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Act 411 PRESENTACION Folios 395

FORMULARIO UNICO DE SOLICITUD DE PATENTE
PCT
ENTRADA EN FASE NACIONAL

SOLICITUD DE:

①

☒ Patente de Invención.☐ Patente de Modelo de Utilidad.☐ Capítulo I☒ Capítulo II

SOLICITANTE (71)

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C.C.



NIT



C.E.



Otro



Cual

Número

③

REPRESENTANTE
O APODERADO (74)

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Número

2.930.616

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2698

④

INVENTOR (ES) (72)

VER ANEXO #1

⑤

PCT (86)

Solicitud Internacional No.

PCT/EP2007/001212

Fecha

13/02/2007

Publicación Internacional No.

WO 2007/093364 A1

Fecha

23/08/2007

⑥

Título (54)

**ARILDIHIDROISOQUINOLINONAS SUSTITUIDAS CON AZACICLILO, PROCEDIMIENTO
PARA SU PREPARACIÓN Y SU USO COMO MEDICAMENTOS**

⑦

Clasificación Internacional (51)

C07D 401/10, A61P 3/10, A61K 31/4355

⑧

Prioridad

(33) País de Origen

(32) Fecha

(31) Número de Solicitud

SI ☒NO ☐

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15/02/2006

10 2006 007 045.3

⑨

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08-21,313 y 08-60,640

Fecha

Marzo 11 y Julio 29 de 2008

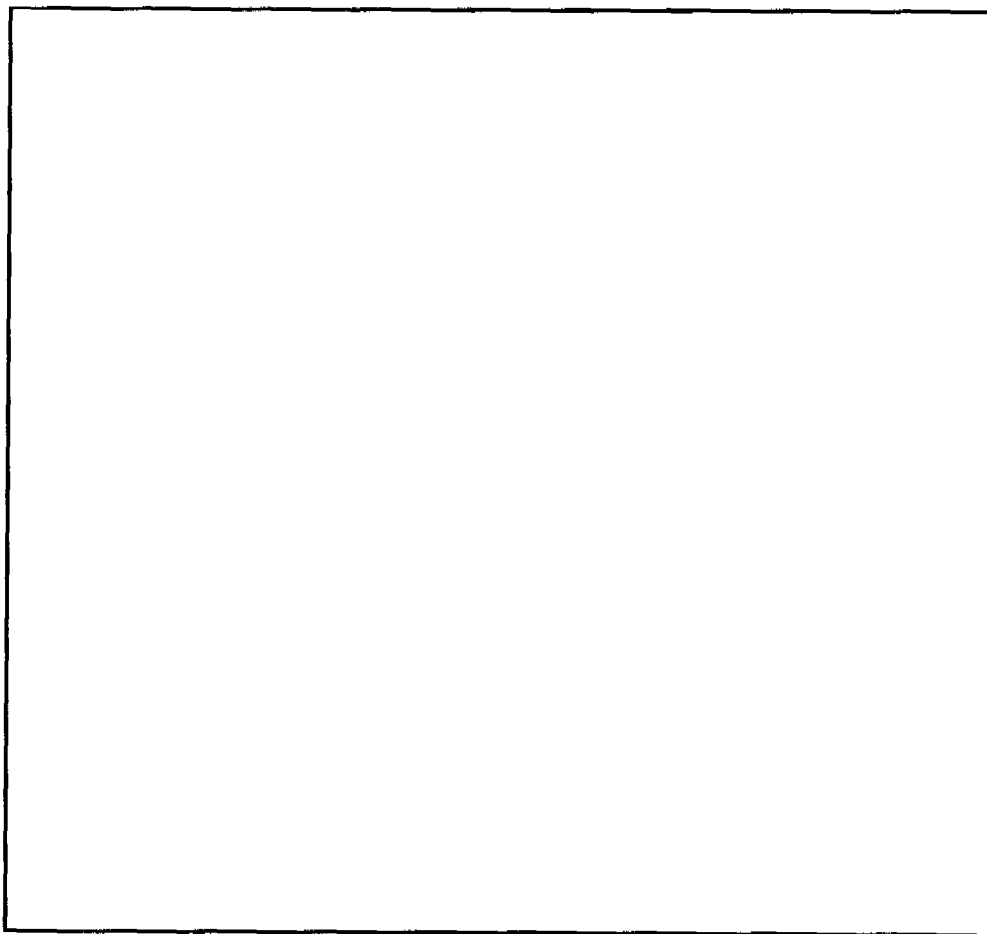
10

Anexos

- ☒ Comprobante de pago de la tasa de presentación de la solicitud.
- ☒ Documento que acredita la existencia y representación legal cuando el solicitante sea persona jurídica.
- ☒ Poderes, si fuere el caso, junto con la sustitución del mismo a mi favor
- ☐ 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 internacional efectuado por la Autoridad Internacional de Examen Preliminar (IPEA).
- ☐ Traducción del examen preliminar internacional efectuado por la IPEA.
- ☐ De ser el caso, copia del contrato de acceso.
- ☐ De ser el caso, documento que acredite la licencia o autorización de uso de conocimientos tradicionales de las comunidades indígenas.
- ☐ De ser el caso, certificado de depósito del material biológico.
- ☐ Arte final 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.
- ☐ De ser el caso, modificaciones efectuadas a la solicitud internacional.
- ☒ Otros **Tarjeta de Propietario y Extracto para la publicación**

11

FIGURA CARACTERISTICA:



12

Solicito la concesión de la patente,

NOMBRE: DR. LUIS PATIÑO LLEYVA

FIRMA:

[Handwritten signature]

C.C. No. 2'930.616 Bogotá - TPA 2.698 C.S.J.

+ -

NIT : 800176089-2

CERTIFICACION DE EXCEDENTE : 8 - 21.313
FECHA : MARZO 11 DE 2008

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



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Tra: 11 PATENTEYII Eve: 379 FASE NACIONALII
Act: 411 PRESENTACION Folios: 395

Ri

***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PAGO	Vr. PAGO
JAIRO SANCHEZ	CONSIGNACION	BANCO DE BOGOTA	062754387	4636880	07/03/2008	158,000.00

***** CONCEPTO *****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-09	OTROS SERVICIOS DE PROPIEDAD I	
		99 OTROS SERVICIOS ADMINISTRATIVOS	158,000.00
		TOTAL :	\$ 158,000.00

SON: CIENTO CINCUENTA Y OCHO MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL ASUNTO No. _____

ESTA CERTIFICACION DE EXCEDENTE DE PAGO SOLO PODRA SER UTILIZADA
COMO PARTE DE LA CANCELACION DE UNA TARIFA VIGENTE Y NO PODRA SER
SUSTITUIDA POR NINGUN RECIBO.

**G.HOLLMANN RESTREPO
ABOGADOS LTDA**

The undersigned SANOFI AVENTIS... , acting on behalf of and representing of ... , domiciled in 174 Avenue de France, 75013 PARIS, FRANCE, hereby

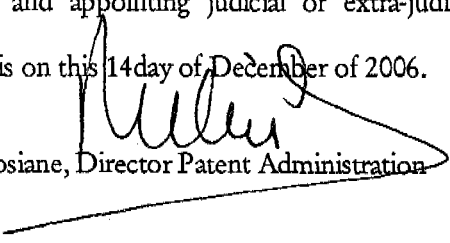
appoint(s) **LUIS PATIÑO LEYVA** and/or **GUSTAVO HOLLMANN RESTREPO**, domiciled in Bogotá D.C., Republic of Colombia , as our true and legal attorney with the necessary powers:

- 1) To apply to the administrative, judicial and police authorities of the Republic of Colombia, in any instance or appeal, for obtaining registration of patents, ~~utility models, industrial designs and models, commercial~~ ~~ensigns and names, trademarks, slogans, health licenses, copyrights and domain names~~ as well as their assignments, extensions, renewals and changes of name;
- 2) To prepare, apply for, obtain, execute and register contracts, licenses, authorizations and registrations of any kind;
- 3) To intervene as plaintiff or defendant, in any instance or appeal, before any judge, court, tribunal, corporation, public officer or authority in any judicial, administrative or police action, such as: action dealing with commercial ensigns and names; oppositions against trademark registrations; caducity and nullity actions; recovery actions, actions arising from obtainment and working of license agreements; actions dealing with unfair competition; criminal actions; actions claiming indemnity for damages, complaints or remarks on all sort of industrial property matters; the performance of precautionary measures, and in any other similar action, measure or appeal related to intellectual property matters.

To this effect, I (we) hereby authorize him to file applications, make descriptions, protests, amendments, declarations, oppositions, cancellations, appeals and claims; to pay taxes, quotas and liens as provided by Law; to waive or abandon granted rights or rights in process of being granted, to receive all kind of documents and securities; to issue the respective releases and, in general, to take, before said authorities, pertinent steps to the above mentioned purposes and take all measures they may deem advisable to protect my (our) interests, with all other necessary legal faculties, and I (we) hereby declare as good and valid whatever the attorneys should do to my (our) benefit.

This power comprises the authority to ratify or confirm on my (our) behalf any action, as well as the faculty of receiving, desisting, transacting, compromising, substituting and revoking substitutions, taking notifications, and appointing judicial or extra-judicial attorneys.

Signed in Paris on this 14 day of December of 2006.


MERLIER Josiane, Director Patent Administration

**G. HOLLMANN RESTREPO
ABOGADOS LTDA**

Yo (nosotros) , obrando en nombre propio y representación de, con domicilio en , nombro(amos) a **LUIS PATIÑO LEYVA** y/o **GUSTAVO HOLLMANN RESTREPO** , con domicilio en Bogotá D.C., República de Colombia, apoderado verdadero y legal, con poder especial, amplio y suficiente:

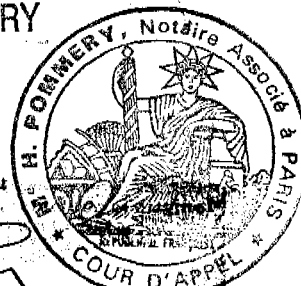
- 1) Para recabar de las oficinas y autoridades colombianas administrativas, judiciales y de policía en cualquier instancia o recurso, la obtención de patentes de invención, modelos de utilidad, dibujos y modelos industriales, registro de marcas, registro de lemas comerciales, depósito de nombres y enseñas comerciales, registros sanitarios, derechos de autor y nombres de dominio así como sus traspasos, prórrogas, renovaciones y cambios de nombre;
- 2) Elaborar, tramitar, solicitar, obtener, realizar, ejecutar y registrar contratos, licencias, autorizaciones y registros de cualesquiera clases;
- 3) Intervenir como demandante o como demandado en cualquier instancia y recurso y ante cualquier juez, entidad, corporación, funcionario público o autoridad en acciones judiciales, administrativas y de policía, tales como acciones derivadas de nombre o enseña comerciales; acciones reivindicatorias; acciones derivadas de la obtención o explotación de licencias; acciones de competencia desleal, demandas penales y civiles; acciones de indemnización de perjuicios, reclamos, u observaciones a cualquier asunto sobre propiedad intelectual; al ejercicio de medidas cautelares y cualesquiera otras acciones, medidas o recursos similares relacionados con la propiedad intelectual.

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Este poder comprende la facultad de ratificar, o confirmar en mi (nuestro) nombre lo actuado, así como la facultad de recibir, desistir, transigir, comprometer, sustituir y revocar sustituciones, recibir notificaciones y nombrar apoderados judiciales o extrajudiciales.

Firmado en Paris el de

Je soussigné Me **Hervé POMMERY**
Notaire à Paris, certifie matériellement
la signature de Madame
Josiane MERLIER
apposée sur le présent document.
Cette certification ne comporte aucune
vérification de l'exactitude des faits et
actes mentionnés dans le présent document



30 JUL 2008

CERTIFICATION

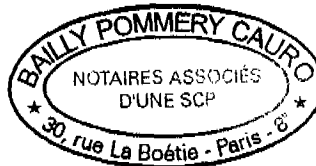
COMPANIES

The undersigned Hervé POMMERY certifies: that the preceding signature(s) reading [Signature] (are) authentic; that the signer(s) at present fill(s) the position of Director of Administrative he (they) is (are) empowered to grant this power; and that said company exists, accomplishes its social object and is organized in FRANCE in accordance with the Laws of FRANCE. All the foregoing facts are known to me, due to my having examined the respective documents to which I attest.

Signed in PARIS on this 19th day of February of 2007.

Hervé POMMERY
NOTAIRE

[Handwritten signature of Hervé Pommery]



CERTIFICACIÓN

SOCIEDADES

El(la) infrascrito(a) _____ certifica: que la(s) firma(s) que antecede(n) y dice(n) _____ es (son) auténtica(s); que el (los) signatario(s) desempeña(n) actualmente el cargo(s) de _____ de _____; que tiene(n) facultad para otorgar este poder; y que dicha compañía existe, cumple su objeto social y está organizada en _____ conforme a las Leyes de _____.

Todos los hechos anteriores le constan, por haber examinado los documentos respectivos y de todo ello da fe.

Firmado en _____ el _____ de _____ de _____.

APOSTILLE

(Convention de La Haye du 5 octobre 1961)

1. République française

Le présent acte public

2. a été signé par Mme POMMERY

3. agissant en qualité de Notaire

4. est revêtu du sceau/timbre de son étude

Attesté

5. à PARIS

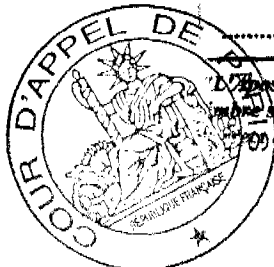
6. le 22/02/2007

7. par le Procureur général près la Cour d'appel de PARIS

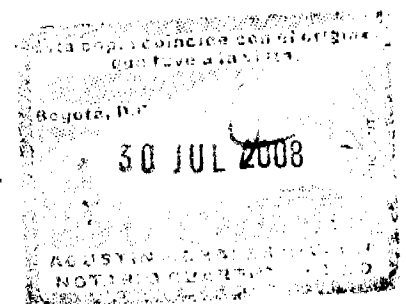
8. sous n° 17350

9. Sceau :

10. Signature :



"L'Apostille confirme seulement l'authenticité de la signature, du sceau ou du timbre sur le document. Elle ne signifie pas que le contenu du document est vrai ou que la République française approuve son contenu."



EDGAR HERMES PAIXÃO PARDO

Traductor oficial - Traducteur assermenté

Español - Français
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Traducción oficial, parcial, de un documento que me fue presentado en lengua francesa, trabajo realizado en función de mi cargo de traductor oficial de esta ciudad de Santafé de Bogotá.

Contenido del documento:

PODER de SANOFI AVENTIS, 174, Avenue de France, 75013 París, Francia, para Luis Patiño Leyva y/o Gustavo Hollmann Restrepo.

Firma ilegible, Josiane Merlier.

El suscrito, Hervé Pommery, notario en París, autentico la firma de Josiane Merlier. Esta autenticación no implica aceptación del contenido del documento. Firma ilegible y sello de la notaría. París, 19 de febrero de 2007.

Apostillas. (Convención de La Haya del 5 de octubre de 1961).

1. República Francesa. El presente documento público. 2. Fue firmado por el señor Pommery. 3. Actuando en calidad de notario. 4. Lleva el sello de la notaría.

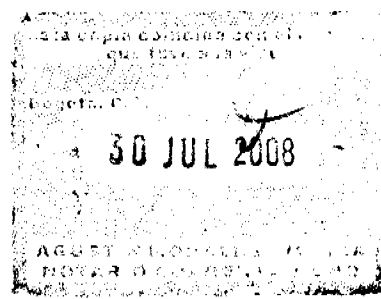
CERTIFICADO:

5. En París, 6. El 20 de diciembre de 2006 y el 22 de febrero de 2007. 7. Por el Procurador General de la Corte de Apelaciones de París, 8. bajo los números 174190 y 173350. 9. Sello de la Corte. 10. Firma ilegible.

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Era todo cuanto contenía el documento. Es una traducción fiel y parcial.

Edgar Hermes Paixão Pardo
Francés - Español
D.E. 1706 Minjusticia



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C07D 413/14 (2006.01)	A61P 3/10 (2006.01)
C07D 417/14 (2006.01)	A61K 31/4355 (2006.01)
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C07D 487/10 (2006.01)	

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(72) Inventors; and

(75) Inventors/Applicants (for US only): **SCHWINK, Lothar** [DE/DE]; Sanofi-Aventis Deutschland GmbH, 65926 Frankfurt am Main (DE). **STENGELIN, Siegfried** [DE/DE]; Sanofi-Aventis Deutschland GmbH, 65929 Frankfurt am Main (DE). **GOSEL, Matthias** [DE/DE]; Sanofi-Aventis Deutschland GmbH, 65929 Frankfurt am

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

(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

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

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: **AZACYCLYL-SUBSTITUTED ARYLDIHYDROISOQUINOLINONES, PROCESS FOR THEIR PREPARATION AND THEIR USE AS MEDICAMENTS**

(57) Abstract: The invention relates to azacyclyl-substituted arylldihydroisoquinolinones and their derivatives, and their physiologically tolerated salts and physiologically functional derivatives, their preparation, medicaments comprising at least one azacyclyl-substituted arylldihydroisoquinolinone of the invention or its derivative, and the use of the azacyclyl-substituted arylldihydroisoquinolinones of the invention and their derivatives as MCH antagonists.

WO 2007/093364 A1

AZACYCLYL-SUBSTITUTED ARYLDIHYDROISOQUINOLINONES, PROCESS FOR THEIR
PREPARATION AND THEIR USE AS MEDICAMENTS

5 The invention relates to azacyclyl-substituted aryldihydroisoquinolinones and their derivatives, and their physiologically tolerated salts and physiologically functional derivatives, their preparation, medicaments comprising at least one azacyclyl-substituted aryldihydroisoquinolinone of the invention or its derivative, and the use of the azacyclyl-substituted aryldihydroisoquinolinones of the invention and their derivatives as medicaments.

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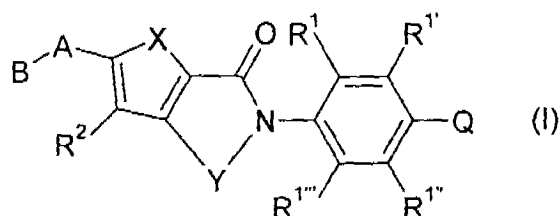
Compounds similar in their overall structure to the azacyclyl-substituted aryl-dihydroisoquinolinones and their derivatives described in the present application and having a pharmacological effect have been described in the prior art. Thus, for example, WO 01/72712 describes inhibitors of factor Xa which have a substituted
15 isoquinolinone basic structure. WO 2005/103039 discloses 2-(3-aminopyrrolidin-1-yl)pyridines having an MCH-antagonistic effect for the treatment of obesity.

Compounds having an MCH-antagonistic effect for the treatment of obesity are described in the prior art (examples: WO2005047293, WO2004092181,
20 WO2005103039, WO2004024702, WO2005042541, WO2003033476, WO2003033480, WO2001021577, WO2003035624, WO2002089729, WO2002006245, WO2002002744, WO2002057233, WO2003045313, WO2003097047, WO2002010146, WO 2003087044).

25 The invention was based on the object of providing compounds which bring about a weight reduction in mammals and which are suitable for the prevention and treatment of obesity and diabetes and of their diverse sequelae.

Surprisingly, a series of compounds which modulate the activity of MCH receptors has
30 been found. In particular, the compounds are notable for an antagonism of the MCH1R.

The invention therefore relates to compounds of the formula I,



5 in which the meanings are

R1, R1', R1'', R1'''

independently of one another H, F, Cl, Br, I, OH, CF₃, NO₂, CN, OCF₃, O-(C₁-C₆)-alkyl, O-(C₁-C₄)-alkoxy-(C₁-C₄)-alkyl, S-(C₁-C₆)-alkyl, (C₁-C₆)-alkyl, (C₂-C₆)-alkenyl, (C₃-C₈)-cycloalkyl, O-(C₃-C₈)-cycloalkyl, (C₃-C₈)-cycloalkenyl, (C₂-C₆)-alkynyl, (C₀-C₈)-alkylene-aryl, O-(C₀-C₈)-alkylene-aryl, S-aryl, N(R3)(R4), SO₂-CH₃, COOH, COO-(C₁-C₆)-alkyl, CON(R5)(R6), N(R7)CO(R8), N(R9)SO₂(R10), CO(R11), (C(R12)(R13))_x-O(R14);

preferably independently of one another H, F, Cl, Br, OH, CF₃, NO₂, CN, OCF₃,

15 O-(C₁-C₆)-alkyl, (C₁-C₄)-alkoxy-(C₁-C₄)-alkyl, S-(C₁-C₆)-alkyl, (C₁-C₆)-alkyl, (C₂-C₆)-alkenyl, (C₃-C₈)-cycloalkyl, O-(C₃-C₈)-cycloalkyl, (C₂-C₆)-alkynyl, O-(C₀-C₈)-alkylene-aryl, CO(C₁-C₆)-alkyl;

particularly preferably H, F, Cl, Br, CF₃, CN, OCF₃, O-(C₁-C₆)-alkyl, (C₁-C₄)-alkoxy-(C₁-C₄)-alkyl, (C₁-C₆)-alkyl;

20 very particularly preferably H, F, Cl, O-(C₁-C₆)-alkyl, (C₁-C₆)-alkyl;

where preferably at least two, particularly preferably at least three or all radicals R1, R1', R1'' and R1''' are H;

R3, R4, R5, R6, R7, R9

25 independently of one another H, (C₁-C₈)-alkyl;

or

R3 and R4, R5 and R6

form independently of one another optionally together with the nitrogen atom to which they are bonded a 5-6 membered ring which, apart from the nitrogen atom,

may also comprise 0-1 further heteroatoms from the group of NH, N-(C₁-C₆)-alkyl, oxygen and sulfur;

R8, R10, R11

5 independently of one another H, (C₁-C₈)-alkyl, aryl; preferably independently of one another H, (C₁-C₈)-alkyl;

R12, R13

independently of one another H, (C₁-C₈)-alkyl;

10

R14 H, (C₁-C₆)-alkyl, aryl; preferably H, (C₁-C₆)-alkyl;

x 0, 1, 2, 3, 4, 5, 6;

15 R2 H, F, Cl, Br, I, OH, CF₃, NO₂, CN, OCF₃, O-(C₁-C₆)-alkyl, O-(C₁-C₄)-alkoxy-(C₁-C₄)-alkyl, S-(C₁-C₆)-alkyl, (C₁-C₆)-alkyl, (C₂-C₆)-alkenyl, (C₃-C₈)-cycloalkyl, O-(C₃-C₈)-cycloalkyl, (C₃-C₈)-cycloalkenyl, (C₂-C₆)-alkynyl, (C₀-C₈)-alkylene-aryl, O-(C₀-C₈)-alkylene-aryl, S-aryl, N(R15)(R16), SO₂-CH₃, COOH, COO-(C₁-C₆)-alkyl, CON(R17)(R18), N(R19)CO(R20), N(R21)SO₂(R22), CO(R23),
20 (C(R24)(R25))_x-O(R26);
preferably H, F, Cl, Br, I, OH, CF₃, NO₂, CN, OCF₃, O-(C₁-C₆)-alkyl, (C₁-C₄)-alkoxy-(C₁-C₄)-alkyl, (C₁-C₆)-alkyl, (C₂-C₆)-alkenyl, (C₂-C₆)-alkynyl;
particularly preferably H, F, Cl, Br, CF₃, CN, OCF₃, O-(C₁-C₆)-alkyl, (C₁-C₄)-alkoxy-(C₁-C₄)-alkyl, (C₁-C₆)-alkyl;
25 very particularly preferably H, F, Cl, O-(C₁-C₆)-alkyl, (C₁-C₆)-alkyl;
in particular very particularly preferably H;

R15, R16, R17, R18, R19, R21

independently of one another H, (C₁-C₈)-alkyl;

30 or

R15 and R16, R17 and R18

form independently of one another and optionally together with the nitrogen atom to which they are bonded a 5-6 membered ring which, apart from the nitrogen atom, may also comprise 0-1 further heteroatoms from the group of NH, N-(C₁-C₆)-alkyl, oxygen and sulfur;

5

R20, R22, R23

independently of one another H, (C₁-C₈)-alkyl, aryl; preferably independently of one another H, (C₁-C₈)-alkyl;

10 R24, R25

independently of one another H, (C₁-C₈)-alkyl;

R26 H, (C₁-C₆)-alkyl, aryl; preferably H, (C₁-C₆)-alkyl;

15 x' 0, 1, 2, 3, 4, 5, 6;

Y C(R27)(R27')C(R28)(R28'), C(R29)=C(R29'); preferably C(R27)(R27')C(R28)(R28');

20 R27, R27', R28, R28', R29, R29'

independently of one another H, F, Cl, Br, CN, (C₁-C₈)-alkyl, (C₂-C₆)-alkenyl, (C₂-C₆)-alkynyl; preferably H, (C₁-C₆)-alkyl, particularly preferably H;

25 X S, O, C(R30)=C(R30'); preferably S, C(R30)=C(R30'); particularly preferably C(R30)=C(R30');

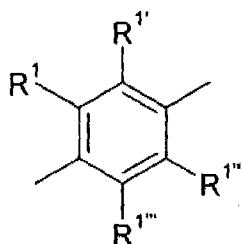
R30, R30'

independently of one another H, F, Cl, Br, I, OH, CF₃, NO₂, CN, OCF₃, O-(C₁-C₆)-alkyl, O-(C₁-C₄)-alkoxy-(C₁-C₄)-alkyl, S-(C₁-C₆)-alkyl, (C₁-C₆)-alkyl, (C₂-C₆)-alkenyl, (C₃-C₈)-cycloalkyl, O-(C₃-C₈)-cycloalkyl, (C₃-C₈)-cycloalkenyl, (C₂-C₆)-alkynyl, (C₀-C₈)-alkylene-aryl, O-(C₀-C₈)-alkylene-aryl, S-aryl, N(R15)(R16), SO₂-CH₃, COOH, COO-(C₁-C₆)-alkyl, CON(R17)(R18), N(R19)CO(R20),

30

oxygen and sulfur;

Q mono-, bi-, tri- or spirocyclic saturated or partly unsaturated ring structure having one nitrogen atom and 0-3 further heteroatoms selected from the group of N, O and S, where the rings of the structure may be spiro-linked, fused or bridged, and where the ring system may be substituted by one or more of the following substituents: F, OH, CF₃, CN, OCF₃, oxo, O-(C₁-C₈)-alkyl, (C₁-C₄)-alkoxy-(C₁-C₄)-alkyl, (C₁-C₆)-alkyl, (C₂-C₆)-alkenyl, (C₂-C₆)-alkynyl, CO(R₄₄), (C(R₄₅)(R₄₆))_o-R₄₇, CO(C(R₄₅)(R₄₆))_p-R₄₈, where Q comprises in total at least two N atoms; Q is preferably linked to the group



via a ring nitrogen atom of the group Q;

R₄₄ H, (C₁-C₈)-alkyl;

R₄₅, R₄₆

independently of one another H, (C₁-C₈)-alkyl, OH, (C₃-C₈)-cycloalkyl, (C₁-C₄)-alkoxy-(C₁-C₄)-alkyl; preferably H, (C₁-C₆)-alkyl; particularly preferably H;

o, p independently of one another 0, 1, 2, 3, 4, 5, 6; preferably 0, 1, 2, 3, 4;

R₄₇, R₄₈

independently of one another OH, F, O-(C₁-C₈)-alkyl, CON(R₄₉)(R₅₀), N(R₅₁)CO(R₅₂), N(R₅₃)(R₅₄), CO₂(R₅₅), SO₂Me, CN, a 3-10 membered ring system having 0 to 3 heteroatoms selected from the group of N, O and S, which may be substituted by one or more of the following substituents: F, Cl, Br, CF₃, (C₁-C₈)-alkyl, O-(C₁-C₈)-alkyl, (C₁-C₄)-alkoxy-(C₁-C₄)-alkyl, CO(R₅₆), oxo, OH;

R₄₉, R₅₀, R₅₁, R₅₂, R₅₅, R₅₆

independently of one another H, (C₁-C₈)-alkyl;

or

R49 and R50

form optionally together with the nitrogen atom to which they are bonded a 5-6
 membered ring which, apart from the nitrogen atom, may also comprise 0-1
 5 further heteroatoms from the group of NH, N-(C₁-C₆)-alkyl, oxygen and sulfur;

R53, R54

independently of one another H, (C₁-C₈)-alkyl, (C₁-C₄)-alkoxy-(C₁-C₄)-alkyl,
 (C₃-C₈)-alkenyl, (C₃-C₈)-alkynyl, CO(R57), (C(R58)(R59))_q-R60,
 10 CO(C(R61)(R62))_r-R63, CO-O(C₁-C₈)-alkyl; or R53 and R54 form together with
 the nitrogen atom to which they are bonded a 4 to 10-membered mono-, bi- or
 spirocyclic ring which, apart from the nitrogen atom, comprises 0 to 3 additional
 heteroatoms selected from the group of N, O and S and may additionally be
 substituted by one or more of the following substituents: F, Cl, Br, CF₃, O-(C₁-C₈)-
 15 alkyl, (C₁-C₆)-alkyl, CO(R64), oxo, OH, (C₁-C₄)-alkoxy-(C₁-C₄)-alkyl, hydroxy-
 (C₁-C₄)-alkyl, CON(R65)(R66), N(R67)CO(R68), N(R69)(R70), CO₂(R71),
 SO₂(C₁-C₆)-alkyl;

