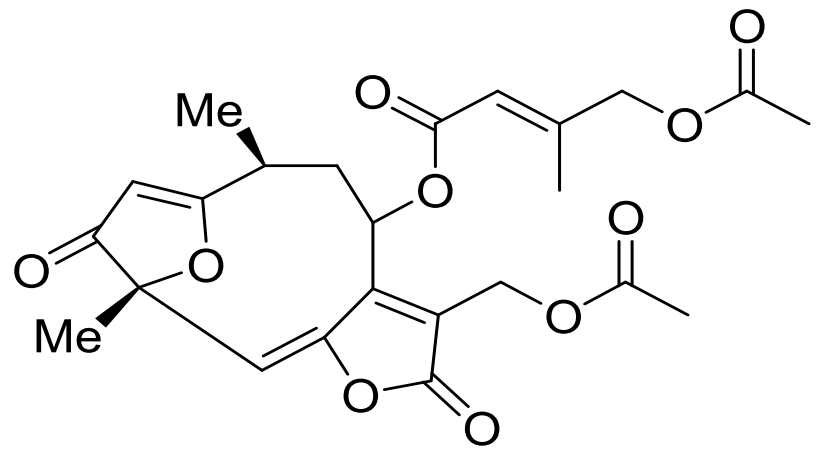
Discovery and development of new biologically active natural products at the University of Cape Town

Kelly Chibale, Peter Smith, David Gammon (and many others)

Towards Structure-Activity Relationships of Antiplasmodial Hirsutinolide Natural Products

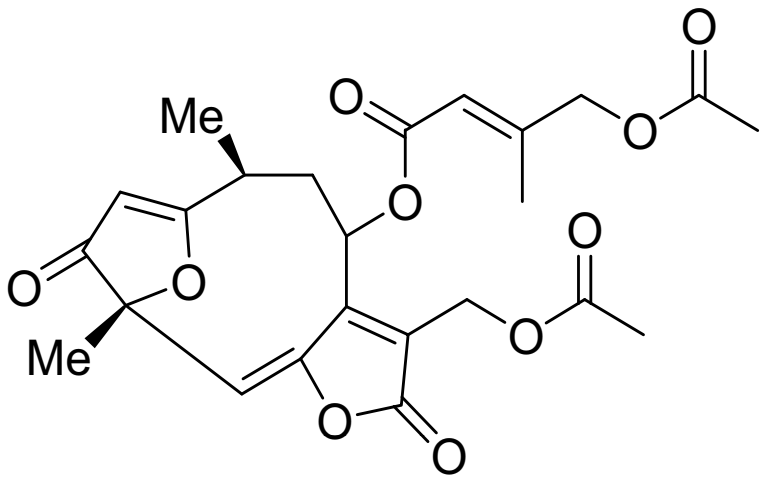
Hirsutinolides



Hirsutinolide (MAL-I-38B)

- Isolated from South African *Vernonia staehelinoides*
- Structures published in 1983 (Bohlmann, F.; Ates, N.; Jakupovic, J. *Phytochemistry* **1983**, *22*, 1159).

Hirsutinolides



Hirsutinolide (MAL-I-38B)

- Not previously Isolated from South African *Vernonia staehelinoides*
- IC_{50} (μg/ml): D10 = 0.24; K1 = 2.6; CHO 0.97
- Not previously reported to possess antiplasmodial properties

