

# Fighting Cancer with Macrocycles: New Molecular Shapes Provide New Treatment Strategies

DEPARTMENT OF  
Chemistry & Biochemistry

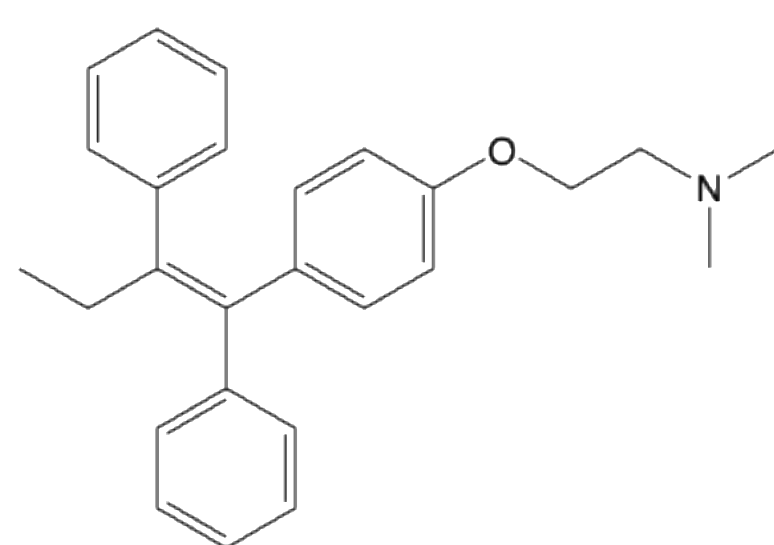
TCU COLLEGE OF  
SCIENCE & ENGINEERING

Graduate Student Presenter: Andrea E. Rangel Faculty Advisor: Eric E. Simanek

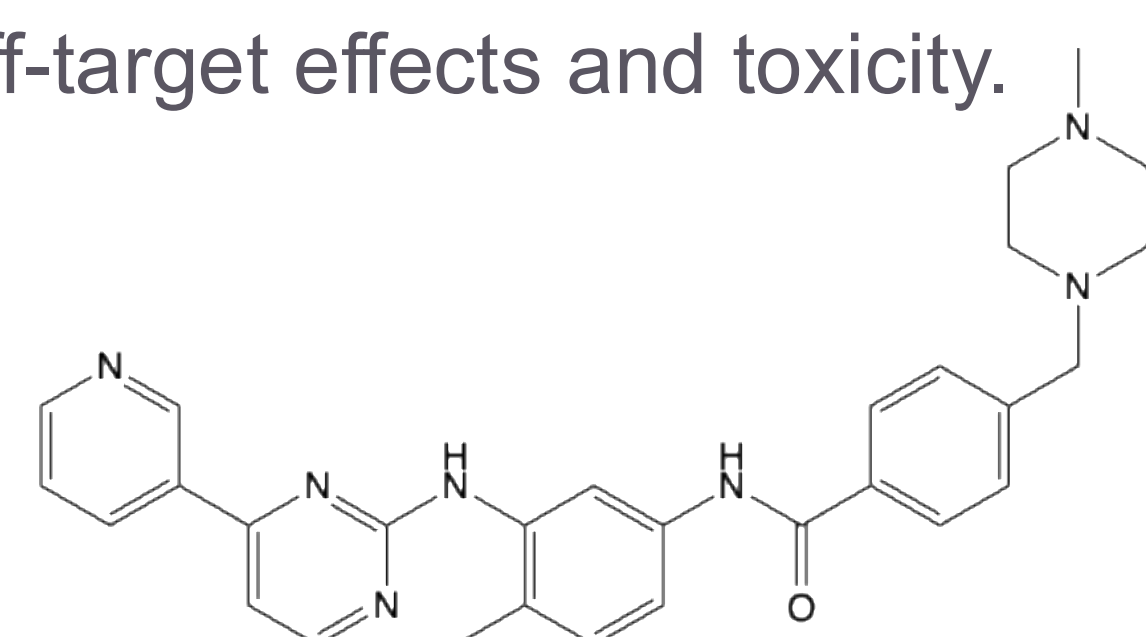
## Background

Chemotherapy relies on two main therapeutic paradigms. The classical approach is seen in many current anti-cancer drugs that rely on small molecules. Their small size can be useful in entering cells to directly stop key cancer-associated proteins. However, not all proteins can be targeted by small molecules due to limitations including off-target effects and toxicity.

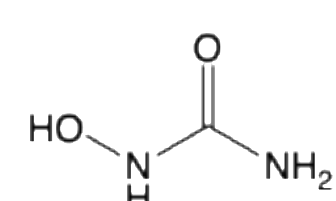
**Figure 1.** Small molecule cancer drugs.



