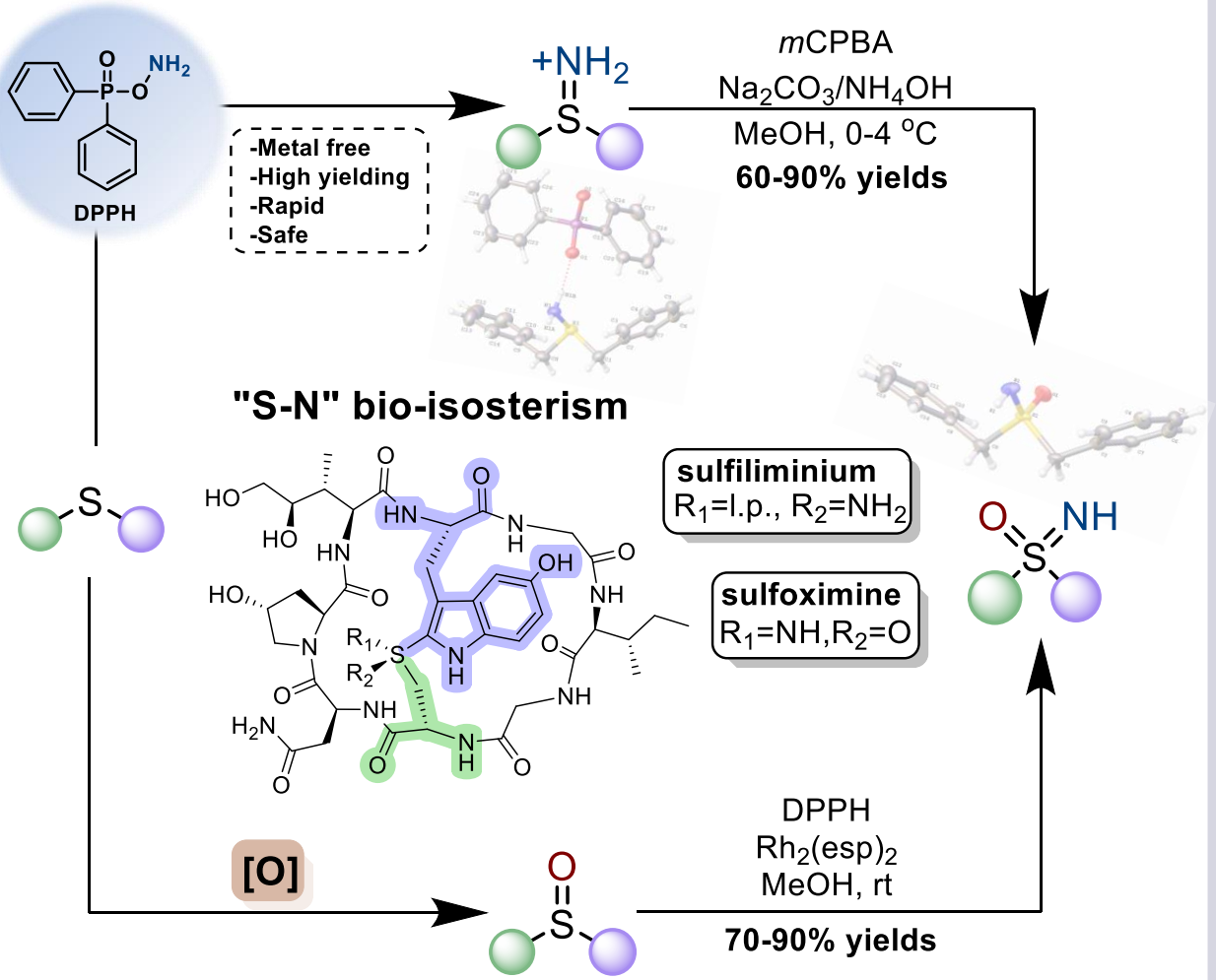


CPPC 2024

2nd Canadian Peptide and Protein Community Virtual Symposium

DECEMBER 16, 2024 | ONLINE

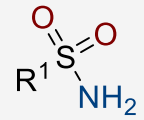
Late-stage peptide modifications through S-imination enable chemoselective installation of free-NH sulfilimines and sulfoximines

Shanal Gunasekera[1], Alla Pryyma[1], Jimin Jung[1], Rebekah Greenwood[1], Brian O. Patrick[1], and David M. Perrin[1*]

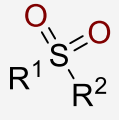
[1]University of British Columbia, 2036 Main Mall, Vancouver, BC, Canada V6T 1Z1

[*]Corresponding author: dperrin@chem.ubc.ca

Sulfur Pharmacophores in Drug Discovery and Design

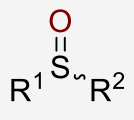


sulfonamides



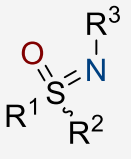
sulfones

(Mainstays in medicinal chemistry)



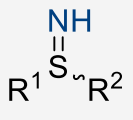
sulfoxides

(Few marketed drugs)

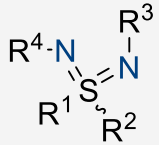


sulfoximines

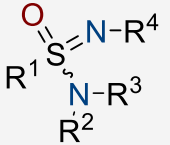
(Few candidates in clinical trials)



sulfilimines



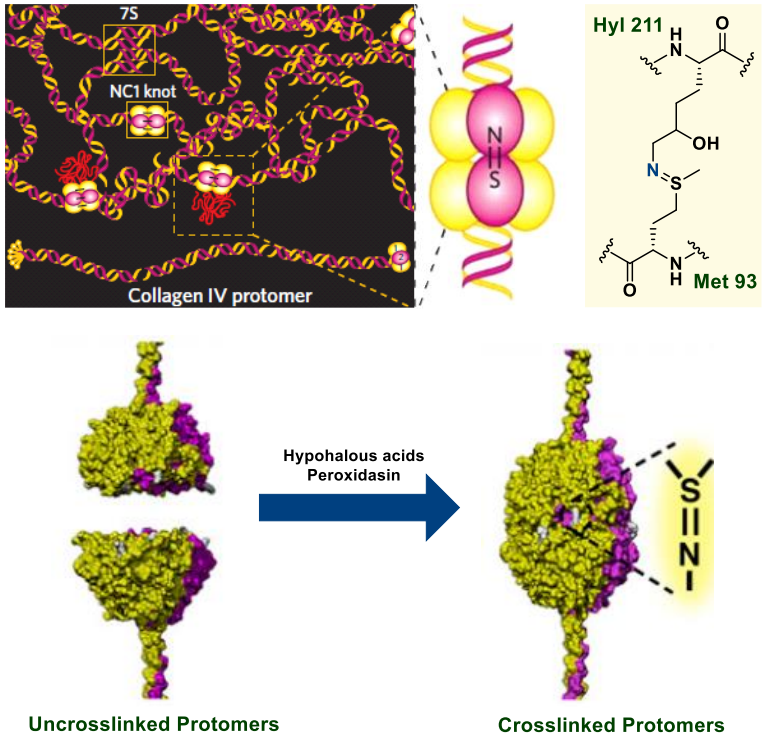
sulfondiimines



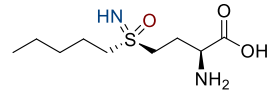
sulfonimidamides

(Underexplored in medicinal chemsitry)

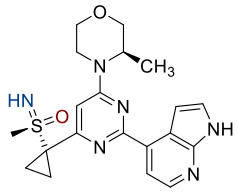
Naturally occurring sulfilimine cross-link



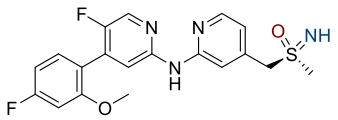
Drug candidates and agrochemicals bearing underexplored sulfur scaffolds



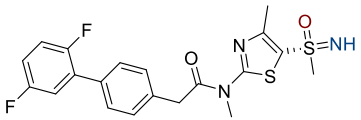
L-Buthionine (*S*)-Sulfoximine (γ-glutamylcysteine synthetase inhibitor, oncology)



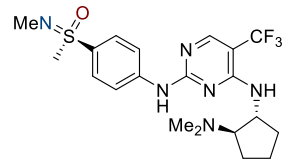
AZD6738/Ceralasertib (ATR Kinasae inhibitor, oncology)



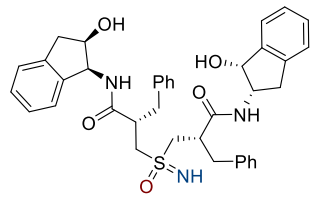
BAY 1251152/Enitociclib (CDK9 inhibitor, oncology)



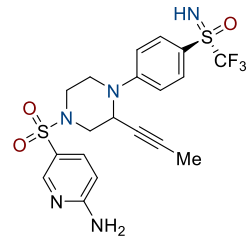
IM-250 (Helicase-primase inhibitor, antiviral)



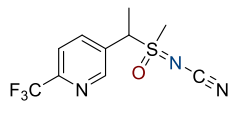
(PYK2 inhibitor, osteoporosis)



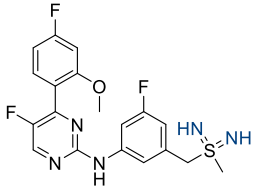
HIV-1 protease inhibitor



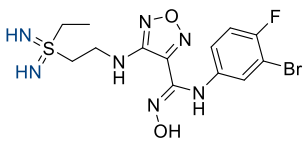
(GKRP inhibitor, diabetes)



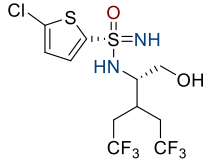
Sulfoxaflor (Commercial insecticide)



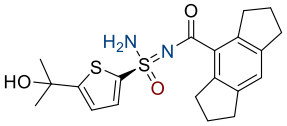
BAY 332 analogue (CDK9 inhibitor, oncology)



(IDO inhibitor, oncology)



(Begacestat analog, Alzheimer's)



DFV890 (NLRP3 inhibitor, Osteoarthritis)

Vanacore et al. *Science* **2009**, *375*, 1230-1237; Tilby, M. J., Willis, M. C. *Expert Opinion on Drug Discovery* **2021**, *16:11*, 1227-1231; Mäder, P., Kattner, L. *J. Med. Chem.* **2020**, 63, 23, 14243–1427; Lücking, U. *Chem. Eur. J.* **2022**, 28, e2022019

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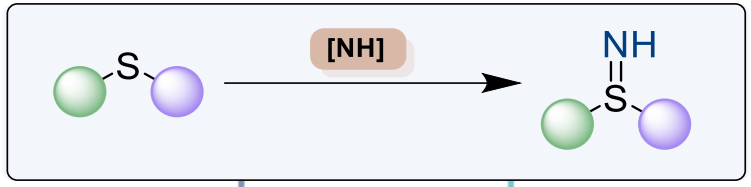
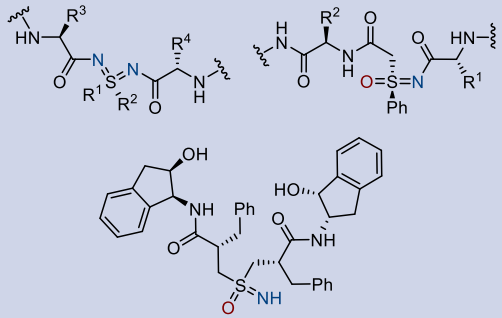
Applications of S-Imination in Medicinal Chemistry

