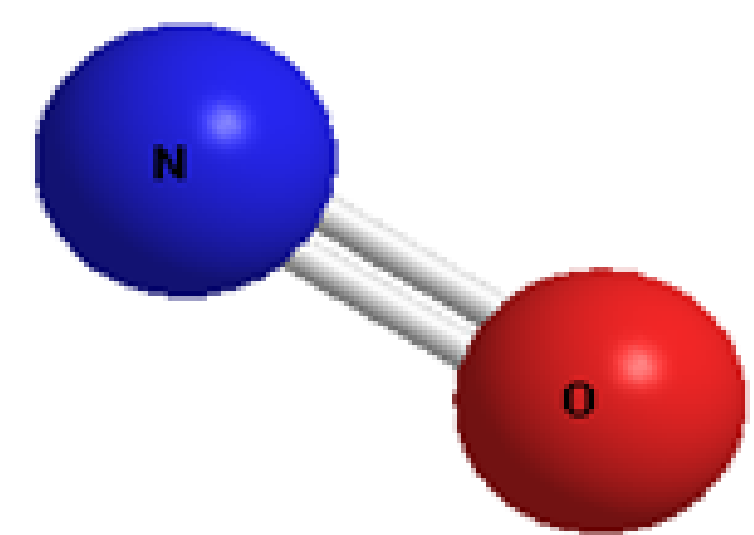


Diazeniumdiolates as nitroxyl (HNO) donors: synthesis and chemical characterization



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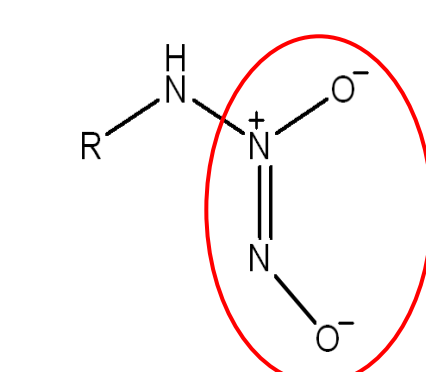


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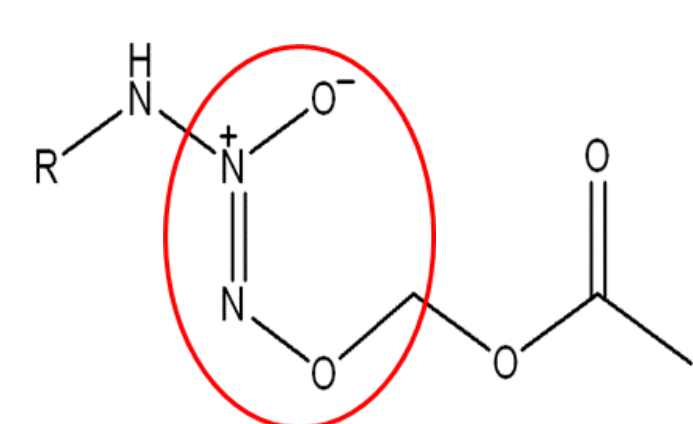
Abstract

Nitroxyl (HNO) donors have emerged as versatile agents in pharmacological research, demonstrating a broad spectrum of therapeutic potential from inducing tumoricidal effects to managing heart failure. However, due to the unstable nature of HNO, which readily dimerizes to form nitrous oxide (N₂O), effective in situ generation of HNO from donor compounds is essential. While secondary amine diazeniumdiolate ions, or NONOates, have been widely utilized for their controlled release of nitric oxide (NO) in various biochemical and pharmacological applications, primary amine diazeniumdiolates have remained less explored. In this study, we present the synthesis and detailed characterization of a series of primary amine-based diazeniumdiolates. These compounds were designed to overcome limitations associated with HNO's fleeting nature by enabling its generation directly from stable precursors. Additionally, we developed acetoxymethyl ester-protected diazeniumdiolates to enhance purification processes and improve cellular uptake. Our findings not only expand the repertoire of diazeniumdiolate-based HNO donors but also offer new tools for probing the biological and therapeutic applications of nitroxyl.

What is a Diazeniumdiolate?



Diazeniumdiolate sodium salt

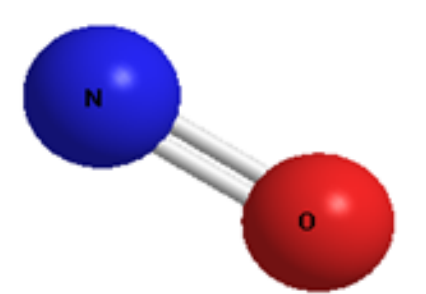


Diazeniumdiolate prodrug

Why Diazeniumdiolates?

