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Identification and synthesis of impurity formed during Dabrafenib Mesylate preparation

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ABSTRACT

Dabrafenib Mesylate (1), a typical anti neo plastic agent drug, is used for the treatment of skin cancer. During the laboratory optimization, formation of an unknown impurity at RRT ~ 0.94 was observed in the final Dabrafenib. Origin of the impurity was possible when chloro pyrimidine intermediate (15) was converted to Dabrafenib (1).In that, the aromatic fluoro group gets converted to amine which leads to the impurity formation (Phenyl amino Dabrafenib impurity (2)). This impurity was prepared and characterized by using spectroscopic techniques. Herein the formation, synthesis and characterization of this impurity is described. Our study will be of immense help to others in obtaining chemically pure Dabrafenib Mesylate.

INTRODUCTION

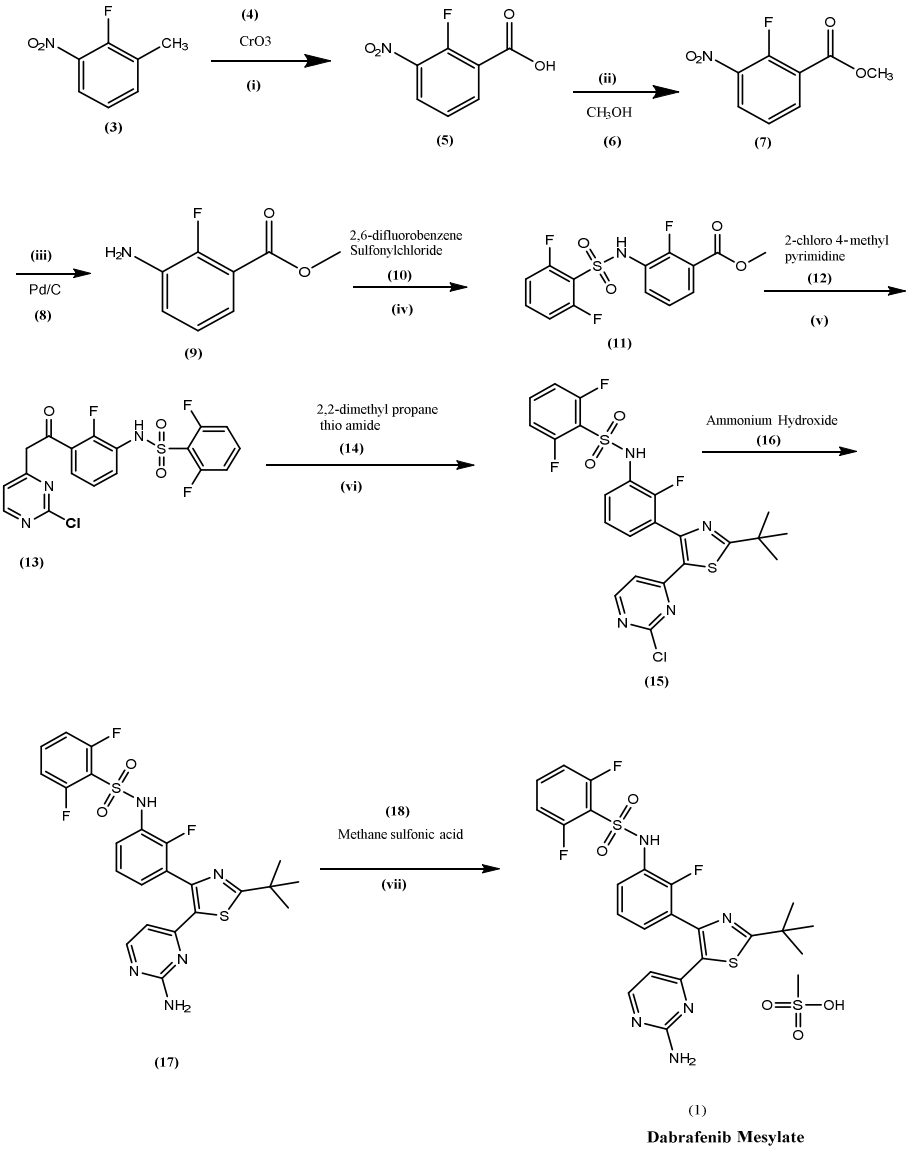
The safety of a drug product is not only dependent on the toxicological properties of the active drug substance (or API), but also on the impurities formed during the various chemical transformations. Therefore, identification, quantification, and control of impurities in the drug substance and drug product are important parts of the drug development for obtaining marketing approval. It is very challenging for an organic chemist to identify the impurities which are formed in very small quantities in a drug substance. Since most of the time it is very difficult to identify and control impurities within acceptable levels in the process, extra purification steps become necessary thereby making the process less competitive. More often than not, the synthesis of impurities are not described in the literature which makes it even more difficult for the organic chemist, who must then design a synthesis, which is time consuming. The development of drug substance is incomplete without the identification of an impurity profile involved in the process. Furthermore, it is not mandatory to design synthetic routes for the impurities. Thus, in our study we explored the formation, identification, synthesis and characterization of impurities found in the preparation for Dabrafenib Mesylate. This study will be of immense help for organic chemists, to understand the potential impurities in Dabrafenib Mesylate synthesis and thereby obtain a pure compound.[1,2]

