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Research Paper

Quantitative Structure-Retention Relationship Studies on a Series of 1,2,4-triazoles using HPTLC

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Abstract: Quantitative structure retention relationship studies have been performed on a series of 1,2,4-triazoles. The retention data was generated from HPTLC in the form of Retardation Factor (RF). Sequential multiple regression analysis was performed for QSRR model generation. Various electronic, topological and steric descriptors contribute to the models. The models generated are found to be robust, predictive and statistically significant.

Keywords: QSRR, HPTLC, 1,2,4-triazole, sequential multiple regression, RF, pRF.

INTRODUCTION

Triazoles constitute an important class of biologically active heterocyclic compounds that have received a great deal of attention since their discovery. The considerable biological importance of triazoles has stimulated a lot of interest in its derivatives. 1,2,4-triazoles, being an important pharmacophores have a wide range of therapeutic properties like antibacterial[1-4], antifungal[5-10], antimycobacterial[11-15], antiviral[16], anti-inflammatory[17-20], anticonvulsant[21-22], antidepressant[23], antitumoral[24-25], antihypertensive[26], analgesic[27], enzyme inhibitor[28], hypoglycemic[29], sedative, hypnotic[30], antiparasitic, herbicidal[31], insecticidal [32-33] and plant growth activities [34-37].

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Quantitative structure–activity relations (QSAR) describe how the molecular structure, in terms of descriptors—lipophilic, electronic and steric—affects the biological activity of a compound. [38-40] Similarly, quantitative structure–retention relations (QSRR) relate these descriptors to chromatographic retention. Quantitative structure retention relationships (QSRR) are among the most extensively studied procedures by which molecular chemical structure is quantitatively correlated with a well-defined physicochemical property of analytes, such as chromatographic retention. Chromatographic retention depends on the net effect of intermolecular interactions between the analyte, the stationary phase and the mobile phase.

The advantages of TLC methods consist in the very small amounts of sample needed

for the estimation and the less strict requirement of purity because the impurities separate during the chromatographic process. They are rapid and relatively simply, low cost and easy to perform. In addition, we have to stress the dynamic aspect of the chromatographic process and the wide choice of stationary phases and developing solvents.

QSRR studies using molecular modeling concentrate two essential points on the description of retention behavior. First one is the selection of meaningful descriptors that can only explain retention behavior, because there are so many available descriptors in QSRR studies, such as topological, geometrical, electronic, physicochemical and intermolecular descriptors. Second, the grouping of solutes is very important process to understand the retention behaviours. In order to get a reliable and precise prediction of retention in a given chromatographic system, it is required to group the structurally similar solutes.

QSRR has been traditionally perceived as a means of establishing correlation between trends in chemical structure modifications and respective changes in retention behaviour of the solutes in a given chromatographic system. Molecular structure is invaded through the generation of descriptors, which are numerical values corresponding to topological, geometric, or electronic structural features. The quantification of responsible physico-chemical properties was done with the help of regression techniques. The major objective of this study is to explore the responsible physico-chemical properties of 1,2,4-triazoles for chromatographic retention and to develop a QSRR equation which can be in future used to predict the chromatographic retention of 1,2,4-triazoles.

Experimental:

The present study comprises of QSRR analysis of a series of 1,2,4-triazoles containing 25 compounds. Earlier we have reported the synthesis and antimicrobial activities of some 1,2,4-triazoles.

For attempting QSRR analysis we needed a data set of compounds with a common pharmacophore with varied substitution. For our study we used the compounds synthesized by us. The HPTLC retention studies were performed using microsyringe (Linomat syringe 659.004, Hamilton-Bonaduz schweiz, Camag, Switzerland), pre-coated silica gel 60 F-254 glass plates (10 · 10 cm with 250 µm, thickness HPTLC; Merck, Germany), linomat 5 applicator, twin trough chamber 20 · 10 cm, saturation pad, UV chamber, TLC scanner III, winCATS version 1.4.0 software (Camag, Muttenz, Switzerland).

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Fixed quantity of each of the 25 compounds equal to 10 mg was dissolved separately in HPLC grade methanol to obtain concentration equal to 100μg/ml. The sample solutions were developed in two separate plates; one containing total 17 samples and another plate containing total 08 samples. Samples were applied to the plates as 5 mm bands, 5 mm apart, 15 mm from the bottom and left edge of the plate using a 100µL microsyringe and linomat 5 applicator. By optimization of the solvent system, cyclohexane: diethyl ether: methanol: ammonia (4:4:1:1) (v/v) was found to be the best system for resolution of the various components. The optimized chamber saturation time was 15 min at room temperature. Ascending development technique was carried out in twin trough chamber. The spots were allowed to dry and then the plates were placed as vertical as possible into the twin trough chamber equilibrated with the mobile phase vapours ensuring that the points of sample spots were above the surface of the mobile phase. A constant application rate of 150 nL s^{-1} was achieved by use of a nitrogen aspirator. The distance covered by the solvent front was 7cm, which took about 8 minutes. After development the plates were dried in a current of air by means of an air-drier. The spots were scanned using TLC scanner 3 in the reflectance/absorbance mode at 254nm and at 366nm and all measurements were made by winCATS software. The R.F. values determined were converted to negative logarithm (pRF) so as to linearize the data for QSRR model building.

Molecular modeling studied were performed using CS ChemOffice and DRAGON software while the regression analysis was performed using VALSTAT[42] program. The 2D structures of all the compounds were constructed in builder module of Chem Draw software. The 2D structures of the compounds were transferred to Chem 3D and were subjected to energy minimization by three different techniques: (1) By MM2 method keeping the RMS gradient at a value of 0.100 kcal/mol, (2) by MMFF94 method keeping the RMS gradient at 0.100 kcal/mol & (3) by GAMESS module using Austin Mechanics – 1 (AM1) method. The energy minimized structures were saved in the form of MDL mol files with .mol extension. The MDL mol files were used for calculation of the physico-chemical descriptors of the compounds with the help of DRAGON software. The calculated descriptors were saved and then used for QSRR model building with the help of VALSTAT program.

The physico-chemical descriptors

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calculates were transferred to the statistical program in order to establish a correlation between physico-chemical parameters as independent variables and pRF as dependent variable employing sequential multiple regression analysis (SQMLR). In sequential multiple linear regression, the program searches for all the permutation and combination sequentially for the given data set. The statistical quality of the SEQ-MLR equations were assessed by parameters like correlation coefficient (r), standard error of estimate (SEE), sequential Fischer test(F) at specified degree of freedom (*df*) and explained variance (r^2_{adj}). The internal predictive powers of the equations were validated by (leave one out or LOO) method using predicted residual sum of squares (PRESS), cross validation squared correlation coefficient (Q^2), standard deviation based on PRESS (S_{PRESS}), total sum of squares (SSY) and standard deviation of error of prediction (S_{DEP}). Chances of fortuitous correlation were tested with the help of Y-scrambled test. The data within the parenthesis is the standard deviation associated with the coefficient of descriptor in regression equation.

Results and Discussion:

In the present study, QSRR analysis has been performed to gain insight into the molecular mechanisms underlying chromatographic separation using Hansch approach. Various univariate, bivariate, trivariate, tetravariate and pentavariate equations were developed. It was observed that a significant increase in the r^2 (correlation coefficient) took place with increase in number of independent variables form 1 to 4 and only a slight increase afterwards. We present here only the tetravaraite and pentavariate regression models that were found statistically significant in all respects. The various descriptors that contributed the developed models are discussed in table 1 and table2.

Model – 1

pRF = [2.974(±0.519)] + **BEHe3** [-0.307 (±0.283)] + **BEHe6** [0.955(±0.198)] + **ATS7p** [-0.684(±0.141)] +**Mor32m**[-0.172(±0.107)] ….(1)

n	=	25
r	=	0.828
r^2	=	0.686
r^2adj	=	0.623
Variance	=	0.027
STD	=	0.165
F	=	7.897

Model – 2

pRF= [3.146(±0.537)] + **BEHe3** [-1.272(±0.283)] + **BEHe6** [0.923(±0.199)] + **ATS7p** [-0.626(±0.149)] + **Mor32m** [-0.119(±0.117)] + **R2v** [-0.242(±0.215)]….(2)

n	=	25
r	=	0.840
r^2	=	0.706
r^2adj	=	0.628
Variance	=	0.027
STD	=	0.164
F	=	9.116

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Model – 3

pRF= [3.230(±0.575)] + **BEHe3** [-1.440(±0.311)] + **BEHe6** [0.992(±0.201)] +**ATS7p** [-0.722(±0.145)] + **Mor32m** [-0.296(±0.161)] + **Mor13p** [-0.148(±0.144)] ……..(3)

n	=	25
r	=	0.838
r^2	=	0.703
r^2adj	=	0.625
Variance	=	0.027
STD	=	0.164
F	=	8.980

Model-1 is a four parametric equation and has a correlation coefficient (0.828), which accounted for 62.3% of variance in the activity. The data showed that overall internal statistical significance level better than 99.9% as it exceeded the tabulated $F_{(5,19\ \alpha\ 0.001)}$ = 6.6226. Sequential Fischer test recommended that equations are applicable for more than 999 times out of 1000.

Model – 1		Model – 2		Model - 3	
Validation parameter	**Value**	**Validation parameter**	**Value**	**Validation parameter**	**Value**
QF	5.032	**QF**	5.138	**QF**	5.099
PE	0.042	**PE**	0.039	**PE**	0.040
FIT	1.066	**FIT**	0.912	**FIT**	0.898
AIC	0.041	**AIC**	0.044	**AIC**	0.044
Bootstrapping r^2	0.677	**Bootstrapping r^2**	0.704	**Bootstrapping r^2**	0.673
Bootstrapping std	0.153	**Bootstrapping std**	0.149	**Bootstrapping std**	0.176
Chance	< 0.001	**Chance**	< 0.001	**Chance**	< 0.001
Standard Fmax value at 95% confidence	8.745	**Standard Fmax value at 95% confidence**	8.765	**Standard Fmax value at 95% confidence**	8.765
Q^2	0.529	**Q^2**	0.539	**Q^2**	0.528
S_{press}	0.202	**S_{press}**	0.205	**S_{press}**	0.207
S_{DEP}	0.180	**S_{DEP}**	0.178	**S_{DEP}**	0.180

Model revealed that the dependent variable can be predicted from a linear combination of the independent variables. The p-value is less than 0.001 for each physico-chemical parameters involved in model generation. We have also made efforts to investigate predictive power of the proposed model by using quality factor (QF) considering Pogliani's method. QF is defined as the ratio of correlation coefficient to standard error of estimation (SEE). The larger value of QF (5.032) signifies better predictive power of the model.

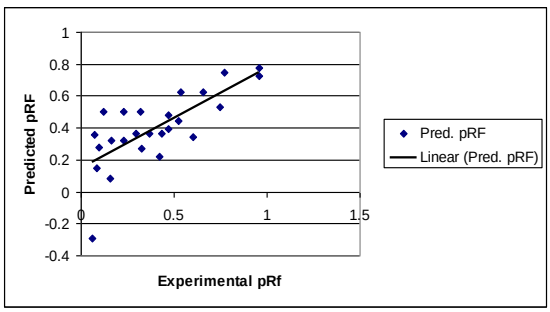

Fig. 1: Graph showing correlation of Experimental pRF with predicted pRF from Model 01.

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For reliability of the model, we have calculated regression associated statistical parameter called probable error of correlation (PE). Goodness of fit is calculated as PE = $2(1-r^2)/3\sqrt{n}$, if the value of correlation coefficient (r) is more than six times of PE than the expression is good and reliable. In model-1 the value of correlation coefficient is significantly higher than 6PE supporting reliability and

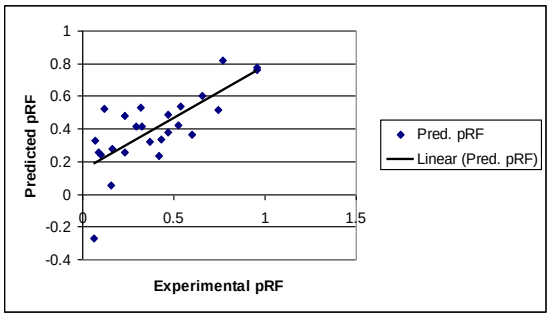

Fig. 2: Graph showing correlation of Experimental pRF with predicted pRF from Model

goodness. The model was further analyzed for the outlier by the Z-score method (Z

Table 1: Values of the calculated descriptors.

Comp. Name	Descriptors						R.F.	Prf
	BeHe3	BeHe6	ATS7p	Mor32m	Mor13p	R2v		
A1	1.945	0	0	0.299	-0.412	1.143	0.37	0.2291
A2	2.56	1.794	1.648	0.513	-1.008	1.15	0.82	0.4202
A3	2.76	1.834	0.796	0.528	-1.047	1.158	0.34	0.7447
A4	3.1	2.009	0.543	0.558	-1.108	1.044	0.25	0.0969
A5	2.755	1.916	1.22	0.662	-1.258	1.246	0.38	0.6576
A6	2.739	1.983	0.974	0.355	-0.797	1.214	0.18	0.4685
A7	2.881	1.978	1.004	0.391	-0.959	1.371	0.85	0.0605
A8	2.891	2.056	1.004	0.595	-0.976	1.393	0.43	0.3665
A9	2.63	1.743	1.03	-0.537	0.575	1.201	0.29	0.1549
A10	3.16	2.299	0.927	0.502	-1.251	1.48	0.59	0.2924
B1	2.055	0	0	0.142	-0.263	1.159	0.69	0.0862
B2	2.241	0.488	0	0.208	-0.396	0.926	0.48	0.0706
B3	2.254	0.824	0	0.233	-0.48	0.769	0.11	0.1192
B4	2.418	1.25	1	0.233	-0.675	0.788	0.47	0.6021
B5	3.254	2.257	1	0.573	-1.535	1.329	0.7	0.3279
C1	2.845	2.055	0.75	0.442	-0.945	1.204	0.22	0.9586
C2	2.945	2.055	0.753	0.545	-1.087	1.26	0.59	0.5229
C3	3.171	2.142	0.632	0.479	-1.115	0.979	0.51	0.1612
C4	2.783	1.654	0.625	0.238	-0.529	1.17	0.3	0.3188
C5	3.044	2.055	0.682	0.538	-1.146	1.202	0.34	0.4685
C6	3.016	2.055	0.632	0.545	-1.142	1.083	0.76	0.5376
C7	3.482	2.257	0.853	0.823	-1.993	1.233	0.87	0.7696
D1	1.958	0	0	1.374	-0.495	1.371	0.8	0.4318
D2	3.254	2.399	0.393	-0.076	-0.384	0.763	0.17	0.2291
D3	1.623	0	0	0.076	-0.195	1.009	0.11	0.9586

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value), the outliers help in the identification of unexplainable structurally diverse analogs. The persuasive QSRR model should not have any outlier. The Z value for individual compounds lies within the specific range (<I2.5I), which indicated the absence of outliers. Test revealed that the model is able to explain the structurally diverse analogs.

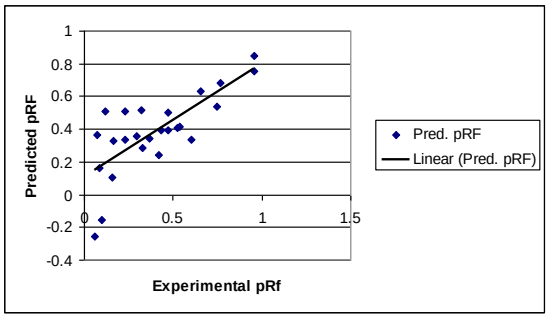

Fig. 3: Graph showing correlation of Experimental rf with predicted rf from Model 03.

Table 2: Details of the descriptors used

S. No.	Descriptor Name & details of the descriptors
1	**BEHe3:** Highest Eigen value n, 3 of burden matrix / weighted by electronic Sanderson electro-negativities. *BEHe3 is* associated with *BCUT* descriptors. *BCUT* descriptors are very powerful, structure-based molecular descriptors. Each *BCUT* combines physicochemical and structural information, derived from 2D or 3D structure, in a single number defined as Eigen values of the modified connectivity matrix, which is also called the Burden matrix B. The property evaluated includes atomic masses, Van der Waals volumes, Sanderson electro-negativities and polarizabilities. *BEHe3 is* 3rd order highest eigen values of Burden matrix corresponding to Sanderson electro-negativity. The ordered sequence of the *n* highest Eigen values of the Burden matrix has high discrimination power, which might be used in the recognition and ordering of molecular structures. The basic assumption was that the highest Eigen values contain contributions from all atoms and thus reflect the topology of the whole molecule. The **negative** contribution of BEHe3 revealed that it is un-favourable for the pRF and hence as the value of BEHe3 increases, the retention decreases.
2	**BeHe6:** Highest Eigen value n, 6 of burden matrix / weighted by electronic Sanderson electro-negativities. *BEHe6 is* 6th order highest Eigen values of Burden matrix corresponding to Sanderson electro-negativity. The basic assumption was that the highest Eigen values contain contributions from all atoms and thus reflect the topology of the whole molecule. The **positive** contribution of BEHe6 revealed that it is favouring the retention of the solutes on the stationary phase.
3	**ATS7p:** The ATS7p come from Broto-Moreau autocorrelation of topological structure (ATS) with polarizabilities (p) as the weighting parameter. The correlation of activity with autocorrelation vectors of lag seven indicate that structural fragment of corresponding lengths are enriched with affinity information. At the same time this descriptor indicates the role of polarizabilities of the compounds in deciding the affinity. The **negative** contribution of ATS7p reveals that the polar moiety would favor for fast elution of the compounds.
4	**Mor32m:** *Mor32m* is 3D molecular representation of structure based on electron diffraction

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	code (*MoRSE* code) *MoRSE* code was calculated by summing atom weights viewed by a different angular scattering function. The values of these code functions were calculated at 32 evenly distributed values of scattering angle(s) in the range of 0-31 Å^{-1} from the three-dimensional atomic coordinates of a molecule. The *3D-MoRSE* codes have great potential for representation of molecular structure. It is worth noting that they reflect the three dimensional arrangement of the atoms of a molecule and do not care about chemical bonds. The 3D-MoRSE code was calculated using following expression: $$I(s) = \sum_{i=2}^{N} \sum_{j=1}^{i-1} A_i A_j \frac{\sin sr_{ij}}{sr_{ij}}$$ Where, *s* is scattering angle, r_{ij} is the inter-atomic distance of i^{th} and j^{th} atom. A_i and A_j are atomic properties of i^{th} and j^{th} atom, respectively, including van der Waals volume, atomic mass, Sanderson atomic electro-negativity and atomic polarizability. The **negative** contribution of *Mor32m* revealed that sum of the properties calculated for the atoms (weighted by atomic mass) from the three-dimensional atomic coordinates at 31 Å^{-1} might enhance van der Walls interaction with mobile phase and enhance elution of the analyte.
5	**Mor13p:** *Mor13p* is 3D molecular representation of structure based on electron diffraction code (*MoRSE* code) *MoRSE* code was calculated by summing atom weights viewed by a different angular scattering function. The values of these code functions were calculated at 32 evenly distributed values of scattering angle(s) in the range of 0-31 Å^{-1} from the three-dimensional atomic coordinates of a molecule. The *3D-MoRSE* codes have great potential for representation of molecular structure. It is worth noting that they reflect the three dimensional arrangement of the atoms of a molecule and do not care about chemical bonds. The 3D-MoRSE code was calculated using following expression: $$I(s) = \sum_{i=2}^{N} \sum_{j=1}^{i-1} A_i A_j \frac{\sin sr_{ij}}{sr_{ij}}$$ Where, *s* is scattering angle, r_{ij} is the inter-atomic distance of i^{th} and j^{th} atom. A_i and A_j are atomic properties of i^{th} and j^{th} atom, respectively, including van der Waals volume, atomic mass, Sanderson atomic electro-negativity and atomic polarizability. The **negative** contribution of **Mor13p** reveals that the polar moiety would favor for fast elution of the compounds.
6	**R2v:** R2v is the GETAWAY class of descriptors represents [GEometry, Topology and Atom-Weights AssemblY] group of descriptors, which are based on a leverage matrix. These molecular descriptors match the three dimensional molecular geometry provided by the molecular influence matrix and atom relatedness by molecular topology, with chemical information by using various atomic weight schemes like atomic mass, polarizability, van der Waals volume, and electro- negativity. Therefore, this class of descriptors is highly sensitive to the 3-dimensional molecular structure. GETAWAY descriptors are used to compare molecules or even conformers taking into account their molecular shape, size, symmetry and atom distributions. **Negative** contribution of R2v descriptor encoding both geometrical information given by the influence molecular matrix and the topological information given by the molecular graph, weighted by Vander Waals volumes is significant for the elution.

The chance of fortuitous correlation is checked with the help of Y-scrambling data test considering Chance parameter, which is evaluated as ratio of the

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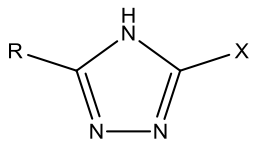
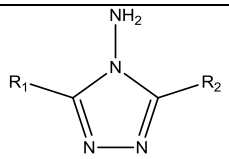
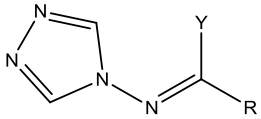
equivalent regression equations to the total number of randomized sets. Chance value of 0.001 corresponds to 0.1% chance of fortuitous correlation. Chance value (less than 0.001) of model-1 revealed that the result was not based on prospective correlation. Internal predictivity of the model-1 was assured with the help of cross-validated constraints like Q^2, S_{PRESS} and S_{DEP} obtained by 'leave one out (LOO)' cross validation method. This model was built by n-1 compounds and the nth compound was predicted. The value of $Q^2 > 0.5$ is the basic requirement for declaring a model to be a valid one. The internal consistency of the model supported by Q^2 (0.529), S_{PRESS} (0.202) and S_{DEP} (0.180) values.

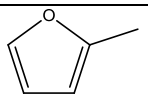
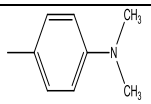
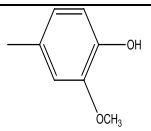
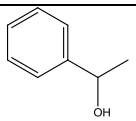
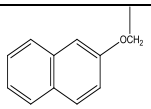
The various statistical validation results of the three models are as follows:

Table 3a: Structures of 1,2,4-triazoles used in the QSRR study.







Compd. Code	Substituent (R)	R.F.	Compd. Code	Substituent (R1)	Substituent (R2)	R.F.	Compd. Code	Substituent (R)	Substituent (Y)	R.F.
A1	CH_3	0.37	**B1**	H	H	0.69	**C1**	C_6H_5	H	0.22
A2 (S11)	C_6H_5	0.82	**B2**	CH_3	CH_3	0.48	**C2**	4-Cl-C_6H_5	H	0.59
A3	4-OH-C_6H_5	0.34	**B3**	C_2H_5	C_2H_5	0.11	**C3**	3-NO_2-C_6H_5	H	0.51
A4	4-NO_2-C_6H_5	0.25	**B4**	C_3H_7	C_3H_7	0.47	**C4**		H	0.3
A5	2,4-Cl_2-C_6H_5	0.38	**B5**	C_6H_5	C_6H_5	0.7	**C5**		H	0.34
A6	$C_6H_5OCH_2$	0.18	--	--	--	--	**C6**		H	0.76
A7	4-Cl-C_6H_5-OCH_2	0.85	--	--	--	--	**C7**		C_6H_5	0.87
A8	2,4-Cl_2- C_6H_5-OCH_2	0.43	--	--	--	--	--	--	--	--
A9	4-pyridyl	0.29	--	--	--	--	--	--	--	--
A10		0.59	--	--	--	--	--	--	--	--

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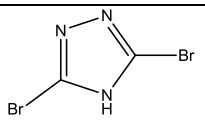
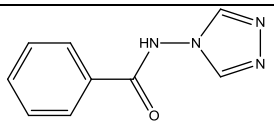
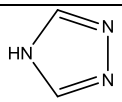
Similarly the models 2 and 3 are also found statistically significant after validation of the models using LOO method.

Table 3b: Miscellaneous compounds of the 1,2,4-triazole class used in QSRR study.

Compd. Code	Structure	R.F.
D1		0.8
D2		0.17
D3	 Purchased preformed from Loba chemie.	0.11

Conclusion: The QSRR analysis of 1,2,4-triazole analogs was successfully carried out to build a statistically significant model possessing a good correlative and predictive capability for the HPTLC retention. The QSRR model was validated by standard statistical means and through observation on how it reproduces and explains the quantitative differences seen in the experimentally known retention data.

The detailed structural investigation revealed that the chromatographic retention is predominantly explained by the **BEHe3**, **BeHe6**, **ATS7p**, **Mor32m, Mor13p,** and **R2v**. The study provided useful clues about the structural requirement for effective chromatographic retention. The identified equations might be used for the prediction of retention factor of the compounds.

The field is further open for study of these compounds with respect to advance QSRR techniques like CoMFA, CoMSIA, MSA, MFA in order to developed improved model for the retention prediction of 1,2,4 triazoles.

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