Photosensitive macrocyclic peptoids functionalized with azobenzenes

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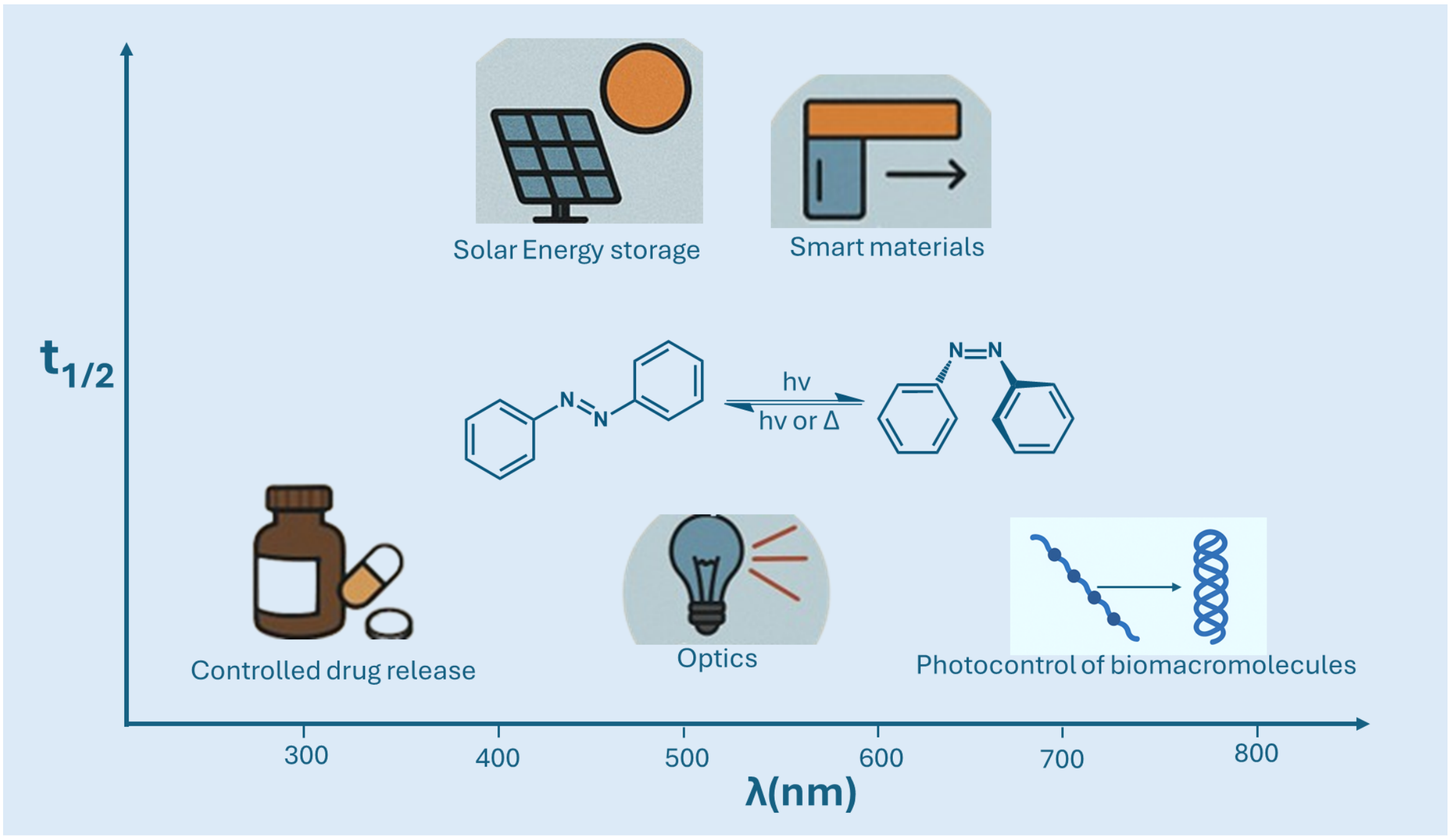


Figure 1. *Photoswitches applications of azobenzenes as a function of wavelength range and half-life time of the ideal cis-isomer [1], [2] .*

Introduction

Azobenzenes are molecular switches that can reversibly switch between the trans and cis forms under the effect of light. This property is exploited in fields such as solar energy storage, smart materials or pharmacology (**Figure 1**) *[1], [2]*. Peptoids are synthetic peptide analogues with high chemical diversity, good stability, and enzyme resistance, making them attractive for biomedical and materials applications *[3]*. Azobenzene derivatives have been previously incorporated all along a peptoid backbone with strong impact on the photoswitching properties (**Figure 2**) *[2]*. Cyclization of peptoids by limiting their conformational flexibility should further affect the photoisomerization processes (**Figure 2**) *[3]*. In this context, the integration of azobenzenes into cyclic peptoids is promising for the design of photoreactive materials and bio-inspired molecules. Their unique structure would represent an ideal and versatile platform to tune the properties of azobenzene. This project explores the integration of a single azobenzene residue into a cyclic peptoid. The photoswitching properties of the obtained original molecule will be investigated using state of the art mass spectrometry methods.