MATERIALS AND METHODS

Dabrafenib Mesylate is designated chemically as *N*-{3-[5-(2-aminopyrimidin-4-yl)-2-*tert*-butyl-1, 3-thiazol-4-yl]-2-fluorophenyl}-2, 6-difluorobenzenesulfonamide. Its literature synthesis **(scheme 1)** (1-8) involves 2-Fluoro-3-nitro toluene **(3)**under goes oxidation with chromium tri oxide **(4)**to leads the product 2-fluoro-3-nitrobenzoic acid**(5)** reacts with methanol**(6)** in presence of sulfuric acid the product Methyl 2-fluoro-3-nitrobenzoate **(7)**reduces with

10% Pd/C**(8)** to give the product Methyl 2-fluoro-3-amino benzoate**(9)** couples with 2,6-difluorobenzene Sulfonylchloride**(10)** the product Methyl 3-{[(2, 6 di fluoro phenyl) sulfonyl] amino}-2-fluoro benzoate**(11)** reacts with 2-chloro 4- methyl pyrimidine**(12)** affords the product N {3-[(2-chloro-4-pyrimidinyl) acetyl]-2-fluoprophenyl-2, 6-difluoro benzene sulfonamide**(13)**reacts with 2,2-propane thioacetamide**(14)** to give the product N {-3-[5-(2-chloro-4-Pyrimidinyl)-2-(1, 1-Dimethylethyl)-1, 3-thiazol-4-yl] -2-flouro phenyl}-2, 6-difluorobenzene sulfonamide**(15)** reacts with ammonium hydroxide**(16)** to afford N-{3-[5-(2-amino-4-pyrimidinyl)-2-(1,1-dimethylethyl)-1,3-thiazol-4-yl]-2-fluorophenyl}-2, 6-difluorobenzenesulfonamide**(17)**which forms Mesylate salt with methane sulfonic acid**(18)** to afford Dabrafenib Mesylate**(1)**

2.1 Scheme-1:



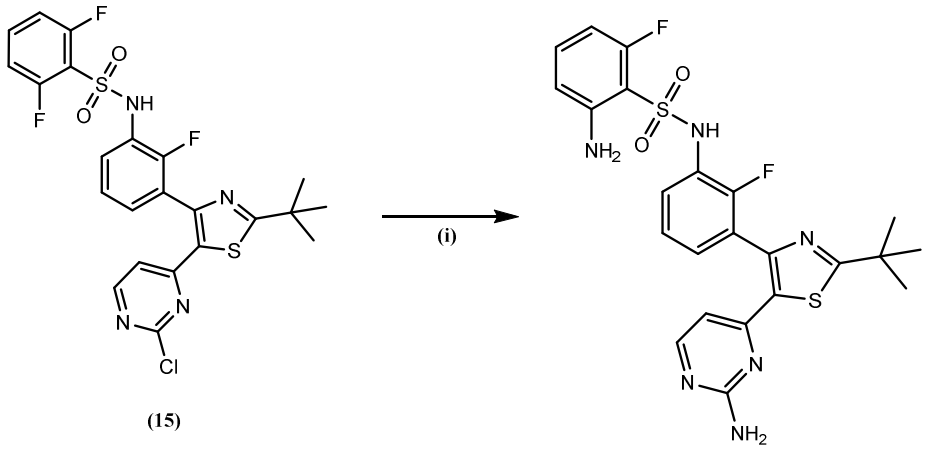
Scheme-I Reagents and conditions: (i) Sulfuric acid, water reflux (ii) Sulfuric acid, reflux (iii) THF, Methanol reflux (iv) Pyridine , Dichloro methane 25-30 ° c (v) 1M LiHMDS in THF 0-5° c (vi) N-bromosuccinimide ,dichloro methane 0-5° c ° c (vii) Iso propyl alcohol 25-30 ° c

