کارگاه های آموزشی مرکز اطلاعات علمی جهاد دانشگاهی

کارگاه آنلاین کاربرد نرم افزار SPSS در پژوهش

کارگاه آنلاین اصول تنظیم قراردادها

کارگاه آنلاین پروپوزال نویسی
RP-HPTLC Retention Data in Correlation with the *In-silico* ADME Properties of a Series of s-triazine Derivatives

Lidija R Jevrić\(^a\), Sanja O Podunavac-Kuzmanović\(^a\), Jaroslava V Švarc-Gajić\(^a\), Strahinja Z Kovačević\(^a\)* and Bratislav Ž Jovanović\(^b\)

\(^a\)Department of Applied and Engineering Chemistry, Faculty of Technology, University of Novi Sad, Serbia. \(^b\)Institute for Chemistry, Technology and Metallurgy, University of Belgrade, Serbia.

**Abstract**

The properties relevant to pharmacokinetics and pharmacodynamics of four series of synthesized s-triazine derivatives have been studied by Quantitative structure-retention relationship (QSRR) approach. The chromatographic behavior of these compounds was investigated by using reversed-phase high performance thin-layer chromatography (RP-HPTLC). Chromatographic retention (\(R_M^0\)) was correlated with selected physicochemical parameters relevant to pharmacokinetics, i.e. ADME (absorption, distribution, metabolism and excretion). In addition, the ability to act as kinase inhibitors and protease inhibitors was predicted for all investigated triazine classes. Also, in order to confirm similarities/dissimilarities between series of examined compounds, principal component analysis (PCA) based on calculated ADME properties was conducted. The \(R_M^0\) values of the s-triazine derivatives have been recommended for description and evaluation of pharmacokinetic properties. According to results of this study, the synthesized s-triazine derivatives meet pharmacokinetic criteria of preselection for drug candidates.

**Keywords:** s-triazine derivatives; *In-silico*; ADME; PCA; Polynomial regression.

**Introduction**

Traditional drug development includes compound synthesis and pre-clinical *in-vitro* and *in-vivo* studies to determine whether such a compound can be considered as a candidate for clinical trial. Such procedures are normally accompanied with enormous costs measured in billions of dollars and more than a decade of interdisciplinary endeavor. In addition to high investments, many of tested candidates in later stages of drug development might demonstrate lack of efficiency, poor pharmacokinetics, animal toxicity and adverse effects in humans. For this, modern process of drug development is based on combinatorial chemistry, genomics, chemometrics and *in-silico* processing. While one group of these computational methods focuses on biological activity, trying to forecast interactions with target receptors (toxicodynamic), others tend to predict the fate of the substance in the human body *i.e.* its absorption, distribution, metabolism and excretion (ADME). Chemometrics has an important place in relating structural or property descriptors of a drug candidate to its biological activity (QSAR - Quantitative structure-activity relationship).
The 1,3,5-triazine (s-triazine) heterocyclic system is today found in a number of bioactive molecules such as herbicides and pharmaceutical products (1). Various triazine substituted molecules exhibit diverse biological activities, having thus been reported as potentially cardiotonic (2,3), anti-HIV (4,5), antitumor (6) and anticancer agents (7).

s-Triazine is a weak base with six-membered heterocyclic ring containing three nitrogens replacing carbon-hydrogen units in the benzene ring. The compound, so as its derivatives, has an excellent potential for the formation of non-covalent bonds, such as coordination and H-bonds, via its nitrogen ion-pairs (8). Non-covalent bonds have a very important role in biological activity of these compounds (9), but also in understanding of their physiological behavior, namely absorption, metabolism and elimination. Furthermore, such chemical properties of s-triazines are responsible for their characteristic chromatographic behaviour.

