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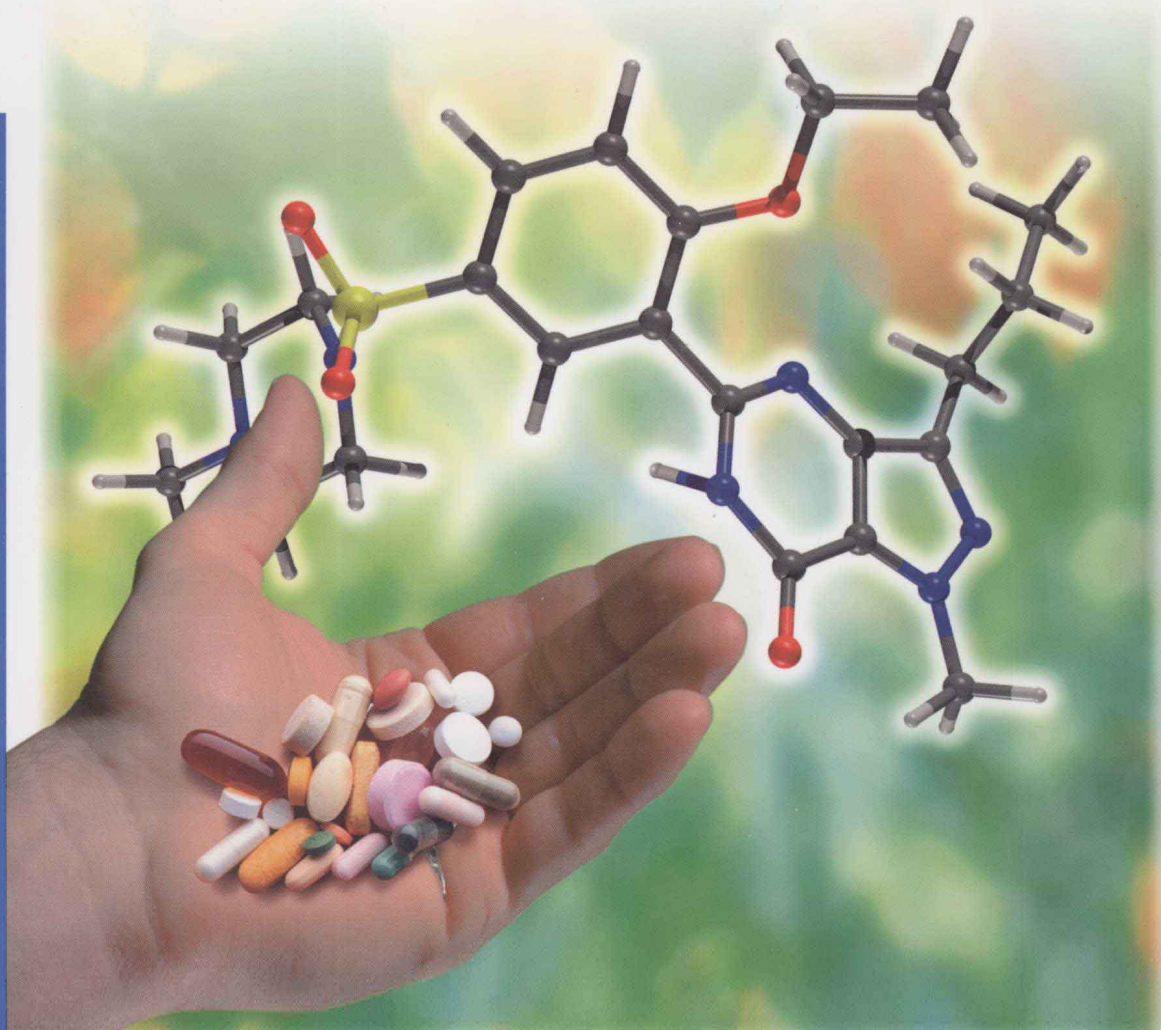
Green Chemistry in the Pharmaceutical Industry



Green Chemistry in the Pharmaceutical Industry

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Foreword

While we all recognize the value and benefits to mankind of the healing drugs that are used worldwide, we often take for granted how these precious materials are discovered and made. The expectations of modern society for improved safety, lower environmental impact, more sustainable practices, and lower energy use at a fair cost place tremendous demands and responsibility on us all, and the complex task of manufacturing pharmaceuticals has to balance current knowledge and the robustness and durability of the chemical and biological processes used with these regulatory pressures and escalating costs. Nevertheless, chemists and production engineers owe it to their profession and to future generations to adopt a charter which promotes the 'Green' agenda.

I therefore welcome this new text, which promotes improved and sustainable practices. It demonstrates clearly how through innovation, understanding, and commitment one can effect change and drive standards even higher. The chapters discuss all the relevant issues of the day as they relate to solvents, energy, new technologies, metrics, and lifecycle appreciation. The articles describing illustrative processes used by the major practitioners for producing worked-up pharmaceutical products amply demonstrate the attitude and advantages that can accrue by a more reflective and committed approach. Clean chemo-enzymatic processes alone, with continuous flow methods and improved optimization protocols, are beginning to make an impact and are certainly trends for the future. Our ability to better and more rapidly profile for impurities and evaluate alternative routes is leading to new opportunities and creating better understanding.

The future image of the industry and society's respect for it will hinge upon a clear demonstration of its belief in and stewardship of the principles of Green Chemistry. Indeed, there is nothing more worthy than our desire to improve our ability to meet healthcare needs for the betterment of everyone through sustainable practices.

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Introduction to Green Chemistry, Organic Synthesis and Pharmaceuticals

Roger Sheldon

1.1
The Development of Organic Synthesis

The well-being of modern society is unimaginable without the myriad products of industrial organic synthesis. Our quality of life is strongly dependent on, *inter alia*, the products of the pharmaceutical industry, such as antibiotics for combating disease and analgesics or anti-inflammatory drugs for relieving pain. The origins of this industry date back to 1935, when Domagk discovered the antibacterial properties of the red dye, prontosil, the prototype of a range of sulfa drugs that quickly found their way into medical practice.

The history of organic synthesis is generally traced back to Wöhler's synthesis of the natural product urea from ammonium isocyanate in 1828. This laid to rest the *vis vitalis* (vital force) theory, which maintained that a substance produced by a living organism could not be produced synthetically. The discovery had monumental significance, because it showed that, in principle, all organic compounds are amenable to synthesis in the laboratory.

The next landmark in the development of organic synthesis was the preparation of the first synthetic dye, mauveine (aniline purple) by Perkin in 1856, generally regarded as the first industrial organic synthesis. It is also a remarkable example of serendipity. Perkin was trying to synthesize the anti-malarial drug quinine by oxidation of *N*-allyl toluidine with potassium dichromate. This noble but naïve attempt, bearing in mind that only the molecular formula of quinine ($C_{20}H_{24}N_2O_2$) was known at the time, was doomed to fail. In subsequent experiments with aniline, fortuitously contaminated with toluidines, Perkin obtained a low yield of a purple-colored product. Apparently, the young Perkin was not only a good chemist but also a good businessman, and he quickly recognized the commercial potential of his finding. The rapid development of the product, and the process to make it, culminated in the commercialization of mauveine, which replaced the natural dye, Tyrian purple. At the time of Perkin's discovery Tyrian purple, which was extracted from a species of Mediterranean snail, cost more per kg than gold.

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