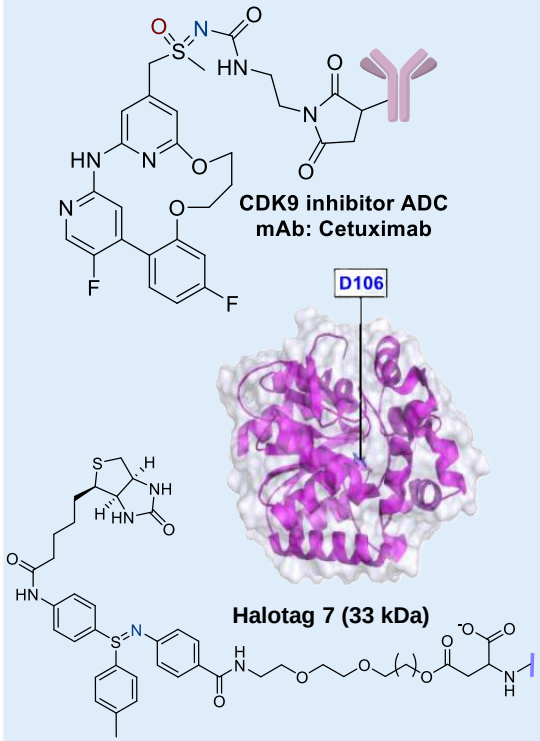


Pseudopeptides and Peptidomimetics



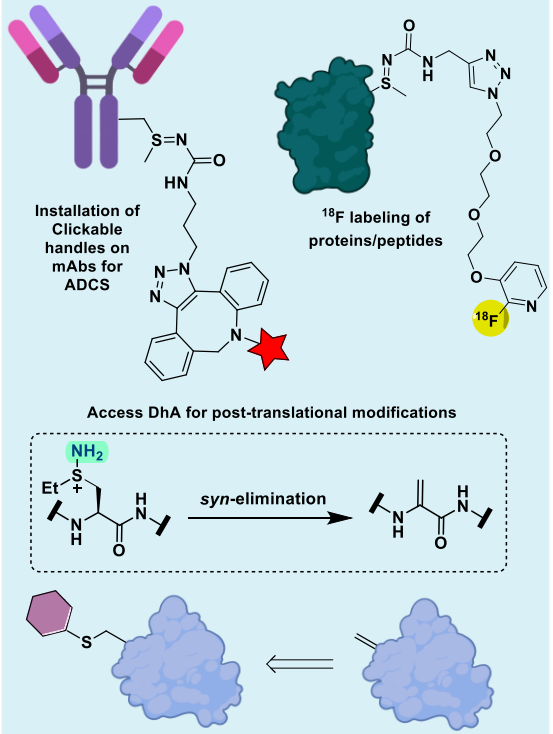
Bolm et al. *Bioorganic and Med. Chem. Letters* **2003**, *13*, 3207-3211; Lu, D., Sham, Y. Y., Vince, R. *Bioorganic and Med. Chem*. **2010**, *18,* 2037-2048

Bioconjugation Handles



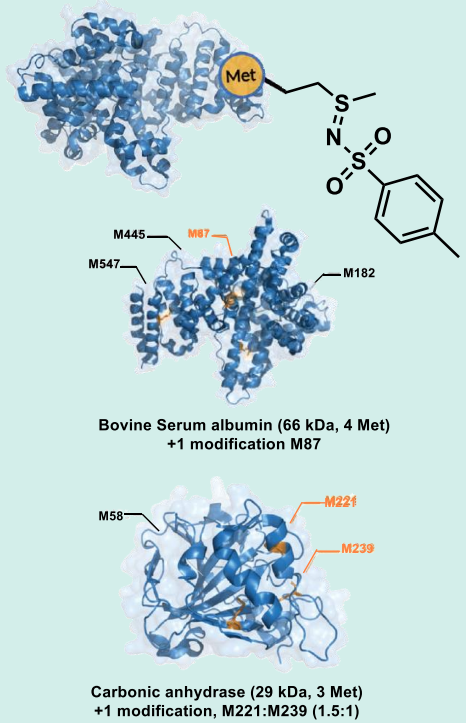
Lücking, U. *Chem. Eur. J.* **2022**, *28*, e2022019; Meng et al. *J. Am. Chem. Soc.* **2022**, *144*, 12476-12487

Protein Modifications



Elledge et al. *Proc Natl Acad Sci USA.* **2020**, *117(11)*, 5733-5740; Lin et al. *Bioconjugate Chem.* **2020**, *31*, 1908-1916; Bernardes et al. *J. Am. Chem. Soc.* **2008**, *130*, 5052-5053

Chemoproteomic profiling of Met



Sahu et al. *Nature Comm.* **2024**, 15, 4243

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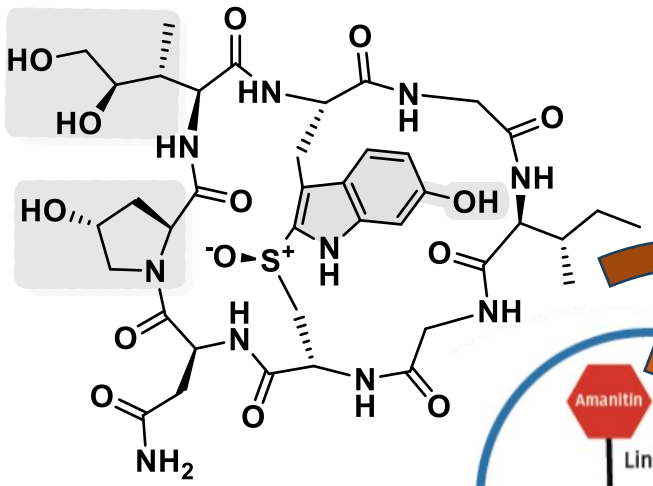
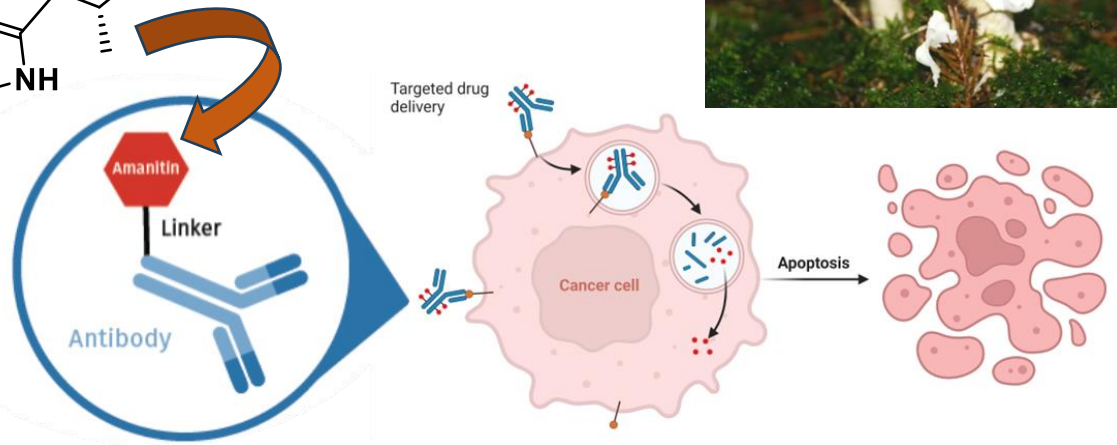
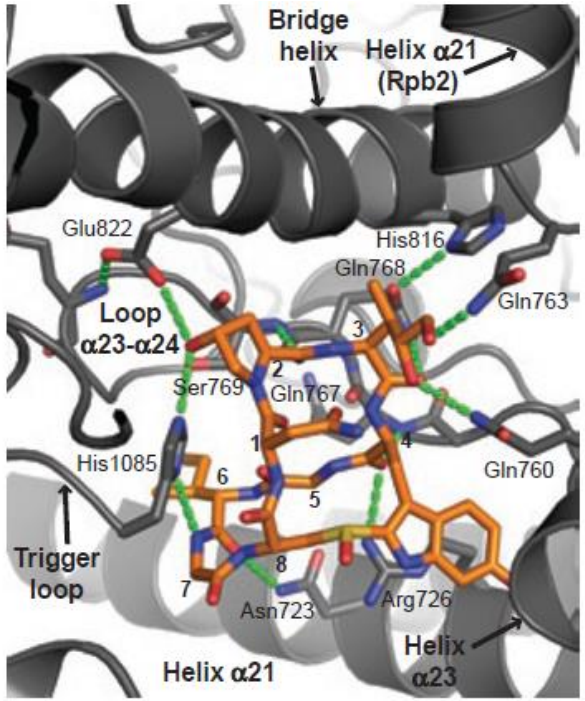
S-N Bio-isosterism in α-amanitin

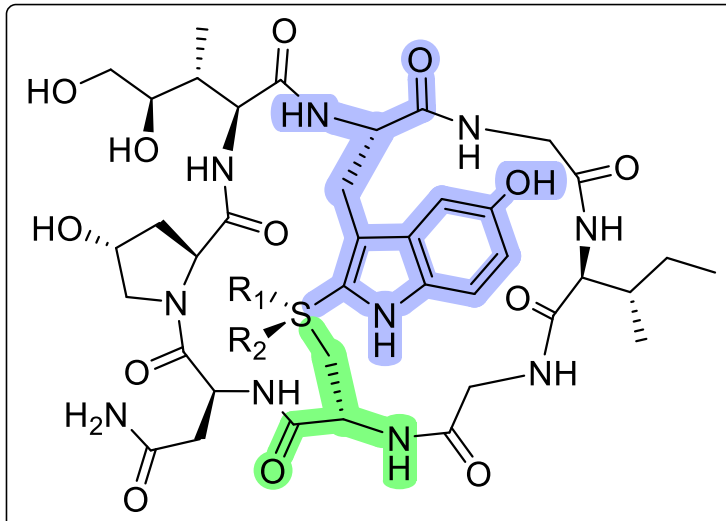


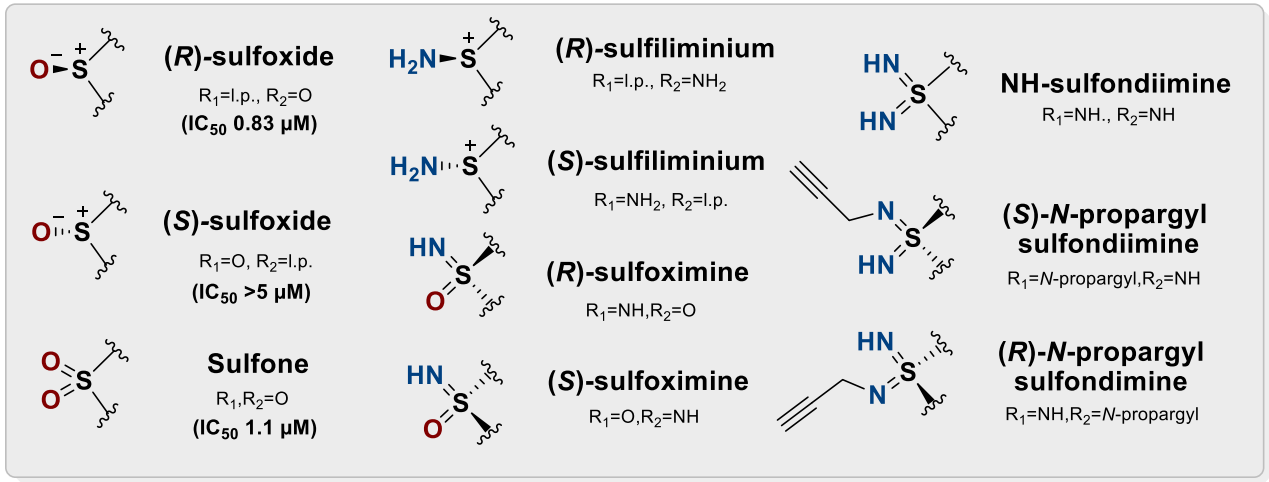
Pahl, A., Lutz, C., Hechler, T. *Drug Discovery Today: Technologies* **2018**, *30*, 85-89

