CLAIMS

What is claimed is:

1. A process for preparing 2-(cyclohexylmethyl)-*N*-{2-[(2S)-1-methylpyrrolidin-2-yl]ethyl}-1,2,3,4-tetrahydroisoquinoline-7-sulfonamide, or a pharmaceutically acceptable salt thereof, or a solvate or hydrate of a pharmaceutically acceptable salt comprising:

a) coupling (-)-2-(2-aminoethyl)-1-methylpyrrolidine with an amine-protected tetrahydroquinoline-7-sulfonyl chloride to give an amine-protected *N*-{2-[(2*S*)-1-methylpyrrolidin-2-yl]ethyl}-1,2,3,4-tetrahydroisoquinoline-7-sulfonamide;

b) deprotecting the amine-protected *N*-{2-[(2S)-1-methylpyrrolidin-2-yl]ethyl}-1,2,3,4-tetrahydroisoquinoline-7-sulfonamide to give *N*-{2-[(2S)-1-methylpyrrolidin-2-yl]ethyl}-1,2,3,4-tetrahydroisoquinoline-7-sulfonamide or a salt thereof;

c) reductively aminating *N*-{2-[(2S)-1-methylpyrrolidin-2-yl]ethyl}-1,2,3,4-tetrahydroisoquinoline-7-sulfonamide or a salt thereof with cyclohexanecarboxaldehyde to form 2-(cyclohexylmethyl)-*N*-{2-[(2S)-1-methylpyrrolidin-2-yl]ethyl}-1,2,3,4-tetrahydroisoquinoline-7-sulfonamide;

d) optionally reacting 2-(cyclohexylmethyl)-*N*-{2-[(2S)-1-methylpyrrolidin-2-yl]ethyl}-1,2,3,4-tetrahydroisoquinoline-7-sulfonamide, or a hydrate or solvate thereof, with a stoichiometric amount or an excess of a salt-forming acid in a solvent to form a salt or a hydrate or solvate thereof; and

e) optionally recrystallizing the product of step d).

2. The process according to claim 1, wherein the amine-protected tetrahydroquinoline-7-sulfonyl chloride is 2-(2,2,2-trifluoroacetyl)-1,2,3,4-tetrahydroisoquinoline-7-sulfonyl chloride and the amine-protected *N*-{2-[(2*S*)-1-methylpyrrolidin-2-yl]ethyl}-1,2,3,4-tetrahydroisoquinoline-7-sulfonamide is 2-(2,2,2-trifluoroacetyl)-*N*-{2-[(2*S*)-1-methylpyrrolidin-2-yl]ethyl}-1,2,3,4-tetrahydroisoquinoline-7-sulfonamide.

3. The process according to claim 1, wherein the coupling in step a) is performed in the presence of an inorganic or organic base and in an inert solvent.

4. The process according to claim 3, wherein the base is selected from the group consisting of sodium hydroxide, potassium hydroxide, lithium hydroxide and triethylamine.

5. The process according to claim 1, wherein deprotecting in step b) is performed under basic conditions and in an alcohol.

6. The process according to claim 1, wherein the reductive amination of step c) is performed in an organic solvent in the presence of a reducing agent.

7. The process according to claim 6, wherein the reducing agent is formic acid.

8. The process according to claim 1, wherein the salt formed in step d) is a pharmaceutically acceptable salt.

9. The process according to claim 1, further comprising formulating 2-(cyclohexylmethyl)-*N*-{2-[(2*S*)-1-methylpyrrolidin-2-yl]ethyl}-1,2,3,4-tetrahydroisoquinoline-7-sulfonamide or a pharmaceutically acceptable salt thereof, or a solvate or hydrate of a pharmaceutically acceptable salt, with one or more pharmaceutically acceptable carrier agents, bulking agents, solvents, diluents and other excipients.

10. The process according to claim 1, wherein the salt-forming acid in step d) is fumaric acid to provide 2-(cyclohexylmethyl)-*N*-{2-[(2*S*)-1-methylpyrrolidin-2-yl]ethyl}-1,2,3,4-tetrahydroisoquinoline-7-sulfonamide difumarate monohydrate.

