
Preface

As part of the series *Topics in Heterocyclic Chemistry*, this volume titled *Bioactive Heterocycles II* presents comprehensive and up-to-date reviews on selected topics concerning flavonoids and anthocyanins in plants, and heterocycles such as bioactive phenothiazines, phenoxazines, and related compounds. The volume is separated into two sections mainly concentrating on these two topics.

There are abundant and diverse flavonoids with carbohydrates and lipids, alkaloids (betalain alkaloids and other alkaloids), phenols (chromones, coumarins, lignans, quinines, and other phenolics), terpenoids (monoterpenoids, sesquiterpene lactones, triperpenoid saponins, carotenoids, and other terpenoids), and minerals as micronutritional phytochemicals in fruits and vegetables of our daily diets. Among these phytochemicals, the flavonoids have specific functionality in relation to age-related diseases such as hypertension, diabetes, cardiac infarction, cataracts, and cancer. The authors of each chapter in the first section have presented their evidence in relation to the mechanism of the preventative and therapeutic ability of the compounds.

The first chapter, “Functionality of Anthocyanins as Alternative Medicine” by Noboru Motohashi and Hiroshi Sakagami, presents their antioxidant mechanism for anthocyanidins, which are present in common foods. It is possible that anthocyanins may have been used both preventatively and clinically as part of many “folklore medicines” worldwide and may have provided health-care benefits since the appearance of mankind some 7.5 million years ago. The review will inform the reader as to their functionality and mechanism.

The second chapter, “Bioactive Mechanism of Interaction between Anthocyanins and Macromolecules Like DNA and Proteins” by Seetharamappa Jaldappagari, Noboru Motohashi, Mamatha P. Gangeenahalli, and James H. Naismith, presents the biological activities of anthocyanins, and the interactions of anthocyanins with DNA and protein. Anthocyanins might protect against damage to health by some types of harmful oxidants through various mechanisms such as their antioxidative activity, protein active site binding, and chelating complex formation. The review presents the interesting interactive mechanism of anthocyanin–DNA complex formation.

The third chapter, “Antibacterial Activity of Artificial Phenothiazines and Isoflavones from Plants” by Asish Dasgupta, Sujata Ghosh Dastidar, Yoshiaki Shirataki, and Noboru Motohashi, presents that synthetic phenothiazines and

isoflavonones are not only powerful antibacterial agents as revealed by their activity in tests with hundreds of bacteria, but often also act as antiviral and anticancer agents. Many such compounds can eliminate drug-resistant plasmids and actively participate in inhibition of efflux pumps in pathogens. This study has opened up a new domain in the field of antimicrobial chemotherapy since these compounds can be administered in humans straight away or may be further improved by structural modifications.

The fourth chapter, "Inhibition of Multidrug Resistance of Cancer Cells by Selected Carotenoids, Flavonoids and Anthocyanins" by Joseph Molnár, Helga Engi, Nóra Gyémánt, Zsuzsanna Schelz, Gabriella Spengler, Imre Ocsóvszki, Miklós Szűcs, Judith Hohmann, Margaret Szabó, Lajos Tanács, Péter Molnár, Joseph Deli, Liselotte Krenn, Masami Kawase, Hidetsugu Wakabayashi, Teruo Kurihara, Yoshiaki Shirataki, Hiroshi Sakagami, Noboru Motohashi, and Remigijus Didiziapetris, tried to indirectly define receptor-structure in the presence of the diverse structurally unrelated carotenoids, flavonoids, isoflavonoids, and terpenoids. This review may contribute to studies of multidrug-resistant (MDR) proteins that belong to the ATP-binding cassette superfamily which are present in a majority of human tumors and are an important final cause of therapeutic failure.

The fifth chapter, "Changes in Polyamine Levels during Cell Death Induced by Heterocycles" by Masaki Kobayashi, Hiroshi Sakagami, Masami Kawase, and Noboru Motohashi, presents changes in polyamine levels during cell death induced by selective properties of diverse heterocycles such as phenoxazines, flavonoids, and other heterocycles. Natural polyamines (putrescine, spermidine, spermine) are aliphatic amines containing two or more amino groups, which play important roles in regulating cell growth and differentiation. Depletion of polyamine in cells has been known to inhibit cell proliferation or induce cell death. This review might help the study of changes in polyamine levels on cell death when induced by heterocycles.

In the second section of the volume, *N*-heterocycles such as phenothiazines, phenoxazines, dihydropyridines, and related compounds are shown also to have interesting biological activity including antitumor activity, vermicide, antibacterial activity, and antischizophrenic activity (i.e. chlorpromazine of the phenothiazine family and its analogs). The activity of phenothiazine and compounds such as phenoxazines and related heterocycles, and also recent bioactive mesoionic heterocycles will be discussed.

The sixth chapter, "Tumor-Specificity and Type of Cell Death Induced by Heterocycles" by Hiroshi Sakagami, Masaki Kobayashi, Mariko Ishihara, Hirotaka Kikuchi, Yukio Nakamura, Masami Kawase, and Noboru Motohashi, presents the tumor specificities of trifluoromethylimidazoles, phenoxazines, 3-formylchromone derivatives, coumarin and its derivatives, and vitamin K₂ derivatives and the type of cell death induced by these heterocycles. This review might beneficially establish a definitive strategy for the exploration of new highly tumor-selective compounds. Also, the screening process of highly

tumor-specific compounds should be introduced before the identification of the type of cell death (either apoptosis, autophagy, or necrosis) and the cell-death induction mechanism.

The seventh chapter, “Advanced Dihydropyridines as Novel Multidrug Resistance Modifiers and Reversing Agents” by Anamik Shah, Jitender Bariwal, Joseph Molnár, Masami Kawase, and Noboru Motohashi, presents a comprehensive review of their synthetic methodology for the preparation of the most-active P-glycoprotein (Pgp) inhibitor dihydropyridine. These “privilege structured” families of compounds are potent inhibitors of P-glycoprotein, which are the main cause of efflux of toxins from the cells. This review might be useful for exploratory future drug development due to the Pgp inhibitory property of the dihydropyridines.

The last chapter, “Theoretical Studies on Phenothiazines, Benzo[*a*]phenothiazines and Benz[*c*]acridines” by Teruo Kurihara, Kazumi Shinohara, Hidet-sugu Wakabayashi, Noboru Motohashi, Hiroshi Sakagami, and Joseph Molnár, presents their quantitative structure–activity relationship (QSAR) analysis for minimum inhibitory concentration (MIC) of phenothiazines and benzo[*a*]phenothiazines. The MIC values of phenothiazines were well correlated to $\Delta\Delta H_f$, HOMO energy, and μG . QSAR may be applicable to predict the MIC of phenothiazines. This review could contribute to prediction of the relationship of structure to biological activity.

It is hoped that this volume will serve as a stimulus for researchers with an interest in the field of biological activity of flavonoids and heterocycles, and also stimulate further development for novel therapeutics.

Tokyo, March 2008

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Bioactive Heterocycles VI

Flavonoids and Anthocyanins in Plants, and Latest

Bioactive Heterocycles I

Motohashi, N. (Ed.)

2008, XIV, 283 p. 178 illus., 14 illus. in color., Hardcover

ISBN: 978-3-540-79217-8