

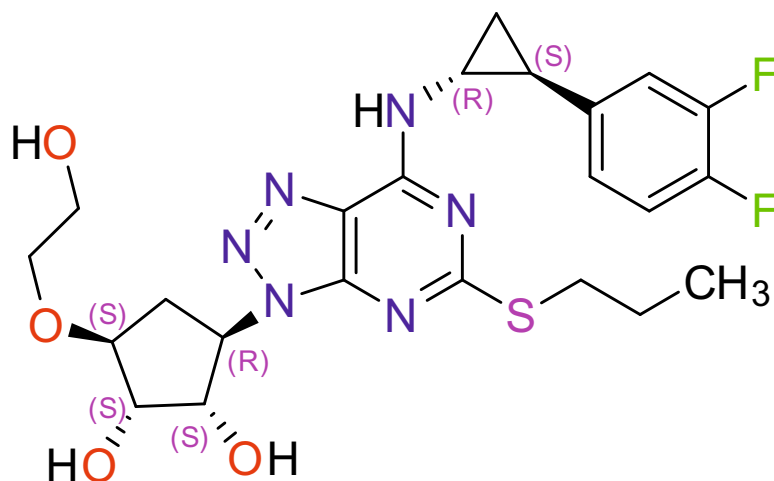
# MSN TICAGRELOR

MSNSS No: 00002



## REACTION OF TICAGRELOR WITH NITROSATING AGENTS PRODUCES 4,5-DIHYDROISOXAZOLE DERIVATIVE, RATHER THAN N-NITROSO TICAGRELOR

### TICAGRELOR – PRODUCT PROFILE



Ticagrelor, known with its IUPAC name as (1S,2S,3R,5S)-3-[7-[[[(1R,2S)-2-(3,4-difluorophenyl)cyclopropyl]amino]-5-(propylthio)-3H-[1,2,3]-triazolo[4,5-d]pyrimidin-3-yl]-5-(2-hydroxyethoxy)cyclopentane-1,2-diol, is P2Y12 platelet inhibitor indicated to reduce the rate of cardiovascular death, myocardial infarction, and stroke in patients with acute coronary syndrome (ACS) or a history of myocardial infarction (MI).

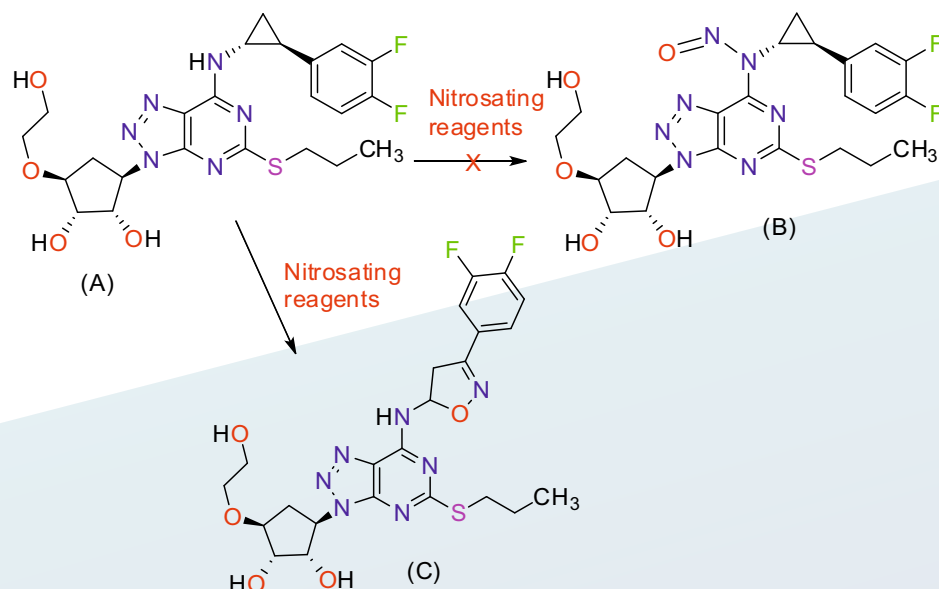
### NEW IMPURITIES IDENTIFICATION IN TICAGRELOR

MSN has a dedicated team for synthesizing impurities like N-Nitrosamine impurities (General, intermediates and NDSRIs), degradation impurities which are formed during API as well as Formulation development and Metabolites. MSN has the capability with state-of-the-art facilities.

