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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
10 August 2006 (10.08.2006)

PCT

(10) International Publication Number
WO 2006/082452 A1

(51) International Patent Classification:
C07C 205/58 (2006.01)

(21) International Application Number:
PCT/HU2006/000003

(22) International Filing Date: 17 January 2006 (17.01.2006)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
P0500157 1 February 2005 (01.02.2005) HU

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

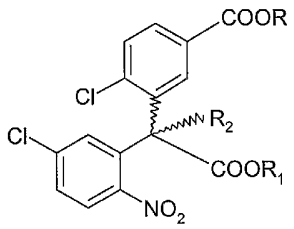
(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT,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

Declaration under Rule 4.17:
— *of inventorship (Rule 4.17(iv))*

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

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

(54) **Title:** OPTICALLY ACTIVE DIARYL ACETIC ACID DERIVATIVES AND PROCESS FOR THEIR PREPARATION



(I)

(57) **Abstract:** The application relates to optically active compounds of the general formula (I): Formula (I) wherein R means a hydrogen atom or a straight or branched alkyl group containing 1-4 carbon atoms, R_1 means a hydrogen atom or a straight or branched alkyi group containing 1-4 carbon atoms, R_2 means a hydrogen atom or a straight or branched alkyl group containing 1-4 carbon atoms- and their salts. Compounds of the general formula (I) are useful intermediates of the therapeutically active compounds described in US-6673790 and in J. Pharmacol. Exp. Ther. 309 p 414 (2004).

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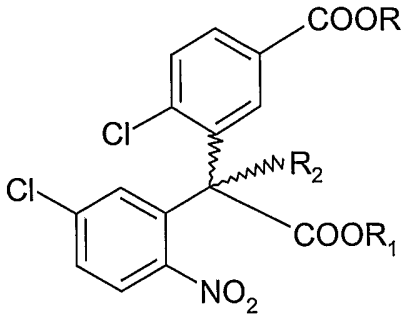
New compounds

This invention relates to the optically active compounds of the general formula (I)

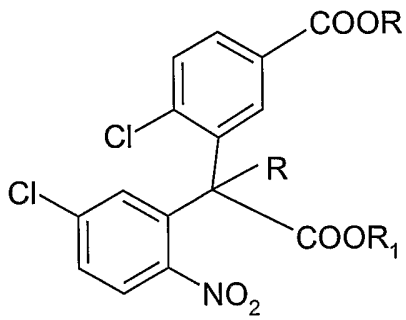


(I)

- wherein R means a hydrogen atom or a straight or branched alkyl group containing 1-4 carbon atoms, R_1 means a hydrogen atom or a straight or branched alkyl group containing 1-4 carbon atoms, R_2 means a hydrogen atom or a straight or branched alkyl group containing 1-4 carbon atoms – and their salts. Furthermore this invention relates to a process for the production of above compounds.

These optically active compounds of the general formula/I/ are useful intermediates during the synthesis of the compounds, which are described in the US-6 673790 and in J. Pharmacol. Exp. Ther. , 309, p 414 /2004/. Content of these citations is hereby incorporated by reference.

It has been found that the optically active compounds of the general formula (I) and their salts may be produced by the resolution of the racemic compounds of the general formula



(Ia)

wherein R means a hydrogen atom or a straight or branched alkyl group containing 1-4 carbon atoms, R_1 means a hydrogen atom or a straight or branched alkyl group containing 1-4 carbon atoms, R_2 means a hydrogen atom or a straight or branched alkyl group containing 1-4 carbon atoms – carried out by using one of the following procedures

a) the racemic compound of the general formula (Ia) –

wherein R means a hydrogen atom or a straight or branched alkyl group containing 1-4 carbon atoms, R_1 means a hydrogen atom or a straight or branched alkyl group containing 1-4 carbon atoms, R_2 means a hydrogen atom or a straight or branched alkyl group containing 1-4 carbon atoms – is separated by chromatography using chiral stationary phase and optically active product thus obtained if desired is partially or totally hydrolized to optically active compounds of the general formula (I) – wherein the meaning of R and/or R_1 is hydrogen, R_2 is as defined above – and optionally their salts are formed or

b) to the racemic compound of the general formula (Ia) - wherein R and R_1 mean hydrogen atoms, R_2 has the meaning as defined above - D-Proline is added and the received D-Proline salt of the (*R*)-enantiomer of compound of the general formula (I) is separated and the (*R*) –enantiomer is optionally deliberated or
L-Proline is added and the received L-Proline salt of the (*S*)-enantiomer of compound of the general formula (I) separated and the (*S*)-enantiomer is optionally deliberated or

c) to the racemic compound of the general formula (Ia) - wherein R and R_1 mean hydrogen atoms, R_2 has the meaning as defined above – (1*S*, 2*R*)-(+)ephedrine is added and the received (1*S*, 2*R*)-(+)-ephedrine salt of the (*R*)-enantiomer of compound of the general formula (I) is separated and optionally the (*R*)-enantiomer is deliberated or
- (1*R*, 2*S*)-(-)-ephedrine is added and the received (1*R*, 2*S*)-(-)-ephedrine salt of the (*S*)-enantiomer of compound of the general formula (I) is separated and optionally the (*S*)-enantiomer is deliberated,
and in case of processes 1b) and 1c) the (R) or the (S) enantiomer is partially or totally esterified to optically active compounds of the general formula (I) wherein R and/or R_1 mean a straight or branched alkyl group containing 1-4 carbonatoms and R_2 means a hydrogen atom or a straight or branched alkyl group containing 1-4 carbon atoms.

In case of the procedure a) the chiral stationary phase may be a derivatized polysaccharide and the mobile phase may be a mixture of a polar solvent and an apolar solvent.
Suitable polar solvent may be isopropanol and the apolar solvent may be n-hexane.

In case of the procedure b) methanol is used as solvent and ethyl-acetate is used for dilution of the reaction mixture. During procedure c) anhydrous ethyl-acetate is the suitable solvent. All the three procedures can be carried out preferably between +10°C and +60°C.

