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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
9 June 2005 (09.06.2005)

PCT

(10) International Publication Number
WO 2005/051933 A1

(51) International Patent Classification[7]: C07D 263/20, 295/205

(21) International Application Number:
PCT/IB2004/003829

(22) International Filing Date:
23 November 2004 (23.11.2004)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
1499/DEL/2003 28 November 2003 (28.11.2003) IN

(71) Applicant *(for all designated States except US)*: **RANBAXY LABORATORIES LIMITED** [IN/IN]; 19, Nehru Place, New Delhi, Delhi 110 019 (IN).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **KUMAR, Yatendra** [IN/IN]; U-26/5, Phase-III, DLF Qutab Enclave, Gurgaon, Haryana 122001 (IN). **KAUL, Vijay, Kumar** [IN/IN]; C-005, Kairali Apartments, Plot No. 10, Sector-3, Dawrka, New Delhi, Delhi 110045 (IN). **SINGH, Nitu** [IN/IN]; B-34/154 A-10, Amravati Nagar Colony, Sunderpur, Varanasi, Uttar Pradesh 221002 (IN). **YADAV, Gyan Chand** [IN/IN]; KA-24, Kaushambi, Ghaziabad, Uttar Pradesh, 201010.

(74) Common Representative: **RANBAXY LABORATORIES LIMITED**; c/o DESHMUKH, Jay R., 600 College Road East, Suite 2100, Princeton, New Jersey 08540 (US).

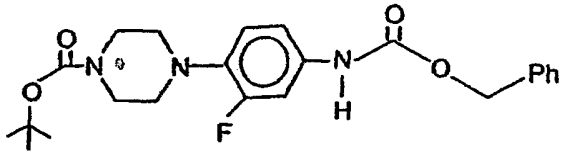
(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR,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

(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, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

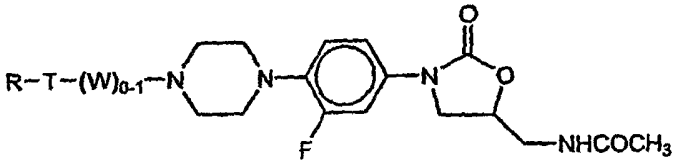
Published:
— *with international search report*

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: AN IMPROVED PROCESS FOR THE SYNTHESIS OF 4-(4-BENZYLOXY-CARBONYLAMINO-2-FLUOROPHENYL)-PIPERAZINE-1-CARBOXYLIC ACID TERT-BUTYL ESTER, A KEY INTERMEDIATE FOR OXAZOLIDINONE ANTIMICROBIALS AND COMPOUNDS PREPARED THEREBY



(I)



(II)

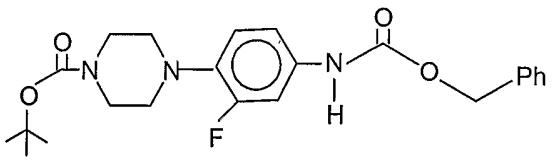
(57) Abstract: Provided herein are process for the synthesis of the 4-(4-benzyloxy-carbonylamino-2-fluorophenyl)-piperazine-1-carboxylic acid tert-butyl ester, which is a key intermediate in the synthesis of oxazolidinone compounds having antibacterial activity. Also provided herein are processes for preparing oxazolidinone compounds. In addition, compounds prepared by the processes provided herein are also encompassed. Formula (I) and Formula (II).

WO 2005/051933 A1

AN IMPROVED PROCESS FOR THE SYNTHESIS OF 4-(4-BENZYLOXY-CARBONYLAMINO-2-FLUOROPHENYL)-PIPERAZINE-1-CARBOXYLIC ACID TERT-BUTYL ESTER, A KEY INTERMEDIATE FOR OXAZOLIDINONE ANTIMICROBIALS AND COMPOUNDS PREPARED THEREBY

Field of the Invention

The present invention relates to processes for the synthesis of the 4-(4-benzyloxy-carbonylamino-2-fluorophenyl)-piperazine-1-carboxylic acid tert-butyl ester of Formula I,



Formula I

which is a key intermediate in the synthesis of oxazolidinone compounds having antibacterial activity.

Background of the Invention

Oxazolidinones are a new class of synthetic antimicrobial agents, which kill gram-positive pathogens by inhibiting a very early stage of protein synthesis. Oxazolidinones inhibit the formation of ribosomal initiation complex involving 30S and 50S ribosomes leading to prevention of initiation complex formation. Due to their novel mechanism of action, these compounds are active against pathogens resistant to other clinically useful antibiotics. For example, phenyloxazolodinones and phenyl piperazinyl oxazolidinones have been disclosed as being useful antimicrobial agents effective against human and veterinary pathogens including gram positive and acid-fast organisms.

A previosly known general method for the synthesis of the intermediate 4-(4-benzyloxy-carbonylamino-2-fluorophenyl)-piperazine-1-carboxylic acid tert-butyl ester of Formula I has been reported, which comprises reacting piperazine with 1,2-difluoro-4-nitrobenzene in acetonitrile to form 1-(2-fluoro-4-nitrophenyl)-piperazine, which is reacted further with di-tert-butoxycarbonyl anhydride in tetrahydrofuran to form 4-(2-fluoro-4-nitrophenyl) piperazin-1-carboxylic acid tert-butyl ester. The resulting nitro compound is

reduced with palladium on carbon in methanol and reacted with benzylchloroformate in tetrahydrofuran to form 4-(4-benzyloxycarbonyl amino-2-fluorophenyl)-piperazin-1-carboxylic acid tert-butyl ester of Formula I.

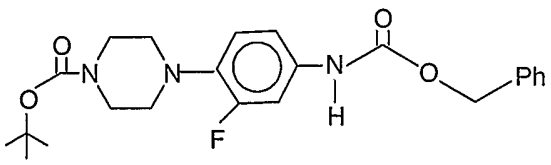
Available methods for the synthesis of compounds of Formula I suffer from a number of limitations and accordingly, are not suitable for commercial production. For example, known methods require the use of acetonitrile, which is highly toxic, inflammable and difficult to handle at commercial scales; and tetrahydrofuran, which is unsafe and burdened with the risk of explosion and fire due to peroxide formation, as well as being an expensive solvent and adds significant factor in the overall cost of preparation of final product. Further, the nitro group reduction is carried out in methanol and tetrahydrofuran and in the presence of ammonium formate-Pd/C catalyst, which is a highly exothermic reaction. This sudden rise in temperature increases the formation of by-products and thereby decreases the overall product yield. In addition, purification of the compound involves column chromatography, which is cumbersome, tedious and not practicable on an industrial scale; the synthesis of the pure compound involves more steps; and the overall yield of the pure compound is poor.

