Clinical Drugs or Natural Products as Leads or Templates for Integrative Organic Synthesis, Medicinal Chemistry and Chemical Biology Explorations

Tentative Seminar Topics

1. **Total Syntheses of Challenging Organic Molecules of High Therapeutic Prospects**
2. **Fixing A Problematic Drug, Plavix: First and Stereoselective Chemical Synthesis of the Intricate Active Metabolite for Overcoming Its Prominent Clinical Resistance and Elucidating Its Unique Action of GPCR Modification and Signaling**
3. **Acylthioenol Click Chemistry: Facile Drug Functionalization for H_2S Delivery and Multicomponent Pharmacotherapy**
4. **Four Distinctive Chemical Approaches for Developing Novel Anticancer Therapeutics**

Yaoqiu Zhu, Ph.D., Assistant Professor, UT-El Paso www.thezhulab.org

Gasotransmitter Symposium at **Pacifichem** 2021 in Hawaii (Dec 16-21, 2021)
Department of Pharmaceutical Sciences, School of Pharmacy, **University of Maryland** (fall, 2021)
Department of Pharmaceutical Sciences, College of Pharmacy, **University of Nebraska Medical Center** (Nov 04, 2021)
Department of Pharmaceutical Sciences, School of Pharmacy, **University of Wisconsin-Madison** (Oct 22, 2021)
Department of Chemistry, **University of Cincinnati** (Oct 15, 2021)
Department of Chemistry, **University of Illinois at Urbana-Champaign** (Oct 11, 2021)
Department of Chemistry, **Texas A&M University** (Sep 30, 2021)
Department of Chemistry, **University of South Florida** (Sep 22, 2021)
Center for Natural Products, Drug Discovery & Development, College of Pharmacy, **University of Florida** (May 26, 2021)
Department of Chemistry, **Brandeis University** (May 17, 2021)
Chemical Biology & Medicinal Chemistry Division, College of Pharmacy, **The University of Texas at Austin** (May 14, 2021)
Department of Biochemistry, **University of Texas Southwestern Medical Center** (May 13, 2021)
Center for Diagnostics & Therapeutics, **Georgia State University** (May 11, 2021)
Department of Medicinal Chemistry and Molecular Pharmacology, **Purdue University** (May 06, 2021)
Department of Pharmacology and Chemical Biology, **Baylor College of Medicine** (Apr 13, 2021)
Department of Pharmacology and Toxicology, College of Pharmacy, **University of Arizona** (Apr 06, 2021)
Department of Chemistry and Biochemistry, **New Mexico State University** (Mar 06, 2020)

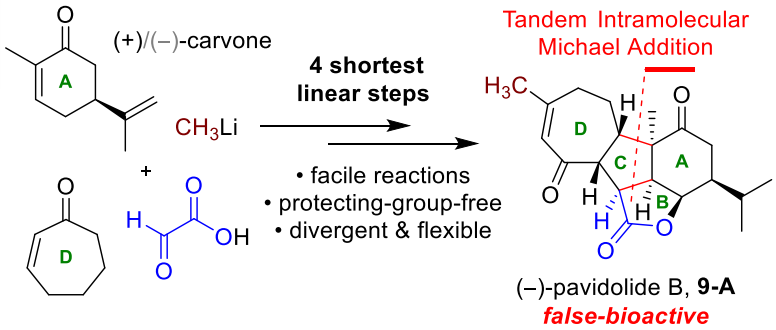
Exploiting Complex Natural Template for Anticancer Lead Discovery

(Elkin) Libo Romero

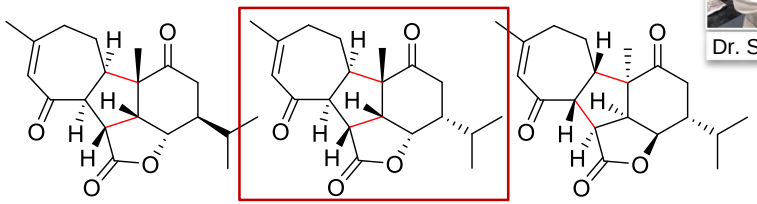
4-Step Facile Total Synthesis of False-Bioactive (−)-Pavidolide B and Its Anticancer Stereoisomers

Zhu, Y.*, Romero, E. L., Kolluru, S., Noriega, E. et al. 2021, under review.