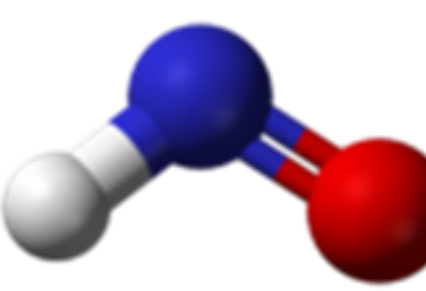
Diazeniumdiolates decompose into NO and HNO

• NO's biological properties



- NO has been shown to slow cancerous tumor growth significantly
- NO causes vasodilation, which causes a decrease in blood pressure

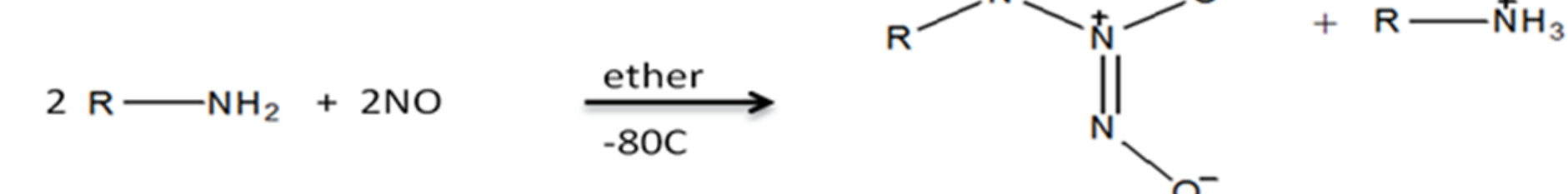
• HNO's biological properties



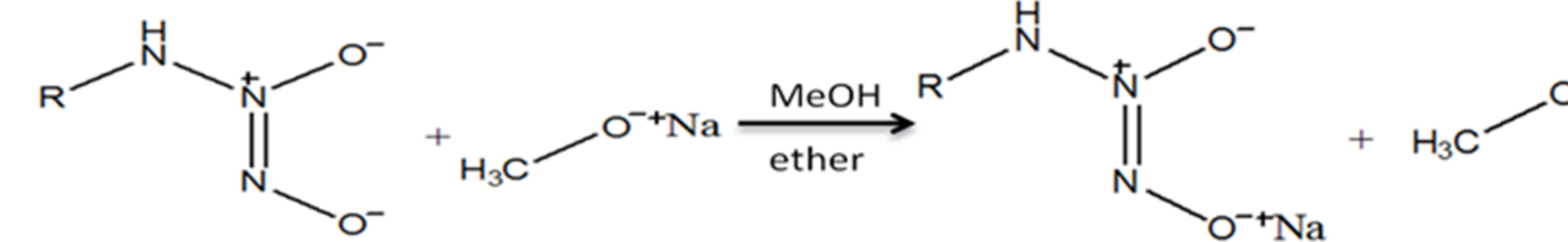
- HNO also causes vasodilation, which causes a decrease in blood pressure
- HNO shows potential in the treatment of heart failure

