(12) STANDARD PATENT (11) Application No. **AU 2001262318 B2**
(19) AUSTRALIAN PATENT OFFICE

(54) Title
Acylphenyl urea derivatives, methods for the production thereof and use thereof as a medicament

(51)[7] International Patent Classification(s)
C07C 275/34 **A61K 031/19**
A61P 003/10 **C07D 307/38**
A61K 031/34 **C07D 295/08**
A61K 031/215

(21) Application No: **2001262318** (22) Date of Filing: **2001.05.26**

(87) WIPO No: **WO01/94300**

(30) Priority Data

(31) Number	(32) Date	(33) Country
10028175	**2000.06.09**	**DE**
10116768	**2001.04.04**	**DE**

(43) Publication Date: **2001.12.17**
(43) Publication Journal Date: **2002.03.07**
(44) Accepted Journal Date: **2005.09.08**

(71) Applicant(s)
Aventis Pharma Deutschland GmbH

(72) Inventor(s)
Defossa, Elisabeth; Baringhaus, Karl-Heinz; Herling, Andreas; Burger, Hans-Joerg; Klabunde, Thomas

(74) Agent / Attorney
Watermark Patent & Trademark Attorneys, 290 Burwood Road, Hawthorn, VIC, 3122

(12) NACH DEM VERTRAG ÜBER DIE INTERNATIONALE ZUSAMMENARBEIT AUF DEM GEBIET DES PATENTWESENS (PCT) VERÖFFENTLICHTE INTERNATIONALE ANMELDUNG

(19) Weltorganisation für geistiges Eigentum
Internationales Büro

(43) Internationales Veröffentlichungsdatum
13. Dezember 2001 (13.12.2001)

PCT

(10) Internationale Veröffentlichungsnummer
WO 01/94300 A1

(51) Internationale Patentklassifikation[7]: C07C 275/34, C07D 295/08, 307/38, A61K 31/19, 31/215, 31/34, A61P 3/10

(21) Internationales Aktenzeichen: PCT/EP01/06030

(22) Internationales Anmeldedatum:
26. Mai 2001 (26.05.2001)

(25) Einreichungssprache: Deutsch

(26) Veröffentlichungssprache: Deutsch

(30) Angaben zur Priorität:
100 28 175.3 9. Juni 2000 (09.06.2000) DE
101 16 768.7 4. April 2001 (04.04.2001) DE

(71) Anmelder: **AVENTIS PHARMA DEUTSCHLAND GMBH** [DE/DE]; Brüningstrasse 50, 65929 Frankfurt (DE).

(72) Erfinder: **DEFOSSA, Elisabeth**; Stolzwiese 20, 65510 Idstein (DE). **KLABUNDE, Thomas**; Liederbacher Str. 1, 65929 Frankfurt (DE). **BURGER, Hans-Joerg**; Am Kreishaus 8A, 65719 Hofheim (DE). **HERLING, Andreas**; Am Walberstück 5, 65520 Bad Camberg (DE). **BARINGHAUS, Karl-Heinz**; Weingartenstrasse 31, 61200 Wölfersheim (DE).

(81) Bestimmungsstaaten *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW.

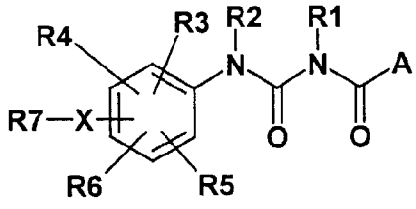
(84) Bestimmungsstaaten *(regional)*: ARIPO-Patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), eurasisches Patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), europäisches Patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI-Patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Veröffentlicht:
— *mit internationalem Recherchenbericht*

Zur Erklärung der Zweibuchstaben-Codes und der anderen Abkürzungen wird auf die Erklärungen ("Guidance Notes on Codes and Abbreviations") am Anfang jeder regulären Ausgabe der PCT-Gazette verwiesen.

(54) **Title:** ACYLPHENYL UREA DERIVATIVES, METHODS FOR THE PRODUCTION THEREOF AND USE THEREOF AS A MEDICAMENT

(54) **Bezeichnung:** ACYLPHENYLHARNSTOFFDERIVATE, VERFAHREN ZU IHRER HERSTELLUNG UND IHRE VERWENDUNG ALS ARZNEIMITTEL



(I)

(57) **Abstract:** The invention relates to acylphenyl urea derivatives and the physiologically compatible salts and physiologically functional derivatives thereof. Such compounds correspond to the formula (I) wherein the radicals have the cited meanings. The invention also relates to a method for producing said compounds. Said compounds can be used, for example, for treating Type II diabetes.

(57) **Zusammenfassung:** Die Erfindung betrifft Acylphenylharnstoffderivate sowie deren physiologisch verträgliche Salze und physiologisch funktionelle Derivate. Es werden Verbindungen der Formel (I), worin die Reste die angegebenen Bedeutungen haben, sowie deren physiologisch verträglichen Salze und Verfahren zu deren Herstellung beschrieben. Die Verbindungen eignen sich z.B. zur Behandlung des Typ II Diabetes.

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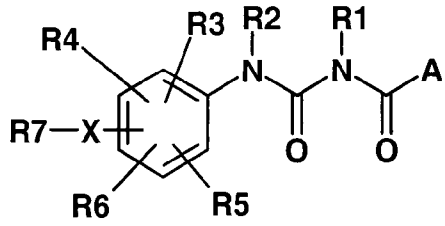
Acylphenylurea derivatives, a process for their preparation and their use as pharmaceuticals.

The invention relates to acylphenylurea derivatives and their physiologically tolerated salts and physiologically functional derivatives.

Acylphenylurea derivatives have already been described in the prior art as insecticides (EP 0 136 745, EP 0 167 197, DE 29 26 480, J. Agric. Food Chem. 1999, 47, 3116-3424).

The invention was based on the object of providing compounds which display a blood glucose-lowering effect which can be exploited therapeutically.

The invention therefore relates to compounds of the formula I



I

in which

A is phenyl, naphthyl, it being possible for the phenyl or naphthyl radical to be substituted up to three times by F, Cl, Br, OH, CF_3, NO_2, CN, OCF_3, O-(C_1-C_6)-alkyl, O-(C_2-C_6)-alkenyl, O-(C_2-C_6)-alkynyl, S-(C_1-C_6)-alkyl, S-(C_2-C_6)-alkenyl, S-(C_2-C_6)-alkynyl, SO-(C_1-C_6)-alkyl, SO_2-(C_1-C_6)-alkyl, SO_2-NH_2, (C_1-C_6)-alkyl, (C_2-C_6)-alkenyl, (C_2-C_6)-alkynyl, (C_3-C_7)-cycloalkyl, (C_3-C_7)-cycloalkyl-(C_2-C_4)-alkylene, (C_0-C_6)-alkylene-COOH, (C_0-C_6)-alkylene-COO(C_1-C_7)-alkyl, $CONH_2$, CONH(C_1-C_6)-alkyl, CON[(C_1-C_6)-alkyl]$_2$, CONH(C_3-C_6)-cycloalkyl, (C_0-C_6)-alkylene-NH_2, (C_0-C_6)-alkylene-NH(C_2-C_6)-alkyl, (C_0-C_6)-alkylene-N[(C_1-C_6)-alkyl]$_2$, NH-CO-(C_1-C_6)-Alkyl, NH-CO-phenyl, NH-SO_2-phenyl, it being possible for the phenyl ring to be substituted up to twice by F, Cl, CN, OH, (C_1-C_6)-alkyl, O-(C_1-C_6)-alkyl, CF_3, OCF_3, COOH, COO(C_1-C_6)-alkyl or $CONH_2$;

R1, R2 are, independently of one another, H, (C_1-C_6)-alkyl, O-(C_1-C_6)-alkyl, CO-(C_1-C_6)-alkyl, COO-(C_1-C_6)-alkyl, (C_1-C_6)-alkylene-COOH, (C_1-C_6)-alkylene-COO-(C_1-C_6)-alkyl;

R3, R4, R5, R6 are, independently of one another, H, F, Cl, Br, OH, CF_3, NO_2, CN, OCF_3, O-(C_1-C_6)-alkyl, O-(C_2-C_6)-alkenyl, O-(C_2-C_6)-alkynyl, S-(C_1-C_6)-alkyl, S-(C_2-C_6)-alkenyl, S-(C_2-C_6)-alkynyl, SO-(C_1-C_6)-alkyl, SO_2-(C_1-C_6)-alkyl, SO_2-NH_2, (C_1-C_6)-alkyl, (C_2-C_6)-alkenyl, (C_2-C_6)-alkynyl, (C_3-C_7)-cycloalkyl, (C_3-C_7)-cycloalkyl-(C_2-C_4)-alkylene, COOH, COO(C_1-C_6)-alkyl, $CONH_2$, CONH(C_1-C_6)-alkyl, CON[(C_1-C_6)-alkyl]$_2$, CONH(C_3-C_7)-cycloalkyl, NH_2, NH(C_1-C_6)-alkyl, N[(C_1-C_6)-alkyl]$_2$, NH-CO-(C_1-C_6)-alkyl, NH-CO-phenyl, NH-SO_2-phenyl, it being possible for the phenyl ring to be substituted up to twice by F, Cl, CN, OH, (C_1-C_6)-Alkyl, O-(C_1-C_6)-alkyl, CF_3, OCF_3, COOH, COO(C_1-C_6)-alkyl or $CONH_2$;

X is O, S;

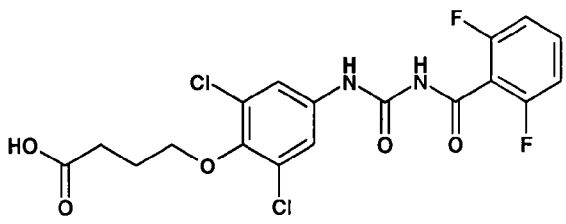
R7 is (C_1-C_{10})-alkylene-COOH, (C_6-C_{10})-alkylene-COO-(C_1-C_6)-alkyl, (C_1-C_{10})-alkylene-$CONH_2$, (C_1-C_{10})-alkylene-CONH-(C_1-C_6)-alkyl, (C_1-C_{10})-alkylene-CON-[(C_1-C_6)-alkyl]$_2$, (C_1-C_{10})-alkylene-NH_2, (C_1-C_{10})-alkylene-NH(C_1-C_6)-alkyl, (C_1-C_{10})-alkylene-N[(C_1-C_6)-alkyl]$_2$, (C_1-C_{10})-alkylene-B;

B is (C_3-C_7)-cycloalkyl, pyrrolyl, Imidazolyl, thiazolyl, azetidinyl, thienyl, piperidinyl, pyrrolidinyl, morpholinyl, pyridyl-methyl or furyl, in which cycloalkyl, phenyl, pyrrolyl, imidazolyl, thiazolyl, azetidinyl, thienyl, piperidinyl, pyrrolidinyl, morpholinyl, pyridyl-methyl or furyl may in each case be substituted up to twice by Cl, F, CN, CF_3, OCF_3, COOH,

$COO-(C_1-C_6)$-alkyl, $CONH_2$, $CONH-(C_1-C_6)$-alkyl, $CON-[(C_1-C_6)\text{-alkyl}]_2$, (C_1-C_6)-alkyl, OH, $O-(C_1-C_6)$-alkyl;

and physiologically tolerated salts thereof,

excepting the compounds of the formula



and compounds of the formula I in which the radicals mean at the same time

A phenyl;

X O;

R1 H;

R7 $-(C_1-C_4)$-alkyl-B;

B (C_3-C_7)-cycloalkyl, heteroaryl.

Preferred compounds of the formula I are those in which

A is phenyl, naphthyl, it being possible for the phenyl or naphthyl radical to be substituted up to three times by F, Cl, Br, OH, CF_3, NO_2, CN, OCF_3, $O-(C_1-C_6)$-alkyl, $O-(C_2-C_6)$-alkenyl, $O-(C_2-C_6)$-alkynyl, $S-(C_1-C_6)$-alkyl, $S-(C_2-C_6)$-alkenyl, $S-(C_2-C_6)$-alkynyl, $SO-(C_1-C_6)$-alkyl, $SO_2-(C_1-C_6)$-alkyl, SO_2-NH_2, (C_1-C_6)-alkyl, (C_2-C_6)-alkenyl, (C_2-C_6)-alkynyl, (C_3-C_7)-cycloalkyl, (C_3-C_7)-cycloalkyl-(C_2-C_4)-alkylene, (C_0-C_6)-alkylene-COOH, (C_0-C_6)-alkylene-$COO(C_1-C_6)$-alkyl, $CONH_2$, $CONH(C_1-C_6)$-alkyl, $CON[(C_1-C_6)\text{-alkyl}]_2$, $CONH(C_3-C_7)$-cycloalkyl, (C_0-C_6)-alkylene-NH_2, (C_0-C_6)-alkylene-$NH(C_2-C_6)$-

alkyl, (C_0-C_6)-alkylene-N[(C_1-C_6)-alkyl]$_2$, NH-CO-(C_1-C_6)-alkyl, NH-CO-phenyl, NH-SO_2-phenyl, it being possible for the phenyl ring to be substituted up to twice by F, Cl, CN, OH, (C_1-C_6)-alkyl, O-(C_1-C_6)-alkyl, CF_3, OCF_3, COOH, COO(C_1-C_6)-alkyl or $CONH_2$;

R1, R2 are, independently of one another, H, (C_1-C_6)-alkyl, O-(C_1-C_6)-alkyl, CO-(C_1-C_6)-alkyl, COO-(C_1-C_6)-alkyl, (C_1-C_6)-alkylene-COOH, (C_1-C_6)-alkylene-COO-(C_1-C_6)-alkyl;

