**The synthesis of Tazverik**

Name

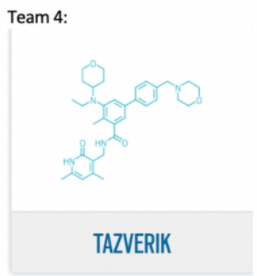
Institution

Course

Instructor

Date

**The synthesis of Tazverik**



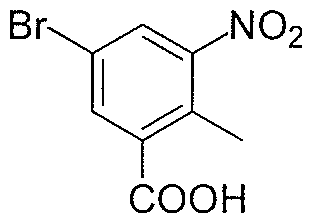
**Tazemetostat - C34H45BrN4O4**

**Introduction**

Tazverik is a brand name for the anticancer drug Tazemetostat. The molecular formula of the drug is C34H45BrN4O4. The molecule is used in the treatment of metastatic cancer in people above 16 years.

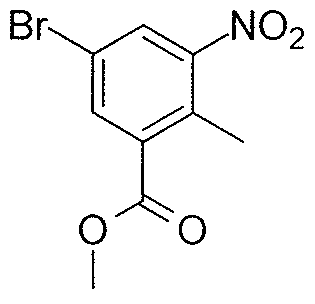
**Synthesis of C34H45BrN4O4.**

1. **The reaction that forms C8H6BrNO4**

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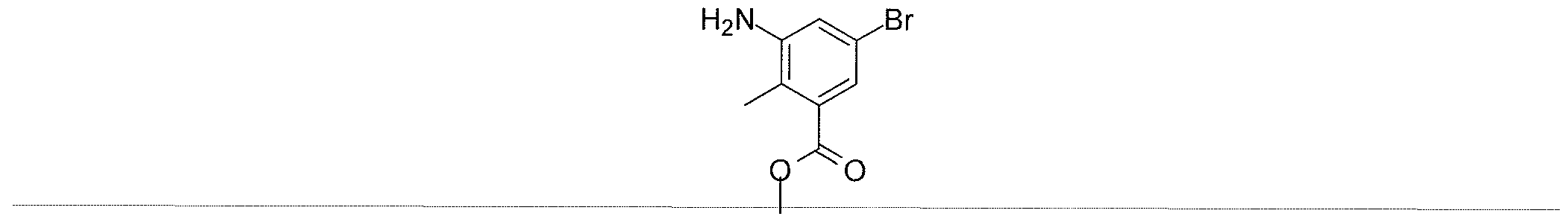
2-methyl-nitro benzoic acid is mixed with Sulphuric acid, and 1, 3-dibromo-5, 5-dimethyl-2, 4-imidazolidine-dione in a ratio of 1:4:3 respectively at room temperature and stirred for five hours. The reacting chamber is then placed in a cold water bath; then, the formed solid is filtered, washed, and dried.

1. **The reaction that forms C9H8BrNO4**

[](http://patentimages.storage.googleapis.com/WO2012142504A1/imgf000222_0003.png)

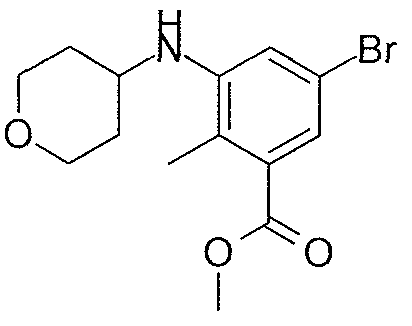
5-Bromo-2-methyl-3-nitrobenzoic acid, sodium carbonate, and methyl iodide are added in 2.8 liters of DMF in the ratio of 1:2:3 respectively and allowed to heat at 60oc for six hours. After the reaction completes, methyl-Bromo-2-methyl-3-nitrobenzoate is formed. Sodium carbonate is then removed and washed with water to remove any product that could be wasted and extracted using ethyl acetate. The organic layers obtained from subsequent washes are combined and dried using anhydrous sodium sulfate.

1. **The reaction that forms C9H10BrNO2**

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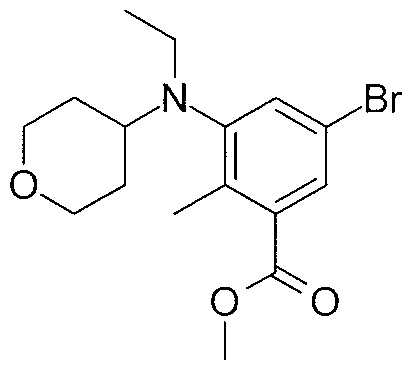
Methyl-Bromo-2methyl-3nitrobenzoate in 1.5l ethanol and aqueous ammonium chloride in 1.5l water are mixed in a ratio of 1:1. The mixture is then heated at 800c for twelve hours when the reaction completes. The product which is, C9H10BrNO2, is filtered and concentrated.

1. **The reaction that forms C14H18BrNO3**

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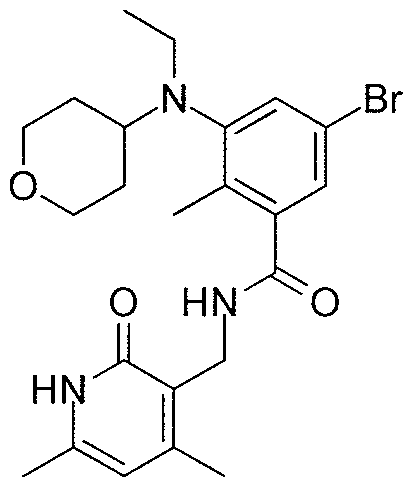
A mixture of step 3’s product, dihydro-2H-pyran-4, 3, - 1 in chloromethane, and acetic acid; a ratio of 2:1:3 respectively, is stirred at 250c for fifteen minutes. The mixture is then cooled to 00c before the addition of sodium tri-acetoxy-borohydride. The reaction is allowed to proceed until the solution reaches a pH of 7 to 8. The product is filtered and concentrated.

