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Synthesis of a Diverse Series of Phosphacoumarins with Biological Activity

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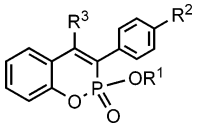
ABSTRACT



We have developed a general and efficient approach to a diverse series of phosphacoumarins as analogues of coumarins with various biological activities, and the inhibitory activity of the synthesized phosphacoumarins against the enzyme SHP-1, a protein tyrosine phosphatases, was tested. Some of them showed moderate to good efficiency.

Coumarins are members of the class of compounds called benzopyrones and have gained considerable synthetic and pharmacological interest for a long time because of their various biological activities, such as antitumor activity,[1] anti-HIV activity,[2] antioxidation,[3] vasorelaxant activity,[4] tumor necrosis factor-α (TNF-α) inhibition,[5] antimicrobial activity,[6] serine protease inhibition,[7] and anticancer activity.[8] In the research field of coumarins, 4-OH coumarin and its derivatives have shown many biological activities, such as inhibition of gyrase B,[9] HIV integrase,[2c] and protein kinase.[10] On the other hand, organophosphorus compounds continue to receive widespread attention due to their ubiquity in biological systems[11] and their potential to serve as novel pharmaceuticals.[12] Phosphonic acids and their derivatives have often exhibited biochemical activity similar to that of naturally occurring carboxylic acids and their derivatives,[13] so we thought that the phosphacoumarins as analogues of coumarins (Figure 1) might have potential biological activities similar to that of coumarins. Chen and Rodios's groups[14] have prepared phosphacoumarins through reaction of salicylalde-

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[||] Equal contribution to this work.

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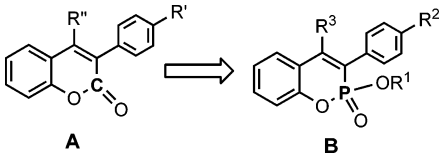
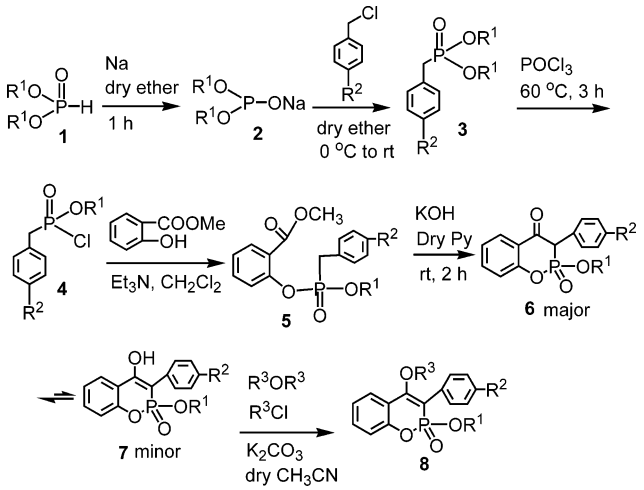


Figure 1. Coumarins (**A**) and the designed phosphacoumarins (**B**) (R′, R″, R^1, R^2, and R^3 are various substituents).

hyde with triethylphosphonoacetate. Unfortunately, only low-yield target products (not more than 21%) were obtained, and major products were phosphonocoumarins. To the best of our knowledge, there is not a general and efficient method for the synthesis of 4-substituted phosphacoumarins so far. Herein, we initiated a program to develop an approach to a diverse series of phosphacoumarins.

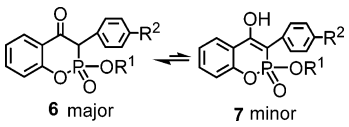
A synthetic route for 4-*O*-substituted phosphacoumarin derivatives is shown in Scheme 1. Reaction of *p*-substituted

Scheme 1. Synthetic Route of 4-*O*-Substituted Phosphacoumarins



benzyl chloride with sodium dialkyl phosphite (**2**), which was prepared from reaction of dialkyl phosphite (**1**) with sodium in dry ether, yielded **3** in 80−85% overall yields from **1** to **3**. Reaction of **3** with phosphoryl chloride produced **4** at 60 °C under nitrogen atmosphere. The excess of phosphoryl chloride and byproducts with low boiling point in the resulting solution were removed by reduced pressure, and the residue was the crude product **4**, which was used in the following reaction without further purification. Reaction of **4** with methyl salicylate produced enantiomers **5** in the presence of triethylamine. Overall yields of the two steps from **3** to **5** are 75−82%. KOH-promoted intramolecular cyclization of **5** in dry pyridine led to major keto-form (**6**) and minor enol-form (**7**) products in 85−90% yields (see Table 1). Cyclization of **5** is the key step during the whole process.