R3, R4, R5, R6 are, independently of one another, H, F, Cl, Br, OH, CF_3, NO_2, CN, OCF_3, O-(C_1-C_6)-alkyl, O-(C_2-C_6)-alkenyl, O-(C_2-C_6)-alkynyl, S-(C_1-C_6)-alkyl S-(C_2-C_6)-alkenyl, S-(C_2-C_6)-alkynyl, SO-(C_1-C_6)-alkyl, SO_2-(C_1-C_6)-alkyl, SO_2-NH_2, (C_1-C_6)-alkyl, (C_2-C_6)-alkenyl, (C_2-C_6)-alkynyl, (C_3-C_7)-cycloalkyl, (C_3-C_7)-cycloalkyl-(C_2-C_4)-alkylene, COOH, COO(C_1-C_6)-alkyl, $CONH_2$, CONH(C_1-C_6)-alkyl, CON[(C_1-C_6)-alkyl]$_2$, CONH(C_3-C_7)-cycloalkyl, NH_2, NH(C_1-C_6)-alkyl, N[(C_1-C_6)-alkyl]$_2$, NH-CO-(C_1-C_6)-alkyl, NH-CO-phenyl, NH-SO_2-phenyl, it being possible for the phenyl ring to be substituted up to twice by F, Cl, CN, OH, (C_1-C_6)-alkyl, O-(C_1-C_6)-alkyl, CF_3, OCF_3, COOH, COO(C_1-C_6)-alkyl or $CONH_2$;

X is O, S;

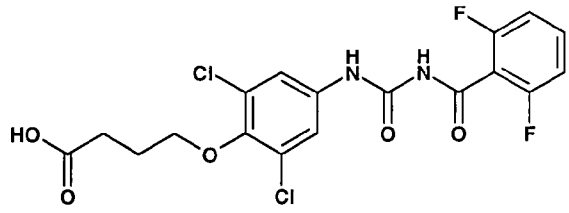
R7 is (C_1-C_{10})-alkylene-COOH, (C_6-C_{10})-alkylene-COO-(C_1-C_6)-alkyl, (C_1-C_{10})-alkylene-$CONH_2$, (C_1-C_{10})-alkylene-CONH-(C_1-C_6)-alkyl, (C_1-C_{10})-alkylene-CON-[(C_1-C_6)-alkyl]$_2$, (C_1-C_{10})-alkylene-NH_2, (C_1-C_{10})-alkylene-NH(C_1-C_6)-alkyl, (C_1-C_{10})-alkylene-N[(C_1-C_6)-alkyl]$_2$, (C_1-C_{10})-alkylene-B;

B is (C_3-C_7)-cycloalkyl, pyrrolyl, imidazolyl, thiazolyl, azetidinyl, thienyl-methyl, piperidinyl, pyrrolidinyl, morpholinyl, pyridyl-

methyl or furyl, in which cycloalkyl, pyrrolyl, imidazolyl, thiazolyl, azetidinyl, thienyl-methyl, piperidinyl, pyrrolidinyl, morpholinyl, pyridyl-methyl or furyl may in each case be substituted up to twice by Cl, F, CN, CF_3, OCF_3, COOH, $COO-(C_1-C_6)$-alkyl, $CONH_2$, $CONH-(C_1-C_6)$-alkyl, $CON-[(C_1-C_6)-alkyl]_2$, (C_1-C_6)-alkyl, OH, $O-(C_1-C_6)$-alkyl

and the physiologically tolerated salts thereof,

excepting the compounds of the formula



and compounds of the formula I in which the radicals are at the same time

A phenyl;

X O;

R1 H;

R7 $-(C_1-C_4)$-alkyl-B;

B (C_3-C_7)-cycloalkyl, heteroaryl.

Particularly preferred compounds of the formula I are those in which

A is phenyl, it being possible for the phenyl radical to be substituted up to twice by F, Cl, Br, $O-(C_1-C_6)$-alkyl;

R1, R2 are, independently of one another, H, (C_1-C_6)-alkyl, $CO-(C_1-C_6)$-alkyl;

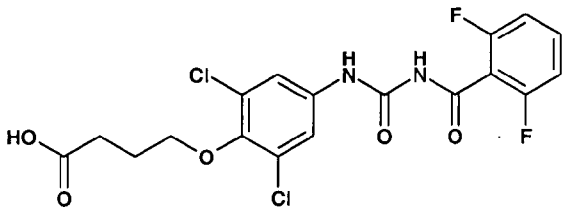
R3, R4, R5, R6 are, independently of one another, H, Cl, F, (C_1-C_6)-alkyl, O-(C_1-C_6)-alkyl, -COO-(C_1-C_6)-alkyl;

X is O;

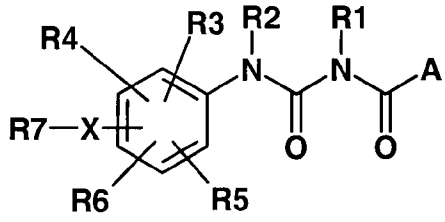
R7 is (C_1-C_{10})-alkylene-COOH, (C_6-C_{10})-alkylene-COO-(C_1-C_6)-alkyl, (C_1-C_{10})-alkylene-$CONH_2$;

and the physiologically tolerated salts thereof,

excepting the compounds of the formula



The invention further relates to the use of compounds of the formula I



I

in which

A is phenyl, naphthyl, it being possible for the phenyl or naphthyl radical to be substituted up to three times by F, Cl, Br, OH, CF_3, NO_2, CN, OCF_3, O-(C_1-C_6)-alkyl, O-(C_2-C_6)-alkenyl, O-(C_2-C_6)-alkynyl, S-(C_1-C_6)-alkyl, S-(C_2-C_6)-alkenyl, S-(C_2-C_6)-alkynyl, SO-(C_1-C_6)-alkyl, SO_2-(C_1-C_6)-alkyl, SO_2-

NH_2, $(C_1$-$C_6)$-alkyl, $(C_2$-$C_6)$-alkenyl, $(C_2$-$C_6)$-alkynyl, $(C_3$-$C_7)$-cycloalkyl, $(C_3$-$C_7)$-cycloalkyl-$(C_2$-$C_4)$-alkylene, $(C_0$-$C_6)$-alkylene-COOH, $(C_0$-$C_6)$-alkylene-COO $(C_1$-$C_6)$-alkyl, $CONH_2$, $CONH(C_1$-$C_6)$-alkyl, $CON[(C_1$-$C_6)$-alkyl$]_2$, $CONH(C_3$-$C_7)$-cycloalkyl, $(C_0$-$C_6)$-alkylene-NH_2, $(C_0$-$C_6)$-alkylene-$NH(C_1$-$C_6)$-alkyl, $(C_0$-$C_6)$-alkylene-$N[(C_1$-$C_6)$-alkyl$]_2$, NH-CO-$(C_1$-$C_6)$-alkyl, NH-CO-phenyl, NH-SO_2-phenyl, it being possible for the phenyl ring to be substituted up to twice by F, Cl, CN, OH, $(C_1$-$C_6)$-alkyl, O-$(C_1$-$C_6)$-alkyl, CF_3, OCF_3, COOH, $COO(C_1$-$C_6)$-alkyl or $CONH_2$;

R1, R2 are, independently of one another, H, $(C_1$-$C_6)$-alkyl, O-$(C_1$-$C_6)$-alkyl, CO-$(C_1$-$C_6)$-alkyl, COO-$(C_1$-$C_6)$-alkyl, $(C_1$-$C_6)$-alkylene-COOH, $(C_1$-$C_6)$-alkylene-COO-$(C_1$-$C_6)$-alkyl;

R3, R4, R5, R6 are, independently of one another, H, F, Cl, Br, OH, CF_3, NO_2, CN, OCF_3, O-$(C_1$-$C_6)$-alkyl, O-$(C_2$-$C_6)$-alkenyl, O-$(C_2$-$C_6)$-alkynyl, S-$(C_1$-$C_6)$-alkyl, S-$(C_2$-$C_6)$-alkenyl, S-$(C_2$-$C_6)$-alkynyl, SO-$(C_1$-$C_6)$-alkyl, SO_2-$(C_1$-$C_6)$-alkyl, SO_2-NH_2, $(C_1$-$C_6)$-alkyl, $(C_2$-$C_6)$-alkenyl, $(C_1$-$C_6)$-alkynyl, $(C_3$-$C_7)$-cycloalkyl, $(C_3$-$C_7)$-cycloalkyl-$(C_2$-$C_4)$-alkylene, COOH, $COO(C_1$-$C_6)$-alkyl, $CONH_2$, $CONH(C_1$-$C_6)$-alkyl, $CON[(C_1$-$C_6)$-alkyl$]_2$, $CONH(C_3$-$C_7)$-cycloalkyl, NH_2, $NH(C_1$-$C_6)$-alkyl, $N[(C_1$-$C_6)$-alkyl$]_2$, NH-CO-$(C_1$-$C_6)$-alkyl, NH-CO-phenyl, NH-SO_2-phenyl, it being possible for the phenyl ring to be substituted up to twice by F, Cl, CN, OH, $(C_1$-$C_6)$-Alkyl, O-$(C_1$-$C_6)$-alkyl, CF_3, OCF_3, COOH, $COO(C_1$-$C_6)$-alkyl or $CONH_2$;

X is O, S;

R7 is $(C_1$-$C_{10})$-alkylene-COOH, $(C_1$-$C_{10})$-alkylene-COO-$(C_1$-$C_6)$-alkyl, $(C_1$-$C_{10})$-alkylene-$CONH_2$, $(C_1$-$C_{10})$-alkylene-CONH-

$(C_1\text{-}C_6)$-alkyl, $(C_1\text{-}C_{10})$-alkylene-CON-$[(C_1\text{-}C_6)\text{-alkyl}]_2$,

$(C_1\text{-}C_{10})$-alkylene-NH_2, $(C_1\text{-}C_{10})$-alkylene-NH$(C_1\text{-}C_6)$-alkyl,

$(C_1\text{-}C_{10})$-alkylene-N$[(C_1\text{-}C_6)\text{-alkyl}]_2$, $(C_1\text{-}C_{10})$-alkylene-B;

B is (C_3-C_7)-cycloalkyl, phenyl, pyrrolyl, imidazolyl, thiazolyl, azetidinyl, thienyl, piperidinyl, pyrrolidinyl, morpholinyl, pyridyl or furyl, in which cycloalkyl, phenyl, pyrrolyl, imidazolyl, thiazolyl, azetidinyl, thienyl, piperidinyl, pyrrolidinyl, morpholinyl, pyridyl or furyl may in each case be substituted up to twice by Cl, F, CN, CF_3, OCF_3, COOH, COO-(C_1-C_6)-alkyl, $CONH_2$, CONH-(C_1-C_6)-alkyl, CON-[(C_1-C_6)-alkyl]$_2$, (C_1-C_6)-alkyl, OH, O-(C_1-C_6)-alkyl;

and physiologically tolerated salts thereof, for producing a medicine for lowering the blood glucose level and treating type II diabetes.

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

The alkyl radicals in the substituents R1, R2, R3, R4, R5, R6, R7, A and B may be both straight-chain and branched.

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

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

The term "physiologically functional derivative" used herein refers to any physiologically tolerated derivative of a compound of the formula I of the invention,

for example an ester, which on administration to a mammal such as, for example, a human is able to form (directly or indirectly) a compound of the formula I or an active metabolite thereof.

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

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

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

The amount of a compound of formula I necessary to achieve the desired biological effect depends on a number of factors, for example the specific compound chosen, the intended use, the mode of administration and the clinical condition of the patient. The daily dose is generally in the range from 0.3 mg to 100 mg (typically from 3 mg and 50 mg) per day and per kilogram of bodyweight, for example 3-10 mg/kg/day. An intravenous dose may be, for example, in the range from 0.3 mg to 1.0 mg/kg, which can suitably be administered as infusion of 10 ng to 100 ng per kilogram and per minute. Suitable infusion solutions for these purposes may contain, for example, from 0.1 ng to 10 mg, typically from 1ng to 10 mg, per milliliter. Single doses may contain, for example, from 1 mg to 10 g of the active ingredient. Thus, ampoules for injections may contain, for example, from 1 mg to 100 mg, and single-dose formulations which can be administered orally, such as, for example, capsules or tablets, may contain, for example, from 1.0 to 1000 mg, typically from 10 to 600 mg. For the therapy of the abovementioned conditions, the compounds of formula I may be used as the compound itself, but they are preferably in the form of a pharmaceutical composition with an acceptable carrier. The carrier must, of course, be acceptable in the sense that it is compatible with the other ingredients of the composition and is not harmful for the patient's health. The carrier may be a solid or a liquid or both and is preferably

formulated with the compound as a single dose, for example as a tablet, which may contain from 0.05% to 95% by weight of the active ingredient. Other pharmaceutically active substances may likewise be preferable, including other compounds of formula I. The pharmaceutical compositions of the invention can be produced by one of the known pharmaceutical methods, which essentially consist of mixing the ingredients with pharmacologically acceptable carriers and/or excipients.

Pharmaceutical compositions of the invention are those suitable for oral, rectal, topical, peroral (for example sublingual) and parenteral (for example subcutaneous, intramuscular, intradermal or intravenous) administration, although the most suitable mode of administration depends in each individual case on the nature and severity of the condition to be treated and on the nature of the compound of formula I used in each case. Coated formulations and coated slow-release formulations also belong within the framework of the invention. Preference is given to acid- and gastric juice-resistant formulations. Suitable coatings resistant to gastric juice comprise cellular acetate phthalate, polyvinal acetate phthalate, hydroxypropylmethylcellulose phthalate and anionic polymers of methacrylic acid and methyl methacrylate.

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

by molding the compound which is in powder form and is moistened with an inert liquid diluent in a suitable machine.