Pristine Azobenzene

- 2 days < $t_{1/2}$ < 4 days
- λ_{max} = 320 nm

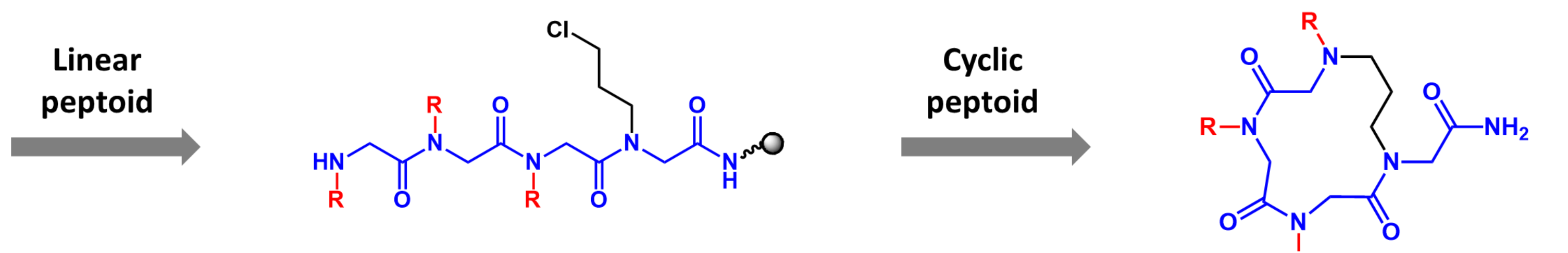


Figure 2. *Incorporating azobenzenes on cyclic peptoids to design new photoreactive materials [2], [3].*

Objectives

- Linear peptoid synthesis
- Cyclization reaction optimization
- Structural characterization (MS, MS/MS, LC-MS and LC-IMS-MS)

Synthetic pathway

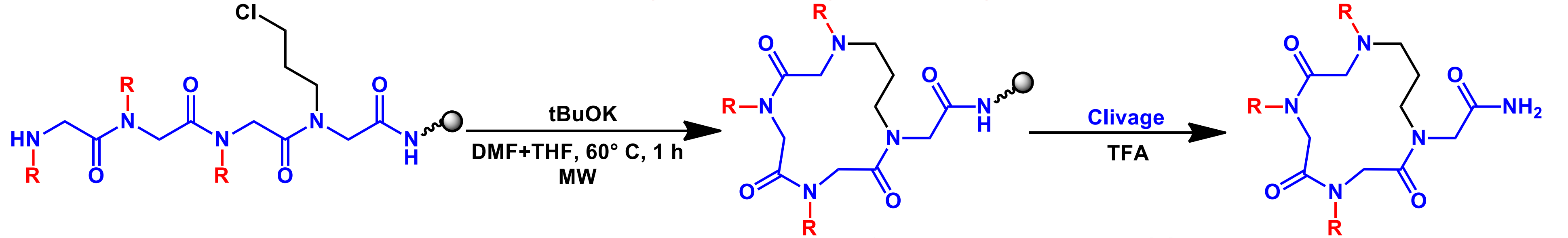


Figure 3. *Microwave-assisted cyclization of peptoids on solid support [3].*

Synthesized peptoids

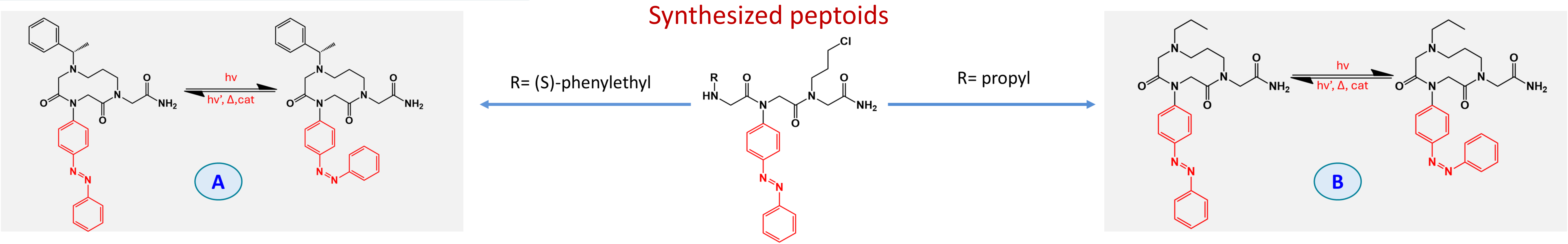


Figure 4. *Cyclic peptoids synthesized from linear precursors; (A): NspeNazoNcp and (B): NpropNazoNcp.*

Linear and cyclic azobenzene-containing peptoid solutions (10^{-5} M) were analyzed by **LC-MS** (C_{18} Agilent Eclipse plus H_2O (0.01 % HCOOH) / ACN gradient) before and after irradiation with a lightningcure LC8 L9588-02A lamp (ca. 220 - 400 nm).

