



Associate Professor Maria Jolanta Mokrosz, Ph.D.
(1949–2001)

OBITUARY

On 2 January 2001 we were bereaved of Assoc. Prof. Maria Jolanta Mokrosz, Ph.D., Head of the Department of Medicinal Chemistry of the Institute of Pharmacology of the Polish Academy of Sciences in Kraków, an eminent specialist in modern medicinal chemistry, a researcher who had been faced with fine perspectives and who could still do a lot for science.

Born on 14 January 1949 in Kraków, Assoc. Professor Maria Mokrosz attended a primary and then a secondary school there. She studied chemistry at the Faculty of Mathematics, Physics and Chemistry of the Jagiellonian University, having received an M.Sc. degree in chemistry in 1972. Immediately upon graduation, she pursued 4-year doctoral studies having joined the Organic Stereochemistry Laboratory at that Faculty. At that time she engaged in the synthesis of spirane systems and investigations into steric effects in those molecules on the basis of changes observed in their UV spectra. In 1976, upon presentation of her dissertation

entitled “Synthesis and stereochemistry of new spirane compounds containing a cyclobutane, as well as an oxa- and a thiaspirane component”, she was granted a Ph.D. degree in chemistry.

For two years (1976–1978) she had been working in the Research Laboratory of the Kraków Pharmaceutical Works POLFA where she dealt with modifications in the oxidation reaction, a step in the vitamin C production cycle.

In 1978 she resumed her research work, having joined the Organic Physicochemistry Laboratory at the Department of Organic Chemistry of the Jagiellonian University. Being a member of that Laboratory, headed by Prof. J. Mirek, she conducted studies into the use of unsaturated nitriles in organic synthesis. Those studies led to elaboration of a simple, one-step cyclization of alkylidenemalononitriles and hydrolysis of the obtained dimers. Her other studies conducted at that time were concerned with the susceptibility of alkylidenemalononitrile dimers to reactions of nucleophilic addition

and electrophilic substitution, as well as with use of those dimers in the synthesis of 3(2H)-pyridazines.

Since 1992 she had been working in the Institute of Pharmacology of the Polish Academy of Sciences in Kraków, strictly speaking in its Department of Medicinal Chemistry (formerly Department of Organic Chemistry), headed by Prof. S. Misztal until 1998. In that Department, having used her hitherto acquired knowledge and experience, she substantially changed her academic interests and direction of research. Since then her studies had been concerned with the synthesis and search for relationships between the chemical structure and the biological activity of new compounds acting on the central nervous system – in particular on one of its neurotransmitter systems, the serotonin system – with special regard to ligands of serotonin 5-HT_{1A} and 5-HT_{2A} receptors.

Her investigations in the field of organic synthesis were mainly concentrated on derivatives of 1,2,3,4-tetrahydro-β-carboline. Thus the Pickett-Spengler reaction between tryptamine derivatives and N-benzyl-4-piperidone afforded a number of spiro[piperidine-4',1-(1,2,3,4-tetrahydro-β-carbolines)]; subsequently, the process itself and the yielded products were used for studying the mechanism of that reaction. It should be added here that for at least 20 years there had been a controversy about that mechanism among chemists, and the above-described and successive studies permitted its final settlement. On the basis of those derivatives there were synthesized poly-heterocyclic systems which were also used in studies into the topographic model of 5-HT_{1A} receptors. An efficient and selective method of oxidation of 1,2,3,4-tetrahydro-β-carbolines to the respective 3,4-dihydro-β-carbolines was also devised.

Assoc. Professor Maria Mokrosz's research into serotonin receptor ligands led to development of a number of biologically active compounds, among others 1-(2-methoxyphenyl)-4-(4-succinimide)-butylpiperazine (MM-77), a new, active postsynaptic antagonist of 5-HT_{1A} receptors, that compound being listed in a catalogue of firms manufacturing tool substances for receptor studies *in vitro*. Her studies on 1,2,3,4-tetrahydroisoquinoline derivatives demonstrated that a nitrogen atom of that amine could mimic the basic N-4 atom of piperazine molecule in reactions with the receptor. In consequence, a tetrahydroisoquinoline analog of

the well-known anti-anxiety drug buspirone, which showed the same activity *in vitro* and the same pharmacological profile, was developed. Thus it was demonstrated that the 1-(2-pyrimidyl)piperazine fragment present in buspirone was not responsible for stabilization of the active ligand-5-HT_{1A} receptor complex.