**Soltamox (Tamoxifen)**  
Used to treat breast cancer

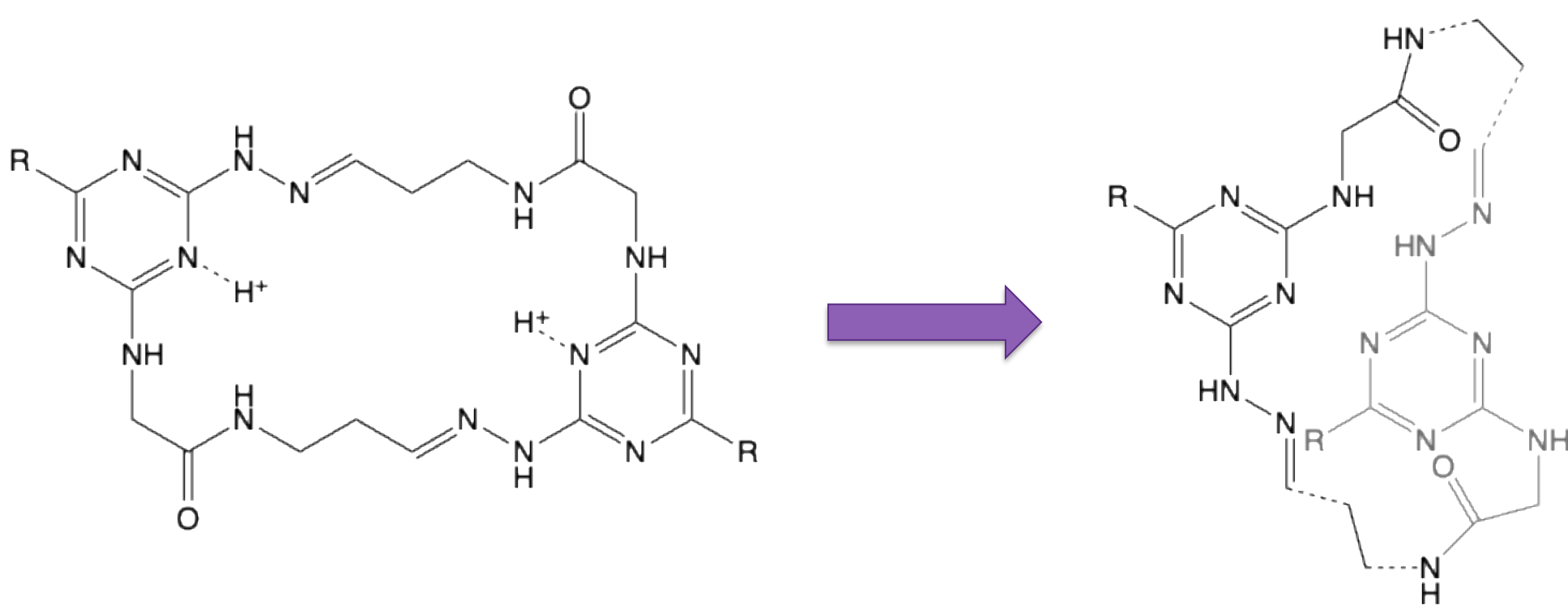


**Imatinib (Gleevec)**  
Used to treat certain cancers like chronic myeloid leukemia



**Hydroxyurea (Hydrea)**  
Used to treat certain cancers and sickle cell disease

As a result, the pharmaceutical industry is now shifting their focus on large molecules that can interfere with protein-protein interactions. But, unlike small molecules, the rules for drug design are not understood for large molecules. Our solution is to use macrocycles with unique folding properties that would allow them to still enter cells and get to their target.