Synthesis

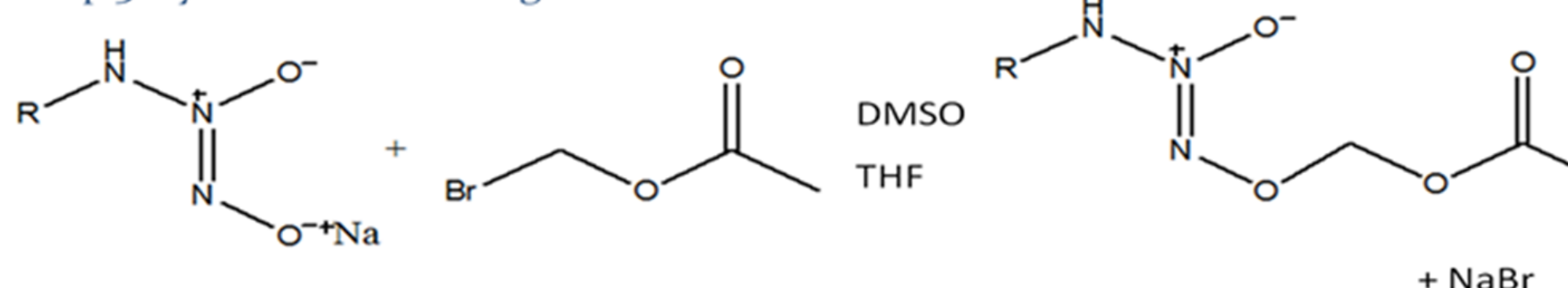
Step 1: Synthesis of Diazeniumdiolate



Step 2: Conversion to Sodium Salt



Step 3: Synthesis of Prodrug



Primary Amine Used

Name	Structure
Isopropylamine	
Cyclopentylamine	
4-methylcyclohexylamine	

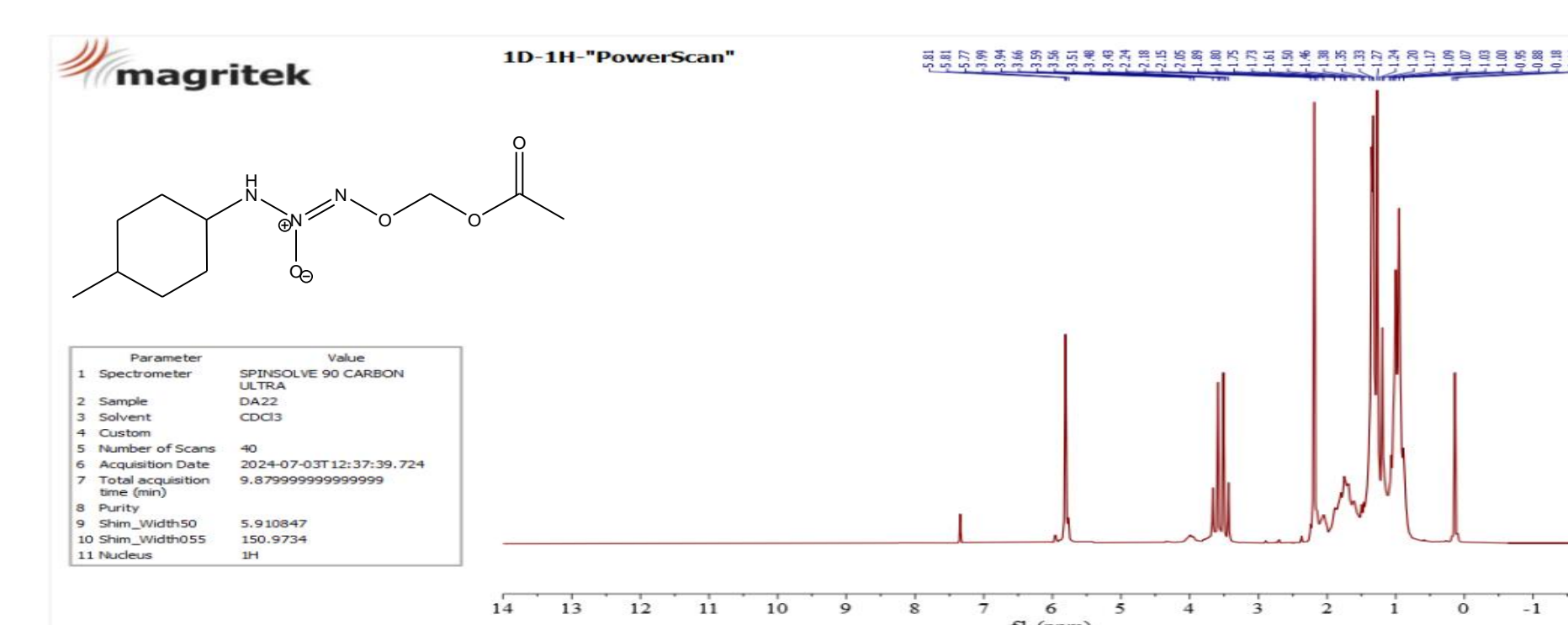
Prodrugs formed



Name	Structure
Isopropylamine diazeniumdiolate prodrug (IPA/NO)	
Cyclopentylamine diazeniumdiolate prodrug (DA-21)	
4-methylcyclohexylamine diazeniumdiolate prodrug (DA-22)	