11. The process according to claim 10, further comprising formulating 2-(cyclohexylmethyl)-*N*-{2-[(2*S*)-1-methylpyrrolidin-2-yl]ethyl}-1,2,3,4-tetrahydroisoquinoline-7-sulfonamide difumarate monohydrate with one or more pharmaceutically acceptable carrier agents, bulking agents, solvents, diluents and other excipients.

12. The process according to claim 1, comprising:

a) coupling (-)-2-(2-aminoethyl)-1-methylpyrrolidine with 2-(2,2,2-trifluoroacetyl)-1,2,3,4-tetrahydroquinoline-7-sulfonyl chloride to give 2-(2,2,2-trifluoroacetyl)-*N*-{2-[(2*S*)-1-methylpyrrolidin-2-yl]ethyl}-1,2,3,4-tetrahydroisoquinoline-7-sulfonamide;

b) deprotecting 2-(2,2,2-trifluoroacetyl)-*N*-{2-[(2*S*)-1-methylpyrrolidin-2-yl]ethyl}-1,2,3,4-tetrahydroisoquinoline-7-sulfonamide to give *N*-{2-[(2*S*)-1-methylpyrrolidin-2-yl]ethyl}-1,2,3,4-tetrahydroisoquinoline-7-sulfonamide, or a salt thereof;

c) reductively aminating *N*-{2-[(2*S*)-1-methylpyrrolidin-2-yl]ethyl}-1,2,3,4-tetrahydroisoquinoline-7-sulfonamide, or a salt thereof with cyclohexanecarboxaldehyde to form 2-(cyclohexylmethyl)-*N*-{2-[(2S)-1-methylpyrrolidin-2-yl]ethyl}-1,2,3,4-tetrahydroisoquinoline-7-sulfonamide;

d) optionally reacting 2-(cyclohexylmethyl)-*N*-{2-[(2S)-1-methylpyrrolidin-2-yl]ethyl}-1,2,3,4-tetrahydroisoquinoline-7-sulfonamide with a stoichiometric amount or an excess of a salt-forming acid in a solvent to form a salt, or a hydrate or solvate thereof; and

e) optionally recrystallizing the product of step d).

13. The process according to claim 12, further comprising formulating 2-(cyclohexylmethyl)-*N*-{2-[(2*S*)-1-methylpyrrolidin-2-yl]ethyl}-1,2,3,4-tetrahydroisoquinoline-7-sulfonamide or a pharmaceutically acceptable salt, or a solvate or hydrate of a pharmaceutically acceptable salt, with one or more pharmaceutically acceptable carrier agents, bulking agents, solvents, diluents and other excipients.

14. The process according to claim 12, wherein the salt-forming acid in step d) is fumaric acid to provide 2-(cyclohexylmethyl)-*N*-{2-[(2*S*)-1-methylpyrrolidin-2-yl]ethyl}-1,2,3,4-tetrahydroisoquinoline-7-sulfonamide difumarate monohydrate.

15. The process according to claim 14, further comprising formulating 2-(cyclohexylmethyl)-*N*-{2-[(2*S*)-1-methylpyrrolidin-2-yl]ethyl}-1,2,3,4-tetrahydroisoquinoline-7-sulfonamide difumarate monohydrate with one or more

pharmaceutically acceptable carrier agents, bulking agents, solvents, diluents and other excipients.

16. The process according to claim 1, comprising:

a) coupling (-)-2-(2-aminoethyl)-1-methylpyrrolidine with an amine-protected tetrahydroquinoline-7-sulfonyl chloride in the presence of a base to give an amine-protected *N*-{2-[(2*S*)-1-methylpyrrolidin-2-yl]ethyl}-1,2,3,4-tetrahydroisoquinoline-7-sulfonamide;

b) deprotecting the amine-protected *N*-{2-[(2*S*)-1-methylpyrrolidin-2-yl]ethyl}-1,2,3,4-tetrahydroisoquinoline-7-sulfona under basic conditions and in a solvent selected from an alcohol and a combination of water with an ethereal solvent, to give *N*-{2-[(2*S*)-1-methylpyrrolidin-2-yl]ethyl}-1,2,3,4-tetrahydroisoquinoline-7-sulfonamide or a salt thereof;

c) reductively aminating *N*-{2-[(2*S*)-1-methylpyrrolidin-2-yl]ethyl}-1,2,3,4-tetrahydroisoquinoline-7-sulfonamide or a salt thereof with cyclohexanecarboxaldehyde in the presence of a reducing agent and in a solvent selected from an alcohol and a combination of water with an ethereal solvent, to form 2-(cyclohexylmethyl)-*N*-{2-[(2S)-1-methylpyrrolidin-2-yl]ethyl}-1,2,3,4-tetrahydroisoquinoline-7-sulfonamide;

