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DERIVADOS DE TETRAHIDROQUINOLINA

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71. SOLICITANTE

AKZO NOBEL N.V.

DOMICILIO

Amsterdam, Holanda

74. APODERADO

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1 SOLICITUD DE:		
☒ Patente de Invención. ☐ Patente de Modelo de Utilidad.		
☐ Capítulo I. ☒ Capítulo II.		
2 SOLICITANTE (71)	Nombre: AKZO NOBEL N.V. sociedad constituida y existente bajo las leyes de Holanda Dirección: Velperweg 76, NL-6824 BM Arnhem, Holanda Domicilio: Arnhem, Holanda	IDENTIFICACION C.C. ☐ NIT ☐ C.E. ☐ Otro ☐ Cual _____ Número: _____
3 REPRESENTANTE APODERADO	Nombre: EMILIO FERRERO Dirección: Carrera 4ª. No. 72-35 Teléfono: 347 36 11 Fax:: 217 92 11 E-mail: clientes@camyp.com. Domicilio: Bogotá, Colombia.	IDENTIFICACION C.C. ☒ NIT ☐ C.E. ☐ Otro ☐ Cual _____ Número: 438.019 T.P. 31.929
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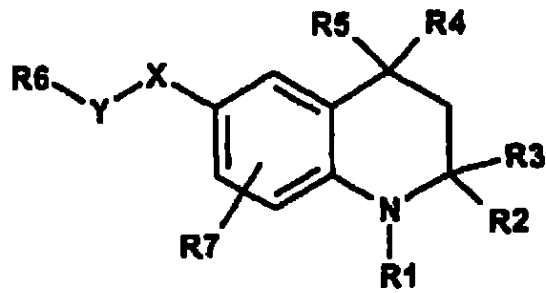
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10	Anexos:
☒	Comprobante de pago de la tasa de presentación de la solicitud por \$ 422.000.00.
☐	Comprobante de pago por reivindicación de prioridad.
☒	Documento que acredite la existencia y representación legal cuando el solicitante sea persona jurídica.
☒	Poderes, si fuere el caso.
☐	Documento de cesión del inventor al solicitante o a su causante.
☐	Declaraciones.
☒	Copia de la solicitud internacional. (Resumen, descripción, reivindicaciones, dibujos)
☒	Traducción de la solicitud internacional al castellano. (Resumen, descripción, reivindicaciones, dibujos)
☒	Copia del examen preliminar efectuado por la IPEA.
☒	Traducción del examen preliminar efectuado por la IPEA.
☐	De ser el caso, copia del contrato de acceso.
☐	De ser el caso, documento que acredite la licencia o autorización de uso de conocimientos tradicionales de las comunidades indígenas.
☐	De ser el caso, certificado de depósito del material biológico.
☒	Arte final 12x12
☐	De ser el caso, información sobre otras solicitudes de patente o títulos obtenidos en el extranjero por el mismo titular o su causante, relacionadas parcial o totalmente con la invención de esta solicitud.
☐	Otros

11

FIGURA CARACTERISTICA:



(I)

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Solicito la concesión de la patente,

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215/08, 413/12, A61K 31/4709, A61P 5/06(74) Agent: VAN WEZENBEEK, P., M., G., F.; P.O. Box 20,
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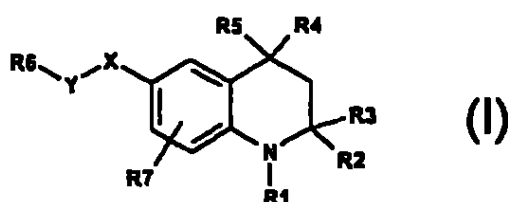
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BH Oss (NL). SCHULZ, Jürgen [DE/GB]; Organon Lab-
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shire, Scotland ML1 5SH (GB).For two-letter codes and other abbreviations, refer to the "Guid-
ance Notes on Codes and Abbreviations" appearing at the begin-
ning of each regular issue of the PCT Gazette.

(54) Title: TETRAHYDROQUINOLINE DERIVATIVES



(57) Abstract: The present invention relates to tetrahydroquino-
line derivatives having general formula (I) or a pharmaceutically
acceptable salt thereof, wherein R¹ is formyl, (1-6C)alkylcarbonyl
or (1-6C)alkylsulfonyl; R² and R³ are H or (1-4C)alkyl;
R⁴ is phenyl; R⁵ is (1-4C)alkyl; Y-X is (CO)-O, (SO)₂-O,
NHC(O)-O, NHC(S)-O, OC(O)-O, bond-O, C(O)-NH, S(O)₂-NH,
NHC(O)-NH, NHC(S)-NH, OC(O)-NH, bond-NH, NH-C(O),
O-C(O), NH-S(O)₂, or O-S(O)₂ or Y-X is a bond; R⁶ is H,
trifluoromethyl, (1-6C)alkyl, 1- or 2-adamantyl, (1-4C)alkyl,
(2-6C)alkenyl, (3-9C)heteroaryl, (3-6C)cycloalkyl, (2-6C)hetero-
cycloalkyl, (1-4C)alkylthio, (1-4C)alkyl, (6-10C)aryl, (1-4C)alkyl,
(3-9C)heteroaryl, (1-4C)alkyl, (3-6C)cycloalkyl, (1-4C)alkyl,
(2-6C)heterocycloalkyl, (1-4C)alkyl, R⁸, R⁹-aminocarbonyl, (1-4C)alkyl, R⁸, R⁹-amino, (1-4C)alkyl, R⁸-oxycarbonyl, (1-4C)alkyl,
R⁸-oxy, (1-4C)alkyl, R⁸-carbonyl, (1-4C)alkyl or (6-10C)aryl; R⁷ is H, (1-4C)alkyl, (1-4C)alkoxy, halogen, trifluoromethyl,
cyano, nitro, hydroxyl; and R⁸ and/or R⁹ is H, (1-4C)alkyl, (2-4C)alkenyl, (2-4C)alkynyl, (6-10C)aryl, (3-9C)heteroaryl,
(6-10C)aryl, (1-4C)alkyl, (3-9C)heteroaryl, (1-4C)alkyl, (3-6C)cycloalkyl, (1-4C)alkyl, (2-6C)heterocycloalkyl, (1-4C)alkyl,
(1-4C)(di)alkylamino, (1-4C)alkyl, (1-4C)alkoxy, (1-4C)alkyl, (1-4C)alkylthio, (1-4C)alkyl, (1-4C)alkylcarbonylamino, (1-4C)alkyl,
(1-4C)alkoxycarbonyl, (1-4C)alkyl, (1-4C)alkoxycarbonylamino, (1-4C)alkyl, (3-6C)cycloalkyl, (2-6C)heterocycloalkyl, or R⁸ and
R⁹ may be joined in a (2-6C)heterocycloalkyl ring. The present invention also relates to pharmaceutical compositions comprising
said derivatives and the use of these derivatives to control fertility.

WO 03/004028 A1

Tetrahydroquinoline derivatives

The invention relates to a compound having FSH modulatory activity, in particular a tetrahydroquinoline derivative, to a pharmaceutical composition containing the same,
5 as well as the use of said compound in medical therapy.

Gonadotropins serve important functions in a variety of bodily functions including metabolism, temperature regulation and the reproductive process. Gonadotropins act on specific gonadal cell types to initiate ovarian and testicular differentiation and
10 steroidogenesis. The hypophyseal gonadotropin FSH (follicle stimulating hormone) for example plays a pivotal role in the stimulation of follicle development and maturation whereas LH (luteinizing hormone) induces ovulation (Sharp, R.M. Clin Endocrinol. 33:787-807, 1990; Dorrington and Armstrong, Recent Prog. Horm. Res. 35:301-342, 1979). Currently, FSH is applied clinically, in combination with LH, for ovarian
15 stimulation i.e. ovarian hyperstimulation for in vitro fertilisation (IVF) and induction of ovulation in infertile anovulatory women (Insler, V., Int. J. Fertility 33:85-97, 1988, Navot and Rosenwaks, J. Vitro Fert. Embryo Transfer 5:3-13, 1988), as well as for male hypogonadism and male infertility.

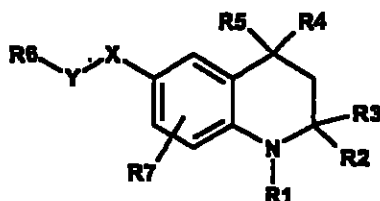
The gonadotropin FSH is released from the anterior pituitary under the influence of
20 gonadotropin-releasing hormone and oestrogens, and from the placenta during pregnancy. In the female, FSH acts on the ovaries promoting development of follicles and is the major hormone regulating secretion of oestrogens. In the male, FSH is responsible for the integrity of the seminiferous tubules and acts on Sertoli cells to support gametogenesis. Purified FSH is used clinically to treat infertility in females and
25 for some types of failure of spermatogenesis in males. Gonadotropins destined for therapeutic purposes can be isolated from human urine sources and are of low purity (Morse et al, Amer. J. Reproduct. Immunol. and Microbiology 17:143, 1988). Alternatively, they can be prepared as recombinant gonadotropins. Recombinant human FSH is available commercially and is being used in assisted reproduction
30 (Olijve et al. Mol. Hum. Reprod. 2:371, 1996; Devroey et al. Lancet 339:1170, 1992).

The actions of the FSH hormone are mediated by a specific plasma membrane receptor that is a member of the large family of G-protein coupled receptors. These receptors consist of a single polypeptide with seven transmembrane domains and are able to
 5 interact with the Gs protein, leading to the activation of adenylate cyclase.

The FSH receptor is a highly specific target in the ovarian follicle growth process and is exclusively expressed in the ovary. Blocking this receptor or inhibiting the signaling which is normally induced after FSH-mediated receptor activation will disturb follicle development and thus ovulation and fertility. Low molecular weight FSH antagonists
 10 could therefore form the basis for new contraceptives. Such FSH antagonists could give rise to diminished follicle development (no ovulation) with still sufficient estrogen production left to avoid adverse effects on e.g. bone mass.

The present invention describes the preparation of low molecular weight hormone analogs that selectively have modulatory activity on the FSH receptor. The compounds
 15 of the invention can either be used as (partial) agonists or (partial) antagonists of the FSH-receptor.

Thus, it has now been found, that the following class of tetrahydroquinoline compounds of formula I or pharmaceutically acceptable salts thereof, have FSH-
 20 modulatory activity:



Formula I

wherein

R¹ is formyl, (1-6C)alkylcarbonyl or (1-6C)alkylsulfonyl;

R² and R³ are H or (1-4C)alkyl;

25 R⁴ is phenyl, optionally substituted with one or more substituents selected from the group hydroxy, amino, halogen, nitro, trifluoromethyl, cyano, (1-4C)alkyl, (2-4C)alkenyl, (2-4C)alkynyl, (1-4C)alkoxy, (1-4C)(di)alkylamino. Preferable position of

substitution is the para-position.

R⁵ is (1-4C)alkyl;

Y-X is C(O)-O, S(O)₂-O, NHC(O)-O, NHC(S)-O, OC(O)-O, bond-O, C(O)-NH, S(O)₂-NH, NHC(O)-NH, NHC(S)-NH, OC(O)-NH, bond-NH, NH-C(O), O-C(O),

5 NH-S(O)₂, or O-S(O)₂ or X-Y is a bond;

R⁶ is H, trifluoromethyl, (1-6C)alkyl, 1- or 2-adamantyl(1-4C)alkyl, (2-6C)alkenyl, (2-6C)alkynyl, (6-10C)aryl, (3-9C)heteroaryl, (3-6C)cycloalkyl, (2-6C)heterocycloalkyl, (1-4C)alkylthio(1-4C)alkyl, (6-10C)aryl(1-4C)alkyl, (3-9C)heteroaryl(1-4C)alkyl, (3-6C)cycloalkyl(1-4C)alkyl, (2-6C)heterocycloalkyl(1-4C)alkyl, R⁸,R⁹-aminocarbonyl(1-4C)alkyl, R⁸,R⁹-amino(1-4C)alkyl, R⁸-oxycarbonyl(1-4C)alkyl, R⁸-oxy(1-4C)alkyl, R⁸-carbonyl(1-4C)alkyl;

10

If R⁶ is H, it is to be noted that X-Y may not be a bond.

If R⁶ is phenyl, phenyl may, in addition to the substituents for (6-10C)aryl groups as mentioned in the definitions, optionally be substituted with (6-10C)aryl, (6-10C)aryloxy, (6-10C)aryl(1-4C)alkoxy, (3-9C)heteroaryl, (3-9C)heteroaryloxy, (3-9C)heteroaryl(1-4C)alkoxy, (1-4C)alkylcarbonylamino, (1-4C)alkylcarbonyloxy, (3-6C)cycloalkylcarbonyloxy, (1-4C)alkoxycarbonyl(1-4C)alkylcarbonyloxy, (1-4C)alkoxy(1-4C)alkylcarbonyloxy, (6-10C)arylcarbonyloxy, (3-9C)heteroarylcarbonyloxy, (1-4C)alkylsulfonyloxy, (6-10C)arylsulfonyloxy, (3-9C)heteroarylsulfonyloxy, (1-4C)(di)alkylcarbamoyl, (6-10C)(di)arylcabamoyl, (2-6C)heterocycloalkylcarbamoyl, (6-10C)(di)arylamino, (3-6C)cycloalkyl, (3-6C)cycloalkyl(1-4C)alkyl, (2-6C)heterocycloalkyl, (2-6)heterocycloalkyl(1-4C)alkyl.

15

20

R⁷ is H, (1-4C)alkyl, (1-4C)alkoxy, halogen, trifluoromethyl, cyano, nitro, hydroxyl; R⁸ and/or R⁹ is H, (1-4C)alkyl, (2-4C)alkenyl, (2-4C)alkynyl, (6-10C)aryl, (3-9C)heteroaryl, (6-10C)aryl(1-4C)alkyl, (3-9C)heteroaryl(1-4C)alkyl, (3-6C)cycloalkyl(1-4C)alkyl, (2-6C)heterocycloalkyl(1-4C)alkyl, (1-4C)(di)alkylamino(1-4C)alkyl, (1-4C)alkoxy(1-4C)alkyl, (1-4C)alkylthio(1-4C)alkyl, (1-4C)alkylcarbonylamino(1-4C)alkyl, (1-4C)alkoxycarbonyl(1-4C)alkyl, (1-4C)alkoxycarbonylamino(1-4C)alkyl, (3-6C)cycloalkyl, (2-6C)heterocycloalkyl, or R⁸ and R⁹ may be joined in a (2-6C)heterocycloalkyl ring.

25

30

The compounds according to the present invention modulate the FSH receptor function and can be used for the same clinical purposes as native FSH if they behave like agonists, with the advantage that they display altered stability properties and may be administered differently. If they block the FSH receptor they can be used e.g. as a
5 contraceptive agent.

Thus, the FSH-receptor modulators of the present invention may be used for treating infertility, for contraception and for treatment of hormone-dependent disorders such as breast cancer, prostate cancer, and endometriosis. Preferably the compounds of the present invention are used to inactivate the FSH-receptor.

10

The term (1-4C)alkyl as used in the definition means a branched or unbranched alkyl group having 1-4 carbon atoms, for example methyl, ethyl, propyl, isopropyl, butyl, sec-butyl and tert-butyl.

The term (1-6C)alkyl as used in the definition means a branched or unbranched alkyl
15 group having 1-6 carbon atoms, for example methyl, ethyl, propyl, isopropyl, butyl, sec-butyl, tert-butyl and hexyl. (1-5C)Alkyl groups are preferred, (1-4C)alkyl being the most preferred.

The term 1- or 2-adamantyl(1-4C)alkyl means an adamantyl group attached at position 1 or 2 to an alkyl group containing 1-4 carbon atoms, with the same meaning as
20 previously defined.

The term (2-4C)alkenyl means a branched or unbranched alkenyl group having 2-4 carbon atoms, such as ethenyl and 2-butenyl.

The term (2-6C)alkenyl means a branched or unbranched alkenyl group having 2-6 carbon atoms, such as ethenyl, 2-butenyl, and n-pentenyl.

25 The term (2-4C)alkynyl means a branched or unbranched alkynyl group having 2-4 carbon atoms, such as ethynyl and propynyl.

The term (2-6C)alkynyl means a branched or unbranched alkynyl group having 2-6 carbon atoms, such as ethynyl, propynyl and n-pentynyl.

The term (3-6C)cycloalkyl means a cycloalkyl group having 3-6 carbon atoms, being cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl.

The term (2-6C)heterocycloalkyl means a heterocycloalkyl group having 2-6 carbon atoms, preferably 3-5 carbon atoms, and at least including one heteroatom selected from N, O and/or S, which may be attached via a heteroatom if feasible, or a carbon atom. Preferred heteroatoms are N or O. Most preferred are piperidine, morpholine and pyrrolidine.

The term (1-4C)alkoxy means an alkoxy group having 1-4 carbon atoms, the alkyl moiety having the same meaning as previously defined. (1-2C)Alkoxy groups are preferred.

The term (6-10C)aryl means an aromatic hydrocarbon group having 6-10 carbon atoms, such as phenyl, naphthyl, tetrahydronaphthyl or indenyl, which may optionally be substituted with one or more substituents selected from hydroxy, amino, halogen, nitro, trifluoromethyl, cyano, (1-4C)alkyl, (2-4C)alkenyl, (2-4C)alkynyl, (1-4C)alkoxy, (1-4C)(di)alkylamino, the alkyl moieties having the same meaning as previously defined. The preferred aromatic hydrocarbon group is phenyl.

The term (3-9C)heteroaryl means a substituted or unsubstituted aromatic group having 3-9 carbon atoms, at least including one heteroatom selected from N, O and/or S, like imidazolyl, thiadiazolyl, pyridyl, (benz)thienyl, (benzo)furyl, quinolyl, tetrahydroquinolyl, quinoxalyl or indolyl. The substituents on the heteroaryl group may be selected from the group of substituents listed for the aryl group. The heteroaryl group may be attached via a carbon atom or a heteroatom, if feasible. Preferred heteroaryl groups are thienyl, furyl and pyridyl.

The term (6-10C)aryloxy means an aryl group containing 6-10 carbon atoms as defined previously, attached to an oxygen atom. (3-9C)Heteroaryloxy groups are analogs of the (6-10C)aryloxy groups, at least including one heteroatom selected from N, O or S.

The term (1-4C)alkoxycarbonyl(1-4C)alkyl means an alkoxycarbonylalkyl group, wherein the alkoxy group contains 1-4 carbon atoms with the same meaning as previously defined and the alkyl group contains 1-4 carbon atoms with the same meaning as previously defined.

The term (1-4C)alkoxy(1-4C)alkyl means an alkoxyalkyl group, wherein the alkoxy group contains 1-4 carbon atoms with the same meaning as previously defined and the alkyl group contains 1-4 carbon atoms with the same meaning as previously defined.

The term (3-6C)cycloalkyl(1-4C)alkyl means a cycloalkyl group of 3-6 carbon atoms
5 attached to an alkyl group of 1-4 carbon atoms, wherein the cycloalkyl group is a (3-6C)cycloalkyl group as previously defined and the alkyl group is a (1-4C)alkyl group as previously defined.

The term (2-6C)heterocycloalkyl(1-4C)alkyl means a heterocycloalkyl group of 2-6 carbon atoms attached to an alkyl group of 1-4 carbon atoms, wherein the
10 heterocycloalkyl group is a (2-6C)heterocycloalkyl group as previously defined and the alkyl group is a (1-4C)alkyl group as previously defined.

The term (1-4C)(di)alkylamino means a (di)alkylamino group, the alkyl groups of which contain 1-4 carbon atoms and have the same meaning as previously defined.

The term (6-10C)(di)aryl amino means a (di)aryl amino group, the aryl groups of which
15 contain 6-10 carbon atoms and have the same meaning as previously defined.

The term (1-4C)(di)alkylamino(1-4C)alkyl means a (di)alkylaminoalkyl group, the alkyl groups of which contain 1-4 carbon atoms and have the same meaning as previously defined.

The term (1-4C)alkylthio(1-4C)alkyl means an alkylthioalkyl group, the alkyl groups
20 of which contain 1 to 4 carbon atoms and have the same meaning as defined previously.

The term aminocarbonyl(1-4C)alkyl in the definition of R^8, R^9 -aminocarbonyl(1-4C)alkyl means an aminocarbonylalkyl group, the alkyl group of which contains 1-4 carbon atoms and has the same meaning as previously defined. The
25 aminocarbonylmethyl group is the preferred aminocarbonylalkyl group.

The term amino(1-4C)alkyl in the definition of R^8, R^9 -amino(1-4C)alkyl means an aminoalkyl group, the alkyl group of which contains 1-4 carbon atoms and has the same meaning as previously defined.

The term oxycarbonyl(1-4C)alkyl in the definition of R^8 -oxycarbonyl(1-4C)alkyl
30 means an oxycarbonylalkyl group, the alkyl group of which contains 1-4 carbon atoms

and has the same meaning as previously defined. The oxycarbonylmethyl group is the preferred oxycarbonylalkyl group.

The term oxy(1-4C)alkyl in the definition of R^8 -oxy(1-4C)alkyl means an oxyalkyl group, the alkyl group of which contains 1-4 carbon atoms and has the same meaning
5 as previously defined.

The term carbonyl(1-4C)alkyl in the definition of R^8 -carbonyl(1-4C)alkyl means a carbonylalkyl group, the alkyl group of which contains 1-4 carbon atoms and has the same meaning as previously defined.

The term (6-10C)aryl(1-4C)alkyl means an arylalkyl group having 7-14 carbon atoms,
10 wherein the alkyl group is a (1-4C)alkyl group and the aryl group is a (6-10C)aryl as previously defined. Phenyl(1-4C)alkyl groups are preferred arylalkyl groups, such as benzyl. (3-9C)Heteroaryl(1-4C)alkyl groups are analogs of the (6-10C)aryl(1-4C)alkyl groups, at least including one heteroatom selected from N, O and/or S, the heteroaryl group of which may be attached via a carbon atom or via a heteroatom if feasible.

15 The term joined in a (2-6C)heterocycloalkyl ring in the definition of NR^8R^9 , where R^8 and R^9 together with the nitrogen atom to which they are attached form a ring, means a ring containing the nitrogen atom and further having at most 2-6 carbon atoms, which ring may contain one or more additional heteroatoms selected from N, O and/or S. Examples of such rings are azetidine, pyrrolidine, piperidine, piperazine, and
20 (thio)morpholine.

The term halogen means fluorine, chlorine, bromine or iodine.

The term (1-6C)alkylcarbonyl means an alkylcarbonyl group, the alkyl group of which contains 1-6 carbon atoms and has the same meaning as previously defined. (1-4C)Alkylcarbonyl groups are preferred.

25 The term (1-4C)alkylcarbonylamino(1-4C)alkyl means an alkylcarbonylaminoalkyl group, the alkyl groups of which contain 1-4 carbon atoms and have the same meaning as previously defined.

The term (6-10C)aryl(1-4C)alkoxy means an aryl group containing 6-10 carbon atoms, as defined previously, attached to an (1-4C)alkoxy group as defined previously. (3-
30 9C)Heteroaryl(1-4C)alkoxy groups are analogs of the (6-10C)aryl(1-4C)alkoxy groups,

at least including one heteroatom selected from N, O or S, the heteroaryl group of which may be attached via a carbon atom or via a heteroatom, if feasible.

The term (1-4C)alkylcarbonyloxy means an alkylcarbonyloxy group the alkyl group of which contains 1-4 carbon atoms. The term (3-6C)cycloalkylcarbonyloxy means a
5 cycloalkylcarbonyloxy group the cycloalkyl group of which contains 3-6 carbon atoms, the cycloalkyl moiety of which has the same meaning as previously defined.

The term (1-4C)alkoxycarbonyl(1-4C)alkylcarbonyloxy means an (1-4C)alkoxycarbonyl group attached to an alkylcarbonyloxy group the alkyl moiety of which contains 1-4 carbon atoms, the alkoxy group of which has the same meaning as
10 previously defined.

The term (1-4C)alkoxy(1-4C)alkylcarbonyloxy means an alkoxy group with 1-4 carbon atoms attached to an alkylcarbonyloxy group with 1-4 carbon atoms, the alkoxy and alkyl groups having the same meaning as previously defined.

The term (1-4C)alkylcarbonylamino means an alkylcarbonylamino group the alkyl
15 group of which contains 1-4 carbon atoms.

The term (1-4C)alkoxycarbonylamino(1-4C)alkyl means an alkoxycarbonyl group containing 1-4 carbon atoms with the same meaning as previously defined, attached to an aminoalkyl group, the alkyl group of which contains 1-4 carbon atoms with the same meaning as previously defined.

20 The term (6-10C)arylcabonyloxy means an arylcarbonyloxy group the aryl group of which contains 6-10 carbon atoms. Preferred arylcarbonyloxy group is a phenylcarbonyloxy group. (3-9C)Heteroarylcabonyloxy groups are analogs of the (6-10C)arylcabonyloxy groups, at least including one heteroatom selected from N, O or S and may be attached via a carbon atom or a heteroatom, if feasible.

25 The term (1-4C)alkylsulfonyl means an alkylsulfonyl group, the alkyl group of which contains 1-4 carbon atoms and has the same meaning as previously defined.

The term (1-6C)alkylsulfonyl means an alkylsulfonyl group, the alkyl group of which contains 1-6 carbon atoms and has the same meaning as previously defined. (1-3C)Alkylsulfonyl groups are preferred.

The term (1-4C)alkylsulfonyloxy means an alkylsulfonyloxy group, the alkyl group of which contains 1-4 carbon atoms and has the same meaning as previously defined. (1-3C)Alkylsulfonyloxy groups are preferred.

The term (6-10C)arylsulfonyloxy means an arylsulfonyloxy group, the aryl group of which contains 6-10 carbon atoms and has the same meaning as previously defined. The phenylsulfonyloxy group is preferred. (3-9C)Heteroarylsulfonyloxy groups are analogs of the (6-10C)arylsulfonyloxy groups, at least including one heteroatom selected from N, O or S, which may be attached via a carbon atom or a heteroatom, if feasible.

10 The term (1-4C)(di)alkylcarbamoyl means a (di)alkylcarbamoyl group, the alkyl groups of which contain 1-4 carbon atoms and have the same meaning as previously defined.

The term (6-10C)(di)arylcabamoyl means a (di)arylcabamoyl group, the aryl moieties of which contains 6-10 carbon atoms and have the same meaning as previously defined.

15 The term (2-6C)heterocycloalkylcarbamoyl means a heterocycloalkylcarbamoyl group, the heterocycloalkyl group of which contains 2-6 carbon atoms and has the same meaning as previously defined.

20 Preferred compounds of the invention are compounds of formula I, wherein Y-X is C(O)-NH, OC(O)-NH, or C(O)-O. More preferred are compounds wherein Y-X is C(O)-NH.

Further preferred are compounds wherein R¹ is (1-4C)alkylcarbonyl, preferably acetyl and/or R² and/or R³ and R⁵ are independently (1-4C)alkyl, more preferably methyl.

25 R⁶ preferably is a bulky group. Preferred compounds are those wherein R⁶ is (6-10C)aryl, (3-9C)heteroaryl, (6-10C)aryl(1-4C)alkyl or (3-9C)heteroaryl(1-4C)alkyl. Most preferred are compounds wherein R⁶ is (6-10C)aryl, even more preferred phenyl. The preferred R⁷ group is H, (1-4C)alkyl or (1-4C)alkoxy. Most preferred are H or (1-4C)alkyl, even more preferred H or methyl. Most preferred are compounds wherein R⁷ is H.

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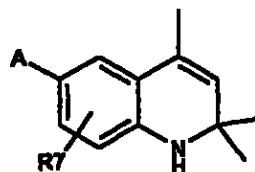
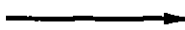
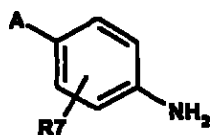
In the most preferred compounds according to the invention R^1 is (1-4C)alkylcarbonyl, R^2 , R^3 , R^5 are independently (1-4C)alkyl, R^4 is phenyl and Y-X is C(O)-NH and R^7 is H. Even more preferred are compounds wherein R^1 is acetyl, R^2 , R^3 , R^5 are independently methyl, R^4 is phenyl and Y-X is C(O)-NH and R^7 is H.

- 5 In the above-mentioned preferred compounds substitutions are allowed as indicated in the definitions of the groups. Phenyl in R^6 can in addition be substituted as indicated in the definition for R^6 .

Excluded from the invention are the compounds 1-acetyl-6-benzoylamino-4-(4-methylphenyl)-1,2,3,4-tetrahydro-2,2,4-trimethylquinoline, 1-acetyl-4-phenyl-1,2,3,4-tetrahydro-2,2,4,6-tetramethylquinoline, 1-acetyl-4-phenyl-1,2,3,4-tetrahydro-2,2,4,6,8-pentamethylquinoline, 1-acetyl-6-methoxy-4-phenyl-1,2,3,4-tetrahydro-2,2,4-trimethylquinoline, 1-acetyl-6-trifluoroacetylamino-4-(4-methylphenyl)-1,2,3,4-tetrahydro-2,2,4-trimethylquinoline, 1-acetyl-6-trifluoroacetylamino-4-phenyl-1,2,3,4-tetrahydro-2,2,4-trimethylquinoline, 1-acetyl-4-(4-chlorophenyl)-1,2,3,4-tetrahydro-2,2,4,6-tetramethylquinoline and 1-acetyl-4-(4-bromophenyl)-1,2,3,4-tetrahydro-2,2,4,6-tetramethylquinoline.

The disclaimer relates to the disclosures in Ref. Zh., Khim. Abstr. No. 1Zh311, 1972; Khim. Geterosikl. Soedin. 7:795, 1971; Ambinter Screening Collection, order nrs 28020-A0839/0039328 (CAS 310456-97-4) and -A0705/0032919 (CAS 327981-38-4); ChemDiv. Inc. order nr 8005-9747 (CAS360760-14-1); ChemStar Product list, order nr CHS0065413 (CAS 299418-67-0); Asinex Compound Collection, order nr BAS0068990 (CAS 299970-20-0).

Suitable methods for the preparation of the compounds of the invention are outlined below.



II-a: A = OAlkyl
 II-b: A = NH(protective group)
 II-c: A = C(O)OAlkyl
 II-d: A = S(O)₂OAlkyl
 II-e: A = (substituted) alkyl, aryl

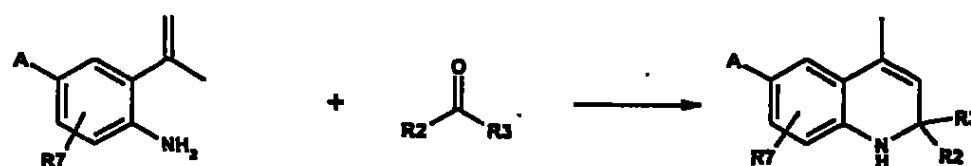
III-a: A = OAlkyl
 III-b: A = NH(protective group)
 III-c: A = C(O)OAlkyl
 III-d: A = S(O)₂OAlkyl
 III-e: A = (substituted) alkyl, aryl

The compounds of the present invention in which R^2 and R^3 are methyl can be prepared starting from (protected) anilines of general formula II-a-e in which R^7 has the same meaning as previously defined, by means of the well-documented Skraup reaction, which yields 1,2-dihydro-2,2,4-trimethylquinoline derivatives of formula III-a-e.

Related Skraup cyclizations are found in literature: A. Knoevenagel, Chem. Ber. 54:1726, 1921; R.L. Atkins and D.E. Bliss, J. Org. Chem. 43:1975, 1978; J.V. Johnson, B.S. Rauckman, D.P. Baccanari and B. Roth, J. Med. Chem. 32:1942, 1989; W.C. Lin, S.-T. Huang and S.-T. Lin, J. Chin. Chem. Soc. 43:497, 1996; J.P. Edwards, S.J. West, K.B. Marschke, D.E. Mais, M.M. Gottardis and T.K. Jones, J. Med. Chem. 41:303, 1998.

The abovementioned reaction is typically conducted at elevated temperature in acetone, mesityl oxide or ethylacetoacetate in the presence of iodine or protic acid such as hydrochloric acid, p-toluenesulfonic acid or aqueous hydrogen iodide. Alternatively, 1,2-dihydro-2,2,4-trimethylquinolines of formula III-a-e can be prepared by reacting the corresponding aniline of formula II-a-e with acetone in the presence of $MgSO_4$, 4-tert-butylcatechol and iodine (L.G. Hamann, R.I. Higuchi, L. Zhi, J.P. Edwards and X.-N. Wang, J. Med. Chem. 41:623, 1998). Starting materials can be either obtained directly from commercial sources or prepared by art-known aromatic ring substitutions, as are described e.g. by H. Cerfontain, Y. Zou and B.H. Bakker, Recl. Trav. Chim. Pays-Bas, 113:403, 1994; A. Coppock, J. Org. Chem. 22:325, 1957; M. Schlosser, J.H. Choi and S. Takagishi, Tetrahedron, 46:5633, 1990.

Alternatively, compounds of general structure VI-a-e, in which R^2 and R^3 are (2-4C)alkyl and R^7 is as previously defined, can generally be synthesized by cyclization of an aniline of formula IV-a-e with an appropriate ketone of formula V.



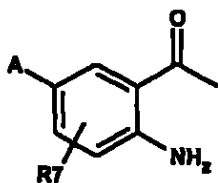
IV-a: A = OAlkyl
 IV-b: A = NH(protective group)
 IV-c: A = C(O)OAlkyl
 IV-d: A = S(O)₂OAlkyl
 IV-e: A = (substituted) alkyl, aryl

V

VI-a: A = OAlkyl
 VI-b: A = NH(protective group)
 VI-c: A = C(O)OAlkyl
 VI-d: A = S(O)₂OAlkyl
 VI-e: A = (substituted) alkyl, aryl

The abovementioned reaction is typically conducted in an inert solvent such as toluene, at elevated temperature using protic or Lewis acids such as, but not limited to, p-toluenesulfonic acid or borontrifluoride to promote the cyclization (H. Walter, H. Sauter and T. Winkler, *Helv. Chim. Acta*, 75:1274, 1992; H. Walter, *Helv. Chim. Acta*, 77:608, 1994; H. Walter and J. Schneider, *Heterocycles*, 41:1251, 1995; J.P. Edwards, J.D. Ringgenberg and T.K. Jones, *Tetrahedron Lett.* 39:5139, 1998).

The requisite building blocks of formula IV-a-e may be prepared by Wittig reaction of ketones of formula VII-a-e. Introduction of substituents A on the aromatic ring can be accomplished using art-known aromatic ring substitutions either in the aniline stage or in the 1,2-dihydro-2,2,4-trimethylquinoline stage, as was mentioned above for compounds of formula II.



VII-a: A = OAlkyl

VII-b: A = NH(protective group)

VII-c: A = C(O)OAlkyl

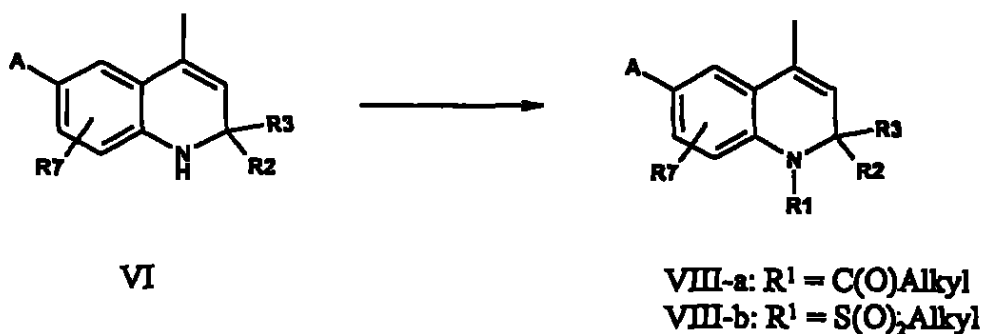
VII-d: A = S(O)₂OAlkyl

VII-e: A = (substituted) alkyl, aryl

In another approach, compounds of formula VI-a-e in which $R^2 = R^3 = H$ can be prepared from anilines of general formula II-a-e by reaction with 1-methylstyrene and formaldehyde in acetonitrile at ambient or elevated temperature. Related cyclizations are described in literature: J.M. Mellor and G.D. Merriman, *Tetrahedron*, 51:6115, 1995.

Subsequent 1-N-acylation or 1-N-sulfonylation of compounds of formula VI wherein R^2 , R^3 , R^7 and A are as previously defined, can be carried out using standard conditions, well known to those skilled in the art. In a typical experiment, compounds of formula VI are reacted in a solvent such as dichloromethane, tetrahydrofuran, toluene or pyridine with an acylhalide or acid anhydride or a sulfonylchloride in the

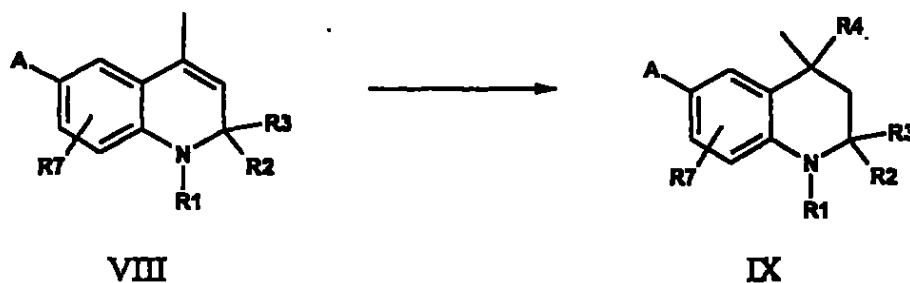
presence of a base such as, but not limited to, *N,N*-diisopropylethylamine, triethylamine, piperidine or sodium hydride to give *N*-acylated or *N*-sulfonylated 1,2-dihydro-4-methylquinoline derivatives of formula VIII-a and VIII-b, respectively.



Related *N*-acylations of a dihydroquinoline scaffold are found in literature: Zh. V. Shmyreva, Kh. S. Shikhaliev and E.B. Shpanig, *Izv. Vyssh. Uchebn. Zaved., Khim. Khim. Tekhnol.* 31:45, 1988; Zh. V. Shmyreva, Kh. S. Shikhaliev, L.P. Zalukaev, Y.A. Ivanov, Y.S. Ryabokobylko and I.E. Pokrovskaya, *Zh. Obshch. Khim.* 59:1391, 1989.

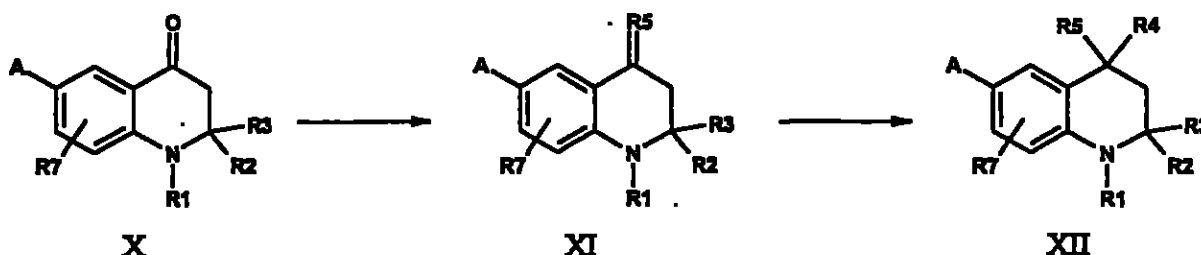
1-*N*-Formylation can be readily established by reaction of dihydroquinoline of formula VI with formic acid in the presence of trifluoroacetic acid at elevated temperature (see for example P. Bouyssou, C. Le Goff and J. Chenault, *J. Heterocycl. Chem.* 29:895, 1992) or with formic acid ethyl ester in the presence of sodium acetate, as was described in literature by e.g. N. Atanea, S. Perez, E. Guitan, L. Castedo and J.M. Saa, *Tetrahedron*, 50:11257, 1994.

Introduction of the requisite phenyl group at position 4 of the dihydroquinoline scaffold can be accomplished via Friedel-Crafts alkylation of (substituted) benzene derivatives with the compounds of general structure VIII, wherein R^1 , R^2 , R^3 , R^7 and A are as previously defined.



The latter reaction is typically conducted at elevated temperatures either in neat (substituted) benzene or in an appropriate inert solvent such as heptane or hexane with (substituted) benzene as reagent, under catalysis of a Lewis acid (e.g. AlCl_3 , AlBr_3 , FeCl_3 or SnCl_4). Friedel-Crafts alkylations with 1,2-dihydro-2,2,4-trimethylquinolines are described in literature by B.A. Lugovik, L.G. Yudin and A.N. Kost, Dokl. Akad. Nauk SSSR, 170:340, 1966; B.A. Lugovik, L.G. Yudin, S.M. Vinogradova and A.N. Kost, Khim. Geterosikl. Soedin, 7:795, 1971.

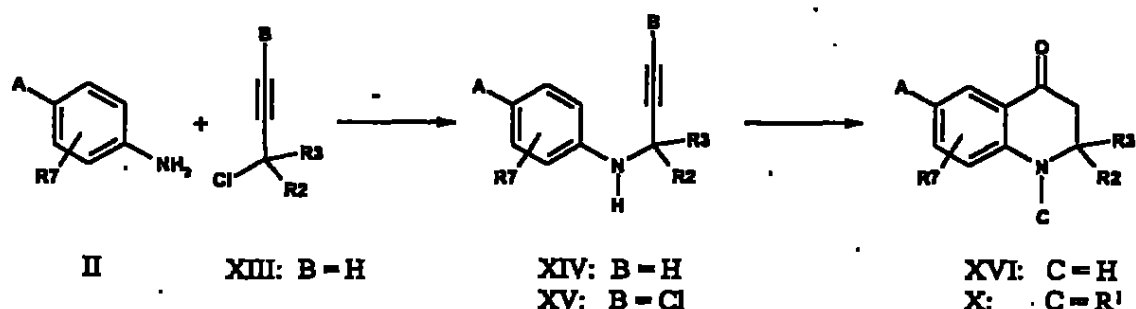
Compounds of the present invention, wherein $\text{R}^5 \neq \text{Me}$ and R^1 , R^2 , R^3 , R^4 , R^7 and A are as previously defined, represented by formula XII, may be synthesized starting from tetrahydroquinoline ketones of formula X. Thus, Wittig reaction of a ketone of formula X with the appropriate Wittig reagent yields the unsaturated derivative represented by formula XI, which in turn is the starting material for a Friedel-Crafts alkylation of (substituted) benzene, *via* the same procedure as was outlined above for the preparation of compounds with general structure IX.



The abovementioned Wittig reaction is well known to those skilled in the art.

The requisite ketone of formula X can be prepared by reaction of an aniline of formula II with 3-chloro-3-methyl-1-butyne (XIII) in diethylether/water in the presence of copper powder and triethylamine which yields an alkyne of formula XIV. Hydrogen-halogen exchange can be carried out by deprotonation of a compound of formula XIV in an inert solvent such as tetrahydrofuran with *n*-butyllithium at temperatures below -50 °C upon addition of *p*-toluenesulfonylchloride to give a chloride of general formula XV. Finally, acid-catalyzed (e.g. sulfuric acid) cyclization can be carried out at elevated temperature in a solvent such as polyethyleneglycol to give compounds of

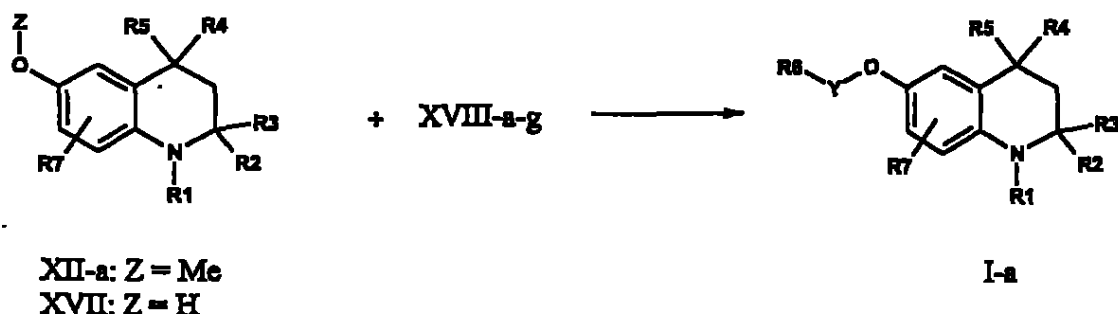
formula XVI, which can be acylated or sulfonylated as was previously described for derivatives of general formula VI



The abovementioned reaction sequence is described in literature: P. Barnettler and H.-
5 J. Hansen, *Helv. Chim. Acta*, 73:1515, 1990 (and references cited in there).

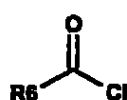
Functionalization of position 6 in tetrahydroquinolines of general structure XII can be accomplished via art-known deprotection-coupling procedures:

Compounds of the present invention wherein $X = O$ and $Y = C(O), S(O)_2, NHC(O),$
 10 $NHC(S), OC(O)$ or a bond, represented by formula I-a, can be prepared from 6-methoxy-containing tetrahydroquinoline of formula XII-a. Demethylation is well known to those skilled in the art.

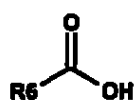


In a typical experiment, demethylation is achieved upon reaction of a compound of formula XII-a with BBr_3 in an inert solvent such as, but not limited to, dichloromethane or tetrahydrofuran at low temperature to give deprotected compounds of general formula XVII. Alternatively, demethylation can be accomplished upon reaction of

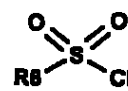
compounds of formula XII-a with $\text{BF}_3 \cdot \text{Me}_2\text{S}$ complex at ambient temperature in an inert solvent as was mentioned for demethylations using BBr_3 .



XVIII-a



XVIII-b



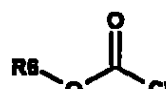
XVIII-c



XVIII-d



XVIII-e



XVIII-f



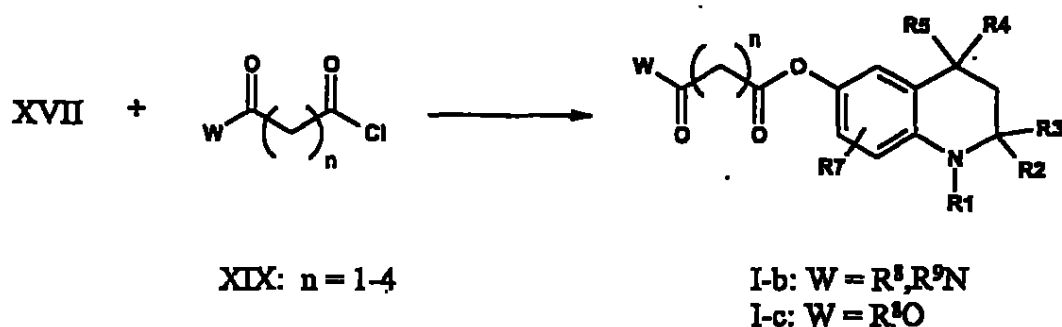
XVIII-g

Subsequent functionalizations of the free OH group in derivatives of formula XVII are also well known to those skilled in the art and can be easily established using reagents of formula XVIII-a-g.

For the halide-containing reagents of formula XVIII, the abovementioned reaction is typically conducted at room temperature in a suitable solvent, e.g. an aprotic solvent such as *N,N*-dimethylformamide, dichloromethane or tetrahydrofuran, in the presence of a base, such as, but not limited to, *N,N*-diisopropylethylamine or sodium hydride. Additives such as *N,N*-dimethylaminopyridine or tetrabutylammoniumiodide may accelerate the latter reaction. Furthermore, utilisation of isocyanates or isothiocyanates of formula XVIII-d and XVIII-e in an inert solvent at ambient or elevated temperatures yields compounds of formula I-a wherein $\text{Y} = \text{NHC}(\text{O})$ or $\text{NHC}(\text{S})$, respectively.

Compounds wherein $\text{Y} = \text{C}(\text{O})$ may also be obtained in an alternative way using carboxylic acids of general formula XVIII-b, using a coupling reagent such as *O*-(benzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium tetrafluoroborate (TBTU), *O*-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (HATU) or bromotripyrrolidinophosphonium hexafluorophosphate (PyBrOP) and a tertiary base, e.g. *N,N*-diisopropylethylamine, in a solvent such as *N,N*-dimethylformamide or dichloromethane at ambient or elevated temperature.

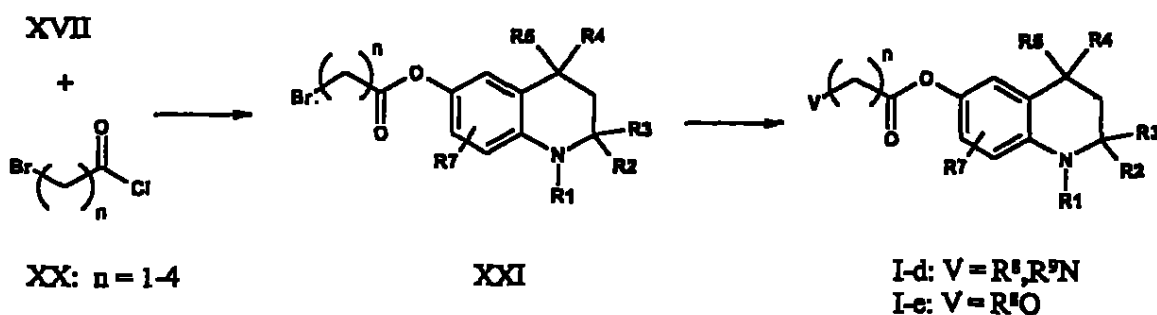
Compounds represented by formula I-b-c, in which $W = R^8, R^9N$ or R^8O , respectively, can be synthesized by reacting compounds of general formula XVII with an acid chloride of formula XIX using standard conditions.



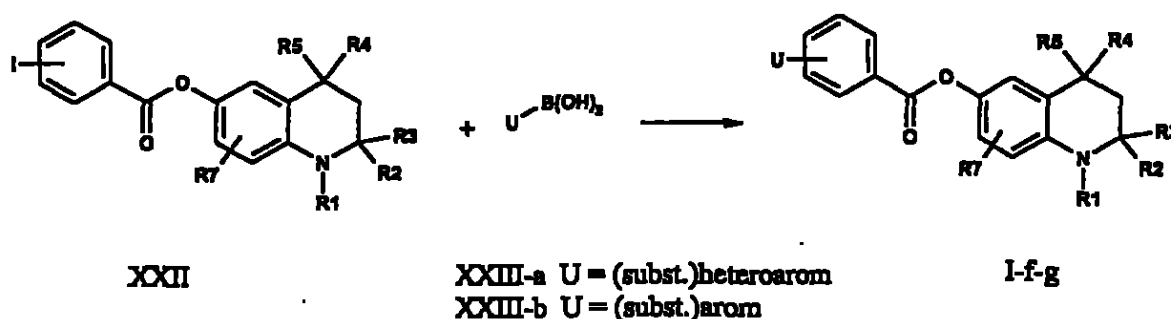
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Alternatively, compounds of structure I-b-c may be prepared from derivatives of formula XVII and an acid chloride of formula XIX in which $W = OBt$, followed by base-mediated (e.g. NaOH) saponification and subsequent condensation of the free carboxylic acid with either amines of general structure R^8, R^9NH or alcohols of general structure R^8OH in the presence of a coupling reagent such as the earlier mentioned TBTU, HATU or PyBrOP and a tertiary base such as *N,N*-diisopropylethylamine.

Compounds represented by formula I-d-e, in which $V = R^8, R^9N$ or R^8O , respectively, can be obtained *via* nucleophilic substitution of a halogen such as Br, present in compounds of formula XXI by amines of general structure R^8, R^9NH or alcohols of general structure R^8OH . In turn, the requisite tetrahydroquinoline of formula XXI can be synthesized from a compound of formula XVII and a bromoacylchloride of general structure XX, using art-known synthetic procedures.



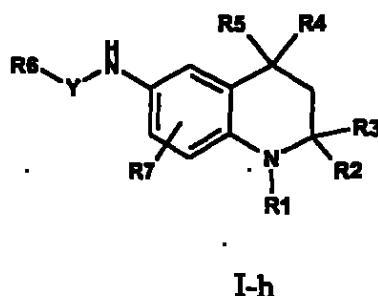
Compounds represented by formula I-f-g, in which U = (substituted) heteroaromatic or (substituted) phenyl, respectively, may be prepared via Suzuki coupling of (substituted) iodobenzoyl derivatives of formula XXII with boronic acids of general formula XXIII-a-b.



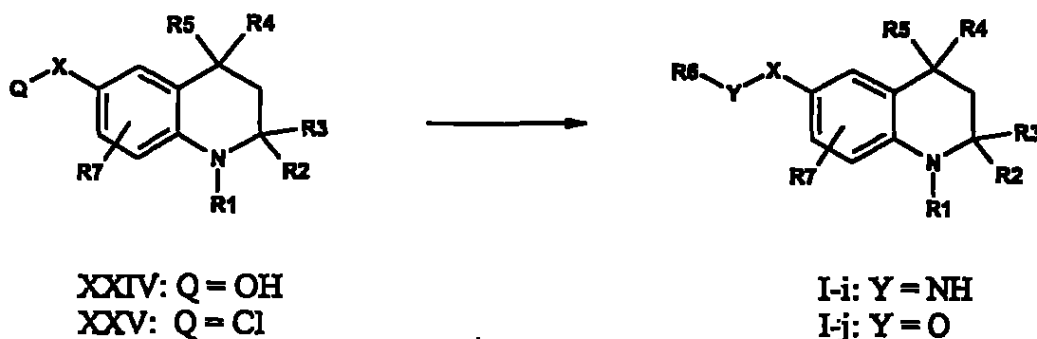
In a typical experiment, an iodide of formula XXII is reacted with a boronic acid of formula XXIII-a-b in a solvent mixture such as dimethoxyethane/ethanol using cesium fluoride and a palladium catalyst such as palladiumtetrakis(triphenylphosphine) or tris(dibenzylideneacetone)dipalladium at elevated temperature under a nitrogen atmosphere. Addition of triphenylphosphine may accelerate the reaction and improve the yield. The abovementioned reaction is described extensively in literature. See for example: A. Suzuki, Acc. Chem. Res. 15:178, 1982; N. Miyaura, T. Ishiyama, H. Sasaki, M. Ishikawa, M. Satoh and A. Suzuki, J. Am. Chem. Soc. 111:314, 1989.

