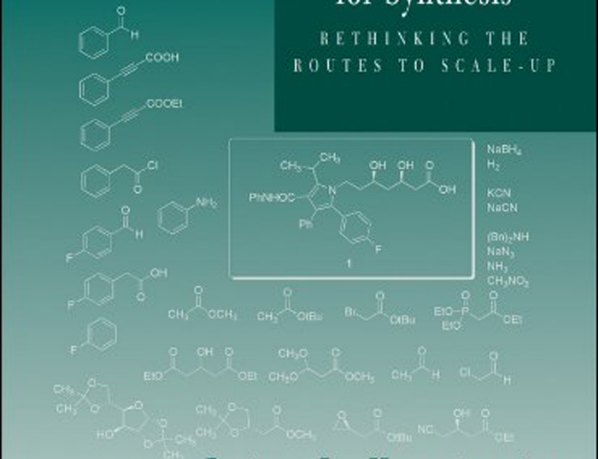
# Pharmaceutical Process Chemistry for Synthesis

## RETHINKING THE ROUTES TO SCALE-UP




*Peter J. Harrington*

WILEY

# PHARMACEUTICAL PROCESS CHEMISTRY FOR SYNTHESIS

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## Rethinking the Routes to Scale-Up

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# 1

# INTRODUCTION

## 1.1 INSPIRATION

This project was first conceptualized at a most unlikely place: at a visit to an *Inspiring Impressionism* exposition at the Denver Art Museum in 2008. The exhibition focused on the impressionists as students of earlier masters. They immersed themselves in these earlier masterpieces and then incorporated the insights they had gained and added their own techniques to convey the same subject matter in profound new ways. My 20 years as a process chemist at Syntex and Roche are much like the years the impressionists spent camped out in front of the works of the masters. The insights gained could be conveyed by presenting the theory and concepts of process research and development, but there are many well-worn reference books that collectively accomplish that objective. My experience has been that process chemistry is a roller-coaster ride, with tremendous highs and lows, where you learn theory and concepts, as needed, on the fly, from your colleagues and from those reference books (while meeting seemingly unattainable milestones and timelines). The aim of this book is to convey some of this experience by immersing the reader in the process chemistry of some of the most valuable pharmaceuticals we are fortunate to have available today. The masterpieces in this book are the top-selling drugs in the United States in 2007–2008. These are Lipitor®, Nexium®, Advair Diskus®, Prevacid®, Plavix®, Singulair®, Seroquel®, Effexor XR®, Lexapro®, and Actos®, all "blockbuster" drugs, generating more than $1 billion in revenue for their owners each year (Figure 1.1).[1]

I have no previous detailed knowledge of chemistry of most of these drugs. Why choose subject matter? First, there is currently intense i process chemistry of these drugs. Second, if I unpublished knowledge about these drugs, I wo by a secrecy agreement to discuss only inform in the public domain. Third, having no financia of these drugs or their process technology, I can ly (and refreshingly) objective. I am not "sellin of any target or proprietary technology to a pat a pharmaceutical manufacturer.

After a detailed review of the process c Plavix® and Nexium®, these will not be in process chemistry for Plavix® is omitted be published and patented process work and h knowledge of the manufacturing process for antiplatelet drug Ticlid® is an adenosine diphos receptor inhibitor with the same thienopyri Plavix® (Figure 1.2).[2] The process chemistry is omitted because Prevacid® and Nexium® h core and there is considerable overlap in t chemistry. Advair Diskus® has two active ing meterol and fluticasone. The process chemistry is included. The process chemistry of fluticaso better presented "in context" with the process other valuable steroids.

With this format, will this book touch on eve aspect of process chemistry in the pharmaceuti If you carefully studied the techniques used masterpieces at the art museum would you be

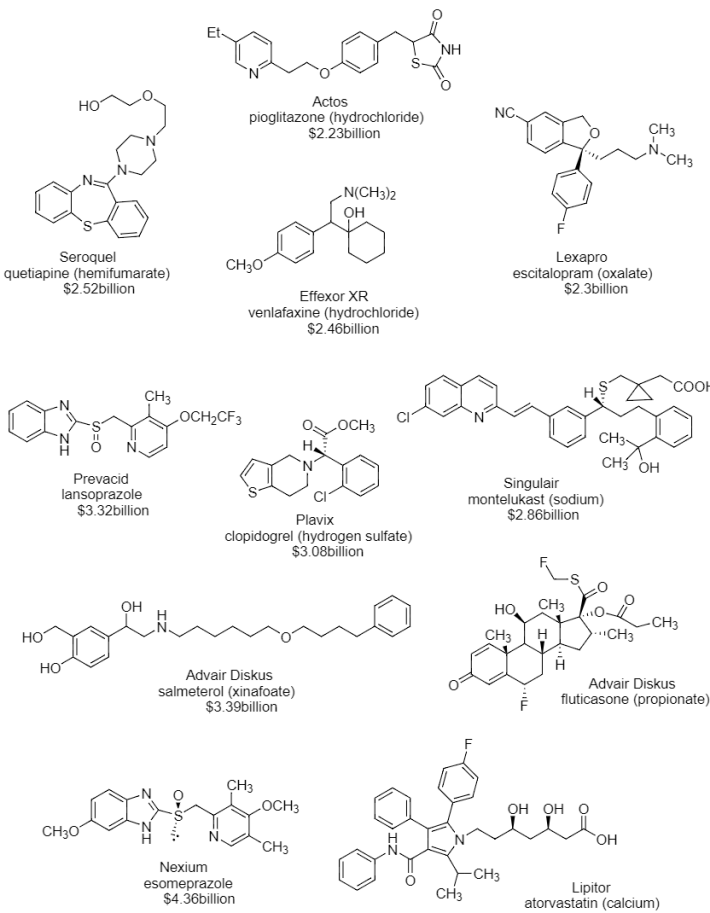
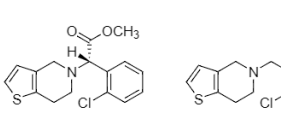



**FIGURE 1.1** The top-selling drugs in the United States in 2007.

expert? Most people would say no. Would you be better able to utilize the techniques in your own paintings? Most people would say yes. The scientific objective of this book is then twofold: to identify one "best" process for manufacturing these blockbuster drugs and to highlight the strategies and methodology that might be useful for expediting



and methodology that might be useful for expediting the process research and development of the blockbusters of the future.

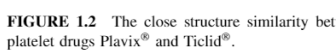


**FIGURE 1.2** The close structure similarity bet
platelet drugs Plavix® and Ticlid®.