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Road, Hallen, Bristol BS10 7ZE (GB). TYLER, Simon, Nicholas, George [GB/GB]; AstraZeneca, Avlon Works, Severn Road, Hallen, Bristol BS10 7ZE (GB).

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(74) Agent: GLOBAL INTELLECTUAL PROPERTY; AstraZeneca AB, S-151 85 Södertälje (SE).

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(71) Applicant (for all designated States except MG, US): ASTRAZENECA AB [SE/SE]; S-151 85 Södertälje (SE).

(71) Applicant (for MG only): ASTRAZENECA UK LIMITED [GB/GB]; 15 Stanhope Gate, London, Greater London W1K 1LN (GB).

(72) Inventors; and

(75) Inventors/Applicants (for US only): CHAFFEY, Julian, Gordon, Knight [GB/GB]; AstraZeneca, Avlon Works, Severn Road, Hallen, Bristol BS10 7ZE (GB). GILDAY, John, Peter [GB/GB]; AstraZeneca, Avlon Works, Severn Road, Hallen, Bristol BS10 7ZE (GB). HOILE, David [GB/GB]; AstraZeneca, Avlon Works, Severn Road, Hallen, Bristol BS10 7ZE (GB). HOPES, Philip [GB/GB]; AstraZeneca, Avlon Works, Severn

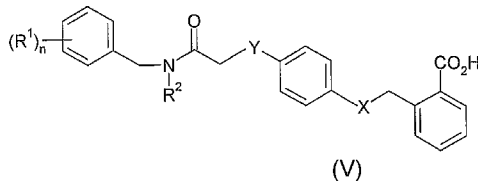
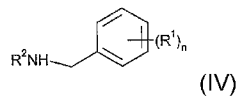
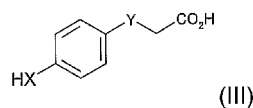
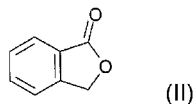
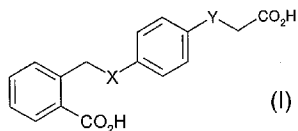
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(54) Title: CHEMICAL PROCESS



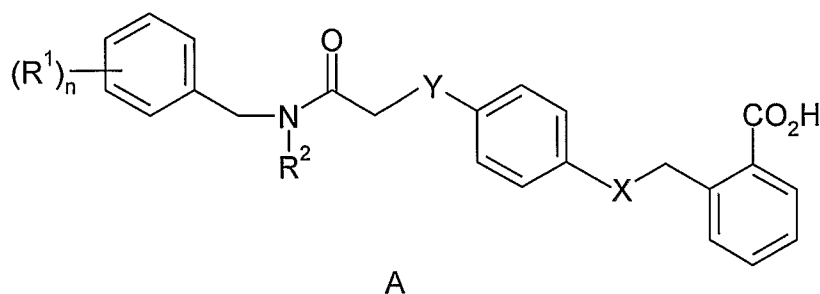
(57) Abstract: A process for the preparation of a compound of formula (I) in which Y is absent or represents methylene, and X is O or S which comprises reacting a compound of formula (II) with a compound of formula (III) in which Y is absent or represents methylene, and X is O or S or a salt thereof optionally in the presence of a base and optionally in the presence of an inert solvent, at a temperature in the range of 0 to 150°C and reaction of the compound of formula (I) with a compound of formula (IV) to give a compound of formula (V) or a salt thereof.

- 1 -

CHEMICAL PROCESS

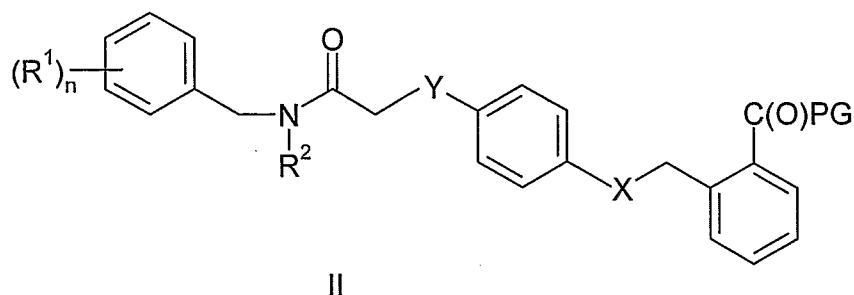
The present invention relates to processes for preparing certain benzoic acid derivatives that have utility in treating clinical conditions associated with insulin resistance and to novel intermediates used in this process.

WO 2004/000790 (PCT/GB02/05743) discloses compounds of formula A



wherein n is 0, 1 or 2 and R¹ represents halo, a C₁₋₄alkyl group which is optionally substituted by one or more fluoro, a C₁₋₄alkoxy group which is optionally substituted by one or more fluoro and wherein when n is 2 the substituents R¹ may be the same or different; R² represents a C₂₋₈alkyl group which is optionally interrupted by oxygen; Y is absent or represents methylene; and X is O or S; and pharmaceutically acceptable salts and prodrugs thereof have utility in treating clinical conditions associated with insulin resistance.