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Likewise, compounds represented by formula I-h wherein X = NH and Y is as previously defined can be synthesized via the same methods as were described above for compounds of general formula Ia-g in which X = O.



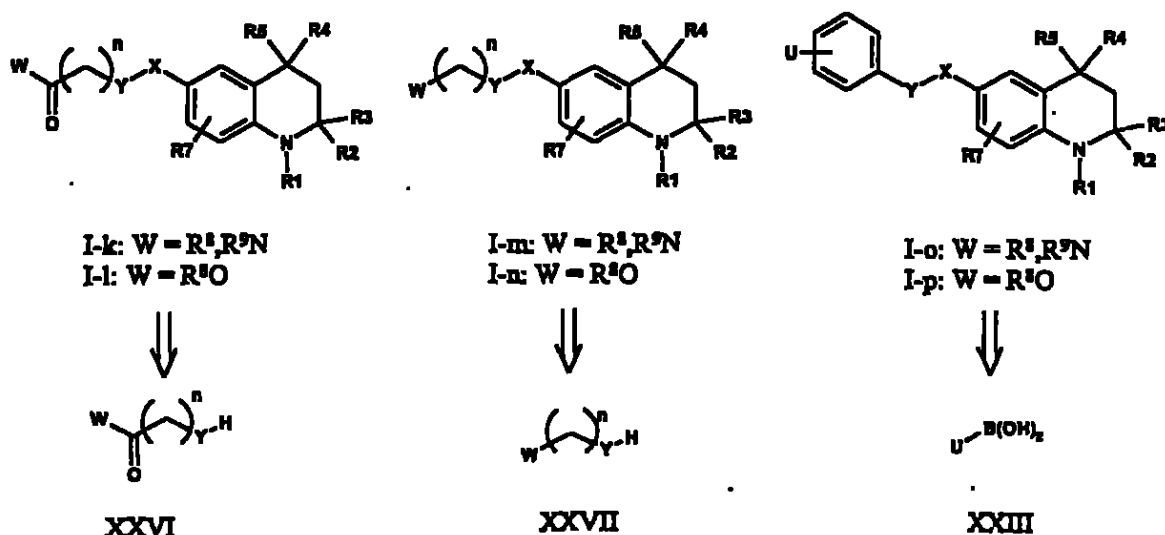
Compounds represented by formula I-i-j in which $X = C(O)$ or $S(O)_2$ and $Y = NH$ or O , respectively, may be obtained *via* reaction of the corresponding acyl or sulfonyl chlorides of formula XXV with amines of general structure R^6NH_2 or alcohols of general structure R^6OH *via* the same method as was described earlier for the preparation of compounds of formula I-a.



The requisite acyl or sulfonyl chlorides of formula XXV can be prepared from the corresponding compounds of formula XXIV by treatment with *e.g.* $POCl_3$, PCl_5 , oxalylchloride, phosgene or $SOCl_2$, in solvents such as toluene, acetonitrile, or *N,N*-dimethylformamide, as is described extensively in literature. See for example M. Bonnat, M. Bradley and J.D. Kilburn, *Tetrahedron Lett.* 37:5409, 1996; J.G. Montana, G.M. Buckley, N. Cooper, H.J. Dyke and L. Gowers, *Bioorg. Med. Chem. Lett.* 8:2635, 1998; J. Hayler, P.D. Kane, D. LeGrand, F. Lugrin, K. Menear, R. Price, M. Allen, X. Cockcroft, J. Ambler, K. Butler and K. Durren, *Bioorg. Med. Chem. Lett.* 10:1567, 2000.

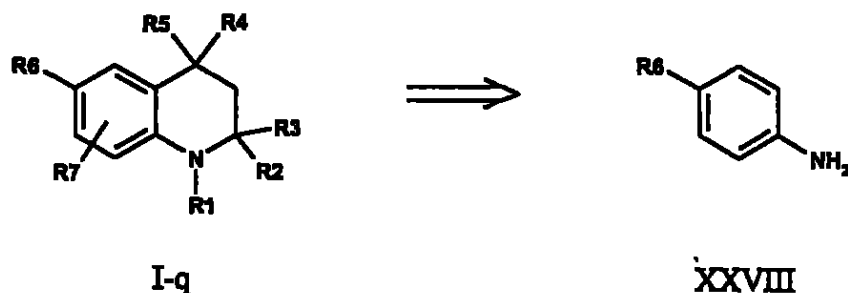
Alternatively, compounds of formula XXIV in which $X = C(O)$ can be used directly as starting materials for the preparation of derivatives of formula I-i-j, using coupling reagents as were mentioned previously.

For compounds represented by formula I-k-p, wherein $X = C(O)$ or $S(O)_2$ and $Y = NH$ or O and $n = 1-4$, art-known synthetic procedures can be followed.

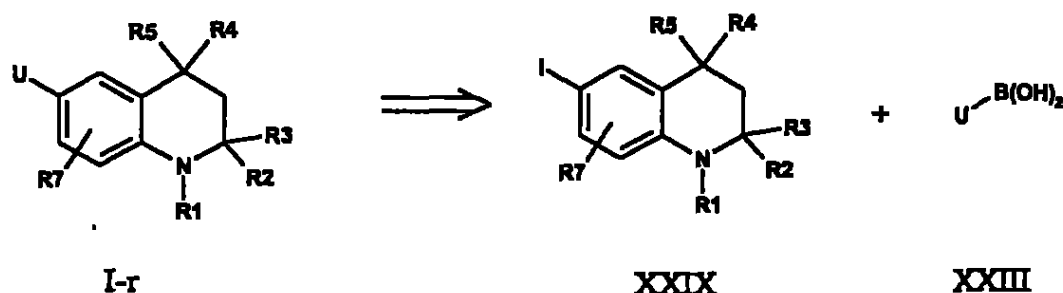


Thus, preparation of tetrahydroquinolines of formula I-k-l can be accomplished by condensing an amine or alcohol represented by formula XXVI ($Y = NH$ or O , respectively) with chlorides of general formula XXV using standard conditions. In a similar approach, amines or alcohols of formula XXVII can be utilized to prepare compounds of formula I-m-n. Finally, the use of the earlier mentioned boronic acids XXIII leads to the preparation of compounds of formula I-o-p *via* the earlier mentioned Suzuki coupling reaction.

- 10 Compounds of the present invention wherein X-Y is a bond, represented by formula I-q, can be prepared directly from commercially available or easily preparable anilines of formula XXVIII *via* the reaction sequence Skraup, acylation and Friedel-Crafts alkylation.



In another approach, compounds represented by formula I-r in which X-Y is a bond and U = (substituted) heteroaromatic or (substituted) phenyl, may be prepared *via* Suzuki condensation of the corresponding 6-iodo tetrahydroquinoline derivatives of formula XXIX with boronic acids of general formula XXIII, as was previously mentioned.



The requisite iodide of formula XXIX can be obtained from the corresponding amine by means of the well-known Sandmeyer reaction.

- Some of the compounds of the invention, which can be in the form of a free base, may be isolated from the reaction mixture in the form of a pharmaceutically acceptable salt. The pharmaceutically acceptable salts may also be obtained by treating the free base of formula I with an organic or inorganic acid such as hydrogen chloride, hydrogen bromide, hydrogen iodide, sulfuric acid, phosphoric acid, acetic acid, propionic acid, glycolic acid, maleic acid, malonic acid, methanesulphonic acid, fumaric acid, succinic acid, tartaric acid, citric acid, benzoic acid, and ascorbic acid.

The compounds of the present invention possess at least one chiral carbon atom and may therefore be obtained as pure enantiomers, or as a mixture of enantiomers, or as a mixture of diastereomers. Methods for obtaining the pure enantiomers are well known in the art, *e.g.* crystallization of salts which are obtained from optically active acids and the racemic mixture, or chromatography using chiral columns. For diastereomers, straight phase or reversed phase columns may be used.

The compounds of the invention may form hydrates or solvates. It is known to those of skill in the art that charged compounds form hydrated species when lyophilized with

water, or form solvated species when concentrated in a solution with an appropriate organic solvent. The compounds of this invention include the hydrates or solvates of the compounds listed.

- 5 For selecting active compounds testing at 10^{-5} M must result in an activity of more than 20% of the maximal activity when FSH is used as a reference. Another criterion might be the EC_{50} value which must be $< 10^{-5}$ M, preferably $< 10^{-7}$ M.

The skilled artisan will recognize that desirable EC_{50} values are dependent on the compound tested. For example, a compound with an EC_{50} which is less than 10^{-5} M is
10 generally considered a candidate for drug selection. Preferably this value is lower than 10^{-7} M. However, a compound which has a higher EC_{50} , but is selective for the particular receptor, may be even a better candidate.

Methods to determine receptor binding, as well as *in vitro* and *in vivo* assays to determine biological activity, of gonadotropins are well known. In general, expressed
15 receptor is contacted with the compound to be tested and binding or stimulation or inhibition of a functional response is measured.

To measure a functional response, isolated DNA encoding the FSH receptor gene, preferably the human receptor, is expressed in suitable host cells. Such a cell might be the Chinese Hamster Ovary cell, but other cells are also suitable. Preferably the cells
20 are of mammalian origin (Jia et al, Mol.Endocrin., 5:759-776, 1991).

Methods to construct recombinant FSH expressing cell lines are well known in the art (Sambrook et al., Molecular Cloning: a Laboratory Manual, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, latest edition). Expression of receptor is attained by expression of the DNA encoding the desired protein. Techniques for site directed
25 mutagenesis, ligation of additional sequences, PCR, and construction of suitable expression systems are all, by now, well known in the art. Portions, or all, of the DNA encoding the desired protein can be constructed synthetically using standard solid phase techniques, preferably to include restriction sites for ease of ligation. Suitable control elements for transcription and translation of the included coding sequence can
30 be provided to the DNA coding sequences. As is well known, expression systems are now available which are compatible with a wide variety of hosts, including prokaryotic

hosts such as bacteria and eukaryotic hosts such as yeast, plant cells, insect cells, mammalian cells, avian cells and the like.

Cells expressing the receptor are then contacted with the test compound to observe binding, or stimulation or inhibition of a functional response.

- 5 Alternatively, isolated cell membranes containing the expressed receptor may be used to measure binding of compound.

For measurement of binding, radioactively labeled or fluorescently labeled compounds may be used. As reference compound human recombinant FSH can be used. In the alternative also competition binding assays can be performed.

- 10 Another assay involves screening for FSH receptor agonist compounds by determining stimulation of receptor mediated cAMP accumulation. Thus, such a method involves expression of the receptor on the cell surface of a host cell and exposing the cell to the test compound. The amount of cAMP is then measured. The level of cAMP will be reduced or increased, depending on the inhibitory or stimulating effect of the test
15 compound upon binding to the receptor.

- In addition to direct measurement of e.g. cAMP levels in the exposed cell, cells lines can be used which in addition to transfection with receptor encoding DNA are also transfected with a second DNA encoding a reporter gene the expression of which responds to the level of cAMP. Such reporter genes might be cAMP inducible or might
20 be constructed in such a way that they are connected to novel cAMP responsive elements. In general, reporter gene expression might be controlled by any response element reacting to changing levels of cAMP. Suitable reporter genes are e.g. LacZ, alkaline phosphatase, firefly luciferase and green fluorescence protein. The principles of such transactivation assays are well known in the art and are described e.g. in
25 Stratowa, Ch., Himmler, A. and Czernilofsky, A.P., (1995) Curr.Opin.Biotechnol. 6:574.

- The present invention also relates to a pharmaceutical composition comprising a tetrahydroquinoline derivative or pharmaceutically acceptable salts thereof having the
30 general formula I in admixture with pharmaceutically acceptable auxiliaries and

optionally other therapeutic agents. The auxiliaries must be "acceptable" in the sense of being compatible with the other ingredients of the composition and not deleterious to the recipients thereof. The pharmaceutical compositions may also comprise the tetrahydroquinoline derivatives 1-acetyl-6-benzoylamino-4-(4-methylphenyl)-1,2,3,4-
5 tetrahydro-2,2,4-trimethylquinoline, 1-acetyl-4-phenyl-1,2,3,4-tetrahydro-2,2,4,6-tetramethylquinoline, 1-acetyl-4-phenyl-1,2,3,4-tetrahydro-2,2,4,6,8-pentamethylquinoline, 1-acetyl-6-methoxy-4-phenyl-1,2,3,4-tetrahydro-2,2,4-trimethylquinoline, 1-acetyl-6-trifluoroacetyl-amino-4-(4-methylphenyl)-1,2,3,4-tetrahydro-2,2,4-trimethylquinoline, 1-acetyl-6-trifluoroacetyl-amino-4-phenyl-1,2,3,4-
10 tetrahydro-2,2,4-trimethylquinoline, 1-acetyl-4-(4-chlorophenyl)-1,2,3,4-tetrahydro-2,2,4,6-tetramethylquinoline and 1-acetyl-4-(4-bromophenyl)-1,2,3,4-tetrahydro-2,2,4,6-tetramethylquinoline.

Compositions include e.g. those suitable for oral, sublingual, subcutaneous,
15 intravenous, intramuscular, local, or rectal administration, and the like, all in unit dosage forms for administration.

For oral administration, the active ingredient may be presented as discrete units, such as tablets, capsules, powders, granulates, solutions, suspensions, and the like.

For parenteral administration, the pharmaceutical composition of the invention may be
20 presented in unit-dose or multi-dose containers, e.g. injection liquids in predetermined amounts, for example in sealed vials and ampoules, and may also be stored in a freeze dried (lyophilized) condition requiring only the addition of sterile liquid carrier, e.g. water, prior to use.

Mixed with such pharmaceutically acceptable auxiliaries, e.g. as described in the
25 standard reference, Gennaro, A.R. et al., Remington: *The Science and Practice of Pharmacy* (20th Edition., Lippincott Williams & Wilkins, 2000, see especially Part 5: Pharmaceutical Manufacturing), the active agent may be compressed into solid dosage units, such as pills, tablets, or be processed into capsules or suppositories. By means of pharmaceutically acceptable liquids the active agent can be applied as a fluid
30 composition, e.g. as an injection preparation, in the form of a solution, suspension, emulsion, or as a spray, e.g. a nasal spray.

- For making solid dosage units, the use of conventional additives such as fillers, colorants, polymeric binders and the like is contemplated. In general any pharmaceutically acceptable additive which does not interfere with the function of the active compounds can be used. Suitable carriers with which the active agent of the invention can be administered as solid compositions include lactose, starch, cellulose derivatives and the like, or mixtures thereof, used in suitable amounts. For parenteral administration, aqueous suspensions, isotonic saline solutions and sterile injectable solutions may be used, containing pharmaceutically acceptable dispersing agents and/or wetting agents, such as propylene glycol or butylene glycol.
- 10 The invention further includes a pharmaceutical composition, as hereinbefore described, in combination with packaging material suitable for said composition, said packaging material including instructions for the use of the composition for the use as hereinbefore described.
- 15 The tetrahydroquinoline derivatives of the invention can also be administered in the form of implantable pharmaceutical devices, consisting of a core of active material, encased by a release rate-regulating membrane. Such implants are to be applied subcutaneously or locally, and will release the active ingredient at an approximately constant rate over relatively large periods of time, for instance from weeks to years.
- 20 Methods for the preparation of implantable pharmaceutical devices as such are known in the art, for example as described in European Patent 0,303,306 (AKZO Nobel N.V.).

The exact dose and regimen of administration of the active ingredient, or a pharmaceutical composition thereof, will necessarily be dependent upon the therapeutic effect to be achieved (treatment of infertility; contraception), and may vary with the particular compound, the route of administration, and the age and condition of the individual subject to whom the medicament is to be administered.

In general parenteral administration requires lower dosages than other methods of administration which are more dependent upon absorption. However, a dosage for humans preferably contains 0.0001-25 mg per kg body weight. The desired dose may be presented as one dose or as multiple subdoses administered at appropriate intervals

throughout the day, or, in case of female recipients, as doses to be administered at appropriate daily intervals throughout the menstrual cycle. The dosage as well as the regimen of administration may differ between a female and a male recipient.

5 Thus, the compounds according to the invention can be used in therapy.

A further aspect of the invention resides in the use of a tetrahydroquinoline derivative compound having the general formula I for the manufacture of a medicament to be used for the treatment of disorders responsive to FSH receptor mediated pathways, preferably for the control of fertility, more preferably for the treatment of infertility or
10 to prevent fertility. The compounds according to the invention can also be used for the treatment of hormone-dependent disorders such as breast cancer, prostate cancer and endometriosis.

The invention is illustrated by the following examples.

15 Examples

Example 1

1-Acetyl-6-(tert-butoxycarbonyl)amino-4-phenyl-1,2,3,4-tetrahydro-2,2,4-trimethylquinoline

(a). 6-(tert-Butoxycarbonyl)amino-1,2-dihydro-2,2,4-trimethylquinoline

20 A mixture of *N*-Boc-1,4-phenylenediamine (5.0 g) and iodine (1.3 g) in mesityl oxide (25 ml) was stirred at 100°C for 2 h. The reaction mixture was concentrated in vacuo and the residue was chromatographed on Al₂O₃ (Alumina B, act. III) in heptane/dichloromethane = 8/2 as eluent.

Yield: 2.9 g. MS-ESI: [M+H]⁺ = 289.2

25

(b). 1-Acetyl-6-(tert-butoxycarbonyl)amino-1,2-dihydro-2,2,4-trimethylquinoline

Acetyl chloride (11.1 ml) and acetic anhydride (11.1 ml) were added dropwise to a solution of 6-(tert-butoxycarbonyl)amino-1,2-dihydro-2,2,4-trimethylquinoline (8.5 g) in pyridine (22 ml) and dichloromethane (212 ml). After stirring for 18 h, the reaction

8

mixture was washed with 2 M HCl and water. The organic layer was dried (MgSO₄); filtered and concentrated in vacuo. The residue was chromatographed on silicagel in heptane/ethyl acetate = 8/2 (v/v) as eluent.

Yield: 6.7 g. MS-ESI: [M+H]⁺ = 331.2

5

(c). 1-Acetyl-6-amino-4-phenyl-1,2,3,4-tetrahydro-2,2,4-trimethylquinoline

A mixture of 1-acetyl-6-(*tert*-butoxycarbonyl)amino-2,2,4-trimethyl-1,2-dihydroquinoline (2.4 g) and AlCl₃ (9.5 g) in benzene (150 ml) was stirred at 70°C for 1 h. The reaction mixture was cooled (0°C) and quenched with water and in addition a
10 solution of 2 M NaOH was added. The organic layer was separated, dried over MgSO₄, filtered and concentrated in vacuo. The residue was chromatographed on silicagel in heptane/ethyl acetate = 8/2 (v/v) as eluent.

Yield: 1.6 g. MS-ESI: [M+H]⁺ = 309.2

15 (d). 1-Acetyl-6-(*tert*-butoxycarbonyl)amino-4-phenyl-1,2,3,4-tetrahydro-2,2,4-trimethylquinoline

A mixture of 1-acetyl-6-amino-4-phenyl-1,2,3,4-tetrahydro-2,2,4-trimethylquinoline (20 mg), (Boc)₂O (30 mg) and *N,N*-diisopropylethylamine (20 l) in tetrahydrofuran (4 ml) was stirred at 60°C for 18 h. The reaction mixture was concentrated in vacuo and
20 the residue was chromatographed on silicagel in dichloromethane/methanol = 1/0 => 95/5 (v/v) as eluent.

Yield: 8 mg. MS-ESI: [M+H]⁺ = 409.2

Example 2

6-Amino-1-butyryl-4-phenyl-1,2,3,4-tetrahydro-2,2,4-trimethylquinoline

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(a). 6-(*tert*-Butoxycarbonyl)amino-1-butyryl-1,2-dihydro-2,2,4-trimethylquinoline

Butyryl chloride (185 l) was added dropwise to a solution of 6-(*tert*-butoxycarbonyl)amino-1,2-dihydro-2,2,4-trimethylquinoline (50 mg) and a catalytic amount of *N,N*-dimethylaminopyridine in pyridine (4 ml). After stirring for 18 h, the
30 reaction mixture was concentrated in vacuo. The residue was dissolved in ethyl acetate and washed with water. The organic layer was separated, dried (MgSO₄) and

concentrated in vacuo. The residue was chromatographed on silicagel in heptane/ethyl acetate = 1/0 $\Rightarrow$ 7/3 (v/v) as eluent.

Yield: 47 mg. MS-ESI: $[M+H]^+ = 359.4$

5 (b). 6-Amino-1-butyryl-4-phenyl-1,2,3,4-tetrahydro-2,2,4-trimethylquinoline

A mixture of 1-butyryl-6-(*tert*-butoxycarbonyl)amino-1,2-dihydro-2,2,4-trimethylquinoline (47 mg) and $AlCl_3$ (52 mg) in benzene (2 ml) was stirred at 60°C for 6 h. The reaction mixture was cooled (0°C) and quenched with water and in addition a solution of 2 M NaOH was added. The organic layer was separated, dried
10 over $MgSO_4$ and concentrated in vacuo. The residue was purified by preparative HPLC.

Yield: 10 mg. MS-ESI: $[M+H]^+ = 337.2$; HPLC: $R_t = 6.97$ min. (method 1)

Example 3

1-Acetyl-6-amino-4-(4-chlorophenyl)-1,2,3,4-tetrahydro-2,2,4-trimethylquinoline

15 A mixture of 1-acetyl-6-(*tert*-butoxycarbonyl)amino-1,2-dihydro-2,2,4-trimethylquinoline (25 mg) and $AlCl_3$ (35 mg) in chlorobenzene (2 ml) was stirred for 1 h. The reaction mixture was quenched with water and in addition a solution of 2 M NaOH and ethyl acetate were added. The organic layer was separated, dried over $MgSO_4$ and concentrated in vacuo.

20 Yield: 20 mg. MS-ESI: $[M+H]^+ = 343.4$; HPLC: $R_t = 6.16$ min. (method 1)

Example 4

1-Acetyl-6-amino-4-(4-fluorophenyl)-1,2,3,4-tetrahydro-2,2,4-trimethylquinoline

Friedel-Crafts alkylation of fluorobenzene (2 ml) with 1-acetyl-6-(*tert*-butoxycarbonyl)amino-1,2-dihydro-2,2,4-trimethylquinoline (25 mg) in the presence of
25 $AlCl_3$ (35 mg) was performed according to the method described in example 3.

Yield: 15 mg. MS-ESI: $[M+H]^+ = 327.4$; HPLC: $R_t = 5.63$ min. (method 1)

Example 5**1-Acetyl-6-amino-1,2,3,4-tetrahydro-4-(4-toloyl)-2,2,4-trimethylquinoline**

Friedel-Crafts alkylation of toluene (2 ml) with 1-acetyl-6-(*tert*-butoxycarbonyl)amino-1,2-dihydro-2,2,4-trimethylquinoline (25 mg) in the presence of AlCl₃ (35 mg) was performed according to the method described in example 3.

Yield: 22 mg. MS-ESI: [M+H]⁺ = 323.2

Example 6**1-Acetyl-6-(4-chlorobenzoyl)amino-4-phenyl-1,2,3,4-tetrahydro-2,2,4-trimethylquinoline**

10 A mixture of 1-acetyl-6-amino-4-phenyl-1,2,3,4-tetrahydro-2,2,4-trimethylquinoline (10 mg), 4-chlorobenzoyl chloride (11 mg) and *N,N*-diisopropylethylamine (22 l) in tetrahydrofuran (1 ml) was stirred for 18 h. The reaction mixture was concentrated in vacuo, the residue was dissolved in ethyl acetate and washed with 0.5 HCl, water, 5% aq. NaHCO₃, water and brine. The organic layer was separated, dried (MgSO₄) and
15 concentrated in vacuo. The residue was chromatographed on silicagel in heptane/ethyl acetate = 1/0 => 0/1 (v/v) as eluent.

Yield: 9.5 mg. MS-ESI: [M+H]⁺ = 447.4; HPLC: R_t = 10.87 min. (method 1)

Example 7**1-Acetyl-6-benzoylamino-4-phenyl-1,2,3,4-tetrahydro-2,2,4-trimethylquinoline**

20 Acylation of 1-acetyl-6-amino-4-phenyl-1,2,3,4-tetrahydro-2,2,4-trimethylquinoline (10 mg) with benzoyl chloride (9.1 mg) and *N,N*-diisopropylethylamine (22 l) in tetrahydrofuran (1 ml) was performed according to the method described in example 6.

Yield: 1.2 mg. MS-ESI: [M+H]⁺ = 413.4; HPLC: R_t = 10.01 min. (method 1)

Example 8

25 **1-Acetyl-4-phenyl-1,2,3,4-tetrahydro-6-(4-[trifluoromethyl]benzoyl)amino-2,2,4-trimethylquinoline**

Acylation of 1-acetyl-6-amino-4-phenyl-1,2,3,4-tetrahydro-2,2,4-trimethylquinoline (10 mg) with 4-trifluoromethylbenzoyl chloride (14 mg) and *N,N*-diisopropylethylamine (22 l) in tetrahydrofuran (1 ml) was performed according to
30 the method described in example 6.

Yield: 8.9 mg. MS-ESI: $[M+H]^+ = 481.4$; HPLC: $R_t = 10.76$ min. (method 1)

Example 9

1-Acetyl-6-(4-nitrobenzoyl)amino-4-phenyl-1,2,3,4-tetrahydro-2,2,4-trimethylquinoline

- 5 Acylation of 1-acetyl-6-amino-4-phenyl-1,2,3,4-tetrahydro-2,2,4-trimethylquinoline (10 mg) with 4-nitrobenzoyl chloride (12 mg) and *N,N*-diisopropylethylamine (22 1) in tetrahydrofuran (1 ml) was performed according to the method described in example 6.

Yield: 8.2 mg. MS-ESI: $[M+H]^+ = 458.4$; HPLC: $R_t = 10.02$ min. (method 1)

10 Example 10

1-Acetyl-4-phenyl-6-(4-*n*-propylbenzoyl)amino-1,2,3,4-tetrahydro-2,2,4-trimethylquinoline

- Acylation of 1-acetyl-6-amino-4-phenyl-1,2,3,4-tetrahydro-2,2,4-trimethylquinoline (10 mg) with 4-*n*-propylbenzoyl chloride (12 mg) and *N,N*-diisopropylethylamine (22
15 1) in tetrahydrofuran (1 ml) was performed according to the method described in example 6.

Yield: 6.7 mg. MS-ESI: $[M+H]^+ = 455.4$; HPLC: $R_t = 11.19$ min. (method 1)

Example 11

- ##### 1-Acetyl-6-(3-bromo-2,6-dimethoxybenzoyl)amino-4-phenyl-1,2,3,4-tetrahydro-2,2,4- 20 trimethylquinoline

- A mixture of 1-acetyl-6-amino-4-phenyl-1,2,3,4-tetrahydro-2,2,4-trimethylquinoline (25 mg), 3-bromo-2,6-dimethoxybenzoic acid (23 mg), *O*-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (HATU) (68 mg) and *N,N*-diisopropylethylamine (32 1) in dichloromethane (4 ml) was stirred for 18 h. The
25 reaction mixture was concentrated in vacuo, the residue was dissolved in ethyl acetate and washed with 0.5 M HCl, water, 5% aq. NaHCO_3 , water and brine. The organic layer was dried (MgSO_4) and concentrated in vacuo. The residue was chromatographed on silicagel in heptane/ethyl acetate = 1/0 $\Rightarrow$ 0/1 (v/v) as eluent.

Yield: 28 mg. MS-ESI: $[M+H]^+ = 551.4$; HPLC: $R_t = 3.75$ min. (method 2)

Example 12**1-Acetyl-4-phenyl-6-(4-phenylbenzoyl)amino-1,2,3,4-tetrahydro-2,2,4-trimethylquinoline**

5 Acylation of 1-acetyl-6-amino-4-phenyl-1,2,3,4-tetrahydro-2,2,4-trimethylquinoline (11 mg) with 4-biphenylcarbonyl chloride (16 mg) and *N,N*-diisopropylethylamine (22 μ l) in tetrahydrofuran (1 ml) was performed according to the method described in example 6.

Yield: 1.0 mg. MS-ESI: $[M+H]^+ = 489.4$; HPLC: $R_t = 11.62$ min. (method 1)

Example 13

10 **1-Acetyl-6-(4-[4-chlorophenyl]benzoyl)amino-4-phenyl-1,2,3,4-tetrahydro-2,2,4-trimethylquinoline**

(a). **1-Acetyl-6-(4-iodobenzoyl)amino-4-phenyl-1,2,3,4-tetrahydro-2,2,4-trimethylquinoline**

15 A mixture of 1-acetyl-6-amino-4-phenyl-1,2,3,4-tetrahydro-2,2,4-trimethylquinoline (300 mg), 4-iodobenzoyl chloride (520 mg) and a catalytic amount of *N,N*-dimethylaminopyridine in pyridine (4 ml) was stirred for 18 h. The reaction mixture was concentrated in vacuo, the residue was dissolved in ethyl acetate and washed with saturated aq. NaHCO_3 , water and brine. The organic layer was dried (MgSO_4) and
20 concentrated in vacuo.

Yield: 460 mg. MS-ESI: $[M+H]^+ = 539.4$; HPLC: $R_t = 10.98$ min. (method 1)

(b). **1-Acetyl-6-(4-[4-chlorophenyl]benzoyl)amino-4-phenyl-1,2,3,4-tetrahydro-2,2,4-trimethylquinoline**

25 A mixture of 1-acetyl-6-(4-iodobenzoyl)amino-4-phenyl-1,2,3,4-tetrahydro-2,2,4-trimethylquinoline (25 mg), 4-chlorobenzeneboronic acid (22 mg), cesium fluoride (14 mg), triphenylphosphine (5.0 mg) and tris(dibenzylideneacetone)dipalladium(0) (4.3 mg) in dimethoxyethane/ethanol 4:1 (5 ml) was stirred for 15 min. as nitrogen was bubbled through the solution. After 3 h. at 80°C the reaction mixture was concentrated

in vacuo, the residue was dissolved in ethyl acetate and washed with 0.5 M HCl, water, 5% aq. NaHCO₃, water and brine. The organic layer was dried (MgSO₄) and concentrated in vacuo. The residue was chromatographed on silicagel in heptane/ethyl acetate = 1/0 => 0/1 (v/v) as eluent.

5 Yield: 16 mg. MS-ESI: [M+H]⁺ = 523.4; HPLC: R_t = 4.40 min. (method 2)

Example 14

1-Acetyl-4-phenyl-6-(4-[3-pyridyl]benzoyl)amino-1,2,3,4-tetrahydro-2,2,4-trimethylquinoline

10 Suzuki cross-coupling of 1-acetyl-6-(4-iodobenzoyl)amino-4-phenyl-1,2,3,4-tetrahydro-2,2,4-trimethylquinoline (25 mg), pyridine-3-boronic acid-1,3-propanediol cyclic ester (23 mg), cesium fluoride (14 mg), triphenylphosphine (5.0 mg) and tris(dibenzylideneacetone)dipalladium(0) (4.3 mg) in dimethoxyethane/ethanol 4:1 (v/v) (5 ml) was performed according to the method described in example 13.

Yield: 17 mg. MS-ESI: [M+H]⁺ = 490.4; HPLC: R_t = 7.11 min. (method 1)

15 Example 15

1-Acetyl-4-phenyl-6-(2-phenyl-5-methoxybenzoyl)amino-1,2,3,4-tetrahydro-2,2,4-trimethylquinoline

20 (a). 1-Acetyl-6-(2-bromo-5-methoxybenzoyl)amino-4-phenyl-1,2,3,4-tetrahydro-2,2,4-trimethylquinoline

Condensation of 1-acetyl-6-amino-4-phenyl-1,2,3,4-tetrahydro-2,2,4-trimethylquinoline (25 mg) with 2-bromo-5-methoxybenzoic acid (21 mg) under the agency of HATU (68 mg) and *N,N*-diisopropylethylamine (32 l) in dichloromethane (4 ml) was performed according to the method described in example 11.

25 Yield: 31 mg. MS-ESI: [M+H]⁺ = 521.4; HPLC: R_t = 3.74 min. (method 2)

(b). 1-Acetyl-4-phenyl-6-(2-phenyl-5-methoxybenzoyl)amino-1,2,3,4-tetrahydro-2,2,4-trimethylquinoline

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Suzuki cross-coupling of 1-acetyl-4-phenyl-6-(2-bromo-5-methoxybenzoyl)amino-1,2,3,4-tetrahydro-2,2,4-trimethylquinoline (30 mg), benzenboronic acid (25 mg), cesium fluoride (21 mg), triphenylphosphine (7.0 mg) and tris(dibenzylideneacetone)dipalladium(0) (6.0 mg) in dimethoxyethane/ethanol 4:1 (v/v) (5 ml) was performed according to the method described in example 13.

Yield: 23 mg. MS-ESI: $[M+H]^+ = 519.4$; HPLC: $R_t = 10.87$ min. (method 1)

Example 16

1-Acetyl-4-phenyl-6-(2-phenyl-3-methylbenzoyl)amino-1,2,3,4-tetrahydro-2,2,4-trimethylquinoline

10

(a). 1-Acetyl-4-phenyl-6-(2-bromo-3-methylbenzoyl)amino-1,2,3,4-tetrahydro-2,2,4-trimethylquinoline

Condensation of 1-acetyl-6-amino-4-phenyl-1,2,3,4-tetrahydro-2,2,4-trimethylquinoline (25 mg) with 2-bromo-3-methylbenzoic acid (19 mg) under the agency of HATU (68 mg) and *N,N*-diisopropylethylamine (32 l) in dichloromethane (4 ml) was performed according to the method described in example 11.

Yield: 16.3 mg. MS ESI: $[M+H]^+ = 505.2$; HPLC: $R_t = 3.80$ min. (method 2)

(b). 1-Acetyl-4-phenyl-6-(2-phenyl-3-methylbenzoyl)amino-1,2,3,4-tetrahydro-2,2,4-trimethylquinoline

20 Suzuki cross-coupling of 1-acetyl-4-phenyl-6-(2-bromo-3-methylbenzoyl)amino-1,2,3,4-tetrahydro-2,2,4-trimethylquinoline (16 mg), benzenboronic acid (25 mg), cesium fluoride (21 mg), triphenylphosphine (7.0 mg) and tris(dibenzylideneacetone)dipalladium(0) (6.0 mg) in dimethoxyethane/ethanol 4:1 (v/v) (5 ml) was performed according to the method described in example 13.

Yield: 4.9 mg. MS-ESI: $[M+H]^+ = 503.3$; HPLC: $R_t = 4.61$ min (method 2)

Example 17**1-Acetyl-4-phenyl-1,2,3,4-tetrahydro-6-(-toluenesulfonyl)amino-2,2,4-trimethylquinoline**

Sulfonylation of 1-acetyl-6-amino-4-phenyl-1,2,3,4-tetrahydro-2,2,4-trimethylquinoline (10 mg) with -toluenesulfonyl chloride (12 mg) and *N,N*-diisopropylethylamine (22 l) in tetrahydrofuran (25 ml) was performed according to the acylation method described in example 6.

Yield: 9.8 mg. MS-ESI: $[M+H]^+ = 463.4$; HPLC: $R_t = 9.49$ min. (method 1)

10 Example 18**1-Acetyl-4-phenyl-6-(phenylaminocarbonyl)amino-1,2,3,4-tetrahydro-2,2,4-trimethylquinoline**

A mixture of 1-acetyl-6-amino-4-phenyl-1,2,3,4-tetrahydro-2,2,4-trimethylquinoline (10 mg), phenyl isocyanate (8.0 mg) and *N,N*-diisopropylethylamine (22 l) in tetrahydrofuran (1 ml) was stirred for 18 h. The reaction mixture was concentrated in vacuo, the residue was dissolved in ethyl acetate and washed with 0.5 M HCl, water, 5% aq. NaHCO_3 , water and brine. The organic layer was dried (MgSO_4) and concentrated in vacuo. The residue was chromatographed on silicagel in heptane/ethyl acetate = 1/0 $\Rightarrow$ 0/1 (v/v) as eluent.

20 Yield: 3.8 mg. MS-ESI: $[M+H]^+ = 428.4$; HPLC: $R_t = 10.39$ min. (method 1)

Example 19**1-Acetyl-6-(tert-butylaminothiocarbonyl)amino-4-phenyl-1,2,3,4-tetrahydro-2,2,4-trimethylquinoline**

Thiourea formation of 1-acetyl-6-amino-4-phenyl-1,2,3,4-tetrahydro-2,2,4-trimethylquinoline (10 mg) with *tert*-butyl isothiocyanate (7.5 mg) and *N,N*-diisopropylethylamine (22 l) in tetrahydrofuran (1 ml) was performed according to the method described in example 18.

25 Yield: 0.50 mg. MS-ESI: $[M+H]^+ = 424.4$; HPLC: $R_t = 5.90$ min. (method 1)

Example 20**1-Acetyl-6-(4-*tert*-butylbenzyl)amino-4-phenyl-1,2,3,4-tetrahydro-2,2,4-trimethylquinoline.trifluoroacetic acid**

A mixture of 1-acetyl-6-amino-4-phenyl-1,2,3,4-tetrahydro-2,2,4-trimethylquinoline
5 (10 mg), 4-(*tert*-butyl)benzylchloride (6.5 mg) and *N,N*-diisopropylethylamine (10 l)
in tetrahydrofuran (1 ml) was stirred at 50°C for 18 h. The reaction mixture was
concentrated in vacuo, the residue was dissolved in ethyl acetate and washed with 0.5
HCl, water, 5% aq. NaHCO₃, water and brine. The organic layer was dried (MgSO₄)
and concentrated in vacuo. The residue was chromatographed on silicagel in
10 heptane/ethyl acetate = 1/0 => 0/1 (v/v) as eluent.

Yield: 3.1 mg. MS-ESI: [M+H]⁺ = 455.4; HPLC: R_t = 10.00 min. (method 1)

Example 21**1-Acetyl-4-phenyl-6-(3-phenylpropionyl)amino-1,2,3,4-tetrahydro-2,2,4-trimethylquinoline**

15 Acylation of 1-acetyl-6-amino-4-phenyl-1,2,3,4-tetrahydro-2,2,4-trimethylquinoline
(10 mg) with 3-phenylpropionyl chloride (11 mg) and *N,N*-diisopropylethylamine (22
l) in tetrahydrofuran (1 ml) was performed according to the method described in
example 6.

Yield: 1.2 mg. MS-ESI: [M+H]⁺ = 441.4; HPLC: R_t = 10.25 min. (method 1)

20 Example 22**1-Acetyl-6-(2-furoyl)amino-4-phenyl-1,2,3,4-tetrahydro-2,2,4-trimethylquinoline**

Acylation of 1-acetyl-6-amino-4-phenyl-1,2,3,4-tetrahydro-2,2,4-trimethylquinoline
(10 mg) with 2-furoyl chloride (8.5 mg) and *N,N*-diisopropylethylamine (22 l) in
tetrahydrofuran (1 ml) was performed according to the method described in example 6.

25 Yield: 7.7 mg. MS-ESI: [M+H]⁺ = 403.4; HPLC: R_t = 8.91 min. (method 1)

Example 23**1-Acetyl-6-(isovaleryl)amino-4-phenyl-1,2,3,4-tetrahydro-2,2,4-trimethylquinoline**

Acylation of 1-acetyl-6-amino-4-phenyl-1,2,3,4-tetrahydro-2,2,4-trimethylquinoline (10 mg) with isovaleryl chloride (7.8 mg) and *N,N*-diisopropylethylamine (22 l) in tetrahydrofuran (1 ml) was performed according to the method described in example 6.

Yield: 5.3 mg. MS-ESI: $[M+H]^+ = 393.4$; HPLC: $R_t = 9.35$ min. (method 1)

Example 24**1-Acetyl-6-(3-(adamantan-1-yl)propionyl)amino-4-phenyl-1,2,3,4-tetrahydro-2,2,4-trimethylquinoline**

Condensation of 1-acetyl-6-amino-4-phenyl-1,2,3,4-tetrahydro-2,2,4-trimethylquinoline (10 mg) with 3-(adamantan-1-yl)propionic acid (10 mg) under the agency of HATU (25 mg) and *N,N*-diisopropylethylamine (22 l) in dichloromethane (1 ml) was performed according to the method described in example 11.

Yield: 6.7 mg. MS-ESI: $[M+H]^+ = 499.4$; HPLC: $R_t = 12.43$ min. (method 1)

Example 25**1-Acetyl-6-(ethyl malonyl)amino-4-phenyl-1,2,3,4-tetrahydro-2,2,4-trimethylquinoline**

Acylation of 1-acetyl-6-amino-4-phenyl-1,2,3,4-tetrahydro-2,2,4-trimethylquinoline (150 mg) with ethyl malonyl chloride (147 mg) and *N,N*-diisopropylethylamine (314 l) in tetrahydrofuran (8 ml) was performed according to the method described in example 6.

Yield: 163 mg. MS-ESI: $[M+H]^+ = 423.2$; HPLC: $R_t = 8.48$ min. (method 1)

Example 26**1-Acetyl-6-([4-methoxybenzylamino]carbonylmethylcarbonyl)amino-4-phenyl-1,2,3,4-tetrahydro-2,2,4-trimethylquinoline**

25

(a). 1-Acetyl-6-(hydroxycarbonylmethylcarbonyl)amino-4-phenyl-1,2,3,4-tetrahydro-2,2,4-trimethylquinoline

A 2 M NaOH solution was added dropwise to a stirred solution of 1-acetyl-6-(ethyl malonyl)amino-4-phenyl-1,2,3,4-tetrahydro-2,2,4-trimethylquinoline (161 mg) in

dioxane/water 4:1 (v/v) (12 ml) until pH 14. After stirring for 3.5 h, the reaction mixture was poured into water and extracted with ethyl acetate at pH 2. The organic layer was washed with water and brine, dried (MgSO₄) and concentrated in vacuo.

Yield: 163 mg. MS-ESI: [M+H]⁺ = 395.2; HPLC: R_t = 7.43 min. (method 1)

5

(b). 1-Acetyl-6-([4-methoxybenzylamino]carbonylmethylcarbonyl)amino-4-phenyl-1,2,3,4-tetrahydro-2,2,4-trimethylquinoline

Condensation of 4-methoxybenzylamine (5.2 mg) with 1-acetyl-6-(hydroxycarbonylmethylcarbonyl)amino-4-phenyl-1,2,3,4-tetrahydro-2,2,4-trimethylquinoline (10 mg), under the agency of HATU (19 mg) and *N,N*-diisopropylethylamine (16 l) in tetrahydrofuran (2 ml) was performed according to the method described in example 11.

Yield: 7.3 mg. MS-ESI: [M+H]⁺ = 514.4; HPLC: R_t = 8.80 min. (method 1)

Example 27

15 1-Acetyl-6-([ethoxycarbonylmethylamino]carbonylmethylcarbonyl)amino-4-phenyl-1,2,3,4-tetrahydro-2,2,4-trimethylquinoline

Condensation of glycine ethyl ester.HCl (5.3 mg) with 1-acetyl-6-(hydroxycarbonylmethylcarbonyl)amino-4-phenyl-1,2,3,4-tetrahydro-2,2,4-trimethylquinoline (10 mg), under the agency of HATU (19 mg) and *N,N*-diisopropylethylamine (16 l) in tetrahydrofuran (2 ml) was performed according to the method described in example 11.

Yield: 4.6 mg. MS-ESI: [M+H]⁺ = 480.6; HPLC: R_t = 7.94 min. (method 1)

Example 28

25 1-Acetyl-6-([*N*-ethyl-*N*-benzylamino]carbonylmethylcarbonyl)amino-4-phenyl-1,2,3,4-tetrahydro-2,2,4-trimethylquinoline

Condensation of *N*-ethylbenzylamine (5.2 mg) with 1-acetyl-6-(hydroxycarbonylmethylcarbonyl)amino-4-phenyl-1,2,3,4-tetrahydro-2,2,4-trimethylquinoline (10 mg), under the agency of HATU (19 mg) and *N,N*-

- 38 -

diisopropylethylamine (16 l) in tetrahydrofuran (2 ml) was performed according to the method described in example 11.

Yield: 7.3 mg. MS-ESI: $[M+H]^+ = 512.6$; HPLC: $R_t = 9.36$ min. (method 1)

Example 29

5 1-Acetyl-6-([2,4-difluorobenzylamino]methylcarbonyl)amino-4-phenyl-1,2,3,4-tetrahydro-2,2,4-trimethylquinoline

(a). 1-Acetyl-6-(bromoacetyl)amino-4-phenyl-1,2,3,4-tetrahydro-2,2,4-trimethylquinoline

10 Acylation of 1-acetyl-6-amino-4-phenyl-1,2,3,4-tetrahydro-2,2,4-trimethylquinoline (130 mg) with bromoacetyl chloride (69 l) and *N,N*-diisopropylethylamine (121 l) in dichloromethane (10 ml) was performed according to the method described in example 6.

Yield: 151 mg. MS-ESI: $[M+H]^+ = 431.2$

15

(b). 1-Acetyl-6-([2,4-difluorobenzylamino]methylcarbonyl)amino-4-phenyl-1,2,3,4-tetrahydro-2,2,4-trimethylquinoline

A mixture of 1-acetyl-6-(bromoacetyl)amino-4-phenyl-1,2,3,4-tetrahydro-2,2,4-trimethylquinoline (10 mg), 2,4-difluorobenzylamine (6.0 mg) and *N,N*-
20 diisopropylethylamine (10 l) in dioxane (2 ml) was stirred at 40°C for 18 h. The reaction mixture was concentrated in vacuo. The residue was chromatographed on silicagel in dichloromethane/methanol = 1/0 => 95/5 (v/v) as eluent.

Yield: 5.5 mg. MS-ESI: $[M+H]^+ = 492.4$; HPLC: $R_t = 6.74$ min. (method 1)

Example 30

25 1-Acetyl-6-([4-{1-phenyl}-piperazinyl]methylcarbonyl)amino-4-phenyl-1,2,3,4-tetrahydro-2,2,4-trimethylquinoline

N-Alkylation of 1-phenylpiperazine (7.0 l) with 1-acetyl-6-(bromoacetyl)amino-4-phenyl-1,2,3,4-tetrahydro-2,2,4-trimethylquinoline (10 mg) and *N,N*-

diisopropylethylamine (10 l) in dioxane (2 ml) was performed according to the method described in example 29.

Yield: 8.4 mg. MS-ESI: $[M+H]^+ = 511.4$; HPLC: $R_t = 7.01$ min. (method 1)

Example 31

5 1-Acetyl-6-([N-morpholino]methylcarbonyl)amino-4-phenyl-1,2,3,4-tetrahydro-2,2,4-trimethylquinoline

N-Alkylation of morpholine (4.0 l) with 1 acetyl-6-(bromoacetyl)amino-4-phenyl-1,2,3,4-tetrahydro-2,2,4-trimethylquinoline (10 mg) and *N,N*-diisopropylethylamine (9.0 l) in dichloromethane (2 ml) was performed according to the method described in
10 example 29.

Yield: 10 mg. MS-ESI: $[M+H]^+ = 436.4$; HPLC: $R_t = 5.64$ min. (method 1)

Example 32

15 1-Acetyl-6-(2-thiophenemethylamino)carbonyl-4-phenyl-1,2,3,4-tetrahydro-2,2,4-trimethylquinoline

(a). 1,2-dihydro-2,2,4-trimethylquinoline-6-carboxylic acid methyl ester

Skraup reaction of methyl 4-aminobenzoate (5.0 g) and iodine (1.7 g) in mesityl oxide (25 ml) was performed according to the method described in example 1.

Yield: 2.3 g. MS-ESI: $[M+H]^+ = 232.2$

20

(b). 1-Acetyl-1,2-dihydro-2,2,4-trimethylquinoline-6-carboxylic acid methyl ester

A mixture of 1,2-dihydro-2,2,4-trimethylquinoline-6-carboxylic acid methyl ester (2.3 g) and a catalytic amount of *N,N*-dimethylaminopyridine in acetic anhydride (60 ml) was stirred at 100°C for 18 h. The reaction mixture was concentrated in vacuo, the
25 residue was dissolved in ethyl acetate and washed with water and brine. The organic layer was dried ($MgSO_4$) and concentrated in vacuo. The residue was chromatographed on silicagel in heptane/ethyl acetate = 1/1 $\Rightarrow$ 1/9 (v/v) as eluent.

Yield: 2.3 g.

(c). 1-Acetyl-4-phenyl-1,2,3,4-tetrahydro-2,2,4-trimethylquinoline-6-carboxylic acid methyl ester

Friedel-Crafts alkylation of benzene (60 ml) with 1-acetyl-1,2-dihydro-2,2,4-trimethylquinoline-6-carboxylic acid methyl ester (2.3 g) in the presence of AlCl_3 (4.4 g) was performed according to the method described in example 3.

Yield: 1.2 g. MS-ESI: $[\text{M}+\text{H}]^+ = 352.4$; HPLC: $R_t = 9.72$ min. (method 1)

(d). 1-Acetyl-4-phenyl-1,2,3,4-tetrahydro-2,2,4-trimethylquinoline-6-carboxylic acid

10 A 2 M NaOH solution was added dropwise to a stirred solution of 1-acetyl-4-phenyl-1,2,3,4-tetrahydro-2,2,4-trimethylquinoline-6-carboxylic acid methyl ester (1.2 g) in dioxane/water 4:1 (v/v) (50 ml) until pH 12. After stirring for 18 h, the reaction mixture was poured into water and extracted with ethyl acetate at pH 2. The organic layer was washed with water and brine, dried (MgSO_4) and concentrated in vacuo.

15 Yield: 891 mg. MS-ESI: $[\text{M}+\text{H}]^+ = 338.2$

(e). 1-Acetyl-6-(2-thiophenemethylamino)carbonyl-4-phenyl-1,2,3,4-tetrahydro-2,2,4-trimethylquinoline

20 Condensation of 2-thiophenemethylamine (5.0 mg) with 1-acetyl-4-phenyl-1,2,3,4-tetrahydro-2,2,4-trimethylquinoline-6-carboxylic acid (10 mg), under the agency of HATU (23 mg) and *N,N*-diisopropylethylamine (19 μl) in dichloromethane (2 ml) was performed according to the method described in example 11.

Yield: 3.0 mg. MS-ESI: $[\text{M}+\text{H}]^+ = 433.4$; HPLC: $R_t = 9.28$ min. (method 1)

Example 33

25 1-Acetyl-6-(2-[4-methoxyphenyl]ethylamino)carbonyl-4-phenyl-1,2,3,4-tetrahydro-2,2,4-trimethylquinoline

Condensation of 2-(4-methoxyphenyl)ethylamine (6.1 mg) with 1-acetyl-4-phenyl-1,2,3,4-tetrahydro-2,2,4-trimethylquinoline-6-carboxylic acid (10 mg), under the

agency of HATU (23 mg) and *N,N*-diisopropylethylamine (19 l)) in dichloromethane (2 ml) was performed according to the method described in example 11.

Yield: 9.9 mg. MS-ESI: $[M+H]^+ = 457.4$; HPLC: $R_t = 9.34$ min. (method 1)

Example 34

5 1-Acetyl-6-(3-isopropoxypropylamino)carbonyl-4-phenyl-1,2,3,4-tetrahydro-2,2,4-trimethylquinoline

Condensation of 3-isopropoxypropylamine (5.2 mg) with 1-acetyl-4-phenyl-1,2,3,4-tetrahydro-2,2,4-trimethylquinoline-6-carboxylic acid (10 mg), under the agency of HATU (23 mg) and *N,N*-diisopropylethylamine (19 l) in dichloromethane (2 ml) was
10 performed according to the method described in example 11.

Yield: 8.8 mg. MS-ESI: $[M+H]^+ = 437.4$; HPLC: $R_t = 8.80$ min. (method 1)

Example 35

1-Acetyl-6-(2-[methylthio]ethylamino)carbonyl-4-phenyl-1,2,3,4-tetrahydro-2,2,4-trimethylquinoline

15 Condensation of 2-(methylthio)ethylamine (4.1 mg) with 1-acetyl-4-phenyl-1,2,3,4-tetrahydro-2,2,4-trimethylquinoline-6-carboxylic acid (10 mg), under the agency of HATU (23 mg) and *N,N*-diisopropylethylamine (19 l) in dichloromethane (2 ml) was performed according to the method described in example 11.

Yield: 10 mg. MS-ESI: $[M+H]^+ = 411.4$; HPLC: $R_t = 3.33$ min. (method 2)

20 **Example 36**

1-Acetyl-6-(4-methoxybenzyloxy)carbonyl-4-phenyl-1,2,3,4-tetrahydro-2,2,4-trimethylquinoline

Condensation of 4-methoxybenzylalcohol (6.2 mg) with 1-acetyl-4-phenyl-1,2,3,4-tetrahydro-2,2,4-trimethylquinoline-6-carboxylic acid (10 mg), under the agency of
25 HATU (23 mg) and *N,N*-diisopropylethylamine (19 l) in dichloromethane (2 ml) was performed according to the method described in example 11.

Yield: 7.2 mg. MS-ESI: $[M+H]^+ = 458.4$; HPLC: $R_t = 3.90$ min. (method 2)

Example 37**1-Acetyl-6-(4-phenylbenzoyl)oxy-4-phenyl-1,2,3,4-tetrahydro-2,2,4-trimethylquinoline****(a). 1,2-Dihydro-6-methoxy-2,2,4-trimethylquinoline**

- 5 Skraup reaction of 4-anisidine (5.0 g) and iodine (1.7 g) in mesityl oxide (25 ml) was performed according to the method described in example 1.

Yield: 2.3 g. MS-ESI: $[M+H]^+ = 204.2$

(b). 1-Acetyl-1,2-dihydro-6-methoxy-2,2,4-trimethylquinoline

- 10 Acetyl chloride (8 ml) was added dropwise to a cooled (0°C) solution of 1,2-dihydro-6-methoxy-2,2,4-trimethylquinoline (1.7 g) and a catalytic amount of *N,N*-dimethylaminopyridine in pyridine (60 ml). After stirring for 18 h, the reaction mixture was concentrated in vacuo. The residue was dissolved in dichloromethane and washed with 1 M HCl, water, 5% aq. NaHCO₃, water and brine. The organic layer was dried
15 (MgSO₄) and concentrated in vacuo. The residue was chromatographed on silicagel in dichloromethane as eluent.

