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# QSAR Study of Substituted Anthracenones Derivatives as Inhibitors of 12-Lipoxygenase Enzymes

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Selective 5-LO enzyme and 12-LO enzyme inhibitors have attracted much attention in recent times in the design of novel anthracenone derivatives, which may be used in cancer and psoriasis. QSAR studies have been done by include a series of 2-arylalkyl substituted anthracenone derivatives having inhibitory action on 12-LO isoforms in epidermal homogenate of mice, bovine platelets and porcine leukocyte by using Openstate 4 version 6.5.1 statistical software. The studies were carried out on 21 analogs. These studies produced good predictive models and give statistically significant correlations with selective 12-LO enzyme inhibition. When available 12-LO enzyme inhibitory data were analyzed, descriptor hydrophobic, F, Ha, $\sigma_m$ gave statistically significant results.

**Key Words: QSAR, 12-LO inhibitors, HETE, Anthracenones, Descriptors.**

## INTRODUCTION

Lipooxygenase catalyzes the stereospecific insertion of molecular oxygen into arachidonic acid, which is further metabolized to hydroxyl derivative as end product. The 5-lipoxygenase pathways has been the major focus of study due to pronounced proinflammatory role in leukotrines synthesis and the approval has been granted for 5-LO inhibitor for the clinical treatment of asthma[1]. Although less well characterized, the 12-LO pathway may play an important role in the progression of human diseases such as cancer and psoriasis. Three isoform of 12-LO have been characterized. They are platelets-type (p12-LO), leukocyte-type (l 12-LO) and the epidermal-type (e 12-LO) 12-lipoxygenase. Such agents can also provide a new therapeutic approach to cure disease such as psoriasis and cancer[2,3]. A series of 2-arylalkyl substituted anthracenones having inhibitory action on 12-LO isoforms in epidermal homogenate of mice, bovine platelets and porcine leukocyte reported by Mullar *et a1.*[4-6] were considered for the

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QSAR analysis. Thus, the main objective of present studies is to design specific inhibitors of 12-LO enzyme inhibitors in the hope that these molecules may be further powerful anticancer and antipsoriasis agents. In view of this anthracenone derivatives were selected for quantitative structure activity relationships (QSAR), for the present study. In addition to this quantitative structure activity analysis has been reported for anthracenone derivatives in 12-LO enzyme inhibition. Thus such studies may help for the design and synthesis of better selective 12-LO enzyme inhibitors.

## EXPERIMENTAL

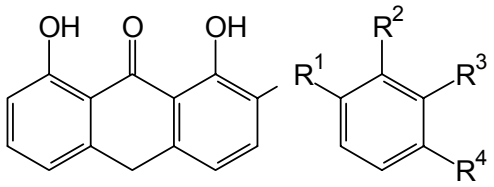
All computational work was performed on Pentium IV workstation-using software Openstate 4 version 6.5.1 statistical software. A total of 21 compounds were selected for the present study (Table-1). Regression analysis correlates independent x variable (physiochemical parameter) and dependently variable (biological data). The correlation coefficient is a relative measure of the quality of fit to the mode, its value depend on the over all variance of the data, $r^2$ is a measure of the explained variance, most often given as a percentage value. The standard deviation is an absolute measure of the quality of fit. The F value is a measure of the statistical significance of the regression model. Often perfect correlations were obtained in PLS analysis, due to usually large numbers of x variables. A cross validation procedure must be used to select the model having the highest predictive values. The served PLS runs are performed in which one (leave one out technique) or several objects are eliminated from the data set. Only the excluded objects are predicted by the corresponding model. The standard deviation $S_{PRESS}$ is taken as the criterion for the optimum number of component. If too many components are extracted, over prediction results and PRESS and $S_{PRESS}$ increase. $S_{DEP}$ corresponds to $S_{PRESS}$, the only difference being that the number of degrees of freedom was not considered in the calculation of the $S_{DEP}$ value. The correlation between the biological activity ($pIC_{50}$) and the descriptors were performed by stepwise regression analysis. Following statistical measures were used: N = number of samples, r = coefficient of correlation, F-test for quality of fit, t-test for test of significance and s = standard deviation, $S_{DEP}$ = standard error of prediction. Leave one- out method was employed for cross-validation of the equation and $Q^2$, cross-validated coefficient of correlation determined.

