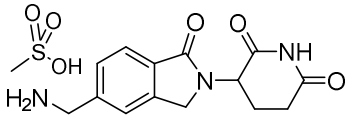
WHAT IS CLAIMED:

1. A process for preparing 2-(4-chlorophenyl)-N-((2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-5-yl)methyl)-2,2-difluoroacetamide comprising contacting Compound M with 2-(4-chlorophenyl)-2,2-difluoroacetic acid in the presence of a base and 1-propylphosphonic anhydride in a solvent, under conditions suitable to provide 2-(4-chlorophenyl)-N-((2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-5-yl)methyl)-2,2-difluoroacetamide, wherein Compound M is selected from methanesulfonate, hydrochloride, sulfate, phosphate and acetate salt of 3-(5-(aminomethyl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione.

2. The process of claim 1, wherein the process comprises contacting Compound L



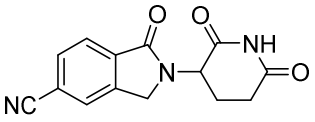
L

with 2-(4-chlorophenyl)-2,2-difluoroacetic acid in the presence of a base and 1-propylphosphonic anhydride in a solvent, under conditions suitable to provide 2-(4-chlorophenyl)-N-((2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-5-yl)methyl)-2,2-difluoroacetamide.

3. The process of claim 1, wherein the base is N-methyl morpholine.

4. The process of claim 1, wherein the solvent is dimethylformamide.

5. The process of claim 1 further comprising contacting Compound G



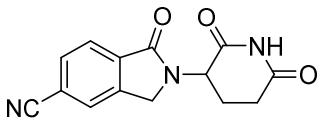
G

with a reducing agent in a solvent followed by contacting with an acid selected from methanesulfonic acid, hydrochloric acid, sulfuric acid, phosphoric acid, or acetic acid, under conditions suitable to provide Compound M.

6. The process of claim 5, wherein the reducing agent is 5% or 10% palladium on carbon.

7. The process of claim 5, wherein the solvent comprises one or more of N-methyl pyrrolidone, 1 propanol, isopropyl alcohol, ethanol and tetrahydrofuran.

8. The process of claim 1 further comprising contacting Compound G



G

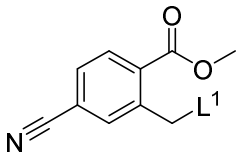
with a reducing agent in a solvent followed by contacting with an methanesulfonic acid, under conditions suitable to provide Compound L.

9. The process of claim 8, wherein the reducing agent comprises 10% palladium on carbon.

10. The process of claim 8, wherein the solvent comprises water and 1-propanol.

11. The process of claim 8, wherein the solvent comprises water and isopropanol.

12. The process of claim 8 further comprising contacting Compound X



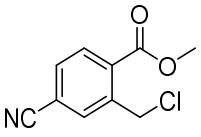
X

wherein L^1 is a leaving group;

with 3-aminopiperidine-2,6-dione hydrochloride in the presence of a salt, followed by a solvent and a base, under conditions suitable to provide Compound G.

13. The process of claim 12, wherein L^1 is halogen or methanesulfonate.

14. The process of claim 8 further comprising contacting Compound D



D

with 3-aminopiperidine-2,6-dione hydrochloride in the presence of a salt, followed by a solvent and a base, under conditions suitable to provide Compound G.

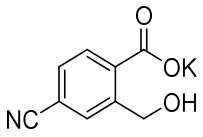
15. The process of any one of claims 12-14, wherein the salt is potassium bromide or potassium iodide.

16. The process of any one of claims 12-14, wherein the base is N,N-diisopropylethylamine.

17. The process of any one of claims 12-14, wherein the solvent comprises acetonitrile.

18. The process of any one of claims 12-14, wherein the solvent comprises acetonitrile and water.

19. The process of any one of claims 12-18 further comprising contacting Compound A



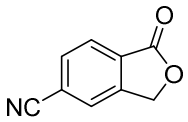
A

with 1) dimethyl sulfate in a solvent; 2) a base; 2) methanesulfonyl chloride; and 4) lithium chloride, under conditions suitable to provide Compound D.

20. The process of claim 14, wherein the base is N-methyl morpholine.

21. The process of claim 14, wherein the solvent is dimethylacetamide.

22. The process of claim 19 further comprising contacting 1-oxo-1,3-dihydroisobenzofuran-5-carbonitrile



with a base in a solvent under conditions suitable to provide Compound A.

23. The process of claim 22, wherein the base is potassium hydroxide.

24. The process of claim 22, wherein the solvent is isopropyl alcohol.