Yield: 1.8 g. MS-ESI: $[M+H]^+ = 246.2$

(c). 1-Acetyl-6-methoxy-4-phenyl-1,2,3,4-tetrahydro-2,2,4-trimethylquinoline

- 20 Fiedel-Crafts alkylation of benzene (25 ml) with 1-acetyl-1,2-dihydro-6-methoxy-2,2,4-trimethylquinoline (1.8 g) in the presence of AlCl₃ (3.0 g) was performed according to the method described in example 3.

Yield: 1.9 g. HPLC: R_t = 9.62 min. (method 1)

- 25 (d). **1-Acetyl-6-hydroxy-4-phenyl-1,2,3,4-tetrahydro-2,2,4-trimethylquinoline**

Boron tribromide (1.30 ml) was added dropwise to a cooled (0°C) solution of 1-acetyl-6-methoxy-4-phenyl-1,2,3,4-tetrahydro-2,2,4-trimethylquinoline (0.9 g) in dichloromethane (75 ml). After stirring for 18 h, the reaction mixture was poured into

water and extracted with ethyl acetate. The organic layer was washed with water, 5% aq. NaHCO₃ and water, dried (MgSO₄) and concentrated in vacuo.

Yield: 950 mg. MS-ESI: [M+H]⁺ = 310.2; HPLC: R_t = 8.41 min. (method 1)

5 (e). 1-Acetyl-4-phenyl-6-(4-phenylbenzoyl)oxy-1,2,3,4-tetrahydro-2,2,4-trimethylquinoline

Acylation of 1-acetyl-6-hydroxy-4-phenyl-1,2,3,4-tetrahydro-2,2,4-trimethylquinoline (10 mg) with 4-biphenylcarbonyl chloride (14 mg) and *N,N*-diisopropylethylamine (28
10 1) in tetrahydrofuran (1 ml) was performed according to the method described in example 6.

Yield: 8.2 mg. MS-ESI: [M+H]⁺ = 490.4; HPLC: R_t = 12.81 min. (method 1)

Example 38

1-Acetyl-6-(*tert*-butylacetyl)oxy-4-phenyl-1,2,3,4-tetrahydro-2,2,4-trimethylquinoline

Acylation of 1-acetyl-6-hydroxy-4-phenyl-1,2,3,4-tetrahydro-2,2,4-trimethylquinoline
15 (10 mg) with *tert*-butylacetyl chloride (9.0 1) and *N,N*-diisopropylethylamine (28 1) in tetrahydrofuran (1 ml) was performed according to the method described in example 6.

Yield: 3.9 mg. MS-ESI: [M+H]⁺ = 408.4; HPLC: R_t = 11.28 min. (method 1)

Example 39

20 1-Acetyl-6-(cyclopropylmethyl)oxy-4-phenyl-1,2,3,4-tetrahydro-2,2,4-trimethylquinoline

A mixture of 1-acetyl-6-hydroxy-4-phenyl-1,2,3,4-tetrahydro-2,2,4-trimethylquinoline (20 mg), cesium carbonate (63 mg), tetrabutylammonium bromide (29 mg) and chloromethylcyclopropane (8.4 1) in acetonitrile (1 ml) was stirred at 50°C for 18 h.
25 The reaction mixture was concentrated in vacuo and the residue was chromatographed on silicagel in heptane/ethyl acetate = 1/0 => 6/4 (v/v) as eluent.

Yield: 10 mg. MS-ESI: [M+H]⁺ = 364.2; HPLC: R_t = 10.73 min. (method 1)

Example 40**1-Acetyl-6-(3-pyridylmethyl)oxy-4-phenyl-1,2,3,4-tetrahydro-2,2,4-trimethylquinoline**

Alkylation of 1-acetyl-6-hydroxy-4-phenyl-1,2,3,4-tetrahydro-2,2,4-trimethylquinoline (20 mg) with 3-picolylchloride.HCl (12 mg), cesium carbonate (63 mg) and
5 tetrabutylammonium bromide (30 mg) acetonitrile (1 ml) was performed according to the method described in example 39.

Yield: 10 mg; MS-ESI: $[M+H]^+ = 401.2$; HPLC: $R_t = 8.40$ min. (method 1)

Example 41**1-Acetyl-6-ethyl-4-phenyl-1,2,3,4-tetrahydro-2,2,4-trimethylquinoline**

10

(a). 1,2-Dihydro-6-ethyl-2,2,4-trimethylquinoline

Skraup reaction of p-ethylaniline (1.0 g) and iodine (0.34 g) in mesityl oxide (5 ml) was performed according to the method described in example 1.

Yield: 800 mg. MS-ESI: $[M+H]^+ = 202.2$

15

(b). 1-Acetyl-6-ethyl-1,2,3,4-tetrahydro-2,2,4-trimethylquinoline

Acylation of 1,2-dihydro-6-ethyl-2,2,4-trimethylquinoline (800 mg) with acetyl chloride (3.5 ml) and a catalytic amount of N,N-dimethylaminopyridine in pyridine (25 ml) was performed according to the method described in example 37.

20 Yield: 410 mg. MS-ESI: $[M+H]^+ = 244.2$

(c). 1-Acetyl-6-ethyl-4-phenyl-1,2,3,4-tetrahydro-2,2,4-trimethylquinoline

Friedel-Crafts alkylation of benzene (10 ml) with 1-acetyl-6-ethyl-1,2,3,4-tetrahydro-2,2,4-trimethylquinoline (410 mg) in the presence of $AlCl_3$ (710 mg) was performed
25 according to the method described in example 3.

Yield: 407 mg. MS-ESI: $[M+H]^+ = 322.4$

Example 42**1-Acetyl-6-(1,1'-biphenyl)-4-phenyl-1,2,3,4-tetrahydro-2,2,4-trimethylquinoline****(a). 1-Acetyl-6-iodo-4-phenyl-1,2,3,4-tetrahydro-2,2,4-trimethylquinoline**

- 5 A sodium nitrite solution (31 mg) was added dropwise to a cooled (0°C) solution of 1-acetyl-6-amino-4-phenyl-1,2,3,4-tetrahydro-2,2,4-trimethylquinoline (128 mg) and sulfuric acid (82 mg) in water (2 ml). After stirring at 0°C for 15 min, a potassium iodide solution (105 mg) was added. After stirring for 18h, the reaction mixture was poured into dichloromethane. The organic layer was separated and washed with 5% aq.
- 10 sodium thiosulfate and water, dried (MgSO₄) and concentrated in vacuo.

Yield: 160 mg. MS-ESI: [M+H]⁺ = 420.0

(b). 1-Acetyl-6-(1,1'-biphenyl-yl)-4-phenyl-1,2,3,4-tetrahydro-2,2,4-trimethylquinoline

- Suzuki cross-coupling of 1-acetyl-6-iodo-4-phenyl-1,2,3,4-tetrahydro-2,2,4-trimethylquinoline (20 mg), (1,1'-biphenyl-4-yl)boronic acid (28 mg), cesium fluoride (15 mg), triphenylphosphine (5 mg) and tris(dibenzylideneacetone)dipalladium(0) (4.5 mg) in dimethoxyethane/ethanol 4:1 (v/v) (5 ml) was performed according to the method described in example 13.
- 15

Yield: 16 mg. MS-ESI: [M+H]⁺ = 446.4; HPLC: R_t = 6.84 min. (method 2)

20 Example 43**1-Acetyl-6-(4-chlorophenyl)-4-phenyl-1,2,3,4-tetrahydro-2,2,4-trimethylquinoline**

- Suzuki cross-coupling of 1-acetyl-6-iodo-4-phenyl-1,2,3,4-tetrahydro-2,2,4-trimethylquinoline (20 mg), 4-chlorophenylboronic acid (22 mg), cesium fluoride (15 mg), triphenylphosphine (5 mg) and tris(dibenzylideneacetone)dipalladium(0) (4.5 mg) in dimethoxyethane/ethanol 4:1 (v/v) (5 ml) was performed according to the method described in example 13.
- 25

Yield: 8.6 mg. MS-ESI: [M+H]⁺ = 404.4; HPLC: R_t = 5.94 min. (method 2)

Example 44**1-Acetyl-6-amino-4-phenyl-1,2,3,4-tetrahydro-2,2,4,7-tetramethylquinoline****(a). 1-Acetyl-6-amino-1,2-dihydro-2,2,4,7-tetramethylquinoline**

- 5 A mixture of *N*-Boc-2-methyl-1,4-phenylenediamine (2.3 g), magnesium sulfate (6.3 g), 4-*tert*-butylcatechol (100 mg) and iodine (300 mg) in acetone (15 ml) was stirred at reflux for 20 h. The reaction mixture was cooled to r.t. and filtered. The filtrate was concentrated in vacuo and the residue was chromatographed on SiO₂ with heptane/ethyl acetate = 1/0 => 3/1 (v/v) as eluent. The product, 6-(*tert*-
10 butoxycarbonyl)amino-1,2-dihydro-2,2,4,7-tetramethylquinoline, was acylated with acetyl chloride (1.0 ml) in a mixture of pyridine (1.0 ml) and toluene (10 ml). After stirring for 1 h, the reaction mixture was washed with 3% aq. citric acid and water. The organic layer was dried (MgSO₄) and concentrated in vacuo. The residue was chromatographed on silicagel in heptane/ethyl acetate = 1/0 => 3/1 (v/v) as eluent.
- 15 Yield: 350 mg. MS-ESI: [M+H]⁺ = 345.4

(b). 1-Acetyl-6-amino-4-phenyl-1,2,3,4-tetrahydro-2,2,4,7-tetramethylquinoline

- AlCl₃ (266 mg) was added to a heated (70°C) solution of 1-acetyl-6-amino-1,2-dihydro-2,2,4,7-tetramethylquinoline (100 mg) in benzene (10 ml). After 3 h, the mixture was
20 cooled and concentrated in vacuo. The residue was dissolved in ethyl acetate and washed with water. The organic layer was separated, dried (MgSO₄) and concentrated in vacuo. The residue was chromatographed on silicagel in heptane/ethyl acetate = 1/0 => 3/1 (v/v) as eluent.

Yield: 75 mg. MS-ESI: [M+H]⁺ = 323.4

25 Example 45**1-Acetyl-6-(4-phenylbenzoyl)amino-4-phenyl-1,2,3,4-tetrahydro-2,2,4,7-tetramethylquinoline**

Acylation of 1-acetyl-6-amino-4-phenyl-1,2,3,4-tetrahydro-2,2,4,7-tetramethylquinoline (20 mg) with 4-biphenylcarbonyl chloride (100 mg) and pyridine

(100 1) in tetrahydrofuran (5 ml) was performed according to the method described in example 6.

Yield: 24 mg. MS-ESI: $[M+H]^+ = 503.4$

Example 46

5 1-Acetyl-6-(4-phenylbenzoyl)amino-8-methoxy-4-phenyl-1,2,3,4-tetrahydro-2,2,4-trimethylquinoline

(a). 1-Acetyl-6-amino-8-methoxy-4-phenyl-1,2,3,4-tetrahydro-2,2,4-trimethylquinoline

Skraup reaction of *N*-Boc-3-methoxy-1,4-phenylenediamine (450 mg), magnesium sulfate (1.0 g), 4-*tert*-butylcatachol (10 mg) and iodine (20 mg) in acetone (10 ml),
10 acylation of the product with acetyl chloride (250 1) and pyridine (250 1) in toluene (10 ml) and subsequent Friedel-Crafts alkylation with $AlCl_3$ (266 mg) were performed according to the methods described in example 44.

Yield: 71 mg. MS-ESI: $[M+H]^+ = 339.4$

15

(b). 1-Acetyl-6-(4-phenylbenzoyl)amino-8-methoxy-4-phenyl-1,2,3,4-tetrahydro-2,2,4-trimethylquinoline

Acylation of 1-acetyl-6-amino-8-methoxy-4-phenyl-1,2,3,4-tetrahydro-2,2,4-trimethylquinoline (20 mg) with 4-biphenylcarbonyl chloride (100 mg) and pyridine
20 (100 1) in tetrahydrofuran (5 ml) was performed according to the method described in example 6.

Yield: 25 mg. MS-ESI: $[M+H]^+ = 519.4$

Example 47

1-Acetyl-6-(2-furoyl)amino-1,2,3,4-tetrahydro-4-toloyl-2,2,4-trimethylquinoline

25 Acylation of 1-acetyl-6-amino-4-toloyl-1,2,3,4-tetrahydro-2,2,4-trimethylquinoline (10 mg) with 2-furoyl chloride (8.1 mg) and *N,N*-diisopropylethylamine (20 1) in tetrahydrofuran (1 ml) was performed according to the method described in example 6.

Yield: 12 mg. MS-ESI: $[M+H]^+ = 417.4$; HPLC: $R_t = 4.90$ min. (method 2)

Example 48**1-Acetyl-6-(4-phenylbenzoyl)amino-1,2,3,4-tetrahydro-4-toloyl-2,2,4-trimethylquinoline**

Acylation of 1-acetyl-6-amino-4-toloyl-1,2,3,4-tetrahydro-2,2,4-trimethylquinoline (10 mg) with 4-biphenylcarbonyl chloride (14 mg) and *N,N*-diisopropylethylamine (20 1) in tetrahydrofuran (1 ml) was performed according to the method described in example 6.

Yield: 9.3 mg. MS-ESI: $[M+H]^+ = 503.4$; HPLC: $R_t = 6.08$ min. (method 2)

Example 49**1-Acetyl-6-(ethyl malonyl)amino-1,2,3,4-tetrahydro-4-toloyl-2,2,4-trimethylquinoline**

10 Acylation of 1-acetyl-6-amino-4-toloyl-1,2,3,4-tetrahydro-2,2,4-trimethylquinoline (10 mg) with ethyl malonyl chloride (9.4 mg) and *N,N*-diisopropylethylamine (20 1) in tetrahydrofuran (1 ml) was performed according to the method described in example 6.

Yield: 12 mg. MS-ESI: $[M+H]^+ = 437.4$; HPLC: $R_t = 4.71$ min. (method 2)

Example 50

15 **1-Acetyl-6-(3,5-dibromobenzoyl)amino-4-phenyl-1,2,3,4-tetrahydro-2,2,4-trimethylquinoline**

HATU condensation of 1-acetyl-6-amino-4-phenyl-1,2,3,4-tetrahydro-2,2,4-trimethylquinoline (10 mg) with 3,5-dibromobenzoic acid (10 mg) and *N,N*-diisopropylethylamine (22 1) in tetrahydrofuran (1 ml) was performed according to the method described in example 11.

Yield: 15.9 mg. MS-ESI: $[M+H]^+ = 470.9$; HPLC: $R_t = 10.11$ min. (method 1)

Example 51**1-Acetyl-6-(5-bromo-2-methylaminobenzoyl)amino-4-phenyl-1,2,3,4-tetrahydro-2,2,4-trimethylquinoline**

25 HATU condensation of 1-acetyl-6-amino-4-phenyl-1,2,3,4-tetrahydro-2,2,4-trimethylquinoline (10 mg) with 5-bromo-2-methylaminobenzoic acid (8.4 mg) and *N,N*-diisopropylethylamine (22 1) in tetrahydrofuran (1 ml) was performed according to the method described in example 11.

Yield: 13.2 mg. MS-ESI: $[M+H]^+ = 522.1$; HPLC: $R_t = 8.95$ min. (method 1)

Example 52**1-Acetyl-6-(3,4,5-trimethoxybenzoyl)amino-4-phenyl-1,2,3,4-tetrahydro-2,2,4-trimethylquinoline**

Acylation of 1-acetyl-6-amino-4-phenyl-1,2,3,4-tetrahydro-2,2,4-trimethylquinoline
5 (10 mg) with 3,4,5-trimethoxybenzoyl chloride (12 mg) and *N,N*-diisopropylethylamine (22 l) in tetrahydrofuran (1 ml) was performed according to the method described in example 6.

Yield: 14.5 mg. MS-ESI: $[M+H]^+ = 503.2$; HPLC: $R_t = 11.26$ min. (method 1)

Example 53**1-Acetyl-6-(3,5-dichloro-2,6-dimethoxybenzoyl)amino-4-phenyl-1,2,3,4-tetrahydro-2,2,4-trimethylquinoline**

HATU condensation of 1-acetyl-6-amino-4-phenyl-1,2,3,4-tetrahydro-2,2,4-trimethylquinoline (10 mg) with 3,5-dichloro-2,6-dimethoxybenzoic acid (9.0 mg) and
15 *N,N*-diisopropylethylamine (22 l) in tetrahydrofuran (1 ml) was performed according to the method described in example 11.

Yield: 15.1 mg. MS-ESI: $[M+H]^+ = 541.1$; HPLC: $R_t = 10.92$ min. (method 1)

Example 54**1-Acetyl-6-(2-acetyloxybenzoyl)amino-4-phenyl-1,2,3,4-tetrahydro-2,2,4-trimethylquinoline**

20 HATU condensation of 1-acetyl-6-amino-4-phenyl-1,2,3,4-tetrahydro-2,2,4-trimethylquinoline (10 mg) with 2-acetyloxybenzoic acid (6.0 mg) and *N,N*-diisopropylethylamine (22 l) in tetrahydrofuran (1 ml) was performed according to the method described in example 11.

Yield: 1.1 mg. MS-ESI: $[M+H]^+ = 471.2$; HPLC: $R_t = 14.35$ min. (method 1)

25 Example 55**1-Acetyl-6-(2-acetamido-5-bromobenzoyl)amino-4-phenyl-1,2,3,4-tetrahydro-2,2,4-trimethylquinoline**

HATU condensation of 1-acetyl-6-amino-4-phenyl-1,2,3,4-tetrahydro-2,2,4-trimethylquinoline (10 mg) with 2-acetamido-5-bromobenzoic acid (6.0 mg) and
30 *N,N*-diisopropylethylamine (22 l) in tetrahydrofuran (1 ml) was performed according to the method described in example 11.

Yield: 2.3 mg. MS-ESI: $[M+H]^+ = 530.2$; HPLC: $R_t = 12.01$ min. (method 1)

Example 56

1-Acetyl-6-(5-bromo-2-*N,N*-dimethylcarbamoylbenzoyl)amino-4-phenyl-1,2,3,4-tetrahydro-2,2,4-trimethylquinoline

- 5 HATU condensation of 1-acetyl-6-amino-4-phenyl-1,2,3,4-tetrahydro-2,2,4-trimethylquinoline (10 mg) with 5-bromosalicylic acid (8.0 mg) and *N,N*-diisopropylethylamine (22 l) in tetrahydrofuran (1 ml) was performed according to the method described in example 11.

Yield: 3.0 mg. MS-ESI: $[M+H]^+ = 580.2$; HPLC: $R_t = 12.53$ min. (method 1)

10 **Example 57**

1-Acetyl-6-(2-[4-toloyloxy]benzoyl)amino-4-phenyl-1,2,3,4-tetrahydro-2,2,4-trimethylquinoline

- HATU condensation of 1-acetyl-6-amino-4-phenyl-1,2,3,4-tetrahydro-2,2,4-trimethylquinoline (10 mg) with 2-[4-toloyloxy]benzoic acid (8.0 mg) and *N,N*-diisopropylethylamine (22 l) in tetrahydrofuran (1 ml) was performed according to the method described in example 11.

Yield: 8.0 mg. MS-ESI: $[M+H]^+ = 519.4$; HPLC: $R_t = 13.11$ min. (method 1)

Example 58

- 1-Acetyl-6-(2-methylsulfonyloxybenzoyl)amino-4-phenyl-1,2,3,4-tetrahydro-2,2,4-trimethylquinoline

- (a). 1-Acetyl-6-(2-methoxybenzoyl)amino-4-phenyl-1,2,3,4-tetrahydro-2,2,4-trimethylquinoline

- Acylation of 1-acetyl-6-amino-4-phenyl-1,2,3,4-tetrahydro-2,2,4-trimethylquinoline (0.60 g) with 2-methoxybenzoyl chloride (1.0 g) and *N,N*-diisopropylethylamine (1.7 ml) in tetrahydrofuran (60 ml) was performed according to the method described in example 6.

Yield: 0.65 g. MS-ESI: $[M+H]^+ = 443.4$

(b). 1-Acetyl-6-(2-hydroxybenzoyl)amino-4-phenyl-1,2,3,4-tetrahydro-2,2,4-trimethylquinoline

BBr₃ (0.69 ml) was added dropwise to a solution of 1-acetyl-6-(2-methoxybenzoyl)amino-4-phenyl-1,2,3,4-tetrahydro-2,2,4-trimethylquinoline (0.64 g) in dichloromethane (40 mL). After stirring for 4 h, TLC indicated complete conversion. Water was added to the reaction mixture and stirring was continued for 15 min. The mixture was washed with 5% aq. NaHCO₃ and water. The organic layer was dried (MgSO₄) and concentrated in vacuo. The resulting product was used without further purification.

Yield: 0.62 g. MS-ESI: [M+H]⁺ = 429.4

(c). 1-Acetyl-6-(2-methylsulfonyloxybenzoyl)amino-4-phenyl-1,2,3,4-tetrahydro-2,2,4-trimethylquinoline

Sulfonylation of 1-acetyl-6-(2-hydroxybenzoyl)amino-4-phenyl-1,2,3,4-tetrahydro-2,2,4-trimethylquinoline (12 mg) with methylsulfonyl chloride (6.5 µl) was performed in pyridine (1 ml). TLC analysis after stirring for 16 h showed conversion to a higher-running product. The mixture was concentrated, the residue was dissolved in dichloromethane and washed with water. The organic layer was dried (Na₂SO₄) and concentrated in vacuo. The crude product was purified by silica gel column chromatography. Eluent: heptane/ethyl acetate = 8/2 (v/v).

Yield: 8.0 mg. MS-ESI: [M+H]⁺ = 507.4; HPLC: R_t = 5.03 min. (method 2)

Example 59

1-Acetyl-6-(2-[3,5-dimethylisoxazole-4-sulfonyl]oxybenzoyl)amino-4-phenyl-1,2,3,4-tetrahydro-2,2,4-trimethylquinoline

Sulfonylation of 1-acetyl-6-(2-hydroxybenzoyl)amino-4-phenyl-1,2,3,4-tetrahydro-2,2,4-trimethylquinoline (20 mg) with 3,5-dimethylisoxazole-4-sulfonyl chloride (27 mg) in pyridine (2 ml) was performed according to the method described in example 58.

Yield: 14 mg. MS-ESI: [M+H]⁺ = 588.4; HPLC: R_t = 14.46 min. (method 1)

Example 60**1-Acetyl-6-(2-methoxycarbonyl-ethyl-carbonyloxybenzoyl)-amino-4-phenyl-1,2,3,4-tetrahydro-2,2,4-trimethylquinoline**

5 Acylation of 1-acetyl-6-(2-hydroxybenzoyl)-amino-4-phenyl-1,2,3,4-tetrahydro-2,2,4-trimethylquinoline (20 mg) with 3-carbomethoxypropionyl chloride (14 mg) and *N,N*-diisopropylethylamine (40 μ l) in tetrahydrofuran (2 ml) was performed according to the method described in example 6.

Yield: 21.4 mg. MS-ESI: $[M+H]^+ = 543.6$; HPLC: $R_t = 6.98$ min. (method 1)

Example 61

10 **1-Acetyl-6-(2-[5-methylisoxazole-3-carbonyl]oxybenzoyl)-amino-4-phenyl-1,2,3,4-tetrahydro-2,2,4-trimethylquinoline**

Acylation of 1-acetyl-6-(2-hydroxybenzoyl)-amino-4-phenyl-1,2,3,4-tetrahydro-2,2,4-trimethylquinoline (15 mg) with 5-methylisoxazole-3-carbonyl chloride (10 mg) and *N,N*-diisopropylethylamine (30 μ l) in tetrahydrofuran (1 ml) was performed according to the method described in example 6.

15 Yield: 4.0 mg. MS-ESI: $[M+H]^+ = 538.4$; HPLC: $R_t = 9.84$ min. (method 1)

Example 62**1-Acetyl-6-(2-[2-oxazolidinone-5-methyl]oxybenzoyl)-amino-4-phenyl-1,2,3,4-tetrahydro-2,2,4-trimethylquinoline**

20 Alkylation of 1-acetyl-6-(2-hydroxybenzoyl)-amino-4-phenyl-1,2,3,4-tetrahydro-2,2,4-trimethylquinoline (20 mg) with 5-chloromethyl-2-oxazolidinone (7 mg), cesium carbonate (63 mg) and tetrabutylammonium bromide (30 mg) in acetonitrile (1 ml) was performed according to the method described in example 39.

Yield: 25 mg. MS-ESI: $[M+H]^+ = 542.4$; HPLC: $R_t = 8.21$ min. (method 1)

25 **Example 63**

1-Acetyl-6-(2-[morpholino-4-carbonyl]oxybenzoyl)-amino-4-phenyl-1,2,3,4-tetrahydro-2,2,4-trimethylquinoline

Acylation of 1-acetyl-6-(2-hydroxybenzoyl)-amino-4-phenyl-1,2,3,4-tetrahydro-2,2,4-trimethylquinoline (15 mg) with morpholino-4-carbonyl chloride (12 μ l) and *N,N*-diisopropylethylamine (30 μ l) in tetrahydrofuran (1 ml) was performed according to the method described in example 6.

30

Yield: 5.4 mg. MS-ESI: $[M+H]^+ = 542.4$; HPLC: $R_t = 10.02$ min. (method 1)

Example 64

1-Acetyl-6-(2-phenylaminobenzoyl)amino-4-phenyl-1,2,3,4-tetrahydro-2,2,4-trimethylquinoline

- 5 HATU condensation of 1-acetyl-6-amino-4-phenyl-1,2,3,4-tetrahydro-2,2,4-trimethylquinoline (15 mg) with *N*-phenylanthranilic acid (21 mg) and *N,N*-diisopropylethylamine (33 μ l) in tetrahydrofuran (1 ml) was performed according to the method described in example 11.

Yield: 5.8 mg. MS-ESI: $[M+H]^+ = 504.4$; HPLC: $R_t = 13.42$ min. (method 1)

10 **Example 65**

1-Acetyl-6-(2-pyrrolidone-*N*-ethylcarbonyl)amino-4-phenyl-1,2,3,4-tetrahydro-2,2,4-trimethylquinoline

(a). 1-Acetyl-6-acryloylamino-4-phenyl-1,2,3,4-tetrahydro-2,2,4-trimethylquinoline

- 15 Acylation of 1-acetyl-6-amino-4-phenyl-1,2,3,4-tetrahydro-2,2,4-trimethylquinoline (0.12 g) with acryloyl chloride (39 μ l) and *N,N*-diisopropylethylamine (0.21 ml) in tetrahydrofuran (10 ml) was performed according to the method described in example 6.

Yield: 0.13 g. MS-ESI: $[M+H]^+ = 363.2$

20

(b). 1-Acetyl-6-(2-pyrrolidone-*N*-ethylcarbonyl)amino-4-phenyl-1,2,3,4-tetrahydro-2,2,4-trimethylquinoline

- To a mixture of 2-pyrrolidone (19 mg) and NaH (18 mg, 60% in oil) in THF (1 mL) was added 1-acetyl-6-acryloylamino-4-phenyl-1,2,3,4-tetrahydro-2,2,4-trimethylquinoline (8 mg) in THF (1 mL). After stirring for 18 h, TLC analysis indicated conversion into a higher-running product. The mixture was diluted with ethyl acetate and washed with water, 0.5 N HCl and water. The organic layer was dried (Na_2SO_4) and concentrated in vacuo. Purification was accomplished by silica gel column chromatography, using heptane/ethyl acetate = 8/2 $\Rightarrow$ 1/1 (v/v) as eluent.
- 25

Yield: 4.6 mg. MS-ESI: $[M+H]^+ = 448.4$; HPLC: $R_t = 4.51$ min. (method 2)

Example 66

1-Acetyl-6-(ethoxyethoxyethylcarbonyl)amino-4-phenyl-1,2,3,4-tetrahydro-2,2,4-trimethylquinoline

- 5 Michael addition of 2-ethoxyethanol (19 mg) and 1-acetyl-6-acryloylamino-4-phenyl-1,2,3,4-tetrahydro-2,2,4-trimethylquinoline (8 mg) in THF (1 mL) was performed according to the method described in example 65.

Yield: 1.0 mg. MS-ESI: $[M+H]^+ = 453.4$; HPLC: $R_t = 5.03$ min. (method 2)

Example 67

- 10 1-Acetyl-6-(2-pyrrolidone-N-methoxycarbonylmethylcarbonyl)amino-4-phenyl-1,2,3,4-tetrahydro-2,2,4-trimethylquinoline

- Condensation of *N*-hydroxymethyl-2-pyrrolidone (22 mg) and 1-acetyl-6-(hydroxycarbonylmethylcarbonyl)amino-4-phenyl-1,2,3,4-tetrahydro-2,2,4-trimethylquinoline (15 mg) under the agency of HATU (29 mg) and *N,N*-diisopropylethylamine (33 1) in tetrahydrofuran (2 ml) was performed according to the method described in example 11.

Yield: 4.6 mg. MS-ESI: $[M+H]^+ = 478.4$; HPLC: $R_t = 5.53$ min. (method 2)

Example 68

- 20 1-Acetyl-6-(tert-butylcarbamoyl-N-[2-ethoxy]carbonylmethylcarbonyl)amino-4-phenyl-1,2,3,4-tetrahydro-2,2,4-trimethylquinoline

- Condensation of *tert*-butyl-*N*-(2-hydroxyethyl)carbamate (29 μ l) and 1-acetyl-6-(hydroxycarbonylmethylcarbonyl)amino-4-phenyl-1,2,3,4-tetrahydro-2,2,4-trimethylquinoline (15 mg) under the agency of HATU (29 mg) and *N,N*-diisopropylethylamine (33 1) in tetrahydrofuran (2 ml) was performed according to the method described in example 11.

Yield: 11 mg. MS-ESI: $[M+H]^+ = 538.4$; HPLC: $R_t = 5.32$ min. (method 2)

Example 69

1-Acetyl-6-(2-furylmethoxycarbonylmethylcarbonyl)amino-4-phenyl-1,2,3,4-tetrahydro-2,2,4-trimethylquinoline

Condensation of furfuryl alcohol (17 μ l) and 1-acetyl-6-(hydroxycarbonylmethylcarbonyl)amino-4-phenyl-1,2,3,4-tetrahydro-2,2,4-trimethylquinoline (15 mg) under the agency of HATU (29 mg) and *N,N*-diisopropylethylamine (33 μ l) in tetrahydrofuran (2 ml) was performed according to the method described in example 11.

Yield: 7.1 mg. MS-ESI: $[M+H]^+ = 475.4$; HPLC: $R_t = 5.30$ min. (method 2)

10 Example 70

1-Acetyl-6-((cyclopropylmethylaminomethylcarbonyl)amino-4-phenyl-1,2,3,4-tetrahydro-2,2,4-trimethylquinoline

Alkylation of cyclopropylmethylamine (4 μ l) with 1-acetyl-6-(bromoacetyl)amino-4-phenyl-1,2,3,4-tetrahydro-2,2,4-trimethylquinoline (10 mg) and *N,N*-diisopropylethylamine (13 μ l) in dichloromethane (1 ml) was performed according to the method described in example 29.

Yield: 6.8 mg. MS-ESI: $[M+H]^+ = 535.6$; HPLC: $R_t = 6.29$ min. (method 2)

Example 71

20 1-Acetyl-4-(2-methoxyphenyl)-6-(4-phenylbenzoyl)amino-1,2,3,4-tetrahydro-2,2,4-trimethylquinoline

(a). 1-Acetyl-6-(4-phenylbenzoyl)amino-1,2-dihydro-2,2,4-trimethylquinoline
1-Acetyl-6-(*tert*-butoxycarbonyl)amino-1,2-dihydro-2,2,4-trimethylquinoline (1.0 g) was dissolved in a mixture of trifluoroacetic acid/ CH_2Cl_2 (1/1, v/v, 25 ml) and stirred
25 for 2 h. The reaction mixture was concentrated in vacuo, diluted with ethyl acetate and washed with 5% aq. $NaHCO_3$. The organic layer was separated, dried ($MgSO_4$) and concentrated. The residue was dissolved in CH_2Cl_2 (25 ml), *N,N*-diisopropylethylamine (5.2 ml) and 4-phenylbenzoyl chloride (2.0 g) were added and the mixture was stirred for 16 h. The mixture was concentrated and chromatographed on silicagel in
30 heptane/ethyl acetate = 1/0 $\Rightarrow$ 0/1 (v/v) as eluent.

Yield: 0.63 g. MS-ESI: $[M+H]^+ = 411.2$

(b). 1-Acetyl-4-(2-methoxyphenyl)-6-(4-phenylbenzoyl)amino-1,2,3,4-tetrahydro-2,2,4-trimethylquinoline and 1-acetyl-4-(4-methoxyphenyl)-6-(4-phenylbenzoyl)amino-1,2,3,4-tetrahydro-2,2,4-trimethylquinoline

Friedel-Crafts alkylation of anisole (25 ml, stored on molecular sieves 3Å) with 1-acetyl-6-(4-phenylbenzoyl)amino-1,2-dihydro-2,2,4-trimethylquinoline (0.50 g) in the presence of $AlCl_3$ (0.50 g) was performed according to the method described in example 3. Purification by silica gel chromatography (eluent: heptane/ethyl acetate = 1/0 $\Rightarrow$ 0/1, v,v) yielded the 2-methoxyphenyl-substituted derivative as minor product and the 4-methoxyphenyl-substituted derivative as the major product.

Yield: 46 mg. MS-ESI: $[M+H]^+ = 518.0$ (2-methoxyphenyl)

Yield: 0.20 g. MS-ESI: $[M+H]^+ = 518.1$ (4-methoxyphenyl)

15 Example 72

1-Acetyl-4-(4-hydroxyphenyl)-6-(4-phenylbenzoyl)amino-1,2,3,4-tetrahydro-2,2,4-trimethylquinoline

To a cooled (0 °C) solution of 1-acetyl-4-(4-methoxyphenyl)-6-(4-phenylbenzoyl)amino-1,2,3,4-tetrahydro-2,2,4-trimethylquinoline (0.46 g) in CH_2Cl_2 was added BBr_3 under a nitrogen atmosphere. Complete conversion was reached after stirring for 3 h at room temperature. The mixture was cooled, 1 M NaOH was added until basic pH, subsequently ethyl acetate was added and the mixture was acidified with 1 M HCl. The organic layer was separated, dried ($MgSO_4$) and concentrated. The residue was chromatographed on silicagel in heptane/ethyl acetate = 1/0 $\Rightarrow$ 0/1 (v/v) as eluent.

Yield: 0.13 g. MS-ESI: $[M+H]^+ = 504.0$

Example 73

1-Acetyl-6-(5-methylnicotinoyl)amino-4-phenyl-1,2,3,4-tetrahydro-2,2,4-trimethylquinoline

Condensation of 1-acetyl-6-amino-4-phenyl-1,2,3,4-tetrahydro-2,2,4-trimethylquinoline (0.10 g) with 5-methyl nicotinic acid (0.13 g) under the agency of

HATU (0.18 g) and *N,N*-diisopropylethylamine (0.28 ml) in dichloromethane (2 ml) was performed according to the method described in example 11.

Yield: 0.12 g. MS-ESI: $[M+H]^+ = 427.0$

5 Example 74

CHO-FSH *in vitro* bioactivity

FSH activity of compounds were tested in Chinese Hamster Ovary (CHO) cells stably transfected with the human FSH receptor and cotransfected with a cAMP responsive element (CRE) / promotor directing the expression of a firefly luciferase reporter gene.

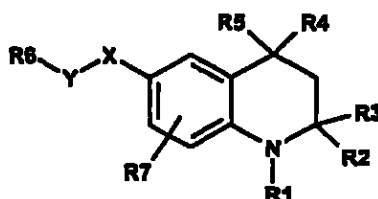
10 Binding of ligand to the Gs-coupled FSH receptor will result in an increase of cAMP, which in turn will induce an increased transactivation of the luciferase reporter construct. The luciferase signal was quantified using a luminescence counter. For test compounds, EC₅₀ values (concentration of test compound causing half-maximal (50 %) stimulation) were calculated. For that purpose the software program GraphPad PRISM,

15 version 3.0 (GraphPad software Inc., San Diego) was used.

Compounds of all examples had an activity (EC₅₀) of less than 10⁻⁵ M. The compounds of examples 1, 6-13, 15, 16, 21-24, 30, 36, 37, 45, 46, 48, 50-53, 55, 57, 58, 61, 63 and 64 showed an EC₅₀ of less than 10⁻⁷ M.

Claims

1. A tetrahydroquinoline derivative compound according to Formula 1,



Formula I

5 or a pharmaceutically acceptable salt thereof, wherein

R^1 is formyl, (1-6C)alkylcarbonyl or (1-6C)alkylsulfonyl;

R^2 and R^3 are H or (1-4C)alkyl;

R^4 is phenyl;

R^5 is (1-4C)alkyl;

10 Y-X is C(O)-O, S(O)₂-O, NHC(O)-O, NHC(S)-O, OC(O)-O, bond-O, C(O)-NH, S(O)₂-NH, NHC(O)-NH, NHC(S)-NH, OC(O)-NH, bond-NH, NH-C(O), O-C(O), NH-S(O)₂, or O-S(O)₂ or X-Y is a bond;

R^6 is H, except for Y-X is a bond, trifluoromethyl, (1-6C)alkyl, 1- or 2-adamantyl, (1-4C)alkyl, (2-6C)alkenyl, (2-6C)alkynyl, (3-9C)heteroaryl, (3-6C)cycloalkyl, (2-6C)heterocycloalkyl, (1-4C)alkylthio(1-4C)alkyl, (6-10C)aryl(1-4C)alkyl, (3-9C)heteroaryl(1-4C)alkyl, (3-6C)cycloalkyl(1-4C)alkyl, (2-6C)heterocycloalkyl(1-4C)alkyl, R^8, R^9 -aminocarbonyl(1-4C)alkyl, R^8, R^9 -amino(1-4C)alkyl, R^8 -oxycarbonyl(1-4C)alkyl, R^8 -oxy(1-4C)alkyl, R^8 -carbonyl(1-4C)alkyl or (6-10C)aryl;

20 R^7 is H, (1-4C)alkyl, (1-4C)alkoxy, halogen, trifluoromethyl, cyano, nitro, hydroxyl; and

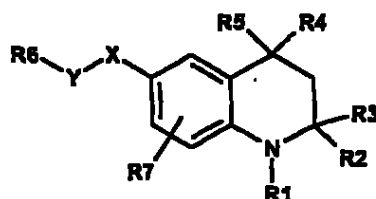
R^8 and/or R^9 is H, (1-4C)alkyl, (2-4C)alkenyl, (2-4C)alkynyl, (6-10C)aryl, (3-9C)heteroaryl, (6-10C)aryl(1-4C)alkyl, (3-9C)heteroaryl(1-4C)alkyl, (3-6C)cycloalkyl(1-4C)alkyl, (2-6C)heterocycloalkyl(1-4C)alkyl, (1-4C)(di)alkylamino(1-4C)alkyl, (1-4C)alkoxy(1-4C)alkyl, (1-4C)alkylthio(1-4C)alkyl, (1-4C)alkylcarbonylamino(1-4C)alkyl, (1-4C)alkoxycarbonyl(1-4C)alkyl, (1-4C)alkoxycarbonylamino(1-4C)alkyl, (3-6C)cycloalkyl, (2-

9X

- 59 -

6C)heterocycloalkyl, or R^8 and R^9 may be joined in a (2-6C)heterocycloalkyl ring for use in therapy.

2. A tetrahydroquinoline derivative compound according to Formula 1,



Formula I

or a pharmaceutically acceptable salt thereof, wherein

R^1 is formyl, (1-6C)alkylcarbonyl or (1-6C)alkylsulfonyl;

R^2 and R^3 are H or (1-4C)alkyl;

R^4 is phenyl;

R^5 is (1-4C)alkyl;

Y-X is C(O)-O, S(O)₂-O, NHC(O)-O, NHC(S)-O, OC(O)-O, bond-O, C(O)-NH, S(O)₂-NH, NHC(O)-NH, NHC(S)-NH, OC(O)-NH, bond-NH, NH-C(O), O-C(O), NH-S(O)₂, or O-S(O)₂ or X-Y is a bond;

R^6 is H, except for Y-X is a bond, trifluoromethyl, (1-6C)alkyl, 1- or 2-adamantyl(1-4C)alkyl, (2-6C)alkenyl, (2-6C)alkynyl, (3-9C)heteroaryl, (3-6C)cycloalkyl, (2-6C)heterocycloalkyl, (1-4C)alkylthio(1-4C)alkyl, (6-10C)aryl(1-4C)alkyl, (3-9C)heteroaryl(1-4C)alkyl, (3-6C)cycloalkyl(1-4C)alkyl, (2-6C)heterocycloalkyl(1-4C)alkyl, R^8, R^9 -aminocarbonyl(1-4C)alkyl, R^8, R^9 -amino(1-4C)alkyl, R^8 -oxycarbonyl(1-4C)alkyl, R^8 -oxy(1-4C)alkyl, R^8 -carbonyl(1-4C)alkyl or (6-10C)aryl

R^7 is H, (1-4C)alkyl, (1-4C)alkoxy, halogen, trifluoromethyl, cyano, nitro, hydroxyl; and

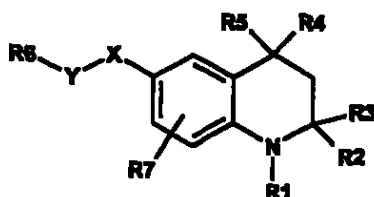
R^8 and/or R^9 is H, (1-4C)alkyl, (2-4C)alkenyl, (2-4C)alkynyl, (6-10C)aryl, (3-9C)heteroaryl, (6-10C)aryl(1-4C)alkyl, (3-9C)heteroaryl(1-4C)alkyl, (3-6C)cycloalkyl(1-4C)alkyl, (2-6C)heterocycloalkyl(1-4C)alkyl, (1-4C)(di)alkylamino(1-4C)alkyl, (1-4C)alkoxy(1-4C)alkyl, (1-4C)alkylthio(1-4C)alkyl, (1-4C)alkylcarbonylamino(1-4C)alkyl, (1-4C)alkoxycarbonyl(1-4C)alkyl, (1-4C)alkoxycarbonylamino(1-4C)alkyl, (3-6C)cycloalkyl, (2-

- 6C)heterocycloalkyl, or R⁸ and R⁹ may be joined in a (2-6C)heterocycloalkyl ring with the proviso that the derivative is 1-acetyl-6-benzoylamino-4-(4-methylphenyl)-1,2,3,4-tetrahydro-2,2,4-trimethylquinoline, 1-acetyl-4-phenyl-1,2,3,4-tetrahydro-2,2,4,6-tetramethylquinoline, 1-acetyl-4-phenyl-1,2,3,4-tetrahydro-2,2,4,6,8-pentamethylquinoline, 1-acetyl-6-methoxy-4-phenyl-1,2,3,4-tetrahydro-2,2,4-trimethylquinoline, 1-acetyl-6-trifluoroacetylamino-4-(4-methylphenyl)-1,2,3,4-tetrahydro-2,2,4-trimethylquinoline, 1-acetyl-6-trifluoroacetylamino-4-phenyl-1,2,3,4-tetrahydro-2,2,4-trimethylquinoline, 1-acetyl-4-(4-chlorophenyl)-1,2,3,4-tetrahydro-2,2,4,6-tetramethylquinoline and 1-acetyl-4-(4-bromophenyl)-1,2,3,4-tetrahydro-2,2,4,6-tetramethylquinoline.
3. The tetrahydroquinoline derivative compound of claim 2 wherein Y-X is C(O)-NH, OC(O)-NH, or C(O)-O.
 4. The tetrahydroquinoline derivative compound of claims 2 or 3 wherein Y-X is C(O)-NH.
 5. The tetrahydroquinoline derivative compound of claims 2-4 wherein R¹ is (1-4C)alkylcarbonyl.
 6. The tetrahydroquinoline derivative compound of claims 2-5 wherein R², R³ and R⁵ are independently (1-4C)alkyl.
 7. The tetrahydroquinoline derivative compound of claims 2-6 wherein R⁶ is (6-10C)aryl, (3-9C)heteroaryl, (6-10C)aryl(1-4C)alkyl or (3-9C)heteroaryl(1-4C)alkyl.
 8. A pharmaceutical composition comprising the compound of any one of claims 2-7 and pharmaceutically suitable auxiliaries.
 9. Use of the compound of any one of claims 2-8 or a pharmaceutically acceptable salt or solvate thereof for the manufacture of a medicament for the control of fertility.

AMENDED CLAIMS

[received by the International Bureau on 12 November 2002 (12.11.02)]

1. A tetrahydroquinoline derivative compound according to Formula 1,



Formula I

or a pharmaceutically acceptable salt thereof, wherein

R^1 is formyl, (1-6C)alkylcarbonyl or (1-6C)alkylsulfonyl;

R^2 and R^3 are H or (1-4C)alkyl;

R^4 is phenyl, optionally substituted with one or more substituents selected from the group hydroxy, amino, halogen, nitro, trifluoromethyl, cyano, (1-4C)alkyl, (2-4C)alkenyl, (2-4C)alkynyl, (1-4C)alkoxy, (1-4C)(di)alkylamino.

R^5 is (1-4C)alkyl;

Y-X is C(O)-O, S(O)₂-O, NHC(O)-O, NHC(S)-O, OC(O)-O, bond-O, C(O)-NH, S(O)₂-NH, NHC(O)-NH, NHC(S)-NH, OC(O)-NH, bond-NH, NH-C(O), O-C(O), NH-S(O)₂, or O-S(O)₂ or X-Y is a bond;

R^6 is H, except for Y-X is a bond, trifluoromethyl, (1-6C)alkyl, 1- or 2-adamantyl(1-4C)alkyl, (2-6C)alkenyl, (2-6C)alkynyl, (3-9C)heteroaryl, (3-6C)cycloalkyl, (2-6C)heterocycloalkyl, (1-4C)alkylthio(1-4C)alkyl, (6-10C)aryl(1-4C)alkyl, (3-9C)heteroaryl(1-4C)alkyl, (3-6C)cycloalkyl(1-4C)alkyl, (2-6C)heterocycloalkyl(1-4C)alkyl, R^8, R^9 -aminocarbonyl(1-4C)alkyl, R^8, R^9 -amino(1-4C)alkyl, R^8 -oxycarbonyl(1-4C)alkyl, R^8 -oxy(1-4C)alkyl, R^8 -carbonyl(1-4C)alkyl or (6-10C)aryl, whereas if (6-10C)aryl is phenyl, phenyl may be optionally substituted with hydroxy, amino, halogen, nitro, trifluoromethyl, cyano, (1-4C)alkyl, (2-4C)alkenyl, (2-4C)alkynyl, (1-4C)alkoxy, (1-4C)(di)alkylamino, (6-10C)aryl, (6-10C)aryloxy, (6-10C)aryl(1-4C)alkoxy, (3-9C)heteroaryl, (3-9C)heteroaryloxy, (3-9C)heteroaryl(1-4C)alkoxy, (1-4C)alkylcarbonylamino, (1-4C)alkylcarbonyloxy, (3-6C)cycloalkylcarbonyloxy,

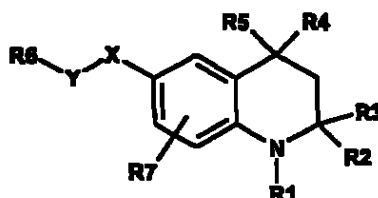
(1-4C)alkoxycarbonyl(1-4C)alkylcarbonyloxy, (1-4C)alkoxy(1-4C)alkylcarbonyloxy, (6-10C)arylcarbonyloxy, (3-9C)heteroarylcarbonyloxy, (1-4C)alkylsulfonyloxy, (6-10C)arylsulfonyloxy, (3-9C)heteroarylsulfonyloxy, (1-4C)(di)alkylcarbamoyl, (6-10C)(di)arylcarbamoyl, (2-6C)heterocycloalkylcarbamoyl, (6-10C)(di)arylamino, (3-6C)cycloalkyl, (3-6C)cycloalkyl(1-4C)alkyl, (2-6C)heterocycloalkyl or (2-6)heterocycloalkyl(1-4C)alkyl,

and whereas all aryl and heteroaryl groups within R⁶ optionally may be substituted with one or more substituents selected from hydroxy, amino, halogen, nitro, trifluoromethyl, cyano, (1-4C)alkyl, (2-4C)alkenyl, (2-4C)alkynyl, (1-4C)alkoxy or (1-4C)(di)alkylamino,

R⁷ is H, (1-4C)alkyl, (1-4C)alkoxy, halogen, trifluoromethyl, cyano, nitro, hydroxyl; and

R⁸ and/or R⁹ is H, (1-4C)alkyl, (2-4C)alkenyl, (2-4C)alkynyl, (6-10C)aryl, (3-9C)heteroaryl, (6-10C)aryl(1-4C)alkyl, (3-9C)heteroaryl(1-4C)alkyl, (3-6C)cycloalkyl(1-4C)alkyl, (2-6C)heterocycloalkyl(1-4C)alkyl, (1-4C)(di)alkylamino(1-4C)alkyl, (1-4C)alkoxy(1-4C)alkyl, (1-4C)alkylthio(1-4C)alkyl, (1-4C)alkylcarbonylamino(1-4C)alkyl, (1-4C)alkoxycarbonyl(1-4C)alkyl, (1-4C)alkoxycarbonylamino(1-4C)alkyl, (3-6C)cycloalkyl, (2-6C)heterocycloalkyl or R⁸ and R⁹ may be joined in a (2-6C)heterocycloalkyl ring for use in therapy.

2. A tetrahydroquinoline derivative compound according to Formula 1,



Formula I

or a pharmaceutically acceptable salt thereof, wherein

R¹ is formyl, (1-6C)alkylcarbonyl or (1-6C)alkylsulfonyl;

R² and R³ are H or (1-4C)alkyl;

R⁴ is phenyl, optionally substituted with one or more substituents selected from

the group hydroxy, amino, halogen, nitro, trifluoromethyl, cyano, (1-4C)alkyl, (2-4C)alkenyl, (2-4C)alkynyl, (1-4C)alkoxy, (1-4C)(di)alkylamino

R⁵ is (1-4C)alkyl;

Y-X is C(O)-O, S(O)₂-O, NHC(O)-O, NHC(S)-O, OC(O)-O, bond-O, C(O)-NH, S(O)₂-NH, NHC(O)-NH, NHC(S)-NH, OC(O)-NH, bond-NH, NH-C(O), O-C(O), NH-S(O)₂, or O-S(O)₂ or X-Y is a bond;

R⁶ is H, except for Y-X is a bond, trifluoromethyl, (1-6C)alkyl, 1- or 2-adamantyl(1-4C)alkyl, (2-6C)alkenyl, (2-6C)alkynyl, (3-9C)heteroaryl, (3-6C)cycloalkyl, (2-6C)heterocycloalkyl, (1-4C)alkylthio(1-4C)alkyl, (6-10C)aryl(1-4C)alkyl, (3-9C)heteroaryl(1-4C)alkyl, (3-6C)cycloalkyl(1-4C)alkyl, (2-6C)heterocycloalkyl(1-4C)alkyl, R⁸,R⁹-aminocarbonyl(1-4C)alkyl, R⁸,R⁹-amino(1-4C)alkyl, R⁸-oxycarbonyl(1-4C)alkyl, R⁸-oxy(1-4C)alkyl, R⁸-carbonyl(1-4C)alkyl or (6-10C)aryl whereas if (6-10C)aryl is phenyl, phenyl may be optionally substituted with hydroxy, amino, halogen, nitro, trifluoromethyl, cyano, (1-4C)alkyl, (2-4C)alkenyl, (2-4C)alkynyl, (1-4C)alkoxy, (1-4C)(di)alkylamino, (6-10C)aryl, (6-10C)aryloxy, (6-10C)aryl(1-4C)alkoxy, (3-9C)heteroaryl, (3-9C)heteroaryloxy, (3-9C)heteroaryl(1-4C)alkoxy, (1-4C)alkylcarbonylamino, (1-4C)alkylcarbonyloxy, (3-6C)cycloalkylcarbonyloxy, (1-4C)alkoxycarbonyl(1-4C)alkylcarbonyloxy, (1-4C)alkoxy(1-4C)alkylcarbonyloxy, (6-10C)arylcabonyloxy, (3-9C)heteroarylcabonyloxy, (1-4C)alkylsulfonyloxy, (6-10C)arylsulfonyloxy, (3-9C)heteroarylsulfonyloxy, (1-4C)(di)alkylcarbamoyl, (6-10C)(di)arylcabamoyl, (2-6C)heterocycloalkylcarbamoyl, (6-10C)(di)arylamino, (3-6C)cycloalkyl, (3-6C)cycloalkyl(1-4C)alkyl, (2-6C)heterocycloalkyl or (2-6)heterocycloalkyl(1-4C)alkyl,

and whereas all aryl and heteroaryl groups within R⁶ optionally may be substituted with one or more substituents selected from hydroxy, amino, halogen, nitro, trifluoromethyl, cyano, (1-4C)alkyl, (2-4C)alkenyl, (2-4C)alkynyl, (1-4C)alkoxy or (1-4C)(di)alkylamino,

R⁷ is H, (1-4C)alkyl, (1-4C)alkoxy, halogen, trifluoromethyl, cyano, nitro, hydroxyl; and

R⁸ and/or R⁹ is H, (1-4C)alkyl, (2-4C)alkenyl, (2-4C)alkynyl, (6-10C)aryl, (3-

- 9C)heteroaryl, (6-10C)aryl(1-4C)alkyl, (3-9C)heteroaryl(1-4C)alkyl, (3-6C)cycloalkyl(1-4C)alkyl, (2-6C)heterocycloalkyl(1-4C)alkyl, (1-4C)(di)alkylamino(1-4C)alkyl, (1-4C)alkoxy(1-4C)alkyl, (1-4C)alkylthio(1-4C)alkyl, (1-4C)alkylcarbonylamino(1-4C)alkyl, (1-4C)alkoxycarbonyl(1-4C)alkyl, (1-4C)alkoxycarbonylamino(1-4C)alkyl, (3-6C)cycloalkyl, (2-6C)heterocycloalkyl, or R⁸ and R⁹ may be joined in a (2-6C)heterocycloalkyl ring with the proviso that the derivative is not 1-acetyl-6-benzoylamino-4-(4-methylphenyl)-1,2,3,4-tetrahydro-2,2,4-trimethylquinoline, 1-acetyl-4-phenyl-1,2,3,4-tetrahydro-2,2,4,6-tetramethylquinoline, 1-acetyl-4-phenyl-1,2,3,4-tetrahydro-2,2,4,6,8-pentamethylquinoline, 1-acetyl-6-methoxy-4-phenyl-1,2,3,4-tetrahydro-2,2,4-trimethylquinoline, 1-acetyl-6-trifluoroacetylamino-4-(4-methylphenyl)-1,2,3,4-tetrahydro-2,2,4-trimethylquinoline, 1-acetyl-6-trifluoroacetylamino-4-phenyl-1,2,3,4-tetrahydro-2,2,4-trimethylquinoline, 1-acetyl-4-(4-chlorophenyl)-1,2,3,4-tetrahydro-2,2,4,6-tetramethylquinoline and 1-acetyl-4-(4-bromophenyl)-1,2,3,4-tetrahydro-2,2,4,6-tetramethylquinoline.
3. The tetrahydroquinoline derivative compound of claim 2 wherein Y-X is C(O)-NH, OC(O)-NH, or C(O)-O.
 4. The tetrahydroquinoline derivative compound of claims 2 or 3 wherein Y-X is C(O)-NH.
 5. The tetrahydroquinoline derivative compound of claims 2-4 wherein R¹ is (1-4C)alkylcarbonyl.
 6. The tetrahydroquinoline derivative compound of claims 2-5 wherein R², R³ and R⁵ are independently (1-4C)alkyl.
 7. The tetrahydroquinoline derivative compound of claims 2-6 wherein R⁶ is (6-10C)aryl, (3-9C)heteroaryl, (6-10C)aryl(1-4C)alkyl or (3-9C)heteroaryl(1-4C)alkyl whereas if (6-10C)aryl is phenyl, phenyl may be optionally substituted with hydroxy, amino, halogen, nitro, trifluoromethyl, cyano, (1-4C)alkyl, (2-4C)alkenyl, (2-4C)alkynyl, (1-4C)alkoxy, (1-4C)(di)alkylamino, (6-10C)aryl, (6-10C)aryloxy, (6-10C)aryl(1-4C)alkoxy, (3-9C)heteroaryl, (3-9C)heteroaryloxy, (3-9C)heteroaryl(1-4C)alkoxy, (1-4C)alkylcarbonylamino, (1-4C)alkylcarbonyloxy, (3-6C)cycloalkylcarbonyloxy, (1-4C)alkoxycarbonyl(1-4C)alkylcarbonyloxy, (1-4C)alkoxy(1-4C)alkylcarbonyloxy, (6-

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- 10C)arylcarbonyloxy, (3-9C)heteroarylcarbonyloxy, (1-4C)alkylsulfonyloxy, (6-10C)arylsulfonyloxy, (3-9C)heteroarylsulfonyloxy, (1-4C)(di)alkylcarbamoyl, (6-10C)(di)arylcarbamoyl, (2-6C)heterocycloalkylcarbamoyl, (6-10C)(di)arylamino, (3-6C)cycloalkyl, (3-6C)cycloalkyl(1-4C)alkyl, (2-6C)heterocycloalkyl or (2-6)heterocycloalkyl(1-4C)alkyl,
- 5 and whereas all aryl and heteroaryl groups within R⁶ optionally may be substituted with one or more substituents selected from hydroxy, amino, halogen, nitro, trifluoromethyl, cyano; (1-4C)alkyl, (2-4C)alkenyl, (2-4C)alkynyl, (1-4C)alkoxy or (1-4C)(di)alkylamino.
- 10 8. A pharmaceutical composition comprising the compound of any one of claims 2-7 and pharmaceutically suitable auxiliaries.
9. Use of the compound of any one of claims 2-8 or a pharmaceutically acceptable salt or solvate thereof for the manufacture of a medicament for the control of fertility.

