivindicación 22, donde las afecciones están seleccionadas del grupo que consiste en rinitis alérgica, congestión, dolor, diarrea, glaucoma, insuficiencia cardíaca congestiva, isquemia cardíaca, trastornos

maníacos, depresión, ansiedad, migraña, incontinencia urinaria inducida por estrés, deterioro neuronal por isquemia y esquizofrenia.

25 El método de la reivindicación 23, donde las afecciones están seleccionadas del grupo que consiste en rinitis alérgica, congesitón, dolor, diarrea, glaucoma, insuficiencia cardíaca congestiva, isquemia cardíaca, trastornos maníacos, depresión, ansiedad, y esquizofrenia.

26. El método de la reivindicación 24, donde la afección es congestión.

27. El método de la reivindicación 25, donde la afección es congestión.

28 El método de la reivindicación 26, donde la congestión está asociada con rinitis alérgica perenne, rinitis alérgica estacional, rinitis no alérgica, rinitis vasomotora, rinitis medicamentosa, sinusitis, rinosinusitis aguda, o rinosinusitis crónica.

29. El método de la reivindicación 26, donde la congestión es causada por pólipos o es inducida viralmente.

30. El método de la reivindicación 27, donde la congestion está asociada con rinitis alérgica perenne, rinitis alérgica estacional, rinitis no alérgica, rinitis vasomotora, rinitis medicamentosa, sinusitis, rinosinusitis aguda, o rinosinusitis crónica.

31. El método de la reivindicación 27, donde la congestión es causada por pólipos o es inducida viralmente.

32. El método de la reivindicación 24, donde la afección es dolor.

33 El método de la reivindicación 32, donde el dolor está asociado con neuropatía, inflamación, artritis o diabetes.

34. El método de la reivindicación 25, donde la afección es dolor.

35. El método de la reivindicación 34, donde el dolor está asociado con neuropatía, inflamación, artritis o diabetes.

36. Un compuesto de la reivindicación 1, en forma aislada y purificada.

p.de: SCHERING CORPORATION * PHARMACOPEIA, INC.

RESUMEN

En sus muchas realizaciones, la presente invención provee una nueva clase de compuestos fenilmorfolina y feniltiomorfolina que son útiles como agonistas del receptor adrenégico α2C, composiciones farmacéuticas que contienen los compuestos, y métodos de tratamiento, prevención, inhibición, o mejoramiento de una o más enfermedades asociadas con los agonistas del receptor adrenérgico α2C, usando dichos compuestos o composiciones farmacéuticas.

Case No: AL06356-01

THE INTERNATIONAL BUREAU OF WIPO

Applicant(s)	: **SCHERING CORPORATION and PHARMACOPEIA, INC.**
International Application No.	: **PCT/US2008/001776**
International Filing Date	: **11 February 2008 (11.02.2008)**
Title	**3,4-DIHYDRO-1, 4-BENZOXAZINE, 3, 4-DIHYDRO-1, 4-BENZOTHIAZINE AND 1,2,3,4-TETRAHYDRO-QUINOXALINE DERIVATIVES AS ALPHA2C ADRENORECEPTOR AGONISTS**

VIA FACSIMILE (011) 41-22 338 8270

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

REQUEST FOR CHANGE OF NAME OF CO-APPLICANT UNDER RULE 92bis

Applicants request that co-applicant's name PHARMACOPEIA, INC. be changed to PHARMACOPEIA, LLC

Respectfully submitted,
SCHERING CORPORATION

By: _____
Mark W. Russell
Agent for Applicants

Dated: August 7, 2009

PATENT COOPERATION TREATY

Date of Submission: 28 August 2008 – via overnight delivery

Applicant's File Reference: AL06356-01

International Application No.: PCT/US2008/001776

International Filing Date: 11 February 2008

Applicant: Schering Corporation

International Bureau of WIPO
34, chemin des Columbettes
1211 Geneva 20, Switzerland
Facsimile No.: (41-22) 740.14.35

Article 19 Amendment

This Amendment is being submitted in response to the Notification of Transmittal of the International Search Report mailed 2 July 2008.

Attached to this Amendment are replacement pages 145-153, which are to be substituted for original pages 145-166. Original claims 1 has been amended to recite the compounds of Examples 63-68 and 273-341. Original claims 2-14, 16, 18, 20, 23, 25, 27, 30 and 31 have been deleted. Original claims 15, 26, 28, 29, and 32-36 have been renumbered as new claims 2-15.

REMARKS

No new matter is believed to have been added to the application by any of the foregoing amendments. New claims 1-14 are supported in the specification by Example 63-68 and 273-341, by the originally filed claims, and elsewhere throughout the application.

Accordingly, Applicants respectfully request that the above amendment be entered of record in the present application and considered by the Examiner.

Respectfully submitted,

Mark W. Russell
Registration No. 37,514
Agent for Applicant

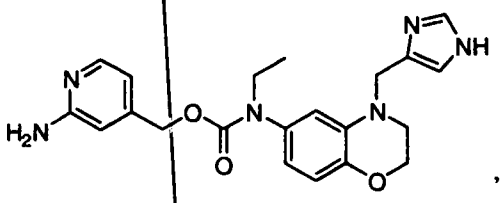
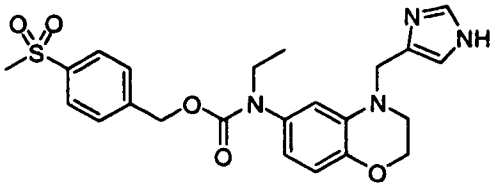
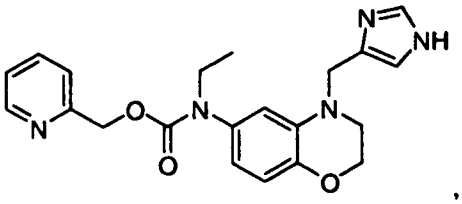
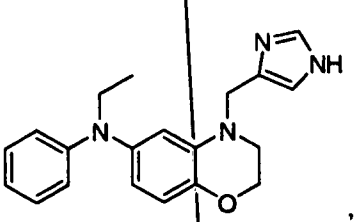
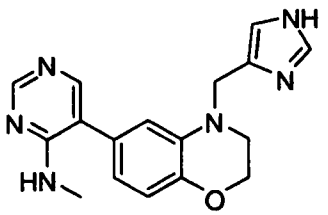
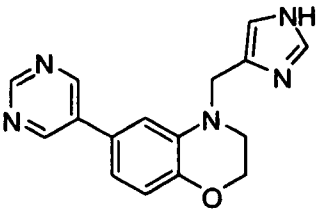
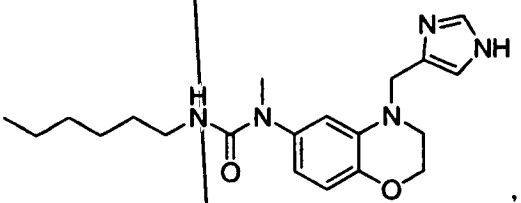
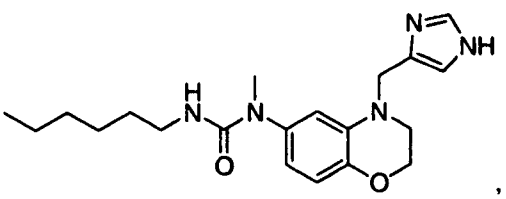
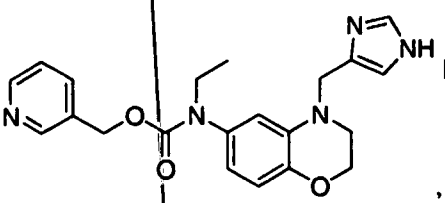
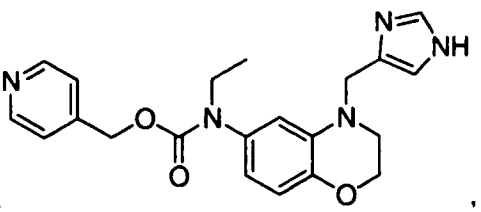
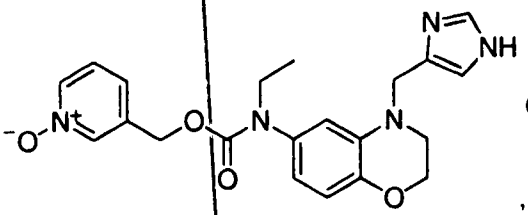
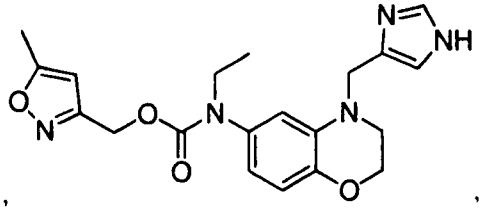
SCHERING CORPORATION
2000 Galloping Hill Rd.
Kenilworth, NJ 07033-0530
United States of America
Telephone No.: (908) 298-5024
Facsimile No.: (908) 298-5388

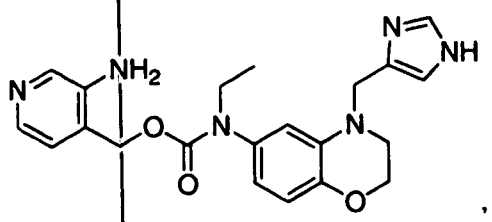
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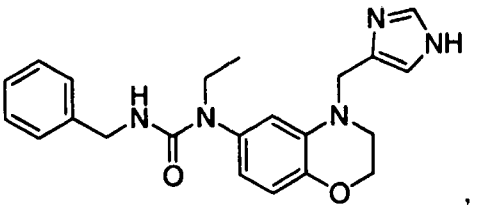
CLAIMS