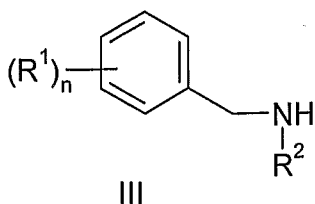
In this application processes for the preparation of compounds of formula A are described as follows. Compounds of formula A may be prepared by reacting a compound of formula II



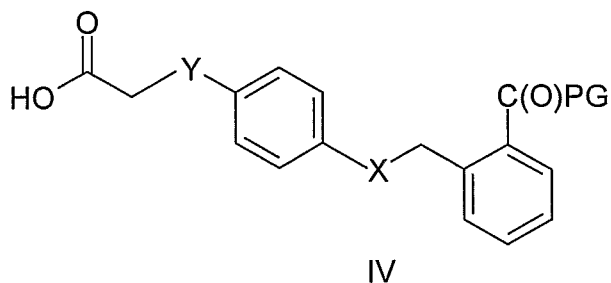
in which R¹, R², X and Y are as previously defined and PG represents a protecting group for a carboxylic hydroxy group as described in the standard text "Protective Groups in Organic Synthesis", 2nd Edition (1991) by Greene and Wuts, with a de-protecting agent.

- 2 -

Compounds of formula II may be prepared by reacting a compound of formula III

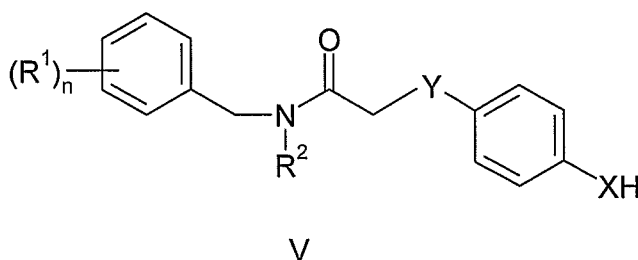


or a salt thereof, for example a hydrochloride salt, in which R^1 , R^2 and n are as previously defined with a compound of formula IV



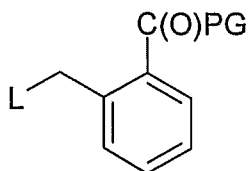
or the acid chloride thereof in which X , Y and PG are as previously defined in an inert solvent, for example dichloromethane, optionally in the presence of a coupling agent, for example 4-dimethylaminopyridine or 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride, at a temperature in the range of -25°C to 150°C .

Compounds of formula II may also be prepared by reacting a compound of formula V



in which R^1 , n , R^2 , X and Y are as previously defined with a compound of formula VI

- 3 -



VI

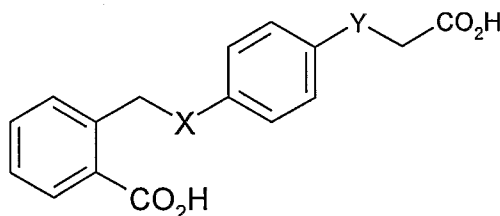
in which PG is as previously defined and L represents a leaving group, for example halo, e.g. bromo, optionally in the presence of solvent, for example acetonitrile, and optionally in the presence of a base, for example potassium carbonate, at a temperature in the range of 0 to 150°C.

J. Med. Chem. 1977, Vol. 20, p66-70 describes the preparation of (4-{[2-(carboxy)benzyl]thio}phenyl)acetic acid in 32% yield from ethyl 4-mercaptophenyl acetate and ethyl 2-bromomethylbenzoate. The (4-{[2-(carboxy)benzyl]thio}phenyl)acetic acid obtained was used in the synthesis of a dibenz[b,e]thiepina-acetic acid.

10

A new process has now been found that reduces the problems encountered in these previously described processes.

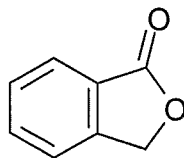
The present invention provides a process for the preparation of a compound of formula I



I

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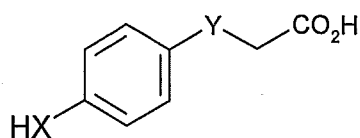
in which Y is absent or represents methylene, and X is O or S which comprises reacting a compound of formula II



II

- 4 -

with a compound of formula III

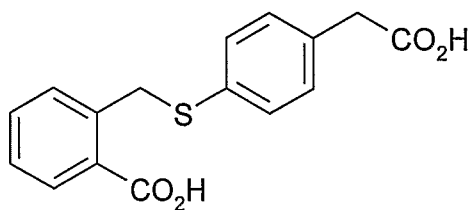


III

in which Y is absent or represents methylene, and X is O or S or a salt thereof optionally
in the presence of a base and optionally in the presence of an inert solvent, at a temperature
5 in the range of 0 to 150°C.

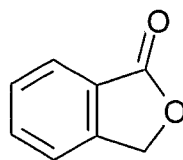
When a base is used the compound of formula I is isolated after acidification of the
reaction mixture.

