# QSAR studies on structurally similar 2-arylidene-4-(4-phenoxy - phenyl) but-3-en-4-olides as anti-inflammatory agents

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**Abstract**
QSAR analysis based on classical Hansch approach was adopted on recently reported novel series of 2-arylidene-4-(4-phenoxy phenyl) but-3-en-4-olides as anti-inflammatory agents. The compounds were divided into training and test sets. The regression analysis demonstrated that the topological parameters kier shape order index ($\kappa_3$) and kiers modified-alpha shape order index ($\kappa\alpha_3$) are important in describing anti-inflammatory activity of butenolides. The developed QSAR model were cross validated by high $q^2$ values obtained by "leave one out" (LOO) method.

**Keywords:** QSAR, butenolides, anti-inflammatory activity, molecular descriptors, linear regression

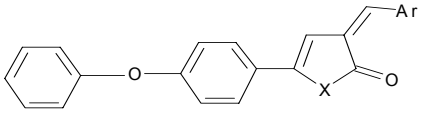
## Introduction

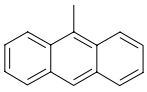
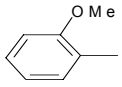
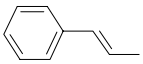
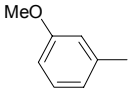
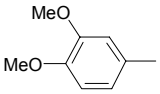
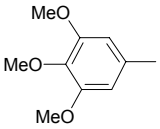
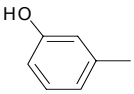
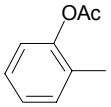
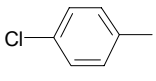
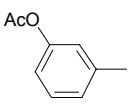
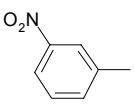
Non- steroidal anti-inflammatory drugs (NSAIDS) are still the most commonly prescribed drugs world wide for the treatment of inflammatory diseases like rheumatoid arthritis, osteoarthritis, orthopedic injuries, post operative pain, acute myalgias etc.[1, 2] The butenolide system in cardiac glycoside shows cardiotonic activity.[3] The synthetic derivatives containing butenolide system reported to posess antiviral, [4, 5] antimicrobial [6] antimalarial[7] and anticancer[8] activities. The butenolides are also reported to have protein tyrosine phosphates (CDC 25) inhibitory and endogenous feeding suppressant activities.[9,10] Recently Husain *et al* reported a series of butenolides with anti-inflammatory potential.[11]

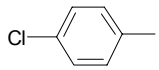
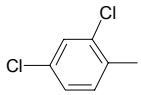
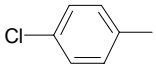
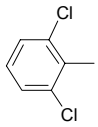
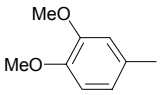
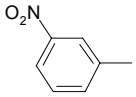
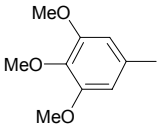
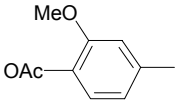
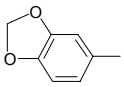
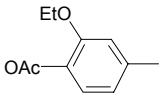
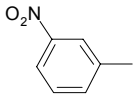
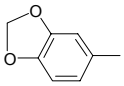
Quantitative Structure activity relationship (QSAR) models are highly effective in describing the structural basis of biological activity.[12] It is now widely used for the prediction of physicochemical properties and biological activities in chemical, environmental and pharmaceutical areas.[13] The success of QSAR approach can be explained by the insight offered into the structural determination of chemical properties, and the possibility to estimate the properties of new chemical compounds without the need to synthesize and test them.[14]. Recently we have reported the development of useful QSAR models for antimicrobial activity [15- 18] and anti-inflammatory activity.[19]

In view of above and as a part of our effort to create QSAR models that show substantial predictive promise, in the present study we report the QSAR study on anti-inflammatory activity of series of 2-arylidene-4-(4-phenoxy-phenyl)but-3-en-4-olide reported by Husain *et al* (Table 1).[11]