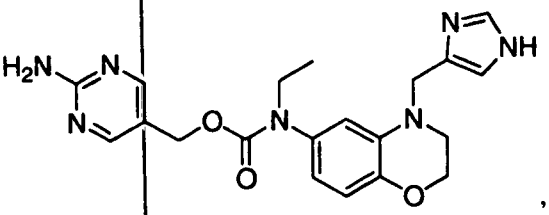
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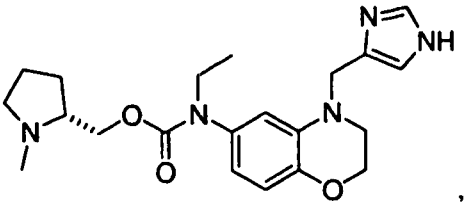
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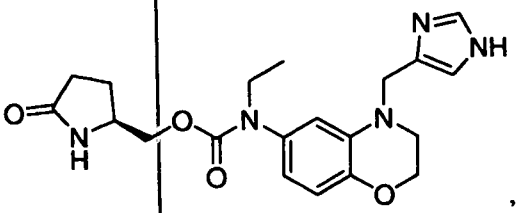

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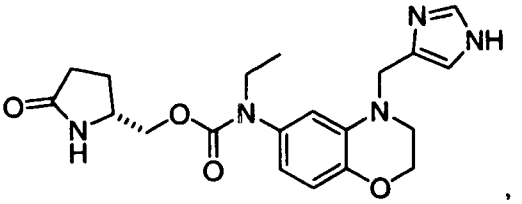