d) optionally reacting 2-(cyclohexylmethyl)-*N*-{2-[(2S)-1-methylpyrrolidin-2-yl]ethyl}-1,2,3,4-tetrahydroisoquinoline-7-sulfonamide with a stoichiometric amount or an excess of a salt-forming acid in a solvent to form a salt or a hydrate or solvate thereof; and

e) optionally recrystallizing the product of step d).

17. The compound 2-(2,2,2-trifluoroacetyl)-*N*-{2-[(2*S*)-1-methylpyrrolidin-2-yl]ethyl}-1,2,3,4-tetrahydroisoquinoline-7-sulfonamide.

18. A process for preparing 2-(2,2,2-trifluoroacetyl)-*N*-{2-[(2*S*)-1-methylpyrrolidin-2-yl]ethyl}-1,2,3,4-tetrahydroisoquinoline-7-sulfonamide comprising coupling 2-(2,2,2-trifluoroacetyl)-1,2,3,4-tetrahydroisoquinoline-7-sulfonyl chloride and (-)-2-(2-aminoethyl)-1-methylpyrrolidine in the presence of a base and in an inert solvent.

19. A process for preparing 2-(cyclohexylmethyl)-*N*-{2-[(2*S*)-1-methylpyrrolidin-2-yl]ethyl}-1,2,3,4-tetrahydroisoquinoline-7-sulfonamide, comprising the step of coupling 2-(2,2,2-trifluoroacetyl)-1,2,3,4-tetrahydroisoquinoline-7-sulfonyl chloride and (-)-2-(2-aminoethyl)-1-methylpyrrolidine in the presence of a base and in an inert solvent.

20. A process for preparing *N*-{2-[(2*S*)-1-methylpyrrolidin-2-yl]ethyl}-1,2,3,4-tetrahydroisoquinoline-7-sulfonamide comprising deprotecting 2-(2,2,2-trifluoroacetyl)-*N*-{2-[(2*S*)-1-methylpyrrolidin-2-yl]ethyl}-1,2,3,4-tetrahydroisoquinoline-7-sulfonamide in the presence of a base.

21. A process for preparing 2-(cyclohexylmethyl)-*N*-{2-[(2*S*)-1-methylpyrrolidin-2-yl]ethyl}-1,2,3,4-tetrahydroisoquinoline-7-sulfonamide, comprising the step of deprotecting 2-(2,2,2-trifluoroacetyl)-*N*-{2-[(2*S*)-1-methylpyrrolidin-2-yl]ethyl}-1,2,3,4-tetrahydroisoquinoline-7-sulfonamide in the presence of a base.

CLAIMS

1. A process for preparing 2-(cyclohexylmethyl)-*N*-{2-[(2S)-1-methylpyrrolidin-2-yl]ethyl}-1,2,3,4-tetrahydroisoquinoline-7-sulfonamide, or a pharmaceutically acceptable salt thereof, or a solvate or hydrate of a pharmaceutically acceptable salt comprising:

a) coupling (-)-2-(2-aminoethyl)-1-methylpyrrolidine with an amine-protected tetrahydroquinoline-7-sulfonyl chloride to give an amine-protected *N*-{2-[(2*S*)-1-methylpyrrolidin-2-yl]ethyl}-1,2,3,4-tetrahydroisoquinoline-7-sulfonamide;

b) deprotecting the amine-protected *N*-{2-[(2S)-1-methylpyrrolidin-2-yl]ethyl}-1,2,3,4-tetrahydroisoquinoline-7-sulfonamide to give *N*-{2-[(2S)-1-methylpyrrolidin-2-yl]ethyl}-1,2,3,4-tetrahydroisoquinoline-7-sulfonamide or a salt thereof;

c) reductively aminating *N*-{2-[(2S)-1-methylpyrrolidin-2-yl]ethyl}-1,2,3,4-tetrahydroisoquinoline-7-sulfonamide or a salt thereof with cyclohexanecarboxaldehyde to form 2-(cyclohexylmethyl)-*N*-{2-[(2S)-1-methylpyrrolidin-2-yl]ethyl}-1,2,3,4-tetrahydroisoquinoline-7-sulfonamide;

d) optionally reacting 2-(cyclohexylmethyl)-*N*-{2-[(2S)-1-methylpyrrolidin-2-yl]ethyl}-1,2,3,4-tetrahydroisoquinoline-7-sulfonamide, or a hydrate or solvate thereof, with a stoichiometric amount or an excess of a salt-forming acid in a solvent to form a salt or a hydrate or solvate thereof; and

e) optionally recrystallizing the product of step d).