R53 is preferably:

H, (C₁-C₈)-alkyl, (C(R58)(R59))_q-R60, (C₁-C₄)-alkoxy-(C₁-C₄)-alkyl, (C₃-C₈)-
 20 alkenyl, (C₃-C₈)-alkynyl, CO-(C₁-C₈)-alkyl, CO-O(C₁-C₈)-alkyl,
 CO(C(R61)(R62))_r-N(R76)(R77);

R54 is preferably:

(C₁-C₈)-alkyl, (C(R58)(R59))_q-R60, (C₁-C₄)-alkoxy-(C₁-C₄)-alkyl, (C₃-C₈)-alkenyl,
 (C₃-C₈)-alkynyl;

25 or

R53 and R54 form preferably together with the nitrogen atom to which they are bonded
 a 4 to 10-membered mono-, bi- or spirocyclic ring which, apart from the nitrogen
 atom, may comprise 0 to 3 additional heteroatoms selected from the group of
 oxygen, nitrogen and sulfur, where the heterocyclic ring system may additionally
 30 be substituted by F, Cl, Br, CF₃, (C₁-C₆)-alkyl, O-(C₁-C₈)-alkyl, (C₁-C₄)-alkoxy-(C₁-
 C₄)-alkyl, hydroxy-(C₁-C₄)-alkyl, oxo, CO(R64), CON(R65)(R66), hydroxy,
 COO(R71), N(R67)CO(C₁-C₆)-alkyl, N(R69)(R70) or SO₂(C₁-C₆)-alkyl;

R53, R54 are very particularly preferably:

(C₁-C₈)-alkyl, (C(R58)(R59))_q-R60, (C₁-C₄)-alkoxy-(C₁-C₄)-alkyl; or R53 and R54 form together with the nitrogen atom to which they are bonded a 4 to 10-membered mono-, bi- or spirocyclic ring which, apart from the nitrogen atom, may comprise 0 to 2 additional heteroatoms selected from the group of oxygen, nitrogen and sulfur, where the heterocyclic ring system may additionally be substituted by F, Cl, Br, CF₃, (C₁-C₆)-alkyl, O-(C₁-C₈)-alkyl, (C₁-C₄)-alkoxy-(C₁-C₄)-alkyl, hydroxy-(C₁-C₄)-alkyl, oxo, CO(R64), hydroxy, N(R67)CO(C₁-C₆)-alkyl, or SO₂(C₁-C₆)-alkyl;

R58, R59

independently of one another H, (C₁-C₆)-alkyl, OH;

R57, R61, R62, R64, R65, R66, R67, R68, R69, R70, R71

independently of one another H, (C₁-C₆)-alkyl;

or

R69 and R70

form optionally together with the nitrogen atom to which they are bonded a 5-6 membered ring which, apart from the nitrogen atom, may also comprise 0-1 further heteroatoms from the group of NH, N-(C₁-C₆)-alkyl, oxygen and sulfur;

q, r independently of one another 0, 1, 2, 3, 4, 5, 6;

R60, R63

independently of one another OH, F, O-(C₁-C₆)-alkyl, CN, COO(R78), N(R74)CO(C₁-C₆)-alkyl, N(R76)(R77), CON(R72)(R73), SO₂(C₁-C₆)-alkyl, 3-12 membered mono-, bi- or spirocyclic ring which may comprise one or more heteroatoms from the group of N, O and S, and the 3-12 membered ring may comprise further substituents such as F, Cl, Br, OH, CF₃, NO₂, CN, OCF₃, oxo, O-(C₁-C₆)-alkyl, (C₁-C₄)-alkoxy-(C₁-C₄)-alkyl, hydroxy-(C₁-C₄)-alkyl, S-(C₁-C₆)-alkyl, (C₁-C₆)-alkyl, (C₂-C₆)-alkenyl, (C₃-C₈)-cycloalkyl, O-(C₃-C₈)-cycloalkyl, (C₃-C₈)-cycloalkenyl, O-(C₃-C₈)-cycloalkenyl, (C₂-C₆)-alkynyl, N(R76)(R77),

COO(R78), SO₂(C₁-C₆)-alkyl and COOH;
preferably OH, F, O-(C₁-C₆)-alkyl, N(R74)CO(C₁-C₆)-alkyl, SO₂(C₁-C₆)-alkyl, 3-12
membered mono-, bi- or spirocyclic ring which may comprise one or more
heteroatoms from the group of N, O and S, and the 3-12 membered ring may
5 comprise further substituents such as F, Cl, Br, OH, CF₃, NO₂, CN, OCF₃, oxo,
O-(C₁-C₆)-alkyl, (C₁-C₄)-alkoxy-(C₁-C₄)-alkyl, (C₁-C₆)-alkyl, (C₂-C₆)-alkenyl,
(C₂-C₆)-alkynyl, N(R76)(R77) and SO₂(C₁-C₆)-alkyl;

R72, R73, R74, R76, R77, R78

10 independently of one another H, (C₁-C₈)-alkyl;

or

R72 and R73, R76 and R77

form independently of one another optionally together with the nitrogen atom to
which they are bonded a 5-6 membered ring which, apart from the nitrogen atom,
15 may also comprise 0-1 further heteroatoms from the group of NH, N-(C₁-C₆)-alkyl,
oxygen and sulfur.

The invention relates to compounds of the formula I in the form of their racemates,
20 enantiomer-enriched mixtures and pure enantiomers, and to their diastereomers and
mixtures thereof.

The compounds of the formula I are notable for exhibiting an improved solubility
compared with compounds of similar structure in aqueous media with at the same time
25 high activity. Preferred compounds of the invention are notable in particular for low
blockade of the hERG channel. Preferred compounds of the invention further exhibit
an improved metabolic stability compared with compounds of the prior art.

The alkyl, alkenyl and alkynyl radicals in the substituents R1, R2, R3, R4, R5, R6, R7,
30 R8, R9, R10, R11, R12, R13, R14, R15, R16, R17, R18, R19, R20, R21, R22, R23,
R24, R25, R26, R27, R27', R28, R28' R29, R29' R30, R30' R31, R32, R33, R34, R34',

R35, R36, R37, R38, R39, R40, R41, R42, R43, R44, R45, R46, R47, R51, R52, R53, R54, R55, R56, R57, R58, R59, R60, R61, R62, R63, R64, R65, R66, R67, R68, R69, R70, R71, R72, R73, R74, R76, R77 and R78 may be either straight-chain, branched and/or optionally substituted by substituents such as (C1-C4)-alkoxy or halogen. This also applies when the alkyl, alkenyl and alkynyl radicals are part of another group, e.g. part of an alkoxy group (such as (C1-C4)-alkoxy-(C1-C4)-alkyl)). Suitable halogens are fluorine, chlorine, bromine and iodine, preferably fluorine, chlorine and bromine, particularly preferably fluorine.

Examples of alkyl groups are: methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl and octyl. Included therein are both the n-isomers of these radicals and branched isomers such as isopropyl, isobutyl, isopentyl, sec-butyl, tert-butyl, neopentyl, 3,3-dimethylbutyl, etc. Unless described otherwise, the term alkyl additionally also includes alkyl radicals which are unsubstituted or optionally substituted by one or more further radicals, for example by 1, 2, 3 or 4 identical or different radicals such as (C1-C4)-alkoxy or halogen. Examples of alkyl groups substituted by halogen are fluorinated alkyl groups such as CF₃, CHF₂, CH₂F, 3-fluoroprop-1-yl, 2,2,1,1-tetrafluoroethyl. It is moreover possible for the additional substituents to appear in any desired position of the alkyl radical. Unless defined otherwise, the alkyl radicals are preferably unsubstituted.

Cycloalkyl means in the context of the present application cycloalkyl and cycloalkylalkyl (alkyl which is in turn substituted by cycloalkyl), where cycloalkyl has at least 3 carbon atoms. Examples of cycloalkyl radicals are: cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclononyl and cyclodecyl. Polycyclic ring systems are also possible where appropriate, such as decalinyl, norbornanyl, bornanyl or adamantanyl. The cycloalkyl radicals may be unsubstituted or optionally substituted by one or more further radicals as listed by way of example above for the alkyl radicals. Unless defined otherwise, the cycloalkyl radicals are preferably unsubstituted.

Examples of alkenyl and alkynyl groups are: vinyl, 1-propenyl, 2-propenyl (allyl), 2-butenyl, 2-methyl-2-propenyl, 3-methyl-2-butenyl, ethynyl, 2-propynyl (propargyl), 2-butyne or 3-butyne.

5

Cycloalkenyl means in the context of the present application cycloalkenyl radicals and cycloalkenylalkyl radicals (alkyl which is substituted by cycloalkenyl), which comprise at least three carbon atoms. Examples of cycloalkenyl are: cyclopentenyl, cyclohexenyl, cycloheptenyl and cyclooctenyl.

10

The alkenyl radicals and cycloalkenyl radicals may have one to three conjugated or non-conjugated double bonds (i.e. also alk-dienyl and alk-trienyl radicals), preferably one double bond in a linear or branched chain. The same applies to the triple bonds for alkynyl radicals. The alkenyl and alkynyl radicals may be unsubstituted or optionally substituted by one or more further radicals as listed by way of example above for the alkyl radicals. Unless defined otherwise, the alkenyl and alkynyl radicals are preferably unsubstituted.

15

20

Aryl refers in the present invention to radicals which are derived from monocyclic or bicyclic aromatic compounds comprising no ring heteroatoms. Where aryl refers to systems which are not monocyclic, the saturated form (perhydro form) or the partly unsaturated form (for example the dihydro form or tetrahydro form) is also possible for the second ring when the respective forms are known and stable. The term aryl also includes in the present invention for example bicyclic radicals in which both rings are aromatic and bicyclic radicals in which only one ring is aromatic. Examples of aryl are: phenyl, naphthyl, indanyl, 1,2-dihydronaphthenyl, 1,4-dihydronaphthenyl, indenyl or 1,2,3,4-tetrahydronaphthyl. Unless defined otherwise, the aryl radicals are preferably unsubstituted. Aryl is particularly preferably phenyl or naphthyl.

25

30

Heteroaryl radicals mean radicals derived from monocyclic or bicyclic aromatic compounds which comprise ring heteroatoms, preferably N, O or S. Otherwise, the

statements made about aryl radicals apply to heteroaryl radicals.

A "tricycle" means structures having 3 rings which are linked together by more than one bond. Examples of such systems are fused systems with 3 rings and spirocycles with fused-on ring system.

5

A polycyclic group (bi-, tri- or spirocyclic ring structure) means in the context of the present application a group which is derived from spiranes, fused ring systems or bridged ring systems. The spiranes are notable for two rings having only one carbon atom in common and the ring planes of the two rings being perpendicular to one another. In the fused ring systems, two rings are linked together in such a way that they have two atoms in common. This type of linkage involves an "ortho fusion". Bridged ring systems are ring systems having a bridge of carbon atoms and/or heteroatoms between two nonadjacent atoms of a ring.

10

15 A "chemically reasonable radical" means in the context of the present invention a radical which is stable at room temperature and atmospheric pressure. In the context of the present invention, a "chemically reasonable radical" in the definition of group A in compounds of the formula I preferably means groups which have no heteroatom-heteroatom bonds between the individual members of the groups.

20

A "nonaromatic" ring means in the context of the present application preferably a ring which is saturated or partly unsaturated. In this connection, a partly unsaturated ring according to the present application has one or, where appropriate, a plurality of double bonds, but the partly unsaturated ring is not aromatic. The term "nonaromatic" 25 in the context of the present application also includes "nonheteroaromatic" rings.

25

The compounds of the formula I may have one or more centers of asymmetry. The compounds of the formula I may therefore exist in the form of their racemates, enantiomer-enriched mixtures, pure enantiomers, diastereomers and mixtures of

diastereomers. The present invention encompasses all these isomeric forms of the compounds of the formula I. These isomeric forms may be obtained by known methods, even if not expressly described in some cases.

5 Pharmaceutically acceptable salts are, because their solubility in water is greater than that of the initial or basic compounds, particularly suitable for medical applications. These salts must have a pharmaceutically acceptable anion or cation. Suitable pharmaceutically acceptable acid addition salts of the compounds of the invention are salts of inorganic acids such as hydrochloric acid, hydrobromic, phosphoric,
10 metaphosphoric, nitric and sulfuric acid, and of organic acids such as, for example, acetic acid, benzenesulfonic, benzoic, citric, ethanesulfonic, fumaric, gluconic, glycolic, isethionic, lactic, lactobionic, maleic, malic, methanesulfonic, succinic, p-toluenesulfonic and tartaric acid. Suitable pharmaceutically acceptable basic salts are ammonium salts, alkali metal salts (such as sodium and potassium salts), alkaline
15 earth metal salts (such as magnesium and calcium salts) and salts of trometamol (2-amino-2-hydroxymethyl-1,3-propanediol), diethanolamine, lysine or ethylenediamine.

Salts with a pharmaceutically unacceptable anion, such as, for example,
20 trifluoroacetate, likewise belong within the framework of the invention as useful intermediates for the preparation or purification of pharmaceutically acceptable salts and/or for use in nontherapeutic, for example in vitro, applications.

The term "physiologically functional derivative" used herein refers to any
25 physiologically tolerated derivative of a compound of the formula I of the invention, for example an ester, which on administration to a mammal such as, for example, a human is able to form (directly or indirectly) a compound of the formula I or an active metabolite thereof.

30 Physiologically functional derivatives also include prodrugs of the compounds of the

invention, as described, for example, in H. Okada et al., Chem. Pharm. Bull. 1994, 42, 57-61. Such prodrugs can be metabolized in vivo to a compound of the invention. These prodrugs may themselves be active or not.

5 The compounds of the invention may also exist in various polymorphous forms, for example as amorphous and crystalline polymorphous forms. All polymorphous forms of the compounds of the invention belong within the framework of the invention and are a further aspect of the invention.

10 All references to "compound(s) of formula I" hereinafter refer to compound(s) of the formula I as described above, and their salts, solvates and physiologically functional derivatives as described herein.

If radicals or substituents may occur more than once in the compounds of the formula
15 I, they may all have the stated meanings independently of one another and be identical or different.

The symbols in compound I preferably have independently of one another the following meanings:

20

R1, R1', R1'', R1'''

independently of one another H, F, Cl, Br, OH, CF₃, NO₂, CN, OCF₃, O-(C₁-C₆)-alkyl, (C₁-C₄)-alkoxy-(C₁-C₄)-alkyl, S-(C₁-C₆)-alkyl, (C₁-C₆)-alkyl, (C₂-C₆)-alkenyl, (C₃-C₈)-cycloalkyl, O-(C₃-C₈)-cycloalkyl, (C₂-C₆)-alkynyl, O-(C₀-C₈)-alkylene-aryl, CO(C₁-C₆)-alkyl;
25

particularly preferably H, F, Cl, Br, CF₃, CN, OCF₃, O-(C₁-C₆)-alkyl, (C₁-C₄)-alkoxy-(C₁-C₄)-alkyl, (C₁-C₆)-alkyl, CO(C₁-C₆)-alkyl;

very particularly preferably H, F, Cl, O-(C₁-C₆)-alkyl, (C₁-C₆)-alkyl, CO(C₁-C₆)-alkyl;

a particularl preferably H, F, methyl, O-methyl, CO-methyl;

where preferably at least two, particularly preferably at least three or all radicals
R1, R1', R1'' and R1''' are H.

R2 H, F, Cl, Br, I, OH, CF₃, NO₂, CN, OCF₃, O-(C₁-C₆)-alkyl, (C₁-C₄)-alkoxy-(C₁-C₄)-
alkyl, (C₁-C₆)-alkyl, (C₂-C₆)-alkenyl, (C₂-C₆)-alkynyl;

particularly preferably H, F, Cl, Br, CF₃, CN, OCF₃, O-(C₁-C₆)-alkyl, (C₁-C₄)-
alkoxy-(C₁-C₄)-alkyl, (C₁-C₆)-alkyl;

very particularly preferably H, F, Cl, O-(C₁-C₆)-alkyl, (C₁-C₆)-alkyl;

in particular very particularly preferably H.

Y C(R27)(R27')C(R28)(R28'); where

R27, R27', R28, R28'

are independently of one another independently of one another H, (C₁-C₈)-
alkyl, (C₂-C₆)-alkenyl, (C₂-C₆)-alkynyl; preferably H, (C₁-C₆)-alkyl, particularly
preferably H.

X S, C(R30)=C(R30'); preferably C(R30)=C(R30'); where

R30, R30'

are independently of one another H, F, Cl, Br, I, OH, CF₃, NO₂, CN, OCF₃,
O-(C₁-C₆)-alkyl, O-(C₁-C₄)-alkoxy-(C₁-C₄)-alkyl, S-(C₁-C₆)-alkyl, (C₁-C₆)-
alkyl, (C₂-C₆)-alkenyl, (C₃-C₈)-cycloalkyl, O-(C₃-C₈)-cycloalkyl, (C₃-C₈)-
cycloalkenyl, (C₂-C₆)-alkynyl, (C₀-C₈)-alkylene-aryl, O-(C₀-C₈)-alkylene-aryl,
S-aryl, N(R15)(R16), SO₂-CH₃, COOH, COO-(C₁-C₆)-alkyl, CON(R17)(R18),
N(R19)CO(R20), N(R21)SO₂(R22), CO(R23), (C(R24)(R25))_x-O(R26);
preferably H, F, Cl, Br, I, OH, CF₃, NO₂, CN, OCF₃, O-(C₁-C₆)-alkyl, O-(C₁-
C₄)-alkoxy-(C₁-C₄)-alkyl, (C₁-C₆)-alkyl, (C₂-C₆)-alkenyl, (C₂-C₆)-alkynyl;
particularly preferably H, F, Cl, Br, CF₃, CN, OCF₃, O-(C₁-C₆)-alkyl, O-(C₁-
C₄)-alkoxy-(C₁-C₄)-alkyl, (C₁-C₆)-alkyl;

very particularly preferably H, F, Cl, O-(C₁-C₆)-alkyl, (C₁-C₆)-alkyl;

in particular very particularly preferably H.

A a bond or a linker having 1 to 6 members, where the members are selected from the group consisting of O, N(R31), CO, C(R32)(R33), C(R34)=C(R34'), C≡C, resulting in a chemically reasonable radical;

particularly preferably a bond or a linker having 1 to 5 members, where the members are selected from the group consisting of O, N(R31), CO, C(R32)(R33), C≡C, resulting in a chemically reasonable radical;

very particularly preferably a bond or a linker having 1 to 5 members, where the members are selected from the group consisting of O, N(R31), CO, C(R32)(R33), C≡C, resulting in a chemically reasonable radical, where the linker comprises no O-CO groups;

in particular preferably a bond, O, NH, CH(OH), CH₂, CO, C≡C, HC=CH, CH₂-O, CH(CH₃)-O, CO-CH(CH₃)-O, CO-NH, NH-CO, N(CH₃)-CO, COCH₂O, CH(OH)CH₂O, O-CO-NH, C(OH)(CH₃)-C≡C, COCH₂CH₂O;

in particular very preferably O, NH, CH(OH), CH₂, CO, C≡C, HC=CH, CH₂-O, CH(CH₃)-O, CO-CH(CH₃)-O, CO-NH, NH-CO, N(CH₃)-CO, COCH₂O, CH(OH)CH₂O, O-CO-NH, C(OH)(CH₃)-C≡C, COCH₂CH₂O; where

R31, R34, R34'

are independently of one another H, (C₁-C₈)-alkyl;

R32, R33

are independently of one another H, (C₁-C₆)-alkyl, OH, O-(C₁-C₆)-alkyl.

B H, hydroxy-(C₁-C₄)-alkyl, (C₁-C₈)-alkyl, (C₁-C₄)-alkoxy-(C₁-C₄)-alkyl, (C₂-C₈)-alkenyl, (C₂-C₈)-alkynyl, a 3 to 10-membered mono-, bi- or spirocyclic ring which may comprise 0 to 4 heteroatoms selected from the group of oxygen, nitrogen and sulfur, where the ring system may additionally be substituted by F, Cl, Br,

CF₃, NO₂, CN, (C₁-C₆)-alkyl, O-(C₁-C₈)-alkyl, (C₁-C₄)-alkoxy-(C₁-C₄)-alkyl, hydroxy-(C₁-C₄)-alkyl, oxo, CO(R37), CON(R38)(R39), hydroxy, COO(R40), N(R41)CO(C₁-C₆)-alkyl, N(R42)(R43) or SO₂CH₃;

particularly preferably H, hydroxy-(C₁-C₄)-alkyl, (C₁-C₈)-alkyl, (C₁-C₄)-alkoxy-(C₁-C₄)-alkyl, a 3 to 10-membered mono-, bi- or spirocyclic ring which may comprise 0 to 3 heteroatoms selected from the group of oxygen, nitrogen and sulfur, where the ring system may additionally be substituted by F, Cl, Br, CF₃, NO₂, CN, (C₁-C₆)-alkyl, O-(C₁-C₈)-alkyl, (C₁-C₄)-alkoxy-(C₁-C₄)-alkyl, hydroxy-(C₁-C₄)-alkyl, oxo, CO(R37), CON(R38)(R39), hydroxy, COO(R40), N(R41)CO(C₁-C₆)-alkyl, N(R42)(R43) or SO₂CH₃;

very particularly preferably H, (C₁-C₈)-alkyl, (C₁-C₄)-alkoxy-(C₁-C₄)-alkyl, a 3 to 10-membered mono-, bi- or spirocyclic ring which may comprise 0 to 3 heteroatoms selected from the group of oxygen, nitrogen and sulfur, where the ring system may additionally be substituted by F, Cl, Br, CF₃, NO₂, CN, (C₁-C₆)-alkyl, O-(C₁-C₈)-alkyl, (C₁-C₄)-alkoxy-(C₁-C₄)-alkyl, hydroxy-(C₁-C₄)-alkyl, oxo, CO(R37), hydroxy, N(R41)CO(C₁-C₆)-alkyl, N(R42)(R43) or SO₂CH₃;

R35, R36, R37, R38, R39, R40, R41, R42, R43

independently of one another H, (C₁-C₈)-alkyl;

or

R38 and R39, R42 and R43

form independently of one another optionally together with the nitrogen atom to which they are bonded a 5-6 membered ring which, apart from the nitrogen atom, may also comprise 0-1 further heteroatoms from the group of NH, N-(C₁-C₆)-alkyl, oxygen and sulfur.

In a preferred embodiment, B is:

B H, N(R35)(R36), hydroxy-(C₁-C₄)-alkyl, (C₁-C₈)-alkyl, (C₁-C₄)-alkoxy-(C₁-C₄)-alkyl, (C₂-C₈)-alkenyl, (C₂-C₈)-alkynyl, a 3 to 10-membered mono-, bi-, tri- or spirocyclic nonaromatic ring which may comprise 0 to 4 heteroatoms selected from the group of oxygen, nitrogen and sulfur, where the ring system may additionally be

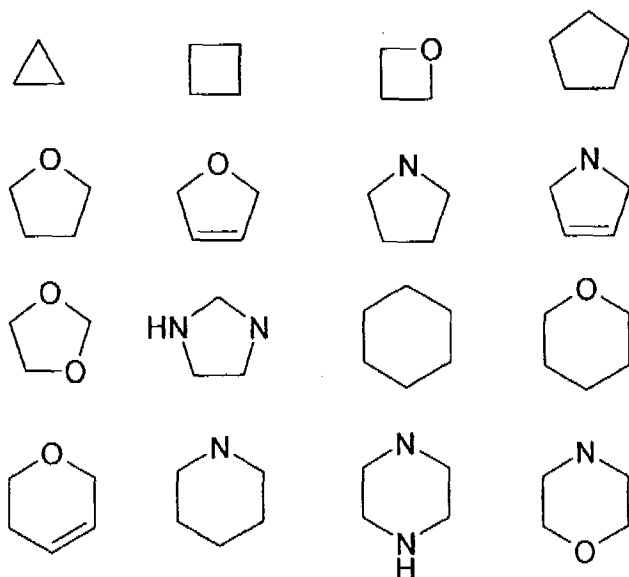
substituted by one or more of the following substituents: F, Cl, Br, CF₃, NO₂, CN, (C₁-C₆)-alkyl, O-(C₁-C₈)-alkyl, (C₁-C₄)-alkoxy-(C₁-C₄)-alkyl, hydroxy-(C₁-C₄)-alkyl, oxo, CO(R37), CON(R38)(R39), hydroxy, COO(R40), N(R41)CO(C₁-C₆)-alkyl, N(R42)(R43), SO₂CH₃, SCF₃ or S-(C₁-C₆)-alkyl;

5 preferably H, hydroxy-(C₁-C₄)-alkyl, (C₁-C₈)-alkyl, (C₁-C₄)-alkoxy-(C₁-C₄)-alkyl, (C₂-C₈)-alkenyl, (C₂-C₈)-alkynyl, a 3 to 10-membered mono-, bi- or spirocyclic nonaromatic ring which may comprise 0 to 4 heteroatoms selected from the group of oxygen, nitrogen and sulfur, where the ring system may additionally be substituted by F, Cl, Br, CF₃, NO₂, CN, (C₁-C₆)-alkyl, O-(C₁-C₈)-alkyl, (C₁-C₄)-alkoxy-(C₁-C₄)-alkyl, hydroxy-(C₁-C₄)-alkyl, oxo, CO(R37), CON(R38)(R39), hydroxy, COO(R40), N(R41)CO(C₁-C₆)-alkyl, N(R42)(R43) or SO₂CH₃;

10 particularly preferably H, (C₁-C₈)-alkyl, (C₁-C₄)-alkoxy-(C₁-C₄)-alkyl, a 3 to 10-membered mono-, bi- or spirocyclic nonaromatic ring which may comprise 0 to 3 heteroatoms selected from the group of oxygen, nitrogen and sulfur, where the ring system may additionally be substituted by F, Cl, Br, CF₃, NO₂, CN, (C₁-C₆)-alkyl, O-(C₁-C₈)-alkyl, (C₁-C₄)-alkoxy-(C₁-C₄)-alkyl, hydroxy-(C₁-C₄)-alkyl, oxo, CO(R37), CON(R38)(R39), hydroxy, COO(R40), N(R41)CO(C₁-C₆)-alkyl, N(R42)(R43) or SO₂CH₃;

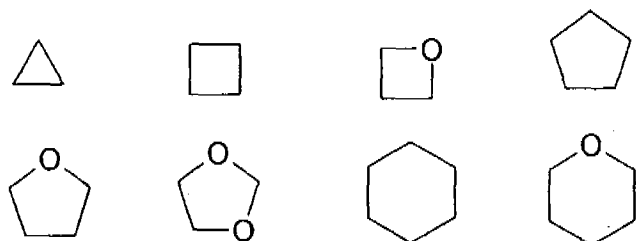
15 very particularly preferably (C₁-C₈)-alkyl, (C₁-C₄)-alkoxy-(C₁-C₄)-alkyl, a 3 to 10-membered mono-, bi- or spirocyclic nonaromatic ring which may comprise 0 to 3 heteroatoms selected from the group of oxygen, nitrogen and sulfur, where the ring system may additionally be substituted by F, Cl, CF₃, (C₁-C₆)-alkyl, O-(C₁-C₈)-alkyl, (C₁-C₄)-alkoxy-(C₁-C₄)-alkyl, hydroxy-(C₁-C₄)-alkyl, oxo, CO(R37), hydroxy, N(R41)CO(C₁-C₆)-alkyl, or SO₂CH₃;

20 in particular preferably hydroxy-(C₁-C₄)-alkyl, (C₁-C₈)-alkyl, (C₁-C₄)-alkoxy-(C₁-C₄)-alkyl, a monocyclic ring, selected from the group:



where the ring system may be substituted one- or two times by F, CF₃, CN, methyl, ethyl, methoxy, oxo, hydroxy, SO₂-methyl;

in particularly very preferably hydroxy-(C₁-C₄)-alkyl, (C₁-C₈)-alkyl, (C₁-C₄)-alkoxy-
 5 (C₁-C₄)-alkyl, a monocyclic ring, selected from the group:

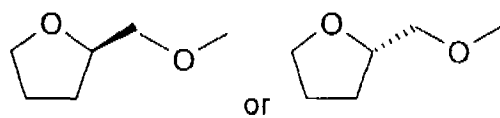


where the ring system may be substituted one- or two times by F, methyl, ethyl, methoxy, hydroxy; where

10

R35, R36, R37, R38, R39, R40, R41, R42, R43 have the meanings mentioned above.

A particularly preferable embodiment is the compound in which B-A has the meanings:

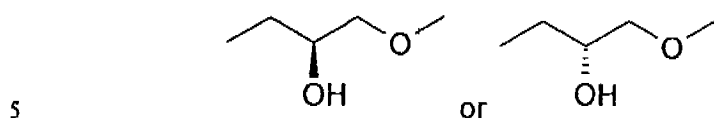


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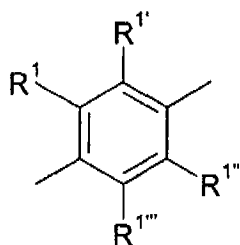
one time by methyl or OH.

