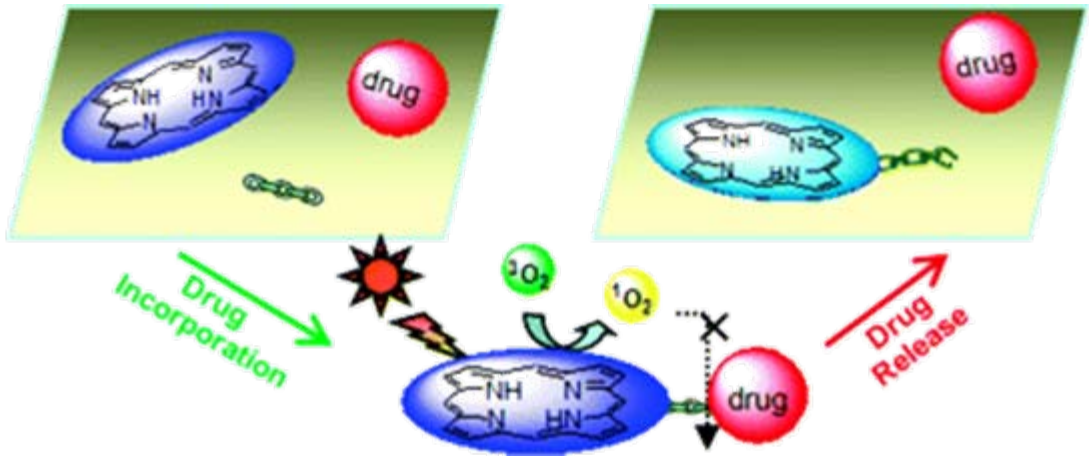
Site-Specific Prodrug Release Using Visible Light



Michael Y. Jiang and David Dolphin*

***J. Am. Chem. Soc.*, 2008, 130 , 4236 -4237**

Li Zhang

Current literature presentation

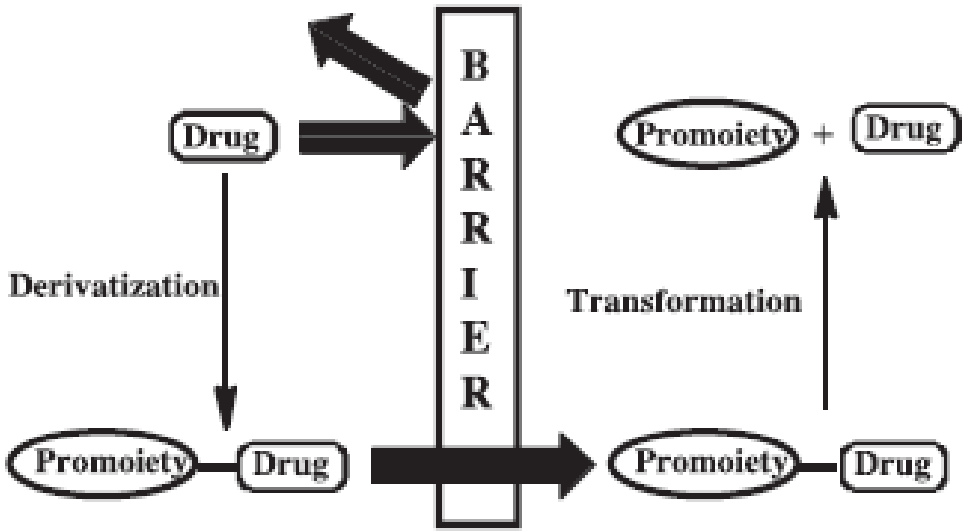
04-26-2008

Li Zhang @ Wipf Group

Background

What are Prodrugs?

