行政院國家科學委員會專題研究計畫成果報告

設計並合成以環丙烷為主體之限制構形/剛性分子及其應用
Design and Synthesis of Cyclopropane-based Conformation-restricted/rigid Molecules and their Applications

計畫編號：NSC 93－2113－M－029－002－
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一、中文摘要

在本年度執行「設計並合成以環丙烷為主體之限制構形/剛性分子及其應用」計劃中的第一部份為設計及合成誘導型限制構形化合物當作氨基醯合成酵素的潛在抑制劑，由於此研究在國際間之競爭相當激烈，當本計劃經國科會核准通過後，又有新型、效果更好之抑制劑被報導出來[1]，因此我們重新執行成效評估後，決定將重點放在本計劃的第二部份，即合成一系列的剛性構形衍生物 dioxabicycle 和 dioxazobicycle 及其應用研究。

本計劃的第二部份又分為四小項分別為：(I) 設計並合成以 dioxobicycle 為骨架之衍生物作為潛在光化學變色物及其光變色性質測試之探討。(II) 設計並合成以 dioxazobicycle 為骨架之衍生物作為潛在的溶劑致變色物探討。(III) 設計並合成以 4-羥基香豆素為主要架構的潛在光化學變色物及其光致變色性質測試之探討。(IV) 設計並合成 diazabicycle 化合物及其切割 DNA 之能力研究。此四小項之研究皆已順利完成。

其中第 I 項，亦即：「設計並合成以 dioxobicycle 為骨架作為潛在的光化學變色物及其光變色性質測試之探討」，我們成功地合成十幾個 dioxobicycle 之衍生物，並鑑定其經照光後生成之產物，其中一衍生物成功地應用於維他命 K 2,3-環氧乙烷還原酵素之抑制，此結果已發表於國際期刊。[2]

其中第 II 項，亦即：「設計並合成以 dioxazobicycle 為骨架之衍生物作為潛在的溶劑致變色物探討」，我們合成出數個具有溶劑致變色性之化合物，唯其結構待 X-ray 結晶作最後之確認。

其中第 III 項，亦即：「設計並合成以 4-羥基香豆素為主要架構的潛在光化學變色物及其光致變色性質測試之探討」，雖然合成出之化合物目前看來並無光致變色性質，但由 NMR 光譜結果顯示，橋頭硝基苯之構形有被固定之現象，我們將對此一有趣現象做進一步研究。

其中第 IV 項，亦即：「設計並合成 diazabicycle 化合物及其切割 DNA 之能力研究」，雖然合成出之化合物目前看來並無光致變色性質，但卻有切割 DNA 之能力，這些研究成果正撰寫成論文發表於國際期刊當中。[3]

關鍵詞：光致變色性，溶劑致變色性，DNA 切割試劑。

Abstract

In our efforts in design and synthesis of potential photochromic, solvatochromic colorants as well as DNA cleavage agents, we have focused on the following four separate topics as proposed in the grant application:

(I).Design and synthesis of a potential photochrome based on the 9-cyano-2,8-dioxa-1-phenylbicyclo[3.3.1]nona-3,6-diene backbone and its photochromic property study.

(II).Design and synthesis of potential photochromes based on the 9,9-dimethyl-8-azo-2-oxa-1-phenylbicyclo[3.3.1]nona-3,6-diene backbone and their solvatochromic property studies.

(III). Design and synthesis of 4-aminocoumarin based potential photochromes and their photochromic property studies.

(IV).Design and synthesis of diazabicycles as potential DNA cleavage agents.

We have finished all of our proposed studies. Some of the results have been published on international journals;[2] some have been submitted for publication.[3]

Keywords: Vitamin K 2,3-epoxide reductase, solvatochromic colorant, acidichromic colorant.