, wherein the ring may be substituted

A further particularly preferable embodiment is the compound in which B-A has the meanings:



- Q mono-, bi-, tri- or spirocyclic saturated or partly unsaturated ring structure having one nitrogen atom and 0-3 further heteroatoms selected from the group of N, O and S, where the rings of the structure may be spiro-linked, fused or bridged, and where the ring system may be substituted by one or more of the following substituents: F, OH, CF₃, CN, OCF₃, oxo, O-(C₁-C₈)-alkyl, (C₁-C₄)-alkoxy-(C₁-C₄)-alkyl, (C₁-C₆)-alkyl, (C₂-C₆)-alkenyl, (C₂-C₆)-alkynyl, CO(R44), (C(R45)(R46))_o-R47, CO(C(R45)(R46))_p-R48, where Q comprises a total of at least two N atoms; Q is preferably linked to the group
- 10
- 15



via a ring nitrogen atom of the group Q; where

R44 is H, (C₁-C₈)-alkyl;

- 20 R45, R46
are independently of one another H, (C₁-C₆)-alkyl; particularly preferably H;

o, p are independently of one another 0, 1, 2, 3, 4;

- 25 R47, R48
are independently of one another OH, F, O-(C₁-C₈)-alkyl, CON(R49)(R50),

N(R51)CO(R52), N(R53)(R54), CO₂(R55), SO₂Me, CN, a 3-10 membered ring system having 0 to 3 heteroatoms selected from the group of N, O and S, which may be substituted by one or more of the following substituents: F, Cl, Br, CF₃, (C₁-C₈)-alkyl, O-(C₁-C₈)-alkyl, (C₁-C₄)-alkoxy-(C₁-C₄)-alkyl, CO(R56), oxo, OH;

5

R49, R50, R51, R52, R55, R56

are independently of one another H, (C₁-C₈)-alkyl;

or

R49 and R50

10 form optionally together with the nitrogen atom to which they are bonded a 5-6 membered ring which, apart from the nitrogen atom, may also comprise 0-1 further heteroatoms from the group of NH, N-(C₁-C₆)-alkyl, oxygen and sulfur;

15 R53 is H, (C₁-C₈)-alkyl, (C(R58)(R59))_q-R60, (C₁-C₄)-alkoxy-(C₁-C₄)-alkyl, (C₃-C₈)-alkenyl, (C₃-C₈)-alkynyl, CO-(C₁-C₈)-alkyl, CO-O(C₁-C₈)-alkyl, CO(C(R61)(R62))_rN(R76)(R77);

R54 is (C₁-C₈)-alkyl, (C(R58)(R59))_q-R60, (C₁-C₄)-alkoxy-(C₁-C₄)-alkyl, (C₃-C₈)-alkenyl, (C₃-C₈)-alkynyl;

or

20 R53 and R54 form preferably together with the nitrogen atom to which they are bonded a 4 to 10-membered mono-, bi- or spirocyclic ring which, apart from the nitrogen atom, may comprise 0 to 3 additional heteroatoms selected from the group of oxygen, nitrogen and sulfur, where the heterocyclic ring system may additionally be substituted by F, Cl, Br, CF₃, (C₁-C₆)-alkyl, O-(C₁-C₈)-alkyl, (C₁-C₄)-alkoxy-(C₁-C₄)-alkyl, hydroxy-(C₁-C₄)-alkyl, oxo, CO(R64), CON(R65)(R66), hydroxy, COO(R71), N(R67)CO(C₁-C₆)-alkyl, N(R69)(R70) or SO₂(C₁-C₆)-alkyl;

25 R53, R54 are very particularly preferably:
(C₁-C₈)-alkyl, (C(R58)(R59))_q-R60, (C₁-C₄)-alkoxy-(C₁-C₄)-alkyl; or R53 and R54
30 form together with the nitrogen atom to which they are bonded a 4 to 10-membered mono-, bi- or spirocyclic ring which, apart from the nitrogen atom, may comprise 0 to 2 additional heteroatoms selected from the group of oxygen, nitrogen and sulfur, where the heterocyclic ring system may additionally be

substituted by F, Cl, Br, CF₃, (C₁-C₆)-alkyl, O-(C₁-C₈)-alkyl, (C₁-C₄)-alkoxy-(C₁-C₄)-alkyl, hydroxy-(C₁-C₄)-alkyl, oxo, CO(R64), hydroxy, N(R67)CO(C₁-C₆)-alkyl, or SO₂(C₁-C₆)-alkyl;

5 R58, R59

are independently of one another H, (C₁-C₆)-alkyl, OH;

R57, R61, R62, R64, R65, R66, R67, R69, R70, R71

are independently of one another H, (C₁-C₆)-alkyl;

10 or

R69 and R70

form optionally together with the nitrogen atom to which they are bonded a 5-6 membered ring which, apart from the nitrogen atom, may also comprise 0-1 further heteroatoms from the group of NH, N-(C₁-C₆)-alkyl, oxygen and sulfur;

15

q, r are independently of one another 0, 1, 2, 3, 4, 5, 6; preferably 0, 1, 2, 3, 4; particularly preferably 0, 1, 2; very particularly preferably 0, 1;

R60 is OH, F, O-(C₁-C₆)-alkyl, N(R74)CO(C₁-C₆)-alkyl, SO₂(C₁-C₆)-alkyl, 3-12

20

membered mono-, bi- or spirocyclic ring which may comprise one or more heteroatoms from the group of N, O and S, and the 3-12 membered ring further substituents such as F, Cl, Br, OH, CF₃, NO₂, CN, OCF₃, oxo, O-(C₁-C₆)-alkyl, (C₁-C₄)-alkoxy-(C₁-C₄)-alkyl, (C₁-C₆)-alkyl, (C₂-C₆)-alkenyl, (C₂-C₆)-alkynyl, N(R76)(R77) and SO₂(C₁-C₆)-alkyl;

25

R72, R73, R74, R76, R77, R78

are independently of one another H, (C₁-C₈)-alkyl;

or

R72 and R73, R76 and R77

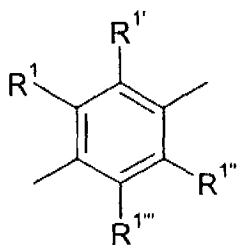
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form independently of one another optionally together with the nitrogen atom to which they are bonded a 5-6 membered ring which, apart from the nitrogen atom, may also comprise 0-1 further heteroatoms from the group of NH, N-(C₁-C₆)-alkyl,

oxygen and sulfur.

In a preferred embodiment Q is:

mono-, bi- or spirocyclic saturated or partly unsaturated ring structure having one
 5 nitrogen atom and 0-3 further heteroatoms selected from the group of N, O and
 S, where the rings of the structure may be spiro-linked, fused or bridged, and
 where the ring system may be substituted by (C(R45)(R46))_o-R47, where Q
 comprises a total of at least two N atoms, and Q is linked to the group



via a ring nitrogen atom of the group Q,

10 where

R45, R46

are independently of one another H, (C₁-C₆)-alkyl; preferably H;

o, p are 0, 1; preferably 0;

15 R47 is N(R53)(R54);

R53, R54 are

(C₁-C₈)-alkyl, (C(R58)(R59))_q-R60, (C₁-C₄)-alkoxy-(C₁-C₄)-alkyl; or R53 and R54
 20 form together with the nitrogen atom to which they are bonded a 4 to 10-
 membered mono-, bi- or spirocyclic ring which, apart from the nitrogen atom, may
 comprise 0 to 2 additional heteroatoms selected from the group of oxygen,
 nitrogen and sulfur, where the heterocyclic ring system may additionally be
 substituted by F, Cl, Br, CF₃, (C₁-C₆)-alkyl, O-(C₁-C₈)-alkyl, (C₁-C₄)-alkoxy-(C₁-
 25 C₄)-alkyl, hydroxy-(C₁-C₄)-alkyl, oxo, CO(R64), hydroxy, N(R67)CO(C₁-C₆)-alkyl,
 or SO₂(C₁-C₆)-alkyl;

R58, R59, R64, R67 are
H, (C₁-C₆)-alkyl, OH;

5 R60 is OH, F, O-(C₁-C₆)-alkyl, N(R74)CO(C₁-C₆)-alkyl, SO₂(C₁-C₆)-alkyl, 3-12
membered mono-, bi- or spirocyclic ring which may comprise one or more
heteroatoms from the group of N, O and S, and the 3-12 membered ring further
substituents such as F, Cl, Br, OH, CF₃, NO₂, CN, OCF₃, oxo, O-(C₁-C₆)-alkyl,
(C₁-C₄)-alkoxy-(C₁-C₄)-alkyl, (C₁-C₆)-alkyl, (C₂-C₆)-alkenyl, (C₂-C₆)-alkynyl,
10 N(R76)(R77) and SO₂(C₁-C₆)-alkyl;

R74, R76, R77
are independently of one another H, (C₁-C₈)-alkyl;

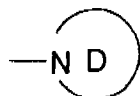
or

15 R76 and R77
form independently of one another optionally together with the nitrogen atom to
which they are bonded a 5-6 membered ring which, apart from the nitrogen atom,
may also comprise 0-1 further heteroatoms from the group of NH, N-(C₁-C₆)-alkyl,
oxygen and sulfur.

20

In a particularly preferred embodiment, Q is:

Q a group of the general formula:

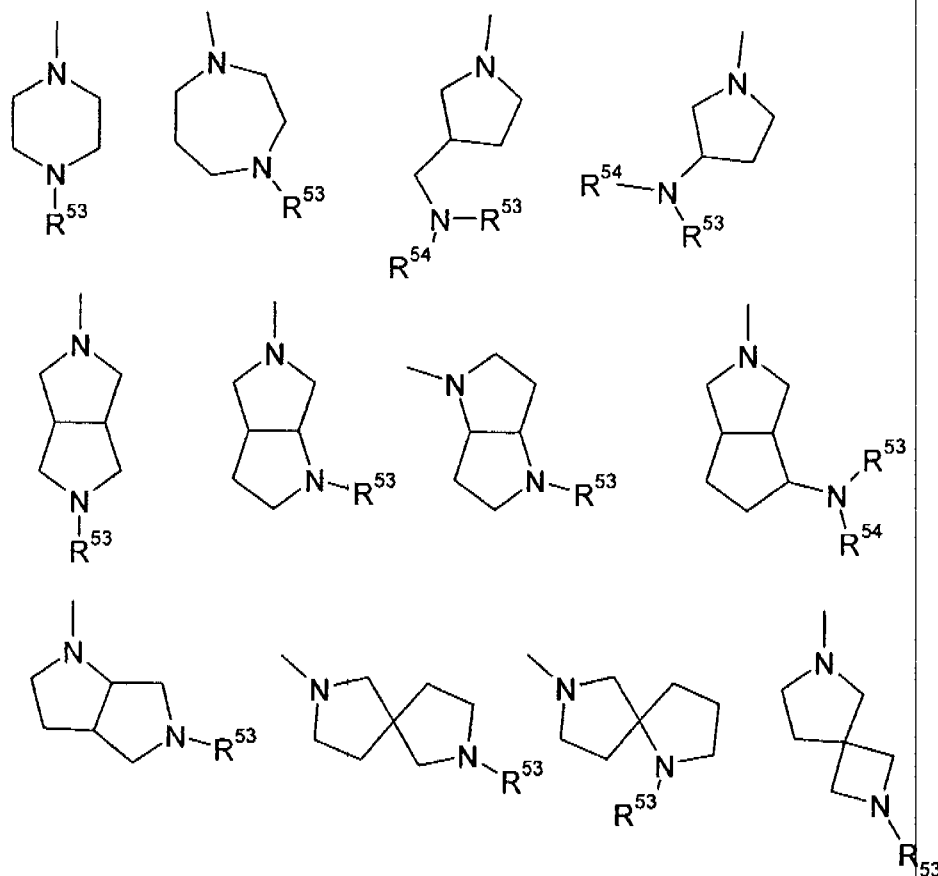


in which the ring D has the following meanings:

25 saturated monocyclic 5-7-membered azacycle which comprises an element
N(R53) or C(R45)((CH₂)_o-N(R53)(R54)); saturated 6-11 membered azabicyclo or
spirocycle which comprises an element N(R53) or C(R45)((CH₂)_o-N(R53)(R54));
Q is preferably:

where the groups may, apart from R⁵³, R⁵⁴, optionally be substituted by one or more substituents selected from F, OH, oxo, (C₁-C₆)-alkyl, O-(C₁-C₆)-alkyl, (C₁-C₄)-alkoxy-(C₁-C₄)-alkyl; the aforementioned groups Q preferably have no further substituents;

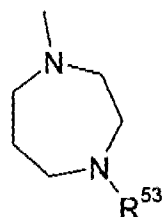
Q is particularly preferably:



5

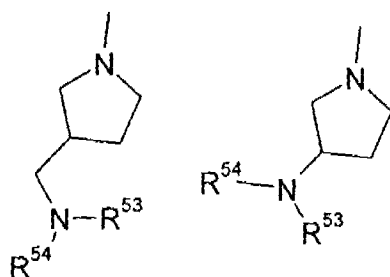
where the groups may optionally be substituted by one or more substituents selected from F, OH, oxo, (C₁-C₆)-alkyl, O-(C₁-C₆)-alkyl, (C₁-C₄)-alkoxy-(C₁-C₄)-alkyl; the aforementioned groups Q preferably have no further substituents;

10 Q is very particularly preferably:



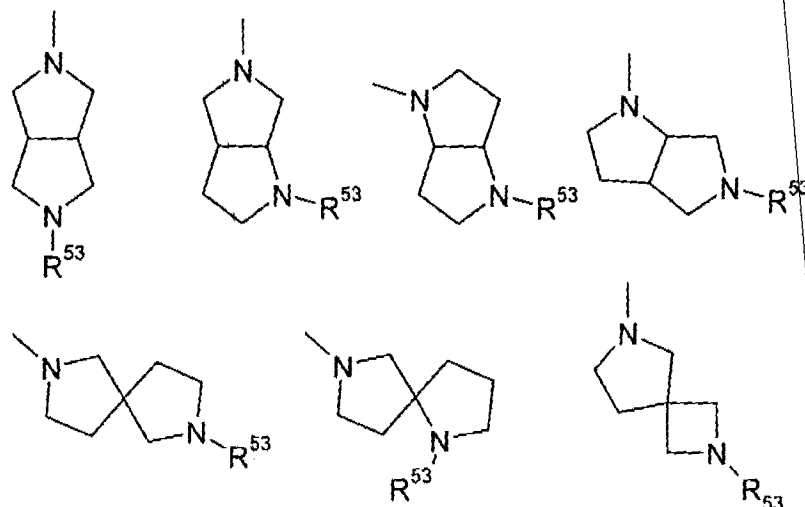
where the group may, apart from R^{53} , optionally be substituted by one or more substituents selected from F, OH, oxo, (C_1-C_6) -alkyl, $O-(C_1-C_6)$ -alkyl, (C_1-C_4) -alkoxy- (C_1-C_4) -alkyl, hydroxy- (C_1-C_4) -alkyl; the aforementioned groups Q preferably have no further substituents;

Further Q is very particularly preferably:



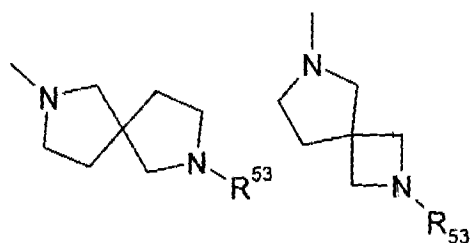
where the groups may, apart from R^{53} , R^{54} , optionally be substituted by one or more substituents selected from F, OH, oxo, (C_1-C_6) -alkyl, $O-(C_1-C_6)$ -alkyl, (C_1-C_4) -alkoxy- (C_1-C_4) -alkyl, hydroxy- (C_1-C_4) -alkyl; the aforementioned groups Q preferably have no further substituents;

Further Q is very particularly preferably:



where the groups may optionally be substituted by one or more substituents selected from F, OH, oxo, (C₁-C₆)-alkyl, O-(C₁-C₆)-alkyl, (C₁-C₄)-alkoxy-(C₁-C₄)-alkyl; the
 5 aforementioned groups Q preferably have no further substituents;

Q is in particular preferably:



where the groups may optionally be substituted by one or more substituents selected
 10 from F, OH, oxo, (C₁-C₆)-alkyl, O-(C₁-C₆)-alkyl, (C₁-C₄)-alkoxy-(C₁-C₄)-alkyl; the
 aforementioned groups Q preferably have no further substituents;

where the radicals R₄₅, R₅₃ and R₅₄ and the index o have the aforementioned meanings.

15

In a further preferred embodiment the meanings are:

R53 H, (C₁-C₈)-alkyl, (C(R58)(R59))_q-R60, (C₁-C₄)-alkoxy-(C₁-C₄)-alkyl,
CO(C(R61)(R62))_r-R63, (C₃-C₈)-alkenyl, (C₃-C₈)-alkynyl, CO-(C₁-C₈)-alkyl,
CO-O(C₁-C₈)-alkyl;

5

R54 (C₁-C₈)-alkyl, (C(R58)(R59))_q-R60, (C₁-C₄)-alkoxy-(C₁-C₄)-alkyl,
CO(C(R61)(R62))_r-R63, (C₃-C₈)-alkenyl, (C₃-C₈)-alkynyl;

or

R53 and R54 form together with the nitrogen atom to which they are bonded a 4 to 10-
membered mono-, bi- or spirocyclic ring which, apart from the nitrogen
atom, comprises 0 to 3 additional heteroatoms selected from the group of N,
O and S and may additionally be substituted by one or more of the following
substituents: F, Cl, Br, CF₃, O-(C₁-C₈)-alkyl, (C₁-C₆)-alkyl, CO(R64), oxo, OH,
(C₁-C₄)-alkoxy-(C₁-C₄)-alkyl, hydroxy-(C₁-C₄)-alkyl, CON(R65)(R66),
N(R67)CO(R68), N(R69)(R70), CO₂(R71), SO₂(C₁-C₆)-alkyl;

15

R45 H, (C₁-C₆)-alkyl;

q, r 0, 1, 2, 3, 4;

20

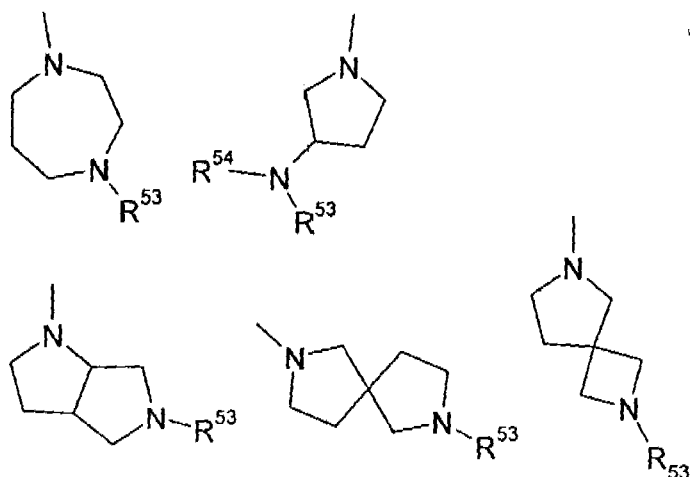
R60, R63

independently of one another OH, F, O-(C₁-C₆)-alkyl, N(R74)CO(C₁-C₆)-
alkyl, SO₂(C₁-C₆)-alkyl, 3-12 membered mono-, bi- or spirocyclic ring which
may comprise one or more heteroatoms from the group of N, O and S, and
the 3-12 membered ring may comprise further substituents such as F, Cl,
Br, OH, CF₃, NO₂, CN, OCF₃, oxo, O-(C₁-C₆)-alkyl, (C₁-C₄)-alkoxy-(C₁-C₄)-
alkyl, hydroxy-(C₁-C₄)-alkyl, (C₁-C₆)-alkyl, (C₂-C₆)-alkenyl, (C₂-C₆)-alkynyl,
N(R76)(R77) and SO₂(C₁-C₆)-alkyl.

25

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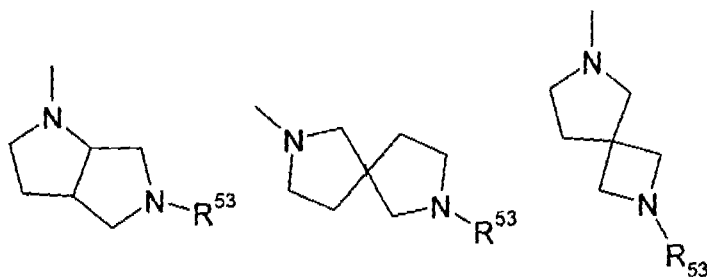
In a further preferred embodiment the meanings are:



where the groups may, apart from R₅₃, R₅₄, optionally be substituted by one or more substituents selected from F, OH, oxo, (C₁-C₆)-alkyl, O-(C₁-C₆)-alkyl, (C₁-C₄)-alkoxy-(C₁-C₄)-alkyl; the aforementioned groups Q preferably have no further substituents;

5

Q is very particularly preferably:



where the groups may, apart from R₅₃, optionally be substituted by one or more substituents selected from F, OH, oxo, (C₁-C₆)-alkyl, O-(C₁-C₆)-alkyl, (C₁-C₄)-alkoxy-(C₁-C₄)-alkyl; the aforementioned groups Q preferably have no further substituents;

10

R₄₅ H, (C₁-C₆)-alkyl; preferably H;

o 0, 1, 2, 3, 4, 5, 6; preferably 0, 1, 2; particularly preferably 0, 1; very particularly preferably 0;

15

R₅₃, R₅₄

independently of one another H, (C₁-C₈)-alkyl, (C₁-C₄)-alkoxy-(C₁-C₄)-alkyl, (C₃-C₈)-alkenyl, (C₃-C₈)-alkynyl, CO(R57), (C(R58)(R59))_q-R60, CO(C(R61)(R62))_r-R63, CO-O(C₁-C₈)-alkyl; or R53 and R54 form together with the nitrogen atom to which they are bonded a 4 to 10-membered mono-, bi- or spirocyclic ring which, apart from the nitrogen atom, comprises 0 to 3 additional heteroatoms selected from the group of N, O and S, and may additionally be substituted by one or more of the following substituents: F, Cl, Br, CF₃, O-(C₁-C₈)-alkyl, (C₁-C₆)-alkyl, CO(R64), oxo, OH, (C₁-C₄)-alkoxy-(C₁-C₄)-alkyl, hydroxy-(C₁-C₄)-alkyl, CON(R65)(R66), N(R67)CO(R68), N(R69)(R70), CO₂(R71), SO₂(C₁-C₆)-alkyl;

R53 is preferably:

H, (C₁-C₈)-alkyl, (C(R58)(R59))_q-R60, (C₁-C₄)-alkoxy-(C₁-C₄)-alkyl, (C₃-C₈)-alkenyl, (C₃-C₈)-alkynyl, CO-(C₁-C₈)-alkyl, CO-O(C₁-C₈)-alkyl, CO(C(R61)(R62))_rN(R76)(R77);

R54 is preferably:

(C₁-C₈)-alkyl, (C(R58)(R59))_q-R60, (C₁-C₄)-alkoxy-(C₁-C₄)-alkyl, (C₃-C₈)-alkenyl, (C₃-C₈)-alkynyl;

or

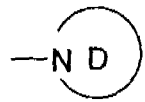
R53 and R54 form preferably together with the nitrogen atom to which they are bonded a 4 to 10-membered mono-, bi- or spirocyclic ring which, apart from the nitrogen atom, may comprise 0 to 3 additional heteroatoms selected from the group of oxygen, nitrogen and sulfur, where the heterocyclic ring system may additionally be substituted by F, Cl, Br, CF₃, (C₁-C₆)-alkyl, O-(C₁-C₈)-alkyl, (C₁-C₄)-alkoxy-(C₁-C₄)-alkyl, hydroxy-(C₁-C₄)-alkyl, oxo, CO(R64), CON(R65)(R66), hydroxy, COO(R71), N(R67)CO(C₁-C₆)-alkyl, N(R69)(R70) or SO₂(C₁-C₆)-alkyl;

R53, R54 are very particularly preferably:

(C₁-C₈)-alkyl, (C(R58)(R59))_q-R60, (C₁-C₄)-alkoxy-(C₁-C₄)-alkyl; or R53 and R54 form together with the nitrogen atom to which they are bonded a 4 to 10-membered mono-, bi- or spirocyclic ring which, apart from the nitrogen atom, may comprise 0 to 2 additional heteroatoms selected from the group of oxygen, nitrogen and sulfur, where the heterocyclic ring system may additionally be substituted by F, Cl, Br, CF₃, (C₁-C₆)-alkyl, O-(C₁-C₈)-alkyl, (C₁-C₄)-alkoxy-(C₁-

in which

X is S or O; preferably S;

Q is , where  has the aforementioned meanings;

5

and the further radicals and groups in the compound of the formula Ib have the aforementioned meanings.

10 In a further embodiment, the present invention relates to compounds of the formula I, in which Y, X and Q have the following meanings:

Y C(R29)=C(R29'); where

R29, R29'

15 are independently of one another H, (C₁-C₈)-alkyl, (C₃-C₆)-alkenyl, (C₃-C₆)-alkynyl; preferably H, (C₁-C₆)-alkyl, particularly preferably H;

X C(R30)=C(R30'); where

20 R30, R30'

are independently of one another H, F, Cl, Br, I, OH, CF₃, NO₂, CN, OCF₃, O-(C₁-C₆)-alkyl, O-(C₁-C₄)-alkoxy-(C₁-C₄)-alkyl, S-(C₁-C₆)-alkyl, (C₁-C₆)-alkyl, (C₂-C₆)-alkenyl, (C₃-C₈)-cycloalkyl, O-(C₃-C₈)-cycloalkyl, (C₃-C₈)-cycloalkenyl, (C₂-C₆)-alkynyl, (C₀-C₈)-alkylene-aryl, O-(C₀-C₈)-alkylene-aryl, S-aryl, N(R15)(R16),
 25 SO₂-CH₃, COOH, COO-(C₁-C₆)-alkyl, CON(R17)(R18), N(R19)CO(R20), N(R21)SO₂(R22), CO(R23), (C(R24)(R25))_x-O(R26);
 preferably H, F, Cl, Br, I, OH, CF₃, NO₂, CN, OCF₃, O-(C₁-C₆)-alkyl, O-(C₁-C₄)-alkoxy-(C₁-C₄)-alkyl, (C₁-C₆)-alkyl, (C₂-C₆)-alkenyl, (C₂-C₆)-alkynyl;

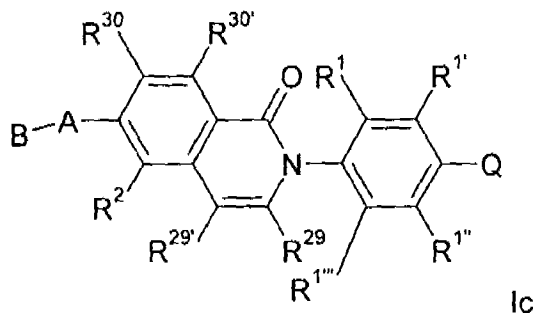
particularly preferably H, F, Cl, Br, CF₃, CN, OCF₃, O-(C₁-C₆)-alkyl, O-(C₁-C₄)-alkoxy-(C₁-C₄)-alkyl, (C₁-C₆)-alkyl;

very particularly preferably H, F, Cl, O-(C₁-C₆)-alkyl, (C₁-C₆)-alkyl;

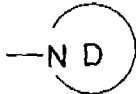
5 in particular very particularly preferably H; and

Q a group , where the group  has the aforementioned meanings.

10 A further aspect of the present invention is thus compounds of the formula Ic



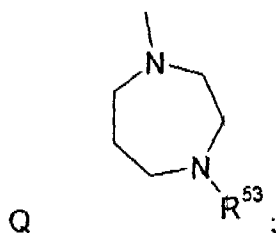
in which the radicals and groups in the compound of the formula Ic have the

aforementioned meanings, where Q is a group of the formula  with the
15 aforementioned meanings.

A very particularly preferred embodiment of the present invention are compounds in which the meanings are:

Y C(R29)=C(R29');

X C(R30)=C(R30') ;



5

R53 H, (C₁-C₈)-alkyl, (C₁-C₄)-alkoxy-(C₁-C₄)-alkyl, (C₃-C₈)-alkenyl, (C₃-C₈)-alkynyl, (C(R58)(R59))_q-R60.

10 A further very particularly preferred embodiment of the present invention are compounds in which the meanings are:

Y C(R29)=C(R29');

X C(R30)=C(R30') ;

15 Q saturated 6-11 membered azaspirocyclic compound which comprises an element N(R53);

R53 H, (C₁-C₈)-alkyl, (C₁-C₄)-alkoxy-(C₁-C₄)-alkyl, (C₃-C₈)-alkenyl, (C₃-C₈)-alkynyl, (C(R58)(R59))_q-R60.

20 A further very particularly preferred embodiment of the present invention are compounds in which the meanings are:

Y C(R29)=C(R29');

X C(R30)=C(R30') ;

Q saturated monocyclic 5-7-membered azacycle which comprises an element $C(R45)((CH_2)_6-N(R53)(R54))$;

5 R53, R54

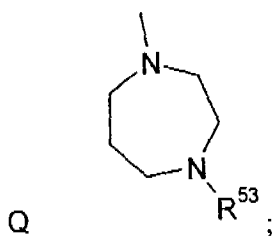
independently of one another H, (C₁-C₈)-alkyl, (C₁-C₄)-alkoxy-(C₁-C₄)-alkyl, (C₃-C₈)-alkenyl, (C₃-C₈)-alkynyl, (C(R58)(R59))_q-R60; or R53 and R54 form together with the nitrogen atom to which they are bonded a 4 to 10-membered mono-, bi- or spirocyclic ring which, apart from the nitrogen atom, comprises 0 to 3 additional heteroatoms selected from the group of N, O and S and may additionally be substituted by one or more of the following substituents: F, Cl, Br, CF₃, O-(C₁-C₈)-alkyl, (C₁-C₆)-alkyl, CO(R64), oxo, OH, (C₁-C₄)-alkoxy-(C₁-C₄)-alkyl, hydroxy-(C₁-C₄)-alkyl, N(R67)CO(R68), SO₂(C₁-C₆)-alkyl.