**Table 1.** Chemical structure and anti-inflammatory potential of structurally similar 2-Arylidene-4-(4-phenoxy -phenyl) but-3-en-4-olides[11]




| Com. No. | Ar | X | % Inhibition of paw edema | Com. No. | Ar | X | % Inhibition of paw edema |
|---|---|---|---|---|---|---|---|
| 1 |  | **O** | 22.58 | 16 |  | **O** | 19.35 |
| 2 |  | **O** | 19.35 | 17 |  | **O** | 25.80 |
| 3 |  | **O** | 25.80 | 18 |  | **NH** | 19.35 |
| 4 |  | **O** | 32.25 | 19 |  | **NH** | 29.03 |
| 5 |  | **O** | 45.16 | 20 |  | **NH** | 25.80 |
| 6 |  | **O** | 48.38 | 21 |  | **NH** | 09.67 |
| 7 |  | **O** | 35.48 | 22 |  | **NH** | 12.90 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| 8 |  | **O** | 25.80 | 23 |  | **NH** | 9.67 |
| 9 |  | **O** | 29.03 | 24 |  | **-N-CH$_2$-Ph** | 35.48 |
| 10 |  | **O** | 22.58 | 25 |  | **-N-CH$_2$-Ph** | 51.61 |
| 11 |  | **O** | 25.80 | 26 |  | **-N-CH$_2$-Ph** | 58.06 |
| 12 |  | **O** | 32.25 | 27 |  | **-N-CH$_2$-Ph** | 32.25 |
| 13 |  | **O** | 45.16 | 28 |  | **-N-CH$_2$-Ph** | 25.80 |
| 14 |  | **O** | 12.90 | 29 |  | **-N-CH$_2$-Ph** | 22.58 |
| 15 |  | **O** | 29.03 | | | | |

## Results and Discussion

The success of QSAR studies mainly depends whether or not the molecular descriptors chosen are appropriate to explain the biological activity. Based on our earlier studies we have used lipophilic parameter, log of octanol water partition co-efficient (log P), [20] molar refractivity (MR) [21] molecular connectivity indices ($\chi^0$,$\chi^1$,$\chi^2$), [22] kiers shape order indices ($\kappa_1$,$\kappa_2$,$\kappa_3$), kiers alpha modified shape indices ($\kappa\alpha_1$,$\kappa\alpha_2$,$\kappa\alpha_3$), [23] Randic [24] and wiener topological indices [25], total energy (Te) and electronic energy (Ele E) as independent variables (Table 2) in the present study. The independent variables are correlated with anti-inflammatory activity of series of 2-arylidene-4-(4-phenoxy-phenyl) but-3-en-4-olides.

