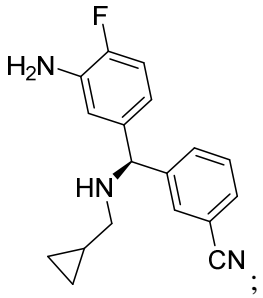
~~We Claim:~~CLAIMS

1. A method, comprising the step of:

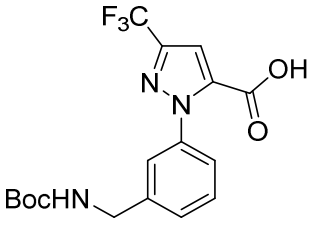
combining compound **C**, or a salt thereof, and compound **F**, or a salt thereof, under conditions sufficient to produce compound **D**, or a salt thereof, wherein:

compound **C** is represented by:



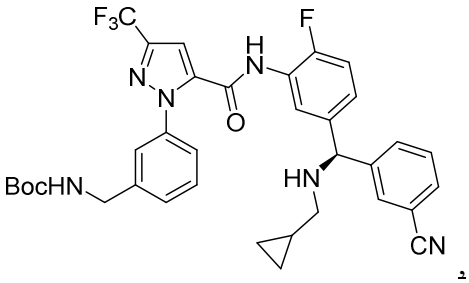
;

compound **F** is represented by:



; and

compound **D** is represented by:



.

wherein:

the conditions sufficient to produce compound **D** comprise an amide-coupling reagent, and a first base;

the amide-coupling reagent is propylphosphonic anhydride (T3P), N,N′-di(isopropyl)carbodiimide, N,N′-di(cyclohexyl)carbodiimide, 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide, or ethyl 2-cyano-2-(hydroxyimino)acetate;

the first base is triethylamine, pyridine, diisopropylethylamine, diisopropylmethylamine, imidazole, pyrimidine, N-methylmorpholine, quinuclidine, or 1,4-diazabicyclo[2.2.2]octane (DABCO); and

compound **C** is used in an amount of at least 1 kg.

~~2. The method of claim 1, wherein the conditions sufficient to produce compound **D** comprise an amide-coupling reagent, and a first base.~~

~~3. The method of claim 2, wherein the amide-coupling reagent is propylphosphonic anhydride (T3P), N,N′-di(isopropyl)carbodiimide, N,N′-di(cyclohexyl)carbodiimide, 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide, or ethyl 2-cyano-2-(hydroxyimino)acetate.~~

~~4~~2. The method of ~~claim 3~~ claim 1, wherein the amide-coupling reagent is propylphosphonic anhydride (T3P).

~~5. The method of any one of claims 2-4, wherein the first base is a first organic base.~~

~~6. The method of any one of claims 2-5, wherein the first base is triethylamine, pyridine, diisopropylethylamine, diisopropylmethylamine, imidazole, pyrimidine, N-methylmorpholine, quinucldine, or 1,4-diazabicyclo[2.2.2]octane (DABCO).~~

~~7~~3. The method of ~~any one of claims 2-6~~ claim 1 or 2, wherein the first base is pyridine.

~~8~~4. The method of any one of claims 1–~~7~~3, wherein the conditions sufficient to produce compound **D** further comprise a first solvent.

~~9~~5. The method of claim ~~8~~4, wherein the first solvent is a polar aprotic solvent.

~~10~~6. The method of claim ~~9~~5, wherein the first solvent is dichloromethane, tetrahydrofuran, acetone, acetonitrile, or ethyl acetate.

~~11~~7. The method of claim ~~9~~ 5 or ~~10~~6, wherein the first solvent is ethyl acetate.

~~12~~8. The method of any one of claims 1-~~11~~7, wherein compound **C** is present as an acid salt; and

the method further comprises the step of combining the acid salt of compound **C** with a second aqueous base, thereby forming the free base of compound **C**;

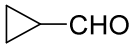
wherein the step of combining the acid salt of compound **C** with a second aqueous base occurs before combining compound **C** and compound **F**.

~~13~~9. The method of claim ~~12~~8, wherein the acid salt of compound **C** is a hydrochloride salt, a hydrobromide salt, a hydroiodide salt, or an oxalic acid salt.