Molecular lipophilicity is one of the major physicochemical properties affecting oral absorption, cell uptake, protein binding, blood-brain penetration, and metabolism of bioactive substances (10). Cell membranes are relatively impermeable to hydrophilic compounds, so these are transported predominantly via paracellular route. Thus lipophilic character of the molecules enables passive diffusion through cell membrane and highly hydrophobic substances enter the cells easily. On the other hand, too high lipophilicity of drugs can be a limiting factor to oral absorption. In order to be absorbed via gut mucose, the substance needs first to be dissolved in hydrophilic mucose. Excessive lipophilicity is, thus, often linked to incomplete drug absorption after oral administration. Other mechanisms of compound transfer across the membrane not involving previous dissolution exist, such as endocytosis, but are mostly characteristic for large molecules (11). It is also generally believed that very lipophilic compounds have greater affinity for plasma-protein binding and are easily transported across the blood-brain barrier (12).

Chromatographic approach has been shown to be quite successful in modeling physicochemical and biological processes (13,14). Owing to its simplicity and efficiency, reversed-phase thin-layer chromatography appears especially attractive for lipophilicity determination (15,16). Taking into consideration that in reversed-phase chromatography solutes distribute between polar and nonpolar phases, calculated retention parameters can be adopted as indirect designators of compounds lipophilicity.

Considering the practical importance of s-triazine derivatives, the main objective of this study was to examine the retention behavior of four classes synthesized s-triazine derivatives in reversed-phase chromatographic systems of five different mobile phases. Novelty of the paper is the correlation between in-silico ADME properties of s-triazine derivatives and its retention behaviour in RP-HPTLC systems.

Chromatographic data were correlated to selected physicochemical properties related to ADME properties, obtained by the established computational medicinal chemistry methods (17). Observed parameters included human intestinal absorption (HIA), plasma protein binding (PPB), blood-brain barrier (BBB) penetration, skin permeability (SP) and oral absorption (expressed as Madin-Darby canine kidney cells (MDCK) and human colorectal carcinoma cells (Caco-2) permeability). In addition, bonding affinities to different receptors (ion channel modulator (ICM), G protein-coupled receptor (GPCR) and nuclear receptor (NRL)) were estimated for studied s-triazine derivatives, as well as protease inhibition (PI) and kinase inhibition (KI) ability.

Statistical validity of established correlation was tested by standard statistical parameters, such as Fisher’s criterion (F), correlation coefficient (r) and standard deviation (s), and cross-validation parameters (cross-validated coefficient of determination - $r^2_{cv}$, adjusted coefficient of determination - $r^2_{adj}$, predicted residual sum of squares - PRESS, total sum of squares - TSS, PRESS/TSS ratio , standard deviation based on predicted residual sum of squares - $S_{PRESS}$).

Principal component analysis (PCA), as a statistical tool for reducing dimensionality of a large number of interrelated variables and revelation of similarities among examined entities, was applied on the set of the calculated ADME properties of studied molecules. With
PCA as a method for identifying the main variation of the data is a crucial task in many fields. Instead of using the original data, new variables (principal components, PC) are defined. These components combine the original data in a way that PC1 captures as much of the variation within the data set as possible. The PC2 describes the maximum amount of residual variation after the PC1 has been taken into consideration, etc (18). The scores plot of the first two PCs is a 2-D map that provides an overview of the data and displays patterns or grouping within the data. The loadings plot shows the relationships between variables that contribute to the positioning of the objects on the scores plot.

**Experimental**

**Synthesis of s-Triazine derivatives**

The investigated compounds were 1,3,5-triazines substituted at positions 4 and 6 by smaller and larger groups with various lipophilic characteristics, chosen for investigation are presented in Table 1. Their melting points experimentaly (19, 20) and theoretical (21) observed, are shown in Table 1. All of investigated s-triazine derivatives were synthesized by the modified procedure of Thurston from cyanuric chloride and corresponding amines (22). In synthesis commercial cyanuric chloride (2,4,6-trichloro-1,3,5-triazine), was used (Fluka, Germany).