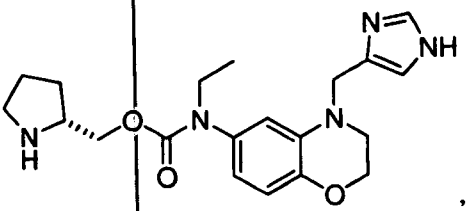


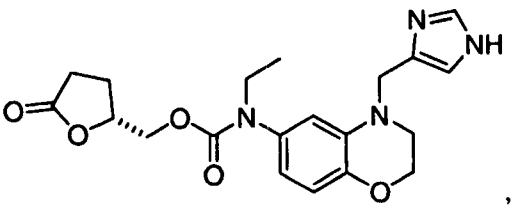


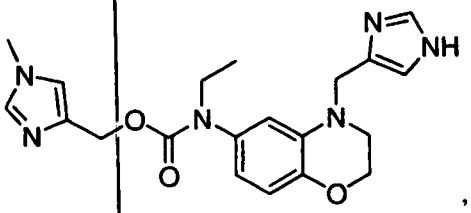


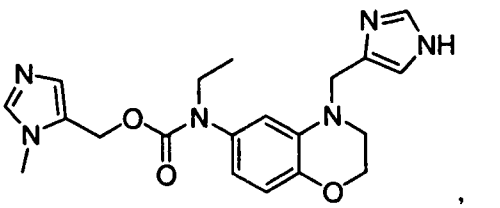


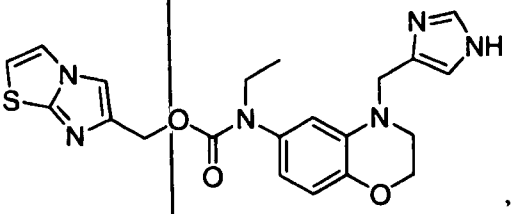


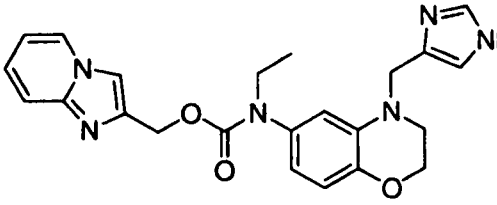


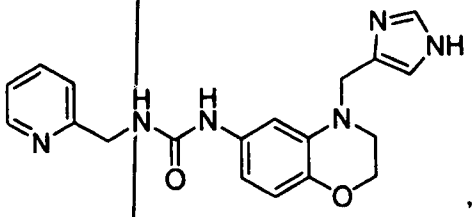


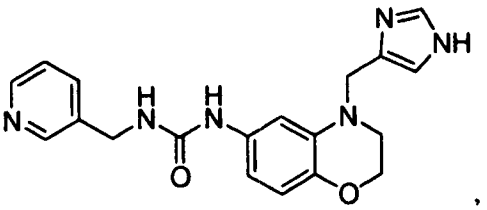


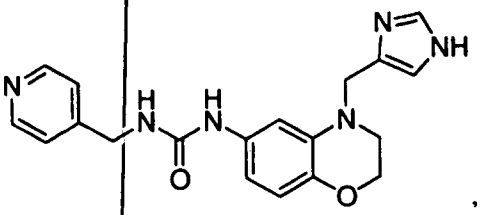


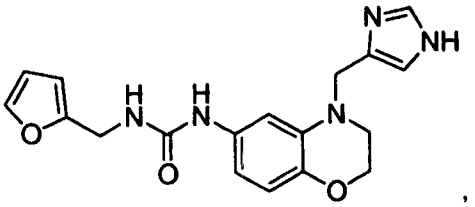


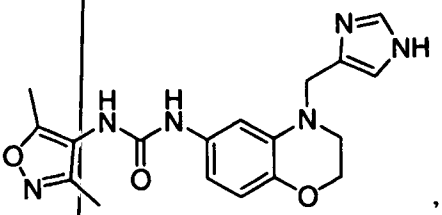


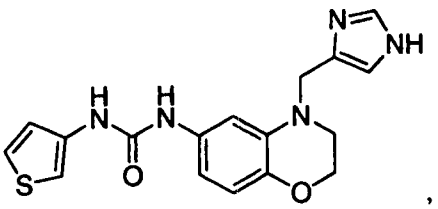


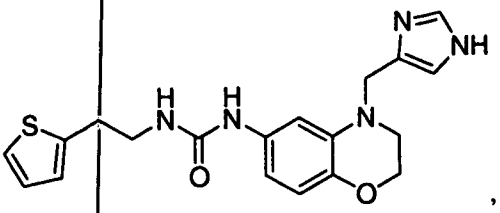


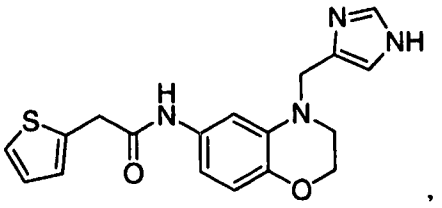


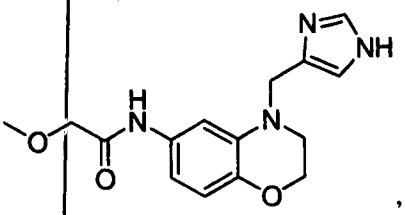


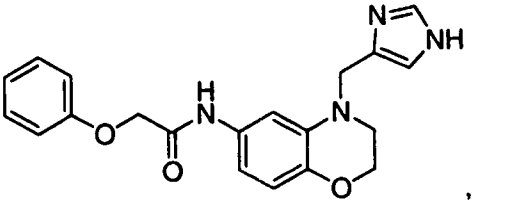


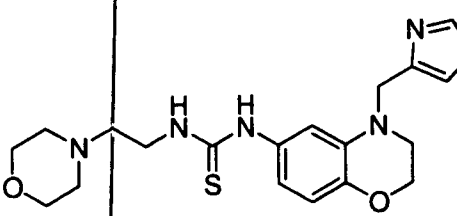


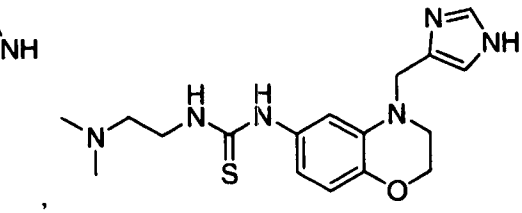


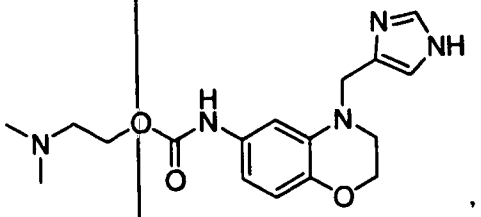


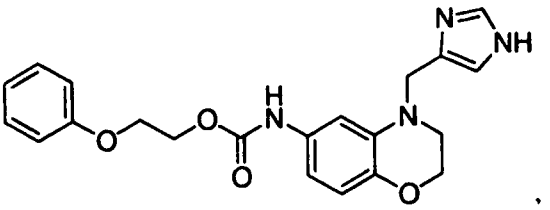


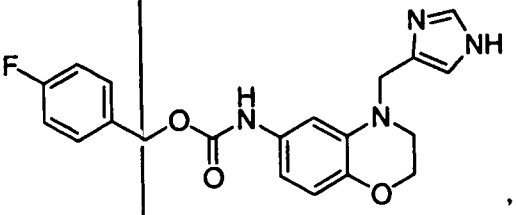


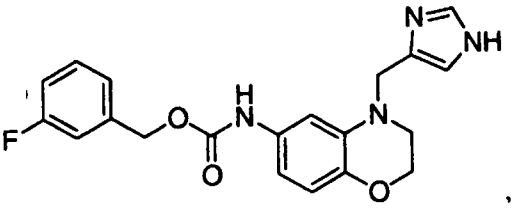


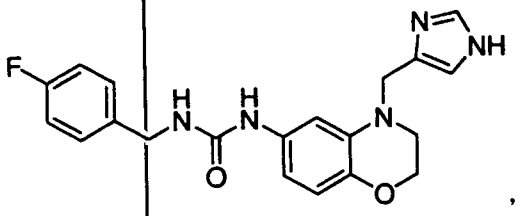


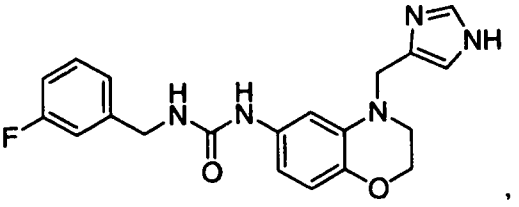


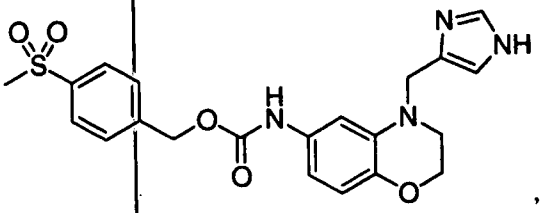


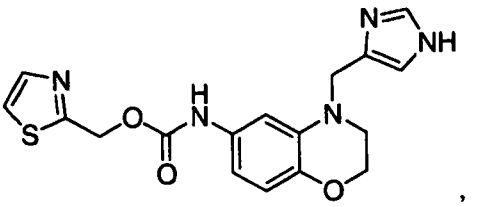


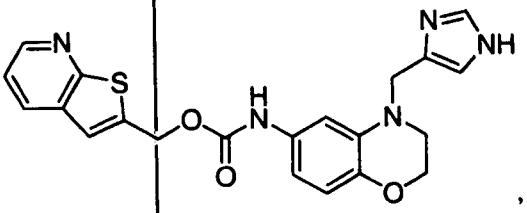


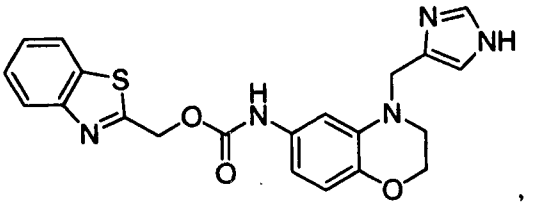


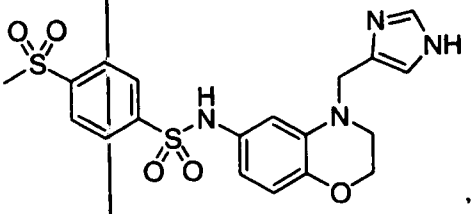


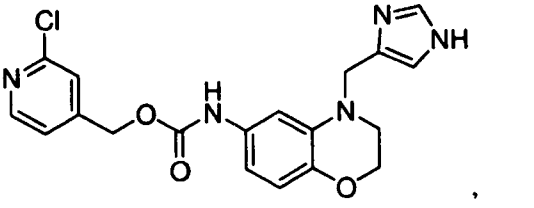


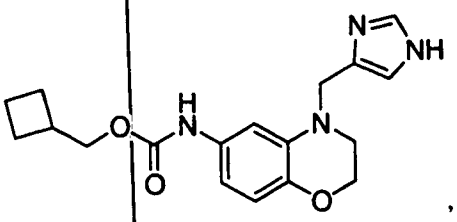


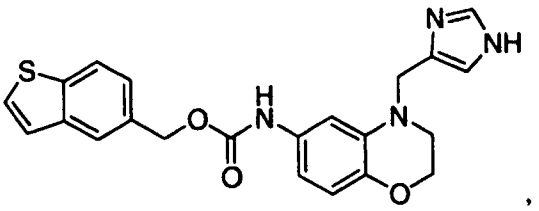


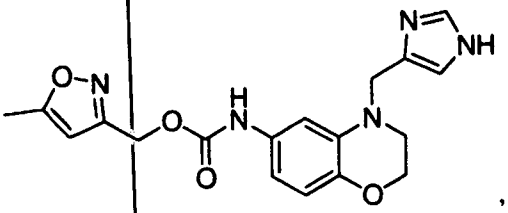


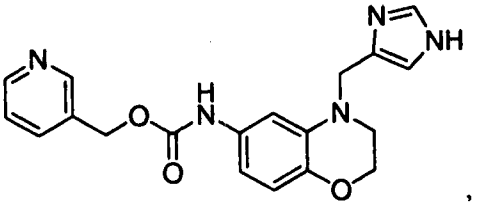


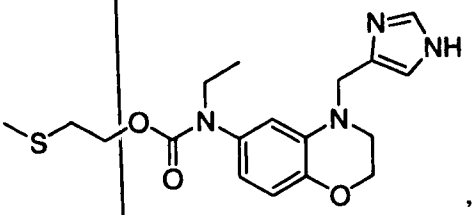


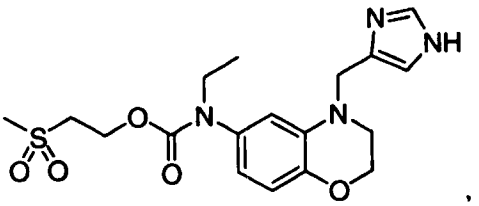


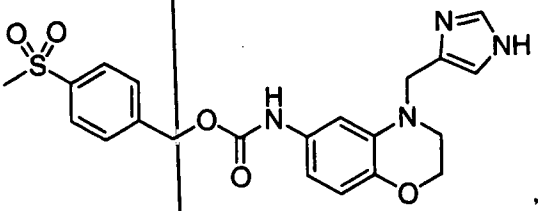


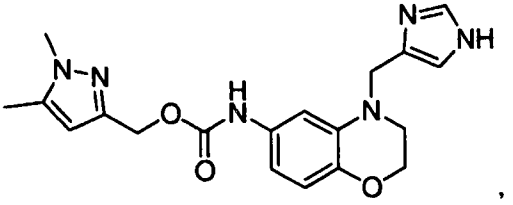


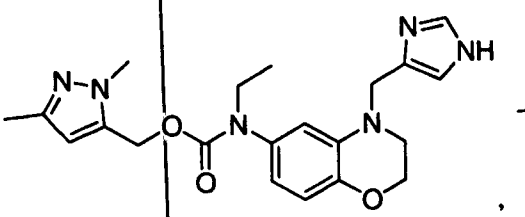


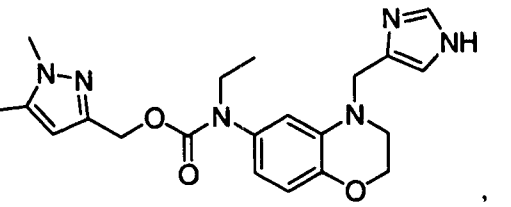


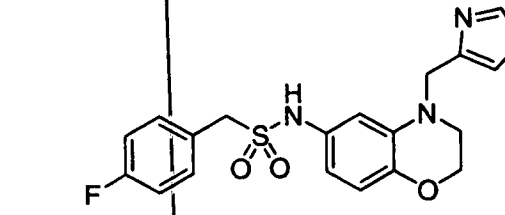


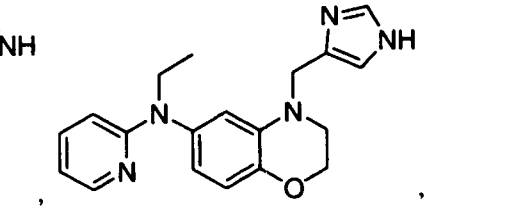




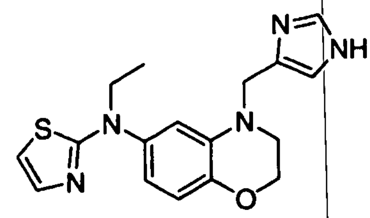


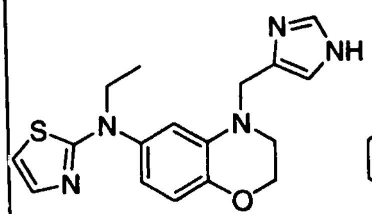
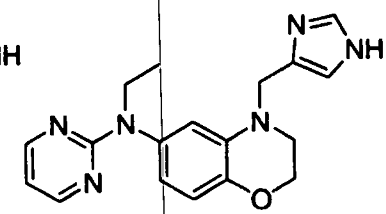


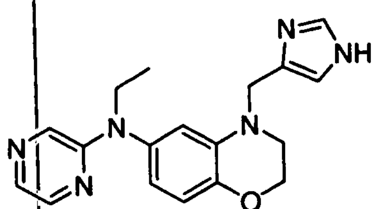
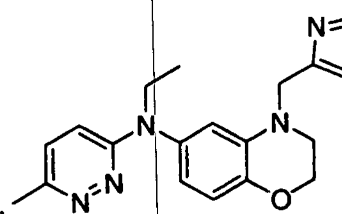


