

SUMMARY

Bioanalytical evaluation plays a pivotal role in preclinical research of new drugs, particularly in investigation of their pharmacokinetics and metabolism. Use of modern analytical approaches is indispensable; chromatography and mass spectrometry are the techniques of choice in this area of research. To obtain reliable data, the analytical methods must be validated. Several authorities – such as European Medicines Agency or Food and Drug Administration – have published recommendations on bioanalytical method validation.

In its theoretical part, this dissertation deals with description of Alzheimer's dementia with special focus on treatment strategies. Further attention is paid to topics that are directly related to the experimental work - liquid chromatography, mass spectrometry, sample preparation, method validation and pharmacokinetics. The experimental part – a commentary on the author's published articles – consists of three units: **I.** bioanalytical evaluation of PC-37 and PC-48 – novel 7-methoxytacrine and donepezil-derived dual cholinesterase inhibitors, **II.** study of the transport of donepezil across the blood-brain barrier with focus on its structure and substructures and **III.** bioanalytical evaluation of S-K1025 and S-K1026 - new 7-methoxytacrine and tryptophan-derived dual cholinesterase inhibitors.

In all three units, the author discusses development and validation of analytical methods, pharmacokinetics and/or metabolism of the studied substances and their transfer to the target organ – the brain. Both PC-37 and PC-48, thanks to the incorporated substituted benzylpiperazine group, are capable of active transport to the brain where they accumulate - the brain concentration exceeded that of plasma. In contrast, both S-K1025 and S-K1026 failed to reach the brain even in trace amounts mainly due to their metabolic instability and non-optimal physicochemical properties. The results discussed in this dissertation provide new information that can contribute to rational development of new, more effective drugs to battle Alzheimer's dementia or drugs with a more convenient pharmacokinetic profile.