Professor Paweł Kafarski

A tribute

Dedicated to Prof. Paweł Kafarski in honor of his scientific achievements within his career

Paweł Kafarski was born in Gdańsk (Poland) on January 13th, 1949. He studied chemistry at Wrocław University of Technology where his scientific adventure started with his M. Sc. thesis, completed in 1971 under the supervision of Prof. Przemysław Mastalerz. Prof. Mastalerz subsequently supervised his scientific career for many years. In his laboratory Paweł Kafarski worked on the synthesis of organophosphorus compounds and their potential biological activitiy. In 1977 he defended his PhD thesis "Synthesis of peptides containing aminophosphonic acids". The synthesis and evaluation of the antibacterial and the plant growth regulating action of these peptides (also called phosphono peptides) became the first benchmark of Paweł Kafarski's scientific activity. In 1976/1977 he interrupted his PhD studies and spent nine months at Marquette University working in the laboratory of Prof. Sheldon E. Cremer on the synthesis of phosphetanes.

When finalizing the topic on antibacterial phosphono dipeptides, their influence on leucine aminopeptidase was tested in the hope that this enzyme might be treated as a model for phosphono peptide degradation in human fluids. It appeared, however, that these compounds were weak ligands and their potency relied on the rate of peptide bond hydrolysis. Thus, it was assumed that the inhibitory effect was derived from the release of α-aminophosphonic acid. Several years of study culminated in the synthesis of over 40 aminophosphonates and the evaluation of their activity towards leucine aminopeptidase and the structurally related, neutral aminopeptidase (then considered as an isoform of LAP). The results, published in 1989, provoked the interest of Prof. Kafarski in the design, synthesis and evaluation of phosphonates as

inhibitors of chosen enzymes. Aminopeptidases were considered as promising targets for the development of new anticancer drugs. Prof. Andrzej Sokalski, from the same faculty, convinced Prof. Kafarski that the application of computer-aided drug design was worth considering, and a commercially available program was applied for this purpose. Initial studies involved validation of this methodology using kinetic data obtained for leucine aminopeptidase in 1989. Subsequently, a series of new inhibitors was synthesized and evaluated towards leucine and neutral aminopeptidases. They appeared to be very promising compounds and consequently Prof. John Dalton at the Technological University of Sydney invited Prof. Kafarski to participate in a project dedicated to search for new anti-malarial drugs. This project was carried out by an international consortium of scientists. Phosphino peptides appeared to be very efficient inhibitors of *Plasmodium falciparum* aminopeptidases and were used to confirm that these enzymes played a vital role in malaria pathogenesis. Finally, one of the compounds – an analogue of homophenylalanylphenylalanine, emerged as a candidate for an effective anti-malarial drug as shown by studies on mice.

This is one example of many studies of enzyme inhibitors (such as: aminopeptidases, cathepsin C, tyrosinase, urease, glutamine synthetase and catechol *O*-methyltransferase) that were interesting medicinally and others (such as: urease, glutamine synthetase, *L*-phenylalanine ammonia lyase, and enzymes of proline and aromatic amino acid biosynthesis) of agrochemical interest. The design of ligands for these molecular targets relied on knowledge of molecular mechanisms of the catalyzed reactions and on three-dimensional structures of these proteins. In many cases the process was computer model assisted. Efforts to synthesize the target compounds were finally undertaken in order to evaluate their biological activity.

Frequently, the preparation of new structures was the most demanding step of these projects. Inhibitors studied by Prof. Kafarski's laboratory usually belonged to the class of organophosphorus compounds containing a C-P bond. Many innovative procedures for their synthesis (including chemoenzymatic approaches with the use of enzymes and whole cells of microorganisms as catalysts) were elaborated, mostly to provide α-aminophosphonic acids and corresponding short peptides. For biological purposes these compounds are required in enantiomerically pure form and therefore methods of enantioseparation as well as techniques for the determination of the optical purity and configuration were developed intensively.