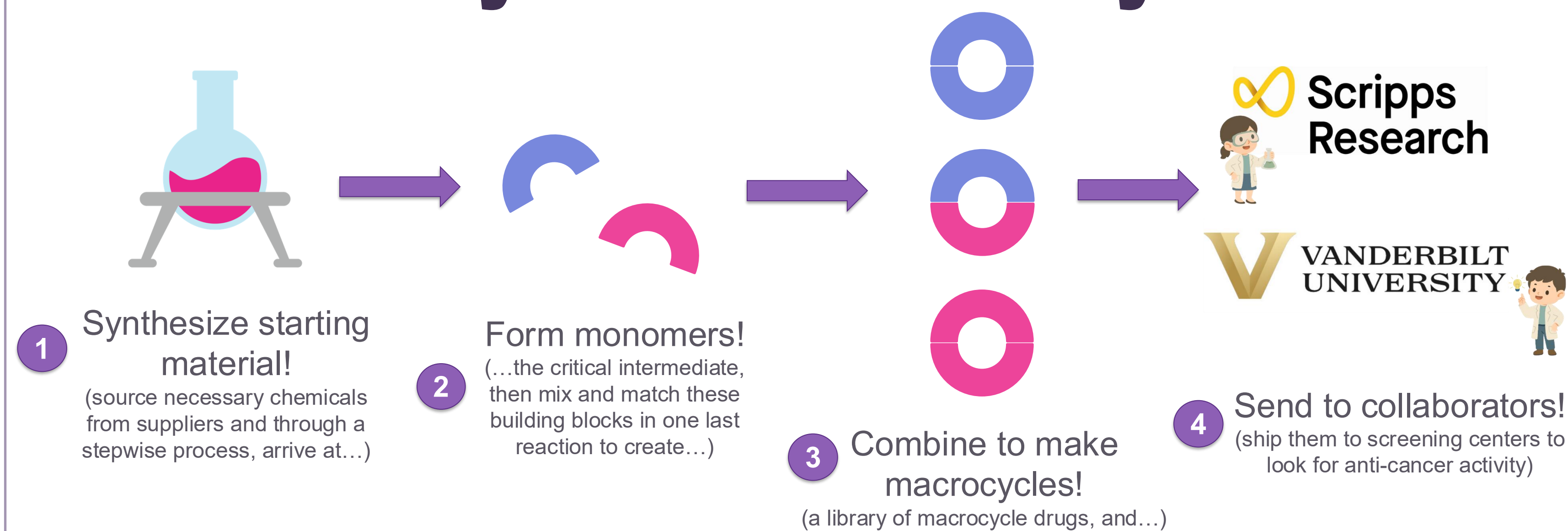


**Figure 2.** Macrocycles can fold to allow them to pass through cell membranes. Well-defined shape allows for computer-aided drug design.

## Objective

Our goal is to create a library of macrocycles using various functional groups attached to the ring. We aim to collaborate with various institutions to test for biological activity.

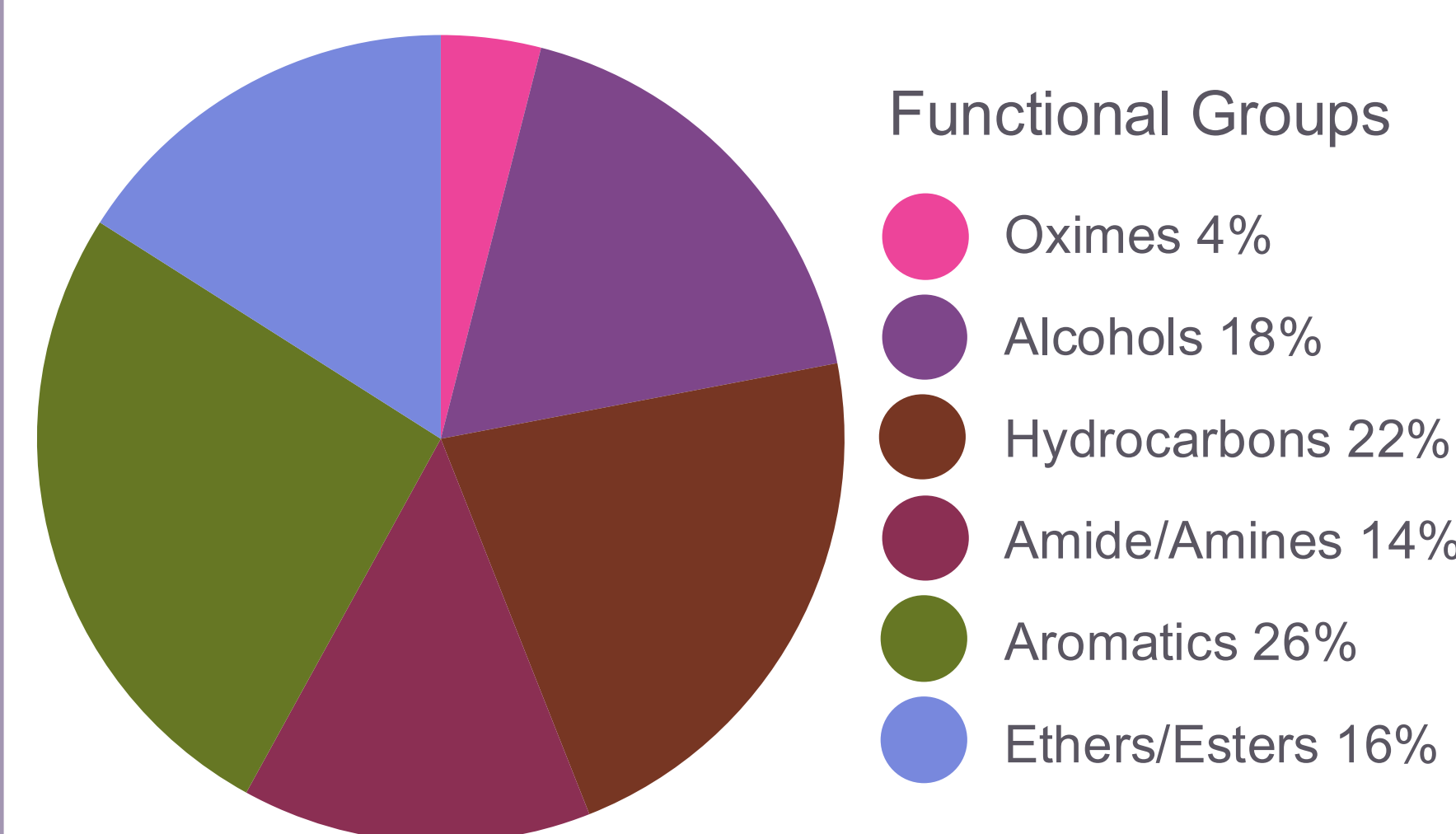
## Synthesis of Library



**Figure 3.** General process for making the macrocycle library and the institutions we are collaborating with to screen these molecules for biological activity.