Prodrugs are bioreversible derivatives of drug molecules that undergo an enzymatic and/or chemical transformation in vivo to release the active parent drug, which can then exert the desired pharmacological effect



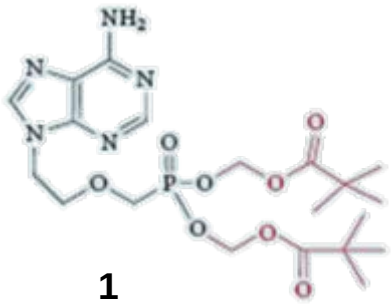
Nat. Rev. Drug Discovery **2008**, 7, 255-270

Prodrugs: Challenges and Rewards (AAPS press/Springer, New York, **2007**)

Applications of Prodrugs

A. Improved oral absorption

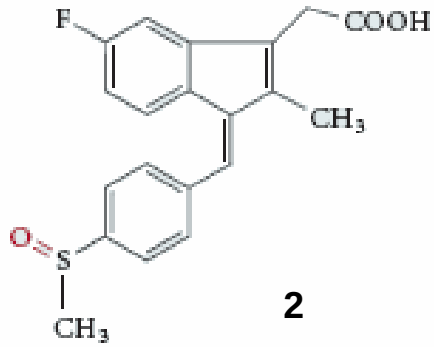
Improved lipophilicity or permeability



1

Adefovir dipivoxil (antiviral)
Bioconversion by esterases and Phosphodiesterases
2002 USA Launched

Improved aqueous solubility



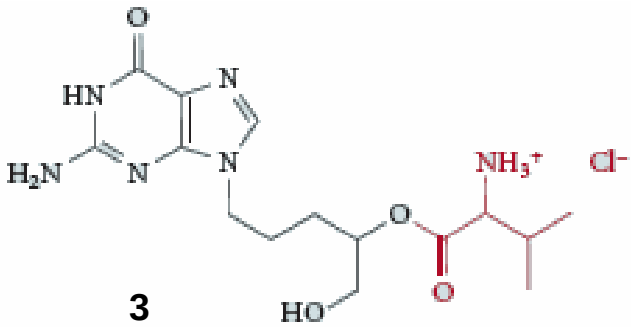
2

Sulindac (non-steroidal antiinflammatory)

Bioprecursor prodrug

1978 USA Launched

Carrier-mediated absorption



3

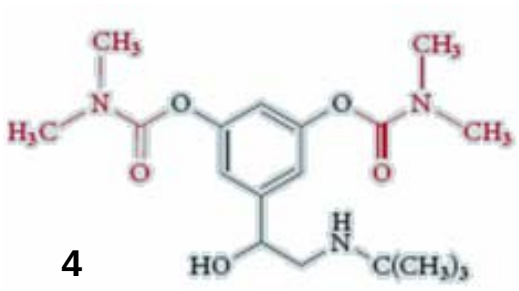
Valganciclovir (antiviral)

Mediated by transporter hPEPT1 expressed in the intestinal epithelial cells

2002 USA Launched

Nat. Rev. Drug Discovery **2008**, 7, 255-270 *J. Pharm. Sci.* **2008**,97,1109-1134

B. Prolonged duration of drug action



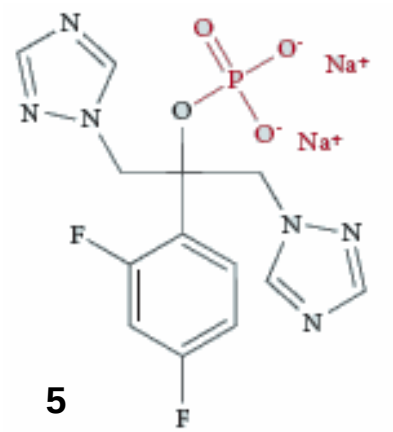
4

Bambuterol
(asthma)

distributes preferentially to lung tissue

1990 Sweden Launched

C. Improved parenteral administration



5

Fosfluconazole
(antifungal)