Reversed-phase high performance thin-layer chromatography

Precoated RP-18W/UV plates (Macherey-Nagel GmbH and Co., Düren, Germany) were used for RP HPTLC analysis. Investigated solvent mixtures used as mobile phases: acetone-water ($\phi = 0.5 - 0.8$; v/v), acetonitrile-water ($\phi = 0.5 - 0.9$; v/v), methanol-water ($\phi = 0.65 - 0.95$; v/v), 2-propanol-water ($\phi = 0.4 - 0.7$; v/v), tetrahydrofuran-water ($\phi = 0.5 - 0.75$; v/v).

The investigated compounds were dissolved in an appropriate solvent, methanol, 1 mg mL$^{-1}$) and the solutions (0.2 μL) were separately spotted

| Table 1. The chemical structures of studied s-triazines. |
| --- |
| **Series I** | **Series II** | **Series III** | **Series VI** |
| **Compound** | **R** | **Melting points °C** | **NMR spectra** | **Compound** | **R** | **n** | **Melting points °C** | **NMR spectra** | **Compound** | **R** | **R$_1$** | **R$_2$** | **Melting points °C** | **NMR spectra** | **Compound** | **R** | **n** | **Melting points °C** | **NMR spectra** |
| I.1 | -CH(CH$_3$)$_2$-C$_6$H$_5$ | 148-150 [21] | 201 [21] | II.1 | -CH(CH$_3$)$_2$-C$_6$H$_5$ | 173-175 [20, 22] | 306 [22] |
| I.2 | -CH(CH$_3$)$_2$-C$_6$H$_5$-4-CH$_3$ | 140-142 [21] | 229 [21] | II.2 | -CH(CH$_3$)$_2$-C$_6$H$_5$ | 158-160 [20, 22] | 327 [22] |
| I.3 | -CH(CH$_3$)$_2$-C$_6$H$_5$-4-Cl | 138-140 [21] | 257 [21] | II.3 | -CH(CH$_3$)$_2$-C$_6$H$_5$ | 121-122 [20, 22] | 365 [22] |
| I.4 | -CH(CH$_3$)$_2$-C$_6$H$_5$-4-Br | 146-148 [21] | 285 [21] | | | | |
| | | | | | | | |
| | | | | | | | |
| | | | | | | | |
| | | | | | | | |
| | | | | | | | |
| | | | | | | | |
| | | | | | | | |
| | | | | | | | |
| | | | | | | | |
| | | | | | | | |
| | | | | | | | |
| | | | | | | | |
| | | | | | | | |
| | | | | | | | |
| | | | | | | | |
| | | | | | | | |
| | | | | | | | |
| | | | | | | | |
| | | | | | | | |
| | | | | | | | |
| | | | | | | | |
| | | | | | | | |
| | | | | | | | |
| | | | | | | | |
| | | | | | | | |
| | | | | | | | |
| | | | | | | | |
| | | | | | | | |
| | | | | | | | |
| | | | | | | | |
| | | | | | | | |
| | | | | | | | |
| | | | | | | | |
| | | | | | | | |
| | | | | | | | |
| | | | | | | | |
| | | | | | | | |
| | | | | | | | |
| | | | | | | | |
| | | | | | | | |
| | | | | | | | |
| | | | | | | | |
| | | | | | | | |
| | | | | | | | |
| | | | | | | | |
| | | | | | | | |
| | | | | | | | |
| | | | | | | | |
| | | | | | | | |
| | | | | | | | |
| | | | | | | | |
| | | | | | | | |
| | | | | | | | |
| | | | | | | | |
| | | | | | | | |
| | | | | | | | |
| | | | | | | | |
| | | | | | | | |
| | | | | | | | |
| | | | | | | | |
| | | | | | | | |
| | | | | | | | |
| | | | | | | | |
| | | | | | | | |
| | | | | | | | |
| | | | | | | | |
| | | | | | | | |
| | | | | | | | |
| | | | | | | | |
| | | | | | | | |
| | | | | | | | |
| | | | | | | | |
| | | | | | | | |
| | | | | | | | |
| | | | | | | | |
| | | | | | | | |
into the plates. All the reagents used were of analytical purity. The plates were developed by the ascending technique at room temperature without previous saturation of the chamber with mobile phase. All measurements were carried out at ambient temperature. After drying of the plates, the spots were visualized under UV light at $\lambda = 254$ nm. $R_F$ values were calculated as average from three measurements for each solute-mobile phase combination. For subsequent calculations mean $R_M$ values were used; these were calculated by using the formula:

$$R_M = \log\left(\frac{1}{R_F} - 1\right)$$  

Equation (1)

