Practical Studies for Medicinal Chemistry—An Integrating Approach for Developing Countries

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reviewed by Paul Erhardt

Every once in a while, we are blessed by the arrival of a seemingly ordinary book that upon purview of just its first few pages, quickly turns into a "must read." *Practical Studies for Medicinal Chemistry* is one of these books. Although written with Latin America and less-developed countries in mind, its broad appeal immediately becomes clear. All experiments are conveyed in English, with most also translated into Spanish or Portuguese. But beyond this universal readability, it is the book's high potential to impact favorably upon education within the field of medicinal chemistry that truly causes it to shine so brightly. Historically, medicinal chemistry has relied upon chemistry courses to expose its budding practitioners to laboratory experiences. Thus, this book represents a first of its kind by its provision of exercises that are representative of medicinal chemistry and often interdisciplinary in nature. Furthermore, it arrives at a time when health science education in general has come to focus more on categorization of its exploding informational base rather than on the rigors of quantifying its long-standing, fundamental principles. Thus, this book also represents a breadth of fresh air as it goes "back to [firmly establish the credentials that will always remain critical for practitioners of medicinal chemistry into] the future."

A total of 41 exercises are arranged in 6 chapters: I. Physicochemical Properties; II. Quantitative Structure-Activity Relationships; III. Molecular Modeling; IV. Toxicity Studies; V. Drug Synthesis; and, VI. Natural Products. These practical experiments in medicinal chemistry do not require expensive starting materials and generally depend only upon low-cost instrumentation. They have been provided by university researchers from 10 countries and are accompanied by statements pertaining to appropriate safety precautions. Some of the exercises are preceded by excellent general lectures of the topic across several pages of text, while all are adequate in their succinct experimental details and referenced descriptions of the concepts and equations associated with the basic principles that are being investigated. Although it is beyond the scope of this review to describe all of the exercises, I am compelled to convey a few of my own favorites while also covering at least one that is representative of each chapter.

The 12 experiments in Chapter I cover the gamut from drug: Dissolution; Lipophilicity; Solvent Effects; Inter- and Intra-Molecular Interactions; Aggregation; Ionization in Relationship to pKa/pH; Free Radicals and Antioxidants; Tautomers; and, Enantiomers and Diastereomeric Relationships. The importance of these parameters on a drug's ADME profile, as well as toward efficacy, is repeatedly emphasized across these studies. One of my favorites was Exercise I.2 Determination of Lipophilicity Substituent Constants of Sulfonamides by Means of Reversed Phase Thin-Layer Chromatography wherein the basic principles behind partition coefficients and π values are delineated while conducting normal and reversed phase TLC experiments. I should add that because of the practical description provided in this experiment, my labs are now making our own reversed phase plates rather than purchasing them from commercial suppliers, and we are more frequently trying them rather than relegating this veritable technique to a last resort attempt at achieving useful separations. And, finally for Chapter I, who could not like Exercise I.9 Determination of Specific Optical Rotation of Naproxen and its Sodium Salt to learn this fundamental technique for specifying compounds having asymmetric centers, while driving home the lesson that one must be very cautious about predicting optical rotation based upon structural similarity (the rotation for the eutomer of naproxen as its acid is +66° whereas that for its sodium salt is -11°).

As their titles imply, Chapters II (with 4 sections) and III (with 5 exercises), cover SAR in a quantitative and modeling capacity, respectively. Within Chapter II, the first section is instead an excellent lecture that serves as an introduction for both chapters. The remaining three sections provide useful exercises involving multivariable correlations that require basic statistical programs; with the last additionally providing a nice introductory lecture and exercise about SPARTAN software. Chapter III likewise begins with an excellent introductory lecture that utilizes the estrogen receptor as a case study and then moves on to exercises involving ChemDraw and Chem3D. Each of the next three sections begin with an excellent lecture and then provide exercises involving: III.2 Molecular Modeling Pro and Chem Site; III.3 PC Model; and, III.4 The Protein Data Bank and Protein Explorer. Given the increasing flow of biology collaborators who approach our own Center for Drug Design

and Development with a protein "target-wannabe" in-hand and in need of small molecule ligands to probe for its therapeutic utility, I found section III.4 to be extremely relevant for today's cutting-edge trends in target identification and validation wherein medicinal chemistry can play a pivotal role at this very early and critical stage of the overall process of drug discovery. Thus, III.4 was my obvious favorite across these two chapters. The final section, III.5, provides a practical QSAR exercise of curve fitting between pKa and electronic parameters for a series of phenols.