In 1982 Prof. Paweł Kafarski was appointed to a position at the University of Opole where some of the above-mentioned studies were performed. The main stream of research in Opole concerns two subjects: biodegradation of aminopolyphosphonates (including the commonly applied herbicide glyphosate) by lower fungi and cyanobacteria and studies on the structure of plant allelochemicals.

Prof. Paweł Kafarski has co-authored over 270 scientific papers, one academic book in Polish (P. Kafarski, B. Lejczak, *Chemia Bioorganiczna*, PWN Warszawa 1994), and 13 chapters in books (4 in Polish), 10 patents and 5 patent applications. These papers have been cited over 2,000 times. He also supervised 21 PhD theses. He acted as the President of the Polish Chemical Society (2005-2010), as Dean of the Faculty of Chemistry at Wrocław University of Technology

(2001-2005), as a member of the Committee of Biotechnology and the Polish Academy of Sciences (1988-2007). He was granted, amongst other, the Jan Hanus medal (Czech Chemical Society, 2005), as Honorary Member of the Slovak Chemical Society (2007), and with the Medal of the National Educational Committee (2007).
In 2010 the Department of Bioorganic Chemistry led by Prof. Kafarski organized the 18th International Conference on Phosphorus Chemistry.

Besides his scientific activities, for many years Paweł Kafarski organized the Festival of Independent Student Songs in the Karkonosze Mountains. Currently, his major hobbies are philately, particularly collecting Polish and Czech pre-war stamps, and mushroom picking. Lastly, he also likes to travel to exotic countries. Being an exceptional story-teller, he always attracts great interest presenting his impressions from these tours. People who were hosted by Paweł Kafarski in Wrocław, undoubtedly remember his passion for the city and its multinational history.

I became a member of Prof. Kafarski's group at the time he took over the leadership after the retirement of Prof. Mastalerz. During my PhD, I received friendly and inspiring guidance and concern from him. This is the usual attitude of Paweł Kafarski to his students and co-workers – professional assistance, but allowing a great deal of scientific independence. The stimulating atmosphere and promotion of young personalities has allowed him to establish a multidisciplinary and creative team. All of his colleagues, friends and students congratulate Paweł Kafarski with the achievements of his scientific career. We also wish him many years of professional activity and satisfaction.

Prof. Artur Mucha
Department of Bioorganic Chemistry,
Institute of Organic Chemistry,
Biochemistry and Biotechnology Technical University of Wroclaw
Wybrzeze Wyspianskiego 27, 50-370 Wroclaw, Poland
E-mail: artur.mucha@pwr.wroc.pl

Selected Publications of Professor Paweł Kafarski

1. Radwan-Olszewska, K.; Palacios, F.; Kafarski, P. Selective synthesis of α-fluoro-β-keto- and α-fluoro-β-aminophosphonates via electrophilic fluorination by Selectfluor. *J. Org. Chem.* **2011**, *76*, 1170.
2. Skinner-Adams, T. S.; Stack, C. M.; Trenholme, K. R.; Brown, C. L.; Grembecka, J.; Lowther, J.; Mucha, A.; Drag, M.; Kafarski, P.; McGowan, S.; Whisstock, J. C.; Gardiner, D. L.; Dalton, J. P. Plasmodium falciparum neutral aminopeptidases: new targets for anti-malarials. *Trends Biochem. Sci.* **2010**, *35*, 53.