10 In particular the present invention provides a process for the preparation of a compound of
formula IA



IA

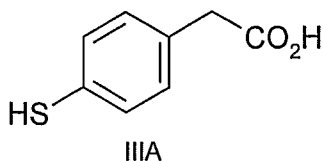
which comprises reacting a compound of formula II



II

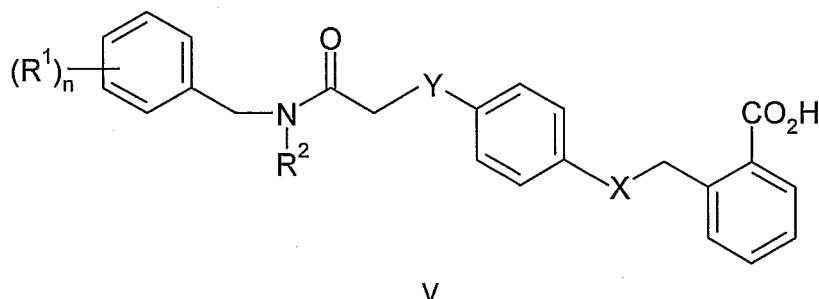
- 5 -

with a compound of formula IIIA



- 5 or a salt thereof optionally in the presence of a base and optionally in the presence of an inert solvent, for example ethanol, at a temperature in the range of 0 to 150°C. These processes provides a considerable saving in cost over previously described processes as they employ commercially available starting materials and use fewer steps. The intermediate has the advantage of being a crystalline material that can be easily purified by
- 10 recrystallisation and this results in an increase in purity of the final product. In previous processes chromatography had to be used to purify intermediate oils. In addition the new processes reduce the use of toxic chemicals eg *N*-bromosuccinimide.

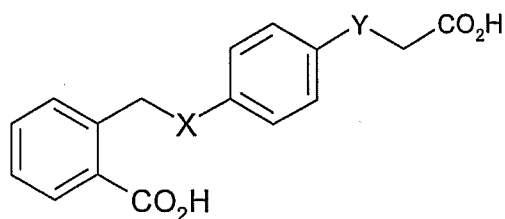
15 In another aspect the present invention provides a process for the preparation of a compound of formula V



wherein n is 0, 1 or 2 and R¹ represents halo, a C₁₋₄alkyl group which is optionally substituted by one or more fluoro, a C₁₋₄alkoxy group which is optionally substituted by one or more fluoro and wherein when n is 2 the substituents R¹ may be the same or

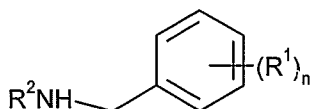
20 different, R² represents a C₂₋₈alkyl group which is optionally interrupted by oxygen, Y is absent or represents methylene and X is O or S, which comprises reacting a compound of formula I

- 6 -



I

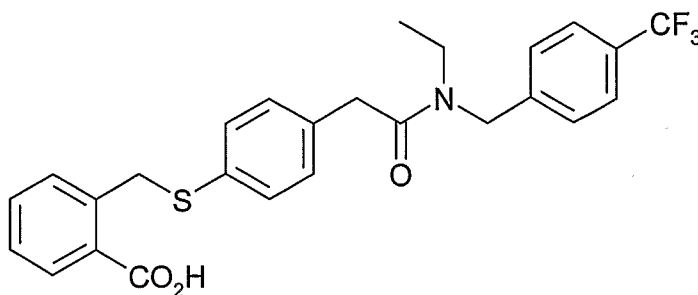
wherein Y is absent or represents methylene and X is O or S with a compound of formula IV



IV

wherein n is 0, 1 or 2 and R¹ represents halo, a C₁₋₄alkyl group which is optionally substituted by one or more fluoro, a C₁₋₄alkoxy group which is optionally substituted by one or more fluoro and wherein when n is 2 the substituents R¹ may be the same or different, R² represents a C₂₋₈alkyl group which is optionally interrupted by oxygen, optionally in the presence of a coupling agent and optionally in the presence of solvent, for example tetrahydrofuran or acetonitrile at a temperature in the range of -100°C to 150°C.

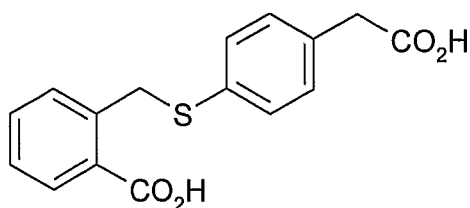
In another aspect the present invention provides a process for the preparation of a compound of formula VA



VA

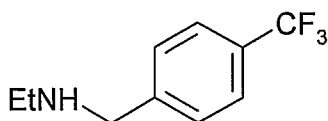
- 7 -

which comprises reacting a compound of formula I A



IA

with a compound of formula IVA

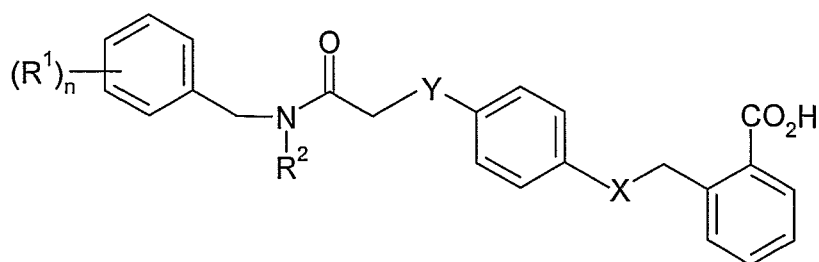


IVA

optionally in the presence of a coupling agent for example 1,1-carbonyl diimidazole and optionally in the presence of solvent, for example tetrahydrofuran, at a temperature in the range of 0 to 150°C.

This process may also be performed using a salt of the compound of formula IV and generating the free amine *in situ* by reaction with a base for example triethylamine or sodium hydroxide.