二、緣由與目的

The photochromism has recently attracted attention both in academic and industry due to the fact that organic photochromic compounds have been recognized to have widespread applications in various photonic devices such as erasable memory media and optical switching. Photochromism is defined as a reversible phototransformation of a chemical species between two forms having different absorption spectra. During the photoisomerization, not only the absorption spectra but also various physicochemical properties change, such as the refractive index, dielectric constant, oxidation/reduction potential, and geometrical structure. These molecular property changes can be applied to various photonic devices, such as erasable optical memory media and photooptical switch components. Although the first finding of photochromic compounds can be traced back to the middle of the 19th century, they are still awaiting their time to go on the stage of photonic devices. The erasable memory media developed so far have been inorganic materials which utilize the magnetooptic effect or phase change as the basis for optical recording. Organic materials have not been considered as viable candidates because of insufficient reliability. However, the situation is dramatically changing. The worldwide acceptance of CD-R (compact disk-recordable), which uses organic dyes as the memory medium, has changed the situation, and photochromic materials are now anticipated as a promising candidate for erasable memory media of the next generation. In optical fiber switch devices, organic polymers, which change their refractive index by thermal heating, are currently used as the switching components. These components can be replaced with photochromic materials, which change their refractive index by photoirradiation. In addition to the above mentioned applications, organic photochromic materials also find many possible applications in different areas like preparing various photoswitchable biomaterials and enzyme active site modifications studies, as well as in photoisomerizable enzyme inhibition studies.

In this proposal, we will focus our efforts in design, synthesis and evaluation of novel dioxobicycle, oxazobicycle and diazobicycle derivatives as potential photochromes on the following four separate topics:

(I).Design and synthesis of a potential photochrome based on the

9-cyano-2,8-dioxa-1-phenylbicyclo[3.3.1]nona-3,6-diene backbone and its photochromic property study.
(II).Design and synthesis of potential photochromes based on the 9,9-dimethyl-8-azo-2-oxa-1-phenylbicyclo[3.3.1]nona-3,6-diene backbone and their solvatochromic property studies.
(III). Design and synthesis of 4-aminocoumarin based potential photochromes and their photochromic property studies.
(IV).Design and synthesis of diazabicycles as potential DNA cleavage agents.

三、結果與討論

In part I, we have successfully synthesized various dioxobicycles, as illustrated in Schemes 1. The two-step preparations started with condensation of acetophenone with 2-hydroxybenzaldehyde, and subsequent dehydration to give the flavylium salt . Coupling of flavylium salt with 4-hydroxycoumarin in methanol and water as co-solvents afforded the desired dioxobicycle. Preliminary UV irradiation experiments suggested that some of the compounds exhibited photochromic behavior. Their UV spectram have been measured and irradiation products have also been characterized.

In part II, several dioxazobicycic derivatives have been synthesized by the similar procedure described in part I, except that 4-hydroxycoumarin was replaced with 4-aminocoumarin, as shown in Scheme 2. These compounds exhibit positive solvatochromic behavior, although the structure of the compound needs to be further confirmed by X-ray crystal studies.

In part III, a novel dioxazobicyclic derivative was prepared in 5 steps as shown in Scheme 3. It started with dehydration of anisidine **11** with 4-nitrobenzaldehyde in the presence of $MgSO_4$ to give imine **12a**. The imine **12a** was then reacted with isobutyraldehyde using $Yb(OTf)_3$ as a Lewis acid catalyst in THF/H_2O for 15 h to afford 1,2,3,4-tetrahydroquinoline **13a**. Subsequent selective methylation on nitrogen of amino alcohol **13a** will be accomplished by treatment of **13a** with methyl iodide and dry potassium carbonate in acetonitrile at room temperature overnight to furnish the tertiary amine **14a**. Final coulping of alcohol **14a** with 4-aminocoumarin in the presence of p-TsOH in 1,2-dichloroethane at 80 ^{o}C generated the target compound **15a**. The X-ray crystal structure of **15a** is shown in Figure 1. Although this compound did not show the expected photochromic behavior so far, the conformation of the nitrophenyl group on the bridgehead of seemed to be restricted, according to proton NMR studies.

In part IV, several diazobicycles have been prepared by the similar procedure described in part III, as shown in Scheme 4. The synthesized compounds were then evaluated by agarose and high resolution polyacrylamide gel electrophoreses for their DNA cleavage properties, as shown in Figures 2 and 3 The preferential cleavage sites consist of single or recurring sequence comprising the purinic triplets 5'-AGG-3' or 5'-AGA-3'.