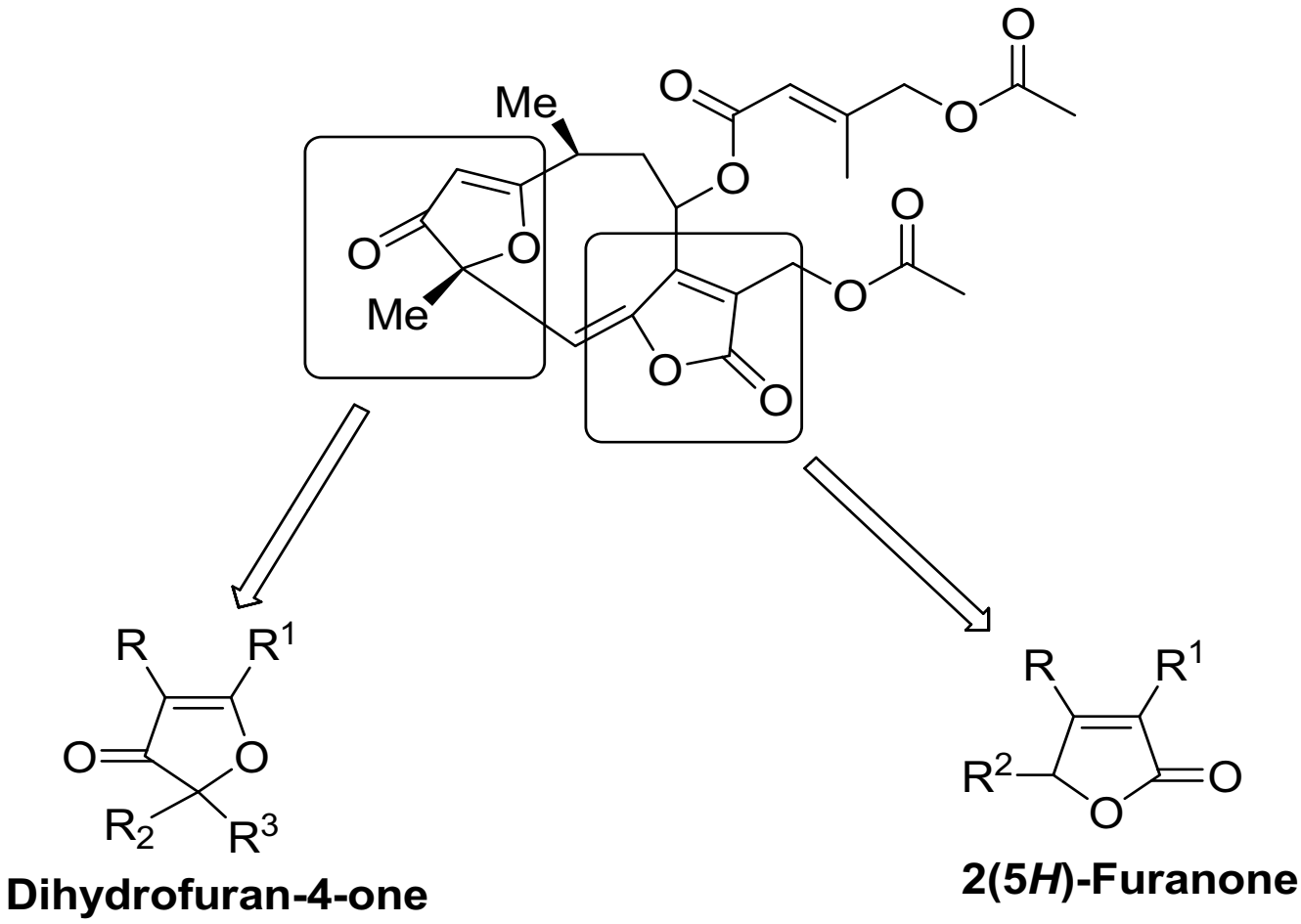
Libraries of Natural Product Derivatives

Total synthesis

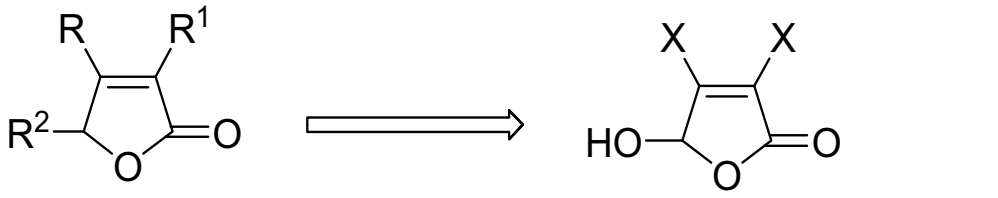
Modification of natural product core structure

Privileged structures identified in natural products as scaffolds

Identification of Privileged Substructures or Potential Pharmacophores in MAL-I-38B