3. Mucha, A.; Drąg, M.; Dalton, J. P.; Kafarski, P. Metallo-aminopeptidase inhibitors. *Biochimie* **2010**, *92*, 1509.
4. Lejczak, B.; Kafarski, P. Biological activity of aminophosphonic acids and their short peptides. *Top. Heterocycl. Chem.* **2009**, *20*, 31.
5. Dąbrowska, E.; Burzyńska, A.; Mucha, A.; Matczak-Jon, E.; Sawka-Dobrowolska, W.; Berlicki, Ł.; Kafarski, P. Insight into the mechanism of three component condensation leading to aminomethylenebisphosphonates. *J. Organomet. Chem.* **2009**, *694*, 3806.
6. Vassiliou, S.; Grabowiecka, A.; Kosikowska, P.; Yiotakis, A.; Kafarski, P.; Berlicki, Ł. Design, synthesis and evaluation of novel organophosphorus inhibitors of bacterial ureases. *J. Med. Chem.* **2008**, *51*, 5736.
7. Latajka, R.; Jewgiński, M.; Makowski, M., Pawełczak, M.; Huber, T.; Sewald, N.; Kafarski, P. Pentapeptides containing two dehydrophenylalanine residues - synthesis, structural studies and evaluation of their activity towards cathepsin C. *J. Pept. Sci.* **2008**, *14*, 1084.
8. Rudzińska, E.; Poliwoda, A.; Berlicki, Ł.; Mucha, A.; Dżygiel, P.; Wieczorek, P. P.; Kafarski, P. Enantiodifferentiation of N-benzyloxycarbonylaminophosphonic and phosphinic acids and their esters using cyclodextrins by means of capillary electrophoresis. *J. Chromat. A* **2007**, *1138*, 284.
9. Młynarz, P.; Rudzińska, E.; Berlicki, Ł.; Kafarski, P. Organophosphorus supramolecular chemistry. Part 2. Organophosphorus receptors. *Curr. Org. Chem.* **2007**, *11*, 1593.
10. Berlicki, Ł.; Kafarski, P. Computer-aided analysis of the interactions of glutamine synthetase with its inhibitors. *Bioorg. Med. Chem.* **2006**, *14*, 4578.
11. Forlani, G.; Obojska, A.; Berlicki, Ł.; Kafarski, P. Phosphinothricin analogues as inhibitors of plant glutamine synthetases. *J. Agric. Food Chem.* **2006**, *54*, 796.
12. Berlicki, Ł.; Rudzińska, E.; Młynarz, P.; Kafarski, P. Organophosphorus supramolecular chemistry. Part 1. Receptors for organophosphorus compounds. *Curr. Org. Chem.* **2006**, *10*, 2285.
13. Latajka, R.; Makowski, M.; Jewgiński, M.; Pawełczak, M.; Koroniak, H.; Kafarski, P. Peptide p-nitrophenylanilides containing (E)-dehydrophenylalanine - synthesis, structural studies and evaluation of their activity towards cathepsin C. *New J. Chem.* **2006**, *30*, 1009.
14. Berlicki, Ł.; Obojska, A.; Forlani, G.; Kafarski, P. Design, synthesis, and activity of analogues of phosphinothricin as inhibitors of glutamine synthetase. *J. Med. Chem.* **2005**, *48*, 6340.
15. Berlicki, Ł.; Kafarski, P. Computer-aided analysis and design of phosphonic and phosphinic enzyme inhibitors as potential drugs and agrochemicals. *Curr. Org. Chem.* **2005**, *9*, 1829.
16. Berlicki, Ł.; Rudzińska, E.; Mucha, A.; Kafarski, P. Cyclodextrins as NMR probes in the study of the enantiomeric compositions of N-benzyloxycarbonylamino-phosphonic and phosphinic acids. *Tetrahedron-Asymmetry* **2004**, *15*, 1597.
17. Kafarski, P.; Lejczak, B. Application of bacteria and fungi as biocatalysts for the preparation of optically active hydroxyphosphonates. *J. Mol. Cat. B-Enzymatic* **2004**, *29*, 99.