四、計劃成果自評

As far as the proposed studies are concerned, we are satisfactory with what we have accomplished in the past year for the second project, especially for the DNA cleavage agents. We have submitted our results to the journal *Chemical Communications* for publication. Moreover, in part I, the design and synthesis of a conformation-restricted vitamin K-2,3-epoxide reductase inhibitor has also been published on *Bioorganic & Medicinal Chemistry Letters* this year (2005).[2] We

are currently writing the manuscripts of part I and II results for publication on international journals.

五、參考文獻

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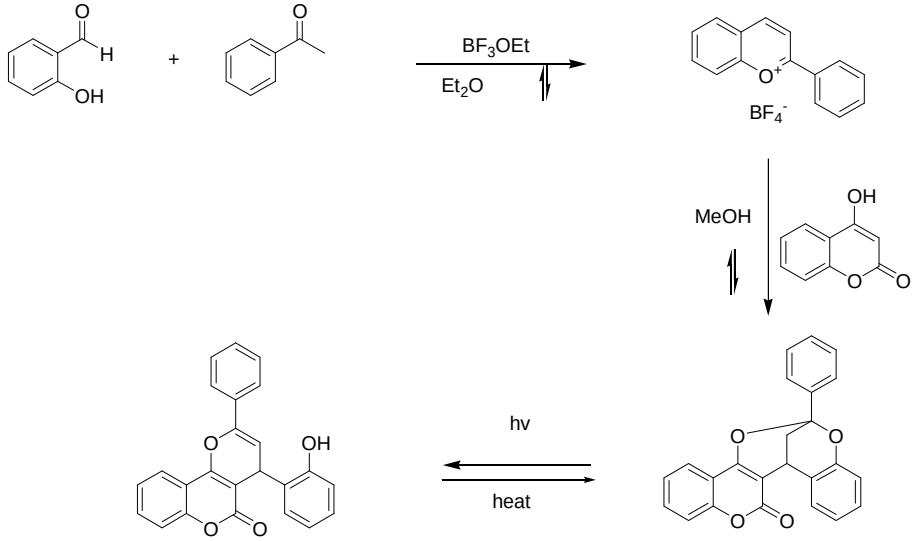
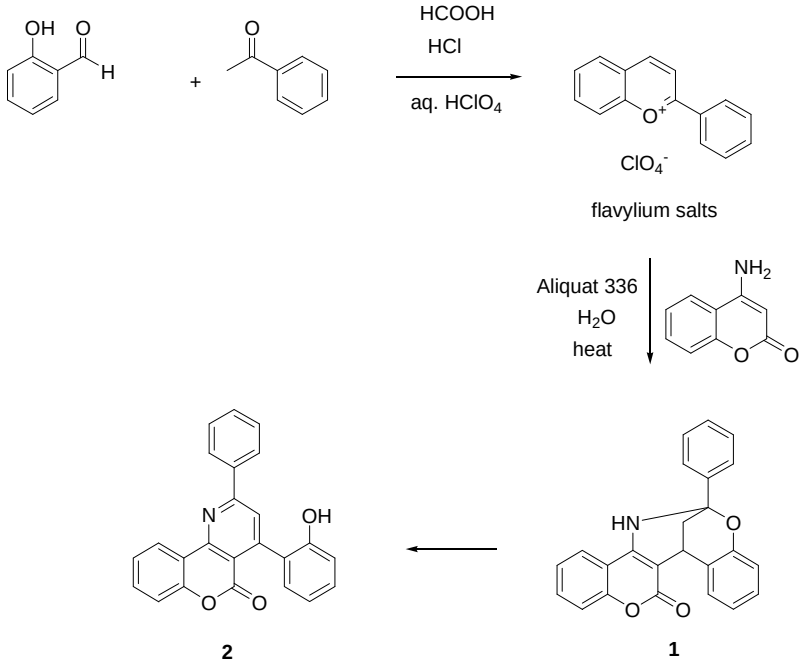
2. Chen,D. U.; Kuo, P. U.; Yang, D. Y. *Bioorg. Med. Chem. Lett*. **2005**, *15*, 2665–2668.
3. Gau, Y. H.;Yang, C. H.; Leung Sheh, L.; Yang, D. Y. Troger's base derivatives, a novel class of sequence-selective DNA cleavage agents, submitted to Chem. Comm.