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INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 02/07053

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61K31/47 C07D215/38 C07D401/12 C07D405/14 C07D417/12
C07D215/48 C07D215/20 C07D215/08 C07D413/12 A61K31/4709
A61P5/06

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D A61K

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

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

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	CHEMICAL ABSTRACTS, vol. 79, no. 9, 3 September 1973 (1973-09-03) Columbus, Ohio, US; abstract no. 53152, LUGOVIK, B. A. ET AL: "Structure of compounds obtained from the interaction of 1,2-dihydroquinolines with alkylbenzenes" XP002185090 cited in the application abstract & TR. OMSK. SEL'SKOKHOZ. INST. (1971), 82, 107-10, ----- -/-	2-9

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents:

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- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
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- *G* document member of the same patent family

Date of the actual completion of the international search

30 September 2002

Date of mailing of the international search report

07/10/2002

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Authorized officer

Scruton-Evans, I

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 02/07053

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	CHEMICAL ABSTRACTS, vol. 77, no. 25, 18 December 1972 (1972-12-18) Columbus, Ohio, US; abstract no. 164415, LUGOVIK, B. A. ET AL: "Reaction of 1,2-dihydroquinolines with benzene and halobenzenes" XP002185091 cited in the application abstract & NAUCH. TR., OMSK. SEL.-KHOZ. INST. (1971), NO. 82, 103-6 FROM: REF. ZH., KHIM. 1972, ABSTR. NO. 1ZH311,	2-9
X	CHEMICAL ABSTRACTS, vol. 105, no. 7, 18 August 1986 (1986-08-18) Columbus, Ohio, US; abstract no. 56990, SHMYREVA, ZH. V. ET AL: "Modification of anion exchanger Duolite A 368 PR for the covalent immobilization of glucoamylase" XP002185092 cited in the application RN 91147-49-8 abstract & TEOR. PRAKT. SORBTSIONNYKH PROTSESSOV (1985), 17, 39-42,	2-9
X	DATABASE CHEMCATS 'Online! CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; XP002185093 ORDER NUMBER 4723-A1028/0048172, 781-A1427/0063514, 28020-A0839/0039328 & "AMBINTER SCREENING COLLECTION" 31 May 2001 (2001-05-31), AMBINTER, 46 QUAI LOUIS BLEROT, PARIS, F-75016, FRANCE	2-7
X	DATABASE CHEMCATS 'Online! CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; XP002185095 ORDER NUMBER VITO003069 & "VITAS-M SCREENING COLLECTION" 22 March 2001 (2001-03-22), VITAS- CENTER OF MOLECULAR MEDICINE, ROOM 208, LABORATORY BUILDING B, MOSCOW, 1192829 RUSSIA	2-7
A	US 6 200 963 B1 (KAO WENLING ET AL) 13 March 2001 (2001-03-13) the whole document	1-9
	-/-	

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 02/07053

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 00 08015 A (APPLIED RESEARCH SYSTEMS ;BUCKLER DAVID (US); EL TAYER NABIL (US);) 17 February 2000 (2000-02-17) the whole document	1-9

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 02/07053

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
US 6200963	B1	13-03-2001	NONE	
WO 0008015	A	17-02-2000	AU 5393199 A	28-02-2000
			EP 1102763 A2	30-05-2001
			JP 2002522433 T	23-07-2002
			WO 0008015 A2	17-02-2000
			US 6235755 B1	22-05-2001
			US 6423723 B1	23-07-2002

PCT

REQUEST

The undersigned requests that the present international application be processed according to the Patent Cooperation Treaty.

For receiving Office use only

International Application No. **B**

International Filing Date

Name of receiving Office and "PCT International Application"

Applicant's or agent's file reference

(if desired) (12 characters maximum)

2001.656 WO

Box No. I TITLE OF INVENTION

"Tetrahydroquinoline derivatives"

Box No. II APPLICANT

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this box is the applicant's State (i.e. country) of residence (if no State of residence is indicated below)

Akzo Nobel N.V.**Velperweg 76****6824 RM ARNHEM****The Netherlands**☐ This person is also inventor

Telephone No.

0412-666380

Facsimile No.

0412-650592

Teleprinter No.

State (i.e. country) of nationality: **NL**State (i.e. country) of residence: **NL**This person is applicant for the purposes of: ☐all designated States ☒all designated States except the United States of America ☐the United States of America only ☐the States indicated in the Supplemental Box ☐

Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this box is the applicant's State (i.e. country) of residence (if no State of residence is indicated below)

VAN STRATEN, Nicole Corine Renée**N.V. Organon****Postbus 20****5340 BH Oss****The Netherlands**

This person is:

☐ applicant only☒ applicant and inventor☐ inventor only (If this check-box is marked, do not fill in below.)State (i.e. country) of nationality: **NL**State (i.e. country) of residence: **NL**This person is applicant for the purposes of: ☐all designated States ☐all designated States except the United States of America ☒the United States of America only ☐the States indicated in the Supplemental Box ☐☒ Further applicants and/or (further) inventors are indicated on a continuation sheet.

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

The person identified below is hereby/has been appointed to act on behalf of the applicant(s) before the competent International Authorities as:

☒

agent

☐

common representative

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

P M G F van Wezenbeek**P.O. Box 20****5340 BH OSS****The Netherlands**

Telephone No.

0412-666219

Facsimile No.

0412-650592

Teleprinter No.

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

Form PCT/RO/101 (first sheet) (January 1997; reprint January 1998)

See Notes to the request form

Continuation of Box No. III FURTHER APPLICANTS AND/OR (FURTHER) INVENTORS	
<i>If none of the following sub-boxes is used, this sheet is not to be included in the request.</i>	
Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this box is the applicant's State (i.e. country) of residence if no State of residence is indicated below) VAN SOMEREN, Rudolf Gijlsbertus N.V. Organon Postbus 20 5340 BH Oss The Netherlands	This person is: ☐ applicant only ☒ applicant and inventor ☐ inventor only (If this check-box is marked, do not fill in below.)
State (i.e. country) of nationality: NL	State (i.e. country) of residence: NL
This person is applicant for the purposes of ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box	
Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this box is the applicant's State (i.e. country) of residence if no State of residence is indicated below) SCHULZ, Jurgén C/O: Organon Laboratories Ltd. New Edinburgh Road Newhouse Lanarkshire ML1 5SH Scotland United Kingdom	This person is: ☐ applicant only ☒ applicant and inventor ☐ inventor only (If this check-box is marked, do not fill in below.)
State (i.e. country) of nationality: DE	State (i.e. country) of residence: GB
This person is applicant for the purposes of ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box	
Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this box is the applicant's State (i.e. country) of residence if no State of residence is indicated below)	This person is: ☐ applicant only ☐ applicant and inventor ☐ inventor only (If this check-box is marked, do not fill in below.)
State (i.e. country) of nationality:	State (i.e. country) of residence:
This person is applicant for the purposes of ☐ all designated States ☐ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box	
Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this box is the applicant's State (i.e. country) of residence if no State of residence is indicated below)	This person is: ☐ applicant only ☐ applicant and inventor ☐ inventor only (If this check-box is marked, do not fill in below.)
State (i.e. country) of nationality:	State (i.e. country) of residence:
This person is applicant for the purposes of ☐ all designated States ☐ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box	
☐ Further applicants and/or (further) inventors are indicated on another continuation sheet.	

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Box No. V DESIGNATION OF STATES

Mark the applicable check-boxes below; at least one must be marked.

The following designations are hereby made under Rule 4.9(a):

Regional Patent

- ☒ AP ARIPO Patent: GH Ghana, GM Gambia, KE Kenya, LS Lesotho, MW Malawi, MZ Mozambique, SD Sudan, SL Sierra Leone, SZ Swaziland, TZ United Republic of Tanzania, UG Uganda, ZM Zambia, ZW Zimbabwe, and any other State which is a Contracting State of the Harare Protocol and of the PCT (If other kind of protection or treatment desired, specify on dotted line)
- ☒ EA Eurasian Patent: AM Armenia, AZ Azerbaijan, BY Belarus, KG Kyrgyzstan, KZ Kazakhstan, MD Republic of Moldova, RU Russian Federation, TJ Tajikistan, TM Turkmenistan, and any other State which is a Contracting State of the Eurasian Patent Convention and of the PCT
- ☒ EP European Patent: AT Austria, BE Belgium, CH & LI Switzerland and Liechtenstein, CY Cyprus, DE Germany, DK Denmark, ES Spain, FI Finland, FR France, GB United Kingdom, GR Greece, IE Ireland, IT Italy, LU Luxembourg, MC Monaco, NL Netherlands, PT Portugal, SE Sweden, TR Turkey, and any other State which is a Contracting State of the European Patent Convention and of the PCT
- ☒ OA OAPI Patent: BF Burkina Faso, BJ Benin, CF Central African Republic, CG Congo, CI Côte d'Ivoire, CM Cameroon, GA Gabon, GN Guinea, GQ Equatorial Guinea, GW Guinea-Bissau, ML Mali, MR Mauritania, NE Niger, SN Senegal, TD Chad, TG Togo, and any other State which is a member State of OAPI and a Contracting State of the PCT (If other kind of protection or treatment desired, specify on dotted line)

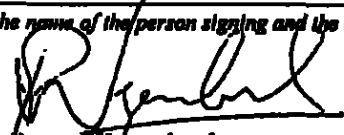
National Patent (If other kind of protection or treatment desired, specify on dotted line):

- | | | |
|---|--|---|
| ☒ AE United Arab Emirates | ☐ GM Gambia | ☒ NZ New Zealand |
| ☒ AG Antigua and Barbuda | ☒ HR Croatia | ☐ OM Oman |
| ☒ AL Albania | ☒ HU Hungary | ☒ PH Philippines |
| ☐ AM Armenia | ☒ ID Indonesia | ☒ PL Poland |
| ☐ AT Austria | ☒ IL Israel | ☐ PT Portugal |
| ☒ AU Australia | ☒ IN India | ☒ RO Romania |
| ☐ AZ Azerbaijan | ☒ IS Iceland | ☒ RU Russian Federation |
| ☒ BA Bosnia and Herzegovina | ☒ JP Japan | ☐ SD Sudan |
| ☒ BB Barbados | ☒ KE Kenya | ☐ SE Sweden |
| ☒ BG Bulgaria | ☐ KG Kyrgyzstan | ☒ SG Singapore |
| ☒ BR Brazil | ☒ KP Democratic People's Republic of Korea | ☒ SI Slovenia |
| ☐ BY Belarus | ☒ KR Republic of Korea | ☒ SK Slovakia |
| ☒ BZ Belize | ☐ KZ Kazakhstan | ☐ SL Sierra Leone |
| ☒ CA Canada | ☒ LC Saint Lucia | ☐ TJ Tajikistan |
| ☐ CH & LI Switzerland and Liechtenstein | ☒ LK Sri Lanka | ☐ TM Turkmenistan |
| ☒ CN China | ☒ LR Liberia | ☐ TN Tunisia |
| ☒ CO Colombia | ☐ LS Lesotho | ☐ TR Turkey |
| ☒ CR Costa Rica | ☒ LT Lithuania | ☒ TT Trinidad and Tobago |
| ☒ CU Cuba | ☐ LU Luxembourg | ☐ TZ United Republic of Tanzania |
| ☒ CZ Czech Republic | ☒ LV Latvia | ☒ UA Ukraine |
| ☐ DE Germany | ☒ MA Morocco | ☐ UG Uganda |
| ☐ DK Denmark | ☐ MD Republic of Moldova | ☒ US United States of America |
| ☒ DM Dominica | ☒ MG Madagascar | ☐ UZ Uzbekistan |
| ☒ EC Ecuador | ☒ MK The former Yugoslav Republic of Macedonia | ☒ VN Viet Nam |
| ☒ EE Estonia | ☒ MN Mongolia | ☒ YU Yugoslavia |
| ☐ ES Spain | ☐ MW Malawi | ☒ ZA South Africa |
| ☐ FI Finland | ☒ MX Mexico | ☐ ZM Zambia |
| ☐ GB United Kingdom | ☒ MZ Mozambique | ☐ ZW Zimbabwe |
| ☒ GD Grenada | ☒ NO Norway | |
| ☒ GE Georgia | | |
| ☐ GH Ghana | | |

Check-boxes below reserved for designating States which have become party to the PCT after issuance of this sheet:

- | | | |
|--------------------------------|--------------------------------|--------------------------------|
| ☐ | ☐ | ☐ |
| ☐ | ☐ | ☐ |

Precautionary Designation Statement: In addition to the designations made above, the applicant also makes under Rule 4.9(b) all other designations which would be permitted under the PCT except any designation(s) indicated in the Supplemental Box as being excluded from the scope of this statement. The applicant declares that those additional designations are subject to confirmation and that any designation which is not confirmed before the expiration of 15 months from the priority date is to be regarded as withdrawn by the applicant at the expiration of that time limit. (Confirmation (including fees) must reach the receiving Office within the 15-month time limit.)

Box No. VI PRIORITY CLAIM		Further priority claims are indicated in the Supplemental Box ☐	
The priority of the following earlier application(s) is hereby claimed:			
Country (in which, or for which, the application was filed)	Filing Date (day/month/year)	Application No.	Office of filing (only for regional or international application)
item (1) EP (designating NL)	02-07-2001	01202531.8	EPO
item (2)			
item (3)			
Mark the following check-box if the certified copy of the earlier application is to be issued by the Office which for the purposes of the present international application is the receiving Office (a fee may be required):			
☒ The receiving Office is hereby requested to prepare and transmit to the International Bureau a certified copy of the earlier application(s) identified above as item(s):			
Box No. VII INTERNATIONAL SEARCHING AUTHORITY			
Choice of International Searching Authority (ISA) (If two or more International Searching Authorities are competent to carry out the international search, indicate the Authority chosen; the two-letter code may be used): ISA /EPO			
Earlier search Fill in where a search (international, international-type or other) by the International Searching Authority has already been carried out or requested and the Authority is now requested to base the international search to the extent possible, on the results of that earlier search. Identify such search or request either by reference to the relevant application (or the translation thereof) or by reference to the search request			
Entry (or regional Office): EP		Date (day/month/year) 02-07-2001	Number: 01202531.8
Box No. VIII CHECK LIST			
This international application contains the following number of sheets: 1. request: 4 sheets 2. description: 57 sheets 3. claims: 3 sheets 4. abstract: 1 sheets 5. drawings: sheets 6. sequence listing: sheets Total : 65 sheets		This international application is accompanied by the item(s) marked below: 1. ☐ separate signed power of attorney 2. ☒ copy of general power of attorney 3. ☐ statement explaining lack of signature 4. ☐ priority document(s) identified in Box No VI as item(s): 5. ☒ fee calculation sheet 6. ☐ separate indications concerning deposited microorganisms 7. ☐ nucleotide and/or amino acid sequence listing (diskette) 8. ☒ other (specify): Request refund Letter / Copy European Search Report.	
Figure No. of the drawings (if any) should accompany the abstract when it is published.			
Box No. IX SIGNATURE OF APPLICANT OR AGENT			
Next to each signature, indicate the name of the person signing and the capacity in which the person signs (if such capacity is not obvious from reading the request)			
 J. van Wezenbeek			

For receiving Office use only	
1. Date of actual receipt of the purported international application:	2. Drawings: ☐ received ☐ not received:
3. Corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application:	
4. Date of timely receipt of the required corrections under PCT Article 11(2):	
5. International Searching Authority specified by the applicant: ISA/	6. ☐ Transmittal of search copy delayed until search fee is paid

For International Bureau use only	
Date of receipt of the record copy by the International Bureau:	

44 ~~7X~~

PCT

FEE CALCULATION SHEET

For receiving Office use only

Annex to the Request

International application No.

Applicant's or agent's
file reference **2001.656 WO**

Date stamp of the receiving Office

Applicant
Akzo Nobel N.V.

CALCULATION OF PRESCRIBED FEES

1. TRANSMITTAL FEE..... **EUR 100,=** **T**

2. SEARCH FEE..... **EUR 945,=** **S**

International search to be carried out by **EPO**
(If two or more International Searching Authorities are competent in relation to the international application, indicate the name of the Authority which is chosen to carry out the international search.)

3. INTERNATIONAL FEE

Basic Fee
The international application contains **65** sheets.
first 30 sheets..... **EUR 444,=** **b₁**

35 **EUR 10,=** **EUR 350,=** **b₂**
remaining sheets additional amount

Add amounts entered at b₁ and b₂ and enter total at B..... **EUR 794,=** **B**

Designation Fees
The international application contains **58** designations

number of designation fees payable (maximum 3) amount of designation fee **EUR 480,=** **D**

Add amounts entered at B and D and enter total at I..... **EUR 1274,=** **I**
(Applicants from certain States are entitled to a reduction of 75% of the international fee. Where the applicant is (or all applicants are) so entitled, the total to be entered at I is 25% of the sum of the amounts entered at B and D.)

4. FEE FOR PRIORITY DOCUMENT..... **EUR 30,=** **P**

5. TOTAL FEES PAYABLE
Add amounts entered at T, S, I and P,
and enter total in the TOTAL box..... **EUR 2349,=**

TOTAL

☐ The designation fee is not paid at this time.

MODE OF PAYMENT

☒ authorization to charge deposit account (see below) ☐ bank draft ☐ coupons
☐ cheque ☐ cash ☐ other (specify):
☐ postal money order ☐ revenue stamps

DEPOSIT ACCOUNT AUTHORIZATION (this mode of payment may not be available at all receiving Offices)

The RO **EPO** ☒ is hereby authorized to charge the total fees indicated above to my deposit account.

☒ is hereby authorized to charge any deficiency or credit any overpayment in the total fees indicated above to my deposit account.

☐ is hereby authorized to charge the fee for preparation and transmittal of the priority document to the International Bureau of WIPO to my deposit account.

2809 0081

24/06/2002

P van Wazerbeek

Deposit Account Number

Date (day/month/year)

Signature **P van Wazerbeek**

Form PCT/RO/101 (Annex) (January 1996; reprint January 1998)

See Notes to the fee calculation sheet

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

IP/EA _____

CHAPTER II

PCT

DEMAND

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

For International Preliminary Examining Authority use only

Identification of IP/EA	Date of receipt of DEMAND
-------------------------	---------------------------

Box No. I IDENTIFICATION OF THE INTERNATIONAL APPLICATION		Applicant's or agent's file reference 2001.656 WO	
International application No. PCT/EP02/07053	International filing date (day/month/year) 25-06-2002	(Earliest) Priority date (day/month/year) 02-07-2001	
Title of invention "TETRAHYDROQUINOLINE DERIVATIVES"			
Box No. II APPLICANT(S)			
Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.) Akzo Nobel N.V. Velperweg 76 6824 RM ARNHEM The Netherlands		Telephone No.: 0412-666380	
		Facsimile No.: 0412-650392	
		Teleprinter No.:	
State (i.e. country) of nationality: NL		State (i.e. country) of residence: NL	
Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.) VAN STRATEN Nicole, Corine, Renée, N.V. Organon Postbus 20 5340 BH OSS The Netherlands			
State (i.e. country) of nationality: NL		State (i.e. country) of residence: NL	
Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.) VAN SOMEREN Rudolf, Gijsbertus N.V. Organon Postbus 20 5340 BH OSS The Netherlands			
State (i.e. country) of nationality: NL		State (i.e. country) of residence: NL	
☒ Further applicants are indicated on a continuation sheet.			

Sheet No. 2.....

International application No.
PCT/EP02/07053

Continuation of Box No. II APPLICANT(S)

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

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

SCHULZ
Jurgen
c/o: Organon Laboratories Ltd.
New Edinburgh Road
Newhouse Lanarkshire
ML1 5SH Scotland
United Kingdom

State (i.e. country) of nationality: **DE**

State (i.e. country) of residence: **GB**

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

State (i.e. country) of nationality:

State (i.e. country) of residence:

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

State (i.e. country) of nationality:

State (i.e. country) of residence:

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

State (i.e. country) of nationality:

State (i.e. country) of residence:



Further applicants are indicated on another continuation sheet.

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

The following person is ☒ agent ☐ common representative
and ☒ has been appointed earlier and represents the applicant(s) also for international preliminary examination.
☐ is hereby appointed and any earlier appointment of (an) agent(s)/common representative is hereby revoked.
☐ is hereby appointed, specifically for the procedure before the International Preliminary Examining Authority, in addition to the agent(s)/common representative appointed earlier.

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

P.M.G.F. van Wezenbeek
P.O. Box 20
5340 BH Oss
The Netherlands

Telephone No.:

0412-666219

Facsimile No.:

0412-650592

Teleprinter No.:

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

Box No. IV STATEMENT CONCERNING AMENDMENTS

The applicant wishes the international Preliminary Examining Authority*

(i) ☒ to start the international preliminary examination on the basis of the international application as originally filed.

(ii) ☐ to take into account the amendments under Article 34 of

☐ the description (amendments attached).

☐ the claims (amendments attached).

☐ the drawings (amendments attached).

(iii) ☐ to take into account any amendments of the claims under Article 19 filed with the International Bureau (a copy is attached).

(iv) ☐ to disregard any amendments of the claims made under Article 19 and to consider them as reversed.

(v) ☐ to postpone the start of the international preliminary examination until the expiration of 20 months from the priority date unless that Authority receives a copy of any amendments made under Article 19 or a notice from the applicant that he does not wish to make such amendments (Rule 69.1(d)). (This check-box may be marked only where the time limit under Article 19 has not yet expired.)

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

Box No. V ELECTION OF STATES

☒ The applicant hereby elects all eligible States (that is, all States which have been designated and which are bound by Chapter II of the PCT) except

(If the applicant does not wish to elect certain eligible States, the name(s) or country code(s) of those States must be indicated above.)

XP

Sheet No. A.

International application No.
PCT/EP02/07053

Box No. VI CHECK LIST

The demand is accompanied by the following documents for the purposes of international preliminary examination:

1. amendments under Article 34

description : sheets
claims : sheets
drawings : sheets

2. letter accompanying amendments under Article 34

: sheets

3. copy of amendments under Article 19

: sheets

4. copy of statement under Article 19

: sheets

5. other (specify):

: sheets

For International Preliminary
Examining Authority use only

received	not received
☐	☐
☐	☐
☐	☐
☐	☐
☐	☐
☐	☐

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

1. ☐ separate signed power of attorney

2. ☐ copy of general power of attorney

3. ☐ statement explaining lack of signature

4. ☒ fee calculation sheet

5. ☐ other (specify):

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

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

P.M.G.F. van Wezenbeek

For International Preliminary Examining Authority use only

1. Date of actual receipt of DEMAND:

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

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

☐ The applicant has been informed accordingly.

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

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

For International Bureau use only

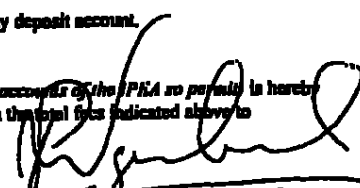
Demand received from IPDA on:

PCT

CHAPTER II

FEE CALCULATION SHEET

Annex to the Demand for international preliminary examination

International application No. PCT/EP02/07053 Applicant's or agent's file reference 2001.656 WO Applicant Akzo Nobel N.V. Calculation of prescribed fees 1. Preliminary examination fee..... EUR 1530,- P 2. Handling fee (<i>Applicants from certain States are entitled to a reduction of 75% of the handling fee. (Where the applicant is (for all applicants are) so entitled, the amount to be entered on H is 25% of the handling fee.)</i>)..... EUR 159,- H 3. Total of prescribed fees Add the amounts entered at P and H and enter total in the TOTAL box..... EUR 1689,- TOTAL Mode of Payment <table style="width: 100%;"> <tr> <td>☒ authorization to charge deposit account with the IPPEA (see below)</td> <td>☐ cash</td> </tr> <tr> <td>☐ cheque</td> <td>☐ revenue stamps</td> </tr> <tr> <td>☐ postal money order</td> <td>☐ coupons</td> </tr> <tr> <td>☐ bank draft</td> <td>☐ other (specify):</td> </tr> </table> Deposit Account Authorization (<i>this mode of payment may not be available at all IPPEAs</i>) The IPPEA / EPO ☒ is hereby authorized to charge the total fees indicated above to my deposit account. ☒ (<i>this check-box may be marked only if the conditions for deposit accounts of the IPPEA so permits</i>) is hereby authorized to charge any deficiency or credit any overpayment in the total fees indicated above to my deposit account. 2802.0012 Deposit Account Number 20-11-2002 Date (day/month/year)  P.M.G.F. van Wexenbeek Signature	☒ authorization to charge deposit account with the IPPEA (see below)	☐ cash	☐ cheque	☐ revenue stamps	☐ postal money order	☐ coupons	☐ bank draft	☐ other (specify):	For International Preliminary Examining Authority use only Date stamp of the IPPEA
☒ authorization to charge deposit account with the IPPEA (see below)	☐ cash								
☐ cheque	☐ revenue stamps								
☐ postal money order	☐ coupons								
☐ bank draft	☐ other (specify):								

PATENT COOPERATION TREATY

70 OKT. 2002

From the INTERNATIONAL SEARCHING AUTHORITY

PCT

NOTIFICATION OF TRANSMITTAL OF
THE INTERNATIONAL SEARCH REPORT
OR THE DECLARATION

(PCT Rule 44.1)

To: VAN WEZENBEEK, P.M.G.F. P.O.Box 20 5340 BH Oss NETHERLANDS		Behandeld door Adm. opgenomen Bericht d.d. aan: Bureau d.d. Algemeen	Date of mailing (day/month/year) 07/10/2002
Applicant's or agent's file reference 2001.656 WO		FOR FURTHER ACTION See paragraphs 1 and 4 below	
International application No. PCT/EP 02/07053		International filing date (day/month/year) 25/06/2002	
Applicant AKZO NOBEL N.V.			

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

Filing of amendments and statement under Article 19:

The applicant is entitled, if he so wishes, to amend the claims of the International Application (see Rule 46):

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

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

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

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

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

☐ the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.☐ no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

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

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

Within 19 months from the priority date, a demand for International preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase until 30 months from the priority date (in some Offices even later).

Within 20 months from the priority date, the applicant must perform the prescribed acts for entry into the national phase before all designated Offices which have not been elected in the demand or in a later election within 19 months from the priority date or could not be elected because they are not bound by Chapter II.

Name and mailing address of the International Searching Authority  European Patent Office, P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Authorized officer Véronique Baillou
--	---

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

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

INSTRUCTIONS CONCERNING AMENDMENTS UNDER ARTICLE 19

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

What parts of the international application may be amended?

Under Article 19, only the claims may be amended.

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

Upon entry into the national phase, all parts of the international application may be amended under Article 28 or, where applicable, Article 41.

When?

Within 2 months from the date of transmittal of the international search report or 18 months from the priority date, whichever time limit expires later. It should be noted, however, that the amendments will be considered as having been received on time if they are received by the International Bureau after the expiration of the applicable time limit but before the completion of the technical preparations for international publication (Rule 46.1).

Where not to file the amendments?

The amendments may only be filed with the International Bureau and not with the receiving Office or the International Searching Authority (Rule 46.2).

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

How?

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

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

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

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

What documents must/may accompany the amendments?

Letter (Section 205(b)):

The amendments must be submitted with a letter.

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

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

✓
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NOTES TO FORM PCT/ISA/220 (continued)

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

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

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

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

"Statement under article 19(1)" (Rule 48.4)

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

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

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

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

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

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

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

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

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

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

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

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference 2001.656 WO	FOR FURTHER ACTION see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, Item 5 below.	
International application No. PCT/EP 02/07053	International filing date (day/month/year) 25/06/2002	(Earliest) Priority Date (day/month/year) 02/07/2001
Applicant AKZO NOBEL - N.V.		

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

This International Search Report consists of a total of 5 sheets.



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

1. Basis of the report

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



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

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



contained in the international application in written form.



filed together with the international application in computer readable form.



furnished subsequently to this Authority in written form.



furnished subsequently to this Authority in computer readable form.



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



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

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

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

4. With regard to the title,



the text is approved as submitted by the applicant.



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

5. With regard to the abstract,



the text is approved as submitted by the applicant.



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

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



as suggested by the applicant.



because the applicant failed to suggest a figure.



because this figure better characterizes the invention.



None of the figures.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 02/07053

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61K31/47 C07D215/38 C07D401/12 C07D405/14 C07D417/12
C07D215/48 C07D215/20 C07D215/08 C07D413/12 A61K31/4709
A61P5/06

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D A61K

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

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

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	CHEMICAL ABSTRACTS, vol. 79, no. 9, 3 September 1973 (1973-09-03) Columbus, Ohio, US; abstract no. 53152, LUGOVIK, B. A. ET AL: "Structure of compounds obtained from the interaction of 1,2-dihydroquinolines with alkylbenzenes" XP002185090 cited in the application abstract & TR. OMSK. SEL'SKOKHOZ. INST. (1971), 82, 107-10, --- -/--	2-9



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

* Special categories of cited documents:

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

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

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

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

"Z" document member of the same patent family

Date of the actual completion of the international search

30 September 2002

Date of mailing of the international search report

07/10/2002

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fac. (+31-70) 340-3016

Authorized officer

Scruton-Evans, I

INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 02/07053

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	CHEMICAL ABSTRACTS, vol. 77, no. 25, 18 December 1972 (1972-12-18) Columbus, Ohio, US; abstract no. 164415, LUGOVIK, B. A. ET AL: "Reaction of 1,2-dihydroquinolines with benzene and halobenzenes" XP002185091 cited in the application abstract & NAUCH. TR., OMSK. SEL.-KHOZ. INST: (1971), NO. 82, 103-6 FROM: REF. ZH., KHIM. 1972, ABSTR. NO. 1ZH311, ---	2-9
X	CHEMICAL ABSTRACTS, vol. 105, no. 7, 18 August 1986 (1986-08-18) Columbus, Ohio, US; abstract no. 56990, SHMYREVA, ZH. V. ET AL: "Modification of anion exchanger Duolite A 368 PR for the covalent immobilization of glucoamylase" XP002185092 cited in the application RN 91147-49-8 abstract & TEOR. PRAKT. SORBTSIONNYKH PROTSESSOV (1985), 17, 39-42, ---	2-9
X	DATABASE CHEMCATS 'Online! CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; XP002185093 ORDER NUMBER 4723-A1028/0048172, 781-A1427/0063514, 28020-A0839/0039328 & "AMBINTER SCREENING COLLECTION" 31 May 2001 (2001-05-31), AMBINTER, 46 QUAI LOUIS BLERiot, PARIS, F-75016, FRANCE ---	2-7
X	DATABASE CHEMCATS 'Online! CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; XP002185095 ORDER NUMBER VIT0003069 & "VITAS-M SCREENING COLLECTION" 22 March 2001 (2001-03-22), VITAS-, CENTER OF MOLECULAR MEDICINE, ROOM 208, LABORATORY BUILDING B, MOSCOW, 1192829 RUSSIA ---	2-7
A	US 6 200 963 B1 (KAO WENLING ET AL) 13 March 2001 (2001-03-13) the whole document ---	1-9

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 02/07053

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 00 08015 A (APPLIED RESEARCH SYSTEMS ;BUCKLER DAVID (US); EL TAYER NABIL (US);) 17 February 2000 (2000-02-17) the whole document -----	1-9

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 02/07053

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 6200963	B1	13-03-2001	NONE
WO 0008015	A	17-02-2000	AU 5393199 A 28-02-2000
			EP 1102763 A2 30-05-2001
			JP 2002522433 T 23-07-2002
			WO 0008015 A2 17-02-2000
			US 6235755 B1 22-05-2001
			US 6423723 B1 23-07-2002

PATENT COOPERATION TREATY

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16 SEP. 2003

Search. chd. acc. *P. L.*

Art. 1. app. nom. *h.*

Script. d.d. *h.*

Beantw. d.d. *h.*

Afgegeven *P. L.*

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Rule 71.1)

To:

VAN WEZENBEEK, P.M.G.F.
P.O.Box 20
5340 BH Oss
PAYS-BAS

Date of mailing
(day/month/year) 12.09.2003

Applicant's or agent's file reference 2001.856 WO		IMPORTANT NOTIFICATION	
International application No. PCT/EP02/07053	International filing date (day/month/year) 25.06.2002	Priority date (day/month/year) 02.07.2001	
Applicant AKZO NOBEL N.V.			

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

4. REMINDER

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

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

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

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

Name and mailing address of the international preliminary examining authority:  European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tlx 523858 epmu d Fax: +49 89 2399 - 4485	Authorized Officer Ambroa, J.R. Tel. +49 89 2399-8012 
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PATENT COOPERATION TREATY

PCT

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

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Applicant's or agent's file reference 2001.656 WO	FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/PEAA/16)	
International application No. PCT/EP0207053	International filing date (day/month/year) 25.06.2002	Priority date (day/month/year) 02.07.2001
International Patent Classification (IPC) or both national classification and IPC A61K31/47		
Applicant AKZO NOBEL N.V.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36. 2. This REPORT consists of a total of 5 sheets, including this cover sheet. ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT). These annexes consist of a total of 5 sheets.
3. This report contains indications relating to the following items: I ☒ Basis of the opinion II ☐ Priority III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability IV ☐ Lack of unity of invention V ☒ Reasoned statement under Rule 66.2(a)(II) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement VI ☐ Certain documents cited VII ☐ Certain defects in the international application VIII ☐ Certain observations on the international application

Date of submission of the demand 22.11.2002	Date of completion of this report 12.09.2003
Name and mailing address of the international preliminary examining authority:  European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tlx 523656 epmu d Fax +49 89 2399 - 4485	Authorized Officer Scruton-Evans, I Telephone No. +49 89 2399-8272 

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. **PCT/EP02/07053**

I. Basis of the report

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

Description, Pages

1-57 as originally filed

Claims, Numbers

1-9 as amended (together with any statement) under Art. 19 PCT

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

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

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

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

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

4. The amendments have resulted in the cancellation of:

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

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

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

6. Additional observations, if necessary:

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**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. **PCT/EP02/07053**

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

1. Statement

Novelty (N)	Yes: Claims	1,3-4,7-9
	No: Claims	2,5,6
Inventive step (IS)	Yes: Claims	
	No: Claims	1-9
Industrial applicability (IA)	Yes: Claims	1-9
	No: Claims	

2. Citations and explanations

see separate sheet

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Re Item V

Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

The following documents cited in the Search Report are referred to in this communication;

- D1: CHEMICAL ABSTRACTS, vol. 79, no. 9, 3 September 1973 (1973-09-03)
Columbus, Ohio, US; abstract no. 53152, LUGOVIK, B. A. ET AL: 'Structure of compounds obtained from the interaction of 1,2-dihydroquinolines with alkylbenzenes' XP002185090 cited in the application & TR. OMSK. SEL'SKOKHOZ. INST. (1971), 82, 107-10,
- D2: CHEMICAL ABSTRACTS, vol. 77, no. 25, 18 December 1972 (1972-12-18)
Columbus, Ohio, US; abstract no. 164415, LUGOVIK, B. A. ET AL: 'Reaction of 1,2-dihydroquinolines with benzene and halobenzenes' XP002185091 cited in the application & NAUCH. TR., OMSK. SEL.-KHOZ. INST. (1971), NO. 82, 103-6 FROM: REF. ZH., KHIM. 1972, ABSTR. NO. 1ZH311,
- D3: CHEMICAL ABSTRACTS, vol. 105, no. 7, 18 August 1986 (1986-08-18)
Columbus, Ohio, US; abstract no. 56990, SHMYREVA, ZH. V. ET AL: 'Modification of anion exchanger Duolite A 368 PR for the covalent immobilization of glucoamylase' XP002185092 cited in the application & TEOR. PRAKT. SORBTSIONNYKH PROTSESSOV (1985), 17, 39-42,
- D4: DATABASE CHEMCATS [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; XP002185093 & 'AMBINTER SCREENING COLLECTION' 31 May 2001 (2001-05-31) , AMBINTER, 46 QUAI LOUIS BLERiot, PARIS, F-75016, FRANCE
- D5: DATABASE CHEMCATS [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; XP002185095 & 'VITAS-M SCREENING COLLECTION' 22 March 2001 (2001-03-22) , VITAS-, CENTER OF MOLECULAR MEDICINE, ROOM 208, LABORATORY BUILDING B, MOSCOW, 1192829 RUSSIA
- D6: US-B1-6 200 963 (KAO WENLING ET AL) 13 March 2001 (2001-03-13)
- D7: WO 00 08015 A (APPLIED RESEARCH SYSTEMS ;BUCKLER DAVID (US); EL TAYER NABIL (US);) 17 February 2000 (2000-02-17)

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/EP02/07053

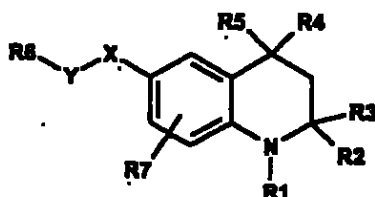
64
63

With regard to the requirement for novelty (Article 33(2) of the PCT); the compound disclosed in D3 (RN 91147-49-8) is prejudicial to the novelty of claims 2,5 and 6, and the compound with RN 339273-93-7 in D4 is also prejudicial to the novelty of the claims 2,5 and 6. The compound RN 332904-33-3 in D5 is also prejudicial to the novelty of claims 2,5 and 6. The other compounds specifically disclosed in the prior arts D1-D5 are excluded by proviso in the compound claim 2. Article 33(2) of the PCT is thus not satisfied for claims 2 5 and 6.

With regard to the requirement for inventive step (Article 33(3) of the PCT), the compounds of the present application are described as having FSH modulatory activity. The documents D1-D5 do not disclose a pharmaceutical activity for the compounds disclosed therein, and thus D6 and D7, which describe the same qualitative activity are to be considered to represent the closest prior art. The man skilled in the art, faced with the problem of providing further novel compounds with FSH modulatory activity would have had no incentive from the prior art to actually prepare the compounds of the present application, expecting them to have this activity, and thus Article 33(3) can in principle be considered to have been satisfied for the examples prepared and a reasonable generalisation thereof, but given the wide scope of the claim, the Applicant is asked to state on which basis the extrapolation to the claimed scope over the examples was made (bioequivalency etc), as the terms heteroaryl for example for the definitions of a substituent on R6 or for R6 itself would allow compounds that could substantially differ from those prepared and the core structure.

Claims

1. A tetrahydroquinoline derivative compound according to Formula 1,



Formula I

or a pharmaceutically acceptable salt thereof, wherein

R^1 is formyl, (1-6C)alkylcarbonyl or (1-6C)alkylsulfonyl;

R^2 and R^3 are H or (1-4C)alkyl;

R^4 is phenyl, optionally substituted with one or more substituents selected from the group hydroxy, amino, halogen, nitro, trifluoromethyl, cyano, (1-4C)alkyl, (2-4C)alkenyl, (2-4C)alkynyl, (1-4C)alkoxy, (1-4C)(di)alkylamino.

R^5 is (1-4C)alkyl;

Y-X is C(O)-O, S(O)₂-O, NHC(O)-O, NHC(S)-O, OC(O)-O, bond-O, C(O)-NH, S(O)₂-NH, NHC(O)-NH, NHC(S)-NH, OC(O)-NH, bond-NH, NH-C(O), O-C(O), NH-S(O)₂, or O-S(O)₂ or X-Y is a bond;

R^6 is H, except for Y-X is a bond, trifluoromethyl, (1-6C)alkyl, 1- or 2-adamantyl, (1-4C)alkyl, (2-6C)alkenyl, (2-6C)alkynyl, (3-9C)heteroaryl, (3-6C)cycloalkyl, (2-6C)heterocycloalkyl, (1-4C)alkylthio(1-4C)alkyl, (6-10C)aryl(1-4C)alkyl, (3-9C)heteroaryl(1-4C)alkyl, (3-6C)cycloalkyl(1-4C)alkyl, (2-6C)heterocycloalkyl(1-4C)alkyl, R^8, R^9 -aminocarbonyl(1-4C)alkyl, R^8, R^9 -amino(1-4C)alkyl, R^8 -oxycarbonyl(1-4C)alkyl, R^8 -oxy(1-4C)alkyl, R^8 -carbonyl(1-4C)alkyl or (6-10C)aryl, [whereas if (6-10C)aryl is phenyl, phenyl may be optionally substituted with hydroxy, amino, halogen, nitro, trifluoromethyl, cyano, (1-4C)alkyl, (2-4C)alkenyl, (2-4C)alkynyl, (1-4C)alkoxy, (1-4C)(di)alkylamino, (6-10C)aryl, (6-10C)aryloxy, (6-10C)aryl(1-4C)alkoxy, (3-9C)heteroaryl, (3-9C)heteroaryloxy, (3-9C)heteroaryl(1-4C)alkoxy, (1-4C)alkylcarbonylamino, (1-4C)alkylcarbonyloxy, (3-6C)cycloalkylcarbonyloxy,

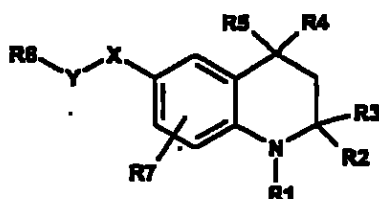
(1-4C)alkoxycarbonyl(1-4C)alkylcarbonyloxy, (1-4C)alkoxy(1-4C)alkylcarbonyloxy, (6-10C)arylcarbonyloxy, (3-9C)heteroarylcarbonyloxy, (1-4C)alkylsulfonyloxy, (6-10C)arylsulfonyloxy, (3-9C)heteroarylsulfonyloxy, (1-4C)(di)alkylcarbamoyl, (6-10C)(di)arylcarbamoyl, (2-6C)heterocycloalkylcarbamoyl, (6-10C)(di)arylamino, (3-6C)cycloalkyl, (3-6C)cycloalkyl(1-4C)alkyl, (2-6C)heterocycloalkyl or (2-6)heterocycloalkyl(1-4C)alkyl,

and whereas all aryl and heteroaryl groups within R^6 optionally may be substituted with one or more substituents selected from hydroxy, amino, halogen, nitro, trifluoromethyl, cyano, (1-4C)alkyl, (2-4C)alkenyl, (2-4C)alkynyl, (1-4C)alkoxy or (1-4C)(di)alkylamino,

R^7 is H, (1-4C)alkyl, (1-4C)alkoxy, halogen, trifluoromethyl, cyano, nitro, hydroxyl; and

R^8 and/or R^9 is H, (1-4C)alkyl, (2-4C)alkenyl, (2-4C)alkynyl, (6-10C)aryl, (3-9C)heteroaryl, (6-10C)aryl(1-4C)alkyl, (3-9C)heteroaryl(1-4C)alkyl, (3-6C)cycloalkyl(1-4C)alkyl, (2-6C)heterocycloalkyl(1-4C)alkyl, (1-4C)(di)alkylamino(1-4C)alkyl, (1-4C)alkoxy(1-4C)alkyl, (1-4C)alkylthio(1-4C)alkyl, (1-4C)alkylcarbonylamino(1-4C)alkyl, (1-4C)alkoxycarbonyl(1-4C)alkyl, (1-4C)alkoxycarbonylamino(1-4C)alkyl, (3-6C)cycloalkyl, (2-6C)heterocycloalkyl or R^8 and R^9 may be joined in a (2-6C)heterocycloalkyl ring for use in therapy.

2. A tetrahydroquinoline derivative compound according to Formula 1,



Formula I

or a pharmaceutically acceptable salt thereof, wherein

R^1 is formyl, (1-6C)alkylcarbonyl or (1-6C)alkylsulfonyl;

R^2 and R^3 are H or (1-4C)alkyl;

R^4 is phenyl, optionally substituted with one or more substituents selected from

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the group hydroxy, amino, halogen, nitro, trifluoromethyl, cyano, (1-4C)alkyl, (2-4C)alkenyl, (2-4C)alkynyl, (1-4C)alkoxy, (1-4C)(di)alkylamino
 $\underline{R^5}$ is (1-4C)alkyl;

Y-X is C(O)-O, S(O)₂-O, NHC(O)-O, NHC(S)-O, OC(O)-O, bond-O, C(O)-NH, S(O)₂-NH, NHC(O)-NH, NHC(S)-NH, OC(O)-NH, bond-NH, NH-C(O), O-C(O), NH-S(O)₂, or O-S(O)₂ or X-Y is a bond;

R^6 is H, except for Y-X is a bond, trifluoromethyl, (1-6C)alkyl, 1- or 2-adamantyl(1-4C)alkyl, (2-6C)alkenyl, (2-6C)alkynyl, (3-9C)heteroaryl, (3-6C)cycloalkyl, (2-6C)heterocycloalkyl, (1-4C)alkylthio(1-4C)alkyl, (6-10C)aryl(1-4C)alkyl, (3-9C)heteroaryl(1-4C)alkyl, (3-6C)cycloalkyl(1-4C)alkyl, (2-6C)heterocycloalkyl(1-4C)alkyl, R^8, R^9 -aminocarbonyl(1-4C)alkyl, R^8, R^9 -amino(1-4C)alkyl, R^8 -oxycarbonyl(1-4C)alkyl, R^8 -oxy(1-4C)alkyl, R^8 -carbonyl(1-4C)alkyl or (6-10C)aryl whereas if (6-10C)aryl is phenyl, phenyl may be optionally substituted with hydroxy, amino, halogen, nitro, trifluoromethyl, cyano, (1-4C)alkyl, (2-4C)alkenyl, (2-4C)alkynyl, (1-4C)alkoxy, (1-4C)(di)alkylamino, (6-10C)aryl, (6-10C)aryloxy, (6-10C)aryl(1-4C)alkoxy, (3-9C)heteroaryl, (3-9C)heteroaryloxy, (3-9C)heteroaryl(1-4C)alkoxy, (1-4C)alkylcarbonylamino, (1-4C)alkylcarbonyloxy, (3-6C)cycloalkylcarbonyloxy, (1-4C)alkoxycarbonyl(1-4C)alkylcarbonyloxy, (1-4C)alkoxy(1-4C)alkylcarbonyloxy, (6-10C)arylcarbonyloxy, (3-9C)heteroarylcarbonyloxy, (1-4C)alkylsulfonyloxy, (6-10C)arylsulfonyloxy, (3-9C)heteroarylsulfonyloxy, (1-4C)(di)alkylcarbamoyl, (6-10C)(di)arylcabamoyl, (2-6C)heterocycloalkylcarbamoyl, (6-10C)(di)arylamino, (3-6C)cycloalkyl, (3-6C)cycloalkyl(1-4C)alkyl, (2-6C)heterocycloalkyl or (2-6)heterocycloalkyl(1-4C)alkyl,

and whereas all aryl and heteroaryl groups within R^6 optionally may be substituted with one or more substituents selected from hydroxy, amino, halogen, nitro, trifluoromethyl, cyano, (1-4C)alkyl, (2-4C)alkenyl, (2-4C)alkynyl, (1-4C)alkoxy or (1-4C)(di)alkylamino,

R^7 is H, (1-4C)alkyl, (1-4C)alkoxy, halogen, trifluoromethyl, cyano, nitro, hydroxyl; and

R^8 and/or R^9 is H, (1-4C)alkyl, (2-4C)alkenyl, (2-4C)alkynyl, (6-10C)aryl, (3-

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- 9C)heteroaryl, (6-10C)aryl(1-4C)alkyl, (3-9C)heteroaryl(1-4C)alkyl, (3-6C)cycloalkyl(1-4C)alkyl, (2-6C)heterocycloalkyl(1-4C)alkyl, (1-4C)(di)alkylamino(1-4C)alkyl, (1-4C)alkoxy(1-4C)alkyl, (1-4C)alkylthio(1-4C)alkyl, (1-4C)alkylcarbonylamino(1-4C)alkyl, (1-4C)alkoxycarbonyl(1-4C)alkyl, (1-4C)alkoxycarbonylamino(1-4C)alkyl, (3-6C)cycloalkyl, (2-6C)heterocycloalkyl, or R⁸ and R⁹ may be joined in a (2-6C)heterocycloalkyl ring with the proviso that the derivative is not 1-acetyl-6-benzoylamino-4-(4-methylphenyl)-1,2,3,4-tetrahydro-2,2,4-trimethylquinoline, 1-acetyl-4-phenyl-1,2,3,4-tetrahydro-2,2,4,6-tetramethylquinoline, 1-acetyl-4-phenyl-1,2,3,4-tetrahydro-2,2,4,6,8-pentamethylquinoline, 1-acetyl-6-methoxy-4-phenyl-1,2,3,4-tetrahydro-2,2,4-trimethylquinoline, 1-acetyl-6-trifluoroacetylamino-4-(4-methylphenyl)-1,2,3,4-tetrahydro-2,2,4-trimethylquinoline, 1-acetyl-6-trifluoroacetylamino-4-phenyl-1,2,3,4-tetrahydro-2,2,4-trimethylquinoline, 1-acetyl-4-(4-chlorophenyl)-1,2,3,4-tetrahydro-2,2,4,6-tetramethylquinoline and 1-acetyl-4-(4-bromophenyl)-1,2,3,4-tetrahydro-2,2,4,6-tetramethylquinoline.
3. The tetrahydroquinoline derivative compound of claim 2 wherein Y-X is C(O)-NH, OC(O)-NH, or C(O)-O.
 4. The tetrahydroquinoline derivative compound of claims 2 or 3 wherein Y-X is C(O)-NH.
 - 20 5. The tetrahydroquinoline derivative compound of claims 2-4 wherein R¹ is (1-4C)alkylcarbonyl.
 6. The tetrahydroquinoline derivative compound of claims 2-5 wherein R², R³ and R⁵ are independently (1-4C)alkyl.
 7. The tetrahydroquinoline derivative compound of claims 2-6 wherein R⁶ is (6-10C)aryl, (3-9C)heteroaryl, (6-10C)aryl(1-4C)alkyl or (3-9C)heteroaryl(1-4C)alkyl whereas if (6-10C)aryl is phenyl, phenyl may be optionally substituted with hydroxy, amino, halogen, nitro, trifluoromethyl, cyano, (1-4C)alkyl, (2-4C)alkenyl, (2-4C)alkynyl, (1-4C)alkoxy, (1-4C)(di)alkylamino, (6-10C)aryl, (6-10C)aryloxy, (6-10C)aryl(1-4C)alkoxy, (3-9C)heteroaryl, (3-9C)heteroaryloxy, (3-9C)heteroaryl(1-4C)alkoxy, (1-4C)alkylcarbonylamino, (1-4C)alkylcarbonyloxy, (3-6C)cycloalkylcarbonyloxy, (1-4C)alkoxycarbonyl(1-4C)alkylcarbonyloxy, (1-4C)alkoxy(1-4C)alkylcarbonyloxy, (6-

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10C)arylcarbonyloxy, (3-9C)heteroarylcarbonyloxy, (1-4C)alkylsulfonyloxy, (6-
10C)arylsulfonyloxy, (3-9C)heteroarylsulfonyloxy, (1-4C)(di)alkylcarbamoyl;
(6-10C)(di)arylcarbamoyl, (2-6C)heterocycloalkylcarbamoyl, (6-
10C)(di)arylamino, (3-6C)cycloalkyl, (3-6C)cycloalkyl(1-4C)alkyl, (2-
5 6C)heterocycloalkyl or (2-6)heterocycloalkyl(1-4C)alkyl,
and whereas all aryl and heteroaryl groups within R⁶ optionally may be
substituted with one or more substituents selected from hydroxy, amino, halogen,
nitro, trifluoromethyl, cyano, (1-4C)alkyl, (2-4C)alkenyl, (2-4C)alkynyl, (1-
4C)alkoxy or (1-4C)(di)alkylamino.