Accordingly, there remains a need for an improved, commercially viable process to synthesize oxazolidinones.

Summary of the Invention

The process provided herein encompass novel methods for the synthesis of the 4-(4-benzyloxy-carbonylamino-2-fluorophenyl)-piperazine-1-carboxylic acid tert-butyl ester of Formula I, which provides improvements over prior methods of synthesis.

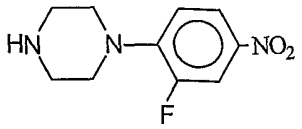
In one aspect, there is provided a process for the synthesis of highly pure 4-(4-benzyloxy-carbonylamino-2-fluorophenyl)-piperazine-1-carboxylic acid tert-butyl ester of Formula I,



Formula I

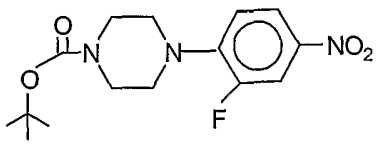
comprising the steps of:

condensing piperazine with 1,2-difluoro-4-nitrobenzene to form 1-(2-fluoro-4-nitro-phenyl)-piperazine of Formula II,



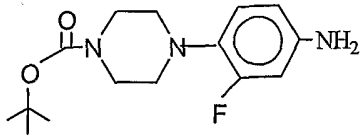
Formula II

contacting the compound of Formula II with di-tert-butoxycarbonyl anhydride to form 4-(2-fluoro-4-nitrophenyl)-piperazine 1-carboxylic acid tert-butyl ester of Formula III,



Formula III

reducing the compound of Formula III to form 4-(4-amino-2-fluorophenyl)-piperazin-1-carboxylic acid tert-butyl ester of Formula IV,



Formula IV

and reacting the compound of Formula IV with benzylchloroformate to form 4-(4-benzyloxy-carbonylamino-2-fluorophenyl)-piperazine-1-carboxylic acid tert-butyl ester of Formula I.

In one aspect, the step of condensing piperazine with 1,2-difluoro-4-nitrobenzene is carried out in an aromatic hydrocarbon, such as toluene, xylene and the like, or mixtures thereof, and at a temperature of, for example, about 40 °C to about 90 °C, or from about 80 °C to about 90 °C.

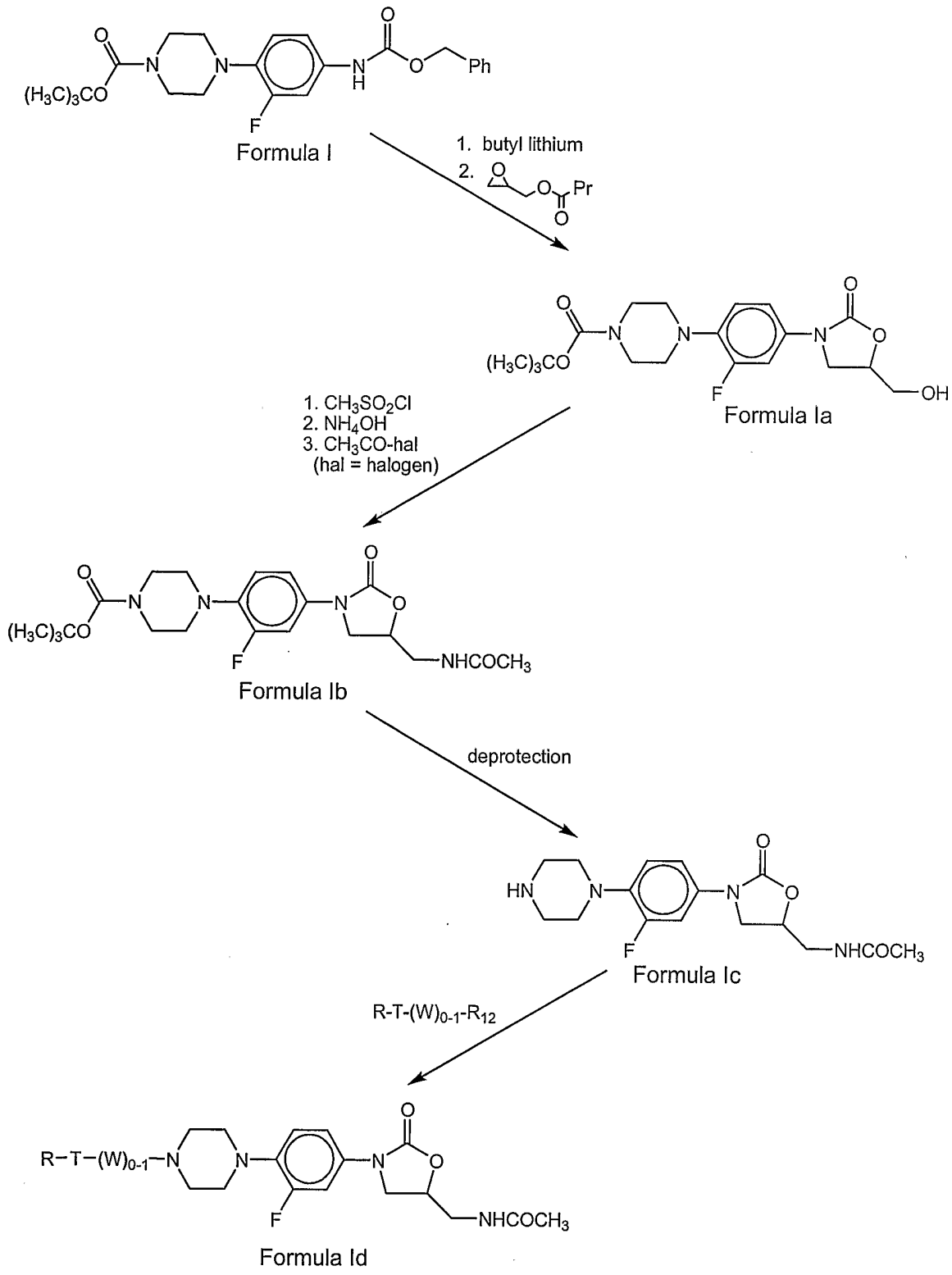
In another aspect, the step of contacting the compound of Formula II with di-tert-butoxycarbonyl anhydride is carried out in an aromatic hydrocarbon, such as toluene, xylene and the like, or mixtures thereof.