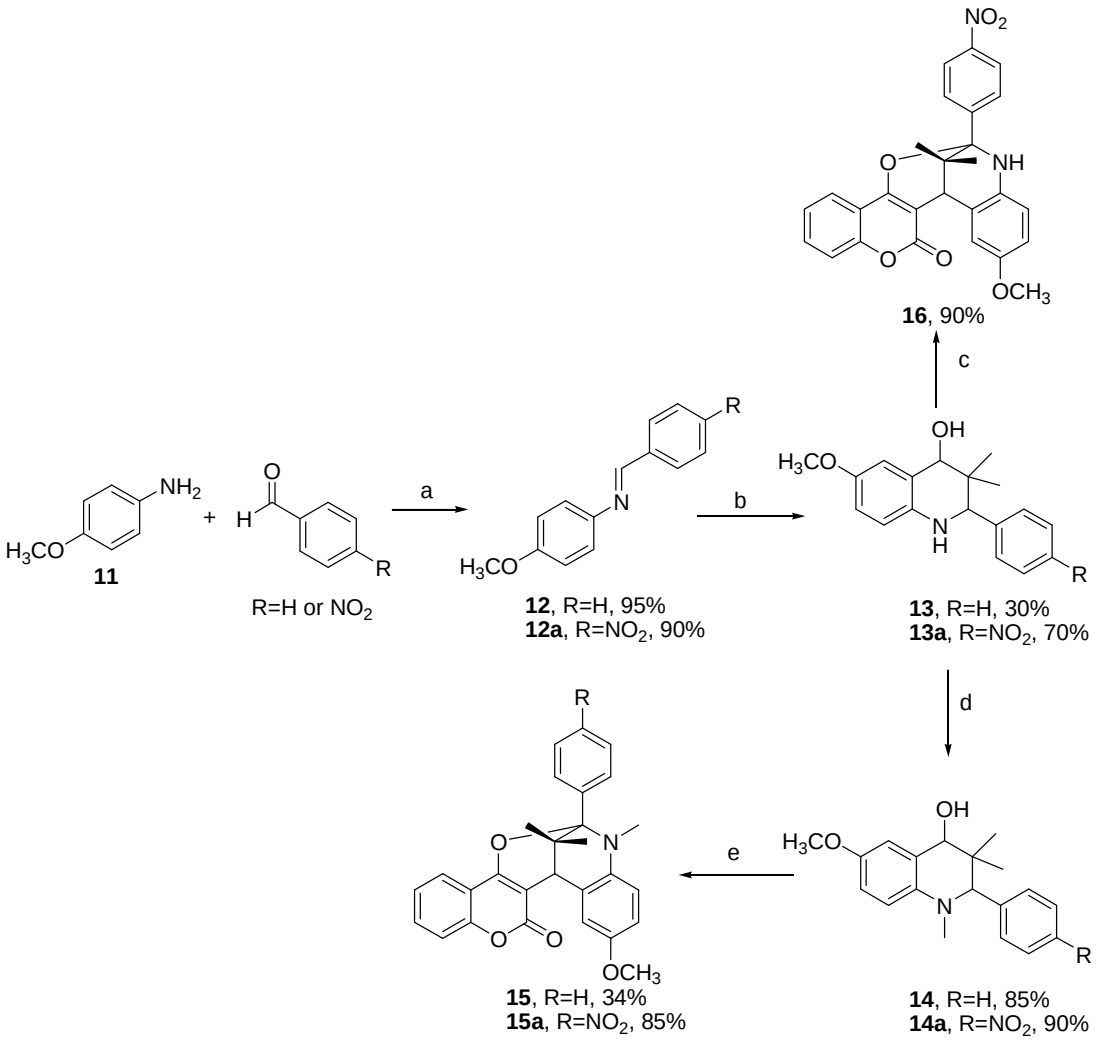
六、圖表



Scheme 1. Preparation of dioxobicycle and its photochromic behavior.



Scheme 2. Preparation of dioxazobicycle **2** as a solvatochromic colorant.



