ANNALS OF "DUNAREA DE JOS" UNIVERSITY OF GALATI
MATHEMATICS, PHYSICS, THEORETICAL MECHANICS
FASCICLE II, YEAR X (XLI) 2018, No. 1

Article DOI: https://doi.org/10.35219/ann-ugal-math-phys-mec.2018.1.03

DETECTING PHENETHYLAMINES ACCORDING TO THEIR PHARMACOLOGICAL ACTIVITY

Stefanut Ciochina[2], Mirela Praisler[1]

[1]*"Dunarea de Jos" University of Galati, Department of Chemistry, Physics and Environment*
[2]*"Dunarea de Jos" University of Galati, Department of Mathematics and Computer Science*
Stefanut.Ciochina@ugal.ro, Mirela.Praisler@ugal.ro

Abstract
We are presenting a chemometrical system designed to detect controlled phenetylamines and classify them according to their pharmacological activity. The system detects these recreational drugs based on their spectra, recorded with a new portable GC - IRAS spectrometer, between 1405 and 1150 cm^1, specific its quantum cascade laser source of infrared radiation (UT8). A w_{TE} feature weight, defined by using the Fisher function, was first determined. A training set formed with the w_{TE} preprocessed spectra of the targeted compounds have then been subjected to Principal Component Analysis (PCA). The scores plots indicate that amphetamines and their main precursors, the ephedrines, are naturally clustering and may be successfully distinguished despite the high similarity of their molecular structures. The remarkable discrimination power of this computerized application recommends its use for forensic purposes and for establishing structure-activity correlations.

Keywords: Amphetamines, ephedrines, pattern recognition.

1. INTRODUCTION

Amphetamine, a methyl homologue of the mammalian neurotransmitter phenethylamine, and many of its analogues are increasingly abused as recreational drugs [1, 2]. Unfortunately, there are currently no effective drugs for treating amphetamine addiction, and drug tolerance develops rapidly in amphetamine abuse [3]. During the last decades, overdose on amphetamine, methamphetamine, and other substituted amphetamines resulted in thousands of deaths worldwide [1]. Therefore, important efforts have been made in the recent past in order to develop analytical instrumentation and data procesing methods that will allow a fast detection of amphetamines [4].

Amphetamine is the parent compound of a large structural class, which includes many psychoactive derivatives: stimulants like amphetamine itself and methamphetamine [5-7], hallucinogens / serotonergic empathogens like 3,4-methylenedioxymethamphetamine (MDMA) [8] and decongestants like ephedrine [9-11], among other subgroups.

As clandestine laboratories are frequently preparing amphetamines as solid salts [1-3], the portable analytical instruments that have been most recently built for *in-situ* scanning for amphetamines are infrared laser spectrometers [12]. We are presenting an artificial intelligence application designed to be embedded on a GC – IRAS portable scanner.

2. EXPERIMENTAL PART

The spectra have been recorded with a UT8 quantum cascade laser (QCL) source of infrared radiation, which emits between 1405 and 1150 cm^1 [13, 14]. The absorption has been measured with a resolution of 5 cm^{-1}. The input database consists of the spectra of 36 substances, i.e. 7 illicit stimulant amphetamines (class code M), 6 ephedrines (class code E), 6 hallucinogenic amphetamines (class code T) and 17 negatives (class code N) representing randomly selected chemicals of forensic interest [15-17]. Class M includes amphetamine and its main analogues (e.g. methamphetamine), class E contains ephedrine and its main analogues and isomers (e.g. pseudoephedrine and norephedrine), while class T is formed by 3,4-methylenedioxyamphetamines and its main analogues.

A w_{TE} feature weight has been calculated, based on the Fisher function, in order to identify the variables having the highest modeling and discrimination power [18-20]. For this purpose, the spectra of the hallucinogenic amphetamines (T) and of the ephedrines (E) included in the database have been included in class I and the spectra of the stimulant amphetamines (M) and of the negatives (N) in class II.