**Table 2.** Calculated molecular descriptors for the compounds used in the present study

| Com. | log P | MR | $\chi^0$ | $\chi^1$ | $\chi^2$ | $\kappa_1$ | $\kappa_2$ | $\kappa_3$ | $\kappa\alpha_1$ | $\kappa\alpha_2$ | $\kappa\alpha_3$ |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Training set** | | | | | | | | | | | |
| 1 | 4.54 | 102.47 | 17.77 | 12.78 | 11.23 | 19.32 | 9.47 | 5.30 | 16.21 | 7.31 | 3.88 |
| 2 | 4.28 | 108.94 | 19.35 | 13.72 | 11.94 | 21.24 | 10.35 | 5.59 | 18.07 | 8.15 | 4.18 |
| 3 | 4.28 | 108.94 | 19.35 | 13.71 | 12.03 | 21.24 | 10.35 | 5.80 | 18.07 | 8.15 | 4.35 |
| 4 | 4.03 | 115.40 | 20.92 | 14.66 | 12.74 | 23.17 | 11.23 | 6.08 | 19.94 | 8.98 | 4.64 |
| 5 | 4.03 | 113.60 | 20.92 | 14.56 | 13.25 | 23.17 | 11.23 | 6.75 | 19.67 | 8.80 | 5.06 |
| 6 | 5.05 | 107.28 | 18.64 | 13.17 | 11.85 | 20.28 | 9.67 | 5.54 | 17.43 | 7.72 | 4.23 |
| 7 | 5.57 | 112.08 | 19.51 | 13.58 | 12.38 | 21.24 | 9.87 | 5.59 | 18.66 | 8.13 | 4.43 |
| 8 | 5.57 | 112.08 | 19.51 | 13.60 | 12.27 | 21.24 | 9.87 | 5.39 | 18.66 | 8.13 | 4.27 |
| 9 | 4.49 | 109.80 | 20.22 | 14.08 | 12.76 | 22.20 | 10.54 | 6.04 | 18.64 | 8.12 | 4.41 |
| 10 | 3.78 | 120.07 | 22.50 | 15.51 | 13.96 | 25.10 | 12.11 | 7.01 | 21.55 | 9.64 | 5.34 |
| 11 | 4.12 | 124.82 | 23.21 | 16.01 | 14.34 | 26.07 | 12.81 | 7.49 | 22.51 | 10.29 | 5.77 |
| 12 | 6.54 | 135.37 | 22.91 | 16.74 | 15.04 | 24.34 | 11.17 | 5.50 | 20.31 | 8.56 | 3.98 |
| 13 | 5.07 | 112.79 | 19.18 | 13.78 | 11.92 | 21.24 | 10.86 | 6.25 | 17.86 | 8.44 | 4.61 |
| 14 | 3.89 | 104.42 | 17.77 | 12.78 | 11.23 | 19.32 | 9.47 | 5.30 | 16.21 | 7.31 | 3.88 |
| 15 | 3.60 | 106.12 | 18.64 | 13.17 | 11.86 | 20.28 | 9.67 | 5.54 | 17.12 | 7.51 | 4.10 |
| 16 | 6.43 | 138.74 | 23.33 | 16.65 | 14.80 | 25.64 | 12.50 | 6.87 | 22.05 | 10.02 | 5.26 |
| 17 | 5.40 | 146.86 | 25.61 | 18.14 | 15.69 | 28.53 | 14.06 | 7.40 | 24.56 | 11.29 | 5.66 |
| 18 | 5.15 | 153.32 | 27.19 | 19.09 | 16.42 | 30.46 | 14.94 | 7.70 | 26.44 | 12.13 | 5.96 |
| 19 | 5.24 | 139.55 | 24.32 | 17.73 | 15.81 | 26.23 | 12.45 | 6.43 | 22.34 | 9.85 | 4.85 |
| **Test set** | | | | | | | | | | | |
| 21 | 3.78 | 121.86 | 22.50 | 15.61 | 13.47 | 25.10 | 12.11 | 6.37 | 21.83 | 9.82 | 4.94 |
| 22 | 4.03 | 113.60 | 20.92 | 14.58 | 13.16 | 23.17 | 11.23 | 6.52 | 19.67 | 8.80 | 4.87 |
| 23 | 3.83 | 101.31 | 17.06 | 12.28 | 10.88 | 18.37 | 8.79 | 4.84 | 15.84 | 7.07 | 3.72 |
| 24 | 3.87 | 108.09 | 19.63 | 14.24 | 12.86 | 20.88 | 9.65 | 5.09 | 17.73 | 7.58 | 3.81 |
| 25 | 3.60 | 106.12 | 18.64 | 13.19 | 11.75 | 20.28 | 9.67 | 5.33 | 17.12 | 7.51 | 3.93 |
| 26 | 4.40 | 109.23 | 18.64 | 13.17 | 11.85 | 20.28 | 9.67 | 5.54 | 17.43 | 7.72 | 4.23 |
| 27 | 3.84 | 111.75 | 20.22 | 14.08 | 12.76 | 22.20 | 10.54 | 6.04 | 18.64 | 8.12 | 4.41 |
| 28 | 3.18 | 103.26 | 17.06 | 12.28 | 10.88 | 18.37 | 8.79 | 4.84 | 15.84 | 7.07 | 3.72 |
| 29 | 5.86 | 141.26 | 24.91 | 17.56 | 15.72 | 27.56 | 13.38 | 7.36 | 23.26 | 10.41 | 5.45 |

The compounds are divided into training and test sets each consisting of 19 and 10 molecules respectively. The training set is used for the model development and test set is used for the cross validation of QSAR model developed by the training set. The inter correlation among the descriptors and their correlation with anti-inflammatory activity is demonstrated by construction of a correlation matrix (Table 3).