Scheme 3. Reagents and conditions: (a) $MgSO_4$, CH_2Cl_2, rt; (b) isobutyraldehyde, $Yb(OTf)_3$, H_2O, THF, rt; (c) 4-hydoxycourmarin, *p*-TsOH, CH_2ClCH_2Cl, 80 ^oC; (d) CH_3I, K_2CO_3, CH_3CN, rt; (e) 4-hydoxycourmarin, *p*-TsOH, CH_2Cl_2, 80 ^oC.

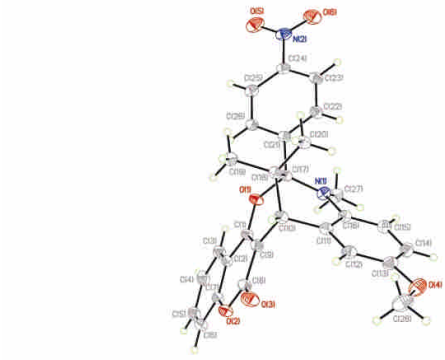
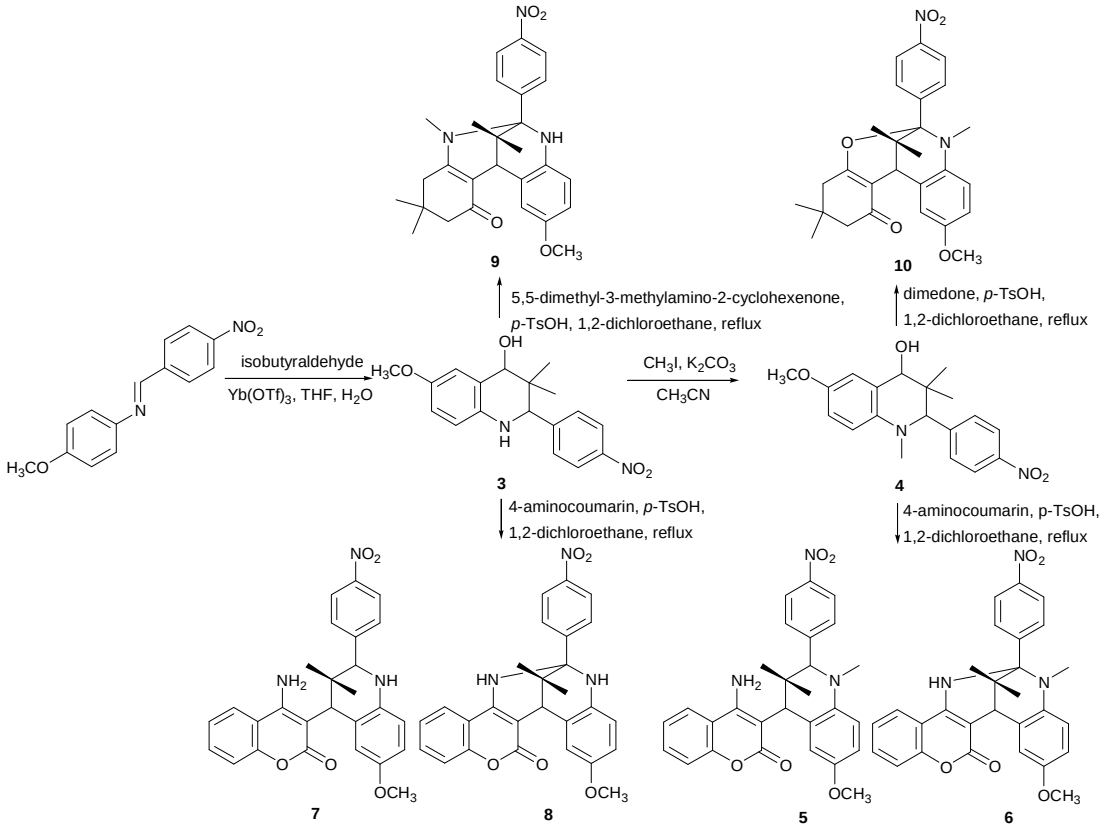


Figure 1. X-ray crystal structure of **15a**.



Scheme 4. Preparation of heterobicycles **5**-**10**.