Chapter IV contains three exercises directed toward better appreciating drug toxicity. These encompass: IV.1 Perturbation of phospholipid bilayers assessed by X-ray diffraction, and of erythrocytes assessed by scanning electron microscopy (SEM); IV.2 Redox properties assessed by the MTT Assay, ELISA plate reading techniques and use of inverted microscopy (IM); and lastly, IV.3 Perturbation of the cell cycle using a colony-forming assay assessed by IM techniques. All of these experiments represent useful exposures for a medicinal chemist so as to further appreciate the associated principles, and to have a better dialogue with other investigators who have specialized in this important aspect of the drug discovery process. In addition, because this chapter flows immediately from the preceding two chapters, it should become clear to a student reader that beyond the pursuit of efficacy, there is a whole world of structure-toxicity relationships (STRs) that need to be explored and elaborated, and that at least some of the tools for that meritorious endeavor have just been laid-out for them.

Chapter V contains 11 exercises directed toward drug synthesis: Sulfasalazine (1 step); Sulfanilamide derivative (3 steps) and Reissert derivative from 6-Nitroquinolone (1 step); Latentiated derivative of Sulfathiazole (1 step); Propranolol (2 steps); Benzodiazepines (2 exercises involving first isolation and identification, and then quantification); Amino Acid derived small molecule Peptidomimetics (3 derivatives using parallel synthesis across 5 steps); Raloxifene (3 step convergent synthesis); Antihistamines (identification); Aspirin (1 step); Chalcones (11 derivatives using 1 step parallel synthesis). The composite of these experiments exposes students to a variety of synthetic strategies, reactions and reaction setups, workups and purification methods including to my own delight the veritable technique of crystallization, and finally, product characterization and quantification. All experiments are done having a drug theme in mind with the last exercise, in particular, culminating in a QSAR study where measured relative lipophilicity (TLC) is plotted versus MCF-7 cancer cell testing data (the latter being provided as a table of data for the student). One of my favorites was the latentiated analog experiment because it presented itself as an interesting twist on the prodrug theme wherein the latter in this case PREVENTS absorption so as to allow slow release for this intestinal antiseptic within the desired GI compartment. I also enjoyed the convergent synthesis and its product purification by crystallization, as well as the final parallel synthesis exercise that became coupled to a QSAR study.

Finally, chapter VI contains six exercises directed toward natural products: Extraction, purification, and derivatization of Podophyllotoxin; Solvatochromic studies of Coumarins; Antioxidant activities of polyphenolic compounds; Antioxidant activities in essential oils relative to levels of menthol determined by extraction; Extraction of Rutin; and, Analysis of Flavonoids in plants. These experiments cover a wide range of techniques such as: Extraction including solid-phase; Partitioning and solvent effects; TLC, column chromatography and HPLC; Derivatization; and, Structural characterization including common instrumentation like UV-Vis and NMR. My favorite is the exercise emphasizing derivatization of podophyllotoxin wherein chemical manipulations are performed to help a chemical characterization, in this case an epimerization reaction, oxidation of an alcohol to a ketone, and preparation of a phenylhydrazone adduct.