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

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

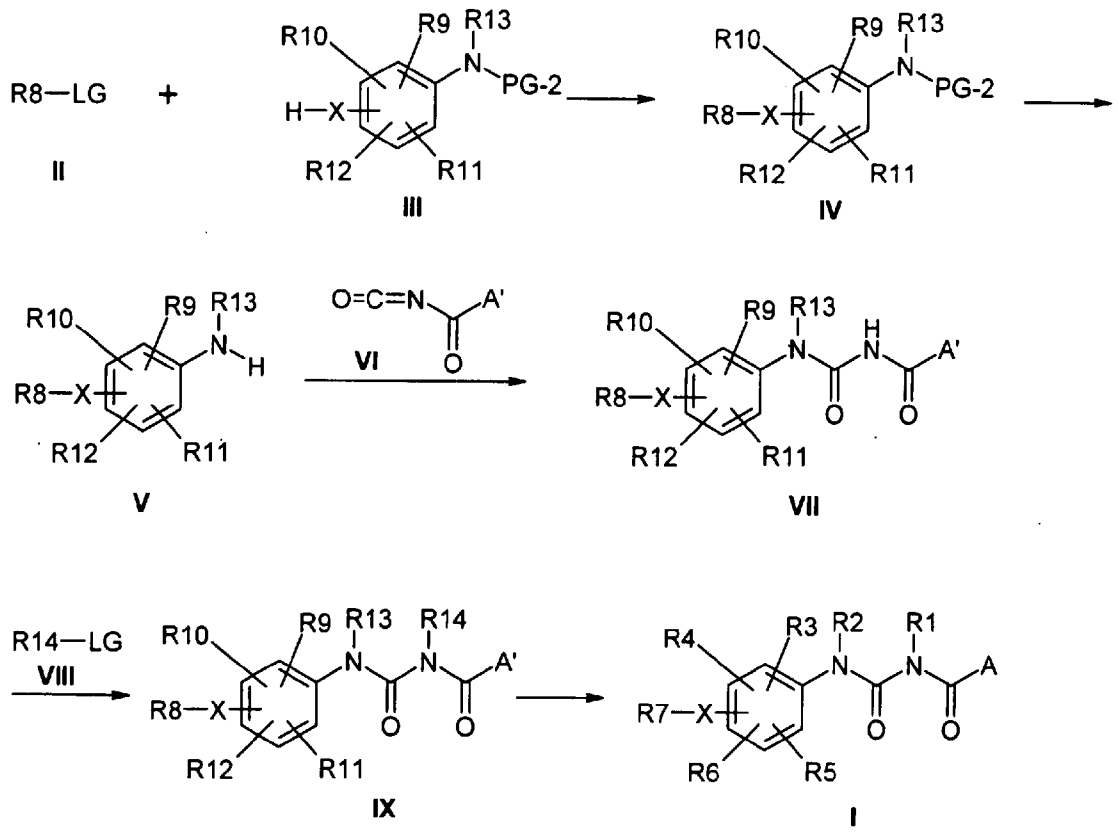
Pharmaceutical compositions suitable for rectal administration are preferably in the form of single-dose suppositories. These can be produced by mixing a compound of the formula I with one or more conventional solid carriers, for example cocoa butter, and shaping the resulting mixture.

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

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

or iontophoresis as described, for example, in Pharmaceutical Research, 2(6): 318 (1986).

The invention further relates to a process for preparing the compounds of the formula I, which comprises obtaining the compounds of the formula I by proceeding as shown in the following reaction:



For this purpose, compounds of the formula II

R8-LG (II)

in which

R8 is $(C_1\text{-}C_{10})$-alkylene-COO-(PG-1), $(C_6\text{-}C_{10})$-alkylene-COO-$(C_1\text{-}C_6)$-alkyl, $(C_1\text{-}C_{10})$-alkylene-CON-$(PG\text{-}2)_2$, $(C_1\text{-}C_{10})$-alkylene-CONH-$(C_1\text{-}C_6)$-alkyl, $(C_1\text{-}C_{10})$-alkylene-CON-$[(C_1\text{-}C_6)\text{-alkyl}]_2$, $(C_1\text{-}C_{10})$-alkylene-N-$(PG\text{-}2)_2$, $(C_1\text{-}C_{10})$-alkylene-NH$(C_1\text{-}C_6)$-alkyl, $(C_1\text{-}C_{10})$-alkylene-N$[(C_1\text{-}C_6)\text{-alkyl}]_2$, $(C_1\text{-}C_{10})$-alkylene-B'

in which

PG-1 is a generally known protective group for esters, such as, for example, $(C_1$-$C_6)$-alkyl, benzyl or p-methoxybenzyl, and

PG-2 is a generally known protective group for amino groups, such as, for example, $(C_1$-$C_6)$-alkylcarbonyl, $(C_1$-$C_6)$-alkyloxycarbonyl or $(C_6$-$C_{12})$-aryl-$(C_1$-$C_4)$-alkyloxycarbonyl, which replaces either both hydrogens or only one hydrogen atom in the amino group, and

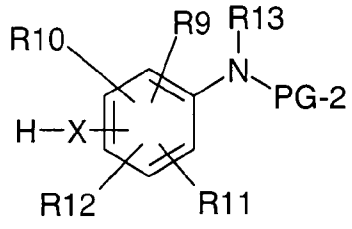
B' is $(C_3$-$C_7)$-cycloalkyl, $(C_3$-$C_7)$-cycloalkyl-$(C_1$-$C_4)$-alkylene, phenyl, pyrrolyl, imidazolyl, thiazolyl, azetidinyl, thienyl, piperidinyl, pyrrolidinyl, morpholinyl, pyridyl and furyl in which cycloalkyl, phenyl, pyrrolyl, imidazolyl, thiazolyl, azetidinyl, thienyl, piperidinyl, pyrrolidinyl, morpholinyl, pyridyl and furyl may in each case be substituted up to twice by Cl, F, CN, CF_3, OCF_3, COO-(PG-1), COO-$(C_1$-$C_6)$-alkyl, CON-$(PG\text{-}2)_2$, CONH-$(C_1$-$C_6)$-alkyl, CON-$[(C_1$-$C_6)$-alkyl$]_2$, $(C_1$-$C_6)$-alkyl, O-(PG-3), O-$(C_1$-$C_6)$-alkyl,

in which PG-3 is a generally known protective group for alcohols, such as, for example, benzyl, allyl, tetrahydropyranyl or tetrahydrofuranyl,

and

LG is a generally known leaving group such as, for example, halogen, arylsulfonyloxy or alkylsulfonyloxy,

are reacted with anilines of the formula III



(III)

in which X and PG-2 have the meaning described above, and

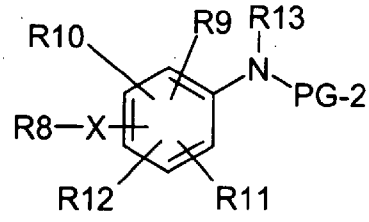
R9, R10, R11, R12 are, independently of one another H, F, Cl, Br, O-(PG-3), CF_3, NO_2, CN, OCF_3, O-(C_1-C_6)-alkyl, O-(C_2-C_6)-alkenyl, O-(C_2-C_6)-alkynyl, S-(C_1-C_6)-alkyl, S-(C_2-C_6)-alkenyl, S-(C_2-C_6)-alkynyl, SO-(C_1-C_6)-alkyl, SO_2-(C_1-C_6)-alkyl, SO_2-N-(PG-2)$_2$, (C_1-C_6)-alkyl, (C_2-C_6)-alkenyl, (C_2-C_6)-alkynyl,(C_3-C_7)-

cycloalkyl, N-(PG-2)$_2$, NH(C_1-C_6)-alkyl, N[(C_1-C_6)-alkyl]$_2$, NH-CO-(C_1-C_6)-alkyl, NH-CO-phenyl, NH-SO_2-phenyl, it being possible for the phenyl ring to be substituted up to twice by F, Cl, CN, O-(PG-3), (C_1-C_6)-alkyl, O-(C_1-C_6)-alkyl, CF_3, OCF_3, COO-(PG-1), COO(C_1-C_6)-alkyl or CON-(PG-2)$_2$;

R13 is H, (C_1-C_6)-alkyl, O-(C_1-C_6)-alkyl, CO-(C_1-C_6)-alkyl, COO-(C_1-C_6)-alkyl, (C_1-C_6)-alkylene-COO-(PG-1), (C_1-C_6)-alkylene-COO-(C_1-C_6)-alkyl,

where PG-1, PG-2 and PG-3 have the meaning described above

using a base such as, for example, potassium or cesium carbonate, in an organic solvent such as, for example, acetone or dimethylformamide, to give compounds of the formula IV

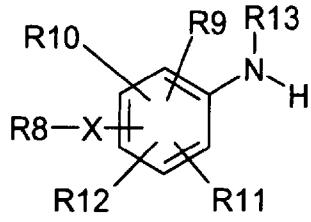


(IV)

in which X, R8, R9, R10, R11, R12, R13 and PG-2 have the meaning described above,

the reaction times are between 2 and 24 hours and the reaction temperature is between 10°C and the boiling point of the solvent used,

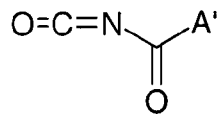
and then, by selective elimination of the protective group PG-2, compounds of the formula V



(V)

in which X, R8, R9, R10, R11, R12, and R13 have the meanings stated above, are obtained,

compounds of the formula V are reacted with isocyanates of the formula VI



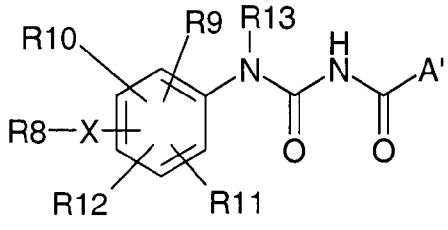
(VI)

in which

A' is phenyl, naphthyl, it being possible for the phenyl or naphthyl radical to be substituted up to three times by F, Cl, Br, O-(PG-3), CF_3, NO_2, CN, OCF_3, O-$(C_1$-$C_6)$-alkyl, O-$(C_2$-$C_6)$-alkenyl, O-$(C_2$-$C_6)$-alkynyl, S-$(C_1$-$C_6)$-alkyl, S-$(C_2$-$C_6)$-alkenyl, S-$(C_2$-$C_6)$-alkynyl, SO-$(C_1$-$C_6)$-alkyl, SO_2-$(C_1$-$C_6)$-alkyl, SO_2-N-$(PG\text{-}2)_2$, $(C_1$-$C_6)$-alkyl, $(C_2$-$C_6)$-alkenyl, $(C_2$-$C_6)$-alkynyl, $(C_3$-$C_7)$-cycloalkyl, $(C_3$-$C_7)$-cycloalkyl-$(C_2$-$C_4)$-alkylene, $(C_0$-$C_6)$-alkylene-COO-(PG-1), $(C_0$-$C_6)$-alkylene-COO$(C_1$-$C_6)$-alkyl, CON-$(PG\text{-}2)_2$, CONH$(C_1$-$C_6)$-alkyl, CON$[(C_1$-$C_6)$-alkyl$]_2$, CONH$(C_3$-$C_7)$-cycloalkyl, $(C_0$-$C_6)$-alkylene-N-$(PG\text{-}2)_2$, $(C_0$-$C_6)$-alkylene-NH$(C_1$-$C_6)$-alkyl, $(C_0$-$C_6)$-alkylene-N$[(C_1$-$C_6)$-alkyl$]_2$, NH-CO-$(C_1$-$C_6)$-alkyl, NH-CO-phenyl, NH-SO_2-phenyl, it being possible for the phenyl ring to be substituted up to twice by F, Cl, CN, O-(PG-3), $(C_1$-$C_6)$-alkyl, O-$(C_1$-$C_6)$-alkyl, CF_3, OCF_3, COO-(PG-1), COO$(C_1$-$C_6)$-alkyl or CON-$(PG\text{-}2)_2$,

where PG-1, PG-2 and PG-3 have the meaning described above,

in anhydrous organic solvents such as, for example, benzene, toluene or acetonitrile, under a protective gas atmosphere, at reaction temperatures between 10°C and the boiling point of the solvent employed, to give compounds of the formula VII



(VII)

in which X, R8, R9, R10, R11, R12, R13 and A' have the meaning described above,

the compounds of the formula VII can, if R1 in compounds of the formula I is not a hydrogen atom, be alkylated by reaction with compounds of the formula VIII

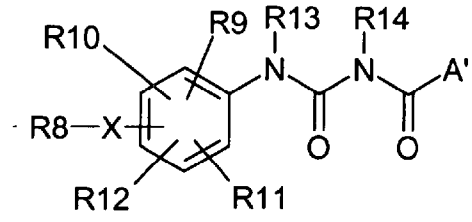
R14-LG (VIII)

in which LG has the meaning described above, and

R14 is H, (C_1-C_6)-alkyl, O-(C_1-C_6)-alkyl, CO-(C_1-C_6)-alkyl, COO-(C_1-C_6)-alkyl, (C_1-C_6)-alkylene-COO-(PG-1), (C_1-C_6)-alkylene-COO-(C_1-C_6)-alkyl

where PG-1 has the meaning described above,

using a base such as, for example, 1,8-diazabicyclo[5.4.0]undec-7-ene, in organic solvents such as, for example, dichloromethane or acetonitrile, to give compounds of the formula IX

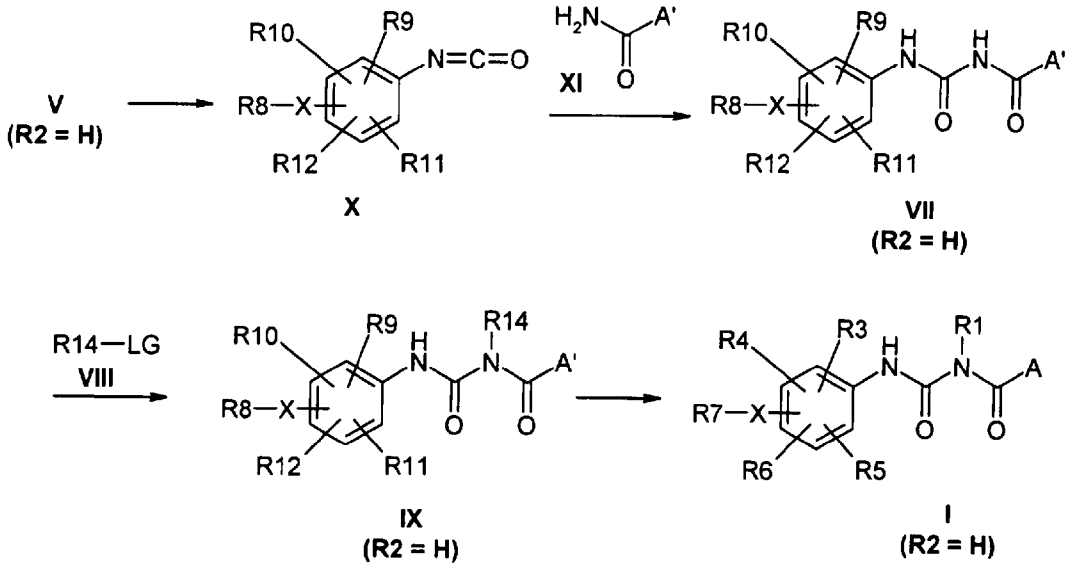


(IX)

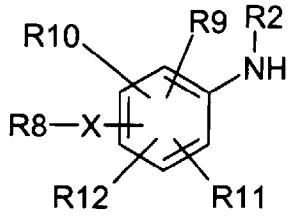
in which X, R8, R9, R10, R11, R12, R13, R14 and A' have the meaning described above,

and, after elimination as disclosed in the literature of all protective groups which may be present in the radicals R8, R9, R10, R11, R12, R13, R14, A' and B', compounds of the formula I are obtained. Conversion of compounds of the formula I into their salts takes place by adding one equivalent to the appropriate acid or base in an organic solvent such as, for example, acetonitrile or dioxane or in water and by subsequent removal of the solvent.

