CLAIMS

What is claimed is:

1. A process for preparing 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 comprising:

a) reductively aminating 1,2,3,4-tetrahydroisoquinoline, or a salt thereof, with cyclohexanecarboxaldehyde to give 2-cyclohexylmethyl-1,2,3,4-tetrahydroisoquinoline, or a salt thereof;

b) reacting 2-cyclohexylmethyl-1,2,3,4-tetrahydroisoquinoline, or a salt thereof, with excess chlorosulfonic acid to give 2-cyclohexylmethyl-1,2,3,4-tetrahydroisoquinoline-7-sulfonyl chloride HX salt, and optionally recrystallizing the 2-cyclohexylmethyl-1,2,3,4-tetrahydroisoquinoline-7-sulfonyl chloride HX salt;

c) coupling 2-cyclohexylmethyl-1,2,3,4-tetrahydroisoquinoline-7-sulfonyl chloride HX salt with (-)-2-(2-aminoethyl)-1-methylpyrrolidine to form 2-(cyclohexylmethyl)-*N*-{2-[(2*S*)-1-methylpyrrolidin-2-yl]ethyl}-1,2,3,4-tetrahydroisoquinoline-7-sulfonamide;

d) optionally reacting 2-(cyclohexylmethyl)-*N*-{2-[(2*S*)-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).

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

3. The process according to claim 2, wherein the reducing agent is selected from the group consisting of sodium triacetoxyborohydride, sodium borohydride, formic acid, and hydrogen with a catalyst.

4. The process according to claim 1 wherein the reaction of step b) is performed in the presence of a co-solvent.

5. The process according to claim 4, wherein the co-solvent is selected from the group consisting of dichloromethane, chloroform, and 1,2-dichloroethane.

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

7. The process according to claim 6, wherein the organic solvent is selected from the group consisting of dichloromethane, chloroform, 1,2-dichloroethane, methyl *t*-butyl ether, and toluene.

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) reductively aminating 1,2,3,4-tetrahydroisoquinoline, or a salt thereof, with cyclohexanecarboxaldehyde in the presence of a reducing agent and in an organic solvent to give 2-cyclohexylmethyl-1,2,3,4-tetrahydroisoquinoline, or a salt thereof;

b) reacting 2-cyclohexylmethyl-1,2,3,4-tetrahydroisoquinoline, or a salt thereof, with excess chlorosulfonic acid optionally in the presence of a co-solvent to give 2-cyclohexylmethyl-1,2,3,4-tetrahydroisoquinoline-7-sulfonyl chloride HX salt, and optionally recrystallizing the 2-cyclohexylmethyl-1,2,3,4-tetrahydroisoquinoline-7-sulfonyl chloride HX salt;

c) coupling 2-cyclohexylmethyl-1,2,3,4-tetrahydroisoquinoline-7-sulfonyl chloride HX salt with (-)-2-(2-aminoethyl)-1-methylpyrrolidine in an organic solvent to form 2-(cyclohexylmethyl)-*N*-{2-[(2*S*)-1-methylpyrrolidin-2-yl]ethyl}-1,2,3,4-tetrahydroisoquinoline-7-sulfonamide;

d) optionally reacting 2-(cyclohexylmethyl)-*N*-{2-[(2*S*)-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 pharmaceutically acceptable 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 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.

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. A process for preparing 2-cyclohexylmethyl-1,2,3,4-tetrahydroisoquinoline-7-sulfonyl chloride HX salt by reacting 2-cyclohexylmethyl-1,2,3,4-tetrahydroisoquinoline with excess chlorosulfonic acid.

17. 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 reacting 2-cyclohexylmethyl-1,2,3,4-tetrahydroisoquinoline with excess chlorosulfonic acid.

18. The process according to claim 17 wherein the reaction is performed in the presence of a co-solvent.

19. A process for preparing 2-(cyclohexylmethyl)-*N*-{2-[(2*S*)-1-methylpyrrolidin-2-yl]ethyl}-1,2,3,4-tetrahydroisoquinoline-7-sulfonamide by coupling 2-cyclohexylmethyl-1,2,3,4-tetrahydroisoquinoline-7-sulfonyl chloride HX salt with (-)-2-(2-aminoethyl)-1-methylpyrrolidine.