18. Berlicki, Ł.; Rudzińska, E.; Kafarski, P. Enantiodifferentiation of aminophosphonic and aminophosphinic acids with α- and β-cyclodextrins. *Tetrahedron-Asymmetry* **2003**, *14*, 1535.
19. Grembecka, J.; Mucha, A.; Cierpicki, T.; Kafarski, P. The most potent organophosphorus inhibitors of leucine aminopeptidase. Structure-based design, chemistry, and activity. *J. Med. Chem.* **2003**, *46*, 2641.
20. Mucha, A.; Kafarski, P. Transesterification of monophenyl phosphonamidates - chemical modelling of serine protease inhibition. *Tetrahedron* **2002**, *58*, 5855.
21. Grembecka, J.; Kafarski, P. Leucine aminopeptidase as a target for inhibitor design. *Mini Rev. Med. Chem.* **2001**, *1*, 133.
22. Kafarski, P.; Lejczak, B. Aminophosphonic acids of potential medical importance. *Curr. Med. Chem. Anti-Canc. Agents* **2001**, *1*, 301.
23. Kafarski, P.; Zoń, J. Synthesis of α-aminoalkanephosphonic and α-aminoalkanephosphinic acids. In *Aminophosphonic and aminophosphinic acids. Chemistry and biological activity.* Kukhar, V. P.; Hudson. H. R.; Eds.; Wiley, Chichester 2000, pp. 33-74.
24. Kafarski, P.; Lejczak, B. Synthesis of phosphono- and phosphinopeptides. In *Aminophosphonic and aminophosphinic acids. Chemistry and biological activity.* Kukhar, V. P.; Hudson. H. R.; Eds.; Wiley, Chichester 2000, pp. 173-203.
25. Grembecka, J.; Sokalski, W. A.; Kafarski, P. Computer-aided design and activity prediction of leucine aminopeptidase inhibitors. *J. Comput. Aid. Mol. Des.* **2000**, *14*, 531.
26. Żymańczyk-Duda, E.; Skwarczyński; M.; Lejczak, B.; Kafarski, P. Accurate assay of enantiopurity of 1-hydroxy- and 2-hydroxyalkylphosphonate esters. *Tetrahedron: Asymmetry.* **1996**, *7*, 1277.
27. Ryglowski, A.; Kafarski, P. Preparation of 1-aminoalkylphosphonic acids and 2-aminoalkylphosphonic acids by reductive amination of oxoalkylphosphonates. *Tetrahedron.* **1996**, *52*, 10685.
28. Mucha, A.; Kafarski, P.; Plenat, F.; Cristau, H.-J. The preparation of phosphono peptides containing a phosphonamidate bond. *Tetrahedron* **1994**, *50*, 12743.
29. Kafarski, P.; Lejczak, B. Biological activity of aminophosphonic acids. *Phosphorus, Sulfur, and Silicon* **1991**, *63*, 193.
30. Kafarski, P.; Lejczak, B. A facile conversion of aminoalkanephosphonic acids into their diethyl esters. The use of unblocked aminophosphonic acids in phosphono peptide synthesis. *Synthesis* **1988**, 307.
31. Kafarski, P.; Lejczak, B.; Mastalerz, P.; Dus, D.; Radzikowski, C. N-(Phosphonoacetyl)amino phosphonates: Phosphonate analogues of N-(phosphonoacetyl)-L-aspartic acid/PALA. *J. Med. Chem.* **1985**, *28*, 1555.
32. Kafarski, P.; Lejczak, B.; Szewczyk, J. Optically active 1-aminoalkanephosphonic acids. Dibenzoyl L-tartaric anhydride as an effective agent for the resolution of racemic diphenyl 1-aminoalkanephosphonates. *Can. J. Chem.* **1983**, *61*, 2425.

33. Kafarski, P.; Lejczak, B.; Mastalerz, P.; Szewczyk, J.; Wasielewski, C. Phosphonodipeptides: synthesis and separation of diastereoisomers. *Can. J. Chem.* **1982**, *60*, 3081.
34. Szewczyk, J.; Lejczak, B.; Kafarski, P. Transesterification of diphenyl phosphonates using potassium fluoride/crown ether/alcohol system; Part 1. Transesterification of diphenyl 1-(benzyloxycarbonylamino)-alkanephosphonates. *Synthesis* **1982**, 409.
35. Zygmunt, J.; Kafarski, P. Preparation of oxoalkanephosphonic acids. *Synthesis* **1978**, 609.

