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# Photo-controlled release of fipronil from a coumarin triggered precursor

Zhenhong Gao [a], Pengtao Yuan [a], Donghui Wang [b], Zhiping Xu [a], Zhong Li [a], Xusheng Shao [a,*]

[a] Shanghai Key Laboratory of Chemical Biology, School of Pharmacy, East China University of Science and Technology, Shanghai 200237, China
[b] College of Life Sciences, Peking University, Beijing 100871, China

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ABSTRACT

Developing efficient controlled release system of insecticide can facilitate the better use of insecticide. We described here a first example of photo-controlled release of an insecticide by linking fipronil with photoresponsive coumarin covalently. The generated coumarin-fipronil (**CF**) precursor could undergo cleavage to release free fipronil in the presence of blue light (420 nm) or sunlight. Photophysical studies of CF showed that it exhibited strong fluorescence properties. The CF had no obvious activity against mosquito larvae under dark, but it can be activated by light inside the mosquito larvae. The released Fip from CF by blue light irradiation *in vitro* retained its activity to armyworm (*Mythimna separate*) with $LC_{50}$ value of 24.64 μmol $L^{-1}$. This photocaged molecule provided an alternative delivery method for fipronil.



Direct delivery of pesticide has many uncontrolled adverse effects such as high toxicity, large application amount and decomposition of active ingredients.[1] To address these issues, methods for conditionally controlling release are needed, since controlled release of pesticides has substantial advantages including enhanced bioavailability, prolonged length of activity, improved physiochemical properties, reduced phytotoxicity and lowering of the environment secondary effects.[1] The previously-developed pesticide-release systems took advantage of nanotechnology,[1,6,7] microencapsulation[2–4,8] and polymer science.[5,9] These methodologies provided slow release of active ingredients, but the release process cannot be easily regulated at spatial and temporal resolution. In this context, a more precise controlled technology is desired to the spatiotemporal control over the pesticide release.

The recent fast-developing photo-triggered technology provides possibilities for controlled release which promises better remote, temporal and spatial control than conventional methods.[10,11] To realize such a photochemical process, a photo-labile protecting (photocaging) group (PPG) is usually used to covalently couple with the molecule being released, generating a caged precursor that can undergo cleavage under light.[12] The advent of photocaged conception creates great opportunities for spatiotemporal manipulation of a variety of processes in chemical, biological and material science.[10,13] Excellent reviews include light-triggered catalysts,[14] organic surfaces,[15] biomedical materials[13] and photocontrol of cellular chemistry[16–18] or gene expression.[19,20] Normally, such photoresponsive system has blocked function in the caged state and can be irreversibly activated upon irradiation to release the functional ingredients. Due to the encouraging advances, this technology thus far has been well applied for the photo-regulated release of bioactive molecules, such as neurotransmitters, enzyme substrates, pheromones, lipids, and second messengers.[10,21,22]

Turning attention back to agrochemical science, the combination of PPG with pesticide provided a promising release method with pioneering work done by N. D. Pradeep Singh et al. Example applications included photo-controlled release of 2,4-D herbicide,[23–25] plant growth regulators,[26] sex pheromone[27] and plant hormone salicylic acid.[28] However, photo-controlled release of an insecticide molecule has not yet been described.

Fipronil (Fip) is a phenylpyrazole insecticide widely used for seed-treatment, sanitary pest control and animal health, but its application was strictly restricted in some districts due to high toxicity to non-target wildlife.[29–32] Fipronil is stable at dark in mildly acidic to neutral water, but is prone to undergo photolysis or biological oxidation or reduction *in vivo* to form desulfinyl, sulfone, sulfide or amide metabolites.[29,33] Its half-life time of photodegradation is 0.33 day (Florida summer sunlight).[34] In a specific case, the persistence of fipronil reduced significantly when exposed to sunlight.[35] As a consequence, two attempts were previously made for controlling release of fipronil using microencapsulation of in situ polymerization or biocompatible silica nanocapsules. Herein, we demonstrated a photochemical method that releases insecticidal fipronil using pulses of light, which enables more precise control and real-time activation. The fipronil was caged using

* Corresponding author.
*E-mail address:* shaoxusheng@ecust.edu.cn (X. Shao).

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coumarin as photoremovable protecting group. The caged compound is stable and would release fipronil only upon irradiation.

The existence of an amino group in fipronil provides the possibility for the installation of PPG. Covalent linking of a PPG with an active molecule is a straightforward way to generate a photocaged molecule. Many factors should be taken into account in designing such a photocaged molecule, such as the solubility, stability, light wavelength, efficiency of desire cleavage reaction, avoidance of photodamage/photodegradation and the toxicity of cleavage product of caging group.[36] Most importantly, a PPG must be subtly selected. Various PPGs have been developed in the past decades. The well-studied and frequently used PPGs include *o*-nitrobenzyl, coumarin-4-ylmethyl and *p*-hydroxylphenacyl.[36] The coumarin phototriggers attract the most attentions recently due to their superior features, such as longer absorption wavelength, large molar coefficients, fast release rates, improved stability, high biocompatibility and fluorescent emitting.[36] Considering the substituent effects on this cages, 7-dialkylamino substituted coumarin was selected here since it has the absorption band at biologically benign region. Thus, the diethylamino-coumarin-4-ylmethyl caged fipronil was prepared for our subsequent investigations (Fig. 1).