Table 1. Yields and Proportions of Cyclization Products (**6** and **7**) from **5**

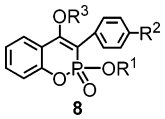


entry	6/7	R^1	R^2	yield (%)[a]	keto/enol[b]
1	**6a/7a**	CH_3	H	90	7.3:1.0
2	**6b/7b**	CH_2CH_3	Cl	85	9.3:1.0
3	**6c/7c**	CH_2CH_3	CH_3	85	2.5:1.0
4	**6d/7d**	CH_2CH_3	CN	88	7.7:1.0

[a] Isolated yields of **6** and **7**. [b] Determined by ^{31}P NMR in $CDCl_3$.

When acetic anhydride (R^3OR^3), methylsulfonyl chloride, diethyl phosphorochloridate, or *p*-toluenesulfonyl chloride (R^3Cl) was added to mixtures of **6** and **7** in dry acetonitrile in the presence of anhydrous K_2CO_3, ^{31}P NMR spectrscopy showed that **6** and **7** almost quantitatively transferred into the corresponding 4-*O*-substituted phosphacoumarins (**8**) at ^{31}P NMR 9−11 ppm, and pure products **8** were obtained in 82−96% yields (see Table 2) after isolation by silica gel

Table 2. Yields of 4-*O*-Substituted Phosphacoumarins



entry	8	R^1	R^2	R^3	yield (%)[c]
1	**8ae**	Me	H	$COCH_3$	92
2	**8be**	Et	Cl	$COCH_3$	95
3	**8ce**	Et	CH_3	$COCH_3$	90
4	**8de**	Et	CN	$COCH_3$	94
5	**8af**	Me	H	SO_2CH_3	96
6	**8bf**	Et	Cl	SO_2CH_3	94
7	**8cf**	Et	CH_3	SO_2CH_3	91
8	**8df**	Et	CN	SO_2CH_3	95
9	**8ag**	Me	H	DEP[a]	82
10	**8bg**	Et	Cl	DEP	84
11	**8ah**	Me	H	Ts[b]	97
12	**8dh**	Et	CN	Ts	95

[a] DEP = diethoxylphosphoryl. [b] Ts = *p*-toluenesulfonyl. [c] Isolated yields.

(12) For examples of phosphorus compounds as pharmaceuticals, see: (a) Kafarski, P.; Lejczak, B. *Curr. Med. Chem.* **2001**, *1*, 301. (b) Colvin, O. M. *Curr. Pharm. Des.* **1999**, *5*, 555. (c) Zon, G. *Prog. Med. Chem.* **1982**, *19*, 205. (d) Stec, W. J. *Organophosphorus Chem.* **1982**, *13*, 145. (e) Mader, M. M.; Bartlett, P. A. *Chem. Rev.* **1997**, *97*, 1281. (f) Kafarski, P.; Lejczak, B. *Phosphorus, Sulfur, Silicon Relat. Elem.* **1991**, *63*, 193.

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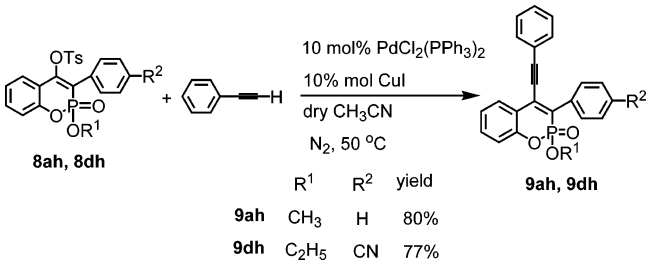
column chromatography. For example, reaction of **6d** and **7d** with acetic anhydride produced 4-*O*-acetyl phosphacoumarin **8de** corresponding to the ^{31}P NMR peak at 9.19 ppm, the pure product **8de** was obtained in 94% yield after purification.