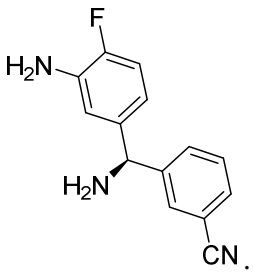
~~14~~10. The method of claim ~~13~~9, wherein the acid salt of compound **C** is an oxalic acid salt.

~~15~~11. The method of any one of claims ~~12~~8-~~14~~10, wherein the second aqueous base comprises potassium hydroxide, sodium hydroxide, ammonium hydroxide, potassium bicarbonate, sodium bicarbonate, potassium carbonate, or sodium carbonate.

~~16~~12. The method of any one of claims ~~12~~8-~~15~~11, wherein the second aqueous base comprises potassium hydroxide.

~~17~~13. The method of any one of claims 1-~~16~~12, further comprising (a) combining compound **B**, or a salt thereof, and  to form a first reaction mixture, then (b) combining the first reaction mixture with a reducing agent under conditions sufficient to form compound **C**, or a salt thereof; wherein:

compound **B** is represented by:



~~18~~14. The method of claim ~~17~~13, wherein the reducing agent is $LiAlH_4$ or $NaBH_4$.

~~19~~15. The method of claim ~~17~~ 13 or ~~18~~14, wherein the reducing agent is $NaBH_4$.

~~20~~16. The method of any one of claims ~~17~~13-~~19~~15, wherein the conditions sufficient to produce compound **C** further comprise a second solvent.

~~21~~17. The method of claim ~~20~~16, wherein the second solvent is a second polar protic solvent.

~~22~~18. The method of claim ~~20~~ 16 or ~~21~~17, wherein the second solvent is methanol, ethanol, or isopropanol.

~~23~~19. The method of any one of claims ~~20~~16-~~22~~18, wherein the second solvent is methanol.

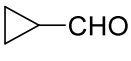
~~24~~20. The method of any one of claims ~~17~~13-~~23~~19, further comprising contacting compound **C** with a first acid to form an acid salt of compound **C**.

~~25~~21. The method of claim ~~24~~20, wherein the first acid is hydrochloric acid, hydrobromic acid, hydroiodic acid, or oxalic acid; and the acid salt of compound **C** is a hydrochloride salt, a hydrobromide salt, a hydroiodide salt, or an oxalic acid salt.

~~26~~22. The method of claim ~~25~~21, wherein the first acid is oxalic acid; and the acid salt of compound **C** is an oxalic acid salt.

~~27~~23. The method of any one of claims ~~17~~13-~~26~~22, wherein compound **B** is present as an acid salt; and

the method further comprises the step of combining the salt of compound **B** with a third organic base, thereby forming the free base of compound **B**;

wherein the step of combining the salt of compound **B** with a third organic base occurs before combining compound **B** and 

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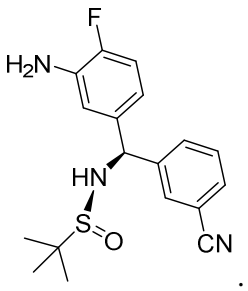
~~28~~24. The method of claim ~~27~~23, wherein the acid salt of compound **B** is a hydrochloride salt, a hydrobromide salt, or a hydroiodide salt.

~~29~~25. The method of claim ~~28~~24, wherein the acid salt of compound **B** is a hydrochloride salt.

~~30~~26. The method of any one of claims ~~27~~23-~~29~~25, wherein the third organic base comprises sodium methoxide.

~~31~~27. The method of any one of claims ~~17~~13-~~30~~26, further comprising (a) combining compound **A** and a second acid under conditions sufficient to form compound **B**, or a salt thereof; wherein:

compound **A** is represented by:



.

~~32~~28. The method of claim ~~31~~27, wherein the second acid is hydrochloric acid, hydrobromic acid, or hydroiodic acid.

~~33~~29. The method of claim ~~32~~28, wherein the second acid is hydrochloric acid.

~~34~~30. The method of any one of claims ~~31~~27-~~33~~29, wherein the conditions sufficient to form compound **B** comprise a third polar protic solvent.

