SALTS OF PAROXETINE

The present invention relates to novel compounds, to processes for preparing them and to their use in treating medical disorders.

Pharmaceutical products with antidepressant and anti-Parkinson properties are described in US-A-3912743 and US-A-4007196. An especially important compound among those disclosed is paroxetine, the (-)*trans* isomer of 4-(4'-fluorophenyl)-3-(3',4'-methylenedioxy-phenoxymethyl)-piperidine. This compound is used in therapy as the hydrochloride salt for the treatment and prophylaxis of *inter alia* depression, obsessive compulsive disorder (OCD) and panic.

We have now surprisingly discovered novel salts of paroxetine which may be used as an alternative to the currently marketed hydrochloride, or as an intermediate in the preparation of the hydrochloride.

According to the present invention there is provided a novel salt of paroxetine with an acid selected from the group consisting of sulphuric, tartaric, oxalic, fumaric, propionic, formic, glutamic, succinic, benzoic, citric, nitric, phosphoric, 4-methylbenzenesulphonic, hypophosphorous, lactic, and mandelic acids and glycine.

Tartaric, glutamic, lactic and mandelic acids exist in enantiomeric forms and this invention includes salts with both the D and L-acids and racemic mixtures thereof, as well as with the symmetric *meso*-tartaric acid.

Sulphuric, tartaric, oxalic, fumaric, glutamic, and succinic acids are dibasic and the invention therefore includes both salts in which the ratio of paroxetine to acid (by mole) is 1:1 and salts in which the ratio of paroxetine to acid (by mole) is 2:1, as well as mixed salts with, for example, an alkali metal or ammonium cation.

Citric and phosphoric acids are tribasic and the invention therefore includes salts in which the ratio of paroxetine to acid (by mole) is 1:1, 2:1, and 3:1 respectively, as well as mixed salts with, for example, an alkali metal or ammonium cation.

In one aspect the novel salts of this invention are provided in non-crystalline form, which may take the form of a solid or an oil. The oil is preferably absorbed on a solid carrier, especially a carrier that is usable as a component of a pharmaceutical composition.

In another aspect the novel salts of this invention are provided in crystalline form. When the crystalline form exists as more than one polymorph, each polymorph forms another aspect of this invention.

Paroxetine salts may be prepared by contacting stoichiometric amounts of the acid (enantiomer or racemic mixture) and paroxetine free base. Preferably the base and/or the acid is in solution, more preferably both are in solution. Mixed salts can be prepared by forming the precursor 1:1 or hydrogen salt (of paroxetine with the acid, or the metal or ammonium ion with the acid) in situ or using it preformed in solution.

Most commonly used solvents are suitable for mobilising paroxetine free base, for example toluene, alcohols such as methanol, ethanol, propan-2-ol, esters such as ethyl acetate, ketones such as acetone and butanone, halogenated hydrocarbons such as dichloromethane, and ethers such as tetrahydrofuran and diethyl ether. The concentration of paroxetine base is preferably in the range 5 to 50% weight/volume, more preferably in the range 10 to 30%.

Suitable solvents for the acids used in accordance with the present invention include water, lower alcohols such as methanol, ethanol and isopropanol, ethers such as diethyl ether and tetrahydrofuran, hydrocarbons such as toluene and benzene, esters such as ethyl acetate, ketones such as acetone, butanone and isobutyl methyl ketone, and halogenated hydrocarbons such as chloroform. The concentration of the acid (other than glutamic acid) is preferably in the range 0.1 to 6.0 molar, for example 0.5 to 4.0 molar, in particular 1.0 to 3.0 molar. Elevated temperatures may be used to enhance solubility. The concentration of glutamic acid is preferably in the range 0.01 to 1.0 molar, in particular 0.1 to 0.5 molar. The acids may also be used in the form of a soluble salt such as the ammonium salt or a salt of an amine, for example ethylamine or diethylamine.

The paroxetine salts may be isolated in solid form by conventional means from a solution thereof obtained as above. For example, the non-crystalline salts may be prepared by precipitation, spray drying, and freeze drying of solutions, or vacuum drying of oils, or solidification of melts obtained from reaction of the free base and the acid.

The crystalline salts may be prepared by directly crystallising from a solvent in which the product has limited solubility, or by triturating or otherwise crystallising a non-crystalline salt. An improved yield of the salt is obtained by evaporation of some or all of the solvent or by crystallisation at elevated temperature followed by controlled cooling, preferably in stages. Careful control of precipitation temperature and seeding may be used to improve the reproducibity of the production process and the particle size distribution and form of the product.

An alternative method of preparing paroxetine salts is to start with a salt of paroxetine with an organic acid, such as acetic acid or maleic acid. Use of another salt of paroxetine as a starting material is suitable for preparation of the crystalline salt or, if a volatile acid such as acetic acid is used, non-crystalline salts by methods that involve evaporation (such as freeze-drying and spray-drying).

Prior to the isolation of the paroxetine salt, water may be removed by azeotropic distillation to avoid the formation of hydrates or to obtain the product in anhydrous form. In that case, suitable solvents for the solution of the salt are those which form an azeotrope with water, such as toluene, pyridine, isopropanol, isobutyl methyl ketone and xylene. It should also be appreciated that mixtures of solvents can also be used to aid the azeotropic removal of water.

More generally, crystallization may be carried out from any solvent which allows formation of the desired crystal structure, using seeds of the desired structure where necessary or desirable. When polymorphs exist, individual polymorphs are preferably crystallized directly from a solution of the salt, although recrystallizing a solution of one polymorph using seeds of another polymorph may also be carried out.

Suitable solvent systems for crystallising/recrystallising salts of the present invention are set out below:

Sulphate: water, butan-1-ol, butan-2-ol.

Tartrates: ethanol, methanol, isopropanol, toluene.

Oxalates: ethanol, methanol, acetone, tetrahydrofuran.

Fumarates: methanol, butanol, tetrahydrofuran.

Propionate: hexane, cyclohexane, chloroform.

Formate: diethyl ether, water, alcohols, toluene, ethyl acetate.

Glutamates: water, methanol, toluene/hexane.

Succinates: toluene, acetone, or lower alcohols followed by precipitation with ethyl acetate, ether, or hexane. Paroxetine succinate may be recrystallised by cooling and optionally seeding hot solutions in suitable solvents such as butan-1-ol or acetonitrile.

Benzoate: As used for salt formation.

Citrate: As used for salt formation.

Nitrate: toluene, toluene/cyclohexane, isopropanol.

Phosphate: toluene, ehtanol, tetrahydrofuran, isopropanol.

4-Methylbenzenesulphonate: toluene or lower alcohols followed by precipitation with ether or hexane.

Hypophosphite: toluene or lower alcohols followed by precipitation with ether or hexane.

Lactate: As used for salt formation.

Mandelate: isopropanol, toluene.

Glycinate: As used for salt formation.

The salt may obtained as a solvate or hydrate, when during isolation from solution it becomes associated with the solvent in which it is dissolved. Any such solvate or hydrate forms a further aspect of this invention. Solvates may be returned to the unsolvated salt by heating, for example by oven-drying, or by treatment with a displacement solvent which does not form a solvate.

