



Industria y Comercio

SUPERINTENDENCIA

Delegatura de Propiedad Industrial

División de Nuevas Creaciones

SOLICITUD

PATENTE DE INVENCION

21. EXPEDIENTE No.

05-53827

54. TITULO

INDOLES UTILES EN EL TRATAMIENTO DE ENFERMEDADES RELACIONADAS

CON ANDROGENOS RECEPTORES

51. CLASIFICACION INTERNACIONAL

A61K31/404
A61P5/24.

71. SOLICITANTE

AKZO NOBEL N.V.

DOMICILIO

Arnhem, Holanda.

74. APODERADO

EMILIO FERRERO

C.C. 438,019 de Usaquén.

22. BOGOTA, D.C.,

02/06/2005.

SS



Industria y Comercio
SUPERINTENDENCIA

PETITORIO

1

REGISTRO DE PATENTES Y MARCAS
Bogotá, D.C. 2003-05-21 17:01:17
Tramite : 011 001-00101 379 0000 001 011 00000000
Remarcas: PARA OTORGAR DE NUEVAS PATENTES

FORMULARIO UNICO DE SOLICITUD DE PATENTE PCT

ENTRADA EN FASE NACIONAL 07-06-2003

SOLICITUD DE:

1

☒ Patente de Invención.
☐ Capítulo I.

☐ Patente de Modelo de Utilidad.
☒ Capítulo II.

2

SOLICITANTE
(71)

Nombre: AKZO NOBEL N.V.
sociedad constituida y existente bajo las
leyes de Holanda
Dirección: Velperweg 76,
6824 BM Arnhem,
Holanda
Domicilio: Arnhem, Holanda

IDENTIFICACIÓN

C.C. ☐ NIT ☐
C.E. ☐ Otro ☐
Cual _____
Número _____

3

**REPRESENTANTE
O APODERADO**

Nombre: EMILIO FERRERO
Dirección: Carrera 4ª. No. 72-35
Teléfono: 347 36 11
Fax: 211 86 50
E-mail: clientes@camvp.com
Domicilio: Bogotá, Colombia.

IDENTIFICACIÓN

C.C. ☒ NIT ☐
C.E. ☐ Otro ☐
Cual _____
Número 438.019 T.P 31.929

4

INVENTOR (ES)
(72)

1. Pedro Harold Han HERMKENS
N.V. Organon, P.O. BOX 20,
NL-5340 BH Oss,
Holanda
3. Neeltje Miranda TEERHUIS
N.V. Organon, P.O. BOX 20,
NL-5340 BH Oss,
Holanda
5. Jaap VAN DER LOUW
N.V. Organon, P.O. BOX 20,
NL-5340 BH Oss,
Holanda

2. Herman Thijl STOCK
N.V. Organon, P.O. BOX 20,
NL-5340 BH Oss,
Holanda
4. Johannes Petrus Maria LOMMERSE
N.V. Organon, P.O. BOX 20,
NL-5340 BH Oss,
Holanda

5

PCT (86)

Solicitud Internacional No. PCT/EP2003/050783

Fecha: 3 de Noviembre de 2003

Publicación Internacional No. WO 2004/041782 A1

Fecha: 21 de Mayo de 2004

6

Título (54)

**INDOLES ÚTILES EN EL TRATAMIENTO DE ENFERMEDADES RELACIONADAS
CON ANDRÓGENOS RECEPTORES**

7

Clasificación Internacional (51) C07D 209/30

A61K31/404
A61P5/24

8

Prioridad

SI ☒ NO ☐

(33) País de Origen

US
EP

(32) Fecha

7 de Noviembre de 2002
7 de Noviembre de 2002

(31) Número de Solicitud

60/424.579
02079648.8

9

C mprobante de pago No.: 05 - 35.940

Fecha: 16 de Mayo de 2005

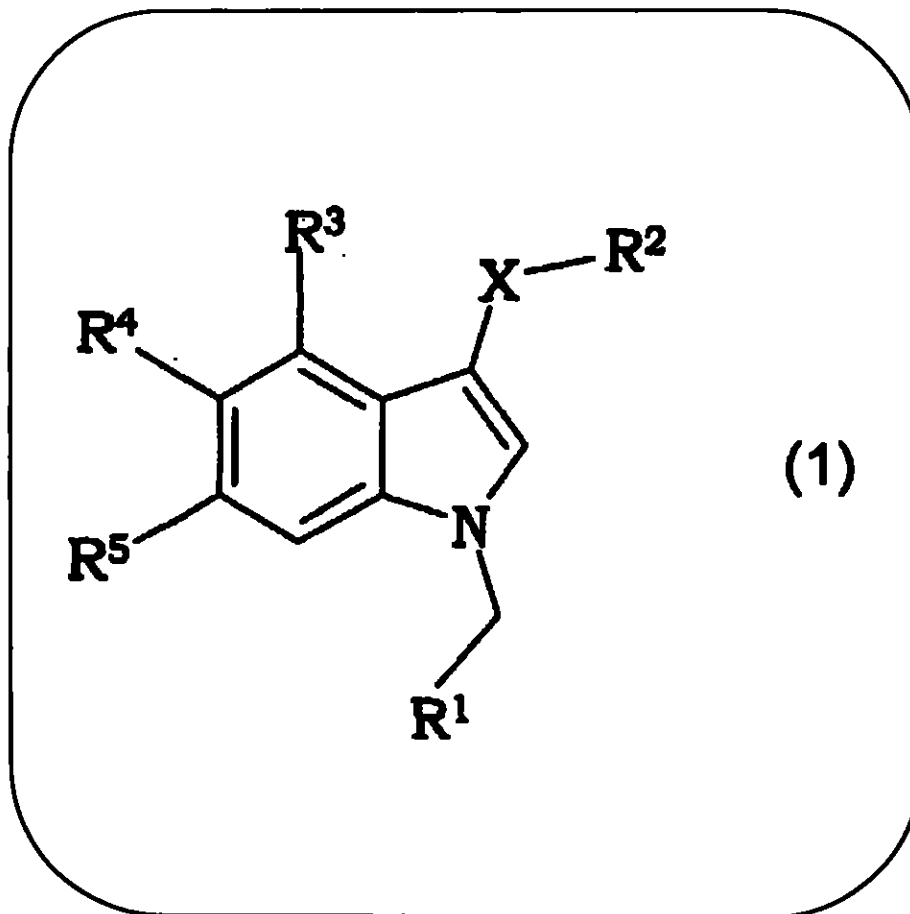
2

10

Anexos:

- ☒ Comprobante de pago de la tasa de presentación de la solicitud por \$ 443.000.00.
- ☐ Comprobante de pago por reivindicación de prioridad.
- ☒ Documento que acredita la existencia y representación legal cuando el solicitante sea persona jurídica.
- ☒ Poderes, si fuere el caso.
- ☒ Documento de cesión del inventor al solicitante o a su causante.
- ☐ Declaraciones.
- ☒ Copia de la solicitud internacional. (Resumen, descripción, reivindicaciones, dibujos)
- ☒ Traducción de la solicitud internacional al castellano. (Resumen, descripción, reivindicaciones, dibujos)
- ☐ Copia del examen preliminar efectuado por la IPEA.
- ☐ Traducción del examen preliminar 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 12x12
- ☐ 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.
- ☒ Otros: VER HOJA DE DOCUMENTOS ANEXOS

11

FIGURA CARACTERÍSTICA

12

Solicito la concesión de la patente,

NOMBRE: EMILIO FERREROFIRMA : 
C.C. 438.019 de Usaquén T.P. 31.929

PRP

ELIER

0197301 CO

For patents, utility models, industrial designs, trademarks, commercial names, trade emblems, slogans.

Para patentes, modelos de utilidad, diseños industriales, marcas de fábrica, nombres comerciales, enseñas, lemas comerciales.

REPRESENTACION Y PODER

REPRESENTATION AND POWER OF ATTORNEY

11214
1538

I (we), the undersigned /Yo (nosotros), abajo firmado (s)

AKZO NOBEL N.V.

of/domiciliado (s) en Velperweg 76, 6824

BM Arnhem, THE NETHERLANDS

por el presente nombramos a EMILIO FERRERO, tpa. 31929; GONZALO PERDOMO, tpa. 831; LUZ CLEMENCIA DE PAEZ, tpa. 23555 y GERMAN CAVELIER, tpa. 832, domiciliados en la Carrera 4ª N° 72-35, Bogotá, Colombia, en obediencia a lo dispuesto en el parágrafo 1º del Artículo 543 del Código de Comercio, el primero como principal y los demás como suplentes, en su orden, como mis (nuestros) representantes en todos los asuntos de propiedad industrial con facultad para recibir notificaciones y nombrar apoderados judiciales o extrajudiciales. El primer representante suplente reemplazará al principal en caso de ausencia o impedimento temporal o definitivo de aquél. La misma regla se aplicará cuando el segundo representante suplente haya de reemplazar al primero, o el tercero al segundo. En tales casos, el representante principal, o el primero, o segundo suplente, en su caso, o ambos, declararán su intención de no ejercer la representación mediante declaración autenticada por Notario Público en Colombia, o por Notario u otro Funcionario Público, o Cónsul de Colombia, en el extranjero; y si se tratare de impedimento, con el certificado respectivo. Si alguno de los nombrados faltare definitivamente, el siguiente tomará su lugar. Cuando cesare la ausencia o impedimento del representante principal, o de su primer o segundo suplentes, en su caso, podrán ejercer la representación, en su orden, uno u otros según el caso, asumiéndola por el solo hecho de ejercerla, cesando en ese momento el ejercicio de la representación por el primero, segundo o tercer suplente en su caso.

Además, confiero (conferimos) poder a los abogados arriba nombrados, para obtener la protección de mi (nuestra) propiedad industrial y contra la competencia desleal, a cuyo efecto autorizo (amos) a los dichos apoderados para que me (nos) representen ante cualesquiera entidades o personas, ejerzan o no jurisdicción, especialmente ante las del orden administrativo, contencioso-administrativo y judicial, así como los tribunales de arbitramento, en todo lo concerniente a los siguientes asuntos: a) Obtención de patentes de invención, modelos de utilidad, y diseños industriales; el registro de marcas de fábrica, colectivas, defensivas, de servicio, lemas comerciales, nombres comerciales, enseñas, variedades vegetales y denominaciones de origen; su renovación, traspaso, cambio de nombre o domicilio, cancelación voluntaria; y el registro de licencias de uso de esos derechos; b) Las acciones de competencia desleal, protección del consumidor, oposiciones u observaciones, cancelación administrativa y judicial, nulidad, medidas cautelares, concesión de licencias, la tutela, la protección de secretos industriales, y en general los juicios civiles, penales, administrativos o contencioso-administrativos relacionados con estos derechos; acciones y procesos que promovamos o se nos promuevan. Y para que en todos los asuntos arriba determinados, puedan sustituir este mandato, transigir, conciliar, admitir los hechos del proceso, desistír, cancelar, recibir, renunciar, y ratificar los actos de agentes oficiosos.

In due compliance with the terms of paragraph 1st. of article 543 of the Commercial Code, do hereby appoint EMILIO FERRERO, tpa. 31929; GONZALO PERDOMO, tpa. 831; LUZ CLEMENCIA DE PAEZ, tpa. 23555 and GERMAN CAVELIER, tpa. 832, domiciled at Carrera 4ª N° 72-35, Bogotá, Colombia, the first as principal and the others as alternates, in the order of their appointment, as our representatives for all industrial property matters with faculty to receive notifications and to appoint attorneys in and out of Court. The first alternate shall replace the principal in case of his absence or of temporal or definitive impediment. The same rule will apply when the second alternate representative is to replace the first one, or when the third is to replace the first or second alternates in their turn, or both of them, second. In such cases, the principal representative, or the first or second alternates in their turn, or both of them, shall state their intention not to act as representatives through a declaration given before a Notary Public in Colombia, or before a Notary or another Public Official or a Colombian Consul abroad; and in case of impediment, the appropriate certificate shall suffice. If any of the appointees were to be definitely absent, the following alternate shall take his place. When the absence or impediment of the principal representative, or of the first or second alternate in their turn ceases, the representation can be taken again in their sequence, by the principal, the first or second alternate depending on case, and the mere fact or its exercise will suffice. The exercise of the representation by the first, second or third alternates in their turn shall end at such time.

In addition, I (we) confer Power of Attorney in favor of the above named attorneys, so that they may obtain the protection of my (our) industrial property and against the unfair competition, for which purpose I (we) authorize the said attorneys to represent me (us) before any authorities or persons, with or without jurisdiction, especially those administrative, administrative, contentious and judicial, as well as before Arbitration Courts, in all matters concerning the following: a) Obtaining of patents, utility models and industrial designs; the registration of trademarks, collective, defensive and service marks, slogans, commercial names, trade emblems, vegetal varieties and denominations of origin; its renewal, assignment, change of name or domicile, voluntary cancellation; and the registration of licenses of use of the above rights; b) Actions of unfair competition, protection to the consumer, oppositions or observations, administrative or Court cancellation, nullity, infringement, granting of licenses, the action for writ mandamus, the protection of trade secrets, and in general the civil, penal, and administrative suits relating to those rights; actions and suits instituted by me (us) or against me (us). And that in all the above matters they may substitute this Power of Attorney, compromise, conciliate, admit the facts of the case, desist, cancel, receive, resign, and ratify acts done by representatives without a power of attorney.

Given and signed this Day of August 1998

F.G.M. Hermans

In/en Director Patents Pharma

E.H. Reerink

Deputy Director

Legal Affairs

Signature

AKZO NOBEL N.V.

© CAVELIER ABOGADOS
WPPERERE-179 (MINUTA N° 12.1.1.2.5)

TRADUCCION No. 18.11.98
MARIA ELVIRA MACÍO LO
Traductora e Intérprete Oficial
Inglés - Español - Inglés
Res. No. 2279 Min. Justicia

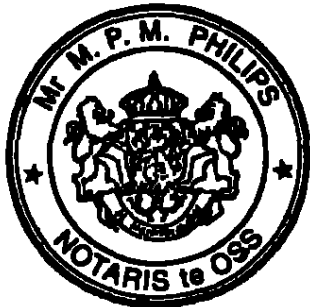
LEGALIZACION

El Señor Cónsul de Colombia debe expedir un certificado consular sobre (1) la existencia legal de la compañía que otorga el poder, (2) que ésta ejerce su objeto social, y (3) que las personas que otorgan el poder están autorizadas para darlo. A este efecto les solicitamos que muestren al Señor Cónsul las pruebas que acreditan esos hechos (1), (2) y (3).

LEGALIZATION

The Colombia Consul must issue a consular certificate on the legal existence of the company, (2) that it is in accordance with the Power-of-Authority, (2) that it is in accordance with the company purposes, and (3) that the persons who execute the Power of Attorney is authorized to do so. To this effect, please show the Consul the evidence to prove the above facts (1), (2) and (3).

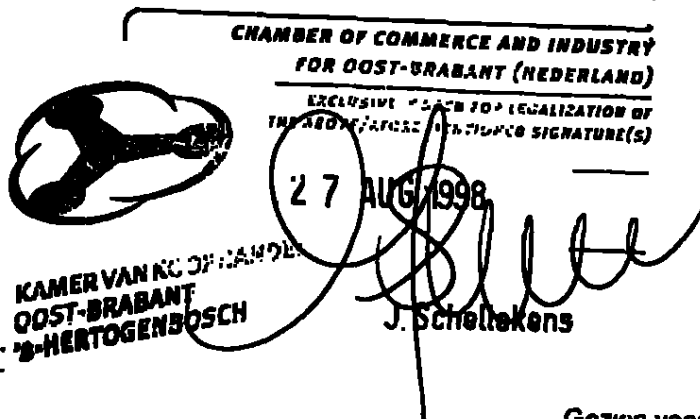
Seen for legalization of the signatures of Mr. F.G.M. Hermans and Mr. E.H. Reerink by me, Mr. Martinus Petrus Maria Philips, notary public at Oss, the Netherlands, on this 26th day of August 1998.



[Handwritten signature of M. P. M. Philips]

TRADUCCION No. 18/1/98
MARIA ELVIRA MARTEL
Traductora e Interprete Oficial
Inglés - Español - Inglés
Res. No. 2879 Min. Justicia

15499



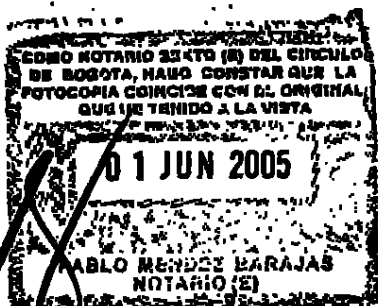
Gezien voor legalisatie van de handtekening van Ghr/mw *[Signature]* Schellekens

's-Gravenhage, 9 SEP 1998



De Minister van
Buitenlandse Zaken
voor deze,

Leges f 20,- H.H. van POORTEN



NOTA PARA EL SEÑOR CONSUL DE COLOMBIA: Según los artículos 65 del C. de P.C. y 480 del C. de Co., si el poderdante es una sociedad, el Señor Cónsul debe certificar que tuvo a la vista las pruebas de su existencia, que ejerce su objeto social y que quien confiere el poder es su representante.



CONSULADO DE COLOMBIA

COLO 11214-801-001-3

El suscrito Cónsul de Colombia en La Haya, Holanda,
vistos los documentos presentados por los interesados,

CERTIFICA:

Que el Señor **Martinus Petrus Maria PHILIPS**, quien como Notario Público de Oss, Países Bajos, autenticó las firmas de los signatarios del poder precedente, ejercía en la fecha las funciones indicadas, y su firma corresponde a la registrada en este Consulado.

Que la Compañía **AKZO NOBEL N.V.** es una Sociedad constituida de acuerdo con las leyes de los Países Bajos, cumple su objeto conforme a las mismas y se halla registrada en la Cámara de Comercio y Fábricas de Centraal Gelderland, Arnhem, bajo el número 09007809;

Que los Señores **Franciscus Guilielmus Maria HERMANS** y **Engbert Harmen REERINK**, signatarios del presente documento, quienes en su carácter de Apoderados de la Empresa **AKZO NOBEL N.V.**, conjuntamente tienen facultad para ello, y cuyas firmas fueron autenticadas ante el Notario Público de Oss, Señor **Martinus Petrus Maria PHILIPS**, son los representantes legales de la citada Empresa en este País.

El Cónsul de Colombia en La Haya, Países Bajos, no asume responsabilidad alguna por el contenido del documento.

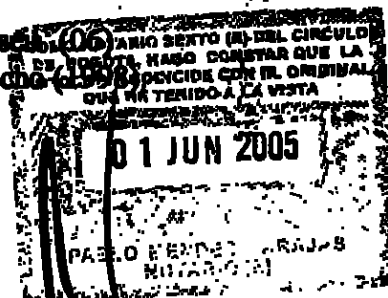
Esta certificación se expide en La Haya, Países Bajos, a los seis (06) días del mes de Noviembre de mil novecientos noventa y ocho (1998).

Impuesto de Timbre	US\$	6.00.
Derechos Consulares	US\$.	100.00
Costo Total Pagado	US\$.	106.00

Certificación No. 206


JOSE IGNACIO VILLEGAS CORTES
CONSUL DE COLOMBIA
LA HAYA

TRADUCCION No. 18.11.98
MARIA ELVIRA MARTELO C.
Traductora e Interprete Oficial
Inglés - Español - Inglés
Res. No. 2879 Min. Justicia



NO SE ASUME
RESPONSABILIDAD DEL TEXTO

MINISTERIO DE RELACIONES
EXTERIORES

90 NOV 19 11:56

300803

JEFE DE LEGACIONES
SANTO DOMINGO D.R.
NOTARIO (E) DEL C.R.
NOTA, HAGO CONSTAR QUE LA
COPIA CONCORDA CON EL ORIGINAL
QUE HE TENIDO A LA VISTA
01 JUN 2005
PABLO MENDEZ BARAJAS
NOTARIO (E)

CUYA FIRMA APARECE EN EL
DOCUMENTO DESEMPEÑA
LAS FUNCIONES INDICADAS

TRADUCCIÓN OFICIAL No. 18.11/98 preparada por María Elvira Martelo, Traductora Oficial debidamente aprobada por el Ministerio de Justicia de Colombia por Resolución 2879 de 1995 y reconocida por el Ministerio de Relaciones Exteriores.

(A continuación se traducen los sellos y legalizaciones de un documento escrito en inglés y español, por el cual AKZO NOBEL N.V. otorga poder a EMILIO FERRERO, GONZALO PERDOMO, LUZ CLEMENCIA DE PAEZ Y GERMAN CAVELIER). Dado y firmado el 6 de agosto de 1998. (Firma ilegible) F.G.M. Hermans, Director de Patentes Farmacéuticas. (Firma ilegible) E.H. Reerink, Subdirector de Asuntos Jurídicos. (Sello Corporativo) AKZO NOBEL N.V.

(Al dorso) Visto por mí, Sr. Martinus Petrus Maria Philips, notario público en Oss, Países Bajos, hoy 25 de agosto de 1998, para legalización de las firmas de F.G.M. Hermans y E.H. Reerink. (Firma ilegible).

(Legalización) CAMARA DE INDUSTRIA Y COMERCIO PARA OOST-BRABANT (PAÍSES BAJOS). Visto exclusivamente para la legalización de la(s) firma(s) que antecede(n). Agosto 27 de 1998. (Firma ilegible) J. Schellenkens.

(Sello en holandés).

(En español) Certificación de las firmas que anteceden y de la existencia legal de AKZO NOBEL N.V. expedida por el Consulado de Colombia en La Haya el día 6 de noviembre de 1998, bajo el No.

206. Firmado JOSE IGNACIO VILLEGAS CORTES, Cónsul de Colombia, La Haya. Pagado impuesto de timbre.

(Al dorso) Legalización de la firma que antecede expedida por el MINISTERIO DE RELACIONES EXTERIORES bajo el No. 300803 del 19 de NOVIEMBRE de 1998, firmado por el Jefe de Legalizaciones.

Es traducción fiel y completa de la cual se deja copia en esta oficina para su confrontación.

COLO 11214-801-001-3

Id. 6

Nov. 20/98

Maria E. Martelo
TRADUCCION No. *NC. 11198*
MARIA ELVIRA MARTELO
Traductora e Interprete Oficial
Inglés - Español - Inglés
Res. No. 2879 Min. Justicia

COMO NOTARIO SEXTO DEL CIRCULO DE SANTAFE DE BOGOTA, HAGO CONSTAR QUE LA(S) ANTERIOR(ES) FIRMA(S) FUE(EN) POR *[Firma]* IDENTIFICADOS CON C.C. No.(s) *[Firma]* ES(SON) AUTENTICA(S) SANTAFE DE BOGOTA, 23 NOV. 1998

COMO NOTARIO SEXTO (S) DEL CIRCULO DE BOGOTA, HAGO CONSTAR QUE LA FOTOCOPIA COINCIDE CON EL ORIGINAL QUE HE TUNIDO A LA VISTA
04 JUN 2005
PABLO MENDEZ PARAJAS
NOTARIO (S)

MINISTERIO DE RELACIONES EXTERIORES
198457
Maria Martelo
SUYA FIRMA APARECE EN EL DOCUMENTO DESEMPEÑA LAS FUNCIONES INDICADAS

NO SE ASUME RESPONSABILIDAD DEL TEXTO
98 NOV 24 PM 12:06
JEFE DE LEGALIZACIONES
SANTAFE DE BOGOTA D.C.

CAVELIER

ABOGADOS
EDIFICIO SISKI
CARRERA 4a Nº 7235
BOGOTÁ, COLOMBIA

374

2002.723 CO

CESSION

ASSIGNMENT

Yo, (nosotros) abajo firmado (a)

I (we), the undersigned

HERMKENS
Pedro, Harold, Han

STOCK
Herman, Thijs

VAN DER LOUW
Jaap

TEERHUIS
Neeltje, Miranda

LOMMERSE
Johannes, Petrus, Maria

domiciliado(s) en

of

N.V. Organon
P.O. Box 20
5340 BH Oss
The Netherlands

declaro(s) bajo juramento ser el/los inventor(es) de la
invención:

state(s) under oath to be sole and true inventor(s) of the invention:

INDOLES USEFUL IN THE TREATMENT OF ANDROGEN-RECEPTOR RELATED DISEASES.

indoles útiles en el tratamiento

de enfermedades relacionadas con el
receptor de andrógenos

declaro(s) mi/ nuestro que cada(una) y transfero(amos), sin
limitación, a favor de la sociedad

state(s) that I/ we assign, without reservations or limitations in favour of

- Akzo Nobel N.V.

constituida y existente de conformidad con las leyes de

a corporation constituted and existing in conformity with the laws of

domiciliada en

Velperweg 78
6824 BM Arnhem
The Netherlands

domicilled in

Todos los derechos inherentes a dicha invención y que la citada compañía queda
facultada para solicitar en su nombre la patente de invención correspondiente en
la República de Colombia.

all rights inherent to said invention and that the above mentioned company hereby
is enabled to apply, in its name, for the corresponding patent invention, in the
Republic of Colombia

Dado y firmado hoy/ Given and signed this

en/ta

Firma

Signature

HERMKENS
Pedro, Harold, Han

STOCK
Herman, Thijs

VAN DER LOUW
Jaap

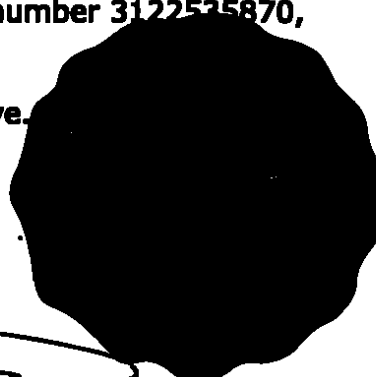
TEERHUIS
Neeltje, Miranda

LOMMERSE
Johannes, Petrus, Maria

Seen by me, mr. Robbert Alexander Gallas, civil-law notary practising in The Hague, for the authentication of the signatures on the attached document of:

- Mr Jaap van der Louw, born on the twenty-first of October of nineteenhundred sixty in Hoorn, The Netherlands, residing at Oss, The Netherlands, holder of a Dutch passport, number M24023283;
- Mrs Neeltje Miranda Teerhuis, born on the twenty-third day of October nineteenhundred sixty-nine in Purmerend, The Netherlands, residing at Wijkchen, The Netherlands, holder of a Dutch driver licence, number 3156380965;
- Mr Johannes Petrus Maria Lommerse, born on the twenty-ninth day of January nineteenhundred sixty-five in Hillegom, The Netherlands, residing at Oss, The Netherlands, holder of a Dutch drivers licence, number 3198737564; and
- Mr Herman Thijs Stock, born on the sixth day of November nineteenhundred sixty-four in Groningen, The Netherlands, residing at Oss, The Netherlands, holder of a Dutch passport, number M12729082;
- Mr Pedro Harold Han Hermkens, born on the first day of February nineteenhundred fifty-eight in Asten, The Netherlands, residing at Oss, The Netherlands, holder of a Dutch divers-licence, number 3122535870,

The Hague, the fourteenth day of April twothousandfive.



All instructions are carried out on the basis of an agreement as meant in Section 400 of Book 7 of the Dutch Civil Code by Pels Rijcken & Droogleevers Fortuijn, a partnership consisting of private companies with limited liability. The agreement is subject to terms of business registered with the District Court at The Hague. A limitation of liability is included in these terms of business. The terms of business will be provided on request. These can also be accessed at www.prdi.nl.

A P O S T I L L E

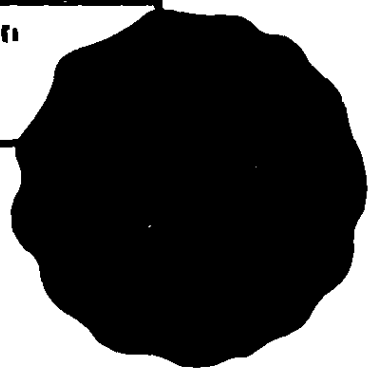
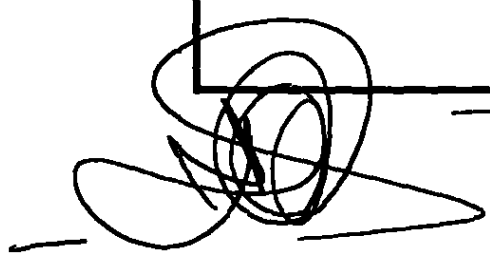
(Convención de La Haya de 5 octubre 1961)

1. País: Países Bajos
2. El presente documento público
3. ha sido firmado por mr. E.A. Gallas
4. Quien actúa en calidad de notario en 's-Gravenhage
5. y está revestido del sello/timbre de el susodicho notario

Certificado

6. La Haya 6. el día 15 april 2005
7. por El secretario Judicial de Tribunal del Distrito
8. bajo el número: 2005-1558
9. Sello/timbre: 10. Firma:

J. Heesterman



TRADUCCIÓN OFICIAL No. 04.22/04b realizada por Diego Vargas, Traductor Oficial, Resolución No. 0001 de 1999 del Ministerio de Justicia, registrado ante el Ministerio de Relaciones Exteriores de Colombia.

A continuación se traducen los sellos y legalizaciones de un documento de Cesión mediante el cual los señores HERMKENS, Pedro, Harold, Han; STOCK Herman, Thijs; VAN DER LOUW Jaap, TEERHUIS Neeltje, Miranda y LOMMERSE Johannes, Petrus, Maria, domiciliados en N.V. Organon, P.O. Box 20, 5340 BH Oss, Países Bajos, declaran bajo juramento ser únicos y verdaderos inventores de la invención: *"Indoles útiles en el tratamiento de enfermedades relacionadas con el receptor de andrógenos"* y declaran así mismo que ceden y transfieren, sin limitación, a favor de Akzo Nobel N.V. una sociedad constituida y existente de conformidad con las leyes de Países Bajos, domiciliada en Velperweg 76, 6824 BM ARNHEM, Países Bajos, todos los derechos inherentes a dicha invención y que dicha Compañía queda facultada para solicitar a su nombre la patente de invención correspondiente en la República de Colombia.

Firma Ilegible 7/4/2005
HERMKENS
Pedro, Harold, Han

Firma Ilegible 7/4/2005
STOCK
Herman, Thijs

Firma Ilegible 7/4/2005
VAN DER LOUW
Jaap

TEERHUIS
Neeltje, Miranda
Firma Ilegible 7/4/2005

LOMMERSE Firma Ilegible
Johannes, Petrus, Maria 7/4/2005

(Anexo)

Examinado por mí, el Señor Robbert Alexander Gallas, Notario Público ejerciendo en La Haya, para la autenticación de las firmas en el adjunto documento de:

- El señor Jaap van der Louw, nacido el veintiuno de octubre de mil novecientos sesenta en Hoorn, Países Bajos, residente en Oss, Países Bajos, portador del pasaporte holandés número M24023283.

- P*
- La señora Neeltje Miranda Teerhius, nacida el veintitrés de Octubre de mil novecientos sesenta y nueve en Purmerend, Países Bajos, residente en Wijchen, Países Bajos, portadora de la licencia de conducción holandesa número 3156380966.
 - El señor Johannes Pedrus Maria Lommerse, nacido el veintinueve de Enero de mil novecientos sesenta y cinco en Hillegom, Países Bajos, residente en Oss, Países Bajos, portador de la licencia de conducción holandesa número 3198737564; y
 - El señor Herman Thijs Stock, nacido el seis de Noviembre de mil novecientos sesenta y cuatro en Groningen, Países Bajos, domiciliado en Oss, Países Bajos, portador del pasaporte holandés número M12729082;
 - El señor Pedro Harold Han Hermkens, nacido el primero de febrero de mil novecientos cincuenta y ocho en Asten, Países Bajos, residente en Oss, Países Bajos, portador de la licencia de conducción holandesa número 3122535870

La Haya, catorce de abril de dos mil cinco.

Sello Notarial: Sr. R.A. GALLAS NOTARIS TE 's-GRAVENHAGE

Firma Ilegible

Sello de oblea ilegible

Todas las instrucciones se realizan basadas en un acuerdo, como se establece en la Sección 400 del Libro 7 del Código Civil Holandés por parte de Pels Rijcken & Droogleever Fortuijn, una sociedad conformada por sociedades privadas de responsabilidad limitada. El acuerdo está sujeto a términos comerciales registrados ante el Tribunal del Distrito en La Haya. Se incluye una limitación de responsabilidad en estos términos comerciales. Los términos comerciales serán suministrados a petición. Estos también pueden ser consultados en www.pdf.nl.

(RESPALDO)

Sello de Apostille expedido por Países Bajos y certificado en La Haya el 15 de abril de 2005 con el número 2005-1558 y firmado por J. Heesterman.

Es traducción fiel y completa de la cual se deja copia en esta oficina para su confrontación.

DVZ/ID-6694/WPCL002G/COLO 11214-841-029-6

Diego F. Vargas
DIEGO F. VARGAS Z.
TRADUCTOR E INTERPRETE OFICIAL
ESPAÑOL - INGLÉS - INGLÉS - ESPAÑOL
RES. 0001 DE ENERO 4 DE 1999
MINISTERIO DE JUSTICIA

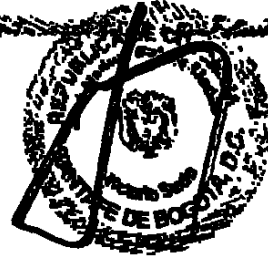
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Diego Jarama
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DOCUMENTO REEMPLAZA
LAS FUNCIONES DE LOS

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JEFE DE LEGALIZACIONES
SANTAFE DE BOGOTA D.C.

COMO NOTARIO SEXTO DEL CIRCULO DE SANTAFE DE
BOGOTA, JUNGO CONSTAR QUE LA(S) FIRMA(S) DE
Diego Jarama
Diego Jarama
COINCIDE(N) CON LA FIRMA REGISTRADA POR
EL (ELLOS) EN ESTA NOTARIA
SANTAFE DE BOGOTA.
29 APR 2005



**DOCUMENTOS ANEXOS**

1. ☒ **Publicación Internacional WO 2004/041782 A1**

Descripción:

Páginas 1-64 en el idioma original

Páginas 1-71 en español

Reivindicaciones: Número (s) 1-20

Figuras: Número (s) _____

2. ☒ **Forma PCT/RO/101. PCT Request**
3. ☐ **Forma PCT/RO/106. Invitation to Correct Defects.**
4. ☒ **Forma PCT/ISA/210. Informe de Búsqueda Internacional.**
5. ☒ **Forma PCT/ISA/220. Notificación De La Transmisión Del Informe De Búsqueda Internacional Y De La Opinión Escrita De La Administración Encargada De La Búsqueda Internacional, O De La Declaración.**
6. ☐ **Forma PCT/ISA/237. Opinión Escrita De La Administración Encargada De La Búsqueda Internacional.**
7. ☐ **Forma PCT/IB/304. Notification Concerning Submission Or Transmittal Of Priority Document.**
8. ☐ **Forma PCT/IB/306. Notification Of The Recoding Of A Change.**
Descripción De Modificación:

9. ☐ **Forma PCT/IB/308. Notice Informing The Applicant Of The Communication Of The International Application To The Designated Offices.**
10. ☐ **Forma PCT/IB/332. Information Concerning Elected Offices Notified Of Their Election.**
11. ☒ **Forma PCT/IPEA/401. PCT Demand**
12. ☐ **Forma PCT/IPEA/402. Notification Of Receipt Of Demand By Competent International Preliminary Examining Authority.**
13. ☐ **Forma PCT/IPEA/408. Written Opinion.**
14. ☒ **Forma PCT/IPEA/416. Notification Of Transmittal Of The International Preliminary Examination Report.**
15. ☒ **Forma PCT/IPEA/409. Informe Del Examen Preliminar Internacional.**
16. ☐ **Traducción Al Español Del Informe Del Examen Preliminar Internacional.**
17. ☐ **Traducción Al Español De Los Anexos Presentados Junto Con El Informe Del Examen Preliminar Internacional.**

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DER LOUW, Jaap [NL/NL]; N.V. Organon, P.O. Box 20,
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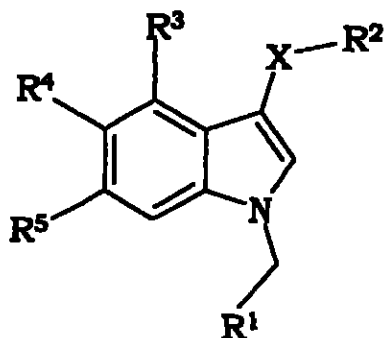
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For two-letter codes and other abbreviations, refer to the "Guid-
ance Notes on Codes and Abbreviations" appearing at the begin-
ning of each regular issue of the PCT Gazette.

(54) Title: INDOLES USEFUL IN THE TREATMENT OF ANDROGEN-RECEPTOR RELATED DISEASES



(1)

(57) Abstract: This invention provides non-steroidal compounds with affinity for the androgen receptor and utility for androgen-receptor related treatments, having a structure according to the formula (1) wherein X is S, SO or SO₂; R¹ is a 5- or 6-membered monocyclic, hetero- or homocyclic, saturated or unsaturated ring structure optionally substituted with one or more substituents selected from the group consisting of halogen, CN, (1C-4C)fluoroalkyl, nitro, (1C-4C)alkyl, (1C-4C)alkoxy or (1C-4C)fluoroalkoxy; R² is 2-nitrophenyl, 2-cyanophenyl, 2-hydroxymethyl-phenyl, pyridin-2-yl, pyridin-2-yl-N-oxide, 2-benzamide, 2-benzoic acid methyl ester or 2-methoxyphenyl; R³ is H, halogen or (1C-4C)alkyl; R⁴ is H, OH, (1C-4C)alkoxy, or halogen; R⁵ is H, OH, (1C-4C)alkoxy, NH₂, CN, halogen, (1C-4C)fluoroalkyl, NO₂, hydroxy(1C-4C)alkyl, CO₂H,

CO₂(1C-6C)alkyl, or R³ is NHR⁶, wherein R⁶ is (1C-6C)acyl optionally substituted with one or more halogens, S(O)₂(1C-4C)alkyl, or S(O)₂aryl optionally substituted with (1C-4C)alkyl or one or more halogens, or R³ is C(O)N(R⁸,R⁹), wherein R⁸ and R⁹ each independently are H, (3C-6C)cycloalkyl, or CH₂R¹⁰, wherein R¹⁰ is H, (1C-5C)alkyl, (1C-5C)alkenyl, hydroxy(1C-3C)alkyl, (1C-4C)alkylester of carboxy(1C-4C)alkyl, (1C-3C)alkoxy(1C-3C)alkyl, (mono- or di(1C-4C)alkyl)aminomethyl, (mono- or di(1C-4C)alkyl)aminocarbonyl, or a 3-, 4-, 5- or 6-membered monocyclic, homo- or heterocyclic, aromatic or non-aromatic ring, or R⁸ and R⁹ form together with the N a heterocyclic 5- or 6-membered saturated or unsaturated ring optionally substituted with (1C-4C)alkyl; or a salt or hydrate form thereof.

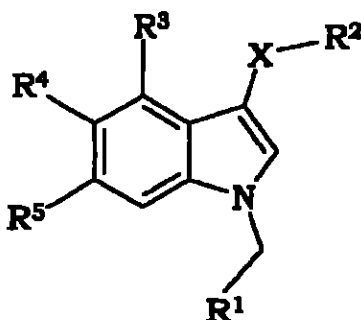
INDOLES USEFUL IN THE TREATMENT OF ANDROGEN-RECEPTOR RELATED DISEASES

The invention relates to indole derivatives, their preparation and their use for the treatment of androgen-receptor related conditions, disorders or diseases and other androgen related treatments.

Compounds possessing androgenic activity are useful in the treatment of men with low endogenous levels of circulating androgenic hormones or men with suppressed androgenic effects. Such treatments are prescribed to older men, to hypogonadal men or men treated with progestagens for male contraception. In addition, potent androgens suppress spermatogenesis and can be used as male contraceptives.

It is thus important to obtain compounds with high affinity for the androgen receptor. Non-steroidal compounds with high affinity for the androgen receptor are particularly useful since they may have different tissue distribution characteristics than steroidal androgens and can be designed by proper choice of substituents to be more or less selective for certain tissues. For example, an action in the brain is usually prevented when compounds are strongly hydrophilic or carry an ionic charge.

The subject invention provides non-steroidal compounds with affinity for the androgen receptor. These compounds are potentially useful for the treatment of androgen-receptor related disorders or disorders which can be treated with androgens. The compounds of the subject invention have a structure according to formula I:



wherein

X is S, SO or SO₂:

R^1 is a 5- or 6-membered monocyclic, hetero- or homocyclic, saturated or unsaturated ring structure optionally substituted with one or more substituents selected from the group consisting of halogen, CN, (1C-4C)fluoroalkyl, nitro, (1C-4C)alkyl, (1C-4C)alkoxy or (1C-4C)fluoroalkoxy;

5 R^2 is 2-nitrophenyl, 2-cyanophenyl, 2-hydroxymethyl-phenyl, pyridin-2-yl, pyridin-2-yl-N-oxide, 2-benzamide, 2-benzoic acid methyl ester or 2-methoxyphenyl;

R^3 is H, halogen or (1C-4C)alkyl;

R^4 is H, OH, (1C-4C)alkoxy, or halogen;

R^5 is H, OH, (1C-4C)alkoxy, NH_2 , CN, halogen, (1C-4C)fluoroalkyl, NO_2 ,

10 hydroxy(1C-4C)alkyl, CO_2H , $CO_2(1C-6C)alkyl$, or R^5 is NHR^6 , wherein R^6 is (1C-6C)acyl optionally substituted with one or more halogens, $S(O)_2(1C-4C)alkyl$, or

$S(O)_2aryl$ optionally substituted with (1C-4C)alkyl or one or more halogens, or

R^5 is $C(O)N(R^8, R^9)$, wherein R^8 and R^9 each independently are H, (3C-6C)cycloalkyl,

or CH_2R^{10} , wherein R^{10} is H, (1C-5C)alkyl, (1C-5C)alkenyl, hydroxy(1C-3C)alkyl,

15 (1C-4C)alkylester of carboxy(1C-4C)alkyl, (1C-3C)alkoxy(1C-3C)alkyl, (mono- or

di(1C-4C)alkyl)aminomethyl, (mono- or di(1C-4C)alkyl)aminocarbonyl, or a 3-, 4-, 5-

or 6-membered monocyclic, homo- or heterocyclic, aromatic or non-aromatic ring, or

R^8 and R^9 form together with the N a heterocyclic 5- or 6-membered saturated or

unsaturated ring optionally substituted with (1C-4C)alkyl;

20 or a salt or hydrate form thereof.

In one embodiment R^1 is a 5- or 6-membered monocyclic, hetero- or homocyclic, saturated or unsaturated ring structure optionally substituted with one or more

substituents selected from the group consisting of halogen, CN, CF_3 , nitro, methoxy,

25 trifluoromethoxy or methyl; R^2 is 2-nitrophenyl, 2-cyanophenyl, 2-hydroxymethyl-

phenyl, pyridin-2-yl, pyridin-2-yl-N-oxide, 2-benzamide, 2-benzoic acid methyl ester or

2-methoxyphenyl; R^3 is H, halogen or (1C-2C)alkyl; R^4 is H or F.

In another embodiment R^5 is H, OH, (1C-4C)alkoxy, CN, halogen, (1C-4C)fluoroalkyl,

30 NO_2 , hydroxy(1C-4C)alkyl, $CO_2(1C-6C)alkyl$, or R^5 is NHR^6 , wherein R^6 is (1C-

6C)acyl optionally substituted with one or more halogens, $S(O)_2(1C-4C)alkyl$, or

$S(O)_2aryl$ optionally substituted with (1C-4C)alkyl or one or more halogens, or

R^5 is $C(O)N(R^8, R^9)$, wherein R^8 and R^9 each independently are H, (3C-6C)cycloalkyl, or CH_2R^{10} , wherein R^{10} is H, (1C-5C)alkyl, (1C-5C)alkenyl, hydroxy(1C-3C)alkyl, (1C-4C)alkylester of carboxy(1C-4C)alkyl, (1C-3C)alkoxy(1C-3C)alkyl, (mono- or di(1C-4C)alkyl)aminomethyl, (mono- or di(1C-4C)alkyl)-aminocarbonyl, or a 3-, 4-, 5- or 6-membered monocyclic, homo- or heterocyclic, aromatic or non-aromatic ring, or R^8 and R^9 form together with the N a heterocyclic 5- or 6-membered saturated or unsaturated ring optionally substituted with (1C-4C)alkyl.

In yet another embodiment R^3 is H or halogen; R^4 is H; R^5 is H, OH, (1C-4C)alkoxy, CN, F, Cl, CF_3 , NO_2 , hydroxy(1C-4C)alkyl, $CO_2(1C-6C)$ alkyl, or R^5 is NHR^6 , wherein R^6 is (1C-3C)acyl optionally substituted with one or more halogens or R^5 is $C(O)N(R^8, R^9)$, wherein R^8 and R^9 each independently are H, (3C-5C)cycloalkyl, or CH_2R^{10} , wherein R^{10} is H, (1C-5C)alkyl, (1C-5C)alkenyl, hydroxy(1C-3C)alkyl, (1C-2C)alkylester of carboxy(1C-2C)alkyl, (1C-3C)alkoxy(1C-3C)alkyl, (mono- or di(1C-4C)alkyl)aminomethyl, (mono- or di(1C-4C)alkyl)aminocarbonyl, (3C-5C)cycloalkyl, or a 5-membered heterocyclic ring.

In yet another embodiment X is S or SO_2 ; R^2 is 2-nitrophenyl, 2-hydroxymethyl-phenyl, 2-benzamide, 2-methoxyphenyl, 2-cyanophenyl or pyridin-2-yl; R^3 is H or F; R^5 is H, OH, (1C-2C)alkoxy, CN, F, Cl, CF_3 , NO_2 , hydroxy(1C-4C)alkyl, $CO_2(1C-4C)$ alkyl, or R^5 is NHR^6 , wherein R^6 is formyl, acetyl, fluoroacetyl, difluoroacetyl, or trifluoroacetyl, or R^5 is $C(O)N(R^8, R^9)$, wherein R^8 is H, and R^9 is H, cyclopropyl or R^9 is CH_2R^{10} , wherein R^{10} is H, (1C-2C)alkyl, hydroxy(1C-2C)alkyl, methoxy(1C-2C)alkyl, cyclopropyl.

In yet another embodiment X is S; R^1 is 3,5-difluorophenyl, pyridin-2-yl, pyridin-3-yl, pyrimidin-5-yl, pyrimidin-4-yl, pyrazin-2-yl, 3-fluorophenyl, 3-cyanophenyl, or 3-nitrophenyl; R^2 is 2-nitrophenyl, 2-hydroxymethyl-phenyl, 2-methoxyphenyl, 2-cyanophenyl or pyridin-2-yl; R^3 is H; R^5 is OH, (1C-2C)alkoxy, CN, CF_3 , NO_2 , hydroxy(1C-4C)alkyl, $CO_2(1C-4C)$ alkyl, or NHR^6 , wherein R^6 is formyl, acetyl, fluoroacetyl, difluoroacetyl, or trifluoroacetyl.

In yet another embodiment R^1 is 3,5-difluorophenyl, pyridin-2-yl, pyridin-3-yl, pyrimidin-5-yl, pyrimidin-4-yl, or pyrazin-2-yl; R^2 is 2-nitrophenyl, or 2-hydroxymethyl-phenyl; R^5 is OH, (1C-2C)alkoxy, CN, hydroxy(1C-4C)alkyl, or NHR^6 , wherein R^6 is formyl, acetyl, fluoroacetyl, difluoroacetyl, or trifluoroacetyl.

5

In yet another embodiment R^1 is 3,5-difluorophenyl, pyridin-2-yl, pyridin-3-yl, pyrimidin-5-yl, or pyrimidin-4-yl; R^2 is 2-nitrophenyl; R^5 is OH, (1C-2C)alkoxy, CN, or NHR^6 , wherein R^6 is formyl, acetyl, fluoroacetyl, difluoroacetyl, or trifluoroacetyl.

- 10 In a specific embodiment the subject invention provides the compounds 6-Methoxy-3-(2-nitro-phenylsulfanyl)-1-pyrimidin-5-ylmethyl-1*H*-indole, 3-(2-Nitro-phenylsulfanyl)-1-pyridin-2-ylmethyl-1*H*-indole-6-carbonitrile, 3-(2-Nitro-phenylsulfanyl)-1-pyridin-2-ylmethyl-1*H*-indole-6-carbonitrile-hydrochloride, 3-(2-Nitro-phenylsulfanyl)-1-pyrimidin-5-ylmethyl-1*H*-indole-6-carbonitrile, 3-(2-Nitro-phenylsulfanyl)-1-pyrimidin-4-ylmethyl-1*H*-indole-6-carbonitrile, *N*-[1-(3,5-Difluoro-benzyl)-3-(2-nitro-phenylsulfanyl)-1*H*-indol-6-yl]-2-fluoro-acetamide, and *N*-[3-(2-Nitro-phenylsulfanyl)-1-pyrimidin-5-ylmethyl-1*H*-indol-6-yl]-formamide.
- 15

- In another embodiment X is S; R^1 is 3,5-difluorophenyl, pyridin-2-yl, pyridin-3-yl, 3-fluorophenyl, 3-cyanophenyl, or 3-nitrophenyl; R^2 is 2-nitrophenyl, 2-hydroxymethyl-phenyl, 2-methoxyphenyl, 2-cyanophenyl or pyridin-2-yl; R^3 is H; R^5 is $C(O)N(R^8, R^9)$, wherein R^8 is H, and R^9 is H, or CH_2R^{10} , wherein R^{10} is H, (1C-2C)alkyl, hydroxy(1C-2C)alkyl, or methoxy(1C-2C)alkyl.
- 20

- 25 In yet another embodiment R^1 is 3,5-difluorophenyl, pyridin-2-yl, or pyridin-3-yl; R^2 is 2-nitrophenyl, or 2-hydroxymethyl-phenyl; R^5 is $C(O)N(R^8, R^9)$, wherein R^8 is H, and R^9 is CH_2R^{10} , wherein R^{10} is H, or (1C-2C)alkyl.

- In a specific embodiment the subject invention provides the compound 1-(3,5-Difluoro-benzyl)-3-(2-nitro-phenylsulfanyl)-1*H*-indole-6-carboxylic acid methylamide.
- 30

In yet another embodiment X is S; R¹ is 3,5-difluorophenyl, pyridin-2-yl, pyridin-3-yl, 3-fluorophenyl, 3-cyanophenyl, or 3-nitrophenyl; R² is 2-nitrophenyl, 2-hydroxymethyl-phenyl, 2-methoxyphenyl, 2-cyanophenyl or pyridin-2-yl; R³ is H; R⁵ is C(O)N(R⁸,R⁹), wherein R⁸ and R⁹ each independently are H or CH₂R¹⁰, wherein R¹⁰ is H, (1C-5C)alkyl, (1C-5C)alkenyl, hydroxy(1C-3C)alkyl, (1C-3C)alkoxy(1C-3C)alkyl, or (mono- or di(1C-4C)alkyl)aminomethyl.

In yet another embodiment R¹ is 3,5-difluorophenyl, pyridin-2-yl, or pyridin-3-yl; R² is 2-nitrophenyl, or 2-hydroxymethyl-phenyl; R⁵ is C(O)N(R⁸,R⁹), wherein R⁸ and R⁹ each independently are H, or CH₂R¹⁰, wherein R¹⁰ is H, (1C-5C)alkyl, hydroxy(1C-3C)alkyl, or (1C-3C)alkoxy(1C-3C)alkyl.

In a specific embodiment the subject invention provides the compound 1-(3,5-Difluorobenzyl)-3-(2-nitro-phenylsulfanyl)-1*H*-indole-6-carboxylic acid dimethylamide.

In those cases that a compound of the invention contains a basic amine function, the compound may be used as a free base or as a pharmaceutically acceptable salt such as hydrochloride, acetate, oxalate, tartrate, citrate, phosphate, maleate or fumarate.

A compound according to the invention is a compound as defined above, a salt thereof, a hydrate thereof or a prodrug thereof.

The terms used in this description have the following meaning:

alkyl is a branched or unbranched alkyl group, for example methyl, ethyl, propyl, isopropyl, butyl, sec-butyl, tert-butyl, hexyl, and the like;

fluoroalkyl is an alkyl group substituted with one or more fluorine atoms;

cycloalkyl is a cyclized unbranched alkyl group, such as cyclopropyl, cyclobutyl, cyclopentyl and the like;

alkenyl is a branched or unbranched alkenyl group, such as ethenyl, 2-butenyl, etc.;

alkoxy is a branched or unbranched alkyloxy group, for example methyloxy, ethyloxy,

propyloxy, isopropyloxy, butyloxy, sec-butyloxy, tert-butyloxy and the like;

fluoroalkoxy is a alkoxy group substituted with one or more fluorine atoms;

aryl is a mono- or polycyclic, homo- or heterocyclic aromatic ring system, such as phenyl, naphthyl or pyridyl; a monocyclic ring with 6 atoms is preferred for use;

acyl is a (substituent-)carbonyl group, such as an aroyl or alkanoyl;

aroyl is arylcarbonyl such as a benzoyl group;

alkanoyl means a formyl or alkylcarbonyl group such as formyl, acetyl and propanoyl;

carboxy is a -COOH substituent, making the compound an organic acid;

carboxylate is a salt of a carboxyl substituent.

- 5 The prefixes (1C-4C), (2C-4C) etc. have the usual meaning to restrict the meaning of the indicated group to those with 1 to 4, 2 to 4 etc. carbon atoms; halogen refers to fluorine, chlorine, bromine and iodine.

10 The androgen receptor affinity and efficacy of the compounds according to the invention make them suitable for use in the treatment of androgen-receptor related disorders, disorders which can be treated with androgens, and in diagnostic methods focussed on the amount and/or location of androgen receptors in various tissues. For the latter purpose it can be preferred to make labelled variants of the compounds according to the invention. Typical androgen receptor-related treatments are those for male
15 contraception and male or female hormone replacement therapy. Thus the invention also pertains to a method of treatment of androgen insufficiency, by administering to a male or female human or animal an effective amount of any of the compounds of the subject invention. The subject invention also lies in the use of any of its compounds for the preparation of a medicine for treating androgen insufficiency. In the context of the
20 invention, the term "androgen insufficiency" is to be understood to pertain to all kinds of diseases, disorders, and symptoms in which a male or a female suffers from too low a testosterone level, such as in hypogonadal men or boys. In particular, the androgen insufficiency to be treated by a compound of the invention is the reduction of the testosterone level which a male individual incurs as a result of age (the compound of the
25 invention is then used for male hormone replacement therapy), or when he is subject to male contraception. In the context of male contraception, the compound of the invention especially serves to neutralise the effect of regimens of male hormone contraception in which a sterilitant such as a progestagen or LHRH (luteinizing hormone releasing hormone) is administered regularly, e.g. daily, or it is used as the sole male
30 contraceptive substance.

Thus, the subject invention provides any one of the compounds of the subject invention for use in therapy.

35 The subject invention further encompasses a pharmaceutical composition comprising a compound of the subject invention and a pharmaceutically acceptable carrier. In an embodiment of the subject invention, the pharmaceutical composition is for the

treatment of a disorder selected from the group consisting of an androgen-receptor related disorder, an androgen related disorder and androgen insufficiency.

The subject invention further provides a use of a compound of the invention for the manufacture of a medicament for the treatment of androgen-receptor related disorders, androgen related disorders and androgen insufficiency.

The subject invention further envisions a method of treating a disorder selected from the group consisting of an androgen-receptor related disorder, an androgen related disorder and androgen insufficiency comprising administering a pharmaceutically effective amount of a compound according to the invention to a subject in need thereof.

The compounds of the invention may further be useful for the treatment of osteoporosis, as well as other bone disorders, bone fraction repair, sarcopenia, frailty, skin aging, male hypogonadism, female sexual dysfunction, postmenopausal symptoms, atherosclerosis, aplastic anemia, muscular atrophy, lipodystrophy, reduced muscle strength and function, side effects of chemotherapy, chronic fatigue syndrome, benign prostate hyperplasia (BPH), cachexia, chronic catabolic state, cognitive impairment, male contraception, and others.

The compounds of the invention may be administered in conjunction with estrogens, progestogen and other androgens.

The compounds of the invention can be produced by various methods known in the art of organic chemistry in general. More specifically the routes of synthesis as illustrated in the following schemes and examples can be used. In the schemes and examples the following abbreviations were used:

DMF = dimethylformamide

mCPBA = *meta* chloro perbenzoic acid

THF = tetrahydrofuran

TBTU = 2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate

DIPEA = diisopropylethylamine

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

HOBt = 1-hydroxybenzotriazole

NMM = N-methylmorpholine

SPE = solid phase extraction

RP-SPE = reversed phase solid phase extraction

5 DMSO = dimethylsulfoxide

DCM = dichloromethane

DHT = 5 α -dihydrotestosterone

NMP = 1-methyl-2-pyrrolidinone

DMS = dimethyl sulfide

10

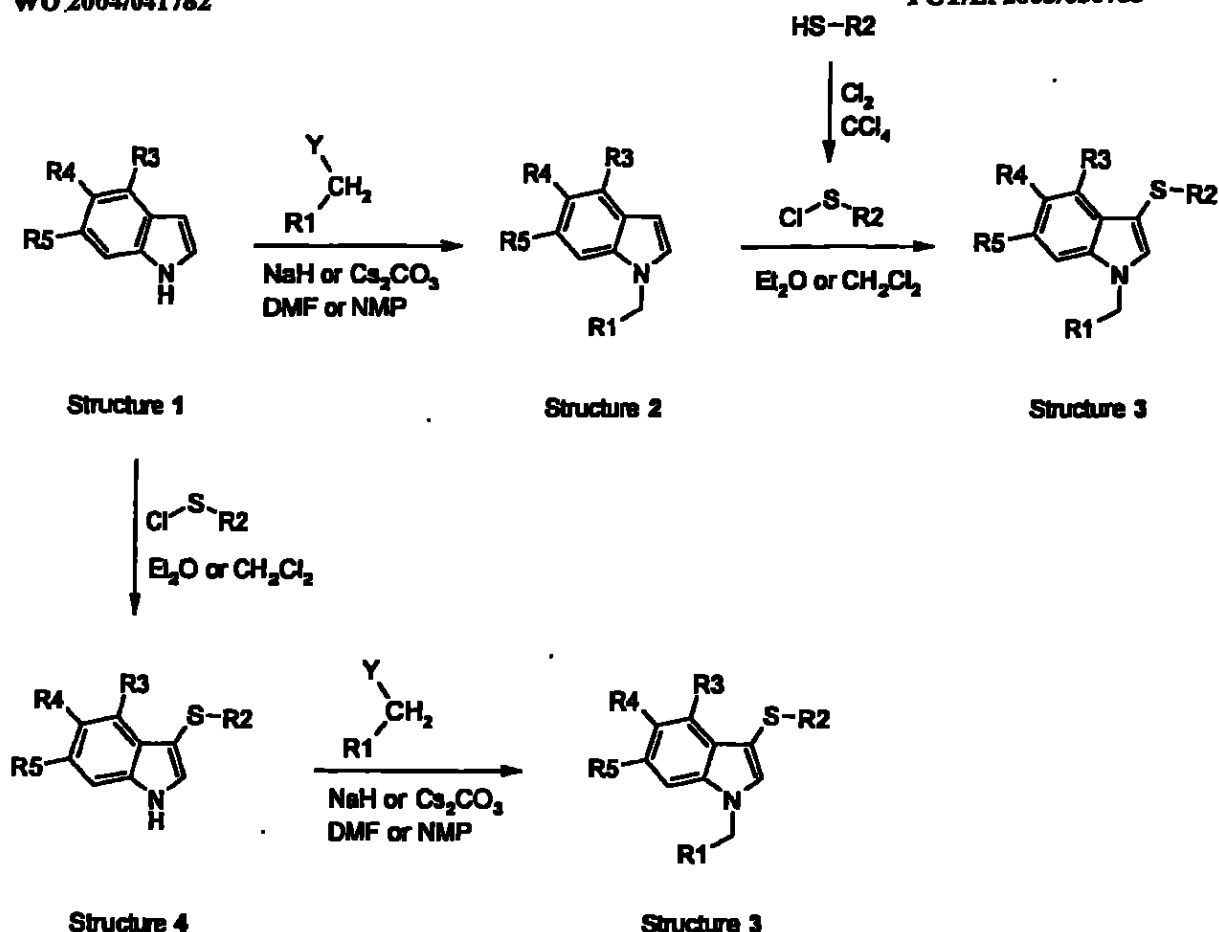
With regard to nomenclature the following trivial names are used interchangeably for substituents R¹ and R²:

	<u>Trivial name</u>	<u>Official name</u>
	2-pyridyl	pyridin-2-yl
15	3-pyridyl	pyridyl-3-yl
	4-pyridyl	pyridyl-4-yl
	3,5-pyrimidyl	pyrimidin-5-yl
	2,4-pyrimidyl	pyrimidin-4-yl
	2,5-pyrazyl	pyrazin-2-yl
20	etc.	

In each of the Schemes I-VII the meanings of the symbols correspond to the definitions given in the previous paragraphs.

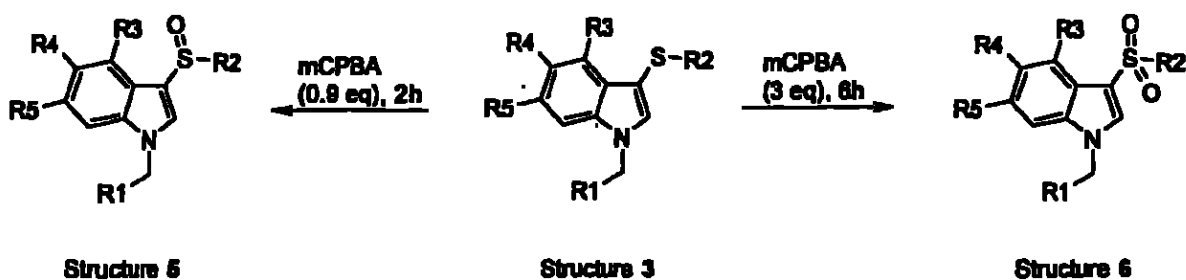
25 Substituted indole compounds of structure 3 were prepared in two steps from the correctly substituted indoles of structure 1, via two different routes. In the first route a correctly substituted indole of structure 1 is N-alkylated with a halide of type R¹CH₂Y, where Y is a halogen, mesylate or tosylate, with NaH or Cs₂CO₃ as a base in DMF or NMP at 0°C to room temperature, to give a compound of structure 2. Structure 2 is then
30 sulfanylated at the C-3 position of the indole ring by reaction with a sulfenyl chloride in either CH₂Cl₂ or diethyl ether at room temperature, to give structure 3. In the second route the two steps of the first route are reversed: the correctly substituted indole of structure 1 is first sulfanylated at the C-3 position of the indole to give structure 4, followed by N-alkylation with R¹CH₂Y to give structure 3 (Scheme I).