The calculated $R_M$ values for different concentrations of organic solvent were used to check the linearity of their relationship with the volume fraction of organic modifier according to the equation (23):

$$R_M = R_M^0 + S\phi$$  

Equation (2)

Where $\phi$ is the volume fraction of organic solvent in the mobile phase, $R_M^0$ is the intercept obtained by extrapolation to $\phi = 0\%$ of modifier, and $S$ is the slope of the linear plot. Equations (1) and (2) served for deriving data for further QSAR studies.

### Statistical methods and descriptors calculation

The complete regression analysis and PCA were carried out by PASS 2005, GESS 2006, NCSS Statistical Softwares and Statistica version 8 program (24). Physicochemical and ADME properties were calculated using the PreADMET (25) and Molinspiration online programs (26).

### Results and Discussion

#### PCA

In order to obtain some basic insight into the similarities/dissimilarities among studied molecules on the basis of their ADME properties, PCA was carried out on the set of the calculated ADME properties. The first principal component (PC1) accounted for 47.31% of data variance and the second one (PC2) for 21.41%.

Score values for PC1 and PC2 are shown in Figure 1. and the mutual projections of the loading vectors in Figure 2. The loading graph reveals that significant negative influence on the PC1 have NRL, KI, PI, GPCR, EI and Caco-2 parameters. PPB, SP and MDCK have positive influence on the PC1. The most positive impact on the PC2 has BBB parameter, while ICM, HIA and MDCK parameters express negative impact on the PC2. Mentioned ADME properties are responsible for distribution of molecules on score plot that shows four well-separated groups.
of studied compounds. On the basis of presented PCA results it can be concluded that groups of examined molecules on the score plot are equal to the groups shown in Table 1 which are based on the molecular structure and substituents present in the examined compounds.

Results from regression analysis using well-known equation (2) according a procedure is described earlier (27). Calculated statistics illustrate that assumed linear dependence correlates very good with experimental data.

**Correlation of $R_M^0$ with biological activity predictors**

PPB, HIA, BBB, SP, MDCK and Caco-2 values (Table 2) were estimated for synthesized s-triazine derivatives by mathematical modeling using the PreADMET program. Molinspiration online program was used for druglikeness calculation (NRL, ICM, KI, PI, EI and GPCR). The retention data, their standard deviations and the characteristics of the $R_M = R_M^0 + S\phi$ equations are presented in Table 2 and Table 3. Calculated
ADME parameters are presented in Table 4.

Correlation analysis showed that the retention parameter correlates the best with KI and PI. Established mathematical models and its basic statistical parameters \( r, F, S \) are presented in Table 5.

Correlation coefficient higher than 0.90 indicates very high correlation between \( R^2 \) and selected ADME properties. F-value is found statistically significant at 99% level since all the calculated \( F \) values are higher as compared to tabulated values.

Equations 3-10 were cross-validated by the leave-one-out method (Table 6). High values of \( R^2_{cv} \) and \( R^2_{adj} \) (higher than 0.5) and PRESS values significantly less than TSS were obtained for all the models indicate that these models have very good predictive power (28). The prediction

