

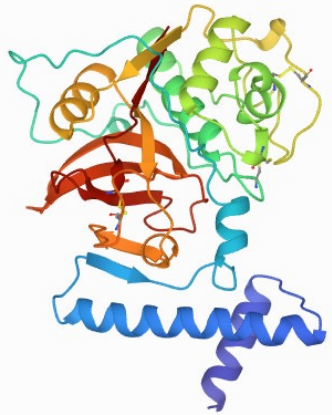

REMOTE WORK RECAP: CYSTEINE PROTEASE INHIBITORS

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AGENDA

- Objective
- Methodology
- Compound Example
- Problems and Solutions
- Summary
- Next Steps

OBJECTIVE

- Create comprehensive list of inhibitors and their properties for three cysteine proteases (as part of Dr. Avalon's F-32 Project):
  - Cathepsins B
  - Cathepsin L
  - Cruzipain/Cruzain
- Data Collections:
  - Compound Name
  - SMILES String, InChI and InChI Key, PubChem ID
  - IC_{50} and/or K_i inhibition values (mM, μM, nM)
  - Natural Product? (Y/N) and Source
  - Publication DOI(s)

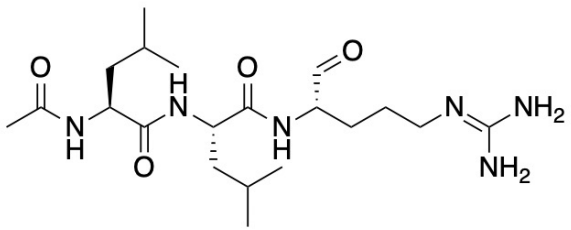
METHODOLOGY

- Initial information provided by Dr. Avalon for compounds Tokaramide A (CatB) and Gallinamide A (CatL)

Tools:

1. Excel
2. Google Scholar
   - Review Articles
3. PubMed
4. ChemDraw
   - Sci-Finder
5. PubChem (If Applicable)

COMPOUND EXAMPLE



Leupeptin

SMILES String	CC(C)C[C@@H](C(=O)N[C@@H](CC(C)C)C(=O)N[C@@H](CCCN=C(N)N)C=O)NC(=O)C
InChI	InChI=1S/C20H38N6O4/c1-12(2)9-16(24-14(5)28)19(30)26-17(10-13(3)4)18(29)25-15(11-27)7-6-8-23-20(21)22/h11-13,15-17H,6-10H2,1-5H3,(H,24,28)(H,25,29)(H,26,30)(H4,21,22,23)/t15-,16-,17-/m0/s1
InChI Key	GDBQQVLCIARPGH-ULQDDVLXSA-N
PubChem ID	72429
IC_{50} value (CatB)	0.001 nM
K_i value	6 nM
Natural Product? (Y/N)	Y
Source of NP	*Streptomyces exfoliatus*
DOI Publication 1	10.1016/B978-0-444-63749-9.00006-2
DOI Publication 2	10.1111/j.1432-1033.1982.tb07017.x

PROBLEMS AND SOLUTIONS #1: 1/19

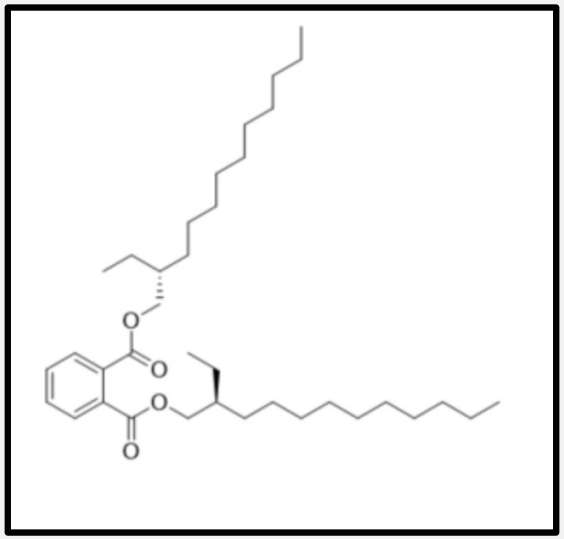
Problem:

- Had to draw molecule in ChemDraw to get SMILES, InChI and InChI Key, and PubChem ID
- ChemDraw introduced stereocenters in hydrocarbon tails
  - Created unnecessary isomeric SMILES string that was incorrect

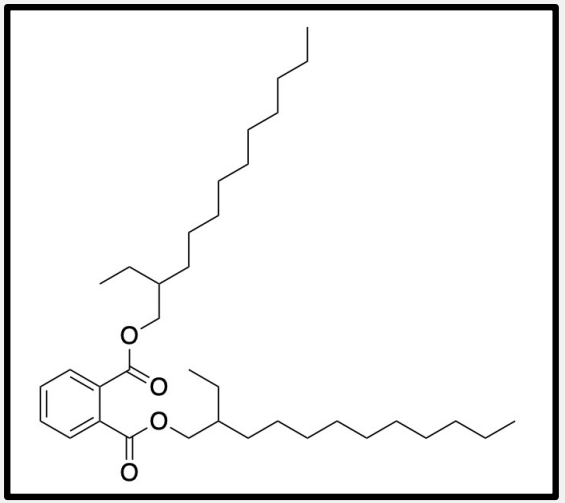
Solution:

- Used Sci-Finder canonical SMILES to locate PubChem profile, confirming data

bis(2-ethyldodecyl) phthalate



SMILES: O=C(OC[C@H](CCCCCCCCCC)CC)C1=CC=CC=C1C(OC[C@@H](CCCCCCCCCC)CC)=O



SMILES: CCCCCCCCCCC(CC)COC(=O)C1=CC=CC=C1C(=O)OCC(CC)CCCCCCCCCC

1. 10.1016/j.bmcl.2008.01.097

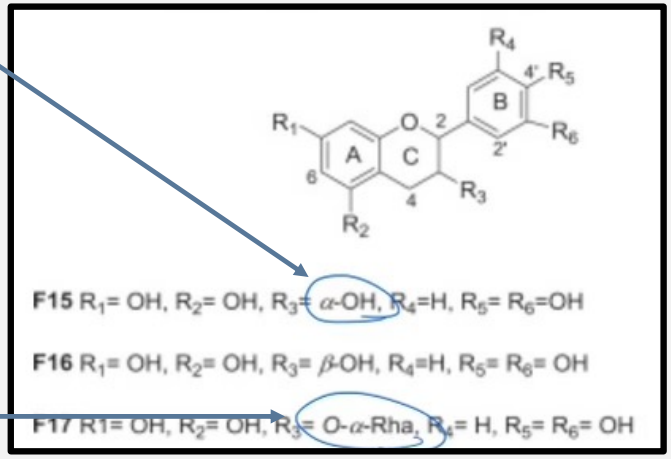
PROBLEMS AND SOLUTIONS #2: 2/02

Problem:

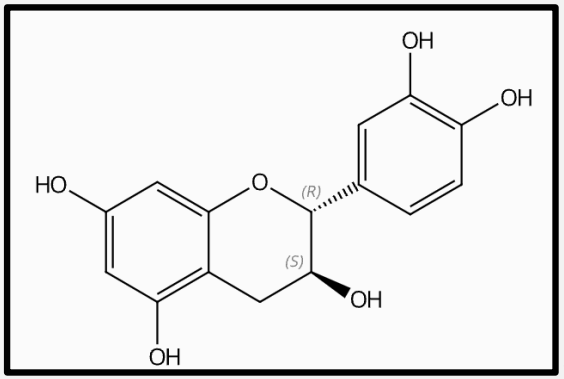
- Unknown substituent notation: α-OH
  - Other substituents were also unfamiliar (O-α-Rha)