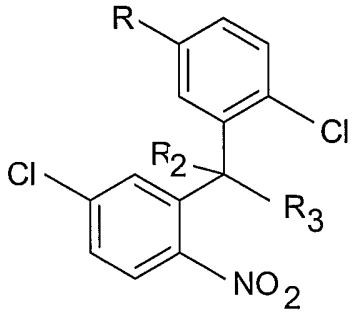
During the resolution processes b) and c) the (R) or (S) enantiomers of the general formula (I) – wherein R and R_1 mean a hydrogen atom, R_2 is a hydrogen atom or a straight or branched alkyl group containing 1-4 carbon atoms, may be deliberated from their salts by addition of acids, for example hydrochloric acid.

The (*R*) or (*S*) enantiomer of the compounds of the general formula (I) – wherein R and R_1 mean a straight or branched alkyl group containing 1-4 carbon atoms – is transformed into the (*R*) or (*S*) enantiomer of the compounds of the general formula (I) – wherein R is a hydrogen atom and R_1 is a straight or branched alkyl group containing 1-4 carbon atoms, R_2 is as defined above, by using of benzyl trimethyl-ammonium hydroxide and a solvent during the procedure a.

The (R) or (S) enantiomer of the compound of the general formula (I) – wherein R and R_1 mean a hydrogen atom, R_2 is as defined above – is treated firstly with thionyl chloride and subsequently with an alkanol –containing 1-4 carbonatoms – and thus the (*R*) or (*S*) enantiomer of the compound of the formula (I) wherein R means a straight or branched alkyl group alkyl group containing 1-4 carbon atoms and R_1 means a hydrogen atom, R_2 is as defined above, is obtained during the procedures b and c.

Preparation of the racemic starting materials of the general formula (Ia) is described in the Hungarian Patent Application No P0500126 filed on 26 January 2005 and in the corresponding Patent Application No ... filed on ... and they are hereby incorporated by reference. Racemic compounds of the general formula (Ia) may be prepared according to the above patent applications by the following synthesis route:

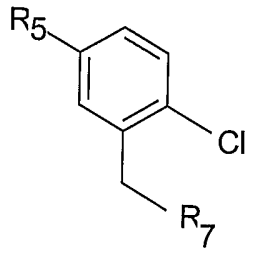
The compounds of the general formula (Ic), which group of compounds contain the group of racemic compounds of the general formula (Ia)



(Ic)

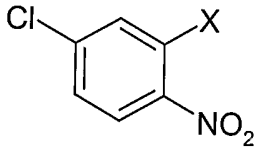
wherein R stands for nitro group or $-COOR^1$ group, wherein R_1 stands for hydrogen atom or C_{1-4} straight or branched alkyl group, R_2 stands for hydrogen atom, C_{1-4} straight or

branched alkyl group and R_3 stands for a -$COOR^4$ group or –CN group, wherein R_4 stands for hydrogen atom or C_{1-4} straight or branched alkyl group, may be prepared by reacting a compound of the general formula (II),



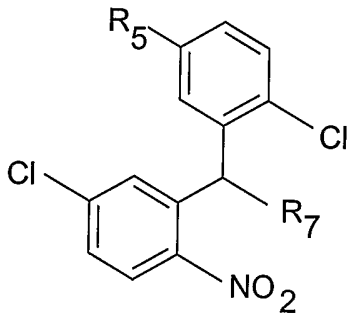
(II)

wherein R_5 stands for nitro group or –$COOR^6$ group, wherein R_6 stands for a straight or branched C_{1-4} alkyl group, R_7 stands for a –$COOR^8$ or –CN group, wherein R_8 stands for a straight or branched C_{1-4} alkyl group, with a nitrobenzene derivative of the formula (III),



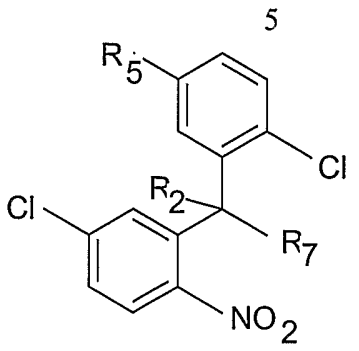
(III)

wherein X stands for a fluorine atom or a chlorine atom, in the presence of solid sodium hydride, alkali metal hydroxide, alkali metal alkoxylate, alkali metal carbonate or bicarbonate in a solvent at low temperature, and if desired reacting a compound of the general formula (IV),



(IV)

wherein R^5 and R^7 have the same meaning as defined above, with an alkylating compound of the formula $(R^9)_nY$, wherein R^9 stands for C_{1-4} straight or branched alkyl group, Y stands for halogen atom, sulphate, sulphonate or phosphate group and n stands for 1, 2 or 3, if desired hydrolyzing the ester groups of a compound of the formula (V),



(V)

wherein R^2 and R^5 have the same meaning as defined above and R^7 stands for $-COOR^8$, wherein R^8 stands for straight or branched C_{1-4} alkyl group in one or two steps and if desired hydrolyzing the –CN group of a compound of the formula (V), wherein R^7 stands for –CN group and R^2 and R^5 are as defined above, and if desired transforming the substituents of the compound of the general formula (I) into each other by known methods.

According to the invention sodium hydroxide or potassium hydroxide might be used as alkali metal hydroxide; sodium methoxide or potassium tertiary butoxide, as alkali metal alkoxylate; potassium carbonate, as alkali metal carbonate; sodium bicarbonate, as alkali metal bicarbonate; dimethylformamide, N-methylpyrrolidone, toluene, tetrahydrofurane, acetone, tertiary-butylalcohol, as solvent.

The X leaving group preferably means fluorine or chlorine atom.

The hydrolysis of the group $-COOR^6$ might be carried out in a protic solvent, preferably methanol in the presence of a base, preferably benzyltrimethylammonium-hydroxide (Triton B).