Brueckner, F., Cramer, P. *Nature Structural and Chemical Biology* **2008**, *15(8)*, 811-818









Pryyma et al. *Chem. Sci.* **2020**, *11*, 11927-11935

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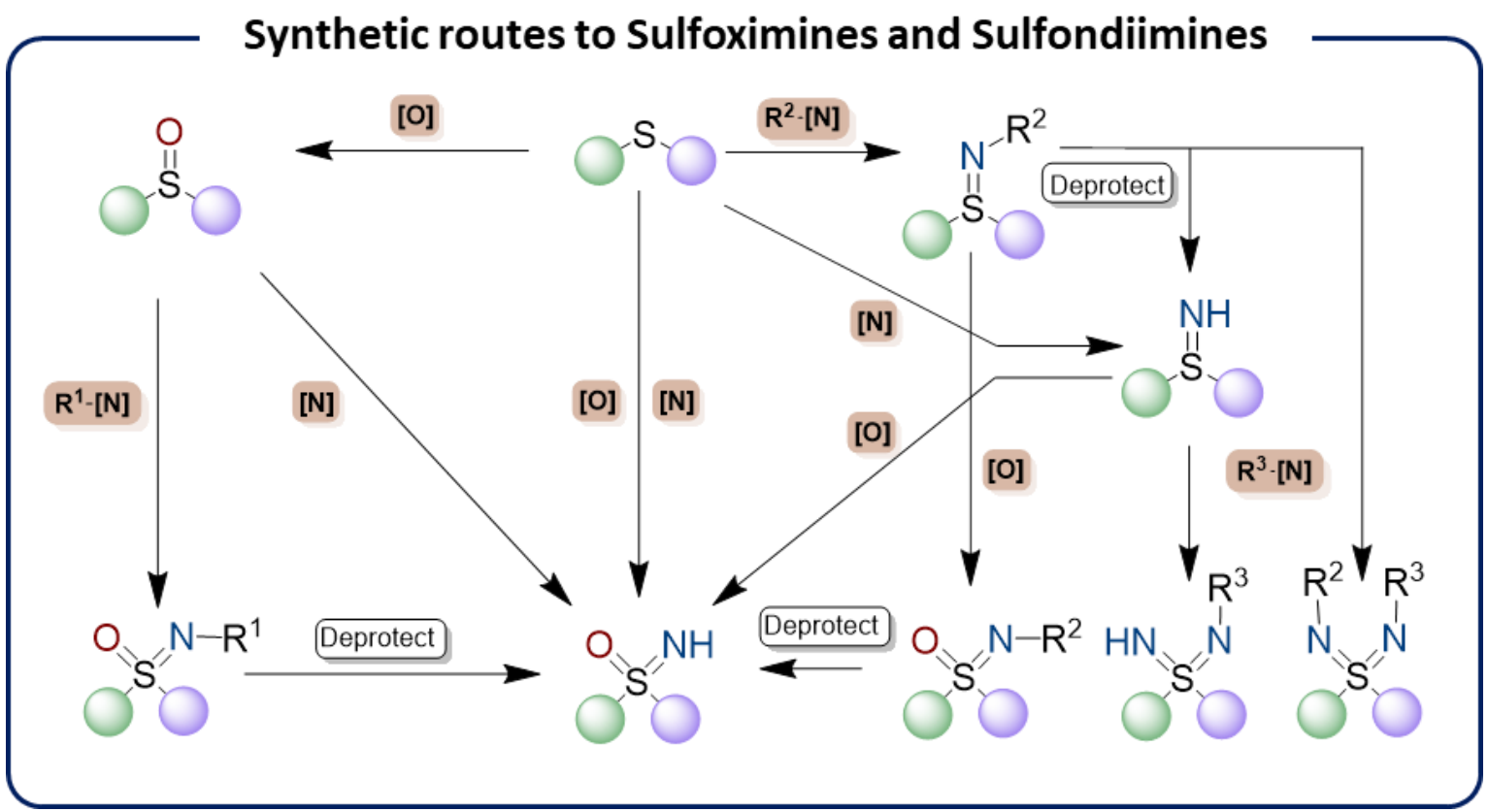
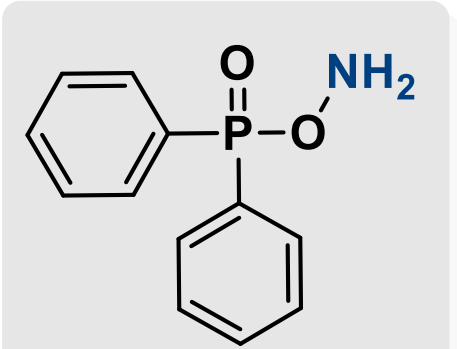
Synthesis Strategies to access Sulfilimines, Sulfoximines, and Sulfondiimines





- ❑ Activated hydroxyl amine
- ❑ Powerful electrophilic aminating agent
- ❑ Unexplored in S-imination
- ❑ Bench-stable reagent
- ❑ Commercial availability and convenient synthesis

Harger, M. J. P. *J. Chem. Soc. Perkin Trans. 1* **1981**, 3284–3288;
Benkovics et al. *Org. Synth.* **2020**, *97*, 54–65

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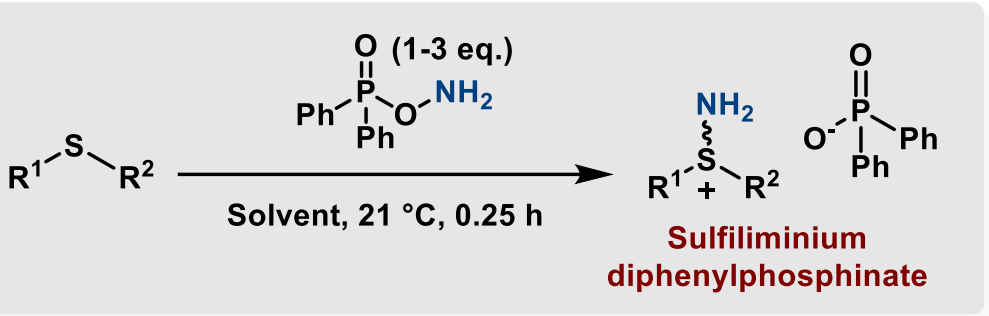
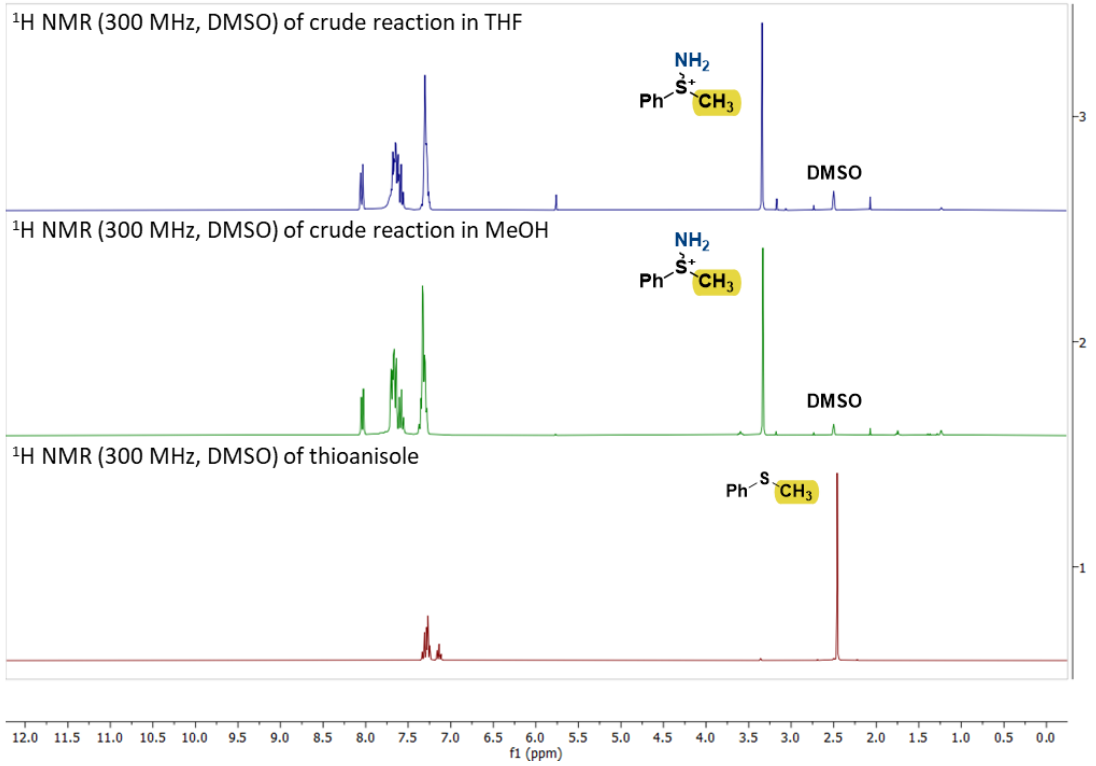
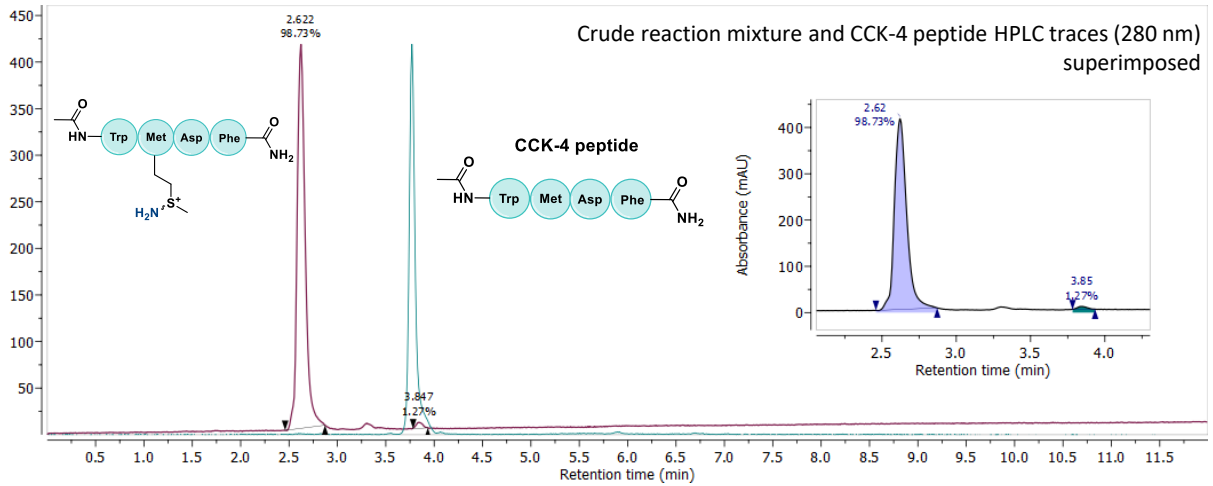
DPPH as an Excellent Iminating Agent to access Sulfiliminium Salts



Entry	Substrate	Solvent	Conversion to Sulfiliminium salt [%][a]
1	Thioanisole	MeOH	Quantitative
2	Thioanisole	CH_2Cl_2	Quantitative
3	Thioanisole	THF	Quantitative
4	Thioanisole	MeCN-d^3	89
5	Thioanisole	DMF	Quantitative
6	Thioanisole	DMSO-d^6	20
7	CCK-4 Peptide	H_2O	99

[a] % Conversion determined using ^{1}H-NMR spectral analysis of crude reaction mixtures and HPLC analysis (at 280 nm) of the crude reaction mixture.