35



Scheme I

- 5 Sulfoxides of structure 5 can be obtained by oxidation of the corresponding sulfide (Structure 3) by reaction with e.g. 0.9 equivalents of mCPBA. Sulfones of structure 6 can be obtained by oxidation of the corresponding sulfide (Structure 3) by reaction with e.g. 3 equivalents of mCPBA (Scheme II).

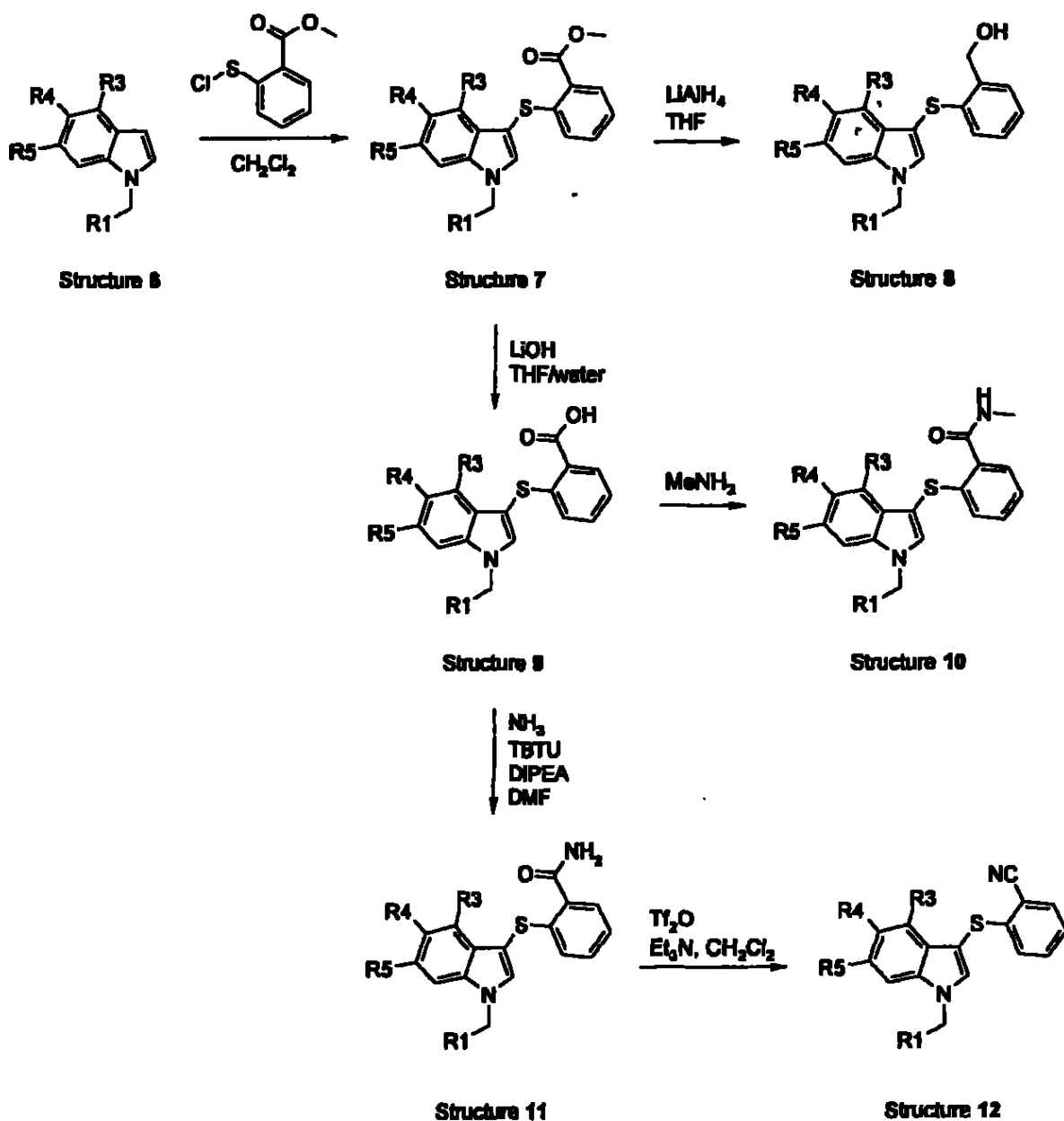


Scheme II

10

Scheme III describes the synthesis of compounds of structure 3, in which the R² group is a phenyl ring substituted on the 2-position with either CO₂Me (Structure 7), CH₂OH

(Structure 8), CO₂H (Structure 9), CONHMe (Structure 10), CONH₂ (Structure 11) or CN (Structure 12).



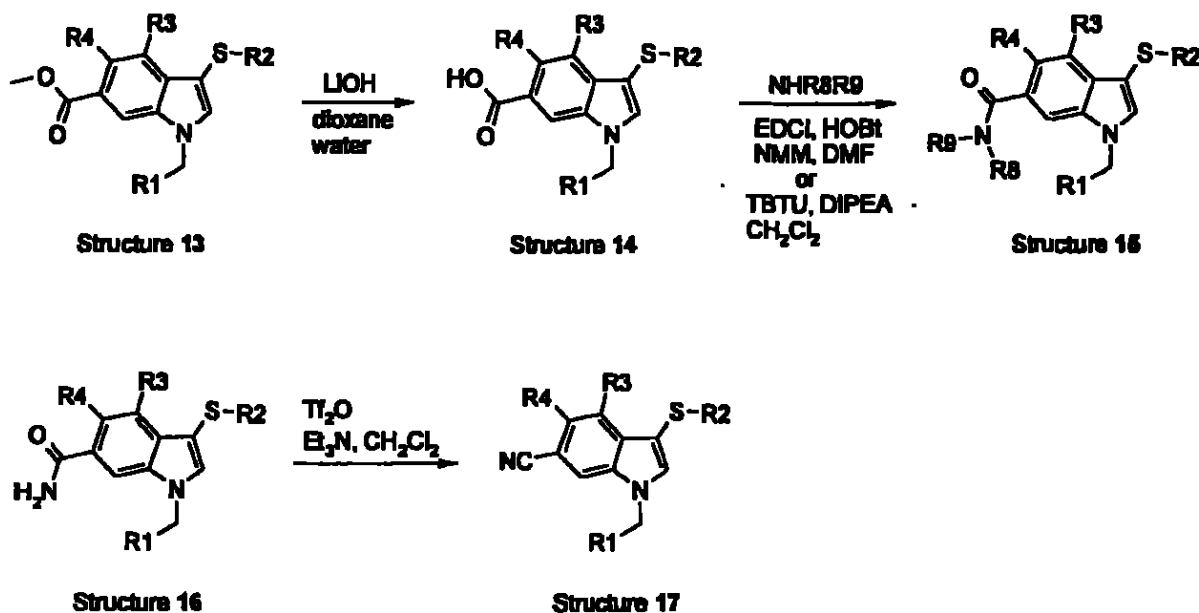
Scheme III

5

In the first step a substituted indole of structure 6 is sulfanylated at the 3-position with 2-(carboxymethyl)-phenylsulfonyl chloride, which was prepared from methylthiosalicylate and chlorine gas, to give a compound of structure 7. Reduction of the methyl ester moiety of compounds of structure 7 with LiAlH₄ gave the corresponding hydroxymethyl compounds of structure 8. Saponification of the methyl

10

ester moiety of compounds of structure 7 with lithium hydroxide gave the corresponding carboxylic acid compounds of structure 9. The carboxylic acid moiety of compounds of structure 9 can be converted to the corresponding carboxamide by reaction with an amine, TBTU and DIPEA in DMF at room temperature. By this method structure 10 was obtained when methylamine was used as the amine and structure 11 was obtained when NH_3 was used as the amine. Dehydration of the benzamide moiety of structure 11 with TiF_4 and triethylamine in CH_2Cl_2 afforded the corresponding benzonitrile compound of structure 12 (Scheme III).

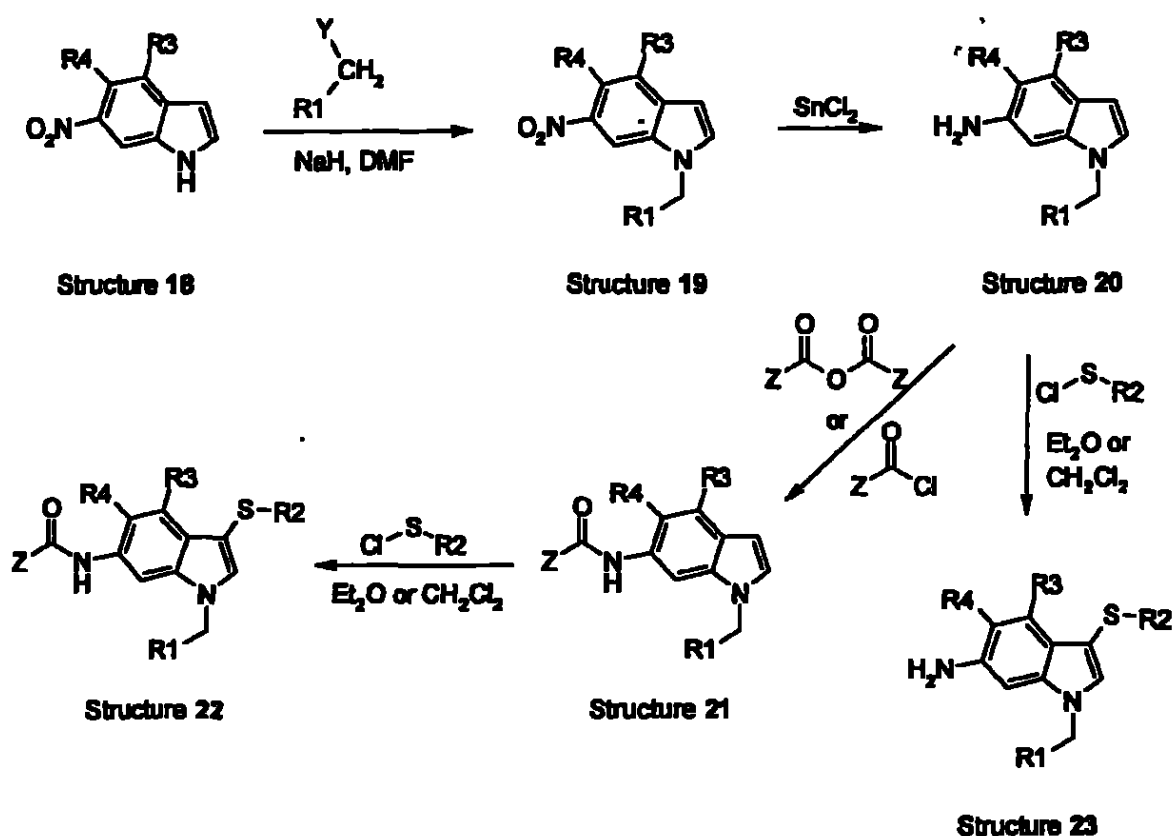


Scheme IV

Scheme IV describes the synthesis of compounds of structure 3, in which the indole ring is substituted at the 6-position with either CO_2Me (Structure 13), CO_2H (Structure 14), CONR^8R^9 (Structure 15), CONH_2 (Structure 16) or CN (Structure 17).

Saponification of the methyl ester moiety of structure 13 with lithium hydroxide afforded the corresponding carboxylic acid of structure 14. The carboxylic acid moiety of structure 14 can be converted to the corresponding carboxamides of structures 15 and 16 by reaction with an amine or amine salt, in the presence of EDCI and HOBT in a mixture of NMM and DMF or in the presence of TBTU and DIPEA in CH_2Cl_2 at room temperature. Dehydration of the benzamide moiety of structure 16 with TiF_4 and

triethylamine in CH_2Cl_2 afforded the corresponding benzonitrile compound of structure 17 (Scheme IV).



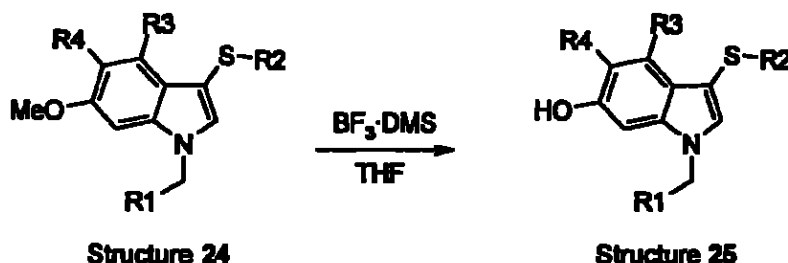
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Scheme V

Scheme V describes the synthesis of compounds of structure 22 containing an acylated amine functionality on the 6-position of the indole ring. These compounds can be synthesised from 6-nitro indoles of structure 18 in 4 steps. In the first step the indole of structure 18 is alkylated on the nitrogen atom by reaction of a halide of type $\text{R}^1\text{CH}_2\text{Y}$, in which Y is halogen, mesylate or tosylate, with NaH as a base in DMF to give compounds of structure 19. In the second step the nitro group of structure 19 is reduced to an amine group by SnCl_2 to give structure 20. Subsequent acylation of the amine group with an acid chloride of type ZCOCl afforded structure 21, which was then sulfanylated at the 3-position of the indole ring by reaction with a sulfonyl chloride in either CH_2Cl_2 or Et_2O as a solvent, at room temperature, to give compounds of structure

22. Direct sulfanylation of a compound of structure 20 with a sulfenyl chloride afforded structure 23

5 In Scheme VI is described how methyl ethers of structure 24 can be cleaved with e.g. $\text{BF}_3 \cdot \text{DMS}$ in THF at room temperature to hydroxy compounds of structure 25.



Scheme VI

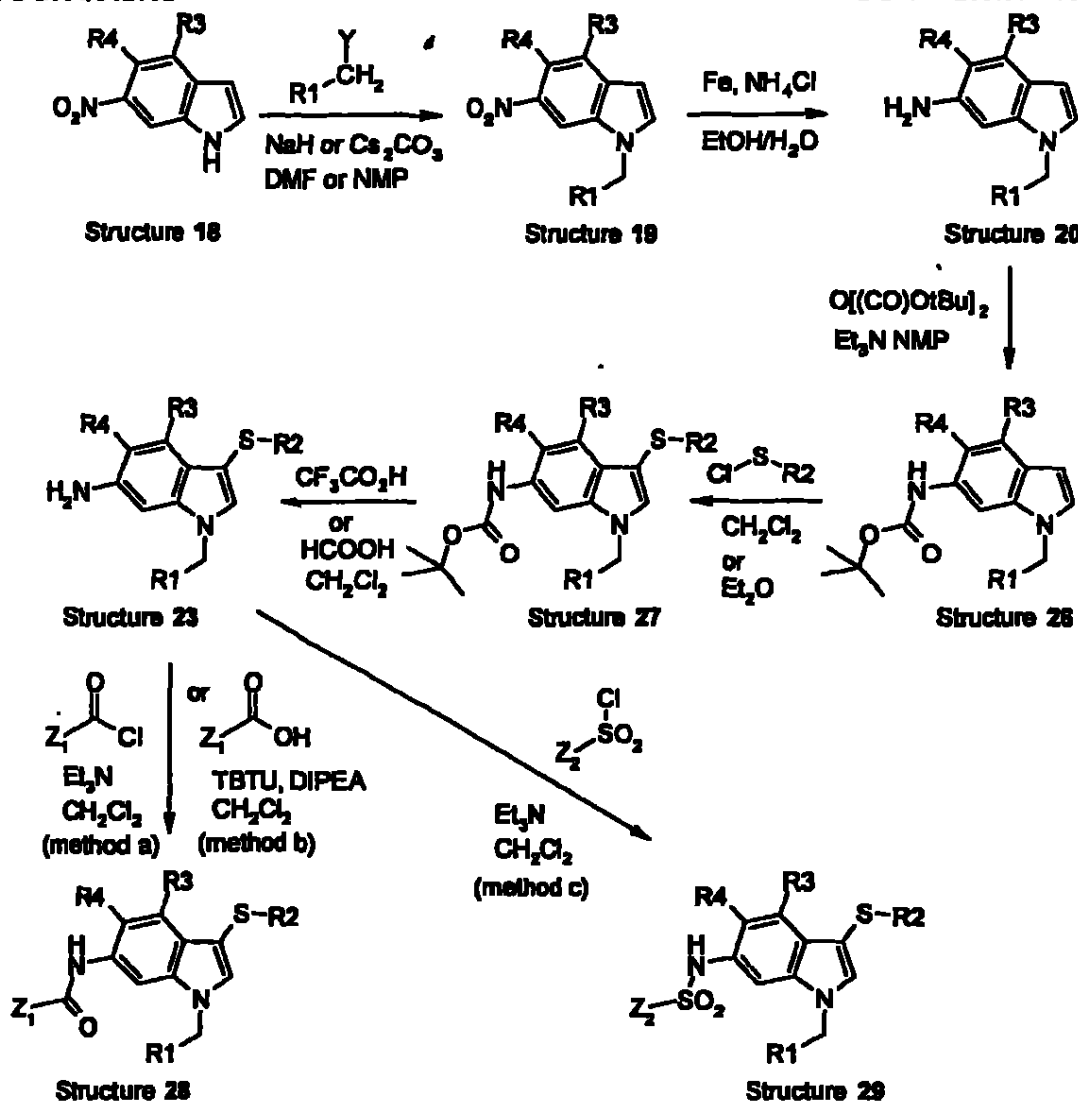
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Scheme VII describes the synthesis of compounds containing either an acylated amine functionality (structure 28) or a sulfonamide functionality (structure 29) at the 6-position of the indole ring. These compounds can be prepared from 6-nitro indoles of structure 18 in 6 steps. In the first step the indole of structure 18 is alkylated on N-1 by reaction of a halide of type $\text{R}^1\text{CH}_2\text{Y}$, in which Y is a halogen, mesylate or tosylate, with NaH or Cs_2CO_3 as a base in either NMP or DMF to give compounds of structure 19. In the second step the nitro group of structure 19 is reduced to an amine group with Fe and NH_4Cl in an ethanol/water mixture to give structure 20. Subsequent acylation of the amine group with di-*tert*-butyl dicarbonate afforded structure 26 which was then sulfanylated at the 3-position of the indole ring by reaction with a sulfenyl chloride in either CH_2Cl_2 or Et_2O to give compounds of structure 27. Then the amide functionality at the 6-position of the indole was cleaved with trifluoroacetic acid or HCOOH to give amines of structure 23. These amines can be converted into amides of structure 28 by reaction with either triethylamine and an acid chloride in CH_2Cl_2 (method a) or an acid, TBTU and DIPEA in CH_2Cl_2 (method b). Sulfonamides of structure 29 can be prepared by reaction of amines of structure 23 with sulfonyl chlorides (method c).

15

20

25



Scheme VII

- 5 The present invention also relates to a pharmaceutical composition comprising the non-steroidal compound according to the invention mixed with a pharmaceutically acceptable auxiliary, such as described in the standard reference Gennaro *et al*, *Remington: The Science and Practice of Pharmacy*, (20th ed., Lippincott Williams & Wilkins, 2000, see especially Part 5: Pharmaceutical Manufacturing). Suitable
- 10 auxiliaries are made available in e.g. the Handbook of Pharmaceutical Excipients (2nd Edition, Editors A. Wade and P.J. Weller; American Pharmaceutical Association; Washington; The Pharmaceutical Press; London, 1994). The mixture of a compound according to the invention and a pharmaceutically acceptable auxiliary may be

compressed into solid dosage units, such as pills, tablets, or be processed into capsules or suppositories. By means of pharmaceutically suitable liquids the compounds can also be applied as an injection preparation in the form of a solution, suspension, emulsion, or as a spray, e.g. nasal spray. For making dosage units, e.g. tablets, the use of
5 conventional additives such as fillers, colorants, polymeric binders and the like is contemplated. In general any pharmaceutically acceptable additive which does not interfere with the function of the active compounds can be used. The compounds of the invention may also be included in an implant, a vaginal ring, a patch, a gel, and any other preparation for sustained release.

10

Suitable carriers with which the compositions can be administered include lactose, starch, cellulose derivatives and the like, or mixtures thereof used in suitable amounts.

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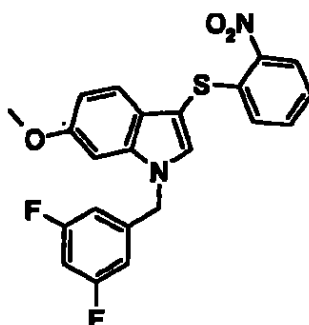
The dosage amounts of the present compounds will be of the normal order for pharmaceutically active compounds, e.g. of the order of 0.001 to 50 mg/kg body weight of the recipient per administration. The recipient can be a human or an animal in need of an androgen receptor-related treatment or an androgen treatment.

The invention is illustrated by the following examples.

Examples

Example 1

- 5 1-(3,5-Difluoro-benzyl)-6-methoxy-3-(2-nitro-phenylsulfanyl)-1H-indole (Compound 63, Structure 3 of Scheme I, where $R^1 = 3,5$ -difluorophenyl, $R^2 = 2$ -nitrophenyl, $R^3 = R^4 = H$, $R^5 = OMe$)



- 10 **General method 1: N-alkylation of a (un)substituted indole of structure 1 to give N-alkylated indole of structure 2, followed by 3-sulfanylation to give substituted indoles of structure 3 (Scheme I).**

(a) 1-(3,5-Difluoro-benzyl)-6-methoxy-1H-indole (Structure 2 of Scheme I, where $R^1 = 3,5$ -difluorophenyl, $R^3 = R^4 = H$, $R^5 = OMe$)

- 15 Under a nitrogen atmosphere: to a cooled (0°C) solution of 6-methoxyindole (863 mg, 5.86 mmol) in DMF (40 mL) was added NaH (60% in oil; 281 mg, 7.03 mmol) in small portions over a 3 minute period. The resulting green suspension was stirred at 0°C for 10 min. Then 3,5-difluorobenzyl bromide (0.91 mL, 7.03 mmol) was added. The mixture was stirred at 0°C for 1 h and then at room temperature for another 21 h. Ethyl acetate (50 mL) was added and the mixture was washed with 3% aqueous citric acid (3x50 mL) and brine (50 mL). The organic phase was dried (MgSO₄) and concentrated *in vacuo* to give a green oil (1.43 g). The crude product was purified over a 20 g silica SPE cartridge (ethyl acetate/heptane 1:9) to give the title compound as a colourless oil (1.23 g, yield = 77%).
- 20
- 25 LCMS: 4.01 min (96.3%, $MH^+ = 274$); TLC (ethyl acetate/heptane 1:4): $R_f = 0.46$; ¹H NMR (CDCl₃): δ 3.80 (s, 3H, OCH₃), 5.24 (s, 2H, NCH₂Ar), 6.51 (dd, 1H, $J_1 = 3.5$ Hz,

J2 = 0.8 Hz), 6.57-6.60 (m, 2H), 6.65 (d, 1H, J = 3.1 Hz), 6.66-6.72 (m, 1H), 6.81 (dd, 1H, J1 = 8.6 Hz, J2 = 3.1 Hz), 7.01 (d, 1H, J = 3.5 Hz), 7.53 (d, 1H, J = 8.6 Hz).

(b) 1-(3,5-Difluoro-benzyl)-6-methoxy-3-(2-nitro-phenylsulfanyl)-1H-indole

5 (Compound 63, Structure 3 of Scheme I, where R¹ = 3,5-difluorophenyl, R² = 2-nitrophenyl, R³=R⁴=H, R⁵=OMe)

To a solution of 1-(3,5-Difluoro-benzyl)-6-methoxy-1H-indole (900 mg, 3.29 mmol) in diethyl ether (20 mL) was added dropwise at room temperature a suspension of 2-nitrobenzenesulfonyl chloride (627 mg, 3.31 mmol) in diethyl ether (10 mL) over a
10 period of 2 min. After stirring at room temperature for 1 h ethyl acetate (50 mL) was added and the mixture was washed with saturated NaHCO₃ solution (2x50 mL) and brine (50 mL). The organic phase was dried (MgSO₄) and concentrated *in vacuo* to give an orange-red oil (1.54 g). The crude product was crystallised from toluene/acetone to give the title compound as orange-red crystalline solid (900 mg, yield = 64%).

15 LCMS: 4.25 min (100%, MH⁺ = 427); HPLC: 4.86 min (98.7%); ¹H NMR (CDCl₃): δ 3.82 (s, 3H, OCH₃), 5.32 (s, 2H, NCH₂Ar), 6.63-6.69 (m, 2H), 6.72-6.79 (m, 1H), 6.75 (d, 1H, J = 2.7 Hz), 6.85 (dd, 1H, J1 = 8.2 Hz, J2 = 2.7 Hz), 6.98 (dd, 1H, J1 = 6.7 Hz, J2 = 1.2 Hz), 7.16-7.20 (m, 1H), 7.26-7.30 (m, 1H) 7.34 (s, 1H), 7.39 (d, 1H, J = 8.2 Hz), 8.27 (dd, 1H, J1 = 8.2 Hz, J2 = 1.6 Hz).

20

According to General method 1 the following compounds were prepared:

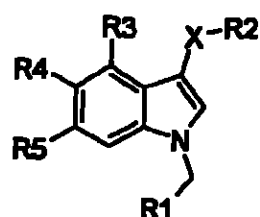


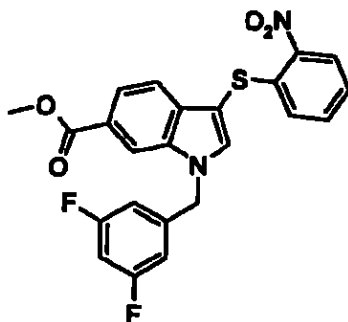
Table 1 Compounds synthesised according to General Method 1

Compound number	X	R ¹	R ²	R ³	R ⁴	R ⁵	MWt	LCMS	LCMS
								(MH ⁺)	ret. Time ^a (min)
21	S	3,5-difluorophenyl	2-methoxyphenyl	H	H	OMe	411.47	446 ^c	5.14 ^b
22	S	3,5-difluorophenyl	2-nitrophenyl	H	H	Br	475.32	476	4.89
23	S	3,5-difluorophenyl	2-nitrophenyl	H	H	CF ₃	464.41	465	5.34 ^b
24	S	3,5-difluorophenyl	2-nitrophenyl	H	H	CH ₂ OH	426.44	Nd	3.88 ^b
25	S	3,5-difluorophenyl	2-nitrophenyl	H	H	Cl	430.86	431	4.89
50	S	3,5-difluorophenyl	2-nitrophenyl	H	H	F	414.40	415	4.79
51	S	3,5-difluorophenyl	2-nitrophenyl	F	H	H	414.40	415	4.72
52	S	3,5-difluorophenyl	2-nitrophenyl	H	H	H	396.41	397	4.22
53	S	3,5-difluorophenyl	2-nitrophenyl	H	F	H	414.40	415	4.75
54	S	3,5-difluorophenyl	2-nitrophenyl	Cl	H	H	430.86	431	5.14 ^b
55	S	3,5-difluorophenyl	2-nitrophenyl	Me	H	H	410.44	411	5.24 ^b
56	S	3,5-difluorophenyl	2-nitrophenyl	H	OH	H	412.41	413	4.50 ^b
60	S	3,5-difluorophenyl	2-nitrophenyl	H	H	NO ₂	441.41	442	4.7
61	S	3,5-difluorophenyl	2-nitrophenyl	H	H	OH	412.41	413	4.54 ^b
63	S	3,5-difluorophenyl	2-nitrophenyl	H	H	OMe	426.45	274 ^d	4.01
66	S	3,5-difluorophenyl	2-pyridyl-N-oxide	H	H	OMe	398.43	399	3.96
90	S	phenyl	2-nitrophenyl	H	H	H	360.43	361	4.19
91	S	phenyl	2-nitrophenyl	H	OMe	H	390.46	391	4.14
92	S	phenyl	2-nitrophenyl	H	H	OMe	390.46	391	4.12

5 a) 7 min LCMS method was used, unless stated otherwise. b) 10 min LCMS method was used. c) M+Cl. nd = not detected. d) $[M-S(PhNO_2)]H^+$.

Example 2

1-(3,5-Difluoro-benzyl)-3-(2-nitro-phenylsulfany)-1*H*-indole-6-carboxylic acid methyl ester (Compound 31, Structure 3 of Scheme I, where $R^1 = 3,5$ -difluorophenyl, $R^2 = 2$ -nitrophenyl, $R^3 = R^4 = H$, $R^5 = CO_2Me$)



(a) 1*H*-Indole-6-carboxylic acid methyl ester (Structure 1 of Scheme I, where $R^3 = R^4 = H$, $R^5 = CO_2Me$)

To a solution of 1*H*-Indole-6-carboxylic acid (1.500 g, 9.31 mmol) in methanol (50 mL) was added concentrated H_2SO_4 (550 μ L, 10.24 mmol). The mixture was stirred overnight at reflux temperature. The mixture was then neutralised to pH 7 by addition of saturated aqueous $NaHCO_3$ and the mixture was extracted twice with ethyl acetate. The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo* to give a yellow powder. The product was recrystallised from heptane/ethyl acetate to give the title compound as green/yellow crystals (688 mg, yield = 53%)

^1H NMR ($CDCl_3$): δ 3.94 (s, 3H, CH_3OCO), 6.60 (m, 1H), 7.37 (t, 1H, $J = 4.7$ Hz), 7.66 (d, 1H, $J = 8.2$ Hz), 7.82 (dd, 1H, $J_1 = 8.2$ Hz, $J_2 = 1.0$ Hz), 8.18 (s, 1H), 8.73 (s, 1H, NH)

(b) 1-(3,5-Difluoro-benzyl)-1*H*-indole-6-carboxylic acid methyl ester (Structure 2 of Scheme I, where $R^1 = 3,5$ -difluorophenyl, $R^3 = R^4 = H$, $R^5 = CO_2Me$)

Under a nitrogen atmosphere: to a solution of 1*H*-indole-6-carboxylic acid methyl ester (367 mg, 2.09 mmol) in DMF (10 mL) was added NaH (60% in oil, 101 mg, 2.52 mmol) at room temperature. After stirring for 15 min 1-bromomethyl-3,5-difluorobenzene (325 μ L, 2.51 mmol) was added and the mixture was stirred at room temperature for 4 h. The reaction was quenched with 3% aqueous citric acid (10 mL)

and ethyl acetate (30 mL) was added. The mixture was washed with 3% aqueous citric acid (3x20 mL) and brine (20 mL). The organic phase was dried (MgSO₄) and concentrated *in vacuo* to give a pale yellow oil (702 mg). The crude product was purified over a 20 g silica SPE cartridge (ethyl acetate/heptane 1:9) to give the title compound as a colourless oil, which slowly crystallised on standing (530 mg, yield = 84%).

LCMS: 4.08 min (99%, MH⁺ = 302); ¹H NMR (CDCl₃): δ 3.92 (s, 3H, CO₂CH₃), 5.37 (s, 2H, NCH₂Ar), 6.54-6.60 (m, 2H), 6.64 (d, 1H, J = 3.1 Hz), 6.67-6.74 (m, 1H), 7.27 (d, 1H, J = 3.1 Hz), 7.68 (d, 1H, J = 8.6 Hz), 7.83 (d, 1H, J = 8.6 Hz), 8.01 (s, 1H).

(c) 1-(3,5-Difluoro-benzyl)-3-(2-nitro-phenylsulfanyl)-1H-indole-6-carboxylic acid methyl ester (Compound 31, Structure 3 of Scheme I, where R¹ = 3,5-difluorophenyl, R² = 2-nitrophenyl, R³=R⁴=H, R⁵=CO₂Me)

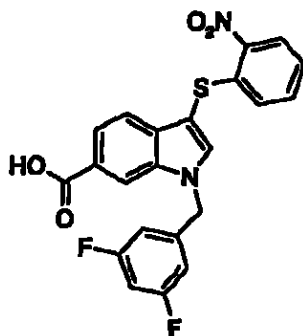
To a solution of 1-(3,5-Difluoro-benzyl)-1H-indole-6-carboxylic acid methyl ester (330 mg, 1.10 mmol) in dichloromethane (30 mL) was added at room temperature a solution of 2-nitrobenzenesulfenyl chloride (210 mg, 1.11 mmol) in dichloromethane (10 mL). The mixture was stirred at room temperature for 4 days. The reaction mixture was concentrated and the crude product was purified over a 20 g silica SPE cartridge (ethyl acetate/heptane 1:5 to 1:2) to give the title compound as a yellow solid (392 mg, yield = 78%).

HPLC: 4.60 min (97.8%); ¹H NMR (CDCl₃): δ 3.93 (s, 3H, CO₂CH₃), 5.45 (s, 2H, NCH₂Ar), 6.63-6.69 (m, 2H), 6.74-6.80 (m, 1H), 6.88 (dd, 1H, J₁ = 8.2 Hz, J₂ = 1.2 Hz), 7.18-7.23 (m, 1H), 7.26-7.30 (m, 1H), 7.57 (d, 1H, J = 7.8 Hz), 7.58 (s, 1H), 7.89 (dd, 1H, J₁ = 7.8 Hz, J₂ = 1.2 Hz), 8.12 (s, 1H), 8.28 (dd, 1H, J₁ = 7.8 Hz, J₂ = 1.2 Hz).

Example 3

1-(3,5-Difluoro-benzyl)-3-(2-nitro-phenylsulfanyl)-1H-indole-6-carboxylic acid (Compound 30, Structure 14 of Scheme IV, where R¹ = 3,5-difluorophenyl, R² = 2-nitrophenyl, R³=R⁴=H)

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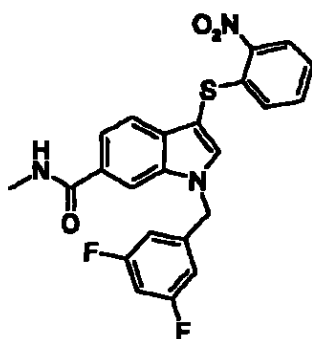


To a solution of 1-(3,5-Difluoro-benzyl)-3-(2-nitro-phenylsulfanyl)-1*H*-indole-6-carboxylic acid methyl ester (150.0 mg, 0.33 mmol) in dioxane (20 mL) and water (15 mL) was added LiOH.H₂O (83.1 mg, 2.0 mmol) in 5 ml water. The reaction mixture was stirred overnight at 60°C. The mixture was then acidified to pH 4 by addition of 15% aqueous HCl and the mixture was extracted twice with ethyl acetate. The combined organic layers were dried over Na₂SO₄ and concentrated *in vacuo* to give a yellow powder. The product was recrystallised from heptane/ethyl acetate to give the title compound as yellow/orange crystals (129.3 mg, *y* = 89%)

¹H NMR (DMSO): δ 5.62 (s, 2H, CH₂Ar), 6.85 (dd, 1H, J₁ = 8.6 Hz, J₂ = br), 7.05 (m, 2H, br), 7.20 (m, 1H, br), 7.32-7.38 (m, 1H), 7.40 (d, 1H, J = 8.2 Hz), 7.44-7.50 (m, 1H), 7.68 (dd, 1H, J₁ = 8.6 Hz, J₂ = br), 7.97 (s, 1H, COOH), 8.20 (s, 1H), 8.26 (s, 1H), 8.28 (d, 1H, J = 8.2)

Example 4

1-(3,5-Difluoro-benzyl)-3-(2-nitro-phenylsulfanyl)-1*H*-indole-6-carboxylic acid methylamide (Compound 47, Structure 15 of Scheme IV, where R¹ = 3,5-difluorophenyl, R² = 2-nitrophenyl, R³=R⁴=R⁵=H, R⁶=Me)



21

General method 2: amidation of 6-carboxyl indoles of structure 14 to give 6-carboxamideindoles of structure 15 (Scheme IV).

Under nitrogen atmosphere: to a solution of 1-(3,5-Difluoro-benzyl)-3-(2-nitro-phenylsulfanyl)-1*H*-indole-6-carboxylic acid (25.1 mg, 57.0 μ mol) in dry DMF (10mL) was added NMM (1 mL), HOBt (9.60 mg, 62.7 μ mol), EDCI (12.1 mg, 62.7 μ mol), and methylammonium chloride (19.2 mg, 285 μ mol). The reaction mixture was stirred overnight at room temperature and then poured into ice water. The resulting precipitate was filtered and the residue was washed with excess water followed by little heptane. The product was dried *in vacuo* at 40°C to give the title compound as a yellow solid (15.2 mg, $y = 60\%$).

LCMS: 4.31 min (100.0%, $MH^+ = 454$); ^1H NMR (DMSO): δ 2.80(d, 3H, $J = 4.3$, CH_3NHCO), 5.63 (s, 2H, CH_2Ar), 6.86 (dd, 1H, $J_1 = 8.2$ Hz, $J_2 = 1.0$ Hz), 7.04 (m, 2H), 7.20 (m, 1H), 7.33-7.37 (m, 1H), 7.41 (d, 1H, 8.6 Hz), 7.46-7.50 (m, 1H), 7.64 (dd, 1H, $J_1 = 8.2$ Hz, $J_2 = 1.0$ Hz), 8.15 (s, 1H), 8.25 (s, 1H), 8.27 (dd, 1H, $J_1 = 8.6$ Hz, $J_2 = 1.0$ Hz), 8.40 (m, 1H, $MeNHCO$).

According to General method 2 the following compounds were prepared:

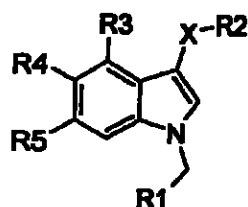


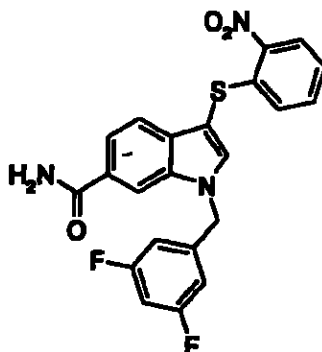
Table 2 Compounds synthesised according to General Method 2

							LCMS	LCMS	
								ret.	
								Time ^a	
Compound number	X	R ¹	R ²	R ³	R ⁴	R ⁵	MWt (MH ⁺)	(min)	
27	S	3,5-difluorophenyl	2-nitrophenyl	H	H	CO(1-pyrrolidinyl)	493.53	494	4.66
28	S	3,5-difluorophenyl	2-nitrophenyl	H	H	CO(4-morpholinyl)	509.53	510	4.50
29	S	3,5-difluorophenyl	2-nitrophenyl	H	H	CO[1-(4-methylpiperazinyl)]	522.57	523	3.81
32	S	3,5-difluorophenyl	2-nitrophenyl	H	H	CONe ₂	495.55	496	4.82
34	S	3,5-difluorophenyl	2-nitrophenyl	H	H	CONHCH ₂ (2-furanyl)	519.53	520	4.74
35	S	3,5-difluorophenyl	2-nitrophenyl	H	H	CONHCH ₂ (3-pyridyl)	530.55	531	3.94
36	S	3,5-difluorophenyl	2-nitrophenyl	H	H	CONHCH ₂ CH ₂ NMe ₂	510.56	511	3.90
37	S	3,5-difluorophenyl	2-nitrophenyl	H	H	CONHCH ₂ CH ₂ OH	483.49	484	4.21
38	S	3,5-difluorophenyl	2-nitrophenyl	H	H	CONHCH ₂ CH ₂ OMe	497.52	498	4.48
39	S	3,5-difluorophenyl	2-nitrophenyl	H	H	CONHCH ₂ CO ₂ Me	511.50	512	4.51
40	S	3,5-difluorophenyl	2-nitrophenyl	H	H	CONHCH ₂ CONMe ₂	524.55	525	4.33
41	S	3,5-difluorophenyl	2-nitrophenyl	H	H	CONHCH ₂ cPr	493.53	494	4.75
42	S	3,5-difluorophenyl	2-nitrophenyl	H	H	CONHCH ₂ iPr	495.55	496	4.85
43	S	3,5-difluorophenyl	2-nitrophenyl	H	H	CONHCH ₂ Ph	529.56	530	4.90
44	S	3,5-difluorophenyl	2-nitrophenyl	H	H	CONHcPr	479.50	480	4.57
45	S	3,5-difluorophenyl	2-nitrophenyl	H	H	CONHt	467.49	468	4.56
46	S	3,5-difluorophenyl	2-nitrophenyl	H	H	CONHiPr	481.52	482	4.71
47	S	3,5-difluorophenyl	2-nitrophenyl	H	H	CONHMe	453.47	454	4.31
48	S	3,5-difluorophenyl	2-nitrophenyl	H	H	CONHnPr	481.52	482	4.75
49	S	3,5-difluorophenyl	2-nitrophenyl	H	H	CONMe ₂	467.49	468	4.30 ^b

a) 7 min LCMS method was used, unless stated otherwise. b) 10 min LCMS method was used.

Example 5

1-(3,5-Difluoro-benzyl)-3-(2-nitro-phenylsulfanyl)-1*H*-indole-6-carboxylic acid amide (Compound 33, Structure 16 of Scheme IV, where $R^1 = 3,5$ -difluorophenyl, $R^2 = 2$ -nitrophenyl, $R^3 = R^4 = H$)



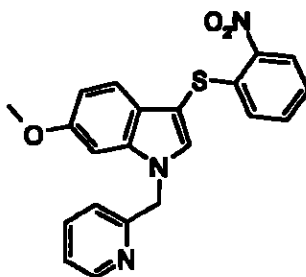
5

The title compound was prepared according to General method 2, using 51.1 mg (116 μ mol) carboxylic acid, 19.5 mg (128 μ mol) HOBt, 24.6 mg (128 μ mol) EDCI and 31.1 mg (581 μ mol) ammonium chloride. The title compound was obtained as a yellow solid (9.0 mg; 18%).

10 LCMS: 4.16 min (100.0%, $MH^+ = 440$); ^1H NMR ($CDCl_3$): δ 5.46 (s, 2H, CH_2Ar), 6.65 (m, 2H), 6.77 (m, 1H), 6.88 (dd, 1H, $J_1 = 8.2$ Hz, $J_2 = 1.0$ Hz), 7.21 (m, 1H), 7.29 (m, 1H), 7.51 (dd, 1H, $J_1 = 7.8$ Hz, $J_2 = 1.0$ Hz), 7.57 (d, 1H, $J = 7.7$ Hz), 7.58 (s, 1H), 8.05 (s, 1H), 8.29 (dd, 1H, $J_1 = 8.2$ Hz, $J_2 = 1.0$ Hz).

15 **Example 6**

6-Methoxy-3-(2-nitro-phenylsulfanyl)-1-pyridin-2-ylmethyl-1*H*-indole (Compound 9, Structure 3 of Scheme I, where $R^1 = 2$ -pyridyl, $R^2 = 2$ -nitrophenyl, $R^3 = R^4 = H$, $R^5 = OMe$)



20

General method 3: 3-sulfanylation of a (un)substituted indole of structure 1 to give substituted indoles of structure 4, followed by indole-*N*-alkylation to give *N*-alkylated indole structure 3 (Scheme I).

(a) 6-Methoxy-3-(2-nitro-phenylsulfanyl)-1*H*-indole (Structure 4 of Scheme I, where $R^2 = 2\text{-nitrophenyl}$, $R^1 = R^3 = R^4 = H$, $R^5 = OMe$)

To a solution of 6-methoxyindole (1.5 g, 10.2 mmol) in Et₂O (100 mL) was added a solution of 2-nitrobenzenesulfonyl chloride (1.93 g, 10.2 mmol) in 50 mL Et₂O dropwise, over a 4 minute period. The resulting yellow solution was stirred at room temperature for 1 h. The solvent was evaporated and the crude product was purified over a silica column (heptane/ethyl acetate 9:1) to give the title compound (3.054 g, yield = 97%).

HPLC : 3.72 min. purity 96.7%, TLC (heptane/ethyl acetate 1:1): $R_f = 0.6$;

¹H NMR (CDCl₃): δ 3.87 (s, 3H, OCH₃), 6.84 (dd, 1H, $J_1 = 7.8$ Hz, $J_2 = 3, 13$ Hz), 6.97 (m, 2H), 7.16 (t, 1H, $J = 7.8$ Hz), 7.25 (t, 1H, $J = 7.8$ Hz), 7.36 (d, 1H, $J = 7.8$ Hz), 7.44 (d, 1H, $J = 2.0$ Hz), 8.26 (d, 1H, $J = 7.8$ Hz), 8.45 (s, 1H, NH).

(b) 6-Methoxy-3-(2-nitro-phenylsulfanyl)-1-pyridin-2-ylmethyl-1*H*-indole (Compound 9, Structure 3 of Scheme I, where $R^1 = 2\text{-pyridyl}$, $R^2 = 2\text{-nitrophenyl}$, $R^3 = R^4 = H$, $R^5 = OMe$)

To a solution of 6-Methoxy-3-(2-nitro-phenylsulfanyl)-1*H*-indole (1.5 g, 5 mmol) in DMF (150 mL) was added NaH (60% in oil; 500 mg, 12.5 mmol) in small portions, over a 4 minute period. The resulting dark solution was stirred for 5 min. at room temperature. Then 2-picolyl chloride hydrochloride (984 mg, 6 mmol) was added in small portions, over a 2 minute period. During stirring at room temperature (2h) the colour of the solution slightly changed from dark to yellow. Ethyl acetate (100 mL) was added and the mixture was washed with 2% aqueous citric acid (2x100 mL) and water (100 mL). The organic phase was dried (MgSO₄) and the solvent was evaporated. The crude product was purified by crystallisation (ethyl acetate/heptane) to give the title compound (1.437 g, yield = 74%).

HPLC : 10.3 min, purity 99.6%, TLC (heptane/ethyl acetate 1:1): $R_f = 0.3$;

¹H NMR (CDCl₃): δ 3.80 (s, 3H, OCH₃), 5.47 (s, 2H, NCH₂), 6.82 (m, 2H), 6.88 (d, 1H, $J = 7.8$ Hz), 7.01 (dd, 1H, $J_1 = 7.8$ Hz, $J_2 = 1, 6$ Hz), 7.15-7.19 (m, 1H), 7.25 (m,

2H), 7.37 (d, 1H, $J = 8.6$ Hz), 7.60-7.64 (m, 1H), 8.26 (dd, 1H, $J_1 = 7.8$ Hz, $J_2 = 1.6$ Hz), 8.63 (d, 1H, $J = 5.88$ Hz).

According to General method 3 the following compounds were prepared:

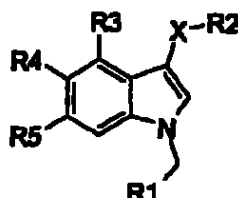


Table 3 Compounds synthesised according to General Method 3

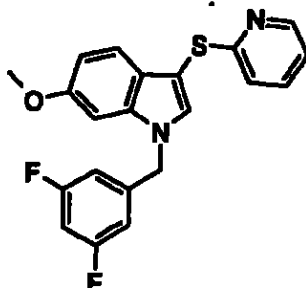
Compound							LCMS	LCMS ret.
number	X	R ¹	R ²	R ³	R ⁴	R ⁵	MWt (MH ⁺)	Time ^a (min)
1	S	2,5-difluorophenyl	2-nitrophenyl	H	H	OMe	426.44	4.07
2	S	2-fluoro,3-methylphenyl	2-nitrophenyl	H	H	OMe	422.48	4.23
3	S	2-chlorophenyl	2-nitrophenyl	H	H	OMe	424.91	4.17
4	S	2-cyanophenyl	2-nitrophenyl	H	H	OMe	415.47	3.97
5	S	2-fluorophenyl	2-nitrophenyl	H	H	OMe	408.45	4.10
6	S	2-methyl,3-nitrophenyl	2-nitrophenyl	H	H	OMe	449.48	4.10
7	S	2-methylphenyl	2-nitrophenyl	H	H	OMe	404.49	4.16
8	S	2-nitrophenyl	2-nitrophenyl	H	H	OMe	435.46	4.08
9	S	2-pyridyl	2-nitrophenyl	H	H	OMe	391.45	10.30 ^b
11	S	2-tetrahydropyranyl	2-nitrophenyl	H	H	OMe	398.48	4.68
12	S	2-trifluoromethylphenyl	2-nitrophenyl	H	H	OMe	458.46	4.29
13	S	3-(5-methylisoxazolyl)	2-nitrophenyl	H	H	OMe	395.44	4.66
14	S	3,4-dichlorophenyl	2-nitrophenyl	H	H	OMe	459.35	4.33
15	S	3,5-dichlorophenyl	2-nitrophenyl	H	H	OMe	459.35	4.36
67	S	3-chlorophenyl	2-nitrophenyl	H	H	OMe	424.91	4.34
68	S	3-cyanophenyl	2-nitrophenyl	H	H	OMe	415.47	3.92
69	S	3-fluoro,5-trifluoromethylphenyl	2-nitrophenyl	H	H	OMe	476.45	4.42
70	S	3-fluoro,6-trifluoromethylphenyl	2-nitrophenyl	H	H	OMe	476.45	4.27
71	S	3-fluorophenyl	2-nitrophenyl	H	H	OMe	408.45	4.22

Compound							LCMS	LCMS ret.
number	X	R ¹	R ²	R ³	R ⁴	R ⁵	MWt (MH ⁺)	Time ^a (min)
72	S	3-methoxyphenyl	2-nitrophenyl	H	H	OMe	420.49	4.04
73	S	3-methylphenyl	2-nitrophenyl	H	H	OMe	404.49	4.16
74	S	3-nitrophenyl	2-nitrophenyl	H	H	OMe	435.46	4.00
75	S	3-pyridyl	2-nitrophenyl	H	H	OMe	391.45	3.28
76	S	3-trifluoromethyl,4-chlorophenyl	2-nitrophenyl	H	H	OMe	492.90	4.33
77	S	3-trifluoromethyloxyphenyl	2-nitrophenyl	H	H	OMe	474.46	4.43
78	S	3-trifluoromethylphenyl	2-nitrophenyl	H	H	OMe	458.46	4.21
79	S	4-(2-methylthiazolyl)	2-nitrophenyl	H	H	OMe	411.50	4.39
80	S	4-(3,5-dimethylisoxazolyl)	2-nitrophenyl	H	H	OMe	409.46	4.49
81	S	4-chlorophenyl	2-nitrophenyl	H	H	OMe	424.91	4.22
82	S	4-cyanophenyl	2-nitrophenyl	H	H	OMe	415.47	3.93
83	S	4-fluorophenyl	2-nitrophenyl	H	H	OMe	408.45	4.07
84	S	4-methoxyphenyl	2-nitrophenyl	H	H	OMe	420.49	4.03
85	S	4-methylphenyl	2-nitrophenyl	H	H	OMe	404.49	4.19
86	S	4-morpholinyl	2-nitrophenyl	H	H	OMe	413.50	3.54
87	S	5-(2-chlorothiazolyl)	2-nitrophenyl	H	H	OMe	431.92	4.61
88	S	5-(2-chlorothiophenyl)	2-nitrophenyl	H	H	OMe	430.93	4.92
89	S	cyclohexyl	2-nitrophenyl	H	H	OMe	396.51	5.11

a) 7 min LCMS method was used unless stated otherwise. b) a 20 min run on an HPLC system was used.

Example 7

1-(3,5-Difluoro-benzyl)-6-methoxy-3-(pyridin-2-ylsulfanyl)-1*H*-indole (Compound 65, Structure 3 of Scheme I, where $R^1 = 3,5$ -difluorophenyl, $R^2 = 2$ -pyridyl, $R^3 = R^4 = H$, $R^5 = OMe$)



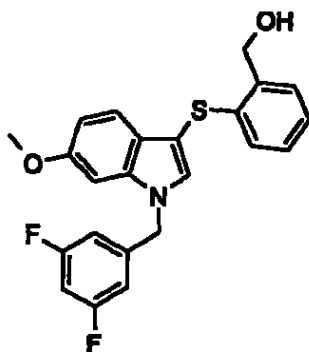
Under a nitrogen atmosphere: to a cooled (-10°C) solution of 2-mercaptopyridine (25 mg, 0.22 mmol) in CCl_4 (2 mL) was passed Cl_2 -gas during a period of 1 minute. The solvent was evaporated and a solution of 1-(3,5-Difluoro-benzyl)-6-methoxy-1*H*-indole (25 mg, 0.09 mmol) in Et_2O (2 mL) was added dropwise. The reaction mixture was concentrated and the crude product was purified by preparative LCMS to give the title compound (7.77 mg, yield = 23%).

LCMS : 3.95 min (100%, MH^+ 383); TLC (heptane/ethyl acetate 1:1): $R_f = 0.6$;

$^1\text{H-NMR}$ (CDCl_3) : δ 2.23 (s, 1H, NH), 3.82 (s, 1H, OCH_3), 6.65 (m, 2H), 6.73 (d, 1H, $J = 2.7$ Hz), 6.73-6.78 (m, 1H), 6.80 (d, 1H, $J = 7.8$ Hz), 6.87 (dd, 1H, $J_1 = 7.8$ Hz, $J_2 = 1.6$ Hz), 7.00 (ddd, 1H, $J_1 = 9.8$ Hz, $J_2 = 4.7$ Hz, $J_3 = 0.8$ Hz), 7.35 (s, 1H), 7.42 (ddd, 1H, $J_1 = J_2 = 7.8$ Hz, $J_3 = 1.6$ Hz), 7.50 (d, 1H, 8.6 Hz), 8.46 (d, 1H, $J = 4.7$ Hz).

Example 8

{2-[1-(3,5-Difluoro-benzyl)-6-methoxy-1*H*-indol-3-ylsulfanyl]-phenyl}-methanol (Compound 16, Structure 8 of Scheme III, where $R^1 = 3,5$ -difluorophenyl, $R^3 = R^4 = H$, $R^5 = OMe$)



- a) 2-[1-(3,5-Difluoro-benzyl)-6-methoxy-1*H*-indol-3-ylsulfanyl]-benzoic acid methyl ester (Compound 19, Structure 7 of Scheme III, where $R^1 = 3,5$ -difluorophenyl, $R^3=R^4=H$, $R^5=OMe$)

Chlorine gas was bubbled through CCl_4 (5 mL) at $-10^\circ C$ for 3 min. Then a solution of methylthiosalicylate (91 μL , 0.66 mmol) in CCl_4 (2 mL) was added. The mixture was stirred at $-10^\circ C$ for 5 min and then at room temperature for 15 min. The mixture was concentrated and redissolved in CH_2Cl_2 (5 mL). To this solution a solution of 1-(3,5-Difluoro-benzyl)-6-methoxy-1*H*-indole (121 mg, 0.443 mmol) in CH_2Cl_2 (3 mL) was added dropwise. The mixture was stirred at room temperature for 2 h and was concentrated. The crude product was purified by column chromatography (ethyl acetate/heptane 1:9) to give the title compound as a white solid (161 mg, 83% yield). LCMS: 4.72 min ($MH^+ = 440$); ^1H -NMR ($CDCl_3$): δ 3.82 (s, 3H, $ArOCH_3$), 3.99 (s, 3H, CO_2CH_3), 5.30 (s, 2H, CH_2Ar), 6.62-6.69 (m, 2H), 6.71-6.77 (m, 2H), 6.83 (dd, 1H, $J_1 = 8.6$ Hz, $J_2 = 2.4$ Hz), 6.87 (dd, 1H, $J_1 = 8.4$ Hz, $J_2 = 1.2$ Hz), 7.06-7.11 (m, 1H, 7.15-7.20 (m, 1H), 7.30 (s, 1H), 7.44 (d, 1H, $J = 8.6$ Hz), 8.02 (dd, 1H, $J_1 = 8.0$ Hz, $J_2 = 1.2$ Hz).

- b) {2-[1-(3,5-Difluoro-benzyl)-6-methoxy-1*H*-indol-3-ylsulfanyl]-phenyl}-methanol (Compound 16, Structure 8 of Scheme III, where $R^1 = 3,5$ -difluorophenyl, $R^3=R^4=H$, $R^5=OMe$)

Under a nitrogen atmosphere: to a solution of 2-[1-(3,5-Difluoro-benzyl)-6-methoxy-1*H*-indol-3-ylsulfanyl]-benzoic acid methyl ester (13.5 mg, 0.031 mmol) in THF (2 mL) was added $LiAlH_4$ (1.0 M in THF, 0.040 mL, 0.040 mmol). The mixture was stirred at room temperature for 3 h. Then ethyl acetate (25 mL) was added and the mixture was washed with 3% aqueous citric acid (2x25 mL) and brine (25 mL). The organic phase was dried ($MgSO_4$) and concentrated to give a colourless oil (15 mg). The crude product

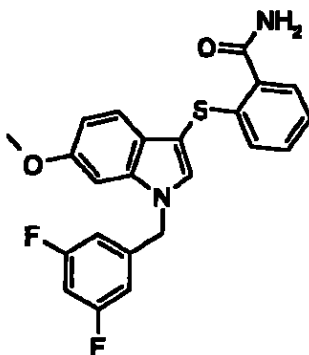
was purified by prep. HPLC to give the title compound as a colourless oil (5.6 mg, 44% yield).

LCMS: 4.47 min (95.6%, $MH^+ = 412$); ^1H -NMR ($CDCl_3$): δ 3.49 (s, 1H, OH), 3.81 (3, 3H, OCH_3), 4.92 (s, 2H, CH_2OH), 5.28 (s, 2H, CH_2Ar), 6.62-6.66 (m, 2H), 6.70-6.77 (m, 2H), 6.83 (dd, 1H, $J_1 = 8.8$ Hz, $J_2 = 2.4$ Hz), 6.89 (dd, 1H, $J_1 = 8.0$ Hz, $J_2 = 1.2$ Hz), 7.02-7.07 (m, 1H), 7.08-7.13 (m, 1H), 7.29 (s, 1H), 7.38 (dd, 1H, $J_1 = 8.0$ Hz, $J_2 = 1.2$ Hz), 7.44 (d, 1H, $J = 8.8$ Hz).

Example 9

2-[1-(3,5-Difluoro-benzyl)-6-methoxy-1*H*-indol-3-ylsulfanyl]-benzamide (Compound 18, Structure 11 of Scheme III, where $R^1 = 3,5$ -difluorophenyl, $R^3=R^4=H$, $R^5=OMe$)

5



a) 2-[1-(3,5-Difluoro-benzyl)-6-methoxy-1*H*-indol-3-ylsulfanyl]-benzoic acid (Structure 9 of Scheme III, where $R^1 = 3,5$ -difluorophenyl, $R^3=R^4=H$, $R^5=OMe$)

- 10 To a solution of 2-[1-(3,5-Difluoro-benzyl)-6-methoxy-1*H*-indol-3-ylsulfanyl]-benzoic acid methyl ester (97 mg, 0.221 mmol) in THF (10 mL) was added a solution of LiOH·H₂O (71 mg, 1.69 mmol) in water (10 mL). The mixture was stirred at room temperature for 17 h and then at 60°C for 24 h and was then acidified with 3% aqueous citric acid. Ethyl acetate (50 mL) was added and the mixture was washed with 3%
- 15 aqueous citric acid (2x50 mL) and brine (50 mL). The organic phase was dried (MgSO₄) and concentrated to give a yellow solid (104 mg). The crude product was recrystallised from ethyl acetate/heptane to give the title compound as a yellow powder (49 mg, 52% yield).

LCMS: 4.37 min ($MH^+ = 426$); ¹H-NMR (CDCl₃): δ 3.77 (s, 3H, OCH₃), 5.51 (s, 2H, CH₂Ar), 6.69 (d, 1H, *J* = 8.0 Hz), 6.76 (dd, 1H, *J*₁ = 8.4 Hz, *J*₂ = 2.4 Hz), 6.98-7.04 (m, 2H), 7.11-7.15 (m, 1H), 7.16-7.25 (m, 4H), 7.83 (s, 1H), 7.92 (dd, 1H, *J*₁ = 8.0 Hz, *J*₂ = 1.6 Hz).

General method 4: Reaction of an amine with a carboxylic acid of structure 9, with

25 TBTU and DIPEA, to give amides of structure 3, in which $R^2 =$ phenyl-2-carboxamide, exemplified by compounds of structure 10 and 11 (Scheme III).

b) 2-[1-(3,5-Difluoro-benzyl)-6-methoxy-1*H*-indol-3-ylsulfanyl]-benzamide

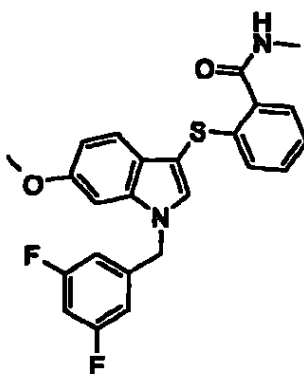
(Compound 18, Structure 11 of Scheme III, where $R^1 = 3,5$ -difluorophenyl, $R^3=R^4=H$, $R^5=OMe$)

Through a solution of 2-[1-(3,5-Difluoro-benzyl)-6-methoxy-1*H*-indol-3-ylsulfanyl]-benzoic acid (36 mg, 0.085 mmol), TBTU (28 mg, 0.087 mmol) and DIPEA (30 μ L, 0.172 mmol) in DMF (1 mL) was bubbled NH_3 gas for 10 min. The mixture was then stirred at room temperature for 3 days. Then 3% aqueous citric acid (0.4 mL) was added and the crude reaction mixture was purified over a RP-SPE cartridge (2g sorbent; 25% aqueous methanol to 100% methanol) to give a white solid (34 mg). The crude product was purified by column chromatography (ethyl acetate) to give the title compound as a colourless oil, which solidifies on standing (31 mg, yield: 86%).

LCMS: 4.20 min ($MH^+ = 425$); ^1H -NMR ($CDCl_3$): δ 3.81 (s, 3H, OCH_3), 5.39 (s, 2H, CH_2Ar), 6.05 (s, br, 1H, NH), 6.28 (s, br, 1H, NH), 6.61-6.67 (m, 2H), 6.70-6.72 (m, 1H), 6.73-6.77 (m, 1H), 6.83 (dd, 1H, $J_1 = 8.8$ Hz, $J_2 = 2.0$ Hz), 6.92 (dd, 1H, $J_1 = 8.0$ Hz, $J_2 = 1.2$ Hz), 7.07-7.17 (m, 2H), 7.31 (s, 1H), 7.45 (d, 1H, $J = 8.8$ Hz), 7.60 (dd, 1H, $J_1 = 8.0$ Hz, $J_2 = 1.2$ Hz).