15

A further very particularly preferred embodiment of the present invention are compounds in which the meanings are:

20 Y C(R27)(R27')C(R28)(R28') ;

X C(R30)=C(R30') ;



25 R53 (C₁-C₄)-alkoxy-(C₁-C₄)-alkyl, (C(R58)(R59))_q-R60;

R58, 59

independently of one another H, OH;

5 q, r independently of one another 1, 2, 3, 4;

R60, R63

independently of one another F, O-(C₁-C₆)-alkyl, N(R74)CO(C₁-C₆)-alkyl, SO₂(C₁-C₆)-alkyl, 3-12 membered mono-, bi- or spirocyclic ring which
10 comprises 0 to 3 additional heteroatoms from the group of O and S, and the 3-12 membered ring may comprise further substituents such as F, Cl, Br, OH, CF₃, NO₂, CN, OCF₃, oxo, O-(C₁-C₆)-alkyl, (C₁-C₄)-alkoxy-(C₁-C₄)-alkyl, hydroxy-(C₁-C₄)-alkyl, (C₁-C₆)-alkyl, (C₂-C₆)-alkenyl, (C₂-C₆)-alkynyl and SO₂(C₁-C₆)-alkyl.

15

A further very particularly preferred embodiment of the present invention are compounds in which the meanings are:

20 Y C(R27)(R27')C(R28)(R28') ;

X C(R30)=C(R30') ;

Q saturated 6-11 membered spirocycle which comprises an element N(R53);

25 R53 (C₁-C₄)-alkoxy-(C₁-C₄)-alkyl, (C(R58)(R59))_q-R60 ;

R58, 59

independently of one another H, OH;

q 1, 2, 3, 4;

R60, R63

independently of one another F, O-(C₁-C₆)-alkyl, N(R74)CO(C₁-C₆)-alkyl,
 5 SO₂(C₁-C₆)-alkyl, 3-12 membered mono-, bi- or spirocyclic ring which
 comprises 0 to 3 additional heteroatoms from the group of O and S, and the
 3-12 membered ring may comprise further substituents such as F, Cl, Br,
 OH, CF₃, NO₂, CN, OCF₃, oxo, O-(C₁-C₆)-alkyl, (C₁-C₄)-alkoxy-(C₁-C₄)-alkyl,
 hydroxy-(C₁-C₄)-alkyl, (C₁-C₅)-alkyl, (C₂-C₆)-alkenyl, (C₂-C₆)-alkynyl and
 10 SO₂(C₁-C₆)-alkyl.

A further very particularly preferred embodiment of the present invention are
 compounds in which the meanings are:

15

Y C(R27)(R27')C(R28)(R28') ;

X C(R30)=C(R30') ;

Q saturated monocyclic 5-7-membered azacycle which comprises an element
 C(R45)((CH₂)_o-N(R53)(R54));

20

R45 H;

o 0, 1, 2;

25

R53 H, (C₁-C₈)-alkyl, (C₁-C₄)-alkoxy-(C₁-C₄)-alkyl, (C₃-C₈)-alkenyl, (C₃-C₈)-
 alkynyl, (C(R58)(R59))_q-R60;

R54 (C(R58)(R59))_q-R60, (C₁-C₄)-alkoxy-(C₁-C₄)-alkyl, CO(R57),
 CO(C(R61)(R62))_r-R63;

30

R58, 59 independently of one another H, OH;

q 1, 2, 3, 4;

5 R60, R63

independently of one another F, O-(C₁-C₆)-alkyl, N(R74)CO(C₁-C₆)-alkyl, SO₂(C₁-C₆)-alkyl, 3-12 membered mono-, bi- or spirocyclic ring which comprises no heteroatoms, and the 3-12 membered ring may comprise further substituents such as F, Cl, Br, OH, CF₃, NO₂, CN, OCF₃, oxo, O-(C₁-C₆)-alkyl, (C₁-C₄)-alkoxy-(C₁-C₄)-alkyl, hydroxy-(C₁-C₄)-alkyl, (C₁-C₆)-alkyl, 10 (C₂-C₆)-alkenyl, (C₂-C₆)-alkynyl and SO₂(C₁-C₆)-alkyl.

A further very particularly preferred embodiment of the present invention are compounds in which the meanings are:

15

Y C(R27)(R27')C(R28)(R28') ;

X C(R30)=C(R30') ;

Q saturated monocyclic 5-7-membered azacycle which comprises an element C(R45)((CH₂)_o-N(R53)(R54));

20

R45 H;

o 0, 1, 2;

25

R53 H, (C₁-C₈)-alkyl, (C₁-C₄)-alkoxy-(C₁-C₄)-alkyl, (C₃-C₈)-alkenyl, (C₃-C₈)-alkynyl, (C(R58)(R59))_q-R60;

R54 (C(R58)(R59))_q-R60';

30

q* 0;

R60' SO₂(C₁-C₆)-alkyl, 3-12 membered mono-, bi- or spirocyclic ring which comprises no heteroatoms, and the 3-12 membered ring is substituted by one or more of the following substituents F, Cl, Br, OH, CF₃, NO₂, CN, OCF₃, oxo, O-(C₁-C₆)-alkyl, (C₁-C₄)-alkoxy-(C₁-C₄)-alkyl, hydroxy-(C₁-C₄)-alkyl, (C₁-C₆)-alkyl, (C₂-C₆)-alkenyl, (C₂-C₆)-alkynyl and SO₂(C₁-C₆)-alkyl.

A further very particularly preferred embodiment of the present invention are compounds in which the meanings are:

10

Y C(R27)(R27')C(R28)(R28') ;

X C(R30)=C(R30') ;

Q saturated monocyclic 5-7-membered azacycle which comprises an element C(R45)((CH₂)_o-N(R53)(R54));

15

R45 H;

o 0, 1, 2;

20

R53 and R54 form together with the nitrogen atom to which they are bonded a 5 to 6-membered monocyclic ring which, apart from the nitrogen atom, comprises 0 to 3 additional heteroatoms selected from the group of N, O and S and is substituted by one or more of the following substituents: F, Cl, Br, CF₃, O-(C₁-C₆)-alkyl, (C₁-C₆)-alkyl, CO(R64), oxo, OH, (C₁-C₄)-alkoxy-(C₁-C₄)-alkyl, hydroxy-(C₁-C₄)-alkyl, N(R67)CO(R68), SO₂(C₁-C₆)-alkyl.

25

A further very particularly preferred embodiment of the present invention are compounds in which the meanings are:

30

Y C(R27)(R27')C(R28)(R28') ;

Formulations

The amount of a compound of formula I necessary to achieve the desired biological effect depends on a number of factors, for example the specific compound chosen, the intended use, the mode of administration and the clinical condition of the patient. The daily dose is generally in the range from 0.001 mg to 100 mg (typically from 0.01 mg to 50 mg) per day and per kilogram of body weight, for example 0.1-10 mg/kg/day. An intravenous dose may be, for example, in the range from 0.001 mg to 1.0 mg/kg, which can suitably be administered as infusion of 10 ng to 100 ng per kilogram and per minute. Suitable infusion solutions for these purposes may contain, for example, from 0.1 ng to 10 mg, typically from 1 ng to 10 mg, per milliliter. Single doses may contain, for example, from 1 mg to 10 g of the active ingredient. Thus, ampoules for injections may contain, for example, from 1 mg to 100 mg, and single-dose formulations which can be administered orally, such as, for example, tablets or capsules, may contain, for example, from 0.05 to 1000 mg, typically from 0.5 to 600 mg. For the therapy of the abovementioned conditions, the compounds of formula I may be used as the compound itself, but they are preferably in the form of a pharmaceutical composition with an acceptable carrier. The carrier must, of course, be acceptable in the sense that it is compatible with the other ingredients of the composition and is not harmful for the patient's health. The carrier may be a solid or a liquid or both and is preferably formulated with the compound as a single dose, for example as a tablet, which may contain from 0.05% to 95% by weight of the active ingredient. Other pharmaceutically active substances may likewise be present, including other compounds of formula I. The pharmaceutical compositions of the invention can be produced by one of the known pharmaceutical methods, which essentially consist of mixing the ingredients with pharmacologically acceptable carriers and/or excipients.

Pharmaceutical compositions of the invention are those suitable for oral, rectal, topical, peroral (for example sublingual) and parenteral (for example subcutaneous, intramuscular, intradermal or intravenous) administration, although the most suitable mode of administration depends in each individual case on the nature and severity of

the condition to be treated and on the nature of the compound of formula I used in each case. Coated formulations and coated slow-release formulations also belong within the framework of the invention. Preference is given to acid- and gastric juice-resistant formulations. Suitable coatings resistant to gastric juice comprise cellulose acetate phthalate, polyvinyl acetate phthalate, hydroxypropylmethylcellulose phthalate
5 acetate phthalate, polyvinyl acetate phthalate, hydroxypropylmethylcellulose phthalate and anionic polymers of methacrylic acid and methyl methacrylate.

Suitable pharmaceutical preparations for oral administration may be in the form of separate units such as, for example, capsules, cachets, suckable tablets or tablets,
10 each of which contains a defined amount of at least one compound of formula I; as powders or granules; as solution or suspension in an aqueous or nonaqueous liquid; or as an oil-in-water or water-in-oil emulsion. These compositions may, as already mentioned, be prepared by any suitable pharmaceutical method which includes a step in which the active ingredient and the carrier (which may consist of one or more
15 additional ingredients) are brought into contact. The compositions are generally produced by uniform and homogeneous mixing of the active ingredient with a liquid and/or finely divided solid carrier, after which the product is shaped if necessary. Thus, for example, a tablet can be produced by compressing or molding a powder or granules of the compound, where appropriate with one or more additional ingredients.
20 Compressed tablets can be produced by tableting the compound in free-flowing form such as, for example, a powder or granules, where appropriate mixed with a binder, glidant, inert diluent and/or one (or more) surface-active/dispersing agent(s) in a suitable machine. Molded tablets can be produced by molding the compound, which is in powder form and is moistened with an inert liquid diluent, in a suitable machine.

25
Pharmaceutical compositions which are suitable for peroral (sublingual) administration comprise suckable tablets which contain at least one compound of formula I with a flavoring, normally sucrose and gum arabic or tragacanth, and pastilles which comprise the compound in an inert base such as gelatin and glycerol or sucrose and
30 gum arabic.

Pharmaceutical compositions suitable for parenteral administration comprise preferably sterile aqueous preparations of at least one compound of formula I, which are preferably isotonic with the blood of the intended recipient. These preparations are preferably administered intravenously, although administration may also take place by subcutaneous, intramuscular or intradermal injection. These preparations can preferably be produced by mixing the compound with water and making the resulting solution sterile and isotonic with blood. Injectable compositions of the invention generally contain from 0.1 to 5% by weight of the active compound.

Pharmaceutical compositions suitable for rectal administration are preferably in the form of single-dose suppositories. These can be produced by mixing at least one compound of the formula I with one or more conventional solid carriers, for example cocoa butter, and shaping the resulting mixture.

Pharmaceutical compositions suitable for topical use on the skin are preferably in the form of ointment, cream, lotion, paste, spray, aerosol or oil. Carriers which can be used are petrolatum, lanolin, polyethylene glycols, alcohols and combinations of two or more of these substances. The active ingredient is generally present in a concentration of from 0.1 to 15% by weight of the composition, for example from 0.5 to 2%.

20

Transdermal administration is also possible. Pharmaceutical compositions suitable for transdermal uses can be in the form of single patches which are suitable for long-term close contact with the patient's epidermis. Such patches suitably contain the active ingredient in an aqueous solution which is buffered where appropriate, dissolved and/or dispersed in an adhesive or dispersed in a polymer. A suitable active ingredient concentration is about 1% to 35%, preferably about 3% to 15%. A particular possibility is for the active ingredient to be released by electrotransport or iontophoresis as described, for example, in *Pharmaceutical Research*, 2(6): 318 (1986).

30

The compounds of the formula I are distinguished by beneficial effects on lipid metabolism, and they are particularly suitable for weight reduction and for maintaining a reduced weight after weight reduction has taken place in mammals and as anorectic agents. The compounds are distinguished as selective MCH1R antagonists by their low toxicity, the small effect on metabolizing enzymes and their few side effects. In particular, preferred compounds of the invention are notable for low blockade of the hERG channel. In addition, preferred compounds of the formula I are noticeably soluble in aqueous systems and thus particularly suitable for pharmaceutical development. The pharmacological effect is moreover achieved in in vivo test models after oral administration from well-tolerated vehicles.

The compounds can be employed alone or in combination with other weight-reducing or anorectic active ingredients. Further anorectic active ingredients of this type are mentioned, for example, in the Rote Liste, chapter 01 under weight-reducing agents/appetite suppressants, and may also include active ingredients which increase the energy turnover of the organism and thus lead to weight reduction or else those which influence the general metabolism of the organism in such a way that an increased calorie intake does not lead to an enlargement of the fat depots and a normal calorie intake leads to a reduction of the fat depots of the organism. The compounds are suitable for the prophylaxis and, in particular, for the treatment of excessive weight or obesity. The compounds are further suitable for the prophylaxis and, in particular, for the treatment of type II diabetes, of arteriosclerosis and for normalizing lipid metabolism and for the treatment of high blood pressure.

25 Combinations with other medicaments

The compounds of the invention can be administered alone or in combination with one or more further pharmacologically active substances which have, for example, beneficial effects on metabolic disturbances or disorders frequently associated therewith. Examples of such medicaments are

1. medicaments which lower blood glucose, antidiabetics,
2. active ingredients for the treatment of dyslipidemias,
3. antiatherosclerotic medicaments,
4. antiobesity agents,
- 5 5. antiinflammatory active ingredients
6. active ingredients for the treatment of malignant tumors
7. antithrombotic active ingredients
8. active ingredients for the treatment of high blood pressure
9. active ingredients for the treatment of heart failure and
- 10 10. active ingredients for the treatment and/or prevention of complications caused
by diabetes or associated with diabetes
11. active ingredients for the treatment neurodegenerative conditions
12. active ingredients for the treatment diseases of the central nervous system
13. active ingredients for the treatment of medicament-, nicotine- or alcohol
- 15 addiction
14. pain killers

They can be combined with the compounds of the invention of the formula I in
20 particular for a synergistic improvement in the effect. Administration of the active
ingredient combination can take place either by separate administration of the active
ingredients to the patient or in the form of combination products in which a plurality of
active ingredients are present in one pharmaceutical preparation.

25 Examples of active ingredients suitable for combination products are listed below:

All antidiabetics which are mentioned in the Rote Liste 2006, chapter 12; all weight-
reducing agents/appetite suppressants which are mentioned in the Rote Liste 2006,
chapter 1; all lipid-lowering agents which are mentioned in the Rote Liste 2006,
30 chapter 58. Most of the active ingredients mentioned hereinafter are disclosed in the
USP Dictionary of USAN and International Drug Names, US Pharmacopeia, Rockville
2001.

Antidiabetics include insulin and insulin derivatives such as, for example, Lantus[®] (see www.lantus.com) or Apidra[®] (HMR 1964) or those described in WO2005005477 (Novo Nordisk), fast-acting insulins (see US 6,221,633), inhalable insulins such as, for example, Exubera[®] or oral insulins such as, for example, IN-105 (Nobex) or Oral-lyn[™] (Generex Biotechnology), GLP-1-derivatives such as, for example, exenatide, liraglutide or those which have been disclosed in WO98/08871 or WO2005027978 of Novo Nordisk A/S, in WO01/04156 of Zealand or in WO00/34331 of Beaufour-Ipsen, Pramlintide Acetate (Symlin; Amylin Pharmaceuticals), and orally effective hypoglycemic active ingredients.

- 10 The active ingredients include preferably
- sulfonylureas,
 - biguanidines,
 - meglitinides,
 - oxadiazolidindiones,
 - 15 thiazolidindiones,
 - glucosidase inhibitors,
 - inhibitors of glycogen phosphorylase,
 - glucagon antagonists,
 - glucokinase activators,
 - 20 inhibitors of fructose-1,6-bisphosphatase
 - modulators of glucose transporter 4 (GLUT4),
 - inhibitors of glutamine-fructose-6-phosphate amidotransferase (GFAT),
 - GLP-1 agonists, potassium channel openers such as, for example, those which have been disclosed in WO 97/26265 and WO 99/03861 of Novo Nordisk A/S,
 - 25 inhibitors of dipeptidylpeptidase IV (DPP-IV),
 - insulin sensitizers,

- inhibitors of liver enzymes involved in stimulating gluconeogenesis and/or glycogenolysis,
modulators of glucose uptake, of glucose transport and of glucose reabsorption,
inhibitors of 11 β -HSD1,
5 inhibitors of protein tyrosine phosphatase 1B (PTP1B),
modulators of the sodium-dependent glucose transporter 1 or 2 (SGLT1, SGLT2),
compounds which alter lipid metabolism such as antihyperlipidemic active ingredients and antilipidemic active ingredients,
compounds which reduce food intake,
10 compounds which increase thermogenesis,
PPAR and RXR modulators and
active ingredients which act on the ATP-dependent potassium channel of the beta cells.
- 15 In one embodiment of the invention, at least one compound of the formula I is administered in combination with an HMGCoA reductase inhibitor such as simvastatin, fluvastatin, pravastatin, lovastatin, atorvastatin, cerivastatin, rosuvastatin or L-659699.
- In one embodiment of the invention, at least one compound of the formula I is
20 administered in combination with a cholesterol absorption inhibitor such as, for example, ezetimibe, tiqeside, pamaqueside, FM-VP4 (sitostanol/campesterol ascorbyl phosphate; Forbes Medi-Tech, WO2005042692), MD-0727 (Microbia Inc., WO2005021497) or with compounds as described in WO2002066464 (Kotobuki Pharmaceutical Co. Ltd.), WO2005062824 (Merck & Co.) or WO2005061451 and
25 WO2005061452 (AstraZeneca AB).

In one embodiment of the invention, at least one compound of the formula I is administered in combination with a PPAR gamma agonist such as, for example,

rosiglitazone, pioglitazone, JTT-501, GI 262570, R-483 or CS-011 (rivoglitazone).

In one embodiment of the invention, at least one compound of the formula I is administered in combination with a PPAR alpha agonist such as, for example,
5 GW9578, GW-590735, K-111, LY-674, KRP-101 or DRF-10945.

In one embodiment of the invention, at least one compound of the formula I is administered in combination with a mixed PPAR alpha/gamma agonist such as, for example, muraglitazar, tesaglitazar, naveglitazar, LY-510929, ONO-5129, E-3030 or
10 as described in WO00/64888, WO00/64876, WO03/020269, WO2004075891, WO2004076402, WO2004075815, WO2004076447, WO2004076428, WO2004076401, WO2004076426, WO2004076427, WO2006018118, WO2006018115, und WO2006018116 or in J.P. Berger et al., TRENDS in Pharmacological Sciences 28(5), 244-251, 2005.

15

In one embodiment of the invention, at least one compound of the formula I is administered in combination with a PPAR delta agonist such as, for example, GW-501516 or as described in WO2005097762, WO2005097786, WO2005097763, und WO2006029699.

20

In one embodiment, at least one compound of the formula I is administered in combination with metaglidasen or with MBX-2044 or other partial PPAR gamma agonists/antagonists.

25 In one embodiment of the invention, at least one compound of the formula I is administered in combination with a fibrate such as, for example, fenofibrate, clofibrate or bezafibrate.

In one embodiment of the invention, at least one compound of the formula I is administered in combination with an MTP inhibitor such as, for example, implitapide, BMS-201038, R-103757 or those described in WO2005085226.

- 5 In one embodiment of the invention, at least one compound of the formula I is administered in combination with a CETP inhibitor such as, for example, torcetrapib or JTT-705.

- 10 In one embodiment of the invention, at least one compound of the formula I is administered in combination with a bile acid absorption inhibitor (see, for example, US 6,245,744, US 6,221,897 or WO00/61568), such as, for example, HMR 1741 or those as described in DE 10 2005 033099.1 and DE 10 2005 033100.9.

- 15 In one embodiment of the invention, at least one compound of the formula I is administered in combination with a polymeric bile acid adsorbent such as, for example, cholestyramine or colesevelam.

- 20 In one embodiment of the invention, at least one compound of the formula I is administered in combination with an LDL receptor inducer (see US 6,342,512), such as, for example, HMR1171, HMR1586 or those as described in WO2005097738.

- In one embodiment, at least one compound of the formula I is administered in combination with Omacor® (omega-3 fatty acids; highly concentrated ethyl esters of eicosapentaenoic acid and of docosahexaenoic acid).

25

In one embodiment of the invention, at least one compound of the formula I is administered in combination with an ACAT inhibitor such as, for example, avasimibe.

In one embodiment of the invention, at least one compound of the formula I is administered in combination with an antioxidant such as, for example, OPC-14117, probucol, tocopherol, ascorbic acid, β -carotene or selenium.

- 5 In one embodiment of the invention, at least one compound of the formula I is administered in combination with a vitamin such as, for example, vitamin B6 or vitamin B12.

- 10 In one embodiment of the invention, at least one compound of the formula I is administered in combination with a lipoprotein lipase modulator such as, for example, ibrolipim (NO-1886).

- 15 In one embodiment of the invention, at least one compound of the formula I is administered in combination with an ATP citrate lyase inhibitor such as, for example, SB-204990.

- 20 In one embodiment of the invention, at least one compound of the formula I is administered in combination with a squalene synthetase inhibitor such as, for example, BMS-188494 or as described in WO2005077907.

- In one embodiment of the invention, at least one compound of the formula I is administered in combination with a lipoprotein(a) antagonist such as, for example, gemcabene (CI-1027).

- 25 In one embodiment of the invention, at least one compound of the formula I is administered in combination with an HM74A receptor agonist such as, for example, nicotinic acid.

In one embodiment of the invention, at least one compound of the formula I is administered in combination with a lipase inhibitor such as, for example, orlistat or cetilistat (ATL-962).

- 5 In one embodiment, at least one compound of the formula I is administered in combination with insulin.

In one embodiment, at least one compound of the formula I is administered in combination with a sulfonylurea such as, for example, tolbutamide, glibenclamide, glipizide or glimepiride.

- 10 In one embodiment, at least one compound of the formula I is administered in combination with a biguanide such as, for example, metformin.

In another embodiment, at least one compound of the formula I is administered in combination with a meglitinide such as, for example, repaglinide or nateglinide.

- 15 In one embodiment, at least one compound of the formula I is administered in combination with a thiazolidinedione such as, for example, troglitazone, ciglitazone, pioglitazone, rosiglitazone or the compounds disclosed in WO 97/41097 of Dr. Reddy's Research Foundation, in particular 5-[[4-[(3,4-dihydro-3-methyl-4-oxo-2-quinazolinylmethoxy)phenyl]methyl]-2,4-thiazolidinedione.

- 20 In one embodiment, at least one compound of the formula I is administered in combination with an α -glucosidase inhibitor such as, for example, miglitol or acarbose.

- In one embodiment, at least one compound of the formula I is administered in combination with an active ingredient which acts on the ATP-dependent potassium channel of the beta cells, such as, for example, tolbutamide, glibenclamide, glipizide, glimepiride or repaglinide.
- 25

In one embodiment, at least one compound of the formula I is administered in combination with more than one of the aforementioned compounds, e.g. in combination with a sulfonylurea and metformin, a sulfonylurea and acarbose, repaglinide and metformin, insulin and a sulfonylurea, insulin and metformin, insulin
5 and troglitazone, insulin and lovastatin, etc.

In one embodiment, at least one compound of the formula I is administered in combination with substances which influence hepatic glucose production, such as, for example an inhibitor of glycogen phosphorylase, such as, for example, PSN-357 or
10 FR-258900 or those as described in WO2003084922, WO2004007455, WO2005073229-31 or WO2005067932.

In one embodiment, at least one compound of the formula I is administered in combination with glucagon receptor antagonists such as, for example, A-770077,
15 NNC-25-2504 or as described in WO2004100875 or WO2005065680.

In one embodiment, at least one compound of the formula I is administered in combination with activators of glucokinase, such as, for example, RO-4389620, LY-2121260 (WO2004063179), PSN-105, PSN-110, GKA-50 or such as described in
20 WO2004072031, WO2004072066, WO 05103021, WO 06016178, WO 00058293, WO 00183465, WO 00183478, WO 00185706, WO 00185707, WO 01044216, GB 02385328, WO 02008209, WO 02014312, WO 0246173, WO 0248106, DE 10259786, WO 03095438, US 04067939, WO 04052869, EP 1532980, WO 03055482, WO 04002481, WO 05049019, WO 05066145, WO 05123132, WO 03080585,
25 WO03097824, WO 04081001, WO 05063738, WO 05090332, WO 04063194, WO 01020327, WO 03000262, WO 03000267, WO 03015774, WO 04045614, WO 04046139, WO 05044801, WO 05054200, WO 05054233, WO 05056530, WO 05080359, WO 05080360 oder WO 05121110.

In one embodiment, at least one compound of the formula I is administered in
30 combination with an inhibitor of gluconeogenesis, such as, for example, FR-225654.

In one embodiment, at least one compound of the formula I is administered in combination with inhibitors of fructose-1,6-bisphosphatase (FBPase), such as, for example, CS-917.

- 5 In one embodiment, at least one compound of the formula I is administered in combination with modulators of glucose transporter 4 (GLUT4), such as, for example, KST-48 (D.-O. Lee et al.: *Arzneim.-Forsch. Drug Res.* 54 (12), 835 (2004)).

- 10 In one embodiment, at least one compound of the formula I is administered in combination with inhibitors of glutamine-fructose-6-phosphate amidotransferase (GFAT), as are described for example in WO2004101528.

- In one embodiment, at least one compound of the formula I is administered in combination with inhibitors of dipeptidylpeptidase IV (DPP-IV), such as, for example, 15 vildagliptin (LAF-237), sitagliptin (MK-0431), saxagliptin (BMS-477118), GSK-823093, PSN-9301, SYR-322, SYR-619, TA-6666, TS-021, GRC-8200, GW-825964X or as are described in WO2003074500, WO2003106456, WO200450658, WO2005058901, WO2005012312, WO2005012308, PCT/EP2005/007821, PCT/EP2005/008005, PCT/EP2005/008002, PCT/EP2005/008004, PCT/EP2005/008283, DE 10 2005 20 012874.2 or DE 10 2005 012873.4.

- In one embodiment, at least one compound of the formula I is administered in combination with inhibitors of 11-beta-hydroxysteroid dehydrogenase 1 (11 β -HSD1), such as, for example, BVT-2733 or those as are described for example in 25 WO200190090-94, WO200343999, WO2004112782, WO200344000, WO200344009, WO2004112779, WO2004113310, WO2004103980, WO2004112784, WO 2003065983, WO2003104207, WO2003104208, WO2004106294, WO2004011410, WO2004033427, WO2004041264, WO2004037251, WO2004056744, WO2004065351, WO2004089367, WO2004089380, 30 WO2004089470-71, WO2004089896, WO2005016877 or WO2005097759.

In one embodiment, at least one compound of the formula I is administered in combination with inhibitors of protein tyrosine phosphatase 1B (PTP1B), as are described for example in WO200119830-31, WO200117516, WO2004506446, WO2005012295, PCT/EP2005/005311, PCT/EP2005/005321, PCT/EP2005/007151,
5 PCT/EP2005/ or DE 10 2004 060542.4.

In one embodiment, at least one compound of the formula I is administered in combination with modulators of the sodium-dependent glucose transporter 1 or 2 (SGLT1, SGLT2), such as, for example, KGA-2727, T-1095, SGL-0010, AVE 2268 and
10 SAR 7226 or as are described for example in WO2004007517, WO200452903, WO200452902, WO2005121161, PCT/EP2005/005959, WO2005085237, JP2004359630 or by A. L. Handlon in Expert Opin. Ther. Patents (2005) 15(11), 1531-1540.

15 In one embodiment, at least one compound of the formula I is administered in combination with modulators of GPR40.

In one embodiment, at least one compound of the formula I is administered in combination with inhibitors of hormone-sensitive lipase (HSL) as described for
20 example in WO01/17981, WO01/66531, WO2004035550, WO2005073199 or WO03/051842.

In one embodiment, at least one compound of the formula I is administered in combination with inhibitors of acetyl-CoA carboxylase (ACC), such as, for example,
25 those as described in WO199946262, WO200372197, WO2003072197 or WO2005044814.

In one embodiment, at least one compound of the formula I is administered in combination with an inhibitor of phosphoenolpyruvate carboxykinase (PEPCK), such
30 as, for example, those as described in WO2004074288.

In one embodiment, at least one compound of the formula I is administered in combination with an inhibitor of glycogen synthase kinase 3 beta (GSK-3 beta), as described for example in US2005222220, WO2005085230, WO2005111018, PCT/EP2005/005346, WO2003078403, WO2004022544, WO2003106410,
5 WO2005058908, US2005038023, WO2005009997, US2005026984, WO2005000836, WO2004106343, EP1460075, WO2004014910, WO2003076442, WO2005087727 or WO2004046117.