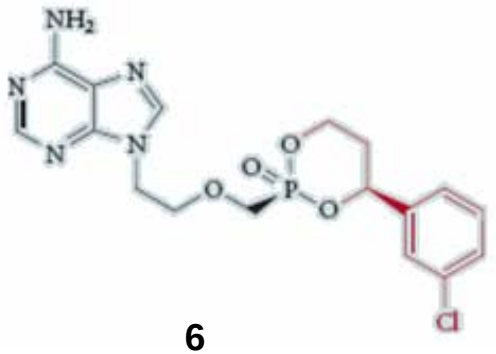
Bioconversion by alkaline phosphatases1

2003 Japan Launched
USA Phase II

Nat. Rev. Drug Discovery **2008**, 7, 255-270 *J. Pharm. Sci.* **2008**,97,1109-1134

D. Site-selective drug delivery

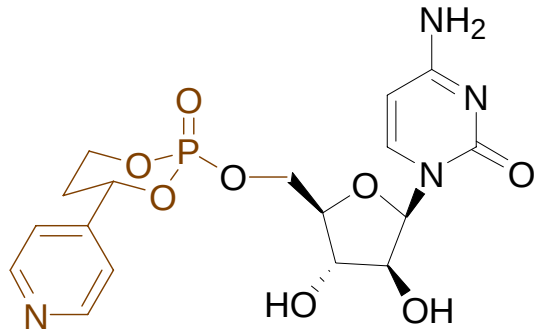
Liver-targeted delivery (liver-specific metabolizing enzymes CYP- activated)



Pradefovir mesylate
(antiviral)

Phase II

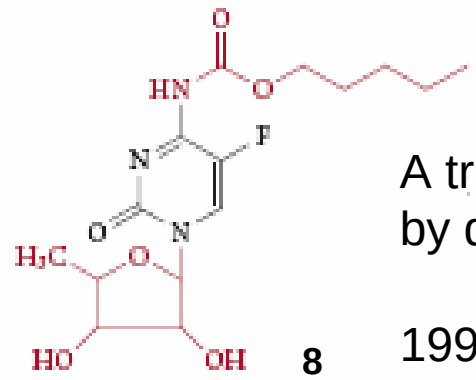
6



7

J. Med. Chem. **2006,** *49,* 7711-7720

Tumour targeting



Capecitabine
(anticancer)