Example 10**2-[1-(3,5-Difluoro-benzyl)-6-methoxy-1*H*-indol-3-ylsulfanyl]-*N*-methyl-benzamide**

(Compound 17, Structure 10 of Scheme III, where $R^1 = 3,5$ -difluorophenyl, $R^3=R^4=H$, $R^5=OMe$)

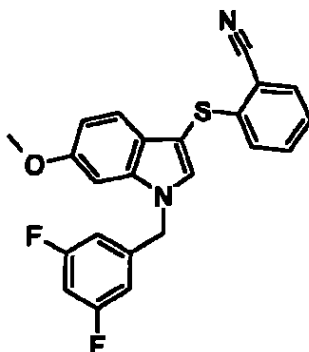


According to general method 4 compound 17 was synthesised from methylamine. LCMS: 4.07 min ($MH^+ = 439$).

Example 11

2-[1-(3,5-Difluoro-benzyl)-6-methoxy-1H-indol-3-ylsulfanyl]-benzonitrile (Compound 20, Structure 12 of Scheme III, where R¹ = 3,5-difluorophenyl, R³=R⁴=H, R⁵=OMe)

5



To a cooled (0°C) solution of 2-[1-(3,5-Difluoro-benzyl)-6-methoxy-1H-indol-3-ylsulfanyl]-benzamide (8 mg, 0.019 mmol) and Et₃N (10 µL, 0.072 mmol) in CH₂Cl₂ (1.5 mL) was added Tf₂O (6 µL, 0.036 mmol). The mixture was stirred at 0°C for 2 h and then at room temperature for 22 h. Water (25 mL) was added and the mixture was extracted with CH₂Cl₂ (2x25 mL). The combined organic phases were dried (Na₂SO₄) and concentrated to give a brown oil (25 mg). The crude product was purified by column chromatography (ethyl acetate/heptane 1:2) to give the title compound as a pale pink oil (3 mg, yield: 39%).

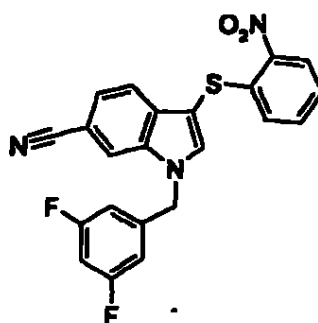
LCMS: 4.57 min (MH⁺ = 407); ¹H-NMR (CDCl₃): δ 3.82 (s, 3H, OCH₃), 5.30 (s, 2H, CH₂Ar), 6.62-6.67 (m, 2H), 6.71-6.73 (m, 1H), 6.74-6.78 (m, 1H), 6.86 (dd, 1H, J₁ = 8.8 Hz, J₂ = 2.0 Hz), 6.91 (d, 1H, J = 8.4 Hz), 7.11-7.15 (m, 1H), 7.26-7.30 (m, 1H), 7.37 (s, 1H), 7.46 (d, 1H, J = 8.8 Hz), 7.57-7.60 (m, 1H).

20

Example 12

1-(3,5-Difluoro-benzyl)-3-(2-nitro-phenylsulfanyl)-1H-indole-6-carbonitrile (Compound 26, Structure 17 of Scheme IV, where R¹ = 3,5-difluorophenyl, R² = 2-nitrophenyl, R³=R⁴=H)

25

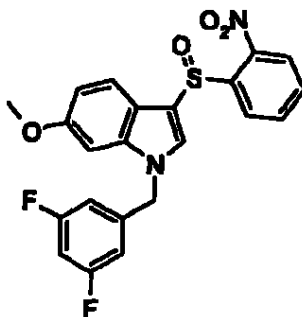


To a cooled (0°C) suspension of 1-(3,5-Difluoro-benzyl)-3-(2-nitro-phenylsulfanyl)-1*H*-indole-6-carboxylic acid amide (15 mg, 0.034 mmol) and Et₃N (10 µL, 0.072 mmol) in CH₂Cl₂ (1.5 mL) was added Tf₂O (13 µL, 0.077 mmol). The mixture was stirred at 0°C for 2 h and then at room temperature for 20 h. Water (25 mL) was added and the mixture was extracted with CH₂Cl₂ (2x25 mL). The combined organic phases were dried (Na₂SO₄) and concentrated to give the title compound as a yellow solid (13 mg, yield: 91%).

LCMS: 4.55 min (MH⁺ = not detectable); ¹H-NMR (CDCl₃): δ 5.42 (s, 2H, CH₂Ar), 6.63-6.69 (m, 2H), 6.78-6.85 (m, 2H), 7.21-7.25 (m, 1H), 7.28-7.33 (m, 1H), 7.44 (dd, 1H, J₁ = 8.4 Hz, J₂ = 1.2 Hz), 7.62 (d, 1H, J = 8.4 Hz), 7.66 (s, 1H), 8.29 (dd, 1H, J₁ = 8.4 Hz, J₂ = 1.6 Hz).

Example 13

1-(3,5-Difluoro-benzyl)-6-methoxy-3-(2-nitro-benzenesulfinyl)-1*H*-indole (Compound 64, Structure 5 of Scheme II, where R¹ = 3,5-difluorophenyl, R² = 2-nitrophenyl, R³=R⁴=H, R⁵=OMe)



To a solution of 1-(3,5-Difluoro-benzyl)-6-methoxy-3-(2-nitro-phenylsulfanyl)-1*H*-indole (40 mg, 0.09 mmol) in CH₂Cl₂ (4 mL) was added meta-chloroperbenzoic acid (14.5, 0.08 mmol). The solution was stirred at room temperature for 2 h. The solvent

was evaporated and the crude product was purified by prep LC-MS to give the title compound (14.3 mg, yield = 34%).

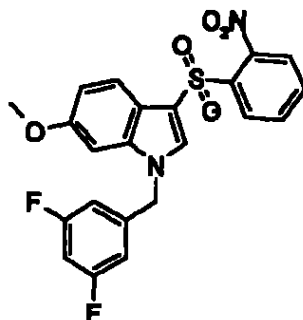
HPLC : 4.13 min, purity 100%; TLC (heptane/ethyl acetate 1:1) : R_f = 0.4; ¹H NMR (CDCl₃): δ 3.66 (s, 3H, OCH₃), 5.12 (s, 2H), 6.57 (m, 3H), 6.75 (m, 2H), 7.47 (d, 1H, J = 7.8 Hz), 7.52 (s, 1H), 7.66-7.70 (m, 1H), 8.28-8.32 (m, 1H), 8.23 (dd, 1H, J₁ = 7.8 Hz, J₂ = 1.9 Hz), 8.80 (dd, 1H, J₁ = 7.8 Hz, J₂ = 3.1 Hz).

5

Example 14

1-(3,5-Difluoro-benzyl)-6-methoxy-3-(2-nitro-benzenesulfonyl)-1H-indole (Compound 62, Structure 6 of Scheme II, where $R^1 = 3,5$ -difluorophenyl, $R^2 = 2$ -nitrophenyl, $R^3 = R^4 = H$, $R^5 = OMe$)

5



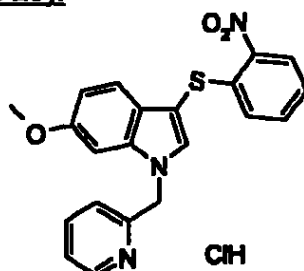
To a solution of 1-(3,5-Difluoro-benzyl)-6-methoxy-3-(2-nitro-phenylsulfanyl)-1H-indole (40 mg, 0.09 mmol) in CH_2Cl_2 (4 mL) was added meta-chloroperbenzoic acid (46.5 mg, 0.27 mmol). The solution was stirred at room temperature for 6 h. The solvent was evaporated and the crude product was purified by LC-MS to give the title compound (14.5 mg, yield = 34%).

HPLC: 4.38 min. purity 100%; TLC (heptane/ethyl acetate 1:1) : $R_f = 0.6$; ^1H NMR ($CDCl_3$): δ 3.71 (s, 3H, OCH₃), 5.25 (s, 2H), 6.58 (d, 1H, $J = 3.1$), 6.62 (m, 1H), 6.07-6.11 (m, 1H), 6.88 (dd, 1H, $J_1 = 7.8$ Hz, $J_2 = 3.1$ Hz), 7.63 (m, 4H), 7.72 (d, 1H, $J = 7.8$ Hz), 7.83 (s, 1H), 8.37 (dd, 1H, $J_1 = 7.8$ Hz, $J_2 = 1.9$ Hz).

Example 15

6-Methoxy-3-(2-nitro-phenylsulfanyl)-1-pyridin-2-ylmethyl-1H-indole monohydrochloride (Compound 10).

20



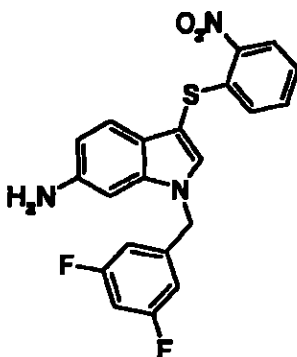
To a solution of 6-Methoxy-3-(2-nitro-phenylsulfanyl)-1-pyridin-2-ylmethyl-1H-indole in methylene chloride was passed HCl-gas till the organic salt crystallised. The title compound was isolated by filtration.

25

LC-MS : 4.04 min ($MH^+ = 392$); ^1H NMR (DMSO): δ 3.78 (s, 3H, OCH₃), 5.78 (s, 2H, NCH₂), 6.77 (dd, 1H, J₁ = 7.8 Hz, J₂ = 2.0 Hz), 6.93 (dd, 1H, J₁ = 7.8 Hz, J₂ = 0.8 Hz), 7.22 (d, 1H, J = 7.8 Hz), 7.26 (d, 1H, J = 2.0 Hz), 7.34 (m, 2H), 7.48-7.52 (m, 1H), 7.59 (t, 1H, J = 7.0 Hz), 7.96 (s, 1H), 8.08 (t, 1H, J = 7.0 Hz), 8.27 (dd, 1H, J₁ = 7.8 Hz, J₂ = 1.6 Hz), 8.74 (d, 1H, J = 6.7 Hz).

Example 16

1-(3,5-Difluoro-benzyl)-3-(2-nitro-phenylsulfanyl)-1H-indol-6-ylamine (Compound 57, Structure 23 of Scheme V, where R¹ = 3,5-difluorophenyl, R² = 2-nitrophenyl, R³=R⁴=H)



a) 1-(3,5-Difluoro-benzyl)-6-nitro-1H-indole (Structure 19 of Scheme V, where R¹ = 3,5-difluorophenyl, R³=R⁴=H)

To a solution of 6-nitroindole (162 mg, 1.0 mmol) in DMF (4 mL) was added NaH (60% dispersion on oil; 80 mg, 2.0 mmol). The resulting dark solution was stirred at room temperature for 15 minutes. 3,5-difluorobenzyl bromide (129 μ L, 1.1 mmol) was added. The reaction mixture was stirred overnight, poured into acidified water and extracted twice with ethyl acetate. The combined organic layers were dried over Na₂SO₄ and concentrated *in vacuo*.

The product was purified over a SiO₂ column (heptane/ethyl acetate 9:1) to give the title compound as a yellow solid (270 mg, yield = 94%).

LCMS: 5.54 min (100.0%, $MH^+ = 289$); ^1H NMR (CDCl₃): δ 5.40 (s, 2H, CH₂Ar), 6.58 (m, 2H), 6.71 (d, 1H, J = 3.5 Hz), 6.75 (m, 1H), 7.26 (s, 1H), 7.41 (d, 1H, J = 3.5 Hz), 7.71 (d, 1H, J = 8.3 Hz), 8.05 (dd, 1H, J₁ = 8.3 Hz, J₂ = 2.0 Hz), 8.21 (d, 1H, J = 2.0 Hz).

b) 1-(3,5-Difluoro-benzyl)-1H-indol-6-ylamine (Structure 20 of Scheme V, where R¹ = 3,5-difluorophenyl, R³=R⁴=H)

To a solution of 1-(3,5-Difluoro-benzyl)-6-nitro-1*H*-indole (144 mg, 0.5 mmol) in ethanol (20 mL) was added hydrochloric acid 37% (80 μ L) and SnCl₂·2H₂O (600 mg). The reaction mixture was stirred at 60 °C for 40 h and was then concentrated *in vacuo*. The residue was poured into ethyl acetate and a concentrated NaHCO₃-solution was added. The two-layer phase system was filtered over decalite to get rid of the tin salts and the filtrate was twice extracted with ethyl acetate. The combined organic layers were dried over Na₂SO₄ and concentrated *in vacuo*. The product was purified over a SiO₂ column (heptane/ethyl acetate 9:1) to give the title compound as a colourless oil (89 mg, yield = 69%).

LCMS: 3.20 min (97.7%, MH⁺ = 259); ¹H NMR (CDCl₃): δ 5.12 (s, 2H, CH₂Ar), 6.52 (m, 2H), 6.56 (d, 1H, J = 3.5 Hz), 6.63 (m, 1H), 7.97 (dd, 1H, J₁ = 8.3 Hz, J₂ = 2.0 Hz), 7.13 (d, 1H, J = 3.5 Hz), 7.17 (d, 1H, J = 2.0 Hz), 7.55 (d, 1H, J = 8.3 Hz).

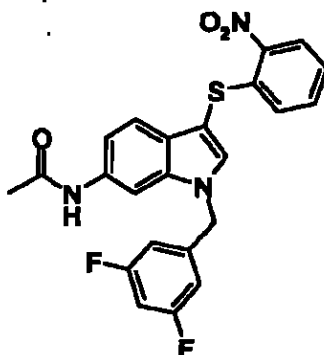
c) 1-(3,5-Difluoro-benzyl)-3-(2-nitro-phenylsulfanyl)-1*H*-indol-6-ylamine (Compound 57, Structure 23 of Scheme V, where R¹ = 3,5-difluorophenyl, R² = 2-nitrophenyl, R³=R⁴=H)

To a solution of 1-(3,5-Difluoro-benzyl)-1*H*-indol-6-ylamine (25 mg, 0.1 mmol) in DCM (4 mL) was added 2-nitrobenzenesulfonyl chloride. The resulting yellow solution was stirred at room temperature for 1 hour. The mixture was concentrated *in vacuo* and purified over a SiO₂ column (heptane/ethyl acetate 9:1) to give the title compound as an orange solid (11.6 mg, yield = 28%).

LCMS: 5.11 min (100.0%, MH⁺ = 412); ¹H NMR (CDCl₃): δ 5.22 (s, 2H, CH₂Ar), 6.56 (m, 2H), 6.65 (m, 1H), 6.84 (dd, 1H, J₁ = 8.2 Hz, J₂ = 1.2 Hz), 7.00 (dd, 1H, J₁ = 8.2 Hz, J₂ = 1.2 Hz), 7.19 (m, 1H), 7.30 (d, 1H, J = 1.2 Hz), 7.31 (s, 1H), 7.37 (d, 1H, J = 8.2 Hz), 7.49 (m, 1H), 8.27 (dd, 1H, J₁ = 8.2 Hz, J₂ = 1.2 Hz).

Example 17

N-[1-(3,5-Difluoro-benzyl)-3-(2-nitro-phenylsulfanyl)-1*H*-indol-6-yl]-acetamide
 (Compound 58, Structure 22 of Scheme V, where $R^1 = 3,5$ -difluorophenyl, $R^2 = 2$ -
 nitrophenyl, $R^3=R^4=H$, $Z = \text{methyl}$)



General method 5: Reaction of an acid anhydride with a 6-aminoindole of structure 20 to give compounds of structure 21, followed by sulfanylation of the indole 3-position to give compounds of structure 22 (Scheme V).

a) *N*-[1-(3,5-Difluoro-benzyl)-1*H*-indol-6-yl]-acetamide (Structure 21 of Scheme V, where $R^1 = 3,5$ -difluorophenyl, $R^3=R^4=H$, $Z = \text{methyl}$)

To a solution of 1-(3,5-Difluoro-benzyl)-1*H*-indol-6-ylamine (25 mg, 0.1 mmol) in DCM (4 mL) was added pyridine (25 μ L) and acetic anhydride (9.8 μ L, 0.11 mmol) and stirred overnight at room temperature. The reaction mixture was poured into 10 mL of water and neutralised with NaHCO_3 and extracted twice with DCM. The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo* to give the crude compound as a off white solid (23.3 mg, yield = 84%). The product was used without further purification.

LCMS: 4.10 min (97.4%, $\text{MH}^+ = 301$); ^1H NMR (CDCl_3): δ 2.18 (s, 3H, CH_3CON), 5.28 (s, 2H, CH_2Ar), 6.53 (d, 1H, $J = 3.1$), 6.58 (m, 2H), 6.68 (m, 1H), 6.87 (dd, 1H, $J_1 = 8.3$ Hz, $J_2 = 1.6$ Hz), 7.07 (d, 1H, $J = 3.1$ Hz), 7.55 (d, 1H, $J = 8.3$ Hz), 7.90 (s, 1H).

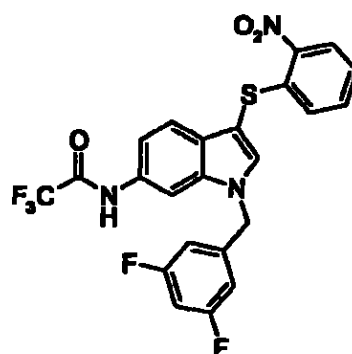
b) *N*-[1-(3,5-Difluoro-benzyl)-3-(2-nitro-phenylsulfanyl)-1*H*-indol-6-yl]-acetamide
 (Compound 58, Structure 22 of Scheme V, where $R^1 = 3,5$ -difluorophenyl, $R^2 = 2$ -
 nitrophenyl, $R^3=R^4=H$, $Z = \text{methyl}$)

To a solution of *N*-[1-(3,5-Difluoro-benzyl)-1*H*-indol-6-yl]-acetamide (23.3 mg, 0.08 mmol) in diethyl ether (4 mL) was added 2-nitrobenzenesulfenyl chloride (14.7 mg,

0.09 mmol). The resulting yellow solution was stirred overnight at room temperature. The mixture was concentrated *in vacuo* and purified over a SiO₂ column (heptane/ethyl acetate 9:1) to give the title compound as a yellow solid (35.0 mg, yield = 96%).
LCMS: 4.26 min (98.6%, MH⁺ = 454); ¹H NMR (DMSO): δ 2.03 (s, 3H, CH₃CON),
5 5.51 (s, 2H, CH₂Ar), 6.89 (dd, 1H, J = 8.3 Hz, J₂ = 1.2 Hz), 6.95 (m, 2H), 7.17 (dd, 1H, J₁ = 8.3 Hz, J₂ = 2.0 Hz), 7.19 (m, 1H), 7.27 (d, 1H, J = 8.3 Hz), 7.34 (m, 1H), 7.49 (m, 1H), 7.97 (d, 1H, J = 1.2 Hz), 8.02 (s, 1H), 8.27 (dd, 1H, J₁ = 8.3 Hz, J₂ = 1.2 Hz).

Example 18

10 *N*-[1-(3,5-Difluoro-benzyl)-3-(2-nitro-phenylsulfanyl)-1*H*-indol-6-yl]-2,2,2-trifluoro-acetamide (Compound 59, Structure 22 of Scheme V, where R¹ = 3,5-difluorophenyl, R² = 2-nitrophenyl, R³=R⁴=H, Z = trifluoromethyl)



15

According to General method 5, step a): *N*-[1-(3,5-Difluoro-benzyl)-1*H*-indol-6-yl]-2,2,2-trifluoro-acetamide was prepared using 1-(3,5-Difluoro-benzyl)-1*H*-indol-6-ylamine (17.7 mg, 69 μmol), pyridine (17 μL) and trifluoroacetic anhydride (9.68 μL, 70 μmol). The compound was purified over a SiO₂ column (heptane/ethyl acetate 9:1) to
20 give the title compound as a white solid (10.9 mg, yield = 61%).

LCMS: 4.41 min (82.1%, MH⁺ = 355)

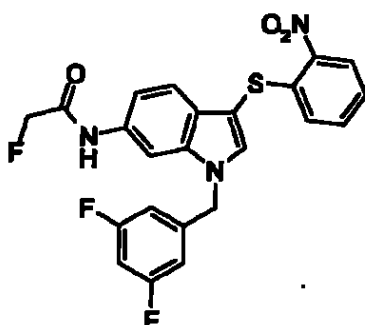
According to General method 5, step b): *N*-[1-(3,5-Difluoro-benzyl)-3-(2-nitro-phenylsulfanyl)-1*H*-indol-6-yl]-2,2,2-trifluoro-acetamide was prepared using *N*-[1-(3,5-Difluoro-benzyl)-1*H*-indol-6-yl]-2,2,2-trifluoro-acetamide (10.9 mg, 31 μmol) and 2-nitrobenzenesulfenyl chloride (5.7 mg, 37 μmol). The compound was purified over an
25 HPLC column (MeCN/H₂O) to give the title compound as a yellow solid (10.2 mg, yield = 65%).

LCMS: 4.65 min (89.0%, MH⁺ = 508); ¹H NMR (DMSO): δ 5.56 (s, 2H, CH₂Ar), 6.87 (dd, 1H, J = 8.3 Hz, J₂ = 1.2 Hz), 7.01 (m, 2H), 7.20 (m, 1H), 7.35 (m, 1H), 7.37 (dd,

1H, J1 = 8.3 Hz, J2 = 2.0 Hz), 7.39 (d, 1H, J = 8.3 Hz), 7.49 (m, 1H), 7.50 (d, 1H, J = 2.0 Hz), 8.15 (s, 1H), 8.28 (dd, 1H, J1 = 8.3 Hz, J2 = 2.0 Hz).

Example 19

- 5 **Compound 97: *N*-[1-(3,5-Difluoro-benzyl)-3-(2-nitro-phenylsulfanyl)-1*H*-indol-6-yl]-2-fluoro-acetamide, structure 28 of Scheme VII, where $R^1 = 3,5$ -difluorophenyl, $R^2 = 2$ -nitrophenyl, $R^3=R^4=H$, $Z^1 =$ monofluoromethyl.**



- 10 **a) 1-(3,5-Difluoro-benzyl)-6-nitro-1*H*-indole, structure 19 of Scheme VII, where $R^1 = 3,5$ -difluorophenyl, $R^2=R^3=R^4=H$.**

To a solution of 6-nitro-1*H*-indole (19.5 g, 120 mmol) in NMP (500 mL) was added at 0 °C cesium carbonate (39.1 g, 120 mmol). After stirring for 30 min at 0 °C 3,5-

15 difluorobenzyl bromide (30.0 g, 144 mmol) was added and the mixture was allowed to warm to room temperature and stirred for 18 hrs. The mixture was poured into saturated aqueous ammonium chloride (1 L) and extracted with ethyl acetate (2 x 500 mL). The combined organic layers were washed with H₂O (2 x 500 mL) and brine (500 mL) and dried (Na₂SO₄) and concentrated to give the title compound (65 g, yellow solid) which
20 was used without further purification.

- b) 1-(3,5-Difluoro-benzyl)-1*H*-indol-6-ylamine, structure 20 of Scheme VII, where $R^1 = 3,5$ -difluorophenyl, $R^2=R^3=R^4=H$.**

EtOH 96% (1L) was added to 1-(3,5-difluoro-benzyl)-6-nitro-1*H*-indole and the
25 mixture was stirred at 60 °C until all material was dissolved. 37% HCl (37 mL) was added followed by tin(II)chloride dihydrate (268 g, 1.19 mol) and stirring was continued at 60 °C for 18 hrs. After the mixture was cooled to room temperature the solvent was removed under reduced pressure. Ethyl acetate (800 mL) was added and the mixture was poured into saturated aqueous NaHCO₃ (1 L) and filtered over kieselguhr.

30 The layers were separated and the organic layer was washed with H₂O (2 x 500 mL) and

brine (500 mL), dried (Na_2SO_4) and concentrated to afford the title compound (54 g, brown oil/solid) which was used without further purification.

c) [1-(3,5-Difluoro-benzyl)-1*H*-indol-6-yl]-carbamic acid *tert*-butyl ester, structure 26 of Scheme VII, where $\text{R}^1 = 3,5\text{-difluorophenyl}$, $\text{R}^2 = \text{R}^3 = \text{R}^4 = \text{H}$.

1-(3,5-Difluoro-benzyl)-1*H*-indol-6-ylamine was dissolved in NMP (1 L) and triethylamine (34 mL, 242 mmol) was added followed by di-*tert*-butyl dicarbonate (53 g, 242 mmol) and the mixture was stirred at room temperature for 18 hrs. The mixture was poured into saturated aqueous NaHCO_3 (1.5 L) and extracted with ethyl acetate (3 x 750 mL). The combined organic layers were washed with H_2O (1 L) and brine (1 L), dried (Na_2SO_4) and concentrated. The crude product was purified using column chromatography (heptane/ethyl acetate 4:1) to afford the title compound (39 g, 109 mmol, 91% (three steps), white solid).

d) [1-(3,5-Difluoro-benzyl)-3-(2-nitro-phenylsulfanyl)-1*H*-indol-6-yl]-carbamic acid *tert*-butyl ester, structure 27 of Scheme VII, where $\text{R}^1 = 3,5\text{-difluorophenyl}$, $\text{R}^2 = 2\text{-nitrophenyl}$, $\text{R}^3 = \text{R}^4 = \text{H}$.

To a solution of [1-(3,5-difluoro-benzyl)-1*H*-indol-6-yl]-carbamic acid *tert*-butyl ester (39 g, 109 mmol) in diethylether (750 mL) was added 2-nitrobenzenesulfonyl chloride (20.4 g, 109 mmol) and the reaction mixture was stirred at room temperature for 18 hrs. The mixture was poured into saturated aqueous NaHCO_3 (1 L) and extracted with ethyl acetate (2 x 300 mL). The combined organic layers were washed with H_2O (400 mL) and brine (400 mL), dried and concentrated to afford the title compound (56 g, yellow solid) which was used without further purification.

e) 1-(3,5-Difluoro-benzyl)-3-(2-nitro-phenylsulfanyl)-1*H*-indol-6-ylamine, structure 23 of Scheme VII, where $\text{R}^1 = 3,5\text{-difluorophenyl}$, $\text{R}^2 = 2\text{-nitrophenyl}$, $\text{R}^3 = \text{R}^4 = \text{H}$.

[1-(3,5-Difluoro-benzyl)-3-(2-nitro-phenylsulfanyl)-1*H*-indol-6-yl]-carbamic acid *tert*-butyl ester was dissolved in CH_2Cl_2 (1 L) and under nitrogen atmosphere trifluoroacetic acid (48 mL, 624 mmol) was added dropwise at room temperature. After stirring for 1 h another portion of trifluoroacetic acid (48 mL, 624 mmol) was added and the reaction mixture was stirred for an additional hour. The mixture was diluted with CH_2Cl_2 (500 mL) and H_2O (1 L) and 3N NaOH solution was added until the pH of the mixture was 11-12. The layers were separated and the organic layer was washed with H_2O (500 mL) and brine (500 mL), dried (Na_2SO_4) and concentrated to afford the crude product. The

product was purified using column chromatography (heptane/ethylacetate 1:1) to give the title compound (28 g, 68 mmol, 63 % (two steps), red/brown solid).

General method 6: Reaction of an acid chloride (method a), carboxylic acid (method b) or sulfonyl chloride (method c) with a 6-aminoindole of structure 23 to give compounds of structure 28 and 29 (Scheme VII).

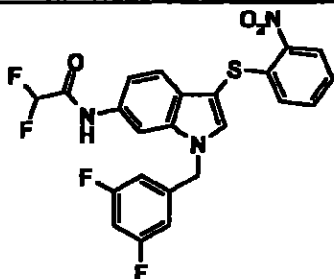
Method a, b and c can all be carried out using the same procedure which is exemplified below for method a.

To a solution of 1-(3,5-difluoro-benzyl)-3-(2-nitro-phenylsulfanyl)-1*H*-indol-6-ylamine (300 mg, 0.73 mmol) in CH₂Cl₂ (7 mL) was added at 0 °C triethylamine (0.12 mL, 0.87 mmol). Subsequently monofluoroacetyl chloride (50 µL, 0.73 mmol) was added and the mixture was stirred at room temperature for 18 hrs. The mixture was concentrated and purified using flash column chromatography (CH₂Cl₂/MeOH 99:1) to afford compound 97 (317 mg, 0.67 mmol, 92%, yellow solid).

¹H NMR (DMSO) δ 4.82 (s, 1H), 5.03 (s, 1H), 5.52 (s, 2H), 6.89 (dd, 1H, J₁ = 7.6 Hz, J₂ = 1.1 Hz), 6.98-7.01 (m, 2H), 7.20 (tt, 1H, J₁ = 9.5 Hz, J₂ = 3.0 Hz), 7.28-7.32 (m, 2H), 7.33-7.37 (m, 1H), 7.46-7.51 (m, 1H), 7.98 (s, 1H), 8.08 (s, 1H), 8.27 (dd, 1H, J₁ = 7.6 Hz, J₂ = 1.1 Hz), 10.15 (s, 1H).

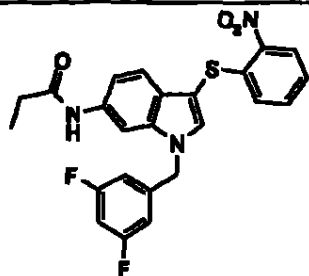
According to general method 6 the following compounds were prepared:

Compound 98: *N*-[1-(3,5-Difluoro-benzyl)-3-(2-nitro-phenylsulfanyl)-1*H*-indol-6-yl]-2,2-difluoro-acetamide, structure 28 of Scheme VII, where R¹ = 3,5-difluorophenyl, R² = 2-nitrophenyl, R³=R⁴=H, Z¹= difluoromethyl. Method a was used.



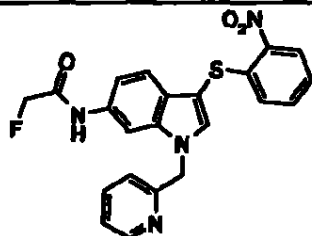
¹H-NMR (DMSO): δ 5.55 (s, 2H), 6.23-6.50 (m, 1H), 6.88 (dd, 1H, J₁ = 7.6 Hz, J₂ = 1.1 Hz), 6.97-7.03 (m, 2H), 7.20 (tt, 1H, J₁ = 9.5 Hz, J₂ = 3.0 Hz), 7.30-7.38 (m, 3H), 7.46-7.51 (m, 1H), 7.98 (d, 1H, J = 1.1 Hz), 8.12 (s, 1H), 8.28 (dd, 1H, J₁ = 7.6 Hz, J₂ = 1.1 Hz), 10.80 (s, 1H).

Compound 99: *N*-[1-(3,5-Difluoro-benzyl)-3-(2-nitro-phenylsulfanyl)-1*H*-indol-6-yl]-propionamide, structure 28 of Scheme VII, where $R^1 = 3,5$ -difluorophenyl, $R^2 = 2$ -nitrophenyl, $R^3=R^4=H$, $Z^1 = \text{ethyl}$. Method b was used.



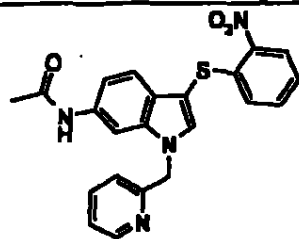
$^1\text{H-NMR}$ (DMSO): δ 1.07 (t, 3H, $J = 7.6$ Hz), 2.31 (q, 2H, $J = 7.6$ Hz), 5.51 (s, 2H), 6.89 (dd, 1H, $J_1 = 7.6$ Hz, $J_2 = 1.1$ Hz), 6.93-6.97 (m, 1H), 7.16-7.23 (m, 3H), 7.27 (d, 1H, $J = 8.4$ Hz), 7.32-7.37 (m, 1H), 7.46-7.51 (m, 1H), 8.01 (d, 1H, $J = 1.1$ Hz), 8.02 (s, 1H), 8.27 (dd, 1H, $J_1 = 7.6$ Hz, $J_2 = 1.1$ Hz), 9.92 (s, 1H).

Compound 100: 2-Fluoro-*N*-[3-(2-nitro-phenylsulfanyl)-1-pyridin-2-ylmethyl-1*H*-indol-6-yl]-acetamide, structure 28 of Scheme VII, where $R^1 = 2$ -pyridyl, $R^2 = 2$ -nitrophenyl, $R^3=R^4=H$, $Z^1 = \text{monofluoromethyl}$. Method a was used.



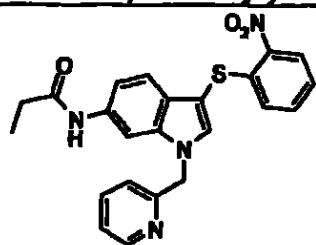
$^1\text{H-NMR}$ (CDCl₃): δ 4.88 (s, 1H), 5.00 (s, 1H), 5.51 (s, 2H), 6.94-6.99 (m, 2H), 7.06 (dd, 1H, $J_1 = 7.6$ Hz, $J_2 = 1.5$ Hz), 7.18 (td, 1H, $J_1 = 8.4$ Hz, $J_2 = 1.5$ Hz), 7.22-7.29 (m, 2H), 7.46 (d, 1H, $J = 8.4$ Hz), 7.55 (s, 1H), 7.64 (td, 1H, $J_1 = 8.4$ Hz, $J_2 = 1.5$ Hz), 8.02 (s, 1H), 8.05 (d, 1H, $J = 2.2$ Hz), 8.27 (dd, 1H, $J_1 = 7.6$ Hz, $J_2 = 1.5$ Hz), 8.62 (d, 1H, $J = 4.6$ Hz).

Compound 101: *N*-[3-(2-Nitro-phenylsulfanyl)-1-pyridin-2-ylmethyl-1*H*-indol-6-yl]-acetamide, structure 28 of Scheme VII, where $R^1 = 2$ -pyridyl, $R^2 = 2$ -nitrophenyl, $R^3=R^4=H$, $Z^1 = \text{methyl}$. Method a was used.



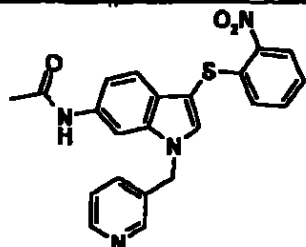
$^1\text{H-NMR}$ (CDCl₃): δ 1.80 (s, 3H), 5.48 (s, 2H), 6.92-6.98 (m, 3H), 7.15-7.30 (m, 4H), 7.40 (d, 1H, $J = 7.6$ Hz), 7.51 (s, 1H), 7.63 (td, 1H, $J_1 = 7.6$ Hz, $J_2 = 2.2$ Hz), 8.04 (d, 1H, $J = 1.5$ Hz), 8.26 (dd, 1H, $J_1 = 7.6$ Hz, $J_2 = 1.5$ Hz), 8.61 (d, 1H, $J = 4.6$ Hz).

Compound 102: *N*-[3-(2-Nitro-phenylsulfanyl)-1-pyridin-2-ylmethyl-1*H*-indol-6-yl]-propionamide, structure 28 of Scheme VII, where $R^1 = 2$ -pyridyl, $R^2 = 2$ -nitrophenyl, $R^3 = R^4 = H$, $Z^1 = \text{ethyl}$). Method b was used.



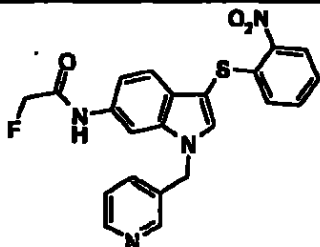
$^1\text{H-NMR}$ (CDCl_3): δ 1.25 (t, 3H, $J = 7.6$ Hz), 2.41 (q, 2H, $J = 7.6$ Hz), 5.49 (s, 2H), 6.92-6.98 (m, 3H), 7.15-7.27 (m, 4H), 7.40 (d, 1H, $J = 8.4$ Hz), 7.51 (s, 1H), 7.63 (td, 1H, $J_1 = 7.6$ Hz, $J_2 = 1.5$ Hz), 8.12 (d, 1H, $J = 1.5$ Hz), 8.26 (dd, 1H, $J_1 = 7.6$ Hz, $J_2 = 1.5$ Hz), 8.61 (d, 1H, $J = 4.6$ Hz).

Compound 103: *N*-[3-(2-Nitro-phenylsulfanyl)-1-pyridin-3-ylmethyl-1*H*-indol-6-yl]-acetamide, structure 28 of Scheme VII, where $R^1 = 3$ -pyridyl, $R^2 = 2$ -nitrophenyl, $R^3 = R^4 = H$, $Z^1 = \text{methyl}$. Method a was used.



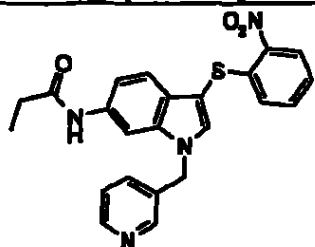
$^1\text{H NMR}$ (CDCl_3) δ 2.20 (s, 3H), 5.40 (s, 2H), 6.86 (dd, 1H, $J_1 = 7.6$ Hz, $J_2 = 2.2$ Hz), 6.72 (dd, 1H, $J_1 = 7.6$ Hz, $J_2 = 1.1$ Hz), 7.16-7.20 (m, 1H), 7.24-7.31 (m, 3H), 7.40 (d, 1H, $J = 8.4$ Hz), 7.42 (s, 1H), 7.49-7.52 (m, 1H), 8.15 (d, 1H, $J = 2.2$ Hz), 8.26 (dd, 1H, $J_1 = 8.4$ Hz, $J_2 = 2.2$ Hz), 8.55 (d, 1H, $J = 3.0$ Hz), 8.58 (dd, 1H, $J_1 = 8.4$ Hz, $J_2 = 2.2$ Hz).

Compound 104: 2-Fluoro-*N*-[3-(2-nitro-phenylsulfanyl)-1-pyridin-3-ylmethyl-1*H*-indol-6-yl]-acetamide, structure 28 of Scheme VII, where $R^1 = 3$ -pyridyl, $R^2 = 2$ -nitrophenyl, $R^3 = R^4 = H$, $Z^1 = \text{monofluoromethyl}$. Method a was used.



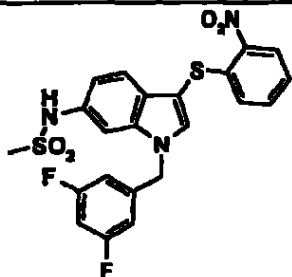
$^1\text{H NMR}$ (CDCl_3) δ 4.88 (s, 1H), 5.00 (s, 1H), 5.42 (s, 2H), 6.92 (dd, 1H, $J_1 = 7.6$ Hz, $J_2 = 1.1$ Hz), 7.00 (dd, 1H, $J_1 = 8.4$ Hz, $J_2 = 1.8$ Hz), 7.17-7.21 (m, 1H), 7.25-7.32 (m, 2H), 7.44-7.47 (d, 1H, $J = 7.6$ Hz), 7.45 (s, 1H), 7.49-7.53 (m, 1H), 8.04 (d, 1H, $J = 4.6$ Hz), 8.15 (d, 1H, $J = 1.8$ Hz), 8.27 (dd, 1H, $J_1 = 8.4$ Hz, $J_2 = 1.8$ Hz), 8.56 (d, 1H, $J = 3.0$ Hz), 8.58 (dd, 1H, $J_1 = 4.6$ Hz, $J_2 = 1.2$ Hz).

Compound 105: *N*-[3-(2-Nitro-phenylsulfanyl)-1-pyridin-3-ylmethyl-1*H*-indol-6-yl]-propionamide, structure 28 of Scheme VII, where $R^1 = 3$ -pyridyl, $R^2 = 2$ -nitrophenyl, $R^3 = R^4 = H$, $Z^1 = \text{ethyl}$. Method b was used.



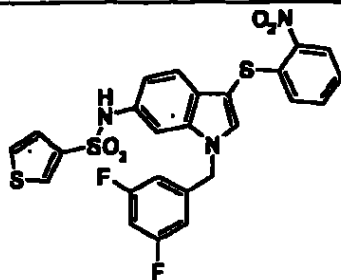
^1H NMR (CDCl_3) δ 1.26 (t, 3H, $J = 7.6$ Hz), 2.42 (q, 2H, $J = 7.6$ Hz), 5.39 (s, 2H), 8.68 (dd, 1H, $J_1 = 8.4$ Hz, $J_2 = 1.8$ Hz), 6.91 (dd, 1H, $J_1 = 8.4$ Hz, $J_2 = 1.1$ Hz), 7.15-7.20 (m, 1H), 7.24-7.30 (m, 3H), 7.38-7.41 (m, 2H), 7.48-7.52 (m, 1H), 8.23 (d, 1H, $J = 1.8$ Hz), 8.27 (dd, 1H, $J_1 = 8.4$ Hz, $J_2 = 1.8$ Hz), 8.55 (d, 1H, $J = 3.0$ Hz), 8.57 (dd, 1H, $J_1 = 4.6$ Hz, $J_2 = 1.1$ Hz).

Compound 106: *N*-[1-(3,5-Difluoro-benzyl)-3-(2-nitro-phenylsulfanyl)-1*H*-indol-6-yl]-methanesulfonamide, structure 29 of Scheme VII, where $R^1 = 3,5$ -difluorophenyl, $R^2 = 2$ -nitrophenyl, $R^3 = R^4 = H$, $Z^2 = \text{Me}$. Method c was used.



^1H -NMR (DMSO): δ 2.95 (s, 3H), 5.54 (s, 2H), 6.90 (dd, 1H, $J_1 = 7.6$ Hz, $J_2 = 1.1$ Hz), 6.98-7.04 (m, 3H), 7.20 (tt, 1H, $J_1 = 9.5$ Hz, $J_2 = 3.0$ Hz), 7.31-7.37 (m, 2H), 7.41 (d, 1H, $J = 1.5$ Hz), 7.47-7.52 (m, 1H), 8.08 (s, 1H), 8.27 (dd, 1H, $J_1 = 7.6$ Hz, $J_2 = 1.1$ Hz), 9.65 (s, 1H).

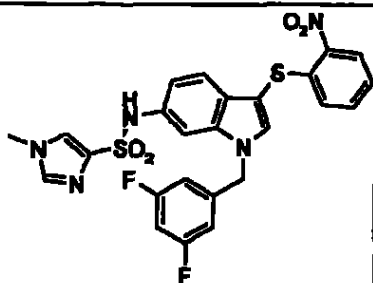
Compound 107: Thiophene-3-sulfonic acid [1-(3,5-difluoro-benzyl)-3-(2-nitro-phenylsulfanyl)-1*H*-indol-6-yl]-amide, structure 29 of Scheme VII, where $R^1 = 3,5$ -difluorophenyl, $R^2 = 2$ -nitrophenyl, $R^3 = R^4 = H$, $Z^1 = 3$ -thiophene. Method c was used.



^1H -NMR (DMSO): δ 5.50 (s, 2H), 6.85 (m, 2H), 6.92-6.97 (m, 2H), 7.13 (dd, 1H, $J_1 = 5.0$, $J_2 = 1.1$ Hz), 7.19-7.26 (m, 2H), 7.31 (d, 1H, $J = 2.2$ Hz), 7.32-7.36 (m, 1H), 7.45-7.50 (m, 1H), 7.61 (dd, 1H, $J_1 = 5.0$ Hz, $J_2 = 3.0$ Hz), 7.97 (dd, 1H, $J_1 = 3.0$ Hz, $J_2 = 1.1$ Hz), 8.05 (s, 1H), 8.26 (dd, 1H, $J_1 = 7.6$ Hz, $J_2 = 1.1$ Hz), 10.20 (s, 1H).

Compound 108: 1-Methyl-1*H*-imidazole-4-sulfonic acid [1-(3,5-difluoro-benzyl)-3-(2-nitro-phenylsulfanyl)-1*H*-indol-6-yl]-amide, structure 29 of Scheme VII, where $R^1 = 3,5$ -difluorophenyl, $R^2 = 2$ -nitrophenyl, $R^3 = R^4 = H$, $Z^2 = 4$ -(1-methyl)-imidazole.

Method c was used.

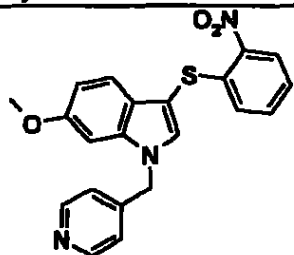


¹H-NMR (DMSO): δ 3.60 (s, 3H), 5.46 (s, 2H), 6.86 (dd, 1H, $J_1 = 7.6$ Hz, $J_2 = 0.7$ Hz), 6.92 (dd, 1H, $J_1 = 7.6$ Hz, $J_2 = 1.5$ Hz), 6.96-7.01 (m, 2H), 7.19 (d, 1H, $J = 7.6$ Hz), 7.23 (tt, 1H, $J_1 = 9.5$ Hz, $J_2 = 3.0$ Hz), 7.31-7.36 (m, 2H), 7.45-7.49 (m, 1H), 7.66-7.69 (m, 2H), 8.02 (s, 1H), 8.26 (dd, 1H, $J_1 = 7.6$ Hz, $J_2 = 0.7$ Hz), 10.20 (s, 1H).

Example 20

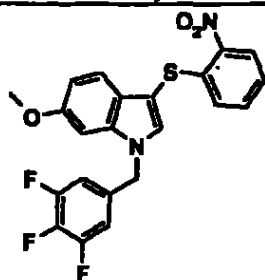
- 5 According to general method 3 the following compounds were prepared:

Compound 93: 6-Methoxy-3-(2-nitro-phenylsulfanyl)-1-pyridin-4-ylmethyl-1*H*-indole, structure 3 of scheme I, where $R^1 = 4$ -pyridyl, $R^2 = 2$ -nitrophenyl, $R^3 = R^4 = H$, $R^5 = OMe$. NaH and DMF were used.



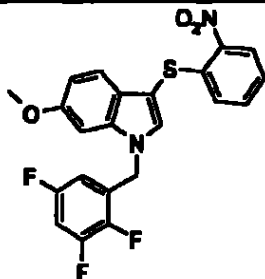
¹H NMR (CDCl₃): δ 3.80 (s, 3H, OCH₃), 5.37 (s, 2H, NCH₂Ar), 6.71 (d, 1H, $J = 2.7$ Hz), 6.86 (dd, 1H, $J_1 = 8.4$ Hz, $J_2 = 2.7$ Hz), 7.00 (dd, 1H, $J_1 = 8.4$ Hz, $J_2 = 1.5$ Hz), 7.04 (m, 2H), 7.19 (td, 1H, $J_1 = 7.6$ Hz, $J_2 = 1.5$ Hz), 7.29 (td, 1H, $J_1 = 7.6$ Hz, $J_2 = 1.5$ Hz), 7.36 (s, 1H), 7.40 (d, 1H, $J = 8.4$ Hz), 8.27 (dd, 1H, $J_1 = 7.6$ Hz, $J_2 = 1.5$ Hz), 8.59 (m, 2H).

Compound 94: 6-Methoxy-3-(2-nitro-phenylsulfanyl)-1-(3,4,5-trifluoro-benzyl)-1*H*-indole, structure 3 of scheme I, where $R^1 = 3,4,5$ -difluorophenyl, $R^2 = 2$ -nitrophenyl, $R^3 = R^4 = H$, $R^5 = OMe$. Cs_2CO_3 and NMP were used.



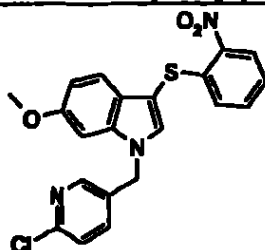
^1H -NMR ($CDCl_3$): δ 3.83 (s, 3H, OCH_3), 5.28 (s, 2H, NCH_2Ar), 6.72 (d, 1H, $J = 2.2$ Hz), 6.75 (d, 1H, $J = 7.6$ Hz), 6.77 (d, 1H, $J = 7.6$ Hz), 6.86 (dd, 1H, $J_1 = 8.4$ Hz, $J_2 = 2.2$ Hz), 6.97 (dd, 1H, $J_1 = 8.4$ Hz, $J_2 = 1.1$ Hz), 7.19 (td, 1H, $J_1 = 7.6$ Hz, $J_2 = 1.1$ Hz), 7.28 (td, 1H, $J_1 = 7.6$ Hz, $J_2 = 1.1$ Hz), 7.33 (s, 1H), 7.40 (d, 1H, $J = 8.4$ Hz), 8.27 (dd, 1H, $J_1 = 8.4$ Hz, $J_2 = 2.2$ Hz).

Compound 95: 6-Methoxy-3-(2-nitro-phenylsulfanyl)-1-(2,3,5-trifluoro-benzyl)-1*H*-indole, structure 3 of scheme I, where $R^1 = 2,3,5$ -difluorophenyl, $R^2 = 2$ -nitrophenyl, $R^3 = R^4 = H$, $R^5 = OMe$. Cs_2CO_3 and NMP were used.



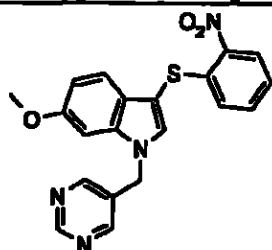
^1H -NMR ($CDCl_3$): δ 3.85 (s, 3H, OCH_3), 5.39 (s, 2H, NCH_2Ar), 6.42 (m, 1H), 6.82 (d, 1H, $J = 2.7$ Hz), 6.86 (dd, 1H, $J_1 = 7.6$ Hz, $J_2 = 2.2$ Hz), 6.90 (m, 1H), 6.96 (dd, 1H, $J_1 = 7.6$ Hz, $J_2 = 2.2$ Hz), 7.18 (td, 1H, $J_1 = 7.6$ Hz, $J_2 = 1.5$ Hz), 7.27 (td, 1H, $J_1 = 7.6$ Hz, $J_2 = 1.5$ Hz), 7.37 (s, 1H), 7.39 (d, 1H, $J = 7.6$ Hz), 8.27 (dd, 1H, $J_1 = 7.6$ Hz, $J_2 = 1.5$ Hz).

Compound 96: 1-(6-Chloro-pyridin-3-ylmethyl)-6-methoxy-3-(2-nitro-phenylsulfanyl)-1*H*-indole, structure 3 of Scheme I, where $R^1 = 4$ -chloro-3-pyridyl, $R^2 = 2$ -nitrophenyl, $R^3 = R^4 = H$, $R^5 = OMe$. Cs_2CO_3 and NMP were used.



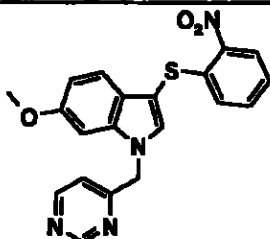
^1H -NMR ($CDCl_3$): δ 3.82 (s, 3H, OCH_3), 5.37 (s, 2H, NCH_2Ar), 6.76 (d, 1H, $J = 2.2$ Hz), 6.84 (dd, 1H, $J_1 = 7.6$ Hz, $J_2 = 2.2$ Hz), 6.96 (dd, 1H, $J_1 = 7.6$ Hz, $J_2 = 1.1$ Hz), 7.18 (td, 1H, $J_1 = 8.4$ Hz, $J_2 = 1.1$ Hz), 7.27 (td, 1H, $J_1 = 8.4$ Hz, $J_2 = 1.1$ Hz), 7.30-7.41 (m, 4H), 8.27 (dd, 1H, $J_1 = 8.4$ Hz, $J_2 = 1.1$ Hz), 8.34 (d, 1H, $J = 3.0$ Hz).

Compound 115: 6-Methoxy-3-(2-nitro-phenylsulfanyl)-1-pyrimidin-5-ylmethyl-1H-indole, structure 3 of Scheme I, where $R^1 = 3,5$ -pyrimidyl, $R^2 = 2$ -nitrophenyl, $R^3=R^4=H$, $R^5=OMe$. NaH and DMF were used. The synthesis of methanesulfonic acid pyrimidin-5-ylmethyl ester is described in example 23a).



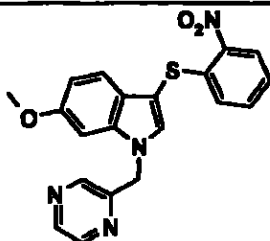
^1H NMR ($CDCl_3$) δ 3.83 (s, 3H), 5.38 (s, 2H), 6.77 (d, 1H, $J = 3.0$ Hz), 6.86 (dd, 1H, $J_1 = 8.4$ Hz, $J_2 = 3.0$ Hz), 6.96 (dd, 1H, $J_1 = 8.4$ Hz, $J_2 = 1.1$ Hz), 7.17-7.21 (m, 1H), 7.26-7.32 (m, 1H), 7.37 (s, 1H), 7.39 (d, 1H, $J = 8.4$ Hz), 8.27 (dd, 1H, $J_1 = 8.4$ Hz, $J_2 = 1.1$ Hz), 8.61 (s, 2H), 9.20 (s, 1H).

Compound 116: 6-Methoxy-3-(2-nitro-phenylsulfanyl)-1-pyrimidin-4-ylmethyl-1H-indole, structure 3 of Scheme I, where $R^1 = 2,4$ -pyrimidyl, $R^2 = 2$ -nitrophenyl, $R^3=R^4=H$, $R^5=OMe$. Cs_2CO_3 and NMP were used.



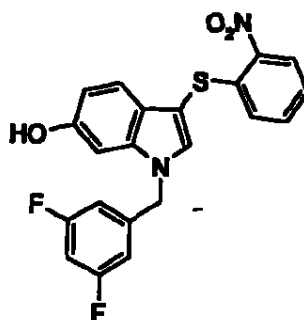
^1H NMR ($CDCl_3$) δ 3.80 (s, 3H), 5.44 (s, 2H), 6.74 (d, 1H, $J = 2.2$ Hz), 6.80 (dd, 1H, $J_1 = 4.6$ Hz, $J_2 = 1.1$ Hz), 6.86 (dd, 1H, $J_1 = 8.4$ Hz, $J_2 = 3.0$ Hz), 7.00 (dd, 1H, $J_1 = 8.4$ Hz, $J_2 = 1.1$ Hz), 7.17-7.21 (m, 1H), 7.26-7.33 (m, 1H), 7.40 (d, 1H, $J = 8.4$ Hz), 7.42 (s, 1H), 8.27 (dd, 1H, $J_1 = 8.4$ Hz, $J_2 = 1.1$ Hz), 8.66 (d, 1H, $J = 4.6$ Hz), 9.24 (d, 1H, $J = 1.1$ Hz).

Compound 117: 6-Methoxy-3-(2-nitro-phenylsulfanyl)-1-pyrazin-2-ylmethyl-1H-indole, structure 3 of Scheme I, where $R^1 = 2,5$ -pyrazyl, $R^2 = 2$ -nitrophenyl, $R^3=R^4=H$, $R^5=OMe$. Cs_2CO_3 and NMP were used.



^1H NMR ($CDCl_3$) δ 3.83 (s, 3H), 5.49 (s, 2H), 6.82-6.86 (m, 2H), 6.99 (dd, 1H, $J_1 = 8.4$ Hz, $J_2 = 1.1$ Hz), 7.16-7.20 (m, 1H), 7.25-7.29 (m, 1H), 7.38 (d, 1H, $J = 8.4$ Hz), 7.46 (s, 1H), 8.26 (dd, 1H, $J_1 = 8.4$ Hz, $J_2 = 1.1$ Hz), 8.35 (d, 1H, $J = 1.1$ Hz), 8.55 (d, 1H, $J = 3.0$ Hz), 8.59-8.61 (m, 1H).

Compound 61: 1-(3,5-Difluoro-benzyl)-3-(2-nitro-phenylsulfanyl)-1*H*-indol-6-ol,
structure 25 of Scheme VI, where $R^1 = 3,5$ -difluorophenyl, $R^2 = 2$ -nitrophenyl,
 $R^3 = R^4 = H$, $R^5 = OH$.

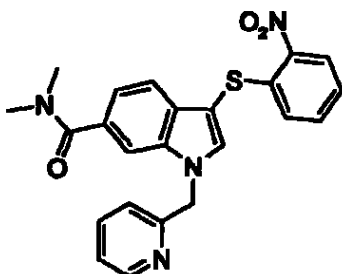


To a solution of compound 63 (240 mg, 0.56 mmol) in CH_2Cl_2 (10 mL) was added at 0 °C boron trifluoride-methyl sulfide complex (2.37 mL, 22.5 mmol). After stirring for 2 hrs at 0 °C the reaction mixture was allowed to warm to room temperature and stirring was continued for another 4 hrs. The reaction mixture was poured into ice water (20 mL) and after addition of ethyl acetate (10 mL) the layers were separated. The organic layer was washed with saturated aqueous $NaHCO_3$ (20 mL) and brine (20 mL) and dried over Na_2SO_4 . Concentration gave the crude product which was purified using flash chromatography (heptane/ethylacetate 3:2) to afford compound 61 as a yellow oil (87 mg, 0.21 mmol, 38%).

^1H NMR ($CDCl_3$) δ 4.75 (2, 1H), 5.29 (s, 2H), 4.66 (m, 1H), 6.72-6.79 (m, 3H), 6.98 (dd, 1H, $J_1 = 8.4$ Hz, $J_2 = 1.5$ Hz), 7.17-7.21 (m, 1H), 7.27-7.31 (m, 1H), 7.35-7.37 (m, 3H), 8.27 (dd, 1H, $J_1 = 8.4$ Hz, $J_2 = 1.5$ Hz).

Example 22

Compound 109: 3-(2-Nitro-phenylsulfanyl)-1-pyridin-2-ylmethyl-1*H*-indole-6-
carboxylic acid dimethylamide, structure 15 of Scheme IV, where $R^1 = 2$ -pyridyl, $R^2 =$
2-nitrophenyl, $R^3 = R^4 = H$, $R^5 = R^6 = Me$.



a) 1-Pyridin-2-ylmethyl-1H-indole-6-carboxylic acid methyl ester.

Under a nitrogen atmosphere: to a solution of 1H-indole-6-carboxylic acid methyl ester (for synthesis see example 2a), 2.47 g, 14.1 mmol) in NMP (140 mL) was added Cs₂CO₃ (10.1 mg, 31 mmol) at 0 °C. After stirring for 15 min 2-picolyl chloride hydrochloride (2.77 g, 16.9 mmol) was added and the mixture was stirred at room temperature for 18 h. Ethyl acetate (200 mL) was added and the mixture was washed with saturated aqueous ammonium chloride (3x150 mL) and brine (200 mL). The organic phase was dried (Na₂SO₄) and concentrated. The crude product was purified using column chromatography (ethyl acetate/heptane 1:3) to give the title compound as a colourless oil, which slowly crystallised on standing (2.72 g, 10.2 mmol, 72%).

b) 3-(2-Nitro-phenylsulfanyl)-1-pyridin-2-ylmethyl-1H-indole-6-carboxylic acid methyl ester, structure 13 of Scheme IV, where R¹ = 2-pyridyl, R² = 2-nitrophenyl, R³=R⁴=H.

To a solution of 1-pyridin-2-ylmethyl-1H-indole-6-carboxylic acid methyl ester (2.72 g, 10.2 mmol) in dichloromethane (75 mL) was added at room temperature a solution of 2-nitrobenzenesulfonyl chloride (1.93 g, 10.2 mmol) in dichloromethane (75 mL). The mixture was stirred at room temperature for 24 hrs. The reaction mixture was concentrated and the crude product was purified using column chromatography (ethyl acetate/heptane 1:5 to 1:2) to give the title compound as a yellow solid (3.21 g, 7.65 mmol, 75%).

c) 3-(2-Nitro-phenylsulfanyl)-1-pyridin-2-ylmethyl-1H-indole-6-carboxylic acid, structure 14 of Scheme IV, where R¹ = 2-pyridyl, R² = 2-nitrophenyl, R³=R⁴=H.

To a suspension of 3-(2-nitro-phenylsulfanyl)-1-pyridin-2-ylmethyl-1H-indole-6-carboxylic acid methyl ester (3.0 g, 6.58 mmol) in dioxane (65 mL) was added a solution of LiOH.H₂O (1.66 g, 39.6 mmol) in water (65 mL). The reaction mixture was stirred overnight at 60°C. The mixture was then acidified to pH 6 by addition of 15%

aqueous HCl and the mixture was extracted with ethyl acetate (2 x 100 mL). The combined organic layers were dried over Na₂SO₄ and concentrated to give a yellow powder. The product was recrystallised from heptane/ethyl acetate to give the title compound as yellow/orange crystals (2.47 g, 6.09 mmol, 93%)

5

General method 7: amidation of 6-carboxyl indoles of structure 14 to give 6-carboxamideindoles of structure 15 (Scheme IV).

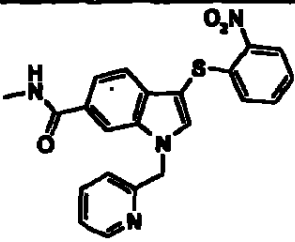
Under nitrogen atmosphere: to a solution of 3-(2-nitro-phenylsulfanyl)-1-pyridin-2-ylmethyl-1*H*-indole-6-carboxylic acid (700 mg, 1.73 mmol) in dry CH₂Cl₂ (70 mL) was added DIPEA (0.9 mL, 5.2 mmol), TBTU (840 mg, 2.6 mmol) and dimethylamine hydrochloride (420 mg, 5.1 mmol). The reaction mixture was stirred overnight at room temperature and then poured into saturated aqueous NaHCO₃ (100 mL). The organic layer was washed with brine (50 mL), dried (Na₂SO₄) and concentrated. The crude product was purified by column chromatography (ethyl acetate/MeOH 95:5) to afford compound 109 (540 mg, 1.25 mmol, 72%, yellow solid).

15

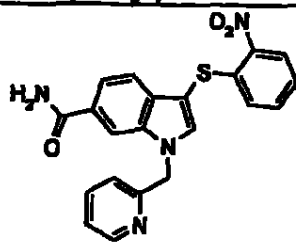
¹H-NMR (CDCl₃): δ 2.97 (s, 3H), 3.11 (s, 3H), 5.53 (s, 2H), 6.90 (dd, 1H, J₁ = 7.6 Hz, J₂ = 1.5 Hz), 6.95 (d, 1H, J = 7.6 Hz), 7.17-7.28 (m, 4H), 7.51 (d, 1H, J = 7.6 Hz), 7.54 (s, 1H), 7.61-7.66 (m, 2H), 8.28 (dd, 1H, J₁ = 8.4 Hz, J₂ = 1.5 Hz), 8.61 (d, 1H, J = 4.6 Hz).

