

Professor Edward Borowski and Molecular Aspects of Chemotherapy

Professor Edward Borowski was born in 1928 in Wilno. He moved to Gdańsk in 1945 to start studying at the Chemical Faculty, Gdańsk University of Technology. As a 3rd-year student, he was in 1948 appointed a Research Assistant at the Department of Organic Chemistry and this date marks the onset of his academic career. His research at that time was focused on discovery of novel antibiotic substances by random screening of soil samples. These studies resulted in discovery of tetaïne, the first ever antibiotic isolated in Poland and in getting PhD for this achievement in 1954. In 1957 Edward Borowski went to the USA where he got a position of a Postdoctoral Fellow at the Institute of Microbiology, Rutgers University, New Brunswick, N.J., in laboratory of the Nobel Prize winner, Professor Selman A. Waxman. In Prof. Borowski's opinion the experience gained at Waxman's lab was of a great importance for his further career. Coming back to the Gdańsk University of Technology in 1960, E. Borowski was given a position of a Head of the Department of Biochemistry (converted later into Department of Pharmaceutical Technology & Biochemistry), and started building his research team. Small at the very beginning, it rapidly expanded and quickly became a large group combining scientists who represented different specializations: organic chemists, biochemists, biophysicists and microbiologists. In the eighties the group was joined by quantum chemists who had been using modern computational technologies for drug design. All these researchers combined their efforts towards studies on molecular basis for the rational design of potential chemotherapeutics for the control of eukaryotic systems, especially antifungal and anticancer agents. Such a multidisciplinary approach was entirely pioneering at that time. Professor Borowski and his Molecular Chemotherapy Group quickly became a leading Polish center of studies on molecular aspects of chemotherapy, well known and appreciated by the world scientific community in this field. In the meantime, Professor Borowski was nominated for several years a Director of the Institute of Organic and Food Chemistry and Technology at his mother faculty. As a matter of fact, he did not enjoy those administrative duties, as they had taken too much time that could be much better spent on doing research.

The scientific record of Professor Borowski is very impressive. It comprises nearly 800 scientific publications, including 340 peer-reviewed articles in journals and books, 380 conference communications and 70 patents. His works were cited by other authors nearly 1100 times in the period 1981–2000. Such a citation record places Prof. Borowski among the most cited Polish scientists. Detailed enumeration of all achievements of Professor Borowski and his research group is undoubtedly beyond the scope of this article but the most important of them include:

1.

Isolation and characterization of original peptide antibiotics: tetaïne [1] and edeine complex [2]. Studies on the mechanism of action of tetaïne led to the proposal of the enzyme, glucosamine-6-phosphate synthase, as a new target for antifungal chemotherapy [3] and to the later rational design and development of highly effective antifungal oligopeptides, containing selective inhibitors of this enzyme [4]. Edeines are well known for their broad spectrum of activity and an unique mode of action as universal inhibitors of translation [5].

2.

Discovery and isolation of 4 polyene macrolide antifungal antibiotics and determination of structures of over 20 polyene macrolides, including Amphotericin B [6], known as a “golden standard” in antifungal chemotherapy. Papers of Borowski and his coworkers constitute about 80% of world scientific bibliography on this subject.

3.

Fundamental works on molecular basis of action and selectivity of antifungal polyene macrolides [7, 8] led to the development of several derivatives of Amphotericin B (AMB) exhibiting qualitatively improved selective toxicity in comparison to the mother antibiotic, including a methyl ester of N-methyl-N-fructopyranosyl-AMB, as the most promising compound [9].

4.

Presentation of a novel concept of mechanism of cardiotoxicity of anthraquinone anticancer agents (AAA). Borowski and coworkers provided evidence for generation of oxygen radicals due to participation of AAA in intracellular single-electron transfer (SET) processes [10] and pointed out that substrate properties of AAA in respect to NADH/NADPH-dependent oxidoreductases are the main factor determining SET potential of these compounds [11].

5.

Demonstration of directions of possible chemical modifications of some clinically useful anticancer agents leading to the development of derivatives highly active against multidrug-resistant cancer cells [12] and new modulators of cancer drug efflux membrane proteins that could be used in combination with existing antitumor drugs.

6.

New technologies of production of several β -lactam antibacterial antibiotics, developed in the seventies of the previous century and a new method of synthesis of an important anticancer agent Novantrone [13], implemented in industrial practice in the nineties.

Some of the above mentioned achievements resulted in part from the international scientific collaboration. Professor Borowski has established highly successful and effective links between his group and more than 20 foreign academic and research institutions. In 1984 he organized in Gdańsk the International Symposium on Molecular Aspects of Chemotherapy as a new forum for the exchange of scientific information among researchers interested in rational drug design. This initiative met with an interest and thus the 1984 conference became the first in the series of eight such events, organized always in Gdańsk in the period of 1984–2001.