In yet another aspect, the step of reducing the compound of Formula III is carried out in the presence of a reducing agent, such as palladium on carbon, and in an aromatic hydrocarbon, such as toluene, xylene and the like, or mixtures thereof.

In another aspect, the reaction of the compound of Formula IV with benzylchloroformate is carried out in the presence of an inorganic base, such as sodium bicarbonate, potassium carbonate or potassium bicarbonate, in an organic solvent, such as toluene, and at a temperature of about 20 °C to about 40 °C.

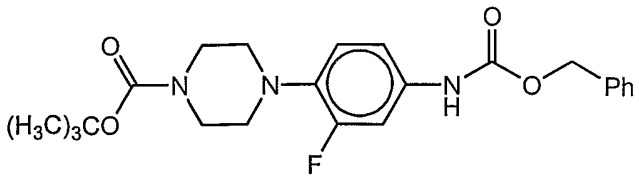
Processes provided herein are advantageous over prior methods because, among other reasons, involve fewer steps, as some steps are carried out *in situ*; the purification of compound need not involve column chromatography, which thus makes the processes convenient to operate at commercial scale; the reduction may be carried out in toluene in the presence of Pd/C, avoiding the exothermicity of the reaction and by-product formation; and the processes need not involve the use of tetrahydrofuran, a material associated with a high risk of fire and explosion.

Oxazolidinone compounds can be prepared from compounds of Formula I using, for example, using methods disclosed in U.S. Patent No. 6,734,307 and PCT Publication Nos. WO 02/06278, WO 03/007870, WO 03/097059, WO04/089944 and WO04/14392, which are incorporated herein by reference. Scheme I below shows a synthetic route starting from a compound of Formula I to oxazolidinone compounds.


Formula I
1. butyl lithium
2.
Pr
Formula Ia
1. CH_3SO_2Cl
2. NH_4OH
3. CH_3CO-hal
(hal = halogen)
Formula Ib
deprotection
Formula Ic
$R\text{-}T\text{-}(W)_{0\text{-}1}\text{-}R_{12}$
Formula Id

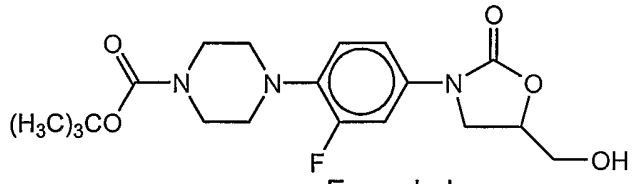
Scheme I

A compound of Formula I



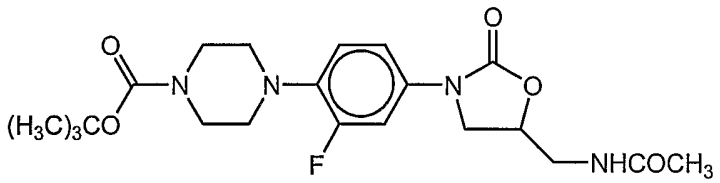
Formula I

can be reacted with a base, *e.g.*, butyl lithium, and glycidyl butyrate to form a compound of Formula Ia.



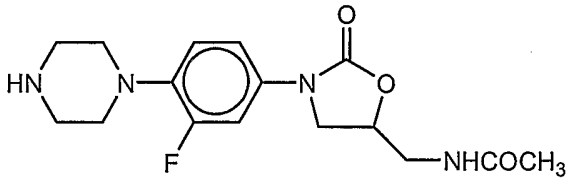
Formula Ia

The compound of Formula Ia can be reacted with methane sulphonyl chloride, followed by ammonium hydroxide, and finally acetyl halide of Formula CH_3CO-hal (wherein hal is Br, Cl or I) to form a compound of Formula Ib.



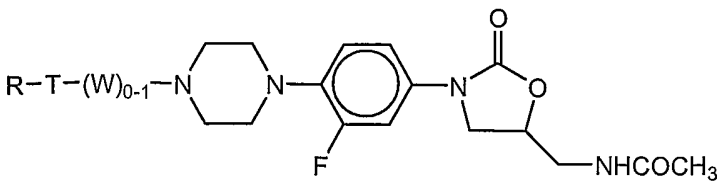
Formula Ib

The compound of Formula Ib can be deprotected to form a compound of Formula Ic.



Formula Ic

The compound of Formula Ic can be reacted with R-T-$(W)_{0-1}$-R_{12} to form a compound of Formula Id



Formula Id

wherein

T can be a five- to seven-membered heterocyclic ring, aryl or substituted aryl, bound to the piperazinyl ring via linker W, wherein the heterocyclic ring can have at least one heteroatom selected from oxygen, nitrogen and sulfur.

Preferred forms of T can be aryl and five-membered heteroaryl, which can be further substituted by a group represented by R, wherein R can be H, CHO, $(C_1\text{-}C_6)$-alkyl, F, Cl, Br, I, -CN, COR_5, $COOR_5$, $N(R_6R_7)$, $CON(R_6R_7)$, CH_2NO_2, NO_2, CH_2R_8, CHR_9, $-CH{=}N\text{-}OR_{10}$, $-C{=}CH\text{-}R_5$, $NHCOC(R_8R_9)$, $NHCOOR_{10}$, $CH(OAc)_2$, OR_5, SR_5, $-C(R_9)NO_2$, $(C_1\text{-}C_{12})$-alkyl substituted with one or more of F, Cl, Br, I, OR_4 or SR_4,

wherein R_5 can be H, optionally substituted $(C_1\text{-}C_{12})$-alkyl, $(C_3\text{-}C_{12})$-cycloalkyl, aryl, heteroaryl, $(C_1\text{-}C_6)$-alkoxy, or $(C_1\text{-}C_6)$-alkyl substituted with one or more of F, Cl, Br, I or OH;