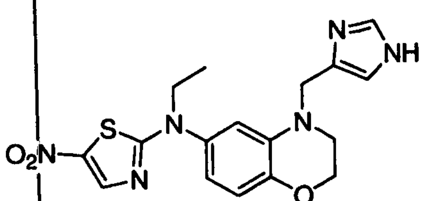
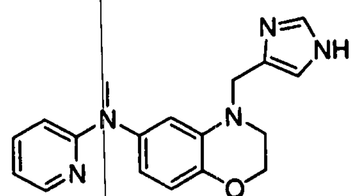


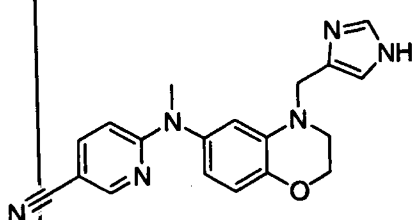
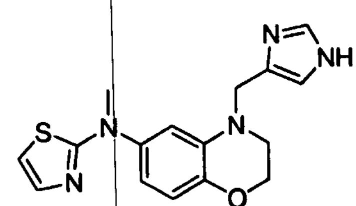


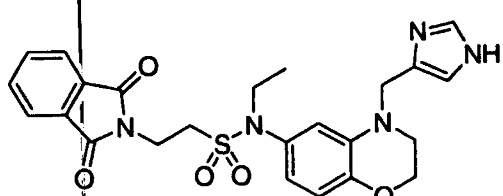
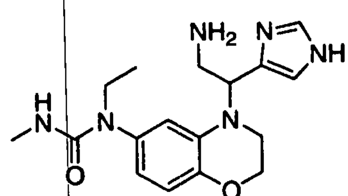

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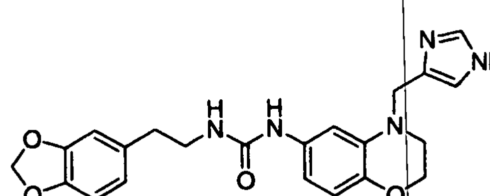


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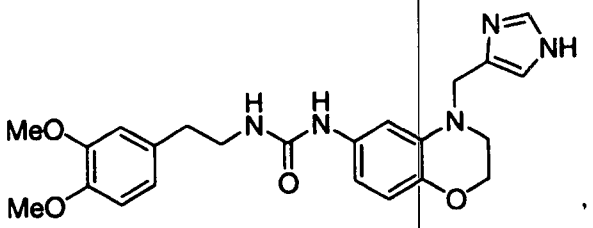

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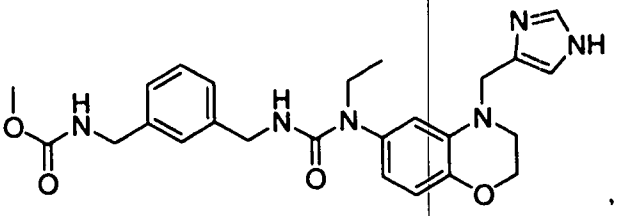

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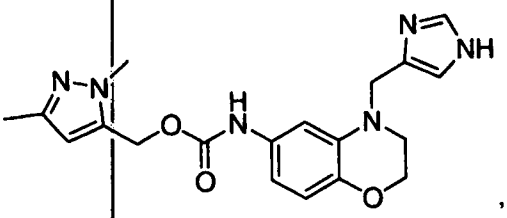

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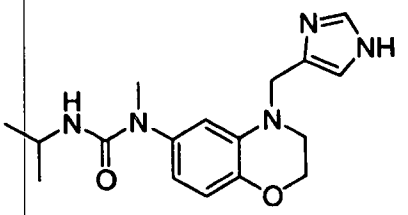

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or a pharmaceutically acceptable salt or solvate thereof.

2. A pharmaceutical composition comprising at least one compound of claim 1, or a pharmaceutically acceptable salt or solvate thereof and at least one pharmaceutically acceptable carrier, adjuvant or vehicle.

3. The pharmaceutical composition of claim 2, further comprising one or more additional therapeutic agents.

4. The pharmaceutical composition of claim 3, wherein said additional therapeutic agents are selected from the group consisting of anti-inflammatory steroids, PDE-4 inhibitors, anti-muscarinic agents, cromolyn sodium, H_1 receptor antagonists, 5-HT_1 agonists, NSAIDs, angiotensin-converting enzyme inhibitors, angiotensin II receptor agonists, β-blockers, β-agonists, leukotriene antagonists, diuretics, aldosterone antagonists, ionotropic agents, and natriuretic peptides.

5. The pharmaceutical composition of claim 3, wherein said additional therapeutic agents are selected from the group consisting of pain management agents, anti-anxiety agents, anti-migraine agents, and therapeutic agents suitable for treating heart conditions, psychotic disorders, and glaucoma.

6. A method for selectively stimulating α2C adrenergic receptors in a cell in need thereof, comprising contacting said cell with a therapeutically effective amount of at least one compound according to claim 1 or a salt or solvate thereof.

7. A method for treating one or more conditions associated with α2C adrenergic receptors, comprising administering to a mammal in need of such treatment at least one compound according to claim 1 or a salt or solvate thereof.

8. The method of claim 7, wherein the conditions are selected from the group consisting of allergic rhinitis, congestion, pain, diarrhea, glaucoma, congestive heart failure, cardiac ischemia, manic disorders, depression, anxiety, migraine, stress-induced urinary incontinence, neuronal damage from ischemia and schizophrenia.

9. The method of claim 8, wherein the condition is congestion.

10. The method of claim 9, wherein the congestion is associated with perennial allergic rhinitis, seasonal allergic rhinitis, non-allergic rhinitis, vasomotor rhinitis, rhinitis medicamentosa, sinusitis, acute rhinosinusitis, or chronic rhinosinusitis.

11. The method of claim 9, wherein the congestion is caused by polyps or is virally induced.

12. The method of claim 9, wherein the congestion is associated with perennial allergic rhinitis, seasonal allergic rhinitis, non-allergic rhinitis, vasomotor rhinitis, rhinitis medicamentosa, sinusitis, acute rhinosinusitis, or chronic rhinosinusitis.

13. The method of claim 8, wherein the condition is pain.

14. The method of claim 12, wherein the pain is associated with neuropathy, inflammation, arthritis or diabetes.

15. A compound of claim 1, in isolated and purified form.

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(71) Applicants *(for all designated States except US)*: **SCHERING CORPORATION** [US/US]; 2000 Galloping Hill Road, Kenilworth, New Jersey 07033-0530 (US). **PHARMACOPEIA, INC.** [US/US]; 3000 Eastpark Boulevard, Cranbury, New Jersey 08512 (US).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **MCCORMICK, Kevin, D.** [US/US]; 15 Brookfield Drive, Basking Ridge, New Jersey 07920 (US). **BOYCE, Christopher, W.** [US/US]; 71 Bonnell Street, Flemington, New Jersey 08822 (US). **SHIH, Neng-yang** [US/US]; 2 Tyler Road, Lexington, Massachusetts 02420 (US). **ASLANIAN, Robert, G.** [US/US]; 144 Philip Drive, Rockaway, New Jersey 07866 (US). **FEVRIER, Salem** [US/US]; 8 Washington Place, Cranford, New Jersey 07016 (US). **MANGIARACINA, Pietro** [US/US]; 4 Montclair Avenue, Monsey, New York 10952 (US). **DE LERA RUIZ, Manuel** [ES/US]; 1236 Magnolia Lane, Branchburg, New Jersey 08876 (US). **YU, Younong** [CN/US]; 280 Bromley Place, East Brunswick, New Jersey 08816 (US). **ZHENG, Junying** [CN/US]; 49 Wexford Way, Bridgewater, New Jersey 08807 (US). **HUANG, Chia-yu** [US/US]; 319 Oak Lane, Princeton Junction, New Jersey 08550 (US). **LIANG, Bo** [CN/US]; 239 Bromley Place, East Brunswick, New Jersey 08816 (US). **LIU, Rong-Qiang** [US/US]; 15 Shepherd Way, Kendall Park, New Jersey 08824 (US). **LIU, Ruiyan** [US/US]; 496 Kings Road, Yardley, Pennsylvania 19067 (US). **GUISE ZAWACKI, Lisa** [US/US]; 1226 Pebble Court, Yardley, Pennsylvania 19067 (US).

(74) Agent: **RUSSELL, Mark, W.**; Schering-Plough Corporation, Patent Department, K-6-1 1990, 2000 Galloping Hill Road, Kenilworth, New Jersey 07033-0530 (US).

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(54) Title: 3,4-DIHYDR0-L4-BENZ0XAZINE, 3, 4-DIHYDR0-1, 4-BENZOTHIAZINE AND 1,2,3,4-TETRAHYDRO-QUINOXALINE DERIVATIVES AS ALPHA2C ADRENORECEPTOR AGONISTS

(57) Abstract: The present invention relates to a novel class of phenylmorpholine and phenyl thiomorpholine compounds useful as alpha2C adrenergic receptor agonists, pharmaceutical compositions containing the compounds, and methods of treatment, prevention, inhibition, or amelioration of one or more diseases associated with the alpha2C adrenergic receptor agonists, such as allergic rhinitis, congestion, pain, diarrhea, glaucoma, congestive heart failure, cardiac ischemia, manic disorders, depression, anxiety and schizophrenia.