Assoc. Professor Maria Mokrosz found in the group of the aforementioned 4,6-diarylpyrimidine derivatives a great number of active 5-HT_{2A} receptor ligands which showed properties of antagonists of those receptors. Having analysed their reaction with 5-HT_{2A} receptors, she observed that the dipole-dipole reactions produced by aromatic and heteroaromatic substituents had the most pronounced effect on stabilization of the active ligand-receptor complex. These reactions are the more effective, the greater co-planarity of the respective fragments of a molecule is. They also depend on local dipole moments that are borne by these fragments. An analysis of a few dozen pyrimidine derivatives, both mono- and disubstituted, permitted determination of a three-point model of a pharmacophore of 5-HT_{2A} receptor antagonists. At the same time, boundary values of the distance between pharmacophoric points, necessary for the optimum affinity of the studied compounds for 5-HT_{2A} receptors, were established. The pertinence of the advanced hypotheses was confirmed by an analysis of N-methylpiperazine derivatives of quinazoline and quinoline, which demonstrated substantial influence of the co-planarity and stereochemistry of a molecule on the affinity for 5-HT_{2A} receptors. Conclusions about the role of a local dipole moment in stabilization of the active complex were also extended to amide derivatives of 1-aryl-4-alkylpiperazine. In the group of those derivatives a linear dependence between the observed affinity for 5-HT_{2A} receptors and the dipole moment of an amide fragment of a molecule was reported. Having analysed 4-(3-furyl)-6-arylpyrimidine derivatives, Assoc. Prof. Maria Mokrosz showed that among reactions stabilizing the active complex – besides the dipole-dipole interactions – a substantial role was played by a hydrogen bond whose acceptor was an oxygen atom of the furyl ring in the ligand molecule. And last but not least, having examined simple 1-arylpiperazines and their N-alkyl derivatives, she also demonstrated that hydrophobic interactions between ligands and 5-HT_{2A} receptors did not play such an

important role as did interactions with 5-HT_{1A} receptors.

Although the majority of those basic studies consisted on the one hand in modifications and improvements of reactions important to processes of synthesis and, on the other, in attempts to determine – in close cooperation with pharmacologists – which fragments of the newly developed substances affected particular brain structures, those studies always had important practical aspects in the background. Development of the above-mentioned compounds, used as the so-called research tools, as well as of a few other substances with a potential therapeutic activity may constitute proof here.

It should also be mentioned that Assoc. Professor Maria Mokrosz conducted all those studies using highly specialized methods and modern research tools which she had devised together with her prematurely deceased husband, Professor Jerzy Mokrosz. Despite her personal tragedy due to her husband's death nearly 5 years before, Maria Mokrosz resumed and carried on their mutual work having expanded the formerly initiated studies. The obtained results were so promising and important to science that on their basis she was qualified as associate professor (habilitation) in chemical sciences in 1998. The title of her dissertation was "An analysis of interactions stabilizing active ligand-5-HT_{2A} receptor complexes in a group of 1-aryl-piperazine derivatives".

Assoc. Professor Maria Mokrosz conducted her investigations not only in Polish research centres. In the 1980ies she paid several visits to some leading foreign scientific institutions in the field of medicinal chemistry, among them twice to the Ruhr University (Bochum, Germany), the University of Florida (Gainesville, USA) and the Georgia State University (Atlanta, USA). During her stay in Gainesville she joined Prof. A. Katritzky's team where she engaged in application of pyridine and pyrimidine salts in the process of synthesis. In Atlanta, she was working under Prof. Strękowski's supervision where the main theme of her studies was synthesis of compounds acting as amplifiers in the bleomycin-mediated degradation of DNA. She was involved in developing a method for synthesizing 2-chloro-4,6-di(heteroaryl)-pyrimidine in a reaction of addition of arylolithium derivatives to 2-chloropyrimidine, which was later on extended also to other diazines such as, e.g., phthalazine and

quinazoline. The resultant chlorodiazines were used as substrates for a synthesis of the respective amine derivatives, the latter being the subject proper of biological studies. It turned out that a considerable number of those derivatives intercalated well with DNA, and thus accelerated the process of its degradation. Using QSAR and molecular modelling methods it was also possible to determine some structural parameters, favorable to those processes, of the molecules studied. Those derivatives were also tested in respect of their activity against the HIV-1 virus, having yielded satisfactory results. Apart from being published in a number of original papers, the results of those studies also brought Assoc. Prof. Maria Mokrosz co-authorship of three American patents.

At the beginning of 1999, being still extremely active and deeply engaged in her own studies – as is best evidenced by her scientific output comprising ca. 120 publications (including over 60 original papers, the substantial majority of which were published in international scientific journals of high renown) – she took up a new challenge, having accepted a position of head of the Department of Medicinal Chemistry at the Institute of Pharmacology. Since then she had been facing new tasks and duties connected with organization of team work, care of scientific development of the staff, struggle for financial support. She always made a good job of those obligations, showing involvement and responsibility so characteristic of her. Assoc. Prof. Maria Mokrosz managed to establish and expand fruitful co-operation with a number of the Institute's research teams. She also searched effectively for research partners outside the Institute, and was herself a most welcome partner. She was equally successful in obtaining grants, and also managed to mobilize her coworkers in such attempts. Assoc. Prof. Maria Mokrosz was in charge of two and co-implemented seven other research projects financed by the State Committee for Scientific Research (KBN).

Being an extremely modest person, during her entire scientific career Assoc. Prof. Maria Mokrosz always seemed to remain in the background and never aspired to be in the front line while designing and taking up all those activities. Until recently, despite her grave and eventually terminal illness, she persisted in performing all those tasks. Almost to the last she was interested in her team's work and remained in steady contact with her colleagues;

furthermore, her health condition permitting, she looked after her little “scientific kingdom” personally.

The premature death of Assoc. Prof. Maria Mokrosz is a severe and painful loss not only to the Institute of Pharmacology of the Polish Academy of Sciences in Kraków and its Department of Medicinal Chemistry. We have been irrevocably be-

rieved of an eminent researcher and scientist, but also of an extremely kind and gentle person who was always ready to help others using all her knowledge and experience, a person who was highly esteemed and much loved. She will be greatly missed by all her friends and coworkers who will devoutly cherish her memory.

Edmund Przegaliński