doi:10.46793/ICCBI21.284C

QSRR MODELING OF LIQUID CHROMATOGRAPHY SEPARATION OF ZIPRASIDONE COMPOUNDS

A. Marija Carapic[1], B. Katarina Nikolic[2], C. Danica Agbaba[2]

[1] Medicines and Medical Devices Agency of Serbia,
Vojvode Stepe 458, 11000, Belgrade, Serbia
e-mail: marija.carapic@alims.gov.rs
[2]Department of Pharmaceutical Chemistry, University of Belgrade - Faculty of Pharmacy
Vojvode Stepe 450, PO Box 146,11000 Belgrade, Serbia
e-mail: knikolic@pharmacy.bg.ac.rs , danica@pharmacy.bg.ac.rs

1. Introduction

Ziprasidone is an atypical antipsychotic drug with an affinity to the adrenergic (α_1), histamine (H_1), serotonin (5-HT_2), and dopamine (D_2) receptors [1]. The first quantitative HPLC analysis of ziprasidone and its five main impurities (I-V) (Figure 1) was developed and validated by our research group [2]. The main aims of the presented chemometric study were to develop the Quantitative Structure Retention Relationship (QSRR) model for the prediction of the chromatographic retention of the other ziprasidone derivatives, or metabolites.

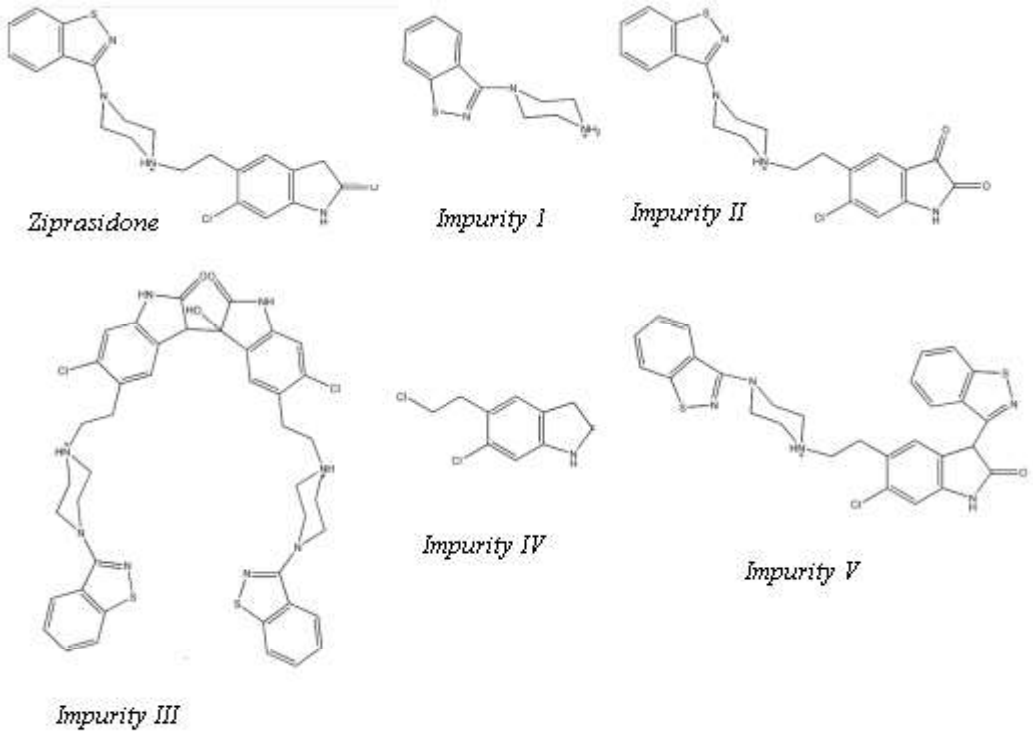

Figure 1. Chemical structures of the dominant forms of ziprasidone and its main impurities at pH 2.5

2.1. Materials and Methods

The minimum energy conformations of the analyzed compounds were obtained by the Molecular Orbital PACkage/Parametric Method Vs.3 (MOPAC/PM_3). Molecular descriptors were computed for the optimized molecular models with use of the MarvinSketch 5.1.5.0 program, the Chem3D Ultra 7.0.0 program, CS Gaussian 98 program [3] using the B3LYP hybrid functional. The QSRR study was performed with use of the Soft Independent Modeling of Class Analogy SIMCA P+ 12.0 program [4], for the Partial Least Square (PLS) Regression analysis [5].