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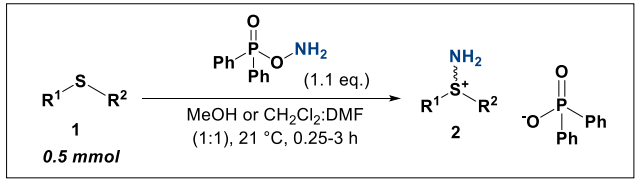
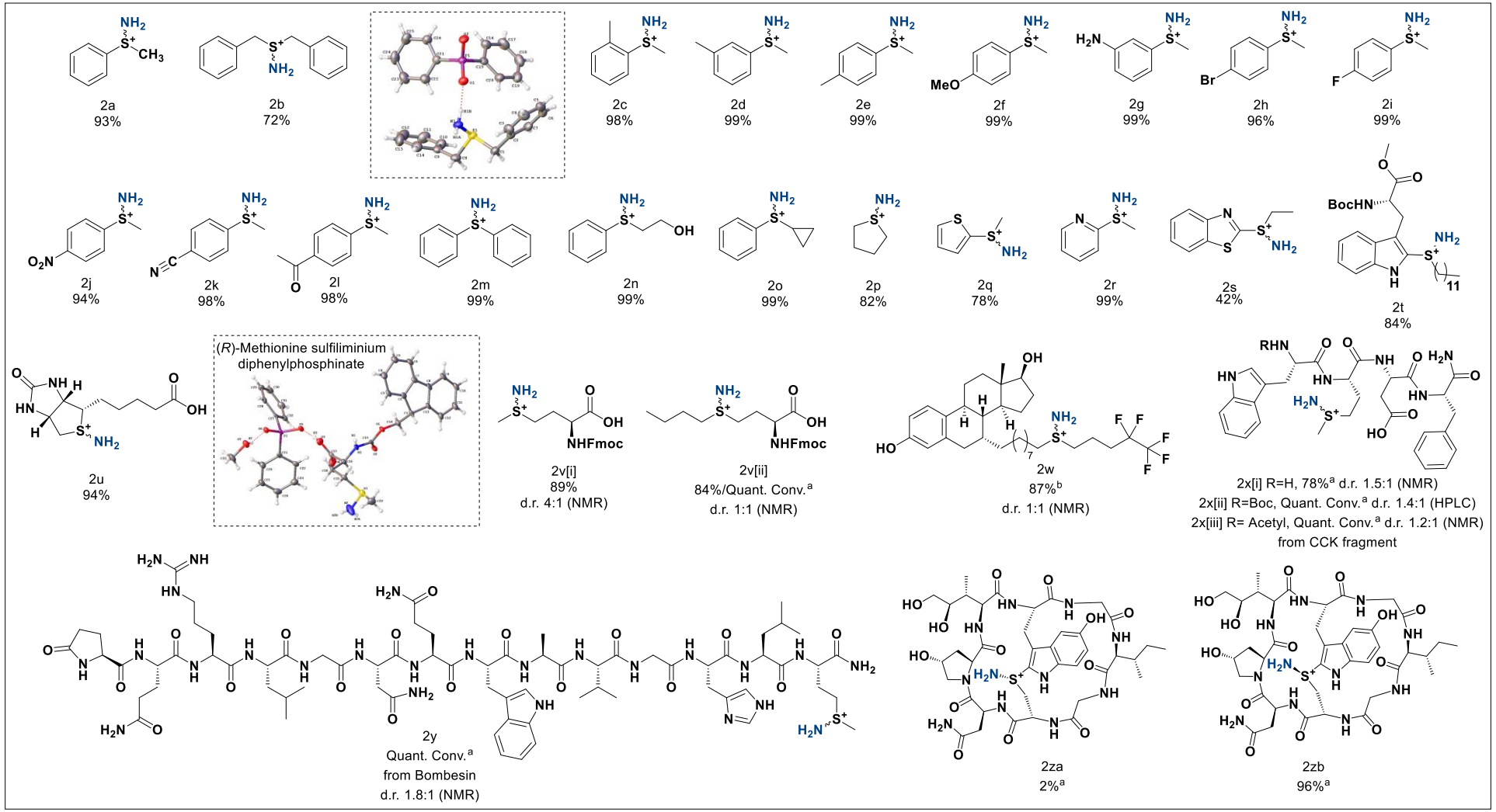
DPPH as an Excellent Iminating Agent to access Sulfiliminium Salts

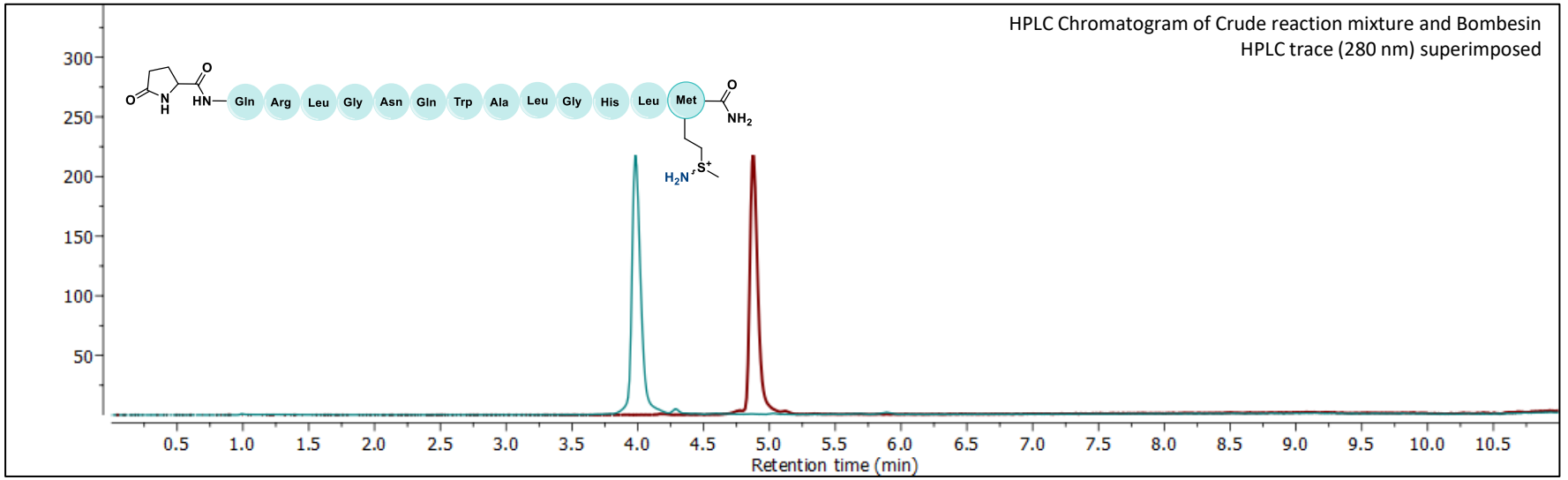


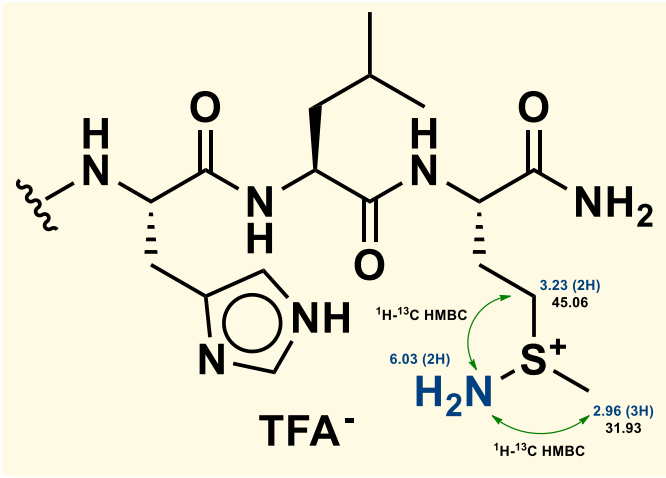


Isolated yields reported for cpds 2a-2w; [a] % conversion determined from reverse-phase HPLC; reactions run in MeOH for cpds 2a-2w, in CH_2Cl_2:DMF (1:1) for cpds 2x-2z

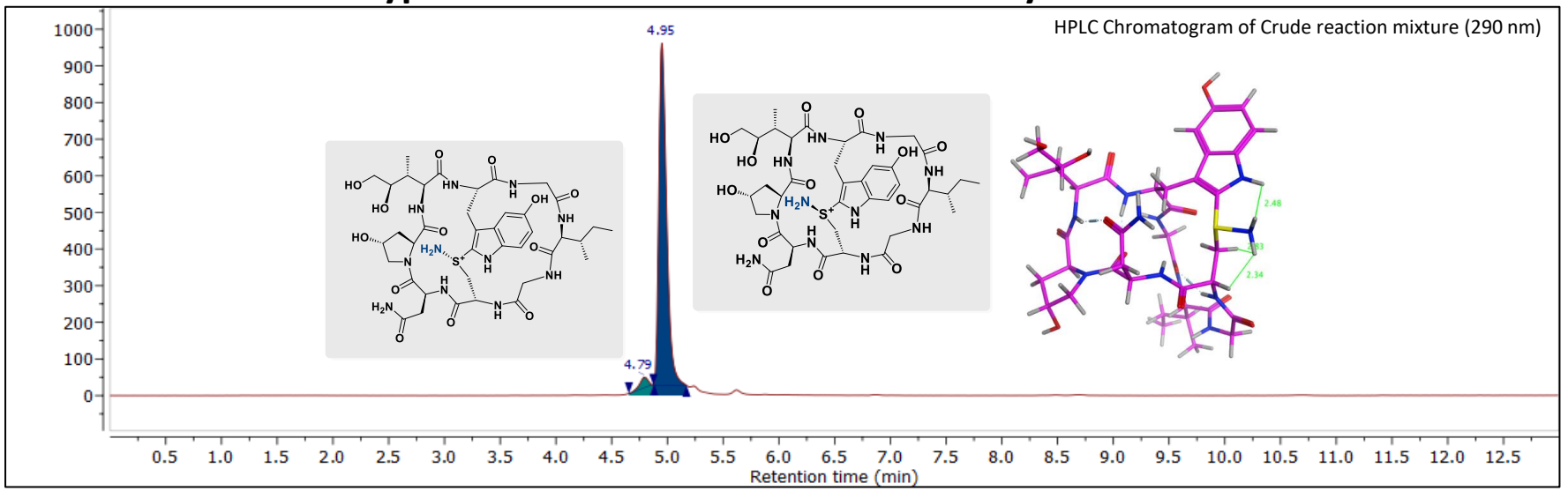
DPPH as an Excellent Iminating Agent to access Sulfiliminium Salts