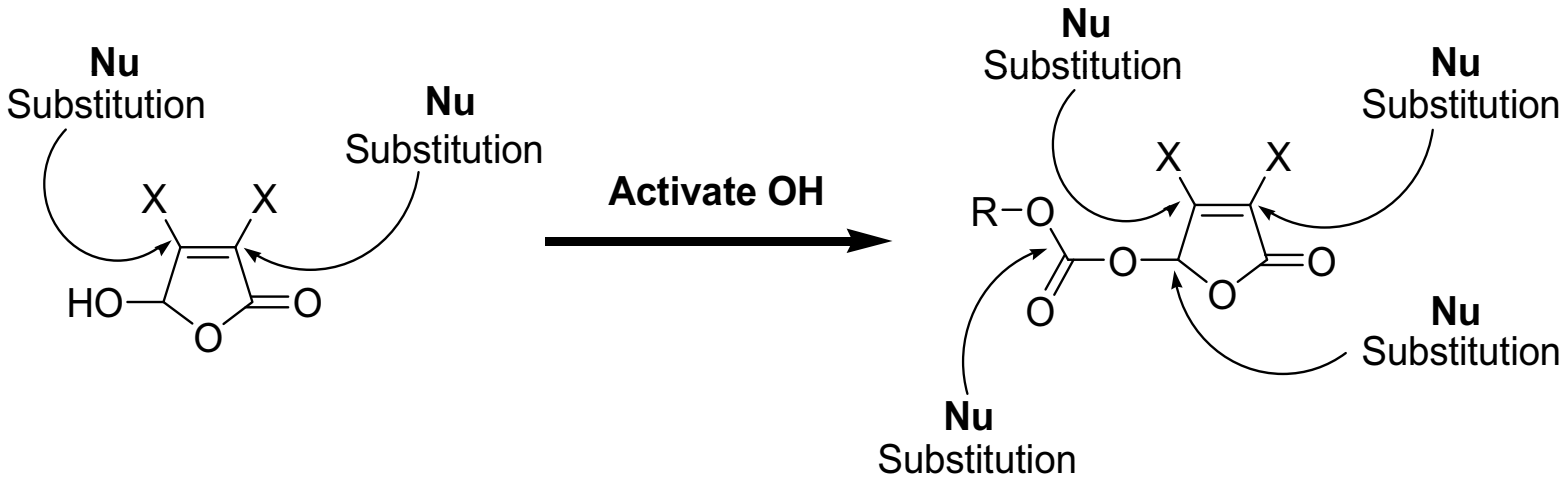


Synthesis of Around the 2(5*H*)-Furanone Basic Structure

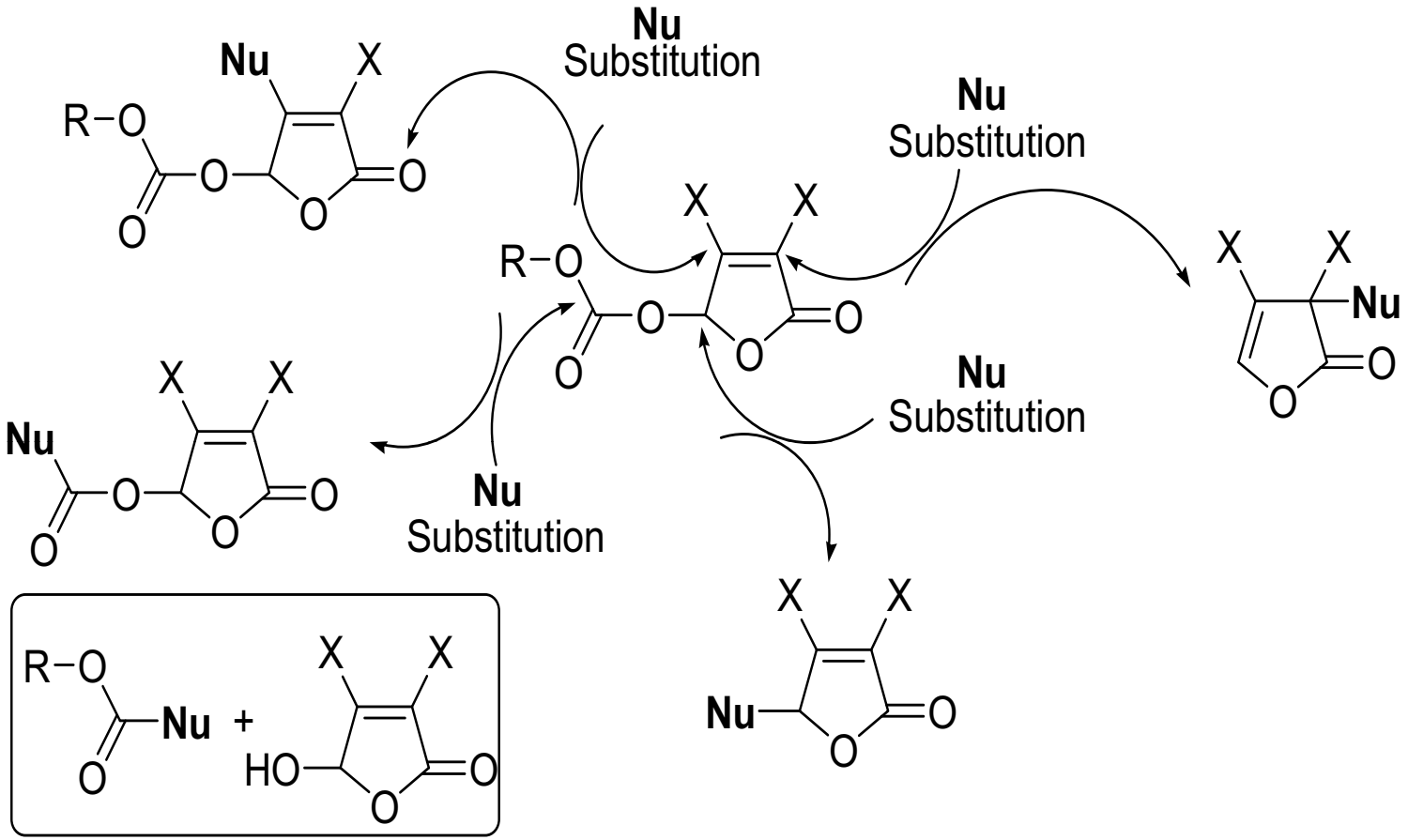


2(5*H*)-Furanone

X = Br: MucoBromic acid
X = Cl: MucoChloric acid



Synthesis of Around the 2(5*H*)-Furanone Basic Structure



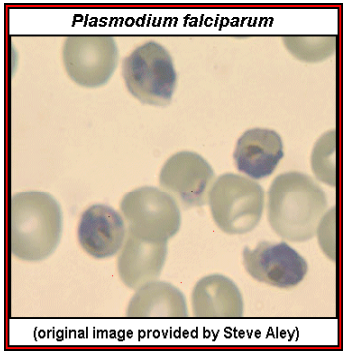
Antiplasmodial Activities of Natural Products and Simplified 2(5*H*)-Furanone Scaffolds