20

The following compounds were prepared using general procedure 7:

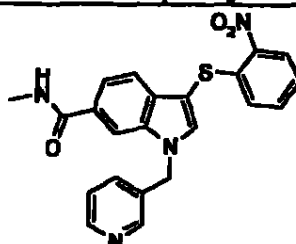
Compound 110: 3-(2-Nitro-phenylsulfanyl)-1-pyridin-2-ylmethyl-1 <i>H</i> -indole-6-carboxylic acid methylamide, structure 15 of Scheme IV, where R ¹ = 2-pyridyl, R ² = 2-nitrophenyl, R ³ =R ⁴ =H, R ⁵ =H, R ⁶ =Me.	
	¹ H-NMR (DMSO): δ 2.78 (d, 3H, J = 4.6 Hz), 5.70 (s, 2H), 6.88 (dd, 1H, J ₁ = 8.4 Hz, J ₂ = 1.5 Hz), 7.19 (d, 1H, J = 7.6 Hz), 7.30-7.37 (m, 2H), 7.41 (d, 1H, J = 8.4 Hz), 7.48-7.53 (m, 1H), 7.62 (dd, 1H, J ₁ = 7.6 Hz, J ₂ = 1.5 Hz), 7.79 (td, 1H, J ₁ = 7.6 Hz, J ₂ = 1.5 Hz), 8.13 (s, 1H), 8.20 (s, 1H), 8.28 (dd, 1H, J ₁ = 8.4 Hz, J ₂ = 1.5 Hz), 8.38 (q, 1H, J = 4.6 Hz), 8.55 (s, 1H, J = 4.6 Hz).

Compound 111: 3-(2-Nitro-phenylsulfanyl)-1-pyridin-2-ylmethyl-1*H*-indole-6-carboxylic acid amide, structure 15 of Scheme IV, where $R^1 = 2$ -pyridyl, $R^2 = 2$ -nitrophenyl, $R^3=R^4=H$, $R^6=R^9=H$.



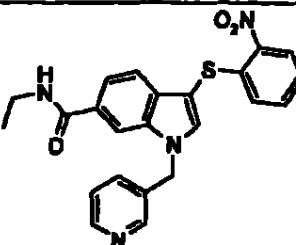
^1H -NMR (DMSO): δ 5.70 (s, 2H), 6.88 (dd, 1H, $J_1 = 8.4$ Hz, $J_2 = 1.5$ Hz), 7.21 (d, 1H, $J = 7.6$ Hz), 7.28-7.37 (m, 3H), 7.39 (d, 1H, $J = 7.6$ Hz), 7.48-7.53 (m, 1H), 7.66 (dd, 1H, $J_1 = 8.4$ Hz, $J_2 = 1.5$ Hz), 7.79 (td, 1H, $J = 7.6$ Hz, $J_2 = 1.5$ Hz), 7.93 (s, 1H), 8.17 (s, 1H), 8.20 (s, 1H), 8.26 (dd, 1H, $J_1 = 7.6$ Hz, $J_2 = 1.5$ Hz), 8.55 (d, 1H, $J = 4.6$ Hz).

Compound 112: 3-(2-Nitro-phenylsulfanyl)-1-pyridin-3-ylmethyl-1*H*-indole-6-carboxylic acid methylamide, structure 15 of Scheme IV, where $R^1 = 3$ -pyridyl, $R^2 = 2$ -nitrophenyl, $R^3=R^4=H$, $R^6=H$, $R^9=Me$. 3-Picolyl chloride hydrochloride was used instead of 2-picolyl chloride hydrochloride.



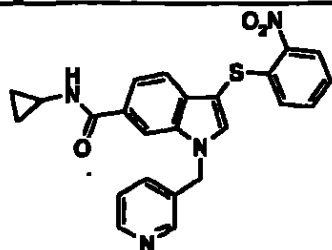
^1H -NMR (DMSO): δ 2.80 (d, 3H, $J = 4.6$ Hz), 5.65 (s, 2H), 6.84 (dd, 1H, $J_1 = 7.6$ Hz, $J_2 = 1.1$ Hz), 7.33-7.42 (m, 3H), 7.46-7.51 (m, 1H), 7.62 (dd, 1H, $J_1 = 8.4$ Hz, $J_2 = 1.1$ Hz), 7.68 (dt, 1H, $J_1 = 7.6$ Hz, $J_2 = 2.2$ Hz), 8.19 (s, 1H), 8.26 (s, 1H), 8.28 (dd, 1H, $J_1 = 7.6$ Hz, $J_2 = 1.1$ Hz), 8.41 (q, 1H, $J = 4.6$ Hz), 8.51 (dd, 1H, $J_1 = 4.6$ Hz, $J_2 = 1.1$ Hz), 8.64 (d, 1H, $J = 3.0$ Hz).

Compound 113: 3-(2-Nitro-phenylsulfanyl)-1-pyridin-3-ylmethyl-1*H*-indole-6-carboxylic acid ethylamide, structure 15 of Scheme IV, where $R^1 = 3$ -pyridyl, $R^2 = 2$ -nitrophenyl, $R^3=R^4=H$, $R^6=H$, $R^9=Et$. 3-Picolyl chloride hydrochloride was used instead of 2-picolyl chloride hydrochloride.



^1H -NMR (DMSO): δ 1.13 (t, 3H, $J = 7.6$ Hz), 3.30 (q, 2H, $J = 7.6$ Hz), 5.66 (s, 2H), 6.83 (dd, 1H, $J_1 = 7.6$ Hz, $J_2 = 1.1$ Hz), 7.33-7.41 (m, 3H), 7.46-7.51 (m, 1H), 7.64 (dd, 1H, $J_1 = 7.6$ Hz, $J_2 = 1.1$ Hz), 7.67 (dt, 1H, $J_1 = 7.6$ Hz, $J_2 = 2.2$ Hz), 8.19 (s, 1H), 8.26 (s, 1H), 8.27 (dd, 1H, $J_1 = 7.6$ Hz, $J_2 = 1.1$ Hz), 8.45 (t, 1H, $J = 5.7$ Hz), 8.52 (dd, 1H, $J_1 = 4.6$ Hz, $J_2 = 1.5$ Hz), 8.64 (d, 1H, $J = 3.0$ Hz).

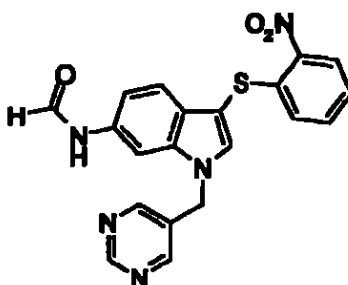
Compound 114: 3-(2-Nitro-phenylsulfanyl)-1-pyridin-3-ylmethyl-1*H*-indole-6-carboxylic acid cyclopropylamide, structure 15 of Scheme IV, where R¹ = 3-pyridyl, R² = 2-nitrophenyl, R³=R⁴=H, R⁵=H, R⁶=cyclopropyl. 3-Picolyl chloride hydrochloride was used instead of 2-picolyl chloride hydrochloride.



¹H-NMR (DMSO): δ 0.54-0.58 (m, 2H), 0.67-0.73 (m, 2H), 2.80-2.87 (m, 1H), 5.66 (s, 2H), 6.82 (d, 1H, J = 7.6 Hz), 7.33-7.41 (m, 3H), 7.46-7.50 (m, 1H), 7.61 (dd, 1H, J₁ = 7.6 Hz, J₂ = 1.1 Hz), 7.67 (dt, 1H, J₁ = 7.6 Hz, J₂ = 1.5 Hz), 8.17 (s, 1H), 8.25 (s, 1H), 8.28 (dd, 1H, J₁ = 7.6 Hz, J₂ = 1.1 Hz), 8.42 (t, 1H, J = 4.6 Hz), 8.52 (dd, 1H, J₁ = 4.6 Hz, J₂ = 1.5 Hz), 8.63 (d, 1H, J = 3.0 Hz).

Example 23

Compound 118: *N*-[3-(2-Nitro-phenylsulfanyl)-1-pyrimidin-5-ylmethyl-1*H*-indol-6-yl]-formamide, structure 28 of Scheme VII, where R¹ = 3,5-pyrimidyl, R² = 2-nitrophenyl, R³=R⁴=H, Z = H



10 a) 6-Nitro-1-pyrimidin-5-ylmethyl-1*H*-indole

5-(Hydroxymethyl)pyrimidine (16.2 g, 147 mmol) was dissolved in 500 mL of CH₂Cl₂ and cooled to -40°C. MsCl (16.0 g, 140 mmol) was added at -40 °C. The mixture was stirred for 1 hour allowing to reach -20°C. The solution was used as such.

6-Nitroindole-1*H*-indole (35.6 g, 220 mmol) was dissolved in 750 mL of DMF and NaH (50%, 12 g, 250 mmol) was added in portions and the mixture was stirred for 1 hour. The mixture was cooled to -40°C and the solution of the mesylate was added dropwise. The mixture was allowed to reach room temperature overnight. The mixture was quenched with water and extracted with ethyl acetate (2x). The combined organic layers were washed with water (2x) and brine and dried over Na₂SO₄. After concentration *in*

vacuo the material was purified by means of column chromatography (silica, heptane/ethyl acetate (1:1)→(1:4)) affording compound the title compound as a yellow solid (14 g, 55 mmol, 39%).

5 b) 1-Pyrimidin-5-ylmethyl-1*H*-indol-6-ylamine.

6-Nitro-1-pyrimidin-5-ylmethyl-1*H*-indole (4.1 g, 16.1 mmol) was dissolved in 100 mL of THF and 100 mL of isopropanol. Pd/C (2 g) was added and the mixture was stirred under an H₂-atmosphere (balloon) for 2 hours. The mixture was filtered over Celite and washed with ethyl acetate affording the title compound after concentration (3.5 g, 15.6 mmol, 97 %).

c) 1-Pyrimidin-5-ylmethyl-1*H*-indol-6-yl)-carbamic acid tert-butyl ester

1-Pyrimidin-5-ylmethyl-1*H*-indol-6-ylamine (5.5 g, 24.6 mmol) was dissolved in 100 mL of NMP and triethylamine (3.5 g, 35 mmol) and di-*tert*-butyl dicarbonate (7.0 g, 32 mmol) were added. The mixture was stirred overnight, quenched with NaHCO₃-sat and extracted with toluene (3x). The combined organic layers were washed with water (4x) and brine and dried over Na₂SO₄. Concentration of the layers afforded the title compound (3.1 g, 39%).

d) [3-(2-Nitro-phenylsulfanyl)-1-pyrimidin-5-ylmethyl-1*H*-indol-6-yl]-carbamic acid tert-butyl ester

1-Pyrimidin-5-ylmethyl-1*H*-indol-6-yl)-carbamic acid tert-butyl ester (3.1 g, 9.6 mmol) was dissolved in 150 mL of CH₂Cl₂ and 2-nitrobenzene sulfenylchloride (1.86 g, 9.8 mmol) was added. The mixture was stirred for 18 hours and quenched with NaHCO₃-sat and extracted with ethyl acetate (2x). The combined organic layers were washed with brine and dried over Na₂SO₄. The product was purified by means of column chromatography (silica, heptane / ethyl acetate (1:1) which gave the title compound as a yellow solid (3.8 g, 83 %).

e) N-[3-(2-Nitro-phenylsulfanyl)-1-pyrimidin-5-ylmethyl-1*H*-indol-6-yl]-formamide

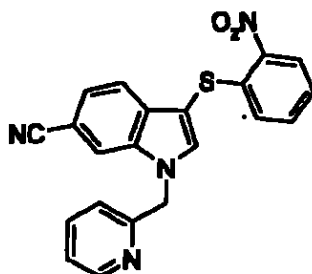
[3-(2-Nitro-phenylsulfanyl)-1-pyrimidin-5-ylmethyl-1*H*-indol-6-yl]-carbamic acid tert-butyl ester (3.8 g, 8.0 mmol) was dissolved in 150 mL of formic acid and stirred for 4 hours. The solution was concentrated *in vacuo*. NaHCO₃-sat was added and the mixture was extracted with CH₂Cl₂ (2x) The combined organic layers were washed with brine and dried over Na₂SO₄. The solution was allowed to stand overnight. The formed solid

was filtered affording a mixture of compound 118 and structure 23 of Scheme VII, where $R^1 = 3,5$ -pyrimidyl, $R^2 = 2$ -nitrophenyl, $R^3 = R^4 = H$ (2.4 g).

Compound 118: ^1H NMR ($CDCl_3$ + drop MeOD) δ 5.47 (s, 2H), 6.91 (dd, 1H, $J_1 = 8.4$ Hz, $J_2 = 1.1$ Hz), 6.99 (dd, 1H, $J_1 = 8.4$ Hz, $J_2 = 1.9$ Hz), 7.19-7.23 (m, 1H), 7.27-7.31 (m, 1H), 7.33 (s, 1H), 7.42 (d, 1H, $J = 8.4$ Hz), 7.49 (s, 1H), 8.22 (d, 1H, $J = 1.9$ Hz), 8.27 (dd, 1H, $J_1 = 8.4$ Hz, $J_2 = 1.1$ Hz), 8.66 (s, 2H), 9.16 (s, 1H).

Example 24

Compound 119: 3-(2-Nitro-phenylsulfanyl)-1-pyridin-2-ylmethyl-1H-indole-6-carbonitrile, structure 3 of scheme I, where $R^1 = 2$ -pyridyl, $R^2 = 2$ -nitrophenyl, $R^3 = R^4 = H$, $R^5 = CN$.



a) To a solution of 1H-indole-6-carbonitrile (1.00 g, 7.04 mmol) in diethyl ether (50 mL) was added at rt 2-nitrobenzenesulfenyl chloride (1.34 g, 7.04 mmol) and the reaction mixture was stirred for 18 hrs. The mixture was concentrated and the crude product was purified using column chromatography (ethyl acetate/heptane 1:4 $\rightarrow$ 4:1) to give 3-(2-Nitro-phenylsulfanyl)-1H-indole-6-carbonitrile (1.62 g, 5.49 mmol, 78%).

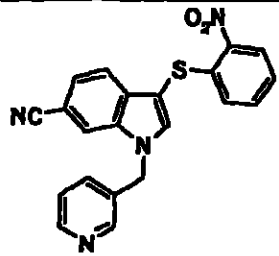
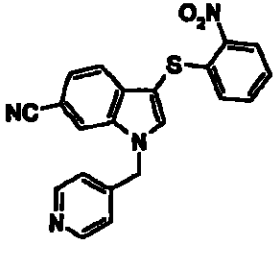
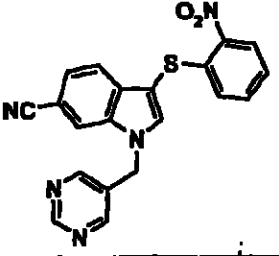
b) To a solution of 3-(2-nitro-phenylsulfanyl)-1H-indole-6-carbonitrile (200 mg, 0.68 mmol) in DMF (5 mL) was added at 0 °C Cs_2CO_3 (442 mg, 1.36 mmol) and the mixture was stirred for 20 min. Subsequently 2-picolylchloride hydrochloride (112 mg, 0.68 mmol) was added and the mixture was stirred for 18 hrs at room temperature. Aqueous saturated $NaHCO_3$ was added and the mixture was extracted with ethyl acetate (2x). The combined organic layers were washed with brine, dried (Na_2SO_4) and concentrated. The crude product was purified using column chromatography to afford compound 119 (223 mg, 0.58 mmol, 85%).

^1H NMR ($CDCl_3$) δ 5.54 (s, 2H), 6.86 (dd, 1H, $J_1 = 8.4$ Hz, $J_2 = 1.1$ Hz), 7.04 (d, 1H, $J = 8.4$ Hz), 7.19-7.23 (m, 1H), 7.26-7.31 (m, 2H), 7.40 (dd, 1H, $J_1 = 8.4$ Hz, $J_2 = 1.1$

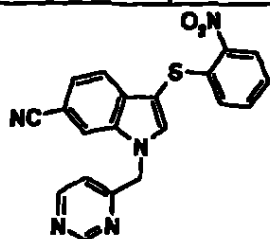
Hz), 7.59 (d, 1H, $J = 8.4$ Hz), 7.70 (td, 1H, $J_1 = 8.4$ Hz, $J_2 = 1.9$ Hz), 7.76 (s, 1H), 7.78 (s, 1H), 8.29 (dd, 1H, $J_1 = 8.4$ Hz, $J_2 = 1.1$ Hz), 8.63 (d, 1H, $J = 3.0$ Hz).

According to general method 3 the following compounds were prepared:

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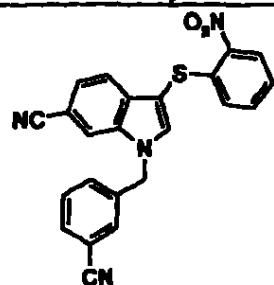
Compound 121: 3-(2-Nitro-phenylsulfanyl)-1-pyridin-3-ylmethyl-1<i>H</i>-indole-6-carbonitrile, structure 3 of scheme I, where $R^1 = 3$-pyridyl, $R^2 = 2$-nitrophenyl, $R^3 = R^4 = H$, $R^5 = CN$. CS_2CO_3 and DMF were used.	
	^1H NMR ($CDCl_3$) δ 5.46 (s, 2H), 6.82 (dd, 1H, $J_1 = 7.6$ Hz, $J_2 = 1.1$ Hz), 7.21-7.25 (m, 1H), 7.27-7.31 (m, 1H), 7.34 (dd, 1H, $J_1 = 8.4$ Hz, $J_2 = 4.6$ Hz), 7.43 (dd, 1H, $J_1 = 7.6$ Hz, $J_2 = 1.1$ Hz), 7.49 (dt, 1H, $J_1 = 8.4$ Hz, $J_2 = 1.9$ Hz), 7.61 (d, 1H, $J = 8.4$ Hz), 7.66 (s, 1H), 7.71 (s, 1H), 8.29 (dd, 1H, $J_1 = 7.6$ Hz, $J_2 = 1.1$ Hz), 8.55 (d, 1H, $J = 3.0$ Hz), 8.64 (dd, 1H, $J_1 = 8.4$ Hz, $J_2 = 1.5$ Hz).
Compound 122: 3-(2-Nitro-phenylsulfanyl)-1-pyridin-4-ylmethyl-1<i>H</i>-indole-6-carbonitrile, structure 3 of scheme I, where $R^1 = 4$-pyridyl, $R^2 = 2$-nitrophenyl, $R^3 = R^4 = H$, $R^5 = CN$.	
	^1H NMR ($CDCl_3$) δ 5.46 (s, 2H), 6.84 (dd, 1H, $J_1 = 8.4$ Hz, $J_2 = 1.1$ Hz), 7.04 (d, 2H, $J = 6.1$ Hz), 7.22-7.26 (m, 1H), 7.28-7.32 (m, 1H), 7.44 (dd, 1H, $J_1 = 7.6$ Hz, $J_2 = 1.1$ Hz), 7.62 (d, 1H, $J = 8.4$ Hz), 7.64 (s, 1H), 7.68 (s, 1H), 8.30 (dd, 1H, $J_1 = 8.4$ Hz, $J_2 = 1.1$ Hz), 8.63-8.65 (m, 2H). CS_2CO_3 and DMF were used.
Compound 123: 3-(2-Nitro-phenylsulfanyl)-1-pyrimidin-5-ylmethyl-1<i>H</i>-indole-6-carbonitrile, structure 3 of scheme I, where $R^1 = 3,5$-pyrimidyl, $R^2 = 2$-nitrophenyl, $R^3 = R^4 = H$, $R^5 = CN$. NaH and DMF were used.	
	^1H NMR ($CDCl_3$) δ 5.48 (s, 2H), 6.81 (dd, 1H, $J_1 = 7.6$ Hz, $J_2 = 1.1$ Hz), 7.22-7.32 (m, 2H), 7.46 (dd, 1H, $J_1 = 7.6$ Hz, $J_2 = 1.1$ Hz), 7.63 (d, 1H, $J = 8.4$ Hz), 7.68 (s, 1H), 7.70 (s, 1H), 8.30 (dd, 1H, $J_1 = 8.4$ Hz, $J_2 = 1.1$ Hz), 8.63 (s, 2H), 9.25 (s, 1H).

Compound 124: 3-(2-Nitro-phenylsulfanyl)-1-pyrimidin-4-ylmethyl-1*H*-indole-6-carbonitrile, structure 3 of scheme I, where $R^1 = 2,4$ -pyrimidyl, $R^2 = 2$ -nitrophenyl, $R^3 = R^4 = H$, $R^5 = CN$. CS_2CO_3 and DMF were used.



^1H NMR ($CDCl_3$) δ 5.52 (s, 2H), 6.86 (dd, 1H, $J_1 = 7.6$ Hz, $J_2 = 1.1$ Hz), 6.97 (dd, 1H, $J_1 = 4.6$ Hz, $J_2 = 1.1$ Hz), 7.22-7.32 (m, 2H), 7.44 (dd, 1H, $J_1 = 8.4$ Hz, $J_2 = 1.1$ Hz), 7.62 (d, 1H, $J = 8.4$ Hz), 7.70 (s, 1H), 7.75 (s, 1H), 8.30 (dd, 1H, $J_1 = 7.6$ Hz, $J_2 = 1.1$ Hz), 8.74 (d, 1H, $J = 4.6$ Hz), 9.24 (d, 1H, $J = 1.1$ Hz).

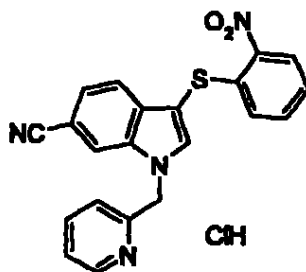
Compound 125: 1-(3-Cyano-benzyl)-3-(2-nitro-phenylsulfanyl)-1*H*-indole-6-carbonitrile, structure 3 of scheme I, where $R^1 = 3$ -cyanophenyl, $R^2 = 2$ -nitrophenyl, $R^3 = R^4 = H$, $R^5 = CN$. CS_2CO_3 and DMF were used.



^1H NMR ($CDCl_3$) δ 5.48 (s, 2H), 6.83 (dd, 1H, $J_1 = 8.4$ Hz, $J_2 = 1.1$ Hz), 7.21-7.26 (m, 1H), 7.30-7.35 (m, 1H), 7.38-7.42 (m, 3H), 7.45 (d, 1H, $J = 8.4$ Hz), 7.53 (d, 1H, $J = 7.6$ Hz), 7.64 (d, 1H, $J = 6.1$ Hz), 7.65 (d, 1H, $J = 3.7$ Hz), 7.66-7.69 (m, 1H), 8.30 (dd, 1H, $J_1 = 8.4$ Hz, $J_2 = 1.1$ Hz).

Example 25

- 5 **Compound 120: 3-(2-Nitro-phenylsulfanyl)-1-pyridin-2-ylmethyl-1*H*-indole-6-carbonitrile monohydrochloride**



- 10 Concentrated hydrochloric acid (0.0225 ml) was added to a solution of compound 119 (0.093 g) in dioxane. The mixture was stirred for 20 min. and then concentrated under reduced pressure, to give compound 120 (0.096 g).

¹H NMR (MeOD) δ 6.01 (s, 2H), 6.98 (dd, 1H, J1 = 7.6 Hz, J2 = 1.1 Hz), 7.28-7.32 (m, 1H), 7.36-7.41 (m, 1H), 7.48 (dd, 1H, J1 = 7.6 Hz, J2 = 1.1 Hz), 7.53 (d, 1H, J = 8.4 Hz), 7.60 (d, 1H, J = 8.4 Hz), 7.93 (t, 1H, J = 6.1 Hz), 8.08 (s, 1H), 8.10 (s, 1H), 8.27 (dd, 1H, J1 = 8.4 Hz, J2 = 1.1 Hz), 8.44 (td, 1H, J1 = 8.4 Hz, J2 = 1.1 Hz), 8.85 (dd, 1H, J1 = 6.1 Hz, J2 = 1.9 Hz).

Compounds were tested for their Androgen Receptor activity in a transactivation assay and in a binding assay.

10

The (anti-)androgenic activity of test compounds (EC50 and intrinsic activity) was determined in an *in vitro* bioassay of Chinese hamster ovary (CHO) cells stably transfected with the human androgen receptor expression plasmid and a reporter plasmid in which the MMTV-promoter is linked to the luciferase reporter gene. The cell-line CHO-AR-pMMTV-LUC 1G12-A5-CA is described in Schoonen et al. (2000), Journal of Steroid Biochemistry and Molecular Biology 74(4):213-222. The antiandrogenic activity of a test compound was determined by the inhibition of the transactivation via the androgen receptor of the enzyme luciferase in the presence of 1 nM DHT (5 α -dihydrotestosterone, 17 β -hydroxy-5 α -androstan-3-one). Intrinsic activity of antiandrogenic activity was determined in the presence of the reference antiandrogen 2-Hydroxy-2-methyl-N-(4-nitro-3-trifluoromethyl-phenyl)-propionamide (Hydroxyflutamide), and set at 100%. For androgenic activity, maximal intrinsic activity in the presence of 100 nM DHT was set at 100%. The results are presented in Table 4.

25

Table 4 Androgen receptor activity

Cpd. number	X	R ¹	R ²	R ³	R ⁴	R ⁵	ago EC50	ago efficacy	ant EC50	ant efficacy
1	S	2,5-difluorophenyl	2-nitrophenyl	H	H	OMe	++	+	-	-
2	S	2-fluoro-3-methylphenyl	2-nitrophenyl	H	H	OMe	+	+	-	-
3	S	2-chlorophenyl	2-nitrophenyl	H	H	OMe	+	+	-	-
4	S	2-cyanophenyl	2-nitrophenyl	H	H	OMe	+	±	++	±
5	S	2-fluorophenyl	2-nitrophenyl	H	H	OMe	+	+	-	-
6	S	2-methyl-3-nitrophenyl	2-nitrophenyl	H	H	OMe	+	+	-	-

Cpd. number	X	R ¹	R ²	R ³	R ⁴	R ⁵	ago EC50	ago efficacy	ant EC50	ant efficacy
7	S	2-methylphenyl	2-nitrophenyl	H	H	OMe	++	++	-	-
8	S	2-nitrophenyl	2-nitrophenyl	H	H	OMe	++	+	-	-
9	S	2-pyridyl	2-nitrophenyl	H	H	OMe	+++	+	+++	±
10	S	2-pyridyl HCl salt	2-nitrophenyl	H	H	OMe	++	+	-	-
11	S	2-tetrahydropyranyl	2-nitrophenyl	H	H	OMe	++	+	-	-
12	S	2-trifluoromethylphenyl	2-nitrophenyl	H	H	OMe	+	+	-	-
13	S	3-(5-methylisoxazolyl)	2-nitrophenyl	H	H	OMe	+	±	-	-
14	S	3,4-dichlorophenyl	2-nitrophenyl	H	H	OMe	+	+	-	-
15	S	3,5-dichlorophenyl	2-nitrophenyl	H	H	OMe	++	++	-	-
16	S	3,5-difluorophenyl	2-(hydroxymethyl)phenyl	H	H	OMe	++	+	++	±
17	S	3,5-difluorophenyl	2-(N-methylbenzamide)	H	H	OMe	-	-	+	+
18	S	3,5-difluorophenyl	2-benzamide	H	H	OMe	++	+	++	±
19	S	3,5-difluorophenyl	2-benzic acid methyl ester	H	H	OMe	+	+	-	-
20	S	3,5-difluorophenyl	2-cyanophenyl	H	H	OMe	++	++	-	-
21	S	3,5-difluorophenyl	2-methoxyphenyl	H	H	OMe	++			
22	S	3,5-difluorophenyl	2-nitrophenyl	H	H	Br	++	++	-	-
23	S	3,5-difluorophenyl	2-nitrophenyl	H	H	CF ₃	+++	++	-	-
24	S	3,5-difluorophenyl	2-nitrophenyl	H	H	CH ₂ OH	++	++	-	-
25	S	3,5-difluorophenyl	2-nitrophenyl	H	H	Cl	+++	++	-	-
26	S	3,5-difluorophenyl	2-nitrophenyl	H	H	CN	+++	++	-	-
27	S	3,5-difluorophenyl	2-nitrophenyl	H	H	CO(1-pyrrolidinyl)	++	+	-	-
28	S	3,5-difluorophenyl	2-nitrophenyl	H	H	CO(4-morpholinyl)	++	+	-	-
29	S	3,5-difluorophenyl	2-nitrophenyl	H	H	CO[1-(4- methylpiperazinyl)]	++	++	-	-
30	S	3,5-difluorophenyl	2-nitrophenyl	H	H	CO ₂ H	+	+	-	-
31	S	3,5-difluorophenyl	2-nitrophenyl	H	H	CO ₂ Me	+++	+	-	-
32	S	3,5-difluorophenyl	2-nitrophenyl	H	H	CONEt ₂	++	+	+	±
33	S	3,5-difluorophenyl	2-nitrophenyl	H	H	CONH ₂	+++	++	-	-
34	S	3,5-difluorophenyl	2-nitrophenyl	H	H	CONHCH ₂ (2-furyl)	++	+	-	-
35	S	3,5-difluorophenyl	2-nitrophenyl	H	H	CONHCH ₂ (3-pyridyl)	++	±	-	-
36	S	3,5-difluorophenyl	2-nitrophenyl	H	H	CONHCH ₂ CH ₂ Nme ₂	++	+	-	-
37	S	3,5-difluorophenyl	2-nitrophenyl	H	H	CONHCH ₂ CH ₂ OH	+++	++	-	-
38	S	3,5-difluorophenyl	2-nitrophenyl	H	H	CONHCH ₂ CH ₂ OMe	+++	++	-	-

Cpd. number	X	R ¹	R ²	R ³	R ⁴	R ⁵	ago EC50	ago efficacy	ant EC50	ant efficacy
39	S	3,5-difluorophenyl	2-nitrophenyl	H	H	CONHCH ₂ CO ₂ Me	++	++	-	-
40	S	3,5-difluorophenyl	2-nitrophenyl	H	H	CONHCH ₂ CONMe ₂	++	+	-	-
41	S	3,5-difluorophenyl	2-nitrophenyl	H	H	CONHCH ₂ cPr	+++	+	-	-
42	S	3,5-difluorophenyl	2-nitrophenyl	H	H	CONHCH ₂ iPr	++	+	-	-
43	S	3,5-difluorophenyl	2-nitrophenyl	H	H	CONHCH ₂ Ph	++	±	+	±
44	S	3,5-difluorophenyl	2-nitrophenyl	H	H	CONHcPr	+++	+	-	-
45	S	3,5-difluorophenyl	2-nitrophenyl	H	H	CONHEt	+++	++	-	-
46	S	3,5-difluorophenyl	2-nitrophenyl	H	H	CONHiPr	++	+	++	±
47	S	3,5-difluorophenyl	2-nitrophenyl	H	H	CONHMe	+++	+	-	-
48	S	3,5-difluorophenyl	2-nitrophenyl	H	H	CONHnPr	++	+	+	±
49	S	3,5-difluorophenyl	2-nitrophenyl	H	H	CONMe ₂	+++	+	-	-
50	S	3,5-difluorophenyl	2-nitrophenyl	H	H	F	++	++	-	-
51	S	3,5-difluorophenyl	2-nitrophenyl	F	H	H	+++	++	-	-
52	S	3,5-difluorophenyl	2-nitrophenyl	H	H	H	++	++	-	-
53	S	3,5-difluorophenyl	2-nitrophenyl	H	F	H	++	++	-	-
54	S	3,5-difluorophenyl	2-nitrophenyl	Cl	H	H	++	++	-	-
55	S	3,5-difluorophenyl	2-nitrophenyl	Me	H	H	++	+	-	-
56	S	3,5-difluorophenyl	2-nitrophenyl	H	OH	H	+++			
57	S	3,5-difluorophenyl	2-nitrophenyl	H	H	NH ₂	+	+	-	-
58	S	3,5-difluorophenyl	2-nitrophenyl	H	H	NHAc	+++	++	-	-
59	S	3,5-difluorophenyl	2-nitrophenyl	H	H	NHCOCF ₃	+++	+	-	-
60	S	3,5-difluorophenyl	2-nitrophenyl	H	H	NO ₂	+++	++	-	-
61	S	3,5-difluorophenyl	2-nitrophenyl	H	H	OH	+++			
62	SO ₂	3,5-difluorophenyl	2-nitrophenyl	H	H	OMe	+++	++	-	-
63	S	3,5-difluorophenyl	2-nitrophenyl	H	H	OMe	+++	++	-	-
64	SO	3,5-difluorophenyl	2-nitrophenyl	H	H	OMe	-	±	+	+
65	S	3,5-difluorophenyl	2-pyridyl	H	H	OMe	++	++	-	-
66	S	3,5-difluorophenyl	2-pyridyl-N-oxide	H	H	OMe	+	+	++	±
67	S	3-chlorophenyl	2-nitrophenyl	H	H	OMe	++	++	-	-
68	S	3-cyanophenyl	2-nitrophenyl	H	H	OMe	+++	++	-	-
69	S	3-fluoro,5-trifluoromethylphenyl	2-nitrophenyl	H	H	OMe	++	++	-	-
70	S	3-fluoro,6-trifluoromethylphenyl	2-nitrophenyl	H	H	OMe	++	+	-	-

Cpd. number	X	R ¹	R ²	R ³	R ⁴	R ⁵	ago EC50	ago efficacy	ant EC50	ant efficacy
71	S	3-fluorophenyl	2-nitrophenyl	H	H	OMe	+++	++	-	-
72	S	3-methoxyphenyl	2-nitrophenyl	H	H	OMe	++	+	-	-
73	S	3-methylphenyl	2-nitrophenyl	H	H	OMe	++	++	-	-
74	S	3-nitrophenyl	2-nitrophenyl	H	H	OMe	+++	++	-	-
75	S	3-pyridyl	2-nitrophenyl	H	H	OMe	+++	++	-	-
76	S	3-trifluoromethyl,4-chlorophenyl	2-nitrophenyl	H	H	OMe	+	+	-	-
77	S	3-trifluoromethyloxyphenyl	2-nitrophenyl	H	H	OMe	++	++	-	-
78	S	3-trifluoromethylphenyl	2-nitrophenyl	H	H	OMe	++	++	-	-
79	S	4-(2-methylthiazolyl)	2-nitrophenyl	H	H	OMe	++	+	-	-
80	S	4-(3,5-dimethylisoxazolyl)	2-nitrophenyl	H	H	OMe	+	±	+	±
81	S	4-chlorophenyl	2-nitrophenyl	H	H	OMe	+	+	+++	+
82	S	4-cyanophenyl	2-nitrophenyl	H	H	OMe	++	+	-	-
83	S	4-fluorophenyl	2-nitrophenyl	H	H	OMe	++	++	-	-
84	S	4-methoxyphenyl	2-nitrophenyl	H	H	OMe	+	±	±	++
85	S	4-methylphenyl	2-nitrophenyl	H	H	OMe	+	+	-	±
86	S	4-morpholinyl	2-nitrophenyl	H	H	OMe	±	±	+	+
87	S	5-(2-chlorothiazolyl)	2-nitrophenyl	H	H	OMe	++	+	-	-
88	S	5-(2-chlorothiophenyl)	2-nitrophenyl	H	H	OMe	++	++	-	-
89	S	Cyclohexyl	2-nitrophenyl	H	H	OMe	++	+	+++	±
90	S	Phenyl	2-nitrophenyl	H	H	H	+	+	-	-
91	S	Phenyl	2-nitrophenyl	H	OMe	H	-	-	±	++
92	S	Phenyl	2-nitrophenyl	H	H	OMe	+++	++	-	-

note 1: EC50 scale: +++ <5 nM; ++ between 5 and 100 nM; + <1000 nM; ± between 1000 and 10000 nM; - >10000 nM

note 2: efficacy scale (maximal intrinsic activity, i.e. intrinsic activity observed in the presence of 100 nM DHT, was set at 1.00): ++ ≥0.80; + between 0.50 and 0.80; ± between 0.20 and 0.50; - <0.20

The androgenic activity (EC50, potency, and efficacy) of the compounds in Table 5 was determined in an *in vitro* bioassay of Chinese hamster ovary (CHO) cells stably transfected with the human androgen receptor expression plasmid and a reporter

plasmid in which the MMTV promotor is linked to the luciferase reporter gene. The cell line CHO-AR-pMMTV-LUC 1G12-A5-CA is described in Schoonen *et al.* (J. Steroid Biochem. Molec. Biol. 2002; 74: 213-222). The androgen receptor activity of compounds was determined in the presence of 0.1 $\mu\text{mol/l}$ onapristone. The maximal efficacy in the presence of 100 nmol/l DHT was set as 100%. The potencies are expressed as percentage of DHT activity.

Table 5 Androgen receptor activity

Cpd. number	X	R ¹	R ²	R ³	R ⁴	R ⁵	ago potency	ago efficacy
93	S	4-pyridyl	2-nitrophenyl	H	H	OMe	±	+
94	S	3,4,5-trifluorophenyl	2-nitrophenyl	H	H	OMe	+	++
95	S	2,3,5-trifluorophenyl	2-nitrophenyl	H	H	OMe	±	++
96	S	4-chloro-3-pyridyl	2-nitrophenyl	H	H	OMe	±	±
97	S	3,5-difluorophenyl	2-nitrophenyl	H	H	NHCOCH ₂ F	+	++
98	S	3,5-difluorophenyl	2-nitrophenyl	H	H	NHCOCHF ₂	++	+
99	S	3,5-difluorophenyl	2-nitrophenyl	H	H	NHCOEt	±	+
100	S	2-pyridyl	2-nitrophenyl	H	H	NHCOCH ₂ F	+	++
101	S	2-pyridyl	2-nitrophenyl	H	H	NHCOMe	+	+
102	S	2-pyridyl	2-nitrophenyl	H	H	NHCOEt	+	+
103	S	3-pyridyl	2-nitrophenyl	H	H	NHCOMe	+	+
104	S	3-pyridyl	2-nitrophenyl	H	H	NHCOCH ₂ F	+	-
105	S	3-pyridyl	2-nitrophenyl	H	H	NHCOEt	+	±
106	S	3,5-difluorophenyl	2-nitrophenyl	H	H	NHSO ₂ Me	+	++
107	S	3,5-difluorophenyl	2-nitrophenyl	H	H	NHSO ₂ -(3-thiophene)	+	++
108	S	3,5-difluorophenyl	2-nitrophenyl	H	H	NHSO ₂ -(1-Me-4-imidazolyl)	+	++
109	S	2-pyridyl	2-nitrophenyl	H	H	CONMe ₂	+	++
110	S	2-pyridyl	2-nitrophenyl	H	H	CONHMe	+	+
111	S	2-pyridyl	2-nitrophenyl	H	H	CONH ₂	±	±
112	S	3-pyridyl	2-nitrophenyl	H	H	CONHMe	+	±
113	S	3-pyridyl	2-nitrophenyl	H	H	CONHEt	+	+
114	S	3-pyridyl	2-nitrophenyl	H	H	CONHcyclopropyl	+	++
115	S	3,5-pyrimidyl	2-nitrophenyl	H	H	OMe	++	+
116	S	2,4-pyrimidyl	2-nitrophenyl	H	H	OMe	+	+

Cpd. number	X	R ¹	R ²	R ³	R ⁴	R ⁵	ago potency	ago efficacy
117	S	2,5-pyrazyl	2-nitrophenyl	H	H	OMe	+	±
118	S	3,5-pyrimidyl	2-nitrophenyl	H	H	NHCHO	++	+
119	S	2-pyridyl	2-nitrophenyl	H	H	CN	++	++
120	S	2-pyridyl HCl salt	2-nitrophenyl	H	H	CN	++	++
121	S	3-pyridyl	2-nitrophenyl	H	H	CN	+	++
122	S	4-pyridyl	2-nitrophenyl	H	H	CN	+	+
123	S	3,5-pyrimidyl	2-nitrophenyl	H	H	CN	++	++
124	S	2,4-pyrimidyl	2-nitrophenyl	H	H	CN	++	++
125	S	3-cyanophenyl	2-nitrophenyl	H	H	CN	+	++

note 1: potency scale: ++ >5%; + between 1% and 5%; ± between 0.1% and 1%.

note 2: efficacy scale (maximal intrinsic activity, i.e. intrinsic activity observed in the presence of 100 nM DHT, was set at 1.00): ++ ≥0.80; + between 0.50 and 0.80; ±

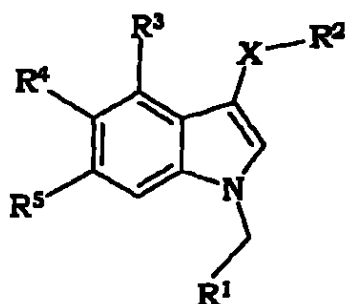
5 between 0.20 and 0.50; - <0.20.

Determination of competitive binding to cytoplasmic human androgen receptor from recombinant CHO cells is used to estimate the relative binding affinity (RBA) of a test compound for androgen receptors present in the cytosol prepared of the recombinant CHO cell-line, CHO-AR-pMMTV-LUC 1G12-A5-CA.

Compound 63 and compound 92 were tested in this binding assay and both compounds were found to have a relative binding affinity >1% relative to DHT.

Claims

1. A compound having the formula



5 wherein

X is S, SO or SO₂;

R¹ is a 5- or 6-membered monocyclic, hetero- or homocyclic, saturated or unsaturated ring structure, optionally substituted with one or more substituents selected from the group consisting of halogen, CN, (1C-4C)fluoroalkyl, nitro, (1C-4C)alkyl, (1C-4C)alkoxy or (1C-4C)fluoroalkoxy;

R² is 2-nitrophenyl, 2-cyanophenyl, 2-hydroxymethyl-phenyl, pyridin-2-yl, pyridin-2-yl-N-oxide, 2-benzamide, 2-benzoic acid methyl ester or 2-methoxyphenyl;

R³ is H, halogen or (1C-4C)alkyl;

R⁴ is H, OH, (1C-4C)alkoxy, or halogen;

15 R⁵ is H, OH, (1C-4C)alkoxy, NH₂, CN, halogen, (1C-4C)fluoroalkyl, NO₂, hydroxy(1C-4C)alkyl, CO₂H, CO₂(1C-6C)alkyl, or

R⁵ is NHR⁶, wherein R⁶ is (1C-6C)acyl optionally substituted with one or more halogens, S(O)₂(1C-4C)alkyl, or S(O)₂aryl optionally substituted with (1C-4C)alkyl or one or more halogens, or

20 R⁵ is C(O)N(R⁸,R⁹), wherein R⁸ and R⁹ each independently are H, (3C-6C)cycloalkyl, or CH₂R¹⁰, wherein R¹⁰ is H, (1C-5C)alkyl, (1C-5C)alkenyl, hydroxy(1C-3C)alkyl, (1C-4C)alkylester of carboxy(1C-4C)alkyl, (1C-3C)alkoxy(1C-3C)alkyl, (mono- or di(1C-4C)alkyl)aminomethyl, (mono- or di(1C-4C)alkyl)aminocarbonyl, or a 3-, 4-, 5- or 6-membered monocyclic, homo- or heterocyclic, aromatic or non-aromatic ring, or R⁸ and R⁹ form

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together with the N a heterocyclic 5- or 6-membered saturated or unsaturated ring optionally substituted with (1C-4C)alkyl;
or a salt or hydrate form thereof.

- 5 2. A compound according to claim 1, characterised in that
 R^1 is a 5- or 6-membered monocyclic, hetero- or homocyclic, saturated or unsaturated ring structure optionally substituted with one or more substituents selected from the group consisting of halogen, CN, CF_3 , nitro, methoxy, trifluoromethoxy or methyl;
- 10 R^2 is 2-nitrophenyl, 2-cyanophenyl, 2-hydroxymethyl-phenyl, pyridin-2-yl, pyridin-2-yl-N-oxide, 2-benzamide, 2-benzoic acid methyl ester or 2-methoxyphenyl;
 R^3 is H, halogen or (1C-2C)alkyl;
 R^4 is H or F.
- 15 3. A compound according to claim 2, characterised in that
 R^5 is H, OH, (1C-4C)alkoxy, CN, halogen, (1C-4C)fluoroalkyl, NO_2 , hydroxy(1C-4C)alkyl, CO_2 (1C-6C)alkyl, or
 R^5 is NHR^6 , wherein R^6 is (1C-6C)acyl optionally substituted with one or more halogens, $S(O)_2$ (1C-4C)alkyl, or $S(O)_2$ aryl optionally substituted with (1C-4C)alkyl or one or more halogens, or
 R^5 is $C(O)N(R^8, R^9)$, wherein R^8 and R^9 each independently are H, (3C-6C)cycloalkyl, or CH_2R^{10} , wherein R^{10} is H, (1C-5C)alkyl, (1C-5C)alkenyl, hydroxy(1C-3C)alkyl, (1C-4C)alkylester of carboxy(1C-4C)alkyl, (1C-3C)alkoxy(1C-3C)alkyl, (mono- or di(1C-4C)alkyl)aminomethyl, (mono- or di(1C-4C)alkyl)-aminocarbonyl, or a 3-, 4-, 5- or 6-membered monocyclic, homo- or heterocyclic, aromatic or non-aromatic ring, or R^8 and R^9 form together with the N a heterocyclic 5- or 6-membered saturated or unsaturated ring optionally substituted with (1C-4C)alkyl.
- 20
25
- 30 4. A compound according to claim 3, characterised in that
 R^3 is H or halogen;
 R^4 is H;

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R^5 is H, OH, (1C-4C)alkoxy, CN, F, Cl, CF_3 , NO_2 , hydroxy(1C-4C)alkyl, CO_2 (1C-6C)alkyl, or

R^5 is NHR^6 , wherein R^6 is (1C-3C)acyl optionally substituted with one or more halogens or

R^5 is $C(O)N(R^8, R^9)$, wherein R^8 and R^9 each independently are H, (3C-5C)cycloalkyl, or CH_2R^{10} , wherein R^{10} is H, (1C-5C)alkyl, (1C-5C)alkenyl, hydroxy(1C-3C)alkyl, (1C-2C)alkylester of carboxy(1C-2C)alkyl, (1C-3C)alkoxy(1C-3C)alkyl, (mono- or di(1C-4C)alkyl)aminomethyl, (mono- or di(1C-4C)alkyl)aminocarbonyl, (3C-5C)cycloalkyl, or a 5-membered heterocyclic ring.

5. A compound according to claim 4, characterised in that

X is S or SO_2 ;

R^2 is 2-nitrophenyl, 2-hydroxymethyl-phenyl, 2-benzamide, 2-methoxyphenyl, 2-cyanophenyl or pyridin-2-yl;

R^3 is H or F;

R^5 is H, OH, (1C-2C)alkoxy, CN, F, Cl, CF_3 , NO_2 , hydroxy(1C-4C)alkyl, CO_2 (1C-4C)alkyl, or

R^5 is NHR^6 , wherein R^6 is formyl, acetyl, fluoroacetyl, difluoroacetyl, or trifluoroacetyl, or

R^5 is $C(O)N(R^8, R^9)$, wherein R^8 is H, and R^9 is H, cyclopropyl or

R^9 is CH_2R^{10} , wherein R^{10} is H, (1C-2C)alkyl, hydroxy(1C-2C)alkyl, methoxy(1C-2C)alkyl, cyclopropyl.

6. A compound according to claim 5, characterised in that

X is S;

R^1 is 3,5-difluorophenyl, pyridin-2-yl, pyridin-3-yl, pyrimidin-5-yl, pyrimidin-4-yl, pyrazin-2-yl, 3-fluorophenyl, 3-cyanophenyl, or 3-nitrophenyl;

R^2 is 2-nitrophenyl, 2-hydroxymethyl-phenyl, 2-methoxyphenyl, 2-cyanophenyl or pyridin-2-yl;

R^3 is H;

R^5 is OH, (1C-2C)alkoxy, CN, CF_3 , NO_2 , hydroxy(1C-4C)alkyl, CO_2 (1C-4C)alkyl, or NHR^6 , wherein R^6 is formyl, acetyl, fluoroacetyl, difluoroacetyl, or trifluoroacetyl.

5 7. A compound according to claim 6, characterised in that

R^1 is 3,5-difluorophenyl, pyridin-2-yl, pyridin-3-yl, pyrimidin-5-yl, pyrimidin-4-yl, or pyrazin-2-yl;

R^2 is 2-nitrophenyl, or 2-hydroxymethyl-phenyl;

10 R^5 is OH, (1C-2C)alkoxy, CN, hydroxy(1C-4C)alkyl, or NHR^6 , wherein R^6 is formyl, acetyl, fluoroacetyl, difluoroacetyl, or trifluoroacetyl.

8. A compound according to claim 7, characterised in that

R^1 is 3,5-difluorophenyl, pyridin-2-yl, pyridin-3-yl, pyrimidin-5-yl, or pyrimidin-4-yl;

15 R^2 is 2-nitrophenyl;

R^5 is OH, (1C-2C)alkoxy, CN, or NHR^6 , wherein R^6 is formyl, acetyl, fluoroacetyl, difluoroacetyl, or trifluoroacetyl.

9. A compound according to claim 8 selected from the group consisting of 6-

20 Methoxy-3-(2-nitro-phenylsulfanyl)-1-pyrimidin-5-ylmethyl-1*H*-indole, 3-(2-Nitro-phenylsulfanyl)-1-pyridin-2-ylmethyl-1*H*-indole-6-carbonitrile, 3-(2-Nitro-phenylsulfanyl)-1-pyridin-2-ylmethyl-1*H*-indole-6-carbonitrile-hydrochloride, 3-(2-Nitro-phenylsulfanyl)-1-pyrimidin-5-ylmethyl-1*H*-indole-6-carbonitrile, 3-(2-Nitro-phenylsulfanyl)-1-pyrimidin-4-ylmethyl-1*H*-indole-6-carbonitrile, *N*-[1-(3,5-Difluoro-benzyl)-3-(2-nitro-phenylsulfanyl)-1*H*-indol-6-yl]-2-fluoro-

25 acetamide, and *N*-[3-(2-Nitro-phenylsulfanyl)-1-pyrimidin-5-ylmethyl-1*H*-indol-6-yl]-formamide.

10. A compound according to claim 5, characterised in that

30 X is S;

R^1 is 3,5-difluorophenyl, pyridin-2-yl, pyridin-3-yl, 3-fluorophenyl, 3-cyanophenyl, or 3-nitrophenyl;

R^2 is 2-nitrophenyl, 2-hydroxymethyl-phenyl, 2-methoxyphenyl, 2-cyanophenyl or pyridin-2-yl;

R^3 is H;

R^5 is $C(O)N(R^8, R^9)$, wherein R^8 is H, and R^9 is H, or CH_2R^{10} , wherein R^{10} is H, (1C-2C)alkyl, hydroxy(1C-2C)alkyl, or methoxy(1C-2C)alkyl.

11. A compound according to claim 10, characterised in that

R^1 is 3,5-difluorophenyl, pyridin-2-yl, or pyridin-3-yl;

R^2 is 2-nitrophenyl, or 2-hydroxymethyl-phenyl;

R^3 is $C(O)N(R^8, R^9)$, wherein R^8 is H, and R^9 is CH_2R^{10} , wherein R^{10} is H, or (1C-2C)alkyl.

12. A compound according to claim 11 which is 1-(3,5-Difluoro-benzyl)-3-(2-nitrophenylsulfanyl)-1*H*-indole-6-carboxylic acid methylamide.

15

13. A compound according to claim 4, characterised in that

X is S;

R^1 is 3,5-difluorophenyl, pyridin-2-yl, pyridin-3-yl, 3-fluorophenyl, 3-cyanophenyl, or 3-nitrophenyl;

R^2 is 2-nitrophenyl, 2-hydroxymethyl-phenyl, 2-methoxyphenyl, 2-cyanophenyl or pyridin-2-yl;

R^3 is H;

R^5 is $C(O)N(R^8, R^9)$, wherein R^8 and R^9 each independently are H, or CH_2R^{10} , wherein R^{10} is H, (1C-5C)alkyl, (1C-5C)alkenyl, hydroxy(1C-3C)alkyl, (1C-3C)alkoxy(1C-3C)alkyl, or (mono- or di(1C-4C)alkyl)aminomethyl.

25

14. A compound according to claim 13, characterised in that

R^1 is 3,5-difluorophenyl, pyridin-2-yl, or pyridin-3-yl;

R^2 is 2-nitrophenyl, or 2-hydroxymethyl-phenyl;

R^5 is $C(O)N(R^8, R^9)$, wherein R^8 and R^9 each independently are H, or CH_2R^{10} , wherein R^{10} is H, (1C-5C)alkyl, hydroxy(1C-3C)alkyl, or (1C-3C)alkoxy(1C-3C)alkyl.

5 15. A compound according to claim 14 which is 1-(3,5-Difluoro-benzyl)-3-(2-nitro-phenylsulfanyl)-1*H*-indole-6-carboxylic acid dimethylamide.

16. The compound of any one of claims 1-15 for use in therapy.

10 17. A pharmaceutical composition comprising a compound according to any one of claims 1-15 and a pharmaceutically acceptable carrier.

18. A pharmaceutical composition according to claim 17 for the treatment of a disorder selected from the group consisting of an androgen-receptor related disorder, an
15 androgen related disorder and androgen insufficiency.

19. A use of a compound according to any one of claims 1-15 for the manufacture of a medicament for the treatment of androgen-receptor related disorders, androgen related disorders and androgen insufficiency.

20

20. A method of treating a disorder selected from the group consisting of an androgen-receptor related disorder, an androgen related disorder and androgen insufficiency comprising administering a pharmaceutically effective amount of a compound according to any one of claims 1-15 to a subject in need thereof.

25

INTERNATIONAL SEARCH REPORT

International Application No.
PCT/EP 03/50783

2/9

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D209/30 C07D401/06 C07D405/06 C07D413/06 C07D401/12
A61K31/404 C07D417/06 C07D409/12 C07D405/12 C07D403/12
C07D403/06 A61P5/24

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D A61K

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

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

EPO-Internal, CHEM ABS Data, WPI Data, BEILSTEIN Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO 03 064387 A (HOFFMANN LA ROCHE) 7 August 2003 (2003-08-07) abstract page 30; example 85 page 31; example 89 page 32; examples 94,95 claims	1-20
A	US 5 767 139 A (FINN PAUL WILLIAM ET AL) 16 June 1998 (1998-06-16) abstract claims examples	1-20
A	DE 25 59 211 A (MCNEILAB INC) 8 July 1976 (1976-07-08) claims	1-20

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

Special categories of cited documents:

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

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

Date of the actual completion of the international search

22 January 2004

Date of mailing of the international search report

30/01/2004

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 851 epo nl,
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Authorized officer

Stix-Malaun, E

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP 03/50783

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

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

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

Although claim 20 is 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 II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

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

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

Remark on Protest

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

INTERNATIONAL SEARCH REPORT

Information on patent family members

International

Location No

PCT/EP 03/50783

50

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 03064387	A	07-08-2003	WO 03064387 A2	07-08-2003
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INTERNATIONAL SEARCH REPORT
interim on patent family members

International Application No.
PCT/EP 03/50783

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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		US 4059583 A	22-11-1977



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6
03 . 2003

Acknowledgement of receipt

We hereby acknowledge receipt of your request for the processing of an international application according to the Patent Cooperation Treaty as follows:

Submission number	8997		
PCT application number	PCT/EP03/50783		
Date of receipt	3 November 2003		
Receiving Office	European Patent Office, The Hague		
Your reference	2002.723_WO		
Applicant	AKZO NOBEL NV		
Number of applicants	6		
Country	NL		
Title	NON-STEROIDAL ANDROGEN COMPOUNDS		
Documents submitted	<table><tr><td>2002.723.zip Fees.PDF add_sheet_representatives.pdf fee-sheet.xml package-data.xml pct101u.GML request.xml</td><td>2002.723_wo_descr.pdf Pct101.PDF application-body.xml general_authorization_59.pdf pct101.GML power-of-attorney1.xml</td></tr></table>	2002.723.zip Fees.PDF add_sheet_representatives.pdf fee-sheet.xml package-data.xml pct101u.GML request.xml	2002.723_wo_descr.pdf Pct101.PDF application-body.xml general_authorization_59.pdf pct101.GML power-of-attorney1.xml
2002.723.zip Fees.PDF add_sheet_representatives.pdf fee-sheet.xml package-data.xml pct101u.GML request.xml	2002.723_wo_descr.pdf Pct101.PDF application-body.xml general_authorization_59.pdf pct101.GML power-of-attorney1.xml		
Submitted by	CN=J. Golsteljn,O=N.V. Organon,C=NL		
Method of submission	Online		
Date and time receipt generated	3 November 2003, 14:57:57		
Digest	32:1E:23:72:96:66:45:82:B9:E7:BA:9D:12:14:34:97:00:0C:DD:44		

Behandeld door	TMC
Adm. organon	ASL
Bericht d.d.	
Bereikt d.d.	
Afgeleverd	TMC

/European Patent Office/

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PCT REQUEST

2002.723_WO

Original (for SUBMISSION) - printed on Monday, 03 November, 2003 02:50:09 PM

0	For receiving Office use only	
0-1	International Application No.	
0-2	International Filing Date	
0-3	Name of receiving Office and "PCT International Application"	
0-4	Form - PCT/ROH01 PCT Request	
0-4-1	Prepared using	epoline® online filing PCT plug-in (updated 03.11.2003)
0-5	Petition The undersigned requests that the present international application be processed according to the Patent Cooperation Treaty	
0-6	Receiving Office (specified by the applicant)	European Patent Office (EPO) (RO/EP)
0-7	Applicant's or agent's file reference	2002.723 WO
I	Title of invention	NON-STEROIDAL ANDROGEN COMPOUNDS
II	Applicant	
II-1	This person is:	applicant only
II-2	Applicant for	all designated States except US
II-4	Name	AKZO NOBEL N.V.
II-5	Address:	Akzo Nobel N.V. Velperweg 76 NL-6824 BM Arnhem Netherlands
II-6	State of nationality	NL
II-7	State of residence	NL
II-8	Telephone No.	+31 (0)412 666380
II-9	Facsimile No.	+31 (0)412 650 592
II-10	e-mail	patent@organon.com
II-11	Applicant's registration No. with the Office	0200751.6
III-1	Applicant and/or inventor	
III-1-1	This person is:	applicant and inventor
III-1-2	Applicant for	US only
III-1-4	Name (LAST, First)	HERMKENS, Pedro, Harold, Han
III-1-5	Address:	N.V. Organon P.O. Box 20 NL-5340 BH Oss Netherlands
III-1-6	State of nationality	NL
III-1-7	State of residence	NL

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2002.723_WO

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III-2	Applicant and/or inventor	
III-2-1	This person is:	applicant and inventor
III-2-2	Applicant for	US only
III-2-4	Name (LAST, First)	STOCK, Herman, Thijs
III-2-5	Address:	N.V. Organon P.O Box 20 NL-5340 BH Oss Netherlands
III-2-6	State of nationality	NL
III-2-7	State of residence	NL
III-3	Applicant and/or inventor	
III-3-1	This person is:	applicant and inventor
III-3-2	Applicant for	US only
III-3-4	Name (LAST, First)	TEERHUIS, Neeltje, Miranda
III-3-5	Address:	N.V. Organon P.O Box 20 NL-5340 BH Oss Netherlands
III-3-6	State of nationality	NL
III-3-7	State of residence	NL
III-4	Applicant and/or inventor	
III-4-1	This person is:	applicant and inventor
III-4-2	Applicant for	US only
III-4-4	Name (LAST, First)	LOMMERSE, Johannes, Petrus, Maria
III-4-5	Address:	N.V. Organon P.O Box 20 NL-5340 BH Oss Netherlands
III-4-6	State of nationality	NL
III-4-7	State of residence	NL
III-5	Applicant and/or inventor	
III-5-1	This person is:	applicant and inventor
III-5-2	Applicant for	US only
III-5-4	Name (LAST, First)	VAN DER LOUW, Jaap
III-5-5	Address:	N.V. ORGANON P.O. Box 20 NL-5340 BH OSS Netherlands
III-5-6	State of nationality	NL
III-5-7	State of residence	NL

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2002.723_WO

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IV-1	Agent or common representative; or address for correspondence The person identified below is hereby/has been appointed to act on behalf of the applicant(s) before the competent International Authorities as:	agent
IV-1-1	Name (LAST, First)	KRAAK, H.
IV-1-2	Address:	P.O. Box 20 NL-5340 BH Oss Netherlands
IV-1-3	Telephone No.	0412 666 380
IV-1-4	Facsimile No.	0412 650 592
IV-1-5	e-mail	patent@organon.com
IV-1-5	Agent's registration No.	073660.3
V	Designation of States	
V-1	Regional Patent (other kinds of protection or treatment, if any, are specified between parentheses after the designation(s) concerned)	AP: GH GM KE LS MW MZ SD SL SZ TZ UG ZM ZW and any other State which is a Contracting State of the Harare Protocol and of the PCT EA: AM AZ BY KG KZ MD RU TJ TM and any other State which is a Contracting State of the Eurasian Patent Convention and of the PCT EP: AT BE BG CH&LI CY CZ DE DK EE ES FI FR GB GR HU IE IT LU MC NL PT RO SE SI SK TR and any other State which is a Contracting State of the European Patent Convention and of the PCT OA: BF BJ CF CG CI CM GA GN GQ GW ML MR NE SN TD TG and any other State which is a member State of OAPI and a Contracting State of the PCT
V-2	National Patent (other kinds of protection or treatment, if any, are specified between parentheses after the designation(s) concerned)	AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH&LI CN CO CR CU CZ DE DK DM DZ EC EE EG ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MY NI NO NZ OM PG PH PL PT RO RU SC SD SE SG SK SL SY TJ TM TN TR TT TZ UA UG US UZ VC VN YU ZA ZM ZW

55

V-5	Precautionary Designation Statement In addition to the designations made under items V-1, V-2 and V-3, the applicant also makes under Rule 4.9(b) all designations which would be permitted under the PCT except any designation(s) of the State(s) indicated under item V-8 below. The applicant declares that those additional designations are subject to confirmation and that any designation which is not confirmed before the expiration of 15 months from the priority date is to be regarded as withdrawn by the applicant at the expiration of that time limit.	
V-8	Exclusion(s) from precautionary designations	NONE
VI-1	Priority claim of earlier national application	
VI-1-1	Filing date	07 November 2002 (07.11.2002)
VI-1-2	Number	60/424,579
VI-1-3	Country	US
VI-2	Priority claim of earlier regional application	
VI-2-1	Filing date	07 November 2002 (07.11.2002)
VI-2-2	Number	02079648.8
VI-2-3	Regional Office	EP
VI-3	Priority document request The receiving Office is requested to prepare and transmit to the International Bureau a certified copy of the earlier application(s) identified above as item(s):	VI-2
VII-1	International Searching Authority Chosen	European Patent Office (EPO) (ISA/EP)
VII-2	Request to use results of earlier search; reference to that search	
VII-2-1	Date	16 December 2002 (16.12.2002)
VII-2-2	Number	02079648.8
VII-2-3	Country (or regional Office)	EP

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2002.723_WO

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VIII		Number of declarations	
VIII-1	Declaration as to the identity of the inventor	-	
VIII-2	Declaration as to the applicant's entitlement, as at the international filing date, to apply for and be granted a patent	-	
VIII-3	Declaration as to the applicant's entitlement, as at the international filing date, to claim the priority of the earlier application	-	
VIII-4	Declaration of inventorship (only for the purposes of the designation of the United States of America)	-	
VIII-5	Declaration as to non-prejudicial disclosures or exceptions to lack of novelty	-	
IX		number of sheets	electronic file(s) attached
IX-1	Check list Request (including declaration sheets)	6	-
IX-2	Description	64	2002.723_wo_descr.pdf
IX-3	Claims	6	2002.723_wo_descr.pdf
IX-4	Abstract	2	2002.723_wo_descr.pdf
IX-2b	Pre-conversion archive	-	2002.723.zip
IX-5	Drawings	0	-
IX-7	TOTAL	78	
		paper document(s) attached	electronic file(s) attached
IX-8	Accompanying items Fee calculation sheet	-	Fees.PDF
IX-11	Copy of general power of attorney	reference no. 59.6	general_authorization_59.pdf
IX-18	Other (specified):	ADDITIONAL SHEET	add_sheet_representatives.pdf
IX-19	Figure of the drawings which should accompany the abstract		
IX-20	Language of filing of the international application	English	
X-1	Signature of applicant, agent or common representative		
X-1-1	Signed by	Subject: NL, N.V. Organon, J. Golsteijn Issuer: DE, D-Trust GmbH, D-Trust for EPO 2.0	
X-1-2	Capacity	AKZO NOBEL N.V. (Applicant 1)	

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PCT REQUEST

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10-1	Date of actual receipt of the purported international application	
10-2	Drawings:	
10-2-1	Received	
10-2-2	Not received	
10-3	Corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application	
10-4	Date of timely receipt of the required corrections under PCT Article 11(2)	
10-5	International Searching Authority	ISA/EP
10-6	Transmittal of search copy delayed until search fee is paid	

FOR INTERNATIONAL BUREAU USE ONLY

11-1	Date of receipt of the record copy by the International Bureau	
------	--	--

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FEE CALCULATION SHEET

2002.723_WO

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(This sheet is not part of and does not count as a sheet of the International application)

0	For receiving Office use only	
0-1	International Application No.	
0-2	Date stamp of the receiving Office	
0-4	Form - PCT/RO/101 (Annex)	
0-4-1	PCT Fee Calculation Sheet Prepared using	epoline® online filing PCT plug-in (updated 03.11.2003)
0-8	Applicant's or agent's file reference	2002.723 WO
2	Applicant	AKZO NOBEL N.V., et al.
12	Calculation of prescribed fees	fee amount/multiplier total amounts (EUR)
12-1	Transmittal fee T	⇒ 100
12-2	Search fee S	⇒ 945
12-3	International fee	
	Basic fee (first 30 sheets) b1	444
12-4	Remaining sheets	48
12-5	Additional amount (X)	10
12-6	Total additional amount b2	480
12-7	b1 + b2 = B	924
12-8	Designation fees	
	Number of designations contained in International application	98
12-9	Number of designation fees payable (maximum 5)	5
12-10	Amount of designation fee (X)	96
12-11	Total designation fees D	480
12-12	epoline® online filing reduction R	-137
12-13	Total International fee (B+D-R) I	⇒ 1,267
12-14	Fee for priority document	
	Number of priority documents requested	1
12-15	Fee per document (X)	30
12-16	Total priority document fee P	⇒ 30
12-17	TOTAL FEES PAYABLE (T+S+B+P)	⇒ 2,342
12-18	Mode of payment	authorization to charge deposit account
12-20	Deposit account instructions	
	The receiving Office:	European Patent Office (EPO) (RO/EP)
12-20-1	Authorization to charge the total fee indicated above.	✓
12-20-2	Authorization to charge any deficiency or credit any overpayment in the total fee indicated above.	✓

FEE CALCULATION SHEET

2002.723_WO

Original (for SUBMISSION) - printed on Monday, 03 November, 2003 02:50:09 PM

12-21	Deposit account No.	28090012
12-22	Date	03 November 2003 (03.11.2003)
12-23	Name and signature	

VALIDATION LOG AND REMARKS

	1.Request	
	2.Series	
	3.Names	
	4.Priority	
	5.Biology	
	6.Declarations	
	7.Contents	
		Green The international application contains no drawings. Please verify.
	8.Fees	
		Green Please confirm that fee schedule utilized is the latest available
	9.Payment	
		Green Please ensure that you have a valid deposit account with the receiving Office selected.
	10.Annotate	

ADDITIONAL SHEET

Additional Representatives:

H. Kraak

P.M.G.F. van Wezenbeek

A.M.A. Rovers

M. Hogenbirk

L.A.G.M. van den Broek

All residing at:

P.O. Box 20
5340 BH OSS
The Netherlands

All authorized under G.A. No. 59

6/

Bitte übermitteln die 3 Blätter 1004.1-3 dem EPA in München, Direction 5.1.1, und beachten Sie Blatt 1004.4, insbesondere Nr.3 b.
Please forward the 3 sheets 1004.1-3 to the EPO at Munich, Directorate 5.1.1 and pay attention to sheet 1004.4, especially point 3 b.
Prière de faire parvenir les 3 feuilles 1004.1-3 à l'OEI à Munich, Direction 5.1.1 et de tenir compte de la feuille 1004.4, notamment du point 3 b.