R_6 and R_7 can be independently selected from H, optionally substituted $(C_1\text{-}C_{12})$-alkyl, $(C_3\text{-}C_{12})$-cycloalkyl, or $(C_1\text{-}C_6)$-alkoxy;

R_8 and R_9 can be independently selected from H, $(C_1\text{-}C_6)$-alkyl, F, Cl, Br, $(C_1\text{-}C_{12})$-alkyl substituted with one or more of F, Cl, Br, I, OR_5, SR_5, $N(R_6R_7)$ wherein R_5, R_6 and R_7 can be the same as defined earlier, R_{10} is H, optionally substituted $(C_1\text{-}C_{12})$-alkyl, $(C_3\text{-}C_{12})$-cycloalkyl, $(C_1\text{-}C_6)$-alkoxy, $(C_1\text{-}C_6)$-alkyl, aryl, or heteroaryl;

W can be selected from CH_2, CO, $-CH_2$ NH-, $-NHCH_2$-, $-CH_2NHCH_2$-, $-CH_2\text{-}N(R_{11})CH_2$-, $-CH_2(R_{11})N$-, $CH(R_{11})$, S, $CH_2(CO)$, NH,

wherein R_{11} can be optionally substituted $(C_1\text{-}C_{12})$-alkyl, $(C_3\text{-}C_{12})$-cycloalkyl, $(C_1\text{-}C_6)$-alkoxy, $(C_1\text{-}C_6)$-alkyl, aryl or heteroaryl; and

R_{12} can be a suitable leaving group well known to one of ordinary skill in the art, for example, fluoro, chloro, bromo, SCH_3, $-SO_2CH_3$, $-SO_2CF_3$ or OC_6H_5 and the like.

Another aspect encompasses compounds prepared by processes provided herein.

Detailed Description of the Invention

In the following section preferred embodiments are described in a way to illustrate the disclosure. However, this does not limit the scope of the present invention.

EXAMPLE Preparation of 4-(4-benzyloxy-carbonylamino-2-fluorophenyl)-piperazine-1-carboxylic acid tert-butyl ester of Formula I

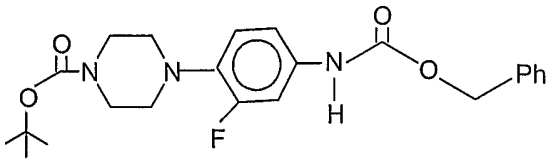
Piperazine (0.77 mol, 66.2 g) was mixed with toluene (500 mL) and stirred at room temperature and subsequently stirred at 50 °C until a homogenous solution was obtained. 1,2-difluoro-4-nitrobenzene (0.314 mol, 50 g) was added to the piperazine/toluene solution and the reaction mixture was stirred at 80-90 °C for 3-6 hours. The reaction mixture then was cooled to 40-45 °C and diluted with deionized water. The organic layer was separated and about 250-350 mL of toluene was evaporated off under reduced pressure at 40 °C. Di-tert-butoxycarbonyl anhydride (0.334mol, 75 g) was then added dropwise to the reaction mixture at room temperature. The resulting reaction mixture was stirred at room temperature for 1-2 hours and then further diluted with hexane (200 mL) and stirred for 15-20 minutes at room temperature. The solid product formed in the reaction mixture was filtered, washed with hexane (150 mL), and dried under reduced pressure at 60-70°C to yield 4-(2-fluoro-4-nitrophenyl)-piperazine-1-carboxylic acid tert butyl ester of Formula III. Yield = 1.8-1.9 (w\w); Purity = 96-98% by HPLC.

The compound of Formula III (0.246 mol, 80 g) was added to toluene (800 mL) followed by the addition of palladium on carbon (4 g) at room temperature with continuous stirring. Hydrogen gas was bubbled into the resulting reaction mixture at a pressure of 72 psi. The reaction mixture was stirred for 12-16 hours and then diluted with toluene (150 mL). The reaction mixture was filtered through a celite pad and washed with toluene (200 mL). Sodium bicarbonate solution was added to the reaction mixture at room temperature with continuous stirring. Benzyl chloroformate (0.310 mol, 103 g) was added dropwise to the reaction mixture with continuous stirring for 2-3 hours. Ethyl acetate (1600 mL) was added to the reaction mixture and stirred for about 30 minutes followed by addition of deionized water (400 mL). The organic layer was separated and the solvent was removed under reduced pressure. The

semi-solid product was washed with hexane (350 mL) to obtain 4-(4-benzyloxy-carbonylamino-2-fluorophenyl)-piperazine-1-carboxylic acid tert-butyl ester of Formula I as a solid. Yield = 1.16-1.23 (w/w); Purity = 97-99% by HPLC.

We Claim:

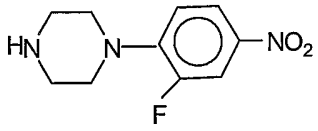
1. A process for the preparation of 4-(4-benzyloxy-carbonylamino-2-fluorophenyl)-piperazin-1-carboxylic acid tert butyl ester of Formula I,



Formula I

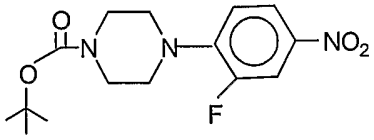
comprising the steps of:

condensing piperazine with 1,2-difluoro-4-nitrobenzene to form a 4-(2-fluoro-4-nitropheyl)-piperazine of Formula II,



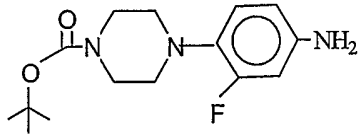
Formula II

contacting the compound of Formula II with di-tert-butyl carboxylic anhydride to form 4-(2-fluoro-4-nitrophenyl)-piperazine-1-carboxylic acid butyl ester of Formula III,



Formula III

reducing the compound of Formula III to form 4-(4-amino-2-fluorophenyl)-piperazin-1-carboxylic acid tert-butyl ester of Formula IV,



Formula IV

and reacting the compound of Formula IV with benzylchloroformate to form a compound 4-(4-benzyloxy-carbonylamino-2-fluorophenyl)-piperazin-1-carboxylic acid tert butyl ester of Formula I.

