Crystallographic Evaluation of Chelidamic Acid Congeners

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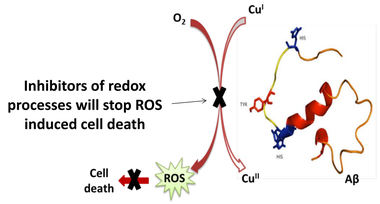
Abstract

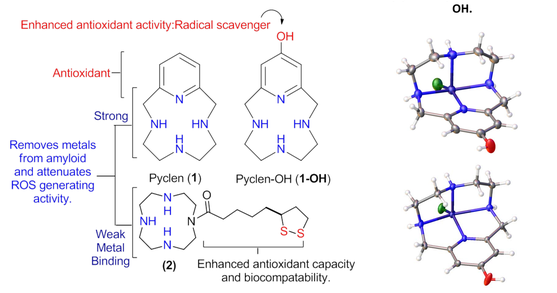
Alzheimer's Disease, a progressive neurodegenerative disorder that takes the lives of approximately 500,000 people per year, still lacks a definitive diagnosis and reliable treatment protocol[1]. Oxidative stress has been shown to be a key factor associated with the molecular markers of the disease. As such, a series of N-heterocyclic amines derived from chelidamic acid have been produced to evaluate these compounds as potential therapeutics for Alzheimer's Disease. We have shown these systems to be both antioxidant and capable of breaking apart the plaques associated with this neurodegenerative disorder[2]. Based on the aforementioned success, this study focuses on the development of new systems based on a chelidamic acid core.

These chelidamic acid derivatives are characterized using X-ray crystallographic methods in order to show how the bond lengths and angles are influenced by the experimental R-groups, which possess a range of donor capacities. By comparing the structural results (bond angles and distances) from the range of proposed compounds, the influence of the varying donors on the aromatic ring can be understood. This information is critical for identifying optimal potential therapeutic agents prior to metallation.

The role of metals in AD



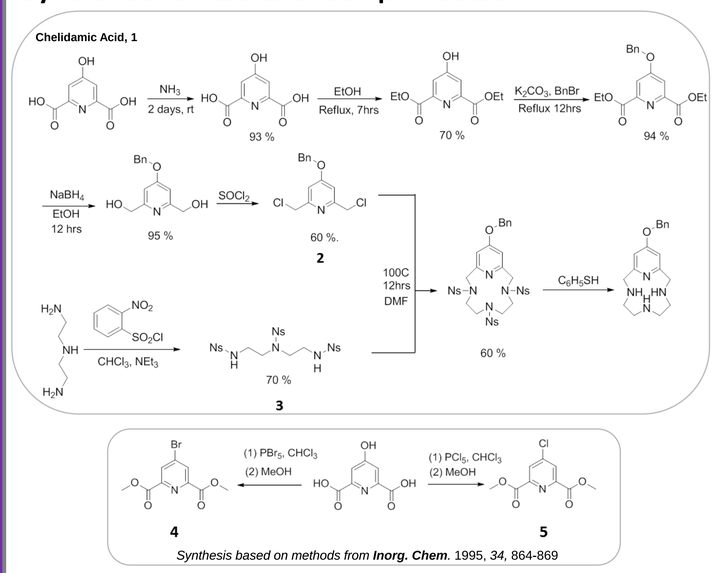
Rational design of hybrid therapeutic molecules in the Green Research Group



Cu(II) and Zn(II) derivatives of 1-OH.