**ALLGEMEINE VOLLMACHT
GENERAL AUTHORISATION
POUVOIR GENERAL**

Nur für amtlichen Gebrauch / For official use only
Cadre réservé à l'administration
Nr. der allgemeinen Vollmacht / General Authorisation No.
N° du pouvoir général

59 (rev.)

Ich (Wir) / (We) / Je (Nous)

Alzo Nobel N.V.
Velperweg 76
6824 BM Arnhem
The Netherlands

bevollmächtigte(n) hiermit / do hereby authorize / autorise (mutualisons) par la présente

Schaikwijk, Pieter Cornelis
Van Deursen, Petrus Hubertus
Quelle-Fontijn, Monique
Hesseling, Dinah E.
Zonneveld, Hendrik Jan
De Vries, Adriaan Jacobus
Alferink, Petrus Johannes Theodorus
Van den Broek, Ludovicus, A.G.M.

Address of place of business:
Alzo Nobel N.V.
Intellectual Property Department (Dept. AIP)
P.O. Box 8300
6800 SB Arnhem
The Netherlands

mich (uns) in den durch das Europäische Patentübereinkommen geschaffenen Verfahren in allen meinen (unseren) Patentangelegenheiten zu vertreten, alle Handlungen für mich (uns) vorzunehmen und Zahlungen für mich (uns) in Empfang zu nehmen.

to represent me (us) in all proceedings established by the European Patent Convention and to act for me (us) in all patent transactions and to receive payments on my (our) behalf.

à me (nous) représenter pour ce qui concerne toutes mes (nos) affaires de brevet dans toute procédure instituée par la Convention sur le brevet européen et, à ce titre, à agir en mon (notre) nom et à recevoir des paiements pour mon (notre) compte.

☒ Die Vollmacht gilt auch für Verfahren nach dem Vertrag über die internationale Zusammenarbeit auf dem Gebiet des Patentrechts.
This authorisation shall also apply to the same extent to any proceedings established by the Patent Cooperation Treaty.
Ce pouvoir s'applique également à toute procédure instituée par le Traité de coopération en matière de brevets.

☒ Weitere Vertreter sind auf einem gesonderten Blatt angegeben. / Additional representatives indicated on supplementary sheet.
Les autres mandataires sont mentionnés sur une feuille supplémentaire.

☒ Untervollmacht kann erteilt werden. / Sub-authorisation may be given. / Le pouvoir pourra être délégué.

☒ Bitte die gelbe Kopie, ergänzt um die Nr. der allgemeinen Vollmacht, an den Vollmachtgeber zurücksenden.
Please return the yellow copy, supplemented by the General Authorisation No., to the authorizer.
Prière de renvoyer la copie jaune au mandant, munie du n° du pouvoir général.

Ort/Place/Lieu Arnhem, the Netherlands

Datum / Date December 4, 2002

Unterschrift(en) / Signature(s)

P.C. Schaikwijk
(Holder of Proxy)

P.H. van Deursen
(Holder of Proxy)

Das Formular muß von dem (den) Vollmachtgeber(n) (bei juristischen Personen vom Unterschriftsberechtigten) eigenhändig unterschrieben sein. Nach der Unterschrift bitte den (die) Namen des (der) Unterschrifteten mit Schreibweise wiederholen (bei juristischen Personen die Stellung des Unterschriftsberechtigten innerhalb der Gesellschaft angeben).

The form must bear the personal signature(s) of the authorizer(s). (In the case of legal persons, that of the officer empowered to sign). After the signature, please type the name(s) of the signatory(ies) adding, in the case of legal persons, his (their) position within the company.

Le formulaire doit être signé de la propre main du (des) mandant(s) (dans le cas de personnes morales, de la personne ayant qualité pour signer). Veuillez ajouter à la machine, après la signature, le (les) nom(s) du (des) signataire(s) en mentionnant, dans le cas de personnes morales, ses (leurs) fonctions au sein de la société.

SUPPLEMENTARY SHEET

This sheet is part of:
concerning:
signed in the name of:
dated:

EPA/EPO/OEB Form 1004 1 04.92
General Authorisation No. 59 (rev.)
Akzo Nobel N.V.
December 4, 2002

Additional representatives:**Address of place of business:**

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63

**Power of Attorney
(Concerning a Given International Application)**

**PATENT CO-OPERATION TREATY
APPOINTMENT OF AGENT OR COMMON REPRESENTATIVE**

POWER OF ATTORNEY

The undersigned applicant(s):

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hereby appoints (appoint) Mr. (Ms., Miss, Mrs.) [Name, address]:

H. Quak

M. Hogenbirk

P.M.G.F. van Wierzbick

A.M.A. Rovers

L.A.G.M. van den Broek

All residing at:

*Postbus 20
5340 BH Oss
The Netherlands*

[X] as agent

[] as common representative

to act on his (her, their) behalf before the competent International Authorities in connection with the international application on [title of the invention, applicant's or agent's file reference, if any has been indicated in the request, international application number, if already available]:

Our ref.: 2002.723 WO

Title: **"NON-STEROIDAL ANDROGENS COMPOUNDS"**

filed with the [name of the Office]: *EPO*
as receiving Office and to make or receive payments on his (her, their) behalf.

Place: *Oss* Date: *17-10-2003*

Signature of the applicant (where there are several applicants, each of them must sign):

17-10-2003

17-10-2003

17/10/2003

17/10/2003

17-10-2003

HERMKENS,
Pedro, Harold, Han

STOCK,
Herman, Thijs

VAN DER LOUW,
Jaap

TEERHUIS,
Neeltje, Miranda

LOMMERSE,
Johannes, Petrus, Maria

[Type the name under the (each) signature and add, in case of legal persons, an indication of the capacity in which the person signs]

PATENT COOPERATION TREATY

6x

From the INTERNATIONAL SEARCHING AUTHORITY

PCT

NOTIFICATION OF TRANSMITTAL OF
THE INTERNATIONAL SEARCH REPORT
OR THE DECLARATION

(PCT Rule 44.1)

To: KRAAK, H. P.O. Box 20 NL-5340 BH Oss NETHERLANDS	30 JAN. 2004 Behandeld door <i>THC</i> Adm. afzender <i>AW</i> Bericht d.d. van: Beantw. d.d. Alleggen <i>THC</i>	<table border="1" style="width: 100%; border-collapse: collapse;"> <tr> <td style="width: 50%;">Date of mailing (day/month/year)</td> <td style="width: 50%;">30/01/2004</td> </tr> </table>	Date of mailing (day/month/year)	30/01/2004
Date of mailing (day/month/year)	30/01/2004			
Applicant's or agent's file reference 2002.723_WO		FOR FURTHER ACTION See paragraphs 1 and 4 below		
International application No. PCT/EP 03/50783		International filing date (day/month/year) 03/11/2003		
Applicant AKZO NOBEL N.V.				

1. ☒ The applicant is hereby notified that the International Search Report has been established and is transmitted herewith.

Filing of amendments and statement under Article 18:
 The applicant is entitled, if he so wishes, to amend the claims of the International Application (see Rule 46):

When? The time limit for filing such amendments is normally 2 months from the date of transmittal of the International Search Report; however, for more details, see the notes on the accompanying sheet.

Where? Directly to the International Bureau of WIPO
 34, chemin des Colombettes
 1211 Geneva 20, Switzerland
 Facsimile No.: (41-22) 740.14.35

→ 30/3/04

For more detailed instructions, see the notes on the accompanying sheet.

2. ☐ The applicant is hereby notified that no International Search Report will be established and that the declaration under Article 17(2)(a) to that effect is transmitted herewith.

3. ☐ With regard to the protest against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

☐ the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.

☐ no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. **Further action(s):** The applicant is reminded of the following:

Shortly after 18 months from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau as provided in Rules 90bis.1 and 90bis.3, respectively, before the completion of the technical preparations for international publication.

Within 18 months from the priority date, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase until 30 months from the priority date (in some Offices even later).

Within 20 months from the priority date, the applicant must perform the prescribed acts for entry into the national phase before all designated Offices which have not been elected in the demand or in a later election within 18 months from the priority date or could not be elected because they are not bound by Chapter II.

Name and mailing address of the International Searching Authority European Patent Office, P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 851 epo nl, Fax (+31-70) 340-3016	Authorized officer Kerstin Gätz
--	---

These Notes are intended to give the basic instructions concerning the filing of amendments under article 19. The Notes are based on the requirements of the Patent Cooperation Treaty, the Regulations and the Administrative Instructions under that Treaty. In case of discrepancy between these Notes and those requirements, the latter are applicable. For more detailed information, see also the PCT Applicant's Guide, a publication of WIPO.

In these Notes, "Article", "Rule", and "Section" refer to the provisions of the PCT, the PCT Regulations and the PCT Administrative Instructions respectively.

INSTRUCTIONS CONCERNING AMENDMENTS UNDER ARTICLE 19

The applicant has, after having received the international search report, one opportunity to amend the claims of the international application. It should however be emphasized that, since all parts of the international application (claims, description and drawings) may be amended during the international preliminary examination procedure, there is usually no need to file amendments of the claims under Article 19 except where, e.g. the applicant wants the letter to be published for the purposes of provisional protection or has another reason for amending the claims before international publication. Furthermore, it should be emphasized that provisional protection is available in some States only.

What parts of the international application may be amended?

Under Article 19, only the claims may be amended.

During the international phase, the claims may also be amended (or further amended) under Article 34 before the International Preliminary Examining Authority. The description and drawings may only be amended under Article 34 before the International Examining Authority.

Upon entry into the national phase, all parts of the international application may be amended under Article 25 or, where applicable, Article 41.

When?

Within 2 months from the date of transmittal of the international search report or 16 months from the priority date, whichever time limit expires later. It should be noted, however, that the amendments will be considered as having been received on time if they are received by the International Bureau after the expiration of the applicable time limit but before the completion of the technical preparations for international publication (Rule 46.1).

Where not to file the amendments?

The amendments may only be filed with the International Bureau and not with the receiving Office or the International Searching Authority (Rule 48.2).

Where a demand for international preliminary examination has been filed, see below.

How?

Either by cancelling one or more entire claims, by adding one or more new claims or by amending the text of one or more of the claims as filed.

A replacement sheet must be submitted for each sheet of the claims which, on account of an amendment or amendments, differs from the sheet originally filed.

All the claims appearing on a replacement sheet must be numbered in Arabic numerals. Where a claim is cancelled, no renumbering of the other claims is required. In all cases where claims are renumbered, they must be renumbered consecutively (Administrative Instructions, Section 205(b)).

The amendments must be made in the language in which the international application is to be published.

What documents must/may accompany the amendments?

Letter (Section 205(b)):

The amendments must be submitted with a letter.

The letter will not be published with the international application and the amended claims. It should not be confused with the "Statement under Article 19(1)" (see below, under "Statement under Article 19(1)").

The letter must be in English or French, at the choice of the applicant. However, if the language of the international application is English, the letter must be in English; if the language of the international application is French, the letter must be in French.

The letter must indicate the differences between the claims as filed and the claims as amended. It must, in particular, indicate, in connection with each claim appearing in the international application (it being understood that identical indications concerning several claims may be grouped), whether

- (i) the claim is unchanged;
- (ii) the claim is cancelled;
- (iii) the claim is new;
- (iv) the claim replaces one or more claims as filed;
- (v) the claim is the result of the division of a claim as filed.

The following examples illustrate the manner in which amendments must be explained in the accompanying letter:

1. [Where originally there were 48 claims and after amendment of some claims there are 51]:
"Claims 1 to 29, 31, 32, 34, 35, 37 to 48 replaced by amended claims bearing the same numbers; claims 30, 33 and 36 unchanged; new claims 49 to 51 added."
2. [Where originally there were 15 claims and after amendment of all claims there are 11]:
"Claims 1 to 15 replaced by amended claims 1 to 11."
3. [Where originally there were 14 claims and the amendments consist in cancelling some claims and in adding new claims]:
"Claims 1 to 6 and 14 unchanged; claims 7 to 13 cancelled; new claims 15, 16 and 17 added." or
"Claims 7 to 13 cancelled; new claims 15, 16 and 17 added; all other claims unchanged."
4. [Where various kinds of amendments are made]:
"Claims 1-10 unchanged; claims 11 to 13, 18 and 19 cancelled; claims 14, 15 and 16 replaced by amended claim 14; claim 17 subdivided into amended claims 15, 16 and 17; new claims 20 and 21 added."

"Statement under article 19(1)" (Rule 46.4)

The amendments may be accompanied by a statement explaining the amendments and indicating any impact that such amendments might have on the description and the drawings (which cannot be amended under Article 19(1)).

The statement will be published with the international application and the amended claims.

It must be in the language in which the international application is to be published.

It must be brief, not exceeding 500 words if in English or if translated into English.

It should not be confused with and does not replace the letter indicating the differences between the claims as filed and as amended. It must be filed on a separate sheet and must be identified as such by a heading, preferably by using the words "Statement under Article 19(1)."

It may not contain any disparaging comments on the international search report or the relevance of citations contained in that report. Reference to citations, relevant to a given claim, contained in the international search report may be made only in connection with an amendment of that claim.

Consequence if a demand for international preliminary examination has already been filed

If, at the time of filing any amendments under Article 19, a demand for international preliminary examination has already been submitted, the applicant must preferably, at the same time of filing the amendments with the International Bureau, also file a copy of such amendments with the International Preliminary Examining Authority (see Rule 62.2(a), first sentence).

Consequence with regard to translation of the international application for entry into the national phase

The applicant's attention is drawn to the fact that, where upon entry into the national phase, a translation of the claims as amended under Article 19 may have to be furnished to the designated/elected Office, instead of, or in addition to, the translation of the claims as filed.

For further details on the requirements of each designated/elected Office, see Volume II of the PCT Applicant's Guide.

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference 2002.723 WO	FOR FURTHER ACTION see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, Item 5 below.	
International application No. PCT/EP 03/50783	International filing date (day/month/year) 03/11/2003	(Earliest) Priority Date (day/month/year) 07/11/2002
Applicant AKZO NOBEL N.V.		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 6 sheets.

☒ It is also accompanied by a copy of each prior art document cited in this report.

1. Basis of the report

- a. With regard to the language, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

☐ the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

- b. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international search was carried out on the basis of the sequence listing:

☐ contained in the international application in written form.

☐ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority in written form.

☐ furnished subsequently to this Authority in computer readable form.

☐ the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

☐ the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

2. ☒ Certain claims were found unsearchable (See Box I).

3. ☐ Unity of invention is lacking (see Box II).

4. With regard to the title,

☐ the text is approved as submitted by the applicant.

☒ the text has been established by this Authority to read as follows:

INDOLES USEFUL IN THE TREATMENT OF ANDROGEN-RECEPTOR RELATED DISEASES

5. With regard to the abstract,

☐ the text is approved as submitted by the applicant.

☒ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the drawings to be published with the abstract is Figure No.

☐ as suggested by the applicant.

☐ because the applicant failed to suggest a figure.

☐ because this figure better characterizes the invention.

☒ None of the figures.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/EP 03/50783

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Box III TEXT OF THE ABSTRACT (Continuation of item 5 of the first sheet)

INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 03/50783

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A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D209/30 C07D401/06 C07D405/06 C07D413/06 C07D401/12
A61K31/404 C07D417/06 C07D409/12 C07D405/12 C07D403/12
C07D403/06 A61P5/24

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D A61K

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

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

EPO-Internal, CHEM ABS Data, WPI Data, BEILSTEIN Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO 03 064387 A (HOFFMANN LA ROCHE) 7 August 2003 (2003-08-07) abstract page 30; example 85 page 31; example 89 page 32; examples 94,95 claims	1-20
A	US 5 767 139 A (FINN PAUL WILLIAM ET AL) 16 June 1998 (1998-06-16) abstract claims examples	1-20
A	DE 25 59 211 A (MCNEILAB INC) 8 July 1976 (1976-07-08) claims	1-20

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

* Special categories of cited documents:

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

"E" earlier document but published on or after the international filing date

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

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

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

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

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

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

"A" document member of the same patent family

Date of the actual completion of the international search

22 January 2004

Date of mailing of the international search report

30/01/2004

Name and mailing address of the ISA

European Patent Office, P.B. 6616 Patentlaan 2
NL - 2280 HV Rijswijk
Tel (+31-70) 340-2040, Tx. 31 651 apo nl,
Fax (+31-70) 340-3018

Authorized officer

Stix-Malaun, E

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP 03/50783

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

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

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Although claim 20 is 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 II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

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

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

Remark on Protest

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

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 03/50783

21

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 03064387	A	07-08-2003	WO 03064387 A2 US 2003220319 A1	07-08-2003 27-11-2003
US 5767139	A	16-06-1998	BR 9305991 A CA 2117610 A1 CZ 9402077 A3 DE 69317651 D1 DE 69317651 T2 EP 0628040 A1 FI 943931 A FI 20001771 A JP 7500347 T NO 943187 A SK 100894 A3 AT 164376 T AU 3497793 A CN 1079465 A DK 628040 T3 WO 9317014 A1 ES 2115053 T3 HR 930227 A1 HU 71126 A2 JP 2540016 B2 MX 9301112 A1 ZA 9301383 A	21-10-1997 02-09-1993 18-01-1995 30-04-1998 09-07-1998 14-12-1994 26-08-1994 09-08-2000 12-01-1995 13-09-1994 12-04-1995 15-04-1998 13-09-1993 15-12-1993 27-04-1998 02-09-1993 16-06-1998 31-10-1996 28-11-1995 02-10-1996 29-07-1994 26-08-1994
DE 2559211	A	08-07-1976	AR 219052 A1 AT 356648 B AT 986075 A AU 505215 B2 AU 8791675 A BE 837199 A1 CA 1065874 A1 CH 622516 A5 DD 125781 A5 DE 2559211 A1 DK 580175 A ES 443935 A1 FI 753669 A ,B, FR 2296413 A1 FR 2315921 A1 GB 1527510 A HU 174948 B HU 174949 B IE 42390 B1 IL 48756 A IN 142735 A1 IT 1052654 B JP 51131872 A NL 7515100 A NO 754313 A ,B, NZ 179580 A PH 12328 A PL 99353 B1 RO 69196 A1 SE 422210 B SE 7514458 A SU 667132 A3	31-07-1980 12-05-1980 15-10-1979 15-11-1979 07-07-1977 30-06-1976 06-11-1979 15-04-1981 18-05-1977 08-07-1976 01-07-1976 16-08-1977 01-07-1976 30-07-1976 28-01-1977 04-10-1978 28-04-1980 28-04-1980 30-07-1980 12-03-1979 20-08-1977 20-07-1981 16-11-1976 02-07-1976 01-07-1976 03-04-1978 16-01-1979 31-07-1978 15-08-1980 22-02-1982 31-07-1976 05-06-1979

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
DE 2559211	A	YU 332275 A1	28-02-1983
		ZA 7508058 A	31-08-1977
		CS 7600126 A2	13-02-1984
		JP 52068175 A	06-06-1977
		JP 60120860 A	28-06-1985
		US 4059583 A	22-11-1977

The demand must be filed directly with the competent International Preliminary Examining Authority or, if two or more Authorities are competent, with the one chosen by the applicant. The full name or two-letter code of that Authority may be indicated by the applicant on the line below:

IPEA/ EPO

PCT

CHAPTER II

DEMAND

under Article 31 of the Patent Cooperation Treaty:
The undersigned requests that the international application specified below be the subject of international preliminary examination according to the Patent Cooperation Treaty.

For International Preliminary Examining Authority use only			
Identification of IPEA		Date of receipt of DEMAND	
Box No. I IDENTIFICATION OF THE INTERNATIONAL APPLICATION		Applicant's or agent's file reference 2002.723 WO	
International application No. PCT/EP03/50783	International filing date (day/month/year) 03-11-2003	(Earliest) Priority date (day/month/year) 07-11-2002	
Title of invention INDOLES USEFUL IN THE TREATMENT OF ANDROGEN-RECEPTOR RELATED DISEASES.			
Box No. II APPLICANT(S)			
Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.) Akzo Nobel N.V. Velperweg 76 6824 BM ARNHEM THE NETHERLANDS		Telephone No. 0412-666380 Facsimile No. 0412-650592 Telexprinter No. Applicant's registration No. with the Office	
State (that is, country) of nationality: NL		State (that is, country) of residence: NL	
Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.) HERMKENS, Pedro, Harold, Han N.V.Organon P.O. Box 20 NL-5340 BH OSS The Netherlands			
State (that is, country) of nationality: NL		State (that is, country) of residence: NL	
Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.) STOCK, Herman, Thijs N.V.Organon P.O. Box 20 NL-5340 BH OSS The Netherlands			
State (that is, country) of nationality: NL		State (that is, country) of residence: NL	
☒ Further applicants are indicated on a continuation sheet.			

Continuation of Box No. II APPLICANT(S)

If none of the following sub-boxes is used, this sheet should not be included in the demand.

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)

TEERHUIS, Neeltje, Miranda
N.V.Organon
P.O. Box 20
NL-5340 BH OSS
The Netherlands

State (that is, country) of nationality:
NL

State (that is, country) of residence:
NL

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)

LOMMERSE, Johannes, Petrus, Marla
N.V.Organon
P.O. Box 20
NL-5340 BH OSS
The Netherlands

State (that is, country) of nationality:
NL

State (that is, country) of residence:
NL

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)

VAN DER LOUW, Jaap
N.V.Organon
P.O. Box 20
NL-5340 BH OSS
The Netherlands

State (that is, country) of nationality:
NL

State (that is, country) of residence:
NL

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)

State (that is, country) of nationality:

State (that is, country) of residence:

☐ Further applicants are indicated on another continuation sheet.

Box No. III AGENT OR COMMON REPRESENTATIVE; OR ADDRESS FOR CORRESPONDENCE

The following person is ☒ agent ☐ common representativeand ☒ has been appointed earlier and represents the applicant(s) also for international preliminary examination.☐ is hereby appointed and any earlier appointment of (an) agent(s)/common representative is hereby revoked.☐ is hereby appointed, specifically for the procedure before the International Preliminary Examining Authority, in addition to the agent(s)/common representative appointed earlier.Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*L.A.G.M. van den Broek
P.O. Box 20
5340 BH OSS
The Netherland

Telephone No.

0412-668456

Facsimile No.

0412-650592

Teleprinter No.

Agent's registration No. with the Office

☐ Address for correspondence: Mark this check-box where no agent or common representative is/has been appointed and the space above is used instead to indicate a special address to which correspondence should be sent.

Box No. IV BASIS FOR INTERNATIONAL PRELIMINARY EXAMINATION

Statement concerning amendments:*

1. The applicant wishes the international preliminary examination to start on the basis of:

☒ the international application as originally filedthe description ☐ as originally filed☐ as amended under Article 34the claims ☐ as originally filed☐ as amended under Article 19 (together with any accompanying statement)☐ as amended under Article 34the drawings ☐ as originally filed☐ as amended under Article 342. ☐ The applicant wishes any amendment to the claims under Article 19 to be considered as reversed.3. ☐ The applicant wishes the start of the international preliminary examination to be postponed until the expiration of the applicable time limit under Rule 69.1(d).4. ☒ The applicant expressly wishes the international preliminary examination to start earlier than at the expiration of the applicable time limit under Rule 54bis.1(a).

* Where no check-box is marked, international preliminary examination will start on the basis of the international application as originally filed or, where a copy of amendments to the claims under Article 19 and/or amendments of the international application under Article 34 are received by the International Preliminary Examining Authority before it has begun to draw up a written opinion or the international preliminary examination report, as so amended.

Language for the purposes of international preliminary examination:

☐ which is the language in which the international application was filed.☐ which is the language of a translation furnished for the purposes of international search.☐ which is the language of publication of the international application.☐ which is the language of the translation (to be) furnished for the purposes of international preliminary examination.

Box No. V ELECTION OF STATES

The filing of this demand constitutes the election of all Contracting States which are designated and are bound by Chapter II of the PCT.

Box No. VI CHECK LIST

The demand is accompanied by the following elements, in the language referred to in Box No. IV, for the purposes of international preliminary examination:

- | | | |
|--|---|--------|
| 1. translation of international application | : | sheets |
| 2. amendments under Article 34 | : | sheets |
| 3. copy (or, where required, translation) of amendments under Article 19 | : | sheets |
| 4. copy (or, where required, translation) of statement under Article 19 | : | sheets |
| 5. letter | : | sheets |
| 6. other (specify) | : | sheets |

For International Preliminary Examining Authority use only
received not received

☐	☐
☐	☐
☐	☐
☐	☐
☐	☐
☐	☐

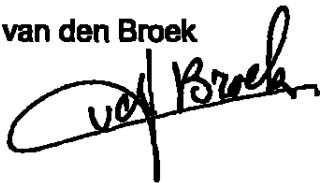
The demand is also accompanied by the item(s) marked below:

- | | |
|--|--|
| 1. ☒ fee calculation sheet | 5. ☐ statement explaining lack of signature |
| 2. ☐ original separate power of attorney | 6. ☐ sequence listing in computer readable form |
| 3. ☐ original general power of attorney | 7. ☐ tables in computer readable form related to a sequence listing |
| 4. ☐ copy of general power of attorney; reference number, if any: | 8. ☐ other (specify): |

Box No. VII SIGNATURE OF APPLICANT, AGENT OR COMMON REPRESENTATIVE

Next to each signature, indicate the name of the person signing and the capacity in which the person signs (if such capacity is not obvious from reading the demand).

L.A.G.M. van den Broek



For International Preliminary Examining Authority use only

1. Date of actual receipt of DEMAND:

2. Adjusted date of receipt of demand due to CORRECTIONS under Rule 60.1(b):

3. ☐ The date of receipt of the demand is AFTER the expiration of 19 months from the priority date and item 4 or 5, below, does not apply.
☐ The applicant has been informed accordingly.

4. ☐ The date of receipt of the demand is WITHIN the time limit of 19 months from the priority date as extended by virtue of Rule 80.5.

5. ☐ Although the date of receipt of the demand is after the expiration of 19 months from the priority date, the delay in arrival is EXCUSED pursuant to Rule 82.

6. ☐ The date of receipt of the demand is AFTER the expiration of the time limit under Rule 54bis.1(a) and item 7 or 8, below, does not apply.

7. ☐ The date of receipt of the demand is WITHIN the time limit under Rule 54bis.1(a) as extended by virtue of Rule 80.5.

8. ☐ Although the date of receipt of the demand is after the expiration of the time limit under Rule 54bis.1(a), the delay in arrival is EXCUSED pursuant to Rule 82.

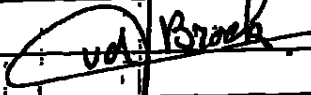
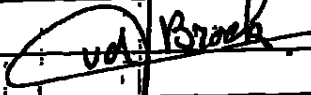
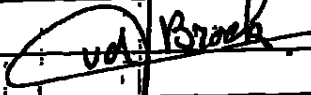
For International Bureau use only

Demand received from IPRA on:

PCT

FEE CALCULATION SHEET

Annex to the Demand

International application No. PCT/EP03/50783	For International Preliminary Examining Authority use only								
Applicant's or agent's file reference 2002.723 WO	Date stamp of the IPRA								
Applicant AKZO NOBEL N.V.									
CALCULATION OF PRESCRIBED FEES									
1. Preliminary examination fee	EURO 1530 P								
2. Handling fee (Applicants from certain States are entitled to a reduction of 75% of the handling fee. Where the applicant is (or all applicants are) so entitled, the amount to be entered at H is 25% of the handling fee.)	EURO 159 H								
3. Total of prescribed fees Add the amounts entered at P and H and enter total in the TOTAL box	EURO 1689 TOTAL								
MODE OF PAYMENT <table style="width: 100%;"> <tr> <td>☒ authorization to charge deposit account with the IPRA (see below)</td> <td>☐ cash</td> </tr> <tr> <td>☐ cheque</td> <td>☐ revenue stamps</td> </tr> <tr> <td>☐ postal money order</td> <td>☐ coupons</td> </tr> <tr> <td>☐ bank draft</td> <td>☐ other (specify):</td> </tr> </table>		☒ authorization to charge deposit account with the IPRA (see below)	☐ cash	☐ cheque	☐ revenue stamps	☐ postal money order	☐ coupons	☐ bank draft	☐ other (specify):
☒ authorization to charge deposit account with the IPRA (see below)	☐ cash								
☐ cheque	☐ revenue stamps								
☐ postal money order	☐ coupons								
☐ bank draft	☐ other (specify):								
AUTHORIZATION TO CHARGE (OR CREDIT) DEPOSIT ACCOUNT (This mode of payment may not be available at all IPRA's) <table style="width: 100%;"> <tr> <td style="vertical-align: top;"> ☒ Authorization to charge the total fees indicated above. ☒ (This check-box may be marked only if the conditions for deposit accounts of the IPRA so permit) Authorization to charge any deficiency or credit any overpayment in the total fees indicated above. </td> <td style="vertical-align: top;"> IPRA/EPO Deposit Account No.: 2809 0012 Date: 09-04-2004 Name: L.A.G.M. van den Broek Signature:  </td> </tr> </table>		☒ Authorization to charge the total fees indicated above. ☒ (This check-box may be marked only if the conditions for deposit accounts of the IPRA so permit) Authorization to charge any deficiency or credit any overpayment in the total fees indicated above.	IPRA/EPO Deposit Account No.: 2809 0012 Date: 09-04-2004 Name: L.A.G.M. van den Broek Signature: 						
☒ Authorization to charge the total fees indicated above. ☒ (This check-box may be marked only if the conditions for deposit accounts of the IPRA so permit) Authorization to charge any deficiency or credit any overpayment in the total fees indicated above.	IPRA/EPO Deposit Account No.: 2809 0012 Date: 09-04-2004 Name: L.A.G.M. van den Broek Signature: 								

PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

VAN DEN BROEK, Ludovicus A. G. M.
P.O. Box 20
NL-5340 BH Oss
PAYS-BAS

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Rule 71.1)

Received date	07.11.2004
Author	CPR 28
Section d.	2
Page	
Branch d.	
Allegat	

Date of mailing
(day/month/year) 07.10.2004

Applicant's or agent's file reference
2002.723_WO

IMPORTANT NOTIFICATION

International application No.
PCT/EP 03/50783

International filing date (day/month/year)
03.11.2003

Priority date (day/month/year)
07.11.2002

Applicant
AKZO NOBEL N.V. et al.

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.
2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.
3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.
4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

The applicant's attention is drawn to Article 33(5), which provides that the criteria of novelty, inventive step and industrial applicability described in Article 33(2) to (4) merely serve the purposes of international preliminary examination and that "any Contracting State may apply additional or different criteria for the purposes of deciding whether, in that State, the claimed inventions is patentable or not" (see also Article 27(5)). Such additional criteria may relate, for example, to exemptions from patentability, requirements for enabling disclosure, clarity and support for the claims.

Name and mailing address of the international
preliminary examining authority:



European Patent Office
D-80298 Munich
Tel. +49 89 2399 - 0 Tlx: 523656 epmu d
Fax: +49 89 2399 - 4485

Authorized Officer

Ambros, J.R.
Tel. +49 89 2399-8012



INTERNATIONAL PRELIMINARY EXAMINATION REPORT
(PCT Article 36 and Rule 70)

79

Applicant's or agent's file reference 2002.723_WO	FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/PEAA18)	
International application No. PCT/EP 03/50783	International filing date (day/month/year) 03.11.2003	Priority date (day/month/year) 07.11.2002
International Patent Classification (IPC) or both national classification and IPC C07D209/30		
Applicant AKZO NOBEL N.V. et al.		
1. This International preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36. 2. This REPORT consists of a total of 5 sheets, including this cover sheet. ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.18 and Section 807 of the Administrative Instructions under the PCT). These annexes consist of a total of sheets.		
3. This report contains indications relating to the following items: I ☒ Basis of the opinion II ☐ Priority III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability IV ☐ Lack of unity of invention V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement VI ☐ Certain documents cited VII ☐ Certain defects in the international application VIII ☐ Certain observations on the international application		
Date of submission of the demand 09.04.2004	Date of completion of this report 07.10.2004	
Name and mailing address of the international preliminary examining authority:  European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tlx 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Stix-Malaun, E Telephone No. +49 89 2399-8057 	

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP 03/50783

I. Basis of the report

1. With regard to the elements of the international application (*Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17):*

Description, Pages

1-64 as originally filed

Claims, Numbers

1-20 as originally filed

2. With regard to the language, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages: ..
- ☐ the claims, Nos.: ..
- ☐ the drawings, sheets: ..

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. **PCT/EP 03/50783**

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:
- ☐ the entire international application,
 - ☒ claims Nos. 20 (Industrial Applicability)
because:
 - ☒ the said international application, or the said claims Nos. 20 relate to the following subject matter which does not require an international preliminary examination (specify):
see separate sheet
 - ☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):
 - ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.
 - ☐ no international search report has been established for the said claims Nos.
2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:
- ☐ the written form has not been furnished or does not comply with the Standard.
 - ☐ the computer readable form has not been furnished or does not comply with the Standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes: Claims	1-20
	No: Claims	
Inventive step (IS)	Yes: Claims	1-20
	No: Claims	
Industrial applicability (IA)	Yes: Claims	1-19
	No: Claims	

2. Citations and explanations

see separate sheet

III NON-ESTABLISHMENT

Claim 20 relates to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

V REASONED STATEMENT**1. PRIOR ART**

The documents cited in the International Search Report

D1: US-A-5 767 139 (FINN PAUL WILLIAM ET AL) 16 June 1998 (1998-06-16)

D2: DE 25 59 211 A (MCNEILAB INC) 8 July 1976 (1976-07-08)

have been considered for the examination procedure.

D3: WO 03/064387 A (HOFFMANN LA ROCHE) 7 August 2003 (2003-08-07) will be relevant in the regional phase. The applicant's comments will be taken into consideration.

2. NOVELTY

The presently claimed subject matter differs from D1 (see formula I of claim 1) and D2 (see formula (I),claims) in the nature of the substituent in position 3. Therefore the requirements of Article 33(2) PCT are fulfilled.

3. INVENTIVE STEP

The problem of the present application may be seen in the provision of further indole derivatives with high affinity for the androgen receptor.

D1 is considered to represent the closest prior art since the compounds being described therein exhibit a similar pharmaceutical activity.

Due to the structural difference as lined out under item 2 the skilled person would not have taken into consideration the presently claimed structures in order to solve the given problem.

The scope of the claims seems to represent a reasonable generalisation of the tested examples.

Therefore the requirements of Article 33(3) PCT are fulfilled.

4. INDUSTRIAL APPLICABILITY

For the assessment of the present Claims 16-20 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

✓ 84

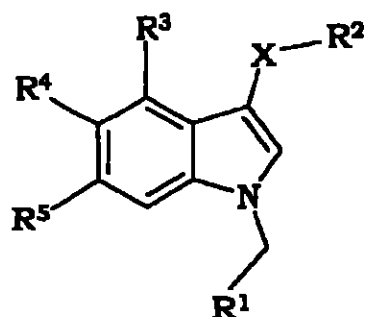
INDOLES UTILES EN EL TRATAMIENTO DE ENFERMEDADES RELACIONADAS CON ANDROGENOS RECEPTORES

La invención se relaciona con derivados del indol, su preparación y su uso para el tratamiento de condiciones, desordenes y enfermedades relacionadas con andrógenos receptores y otros tratamientos relacionados.

Los compuestos que poseen actividades androgénicas son útiles en el tratamiento de hombres con bajos niveles endógenos en las hormonas andrógenas circulantes u hombres con efectos androgenicos suspendidos. Tales tratamientos son prescritos a hombres de edad, a hombres hipogonadales u hombres tratados con progestagenos para anticoncepción masculina. En adición, andrógenos potentes suprimen la espermatogenesis y pueden ser usados como anticonceptivos masculinos.

Es por lo tanto importante obtener compuestos con una alta afinidad por el receptor andrógeno. Compuestos no esteroides con alta afinidad por el receptor andrógeno son particularmente útiles porque ellos pueden tener diferentes características de distribución en los tejidos que los andrógenos esteroides y pueden ser diseñados por escogencia apropiada de sustituyentes para ser mas o menos selectivos de ciertos tejidos. Por ejemplo, una acción en el cerebro es usualmente prevenida cuando los compuestos son fuertemente hidrofílicos o llevan una carga iónica.

El sujeto de la invención provee compuestos no-esteroides con afinidad por el receptor andrógeno. Estos compuestos son potencialmente útiles para el tratamiento de desordenes o desordenes relacionados con los receptores andrógenos los cuales pueden ser tratados con andrógenos. Los compuestos de la invención tienen una Estructura de acuerdo a la formula I



Donde.

X es S, SO o So₂

R¹ es una estructura anular no saturada o saturada, monociclica, hetero u homociclica, de 5- o 6- miembros, opcionalmente sustituida con uno o mas sustituyentes seleccionados de los grupos de halógenos, CN, (1C-4C)fluoroalkil, nitro, (1C-4C)alkil, (1C-4C)alkoxi o (1C-4C)fluoroalkoxi.

R² es 2-nitrofenil, 2-cianofenil, 2-hidroximetil-fenil, piridina-2-il, piridina-2-il-N-oxido, 2-benzamida, 2- metil éster de ácido benzoico o 2-metoxifenil;

R³ es H, halogeno o (1C-4C)alkil;

R⁴ es H, OH, (1C-4C)alkoxi o halógeno;

R⁵ es H, OH, (1C-4C)alkoxi; NH₂, CN, halógeno, (1C-4C)fluoroalkil, NO₂, hidroxil (1C-4C)alkil, CO₂H, CO₂(1C-6C)alkil, o R⁵ es NHR⁶, donde R⁶ es (1C-6C)acil opcionalmente sustituido con uno o mas halógenos, S(O)₂(1C-4C)alkil, o S(O)₂aril opcionalmente sustituido con (1C-4C)alkil o uno o más halógenos, o R⁵ es C(O)N(R⁸ o R⁹) donde R⁸ y R⁹ cada uno independientemente son H, (3C-6C)cicloalkil, o CH₂R¹⁰, donde R¹⁰ es H, (1C-5C)alkil, (1C-5C)alkenil, hidroxil(1C-3C)alkil, (1C-4C)alkilester de carboxil(1C-4C)alkil, (1C-3C)alkoxil(1C-3C)alkil, (mono o di(1C-4C)alkil)aminometil, (mono- o di(1C-4C)alkil)aminocarbonil, o un anillo no aromático o aromático, monociclico, hetero u homocíclico de 3-, 4-, 5- o 6- miembros, o R⁸ y R⁹ forman conjuntamente con el N un anillo no saturado o saturado, heterocíclico de 5 o 6 miembros opcionalmente sustituidos con (1C-4C)alkil; o sales o hidratos a partir de ellos.

/ 26

En una incorporación R^1 es una estructura anular no saturada o saturada, monocíclica, hetero u homocíclica de 5-o 6-miembros, opcionalmente sustituida con uno o mas sustituyentes seleccionados del grupo de halógeno, CN, CF_3 , nitro, metoxi, trifluorometoxi o metil; R^2 es 2-nitrofenil, 2-cianofenil, 2-hidroximetil-fenil, piridina-2-il, piridina-2-il-N-oxido, 2-benzamida, metil éster de ácido 2-benzoico o 2-metoxifenil; R^3 es H, halógeno o (1C-2C)alkil; R^4 es H o F.

En otra incorporación R^5 es H, OH, (1C-4C)alkoxi, CN, halógeno, (1C-4C)fluoroalkil, NO_2 , hidroxil(1C-4C)alkil, $CO_2(1C-6C)alkil$, o R^5 es NHR^6 , donde R^6 es (1C-6C)acil opcionalmente sustituido con uno o mas halógenos, $S(O)_2(1C-4C)alkil$ o $S(O)_2aril$ opcionalmente sustituido con (1C-4C)alkil o uno o mas halógenos, o R^5 es $C(O)N(R^8, R^9)$, donde R^8 y R^9 cada uno independientemente son H, (3C-6C)cicloalkil, o CH_2R^{10} , donde R^{10} es H, (1C-5C)alkil, (1C-5C)alkenil, hidroxil(1C-3C)alkil, (1C-4C)alkilester de carboxil(1C-4C)alkil, (1C-3C)alkoxil(1C-3C)alkil, (mono- o di(1C-4C)alkil)aminometil, (mono- o di(1C-4C)alkil)-aminocarbonil, o un anillo no aromático o aromático, monocíclico, hetero u homocíclico de 3-, 4-, 5- o 6- miembros, o R^8 y R^9 forman conjuntamente con el N un anillo no saturado o saturado, heterocíclico de 5 o 6 miembros opcionalmente sustituido con (1C-4C)alkil.

En todavía otra incorporación R^3 es H o halógeno; R^4 es H; R^5 es H, OH, (1C-4C)alkoxi, CN, F, Cl, CF_3 , NO_2 , hidroxil(1C-4C)alkil, $CO_2(1C-6C)alkil$, o R^5 es NHR^6 , donde R^6 es (1C-6C)acil opcionalmente sustituido con uno o mas halógenos o R^5 es $C(O)N(R^8, R^9)$, donde R^8 y R^9 cada uno independientemente son H, (3C-6C)cicloalkil, o CH_2R^{10} , donde R^{10} es H, (1C-5C)alkil, (1C-5C)alkenil, hidroxil(1C-3C)alkil, (1C-2C)alkilester de carboxil(1C-4C)alkil, (1C-3C)alkoxil(1C-3C)alkil, (mono- o di(1C-4C)alkil)aminometil, (mono- o di(1C-4C)alkil)aminocarbonil, (3C-5C)cicloalkil, o un anillo heterocíclico de 5- miembros.

07

En todavía otra incorporación X es S o SO₂; R² es 2-nitrofenil, 2-hidroximetil-fenil, 2-benzamida, 2-metoxifenil, 2-cianofenil o piridina-2-il; R³ es H o F; R⁵ es H, OH, (1C-2C)alkoxi, CN, F, Cl, CF₃, NO₂, hidroxi(1C-4C)alkil, CO₂(1C-4C)alkil, o R⁵ es NHR⁶, donde R⁶ formil, acetil, fluoroacetil, difluoroacetil o trifluoroacetil, o R⁵ es C(O)N(R⁸,R⁹), donde R⁸ es H, y R⁹ es H, ciclopropil o R⁹ es CH₂R¹⁰, donde R¹⁰ es H, (1C-2C)alkil, hidroxi(1C-2C)alkil, metoxi(1C-2C)alkil, ciclopropil.

En todavía otra incorporación X es S; R¹ es 3,5 difluorofenil, piridina-2-il, piridina-3-il, pirimidina-5-il, pirimidina-4-il, pirazina-2-il, 3-fluorofenil, 3-cianofenil, o 3-nitrofenil; R² es 2-nitrofenil, 2-hidroximetil-fenil, 2-metoxifenil, 2-cianofenil o piridina-2-il; R³ es H; R⁵ es OH, (1C-2C)alkoxi, CN, CF₃, NO₂, hidroxi(1C-4C)alkil, CO₂(1C-4C)alkil, o NHR⁶ donde R⁶ es formil, acetil, fluoroacetil, difluoroacetil, o trifluoroacetil.

En todavía otra incorporación R¹ es 3,5 difluorofenil, piridina-2-il, piridina-3-il, pirimidina-5-il, pirimidina-4-il, o pirazina-2-il; R² es 2-nitrofenil, o 2-hidroximetil-fenil; R⁵ es OH, (1C-2C)alkoxi, CN, hidroxi(1C-4C)alkil, o NHR⁶ donde R⁶ es formil, acetil, fluoroacetil, difluoroacetil, o trifluoroacetil.

En todavía otra incorporación R¹ es 3,5 difluorofenil, piridina-2-il, piridina-3-il, pirimidina-5-il o pirimidina-4-il; R² es 2-nitrofenil; R⁵ es OH, (1C-2C)alkoxi, CN, o NHR⁶ donde R⁶ es formil, acetil, fluoroacetil, difluoroacetil, o trifluoroacetil.

En una incorporación específica el sujeto de la invención provee el compuesto 6-Metoxi-3-(2-nitro-fenilsulfanil)-1-pirimidina-5-ilmetil-1H-indol, 3-(2-Nitro-fenilsulfanil)-1-piridina-2-ilmetil-1H-indol-6-carbonitrilo, 3-(2-Nitro-fenilsulfanil)-1-piridina-2-ilmetil-1H-indol-6-carbonitrilo-clorhidrato, 3-(2-Nitro-fenilsulfanil)-1-pirimidina-5-ilmetil-1H-indol-6-carbonitrilo, 3-(2-Nitro-fenilsulfanil)-1-pirimidina-4-ilmetil-1H-indol-6-carbonitrilo, N-[1-(3,5 difluorobencil)-3-(2-nitro-fenilsulfanil)-1-H-indol-6-il]-2-fluoro-acetamida, y N-[3-(2-Nitro-fenilsulfanil)-1-pirimidina-5-ilmetil-1H-indol-6-il]-formamida.

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En otra incorporación X es S; R¹ es 3,5 difluorofenil, piridina-2-il, piridina-3-il, 3-fluorofenil, 3-cianofenil, o 3-nitrofenil; R² es 2-nitrofenil, o 2-hidroximetil-fenil, 2-metoxifenil, 2-cianofenil o piridina-2-il; R³ es H; R⁵ es C(O)N(R⁸,R⁹), donde R⁸ es H, y R⁹ es H o CH₂R¹⁰, donde R¹⁰ es H, (1C-2C)alkil, hidroxi(1C-2C)alkil, o metoxi(1C-2C)alkil.

En todavía otra incorporación R¹ es 3,5 difluorofenil, piridina-2-il o piridina-3-il; R² es 2-nitrofenil, o 2-hidroximetil-fenil; R⁵ es C(O)N(R⁸,R⁹), donde R⁸ es H, y R⁹ es H y R⁹ es CH₂R¹⁰, donde R¹⁰ es H, (1C-2C)alkil.

En una incorporación específica el sujeto de la invención provee el compuesto metilamida del ácido 1-(3,5-Difluoro-bencil)-3-(2-nitro-fenilsulfanil)-1*H*-indol-6-carboxílico.

En todavía otra incorporación X es S; R¹ es 3,5 difluorofenil, piridina-2-il, piridina-3-il, 3-fluorofenil, 3-cianofenil, o 3-nitrofenil; R² es 2-nitrofenil, 2-hidroximetil-fenil, 2-metoxifenil, 2-metoxifenil, 2-cianofenil o piridina-2-il; R³ es H; R⁵ es C(O)N(R⁸,R⁹), donde R⁸ y R⁹ cada uno independientemente son H o CH₂R¹⁰, donde R¹⁰ es H, (1C-5C)alkil,(1C-5C)alkenil, hidroxi(1C-3C)alkil, (1C-3C)alkoxi(1C-3C)alkil o (mono- o di(1C-4C)alkil)aminometil.

En todavía otra incorporación R¹ es 3,5 difluorofenil, piridina-2-il o piridina-3-il; R² es 2-nitrofenil, o 2-hidroximetil-fenil; R⁵ es C(O)N(R⁸,R⁹), donde R⁸ y R⁹ cada uno independientemente son H o CH₂R¹⁰, donde R¹⁰ es H, (1C-5C)alkil, hidroxi(1C-3C)alkil, o (1C-3C)alkoxi(1C-3C)alkil.

En una incorporación específica el sujeto de la invención provee el compuesto dimetilamida del ácido 1-(3,5-Difluoro-bencil)-3-(2-nitro-fenilsulfanil)-1*H*-indol-6-carboxílico.

En aquellos casos en que un compuesto de la invención contiene una función amina básica, el compuesto puede ser usado como una base libre o como una sal farmacéuticamente aceptable tales como clorhidrato, acetato, oxalato, tartrato, citrato, fosfato, maleato o fumarato.

Un compuesto de acuerdo con la invención es un compuesto como se definió arriba, una sal a partir de ellos, un hidrato a partir de ellos o una prodroga a partir de ellos.

Los términos usados en esta descripción tienen los siguientes significados:

alkil es un grupo alkil ramificado o sin ramificar, por ejemplo metil, etil, propil, isopropil, butil, sec-butil, tert-butil, hexil y similares.

fluoroalkil es un grupo alkil sustituido con uno o mas átomos de fluor,

cicloalkil es un grupo alkil ciclado no ramificado, tal como ciclopropil, ciclobutil, ciclopentil y similares;

alkenil es un grupo alkenil ramificado o no ramificado, tal como etenil, 2-butenil, etc;

alkoxi es un grupo alkoxi ramificado o no ramificado, por ejemplo, metiloxi, etiloxi, propiloxi, isopropiloxi, butiloxi, sec-butiloxi, tert-butiloxi y similares;

fluoroalkoxi es un grupo alkoxi sustituido con uno o mas átomos de fluor:

aril es un sistema anillar aromático mono- o policíclico, homo- o heterocíclico, tal como fenil, naftil o piridil; un anillo monocíclico con 6 átomos es el preferido para usar;

acil es un (sustituyente-) grupo carbonil, tal como un aroil o alkanoil;

aroil es aricarbonil tal como un grupo benzoil:

alkanoil significa un grupo formil o alkilcarbonil tal como formil, acetil y propanoil;

carboxi es un sustituyente -COOH , que hace del compuesto un ácido orgánico;

carboxilato es una sal de un sustituyente carboxil.

Los prefijos (1C-4C), (2C-4C) etc. Tienen el significado usual de restringir el significado del grupo indicado a esos con 1 a 4 , 2 a 4 etc, átomos de carbono;

halógeno se refiere a fluor, cloro, bromo o yodo.

La afinidad al receptor andrógeno y eficacia del compuesto de acuerdo a la invención lo hace adecuado para uso en el tratamiento de desordenes relacionados con el receptor andrógeno, desordenes que pueden ser tratados con andrógenos, y en métodos de diagnóstico centrados en la cantidad y/o localización de los receptores andrógenos en diferentes tejidos. Para el último propósito puede preferirse hacer variantes marcadas de los compuestos de acuerdo a la invención. Los tratamientos típicos receptor andrógeno relacionados son esos para anticoncepción masculina y terapias de reemplazo hormonal masculina y femenina. Así a la invención también le pertenece un método de tratamiento de insuficiencia andrógena, mediante la administración a un macho o una hembra humana o animal de una cantidad efectiva de cualquiera de los compuestos del sujeto de la invención. El sujeto de la invención también descansa en el uso de cualquiera de sus compuestos para la preparación de una medicina para tratar la insuficiencia andrógena. En el contexto de la invención, el término " insuficiencia andrógena " debe ser entendido para incluir (pertain to) toda clase de enfermedades, desordenes, y síntomas en los cuales un macho o una hembra sufre de un muy bajo nivel de testosterona, tal como en hombre o nichos hipogonadales. En particular, la insuficiencia andrógena a ser tratada por un compuesto de la invención es la reducción del nivel de testosterona en el que un individuo masculino incurre como resultado de la edad (el compuesto de la invención es en consecuencia usado para terapia de reemplazo hormonal masculina), o cuando el es sujeto a anticoncepción masculina. En el contexto de la anticoncepción masculina, el compuesto de la invención sirve especialmente para neutralizar el efecto de regimenes de anticoncepción de hormonas masculinas en las cuales un esterilizante tales como el prostageno o LHRH (hormona liberadora de hormona luteinizante) es administrado regularmente , por ejemplo diariamente, o es usado como la única sustancia anticonceptiva masculina.

Así el sujeto de la invención provee cualquiera de los compuestos de la invención para uso en terapia.

El sujeto de la invención encompassa además una composición farmacéutica que comprende un compuesto del sujeto de la invención y un vehículo farmacéuticamente aceptable. En una incorporación de la presente invención, la composición farmacéutica es para el tratamiento de un desorden seleccionado de un grupo que consiste de desorden relacionado con receptor andrógeno, desorden relacionado con andrógeno e insuficiencia andrógena.

El sujeto de la invención envuelve además un método para tratar un desorden seleccionado de un grupo consistente en un desorden relacionado con receptor andrógeno, un desorden relacionado con andrógeno e insuficiencia andrógena que comprende la administración de una cantidad farmacéuticamente efectiva de un compuesto de acuerdo a la invención a un sujeto en necesidad de ellos.

El compuesto de la invención puede ser además útil en el tratamiento de osteoporosis, así como otros desordenes óseos, reparación de rotura de huesos, sarcopenia, fragilidad, envejecimiento de la piel, hipogonadismo masculino, disfunción sexual femenina, síntomas postmenopausicos, aterosclerosis, anemia aplástica, atrofia muscular, lipodistrofia, reducción de función y resistencia muscular, efectos secundarios de la quimioterapia, síndrome de fatiga crónica, hiperplasia benigna de la próstata (BPH), cachexi, estado catabólico crónico, alteración del conocimiento, contracepción masculina, y otros.

Los compuestos de la invención pueden ser administrados en conjunto con estrógenos, progestogenos y otros andrógenos.

Los compuestos de la invención pueden ser producidos por varios métodos conocidos en el arte de la química orgánica en general. Mas específicamente las

rutas de síntesis como son ilustradas en los siguientes Esquemas y ejemplos pueden ser usadas. En los esquemas y ejemplos las siguientes abreviaturas son usadas

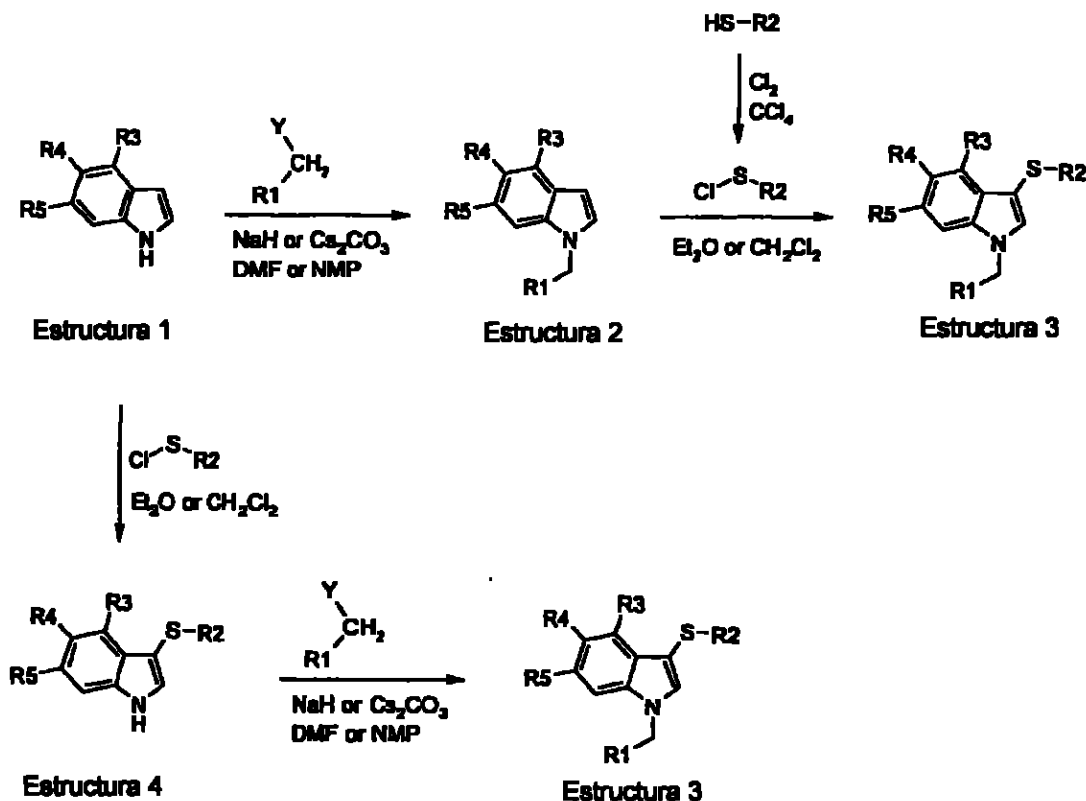
DMF=	dimetilformamida
mCPBA=	ácido <i>meta</i> cloro perbenzoico
THF=	tetrahidrofuran
TBTU=	2-(1H-benzotriazol-1-il)-1,1,3,3-tetrametilluronium tetrafluorobato
DIPEA=	diisopropiletilamina
EDCI=	1-(3-dimetilaminopropil)-3-clorhidrato de etilcarbodiimida
HOBt=	1-hidroxibenzotriazol
NMM=	N-metilmorfolina
SPE=	Extracción de fase sólida
RP-SPE=	fase reversa de extracción de fase sólida
DMSO=	dimetilsulfoxido
DMS=	diclorometano
DHT=	5 α -dihidrotestosterona
NMP=	1-metil-2-pirrolidinona
DMS=	sufuro de dimetil

En relación con la nomenclatura los siguientes nombres triviales son usados intercambiabilmente para los sustituyentes R¹ y R²:

<u>Nombre Trivial</u>	<u>Nombre Oficial</u>
2-piridil	piridina-2-il
3-piridil	piridil-3-il
4-piridil	piridil-4-il
3,5-pirimidil	pirimidina-5-il
2,4-pirimidil	pirimidina-4-il
2,5-pirazil	pirazina-4-il
etc.	

En cada uno de los Esquemas I-VII los significados de los símbolos corresponden a las definiciones dadas en los párrafos previos.