2. The process of claim 1, wherein the reaction of piperazine with 1,2-difluoro-4-nitrobenzene to form Formula II is carried out in an aromatic hydrocarbon.

3. The process of claim 2, wherein the aromatic hydrocarbon is selected from toluene, xylene, and mixtures thereof.

4. The process of claim 2, wherein the aromatic hydrocarbon is toluene.

5. The process of claim 1, wherein the reaction of piperazine with 1,2-difluoro-4-nitrobenzene is carried out at a temperature of about 40 °C to about 90 °C.

6. The process of claim 5, wherein the reaction of piperazine with 1,2-difluoro-4-nitrobenzene is carried out at a temperature of about 80 °C to about 90 °C.

7. The process of claim 1, wherein the reaction of a compound of Formula II with di-tert-butoxycarbonyl anhydride to form a compound of Formula III is carried out in an aromatic hydrocarbon.

8. The process of claim 7, wherein the aromatic hydrocarbon is selected from toluene, xylene, and mixtures thereof.

9. The process of claim 8, wherein the aromatic hydrocarbon is toluene.

10. The process of claim 1, wherein the reduction of a compound of Formula III to form a compound of Formula IV is carried out in an aromatic hydrocarbon.

11. The process of claim 10, wherein the aromatic hydrocarbon is selected from toluene, xylene, and mixtures thereof.

12. The process of claim 11, wherein the aromatic hydrocarbon is toluene.

13. The process of claim 1 wherein the reduction of a compound of Formula III to form a compound of Formula IV is carried out in the presence of a reducing agent.

14. The process of claim 13, wherein the reducing agent is palladium on carbon.

15. The process of claim 1, wherein the reaction of a compound of Formula IV with benzylchloroformate to form a compound of Formula I is carried out in an organic solvent.

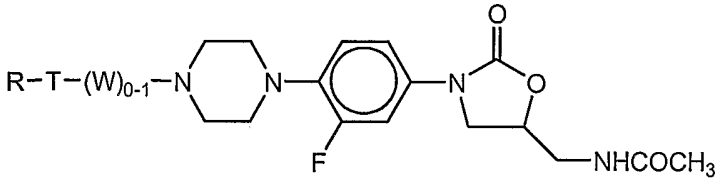
16. The process of claim 15, wherein the organic solvent is toluene.

17. The process of claim 1, wherein the reaction of a compound of Formula IV with benzylchloroformate is carried out in the presence of an inorganic base.

18. The process of claim 17, wherein the inorganic base is selected from sodium bicarbonate, potassium carbonate, and potassium bicarbonate.

19. The process of claim 18, wherein the inorganic base is sodium bicarbonate.

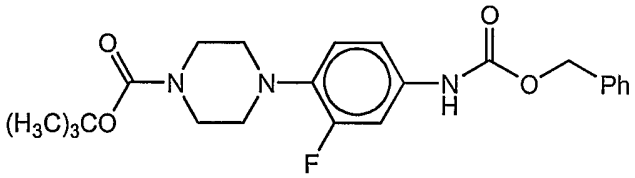
20. A process for the preparation of oxazolidinone compounds of Formula Id



Formula Id

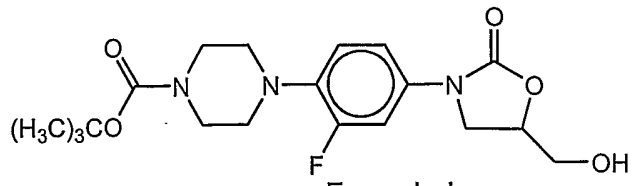
comprising the steps of:

a. reacting a compound of Formula I



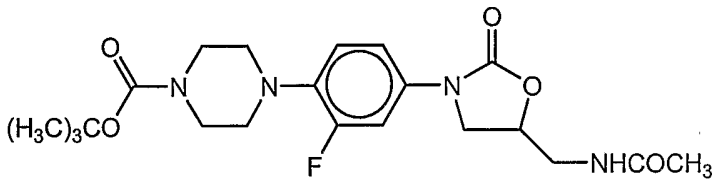
Formula I

with butyl lithium and glycidyl butyrate to form a compound of Formula Ia,



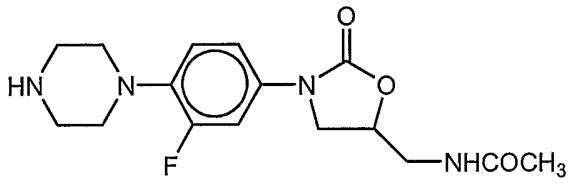
Formula Ia

b. reacting the compound of Formula Ia with methane sulphonyl chloride, ammonium hydroxide and an acetyl halide of Formula CH_3CO-hal, wherein hal is Br, Cl or I, to form a compound of Formula Ib,



Formula Ib

c. deprotecting the compound of Formula Ib to form a compound of Formula Ic, and



Formula Ic

d. reacting the compound of Formula Ic with R-T-$(W)_{0-1}$-R_{12} to form the compound of Formula Id,

wherein

T is a five- to seven-membered heterocyclic ring, aryl or substituted aryl, bound to the piperazinyl ring via linker W,

wherein the heterocyclic ring has at least one heteroatom selected from oxygen, nitrogen and sulfur, and T is further substituted by a group represented by R, wherein R is H, CHO, (C_1-C_6)-alkyl, F, Cl, Br, I, -CN, COR_5, $COOR_5$, $N(R_6R_7)$, $CON(R_6R_7)$, CH_2NO_2, NO_2, CH_2R_8, CHR_9, -CH=N-OR_{10}, -C=CH-R_5, $NHCOC(R_8R_9)$, $NHCOOR_{10}$, $CH(OAc)_2$, OR_5, SR_5, $-C(R_9)NO_2$, (C_1-C_{12})-alkyl substituted with one or more of F, Cl, Br, I, OR_4 or SR_4,

wherein R_5 is H, optionally substituted (C_1-C_{12})-alkyl, (C_3-C_{12})-cycloalkyl, aryl, heteroaryl, (C_1-C_6)-alkoxy, or (C_1-C_6)-alkyl substituted with one or more of F, Cl, Br, I or OH;

