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NDMA: WHAT AN IMPURITY CAN DO TO THE AGE-OLD WIDELY USED DRUGS

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ABSTRACT

USFDA wants ranitidine, a household name all over the world for the treatment of hyperacidity, to be taken out from the market because of the presence of N-nitrosodimethylamine, a carcinogenic impurity.Chemically, N-nitrosodimethylamine (NDMA) is a nitrosamine. At the same time, along with NDMA another nitrosamine by name N-nitrosodiethylamine (NDEA) is drawing regulatory headwinds for valsartan formulations for a similar reason. Many pharma companies have received 483s and warning letters due to the presence of more than permissible levels of either of these impurities. Some companies have voluntarily recalled products. The N-nitrosamines altogether are making the pharmaceutical companies to seriously re-look at their development strategies - synthetic route development to formulation development to quality risk management and regulatory approaches. This research paper explores the scientific and regulatory aspects associated with the N-Nitrosamine impurities.

INTRODUCTION

N-nitrosodimethylamine is found in ranitidine, a household name for the treatment of gastritis and heartburn. It is a process related impurity in the bulk drug. Consequently, it is found in ranitidine formulations as well. Along with NDMA, NDEA is found as process related impurity in valsartan bulk drug. Both are claimed as human carcinogens by IARC.USFDA have decided to withdraw permission for marketing of ranitidine. This is the worst thing that can happen to any drug. Especially USFDA has specified the zantac brand, a global brand manufactured by Sanofi[1].Ranitidine is a histamine receptor antagonist introduced to the market in 1981. It hinders acid production in stomach and was first developed by Glaxo (GlaxoSmithKline)[2].

Valsartan was first approved in1996 in Europe and later in US in 1997. It is used for the treatment of hypertension [3].Text book version of synthetic route focuses on main path of reaction. However, the practical experience is somewhat different. By-products have to be anticipated. Sometimes, purity of reactants can make or break a synthetic route when it comes to regulatory requirement. The purification procedures are critical in controlling the level of impurities in the final product i.e., the bulk drug. It is prudent to mention here that the impurities are of several types as mentioned in Fig.1[4]. The classification pictorially and broadly outlines the sources of different classes of impurities. In an open accessed peer reviewed chapter, Kung-Tien Liu and Chien – Hsin, have described API based impurities as

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'potentially genotoxic, mutagenic and carcinogenic due to their structure activity relationship [4]. Ranitidine and valsartan are age old drugs prescribed globally for the treatment of gastritis and blood pressure respectively. These drugs are in the news due to regulatory headwinds – ranitidine for the presence of NDMA impurity and valsartan for NDMA and NDEA. The issue involves voluntary recalls, 483s and even a warning letter.

Current trend related to NDMA:

Zhejiang Huahai Pharmaceuticals (ZHP) in china is an API manufacturing company. Nitrosamine impurity was first identified in ZHP after receiving a complaint from a customer in June 2018 in Valsartan's API. Thereafter, all the companies who were importing valsartan API from ZHP have recalled their finished product from the market. [5]GSK declared closure of vemagal plant. One of the main reasons is perceived to be company's bitter experience with its bread and butter product "zantac". The product has ranitidine Hydrochloride as the API. Zantac faced regulatory headwinds due to the impurity N-nitrosodimethylamine (NDMA). At the same time, some other pharma majors had no issues with their equivalent products. This is because of the origin of NDMA, a process related impurity[6]. An aqueous solution of (I) and (II) in figure 3, is heated to 45-50°C with stirring for 3-4 hours. The reaction mixture is acidified and extracted with a suitableorganic solvent (bulk drug companies use different solvents as per the in-house procedures).During this process, any small amount of nitric oxide present as an impurity in any of the solvent or catalyst used can react with(II) t*o form N,N-nitrosodimethylamine. It is showed in figure 3 and 4 [7]*.

Valsartan is synthesized by,

Here in the step 4 of synthesis of valsartan, Sodium azide is used for cyclization, Excess of sodium azide is wiped by sodium nitrite. Under acidic condition the nitrite forms nitrous acid that could react with trace amount of dimethylamine, degradate of the solvent called dimethylformamide. The synthetic reaction is showed in figure 6.