In one embodiment, at least one compound of the formula I is administered in
10 combination with an inhibitor of protein kinase C beta (PKC beta), such as, for example, ruboxistaurin.

In one embodiment, at least one compound of the formula I is administered in combination with an endothelin A receptor antagonist such as, for example, avosentan
15 (SPP-301).

In one embodiment, at least one compound of the formula I is administered in combination with inhibitors of "I-kappaB kinase" (IKK inhibitors), as are described for example in WO2001000610, WO2001030774, WO2004022553 or WO2005097129.
20

In one embodiment, at least one compound of the formula I is administered in combination with modulators of the glucocorticoid receptor, like those described for example in WO2005090336.

25 In a further embodiment, at least one compound of the formula I is administered in combination with CART modulators (see "Cocaine-amphetamine-regulated transcript influences energy metabolism, anxiety and gastric emptying in mice" Asakawa, A. et al.: Hormone and Metabolic Research (2001), 33(9), 554-558);

NPY antagonists such as, for example, naphthalene-1-sulfonic acid {4-[(4-amino-

quinazolin-2-ylamino)methyl]cyclohexylmethyl]amide hydrochloride (CGP 71683A);
peptide YY 3-36 (PYY3-36) or analogous compounds, such as, for example, CJC-1682
(PYY3-36 conjugated with human serum albumin via Cys34), CJC-1643 (derivative of
PYY3-36 which conjugates in vivo to serum albumin) or those as are described in
5 WO2005080424;

cannabinoid receptor 1 antagonists (such as, for example, rimonabant, SR147778 or
those as are described for example in EP 0656354, WO 00/15609, WO02/076949,
WO2005080345, WO2005080328, WO2005080343, WO2005075450,
WO2005080357, WO200170700, WO2003026647-48, WO200302776,
10 WO2003040107, WO2003007887, WO2003027069, US6,509,367, WO200132663,
WO2003086288, WO2003087037, WO2004048317, WO2004058145,
WO2003084930, WO2003084943, WO2004058744, WO2004013120,
WO2004029204, WO2004035566, WO2004058249, WO2004058255,
WO2004058727, WO2004069838, US20040214837, US20040214855,
15 US20040214856, WO2004096209, WO2004096763, WO2004096794,
WO2005000809, WO2004099157, US20040266845, WO2004110453,
WO2004108728, WO2004000817, WO2005000820, US20050009870,
WO200500974, WO2004111033-34, WO200411038-39, WO2005016286,
WO2005007111, WO2005007628, US20050054679, WO2005027837,
20 WO2005028456, WO2005063761-62, WO2005061509 or WO2005077897);

MC4 agonists (e.g. 1-amino-1,2,3,4-tetrahydronaphthalene-2-carboxylic acid [2-(3a-
benzyl-2-methyl-3-oxo-2,3,3a,4,6,7-hexahydropyrazolo[4,3-c]pyridin-5-yl)-1-(4-chloro-
phenyl)-2-oxoethyl]amide; (WO 01/91752)) or LB53280, LB53279, LB53278 or THIQ,
MB243, RY764, CHIR-785, PT-141 or those that are described in WO2005060985,
25 WO2005009950, WO2004087159, WO2004078717, WO2004078716,
WO2004024720, US20050124652, WO2005051391, WO2004112793,
WOUS20050222014, US20050176728, US20050164914, US20050124636,
US20050130988, US20040167201, WO2004005324, WO2004037797,
WO2005042516, WO2005040109, WO2005030797, US20040224901,
30 WO200501921, WO200509184, WO2005000339, EP1460069, WO2005047253,
WO2005047251, EP1538159, WO2004072076 or WO2004072077;

orexin receptor antagonists (e.g. 1-(2-methylbenzoxazol-6-yl)-3-[1,5]naphthyridin-4-ylurea hydrochloride (SB-334867-A) or those as are described for example in WO200196302, WO200185693, WO2004085403 or WO2005075458);

histamine H3 receptor agonists (e.g. ABT-834, ABT-239, 3-cyclohexyl-1-(4,4-dimethyl-1,4,6,7-tetrahydroimidazo[4,5-c]pyridin-5-yl)propan-1-one oxalic acid salt (WO 00/63208) or those as are described in WO200064884, WO2005082893, FR2870846 WO2005037810, Celanire, S., et al. Drug Discovery Today 2005, 10, 1613-1627);

CRF antagonists (e.g. [2-methyl-9-(2,4,6-trimethylphenyl)-9H-1,3,9-triazafluoren-4-yl]dipropylamine (WO 00/66585));

10 CRF BP antagonists (e.g. urocortin);

urocortin agonists;

β 3 agonists (such as, for example, 1-(4-chloro-3-methanesulfonylmethylphenyl)-2-[2-(2,3-dimethyl-1H-indol-6-yloxy)ethylamino]ethanol hydrochloride (WO 01/83451));

MSH (melanocyte-stimulating hormone) agonists;

15 MCH (melanin-concentrating hormone) receptor antagonists (such as, for example, NGD-4715, AMG-076, NBI-845, A-761, A-665798, A-798, ATC-0175, T-226296, T-71, GW-803430 or compounds such as are described in WO2003/15769, WO2005085200, WO2005019240, WO2004011438, WO2004012648, WO2003015769, WO2004072025, WO2005070898, WO2005070925, WO2004039780, WO2003033476, WO2002006245, WO2002002744, WO2003004027 or FR2868780);

CCK-A agonists (such as, for example, {2-[4-(4-chloro-2,5-dimethoxyphenyl)-5-(2-cyclohexylethyl)thiazol-2-yl]carbonyl}-5,7-dimethylindol-1-yl}acetic acid trifluoroacetic acid salt (WO 99/15525), SR-146131 (WO 0244150) or SSR-125180);

25 serotonin reuptake inhibitors (e.g. dexfenfluramine);

mixed serotonergic and noradrenergic compounds (e.g. WO 00/71549);

5-HT receptor agonists, e.g. 1-(3-ethylbenzofuran-7-yl)piperazine oxalic acid salt (WO 01/09111);

5-HT_{2C} receptor agonists (such as, for example, APD-356, BVT-933 or those as are

described in WO200077010, WO20077001-02, WO2005019180, WO2003064423, WO200242304 or WO2005082859);

5-HT6 receptor antagonists as are described for example in WO2005058858;

bombesin receptor agonists (BRS-3 agonists);

5 galanin receptor antagonists;

growth hormone (e.g. human growth hormone or AOD-9604);

growth hormone-releasing compounds (tertiary butyl 6-benzyloxy-1-(2-diisopropyl-aminoethylcarbamoyl)-3,4-dihydro-1H-isoquinoline-2-carboxylate (WO 01/85695));

10 growth hormone secretagogue receptor antagonists (ghrelin antagonists) such as, for example, A-778193 or those as are described in WO2005030734;

TRH agonists (see, for example, EP 0 462 884);

uncoupling protein 2 or 3 modulators;

15 leptin agonists (see, for example, Lee, Daniel W.; Leinung, Matthew C.; Rozhavskaya-Arena, Marina; Grasso, Patricia. Leptin agonists as a potential approach to the treatment of obesity. Drugs of the Future (2001), 26(9), 873-881);

DA agonists (bromocriptine or Doprexin);

lipase/amylase inhibitors (like those described for example in WO 00/40569);

20 inhibitors of diacylglycerol O-acyltransferases (DGATs) as described for example in US2004/0224997, WO2004094618, WO200058491, WO2005044250, WO2005072740, JP2005206492 or WO2005013907;

inhibitors of fatty acid synthase (FAS) such as, for example, C75 or those as described in WO2004005277;

oxyntomodulin;

oleoyl-estrone;

25

or thyroid hormone receptor agonists such as, for example: KB-2115 or those as described in WO20058279, WO200172692, WO200194293, WO2003084915, WO2004018421 or WO2005092316.

In one embodiment, the further active ingredient is leptin;

see, for example, "Perspectives in the therapeutic use of leptin", Salvador, Javier; Gomez-Ambrosi, Javier; Fruhbeck, Gema, Expert Opinion on Pharmacotherapy (2001), 2(10), 1615-1622.

5

In one embodiment, the further active ingredient is dexamphetamine or amphetamine.

In one embodiment, the further active ingredient is fenfluramine or dexfenfluramine.

In another embodiment, the further active ingredient is sibutramine.

In one embodiment, the further active ingredient is mazindole or phentermine.

10

In one embodiment, at least one compound of the formula I is administered in combination with bulking agents, preferably insoluble bulking agents (see, for example, Carob/Caromax® (Zunft H J; et al., Carob pulp preparation for treatment of hypercholesterolemia, ADVANCES IN THERAPY (2001 Sep-Oct), 18(5), 230-6).

15 Caromax is a carob-containing product from Nutrinova, Nutrition Specialties & Food Ingredients GmbH, Industriepark Höchst, 65926 Frankfurt/Main. Combination with Caromax® is possible in one preparation or by separate administration of compounds of the formula I and Caromax®. Caromax® can in this connection also be administered in the form of food products such as, for example, in bakery products or
20 muesli bars.

In one embodiment, at least one compound of the formula I is administered in combination with PDE (Phosphodiesterase) inhibitors such as, for example, described in WO2003/077949 or WO2005012485.

25

In one embodiment, at least one compound of the formula I is administered in combination with NAR-1 (Nicotinic acid receptor) agonists such as for example described in WO2004094429.

- 5 In one embodiment, at least one compound of the formula I is administered in combination with CB2 (Cannabinoid receptor 2) agonists such as for example described in US2005/143448.

- 10 In one embodiment, at least one compound of the formula I is administered in combination with H1 (Histamine receptor 1) agonists such as for example described in WO2005101979.

In one embodiment, at least one compound of the formula I is administered in combination with Bupropion, such as for example described in WO2006017504.

15

In one embodiment, at least one compound of the formula I is administered in combination with Opiat receptor-antagonists such as for example described in WO2005107806 or WO2004094429.

- 20 In one embodiment, at least one compound of the formula I is administered in combination with inhibitors of the neutral Endopeptidase such as for example described in WO200202513, WO2002/06492, WO 2002040008, WO2002040022 or WO2002047670.

- 25 In one embodiment, at least one compound of the formula I is administered in combination with NPY (Neuropeptide Y) modulators such as for example described in WO2002047670.

In one embodiment, at least one compound of the formula I is administered in combination with a inhibitor of the sodium/hydrogen replacement protein such as described for example in WO2003092694.

- 5 In one embodiment, at least one compound of the formula I is administered in combination with modulators of the glucocorticoid receptor such as for example described in WO2005090336.

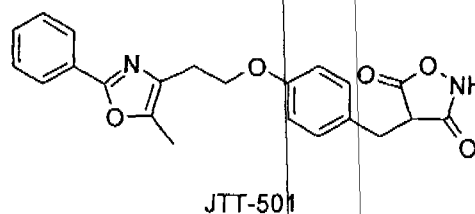
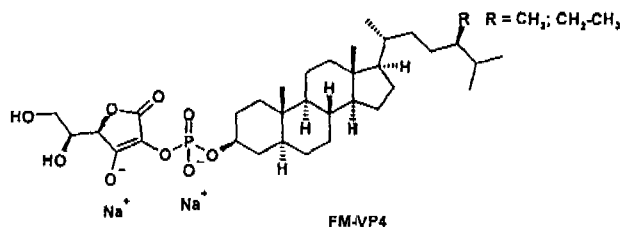
- 10 In one embodiment, at least one compound of the formula I is administered in combination with nicotin receptor-agonists such as for example described in WO2004094429.

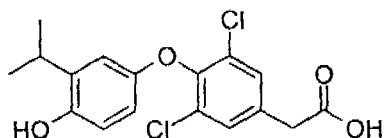
- 15 In one embodiment, at least one compound of the formula I is administered in combination with NRIs (Norepinephrine reuptake inhibitor) such as for example described in WO2002053140.

- In one embodiment, at least one compound of the formula I is administered in combination with MOA (E-beta-Methoxyacrylate), such as for example segeline, or such as for example described in WO2002053140.

20

In one embodiment, at least one compound of the formula I is administered in combination with an antithrombotic active ingredient such as for example Clopidrogel.





KB-2115

5 In one embodiment, the compounds of the formula I are administered in combination with medicaments having effects on the coronary circulation and the vascular system, such as, for example, ACE inhibitors (e.g. ramipril), medicaments which act on the angiotensin-renin system, calcium antagonists, beta blockers etc.

10 In one embodiment, the compounds of the formula I are administered in combination with medicaments having an antiinflammatory effect.

In one embodiment, the compounds of the formula I are administered in combination with medicaments which are employed for cancer therapy and cancer prevention.

15 It will be appreciated that every suitable combination of the compounds of the invention with one or more of the aforementioned compounds and optionally one or more other pharmacologically active substances is regarded as falling within the protection conferred by the present invention.

20

Test models

Suitability of the compounds of the invention as active pharmaceutical ingredient can be tested by means of various test models. Descriptions are given of such test models by way of example below.

25

Influence on the MCH receptor in vitro; determination of functional IC₅₀ values of MCH1R antagonists

Cloning of the cDNA for the human MCH receptor, preparation of a recombinant
5 HEK293 cell line which expresses the human MCH receptor, and functional
measurements with the recombinant cell line took place in analogy to the description
by Audinot et al. (J. Biol. Chem. 276, 13554-13562, 2001). A difference from the
reference was, however, the use of the plasmid pEAK8 from EDGE Biosystems (USA)
for the construction of the expression vector. The host used for the transfection was a
10 transformed HEK cell line named "PEAK Stable Cells" (likewise from EDGE
Biosystems). Functional measurements of the cellular calcium flux after addition of
agonist (MCH) in the presence of ligand of the invention took place with the aid of the
FLIPR apparatus from Molecular Devices (USA), using protocols of the apparatus
manufacturer. The compounds of the invention show a significant inhibition (>30%) of
15 the signal induced by the agonist at a concentration of 100 μ M, preferably at 10 μ M,
particularly preferably at 1 μ M, very particularly preferably at 100 nM and very very
particularly preferably at 10 nM.

Besides the functional activity it is also possible to determine the affinity for the
MCH1R according to Audinot et al. (Br. J. Pharmacol. 2001, 133, 371-378). Preferred
20 compounds of the invention show an IC₅₀ of less than 1 μ M, particularly preferably of
less than 100 nM, very particularly preferably of less than 10 nM and very very
particularly preferably of less than 1 nM.

Milk intake by female NMRI mice

25 The anorectic effect is tested on female NMRI mice. After withdrawal of feed for
24 hours, the test substance is administered intraperitoneally or preferably orally by
gavage. The animals are housed singly with free access to drinking water and, 30
minutes after administration of product, are offered condensed milk. The condensed
milk consumption is determined every half hour for 7 hours, and the general condition
30 of the animals is observed. The measured milk consumption is compared with the
vehicle-treated control animals.

The vehicle itself has no influence on feed intake. Preferred tolerated vehicles for the administration are, for example, hydroxyethylcellulose (0.5% in water) or Solutol HS15 (5% in hydroxyethylcellulose (0.5% in water)).

5 Feed and water intake of female Wistar rats

As alternative to testing the anorectic effect on NMRI mice, it is also possible analogously to use female Wistar rats weighing about 220-250 g. The animals are accustomed to the experimental environment before the start of the study. In one embodiment, the animals have free access to feed and water up to the start of the experiment. In another embodiment, access of the animals to feed is withdrawn 24 hours before the administration. For the investigation of the test substance, the animals are housed singly with free access to feed and water. Feed intake and water intake are measured continuously every 30 minutes over a period of 22 hours using a computer-assisted system (TSE Drinking & Feeding Monitor). The measured feed and water consumption is compared with the vehicle-treated control animals.

Body weight gain of diet-induced obese and standard-fed mice

For these investigations, male C57BL6J mice 5 weeks old (weaning age) are accustomed either to a standard maintenance diet or to a high-fat and thus high-energy diet. After 12 weeks, the normally fed, slim mice have typically reached a body weight of about 25 g, and the fat-fed mice have reached one of about 35 g. The animals are housed singly, and the feed intake and water intake are determined individually. There is free access to feed and water during the experiment.

The test substances are administered orally in a vehicle and always tested by comparison with the vehicle control which is included in parallel. The vehicle itself has no influence on the feed intake, and is normally hydroxyethylcellulose (0.5% in water) or Solutol HS15 (5% in hydroxyethylcellulose (0.5% in water)). A corresponding group of slim mice is kept for each group of diet-induced obese mice.

Feed consumption and water consumption are determined each day in the first week and then once per week by reweighing the offered feed and water, respectively. The

body weight is measured each day.

Blood samples are taken before and at the end of the treatment in order to determine serum parameters which provide information about changes in intermediary metabolism. It is additionally possible to determine the body fat content on the living
5 animal by means of an impedance measurement (TOBEC method).

Micronucleus test (in vitro)

The aim of the micronucleus test (in vitro) is to examine whether a test compound has
10 the potential to elicit the formation of micronuclei (small membrane-bound DNA fragments) in various cell lines or primary cultures, with or without metabolic activation by S9 liver homogenate. The test system allows differentiation between the clastogenic and aneugenic potential of a test compound by an immunochemical labeling of the kinetochores or by staining the DNA fragments by the FISH (fluorescence in situ
15 hybridization) method.

Brief description: The cells are treated in a 96-well microtiter plate with the test compound. The treatment time is typically 3 hours with metabolic activation or 24 hours without metabolic activation. Twenty four hours after the end of the treatment, the cells are isolated, fixed and stained. The cytotoxicity of the test compound is
20 assessed according to the relative cell growth expressed as percentage growth or taking account of the doubling time as population doubling compared with the negative control. The highest test concentration should show not less than 30% surviving cells, or should be the concentration at which a precipitate of the test compound is observed. Duplicate determinations should be carried out with each test concentration. An
25 accurate detailed description of the experiment is to be found in Kirsch-Volders et al. (Mutation Res. 2003, 540, 153-163).

Evaluation: The structural or numerical chromosomal damage is reported as the increase in the number of cells with micronuclei in an ensemble of 1000 cells at three analyzable test concentrations. The test is regarded as positive in the following cases:

- 30 a) the increase in the number of cells with micronuclei is significant by comparison with the negative control (solvent or untreated), or

- b) the number of micronuclei is increased to a biologically relevant extent, concentration-dependently by comparison with the negative control.

A positive control must show a clear statistically significant effect by comparison with the negative control.

- 5 Preferred compounds of the invention are negative in the micronucleus test.

AMES II test

The aim of the AMES II test is to examine whether a test compound has mutagenic potential.

- 10 Brief description: A mixed bacterial strain (mixed strains, 6 different Salmonella typhimurium strains with in each case a missence point mutation in the histidine operon) and the Salmonella typhimurium strain TA98 for detecting frame shift mutations is treated in a 384-well microtiter plate with various concentrations of the test substance with or without metabolic activation through addition of S9 liver homogenate
15 (accurate descriptions of the experiment are to be found in the literature: P. Gee, D.M. Maron, B.N. Ames; Proc. Natl. Acad. Sci. USA 1994, 91, 11606 and Flückiger-Isler et al.; Mutation Res. 2004, 558, 181 and cit. lit.).

- Mutagenic test compounds cause back-mutations and thus restore the functionality of endogenous histidine biosynthesis. Mutated bacteria are thus able to divide and
20 expand to bacterial colonies.

- Evaluation: If there is enhanced bacterial growth owing to mutations of the bacteria, then enzymes are digested in the growth medium. As a result, the pH in the medium falls and the color of the added indicator (bromocresol purple) changes from pale violet to yellow. The test is regarded as positive if the number of wells in which a color
25 change is observed per concentration increases significantly by comparison with the control.

Preferred compounds of the invention are negative in the AMES II test.

Cytotoxicity tests

a) LDH release

- 5 The aim of the test for LDH (lactate dehydrogenase) release is to examine whether a compound damages the integrity of the cell wall and may thus cause cell death.

Brief description: The LDH activity which enters the cell supernatant from the cytosol due to cell damage is measured by colorimetry. The cells are treated with the test compound. Fifty microliters of the culture supernatant are removed and mixed with the
10 reaction solution (LDH kit, Roche, Mannheim) in accordance with the manufacturer's information. LDH catalyzes the conversion of lactate into pyruvate. During this, NAD⁺ is reduced to NADH/H⁺. The latter in turn reduces, under the influence of the added diaphorase, a likewise added yellow tetrazolium salt to the red formazan.

Evaluation: The formazan is quantified by measuring the absorption at 492 nm (e.g.
15 with TECAN SPECTRAFluor Plus).

Preferred compounds of the invention show no significant increase in LDH activity at concentrations below 10 μ M. Particularly preferred compounds show no increase below a concentration of 50 μ M. Even further preferred compounds show no increase below a concentration of 250 μ M.

20

b) Intracellular ATP content

The aim of the test is to determine the total intracellular ATP content, which is a measure of the energy level and thus the vitality of a cell.

Brief description: 100 μ L of cell culture medium are mixed in a well of a microtiter plate
25 with 100 μ L of the CellTiter-Glo reagent (following the manufacturer's instructions: Promega Technical Bulletin No. 228, CellTiter-Glo Luminescent Cell Viability Assay). The cultures are shaken at room temperature for 2 minutes and then incubated for 10 minutes until the luminescence signal has stabilized.

Evaluation: The luminescence is recorded, integrating over one second (e.g. with
30 TECAN SPECTRAFluor Plus).

Preferred compounds of the invention show no significant reduction in the ATP levels at concentrations below 10 μ M. Particularly preferred compounds show no reduction below a concentration of 50 μ M. Even further preferred compounds show no reduction below a concentration of 250 μ M.

5

c) Neutral red uptake

The aim of the test is to measure the uptake of neutral red (NR) into the lysosomes/endosomes and vacuoles of living cells, which is a quantitative measure of the number and vitality of the cells.

- 10 Brief description: The cells are washed with 150 μ L of a preheated phosphate buffer solution (PBS) and incubated with 100 μ L of the NR medium at 37°C in a humidified atmosphere with 7.5% carbon dioxide for 3 hours. After the incubation, the NR medium is removed and the cells are washed with 150 μ L of PBS. Removal of the PBS is followed by addition of exactly 150 μ L of an ethanol/glacial acetic acid solution. After
- 15 shaking for 10 minutes, the dye is extracted from the cells to give a homogeneous dye solution. An exact description of the test is to be found in the literature (E. Borenfreund, J.A. Puerner, Toxicol. Lett. 1985, 24(2-3), 119-124).

- Evaluation: The absorption of the dye solution is determined at 540 nm using a microtiter plate reader as difference from the absorption of the ethanol/glacial acetic acid solution.
- 20

HERG channel blockade

- The aim of the test is to determine the concentration range in which the test compound blocks the cardiac hERG channel. Blockade of the hERG channel, which is responsible for the I_{Kr} current in the human heart, is associated with potentially fatal arrhythmias.
- 25

- For expression of the cDNA encoding the hERG channel it was cloned into the pCDNA3 vector (Invitrogen). Chinese hamster oocytes (CHO, American Type Culture Collection, Rockville, MD) were transfected using lipofectamine (GIBCO/BRL, Grand
- 30

Island, NY) with the hERG cDNA and selected using G418 (GIBCO/BRL, Grand Island, NY; 500 µg/mL). CHO cells with stable expression of the hERG channel were cultured on a HAM F-12 medium which was supplemented with 10% native bovine serum, 1X penicillin/streptomycin and 500 µg/mL G418 in an atmosphere of 95%
5 air/5% carbon dioxide.

The cells selected for the patch clamp experiment are seeded on a plastic support 18-24 hours before the experiment. HERG channel currents are recorded at room temperature by the whole-cell variant of the patch clamp technique using an Axopatch 200B amplifier (Axon Instruments, Foster City, CA). The electrodes (3-6 megaohms
10 resistance) are prepared from TW150F glass capillaries (World Precision Instruments, Sarasota, FL) and filled with the pipette solution (120 mM potassium aspartate, 20 mM KCl, 4 mM Na₂ATP, 5 mM HEPES, 1 mM MgCl₂; adjusted to pH 7.2 with KOH). The hERG channel currents are induced by a positive voltage pulse (20 mV) followed by a negative pulse (-40 mV) and are recorded for later analysis. As soon as the hERG
15 channel current of the cell flushed with the control solution (130 mM NaCl, 5 mM KCl, 2.8 mM NaOAc, 1 mM MgCl₂, 10 mM HEPES; 10 mM glucose, 1 mM CaCl₂; adjusted to pH 7.4 with NaOH) is stable, the cell is perfused with the test compound dissolved in the above control solution (by dilution of a 10 or 100 mM DMSO solution of the test compound so that the DMSO content is no more than 0.1%). The current is followed
20 continuously until no further changes occur. The same procedure is repeated with increasing concentrations of the test compound. The maximum amplitude of the hERG current is measured in picoAmperes (pA) for each concentration and for each cell. The maximum amplitude in pA for each concentration of the test compound is compared with that of the pure control solution in the same cell and calculated as % of the control
25 value.

Evaluation: The test compound is tested at various concentrations in 3-5 CHO cells which express hERG channel. The IC₅₀ is obtained by use of nonlinear least squares regression (GraphPAD Software, San Diego, CA).

General selectivity

30 In order to minimize the risk of unwanted side effects, it is desirable to keep the

nonselective effect on biologically important functional units (e.g. receptors, ion channels and enzymes; for lists, see, for example, Whitebread, S. et al.; Drug Discovery Today 2005, 10, 1421-33 and Rolland, C. et al.; J. Med. Chem. 2005, 48, 6563-6574) by an active pharmaceutical ingredient as small as possible. General
5 selectivity tests in a large number of in vitro test systems can be carried out by various specialized services (e.g. Cerep, Panlabs).

The compounds of the invention of the formula I exhibit, as selective MCH1R antagonists, selectivity factors of at least 30, preferably of 100, more preferably of 300 and even more preferably of 1000 vis à vis the affinity to other proteins. Examples of
10 such proteins are serotonin receptor subtypes (e.g. the 5-HT_{2a} receptor), muscarine receptor subtypes (e.g. the M1 receptor), adrenergic receptor subtypes (e.g. AR alpha_{1a}), sodium and calcium channels (e.g. the L-type calcium channel).

Solubility in aqueous systems

15 Adequate solubility of a substance in aqueous solvent systems is an important prerequisite for a (reproducible) pharmacological effect. Solubilities in aqueous systems can be determined by various methods. Suitable examples of solution precipitation methods ("kinetic solubility") and methods which investigate the dissolution of a solid sample until an equilibrium is set up ("thermodynamic solubility").

20 a) Kinetic solubility

A DMSO solution of the test compound (2.5 mM; 0.5 µL) is pipetted into 200 µL of an aqueous test solution (e.g. phosphate-buffered saline, 10x, 1M, Sigma, adjusted to 10 mM, pH 7.4) in a 96-well microtiter plate, and the turbidity is measured at the resulting theoretical concentration for the test compound of 6.25 µM using a
25 nephelometer (e.g. Nephelostar Galaxy, BMG Labtech). The concentration of the test compound in the aqueous test solution is then raised to a theoretical 12.5 µM by adding further DMSO solution (2.5 mM; 0.5 µL), and the turbidity measurement is repeated. Further additions of DMSO solutions (1 µL, 2.5 mM; 0.5 µL, 10 mM; then 9x 1 µL, 10 mM resulting in theoretical concentrations of 25 µM, 50 µM, 100 µM, 150 µM,
30 200 µM, 250 µM, 300 µM, 350 µM, 400 µM, 450 µM and 500 µM) with turbidity

measurement in between complete the measurement process.

Evaluation: The turbidity values from the nephelometer are plotted against the theoretical concentration of the test compound in the aqueous test solution. As soon as a significant turbidity is detected (e.g. 5 times above the control value of the aqueous test solution) at a theoretical concentration, the level of concentration below this is stated to be the solubility limit of the test compound in the test solution. Thus, the maximum possible measurement range emerges as values $<6.25 \mu\text{M}$, $6.25 - 500 \mu\text{M}$ and $>500 \mu\text{M}$.

Preferred compounds of the invention show a kinetic solubility in phosphate buffer (pH 7.4) of at least $12.5 \mu\text{M}$; more preferably of at least $50 \mu\text{M}$ and even more preferably of at least $250 \mu\text{M}$.

b) Thermodynamic solubility

The integrated UV absorption from HPLC UV measurement of serial dilutions of the test compound in DMSO ($500 \mu\text{M}$, $100 \mu\text{M}$, $50 \mu\text{M}$, $10 \mu\text{M}$ and $1 \mu\text{M}$) shows a linear correlation with the concentration in a calibration line. The test compound ($500 \mu\text{g}$) is shaken together with the aqueous test solution ($250 \mu\text{L}$) in a closed vessel (capacity: 1.5 mL) for 16 hours (Eppendorf thermoshaker, 1400 rpm , 25°C , covering to protect from light). The sample is then centrifuged at maximum rotational speed, and the supernatant is finally filtered. A sample of the filtered supernatant is analyzed directly by HPLC UV measurement (see above). A further sample is analyzed after dilution (1 part by volume of supernatant, 39 parts by volume of test solution).

Evaluation: The concentration of the test compound in the undiluted supernatant is calculated from the resulting integrated UV absorptions of the supernatant samples on the basis of the constructed calibration lines and stated as solubility of the test compound in the respective aqueous test solution.