In another aspect the present invention provides a process for the preparation of a compound of formula V



V

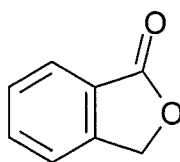
- 8 -

wherein n is 0, 1 or 2 and R¹ represents halo, a C₁₋₄alkyl group which is optionally substituted by one or more fluoro, a C₁₋₄alkoxy group which is optionally substituted by one or more fluoro and wherein when n is 2 the substituents R¹ may be the same or different, R² represents a C₂₋₈alkyl group which is optionally interrupted by oxygen,

5 Y is absent or represents methylene and X is O or S ,

which comprises

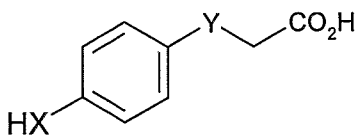
a) reacting a compound of formula II



II

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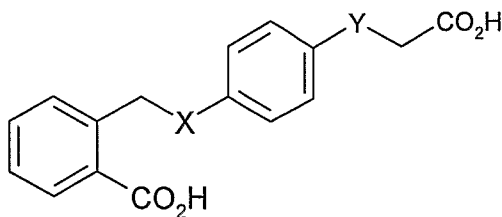
with a compound of formula III



III

15

wherein Y is absent or represents methylene and X is O or S or a salt thereof optionally in the presence of a base for example sodium ethoxide and optionally in the presence of solvent, for example ethanol, at a temperature in the range of 0 to 150°C to give a compound of formula I



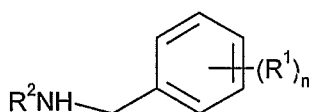
I

20

- 9 -

wherein Y is absent or represents methylene and X is O or S and then

b) reacting the compound of formula I with a compound of formula IV



IV

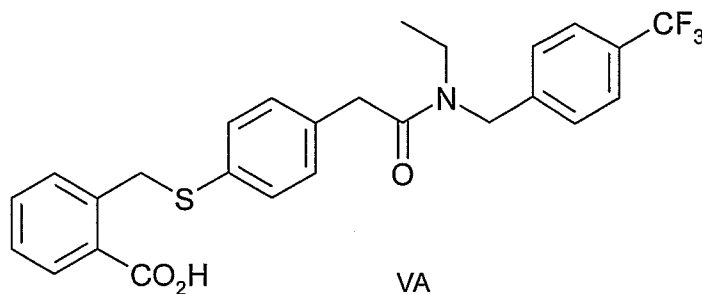
5

wherein n is 0, 1 or 2 and R¹ represents halo, a C₁₋₄alkyl group which is optionally substituted by one or more fluoro, a C₁₋₄alkoxy group which is optionally substituted by one or more fluoro and wherein when n is 2 the substituents R¹ may be the same or different, R² represents a C₂₋₈alkyl group which is optionally interrupted by oxygen,
 10 wherein n is 0, 1 or 2 and R¹ represents halo, a C₁₋₄alkyl group which is optionally substituted by one or more fluoro, a C₁₋₄alkoxy group which is optionally substituted by one or more fluoro and wherein when n is 2 the substituents R¹ may be the same or different, R² represents a C₂₋₈alkyl group which is optionally interrupted by oxygen, optionally in the presence of a coupling agent and optionally in the presence of solvent,
 15 for example tetrahydrofuran, at a temperature in the range of 0 to 150°C .

This process may also be performed using a salt of the compound of formula IV and generating the free amine *in situ* by reaction with a base for example optionally in the presence of a base for example sodium ethoxide

20

In another aspect the present invention provides a process for the preparation of a compound of formula VA

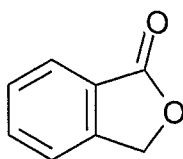


VA

- 10 -

which comprises

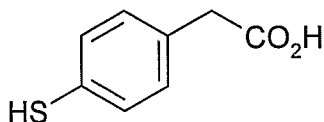
a) reacting a compound of formula II



II

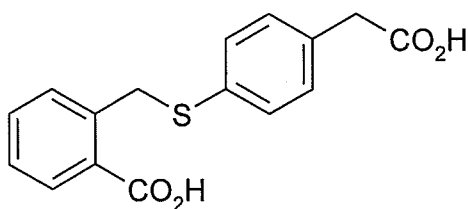
5

with a compound of formula IIIA



IIIA

10 or a salt thereof optionally in the presence of a base for example sodium ethoxide and optionally in the presence of solvent, for example ethanol, at a temperature in the range of 0 to 150°C to give a compound of formula IA



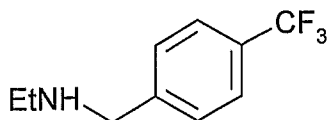
IA

15

and then

b) reacting the compound of formula IA with a compound of formula IVA

- 11 -

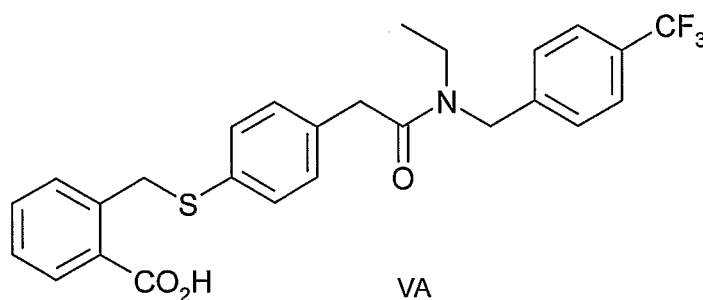


IVa

optionally in the presence of a coupling agent for example a 1,1-carbonyl diimidazole and optionally in the presence of solvent, for example tetrahydrofuran, at a temperature in the range of 0 to 150°C and optionally step c)