Toxicology data of Nitrosamines [12, 13, 14]:

The approved and allowable daily intake of NDMA is 96.0ng. It is 26.5ng for NDEA.

As per WHO Classification "NDMA and NDEA belong to the so-called **'cohort of concern',** which is a group of highly potent mutagenic carcinogens". NDMA is categorised as a likely human carcinogen based totally on results from laboratory tests. It is a regarded environmental contaminant. It is observed in water and foods, inclusive of meats, dairy products and vegetables. NDMA causes liver cancer, whereas a number of tobacco particular nitrosamines reasons lung cancer. Volatile N-nitrosamines set off tumors in a lot of human organs, consisting of the tongue, oesophagus, lung, pancreas, liver, kidneys and bladder.Although categorized as a likely carcinogen, NDMA may cause cancer most effective after exposure to excessive doses over a long duration of time. NDMA is one of the equal impurities that was located in positive coronary heart medicinal drugs beginning final 12 months and that ended in the bear in mind of many products. The O (6)-methyl guanine fashioned in human twine blood in mothers highly exposed to such merchandise implicates. NDMA exposure of the foetus. According to this have a look at and the literature, NDMA is not metabolized in full-term human placenta from healthful non-smoking, non-consuming mothers.

Primary use of **NDEA** is as a research chemical. Formerly it was used in the production of rocket fuels. Acute exposure of NDEA can cause liver damage in humans. It has found that NDEA can cause cancer.

RESULTS AND DISCUSSION:

NDMA and NDEA are found as carcinogenic impurities emerging from the synthetic routes of bulk drugs namely ranitidine and valsartan respectively. These impurities are neither the intermediates in the synthetic route nor structurally related to ranitidine and valsartan. NDMA is formed when nitric oxide, a solvent impurity reacts with an intermediate during the synthesis of ranitidine bulk drug. Where in case of valsartan NDMA is formed when sodium nitrite is added to remove excess of DMF, reacts with (E)-8-(benzyloxy)-N-(4-(triflouromethyl) phenyl) quinolone-5-carbimidoyl chloride during the synthesis of

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valsartan drug. There is nitric oxide which is solvent impurity that react with solvent impurity. Therefore, one has to consider the impurity right from the stage of bulk drug synthetic route development to quality risk management to stability studies to formulation development to analytical development and regulatory practice. All the functional departments will have to understand the importance of these impurities.