R_6 and R_7 is independently selected from H, optionally substituted (C_1-C_{12})-alkyl, (C_3-C_{12})-cycloalkyl, or (C_1-C_6)-alkoxy;

R_8 and R_9 is independently selected from H, (C_1-C_6)-alkyl, F, Cl, Br, (C_1-C_{12})-alkyl substituted with one or more of F, Cl, Br, I, OR_5, SR_5, $N(R_6R_7)$ wherein R_5, R_6 and R_7 is the same as defined earlier, R_{10} is H, optionally substituted (C_1-C_{12})-alkyl, (C_3-C_{12})-cycloalkyl, (C_1-C_6)-alkoxy, (C_1-C_6)-alkyl, aryl, or heteroaryl; and

W is CH_2, CO, -CH_2 NH-, -$NHCH_2$-, -CH_2NHCH_2-, -CH_2-$N(R_{11})CH_2$-, -$CH_2(R_{11})$N-, $CH(R_{11})$, S, CH_2(CO), NH,

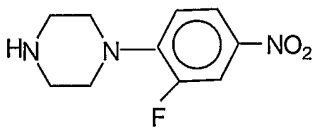
wherein R_{11} is optionally substituted (C_1-C_{12})-alkyl, (C_3-C_{12})-cycloalkyl, (C_1-C_6)-alkoxy, (C_1-C_6)-alkyl, aryl or heteroaryl; and

R_{12} is a leaving group.

21. The process of claim 20, wherein the leaving group is fluoro, chloro, bromo, SCH_3, -SO_2CH_3, -SO_2CF_3 or OC_6H_5.

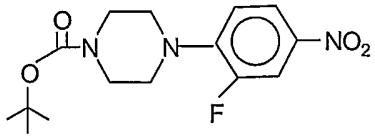
22. The process of claim 20, wherein the compound of Formula I is prepared by a process comprising the steps of:

a. condensing piperazine with 1,2-difluoro-4-nitrobenzene to form a 4-(2-fluoro-4-nitropheyl)-piperazine of Formula II,



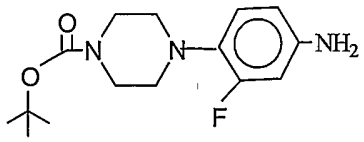
Formula II

b. contacting the compound of Formula II with di-tert-butyl carboxylic anhydride to form 4-(2-fluoro-4-nitrophenyl)-piperazine-1-carboxylic acid butyl ester of Formula III,



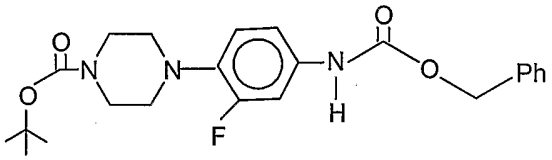
Formula III

c. reducing the compound of Formula III to form 4-(4-amino-2-fluorophenyl)-piperazin-1-carboxylic acid tert-butyl ester of Formula IV, and



Formula IV

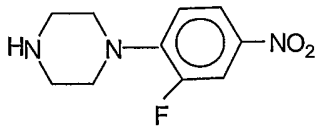
d. reacting the compound of Formula IV with benzylchloroformate to form a compound 4-(4-benzyloxy-carbonylamino-2-fluorophenyl)-piperazin-1-carboxylic acid tert butyl ester of Formula I.



Formula I

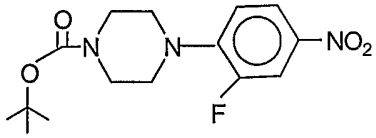
23. A compound prepared by a process comprising the steps of:

condensing piperazine with 1,2-difluoro-4-nitrobenzene to form a 4-(2-fluoro-4-nitropheyl)-piperazine of Formula II,



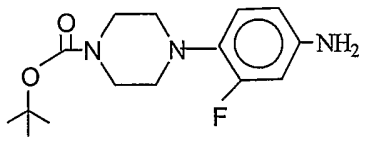
Formula II

contacting the compound of Formula II with di-tert-butyl carboxylic anhydride to form 4-(2-fluoro-4-nitrophenyl)-piperazine-1-carboxylic acid butyl ester of Formula III,



Formula III

reducing the compound of Formula III to form 4-(4-amino-2-fluorophenyl)-piperazin-1-carboxylic acid tert-butyl ester of Formula IV,

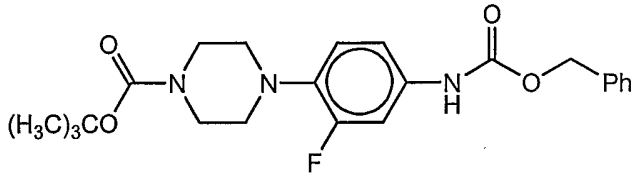


Formula IV

and reacting the compound of Formula IV with benzylchloroformate.

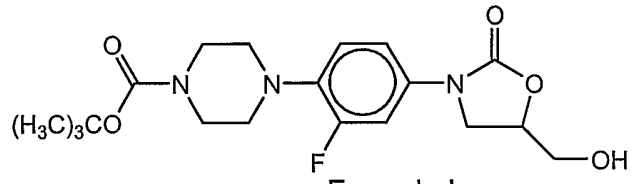
24. A compound prepared by a process comprising the steps of:

a. reacting a compound of Formula I



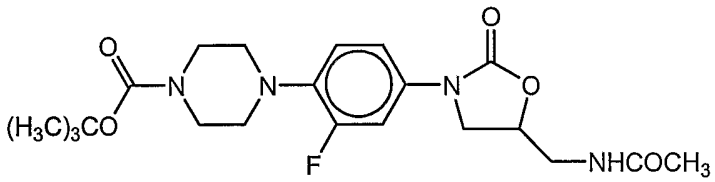
Formula I

with butyl lithium and glycidyl butyrate to form a compound of Formula Ia,



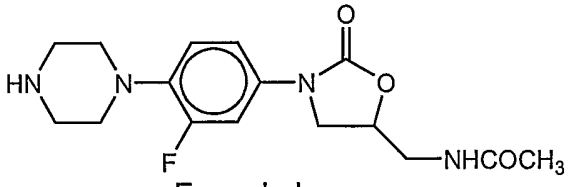
Formula Ia

b. reacting the compound of Formula Ia with methane sulphonyl chloride, ammonium hydroxide and an acetyl halide of Formula CH_3CO-hal, wherein hal is Br, Cl or I, to form a compound of Formula Ib,



