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NSF-Funded Green Drug Discovery Research Program Based on a 90MHz NMR Spectrometer

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Mini Review

My ongoing research is focused on green Diels-Alder nanosynthesis of bioactive chalcones [1] derived from medicinal plants endemic to Kenya [2-5]. The versatile Diels-Alder [4+2] cycloaddition [6] is an enviable asset in the organic chemist's toolbox because it triggers the simultaneous setting of asymmetric centers, ring(s), and functional groups. Cong and co-workers [7] were the first to report the use of silver nanoparticle (AgNP) catalysts in the Diels-Alder total synthesis of the cytotoxic chalcone-based natural product panduratin A. The poorly reactive but electron-rich *trans*-2'-hydroxychalcone was used as a dienophile. Their initial studies revealed that *trans*-2'-hydroxychalcone and 1-phenyl-3-methylbutadiene in the presence of a mixture of 30 mol % $AgBF_4$ and 10 mol % Bu_4NBH_4 gave the desired [4+2] cycloadduct in 98% yield as a single Regio isomer. Conversions ("yields") and the *endo/exo* ratios were calculated based on 1H-NMR integration. Catalytically active AgNPs were fixed onto chromatography-grade silica gel in simple steps: A 3:1 $AgBF_4$/Bu_4NBH_4 supernatant in CH_2Cl_2 was stirred with silica gel for three hours at 25°C. The resulting light brown silica-supported AgNPs catalyzed the cycloaddition of acetylated chalcone and the labile diene (*trans*-β-ocimene) affording the desired endo cycloadduct (panduratin A) in 98% yield. Panduratin A and its regioisomer (1'R,2'S,6'R)-2-hydroxyisopanduratin A) have been isolated [8] from the rhizomes of Thai ginger, *Boesenbergia pandurata*. Both compounds showed significant preferential cytotoxicity against human pancreatic PANC-1 cancer cells in nutrient-deprived medium.

In my research group, we have implemented successful nanosynthetic protocols [6-9] in the preparation of new [4+2] cycloadducts based on chalcones and dienes (Figure 1). The polar organic solvents used in the cycloaddition reaction [7] have been replaced with environmentally benign water, poly (ethylene glycol) (PEG), or ionic liquids (ILs). ILs were synthesized as described in the literature [10]. Breslow & Zhu [11] discovered that Diels-Alder reactions proceed faster in water (as high as 700-fold) and with a higher endo/exo selectivity than in organic solvents. The first study using ILs in Diels-Alder cycloaddition was the reaction of cyclopentadiene with two dienophiles (i.e., methyl acrylate and methylvinyl ketone) in ethylammonium nitrate ($[EtNH_3]$ $[NO_3]$) [12]. These cycloadditions lead to a mixture of exo and endo products with a preference for the endo product. We have synthesized various chalcones through green synthetic methods [13]. Additional chalcones were purchased from common chemical suppliers (e.g., Sigma-Aldrich) and used as dienophiles.

Hundreds of chalcone-containing natural products continue to be discovered each year [8]. Retro-Diels-Alder (rDA) [14] of bioactive chalcone-based synthetic and natural products containing cyclohexenyl nucleus has guided us in selecting the additional dienes [15]. We are currently evaluating how cycloadditions of chalcones and a range of mono-, di-, tri-, and tetrasubstituted dienes (Figure 1) affect the yields of reactions and bioactivities. Our potentially transformative Diels-Alder reactions are clearly bioinspired because the cycloadducts (Figure 1) are analogues of the bioactive prenylated chalcones natural products,

(-)-panduratin A and nicolaioidesin C [16]. A library of biologically relevant chalcone scaffolds generated from Diels-Alder reactions will be bio-tested against several biological targets (human cancer cell lines, *Caenorhabditis elegans, mosquitoes, Drosophila melanogaster, Mycobacterium smegmatis*, etc.) to decipher the structure-activity relationships (SAR).

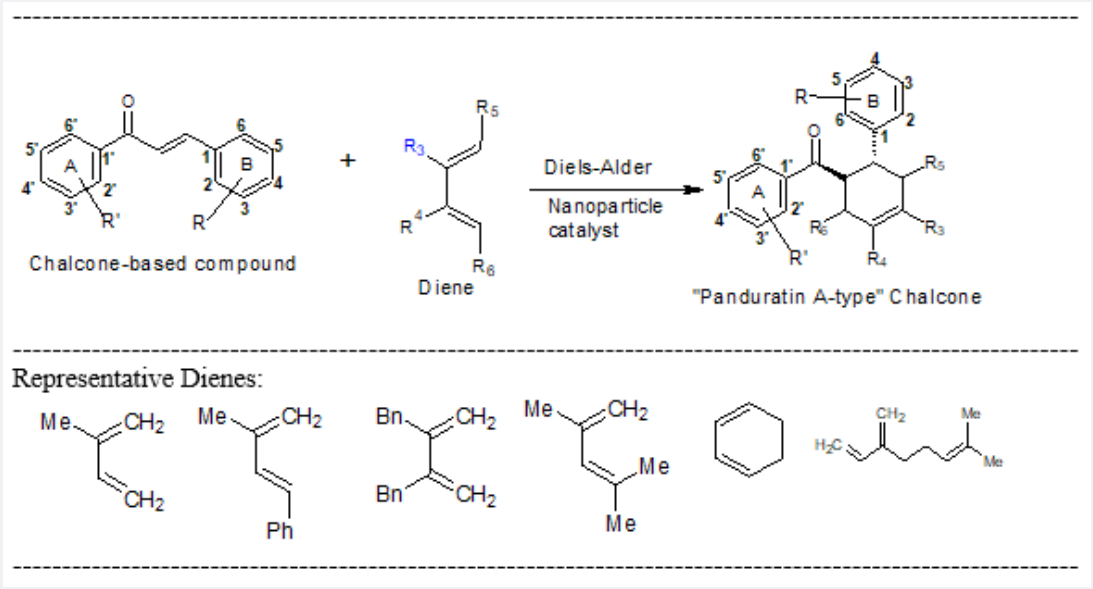

Figure 1: Diels-alder green nanosynthesis of chalcones.

This NSF-funded chalcone project is a minefield for generating interesting research data. Undergraduate and graduate students are already synthesizing the beautiful and inspiring "Pina's-type" [17] crystalline compounds of the anthocyanin family. They are learning important research skills including green nanosynthesis, chromatographic purification, and characterization of compounds using NMR spectroscopy. In our research, [18,19] we have used Anasazi's Fourier Transform (FT) [20] 90MHz NMR spectrometer [21] as a "workhorse" instrument for both research and teaching purposes. Despite the inherent drawbacks of low sensitivity and low resolution, the permanent magnet spectrometer can be used for a robust drug discovery project like ours. It is important to emphasize that the compound(s) of interest must be synthesized in gram quantities to reduce data acquisition time. Advantages of the permanent magnet are numerous including durability, low power consumption, user-friendly, ability to do various 1D/2D NMR experiments, and low maintenance (does not require cryogens, an NMR technician, etc.).

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