Dr. Srinivas Kolluru



synthetic anticancer stereoisomers beyond biogenesis



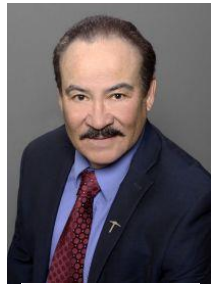
9-B *bioactive*

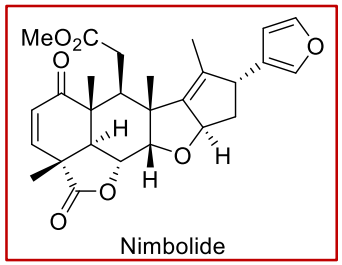
9-C *bioactive*

9-D *bioactive*

Baylor College of Medicine

	Lab-1, IC_{50} (μM)							Lab-2, CC_{50} (μM)			
	A549	BT474	MDA-MB-231	HepG2	Jeko	Mino	MOLM-14	Hela	SH-SY5Y	CEM	HL60
9-A	>100	>100	>100	>100	>100	>100	>100	>100	>100	>100	>100
9-B	>100	54	45	>100	>100	>100	>100	>100	>100	>100	>100
9-C	>100	>100	>100	>100	29	4.4	27	35	47	6.3	25
9-D	>100	>100	>100	>100	>100	>100	>100	>100	>100	53	>100



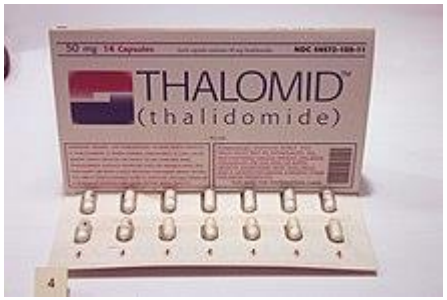


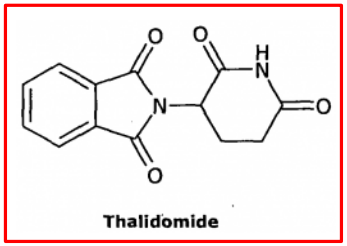
Harnessing the anticancer natural product nimbolide for targeted protein degradation

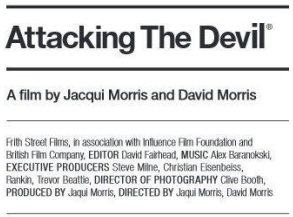
Maimone & Nomura

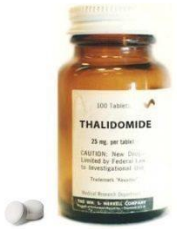
Nature Chemical Biology 2019, 15, 747-755.

The human body is the ultimate subject of biochemistry while its complex nature are portrayed by the diverse and mysterious outcomes of pharmacotherapy. **Mechanistic quest on the clinical puzzles of a drug molecule represents one of the greatest challenges to biochemists**. One recent example is the 60-year pursuit on thalidomide that does not only unlock its tragic past of teratogenesis but also bring it forward as a new treatment for cancer.