Professor Borowski has built a well recognized scientific school. He has been a supervisor of 42 PhD thesis, his 7 co-workers got the DSc degree and 3 of them became full professors. For his academic achievements Professor Borowski has been awarded many times in Poland and abroad. In 1997 he was the first ever laureate of the Hevelius Award, established to honor especially distinguished scientist of the Pomeranian region. Member of editorial boards of several scientific periodicals, including a highly prestigious journal *Antimicrobial Agents & Chemotherapy* and *Polish Journal of Chemistry*. Elected many times a member of Scientific Councils of many research institutes and a current member of the Committee of Drug Science, Polish Academy of Sciences. Despite the fact that science is Professor Borowski's primary love, he has also found some time to be a very active President of the Gdańsk branch of the Association of Friends of Wilno and the Wilno Region (Professor Borowski's homeland, now in Lithuania). In his free time he has enjoyed hunting and farming.

In 1998 Professor Borowski celebrated the 50th anniversary of beginning of his scientific career. In the same year he passed the position of a head of the department to Professor Jerzy Konopa but remained a leader of the Molecular Chemotherapy Group. For those who know Professor Borowski a bit closer it was obvious that his formal retirement could not mean any real abandonment of the scientific activity, so that nobody should be surprised that this activity has never actually decreased. His current subject of special scientific interest is a phenomenon of multidrug resistance and chemotherapeutic strategies of its overcoming. Professor Borowski is highly active in arrangements of scientific consortia for the purpose of participation in the 6 Framework Programme of EU.

The members of the Professor Borowski's research group, including myself, have always known that our joint work is difficult from time to time but always interesting. The Professor's ideas are sometimes controversial but always stimulating. Following them has been for us a kind of a scientific adventure – may be sometimes not highly practical but often exciting. Professor Borowski has inoculated at least some of us with his a bit romantic attitude to science – not so abundant nowadays. We are highly grateful to him for this gift.

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Genomic Maps and Novel Approaches to Sequencing of Repetitive *versus* Non-repetitive DNA

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As first demonstrated by Avery *et al.*, DNA is a macromolecule which governs most aspects of life [1]. Thus our role as chemists was to determine the structure of this macromolecule, synthesize it, and possibly relate its structure to the genetic function. The first task was to determine the subunit structure of DNA, namely the structure of bases and their organization in relation to the deoxyribose and phosphate backbone. This was done in decades around the 1950-s. Independently, and around the same time, the concept of genes and the gene maps emerged as to relate the linear structure of DNA to its function. Next came the visualization of DNA by electron microscopy (EM) and its physical mapping using the heteroduplexes between DNA strands of various mutants. This permitted a precise way of measuring the length of DNA, positioning various deletions or other rearrangements and relating these to the genetic and transcriptional maps. The final step was the precise sequencing of DNA, either by the now abandoned chemical based method or by the presently used enzymatic procedure, which led to progressively more genomes being sequenced. Taken together, all this important scientific milestones led to our present day understanding of the chemical structure and function of DNA in relation to the 'puzzle of life'!

However, it was soon realized that the precise entire sequence of DNA could not be determined for many genomes, especially the eukaryotic ones, because they contain numerous long stretches of highly repetitive sequences, which defy the present computerized overlap procedure required for aligning of fragments and determining the final sequence. Therefore, we had to develop novel strategies to accurately sequence repetitive elements of DNA, as outlined here. These comprise construction and use of special transposons and pBAC/oriV vectors, both equipped with very rare cutting sites. Transposons (Tn) allow determination of 500–1000 nucleotide (nt) sequences on both sides of their insertion, whereas the very rare cutting sites (like I-SceI, PI-SceI or our Achilles heel cleavage sites) allow precise mapping of the positions of the insertions, using pulsed field gel electrophoresis (PFGE) or other physical means, including electron microscopic (EM) mapping. Thus we had to return to some of our earlier methods of physical mapping, which together with transposon-associated priming would allow sequencing of large eukaryotic genomes to be completed. This would be the final triumph of the structural chemistry of the DNA macromolecules which are the essence of genomes and genomics.

Rational Design, Synthesis and Biological Evaluation of 3*H*-Naphtho[1,2,3-*de*]quinoline-2,7-diones: a New Class of Potential Antitumor Agents

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A series of novel potential DNA-binding antitumor agents, 6-[(ω -aminoalkyl)amino]-3*H*-naphtho[1,2,3-*de*]quinoline-2,7-diones **3a–j**, has been prepared by nucleophilic substitution of commercially available 6-bromo-4-methyl-1-phenyl-3*H*-naphtho[1,2,3-*de*]quinoline-2,7-dione with the suitable 1-[(ω -(alkylamino)alkyl]amine. *In vitro* cytotoxic potencies of these derivatives toward six tumor cell lines, including human colon adenocarcinoma (HT29) and human ovarian carcinoma (A2780 sensitive, A2780cisR cisplatin-resistant, CH1, CH1cisR cisplatin-resistant, and SKOV-3), are described and compared to that of reference drugs. The 6-[3-(diethylamino)propyl]-3*H*-naphtho[1,2,3-*de*]quinoline-2,7-diones (**3e**), which possesses good cytotoxicity and low or none cross resistance with Cs on resistant cell lines, can be regarded as a new lead in the development of intercalating anticancer derivatives.