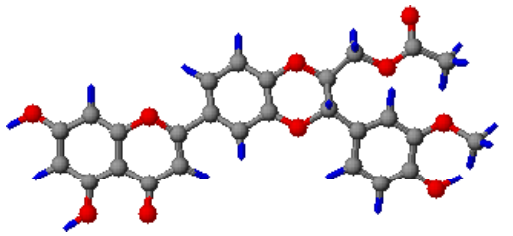
Tested sample	**D10 IC_{50} (ng/ml)**	**K1 IC_{50} (ng/ml)**	**CHO IC_{50} (µg/ml)**	**SI***
Chloroquine	12	182	18.5	1542
MAL-I-38A	260	1800	2.9	11
MAL-I-38B	240	2600	0.9	4
Mucochloric acid	152	137	4.8	32
Mucobromic acid	422	359	6.3	15
Emetine			0.06	

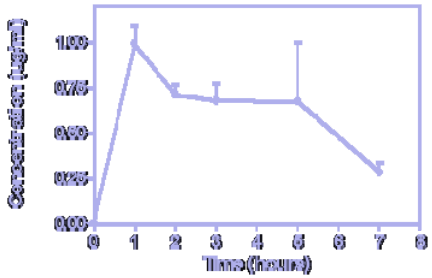
* SI = cytotoxicity CHO IC_{50}/antiplasmodial D10 IC_{50}

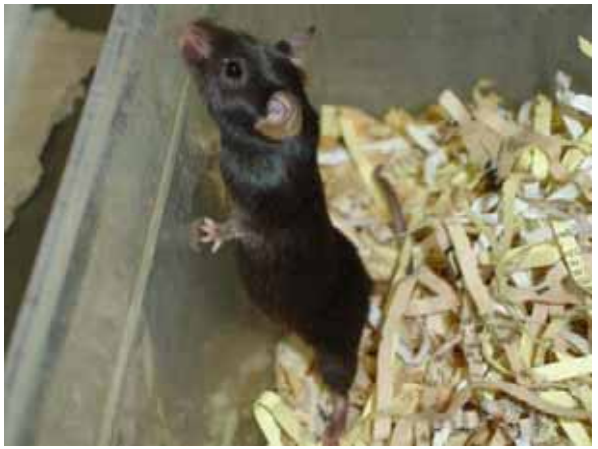
P. Pillay, R. Vleggaar, V. J. Maharaj, P. J. Smith, C. A. Lategan,. F. Chouteau, K. Chibale
Phytochemistry **2007**, *68*, 1200-1205