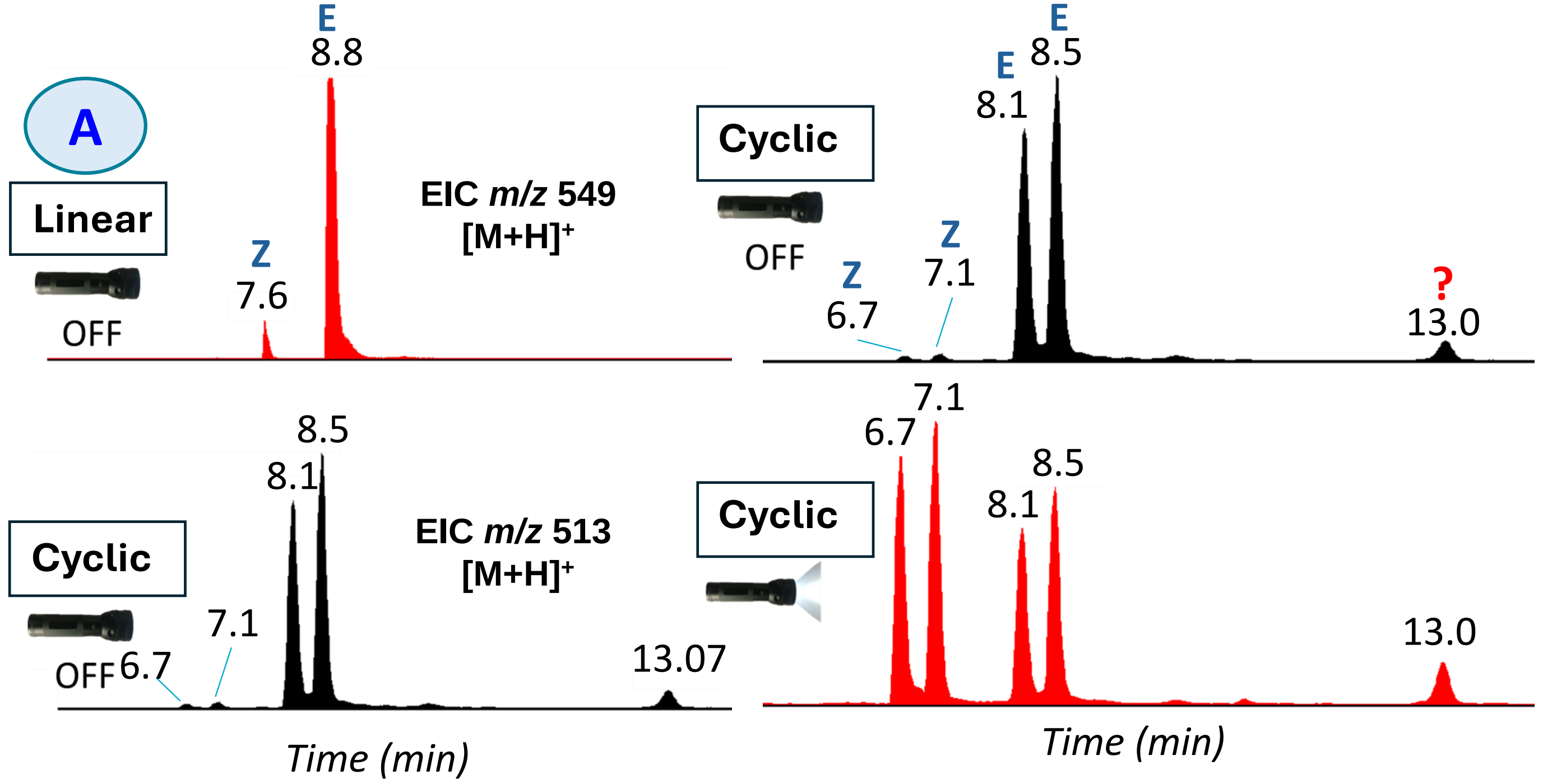


Figure 5. LC-MS analyses : *EIC of linear and cyclic peptoid A with and without irradiation*