Synthesis, Pharmacological Properties and SAR of New 1,4-Disubstituted Piperazine Derivatives with Hypnotic-Sedative Activity

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Synthesis, chromatographic behaviour, pharmacological data and structure activity relationship (SAR) studies of some 1-(pyrimidin-2-yl)piperazine derivatives **1–13** are reported. The hydrophobic indices and chromatographic retention factors of the compounds exhibited statistically significant linear correlation with the calculated lipophilicities. The highest hypnotic-sedative activity as measured in loss of the righting reflex, rota-rod and spontaneous locomotor activity tests exhibited compound **6** possessing *n*-hexyl R substituent. The hypnotic activity of compounds **1–13** measured in loss of the righting reflex test could be described with the aid of hydrophobic indices in terms of Hansch parabolic relationship for structurally related group of compounds (separately for compounds with R = alkyl or R = cycloalkyl). The necessity to describe the pharmacological activity for aliphatic and alicyclic series with 2 different equations corresponded well to the observed difference in the pharmacological properties between the both groups of compounds.

Synthesis of Block and Random Copolymers of Isoprene via Two-Electron Transfer Mechanism

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Supramolecular complexes of alkali metals, capable of two electron transfer and generation of carbanions have been utilized in the polymerization of isoprene. The “living” polyisoprene blocks were subsequently used to react with styrene to produce the relevant block copolymers. The polyisoprene-polystyrene random copolymers were also obtained. The novel type of anionic polymerization initiated *via* novel supramolecular catalyst yields polyisoprene copolymers with well defined structure and properties.

Combined pH/Organic Modifier Double Gradient Reversed-Phase HPLC

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A new procedure of a combined pH and organic solvent double gradient reversed-phase high-performance liquid chromatography (RP HPLC) has been proposed. The procedure is technically feasible and theoretically proved. The method is demonstrated to outstandingly enhance separation of ionizable analytes. The approach consists in simultaneous developing of linear gradients of pH and of the organic modifier in the mobile phase. An extraordinary, systematically increasing eluting power of the mobile phase leads to a remarkable analyte peak compression, accompanied by a strongly reduced peak tailing.

Transient Permeability Induced by Cationic Derivatives of Amphotericin B in Lipid Membranes

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Individual ionic channels were shown to be formed through brain phospholipid membranes containing cholesterol, by two-sided addition of cationic derivatives of amphotericin B. At concentrations between 10^{-8} and 10^{-7} M, the resulting conductance appeared to be transient. Equilibrium between different antibiotic assemblies inside the membrane was demonstrated by the kinetics of conductance decrease following washing out the antibiotic. To explain the transient characteristics of the induced conductance, it is proposed that the antibiotic, present in solution under self-associated form, binds the membrane and forms pores, then dissociates in the bilayer in a non active monomeric form. This observation may be of importance to explain the delivery of oligonucleotides into mammalian cells, by cationic derivatives of amphotericin B.

A Facile Synthesis of Primary and Secondary Amines

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A facile synthesis of primary amines (R-CH₂-NH₂, where R = napht-2-yl, anthr-9-yl, phenyl, *p*-nitrophenyl) and secondary amines (R-NH-R', where R is as mentioned above for primary amines and R' = methyl) is described. The primary amines were obtained by alkylation of di-*tert*-butyl imidodicarbonate (Boc₂NH) under phase-transfer catalysis (PTC) conditions, followed by acidolytic removal of the amine protecting groups. The secondary amines were obtained from the appropriate primary amines by alkylation of their *N-tert*-butoxycarbonyl derivatives (Boc-NH-R), followed by Boc group acidolysis. It is worth emphasizing that the substrates for synthesis of secondary amines (Boc-NH-R) were obtained *via* selective removal of one of the *tert*-butoxycarbonyl groups from the alkylated di-*tert*-butyl imidodicarbonates (Boc₂N-R).

***Mycobacterium kansasii* Phagocytosis Inhibition by the Oligopeptides Derived from Systemine, Cecropin A and BRCT-1 Protein Sequences**

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In this work the results of investigations of the influence of three series of peptides on the inhibition of the *Mycobacterium kansasii* phagocytosis are presented. The peptides are the fragments of systemine (the plant signaling protein), antimicrobial peptide cecropine A, and the active fragment GRGDVVNGRG of the BRCT protein. It was found that KRDVY is a weaker inhibitor of phagocytosis than its analog RKDVY. Introduction of the sequence RDG in the place of RGD (present in cecropine A) decreases the anti-phagocytic activity in comparison with the RGDVY peptide. Very interesting is a high biological activity of the palindromic peptide GRGNVVNGRG, while its parent peptide, indicated above, is inactive.

**A Convenient Synthesis of
(S)-O-Benzyl-N-tert-butoxycarbonyl- β -tyrosine**

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