2.2Preparation of phenyl amino Dabrafenib impurity (2):

The preparation of Phenyl fluoro Dabrafenib is as illustrated here: chloro pyrimidine intermediate (15) was reacted with excess ammonium hydroxide in pressure flask for 40 hours to give phenyl amino Dabrafenib impurity and this

contains ~50-60% of phenyl amino Dabrafenib impurity (2), which was further purified using Prep. HPLC to get the pure phenyl amino Dabrafenib impurity. The synthetic scheme (2) is as follows.

2.3 Scheme-2:



Scheme-2 Reagents and conditions: (i) Excess Ammonium hydroxide, 98-103° C for 40 hours in pressure flask

RESULTS AND DISCUSSION

During the laboratory optimization, formation of unknown impurity at RRT ~ 0.94 was observed in the final Dabrafenib when chloro pyrimidine intermediate (15) is converted to Dabrafenib (1). In that aromatic fluoro group is getting converted to amine which leads to the impurity formation.**(Phenyl amino Dabrafenib impurity (2))**.

The mass spectroscopic data and NMR analysis data of the impurity are as given below:
Mass m/z = 517.12 (M+ 1)

NMR (DMSO – d_6, 300 MHz)

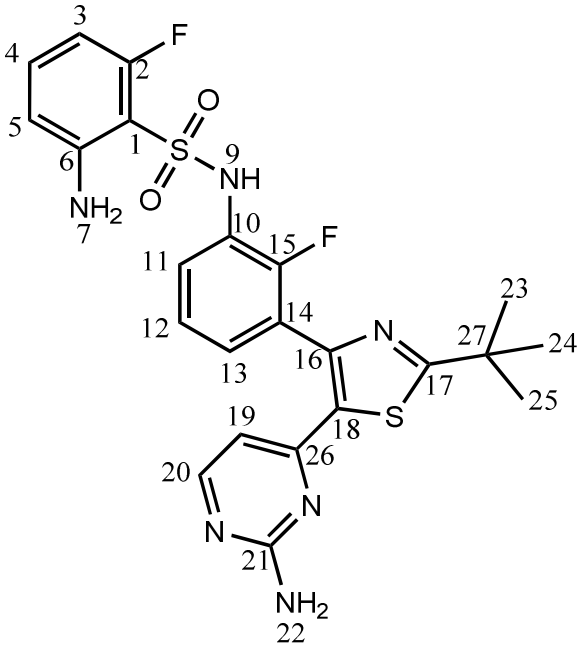


Table 1: NMR data

Position	1H	δ (ppm)	multiplicity	^{13}C	DEPT
1	-	-	-	137.44	-
2	-	-	-	159.38	-
3	1H	6.92	d	117.15	CH
4	1H	7.15	dd	131.4	CH
5	1H	6.6	d	111.3	CH
6	-	-	-	147.2	-
7	NH_2	5.820	br. s	-	-
9	NH	10.365-10.391	br. s	-	-
10		-	-	143.49	-
11	1H	6.9	d	115.42	CH
12	1H	6.85	dd	127.30	CH
13	1H	7.983-8.000	d	130.23	CH
14	-	-	-	120.22	-
15	-	-	-	161.05	-
16	-	-	-	149.23	-
17	-	-	-	184.34	-
18	-	-	-	134.06	-
19	1H	7.49	d	108.99	CH
20	1H	8.2	d	158.60	CH
21	-	-	-	163.62	-
22	NH_2	6.261	br. s	-	-
23, 24, 25	9H	1.405	s	30.5	CH_3
26	-	-	-	152.96	-
27	-	-	-	39.50	-

CONCLUSION

It is difficult to remove the Phenyl amino Dabrafenib impurity from Dabrafenib without significant loss in yield. Hence this impurity was prepared and characterized to help improve the yield of pure Dabrafenib. It was seen that when the process was stopped and carried forward at the appropriate time, formation of the impurity as well as yield loss was minimized.

REFERENCES

[1] Drugs of the Future **2012**, 37(7) ,469-474
[2] US 7994185 B2