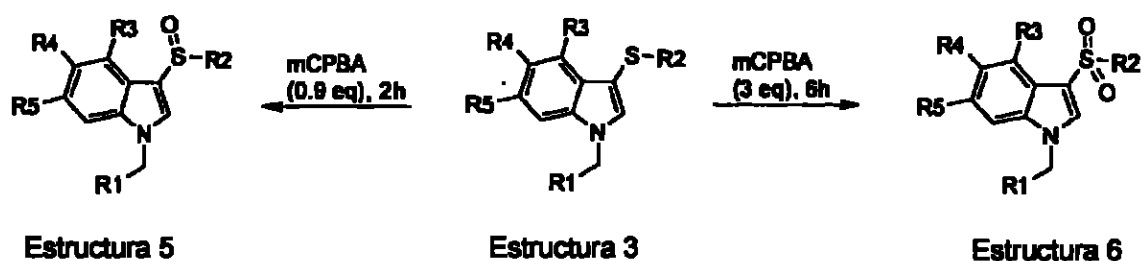
Los compuestos de indol sustituidos de Estructura 3 fueron preparados en dos pasos de los indoles correctamente sustituidos de Estructura 1, a través de dos rutas diferentes. En la primera ruta un indole correctamente sustituido de Estructura 1 es N-alkilado con un haluro de tipo R^1CH_2Y , donde Y es halógeno, mesilato o tosilato, con NaH o Ca_2CO_3 como una base en DMF o NMP a 0 °C a temperatura ambiente, para dar un compuesto de Estructura 2. La Estructura 2 es luego sulfanilada en la posición C-3 del anillo de indol por reacción con un cloruro de sulfenil en CH_2Cl_2 o eter dietil a temperatura ambiente, para dar la Estructura 3. En la segunda ruta los dos pasos de la primera ruta son reversados: el correctamente sustituido indol de la Estructura 1 es primero sulfanilado en la posición C-3 del indol para dar la estructura 4, seguido por N-alkilación con R^1CH_2Y para dar la Estructura 3 (Esquema I).



Esquema I

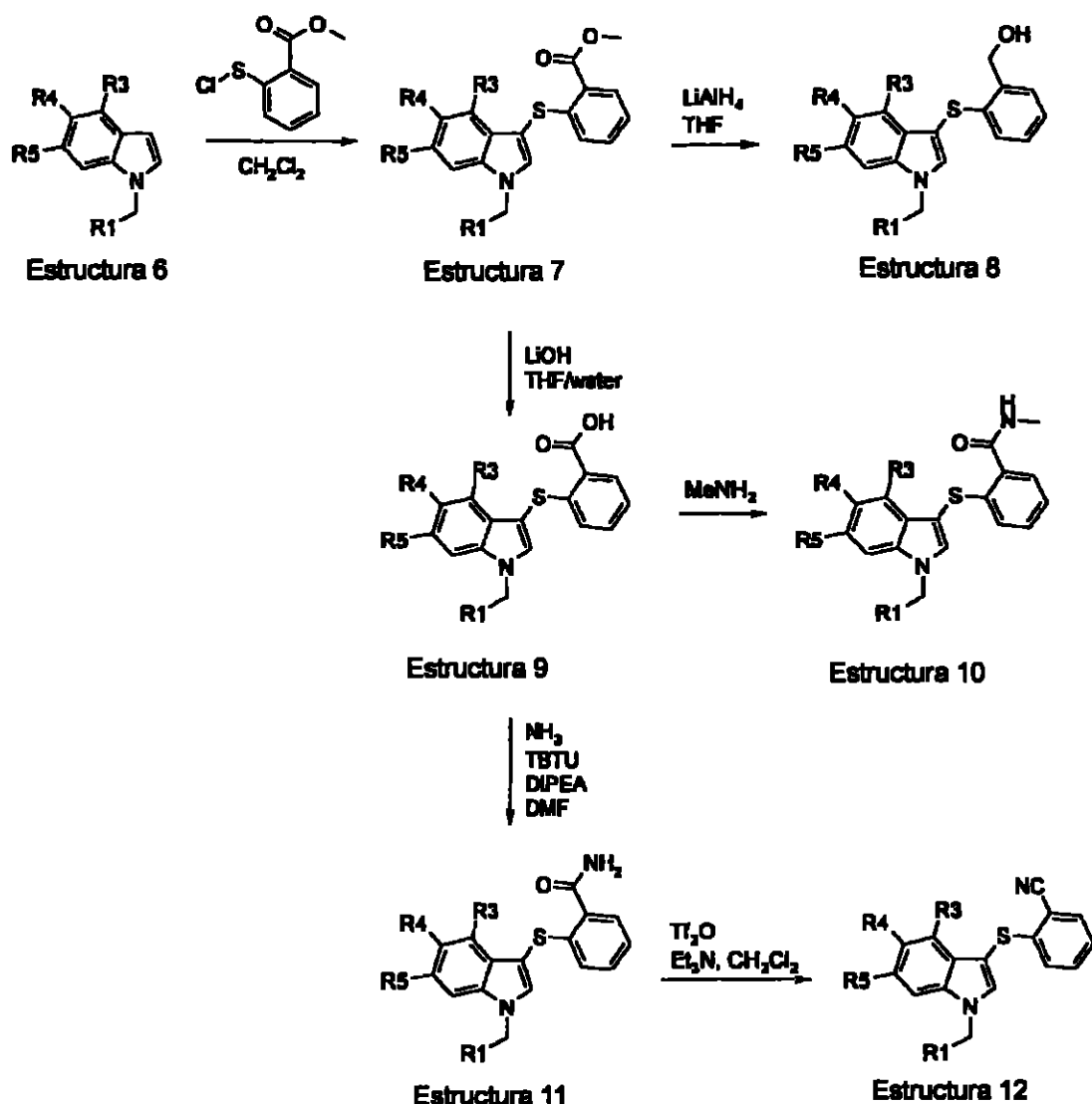
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Los sulfoxidos de la Estructura 5 pueden ser obtenidos por oxidación del sulfuro correspondiente (Estructura 3) por reacción con, por ejemplo, 0.9 equivalentes de mCPBA. Las sulfonas de la Estructura 6 pueden ser obtenidas por oxidación del correspondiente sulfuro (Estructura 3) por reacción con, por ejemplo, 3 equivalentes de mCPBA (Esquema II)



Esquema II

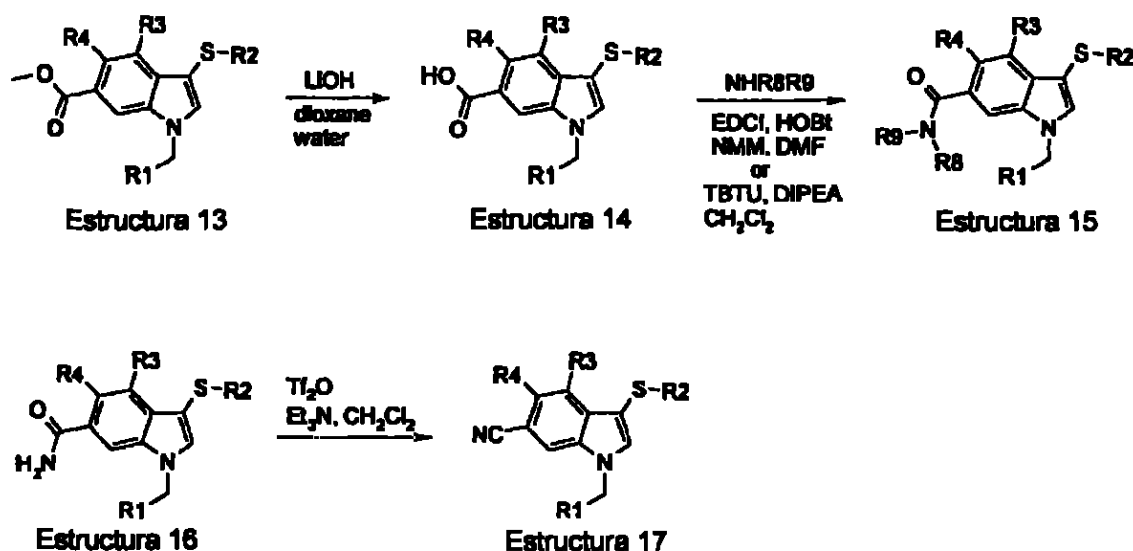
El Esquema III describe la síntesis de los compuestos de Estructura 3, en los cuales el grupo R² es un anillo de fenil sustituido en la posición-2 con o CO₂Me (Estructura 7), CH₂OH (Estructura 8), CO₂H (Estructura 9), CONAME (Estructura 10), CONH₂ (Estructura 11) o CN (Estructura 12)



Esquema III

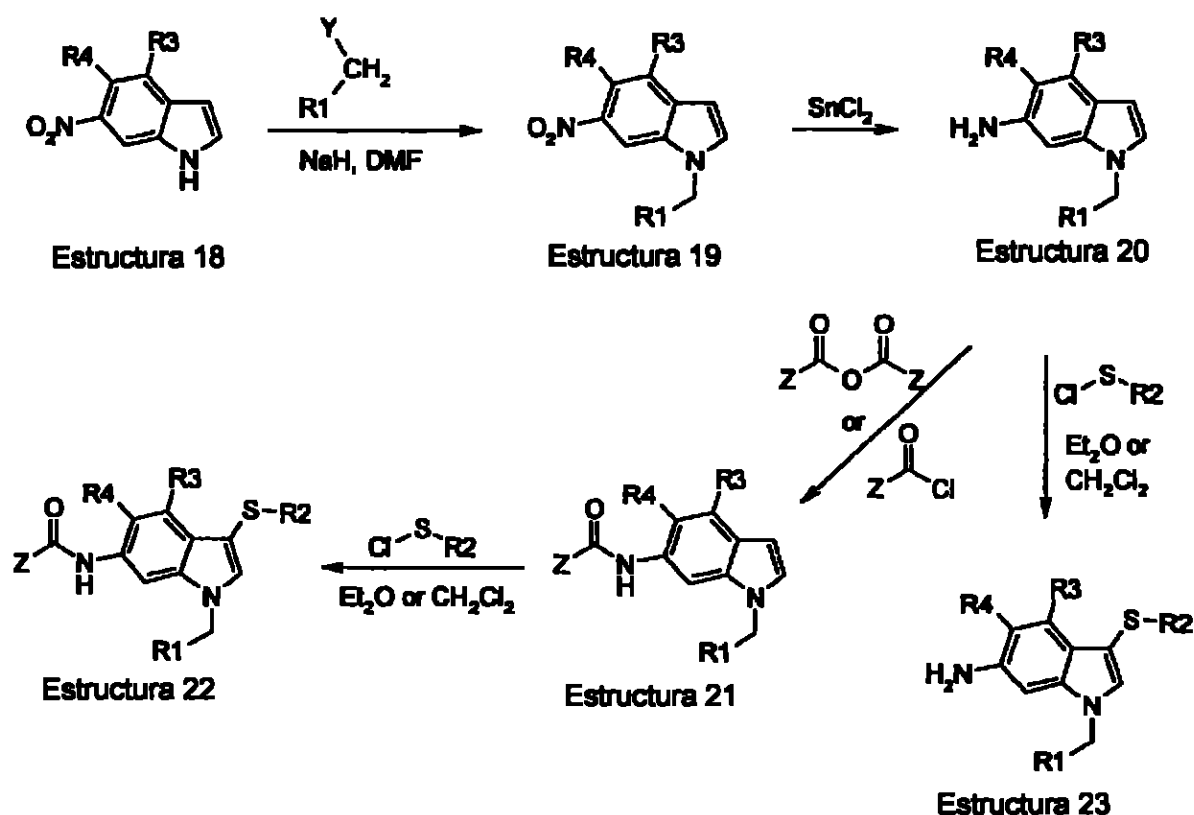
En el primer paso un indol sustituido de la Estructura 6 es sulfanilado en la posición-3 con 2-(carboximetil)-cloruro de fenilsulfenil, el cual fue preparado de metiltiosalicilato y gas de cloro, para dar un compuesto de Estructura 7. La reducción del moiety de metil éster de los compuestos de la Estructura 7 con LiAlH₄ dieron los correspondientes compuestos de hidroximetil de Estructura 8. Saponification del moiety de metil éster de los compuestos de Estructura 7 con hidróxido de litio dio los compuestos ácido carboxílicos correspondientes de la Estructura 9. El moiety de ácido carboxílico de los compuestos de Estructura 9 puede ser convertido al correspondiente carboxamida por reacción con una amina, TBTU y DIPEA en DMF a temperatura ambiente. Por este método la Estructura 10 fue obtenida cuando la metilamina fue usada como la amina y la Estructura 11 fue obtenida cuando NH₃ fue

usado como la amina. Deshidratación del moiety de benzamida de Estructura 11 con Ti_2O y trietilamina en CH_2Cl_2 obtuvo el correspondiente compuesto de benzonitrilo de la Estructura 12. (Esquema III)



Esquema IV

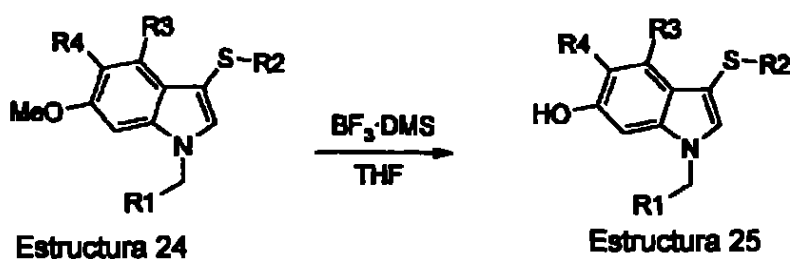
El Esquema IV describe la síntesis de compuestos de Estructura 3 en los cuales el anillo de indole es sustituido en la posición-6 con o CO_2Me (Estructura 13), CO_2H (Estructura 14), CONR^8R^9 (Estructura 15), CONH_2 (Estructura 16) o CN (Estructura 17). Saponificación del moiety de metil éster de la Estructura 13 con hidróxido de litio obtuvo el correspondiente ácido carboxílico de la Estructura 14. El moiety de ácido carboxílico de la Estructura 14 puede ser convertido a las correspondientes carboxamidas de la Estructura 15 y 16 por reacción con una amina o una sal de amina, en la presencia de EDCI y HOBt en una mezcla de NMM y DMF o en presencia de TBTU y DIPEA en CH_2Cl_2 a temperatura ambiente. Deshidratación del moiety de benzamida de Estructura 16 con Ti_2O y trietilamina en CH_2Cl_2 obtuvo el correspondiente compuesto de benzonitrilo de Estructura 17 (Esquema IV)



Esquema V

El Esquema V describe la síntesis de compuestos de Estructura 22 que contiene una funcionalidad amina acilada en la posición-6 del anillo de indol. Estos compuestos pueden ser sintetizados de 6-nitro indoles de Estructura 18 en 4 pasos. En el primer paso el indol de la Estructura 18 es alquilado en el átomo de nitrógeno por reacción de un haluro del tipo $\text{R}^1\text{CH}_2\text{Y}$, en el cual Y es halógeno, mesilato o tosilato, con NaH como una base en DMF para dar los compuestos de Estructura 19. En el segundo paso el grupo nitro de la Estructura 19 es reducido a un grupo amina por SnCl_2 para dar la Estructura 20. Subsecuentemente acilación del grupo amina con un cloruro de ácido del tipo ZCOCl obtuvo la Estructura 21, que luego fue sulfenilada en la posición 3 del anillo de indol por reacción con cloruro de sulfenil en CH_2Cl_2 o Et_2O como un solvente, a temperatura ambiente, para dar los compuestos de 22. Sulfenilación directa del compuesto de la Estructura 20 con cloruro de sulfenil obtuvo la Estructura 23.

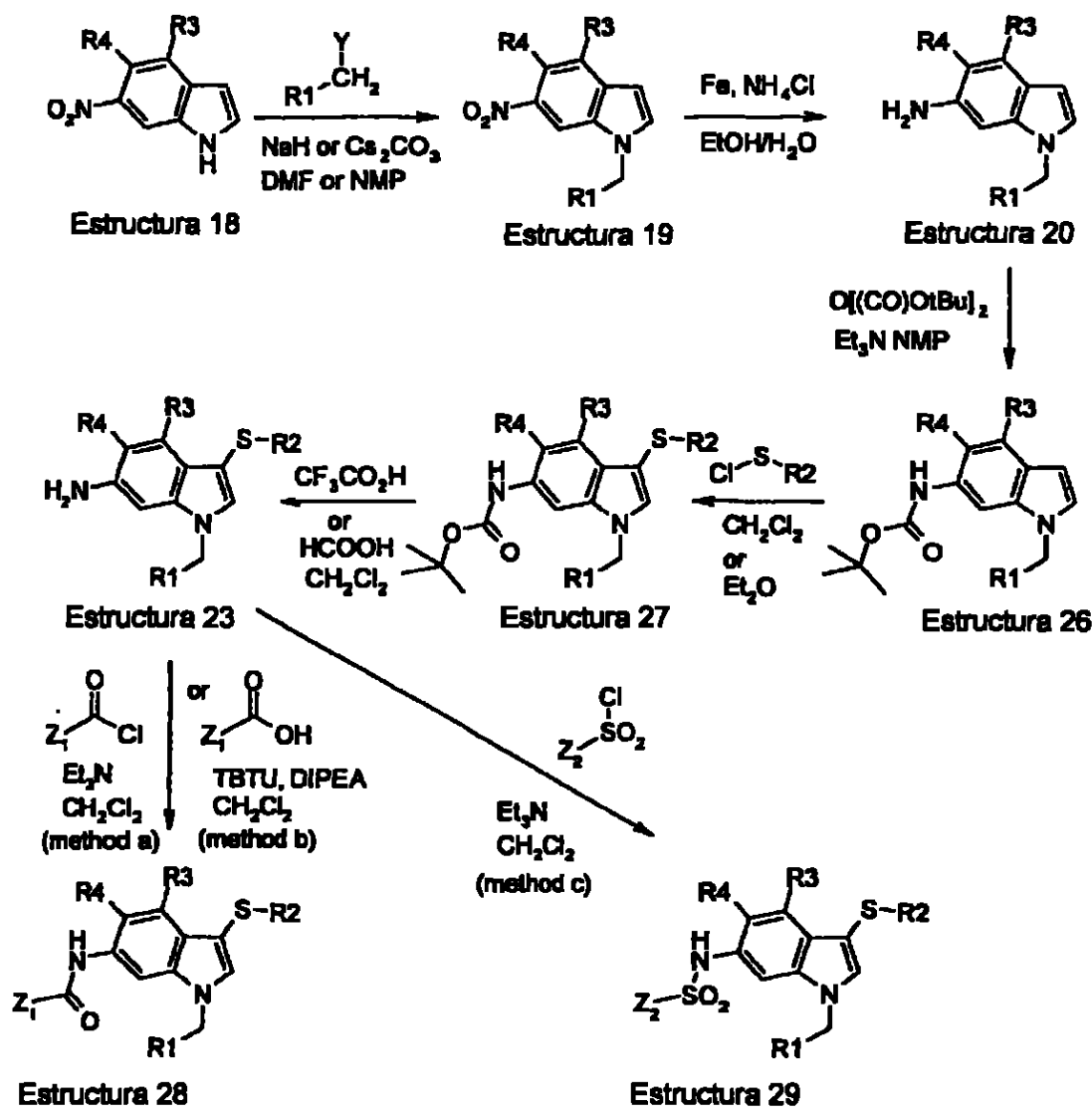
En el Esquema VI es descrito como metil ésteres de la Estructura 24 pueden ser partidos con, por ejemplo, $\text{BF}_3 \cdot \text{DMS}$ en THF a temperatura ambiente a los compuestos hidroxi de la Estructura 25.



Esquema VI

El Esquema VII describe la síntesis de los productos que contienen una funcionalidad amino acilada (Estructura 28) o una funcionalidad sulfonamida (Estructura 29) en la posición 6 del anillo de indol. Estos compuestos pueden ser preparados de 6-nitro indoles de Estructura 18 en 6 pasos. En el primero paso el indol de Estructura 18 es alquilado en N-1 por reacción de un haluro del tipo $\text{R}^1\text{CH}_2\text{Y}$, en el cual Y es un halógeno, mesilato o tosilato, con NaH o Cs_2CO_3 como una base en NMP o DMF para dar los compuestos de Estructura 19. En el segundo paso el grupo nitró de la Estructura 19 es reducido a un grupo amino con Fe y NH_4Cl en una mezcla etanol/agua para dar la Estructura 20. Acilación subsiguiente del grupo amino con dicarbonato de di-*tert*-butil obtuvo la Estructura 26 la cual fue luego sulfenilada en la posición 3 del anillo de indol por reacción con cloruro de sulfenil en CH_2Cl_2 o Et_2O para dar compuestos de Estructura 27. Luego la funcionalidad amina en la posición 6 del indol fue arrancada con ácido trifluoroacético o HCOOH para dar aminos de Estructura 23. Estos aminos pueden ser convertidos en aminos de Estructura 28 por reacción con trietilamina y un cloruro de ácido en CH_2Cl_2 (método a) o un ácido, TBTU y DIPEA en CH_2Cl_2 (método b). Las sulfonamidas de Estructura 29 pueden ser

preparadas por reacción de las aminas de la Estructura 23 con cloruros de sulfonil (método c).



Esquema VII

La presente invención también se relaciona con una composición farmacéutica que comprende el compuesto no-esteroide de acuerdo a la invención mezclado con un auxiliar farmacéuticamente aceptable, tal como se describe en el referencia estándar Gennaro *et al*, *Remmington: The Science and Practice of Pharmacy*, (20 th ed., Lippincott Williams & Wilkins, 2000, ver especialmente la parte 5: Manufactura Farmacéutica). Auxiliares adecuados están disponibles en, por ejemplo, The Handbook of Pharmaceutical Excipients (2nd Edition, Editors A. Wade and P.J.



Séller, American Pharmaceutical Association; Washington; The Pharmaceutical Press; London, 1994). La mezcla de un compuesto de acuerdo con la presente invención y un auxiliar farmacéuticamente aceptable puede ser comprimida en unidades de dosificación sólidas, tales como píldoras, tabletas, o ser procesadas en cápsulas o supositorios. Por medio de líquidos farmacéuticamente adecuados los compuestos pueden ser aplicados como una preparación inyectable en la forma de una solución, suspensión, emulsión, o como un atomizador, por ejemplo, un atomizador nasal. Para hacer las unidades de dosificación, por ejemplo, tabletas, el uso de aditivos convencionales tales como llenantes, colorantes, aglomerantes poliméricos y similares es contemplado. En general cualquier aditivo farmacéuticamente aceptable que no interfiera con la función del compuesto activo puede ser usado. Los compuestos de la invención pueden también ser incluidos en un implante, un anillo vaginal, un parche, un gel y cualquier otra preparación para una liberación sostenida.

Vehículos adecuados con los cuales la composición puede ser administrada incluye lactosa, almidón, derivados de celulosa y similares, o mezclas de ellos en cantidades adecuadas.

Las cantidades de dosificación de los presentes compuestos serán del orden normal para compuestos farmacéuticamente activos, por ejemplo, del orden de 0.001 a 50 mg/kg de peso de cuerpo del receptor por administración. El receptor puede ser un humano o un animal en necesidad de un tratamiento relacionado con el andrógeno-receptor o un tratamiento andrógeno.

El invento es ilustrado por los siguientes ejemplos.

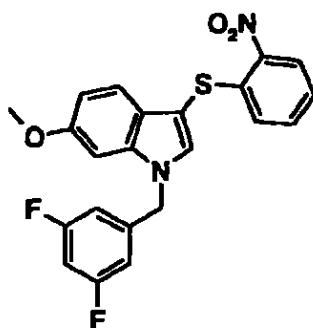
Ejemplos

Ejemplo 1

1-(3,5-Difluoro-bencil)-6-metoxi-3-(2-nitro-fenilsulfanil)-1-H-indol (Compuesto 63,

Estructura 3 del Esquema 1, donde $R^1=3,5$ -difluorofenil, $R^2=2$ -nitrofenil, $R^3=R^4=H$,

$R^5=OMe$)



Método General 1 : N-alkilación de un indol (no) sustituido de Estructura 1 para dar indole N-alkilatado de Estructura 2, seguido por 3-sulfanilación para dar indol sustituidos de Estructura 3 (Esquema I)

(a) 1-(3,5-Difluoro-bencil)-6-metoxi-1-H-indol (Estructura 2 del Esquema I, donde

$R^1=3,5$ -difluorofenil, $R^3=R^4=H$, $R^5=OMe$)

Bajo una atmósfera de nitrógeno: a una solución enfriada (0 °C) de 6-metoxiindol (863 mg, 5.86 mmol) en DMF (40 mL) fue adicionada NaH (60% en aceite; 281 mg, 7.03 mmol) en pequeñas porciones por un período de 3 minutos. La suspensión verde resultante fue agitada a 0 °C por 10 minutos. Luego bromuro de 3,5-difluorobencil (0.91 mL, 7.03 mmol) fue adicionado. La mezcla fue agitada a 0 °C por i hora y luego a temperatura ambiente por otras 21 horas. Acetato de etil (50 mL) fue adicionado y la mezcla fue lavada con solución acuosa de ácido cítrico al 3 % (

3X50mL) y salmuera (50 mL). La fase orgánica fue secada (MgSO_4) y concentrada en vacío para dar una aceite verde (1.43 g). El producto crudo fue purificado sobre un cartucho de 20 g. de SPE silica (acetato de etil/heptano 1:9) para dar el compuesto del título como un aceite incoloro (1.23 g, rendimiento 77%).

LCMS: 4.01 min (96.3 %, $\text{MH}^+ = 274$); TLC (acetato de etil/heptano 1:4): $R_f = 0.46$; ^1H NMR(CDCl_3): δ 3.80 (s, 3H, OCH_3), 5.24 (s, 2H, NCH_2Ar), 6.51 (dd, 1H, $J_1 = 3.5$ Hz, $J_2 = 0.8$ Hz), 6.57-6.60 (m, 2H), 6.65 (d, 1H, $J = 3.1$ Hz), 6.66-6.72 (m, 1H), 6.81 (dd, 1H, $J_1 = 8.6$ Hz, $J_2 = 3.1$ Hz), 7.01 (d, 1H, $J = 3.5$ Hz), 7.53 (d, 1H, 8.6 Hz).

(b) 1-(3,5-Difluoro-bencil)-6-metoxi-3-(2-nitro-fenilsulfenil)-1-H-indol (Compuesto 63, Estructura 3 del Esquema I, donde $R^1 = 3,5$ -difluorofenil, $R^2 = 2$ -nitrofenil, $R^3 = R^4 = \text{H}$, $R^5 = \text{OMe}$)

A una solución de 1-(3,5-Difluoro-bencil)-6-metoxi-1H-indol (900 mg, 3.29 mmol) en dietil éter (20 mL) fue adicionada por goteo a temperatura ambiente una suspensión de 2-cloruro de nitrobenzenosulfenil (637 mg, 3.31 mmol) en dietil éter (10 mL) en un período de dos horas. Después de agitar a temperatura ambiente por 1 hora, acetato de etil (50 mL) fue adicionado y la mezcla fue lavada con una solución saturada de NaHCO_3 (2X50 mL) y salmuera (50 mL). La fase orgánica fue secada (MgSO_4) y concentrada en vacío para dar una aceite naranja-rojo (1.54 g). El producto crudo fue cristalizado a partir de tolueno/acetona para dar el compuesto del título como un sólido cristalino naranja-rojo (900 mg, rendimiento 64 %)

LCMS: 4.25 min (100 %, $\text{MH}^+ = 427$); HPLC: 4.86 min (98.7 %); ^1H NMR(CDCl_3): δ 3.82 (s, 3H, OCH_3), 5.32 (s, 2H, NCH_2Ar), 6.63-6.69 (m, 2H), 6.72 – 6.69 (m. 1 H), 6.75 (d, 1H, $J = 2.7$), 6.85 (dd, 1H, $J_1 = 8.2$ Hz, $J_2 = 2.7$ Hz), 6.98 (dd, 1H, $J_1 = 6.7$ Hz, $J_2 = 1.2$ Hz), 7.16 – 7.20 (m, 1H), 7.26 – 7.30 (m, 1H), 7.34 (s, 1H), 7.39 (d, 1H, $J = 8.2$ Hz), 8.27 (dd, 1H, $J_1 = 8.6$ Hz, $J_2 = 1.6$ Hz).

De acuerdo al Método General 1 el siguiente compuesto fue preparado:

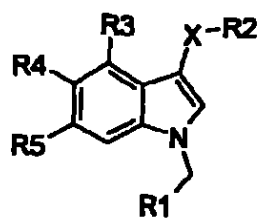


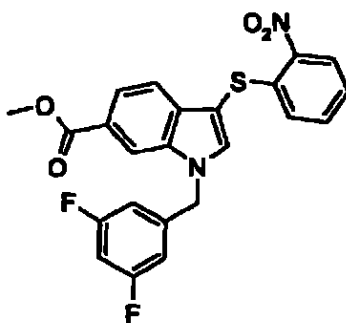
Tabla 1 Compuestos sintetizados de acuerdo al Método General 1.

Compuesto Numero	X	R ¹	R ²	R ³	R ⁴	R ⁵	Mwt	LCMS MH ⁺	LCMS ret Time ^a (min)
21	S	3,5-difluorofenil	2- metoxifenil	H	H	Ome	411.47	446 ^a	5.14 ^b
22	S	3,5-difluorofenil	2- nitrofenil	H	H	Br	475.32	476	4.89
23	S	3,5-difluorofenil	2- nitrofenil	H	H	CF3	464.41	465	5.34 ^b
24	S	3,5-difluorofenil	2- nitrofenil	H	H	CH2OH	426.44	Nd	3.88 ^b
25	S	3,5-difluorofenil	2- nitrofenil	H	H	Cl	430.86	431	4.89
50	S	3,5-difluorofenil	2- nitrofenil	H	H	F	414.40	415	4.79
51	S	3,5-difluorofenil	2- nitrofenil	F	H	H	414.40	415	4.72
52	S	3,5-difluorofenil	2- nitrofenil	H	H	H	396.41	397	4.22
53	S	3,5-difluorofenil	2- nitrofenil	H	F	H	414.40	415	4.75
54	S	3,5-difluorofenil	2- nitrofenil	Cl	H	H	430.86	431	5.14 ^b
55	S	3,5-difluorofenil	2- nitrofenil	Me	H	H	410.44	411	5.24 ^b
56	S	3,5-difluorofenil	2- nitrofenil	H	OH	H	412.41	413	4.50 ^b
60	S	3,5-difluorofenil	2- nitrofenil	H	H	NO2	441.41	442	4.7
61	S	3,5-difluorofenil	2- nitrofenil	H	H	OH	412.41	413	4.54 ^b
63	S	3,5-difluorofenil	2- nitrofenil	H	H	OMe	426.45	274 ^a	4.01
66	S	3,5-difluorofenil	2-piridil-N- oxido	H	H	OMe	398.43	399	3.96
90	S	Fenil	2- nitrofenil	H	H	H	360.43	361	4.19
91	S	Fenil	2- nitrofenil	H	OMe	H	390.46	391	4.14
92	S	Fenil	2- nitrofenil	H	H	OMe	390.46	391	4.12

a) 7 min método LCMS fue usado, a menos que se establezca de otra manera, b) 10 min. Método fue usado c) M+Cl . nd= no detectado. d) =[M-S(PhNO₂)]H⁺

Ejemplo 2

Metil ester del ácido 1-(3,5-Difluoro-bencil)-3-(2-nitro-fenilsulfanil)-1-*H*-indol-6-carboxílico (Compuesto 31, Estructura 3 del Esquema I, donde $R^1=3,5$ -difluorofenil, $R^2=2$ -nitrofenil, $R^3=R^4=H$, $R^5=CO_2Me$)



(a) Metil ester del ácido 1-*H*-indol-6-carboxílico (Estructura 1 del Esquema I, donde $R^3=R^4=H$, $R^5=CO_2Me$)

A una solución de 1-*H*-indol-6-ácido carboxílico (1500 g, 9.31 mmol) en metanol (50 mL) le fue adicionado H_2SO_4 concentrado (550 μ L, 10.24 mmol). La mezcla fue agitada de un día al otro a temperatura de reflujo. La mezcla fue luego neutralizada a pH 7 por adiciones de solución acuosa saturada de $NaHCO_3$ y la mezcla fue luego extraída dos veces con acetato de etil. Las capas orgánicas combinadas fueron secadas sobre Na_2SO_4 y concentradas en vacio para obtener un polvo amarillo. El producto fue recristalizado desde heptano/ acetato de etil para dar el compuesto del título como unos cristales verde/amarillo (68 mg, rendimiento 53%)

^1H NMR ($CDCl_3$): δ 3.94 (s, 3H, CH_3OCO), 6.60 (m, 1H), 7.37 (t, 1H, $J=4.7$ Hz), 7.66 (d, 1H, $J=8.2$ Hz), 7.82 (dd, 1H, $J_1=3.1$ Hz, $J_2=1.0$ Hz), 8.18 (s, 1H), 8.73 (s, 1H, NH).

2
85

(b) Metil ester del ácido 1-(3,5-Difluoro-bencil)-3-(2-nitro-fenilsulfanil)-1-*H*-indol-6-carboxílico (Estructura 2 del Esquema I, donde $R^1=3,5$ -difluorofenil, $R^3=R^4=H$, $R^5=CO_2Me$)

Bajo una atmósfera de nitrógeno: a una solución de metil ester del ácido 1-*H*-indol-6-carboxílico (367 mg, 2.09 mmol) en DMF (10 mL) fue adicionado NaH (60% en aceite, 101 mg, 2.52 mmol) a temperatura ambiente. Después de agitar por 15 minutos 1-bromoetil-3,5-difluoro-benceno (325 μ L, 2.51 mmol) fue adicionado y la mezcla fue agitada a temperatura ambiente por 4 horas. La reacción fue apagada con solución acuosa de ácido cítrico al 3 % (10 mL) y acetato de etil (30 mL) fue adicionado. La mezcla fue lavada con solución acuosa de ácido cítrico al 3 % (3X20 mL) y salmuera (20 mL). La fase orgánica fue secada ($MgSO_4$) y concentrada en vacío para dar un aceite amarillo pálido (702 mg). El producto crudo fue purificado sobre un cartucho de SPE sílice de 20g (acetato de etil/heptano 1:9) para obtener el compuesto del título como un aceite incoloro, que lentamente se cristalizó en reposo (530 mg, rendimiento= 84%).

LCMS: 4.08 min (99 %, $MH^+ = 302$); ^1H NMR($CDCl_3$): δ 3.92 (3, 3H, CO_2CH_3), 5.37 (s,2H, NCH_2Ar), 6.54-6.60 (m, 2H), 6.64 (d,1H, $J = 3.1$ Hz), 6.67 – 6.74 (m, 1H), 7.27 (d,1H, $J = 3.1$ Hz), 7.68 (d,1H, $J = 8.6$ Hz), 7.83 (d,1H, $J = 8.6$ Hz), 8.01 (s, 1H).

(c) Metil ester del ácido 1-(3,5-Difluoro-bencil)-3-(2-nitro-fenilsulfanil)-1-*H*-indol-6-carboxílico (Compuesto 31, Estructura 3 del Esquema I, donde $R^1=3,5$ -difluorofenil, $R^2=2$ -nitrofenil, $R^3=R^4=H$, $R^5=CO_2Me$)

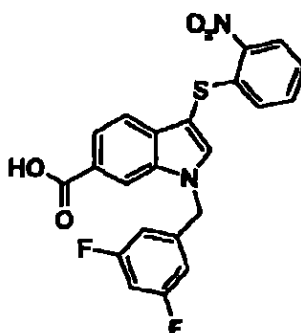
A una solución de metil ester del ácido 1-(3,5-Difluoro-bencil)-1-*H*-indol-6- carboxílico (330 mg, 1.10 mmol) en diclorometano (30 mL) fue adicionado a temperatura ambiente una solución de cloruro de 2-nitrobencenosulfenil (210 mg, 1.11 mmol) en diclorometano (10 mL), La mezcla fue agitada a temperatura ambiente durante 4 días. La mezcla de la reacción fue concentrada y el producto crudo fue purificado

sobre un cartucho de SPE sílice de 20 gramos (acetato de etil/heptano 1:5 a 1: 2) para dar el compuesto del título como un sólido amarillo (392 mg, rendimiento= 78 %).

HPLC: 4.60 min (97.8 %); ^1H NMR(CDCl_3): δ 3.93 (s, 3H, CO_2CH_3), 5.45 (s,2H, NCH_2Ar), 6.63-6.69 (m, 2H), 6.74-6.80 (m, 1H), 6.88 (dd,1H, $J_1 = 8.2$ Hz, $J_2 = 1.2$ Hz), 7.18 – 7.23 (m, 1H), 7.26 – 7.30 (m, 1H), 7.57 (d,1H, $J = 7.8$ Hz), 7.89 (s, 1H), 7.89 (dd,1H, $J_1 = 7.8$ Hz, $J_2 = 1.2$ Hz), 8.12 (s, 1H), 8.28 (dd,1H, $J_1 = 7.8$ Hz, $J_2 = 1.2$ Hz).

Ejemplo 3

1-(3,5-Difluoro-bencil)-3-(2-nitro-fenilsulfanil)-1-*H*-indol-6-ácido carboxílico
(Compuesto 30. Estructura 14 del Esquema IV, donde $\text{R}^1=3,5\text{-difluorofenil}$, $\text{R}^2=2\text{-nitrofenil}$, $\text{R}^3=\text{R}^4=\text{H}$)

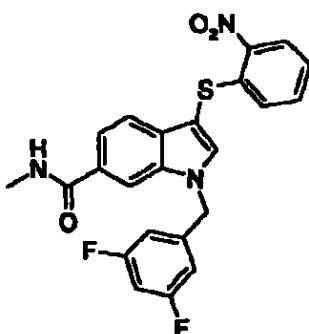


A una solución de metil ester del ácido1-(3,5-Difluoro-bencil)-3-(2-nitro-fenilsulfanil)-1-*H*-indol-6-carboxílico (150.0 mg, 0.33 mmol) en dioxano (20 mL) y agua (15 mL) fue adicionada $\text{LiOH}\cdot\text{H}_2\text{O}$ (83.1 mg, 2.0 mmol) en 5 ml de agua. La mezcla de la reacción fue agitada de un día al otro a 60 °C. La mezcla fue luego acidificada a pH 4 mediante la adición de solución acuosa de HCl al 15% y la mezcla fue extraída dos veces con acetato de etil. La capas orgánicas combinadas fueron secadas sobre Na_2SO_4 y concentradas en vacío para obtener un polvo amarillo. El producto fue recrystalizado a partir de heptano/acetato de etil para dar el compuesto del título como cristales amarillo/naranja (129.3 mg, rendimiento = 89%).

^1H NMR(DMSO): δ 5.62 (s, 2H, CH_2Ar), 6.85 (dd, 1H, $J_1 = 8.6$ Hz, $J_2 = \text{br}$), 7.05 (m, 2H, br), 7.20 (m, 1H, br), 7.32-7.38 (m, 1H), 7.40 (d, 1H, $J = 8.2$ Hz), 7.44-7.50 (m, 1H), 7.68 (dd, 1H, $J_1 = 8.6$ Hz, $J_2 = \text{br}$), 7.97 (s, 1H, COOH), 8.20 (s, 1H), 8.26 (s, 1H), 8.28 (d, 1H, $J = 8.2$).

Ejemplo 4

Metilamida del ácido 1-(3,5-Difluoro-bencil)-3-(2-nitro-fenilsulfanil)-1-*H*-indol-6-carboxílico (Compuesto 47, Estructura 15 del Esquema IV, donde $\text{R}^1 = 3,5$ -difluorofenil, $\text{R}^2 = 2$ -nitrofenil, $\text{R}^3 = \text{R}^4 = \text{R}^5 = \text{H}$, $\text{R}^6 = \text{Me}$)



Método General 2: amidación de indoles 6-carboxil de estructura 14 para obtener 6-carboxamideindoles de estructura 15 (Esquema IV)

Bajo atmósfera de nitrógeno : a una solución de 1-(3,5-Difluoro-bencil)-3-(2-nitro-fenilsulfanil)-1-*H*-indol-6-ácido carboxílico (25.1 mg, 57.0 μmol) en DMF seco (10 mL) fue adicionado NMM (1 mL), HOBT (9.60 mg, 62.7 μmol), EDCI (12.1 mg, 62.7 μmol), y cloruro de metilamonio (19.2 mg, 285 μmol). La mezcla de la reacción fue agitada de un día al otro a temperatura ambiente y luego vertida sobre agua congelada. El precipitado resultante fue filtrado y el residuo fue lavado con agua de exceso seguido por un poco de heptano.. El producto fue secado en vacío a 40 °C para dar el compuesto del título como un sólido amarillo (15.2 mg, $y = 60\%$).

LCMS: 4.31 min (100.0 %, MH⁺ =454); ¹H NMR(DMSO): δ 2.80 (d, 3H, J= 4.3, CH₃NHCO), 5.63 (s, 2H, CH₂Ar), 6.86 (dd ,1H,J1 = 8.2 Hz, J2= 1.0 Hz), 7.04 (m, 2H), 7.20 (m,1H), 7.33-7.37 (m, 1H), 7.41 (d,1H,J 8.6 Hz), 7.46-7.50(m,1H), 7.64 (dd,1H,J1= 8.2 Hz, J2= 1.0 Hz), 8.15 (s, 1H), 8.25 (s,1H), 8.27 (dd, 1H, J1= 8.6 Hz, J2=1.0 Hz), 8.40 (m,1H, MeNHCO).

De acuerdo con el Método General 2 el siguiente compuesto fue preparado

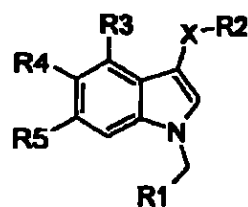


Tabla 2 Compuestos sintetizados de acuerdo al Método General 2.

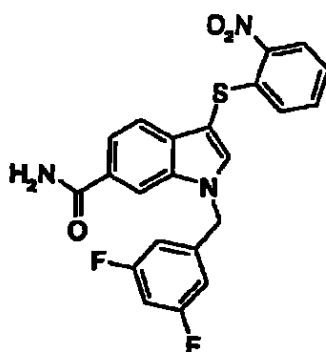
Compuesto Numero	X	R ¹	R ²	R ³	R ⁴	R ⁵	Mwt	LCMS MH ⁺	LCMS ret Time ^a (min)
27	S	3,5-difluorofenil	2- nitrofenil	H	H	CO(1-pirrolidina)	493.53	494	4.66
28	S	3,5-difluorofenil	2- nitrofenil	H	H	CO(4-morfolinil)	509.53	510	4.50
29	S	3,5-difluorofenil	2- nitrofenil	H	H	CO[1-(4-metilpiperazinil)]	522.57	523	3.81
32	S	3,5-difluorofenil	2- nitrofenil	H	H	CONEt2	495.55	496	4.82
34	S	3,5-difluorofenil	2- nitrofenil	H	H	CONHCH2(2-furanil)	519.53	520	4.74
35	S	3,5-difluorofenil	2- nitrofenil	H	H	CONHCH2(3-piridil)	530.55	531	3.94
36	S	3,5-difluorofenil	2- nitrofenil	H	H	CONHCH2CH2NMe 2	510.56	511	3.90
37	S	3,5-difluorofenil	2- nitrofenil	H	H	CONHCH2CH2OH	483.49	484	4.21
38	S	3,5-difluorofenil	2- nitrofenil	H	H	CONHCH2CH2OMe	497.52	498	4.48
39	S	3,5-difluorofenil	2- nitrofenil	H	H	CONHCH2CO2Me	511.50	412	4.51
40	S	3,5-difluorofenil	2- nitrofenil	H	H	CONHCH2CONMe2	524.55	525	4.33
41	S	3,5-difluorofenil	2- nitrofenil	H	H	CONHCH2cPr	493.53	494	4.75
42	S	3,5-difluorofenil	2- nitrofenil	H	H	CONHCH2iPr	495.55	496	4.85
43	S	3,5-difluorofenil	2- nitrofenil	H	H	CONHCH2Ph	529.56	530	4.90
44	S	3,5-difluorofenil	2- nitrofenil	H	H	CONHcPr	479.50	480	4.57
45	S	3,5-difluorofenil	2-piridil-N-oxido	H	H	CONHEt	529.56	468	4.56

46	S	3,5-difluorofenil	2- nitrofenil	H	H	CONHPr	479.50	482	4.71
47	S	3,5-difluorofenil	2- nitrofenil	H	H	CONHMe	467.49	454	4.31
48	S	3,5-difluorofenil	2- nitrofenil	H	H	CONHnPr	481.52	482	4.75
49	S	3,5-difluorofenil	2- nitrofenil	H	H	CONMe	467.49	468	4.30 ^b

a) 7 min método LCMS fue usado, a menos que se establezca de otra manera, b) 10 min. Método fue usado .

Ejemplo 5

Amida del ácido 1-(3,5-Difluoro-bencil)-3-(2-nitro-fenilsulfanil)-1-*H*-indol-6-carboxílico
(Compuesto 33, Estructura 16 del Esquema IV, donde R¹=3,5-difluorofenil, R²=2-nitrofenil, R³=R⁴= H)



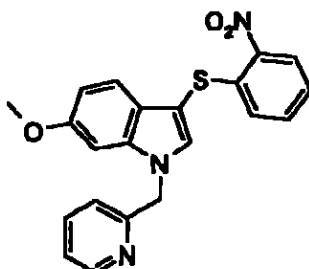
El compuesto del título fue preparado de acuerdo al método general 2, usando 51.1 mg (116 μ mol) de ácido carboxílico, 19.5 mg (128 μ mol) de HOBt, 24.6 mg (128 μ mol) de EDCI y 31.1 mg (581 μ mol) de cloruro de amonio. El título del compuesto fue obtenido como un sólido amarillo (9.0 mg, 18 %).

LCMS: 4.16 min (100.0 %, MH⁺ =440); ¹H NMR(CDCl₃): δ 5.46 (s, 2H, CH₂Ar), 6.65 (m, 2H), 6.77 (m, 2H), 6.88 (dd ,1H,J1 = 8.2 Hz, J2= 1.0 Hz), 7.21 (m, 1H), 7.29 (m,1H), 7.51 (dd,1H,J1= 7.8 Hz, J2= 1.0 Hz), 7.57 (d,1H,J= 7.7 Hz), 7.58 (s, 1H), 8.05 (s,1H), 8.29 (dd, 1H, J1= 8.2 Hz, J2=1.0 Hz).

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Ejemplo 6

6-Metoxi-3-(2-nitro-fenilsulfanil)-1H-indol (Compuesto 9, Estructura 3 del Esquema I, donde $R^1 = 2$ -piridil, $R^2 = 2$ -nitrofenil, $R^3 = R^4 = H$, $R^5 = OMe$)



Método General 3: 3-sulfanilación de un indole (no) sustituido de estructura 1 para obtener indoles sustituidos de estructura 4, seguido por N-alkilación de indole para obtener indoles N-alkilatado de estructura 3 (Esquema I)

(a) 6-Metoxi-3-(2-nitro-fenilsulfanil)-1H-indol (Estructura 4 del Esquema I, donde $R^2 = 2$ -nitrofenil, $R^1 = R^3 = R^4 = H$, $R^5 = OMe$)

A una solución de 6-metoxiindol (1.5 g, 10.2 mmol) en Et₂O (100mL) fue adicionado una solución de cloruro de 2-nitrobencenosulfenil (1.93 g, 10.2 mmol) en 50 ml de Et₂O por goteo, por un período de 4 minutos. La solución amarilla resultante fue agitada a temperatura ambiente por 1 horas. El solvente fue evaporado y el producto crudo fue purificado sobre una columna de silica (heptano/ acetato de etil 9:1) para dar el compuesto del título (3.054 g, rendimiento=97%).

HPLC: 3.72 min, pureza 96.7% TLC (heptano/acetato de etil 1:1): $R_f = 0.6$ ¹H NMR(CDCl₃): δ 3.87 (s, 3H, OCH₃), 6.84 (dd ,1H, $J_1 = 7.8$ Hz, $J_2 = 3.13$ Hz), 6.97 (m, 2H), 7.16 (t,1H, $J = 7.8$ Hz), 7.25 (t,1H, $J = 7.8$ Hz), 7.36(d, 1H, $J = 7.8$ Hz), 7.44 (d, 1H, $J = 2.0$ Hz), 8.26 (d,1H, $J = 7.8$ Hz), 8.45 (s, 1H, NH).

(b) 6-Metoxi-3-(2-nitro-fenilsulfanil)-1-piridina-2-ilmetil-1*H*-indol (Compuesto 9, Estructura 3 del Esquema I, donde R¹= 2-piridil, R²=2-nitrofenil, R³=R⁴= H, R⁵=OMe)

A una solución de 6-Metoxi-3-(2-nitro-fenilsulfanil)-1*H*-indol (1.5 g, 5 mmol) en DMF (150 mL) fue adicionada NaH (60 % en aceite, 500 mg, 12.5 mmol) en pequeñas porciones, por un período de 4 minutos. La solución oscura resultante fue agitada por 5 minutos a temperatura ambiente. Luego clorhidrato de 2-picolil cloruro (984 mg, 6 mmol) fue adicionado en pequeñas porciones por un período de 2 minutos. Durante la agitación a temperatura ambiente (2h) el color de la solución cambio ligeramente de oscuro a amarillo. Acetato de etil (100 mL) fue adicionado a la mezcla y lavado con solución acuosa de ácido cítrico al 2 % (2X100 mL) y agua (100 mL). La fase orgánica fue secada (MgSO₄) y el solvente fue evaporado. El producto crudo fue purificado por cristalización (acetato de etil/ heptano) para obtener el compuesto del título (1.437 g, rendimiento 74%).

HPLC: 10.3 min, pureza 99.6% TLC (heptano/acetato de etil 1:1): R_f= 0.3

¹H NMR(CDCl₃): δ 3.80 (s, 3H, OCH₃), 5.47 (s, 2H, NCH₂), 6.82 (m, 2H), 6.88 (d ,1H,J = 7.8 Hz), 7.01 (dd,1H, J1= 7.8 Hz, J2= 1.6 Hz), 7.15-7.19 (m, 1H), 7.25 (m,2H), 7.37 (d, 1H, J= 8.6 Hz), 7.60 –7.44 (m, 1H), 8.26 (d,1H, J1=7.8 Hz, J2= 1.6 Hz), 8.63 (d, 1H, J = 5.88 Hz).

De acuerdo al Método General 3 los siguientes compuestos fueron preparados

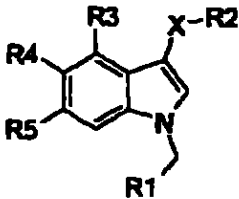


Tabla3 Compuestos Sintetizados de acuerdo al Método General 3

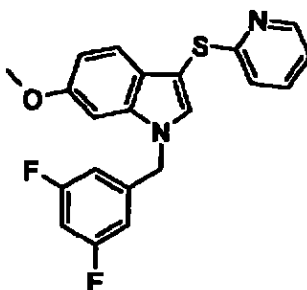
Compuesto Numero	X	R ¹	R ²	R ³	R ⁴	R ⁵	Mwt	LCMS MH ⁺	LCMS ret Time ^a (min)
1	S	2,5-difluorofenil	2- nitrofenil	H	H	OMe	426.44	427	4.07
2	S	2, fluoro, 3-metilfenil	2- nitrofenil	H	H	OMe	422.48	423	4.23
3	S	2 clorofenil	2- nitrofenil	H	H	OMe	424.91	425	4.17
4	S	2 clanofenil	2- nitrofenil	H	H	OMe	415.47	416	3.97
5	S	2-fluorofenil	2- nitrofenil	H	H	OMe	408.45	409	4.10
6	S	2-metil,3-nitrofenil	2- nitrofenil	H	H	OMe	449.48	450	4.10
7	S	2-metilfenil	2- nitrofenil	H	H	OMe	404.49	405	4.16
8	S	2-nitrofenil	2- nitrofenil	H	H	OMe	435.46	436	4.08
9	S	2-piridil	2- nitrofenil	H	H	OMe	391.45		10.30 ^b
11	S	2-tetrahidropiraniil	2- nitrofenil	H	H	OMe	398.48	399	4.68
12	S	2-trifluorometilfenil	2- nitrofenil	H	H	OMe	458.48	459	4.29
13	S	3-(5.metilisoxazolil)	2- nitrofenil	H	H	OMe	395.44	396	4.66
14	S	3,4 diclorofenil	2- nitrofenil	H	H	OMe	459.35	459	4.33
15	S	3,5-diclorofenil	2- nitrofenil	H	H	OMe	459.35	459	4.36
67	S	3-clorofenil	2- nitrofenil	H	H	OMe	424.91	425	4.34
68	S	3-clanofenil	2- nitrofenil	H	H	OMe	415.47	416	3.92
69	S	3-fluoro,5-trifluorometilfenil	2- nitrofenil	H	H	OMe	476.45	477	4.42
70	S	3-fluoro,6-trifluorometilfenil	2- nitrofenil	H	H	OMe	476.45	477	4.27
71	S	3-fluorofenil	2- nitrofenil	H	H	OMe	408.45	409	4.22
72	S	3-metoxifenil	2- nitrofenil	H	H	OMe	420.49	421	4.04
73	S	3-metilfenil	2- nitrofenil	H	H	OMe	404.49	405	4.16
74	S	3-nitrofenil	2- nitrofenil	H	H	OMe	435.46	436	4.00
75	S	3-piridil	2- nitrofenil	H	H	OMe	391.45	392	3.26
76	S	3-trifluorometil,4-clorofenil	2- nitrofenil	H	H	OMe	492.40	493	4.33
77	S	3-trifluorometiloxifenil	2- nitrofenil	H	H	OMe	474.48	475	4.43
78	S	3-trifluorometilfenil	2- nitrofenil	H	H	OMe	458.48	459	4.21
79	S	4-(2.metiltiazolil)	2- nitrofenil	H	H	OMe	411.50	412	4.39
80	S	4-(3,5-dimetilisoxazolil)	2- nitrofenil	H	H	OMe	409.46	410	4.49
81	S	4-clorofenil	2- nitrofenil	H	H	Me	424.91	425	4.22

82	S	4-cianofenil	2- nitrofenil	H	H	OMe	415.47	416	3.93
83	S	4-fluorofenil	2- nitrofenil	H	H	OMe	408.45	409	4.07
84	S	4-metoxifenil	2- nitrofenil	H	H	OMe	420.49	421	4.03
85	S	4-metilfenil	2- nitrofenil	H	H	OMe	404.49	405	4.19
86	S	4-morfolinil	2- nitrofenil	H	H	OMe	413.50	414	3.54
87	S	5-2(-clorotiazolil)	2- nitrofenil	H	H	OMe	431.92	432	4.61
88	S	5-(2-clorotiofenil)	2- nitrofenil	H	H	OMe	430.93	431	4.92
89	S	ciclohexil	2- nitrofenil	H	H	OMe	396.51	397	5.11

a) 7 min Método LCMS fue usado a menos que se establezca de otra manera, b) una carrera de 20 minutos en un sistema HPLC fue usada.

Ejemplo 7

{2-[1-(3,5-Difluoro-bencil)-6-metoxi-3-(piridina-2-ilsulfanil)-1-*H*-indol (Compuesto 65, Estructura 3 del Esquema I, donde $R^1=3,5$ -difluorofenil, $R^2=2$ -piridil, $R^3=R^4=H$, $R^5=OMe$)



Bajo una atmósfera de nitrógeno: a una solución enfriada (-10 °C) de 2-mercaptopiridina (25 mg, 0.22 mmol) en CCl₄ (2mL) le fue pasado gas Cl₂ durante un período de 1 minuto. El solvente fue evaporado y una solución de 1-(3,5-Difluoro-bencil)-6-metoxi-1*H*-indol (25 mg, 0.09 mmol) en Et₂O (2mL) fue adicionada por goteo. La mezcla de la reacción fue concentrada y el producto crudo fue purificado

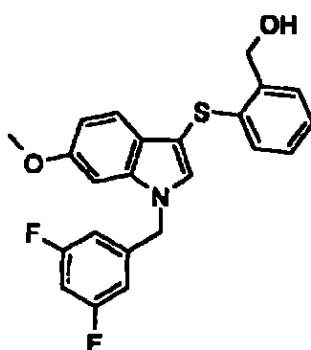
mediante el preparativo LCMS para dar el compuesto del título (7.77 mg, rendimiento 23 %).

LCMS: 3.95 min (100.0 %, $MH^+ = 383$); TLC (heptano/acetato de etil 1:1): $R_f=0.6$

^1H NMR($CDCl_3$): δ 2.23(s, 2H, NH), 3.82 (s, 1H, OCH_3), 6.65 (m, 2H), 6.73 (d, 1H, $J = 2.7$ Hz), 6.73 – 6.78 (m, 1H), 6.80 (d, 1H, $J=7.8$ Hz), 6.87 (dd, 1H, $J_1= 7.8$ Hz, $J_2=1.6$ Hz), 7.00 (ddd, 1H, $J_1= 9.8$ Hz, $J_2= 4.7$ Hz, $J_3= 0.8$ Hz), 7.35 (s, 1H), 7.42 (ddd, 1H, $J_1= J_2= 7.8$ Hz, $J_3= 1.6$ Hz), 7.50 (d, 1H, $J= 8.6$ Hz), 8.46 (d, 1H, $J= 4.7$ Hz).

Ejemplo 8

{2-[1-(3,5-Difluoro-bencil)-6-metoxi-1-*H*-indol-3-il-sulfanil]-fenil}-metanol (Compuesto 16, Estructura 8 del Esquema III, donde $R^1=3,5$ -difluorofenil, $R^3=R^4= H$, $R^5= OMe$)



a) Metil ester del ácido {2-[1-(3,5-Difluoro-bencil)-6-metoxi-1-*H*-indol-3-il-sulfanil]-benzoico (Compuesto 19, Estructura 7 del Esquema III, donde $R^1=3,5$ -difluorofenil, $R^3=R^4= H$, $R^5= OMe$)

Gas de cloro fue burbujeado a través de CCl_4 (5mL) a -10 °C por 3 minutos. Luego una solución de metiltiosalicilato (91 μ L, 0.66 mmol) en CCl_4 (2mL) fue adicionada. La mezcla fue agitada a -10 °C por 5 minutos y luego a temperatura ambiente por 15 minutos. La mezcla fue concentrada y redisoluelta en CH_2Cl_2 (5 mL). A esta solución una solución de 1-(3,5-Difluoro-bencil)-6-metoxi-1*H*-indole (121 mg, 0.443 mmol) en CH_2Cl_2 (3 mL) fue adicionada por goteo. La mezcla fue agitada a temperatura

ambiente por 2 horas y fue concentrada. El producto crudo fue purificado mediante cromatografía de columna (acetato de etil/ heptano 1:9) para obtener el compuesto del título como un sólido blanco (161 mg, rendimiento del 83%).

LCMS: 4.72 min ($MH^+ = 440$); ^1H NMR($CDCl_3$): δ 3.82 (s, 3H, $ArOCH_3$), 3.99 (s, 3H, CO_2CH_3), 5.30 (s, 2H, CH_2Ar), 6.62 – 6.69 (m, 2H), 6.71-6.77 (m, 2H), 6.83 (dd, 1H, $J_1=7.8$ Hz, $J_2= 2.4$ Hz), 6.87 (dd, 1H, $J_1= 8.4$ Hz, $J_2=1.2$ Hz), 7.06-7.11 (m, 1H), 7.15 – 7.20 (m, 1H), 7.30 (s, 1H), 7.44 (dd, 1H, $J_1= 8.4$ Hz, $J_2= 1.2$ Hz), 8.02 (dd, 1H, $J_1= 8.0$ Hz, $J_2= 1.2$ Hz).

b) {2-[1-(3,5-Difluoro-bencil)-6-metoxi-1-*H*-indol-3-il-sulfanil]-fenil]-metanol
(Compuesto 16, Estructura 8 del Esquema III, donde $R^1=3,5$ -difluorofenil, $R^3=R^4= H$, $R^5= OMe$)

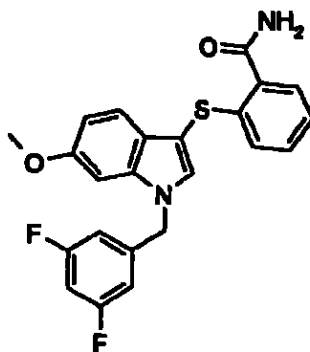
Bajo una atmósfera de nitrógeno: a una solución de metil ester del ácido 2-[1-(3,5-Difluoro-bencil)-6-metoxi-1-*H*-indol-3-il-sulfanil]-benzoico (13.5 mg, 0.031 mmol) en THF (2mL) fue adicionado $LiAlH_4$ (1.0 M en THF, 0.040 mL, 0.040 mmol). La mezcla fue agitada a temperatura ambiente por 3 horas. Luego acetato de etil (25 mL) fue adicionado y la mezcla fue lavada con solución acuosa de ácido cítrico al 3 % (2X 25mL) y salmuera (25 mL). La fase orgánica fue secada ($MgSO_4$) y concentrada para obtener un aceite incoloro (15 mg). El producto crudo fue purificado mediante la preparación HPLC para obtener el compuesto del título como un aceite incoloro (5.6 mg, rendimiento 44 %).

LCMS: 4.47 min (95.6 %, $MH^+ = 412$); ^1H -NMR($CDCl_3$): δ 3.49 (s, 1H, OH), 3.81 (3, 3H, OCH_3), 4.92 (s, 2H, CH_2OH), 5.28 (s, 2H, CH_2Ar), 6.62-6.66 (m, 2H), 6.70 – 6.77 (m, 2H), 6.83 (dd, 1H, $J_1=8.8$ Hz, $J_2= 2.4$ Hz), 6.89 (dd, 1H, $J_1= 8.0$ Hz, $J_2=1.2$ Hz), 7.02-7.07 (m, 1H), 7.08 – 7.13 (m, 1H), 7.29 (s, 1H), 7.38 (dd, 1H, $J_1= 8.0$ Hz, $J_2= 1.2$ Hz), 7.44 (d, 1H, $J= 8.8$ Hz).

Ejemplo 9

2-[1-(3,5-Difluoro-bencil)-6-metoxi-1-*H*-indol-3-ilsulfanil]-benzamida (Compuesto 18,

Estructura 11 del Esquema III, donde $R^1=3,5$ -difluorofenil, $R^3=R^4=H$, $R^5=OMe$)



a) 2-[1-(3,5-Difluoro-bencil)-6-metoxi-1-*H*-indol-3-ilsulfanil]- ácido benzoico

(Estructura 9 del Esquema III, donde $R^1=3,5$ -difluorofenil, $R^3=R^4=H$, $R^5=OMe$)

A una solución de metil éster del ácido 2-[1-(3,5-Difluoro-bencil)-6-metoxi-1-*H*-indol-3-ilsulfanil]-benzoico (97 mg, 0.221 mmol) en THF (10 mL) fue adicionada una solución de LiOH.H₂O (71 mg, 1.69 mmol) en agua (10 mL) . La mezcla fue agitada a temperatura ambiente por 17 horas y luego a 60 °C por 24 horas y luego fue acidificada con solución acuosa de ácido cítrico al 3 % . Acetato de etil (50 mL) fue adicionado y la mezcla fue lavada con solución acuosa de ácido cítrico al 3 % (2X50 mL) y salmuera (50 mL). La fase orgánica fue secada (Mg SO₄) y concentrada para obtener un sólido amarillo (104 mg). El producto crudo fue recristalizado desde acetato de etil/heptano para obtener el compuesto del título como un polvo amarillo (49 mg, 52 % de rendimiento).