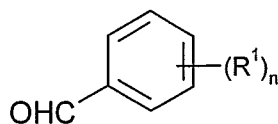
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c) reacting a compound of formula VA



VA

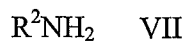
10 with 2-methylpropan-2-amine (t-butylamine) in a diluent (for example acetonitrile) at a temperature in the range of 0 to 100°C to give 2-((4-(2-((2-ethyl-4-(trifluoromethyl)benzyl)amino)-2-oxoethyl)phenyl)thio)methyl)benzoic acid 2-methylpropan-2-amine salt (1:1). Compounds of formula IV may be prepared by reacting a compound of formula VI



VI

15

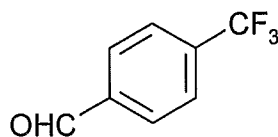
with a compound of formula VII



- 12 -

in an inert solvent for example toluene and then reducing the imine obtained for example by catalytic hydrogenation e.g under pressure or by use of a hydride e.g sodium borohydride.

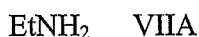
Compounds of formula IVA may be prepared by reacting a compound of formula VIA



VIA

5

with a compound of formula VIIA



10 in an inert solvent for example toluene and then reducing the imine obtained for example by catalytic hydrogenation e.g. under pressure.

Suitable bases include a carbonate base (e.g sodium carbonate or potassium carbonate optionally in a finely divided state e.g. 235 mesh), an alkali metal C₁₋₄ alkoxide (e.g.

15 sodium methoxide, lithium methoxide, potassium methoxide, sodium ethoxide, lithium ethoxide, potassium ethoxide, sodium propoxide, lithium propoxide, potassium propoxide, sodium *isopropoxide*, lithium *isopropoxide*, potassium *isopropoxide*, sodium *tert*-butoxide, lithium *tert*-butoxide or potassium *tert*-butoxide), an alkali metal hydroxide (e.g. sodium hydroxide, lithium hydroxide or potassium methoxide), an alkali metal hydride (for
20 example sodium hydride) or a base such as lithium diisopropylamide (LDA) or lithium (bistrimethylsilylamide (LiHMDS). A particular base is sodium ethoxide.

The expression "inert solvent" refers to a solvent that does not react with the starting materials, reagents, intermediates or products in a manner that adversely affects the yield
25 of the desired product. Suitable inert solvents include C₁₋₄ alkanol (e.g.methanol, ethanol, propanol *isopropanol*, *tert*-butanol), acetonitrile, *N*-methylpyrrolidin-2-one (NMP), dimethylsulfoxide (DMSO), *N,N*-dimethylformamide (DMF), *N,N*-dimethylacetamide (DMA), tetrahydrofuran (THF), methyl *tert*-butyl ether (MTBE) or 1,2-dimethoxyethane (DME).

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Suitable coupling agents include 1,1-carbonyl diimidazole, a carbodiimide (e.g. (1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDCI) or dicyclohexylcarbodiimide (DCCI)), O-[(Ethoxycarbonyl)-cyanomethyleneamino]-N,N,N,N-tetramethyluronium BF₄ (TBTU), O-(benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (HBTU), O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (HATU), isobutylchloroformate and thionyl chloride. A particular coupling agent is 1,1-carbonyl diimidazole.

Examples

Example 1

A mixture of 4-mercaptophenylacetic acid (40.40g) and ethanol (395g) was degassed and then a degassed solution of sodium ethoxide in ethanol (152g of a 21% w/w solution) was added. The mixture was again degassed and then phthalide (31.92g) was added and the reaction mixture was boiled under reflux for 5 days. The thick slurry was distilled under nitrogen, then degassed water (300ml) was added and distillation continued until the reaction solvent had been changed from ethanol to water. The clear solution was cooled to 22°C and extracted with ethyl acetate (2x100ml). After screening through a filtration aid (harborlite), the ethyl acetate phase was discarded. Tetrahydrofuran (200ml) was added, followed by 37% hydrochloric acid (38.6 ml) and sodium chloride (72.6g). The aqueous phase was discarded. The organic phase was distilled, further tetrahydrofuran (4x200ml) was added and the distillation continued until the batch was dry. Acetonitrile (510ml) was added and the distillation continued until the tetrahydrofuran has been distilled out. (4-{[2-(carboxy)benzyl]thio}phenyl)acetic acid crystallised out during the solvent exchange. The resultant slurry was cooled to 22°C and the product isolated by filtration, washed with acetonitrile and dried in a vacuum oven at 40°C.