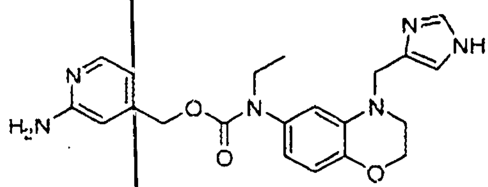
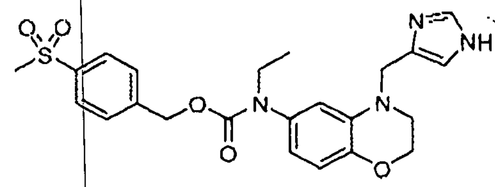
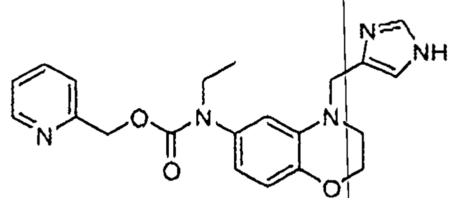
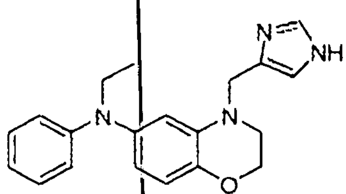
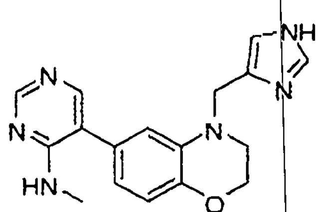
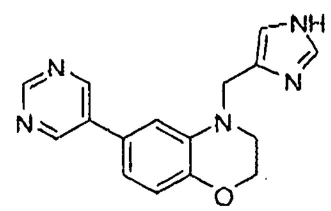
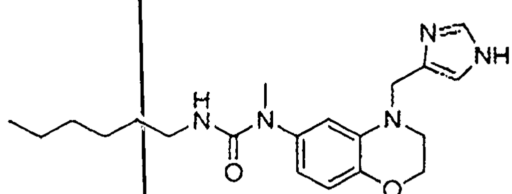
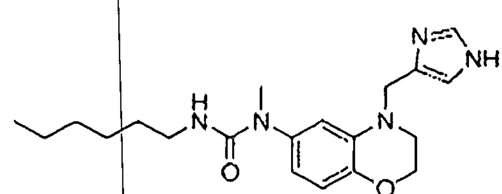
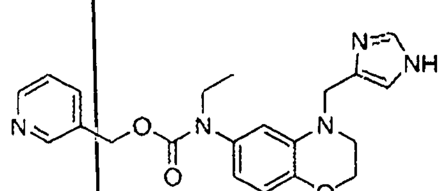
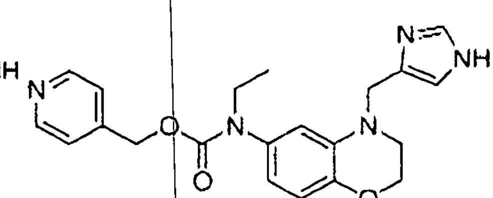
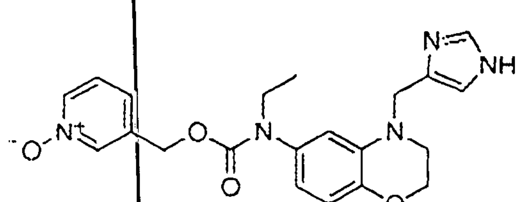
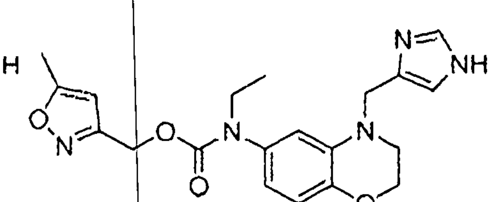
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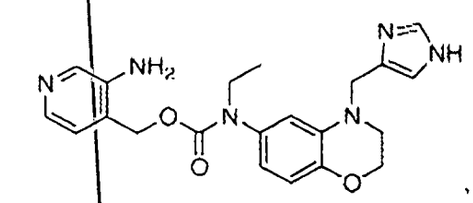
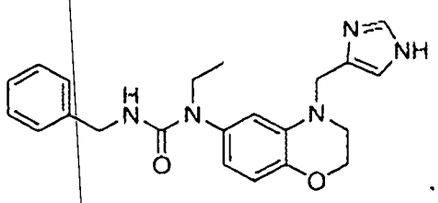
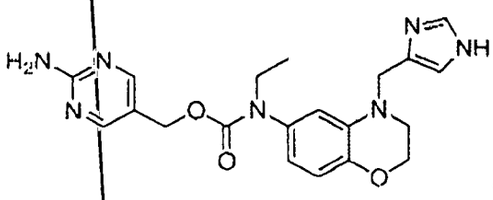
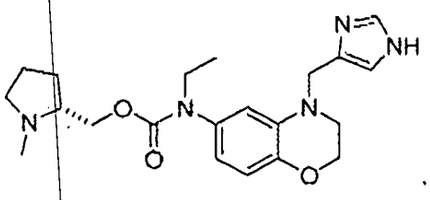
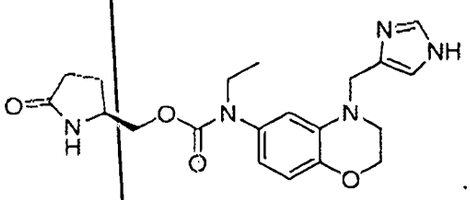
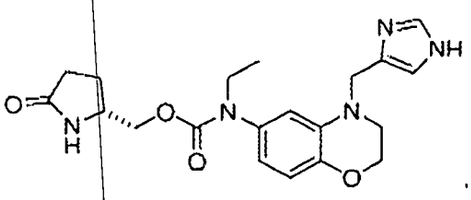
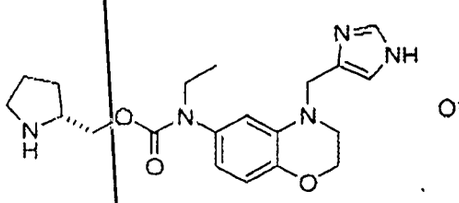
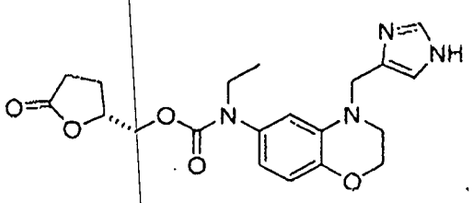
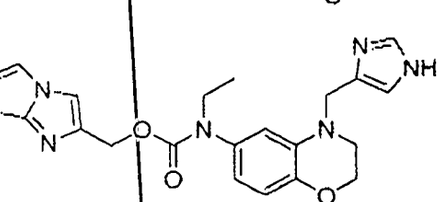
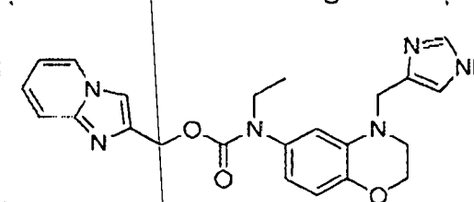
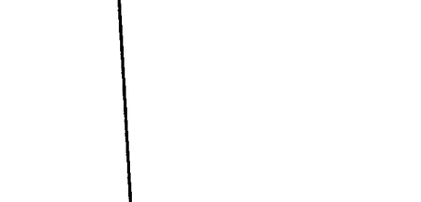
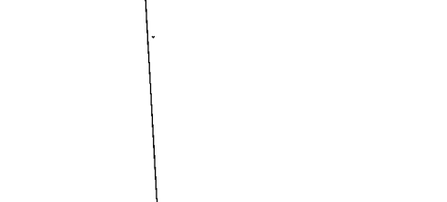
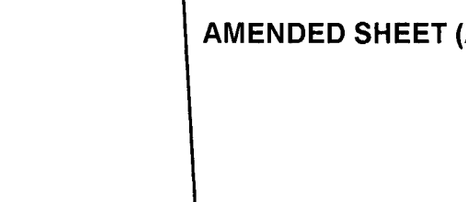
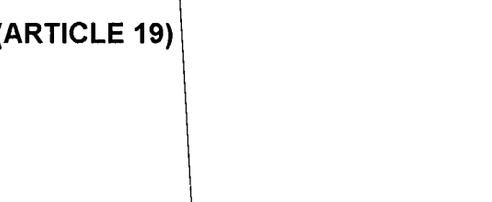
AMENDED CLAIMS

received by the International Bureau on 28 August 2008 (28.08.2008)

