Abstract

Physicochemical and Pharmacokinetic Properties of New Dual-Acting Compounds for the Treatment of Mental Disorders †

Agnieszka Zagórska 1,*, Paweł Żmudzki 1, Paulina Janiszewska 1 and Maria Walczak 2

1 Department of Medicinal Chemistry, Jagiellonian University Medical College Medyczna 9 Str, 30-688 Kraków, Poland
2 Department of Toxicology, Jagiellonian University Medical College Medyczna 9 Str, 30-688 Kraków, Poland
* Correspondence: agnieszka.zagorska@uj.edu.pl

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Abstract: Physicochemical and pharmacokinetic properties of compounds marked with acronyms PQA-AZ-4 and PQA-AZ-6 were studied using experimental methods. Selected compounds (dual-active effective inhibitors of phosphodiesterase (PDE) 10A and serotonin 5-HT1A and 5-HT7 receptor ligands) in prescreening pharmacological studies revealed antipsychotic-like, antidepressant-like, and anxiolytic activities. The liquid chromatographic–tandem mass spectrometric method with electrospray ionization (LC/ESI-MS/MS) system was calibrated and validated for lipophilicity studies. Lipophilicity was assessed from the y axis intercept ($y_0$) of the linear regression line of $\ln((t−t_0)/t_0)$ against % concentration of organic eluent. Finally, lipophilicity was calculated using a linear regression equation of the logP value against $y_0$ values obtained for the reference compounds in the same experimental conditions. Next, the thermodynamic aqueous solubility of selected compounds was detected with UPLC detection. The LC/ESI-MS/MS system was used for the simultaneous determination of PQA-AZ-4 and PQA-AZ-6 in mouse plasma, hippocampus, striatum, and frontal cortex, developed and validated according to GLP procedures. Finally, drug-likeness properties of selected compounds were evaluated using a predictive bioavailability radar model from the SwissADME web tool. The descriptors of physicochemical properties (lipophilicity, size, polarity, solubility, flexibility, and saturation) for selected compounds were projected next on the optimal range for each property to be considered drug-like.

Keywords: PDE inhibitors; 5-HT1A receptor ligands; 5-HT7 receptor ligands; antipsychotics; antidepressants; anxiolytics

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