- 10 8. A pharmaceutical composition comprising the compound of any one of claims 2-
7 and pharmaceutically suitable auxiliaries.
9. Use of the compound of any one of claims 2-8 or a pharmaceutically acceptable
salt or solvate thereof for the manufacture of a medicament for the control of
fertility.

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Traducción

TRATADO DE COOPERACIÓN DE PATENTES
PCT
INFORME DE EXAMEN PRELIMINAR INTERNACIONAL
(Artículo 36 y Regla 70 del PCT)

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Referencia del expediente del agente o solicitante 2001.656 WO	PARA ACTUACIONES ADICIONALES	Ver notificación de Transmisión del Reporte de Examen Preliminar (Formato PCT/IPEA416)
Solicitud Internacional No. PCT/EP02/07053	Fecha de presentación internacional (día/mes/año) 25.08.2002	Fecha de prioridad (día/mes/año) 02.07.2001
Clasificación Internacional de Patentes (IPC) o clasificación nacional e IPC A61K 31/47		
Solicitante AKZO NOBEL N.V.		

1. Este informe de examen preliminar internacional ha sido preparado por esta Administración encargada del Examen Preliminar Internacional y se envía al solicitante en concordancia con el artículo 36.

2. Este INFORME consta de una total de 5 hojas, incluyendo la portada

☒ Este informe también se acompaña de ANEXOS, esto es documentos de la descripción, reivindicaciones y/o dibujos que han sido corregidos y que son la base de este Informe y/o documentos que contienen rectificaciones realizadas ante esta Administración (Ver Regla 70.16 y Sección 607 de las Instrucciones Administrativas según el PCT)

Estos anexos constan de un total de 5 hojas.

3. Este informe contiene indicaciones relativas a los siguientes aspectos:

I ☒ Fundamentos del Informe

II ☐ Prioridad

III ☐ No se establece concepto relativo a la novedad, nivel inventivo y aplicación industrial

IV ☐ Carencia de unidad de la invención

V ☒ Declaración razonada según el artículo 35(2), en relación con la novedad, nivel inventivo o aplicación industrial; citaciones y explicaciones que soportan dicha declaración

VI ☐ Ciertos documentos citados

VII ☐ Ciertos defectos de la solicitud internacional

VIII ☐ Ciertas observaciones respecto a la solicitud internacional

Fecha de presentación de la demanda 22.11.2002	Fecha de terminación de este reporte 12.09.2003
Nombre y dirección de correo de la autoridad encargada del examen preliminar Oficina de Patentes Europea D-80298 Munich Tel. +49 89 2399-0 Tx: 523656 epmu d	Funcionario Autorizado Scruton-Evans, I Teléfono No. +49 89 2399 - 8272

Formato PCT/IPEA/409 (portada) (julio 1998)

02/07

I. Base del Informe

1. Respecto a los elementos de la solicitud internacional: *(Las hojas de reemplazo que han sido entregadas a la Oficina receptora en respuesta a la invitación bajo el Artículo 14 se referirán en este informe como "originalmente presentadas" y no se anexan a este informe ya que ellas no contienen modificaciones (Regla 70.16 y 70.17).*

☐ La descripción:
páginas 1 - 57, como se presentaron originalmente

☐ Las reivindicaciones:
números 1 - 9, como se modificaron (junto con cualquier declaración) bajo el artículo 19 del PCT

2. Respecto al lenguaje, todos los elementos marcados anteriormente estuvieron disponibles o fueron enviados a la Administración en el lenguaje en que se presentó la solicitud internacional, a menos que se indique otra cosa en este punto.

Estos elementos estuvieron disponibles o fueron enviados a esta Administración en el siguiente lenguaje _____ el cual es:

- ☐ el lenguaje de la traducción enviada para propósitos de la búsqueda internacional (bajo Regla 23.1 (b)).
☐ el lenguaje de la publicación de la solicitud internacional (bajo Regla 48.3(b)).
☐ el lenguaje de la traducción entregada con propósitos del examen preliminar internacional (bajo Regla 55.2 y/o 55.3).

3. Respecto a cualquier secuencia de nucleótido y/o amino ácidos divulgada en la solicitud internacional, el examen preliminar internacional se llevó a cabo con base en el listado de secuencias:

- ☐ contenido en la solicitud internacional en forma escrita
☐ presentado junto con la solicitud internacional en forma legible por computador
☐ entregado posteriormente a esta Administración en forma legible por computador
☐ La declaración de que el listado de secuencias posteriormente entregado no va más allá de lo divulgado en la solicitud internacional originalmente presentada, ha sido entregada.
☐ La declaración de que la información grabada en la forma legible por computador es idéntica al listado de secuencias escrito que se ha entregado.

4. Las modificaciones han dado como resultado la cancelación de:

- ☐ la descripción, páginas _____,
☐ las reivindicaciones, Nos. _____,
☐ los dibujos, página _____.

5. ☐ Este reporte ha sido establecido como si (parte de) las modificaciones no se hubieran realizado, ya que éstas han sido consideradas como una ampliación de lo inicialmente divulgado como se indica en la Casilla Suplementaria (Regla 70.2(c)). *(Cualquier hoja de reemplazo que contenga dichas modificaciones deberá ser referida bajo el punto 1 y anexada a este informe.)*

6. Observaciones adicionales, si necesarias:

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V. Declaración motivada según el Artículo 35(2) en cuanto a la novedad, el nivel inventivo y la aplicación industrial; citas y explicaciones que apoyan esta declaración.

1. Declaración

Novedad (N)	Reivindicaciones	1, 3 - 4, 7 - 9	SI
	Reivindicaciones	2, 5, 6	NO
Nivel inventivo (NI)	Reivindicaciones		SI
	Reivindicaciones	1 - 9	NO
Aplicación Industrial (AI)	Reivindicaciones	1 - 9	SI
	Reivindicaciones		NO

2. Citas y explicaciones (Regla 70.7)

ver hoja deparada

Recuadro Suplementario

(Para ser usado cuando el espacio en alguno de los cuadros anteriores no es suficiente)

Continuación de:

Referente al punto V

Declaración motivada según el Artículo 35(2) en cuanto a la novedad, el nivel inventivo y la aplicación Industrial; citas y explicaciones que apoyan esta declaración

Se hace referencia en esta comunicación a los siguientes documentos citados en el Informe de Búsqueda;

- D1: CHEMICAL ABSTRACTS, vol. 79, no. 9, 3 de septiembre de 1973 (1973-09-03) Columbus, Ohio, US; resumen no. 53152, LUGOVIK, B. A. ET AL: 'Structure of compounds obtained from the interaction of 1, 2-dihydroquinolines with alkylbenzenes' XP002185090 citado en la solicitud & TR. OMSK. SEL'SKOKHOZ. INST. (1971), 82, 107-10,
- D2: CHEMICAL ABSTRACTS, vol. 77, no. 25, 18 de diciembre de 1972 (1972-12-18) Columbus, Ohio, US; resumen no. 164415, LUGOVIK, B.A. ET AL: 'Reaction of 1, 2-dihydroquinolines with benzene and halobenzenes' XP002185091 citado en la solicitud & NAUCH. TR., OMSK. SEL. -KHOZ. IST. (1971) NO. 82, 103-6 FROM: REF. ZH., KHIM.1972, ABSTR. NO. 1ZH311,
- D3: CHEMICAL ABSTRACTS, vol. 105, no. 7, 18 de agosto de 1986 (1986-08-18) Columbus, Ohio, US; resumen no. 56990, SHMYREVA, ZH. V. ET AL: 'Modification of anion exchanger Duolite A 368 PR for the covalent immobilization of glucoamylase' XP002185092 citado en la solicitud & TEOR. PRAKT. SIRBTSIONNYKH PROTSESSOV (1985), 17, 39- 42,
- D4: DATABASE CHEMCATS [Online] CHEMICAL ABSTRACTS SERVICE, Columbus, Ohio, US; XP002185093 & 'Ambinter Screening Collection' 31 de mayo de 2001 (2001-05-31), Ambinter, 46 Quai Louis Bleriot, Paris, F-75016, Francia
- D5: DATABASE CHEMCATS [Online] CHEMICAL ABSTRACTS SERVICE, Columbus, Ohio, US; XP002185095 & 'Vitas-M Screening Collection' 22 de marzo de 2001 (2001-03-22), Vitas-, Center of Molecular Medicine, Room 208, Laboratory Building B, Moscow, 1192829 Rusia
- D6: US-B1-6 200 963 (KAO WENLING ET AL) 13 de marzo 2001 (2001-03-13)
- D7: WO 00 08015 A (APPLIED RESEARCH SYSTEMS; BUCKLER DAVID (US); EL TAYER NABIL (US);) 17 de febrero de 2000 (2000-02-17)

Respecto al requerimiento de novedad (artículo 33(2) del PCT); el compuesto revelado en el documento D3 (RN 91147-49-8) es perjudicial a la novedad de las reivindicaciones 2, 5 y 6, y el compuesto con RN 339273-93-7 en el documento D4 también perjudica la novedad de las reivindicaciones 2, 5 y 6. El compuesto RN 332904-33-3 en el documento D5 también es perjudicial para la novedad de las reivindicaciones 2, 5, y 6. Los otros compuestos revelados específicamente en los estados del arte D1 – D5 están excluidos de proviso en el compuesto de la reivindicación 2. Por lo tanto el artículo 33(2) del PCT no está satisfecho por las reivindicaciones 2, 5 y 6.

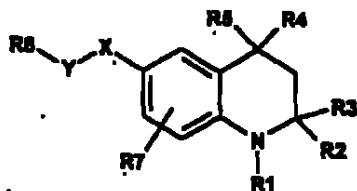
Respecto al requerimiento de nivel inventivo (artículo 33(3) del PCT), los compuestos de la presente solicitud están descritos como que tienen actividad moduladora de FSH. Los documentos D1 – D5 no revelan una actividad farmacéutica para los compuestos revelados en ellos, y por lo tanto los documentos D6 y D7, los cuales describen la misma actividad cualitativa se consideran que representan el estado del arte más cercano. La persona versada en la materia técnica, enfrentada con el problema de proporcionar otros compuestos novedosos con actividad moduladora de FSH no hubiera tenido ningún incentivo del estado del arte para de hecho preparar los compuestos de la presente solicitud, con la expectativa de que estos tengan esa actividad, y por lo tanto el artículo 33(3) puede en principio ser considerado como satisfecho por los ejemplos preparados y una generalización razonable de lo mismo, pero dado el amplio alcance de la reivindicación, se le pide al solicitante que establezca sobre que base se hizo la extrapolación del alcance reivindicado sobre los ejemplos (bioequivalencia, etc., como los términos, por ejemplo, heteroarilo para las definiciones de un sustituyente en R6 o para R6 mismo permitiría compuestos que podrían diferenciarse sustancialmente de aquellos preparados y la estructura núcleo.

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REIVINDICACIONES CORREGIDAS

(ARTICULO 19 DEL PCT)

1. Un compuesto derivado de tetrahydroquinolina CARACTERIZADO porque tiene la fórmula I:



Formula I

o una sal farmacéuticamente aceptable del mismo,
donde

R^1 es formilo, (1-6C)alquilcarbonilo o (1-6C)-alquilsulfonilo;

R^2 y R^3 son H ó (1-4C)alquilo;

R^4 es fenilo, opcionalmente substituido con uno o más substituyentes seleccionados del grupo hidroxilo, amino, halógeno, nitro, trifluorometilo, ciano, (1-4C)alquilo, (2-4C)alquenilo, (2-4C)alquinilo, (1-4C)alcoxi, (1-4C) (di)alquilamino;

R^5 es (1-4C)alquilo;

Y-X es C(O)-O, S(O)₂-O, NHC(O)-O, NHC(S)-O, OC(O)-O, enlace-O, C(O)-NH, S(O)₂-NH, NHC(O)₂-NH, NHC(S)-NH, OC(O)-NH, enlace-NH, NH-C(O), O-C(O), NH-S(O)₂ u O-S(O)₂, o bien X-Y es un enlace;

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R^6 es H, excepto cuando Y-X es un enlace, trifluorometilo, (1-6C)alquilo, 1-6 2-adamantil(1-4C)alquilo, (2-6C)alquenilo, (2-6C)alquinilo, (3-9C)heteroarilo, (3-6C)-cicloalquilo, (2-6C)heterocicloalquilo, (1-4C)alquiltio(1-4C)-alquilo, (6-10C)aril(1-4C)alquilo, (3-9C)heteroaril(1-4C)-alquilo, (3-6C)cicloalquil(1-4C)alquilo, (2-6C)heterocicloalquil(1-4C)alquilo, R^8 , R^9 -aminocarbonil(1-4C)alquilo, R^8 , R^9 -amino(1-4C)alquilo, R^8 -oxicarbonil(1-4C)alquilo, R^8 -oxi(1-4C)alquilo, R^8 -carbonil(1-4C)alquilo o (6-10C)arilo, en donde si (6-10C)arilo es fenilo, fenilo puede ser opcionalmente substituido con hidroxilo, amino, halógeno, nitro, trifluorometilo, ciano, (1-4C)alquilo, (2-4C)alquenilo, (2-4C)alquinilo, (1-4C)alcoxi, (1-4C)(di)alquilamino, (6-10C)arilo, (6-10C)ariloxi, (6-10C)aril(1-4C)alcoxi, (3-9C)heteroarilo, (3-9C)heteroariloxi, (3-9C)heteroaril(1-4C)alcoxi, (1-4C)alquilcarbonilamino, (1-4C)alquilcarboniloxi, (3-6C)cicloalquilcarboniloxi, (1-4C)alcoxycarbonil(1-4C)alquilcarboniloxi, (1-4C)alcoxi(1-4C)alquilcarboniloxi, (6-10C)arilcarboniloxi, (3-9C)heteroarilcarboniloxi, (1-4C)alquilsulfoniloxi, (6-10C)arilsulfoniloxi, (3-9C)heteroarilsulfoniloxi, (1-4C)(di)alquilcarbamoil, (6-10C)(di)arilcarbamoil, (2-6C)heterocicloalquilcarbamoil, (6-10C)(di)arilamino, (3-6C)cicloalquil, (3-6C)cicloalquil(1-4C)alquil, (2-6C)heterocicloalquil o (2-6)heterocicloalquil(1-4C)alquil,

y en donde todos los grupos arilo y heteroarilo dentro de R^6 opcionalmente pueden estar substituidos con uno o más substituyentes seleccionados de hidroxilo, amino, halógeno, nitro, trifluorometilo, ciano, (1-4C)alquilo, (2-4C)alquenilo, (2-4C)alquinilo, (1-4C)alcoxi o (1-4C)(di)alquilamino,

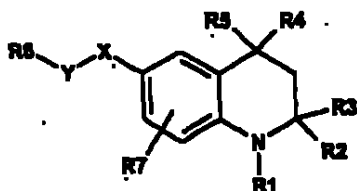
R^7 es H, (1-4C)alquilo, (1-4C)alcoxi, halógeno, trifluorometilo, ciano, nitro, hidroxilo; y

R^8 y/o R^9 es H, (1-4C)alquilo, (2-4C)alquenilo, (2-4C)alquinilo, (6-10)arilo, (3-9C)heteroarilo, (6-10C)-aril(1-

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4C)alquilo, (3-9C)heteroaril(1-4C)alquilo, (3-6C)-cicloalquil(1-4C)alquilo, (2-6C)heterocicloalquil(1-4C)-alquilo, (1-4C)(di)alquilamino(1-4C)alquilo, (1-4C)alcoxi(1-4C)alquilo, (1-4C)alquiltio(1-4C)alquilo, (1-4C)alquilcarbonilamino(1-4C)alquilo, (1-4C)alcoxycarbonil(1-4C)alquilo, (1-4C)alcoxycarbonilamino(1-4C)alquilo, (3-6C)cicloalquilo, (2-6C)heterocicloalquilo, o bien R⁸ y R⁹ pueden estar unidos en un anillo (2-6C)heterocicloalquilo, para el uso en terapia.

2. Un compuesto derivado de tetrahydroquinolina CARACTERIZADO porque tiene la fórmula I



Formula I

o una sal farmacéuticamente aceptable del mismo, donde

R¹ es formilo, (1-6C)alquilcarbonilo o (1-6C)-alquilsulfonilo;

R² y R³ son H ó (1-4C)alquilo;

R⁴ es fenilo, opcionalmente substituido con uno o más substituyentes seleccionados del grupo hidroxí, amino, halógeno, nitro, trifluorometilo, ciano, (1-4C)alquilo, (2-4C)alquenilo, (2-4C)alquinilo, (1-4C)alcoxi, (1-4C)(di)alquilamino;

R⁵ es (1-4C)alquilo;

Y-X es C(O)-O, S(O)₂-O, NHC(O)-O, NHC(S)-O, OC(O)-O, enlace-O, C(O)-NH, S(O)₂-NH, NHC(O)-NH, NHC(S)-NH,

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OC(O)-NH, enlace-NH, NH-C(O), O-C(O), NH-S(O)₂ u O-S(O)₂, o bien X-Y es un enlace;

R⁶ es H, excepto cuando Y-X es un enlace, trifluorometilo, (1-6C)alquilo, 1- ó 2-adamantil(1-4C)alquilo, (2-6C)alquenilo, (2-6C)alquinilo, (3-9C)heteroarilo, (3-6C)cicloalquilo, (2-6C)heterocicloalquilo, (1-4C)alquiltio(1-4C)alquilo, (6-10C)aril(1-4C)alquilo, (3-9C)heteroaril(1-4C)alquilo, (3-6C)cicloalquil(1-4C)alquilo, (2-6C)heterocicloalquil(1-4C)alquilo, R⁸, R⁹-aminocarbonil(1-4C)alquilo, R⁸, R⁹-amino(1-4C)alquilo, R⁸-oxicarbonil(1-4C)alquilo, R⁸-oxi(1-4C)alquilo, R⁸-carbonil(1-4C)alquilo o (6-10C)arilo, en donde si (6-10C)arilo es fenilo, fenilo puede ser opcionalmente substituido con hidroxilo, amino, halógeno, nitro, trifluorometilo, ciano, (1-4C)alquilo, (2-4C)alquenilo, (2-4C)alquinilo, (1-4C)alcoxi, (1-4C)(di)alquilamino, (6-19C)arilo, (6-10C)ariloxi, (6-10C)aril(1-4C)alcoxi, (3-9C)heteroarilo, (3-9C)heteroariloxi, (3-9C)heteroaril(1-4C)alcoxi, (1-4C)alquilcarbonilamino, (1-4C)alquilcarboniloxi, (3-6C)cicloalquilcarboniloxi, (1-4C)alcoxycarbonil(1-4C)alquilcarboniloxi, (1-4C)alcoxi(1-4C)alquilcarboniloxi, (6-10C)arilcarboniloxi, (3-9C)heteroarilcarboniloxi, (1-4C)alquilsulfoniloxi, (6-10C)arilsulfoniloxi, (3-9C)heteroarilsulfoniloxi, (1-4C)(di)alquilcarbamoil, (6-10C)(di)arilcarbamoil, (2-6C)heterocicloalquilcarbamoil, (6-10C)(di)arilamino, (3-6C)cicloalquil, (3-6C)cicloalquil(1-4C)alquil, (2-6C)heterocicloalquil o (2-6)heterocicloalquil(1-4C)alquil,

y en donde todos los grupos arilo y heteroarilo dentro de R⁶ opcionalmente pueden estar substituidos con uno o más substituyentes seleccionados de hidroxilo, amino, halógeno, nitro, trifluorometilo, ciano, (1-4C)alquilo, (2-4C)alquenilo, (2-4C)alquinilo, (1-4C)alcoxi o (1-4C)(di)alquilamino;

R⁷ es H, (1-4C)alquilo, (1-4C)alcoxi, halógeno, trifluorometilo, ciano, nitro, hidroxilo; y

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R^8 y/o R^9 es H, (1-4C)alquilo, (2-4C)alquenilo, (2-4C)alquinilo, (6-10C)arilo, (3-9C)heteroarilo, (6-10C)aril(1-4C)alquilo, (3-9C)heteroaril(1-4C)alquilo, (3-6C)cicloalquil(1-4C)alquilo, (2-6C)heterocicloalquil(1-4C)alquilo, (1-4C)(di)alquilamino(1-4C)alquilo, (1-4C)alcoxi(1-4C)alquilo, (1-4C)alquiltio(1-4C)alquilo, (1-4C)alquilcarbnilamino(1-4C)alquilo, (1-4C)alcoxycarbonil(1-4C)alquilo, (1-4C)alcoxycarbonilamino(1-4C)alquilo, (3-6C)cicloalquilo, (2-6C)heterocicloalquilo, o bien R^8 y R^9 pueden estar unidos en un anillo (2-6C)heterocicloalquilo, con la salvedad de que el derivado no es 1-acetil-6-benzoilamino-4-(4-metilfenil)-1, 2, 3, 4-tetrahidro-2, 2, 4-trimetilquinolina, 1-acetil-4-fenil-1, 2, 3, 4-tetrahidro-2, 2, 4, 6-tetrametilquinolina, 1-acetil-4-fenil-1, 2, 3, 4-tetrahidro-2, 2, 4, 6, 8-pentametilquinolina, 1-acetil-6-metoxi-4-fenil-1, 2, 3, 4-tetrahidro-2, 2, 4-trimetilquinolina, 1-acetil-6-trifluoroacetilamino-4-(4-metilfenil)-1, 2, 3, 4-tetrahidro-2, 2, 4-trimetilquinolina, 1-acetil-6-trifluoroacetilamino-4-fenil-1, 2, 3, 4-tetrahidro-2, 2, 4-trimetilquinolina, 1-acetil-4-(4-clorofenil)-1, 2, 3, 4-tetrahidro-2, 2, 4, 6-tetrametilquinolina y 1-acetil-4-(4-bromofenil)-1, 2, 3, 4-tetrahidro-2, 2, 4, 6-tetrametilquinolina.

3. El compuesto derivado de tetrahydroquinolina de la reivindicación 2, CARACTERIZADO porque Y-X es C(O)-NH, OC(O)-NH ó C(O)-O.

4. El compuesto derivado de tetrahydroquinolina de las reivindicaciones 2 ó 3, CARACTERIZADO porque Y-X es C(O)-NH.

5. El compuesto derivado de tetrahydroquinolina de las reivindicaciones 2-4, CARACTERIZADO porque R^1 es (1-4C)-alquilcarbonilo.

6. El compuesto derivado de tetrahydroquinolina de las reivindicaciones 2-5, CARACTERIZADO porque R^2 , R^3 y R^5 son independientemente (1-4C)alquilo.

7. El compuesto derivado de tetrahydroquinolina de las reivindicaciones 2.6, CARACTERIZADO porque R^6 es (6-10C)-arilo, (3-9C)heteroarilo, (6-10C)aril(1-4C)alquilo o (3-9C)-heteroaril(1-4C)alquilo, , en donde si (6-10C)arilo es fenilo, fenilo puede ser opcionalmente substituido con hidroxilo, amino, halógeno, nitro, trifluorometilo, ciano, (1-4C)alquilo, (2-4C)alquenilo, (2-4C)alquinilo, (1-4C)alcoxi, (1-4C)(di)alquilamino, (6-10C)arilo, (6-10C)ariloxi, (6-10C)aril(1-4C)alcoxi, (3-9C)heteroarilo, (3-9C)heteroariloxi, (3-9C)heteroaril(1-4C)alcoxi, (1-4C)alquilcarbonilamino, (1-4C)alquilcarboniloxi, (3-6C)cicloalquilcarboniloxi, (1-4C)alcoxycarbonil(1-4C)alquilcarboniloxi, (1-4C)alcoxi(1-4C)alquilcarboniloxi, (6-10C)arilcarboniloxi, (3-9C)heteroarilcarboniloxi, (1-4C)alquilsulfoniloxi, (6-10C)arilsulfoniloxi, (3-9C)heteroarilsulfoniloxi, (1-4C)(di)alquilcarbamoil, (6-10C)(di)arilcarbamoil, (2-6C)heterocicloalquilcarbamoil, (6-10C)(di)arilamino, (3-6C)cicloalquil, (3-6C)cicloalquil(1-4C)alquil, (2-6C)heterocicloalquil o (2-6)heterocicloalquil(1-4C)alquil, y en donde todos los grupos arilo y heteroarilo dentro de R^6 opcionalmente pueden estar substituidos con uno o más substituyentes seleccionados de hidroxilo, amino, halógeno, nitro, trifluorometilo, ciano, (1-4C)alquilo, (2-4C)alquenilo, (2-4C)alquinilo, (1-4C)alcoxi o (1-4C)(di)alquilamino.

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8. Una composición farmacéutica CARACTERIZADA porque comprende el compuesto de cualquiera de las reivindicaciones 2-7 y auxiliares farmacéuticamente adecuados.

9. Uso del compuesto de cualquiera de las reivindicaciones 2-8, o una sal o solvato farmacéuticamente aceptable del mismo, CARACTERIZADO porque sirve para fabricar un medicamento para el control de la fertilidad.

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DERIVADOS DE TETRAHIDROQUINOLINA

MEMORIA DESCRIPTIVA

La invención se refiere a un compuesto que tiene actividad moduladora de la FSH, en particular un derivado de tetrahidroquinolina, a una composición farmacéutica que lo contiene, y también al uso de dicho compuesto en terapia médica.

Las gonadotrofinas cumplen importantes funciones en una variedad de funciones corporales, incluyendo el metabolismo, la regulación de la temperatura y el proceso reproductivo. Las gonadotrofinas actúan sobre tipos específicos de células gonadales para iniciar la diferenciación ovárica y testicular y la esteroidogénesis. La gonadotrofina hipofisiaria FSH (hormona folículo estimulante), por ejemplo, juega un rol fundamental en la estimulación del desarrollo y la maduración de los folículos, en tanto que la LH (hormona luteinizante) induce la ovulación (Sharp, R.M. Clin Endocrinol. 33:787-807, 1990; Dorrington y Armstrong, Recent Prog. Horm. Res. 35:301-342, 1979). Actualmente, la FSH se aplica en clínica, en combinación con LH, para la estimulación ovárica, o sea la hiperestimulación ovárica para la fertilización in vitro (IVF) y la inducción de la ovulación en mujeres anovulatorias infértiles (Insler, V., Int. J. Fertility 33:85-97, 1988; Navot y Rosenwaks, J. Vitro Fert. Embryo Transfer 5:3-13, 1988), y también para el hipogonadismo masculino y la infertilidad masculina.

La gonadotrofina FSH es liberada desde la pituitaria anterior, bajo la influencia de la hormona liberadora de



gonadotrofinas y los estrógenos, y desde la placenta durante el embarazo. En la hembra, la FSH actúa sobre los ovarios promoviendo el desarrollo de los folículos, y es la principal hormona que regula la secreción de estrógenos. En el macho, la FSH es responsable de la integridad de los túbulos seminíferos y actúa sobre las células de Sertoli para apoyar la gametogénesis. La FSH purificada se usa en clínica para tratar la infertilidad en la hembra y para algunos tipos de falla de la espermatogénesis en el macho. Las gonadotrofinas destinadas a propósitos terapéuticos pueden ser aisladas de fuentes de orina humana y son de baja pureza (Morse et al, Amer. J. Reproduct. Immunol. and Microbiology 17:143, 1988). Alternativamente, pueden ser preparadas como gonadotrofinas recombinantes. La FSH humana recombinante está disponible en el comercio y está siendo usada en la reproducción asistida (Olijve et al. Mol. Hum. Reprod. 2:371, 1996; Devroey et al. Lancet 339:1170, 1992).

Las acciones de la hormona FSH son mediadas por un receptor específico de la membrana plasmática que es un miembro de la gran familia de receptores acoplados a proteína G. Estos receptores consisten en un polipéptido único con siete dominios transmembrana, y son capaces de interactuar con las proteínas G, lo que lleva a la activación de la adenilato ciclasa.

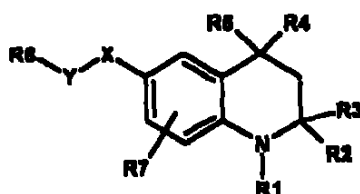
El receptor de FSH es un blanco altamente específico en el proceso de crecimiento de los folículos ováricos, y se expresa exclusivamente en el ovario. Bloquear este receptor o inhibir la señalización que es inducida normalmente después de la activación del receptor mediada por FSH, alterará el

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desarrollo de los folículos y, así, la ovulación y la fertilidad. Por lo tanto, los antagonistas de FSH de bajo peso molecular podrían formar la base de nuevos anticonceptivos. Estos antagonistas de FSH podrían dar origen a un desarrollo disminuido de los folículos (no hay ovulación), quedando todavía suficiente producción de estrógenos como para evitar los efectos adversos, por ejemplo sobre la masa ósea.

La presente invención describe la preparación de análogos de hormonas de bajo peso molecular que selectivamente tienen actividad moduladora sobre el receptor de FSH. Los compuestos de la invención pueden usarse ya sea como agonistas (parciales) o antagonistas (parciales) del receptor de FSH.

Por lo tanto, se ha encontrado ahora que la siguiente clase de compuestos de tetrahidroquinolina de fórmula I o sus sales farmacéuticamente aceptables, tienen actividad moduladora de FSH:



Fórmula I

donde

R^1 es formilo, (1-6C)alquilcarbonilo o (1-6C)-alquilsulfonilo;

R^2 y R^3 son H ó (1-4C)alquilo;

R^4 es fenilo, opcionalmente substituido con uno o más substituyentes seleccionados del grupo de hidroxí, amino,

halógeno, nitro, trifluorometilo, ciano, (1-4C)alquilo, (2-4C)alquenilo, (2-4C)alquinilo, (1-4C)alcoxi, (1-4C)(di)-alquilamino. La posición de substitución preferida es la posición para;

R^5 es (1-4C)alquilo;

Y-X es C(O)-O, S(O)₂-O, NHC(O)-O, NHC(S)-O, OC(O)-O, enlace-O, C(O)-NH, S(O)₂-NH, NHC(O)-NH, NHC(S)-NH, OC(O)-NH, enlace-NH, NH-C(O), O-C(O), NH-S(O)₂, u O-S(O)₂, o bien X-Y es un enlace;

R^6 es H, trifluorometilo, (1-6C)alquilo, 1- ó 2-adamantil(1-4C)alquilo, (2-6C)alquenilo, (2-6C)alquinilo, (6-10C)arilo, (3-9C)heteroarilo, (3-6C)cicloalquilo, (2-6C)-heterocicloalquilo, (1-4C)alquiltio(1-4C)alquilo, (6-10C)-aril(1-4C)alquilo, (3-9C)heteroaril(1-4C)alquilo, (3-6C)-cicloalquil(1-4C)alquilo, (2-6C)heterocicloalquil(1-4C)-alquilo, R^8, R^9 -aminocarbonil(1-4C)alquilo, R^8, R^9 -amino(1-4C)alquilo, R^8 -oxicarbonil(1-4C)alquilo, R^8 -oxi(1-4C)-alquilo, R^8 -carbonil(1-4C)alquilo;

si R^6 es H, debe hacerse notar que X-Y puede no ser un enlace;

si R^6 es fenilo, el fenilo, además de los substituyentes para los grupos (6-10C)arilo mencionados en las definiciones, puede estar opcionalmente substituido con (6-10C)arilo, (6-10C)ariloxi, (6-10C)aril(1-4C)alcoxi, (3-9C)-heteroarilo, (3-9C)heteroariloxi, (3-9C)heteroaril(1-4C)-alcoxi, (1-4C)alquilcarbonilamino, (1-4C)alquilcarboniloxi, (3-6C)cicloalquilcarboniloxi, (1-4C)alcoxicarbonil(1-4C)-alquilcarboniloxi, (1-4C)alcoxi(1-4C)alquilcarboniloxi, (6-10C)arilcarboniloxi, (3-9C)heteroarilcarboniloxi, (1-4C)-

alquilsulfoniloxi, (6-10C)arilsulfoniloxi, (3-9C)hetero-
arilsulfoniloxi, (1-4C)(di)alquilcarbamoilo, (6-10C)(di)aril-
carbamoilo, (2-6C)heterocicloalquilcarbamoilo, (6-10C)(di)-
arilamino, (3-6C)cicloalquilo, (3-6C)cicloalquil(1-4C)alquilo,
(2-6C)heterocicloalquilo, (2-6)heterocicloalquil(1-4C)alquilo;

R^7 es H, (1-4C)alquilo, (1-4C)alcoxi, halógeno,
trifluorometilo, ciano, nitro, hidroxilo;

R^8 y/o R^9 es H, (1-4C)alquilo, (2-4C)alquenilo,
(2-4C)alquinilo, (6-10C)arilo, (3-9C)heteroarilo, (6-10C)-
aril(1-4C)alquilo, (3-9C)heteroaril(1-4C)alquilo, (3-6C)-
cicloalquil(1-4C)alquilo, (2-6C)heterocicloalquil(1-4C)-
alquilo, (1-4C)(di)alquilamino(1-4C)alquilo, (1-4C)alcoxi(1-
4C)alquilo, (1-4C)alquiltio(1-4C)alquilo, (1-4C)alquil-
carbonilamino(1-4C)alquilo, (1-4C)alcoxycarbonil(1-4C)alquilo,
(1-4C)alcoxycarbonilamino(1-4C)alquilo, (3-6C)cicloalquilo,
(2-6C)heterocicloalquilo, o bien R^8 y R^9 pueden estar unidos
en un anillo (2-6C)heterocicloalquilo.

Los compuestos de acuerdo con la presente invención
modulan la función del receptor de FSH y pueden usarse para
los mismos propósitos clínicos que la FSH nativa si se
comportan como agonistas, con la ventaja de que presentan
propiedades de estabilidad alteradas y pueden ser
administrados en forma diferente. Si bloquean el receptor de
FSH pueden usarse, por ejemplo, como un agente anticonceptivo.

Por lo tanto, los moduladores del receptor de FSH de
la presente invención pueden usarse para tratar la
infertilidad, para la anticoncepción y para el tratamiento de
trastornos dependientes de hormonas, tales como cáncer de

mama, cáncer de próstata y endometriosis. De preferencia, los compuestos de la presente invención se usan para inactivar el receptor de FSH.

El término (1-4C)alquilo, como se usa en la definición, significa un grupo alquilo ramificado o no ramificado que tiene 1-4 átomos de carbono, por ejemplo metilo, etilo, propilo, isopropilo, butilo, sec-butilo y ter-butilo.

El término (1-6C)alquilo, como se usa en la definición, significa un grupo alquilo ramificado o no ramificado que tiene 1-6 átomos de carbono, por ejemplo metilo, etilo, propilo, isopropilo, butilo, sec-butilo, ter-butilo y hexilo. Son preferidos los grupos (1-5C)alquilo, siendo (1-4C)alquilo el más preferido.

El término 1- ó 2-adamantil(1-4C)alquilo significa un grupo adamantilo unido en la posición 1 ó 2 a un grupo alquilo que contiene 1-4 átomos de carbono, con el mismo significado definido anteriormente.

El término (2-4C)alquenilo significa un grupo alquenilo ramificado o no ramificado que tiene 2-4 átomos de carbono, tal como etenilo y 2-butenilo.

El término (2-6C)alquenilo significa un grupo alquenilo ramificado o no ramificado que tiene 2-6 átomos de carbono, tal como etenilo, 2-butenilo y n-pentenilo.

El término (2-4C)alquinilo significa un grupo alquinilo ramificado o no ramificado que tiene 2-4 átomos de carbono, tal como etinilo y propinilo.

El término (2-6C)alquinilo significa un grupo alquinilo ramificado o no ramificado que tiene 2-6 átomos de carbono, tal como etinilo, propinilo y n-pentinilo.

El término (3-6C)cicloalquilo significa un grupo cicloalquilo que tiene 3-6 átomos de carbono, y que es ciclopropilo, ciclobutilo, ciclopentilo y ciclohexilo.

El término (2-6C)heterocicloalquilo significa un grupo heterocicloalquilo que tiene 2-6 átomos de carbono, de preferencia 3-5 átomos de carbono, e incluye al menos un heteroátomo seleccionado entre N, O y/o S, que puede estar unido a través de un heteroátomo si es factible, o un átomo de carbono. Los heteroátomos preferidos son N u O. Los más preferidos son piperidina, morfolina y pirrolidina.

El término (1-4C)alcoxi significa un grupo alcoxi que tiene 1-4 átomos de carbono, teniendo la porción alquilo el mismo significado definido anteriormente. Son preferidos los grupos (1-2C)alcoxi.

El término (6-10C)arilo significa un grupo hidrocarburo aromático que tiene 6-10 átomos de carbono, tal como fenilo, naftilo, tetrahidronaftilo o indenilo, que puede estar opcionalmente substituido con uno o más substituyentes seleccionados entre hidroxil, amino, halógeno, nitro, trifluorometilo, ciano, (1-4C)alquilo, (2-4C)alquenilo, (2-4C)alquinilo, (1-4C)alcoxi, (1-4C)(di)alquilamino, donde las porciones alquilo tienen el mismo significado definido anteriormente. El grupo hidrocarburo aromático preferido es fenilo.

El término (3-9C)heteroarilo significa un grupo aromático substituido o no substituido que tiene 3-9 átomos de

carbono, incluyendo al menos un heteroátomo seleccionado entre N, O y/o S, como imidazolilo, tiadiazolilo, piridilo, (benzo)tienilo, (benzo)furilo, quinolilo, tetrahydroquinolilo, quinoxalilo o indolilo. Los sustituyentes en el grupo heteroarilo pueden seleccionarse del grupo de sustituyentes enumerados para el grupo arilo. El grupo heteroarilo puede estar unido a través de un átomo de carbono o un heteroátomo, si es factible. Los grupos heteroarilo preferidos son tienilo, furilo y piridilo.

El término (6-10C)ariloxi significa un grupo arilo que contiene 6-10 átomos de carbono como se definió anteriormente, unido a un átomo de oxígeno. Los grupos (3-9C)heteroariloxi son análogos de los grupos (6-10C)ariloxi, incluyendo al menos un heteroátomo seleccionado entre N, O ó S.

El término (1-4C)alcoxycarbonil(1-4C)alquilo significa un grupo alcoxycarbonilalquilo, donde el grupo alcoxi contiene 1-4 átomos de carbono y tiene el mismo significado definido anteriormente, y el grupo alquilo contiene 1-4 átomos de carbono y tiene el mismo significado definido anteriormente.

El término (1-4C)alcoxi(1-4C)alquilo significa un grupo alcoxialquilo, donde el grupo alcoxi contiene 1-4 átomos de carbono y tiene el mismo significado definido anteriormente, y el grupo alquilo contiene 1-4 átomos de carbono y tiene el mismo significado definido anteriormente.

El término (3-6C)cicloalquil(1-4C)alquilo significa un grupo cicloalquilo de 3-6 átomos de carbono unido a un grupo alquilo de 1-4 átomos de carbono, donde el grupo

cicloalquilo es un grupo (3-6C)cicloalquilo como el definido anteriormente, y el grupo alquilo es un grupo (1-4C)alquilo como el definido anteriormente.

El término (2-6C)heterocicloalquil(1-4C)alquilo significa un grupo heterocicloalquilo de 2-6 átomos de carbono unido a un grupo alquilo de 1-4 átomos de carbono, donde el grupo heterocicloalquilo es un grupo (2-6C)heterocicloalquilo como el definido anteriormente, y el grupo alquilo es un grupo (1-4C)alquilo como el definido anteriormente.

El término (1-4C)(di)alquilamino significa un grupo (di)alquilamino, cuyos grupos alquilo contienen 1-4 átomos de carbono y tienen el mismo significado definido anteriormente.

El término (6-10C)(di)arilamino significa un grupo (di)arilamino, cuyos grupos arilo contienen 6-10 átomos de carbono y tienen el mismo significado definido anteriormente.

El término (1-4C)(di)alquilamino(1-4C)alquilo significa un grupo (di)alquilaminoalquilo, cuyos grupos alquilo contienen 1-4 átomos de carbono y tienen el mismo significado definido anteriormente.

El término (1-4C)alquiltio(1-4C)alquilo significa un grupo alquiltioalquilo, cuyos grupos alquilo contienen 1-4 átomos de carbono y tienen el mismo significado definido anteriormente.

El término aminocarbonil(1-4C)alquilo en la definición de R^8, R^9 -aminocarbonil(1-4C)alquilo significa un grupo aminocarbonilalquilo, cuyo grupo alquilo contiene 1-4 átomos de carbono y tiene el mismo significado definido anteriormente. El grupo aminocarbonilmetilo es el grupo aminocarbonilalquilo preferido.

El término amino(1-4C)alquilo en la definición de R^8, R^9 -amino(1-4C)alquilo significa un grupo aminoalquilo, cuyo grupo alquilo contiene 1-4 átomos de carbono y tiene el mismo significado definido anteriormente.

El término oxicarbonil(1-4C)alquilo en la definición de R^8 -oxicarbonil(1-4C)alquilo significa un grupo oxicarbonilalquilo, cuyo grupo alquilo contiene 1-4 átomos de carbono y tiene el mismo significado definido anteriormente. El grupo oxicarbonilmetilo es el grupo oxicarbonilalquilo preferido.

El término oxi(1-4C)alquilo en la definición de R^8 -oxi(1-4C)alquilo significa un grupo oxialquilo, cuyo grupo alquilo contiene 1-4 átomos de carbono y tiene el mismo significado definido anteriormente.

El término carbonil(1-4C)alquilo en la definición de R^8 -carbonil(1-4C)alquilo significa un grupo carbonilalquilo, cuyo grupo alquilo contiene 1-4 átomos de carbono y tiene el mismo significado definido anteriormente.

El término (6-10C)aril(1-4C)alquilo significa un grupo arilalquilo que tiene 7-14 átomos de carbono, donde el grupo alquilo es un grupo (1-4C)alquilo y el grupo arilo es un grupo (6-10C)arilo, definidos anteriormente. Los grupos fenil(1-4C)alquilo, tal como bencilo, son grupos arilalquilo preferidos. Los grupos (3-9C)heteroaril(1-4C)alquilo son análogos de los grupos (6-10C)aril(1-4C)alquilo, incluyendo al menos un heteroátomo seleccionado entre N, O y/o S, cuyo grupo heteroarilo puede estar unido a través de un átomo de carbono o a través de un heteroátomo, si es factible.

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El término unidos en un anillo (2-6C)heterocicloalquilo en la definición de NR^8R^9 , donde R^8 y R^9 junto con el átomo de nitrógeno al cual están unidos forman un anillo, significa un anillo que contiene el átomo de nitrógeno y además tiene como máximo 2-6 átomos de carbono, cuyo anillo puede contener uno o más heteroátomos adicionales seleccionados entre N, O y/o S. Ejemplos de estos anillos son azetidina, pirrolidina, piperidina, piperazina y (tio)morfolina.

El término halógeno significa flúor, cloro, bromo o yodo.

El término (1-6C)alquilcarbonilo significa un grupo alquilcarbonilo, cuyo grupo alquilo contiene 1-6 átomos de carbono y tiene el mismo significado definido anteriormente. Son preferidos los grupos (1-4C)alquilcarbonilo.

El término (1-4C)alquilcarbonilamino(1-4C)alquilo significa un grupo alquilcarbonilaminoalquilo, cuyos grupos alquilo contienen 1-4 átomos de carbono y tienen el mismo significado definido anteriormente.

El término (6-10C)aril(1-4C)alcoxi significa un grupo arilo que contiene 6-10 átomos de carbono como se definió anteriormente, unido a un grupo (1-4C)alcoxi como se definió anteriormente. Los grupos (3-9C)heteroaril(1-4C)alcoxi son análogos de los grupos (6-10C)aril(1-4C)-alcoxi, incluyendo al menos un heteroátomo seleccionado entre N, O ó S, cuyo grupo heteroarilo puede estar unido a través de un átomo de carbono o a través de un heteroátomo, si es factible.

El término (1-4C)alquilcarboniloxi significa un grupo alquilcarb niloxi, cuyo grupo alquilo contiene 1-4 átomos de carbono. El término (3-6C)cicloalquilcarboniloxi significa un grupo cicloalquilcarboniloxi, cuyo grupo cicloalquilo contiene 3-6 átomos de carbono, y cuya porción cicloalquilo tiene el mismo significado definido anteriormente.

El término (1-4C)alcoxycarbonil(1-4C)alquilcarboniloxi significa un grupo (1-4C)alcoxycarbonilo unido a un grupo alquilcarboniloxi cuya porción alquilo contiene 1-4 átomos de carbono, y cuyo grupo alcoxí tiene el mismo significado definido anteriormente.

El término (1-4C)alcoxí(1-4C)alquilcarboniloxi significa un grupo alcoxí con 1-4 átomos de carbono unido a un grupo alquilcarboniloxi con 1-4 átomos de carbono, teniendo los grupos alcoxí y alquilo el mismo significado definido anteriormente.

El término (1-4C)alquilcarbonilamino significa un grupo alquilcarbonilamino, cuyo grupo alquilo contiene 1-4 átomos de carbono.

El término (1-4C)alcoxycarbonilamino(1-4C)alquilo significa un grupo alcoxycarbonilo que contiene 1-4 átomos de carbono y tiene el mismo significado definido anteriormente, unido a un grupo aminoalquilo, cuyo grupo alquilo contiene 1-4 átomos de carbono y tiene el mismo significado definido anteriormente.

El término (6-10C)arilcarboniloxi significa un grupo arilcarboniloxi, cuyo grupo arilo contiene 6-10 átomos de carbono. El grupo arilcarboniloxi preferido es un grupo

fenilcarboniloxi. Los grupos (3-9C)heteroarilcarboniloxi son análogos de los grupos (6-10C)arilcarboniloxi, incluyendo al menos un heteroátomo seleccionado entre N, O ó S, y pueden estar unidos a través de un átomo de carbono o un heteroátomo, si es factible.

El término (1-4C)alquilsulfonilo significa un grupo alquilsulfonilo, cuyo grupo alquilo contiene 1-4 átomos de carbono y tiene el mismo significado definido anteriormente.

El término (1-6C)alquilsulfonilo significa un grupo alquilsulfonilo, cuyo grupo alquilo contiene 1-6 átomos de carbono y tiene el mismo significado definido anteriormente. Son preferidos los grupos (1-3C)alquilsulfonilo.

El término (1-4C)alquilsulfoniloxi significa un grupo alquilsulfoniloxi, cuyo grupo alquilo contiene 1-4 átomos de carbono y tiene el mismo significado definido anteriormente. Son preferidos los grupos (1-3C)alquilsulfoniloxi.

El término (6-10C)arilsulfoniloxi significa un grupo arilsulfoniloxi, cuyo grupo arilo contiene 6-10 átomos de carbono y tiene el mismo significado definido anteriormente. Es preferido el grupo fenilsulfoniloxi. Los grupos (3-9C)heteroarilsulfoniloxi son análogos de los grupos (6-10C)arilsulfoniloxi, incluyendo al menos un heteroátomo seleccionado entre N, O ó S, que pueden estar unidos a través de un átomo de carbono o un heteroátomo, si es factible.

El término (1-4C)(di)alquilcarbamoilo significa un grupo (di)alquilcarbamoilo, cuyos grupos alquilo contienen 1-4 átomos de carbono y tienen el mismo significado definido anteriormente.

El término (6-10C)(di)arilcarbamoílo significa un grupo (di)arilcarbamoílo, cuyas porciones arilo contienen 6-10 átomos de carbono y tienen el mismo significado definido anteriormente.

El término (2-6C)heterocicloalquilcarbamoílo significa un grupo heterocicloalquilcarbamoílo, cuyo grupo heterocicloalquilo contiene 2-6 átomos de carbono y tiene el mismo significado definido anteriormente.

Los compuestos preferidos de la invención son compuestos de fórmula I, donde Y-X es C(O)-NH, OC(O)-NH ó C(O)-O. Más preferidos son los compuestos en que Y-X es C(O)-NH.

Más preferidos son los compuestos donde R¹ es (1-4C)alquilcarbonilo, de preferencia acetilo, y/o R² y/o R³ y R⁵ son independientemente (1-4C)alquilo, de mayor preferencia metilo.

De preferencia, R⁶ es un grupo voluminoso. Los compuestos preferidos son aquéllos donde R⁶ es (6-10C)arilo, (3-9C)heteroarilo, (6-10C)aril(1-4C)alquilo o (3-9C)-heteroaril(1-4C)alquilo. Los más preferidos son los compuestos donde R⁶ es (6-10C)arilo, más preferido aún fenilo. El grupo R⁷ preferido es H, (1-4C)alquilo o (1-4C)alcoxí. Los más preferidos son H ó (1-4C)alquilo, más preferido aún H ó metilo. Los más preferidos son los compuestos donde R⁷ es H.

En los compuestos más preferidos de acuerdo con la invención, R¹ es (1-4C)alquilcarbonilo, R², R³, R⁵ son independientemente (1-4C)alquilo, R⁴ es fenilo, Y-X es C(O)-NH y R⁷ es H. Aún más preferidos son los compuestos donde R¹

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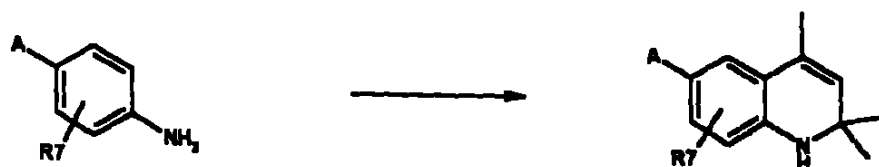
es acetilo, R^2 , R^3 , R^5 son independientemente metilo, R^4 es fenilo, Y-X es C(O)-NH y R^7 es H.

En los compuestos preferidos mencionados más arriba, se permiten substituciones como se indica en las definiciones de los grupos. El fenilo en R^6 puede además estar substituido como se indicó en la definición de R^6 .

Están excluidos de la invención los compuestos 1-acetil-6-benzoilamino-4-(4-metilfenil)-1,2,3,4-tetrahidro-2,2,4-trimetilquinolina, 1-acetil-4-fenil-1,2,3,4-tetrahidro-2,2,4,6-tetrametilquinolina, 1-acetil-4-fenil-1,2,3,4-tetrahidro-2,2,4,6,8-pentametilquinolina, 1-acetil-6-metoxi-4-fenil-1,2,3,4-tetrahidro-2,2,4-trimetilquinolina, 1-acetil-6-trifluoroacetilamino-4-(4-metilfenil)-1,2,3,4-tetrahidro-2,2,4-trimetilquinolina, 1-acetil-6-trifluoroacetilamino-4-fenil-1,2,3,4-tetrahidro-2,2,4-trimetilquinolina, 1-acetil-4-(4-clorofenil)-1,2,3,4-tetrahidro-2,2,4,6-tetrametilquinolina y 1-acetil-4-(4-bromofenil)-1,2,3,4-tetrahidro-2,2,4,6-tetrametilquinolina.

La renuncia se refiere a las enseñanzas en Ref. Zh., Khim. Abstr. No. 1Zh311, 1972; Khim. Geterosikl. Soedin. 7:795, 1971; Ambinter Screening Collection, números de orden 28020-A0839/0039328 (CAS 310456-97-4) y -A0705/0032919 (CAS 327981-38-4); ChemDiv. Inc. número de orden 8005-9747 (CAS 60760-14-1); ChemStar Product list, número de orden CHS0065413 (CAS 299418-67-0); Asinex Compound Collection, número de orden BAS0068990 (CAS 299970-20-0).

Los métodos adecuados para la preparación de los compuestos de la invención se resumen a continuación.



II-a: A = OAlquilo
 II-b: A = NH(grupo protector)
 II-c: A = C(O)OAlquilo
 II-d: A = S(O)₂OAlquilo
 II-e: A = alquilo(substituido), arilo

III-a: A = OAlquilo
 III-b: A = NH(grupo protector)
 III-c: A = C(O)OAlquilo
 III-d: A = S(O)₂OAlquilo
 III-e: A = alquilo(substituido), arilo

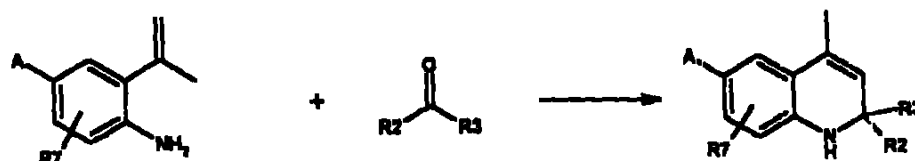
Los compuestos de la presente invención donde R^2 y R^3 son metilo pueden prepararse partiendo de anilinas (protegidas) de fórmula general II-a-e, donde R^7 tiene el mismo significado definido anteriormente, por medio de la bien documentada reacción de Skraup, que da derivados de 1,2-dihidro-2,2,4-trimetilquinolina de fórmula III-a-e.

Ciclaciones de Skraup relacionadas se encuentran en la literatura: A. Knoevenagel, Chem. Ber. 54:1726, 1921; R.L. Atkins y D.E. Bliss, J. Org. Chem. 43:1975, 1978; J.V. Johnson, B.S. Rauckman, D.P. Baccanari y B. Roth, J. Med. Chem. 32:1942, 1989; W.C. Lin, S.T. Huang y S.T. Lin, J. Chin. Chem. Soc. 43:497, 1996; J.P. Edwards, S.J. West, K.B. Marschke, D.E. Mais, M.M. Gottardis y T.K. Jones, J. Med. Chem. 41:303, 1998.