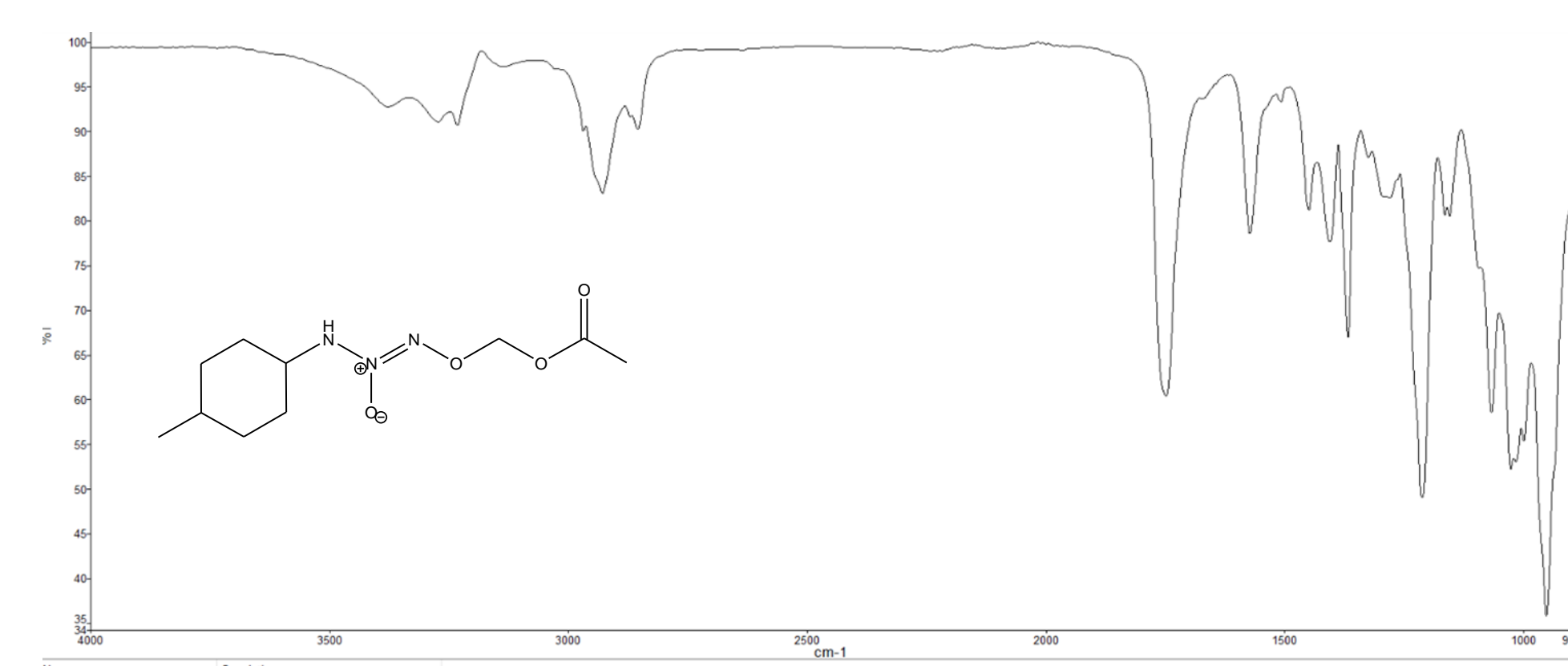
Chemical Characterization

NMR

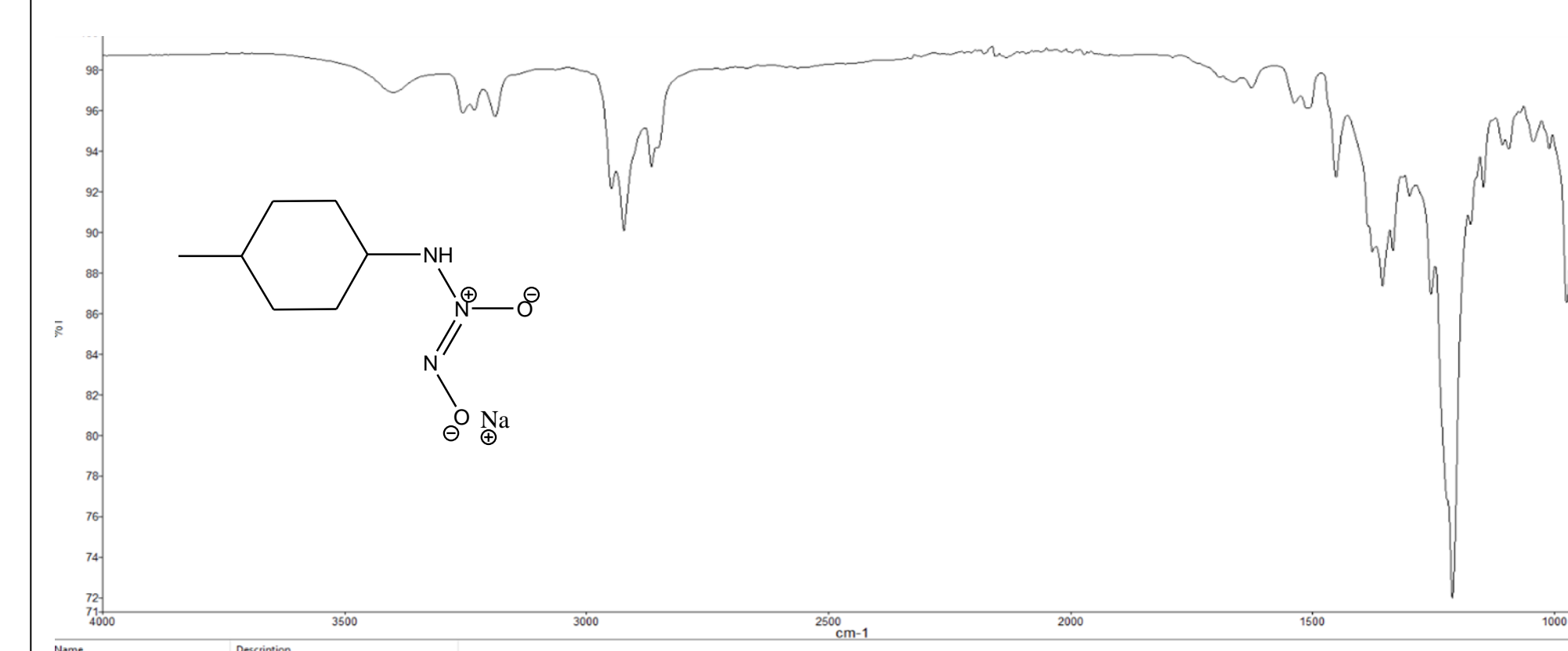