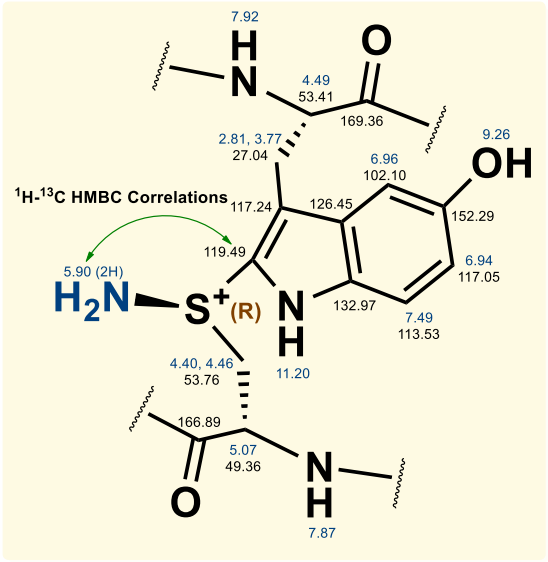
- **Chemoselective Methionine sulfimination of Bombesin**





- **Chemoselective Tryptathionine sulfimination of S-deoxy amanitin**





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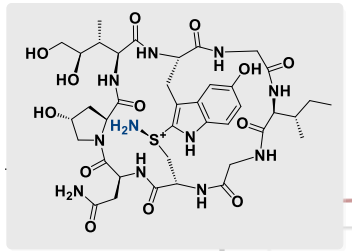
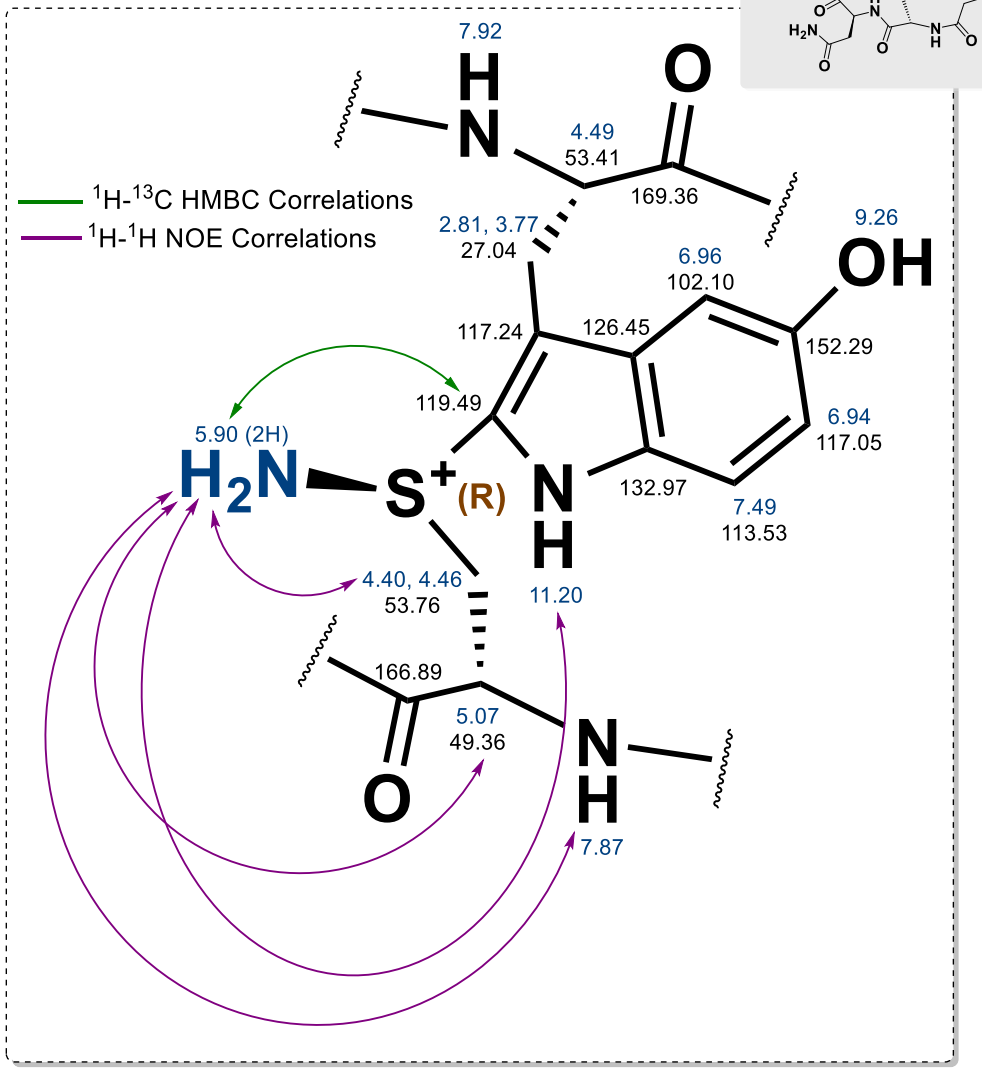
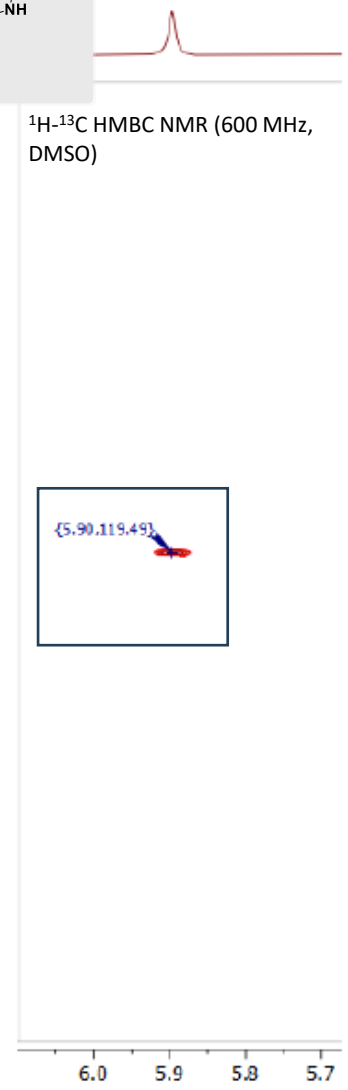
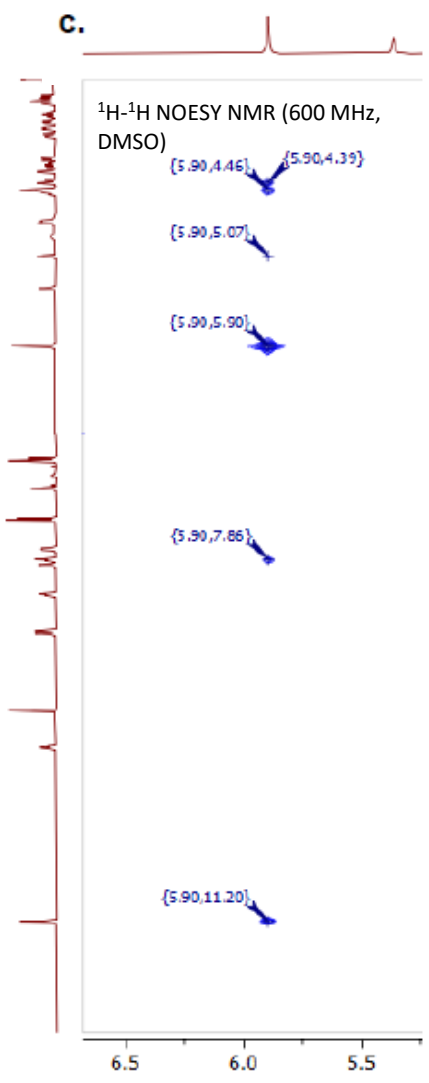
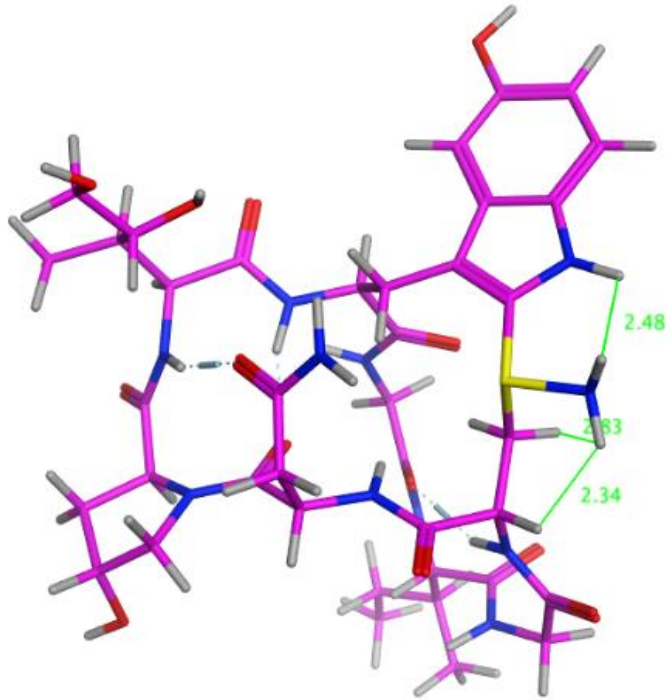
Stereochemical assignment of 5-OH Ama Sulfiliminium salt (Major diastereomer)











- Energy minimized model for (*R*)-sulfiliminium analogue of 5′-OH(Trp) Amanitin constructed using molecular operating environment (MOE) program
- Highlighted in green lines are inter-Hydrogen distances (10^{-10} m)