A triple prodrug,
by dThdPase in tumors

1998 USA Launched

8

Antibody-directed enzyme prodrug therapy (ADEPT) Phase I

Gene-directed enzyme prodrug therapy (GDEPT) Phase III

Light-Triggered Strategy

Nat. Rev. Drug Discovery **2008**, 7, 255-270

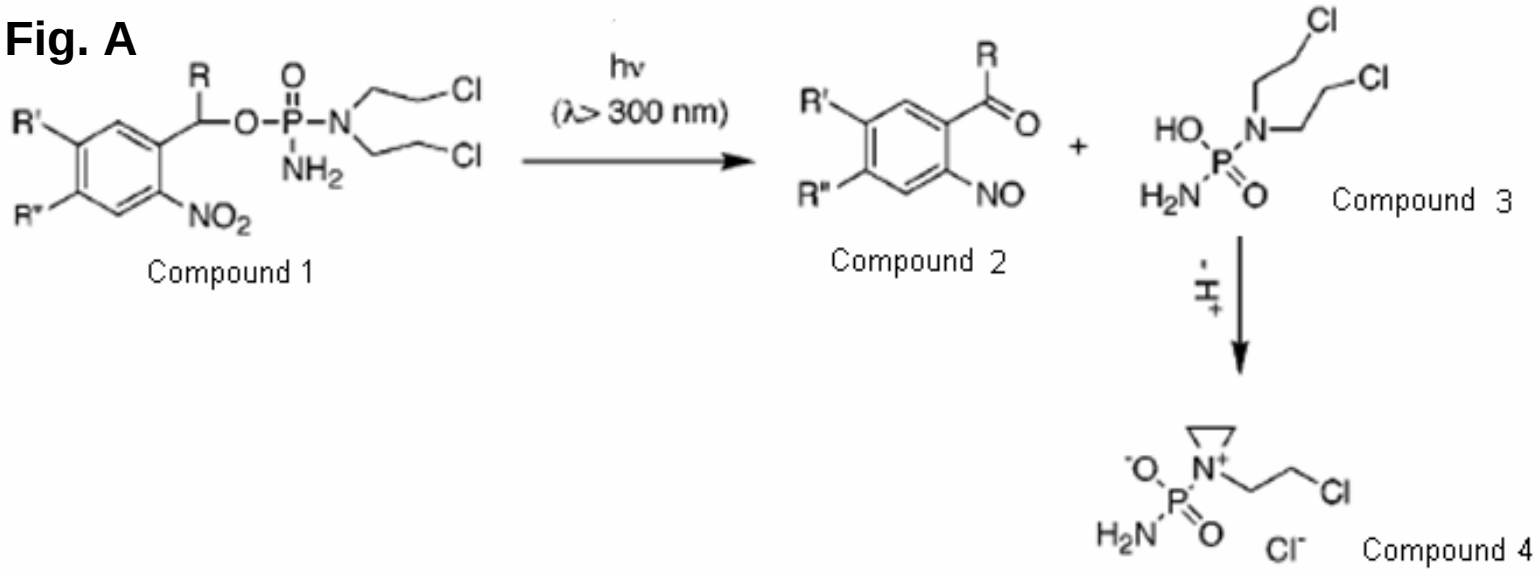
J. Pharm. Sci. **2008**,97,1109-1134

Site-Specific Prodrug Release by Light-Triggered Strategy

Nonenzymatic Activation
Photolysis can be temporally and spatially controlled

UV light triggerable prodrugs

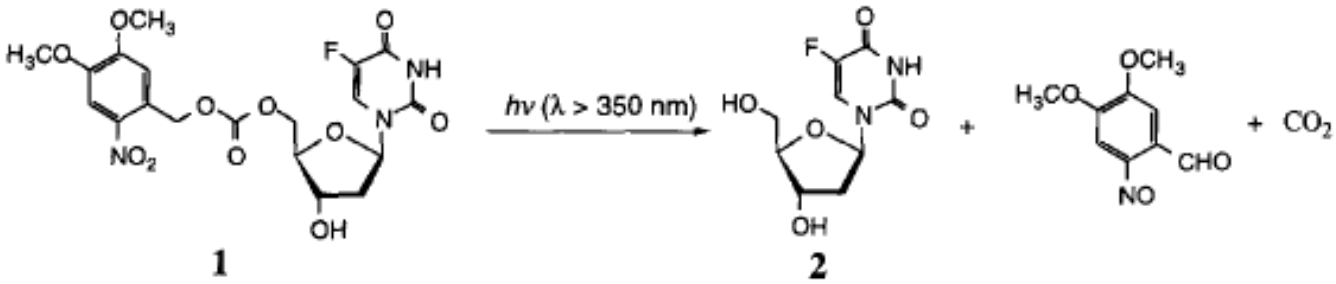
Fig. A



Aziridinium cation compound 4 is the active alkylating species of cyclophosphamide