LCMS: 4.37 min (MH⁺ = 426); ¹H-NMR(CDCl₃): δ 3.77 (s, 3H, OCH₃), 5.51 (s, 2H, CH₂ Ar), 6.69 (d, 1H, J=8.0 Hz), 6.76 (dd, 1H, J₁= 8.4 Hz, J₂=2.4 Hz), 6.98-7.04 (m, 2H), 7.11 – 7.15 (m, 1H), 7.16-7.25 (s, 4H), 7.83 (s, 1H), 7.92 (dd, 1H, J₁= 8.0 Hz, J₂= 1.6 Hz).

Método General 4 : Reacción de una amina con un ácido carboxílico de estructura 9, con TBTU y DIPEA, para obtener amidas de estructura 3, en la cual R^2 = fenil-2-carboxamida, ejemplarizada por los compuestos de estructura 10 y 11 (Esquema III).

b) 2-[1-(3,5-Difluoro-bencil)-6-metoxi-1-*H*-indol-3-ilsulfanil]-benzamida (Compuesto 18, Estructura 11 del Esquema III, donde R^1 =3,5-difluorofenil, $R^3=R^4$ = H, R^5 = OMe)

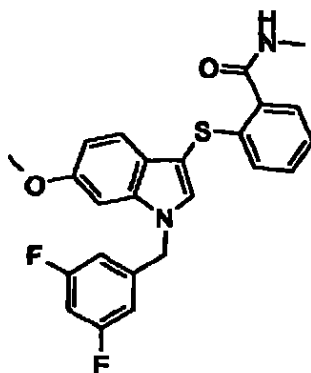
A través de una solución de 2-[1-(3,5-Difluoro-bencil)-6-metoxi-1-*H*-indol-3-ilsulfanil]-ácido benzoico (36 mg, 0.085 mmol), TBTU (28 mg, 0.087 mmol) y DIPEA (30 μ L, 0.172 mmol) en DMF (1mL) fue burbujeado gas de NH_3 por 10 minutos. La mezcla fue luego agitada a temperatura ambiente por 3 días. Luego solución acuosa de ácido cítrico al 3 % (0.4 mL) y la mezcla cruda de la reacción fue purificada sobre un cartucho de RP-SPE (2g sorbente; solución acuosa de 25% metanol a 100% metanol) para obtener un sólido blanco (34 mg). El producto crudo fue purificado por medio de cromatografía de columna (acetato de etil) para dar el compuesto del título como un aceite incoloro, que se solidifica en reposo (31 mg, rendimiento: 86 %).

LCMS: 4.20 min (MH^+ = 425); ^1H -NMR($CDCl_3$): δ 3.81 (s, 3H, OCH_3), 5.39 (s, 2H, CH_2 Ar), 6.05 (s, br, 1H, NH), 6.28 (s, br, 1H, J_1 = 8.8 Hz, J_2 =2.0 Hz), 6.92 (dd, 1H, J_1 =8.0, J_2 = 1.2 Hz), 7.07 – 7.17 (m, 2H), 7.31 (s, 1H), 7.45 (d, 1H, J =8.8 Hz), 7.60 (dd, 1H, J_1 = 8.0 Hz, J_2 = 1.2 Hz).

Ejemplo 10

2-[1-(3,5-Difluoro-bencil)-6-metoxi-1-*H*-indol-3-ilsulfanil]-*N*-metil-benzamida

(Compuesto 17, Estructura 10 del Esquema III, donde R^1 =3,5-difluorofenil, $R^3=R^4$ = H, R^5 = OMe)



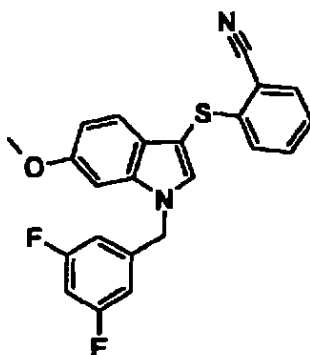
De acuerdo al Método general 4 el compuesto 17 fue sintetizado de metilamina

LCMS: 4.07 minutos ($MH^+ = 439$).

Ejemplo 11

2-[1-(3,5-Difluoro-bencil)-6-metoxi-1-*H*-indol-3-ilsulfanil]-benzonitrilo (Compuesto 20,

Estructura 12 del Esquema III, donde $R^1=3,5$ -difluorofenil, $R^3=R^4=H$, $R^5=OMe$)



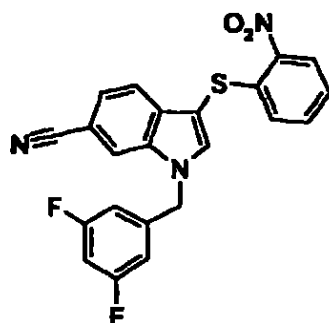
A una solución enfriada (0 °C) de 2-[1-(3,5-Difluoro-bencil)-6-metoxi-1-*H*-indol-3-ilsulfanil]-benzamida (8 mg, 0.019 mmol) y Et_3N (10 μ L, 0.072 mmol) en CH_2Cl_2 (1.5 mL) fue adicionado Tf_2O (6 μ L, 0.036 mmol). La mezcla fue agitada a 0 °C por 3 horas y luego a temperatura ambiente por 22 horas. Agua (25 mL) fue adicionada y la mezcla fue extraída con CH_2Cl_2 (2X 25 mL). Las fases orgánicas combinadas fueron secadas (Na_2SO_4) y concentradas para obtener un aceite marrón (25 mg). El producto crudo fue purificado por cromatografía de columna (etil acetato/heptano 1:2)

para obtener el compuesto del título como un aceite rosado pálido (3 mg, rendimiento: 39 %).

LCMS: 4. 57 min ($MH^+ = 407$); ^1H -NMR($CDCl_3$): δ 3.82 (s, 3H, OCH_3), 5.30 (s, 2H, CH_2 Ar), 6.62-6.67(m, 2H), 6.71-6.73 (m, 1H), 6.74-6.78 (m, 1H), 6.86 (dd, 1H, $J_1=8.8$, $J_2= 2.0$ Hz), 6.91 (d, 1H, $J=8.4$ Hz), 7.11 – 7.15 (m, 1H), 7.26-7.30 (m, 1H), 7.37 (s, 1H), 7.46 (d, 1H, $J = 8.8$ Hz), 7.57-7.60 (m, 1H).

Ejemplo 12

1-(3,5-Difluoro-bencil)-3-(2-nitro-fenilsulfanil)-1-*H*-indol-6-carbonitrilo (Compuesto 26, Estructura 17 del Esquema IV, donde $R^1=3,5$ -difluorofenil , $R^2= 2$ -nitrofenil, $R^3=R^4=H$)



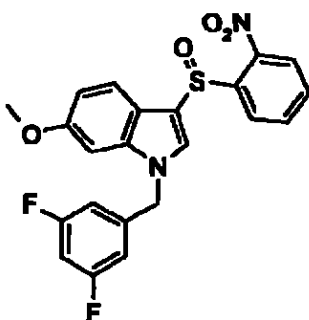
A una suspensión enfriada (0 °C) de amida del ácido 1-(3,5-Difluoro-bencil)-3-(2-nitro-fenilsulfanil)-1-*H*-indol-6-carboxílico (15 mg, 0.034 mmol) y Et_3N (10 μ L, 0.072 mmol) en CH_2Cl_2 (1.5 mL) fue adicionado Tf_2O (13 μ L, 0.077 mmol). La mezcla fue agitada a 0 °C por 2 horas y luego a temperatura ambiente por 20 horas. Agua (25 mL) fue adicionada y la mezcla fue extraída con CH_2Cl_2 (2X 25 mL). Las fases orgánicas combinadas fueron secadas (Na_2SO_4) y concentradas para obtener el compuesto del título como un sólido amarillo (13 mg, rendimiento 91 %).

LCMS: 4. 55 min ($MH^+ =$ no detectable); ^1H -NMR($CDCl_3$): δ 5.42 (s, 2H, CH_2 Ar), 6.63-6.69 (m, 2H), 6.78-6.85 (m, 2H), 7.21- 7.25 (m, 1H), 7.28 –7.33 (m, 1H), 7.44

(dd, 1H, J1=8.4, J2= 1.2 Hz), 7.62 (d, 1H, J=8.4 Hz), 7.66 (s, 1H), 8.29 (dd, 1H, J1 = 8.4 Hz, J2= 1.6 Hz).

Ejemplo 13

1-(3,5-Difluoro-bencil)-6-metoxi-3-(2-nitro-bencenosulfinil)-1-H-indol (Compuesto 64, Estructura 5 del Esquema II, donde R¹=3,5-difluorofenil, R²= 2-nitrofenil, R³=R⁴= H, R⁵ = OMe)



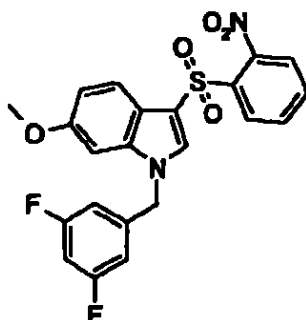
A una solución de 1-(3,5-Difluoro-bencil)-6-metoxi-3-(2-nitro-fenilsulfanil)-1-H-indol (40 mg, 0.09 mmol) en CH₂Cl₂ (4 mL) fue adicionado ácido meta-cloroperbenzoico (14.5 , 0.08 mmol). La solución fue agitada a temperatura ambiente por 2 horas. El solvente fue evaporado y el producto crudo fue purificado por preparación LC-MS para dar el compuesto del título (14.3 mg, rendimiento= 34 %).

HPLC: 4. 13 min, pureza 100% ; TLC (heptano/acetato de etil 1:1): R_f= 0.4;

¹H-NMR(CDCl₃): δ 3.66 (s, 3H, OCH₃), 5.12 (s, 2H), 6.57 (m, 3H), 6.75 (m, 2H), 7.47 (d, 1H, J =7.8 Hz), 7.52 (s, 1H), 7.66-7.70 (m, 1H), 8.28-8.32 (m, 1H), 8.23 (dd, 1H, J1=7.8 Hz, J2= 1.9 Hz), 8.80 (dd, 1H, J1 = 7.8 Hz, J2= 3.1 Hz).

Ejemplo 14

1-(3,5-Difluoro-bencil)-6-metoxi-3-(2-nitro-bencenosulfinil)-1-H-indol (Compuesto 62, Estructura 6 del Esquema II, donde R¹=3,5-difluorofenil, R²= 2-nitrofenil, R³=R⁴= H, R⁵ = OMe)



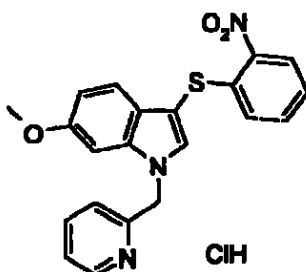
A una solución de 1-(3,5-Difluoro-bencil)-6-metoxi-3-(2-nitro-fenilsulfanil)-1-*H*-indol (40 mg, 0.09 mmol) en CH₂Cl₂ (4 mL) fue adicionado ácido meta-cloroperbenzoico (46.5 mg, 0.27 mmol) . La solución fue agitada a temperatura ambiente por 6 horas. El solvente fue evaporado y el producto crudo fue purificado por LC-MS para dar el compuesto del título (14.5 mg, rendimiento 34 %).

HPLC: 4. 38 min, pureza 100% ; TLC (heptano/acetato de etil 1:1): R_f= 0.6;

¹H-NMR(CDCl₃): δ 3.71 (s, 3H, OCH₃), 5.25 (s, 2H), 6.58 (d, 1H, J= 3.1), 6.62 (m, 1H), 6.07-6.11 (m, 1 H), 6.88 (dd, 1H, J₁ =7.8 Hz, J₂= 3.1 Hz), 7.63 (m, 4H), 7.72 (d, 1H, J= 7.8 Hz), 7.83 (s, 1H), 8.37 (dd, 1H, J₁=7.8 Hz, J₂= 1.9 Hz).

Ejemplo 15

Monoclorhidrato de 6-metoxi-3-(2-nitro-bencenosulfanil)-1-piridina-2-ilmetil-1H-indol
(Compuesto 10)

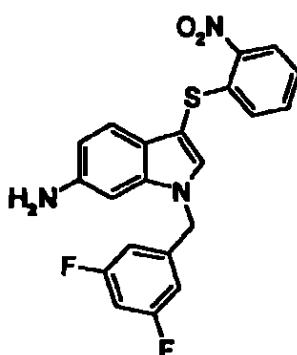


A una solución de 6-Metoxi-3-(2-nitro-fenilsulfanil)-1-piridina-2-ilmetil-1-*H*-indol en cloruro de metileno le fue pasado gas HCl hasta que la sal orgánica se cristalizó. El compuesto del título fue aislado por filtración.

LC-MS: 4.04 min ($MH^+ = 392$); ^1H -NMR(DMSO): δ 3.78 (s, 3H, OCH₃), 5.78 (s, 2H, NCH₂), 6.77 (dd, 1H, J₁ = 7.8 Hz, J₂ = 2.0 Hz), 6.93 (dd, 1H, J₁ = 7.8 Hz, J₂ = 0.8 Hz), 7.22 (d, 1H, J = 7.8 Hz), 7.26 (d, 1H, J = 2.0 Hz), 7.34 (m, 2H), 7.48 – 7.52 (m, 1H), 7.59 (t, 1H, J = 7.0 Hz), 7.96 (s, 1H), 8.08 (t, 1H, J = 7.0 Hz), 8.27 (dd, 1H, J₁ = 7.8 Hz, J₂ = 1.6 Hz), 8.74 (d, 1H, J = 6.7 Hz).

Ejemplo 16

1-(3,5-Difluoro-bencil)-3-(2-nitro-fenilsulfanil)-1-H-indol-6-ilamina (Compuesto 57, Estructura 23 del Esquema V, donde R¹=3,5-difluorofenil, R²= 2-nitrofenil, R³=R⁴= H)



a) 1-(3,5-Difluoro-bencil)-6-nitro-1-H-indol (Estructura 19 del Esquema V, donde R¹=3,5-difluorofenil, R³=R⁴= H)

A una solución de 6-nitroindol (162 mg, 1.0 mmol) en DMF (4 mL) fue adicionado NaH (dispersión al 60% en aceite; 80 mg, 2.0 mmol). La solución oscura resultante fue agitada a temperatura ambiente por 15 minutos, bromuro de 3,5- difluorobencil (129 μ L, 1.1 mmol) fue adicionado. La mezcla de la reacción fue agitada de un día al otro, vertida dentro de agua acidificada y extraída dos veces con acetato de etil. Las capas orgánicas combinadas fueron secadas sobre Na₂SO₄ y concentradas en vacío. El producto fue purificado sobre una columna de SiO₂ (heptano/acetato de etil 9:1) para obtener el compuesto del título como un sólido amarillo (270 mg, rendimiento 94 %).

LCMS: 5.54 min (100.0 %, $MH^+ = 289$); ^1H -NMR($CDCl_3$): δ 5.40 (s, 2H, CH_2Ar), 6.58 (m, 2H), 6.71 (d, 1H, $J = 3.5$ Hz), 6.75 (m, 1H), 7.26 (s, 1H), 7.41 (d, 1H, $J = 3.5$ Hz), 7.71 (d, 1H, $J = 8.3$ Hz), 8.05 (dd, 1H, $J_1 = 8.3$ Hz, $J_2 = 2.0$ Hz), 8.21 (d, 1H, $J = 2.0$ Hz).

b) 1-(3,5-Difluoro-bencil)-1-*H*-indol-6-ilamina (Estructura 20 del Esquema V, donde $R^1 = 3,5$ -difluorofenil, $R^3 = R^4 = H$).

A una solución de 1-(3,5-Difluoro-bencil)-6-nitro-1*H*-indol (144 mg, 0.5 mmol) en etanol (20 mL) fue adicionado ácido clorhídrico al 37 % (80 μ L) y $SnCl_2 \cdot 2H_2O$ (600 mg). La mezcla de reacción agitada a 60 °C por 40 horas y luego fue concentrada en vacío. El residuo fue vertido en acetato de etil y una solución concentrada de $NaHCO_3$ fue adicionada. El sistema de fases de dos capas fue filtrado sobre decalita para eliminar las sales de estaño y el filtrado fue extraído dos veces con acetato de etil. Las capas orgánicas combinadas fueron secadas sobre Na_2SO_4 y concentrada en vacío. El producto fue purificado sobre una columna de SiO_2 (heptano/acetato de etil 9:1) para dar el compuesto del título como un aceite incoloro (89 mg, rendimiento = 69%).

LCMS: 3.20 min (97.7 %, $MH^+ = 259$); ^1H -NMR($CDCl_3$): δ 5.12 (s, 2H, CH_2Ar), 6.52 (m, 2H), 6.56 (d, 1H, $J = 3.5$ Hz), 6.63 (m, 1H), 7.97 (dd, 1H, $J_1 = 8.3$ Hz, $J_2 = 2.0$ Hz), 7.13 (d, 1H, $J = 3.5$ Hz), 7.17 (d, 1H, $J = 2.0$ Hz), 7.55 (d, 1H, $J = 8.3$ Hz).

c) 1-(3,5-Difluoro-bencil)-3-(2-nitro-fenilsulfenil)-1-*H*-indol-6-ilamina (Compuesto 57, Estructura 23 del Esquema V, donde $R^1 = 3,5$ -difluorofenil, $R^2 = 2$ -nitrofenil, $R^3 = R^4 = H$)

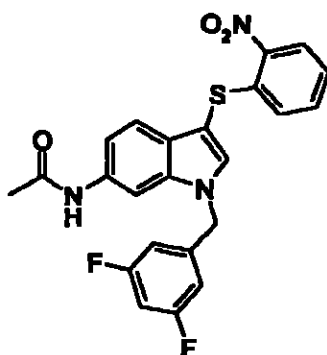
A una solución de 1-(3,5-Difluoro-bencil)-1-*H*-indol-6-ilamina (25 mg, 0.1 mmol) en DCM (4 mL) fue adicionado cloruro de 2-nitrobenzenosulfenil. La solución amarilla resultante fue agitada a temperatura ambiente por 1 hora. La mezcla fue concentrada en vacío y purificada sobre una columna de SiO_2 (heptano/ acetato de etil 9:1) para dar el compuesto del título como un sólido naranja (11.6 mg, rendimiento = 28 %).

LCMS: 5.11 min (100 %, $MH^+ = 412$); ^1H -NMR($CDCl_3$): δ 5.22 (s, 2H, CH_2Ar), 6.56 (m, 2H), 6.65 (m, 1H), 6.84 (dd, 1H, $J_1 = 8.2$ Hz, $J_2 = 1.2$ Hz), 7.00 (dd, 1H, $J_1 = 8.2$

Hz, $J_2 = 1.2$ Hz), 7.19 (m, 1H), 7.30 (d, 1H, $J = 1.2$ Hz), 7.31 (s, 1H), 7.37 (d, 1H, $J = 8.2$ Hz), 7.49 (m, 1H), 8.27 (dd, 1H, $J_1 = 8.2$ Hz, $J_2 = 1.2$ Hz).

Ejemplo 17

N-[1-(3,5-Difluoro-bencil)-3-(2-nitro-fenilsulfanil)-1-*H*-indol-6-il]-acetamida (Compuesto 58, Estructura 22 del Esquema V, donde $R^1 = 3,5$ -difluorofenil, $R^2 = 2$ -nitrofenil, $R^3 = R^4 = H$, $Z = \text{metil}$)



Método General 5: Reacción de un anhídrido ácido con una 6-aminoindol de estructura 20 para obtener el compuesto de estructura 21 seguido por sulfanilación del indole de posición 3 para dar compuestos de estructura 22 (Esquema V)

a) N-[1-(3,5-Difluoro-bencil)-1-*H*-indol-6-il]-acetamida (Estructura 22 del Esquema V, donde $R^1 = 3,5$ -difluorofenil, $R^3 = R^4 = H$, $Z = \text{metil}$)

A una solución de 1-(3,5-Difluoro-bencil)-1-*H*-indol-6-ilamina (25 mg, 0.1 mmol) en DCM (4 mL) fue adicionada piridina (25 μL) y anhídrido acético (9.8 μL , 0.11 mmol) y revuelto de un día al otro a temperatura ambiente. La mezcla de la reacción fue vertida en 10 mL de agua y neutralizada con NaHCO_3 y concentrada en vacío para dar el compuesto crudo como un sólido blancuzco (23.3 mg, rendimiento = 84%). El producto fue usado sin más purificación.

LCMS: 4.10 min (97.4 %, $\text{MH}^+ = 301$); $^1\text{H-NMR}(\text{CDCl}_3)$: δ 2.18 (s, 3H, CH_3CON), 5.28 (s, 2H, CH_2Ar), 6.53 (d, 1H, $J = 3.1$), 6.58 (m, 2H), 6.68 (m, 1H), 6.87 (dd, 1H,

J1= 8.3 Hz, J2=1.6 Hz), 7.07 (d, 1H, J = 3.1 Hz), 7.55 (d, 1H, J =8.3 Hz), 7.90 (s, 1H).

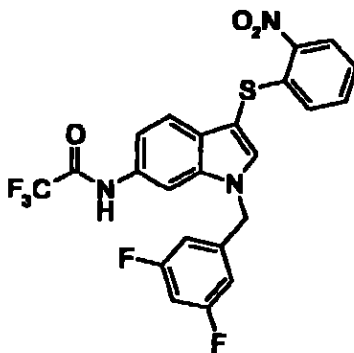
b) N-[1-(3,5-Difluoro-bencil)-3-(2-nitro-fenilsulfanil)-1-H-indol-6-il]-acetamida (Compuesto 58, Estructura 22 del Esquema V, donde R¹=3,5-difluorofenil , R²= 2-nitrofenil, R³=R⁴= H, Z= metil)

A una solución de N-[1-(3,5-Difluoro-bencil)-1-H-indol-6-il]-acetamida (23.3 mg, 0.08 mmol) en dietil éter (4 mL) fue adicionado cloruro de 2-nitrobencenosulfenil (14.7 mg, 0.09 mmol). La solución amarilla resultante fue agitada de una día al otro a temperatura ambiente. La mezcla fue concentrada en vacío y purificada sobre una columna de SiO₂ (heptano/acetato de etil 9:1) para dar el compuesto del título como un sólido amarillo (35.0 mg, rendimiento = 96 %).

LCMS: 4.26 min (98.6 %, MH⁺= 454); ¹H-NMR(DMSO): δ 2.03 (s, 3H, CH₃CON), 5.51 (s, 2H, CH₂Ar), 6.89 (dd, 1H, J= 8.3 Hz, J2= 1.2 Hz), 6.95 (m, 2H), 7.17 (dd, 1H, J1= 8.3 Hz, J2=2.0 Hz), 7.19 (m, 1H), 7.27 (d, 1H, J = 8.3 Hz), 7.34 (m, 1H), 7.49 (m, 1H), 7.97 (d, 1H, J =1.2 Hz), 8.02 (s, 1H), 8.27 (dd, 1H, J1= 8.3 Hz, J2=1.2 Hz).

Ejemplo 18

N-[1-(3,5-Difluoro-bencil)-3-(2-nitro-fenilsulfanil)-1-H-indol-6-il]-2,2,2-trifluoroacetamida (Compuesto 59, Estructura 22 del Esquema V, donde R¹=3,5-difluorofenil , R²= 2-nitrofenil, R³=R⁴= H, Z= trifluorometil)



De acuerdo al método general 5, paso a) N-[1-(3,5-Difluoro-bencil)-1-*H*-indol-6-il]-2,2,2-trifluoro-acetamida fue preparada usando 1-(3,5-Difluoro-bencil)-1-*H*-indol-6-ilamina (17.7 mg, 69 μmol), piridina (17 μL) y anhídrido trifluoroacético (9.68 μL , 70 μmol). El compuesto fue purificado sobre una columna de SiO_2 (heptano/acetato de etil 9:1) para obtener el compuesto del título como un sólido blanco (10.9 mg, rendimiento= 61 %).

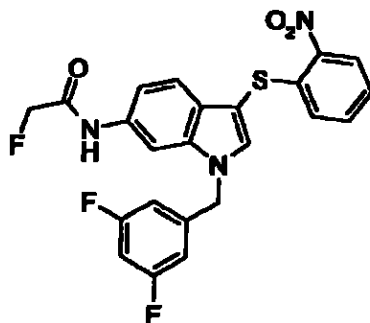
LCMS: 4.41 minutos (82.1 %, $\text{MH}^+ = 355$)

De acuerdo con el método general 5, paso b) N-[1-(3,5-Difluoro-bencil)-3-(2-nitro-fenilsulfanil)-1-*H*-indol-6-il]-2,2,2-trifluoro-acetamida fue preparada usando N-[1-(3,5-Difluoro-bencil)-1-*H*-indol-6-il]-2,2,2-trifluoro-acetamida (10.9 mg, 31 μmol) y cloruro de 2-nitrobencenosulfenil (5.7 mg, 37 μmol). El compuesto fue purificado sobre una columna HPLC (MeCN/ H_2O) para obtener el compuesto del título como un sólido amarillo (10.3 mg, rendimiento 65 %).

LCMS: 4.65 min (89.0 %, $\text{MH}^+ = 508$); $^1\text{H-NMR}(\text{DMSO})$: δ 5.56 (s, 2H, CH_2Ar), 6.87 (dd, 1H, $J=8.3$ Hz, $J_2=1.2$ Hz), 7.01 (m, 2H), 7.20 (m, 1H), 7.35 (m, 1H), 7.37 (dd, 1H, $J_1=8.3$ Hz, $J_2=2.0$ Hz), 7.39 (d, 1H, $J=8.3$ Hz), 7.49 (m, 1H), 7.50 (d, 1H, $J=2.0$ Hz), 8.15 (s, 1H), 8.28 (dd, 1H, $J_1=8.3$ Hz, $J_2=2.0$ Hz).

Ejemplo 19

Compuesto 97: N-[1-(3,5-Difluorobencil)-3-(2-nitro-fenilsulfanil)-1*H*-indol-6-yl]-2-fluoro-acetamida, estructura 28 del esquema VII, donde $\text{R}^1 = 3,5$ -difluorofenil, $\text{R}^2 = 2$ -nitrofenil, $\text{R}^3=\text{R}^4=\text{H}$, $\text{Z}^1 = \text{monofluorometil}$.



a) 1-(3,5-Difluorobencil)-6-nitro-1*H*-indol, estructura 19 del Esquema VII, donde $R^1 =$ 3,5-difluorofenil, $R^2=R^3=R^4=H$.

A una solución de 6-nitro-1*H*-indol (19.5 g, 120 mmol) en NMP (500 mL) fue adicionado a 0°C carbonato de cesio (39.1 g, 120 mmol). Después de agitar por 30 min a 0°C se agregó bromuro de 3,5-difluorobencil (30.0 g, 144 mmol) y la mezcla fue dejada calentar a temperatura ambiente y agitada por 18 hrs. La mezcla fue vertida dentro de una solución acuosa saturada de cloruro amónico (1 L) y extractada con acetato de etilo (2 x 500 mL). Las capas orgánicas fueron lavadas con H₂O (2 x 500 mL) y salmuera (500 mL) y secada (Na₂SO₄) y concentrada para obtener el compuesto del título (65 g, sólido amarillo) el cual fue utilizado sin purificación adicional.

b) 1-(3,5-Difluorobencil)-1*H*-indol-6-ilamina, estructura 20 del Esquema VII, donde $R^1 =$ 3,5-difluorofenil, $R^2=R^3=R^4=H$.

EtOH 96% (1L) fue adicionada a 1-(3,5-difluorobencil)-6-nitro-1*H*-indol y la mezcla fue agitada a 60°C hasta que todos los materiales fueron disueltos. Se adicionó HCl al 37% (37 mL) seguido por cloruro de estaño (II) dihidrato (268 g, 1.19 mol) y se continuó la agitación a 60°C por 18 hrs. Después de que la mezcla fue enfriada a temperatura ambiente el solvente fue removido bajo presión reducida. Se adicionó acetato de etilo (800 mL) y la mezcla fue vertida en NaHCO₃ (1 L) acuoso saturado y filtrado sobre kieselguhr.

Las capas fueron separadas y la capa orgánica fue lavada con H₂O (2 x 500 mL) y salmuera (500 mL), secada (Na₂SO₄) y concentrada para producir el compuesto del título (54 g, aceite/sólido café) el cual fue utilizado sin purificación adicional.

c) Terbutil éster del ácido [1-(3,5-Difluorobencil)-1*H*-indol-6-yl]-carbámico, estructura 26 del Esquema VII, donde $R^1 =$ 3,5-difluorofenil, $R^2=R^3=R^4=H$.

1-(3,5-Difluorobencil)-1*H*-indol-6-ilamina fue disuelta en NMP (1 L) y adicionada con trietilamina (34 mL, 242 mmol) seguida de dicarbonato de diterbutilo (53 g, 242 mmol) y la mezcla fue agitada a temperatura ambiente por 18 hrs. La mezcla fue vertida en NaHCO₃ (1 L) acuoso saturado (1.5 L) y extractada con acetato de etilo (3 x 750 mL). Las capas orgánicas combinadas fueron lavadas con H₂O (1 L) y salmuera (1 L), secadas (Na₂SO₄) y concentrada. El producto crudo fue purificado utilizando un cromatografía de columna (acetato heptano/etil 4:1) para producir el compuesto del título (39 g, 109 mmol, 91% (tres pasos), sólido blanco).

d) Terbutil éster del ácido [1-(3,5-Difluorobencil)-3-(2-nitro-fenilsulfanil)-1*H*-indol-6-yl]-carbámico, estructura 27 del Esquema VII, donde R¹ = 3,5-difluorofenil, R²=2-nitrofenil, R³=R⁴=H.

A una solución de [1-(3,5-Difluorobencil)-1*H*-indol-6-yl]-ácido carbámico *tert*-butil éster (39 g, 109 mmol) en éter dietílico (750 mL) fue adicionado cloruro de 2-nitrobencenosulfenil (20.4 g, 109 mmol) y la mezcla de reacción fue agitada a temperatura ambiente durante 18 hrs. La mezcla fue vertida en NaHCO₃ saturada acuosa (1 L) y extractada con acetato de etilo (2 x 300 mL). Las capas orgánicas combinadas fueron lavadas con H₂O (400 mL) y salmuera (400 mL), secada y concentrada para obtener el compuesto del título (56 g, sólido amarillo) el cual fue utilizado sin purificación adicional.

e) 1-(3,5 Difluorobencil)-3-(2-nitro-fenilsufanil)-1*H*-indol-6-ilamina, estructura 23 del Esquema VII, donde R¹ = 3,5 difluorofenil, R² = 2-nitrofenil, R³=R⁴=H.

Terbutil éster de ácido [1-(3,5-Difluorobencil)-3-(2-nitro-fenilsulfanil)-1*H*-idol-6-yl]-carbámico fue disuelto en CH₂Cl₂ (1 L) y bajo atmósfera de nitrógeno fue adicionado ácido trifluoroacético (48 mL, 624 mmol) por goteo a temperatura ambiente. Después de agitar por 1 h fue adicionada otra porción de trifluoroacético (48 mL, 624 mmol) y la mezcla de reacción fue agitada por una hora adicional. La mezcla fue diluida con CH₂Cl₂ (500 mL) y H₂O (1 L) y se adicionó una solución 3N NaOH hasta que el pH de

la mezcla fue 11-12. Las capas fueron separadas y la capa orgánica fue lavada con H₂O (500 mL) y salmuera (500 mL), secada (Na₂SO₄) y concentrada para obtener el producto crudo. El producto fue purificado utilizando cromatografía de columna (heptano/acetato de etilo 1:1) para obtener el compuesto del título (28 g, 68 mmol, 63 % (dos pasos), sólido rojo/café).

Método general 6: Reacción de un ácido clorhídrico (método a), ácido carboxílico (método b) o cloruro de sulfonil (método c) con 6-aminoindol de estructura **23** para obtener compuestos de estructura **28** y **29** (Esquema VII).

Los métodos a, b y c se pueden llevar a cabo utilizando el mismo procedimiento, el cual se ejemplifica en seguida para el método a.

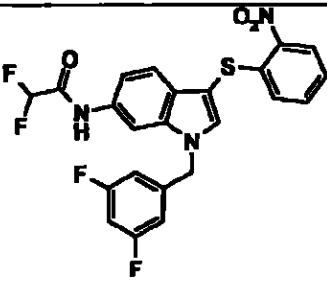
A una solución de 1-(3,5-difluorobencil)-3-(2-nitro-fenilsulfanil)-1*H*-indol-6-ilamina (300 mg, 0.73 mmol) en CH₂Cl₂ (7 ml) se adicionó a 0°C trietilamina (0.12 mL, 0.87 mmol). A continuación fue adicionado cloruro de monofluoroacetil (50 µL, 0.73 mmol) y la mezcla fue agitada a temperatura ambiente por 18 hrs. La mezcla fue concentrada y purificada utilizando cromatografía flash de columna (CH₂Cl₂/MeOH 99:1) para obtener el compuesto **97** (317 mg, 0.67 mmol, 92%, sólido amarillo).

¹H NMR (DMSO) δ 4.82 (s, 1H), 5.03 (s, 1H), 5.52 (s, 2H), 6.89 (dd, 1H, J₁ = 7.6 Hz, J₂ = 1.1 Hz), 6.98-7.01 (m, 2H), 7.20 (tt, 1H, J₁ = 9.5 Hz, J₂ = 3.0 Hz), 7.28-7.32 (m, 2H), 7.33-7.37 (m, 1H), 7.46-7.51 (m, 1H), 7.98 (s, 1H), 8.08 (s, 1H), 8.27 (dd, 1H, J₁ = 7.6 Hz, J₂ = 1.1 Hz), 10.15 (s, 1H).

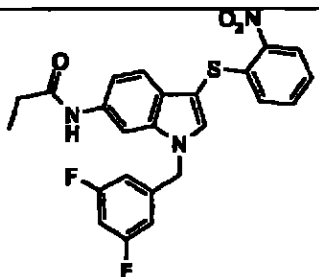
De acuerdo al método general 6 se prepararon los siguientes compuestos:

130

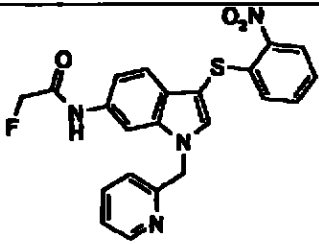
Compuesto 98: *N*-[1-(3,5 Difluorobencil)-3-(2-nitro-fenilsufanil)-1*H*-indol-6-yl]-2,2-difluoro-acetamida, estructura 28 del Esquema VII, donde $R^1 = 3,5$ difluorofenil, $R^2 = 2$ -nitrofenil, $R^3=R^4=H$, $Z^1 =$ difluorometil. Fue usado el método a.

	¹ H-NMR (DMSO): δ 5.55 (s, 2H), 6.23-6.50 (m, 1H), 6.88 (dd, 1H, $J_1 = 7.6$ Hz, $J_2 = 1.1$ Hz), 6.97-7.03 (m, 2H), 7.20 (tt, 1H, $J_1 = 9.5$ Hz, $J_2 = 3.0$ Hz), 7.30-7.38 (m, 3H), 7.46-7.51 (m, 1H), 7.98 (d, 1H, $J = 1.1$ Hz), 8.12 (s, 1H), 8.28 (dd, 1H, $J_1 = 7.6$ Hz, $J_2 = 1.1$ Hz), 10.80 (s, 1H).
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Compuesto 99: *N*-[1-(3,5 Difluorobencil)-3-(2-nitro-fenilsufanil)-1*H*-indol-6-yl]-propionamida, estructura 28 del Esquema VII, donde $R^1 = 3,5$ difluorofenil, $R^2 = 2$ -nitrofenil, $R^3=R^4=H$, $Z^1 =$ etil. Fue usado el método b.

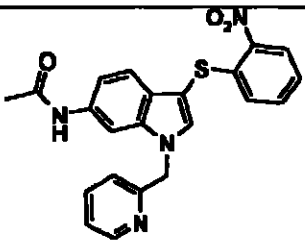
	¹ H-NMR (DMSO): δ 1.07 (t, 3H, $J = 7.6$ Hz), 2.31 (q, 2H, $J = 7.6$ Hz), 5.51 (s, 2H), 6.89 (dd, 1H, $J_1 = 7.6$ Hz, $J_2 = 1.1$ Hz), 6.93-6.97 (m, 1H), 7.16-7.23 (m, 3H), 7.27 (d, 1H, $J = 8.4$ Hz), 7.32-7.37 (m, 1H), 7.46-7.51 (m, 1H), 8.01 (d, 1H, $J = 1.1$ Hz), 8.02 (s, 1H), 8.27 (dd, 1H, $J_1 = 7.6$ Hz, $J_2 = 1.1$ Hz), 9.92 (s, 1H).
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Compuesto 100: 2-Fluoro-*N*-[3-(2-nitro-fenilsufanil)-1-piridin-2-ilmetil-1*H*-indol-6-yl]-acetamida, estructura 28 del Esquema VII, donde $R^1 = 2$ -piridil, $R^2 = 2$ -nitrofenil, $R^3=R^4=H$, $Z^1 =$ monofluorometil. Fue usado el método a.

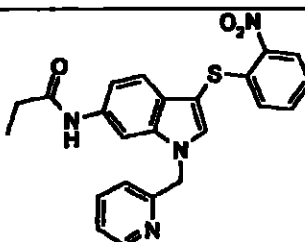
	¹ H-NMR (CDCl ₃): δ 4.88 (s, 1H), 5.00 (s, 1H), 5.51 (s, 2H), 6.94-6.99 (m, 2H), 7.06 (dd, 1H, $J_1 = 7.6$ Hz, $J_2 = 1.5$ Hz), 7.18 (td, 1H, $J_1 = 8.4$ Hz, $J_2 = 1.5$ Hz), 7.22-7.29 (m, 2H), 7.46 (d, 1H, $J = 8.4$ Hz), 7.55 (s, 1H), 7.64 (td, 1H, $J_1 = 8.4$ Hz, $J_2 = 1.5$ Hz), 8.02 (s, 1H), 8.05 (d, 1H, $J = 2.2$ Hz), 8.27 (dd, 1H, $J_1 = 7.6$ Hz, $J_2 = 1.5$ Hz), 8.62 (d, 1H, $J = 4.6$ Hz).
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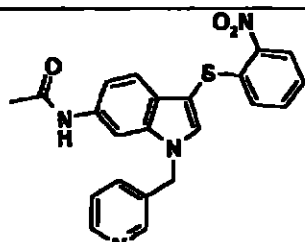
Compuesto 101: *N*-[3-(2-Nitro-fenilsufanil)-1-piridin-2-ilmetil-1*H*-indol-6-yl]- acetamida, estructura 28 del Esquema VII, donde $R^1 = 2$ -piridil, $R^2 = 2$ -nitrofenil, $R^3=R^4=H$, $Z^1 =$ metil. Fue usado el método a.

	$^1\text{H-NMR}$ (CDCl_3): δ 1.80 (s, 3H), 5.48 (s, 2H), 6.92-6.98 (m, 3H), 7.15-7.30 (m, 4H), 7.40 (d, 1H, $J = 7.6$ Hz), 7.51 (s, 1H), 7.63 (td, 1H, $J_1 = 7.6$ Hz, $J_2 = 2.2$ Hz), 8.04 (d, 1H, $J = 1.5$ Hz), 8.26 (dd, 1H, $J_1 = 7.6$ Hz, $J_2 = 1.5$ Hz), 8.61 (d, 1H, $J = 4.6$ Hz).
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Compuesto 102: *N*-[3-(2-Nitro-fenilsufanil)-1-piridin-2-ilmetil-1*H*-indol-6-yl]-propionamida, estructura 28 del Esquema VII, donde $R^1 = 2$ -piridil, $R^2 = 2$ -nitrofenil, $R^3=R^4=H$, $Z^1 =$ etil. Fue usado el método b.

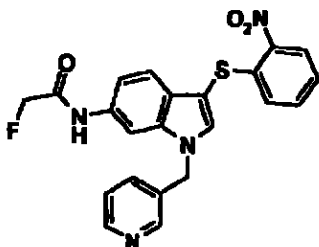
	$^1\text{H-NMR}$ (CDCl_3): δ 1.25 (t, 3H, $J = 7.6$ Hz), 2.42 (q, 2H, $J = 7.6$ Hz), 5.49 (s, 2H), 6.92-6.98 (m, 3H), 7.15-7.27 (m, 4H), 7.40 (d, 1H, $J = 8.4$ Hz), 7.51 (s, 1H), 7.63 (td, 1H, $J_1 = 7.6$ Hz, $J_2 = 1.5$ Hz), 8.12 (d, 1H, $J = 1.5$ Hz), 8.26 (dd, 1H, $J_1 = 7.6$ Hz, $J_2 = 1.5$ Hz), 8.61 (d, 1H, $J = 4.6$ Hz).
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Compuesto 103: *N*-[3-(2-Nitro-fenilsufanil)-1-piridin-3-ilmetil-1*H*-indol-6-yl]-acetamida, estructura 28 del Esquema VII, donde $R^1 = 2$ -piridil, $R^2 = 2$ -nitrofenil, $R^3=R^4=H$, $Z^1 =$ metil. Fue usado el método a.

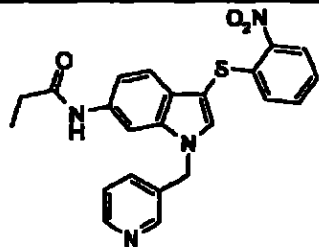
	$^1\text{H NMR}$ (CDCl_3) δ 2.20 (s, 3H), 5.40 (s, 2H), 6.86 (dd, 1H, $J_1 = 7.6$ Hz, $J_2 = 2.2$ Hz), 6.72 (dd, 1H, $J_1 = 7.6$ Hz, $J_2 = 1.1$ Hz), 7.16-7.20 (m, 1H), 7.24-7.31 (m, 3H), 7.40 (d, 1H, $J = 8.4$ Hz), 7.42 (s, 1H), 7.49-7.52 (m, 1H), 8.15 (d, 1H, $J = 2.2$ Hz), 8.26 (dd, 1H, $J_1 = 8.4$ Hz, $J_2 = 2.2$ Hz), 8.55 (d, 1H, $J = 3.0$ Hz), 8.58 (dd, 1H, $J_1 = 8.4$ Hz, $J_2 = 2.2$ Hz).
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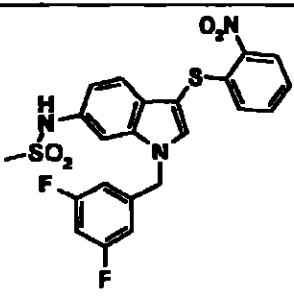
Compuesto 104: 2-Fluoro-*N*-[3-(2-nitro-fenilsufanil)-1-piridin-3-ilmetil-1*H*-indol-6-yl]-acetamida, estructura 28 del Esquema VII, donde $R^1 = 3$ -piridil, $R^2 = 2$ -nitrofenil, $R^3=R^4=H$, $Z^1 =$ monofluorometil. Fue usado el método a.

	$^1\text{H NMR (CDCl}_3\text{)}$ δ 4.88 (s, 1H), 5.00 (s, 1H), 5.42 (s, 2H), 6.92 (dd, 1H, $J_1 = 7.6$ Hz, $J_2 = 1.1$ Hz), 7.00 (dd, 1H, $J_1 = 8.4$ Hz, $J_2 = 1.8$ Hz), 7.17-7.21 (m, 1H), 7.25-7.32 (m, 2H), 7.44-7.47 (d, 1H, $J = 7.6$ Hz), 7.45 (s, 1H), 7.49-7.53 (m, 1H), 8.04 (d, 1H, $J = 4.6$ Hz), 8.15 (d, 1H, $J = 1.8$ Hz), 8.27 (dd, 1H, $J_1 = 8.4$ Hz, $J_2 = 1.8$ Hz), 8.56 (d, 1H, $J = 3.0$ Hz), 8.58 (dd, 1H, $J_1 = 4.6$ Hz, $J_2 = 1.2$ Hz).
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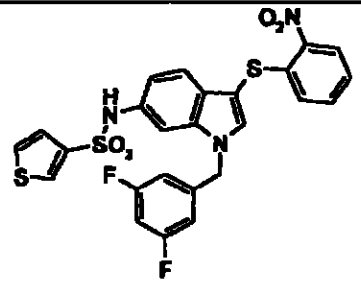
Compuesto 105: *N*-[3-(2-Nitro-fenilsufanil)-1-piridin-3-ilmetil-1*H*-indol-6-yl]-propionamida, estructura 28 del Esquema VII, donde $R^1 = 3$ -piridil, $R^2 = 2$ -nitrofenil, $R^3=R^4=H$, $Z^1 =$ etil. Fue usado el método b.

	$^1\text{H NMR (CDCl}_3\text{)}$ δ 1.26 (t, 3H, $J = 7.6$ Hz), 2.42 (q, 2H, $J = 7.6$ Hz), 5.39 (s, 2H), 8.68 (dd, 1H, $J_1 = 8.4$ Hz, $J_2 = 1.8$ Hz), 6.91 (dd, 1H, $J_1 = 8.4$ Hz, $J_2 = 1.1$ Hz), 7.15-7.20 (m, 1H), 7.24-7.30 (m, 3H), 7.38-7.41 (m, 2H), 7.48-7.52 (m, 1H), 8.23 (d, 1H, $J = 1.8$ Hz), 8.27 (dd, 1H, $J_1 = 8.4$ Hz, $J_2 = 1.8$ Hz), 8.55 (d, 1H, $J = 3.0$ Hz), 8.57 (dd, 1H, $J_1 = 4.6$ Hz, $J_2 = 1.1$ Hz).
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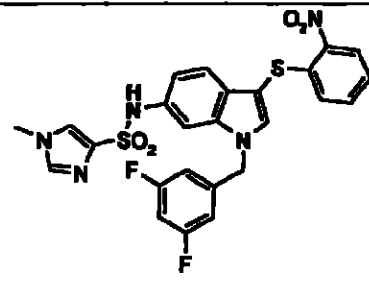
Compuesto 106: *N*-[1-(3,5-Difluorobencil)-3-(2-nitro-fenilsulfanil)-1*H*-indol-6-yl]-metanesulfonamida, estructura **29** del Esquema VII, donde $R^1 = 3,5$ -difluorofenil, $R^2 = 2$ -nitrofenil, $R^3=R^4=H$, $Z^2 = Me$. Fue usado el método c.

	¹ H-NMR (DMSO): δ 2.95 (s, 3H), 5.54 (s, 2H), 6.90 (dd, 1H, $J_1 = 7.6$ Hz, $J_2 = 1.1$ Hz), 6.98-7.04 (m, 3H), 7.20 (tt, 1H, $J_1 = 9.5$ Hz, $J_2 = 3.0$ Hz), 7.31-7.37 (m, 2H), 7.41 (d, 1H, $J = 1.5$ Hz), 7.47-7.52 (m, 1H), 8.08 (s, 1H), 8.27 (dd, 1H, $J_1 = 7.6$ Hz, $J_2 = 1.1$ Hz), 9.65 (s, 1H).
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Compuesto 107: Acido tiofeno-3-sulfónico de [1-(3,5-difluorobencil)-3-(2-nitro-fenilsulfanil)-1*H*-indol-6-yl]-amida, estructura **29** del Esquema VII, donde $R^1 = 3,5$ -difluorofenil, $R^2 = 2$ -nitrofenil, $R^3=R^4=H$, $Z^1 = 3$ -tiofeno. Fue usado el método c.

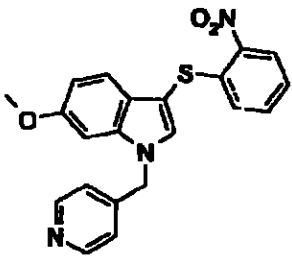
	¹ H-NMR (DMSO): δ 5.50 (s, 2H), 6.85 (m, 2H), 6.92-6.97 (m, 2H), 7.13 (dd, 1H, $J_1 = 5.0$, $J_2 = 1.1$ Hz), 7.19-7.26 (m, 2H), 7.31 (d, 1H, $J = 2.2$ Hz), 7.32-7.36 (m, 1H), 7.45-7.50 (m, 1H), 7.61 (dd, 1H, $J_1 = 5.0$ Hz, $J_2 = 3.0$ Hz), 7.97 (dd, 1H, $J_1 = 3.0$ Hz, $J_2 = 1.1$ Hz), 8.05 (s, 1H), 8.26 (dd, 1H, $J_1 = 7.6$ Hz, $J_2 = 1.1$ Hz), 10.20 (s, 1H).
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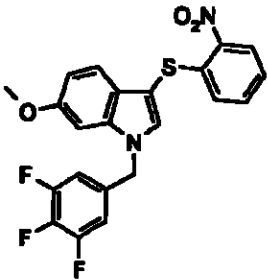
Compuesto 108: Acido 1-Metil-1*H*-imidazol-4-sulfónico de [1-(3,5-difluorobencil)-3-(2-nitro-fenilsulfanil)-1*H*-indol-6-yl]-amida, estructura **29** del Esquema VII, donde $R^1 = 3,5$ -difluorofenil, $R^2=2$ -nitrofenil, $R^3=R^4=H$, $Z^2 = 4$ -(1-metil)-imidazol. Fue usado el método c.

	¹ H-NMR (DMSO): δ 3.60 (s, 3H), 5.46 (s, 2H), 6.86 (dd, 1H, $J_1 = 7.6$ Hz, $J_2 = 0.7$ Hz), 6.92 (dd, 1H, $J_1 = 7.6$ Hz, $J_2 = 1.5$ Hz), 6.96-7.01 (m, 2H), 7.19 (d, 1H, $J = 7.6$ Hz), 7.23 (tt, 1H, $J_1 = 9.5$ Hz, $J_2 = 3.0$ Hz), 7.31-7.36 (m, 2H), 7.45-7.49 (m, 1H), 7.66-7.69 (m, 2H), 8.02 (s, 1H), 8.26 (dd, 1H, $J_1 = 7.6$ Hz, $J_2 = 0.7$ Hz), 10.20 (s, 1H).
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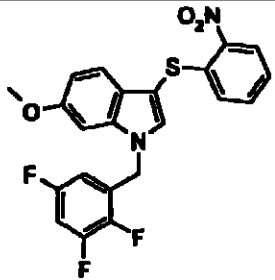
Ejemplo 20

De acuerdo con el método general 3 se prepararon los siguientes compuestos:

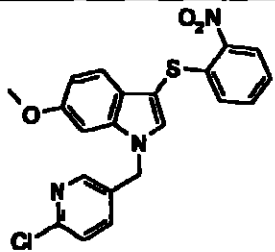
Compuesto 93: 6-Metoxy-3-(2-nitro-fenilsulfanil)-1-piridin-4-ilmetil-1<i>H</i>-indol, estructura 3 del Esquema I, donde $R^1 = 4\text{-piridil}$, $R^2 = 2\text{-nitrofenil}$, $R^3=R^4=H$, $R^5 = \text{OMe}$. Fueron utilizados NaH y DMF.	
	^1H NMR (CDCl_3): δ 3.80 (s, 3H, OCH_3), 5.37 (s, 2H, NCH_2Ar), 6.71 (d, 1H, $J = 2.7$ Hz), 6.86 (dd, 1H, $J_1 = 8.4$ Hz, $J_2 = 2.7$ Hz), 7.00 (dd, 1H, $J_1 = 8.4$ Hz, $J_2 = 1.5$ Hz), 7.04 (m, 2H), 7.19 (td, 1H, $J_1 = 7.6$ Hz, $J_2 = 1.5$ Hz), 7.29 (td, 1H, $J_1 = 7.6$ Hz, $J_2 = 1.5$ Hz), 7.36 (s, 1H), 7.40 (d, 1H, $J = 8.4$ Hz), 8.27 (dd, 1H, $J_1 = 7.6$ Hz, $J_2 = 1.5$ Hz), 8.59 (m, 2H).

Compuesto 94: 6-Metoxy-3-(2-nitro-fenilsulfanil)-1-(3,4,5-trifluoro-bencil)-1<i>H</i>-indol, estructura 3 del Esquema I, donde $R^1 = 3,4,5\text{-difluorofenil}$, $R^2 = 2\text{-nitrofenil}$, $R^3=R^4=H$, $R^5 = \text{OMe}$. Fueron utilizados Cs_2CO_3 y NMP.	
	^1H-NMR (CDCl_3): δ 3.83 (s, 3H, OCH_3), 5.28 (s, 2H, NCH_2Ar), 6.72 (d, 1H, $J = 2.2$ Hz), 6.75 (d, 1H, $J = 7.6$ Hz), 6.77 (d, 1H, $J = 7.6$ Hz), 6.86 (dd, 1H, $J_1 = 8.4$ Hz, $J_2 = 2.2$ Hz), 6.97 (dd, 1H, $J_1 = 8.4$ Hz, $J_2 = 1.1$ Hz), 7.19 (td, 1H, $J_1 = 7.6$ Hz, $J_2 = 1.1$ Hz), 7.28 (td, 1H, $J_1 = 7.6$ Hz, $J_2 = 1.1$ Hz), 7.33 (s, 1H), 7.40 (d, 1H, $J = 8.4$ Hz), 8.27 (dd, 1H, $J_1 = 8.4$ Hz, $J_2 = 2.2$ Hz).

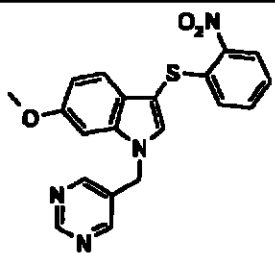
Compuesto 95: 6-Metoxy-3-(2-nitro-fenilsulfanil)-1-(2,3,5-trifluoro bencil)-1*H*-indol, estructura 3 del Esquema I, donde $R^1 = 2,3,5$ -difluorofenil, $R^2 = 2$ -nitrofenil, $R^3=R^4=H$, $R^5 = OMe$. Fueron utilizados Cs_2CO_3 y NMP.

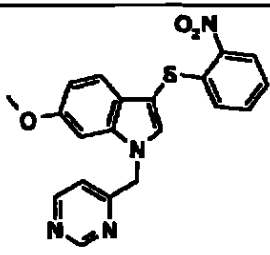
	^1H -NMR ($CDCl_3$): δ 3.85 (s, 3H, OCH_3), 5.39 (s, 2H, NCH_2Ar), 6.42 (m, 1H), 6.82 (d, 1H, $J = 2.7$ Hz), 6.86 (dd, 1H, $J_1 = 7.6$ Hz, $J_2 = 2.2$ Hz), 6.90 (m, 1H), 6.96 (dd, 1H, $J_1 = 7.6$ Hz, $J_2 = 2.2$ Hz), 7.18 (td, 1H, $J_1 = 7.6$ Hz, $J_2 = 1.5$ Hz), 7.27 (td, 1H, $J_1 = 7.6$ Hz, $J_2 = 1.5$ Hz), 7.37 (s, 1H), 7.39 (d, 1H, $J = 7.6$ Hz), 8.27 (dd, 1H, $J_1 = 7.6$ Hz, $J_2 = 1.5$ Hz).
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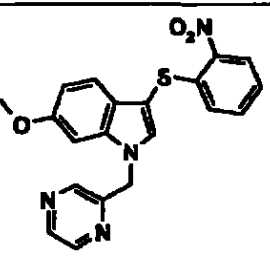
Compuesto 96: 1-(6-Cloro-piridin-3-ilmetil)-6-metoxo-3-(2-nitro-fenilsulfanil)-1*H*-indol, estructura 3 del Esquema I, donde $R^1 = 4$ -cloro-3-piridil, $R^2 = 2$ -nitrofenil, $R^3=R^4=H$, $R^5 = OMe$. Fueron utilizados Cs_2CO_3 y NMP.

	^1H -NMR ($CDCl_3$): δ 3.82 (s, 3H, OCH_3), 5.37 (s, 2H, NCH_2Ar), 6.76 (d, 1H, $J = 2.2$ Hz), 6.84 (dd, 1H, $J_1 = 7.6$ Hz, $J_2 = 2.2$ Hz), 6.96 (dd, 1H, $J_1 = 7.6$ Hz, $J_2 = 1.1$ Hz), 7.18 (td, 1H, $J_1 = 8.4$ Hz, $J_2 = 1.1$ Hz), 7.27 (td, 1H, $J_1 = 8.4$ Hz, $J_2 = 1.1$ Hz), 7.30-7.41 (m, 4H), 8.27 (dd, 1H, $J_1 = 8.4$ Hz, $J_2 = 1.1$ Hz), 8.34 (d, 1H, $J = 3.0$ Hz).
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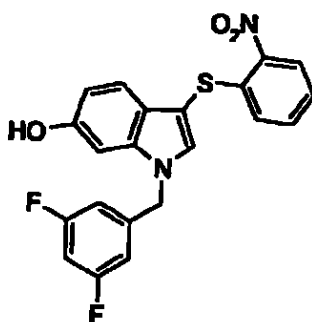
Compuesto 115: 6-Metoxo-3-(2-nitro-fenilsulfanil)-1-pirimidin-5-ilmetil-1*H*-indol, estructura 3 del Esquema I, donde $R^1 = 3,5$ -pirimidil, $R^2 = 2$ -nitrofenil, $R^3=R^4=H$, $R^5 = OMe$. Fueron utilizados Cs_2CO_3 y NMP.

	^1H NMR ($CDCl_3$): δ 3.83 (s, 3H), 5.38 (s, 2H), 6.77 (d, 1H, $J = 3.0$ Hz), 6.86 (dd, 1H, $J_1 = 8.4$ Hz, $J_2 = 3.0$ Hz), 6.96 (dd, 1H, $J_1 = 8.4$ Hz, $J_2 = 1.1$ Hz), 7.17-7.21 (m, 1H), 7.26-7.32 (m, 1H), 7.37 (s, 1H), 7.39 (d, 1H, $J = 8.4$ Hz), 8.27 (dd, 1H, $J_1 = 8.4$ Hz, $J_2 = 1.1$ Hz), 8.61 (s, 2H), 9.20 (s, 1H).
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Compuesto 116: 6-Metoxy-3-(2-nitro-fenilsulfanil)-1-pirimidin-4-ilmetil-1<i>H</i>-indol. estructura 3 del Esquema I, donde $R^1 = 2,4$-pirimidil, $R^2 = 2$-nitrofenil, $R^3=R^4=H$, $R^5 = OMe$. Fueron utilizados Cs_2CO_3 y NMP.	 ^1H NMR ($CDCl_3$): δ 3.80 (s, 3H), 5.44 (s, 2H), 6.74 (d, 1H, $J = 2.2$ Hz), 6.80 (dd, 1H, $J_1 = 4.6$ Hz, $J_2 = 1.1$ Hz), 6.86 (dd, 1H, $J_1 = 8.4$ Hz, $J_2 = 3.0$ Hz), 7.00 (dd, 1H, $J_1 = 8.4$ Hz, $J_2 = 1.1$ Hz), 7.17-7.21 (m, 1H), 7.26-7.33 (m, 1H), 7.40 (d, 1H, $J = 8.4$ Hz), 7.42 (s, 1H), 8.27 (dd, 1H, $J_1 = 8.4$ Hz, $J_2 = 1.1$ Hz), 8.66 (d, 1H, $J = 4.6$ Hz), 9.24 (d, 1H, $J = 1.1$ Hz).
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Compuesto 117: 6-Metoxy-3-(2-nitro-fenilsulfanil)-1-pirazin-2-ilmetil-1<i>H</i>-indol. estructura 3 del Esquema I, donde $R^1 = 2,5$-pirazil, $R^2 = 2$-nitrofenil, $R^3=R^4=H$, $R^5 = OMe$. Fueron utilizados Cs_2CO_3 y NMP.	 ^1H NMR ($CDCl_3$): δ 3.83 (s, 3H), 5.49 (s, 2H), 6.82-6.86 (m, 2H), 6.99 (dd, 1H, $J_1 = 8.4$ Hz, $J_2 = 1.1$ Hz), 7.16-7.20 (m, 1H), 7.25-7.29 (m, 1H), 7.38 (d, 1H, $J = 8.4$ Hz), 7.46 (s, 1H), 8.26 (dd, 1H, $J_1 = 8.4$ Hz, $J_2 = 1.1$ Hz), 8.35 (d, 1H, $J = 1.1$ Hz), 8.55 (d, 1H, $J = 3.0$ Hz), 8.59-8.61 (m, 1H).
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Compuesto 61: 1-(3,5-Difluorobencil)-3-(2-nitro-fenilsulfanil)-1*H*-indol-6-ol, estructura 25 del Esquema VI, donde $R^1 = 3,5$ -difluorofenil, $R^2=2$ -nitrofenil, $R^3=R^4=H$, $R^5=OH$.



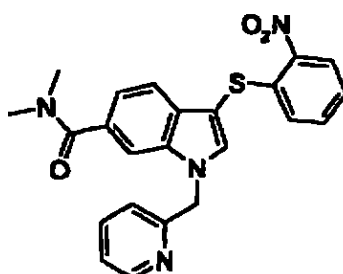
137

A una solución del compuesto **63** (240 mg, 0.56 mmol) en CH_2Cl_2 (10 mL) fue adicionado a 0°C complejo de sulfuro trifluoride-metil de boro (2.37 mL, 22.5 mmol). Después de agitar por 2 Hrs a 0°C la mezcla de reacción fue dejada calentar a temperatura ambiente y se continuó con la agitación durante otras 4 hrs. La mezcla de reacción fue vertida dentro de agua helada (20 mL) y después de la adición de acetato de etilo (10 mL) las capas se separaron. La capa orgánica fue lavada con NaHCO_3 acuoso saturado (20 mL) y salmuera (20 mL) y secada sobre Na_2SO_4 . La concentración dio el producto crudo el cual fue purificado utilizando cromatografía flash (heptano/etilactato 3:2) para obtener el compuesto **61** como un aceite amarillo (87 mg, 0.21 mmol, 38%).