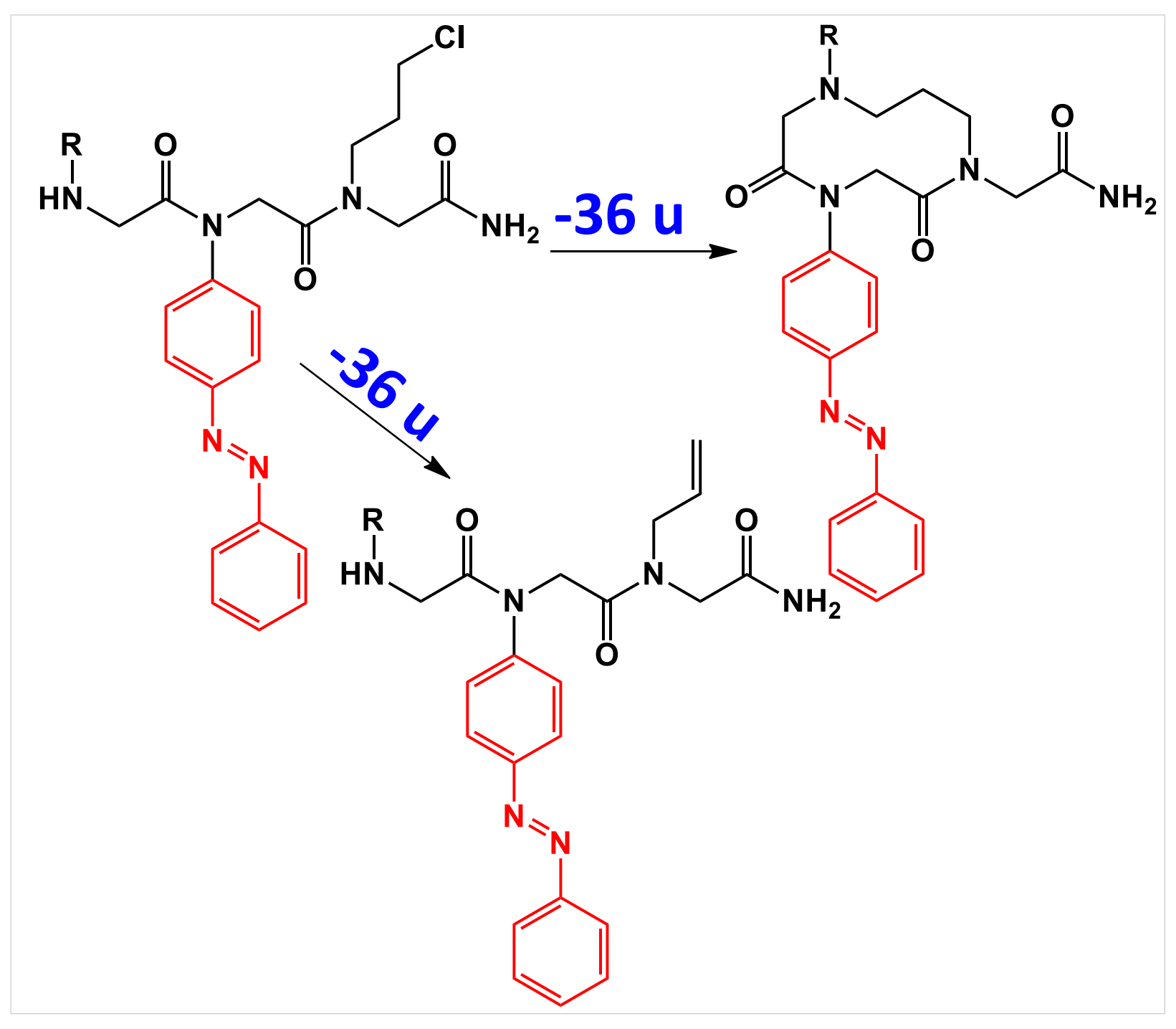


Figure 7. Different *isomers may be produced by the HCl loss