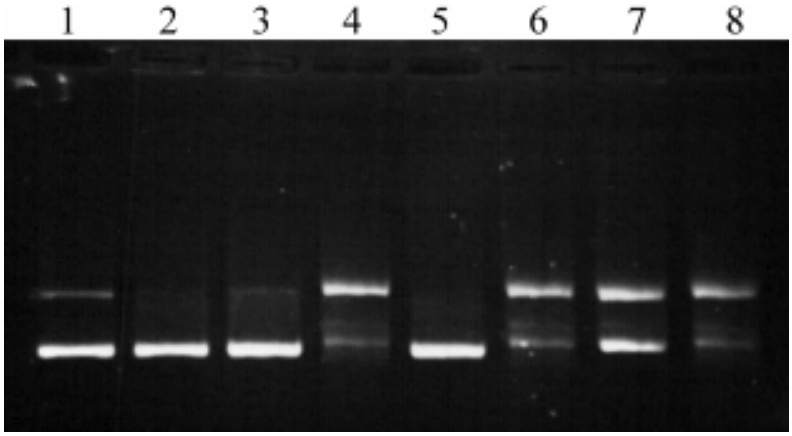


Figure 2. Nicking of supercoiled pBR322 DNA induced by Troger's base derivatives (500 μM) after incubation at 65 °C for 30 min as monitored by agarose gel electrophoresis. The upper band represents the open-circular form, and the lower band the supercoiled form. Lane 1: DNA alone in 10 mM Tris buffer, pH 8. Lane 2: DNA in 10% DMSO/10mM Tris buffer, pH 8. Lane 3-8: DNA incubated with heterobicycles **7**, **8**, **5**, **6**, **9**, **10** in 10% DMSO/10 mM Tris buffer, pH 8, respectively.

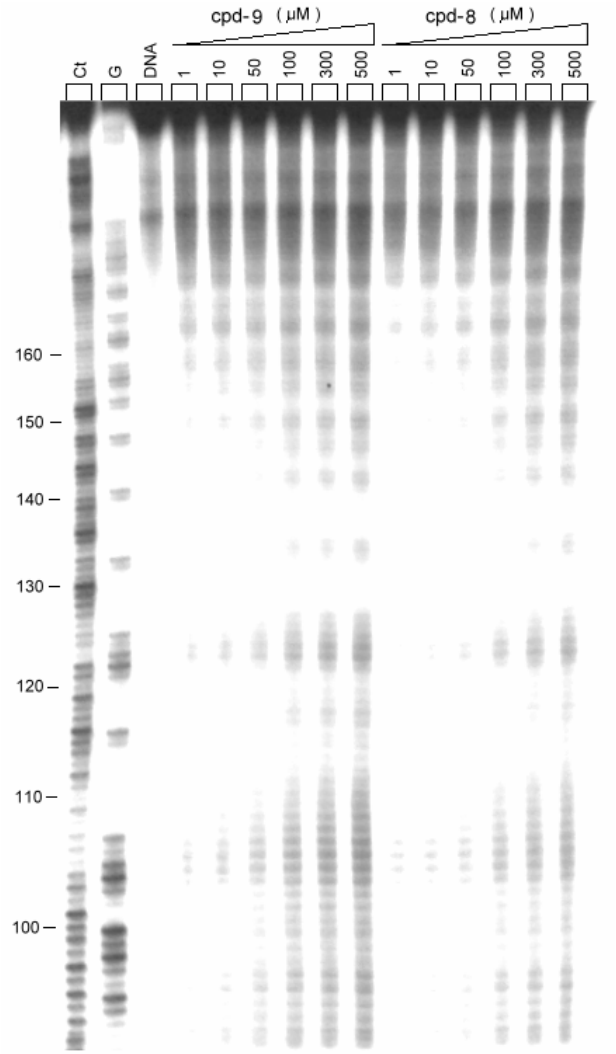


Figure 3 Autoradiograph showing sequence-selective cleavage of 5'-^{32}P-labeled 158-mer DNA duplex induced by Troger's base derivatives. Heterobicycles **8** and **9** were incubated with DNA for 30 min at 65 °C. G represents Maxam-Gilbert purine sequencing tracks and Ct is a DNase I digestion control lane.