2.2. Results

The retention times (t_R) of ziprasidone and its impurities (obtained with the developed HPLC gradient method) [2], and the computed molecular parameters of the examined compounds were used to build the QSRR models. Descriptors with the highest Variable Importance in the Projection (VIP) values were selected for PLS-QSRR model building. Optimal combination of the most relevant descriptors (MS, SAS, LogP, $LogD_{pH\ 2.5}$, $LogD_{pH\ 1.5}$ and $LogD_{pH\ 4.0}$) for PLS models building were chosen on basis of the R^2, Q^2, Root Mean Square Error of Prediction (RMSEP) values of the obtained PLS models. The obtained statistical parameters of the **PLS-QSRR model** (r^2=0.913) pointed out to a good prognostic capacity of the developed QSRR model (Table 1).

Table 1. Molecular parameters of ziprasidone and its five main impurities, and the predicted retention time (t_R) values obtained with use of the developed **QSRR-PLS model** (2 significant components)

STRUCTURE	SAS	MS	LogD pH 1.5	LogD pH 2.5
Imp I	399.318	205.444	-2.02	-1.31
Imp II	578.710	331.072	0.71	1.41
Ziprasidone	649.768	359.486	0.17	0.71
Imp III	892.016	567.532	-0.53	0.57
Imp IV	390.659	197.267	2.55	2.55
Imp V	770.858	444.459	2.24	2.84
STRUCTURE	LogD pH 4.0	LogP	Experimental t_R [min]	Predicted t_R [min] by PLS-QSRR model
Imp I	-1.03	2.21	3.651	2.5409
Imp II	2.64	4.83	7.290	10.4748
Ziprasidone	1.35	4.30	7.860	8.6666
Imp III	1.89	7.75	10.197	9.7429
Imp IV	2.55	2.55	12.573	11.9067
Imp V	3.49	6.43	16.056	14.2951
r^2, obs vs. pred				0.91315
MSEP*				2.62946
RMSEP				1.62156

* Mean Square Error of Prediction

The developed PLS-QSRR model was used to predict separation of ten (TS1-TS10) ziprasidone derivatives (organic impurities, metabolites and potential degradation products) in RP-HPLC system (Figure 2).