UCT Division of Pharmacology

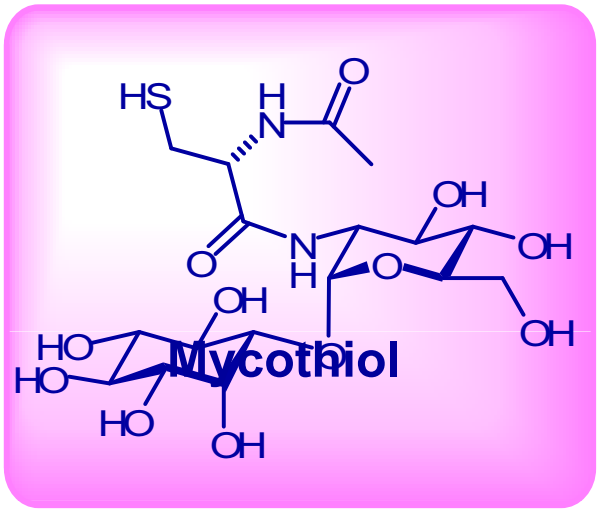








Newton *et* al., *Microbiol & Mol Biol* Reviews, Sept. 2008, p. 471–494

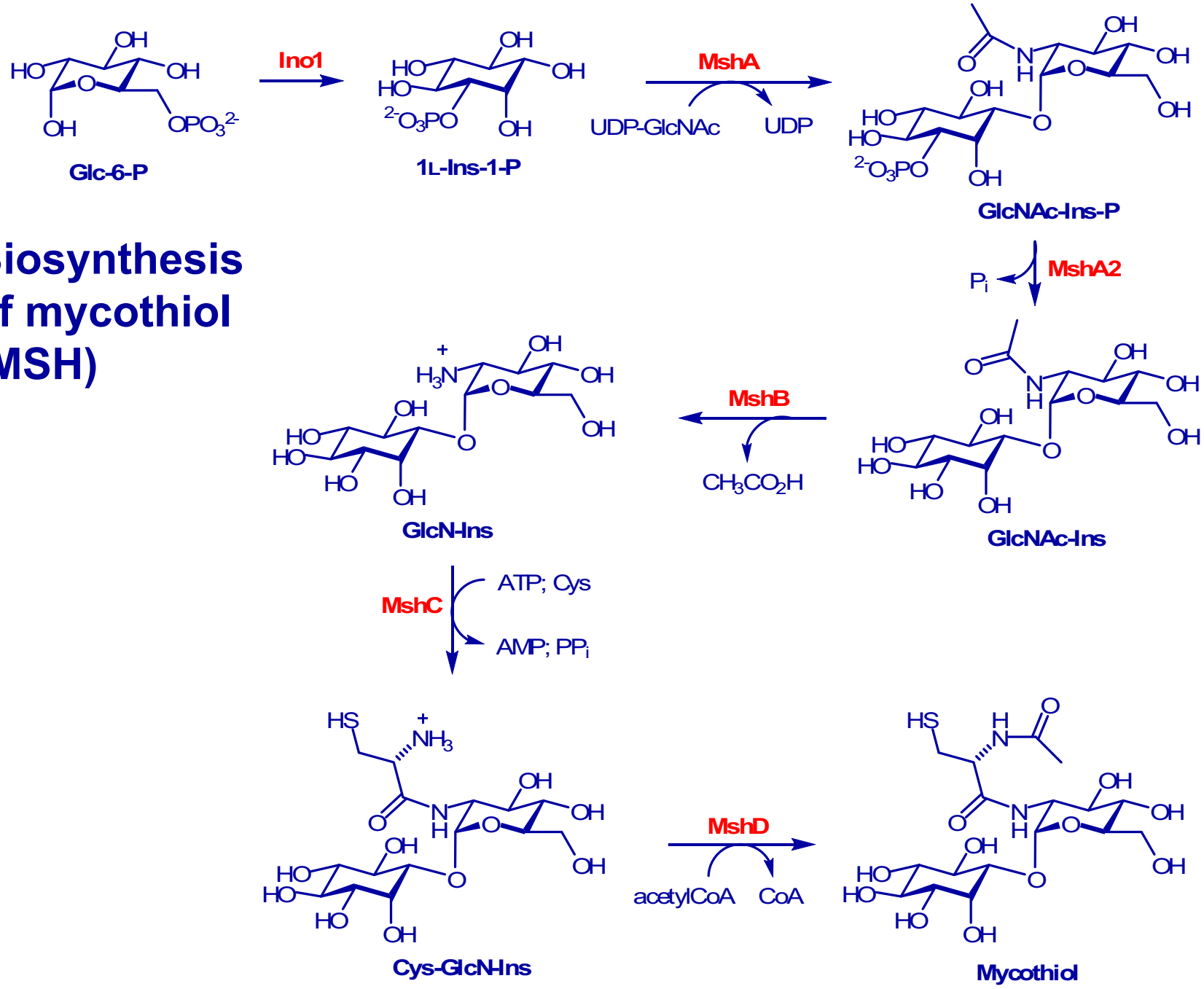


- produced by the gram +ve *Actinobacteria*, including ***M. tuberculosis***;

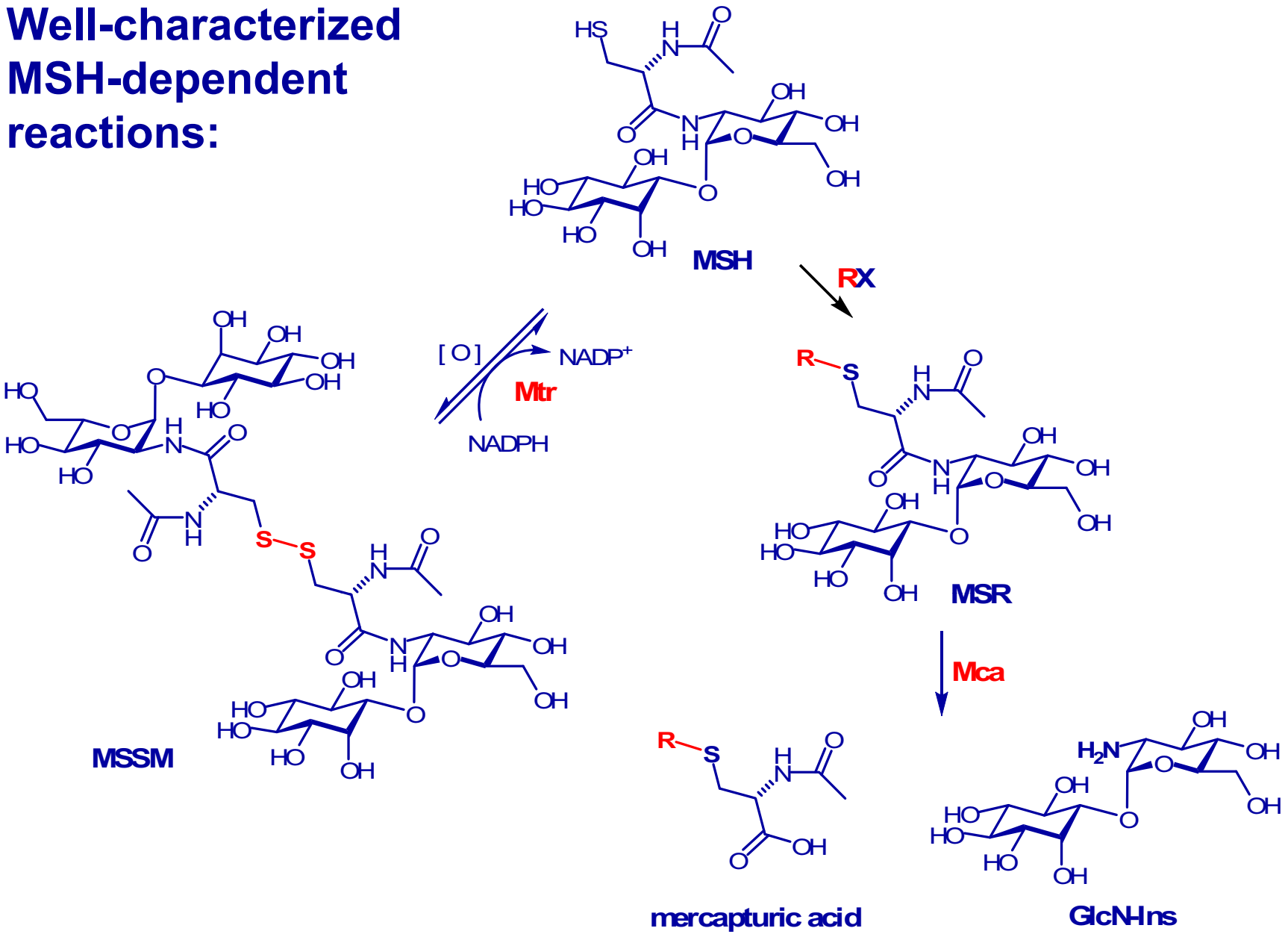
  analogue of glutathione in the gram -ve bacteria

