Site-Specific Prodrug Release Using Visible Light

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Prodrug approaches are widely used in drug discovery, and the release of the parent drugs is generally through enzymatic activation and can be site-specific when unique activating enzymes and appropriate chemical environment are present at the target site. An external and nonenzymatic activation providing more direct controls over the course of drug release would be attractive. Herein, we report a novel site-specific prodrug system, in which visible light is employed to trigger drug release.

UV light triggerable prodrugs have been reported. However, the poor tissue-penetrating nature of UV light, less than 1 mm, hampers their clinical utility. In fact, only visible light between 650 to 800 nm can penetrate tissue effectively, and some photosensitizers with a strong absorption band within this range have been developed as photomedicines using photodynamic therapy (PDT). The chemical basis of PDT relates to the ability of the visible-light-activated photosensitization to convert normal triplet oxygen into singlet oxygen, which reacts with various biomolecules to cause cell modification or death. Taking advantage of the reactivity of singlet oxygen, especially its [2 + 2] cycloaddition with double bonds to ultimately give carbonyl fragments via a dioxetane intermediate, Breslow and co-workers have developed photocleavable cyclodextrin carriers for photosensitizers. Using the similar photosensitization—singlet oxygenation—dioxetane decomposition trilogy, we envisioned that a “photodynamic” prodrug system could be engineered to release drugs bearing carbonyl functionalities.

In our system, a drug bearing a carbonyl group is incorporated onto the periphery of a photosensitizer, by a linker, to furnish a sensitizer–drug complex. The carbonyl group of the drug becomes part of the double bond linkage. After systemic administration, selective irradiation at the diseased site by visible light triggers the photosensitizing moieties of the local complex to generate singlet oxygen, which then migrates and oxidatively cleaves the olefin linkage to release the drug (Scheme 1). Due to the fact that the [2 + 2] cycloaddition generally competes ineffectively with the “ene” reaction and the [4 + 2] cycloaddition in singlet oxygenation of alkenes, our major challenge was the elaboration of an olefin linkage to ensure the desired chemoselectivity during photooxygenation. Highly electron-rich alkenes, such as those heavily substituted by hetero groups, have been reported to favor the [2 + 2] mode. Furthermore, hetero substituents tend to direct the attack of the singlet oxygen to the side of the double bond, a phenomenon known as the “cis-directing effect”, which can be used to secure the [2 + 2] selectivity if that side of the olefin lacks an abstractable allylic hydrogen. Based on these considerations, a 1,2-dihetero substituted alkene, preferably in Z-configuration, presents itself as an ideal olefin linkage for our system. These species can be readily generated from esters or amides by a recently reported alkoxymethyleneation methodology using a titanium carbene complex.

A linker was designed to have functional groups (A and B) at either end of a spacer arm (Scheme 1). A is a dithioorthoformate to alkoxymethylenate carbonyl-bearing drugs, while B is a silyl-protected hydroxyl to esterify carbonyl-bearing photosensitizers. Simple alkyl chains or complex structures like steroids can be used as spacers to fine-tune the pharmacokinetic (PK) profile of the complexes.

As proof-of-principle, linker I was readily prepared by a three-step synthesis from 1,5-pentandiol (Scheme 2). Simple esters (aliphatic, aromatic and lactone) and amides as drug mimics and methyl esters of NSAIDs (ibuprofen and naproxen) were connected with photosensitizers of a tetraphenylporphyrin monoacid derivative (TPPAD) or benzophenylporphyrin monoacid derivative (BPAD, verteporfin analogue) to give complexes 2 to 9, comprising both Z- and E-isomers (Scheme 2).