**Table 3.** Correlation matrix of anti-inflammatory activity of butenolides

| | logBA | log P | MR | $\chi^0$ | $\kappa_1$ | $\kappa_2$ | $\kappa_3$ | $\kappa\alpha_1$ | $\kappa\alpha_2$ | $\kappa\alpha_3$ | R | W |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| logBA | 1.000 | | | | | | | | | | | |
| log P | 0.050 | 1.000 | | | | | | | | | | |
| MR | 0.710 | 0.549 | 1.000 | | | | | | | | | |
| $\chi^0$ | 0.801 | 0.377 | 0.967 | 1.000 | | | | | | | | |
| $\kappa_1$ | 0.844 | 0.316 | 0.946 | 0.995 | 1.000 | | | | | | | |
| $\kappa_2$ | 0.874 | 0.246 | 0.917 | 0.967 | 0.985 | 1.000 | | | | | | |
| $\kappa_3$ | 0.924 | 0.029 | 0.733 | 0.839 | 0.884 | 0.927 | 1.000 | | | | | |
| $\kappa\alpha_1$ | 0.863 | 0.322 | 0.936 | 0.987 | 0.995 | 0.979 | 0.884 | 1.000 | | | | |
| $\kappa\alpha_2$ | 0.897 | 0.264 | 0.909 | 0.960 | 0.981 | 0.992 | 0.923 | 0.987 | 1.000 | | | |
| $\kappa\alpha_3$ | 0.946 | 0.069 | 0.732 | 0.836 | 0.882 | 0.917 | 0.987 | 0.897 | 0.933 | 1.000 | | |
| R | 0.740 | 0.437 | 0.985 | 0.990 | 0.974 | 0.945 | 0.783 | 0.959 | 0.930 | 0.771 | 1.000 | |
| W | 0.788 | 0.372 | 0.971 | 0.996 | 0.989 | 0.967 | 0.831 | 0.976 | 0.954 | 0.820 | 0.994 | 1.000 |

From Table -3, it is clear that each parameter is highly correlated with biological activity as well highly correlated with each other except with log P. The high interrelationship among the parameters indicates that they should not be combined in multiple linear regressions (MLR) which may lead to be model suffering from the problem of colinearity.[14]

The multi co-linearity occurs when two independent variables are correlated with each other indicated by the change in signs of the co-efficient, a change in values of the previous co-efficient, change of significant variable into insignificant one or an increase in standard error of the estimate on addition of an additional parameter to the model. The different mono-parametric models developed for the anti-inflammatory activity of butenolides are presented in Table 4.

Among the different mono parametric models developed the model containing the topological parameter kiers shape third order index ($\kappa_3$) and kiers alpha modified third order shape index ($\kappa\alpha_3$) have high statistical significance (Eq-1 and Eq-2).

$Log_{BA} = 0.197\kappa\alpha_3 + 0.542$ (1)

n=19 r=0.945 $q^2$=0.865 F=113.84 s=0.045

$Log_{BA} = 0.158\kappa_3 + 0.484$ (2)

n=19 r=0.924 $q^2$=0.817 F=99.86 s=0.054

The positive co-efficient of $\kappa\alpha_3$ in Eq-1 indicates that the anti-inflammatory potential of substituted butenolides increases with increase in the magnitude of $\kappa\alpha_3$. The compound no.18 of training set having maximum $\kappa\alpha_3$ value of 5.96 is the most active compound (Log BA=1.76) among the training set and the compound no. 14 having a low $\kappa\alpha_3$ value 3.88 is being the least active one (Log BA=1.29). The similar trend was observed with anti-inflammatory activity of substituted butenolides and kiers third order shape index ($\kappa_3$).