The hydrolysis of the groups –COOR6 and –COOR8 together is preferably performed in a protic solvent, preferably isopropanol in the presence of a base, preferably alkali hydroxide, preferably potassium hydroxide.

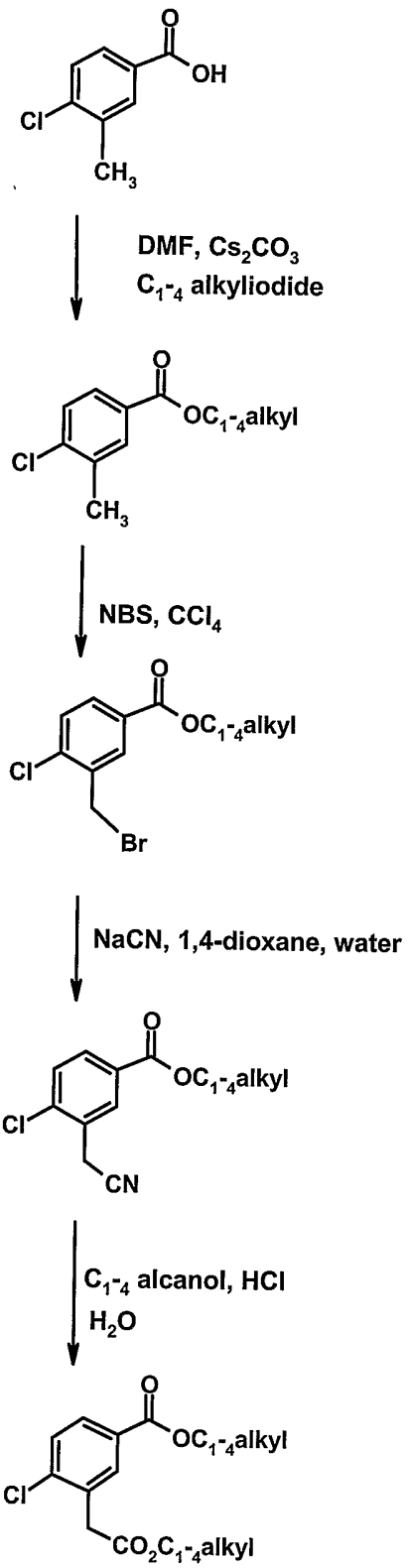
The arylation with 2,4-dichloro-nitrobenzene is preferably carried out at a temperature between (-20 °C) and 0 °C, preferably (-10 °C) and (-8 °C), while using 2-chloro-4-fluoro-nitrobenzene the preferable temperature is between (-10 °C) and (+20 °C).

Compounds of the general formula (II) are new compounds, which may be prepared according to methods known per se, e.g. by methods given in reaction schemes 1 and 2.

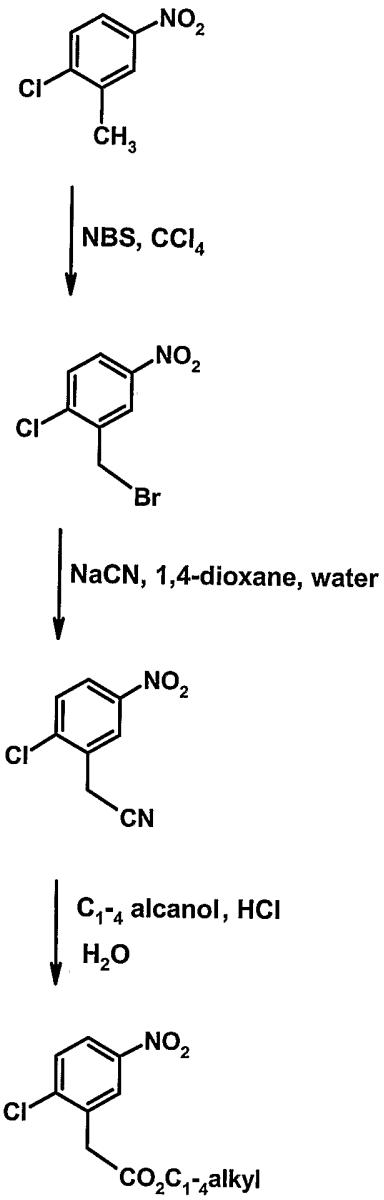
The used resolution agents and reagents are commercial products.

Further details of this invention are illustrated by the following examples without limitation of the scope of claims to the content of these examples.

1. Reaction scheme



2. Reaction scheme



EXAMPLES

EXAMPLE 1

Separation of the enantiomers of 3-[1-methoxycarbonyl-1-(5-chloro-2-nitrophenyl)ethyl]-4-chlorobenzoic acid methyl ester was done using a Chiralpak® AD (Product of Daicel Chem. Corp.) 20 (m preparative column (250 x 50 mm) (Chiral Technologies Europe, France) and isocratic mobile phase consisting of n-hexane - 2-propanol (v/v 900 : 100) and UV detection at 240 nm.

Racemic 3-[1-methoxycarbonyl-1-(5-chloro-2-nitrophenyl)ethyl]-4-chlorobenzoic acid methyl ester (10 g) was dissolved in chloroform (150 ml) and the solution was diluted by the eluent to 1000 ml. Prior the injection of the solution to the preparative column it should be degassed. Each time 100 mL of the above mentioned solution was injected into the column. Running time was 30 min in each case.

The (R)-3-[1-methoxycarbonyl-1-(5-chloro-2-nitrophenyl)ethyl]-4-chlorobenzoic acid methyl ester was obtained from the eluent collected between 7 and 13 min running time, by evaporation of the combined eluent. Yield: 4.95 g

Mp.: 97-99 °C, [(]20589 = +32.59° (c=1, MeOH)

Anal. Calcd for C18H15Cl2NO6: C, 52.45; H, 3.67; N, 3.40; Cl, 17.20.

Found: C, 52.66; H, 3.45; N, 3.30; Cl, 17.37.