"Inhibition of MSH production simultaneously inactivates all MSH-dependent metabolic processes, **so the enzymes of MSH biosynthesis would appear to be prime drug targets**."

Biosynthesis of mycothiol (MSH)



Well-characterized MSH-dependent reactions:



gene knockout experiments:

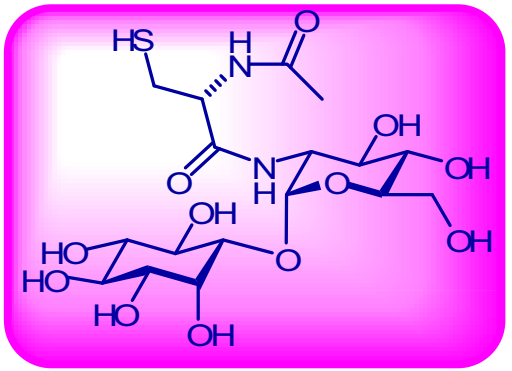
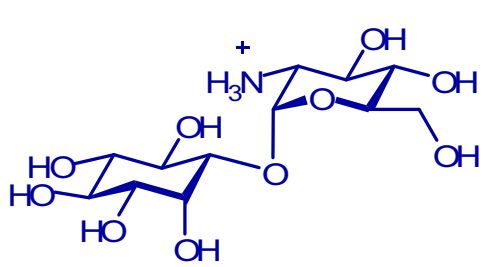


TABLE 3. Production of MSH and MSH intermediates by *M. smegmatis* mutants

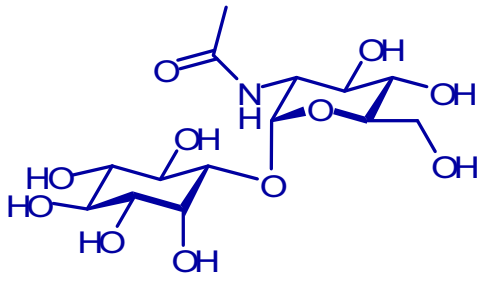
Enzyme	Strain	Concn (μmol/g dry weight) of MSH or intermediate			
		GlcNAc-Ins	GlcN-Ins	Cys-GlcN-Ins	MSH
Wild type[a]	mc^{2}155	<0.1	0.2–1.0	~0.008	10 ± 3
MshA[b]	*mshA*::Tn*5*	<0.01	<0.01	<0.01	<0.01
MshB[c]	Myco504	2.6 ± 0.2	<0.01	<0.02	1.0 ± 0.2
MshC[d]	Tn*1*	ND[e]	2.6	<0.002	<0.004
MshD[f]	*mshD*::Tn*5*	ND	0.35 ± 0.05	0.6–2	0.12 ± 0.01[g]

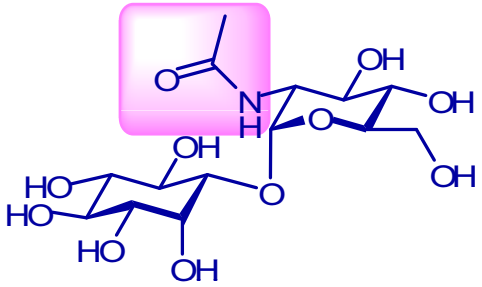
Search for enzyme inhibitors: key early results on MshB