- 4-methylcyclohexylamine prodrug derivative

IR



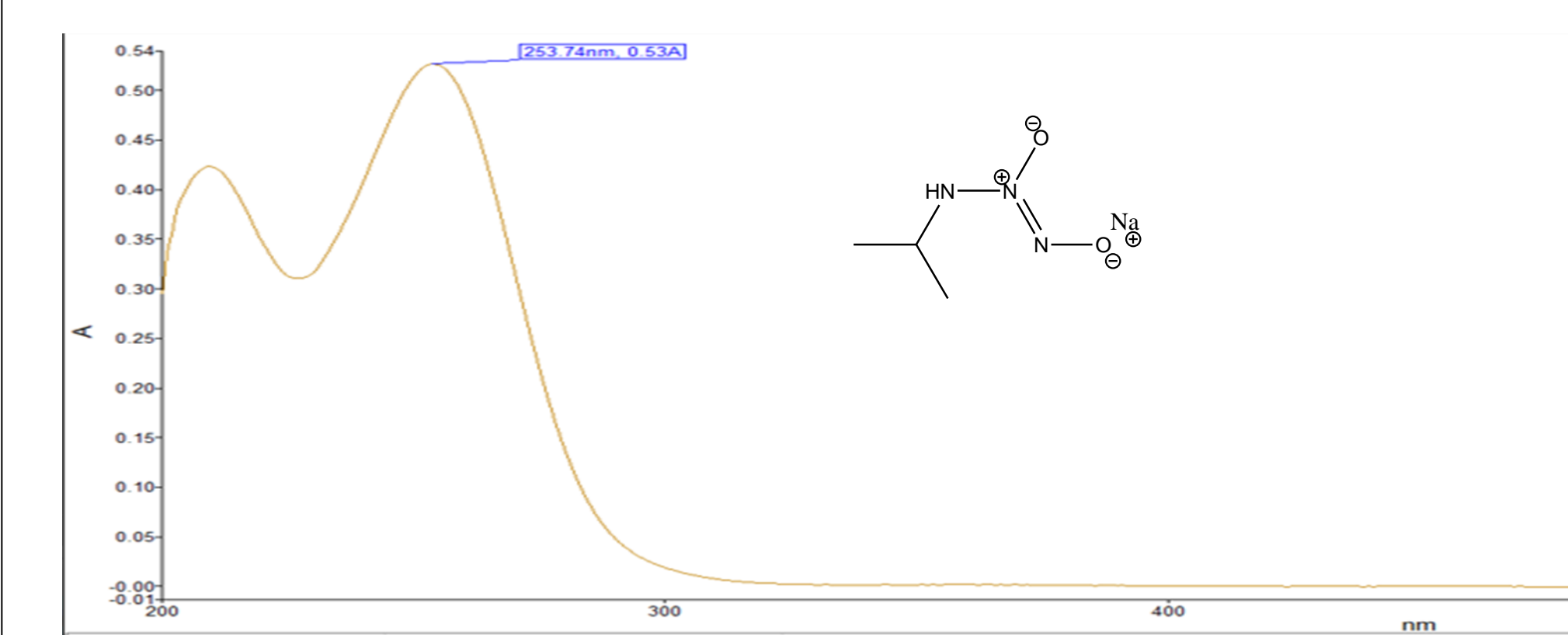
- 4-methylcyclohexylamine prodrug derivative