**Table 4.** Best QSAR models for anti-inflammatory potential of 2-Arylidene-4-(4-phenoxy -phenyl) but-3-en-4-olides

| QSAR model No. | QSAR Models ($Log_{BA}$ = ) | n | r | $q^2$ | F ($p < 0.01$) | S |
|---|---|---|---|---|---|---|
| 1 | 0.006(±0.0968) MR+ 0.716(±1.464) | 19 | 0.709 | 0.369 | 17.25 | 0.098 |
| 2 | 0.040(±0.109)$\chi^0$+ 0.615(±1.464) | 19 | 0.800 | 0.562 | 30.33 | 0.084 |
| 3 | 0.0496(±0.107)$^v\chi^0$ + 0.688(±1.464) | 19 | 0.785 | 0.536 | 27.34 | 0.87 |
| 4 | 0.052(±0.0101)$\chi^1$ +0.686(±1.464) | 19 | 0.739 | 0.423 | 20.54 | 0.095 |
| 5 | 0.072(±0.096)$^v\chi^1$ +0.755 | 19 | 0.706 | 0.355 | 16.89 | 0.099 |
| 6 | 0.060(±0.099)$\chi^2$ +0.675 | 19 | 0.722 | 0.370 | 18.57 | 0.097 |
| 7 | 0.086(±0.087)$^v\chi^2$ +0.859 | 19 | 0.636 | 0.225 | 11.59 | 0.108 |
| 8 | 0.383(±0.097)$\chi^3$ +0.790 | 19 | 0.711 | 0.387 | 17.40 | 0.098 |
| 9 | 0.538(±0.072)$^v\chi^3$ +1.093 | 19 | 0.534 | 0.112 | 6.78 | 0.118 |
| 10 | 0.036(±0.115)$\kappa_1$ +0.612 | 19 | 0.844 | 0.660 | 42.13 | 0.075 |
| 11 | 0.075(±0.119)$\kappa_2$ +0.621 | 19 | 0.875 | 0.725 | 55.26 | 0.068 |
| 12 | 0.158(±0.1266)$\kappa_3$ +0.484 | 19 | 0.924 | 0.817 | 99.86 | 0.054 |
| 13 | 0.042(±0.118)$\kappa\alpha_1$ +0.631 | 19 | 0.863 | 0.702 | 49.78 | 0.070 |
| 14 | 0.091(±0.122)$\kappa\alpha_2$+0.655 | 19 | 0.897 | 0.804 | 70.07 | 0.062 |
| 15 | 0.197(±0.129) $\kappa\alpha_3$+0.542 | 19 | 0.945 | 0.865 | 143.84 | 0.045 |
| 16 | 0.052(±0.100)R +0.686 | 19 | 0.739 | 0.423 | 20.54 | 0.095 |
| 17 | 0.0001(±0.107)W +1.133 | 19 | 0.787 | 0.533 | 27.85 | 0.086 |
| 18 | -0.0001(±0.113)Te +0.591 | 19 | 0.829 | 0.623 | 37.55 | 0.078 |
| 19 | -0.1288 (±0.107)Ele E +0.984 | 19 | 0.790 | 0.549 | 28.39 | 0.085 |

The developed models are cross validated by leave one out method .The high $q^2$ values observed in case of Eq-1 ($q^2$=0.865) and Eq-2 ($q^2$=0.817) are indicative of their reliability in prediction of anti-inflammatory activity of substituted butenolides. The predictive ability of Eq-1 was validated by predicting the anti inflammatory activity of test set which has excluded from the development of QSAR model. The low residual activity observed in case of training as well as test sets in Table-5 indicates the reliability of the QSAR model expressed by Eq-1.

Even though the number of compounds and 'rule of thumb' allowed us to go for multi-parametric models the high inter-relationship among the parameters restricted us to go stick to the development of monoparametric models. Further the plot of QSAR predicted Log BA Vs observed Log BA (Figure-1) is also in favor of the model expressed by Eq-1.