Paroxetine free base may be prepared according to the procedures generally outlined in US Patent No 4,007,196 and EP-B-0223403. The acids are commercially available.

The compounds of this invention may be used to treat and prevent the following disorders:

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
Substance Abuse	

These disorders are herein after referred to as "the Disorders".

The present invention further provides a method for treating and/or preventing any one or more of the Disorders by administering an effective and/or prophylactic amount of a salt of the invention to a sufferer in need thereof.

The present invention further provides a pharmaceutical composition for use in the treatment and/or prevention of the Disorders which comprises an admixture of a salt of the invention with a pharmaceutically acceptable carrier.

The present invention also provides the use of a salt of the invention for treating and/or preventing the Disorders.

The present invention also provides the use of a salt of the invention in the manufacture of a medicament for treating and/or preventing the Disorders.

Most suitably the present invention is applied to the treatment of depression, OCD and panic.

The compositions of 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 200 mg of active ingredient calculated on a free base basis, more usually from 5 to 100mg, for example 10 to 50mg such as 10, 12.5, 15, 20, 25, 30 or 40mg by a human patient. Most preferably unit doses contain 20mg 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 400mg 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.

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 utilized in conventional manner, for example in a manner similar to that already used for marketed anti-depressant agents.

Specific examples of pharmaceutical compositions include those described EP-B-0223403, and US 4,007,196 in which the products of the present invention may be used as the active ingredients.

The following Examples illustrate the present invention:

Example 1: preparation of tablets

INGREDIENTS	**20 mg Tablet**	**30mg Tablet**
Paroxetine salt	20.00 mg (calc. as free base)	30.0 mg (calc. as free base)
Dicalcium Phosphate (DCP)	83.34 mg	125.0 mg
Microcrystalline Cellulose	50.67 mg	76.0 mg
Sodium Starch Glycollate	8.34 mg	12.5 mg
Magnesium Stearate	1.67 mg	2.5 mg

Commercial source of the ingredients

Dicalcium Phosphate Dihydrate	-	Emcompress or Ditab*
Microcrystalline Cellulose	-	Avicel PH 102*
Sodium Starch Glycollate	-	Explotab.*

* Trade names

Method

1. Pass DCP through a screen and weigh it into a Planetary mixer.
2. Add 30 mesh Paroxetine salt to the bowl.
3. Add 20 mesh Avicel and Explotab and mix all the powders for 10 minutes.
4. Add magnesium stearate and mix for 5 minutes.

Tablet into Pentagonal Tablets using the following punches:

30 mg Tablet	9.5 mm	Circumcircle
20 mg Tablet	8.25 mm	Circumcircle

The tablets are made satisfactorily on a single punch or a Rotary press.

Example 2 : preparation of tablets

INGREDIENTS	10 mg Tablet	20 mg Tablet	30mg Tablet
Paroxetine salt	10 mg (calc.as free base)	20 mg (calc.as free base)	30 mg (calc.as free base)
Sodium Starch Glycollate	2.98 mg	5.95 mg	8.93 mg
Granular Dicalcium Phosphate (DITAB) or Dicafos	158.88 mg	317.75 mg	476.63 mg
Magnesium Stearate	1.75 mg	3.50 mg	5.25 mg

Method

1. Paroxetine salt, Sodium Starch Glycollate and Dicalcium Phosphate Dihydrate are screened and mixed together in a suitable mixer.
   (Planetary, Cuble or High Energy Shear mixer.)
2. Add Magnesium Stearate and compress it into a tablet using a single punch or Rotary Tablet machine.

Example 3 : Paroxetine sulphate 1:1 salt.

Aqueous sulphuric acid (1.5 ml , 2 molar) was added to a solution of paroxetine free base (1.0 g) in propan-2-ol (10 ml) and the mixture stirred at ambient temperature for three hours. The solvent was removed by evaporation and the residue was stirred in a mixture of hexane (10 ml) and butan-1-ol (10 ml) until the product crystallised. Finally, the crystals were filtered, washed with hexane and dried *in vacuo*.

m.pt 128-130°C

IR nujol mull:

Bands at 1632, 1500, 1324, 1114, 1065, 1005, 925, 884, 844, 761, 672, 614, 578 cm^{-1}.

X-ray powder diffractogram (Cu $K_{2\alpha}$):

Angle [°2θ]	Rel. Int
9.3	10.1
14.3	26.4
14.8	13.5

15.3	19.0
16.9	33.3
17.7	22.6
18.7	44.4
19.2	100.0
20.3	65.4
20.9	27.3
21.5	11.5
22.3	15.6
23.415	10.8
23.720	16.9
24.325	25.9
24.475	26.8
25.640	62.5
26.950	40.2
28.340	36.5
30.335	20.4

Example 4 : Paroxetine sulphate 2:1 salt.

Aqueous sulphuric acid (1.5 ml , 2 molar) was added to a solution of paroxetine free base (2.1 g) in toluene (20 ml) with vigorous stirring. Almost immediately a solid began to separate out. The mixture was diluted with hexane (40 ml) and butanol (20 ml) and stirred rapidly, as a result the form of the crystalline solid improved. After stirring for 1 hour the crystals were filtered, washed with hexane and dried *in vacuo*.

m.pt 247-250°C

IR nujol mull:

Bands at 1627, 1511, 1230, 1161, 1040, 958, 825, 779, 613, 593 cm^{-1}.

X-ray powder diffractogram (Cu K_{2a}):

Angle [°2θ]	**Rel. Int [%]**
5.300	25.3
13.215	9.6
15.185	27.3

17.595	46.7
18.290	100.0
18.980	35.0
19.465	44.3
20.755	39.2
21.420	53.0
21.635	64.3
22.305	21.8
24.875	54.7
26.075	28.2
26.615	59.1
30.355	26.5
31.710	16.3

Example 5 - Paroxetine sulphate 2:1 salt

Paroxetine base (54.9 g) was dissolved in a mixture of propan-2-ol (500 ml) and water (20 ml). To the stirred, clear solution was added slowly a mixture of sulphuric acid (8.3 g, 98%), water (20 ml), and propan-2-ol (200 ml); during the course of the addition seeds of paroxetine sulphate (2:1) were added to induce crystallisation. After stirring for 2 hours, the mixture was stored overnight at 4°C, then filtered, washed with propan-2-ol (100 ml) and dried in an air oven.

Yield 54.8 g.

Example 6 - Preparation of non-crystalline paroxetine sulphate (2:1)

Concentrated sulphuric acid (1.6 g) was diluted to 10 ml with water, and the solution added slowly to a stirred mixture of paroxetine base (11.0 g) and water (20 ml). The clear solution was evaporated at reduced pressure to form a white, crisp glassy solid.

Example 7 - Preparation of paroxetine sulphate (2:1)

Concentrated sulphuric acid (16 g) was diluted to 100 ml with water, and the solution added slowly to a stirred mixture of paroxetine base (109.8 g) and water (200 ml). The clear solution was cooled overnight, then stirred and seeded until crystallisation was complete. The product was collected by filtration, washed with propan-2-ol, and dried under vacuum.

Yield 96.7 g.