A new database, created by preprocessing the spectra with the w_{TE} function, was subjected to Principal Component Analysis (PCA) [21], which was performed with the MATLAB software package. The analysis of the cumulated explained variance has indicated that the three principal components (PCs) are enough for obtaining relevant score and loading plots.

The score plots have been analyzed in order to assess which clusters may be clearly distinguished [22]. The loading plots have been analyzed in order to identify which absorption bands are crucial for the recognition of each class identity.

The PCA scores obtained for the first three PCs and kernel density estimations have been then used in order to evaluate the potential overlap of the clusters identified in the score plots.

3. RESULTS AND DISCUSSION

The w_{TE} feature weight obtained as mentioned above is presented in Fig. 1. Its effect of the original spectra of the modeled compounds is illustrated in Fig.2. Corroborating these figures, we may conclude that the main effect of spectra preprocessing with the w_{TE} function is the enhancement of the intensity of the absorption bands found at 1245 and 1190-1195 cm^{-1} in the spectra of the hallucinogenic amphetamines. Indeed, these bands are very specific, as they are very stable in both position and shape [13-17]. Secondly, we should notice that the w_{TE} preprocessed spectra of hallucinogens and of ephedrines display much stronger bands in the 1405 - 1150 cm^1 spectral domain than their M and N counterparts.

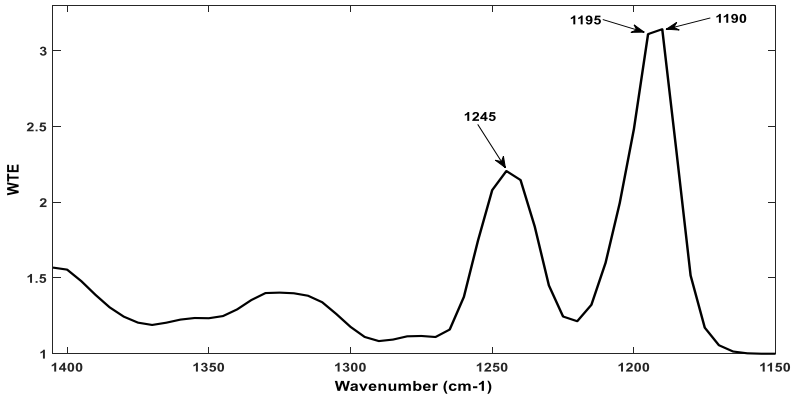

Figure 1. w_{TE} feature weight used for preprocessing the infrared spectra.