We thought that phosphacoumarins conjugated with alkynes could be further utilized as precursors to construct even more complex molecules, so 4-alkynylphosphacoumarins were prepared through Sonogashira reaction as shown in Scheme 2. Reaction of **8ah** or **8dh** with phenyl acetylene

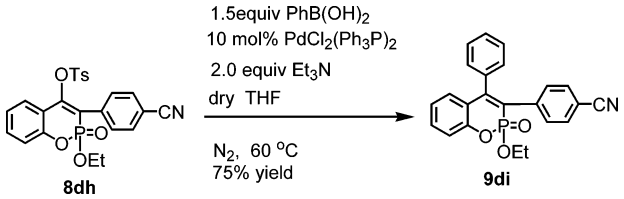
Scheme 2. Sonogashira Coupling of 4-Tosylphosphacoumarins with Phenylacetylene



in the presence of triethylamine and catalytic amounts of $PdCl_2(PPh_3)_2$ (10% mol) and CuI (10% mol) in acetonitrile at 50 °C produced **9ah** or **9dh** in 77% and 80% yields, respectively, after isolation by column chromatography on silica gel.

4-Phenylphosphacoumarin (**9di**) was also made as shown in Scheme 3. Reaction of **8dh** with phenylboronic acid in

Scheme 3. Suzuki Coupling of 4-Tosylphosphacoumarin with Phenylboronic Acid



dry THF produced **9di** in the presence of 10% mol $PdCl_2(PPh_3)_2$ and triethylamine at 60 °C under nitrogen atmosphere, and the pure compound **9di** was obtained in 75% yield after isolation by column chromatography on silica gel.

The structures of the synthesized compounds **6**−**9** were identified by the shifts and *J* values of ^{1}H, ^{13}C, and ^{31}P NMR spectroscopy (see Supporting Information).

In addition, 4-diethylphosphonooxyphosphacoumarins (**8ag** and **8bg**) can be important precursors and can be used to prepare 4-substituted phosphacoumarins such as 4-diethylphosphonooxycoumarins using organozinc reagents as partners of nickel-catalyzed cross-coupling reactions.[15] So these synthesized 4-*O*-substituted phosphacoumarins can be used as precursors of a phosphacoumarin library.

To probe whether the synthesized phosphacoumarins are of biological activities, we tested their inhibitory activity against the enzyme SHP-1, one of the protein tyrosine phosphatases (PTPs). Protein tyrosine phosphatases (PTPs) catalyze the hydrolysis of phosphotyrosyl (pY) proteins to produce tyrosyl proteins and inorganic phosphate. Specific and cell-membrane-permeable PTP inhibitors would likely provide such tools for studying the function of these enzymes. Aberrant action of PTPs is often linked to cellular dysfunction and implicated in a diversity of diseases including diabetes, obesity, autoimmune disease, infectious diseases, inflammation, cancer, osteoporosis, and neurodegeneration.[16] Thus, PTP inhibitors could also provide potential therapeutic agents against those diseases. As shown in Table 3, most of the phosphacoumarins showed certain inhibitory

Table 3. Inhibition Constants of the Phosphacoumarin Derivatives against SHP-1 (ΔSH2)

compound	K_i (μM)	compound	K_i (μM)
6a/7a	350	**8af**	130
6b/7b	600	**8bf**	730
6c/7c	510	**8cf**	280
6d/7d	570	**8df**	430
8ae	ND[a]	**8ag**	90
8be	620	**8bg**	10
8ce	820	**8ah**	60
8de	250	**8dh**	130

[a] ND: not detected.

activity, and compound **8bg** was the most potent inhibitor, with a K_i value of 10 μM. This represents the first example using the phosphacoumarins as membrane-permeable PTP inhibitors, which provides a new class of core structures for the further development of PTP inhibitors.

The synthesized phosphacoumarin derivatives may potentially have biological and medicinal activities similar to those of coumarin derivatives, but further studies are needed to confirm this possibility.

In summary, a general and efficient approach to a diverse series of phosphacoumarins has been developed. The methods could provide valuable routes to various phosphorus heterocycles and enrich the organic and medicinal chemistry of coumarins. The synthesized phosphacoumarin derivatives showed moderate to good inhibitory activity against SHP-1, which provides a lead structures for further design and development of novel PTP inhibitors as potential therapeutic reagents.

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Supporting Information Available: Detailed experimental procedures; characterization data for compounds **5**−**9**; ^{1}H, ^{13}C, and ^{31}P NMR spectra of compounds **6**, **7**; and ^{1}H and ^{13}C NMR spectra of compounds **8** and **9**. This material is available free of charge via the Internet at http://pubs.acs.org.

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