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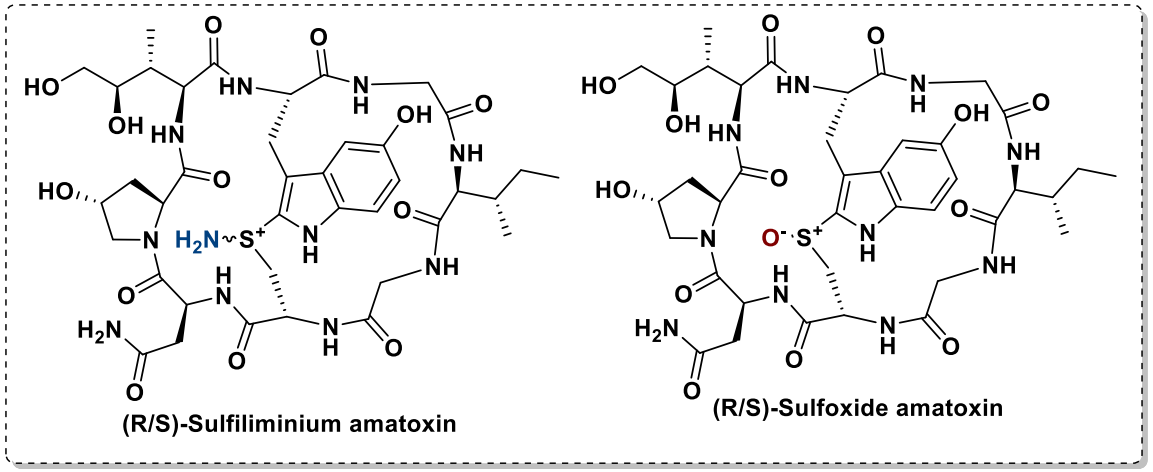
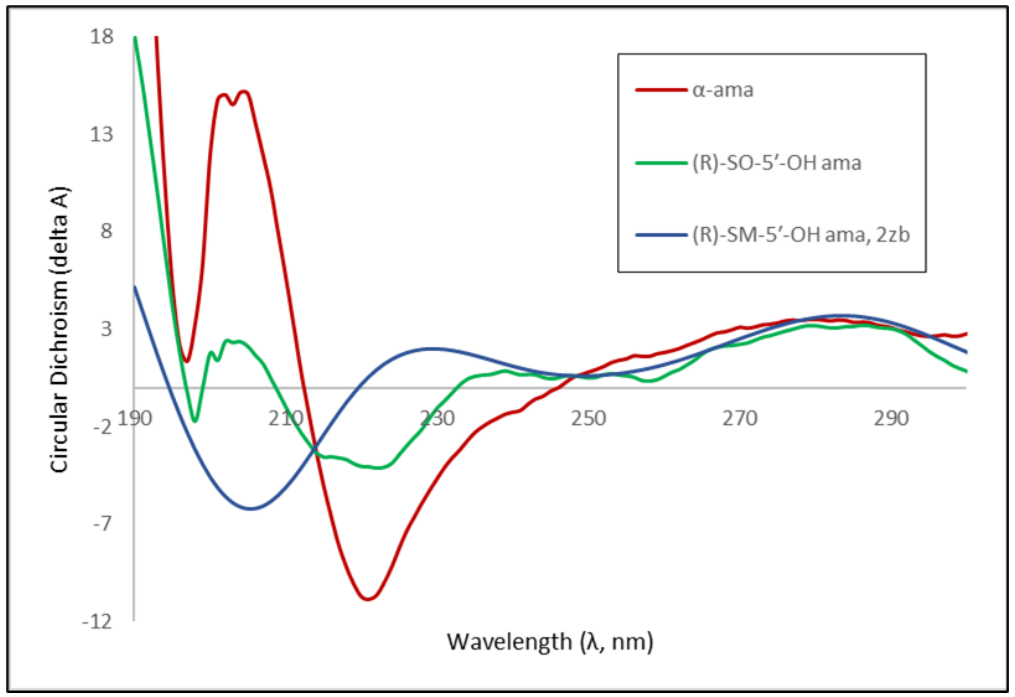
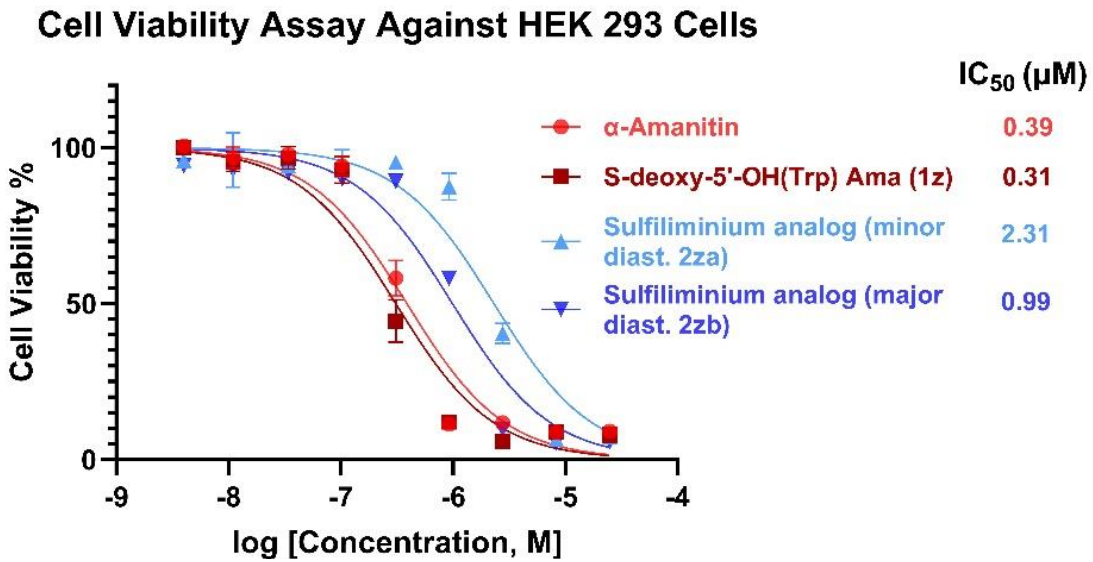
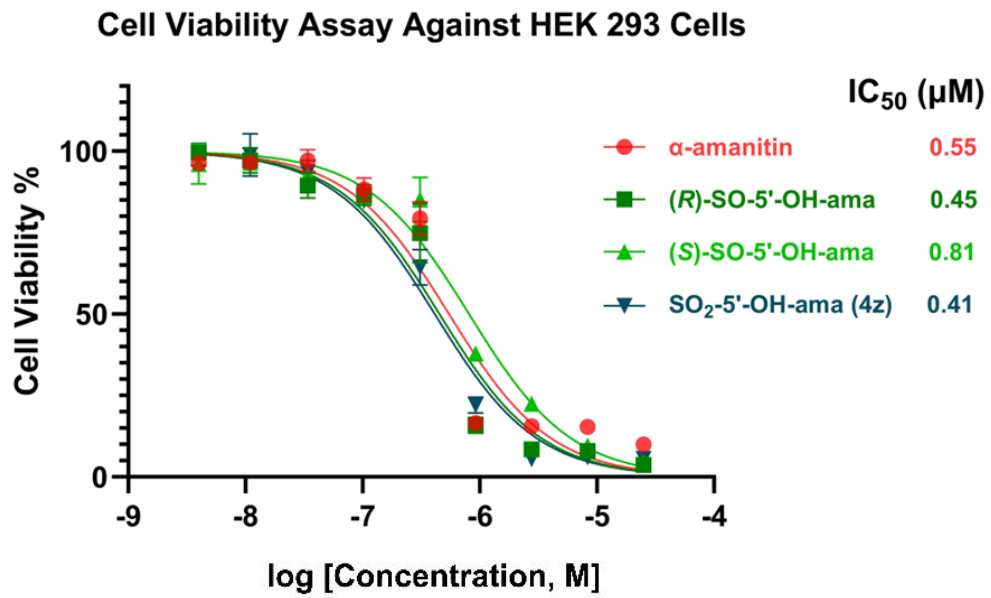
Bioisosterism: Sulfiliminium vs Sulfoxide









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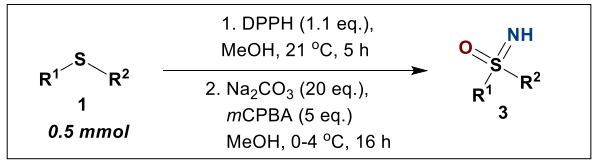
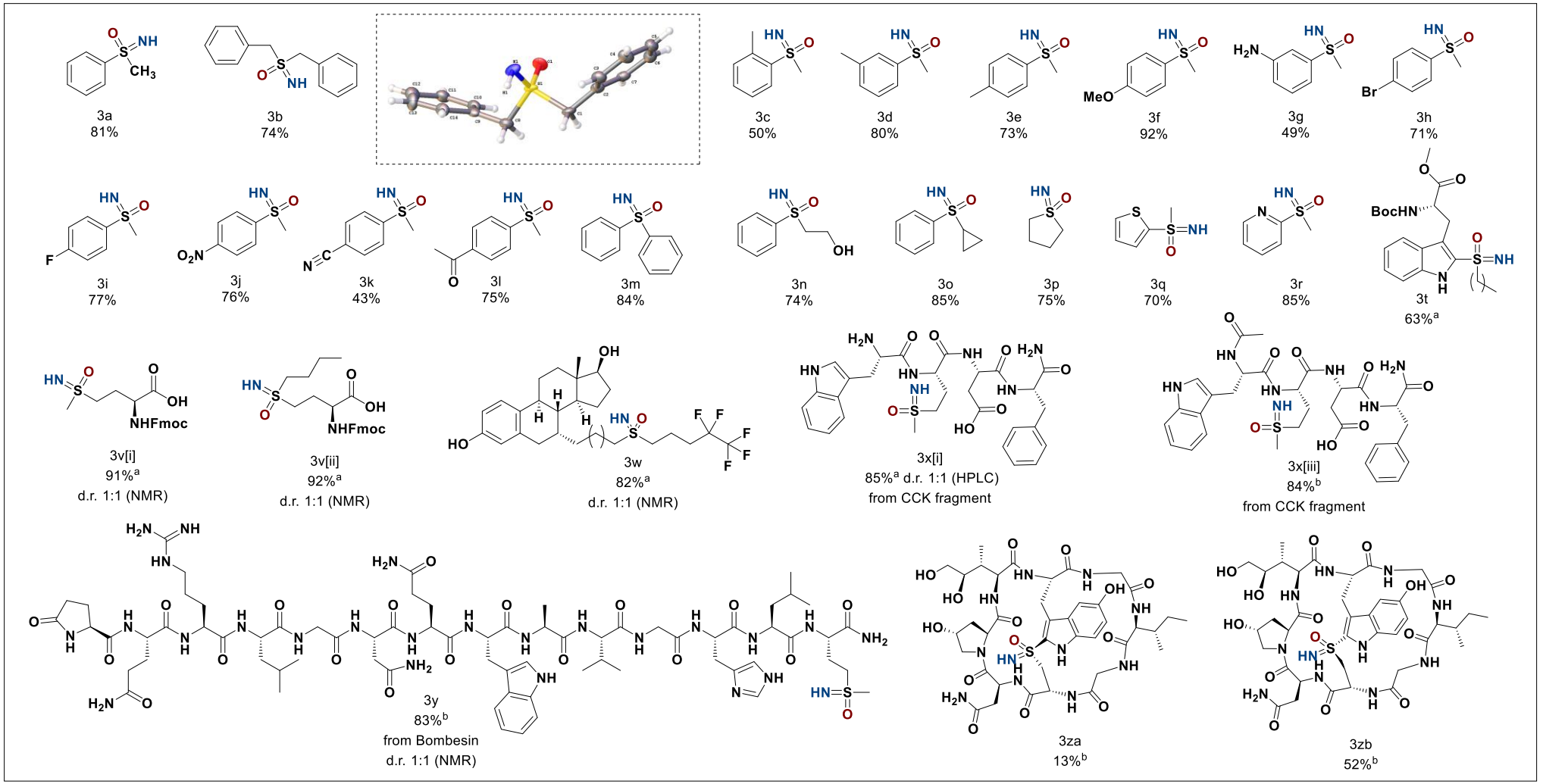
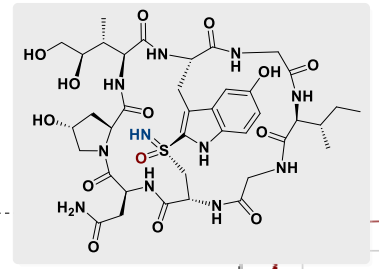
DPPH mediated access to free-NH Sulfoximines