(1) Lincoln, K. M.; Gonzalez, P.; Richardson, T. E.; Rutter, L.; Julovich, D. A.; Simpkins, J. W.; Green, K. N. *ACS Chem. Neurosci*. **2012**, *3*, 919-927. (2) Lincoln, K. M.; Gonzalez, P.; Richardson, T. E.; Rutter, L.; Julovich, D. A.; Simpkins, J. W.; Green, K. N. *Chem. Commun*. **2013**, *49*, 2712-2714. Gonzalez, P.; da Costa, V. C. P.; Hyde, K.; Wu, Q.; Annunziata, O.; Rizo, J.; Akkaraju, G.; Green, K. A. *Metallomics*, **2014**, *6*, 2072-2082

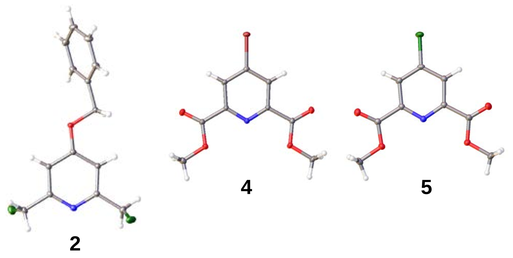
Synthesis and Results for compounds 2-5

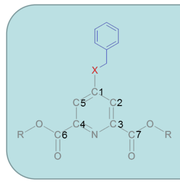


Experimental Details for 2-5

Complex	2	3	4	5
Chemical Formula	$C_{14}H_{13}Cl_2NO$	$C_{28}H_{22}O_{12}S_3N_4$	$C_{18}H_{16}Br_2N_2O_8$	$C_9H_8NO_4Cl$
Formula Weight (g/mol)	282.15	661.68	548.15	229.62
Crystal System	Monoclinic	Monoclinic	Triclinic	Monoclinic
Space Group	P 1 21/c 1	P 21/c	P -1	P21/n
a (Å)	13.8984(16)	17.180(17)	3.9490(4)	3.8202(12)
b (Å)	7.9572(9)	12.454(11)	13.6106(15)	13.770(4)
c (Å)	12.2990(14)	12.337(13)	18.741(2)	18.224(6)
α (°)	90	90	98.424(3)	90
β (°)	110.485(2)	92.57(3)	92.952(3)	91.070(8)
γ (°)	90	90	97.707(3)	90
Volume (Å^3)	1274.2(3)	2637(4)	984.82(18)	958.5(5)
Z	4	4	2	4
Density (g/cm^3)	1.471	1.666	1.848	1.5911
Reflections Collected	30281	171912	50238	19228
Independent Reflections	5408 [R_{int} = 0.0215]	14843 [R_{int} = 0.0482, Rsigma = 0.0409]	9622 [R_{int} = 0.0401]	2919 [R_{int} = 0.0398, R_{sigma} = 0.0257]
Goodness-of-fit on F2	0.996	1.093	1.082	1.116
R1 I>2σ(I)	0.0282	0.0489	0.0322	0.0328
wR2 I>2σ(I)	0.0799	0.1399	0.0693	0.0863
R1	0.03	0.0851	0.0437	0.0438
wR2	0.0818	0.1627	0.0740	0.0983

50% TELP for 2, 4, and 5





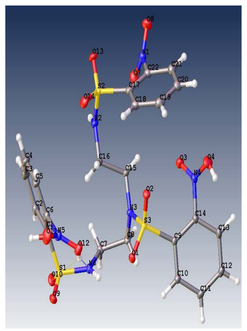
Labeling Scheme adopted for crystallographic data of **2**, **4** and **5.**

Bond Lengths for 2, 4, and 5

Bond	2	4	5
C1-X	[X=OBz] 1.3561(7)	[X=Br] 1.8818(13)	[X=Cl] 1.7369(5)
C1-C2	1.3968(9)	1.3882(19)	1.3860(3)
C2-C3	1.3903(9)	1.3952(19)	1.3987(4)
C3-N	1.3421(8)	1.3348(18)	1.3387(3)
N-C4	1.3411(8)	1.3395(17)	1.3393(3)
C4-C5	1.3954(9)	1.3956(19)	1.4011(4)
C5-C1	1.3977(9)	1.385(2)	1.3881(3)
C3-C7	1.5005(9)	1.5069(18)	1.5071(4)
C4-C6	1.4994(9)	1.4993(19)	1.5096(4)

The triply Ns-protected derivative of diethylene triamine (Ns_3-DETA) is a staple in the heterocyclic literature. However, and to the best of our knowledge, this is the first X-ray crystallographic characterization to date.