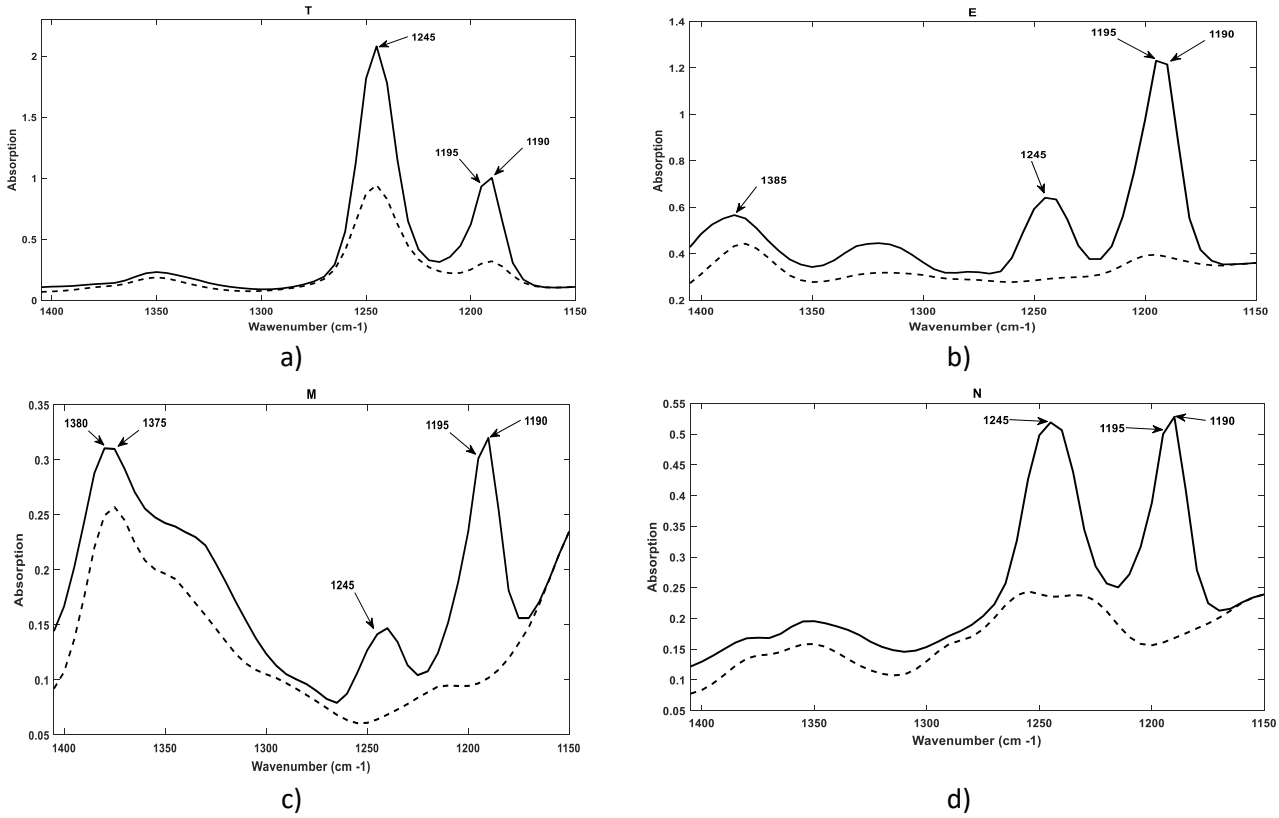

Figure 2. Mean spectra of: a) hallucinogenic amphetamines (class T); b) ephedrines (class E; c) stimulant amphetamines (class M); negatives (class N) unprocessed (- - -) and preprocessed with the w_{TE} selective amplifier (___).

The number of principal components (PCs) needed for obtaining good quality clustering has been established based on the explained variance characterizing the first PCs. As shown in Fig. 3, the first three PCs are cumulating most of the explained variance. Hence, the score plots have been determined for the first three PCs.

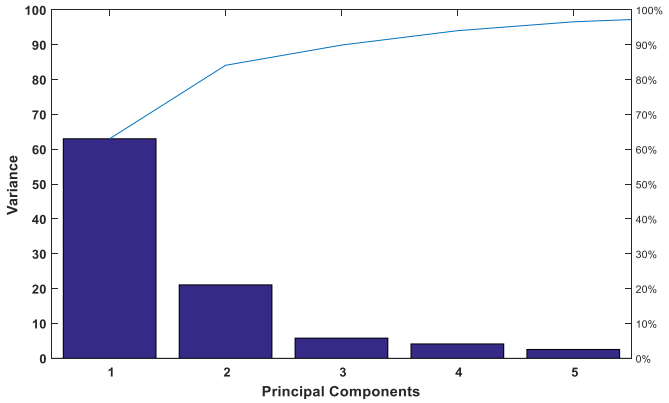

Figure 3. Explained variance obtained with the w_{TE} preprocessed spectra.

The resulting score and loading plots obtained for PC1 and PC2 are presented in Fig. 4. The score plot (see Fig. 4a) indicates that the hallucinogens (T) form a dense cluster in quadrant I. The loading plot indicates that the most important absorptions that are generating this cluster are those around 1245 cm^{-1}. Taking into account that all the wavenumbers between 1260 and 1235 cm^{-1} are

contributing to this cluster, we may conclude that the class identity is assigned not based on the presence of the 1245 cm^{-1} peak, but also by taking into account the shape (envelope) of this absorption band.