Solution:

- Sci-Finder and detailed supplemental material gave molecule names to use in PubChem search



[2]


[3]

F15: Catechin

2. 10.1016/B978-0-444-63749-9.00006-2
3. 10.1080/14786419.2014.1002404

PROBLEMS AND SOLUTIONS #3

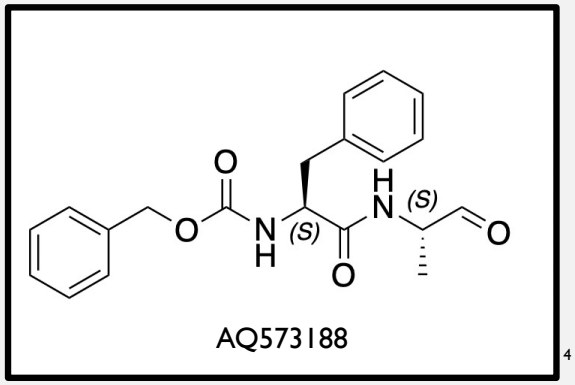
Problem:

- Sci-Finder seldom displayed IUPAC names for compounds
  - Example: Rhenium, chlorooxo[2,6-pyridinedimethanethiolato(2-)-κN1,κS2,κS6]-, (SP-5-34)- (9CI)

Solution:

- Data from Sci-Finder used to find PubChem profile
- ChemDraw naming function

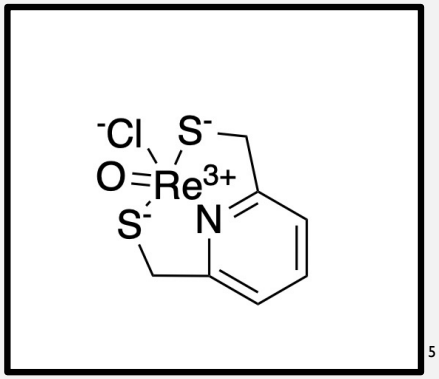
Good



[4]

ChemDraw Example: benzyl ((*S*)-1-oxo-1-(((*S*)-1-oxopropan-2-yl)amino)-3-phenylpropan-2-yl)carbamate

Bad



[5]

Unidentifiable Compound

4. 10.1016/j.bmc.2004.12.053
5. 10.1021/jm060357z

SUMMARY

- Sci-Finder is a godsend
- Academia is very confusing and requires great attention to fine detail
  - The potential for creating new inhibitors is far greater than I thought
- The skills I gained from this work greatly enhanced my studies
- Total Number of Compounds
  - Cathepsin B: 125
  - Cathepsin L: 134
  - Cruzipain: 100

NEXT STEPS

- Look for more DOI Publications for compounds in spreadsheet
- Natural product inhibitors of cruzipain
- Revisit papers with unidentifiable compounds

THANK YOU

- Dr. Avalon
- Dr. Gerwicks
- The Gerwick Lab

CITATIONS

BAICI, A., & GYGER-MARAZZI, M. (1982). The slow, tight-binding inhibition of cathepsin B by leupeptin. A hysteretic effect. *European Journal of Biochemistry*, *129*(1), 33–41. https://doi.org/10.1111/j.1432-1033.1982.tb07017.x

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Hoang, V. L. T., Li, Y., & Kim, S.-K. (2008). Cathepsin B inhibitory activities of phthalates isolated from a marine pseudomonas strain. *Bioorganic & Medicinal Chemistry Letters*, *18*(6), 2083–2088. https://doi.org/10.1016/j.bmcl.2008.01.097

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The Protein Data Bank Silva, E. B., Dall, E., Rodrigues, F. T. G., Ferreira, R. S., & Brandstetter, H. (2019). Crystal structure of Apo-Cruzain. https://doi.org/10.2210/pdb6n3s/pdb

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