La reacción mencionada más arriba se efectúa típicamente a temperatura elevada en acetona, óxido de mesitilo o acetoacetato de etilo, en presencia de yodo o un ácido prótico tal como ácido clorhídrico, ácido p-toluenosulfónico o yoduro de hidrógeno acuoso. Alternativamente, las 1,2-dihidro-2,2,4-trimetilquinolinas de fórmula III-a-e pueden

prepararse haciendo reaccionar la anilina correspondiente de fórmula II-a-e con acetona, en presencia de MgSO_4 , 4-terbutilcatecol y yodo (L.G. Hamann, R.I. Higuchi, L. Zhi, J.P. Edwards y X.N. Wang, J. Med. Chem, 41:623, 1998). Los materiales de partida pueden obtenerse directamente de fuentes comerciales, o bien pueden prepararse por substituciones en el anillo aromático conocidas en el arte, como se describe por ejemplo en H. Carfontain, Y. Zou y B.H. Bakker, Recl. Trav. Chim. Pays-Bas, 113:403, 1994; A. Coppock, J. Org. Chem. 22:325, 1957; M. Schlosser, J.H. Choi y S. Takagishi, Tetrahedron, 46:5633, 1990.

Alternativamente, los compuestos de la estructura general VI-a-e, donde R^2 y R^3 son (2-4C)alquilo y R^7 es como se definió anteriormente, pueden sintetizarse en general por ciclación de una anilina de fórmula IV-a-e con una cetona apropiada de fórmula V.



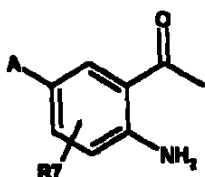
IV-a: A = OAlquilo
IV-b: A = NH(grupo protector)
IV-c: A = C(O)OAlquilo
IV-d: A = S(O)₂OAlquilo
IV-e: A = alquilo(substituido). arilo

VI-a: A = OAlquilo
VI-b: A = NH(grupo protector)
VI-c: A = C(O)OAlquilo
VI-d: A = S(O)₂OAlquilo
VI-e: A = alquilo(substituido). arilo

La reacción mencionada más arriba se efectúa típicamente en un solvente inerte tal como tolueno, a temperatura elevada usando ácidos próticos o de Lewis tales

como, pero no limitados a, ácido p-toluenosulfónico o trifluoruro de boro, para promover la ciclación (H. Walter, H. Sauter y T. Winkler, *Helv. Chim. Acta*, 75:1274, 1992; H. Walter, *Helv. Chim. Acta*, 77:608, 1994; H. Walter y J. Schneider, *Heterocycles*, 41:1251, 1995; J.P. Edwards, J.D. Ringgenberg y T.K. Jones, *Tetrahedron Lett.* 39:5139, 1998).

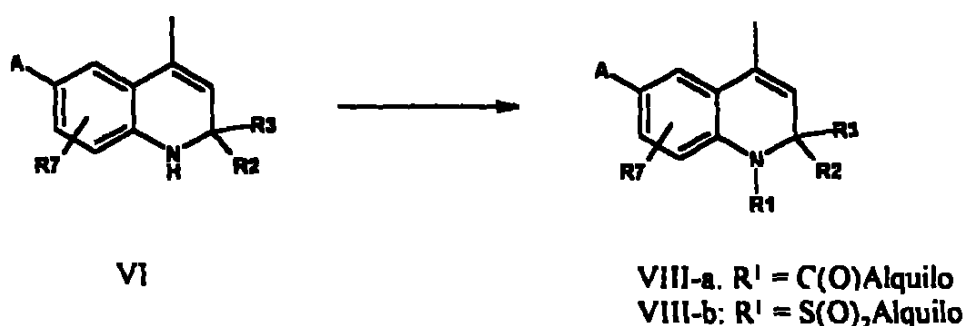
Los bloques de construcción requeridos de fórmula IV-a-e pueden prepararse por reacción de Wittig de cetonas de fórmula VII-a-e. La introducción de los substituyentes A en el anillo aromático puede efectuarse usando substituciones en el anillo aromático conocidas en el arte, ya sea en la etapa de anilina o en la etapa de 1,2-dihidro-2,2,4-trimetilquinolina, como se mencionó más arriba para los compuestos de fórmula II.



- VII-a: A = OAlquilo
- VII-b: A = NH(grupo protector)
- VII-c: A = C(O)OAlquilo
- VII-d: A = S(O)₂OAlquilo
- VII-e: A = alquilo(substituido), arilo

En otra propuesta, los compuestos de fórmula VI-a-e donde $R^2 = R^3 = H$ pueden prepararse a partir de anilinas de fórmula general II-a-e, por reacción con 1-metilestireno y formaldehído en acetonitrilo, a temperatura ambiente o elevada. Ciclaciones relacionadas se describen en la

literatura: J.M. Mellor y G.D. Merriman, Tetrahedron, 51:6115, 1995.



La 1-N-acilación o 1-N-sulfonilación subsiguiente de los compuestos de fórmula VI donde R^2 , R^3 , R^7 y A son como se definió anteriormente, puede efectuarse usando condiciones estándar, bien conocidas para los expertos en el arte. En un experimento típico, los compuestos de fórmula VI se hacen reaccionar en un solvente tal como diclorometano, tetrahidrofurano, tolueno o piridina, con un acilhaluro o anhídrido de ácido o un sulfonilcloruro, en presencia de una base tal como, pero no limitada a, N,N-diisopropiletilamina, trietilamina, piperidina o hidruro de sodio, para dar derivados N-acilados o N-sulfonilados de 1,2-dihidro-4-metilquinolina de las fórmulas VIII-a y VIII-b, respectivamente.

N-acilaciones relacionadas de un andamiaje de dihidroquinolina se encuentran en la literatura: Zh. V. Shmyreva, Kh. S. Shikhaliev y E.B. Shpanig, Izv. Vyssh. Uchebn. Zaved., Khim. Khim. Tekhnol. 31:45, 1988; Zh. V. Shmyreva, Kh. S. Shikhaliev, L.P. Zalukaev, Y.A. Ivanov, Y.S. Ryabokobylko e I.E. Pokrovskaya, Zh. Obshch. Khim. 59:1391, 1989.

La 1-N-formilación puede efectuarse fácilmente por reacción de una dihidroquinolina de fórmula VI con ácido fórmico, en presencia de ácido trifluoroacético a temperatura elevada (véase por ejemplo P. Bouyssou, C. Le Goff y J. Chenault, J. Heterocycl. Chem. 29:895, 1992) o con étil éster de ácido fórmico en presencia de acetato de sodio, como está descrito en la literatura, por ejemplo en N. Atanes, S. Perez, E. Guitan, L. Castedo y J.M. Saa, Tetrahedron, 50:11257, 1994.

La introducción del grupo fenilo requerido en la posición 4 del andamiaje de dihidroquinolina puede efectuarse por alquilación de Friedel-Crafts de derivados de benceno (sustituido) con los compuestos de estructura general VIII, donde R^1 , R^2 , R^3 , R^7 y A son como se definió anteriormente.

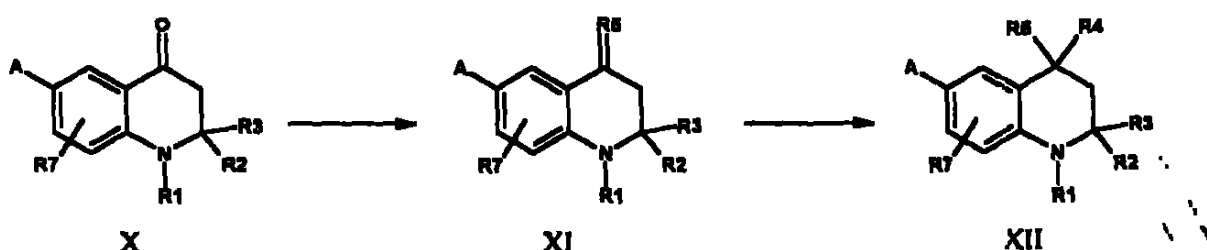


Esta última reacción se efectúa típicamente a temperaturas elevadas ya sea en benceno (sustituido) puro o en un solvente inerte apropiado tal como heptano o hexano con benceno (sustituido) como reactivo, bajo la catálisis de un ácido de Lewis (por ejemplo $AlCl_3$, $AlBr_3$, $FeCl_3$ ó $SnCl_4$). Alquilaciones de Friedel-Crafts con 1,2-dihidro-2,2,4-trimetilquinolinas se describen en la literatura en B.A. Lugovik, L.G. Yudin y A.N. Kost, Dokl. Akad. Nauk SSSR,

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170:340, 1966; B.A. Lugovik, L.G. Yudin, S.M. Vinogradova y A.N. Kost, Khim. Geterosikl. Soedin, 7:795, 1971.

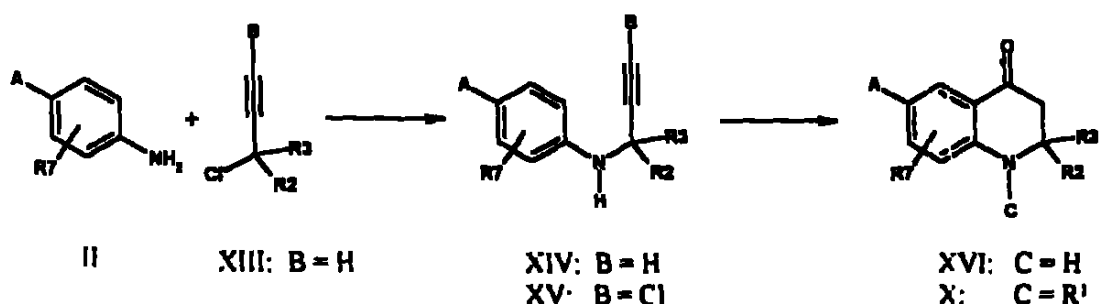
Los compuestos de la presente invención, donde $R^5 \neq Me$ y R^1, R^2, R^3, R^4, R^7 y A son como se definió anteriormente, representados por la fórmula XII, pueden sintetizarse partiendo de tetrahidroquinolina cetonas de fórmula X. Así, la reacción de Wittig de una cetona de fórmula X con el reactivo de Wittig apropiado, da el derivado insaturado representado por la fórmula XI, que a su vez es el material de partida para una alquilación de Friedel-Crafts de benceno (sustituido), por el mismo procedimiento descrito más arriba para la preparación de los compuestos con la estructura general IX.



La reacción de Wittig mencionada más arriba es bien conocida para los expertos en el arte.

La cetona requerida de fórmula X puede prepararse por reacción de una anilina de fórmula II con 3-cloro-3-metil-1-butino (XIII) en dietiléter/agua, en presencia de cobre en polvo y trietilamina, lo que da un alquino de fórmula XIV. El intercambio hidrógeno-halógeno puede efectuarse por desprotonación de un compuesto de fórmula XIV en un solvente inerte tal como tetrahidrofurano con n-butil litio a

temperaturas bajo -50°C , con la adición de p-tolueno-sulfonilcloruro para dar un cloruro de fórmula general XV. Finalmente, la ciclación catalizada por ácido (por ejemplo ácido sulfúrico) puede efectuarse a temperatura elevada en un solvente tal como polietilenglicol, para dar compuestos de fórmula XVI, que pueden ser acilados o sulfonilados como se describió anteriormente para los derivados de fórmula general VI.

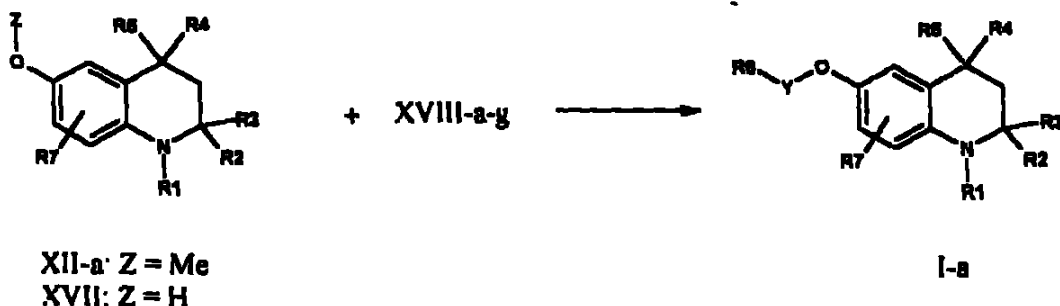


La secuencia de reacciones mencionada más arriba está descrita en la literatura: P. Barmettler y H.J. Hansen, *Helv. Chim. Acta*, 73:1515, 1990 (y las referencias allí citadas).

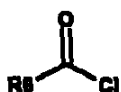
La funcionalización de la posición 6 en las tetrahydroquinolinas de estructura general XII puede efectuarse por procedimientos de desprotección-acoplamiento conocidos en el arte:

Los compuestos de la presente invención donde $X = O$ e $Y = C(O)$, $S(O)_2$, $NHC(O)$, $NHC(S)$, $OC(O)$ o un enlace, representados por la fórmula I-a, pueden prepararse a partir de la tetrahydroquinolina que contiene 6-metoxi de fórmula XII-a. La desmetilación es bien conocida para los expertos en el arte.

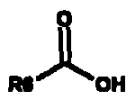
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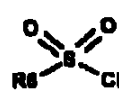
En un experimento típico, la desmetilación se efectúa por reacción de un compuesto de fórmula XII-a con BBr_3 en un solvente inerte tal como, pero no limitado a, diclorometano o tetrahidrofurano a baja temperatura, para dar los compuestos desprotegidos de fórmula general XVII. Alternativamente, la desmetilación puede efectuarse por la reacción de compuestos de fórmula XII-a con el complejo $\text{BF}_3 \cdot \text{Me}_2\text{S}$ a temperatura ambiente en un solvente inerte, como se mencionó para las desmetilaciones usando BBr_3 .



XVIII-a



XVIII-b



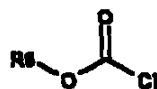
XVIII-c



XVIII-d



XVIII-e



XVIII-f



XVIII-g

Las funcionalizaciones subsiguientes del grupo OH libre en los derivados de fórmula XVII también son bien

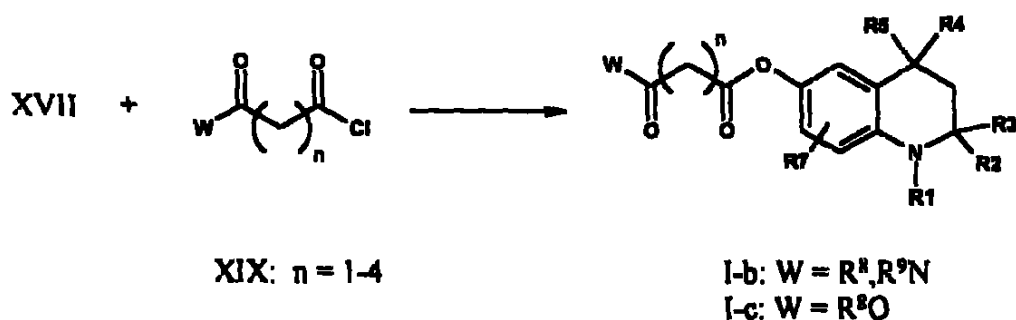
conocidas para los expertos en el arte, y pueden establecerse fácilmente usando reactivos de fórmula XVIII-a-g.

Para los reactivos que contienen haluro de fórmula XVIII, la reacción mencionada más arriba se efectúa típicamente a temperatura ambiente en un solvente adecuado, por ejemplo un solvente aprótico tal como N,N-dimetilformamida, diclorometano o tetrahidrofurano, en presencia de una base tal como, pero no limitada a, N,N-diisopropiletilamina o hidruro de sodio. Aditivos tales como N,N-dimetilaminopiridina o yoduro de tetrabutilamonio pueden acelerar esta última reacción. Además, la utilización de isocianatos o isotiocianatos de fórmula XVIII-d y XVIII-e en un solvente inerte a temperaturas ambientes o elevadas, de los compuestos de fórmula I-a donde $Y = \text{NHC(O)} \text{ ó } \text{NHC(S)}$, respectivamente.

Los compuestos donde $Y = \text{C(O)}$ también pueden obtenerse de una manera alternativa usando ácidos carboxílicos de fórmula general XVIII-b, usando un reactivo de acoplamiento tal como tetrafluoroborato de O-(benzotriazol-1-il)-N,N,N',N'-tetrametiluronio (TBTU), hexafluorofosfato de O-(7-azabenzotriazol-1-il)-N,N,N',N'-tetrametiluronio (HATU) o hexafluorofosfato de bromotripirrolidinofosfonio (PyBrOP) y una base terciaria, por ejemplo N,N-diisopropiletilamina, en un solvente como N,N-dimetilformamida o diclorometano, a temperatura ambiente o elevada.

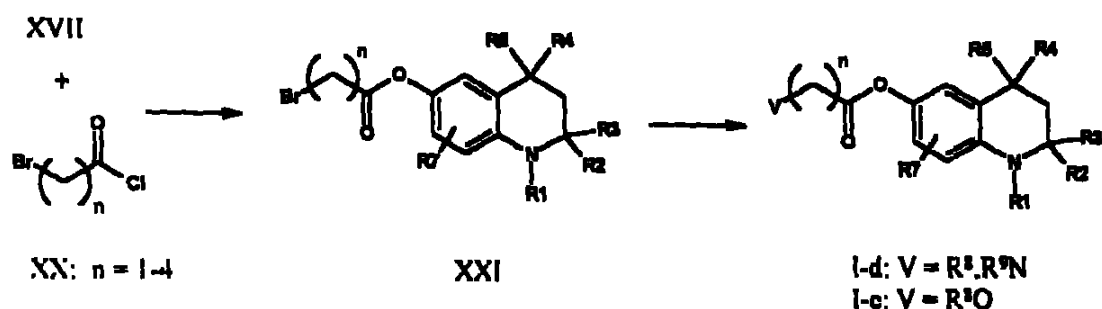
Los compuestos representados por la fórmula I-b-c, donde $W = \text{R}^8, \text{R}^9\text{N} \text{ ó } \text{R}^8\text{O}$, respectivamente, pueden sintetizarse haciendo reaccionar compuestos de fórmula general XVII con un cloruro de ácido de fórmula XIX, usando condiciones estándar.

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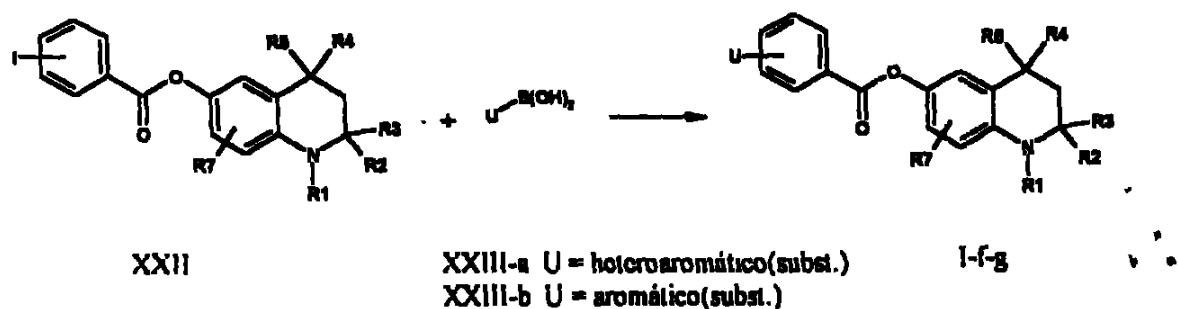


Alternativamente, los compuestos de la estructura I-b-c pueden prepararse a partir de derivados de fórmula XVII y un cloruro de ácido de fórmula XIX donde $\text{W} = \text{OEt}$, seguido por saponificación mediada por base (por ejemplo NaOH) y posterior condensación del ácido carboxílico libre, ya sea con aminas de estructura general $\text{R}^8, \text{R}^9\text{NH}$ o alcoholes de estructura general R^8OH , en presencia de un reactivo de acoplamiento tal como TBTU, HATU ó PyBrOP mencionados anteriormente, y una base terciaria tal como N,N-diisopropiletilamina.

Los compuestos representados por la fórmula I-d-e, donde $\text{V} = \text{R}^8, \text{R}^9\text{N}$ ó R^8O , respectivamente, pueden obtenerse por substitución nucleofílica de un halógeno tal como Br, presente en los compuestos de fórmula XXI, por aminas de estructura general $\text{R}^8, \text{R}^9\text{NH}$ o alcoholes de estructura general R^8OH . A su vez, la tetrahydroquinolina requerida de fórmula XXI puede sintetizarse a partir de un compuesto de fórmula XVII y un bromoacilcloruro de estructura general XX, usando procedimientos sintéticos conocidos en el arte.



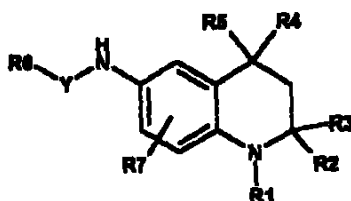
Los compuestos representados por la fórmula I-f-g, donde U = heteroaromático (sustituido) o fenilo (sustituido), respectivamente, pueden prepararse por acoplamiento de Suzuki de yodobenzóil derivados (sustituidos) de fórmula XXII con ácidos borónicos de fórmula general XXIII-a-b.



En un experimento típico, un yoduro de fórmula XXII se hace reaccionar con un ácido borónico de fórmula XXIII-a-b en una mezcla de solventes tal como dimetoxietano/etanol, usando fluoruro de cesio y un catalizador de paladio tal como tetrakis(trifenilfosfina) paladio o tris(dibenciliden-acetona)dipaladio, a temperatura elevada bajo una atmósfera de nitrógeno. La adición de trifenilfosfina puede acelerar la reacción y mejorar el rendimiento. La reacción mencionada más

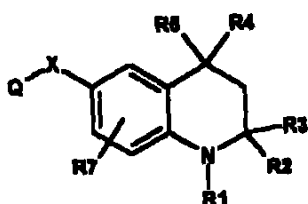
arriba está descrita extensamente en la literatura. Véase por ejemplo: A. Suzuki, Acc. Chem. Res. 15:178, 1982; N. Miyaura, T. Ishiyama, H. Sasaki, M. Ishikawa, M. Satoh y A. Suzuki, J. Am. Chem. Soc. 111:314, 1989.

De manera similar, los compuestos representados por la fórmula I-h donde X = NH e Y es como se definió anteriormente, pueden sintetizarse por los mismos métodos descritos más arriba para los compuestos de fórmula general Ia-g donde X = O.

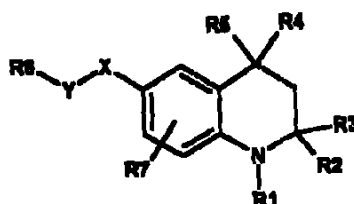


I-h

Los compuestos representados por la fórmula I-i-j donde X = C(O) ó S(O)₂ e Y = NH u O, respectivamente, pueden obtenerse por la reacción de los acil o sulfonyl cloruros, correspondientes de fórmula XXV, con aminas de estructura general R⁶NH₂ o alcoholes de estructura general R⁶OH, por el mismo método que se describió anteriormente para la preparación de los compuestos de fórmula I-a.



XXIV. Q = OH
XXV. Q = Cl

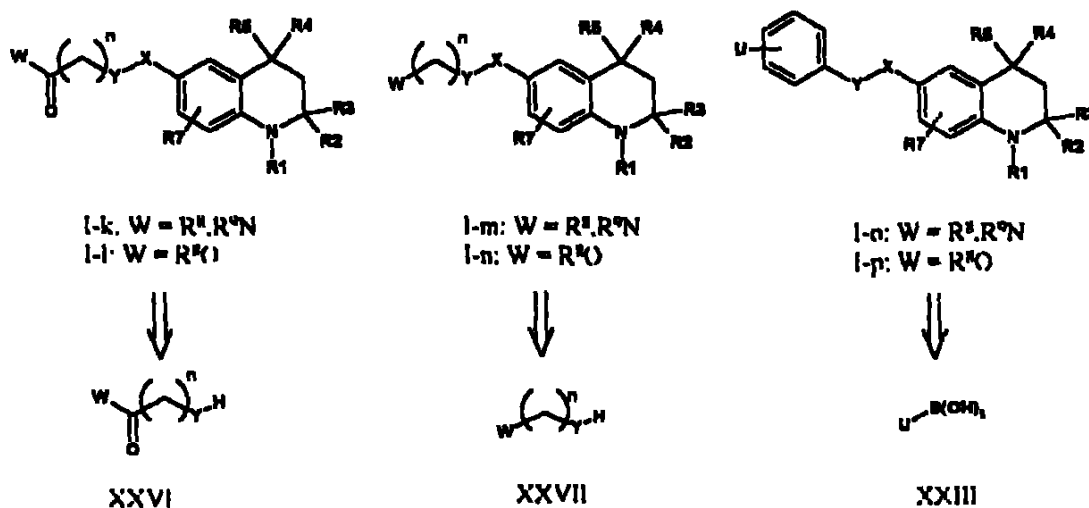


I-i: Y = NH
I-j: Y = O

Los acil o sulfonyl cloruros requeridos de fórmula XXV pueden prepararse a partir de los compuestos correspondientes de fórmula XXIV, por tratamiento por ejemplo con POCl_3 , PCl_5 , oxalilcloruro, fosgeno o SOCl_2 , en solventes tales como tolueno, acetonitrilo o N,N-dimetilformamida, como está descrito extensamente en la literatura. Véase por ejemplo M. Bonnat, M. Bradley y J.D. Kilburn, *Tetrahedron Lett.* 37:5409, 1996; J.G. Montana, G.M. Buckley, N. Cooper, H.J. Dyke y L. Gowers, *Bioorg. Med. Chem. Lett.* 8:2635, 1998; J. Hayler, P.D. Kane, D. LeGrand, F. Lugin, K. Menear, R. Price, M. Allen, X. Cockcroft, J. Ambler, K. Butler y K. Durren, *Bioorg. Med. Chem. Lett.* 10:1567, 2000.

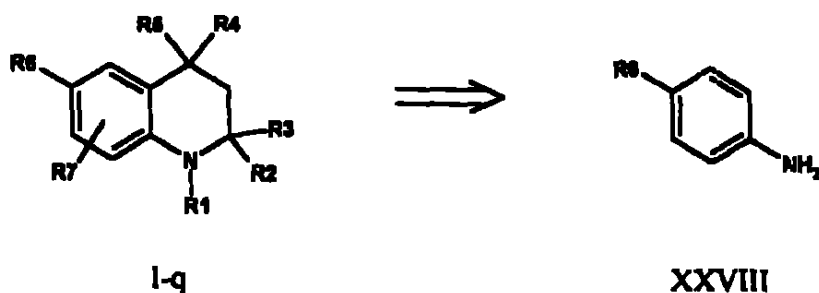
Alternativamente, los compuestos de fórmula XXIV donde $X = \text{C}(\text{O})$ pueden usarse directamente como materiales de partida para la preparación de derivados de fórmula I-1-j, usando reactivos de acoplamiento como los mencionados anteriormente.

Para los compuestos representados por la fórmula I-k-p, donde $X = \text{C}(\text{O})$ ó $\text{S}(\text{O})_2$ e $Y = \text{NH}$ u O , y $n = 1-4$, pueden seguirse procedimientos sintéticos conocidos en el arte.

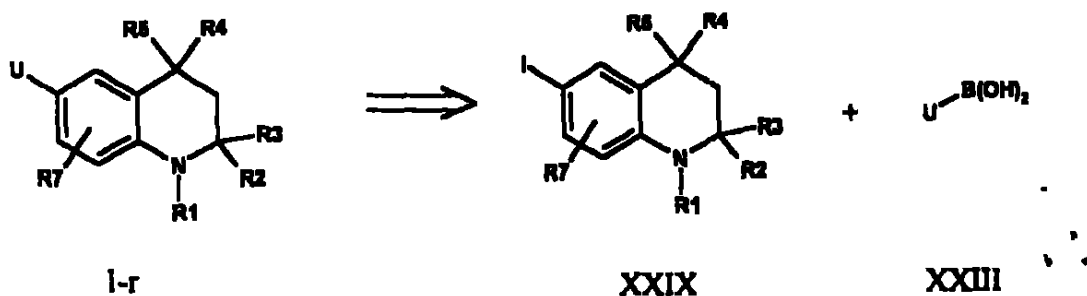


Así, la preparación de tetrahidroquinolinas de fórmula I-k-l puede efectuarse condensando una amina o alcohol representado por la fórmula XXVI (Y = NH u O, respectivamente) con cloruros de fórmula general XXV, usando condiciones estándar. En una propuesta similar, aminas o alcoholes de fórmula XXVII pueden utilizarse para preparar compuestos de fórmula I-m-n. Finalmente, el uso de los ácidos borónicos XXVIII mencionados anteriormente lleva a la preparación de compuestos de fórmula I-o-p, mediante la reacción de acoplamiento de Suzuki mencionada anteriormente.

Los compuestos de la presente invención donde X-Y es un enlace, representados por la fórmula I-q, pueden prepararse directamente a partir de anilinas de fórmula XXVIII disponibles en el comercio o que se pueden preparar fácilmente, mediante la secuencia de reacciones de Skraup, acilación y alquilación de Friedel-Crafts.



En otra propuesta, los compuestos representados por la fórmula I-r donde X-Y es un enlace y U = heteroaromático (substituido) o fenilo (substituido), pueden prepararse por condensación de Suzuki de los 6-yodo tetrahidroquinolina derivados correspondientes de fórmula XXIX con ácidos borónicos de fórmula general XXIII, como se mencionó anteriormente.



El yoduro requerido de fórmula XXIX puede obtenerse a partir de la amina correspondiente por medio de la bien conocida reacción de Sandmeijer.

Algunos de los compuestos de la invención, que pueden estar en la forma de una base libre, pueden ser aislados de la mezcla de reacción en la forma de una sal farmacéuticamente aceptable. Las sales farmacéuticamente aceptables también pueden obtenerse tratando la base libre de fórmula I con un ácido orgánico o inorgánico tal como cloruro

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de hidrógeno, bromuro de hidrógeno, yoduro de hidrógeno, ácido sulfúrico, ácido fosfórico, ácido acético, ácido propiónico, ácido glicólico, ácido maleico, ácido malónico, ácido metanosulfónico, ácido fumárico, ácido succínico, ácido tartárico, ácido cítrico, ácido benzoico y ácido ascórbico.

Los compuestos de la presente invención poseen al menos un átomo de carbono quiral y, por lo tanto, pueden obtenerse como enantiómeros puros o como una mezcla de enantiómeros, o como una mezcla de diastereómeros. Los métodos para obtener los enantiómeros puros son bien conocidos en el arte, por ejemplo cristalización de sales que se obtienen de ácidos ópticamente activos y la mezcla racémica, o cromatografía usando columnas quirales. Para los diastereómeros, pueden usarse columnas de fase directa o fase inversa.

Los compuestos de la invención pueden formar hidratos o solvatos. Es sabido por los expertos en el arte que los compuestos cargados forman especies hidratadas cuando son liofilizados con agua, o forman especies solvatadas cuando son concentrados en una solución con un solvente orgánico apropiado. Los compuestos de esta invención incluyen los hidratos o solvatos de los compuestos presentados.

Para seleccionar compuestos activos, el análisis a 10^{-5} M debe dar como resultado una actividad de más del 20% de la actividad máxima, cuando se usa FSH como referencia. Otro criterio podría ser el valor EC_{50} , que debe ser $< 10^{-5}$ M, de preferencia $< 10^{-7}$ M.

El experto en el arte podrá reconocer que los valores deseables de EC_{50} son dependientes del compuesto

analizado. Por ejemplo, un compuesto con una EC_{50} que es menor de 10^{-5} M, generalmente se considera candidato para la selección de fármacos. De preferencia, este valor es menor que 10^{-7} M. Sin embargo, un compuesto que tiene una EC_{50} más alta pero es selectivo para el receptor particular, puede ser un candidato aún mejor.

Los métodos para determinar la unión al receptor, y también los ensayos in vitro e in vivo para determinar la actividad biológica, de las gonadotrofinas, son bien conocidos. En general, el receptor expresado se pone en contacto con el compuesto que será analizado, y se mide la unión, o la estimulación o inhibición de una respuesta funcional.

Para medir una respuesta funcional, DNA aislado que codifica el gen del receptor de FSH, de preferencia el receptor humano, es expresado en células huéspedes adecuadas. Esta célula puede ser la célula de ovario de hámster chino, pero otras células también son adecuadas. De preferencia, las células son de origen de mamífero (Jia et al, Mol. Endocrin., 5:759-776, 1991).

Los métodos para construir líneas celulares que expresan FSH recombinante son bien conocidas en el arte (Sambrook et al., Molecular Cloning: a Laboratory Manual, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, última edición). La expresión del receptor se obtiene por la expresión del DNA que codifica para la proteína deseada. Las técnicas para mutagénesis dirigida al sitio, ligazón de secuencias adicionales, PCR y construcción de sistemas de expresión adecuados son todas, hoy en día, bien conocidas en

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el arte. Porciones, o el total, del DNA que codifica para la proteína deseada pueden construirse sintéticamente usando técnicas estándar de fase sólida, de preferencia incluyendo sitios de restricción para facilitar la ligazón. Elementos de control adecuados para la transcripción y traducción de la secuencia de codificación incluida, pueden ser proporcionados a las secuencias de codificación del DNA. Como es bien sabido, actualmente hay disponibles sistemas de expresión que son compatibles con una amplia variedad de huéspedes, incluyendo huéspedes procarióticos tales como bacterias y huéspedes eucarióticos tales como levadura, células vegetales, células de insectos, células de mamíferos, células de aves y similares.

Enseguida, las células que expresan el receptor se ponen en contacto con el compuesto de prueba para observar la unión, o la estimulación o inhibición de una respuesta funcional.

Alternativamente, membranas celulares aisladas que contienen el receptor expresado, pueden usarse para medir la unión del compuesto.

Para la medición de la unión, pueden usarse compuestos marcados con radioactividad o marcados con fluorescencia. Como compuesto de referencia, puede usarse FSH recombinante humana. Como alternativa, también pueden efectuarse ensayos de unión por competencia.

Otro ensayo involucra sondear para compuestos agonistas del receptor de FSH determinando la estimulación de la acumulación de cAMP mediada por el receptor. Así, este método involucra la expresión del receptor en la superficie

celular de una célula huésped, y exponer la célula al compuesto de prueba. Enseguida, se mide la cantidad de cAMP. El nivel de cAMP estará reducido o aumentado, dependiendo del efecto inhibitor o estimulante del compuesto de prueba sobre la unión al receptor.

Además de la medición directa, por ejemplo de los niveles de cAMP en la célula expuesta, pueden usarse líneas celulares que además de la transfección con el DNA que codifica para el receptor, también son transfectadas con un segundo DNA que codifica para un gen reportero, cuya expresión responde al nivel de cAMP. Estos genes reporteros podrían ser inducibles por cAMP o podrían ser contruidos de manera tal que estén conectados con nuevos elementos que responden a cAMP. En general, la expresión de los genes reporteros podría ser controlada por cualquier elemento de respuesta que reaccione a niveles cambiantes de cAMP. Genes reporteros adecuados son por ejemplo LacZ, fosfatasa alcalina, luciferasa de luciérnaga y proteína con fluorescencia verde. Los principios de estos ensayos de transactivación son bien conocidos en el arte y están descritos por ejemplo en Stratowa, Ch., Himmler, A. y Czernilofsky, A.P., (1995) Curr. Opin. Biotechnol. 6:574.

La presente invención también se refiere a una composición farmacéutica que comprende un derivado de tetrahydroquinolina o sus sales farmacéuticamente aceptables que tienen la fórmula general I, mezclado con auxiliares farmacéuticamente aceptables y opcionalmente otros agentes terapéuticos. Los auxiliares deben ser "aceptables" en el sentido de ser compatibles con los otros ingredientes de la

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composición y no ser dañinos para los sujetos receptores de la misma. Las composiciones farmacéuticas también pueden comprender los derivados de tetrahydroquinolina 1-acetil-6-benzoylamino-4-(4-metilfenil)-1,2,3,4-tetrahydro-2,2,4-trimetilquinolina, 1-acetil-4-fenil-1,2,3,4-tetrahydro-2,2,4,6-tetrametilquinolina, 1-acetil-4-fenil-1,2,3,4-tetrahydro-2,2,4,6,8-pentametilquinolina, 1-acetil-6-metoxi-4-fenil-1,2,3,4-tetrahydro-2,2,4-trimetilquinolina, 1-acetil-6-trifluoroacetilamino-4-(4-metilfenil)-1,2,3,4-tetrahydro-2,2,4-trimetilquinolina, 1-acetil-6-trifluoroacetilamino-4-fenil-1,2,3,4-tetrahydro-2,2,4-trimetilquinolina, 1-acetil-4-(4-clorofenil)-1,2,3,4-tetrahydro-2,2,4,6-tetrametilquinolina y 1-acetil-4-(4-bromofenil)-1,2,3,4-tetrahydro-2,2,4,6-tetrametilquinolina.

Las composiciones incluyen, por ejemplo, aquéllas adecuadas para administración oral, sublingual, subcutánea, intravenosa, intramuscular, local o rectal y similares, todas en formas de dosificación unitarias para administración.

Para la administración oral, el ingrediente activo puede ser presentado como unidades separadas tales como tabletas, cápsulas, polvos, granulados, soluciones, suspensiones y similares.

Para la administración parenteral, la composición farmacéutica de la invención puede ser presentada en contenedores de dosis unitarias o de dosis múltiples, por ejemplo líquidos para inyección en cantidades predeterminadas, por ejemplo en frascos sellados y ampollas, y también puede ser almacenada en un estado secado por congelación

(liofilizado) que requiere sólo de la adición de un vehículo líquido estéril, por ejemplo agua, antes del uso.

Mezclado con los auxiliares farmacéuticamente aceptables, por ejemplo los descritos en la referencia estándar, Gennaro, A.R. y colaboradores, Remington: "The Science and Practice of Pharmacy" (20a. Edición, Lippincott Williams & Wilkins, 2000, véase especialmente Parte 5: "Pharmaceutical Manufacturing"), el agente activo puede ser comprimido para formar unidades de dosificación sólidas tales como píldoras y tabletas, o puede ser procesado para formar cápsulas o supositorios. Mediante líquidos farmacéuticamente aceptables, el agente activo puede ser aplicado como una composición fluida, por ejemplo como una preparación inyectable, en la forma de una solución, suspensión o emulsión, o como un rocío, por ejemplo un rocío nasal.

Para fabricar unidades de dosificación sólidas, se contempla el uso de aditivos convencionales tales como rellenos, colorantes, aglutinantes poliméricos y similares. En general, puede usarse cualquier aditivo farmacéuticamente aceptable que no interfiera con la función de los compuestos activos. Los vehículos adecuados con los cuales el agente activo de la invención puede ser administrado en composiciones sólidas, incluyen lactosa, almidón, derivados de celulosa y similares, o mezclas de los mismos, usados en cantidades adecuadas. Para la administración parenteral, pueden usarse suspensiones acuosas, soluciones salinas isotónicas y soluciones inyectables estériles, conteniendo agentes dispersantes y/o agentes humectantes farmacéuticamente aceptables, tales como propilenglicol o butilenglicol.

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La invención además incluye una composición farmacéutica, como se describió anteriormente, en combinación con material de envase adecuado para dicha composición, incluyendo dicho material de envase instrucciones para el uso de la composición, como se describió anteriormente.

Los derivados de tetrahydroquinolina de la invención también pueden ser administrados en la forma de dispositivos farmacéuticos implantables, que consisten en un núcleo de material activo, encerrado por una membrana que regula la velocidad de liberación. Estos implantes son para ser aplicados en forma subcutánea o local, y liberarán el ingrediente activo a una velocidad aproximadamente constante durante periodos de tiempo relativamente largos, por ejemplo desde semanas hasta años. Los métodos para la preparación de dispositivos farmacéuticos implantables son bien conocidos en el arte, por ejemplo como se describe en la patente europea 0.303.306 (AKZO Nobel N.V.).

La dosis exacta y el régimen de administración del ingrediente activo, o de una composición farmacéutica del mismo, necesariamente serán dependientes del efecto terapéutico que se debe lograr (tratamiento de la infertilidad; contracepción), y pueden variar con el compuesto particular, la vía de administración, y la edad y condición del sujeto individual al que será administrado el medicamento.

En general, la administración parenteral requiere dosificaciones más bajas que otros métodos de administración que son más dependientes de la absorción. Sin embargo, una dosificación para seres humanos de preferencia contiene 0,0001-25 mg por kg de peso corporal. La dosis deseada puede

ser presentada como una sola dosis o como subdosis múltiples, administradas a intervalos apropiados a través del día o, en el caso de sujetos receptores hembras, como dosis para ser administradas a intervalos diarios apropiados a través del ciclo menstrual. La dosificación y también el régimen de administración pueden diferir entre un sujeto receptor hembra y uno macho.

Así, los compuestos de acuerdo con la invención pueden ser usados en terapia.

Otro aspecto de la invención reside en el uso de un compuesto derivado de tetrahydroquinolina que tiene la fórmula general I, para la fabricación de un medicamento para ser usado para el tratamiento de trastornos que responden a las rutas mediadas por el receptor de FSH, de preferencia para el control de la fertilidad, de mayor preferencia para el tratamiento de la infertilidad o para impedir la fertilidad. Los compuestos de acuerdo con la invención también pueden usarse para el tratamiento de trastornos dependientes de hormonas, tales como cáncer de mama, cáncer de próstata y endometriosis.

La invención se ilustra por los siguientes ejemplos.

EJEMPLOS

Ejemplo 1

1-Acetil-6-(ter-butoxicarbonil)amino-4-fenil-1,2,3,4-tetrahydro-2,2,4-trimetilquinolina

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(a). 6-(ter-Butoxicarbonil)amino-1,2-dihidro-2,2,4-trimetil-quinolina

Una mezcla de N-Boc-1,4-fenilendiamina (5,0 g) y yodo (1,3 g) en óxido de mesitilo (25 ml) fue agitada a 100°C por 2 horas. La mezcla de reacción fue concentrada al vacío y el residuo fue sometido a cromatografía en Al₂O₃ (Alumina B, act. III), en heptano/diclorometano = 8/2 como eluyente.

Rendimiento: 2,9 g. MS-ESI: [M+H]⁺ = 289,2.

(b). 1-Acetil-6-(ter-butoxicarbonil)amino-1,2-dihidro-2,2,4-trimetilquinolina

Acetil cloruro (11,1 ml) y anhídrido acético (11,1 ml) fueron agregados gota a gota a una solución de 6-(ter-butoxicarbonil)amino-1,2-dihidro-2,2,4-trimetilquinolina (8,5 g) en piridina (22 ml) y diclorometano (212 ml). Después de agitar por 18 horas, la mezcla de reacción fue lavada con HCl 2 M y agua. La capa orgánica fue secada (MgSO₄), filtrada y concentrada al vacío. El residuo fue sometido a cromatografía en sílica gel, en heptano/acetato de etilo = 8/2 (v/v) como eluyente.

Rendimiento: 6,7 g. MS-ESI: [M+H]⁺ = 331,2.

(c). 1-Acetil-6-amino-4-fenil-1,2,3,4-tetrahidro-2,2,4-trimetilquinolina

Una mezcla de 1-acetil-6-(ter-butoxicarbonil)amino-2,2,4-trimetil-1,2-dihidroquinolina (2,4 g) y AlCl₃ (9,5 g) en benceno (150 ml) fue agitada a 70°C por 1 hora. La mezcla de reacción fue enfriada (0°C) y extinguida con agua, y además se le agregó una solución de NaOH 2 M. La capa orgánica fue

separada, secada sobre MgSO_4 , filtrada y concentrada al vacío. El residuo fue sometido a cromatografía en sílica gel, en heptano/acetato de etilo = 8/2 (v/v) como eluyente.

Rendimiento: 1,6 g. MS-ESI: $[\text{M}+\text{H}]^+ = 309,2$.

(d). 1-Acetil-6-(ter-butoxicarbonil)amino-4-fenil-1,2,3,4-tetrahidro-2,2,4-trimetilquinolina

Una mezcla de 1-acetil-6-amino-4-fenil-1,2,3,4-tetrahidro-2,2,4-trimetilquinolina (20 mg), $(\text{Boc})_2\text{O}$ (30 mg) y N,N-diisopropiletilamina (20 μl) en tetrahidrofurano (4 ml) fue agitada a 60°C por 18 horas. La mezcla de reacción fue concentrada al vacío y el residuo fue sometido a cromatografía en sílica gel, en diclorometano/metanol = 1/0 $\Rightarrow$ 95/5 (v/v) como eluyente.

Rendimiento: 8 mg. MS-ESI: $[\text{M}+\text{H}]^+ = 409,2$.

Ejemplo 2

6-Amino-1-butiril-4-fenil-1,2,3,4-tetrahidro-2,2,4-trimetilquinolina

(a). 6-(ter-Butoxicarbonil)amino-1-butiril-1,2-dihidro-2,2,4-trimetilquinolina

Butiril cloruro (185 μl) fue agregado gota a gota a una solución de 6-(ter-butoxicarbonil)amino-1,2-dihidro-2,2,4-trimetilquinolina (50 mg) y una cantidad catalítica de N,N-dimetilaminopiridina en piridina (4 ml). Después de agitar por 18 horas, la mezcla de reacción fue concentrada al vacío. El residuo fue disuelto en acetato de etilo y lavado con agua.

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La capa orgánica fue separada, secada (MgSO_4) y concentrada al vacío. El residuo fue sometido a cromatografía en sílica gel, en heptano/acetato de etilo = 1/0 $\Rightarrow$ 7/3 (v/v) como eluyente. Rendimiento: 47 mg. MS-ESI: $[\text{M}+\text{H}]^+ = 359,4$.

(b). 6-Amino-1-butil-4-fenil-1,2,3,4-tetrahidro-2,2,4-trimetilquinolina

Una mezcla de 1-butil-6-(ter-butoxicarbonil)amino-1,2-dihidro-2,2,4-trimetilquinolina (47 mg) y AlCl_3 (52 mg) en benceno (2 ml), fue agitada a 60°C por 6 horas. La mezcla de reacción fue enfriada (0°C) y extinguida con agua, y además se le agregó una solución de NaOH 2 M. La capa orgánica fue separada, secada sobre MgSO_4 y concentrada al vacío. El residuo fue purificado por HPLC preparativa.

Rendimiento: 10 mg. MS-ESI: $[\text{M}+\text{H}]^+ = 337,2$; HPLC: $R_t = 6,97$ min. (método 1).

Ejemplo 3

1-Acetil-6-amino-4-(4-clorofenil)-1,2,3,4-tetrahidro-2,2,4-trimetilquinolina

Una mezcla de 1-acetil-6-(ter-butoxicarbonil)amino-1,2-dihidro-2,2,4-trimetilquinolina (25 mg) y AlCl_3 (35 mg) en clorobenceno (2 ml) fue agitada por 1 hora. La mezcla de reacción fue extinguida con agua y además se le agregó una solución de NaOH 2 M y acetato de etilo. La capa orgánica fue separada, secada sobre MgSO_4 y concentrada al vacío.

Rendimiento: 20 mg. MS-ESI: $[\text{M}+\text{H}]^+ = 343,4$; HPLC: $R_t = 6,16$ min. (método 1).

Ejemplo 4

1-Acetil-6-amino-4-(4-fluorofenil)-1,2,3,4-tetrahidro-2,2,4-trimetilquinolina

La alquilación de Friedel-Crafts de fluorobenceno (2 ml) con 1-acetil-6-(ter-butoxicarbonil)amino-1,2-dihidro-2,2,4-trimetilquinolina (25 mg) en presencia de AlCl_3 (35 mg), se efectuó de acuerdo con el método descrito en el Ejemplo 3.

Rendimiento: 15 mg. MS-ESI: $[\text{M}+\text{H}]^+ = 327,4$; HPLC: $R_t = 5,63$ min. (método 1).

Ejemplo 5

1-Acetil-6-amino-1,2,3,4-tetrahidro-4-(4-toliloil)-2,2,4-trimetilquinolina

La alquilación de Friedel-Crafts de tolueno (2 ml) con 1-acetil-6-(ter-butoxicarbonil)amino-1,2-dihidro-2,2,4-trimetilquinolina (25 mg) en presencia de AlCl_3 (35 mg), se efectuó de acuerdo con el método descrito en el Ejemplo 3.

Rendimiento: 22 mg. MS-ESI: $[\text{M}+\text{H}]^+ = 323,2$.

Ejemplo 6

1-Acetil-6-(4-clorobenzoil)amino-4-fenil-1,2,3,4-tetrahidro-2,2,4-trimetilquinolina

Una mezcla de 1-acetil-6-amino-4-fenil-1,2,3,4-tetrahidro-2,2,4-trimetilquinolina (10 mg), 4-clorobenzoil cloruro (11 mg) y N,N-diisopropiletilamina (22 μl) en tetrahidrofurano (1 ml), fue agitada por 18 horas. La mezcla de reacción fue concentrada al vacío, el residuo fue disuelto en acetato de etilo y lavado con HCl 0,5 N, agua, NaHCO_3

acuoso al 5%, agua y solución salina. La capa orgánica fue separada, secada (MgSO_4) y concentrada al vacío. El residuo fue sometido a cromatografía en sílica gel, en heptano/acetato de etilo = 1/0 $\Rightarrow$ 0/1 (v/v) como eluyente.

Rendimiento: 9,5 mg. MS-ESI: $[\text{M}+\text{H}]^+ = 447,4$; HPLC: $R_t = 10,87$ min. (método 1).

Ejemplo 7

1-Acetil-6-benzoilamino-4-fenil-1,2,3,4-tetrahydro-2,2,4-trimetilquinolina

La acilación de 1-acetil-6-amino-4-fenil-1,2,3,4-tetrahydro-2,2,4-trimetilquinolina (10 mg) con benzoil cloruro (9,1 mg) y N,N-diisopropiletilamina (22 μl) en tetrahydrofurano (1 ml), se efectuó de acuerdo con el método descrito en el Ejemplo 6.

Rendimiento: 1,2 mg. MS-ESI: $[\text{M}+\text{H}]^+ = 413,4$; HPLC: $R_t = 10,01$ min. (método 1).

Ejemplo 8

1-Acetil-4-fenil-1,2,3,4-tetrahydro-6-(4-(trifluorometil)-benzoil)amino-2,2,4-trimetilquinolina

La acilación de 1-acetil-6-amino-4-fenil-1,2,3,4-tetrahydro-2,2,4-trimetilquinolina (10 mg) con 4-trifluorometilbenzoil cloruro (14 mg) y N,N-diisopropiletilamina (22 μl) en tetrahydrofurano (1 ml), se efectuó de acuerdo con el método descrito en el Ejemplo 6.

Rendimiento: 8,9 mg. MS-ESI: $[\text{M}+\text{H}]^+ = 481,4$; HPLC: $R_t = 10,76$ min. (método 1).

Ejemplo 9

1-Acetil-6-(4-nitrobenzoil)amino-4-fenil-1,2,3,4-tetrahidro-2,2,4-trimetilquinolina

La acilación de 1-acetil-6-amino-4-fenil-1,2,3,4-tetrahidro-2,2,4-trimetilquinolina (10 mg) con 4-nitrobenzoil cloruro (12 mg) y N,N-diisopropiletilamina (22 µl) en tetrahidrofurano (1 ml), se efectuó de acuerdo con el método descrito en el Ejemplo 6.

Rendimiento: 8,2 mg. MS-ESI: $[M+H]^+$ = 458,4; HPLC: R_t = 10,02 min. (método 1).

Ejemplo 10

1-Acetil-4-fenil-6-(4-n-propilbenzoil)amino-1,2,3,4-tetrahidro-2,2,4-trimetilquinolina

La acilación de 1-acetil-6-amino-4-fenil-1,2,3,4-tetrahidro-2,2,4-trimetilquinolina (10 mg) con 4-n-propilbenzoil cloruro (12 mg) y N,N-diisopropiletilamina (22 µl) en tetrahidrofurano (1 ml), se efectuó de acuerdo con el método descrito en el Ejemplo 6.

Rendimiento: 6,7 mg. MS-ESI: $[M+H]^+$ = 455,4; HPLC: R_t = 11,19 min. (método 1).

Ejemplo 11

1-Acetil-6-(3-bromo-2,6-dimetoxibenzoil)amino-4-fenil-1,2,3,4-tetrahidro-2,2,4-trimetilquinolina

Una mezcla de 1-acetil-6-amino-4-fenil-1,2,3,4-tetrahidro-2,2,4-trimetilquinolina (25 mg), ácido 3-bromo-2,6-dimetoxibenzoico (23 mg), hexafluorofosfato de O-(7-azabenzotriazol-1-il)-N,N,N',N'-tetrametiluronio (HATU) (68

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mg) y N,N-diisopropiletilamina (32 µl) en diclorometano (4 ml), fue agitada por 18 horas. La mezcla de reacción fue concentrada al vacío, el residuo fue disuelto en acetato de etilo y lavado con HCl 0,5 M, agua, NaHCO₃ acuoso al 5%, agua y solución salina. La capa orgánica fue secada (MgSO₄) y concentrada al vacío. El residuo fue sometido a cromatografía en sílica gel, en heptano/acetato de etilo = 1/0 => 0/1 (v/v) como eluyente.

Rendimiento: 28 mg. MS-ESI: [M+H]⁺ = 551,4; HPLC: R_t = 3,75 min. (método 2).

Ejemplo 12

1-Acetil-4-fenil-6-(4-fenilbenzoil)amino-1,2,3,4-tetrahidro-2,2,4-trimetilquinolina

La acilación de 1-acetil-6-amino-4-fenil-1,2,3,4-tetrahidro-2,2,4-trimetilquinolina (11 mg) con 4-bifenil-carbonil cloruro (16 mg) y N,N-diisopropiletilamina (22 µl) en tetrahidrofurano (1 ml), se efectuó de acuerdo con el método descrito en el Ejemplo 6.

Rendimiento: 1,0 mg. MS-ESI: [M+H]⁺ = 489,4; HPLC: R_t = 11,62 min. (método 1).

Ejemplo 13

1-Acetil-6-(4-[4-clorofenil]benzoil)amino-4-fenil-1,2,3,4-tetrahidro-2,2,4-trimetilquinolina

(a). 1-Acetil-6-(4-yodobenzoil)amino-4-fenil-1,2,3,4-tetrahidro-2,2,4-trimetilquinolina

Una mezcla de 1-acetil-6-amino-4-fenil-1,2,3,4-tetrahidro-2,2,4-trimetilquinolina (300 mg), 4-yodobenzoil cloruro (520 mg) y una cantidad catalítica de N,N-dimetilaminopiridina en piridina (4 ml), fue agitada por 18 horas. La mezcla de reacción fue concentrada al vacío, el residuo fue disuelto en acetato de etilo y lavado con NaHCO₃ acuoso saturado, agua y solución salina. La capa orgánica fue secada (MgSO₄) y concentrada al vacío.