The lipophilic parameter log P has showed poor correlation with the studied biological activity (Eq.3) when studied alone.

$Log_{BA}$= -0.007 log P + 1.427 (3)

n=19 r=0.050 $q^2$=-0.222 F=0.042 s=0.140

When log P has combined with molar refractivity and valence molecular connectivity indices $^{0}\chi^{v}$ and $^{1}\chi^{v}$ an improvement in the r values were observed (Eq.4 –Eq. 6) when compared to QSAR model No. 1, 5 and 7 of Table 4. But its combination with shape indices produced a marginal increase in r value. (Eq. 7 –Eq.10 when compared to QSAR model No. 10, 11, 13 and 14 of Table 4).

$Log_{BA}$= -0.077 log P + 0.008 MR + 0.804 (4)
n=19 r=0.817 $q^2$=0.494 F=16.14 s=0.083

$Log_{BA}$= -0.067 log P + 0.058 $^{0}\chi^{v}$ + 0.809 (5)
n=19 r=0.868 $q^2$=0.630 F=24.45 s=0.071

$Log_{BA}$= -0.081 log P + 0.101 $^{1}\chi^{v}$ + 0.853 (6)
n=19 r=0.821 $q^2$=0.500 F=16.66 s=0.082

$Log_{BA}$= -0.032 log P + 0.125 $\kappa_1$ + 1.465 (7)
n=19 r=0.874 $q^2$=0.677 F=26.01 s=0.070

$Log_{BA}$= -0.028 log P + 0.079 $\kappa_2$ + 0.713 (8)
n=19 r=0.891 $q^2$=0.684 F=30.80 s=0.066

$Log_{BA}$= -0.040 log P + 0.046 $\kappa\alpha_1$ + 0.745 (9)
n=19 r=0.896 $q^2$=0.703 F=32.70 s=0.064

$Log_{BA}$= -0.031 log P + 0.096 $\kappa\alpha_2$ + 0.759 (10)
n=19 r=0.918 $q^2$=0.842 F=42.77 s=0.057