The (S)-3-[1-methoxycarbonyl-1-(5-chloro-2-nitrophenyl)ethyl]-4-chlorobenzoic acid methyl ester was obtained from the eluent collected between 14 and 22 min running time, by evaporation of the combined eluent. Yield: 4.23 g.

Mp.: 100-101°C, [(]20589 = -32.67° (c=1, MeOH)

Anal. Calcd for C18H15Cl2NO6: C, 52.45; H, 3.67; N, 3.40; Cl, 17.20.

Found: C, 52.56; H, 3.50; N, 3.37; Cl, 17.17.

EXAMPLE 2

Racemic 3-[1-carboxy-1-(5-chloro-2-nitrophenyl)ethyl]-4-chlorobenzoic acid (50.7 g), D-proline (15.2 g) in methanol (255 mL) were heated at 50 °C with vigorous stirring. This reaction mixture was then diluted with ethyl acetate (306 mL). After cooling to room temperature the reaction mixture was stirred overnight. The precipitated solid was filtered off and the cake was washed with a 5 : 6 mixture of methanol and ethyl acetate (3x25 mL),

and dried to give 18.94g (28.6 %) of D-proline salt of (*R*)-3-[1-carboxy-1-(5-chloro-2-nitrophenyl)ethyl]-4-chlorobenzoic acid as a white crystalline solid.

Mp.: 184-187 °C, $[\alpha]^{20}_{589}$ = +6.96° (c=1, MeOH)

Anal. Calcd for $C_{21}H_{20}Cl_2N_2O_8$: C, 50.52; H, 4.04; N, 5.61; Cl, 14.20.

Found: C, 50.46; H, 4.10; N, 5.47; Cl, 14.15.

EXAMPLE 3

D-Proline salt of (*R*)-3-[1-carboxy-1-(5-chloro-2-nitrophenyl)ethyl]-4-chlorobenzoic acid (18.94 g), obtained in Example 2 was added to water (270 mL) and concentrated hydrochloric acid (8 mL) was dropwise added to the solution at 50°C. The mixture was stirred for 1 hour at room temperature and the precipitate was filtered and washed with water (3x130 mL) to give (*R*)-3-[1-carboxy-1-(5-chloro-2-nitrophenyl)ethyl]-4-chlorobenzoic acid (14.0 g), yield 26.6 %.

Mp.: 199-201 °C, $[\alpha]^{20}_{589}$ = -6.97° (c=1, MeOH)

Anal. Calcd for $C_{16}H_{11}Cl_2NO_6$: C, 50.02; H, 2.89; N, 3.65; Cl, 18.46.

Found: C, 50.06; H, 2.80; N, 3.57; Cl, 18.37.

EXAMPLE 4

Racemic 3-[1-carboxy-1-(5-chloro-2-nitrophenyl)ethyl]-4-chlorobenzoic acid (20 g), L-proline (6 g) in methanol (100 mL) were heated at 50 °C with vigorous stirring. This reaction mixture was then diluted with ethyl acetate (120 mL). After cooling to room temperature the reaction mixture was stirred overnight. The precipitated solid was filtered off and the cake was washed with a 5:6 mixture of methanol and ethyl acetate (3x15 mL), and dried to give 5.76g (28.6 %) of L-proline salt of (*S*)-3-[1-carboxy-1-(5-chloro-2-nitrophenyl)ethyl]-4-chlorobenzoic acid as a white crystalline solid.

Mp.: 182-184 °C, $[\alpha]^{20}_{589}$ = -6.47° (c=1, MeOH)

Anal. Calcd for $C_{21}H_{20}Cl_2N_2O_8$: C, 50.52; H, 4.04; N, 5.61; Cl, 14.20.

Found: C, 50.39; H, 4.10; N, 5.53; Cl, 14.09.

EXAMPLE 5

The filtrate of Example 4 was evaporated and the residue was dissolved in hot ethanol (23 ml). The solution was diluted with water (23 ml) and it was acidified with concentrated hydrochloric acid (10 ml). The reaction mixture was cooled to room temperature and the crystals were collected by filtration and washed with aqueous ethyl alcohol (50 v%, 10

mL) and dried to give racemic 3-[1-carboxy-1-(5-chloro-2-nitrophenyl)ethyl]-4-chlorobenzoic acid (10.85 g, mp.: 241-246°C, ee: 3.4).

The filtrate was evaporated until crystallization was observed. The reaction mixture was cooled to room temperature and the crystals were collected by filtration to give (*R*)-3-[1-carboxy-1-(5-chloro-2-nitrophenyl)ethyl]-4-chlorobenzoic acid (3.3 g.).

Mp.: 204-210°C, $[\alpha]^{20}_{589}$ = -7.0° (c=1, MeOH)

Anal. Calcd for $C_{16}H_{11}Cl_2NO_6$: C, 50.02; H, 2.89; N, 3.65; Cl, 18.46.

Found: C, 50.06; H, 2.80; N, 3.57; Cl, 18.37.

EXAMPLE 6

L-Proline salt of (*S*)-3-[1-carboxy-1-(5-chloro-2-nitrophenyl)ethyl]-4-chlorobenzoic acid (5.76 g), obtained in Example 4 was added to water (80 mL) and concentrated hydrochloric acid (2.5 mL) was dropwise added to the solution at 50°C. The mixture was stirred for 1 hour at room temperature and the precipitate was filtered and washed with water (3x40 mL) to give (*S*)-3-[1-carboxy-1-(5-chloro-2-nitrophenyl)ethyl]-4-chlorobenzoic acid (3.1 g), yield 26.6 %,.

Mp.: 202-208°C, $[\alpha]^{20}_{589}$ = +7.0° (c=1, MeOH)

Anal. Calcd for $C_{16}H_{11}Cl_2NO_6$: C, 50.02; H, 2.89; N, 3.65; Cl, 18.46.

Found: C, 50.21; H, 2.50; N, 3.37; Cl, 17.17.