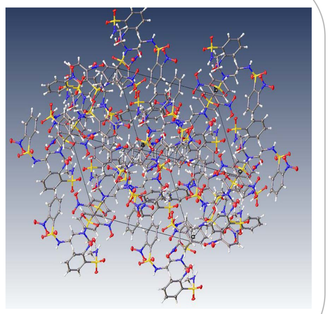
Crystals were obtained by slow evaporation in organic solvents.



50% TELP for 3 with labels

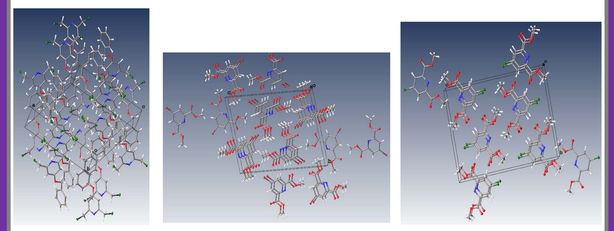
S1	O9	1.4275(15)	C6	N5	1.463(2)
S1	O10	1.4261(15)	C1	C2	1.385(2)
S1	C1	1.775(2)	N6	C7	1.4651(19)
S1	N6	1.6131(16)	C7	C8	1.520(2)
S2	O13	1.4302(15)	C8	N3	1.4707(18)
S2	N2	1.6147(17)	N3	C15	1.4677(18)
S2	C17	1.7715(18)	C15	C16	1.5279(19)
S2	O14	1.4236(14)	C16	N2	1.4625(19)
S3	O1	1.4351(12)	C17	C18	1.387(2)
S3	O2	1.4289(15)	C17	C22	1.398(2)
S3	N3	1.6114(18)	C18	C19	1.394(2)
S3	C9	1.7817(16)	C19	C20	1.382(2)
O3	N4	1.2207(17)	C20	C21	1.386(2)
O4	N4	1.2193(16)	C9	C14	1.3979(19)
O7	N1	1.2293(17)	C9	C10	1.391(2)
O8	N1	1.2190(17)	C14	C13	1.3827(19)
O11	N5	1.2230(16)	C14	N4	1.468(2)
O12	N5	1.2220(16)	C13	C12	1.390(2)
C4	C5	1.385(2)	C12	C11	1.389(2)
C4	C3	1.376(2)	C11	C10	1.3885(19)
C5	C6	1.379(2)	C21	C22	1.377(2)
C6	C1	1.398(2)	C22	N1	1.467(2)
			C2	C3	1.396(2)

Bond Lengths for 3



Unit Cell Packing Scheme for 3

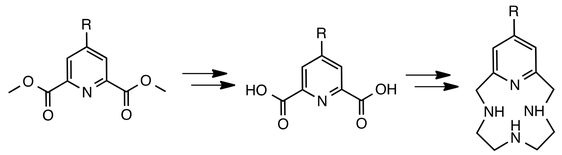
Unit Cell Packing Schemes for 2, 4, and 5



Conclusions

We have produced a library of chelidamic acid derivatives and determined their crystallographic structures using XRD analysis. In addition the Ns_3-DETA solid state structure was obtained. Overall these results will assist in determining electronic effects on structure, electrochemistry and reactivity in biological and catalysis activity that the Green Group is currently exploring.

Future Research



Long-Term Goals

- Continue exploring the functionalization of the pyridol core and analyzing the bond lengths and angles via X-ray crystallographic methods.
- Synthesize the structures shown above and isolate crystals suitable for XRD analysis for each compound synthesized.
- Continue comparing the bond lengths and angles for these newly synthesized compounds with those of compounds **2**, **3**, **4**, and **5**.

Acknowledgements

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