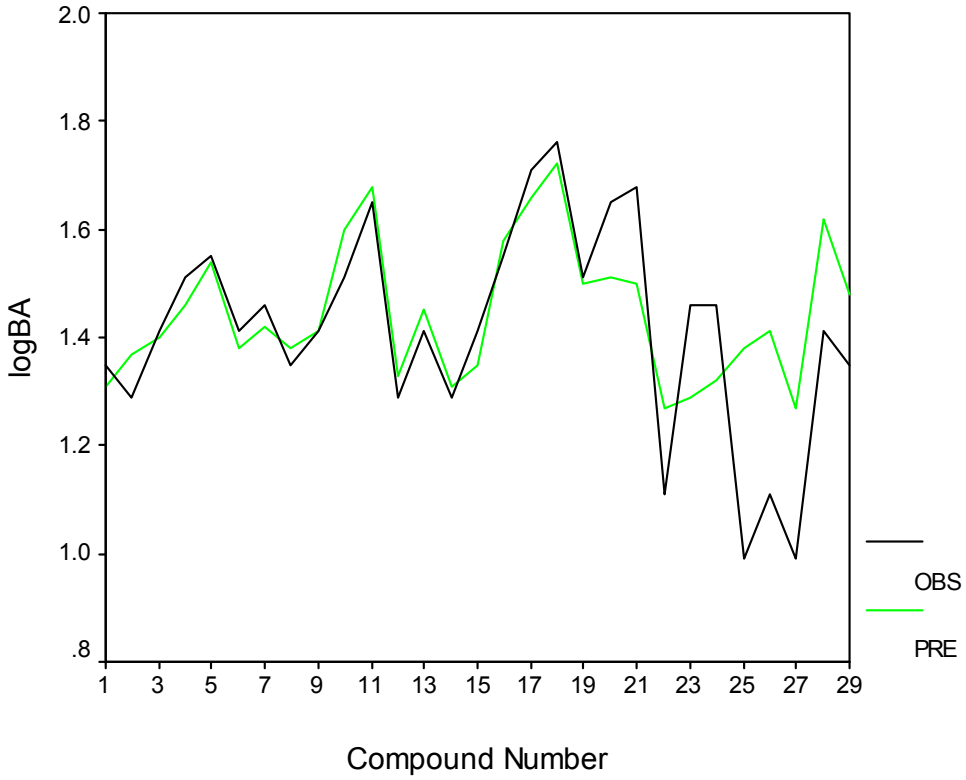



**Figure 1.** Comparison of observed logBA and QSAR predicted logBA

**Table 5.** Observed (Obs), calculated (cal), residual values obtained using Eq. 1

| Comp. | Observed | Predicted | Residual |
|---|---|---|---|
| | Training set | | |
| 1 | 1.35 | 1.31 | 0.04 |
| 2 | 1.29 | 1.37 | -0.08 |
| 3 | 1.41 | 1.40 | 0.01 |
| 4 | 1.51 | 1.46 | 0.05 |
| 5 | 1.55 | 1.54 | 0.01 |
| 6 | 1.41 | 1.38 | 0.03 |
| 7 | 1.46 | 1.42 | 0.04 |
| 8 | 1.35 | 1.38 | -0.03 |
| 9 | 1.41 | 1.41 | 0.00 |
| 10 | 1.51 | 1.60 | -0.09 |
| 11 | 1.65 | 1.68 | -0.03 |
| 12 | 1.29 | 1.33 | -0.04 |
| 13 | 1.41 | 1.45 | -0.04 |
| 14 | 1.29 | 1.31 | -0.02 |
| 15 | 1.41 | 1.35 | 0.06 |
| 16 | 1.55 | 1.58 | -0.03 |
| 17 | 1.71 | 1.66 | 0.05 |
| 18 | 1.76 | 1.72 | 0.04 |
| 19 | 1.51 | 1.50 | 0.01 |
| | Test set | | |
| 20 | 1.65 | 1.51 | 0.14 |
| 21 | 1.68 | 1.50 | 0.18 |
| 22 | 1.11 | 1.27 | -0.16 |
| 23 | 1.46 | 1.29 | 0.17 |
| 24 | 1.46 | 1.32 | 0.14 |
| 25 | 0.99 | 1.38 | -0.39 |
| 26 | 1.11 | 1.41 | -0.30 |
| 27 | 0.99 | 1.27 | -0.28 |
| 28 | 1.41 | 1.62 | -0.21 |
| 29 | 1.35 | 1.48 | -0.13 |

## Conclusions

The results and discussion made above lead to the conclusion that the anti inflammatory activity of series of 2-arylidene-4-(4-phenoxy-phenyl)but-3-en-4-olides can be successfully modeled using topological indices. It was also observed that out of the topological indices selected the

kiers third order shape index ($\kappa_3$) and kiers alpha modified third order shape index ($\kappa\alpha_3$) are most useful for this purpose.

## Experimental Section

**Anti-inflammatory activity**

The % inhibition of carrageenan induced paw edema was adopted from the work of Husain *et al.* We have converted the % inhibition into log units for use in QSAR model development.

**Calculation of molecular descriptors and regression**

The calculation of molecular descriptors of substituted butenolides as well as the regression analyses were carried out using the molecular package TSAR 3D version 3.3 for windows.[26] The details of the descriptors are available in the literature [20-25] and therefore they are not described over here.

**Cross-validation**

The models were cross-validated by 'leave one out' scheme [27] where a model is built with N-1 compounds and the $N^{th}$ compound is predicted. Each compound is left out of the model derivation and predicted in turn. An indication of the performance of the model is obtained from the cross-validated (or predictive $q^2$) method which is defined as

$q^2$= (SD-PRESS/SD)

Where SD is the sum of squares deviation for each activity from the mean. PRESS (or predictive sum-of -squares) is the sum of the squared difference between the actual and that of the predicted values when the compound is omitted from the fitting process. The model with high $q^2$ value is said to have high predictability.

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