| Molecule | HIA% | Caco-2 (nm/sec) | MDCK (nm/sec) | SP \((-\log Kp)\) | PPB% | BBB \((C_{total}/C_{inter})\) | GPCR | ICM | KI | NRL | PI | EI |
|----------|------|----------------|---------------|-----------------|------|----------------------------|-------|-----|----|-----|----|----|
| I.1      | 95.01| 29.72          | 0.20          | -2.30           | 89.27| 4.47                       | 0.07  | 0.12| 0.10| -0.20| -0.35| -0.09|
| I.2      | 95.28| 31.99          | 0.13          | -1.24           | 88.82| 7.21                       | 0.03  | 0.17| 0.06| -0.21| -0.38| -0.13|
| I.3      | 95.95| 44.38          | 0.09          | -2.22           | 93.61| 7.94                       | 0.06  | 0.12| 0.08| -0.20| -0.35| -0.10|
| I.4      | 96.22| 47.80          | 0.02          | -2.12           | 100.00| 8.32                       | 0.03  | -0.19| 0.01| -0.03| -0.32| -0.03|
| II.1     | 92.84| 24.25          | 1.79          | -2.40           | 100.00| 5.62                       | 0.14  | -0.19| 0.01| -0.03| -0.32| -0.03|
| II.2     | 93.28| 26.82          | 0.52          | -1.95           | 100.00| 7.36                       | 0.15  | -0.17| 0.02| 0.04  | -0.26| -0.08|
| II.3     | 93.70| 30.23          | 11.18         | -1.59           | 100.00| 8.75                       | 0.15  | -0.16| 0.02| 0.05  | -0.21| -0.07|
| III.1    | 92.85| 24.86          | 0.55          | -2.99           | 100.00| 6.62                       | 0.23  | -0.03| 0.16| -0.02| -0.24| 0.10 |
| III.2    | 97.69| 51.33          | 0.25          | -2.58           | 91.59 | 1.21                       | 0.34  | 0.02| 0.12| -0.03| -0.18| 0.15 |
| III.3    | 97.61| 52.76          | 1.49          | -2.53           | 92.25 | 1.87                       | 0.39  | -0.08| 0.26| -0.01| -0.20| 0.10 |
| III.4    | 98.03| 53.78          | 20.59         | -1.98           | 92.75 | 3.02                       | 0.26  | -0.07| 0.10| -0.04| -0.17| 0.05 |
| IV.1     | 95.36| 26.68          | 14.97         | -2.16           | 100.00| 2.10                       | 0.02  | -0.07| 0.11| -0.39| -0.39| -0.78|
| IV.2     | 95.41| 7.91           | 6.83          | -1.99           | 100.00| 2.10                       | 0.02  | -0.07| 0.11| -0.39| -0.39| -0.78|
| IV.3     | 95.46| 8.93           | 18.92         | -1.83           | 100.00| 2.99                       | 0.01  | -0.08| 0.30| -0.30| -0.67| -0.15|

Table 4. In silico ADME characteristics of studied compounds.

| Modifier | Acetone | Acetonitrile | Methanol | 2-Propanol | Tetrahydrofuran |
|----------|---------|--------------|----------|------------|-----------------|
| I. 1     | 0.0475  | 0.0705       | 0.0703   | 0.9303     | 0.0922          |
| I. 2     | 0.2228  | 0.3162       | 0.1381   | 0.1918     | 0.0950          |
| I. 3     | 0.1292  | 0.1916       | 0.1236   | 0.1717     | 0.1940          |
| I. 4     | 0.1341  | 0.1990       | 0.0610   | 0.0846     | 0.3027          |
| II. 1    | 0.1286  | 0.1828       | 0.1090   | 0.1513     | 0.3633          |
| II. 2    | 0.1399  | 0.2076       | 0.0967   | 0.1342     | 0.1077          |
| II. 3    | 0.2048  | 0.3038       | 0.1993   | 0.2767     | 0.0828          |
| III. 1   | 0.4059  | 0.6023       | 0.1985   | 0.2756     | 0.3306          |
| III. 2   | 0.2187  | 0.3246       | 0.1007   | 0.1398     | 0.1800          |
| III. 3   | 0.1401  | 0.2079       | 0.0901   | 0.1252     | 0.2069          |
| III. 4   | 0.2511  | 0.3727       | 0.2038   | 0.2830     | 0.1744          |
| IV. 1    | 0.1121  | 0.1737       | 0.3298   | 0.4579     | 0.4987          |
| IV. 2    | 0.1443  | 0.2235       | 0.0744   | 0.1033     | 0.0853          |
| IV. 3    | 0.3347  | 0.4757       | 0.0944   | 0.1311     | 0.2832          |
Table 5. Polynomial correlations between retention parameter ($R_M^0$) and ADME descriptors of studied compounds.

| Modifier       | Dependent variable | Polynomial regression: $Y = a \cdot (R_M^0)^2 + b \cdot R_M^0 + c$ | Eq.       |
|----------------|--------------------|---------------------------------------------------------------|-----------|
| Methanol       | KI                 | $a = -0.0807 \quad b = 0.6604 \quad c = -1.2173 \quad r = 0.9200 \quad F = 30.3 \quad s = 0.0903 \quad 3$ |
| Acetone        | KI                 | $a = -0.0885 \quad b = 0.7579 \quad c = -1.5169 \quad r = 0.9407 \quad F = 42.3 \quad s = 0.0782 \quad 4$ |
| Tetrahydrofuran| KI                 | $a = -0.1545 \quad b = 1.1238 \quad c = -1.9476 \quad r = 0.9481 \quad F = 48.8 \quad s = 0.0733 \quad 5$ |
| Methanol       | PI                 | $a = -0.0657 \quad b = 0.5851 \quad c = -1.5263 \quad r = 0.9153 \quad F = 28.4 \quad s = 0.0899 \quad 6$ |
| 2-Propanol     | PI                 | $a = -0.1967 \quad b = 1.1643 \quad c = -1.9652 \quad r = 0.9002 \quad F = 23.5 \quad s = 0.1069 \quad 7$ |
| Acetone        | PI                 | $a = -0.0524 \quad b = 0.5535 \quad c = -1.6536 \quad r = 0.9528 \quad F = 54.2 \quad s = 0.0745 \quad 8$ |
| Acetonitrile   | PI                 | $a = -0.1739 \quad b = 1.724 \quad c = -2.1923 \quad r = 0.9040 \quad F = 24.6 \quad s = 0.1049 \quad 9$ |
| Tetrahydrofuran| PI                 | $a = -0.0548 \quad b = 0.5981 \quad c = -1.7104 \quad r = 0.9507 \quad F = 51.7 \quad s = 0.0761 \quad 10$ |
| Methanol       | Caco-2             | $a = 0.1015 \quad b = 9.8956 \quad c = -1.2877 \quad r = 0.8045 \quad F = 10.906 \quad s = 0.7347 \quad 11$ |
| Acetone        | GPCR               | $a = 0.0108 \quad b = 0.0520 \quad c = -0.2221 \quad r = 0.7534 \quad F = 7.2244 \quad s = 0.1097 \quad 12$ |
| 2-Propanol     | NRL                | $a = -0.1709 \quad b = 0.9461 \quad c = -1.375 \quad r = 0.8013 \quad F = 9.8696 \quad s = 0.1149 \quad 13$ |
| Acetonitrile   | BBB%               | $a = -5.1906 \quad b = 26.874 \quad c = -28.0 \quad r = 0.7433 \quad F = 6.7929 \quad s = 2.0227 \quad 14$ |
| Acetone        | MDCK               | $a = 5.6721 \quad b = -38.794 \quad c = 66.88 \quad r = 0.6624 \quad F = 4.3025 \quad s = 6.2033 \quad 15$ |

Errors of the best equations (3-10) are presented in Table 7.

The main purpose of the conducted correlation analysis was to determine the ability to predict ADME properties of these molecules using chromatographic retention data, since the chromatography has been shown to be quite successful in modeling physicochemical and biological properties. ADME processes are dynamic in nature, as the chromatographic separations are (29).

Conclusion

Retention constants in reverse-phase chromatography of proposed synthesized $\pi$-triazine derivatives have been shown to be a useful and simple way in predicting biological activity and drug likeness. For all investigated derivatives, experimentally determined retention parameters, $R_M^0$, could be reliably correlated with some of the ADME properties. It was found that experimentally determined
retention parameter \( (R_m) \) of studied s-triazine derivatives was reliably correlated with in-silico calculated protease inhibition (PI) and kinase inhibition (KI) ability. Standard statistical measures and cross-validation parameters indicate that the established mathematical dependences between retention parameters and ADME properties are statistically valid. Also, PCA applied on both the retention parameters and calculated ADME properties showed similar grouping of molecules. That could indicate the similarity between retention behaviour and ADME properties of the examined molecules. On the basis of presented results it can be concluded that the retention parameters obtained by RP HPTLC could be successfully used for prediction of some in-silico ADME properties of studied compounds.

Acknowledgement

These results are part of the projects No. 114-451-2707/2012-01, financially supported by the Provincial Secretariat for Science and Technological Development of Vojvodina and project No. 31055, No. 172012, No. 172013 and No. 172014 supported by the Ministry of Science and Technological Development of the Republic of Serbia, 2011-2014.

References

(1) Blotny G. Recent applications of 2,4,6-trichloro-1,3,5-triazine and its derivatives in organic synthesis. Tetrahedron (2006) 62: 9507-9522.
(2) Kosary J, Kasztreiner E, Rabloczky G and Kurthy M. Synthesis and cardiotonic activity of 2,4-diamino-1,3,5-triazines. Eur. J. Med. Chem. (1989) 24: 97-99.
(3) Barraclough P, Firmin D, Lindon JC, Nobbs MS, Sanderson PN, Smith S and Gillam JM. Sites of protonation in cardiotonic polyazaindolizines by NMR spectroscopy. Magn. Reson. Chem. (1991) 29: 468-475.
(4) Patel RV, Kumari P, Rajani DP, Pannecoque C, De Clercq E and Chikhalia KH. Antimicrobial, anti-TB, anticancer and anti-HIV evaluation of new s-triazine-based heterocycles. Future Med. Chem. (2012) 4: 1053-1065.
(5) Desai NC, Bhatt JJ, Shah BR, Trivedi PB and Undavla NK. Anti-HIV activity of some non-nucleoside s-triazine derivatives (Part-IV). Indian J. Exp. Biol. (1996) 34: 584-587.
(6) Brzozowski Z, Saczewski F and Gdaniec M. Synthesis, structural characterization and antitumor activity of novel 2,4-diamino-1,3,5-triazine derivatives. Eur. J. Med. Chem. (2000) 35: 1053-1064.
(7) Corbett TH, Leopold WR, Dykes DJ, Roberts BJ, Griswold DP Jr and Schabel FM Jr. Toxicity and anticancer activity of a new triazine antifolate (NSC 127755). Cancer Res. (1982) 42: 1707-1715.
(8) Mooibroek TJ and Gamar P. The s-triazine ring, a remarkable unit to generate supramolecular interactions. Inorg. Chim. Acta. (2007) 360: 381-404.
(9) Ma JC and Dougherty DA. The Cation-π Interaction.
Chem. Rev. (1997) 97: 1303-1324.
(10) Waltber B, Vis P and Taylor A. In: Lipophilicity in Drug Action and Toxicology. V Pliska, B Testa and H Van de Waterbeemd (eds.) VCH, Weinheim (1996) 253-261.
(11) Švarc-Gajić J. General Toxicology. Novascience Publishers. New York (2009) 1-11.
(12) Mornar A, Medić-Šarić M and Jasparica I. ADME data for polyphenols characterized by reversed-phase thin-layer chromatography. J. Planar Chromatogr. (2006) 19: 409-417.