from linear peptoids.*

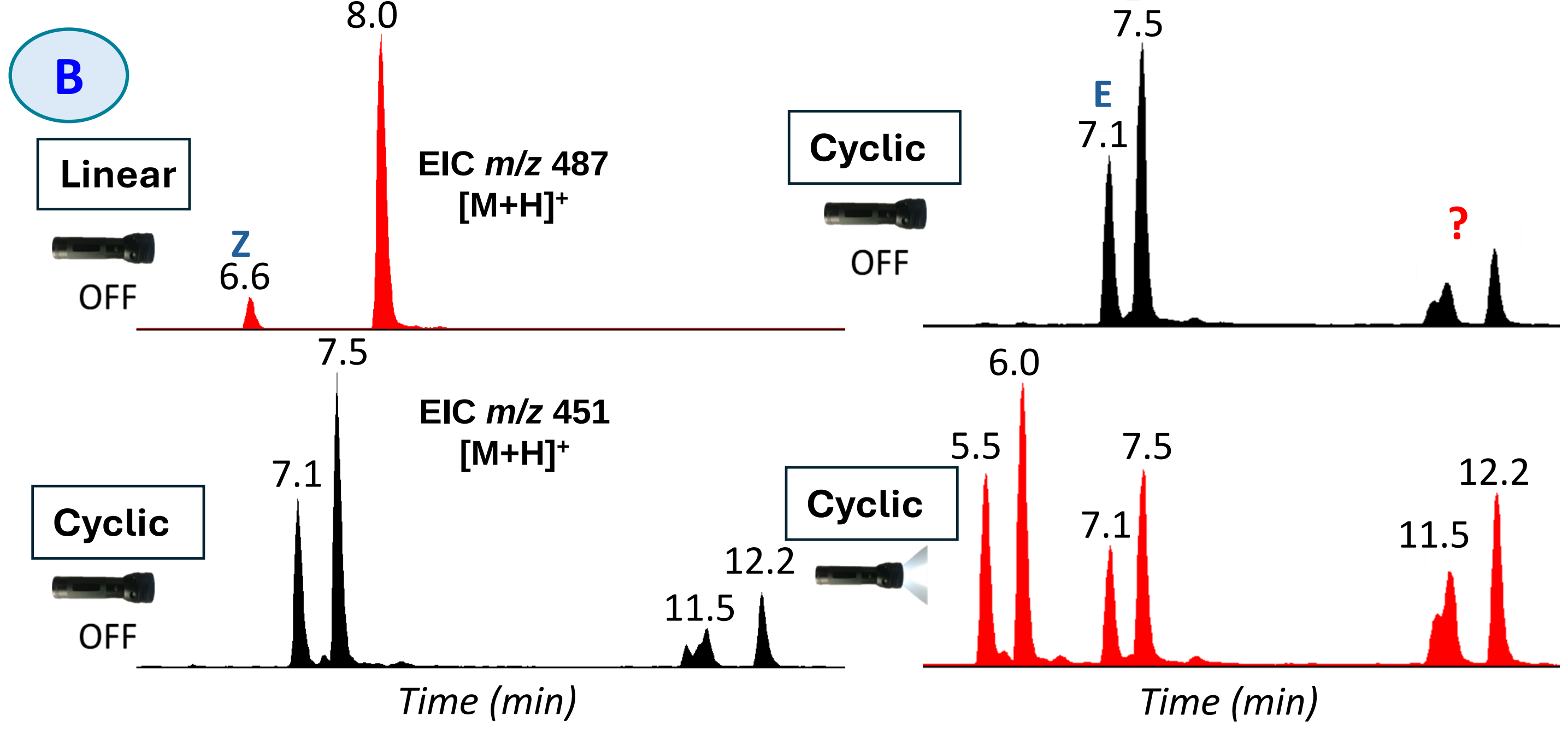
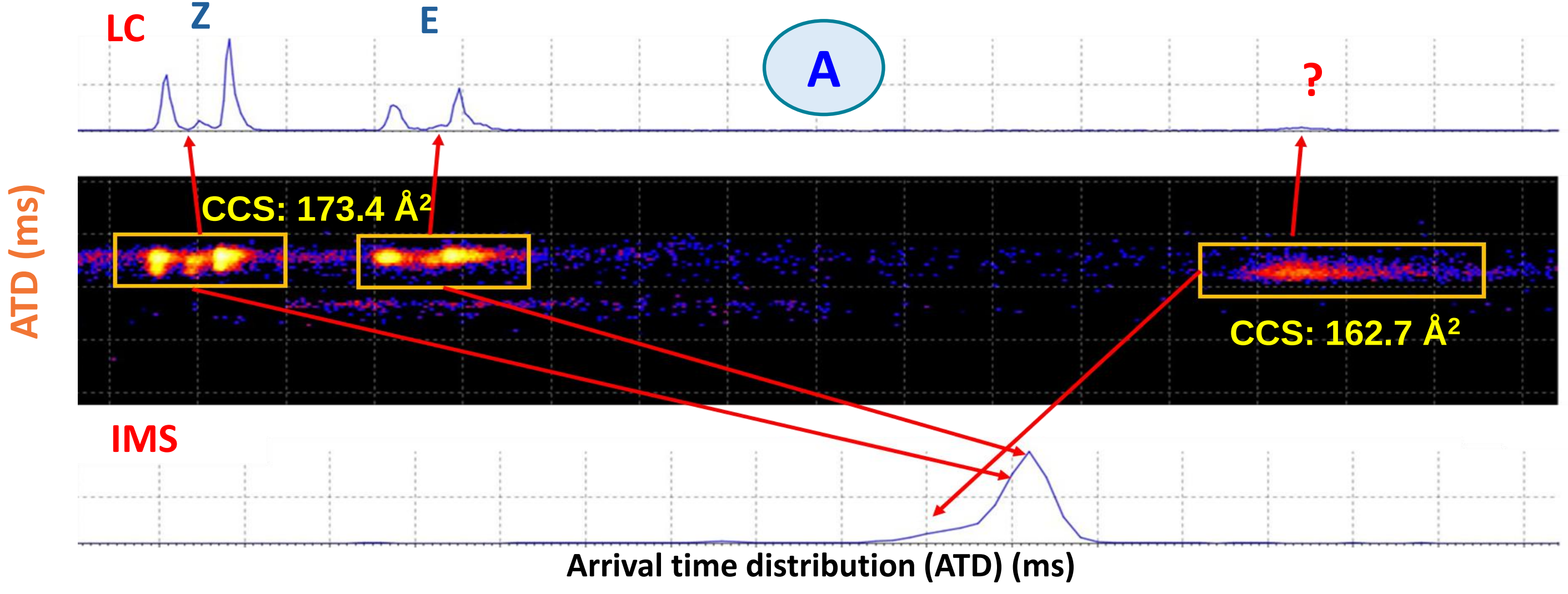