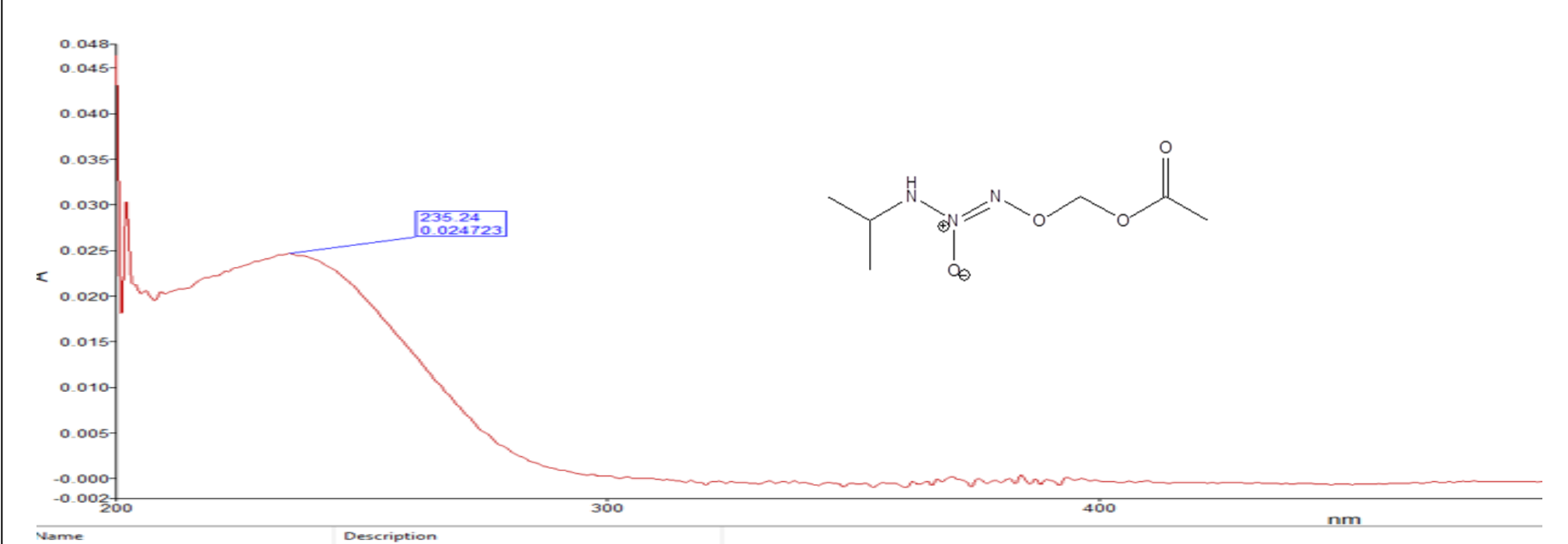
- 4-methylcyclohexylamine sodium salt derivative

Chemical Characterization

UV



- IPA/NO sodium salt



- IPA/NO prodrug

Conclusions

- Primary amine-based diazeniumdiolates have been developed as effective HNO donors, with acetoxymethyl ester-protected derivatives improving purification and cellular delivery, paving the way for future HNO pharmacological studies.

Acknowledgements

1. Chemistry Department, Dominican University, River Forest, IL
2. URSCI program, Dominican University, River Forest, IL
3. PUMA stem, Elmhurst University, Prospect Ave, IL

References

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