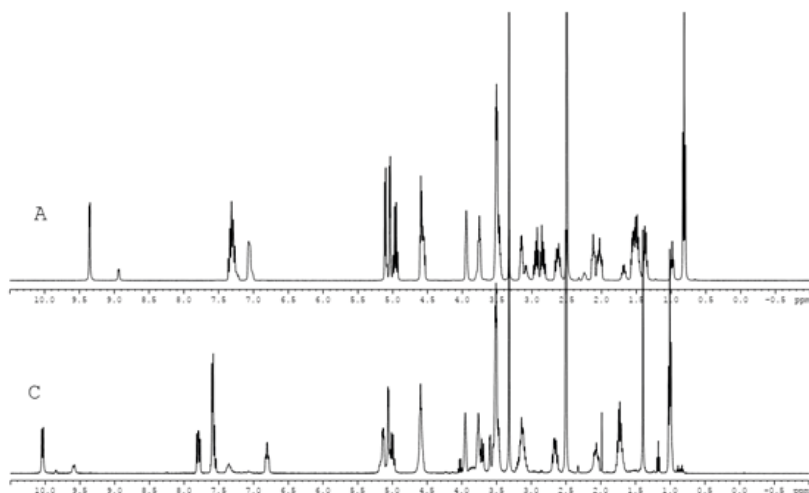
# Reaction of Ticagrelor with Nitrosating Agents Produces 4,5-Dihydroisoxazole Derivative, Rather Than N-Nitroso Ticagrelor

Recently, many pharmaceutical companies withdrew a few finished products from the US market due to the presence of unacceptable level of the “probably carcinogenic” Nitrosamine Drug Substance-Related Impurities (NDSRIs). In view of this, MSN has started the synthesis of NDSRI of Ticagrelor for evaluation in Ticagrelor Drug substance and Ticagrelor Drug product. MSN performed a set of reactions of Ticagrelor with different nitrosating agents under different conditions to make “N-Nitroso Ticagrelor” and analysed the obtained product by LCMS. The product mass is consistent with the “N-Nitroso Ticagrelor”. The pure product isolated by column chromatography is further studied by spectroscopic techniques like 1D (<sup>1</sup>H, <sup>13</sup>C, DEPT) and 2D (COSY, HSQC and HMBC). The spectral data confirms that the product formed is in fact 4,5-Dihydroisoxazole derivative and not the “N-Nitroso Ticagrelor” which otherwise is intended to be prepared. No traces of so called “N-Nitroso Ticagrelor” is observed either in the reaction product of Ticagrelor with nitrosating agents or in commercial batches of Ticagrelor manufactured by MSN as per the spectral data in addition to LCMS.

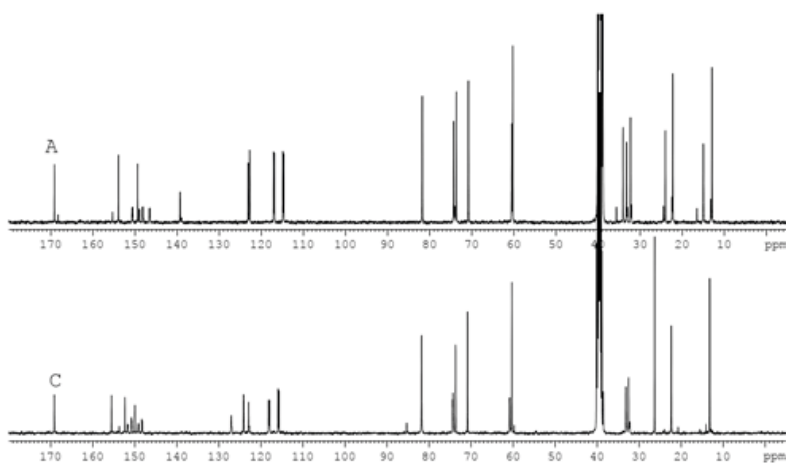
## SCHEMATIC REPRESENTATION AND THE STRUCTURE OF THE 4,5-DIHYDROISOXAZOLE DERIVATIVE