Example 8 - crystallisation of non-crystalline paroxetine sulphate (2:1)

The non-crystalline paroxetine sulphate prepared in Example 6 was suspended in propan-2-ol (200 ml), stirred vigorously, and gradually heated to reflux. After 2 hours the paroxetine sulphate could be seen to have changed form, so the mixture was cooled, filtered, washed with cold propan-2-ol, and dried under vacuum to give crystalline paroxetine sulphate (2:1).

Yield 8.5 g.

Example 9 : Paroxetine L(+) tartrate 1:1 salt.

L(+)-tartaric acid (1.25 g) was dissolved in propan-2-ol (10 ml) with heating, and mixed with a stirred solution of paroxetine base (2 g) in toluene (20 ml). A crystalline suspension formed which was stirred for a further 1 hour at room temperature. Finally, the product was filtered, washed with acetone and dried under reduced pressure. Yield 2.65 g.

Example 10 : Paroxetine L(+) tartrate 1:1 salt.

A solution of L(+)-tartaric acid (1.0 g) in methanol (10 ml) was mixed with a solution of paroxetine base (1.75 g) in methanol (15ml) and the mixture stirred at ambient temperature. Crystals separated within a few minutes and the suspension was stirred for a further 1 hour at ambient temperature. Finally the crystals were filtered, washed with acetone and dried under reduced pressure. Yield 2.01 g.

Example 11 : Larger scale preparation of paroxetine L(+) tartrate 1:1 salt.

L(+) tartaric acid (25 g) was dissolved in propan-2-ol (200 ml) with heating and mixed with a solution of paroxetine base (42 g) in toluene (400 ml). A crystalline precipitate formed, which was stirred for 1 hour at ambient temperature then at 0°C for a further 1 hour. Finally the crystals were filtered, washed with acetone and dried under reduced pressure. Yield 59.88g.

m.pt 176-178°C.

IR nujol mull:

Bands at *1718, 1602, 1504, 1490, 1465, 1242, 1190, 1106, 833, 780, 650 cm^{-1}*

X-ray powder diffractogram ($CuK_{2\alpha}$)

Angle [°2θ]	Rel. Int [%]
6.1	12.8
14.2	44.7

16.2	25.7
17.3	42.6
17.9	100.0
20.1	24.0
20.4	30.6
21.9	34.5
22.3	48.6
22.6	48.6
23.0	33.0
24.0	42.2
25.1	36.9
25.7	52.5
26.1	59.5
27.3	27.8
28.6	21.3
34.3	24.2

Example 12 : Paroxetine D(-) tartrate 1:1 salt.

D(-)-tartaric acid (1.25 g) was dissolved in propan-2-ol (10 ml) with heating, and mixed with a stirred solution of paroxetine base (2.1 g) in toluene (20 ml). A crystalline suspension soon formed which was stirred for another hour at room temperature. The product was then filtered, washed with acetone and dried under reduced pressure. Yield 2.70 g.

Example 13 : Larger scale preparation of paroxetine D(-)-tartrate 1:1 salt.

D(-) tartaric acid (25 g) was dissolved in propan-2-ol (200 ml) by heating and added rapidly to a solution of paroxetine base (42 g) in toluene (400 ml). A crystalline precipitate soon formed, and was stirred for 1 hour at ambient temperature then at 0°C for a further 1 hour. The crystals were then filtered, washed with toluene and dried under reduced pressure. Yield 57.59g.

m. pt 174-176°C.

IR nujol mull:

Bands at *3489, 3354, 1726, 1616, 1462, 1184, 1097, 936, 831, 794, 694* cm^{-1}.

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

Angle [°2θ]	Rel. Int [%]
4.4	100.0
16.5	11.6
16.8	27.7
17.3	70.9
17.6	52.9
20.5	15.1
24.3	13.3
25.2	10.6
25.9	10.4
26.3	18.5
26.4	15.4
28.5	12.7
28.8	15.9

Example 14 : Preparation of non-crystalline 2:1 salt with L(+)-tartaric acid.

L(+) tartaric acid (1.0 g) was heated in propan-2-ol (10 ml) to form a solution, and mixed with a solution of paroxetine base (5.0 g) in toluene (20 ml). The resulting solution was stirred at ambient temperature and then hexane (50 ml) was added.and a white solid precipitated. The suspension was stirred for a further 1 hour then the solid was filtered, washed with hexane and dried under reduced pressure. This solid was shown by X-ray diffraction to be non-crystalline.

Yield 4.32g.

Example 15 : Preparation of crystalline 2:1 salt with D(-)-tartaric acid.

D(-) tartaric acid (1 g) was heated in propan-2-ol to form a solution. This solution was mixed with a stirred solution of paroxetine base (5.0 g) in toluene (20 ml). Crystallization commenced within two minutes, and the suspension was stirred at ambient temperature for a further 1 hour. Finally the product was filtered, washed with toluene and dried under reduced pressure. Yield 5.69 g.

Example 16 : Larger scale preparation of crystalline 2:1 salt with D(-)-tartaric acid.

D(-) tartaric acid (10 g) was dissolved in propan-2-ol (100 ml) by heating and then mixed with a stirred solution of paroxetine base (50.4 g) in toluene (200 ml). Within 5 minutes

crystals had precipitated, and the suspension was stirred at ambient temperature for an hour then a further hour in an ice/water bath. Finally, the crystals were filtered, washed with toluene and dried under reduced pressure. Yield 57.12g.

m.pt 190-192°C.

IR nujol mull:

Bands at *3436, 1650, 1556, 1491, 1221, 1120, 1035, 931, 832, 783, 631, 538* cm^{-1}

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

Angle [°2θ]	Rel. Int [%]
3.6	35.1
5.5	33.8
15.6	20.6
16.5	24.4
16.9	53.0
17.1	51.5
17.6	67.7
18.0	57.6
18.7	100.0
19.2	65.2
19.5	74.4
20.1	55.5
21.1	76.1
21.6	38.8
22.9	70.5
23.2	59.7
23.5	53.3
24.3	40.1
27.2	35.3
27.8	27.6
28.7	38.0
28.9	33.6

31.8	27.6

Example 17 : Preparation of crystalline 2:1 salt with L(+)-tartaric acid.

L(+)-potassium hydrogen tartrate (1.0 g) was heated in a mixture of ethanol (120 ml) and water (40 ml) to form a solution. Paroxetine base (4.2 g) in toluene (10 ml) was added and the mixture stirred at ambient temperature for several hours but remained clear. The solvent was therefore removed by evaporation and the residue redissolved in toluene. The evaporation procedure was repeated and the residue stirred with fresh toluene for 30 minutes to form a crystalline product, which was filtered, washed in toluene and dried under reduced pressure. Yield 2.18 g.

IR nujol mull:

Bands at *1572, 1463, 1226, 1187, 1098, 1035, 943, 835, 781, 721, 598, 542* cm^{-1}.