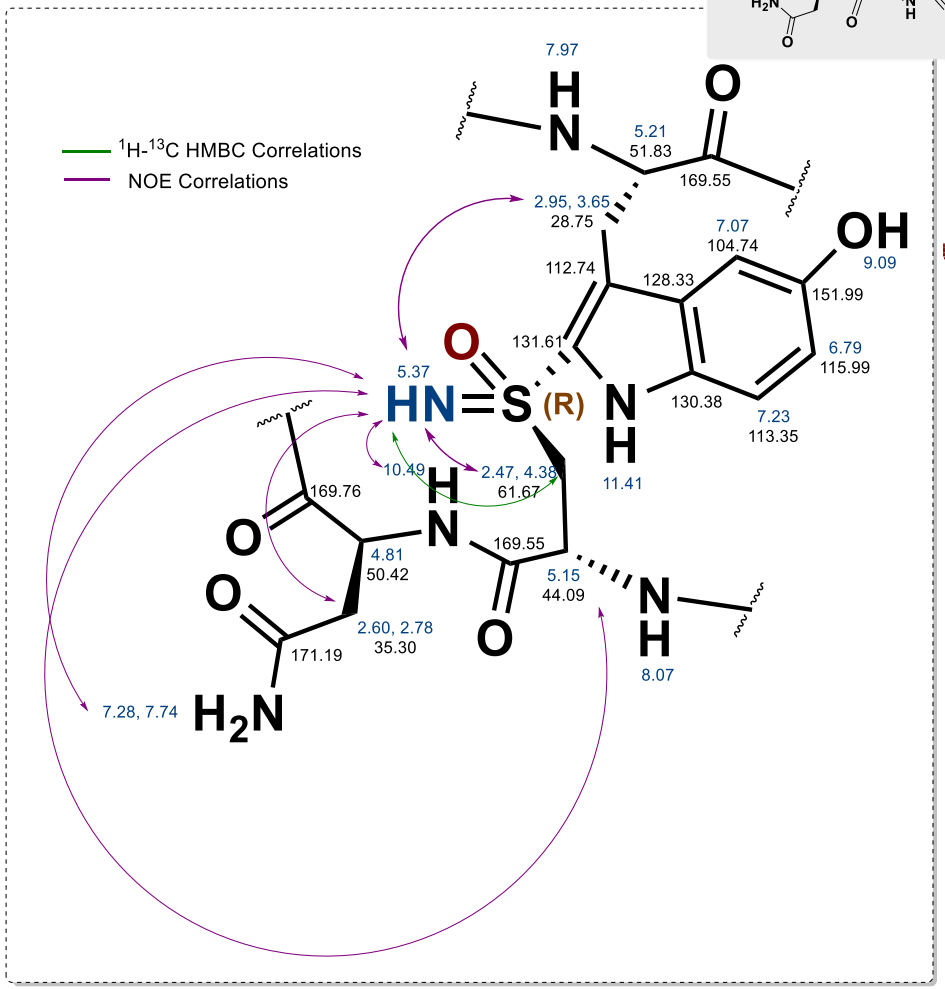


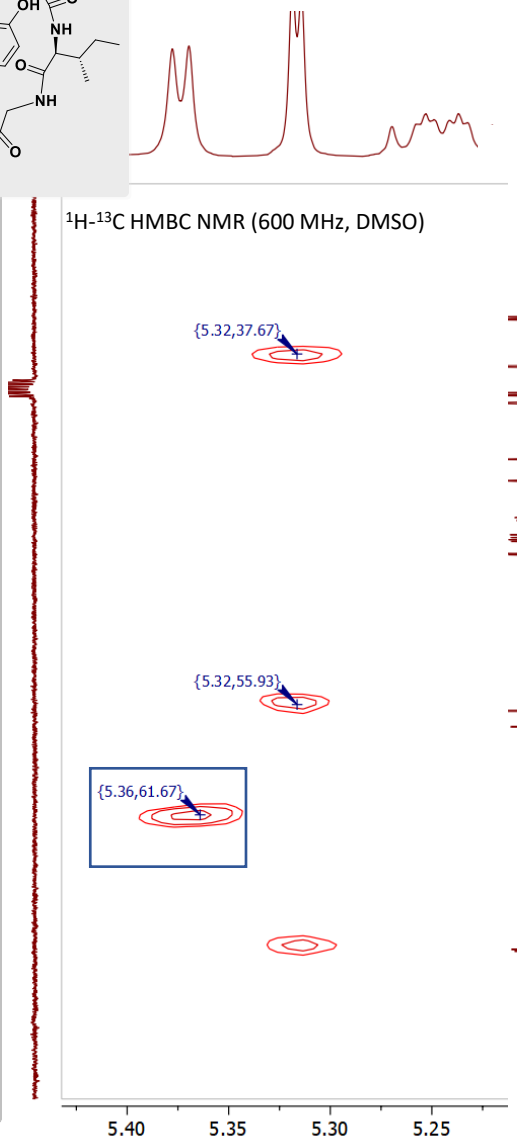


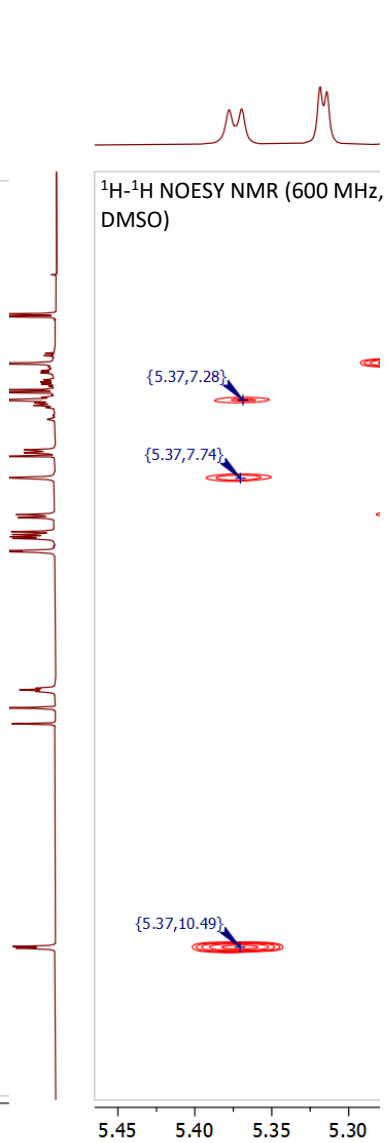
Isolated yields reported for cpds 3a-3r and 3w; [a] % conversion determined from reverse-phase HPLC; [b] one-pot imination and then oxidation method in which the imination solvent was removed by evaporation or lyophilization followed by oxidation in the presence of Na_2CO_3

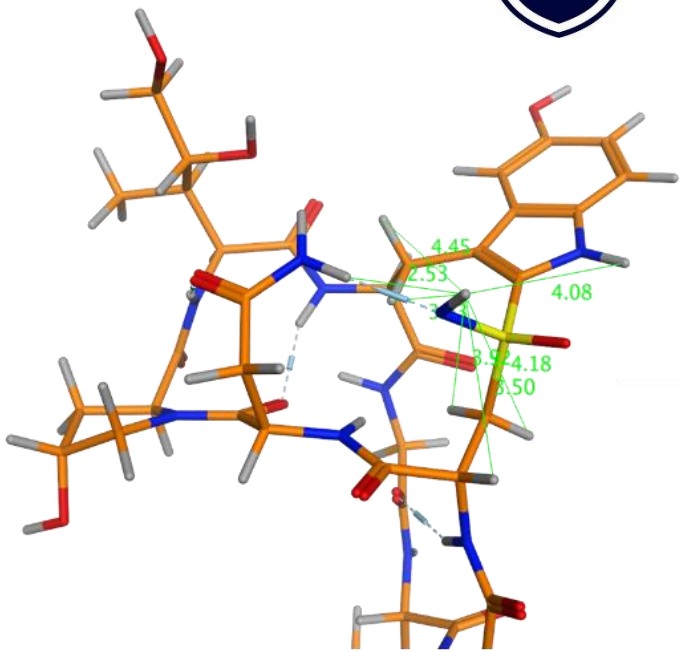
Stereochemical assignment of 5-OH Ama Sulfoximine (Major Diastereomer)