The biological activity data for the QSAR analysis was obtained from, Mullar *et al.*[5] (Table-1). The biological activities of the anthracenones derivatives (Fig. 1) are given as $IC_{50}$ for inhibitory action on 12-LO isoforms in epidermal homogenate of mice, bovine platelets and porcine leukocyte. The biological activities were converted in to -log $IC_{50}$. The physicochemi-

TABLE-1
SUBSTITUTION ON THE PARENT NUCLEUS AND BIOLOGICAL DATA OF THE SERIES

| Compd. No. | $R^1$ | $R^2$ | $R^3$ | $R^4$ | Cytotoxicity | | | -log $IC_{50}$ | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | Mouse EH | Bovine platelet | Porcine leucocyte | Mouse EH | Bovine platelet | Porcine leucocyte |
| 1 | $CH_2$ | H | H | H | >30 | 13 | >30 | – | -1.1139 | – |
| 2 | $(CH_2)_2$ | H | H | H | 7 | 7 | 9 | -0.845 | -0.8450 | -0.9542 |
| 3 | $(CH_2)_2$ | H | Cl | H | 23 | 14 | 11 | -1.361 | -1.1460 | -1.0400 |
| 4 | $(CH_2)_2$ | H | CN | H | 18 | 7 | 24 | -1.255 | -0.8450 | -1.3800 |
| 5 | $(CH_2)_2$ | H | $CH_3$ | H | 16 | 12 | 21 | -1.204 | -1.0790 | -1.3220 |
| 6 | $(CH_2)_2$ | $OC_4H_9$ | $OC_4H_9$ | H | 30 | >30 | >30 | -1.477 | – | – |
| 7 | $(CH_2)_2$ | $OCH_3$ | $OCH_3$ | H | 6 | 6 | 5 | -0.778 | -0.7780 | -0.6980 |
| 8 | $(CH_2)_2$ | OH | $OCH_3$ | H | 6 | 6 | 4 | -0.778 | -0.7780 | -0.6020 |
| 9 | $(CH_2)_2$ | H | OH | H | 12 | 6 | 16 | -1.079 | -0.9030 | -1.2040 |
| 10 | $(CH_2)_2$ | OH | OH | H | 5 | 4 | 5 | -0.698 | -0.6020 | -0.6980 |
| 11 | E-CH=CH | H | $CH_3$ | H | >30 | >30 | >30 | – | – | – |
| 12 | $(CH_2)_3$ | H | H | H | 12 | 10 | 13 | -1.079 | -1.0000 | -1.1130 |
| 13 | $(CH_2)_3$ | H | $OCH_3$ | H | 14 | 4 | 14 | -1.146 | -0.6020 | -1.1460 |
| 14 | $(CH_2)_3$ | $OCH_3$ | $OCH_3$ | $OCH_3$ | >30 | 9 | 7 | – | -0.9540 | -0.8450 |
| 15 | $(CH_2)_3$ | H | OH | H | 11 | 8 | 6 | -1.040 | -0.9030 | -0.7780 |
| 16 | $(CH_2)_3$ | OH | OH | OH | 7 | 5 | 4 | -0.845 | -0.6980 | -0.6020 |
| 17 | $(CH_2)_4$ | H | H | H | 19 | 7 | 16 | -1.278 | -0.8450 | -1.2040 |
| 18 | CO | H | H | H | 16 | 6 | 18 | -1.204 | -0.7780 | -1.2550 |
| 19 | CO | H | CN | H | 8 | 4 | 11 | -0.903 | -0.6020 | -1.0400 |
| 20 | CO | H | COOH | H | 7 | 11 | 14 | -0.845 | -1.0400 | -1.1460 |
| 21 | CO | H | $COOCH_3$ | H | 30 | 27 | >30 | -1.477 | -1.4310 | – |

cal descriptors were calculated from *The substituents constants for correlation analysis in chemistry and biology developed by Corwin Hansch and Albert Leo*. The physicochemical parameters and -log $IC_{50}$ values were loaded into the MS excel worksheet and saved as coma delimited file. Openstat 4 version 6.5.1 software was used to derive the regression equations between physicochemical descriptors and biological activity of the compounds. The statistical parameters that were considered for the analysis are correlation coefficient (r), squared correlation coefficient ($r^2$), F test value, $Q^2$, $S_{DEP}$ and VIF. The selected significant equations were validated by leave one out method (LOO).