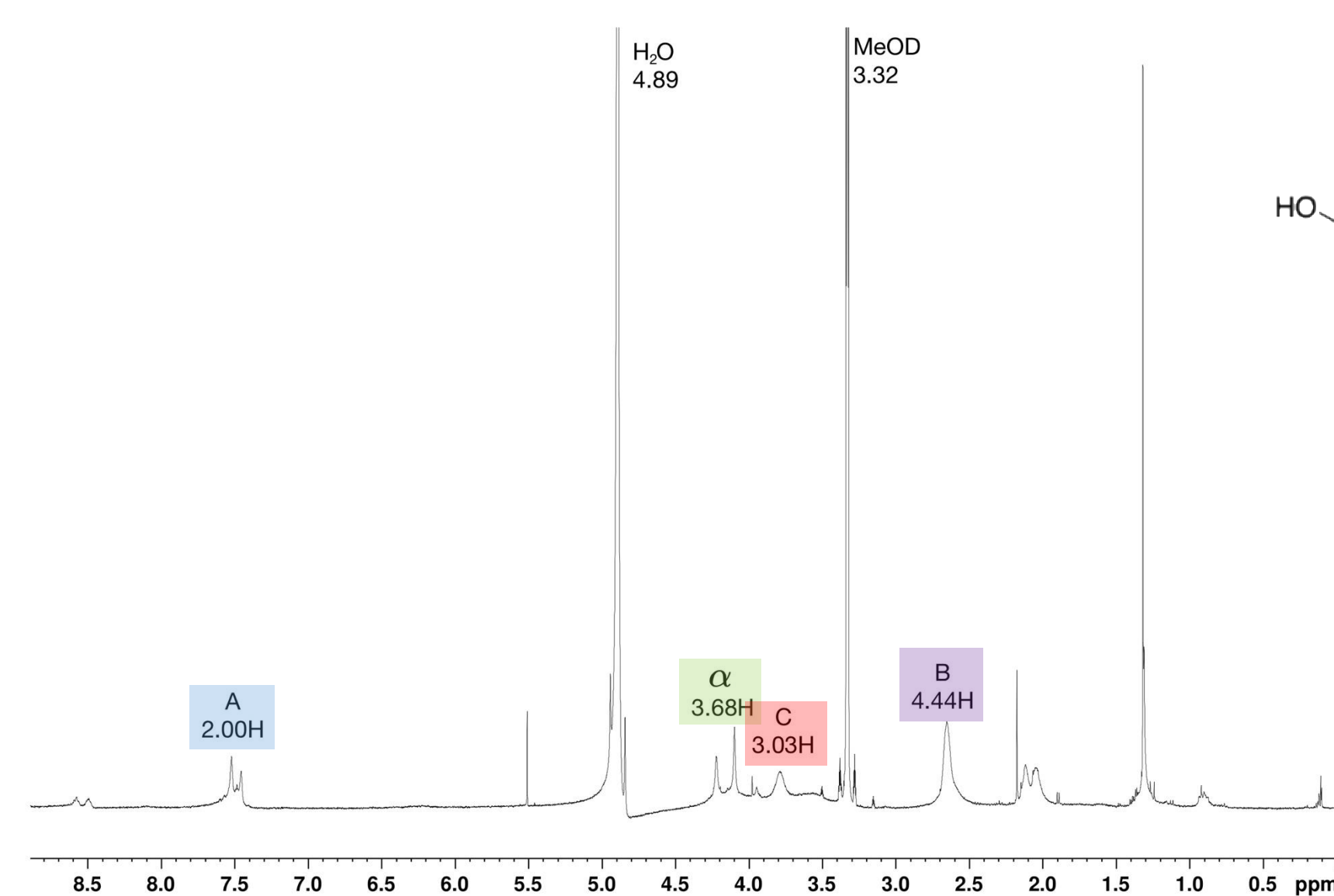
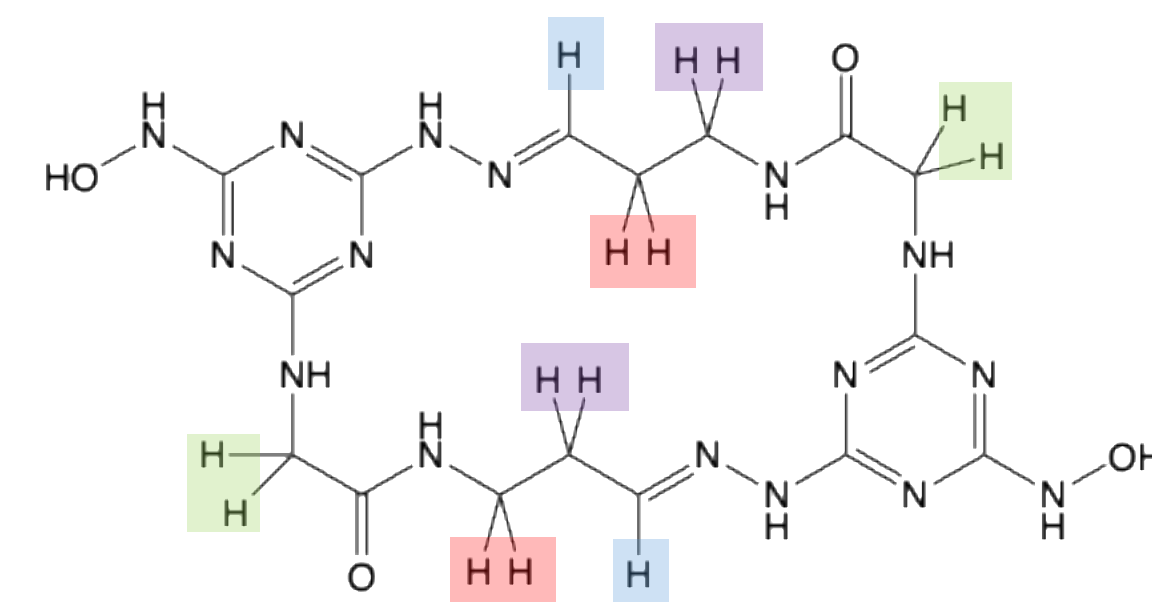
## Results