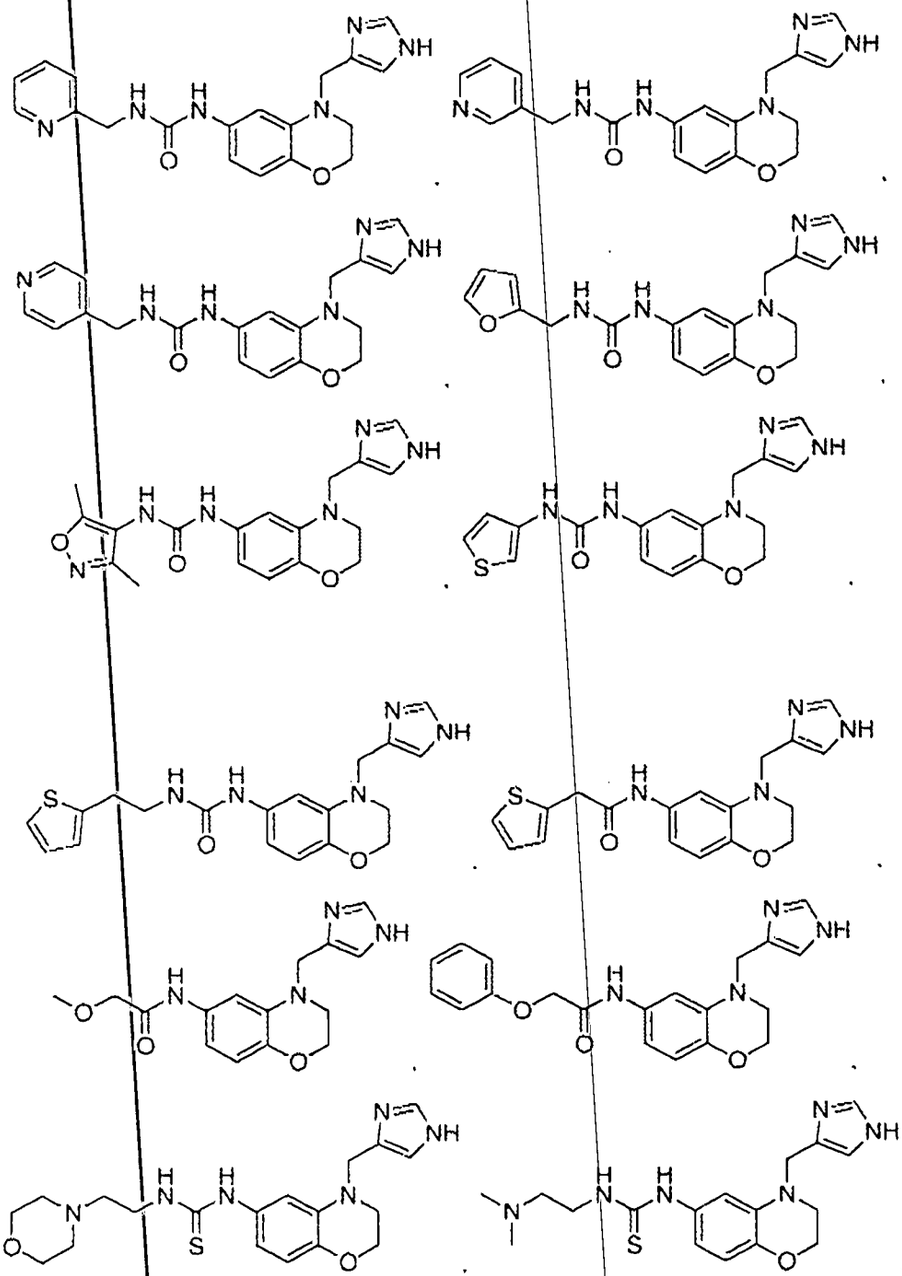
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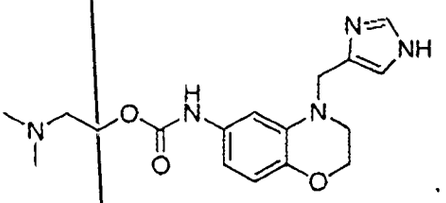
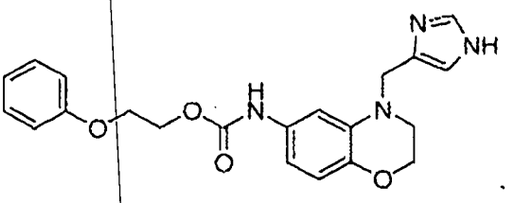
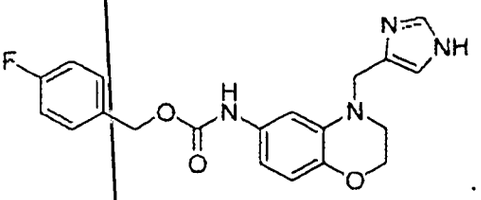
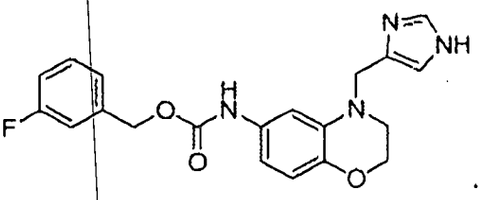
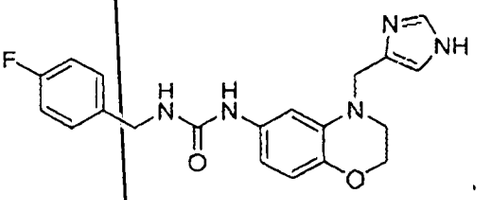
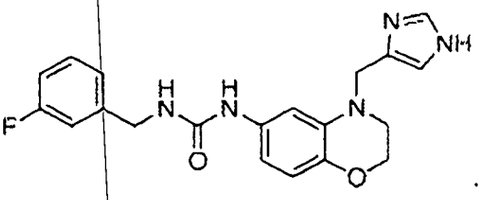
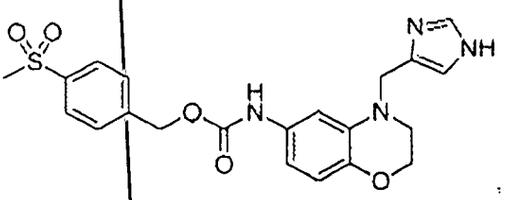
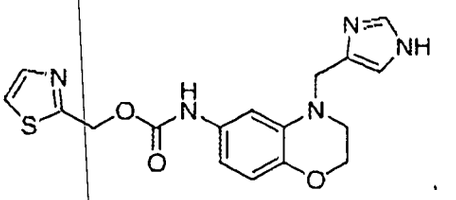
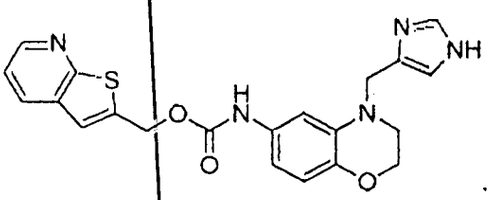
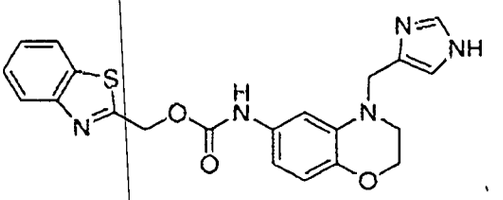
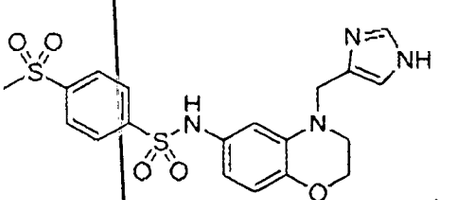
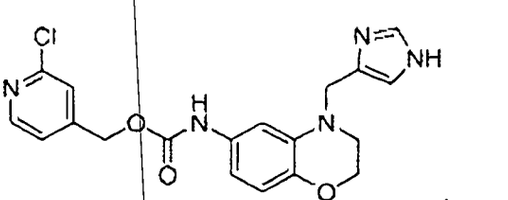
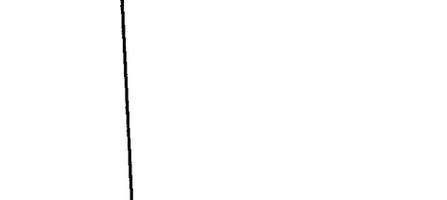
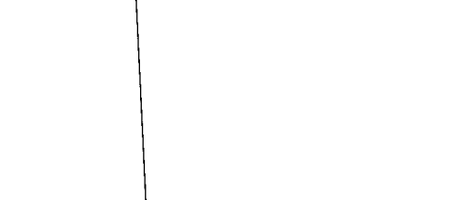
1. A compound selected from the group consisting of