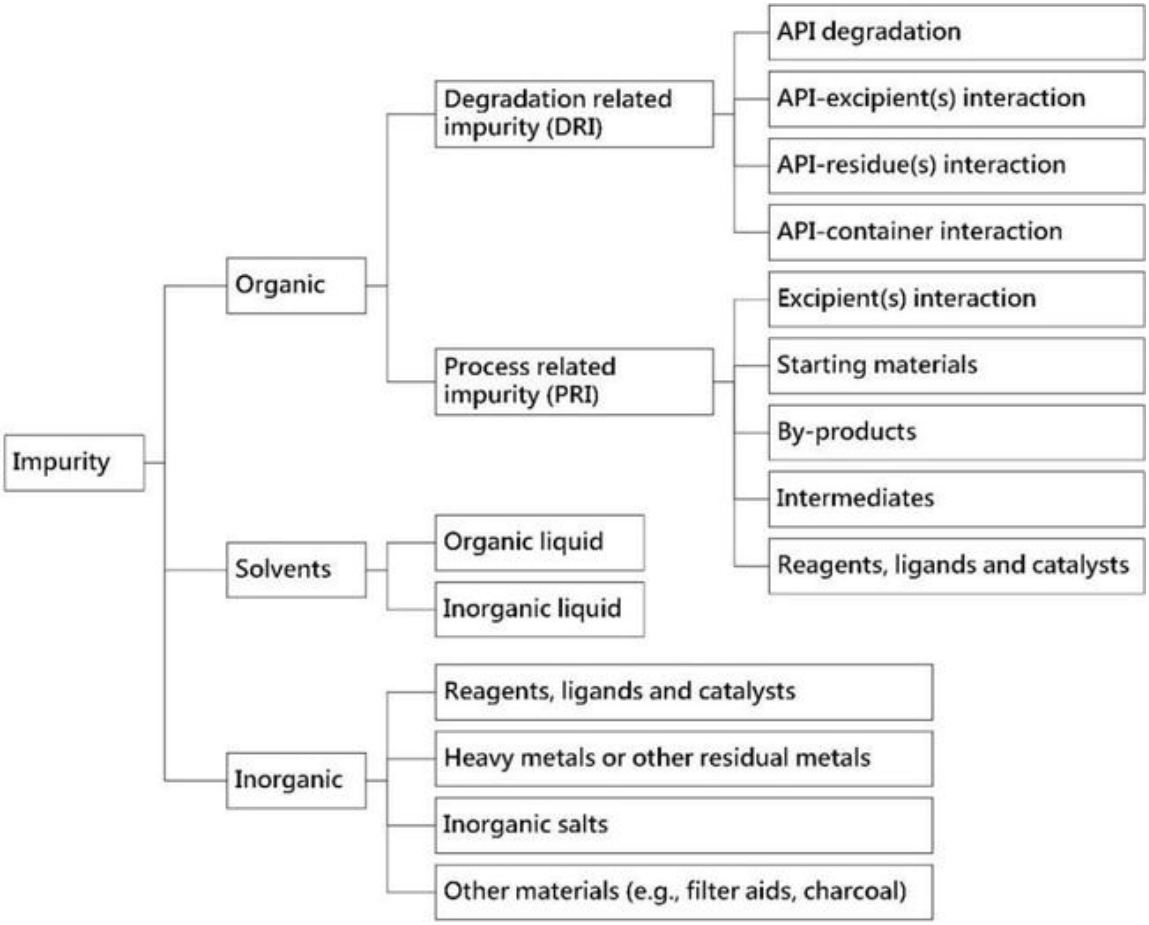
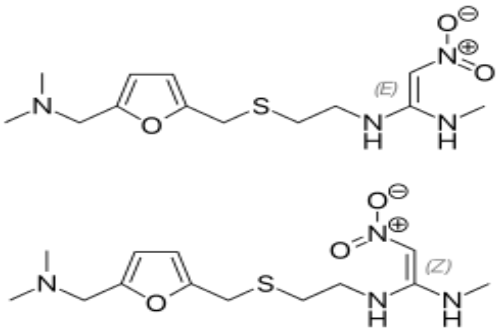


Figure 1. Classification of impurities

Figure 2 Ranitidine Impurity profile



E and Z isomers of Dimethyl [(5-{[(2-{[1-(methylamino)-2-nitroethenyl] amino} ethyl) sulfanyl] methyl} furan-2-yl) methyl] amine.

Formula	$C_{13}H_{22}N_4O_3S$
Molar mass	314.40 g·mol^{-1}

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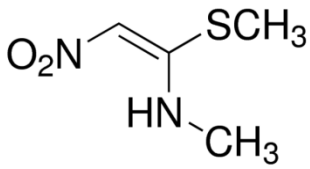
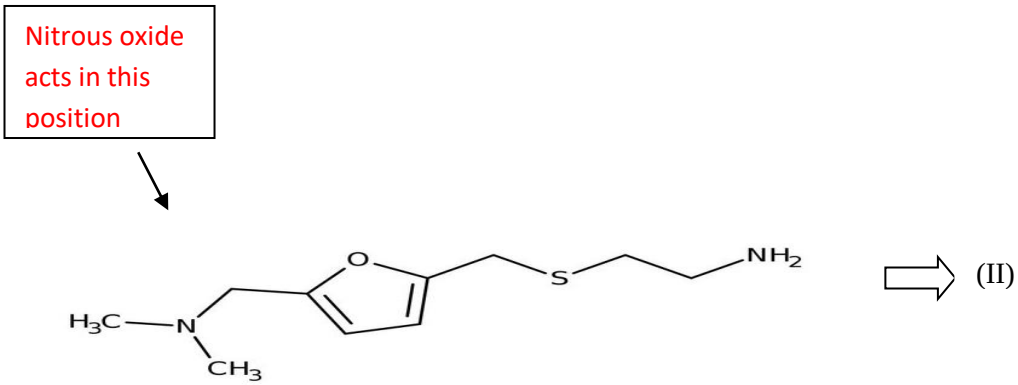
Ranitidine is manufactured by a reaction between: See figure 3.