X-ray powder diffractogram major peaks:

Angle [$^{o}2\theta$]	**Rel. Int [%]**
6.0	41.9
13.0	29.7
15.6	75.8
15.9	40.5
16.7	49.9
17.8	69.3
18.0	61.3
19.1	37.6
20.7	63.4
21.2	57.5
21.9	53.2
22.4	80.1
23.1	39.0
24.7	55.5
24.9	59.2
25.5	49.4
26.0	32.7
26.6	57.2

27.6	38.1
28.0	30.9
28.9	25.3
33.1	23.6

Example 18 : Preparation of paroxetine 1:1 *meso*-tartrate

A solution of *meso*-tartaric acid (2.14 g) in water (19 ml) was prepared by heating to reflux temperature. Propan-2-ol (20 ml) and paroxetine base (4.2 g) in toluene (20 ml) were added and the mixture stirred, then the solvents were removed by distillation at reduced pressure. Toluene (20 ml) was added and the distillation repeated to yield the 1:1 meso-tartrate as a non-crystalline solid. Trituration with heptane caused the solid to crystallise, and the white powdery product was filtered, washed with heptane and dried under reduced pressure.

Yield 3.52 g

Melting point 168-171°C

IR nujol mull:

Bands at *1725, 1622, 1463, 1378, 1267, 1104, 944, 824, 779, 677* cm^{-1}.

X-ray powder diffractogram (Cu K2α):

Angle [°2θ]	Rel. Int [%]
4.7	71.2
9.4	20.6
11.1	2.1
12.8	2.6
14.6	25.9
15.2	16.9
15.7	15.1
16.6	44.5
17.4	70.0
17.9	44.0
16.7	55.8
19.1	100.0
19.7	49.4
20.7	34.7

21.0	47.3
21.6	3.1
22.4	37.6
23.0	45.3
23.4	56.1
23.7	52.5
24.8	45.3
25.3	50.7
25.8	36.7
26.1	16.3
27.0	5.1
27.5	14.5
28.1	30.1
29.4	7.2
29.9	29.5
30.2	21.1
31.0	7.9
31.5	15.2
31.9	13.8
32.4	13.1
33.2	4.0
33.6	10.9

Example 19 : Preparation of paroxetine oxalate (1:1)

Oxalic acid (1.15 g) was dissolved in methanol (50 ml) with heating. A solution of paroxetine base in toluene (4.2 g in 20 ml) was added and the reaction mixture stirred at room temperature. The solvents were removed *in vacuo* to afford a white glassy solid of non-crystalline paroxetine oxalate. Trituration with heptane caused the produce to crystallise to a white powdery solid, which was filtered, washed with heptane and dried at reduced pressure.

Yield 2.93g

Melting point 122-134°C

IR nujol mull:

Bands at *1732, 1634, 1505, 1376, 1038, 930, 835, 720, 538 cm^{-1}.*

X-ray powder diffractogram (Cu K2α):

Angle [°2θ]	Rel. Int [%]
8.1	3.1
10.6	2.7
12.9	9.2
13.8	18.8
15.7	30.1
16.3	34.4
19.1	100.0
19.7	77.1
20.1	63.1
21.4	65.2
22.6	54.9
23.1	44.1
24.8	38.4
26.1	44.3
26.7	47.0
27.3	38.9
28.9	31.3
30.5	24.8
32.1	27.3
33.0	27.7
34.6	54.6

Example 20 : Preparation of paroxetine oxalate (2:1)

Oxalic acid (1.15 g) was added to methanol (40 ml) and the mixture heated to achieve total dissolution of the acid. Paroxetine base in toluene (8.4 g in 40 ml) was added and the solution stirred at room temperature. White crystals separated rapidly. The product was filtered, washed with heptane and dried at reduced pressure.

Yield 7.34 g.

Melting point 207-211°C

IR nujol mull:

Bands at *1585, 1509, 1377, 1286, 1081, 926, 831, 761, 604, 574* cm^{-1}.

X-ray powder diffractogram (Cu K2α):

Angle [°2θ]	Rel. Int [%]
5.4	3.9
6.3	2.8
8.4	7.3
11.1	8.1
12.6	11.3
13.4	7.1
14.2	27.8
14.9	23.3
16.0	54.4
16.4	59.6
16.7	86.3
17.2	38.8
18.4	81.8
18.6	77.4
19.4	51.2
19.9	53.0
20.5	63.1
21.6	100.0
22.2	40.6
22.7	40.3
23.1	37.5
23.4	29.3
25.4	95.6
26.9	55.2
27.8	41.2
30.1	34.6

31.8	27.3
32.6	25.5
34.0	23.1

Example 21: Preparation of 1:1 salt.

Fumaric acid (0.3 g) was heated in a mixture of toluene (5 ml) and propan-2-ol (5 ml) to form a solution. This solution was mixed with a solution of paroxetine free base (1 g) in toluene (10 ml) while stirring. Crystals separated within 2 minutes and the suspension was stirred at ambient temperature for a further 1 hour. Finally the product was filtered, washed in toluene and dried at reduced pressure.

Molar ratio of paroxetine to fumaric acid = 1:1.

Example 22: Larger scale preparation of 1:1 salt.

Fumaric acid (30 g) was heated in propan-2-ol until the solid dissolved and the warm solution was mixed with a solution of paroxetine free base (84 g) in toluene (500 ml) with stirring. Crystals separated rapidly and the suspension was stirred for 1 hour at ambient temperature then 1 hour at 0°C (ice/water bath). Finally the crystals were filtered. washed in toluene and dried at reduced pressure.

Yield 102.31g.

Molar ratio of paroxetine to fumaric acid = 1:1.

Paroxetine Fumarate 1:1 salt characterising data:

m. pt 180-182°C.

IR nujol mull:

Bands at 1706, 1659, 1504, 1487, 1466, 1295, 1184, 1032, 833, 792, 636cm^{-1}

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

Angle [°2θ]	**Rel. Int [%]**
4.8	11.8
14.4	58.0
16.4	53.7
16.9	16.7
17.9	100.0
19.0	20.1
19.2	24.9

20.0	55.8
20.2	25.2
21.6	27.1
24.0	62.6
24.3	60.4
26.6	46.5
28.3	58.2
29.0	40.5
32.9	19.4

Example 23: Preparation of 2:1 salt.

Fumaric acid (0.3 g) was heated in propan-2-ol (10 ml) until the solid dissolved and this solution was mixed with paroxetine free base (2.1 g) in toluene (20 ml). The mixture was stirred for 1 hour at room temperature and a gel began to separate. Diethyl ether (20 ml) was added and the product crystallised. The suspension was stirred for a further 1 hour. Finally the crystals were filtered, washed in diethyl ether and dried at reduced pressure. Yield 1.79g.

Molar ratio of paroxetine to fumaric acid = 2:1.

Example 24: Larger scale preparation of 2:1 salt.

Fumaric acid (9 g) was heated in propan-2-ol (200 ml) until the solid dissolved, and the warm solution was added to a solution of paroxetine free base (63 g) in toluene (600 ml). The mixture was stirred at ambient temperature and the product crystallised. After 1 hour it was necessary to add more toluene to enable the crystals to be collected by filtration. The prouct waswashed in toluene and dried at reduced pressure.

Yield 58.86g.

Molar ratio of paroxetine to fumaric acid = 2:1.

Example 25: Preparation of non-crystalline salt.