EXAMPLE 7

Racemic 3-[1-carboxy-1-(5-chloro-2-nitrophenyl)ethyl]-4-chlorobenzoic acid (70 g), (1*S*,2*R*)-(+)-ephedrine (31.5 g) in ethyl acetate (700 mL) were heated at 55°C with stirring. After cooling to room temperature the reaction mixture was stirred overnight. The precipitated solid was filtered off and the cake was washed with ethyl acetate (2x50 mL), and dried to give 44.93g (45 %) of (1*S*,2*R*)-(+)-ephedrine salt of (*R*)-3-[1-carboxy-1-(5-chloro-2-nitrophenyl)ethyl]-4-chlorobenzoic acid as a white crystalline solid.

Mp.: 151°C, $[\alpha]^{20}_{589}$= -45.0° (c=1, MeOH)

Anal. Calcd for $C_{26}H_{26}Cl_2N_2O_7$: C, 56.84; H, 4.77; N, 5.10; Cl, 12.91.

Found: C, 56.50; H, 4.59; N, 5.02; Cl, 12.80.

EXAMPLE 8

Racemic 3-[1-carboxy-1-(5-chloro-2-nitrophenyl)ethyl]-4-chlorobenzoic acid (50 g), (1*S*,2*R*)-(+)-ephedrine (21.5 g) in ethyl acetate (1L) were heated to 55°C with stirring. The solution was seeded with a small amount of the desired (*R*)-acid ephedrine salt, and the reaction mixture was stirred overnight at the same temperature. The solid was filtered off and the cake was washed with ethyl acetate (2x40 mL) and dried to give 22.64 g (31 %) of (1*S*,2*R*)-(+)-ephedrine salt of (*R*)-3-[1-carboxy-1-(5-chloro-2-nitrophenyl)ethyl]-4-chlorobenzoic acid as a white crystalline solid.

Mp.: 154-155°C, $[\alpha]^{20}_{589}$= -46.0° (c=1, MeOH)

Anal. Calcd for $C_{26}H_{26}Cl_2N_2O_7$: C, 56.84; H, 4.77; N, 5.10; Cl, 12.91.

Found: C, 56.61; H, 4.81; N, 5.05; Cl, 12.81.

EXAMPLE 9

Racemic 3-[1-carboxy-1-(5-chloro-2-nitrophenyl)ethyl]-4-chlorobenzoic acid (20 g), (1*S*,2*R*)-(+)-ephedrine (4.5 g) in ethyl acetate (200 mL) were heated to 55°C. The suspension was stirred for 3 hours at this temperature. The solid formed was filtered off and the cake was washed with ethyl acetate (2x50 mL), and dried to give 8.2 g (37 %) of (1*S*,2*R*)-(+)-ephedrine salt of (*R*)-3-[1-carboxy-1-(5-chloro-2-nitrophenyl)-ethyl]-4-chlorobenzoic acid as white crystalline solid.

Mp.: 155-156°C, $[\alpha]^{20}_{589}$= -45.0° (c=1, MeOH)

Anal. Calcd for $C_{26}H_{26}Cl_2N_2O_7$: C, 56.84; H, 4.77; N, 5.10; Cl, 12.91.

Found: C, 56.51; H, 4.62; N, 5.00; Cl, 12.8.

EXAMPLE 10

Racemic 3-[1-carboxy-1-(5-chloro-2-nitrophenyl)ethyl]-4-chlorobenzoic acid (20 g), (1*R*,2*S*)-(-)-ephedrine (9,08 g) in ethyl acetate (100 mL) were heated to 55°C with stirring. The solution was seeded with a small amount of pure (*S*)-acid ephedrine salt, the mixture allowed to crystallize overnight while stirring was maintained for 18 hours at room temperature. The solid was filtered off and the cake was washed with ethyl acetate (2x25 mL), and dried to give 13.3 g (46.5 %) of (1*R*,2*S*)-(-)-ephedrine salt of (*S*)-3-[1-carboxy-1-(5-chloro-2-nitrophenyl)ethyl]-4-chlorobenzoic acid as white crystalline solid.

Mp.: 156-157°C, $[\alpha]^{20}_{589}$= +43.0° (c=1, MeOH)

Anal. Calcd for $C_{26}H_{26}Cl_2N_2O_7$: C, 56.84; H, 4.77; N, 5.10; Cl, 12.91.

Found: C, 56.47; H, 4.59; N, 5.07; Cl, 12.8.

EXAMPLE 11

The mother liquid of Example 10 was concentrated in vacuum to give pale yellow foam of (1*R*,2*S*)-(-)-ephedrine salt of (*R*)-3-[1-carboxy-1-(5-chloro-2-nitrophenyl)ethyl]-4-chlorobenzoic acid (15.4 g). This salt (15.3 g) was converted to the corresponding (*R*)-3-[1-carboxy-1-(5-chloro-2-nitro-phenyl)ethyl]-4-chlorobenzoic acid with diluted hydrochloric acid (18.5 mL). The obtained white powder was 10.5 g (98 % yield).

Mp.: 201-202°C, $[\alpha]^{20}_{589}$= - 7.0° (c=1, MeOH)

Anal. Calcd for $C_{16}H_{11}Cl_2NO_6$: C, 50.02; H, 2.89; N, 3.65; Cl, 18.46.

Found: C, 49.56; H, 2.75; N, 3.6; Cl, 18.28.

EXAMPLE 12

Racemic 3-[1-carboxy-1-(5-chloro-2-nitrophenyl)ethyl]-4-chlorobenzoic acid (2.0 g), (1*S*,2*R*)-(+)-ephedrine (0.45 g) and ethyl acetate (25 mL) were heated to 60°C with stirring to dissolve the solids. Stirring was maintained for 3 hours at this temperature then the precipitated solid was filtered off and the cake was washed with cold ethyl acetate (2x5 mL) and dried to give 0.41 g (29 %) of (1*S*,2*R*)-(+)-ephedrine salt of (*R*)-3-[1-carboxy-1-(5-chloro-2-nitrophenyl)ethyl]-4-chlorobenzoic acid as white, crystalline solid.