~~35~~31. The method of claim ~~34~~30, wherein the third polar protic solvent is methanol, ethanol, or isopropanol.

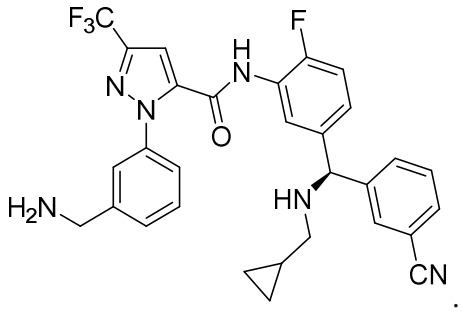
~~36~~32. The method of claim ~~34~~ 30 or ~~35~~31, wherein the third polar protic solvent is isopropanol.

~~37~~33. The method of any one of claims ~~31~~27-~~36~~32, wherein compound **B** is formed as an acid salt.

~~38~~34. The method of claim ~~37~~33, wherein the acid salt of compound **B** is a hydrochloride salt, a hydrobromide salt, or a hydroiodide salt.

~~39~~35. The method of claim ~~38~~34, wherein the acid salt of compound **B** is a hydrochloride salt.

~~40~~36. The method of any one of claims 1-~~39~~35, further comprising (c) combining compound **D** and a deprotecting reagent to form a second reaction mixture, then (d) exposing the second reaction mixture to conditions sufficient to form Compound **I** as a free base; wherein:
Compound **I** is represented by:



~~41~~37. The method of claim ~~40~~36, wherein the deprotecting reagent is a third acid.

~~42~~38. The method of claim ~~41~~37, wherein the third acid is hydrochloric acid, hydrobromic acid, or hydroiodic acid.

~~43~~39. The method of claim ~~42~~38, wherein the third acid is hydrochloric acid.

~~44~~40. The method of any one of claims ~~40~~36-~~43~~39, wherein the conditions sufficient to form Compound **I** as a free base comprise a fourth base.

~~45~~41. The method of claim ~~44~~40, wherein the fourth base is aqueous ammonia.

~~46~~42. The method of any one of claims ~~40~~36-~~45~~41, further comprising:
e) providing a first freebase mixture of Compound I as a free base in a fourth organic solvent;
f) combining the freebase mixture with a first reagent solution comprising a fourth acid and a fifth organic solvent under conditions sufficient to form a third reaction mixture comprising a salt of Compound I; and
g) crystallizing the salt of Compound I from the mixture comprising a salt of Compound I.

~~47~~43. The method of claim ~~46~~42, wherein the crystalline salt is a hydrochloride salt.

~~48~~44. The method of claim ~~46~~42, wherein the crystalline salt is a bis(hydrochloride) salt.

~~49~~45. The method of any one of claims ~~46~~42-~~48~~44, wherein the fourth organic solvent comprises a fouth polar aprotic solvent.

~~50~~46. The method of claim ~~49~~45, wherein the fourth polar aprotic solvent is methyl tert-butyl ether.

~~51~~47. The method of claim ~~49~~ 45 or ~~50~~46, wherein the fourth organic solvent further comprises a fourth non-polar solvent.

~~52~~48. The method of claim ~~51~~47, wherein the fourth non-polar solvent is toluene.

~~53~~49. The method of any one of claims ~~46~~42-~~52~~48, wherein the fourth acid is hydrochloric acid.

~~54~~50. The method of any one of claims ~~41~~37-~~48~~44, wherein the fifth organic solvent is a fifth polar protic solvent.

~~55~~51. The method of claim ~~54~~50, wherein the fifth polar protic solvent is methanol.

~~56~~52. The method of any one of claims 1-~~55~~51, wherein compound **C** is used in an amount of ~~at least 1 kg,~~ at least 5 kg, at least 10 kg, at least 15 kg, at least 20 kg, at least 25 kg, at least 30 kg, at least 35 kg, at least 40 kg, at least 45 kg, at least 50 kg, at least 55 kg, or at least 60 kg.

~~57~~53. The method of any one of claims 1-~~56~~52, wherein compound **C** is used in an amount of at least 50 kg.