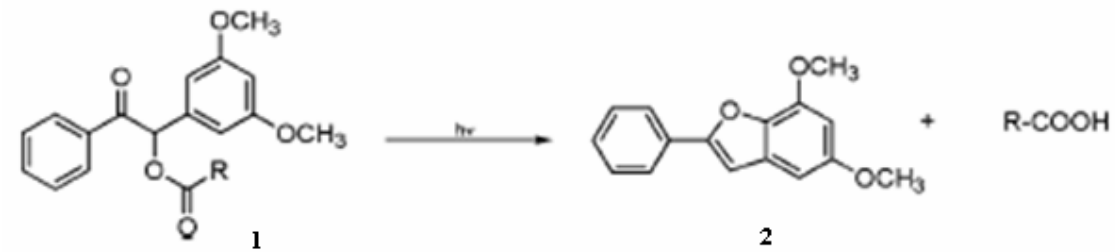
J. Org. Chem. **1998,** 63, 2434-2441

Fig. B



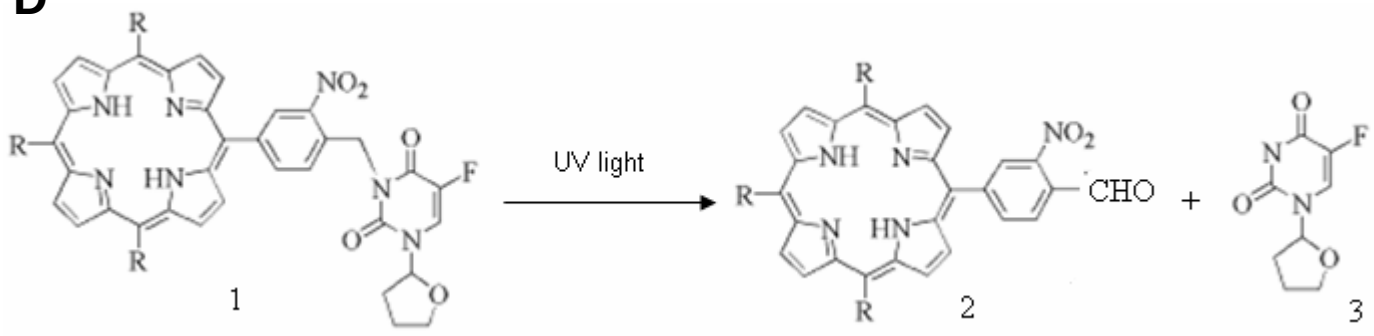
Bioorganic & Medicinal Chemistry Letters **1998**, 8, 2419-2422

Fig. C



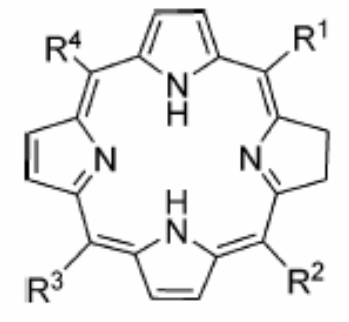
J. AM. CHEM. SOC. **2007**, 129, 9572-9573

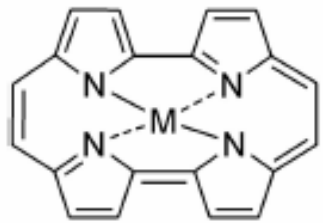
Fig. D

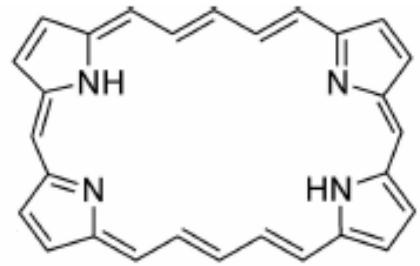


Eur. J. Org. Chem. **2008**, 793–796

Porphyrins







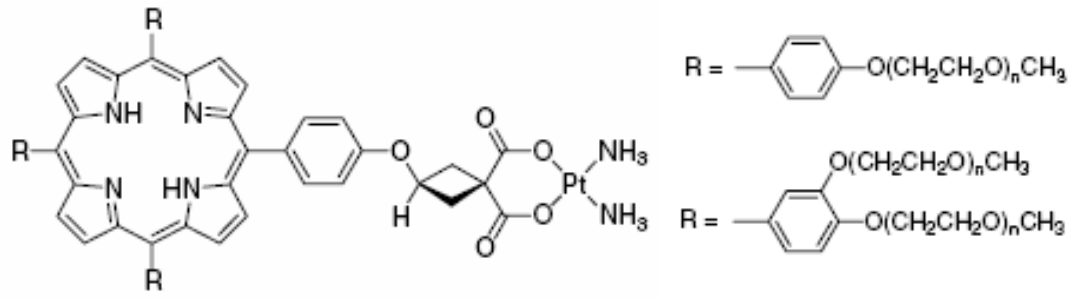
Porphyrins are a class of photosensitizers used in photodynamic Therapy (PDT).