The cluster formed by the ephedrines (E) may also be easily distinguished. Found in quadrant IV, ephedrines are the only compounds characterized by small positive PC1 scores and large negative PC2 scores (see Fig. 4a). Their discrimination is ensured by the presence of the 1190 – 1195 cm^{-1} peak and the *lack* of the absorption band specific to the hallucinogens, i.e. 1245 cm^{-1} (see Fig 4b, Fig. 2b and Fig. 2a).

On the other hand, the cluster formed by the stimulant amphetamines (M), found at the border between the quadrants II and III, is closely surrounded by a cloud of negatives (N). Hence, these two classes of compounds may not be easily distinguished based on their (PC1, PC2) scores.

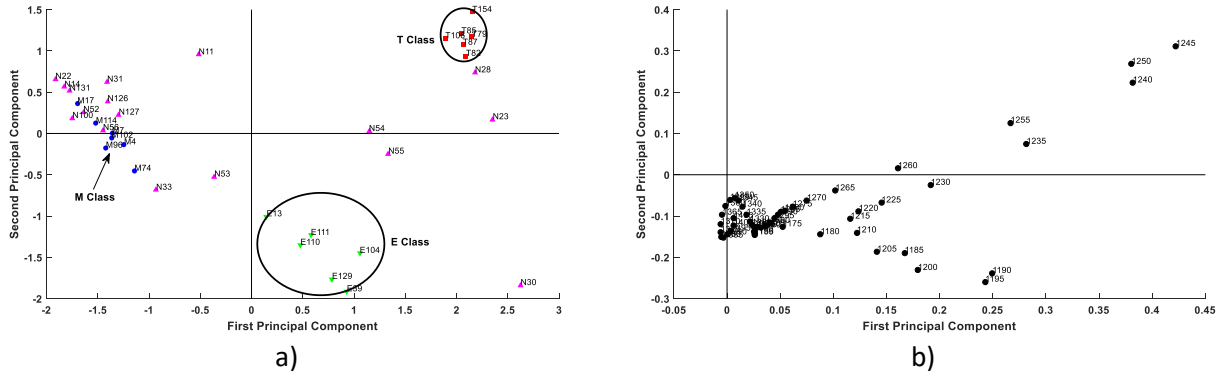

Figure 4. Principal Component Analysis for the first two principal components characterizing stimulant amphetamines (M), hallucinogenic amphetamines (T) and negatives (N): a) score plot; b) loading plot.

The PC1 vs. PC3 score and loading plots are presented in Figure 5. The T and E clusters are still well defined, although they are now both located in quadrant IV and closer one to each other than in the PC1 vs. PC2 score plot. The third PC does not improve the discrimination of the M and N clusters (see Fig. 5 and 6).