Total number of macrocycles:  
1275

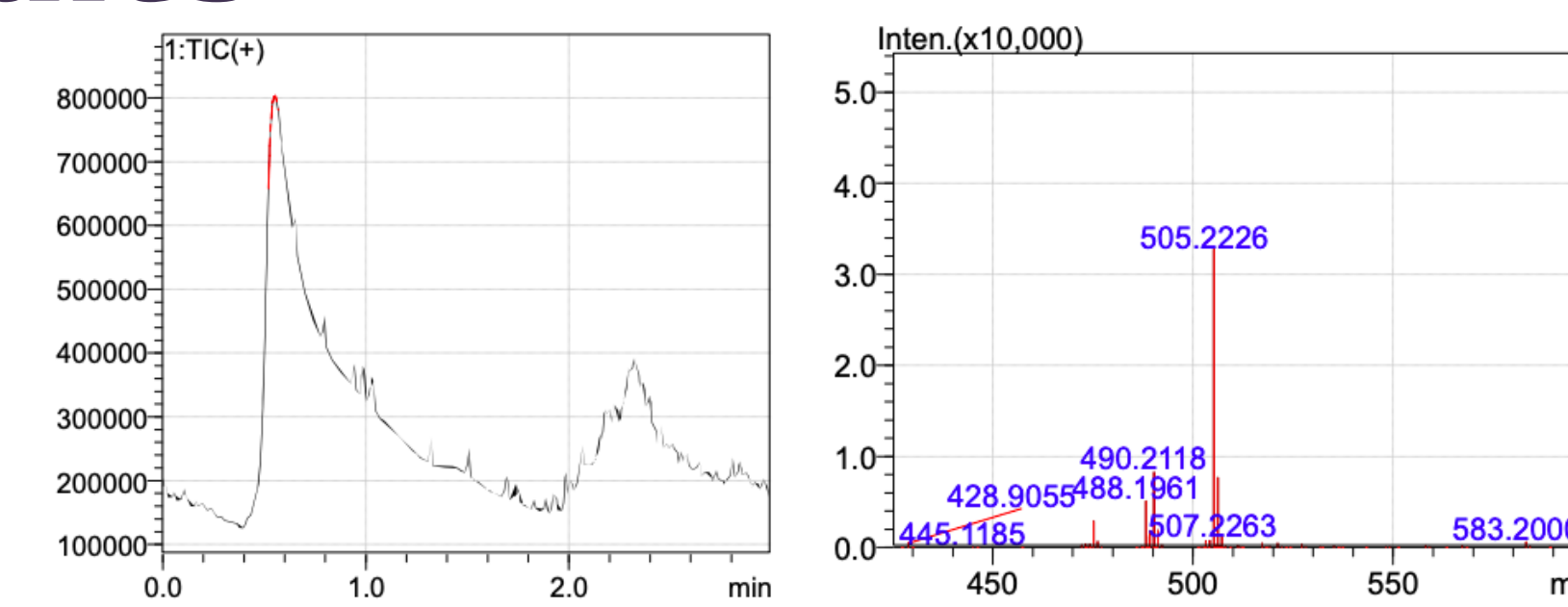


Monomer composition

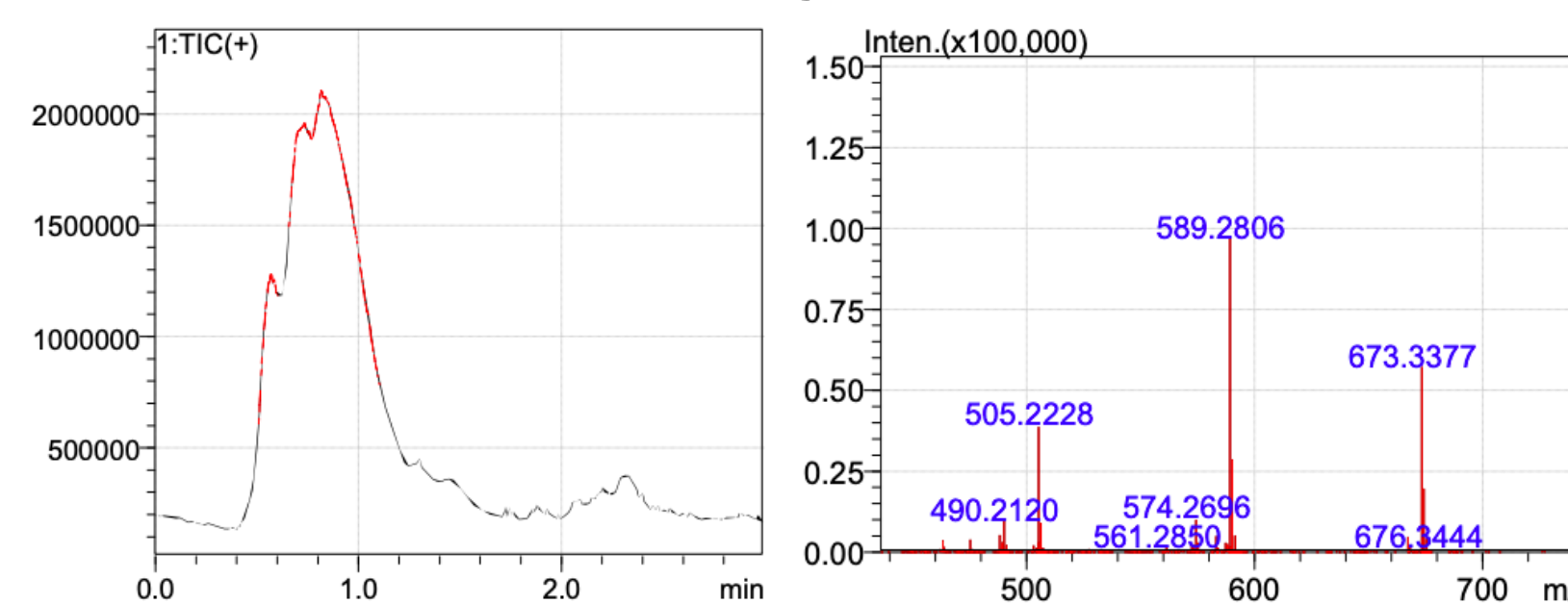