2. The process according to claim 1, wherein the amine-protected tetrahydroquinoline-7-sulfonyl chloride is 2-(2,2,2-trifluoroacetyl)-1,2,3,4-tetrahydroisoquinoline-7-sulfonyl chloride and the amine-protected N-{2-[(2S)-1-methylpyrrolidin-2-yl]ethyl}-1,2,3,4-tetrahydroisoquinoline-7-sulfonamide is 2-(2,2,2-trifluoroacetyl)-N-{2-[(2S)-1-methylpyrrolidin-2-yl]ethyl}-1,2,3,4-tetrahydroisoquinoline-7-sulfonamide.

3. The process according to claim 1, wherein the coupling in step a) is performed in the presence of an inorganic or organic base and in an inert solvent.

4. The process according to claim 3, wherein the base is selected from the group consisting of sodium hydroxide, potassium hydroxide, lithium hydroxide and triethylamine.

5. The process according to claim 1, wherein deprotecting in step b) is performed under basic conditions and in an alcohol.

6. The process according to claim 1, wherein the reductive amination of step c) is performed in an organic solvent in the presence of a reducing agent.

7. The process according to claim 6, wherein the reducing agent is formic acid.

8. The process according to claim 1, wherein the salt formed in step d) is a pharmaceutically acceptable salt.

9. The process according to claim 1, further comprising formulating 2-(cyclohexylmethyl)-N-{2-[(2S)-1-methylpyrrolidin-2-yl]ethyl}-1,2,3,4-tetrahydroisoquinoline-7-sulfonamide or a pharmaceutically acceptable salt thereof, or a solvate or hydrate of a pharmaceutically acceptable salt, with one or more pharmaceutically acceptable carrier agents, bulking agents, solvents, diluents and other excipients.

10. The process according to claim 1, wherein the salt-forming acid in step d) is fumaric acid to provide 2-(cyclohexylmethyl)-N-{2-[(2S)-1-methylpyrrolidin-2-yl]ethyl}-1,2,3,4-tetrahydroisoquinoline-7-sulfonamide difumarate monohydrate.

11. The process according to claim 10, further comprising formulating 2-(cyclohexylmethyl)-N-{2-[(2S)-1-methylpyrrolidin-2-yl]ethyl}-1,2,3,4-tetrahydroisoquinoline-7-sulfonamide difumarate monohydrate with one or more pharmaceutically acceptable carrier agents, bulking agents, solvents, diluents and other excipients.

12. The process according to claim 1, comprising:

a) coupling (-)-2-(2-aminoethyl)-1-methylpyrrolidine with 2-(2,2,2-trifluoroacetyl)-1,2,3,4-tetrahydroquinoline-7-sulfonyl chloride to give 2-(2,2,2-trifluoroacetyl)-N-{2-[(2S)-1-methylpyrrolidin-2-yl]ethyl}-1,2,3,4-tetrahydroisoquinoline-7-sulfonamide;

b) deprotecting 2-(2,2,2-trifluoroacetyl)-N-{2-[(2S)-1-methylpyrrolidin-2-yl]ethyl}-1,2,3,4-tetrahydroisoquinoline-7-sulfonamide to give N-{2-[(2S)-1-methylpyrrolidin-2-yl]ethyl}-1,2,3,4-tetrahydroisoquinoline-7-sulfonamide, or a salt thereof;

c) reductively aminating N-{2-[(2S)-1-methylpyrrolidin-2-yl]ethyl}-1,2,3,4-tetrahydroisoquinoline-7-sulfonamide, or a salt thereof with cyclohexanecarboxaldehyde to form 2-(cyclohexylmethyl)-N-{2-[(2S)-1-methylpyrrolidin-2-yl]ethyl}-1,2,3,4-tetrahydroisoquinoline-7-sulfonamide;

d) optionally reacting 2-(cyclohexylmethyl)-N-{2-[(2S)-1-methylpyrrolidin-2-yl]ethyl}-1,2,3,4-tetrahydroisoquinoline-7-sulfonamide with a stoichiometric amount or an excess of a salt-forming acid in a solvent to form a salt, or a hydrate or solvate thereof; and

e) optionally recrystallizing the product of step d).