Figure 6. LC-MS analyses : *EIC of linear and cyclic peptoid B with and without irradiation.*

Separation of protonated isomers according to their three-dimensional structure by ion mobility spectrometry coupled to liquid chromatography and mass spectrometry (**LC-IMS-MS**).



C_{18} Acquity UPLC
H_2O (0.01 % HCOOH) /
ACN gradient

Two ATD are observed : linear and cyclic isomers ?

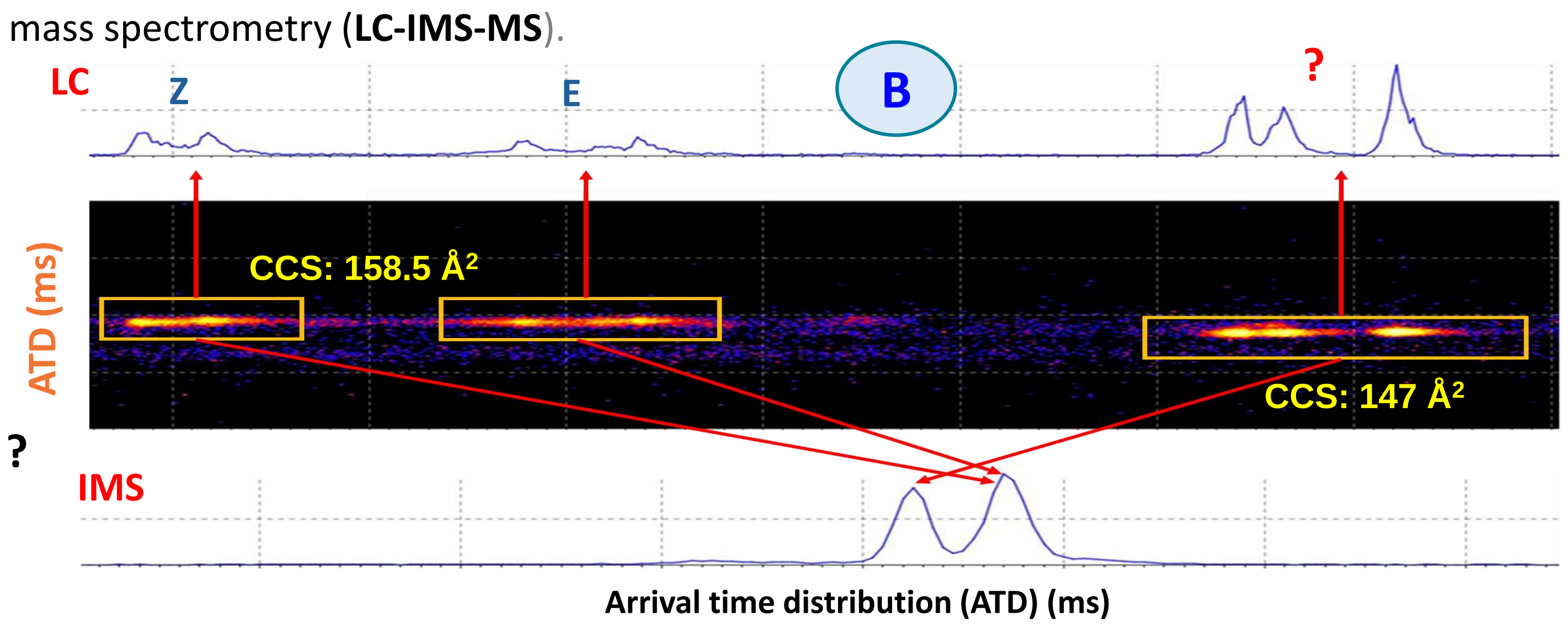
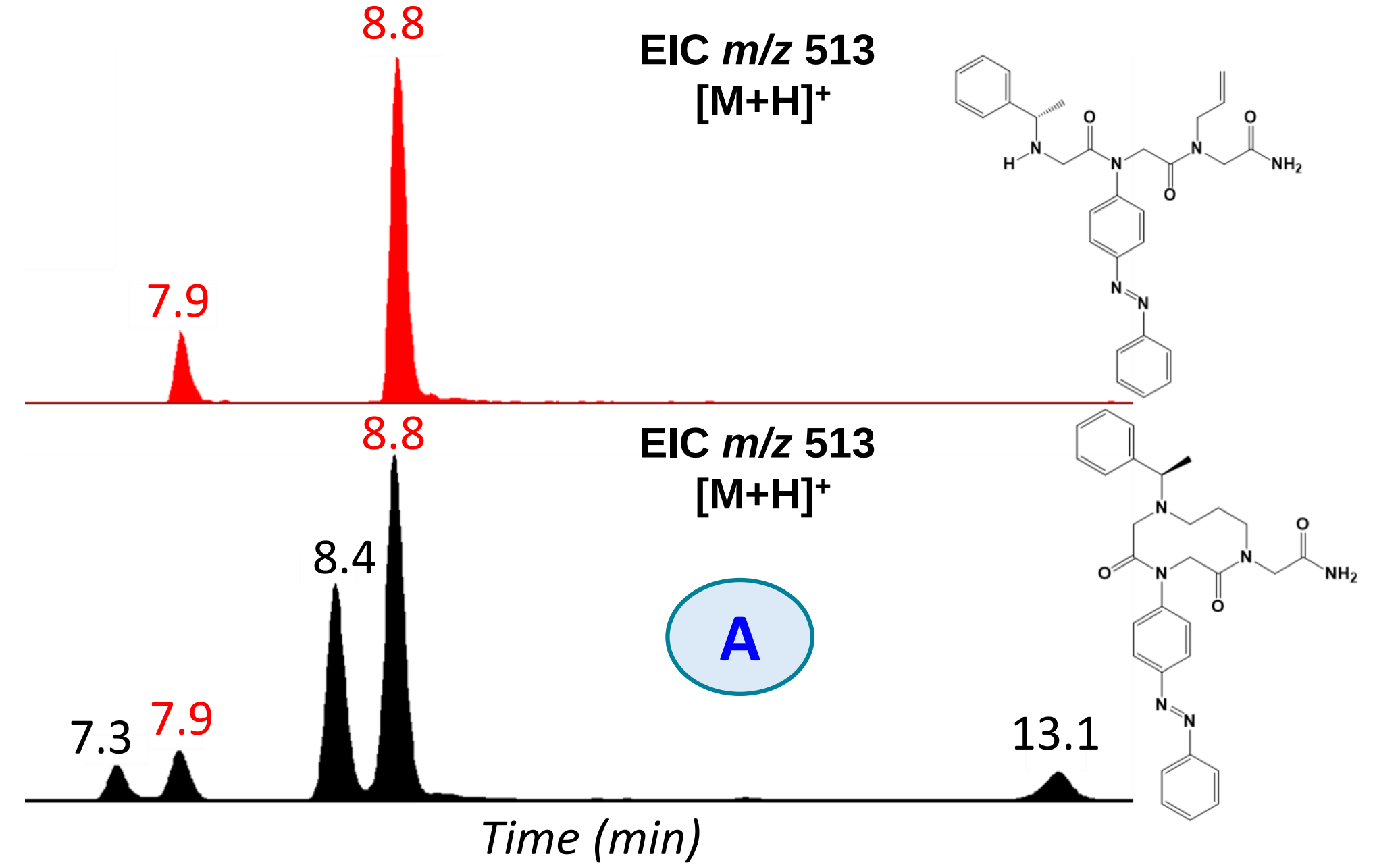


Figure 8. *LC-IMS-MS of cyclic peptoids (A) and (B). Isomers observed at low retention times in the chromatogram have a higher CCS than those at high retention times.*



Synthesis and analysis of a linear peptoids similar to the isomers obtained by the elimination reaction from the precursor linear peptoids (**Figure 7**).

