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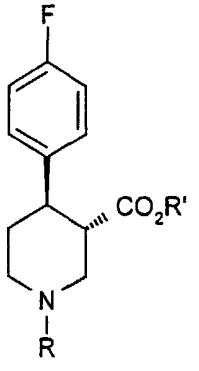
(54) Title: PROCESS FOR THE PREPARATION OF 4-(FLUOROPHENYL)PIPERIDINE ESTERS



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(57) **Abstract:** Firstly a process for the preparation of the (-) trans ester of structure (4), [a valuable intermediate in the preparation of paroxetine] comprising resolution of the corresponding racemic cis ester by the formation of a salt with a chiral acid to give the (+) cis ester, followed by epimerisation of the (+) cis ester with a strong base. Secondly a process for the preparation of a crystalline salt of a racemic trans compound of structure (4) comprising contacting a solution of racemic trans compound of structure (4) with a suitable acidic component, isolating the crystalline product and optionally recrystallising the product. Thirdly a process for the preparation of the (-) trans ester of structure (4) which comprises forming a solution of the product of the process of the second aspect of this invention and a chiral acid, and seeding the solution with a crystalline salt formed from the (-) trans product of the process of the first aspect of this invention and the same chiral acid.

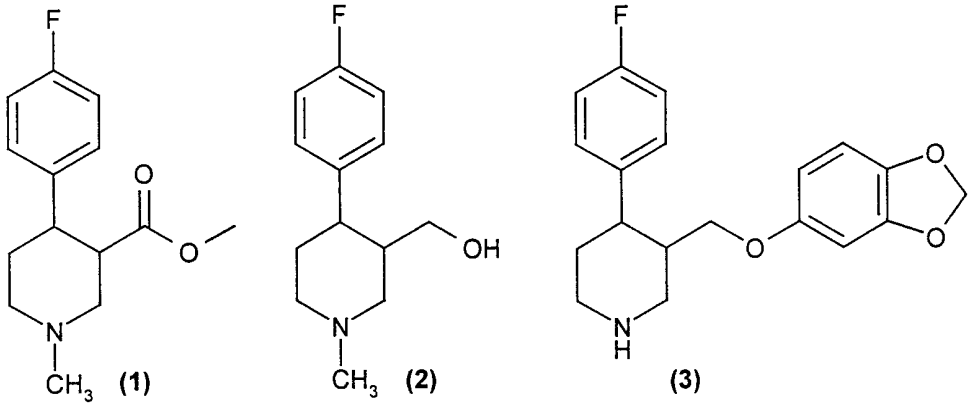
WO 01/29002 A1

PROCESS FOR THE PREPARATION OF 4-(FLUOROPHENYL)PIPERIDINE ESTERS

The present invention relates to novel piperidine compounds which are valuable intermediates for preparing pharmaceutically active compounds, and processes thereto.

Pharmaceutical products with antidepressant and anti-Parkinson properties are described in US 3,912,743 and US 4,007,196. An especially important compound among those disclosed is paroxetine, the (-) *trans* isomer of 4-(4'-fluorophenyl)-3- (3',4'-methylene dioxyphenoxymethyl)piperidine. This compound is used in therapy as the hydrochloride salt to treat *inter alia* depression, obsessive compulsive disorder (OCD) and panic.

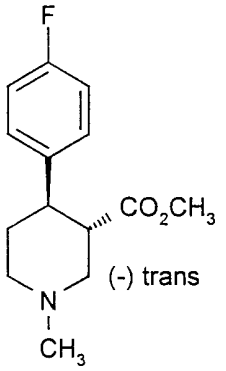
Piperidine compounds of structure (1) and (2) are described in US 4,007,196, EP 0219934, and Acta Chemica Scandinavica (1996) volume 50 page 164 as chemical intermediates useful for the manufacture of paroxetine (3).



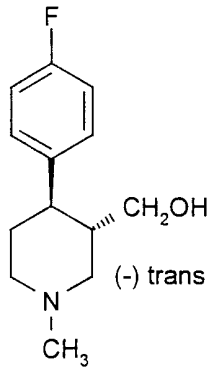
Thus in the process described in US-A-4007196, arecoline base is liberated from the hydrobromide salt and reacted with the Grignard reagent 4-fluorophenyl magnesium bromide to give a piperidine ester of structure (1). This piperidine ester is converted to a piperidine carbinol of structure (2), which is coupled with sesamol, then deprotected, to give paroxetine (3).

Paroxetine is the (-) trans isomer of 4-(4'-fluorophenyl)-3-(3',4'-methylenedioxy-phenoxymethyl)-piperidine. The above described processes produce compounds of structure (1) as a mixture of enantiomers, and conversion of compounds of structure (1) to useful pharmaceuticals will normally require a resolution stage.

Particularly useful compounds of structure (1) and (2) are therefore those where the stereo-configuration is (-) *trans*-, that is a compounds of structure (A) and (B), as this configuration corresponds to that of paroxetine.



(A)



(B)

There are two possible approaches to the preparation of the (-) trans carbinol, compound (B). One approach is to reduce compound (1) to compound (2), and then carry out a resolution step to give compound (B). Such an approach is described in Examples 5 and 8 of EP 0223, 334, where a racemic carbinol of structure (2) is resolved using either nitrotartanilic acid or di-p-toluoyl tartaric acid.

The second approach is to first produce the (-) trans ester compound (A), and subsequently reduce this to compound (B). The second approach is clearly advantageous, as only half the quantity of hydride reducing agent is required, representing a significant cost saving.

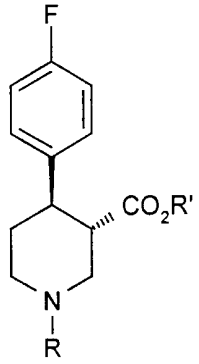
This application provides processes which enable the second approach to be carried out on a manufacturing scale. This application further provides novel salts of piperidine esters which are useful in the isolation, purification and resolution of such piperidine esters.