^1H NMR (CDCl_3) δ 4.75 (2, 1H), 5.29 (s, 2H), 4.66 (m, 1H), 6.72-6.79 (m, 3H), 6.98 (dd, 1H, $J_1 = 8.4$ Hz, $J_2 = 1.5$ Hz), 7.17-7.21 (m, 1H), 7.27-7.31 (m, 1H), 7.35-7.37 (m, 3H), 8.27 (dd, 1H, $J_1 = 8.4$ Hz, $J_2 = 1.5$ Hz).

Ejemplo 22

Compuesto 109: Dimetilamida del ácido 3-(2-Nitro-fenilsulfanil)-1-piridin-2-ilmetil-1H-indol-6-carboxílico, estructura 15 del Esquema IV, donde $\text{R}^1 = 2\text{-piridil}$, $\text{R}^2 = 2\text{-nitrofenil}$, $\text{R}^3 = \text{R}^4 = \text{H}$, $\text{R}^5 = \text{R}^6 = \text{Me}$.



a) Metil éster del ácido 1-Piridin-2-ilmetil-1*H*-indol-6-carboxílico.

Bajo atmósfera de nitrógeno: a una solución de metil éster del ácido 1*H*-indol-6-carboxílico (para síntesis ver ejemplo 2a), 2.47g, 14.1 mmol) en NMP (140 mL) fue adicionado Cs_2CO_3 (10.1 mg, 31 mmol) a 0°C. Después de agitar por 15 min se adicionó clorhidrato de 2-picolil cloruro (2.77 g, 16.9 mmol) y la mezcla fue agitada a temperatura ambiente por 18 hrs. Se adicionó acetato de etilo (200 mL) y la mezcla fue lavada con solución acuosa saturada de cloruro amónico (3x150 mL) y salmuera (200 mL). La fase orgánica fue secada (Na_2SO_4) y concentrada. El producto crudo fue purificado utilizando cromatografía de columna (acetato de etilo/heptano 1:3) para dar el compuesto del título como un aceite incoloro, el cual se cristaliza lentamente en reposo (2.72 g, 10.2 mmol, 72%).

b) Metil éster de ácido 3-(2-Nitrofenil sulfanil)-1-piridin-2-ilmetil-1*H*-indol-6-carboxílico, estructura 13 del Esquema IV donde $\text{R}^1 = 2\text{-piridil}$, $\text{R}^2 = 2\text{-nitrofenil}$, $\text{R}^3 = \text{R}^4 = \text{H}$.

A una solución de metil éster de ácido 1-piridin-2-ilmetil-1*H*-indol-6-carboxílico (2.72g, 10.2 mmol) en diclorometano (75 mL) fue adicionada a temperatura ambiente una solución cloruro de 2-nitrobenzen sulfenil (1.93 g, 10.2 mmol) en diclorometano (75 mL). La mezcla fue agitada a temperatura ambiente por 24 hrs. La mezcla de reacción fue concentrada y el producto crudo fue purificado utilizando cromatografía de columna (acetato de etilo/heptano 1:5 a 1:2) para dar el compuesto del título como un sólido amarillo (3.21 g, 7.65 mmol, 75%).

c) Ácido 3-(2-Nitrofenil sulfanil)-1-piridin-2-ilmetil-1*H*-indol-6-carboxílico, estructura 14 del Esquema IV donde $\text{R}^1 = 2\text{-piridil}$, $\text{R}^2 = 2\text{-nitrofenil}$, $\text{R}^3 = \text{R}^4 = \text{H}$.

A una suspensión metil éster del ácido 3-(2-nitrofenil sulfanil)-1-piridin-2-ilmetil-1*H*-indol-6-carboxílico (3.0 g, 6.58 mmol) en dioxano (65 mL) se adicionó una solución de $\text{LiOH} \cdot \text{H}_2\text{O}$ (1.66 g, 39.6 mmol) en agua (65 mL). La mezcla de reacción fue agitada de un día para otro a 60°C. La mezcla fue entonces acidificada hasta un pH de 6 por la adición de HCl 15% acuoso y la mezcla fue extractada con acetato de

etilo (2 x 100 mL). Las capas orgánicas combinadas fueron secadas sobre Na₂SO₄ y concentradas para obtener un polvo amarillo. El producto fue recristalizado desde heptano/acetato de etilo para obtener el compuesto del título como cristales amarillo/naranja (2.47 g, 6.09 mmol, 93%).

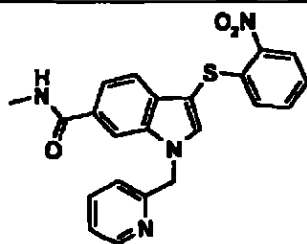
Método general 7: Amidación de indols 6-carboxil de estructura **14** para obtener indols 6-carboxamida de estructura **15** (Esquema IV).

Bajo atmósfera de nitrógeno: a una solución de ácido 3-(2-nitrofenil sulfanil)-1-piridin-2-ilmetil-1*H*-indol-6-carboxílico (700 mg, 1.73 mmol) en CH₂Cl₂ seco (70 mL) fue agregado DIPEA (0.9 mL, 5.2 mmol), TBTU (840 mg, 2.6 mmol) e clorhidrato de dimetilamina (420 mg, 5.1 mmol). La mezcla de reacción fue agitada de un día para otro a temperatura ambiente y después vertida dentro de NaHCO₃ saturado acuoso (100 mL). La capa orgánica fue lavada con salmuera (50 mL), secada (Na₂SO₄) y concentrada. El producto crudo fue purificado por cromatografía de columna (acetato de etilo/MeOH 95:5) para obtener el compuesto **109** (540 mg, 1.25 mmol, 72%, sólido amarillo).

¹H-NMR (CDCl₃): δ 2.97 (s, 3H), 3.11 (s, 2H), 5.53 (s, 2H), 6.90 (dd, 1H, J₁ = 7.6 Hz, J₂ = 1.5 Hz), 6.95 (d, 1H, J = 7.6 Hz), 7.17-7.28 (m, 4H), 7.51 (d, 1H, J = 7.6 Hz), 7.54 (s, 1H), 7.61-7.66 (m, 2H), 8.26 (dd, 1H, J₁ = 8.4 Hz, J₂ = 1.5 Hz), 8.61 (d, 1H, J = 4.6 Hz).

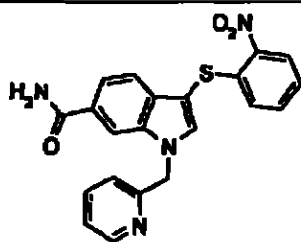
Los siguientes compuestos fueron preparados utilizando el procedimiento general 7:

Compuesto 110: Metilamida de ácido 3-(2-Nitro-fenilsulfanil)-1-piridin-2-ilmetil-1*H*-indol-6-carboxílico, estructura 15 del Esquema IV, donde $R^1 = 2\text{-piridil}$, $R^2 = 2\text{-nitrofenil}$, $R^3=R^4=H$, $R^6 = H$, $R^8=Me$.



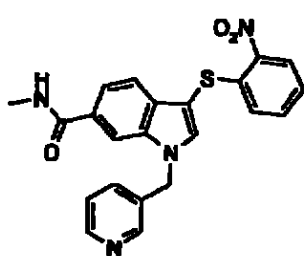
$^1\text{H-NMR}$ (DMSO): δ 2.78 (d, 3H, $J = 4.6$ Hz), 5.70 (s, 2H), 6.88 (dd, 1H, $J_1 = 8.4$ Hz, $J_2 = 1.5$ Hz), 7.19 (d, 1H, $J = 7.6$ Hz), 7.30-7.37 (m, 2H), 7.41 (d, 1H, $J = 8.4$ Hz), 7.48-7.53 (m, 1H), 7.62 (dd, 1H, $J_1 = 7.6$ Hz, $J_2 = 1.5$ Hz), 7.79 (td, 1H, $J_1 = 7.6$ Hz, $J_2 = 1.5$ Hz), 8.13 (s, 1H), 8.20 (s, 1H), 8.28 (dd, 1H, $J_1 = 8.4$ Hz, $J_2 = 1.5$ Hz), 8.38 (q, 1H, $J = 4.6$ Hz), 8.55 (s, 1H, $J = 4.6$ Hz).

Compuesto 111: Amida de ácido 3-(2-Nitro-fenilsulfanil)-1-piridin-2-ilmetil-1*H*-indol-6-carboxílico, estructura 15 del Esquema IV, donde $R^1 = 2\text{-piridil}$, $R^2 = 2\text{-nitrofenil}$, $R^3=R^4=H$, $R^6 = R^8=H$.



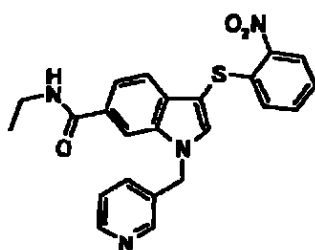
$^1\text{H-NMR}$ (DMSO): δ 5.70 (s, 2H), 6.88 (dd, 1H, $J_1 = 8.4$ Hz, $J_2 = 1.5$ Hz), 7.21 (d, 1H, $J = 7.6$ Hz), 7.28-7.37 (m, 3H), 7.39 (d, 1H, $J = 7.6$ Hz), 7.48-7.53 (m, 1H), 7.66 (dd, 1H, $J_1 = 8.4$ Hz, $J_2 = 1.5$ Hz), 7.79 (td, 1H, $J = 7.6$ Hz, $J_2 = 1.5$ Hz), 7.93 (s, 1H), 8.17 (s, 1H), 8.20 (s, 1H), 8.26 (dd, 1H, $J_1 = 7.6$ Hz, $J_2 = 1.5$ Hz), 8.55 (d, 1H, $J = 4.6$ Hz).

Compuesto 112: Metilamida de ácido 3-(2-Nitro-fenilsulfanil)-1-piridin-3-ilmetil-1H-indol-6-carboxílico, estructura 15 del Esquema IV, donde $R^1 = 3$ -piridil, $R^2 = 2$ -nitrofenil, $R^3=R^4=H$, $R^5 = H$, $R^6=Me$. Fue utilizado clorhidrato de 3-picolil cloruro en lugar de clorhidrato de 2-picolil.



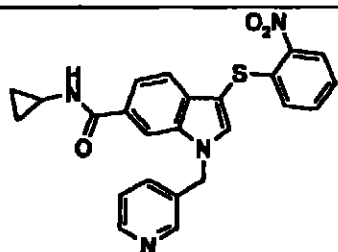
^1H -NMR (DMSO): δ 2.80 (d, 3H, $J = 4.6$ Hz), 5.65 (s, 2H), 6.84 (dd, 1H, $J_1 = 7.6$ Hz, $J_2 = 1.1$ Hz), 7.33-7.42 (m, 3H), 7.46-7.51 (m, 1H), 7.62 (dd, 1H, $J_1 = 8.4$ Hz, $J_2 = 1.1$ Hz), 7.68 (dt, 1H, $J_1 = 7.6$ Hz, $J_2 = 2.2$ Hz), 8.19 (s, 1H), 8.26 (s, 1H), 8.28 (dd, 1H, $J_1 = 7.6$ Hz, $J_2 = 1.1$ Hz), 8.41 (q, 1H, $J = 4.6$ Hz), 8.51 (dd, 1H, $J_1 = 4.6$ Hz, $J_2 = 1.1$ Hz), 8.64 (d, 1H, $J = 3.0$ Hz).

Compuesto 113: Etilamida de ácido 3-(2-Nitro-fenilsulfanil)-1-piridin-3-ilmetil-1H-indol-6-carboxílico, estructura 15 del Esquema IV, donde $R^1 = 3$ -piridil, $R^2 = 2$ -nitrofenil, $R^3=R^4=H$, $R^5 = H$, $R^6=Et$. Fue utilizado clorhidrato de 3-picolil cloruro en lugar de clorhidrato de 2-picolil.



^1H -NMR (DMSO): δ 1.13 (t, 3H, $J = 7.6$ Hz), 3.30 (q, 2H, $J = 7.6$ Hz), 5.66 (s, 2H), 6.83 (dd, 1H, $J_1 = 7.6$ Hz, $J_2 = 1.1$ Hz), 7.33-7.41 (m, 3H), 7.46-7.51 (m, 1H), 7.64 (dd, 1H, $J_1 = 7.6$ Hz, $J_2 = 1.1$ Hz), 7.67 (dt, 1H, $J_1 = 7.6$ Hz, $J_2 = 2.2$ Hz), 8.19 (s, 1H), 8.26 (s, 1H), 8.27 (dd, 1H, $J_1 = 7.6$ Hz, $J_2 = 1.1$ Hz), 8.45 (t, 1H, $J = 5.7$ Hz), 8.52 (dd, 1H, $J_1 = 4.6$ Hz, $J_2 = 1.5$ Hz), 8.64 (d, 1H, $J = 3.0$ Hz).

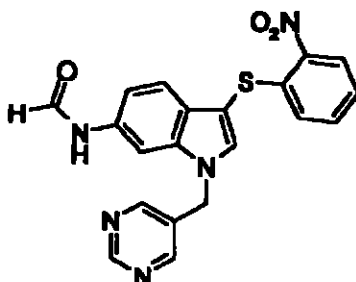
Compuesto 114: Ciclopropilamida ácido de 3-(2-Nitro-fenilsulfanil)-1-piridin-3-ilmetil-1H-indol-6-carboxílico, estructura 15 del Esquema IV, donde $R^1 = 3\text{-piridil}$, $R^2 = 2\text{-nitrofenil}$, $R^3=R^4=H$, $R^6 = H$, $R^9=\text{ciclopropil}$. Fue utilizado clorhidrato de 3-picolil cloruro en lugar de clorhidrato de 2-picolil.



$^1\text{H-NMR}$ (DMSO): δ 0.54-0.58 (m, 2H), 0.67-0.73 (m, 2H), 2.80-2.87 (m, 1H), 5.66 (s, 2H), 6.82 (d, 1H, $J = 7.6$ Hz), 7.33-7.41 (m, 3H), 7.46-7.50 (m, 1H), 7.61 (dd, 1H, $J_1 = 7.6$ Hz, $J_2 = 1.1$ Hz), 7.67 (dt, 1H, $J_1 = 7.6$ Hz, $J_2 = 1.5$ Hz), 8.17 (s, 1H), 8.25 (s, 1H), 8.28 (dd, 1H, $J_1 = 7.6$ Hz, $J_2 = 1.1$ Hz), 8.42 (t, 1H, $J = 4.6$ Hz), 8.52 (dd, 1H, $J_1 = 4.6$ Hz, $J_2 = 1.5$ Hz), 8.63 (d, 1H, $J = 3.0$ Hz).

Ejemplo 23

Compuesto 118: N-[3-(2-Nitro-fenilsulfanil)-1-pirimidin-5-ilmetil-1H-indol-6-yl]-formamida, estructura 28 del Esquema VII, donde $R^1 = 3,5\text{-pirimidil}$, $R^2 = 2\text{-nitrofenil}$, $R^3=R^4=H$, $Z = H$



a) 6-Nitro-1-pirimidin-5-ilmetil-1H-indol

5-(Hidroximetil) pirimidina (16.2 g, 147 mmol) fue disuelto en 500 mL de CH_2Cl_2 y enfriado a -40°C . Se adicionó MsCl (16.0 g, 140 mmol) a -40°C . La mezcla fue agitada durante 1 hora permitiendo alcanzar -20°C . La solución fue usada como tal. 6-Nitroindol-1H-indol (35.6 g, 220 mmol) fue disuelto en 750 mL de DMF y se agregó NaH (50%, 12 g, 250 mmol) en porciones y la mezcla fue agitada por 1 hora. La

mezcla fue enfriada a -40°C y la solución del mesilato fue agregada por goteo. La mezcla fue dejada de un día para otro hasta alcanzar la temperatura ambiente. La mezcla fue apagada con agua y extractada con acetato de etilo (2x). Las capas orgánicas combinadas fueron lavadas con agua (2x) y salmuera y secadas sobre Na_2SO_4 . Después de la concentración *en vacío* el material fue purificado por medio de cromatografía de columna (sílica, heptano/acetato de etilo (1:1) $\rightarrow$ (1:4)) produciendo el compuesto del título como un sólido amarillo (14 g, 55 mmol, 39%).

b) 1-Pirimidin-5-ilmetil-1*H*-indol-6-ilamina.

6-Nitro-1-pirimidin-5-ilmetil-1*H*-indol (4.1 g, 16.1 mmol) fue disuelto en 100 mL de THF y 100 mL de isopropanol. Se adicionó Pd/C (2 g) y la mezcla fue agitada bajo una atmósfera H_2 (globo) por 2 horas. La mezcla fue filtrada sobre Celita y lavada con acetato de etilo produciendo el compuesto del título después de concentración (3.5 g, 15.6 mmol, 97 %).

c) Terbutil éster de ácido 1-Pirimidin-5-ilmetil-1*H*-indol-6-yl)-carbámico.

1-Pirimidin-5-ilmetil-1*H*-indol-6-ilamina (5.5. g, 24.6 mmol) fue disuelto en 100 mL de NMP y trietilamina (3.5 g, 35 mmol) y fue adicionado dicarbonato de diterbutil (7.0 g, 32 mmol). La mezcla fue agitada de un día para otro, apagada con NaHCO_3 -sat y extractada con tolueno (3x). Las capas orgánicas combinadas fueron lavadas con agua (4x) y salmuera y secadas sobre Na_2SO_4 . La concentración de las capas produjeron el compuesto del título (3.1 g, 39%).

d) Terbutil éster del ácido [3-(2-Nitro-fenilsulfanil)-1-pirimidin-5-ilmetil-1*H*-indol-6-yl]-carbámico

Terbutil éster del ácido 1-pirimidin-5-ilmetil-1*H*-indol-6-yl)-carbámico (3.1 g, 9.6 mmol) fue disuelto en 150 mL de CH_2Cl_2 y se adicionó sulfenilcloruro de 2-nitrobenceno (1.86 g, 9.8 mmol). La mezcla fue agitada por 18 horas y apagada con NaHCO_3 -sat y extractada con acetato de etilo (2x). Las capas orgánicas combinadas fueron

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lavadas con salmuera y secadas sobre Na_2SO_4 . El producto fue purificado por medio cromatografía de columna (sílica, heptano/acetato de etilo (1:1) la cual dio el compuesto del título como un sólido amarillo (3.8 g, 83%).

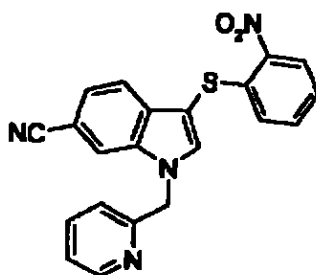
e) N-[3-(2-Nitro-fenilsulfanil)-1-pirimidin-5-ilmetil-1H-indol-6-yl]-formamida.

Tertbutil éster de ácido [3-(2-Nitro-fenilsulfanil)-1-pirimidin-5-ilmetil-1H-indol-6-yl]-carbámico (3.8 g, 8.9 mmol) fue disuelto en 150 mL de ácido fórmico y agitado por 4 horas. La solución fue concentrada *en vacío*. Fue adicionado NaHCO_3 -sat y la mezcla fue extractada con CH_2Cl_2 (2x). Las capas orgánicas combinadas fueron lavadas con salmuera y secada sobre Na_2SO_4 . La solución fue dejada en reposo de un día para otro. El sólido formado fue filtrado produciendo la mezcla del compuesto **118** y estructura **23** del Esquema VII, donde $\text{R}^1 = 3,5$ -pirimidil, $\text{R}^2 = 2$ -nitrofenil, $\text{R}^3 = \text{R}^4 = \text{H}$ (2.4 g).

Compuesto **118**: $^1\text{H-NMR}$ (CDCl_3 + una gota MeOD) δ 5.47 (s, 2H), 6.91 (dd, 1H, $J_1 = 8.4$ Hz, $J_2 = 1.1$ Hz), 6.99 (dd, 1H, $J_1 = 8.4$ Hz, $J_2 = 1.9$ Hz), 7.19-7.23 (m, 1H), 7.27-7.31 (m, 1H), 7.33 (s, 1H), 7.42 (d, 1H, $J = 8.4$ Hz), 7.49 (s, 1H), 8.22 (d, 1H, $J = 1.9$ Hz), 8.27 (dd, 1H, $J_1 = 8.4$ Hz, $J_2 = 1.1$ Hz), 8.66 (s, 2H), 9.16 (s, 1H).

Ejemplo 24

Compuesto 119: 3-(2-Nitro-fenilsulfanil)-1-piridin-2-ilmetil-1H-indol-6-carbonitrilo,
estructura 3 del esquema I, donde $\text{R}^1 = 2$ -piridil, $\text{R}^2 = 2$ -nitrofenil, $\text{R}^3 = \text{R}^4 = \text{H}$, $\text{R}^5 = \text{CN}$.



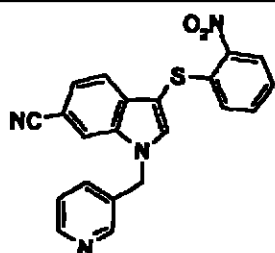
a) A una solución de 1 *H*-indol-6-carbonitrilo (1.00 g, 7.04 mmol) en éter dietílico (50 mL) fue adicionado a temperatura ambiente cloruro de 2-nitrobenzenosulfenil (1.34 g, 7.04 mmol) y la mezcla de reacción fue agitada por 18 hrs. La mezcla fue concentrada y el producto crudo fue purificado utilizando cromatografía de columna (acetato de etilo/heptano 1:4 → 4:1) para dar 3-(2-Nitro-fenilsulfanil)-1*H*-indol-6-carbonitrilo (1.62 g, 5.49 mmol, 78%).

b) A una solución de 3-(2-nitro-fenilsulfanil)-1*H*-indol-6-carbonitrilo (200 mg, 0.68 mmol) en DMF (5 mL) fue adicionado a 0°C Cs₂CO₃ (442 mg, 1.36 mmol) y la mezcla fue agitada por 20 min. Posteriormente se adicionó clorhidrato de 2-picolil cloruro (112 g, 0.68 mmol) y la mezcla fue agitada por 18 hrs a temperatura ambiente. Se adicionó NaHCO₃ acuoso saturado y la mezcla fue extractada con acetato de etilo (2x). Las capas orgánicas combinadas fueron lavadas con salmuera, secadas (Na₂SO₄) y concentrada. El producto crudo fue purificado usando columna cromatográfica para obtener el compuesto **119** (223 mg, 0.58 mmol, 85%).

¹H NMR (CDCl₃) δ 5.54 (s, 2H), 6.86 (dd, 1H, J₁ = 8.4 Hz, J₂ = 1.1 Hz), 7.04 (d, 1H, J = 8.4 Hz), 7.19-7.23 (m, 1H), 7.26-7.31 (m, 2H), 7.40 (dd, 1H, J₁ = 8.4 Hz, J₂ = 1.1 Hz), 7.59 (d, 1H, J = 8.4 Hz), 7.70 (td, 1H, J₁ = 8.4 Hz, J₂ = 1.9 Hz), 7.76 (s, 1H), 7.78 (s, 1H), 8.29 (dd, 1H, J₁ = 8.4 Hz, J₂ = 1.1 Hz), 8.63 (d, 1H, J = 3.0 Hz).

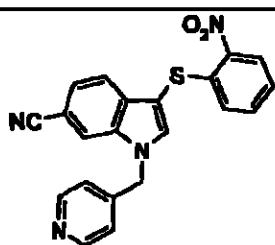
De acuerdo con el método general 3 se prepararon los siguientes compuestos:

Compuesto 121: 3-(2-Nitro-fenilsulfanil)-1-piridin-3-ilmetil-1*H*-indol-6-carbonitrilo.
 estructura 3 del esquema I, donde $R^1 = 3\text{-piridil}$, $R^2 = 2\text{-nitrofenil}$, $R^3=R^4=H$, $R^5 = CN$.
 Fueron utilizados Cs_2CO_3 y DMF.



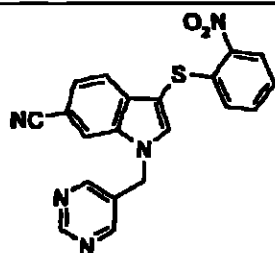
$^1H\text{-NMR}$ ($CDCl_3$) δ 5.46 (s, 2H), 6.82 (dd, 1H, $J_1 = 7.6$ Hz, $J_2 = 1.1$ Hz), 7.21-7.25 (m, 1H), 7.27-7.31 (m, 1H), 7.34 (dd, 1H, $J_1 = 8.4$ Hz, $J_2 = 4.6$ Hz), 7.43 (dd, 1H, $J_1 = 7.6$ Hz, $J_2 = 1.1$ Hz), 7.49 (dt, 1H, $J_1 = 8.4$ Hz, $J_2 = 1.9$ Hz), 7.61 (d, 1H, $J = 8.4$ Hz), 7.66 (s, 1H), 7.71 (s, 1H), 8.29 (dd, 1H, $J_1 = 7.6$ Hz, $J_2 = 1.1$ Hz), 8.55 (d, 1H, $J = 3.0$ Hz), 8.64 (dd, 1H, $J_1 = 8.4$ Hz, $J_2 = 1.5$ Hz).

Compuesto 122: 3-(2-Nitro-fenilsulfanil)-1-piridin-4-ilmetil-1*H*-indol-6-carbonitrilo.
 estructura 3 del esquema I, donde $R^1 = 4\text{-piridil}$, $R^2 = 2\text{-nitrofenil}$, $R^3=R^4=H$, $R^5 = CN$.



^1H NMR ($CDCl_3$) δ 5.46 (s, 2H), 6.84 (dd, 1H, $J_1 = 8.4$ Hz, $J_2 = 1.1$ Hz), 7.04 (d, 2H, $J = 6.1$ Hz), 7.22-7.26 (m, 1H), 7.28-7.32 (m, 1H), 7.44 (dd, 1H, $J_1 = 7.6$ Hz, $J_2 = 1.1$ Hz), 7.62 (d, 1H, $J = 8.4$ Hz), 7.64 (s, 1H), 7.68 (s, 1H), 8.30 (dd, 1H, $J_1 = 8.4$ Hz, $J_2 = 1.1$ Hz), 8.63-8.65 (m, 2H).
 Fueron utilizados Cs_2CO_3 y DMF.

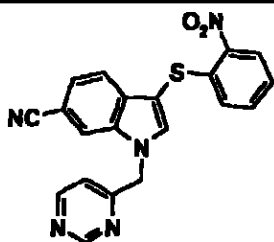
Compuesto 123: 3-(2-Nitro-fenilsulfanil)-1-pirimidin-5-ilmetil-1*H*-indol-6-carbonitrilo.
 estructura 3 del esquema I, donde $R^1 = 3,5\text{-pirimidil}$, $R^2 = 2\text{-nitrofenil}$, $R^3 = R^4 = H$, $R^5 = CN$. Fueron utilizados NaH y DMF.



^1H NMR ($CDCl_3$) δ 5.48 (s, 2H), 6.81 (dd, 1H, $J_1 = 7.6$ Hz, $J_2 = 1.1$ Hz), 7.22-7.32 (m, 2H), 7.46 (dd, 1H, $J_1 = 7.6$ Hz, $J_2 = 1.1$ Hz), 7.63 (d, 1H, $J = 8.4$ Hz), 7.68 (s, 1H), 7.70 (s, 1H), 8.30 (dd, 1H, $J_1 = 8.4$ Hz, $J_2 = 1.1$ Hz), 8.63 (s, 2H), 9.25 (s, 1H).

Compuesto 124: 3-(2-Nitro-fenilsulfanil)-1-pirimidin-4-ilmetil-1H-indol-6-carbonitrilo.

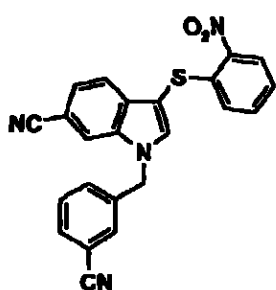
estructura 3 del esquema I, donde $R^1 = 2,4$ -pirimidil, $R^2 = 2$ -nitrofenil, $R^3 = R^4 = H$, $R^5 = CN$. Fueron utilizados Cs_2CO_3 y DMF.



^1H NMR ($CDCl_3$) δ 5.52 (s, 2H), 6.86 (dd, 1H, $J_1 = 7.6$ Hz, $J_2 = 1.1$ Hz), 6.97 (dd, 1H, $J_1 = 4.6$ Hz, $J_2 = 1.1$ Hz), 7.22-7.32 (m, 2H), 7.44 (dd, 1H, $J_1 = 8.4$ Hz, $J_2 = 1.1$ Hz), 7.62 (d, 1H, $J = 8.4$ Hz), 7.70 (s, 1H), 7.75 (s, 1H), 8.30 (dd, 1H, $J_1 = 7.6$ Hz, $J_2 = 1.1$ Hz), 8.74 (d, 1H, $J = 4.6$ Hz), 9.24 (d, 1H, $J = 1.1$ Hz).

Compuesto 125: 1-(3-Cianobencil)-3-(2-nitro-fenilsulfanil)-1H-indol-6-carbonitrilo.

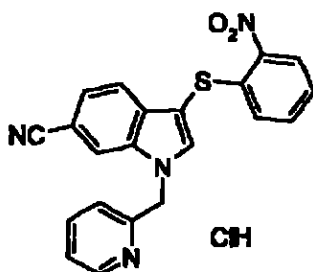
estructura 3 del esquema I, donde $R^1 = 3$ -cianofenil, $R^2 = 2$ -nitrofenil, $R^3 = R^4 = H$, $R^5 = CN$. Fueron utilizados Cs_2CO_3 y DMF.



^1H NMR ($CDCl_3$) δ 5.48 (s, 2H), 6.83 (dd, 1H, $J_1 = 8.4$ Hz, $J_2 = 1.1$ Hz), 7.21-7.26 (m, 1H), 7.30-7.35 (m, 1H), 7.38-7.42 (m, 3H), 7.45 (d, 1H, $J = 8.4$ Hz), 7.53 (d, 1H, $J = 7.6$ Hz), 7.64 (d, 1H, $J = 6.1$ Hz), 7.65 (d, 1H, $J = 3.7$ Hz), 7.66-7.69 (m, 1H), 8.30 (dd, 1H, $J_1 = 8.4$ Hz, $J_2 = 1.1$ Hz).

Ejemplo 25

Compuesto 120: Monoclorhidrato de 3-(2-Nitro-fenilsulfanil)-1-piridin-2-ilmetil-1H-indol-6-carbonitrilo.



Ácido clorhídrico concentrado (0.0225 ml) fue adicionado a una solución del compuesto **119** (0.093 g) en dioxano. La mezcla fue agitada por 20 min. y después concentrada bajo reducción de presión, para dar el compuesto **120** (0.096 g).

^1H NMR (MeOD) δ 6.01 (s, 2H), 6.98 (dd, 1H, $J_1 = 7.6$ Hz, $J_2 = 1.1$ Hz), 7.28-7.32 (m, 1H), 7.36-7.41 (m, 1H), 7.48 (dd, 1H, $J_1 = 7.6$ Hz, $J_2 = 1.1$ Hz), 7.53 (d, 1H, $J = 8.4$ Hz), 7.60 (d, 1H, $J = 8.4$ Hz), 7.93 (t, 1H, $J = 6.1$ Hz), 8.08 (s, 1H), 8.10 (s, 1H), 8.27 (dd, 1H, $J_1 = 8.4$ Hz, $J_2 = 1.1$ Hz), 8.44 (td, 1H, $J_1 = 8.4$ Hz, $J_2 = 1.1$ Hz), 8.85 (dd, 1H, $J_1 = 6.1$ Hz, $J_2 = 1.9$ Hz).

Los compuestos fueron ensayados para su actividad como Andrógeno Receptor en un ensayo de transactivación y en un ensayo de fijación.

La actividad (anti-) androgénica de los compuestos probados (EC_{50} y actividad intrínseca) fue determinada en un bioensayo *in vitro* de células de ovarios de hamster Chino (CHO) establemente transfectadas con plásmido de expresión del andrógeno receptor humano y un plásmido reportero en el cual el MMTV-promotor es vinculado al gen reportero de luciferasa. La línea de células CHO-AR-pMMTV-LUC 1G12-A5-CA es descrita en Schoonen et al. (2000), Journal of Steroid Biochemistry and Molecular Biology 74(4):213-222. La actividad antiandrogénica de un compuesto de ensayo fue determinada por la inhibición de la transactivación vía el andrógeno receptor de la encima luciferasa en la presencia de 1 nM DHT (5α -dihidrotestosterona, 17β -hidroxi- 5α -androstan-3-uno). La actividad intrínseca de la actividad antiandrogénica fue determinada en la presencia del antiandrógeno de referencia 2-Hidroxi-2-metil-*N*-(4-nitro-3-trifluorometil-fenil)-propionamida (Hidroxiflutamida), y fijado en 100%. Para actividad androgénica, la máxima actividad intrínseca en la presencia de 100 nM DHT fue fijada en 100%. Los resultados se presentan en la Tabla 4.

Tabla 4 Actividad del andrógeno receptor

Comp. Numero	X	R ¹	R ²	R ³	R ⁴	R ⁵	ago EC50	ago eficacia	ant EC50	ant eficacia
1	S	2,5-difluorofenil	2-nitrofenil	H	H	OMe	++	+	-	-
2	S	2, fluoro, 3-metilfenil	2-nitrofenil	H	H	OMe	+	+	-	-
3	S	2-clorofenil	2-nitrofenil	H	H	OMe	+	+	-	-
4	S	2-cianofenil	2-nitrofenil	H	H	OMe	+	±	++	±
5	S	2-fluorofenil	2-nitrofenil	H	H	OMe	+	+	-	-
6	S	2-metil,3-nitrofenil	2-nitrofenil	H	H	OMe	+	+	-	-
7	S	2-metilfenil	2-nitrofenil	H	H	OMe	++	++	-	-
8	S	2-nitrofenil	2-nitrofenil	H	H	OMe	++	+	-	-
9	S	2-piridil	2-nitrofenil	H	H	OMe	+++	+	+++	±
10	S	2-piridil HCl sal	2-nitrofenil	H	H	OMe	++	+	-	-
11	S	2-tetrahidropiranil	2-nitrofenil	H	H	OMe	++	+	-	-
12	S	2-trifluorometilfenil	2-nitrofenil	H	H	OMe	+	+	-	-
13	S	3-(5.metilisoxazolil)	2-nitrofenil	H	H	OMe	+	±	-	-
14	S	3,4 diclorofenil	2-nitrofenil	H	H	OMe	+	+	-	-
15	S	3,5-diclorofenil	2-nitrofenil	H	H	OMe	++	++	-	-
16	S	3,5-difluorofenil	2-(hidroxi metilfenil)	H	H	OMe	++	+	++	±
17	S	3,5-difluorofenil	2-(N-metilbenzamida)	H	H	OMe	-	-	+	+
18	S	3,5-difluorofenil	2-benzamida	H	H	OMe	++	+	++	±
19	S	3,5-difluorofenil	2-ácido benzoico metil ester	H	H	OMe	+	+	-	-
20	S	3,5-difluorofenil	2-cianofenil	H	H	OMe	++	++	-	-
21	S	3,5-difluorofenil	2-metoxifenil	H	H	OMe	++			
22	S	3,5-difluorofenil	2-nitrofenil	H	H	Br	++	++	-	-
23	S	3,5-difluorofenil	2-nitrofenil	H	H	CF3	+++	++	-	-
24	S	3,5-difluorofenil	2-nitrofenil	H	H	CH2OH	++	++	-	-
25	S	3,5-difluorofenil	2-nitrofenil	H	H	Cl	+++	++	-	-
26	S	3,5-difluorofenil	2-nitrofenil	H	H	CN	+++	++	-	-

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Comp. Numero	X	R ¹	R ²	R ³	R ⁴	R ⁵	ago EC50	ago eficacia	ant EC50	ant eficacia
27	S	3,5-difluorofenil	2-nitrofenil	H	H	CO(1-pirrolidinil)	++	+	-	-
28	S	3,5-difluorofenil	2-nitrofenil	H	H	CO(4-morfolinil)	++	+	-	-
29	S	3,5-difluorofenil	2-nitrofenil	H	H	CO[1-(4-metilpipera- cetil)]	++	++	-	-
30	S	3,5-difluorofenil	2-nitrofenil	H	H	CO ₂ H	+	+	-	-
31	S	3,5-difluorofenil	2-nitrofenil	H	H	CO ₂ Me	+++	+	-	-
32	S	3,5-difluorofenil	2-nitrofenil	H	H	CONEt ₂	++	+	+	±
33	S	3,5-difluorofenil	2-nitrofenil	H	H	CONH ₂	+++	++	-	-
34	S	3,5-difluorofenil	2-nitrofenil	H	H	CONHCH ₂ (2-furanil)	++	+	-	-
35	S	3,5-difluorofenil	2-nitrofenil	H	H	CONHCH ₂ (2-piridil)	++	±	-	-
36	S	3,5-difluorofenil	2-nitrofenil	H	H	CONHCH ₂ CH ₂ Nme ₂	++	+	-	-
37	S	3,5-difluorofenil	2-nitrofenil	H	H	CONHCH ₂ CH ₂ OH	+++	++	-	-
38	S	3,5-difluorofenil	2-nitrofenil	H	H	CONHCH ₂ CH ₂ OMe	+++	++	-	-
39	S	3,5-difluorofenil	2-nitrofenil	H	H	CONHCH ₂ CH ₂ OMe	++	++	-	-
40	S	3,5-difluorofenil	2-nitrofenil	H	H	CONHCH ₂ CONMe ₂	++	+	-	-
41	S	3,5-difluorofenil	2-nitrofenil	H	H	CONHCH ₂ cPr	+++	+	-	-
42	S	3,5-difluorofenil	2-nitrofenil	H	H	CONHCH ₂ iPr	++	+	-	-
43	S	3,5-difluorofenil	2-nitrofenil	H	H	CONHCH ₂ Ph	++	±	+	±
44	S	3,5-difluorofenil	2-nitrofenil	H	H	CONHcPr	+++	+	-	-
45	S	3,5-difluorofenil	2-nitrofenil	H	H	CONHEt	+++	++	-	-
46	S	3,5-difluorofenil	2-nitrofenil	H	H	CONHiPr	++	+	++	±
47	S	3,5-difluorofenil	2-nitrofenil	H	H	CONHMe	+++	+	-	-
48	S	3,5-difluorofenil	2-nitrofenil	H	H	CONHnPr	++	+	+	±
49	S	3,5-difluorofenil	2-nitrofenil	H	H	CONMe ₂	+++	+	-	-
50	S	3,5-difluorofenil	2-nitrofenil	H	H	F	++	++	-	-
51	S	3,5-difluorofenil	2-nitrofenil	F	H	H	+++	++	-	-
52	S	3,5-difluorofenil	2-nitrofenil	H	H	H	++	++	-	-
53	S	3,5-difluorofenil	2-nitrofenil	H	F	H	++	++	-	-
54	S	3,5-difluorofenil	2-nitrofenil	Cl	H	H	++	++	-	-
55	S	3,5-difluorofenil	2-nitrofenil	Me	H	H	++	+	-	-

Comp. Numero	X	R ¹	R ²	R ³	R ⁴	R ⁵	ago EC50	ago eficacia	ant EC50	ant eficacia
56	S	3,5-difluorofenil	2-nitrofenil	H	OH	H	+++			
57	S	3,5-difluorofenil	2-nitrofenil	H	H	NH ₂	+	+	-	-
58	S	3,5-difluorofenil	2-nitrofenil	H	H	NHAc	+++	++	-	-
59	S	3,5-difluorofenil	2-nitrofenil	H	H	NHCOCF ₃	+++	+	-	-
60	S	3,5-difluorofenil	2-nitrofenil	H	H	NO ₂	+++	++	-	-
61	S	3,5-difluorofenil	2-nitrofenil	H	H	OH	+++			
62	SO ₂	3,5-difluorofenil	2-nitrofenil	H	H	OMe	+++	++	-	-
63	S	3,5-difluorofenil	2-nitrofenil	H	H	OMe	+++	++	-	-
64	SO	3,5-difluorofenil	2-nitrofenil	H	H	OMe	-	±	+	+
65	S	3,5-difluorofenil	2-piridil	H	H	OMe	++	++	-	-
66	S	3,5-difluorofenil	2-piridil-N-oxido	H	H	OMe	+	+	++	±
67	S	3-clorofenil	2-nitrofenil	H	H	OMe	++	++	-	-
68	S	3-clanofenil	2-nitrofenil	H	H	OMe	+++	++	-	-
69	S	3-fluoro,5-trifluorometilfenil	2-nitrofenil	H	H	OMe	++	++	-	-
70	S	3-fluoro,6-trifluorometilfenil	2-nitrofenil	H	H	OMe	++	+	-	-
71	S	3-fluorofenil	2-nitrofenil	H	H	OMe	+++	++	-	-
72	S	3-metoxifenil	2-nitrofenil	H	H	OMe	++	+	-	-
73	S	3-metilfenil	2-nitrofenil	H	H	OMe	++	++	-	-
74	S	3-nitrofenil	2-nitrofenil	H	H	OMe	+++	++	-	-
75	S	3-piridil	2-nitrofenil	H	H	OMe	+++	++	-	-
76	S	3-trifluorometil,4-clorofenil	2-nitrofenil	H	H	OMe	+	+	-	-
77	S	3-trifluorometiloxifenil	2-nitrofenil	H	H	OMe	++	++	-	-
78	S	3-trifluorometilfenil	2-nitrofenil	H	H	OMe	++	++	-	-
79	S	4-(2-metilfiazoli)	2-nitrofenil	H	H	OMe	++	+	-	-
80	S	4-(3,5-dimetilisoxazoli)	2-nitrofenil	H	H	OMe	+	±	+	±
81	S	4-clorofenil	2-nitrofenil	H	H	OMe	+	+	+++	+
82	S	4-cianofenil	2-nitrofenil	H	H	OMe	++	+	-	-
83	S	4-fluorofenil	2-nitrofenil	H	H	OMe	++	++	-	-
84	S	4-metoxifenil	2-nitrofenil	H	H	OMe	+	±	±	++
85	S	4-metilfenil	2-nitrofenil	H	H	OMe	+	+	-	±

Comp. Numero	X	R ¹	R ²	R ³	R ⁴	R ⁵	ago EC50	ago eficacia	ant EC50	ant eficacia
86	S	4-morfolinil	2-nitrofenil	H	H	OMe	±	±	+	+
87	S	5-(2-clorotiazolil)	2-nitrofenil	H	H	OMe	++	+	-	-
88	S	5-(2-clorotiofenil)	2-nitrofenil	H	H	OMe	++	++	-	-
89	S	Ciclohexil	2-nitrofenil	H	H	OMe	++	+	+++	±
90	S	Fenil	2-nitrofenil	H	H	H	+	+	-	-
91	S	Fenil	2-nitrofenil	H	OMe	H	-	-	±	++
92	S	Fenil	2-nitrofenil	H	H	OMe	+++	++	-	-

nota 1: Escala EC50: +++ <5 nM; ++ entre 5 y 100 nM; + <1000; ± entre 1000 y 10000 nM; ->10000 nM.

nota 2: escala de eficacia (máxima actividad intrínseca, por ejemplo actividad intrínseca observada en la presencia de 100 nM DHT, fue fijada en 1.00): ++ ≥0.80: + entre 0.50 y 0.80; ± entre 0.20 y 0.50; -<0.20

La actividad androgénica (EC50, potencia y eficacia) de los compuestos en la Tabla 5 fue determinada en un bioensayo *in vitro* de células de ovarios de hamster Chino (CHO) establemente transfectadas con plásmido de expresión del andrógeno receptor humano y un plásmido reportero en el cual el MMTV promotor es vinculado al gen reportero de luciferasa. La línea de células CHO-AR-pMMTV-LUC 1G12-A5-CA es descrita en Schoonen et al. (J. Steroid Biochem. Molec. Biol. 2002; 74: 213-222). La actividad del andrógeno receptor de los compuestos fue determinada en la presencia de 0.1 µmol/l onapristone. La máxima eficacia en la presencia de 100 nmol/l DHT fue fijada como 100%. Las potencias son expresadas como porcentaje de actividad DHT.

Tabla 5 Actividad del andrógeno receptor

Compuesto Numero	X	R ¹	R ²	R ³	R ⁴	R ⁵	ago potencia	ago eficacia
93	S	4-píridil	2-nitrofenil	H	H	OMe	±	+
94	S	3,4,5-trifluorofenil	2-nitrofenil	H	H	OMe	+	++
95	S	2,3,5-trifluorofenil	2-nitrofenil	H	H	OMe	±	++
96	S	4-clor-3-píridil	2-nitrofenil	H	H	OMe	±	±
97	S	3,5-difluorofenil	2-nitrofenil	H	H	NHCOCH ₂ F	+	++
98	S	3,5-difluorofenil	2-nitrofenil	H	H	NHCOCHF ₂	++	+
99	S	3,5-difluorofenil	2-nitrofenil	H	H	NHCOEt	±	+
100	S	2-píridil	2-nitrofenil	H	H	NHCOCH ₂ F	+	++
101	S	2-píridil	2-nitrofenil	H	H	NHCOMe	+	+
102	S	2-píridil	2-nitrofenil	H	H	NHCOEt	+	+
103	S	3-píridil	2-nitrofenil	H	H	NHCOMe	+	+
104	S	3-píridil	2-nitrofenil	H	H	NHCOCH ₂ F	+	-
105	S	3-píridil	2-nitrofenil	H	H	NHCOEt	+	±
106	S	3,5-difluorofenil	2-nitrofenil	H	H	NHSO ₂ Me	+	++
107	S	3,5-difluorofenil	2-nitrofenil	H	H	NHSO ₂ -(3-tiofeno)	+	++
108	S	3,5-difluorofenil	2-nitrofenil	H	H	NHSO ₂ -(1-Me-4-imidazolil)	+	++
109	S	2-píridil	2-nitrofenil	H	H	CONMe ₂	+	++
110	S	2-píridil	2-nitrofenil	H	H	CONHMe	+	+
111	S	2-píridil	2-nitrofenil	H	H	CONH ₂	±	±
112	S	3-píridil	2-nitrofenil	H	H	CONHMe	+	±
113	S	3-píridil	2-nitrofenil	H	H	CONHEt	+	+
114	S	3-píridil	2-nitrofenil	H	H	CONH ciclopropil	+	++
115	S	3,5-pirimidil	2-nitrofenil	H	H	OMe	++	+
116	S	2,4-pirimidil	2-nitrofenil	H	H	OMe	+	+
117	S	2,5-piracil	2-nitrofenil	H	H	OMe	+	+
118	S	3,5-pírimidil	2-nitrofenil	H	H	NHCHO	++	+
119	S	2-píridil	2-nitrofenil	H	H	CN	++	++
120	S	2-píridil HCl sal	2-nitrofenil	H	H	CN	++	++

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Compuesto Numero	X	R ¹	R ²	R ³	R ⁴	R ⁵	ago potencia	ago eficacia
121	S	3-piridil	2-nitrofenil	H	H	CN	+	++
122	S	4-piridil	2-nitrofenil	H	H	CN	+	+
123	S	3,5-pirimidil	2-nitrofenil	H	H	CN	++	++
124	S	2,4-pirimidil	2-nitrofenil	H	H	CN	++	++
125	S	3-cianofenil	2-nitrofenil	H	H	CN	+	++

nota 1: escala de potencia: ++>5%; + entre 1% y 5%; ± entre 0.1% y 1%.

nota 2: escala de eficacia (máxima actividad intrínseca, por ejemplo actividad intrínseca observada en la presencia de 100 nM DHT, fue fijada en 1.00): ++ ≥0.80; + entre 0.50 y 0.80; ± entre 0.20 y 0.50; -<0.20

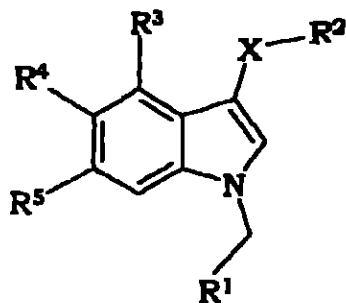
La determinación de enlazamiento competitivo al andrógeno receptor humano citoplásmico desde células recombinantes CHO es utilizado para estimar la afinidad de enlazamiento (RBA) de un compuesto de ensayo para receptores andrógenos presentes en el citosol preparado de la línea de célula recombinante CHO, CHO-AR-PMMTV-LUC 1G12-A5-CA.

Compuesto 63 y compuesto 92 fueron ensayados en este ensayo de enlace y se encontró que ambos compuestos tienen una afinidad de enlace relativa >1% relativa a DHT.

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REVINDICACIONES

1. Un compuesto que tiene la formula



Donde

X es S, SO o SO₂

R¹ es una estructura anular no saturada o saturada, monociclica, hetero u homociclica, de 5- o 6- miembros opcionalmente sustituida con uno o mas sustituyentes seleccionados de los grupos de halógenos, CN, (1C-4C)fluoroalkil, nitro, (1C-4C)alkil, (1C-4C)alkoxi o (1C-4C)fluoroalkoxi.

R² es 2-nitrofenil, 2-cianofenil, 2-hidroximetil-fenil, piridina-2-il,piridina-2-il-N-oxido,2-benzamida, metil ester del ácido 2- benzoico o 2-metoxifenil;

R³ es H, halógeno o (1C-4C)alkil;

R⁴ es H, OH, (1C-4C)alkoxi o halógeno;

R⁵ es H, OH, (1C-4C)alkoxi; NH₂, CN, halógeno, (1C-4C)fluoroalkil, NO₂, hidroxi (1C-4C)alkil, CO₂H, CO₂(1C-6C)alkil, o

R⁵ es NHR⁶, donde R⁶ es (1C-6C)acil opcionalmente sustituido con uno o mas halógenos, S(O)₂(1C-4C)alkil, o S(O)₂aril opcionalmente sustituido con (1C-4C)alkil o uno o más halógenos.

R⁵ es C(O)N(R⁸ o R⁹) donde R⁸ y R⁹ cada uno independientemente son H,(3C-6C)cicloalkil, o CH₂R¹⁰, donde R¹⁰ es H, (1C-5C)alkil, (1C-5C)alkenil, hidroxi(1C-3C)alkil, (1C-4C)alkilester de carboxi(1C-4C)alkil,(1C-3C)alkoxi(1C-3C)alkil, (mono o di(1C-4C)alkil)aminometil, (mono- o di(1C-4C)alkil)aminocarbonil, o un

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anillo no aromático o aromático, monocíclico, hetero u homocíclico, de 3-, 4-, 5- o 6- miembros o R^8 y R^9 forman conjuntamente con el N un anillo no saturado o saturado, heterocíclico de 5 o 6 miembros opcionalmente sustituido con (1C-4C)alkil; o una sal o forma hidratada a partir de ellos.

2. Un compuesto de acuerdo con la reivindicación 1, caracterizado en que

R^1 es una estructura anular no saturada o saturada, monocíclica, hetero u homocíclica de 5-o 6-miembros, opcionalmente sustituida con uno o mas sustituyentes seleccionados del grupo de halógeno, CN, CF_3 , nitro, metoxi, trifluorometoxi o metil;

R^2 es 2-nitrofenil, 2-cianofenil, 2-hidroximetil-fenil, piridina-2-il, piridina-2-il-N-oxido, 2-benzamida, 2- metil éster de ácido benzoico o 2-metoxifenil;

R^3 es H, halogeno o (1C-2C)alkil;

R^4 es H o F.

3. Un compuesto de acuerdo a la reivindicación 2, caracterizado en que:

R^5 es H, OH, (1C-4C)alkoxi, CN, halógeno, (1C-4C)fluoroalkil, NO_2 , hidroxil(1C-4C)alkil, $CO_2(1C-6C)alkil$, o

R^5 es NHR^6 , donde R^6 es (1C-6C)acil opcionalmente sustituido con uno o mas halógenos, $S(O)_2(1C-4C)alkil$ o $S(O)_2aril$ opcionalmente sustituido con (1C-4C)alkil o uno o mas halógenos, o

R^5 es $C(O)N(R^8, R^9)$, donde R^8 y R^9 cada uno independientemente son H, (3C-6C)cicloalkil, o CH_2R^{10} , donde R^{10} es H, (1C-5C)alkil, (1C-5C)alkenil, hidroxil(1C-3C)alkil, (1C-4C)alkilester de carboxil(1C-4C)alkil, (1C-3C)alkoxil(1C-3C)alkil, (mono- o di(1C-4C)alkil)aminometil, (mono- o di(1C-4C)alkil)-aminocarbonil, o un anillo no aromático o aromático, monocíclico, hetero u homocíclico de 3-, 4-, 5- o 6- miembros, o R^8 y R^9 forman conjuntamente con el N un anillo no saturado o saturado, heterocíclico de 5 o 6 miembros opcionalmente sustituido con (1C-4C)alkil.

4. Un compuesto de acuerdo con la reivindicación 3, caracterizado en que

R^3 es H o halógeno;

R^5 es H, OH, (1C-4C)alkoxi, CN, F, Cl, CF_3 , NO_2 , hidroxi(1C-4C)alkil, CO_2 (1C-6C)alkil, o

R^5 es NHR^8 , donde R^8 es (1C-6C)acil opcionalmente sustituido con uno o mas halógenos o

R^5 es $C(O)N(R^8, R^9)$, donde R^8 y R^9 cada uno independientemente son H, (3C-6C)cicloalkil, o CH_2R^{10} , donde R^{10} es H, (1C-5C)alkil, (1C-5C)alkenil, hidroxi(1C-3C)alkil, (1C-2C)alkilester de carboxi(1C-4C)alkil, (1C-3C)alkoxi(1C-3C)alkil, (mono- o di(1C-4C)alkil)aminometil, (mono- o di(1C-4C)alkil)aminocarbonil, (3C-5C)cicloalkil, o un anillo heterocíclico de 5- miembros.

5. Un compuesto de acuerdo a la reivindicación 4, caracterizado en que

X es S o SO_2 ;

R^2 es 2-nitrofenil, 2-hidroximetil-fenil, 2-benzamida, 2-metoxifenil, 2-cianofenil o piridina-2-il;

R^3 es H o F;

R^5 es H, OH, (1C-2C)alkoxi, CN, F, Cl, CF_3 , NO_2 , hidroxi(1C-4C)alkil, CO_2 (1C-4C)alkil, o

R^5 es NHR^8 , donde R^8 formil, acetil, fluoroacetil, difluoroacetil o trifluoroacetil o

R^5 es $C(O)N(R^8, R^9)$, donde R^8 es H, y R^9 es H, ciclopropil o R^9 es CH_2R^{10} , donde R^{10} es H, (1C-2C)alkil, hidroxi(1C-2C)alkil, metoxi(1C-2C)alkil, ciclopropil.

6. Un compuesto de acuerdo a la reivindicación 5 caracterizado en que:

X es S;

R^1 es 3,5 difluorofenil, piridina-2-il, piridina-3-il, pirimidina-5-il, pirimidina-4-il, pirazina-2-il, 3-fluorofenil, 3-cianofenil, o 3-nitrofenil;

R^2 es 2-nitrofenil, 2-hidroximetil-fenil, 2-metoxifenil, 2-cianofenil o piridina-2-il;

R^3 es H;

R^5 es OH, (1C-2C)alkoxi, CN, CF_3 , NO_2 , hidroxil(1C-4C)alkil, $CO_2(1C-4C)alkil$, o NHR^6 donde R^6 es formil, acetil, fluoroacetil, difluoroacetil, o trifluoroacetil.

7. Un compuesto de acuerdo a la reivindicación 6 caracterizado en que:

R^1 es 3,5 difluorofenil, piridina-2-il, piridina-3-il; pirimidina-5-il, pirimidina-4-il, o pirazina-2-il;

R^2 es 2-nitrofenil, o 2-hidroximetil-fenil;

R^5 es OH, (1C-2C)alkoxi, CN, hidroxil(1C-4C)alkil, o NHR^6 donde R^6 es formil, acetil, fluoroacetil, difluoroacetil, o trifluoroacetil.

8. Un compuesto de acuerdo a la reivindicación 7 caracterizado en que:

R^1 es 3,5 difluorofenil, piridina-2-il, piridina-3-il, pirimidina-5-il o pirimidina-4-il;

R^2 es 2-nitrofenil;

R^5 es OH, (1C-2C)alkoxi, CN, o NHR^6 donde R^6 es formil, acetil, fluoroacetil, difluoroacetil, o trifluoroacetil.

9. Un compuesto de acuerdo a la reivindicación 8 seleccionado del grupo consistente de 6-Metoxi-3-(2-nitro-fenilsulfanil)-1-pirimidina-5-ilmetil-1H-indol, 3-(2-Nitro-fenilsulfanil)-1-piridina-2-ilmetil-1H-indol-6-carbonitrilo, 3-(2-Nitro-fenilsulfanil)-1-piridina-2-ilmetil-1H-indol-6-carbonitrilo-clorhidrato, 3-(2-Nitro-fenilsulfanil)-1-pirimidina-5-ilmetil-1H-indol-6-carbonitrilo, 3-(2-Nitro-fenilsulfanil)-1-pirimidina-4-ilmetil-1H-indol-6-carbonitrilo, N-[1-(3,5 difluoro-bencil)-3-(2-nitro-fenilsulfanil)-1-H-indol-6-il]-2-fluoro-acetamida, y N-[3-(2-Nitro-fenilsulfanil)-1-pirimidina-5-ilmetil-1H-indol-6-il]-formamida.

10. Un compuesto de acuerdo a la reivindicación 5, caracterizado en que:

X es S;

R¹ es 3,5 difluorofenil, piridina-2-il, piridina-3-il, 3-fluorofenil, 3-cianofenil, o 3-nitrofenil;

R² es 2-nitrofenil, o 2-hidroximetil-fenil, 2-metoxifenil, 2-cianofenil o piridina-2-il;

R³ es H;

R⁵ es C(O)N(R⁸,R⁹), donde R⁸ es H, y R⁹ es H o CH₂R¹⁰, donde R¹⁰ es H, (1C-2C)alkil, hidroxi(1C-2C)alkil, o metoxi(1C-2C)alkil.

11. Un compuesto de acuerdo a la reivindicación 10, caracterizado en que

R¹ es 3,5 difluorofenil, piridina-2-il o piridina-3-il;

R² es 2-nitrofenil, o 2-hidroximetil-fenil;

R⁵ es C(O)N(R⁸,R⁹), donde R⁸ es H, y R⁹ es H y R⁹ es CH₂R¹⁰, donde R¹⁰ es H, (1C-2C)alkil

12. Un compuesto de acuerdo a la reivindicación 11 el cual es metilamida del ácido 1-(3,5-Difluoro-bencil)-3-(2-nitro-fenilsulfanil)-1H-indol-6-carboxílico.

13. Un compuesto de acuerdo a la reivindicación 4, caracterizado en que

X es S;

R¹ es 3,5 difluorofenil, piridina-2-il, piridina-3-il, 3-fluorofenil, 3-cianofenil, o 3-nitrofenil;

R² es 2-nitrofenil, 2-hidroximetil-fenil, 2-metoxifenil, 2-metoxifenil, 2-cianofenil o piridina-2-il;

R³ es H;

R⁵ es C(O)N(R⁸,R⁹), donde R⁸ y R⁹ cada uno independientemente son H o CH₂R¹⁰,

donde R¹⁰ es H, (1C-5C)alkil,(1C-5C)alkenil, hidroxi(1C-3C)alkil, (1C-3C)alkoxi(1C-3C)alkil o (mono- o di(1C-4C)alkil)aminometil

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relacionado e insuficiencia andr6gena., que comprende la administraci6n de una cantidad farmac6uticamente efectiva de un compuesto de acuerdo a cualquiera de las reivindicaciones 1 –15 a un sujeto en necesidad de ellos.

Traducido por : Guillermo Angel Reyes

FORMATO DE DIGITALIZACION
RELACION DE ANEXOS



Royal
Technologies S.A.
Bogotá, Colombia - República de Colombia

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Expediente No		050.53 827	No de Folio
Item		No de Unidades	
1	CD		
2	DVD		
3	REVISTA		
4	LIBRO		
5	PERIODICO		
6	DISQUETES		
7	SOBRE DE MANILA		
8	SOBRE BLANCO TAMAÑO CARTA	7	✓
9	SOBRE BLANCO TAMAÑO OFICIO		
10	OTROS:		

Observaciones:

Contiene Art. final

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SUPERINTENDENCIA Y PROTECCIÓN
Radicación : 850176089-2
Fecha (AMBI): 2005-05-16 17:01:17
Tipo : R11 D11-001001 70 C000 N001 411 DOCUMENTOS
Folios: 142

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 05 - 35,940
FECHA : MAYO 16 DE 2005

***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
CAVELIER ABOGADOS	CONSIGNACION	BANCO POPULAR	050-00110-6	40116714	16/05/2005	39,471,000.00

***** CONCEPTO *****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-01 SOLICITUDES	1 TRAMITES DE SOL. DE PATENTE DE IN	443,000.00
		TOTAL :	\$ 443,000.00

SON: CUATROCIENTOS CUARENTA Y TRES MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____

66 11214-841-029-6

REQUISITOS NECESARIOS PARA PRESENTACION Y AGILIZACION DEL TRAMITE

	USUARIO	RADICADOR
PATENTE DE INVENCION ✓	()	() ✓
- Indicación de que se solicita la concesión de una patente.	()	() ✓
- Datos de identificación del solicitante o de la persona que se 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 o 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 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 de trazado	()	()
- Comprobante de pago de las tasas establecidas.	()	()

COMPLETA () INCOMPLETA ()

Firma Responsable:

Fecha:

165

Industria y Comercio
SUPERINTENDENCIA

Folio 165

2020
Bogotá DC

Doctor(a)
EMILIO FERRERO
Apoderado(a) y/o Representante
AKZO NOBEL N.V.

REFERENCIA:	Radicación No.	05 53827
	Solicitud Internacional	PCT/EP2003/050783
	Fecha límite inicio fase Nacional	07 - 08 - 2005
	Trámite	011
	Evento	379
	Actuación	416
	Oficio No.	793
	Folios	001

Teniendo en cuenta que la solicitud de privilegio de patente que se tramita bajo el expediente indicado en la referencia, reúne los requisitos de forma establecidos en la Decisión 486 de la Comisión de la Comunidad Andina, el Tratado de Cooperación en Materia de Patentes (PCT), el Reglamento y la Circular Única de la Superintendencia de Industria y Comercio, se envía el extracto de la solicitud a la Oficina de Comunicaciones para efecto de su publicación en la Gaceta de Propiedad Industrial.

Cúmplase
Dado en Bogotá DC

13 SET. 2005

ALIX CESPEDÉS DE VERGEL
Jefe de la División de Nuevas Creaciones

Al contestar favor indque el número de
radicación consignado en el sticker

Sede Centro: Carrera 13 No. 27-00 Pisos 2, 5, 7 y 10
Commutador: 3 820840 Fax: 3 505220
Sede CAN: Tr. 40A No. 38-50 3153265 al 69
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Bogotá D.C. - Colombia