1. **The reaction that forms C14H18BrNO3**

[](http://patentimages.storage.googleapis.com/WO2012142504A1/imgf000224_0001.png)

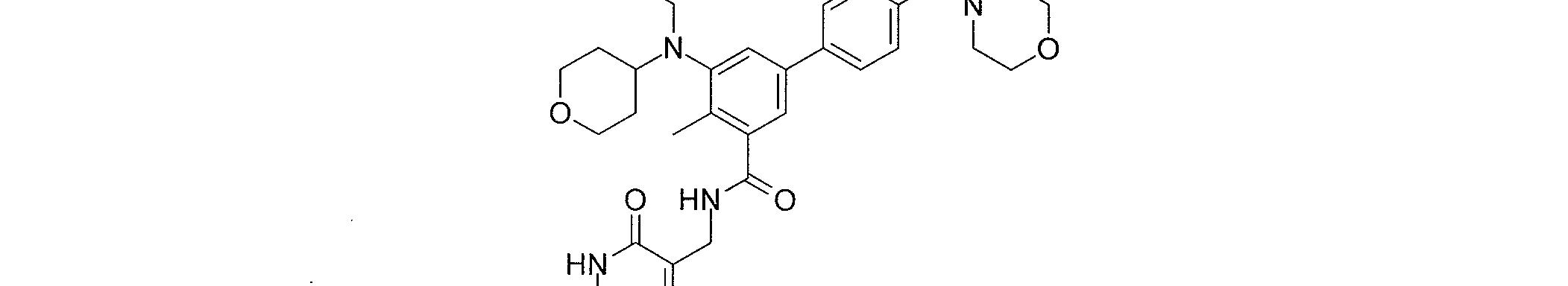
Step 5’s product in di-chloroethane is mixed with acetaldehyde and acetic acid in the ratio of 5:1:1, respectively. The mixture is stirred for approximately fifteen minutes at 250c then allowed to cool up to 00c. After cooling, sodium tri-acetoxyl - borohydride is added and stirred at 250c until the solution attains a pH of 7 to 8. The compound obtained from the reaction is filtered, concentrated, and purified.

1. **The reaction that forms C16H22BrNO3**

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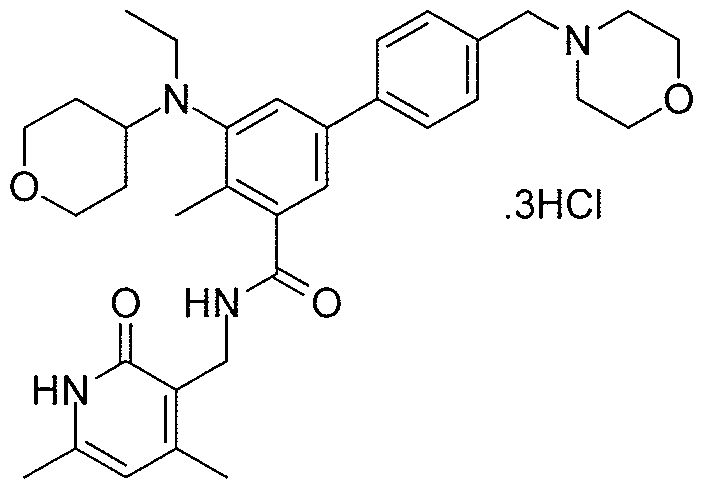
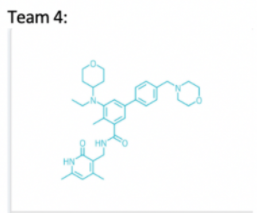
The product in step 5 is added to sodium hydroxide in a ratio of 7:1 to completion under 600c. The reaction solution is then acidified using hydrochloric acid and citric acid to a pH of 5. This acidified product is then mixed with DMSO and 3 - (amino-methyl) - 4, 6-dimethyl pyridine-2(l H)-1 in a ratio of 1:5:1, respectively. The solution is stirred at 250c before the addition of PYBOP. The solution is left to proceed overnight. After completion, the reaction chamber is cooled using a cold water bath. The precipitate is filtered, washed, and dried.

1. **The reaction that produces C34H44N4O4**

[[](http://patentimages.storage.googleapis.com/WO2012142504A1/imgf000226_0001.png)](http://patentimages.storage.googleapis.com/WO2012142504A1/imgf000226_0001.png)

The product in step 6 dissolved in water is added to 4-(4-4,4,5, 5-tetramethyl 1,3,2-di-oxaborolan-2-) Benzyl-Morpholine and sodium bicarbonate in the ratio of 1:1:1 with stirring. Argon is passed through the mixture for fifteen minutes, Palladium is added, and more argon is passed through the mixture. The reaction is then heated at 100oc, and the completion is monitored using TLC. Extraction is performed on the mixture using DCM and drying done on the organic phase using anhydrous sodium sulfate.

1. **The reaction that forms C34H45BrN4O4**

[](http://patentimages.storage.googleapis.com/WO2012142504A1/imgf000227_0001.png)

The product in step seven dissolved in methanolic HC1 and allowed to react at 25oc for about three hours. After the reaction completes, the solution is concentrated and the precipitate dissolved in ether to obtain the drug molecule as a salt.