In the process described in US 4,007,196 and Acta Chemica Scandinavica (1996) volume 50 page 164, arecoline is reacted with 4-fluorophenylmagnesium bromide to give a compound of structure (1) as a mixture of racemic cis- and trans isomers, which is converted to a racemic trans-compound of structure (1) by reaction with sodium methoxide in an organic solvent at elevated temperature.

In the process described in EP 0219934, reduction of a quaternary pyridinium salt produces a compound of structure (1) exclusively in the racemic cis- configuration. This is similarly epimerised to a racemic trans-compound of structure (1) by reaction with sodium methoxide in an organic solvent at elevated temperature.

An outline method for the chemical resolution of trans 1-methyl-3-carbomethoxy-4-(4'-fluorophenyl) piperidine using unspecified optical forms of mandelic acid or dibenzoyl tartaric acid has been described in the literature in the form of a flowchart [Acta Chemica Scandinavica (1996) volume 50 page 164], but no details of the conditions are given. The same flowchart outlines the reduction of the (-) trans ester (A) to the (-) trans carbinol (B).

We have made numerous attempts carry out this resolution procedure but have been unable to obtain any crystallise salts using either mandelic acid or dibenzoyl tartaric acid in a wide range of organic solvents. In addition, no chemical or physical properties for the individual (+) and (-) optical isomers of trans 1-methyl-3-carbomethoxy-4-(4'-fluorophenyl) piperidine or analogous trans compounds of structure (4) below, in which R and R' are independently an alkyl, aryl, or arylalkyl group, most suitably lower alkyl, have been reported, either as salts or in the free base form.



(4)

We therefore conclude that no workable process for obtaining (-) trans 1-methyl-3-carbomethoxy-4-(4'-fluorophenyl) piperidine (A) or analogous resolved trans compounds of structure (4) is available in the prior art.

In addition, no description or preparation of the individual (+) and (-) isomers of cis 1-methyl-3-carbomethoxy-4-(4'-fluorophenyl) piperidine or analogous resolved cis compounds corresponding to structure (4) has previously been described.

In a first aspect, the present invention is based on the discovery that salts of the cis ester of structure (1) with chiral acids may be prepared and used to generate novel (+) cis and (-) cis isomers of compound (1).

In addition we have surprisingly found that the desired (-) trans ester of structure (A) can be obtained from the racemic cis ester by a novel procedure which comprises resolution of the racemic cis ester by the formation of a salt with a chiral acid to give the (+) cis form, followed by an epimerisation reaction with a strong base. In this process inversion of configuration occurs, providing the (-) trans ester in good yield and high optical purity, suitable for reduction to the (-) trans form of the carbinol, compound (B).

Accordingly the first aspect of the present invention provides a process for the preparation of the (-) trans ester of structure (4), the process comprising resolution of the corresponding racemic cis ester by the formation of a salt with a chiral acid to give the (+) cis ester, followed by epimerisation of the (+) cis ester with a strong base.

In structure (4), R' may be any group that is easily removable, for example by hydrolysis or reduction, for example using lithium aluminium hydride, to generate the corresponding carbinol. Suitable groups include methyl and ethyl. Similarly R may be any N-protecting group that is easily removable. Suitable groups include methyl and benzyl.

The process of the first aspect of this invention is particularly convenient as the racemic cis ester starting material is a crystalline solid which can be readily isolated. The racemic cis ester may be prepared as in EP 0219934 mentioned above. Alternatively a mixture of racemic cis and trans esters may be prepared as in US 4,007,196 and Acta Chemica Scandinavica (1996) volume 50 page 164 mentioned above, and the racemic cis ester isolated as a crystalline salt. Surprisingly we have found that treatment of the racemic

cis/trans mixture with a chiral acid results initially in crystallisation of a racemic cis salt, which on recrystallisation yields predominantly (+) cis salt.

Accordingly in a typical procedure, the racemic cis ester is obtained by treating a racemic cis/trans mixture of the ester with a chiral acid to obtain a crystalline salt of the racemic cis ester and the chiral acid, and recrystallising the salt to obtain a salt of the (+) cis ester, which is treated with a base to recover the (+) cis ester for epimerisation.

Crystalline chiral acid salts of the racemic cis-ester of structures (4) and (1), and of the (+) and (-) isomers, are believed to be novel.

The racemic cis-ester may be liberated from the racemic cis-ester salt by treatment in solution with a base, such as aqueous sodium hydroxide, and isolated. Treatment of a solution of the racemic cis-ester with appropriate chiral acids allows the formation of crystalline salts of the individual (+) isomers (for example with L(-) dibenzoyl tartaric acid or (+)-di-p-toluoyl-D-tartaric acid) and (-) isomers (for example with (-)-di-p-toluoyl-L-tartaric acid).

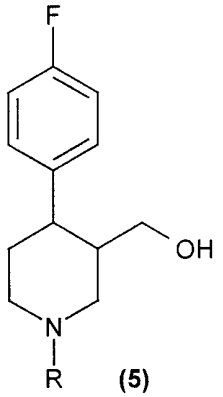
The (+) and (-) isomers of the cis-compound of structures (4) and (1) liberated from the chiral salts by treatment with a base are also believed to be novel.

The (-) cis esters of structures (4) and (1) may be epimerised with a strong base to obtain the corresponding (+) trans esters, which are also believed to be novel.

In a second aspect, the present invention is based on the surprising discovery that, despite the failure of the racemic trans ester to form salts directly with chiral acids, a limited number of non-chiral acids, for example citric acid, oxalic acid, phosphoric acid hydrobromic acid and hydroiodic acid can be used to form crystalline salts with the crude racemic trans ester.