1,8-Dihydroxy-2-phenyl alkyl-9(10H)-anthracenone

Fig. 1. Parent structure of the anthracenone series

## RESULTS AND DISCUSSION

21 Compounds belonging to anthracenone category were taken for the present study. The biological activities data for anthracenone derivatives were taken from literature. The $IC_{50}$ values for inhibitory action on 12-LO isoforms in epidermal homogenate of mice, bovine platelets and porcine leukocyte were transformed into -log $IC_{50}$. Stepwise regression analysis was performed by taking -log $IC_{50}$ as dependent variable and descriptors as independent variables. From the analysis significant equations were selected which were validated by leave one out method. The significant regression equations are:

$$\text{-log } IC_{50} = -1.343\ (\pm 0.23)\ R^2_{\pi}\ p\text{-}1.132 \quad (1)$$

n = 17, F = 34.091, R = 0.833, $R^2$ = 0.694, VIF = 1,
PRESS = 0.421, $Q^2$ = 0.7137, $S_{DEP}$ = 0.02

$$\text{-log } IC_{50} = 1.605\ (\pm 0.281)\ R^2\ f\text{-}1.133 \quad (2)$$

n = 17, F = 32.637, R = 0.828, $R^2$ = 0.685, VIF = 1,
PRESS = 0.375, $Q^2$ = 0.684, $S_{DEP}$ = 0.242

$$\text{-log } IC_{50} = 0.443\ (\pm 0.08)\ R^2\ Ha\text{-}1.132 \quad (3)$$

n = 17, F = 30.791, R = 0.821, $R^2$ = 0.672, VIF = 1,
PRESS = 0.409, $Q^2$ = 0.788, $S_{DEP}$ = 0.155

$$\text{-log } IC_{50} = 3.691\ (\pm 0.665)\ R^2\ \sigma_m\ \text{-}1.132 \quad (4)$$

n = 17, F = 30.791, R = 0.820, $R^2$ = 0.672, VIF = 1,
PRESS = 0.488, $Q^2$ = 0.5879, SDEP = 0.169

Total 17 compounds are taken for the study due to unavailability of the biological data of 4 compounds. From above equations it is clear that group at position 2 effects biological activity of the parent compound significantly. Descriptors effects the biological activity significantly are lipophilicity, field effect, inductive effect and hydrogen acceptor in the pool of descriptors, taken for study. These are also cross validated by PRESS, $Q^2$, SDEP values.

**Conclusion**

The results obtained from the regression equation shows that the physicochemical properties in $R^2$ position of the compound has contributed significantly with 12(s)-HETE biosynthesis in porcine leukocytes in monoparametric analysis. Other than hydrophobic descriptor, F, Ha and $\sigma_m$ were positively contributed for activity. In multiparametric analysis, no significant increase in correlation coefficient values was obtained. Validation results also concluded that the selected equations are significant. Epidermal homogenate of mice and bovine platelets are having insignificant correlation with physicochemical properties. It is concluded that electronic hydrophobic and steric properties in $R^2$ position of the compound is important for 12(s)-HETE biosynthesis inhibitory activity.

These initial results are promising for the development of some novel anthracenones, which are selective 12-LO enzyme inhibitors without renal or gastric toxicity. Further extended research in this work could lead to the development of new selective 12-LO enzyme inhibitors.

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## REFERENCES

1. A.R. Brash, *J. Biol. Chem.*, **274**, 23679 (1999).
2. C.D. Funk, D.S. Keeney and A.R. Brash, *J. Biol. Chem.*, **271**, 23338 (1996).
3. R.N. Young, *Eur. J. Med. Chem.*, **34**, 671 (1999).
4. K. Mullar, R. Altmann and H. Prinz, *Eur. J. Med. Chem.*, **33**, 209 (1998).
5. K. Mullar, R. Altmann and H. Prinz, *Eur. J. Med. Chem.*, **36**, 569 (2001).
6. K. Mullar, H. Reindle and I. Gawlik, *Eur. J. Med. Chem.*, **33**, 969 (1998).

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