Examples of aqueous test solutions are deionized water or aqueous phosphate buffer with various pH values (e.g. pH 1.2; pH 4.0; pH 6.8; pH 7.4; pH 9.0) which can be prepared from the commercial solution (phosphate buffered saline, $10\times$, Sigma) by dilution and adjustment with phosphoric acid or sodium hydroxide solution by standard

methods.

Preferred compounds of the invention show a solubility in phosphate buffer (pH 7.4) of at least 12.5 μM ; more preferably of at least 50 μM and even more preferably of at least 250 μM .

5

Permeability

The test for permeability is carried out in CACO-2/TC7 cells which have been cultured (DMEM/Glutamax I/Gibco with high glucose content, HEPES 25 mM, 1% NEAA, 10% FBS, 40 $\mu\text{g/mL}$ gentamycin; 37°C surrounding temperature; 95% humidity and 10% CO₂ content) on Becton Dickinson filters (24-well, uncoated) for 21 days. The permeability is tested at a concentration of 20 μM for the test compound (1% DMSO in HBSS) with a pH gradient (apical: pH 6.5 and 0.5% BSA; basolateral: pH 7.4 and 5% BSA). Analysis takes place by means of LCMS/MS. Further descriptions of the test system and references for the experimental procedure are to be found in Balimane, P.V.; Drug Discovery Today 2005, 10(5), 335-343.

15

Inhibition of CYP enzymes

The inhibition of CYP enzymes is determined on recombinant enzymes (obtained from Becton Dickinson) and fluorescent substrates (BD/Gentest) as recommended by the manufacturer (see Website <http://www.bdbiosciences.com>). Further descriptions of the test system and references for the experimental procedure are to be found in Zlokarnik, G.; Drug Discovery Today 2005, 10(21), 1443-1450.

25

Metabolic stability

The metabolic stability is determined by incubating the test compound (5 μM) with microsomal liver fractions (1 mg/mL protein with 0.1% w/v BSA; 1 mM NADPH, 0.5% DMSO) at 37°C. Analysis at an incubation time of 0 and 20 minutes takes place by means of LCMS/MS. Further descriptions of the test system and references for the

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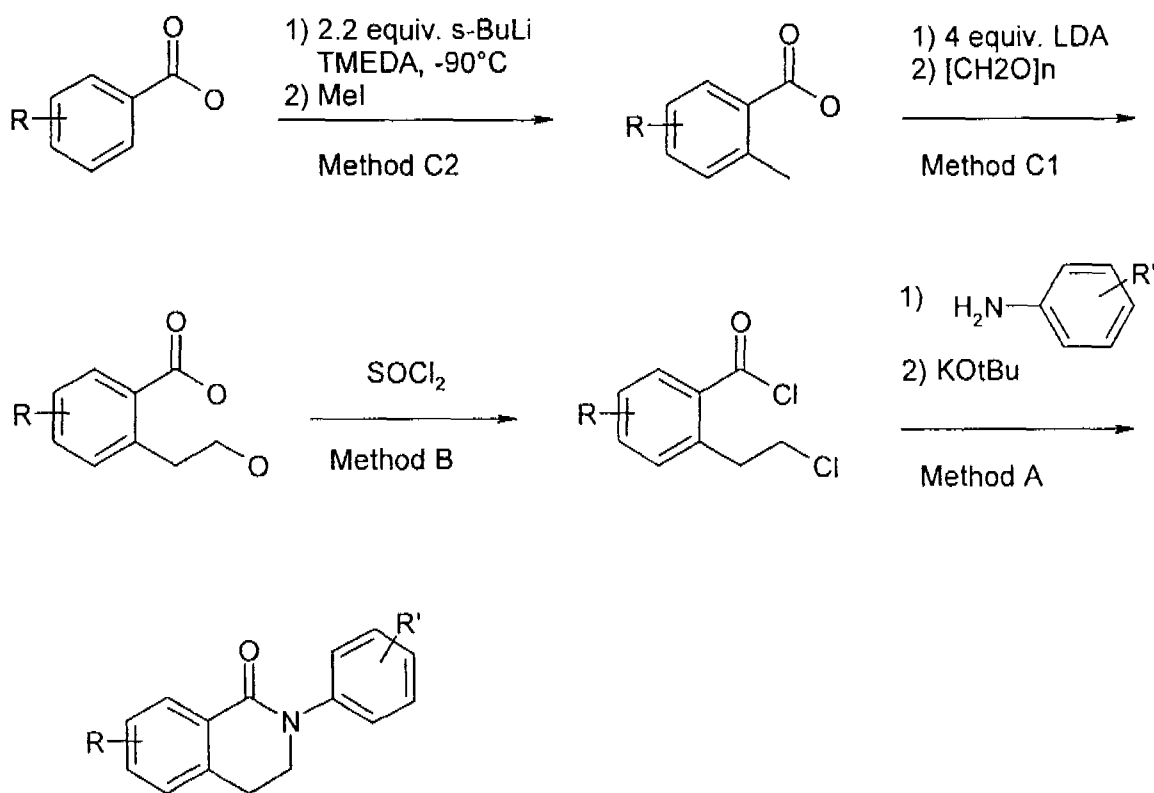
experimental procedure are to be found in Plant, N.; Drug Discovery Today 2004, 9(7), 328-336 and Lau, Y.Y. et al.; Pharmaceutical Res. 2002, 19(11), 1606-1610.

5 Examples

The examples and methods of production given below are for the purpose of explaining the invention, but without limiting it. The symbol R in following schemes represents the variables B-A and R' the variables R1, R1', R1'', R1''' and Q.

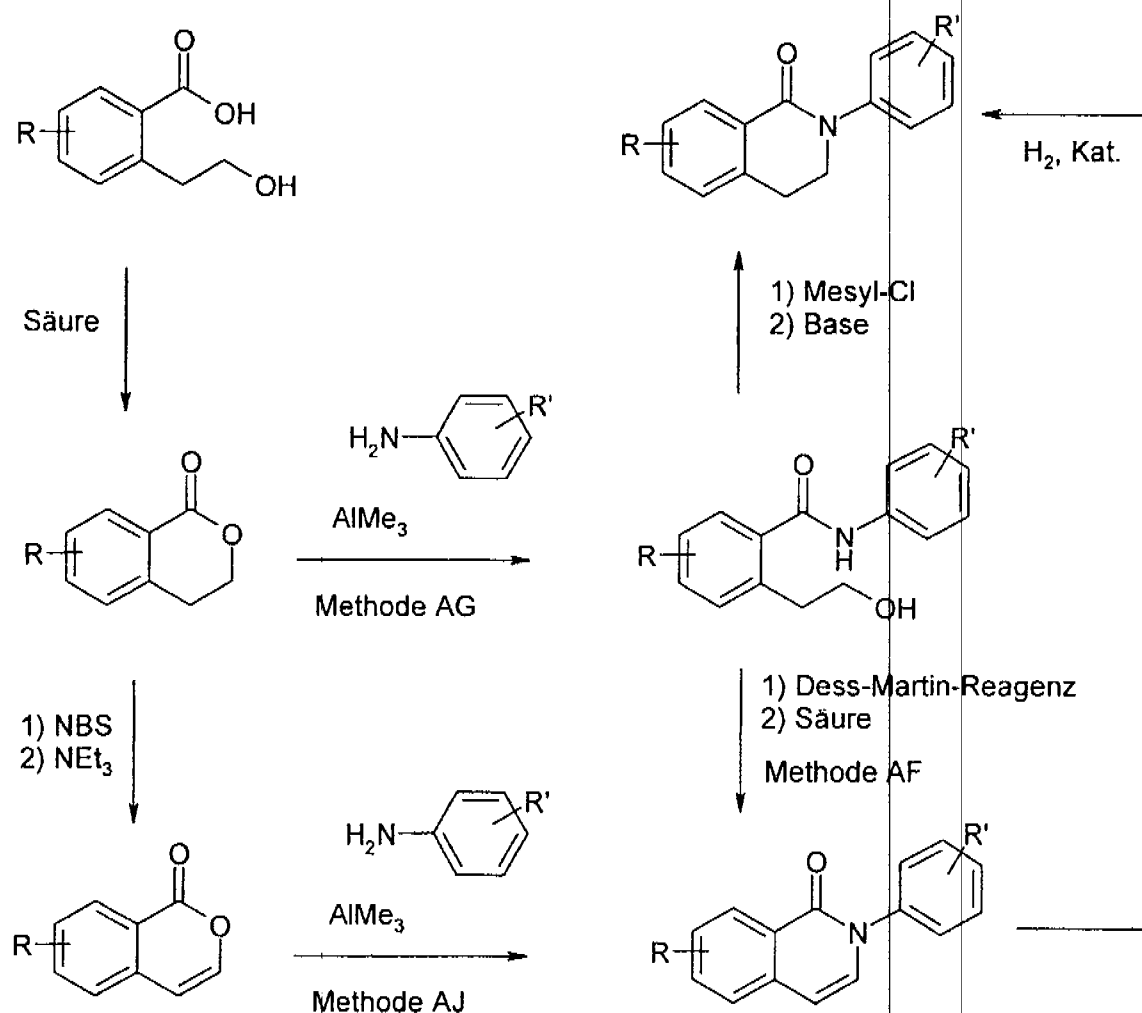
- 10 The compounds according to the invention of Formula I can be produced using reactions that are known in principle. Thus, isoquinolones for example can be produced according to the method described by Alvarez, M. et al., Science of Synthesis 2005, 15, 839-906. A novel reaction sequence (Scheme 1) for the production of isoquinolones comprises first submitting substituted derivatives of
- 15 benzoic acid to an ortho-metallation and capturing the dianion that forms with e.g. methyl iodide (Method C2). The 2-methyl-benzoic acids thus obtained can be metallated twice more and this time the dianion is captured with e.g. paraformaldehyde (Method C1). Reaction of the 2-(2-hydroxyethyl)-benzoic acids, or of the bicyclic lactones resulting from them by acid-catalyzed intramolecular dehydration, with thionyl
- 20 chloride yields 2-(2-chloroethyl)-benzoyl chlorides as main intermediate (Method B). These are cyclized to the desired isoquinolones by reaction with primary (aromatic) amines and then addition of strong bases (e.g. sodium hydride or potassium tert.-butylate) to the reaction mixture (Method A).

Scheme 1

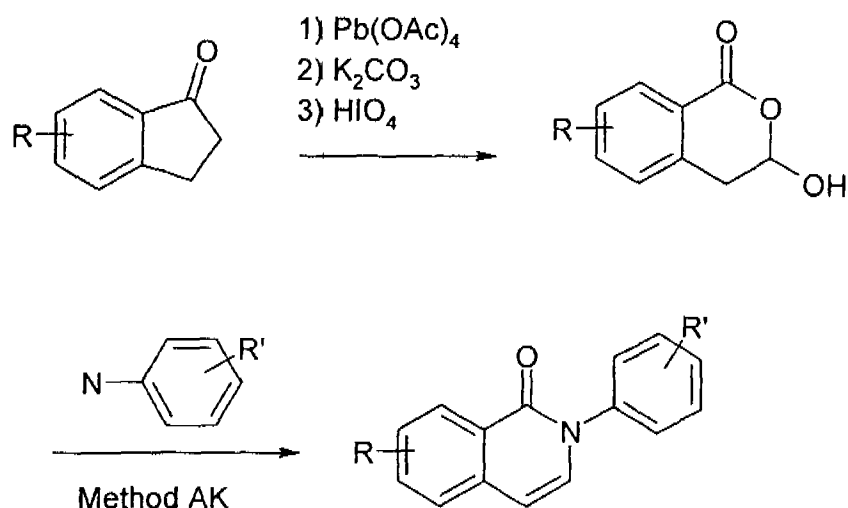


Alternatively isoquinolones can be obtained from 2-(2-hydroxyethyl)-benzoic acids by the routes shown in Scheme 1a. Treating the 2-(2-hydroxyethyl)-benzoic acids with acid produces the corresponding isochromanones, which can be treated for example with N-bromosuccinimide (NBS) to effect benzylic bromination, and can then be reacted to the corresponding isochromenone by treatment for example with triethylamine. Trimethylaluminum-catalyzed opening of the isochromanones with aromatic amines leads to 2-(2-hydroxyethyl)benzanilides (Method AG), which on the one hand can be converted to dihydroisoquinolones by transfer of the alcohol function to a leaving group (e.g. mesylate) and then treatment with a base. Furthermore, the 2-(2-hydroxyethyl)benzanilides can first be oxidized with oxidizing agents such as the Dess-Martin reagent and then reacted to isoquinolones by treatment with acid (Method AF). Isochromenones can also be converted directly to isoquinolones by means of trimethylaluminum after treatment with acid (Method AJ). Furthermore isochinolinones can be converted to dihydroisochinolinones by hydrogenation.

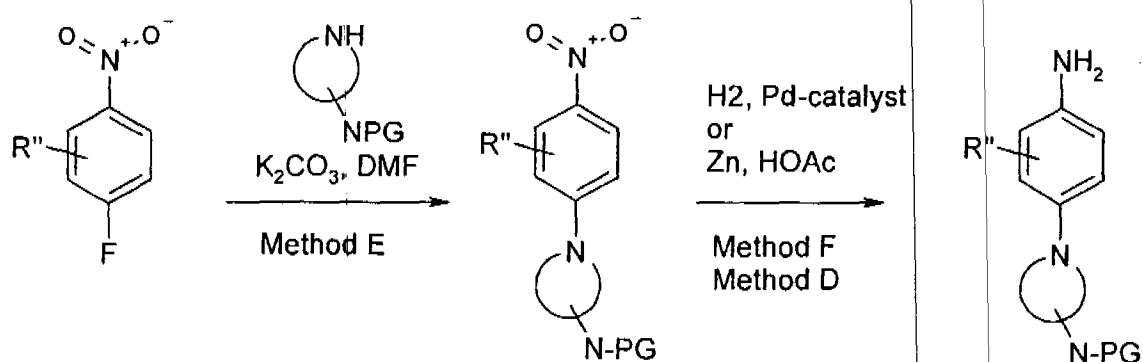
Schema 1a



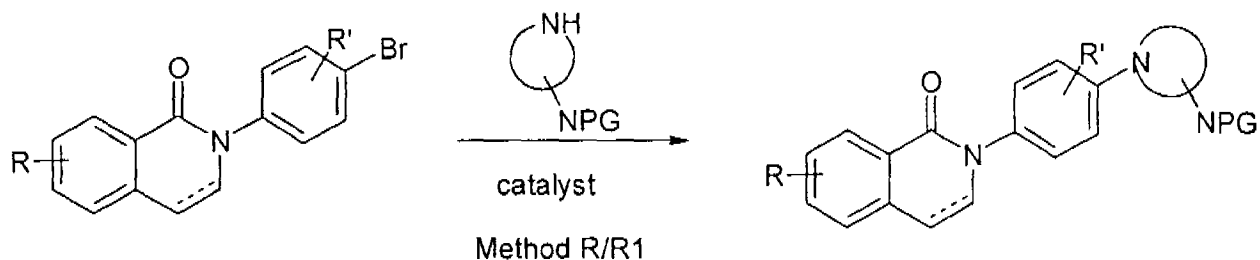
In a further variant for the synthesis of isoquinolones (Scheme 1b), 2-methyl-benzoic acids can be reacted with aromatic amines first to 2-methyl-benzanilides according to one of the many methods of amide linkage (for example via the acid chloride or TOTU-mediated; Method P). These can then be doubly deprotonated with a strong base (for example lithium 2,2,6,6-tetramethyl piperidide (LTMP)) and reacted with acylating reagents (for example N-formylmorpholine or N-methoxy-N-methyl-acetamides). Then treatment with acid produces the desired isoquinolones (Method Q).

Scheme 1c

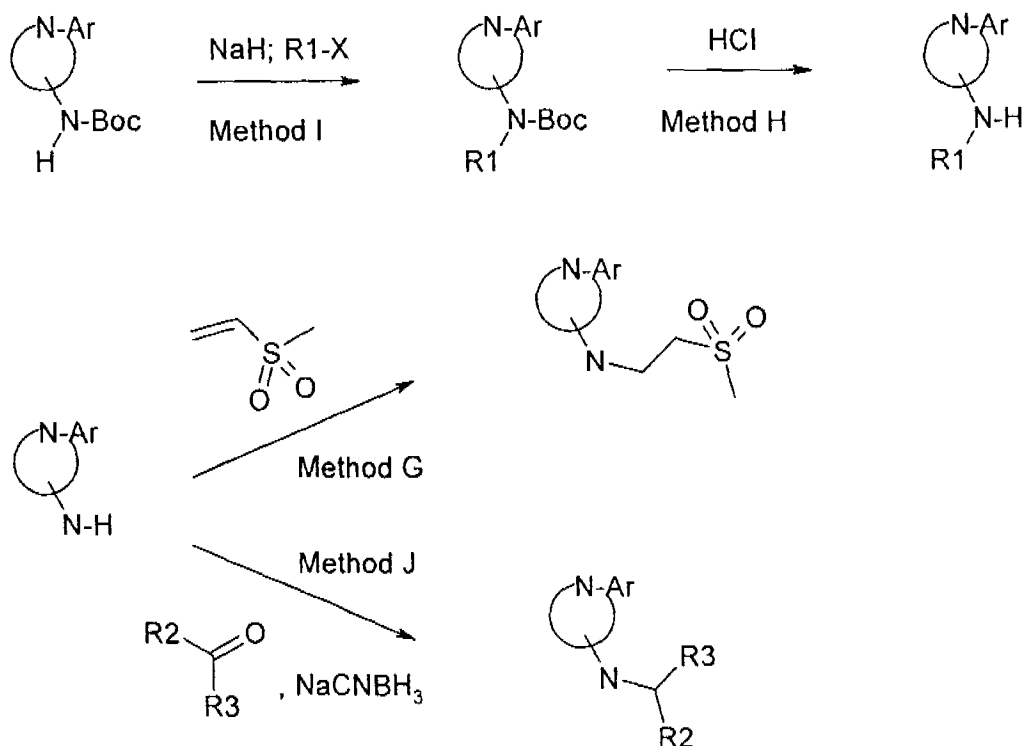
The necessary substituted aromatic amines can be obtained by nucleophilic substitution with aza cycles (Method E) on suitable fluoro-nitrobenzenes and then reduction of the nitro group (Methods D or F) (Scheme 2). In this case PG is (also a
5 cleavable group) a group that is generally unreactive with respect to the conditions of methods E, F or D. Examples include alkyl groups and carbamates.

Scheme 2

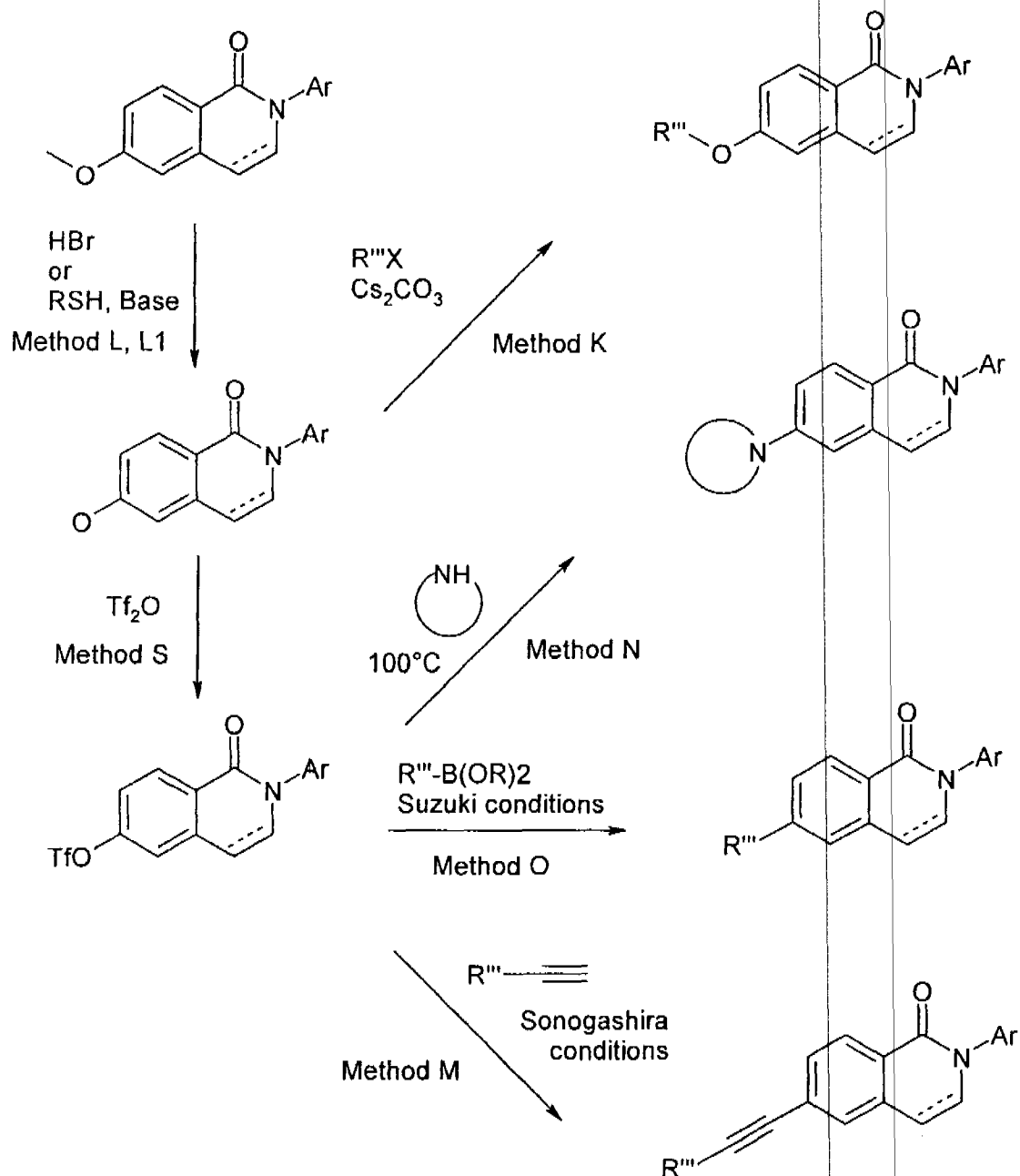
As a variant of the aza cycles, it is also possible to carry out transition metal-mediated aminations on the corresponding halogen-substituted isoquinolinones (Scheme 2a,
10 Method R or R1).

Scheme 2a

The N-PG group can be modified in various ways by known methods (see e.g. Scheme 3). Carbamate alkylation (Method I) followed by carbamate cleavage (Method H) may be mentioned as an example. Compounds obtained by carbamate cleavage with a basic N-H group react with a great many electrophiles (e.g. vinyl sulfone; Method G) or in the sense of a reductive alkylation (Method J).

Scheme 3

Scheme 4

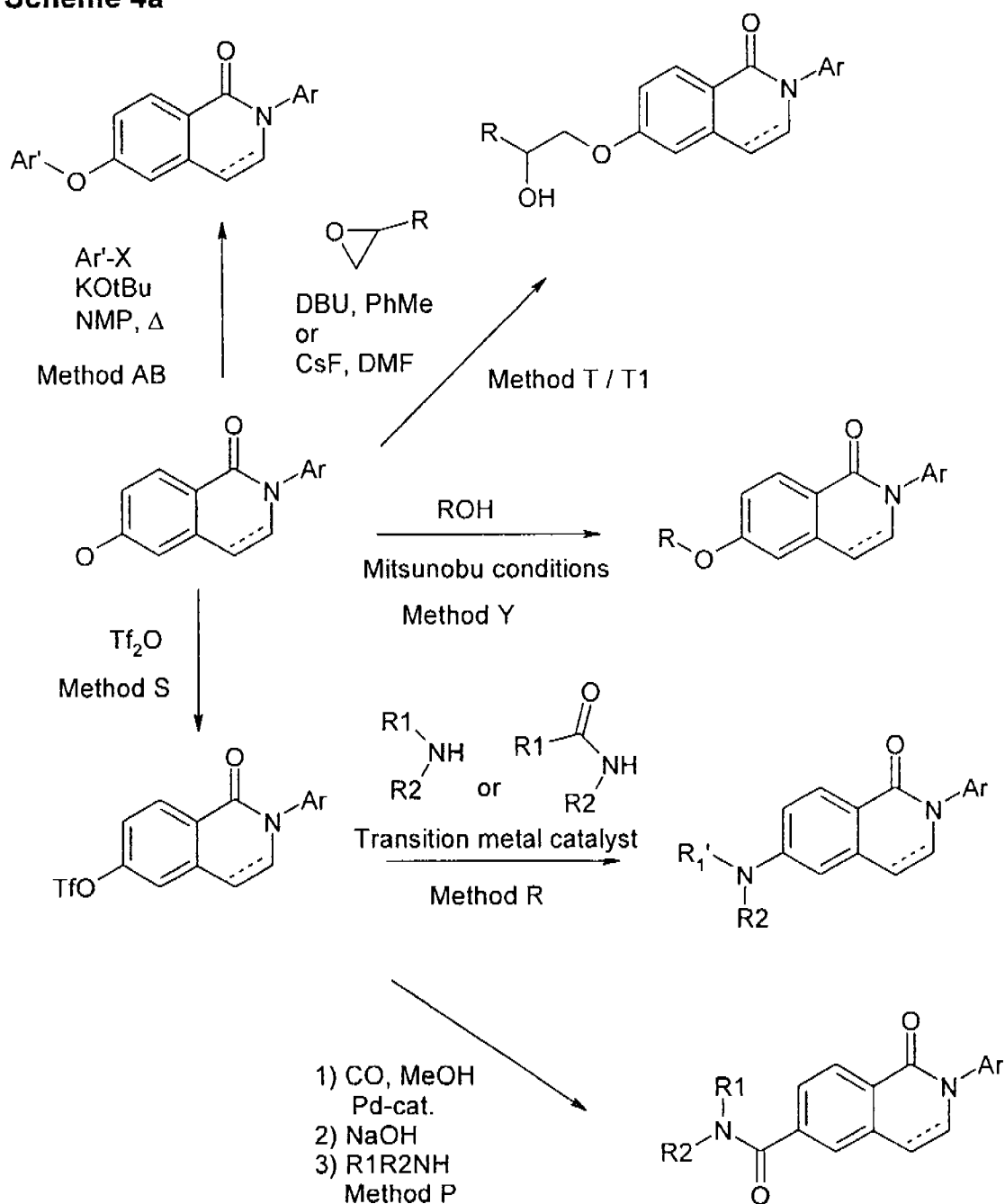


Alternatively, according to Scheme 4a, hydroxy-isoquinolinones can be functionalized by reaction with electrophiles Ar-X, which are accessible for nucleophilic aromatic substitution (Method AB). Electrophiles such as epoxides (Method T) and alcohols, which were activated under Mitsunobu conditions (Method Y), are equally suitable.

5 Trifluoromethane sulfonates also offer further possible variants. For example, after

palladium-catalyzed alkoxylation and saponification of the ester thus obtained, a carboxylic acid is formed, which can be converted for example by Method P to the corresponding amides. The trifluoromethane sulfonate group can also be exchanged for amines and amides under transition-metal catalysis (Method R).

Scheme 4a



Descriptions of the general methods used can be found for example in the following places:

Method A, B, C1, C2, D, E in Example 1;

Method F, G and H according to Table 1;

5 Method I in Example 13;

Method J/J1 in Example 15/253;

Method K/K1 in Example 17/253;

Method L/L1 in Example 17/270;

Method N in Example 24;

10 Method M in Example 27;

Method O in Example 37;

Method P in Example 46;

Method Q in Example 66;

Method R/R1 in Example 90/340;

15 Method S in Example 24;

Method T/T1 in Example 141/274;

Method U, V, W and X according to Table 11;

Method Y according to Example 212;

Method Z according to Example 230;

Method AA according to Example 235;

Method AB according to Example 237;

Method AC, AD and AE in Example 253;

5 Method AF and AG in Example 288;

Method AH/AH1 according to Table 15/in Example 338;

Method AI according to Table 19;

Method AJ in Example 322;

Method AK in Example 357.

10 Method AL in Example 358.

General explanations

a) Mode of drawing the structural formulae

15 Only non-hydrogen atoms are depicted for clarity in the structural formulae of the given examples.

b) Salt forms

Many of the compounds of the invention are bases and can form salts with
20 appropriately strong acids. The compounds can in particular be in the form of hydrotrifluoroacetates after purification by HPLC chromatography using a mobile

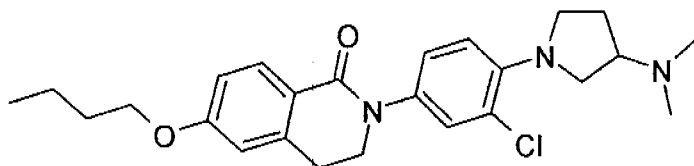
phase containing trifluoroacetic acid. These can be converted into the free bases shown by simple treatment of a solution of the salts for example with sodium carbonate solution.

5 c) Units of the characterizing data

The unit of the indicated molecular weights is "g/mol". Peaks observed in the mass spectrum are stated as integral quotient of the molar molecular ion mass and the charge of the molecular ion (m/z).