Another possibility for preparing compounds of the formula I in which R2 is a hydrogen atom is depicted in the following scheme:

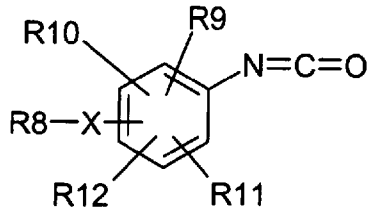


which entails converting compounds of the formula V in which R2 is a hydrogen atom



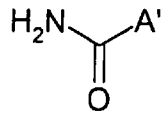
(V)

and X, R8, R9, R19, R11 and R12 have the meaning described above, into isocyanates of the formula X



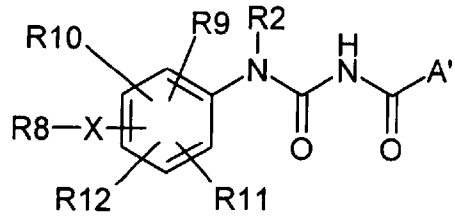
(X)

by known methods such as, for example, a reaction with oxalyl chloride in organic solvents such as, for example, 1,2-dichlorethane or dichloromethane, at reaction temperatures between room temperature and the boiling point of the solvent, reacting the isocyanates of the formula X with amides of the formula XI



(XI)

in which A' has the meaning described above,
to result in compounds of the formula VII in which R2 is a hydrogen atom,

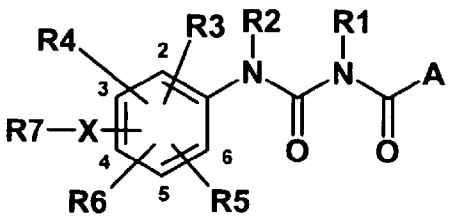


(VII)

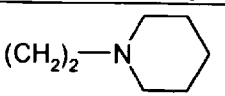
and X, R8, R9, R10, R11 and R12 have the meaning described above; compounds of the formula VII can, if R1 is not a hydrogen atom, be converted as already described above by alkylation with compounds of the formula VIII into compounds of the formula IX, and, if necessary, by subsequent elimination of the protective groups into compounds of the formula I. Conversion of compounds of the formula I into their salts takes place by adding one equivalent of the appropriate acid or base in an organic solvent such as, for example, acetonitrile or dioxane or in water and by subsequent removal of the solvent.

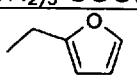
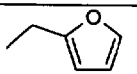
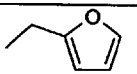
The examples listed hereinafter serve to illustrate the invention without, however, restricting it. The measured solidification or decomposition points (m.p.) have not been corrected and generally depend on the heating rate.

Table 1: Examples

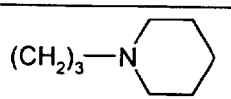


Formula I

Ex.	A	R1	R2	R3	R4	R5	R6	R7	X	Salt	m.p. [°C]	MS*
1	phenyl-2-Cl	H	H	2-H	3-Cl	6-H	5-Cl	$(CH_2)_5$-COOH	4-O	-	164	ok
2	phenyl-2-Cl	H	H	2-H	3-Cl	6-H	5-Cl	$(CH_2)_5$-COONa	4-O	-	177-179	ok
3	phenyl-2-Cl	H	H	2-H	3-Cl	6-H	5-Cl	$(CH_2)_5$-COOH	4-O	bis-2-hydroxyethylamine		ok
4	phenyl-2-Cl	H	H	2-H	3-Cl	6-H	5-Cl	$(CH_2)_5$-COOH	4-O	3-hydroxy-1-(2-hydroxyethyl)-1-hydroxymethyl-propylamine	163-165	ok
5	phenyl-2-Cl	H	H	2-H	3-Cl	6-H	5-Cl	$(CH_2)_5$-COOH	4-O	lysine	170-172	ok
6	phenyl-2-Cl	H	H	2-H	3-Cl	6-H	5-H	CH_2COOCH_3	4-S	-	168-169	ok
7	phenyl-2,6-F_2	H	H	H	H	H	H	CH_2COOCH_3	4-S	-	152	ok
8	phenyl	H	H	H	H	H	H		4-O	fumaric acid	182	ok

9	phenyl	CH_3	H	H	H	H	H	$(CH_2)_2$—N⟨ ⟩	4-O	HCl	82	ok
10	phenyl-2-Cl	H	$COCH_3$	2-H	3-Cl	6-H	5-Cl	$(CH_2)_5$-COOH	4-O	-	137-139	ok
11	phenyl	H	H	2-H	3-Cl	6-H	5-Cl	$(CH_2)_5$-COOH	4-O	-	189-191	ok
12	phenyl-2,4-Cl_2	H	H	2-H	3-Cl	6-H	5-Cl	$(CH_2)_5$-COOH	4-O	-	202-204	ok
13	phenyl-2-Cl	H	H	2-H	3-Cl	6-H	5-Cl	$(CH_2)_5$-$COOC_2H_5$	4-O	-	119-121	ok
14	phenyl-4-OCH_3	H	H	2-H	3-Cl	6-H	5-Cl	$(CH_2)_5$-COOH	4-O	-	188-190	ok
15	phenyl-3-F	H	H	2-H	3-Cl	6-H	5-Cl	$(CH_2)_5$-COOH	4-O	-	210-214	ok
16	phenyl-2-F	H	H	2-H	3-Cl	6-H	5-Cl	$(CH_2)_5$-COOH	4-O	-	147-151	ok
17	phenyl-2-OCH_3	H	H	2-H	3-Cl	6-H	5-Cl	$(CH_2)_5$-COOH	4-O	-	149-153	ok
18	phenyl-2,3-Cl_2	H	H	2-H	3-Cl	6-H	5-Cl	$(CH_2)_5$-COOH	4-O	-	170-172	ok
19	phenyl-2-F	H	H	H	H	H	H		4-S	-	139-143	
20	phenyl-2,6-F_2	H	H	H	H	H	H		4-S	-	162-163	
21	phenyl-2,6-F_2	H	H	2-H	3-Cl	6-H	5-Cl		4-S	-	152	
22	phenyl-2-Cl	H	H	H	H	H	H	CH_2-$COOCH_3$	4-S	-	125-126	
23	phenyl-3-OCH_3	H	H	2-H	3-Cl	6-H	5-Cl	$(CH_2)_5$-COOH	4-O	-	136	ok
24	phenyl-2,4-Cl_2	H	H	2-H	3-Cl	6-H	5-Cl	$(CH_2)_2$—N⟨ ⟩	4-O	-	189	ok
25	phenyl-3-F	H	H	2-H	3-Cl	6-H	5-Cl	$(CH_2)_2$—N⟨ ⟩	4-O	-	204	ok

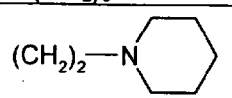
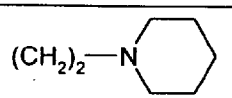
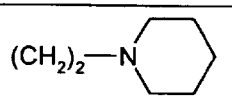
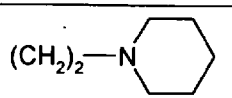
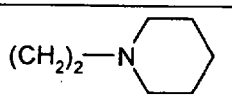
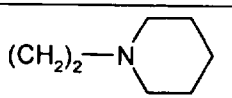
26	phenyl-2,3-Cl_2	H	H	2-H	3-Cl	6-H	5-Cl	$(CH_2)_2$—N⟨ ⟩	4-O	-	182	ok
27	phenyl-3-OCH_3	H	H	2-H	3-Cl	6-H	5-Cl	$(CH_2)_2$—N⟨ ⟩	4-O	-	176	ok
28	phenyl-2-F	H	H	2-H	3-Cl	6-H	5-Cl	$(CH_2)_2$—N⟨ ⟩	4-O	-	144	ok
29	phenyl	H	H	2-H	3-Cl	6-H	5-Cl	$(CH_2)_2$—N⟨ ⟩	4-O	-	204	ok
30	phenyl-4-OCH_3	H	H	2-H	3-Cl	6-H	5-Cl	$(CH_2)_2$—N⟨ ⟩	4-O	TFA		ok
31	phenyl-2-OCH_3	H	H	2-H	3-Cl	6-H	5-Cl	$(CH_2)_2$—N⟨ ⟩	4-O	TFA		ok
32	phenyl-2-Cl	H	H	2-H	3-Cl	6-H	5-Cl	$(CH_2)_3$-COOH	4-O	-		ok
33	phenyl-2-Cl	H	H	2-H	3-Cl	6-H	5-Cl	$(CH_2)_4$-COOH	4-O	-		ok
34	phenyl-2-Cl	H	H	2-H	3-Cl	6-H	5-Cl	$(CH_2)_6$-COOH	4-O	-		ok
35	phenyl-2-Cl	H	H	2-H	3-Cl	6-H	5-Cl	$(CH_2)_7$-COOH	4-O	-		ok
36	phenyl-2-Cl	CH_3	H	2-H	3-Cl	6-H	5-Cl	$(CH_2)_5$-COOH	4-O	-		ok
37	phenyl-2-Cl	H	H	2-H	3-Cl	6-H	5-Cl	$(CH_2)_3$-COOH	4-O	3-hydroxy-1-(2-hydroxyethyl)-1-hydroxymethyl-propylamine		ok
38	phenyl-2-Cl	H	H	2-H	3-Cl	6-H	5-Cl	$(CH_2)_4$-COOH	4-O	3-hydroxy-1-(2-hydroxyethyl)-1-hydroxymethyl-propylamine		ok

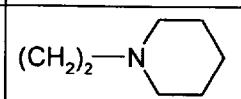
39	phenyl-2-Cl	H	H	2-H	3-Cl	6-H	5-Cl	$(CH_2)_6$-COOH	4-O	3-hydroxy-1-(2-hydroxyethyl)-1-hydroxymethyl-propylamine		ok
40	phenyl-2-Cl	H	H	2-H	3-Cl	6-H	5-Cl	$(CH_2)_7$-COOH	4-O	3-hydroxy-1-(2-hydroxyethyl)-1-hydroxymethyl-propylamine		ok
41	phenyl-2,4-Cl_2	H	H	2-H	3-Cl	6-H	5-Cl	$(CH_2)_3$-COOH	4-O	3-hydroxy-1-(2-hydroxyethyl)-1-hydroxymethyl-propylamine		ok
42	phenyl-2,4-Cl_2	H	H	2-H	3-Cl	6-H	5-Cl	$(CH_2)_4$-COOH	4-O	3-hydroxy-1-(2-hydroxyethyl)-1-hydroxymethyl-propylamine		ok
43	phenyl-2,4-Cl_2	H	H	2-H	3-Cl	6-H	5-Cl	$(CH_2)_6$-COOH	4-O	3-hydroxy-1-(2-hydroxyethyl)-1-hydroxymethyl-propylamine		ok
44	phenyl-2,4-Cl_2	H	H	2-H	3-Cl	6-H	5-Cl	$(CH_2)_7$-COOH	4-O	3-hydroxy-1-(2-hydroxyethyl)-1-hydroxymethyl-propylamine		ok
45	phenyl-2-Cl	H	H	2-H	3-Cl	6-H	5-Cl		4-O	HCl		ok

46	phenyl-2,4-Cl_2	H	H	2-H	3-Cl	6-H	5-Cl	$(CH_2)_3$—N⟨ ⟩	4-O	HCl	182	ok
47	phenyl-2-CH_3	H	H	2-H	3-Cl	6-H	5-Cl	$(CH_2)_5$-COOH	4-O	3-hydroxy-1-(2-hydroxyethyl)-1-hydroxymethyl-propylamine		ok
48	phenyl-4-CH_3	H	H	2-H	3-Cl	6-H	5-Cl	$(CH_2)_5$-COOH	4-O	3-hydroxy-1-(2-hydroxyethyl)-1-hydroxymethyl-propylamine		ok
49	phenyl-3-CH_3	H	H	2-H	3-Cl	6-H	5-Cl	$(CH_2)_5$-COOH	4-O	3-hydroxy-1-(2-hydroxyethyl)-1-hydroxymethyl-propylamine		ok
50	phenyl-4-F	H	H	2-H	3-Cl	6-H	5-Cl	$(CH_2)_5$-COOH	4-O	3-hydroxy-1-(2-hydroxyethyl)-1-hydroxymethyl-propylamine		ok
51	phenyl-3-Cl	H	H	2-H	3-Cl	6-H	5-Cl	$(CH_2)_5$-COOH	4-O	3-hydroxy-1-(2-hydroxyethyl)-1-hydroxymethyl-propylamine		ok
52	phenyl-2-Cl	H	H	2-H	3-Cl	6-H	5-Cl	$(CH_2)_5$-COOK	4-O	-		ok
53	phenyl-4-Br	H	H	2-H	3-Cl	6-H	5-Cl	$(CH_2)_5$-COOH	4-O	3-hydroxy-1-(2-hydroxyethyl)-1-hydroxymethyl-propylamine		ok