Mp.: 156-157°C, $[\alpha]^{20}_{589}$= -45.0° (c=1, MeOH)

Anal. Calcd for $C_{26}H_{26}Cl_2N_2O_7$: C, 56.84; H, 4.77; N, 5.10; Cl, 12.91.

Found: C, 56.66; H, 4.57; N, 5.05; Cl, 12.8.

EXAMPLE 13

(*R*)-3-[1-carboxy-1-(5-chloro-2-nitrophenyl)-ethyl]-4-chlorobenzoic acid (2.0 g), (1*S*,2*R*)-(+)-ephedrine (0.45 g) and ethyl acetate (20 mL) were heated at 55°C with stirring to dissolve the solids. The solution was seeded with a small amount of title compound. After being allowed to cool to room temperature and stirring overnight the solid was filtered off and the cake was washed with ethyl acetate (2x5 mL), and dried to give 1.35 g (47 %) of (1*R*,2S)-(+)-ephedrine salt of (*R*)-3-[1-carboxy-1-(5-chloro-2-nitrophenyl)-ethyl]-4-chlorobenzoic acid ephedrine salt as a white, crystalline solid.

Mp.: 148-149°C, $[\alpha]^{20}_{589}$= -46.0° (c=1, MeOH)

Anal. Calcd for $C_{26}H_{26}Cl_2N_2O_7$: C, 56.84; H, 4.77; N, 5.10; Cl, 12.91.

Found: C, 56.75; H, 4.65; N, 5.05; Cl, 12.80.

EXAMPLE 14

(*S*)-3-[1-carboxy-1-(5-chloro-2-nitrophenyl)-ethyl]-4-chlorobenzoic acid (2.0 g), (1*S*,2*R*)-(+)-ephedrine (0.45 g) and ethyl acetate (20 mL) were heated at 55°C with stirring to dissolve the solids. The solution was seeded with a small amount of title compound. After being allowed to cool to room temperature and stirred overnight the solid was filtered off and the cake was washed with ethyl acetate (2x5 mL), and dried to give 1.41g (48 %) of (1*S*,2R)-(+)-ephedrine salt of (*S*)-3-[1-carboxy-1-(5-chloro-2-nitrophenyl)-ethyl]-4-chlorobenzoic acid as a white, crystalline and

vaxy solid , $[\alpha]^{20}_{589}$=+ 45.0° (c=1, MeOH)

Anal. Calcd for $C_{26}H_{26}Cl_2N_2O_7$: C, 56.84; H, 4.77; N, 5.10; Cl, 12.91.

Found: C, 56.78; H, 4.70; N, 5.,00; Cl, 12.80.

EXAMPLE 15

(1*S*,2*R*)-Ephedrine salt of (*R*)-3-[1-carboxy-1-(5-chloro-2-nitrophenyl)ethyl]-4-chlorobenzoic acid (31.73 g), obtained in Example 7 was added to a diluted hydrochloric acid (37 mL) at room temperature. The mixture was stirred for 2 hours then the resulting precipitate was collected by filtration to give (*R*)-3-[1-carboxy-1-(5-chloro-2-nitrophenyl)ethyl]-4-chlorobenzoic acid 21.78 g (yield 98 %).

Mp.: 199-201°C, $[\alpha]^{20}_{589}$= -8.0° (c=1, MeOH)

Anal. Calcd for $C_{16}H_{11}Cl_2NO_6$: C, 50.02; H, 2.89; N, 3.65; Cl, 18.46.

Found: C, 49.75; H, 2.81; N, 3.60; Cl,18.36.

EXAMPLE 16

(*R*)-3-[1-methoxycarbonyl-1-(5-chloro-2-nitrophenyl)ethyl]-4-chlorobenzoic acid methyl ester (2.5 g) (obtained in Example 1) and Triton B(benzyl-trimethyl-ammonium hydroxide) (7.5 mL) in methanol (25 mL) are refluxed for 4 hours. The solvent is removed in vacuum. The residue is diluted with water (25 mL), acidified with hydrochloric acid. The solution is poured off from the separated oil. The residue is treated with methanol (7.5 mL) the precipitated is filtered off, washed and dried. It yields 2.01 g (83 %) of (R)-3-[1-methoxy-carbonyl-1-(5-chloro-2-nitrophenyl)-ethyl]-4-chloro-benzoic acid.

Mp.: 174-175°C, $[\alpha]^{20}_{589}$ = +61,5° (c=1, DMSO)

Anal. Calcd for $C_{17}H_{13}Cl_2NO_6$: C, 51.28; H, 3.29; N, 3.52; Cl, 17.81.

Found: C, 51.18; H, 3.27; N, 3.4; Cl, 17.80.

EXAMPLE 17

(*S*)-3-[1-methoxycarbonyl-1-(5-chloro-2-nitrophenyl)ethyl]-4-chlorobenzoic acid methyl ester (2.5 g) (obtained in Example 1) and Triton B (7.5 mL) in methanol (25 mL) were refluxed for 4 hours. The solvent was removed in vacuum. The residue was diluted with water (25 mL), acidified with hydrochloric acid. The solution was poured off from the separated oil. The residue was treated with methanol (7.5 mL) the precipitated was filtered off, washed and dried. It yielded 0.6 g (79%) of (S)-3-[1-methoxy-carbonyl-1-(5-chloro-2-nitrophenyl)-ethyl]-4-chloro-benzoic acid.

Mp.: 172-174°C, $[\alpha]^{20}_{589}$ = -63.0° (c=1, DMSO)

Anal. Calcd for $C_{17}H_{13}Cl_2NO_6$: C, 51.28; H, 3.29; N, 3.52; Cl, 17.81.

Found: C, 52.03; H, 3.39; N, 3.44; Cl, 17.64.