10 Example 1

6-Butoxy-2-[3-chloro-4-(3-dimethylaminopyrrolidin-1-yl)phenyl]-3,4-dihydro-2H-isoquinolin-1-one



Method A

15 A solution of [1-(4-amino-2-chlorophenyl)pyrrolidin-3-yl]dimethylamine (98 mg) in THF (3 mL) was added dropwise to a solution of 4-butoxy-2-(2-chloroethyl)benzoyl chloride (100 mg) in THF (4 mL). Sodium hydride (55% in oil; 40 mg) was added to the resulting suspension and heated at 60°C for 3 hours. An alternative possibility is also to employ potassium tert-butoxide as base at room temperature. After cooling, the
20 precipitate was removed by filtration and the filtrate was concentrated. The residue was purified by preparative HPLC. The product with the molecular weight of 442.01 (C₂₅H₃₂ClN₃O₂) was obtained in this way; MS (ESI): 442 (M+H⁺).

Method B

25 4-Butoxy-2-(2-chloroethyl)benzoyl chloride

Thionyl chloride (5 g) was cooled to -10°C, and 4-butoxy-2-(2-hydroxyethyl)benzoic acid (1.0 g) was added in portions so that the internal temperature did not rise above

-3°C. After 20 minutes at 0°C, the mixture was heated to reflux for 4 hours. Volatiles were removed in a rotary evaporator, and the residue was mixed twice with toluene (20 mL) and reevaporated. The resulting oil was reacted further without further purification.

5

Method C1

4-Butoxy-2-(2-hydroxyethyl)benzoic acid

A solution of 4-butoxy-2-methylbenzoic acid (2.5 g) in THF (15 mL) was added dropwise to a solution of LDA (freshly prepared from diisopropylamine (4.86 g) and n-butyllithium (32 mL; 1.5 M in hexane)) in THF (50 mL) at -78°C. After 10 minutes, paraformaldehyde (1.44 g) was added, and the mixture was allowed slowly to warm to room temperature. After 4 hours, water (10 mL) was added, and the volatile organic constituents were removed in a rotary evaporator. The residue was partitioned between water and diethyl ether. The aqueous phase was mixed with dichloromethane and cautiously acidified with hydrochloric acid at 0°C. Concentration of the organic phase afforded the desired product with the molecular weight of 238.29 (C₁₃H₁₈O₄); MS (ESI): 239 (M+H⁺).

Method C2

4-Butoxy-2-methylbenzoic acid

A mixture of 4-butoxybenzoic acid (10 g), N,N,N',N'-tetramethylethylenediamine (13.2 g) and THF (75 mL) was cooled to -90°C, and sec-butyllithium (81 mL; 1.4 M in hexane) was added over the course of 30 minutes. After a further 30 minutes, the mixture was warmed to -78°C, and a solution of methyl iodide (12.8 mL) in THF (10 mL) was added dropwise. The reaction solution was allowed to warm to room temperature and the mixture was hydrolyzed with water and extracted with ethyl acetate. The organic phase was dried over magnesium sulfate and concentrated. The residue was purified by chromatography on silica gel. The product with the molecular weight of 208.26 (C₁₂H₁₆O₃) was obtained in this way; MS (ESI): 209 (M+H⁺).

30

Method D

[1-(4-Amino-2-chlorophenyl)pyrrolidin-3-yl]dimethylamine

Zinc powder (3.0 g) was added in portions to a solution of [1-(2-chloro-4-nitrophenyl)-pyrrolidin-3-yl]dimethylamine (1.9 g) in glacial acetic acid (50 mL) cooled to 0°C. After
 5 the addition was complete, the mixture was stirred at room temperature for 30 minutes and then insolubles were filtered off with suction. The filtrate was concentrated in a rotary evaporator, and the residue was partitioned between sodium hydroxide solution and ethyl acetate. The organic phase was dried over magnesium sulfate and concentrated. The product with the molecular weight of 239.75 (C₁₂H₁₈ClN₃) was
 10 obtained in this way; MS (ESI): 240 (M+H⁺).

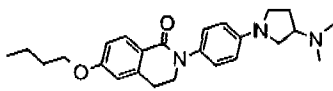
Method E

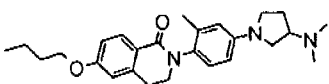
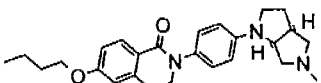
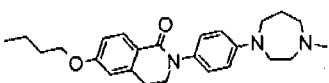
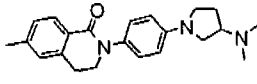
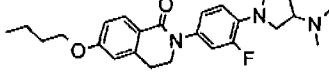
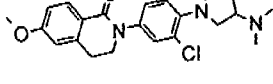
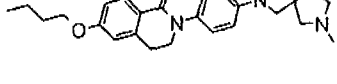
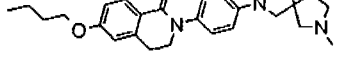
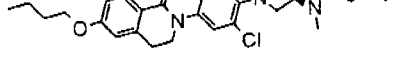
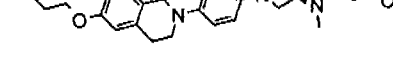
[1-(2-Chloro-4-nitrophenyl)pyrrolidin-3-yl]dimethylamine

A mixture of 2-chloro-1-fluoro-4-nitrobenzene (4.79 g), dimethylpyrrolidin-3-ylamine
 15 (2.60 g), potassium carbonate (3.82 g) and DMF (35 mL) was stirred at room temperature for 4 hours. The reaction mixture was partitioned between water and ethyl acetate. The organic phase was extracted with hydrochloric acid (2 M), and the extract was basified with sodium hydroxide solution (2M). Extraction with ethyl acetate afforded an organic phase which was dried and concentrated. The product with the
 20 molecular weight of 269.73 (C₁₂H₁₆ClN₃O₂) was obtained in this way; MS (ESI): 270 (M+H⁺).

The exemplary compounds in table 1 were obtained by method A from the appropriate
 25 2-(2-chloroethyl)benzoyl chlorides and the appropriate anilines.

Table 1.

Ex. No.	Structure	Molecular formula	Molecular weight	ESI-MS [M+H] ⁺
2		C ₂₅ H ₃₃ N ₃ O ₂	407.56	408

3		C26H35N3O2	421.59	422
4		C26H33N3O2	419.57	420
5		C25H33N3O2	407.56	408
6		C22H27N3O	349.48	350
7		C25H32FN3O2	425.55	426
8		C22H26ClN3O2	399.92	400
9		C27H35N3O2	433.60	434
10		C27H34ClN3O2	468.04	468
11		C27H36ClN3O4 S	534.12	534
12		C27H37N3O4S	499.68	500

4-Methoxy-2-(2-chloroethyl)benzoyl chloride

4-Methoxy-2-methylbenzoic acid was firstly reacted with paraformaldehyde by method C, and the product was then reacted with thionyl chloride by method B.

4-Methyl-2-(2-chloroethyl)benzoyl chloride was obtained analogously.

5

Method F

[1-(4-Aminophenyl)pyrrolidin-3-yl]dimethylamine

A suspension of dimethyl[1-(4-nitrophenyl)pyrrolidin-3-yl]amine (5.0 g) and
10 palladium(II) hydroxide (20% on carbon; 0.9 g) in ethanol (150 mL) was vigorously stirred under a hydrogen atmosphere (atmospheric pressure) for 3 hours. The catalyst was then removed by filtration and the filtrate was concentrated. The product with the molecular weight of 205.31 (C₁₂H₁₉N₃) was obtained in this way; MS (ESI): 206 (M+H⁺). Dimethyl[1-(4-nitrophenyl)pyrrolidin-3-yl]amine was obtained by method E
15 from 1-fluoro-4-nitrobenzene and dimethylpyrrolidin-3-ylamine.

The following anilines were prepared analogously by method F:

[1-(4-amino-3-methylphenyl)pyrrolidin-3-yl]dimethylamine;

4-((3aS*,6aS*)-5-methylhexahydropyrrolo[3,4-b]pyrrol-1-yl)phenylamine;

4-(4-methyl[1,4]diazepan-1-yl)phenylamine;

20 [1-(4-amino-2-fluorophenyl)pyrrolidin-3-yl]dimethylamine;

4-(7-methyl-2,7-diazaspiro[4.4]non-2-yl)phenylamine;

3-chloro-4-(7-methyl-2,7-diazaspiro[4.4]non-2-yl)phenylamine (the reduction by method F with palladium (10% on carbon) took place in ethyl acetate with addition of zinc bromide (10 mol%).

25

[(R)-1-(4-Aminophenyl)pyrrolidin-3-yl]-(2-methanesulfonylethyl)methylamine

[(R)-1-(2-Chloro-4-nitrophenyl)pyrrolidin-3-yl]-(2-methanesulfonylethyl)methylamine

was dechlorinated and the nitro group was reduced to the amine under the conditions of method F. The crude product was purified by preparative HPLC. The product with
30 the molecular weight of 297.42 (C₁₄H₂₃N₃O₂S) was obtained in this way; MS (ESI): 298 (M+H⁺). Since the dehalogenation reaction was incomplete, [(R)-1-(4-amino-2-chlorophenyl)pyrrolidin-3-yl]-(2-methanesulfonylethyl)methylamine was also isolated.

The product with the molecular weight of 331.87 (C₁₄H₂₂ClN₃O₂S) was obtained in this way; MS (ESI): 332 (M+H⁺).

Method G

5 [(R)-1-(2-Chloro-4-nitrophenyl)pyrrolidin-3-yl]-(2-methanesulfonylethyl)methylamine
A mixture of [(R)-1-(2-chloro-4-nitrophenyl)pyrrolidin-3-yl]methylamine (384 mg), methanesulfonylethene (318 mg) and methanol (5 mL) was stirred at room temperature for 12 hours. Volatiles were evaporated off and the residue was purified by preparative HPLC. The product with the molecular weight of 361.85
10 (C₁₄H₂₀ClN₃O₄S) was obtained in this way; MS (ESI): 362 (M+H⁺).

Method H

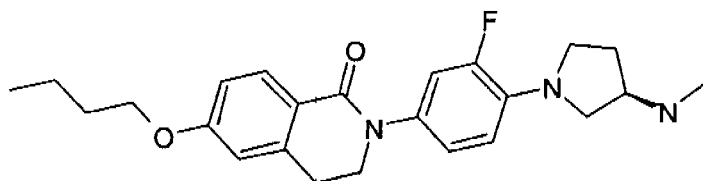
[(R)-1-(2-Chloro-4-nitrophenyl)pyrrolidin-3-yl]methylamine
A solution of [(R)-1-(2-chloro-4-nitrophenyl)pyrrolidin-3-yl]methylcarbamate tert-butyl ester (560 mg) in dichloromethane (2 mL) was mixed with trifluoroacetic acid
15 (2 mL; alternatively a solution of HCl in dioxane or propanol-2 can be used) and stirred at room temperature for 5 hours. The reaction mixture was partitioned between dichloromethane and sodium carbonate solution. The organic phase was dried and concentrated. The product with the molecular weight of 255.71 (C₁₁H₁₄ClN₃O₂) was
20 obtained in this way; MS (ESI): 256 (M+H⁺).

[(R)-1-(2-Chloro-4-nitrophenyl)pyrrolidin-3-yl]methylcarbamate tert-butyl ester was obtained from 2-chloro-1-fluoro-4-nitrobenzene and methyl-(R)-pyrrolidin-3-ylcarbamate tert-butyl ester by method E.

25

Example 13

6-Butoxy-2-[3-fluoro-4-((R)-3-methylaminopyrrolidin-1-yl)phenyl]-3,4-dihydro-2H-isoquinolin-1-one



The carbamate was cleaved using hydrogen chloride (6N in isopropanol) to give {(R)-1-[4-(6-butoxy-1-oxo-3,4-dihydro-1H-isoquinolin-2-yl)-2-fluorophenyl]pyrrolidin-3-yl}methylcarbamic acid tert-butyl ester. The product with the molecular weight of 411.52 (C₂₄H₃₀FN₃O₂) was obtained in this way; MS (ESI): 412 (M+H⁺).

{(R)-1-[4-(6-Butoxy-1-oxo-3,4-dihydro-1H-isoquinolin-2-yl)-2-fluorophenyl]pyrrolidin-3-yl}methylcarbamic acid tert-butyl ester

4-Butoxy-2-(2-chloroethyl)benzoyl chloride was reacted by method A with [(R)-1-(4-amino-2-fluorophenyl)pyrrolidin-3-yl]methylcarbamic acid tert-butyl ester. The product with the molecular weight of 511.64 (C₂₉H₃₈FN₃O₄) was obtained in this way; MS (ESI): 512 (M+H⁺).

[(R)-1-(4-Amino-2-fluorophenyl)pyrrolidin-3-yl]methylcarbamic acid tert-butyl ester
[(R)-1-(2-Fluoro-4-nitrophenyl)pyrrolidin-3-yl]methylcarbamic acid tert-butyl ester was hydrogenated under the conditions of method F. The product with the molecular weight of 309.39 (C₁₆H₂₄FN₃O₂) was obtained in this way; MS (ESI): 310 (M+H⁺).

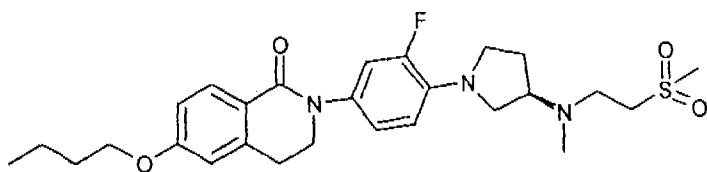
Method I

[(R)-1-(2-Fluoro-4-nitrophenyl)pyrrolidin-3-yl]methylcarbamic acid tert-butyl ester
Sodium hydride (0.6 g) was added in portions to a solution of [(R)-1-(2-fluoro-4-nitrophenyl)pyrrolidin-3-yl]carbamic acid tert-butyl ester (4.09 g) in DMF (10 mL). After gas evolution ceased, iodomethane (2.37 mL) was added dropwise. After 12 hours, the mixture is partitioned between water and ethyl acetate/hexane (1:1), and the organic phase is dried and concentrated. The product with the molecular weight of 339.37 (C₁₆H₂₂FN₃O₄) was obtained in this way; MS (ESI): 340(M+H⁺).

[(R)-1-(2-Fluoro-4-nitrophenyl)pyrrolidin-3-yl]carbamic acid tert-butyl ester was obtained by method E from 1,2-difluoro-4-nitrobenzene and (R)-pyrrolidin-3-ylcarbamic acid tert-butyl ester.

5 Example 14

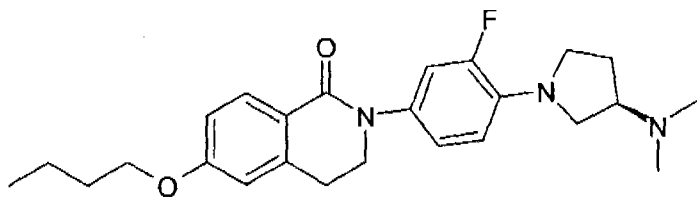
6-Butoxy-2-(3-fluoro-4-((R)-3-[(2-methanesulfonyl)ethyl]methylamino)pyrrolidin-1-yl)phenyl]-3,4-dihydro-2H-isoquinolin-1-one



6-Butoxy-2-[3-fluoro-4-((R)-3-methylaminopyrrolidin-1-yl)phenyl]-3,4-dihydro-2H-isoquinolin-1-one was reacted with methanesulfonylethene by method G. The product with the molecular weight of 517.67 (C₂₇H₃₆FN₃O₄S) was obtained in this way; MS (ESI): 518 (M+H⁺).

Example 15

6-Butoxy-2-[4-((R)-3-dimethylaminopyrrolidin-1-yl)-3-fluorophenyl]-3,4-dihydro-2H-isoquinolin-1-one



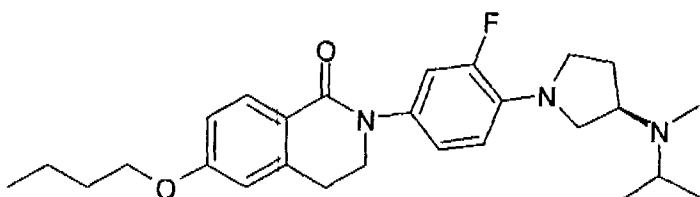
Method J

20 N,N-Diisopropylethylamine (11.5 mg), acetic acid (5.3 mg), formaldehyde (37% in water; 7.2 mg) and sodium cyanoborohydride (5.6 mg; polymer-bound material can also be employed as an alternative) were successively added to a solution of a 6-butoxy-2-[3-fluoro-4-((R)-3-methylaminopyrrolidin-1-yl)phenyl]-3,4-dihydro-2H-isoquinolin-1-one (hydrochloride; 40 mg) in THF (2 mL). After 12 hours, volatiles were removed and the residue was purified by preparative HPLC. The product with the

molecular weight of 425.55 (C₂₅H₃₂FN₃O₂) was obtained in this way; MS (ESI): 426 (M+H⁺).

Example 16

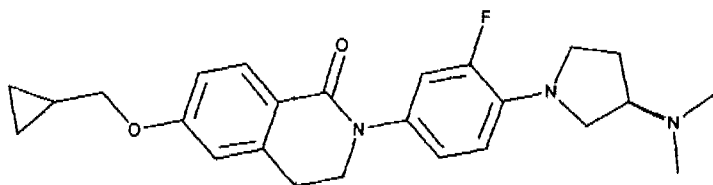
- 5 6-Butoxy-2-[3-fluoro-4-[(R)-3-(isopropylmethylamino)pyrrolidin-1-yl]phenyl]-3,4-dihydro-2H-isoquinolin-1-one



- 10 6-Butoxy-2-[3-fluoro-4-((R)-3-methylaminopyrrolidin-1-yl)phenyl]-3,4-dihydro-2H-isoquinolin-1-one (hydrochloride) was reductively alkylated with acetone by method J. The product with the molecular weight of 453.61 (C₂₇H₃₆FN₃O₂) was obtained in this way; MS (ESI): 454 (M+H⁺).

Example 17

- 15 6-Cyclopropylmethoxy-2-[4-((R)-3-dimethylaminopyrrolidin-1-yl)-3-fluorophenyl]-3,4-dihydro-2H-isoquinolin-1-one



Method K

- 20 A solution of 2-[4-((R)-3-dimethylaminopyrrolidin-1-yl)-3-fluorophenyl]-6-hydroxy-3,4-dihydro-2H-isoquinolin-1-one (50 mg) in NMP (1.5 mL) was mixed with cesium carbonate (44 mg) and cyclopropylmethyl bromide (18.3 mg) and heated at 60°C for 5 hours. The reaction mixture was filtered and concentrated. The residue was purified by preparative HPLC. The product with the molecular weight of 423.54 (C₂₅H₃₀FN₃O₂) was obtained in this way; MS (ESI): 424 (M+H⁺).

Method L

2-[4-((R)-3-Dimethylaminopyrrolidin-1-yl)-3-fluorophenyl]-6-hydroxy-3,4-dihydro-2H-isoquinolin-1-one

A mixture of 2-[4-((R)-3-dimethylaminopyrrolidin-1-yl)-3-fluorophenyl]-6-methoxy-3,4-dihydro-2H-isoquinolin-1-one (9.3 g) and hydrogen bromide (48% strength in water; 140 mL) was heated at 100°C for 12 hours. The cooled reaction solution was adjusted to pH 10 with sodium hydroxide solution (4N). The precipitate was filtered off with suction, washed with water until neutral and dried. The product with the molecular weight of 369.44 (C₂₁H₂₄FN₃O₂) was obtained in this way; MS (ESI): 370 (M+H⁺).

2-[4-((R)-3-Dimethylaminopyrrolidin-1-yl)-3-fluorophenyl]-6-methoxy-3,4-dihydro-2H-isoquinolin-1-one

2-(2-Chloroethyl)-4-methoxybenzoyl chloride was reacted with [(R)-1-(4-amino-2-fluorophenyl)pyrrolidin-3-yl]dimethylamine by method A. The product with the molecular weight of 383.47 (C₂₂H₂₆FN₃O₂) was obtained in this way; MS (ESI): 384 (M+H⁺).

[(R)-1-(4-Amino-2-fluorophenyl)pyrrolidin-3-yl]dimethylamine

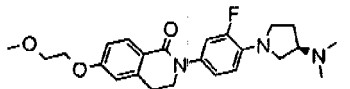
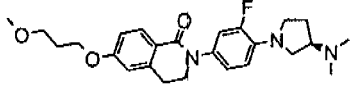
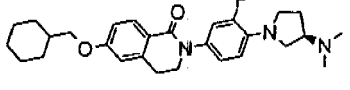
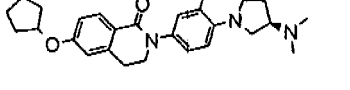
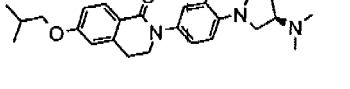
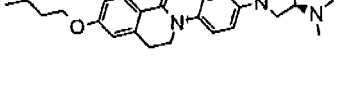
[(R)-1-(2-Fluoro-4-nitrophenyl)pyrrolidin-3-yl]dimethylamine was hydrogenated by method F. The product with the molecular weight of 223.30 (C₁₂H₁₈FN₃) was obtained in this way; MS (ESI): 224 (M+H⁺).

[(R)-1-(2-Fluoro-4-nitrophenyl)pyrrolidin-3-yl]dimethylamine

2-Difluoro-4-nitrobenzene was reacted with dimethyl-(R)-pyrrolidin-3-ylamine by method E. The product with the molecular weight of 253.28 (C₁₂H₁₆FN₃O₂) was obtained in this way; MS (ESI): 254 (M+H⁺).

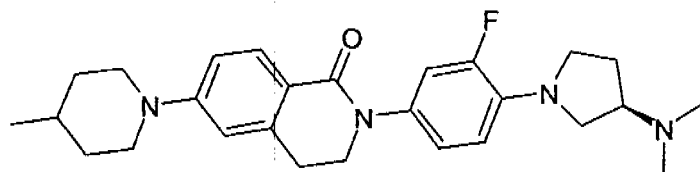
1,2-[4-((R)-3-Dimethylaminopyrrolidin-1-yl)-3-fluorophenyl]-6-hydroxy-3,4-dihydro-2H-isoquinolin-1-one was reacted with the appropriate alkyl halides by method K, and the exemplary compounds in table 2 were obtained.

Table 2.

Ex. No.	Structure	Molecular formula	Molecular weight	ESI-MS [M+H] ⁺
18		C ₂₄ H ₃₀ FN ₃ O ₃	427.52	428
19		C ₂₅ H ₃₂ FN ₃ O ₃	441.55	442
20		C ₂₈ H ₃₆ FN ₃ O ₂	465.62	466
21		C ₂₆ H ₃₂ FN ₃ O ₂	437.56	438
22		C ₂₅ H ₃₂ FN ₃ O ₂	425.55	426
23		C ₂₆ H ₃₄ FN ₃ O ₂	439.58	440

Example 24

- 5 2-[4-((R)-3-Dimethylaminopyrrolidin-1-yl)-3-fluorophenyl]-6-(4-methylpiperidin-1-yl)-3,4-dihydro-2H-isoquinolin-1-one



Method N

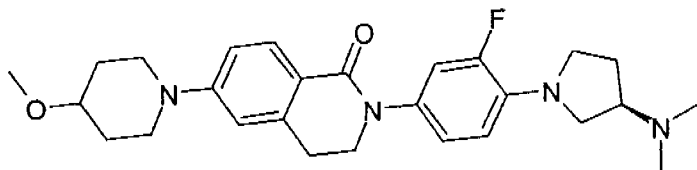
A mixture of trifluoromethanesulfonic acid 2-[4-((R)-3-dimethylaminopyrrolidin-1-yl)-3-fluorophenyl]-1-oxo-1,2,3,4-tetrahydroisoquinolin-6-yl ester (75 mg) and 4-methylpiperidine (0.7 mL) was heated at 100°C for 4 hours. Volatiles were
5 evaporated off. The residue was purified by preparative HPLC. The product with the molecular weight of 450.60 (C₂₇H₃₅FN₄O) was obtained in this way; MS (ESI): 451 (M+H⁺).

Method S

10 Trifluoromethanesulfonic acid 2-[4-((R)-3-dimethylaminopyrrolidin-1-yl)-3-fluorophenyl]-1-oxo-1,2,3,4-tetrahydroisoquinolin-6-yl ester
Trifluoromethanesulfonic anhydride (2.06 g) was added to a solution of 2-[4-((R)-3-dimethylaminopyrrolidin-1-yl)-3-fluorophenyl]-6-hydroxy-3,4-dihydro-2H-isoquinolin-1-one (1.5 g) and pyridine (0.64 g) in dichloromethane (40 mL) at 0°C. After 30 minutes,
15 the mixture was partitioned between water and dichloromethane, and the organic phase was dried over magnesium sulfate and concentrated. The product with the molecular weight of 501.50 (C₂₂H₂₃F₄N₃O₄S) was obtained in this way; MS (ESI): 502 (M+H⁺).

20 Example 25

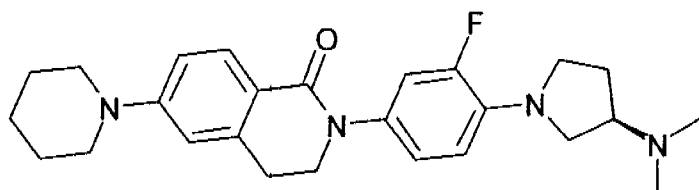
2-[4-((R)-3-Dimethylaminopyrrolidin-1-yl)-3-fluorophenyl]-6-(4-methoxypiperidin-1-yl)-3,4-dihydro-2H-isoquinolin-1-one



Trifluoromethanesulfonic acid 2-[4-((R)-3-dimethylaminopyrrolidin-1-yl)-3-fluorophenyl]-
25 1-oxo-1,2,3,4-tetrahydroisoquinolin-6-yl ester was reacted with 4-methoxypiperidine by method N. The product with the molecular weight of 466.60 (C₂₇H₃₅FN₄O₂) was obtained in this way; MS (ESI): 467 (M+H⁺).

Example 26

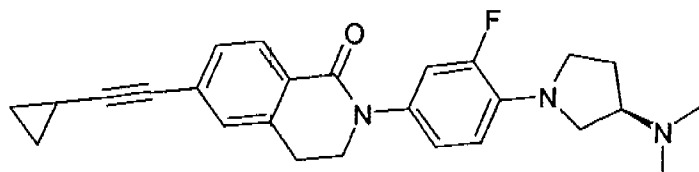
2-[4-((R)-3-Dimethylaminopyrrolidin-1-yl)-3-fluorophenyl]-6-piperidin-1-yl-3,4-dihydro-2H-isoquinolin-1-one



- 5 Trifluoromethanesulfonic acid 2-[4-((R)-3-dimethylaminopyrrolidin-1-yl)-3-fluorophenyl]-1-oxo-1,2,3,4-tetrahydroisoquinolin-6-yl ester was reacted with piperidine by method N. The product with the molecular weight of 436.58 (C₂₆H₃₃FN₄O) was obtained in this way; MS (ESI): 437 (M+H⁺).

10 Example 27

6-Cyclopropylethynyl-2-[4-((R)-3-dimethylaminopyrrolidin-1-yl)-3-fluorophenyl]-3,4-dihydro-2H-isoquinolin-1-one



Method M

- 15 Ethynylcyclopropane (10.5 mg), triphenylphosphine (8.4 mg), cesium carbonate (104 mg), bis(triphenylphosphine)palladium(II) chloride (5.6 mg) and copper(I) iodide (6.1 mg) were successively added to a solution of trifluoromethanesulfonic acid 2-[4-((R)-3-dimethylaminopyrrolidin-1-yl)-3-fluorophenyl]-1-oxo-1,2,3,4-tetrahydroisoquinolin-6-yl ester (80 mg) in NMP (2 mL). The mixture was heated at
20 85°C for 4 hours. The reaction solution was concentrated. The residue was purified by preparative HPLC. The product with the molecular weight of 417.53 (C₂₆H₂₈FN₃O) was obtained in this way; MS (ESI): 418 (M+H⁺).

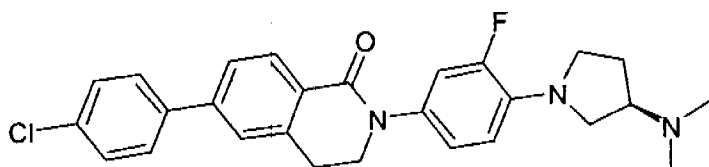
- 25 Reaction of trifluoromethanesulfonic acid 2-[4-((R)-3-dimethylaminopyrrolidin-1-yl)-3-fluorophenyl]-1-oxo-1,2,3,4-tetrahydroisoquinolin-6-yl ester with the appropriate alkynes by method M resulted in the exemplary compounds in table 3.

Table 3.