Paroxetine fumarate (2 g) (prepared as Example 22) was heated in methanol (50 ml) to form a solution. The solvent was removed by evaporation at a water bath temperature of between 70 and 80°C. The product was a glassy solid which was shown by X-ray diffraction to be non-crystalline.

Paroxetine Fumarate 2:1 salt characterising data:

m. pt 164-165°C.

IR nujol mull:

Bands at 1644, 1508, 1464, 1246, 1205, 1138, 1044, 934, 836, 835, 722, 674 cm^{-1}

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

Angle [$^{o}2\theta$]	Rel. Int [%]
11.4	3.8
12.4	9.4
12.9	3.9
15.3	5.4
15.8	6.9
16.5	11.8
18.2	25.8
19.4	100.0
19.8	41.9
21.7	32.6
22.6	31.4
23.0	39.2
27.8	38.2
28.4	14.3
33.4	12.1

Example 26.

Propionic acid (0.5 ml) was added to a solution of paroxetine free base (2 g) in toluene (20 ml). No crystals separated until the solution was diluted with hexane (40 ml) when an oil formed which crystallised within 1 hour. The suspension was stirred for a further 1 hour at ambient temperature. Finally the crystals were filtered, washed with hexane and dried at reduced pressure.

Yield 0.60g.

Example 27.

Propionic acid (15 ml) was added to a solution of paroxetine free base (63 g) in toluene (150 ml). The mixture was diluted with hexane (1500 ml) and an oil formed which began to crystallise within a few minutes. The suspension was stirred for 1 hour at ambient temperature then 1 hour at 0°C (ice/water bath). The product was filtered, washed with

hexane and dried at reduced pressure. Since some of the oil had not crystallised, more hexane was added and the mixture was stirred overnight at ambient temperature. Finally the product was filtered, washed with hexane and dried at reduced pressure.

Yield 60.0g.

Paroxetine Propionate characterising data:

m. pt 89-91°C.

IR nujol mull:

Bands at 1634, 1604, 1464, 1289, 1249, 1223, 1193, 1036, 979, 870, 808, 721, 671 cm^{-1}.

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

Angle [°2θ]	Rel. Int. [%]
5.7	37.8
8.1	29.2
16.2	40.6
16.6	69.8
17.1	100.0
18.9	83.0
19.2	24.1
19.7	23.6
21.7	98.5
22.2	20.7
22.5	42.3
22.6	38.4
22.9	21.6
23.3	45.3
23.7	70.0
25.2	54.2
27.3	20.6
27.8	46.2
28.1	44.4
29.5	29.0

32.0	21.1

Example 28: Preparation of crystalline paroxetine formate

A solution of paroxetine base in toluene (2 ml, 2.55 mmol) was added to a solution of formic acid (0.12g, 2.50 mmol) in toluene (10 ml). The solvent was removed at reduced pressure to yield a white solid. Trituration with diethyl ether (*c.* 10 ml) and filtration under nitrogen gave a white solid which was washed with diethyl ether (2 × 10 ml) and dried.

Yield 0.84g.

Example 29: Larger scale preparation of crystalline salt.

A solution of paroxetine base in toluene (120 ml, 153.0 mmol) was added to a solution of formic acid (7.2g, 156.0 mmol) in toluene (300 ml). The solvent was removed at reduced pressure to yield a white solid. Trituration with diethyl ether (*c.* 400 ml) and filtration gave a white solid which was washed with diethyl ether (2 × 100 ml) and dried at reduced pressure. Yield 56.10g.

^{1}H NMR ($CDCl_3$) showed a ratio between formic acid and paroxetine of 1:1.

m.p. 100 - 103°C.

IR nujol mull:

Bands at 1638, 1574, 1508, 1490, 1462, 1377, 1342, 1279, 1246, 1204, 1136, 1090, 1044, 934, 913, 836, 826, 804, 786, 762, 722, 674, 603, 577, 542 cm^{-1}.

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

Angle [°2θ]	**Rel. Int [%]**
12.6	16.3
16.3	11.4
16.8	29.8
16.9	29.8
18.6	10.1
19.5	100.0
20.2	20.9
20.4	16.9
21.0	13.5

21.5	11.8
22.1	32.8
22.7	30.4
23.1	42.3
25.8	13.6
27.8	41.6
28.7	11.3
29.0	14.2
29.7	10.6
32.6	11.4
34.0	12.1

Example 30 : Preparation of non-crystalline paroxetine L-glutamate

A solution of paroxetine base in toluene (5 ml, 6.38 mmol) was added to a suspension of L-glutamic acid (0.94 g, 6.38 mmol) in hot methanol (45 ml). The mixture was heated at reflux for 1 hour, allowed to cool, filtered and the solvent was removed at reduced pressure. The residual oil was diluted with toluene (15 ml) and the solvent removed at reduced pressure. Trituration with diethyl ether (c. 20 ml) and filtration under nitrogen gave a white powder which was washed with diethyl ether (2 × 10 ml) and dried (yield 2.64 g, 87%).

^{1}H NMR (DMSO) shows a ratio between L-glutamic acid and paroxetine of 1:1.

IR nujol mull:

Bands at 1465, 1377, 1223, 1186, 1037, 931, 831, 721, 541.

Example 31 : Preparation of non-crystalline paroxetine D-glutamate

A solution of paroxetine base in toluene (5 ml, 6.38 mmol) was added to a suspension of D-glutamic acid (0.94 g, 6.38 mmol) in hot methanol (45 ml). The mixture was heated at reflux for 1hour, allowed to cool, filtered and the solvent removed at reduced pressure. The residual oil was diluted with toluene (30 ml) and the solvent removed at reduced pressure. Trituration with diethyl ether (c. 20 ml) and filtration under nitrogen gave a pale brown solid which was washed with diethyl ether (2 × 10 ml) and vacuum dried. Yield 2.65g.

^{1}H NMR (DMSO) shows a ratio between D-glutamic acid and paroxetine of 1:1.

IR nujol mull:

Bands at 1558, 1465, 1377, 1224, 1187, 1038, 931, 832, 722, 541.

Example 32 : Preparation of crystalline 1:1 salt with L-glutamic acid.

Paroxetine free base (2.1 g) in toluene (5 ml) was added to a suspension of L-glutamic acid (0.8 g) in propan-2-ol (90 ml) and water (15 ml), stirred, and diluted further with toluene (100 ml). The mixture was gently heated to dissolve the acid, and the solution evaporated. The residue from evaporation was stirred at ambient temperature with a mixture of toluene (50 ml) and n-hexane (50 ml) until the product appeared to have crystallised and then for another hour. Finally, the crystals were collected by filtration, washed with hexane and dried at reduced pressure.

m.pt 92-98°C.

IR nujol mull:

Bands at 1650, 1598, 1573, 1507, 1207, 1043, 933, 826, 804, 648, 540cm^{-1}.