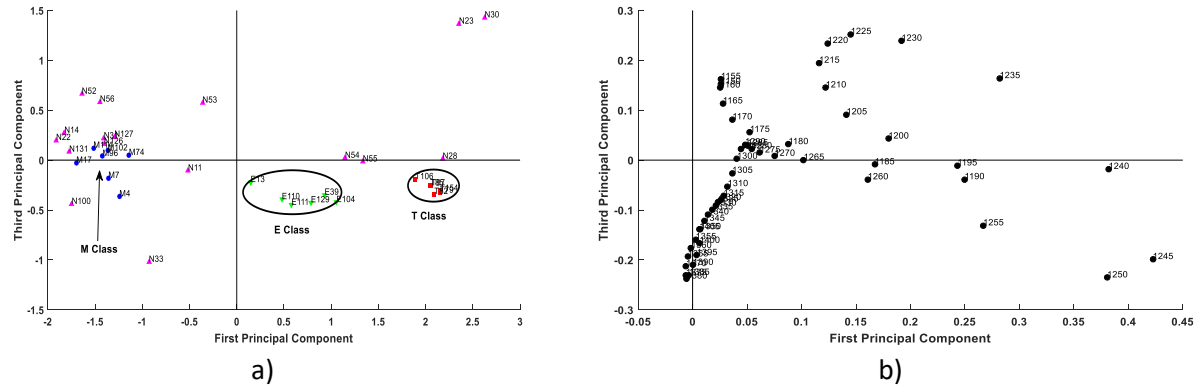

Figure 5. Principal Component Analysis for the first and third principal components characterizing stimulant amphetamines (M), hallucinogenic amphetamines (T) and negatives (N): a) score plot; b) loading plot.

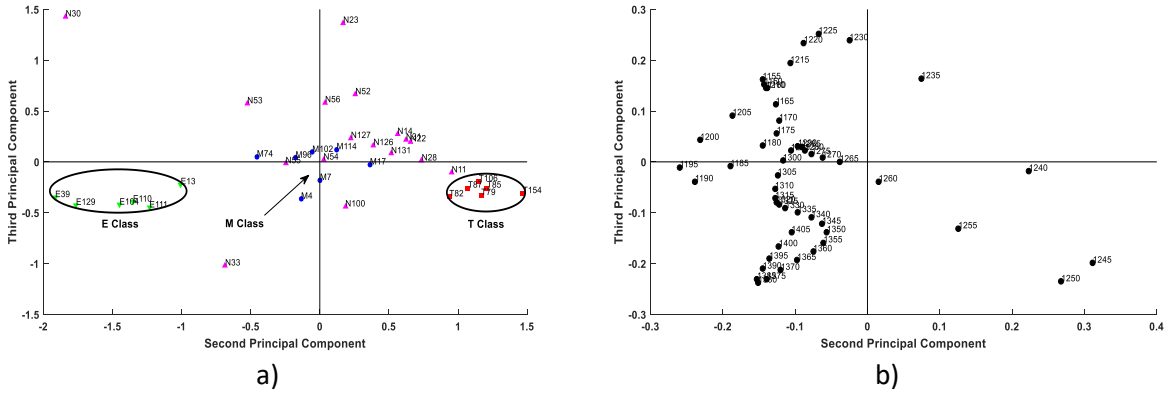

Figure 6. Principal Component Analysis for the second and third principal components characterizing stimulant amphetamines (M), hallucinogenic amphetamines (T) and negatives (N): a) score plot; b) loading plot.

The potential overlap of the clusters, evaluated by using kernel density estimations, is presented in Fig. 5. We may notice that, due to the fact that the negatives have very different molecular structures and thus very different spectra, their associated points present in the score plots cover the whole range of PC1, PC2 and PC3 scores. However, the probability of misclassifying negatives as (false) hallucinogenic amphetamines (T) or as (false) ephedrines (E) is very low. These plots confirm that the highest probability of misclassification appears for the negatives (N) and stimulant amphetamines (M).