(13) Djaković-Sekulić T and Smoliński A. Chemometric characterization of s-triazine derivatives in relation to structural parameters and biological activity. Drug Dev. Ind. Pharm. (2010) 36: 954-961.
(14) Perišić-Janjić N, Kaliszan R, Wiczling P, Milošević N, Usurmilić G and Banjac R. Reversed-Phase TLC and HPLC Retention Data in Correlation Studies with in Silico Molecular Descirptors and Druglikeness Properties of Newly Synthesized Anticonvulsant Succinimide Derivatives. Mol. Pharmaceut. (2011) 8: 555-563.
(15) Jevrić L, Jovanović BZ, Velimirović S, Tepić A, Koprivica G and Mišljenović N. Application of lipophilicity parameters and biological activity. Chem. Ind. (2011) 65: 533-540.
(16) Jevrić L, Velimirović S, Koprivica G, Mišljenović N, Kuljanić T and Tepić A. Prediction og s-triazine components lipophilicity of total herbicides. Rom. Biotechnol. Lett. (2012) 17: 6882-6892.
(17) Buchwald Pand Bodor N. Computer-aided drug design: The role of quantitative structure-property, structure-activity, and structure-metabolism relationships (QSPR/QSAR/QSMR). Drug Future. (2002) 27: 577-588.
(18) Djaković Sekulić T and Perišić Janjić N. Study of the characteristics and separating power of unconventional tlc supports. ii. principal-components analysis. J. Planar Chromatogr. (2007) 20: 711.
(19) Carić GB. Thermal dealkylation of N-alkylamino of s-triazine derivatives. Correlation between mass spectrometry and pyrolytic reactivity, Faculty of Technology and Metallurgy, University of Belgrade, Serbia (1985) 59-67.
(20) Jovanović BZ. Study the kinetics of reactions of thermal dealkylation of 2,4-bis-(alkylamino)-6-chloro-s-triazine, Faculty of Technology and Metallurgy, University of Belgrade, Serbia (1978) 51-56.
(21) Muškalović MD, Jovanović BZ, Carić GB and Tadić ZD. Thermal Dealkylation of 2,4-Bis(alkylamino)-6-chloro s-triazines. effect of ring size on formation of Alicyclic Olefins. J. C. S. Perkin II (1978) 9: 948-951.
(22) Thurston T, Dudley R, Kaiser W, Hechenbleikner I, Schaefer C and Holm-Hansen J. Cianuric Chloride Derivatives. 1. (Aminochloro)-s-triazines. J. Am. Chem. Soc. (1951) 73: 2981-2983.
(23) Soczewinski E and Wachtmeister CAJ. The relation between the composition of certain ternary two-phase solvent systems and Rv values. Chromatogr. (1962) 7: 311-320.
(24) NCSS. NCSS 8 - Statistical Analysis & Graphics Software. [cited 2012 December 14]. Available from: URL: http://www.ncss.com/software/ncss.
(25) Preadmet. Web-based Application for Predicting ADME Data and Building Drug-like Library Using In-silico Method. [cited 2012 December 14]. Available from: URL: http://preadmet.bmdrc.org.
(26) Molinspiration Cheminformatics. Calculation of Molecular Properties and Bioactivity Score. [cited 2012 December 14]. Available from: URL: http://molinspiration.com.
(27) Perišić-Janjić N, Đaković-Sekulić T, Jevrić L and Jovanović B. Study of quantitative structure-retention relationships for s-triazine derivatives in different RP HPTLC systems. J. Planar Chromatogr. (2005) 18: 212-216.
(28) Podunavac Kuzmanović SO, Jevrić LR, Kovačević SZ and Kalajdžija ND. Chemometric Approach for Prediction of Antifungal Activity of some Benzoxazole Derivatives Against Candida albicans. Aptej (2012) 43: 273-282.
(29) Kaliszan R. QSPR: Quantitative Structure-(Chromatographic) Retention Relationships. Chem. Rev. (2007) 107: 3212-3246.

This article is available online at http://www.ijpr.ir
کارگاه‌های آموزشی مرکز اطلاعات علمی جهاد دانشگاهی

کارگاه آنلاین
کاربرد ویژه SPSS در پژوهش

کارگاه آنلاین
اصول تنظیم قراردادها

کارگاه آنلاین
بروپوزال نویسی