X-ray powder diffractogram ($CuK_{2\alpha}$):

Angle [°2θ]	Rel. Int [%]
13.4	11.9
15.7	18.4
17.4	38.9
17.5	33.1
19.1	100.0
19.7	55.0
20.2	31.6
20.8	32.9
21.5	44.1
22.5	66.5
22.7	60.0
24.0	38.0
24.4	24.1
27.3	35.9
29.2	20.6
30.5	14.6
32.2	15.2

33.2	15.7
34.0	23.5

Example 33: Preparation of crystalline paroxetine D-glutamate 1:1 salt

A solution of paroxetine base (4.2 g) in toluene (10 ml) was added to a suspension of D-glutamic acid (1.88 g, 12.76 mmoles) in water (35 ml) and toluene (40 ml). The reaction mixture was stirred and brought to reflux temperature and all of the water was removed using a Dean and Stark apparatus. Almost immediately a solid separated. The mixture was cooled to 0°C, and the reaction mixture was diluted with propan-2-ol (80 ml) with stirring, to afford paroxetine D-glutamate 1:1 salt as a white crystalline solid. The product was filtered off under a nitrogen atmosphere, and dried at reduced pressure.

Melting point = 195°C

Molar ratio by ^{1}H NMR of paroxetine to D-glutamic acid = 1:1

IR Nujol Mull:

Bands at 2741, 1642, 1584, 1510, 1315, 1150, 1078, 947, 867, 675 538 cm-1.

X-ray diffractogrm (Cu $K_{2\alpha}$):

Angle [°2θ]	Relative intensity [%]
3.8	44.3
6.2	3.1
6.9	2.8
9.7	10.9
11.5	35.7
11.9	17.8
12.5	5.5
13.2	11.1
14.2	22.8
14.7	3.7
15.3	12.8
16.0	28.9
16.3	12.4
16.8	9.2
17.6	9.0
18.3	78.5
18.6	37.8
19.3	74.8
19.9	51.8
20.3	36.2
20.8	27.3
22.3	27.9
22.7	100.0
23.5	66.6

23.9	41.2
24.4	33.9
25.0	19.4
26.1	13.9
26.6	10.8
27.1	19.6
27.9	48.2
28.7	30.4
31.0	14.4
31.6	15.7
32.2	16.3
33.3	24.1
34.4	22.6

Example 34 : Preparation of crystalline 1:1 paroxetine succinate

Succinic acid (0.35 g) was dissolved in propan-2-ol (5 ml) with heating and mixed with a solution of paroxetine base (1 g) in toluene (10 ml). The solution was diluted with ethyl acetate (15 ml) and hexane (20 ml). An oil formed initially, but this crystallised within 15 minutes following scratching and ultrasonication. The suspension was stirred at approximately 20°C for a further hour then the crystals were filtered, washed with ethyl acetate and dried at reduced pressure.

Yield 0.92 g.

Example 35 : Larger scale preparation of crystalline 1:1 paroxetine succinate.

Succinic acid (20 g) was dissolved in propan-2-ol (300 ml) with heating and then mixed witht a solution of paroxetine base (60 g) in toluene 500 ml. The warm solution was diluted with ethyl acetate (500 ml) and hexane (800 ml) and stirred vigorously. Crystals began to separate out within a few minutes, and stirring at approximately 20°C was continues for an hour, and then at 0°C for a further hour. Finally the crystals were filtered, washed with ethyl acetate and dried at reduced pressure.

Yield 66.24g.

m. pt 116-117°C.

IR nujol mull:

Bands at *1713, 1573, 1488, 1464, 1272, 1185, 1032, 833, 793, 721, 627* cm^{-1}.

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

Angle [°2θ]	Rel. Int [%]

4.8	6.0
11.3	15.8
14.4	33.7
16.3	60.1
17.8	99.3
19.2	25.1
19.9	61.4
21.6	20.5
21.8	26.8
23.9	72.8
24.1	100.0
24.5	25.9
25.5	34.6
26.4	72.6
27.1	28.4
27.3	26.7
28.2	32.4
28.6	21.9
29.0	27.4
29.4	35.8
32.8	17.5

Example 36 : Alternative preparation of crystalline 1:1 paroxetine succinate.

Succinic acid (0.7 g) was heated in propan-2-ol (10 ml) to form a solution, which was then added to a solution of paroxetine free base (4.2 g) in toluene (10 ml). The mixture was diluted with diethyl ether (30 ml) and hexane (30 ml) and the resulting oil was scratched and ultrasonicated until it crystallised. The suspension was stirred for a further 1 hour, filtered, washed with diethyl ether and dried at reduced pressure.

Yield 0.99g.

Example 37 : Preparation of crystalline 1:1 paroxetine succinate.

A solution of succinic acid (0.35 g) in hot propan-2-ol was mixed with a solution of paroxetine base (1 g) in toluene (10 ml). The mixture was stirred at approximately 20°C

and then diluted with hexane (15 ml) when an oil formed which crystallised on standing. The solid was filtered, washed with hexane and dried at reduced pressure.

Yield 0.6g.

Example 38 : Preparation of 2:1 paroxetine succinate.

A solution of succinic acid (0.35 g) in methanol (10 ml) was added to a solution of paroxetine free base (2.1g) in toluene (10 ml). The solvent was removed by evaporation under reduced pressure to yield a white crisp foam. Diethyl ether (25 ml) and hexane (25 ml) were added and the solid triturated to give a solid, easily stirrable product. After stirring for 30 minutes, the product was filtered, washed in diethyl ether and dried at reduced pressure.

Example 39 : Preparation of paroxetine benzoate

Paroxetine base (2.1 g) in toluene (5 ml) was added to a suspension of benzoic acid (0.78 g, 6.38 mmol) in toluene (15 ml) and stirred vigorously. The solvent was removed from the resulting clear solution by evaporation under high vacuum to afford paroxetine benzoate.

Yield 2.9g

Molar ratio of paroxetine to benzoic acid = 1:1

IR nujol mull:

Bands at *2879, 1627, 1509, 1376, 1037, 932, 830, 799, 695* cm^{-1}.

Example 40: Preparation of paroxetine citrate (1:1)

A solution of paroxetine base (4.2 g) in toluene (25 ml) was added to a suspension of citric acid (2.45 g) in water (4 ml), and the mixture was heated to reflux to form a clear solution. The water was removed by heating at reflux in a Dean and Stark apparatus, then the mixture was cooled and the solvent decanted. Fresh toluene (20 ml) was added to the solid residue, and the mixture heated once again at reflux in a Dean and Stark apparatus. Finally the toluene was removed at reduced pressure and the residue stirred with heptane overnight, filtered and dried to produce paroxetine citrate 1:1 salt as a yellowish powder.

Example 41: Preparation of paroxetine citrate (2:1)

A solution of paroxetine base (4.2 g) in toluene (30 ml) was added to a suspension of citric acid (1.23 g) in water (2 ml), and the mixture was heated to reflux to form a clear solution. The water was removed by heating at reflux in a Dean and Stark apparatus, then the mixture was cooled and the solvent decanted. Propan-2-ol (30 ml) was added to the solid residue and the mixture stirred and heated to reflux temperature for 30 minutes, then cooled to room temperature (approximately 22°C), whereupon a yellowish precipitate was

produced. The produce, paroxetine citrate 2:1, was collected by filtration under an atmosphere of nitrogen and dried under vacuum.