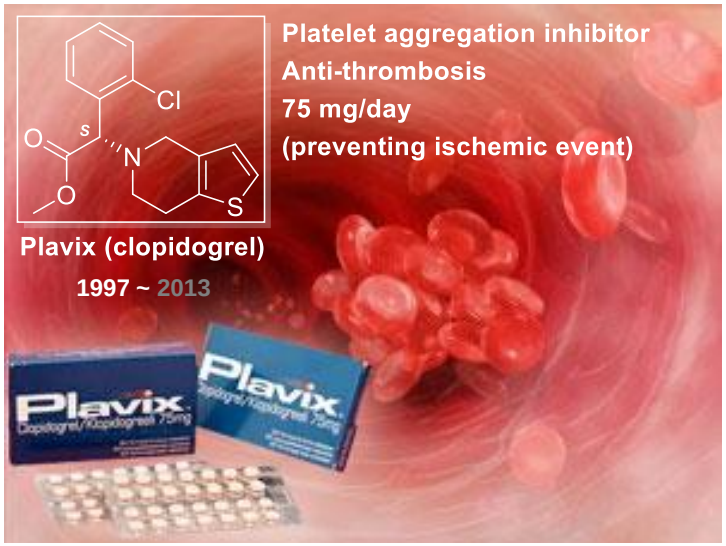


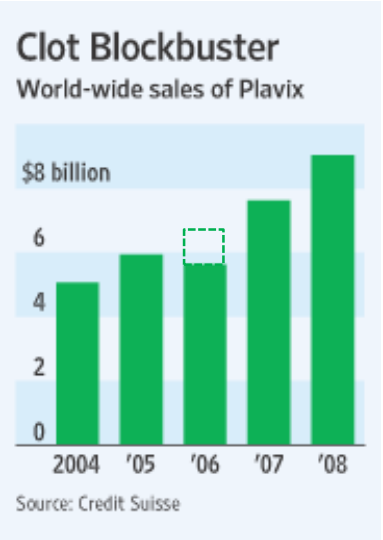




Ref: (1) *Science* ***2010****, 327, 1345- 1350*. (2) *Science* **2015***, 348*, 1376-1381. (3) *Nat. Med.* **2016**, *22*, 735-743.
(4) “Attacking the Devil”, documentary movie, initial release: June 9, 2014 (United Kingdom)

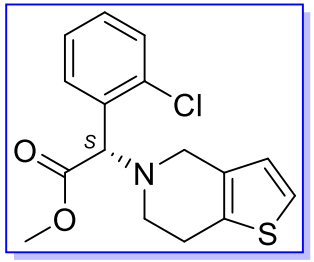
The Serendipitous & Problematic Antiplatelet - Clopidogrel

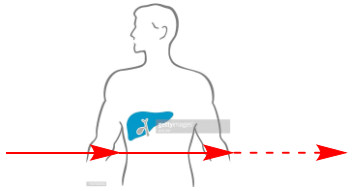




The ***Billion Dollar Prodrug***

Clopidogrel (Plavix®)

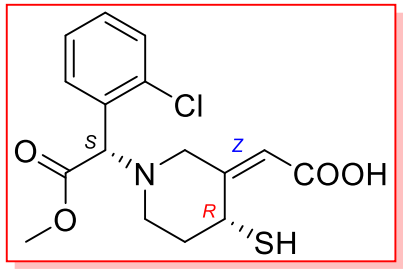




Problematic activation in patient's liver ***(0-1% of oral dose)***

The ***Billion Dollar Baby***

Active metabolite (**H4**)



The serendipitous & problematic drug

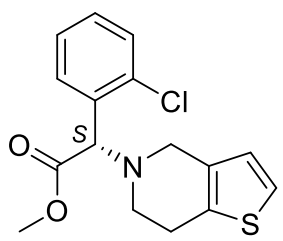
- Tedious and vulnerable metabolic activation in liver
- Prominent resistance confers high risk of ischemia
- Long-standing mainstay antiplatelet treatment

A high-profile synthetic target

- Enormous biomedical significance
- Rare and elusive structure
- Reactive and unstable
- Underestimated challenges

A 10-Step First & Stereoselective Chemical Synthesis

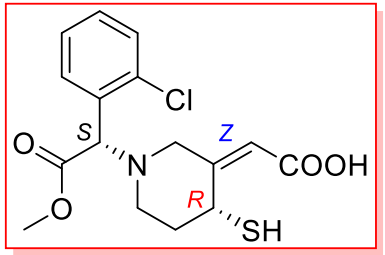
- Overall 16% Yield
- Enabled by a series of nontraditional approaches
- Convenient & flexible conversion to stable and releasable derivatives