54	phenyl	H	H	2-H	3-Cl	6-H	5-Cl	$(CH_2)_5$-COOH	4-O	3-hydroxy-1-(2-hydroxyethyl)-1-hydroxymethyl-propylamine	172	ok
55	phenyl-3-F	H	H	2-H	3-Cl	6-H	5-Cl	$(CH_2)_5$-COOH	4-O	3-hydroxy-1-(2-hydroxyethyl)-1-hydroxymethyl-propylamine	170	ok
56	phenyl-2-OCH_3	H	H	2-H	3-Cl	6-H	5-Cl	$(CH_2)_5$-COOH	4-O	3-hydroxy-1-(2-hydroxyethyl)-1-hydroxymethyl-propylamine	119	ok
57	phenyl-2,3-Cl_2	H	H	2-H	3-Cl	6-H	5-Cl	$(CH_2)_5$-COOH	4-O	3-hydroxy-1-(2-hydroxyethyl)-1-hydroxymethyl-propylamine	160	ok
58	phenyl-4-Cl	H	H	2-H	3-Cl	6-H	5-Cl	$(CH_2)_5$-COOH	4-O	3-hydroxy-1-(2-hydroxyethyl)-1-hydroxymethyl-propylamine		ok
59	phenyl-2,4-Cl_2	H	H	2-H	3-Cl	6-H	5-Cl	$(CH_2)_5$-COOH	4-O	3-hydroxy-1-(2-hydroxyethyl)-1-hydroxymethyl-propylamine		ok
60	phenyl-2-CH_3	H	H	2-H	3-Cl	6-H	5-Cl	$(CH_2)_3$-COOH	4-O	-	207	ok
61	phenyl-2-CH_3	H	H	2-H	3-Cl	6-H	5-Cl	$(CH_2)_4$-COOH	4-O	-	167	ok
62	phenyl-2-CH_3	H	H	2-H	3-Cl	6-H	5-Cl	$(CH_2)_6$-COOH	4-O	-	185	ok
63	phenyl-2-CH_3	H	H	2-H	3-Cl	6-H	5-Cl	$(CH_2)_7$-COOH	4-O	-	153	ok

64	phenyl-2,4-Cl_2	H	H	2-H	3-F	6-H	5-H	$(CH_2)_3$-COOH	4-O	-		ok
65	phenyl-2,4-Cl_2	H	H	2-H	3-F	6-H	5-H	$(CH_2)_4$-COOH	4-O	-		ok
66	phenyl-2,4-Cl_2	H	H	2-H	3-F	6-H	5-H	$(CH_2)_5$-COOH	4-O	-		ok
67	phenyl-2,4-Cl_2	H	H	2-H	3-F	6-H	5-H	$(CH_2)_6$-COOH	4-O	-		ok
68	phenyl-2,4-Cl_2	H	H	2-H	3-F	6-H	5-H	$(CH_2)_7$-COOH	4-O	-		ok
69	phenyl-2,4-Cl_2	H	H	2-CH_3	4-H	6-H	5-H	$(CH_2)_3$-COOH	3-O	-		ok
70	phenyl-2,4-Cl_2	H	H	2-CH_3	4-H	6-H	5-H	$(CH_2)_4$-COOH	3-O	-		ok
71	phenyl-2,4-Cl_2	H	H	2-CH_3	4-H	6-H	5-H	$(CH_2)_5$-COOH	3-O	-		ok
72	phenyl-2,4-Cl_2	H	H	2-CH_3	4-H	6-H	5-H	$(CH_2)_6$-COOH	3-O	-		ok
73	phenyl-2,4-Cl_2	H	H	2-CH_3	4-H	6-H	5-H	$(CH_2)_7$-COOH	3-O	-		ok
74	phenyl-2,4-Cl_2	H	H	2-CH_3	3-H	6-H	5-H	$(CH_2)_3$-COOH	4-O	-		ok
75	phenyl-2,4-Cl_2	H	H	2-CH_3	3-H	6-H	5-H	$(CH_2)_4$-COOH	4-O	-		ok
76	phenyl-2,4-Cl_2	H	H	2-CH_3	3-H	6-H	5-H	$(CH_2)_5$-COOH	4-O	-		ok
77	phenyl-2,4-Cl_2	H	H	2-CH_3	3-H	6-H	5-H	$(CH_2)_6$-COOH	4-O	-		ok
78	phenyl-2,4-Cl_2	H	H	2-CH_3	3-H	6-H	5-H	$(CH_2)_7$-COOH	4-O	-		ok
79	phenyl-2,4-Cl_2	H	H	2-H	3-CH_3	6-H	5-CH_3	$(CH_2)_3$-COOH	4-O	-		ok
80	phenyl-2,4-Cl_2	H	H	2-H	3-CH_3	6-H	5-CH_3	$(CH_2)_4$-COOH	4-O	-		ok
81	phenyl-2,4-Cl_2	H	H	2-H	3-CH_3	6-H	5-CH_3	$(CH_2)_5$-COOH	4-O	-		ok

82	phenyl-2,4-Cl_2	H	H	2-H	3-CH_3	6-H	5-CH_3	$(CH_2)_6$-COOH	4-O	-		ok
83	phenyl-2,4-Cl_2	H	H	2-H	3-CH_3	6-H	5-CH_3	$(CH_2)_7$-COOH	4-O	-		ok
84	phenyl-2,4-Cl_2	H	H	H	H	H	H	$(CH_2)_3$-COOH	3-O	-		ok
85	phenyl-2,4-Cl_2	H	H	H	H	H	H	$(CH_2)_4$-COOH	3-O	-		ok
86	phenyl-2,4-Cl_2	H	H	H	H	H	H	$(CH_2)_5$-COOH	3-O	-		ok
87	phenyl-2,4-Cl_2	H	H	H	H	H	H	$(CH_2)_7$-COOH	3-O	-		ok
88	phenyl-2,4-Cl_2	H	H	H	H	H	H	$(CH_2)_3$-COOH	4-O	-		ok
89	phenyl-2,4-Cl_2	H	H	H	H	H	H	$(CH_2)_4$-COOH	4-O	-		ok
90	phenyl-2,4-Cl_2	H	H	H	H	H	H	$(CH_2)_5$-COOH	4-O	-		ok
91	phenyl-2,4-Cl_2	H	H	H	H	H	H	$(CH_2)_6$-COOH	4-O	-		ok
92	phenyl-2,4-Cl_2	H	H	H	H	H	H	$(CH_2)_7$-COOH	4-O	-		ok
93	phenyl-3,4-Cl_2	H	H	2-H	3-Cl	6-H	5-Cl	$(CH_2)_5$-COOH	4-O	-		ok
94	phenyl-2,4-Cl_2	H	H	2-H	3-Cl	6-H	5-Cl		4-O	HCl		ok
95	phenyl-3-F	H	H	2-H	3-Cl	6-H	5-Cl		4-O	HCl		ok
96	phenyl-2,3-Cl_2	H	H	2-H	3-Cl	6-H	5-Cl		4-O	HCl		ok
97	phenyl-3-OCH_3	H	H	2-H	3-Cl	6-H	5-Cl		4-O	HCl		ok
98	phenyl-2-F	H	H	2-H	3-Cl	6-H	5-Cl		4-O	HCl		ok
99	phenyl	H	H	2-H	3-Cl	6-H	5-Cl		4-O	HCl		ok

100	phenyl-3-SO_2CH_3	H	H	2-H	3-Cl	6-H	5-Cl	$(CH_2)_5$-COOH	4-O	-		ok
101	phenyl-2-SO_2CH_3	H	H	2-H	3-Cl	6-H	5-Cl	$(CH_2)_5$-COOH	4-O	-		ok
102	phenyl-2-Cl-4-SO_2CH_3	H	H	2-H	3-Cl	6-H	5-Cl	$(CH_2)_5$-COOH	4-O	-		ok
103	phenyl-2,4-$(CH_3)_2$	H	H	2-H	3-Cl	6-H	5-Cl	$(CH_2)_5$-COOH	4-O	-		ok
104	phenyl-4-Cl-2-F	H	H	2-H	3-Cl	6-H	5-Cl	$(CH_2)_5$-COOH	4-O	-		ok
105	phenyl-2-Cl-4-F	H	H	2-H	3-Cl	6-H	5-Cl	$(CH_2)_5$-COOH	4-O	-		ok
106	phenyl-4-$COOCH_3$	H	H	2-H	3-Cl	6-H	5-Cl	$(CH_2)_5$-COOH	4-O	-		ok
107	phenyl-4-SO_2CH_3	H	H	2-H	3-Cl	6-H	5-Cl	$(CH_2)_5$-COOH	4-O	-		ok
108	phenyl-2-Cl	H	H	2-H	3-Cl	6-H	5-Cl		4-O	-		ok
109	phenyl-4-Cl-2-CH_3	H	H	2-H	3-Cl	6-H	5-Cl	$(CH_2)_5$-COOH	4-O	-		ok
110	phenyl-3-F-4-NO_2	H	H	2-H	3-Cl	6-H	5-Cl	$(CH_2)_5$-COOH	4-O	-		ok
111	phenyl-2-$COOCH_3$	H	H	2-H	3-Cl	6-H	5-Cl	$(CH_2)_5$-COOH	4-O	-		ok
112	phenyl-3-$COOCH_3$-5-NO_2	H	H	2-H	3-Cl	6-H	5-Cl	$(CH_2)_5$-COOH	4-O	-		ok
113	phenyl-3-CF_3	H	H	2-H	3-Cl	6-H	5-Cl	$(CH_2)_5$-COOH	4-O	-		ok

114	phenyl-2,4-Cl_2	H	H	H	H	H	H	$(CH_2)_6$-COOH	3-O	-		ok
115	phenyl-2,4-Cl_2	H	H	2-H	3-Cl	6-H	5-H	$(CH_2)_4$-COOH	4-O	-		ok
116	phenyl-2,4-Cl_2	H	H	2-F	3-H	6-H	5-H	$(CH_2)_5$-COOH	4-O	-		ok
117	phenyl-4-CF_3	H	H	2-H	3-Cl	6-H	5-Cl	$(CH_2)_5$-COOH	4-O	-		ok
118	phenyl-2-Cl	H	H	2-H	3-Cl	6-H	5-Cl	$(CH_2)_5$-$CONH_2$	4-O	-		ok
119	phenyl-2,4-Cl_2	H	H	2-CH_3	3-H	6-CH_3	5-H	$(CH_2)_4$-COOH	4-O	-		ok
120	phenyl-2,4-Cl_2	H	H	2-H	4-CH_3	6-H	5-H	$(CH_2)_4$-COOH	3-O	-		ok
121	phenyl-2,4-Cl_2	H	H	2-H	4-OCH_3	6-H	5-H	$(CH_2)_4$-COOH	3-O	-		ok
122	phenyl-2,4-Cl_2	H	H	2-H	3-$COOCH_3$	6-H	5-H	$(CH_2)_4$-COOH	4-O	-		ok
123	phenyl-2,4-Cl_2	H	H	2-Cl	3-H	6-H	5-H	$(CH_2)_4$-COOH	4-O	-		ok
124	phenyl-2,4-Cl_2	H	H	2-H	3-cHexyl	6-H	5-H	$(CH_2)_4$-COOH	4-O	-		ok
125	phenyl-2,4-Cl_2	H	H	2-CH_3	3-CH_3	6-H	5-H	$(CH_2)_4$-COOH	4-O	-		ok
126	phenyl-2,4-Cl_2	H	H	2-CH_3	3-H	6-CH_3	5-H	$(CH_2)_5$-COOH	4-O	-		ok
127	phenyl-2,4-Cl_2	H	H	2-H	4-CH_3	6-H	5-H	$(CH_2)_5$-COOH	3-O	-		ok
128	phenyl-2,4-Cl_2	H	H	2-H	4-OCH_3	6-H	5-H	$(CH_2)_5$-COOH	3-O	-		ok
129	phenyl-2,4-Cl_2	H	H	2-H	3-$COOCH_3$	6-H	5-H	$(CH_2)_5$-COOH	4-O	-		ok
130	phenyl-2,4-Cl_2	H	H	2-Cl	3-H	6-H	5-H	$(CH_2)_5$-COOH	4-O	-		ok
131	phenyl-2,4-Cl_2	H	H	2-H	3-cHexyl	6-H	5-H	$(CH_2)_5$-COOH	4-O	-		ok

132	phenyl-2,4-Cl_2	H	H	2-CH_3	3-H	6-H	5-CH_3	$(CH_2)_5$-COOH	4-O	-		ok
133	phenyl-2,4-Cl_2	H	H	2-CH_3	3-CH_3	6-H	5-H	$(CH_2)_5$-COOH	4-O	-		ok
134	phenyl-2,4-Cl_2	H	H	2-CH_3	3-H	6-CH_3	5-H	$(CH_2)_7$-COOH	4-O	-		ok
135	phenyl-2,4-Cl_2	H	H	2-H	4-CH_3	6-H	5-H	$(CH_2)_7$-COOH	3-O	-		ok
136	phenyl-2,4-Cl_2	H	H	2-H	4-OCH_3	6-H	5-H	$(CH_2)_7$-COOH	3-O	-		ok
137	phenyl-2,4-Cl_2	H	H	2-H	3-$COOCH_3$	6-H	5-H	$(CH_2)_7$-COOH	4-O	-		ok
138	phenyl-2,4-Cl_2	H	H	2-Cl	3-H	6-H	5-H	$(CH_2)_7$-COOH	4-O	-		ok
139	phenyl-2,4-Cl_2	H	H	2-CH_3	3-H	6-H	5-CH_3	$(CH_2)_7$-COOH	4-O	-		ok
140	phenyl-2,4-Cl_2	H	H	2-CH_3	3-CH_3	6-H	5-H	$(CH_2)_7$-COOH	4-O	-		ok
141	phenyl-2,4-Cl_2	H	H	2-CH_3	3-H	6-CH_3	5-H	$(CH_2)_3$-COOH	4-O	-		ok
142	phenyl-2,4-Cl_2	H	H	2-H	4-CH_3	6-H	5-H	$(CH_2)_3$-COOH	3-O	-		ok
143	phenyl-2,4-Cl_2	H	H	2-H	4-OCH_3	6-H	5-H	$(CH_2)_3$-COOH	3-O	-		ok
144	phenyl-2,4-Cl_2	H	H	2-H	3-$COOCH_3$	6-H	5-H	$(CH_2)_3$-COOH	4-O	-		ok
145	phenyl-2,4-Cl_2	H	H	2-Cl	3-H	6-H	5-H	$(CH_2)_3$-COOH	4-O	-		ok
146	phenyl-2,4-Cl_2	H	H	2-H	3-cHexyl	6-H	5-H	$(CH_2)_3$-COOH	4-O	-		ok
147	phenyl-2,4-Cl_2	H	H	2-CH_3	3-H	6-H	5-CH_3	$(CH_2)_3$-COOH	4-O	-		ok