13. The process according to claim 12, further comprising formulating 2-(cyclohexylmethyl)-N-{2-[(2S)-1-methylpyrrolidin-2-yl]ethyl}-1,2,3,4-tetrahydroisoquinoline-7-sulfonamide or a pharmaceutically acceptable salt, or a solvate or hydrate of a pharmaceutically acceptable salt, with one or more pharmaceutically acceptable carrier agents, bulking agents, solvents, diluents and other excipients.

14. The process according to claim 12, wherein the salt-forming acid in step d) is fumaric acid to provide 2-(cyclohexylmethyl)-N-{2-[(2S)-1-methylpyrrolidin-2-yl]ethyl}-1,2,3,4-tetrahydroisoquinoline-7-sulfonamide difumarate monohydrate.

15. The process according to claim 14, further comprising formulating 2-(cyclohexylmethyl)-N-{2-[(2S)-1-methylpyrrolidin-2-yl]ethyl}-1,2,3,4-tetrahydroisoquinoline-7-sulfonamide difumarate monohydrate with one or more pharmaceutically acceptable carrier agents, bulking agents, solvents, diluents and other excipients.

16. The process according to claim 1, comprising:

a) coupling (-)-2-(2-aminoethyl)-1-methylpyrrolidine with an amine-protected tetrahydroquinoline-7-sulfonyl chloride in the presence of a base to give an amine-protected N-{2-[(2S)-1-methylpyrrolidin-2-yl]ethyl}-1,2,3,4-tetrahydroisoquinoline-7-sulfonamide;

b) deprotecting the amine-protected N-{2-[(2S)-1-methylpyrrolidin-2-yl]ethyl}-1,2,3,4-tetrahydroisoquinoline-7-sulfona under basic conditions and in a solvent selected from an alcohol and a combination of water with an ethereal solvent, to give N-{2-[(2S)-1-methylpyrrolidin-2-yl]ethyl}-1,2,3,4-tetrahydroisoquinoline-7-sulfonamide or a salt thereof;

c) reductively aminating N-{2-[(2S)-1-methylpyrrolidin-2-yl]ethyl}-1,2,3,4-tetrahydroisoquinoline-7-sulfonamide or a salt thereof with cyclohexanecarboxaldehyde in the presence of a reducing agent and in a solvent selected from an alcohol and a combination of water with an ethereal solvent, to form 2-(cyclohexylmethyl)-N-{2-[(2S)-1-methylpyrrolidin-2-yl]ethyl}-1,2,3,4-tetrahydroisoquinoline-7-sulfonamide;

d) optionally reacting 2-(cyclohexylmethyl)-N-{2-[(2S)-1-methylpyrrolidin-2-yl]ethyl}-1,2,3,4-tetrahydroisoquinoline-7-sulfonamide with a stoichiometric amount or an excess of a salt-forming acid in a solvent to form a salt or a hydrate or solvate thereof; and

e) optionally recrystallizing the product of step d).

17. A process for preparing 2-(cyclohexylmethyl)-N-{2-[(2S)-1-methylpyrrolidin-2-yl]ethyl}-1,2,3,4-tetrahydroisoquinoline-7-sulfonamide, comprising the step of coupling 2-(2,2,2-trifluoroacetyl)-1,2,3,4-tetrahydroisoquinoline-7-sulfonyl chloride and (-)-2-(2-aminoethyl)-1-methylpyrrolidine in the presence of a base and in an inert solvent.

18. A process for preparing 2-(cyclohexylmethyl)-N-{2-[(2S)-1-methylpyrrolidin-2-yl]ethyl}-1,2,3,4-tetrahydroisoquinoline-7-sulfonamide, comprising the step of deprotecting 2-(2,2,2-trifluoroacetyl)-N-{2-[(2S)-1-methylpyrrolidin-2-yl]ethyl}-1,2,3,4-tetrahydroisoquinoline-7-sulfonamide in the presence of a base.