Clopidogrel (Plavix)

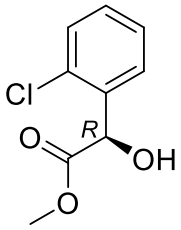
problematic activation in patient's liver

(0-1% of oral dose)



Active metabolite (**H4**)

methyl 2-chloro-*D*-mandelate ($16/g)



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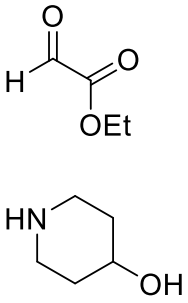
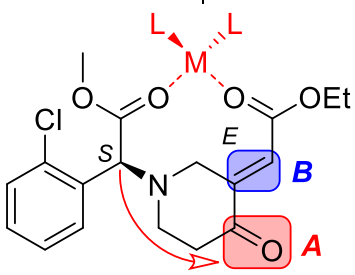


5 steps

5 steps



A high-profile target for organic synthesis:

- Enormous biomedical significance
- Elusive structure
- Reactive and unstable
- Underestimated synthetic challenges

Unprecedented synthetic approaches:

- Mitigating the (*Z*)-double bond disadvantages - furnishing (*E*)-intermediates for isomerization
- **A**. Asymmetric ketone reduction
  Metal ion-promoted chirality extension
- **B**. Double bond (*E*)-to-(*Z*) isomerization
  biomimetic reversible Michael addition