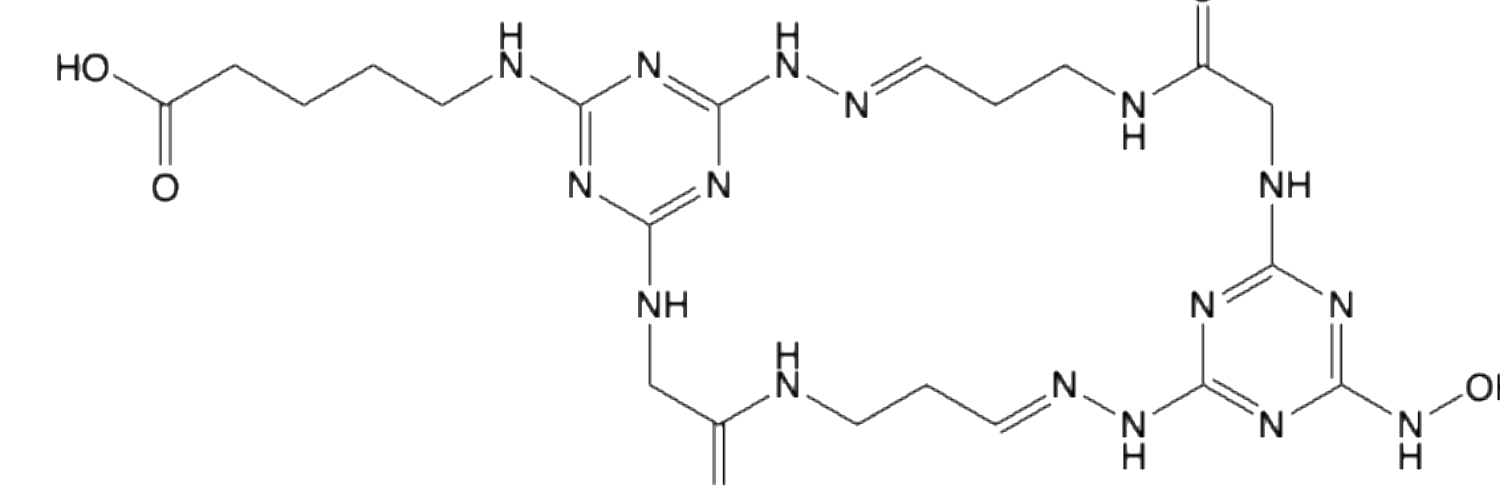
**Figure 4.** Monomer R-group composition for the macrocycle library.