C_{18} Agilent Eclipse plus
H_2O (0.01 % HCOOH) /
ACN gradient

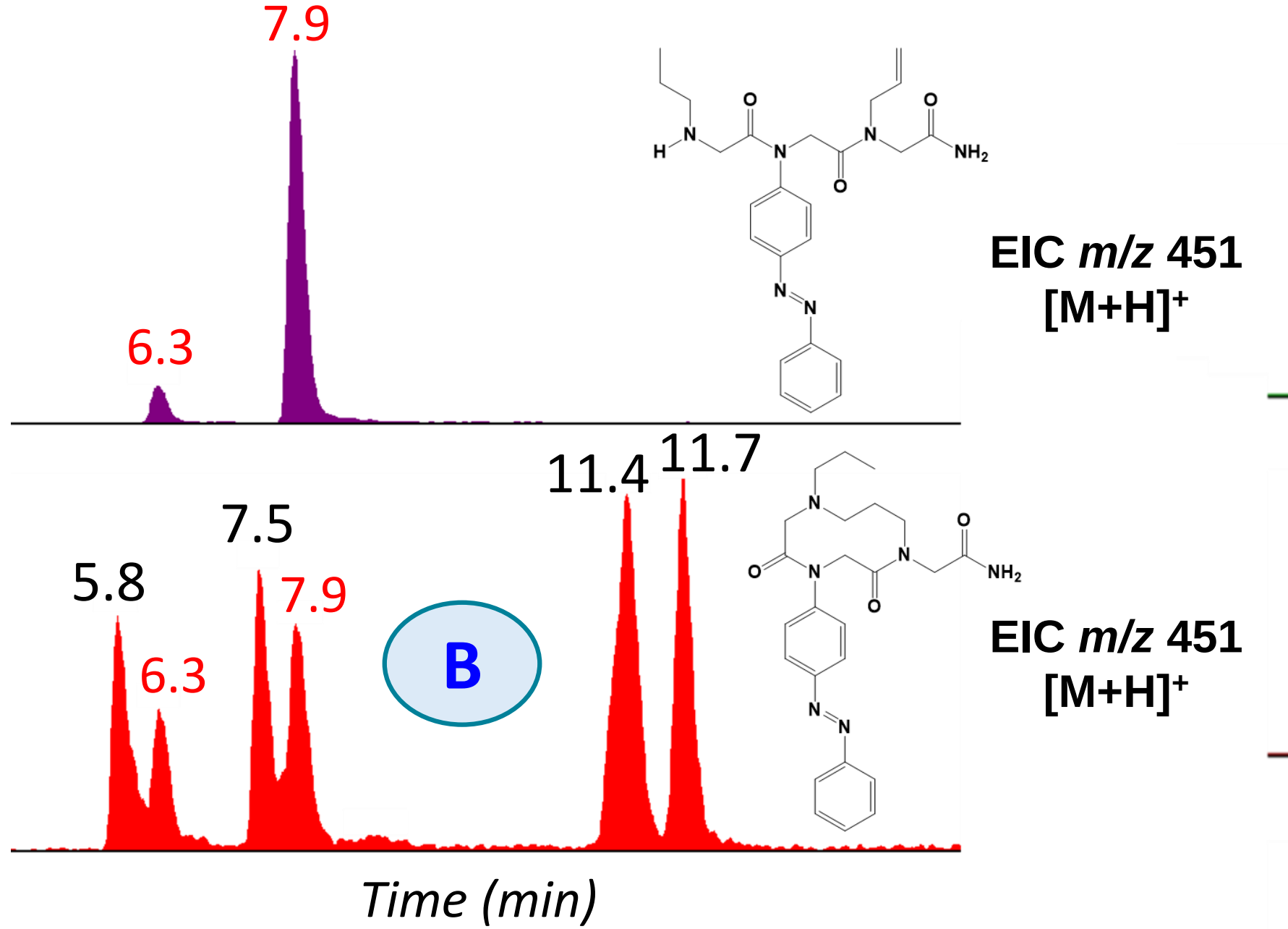


Figure 9. LC-MS analysis : *comparison of the cyclization isomer populations and the referent allyl-containing linear peptoids*

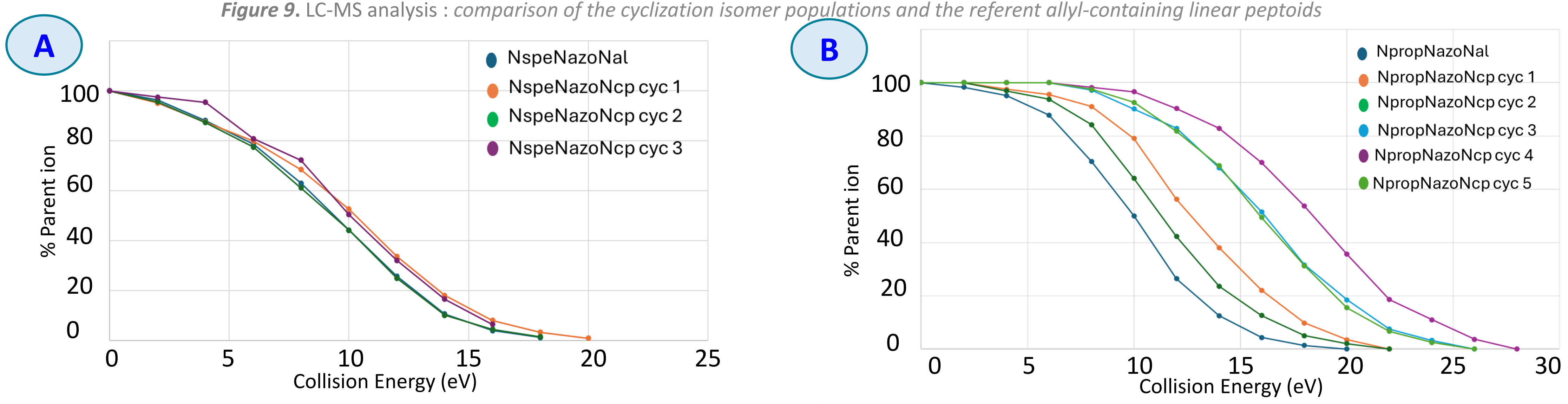


Figure 10. LC-MSMS analyses: Survival yields of all the isomeric peptoid (trans) ions generated during the cyclization reaction and the referent linear peptoids

What do the other peaks in the chromatogram correspond to?