N*-Methyl-1-(methylthio)-2-nitroethenamine (I)and*
2-[[[***5***-[(***Dimethylamino***) ***methyl***]-***2-furyl***] ***methyl***] thio] ***ethylamine (II)***



(I)

Molecular Weight: 148.19 g/mol



(II)

(Traces of Nitrous oxide attack at this position and cause lysis of the bond to formNDMA)
Figure 3. Ranitidine manufacturing process.

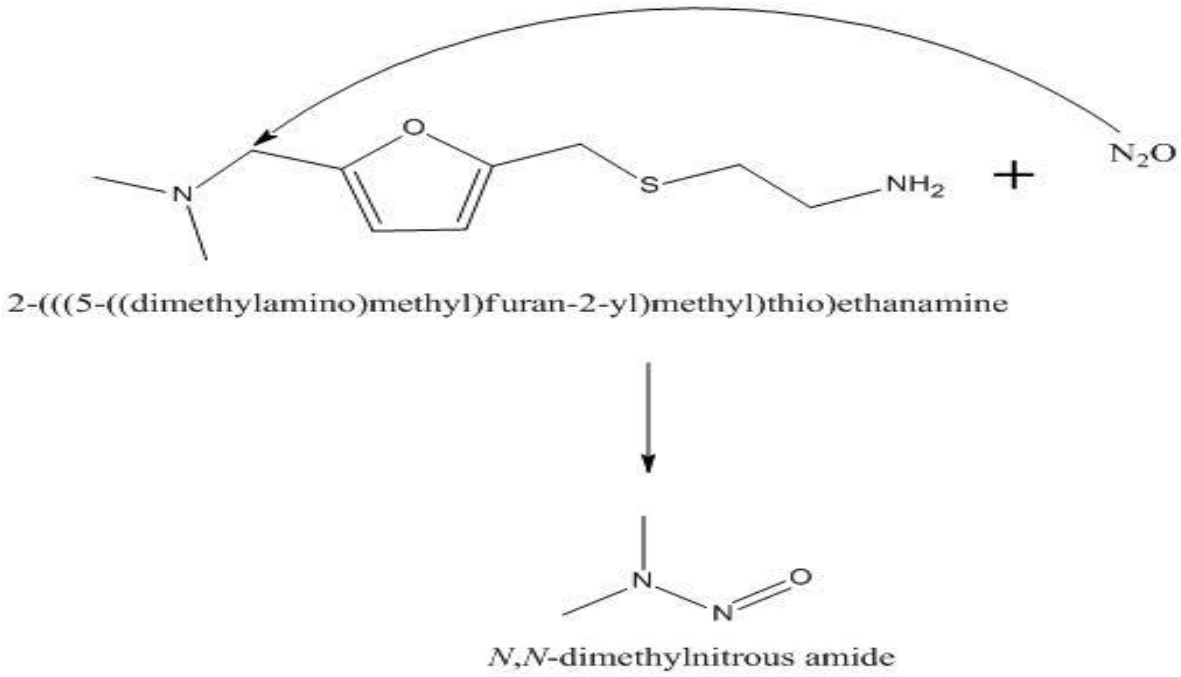


Figure 4. Formation of NDMA in Ranitidine.

Possible route of NDMA in valsartan[5]:

Possible route of NDMA impurity in valsartan is explained in below figure 5.