Porphyrins tend to accumulate in neoplastic tissue to higher concentrations than in surrounding normal tissue.

Upon irradiation by light, porphyrins may be initially excited and further convert normal triplet oxygen into singlet oxygen, which reacts with various biomolecules to cause cell modification or death

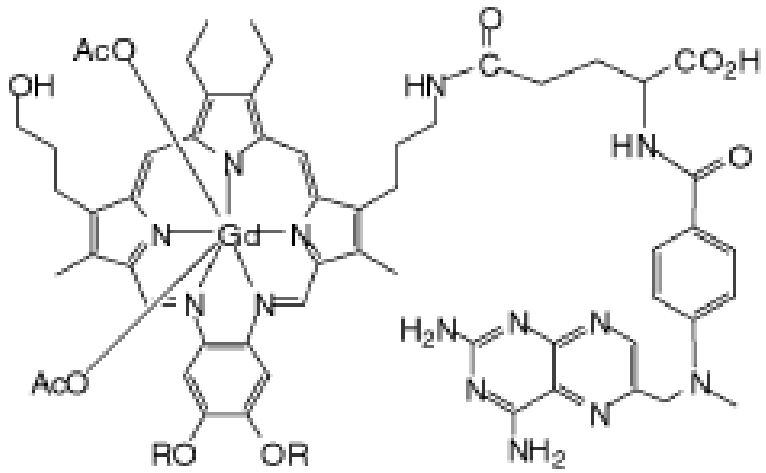
T **1998**, 54, 4151--4202 *Cancer research* **1981**, 41, 4606-4612

Porphyrin–drug conjugates as anticancer drugs



porphyrin–platinum complexes

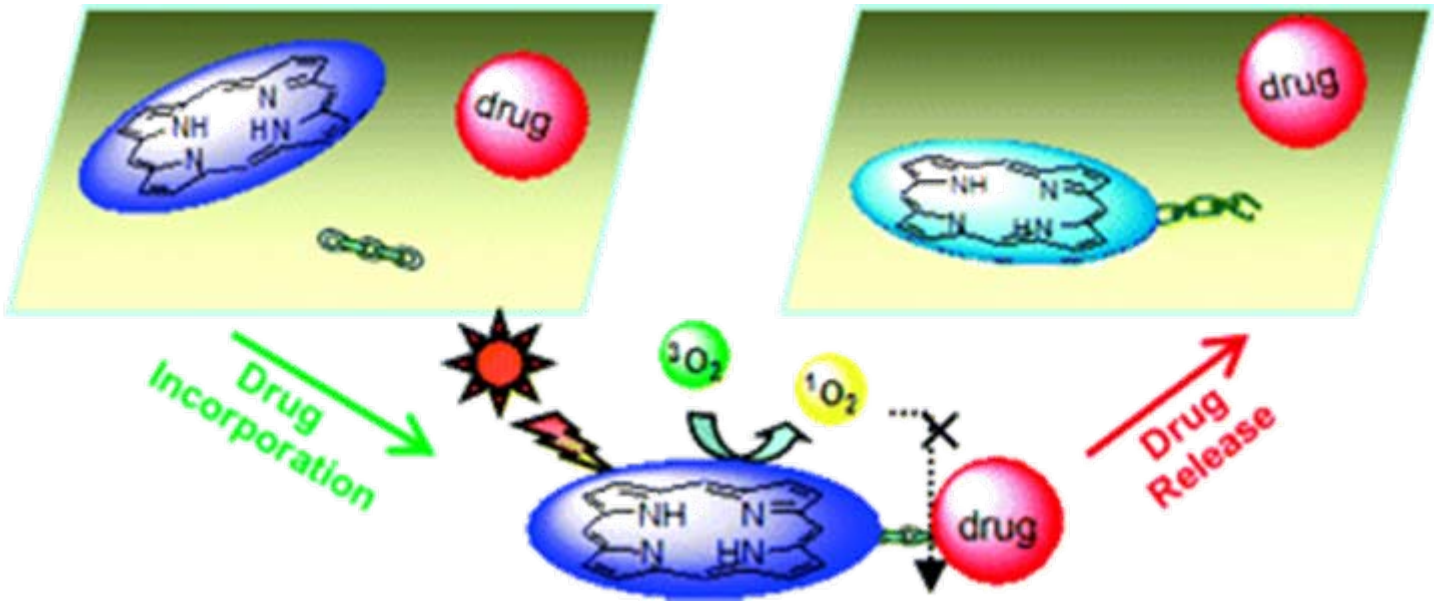
Inorganica Chimica Acta **2004**, 357, 4423–4451