148	phenyl-2,4-Cl_2	H	H	2-CH_3	3-CH_3	6-H	5-H	$(CH_2)_3$-COOH	4-O	-		ok
149	phenyl-2,6-Cl_2	H	H	2-H	3-Cl	6-H	5-Cl	$(CH_2)_5$-COOH	4-O	-		ok
150	phenyl-6-Cl-3-COOH	H	H	2-H	3-Cl	6-H	5-Cl	$(CH_2)_3$-COOH	4-O	-		ok
151	phenyl-2,4-Cl_2	H	H	2-CH_3	4-H	6-H	5-H	$(CH_2)_4$-COOH	3-O	bis-2-hydroxyethylamine		ok
152	phenyl-2,4-Cl_2	H	H	2-Cl	3-H	6-H	5-H	$(CH_2)_3$-COOH	4-O	bis-2-hydroxyethylamine		ok
153	phenyl-2,4-Cl_2	H	H	2-CH_3	3-CH_3	6-H	5-H	$(CH_2)_3$-COOH	4-O	bis-2-hydroxyethylamine		ok
154	phenyl-2,4-Cl_2	H	H	2-H	4-OCH_3	6-H	5-H	$(CH_2)_2$-N-$(C_2H_5)_2$	3-O	-		ok
155	phenyl-2,4-Cl_2	H	H	H	H	H	H	$(CH_2)_2$-N-$(C_2H_5)_2$	4-O	-		ok

* The statement "MS is ok " means that a mass spectrum was recorded and the molecular peak (molecular mass + H^+) was detected therein.

The compounds of the formula I are distinguished by beneficial effects on glucose metabolism; in particular, they lower the blood glucose level and are suitable for treating type II diabetes. The compounds can be employed alone or in combination with other blood glucose-lowering active ingredients. Examples of such other blood glucose-lowering active ingredients are sulfonylureas (such as, for example, glimerpiride, glibenclamide), glitazones (such as, for example, troglitazone, rosiglitazone), alpha-glucosidase inhibitors (such as, for example, acarbose, miglitol) or insulins.

The activity of the compounds was assayed as follows:

Glycogen phophorylase a activity assay

The effect of compounds on the activity of the active form of glycogen phosphorylase (GPa) was measured in the reverse direction by following the synthesis of glycogen from glucose 1-phosphate by determining the liberation of inorganic phosphate. All the reactions were carried out as duplicate determinations in microtiter plates with 96 wells (Half Area Plates, Costar No 3696), measuring the change in absorption owing to the formation of the reaction product at the wavelength specified hereinafter in a Multiskan Ascent Elisa Reader (Lab Systems, Finland).

In order to measure the GPa enzymic activity in the reverse direction, the general method of Engers et al. (Engers HD, Shechosky S, Madsen NB, Can J Biochem 1970 Jul;48(7):746-754) was used to measure the conversion of glucose 1-phosphate into glycogen and inorganic phosphate, with the following modifications: human glycogen phosphorylase a (for example with 0.76 mg of protein/ml (Aventis Pharma Deutschland GmbH), dissolved in buffer solution E (25 mM β-glycerophosphate, pH 7.0, 1 mM EDTA and 1 mM dithiotreitol) was diluted with buffer T (50 mM Hepes, pH 7.0, 100 mM KCl, 2.5 mM EDTA, 2.5 mM $MgCl_2 \cdot 6H_2O$) and addition of 5 mg/ml glycogen to a concentration of 10 µg of protein/ml. Test substances were prepared as 10 mM solution in DMSO and diluted to 50 µM with buffer solution T. To 10 µl of this solution were added 10 µl of 37.5 mM glucose, dissolved in buffer solution T, and 5 mg/ml glycogen, plus 10 µl of a solution of human glycogen phosphorylase a (10 µg of protein /ml) and 20 µl of glucose 1-phosphate, 2,5 mM. The baseline glycogen phosphorylase a activity in the absence of test substance was determined by adding 10 µl of buffer solution T (0.1% DMSO). The mixture was incubated at room temperature for 40 minutes, and the liberated organic phosphate was measured by the

general method of Drueckes et al. (al (Drueckes P, Schinzel R, Palm D, *Anal Biochem* 1995 Sep 1;230(1):173-177) with the following modifications: 50 µl of a stop solution of 7.3 mM ammonium molybdate, 10.9 mM zinc acetate, 3.6% ascorbic acid, 0.9% SDS are added to 50 µl of the enzyme mixture. After incubation at 45°C for 60 minutes, the absorption at 820 nm was measured. To determine the background absorption, in a separate mixture the stop solution was added immediately after addition of the glucose 1-phosphate solution.

This test was carried out with a concentration of 10 µM of the test substance in order to determine the particular inhibition of glycogen phosphorylase a in vitro by the test substance.

Table 2: Biological activity:

Ex.	**% inhibition at 10 µM**
1	87
2	73
3	75
4	79
5	77
12	92
20	35
29	78
30	76
31	86
41	50
44	11
46	36
47	46
49	13
51	36
53	22
60	36
70	86
75	41

80	50
84	44
89	90
90	34
100	78
101	93
102	14
106	35
111	88
112	100
116	100
117	99
118	70
119	97
120	40
122	12
128	95
147	88
149	76

It is evident from the table that the compounds of the formula I inhibit the activity of glycogen phosphorylase a and thus are very suitable for lowering the blood glucose level.

The preparation of some examples is described in detail below, and the other compounds of the formula I were obtained analogously:
Experimental part:

Example 1:

6-{2,6-Dichloro-4-[(2-chlorobenzoyl)aminocarbamoyl]phenoxy}hexanoic acid

a) Ethyl 6-(4-acetylamino-2,6-dichlorophenoxy)hexanoate
13.3 ml (74.9mmol) of ethyl 6-bromohexanoate and 52.1 g (160 mmol) of cesium carbonate are added to a solution of 15.0 g (68.1 mmol) of N-(3,5-dichloro-4-hydroxyphenyl)acetamide in 300 ml of acetone. The suspension is boiled under reflux for 8 hours. Then 600 ml of water are added, and the mixture is extracted twice with 400 ml of dichloromethane and with 400 ml of MTB ether each time. The combined organic phases are washed with water and concentrated in a rotary evaporator. The product is employed in the next step without purification. Crude yield: 30 g

b) 6-(4-Acetylamino-2,6-dichlorophenoxy)hexanoic acid

30 g of crude material from step a) are mixed with 800 ml of 1 M potassium hydroxide solution and stirred at room temperature for 3 days. Then 600 ml of water are added and the pH is adjusted to 5.5 with about 80 ml of glacial acetic acid. The precipitated product is filtered off with suction and washed twice with 40 ml of water each time. The precipitate is dried under high vacuum and affords 14.6 g of the required compound.

c) 6-(4-Amino-2,6-dichlorophenoxy)hexanoic acid

7.5 g (22.4 mmol) of 6-(4-acetylamino-2,6-dichlorophenoxy)hexanoic acid in 140 ml of 1 m potassium hydroxide solution in methanol/water (3:1) [lacuna] boiled under reflux overnight. The methanol is removed in a rotary evaporator, and the residue is diluted with about 30 ml of water and acidified to pH 5 with glacial acetic acid. The mixture is stirred in an ice bath for 30 minutes and then filtered with suction. The crude product is subjected to column chromatography using

n-heptane/ethyl acetate = 1/1 and affords 4.3 g (14.7 mmol, 66%) of the required product.

d) 6-{2,6-Dichloro-4-[(2-chlorobenzoyl)ureido]phenoxy}hexanoic acid

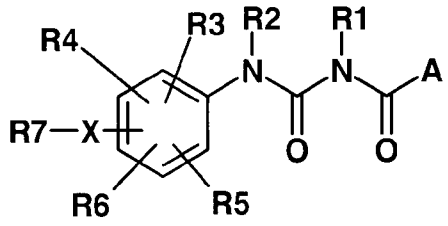
A solution of 7.5 g (41.1 mmol) of 2-chlorobenzoyl isocyanate in 300 ml of acetonitrile is added to a suspension of 10.0 g (34.2 mmol) of 6-(4-amino-2,6-dichlorophenoxy)hexanoic acid in 700 ml of dry acetonitrile under a protective gas atmosphere at room temperature. The mixture is boiled under reflux for 2 hours and cooled to room temperature. The resulting precipitate is filtered off with suction and washed with 50 ml of acetonitrile. The residue is stirred with 100 ml of methanol, filtered off with suction, washed with a little methanol and dried at 40°C under vacuum overnight. 13.7 g (28.9 mmol, 85%) of the required product are obtained.

Melting point: 171-173°C

Comprises/comprising and grammatical variations thereof when used in this specification are to be taken to specify the presence of stated features, integers, steps or components or groups thereof, but do not preclude the presence or addition of one or more other features, integers, steps, components or groups thereof.

THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:

1. A compound of the formula I



I

in which

A is phenyl, naphthyl, it being possible for the phenyl or naphthyl radical to be substituted up to three times by F, Cl, Br, OH, CF_3, NO_2, CN, OCF_3, O-(C_1-C_6)-alkyl, O-(C_2-C_6)-alkenyl, O-(C_2-C_6)-alkynyl, S-(C_1-C_6)-alkyl, S-(C_2-C_6)-alkenyl, S-(C_2-C_6)-alkynyl, SO-(C_1-C_6)-alkyl, SO_2-(C_1-C_6)-alkyl, SO_2-NH_2, (C_1-C_6)-alkyl, (C_2-C_6)-alkenyl, (C_2-C_6)-alkynyl, (C_3-C_7)-cycloalkyl, (C_3-C_7)-cycloalkyl-(C_2-C_4)-alkylene, (C_0-C_6)-alkylene-COOH, (C_0-C_6)-alkylene-COO(C_1-C_7)-alkyl, $CONH_2$, CONH(C_1-C_6)-alkyl, CON[(C_1-C_6)-alkyl]$_2$, CONH(C_3-C_6)-cycloalkyl, (C_0-C_6)-alkylene-NH_2, (C_0-C_6)-alkylene-NH(C_2-C_6)-alkyl, (C_0-C_6)-alkylene-N[(C_1-C_6)-alkyl]$_2$, NH-CO-(C_1-C_6)-alkyl, NH-CO-phenyl, NH-SO_2-phenyl, it being possible for the phenyl ring to be substituted up to twice by F, Cl, CN, OH, (C_1-C_6)-alkyl, O-(C_1-C_6)-alkyl, CF_3, OCF_3, COOH, COO(C_1-C_6)-alkyl or $CONH_2$;

R1, R2 are, independently of one another, H, (C_1-C_6)-alkyl, O-(C_1-C_6)-alkyl, CO-(C_1-C_6)-alkyl, COO-(C_1-C_6)-alkyl, (C_1-C_6)-alkylene-COOH, (C_1-C_6)-alkylene-COO-(C_1-C_6)-alkyl;

R3, R4, R5, R6 are, independently of one another, H, F, Cl, Br, OH, CF_3, NO_2, CN, OCF_3, O-(C_2-C_6)-alkyl, O-(C_2-C_6)-alkenyl, O-(C_2-C_6)-alkynyl, S-(C_1-C_6)-alkyl, S-(C_2-C_6)-alkenyl, S-(C_2-C_6)-alkynyl, SO-(C_1-C_6)-alkyl, SO_2-(C_1-C_6)-alkyl, SO_2-NH_2, (C_1-C_6)-alkyl, (C_2-C_6)-alkenyl, (C_2-C_6)-alkynyl, (C_3-C_7)-cycloalkyl, (C_3-C_7)-cycloalkyl-(C_2-C_4)-alkylene, COOH, $COO(C_1$-$C_6)$-alkyl, $CONH_2$, $CONH(C_1$-$C_6)$-alkyl, $CON[(C_1$-$C_6)$-alkyl$]_2$, $CONH(C_3$-$C_7)$-cycloalkyl, NH_2, $NH(C_1$-$C_6)$-alkyl, $N[(C_1$-$C_6)$-alkyl$]_2$, NH-CO-(C_1-C_6)-alkyl, NH-CO-phenyl, NH-SO_2-phenyl, it being possible for the phenyl ring to be substituted up to twice by F, Cl, CN, OH, (C_1-C_6)-Alkyl, O-(C_1-C_6)-alkyl, CF_3, OCF_3, COOH, $COO(C_1$-$C_6)$-alkyl or $CONH_2$;

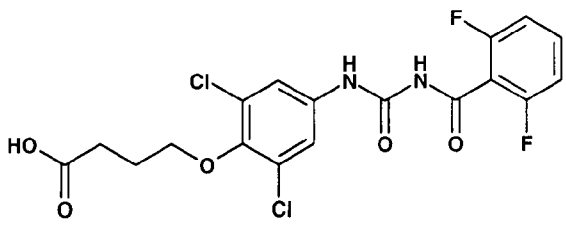
X is O, S;

R7 is (C_1-C_{10})-alkylene-COOH, (C_6-C_{10})-alkylene-COO-(C_1-C_6)-alkyl, (C_1-C_{10})-alkylene-$CONH_2$, (C_1-C_{10})-alkylene-CONH-(C_1-C_6)-alkyl, (C_1-C_{10})-alkylene-CON-$[(C_1$-$C_6)$-alkyl$]_2$, (C_1-C_{10})-alkylene-NH_2, (C_1-C_{10})-alkylene-$NH(C_1$-$C_6)$-alkyl, (C_1-C_{10})-alkylene-$N[(C_1$-$C_6)$-alkyl$]_2$, (C_1-C_{10})-alkylene-B;

B is (C_3-C_7)-cycloalkyl, pyrrolyl, Imidazolyl, thiazolyl, azetidinyl, thienyl, piperidinyl, pyrrolidinyl, morpholinyl, pyridyl-methyl or furyl, in which cycloalkyl, pyrrolyl, imidazolyl, thiazolyl, azetidinyl, thienyl, piperidinyl, pyrrolidinyl, morpholinyl, pyridyl-methyl or furyl may in each case be substituted up to twice by Cl, F, CN, CF_3, OCF_3, COOH, COO-(C_1-C_6)-alkyl, $CONH_2$, CONH-(C_1-C_6)-alkyl, CON-$[(C_1$-$C_6)$-alkyl$]_2$, (C_1-C_6)-alkyl, OH, O-(C_1-C_6)-alkyl;

and physiologically tolerated salts thereof,

excepting the compounds of the formula



and compounds of the formula I in which the radicals mean at the same time

A phenyl;

X O;

R1 H;

R7 -(C_1-C_4)-alkyl-B;

B (C_3-C_7)-cycloalkyl, heteroaryl.