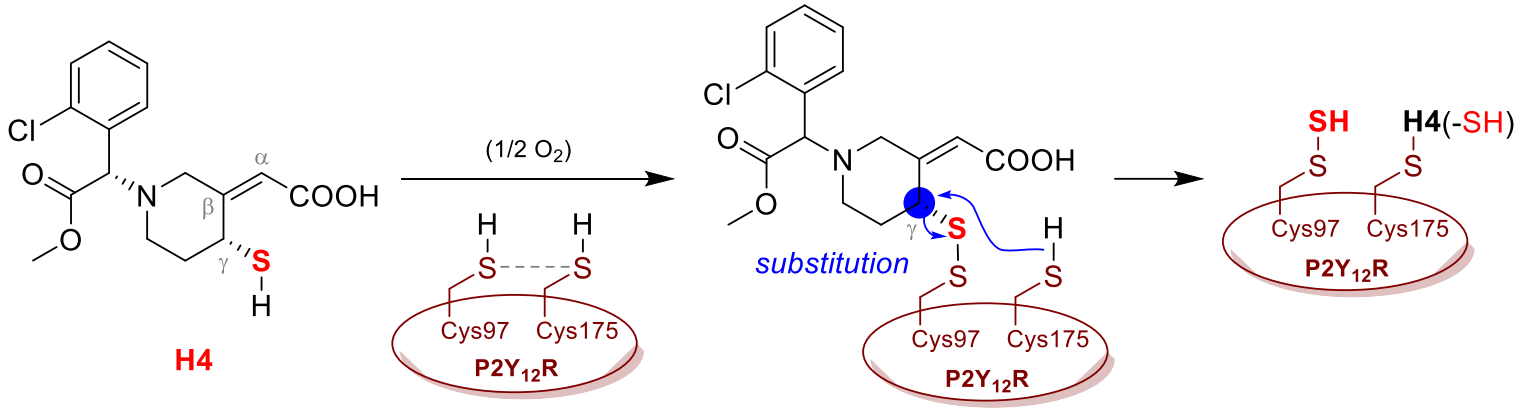
Dr. Suresh Kurhade

Commercialization Development

Shineage Therapeutics

(Elkin) Libo Romero

Unprecedented Mechanism of GPCR Protein Signaling



Novel mercapto activation

- unconventional on & off reactivity
- unprecedented S_N2 reaction

Intriguing protein interception

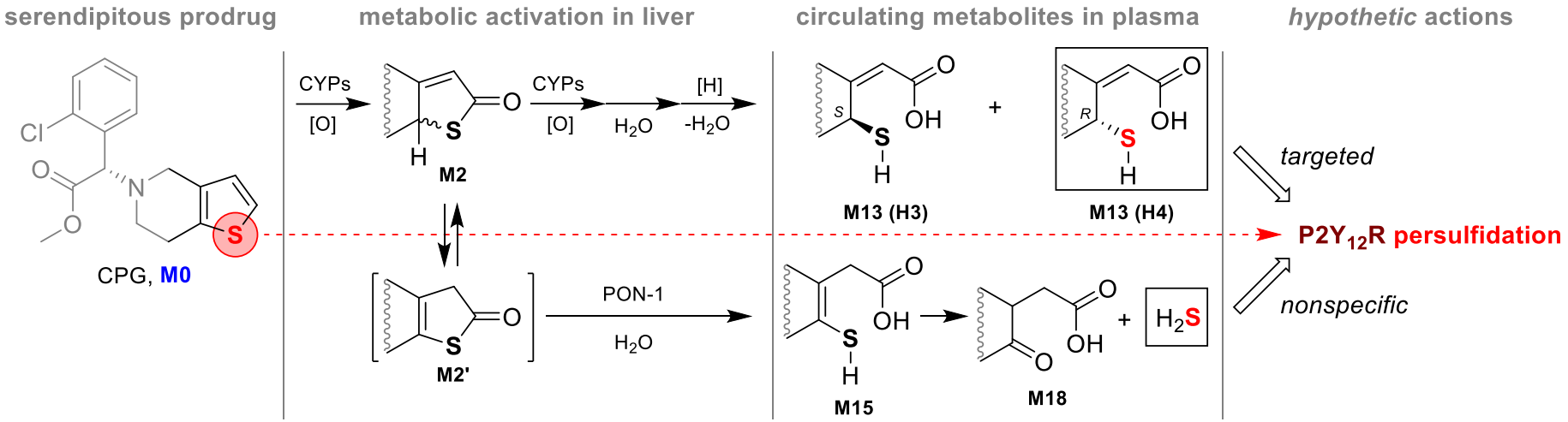
- sequential modification
- protein persulfidation

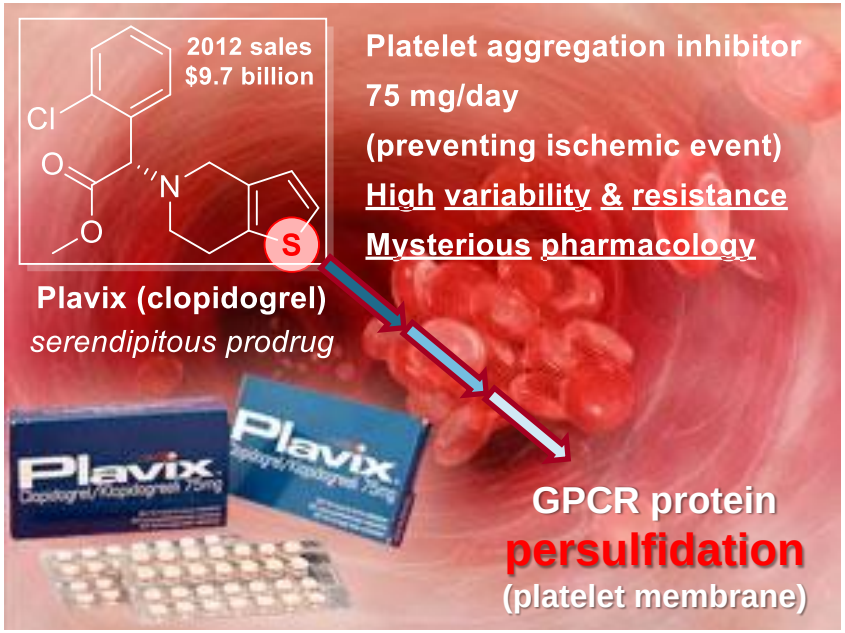
- Upon disulfide adduct formation with Cys97, the unconventional reactivity of H4 might compel itself to an intraprotein S_N2 reaction with another cysteine residue, which does not only persulfate the receptor to signal its disruption and translocation, but also in return confer H4 the observed (4*R*)-specific potency.
- Persulfidation is a known regulatory pathway of protein structure and function.
- A major signaling pathway of gasotransmitter H_2S is through persulfidation of cysteine residues, which has been shown to destabilize protein monomers and signal the translocation of certain membrane-bound protein.
- H_2S has been established as an antiplatelet agent with a proposed role of antagonizing $P2Y_{12}R$ through modifying its extracellular cysteine.