20. The product prepared by reacting 2-cyclohexylmethyl-1,2,3,4-tetrahydroisoquinoline with excess chlorosulfonic acid.

21. The compound 2-cyclohexylmethyl-1,2,3,4-tetrahydroisoquinoline-7-sulfonyl chloride HX salt.

CLAIMS

1. A process for preparing 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 comprising:

a) reductively aminating 1,2,3,4-tetrahydroisoquinoline, or a salt thereof, with cyclohexanecarboxaldehyde to give 2-cyclohexylmethyl-1,2,3,4-tetrahydroisoquinoline, or a salt thereof;

b) reacting 2-cyclohexylmethyl-1,2,3,4-tetrahydroisoquinoline, or a salt thereof, with excess chlorosulfonic acid to give 2-cyclohexylmethyl-1,2,3,4-tetrahydroisoquinoline-7-sulfonyl chloride HX salt;

c) coupling 2-cyclohexylmethyl-1,2,3,4-tetrahydroisoquinoline-7-sulfonyl chloride HX salt with (-)-2-(2-aminoethyl)-1-methylpyrrolidine to form 2-(cyclohexylmethyl)-*N*-{2-[(2*S*)-1-methylpyrrolidin-2-yl]ethyl}-1,2,3,4-tetrahydroisoquinoline-7-sulfonamide;

d) optionally reacting 2-(cyclohexylmethyl)-*N*-{2,[(2*S*)-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).

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

3. The process according to claim 2, wherein the reducing agent is selected from the group consisting of sodium triacetoxyborohydride, sodium borohydride, formic acid, and hydrogen with a catalyst.

4. The process according to claim 1 wherein the reaction of step b) is performed in the presence of a co-solvent.

5. The process according to claim 4, wherein the co-solvent is selected from the group consisting of dichloromethane, chloroform, and 1,2-dichloroethane.

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

7. The process according to claim 6, wherein the organic solvent is selected from the group consisting of dichloromethane, chloroform, 1,2-dichloroethane, methyl, *t*-butyl ether, and toluene.

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) reductively aminating 1,2,3,4-tetrahydroisoquinoline, or a salt thereof, with cyclohexanecarboxaldehyde in the presence of a reducing agent and in an organic solvent to give 2-cyclohexylmethyl-1,2,3,4-tetrahydroisoquinoline, or a salt thereof;

b) reacting 2-cyclohexylmethyl-1,2,3,4-tetrahydroisoquinoline, or a salt thereof, with excess chlorosulfonic acid optionally in the presence of a co-solvent to give 2-cyclohexylmethyl-1,2,3,4-tetrahydroisoquinoline-7-sulfonyl chloride HX salt, and

optionally recrystallizing the 2-cyclohexylmethyl-1,2,3,4-tetrahydroisoquinoline-7-sulfonyl chloride HX salt;

c) coupling 2-cyclohexylmethyl-1,2,3,4-tetrahydroisoquinoline-7-sulfonyl chloride HX salt with (-)-2-(2-aminoethyl)-1-methylpyrrolidine in an organic solvent to form 2-(cyclohexylmethyl)-*N*-{2-[(2*S*)-1-methylpyrrolidin-2-yl]ethyl}-1,2,3,4-tetrahydroisoquinoline-7-sulfonamide;

d) optionally reacting 2-(cyclohexylmethyl)-*N*-{2,[(2*S*)-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 pharmaceutically acceptable 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 thereof, or a solvate or hydrate of 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. 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 reacting 2-cyclohyexylmethyl-1,2,3,4-tetrahydroisoquinoline with excess chlorosulfonic acid.

17. The process according to claim 16 wherein the reaction is performed in the presence of a co-solvent.

18. A process for preparing 2-(cyclohexylmethyl)-*N*-{2-[(2*S*)-1-methylpyrrolidin-2-yl]ethyl}-1,2,3,4-tetrahydroisoquinoline-7-sulfonamide coupling 2-cyclohyexylmethyl-1,2,3,4-tetrahydroisoquinoline-7-sulfonyl chloride HX salt with (-)-2-(2-aminoethyl)-1-methylpyrrolidine.