Example 2

(4-{[2-(Carboxy)benzyl]thio}phenyl)acetic acid (15.0g) was dissolved in degassed THF (150ml). The solution was distilled under nitrogen to remove water by collecting approximately 75 ml of THF as distillate. Meanwhile 1,1-carbonyl di-imidazole (CDI) (16.32g) was added to THF (105ml) with stirring under nitrogen to form a slurry. The solution of the acid was added to the stirred CDI slurry under nitrogen at such a rate as to control the rate of evolution of liberated carbon dioxide (approximately 2 hours) as 1-[(4-

- 14 -

{2-(1H-imidazol-1-ylcarbonyl)benzyl]thio}phenylacetyl]-1H-imidazole was formed. A solution of *N*-ethyl-[4-(trifluoromethyl)benzyl]amine (11.17g) in THF (15ml) was added over 2 hours at 22°C. After stirring for 3 hours the THF solution containing *N*-ethyl-2-(4-{2-(1H-imidazol-1-ylcarbonyl)benzyl]thio}phenyl)-*N*-[4-(trifluoromethyl)benzyl]-acetamide was slowly added to 2M hydrochloric acid (94.3ml) with stirring under nitrogen over approximately 4 hours. After overnight stirring sodium chloride (19.2g) was added to saturate the aqueous phase. The aqueous phase was then separated off. The THF layer was evaporated on a rotary evaporator. The resultant oil was dissolved in methyl *tert*-butyl ether (MTBE) (60ml) and water (105ml) added followed by 2M sodium hydroxide (30.6ml). The MTBE layer was discarded. Fresh MTBE (120ml) was added, followed by 37% w/w hydrochloric acid (3.87ml). After washing with water the MTBE solution of the product was set to distillation and the solvent exchanged by acetonitrile. *Tert*-butylamine was added at 30°C. The solution was then heated to 45°C and seeded with finely ground product. After holding for 5 hours the batch was cooled to 22°C. The resultant slurry was filtered, washed with acetonitrile and dried at 40°C to give an off-white solid. The crude product was recrystallised from isopropanol with seeding to give 2-({[4-(2-{ethyl[4-(trifluoromethyl)benzyl]amino}-2-oxoethyl)phenyl]thio}methyl)benzoic acid 2-methylpropan-2-amine salt (1:1). Melting point onset (DSC) is 136°C. The process to prepare this compound forms part of the present invention that is a process wherein the compound of formula VA is reacted with 2-methylpropan-2-amine in an inert solvent at a temperature in the range of 0°C to 100°C to give 2-({[4-(2-{ethyl[4-(trifluoromethyl)benzyl]amino}-2-oxoethyl)phenyl]thio}methyl)benzoic acid 2-methylpropan-2-amine salt (1:1).

¹H NMR (DMSO)

7.728-7.708 d (I=1), 7.678-7.636 t (I=2), 7.425-7.405 d (I=2), 7.286 - 7.265 d (I=1), 7.241-7.114 m (I=5), 7.0878-7.067 d (I=1), 4.709-4.695 s (I=2) (rotamers), 4.585 s (I=2) rotamers, 3.747 - 3.604 s (I=2) rotamers, 3.373 - 3.244 s (I=2) rotamers, 1.242 s (I=9), 1.082 - 0.970 t (I=3) rotamers

¹³C NMR (DMSO)

171.15, 170.34, 143.41, 143.0, 140.0, 135.92, 135.4, 132.98, 129.57, 129.52, 129.46, 129.32, 127.98, 127.88, 127.78, 127.63, 127.33, 126.19, 125.42, 125.18, 125.14, 123.0, 50.05, 47.15, 42.2, 40.5, 34.97, 28.5, 13.8, 12.47.

- 15 -

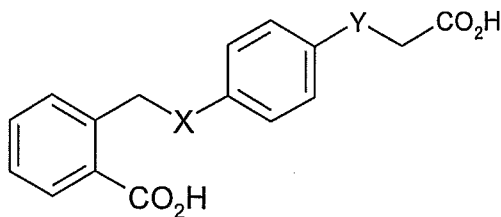
Preparation of Starting Material

Ethylamine hydrochloride (42.8g,1.23 equivalents), 4-trifluoromethyl benzaldehyde (75.3g, 1.00 equivalent) and toluene (188.4mL,2.55 volumes) were stirred and 4M sodium hydroxide solution (129.8 mL,1.23 equivalents) was added over 30 minutes to liberate the ethylamine. The mixture was held at ambient temperature until the reaction to the imine was complete. The biphasic liquor was separated. Water (18.2 mL) was added to the toluene phase and this imine liquor was hydrogenated with 5% Palladium on carbon (73.8mg -weight of palladium employed) as catalyst under a head of hydrogen of 200 kpascals (1 BarG) . The hydrogenated liquor was screened to remove catalyst, separated, washed with water and evaporated to give *N*-ethyl-4-trifluoromethylbenzylamine.

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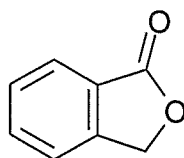
Claims

1. A process for the preparation of a compound of formula I



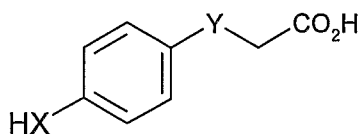
I

- 5 in which Y is absent or represents methylene, and X is O or S which comprises reacting a compound of formula II



II

with a compound of formula III



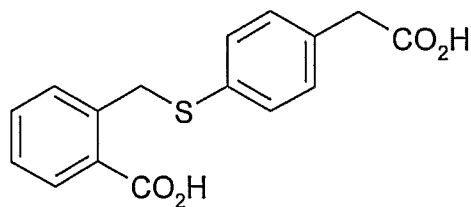
III

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in which Y is absent or represents methylene and X is O or S or a salt thereof optionally in the presence of a base and optionally in the presence of an inert solvent, at a temperature in the range of 0 to 150°C.