Rendimiento: 460 mg. MS-ESI: $[M+H]^+$ = 539,4; HPLC: R_t = 10,98 min. (método 1).

(b). 1-Acetil-6-(4-[4-clorofenil]benzoil)amino-4-fenil-1,2,3,4-tetrahidro-2,2,4-trimetilquinolina

Una mezcla de 1-acetil-6-(4-yodobenzoil)amino-4-fenil-1,2,3,4-tetrahidro-2,2,4-trimetilquinolina (25 mg), ácido 4-clorobencenoborónico (22 mg), fluoruro de cesio (14 mg), trifenilfosfina (5,0 mg) y tris-(dibencilidenacetona)dipaladio(0) (4,3 mg) en dimetoxi-etano/etanol 4:1 (5 ml) fue agitada por 15 minutos, a medida que se hacía burbujear nitrógeno a través de la solución. Después de 3 horas a 80°C, la mezcla de reacción fue concentrada al vacío, el residuo fue disuelto en acetato de etilo y lavado con HCl 0,5 M, agua, NaHCO₃ acuoso al 5%, agua y solución salina. La capa orgánica fue secada (MgSO₄) y concentrada al vacío. El residuo fue sometido a cromatografía en sílica gel, en heptano/acetato de etilo = 1/0 => 0/1 (v/v) como eluyente.

Rendimiento: 16 mg. MS-ESI: $[M+H]^+$ = 523,4; HPLC: R_t = 4,40 min. (método 2).

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Ejemplo 14

1-Acetil-4-fenil-6-(4-[3-piridil]benzoil)amino-1,2,3,4-tetrahidro-2,2,4-trimetilquinolina

El acoplamiento cruzado de Suzuki de 1-acetil-6-(4-yodobenzoil)amino-4-fenil-1,2,3,4-tetrahidro-2,2,4-trimetilquinolina (25 mg), éster cíclico de 1,3-propanodiol de ácido piridina-3-borónico (23 mg), fluoruro de cesio (14 mg), trifenilfosfina (5,0 mg) y tris(dibencilidenacetona)-dipaladio(0) (4,3 mg) en dimetoxietano/etanol 4:1 (v/v) (5 ml), se efectuó de acuerdo con el método descrito en el Ejemplo 13.

Rendimiento: 17 mg. MS-ESI: $[M+H]^+$ = 490,4; HPLC: R_t = 7,11 min. (método 1).

Ejemplo 15

1-Acetil-4-fenil-6-(2-fenil-5-metoxibenzoil)amino-1,2,3,4-tetrahidro-2,2,4-trimetilquinolina(a). 1-Acetil-6-(2-bromo-5-metoxibenzoil)amino-4-fenil-1,2,3,4-tetrahidro-2,2,4-trimetilquinolina

La condensación de 1-acetil-6-amino-4-fenil-1,2,3,4-tetrahidro-2,2,4-trimetilquinolina (25 mg) con ácido 2-bromo-5-metoxibenzoico (21 mg), por acción de HATU (68 mg) y N,N-diisopropiletilamina (32 μ l) en diclorometano (4 ml), se efectuó de acuerdo con el método descrito en el Ejemplo 11.

Rendimiento: 31 mg. MS-ESI: $[M+H]^+$ = 521,4; HPLC: R_t = 3,74 min. (método 2).

(b). 1-Acetil-4-fenil-6-(2-fenil-5-metoxibenzoil)amino-1,2,3,4-tetrahidro-2,2,4-trimetilquinolina

El acoplamiento cruzado de Suzuki de 1-acetil-4-fenil-6-(2-bromo-5-metoxibenzoil)amino-1,2,3,4-tetrahidro-2,2,4-trimetilquinolina (30 mg), ácido bencenoborónico (25 mg), fluoruro de cesio (21 mg), trifenilfosfina (7,0 mg) y tris(dibencilidenacetona)dipaladio(0) (6,0 mg) en dimetoxietano/etanol 4:1 (v/v) (5 ml), se efectuó de acuerdo con el método descrito en el Ejemplo 13.

Rendimiento: 23 mg. MS-ESI: $[M+H]^+$ = 519,4; HPLC: R_t = 10,87 min. (método 1).

Ejemplo 16

1-Acetil-4-fenil-6-(2-fenil-3-metilbenzoil)amino-1,2,3,4-tetrahidro-2,2,4-trimetilquinolina

(a). 1-Acetil-4-fenil-6-(2-bromo-3-metilbenzoil)amino-1,2,3,4-tetrahidro-2,2,4-trimetilquinolina

La condensación de 1-acetil-6-amino-4-fenil-1,2,3,4-tetrahidro-2,2,4-trimetilquinolina (25 mg) con ácido 2-bromo-3-metilbenzoico (19 mg), por acción de HATU (68 mg) y N,N-diisopropiletilamina (32 μ l) en diclorometano (4 ml), se efectuó de acuerdo con el método descrito en el Ejemplo 11.

Rendimiento: 16,3 mg. MS ESI: $[M+H]^+$ = 505,2; HPLC: R_t = 3,80 min. (método 2).

(b). 1-Acetil-4-fenil-6-(2-fenil-3-metilbenzoil)amino-1,2,3,4-tetrahidro-2,2,4-trimetilquinolina

El acoplamiento cruzado de Suzuki de 1-acetil-4-fenil-6-(2-bromo-3-metilbenzoil)amino-1,2,3,4-tetrahidro-2,2,4-trimetilquinolina (16 mg), ácido bencenoborónico (25 mg), fluoruro de cesio (21 mg), trifenilfosfina (7,0 mg) y tris(dibencilidenacetona)dipaladio(0) (6,0 mg) en dimetoxietano/etanol 4:1 (v/v) (5 ml), se efectuó de acuerdo con el método descrito en el Ejemplo 13.

Rendimiento: 4,9 mg. MS-ESI: $[M+H]^+$ = 503,3; HPLC: R_t = 4,61 min (método 2).

Ejemplo 17

1-Acetil-4-fenil-1,2,3,4-tetrahidro-6-(α -toluenosulfonyl)-amino-2,2,4-trimetilquinolina

La sulfonilación de 1-acetil-6-amino-4-fenil-1,2,3,4-tetrahidro-2,2,4-trimetilquinolina (10 mg) con α -toluenosulfonyl cloruro (12 mg) y N,N-diisopropiletilamina (22 μ l) en tetrahidrofurano (25 ml), se efectuó de acuerdo con el método de acilación descrito en el Ejemplo 6.

Rendimiento: 9,8 mg. MS-ESI: $[M+H]^+$ = 463,4; HPLC: R_t = 9,49 min. (método 1).

Ejemplo 18

1-Acetil-4-fenil-6-(fenilaminocarbonil)amino-1,2,3,4-tetrahidro-2,2,4-trimetilquinolina

Una mezcla de 1-acetil-6-amino-4-fenil-1,2,3,4-tetrahidro-2,2,4-trimetilquinolina (10 mg), isocianato de fenilo (8,0 mg) y N,N-diisopropiletilamina (22 μ l) en tetrahidrofurano (1 ml), fue agitada por 18 horas. La mezcla de reacción fue concentrada al vacío, el residuo fue disuelto

en acetato de etilo y lavado con HCl 0,5 M, agua, NaHCO₃ acuoso al 5%, agua y solución salina. La capa orgánica fue secada (MgSO₄) y concentrada al vacío. El residuo fue sometido a cromatografía en sílica gel, en heptano/acetato de etilo = 1/0 => 0/1 (v/v) como eluyente.

Rendimiento: 3,8 mg. MS-ESI: $[M+H]^+$ = 428,4; HPLC: R_t = 10,39 min. (método 1).

Ejemplo 19

1-Acetil-6-(ter-butilaminotiocarbonil)amino-4-fenil-1,2,3,4-tetrahydro-2,2,4-trimetilquinolina

La formación de tiourea de 1-acetil-6-amino-4-fenil-1,2,3,4-tetrahydro-2,2,4-trimetilquinolina (10 mg) con isotiocianato de ter-butilo (7,5 mg) y N,N-diisopropiletilamina (22 µl) en tetrahydrofurano (1 ml), se efectuó de acuerdo con el método descrito en el Ejemplo 18.

Rendimiento: 0,50 mg. MS-ESI: $[M+H]^+$ = 424,4; HPLC: R_t = 5,90 min. (método 1).

Ejemplo 20

1-Acetil-6-(4-ter-butilbencil)amino-4-fenil-1,2,3,4-tetrahydro-2,2,4-trimetilquinolina.ácido trifluoroacético

Una mezcla de 1-acetil-6-amino-4-fenil-1,2,3,4-tetrahydro-2,2,4-trimetilquinolina (10 mg), 4-(ter-butil)-bencilcloruro (6,5 mg) y N,N-diisopropiletilamina (10 µl) en tetrahydrofurano (1 ml), fue agitada a 50°C por 18 horas. La mezcla de reacción fue concentrada al vacío, el residuo fue disuelto en acetato de etilo y lavado con HCl 0,5 M, agua, NaHCO₃ acuoso al 5%, agua y solución salina. La capa orgánica

fue secada (MgSO_4) y concentrada al vacío. El residuo fue sometido a cromatografía en sílica gel, en heptano/acetato de etilo = 1/0 $\Rightarrow$ 0/1 (v/v) como eluyente.

Rendimiento: 3,1 mg. MS-ESI: $[\text{M}+\text{H}]^+ = 455,4$; HPLC: $R_t = 10,00$ min. (método 1).

Ejemplo 21

1-Acetil-4-fenil-6-(3-fenilpropionil)amino-1,2,3,4-tetrahidro-2,2,4-trimetilquinolina

La acilación de 1-acetil-6-amino-4-fenil-1,2,3,4-tetrahidro-2,2,4-trimetilquinolina (10 mg) con 3-fenilpropionil cloruro (11 mg) y N,N-diisopropiletilamina (22 μl) en tetrahidrofurano (1 ml), se efectuó de acuerdo con el método descrito en el Ejemplo 6.

Rendimiento: 1,2 mg. MS-ESI: $[\text{M}+\text{H}]^+ = 441,4$; HPLC: $R_t = 10,25$ min. (método 1).

Ejemplo 22

1-Acetil-6-(2-furoil)amino-4-fenil-1,2,3,4-tetrahidro-2,2,4-trimetilquinolina

La acilación de 1-acetil-6-amino-4-fenil-1,2,3,4-tetrahidro-2,2,4-trimetilquinolina (10 mg) con 2-furoil cloruro (8,5 mg) y N,N-diisopropiletilamina (22 μl) en tetrahidrofurano (1 ml), se efectuó de acuerdo con el método descrito en el Ejemplo 6.

Rendimiento: 7,7 mg. MS-ESI: $[\text{M}+\text{H}]^+ = 403,4$; HPLC: $R_t = 8,91$ min. (método 1).

Ejemplo 23

1-Acetil-6-(isovaleril)amino-4-fenil-1,2,3,4-tetrahidro-2,2,4-trimetilquinolina

La acilación de 1-acetil-6-amino-4-fenil-1,2,3,4-tetrahidro-2,2,4-trimetilquinolina (10 mg) con isovaleril cloruro (7,8 mg) y N,N-diisopropiletilamina (22 μ l) en tetrahidrofurano (1 ml), se efectuó de acuerdo con el método descrito en el Ejemplo 6.

Rendimiento: 5,3 mg. MS-ESI: $[M+H]^+ = 393,4$; HPLC: $R_t = 9,35$ min. (método 1).

Ejemplo 24

1-Acetil-6-(3-[adamantan-1-il]propionil)amino-4-fenil-1,2,3,4-tetrahidro-2,2,4-trimetilquinolina

La condensación de 1-acetil-6-amino-4-fenil-1,2,3,4-tetrahidro-2,2,4-trimetilquinolina (10 mg) con ácido 3-(adamantan-1-il)propiónico (10 mg), por acción de HATU (25 mg) y N,N-diisopropiletilamina (22 μ l) en diclorometano (1 ml), se efectuó de acuerdo con el método descrito en el Ejemplo 11.

Rendimiento: 6,7 mg. MS-ESI: $[M+H]^+ = 499,4$; HPLC: $R_t = 12,43$ min. (método 1).

Ejemplo 25

1-Acetil-6-(etilmalonil)amino-4-fenil-1,2,3,4-tetrahidro-2,2,4-trimetilquinolina

La acilación de 1-acetil-6-amino-4-fenil-1,2,3,4-tetrahidro-2,2,4-trimetilquinolina (150 mg) con etil malonil cloruro (147 mg) y N,N-diisopropiletilamina (314 μ l) en

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tetrahidrofurano (8 ml), se efectuó de acuerdo con el método descrito en el Ejemplo 6.

Rendimiento: 163 mg. MS-ESI: $[M+H]^+ = 423,2$; HPLC: $R_t = 8,48$ min. (método 1).

Ejemplo 26

1-Acetil-6-([4-metoxibencilamino]carbonilmetilcarbonil)amino-4-fenil-1,2,3,4-tetrahidro-2,2,4-trimetilquinolina

(a). 1-Acetil-6-(hidroxicarbonilmetilcarbonil)amino-4-fenil-1,2,3,4-tetrahidro-2,2,4-trimetilquinolina

Una solución de NaOH 2 M fue agregada gota a gota a una solución con agitación de 1-acetil-6-(etil malonil)amino-4-fenil-1,2,3,4-tetrahidro-2,2,4-trimetilquinolina (161 mg) en dioxano/agua 4:1 (v/v) (12 ml), hasta pH 14. Después de agitar por 3,5 horas, la mezcla de reacción fue vertida en agua y extraída con acetato de etilo a pH 2. La capa orgánica fue lavada con agua y solución salina, secada ($MgSO_4$) y concentrada al vacío.

Rendimiento: 163 mg. MS-ESI: $[M+H]^+ = 395,2$; HPLC: $R_t = 7,43$ min. (método 1).

(b). 1-Acetil-6-([4-metoxibencilamino]carbonilmetilcarbonil)amino-4-fenil-1,2,3,4-tetrahidro-2,2,4-trimetilquinolina

La condensación de 4-metoxibencilamina (5,2 mg) con 1-acetil-6-(hidroxicarbonilmetilcarbonil)amino-4-fenil-1,2,3,4-tetrahidro-2,2,4-trimetilquinolina (10 mg), por acción de HATU (19 mg) y N,N-diisopropiletilamina (16 μ l) en

tetrahidrofurano (2 ml), se efectuó de acuerdo con el método descrito en el Ejemplo 11.

Rendimiento: 7,3 mg. MS-ESI: $[M+H]^+$ = 514,4; HPLC: R_t = 8,80 min. (método 1).

Ejemplo 27

1-Acetil-6-([etoxicarbonilmetilamino]carbonilmetilcarbonil)-amino-4-fenil-1,2,3,4-tetrahydro-2,2,4-trimetilquinolina

La condensación de etil éster de glicina.HCl (5,3 mg) con 1-acetil-6-(hidroxicarbonilmetilcarbonil)amino-4-fenil-1,2,3,4-tetrahydro-2,2,4-trimetilquinolina (10 mg), por acción de HATU (19 mg) y N,N-diisopropiletilamina (16 μ l) en tetrahidrofurano (2 ml), se efectuó de acuerdo con el método descrito en el Ejemplo 11.

Rendimiento: 4,6 mg. MS-ESI: $[M+H]^+$ = 480,6; HPLC: R_t = 7,94 min. (método 1).

Ejemplo 28

1-Acetil-6-([N-etil-N-bencilamino]carbonilmetilcarbonil)amino-4-fenil-1,2,3,4-tetrahydro-2,2,4-trimetilquinolina

La condensación de N-etilbencilamina (5,2 mg) con 1-acetil-6-(hidroxicarbonilmetilcarbonil)amino-4-fenil-1,2,3,4-tetrahydro-2,2,4-trimetilquinolina (10 mg), por acción de HATU (19 mg) y N,N-diisopropiletilamina (16 μ l) en tetrahidrofurano (2 ml), se efectuó de acuerdo con el método descrito en el Ejemplo 11.

Rendimiento: 7,3 mg. MS-ESI: $[M+H]^+$ = 512,6; HPLC: R_t = 9,36 min. (método 1).

Ejemplo 29

1-Acetil-6-([2,4-difluorobencilamino]metilcarbonil)amino-4-fenil-1,2,3,4-tetrahidro-2,2,4-trimetilquinolina

(a). 1-Acetil-6-(bromoacetil)amino-4-fenil-1,2,3,4-tetrahidro-2,2,4-trimetilquinolina

La acilación de 1-acetil-6-amino-4-fenil-1,2,3,4-tetrahidro-2,2,4-trimetilquinolina (130 mg) con bromoacetil cloruro (69 μ l) y N,N-diisopropiletilamina (121 μ l) en diclorometano (10 ml), se efectuó de acuerdo con el método descrito en el Ejemplo 6.

Rendimiento: 151 mg. MS-ESI: $[M+H]^+ = 431,2$.

(b). 1-Acetil-6-([2,4-difluorobencilamino]metilcarbonil)-amino-4-fenil-1,2,3,4-tetrahidro-2,2,4-trimetilquinolina

Una mezcla de 1-acetil-6-(bromoacetil)amino-4-fenil-1,2,3,4-tetrahidro-2,2,4-trimetilquinolina (10 mg), 2,4-difluorobencilamina (6,0 mg) y N,N-diisopropiletilamina (10 μ l) en dioxano (2 ml), fue agitada a 40°C por 18 horas. La mezcla de reacción fue concentrada al vacío. El residuo fue sometido a cromatografía en sílica gel, en diclorometano/metanol = 1/0 => 95/5 (v/v) como eluyente.

Rendimiento: 5,5 mg. MS-ESI: $[M+H]^+ = 492,4$; HPLC: $R_t = 6,74$ min. (método 1).

Ejemplo 30

1-Acetil-6-([4-{1-fenil}-piperazinil]metilcarbonil)amino-4-fenil-1,2,3,4-tetrahidro-2,2,4-trimetilquinolina

La N-alquilación de 1-fenilpiperazina (7,0 μ l) con 1-acetil-6-(bromoacetil)amino-4-fenil-1,2,3,4-tetrahidro-2,2,4-trimetilquinolina (10 mg) y N,N-diisopropiletilamina (10 μ l) en dioxano (2 ml), se efectuó de acuerdo con el método descrito en el Ejemplo 29.

Rendimiento: 8,4 mg. MS-ESI: $[M+H]^+ = 511,4$; HPLC: $R_t = 7,01$ min. (método 1).

Ejemplo 31

1-Acetil-6-([N-morfolino]metilcarbonil)amino-4-fenil-1,2,3,4-tetrahidro-2,2,4-trimetilquinolina

La N-alquilación de morfolina (4,0 μ l) con 1-acetil-6-(bromoacetil)amino-4-fenil-1,2,3,4-tetrahidro-2,2,4-trimetilquinolina (10 mg) y N,N-diisopropiletilamina (9,0 μ l) en diclorometano (2 ml), se efectuó de acuerdo con el método descrito en el Ejemplo 29.

Rendimiento: 10 mg. MS-ESI: $[M+H]^+ = 436,4$; HPLC: $R_t = 5,64$ min. (método 1).

Ejemplo 32

1-Acetil-6-(2-tiofenmetilamino)carbonil-4-fenil-1,2,3,4-tetrahidro-2,2,4-trimetilquinolina

(a). Metil éster del ácido 1,2-dihidro-2,2,4-trimetilquinolina-6-carboxílico

La reacción de Skraup de 4-aminobenzoato de metilo (5,0 g) y yodo (1,7 g) en óxido de mesitilo (25 ml), se efectuó de acuerdo con el método descrito en el Ejemplo 1.

Rendimiento: 2,3 g. MS-ESI: $[M+H]^+ = 232,2$.

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(b). Metil éster del ácido 1-acetil-1,2-dihidro-2,2,4-trimetilquinolina-6-carboxílico

Una mezcla de metil éster del ácido 1,2-dihidro-2,2,4-trimetilquinolina-6-carboxílico (2,3 g) y una cantidad catalítica de N,N-dimetilaminopiridina en anhídrido acético (60 ml), fue agitada a 100°C por 18 horas. La mezcla de reacción fue concentrada al vacío, el residuo fue disuelto en acetato de etilo y lavado con agua y solución salina. La capa orgánica fue secada (MgSO₄) y concentrada al vacío. El residuo fue sometido a cromatografía en sílica gel, en heptano/acetato de etilo = 1/1 => 1/9 (v/v) como eluyente.

Rendimiento: 2,3 g.

(c). Metil éster del ácido 1-acetil-4-fenil-1,2,3,4-tetrahidro-2,2,4-trimetilquinolina-6-carboxílico

La alquilación de Friedel-Crafts de benceno (60 ml) con metil éster del ácido 1-acetil-1,2-dihidro-2,2,4-trimetilquinolina-6-carboxílico (2,3 g) en presencia de AlCl₃ (4,4 g), se efectuó de acuerdo con el método descrito en el Ejemplo 3.

Rendimiento: 1,2 g. MS-ESI: [M+H]⁺ = 352,4; HPLC: R_t = 9,72 min. (método 1).

(d). Acido 1-acetil-4-fenil-1,2,3,4-tetrahidro-2,2,4-trimetilquinolina-6-carboxílico

Una solución de NaOH 2 M fue agregada gota a gota a una solución con agitación de metil éster del ácido 1-acetil-4-fenil-1,2,3,4-tetrahidro-2,2,4-trimetilquinolina-6-

carboxílico (1,2 g) en dioxano/agua 4:1 (v/v) (50 ml), hasta pH 12. Después de agitar por 18 horas, la mezcla de reacción fue vertida en agua y extraída con acetato de etilo a pH 2. La capa orgánica fue lavada con agua y solución salina, secada (MgSO_4) y concentrada al vacío.

Rendimiento: 891 mg. MS-ESI: $[\text{M}+\text{H}]^+ = 338,2$.

(e). 1-Acetil-6-(2-tiofenmetilamino)carbonil-4-fenil-1,2,3,4-tetrahidro-2,2,4-trimetilquinolina

La condensación de 2-tiofenmetilamina (5,0 mg) con ácido 1-acetil-4-fenil-1,2,3,4-tetrahidro-2,2,4-trimetilquinolina-6-carboxílico (10 mg), por acción de HATU (23 mg) y N,N-diisopropiletilamina (19 μl) en diclorometano (2 ml), se efectuó de acuerdo con el método descrito en el Ejemplo 11.

Rendimiento: 3,0 mg. MS-ESI: $[\text{M}+\text{H}]^+ = 433,4$; HPLC: $R_t = 9,28$ min. (método 1).

Ejemplo 33

1-Acetil-6-(2-[4-metoxifenil]etilamino)carbonil-4-fenil-1,2,3,4-tetrahidro-2,2,4-trimetilquinolina

La condensación de 2-(4-metoxifenil)etilamina (6,1 mg) con ácido 1-acetil-4-fenil-1,2,3,4-tetrahidro-2,2,4-trimetilquinolina-6-carboxílico (10 mg), por acción de HATU (23 mg) y N,N-diisopropiletilamina (19 μl) en diclorometano (2 ml), se efectuó de acuerdo con el método descrito en el Ejemplo 11.

Rendimiento: 9,9 mg. MS-ESI: $[\text{M}+\text{H}]^+ = 457,4$; HPLC: $R_t = 9,34$ min. (método 1).

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Ejemplo 34**1-Acetil-6-(3-isopropoxipropilamino)carbonil-4-fenil-1,2,3,4-tetrahidro-2,2,4-trimetilquinolina**

La condensación de 3-isopropoxipropilamina (5,2 mg) con ácido 1-acetil-4-fenil-1,2,3,4-tetrahidro-2,2,4-trimetilquinolina-6-carboxílico (10 mg), por acción de HATU (23 mg) y N,N-diisopropiletilamina (19 µl) en diclorometano (2 ml), se efectuó de acuerdo con el método descrito en el Ejemplo 11.

Rendimiento: 8,8 mg. MS-ESI: $[M+H]^+$ = 437,4; HPLC: R_t = 8,80 min. (método 1).

Ejemplo 35**1-Acetil-6-(2-[metiltio]etilamino)carbonil-4-fenil-1,2,3,4-tetrahidro-2,2,4-trimetilquinolina**

La condensación de 2-(metiltio)etilamina (4,1 mg) con ácido 1-acetil-4-fenil-1,2,3,4-tetrahidro-2,2,4-trimetilquinolina-6-carboxílico (10 mg), por acción de HATU (23 mg) y N,N-diisopropiletilamina (19 µl) en diclorometano (2 ml), se efectuó de acuerdo con el método descrito en el Ejemplo 11.

Rendimiento: 10 mg. MS-ESI: $[M+H]^+$ = 411,4; HPLC: R_t = 3,33 min. (método 2).

Ejemplo 36**1-Acetil-6-(4-metoxibenciloxi)carbonil-4-fenil-1,2,3,4-tetrahidro-2,2,4-trimetilquinolina**

La condensación de alcohol 4-metoxibencílico (6,2 mg) con ácido 1-acetil-4-fenil-1,2,3,4-tetrahidro-2,2,4-trimetilquinolina-6-carboxílico (10 mg), por acción de HATU

(23 mg) y N,N-diisopropiletilamina (19 μ l) en diclorometano (2 ml), se efectuó de acuerdo con el método descrito en el Ejemplo 11.

Rendimiento: 7,2 mg. MS-ESI: $[M+H]^+$ = 458,4; HPLC: R_t = 3,90 min. (método 2).

Ejemplo 37

1-Acetil-6-(4-fenilbenzoil)oxi-4-fenil-1,2,3,4-tetrahidro-2,2,4-trimetilquinolina

(a). 1,2-Dihidro-6-metoxi-2,2,4-trimetilquinolina

La reacción de Skraup de 4-anisidina (5,0 g) y yodo (1,7 g) en óxido de mesitilo (25 ml), se efectuó de acuerdo con el método descrito en el Ejemplo 1.

Rendimiento: 2,3 g. MS-ESI: $[M+H]^+$ = 204,2.

(b). 1-Acetil-1,2-dihidro-6-metoxi-2,2,4-trimetilquinolina

Acetil cloruro (8 ml) fue agregado gota a gota a una solución enfriada (0°C) de 1,2-dihidro-6-metoxi-2,2,4-trimetilquinolina (1,7 g) y una cantidad catalítica de N,N-dimetilaminopiridina en piridina (60 ml). Después de agitar por 18 horas, la mezcla de reacción fue concentrada al vacío. El residuo fue disuelto en diclorometano y lavado con HCl 1 M, agua, NaHCO_3 acuoso al 5%, agua y solución salina. La capa orgánica fue secada (MgSO_4) y concentrada al vacío. El residuo fue sometido a cromatografía en sílica gel, en diclorometano como eluyente.

Rendimiento: 1,8 g. MS-ESI: $[M+H]^+$ = 246,2.

(c). 1-Acetil-6-metoxi-4-fenil-1,2,3,4-tetrahidro-2,2,4-trimetilquinolina

La alquilación de Friedel-Crafts de benceno (25 ml) con 1-acetil-1,2-dihidro-6-metoxi-2,2,4-trimetilquinolina (1,8 g) en presencia de AlCl_3 (3,0 g), se efectuó de acuerdo con el método descrito en el Ejemplo 3.

Rendimiento: 1,9 g. HPLC: $R_t = 9,62$ min. (método 1).

(d). 1-Acetil-6-hidroxi-4-fenil-1,2,3,4-tetrahidro-2,2,4-trimetilquinolina

Tribromuro de boro (1,30 ml) fue agregado gota a gota a una solución enfriada (0°C) de 1-acetil-6-metoxi-4-fenil-1,2,3,4-tetrahidro-2,2,4-trimetilquinolina (0,9 g) en diclorometano (75 ml). Después de agitar por 18 horas, la mezcla de reacción fue vertida en agua y extraída con acetato de etilo. La capa orgánica fue lavada con agua, NaHCO_3 acuoso al 5% y agua, secada (MgSO_4) y concentrada al vacío.

Rendimiento: 950 mg. MS-ESI: $[\text{M}+\text{H}]^+ = 310,2$; HPLC: $R_t = 8,41$ min. (método 1).

(e). 1-Acetil-4-fenil-6-(4-fenilbenzoil)oxi-1,2,3,4-tetrahidro-2,2,4-trimetilquinolina

La acilación de 1-acetil-6-hidroxi-4-fenil-1,2,3,4-tetrahidro-2,2,4-trimetilquinolina (10 mg) con 4-bifenil-carbonil cloruro (14 mg) y N,N-diisopropiletilamina (28 μl) en tetrahidrofurano (1 ml), se efectuó de acuerdo con el método descrito en el Ejemplo 6.

Rendimiento: 8,2 mg. MS-ESI: $[\text{M}+\text{H}]^+ = 490,4$; HPLC: $R_t = 12,81$ min. (método 1).

Ejemplo 38

1-Acetil-6-(ter-butilacetil)oxi-4-fenil-1,2,3,4-tetrahidro-2,2,4-trimetilquinolina

La acilación de 1-acetil-6-hidroxi-4-fenil-1,2,3,4-tetrahidro-2,2,4-trimetilquinolina (10 mg) con ter-butilacetil cloruro (9,0 μ l) y N,N-diisopropiletilamina (28 μ l) en tetrahidrofurano (1 ml), se efectuó de acuerdo con el método descrito en el Ejemplo 6.

Rendimiento: 3,9 mg. MS-ESI: $[M+H]^+$ = 408,4; HPLC: R_t = 11,28 min. (método 1).

Ejemplo 39

1-Acetil-6-(ciclopropilmetil)oxi-4-fenil-1,2,3,4-tetrahidro-2,2,4-trimetilquinolina

Una mezcla de 1-acetil-6-hidroxi-4-fenil-1,2,3,4-tetrahidro-2,2,4-trimetilquinolina (20 mg), carbonato de cesio (63 mg), bromuro de tetrabutilamonio (29 mg) y clorometilciclopropano (8,4 μ l) en acetonitrilo (1 ml), fue agitada a 50°C por 18 horas. La mezcla de reacción fue concentrada al vacío y el residuo fue sometido a cromatografía en sílica gel, en heptano/acetato de etilo = 1/0 $\Rightarrow$ 6/4 (v/v) como eluyente.

Rendimiento: 10 mg. MS-ESI: $[M+H]^+$ = 364,2; HPLC: R_t = 10,73 min. (método 1).

Ejemplo 40

1-Acetil-6-(3-piridilmetil)oxi-4-fenil-1,2,3,4-tetrahidro-2,2,4-trimetilquinolina

La alquilación de 1-acetil-6-hidroxi-4-fenil-1,2,3,4-tetrahidro-2,2,4-trimetilquinolina (20 mg) con 3-picolilcloruro.HCl (12 mg), carbonato de cesio (63 mg) y bromuro de tetrabutilamonio (30 mg) en acetonitrilo (1 ml), se efectuó de acuerdo con el método descrito en el Ejemplo 39. Rendimiento: 10 mg. MS-ESI: $[M+H]^+$ = 401,2; HPLC: R_t = 8,40 min. (método 1).

Ejemplo 41

1-Acetil-6-etil-4-fenil-1,2,3,4-tetrahidro-2,2,4-trimetil-quinolina

(a). 1,2-Dihidro-6-etil-2,2,4-trimetilquinolina

La reacción de Skraup de p-etilanilina (1,0 g) y yodo (0,34 g) en óxido de mesitilo (5 ml), se efectuó de acuerdo con el método descrito en el Ejemplo 1.

Rendimiento: 800 mg. MS-ESI: $[M+H]^+$ = 202,2.

(b). 1-Acetil-6-etil-1,2,3,4-tetrahidro-2,2,4-trimetil-quinolina

La acilación de 1,2-dihidro-6-etil-2,2,4-trimetil-quinolina (800 mg) con acetil cloruro (3,5 ml) y una cantidad catalítica de N,N-dimetilaminopiridina en piridina (25 ml), se efectuó de acuerdo con el método descrito en el Ejemplo 37.

Rendimiento: 410 mg. MS-ESI: $[M+H]^+$ = 244,2.

(c). 1-Acetil-6-etil-4-fenil-1,2,3,4-tetrahidro-2,2,4-trimetilquinolina

La alquilación de Friedel-Crafts de benceno (10 ml) con 1-acetil-6-etil-1,2,3,4-tetrahidro-2,2,4-trimetilquinolina (410 mg) en presencia de AlCl_3 (710 mg), se efectuó de acuerdo con el método descrito en el Ejemplo 3.

Rendimiento: 407 mg. MS-ESI: $[\text{M}+\text{H}]^+ = 322,4$.

Ejemplo 42

1-Acetil-6-(1,1'-bifenil)-4-fenil-1,2,3,4-tetrahidro-2,2,4-trimetilquinolina

(a). 1-Acetil-6-yodo-4-fenil-1,2,3,4-tetrahidro-2,2,4-trimetilquinolina

Una solución de nitrito de sodio (31 mg) fue agregada gota a gota a una solución enfriada (0°C) de 1-acetil-6-amino-4-fenil-1,2,3,4-tetrahidro-2,2,4-trimetilquinolina (128 mg) y ácido sulfúrico (82 mg) en agua (2 ml). Después de agitar a 0°C por 15 minutos, se agregó una solución de yoduro de potasio (105 mg). Después de agitar por 18 horas, la mezcla de reacción fue vertida en diclorometano. La capa orgánica fue separada y lavada con tiosulfato de sodio acuoso al 5% y agua, secada (MgSO_4) y concentrada al vacío.

Rendimiento: 160 mg. MS-ESI: $[\text{M}+\text{H}]^+ = 420,0$.

(b). 1-Acetil-6-(1,1'-bifenil-11)-4-fenil-1,2,3,4-tetrahidro-2,2,4-trimetilquinolina

El acoplamiento cruzado de Suzuki de 1-acetil-6-yodo-4-fenil-1,2,3,4-tetrahidro-2,2,4-trimetilquinolina (20 mg), ácido (1,1'-bifenil-4-il)borónico (28 mg), fluoruro de cesio (15 mg), trifenilfosfina (5 mg) y tris-

(dibencilidenacetona)dipaladio(0) (4,5 mg) en dimetoxietano/etanol 4:1 (v/v) (5 ml), se efectuó de acuerdo con el método descrito en el Ejemplo 13.

Rendimiento: 16 mg. MS-ESI: $[M+H]^+$ = 446,4; HPLC: R_t = 6,84 min. (método 2).

Ejemplo 43

1-Acetil-6-(4-clorofenil)-4-fenil-1,2,3,4-tetrahidro-2,2,4-trimetilquinolina

El acoplamiento cruzado de Suzuki de 1-acetil-6-yodo-4-fenil-1,2,3,4-tetrahidro-2,2,4-trimetilquinolina (20 mg), ácido 4-clorofenilborónico (22 mg), fluoruro de cesio (15 mg), trifenilfosfina (5 mg) y tris(dibencilidenacetona)-dipaladio(0) (4,5 mg) en dimetoxietano/etanol 4:1 (v/v) (5 ml), se efectuó de acuerdo con el método descrito en el Ejemplo 13.

Rendimiento: 8,6 mg. MS-ESI: $[M+H]^+$ = 404,4; HPLC: R_t = 5,94 min. (método 2).

Ejemplo 44

1-Acetil-6-amino-4-fenil-1,2,3,4-tetrahidro-2,2,4,7-tetrametilquinolina

(a). 1-Acetil-6-amino-1,2-dihidro-2,2,4,7-tetrametilquinolina

Una mezcla de N-Boc-2-metil-1,4-fenilendiamina (2,3 g), sulfato de magnesio (6,3 g), 4-ter-butilcatecol (100 mg) y yodo (300 mg) en acetona (15 ml), fue agitada a reflujo por 20 horas. La mezcla de reacción fue enfriada hasta temperatura ambiente y filtrada. El filtrado fue concentrado al vacío y el

residuo fue sometido a cromatografía en SiO_2 , con heptano/acetato de etilo = 1/0 => 3/1 (v/v) como eluyente. El producto, 6-(ter-butoxicarbonil)amino-1,2-dihidro-2,2,4,7-tetrametilquinolina, fue acilado con acetyl cloruro (1,0 ml) en una mezcla de piridina (1,0 ml) y tolueno (10 ml). Después de agitar por 1 hora, la mezcla de reacción fue lavada con ácido cítrico acuoso al 3% y agua. La capa orgánica fue secada (MgSO_4) y concentrada al vacío. El residuo fue sometido a cromatografía en sílica gel, en heptano/acetato de etilo = 1/0 => 3/1 (v/v) como eluyente.

Rendimiento: 350 mg. MS-ESI: $[\text{M}+\text{H}]^+ = 345,4$

(b). 1-Acetil-6-amino-4-fenil-1,2,3,4-tetrahidro-2,2,4,7-tetrametilquinolina

AlCl_3 (266 mg) fue agregado a una solución caliente (70°C) de 1-acetil-6-amino-1,2-dihidro-2,2,4,7-tetrametilquinolina (100 mg) en benceno (10 ml). Después de 3 horas, la mezcla fue enfriada y concentrada al vacío. El residuo fue disuelto en acetato de etilo y lavado con agua. La capa orgánica fue separada, secada (MgSO_4) y concentrada al vacío. El residuo fue sometido a cromatografía en sílica gel, en heptano/acetato de etilo = 1/0 => 3/1 (v/v) como eluyente.

Rendimiento: 75 mg. MS-ESI: $[\text{M}+\text{H}]^+ = 323,4$.

Ejemplo 45

1-Acetil-6-(4-fenilbenzoil)amino-4-fenil-1,2,3,4-tetrahidro-2,2,4,7-tetrametilquinolina

La acilación de 1-acetil-6-amino-4-fenil-1,2,3,4-tetrahidro-2,2,4,7-tetrametilquinolina (20 mg) con 4-

bifenilcarbonil cloruro (100 mg) y piridina (100 µl) en tetrahidrofurano (5 ml), se efectuó de acuerdo con el método descrito en el Ejemplo 6.

Rendimiento: 24 mg. MS-ESI: $[M+H]^+$ = 503,4.

Ejemplo 46

1-Acetil-6-(4-fenilbenzoil)amino-8-metoxi-4-fenil-1,2,3,4-tetrahidro-2,2,4-trimetilquinolina

(a). 1-Acetil-6-amino-8-metoxi-4-fenil-1,2,3,4-tetrahidro-2,2,4-trimetilquinolina

La reacción de Skraup de N-Boc-3-metoxi-1,4-fenilendiamina (450 mg), sulfato de magnesio (1,0 g), 4-ter-butilcatecol (10 mg) y yodo (20 mg) en acetona (10 ml), la acilación del producto con acetil cloruro (250 µl) y piridina (250 µl) en tolueno (10 ml), y la alquilación de Friedel-Crafts subsiguiente con $AlCl_3$ (266 mg), se efectuaron de acuerdo con los métodos descritos en el Ejemplo 44.

Rendimiento: 71 mg. MS-ESI: $[M+H]^+$ = 339,4.

(b). 1-Acetil-6-(4-fenilbenzoil)amino-8-metoxi-4-fenil-1,2,3,4-tetrahidro-2,2,4-trimetilquinolina

La acilación de 1-acetil-6-amino-8-metoxi-4-fenil-1,2,3,4-tetrahidro-2,2,4-trimetilquinolina (20 mg) con 4-bifenilcarbonil cloruro (100 mg) y piridina (100 µl) en tetrahidrofurano (5 ml), se efectuó de acuerdo con el método descrito en el Ejemplo 6.

Rendimiento: 25 mg. MS-ESI: $[M+H]^+$ = 519,4.

Ejemplo 47

1-Acetil-6-(2-furoil)amino-1,2,3,4-tetrahidro-4-toloil-2,2,4-trimetilquinolina

La acilación de 1-acetil-6-amino-4-toloil-1,2,3,4-tetrahidro-2,2,4-trimetilquinolina (10 mg) con 2-furoil cloruro (8,1 mg) y N,N-diisopropiletilamina (20 µl) en tetrahidrofurano (1 ml), se efectuó de acuerdo con el método descrito en el Ejemplo 6.

Rendimiento: 12 mg. MS-ESI: $[M+H]^+$ = 417,4; HPLC: R_t = 4,90 min. (método 2).

Ejemplo 48

1-Acetil-6-(4-fenilbenzoil)amino-1,2,3,4-tetrahidro-4-toloil-2,2,4-trimetilquinolina

La acilación de 1-acetil-6-amino-4-toloil-1,2,3,4-tetrahidro-2,2,4-trimetilquinolina (10 mg) con 4-bifenilcarbonil cloruro (14 mg) y N,N-diisopropiletilamina (20 µl) en tetrahidrofurano (1 ml), se efectuó de acuerdo con el método descrito en el Ejemplo 6.

Rendimiento: 9,3 mg. MS-ESI: $[M+H]^+$ = 503,4; HPLC: R_t = 6,08 min. (método 2).

Ejemplo 49

1-Acetil-6-(etilmalonil)amino-1,2,3,4-tetrahidro-4-toloil-2,2,4-trimetilquinolina

La acilación de 1-acetil-6-amino-4-toloil-1,2,3,4-tetrahidro-2,2,4-trimetilquinolina (10 mg) con etil malonil cloruro (9,4 mg) y N,N-diisopropiletilamina (20 µl) en tetrahidrofurano (1

ml), se efectuó de acuerdo con el método descrito en el Ejemplo 6.

Rendimiento: 12 mg. MS-ESI: $[M+H]^+$ = 437,4; HPLC: R_t = 4,71 min. (método 2).

Ejemplo 50

1-Acetil-6-(3,5-dibromobenzoil)amino-4-fenil-1,2,3,4-tetrahidro-2,2,4-trimetilquinolina

La condensación con HATU de 1-acetil-6-amino-4-fenil-1,2,3,4-tetrahidro-2,2,4-trimetilquinolina (10 mg) con ácido 3,5-dibromobenzoico (10 mg) y N,N-diisopropiletilamina (22 μ l) en tetrahidrofurano (1 ml), se efectuó de acuerdo con el método descrito en el Ejemplo 11.

Rendimiento: 15,9 mg. MS-ESI: $[M+H]^+$ = 470,9; HPLC: R_t = 10,11 min. (método 1).

Ejemplo 51

1-Acetil-6-(5-bromo-2-metilaminobenzoil)amino-4-fenil-1,2,3,4-tetrahidro-2,2,4-trimetilquinolina

La condensación con HATU de 1-acetil-6-amino-4-fenil-1,2,3,4-tetrahidro-2,2,4-trimetilquinolina (10 mg) con ácido 5-bromo-2-metilaminobenzoico (8,4 mg) y N,N-diisopropiletilamina (22 μ l) en tetrahidrofurano (1 ml), se efectuó de acuerdo con el método descrito en el Ejemplo 11.

Rendimiento: 13,2 mg. MS-ESI: $[M+H]^+$ = 522,1; HPLC: R_t = 8,95 min. (método 1).

Ejemplo 52

1-Acetil-6-(3,4,5-trimetoxibenzoil)amino-4-fenil-1,2,3,4-tetrahydro-2,2,4-trimetilquinolina

La acilación de 1-acetil-6-amino-4-fenil-1,2,3,4-tetrahydro-2,2,4-trimetilquinolina (10 mg) con 3,4,5-trimetoxibenzoil cloruro (12 mg) y N,N-diisopropiletilamina (22 µl) en tetrahydrofurano (1 ml), se efectuó de acuerdo con el método descrito en el Ejemplo 6.

Rendimiento: 14,5 mg. MS-ESI: $[M+H]^+$ = 503,2; HPLC: R_t = 11,26 min. (método 1).

Ejemplo 53

1-Acetil-6-(3,5-dicloro-2,6-dimetoxibenzoil)amino-4-fenil-1,2,3,4-tetrahydro-2,2,4-trimetilquinolina

La condensación con HATU de 1-acetil-6-amino-4-fenil-1,2,3,4-tetrahydro-2,2,4-trimetilquinolina (10 mg) con ácido 3,5-dicloro-2,6-dimetoxibenzoico (9,0 mg) y N,N-diisopropiletilamina (22 µl) en tetrahydrofurano (1 ml), se efectuó de acuerdo con el método descrito en el Ejemplo 11.

Rendimiento: 15,1 mg. MS-ESI: $[M+H]^+$ = 541,1; HPLC: R_t = 10,92 min. (método 1).

Ejemplo 54

1-Acetil-6-(2-acetiloxibenzoil)amino-4-fenil-1,2,3,4-tetrahydro-2,2,4-trimetilquinolina

La condensación con HATU de 1-acetil-6-amino-4-fenil-1,2,3,4-tetrahydro-2,2,4-trimetilquinolina (10 mg) con ácido 2-acetiloxibenzoico (6,0 mg) y N,N-diisopropiletilamina

(22 μ l) en tetrahydrofurano (1 ml), se efectuó de acuerdo con el método descrito en el Ejemplo 11.

Rendimiento: 1,1 mg. MS-ESI: $[M+H]^+$ = 471,2; HPLC: R_t = 14,35 min. (método 1).

Ejemplo 55

1-Acetil-6-(2-acetamido-5-bromobenzoil)amino-4-fenil-1,2,3,4-tetrahydro-2,2,4-trimetilquinolina

La condensación con HATU de 1-acetil-6-amino-4-fenil-1,2,3,4-tetrahydro-2,2,4-trimetilquinolina (10 mg) con ácido 2-acetamido-5-bromobenzoico (6,0 mg) y N,N-diisopropiletilamina (22 μ l) en tetrahydrofurano (1 ml), se efectuó de acuerdo con el método descrito en el Ejemplo 11.

Rendimiento: 2,3 mg. MS-ESI: $[M+H]^+$ = 530,2; HPLC: R_t = 12,01 min. (método 1).

Ejemplo 56

1-Acetil-6-(5-bromo-2-N,N-dimetilcarbamoylbenzoil)amino-4-fenil-1,2,3,4-tetrahydro-2,2,4-trimetilquinolina

La condensación con HATU de 1-acetil-6-amino-4-fenil-1,2,3,4-tetrahydro-2,2,4-trimetilquinolina (10 mg) con ácido 5-bromosalicílico (8,0 mg) y N,N-diisopropiletilamina (22 μ l) en tetrahydrofurano (1 ml), se efectuó de acuerdo con el método descrito en el Ejemplo 11.

Rendimiento: 3,0 mg. MS-ESI: $[M+H]^+$ = 580,2; HPLC: R_t = 12,53 min. (método 1).

Ejemplo 57

1-Acetil-6-(2-[4-toloiilo]benzoil)amino-4-fenil-1,2,3,4-tetrahydro-2,2,4-trimetilquinolina

La condensación con HATU de 1-acetil-6-amino-4-fenil-1,2,3,4-tetrahydro-2,2,4-trimetilquinolina (10 mg) con ácido 2-[4-toloiilo]benzoico (8,0 mg) y N,N-diisopropiletilamina (22 µl) en tetrahydrofurano (1 ml), se efectuó de acuerdo con el método descrito en el Ejemplo 11.

Rendimiento: 8,0 mg. MS-ESI: $[M+H]^+$ = 519,4; HPLC: R_t = 13,11 min. (método 1).

Ejemplo 58

1-Acetil-6-(2-metilsulfonilo]benzoil)amino-4-fenil-1,2,3,4-tetrahydro-2,2,4-trimetilquinolina(a). 1-Acetil-6-(2-metoxibenzoil)amino-4-fenil-1,2,3,4-tetrahydro-2,2,4-trimetilquinolina

La acilación de 1-acetil-6-amino-4-fenil-1,2,3,4-tetrahydro-2,2,4-trimetilquinolina (0,60 g) con 2-metoxibenzoil cloruro (1,0 g) y N,N-diisopropiletilamina (1,7 ml) en tetrahydrofurano (60 ml), se efectuó de acuerdo con el método descrito en el Ejemplo 6.

Rendimiento: 0,65 g. MS-ESI: $[M+H]^+$ = 443,4.

(b). 1-Acetil-6-(2-hidroxibenzoil)amino-4-fenil-1,2,3,4-tetrahydro-2,2,4-trimetilquinolina

BBr₃ (0,69 ml) fue agregado gota a gota a una solución de 1-acetil-6-(2-metoxibenzoil)amino-4-fenil-1,2,3,4-tetrahydro-2,2,4-trimetilquinolina (0,64 g) en diclorometano

(40 mL). Después de agitar por 4 horas, el análisis TLC indicó una conversión completa. Se agregó agua a la mezcla de reacción y la agitación se continuó por 15 minutos. La mezcla fue lavada con NaHCO_3 acuoso al 5% y agua. La capa orgánica fue secada (MgSO_4) y concentrada al vacío. El producto resultante fue usado sin mayor purificación.

Rendimiento: 0,62 g. MS-ESI: $[\text{M}+\text{H}]^+ = 429,4$.

(c). 1-Acetil-6-(2-metilsulfoniloxibenzoil)amino-4-fenil-1,2,3,4-tetrahidro-2,2,4-trimetilquinolina

La sulfonilación de 1-acetil-6-(2-hidroxibenzoil)-amino-4-fenil-1,2,3,4-tetrahidro-2,2,4-trimetilquinolina (12 mg) con metilsulfonil cloruro (6,5 μl), se efectuó en piridina (1 ml). El análisis TLC después de agitar por 16 horas, mostró la conversión a un producto que subía más alto. La mezcla fue concentrada, el residuo fue disuelto en diclorometano y lavado con agua. La capa orgánica fue secada (Na_2SO_4) y concentrada al vacío. El producto crudo fue purificado por cromatografía en columna en sílica gel. Eluyente: heptano/acetato de etilo = 8/2 (v/v).

Rendimiento: 8,0 mg. MS-ESI: $[\text{M}+\text{H}]^+ = 507,4$; HPLC: $R_t = 5,03$ min. (método 2).

Ejemplo 59

1-Acetil-6-(2-[3,5-dimetilisoxazol-4-sulfonil]oxibenzoil)-amino-4-fenil-1,2,3,4-tetrahidro-2,2,4-trimetilquinolina

La sulfonilación de 1-acetil-6-(2-hidroxibenzoil)-amino-4-fenil-1,2,3,4-tetrahidro-2,2,4-trimetilquinolina (20 mg) con 3,5-dimetilisoxazol-4-sulfonil cloruro (27 mg) en

piridina (2 ml), se efectuó de acuerdo con el método descrito en el Ejemplo 58.

Rendimiento: 14 mg. MS-ESI: $[M+H]^+$ = 588,4; HPLC: R_t = 14,46 min. (método 1).

Ejemplo 60

1-Acetil-6-(2-metoxycarboniletilcarboniloxibenzoil)amino-4-fenil-1,2,3,4-tetrahidro-2,2,4-trimetilquinolina

La acilación de 1-acetil-6-(2-hidroxibenzoil)amino-4-fenil-1,2,3,4-tetrahidro-2,2,4-trimetilquinolina (20 mg) con 3-carbometoxipropionil cloruro (14 mg) y N,N-diisopropiletilamina (40 µl) en tetrahidrofurano (2 ml), se efectuó de acuerdo con el método descrito en el Ejemplo 6.

Rendimiento: 21,4 mg. MS-ESI: $[M+H]^+$ = 543,6; HPLC: R_t = 6,98 min. (método 1).

Ejemplo 61

1-Acetil-6-(2-[5-metilisoxazol-3-carbonil]oxibenzoil)amino-4-fenil-1,2,3,4-tetrahidro-2,2,4-trimetilquinolina

La acilación de 1-acetil-6-(2-hidroxibenzoil)amino-4-fenil-1,2,3,4-tetrahidro-2,2,4-trimetilquinolina (15 mg) con 5-metilisoxazol-3-carbonil cloruro (10 mg) y N,N-diisopropiletilamina (30 µl) en tetrahidrofurano (1 ml), se efectuó de acuerdo con el método descrito en el Ejemplo 6.

Rendimiento: 4,0 mg. MS-ESI: $[M+H]^+$ = 538,4; HPLC: R_t = 9,84 min. (método 1).

Ejemplo 62**1-Acetil-6-(2-(2-oxazolidinona-5-metil)oxibenzoil)amino-4-fenil-1,2,3,4-tetrahidro-2,2,4-trimetilquinolina**

La alquilación de 1-acetil-6-(2-hidroxibenzoil)-amino-4-fenil-1,2,3,4-tetrahidro-2,2,4-trimetilquinolina (20 mg) con 5-clorometil-2-oxazolidinona (7 mg), carbonato de cesio (63 mg) y bromuro de tetrabutilamonio (30 mg) en acetonitrilo (1 ml), se efectuó de acuerdo con el método descrito en el Ejemplo 39.

Rendimiento: 25 mg. MS-ESI: $[M+H]^+$ = 542,4; HPLC: R_t = 8,21 min. (método 1).

Ejemplo 63**1-Acetil-6-(2-(morfolino-4-carbonil)oxibenzoil)amino-4-fenil-1,2,3,4-tetrahidro-2,2,4-trimetilquinolina**

La acilación de 1-acetil-6-(2-hidroxibenzoil)amino-4-fenil-1,2,3,4-tetrahidro-2,2,4-trimetilquinolina (15 mg) con morfolino-4-carbonil cloruro (12 μ l) y N,N-diisopropil-etilamina (30 μ l) en tetrahidrofurano (1 ml), se efectuó de acuerdo con el método descrito en el Ejemplo 6.

Rendimiento: 5,4 mg. MS-ESI: $[M+H]^+$ = 542,4; HPLC: R_t = 10,02 min. (método 1).

Ejemplo 64**1-Acetil-6-(2-fenilaminobenzoil)amino-4-fenil-1,2,3,4-tetrahidro-2,2,4-trimetilquinolina**

La condensación con HATU de 1-acetil-6-amino-4-fenil-1,2,3,4-tetrahidro-2,2,4-trimetilquinolina (15 mg) con ácido N-fenilntranílico (21 mg) y N,N-diisopropiletilamina

(33 μ l) en tetrahydrofurano (1 ml), se efectuó de acuerdo con el método descrito en el Ejemplo 11.

Rendimiento: 5,8 mg. MS-ESI: $[M+H]^+$ = 504,4; HPLC: R_t = 13,42 min. (método 1).