The photoresponsive **CF** was prepared from a three-steps route starting from commercially available 7-(diethylamino)-4-methyl-2*H*-chromen-2-one **1** (Fig. 1). Oxidation of **1** with Selenium dioxide and the following reduction by Sodium borohydride ($NaBH_4$) afforded alcohol intermediate **2** (Cou). Alcohol **2** then condensed with *p*-nitrophenyl chloroformate to furnish intermediate **3** under catalysis of DIPEA. Finally, **3** reacted with Fip at presence of DMAP to present the target caged product **CF**.

With successful obtaining of coumarin-caged fipronil, its photophysical properties were studied first. The absorption and emission maximum wavelength, molar absorption coefficient, Stokes shift and fluorescence quantum yield of **CF** were summarized in Table 1. In UV–Vis spectra, **CF** features two obvious absorption bands

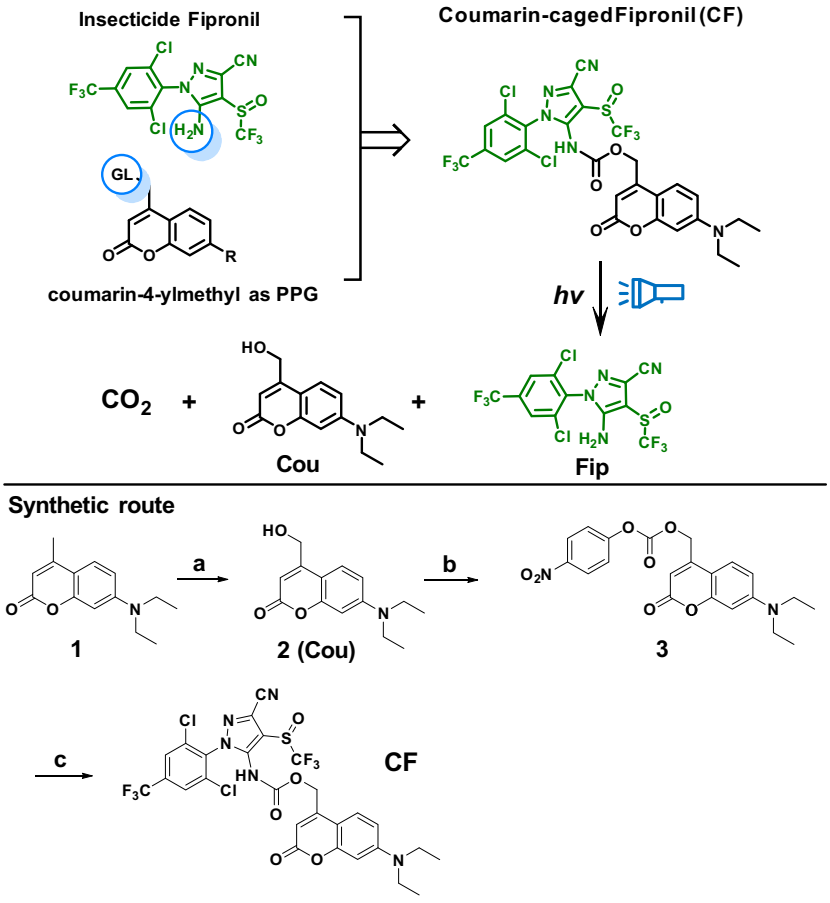


**Fig. 1.** Molecular design of photoresponsive coumarin-caged fipronil and its synthetic route. Reagents and condition: a) 1. $SeO_2$, Ar, *p*-xylene, reflux, 53 h; 2. $NaBH_4$, $CH_3OH$, r. t., 4 h, 26%. b) *p*-nitrophenyl chloroformate, DIPEA, Ar, dry dichloromethane, r. t., 20 h, 50%. c) fipronil, DMAP, Ar, dry dichloromethane, r. t., 48 h, 24%.

**Table 1**
UV–Vis and fluorescence data for **CF**.

| Compound | UV–Vis | | Fluorescence | | |
|---|---|---|---|---|---|
| | $\lambda_{max}$[a] (nm) | $\varepsilon$[b] ($10^4 M^{-1} cm^{-1}$) | $\lambda_{max}$[c] (nm) | Stokes shift[d] (nm) | $\varphi_f$[e] |
| CF | 390 | 1.6 | 475 | 85 | 0.2 |

[a] Maximum absorption wavelength.
[b] Molar absorption coefficient ($M^{-1} cm^{-1}$) at the wavelength of 390 nm.
[c] Maximum emission wavelength.
[d] Difference between wavelengths of the maximal emission and excitation.
[e] Fluorescence quantum yield.