EXAMPLE 18

(*R*)-3-[1-carboxy-1-(5-chloro-2-nitrophenyl)ethyl]-4-chlorobenzoic acid (1.0 g) (obtained in Example 3) was stirred with thionyl chloride (2.0 mL). After the completion of the acyl chloride formation the excess of reagent was evaporated under reduced pressure. The residue was treated with methanol (5 mL) and was refluxed for one hour. The precipitated solid material was filtered off, washed with hot methanol and dried. It yielded (R)-3-[1-carboxy-1-(5-chloro-2-nitrophenyl)-ethyl]-4-chloro-benzoic acid-methyl-ester (0.77 g).

Mp.: 243-245°C, $[\alpha]^{20}_{589}$ = +21,78 °(c=1, DMSO)

Anal. Calcd for $C_{17}H_{13}Cl_2NO_6$: C, 51.28, H, 3.29; N, 3.52; Cl, 17.81.

Found: C, 51.10; H, 3.17; N, 3.48; Cl, 17.79.

EXAMPLE 19

(*S*)-3-[1-carboxy-1-(5-chloro-2-nitrophenyl)ethyl]-4-chlorobenzoic acid (1.0 g) (obtained in Example 4) was stirred with thionyl chloride (2 mL). After the completion of the acyl chloride formation the excess of reagent was evaporated under reduced pressure. The residue was treated with methanol (5 mL) and was refluxed for one hour. The precipitated solid material was filtered off, washed with hot methanol and dried. It yielded (S)-3-[1-carboxy-1-(5-chloro-2-nitrophenyl)-ethyl]-4-chloro-benzoic acid-methyl-ester (0.81 g).

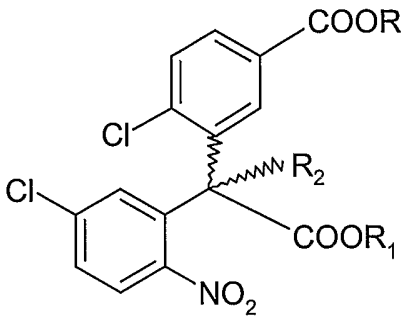
Mp.: 245-246°C, $[\alpha]^{20}_{589}$ = -21,78 °(c=1, DMSO)

Anal. Calcd for $C_{17}H_{13}Cl_2NO_6$: C, 51.28; H, 3.29; N, 3.52; Cl, 17.81.

Found: C, 51.19; H, 3.14; N, 3.40; Cl, 17.69.

CLAIMS

1. Optically active compounds of the general formula (I)



(I)

wherein R means a hydrogen atom or a straight or branched alkyl group containing 1-4 carbon atoms, R_1 means a hydrogen atom or a straight or branched alkyl group containing 1-4 carbon atoms, R_2 means a hydrogen atom or a straight or branched alkyl group containing 1-4 carbon atoms– and their salts.

2. (*R*)-enantiomers of the compounds of the general formula (I) – wherein R, R_1 and R_2 independently from each other mean hydrogen atom or a straight or branched alkyl group alkyl group containing 1-4 carbon atoms – and their salts.

3. (*S*)-enantiomers of the compounds of the general formula (I) – wherein R, R_1 and R_2 independently from each other mean a hydrogen atom or a straight or branched alkyl group containing 1-4 carbon atoms – and their salts.

4. A compound or its diastereoisomeric salt according to any of claims 1 to 3 selected from the group consisting of

Methyl (*R*)-3-[1-methoxycarbonyl-1-(5-chloro-2-nitrophenyl)ethyl]-4-chlorobenzoate;

Methyl (*S*)-3-[1-methoxycarbonyl-1-(5-chloro-2-nitrophenyl)ethyl]-4-chlorobenzoate;

(1*R*,2*S*)-Ephedrine salt of (R)-3-[1-carboxy-1-(5-chloro-2-nitrophenyl)ethyl]-4-chlorobenzoic acid;

(1*S*,2*R*)-Ephedrine salt of (*S*)-3-[1-carboxy-1-(5-chloro-2-nitrophenyl)ethyl]-4-chlorobenzoic acid;

L-proline salt of (*S*)-3-[1-carboxy-1-(5-chloro-2-nitrophenyl)ethyl]-4-chlorobenzoic acid;.

D-proline salt of (*R*)-3-[1-carboxy-1-(5-chloro-2-nitrophenyl)ethyl]-4-chlorobenzoic acid;

(*S*)-3-[1-carboxy-1-(5-chloro-2-nitrophenyl)ethyl]-4-chlorobenzoic acid;

(*R*)-3-[1-carboxy-1-(5-chloro-2-nitrophenyl)ethyl]-4-chlorobenzoic acid;

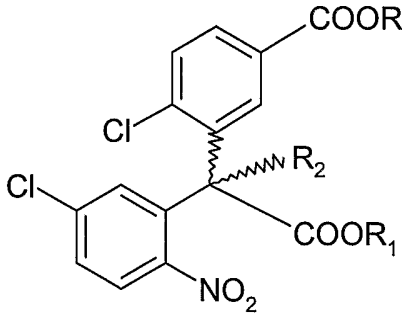
(*R*)-3-[1-methoxy-carbonyl-1-(5-chloro-2-nitrophenyl)-ethyl]-4-chloro-benzoic acid;

(*S*)-3-[1-methoxy-carbonyl-1-(5-chloro-2-nitrophenyl)ethyl]-4-chloro-benzoic acid;

(R)-3-[1-carboxy-1-(5-chloro-2-nitrophenyl)-ethyl]-4-chloro-benzoic acid-methylester;

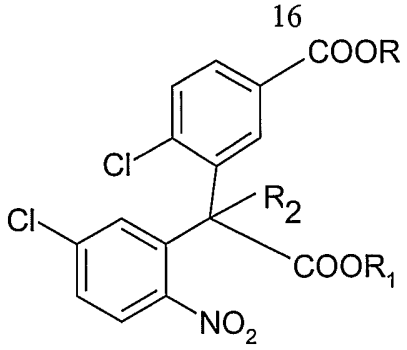
(S)-3-[1-carboxy-1-(5-chloro-2-nitrophenyl)-ethyl]-4-chloro-benzoic acid-methyl ester;