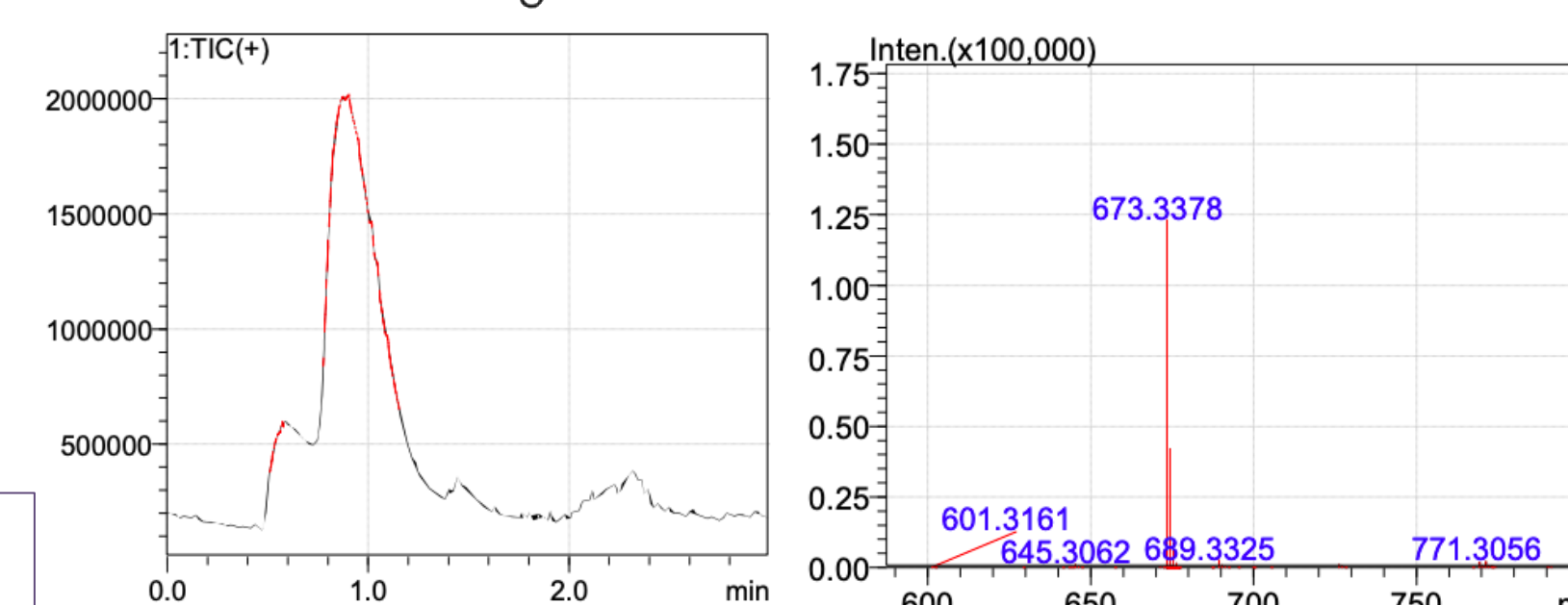
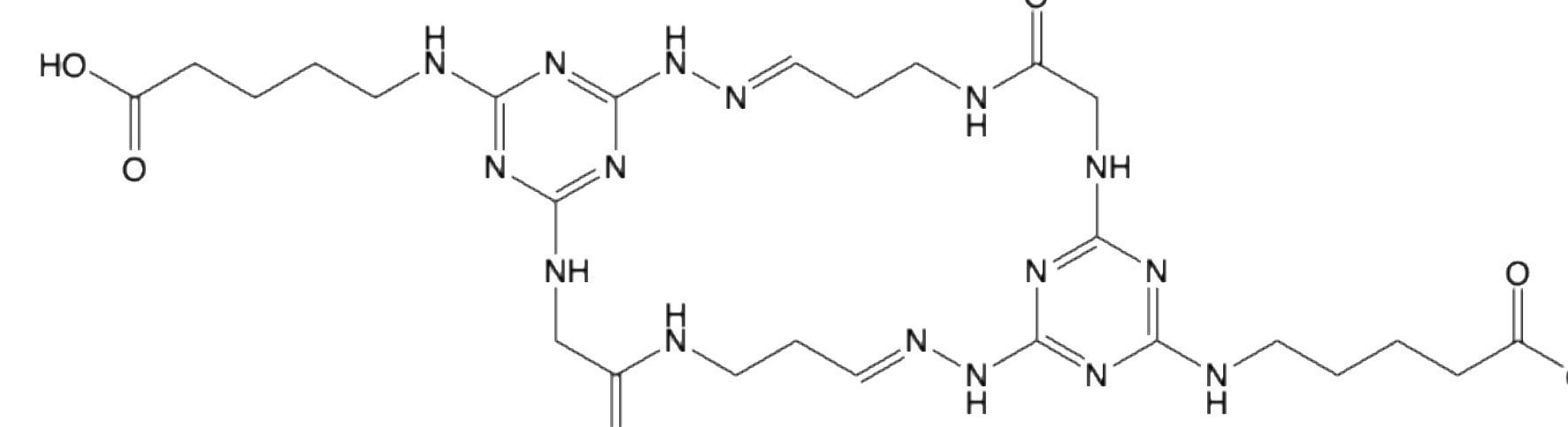
**Figure 5.** <sup>1</sup>H NMR of G21G21 macrocycle (homodimer) that was made. Note the similarity to hydroxyurea.