Such crystalline salts are useful and convenient intermediates for the large scale isolation and purification of the racemic trans ester, the free base of which is an oil and otherwise

difficult to isolate in pure form. The purified racemic trans ester of structure (4) may be used to prepare the racemic trans carbinol of structure (5) which may be resolved and converted to paroxetine by known methods.



(5)

Accordingly the second aspect of the present invention provides a process for the preparation of a crystalline salt of a racemic trans compound of structure (4) which comprises contacting a solution of racemic trans compound of structure (4) with a suitable acidic component, isolating the crystalline product and optionally recrystallising the product.

We have found that citric acid, oxalic acid phosphoric acid hydrobromic acid and hydroiodic acid are especially suitable for the formation of such salts, particularly for compounds of structure (1) i.e. structure (4) where R is methyl.

Crystalline salts of the racemic trans compound of structures (4) and (1) are believed to be novel.

Similarly formed salts of the racemic cis esters with non-chiral acids are also believed to be novel.

Preferably the acidic component or a solution thereof is added to a solvent extract of the racemic trans compound of structure (4) from the previous reaction step. Suitable solvents include toluene, optionally with an additional solvent such as acetone.

The racemic trans compound of structure (4) may be liberated in purified form from the crystalline salt by conventional means, for example by treatment with an inorganic base followed by extraction with a solvent such as toluene. In a particularly useful aspect of the invention the extract of the purified racemic trans compound is used directly in the reduction step to generate a racemic trans carbinol of structure (5). This reduction may be carried out with a reducing agent such as lithium aluminium hydride, optionally employing an additional solvent such as tetrahydrofuran.

In a third aspect, the present invention is based on the surprising discovery that the pure (-) trans ester of structure (4) or (1) produced in accordance with the first aspect of this invention may be used to form crystalline salts with non-chiral and chiral acids. The chiral acid salts may be used as seed crystals to enable the otherwise extremely difficult resolution of racemic trans ester with chiral acids to be carried out, particularly when the racemic trans ester has first been purified using the second aspect of this invention.

We have surprisingly found that although a crystalline salt could not be generated by reaction of the pre-formed (-) trans ester of structure (1) with dibenzoyl tartaric acid, the acid allegedly employed in the prior art, it was possible to form a crystalline salt between the pre-formed (-) trans ester of structure (1) and di-toluoyl tartaric acid. In addition , we have been able to carry out a resolution of the racemic trans ester of structure (1) using the aforementioned di-toluoyl tartaric acid salt as seeds.

Accordingly the third aspect of the present invention provides a process for the preparation of the (-) trans ester of structure (4) which comprises forming a solution of the product of the process of the second aspect of this invention and a chiral acid, and seeding the solution with a crystalline salt formed from the (-) trans product of the process of the first aspect of this invention and the same chiral acid.

Similarly, a crystalline salt formed directly between a (+) trans ester isomer (obtained by epimerisation of a (-) cis ester isomer as described previously) and a chiral acid may be used as seed to obtain a crystalline (+) ester salt from a solution of the racemic ester salt.

Crystalline salts of the (-) trans and (+) trans compound of structures (4) and (1) are believed to be novel.

Compounds of structure (4) may be converted to the active compound paroxetine using conventional procedures disclosed in US-A-3912743 or US-A-4007196, whereby the piperidine ester of structure (4) is reduced to a piperidine carbinol of structure (5), which is coupled with sesamol, then deprotected, to give paroxetine (3).

The present invention includes within its scope the compound paroxetine and its pharmaceutically acceptable salts, particularly paroxetine hydrochloride, especially as an anhydrate or the hemihydrate, and paroxetine methanesulphonate, when obtained via any aspect of this invention, and any novel intermediates resulting from the described procedures.

Paroxetine free base may be converted to paroxetine methanesulphonate by treatment with methanesulphonic acid or a labile derivative thereof, for example a soluble salt such as ammonium methanesulphonate. Paroxetine hydrochloride may be prepared by treatment of paroxetine free base with a source of hydrogen chloride, for example gaseous hydrogen chloride, or a solution thereof, or aqueous hydrochloric acid.

Paroxetine and its salts obtained using this invention may be formulated for therapy in the dosage forms described in EP-A-0223403 or WO96/24595, either as solid formulations or as solutions for oral or parenteral use.

Therapeutic uses of paroxetine, especially paroxetine hydrochloride or methanesulphonate, obtained using this invention include treatment of: alcoholism, anxiety, depression, obsessive compulsive disorder, panic disorder, chronic pain, obesity, senile dementia, migraine, bulimia, anorexia, social phobia, pre-menstrual syndrome (PMS), adolescent depression, trichotillomania, dysthymia, and substance abuse, referred to below as "the Disorders".

Pharmaceutical compositions using active compounds prepared in accordance with this invention are usually adapted for oral administration, but formulations for dissolution for parental administration are also within the scope of this invention.

The composition is usually presented as a unit dose composition containing from 1 to 200mg of active ingredient calculated on a free base basis, more usually from 5 to 100 mg, for example 10 to 50 mg such as 10, 12.5, 15, 20, 25, 30 or 40 mg by a human patient. Most preferably unit doses contain 20 mg of active ingredient calculated on a free base basis. Such a composition is normally taken from 1 to 6 times daily, for example 2, 3 or 4 times daily so that the total amount of active agent administered is within the range 5 to 400 mg of active ingredient calculated on a free base basis. Most preferably the unit dose is taken once a day.

Preferred unit dosage forms include tablets or capsules, including formulations adapted for controlled or delayed release.

The compositions of this invention may be formulated by conventional methods of admixture such as blending, filling and compressing. Suitable carriers for use in this invention include a diluent, a binder, a disintegrant, a colouring agent, a flavouring agent and/or preservative. These agents may be utilised in conventional manner, for example in a manner similar to that already used for marketed anti-depressant agents.