Upon winding-down this "must read," you're actually left "wanting for" yet another experiment. Simply put, these exercises are truly that entertaining in dialogue, and meaningful as an educational experience. As I mentioned in several places, we have adopted several of them into our own programs, some as part of an advanced training lab for undergraduates and early graduate students in medicinal chemistry, and others as new protocols within our daily practice of synthetic medicinal chemistry research and drug discovery. Such personal adoption is, in itself, probably the best testimonial for this book that one can offer. For those who may not want to purchase a published hardcopy, "thanks" to IUPAC, this complete book has open access and is freely available on line at: http://media.iupac.org/publications/cd/medicinal_chemistry.

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Macromolecular Symposia

Recent volumes of *Macromolecular Symposia* include contributions from recent IUPAC–sponsored conferences. See MS online at http://onlinelibrary.wiley.com/journal/10.1002/(ISSN)1521-3900.

Macromolecular Complexes

Macromolecular Symposia Vol 317–318, August 2012
edited by Vladimir Aseyev and Heikki Tenhu

This edition of *Macromolecular Symposia* includes presentations made at the 14th IUPAC International Symposium on MacroMolecular Complexes MMC-14, organized 14–17 August 2011 in Helsinki.

Various aspects of the complexes between macromolecules and metals have been studied for several decades. Mechanisms of the complex formation, as well as the structures of the complexes are an important research problem as such, but detailed knowledge of all these factors is needed for applications of the materials as catalysts, photoactive and electrically conducting materials. Macromolecular complexes are promising materials for high-performance energy devices. There are several examples of the use of macromolecular metal complexes in cancer therapy. Because macromolecules may be tailored to contain several functionalities they may be used to bind various toxic metals or organic substances from water. Owing to the remarkable advances in the methods of polymer synthesis, functional polymers can be used in advanced applications such as controlled drug delivery or delivery of active substances, from magnetic nanoparticles to human growth factor.

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Ionic Polymerization

Macromolecular Symposia Vol 323, January 2013
edited by Goy Teck Lim

This edition of *Macromolecular Symposia* collects 10 of the keynote and invited lectures presented at IP'11. These invited papers, authored by the leading researchers in the field of ionic (anionic and cationic) and radical polymerization, present research related to reaction control, reaction kinetics, chain functionalization, polymer morphology, and material characterization. The "International Symposium on Ionic Polymerization" (IP'11) was held 10–15 July 2011 in Akron, Ohio, USA.

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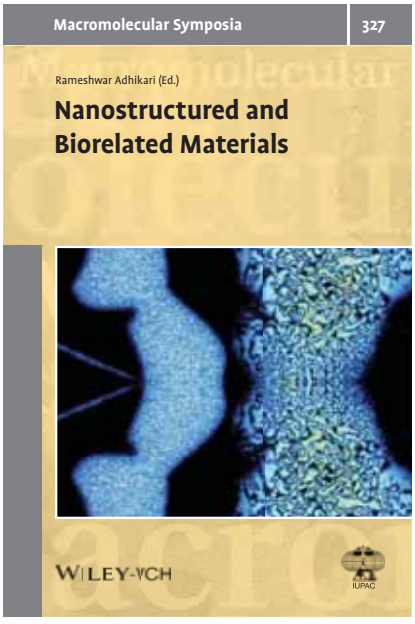

Nanostructured and Biorelated Materials

Macromolecular Symposia
Vol 327, May 2013
edited by Rameshwar Adhikari

This special issue of *Macromolecular Symposia* is devoted to new series of international conferences to be organized biannually in Kathmandu under the banner of "Kathmandu Symposia on Advanced Materials." KaSAM–2012 was held 9–12 May 2012 and hosted by the Nepal Polymer Institute (NPI) in association with Tribhuvan University, Kathmandu; Kathmandu University, Kavre and Universite´ de Rouen, Rouen (France) under the sponsorship of IUPAC. The conference series is aimed at strengthening the relationships among materials scientists from South Asian countries and the rest of the world. With the motto "CrossLinking Science and Virtues," KaSAM has the goal of promoting education and research in advanced materials in Nepal, with a particular focus on applied nanoscience and nanotechnology.

For a report on KaSAM 2012, see www.iupac.org/publications/ci/2013/3502/cc5_090512.html.

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