Yield 3.1 g

IR spectrum (nujol mull):

Bands at *2970, 2360, 1738, 1622, 1487, 1134, 929, 830, 668 cm^{-1}.*

Example 42: Preparation of paroxetine citrate (3:1)

A solution of paroxetine base (6.3 g) in toluene (25 ml) was added to a suspension of citric acid (1.23 g) in water (2.5 ml), and the mixture was heated to reflux to form a clear solution. The water was removed by heating at reflux in a Dean and Stark apparatus, then the mixture was cooled and the solvent decanted. Residual toluene was removed at reduced pressure and the solid product stirred with heptane overnight, filtered and dried at reduced pressure to give paroxetine citrate 3:1 salt as a yellowish powder.

Yield 5.1 g

IR spectrum (nujol mull):

Bands at *2970, 2359, 1738, 1558, 1487, 1366, 1035, 929, 720 cm^{-1}.*

Example 43. Preparation of paroxetine nitrate

Concentrated nitric acid (1.7 g, 1.2 ml, 19.14 mmol) was diluted with water (28 ml), and the solution mixed with a solution of paroxetine base (6.3 g) in toluene (15 ml). The mixture was heated at reflux in a Dean and Stark apparatus under nitrogen until all the water had been removed, and the resulting solution cooled to room temperature and evaporated to an oil. On diluting the oil with toluene (10 ml), the product crystallised; heptane (100 ml) was added to the crystals and the suspension was stirred at ambient temperature. Finally, the crystals were collected by filtration, washed with heptane and dried *in vacuo*.

Yield 6.1 g.

Melting point 95-99°C

IR nujol mull:

Bands at 1630, 1504, 1458, 1321, 1037, 930, 834, 719, 574cm^{-1}.

X-ray powder diffractogram (Cu K2α):

Angle [°2θ]	Rel. Int [%]
6.5	1.3

8.1	0.3
9.7	1.3
11.5	1.0
13.0	19.5
13.7	12.9
14.0	7.8
14.5	4.6
15.8	11.8
16.7	17.1
18.0	52.4
19.1	76.9
19.4	100.0
21.0	17.2
23.1	39.3
23.9	27.4
24.2	32.3
24.7	17.5
25.9	14.7
26.9	40.3
27.2	38.4
28.1	23.1
28.8	26.6
29.7	15.7
31.0	11.8
32.0	17.5
33.5	10.4

Example 44 : Paroxetine phosphate 1:1 salt.

A solution of paroxetine base (2.1 g) in toluene (20 ml) was diluted with acetone (20 ml). Orthophosphoric acid in propan-2-ol (1.5 ml, 3.675molar) was added and the mixture diluted further with propan-2-ol (20 ml) and stirred for 1 hour at ambient temperature. The product crystallised and was filtered, washed with propan-2-ol and dried *in vacuo*. Yield 1.92 g.

Example 45 : Larger scale preparation of paroxetine phosphate 1:1 salt.

Orthophosphoric acid in propan-2-ol (45 ml, 3.675 molar) was added to a solution of paroxetine base (63 g) in toluene (600 ml). The mixture was stirred for 1 hour, and then diluted with acetone (600 ml). Crystallisation began within a few minutes, and the suspension was stirred for 1 hour at ambient temperature and for a further 1 hour in an ice/water bath. The crystalline product was filtered, washed with propan-2-ol and dried *in vacuo*. Yield 74.53 g.

m. pt 207-210°C.

IR nujol mull:

1606, 1512, 1466, 1225, 1190, 1079, 1040, 953, 831, 722, 608, 577 cm^{-1}.

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

Angle [°2θ]	Rel. Int. [%]
14.0	48.6
17.4	80.1
19.8	71.4
21.4	96.3
23.6	65.3
24.8	100.0
26.2	48.6

Example 46 : Preparation of paroxetine phosphate 2:1 salt.

A solution of paroxetine base (4.2 g) in toluene (20 ml) was treated with a solution of orthophosphoric acid in propan-2-ol (1.5 ml, 3.675 molar). Propan-2-ol (20 ml) was added and a white solid precipitated. The suspension was stirred for 1 hour at ambient temperature, and then the product was filtered, washed with propan-2-ol and dried *in vacuo*. Yield 3.40 g.

IR nujol mull:

Bands at *1573, 1466, 1225, 1189, 1039, 876, 834, 782, 720, 547 cm^{-1}.*

Example 47: Preparation of non-crystalline paroxetine phosphate 2:1 salt.

Paroxetine base (4.2 g) in toluene (10 ml) was added to a suspension of aqueous orthophosphoric acid (0.37 ml, 14.6 molar, 85%) in methanol (50 ml), with stirring to form a clear solution. The solvents were removed by distillation *in vacuo* to produce an oil, which was dissolved in toluene (30 ml) and the solvent removed once more. The resulting

glassy solid was triturated with heptane (50 ml) to give a white powdery non-crystalline solid, which was filtered, washed with heptane and dried *in vacuo*.
Yield = 2.51 g.

Example 48: Crystallisation of paroxetine phosphate 2:1 salt.

The non-crystalline paroxetine phosphate prepared in Example 47 (1 g) was suspended in a mixture of ethanol (18 ml) and propan-2-ol (20 ml) and heated to reflux temperature with stirring. After 30 minutes the mixture was allowed to cool, then was collected by filtration and dried *in vacuo*. The product was found to be crystalline paroxetine phosphate 2:1 salt.
Yield = 0.89 g.

Molar ratio of paroxetine to phosphoric acid = 2:1
IR nujoll mull:
Bands at *1606, 1468, 1377, 1225, 1040, 952, 783, 609, 578* cm^{-1}.
X-ray powder diffractogram (Cu $K_{2\alpha}$):

Angle [°2θ]	Relative Intensity [%]
4.6	70.2
8.3	2.3
11.3	8.9
12.5	10.7
14.0	100.0
14.5	16.5
15.3	39.9
15.6	29.8
16.0	25.5
17.4	90.7
17.7	74.6
18.2	49.2
19.2	52.4
20.4	60.0
20.6	50.6
21.5	77.3
21.8	83.6
22.7	40.7
23.5	60.0
24.3	41.5
24.8	78.4
26.2	39.9
28.3	11.3
30.7	8.5
31.5	6.9
33.6	1.5

Example 49 : Preparation of crystalline paroxetine 4-methylbenzenesulphonate

A solution of paroxetine base in toluene (2.1 g in 5 ml) was mixed with a solution of 4-methylbenzenesulphonic acid monohydrate (1.21g) in methanol (15 ml). The solvent was removed *in vacuo*, replaced with fresh toluene (10 ml), and evaporated again. The residue was triturated with diethyl ether (15 ml) to produce a white crystalline solid, which was filtered, washed with diethyl ether (2 × 10 ml) and dried in a vacuum desiccator.

Yield 3.09g.

Example 50 : Preparation of crystalline paroxetine 4-methylbenzenesulphonate

A solution of paroxetine base in toluene (42 g in 100 ml) was added to a solution of 4-methylbenzenesulphonic acid (24.2 g) in methanol (300 ml). The solvent was removed *in vacuo*, the residue diluted with toluene (200 ml) and the solvent again removed *in vacuo*. Trituration with diethyl ether (*c.* 300 ml) gave a white crystalline solid which was filtered, washed with diethyl ether (2 × 50 ml) and dried in a vacuum desiccator.