**Figure 6.** Total ion chromatogram (left) and mass spectrum (right) of G21G21 macrocycle.



**Figure 7.** Total ion chromatogram (left) and mass spectrum (right) of G76G21 macrocycle (top).



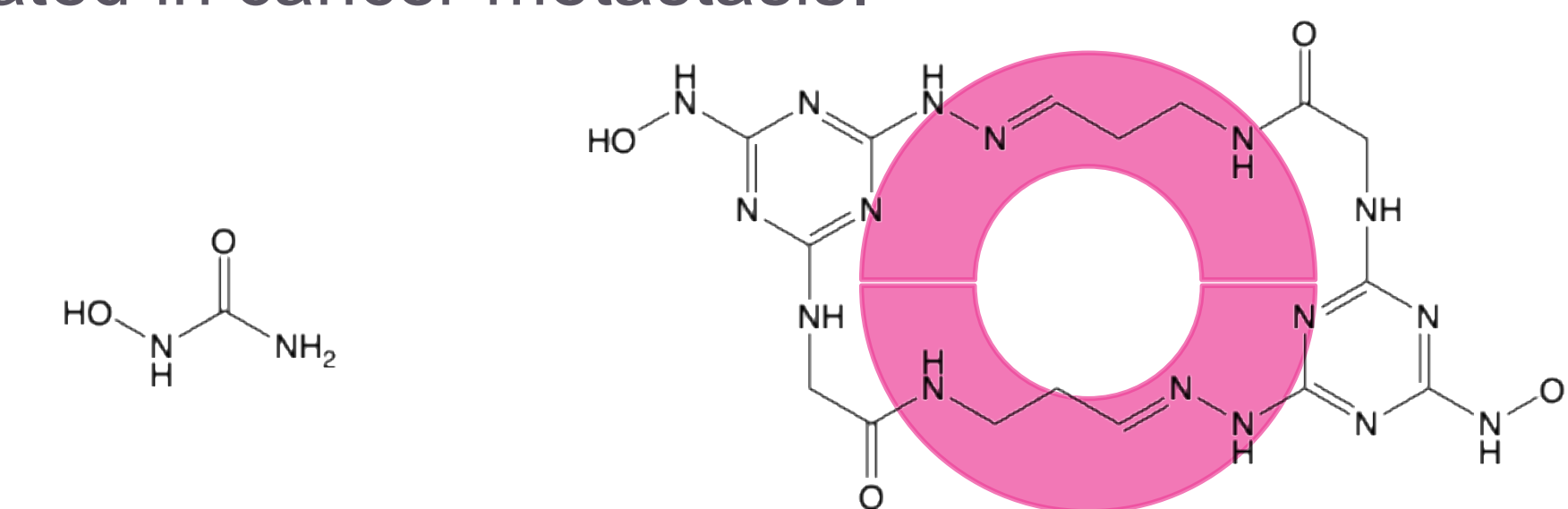
**Figure 8.** Total ion chromatogram (left) and mass spectrum (right) of G76G76 macrocycle (top).

## Conclusion

A library of 1,275 macrocycles was made using 50 different monomers. Various drug-like groups were used to maximize the chance of finding an “undruggable” target. Liquid chromatography-mass spectroscopy confirmed presence of the expected three isomers with > 99.9% purity. The library has been shipped to the drug screening facility at Vanderbilt University as well as a screening center in Florida.

## Future Directions

Macrocycle G21G21, presenting a group similar to hydroxyurea, will be prepared and studied at TCU for activity against specific protein targets that are implicated in cancer metastasis.



**Figure 6.** FDA approved drug “Hydrea” and the G21G21 macrocycle containing hydroxylamine group.

## About the Presenter

Andrea Rangel is a first-generation first-year Chemistry PhD student working in the Simanek Lab. She graduated with a B.S in Biochemistry from the University of San Diego. Andrea was born and raised in Fort Worth and is excited to be back home to pursue her graduate studies at TCU! Dr. Simanek is the Robert A. Welch Chair of Chemistry.

## Acknowledgments

Several undergraduate students worked on this project under the mentorship of graduate student Liam Claton and post-doc Dr. Harsha Vardhan Reddy. The work is funded by the National Institutes of Health.

NIH National Institutes of Health

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