Chromatography Solutions

Application note #7590

Analysis of Azido Impurities using the Avantor® ACE® C18-PFP

INTRODUCTION

There have been recent concerns surrounding the detection of potentially mutagenic azido impurities in some Sartan-containing products.

Sartan medicines are angiotensin II receptor blockers (ARB) which are typically used in the treatment of conditions including high blood pressure (hypertension) and heart failure. They function by helping to relax and widen the blood vessels, leading to lower blood pressure and improved supply of blood and oxygen.[1,2,3]

In 2021 the MHRA (Medicines and Healthcare products Regulatory Agency) issued several recalls for specific batches of Irbesartan-containing and Losartan-containing products as a precautionary measure. The batches were found to contain levels of an impurity known as 5-(4′-(azidomethyl)-[1,1′-biphenyl]-2yl)-1H-tetrazole (AZBT) above the acceptable limit permitted for this product. They reported that long-term exposure to AZBT at those levels may have the potential to increase the risk of cancer over time. [3,4,5]

The European Directorate for the Quality of Medicines and Healthcare (EDQM) reported that investigations had also identified another azido impurity in losartan potassium called 5-[4′-[(5-(azidomethyl)-2-butyl-4-chloro-1H-imidazol-1-yl)methyl]-[1,1′-biphenyl]2-yl]-1H-tetrazole. [6] This is also known as 'losartan azide impurity'.

An LC-MS analytical method has been developed for determination of 3 azido impurities using the Avantor® ACE® C18-PFP phase. The ACE® C18-PFP combines both C18 and pentafluorophenyl (PFP) functionalities, thereby bringing together the hydrophobicity, stability and low bleed characteristics of the ACE® C18 with the additional shape selectivity, π-π and dipole-dipole interactions of the PFP group.

Method Details

CONDITIONS

Columns: Avantor® ACE® Excel 3 C18-PFP

Particle Size: 3 µm

Dimensions: 150 x 3.0 mm

Mobile Phase : A: H_2O + 0.1% Formic Acid

B: MeCN/H_2O (95:5) + 0.1% Formic Acid

Gradient:

Time (mins)	% B
0	40
6	40
12	100
15	100
15.1	40
20	40

Flow Rate: 0.8 mL/min

Injection Volume: 5 µL

Temperature: 40 °C

UV Detection: UV, 220 nm

MS Detection AB Sciex API 3200 LC-MS/MS

Polarity: Positive

Ion Source: ESI

Scan Type: MRM

Curtain gas: 30

Temperature: 500 °C

GS1: 40

GS2: 50

CAD: 9

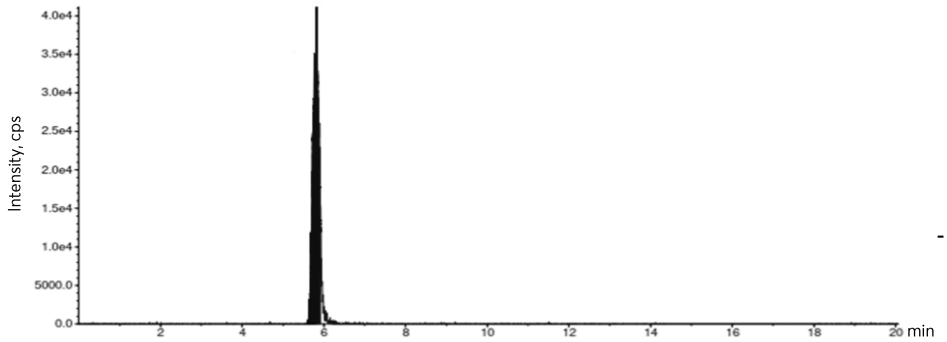
Ion Spray Voltage: 5500

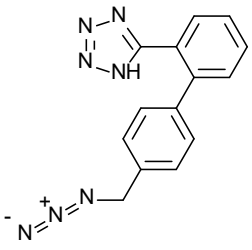
Entrance Potential: 12

MRM TRANSITIONS

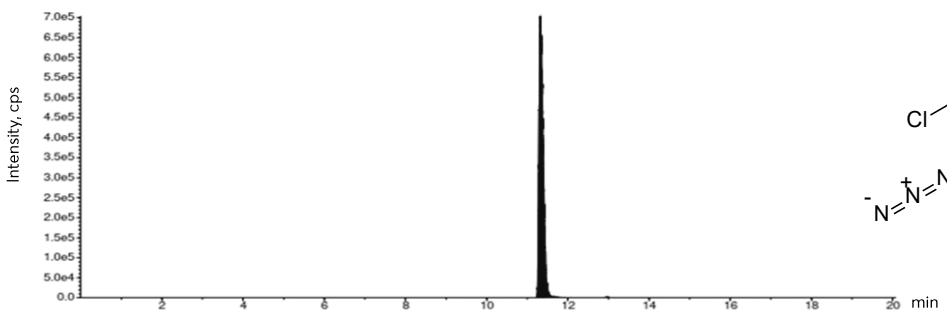
Analyte	CAS No.	Abbreviation	t_R (mins)	Q1	Q3
5-[4′-(Azidomethyl)[1,1′-biphenyl]-2-yl]-1H-tetrazole (Irbesartan Impurity 15)	152708-24-2	AZBT	5.83	278.0	180.0
5-(4′-((5-(azidomethyl)-2-butyl-4-chloro-1H-imidazol-1-yl) methyl)-[1,1′-biphenyl]-2-yl)-1H-tetrazole (Losartan Azide Impurity)	727718-93-6	AZLS	11.32	448.2	207.2
4′-(azidomethyl)-[1,1′-biphenyl]-2-carboxamide	N/A	AZBX	4.88	253.0	210.0

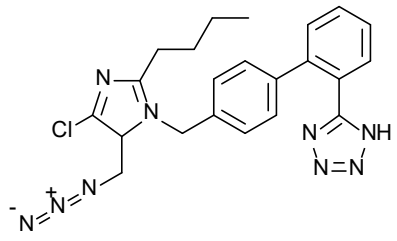
LC-MS/MS CHROMATOGRAMS



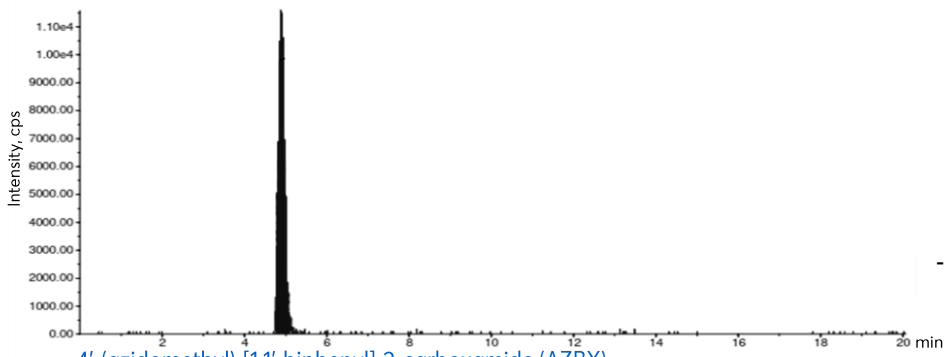


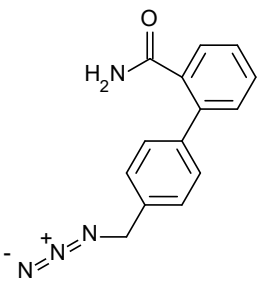
5-[4′-(Azidomethyl)[1,1′-biphenyl]-2-yl]-1H-tetrazole (AZBT)





5-(4′-((5-(azidomethyl)-2-butyl-4-chloro-1H-imidazol-1-yl) methyl)-[1,1′-biphenyl]-2-yl)-1H-tetrazole (AZLS)





4′-(azidomethyl)-[1,1′-biphenyl]-2-carboxamide (AZBX)

REFERENCES

1. "NHS: About losartan" (https://www.nhs.uk/medicines/losartan/about-losartan/). Accessed March 2022.
2. "NHS: About irbesartan" (https://www.nhs.uk/medicines/irbesartan/about-irbesartan/). Accessed March 2022.
3. "Press release: Precautionary recall of specific batches of blood pressure drug irbesartan" (https://www.gov.uk/government/news/precautionary-recall-of-specific-batches-of-blood-pressure-drug-irbesartan). Accessed March 2022.
4. "Press Release: MHRA recalls contaminated Irbesartan-batches as precautionary measure". (https://www.gov.uk/government/news/mhra-recalls-contaminated-irbesartan-batches-as-precautionary-measure). Accessed March 2022.
5. "Class 2 Medicines Recall: Bristol Laboratories Limited, Brown & Burk UK Ltd, Teva UK Ltd, Irbesartan-containing and Losartan-containing products, EL (21)A/14" (https://www.gov.uk/drug-device-alerts/class-2-medicines-recall-bristol-laboratories-limited-brown-and-burk-uk-ltd-teva-uk-ltd-irbesartan-containing-and-losartan-containing-products-el-21-a-slash-14).Accessed March 2022.
6. "Risk of presence of mutagenic azido impurities in sartan active substances with a tetrazole ring". (https://www.edqm.eu/en/news/risk-presence-mutagenic-azido-impurities-losartan-active-substance). Accessed March 2022.

ORDERING TABLE

Product	Details	Size	Part number
Avantor® ACE® Excel 3 C18-PFP	HPLC Column	150 x 3.0 mm	EXL-1110-1503U

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