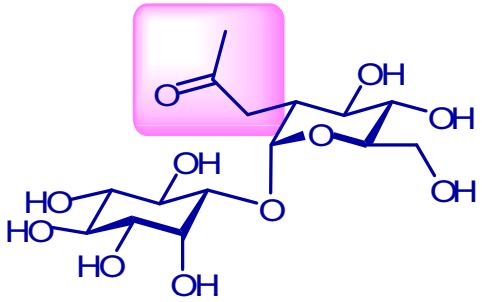
MshB

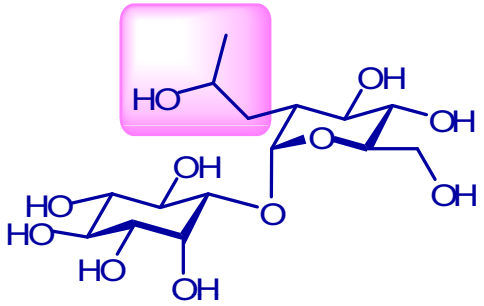
CH_3CO_2H





substrate



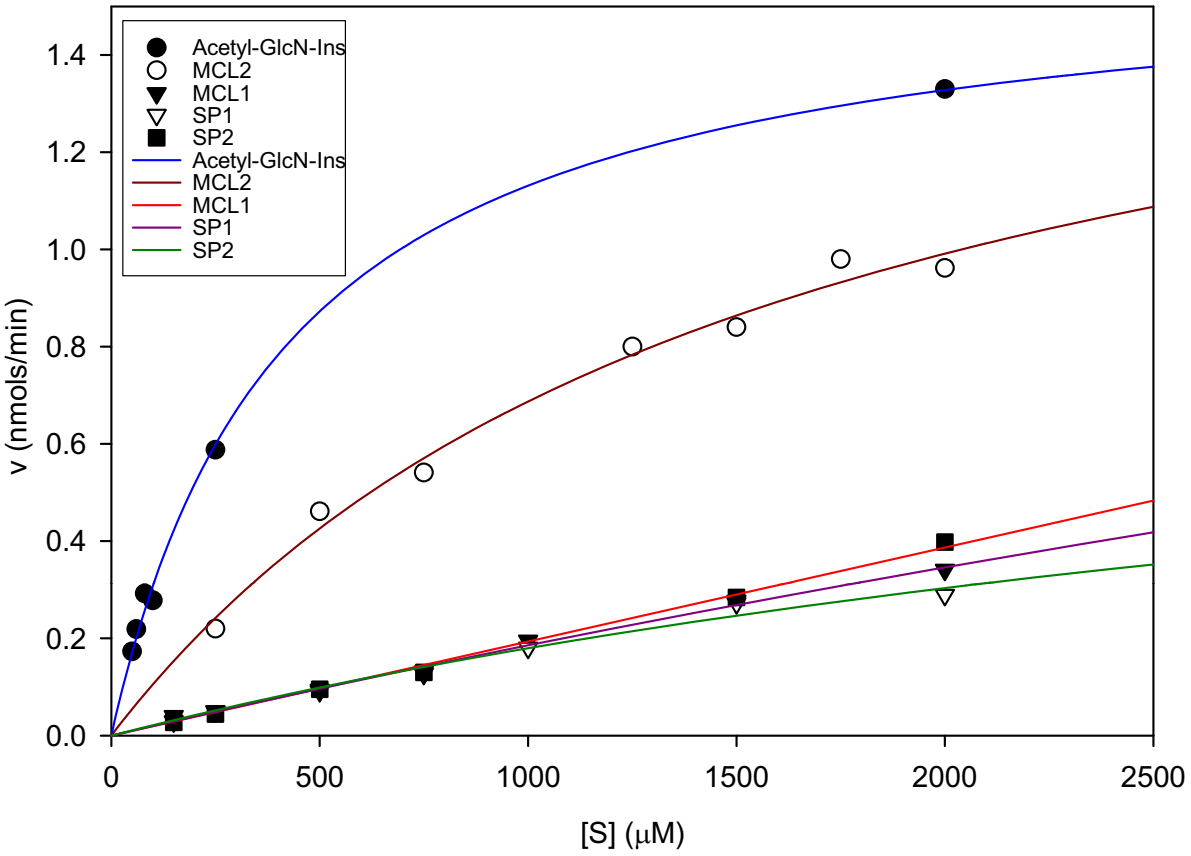


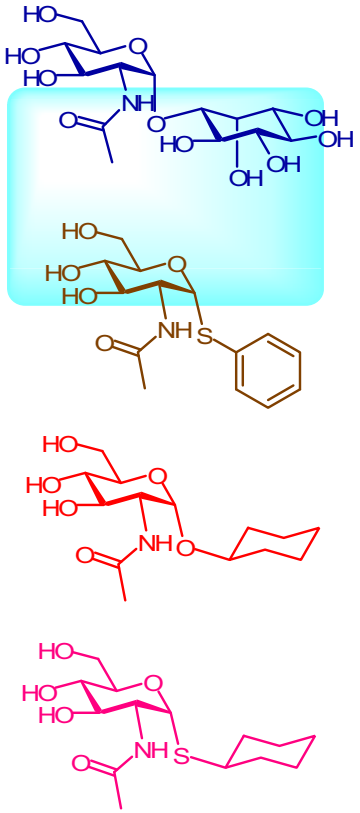
inhibitors

D.W. Gammon, M. Jardine, C.M. Nkambule, H.S.C.Spies and D.J. Steenkamp, *Bioorganic & Medicinal Chemistry*, 2002, **10**(4), 875-881.

D.W. Gammon, R. Hunter, D.J. Steenkamp and T.T. Mudzunga, *Bioorganic & Medicinal Chemistry Letters*, 2003, **13(12)**, 2045 - 2049.