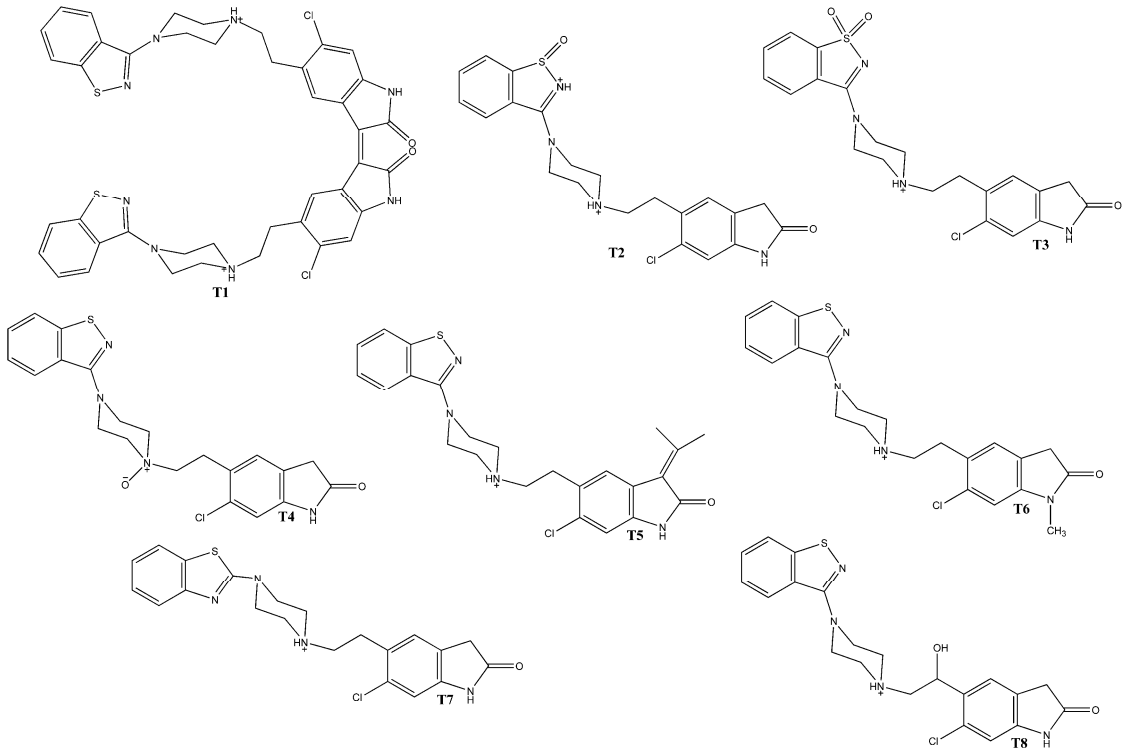

Figure 2. Chemical structures of the dominant forms of the ziprasidone derivatives (TS1-TS10), impurities and/or metabolites, at pH 2.5.

Based on the obtained results, the PLS-QSRR model proposed two structures (TS1 and TS5) as potential for *unknown impurity* (t_R: 11.270 min) in the test solution [2] (Table 2), and one of them (TS1) was confirmed by Ultra-High-Pressure Liquid Chromatography-tandem Mass Spectrometry (UPLC-MS-MS) study [6,7].

Table 2. The predicted retention time (t_R) values of the remaining ziprasidone derivatives (TS1-TS10), obtained with use of the developed QSRR-PLS model.

Ziprasidone derivatives (impurities/metabolites)	Predicted t_R [min] by PLS-QSRR model
TS1	**12.055**
TS2	2.211
TS3	6.523
TS4	13.881
TS5	**11.780**
TS6	8.402
TS7	9.045
TS8	6.665
TS9	8.815
TS10	6.302
Unknown impurity, experimental t_R	**11.270**

3. Conclusion

The high agreement between LC-MS results and the QSRR prediction have confirmed good prognostic potential of the created QSRR models. Furthermore, the predicted t_R values for **TS1-TS10** basically differed from those for ziprasidone and its impurities (I-V) which indicates that the developed

QSRR model can be successfully used for the separation of ziprasidone from the other ziprasidone derivatives.

Acknowledgments

This work was supported by the Ministry of Education and Science of the Republic of Serbia Contract No. 172033 and COST action CM1103.

References

[1] Harrison, T.S.; Scott, L.J. Ziprasidone: A review of its use in schizophrenia and schizoaffective disorder . *CNS Drugs*, 2009, 20 (12), 1027-1052.
[2] Pavlovic, M.; Malesevic, M.; Nikolic, K.; Agbaba, D. Development and validation of an HPLC method for determination of ziprasidone and its impurities in pharmaceutical dosage forms. *J. AOAC Int.*, 2010, 94 (3), 713-722.
[3] Gaussian 98 (Revision A.7), M. J. Frisch at al., Gaussian, Inc., Pittsburgh PA, **1998**.
[4] SIMCA P+ program, Version 12.0, Umetrics AB, Umea, Sweden, May 2008, www.umetrics.com
[5] Eriksson, L.; Johansson, E.; Kettaneh-Wold, N.; Trygg, J.; Wikstrom, C.; Wold, S. (Eds.) In: *Multi- and Megavariate Data Analysis. Basic Principles and Applications I*, 2nd ed., Umetrics Academy, Umeå, 2001, pp. 39-65.
[6] Nikolic K., Pavlovic M., Smoliński A., Agbaba D. The Chemometric Study and Quantitative Structure Retention Relationship modeling of Liquid Chromatography separation of Ziprasidone components. *Combinatorial Chemistry & High Throughput Screening* **2012**, 15, 730-744.
[7] Čarapić M, Nikolic K, Marković B, Petković M, Pavlovic M, Agbaba D.
Ultra-performance liquid chromatography tandem mass spectrometryfor the rapid, simultaneous analysis of ziprasidone and its impurities. Biomedical Chromatography. 2018;e4384. https://doi.org/10.1002/ bmc.4384