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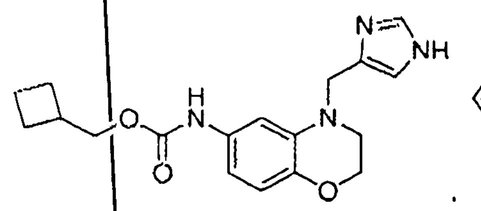
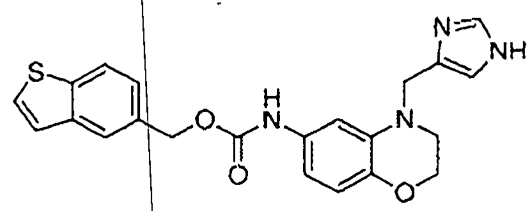
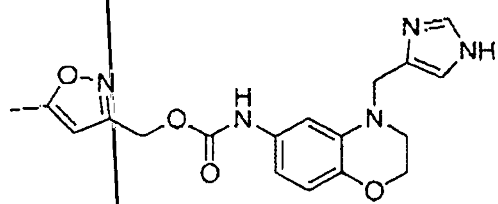
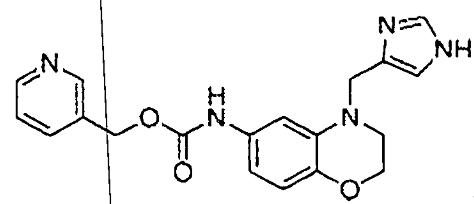
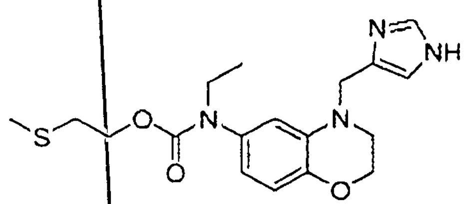
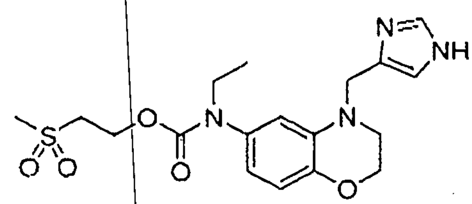
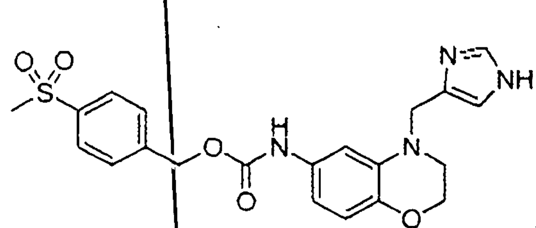
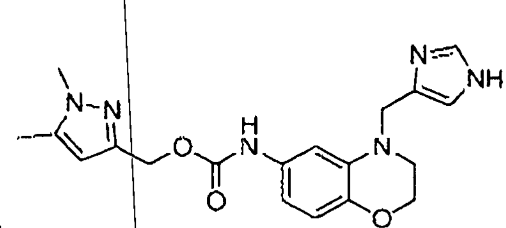
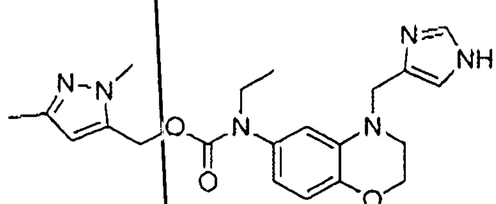
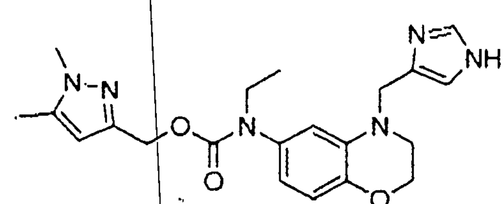
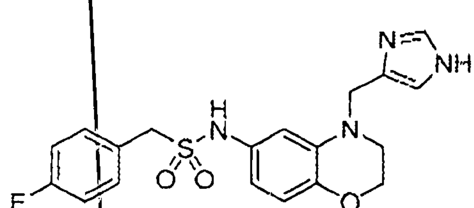
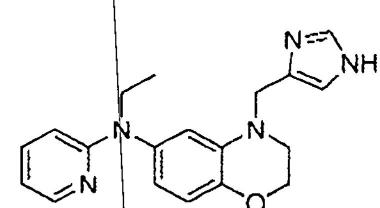















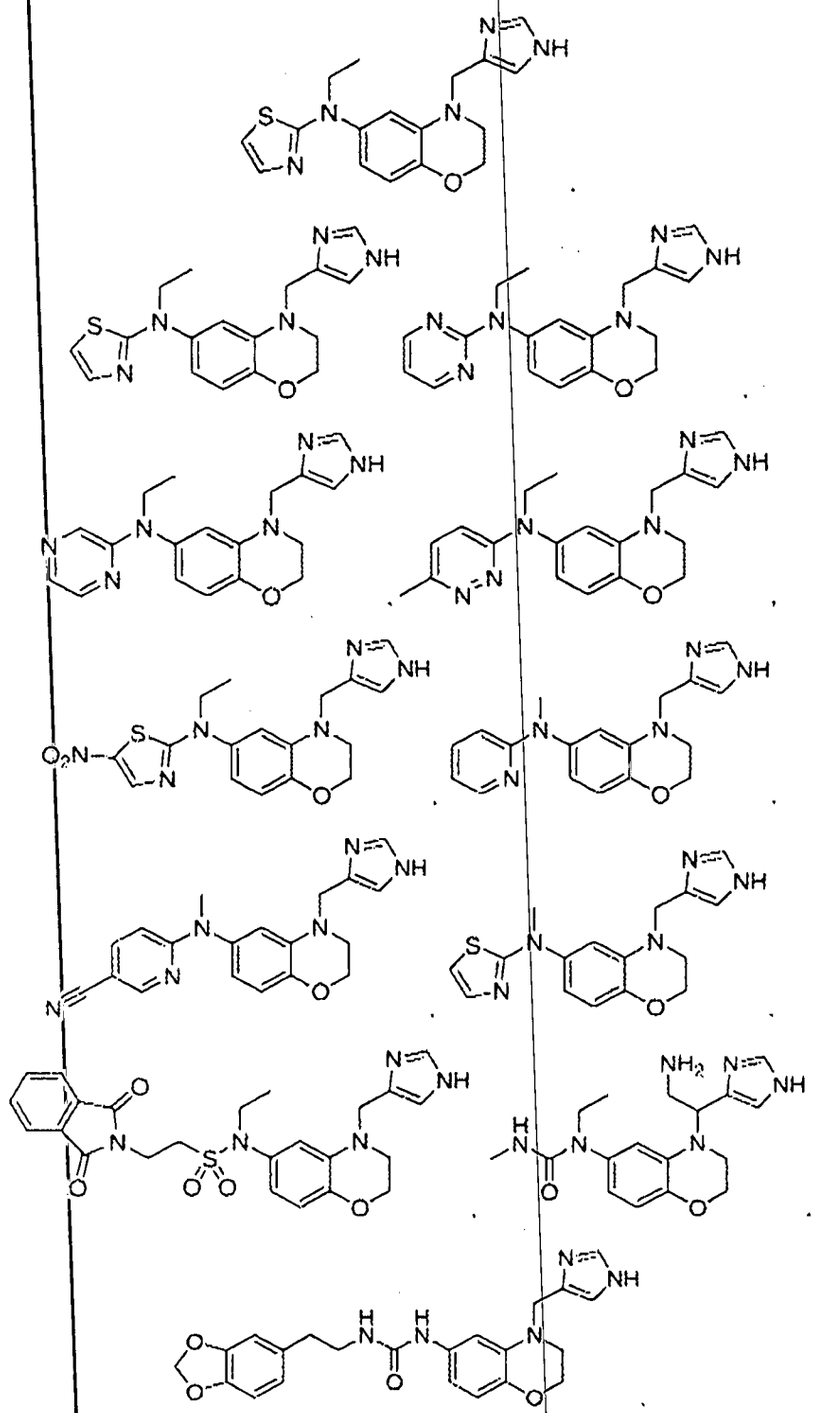
AMENDED SHEET (ARTICLE 19)



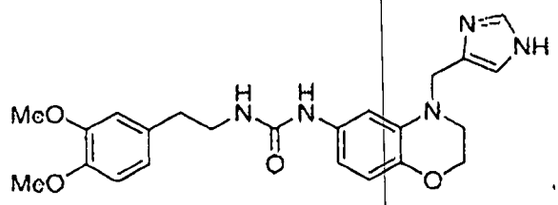















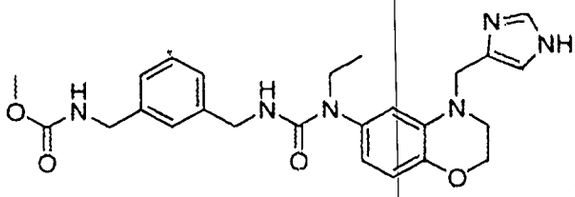
AMENDED SHEET (ARTICLE 19)

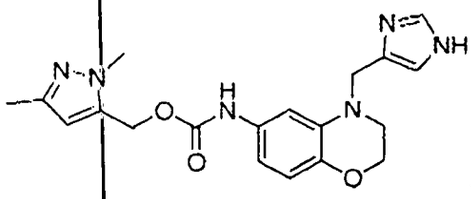















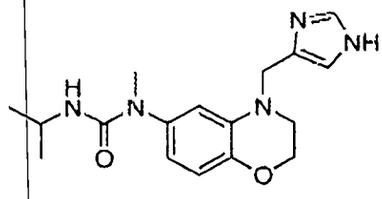
AMENDED SHEET (ARTICLE 19)







. and



or a pharmaceutically acceptable salt or solvate thereof.

2. A pharmaceutical composition comprising at least one compound of claim 1, or a pharmaceutically acceptable salt or solvate thereof and at least one pharmaceutically acceptable carrier, adjuvant or vehicle.

3. The pharmaceutical composition of claim 2, further comprising one or more additional therapeutic agents.

4. The pharmaceutical composition of claim 3, wherein said additional therapeutic agents are selected from the group consisting of anti-inflammatory steroids, PDE-4 inhibitors, anti-muscarinic agents, cromolyn sodium, H_1 receptor antagonists, 5-HT_1 agonists, NSAIDs, angiotensin-converting enzyme inhibitors, angiotensin II receptor agonists, β-blockers, β-agonists, leukotriene antagonists, diuretics, aldosterone antagonists, ionotropic agents, and natriuretic peptides.

AMENDED SHEET (ARTICLE 19)

5. The pharmaceutical composition of claim 3, wherein said additional therapeutic agents are selected from the group consisting of pain management agents, anti-anxiety agents, anti-migraine agents, and therapeutic agents suitable for treating heart conditions, psychotic disorders, and glaucoma.

6. A method for selectively stimulating α2C adrenergic receptors in a cell in need thereof, comprising contacting said cell with a therapeutically effective amount of at least one compound according to claim 1 or a salt or solvate thereof.

7. A method for treating one or more conditions associated with α2C adrenergic receptors, comprising administering to a mammal in need of such treatment at least one compound according to claim 1 or a salt or solvate thereof.