Accordingly, the present invention also provides:
a pharmaceutical composition for treatment or prophylaxis of one or more of the Disorders comprising paroxetine or a pharmaceutically acceptable salt such as the mesylate or hydrochloride obtained using the process of this invention and a pharmaceutically acceptable carrier;
the use of paroxetine or a pharmaceutically acceptable salt such as the mesylate or hydrochloride obtained using the process of this invention to manufacture a medicament for the treatment or prophylaxis of one or more of the Disorders; and
a method of treating the Disorders which comprises administering an effective or prophylactic amount of paroxetine or a pharmaceutically acceptable salt such as the

mesylate or hydrochloride obtained using the process of this invention to a person suffering from one or more of the Disorders.

This invention is illustrated by the following Examples.

Analytical Procedures

The stereo configuration of piperidine esters of structure (1) may be determined by conventional means, for example by NMR. The cis ester of structure (1) gives an NMR signal in deuterochloroform at ca δ 3.51 ppm for the methyl protons of the ester group, whereas the trans ester of structure (1) has a signal at ca δ 3.44.

The optical purity of piperidine esters of structure (1) may be assessed by measurement of optical rotation, or by chiral HPLC or preferably by chiral capillary electrophoresis. A review entitled "Separation of optically active pharmaceuticals using capillary electrophoresis" by T.J. Ward, and K. D. Ward has been published in Chem. Anal. (N. Y.) (1997), volume 142 pages 317-344.

Example 1

Preparation of trans-1-methyl-3-carbomethoxy-4-(4'-fluorophenyl) piperidine oxalate

Crude trans-1-methyl-3-carbomethoxy-4-(4'-fluorophenyl)piperidine (2.60g) was added to a solution of oxalic acid (0.95g) in ethanol (30 ml) and stirred to give a clear solution. The solution was diluted with hexane (30 ml) and diethyl ether (60 ml), stirred for 1 hour at ambient temperature then stored at 5 °C for a further 1 hour. The resulting crystals were collected by filtration, washed with diethyl ether (20 ml) and dried.

Yield 1.98g.

The IR spectrum (attenuated total reflectance) showed bands at *inter alia* 3038, 2951, 1734, 1601, 1512, 1436, 1330, 1225, 1173, 1161, 1140, 1000, 959, 797, 754, 711 cm^{-1}.

X-ray diffractogram, major peaks ($CuK_{2\alpha}$):

Angle [$^0 2\theta$]	Rel. Int [%]
7.77	24.8
8.98	37.0
12.61	41.7
14.84	24.5
16.45	84.8
18.17	95.2
20.10	33.7
23.63	100.0
25.68	32.5
26.73	37.8
28.60	29.9

Example 2

Regeneration of trans-1-methyl-3-carbomethoxy-4-(4'-fluorophenyl) piperidine from the oxalate salt

Trans-1-methyl-3- carbomethoxy-4-(4'-fluorophenyl)piperidine oxalate (1.0g) was suspended in ethyl acetate (20 ml) and 10%w/v aqueous sodium hydroxide (10 ml) was added to dissolve the solid. The layers were separated and the aqueous layer was extracted again with ethyl acetate (20 ml). The combined organic layers were dried over magnesium sulphate, and the solvent removed by evaporation to give pure trans –1-methyl-3-carbomethoxy-4-(4'-fluorophenyl)piperidine as an oil.

Yield 0.59 g.

Example 3

Preparation of trans-1-methyl-3-carbomethoxy-4-(4'-fluorophenyl)-piperidine hydrobromide.

48% aqueous hydrobromic acid (0.36 g) was added to a solution of trans-1-methyl-3-carbomethoxy-4-(4'-fluorophenyl)-piperidine (0.50 g) in ethanol (15 ml) and mixture stirred for 2 hours. The resulting suspension was stored at 5°C for 72 hours then the crystals were filtered and dried in vacuum.

Yield 0.30 g.

The IR spectrum (attenuated total reflectance) showed bands at *inter alia* 2949, 2675, 1735, 1512, 1433, 1331, 1209, 1168, 1143, 961, 831, 796 cm^{-1}.

The X-ray powder diffractogram ($CuK_{2\alpha}$) showed the following significant peaks

Angle [$^{o}2\theta$]	Counts
7.4	182
9.0	269
13.9	224
16.4	1319
18.3	677
18.6	289
21.2	191
22.0	585
23.3	882
25.1	729
26.9	250
27.2	265
27.9	426
29.1	295
31.0	383
32.1	173
32.7	186
34.2	404

Example 4

Preparation of hydroiodic acid salt of trans-1-methyl-3-carbomethoxy-4-(4'-fluorophenyl)piperidine

A solution of 55% hydroiodic acid (0.19 g) in ethanol (5 ml) was mixed with a solution of trans-1-methyl-3-carbomethoxy-4-(4'-fluorophenyl)piperidine (0.20 g) in ethanol (5 ml) and the clear solution was stirred well. The solvent was removed by evaporation to give the product as a yellow solid, whiich was recrystallised from ethyl acetate.

The IR spectrum (attenuated total reflectance) showed bands at *inter alia* 2932, 2701, 1735, 1511, 1329, 1226, 1163, 959 and 794 cm^{-1}.

The X-ray powder diffractogram ($CuK_{2\alpha}$) showed the following significant peaks

Angle [°2θ]	Counts
7.4	123
12.9	57
13.6	69
15.9	288
17.7	140
18.3	282
20.2	85
21.2	223
22.5	460
23.9	122
24.8	458
26.8	153
27.2	266
28.4	136
29.4	137
30.0	115
31.8	108
32.1	129
33.0	98
33.7	146

Example 5

Preparation of the citric acid salt of trans-1-methyl-3-carbomethoxy-4-(4'-fluorophenyl)piperidine

A solution of citric acid (0.20 g) in acetone (5 ml) was added to trans-1-methyl-3-carbomethoxy-4-(4'-fluorophenyl)piperidine (0.25 g) and stirred well to give a clear solution. The solution was concentrated to approximately 3 ml by evaporation under reduced pressure, whereupon crystals began to form. The crystalline salt was collected by filtration, washed with acetone (5 ml) and dried under vacuum

Yield 0.30 g.