2. A compound of the formula I as claimed in claim 1, wherein

A is phenyl, naphthyl, it being possible for the phenyl or naphthyl radical to be substituted up to three times by F, Cl, Br, OH, CF_3, NO_2, CN, OCF_3, O-(C_1-C_6)-alkyl, O-(C_2-C_6)-alkenyl, O-(C_2-C_6)-alkynyl, S-(C_1-C_6)-alkyl, S-(C_2-C_6)-alkenyl, S-(C_2-C_6)-alkynyl, SO-(C_1-C_6)-alkyl, SO_2-(C_1-C_6)-alkyl, SO_2-NH_2, (C_1-C_6)-alkyl, (C_2-C_6)-alkenyl, (C_2-C_6)-alkynyl, (C_3-C_7)-cycloalkyl, (C_3-C_7)-cycloalkyl-(C_2-C_4)-alkylene, (C_0-C_6)-alkylene-COOH, (C_0-C_6)-alkylene-COO(C_1-C_6)-alkyl, $CONH_2$, CONH(C_1-C_6)-alkyl, CON[(C_1-C_6)-alkyl]$_2$, CONH(C_3-C_7)-cycloalkyl, (C_0-C_6)-alkylene-NH_2, (C_0-C_6)-alkylene-NH(C_2-C_6)-alkyl, (C_0-C_6)-alkylene-N[(C_1-C_6)-alkyl]$_2$, NH-CO-(C_1-C_6)-alkyl, NH-CO-phenyl, NH-SO_2-phenyl, it being possible for the phenyl ring to be substituted up to twice by F, Cl, CN, OH, (C_1-C_6)-alkyl, O-(C_1-C_6)-alkyl, CF_3, OCF_3, COOH, COO (C_1-C_6)-alkyl or $CONH_2$;

R1, R2 are, independently of one another, H, (C_1-C_6)-alkyl, O-(C_1-C_6)-alkyl, CO-(C_1-C_6)-alkyl, COO-(C_1-C_6)-alkyl, (C_1-C_6)-alkylene-COOH, (C_1-C_6)-alkylene-COO-(C_1-C_6)-alkyl;

R3, R4, R5, R6 are, independently of one another, H, F, Cl, Br, OH, CF_3, NO_2, CN, OCF_3, O-(C_1-C_6)-alkyl, O-(C_2-C_6)-alkenyl, O-(C_2-C_6)-alkynyl, S-(C_1-C_6)-alkyl, S-(C_2-C_6)-alkenyl, S-(C_2-C_6)-alkynyl, SO-(C_1-C_6)-alkyl, SO_2-(C_1-C_6)-alkyl, SO_2-NH_2, (C_1-C_6)-alkyl, (C_2-C_6)-alkenyl, (C_2-C_6)-alkynyl, (C_3-C_7)-cycloalkyl, (C_3-C_7)-cycloalkyl-(C_2-C_4)-alkylene, COOH, COO(C_1-C_6)-alkyl, $CONH_2$, CONH(C_1-C_6)-alkyl, CON$[(C_1-C_6)$-alkyl$]_2$, CONH(C_3-C_7)-cycloalkyl, NH_2, NH(C_1-C_6)-alkyl, N$[(C_1-C_6)$-alkyl$]_2$, NH-CO-(C_1-C_6)-alkyl, NH-CO-phenyl, NH-SO_2-phenyl, it being possible for the phenyl ring to be substituted up to twice by F, Cl, CN, OH, (C_1-C_6)-alkyl, O-(C_1-C_6)-alkyl, CF_3, OCF_3, COOH, COO(C_1-C_6)-alkyl or $CONH_2$;

X is O, S;

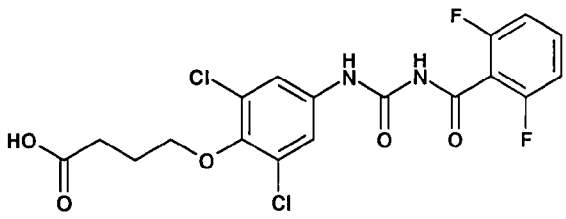
R7 is (C_1-C_{10})-alkylene-COOH, (C_6-C_{10})-alkylene-COO-(C_1-C_6)-alkyl, (C_1-C_{10})-alkylene-$CONH_2$, (C_1-C_{10})-alkylene-CONH-(C_1-C_6)-alkyl, (C_1-C_{10})-alkylene-CON-$[(C_1-C_6)$-alkyl$]_2$, (C_1-C_{10})-alkylene-NH_2, (C_1-C_{10})-alkylene-NH(C_1-C_6)-alkyl, (C_1-C_{10})-alkylene-N$[(C_1-C_6)$-alkyl$]_2$, (C_1-C_{10})-alkylene-B;

B is (C_3-C_7)-cycloalkyl, pyrrolyl, imidazolyl, thiazolyl, azetidinyl, thienyl-methyl, piperidinyl, pyrrolidinyl, morpholinyl, pyridyl-methyl or furyl, in which cycloalkyl, pyrrolyl, imidazolyl, thiazolyl, azetidinyl, thienyl-methyl, piperidinyl, pyrrolidinyl, morpholinyl, pyridyl-methyl or furyl may in each case be substituted up to twice by Cl, F, CN, CF_3, OCF_3, COOH,

$COO-(C_1-C_6)$-alkyl, $CONH_2$, $CONH-(C_1-C_6)$-alkyl, $CON-[(C_1-C_6)\text{-alkyl}]_2$, (C_1-C_6)-alkyl, OH, $O-(C_1-C_6)$-alkyl

and the physiologically tolerated salts thereof,

excepting the compounds of the formula



and compounds of the formula I in which the radicals are at the same time

A phenyl;

X O;

R1 H;

R7 $-(C_1-C_4)$-alkyl-B;

B (C_3-C_7)-cycloalkyl, heteroaryl.

3. A compound of the formula I as claimed in claim 1 or 2, wherein

A is phenyl, it being possible for the phenyl radical to be substituted up to twice by F, Cl, Br, $O-(C_1-C_6)$-alkyl;

R1, R2 are, independently of one another, H, (C_1-C_6)-alkyl, $CO-(C_1-C_6)$-alkyl;

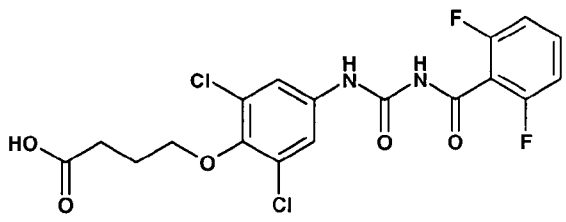
R3, R4, R5, R6 are, independently of one another, H, Cl, F, (C_1-C_6)-alkyl, $O-(C_1-C_6)$-alkyl, $-COO-(C_1-C_6)$-alkyl;

X is O;

R7 is $(C_1\text{-}C_{10})$-alkylene-COOH, $(C_6\text{-}C_{10})$-alkylene-COO-$(C_1\text{-}C_6)$-alkyl, $(C_1\text{-}C_{10})$-alkylene-$CONH_2$;

and the physiologically tolerated salts thereof,

excepting the compounds of the formula



4. A compound of the formula I according to claim 1 and substantially as hereinbefore described with reference to any one of the Examples.

5. A pharmaceutical comprising one or more of the compounds as claimed in any one or more of claims 1 to 4.

6. A pharmaceutical comprising one or more of the compounds as claimed in any one or more of claims 1 to 4 and one or more blood glucose-lowering active ingredients.

7. The use of the compounds as claimed in any one or more of claims 1 to 4 for producing a medicine for lowering blood glucose.

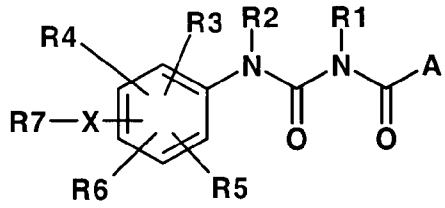
8. The use of the compounds as claimed in any one or more of claims 1 to 4 for producing a medicine for treating type II diabetes.

9. The use of the compounds as claimed in any one or more of claims 1 to 4 in combination with at least one other blood glucose-lowering active ingredient for producing a medicine.

10. A process for producing a pharmaceutical comprising one or more of the compounds as claimed in one or more of claims 1 to 4, which process comprises

mixing the active ingredient with a pharmaceutically acceptable carrier, and converting this mixture into a form suitable for administration.

11. The use of the compound of the formula I



I

in which

A is phenyl, naphthyl, it being possible for the phenyl or naphthyl radical to be substituted up to three times by F, Cl, Br, OH, CF_3, NO_2, CN, OCF_3, O-(C_2-C_6)-alkyl, O-(C_2-C_6)-alkenyl, O-(C_2-C_6)-alkynyl, S-(C_1-C_6)-alkyl, S-(C_2-C_6)-alkenyl, S-(C_2-C_6)-alkynyl, SO-(C_1-C_6)-alkyl, SO_2-(C_1-C_6)-alkyl, SO_2-NH_2, (C_1-C_6)-alkyl, (C_2-C_6)-alkenyl, (C_2-C_6)-alkynyl, (C_3-C_7)-cycloalkyl, (C_3-C_7)-cycloalkyl-(C_2-C_4)-alkylene, (C_0-C_6)-alkylene-COOH, (C_0-C_6)-alkylene-COO(C_1-C_6)-alkyl, $CONH_2$, CONH(C_1-C_6)-alkyl, CON[(C_1-C_6)-alkyl]$_2$, CONH(C_3-C_7)-cycloalkyl, (C_0-C_6)-alkylene-NH_2, (C_0-C_6)-alkylene-NH(C_1-C_6)-alkyl, (C_0-C_6)-alkylene-N[(C_1-C_6)-alkyl]$_2$, NH-CO-(C_1-C_6)-Alkyl, NH-CO-phenyl, NH-SO_2-phenyl, it being possible for the phenyl ring to be substituted up to twice by F, Cl, CN, OH, (C_1-C_6)-alkyl, O-(C_1-C_6)-alkyl, CF_3, OCF_3, COOH, COO(C_1-C_6)-alkyl or $CONH_2$;

R1, R2 are, independently of one another, H, (C_1-C_6)-alkyl, O-(C_1-C_6)-alkyl, CO-(C_1-C_6)-alkyl, COO-(C_1-C_6)-alkyl, (C_1-C_6)-alkylene-COOH, (C_1-C_6)-alkylene-COO-(C_1-C_6)-alkyl;

R3, R4, R5, R6 are, independently of one another, H, F, Cl, Br, OH, CF_3, NO_2, CN, OCF_3, O-(C_1-C_6)-alkyl, O-(C_2-C_6)-alkenyl, O-(C_2-C_6)-alkynyl, S-(C_1-C_6)-alkyl, S-(C_2-C_6)-alkenyl, S-(C_2-C_6)-alkynyl,

SO-(C_1-C_6)-alkyl, SO_2-(C_1-C_6)-alkyl, SO_2-NH_2, (C_1-C_6)-alkyl, (C_2-C_6)-alkenyl, (C_2-C_6)-alkynyl, (C_3-C_7)-cycloalkyl, (C_3-C_7)-cycloalkyl-(C_2-C_4)-alkylene, COOH, COO(C_1-C_6)-alkyl, $CONH_2$, CONH(C_1-C_6)-alkyl, CON[(C_1-C_6)-alkyl]$_2$, CONH(C_3-C_7)-cycloalkyl, NH_2, NH(C_1-C_6)-alkyl, N[(C_1-C_6)-alkyl]$_2$, NH-CO-(C_1-C_6)-alkyl, NH-CO-phenyl, NH-SO_2-phenyl, it being possible for the phenyl ring to be substituted up to twice by F, Cl, CN, OH, (C_1-C_6)-Alkyl, O-(C_1-C_6)-alkyl, CF_3, OCF_3, COOH, COO(C_1-C_6)-alkyl or $CONH_2$;

X is O, S;

R7 is (C_1-C_{10})-alkylene-COOH, (C_1-C_{10})-alkylene-COO-(C_1-C_6)-alkyl, (C_1-C_{10})-alkylene-$CONH_2$, (C_1-C_{10})-alkylene-CONH-(C_1-C_6)-alkyl, (C_1-C_{10})-alkylene-CON-[(C_1-C_6)-alkyl]$_2$, (C_1-C_{10})-alkylene-NH_2, (C_1-C_{10})-alkylene-NH(C_1-C_6)-alkyl, (C_1-C_{10})-alkylene-N[(C_1-C_6)-alkyl]$_2$, (C_1-C_{10})-alkylene-B;

B is (C_3-C_7)-cycloalkyl, phenyl, pyrrolyl, Imidazolyl, thiazolyl, azetidinyl, thienyl, piperidinyl, pyrrolidinyl, morpholinyl, pyridyl or furyl, in which cycloalkyl, phenyl, pyrrolyl, imidazolyl, thiazolyl, azetidinyl, thienyl, piperidinyl, pyrrolidinyl, morpholinyl, pyridyl or furyl may in each case be substituted up to twice by Cl, F, CN, CF_3, OCF_3, COOH, COO-(C_1-C_6)-alkyl, $CONH_2$, CONH-(C_1-C_6)-alkyl, CON-[(C_1-C_6)-alkyl]$_2$, (C_1-C_6)-alkyl, OH, O-(C_1-C_6)-alkyl;

and physiologically tolerated salts thereof,

for producing a medicine for lowering the blood glucose level.