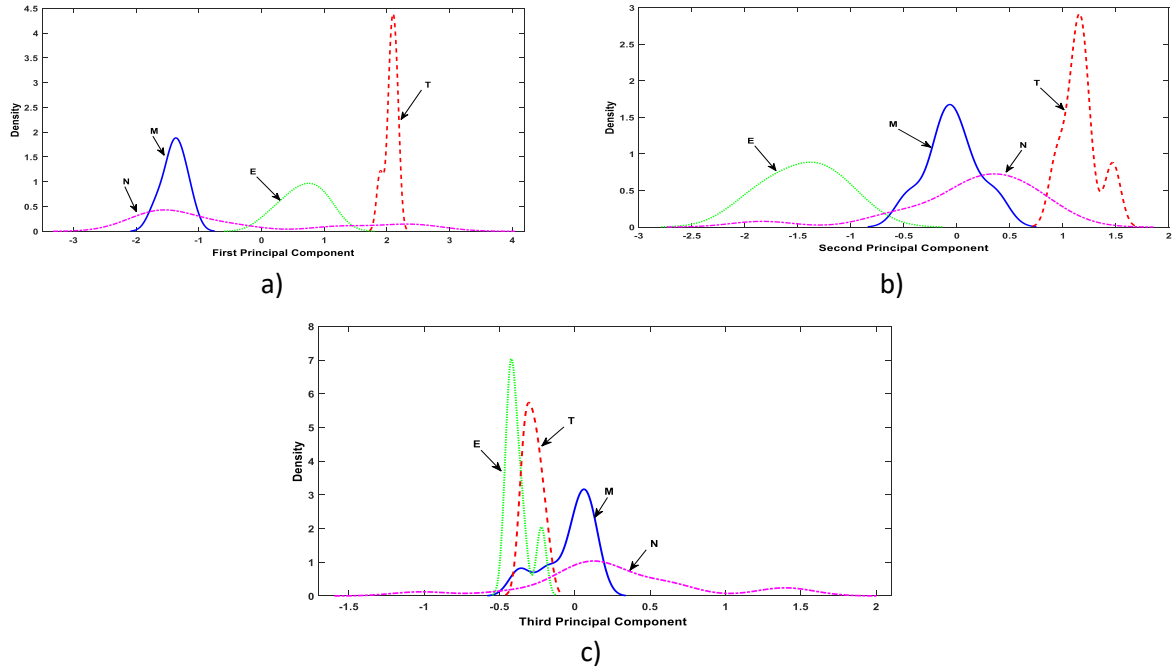

Figure 5. Estimated density associated to the PC scores of stimulant amphetamines (M), ephedrines (E), hallucinogenic amphetamines (T) and negatives (N): a) PC1; b) PC2; c) PC3.

4. CONCLUSION

The broad range of chemicals that cause the "amphetamine use disorder" contains amphetamine as a backbone and derivatives that are formed by replacing one or more hydrogen atoms

in the amphetamine core structure with small chemical groups. The results presented in this study indicate that PCA is a useful tool for distinguishing hallucinogenic amphetamines and ephedrines from other types of compounds, as well as among themselves. With this system, once a compound is classified as a negative, it may as well be a compound belonging to the class of stimulant amphetamines (M). Therefore, further analysis is necessary in order to distinguish the latter controlled substances.

Acknowledgements

Part of the research has been funded by EC under the grant agreement n FP7-SEC-2009-242309 DIRAC. The work of Stefanut Ciochina has been funded by the Romanian Ministry of European Funds within the POSDRU/107/1.5/S/76822 project. The authors are grateful for the financial support.