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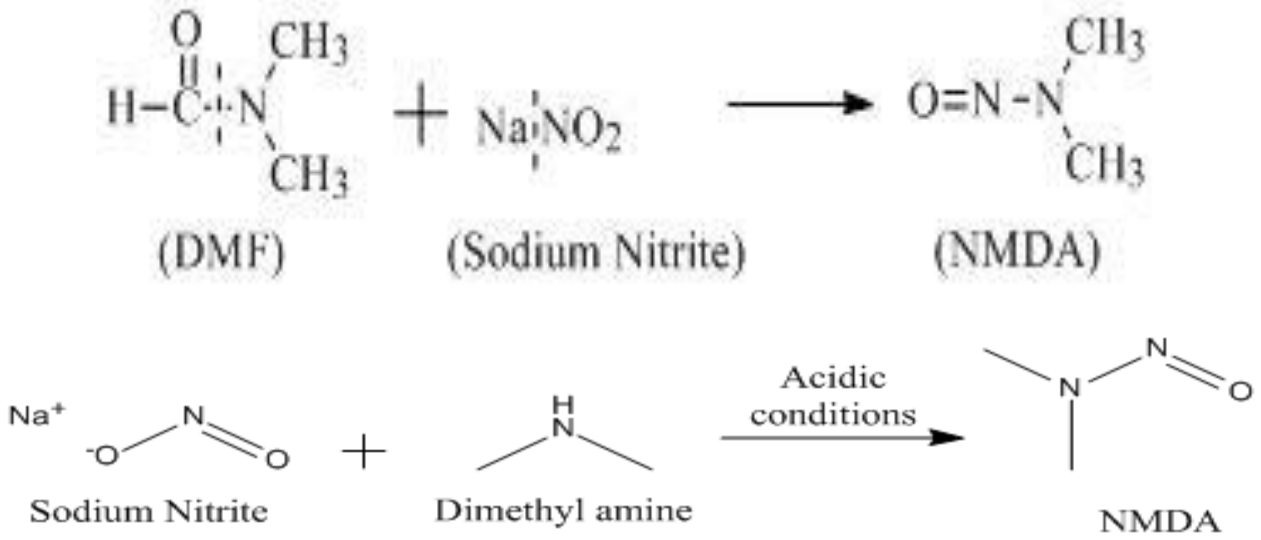

Figure 5. Possible route of NDMA in Valsartan.

483s issued to ranitidine and valsartan bulk drugs due to the presence of exceeded amount of NDMA impurity is examined in the below table 1[8].

Table 1. List of 483's issued to Ranitidine and Valsartan.

Sl. No.	Ranitidine	Valsartan
1	-	Mylan Laboratories limited

Warning letters issued by FDA is demonstrated in below table 2[9].

Table 2. Warning Letters issued by FDA.

Sl. No.	Ranitidine	Valsartan
1	-	Mylan laboratories Limited
2	-	Lantech pharmaceuticals limited
3	-	Emtech Pharmaceuticals

Voluntary recalls are listed in the below table 3[5, 10, 11].

Table 3. List of Voluntary Recalls by the companies.

Sl. No.	Ranitidine	Valsartan
1	Denton pharma, Inc, dba northwind pharmaceuticals	Prinston pharmaceuticals
2	Mylan laboratories	Teva Pharmaceuticals
3	Apco pharma LLC	Camber Pharmaceuticals
4	Glenmark pharmaceuticals Inc., USA	ScieGen
5	Precision dose Inc, oral solution	Torrent Pharmaceuticals
6	Golden state medical supply, Inc.	Pfizer Pharmaceuticals
7	Amneal pharmaceuticals, LLC	Hetero Labs
8	American health packaging	Mylan Laboratories
9	GSK pharmaceuticals limited	Aurobindo Pharma