Analysis by NMR showed that the molar ratio of citric acid to trans-1-methyl-3-carbomethoxy-4-(4'-fluorophenyl)piperidine was 1:1.

The IR spectrum (attenuated total reflectance) showed bands *inter alia* at 1727, 1583, 1512, 1436, 1330, 1208, 1174, 1139, 1084, 963, 831, 796, 773, 721 and 664 cm^{-1}.

The X-ray powder diffractogram ($CuK_{2\alpha}$) showed the following significant peaks

Angle [°2θ]	Rel. Int [%]
3.9	100.0
7.5	17.0
10.2	42.5
12.7	71.6
13.4	28.3
14.9	84.9
16.3	74.9
17.5	57.8
19.0	50.1
20.6	71.0
21.5	72.3
26.3	44.4
34.0	56.7

Example 6

Preparation of the phosphate salt of trans-1-methyl-3-carbomethoxy-4-(4'-fluorophenyl)piperidine.

A 10% v/v solution of orthophosphoric acid in propan-2-ol (0.68 ml) was added to a solution of trans-1-methyl-3-carbomethoxy-4-(4'-fluorophenyl)piperidine (0.25 g) in propan-2-ol (5 ml) to give a white oil. Crystallisation was induced by stirring with additional propan-2-ol (10 ml) and n-hexane (15 ml) for 1 hour at ambient temperature. The suspension was stored at 4°C overnight, then the crystalline salt was collected by filtration and dried under vacuum.

Yield 0.23g.

Analysis by ion chromatography showed that the ratio of phosphoric acid to trans-1-methyl-3-carbomethoxy-4-(4'-fluorophenyl)piperidine was approximately 1:1.

The IR spectrum (attenuated total reflectance) showed bands *inter alia* at 1726, 1603, 1513, 1437, 1331, 1256, 1221, 1169, 1101, 1049, 888, 847, 796, 771 and 755 cm^{-1}.

The X-ray powder diffractogram ($CuK_{2\alpha}$) showed the following significant peaks:

Angle [$^{o}2\theta$]	Rel. Int [%]
5.5	16.6
13.4	38.2
14.0	50.2
15.0	7.9
16.1	4.5
18.5	100.0
20.2	69.7
22.9	20.2
24.4	77.6
25.5	22.5
26.5	9.0
28.1	28.5
29.8	9.8

Example 7

Resolution of cis 1-methyl-3-carbomethoxy-4-(4'-fluorophenyl)piperidine using L(-) dibenzoyl tartaric acid

i) Cis/trans 1-methyl-3-carbomethoxy-4-(4'-fluorophenyl)piperidine (2.18 g), prepared by the method of Example 1 of US 4,007,196, was dissolved in acetone (40 ml) and treated with L(-)-dibenzoyl tartaric acid (4.0 g). The mixture was allowed to stand at 5°C for several days, then the crystals were collected, washed with acetone and dried in vacuum.

Yield 2.73 g

NMR analysis confirmed that only the salt of the cis-form had crystallised. Analysis by chiral capillary electrophoresis showed that the ratio of (+) cis to (-) cis was 1:1.

ii) 1.0 g of the above salt was recrystallised by warming in methanol (10 ml) and storing the solution at 5 C for 18 hours. The resulting crystals were collected by filtration, washed with methanol and dried in vacuum. Chiral capillary electrophoresis showed that the ratio of (+) cis to (-) cis was 91:9.

(+) cis 1-methyl-3-carbomethoxy-4-(4'-fluorophenyl)piperidine L(-)-dibenzoyl tartrate may aso be prepared directly from racemic cis 1-methyl-3-carbomethoxy-4-(4'-fluorophenyl)piperidine by heating with L(-)-dibenzoyl tartaric acid in acetonitrile and allowing the mixture to cool.

Example 8

Preparation of (+)cis-1-methyl-3-carbomethoxy-4-(4'-fluorophenyl) piperidine (+)-di-p-toluoyl-D-tartrate from crude cis/trans ester.

i) Crude cis/trans-1-methyl-3-carbomethoxy-4-(4'-fluorophenyl)piperidine (20 g) was dissolved in acetone (100 ml) and mixed with a solution of (+)-di-p-toluoyl-D -tartaric acid monohydrate (33 g) in acetone (50 ml). The flask was sealed and stored at 5°C for 18 hours. The crystals were collected by filtration, washed with acetone (25 ml) and dried under vacuum.

Yield 28.31g

Chiral capillary electrophoresis showed that the ratio of (+) cis to (-) cis was approximately 1:1

ii) Cis-1-methyl-3-carbomethoxy-4-(4'-fluorophenyl)piperidine (+)-di-p-toluoyl- D-tartrate (25 g) was dissolved in boiling methanol (50 ml) then allowed to cool to room temperature. The flask was sealed and stored at 5°C for 4 days during which time crystals separated. These were collected by filtration, washed with acetone (10 ml) and dried under vacuum.

Yield 7.36g

Chiral capillary electrophoresis showed that the ratio of (+) cis to (-) cis was approximately 75:25

Example 9

Preparation of (+)cis-1-methyl-3-carbomethoxy-4-(4'-fluorophenyl) piperidine

Recrystallised (+) cis-1-methyl-3-carbomethoxy-4-(4'-fluorophenyl)piperidine (+)-di-p-toluoyl-D-tartrate (7 g) was suspended in a mixture of ethyl acetate (120 ml) and water (60 ml), and 10% w/v aqueous sodium hydroxide (10 ml) was added to dissolve the salt. The layers were separated and the aqueous phase was extracted again with ethyl acetate (60 ml). The combined ethyl acetate layers were dried over magnesium sulphate, and the solvent evaporated under reduced pressure to give (+) cis-1-methyl-3-carbomethoxy-4-(4'-fluorophenyl) piperidine as a crystalline solid.