Formula Ib

c. deprotecting the compound of Formula Ib to form a compound of Formula Ic, and



Formula Ic

d. reacting the compound of Formula Ic with R-T-$(W)_{0-1}$-R_{12},

wherein

T is a five- to seven-membered heterocyclic ring, aryl or substituted aryl, bound to the piperazinyl ring via linker W,

wherein the heterocyclic ring has at least one heteroatom selected from oxygen, nitrogen and sulfur, and T is further substituted by a group represented by R, wherein R is H, CHO, (C_1-C_6)-alkyl, F, Cl, Br, I, -CN, COR_5, $COOR_5$, $N(R_6R_7)$, $CON(R_6R_7)$, CH_2NO_2, NO_2, CH_2R_8, CHR_9, -CH=N-OR_{10}, -C=CH-R_5, $NHCOC(R_8R_9)$, $NHCOOR_{10}$, $CH(OAc)_2$, OR_5, SR_5, $-C(R_9)NO_2$, (C_1-C_{12})-alkyl substituted with one or more of F, Cl, Br, I, OR_4 or SR_4,

wherein R_5 is H, optionally substituted (C_1-C_{12})-alkyl, (C_3-C_{12})-cycloalkyl, aryl, heteroaryl, (C_1-C_6)-alkoxy, or (C_1-C_6)-alkyl substituted with one or more of F, Cl, Br, I or OH;

R_6 and R_7 is independently selected from H, optionally substituted (C_1-C_{12})-alkyl, (C_3-C_{12})-cycloalkyl, or (C_1-C_6)-alkoxy;

R_8 and R_9 is independently selected from H, (C_1-C_6)-alkyl, F, Cl, Br, (C_1-C_{12})-alkyl substituted with one or more of F, Cl, Br, I, OR_5, SR_5, $N(R_6R_7)$ wherein R_5, R_6 and R_7 is the same as defined earlier, R_{10} is H, optionally substituted (C_1-C_{12})-alkyl, (C_3-C_{12})-cycloalkyl, (C_1-C_6)-alkoxy, (C_1-C_6)-alkyl, aryl, or heteroaryl; and

W is CH_2, CO, -CH_2 NH-, -$NHCH_2$-, -CH_2NHCH_2-, -CH_2-$N(R_{11})CH_2$-, -$CH_2(R_{11})$N-, $CH(R_{11})$, S, $CH_2(CO)$, NH,

wherein R_{11} is optionally substituted (C_1-C_{12})-alkyl, (C_3-C_{12})-cycloalkyl, (C_1-C_6)-alkoxy, (C_1-C_6)-alkyl, aryl or heteroaryl; and

R_{12} is a leaving group.

INTERNATIONAL SEARCH REPORT

IB2004/003829

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D263/20 C07D295/205

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D

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, BEILSTEIN Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 93/23384 A (THE UPJOHN COMPANY) 25 November 1993 (1993-11-25)	1,5,6, 13-15, 23,24
Y	page 33 - page 36; claims 1,2,4,5,7,9; examples 1,7,21,25	2-4, 7-12, 16-22
X	WO 02/06278 A (RANBAXY LABORATORIES LIMITED; MEHTA, ANITA; ARORA, SUDERSHAN, K; DAS,) 24 January 2002 (2002-01-24) cited in the application	24
Y	claims 1-3,7-24; example 55	1-23

-/--

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

[X] Patent family members are listed in annex.

° Special categories of cited documents :

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

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

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

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

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

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

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

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

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
14 February 2005	24/02/2005

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	Hanisch, I

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 03/007870 A (RANBAXY LABORATORIES LIMITED; MEHTA, ANITA; ARORA, SUDERSHAN, K; DAS,) 30 January 2003 (2003-01-30) cited in the application	24
Y	page 9, line 11 - page 10, line 24; claims 1-5,17-34; example 55	1-23
X	WO 03/002560 A (VITA-INVEST, S.A; MOURELLE MANCINI, MARISABEL; HUGUET CLOTET, JUAN; HI) 9 January 2003 (2003-01-09)	1,5,6, 13-15, 17-19,23
Y	* page 26 - page 28; reference examples 1-3, 8, 18, 20, 23, 29, 36	2-4, 7-12,16
X	TUCKER J A ET AL: "PIPERAZINYL OXAZOLIDINONE ANTIBACTERIAL AGENTS CONTAINING A PYRIDINE, DIAZENE, OR TRIAZENE HETEROAROMATIC RING" JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY. WASHINGTON, US, vol. 41, no. 19, 1998, pages 3727-3735, XP001203467 ISSN: 0022-2623	24
Y	* page 3727, column 2; scheme 1; table 1 *	1-23
X	PAE A N ET AL: "Synthesis and In Vitro Activity of new Oxazolidinone Antibacterial Agents Having Substituted Isoxazoles" BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, OXFORD, GB, vol. 9, 1999, pages 2679-2684, XP002301080 ISSN: 0960-894X page 2680; compounds 6A-6L,8A-8R	24
X	PAE A N ET AL: "3D QSAR studies on new oxazolidinone antibacterial agents by comparative molecular field analysis" BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, OXFORD, GB, vol. 9, no. 18, 20 September 1999 (1999-09-20), pages 2685-2690, XP004179952 ISSN: 0960-894X page 2685; tables 2,3	24
X	WO 97/30981 A (PHARMACIA & UPJOHN COMPANY; GADWOOD, ROBERT, C; BARBACHYN, MICHAEL, R;) 28 August 1997 (1997-08-28) claims 1-5; examples 2,5,11-31	24
X	WO 98/01447 A (ZENECA LIMITED; BETTS, MICHAEL, JOHN; DARBYSHIRE, CATHERINE, JANE) 15 January 1998 (1998-01-15) the whole document	24