References

1. United Nations Office on Drugs and Crime (UNODC), *World Drug Report 2017, Part 4: Market analysis of synthetic drugs: Amphetamine-type stimulants, new psychoactive substances*, United Nations, 2017.
2. European Monitoring Centre for Drugs and Drug Addiction (EMCDDA), *European Drug Report 2017: Trends and developments*, 2017.
3. S. Karch, *Drug of Abuse Handbook*, 2nd ed. Boca Raton: CRC Press, 2007.
4. European Monitoring Centre for Drugs and Drug Addiction (EMCDDA), *Drug supply reduction: an overview of policies and measures*, 2017.
5. A.H. Ashok, Y. Mizuno, N. D. Volkow, and O. D. Howes, Association of Stimulant Use with Dopaminergic Alterations in Users of Cocaine, Amphetamine, or Methamphetamine: A Systematic Review and Meta-analysis, *JAMA Psychiatry* 74 (2017) 511-519.
6. W. P. Knapp, B. G. O. Soares, M. Farrel, and M. S. Lima, Psychosocial interventions for cocaine and psychostimulant amphetamines related disorders, *Cochrane Database of Systematic Reviews* 3 (2007) CD003023.
7. A. Turcant, M. Deguigne, S. Ferec, C. Bruneau, I. Leborgne, B. Lelievre, C. Gegu, F. Jegou, C. Abbara, G. Le Roux, and D. Boels, A 6-year review of new psychoactive substances at the Centre antipoison Grand-Ouest d'Angers: Clinical and biological data, *Toxicologie Analytique et Clinique*, vol. 29 (2017) 18-33.
8. R. Laing (Ed,), *Hallucinogens. A Forensic Drug Handbook*, London: Academic Press, 2003.
9. A. Momaya, M. Fawal, and R. Estes, Performance-Enhancing Substances in Sports: A Review of the Literature, *Sports Medicine* 45 (2015) 517-531.
10. H. U. Yavuz and D. Ozkum, Herbs Potentially Enhancing Sports Performance, *Current Topics in Nutraceutical Research* 12 (2014) 25-34.
11. J. C. Wagner, Enhancement of Athletic Performance with Drugs - An Overview, *Sports Medicine* 12 (1991) 250-265.
12. J. M. Chalmers, H. G. M. Edwards, M. D. Hargreaves, *Infrared and Raman Spectroscopy in Forensic science*, Chichester: Wiley, 2012.
13. M. Praisler, S. Ciochina, C. Negoita, Improved Selectivity in Detecting Controlled Amphetamines and their Main Precursors based on Laser Infrared Spectra, *2017 E-Health and Bioengineering Conference, EHB 2017*, 28 July 2017, pp. 233-236. Article number 7995404.
14. S. Ciochina, M. Praisler, C. Negoita, Cluster Analysis Evaluating the Automated Detection of Drugs of Abuse with a New Hollow Fiber based Quantum Cascade Laser Infrared Spectrometer, *2017 E-Health and Bioengineering Conference, EHB 2017*, 28 July 2017, pp. 237-240. Article number 7995405.

15. M. Praisler, S. Ciochina, M. Coman, Screening for Illicit Psychoactive Drugs Based on Pattern Recognition Methods, *5th International Symposium on Electrical and Electronics Engineering, ISEEE 2017*, 20-22 October 2017, Galati, Romania
16. S. Ciochina, M. Praisler, M. Coman, Hierarchical Cluster Analysis Applied for the Automated Recognition of Psychoactive Substances and of Their Main Precursors, 2017 5th International Symposium on Electrical and Electronics Engineering (ISEEE), 20-22 October 2017, Galati, Romania.
17. M. Praisler, S. Ciochina, M. Coman, Hunting for Illicit Psychoactive Substances and Precursors: a Multivariate Approach, in Kloetzer, M; Ferariu, L. (Eds), *2017 21st International Conference On System Theory, Control And Computing (ICSTCC),* Book Series: International Conference on System Theory Control and Computing, 2017, pp. 248-253. Article number 8107042.
18. S. Gosav, M. Praisler, D. O. Dorohoi, G. Popa, Structure – Activity Correlations for Illicit Amphetamines Using ANN and Constitutional Descriptors, *Talanta -The International Journal of Pure and Applied Chemistry* 70 (2006) 922-928.
19. S. Gosav, M. Praisler, D. O. Dorohoi, ANN Expert System Screening for Illicit Amphetamines using Molecular Descriptors, *Journal of Molecular Structure* 834-836 (2007) 188-194.
20. S. Gosav, M. Praisler, Artificial Neural Networks Built for the Recognition of Illicit Amphetamines Using a Concatenated Database, *Romanian Reports of Physics* 54-9/10 (2009) 929–935.
21. I. T. Jolliffe, *Principal Component Analysis*, 2nd ed. New York: Springer, 2002.
22. M. Praisler, S. Ciochina, Global clustering quality coefficient assessing the efficiency of PCA class identity assignment, *Journal of Analytical Methods in Chemistry*, volume 2014 (2014), Article ID 342497.