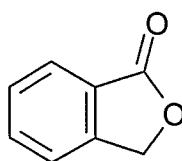
- 15 2. A process for the preparation of a compound of formula IA

- 17 -



IA

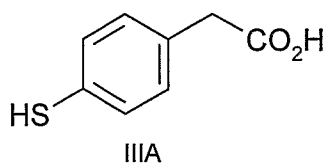
which comprises reacting a compound of formula II



II

5

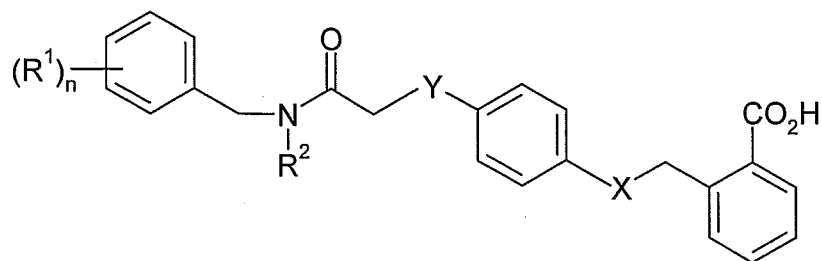
with a compound of formula IIIA



IIIA

10 or a salt thereof optionally in the presence of a base, optionally in the presence of an inert solvent at a temperature in the range of 0 to 150°C.

3. A process for the preparation of a compound of formula V

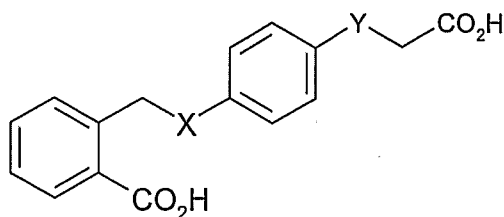


V

15 wherein n is 0, 1 or 2 and R¹ represents halo, a C₁₋₄alkyl group which is optionally substituted by one or more fluoro, a C₁₋₄alkoxy group which is optionally substituted by

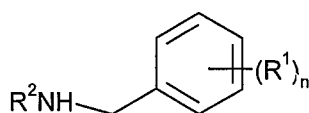
- 18 -

one or more fluoro and wherein when n is 2 the substituents R^1 may be the same or different, R^2 represents a C_{2-8} alkyl group which is optionally interrupted by oxygen, Y is absent or represents methylene and X is O or S, which comprises reacting a compound of formula I



I

wherein Y is absent or represents methylene and X is O or S with a compound of formula IV

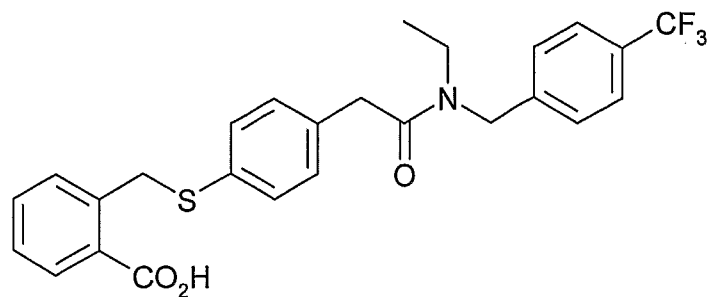


IV

wherein n is 0, 1 or 2 and R^1 represents halo, a C_{1-4} alkyl group which is optionally substituted by one or more fluoro, a C_{1-4} alkoxy group which is optionally substituted by one or more fluoro and wherein when n is 2 the substituents R^1 may be the same or different, R^2 represents a C_{2-8} alkyl group which is optionally interrupted by oxygen, optionally in the presence of a coupling agent and optionally in the presence of solvent at a temperature in the range of -100°C to 150°C .

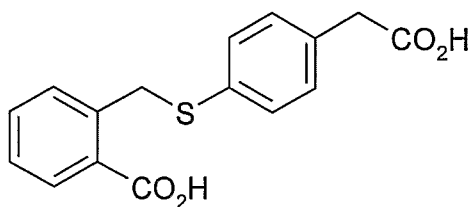
4. A process for the preparation of a compound of formula VA

- 19 -



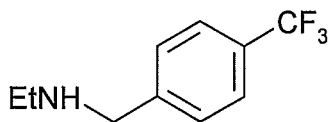
VA

which comprises reacting a compound of formula I A



IA

with a compound of formula IVA

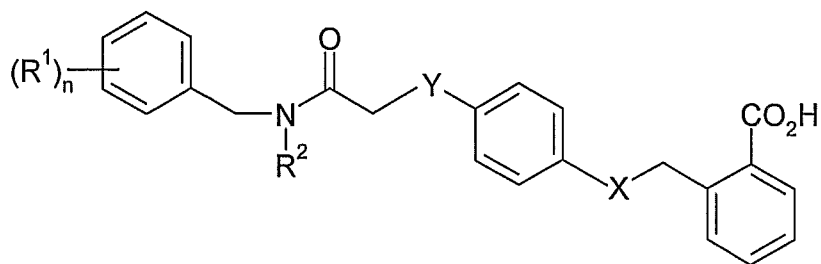


IVA

optionally in the presence of a coupling agent and optionally in the presence of solvent at a temperature in the range of 0 to 150°C.