Ex. No.	Structure	Molecular formula	Molecular weight	ESI-MS [M+H] ⁺
28		C ₂₆ H ₃₀ FN ₃ O	419.55	420
29		C ₂₅ H ₂₈ FN ₃ O ₂	421.52	422
30		C ₂₇ H ₃₂ FN ₃ O	433.57	434
31		C ₂₈ H ₃₂ FN ₃ O	445.59	446
32		C ₂₆ H ₃₀ FN ₃ O ₂	435.55	436
33		C ₂₇ H ₃₂ FN ₃ O ₂	449.57	450
34		C ₂₆ H ₃₀ FN ₃ O ₂	435.55	436
35		C ₂₉ H ₂₈ FN ₃ O	453.56	454
36		C ₂₅ H ₂₈ FN ₃ O ₂	421.52	422

Example 37

6-(4-Chlorophenyl)-2-[4-((R)-3-dimethylamino-pyrrolidin-1-yl)-3-fluorophenyl]-3,4-dihydro-2H-isoquinolin-1-one

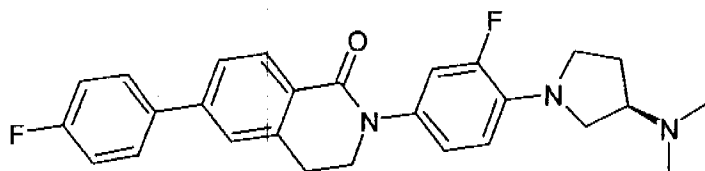


Method O

4-Chlorophenylboronic acid (18.7 mg), cesium carbonate (39 mg) in water/ethanol (0.5 mL/0.5 mL) and tetrakis(triphenylphosphine)palladium (13.8 mg) were successively added to a solution of trifluoromethanesulfonic acid 2-[4-((R)-3-dimethylaminopyrrolidin-1-yl)-3-fluorophenyl]-1-oxo-1,2,3,4-tetrahydroisoquinolin-6-yl ester (60 mg) in toluene (2 mL). The mixture was heated to reflux for 2 hours. After cooling, the organic phase was separated off and concentrated. The residue was purified by preparative HPLC. The product with the molecular weight of 463.99 (C₂₇H₂₇ClFN₃O) was obtained in this way; MS (ESI): 464 (M+H⁺).

Example 38

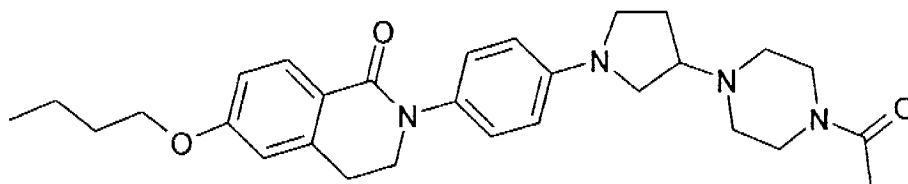
2-[4-((R)-3-Dimethylaminopyrrolidin-1-yl)-3-fluorophenyl]-6-(4-fluorophenyl)-3,4-dihydro-2H-isoquinolin-1-one



Trifluoromethanesulfonic acid 2-[4-((R)-3-dimethylaminopyrrolidin-1-yl)-3-fluorophenyl]-1-oxo-1,2,3,4-tetrahydroisoquinolin-6-yl ester was reacted with 4-fluorophenylboronic acid by method O. The product with the molecular weight of 447.53 (C₂₇H₂₇F₂N₃O) was obtained in this way; MS (ESI): 448 (M+H⁺).

Example 39

2-{4-[3-(4-Acetylpiperazin-1-yl)pyrrolidin-1-yl]phenyl}-6-butoxy-3,4-dihydro-2H-isoquinolin-1-one



5

6-Butoxy-2-[4-(3-oxopyrrolidin-1-yl)phenyl]-3,4-dihydro-2H-isoquinolin-1-one was reacted with 1-piperazin-1-ylethanone by method J. The product with the molecular weight of 490.65 (C₂₉H₃₈N₄O₃) was obtained in this way; MS (ESI): 491 (M+H⁺).

10

6-Butoxy-2-[4-(3-oxopyrrolidin-1-yl)phenyl]-3,4-dihydro-2H-isoquinolin-1-one

A mixture of 6-butoxy-2-[4-(1,4-dioxo-7-azaspiro[4.4]non-7-yl)phenyl]-3,4-dihydro-2H-isoquinolin-1-one (1.40 g), p-toluenesulfonic acid (57 mg) and acetone (40 mL) was boiled under reflux for 12 hours and then concentrated. The residue was partitioned between sodium carbonate solution and ethyl acetate. The organic phase was dried and concentrated. The product with the molecular weight of 378.48 (C₂₃H₂₆N₂O₃) was obtained in this way; MS (ESI): 379 (M+H⁺).

15

6-Butoxy-2-[4-(1,4-dioxo-7-azaspiro[4.4]non-7-yl)phenyl]-3,4-dihydro-2H-isoquinolin-1-one

20

4-(1,4-Dioxo-7-azaspiro[4.4]non-7-yl)phenylamine was reacted with 4-butoxy-2-(2-chloroethyl)benzoyl chloride by method A. The product with the molecular weight of 438.57 (C₂₆H₃₄N₂O₄) was obtained in this way; MS (ESI): 439 (M+H⁺).

4-(1,4-Dioxo-7-azaspiro[4.4]non-7-yl)phenylamine

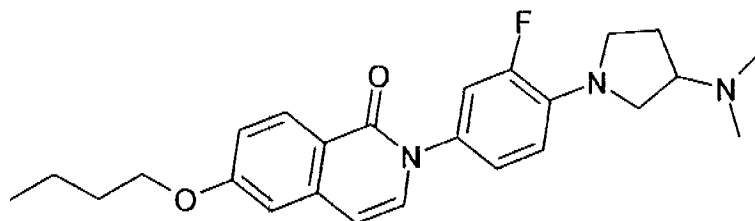
25

Trimethylchlorosilane (9.3 g) was slowly added to a solution of 1-benzyl-3-pyrrolidinone (5.0 g) in dichloromethane (30 mL) and ethylene glycol (2.67 g). After 18 hours, the mixture was poured into sodium hydroxide solution (1N). The organic phase was separated off, dried over magnesium sulfate and concentrated. The residue was dissolved in methanol (30 mL), and ammonium formate (5.2 g) and palladium

Triethylamine (1.0 g) and then Pd(dppf)Cl₂ (365 mg) were added to a mixture of trifluoromethanesulfonic acid 2-[4-((R)-3-dimethylaminopyrrolidin-1-yl)-3-fluorophenyl]-1-oxo-1,2,3,4-tetrahydroisoquinolin-6-yl ester (2.5 g), DMF (50 mL) and methanol (25 mL). The mixture was heated at 50°C in an autoclave under a CO atmosphere (5 bar) for 6 hours. The cooled and decompressed reaction mixture was partitioned between water and ethyl acetate. The organic phase was dried over sodium sulfate and concentrated. The residue was purified by preparative HPLC. The product with the molecular weight of 411.48 (C₂₃H₂₆FN₃O₃) was obtained in this way; MS (ESI): 412 (M+H⁺).

Example 47

6-Butoxy-2-[4-(3-dimethylaminopyrrolidin-1-yl)-3-fluorophenyl]-2H-isoquinolin-1-one



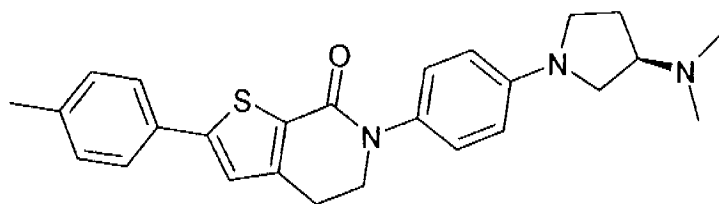
n-Butyllithium (2.6M in toluene; 0.70 mL) was added to a solution of N,N-diisopropylamine (184 mg) in THF (30 mL) at -78°C. After 10 minutes, 4-butoxy-N-[4-(3-dimethylaminopyrrolidin-1-yl)-3-fluorophenyl]-2-methylbenzamide (0.30 g) was added, and the mixture was stirred at -78°C for 30 minutes and then warmed to -20°C. DMF (53 mg) was added, and the reaction mixture was hydrolyzed after a further 30 minutes with hydrochloric acid. The reaction mixture was partitioned between sodium carbonate solution and ethyl acetate. The organic phase was dried over sodium sulfate and concentrated. The residue was purified by preparative HPLC. The product with the molecular weight of 423.54 (C₂₅H₃₀FN₃O₂) was obtained in this way; MS (ESI): 424 (M+H⁺).

4-Butoxy-N-[4-(3-dimethylaminopyrrolidin-1-yl)-3-fluorophenyl]-2-methylbenzamide
4-Butoxy-2-methylbenzoic acid was reacted with [1-(4-amino-2-fluorophenyl)pyrrolidin-3-yl]dimethylamine by method P. The product with the molecular weight of 413.54 (C₂₄H₃₂FN₃O₂) was obtained in this way; MS (ESI): 414 (M+H⁺).

5

Example 48

6-[4-((R)-3-Dimethylaminopyrrolidin-1-yl)phenyl]-2-p-tolyl-5,6-dihydro-4H-thieno[2,3-c]pyridin-7-one



10

Firstly 3-methyl-5-p-tolylthiophene-2-carboxylic acid was reacted with paraformaldehyde by method C1, and then the product was treated with thionyl chloride by method B. The resulting 3-(2-chloroethyl)-5-p-tolylthiophene-2-carbonyl chloride was finally reacted with [(R)-1-(4-aminophenyl)pyrrolidin-3-yl]dimethylamine by method A. The product with the molecular weight of 431.60 (C₂₆H₂₉N₃OS) was obtained in this way; MS (ESI): 432 (M+H⁺).

15

3-Methyl-5-p-tolylthiophene-2-carboxylic acid

A solution of 3-methyl-5-p-tolylthiophene-2-carbaldehyde (2.6 g) in 1,4-dioxane (30 mL) was mixed with a solution of sodium dihydrogenphosphate (5.77 g) in water, and sulfamic acid (1.87 g) was added. At 10°C, a solution of sodium chlorite (1.52 g) in water (20 mL) was added dropwise in such a way that the temperature did not rise above 10°C. Twenty minutes after the addition was complete, sodium sulfite (1.98 g) was added and the mixture was stirred for 15 minutes. The reaction mixture was acidified with hydrochloric acid and extracted with ethyl acetate. The organic phase

20

25

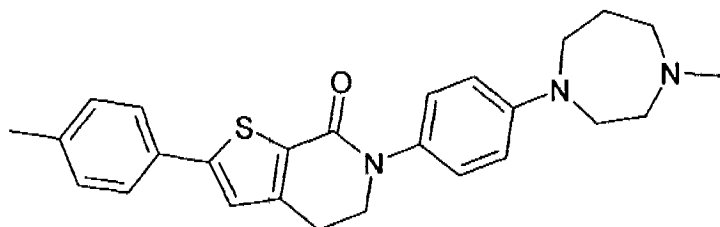
was dried and concentrated. The product with the molecular weight of 232.30 (C₁₃H₁₂O₂S) was obtained in this way; MS (ESI): 233 (M+H⁺).

3-Methyl-5-p-tolylthiophene-2-carbaldehyde

- 5 5-Bromo-3-methylthiophene-2-carbaldehyde (Spinelli, D. et al., J. Chem Soc. Perkin Trans. 2, 1972, (12), 1866-9) was reacted with 4-methylphenylboronic acid by method J. The product with the molecular weight of 216.30 (C₁₃H₁₂O₂S) was obtained in this way; MS (ESI): 217 (M+H⁺).

10 Example 49

6-[4-(4-Methyl-[1,4]diazepan-1-yl)phenyl]-2-p-tolyl-5,6-dihydro-4H-thieno[2,3-c]pyridin-7-one



- 15 3-(2-Chloroethyl)-5-p-tolylthiophene-2-carbonyl chloride was reacted with 4-(4-methyl-[1,4]diazepan-1-yl)phenylamine by method A. The product with the molecular weight of 431.60 (C₂₆H₂₉N₃O₂S) was obtained in this way; MS (ESI): 432 (M+H⁺).

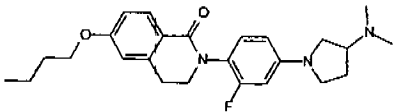
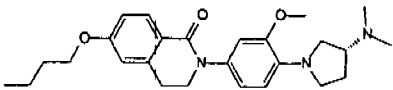
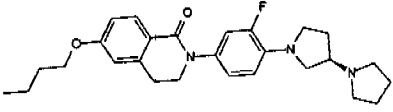
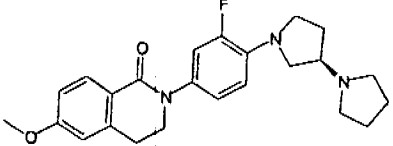
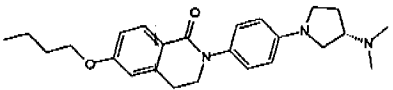
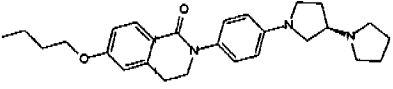
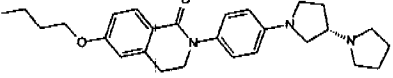
- 20 According to Method N, trifluoro-methanesulfonic acid 2-[4-((R)-3-dimethylamino-pyrrolidin-1-yl)-3-fluorophenyl]-1-oxo-1,2,3,4-tetrahydro-isoquinolin-6-yl ester was reacted with various amines. The compounds presented in Table 5 were obtained.

Table 5.

Ex. No.	Structure	Empirical formula	Molecular weight	ESI-MS [M+H] ⁺
50		C ₂₇ H ₃₄ FN ₅ O ₂	479,60	480
51		C ₂₅ H ₃₁ FN ₄ O ₂	438,55	439
52		C ₂₇ H ₃₂ FN ₅ O	461,59	462
53		C ₂₅ H ₃₀ FN ₅ O ₂	451,55	452
54		C ₂₆ H ₃₃ FN ₄ O ₃ S	500,64	501
55		C ₂₆ H ₃₂ FN ₅ O ₂	465,58	466
56		C ₂₈ H ₃₅ FN ₄ O ₃	494,62	495
57		C ₂₇ H ₃₄ FN ₅ O ₂	479,60	480
58		C ₂₆ H ₃₃ FN ₄ O ₂	452,58	453

The example compounds in Table 6 were obtained by Method A from the
 5 corresponding 2-(2-chloroethyl)-benzoyl chlorides and the corresponding anilines.

Table 6.

Ex. No.	Structure	Empirical formula	Molecular weight	ESI-MS [M+H] ⁺
59		C ₂₅ H ₃₂ FN ₃ O ₂	425,55	426
60		C ₂₆ H ₃₅ N ₃ O ₃	437,59	438
61		C ₂₇ H ₃₄ FN ₃ O ₂	451,59	452
62		C ₂₄ H ₂₈ FN ₃ O ₂	409,51	410
63		C ₂₅ H ₃₃ N ₃ O ₂	407,56	408
64		C ₂₇ H ₃₅ N ₃ O ₂	433,60	434
65		C ₂₇ H ₃₅ N ₃ O ₂	433,60	434

The anilines required were prepared according to Methods E and F by substitution on
 5 suitable 4-fluoro-nitrobenzenes with the corresponding amines followed by catalytic
 hydrogenation of the nitro function.

Preparation of (R)-[1,3']bipyrrolidinyl

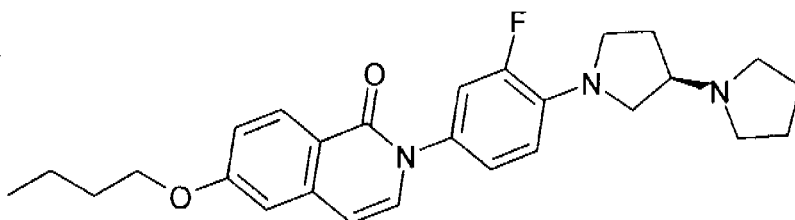
Methanesulfonic acid chloride (24.5 g) was added dropwise to a solution of (S)-3-hydroxypyrrolidine-1-carboxylic acid tert-butyl ester (40 g) and pyridine (17 g) in dichloromethane (200 mL) cooled on an ice bath, and the ice bath was removed after
5 15 minutes. After a further 2 hours at room temperature, the mixture was distributed between ethyl acetate and water. The organic phase was washed with dilute hydrochloric acid, dried over magnesium sulfate and concentrated. Pyrrolidine (20 mL) was added to the raw mesylate ((S)-3-methanesulfonyloxy-pyrrolidine-1-carboxylic acid tert-butyl ester) and heated at 100°C oil-bath temperature. After cooling, the
10 mixture was distributed between ethyl acetate and water. The organic phase was concentrated. The residue was dissolved in dichloromethane (150 mL) and an excess of hydrochloric acid (5 N in 2-propanol) was added. After 12 hours, volatile components were removed in the rotary evaporator. In this way the product was obtained with molecular weight 140.23 (C₈H₁₆N₂); MS (ESI): 141 (M+H⁺) as
15 dihydrochloride.

(S)-[1,3']Bipyrrolidinyl was obtained similarly (as dihydrochloride) from (R)-3-hydroxypyrrolidine-1-carboxylic acid tert-butyl ester.

By use of (S)-2-methyl-pyrrolidine in the substitution reaction step (2S, 3'S)-2-methyl-[1,3']bipyrrolidinyl is obtained.

Example 66

2-((R)-4-[1,3']Bipyrrolidinyl-1'-yl-3-fluorophenyl)-6-butoxy-2H-isoquinolin-1-one



Method Q

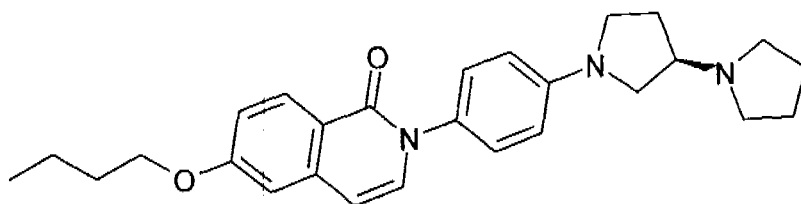
25 n-Butyllithium (2.6 M in toluene; 5.0 mL) was added, at -78°C, to a solution of 2,2,6,6-tetramethyl piperidine (2.2 mL) in THF (30 mL). After 10 minutes, 4-N-((R)-4-[1,3']bipyrrolidinyl-1'-yl-3-fluorophenyl)-4-butoxy-2-methyl-benzamide (1.8 g) in THF

(10 mL) was added and the mixture was stirred for 40 minutes at -78°C. N-Formylmorpholine (1.2 g) was added to the deep-red solution, and after a further 30 minutes the reaction mixture was heated to room temperature and hydrochloric acid (6 N in water, 10 mL) was added. After 4 hours, the THF was removed by distillation in the rotary evaporator and the residue was distributed between sodium carbonate solution and ethyl acetate. The organic phase was dried over sodium sulfate and concentrated. The residue was purified by chromatography on silica gel. In this way the product was obtained with molecular weight 449.57 (C₂₇H₃₂FN₃O₂); MS (ESI): 450 (M+H⁺).

N-((R)-4-[1,3']Bipyrrolidinyl-1'-yl-3-fluorophenyl)-4-butoxy-2-methyl-benzamide
4-Butoxy-2-methyl-benzoic acid was reacted with (R)-4-[1,3']bipyrrolidinyl-1'-yl-3-fluorophenylamine according to Method P. In this way the product was obtained with molecular weight 439.58 (C₂₆H₃₄FN₃O₂); MS (ESI): 440 (M+H⁺).

Example 67

2-((R)-4-[1,3']Bipyrrolidinyl-1'-yl-phenyl)-6-butoxy-2H-isoquinolin-1-one

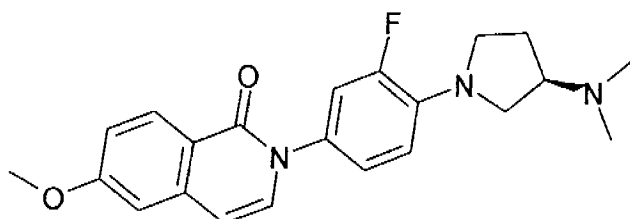


Firstly, 4-butoxy-2-methyl-benzoic acid was reacted with (R)-4-[1,3']bipyrrolidinyl-1'-yl-3-phenylamine according to Method P. The amide obtained was reacted with N-formylmorpholine according to Method Q. In this way the product was obtained with molecular weight 431.58 (C₂₇H₃₃N₃O₂); MS (ESI): 432 (M+H⁺).

Similarly, 4-methoxy-2-methyl-benzoic acid was reacted to 2-((R)-4-[1,3']bipyrrolidinyl-1'-yl-phenyl)-6-methoxy-2H-isoquinolin-1-one. In this way the product was obtained with molecular weight 389.50 (C₂₄H₂₇N₃O₂); MS (ESI): 390 (M+H⁺).

Example 68

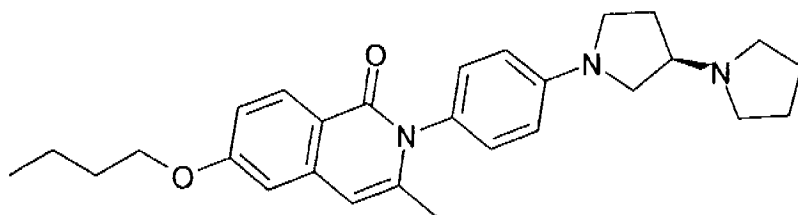
2-[4-((R)-3-Dimethylamino-pyrrolidin-1-yl)-3-fluorophenyl]-6-methoxy-2H-isoquinolin-1-one



- 5 Firstly, 4-methoxy-2-methyl-benzoic acid was reacted with [(R)-1-(4-amino-2-fluorophenyl)-pyrrolidin-3-yl]-dimethylamine according to Method P. The amide obtained was reacted with N-formylmorpholine according to Method Q. In this way the product was obtained with molecular weight 381.45 (C₂₂H₂₄FN₃O₂); MS (ESI): 382 (M+H⁺).
- 10 Similarly, using (R)-4-[1,3']bipyrrolidinyl-1'-yl-3-fluorophenylamine, the product 2-((R)-4-[1,3']bipyrrolidinyl-1'-yl-3-fluorophenyl)-6-methoxy-2H-isoquinolin-1-one was obtained (molecular weight 407.49 (C₂₄H₂₆FN₃O₂); MS (ESI): 408 (M+H⁺)).

Example 69

- 15 2-((R)-4-[1,3']Bipyrrolidinyl-1'-yl-phenyl)-6-butoxy-3-methyl-2H-isoquinolin-1-one

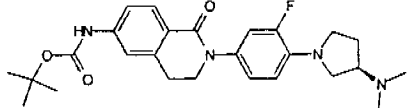
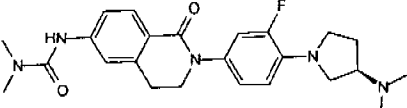
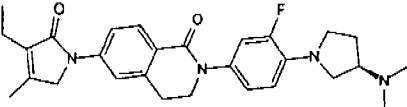
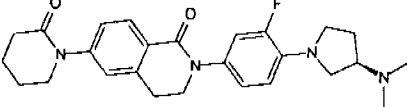
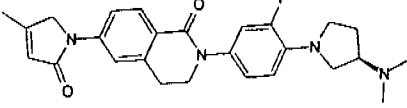
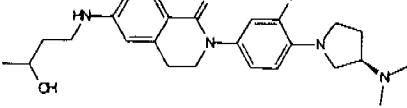
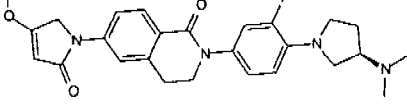
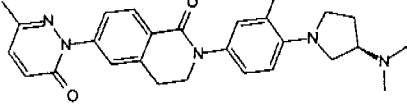
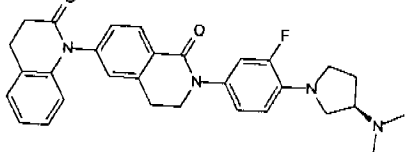


- n-Butyllithium (2.6 m in toluene; 1.2 mL) was added at -78°C to a solution of 2,2,6,6-tetramethyl piperidine (0.51 mL) in THF (30 mL). After 10 minutes, 4-N-((R)-4-[1,3']bipyrrolidinyl-1'-yl-phenyl)-4-butoxy-2-methyl-benzamide (0.4 g) in THF (5 mL)
- 20 was added and the mixture was stirred for 20 minutes at -78°C. N-Methoxy-N-methylacetamide (207 mg) was added to the deep-red solution and after a further 30 minutes the reaction mixture was heated to room temperature. After 2 hours the THF was removed by distillation in the rotary evaporator and the residue was distributed between water and ethyl acetate. The organic phase was dried over sodium sulfate

Ex. No.	Structure	Empirical formula	Molecular weight	ESI-MS [M+H]
77		C ₂₂ H ₂₄ FN ₃ O ₄	413,45	414
78		C ₂₆ H ₃₀ FN ₃ O ₃	451,55	452
79		C ₂₄ H ₂₆ FN ₃ O ₄	439,49	440
80		C ₂₇ H ₂₈ FN ₃ O ₂	445,54	446
81		C ₂₆ H ₂₇ FN ₄ O ₂	446,53	447
82		C ₂₃ H ₂₆ FN ₃ O ₃	411,48	412
83		C ₂₄ H ₂₈ FN ₃ O ₃	425,51	426
84		C ₂₅ H ₂₈ FN ₃ O ₄	453,52	454
85		C ₂₃ H ₂₈ FN ₃ O ₃	413,50	414
86		C ₂₄ H ₂₉ FN ₄ O ₃	440,52	441

Table 9.

Ex. No.	Structure	Empirical formula	Molecular weight	ESI-MS [M+H] ⁺
91		C ₂₈ H ₂₉ FN ₄ O ₂	472,57	473 5
92		C ₂₅ H ₂₉ FN ₄ O ₂	436,53	437
93		C ₂₄ H ₂₉ FN ₄ O ₂	424,52	425
94		C ₂₈ H ₃₅ FN ₄ O ₂	478,62	479
95		C ₂₅ H ₃₁ FN ₄ O ₂	438,55	439
96		C ₂₅ H ₃₁ FN ₄ O ₂	438,55	439
97		C ₂₆ H ₃₀ FN ₅ O ₂	463,56	464
98		C ₂₆ H ₃₂ FN ₅ O ₂	465,58	466
99		C ₂₇ H ₃₂ FN ₅ O ₂	477,59	478
100		C ₂₆ H ₃₀ FN ₅ O ₂	463,56	464

Ex. No.	Structure	Empirical formula	Molecular weight	ESI-MS [M+H] ⁺
101		C ₂₆ H ₃₃ FN ₄ O ₃	468,58	469
102		C ₂₄ H ₃₀ FN ₅ O ₂	439,54	440
103		C ₂₈ H ₃₃ FN ₄ O ₂	476,60	477
104		C ₂₆ H ₃₁ FN ₄ O ₂	450,56	451
105		C ₂₆ H ₂₉ FN ₄ O ₂	448,55	449
106		C ₂₅ H ₃₃ FN ₄ O ₂	440,57	441
107		C ₂₆ H ₂₉ FN ₄ O ₃	464,54	465
108		C ₂₆ H ₂₈ FN ₅ O ₂	461,54	462
109		C ₃₀ H ₃₁ FN ₄ O ₂	498,61	499

Ex. No.	Structure	Empirical formula	Molecular weight	ESI-MS [M+H] ⁺
114		C ₂₈ H ₃₂ FN ₃ O ₂	461,59	462
115		C ₂₇ H ₃₂ FN ₃ O ₂	449,57	450
116		C ₂₈ H ₃₂ FN ₃ O ₂	461,59	462
117		C ₂₈ H ₃₄ FN ₃ O ₂	463,60	464
118		C ₂₈ H ₃₄ FN ₃ O ₂	463,60	464
119		C ₂₆ H ₃₀ FN ₃ O	419,55	420
120		C ₂₇ H ₃₂ FN ₃ O ₂	449,57	450
121		C ₂₆ H ₃₁ FN ₄ O	434,56	435
122		C ₂₄ H ₂₅ FN ₄ O ₂	420,49	421
123		C ₂₅ H ₂₈ FN ₅ O ₂	449,53	450
124		C ₂₈ H ₃₃ FN ₄ O ₃	492,60	493

Ex. No.	Structure	Empirical formula	Molecular weight	ESI-MS [M+H] ⁺
125		C ₂₇ H ₃₂ FN ₃ O ₂	449,57	450
126		C ₂₆ H ₃₀ FN ₃ O ₂	435,55	436
127		C ₂₆ H ₃₁ FN ₄ O	434,56	435
128		C ₂₈ H ₃₂ FN ₃ O ₂	461,59	462
129		C ₂₇ H ₃₀ FN ₃ O ₂	447,56	448
130		C ₂₈ H ₃₀ FN ₃ O ₂	459,57	460
131		C ₂₇ H ₂₈ FN ₃ O ₂	445,54	446
132		C ₂₇ H ₃₀ FN ₃ O ₂	447,56	448
133		C ₂₇ H ₃₀ FN ₃ O ₂	447,56	448
134		C ₂₈ H ₃₂ FN ₃ O ₂	461,59	462
135		C ₂₈ H ₃₂ FN ₃ O ₂	461,59	462

octahydro-pyrimido[1,2-a]azepine (21 mg) and toluene (1 mL) was heated at 120°C bath temperature. After 4 hours, the same amounts of epoxide and auxiliary base were added once again, heating for a further 8 hours at 120°C. The cooled reaction mixture was concentrated and purified by preparative HPLC. In this way the product was
5 obtained with molecular weight 455.58 (C₂₆H₃₄FN₃O₃); MS (ESI): 456 (M+H⁺). Alternatively cesium fluoride in DMF as solvent can also be used as auxiliary base.

The products presented in Table 11 were obtained according to Method T by reaction of the corresponding phenol with the corresponding epoxide.