(1) Chem. Rev. **2018**, *118*, 1253-1337. (2) *Free Radic. Biol. Med.* **2017**, *104*, 262-271.
(3) *Eur. J. Pharmacol.* **2007**, *559*, 65-68. (4) *Arterioscler. Thromb. Vasc. Biol.* **2012**, 32, 2884-2891.

The Tale of Plavix – *It Is All About that Sulfur*

A Human Subject-Oriented Research Endeavor



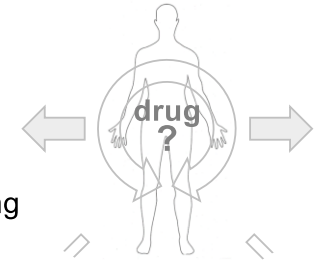


The Extra – *A Perspective*

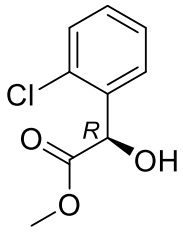
The ‘top-down’ research paradigm based on clinical drugs
- aligning basic research with its ultimate subject of human body (drug-as-probe)
- alleviating the R&D bottleneck in drug development (drug-as-lead)

Biochemical Research** directly addressing **Human Subject Conundrums

The puzzling and formidable subject of H4:
- Reactive, labile and intricate degradation structure with unknown bioactive configuration
- Unique and elusive action on receptor signaling



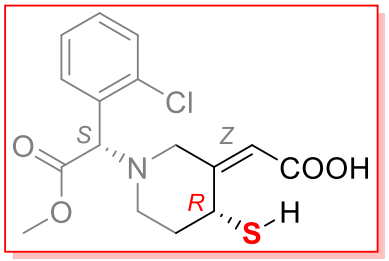
The mysterious and problematic clinical drug:
- Tedious and vulnerable metabolic activation
- Prominent resistance confers high risk of ischemia
- Long-standing mainstay antiplatelet treatment



methyl 2-chloro-*D*-mandelate ($16/g)

First chemical synthesis

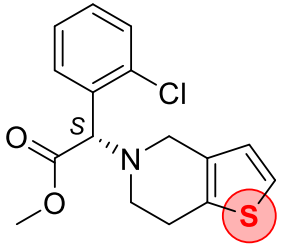
nontraditional approaches



Active metabolite (**H4**)
stable & releasable derivatives

Problematic activation

in patient's liver



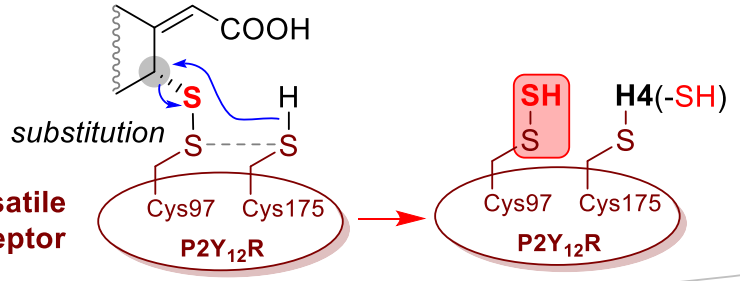
Clopidogrel (Plavix)
serendipitous prodrug

drug as lead

drug as probe

Clinically established entities for ***Drug Development:*** **revitalized** & **repurposed** medicines targeting **$P2Y_{12}R$**

versatile receptor



Clinically derived & aligned ***New Sciences:*** **sulfur** activation & protein **persulfidation**