

Preface

As part of the *Topics in Current Chemistry* series, this volume, entitled “Chemistry of Opioids,” presents the progress made in opioid research over the past 5 years in the synthesis and pharmacology of opioids.

In 1803, morphine was first isolated by a German pharmacologist, Sertürner, and its structure was later determined. Since then, many research groups have tried to synthesize an ideal analgesic without addictive properties. In the course of those studies, a number of opioids were synthesized. Morphine has a unique 4,5-epoxymorphinan skeleton, which comprises five sequential asymmetric centers and a phenolic hydroxy group, a 4,5-epoxy ring, and a basic nitrogen. Due to this complex structure, early research groups could not synthesize morphine. Therefore, they tried to design drugs with simpler structures that could be manufactured as an industrial product. These trials produced many drugs, including pentazocine (benzomorphane), butorphanol, levorphanol (morphinan), pethidine (phenylpiperidine), fentanyl (anilino-piperidine), etc. However, these compounds could not provide analgesics without addiction. In 1975, when endogenous opioids were isolated, many researchers expected to be able to produce a drug without addictive properties, and many peptide derivatives were synthesized. Unfortunately, these opioid peptide mimetics also had addictive properties, despite the fact that they were derived from endogenous substances.

Nevertheless, opioid researchers did not give up their dreams. The first clue was that there were three types of opioid receptors (μ , δ , κ). This explained the diverse pharmacological effects of the many synthetic drugs. Many of the syntheses and pharmacologies of drugs produced before the early 1980s have been described in detail in two excellent books published in 1986, entitled *Opioid Analgesics; Chemistry and Receptor* and *Opiates*. After that, research focused on the κ and δ opioid receptor types. In the 1990s, extensive research was conducted in multiple efforts to synthesize κ selective agonists. However, there is no current book regarding the progress in the whole opioid field of δ - and κ -type selective ligands. In particular, in the 1990s, a vast number of U-50,488H (discovered by Upjohn Company) derivatives were synthesized to produce a nonaddictive drug. Unfortunately, these derivatives showed aversive effects (psychotomimetics), and development was suspended in the early stages, both as an analgesic and as an antipruritic

drug. Consequently, there have been no reports on U-50,488H derivatives in the last 5 years.

This book describes the progress made in the opioid field over the last 5 years with a focus on the work of 14 representative researchers in the opioid field.

The first chapter, "Recent Advances in the Synthesis of Morphine and Related Alkaloids," by Noritaka Chida, presents the racemic synthesis of morphine and related alkaloids by four research groups, and the chiral synthesis of those alkaloids by four research groups. This work has greatly contributed to progress in Organic Chemistry and Medicinal Chemistry.

The second chapter, "Opioids in Preclinical and Clinical Trials," by Hiroshi Nagase and Hideaki Fujii, provides a short survey of opioid ligands in development. They also give a detailed history of the drugs, TRK-851 (δ -antagonist) and TRK-820 (nalfurafine hydrochloride, κ -agonist), which were discovered by their team.

The third chapter, "Synthesis of 14-Alkoxymorphinan Derivatives and Their Pharmacological Actions," by Helmut Schmidhammer and Mariana Spetea, presents recent advances in the chemistry, ligand-based structure activity relationships, and pharmacology of 14-alkoxymorphinans.

The fourth chapter, "14-Amino-4,5-epoxymorphinan Derivatives and Their Pharmacological Actions," by John W. Lewis and Stephen M. Husbands, presents the recent extensive studies on the chemistry, structure–activity relationships, and pharmacology of 14-acylamino- and 14-alkylamino-derivatives.

The fifth chapter, "Nonpeptidic δ Opioid Agonists and Antagonists of the Diarylmethylpiperazine Class: What Have We Learned?" by Silvia N. Calderon, presents the major advances in the field of δ -opioid ligands and the extensive research performed to uncover the SAR of SNC-80 derivatives. Furthermore, synthetic methods are described for these compounds.

The sixth chapter, "Synthesis of Neoclerodane Diterpenes and Their Pharmacological Effects," by Kimberly M. Lovell, Katherine M. Prevatt-Smith, Anthony Lozama, and Thomas E. Prisinzano, describes the total synthesis of Salvinorin A and current research efforts focused on structure modifications of Salvinolin A derivatives.

The seventh chapter, "Synthesis of Novel Basic Skeletons Derived from Naltrexone," by Hiroshi Nagase and Hideaki Fujii, describes the many novel reactions that were discovered in the course of synthesizing naltrexone derivatives and the characteristics of those naltrexone derivatives. Some of the new reactions were expanded into general reactions.

The eighth chapter, "Twin and Triplet Drugs in Opioid Research," by Hideaki Fujii, presents opioid research that used dimer and trimer ligands as a tool for investigating opioid receptors. The dimer and trimer constructs were able to increase ligand activity and selectivity.

The ninth chapter, "3D-Pharmacophore Identification for κ -Opioid Agonists Using Ligand-Based Drug-Design Techniques," by Noriyuki Yamaotsu and Shuichi Hirono, presents a summary of previous efforts in identifying the pharmacophore in κ -opioid agonists and a proposal for a new model that encompasses the activities of all class κ -agonists.

I would like to thank all those who have contributed to making this volume a collection of expert articles. I hope that our readers find this volume a useful guide to the current progress in opioid research.

Tokyo, Summer 2010

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