Yield 2.18g.

$[\alpha]^{26}_{D}$ + 40° (c = 1, methanol)

(+) cis-1-methyl-3-carbomethoxy-4-(4'-fluorophenyl)piperidine be similarly liberated from the recrystallised L (-)-dibenzoyl tartrate salt as prepared in Example 7.

Example 10

Preparation of (+)cis-1-methyl-3-carbomethoxy-4-(4'-fluorophenyl) piperidine (+)-di-p-toluoyl-D-tartrate from the cis ester.

i) Cis-1-methyl-3-carbomethoxy-4-(4'-fluorophenyl)piperidine (1.0 g) prepared by the method of Example 2 of EP 0219934, was dissolved in acetone (5 ml) and mixed with a solution of (+)-di-p-toluoyl-D- tartaric acid monohydrate (1.6g) in acetone (5 ml). Crystals separated on stirring and the suspension was left to stand for several hours. The crystals were collected by filtration, washed with acetone (5 ml) and dried under vacuum.

Yield 2.11g.

Chiral capillary electrophoresis showed that the ratio of (+) cis to (-) cis was approximately 1:1

ii) Cis-1-methyl-3-carbomethoxy-4-(4'-fluorophenyl)piperidine (+)-di-p-toluoyl-D-tartrate (1.0 g) was dissolved in hot methanol (5 ml) then allowed to cool. The flask was stored at 5°C for 18 hours during which time crystals separated. The crystals were collected, washed with methanol (5 ml) and dried under vacuum

Chiral capillary electrophoresis showed that the ratio of (+) cis to (-) cis was approximately 90:10.

Example 11

Preparation of (-)cis-1-methyl-3-carbomethoxy-4-(4'-fluorophenyl)piperidine (-)-di-p-toluoyl-L-tartrate from the cis ester.

i) Cis-1-methyl-3-carbomethoxy-4-(4'-fluorophenyl)piperidine (1.0g) was dissolved in acetone (5 ml) and mixed with a solution of L(-)-di-p-toluoyl tartaric acid (1.52g) in acetone (5 ml). Crystals separated on stirring and the suspension was left to stand for several hours. The crystals were collected by filtration, washed with acetone (5 ml) and dried under vacuum.

Yield 1.79g.

ii) Cis-1-methyl-3-carbomethoxy-4-(4'-fluorophenyl)piperidine (-)-di-p-toluoyl-L-tartrate (1.0 g) was dissolved in hot methanol (5 ml) then allowed to cool. The flask was sealed and stored at 5°C for 7 hours during which time crystals separated. The crystals were collected by filtration, washed with methanol (5 ml) and dried under vacuum.

Yield 0.21g

Chiral capillary electrophoresis showed that the ratio of (-) cis to (+) cis was approximately 89 : 11

Example 12

Preparation of (-)cis-1-methyl-3-carbomethoxy-4-(4'-fluorophenyl)piperidine

(-) cis-1-methyl-3-carbomethoxy-4-(4'-fluorophenyl)piperidine is regenerated from the (-) cis-1-methyl-3-carbomethoxy-4-(4'-fluorophenyl)piperidine (-)-di-p-toluoyl-L-tartrate produced in Example 11 (ii) using the procedure of Example 9.

(-) cis-1-methyl-3-carbomethoxy-4-(4'-fluorophenyl)piperidine may also be prepared by employing D(+)-dibenzoyl tartaric acid in place of L(-)-dibenzoyl tartaric in the procedure described in Example 7, to give (-) cis-1-methyl-3-carbomethoxy-4-(4'-fluorophenyl)piperidine D(+)-dibenzoyl tartrate, and liberating the product from this salt using the procedure of Example 9.

The product has an optical rotation, $[\alpha]^{26}_{D}$ (c = 1, methanol), of about - 40°

Example 13

Preparation of (-) trans -1-methyl-3-carbomethoxy-4-(4'-fluorophenyl)-piperidine

(+) cis-1-methyl-3-carbomethoxy-4-(4'-fluorophenyl)piperidine, as prepared in Example 9, (0.35g), is dissolved in dry toluene (10 ml) and treated with sodium methoxide (0.15g). The mixture is heated to reflux under nitrogen for 2 hours, then allowed to cool to ambient temperature. The solution is washed with water (10 ml) followed by saturated aqueous sodium chloride (10 ml) and the toluene is evaporated under reduced pressure to give (-)-trans-1-methyl-3-carbomethoxy-4-(4'-fluorophenyl)piperidine as an oil. A yield of about 0.30g is obtained, having the following properties:

N.M.R. δ (CDCl3) ~ 7.15 (m, 2H), 6.95 (q, 2H), 3.44 (s, 3H, methyl ester), 3.10 (m, 1H), 2.88 (m, 2H), 2.75 (m, 1H), 2.18 (m, 2H), 1.80 (m, 2H).

Optical rotation $[\alpha]^{26}_{D}$ ca. - 44 ^{0} (c =1, methanol)

Example 14

Preparation of (+) trans -1-methyl-3-carbomethoxy-4-(4'-fluorophenyl)-piperidine

(-) cis-1-methyl-3-carbomethoxy-4-(4'-fluorophenyl)piperidine, as prepared in Example 12, (0.35g), is dissolved in dry toluene (10 ml) and treated with sodium methoxide (0.15g). The mixture is heated to reflux under nitrogen for 2 hours, then allowed to cool to ambient temperature. The solution is washed with water (10 ml) followed by saturated aqueous sodium chloride (10 ml) and the toluene is evaporated under reduced pressure to give (+)-trans-1-methyl-3-carbomethoxy-4-(4'-fluorophenyl)piperidine as an oil. A yield of about 0.30g is obtained, having the following properties:

N.M.R. δ (CDCl3) ~ 7.15 (m, 2H), 6.95 (q, 2H), 3.44 (s, 3H, methyl ester), 3.10 (m, 1H), 2.88 (m, 2H), 2.75 (m, 1H), 2.18 (m, 2H), 1.80 (m, 2H).