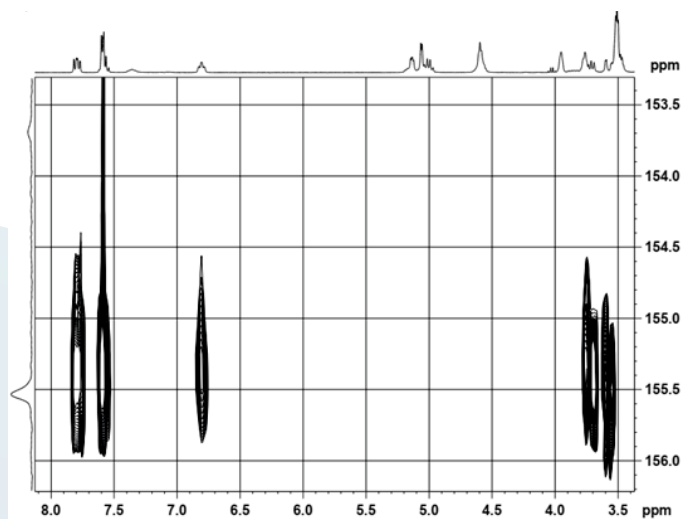
# CHARACTERIZATION DATA OF TICAGRELOR AND 4,5-DIHYDROISOXAZOLE DERIVATIVE:



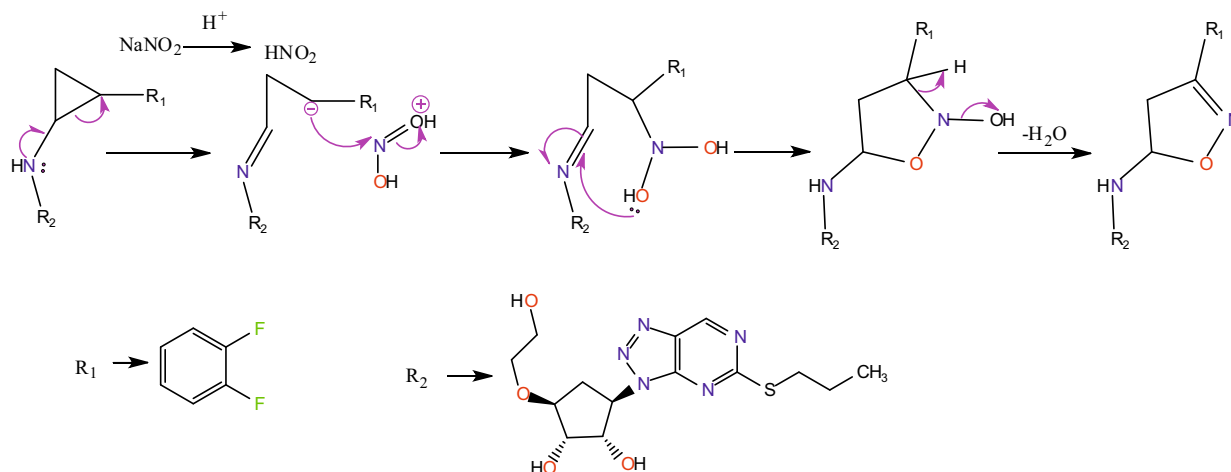
Overlaid <sup>1</sup>H-NMR spectra of the Ticagrelor (A) and the 4,5-Dihydroisoxazole Derivative ©



Overlaid <sup>13</sup>C-NMR spectra of Ticagrelor (A) and the 4,5-Dihydroisoxazole Derivative ©



Key HMBC correlations of 4,5-Dihydroisoxazole Derivative ©



## REACTION MECHANISM FOR THE FORMATION OF 4,5-DIHYDROISOXAZOLE DERIVATIVE

# EXECUTIVE SUMMARY OF MSN TICAGRELOR IMPURITY

- Through the systematic study of the reactions between Ticagrelor and nitrosating agents, the reaction product formed is found to be the 4,5-Dihydroisoxazole Derivative.
- No trace of so called "N-Nitroso Ticagrelor" is observed either in the reaction product of Ticagrelor with nitrosating agents or in the commercial batches of Ticagrelor.

MSN has the capabilities with a team of Process and Analytical experts, who can draw on their integrated understanding of IP, Regulatory affairs of multiple regulatory bodies, process development (API & formulation) and API manufacturing skills to ensure early and risk free entry into the world-wide markets.

*Disclaimer: This 'MSN SCIENTIFIC SPARKLES' is meant only to showcase MSN's capabilities. Products under patent protection would be offered and supplied by MSN only for development, testing and regulatory submission related activities which are covered under Bolar Exemption or Experimental use exception available in respective countries and as provided under Section 107A of the Indian Patents Act, 2005.*