12. A process for preparing the compounds as claimed in any one or more of claims 1 to 4, wherein, in accordance with the following formula diagram.

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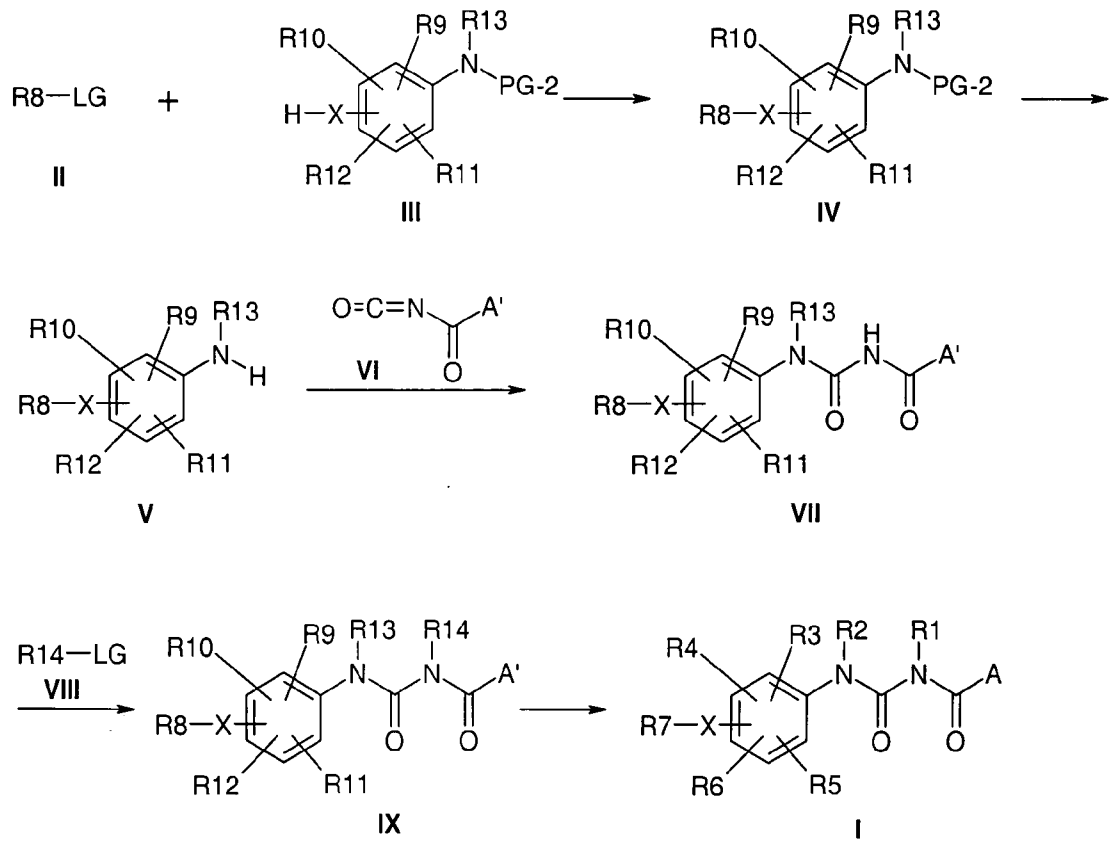


the compound of the formula II

R8-LG (II)

in which

R8 is (C_1-C_{10})-alkylene-COO-(PG-1), (C_6-C_{10})-alkylene-COO-(C_1-C_6)-alkyl, (C_1-C_{10})-alkylene-CON-(PG-2)$_2$, (C_1-C_{10})-alkylene-CONH-(C_1-C_6)-alkyl, (C_1-C_{10})-alkylene-CON-[(C_1-C_6)-alkyl]$_2$, (C_1-C_{10})-alkylene-N-(PG-2)$_2$, (C_1-C_{10})-alkylene-NH(C_1-C_6)-alkyl, (C_1-C_{10})-alkylene-N[(C_1-C_6)-alkyl]$_2$, (C_1-C_{10})-alkylene-B'

PG-1 is a generally known protective group for esters, such as, for example, (C_1-C_6)-alkyl, benzyl or p-methoxybenzyl, and

PG-2 is a generally known protective group for amino groups, such as, for example, $(C_1$-$C_6)$-alkylcarbonyl, $(C_1$-$C_6)$-alkyloxycarbonyl or $(C_6$-$C_{12})$-aryl-$(C_1$-$C_4)$-alkyloxycarbonyl, which replaces either both hydrogens or only one hydrogen atom in the amino group,

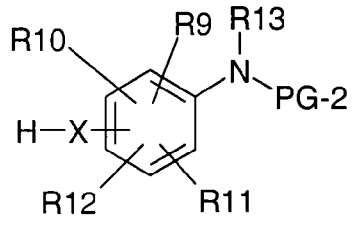
B' is $(C_3$-$C_7)$-cycloalkyl, $(C_3$-$C_7)$-cycloalkyl-$(C_2$-$C_4)$-alkylene, phenyl, pyrrolyl, imidazolyl, thiazolyl, azetidinyl, thienyl, piperidinyl, pyrrolidinyl, morpholinyl, pyridyl and furyl in which cycloalkyl, phenyl, pyrrolyl, imidazolyl, thiazolyl, azetidinyl, thienyl, piperidinyl, pyrrolidinyl, morpholinyl, pyridyl and furyl may in each case be substituted up to twice by Cl, F, CN, CF_3, OCF_3, COO-(PG-1), COO-$(C_1$-$C_6)$-alkyl, CON-$(PG\text{-}2)_2$, CONH-$(C_1$-$C_6)$-alkyl, CON-$[(C_1$-$C_6)$-alkyl$]_2$, $(C_1$-$C_6)$-alkyl, O-(PG-3), O-$(C_1$-$C_6)$-alkyl,

PG-3 is a generally known protective group for alcohols, such as, for example, benzyl, allyl, tetrahydropyranyl or tetrahydrofuranyl,

and

LG is a generally known leaving group such as, for example, halogen, arylsulfonyloxy or alkylsulfonyloxy,

is reacted with anilines of the formula III



(III)

in which X and PG-2 have the meaning described above, and in which

R9, R10, R11, R12 are, independently of one another H, F, Cl, Br, O-(PG-3), CF_3, NO_2, CN, OCF_3, O-$(C_1$-$C_6)$-alkyl, O-$(C_2$-$C_6)$-alkenyl, O-$(C_2$-$C_6)$-alkynyl, S-$(C_1$-$C_6)$-alkyl, S-

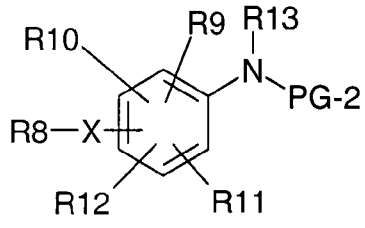
$(C_2$-$C_6)$-alkenyl, S-$(C_2$-$C_6)$-alkynyl, SO-$(C_1$-$C_6)$-alkyl, SO_2-$(C_1$-$C_6)$-alkyl, SO_2- N-$(PG\text{-}2)_2$, $(C_1$-$C_6)$-alkyl, $(C_2$-$C_6)$-alkenyl, $(C_2$-$C_6)$-alkynyl, $(C_3$-$C_7)$-cycloalkyl, $(C_3$-$C_7)$-cycloalkyl-$(C_2$-$C_4)$-alkylene, COO-(PG-1), $COO(C_1$-$C_6)$-alkyl, CON-$(PG\text{-}2)_2$, $CONH(C_1$-$C_6)$-alkyl, $CON[(C_1$-$C_6)$-alkyl$]_2$, $CONH(C_3$-$C_7)$-cycloalkyl, N-$(PG\text{-}2)_2$, $NH(C_1$-$C_6)$-alkyl, $N[(C_1$-$C_6)$-alkyl$]_2$, NH-CO-$(C_1$-$C_6)$-alkyl, NH-CO-phenyl, NH-SO_2-phenyl, it being possible for the phenyl ring to be substituted up to twice by F, Cl, CN, O-(PG-3), $(C_1$-$C_6)$-alkyl, O-$(C_1$-$C_6)$-alkyl, CF_3, OCF_3, COO-(PG-1), $COO(C_1$-$C_6)$-alkyl or CON-$(PG\text{-}2)_2$;

R13 is H, $(C_1$-$C_6)$-alkyl, O-$(C_1$-$C_6)$-alkyl, CO-$(C_1$-$C_6)$-alkyl, COO-$(C_1$-$C_6)$-alkyl, $(C_1$-$C_6)$-alkylene-COO-(PG-1), $(C_1$-$C_6)$-alkylene-COO-$(C_1$-$C_6)$-alkyl,

where PG-1, PG-2 and PG-3 have the meaning described above

using a base such as, for example, potassium or cesium carbonate, in an organic solvent such as, for example, acetone or dimethylformamide,

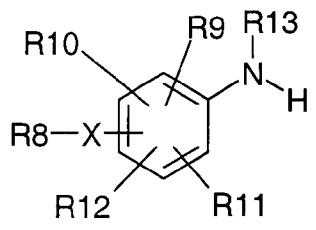
to give compounds of the formula IV



(IV)

in which X, R8, R9, R10, R11, R12, R13 and PG-2 have the meaning described above,

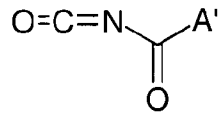
and then, by selective elimination of the protective group PG-2, compounds of the formula V



(V)

in which X, R8, R9, R10, R11, R12, and R13 have the meanings stated above, are obtained,

compounds of the formula V are reacted with isocyanates of the formula VI

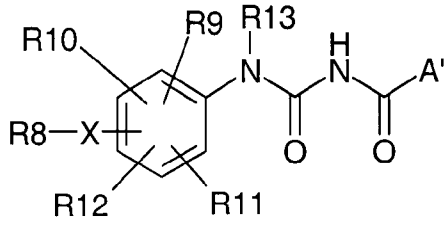


(VI)

in which

A' is phenyl, naphthyl, it being possible for the phenyl or naphthyl radical to be substituted up to three times by F, Cl, Br, O-(PG-3), CF_3, NO_2, CN, OCF_3, O-(C_1-C_6)-alkyl, O-(C_2-C_6)-alkenyl, O-(C_2-C_6)-alkynyl, S-(C_1-C_6)-alkyl, S-(C_2-C_6)-alkenyl, S-(C_2-C_6)-alkynyl, SO-(C_1-C_6)-alkyl, SO_2-(C_1-C_6)-alkyl, SO_2-N-(PG-2)$_2$, (C_1-C_6)-alkyl, (C_2-C_6)-alkenyl, (C_2-C_6)-alkynyl, (C_3-C_7)-cycloalkyl, (C_3-C_7)-cycloalkyl-(C_2-C_4)-alkylene, (C_0-C_6)-alkylene-COO-(PG-1), (C_0-C_6)-alkylene-COO(C_1-C_6)-alkyl, CON-(PG-2)$_2$, CONH(C_1-C_6)-alkyl, CON[(C_1-C_6)-alkyl]$_2$, CONH(C_3-C_7)-cycloalkyl, (C_0-C_6)-alkylene-N-(PG-2)$_2$, (C_0-C_6)-alkylene-NH(C_1-C_6)-alkyl, (C_0-C_6)-alkylene-N[(C_1-C_6)-alkyl]$_2$, NH-CO-(C_1-C_6)-alkyl, NH-CO-phenyl, NH-SO_2-phenyl, it being possible for the phenyl ring to be substituted up to twice by F, Cl, CN, O-(PG-3), (C_1-C_6)-alkyl, O-(C_1-C_6)-alkyl, CF_3, OCF_3, COO-(PG-1), COO(C_1-C_6)-alkyl or CON-(PG-2)$_2$,

and PG-1, PG-2 and PG-3 have the meaning described above,
to give compounds of the formula VII



(VII)

in which X, R8, R9, R10, R11, R12, R13 and A' have the meaning described above,

the compounds of the formula VII can, if R1 in compounds of the formula I is not a hydrogen atom, be alkylated by reaction with compounds of the formula VIII

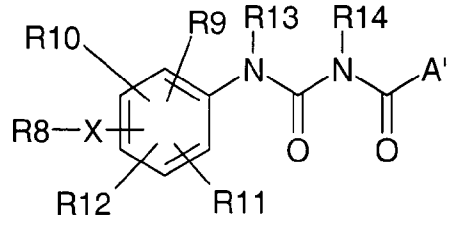
R14-LG (VIII)

in which LG has the meaning described above, and in which

R14 is H, (C_1-C_6)-alkyl, O-(C_1-C_6)-alkyl, CO-(C_1-C_6)-alkyl, COO-(C_1-C_6)-alkyl, (C_1-C_6)-alkylene-COO-(PG-1), (C_1-C_6)-alkylene-COO-(C_1-C_6)-alkyl

where PG-1 has the meaning described above,

using a base such as, for example, 1,8-diazabicyclo[5.4.0]undec-7-ene to give compounds of the formula IX



(IX)

in which X, R8, R9, R10, R11, R12, R13, R14 and A' have the meaning described above,

and, where appropriate, the protective groups which are present in the radicals R8, R9, R10, R11, R12, R13, R14, A' and B' are eliminated and, where appropriate, the compounds of the formula I obtained in this way are converted into the salts thereof by adding one equivalent of the appropriate acid or base.

13. A method for lowering blood glucose, which method comprises administering to a patient a therapeutically effective amount of the compounds as claimed in any one or more of claims 1 to 4 or of a pharmaceutical as claimed in claim 5.

14. A method as claimed in claim 13 for treating type II diabetes.

DATED this 22nd day of August 2005

WATERMARK PATENT & TRADE MARK ATTORNEYS