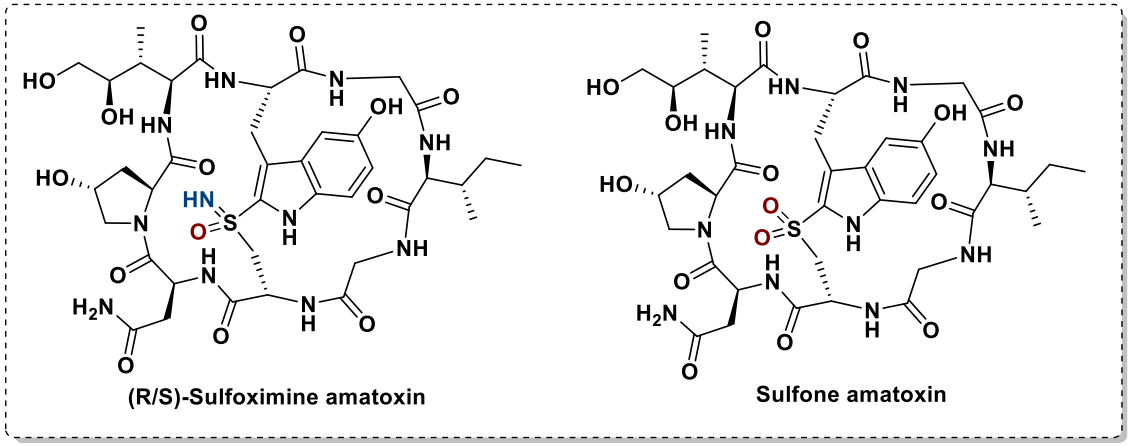


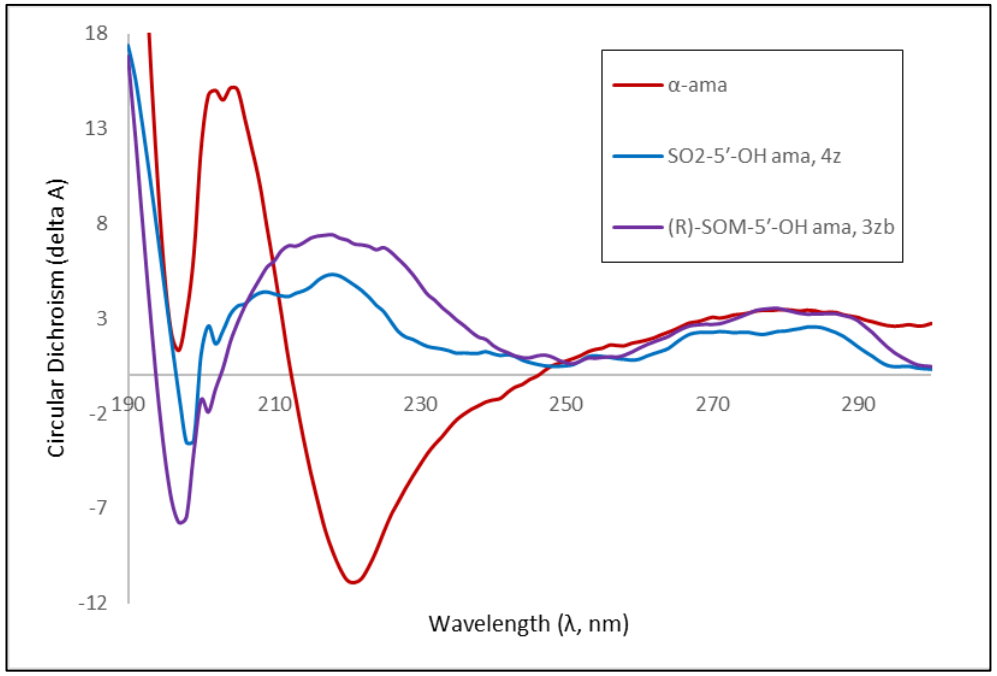


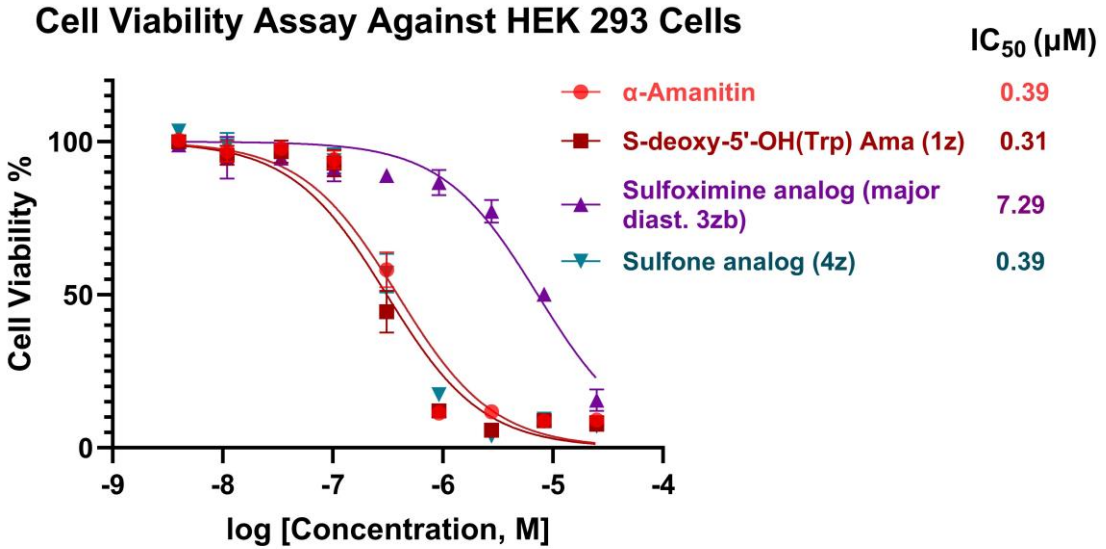
- Energy minimized model for (*R*)-sulfoximine analogue of 5'-OH(Trp) Amanitin constructed using molecular operating environment (MOE) program
- Highlighted in green lines are inter-Hydrogen distances (10^{-10} m)

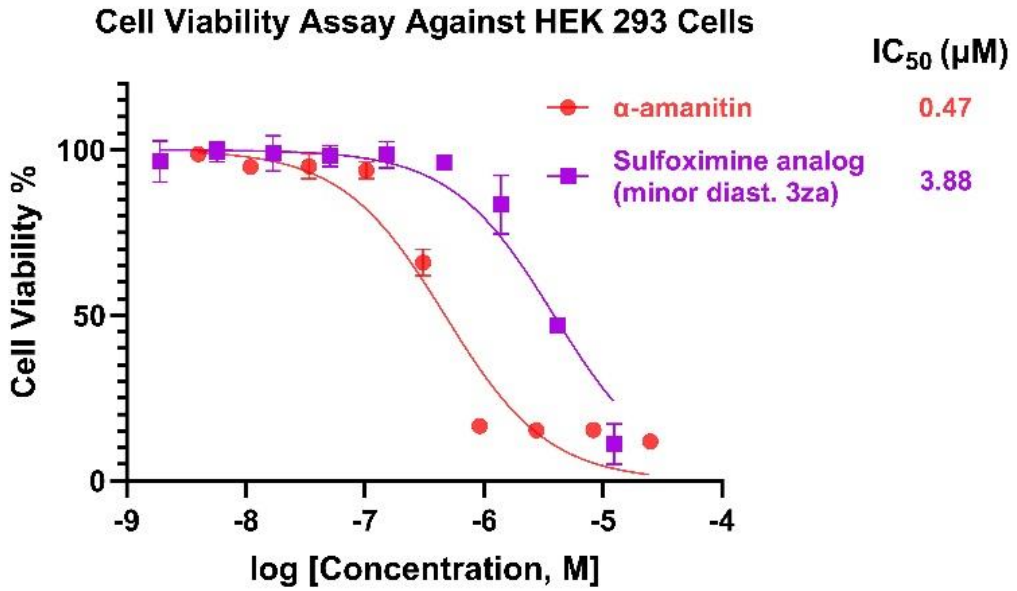
CPPC 2024

Bioisosterism: Sulfoximine vs Sulfone









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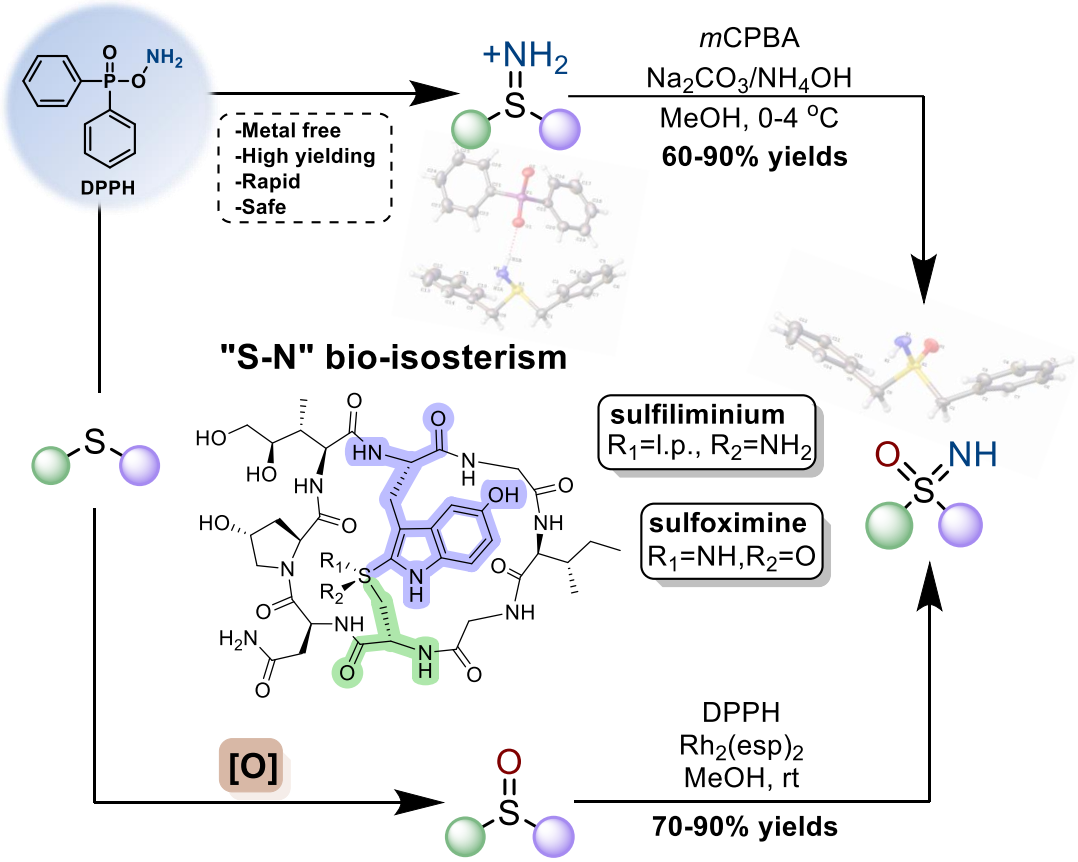
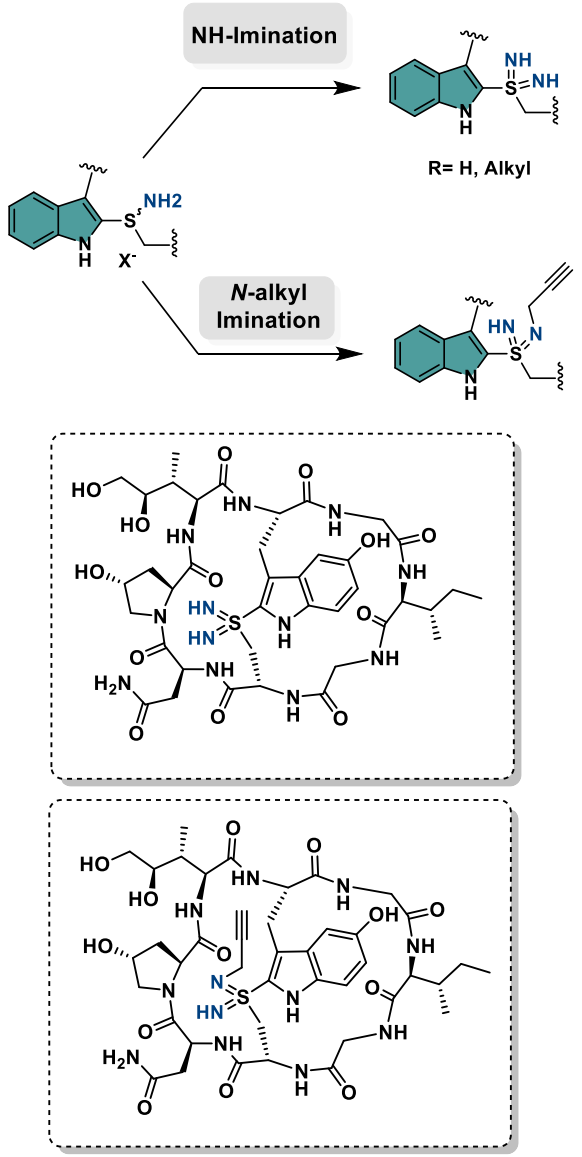
Conclusions and Future Directions



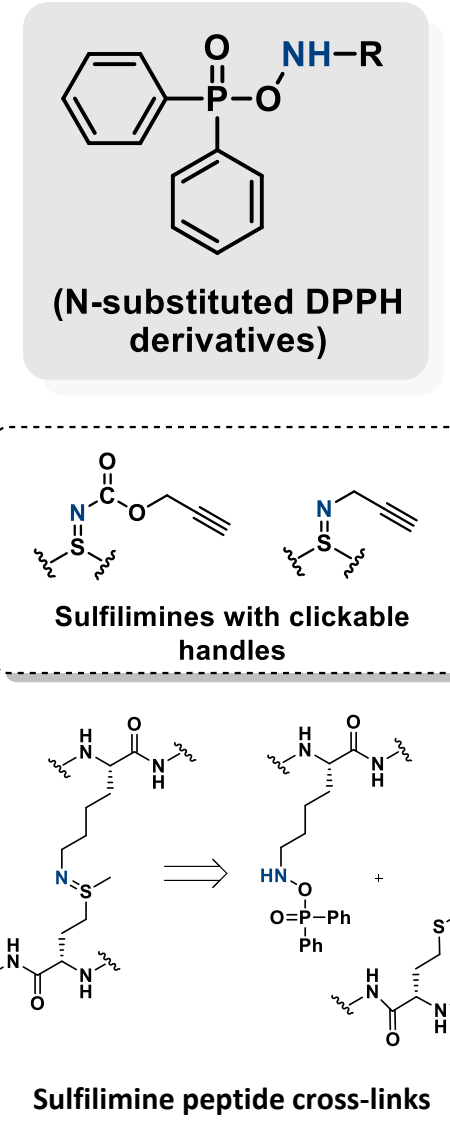
Gunasekera et al. *Angew. Chem. Int. Ed.* **2024**, *63*, e202314906

- DPPH serves as a safe, bench-stable, highly efficient iminating agent for facile and biomolecule compatible sulfimination and sulfoximination

Synthetic access to Sulfondiimines



N-substituted Sulfilimines



CPPC 2024

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CIHR IRSC Canadian Institutes of Health Research / Instituts de recherche en santé du Canada

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