5. A process for the preparation of the optically active compounds of the general formula (I)



(I)

wherein R, R_1 and R_2 independently from each other mean a hydrogen atom or a straight or branched alkyl group containing 1-4 carbonatoms – and their salts by the resolution of racemic compounds of the general formula (Ia) –



(Ia)

wherein R, R_1 and R_2 independently from each other mean a hydrogen atom or a straight or branched alkyl group containing 1-4 carbon atoms - characterized in that

a) the racemic compound of the general formula (Ia) –

wherein R and R_1 mean a straight or branched alkyl groups containing 1-4 carbonatoms, R_2 means a hydrogen atom or a straight or branched alkyl group containing 1-4 carbon atoms – is separated by chromatography using chiral stationary phase and optically active product thus obtained if desired is partially or totally hydrolized to optically active compounds of the general formula (I) – wherein the meaning of R and/or R_1 is hydrogen and R_2 has the above mentioned meaning – and optionally their salts are formed or

b) to the racemic compound of the general formula (Ia) - wherein R and R_1 mean hydrogen atoms, R_2 means a hydrogen atom or a straight or branched alkyl grooup containing 1-4 carbon atoms - D-Proline is added and the received D-Proline salt of the (*R*)-enantiomer of compound of the general formula (I) is separated and the (*R*) – enantiomer is optionally deliberated or

L-Proline is added and the received L-Proline salt of the (*S*)-enantiomer of compound of the general formula (I) separated and the (*S*)-enantiomer is optionally deliberated or

c) to the racemic compound of the general formula (Ia) - wherein R and R_1 mean hydrogen atoms and R_2 has the above meaning – (1*S*, 2*R*)-(+)ephedrine is added and the received (1*S*, 2*R*)-(+)-ephedrine salt of the (*R*)-enantiomer of compound of the general formula (I) is separated and optionally the (*R*)-enantiomer is deliberated or

- (1*R*, 2*S*)-(-)-ephedrine is added and the received (1*R*, 2*S*)-(-)-ephedrine salt of the (*S*)-enantiomer of compound of the general formula (I) is separated and optionally the (*S*)-enantiomer is deliberated,

and in case of processes 1b) and 1c) the (R) or the (S) enantiomer is partially or totally esterified to optically active compounds of the general formula (I) wherein R and/or R_1

mean a straight or branched alkyl group containing 1-4 carbon atoms and R_2 has the above meaning.

6. A process according to claim 1a), characterized in that, the chiral stationary phase is a derivatized polysaccharide and the mobile phase is a mixture of a polar solvent and an apolar solvent.

7. A process according to claim 1b), characterized in that, methanol is used as solvent and ethyl-acetate is used for dilution of the reaction mixture.

8. A process according to claim 1c), characterized in that, anhydrous ethyl-acetate is used as solvent.

9. A process according to claim 1a) or 1b) or 1c), characterized in that, the process is carried out between +10°C and +60°C.

10. A process according to claim 1b) or 1c), characterized in that, the deliberation of the (*R*) or (*S*) enantiomers of the compounds of the general formula (I) – wherein R and R_1 mean a hydrogen atom, R_2 has the same meaning as it is defined in claim 1 – from their salts - is carried out by addition of hydrochloric acid.

11. A process according to claim 1a), characterized in that, the (*R*) or (*S*) enantiomer of the compounds of the general formula (I) – wherein R and R_1 mean a straight or branched alkyl group containing 1-4 carbon atoms, R_2 has the same meaning as it is defined in claim 1 – is transformed into the (*R*) or (*S*) enantiomer of the compounds of the general formula (I) – wherein R is hydrogen atom and R_1 is a straight or branched alkyl group containing 1-4 carbonatoms, R_2 has the same meaning as it is defined in claim 1, by using of benzyl trimethyl-ammonium hydroxide and a solvent.

12. A process according to claim 1b) or 1c), characterized in that, the (R) or (S) enantiomer of the compound of the general formula (I) – wherein R and R_1 mean hydrogen atom and R_2 has the same meaning as it is defined in claim 1 – is treated firstly with thionyl chloride and subsequently with an alkanol –containing 1-4 carbon atoms – and thus the (*R*) or (*S*) enantiomer of the compound of the formula (I) wherein

R means a straight or branched alkyl group alkyl group containing 1-4 carbonatoms, R_1 means hydrogenatom and R_2 has the same meaning as it is defined in claim 1, is obtained.

INTERNATIONAL SEARCH REPORT

International application No
PCT/HU2006/000003

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07C205/58

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)
C07C

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

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

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	HEWAWASAM P ET AL: "The synthesis and characterization of BMS-204352 (MaxiPostTM) and related 3-fluorooxindoles as openers of maxi-K potassium channels" BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, OXFORD, GB, vol. 12, no. 7, 8 April 2002 (2002-04-08), pages 1023-1026, XP002380786 ISSN: 0960-894X abstract Scheme 2 page 1025, column 2, paragraph 2 ----- -/--	1-12

[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

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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

"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.

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Date of the actual completion of the international search	Date of mailing of the international search report
27 June 2006	05/07/2006

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Kiernan, A

INTERNATIONAL SEARCH REPORT

International application No
PCT/HU2006/000003

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	LAWRENCE N J ET AL: "Synthesis of Diaryl Acetates and Oxoindoles via a Sequential VNSAR-SNAR Three-Component Coupling reaction" ORGANIC LETTERS, AMERICAN CHEMICAL SOCIETY, US, vol. 6, no. 26, 24 November 2004 (2004-11-24), pages 4957-4960, XP002380787 ISSN: 1523-7060 the whole document	1-4
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A	example 1	1-4
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Information on patent family members

International application No
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