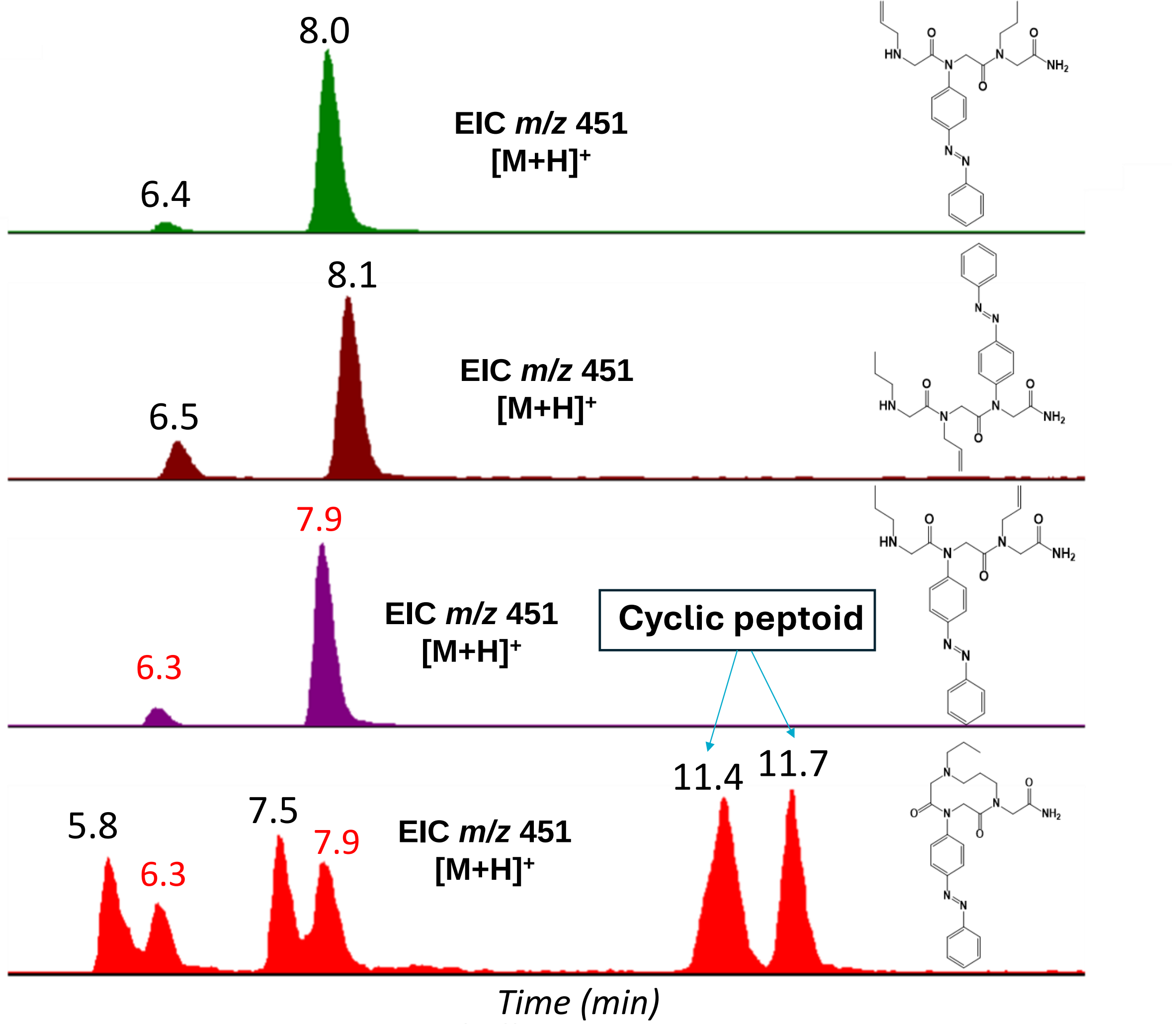


Figure 11. LC-MS analyses : *EIC of different isomers with varying side-chain positions.*

The peaks in the chromatograms of the isomers resulting from the change in side-chain position correspond neither to the second pair observed, nor to the peaks with high retention times after cyclization.

Conclusions

This work, which combines synthesis, MS, MS/MS, LC-MS and LC-IMS-MS analyses, demonstrates that it is possible to separate and identify several isomers. We observed linear peptoids resulting from a side elimination reaction together with the targeted cyclic peptoids. However, several isomers still need to be identified toward the optimization of the cyclization process.

Acknowledgments

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References

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[2] B. Tassignon, Z. Wang, A. Galanti, J. De Winter, P. Samori, J. Cornil, K. Moth-Poulsen, P. Gerbaux; Chem. Eur. J., 29, (2023)
[3] P.J. Kaniraj, G. Maayan; Org. Lett., 17, 2110-2113 (2015)