Optical rotation $[\alpha]^{26}_{D}$ ca. + 44 ^{0} (c =1, methanol)

Example 15

Preparation of L(-)-di-p-toluoyl tartaric acid salt of (-)-trans-1-methyl-3-carbomethoxy-4-(4'-fluorophenyl)piperidine.

L(-)-di-p-toluoyl tartaric acid (0.154 g) was added to (-)-trans-1-methyl-3-carbomethoxy-4-(4'-fluorophenyl)piperidine (0.10 g) and the mixture was stirred well in acetone (5 ml). The solvent was removed by evaporation to give an oil. Ethanol (5 ml) and water (10 ml) were added and crystallisation was induced by stirring. The crystals were collected by filtration dried under vacuum

Yield 0.14 g.

NMR indicated that a 1:1 salt had been formed

The IR spectrum showed bands *inter alia* at 1721,1610,1511,1436,1378,1331,1263,1177, 1105,1042,1020, 960, 899, 833, and 693 cm^{-1}.X-ray diffractogram major peaks ($CuK_{2\alpha}$):

Angle [°2θ]	Rel. Int [%]
8.4	10.8
11.6	12.2
12.6	52.3
13.2	59.7
14.1	85.6
15.5	10.4
16.7	86.1
18.4	100.0
20.3	56.1
21.2	57.0
21.7	87.7
22.5	73.3
24.2	56.6
26.6	35.6
27.3	50.7
29.5	33.2
30.9	29.4
31.7	26.0
33.1	31.9

Example 16

Preparation of D(+)-di-p-toluoyl tartaric acid salt of (+)-trans-1-methyl-3-carbomethoxy-4-(4'-fluorophenyl)piperidine

This salt may be prepared from (+)-trans-1-methyl-3-carbomethoxy-4-(4'-fluorophenyl)piperidine by following the procedure of Example 15 and replacing L(-)-di-p-toluoyl tartaric acid with D(+)-di-p-toluoyl tartaric acid.

Example 17

Resolution of trans-1-methyl-3-carbomethoxy-4-(4'-fluorophenyl)piperidine using seeds

A solution of L(-)-di-p-toluoyl tartaric acid (0.39 g) in ethyl acetate (12.5 ml) was mixed with a solution of racemic trans-1-methyl-3-carbomethoxy-4-(4'-fluorophenyl)piperidine (0.25 g) in o-xylene (12.5 ml) and the mixture was stirred well to give a clear solution. This solution was seeded with (-)-trans-1-methyl-3-carbomethoxy-4-(4'-fluorophenyl)piperidine L(-)-di-p-toluoyl tartrate (5 mg) and stirred for several hours. The

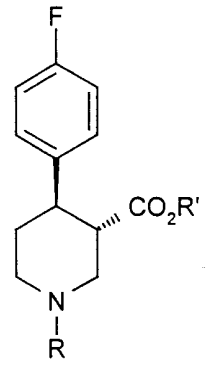
cloudy mixture was stored at 4°C for six days during which time more crystals formed. These were filtered and dried under vacuum.

Yield 0.17g.

Chiral capillary electrophoresis showed that the ratio of (-) trans to (+) trans was 90:10

CLAIMS

1. A process for the preparation of the (-) trans ester of structure (4)

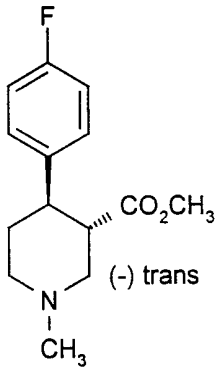


(4)

in which R and R' are independently an alkyl, aryl, or arylalkyl group, most suitably lower alkyl, the process comprising resolution of the corresponding racemic cis ester by the formation of a salt with a chiral acid to give the (+) cis ester, followed by epimerisation of the (+) cis ester with a strong base.

2. A process according to claim 1 in which the racemic cis ester is obtained by treating a racemic cis/trans mixture of the ester with a chiral acid to obtain a crystalline salt of the racemic cis ester and the chiral acid, and recrystallising the salt to obtain a salt of the (+) cis ester, which is treated with a base to recover the (+) cis ester for epimerisation.

3. A process according to claim 1 or 2 for the preparation of the (-) trans ester of structure (A)



(A)

4. (-) trans -1-methyl-3-carbomethoxy-4-(4'-fluorophenyl)-piperidine.

5. A process for the preparation of a crystalline salt of the racemic cis ester corresponding to structure (4) which comprises treating a solution of a racemic cis/trans mixture of the ester with a chiral acid and crystallising a salt of the racemic cis ester and the chiral acid.

6. (±) cis 1-methyl-3-carbomethoxy-4-(4'-fluorophenyl)piperidine L(-) dibenzoyl tartrate.

7. (±) cis-1-methyl-3-carbomethoxy-4-(4'-fluorophenyl) piperidine (+)-di-p-toluoyl-D-tartrate.

8. A process according to claim 4, further comprising recrystallising the salt to obtain a salt of the (+) cis ester.

9. A process for the preparation of a crystalline salt of the (+) cis ester corresponding to structure (4) which comprises treating a solution of the racemic cis ester with a chiral acid and crystallising a salt of the (+) cis ester and the chiral acid.

10. (+)cis 1-methyl-3-carbomethoxy-4-(4'-fluorophenyl)piperidine L(-) dibenzoyl tartrate.