Ejemplo 65

1-Acetil-6-(2-pirrolidona-N-etilcarbonil)amino-4-fenil-1,2,3,4-tetrahydro-2,2,4-trimetilquinolina

(a). 1-Acetil-6-acriloilamino-4-fenil-1,2,3,4-tetrahydro-2,2,4-trimetilquinolina

La acilación de 1-acetil-6-amino-4-fenil-1,2,3,4-tetrahydro-2,2,4-trimetilquinolina (0,12 g) con acrilóil cloruro (39 μ l) y N,N-diisopropiletilamina (0,21 ml) en tetrahydrofurano (10 ml), se efectuó de acuerdo con el método descrito en el Ejemplo 6.

Rendimiento: 0,13 g. MS-ESI: $[M+H]^+$ = 363,2.

(b). 1-Acetil-6-(2-pirrolidona-N-etilcarbonil)amino-4-fenil-1,2,3,4-tetrahydro-2,2,4-trimetilquinolina

A una mezcla de 2-pirrolidona (19 mg) y NaH (18 mg, al 60% en aceite) en THF (1 mL), se agregó 1-acetil-6-acriloilamino-4-fenil-1,2,3,4-tetrahydro-2,2,4-trimetilquinolina (8 mg) en THF (1 mL). Después de agitar por 18 horas, el análisis TLC indicó la conversión a un producto que subía más alto. La mezcla fue diluida con acetato de etilo y lavada con agua, HCl 0,5 N y agua. La capa orgánica fue secada (Na_2SO_4) y concentrada al vacío. La purificación se

efectuó por cromatografía en columna en sílica gel, usando heptano/acetato de etilo = 8/2 $\Rightarrow$ 1/1 (v/v) como eluyente.

Rendimiento: 4,6 mg. MS-ESI: $[M+H]^+$ = 448,4; HPLC: R_t = 4,51 min. (método 2).

Ejemplo 66

1-Acetil-6-(etoxietoxietilcarbonil)amino-4-fenil-1,2,3,4-tetrahidro-2,2,4-trimetilquinolina

La adición de Michael de 2-etoxietanol (19 mg) y 1-acetil-6-acrilolilamino-4-fenil-1,2,3,4-tetrahidro-2,2,4-trimetilquinolina (8 mg) en THF (1 mL), se efectuó de acuerdo con el método descrito en el Ejemplo 65.

Rendimiento: 1,0 mg. MS-ESI: $[M+H]^+$ = 453,4; HPLC: R_t = 5,03 min. (método 2).

Ejemplo 67

1-Acetil-6-(2-pirrolidona-N-metoxycarbonilmetilcarbonil)amino-4-fenil-1,2,3,4-tetrahidro-2,2,4-trimetilquinolina

La condensación de N-hidroximetil-2-pirrolidona (22 mg) y 1-acetil-6-(hidroxicarbonilmetilcarbonil)amino-4-fenil-1,2,3,4-tetrahidro-2,2,4-trimetilquinolina (15 mg), por acción de HATU (29 mg) y N,N-diisopropiletilamina (33 μ l) en tetrahidrofurano (2 ml), se efectuó de acuerdo con el método descrito en el Ejemplo 11.

Rendimiento: 4,6 mg. MS-ESI: $[M+H]^+$ = 478,4; HPLC: R_t = 5,53 min. (método 2).

Ejemplo 68

1-Acetil-6-(ter-butilcarbamoil-N-[2-etoxi]carbonilmetil-carbonil)amino-4-fenil-1,2,3,4-tetrahidro-2,2,4-trimetil-quinolina

La condensación de carbamato de ter-butil-N-(2-hidroxietilo) (29 μ l) y 1-acetil-6-(hidroxicarbonilmetil-carbonil)amino-4-fenil-1,2,3,4-tetrahidro-2,2,4-trimetil-quinolina (15 mg), por acción de HATU (29 mg) y N,N-diisopropiletilamina (33 μ l) en tetrahidrofurano (2 ml), se efectuó de acuerdo con el método descrito en el Ejemplo 11. Rendimiento: 11 mg. MS-ESI: $[M+H]^+$ = 538,4; HPLC: R_t = 5,32 min. (método 2).

Ejemplo 69

1-Acetil-6-(2-furilmetoxycarbonilmetilcarbonil)amino-4-fenil-1,2,3,4-tetrahidro-2,2,4-trimetilquinolina

La condensación de alcohol furfurílico (17 μ l) y 1-acetil-6-(hidroxicarbonilmetilcarbonil)amino-4-fenil-1,2,3,4-tetrahidro-2,2,4-trimetilquinolina (15 mg), por acción de HATU (29 mg) y N,N-diisopropiletilamina (33 μ l) en tetrahidrofurano (2 ml), se efectuó de acuerdo con el método descrito en el Ejemplo 11.

Rendimiento: 7,1 mg. MS-ESI: $[M+H]^+$ = 475,4; HPLC: R_t = 5,30 min. (método 2).

Ejemplo 70

1-Acetil-6-([ciclopropilmetilamino]metilcarbonil)amino-4-fenil-1,2,3,4-tetrahidro-2,2,4-trimetilquinolina

La alquilación de ciclopropilmetilamina (4 μ l) con 1-acetil-6-(bromoacetil)amino-4-fenil-1,2,3,4-tetrahidro-2,2,4-trimetilquinolina (10 mg) y N,N-diisopropiletilamina (13 μ l) en diclorometano (1 ml), se efectuó de acuerdo con el método descrito en el Ejemplo 29.

Rendimiento: 6,8 mg. MS-ESI: $[M+H]^+ = 535,6$; HPLC: $R_t = 6,29$ min. (método 2).

Ejemplo 71

1-Acetil-4-(2-metoxifenil)-6-(4-fenilbenzoil)amino-1,2,3,4-tetrahidro-2,2,4-trimetilquinolina

(a). 1-Acetil-6-(4-fenilbenzoil)amino-1,2-dihidro-2,2,4-trimetilquinolina

Se disolvió 1-acetil-6-(ter-butoxicarbonil)amino-1,2-dihidro-2,2,4-trimetilquinolina (1,0 g) en una mezcla de ácido trifluoroacético/ CH_2Cl_2 (1/1, v/v, 25 ml) y se agitó por 2 horas. La mezcla de reacción fue concentrada al vacío, diluida con acetato de etilo y lavada con $NaHCO_3$ acuoso al 5%. La capa orgánica fue separada, secada ($MgSO_4$) y concentrada. El residuo fue disuelto en CH_2Cl_2 (25 ml), se agregó N,N-diisopropiletilamina (5,2 ml) y 4-fenilbenzoil cloruro (2,0 g), y la mezcla fue agitada por 16 horas. La mezcla fue concentrada y sometida a cromatografía en sílica gel, en heptano/acetato de etilo = 1/0 $\Rightarrow$ 0/1 (v/v) como eluyente.

Rendimiento: 0,63 g. MS-ESI: $[M+H]^+ = 411,2$.

(b). 1-Acetil-4-(2-metoxifenil)-6-(4-fenilbenzoil)amino-1,2,3,4-tetrahidro-2,2,4-trimetilquinolina y 1-acetil-4-(4-metoxifenil)-6-(4-fenilbenzoil)amino-1,2,3,4-tetrahidro-2,2,4-trimetilquinolina

La alquilación de Friedel-Crafts de anisol (25 ml, almacenado en tamices moleculares de 3Å) con 1-acetil-6-(4-fenilbenzoil)amino-1,2-dihidro-2,2,4-trimetilquinolina (0,50 g) en presencia de AlCl_3 (0,50 g), se efectuó de acuerdo con el método descrito en el Ejemplo 3. La purificación por cromatografía en sílica gel (eluyente: heptano/acetato de etilo = 1/0 $\Rightarrow$ 0/1, v,v) dio el derivado 2-metoxifenil-substituido como producto minoritario y el derivado 4-metoxifenil-substituido como el producto mayoritario.

Rendimiento: 46 mg. MS-ESI: $[\text{M}+\text{H}]^+ = 518,0$ (2-metoxifenil).

Rendimiento: 0,20 g. MS-ESI: $[\text{M}+\text{H}]^+ = 518,1$ (4-metoxifenil).

Ejemplo 72

1-Acetil-4-(4-hidroxifenil)-6-(4-fenilbenzoil)amino-1,2,3,4-tetrahidro-2,2,4-trimetilquinolina

A una solución enfriada (0°C) de 1-acetil-4-(4-metoxifenil)-6-(4-fenilbenzoil)amino-1,2,3,4-tetrahidro-2,2,4-trimetilquinolina (0,46 g) en CH_2Cl_2 , se agregó BBr_3 bajo una atmósfera de nitrógeno. La conversión completa se obtuvo después de agitar por 3 horas a temperatura ambiente. La mezcla fue enfriada, se agregó NaOH 1 M hasta pH básico, posteriormente se agregó acetato de etilo y la mezcla fue acidificada con HCl 1 M. La capa orgánica fue separada, secada (MgSO_4) y concentrada. El residuo fue sometido a

cromatografía en sílica gel, en heptano/acetato de etilo = 1/0
⇒ 0/1 (v/v) como eluyente.

Rendimiento: 0,13 g. MS-ESI: $[M+H]^+$ = 504,0.

Ejemplo 73

1-Acetil-6-(5-metilnicotinoil)amino-4-fenil-1,2,3,4-tetrahidro-2,2,4-trimetilquinolina

La condensación de 1-acetil-6-amino-4-fenil-1,2,3,4-tetrahidro-2,2,4-trimetilquinolina (0,10 g) con ácido 5-metil nicotínico (0,13 g), por acción de HATU (0,18 g) y N,N-diisopropiletilamina (0,28 ml) en diclorometano (2 ml), se efectuó de acuerdo con el método descrito en el Ejemplo 11.

Rendimiento: 0,12 g. MS-ESI: $[M+H]^+$ = 427,0.

Example 74

Bioactividad in vitro de CHO-FSH

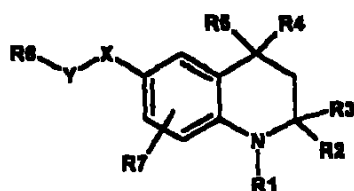
La actividad de FSH de los compuestos se determinó en células de ovario de hámster chino (CHO) transfectadas en forma estable con el receptor de FSH humano, y cotransfectadas con un promotor/elemento que responde a cAMP (CRE), que dirige la expresión de un gen reportero de luciferasa de luciérnaga. La unión del ligando al receptor de FSH acoplado con Gs dará como resultado un aumento de cAMP, que a su vez inducirá una transactivación aumentada del constructo reportero de luciferasa. La señal de luciferasa fue cuantificada usando un contador de luminiscencia. Para los compuestos de prueba, se calcularon los valores de EC₅₀ (concentración del compuesto de prueba que causa una estimulación semi-máxima (50%)). Para ese

propósito, se usó el programa de software GraphPad PRISM, versión 3.0 (GraphPad Software Inc., San Diego).

Los compuestos de todos los ejemplos tenían una actividad (EC_{50}) de menos de 10^{-5} M. Los compuestos de los ejemplos 1, 6-13, 15, 16, 21-24, 30, 36, 37, 45, 46, 48, 50-53, 55, 57, 58, 61, 63 y 64 presentaron una EC_{50} de menos de 10^{-7} M.

REIVINDICACIONES

1. Un compuesto derivado de tetrahidroquinolina
CARACTERIZADO porque tiene la fórmula I:



Fórmula I

o una sal farmacéuticamente aceptable del mismo,
donde

R^1 es formilo, (1-6C)alquilcarbonilo o (1-6C)-
alquilsulfonilo;

R^2 y R^3 son H ó (1-4C)alquilo;

R^4 es fenilo;

R^5 es (1-4C)alquilo;

Y-X es C(O)-O, S(O)₂-O, NHC(O)-O, NHC(S)-O, OC(O)-
O, enlace-O, C(O)-NH, S(O)₂-NH, NHC(O)-NH, NHC(S)-NH, OC(O)-
NH, enlace-NH, NH-C(O), O-C(O), NH-S(O)₂ u O-S(O)₂, o bien
X-Y es un enlace;

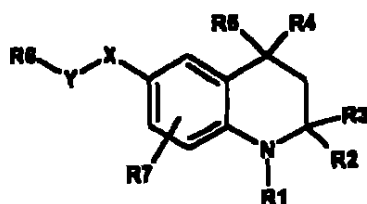
R^6 es H, excepto cuando Y-X es un enlace,
trifluorometilo, (1-6C)alquilo, 1- ó 2-adamantil(1-4C)alquilo,
(2-6C)alquenilo, (2-6C)alquinilo, (3-9C)heteroarilo, (3-6C)-
cicloalquilo, (2-6C)heterocicloalquilo, (1-4C)alquiltio(1-4C)-
alquilo, (6-10C)aril(1-4C)alquilo, (3-9C)heteroaril(1-4C)-
alquilo, (3-6C)cicloalquil(1-4C)alquilo, (2-6C)hetero-
cicloalquil(1-4C)alquilo, R^8, R^9 -aminocarbonil(1-4C)alquilo,

R^8, R^9 -amino(1-4C)alquilo, R^8 -oxicarbonil(1-4C)alquilo, R^8 -oxi(1-4C)alquilo, R^8 -carbonil(1-4C)alquilo o (6-10C)arilo;

R^7 es H, (1-4C)alquilo, (1-4C)alcoxi, halógeno, trifluorometilo, ciano, nitro, hidroxilo; y

R^8 y/o R^9 es H, (1-4C)alquilo, (2-4C)alquenilo, (2-4C)alquinilo, (6-10C)arilo, (3-9C)heteroarilo, (6-10C)-aril(1-4C)alquilo, (3-9C)heteroaril(1-4C)alquilo, (3-6C)-cicloalquil(1-4C)alquilo, (2-6C)heterocicloalquil(1-4C)-alquilo, (1-4C)(di)alquilamino(1-4C)alquilo, (1-4C)alcoxi-(1-4C)alquilo, (1-4C)alquiltio(1-4C)alquilo, (1-4C)alquil-carbonilamino(1-4C)alquilo, (1-4C)alcoxicarbonil(1-4C)alquilo, (1-4C)alcoxicarbonilamino(1-4C)alquilo, (3-6C)cicloalquilo, (2-6C)heterocicloalquilo, o bien R^8 y R^9 pueden estar unidos en un anillo (2-6C)heterocicloalquilo, para el uso en terapia.

2. Un compuesto derivado de tetrahidroquinolina CARACTERIZADO porque tiene la fórmula I



Fórmula I

o una sal farmacéuticamente aceptable del mismo, donde

R^1 es formilo, (1-6C)alquilcarbonilo o (1-6C)-alquilsulfonilo;

R^2 y R^3 son H ó (1-4C)alquilo;

R^4 es fenilo;

R^5 es (1-4C)alquilo;

Y-X es C(O)-O, S(O)₂-O, NHC(O)-O, NHC(S)-O, OC(O)-O, enlace-O, C(O)-NH, S(O)₂-NH, NHC(O)-NH, NHC(S)-NH, OC(O)-NH, enlace-NH, NH-C(O), O-C(O), NH-S(O)₂ u O-S(O)₂, o bien X-Y es un enlace;

R^6 es H, excepto cuando Y-X es un enlace, trifluorometilo, (1-6C)alquilo, 1- ó 2-adamantil(1-4C)alquilo, (2-6C)alquenilo, (2-6C)alquinilo, (3-9C)heteroarilo, (3-6C)-cicloalquilo, (2-6C)heterocicloalquilo, (1-4C)alquiltio-(1-4C)alquilo, (6-10C)aril(1-4C)alquilo, (3-9C)heteroaril-(1-4C)alquilo, (3-6C)cicloalquil(1-4C)alquilo, (2-6C)heterocicloalquil(1-4C)alquilo, R^8, R^9 -aminocarbonil(1-4C)alquilo, R^8, R^9 -amino(1-4C)alquilo, R^8 -oxicarbonil(1-4C)alquilo, R^8 -oxi(1-4C)alquilo, R^8 -carbonil(1-4C)alquilo o (6-10C)arilo;

R^7 es H, (1-4C)alquilo, (1-4C)alcoxi, halógeno, trifluorometilo, ciano, nítro, hidroxilo; y

R^8 y/o R^9 es H, (1-4C)alquilo, (2-4C)alquenilo, (2-4C)alquinilo, (6-10C)arilo, (3-9C)heteroarilo, (6-10C)aril(1-4C)alquilo, (3-9C)heteroaril(1-4C)alquilo, (3-6C)-cicloalquil(1-4C)alquilo, (2-6C)heterocicloalquil(1-4C)-alquilo, (1-4C)(di)alquilamino(1-4C)alquilo, (1-4C)alcoxi-(1-4C)alquilo, (1-4C)alquiltio(1-4C)alquilo, (1-4C)alquil-carbonilamino(1-4C)alquilo, (1-4C)alcoxicarbonil(1-4C)alquilo, (1-4C)alcoxicarbonilamino(1-4C)alquilo, (3-6C)cicloalquilo, (2-6C)heterocicloalquilo, o bien R^8 y R^9 pueden estar unidos en un anillo (2-6C)heterocicloalquilo, con la salvedad de que el derivado no es 1-acetil-6-benzoilamino-4-(4-metilfenil)-1,2,3,4-tetrahidro-2,2,4-trimetilquinolina, 1-acetil-4-fenil-1,2,3,4-tetrahidro-2,2,4,6-tetrametilquinolina, 1-acetil-4-

fenil-1,2,3,4-tetra-hidro-2,2,4,6,8-pentametilquinolina,
 1-acetil-6-metoxi-4-fenil-1,2,3,4-tetrahidro-2,2,4-trimetil-
 quinolina, 1-acetil-6-trifluoroacetilamino-4-(4-metilfenil)-
 1,2,3,4-tetrahidro-2,2,4-trimetilquinolina, 1-acetil-6-
 trifluoroacetilamino-4-fenil-1,2,3,4-tetrahidro-2,2,4-tri-
 metilquinolina, 1-acetil-4-(4-clorofenil)-1,2,3,4-tetrahidro-
 2,2,4,6-tetrametilquinolina y 1-acetil-4-(4-bromofenil)-
 1,2,3,4-tetrahidro-2,2,4,6-tetrametilquinolina.

3. El compuesto derivado de tetrahydroquinolina de la reivindicación 2, CARACTERIZADO porque Y-X es C(O)-NH, OC(O)-NH ó C(O)-O.

4. El compuesto derivado de tetrahydroquinolina de las reivindicaciones 2 ó 3, CARACTERIZADO porque Y-X es C(O)-NH.

5. El compuesto derivado de tetrahydroquinolina de las reivindicaciones 2-4, CARACTERIZADO porque R^1 es (1-4C)-alquilcarbonilo.

6. El compuesto derivado de tetrahydroquinolina de las reivindicaciones 2-5, CARACTERIZADO porque R^2 , R^3 y R^5 son independientemente (1-4C)alquilo.

7. El compuesto derivado de tetrahydroquinolina de las reivindicaciones 2-6, CARACTERIZADO porque R^6 es (6-10C)-arilo, (3-9C)heteroarilo, (6-10C)aril(1-4C)alquilo o (3-9C)-heteroaril(1-4C)alquilo.

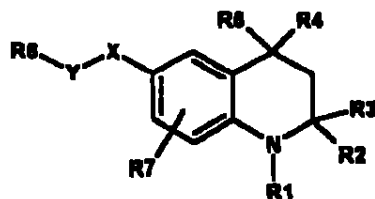
8. Una composición farmacéutica CARACTERIZADA porque comprende el compuesto de cualquiera de las reivindicaciones 2-7 y auxiliares farmacéuticamente adecuados.

9. Uso del compuesto de cualquiera de las reivindicaciones 2-8, o una sal o solvato farmacéuticamente aceptable del mismo, CARACTERIZADO porque sirve para fabricar un medicamento para el control de la fertilidad.

803.525

RESUMEN

La presente invención se refiere a derivados de tetrahidroquinolina que tienen la fórmula general I



Fórmula I

o una sal farmacéuticamente aceptable del mismo, donde R^1 es formilo, (1-6C)alquilcarbonilo o (1-6C)alquilsulfonilo; R^2 y R^3 son H ó (1-4C)alquilo; R^4 es fenilo; R^5 es (1-4C)-alquilo; Y-X es C(O)-O, S(O)₂-O, NHC(O)-O, NHC(S)-O, OC(O)-O, enlace-O, C(O)-NH, S(O)₂-NH, NHC(O)-NH, NHC(S)-NH, OC(O)-NH, enlace-NH, NH-C(O), O-C(O), NH-S(O)₂ u O-S(O)₂, o bien Y-X es un enlace; R^6 es H, trifluorometilo, (1-6C)alquilo, 1- ó 2-adamantil(1-4C)alquilo, (2-6C)alquenilo, (2-6C)-alquinilo, (3-9C)heteroarilo, (3-6C)cicloalquilo, (2-6C)-heterocicloalquilo, (1-4C)alquiltio(1-4C)alquilo, (6-10C)-aril(1-4C)alquilo, (3-9C)heteroaril(1-4C)alquilo, (3-6C)-cicloalquil(1-4C)alquilo, (2-6C)heterocicloalquil(1-4C)-alquilo, R^8, R^9 -aminocarbonil(1-4C)alquilo, R^8, R^9 -amino-(1-4C)alquilo, R^8 -oxicarbonil(1-4C)alquilo, R^8 -oxi(1-4C)-alquilo, R^8 -carbonil(1-4C)alquilo o (6-10C)arilo; R^7 es H, (1-4C)alquilo, (1-4C)alcoxi, halógeno, trifluorometilo, ciano, nitro, hidroxilo; y R^8 y/o R^9 es H, (1-4C)alquilo, (2-4C)-alquenilo, (2-4C)alquinilo, (6-10C)arilo, (3-9C)heteroarilo,

(6-10C)aril(1-4C)alquilo, (3-9C)heteroaril(1-4C)alquilo, (3-6C)cicloalquil(1-4C)alquilo, (2-6C)heterocicloalquil(1-4C)-alquilo, (1-4C)(di)alquilamino(1-4C)alquilo, (1-4C)alcoxi-(1-4C)alquilo, (1-4C)alquiltio(1-4C)alquilo, (1-4C)alquil-carbonilamino(1-4C)alquilo, (1-4C)alcoxicarbonil(1-4C)alquilo, (1-4C)alcoxicarbonilamino(1-4C)alquilo, (3-6C)cicloalquilo, (2-6C)heterocicloalquilo, o bien R^8 y R^9 pueden estar unidos en un anillo (2-6C)heterocicloalquilo.

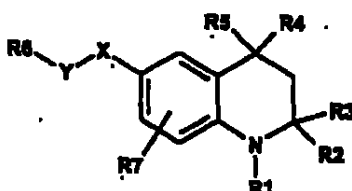
La presente invención también se refiere a composiciones farmacéuticas que comprenden dichos derivados y al uso de estos derivados para controlar la fertilidad.

Título

Derivados de tetrahydroquinolina y su uso para controlar la fertilidad.

REIVINDICACIONES CORREGIDAS
(ARTICULO 19 DEL PCT)

1. Un compuesto derivado de tetrahydroquinolina CARACTERIZADO porque tiene la fórmula I:



Formula I

o una sal farmacéuticamente aceptable del mismo,
donde

R^1 es formilo, (1-6C)alquilcarbonilo o (1-6C)-alquilsulfonilo;

R^2 y R^3 son H ó (1-4C)alquilo;

R^4 es fenilo, opcionalmente substituído con uno o más substituyentes seleccionados del grupo hidroxí, amino, halógeno, nitro, trifluorometilo, ciano, (1-4C)alquilo, (2-4C)alquenilo, (2-4C)alquinilo, (1-4C)alcoxi, (1-4C) (di)alquilamino;

R^5 es (1-4C)alquilo;

Y-X es C(O)-O, S(O)₂-O, NHC(O)-O, NHC(S)-O, OC(O)-O, enlace-O, C(O)-NH, S(O)₂-NH, NHC(O)₂-NH, NHC(S)-NH, OC(O)-NH, enlace-NH, NH-C(O), O-C(O), NH-S(O)₂ u O-S(O)₂, o bien X-Y es un enlace;

R^6 es H, excepto cuando Y-X es un enlace, trifluorometilo, (1-6C)alquilo, 1-6 2-adamantil(1-4C)alquilo, (2-6C)alquenilo, (2-6C)alquinilo, (3-9C)heteroarilo, (3-6C)-cicloalquilo, (2-6C)heterocicloalquilo, (1-4C)alquiltio(1-4C)-alquilo, (6-10C)aril(1-4C)alquilo, (3-9C)heteroaril(1-4C)-alquilo, (3-6C)cicloalquil(1-4C)alquilo, (2-6C)heterocicloalquil(1-4C)alquilo, R^8 , R^9 -aminocarbonil(1-4C)alquilo, R^8 , R^9 -amino(1-4C)alquilo, R^8 -oxicarbonil(1-4C)alquilo, R^8 -oxi(1-4C)alquilo, R^8 -carbonil(1-4C)alquilo o (6-10C)arilo, en donde si (6-10C)arilo es fenilo, fenilo puede ser opcionalmente substituido con hidroxilo, amino, halógeno, nitro, trifluorometilo, ciano, (1-4C)alquilo, (2-4C)alquenilo, (2-4C)alquinilo, (1-4C)alcoxi, (1-4C)(di)alquilamino, (6-10C)arilo, (6-10C)ariloxi, (6-10C)aril(1-4C)alcoxi, (3-9C)heteroarilo, (3-9C)heteroariloxi, (3-9C)heteroaril(1-4C)alcoxi, (1-4C)alquilcarbonilamino, (1-4C)alquilcarboniloxi, (3-6C)cicloalquilcarboniloxi, (1-4C)alcoxycarbonil(1-4C)alquilcarboniloxi, (1-4C)alcoxi(1-4C)alquilcarboniloxi, (6-10C)arilcarboniloxi, (3-9C)heteroarilcarboniloxi, (1-4C)alquilsulfoniloxi, (6-10C)arilsulfoniloxi, (3-9C)heteroarilsulfoniloxi, (1-4C)(di)alquilcarbamoil, (6-10C)(di)arilcarbamoil, (2-6C)heterocicloalquilcarbamoil, (6-10C)(di)arilamino, (3-6C)cicloalquil, (3-6C)cicloalquil(1-4C)alquil, (2-6C)heterocicloalquil o (2-6)heterocicloalquil(1-4C)alquil,

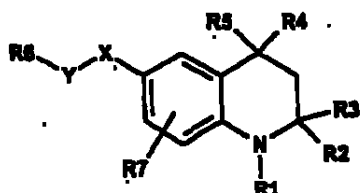
y en donde todos los grupos arilo y heteroarilo dentro de R^6 opcionalmente pueden estar substituidos con uno o más substituyentes seleccionados de hidroxilo, amino, halógeno, nitro, trifluorometilo, ciano, (1-4C)alquilo, (2-4C)alquenilo, (2-4C)alquinilo, (1-4C)alcoxi o (1-4C)(di)alquilamino,

R^7 es H, (1-4C)alquilo, (1-4C)alcoxi, halógeno, trifluorometilo, ciano, nitro, hidroxilo; y

R^8 y/o R^9 es H, (1-4C)alquilo, (2-4C)alquenilo, (2-4C)alquinilo, (6-10)arilo, (3-9C)heteroarilo, (6-10C)-aril(1-

4C)alquilo, (3-9C)heteroaril(1-4C)alquilo, (3-6C)-cicloalquil(1-4C)alquilo, (2-6C)heterocicloalquil(1-4C)-alquilo, (1-4C)(di)alquilamino(1-4C)alquilo, (1-4C)alcoxi(1-4C)alquilo, (1-4C)alquiltio(1-4C)alquilo, (1-4C)alquilcarbonilamino(1-4C)alquilo, (1-4C)alcoxycarbonil(1-4C)alquilo, (1-4C)alcoxycarbonilamino(1-4C)alquilo, (3-6C)cicloalquilo, (2-6C)heterocicloalquilo, o bien R⁸ y R⁹ pueden estar unidos en un anillo (2-6C)heterocicloalquilo, para el uso en terapia.

2. Un compuesto derivado de tetrahydroquinolina CARACTERIZADO porque tiene la fórmula I



Formula I

o una sal farmacéuticamente aceptable del mismo, donde

R¹ es formilo, (1-6C)alquilcarbonilo o (1-6C)-alquilsulfonilo;

R² y R³ son H ó (1-4C)alquilo;

R⁴ es fenilo, opcionalmente substituido con uno o más substituyentes seleccionados del grupo hidroxí, amino, halógeno, nitro, trifluorometilo, ciano, (1-4C)alquilo, (2-4C)alquenilo, (2-4C)alquinilo, (1-4C)alcoxi, (1-4C)(di)alquilamino;

R⁵ es (1-4C)alquilo;

Y-X es C(O)-O, S(O)₂-O, NHC(O)-O, NHC(S)-O, OC(O)-O, enlace-O, C(O)-NH, S(O)₂-NH, NHC(O)-NH, NHC(S)-NH,

OC(O)-NH, enlace-NH, NH-C(O), O-C(O), NH-S(O)₂ u O-S(O)₂, o bien X-Y es un enlace;

R⁶ es H, excepto cuando Y-X es un enlace, trifluorometilo, (1-6C)alquilo, 1- ó 2-adamantil(1-4C)alquilo, (2-6C)alquenilo, (2-6C)alquinilo, (3-9C)heteroarilo, (3-6C)cicloalquilo, (2-6C)heterocicloalquilo, (1-4C)alquiltio(1-4C)alquilo, (6-10C)aril(1-4C)alquilo, (3-9C)heteroaril(1-4C)alquilo, (3-6C)cicloalquil(1-4C)alquilo, (2-6C)heterocicloalquil(1-4C)alquilo, R⁸, R⁹-aminocarbonil(1-4C)alquilo, R⁸, R⁹-amino(1-4C)alquilo, R⁸-oxicarbonil(1-4C)alquilo, R⁸-oxi(1-4C)alquilo, R⁸-carbonil(1-4C)alquilo o (6-10C)arilo, en donde si (6-10C)arilo es fenilo, fenilo puede ser opcionalmente substituido con hidroxilo, amino, halógeno, nitro, trifluorometilo, ciano, (1-4C)alquilo, (2-4C)alquenilo, (2-4C)alquinilo, (1-4C)alcoxi, (1-4C)(di)alquilamino, (6-19C)arilo, (6-10C)ariloxi, (6-10C)aril(1-4C)alcoxi, (3-9C)heteroarilo, (3-9C)heteroariloxi, (3-9C)heteroaril(1-4C)alcoxi, (1-4C)alquilcarbonilamino, (1-4C)alquilcarboniloxi, (3-6C)cicloalquilcarboniloxi, (1-4C)alcoxycarbonil(1-4C)alquilcarboniloxi, (1-4C)alcoxi(1-4C)alquilcarboniloxi, (6-10C)arilcarboniloxi, (3-9C)heteroarilcarboniloxi, (1-4C)alquilsulfoniloxi, (6-10C)arilsulfoniloxi, (3-9C)heteroarilsulfoniloxi, (1-4C)(di)alquilcarbamoil, (6-10C)(di)arilcarbamoil, (2-6C)heterocicloalquilcarbamoil, (6-10C)(di)arilamino, (3-6C)cicloalquil, (3-6C)cicloalquil(1-4C)alquil, (2-6C)heterocicloalquil o (2-6)heterocicloalquil(1-4C)alquil,

y en donde todos los grupos arilo y heteroarilo dentro de R⁶ opcionalmente pueden estar substituidos con uno o más substituyentes seleccionados de hidroxilo, amino, halógeno, nitro, trifluorometilo, ciano, (1-4C)alquilo, (2-4C)alquenilo, (2-4C)alquinilo, (1-4C)alcoxi o (1-4C)(di)alquilamino;

R⁷ es H, (1-4C)alquilo, (1-4C)alcoxi, halógeno, trifluorometilo, ciano, nitro, hidroxilo; y

R^8 y/o R^9 es H, (1-4C)alquilo, (2-4C)alquenilo, (2-4C)alquinilo, (6-10C)arilo, (3-9C)heteroarilo, (6-10C)aril(1-4C)alquilo, (3-9C)heteroaril(1-4C)alquilo, (3-6C)cicloalquil(1-4C)alquilo, (2-6C)heterocicloalquil(1-4C)alquilo, (1-4C)(di)alquilamino(1-4C)alquilo, (1-4C)alcoxi(1-4C)alquilo, (1-4C)alquiltio(1-4C)alquilo, (1-4C)alquilcarbnilamino(1-4C)alquilo, (1-4C)alcoxycarbonil(1-4C)alquilo, (1-4C)alcoxycarbonilamino(1-4C)alquilo, (3-6C)cicloalquilo, (2-6C)heterocicloalquilo, o bien R^8 y R^9 pueden estar unidos en un anillo (2-6C)heterocicloalquilo, con la salvedad de que el derivado no es 1-acetil-6-benzoilamino-4-(4-metilfenil)-1, 2, 3, 4-tetrahidro-2, 2, 4-trimetilquinolina, 1-acetil-4-fenil-1, 2, 3, 4-tetrahidro-2, 2, 4, 6-tetrametilquinolina, 1-acetil-4-fenil-1, 2, 3, 4-tetrahidro-2, 2, 4, 6, 8-pentametilquinolina, 1-acetil-6-metoxi-4-fenil-1, 2, 3, 4-tetrahidro-2, 2, 4-trimetilquinolina, 1-acetil-6-trifluoroacetilamino-4-(4-metilfenil)-1, 2, 3, 4-tetrahidro-2, 2, 4-trimetilquinolina, 1-acetil-6-trifluoroacetilamino-4-fenil-1, 2, 3, 4-tetrahidro-2, 2, 4-trimetilquinolina, 1-acetil-4-(4-clorofenil)-1, 2, 3, 4-tetrahidro-2, 2, 4, 6-tetrametilquinolina y 1-acetil-4-(4-bromofenil)-1, 2, 3, 4-tetrahidro-2, 2, 4, 6-tetrametilquinolina.

3. El compuesto derivado de tetrahydroquinolina de la reivindicación 2, CARACTERIZADO porque Y-X es C(O)-NH, OC(O)-NH ó C(O)-O.

4. El compuesto derivado de tetrahydroquinolina de las reivindicaciones 2 ó 3, CARACTERIZADO porque Y-X es C(O)-NH.

5. El compuesto derivado de tetrahydroquinolina de las reivindicaciones 2-4, CARACTERIZADO porque R^1 es (1-4C)-alquilcarbonilo.

6. El compuesto derivado de tetrahydroquinolina de las reivindicaciones 2-5, CARACTERIZADO porque R^2 , R^3 y R^5 son independientemente (1-4C)alquilo.

7. El compuesto derivado de tetrahydroquinolina de las reivindicaciones 2.6, CARACTERIZADO porque R^6 es (6-10C)-arilo, (3-9C)heteroarilo, (6-10C)aril(1-4C)alquilo o (3-9C)-heteroaril(1-4C)alquilo, , en donde si (6-10C)arilo es fenilo, fenilo puede ser opcionalmente substituido con hidroxilo, amino, halógeno, nitro, trifluorometilo, ciano, (1-4C)alquilo, (2-4C)alqueno, (2-4C)alquino, (1-4C)alcoxi, (1-4C)(di)alquilamino, (6-10C)arilo, (6-10C)ariloxi, (6-10C)aril(1-4C)alcoxi, (3-9C)heteroarilo, (3-9C)heteroariloxi, (3-9C)heteroaril(1-4C)alcoxi, (1-4C)alquilcarbonilamino, (1-4C)alquilcarboniloxi, (3-6C)cicloalquilcarboniloxi, (1-4C)alcoxycarbonil(1-4C)alquilcarboniloxi, (1-4C)alcoxi(1-4C)alquilcarboniloxi, (6-10C)arilcarboniloxi, (3-9C)heteroarilcarboniloxi, (1-4C)alquilsulfoniloxi, (6-10C)arilsulfoniloxi, (3-9C)heteroarilsulfoniloxi, (1-4C)(di)alquilcarbamoilo, (6-10C)(di)arilcarbamoilo, (2-6C)heterocicloalquilcarbamoilo, (6-10C)(di)arilamino, (3-6C)cicloalquil, (3-6C)cicloalquil(1-4C)alquil, (2-6C)heterocicloalquil o (2-6)heterocicloalquil(1-4C)alquil, y en donde todos los grupos arilo y heteroarilo dentro de R^6 opcionalmente pueden estar substituidos con uno o más substituyentes seleccionados de hidroxilo, amino, halógeno, nitro, trifluorometilo, ciano, (1-4C)alquilo, (2-4C)alqueno, (2-4C)alquino, (1-4C)alcoxi o (1-4C)(di)alquilamino.

8. Una composición farmacéutica CARACTERIZADA porque comprende el compuesto de cualquiera de las reivindicaciones 2-7 y auxiliares farmacéuticamente adecuados.

9. Uso del compuesto de cualquiera de las reivindicaciones 2-8, o una sal o solvato farmacéuticamente aceptable del mismo, CARACTERIZADO porque sirve para fabricar un medicamento para el control de la fertilidad.

COLO 11214 841 013 0
DLM/ID-000000280/WPC11214

CAVELIER

ABOGADOS
EDIFICIO 616K1
CARRERA 4a N° 7235
BOGOTÁ, C- COLOMBIA

374

2001.656 CO

CESSION

ASSIGNMENT

Yo, (nosotros) abajo firmante (s)

I (we), the undersigned

VAN STRATEN
Nicole Corine Renée

VAN SOMEREN
Rudolf Gijbertus

SCHULZ
Jurgen

domiciliado(s) en

of

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

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

c/o: Organon Laboratories Ltd.
New Edinburgh Road
Newhouse, Lanarkshire
Scotland, ML1 5SH
United Kingdom

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

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

derivados tetrahidroquinolina

Tetrahydroquinoline derivatives

declaro(amos) así mismo que cedo(amos) y transfero(amos), sin
limitación, a favor de la sociedad

state as well, that assign, without reservations or limitations in favour of

- Akzo Nobel N.V.

constituida y existente de conformidad con las leyes de

a corporation constituted and existing in conformity with the laws of

domiciliada en
Velperweg 76
6824 BM Arnhem
The Netherlands

located in

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

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

Dado y firmado hoy/ Given and signed this

en/ in

Firma

Signature


VAN STRATEN
Nicole Corine Renée

ass,
9 dec
03


VAN SOMEREN
Rudolf Gijbertus

SCHULZ
Jurgen

AUTENTICACION NOTARIAL (INDIVIDUO)

A los _____ días del mes de _____ de
200__ ante mí, Notario Público de _____
compareció(ron) personalmente _____

a quien(es) doy fe de conocer y me consta que es(son) la(s) persona(s)
firmante(s) del documento que presenta, y quien(es) tiene(n) capacidad
legal para otorgarlo.

NOTARIAL AUTHENTICATION (INDIVIDUAL)

On this _____ day of _____, 200__
before me, a Notary Public of _____
personally appeared _____

to me known, and known to me to be the person(s) who executed the
foregoing document, and who has (have) legal capacity to execute it.

Notario Público / Notary Public

APOSTILLE

(Convention de La Haye du 5 octobre 1961)

1. Country:
- This public document
2. has been signed by
3. acting in the capacity of
4. bears the seal/stamp of

Certified

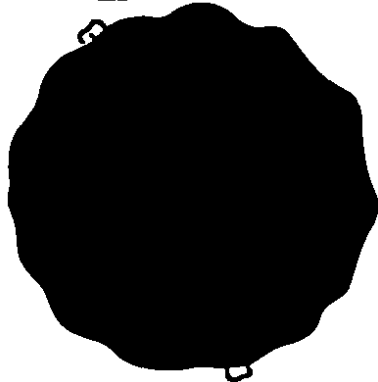
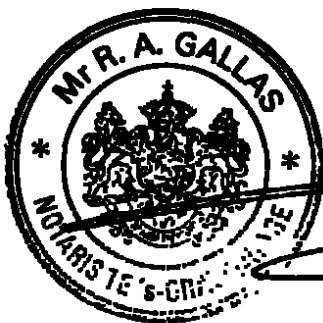
- | | |
|---------------|---------------|
| 5. at | 6. the |
| 7. by | |
| 8. No. | |
| 9. Seal/stamp | 10. Signature |

.....

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

- Mr Rudolf Gijsbertus van Someren, born on the twenty-fifth of August nineteenhundred seventy-three in Vught, The Netherlands, residing at Nieuwegeln, The Netherlands, holder of a Dutch passport, number M05303992; and
- Mrs. Nicole Corine Renée van Straten, born on the tenth of December nineteenhundred sixty-nine in Hoeven, The Netherlands, residing at Oss, The Netherlands, holder of a Dutch passport, number NB5786820,

The Hague, the fifteenth day of December twothousandthree.



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

A P O S T I L L E

(Convention de La Haye du 5 octobre 1961)

1. Country: THE NETHERLANDS
This public document
2. has been signed by mr. R.A. Gallas
3. acting in the capacity of notary at 's-Gravenhage
4. bears the seal/stamp of aforesaid notary

Certified

5. at 's-GRAVENHAGE 6. the 17 december 2003
7. by the registrar of the court (rechtbank)
8. no. 2003-4906
9. Seal/stamp:
10. Signature:

S. Petronilla



TRADUCCIÓN OFICIAL 216/2003 DE UN DOCUMENTO ESCRITO EN INGLÉS Y EN ESPAÑOL, REALIZADA POR EDUARDO CALADO NOGUERA, TRADUCTOR OFICIAL APROBADO POR RESOLUCIÓN 541 DEL 27 DE FEBRERO DE 1976 POR EL MINISTERIO DE JUSTICIA Y DEBIDAMENTE REGISTRADO ANTE EL MINISTERIO DE RELACIONES EXTERIORES DE LA REPÚBLICA DE COLOMBIA Y MEDIANTE EL CUAL NICOLE CORINE RENÉE, RUDOLF GIJSBERTUS VAN SOMEREN Y JURGEN SCHULZ, DOMICILIADOS RESPECTIVAMENTE EN N.V. ORGANON, P.O. BOX 20, 5340 BH OSS, THE NETHERLANDS, N.V. ORGANON P.O. BOX 20, 5340 BH OSS, THE NETHERLANDS Y C/O: ORGANON LABORATORIES LTD. NEWHOUSE, LANARKSHIRE, SCOTLAND, ML1 5SH, UNITED KINGDOM INVENTORES ÚNICOS Y VERDADEROS DE LA INVENCION: DERIVADOS TETRAHIDROQUINOLONA , DECLARAN POR EL PRESENTE QUE CEDEN DICHA INVENCION A AKZO NOBEL N.V., EMPRESA DOMICILIADA EN VELPERWEG 76, 6824 BM ARNHEM, THE NETHERLANDS (HOLANDA), JUNTO CON TODOS LOS DERECHOS INHERENTES Y QUE DICHA COMPAÑIA QUEDA FACULTADA PARA SOLICITAR EN SU NOMBRE LA PATENTE CORRESPONDIENTE EN LA REPUBLICA DE COLOMBIA.

DADO Y FIRMADO HOY 9 DE DICIEMBRE DE 2003.

FIRMAS ILEGIBLES: NICOLE CORINE RENÉE, RUDOLF GIJSBERTUS Y JURGEN SCHULZ

VISTO POR MÍ, ROBERT ALEXANDER GALLAS, NOTARIO DE LEY CIVIL QUE PRACTICA EN LA HAYA, PARA LA AUTENTICACION DE LAS FIRMAS QUE APARECEN EN EL DOCUMENTO ADJUNTO Y QUE CORRESPONDE A:

- RUDOLF GIJSBERTUS VAN SOMEREN, NACIDO EL 25 DE AGOSTO DE MIL NOVECIENTOS SETENTA Y TRES EN VUGHT, HOLANDA, RESIDENTE EN NIEUWEGEIN, HOLANDA, PORTADOR DE UN PASAPORTE HOLANDÉS, CON NÚMERO M05303992 Y

- A LA SEÑORA NICOLE CORINE RENÉE VAN STRATEN, NACIDA EL DIEZ DE DICIEMBRE DE MIL NOVECIENTOS SESENTA Y NUEVE EN HOEVEN, HOLANDA, RESIDENTE EN OSS, HOLANDA, PORTADORA DEL PASAPORTE HOLANDÉS NÚMERO NB5786820.

- LA HAYA, QUINCE DE DICIEMBRE DE DOS MIL TRES

FIRMA ILEGIBLE:

SELLO: MR. R. A. GALLAS, NOTARIO

TODAS LAS INSTRUCCIONES SE LLEVAN A CABO CON BASE EN UN CONVENIO DE ACUERDO CON LA SECCIÓN 400 DEL LIBRO 7 DEL CÓDIGO CIVIL HOLANDÉS POR PELS RIJCKEN & DROOGLEEVER FORTUIJN, UNA SOCIEDAD FORMADA POR COMPAÑÍAS PRIVADAS CON RESPONSABILIDAD LIMITADA. EL CONVENIO ESTÁ SUJETO A LAS CONDICIONES DE NEGOCIO REGISTRADAS ANTE LA CORTE DE DISTRITO DE LA HAYA. EN ESTOS TÉRMINOS Y CONDICIONES EMPRESARIALES SE INCLUYE UNA LIMITACIÓN DE RESPONSABILIDAD. DICHOS TÉRMINOS Y CONDICIONES SE SUMINISTRARÁN CUANDO ASÍ SE SOLICITE. TAMBIÉN SE PUEDEN CONSULTAR EN LA DIRECCIÓN DE INTERNET www.prd.f.nl.

APOSTILLA:

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

1. País: LOS PAÍSES BAJOS

Este documento público

2. ha sido firmado por R.A. GALLAS

3. quien actúa en su calidad de NOTARIO PÚBLICO DE GRAVENHAGE

4. lleva el sello de dicho NOTARIO PÚBLICO,

CERTIFICADO

5. en GRAVENHAGE

6. el 17 de diciembre de 2003

12/30

7. por el registrador de la corte

8. Número 2003-4006

9. Sello: CORTE DE GRAVENHAGE

10. Firma: (ILEGIBLE) NOMBRE: S. PETRONILLA

COLO-11214-841-013-0

WPCL002G. ID 5189

Bogotá, 29 de diciembre de 2003.

Eduardo Calado R.

Eduardo Calado Negrete
TRADUCTOR OFICIAL
ESPAÑOL - INGLÉS - FRANCÉS
Bos 541 Febrero de 1999

NO SE ASUME
RESPONSABILIDAD DEL LEYER

2003 DEC 30 P 2:31

Eduardo Calado
E DE LEGALIZACION
LA FE DE BOGOTA D.C.

COMO NOTARIO SEXTO DEL CIRCULO DE SANTA
BOGOTA, HAGO CONSTAR QUE LA(S) FICHA(S)
Eduardo Calado
Rogues
CON LA FIRMA REGISTRADA POR
EN ESTA NOTARIA
30 DIC. 2003

513548
Eduardo Calado
LUGAR DE FIRMAR EL
DOCUMENTO EN EL
LAS FOLIOS

NOTARIA SEXTA
PABLO MENDEZ
BARAJAS
Circulo Santo Eduardo

Expediente No		No de Folia
04007751		139
No de unidades		✓
Item		
1	CD	
2	DVD	
3	REVISTA	
4	LIBRO	
5	PERIODICO	
6	DISQUETES	
7	SOBRE DE MANILA	
8	SOBRE BLANCO TAMAÑO CARTA	
9	SOBRE BLANCO TAMAÑO OFICIO	
10	OTROS:	

Observaciones:

Contiene 2 figuras

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

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

REPRESENTACION Y PODER

REPRESENTATION AND POWER OF ATTORNEY

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

AKZO NOBEL N.V.

of/domicillado (a) en Velperweg 76, 6824

BM Arnhem, THE NETHERLANDS

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

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

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

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

Given and signed this Day and Month of 6 AUG 1998

F.G.M. Hermans

in/en Director Patents Pharma

Signature

AKZO NOBEL N.V.

E.H. Reerink

Deputy Director
Legal Affairs

CAVELIER ABOGADOS
WPPERRE-179 (MINUTA N° 12.1.12.5)

TRADUCCION No. 18.11/98
MARIA ELVIRA MASCLO
Traductora e Interprete Oficial
Inglés - Español - Inglés
Res. No. 2079 Min. Justicia

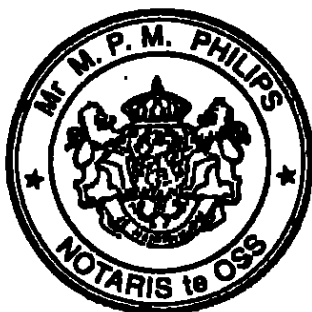
LEGALIZACION

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

LEGALIZATION

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

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



TRADUCCION No: 18.11/98
MARIA ELVIRA MARTELO
Traductora e Interprete Oficial
Inglés - Español - Inglés
Res. No. 2879 Min. Justicia

15499



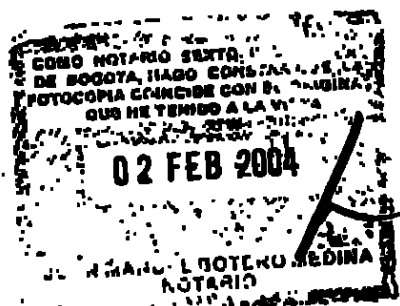
CHAMBER OF COMMERCE AND INDUSTRY
FOR OOST-BRABANT (NEDERLAND)

EXCLUSIVE PLACE FOR LEGALIZATION OF
THE SIGNATURE(S)

27 AUG 1998

KAMER VAN KOOPHANDEL
OOST-BRABANT
's-HERTOGENBOSCH

J. Scheldkens



Gezien voor legalisatie van de handtekening
van dhr/mw J. Scheldkens

's-Gravenhage, 9 SEP 1998



De Minister van
Buitenlandse Zaken
voordeze,

Leges f 20,- H.H. van POORTEN

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



CONSULADO DE COLOMBIA

C 260 112 11-201-001-3

112 11-201-001-3

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

CERTIFICA:

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

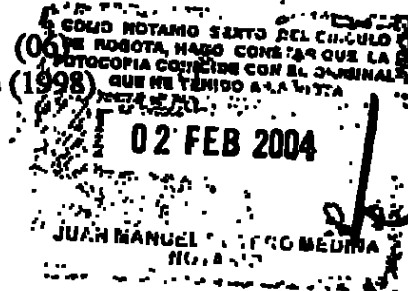
Que la Compañía **AKZO NOBEL N.V.** es una Sociedad constituida de acuerdo con las leyes de los Países Bajos, cumple su objeto conforme a las mismas y se halla registrada en la Cámara de Comercio y Fábricas de Centraal Gelderland, Arnhem, bajo el número 09007809;

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

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

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

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



Certificación No. 206

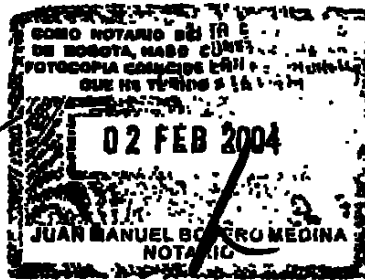
JOSE IGNACIO VILLEGAS CORTES
CONSUL DE COLOMBIA
LA HAYA

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

NO SE ASUME
RESPONSABILIDAD DEL TEXTO

98 NOV 19 11:56

JEFE DE LEGALIZACIONES
SANTAFE DE BOGOTA D.C.



MINISTERIO DE RELACIONES
EXTERIORES

300803

CUYA FIRMA APARECE EN EL
DOCUMENTO DESEMPENA
LAS FUNCIONES INDICADAS

14/3 142

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

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

(Al dorso) Visto por mí, Sr. Martinus Petrus Maria Philips, notario público en Oss, Países Bajos, hoy 26 de agosto de 1998, para legalización de las firmas de F.G.M. Hermans y E.H. Reerink. (Firma ilegible).

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

(Sello en holandés).

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

143
18X

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

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

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

COLO 11214-801-001-3

Id. 6

Nov. 20/98

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

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



COMO NOTARIO SEXTO DEL CIRCULO DE SANTA FE DE BOGOTA, HAGO CONSTAR QUE FOTOCOPIA CONCORDA CON EL ORIGINAL QUE HE TENIDO A LA VISTA
02 FEB 2004
JUAN

MINISTERIO DE RELACIONES EXTERIORES
198457
Maria E. Martelo
Cuya firma aparece en el documento desempeña las funciones indicadas
NO SE ASUME RESPONSABILIDAD DEL TEXTO
98 NOV 24 PM 12:06
JEFE DE LEGALIZACIONES
SANTA FE DE BOGOTA D.C.

144
145

Radicacion : 04007731 00000000
Fecha (MM): 2004-02-02 17:06:07
Trámite : 011 PCI +000000 179 F02.0001 11 P.000000
Dependencia: 2000 DIVISION DE Nuevos Lugares

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 04 - 2,394
FECHA : ENERO 13 DE 2004

***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO.	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
CAVELIER ABOGADOS	CONSIGNACION	BANCO POPULAR	050-00110-6	10497412	13/01/2004	31,278,400.00

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

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-01 SOLICITUDES	7 TRAMITES DE SOL. DE DISENOS INDUS	422,000.00
		TOTAL :	\$ 422,000.00

SON: CUATROCIENTOS VEINTIDOS MIL PESOS

RESPONSABLE : 

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____

Colo 11214-841-013-0

REQUISITOS NECESARIOS PARA PRESENTACION Y AGILIZACION DEL TRAMITE

		USUARIO	RADICADOR
PATENTE DE INVENCIÓN	MODELO DE UTILIDAD	()	(x)
- Indicación de que se solicita la concesión de una patente.		()	(x)
- Datos de identificación del solicitante o de la persona que se presenta la solicitud.		()	(x)
- Descripción de la invención.		()	()
- Dibujos de ser estos pertinentes.		()	(x)
- Comprobante de Pago de las tasas establecidas.			
COMPLETA	()	INCOMPLETA	()
DISEÑO INDUSTRIAL ()			
- Indicación de que se solicita el registro de Diseño Industrial		()	()
- Datos de identificación del solicitante o de la persona que presenta la solicitud.		()	()
- Representación gráfica y fotográfica del Diseño Industrial o muestra del Material que incorpora el diseño.		()	()
- Comprobante de pago de las tasas establecidas		()	()
COMPLETA	()	INCOMPLETA	()
ESQUEMA DE TRAZADO ()			
- Indicación de que solicita el registro de un Esquema de trazado.		()	()
- Datos de identificación del solicitante o de la persona que presenta La solicitud.		()	()
- Representación gráfica del esquema de trazado		()	()
- Comprobante de pago de las tasas establecidas.		()	()
COMPLETA	()	INCOMPLETA	()

Firma Responsable:
Fidel Naranjo
Fecha: 02-02-2004