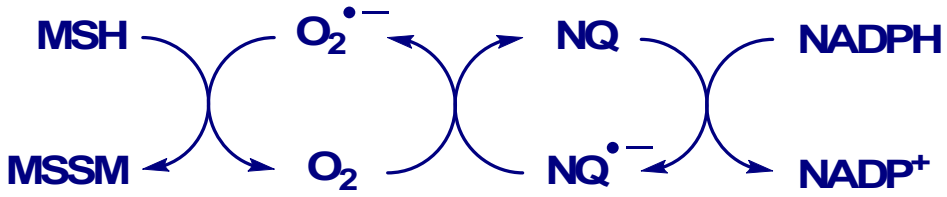
Substrate specificity: MshB



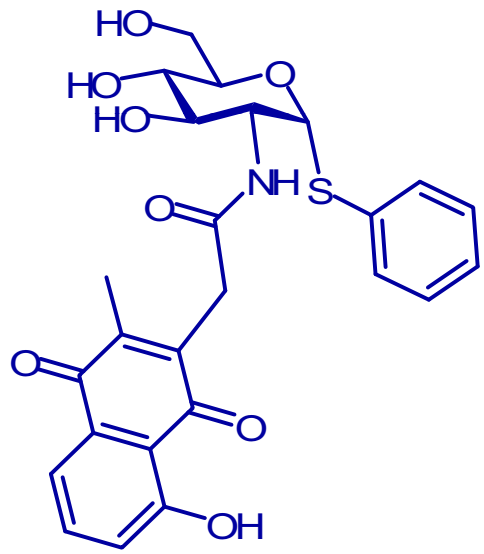


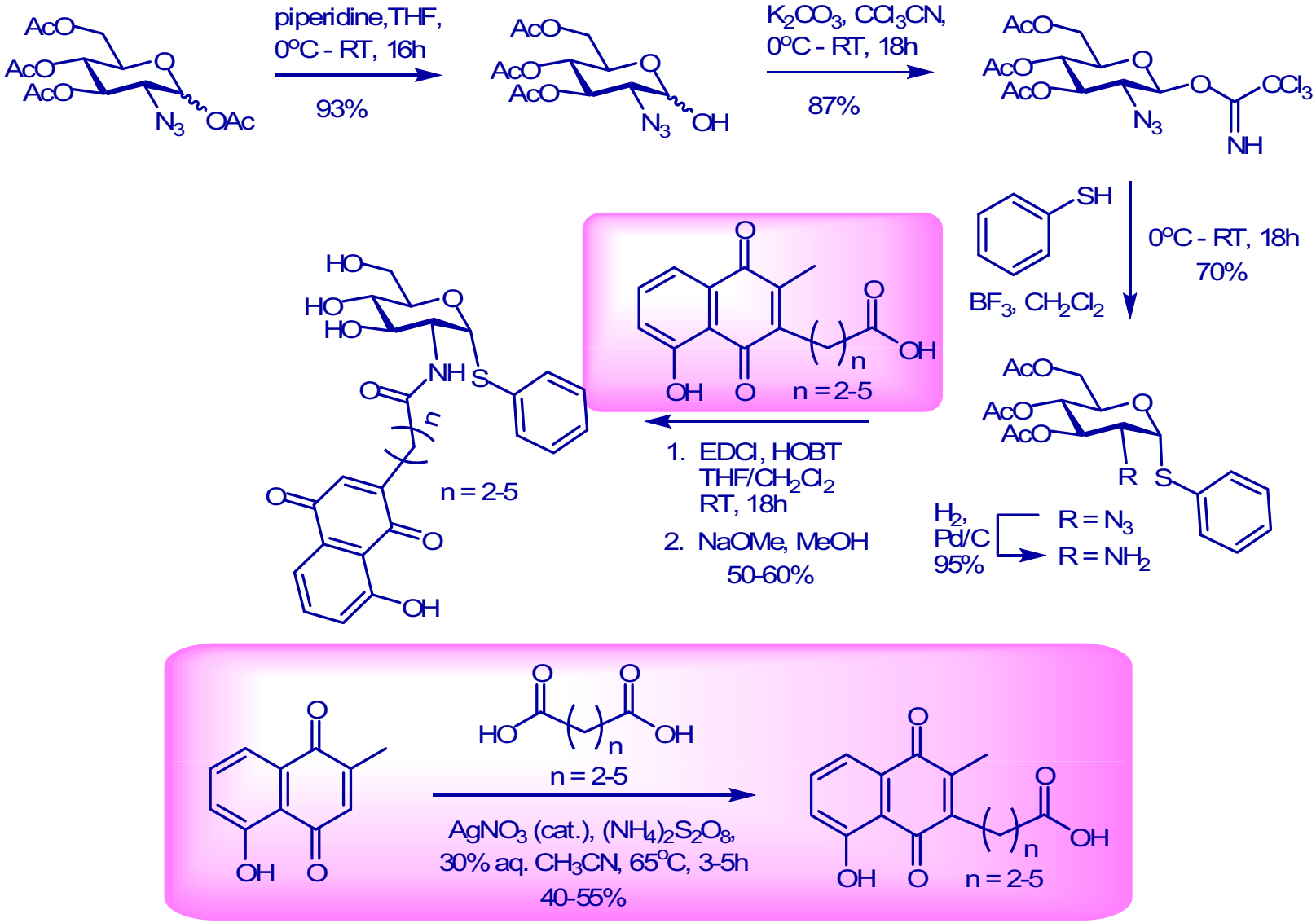
Synthesis of potential suicide substrates of mycothione reductase (Mtr) – and some surprising results!

By analogy with work done on the trypanothione reductase, naphthoquinones can act as suicide substrates of these enzymes:



Target molecules:





J.M. Anderson and J.K. Kochi, *JACS*, 1970, 92(6), 1651-1659

Inhibition of MshB: