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# QSAR analysis on inhibitors of human dihydroorotate dehydrogenase (*h*DHODH): The aryl carboxylic acid amide derivatives

Vivek K Vyas* & Manjunath Ghate

Department of Pharmaceutical Chemistry, Institute of Pharmacy, Nirma University, Ahmedabad 382 481, India

E-mail: vicky_1744@yahoo.com

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Structural and physicochemical requirements of aryl carboxylic acid amide derivatives for the inhibition of human dihydroorotate dehydrogenase (*h*DHODH) are explored in this QSAR study. The calculated molecular descriptors (electronic and thermodynamic) have been used to derive QSAR models between *h*DHODH inhibitory activity and structural properties. The best model for prediction of *h*DHODH inhibitory activity is obtained by applying sequential multiple linear regression (SMLR) analysis. Regression coefficient of all the descriptors is significant at more than 99% and statistically significant model with $r^2 > 0.87$ is obtained. Selected QSAR model emphasized the importance of logP, torsion energy (Et), 1,4-dihedral van der Waals interaction (1,4-VDWE) and electronic descriptor like lowest unoccupied molecular orbital (LUMO) on *h*DHODH inhibitory activity. Results of QSAR analysis show that logP and LUMO are the principle descriptors for inhibition of *h*DHODH. QSAR model has also been tested successfully for internal ($q^2 > 0.753$) and external ($r^2_{pred} > 0.621$) validation criteria. It is believed that the results of this study will be helpful in the design of more potent and selective *h*DHODH inhibitors.

**Keywords**: QSAR, dihydroorotate dehydrogenase (DHODH), aryl carboxylic acid amides, *h*DHODH inhibitors, logP, LUMO

Dihydroorotate dehydrogenase (DHODH)[EC 1.3.99.11] (Ref 1) is the fourth enzyme of pyrimidine *de-novo* synthesis that catalyses the conversion of dihydroorotate to orotate using co-factors flavin mononucleotide (FMN) and ubiquinone (CoQ) in redox process, which is a rate-limiting step in pyrimidine biosynthesis (**Figure 1**)[2]. Pyrimidines are required for the biosynthesis of DNA, RNA, glycolproteins and phospholipids[3]. Most of the organisms acquire pyrimidines either through *de novo* synthesis or by salvage pathway. Rapidly proliferating human cells such as activated T lymphocytes[4] and cancer cells[5] are heavily dependent on *de novo* nucleotide synthesis to meet their growth requirements[6]; therefore, *de novo* pyrimidine biosynthesis represents an attractive and selective target for the development of new therapeutics as anticancer, antimalarial and anti-microbial agents. Inhibitors of *h*DHODH have proven efficacy for the treatment of cancer[7,8] and immunological disorders, such as rheumatoid arthritis and multiple sclerosis[9-12]. Leflunomide for the treatment of rheumatoid arthritis[13,14] and brequinar (antitumor and immunosuppressive agent)[15] are two well-described inhibitors of *h*DHODH. DHODH enzymes are divided into two family based upon their localization, amino acid sequence, substrate/cofactor dependence, and cellular localization[16]. Family-1 enzymes are located in the cytosol; utilize fumarate or $NAD^+$ as the terminal electron acceptor whereas family-2 enzymes transfer electrons to ubiquinone (CoQ), to which *h*DHODH belongs[17,18]. To correlate mathematically chemical structures with biological activity induced by sets of congener molecules is generally referred to as QSAR. The main object of QSAR is to predict the desired property of a newly synthesized or a hypothetical molecule[19,20]. QSAR is being used to gain insight into the interaction of molecules with macromolecules and macromolecular systems and by modifying the molecular structures to predict the desired property could be helpful in designing of more potent and selective drug candidate. We have compiled the literature pertaining recent advancements in the medicinal chemistry of DHODH inhibitors[21]. In search for selective *h*DHODH inhibitors, an attempt has been made to quantify necessary structural and physico-chemical requirements for inhibition of *h*DHODH, which is the first of its kind and of high statistical

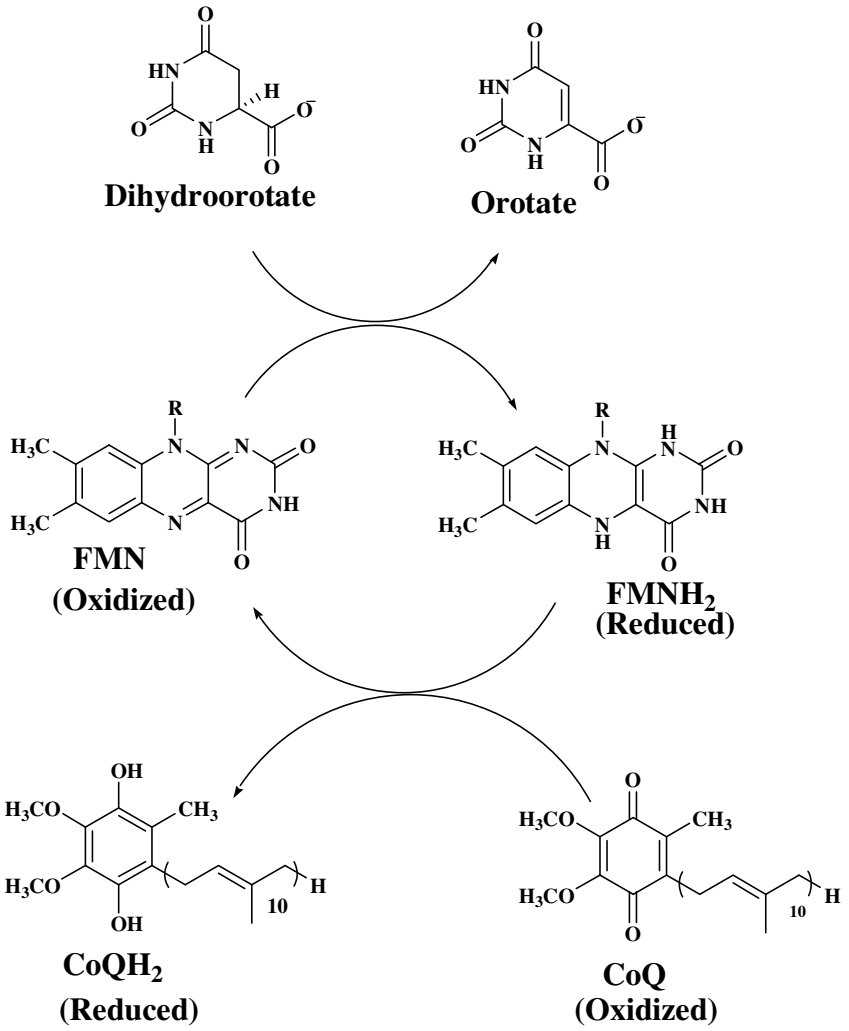



**Figure 1** — Reactions catalyzed by DHODH

quality and it was examined with variety of statistical parameters.

## Materials and Methods

The main steps for the development of a QSAR model is described in the following section as: data preparation, statistical methods and model validation.

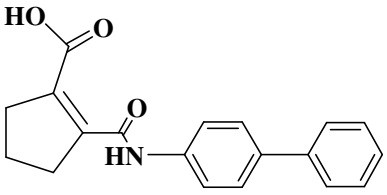
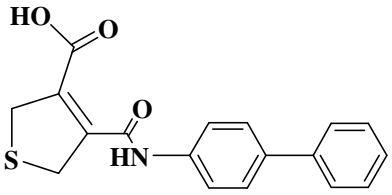
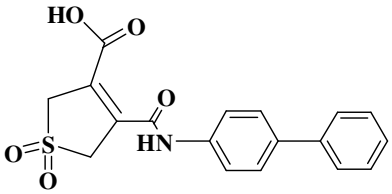
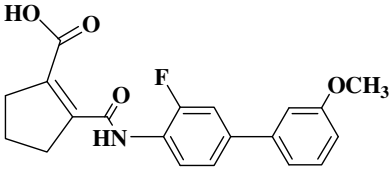
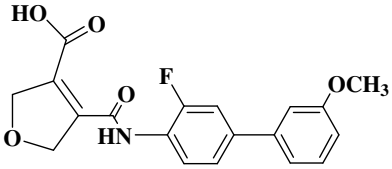
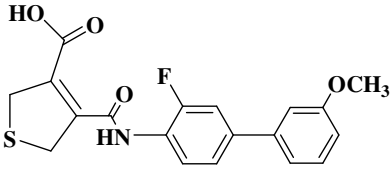
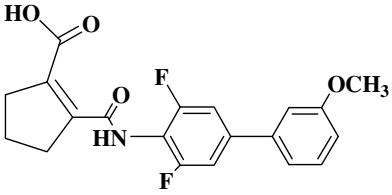
### Data preparation

A data set of 34 compounds (*h*DHODH inhibitors) was collected from the literatures[22,23]. The experimental $IC_{50}$ values (50% inhibitory concentration of the enzyme) were evaluated by Leban, *et al.*[22,23] in an enzyme assay by using N-terminally truncated re-combinant *h*DHODH. The enzyme inhibition data $IC_{50}$ values were converted to $pIC_{50}$ and subsequently used as the dependent variable for QSAR study (**Table I**).

### Model building

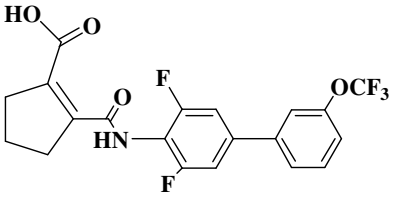
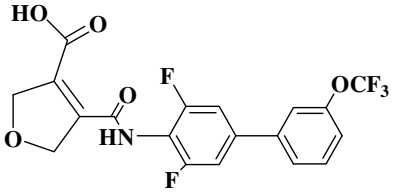
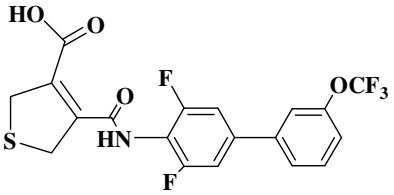
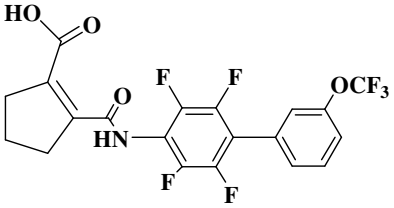
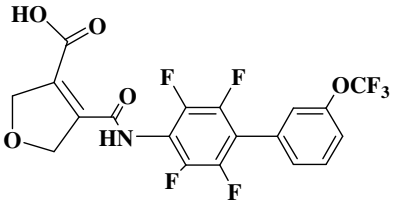
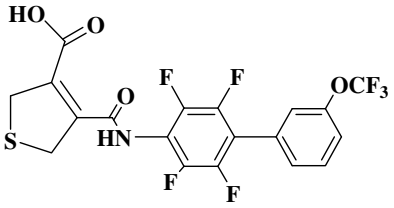
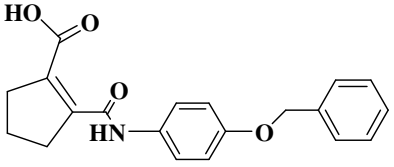
All the calculation to draw out molecular descriptor was done on P-IV processor using CS Chem office[24] and in order to perform correlation analysis VALSTAT[25] software was used. The structures of aryl carboxylic acid amide derivatives were drawn in Chem draw and copied to Chem 3D ultra to create 3D model, which was served as template model, for every compound. Template compound was suitably modified considering its structural feature so that every compound maintains same sequence of atoms. Minimized molecules are than subjected to re-optimization *via* Austin model-1 (AM1) method using closed shell restricted wave function of MOPAC module until the root mean square (RMS) gradient attained a value less than 0.0001 kcal/mol Å. The geometric optimization of the lowest energy structure

**Table I** — Structures, physicochemical properties and activity of aryl carboxylic acid amide derivatives— *Contd*

| Compd | Compd structure | m.p. (K) | logP | Et (Kcal/mol) | 1,4-VDWE (Kcal/mol) | N1,4-VDWE (Kcal/mol) | *h*DHODH Inhibitory activity $IC_{50}$ [a] | $pIC_{50}$ [b] |
|---|---|---|---|---|---|---|---|---|
| **1** |  | 736.5 | 3.182 | -7.048 | 10.844 | 0.453 | 0.41 µM | 6.387 |
| **2** |  | 774.4 | 2.651 | -12.078 | 12.091 | -1.75 | 0.667 µM | 6.176 |
| **3** |  | 773.21 | 0.588 | -6.967 | 9.575 | 0.399 | 3.8µM | 5.42 |
| **4** |  | 795.63 | 3.214 | 4.576 | 13.299 | -0.712 | 0.134 µM | 6.873 |
| **5** |  | 810.93 | 1.807 | 3.553 | 13.208 | -0.327 | 0.36 µM | 6.444 |
| **6** |  | 867.81 | 2.528 | -11.295 | 11.532 | 1.4905 | 0.131 µM | 6.883 |
| **7** |  | 808.74 | 3.372 | -7.242 | 12.259 | 3.549 | 0.011 µM | 7.959 |

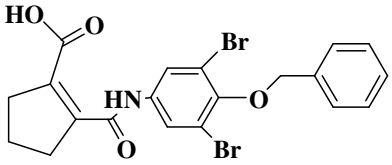
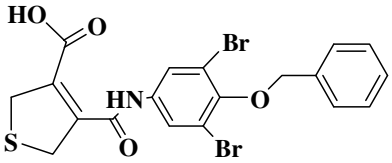
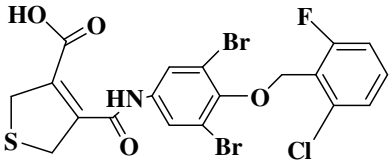
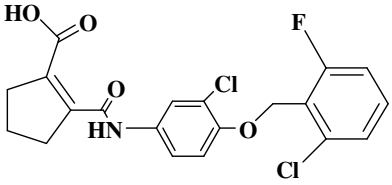
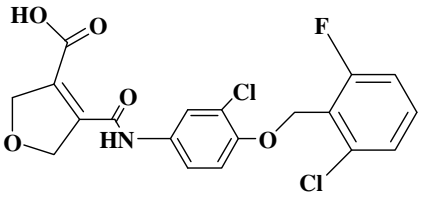
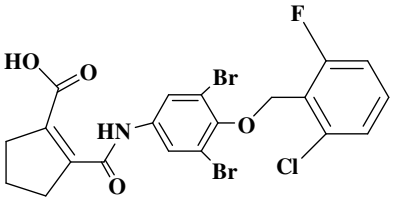
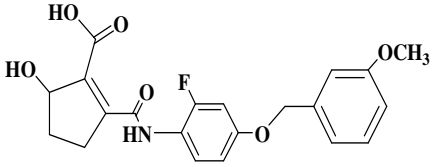
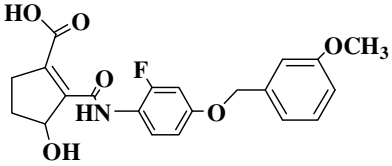
— *Contd*

**Table I** — Structures, physicochemical properties and activity of aryl carboxylic acid amide derivatives— *Contd*

| Compd | Compd structure | m.p. (K) | logP | Et (Kcal/mol) | 1,4-VDWE (Kcal/mol) | N1,4-VDWE (Kcal/mol) | *h*DHODH Inhibitory activity $IC_{50}$ [a] | $pIC_{50}$ [b] |
|---|---|---|---|---|---|---|---|---|
| **8** |  | 812.93 | 5.025 | -4.303 | 11.435 | -2.333 | 0.033 µM | 7.481 |
| **9** |  | 828.23 | 3.618 | 6.498 | 11.912 | -2.144 | 0.205 µM | 6.688 |
| **10** |  | 885.11 | 4.34 | 10.935 | 10.33 | -2.162 | 0.015 µM | 8.155 |
| **11** |  | 839.15 | 5.342 | 6.188 | 11.659 | -2.054 | 0.007 µM | 7.237 |
| **12** |  | 854.45 | 3.934 | 2.945 | 11.48 | -2.612 | 0.058 µM | 7.237 |
| **13** |  | 911.33 | 4.6559 | 7.53618 | 9.91312 | -2.23212 | 0.004 µM | 8.398 |
| **14** |  | 770 | 3.113 | -4.19 | 13.458 | 1.524 | 2 µM | 5.699 |

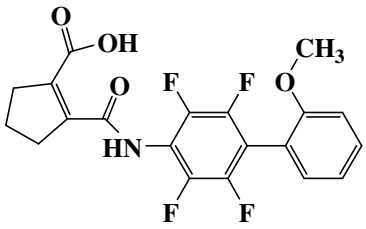
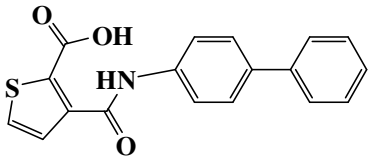
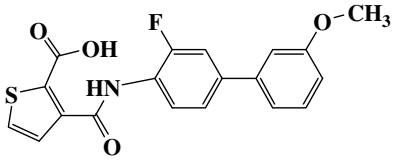
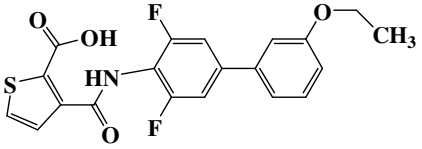
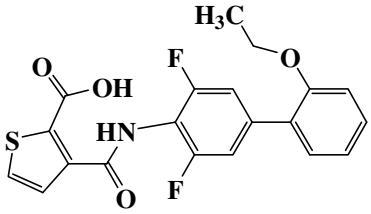
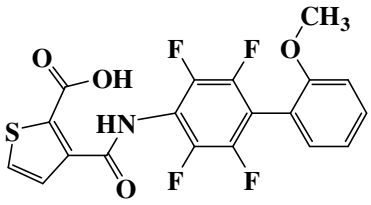
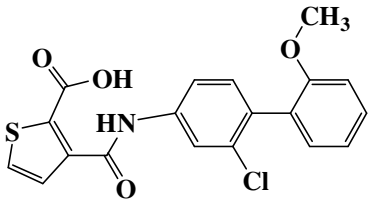
*—Contd*

**Table I** — Structures, physicochemical properties and activity of aryl carboxylic acid amide derivatives— *Contd*

| Compd | Compd structure | m.p. (K) | logP | Et (Kcal/mol) | 1,4-VDWE (Kcal/mol) | N1,4-VDWE (Kcal/mol) | *h*DHODH Inhibitory activity $IC_{50}$ [a] | $pIC_{50}$ [b] |
|---|---|---|---|---|---|---|---|---|
| **15** |  | 914.64 | 4.771 | 1.521 | 14.651 | -1.4001 | 0.127 µM | 6.896 |
| **16** |  | 986.82 | 4.086 | 2.963 | 13.054 | -1.37 | 0.173 µM | 6.762 |
| **17** |  | 1042.3 | 4.802 | 3.061 | 13.268 | -1.853 | 0.105 µM | 6.979 |
| **18** |  | 867.99 | 4.388 | 2.377 | 13.603 | -1.73 | 0.011 µM | 7.959 |
| **19** |  | 883.29 | 2.98 | -2.889 | 13.84 | -1.308 | 0.041 µM | 7.387 |
| **20** |  | 970.19 | 5.488 | 3.209 | 14.655 | -1.06 | 0.11 µM | 6.959 |
| **21** |  | 885.71 | 2.054 | 17.115 | 16.611 | 0.797 | 0.68 µM | 6.167 |
| **22** |  | 885.71 | 2.054 | 9.496 | 16.888 | 0.373 | 1.46 µM | 5.836 |

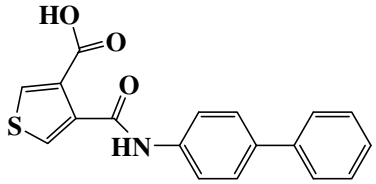
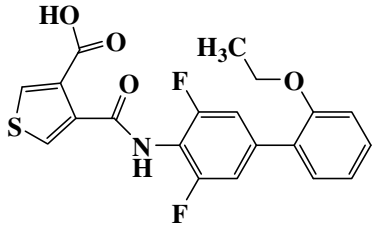
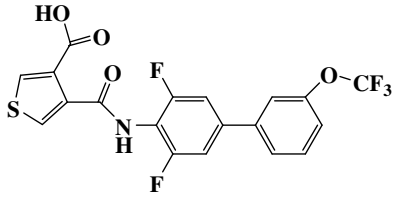
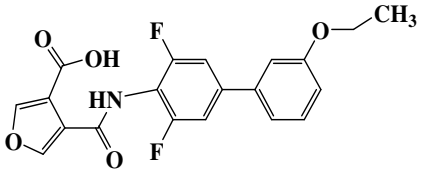
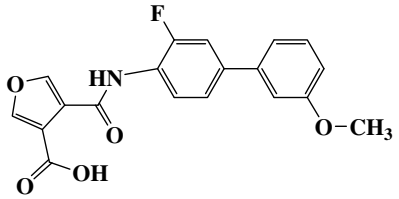
*—Contd*

**Table I** — Structures, physicochemical properties and activity of aryl carboxylic acid amide derivatives— *Contd*

| Compd | Compd structure | m.p. (K) | logP | Et (Kcal/mol) | 1,4-VDWE (Kcal/mol) | N1,4-VDWE (Kcal/mol) | *h*DHODH Inhibitory activity $IC_{50}$ [a] | $pIC_{50}$ [b] |
|---|---|---|---|---|---|---|---|---|
| **23** |  | 834.96 | 3.688 | 10.78 | 12.282 | -2.223 | 8 nM | 8.097 |
| **24** |  | 809.44 | 4.053 | -3.183 | 8.861 | 0.423 | 303 nM | 6.519 |
| **25** |  | 868.57 | 4.085 | -2.498 | 10.892 | 1.848 | 44 nM | 7.357 |
| **26** |  | 892.95 | 4.581 | -5.742 | 11.562 | 4.496 | 3 nM | 8.523 |
| **27** |  | 892.95 | 4.581 | 15.345 | 11.57 | 0.456 | 9 nM | 8.047 |
| **28** |  | 907.9 | 4.559 | 14.221 | 10.366 | -2.859 | 1 nM | 9 |
| **29** |  | 897.9 | 4.485 | 2.486 | 11.983 | 0.915 | 12 nM | 7.921 |

— *Contd*

**Table I** — Structures, physicochemical properties and activity of aryl carboxylic acid amide derivatives— *Contd*

| Compd | Compd structure | m.p. (K) | logP | Et (Kcal/mol) | 1,4-VDWE (Kcal/mol) | N1,4-VDWE (Kcal/mol) | *h*DHODH Inhibitory activity $IC_{50}$ [a] | $pIC_{50}$ [b] |
|---|---|---|---|---|---|---|---|---|
| **30** |  | 809.44 | 3.998 | 0.978 | 8.804 | 0.224 | 1000 nM | 6 |
| **31** |  | 892.95 | 4.525 | 3.29 | 10.876 | -3.319 | 10 nM | 8 |
| **32** |  | 885.87 | 5.84 | 19.474 | 10.568 | -1.329 | 10 nM | 8 |
| **33** |  | 836.07 | 3.159 | 8.128 | 12.081 | 0.168 | 16 nM | 7.796 |
| **34** |  | 811.69 | 2.663 | -1.408 | 11.283 | 1.74 | 340 nM | 6.469 |

[a] Experimental *h*DHODH inhibitory activity ($IC_{50}$ μM/nM)
[b] Negative logarithm of $IC_{50}$ (μM/nM) ($pIC_{50}$)

was carried out with eigenvector (EF) routine. The energy minimized geometry was used for the calculation of descriptor and extended Huckel charges of different atoms. The descriptor values were calculated using ''compute properties'' module of the program. Total number of descriptors calculated was about 48. Calculated thermodynamic descriptors included critical temperature ($T_c$), ideal gas thermal capacity ($C_p$), critical pressure ($P_c$), boiling point (BP), Henry's law constant (H), bond energy ($E_b$), heat of formation ($H_f$), total energy (TE), partition coefficient (PC) and melting point (m.p.). Steric descriptors were also derived like connolly accessible area (CAA), connolly molecular area (CMA), connolly solvent excluded volume (CSEV), exact mass (EM), molecular weight (MW), principal moment of inertia-X component (PMI-X), principal moment of inertia-Y component (PMI-Y) and principal moment of inertia-Z component (PMI-Z), molar refractivity (MR) and ovality (OVAL). Electronic descriptors such as dipole (DIP), electronic energy (ElcE), highest occupied molecular orbital energy (HOMO), lowest unoccupied

molecular orbital energy (LUMO), repulsion energy (NRE), VDW-1,4-energy (1,4-VDWE), Non-1,4-VDW energy (N1,4-VDWE) and total energy were calculated. Some of the descriptors used in QSAR study are listed in **Table I**.

**Selection of the training and test sets**

Training set plays a vital role in the development of QSAR model, since the more similar molecules for training a model; the more accurate are predictable results. Thus, selection of training and test sets is one of the most important steps in QSAR modeling. An ideal division of a training and test set will lead to data sets with resemblance of all the compounds of the test set in multidimensional descriptor space to the training set and resemblance of all representative compounds of a training set to a test set. Simply, an ideal splitting leads to a test set in which each of its members is close to at least one member of a training set[26]. In present QSAR study all the compounds were divided into a training set of 25 compounds (**11, 13, 26, 10, 15, 25, 32, 28, 34, 21, 16, 17, 31, 29, 20, 27, 30, 6, 7, 14, 33, 19, 3, 4, 8**) and test set of 9 compounds (**5, 22, 24, 1, 9, 18, 2, 12, 23**) by straightforward random selection through activity sampling automatically by VALSTAT.

**Statistical analysis**

Sequential multiple linear regression (SMLR) analysis was carried out to develop QSAR models. The data was transferred to the statistical program (VALSTAT) in order to establish the correlation between physiochemical descriptors as independent variable and *h*DHODH inhibitory activity as dependent variable. The ± data within the parentheses are the standard deviation, associated with coefficient of descriptors in regression equations. Statistical quality of SMLR equation were judged by parameter like observed squared correlation coefficient ($r^2$), standard error of estimate (SE), sequential Fischer test (F), bootstrapping squared correlation coefficient ($r^2_{bs}$), bootstrapping standard deviation ($S_{bs}$), chance statistics evaluated as the ratio of the equivalent regression equations to the total number of randomized sets; a chance value of 0.001 corresponds to 0.1% chance of fortuitous correlation), outliers on the basis of Z-score value[27].

**Validation of QSAR model**

The definitive validity of QSAR model was examined by mean of external validation ($q^2$), which evaluates how well an equation generalizes. Training set was used to derive an adjustment model that was used to predict the activity of a test set. The predicted power of equations was validated using predictive squared correlation coefficients ($r^2_{pred}$).

**Results and Discussion**

Thirty four compounds were identified for QSAR analysis and further subjected to molecular modeling studies in order to explore physicochemical properties of the molecules which are responsible for *h*DHODH inhibition. Training set of 25 compounds was used to explore conformational and geometrical related physicochemical properties, when training set was subjected to SMLR to develop QSAR models, various statistical equations were obtained.

$pIC_{50}$ = [7.078 (± 0.381)] +MP [0.024 (± 0.004)] +N1,4-VDWE [-0.516 (± 0.040)] + VDW14E [-0.213 (± 0.164)] +LUMO [1.052 (± 0.249)] ... (1)

where, n = $25_{training}$ and $9_{test}$, r = 0.935, $r^2$ = 0.875, SD = 0.371, F = 23.426, $q^2$ = 0.695, $r^2_{pred}$ = 0.386

$pIC_{50}$ = [6.490 (± 0.028)] + $C_p$ [0.013(± 0.013)] + N1,4-VDWE [-0.407(± 0.017)] + 1,4-VDWE [-0.241(± 0.087)] + LUMO [1.132(± 0.212)] ... (2)

where, n = $25_{training}$ and $9_{test}$, r = 0.934, $r^2$ = 0.873, SD = 0.374, F= 23.150, $q^2$ = 0.681, $r^2_{pred}$ = 0.427

$pIC_{50}$ = [7.081(± 0.275)] +logP [0.063 (± 0.175)] +Et [0.074(± 0.041)] +1,4VDWE [-0.260(± 0.146)] +LUMO [0.750(± 0.176)] ... (3)

where, n = $25_{training}$ and $9_{test}$, r = 0.935, $r^2$=0.873, SD = 0.373, F= 24.248, $q^2$ = 0.753, $r^2_{pred}$ = 0.621

Where n is a number of compounds, r is a correlation coefficient which measures quality of fit of model, $r^2$ is a squared correlation coefficient used to describe goodness of fit of the data, SD is standard deviation, a square root of variance and measure of magnitude of residuals, accounting for accuracy, F is a Fischer ratio values between variances of calculated and observed activities which is used to measure levels of statistical significance of regression model.

Statistical significance of QSAR models was further supported by a plot of calculated *vs*. predicted activity (**Figure 2**) of training set compounds and provides an idea about how fit model was trained and how well it predict the activity of a test set.

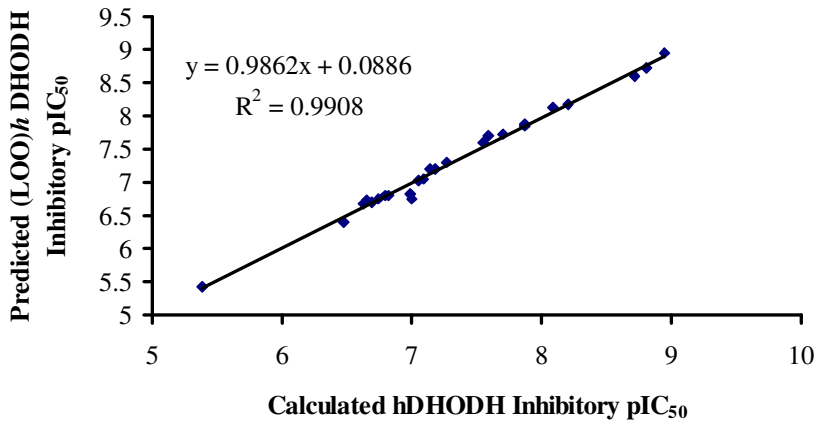



**Figure 2** — Plot of calculated *vs.* predicted (LOO) $pIC_{50}$

**Table II** — Calculated and predicted $pIC_{50}$ by LOO method with residual and Z-score value

| Compd | Calculated $pIC_{50}$ | Residual | Z-value | Predicted $pIC_{50}$ (LOO) | Residual (LOO) |
|---|---|---|---|---|---|
| **11** | 8.599 | -0.862 | -0.761 | 8.715 | -1.478 |
| **13** | 8.716 | -0.318 | -0.76 | 8.809 | -0.411 |
| **26** | 8.133 | -0.776 | 0.934 | 8.096 | -0.739 |
| **10** | 7.867 | 0.288 | -0.103 | 7.872 | 0.283 |
| **15** | 6.71 | 0.186 | 0.446 | 6.696 | 0.201 |
| **25** | 7.192 | 0.165 | 0.395 | 7.182 | 0.175 |
| **32** | 7.692 | 0.309 | 0.738 | 7.589 | 0.411 |
| **28** | 8.959 | 0.041 | 0.098 | 8.944 | 0.056 |
| **34** | 7.047 | -0.579 | -1.386 | 7.092 | -0.623 |
| **21** | 6.742 | -0.575 | -1.374 | 6.996 | -0.829 |
| **16** | 6.811 | -0.049 | -0.118 | 6.818 | -0.055 |
| **17** | 6.683 | 0.296 | 0.709 | 6.622 | 0.357 |
| **31** | 7.589 | 0.411 | 0.984 | 7.557 | 0.443 |
| **29** | 7.732 | 0.189 | 0.453 | 7.705 | 0.216 |
| **20** | 6.759 | 0.2 | 0.477 | 6.742 | 0.217 |
| **27** | 8.178 | -0.132 | -0.316 | 8.199 | -0.153 |
| **30** | 6.827 | -0.827 | -1.978 | 6.986 | -0.986 |
| **6** | 7.03 | -0.147 | -0.353 | 7.045 | -0.162 |
| **7** | 7.212 | 0.748 | 1.787 | 7.145 | 0.814 |
| **14** | 6.395 | -0.696 | -1.668 | 6.473 | -0.774 |
| **33** | 7.296 | 0.501 | 1.195 | 7.275 | 0.522 |
| **19** | 6.727 | 0.66 | 1.579 | 6.653 | 0.734 |
| **3** | 5.415 | 0.005 | 0.014 | 5.379 | 0.041 |
| **4** | 6.807 | 0.066 | 0.159 | 6.798 | 0.075 |
| **8** | 7.838 | -0.357 | -0.853 | 7.878 | -0.396 |

Nearness of experimental and predicted activity reported in **Table II** also adds to this fact. Equations 1–3 were screened on the basis of inter correlation within the descriptors (< 0.46) as mentioned in **Table III**; leave-one-out (LOO) cross validated squared correlation coefficient > 0.75 and intercept of best fit line. Equation 3 was considered as best model for *h*DHODH inhibition with $r^2 > 0.87$, standard

**Table III** — Correlation matrix of descriptors used in QSAR model 3

| | logP | Et | 1,4-VDWE | LUMO |
|---|---|---|---|---|
| logP | 1.000000 | | | |
| Et | 0.029049 | 1.000000 | | |
| 1,4-VDWE | 0.072969 | 0.459634 | 1.000000 | |
| LUMO | 0.059161 | 0.076151 | 0.428572 | 1.000000 |

**Table IV** — QSAR statistics of equations 1-3

| $Eq^n$ | $r^2$ | SD | F | $r^2_{bs}$ | $s_{bs}$ | Chance | $q^2$ | $S_{PRESS}$ | $S_{DEP}$ | $r^2_{pred}$ |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 0.874 | 0.371 | 23.426 | 0.901 | 0.05 | 0.001 | 0.695 | 0.478 | 0.472 | 0.386 |
| 2 | 0.872 | 0.374 | 23.150 | 0.902 | 0.07 | 0.001 | 0.681 | 0.491 | 0.483 | 0.427 |
| 3 | 0.873 | 0.373 | 24.248 | 0.893 | 0.07 | 0.001 | 0.753 | 0.421 | 0.425 | 0.621 |

deviation < 0.38, chance correlation < 0.01 and better statistical significance > 99% with $F_{(4, 25\ \alpha\ 0.001)}$ = 24.248. The generated model shows 87% variance in the activity. Model was tested for outlier by Z-score method; there is no outlier in QSAR study. To ascertain the predictivity of the model, internal validation using leave-one-out cross validation process, bootstrapping technique and randomization test were performed. The satisfactory values of internal validation, LOO cross validated squared correlation coefficient ($q^2$) > 0.75, standard deviation of prediction ($S_{press}$) = 0.421, standard deviation of error of predictions ($S_{DEP}$) = 0.425, bootstrapping squared correlation coefficient ($r^2_{bs}$) = 0.893 and chance correlation < 0.01 in the randomize biological activity test revealed that the results were not based on chance correlation. The model's $q^2$ > 0.75 supported the predictive ability and significance of the model (**Table IV**). QSAR model shows predictive squared correlation coefficient ($r^2_{pred}$) of 0.621. (**Table IV**). Equation 3 revealed that thermodynamic descriptors like logP, torsion energy (Et) and electronic descriptor like lowest unoccupied molecular orbital (LUMO) energy were contributed positively to the model, where thermodynamic descriptor like 1,4-dihedral van der Waals interaction (1,4-VDWE) energy was contributed negatively to the model. LUMO energy is a very popular quantum chemical descriptor. LUMO is the lowest energy level in a molecule that contains no electrons. LUMO energy[28] plays a major role in governing many chemical reactions and determining electronic band gaps in molecules; it is also responsible for the formation of many charge transfer complexes[29]. According to frontier molecular orbital theory (FMO) of chemical reactivity, the formation of a transition state is due to an interaction between the frontier orbital (LUMO) of reacting species. Hard electrophiles have a high LUMO energy; and soft electrophiles have a low LUMO energy. DHODH catalyzes conversion of dihydroorotate (DHO) to orotate (ORO) by utilizing an FMN cofactor in the redox reaction for pyrimidine biosynthesis. Human DHODH belongs to the family-2 that utilizes flavin as a redox cofactor that uses respiratory quinones as terminal electron acceptors. LUMO which is indicative of π-bonding interaction of species is crucial for the electrophilicity of the molecules, suggested that molecules are able to interact with electron rich area at the target site. The substitutions which enhance electrophilicity of a molecule might be helpful for development of potent *h*DHODH inhibitors. Literature survey[21] suggested that all the inhibitors of *h*DHODH published to date binds to the putative ubiquinone (CoQ) binding channel and display favorable antiproliferative activity, shown to be most pronounced during T-cell proliferation[30]. The octanol/water partition coefficient (logP) is the standard quantity to characterize the hydrophobicity/hydrophilicity of a molecule; a property is of major importance in biomedical applications. Atomic charge density has been proposed as the basis for calculating octanol/water partition coefficients[31]. Oral bioavailability and membrane permeability have regularly been correlated to logP in a molecule, thus logP is an important property in describing the affinity of the compounds in terms of their partitioning the biological membranes. Thus by increasing lipohilicity of whole molecule by introducing a suitable lipophilic

group would surely lead to the development of inhibitors with good activity. Human DHODH is an integral membrane protein localized in the inner mitochondrial membrane with the active site facing the inner membrane space. DHODH is capped by hydrophobic cavity and inhibitors have to diffuse through a very hydrophobic environment, hence increase in lipophilicity might increase inhibitory activity. Torsion energy (Et) is defined as the sum of dihedral bond rotational energy term of the force-field equation. Torsion energy (Et) is a thermodynamic parameter, which represents the energy associated with deforming torsion angles in the molecules from their ideal values. Torsion energy ($E_t$) contributes positively to QSAR model which suggested that absence of conjugation would be conducive for inhibitory activity of the compounds. 1,4-Dihedral van der Waals interaction (1,4-VDWE) energy term is defined as sum of pair wise van der Waals interaction energy for the atoms separated by exactly three chemical bonds, which explains depth of attraction potential energy well and how easy it is to push atoms together. Negative coefficient of 1,4-VDWE indicate that substitution which decreases the energy of this interaction generally lead to higher activity.

## Conclusions

QSAR study suggested some important structural features responsible for better *h*DHODH inhibitory activity of the studied compounds. QSAR analysis revealed that selective inhibition is dependent on calculated electronic and thermodynamic descriptors. The linear models developed in this work are easily calculated and suitable for the rapid prediction of *h*DHODH inhibitory activity, and internal and external validation of QSAR models supported this claim. The $\pi$ electron density of aromatic system decrease along with the LUMO energy of the system, therefore, substitution of electron withdrawing groups in the molecules will impart a positive influence on *h*DHODH inhibitory activity, and it may be helpful for designing of less toxic and more potent inhibitors. Partition coefficient (logP) was contributed positively to QSAR model, which means a group that increases hydrophobic nature might be helpful for good inhibitory activity. The study revealed that substitution on aromatic portion of the molecules results in interaction with a hydrophobic pocket at receptor site, which have an influence on the selectivity and activity. Thus, it can be concluded that introduction of suitable functional groups, which increases electronic effect like LUMO energy and the groups which results in increased torsion energy (Et) and lipophiliity (logP) have significant deficit in terms of accuracy of molecular structures, while substitutions which decreases 1,4-VDW energy can be used to optimize *h*DHODH inhibitory activity of aryl carboxylic acid amide derivatives.

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