Yield 61.13g.

m. p. 105 - 109°C.

IR nujol mull:

Bands at *1603, 1504, 1465, 1377, 1224, 1188, 1159, 1119, 1030, 999, 930, 830, 779, 722, 684, 564* cm^{-1}.

X-ray powder diffractogram major peaks (CuK_{2a}):

Angle [°2θ]	Rel. Int [%]
4.9	32.8
7.3	21.6
9.9	14.6
12.9	22.3
14.9	22.8
15.9	18.2
16.3	28.0
17.0	17.2
17.3	23.3
17.8	21.1
18.5	34.7

19.0	19.0
19.4	31.2
19.8	45.0
20.5	28.6
20.8	15.7
22.1	100.00
28.0	15.1

Example 51: Preparation of paroxetine hypophosphite

Paroxetine base (4.2 g) in toluene (10 ml) was added to a 50% aqueous solution of hypophosphorous acid (1.32 ml, 9.7 molar) and the mixture stirred at approximately 20°C. The solvents were then removed by distillation at reduced pressure to produce non-crystalline paroxetine hypophosphite as a crisp glassy solid. This solid was triturated with heptane to form the crystalline salt as a white solid, which was filtered under nitrogen and dried *in vacuo*.

Yield 5.1 g.
Molar ratio of paroxetine to hypophosphorous acid = 1:1
IR nujol mull:
Bands at *2352, 1602, 1466, 1377, 1151, 1975, 836, 722, 539* cm^{-1}.
X-ray diffractogram ($CuK_{2\alpha}$)

Angle [°2θ]	Rel. Int [%]
8.2	6.2
9.9	1.1
12.9	1.7
15.6	30.3
16.4	46.1
17.5	17.8
18.6	22.9
19.2	67.1
19.5	36.4
21.2	100.0
21.8	41.0
22.5	24.2
22.6	21.3
23.5	11.6
24.2	73.6
24.9	70.3
25.5	17.7
26.1	9.0

27.6	35.7
28.8	40.0
29.3	11.7
29.9	15.4
31.5	13.5
32.7	14.2
33.1	19.0
34.3	8.6

Example 52 Preparation of paroxetine L-(+)-lactate

Paroxetine base (2.1 g) in toluene (5 ml) was added to a suspension of L-(+)-lactic acid (0.63 g, 6.38 mmoles) in methanol (10 ml) and stirred at approximately 20°C until a clear solution formed. The solvents were then removed by evaporation *in vacuo* to afford a white glassy non-crystalline salt of paroxetine L-(+)-lactate. This solid was triturated with heptane and the white powdery solid of crystalline paroxetine L-(+)-lactate was filtered, washed with heptane and dried *in vacuo*.

Melting point = 98-103°C.

IR nujol mull: Bands at *1647, 1588, 1464, 1377, 1195, 1038, 930, 785, 721cm^{-1}*.

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

Angle [°2θ]	Rel. Int [%]
5.4	6.2
7.8	50.7
8.4	1.2
9.4	0.1
10.4	3.6
11.9	1.3
15.6	39.6
16.3	100.0
16.5	95.2
17.4	61.8
17.7	58.3
18.7	37.4
18.9	14.3
19.6	19.0
20.0	4.5
20.9	8.4
21.4	38.8
21.9	93.4
22.1	61.5

22.9	48.2
23.6	45.7
24.0	28.2
24.8	9.1
25.1	11.8
25.6	7.9
26.2	9.4
26.8	18.2
27.8	40.5
28.4	40.7
29.3	11.0
29.6	15.1
30.1	13.2
31.2	8.0
31.6	10.6
32.2	30.2
32.6	15.7
33.0	10.1
33.7	12.1
34.4	12.1

Example 53 - Preparation of paroxetine R-(-)-mandelate

Paroxetine base (4.2 g) in toluene (10 ml) was added to a suspension of R-(-)-mandelic acid (1.94 g, 12.76 mmoles) in methanol (20 ml), and stirred at approximately 20°C until a clear solution was formed. The solvents were removed by low pressure evaporation to produce an off-white glassy solid of non-crystalline paroxetine mandelate. This solid was triturated with heptane (50 ml) and the white powdery crystalline solid was filtered, washed with heptane and dried *in vacuo*. Yield 3.9 g

melting point = 78-83°C

IR nujol mull: Bands at *1617, 1463, 1267, 1183, 1015, 984, 870, 735, 539, 516 cm^{-1}*.

X-ray diffractogram major peaks (Cu $K_{2\alpha}$):

Angle [°2θ]	Rel. Int [%]
3.6	8.7
9.1	8.2
9.5	29.1
10.5	2.7
13.5	7.9
15.5	10.6
18.2	27.3
18.4	28.9

19.1	100.0
19.5	40.5
20.4	66.4
21.6	30.5
23.0	24.9
23.6	24.7
25.3	18.5
27.2	32.1
27.7	24.9
28.0	20.7
28.8	22.0
29.3	19.9
31.9	15.9
34.1	11.3

Claims

1. A salt of paroxetine with an acid selected from the group consisting of sulphuric, tartaric, oxalic, fumaric, propionic, formic, glutamic, succinic, benzoic, citric, nitric, phosphoric, 4-methylbenzenesulphonic, hypophosphorous, lactic, and mandelic acids and glycine.

2 A salt of paroxetine with sulphuric, tartaric, *meso*-tartaric, oxalic, fumaric, glutamic, succinic, citric or phosphoric acid, in which the ratio of paroxetine to the acid (by mole) is 1:1, 2:1 or 3:1 and, in the case where the ratio is less than the theoretical maximum, the salt is a hydrogen salt or a mixed salt with a cation other than hydrogen.

3. A salt of paroxetine with tartaric, glutamic, lactic or mandelic acid, in which the acid is in the D or L-form or a racemic mixture thereof.

4. A compound according to any one of the preceding claims, in non-crystalline form.

5. A compound according to claim 1, 2, or 3, in crystalline form.

6. A process for the preparation of a compound as claimed in any preceding claim, by precipitation, spray drying or freeze drying a solution of a paroxetine salt, or by vacuum drying of oils of a paroxetine salt, or solidification of a melt of a paroxetine salt.

7. A process for the preparation of a compound as claimed in any one of claims 1 to 5, by crystallization or re-crystallization from a solution of a paroxetine salt.

8. A process according to claim 6 or 7 in which the solution, oil or melt of a paroxetine salt is prepared by treating paroxetine free base or an organic acid salt thereof with an acid or a salt thereof (including a hydrogen salt), or by contacting a paroxetine hydrogen salt with a cation other than hydrogen.

9. A method for treating and/or preventing any one or more of the Disorders by administering an effective and/or prophylactic amount of a compound according to any one of claims 1 to 5 to a sufferer in need thereof.

10. A pharmaceutical composition for use in the treatment and/or prevention of the Disorders which comprises a compound according to any one of claims 1 to 5 or a product of the process of any one of claims 6 to 8, together with a pharmaceutically acceptable carrier.