11. (+)cis-1-methyl-3-carbomethoxy-4-(4'-fluorophenyl) piperidine (+)-di-p-toluoyl-D-tartrate.

12. A process for the preparation of a crystalline salt of the (-) cis ester corresponding to structure (4) which comprises treating a solution of the racemic cis ester with a chiral acid and crystallising a salt of the (-) cis ester and the chiral acid.

13. (-) cis-1-methyl-3-carbomethoxy-4-(4'-fluorophenyl)piperidine (-)-di-p-toluoyl-L-tartrate.

14. A process for the preparation of the (+) or (-) cis ester corresponding to structure (4) which comprises treating a crystalline salt of the (+) or (-) cis ester and a chiral acid with a base.

15. (+) cis-1-methyl-3-carbomethoxy-4-(4'-fluorophenyl) piperidine.

16. (-) cis-1-methyl-3-carbomethoxy-4-(4'-fluorophenyl) piperidine.

17. A process for the preparation of the (+) trans ester corresponding to structure (4) which comprises epimerising the (-) cis ester with a strong base.

18. (+) trans-1-methyl-3-carbomethoxy-4-(4'-fluorophenyl) piperidine.

19. A process for the preparation of a crystalline salt of a racemic trans or cis compound of structure (4) which comprises contacting a solution of the racemic trans or cis compound of structure (4) with a suitable acidic component, isolating the crystalline product and optionally recrystallising the product.

20. A process according to claim 19 for the preparation of a crystalline salt of the racemic trans or cis ester of structure (A).

21. A process according to claim 19 or 20 in which the acidic component is oxalic acid, hydrobromic acid, hydroiodic acid, citric acid or phosphoric acid.

22. (±) trans-1-methyl-3-carbomethoxy-4-(4'-fluorophenyl) piperidine oxalate.

23. (±) trans-1-methyl-3-carbomethoxy-4-(4'-fluorophenyl)-piperidine hydrobromide.

24. (±) trans-1-methyl-3-carbomethoxy-4-(4'-fluorophenyl)-piperidine hydroiodide.

25. (±) trans-1-methyl-3-carbomethoxy-4-(4'-fluorophenyl)-piperidine citrate.

26. (±) trans-1-methyl-3-carbomethoxy-4-(4'-fluorophenyl)-piperidine phosphate.

27. A process for the preparation of the (-) trans ester of structure (4) or (A) which comprises forming a solution of the trans ester salt of claim 19, 20 or 21, or of the free ester liberated therefrom, and a chiral acid, and seeding the solution with a crystalline salt formed from the product of claim 1, 2 or 3 and the same chiral acid.

28. (-)-trans-1-methyl-3-carbomethoxy-4-(4'-fluorophenyl)piperidine L(-)-di-p-toluoyl tartarate.

29. (+)-trans-1-methyl-3-carbomethoxy-4-(4'-fluorophenyl)piperidine D(+)-di-p-toluoyl tartarate.

30. A process for preparing paroxetine in which the (-) trans ester product of claim 1 or 17 is reduced to a carbinol, coupled with sesamol and deprotected.

31. A process for preparing paroxetine in which the racemic trans ester liberated from the product of claim 19 is reduced to a racemic carbinol, the racemic carbinol is resolved to the (-) trans isomer, coupled with sesamol and deprotected.

32. Paroxetine whenever obtained by a process as claimed in claim 30 or 31, or a pharmaceutically acceptable salt thereof.

33. A method of treating the Disorders which comprises administering an effective or prophylactic amount of paroxetine or a pharmaceutically acceptable salt such as the mesylate or hydrochloride of claim 32 to a person suffering from one or more of the Disorders.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB 00/04058

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D211/60

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, WPI Data, 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.
X	EP 0 219 934 A (BEECHAM GROUP PLC) 29 April 1987 (1987-04-29) cited in the application column 3, line 39 - line 47; example 2 ---	1-18, 28-33
Y	WO 98 45263 A (KOZIKOWSKI ALAN P ;UNIV GEORGETOWN (US); ARALDI GIAN LUCA (US)) 15 October 1998 (1998-10-15)	1-18, 28-33
A	page 11, line 16 -page 12, line 13; claims 11,13; figures 1,2; examples 1-4,11,12 --- -/--	19-26

[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
31 January 2001	08. 02. 01

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	Seymour, L

2

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INTERNATIONAL SEARCH REPORT

In ational Application No
PCT/GB 00/04058

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
A	ENGELSTOFT M ET AL: "SYNTHESIS AND 5HT MODULATING ACTIVITY OF STEREOISOMERS OF 3-PHENOXYMETHYL-4-PHENYLPIPERIDINES" ACTA CHEMICA SCANDINAVICA,DK,MUNKSGAARD, COPENHAGEN, vol. 50, no. 2, 1996, pages 164-169, XP002074608 ISSN: 0904-213X cited in the application schemes 2,4 ---	1-18, 28-33
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P,Y	WO 00 20390 A (UNIV GEORGETOWN) 13 April 2000 (2000-04-13) figures 14,15; examples 34,35,42-44 ---	1-18, 28-33
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A	EP 0 416 736 A (LILLY CO ELI) 13 March 1991 (1991-03-13) claim 1 ---	27
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2

INTERNATIONAL SEARCH REPORT

International application No.
PCT/GB 00/04058

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☒ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☒ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: 1-18, 28-30, 32 (part) and 33 (part)

   Synthesis of (-) or (+) trans esters of formula 4 starting from the racemic cis esters involving resolution with a chiral acid and an epimerisation step.

2. Claims: 19 - 27, 31, 32 (part) and 33 (part)

   Provision of salts of racemic trans or cis esters of formula 4 and resolution of solutions thereof by seeding.

INTERNATIONAL SEARCH REPORT

Information on patent family members

I. national Application No
PCT/GB 00/04058

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INTERNATIONAL SEARCH REPORT

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International Application No
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