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RESEARCH ARTICLE

Drug penetration enhancement via skin in transdermal drug delivery through stratum corneum- QSAR Modeling

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Abstract:
The objective of this work was to develop a Quantitative Structure Activity Relationship (QSAR) model for understanding the effect of topological polar surface area, lipo-affinity index, fragment complexity and MLogP on the drug penetration power of penetration enhancers. For developing the model, Multiple Linear Regression (MLR) has been employed as an effective and efficient method and this model has been validated with statistical analysis such as fraction of variance, cross validation test, quality factor, standard deviation, and internal validation test. A regression based QSAR model has been developed with cross validation test $q^2 = 0.914$ and fraction of variance $r^2 = 0.913$, i.e. >90% predictive efficiency and all the statistical tests have validated this model.

Keywords: penetration enhancer; partition coefficient, topological polar surface area; lipo-affinity index; Fragment Complexity.

Introduction

The penetration enhancers are agents, which increase the permeability of the skin or temporally reduce the impermeability of the skin. Penetration enhancers or promoters are agents that have no therapeutic properties of their own but can transport the sorption of drugs from drug delivery system onto the skin[1]. There is considerable interest in the skin as a site of drug application both for local and systemic effect. However, the skin, in particular the stratum corneum, poses a formidable barrier to drug penetration thereby limiting topical and transdermal bioavailability[2]. The transdermal route now ranks with oral treatment as the most successful innovative research area in drug delivery, with around 40% of the drug delivery candidate products under clinical evaluation related to transdermal or dermal system.

Transdermal drug delivery is the administration of a therapeutic agent through intact skin for systemic effect. Transdermal drug delivery offers the following advantages over the oral route for controlled drug delivery- avoidance of hepatic first pass metabolism, ability to discontinue administration by removal of the system, ability to control drug delivery for a longer time than the usual gastrointestinal transit of oral dosage form, ability to modify the properties of the biological barrier to absorption[3].

In the present study, we developed a QSAR model on a series of penetration enhancer with respect to their logK. The QSAR studies are perfect tool for understanding the drug design process in terms of their chemical-pharmacological activity interaction, along with it is also used in toxicology and pesticide research. It can also be used for the evaluation of the metabolism, absorption, distribution and excretion phenomena.

The QSAR methodology comprises of computationally derived descriptors to correlate with pharmacological activities. These descriptors are principally of four types such as electronic, stearic, hydrophobic and topological indices [4]. The descriptors used for developing the QSAR model are topological polar surface area (TPSA); lifo-affinity index (LAI); fragment complexity (FC)[5], and MLogP.

Materials and method

Modeling parameters and structure optimization

The 2D structure construction, energy minimization and geometry optimization of the penetration enhancer were carried out by using ChemDraw Ultra 7.0 and Chem3D Pro 7.0 (CambridgeSoft Corporation, 100 CambridgePark Drive, Cambridge MA, 02140 USA) on an Intel(R) Core(TM)2 Duo Central Processing Unit T6670 @ 2.20 GHz and 4.00 GB of RAM, running the Windows 7 Home Basic, 64-bit compatible operating system. The energy minimization was carried out to minimum RMS Gradient of 0.100, with step interval of 2.0 Fs and frame interval of 10.

Descriptor selection

The selection of descriptors among the calculated descriptors for the multiple linear regression analysis is based on the correlation matrix. This matrix is prepared and analyzed for the least correlated descriptors.
All the bioactivity values and information about 2D structure of penetration enhancer were taken from literature[6]. LogK is variable that comprises the parameter for the QSAR model. In order to calculate the 2D molecular descriptors, PaDEL descriptor software[7, 8] which incorporates CDK library has been used. For the development of QSAR model, multiple linear regression analysis was employed[9].

Molecular descriptors Topological polar surface area (TPSA)

Topological polar surface area is calculated from molecular bonding information only. Hou et. al. has used the solvent-accessible surface area for calculating the topological polar surface area. Different procedures of surface calculations, even different calculation parameters may generate different TPSA[10].

Partition co-efficient (MLogP)

The partition coefficient is a ratio of concentrations of un-ionized compound between the two solutions. To measure the partition coefficient of ionizable solutes, the pH of the aqueous phase is adjusted such that the predominant form of the compound is un-ionized. The logarithm of the ratio of the concentrations of the un-ionized solute in the solvents is called log P. The log P value is also known as a measure of lipophilicity. MlogP is termed as molecular logP.

Lipo-affinity index (LAI)

The descriptor was defined based on Kier and Hall's atom-type electrotopological state indices. Its evaluation requires 2D molecular bonding information only[11].

Statistical parameters

In the QSAR model, number of data points is denoted as n, squared correlation coefficient as r^2 (fraction of variance), cross-validated r^2 is denoted as q^2, s is standard deviation. Q is quality factor, where $Q = r/s$ (here r is correlation coefficient and s is standard deviation).

Model validation

The QSAR model validation was carried with statistical analysis and with internal validation.

Results and Discussion

The 2D structure of penetration enhancers for which the QSAR model has been developed is shown in Figure 1. From the data in Table 1, QSAR equation was developed where number of data point (n) is 68 and number of descriptors used are 4. The derived QSAR model is given below. Here 95% confidence intervals are given in parantheses.

Validation of QSAR model

A quantitative assessment of model robustness has been performed through model validation. All the statistical results of model validation have been given in Table 2.

Statistical analysis

n/p ratio*: *n/p* = ≥ *4, where *n* is the number of data points and *p* is the number of descriptors used in the QSAR model. The model obeys the condition.

***Fraction of variance (r^2)*:** The value of fraction of variance may vary between 0 (means model without explanatory power) and 1 (means perfect model). QSAR model having $r^2 > 0.6$ will only be considered for validation[4, 12-16]. The value for this QSAR model is 0.913.

***Cross-Validation Test (q^2: LOO-leave one out; $q_f{}^2$: LFO-leave five out)*:** A QSAR model must have $q^2 > 0.5$

for the predictive ability[4, 12-16]. The value of q^2 for this QSAR model is 0.914.

***(r^2-q^2, q_f^2)< 0.3*:** The difference between r^2 and q^2 should never be exceeding by 0.3. A large difference suggests the following: presence of outliers, over-fitted model, and presence of irrelevant variables in data[4, 12-16]. The value of r^2-q^2 for this QSAR model is 0.0003.

***Quality Factor (Q)*:** Over fitting and chance correlation, due to excess number of descriptors, can be detected by Q value. Positive value for this QSAR model suggests its high predictive power and lack of overfitting[4, 12-16].

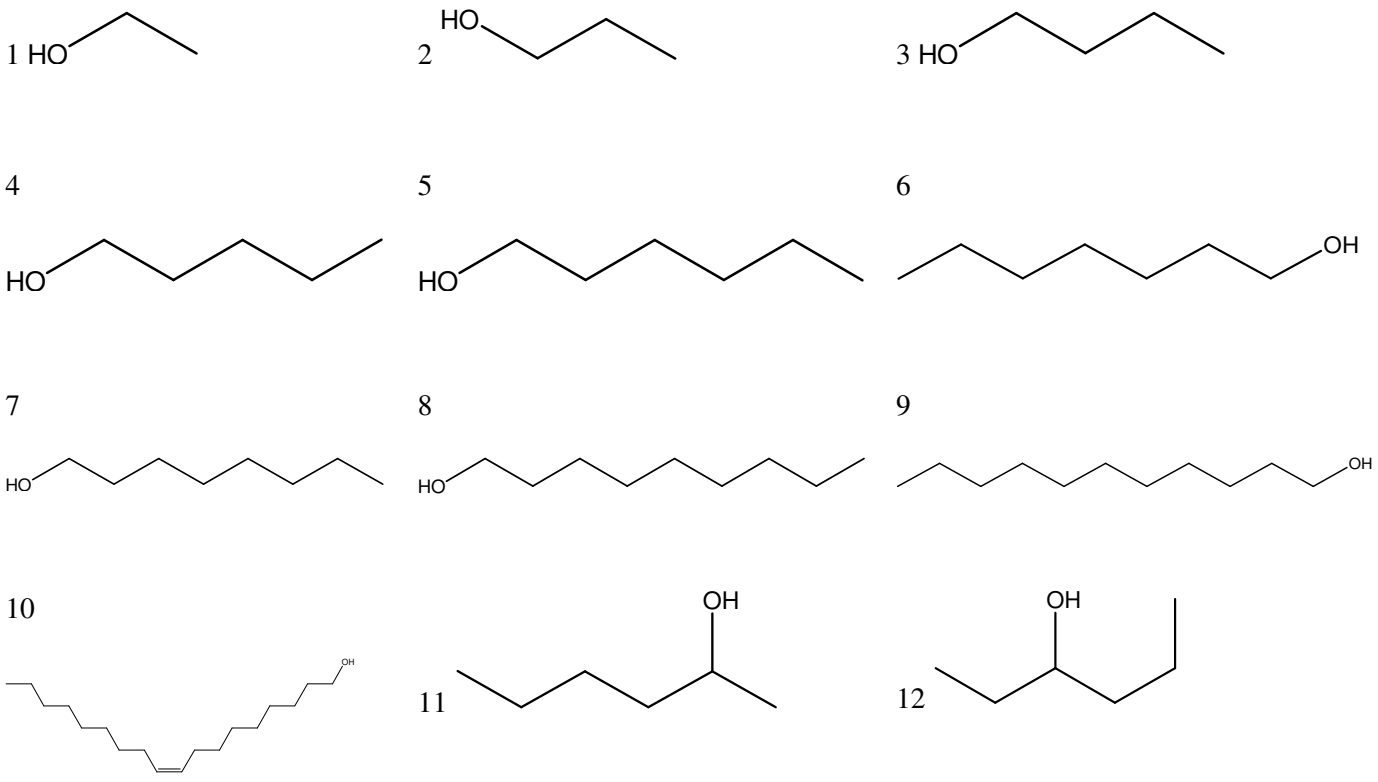
Internal Validation

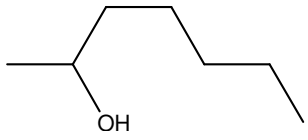
Y-Randomization Test: To establish the QSAR model robustness, this technique is being used widely. For this test, the dependent variable vector is randomly shuffled, and a new QSAR model is developed using the unchanged independent variable. This process was repeated for five times. The statistical data of r^2 for five runs are given in Table 3. The values r^2<0.6 in Y-randomization test confirm the robustness of this QSAR model[4, 12-16].

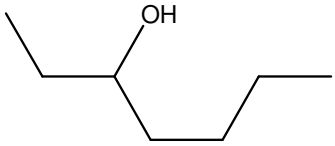
Conclusion

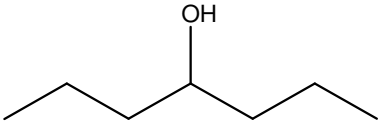
With deluged data of QSAR studies of penetration enhancer, we could draw a number of conclusions. On the basis of discussion given earlier we could conclude that for developing the novel penetration enhancer for transdermal drug delivery on the basis of TPSA, LAI, FC, and MLogP, we have to select such groups or substituent which increases the LAI (lipo-affinity index) and MLogP of the novel penetration enhancer molecules and we can evaluate the novel molecules for their logK values on the basis of the derived QSAR equation. For developing a molecule like penetration enhancer, it is necessary to alter the partition coefficient of novel molecule; in this regard the derived model suggests that partition coefficient should be increased according to the model. As far as topological polar surface area and fragment complexity are concerned, these should be kept low or negative in order to increase the penetration power of solvent. So, with the help of the developed model we can identify the logK values of novel designed molecules and alter their structural properties accordingly before synthesizing them.

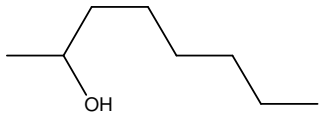
$$\log K = -5.12215(\pm 2.743785) - 0.053906\ (\pm 0.0223418)(TPSA) + 0.971232(\pm 0.3866824)(LAI) - 0.0019202\ (\pm 0.0011573)(FC) + 1.512311\ (\pm 1.722836)(MLogP)$$

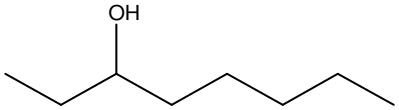


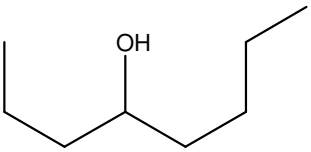
13 

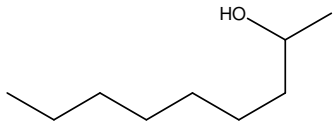
14 

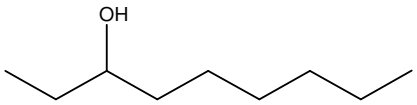
15 

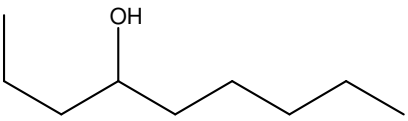
16 

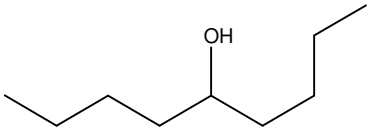
17 

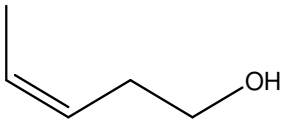
18 

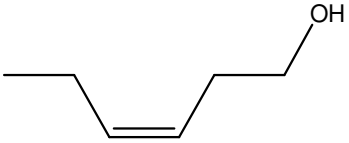
19 

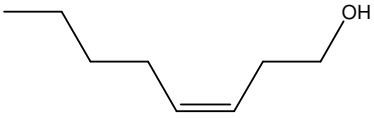
20 

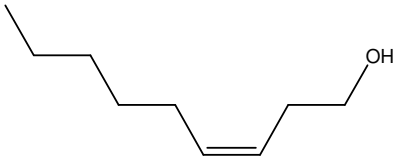
21 

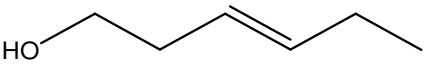
22 

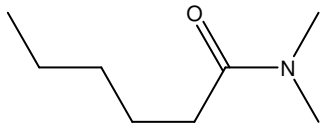
23 

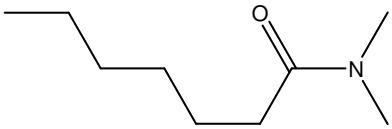
24 

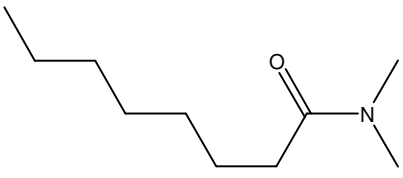
25 

26 

27 

28 

29 

30 

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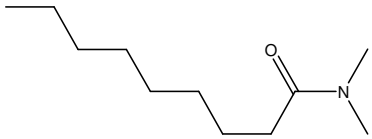

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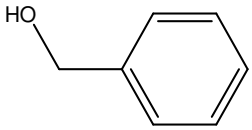

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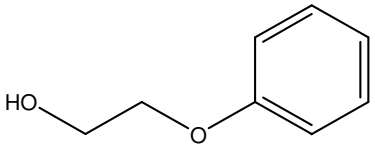

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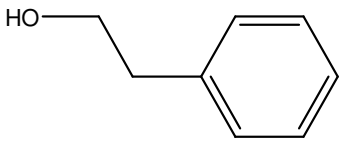

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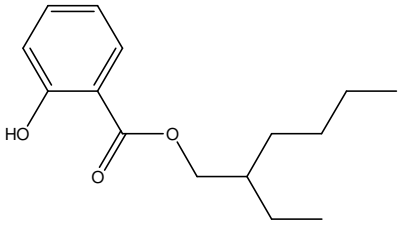

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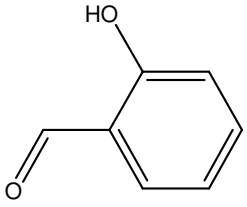

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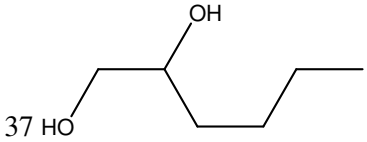

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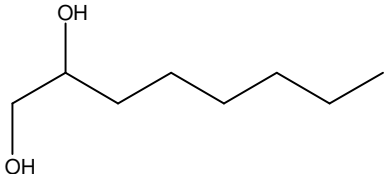

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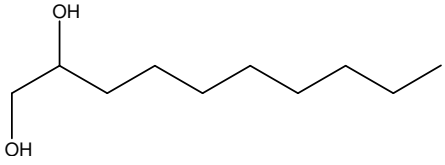

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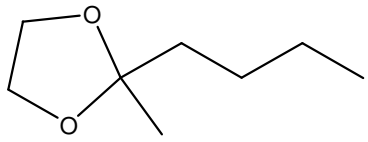

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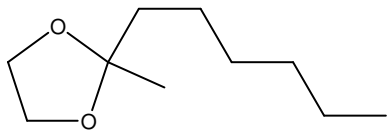

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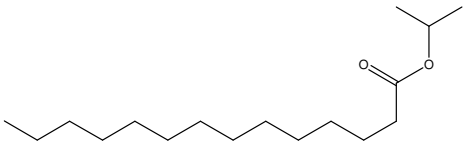

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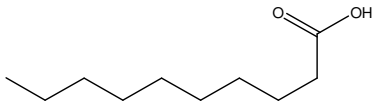

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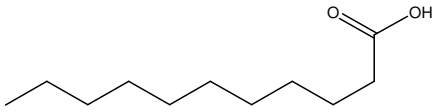

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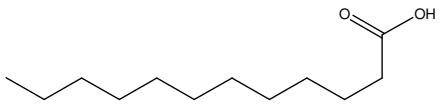

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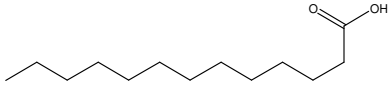

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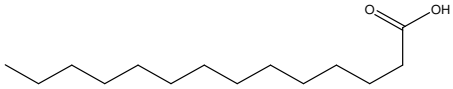

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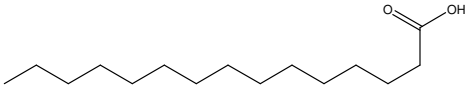

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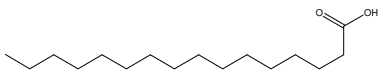

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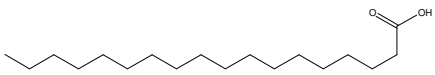

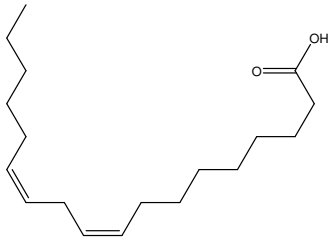

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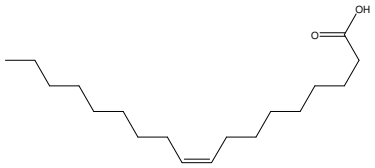

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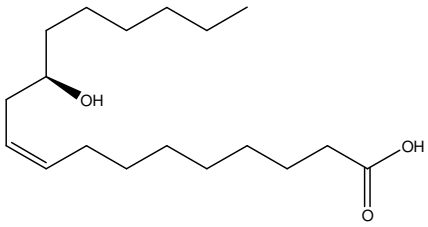

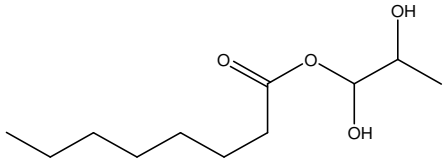

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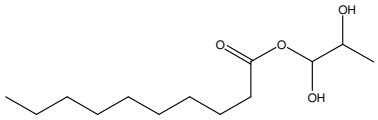

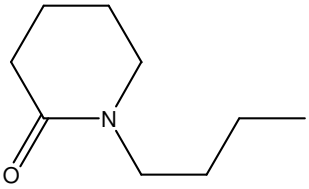

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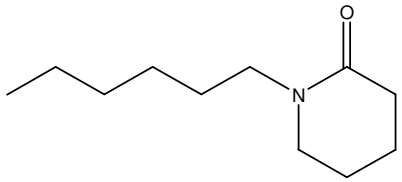

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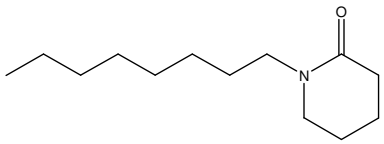

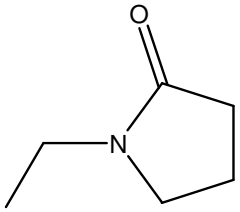

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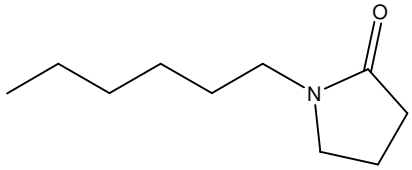

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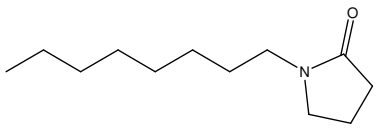

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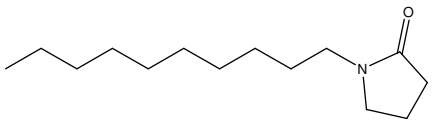

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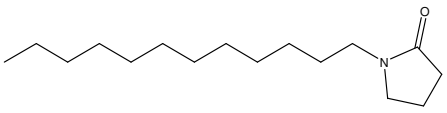

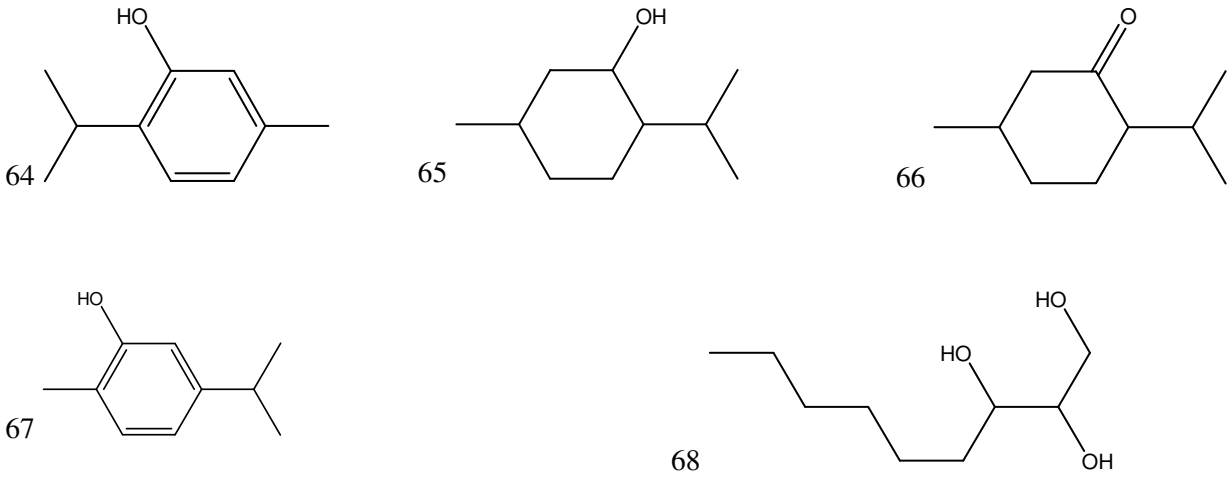

Fig. 1. Structure of penetration enhancer for developing the QSAR model

Table 1. logK and descriptors of penetration enhancer used to derive QSAR equation.

Compound S. No.	logK			TPSA	LAI	FC	MLogP
	Observed	Predicted	Residuals				
1	-0.3	-0.9465	0.646546	20.23	0.8465	58.01	1.57
2	7	7.1145	-0.11455	20.23	11.3801	2574.01	3.33
3	1.83	1.4810	0.348989	20.23	3.2539	358.01	2.01
4	1.81	1.3906	0.419344	20.23	3.1609	358.01	2.01
5	2.43	2.0812	0.348738	20.23	3.9280	473.01	2.12
6	2.42	1.9732	0.446785	20.23	3.8168	473.01	2.12
7	2.32	1.9427	0.377238	20.23	3.7854	473.01	2.12
8	3.03	2.6623	0.36764	20.23	4.6140	604.01	2.23
9	2.94	2.5431	0.396898	20.23	4.4913	604.01	2.23
10	2.88	2.4949	0.385044	20.23	4.4417	604.01	2.23
11	3.48	3.2205	0.259475	20.23	5.3081	751.01	2.34
12	0.25	-0.3311	0.581103	20.23	1.4097	109.01	1.68
13	3.47	3.0937	0.376292	20.23	5.1775	751.01	2.34
14	3.46	3.0343	0.425648	20.23	5.1164	751.01	2.34
15	3.42	3.0166	0.40334	20.23	5.0982	751.01	2.34
16	1.08	0.8248	0.255149	20.23	2.4273	195.01	1.9
17	1.63	1.4395	0.19045	20.23	3.0610	282.01	2.01
18	2.71	2.65747	0.05253	20.23	4.4113	504.01	2.23
19	3.25	3.2373	0.012697	20.23	5.1039	639.01	2.34
20	1.76	1.4395	0.32045	20.23	3.0610	282.01	2.01
21	1.4	2.3434	-0.94349	20.31	4.4170	586.02	2.12
22	1.9	2.8807	-0.98073	20.31	5.0856	731.02	2.23
23	0.84	0.3133	0.52662	20.23	2.0344	176.01	1.79
24	2.6	3.3990	-0.79908	20.31	5.7663	892.02	2.34
25	1.9	3.8949	-1.99496	20.31	6.4555	1069.02	2.45
26	1.1	1.3136	-0.21365	20.23	2.5979	200.01	2.12
27	1.2	1.7315	-0.53155	29.46	2.7334	310.02	2.12
28	1.6	1.7979	-0.19791	20.23	3.1012	289.01	2.23

29	6	5.1193	0.88065	46.53	6.1919	1294.03	2.78
30	2	1.4937	0.506295	37.3	1.9143	153.02	2.01
31	0.78	1.1250	-0.34509	40.46	1.9893	385.02	1.9
32	2.1	2.2301	-0.13016	40.46	3.2867	639.02	2.12
33	3.2	3.2665	-0.0665	40.46	4.6399	957.02	2.34
34	1.5	0.9578	0.542164	20.23	2.6908	259.01	1.9
35	2.1	1.9789	0.121025	18.46	4.1444	586.02	2.12
36	3.5	3.0523	0.447622	18.46	5.5120	892.02	2.34
37	7.3	6.0693	1.230674	26.3	9.8905	2362.02	3.11
38	4	3.8947	0.105281	37.3	5.2091	829.02	2.34
39	4.5	4.3996	0.100357	37.3	5.8957	1000.02	2.45
40	5	4.8792	0.120789	37.3	6.5879	1187.02	2.56
41	5.5	5.3322	0.167716	37.3	7.2845	1390.02	2.67
42	6	5.7580	0.241978	37.3	7.9845	1609.02	2.78
43	6.5	6.1557	0.344204	37.3	8.6874	1844.02	2.89
44	7	6.5251	0.474877	37.3	9.3927	2095.02	3
45	2.1	1.5894	0.510532	20.23	3.3656	358.01	2.01
46	7.9	7.1770	0.722992	37.3	10.8087	2645.02	3.22
47	7.5	7.1724	0.327541	37.3	9.9657	2221.02	3.22
48	7.6	7.1614	0.438532	37.3	10.36568593	2429.02	3.22
49	6.2	6.2015	-0.00153	57.53	8.558258358	2496.03	3.11
50	2.4	2.9097	-0.50975	66.76	3.23927854	1086.04	2.23
51	3.1	3.7432	-0.64326	66.76	4.557607152	1492.04	2.45
52	1.4	2.3750	-0.97508	20.31	4.452280945	674.02	2.23
53	2.6	3.3865	-0.78654	20.31	5.795666188	1000.02	2.45
54	3.4	4.3130	-0.91304	20.31	7.178100809	1390.02	2.67
55	-0.04	0.7955	-0.83551	20.31	2.610231944	305.02	1.9
56	2.5	2.2017	0.29826	20.23	4.052117268	473.01	2.12
57	2.1	2.9705	-0.87051	20.31	5.200508271	829.02	2.34
58	3	3.9583	-0.95837	20.31	6.582866504	1187.02	2.56
59	4.1	4.8429	-0.74293	20.31	7.985387597	1609.02	2.78
60	4.9	5.6160	-0.71609	20.31	9.399743526	2095.02	3
61	2.5	2.6488	-0.14881	20.23	4.081625463	515.01	2.45
62	3.4	3.2852	0.114792	20.23	5.401167361	851.01	2.45
63	2.9	2.8838	0.016188	17.07	4.926021898	731.01	2.45
64	2.5	2.7004	-0.20043	20.23	4.134772407	515.01	2.45
65	1.6	2.0866	-0.48662	60.69	2.391822055	829.03	2.12
66	3.1	2.7909	0.309043	20.23	4.746502684	604.01	2.23
67	3.5	3.3548	0.145128	20.23	5.446469598	751.01	2.34
68	4.2	4.4014	-0.20148	20.23	6.857677366	1093.01	2.56

A comparison (multiple linear regression curve) of observed values and predicted values of *logK* for penetration enhancers used for development of QSAR equation is shown in Figure 2 and multiple linear graph is shown in Figure 3.

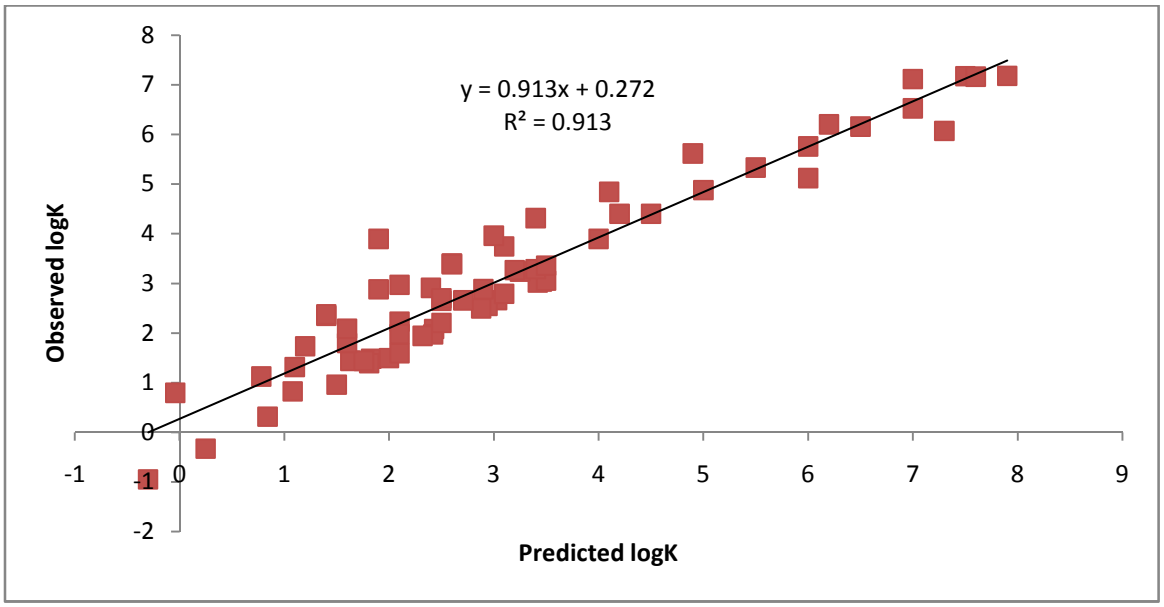

Fig. 2 Multiple linear regression plot

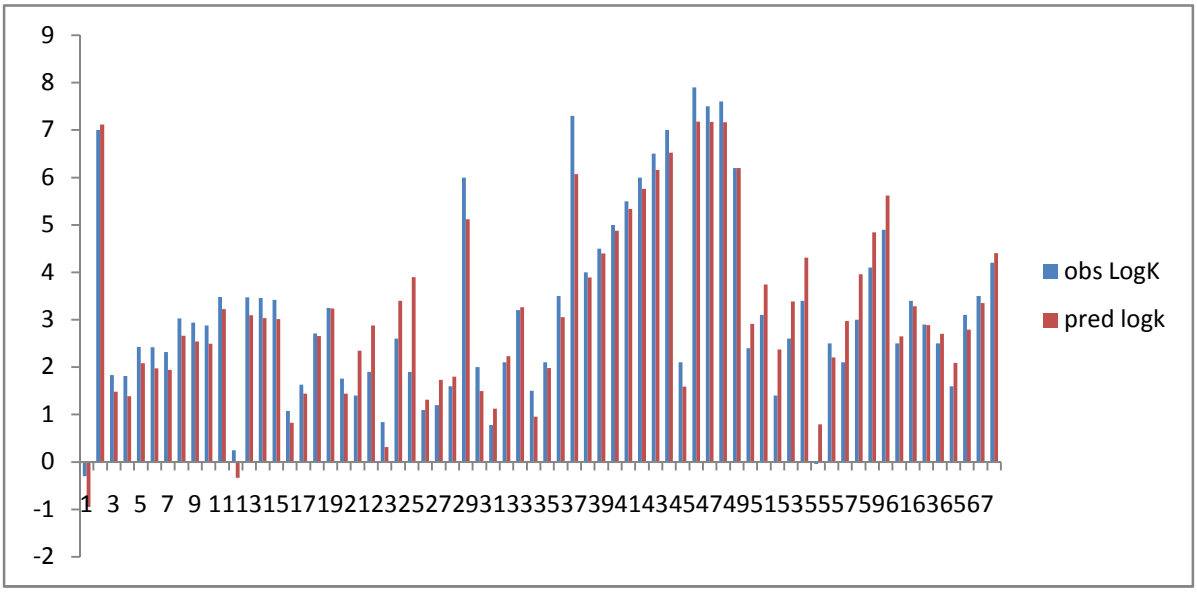

Fig. 3 Multiple linear graph between observed LogK and predicted LogK

Table 2. Statistical results of model validation

n/p(>=4)	r^2	q^2	q_f^2	$r^2-q^2 < 0.3$	$r^2-q_f^2 < 0.3$	RMSD	Variance	Q
17	0.913	0.914	0.917	-0.001	-0.004	0.0684	0.3438	0.5

Table 3: Results of internal validation: Y-randomization test (5 runs)

	Run 1	Run 2	Run 3	Run 4	Run 5
r^2	0.29	0.48	0.42	0.45	0.19

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