-/--

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 02/48139 A (PHARMACIA & UPJOHN COMPANY; THOMASCO, LISA, MARIE; GADWOOD, ROBERT, C) 20 June 2002 (2002-06-20) claim 1; examples 2,4	24
X	DU YU ET AL: "Synthesis and antibacterial activity of linezolid analogUES" BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, OXFORD, GB, vol. 12, 2002, pages 857-859, XP002245432 ISSN: 0960-894X figure 1; compounds 1A-1C	24
X	IN HWA CHUNG ET AL: "SYNTHESIS AND IN VITRO ANTIBACTERIAL ACTIVITY OF QUATERNARY AMMONIUM CEPHALOSPORIN DERIVATIVES BEARING OXAZOLIDINONE MOIETY" ARCHIVES OF PHARMACAL RESEARCH, NATL. FISHERIES UNIVERSITY, PUSAN, KR, vol. 22, no. 6, 1999, pages 579-584, XP001037701 ISSN: 0253-6269 figure 2; compound 3	24
P,X	WO 2004/018439 A (ORCHID CHEMICALS & PHARMACEUTICALS LTD; AGARWAL, SHIV, KUMAR; GUHA, MR) 4 March 2004 (2004-03-04) page 30, line 7 - page 43, line 18; claim 1; example 50	1,5,6, 13-15, 22-24

INTERNATIONAL SEARCH REPORT

IB2004/003829

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9323384 A	25-11-1993	AT 219770 T	15-07-2002
		AU 668733 B2	16-05-1996
		AU 4287793 A	13-12-1993
		CA 2133079 A1	25-11-1993
		CN 1079964 A ,C	29-12-1993
		CZ 9402505 A3	16-08-1995
		DE 69332061 D1	01-08-2002
		DE 69332061 T2	07-11-2002
		DK 640077 T3	14-10-2002
		EP 0640077 A1	01-03-1995
		ES 2180545 T3	16-02-2003
		FI 945246 A	08-11-1994
		HU 72296 A2	29-04-1996
		HU 9500659 A3	28-11-1995
		IL 105555 A	15-07-1998
		JP 3255920 B2	12-02-2002
		JP 7506829 T	27-07-1995
		MX 9302665 A1	01-11-1993
		NO 944237 A	04-01-1995
		PL 174909 B1	30-10-1998
		PL 174850 B1	30-09-1998
		PT 640077 T	29-11-2002
		RU 2105003 C1	20-02-1998
		SK 133794 A3	07-06-1995
		WO 9323384 A1	25-11-1993
		US 5547950 A	20-08-1996
		US 5700799 A	23-12-1997
		ZA 9302855 A	24-10-1994
WO 0206278 A	24-01-2002	AU 6937001 A	30-01-2002
		BR 0112826 A	24-06-2003
		CA 2415965 A1	24-01-2002
		CN 1447808 T	08-10-2003
		CZ 20030228 A3	18-06-2003
		EP 1303511 A1	23-04-2003
		HU 0302918 A2	29-12-2003
		WO 0206278 A1	24-01-2002
		JP 2004504321 T	12-02-2004
		MX PA03000503 A	14-10-2003
		NZ 523700 A	26-11-2004
		SK 1402003 A3	05-08-2003
		US 2004242591 A1	02-12-2004
		US 2002103186 A1	01-08-2002
		ZA 200300471 A	29-10-2003
WO 03007870 A	30-01-2003	AU 6937001 A	30-01-2002
		BR 0112826 A	24-06-2003
		CA 2415965 A1	24-01-2002
		EP 1303511 A1	23-04-2003
		EP 1409465 A2	21-04-2004
		EP 1409464 A1	21-04-2004
		HU 0302918 A2	29-12-2003
		WO 03008389 A1	30-01-2003
		WO 03007870 A2	30-01-2003
		JP 2004504321 T	12-02-2004
		MX PA03000503 A	14-10-2003
		NZ 523700 A	26-11-2004
		SK 1402003 A3	05-08-2003

INTERNATIONAL SEARCH REPORT

IB2004/003829

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 03007870 A		US 2004254162 A1	16-12-2004
		US 2004242591 A1	02-12-2004
WO 03002560 A	09-01-2003	ES 2186550 A1	01-05-2003
		BR 0210667 A	05-10-2004
		CA 2450982 A1	09-01-2003
		CZ 20040101 A3	14-07-2004
		EE 200400004 A	16-02-2004
		EP 1401834 A1	31-03-2004
		HR 20031063 A2	30-04-2004
		HU 0400370 A2	30-08-2004
		WO 03002560 A1	09-01-2003
		JP 2004521147 T	15-07-2004
		MX PA04000185 A	18-03-2004
		SK 572004 A3	03-08-2004
		US 2004147545 A1	29-07-2004
WO 9730981 A	28-08-1997	AT 221521 T	15-08-2002
		AU 703831 B2	01-04-1999
		AU 1954797 A	10-09-1997
		CA 2243706 A1	28-08-1997
		CN 1206410 A ,C	27-01-1999
		DE 69714418 D1	05-09-2002
		DE 69714418 T2	16-01-2003
		DK 883611 T3	02-12-2002
		EP 0883611 A1	16-12-1998
		ES 2180945 T3	16-02-2003
		HK 1017033 A1	02-08-2002
		ID 18467 A	09-04-1998
		JP 2000505084 T	25-04-2000
		NZ 331011 A	28-04-2000
		PT 883611 T	31-12-2002
		SI 883611 T1	31-12-2002
		TW 442460 B	23-06-2001
		WO 9730981 A1	28-08-1997
		US 5736545 A	07-04-1998
		ZA 9701287 A	14-08-1998
WO 9801447 A	15-01-1998	AU 3352197 A	02-02-1998
		EP 0918770 A1	02-06-1999
		WO 9801447 A1	15-01-1998
		JP 2000514084 T	24-10-2000
		ZA 9705951 A	06-01-1998
WO 0248139 A	20-06-2002	US 2003073696 A1	17-04-2003
		AU 3401602 A	24-06-2002
		CA 2432739 A1	20-06-2002
		EP 1368326 A2	10-12-2003
		JP 2004520298 T	08-07-2004
		WO 0248139 A2	20-06-2002
		US 2003232840 A1	18-12-2003
		US 2003232008 A1	18-12-2003
WO 2004018439 A	04-03-2004	WO 2004018439 A1	04-03-2004