8. The method of claim 7, wherein the conditions are selected from the group consisting of allergic rhinitis, congestion, pain, diarrhea, glaucoma, congestive heart failure, cardiac ischemia, manic disorders, depression, anxiety, migraine, stress-induced urinary incontinence, neuronal damage from ischemia and schizophrenia.

9. The method of claim 8, wherein the condition is congestion.

10. The method of claim 9, wherein the congestion is associated with perennial allergic rhinitis, seasonal allergic rhinitis, non-allergic rhinitis, vasomotor rhinitis, rhinitis medicamentosa, sinusitis, acute rhinosinusitis, or chronic rhinosinusitis.

11. The method of claim 9, wherein the congestion is caused by polyps or is virally induced.

12. The method of claim 9, wherein the congestion is associated with perennial allergic rhinitis, seasonal allergic rhinitis, non-allergic rhinitis, vasomotor rhinitis, rhinitis medicamentosa, sinusitis, acute rhinosinusitis, or chronic rhinosinusitis.

13. The method of claim 8, wherein the condition is pain.

14. The method of claim 12, wherein the pain is associated with neuropathy, inflammation, arthritis or diabetes.

15. A compound of claim 1, in isolated and purified form.

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2008/001776

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K31/4985 A61K31/5383 A61K31/542 C07D403/06 C07D413/06
C07D413/14 C07D417/06 C07D471/04 C07D498/04 A61P11/02
A61P29/00 A61P25/24 A61P27/06

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D

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

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2005/089515 A (BRIGHAM & WOMENS HOSPITAL [US]; LANSBURY PETER T [US]; LIU ZHIHUA [US]) 29 September 2005 (2005-09-29) page 144, lines 31,32	1-3,5,6, 15
X	WO 97/30992 A (SQUIBB BRISTOL MYERS CO [US]) 28 August 1997 (1997-08-28) examples 93,413 page 377, lines 29-31 page 392, lines 27,28 page 387, lines 11,12	1-3,5,6, 15

-/--

[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

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

'E' earlier document but published on or after the international filing date

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

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

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

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

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

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

'&' document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
24 June 2008	02/07/2008

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Schuemacher, Anne

Form PCT/ISA/210 (second sheet) (April 2005)

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2008/001776

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	CHANG WONG-JIN ET AL: "Microwave-assisted soluble polymer-supported synthesis of benzopiperazinones" SYNLETT, THIEME INTERNATIONAL, STUTTGART, DE, no. 11, 1 January 2003 (2003-01-01), pages 1688-1692, XP002420369 ISSN: 0936-5214 page 1690; table 1; compound 9H	1
X	FENG G ET AL: "ONE-POT REGIOSELECTIVE ANNULATION TOWARD 3,4-DIHYDRO-3-OXO-2H-1,4-BEN ZOXAZINE SCAFFOLDS UNDER CONTROLLED MICROWAVE HEATING" TETRAHEDRON, ELSEVIER SCIENCE PUBLISHERS, AMSTERDAM, NL, vol. 62, 1 January 2006 (2006-01-01), pages 4635-4642, XP002420370 ISSN: 0040-4020 page 4636; table 2; compounds 5A-5C, 5E-5H	1
A	WO 01/00586 A (ALLERGAN SALES INC [US]; CHOW KEN [US]; GIL DANIEL W [US]; BURKE JAMES) 4 January 2001 (2001-01-04) abstract; claims 1,57	1-36
P,X	WO 2007/024949 A (SCHERING CORP [US]; PHARMACOPEIA DRUG DISCOVERY [US]; MCCORMICK KEVIN) 1 March 2007 (2007-03-01) the whole document	1-36

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2008/001776

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 14 and 21-35 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

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

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers allsearchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search reportcovers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

[ ] The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2008/001776

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2005089515 A	29-09-2005	US 2005272722 A1	08-12-2005
WO 9730992 A	28-08-1997	AU 718676 B2	20-04-2000
		AU 2136697 A	10-09-1997
		BG 64951 B1	31-10-2006
		BG 102738 A	30-09-1999
		BR 9707614 A	27-07-1999
		CA 2239187 A1	28-08-1997
		CN 1347881 A	08-05-2002
		CN 1214685 A	21-04-1999
		CZ 9802696 A3	13-10-1999
		EE 9800262 A	15-02-1999
		EP 1481975 A1	01-12-2004
		EP 0892797 A1	27-01-1999
		HU 9902016 A2	28-09-1999
		IL 124197 A	24-06-2003
		IL 141908 A	10-04-2003
		JP 2000502356 T	29-02-2000
		LV 12150 A	20-10-1998
		NO 983892 A	25-08-1998
		NZ 330287 A	27-03-2000
		PL 328868 A1	01-03-1999
		RO 121118 B1	29-12-2006
		RU 2225405 C2	10-03-2004
		SK 117398 A3	11-12-2000
		TW 496863 B	01-08-2002
WO 0100586 A	04-01-2001	AT 283843 T	15-12-2004
		AU 773668 B2	03-06-2004
		AU 5474900 A	31-01-2001
		CZ 20010864 A3	12-09-2001
		DE 60016359 D1	05-01-2005
		DE 60016359 T2	01-12-2005
		EP 1104407 A1	06-06-2001
		ES 2228544 T3	16-04-2005
		HK 1035724 A1	13-05-2005
		HU 0104390 A2	29-04-2002
		RU 2232154 C2	10-07-2004
		TW 283669 B	11-07-2007
WO 2007024949 A	01-03-2007	AR 057771 A1	19-12-2007
		AU 2006283109 A1	01-03-2007
		CA 2620173 A1	01-03-2007

Industria y Comercio
SUPERINTENDENCIA

REQUISITOS MÍNIMOS PARA ADMISIÓN A TRAMITE
PCT

PATENTE DE INVENCIÓN [✓] MODELO DE UTILIDAD [ ]

- Indicación de que se solicita la concesión de una patente [✓]
- Datos de identificación del solicitante o de la persona que presenta la solicitud [✓]
- Descripción de la invención [✓]
- Dibujos de ser estos pertinentes [ ]
- Comprobante de pago de las tasas establecidas [✓]

COMPLETA [ ] INCOMPLETA [ ]

DISEÑO INDUSTRIAL [ ]

- Indicación de que se solicita el registro de Diseño Industrial [ ]
- Datos de identificación del solicitante o de la persona que presenta la solicitud [ ]
- Representación gráfica y fotográfica del Diseño Industrial o muestra del material que incorpora el diseño [ ]
- Comprobante de pago de las tasas establecidas [ ]

COMPLETA [ ] INCOMPLETA [ ]

ESQUEMA DE TRAZADO [ ]

- Indicación de que se solicita el registro de un Esquema de Trazado [ ]
- Datos de identificación del solicitante o de la persona que presenta la solicitud [ ]
- Representación gráfica del esquema trazado [ ]
- Comprobante de pago de las tasas establecidas [ ]

COMPLETA [ ] INCOMPLETA [ ]

Firma Responsable

Fecha_

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 09-084452- -00000-0000
Fecha: 2009-08-12 17:47:12 Dep. 2020 NUECREACIONI
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 380

arrera 13 No. 27-00 Piso 5,7y10´
Conmutador: 3 82 0840
Fax: 3505220
E-mail: info@sic.gov.co
www.sic.gov.co
Bogotá D.C. - Colombia

REPUBLICA DE COLOMBIA
SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

Bogotá,
2020

Doctor(a)
OLARTE GARCIA CARLOS REYNALDO
Apoderado(a) y/o Representante de
SCHERING - CORPORATION
PHARMACOPEIA LLC

REFERENCIA	Radicación No.	9 84452
	Solicitud internacional	PCT/US2008/001776
	Fecha inicio fase nacional	13/09/2009
	Trámite	11
	Evento	378
	Actuación	430
	Oficio No.	11097

Como resultado del examen de forma, realizado con fundamento en el artículo 38 de la Decisión 486 de la Comisión de la Comunidad Andina, artículo 27 del Tratado de Cooperación en Materia de Patentes (PCT), regla 51 bis del Reglamento y Circular Única de la Superintendencia de Industria y Comercio, se le comunica que:

1. La solicitud no contiene la copia del documento en que consta la cesión del derecho a la patente del inventor al solicitante o a su causante, conforme a lo establecido por el artículo 26 literal k) de la Decisión 486 de la Comisión de la Comunidad Andina. Cuando se trate de documentos otorgados en el extranjero, estos deberán legalizarse de conformidad con lo dispuesto por los artículos 259 y 260 del Código de Procedimiento Civil. Cuando se trate de las declaraciones a que hace referencia la Regla 4.17 ii) del Tratado de Cooperación en Materia de Patentes PCT., el alcance de las tales declaraciones se determinará según indiquen claramente una cesión de derechos del inventor al solicitante o su causante, de conformidad con lo dispuesto en el numeral 5.2.15 del Capítulo Quinto, Título X de la Circular Única de Superintendencia de Industria y Comercio.

En cumplimiento de lo dispuesto por el artículo 39 de la Decisión 486, se le requiere para que dentro del término de dos meses siguientes a la fecha de notificación del presente oficio, complete los requisitos anteriormente enunciados. En caso de no dar cumplimiento al presente requerimiento, la solicitud se considerará abandonada y perderá su prelación.

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

Continua en la página siguiente...

REPUBLICA DE COLOMBIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

Radicación No.:9 84452

ALIX CARMENZA CESPEDES DE VERGEL
Jefe de la división de Nuevas Creaciones

El anterior requerimiento fue notificado por fijación en lista de fecha 02 OCT. 2009
adpa11