5. A process for the preparation of a compound of formula V

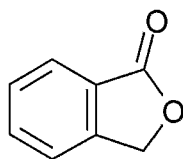
- 20 -



V

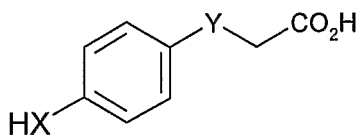
wherein n is 0, 1 or 2 and R¹ represents halo, a C₁₋₄alkyl group which is optionally substituted by one or more fluoro, a C₁₋₄alkoxy group which is optionally substituted by one or more fluoro and wherein when n is 2 the substituents R¹ may be the same or
 5 different, R² represents a C₂₋₈alkyl group which is optionally interrupted by oxygen, Y is absent or represents methylene and X is O or S ,
 which comprises

a) reacting a compound of formula II



II

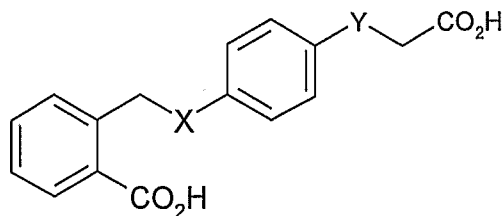
with a compound of formula III



III

15 wherein Y is absent or represents methylene and X is O or S or a salt thereof optionally in the presence of a base and optionally in the presence of solvent at a temperature in the range of 0 to 150°C to give a compound of formula I

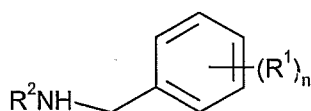
- 21 -



I

wherein Y is absent or represents methylene and X is O or S and then

- 5 b) reacting the compound of formula I with a compound of formula IV

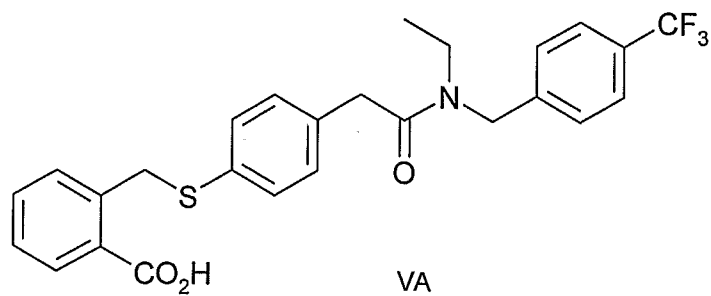


IV

- wherein n is 0, 1 or 2 and R¹ represents halo, a C₁₋₄alkyl group which is optionally substituted by one or more fluoro, a C₁₋₄alkoxy group which is optionally substituted by one or more fluoro and wherein when n is 2 the substituents R¹ may be the same or different, R² represents a C₂₋₈alkyl group which is optionally interrupted by oxygen, wherein n is 0, 1 or 2 and R¹ represents halo, a C₁₋₄alkyl group which is optionally substituted by one or more fluoro, a C₁₋₄alkoxy group which is optionally substituted by one or more fluoro and wherein when n is 2 the substituents R¹ may be the same or different, R² represents a C₂₋₈alkyl group which is optionally interrupted by oxygen, optionally in the presence of a coupling agent and optionally in the presence of solvent, at a temperature in the range of 0 to 150°C .

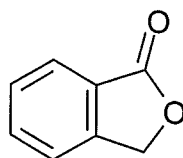
6. A process for the preparation of a compound of formula VA

- 22 -



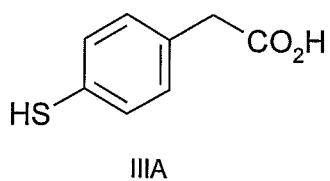
which comprises

- a) reacting a compound of formula II



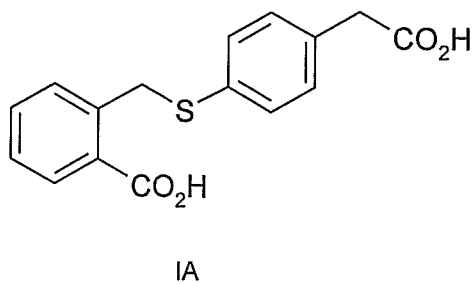
5

with a compound of formula IIIA



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or a salt thereof optionally in the presence of a base and optionally in the presence of solvent at a temperature in the range of 0 to 150°C to give a compound of formula IA

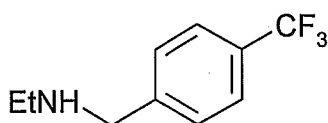


15

- 23 -

and then

- b) reacting the compound of formula IA with a compound of formula IVA



IVA

5

optionally in the presence of a coupling agent and optionally in the presence of solvent at a temperature in the range of 0 to 150°C .

7. A process according to claim 6 wherein the compound of formula VA is reacted
10 with 2-methylpropan-2-amine in an inert solvent at a temperature in the range of 0°C to 100°C to give 2-({[4-(2-{ethyl[4-(trifluoromethyl)benzyl]amino}-2-oxoethyl)phenyl]thio}methyl)benzoic acid 2-methylpropan-2-amine salt (1:1) .