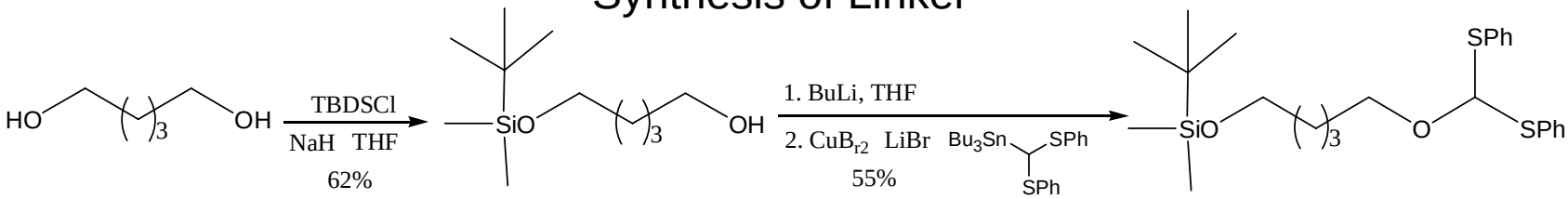
Texaphyrin-methotrexate conjugate

Pure appl.chem **2004**,76, 365-374

Site-Specific Prodrug Release Using Visible Light



Synthesis of Linker



J. Am. Chem. Soc., **2008**, 130 , 4236 -4237

Site-Specific Prodrug Release Using Visible Light

Advantages:

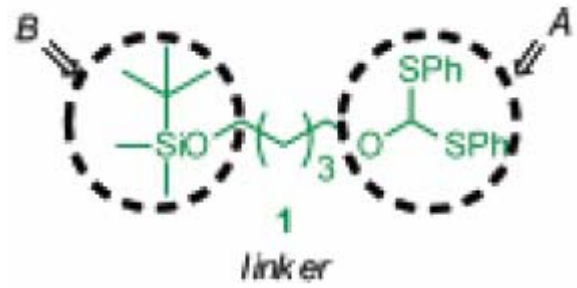
◆External and nonenzymatic activation providing more direct controls over drug release

◆Visible light between 650 to 800 nm can penetrate tissue effectively. Poor tissue-penetrating nature of UV light, less than 1 mm, hampers clinical utility of UV light triggerable prodrugs

◆ PK and clinical profiles of wellestablished photosensitizers using photodynamic therapy (PDT) can be as good reference points for new photosensitizer-drug complexes

◆Visible-light-activated photosensitization could convert triplet oxygen into singlet oxygen. **Singlet oxygen's [2 + 2] cycloaddition with double bonds can give carbonyl fragments**