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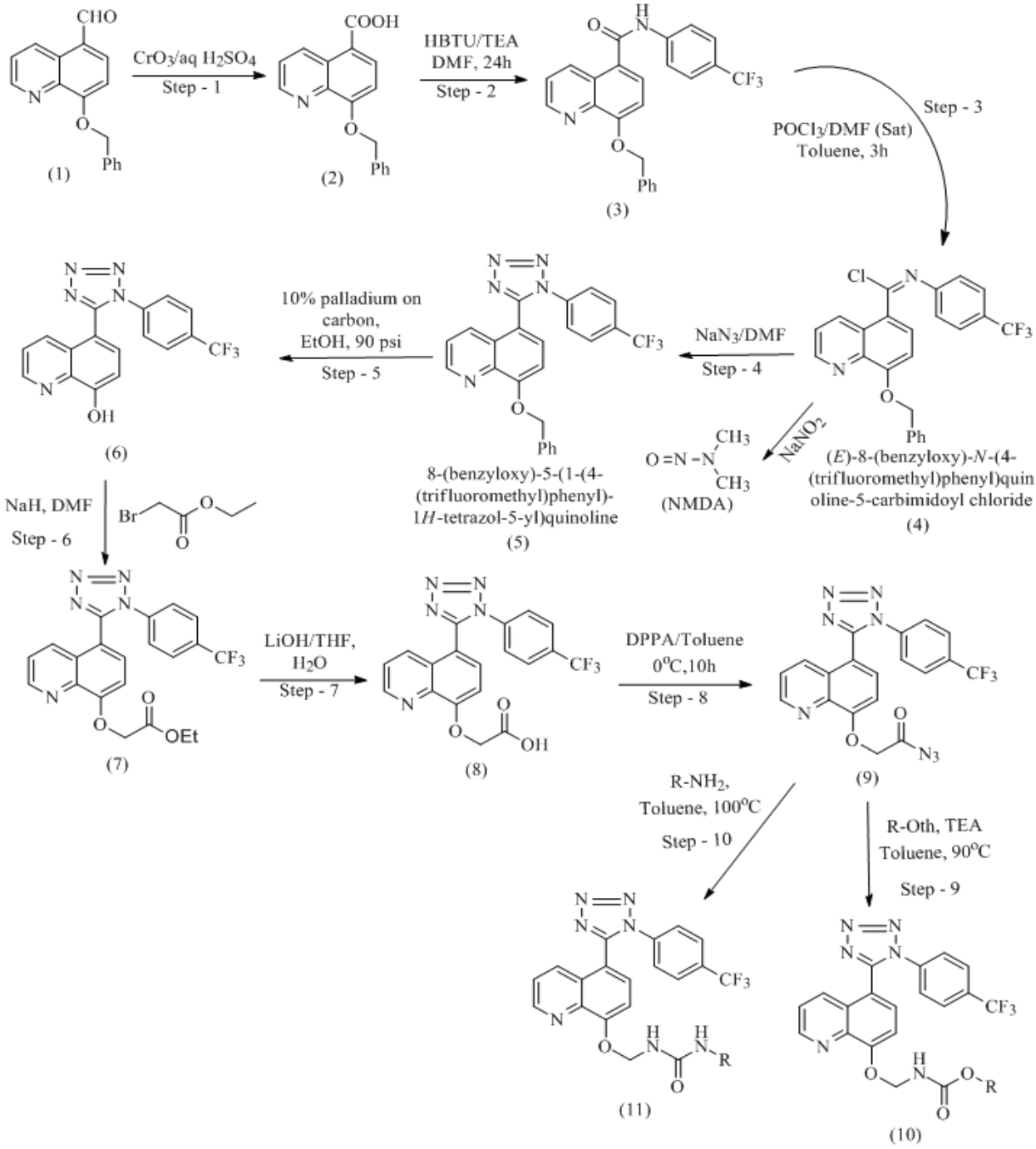

Figure 6. Formation of NDMA in synthesis of Valsartan.

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CONCLUSION:

From the above discussion we can say that an impurity can decide the existence of drug itself. Ranitidine an age old drug used for generations and all over the world is out of the shelf now due to the solvents used in the synthesis. Now onwards impurities will be taken up even more seriously than ever before. This enhances the responsibility on the shoulder of scientists in bulk drug synthetic route development. Henceforth this

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nitrosamines issue will make synthetic route development even more challenging. And the analytical method development will have to become even more sensitive and have to lead even more sensitive method than existing methods.

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