Photoirradiation of the final complexes was carried out in NMR tubes at room temperature using filtered visible light. Progress of the reactions was monitored and quantified by NMR and GC with internal standardization. Since dioxetanes decompose instantly at the injection temperature (220 °C), GC offers the advantage of showing the total amount of releasable drug from the complex. The step-by-step NMR spectra of the photoirradiation show the rapid decay of the starting complex, accompanied by the increase of the released drug and the remaining dioxetane. Signals of the porphyrin and released drug and the remaining dioxetane. Signals of the porphyrin backbone are barely changed as the photooxygenation took place.
The high yields of the visible-light-triggered drug release were solvent-independent, as evident by the photooxygenation of 2Z in solvents of varied polarity (Table 1, entries 1 to 4). The involvement of singlet oxygen in drug release was confirmed as the progression of the photooxygenation of 2Z in deuterated acetone was severally hampered when 1,4-diazabicyclo[2.2.2]octane (DABCO), a singlet oxygen quencher, was added (entry 5). Quantitative and rapid releases of ethyl benzoate, \( \delta \)-valerolactone, methyl esters of ibuprofen, and naproxen were observed in the photooxygenation of 3Z to 8Z (entries 6 to 11). It is remarkable that the competing “ene” reaction and the \([4+2]\) cycloaddition were completely suppressed in these reactions. The equal efficiency of drug release from either TPPAD or BPAD based complexes indicated the choice of drug release exclusively on the side chain, leaving the chromophore intact. The dioxygenamine intermediate was confirmed by ESI-MS.

In conclusion, a proof-of-principle photodynamic prodrug system has been established, which allows for rapid drug incorporation and highly efficient drug release upon visible light irradiation. The advantages of this system are multifold: (1) the external, light-triggered activation would provide superior controls over the location and the onset of drug release; (2) the system itself is sufficiently flexible that both the linker and the photosensitizer can be rationally modified or functionalized; (3) as shown here, well-established photosensitizers such as verteporfin can be directly utilized so that their PK and clinical profiles can serve as good reference points for new photosensitizer-drug complexes; (4) since esters and amides provide some of the most common prodrug derivatives, our system provides a solution to deliver these prodrugs site-specifically; (5) from a PDT perspective, bifunctional drugs can be developed to have the complementary drug simultaneously released at the site where PDT is performed, to bring about a synergistic therapeutic effect.

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Supporting Information Available: Experimental details and compound characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

Table 1. Visible-Light-Triggered Drug Release

<table>
<thead>
<tr>
<th>entry</th>
<th>complex</th>
<th>solvent</th>
<th>concn (mM)</th>
<th>time (min)</th>
<th>yield by NMR (%)</th>
<th>yield by GC (%)</th>
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<tr>
<td>1</td>
<td>2Z</td>
<td>CDCl(_3)</td>
<td>7</td>
<td>4</td>
<td>93</td>
<td>94</td>
</tr>
<tr>
<td>2</td>
<td>2Z</td>
<td>CDCl(_3)</td>
<td>3</td>
<td>3</td>
<td>91</td>
<td>&gt;95</td>
</tr>
<tr>
<td>3</td>
<td>2Z</td>
<td>CDCl(_3)/CD(_3)OD = 4:1</td>
<td>4</td>
<td>3</td>
<td>93</td>
<td>&gt;95</td>
</tr>
<tr>
<td>4</td>
<td>2Z</td>
<td>CDCl(_3)/CD(_3)COCD(_3)</td>
<td>4</td>
<td>8</td>
<td>&gt;95</td>
<td>&gt;95</td>
</tr>
<tr>
<td>5</td>
<td>2Z</td>
<td>CD-CD-COCD(_3)</td>
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<td>60</td>
<td>&gt;95</td>
<td>&gt;95</td>
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<tr>
<td>6</td>
<td>3Z</td>
<td>CDCl(_3)</td>
<td>3</td>
<td>1</td>
<td>&gt;95</td>
<td>91</td>
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<tr>
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<td>CDCl(_3)</td>
<td>10</td>
<td>3</td>
<td>94</td>
<td>90</td>
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<td>CDCl(_3)</td>
<td>15</td>
<td>2</td>
<td>92</td>
<td>&gt;95</td>
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<tr>
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<td>6Z</td>
<td>CDCl(_3)</td>
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<td>CDCl(_3)</td>
<td>8</td>
<td>7</td>
<td>88</td>
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<tr>
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<td>1</td>
<td>35(^e)</td>
<td>33</td>
</tr>
<tr>
<td>13</td>
<td>9(^e)</td>
<td>CDCl(_3)</td>
<td>8</td>
<td>5</td>
<td>&gt;95</td>
<td>88</td>
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</table>

\(^a\) All the experiments were carried out at room temperature, and yields are based on conversions \( \geq 95\). \(^b\) Yield of the total \([2+2]\) cycloaddition products. \(^c\) Yield of total releasable esters or amides. \(^d\) DABCO (6 equiv) was added. \(^e\) “ene” products were generated in 56\% yield. \(^f\) A ZIE = 4:1 mixture was used as starting materials.

References


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