Synthesis of Photosensitizer-Drug Complexes

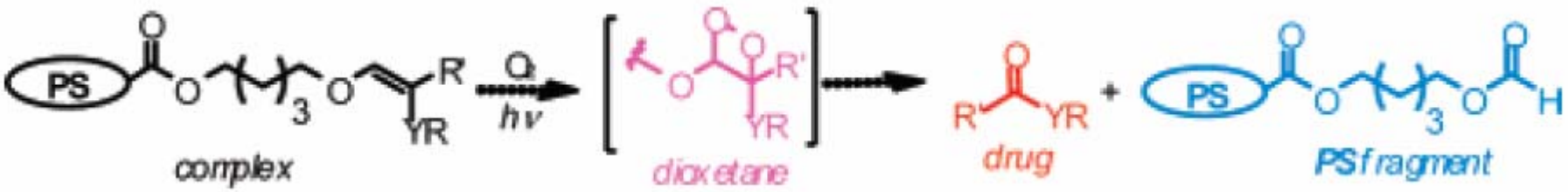


Y = O, N ;

PS-COOH = TPPAD or BPAD

	PS-COOH	YR	R*
2	TPPAD	OEt	n-Pr
3	TPPAD	OEt	Ph
4	TPPAD		
5	TPPAD		
6	BPAD		
7	TPPAD		
8	BPAD		
9	TPPAD	NMe	Ph

Visible-Light-Triggered Drug Release



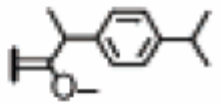
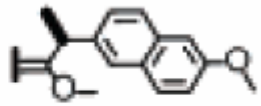
Linker is designed elaborately to ensure the desired [2 + 2] chemoselectivity during photooxygenation

Avoid competing ineffectively with the "ene"reaction and the [4 + 2] cycloaddition in singlet oxygenation of alkenes

Basis:
Highly electron-rich alkenes (heavily substituted by hetero groups) tend to direct the attack of the singlet oxygen to the side of the double bond by cis-directing effect

Result Analysis

entry[a]	complex	solvent	concn (mM)	time (min)	yield by NMR[b] (%)	yield by GC[c] (%)
1	**2Z**	C_6D_6	7	4	93	94
2	**2Z**	$CDCl_3$	3	3	91	>95
3	**2Z**	$CDCl_3/CD_3OD = 4:1$	4	3	93	>95
4	**2Z**	CD_3COCD_3	4	8	>95	>95
5[d]	**2Z**	CD_3COCD_3	5	60	>95	>95
6	**3Z**	C_6D_6	3	1	>95	91
7	**4Z**	C_6D_6	10	3	94	90
8	**5Z**	C_6D_6	15	2.5	92	>95
9	**6Z**	C_6D_6	4	6	94	>95
10	**7Z**	C_6D_6	8	7	88	>95
11	**8Z**	C_6D_6	7	3	>95	86
12	**2E**	$CDCl_3$	2	1	35[e]	33
13	**9**[f]	C_6D_6	8	5	>95	88

	PS-COOH	YR	R'
2	TPPAD	OEt	n-Pr
3	TPPAD	OEt	Ph
4	TPPAD		
5	TPPAD		
6	BPAD		
7	TPPAD		
8	BPAD		
9	TPPAD		Ph

- **Entries 1 to 4: solvent-independent visible-light-triggered drug release**
- **Entry 5: Confirmed the involvement of singlet oxygen in drug release because a singlet oxygen quencher (DABCO) was added to severely hamper the progression of the photooxygenation of 2Z**
- **Entries 6 to 11: photosensitizer can be flexible**
  Z-configured suppressed the "ene" reaction and the [4 + 2] cycloaddition
- **Entries 12: 2E gave the [2 + 2] cycloaddition products in only 35% yield**

Summary

Establishing a proof-of-principle visible light photodynamic prodrug system

Providing superior controls over the location and the onset of drug release

Site-specifically delivering esters and amides prodrugs

Flexible system - both the linker and the photosensitizer can be rationally modified or functionalized

PK and clinical profiles of wellestablished photosensitizers as good reference points for new photosensitizer-drug complexes

Synergistic therapeutic effect