Computational prediction and validation studies on a diverse dataset of cox-2 inhibitors

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Abstract: In linear regression analysis, when data was derived from various reference sources, the experimental quality of such data has to be assessed. Significant variables based on the statistical data of analysis were chosen. Based on the parameters like correlation coefficient (r), F-value, cross-validation r² etc quality of the generated equation was judged. An additional condition for high predictive ability of regression model is based on external set cross-validation r² (R²cv,ext) and the regression of observed activities against predicted activities and vice versa for validation set. Multivariate regression analysis using python program resulted in few influential parameters displayed significant positive and negative contribution towards biological activity of COX-2 inhibitors. A new regression model was attempted by dividing the complete set (n=64) as a 58 molecule training set and a 6 molecule validation set based on selection criteria after rejecting outliers from the data set.

Index Terms: Linear regression, COX-2, regression model, correlation

1. Introduction

Arachidonic acid is converted to prostaglandins (PGs) and exists in two isoforms, COX-1 and COX-2 [1]. Cyclo-oxygenase-2 (COX-2), a rate-limiting enzyme for prostanoid synthesis, is induced during inflammation and participates in inflammation mediated cytotoxicity. Cerebral ischemia is followed by an inflammatory reaction that plays a role in the evolution of the tissue damage [2]. Celecoxib, an anti arthritic agent that inhibits COX-2 but spares COX-1 at therapeutic doses, is expected to have minimal effects on platelet function compared to the effects on platelet function of a supratherapeutic dose of celecoxib with a standard dose of naproxen a conventional NSAID [3 and 4]. The discovery of at least 2 cyclo-oxygenase (COX) isoenzymes, referred to as COX-1 and COX-2, has updated our knowledge of non steroidal anti-inflammatory drugs (NSAIDs) [5]. The 2 COX isoenzymes share structural and enzymatic similarities, but are specifically regulated at the molecular level and may be distinguished apart in their functions, although some physiological overlap between them does occur. The major goal in developing selective COX inhibitors is to improve NSAID tolerability [6]. Celecoxib, in the 1,5-diarylpyrazole class of compound [7], was the first launched selective COX-2 inhibitor and has excellent selectivity and potent anti-inflammatory activity; however, its aqueous solubility is relatively low, which decreases its oral bioavailability [8]. One approach to address this problem is to convert the compound into a pro drug that is readily soluble in water. Recent studies have
indicated that the relationships between polyunsaturated fatty acid metabolism and carcinogenesis have led to new targets for the design of mechanism based drugs in cancer chemoprevention research [9, 10 and 11]. Encouraged by these observations we performed computational linear regression analysis using python code on a set of 79 compounds with dihydropyrazole sulphonamides, pyrazole thiadiazoles and triarylpyrazoline derivatives and all statistical validation procedures were met.

2. Material and methods

2.1 Data set
To obtain a consistent and robust linear regression equation, it is essential to consider a dataset that consists of chemically diverse molecules with experimental biological activity. Therefore, a set of 79 compounds with dihydropyrazole sulphonamides and triarylpyrazoline derivatives were considered [12, 13, 14, and 15]. The structures along with bioactivities of all compounds were given in Table 1. The inhibitory activities of these derivatives reported in terms of IC50 in micro molar were transformed into their corresponding concentration values in order to overcome overlapping data. The structures were sketched using ISIS Draw 2.3 (www.mdli.com) software and the descriptors were calculated.

2.2 Conversion of dependent variable to its respective log values
In regression analysis, it is imperative that the biological data be both accurate and precise to develop a meaningful model. It must be realized that any resulting regression equation obtained that is developed is only as valid statistically as the data that led to its development.

2.3 Linear Regression Analysis using Python Statmodels, pandas, numpy, matplotlib
The construction of linear regression models on complete and training sets respectively is implemented. Linear regression analysis establishes the relationship between dependent variable (log 1/IC50) and independent variables. Based on the statistical data of analysis significant descriptors were chosen.

Table 1: Structures and activity data of triarylpyrazolines and dihydropyrazole sulphonamide, pyrazole thiadiazoles and pyrazoline derivatives.

| S. No. | Inhibitor from article | Activity IC50 (uM) |
|-------|------------------------|-------------------|
|       | X Ar                   |                   |
| 1     | 10a O                  | 4.13              |
| 2     | 10b S                  | 2-furyl 6.11      |
| 3     | 10c O                  | 2-thienyl 3.65    |
| 4     | 10d S                  | 2-thienyl 3.89    |
| 5     | 10e O                  | C6H5 1.98         |
| 6     | 10f O                  | 4-OCH3C6H4 4.33   |
| 7     | 10g S                  | 4-OCH3C6H4 1.52   |
| 8     | 10h O                  | 4-ClC6H4 2.64     |
| 9     | 10i S                  | 4-ClC6H4 0.56     |
| 10    | 10j O                  | 4-CF3C6H4 0.97    |
| 11    | 10k S                  | 4-CF3C6H4 1.97    |
| 12    | 10l O                  | 3,4,5-(OCH3)3C6H2 6.34 |
|   |   | 3,4,5-(OCH₃)₃C₆H₂ |   |
|---|---|-------------------|---|
|13 | 10m| S                 | 0.98|
|   |   | ![Chemical Structure](image)

| R  | Ar     |
|----|--------|
|14  | 8a     | COOH | C₆H₅  |
|15  | 8b     | COOH | 4-FC₆H₄ |
|16  | 8c     | COOH | 4-ClC₆H₄ |
|17  | 8d     | COOH | 3-OCH₃C₆H₄ |
|18  | 8e     | COOH | 4-OCH₃C₆H₄ |
|19  | 8f     | COOH | 3,4-(OCH₃)₂C₆H₃ |
|20  | 8g     | COOH | 3,4,5-(OCH₃)₃C₆H₂ |
|21  | 8h     | COOH | 2-thienyl |
|22  | 8i     | SO₂NH₂ | C₆H₅ |
|23  | 8j     | SO₂NH₂ | 4-FC₆H₄ |
|24  | 8k     | SO₂NH₂ | 4-ClC₆H₄ |
|25  | 8l     | SO₂NH₂ | 3-OCH₃C₆H₄ |
|26  | 8m     | SO₂NH₂ | 4-OCH₃C₆H₄ |
|27  | 8n     | SO₂NH₂ | 3,4-(OCH₃)₂C₆H₃ |
|28  | 8o     | SO₂NH₂ | 3,4,5-(OCH₃)₃C₆H₂ |
|29  | 8p     | SO₂NH₂ | 2-thienyl |

|   |   | ![Chemical Structure](image)

| X=C | R1 | R2 | R3 | R4 | R5 |
|-----|----|----|----|----|----|
|30   | H  | H  | H  | H  | H  | 3.28|
|31   | H  | CH₃| H  | H  | H  | 2.48|
|32   | H  | CH₃| H  | H  | H  | 2.16|
|33   | H  | H  | CH₃| H  | H  | 2.63|
|34   | OCH₃| H  | H  | H  | H  | 1.12|
|35   | H  | OCH₃| H  | H  | H  | 11.89|
|36   | F  | H  | H  | H  | H  | 4.83|
|37   | H  | F  | H  | H  | H  | 15.32|
|38   | H  | H  | F  | H  | H  | 4.92|
|39   | Cl | H  | H  | H  | H  | 12.68|
|40   | Br | H  | H  | H  | H  | 3.48|
|41   | H  | Br | H  | H  | H  | 26.34|
|42   | H  | H  | Br | H  | H  | 1.76|
|43   | H  | OH | H  | H  | H  | 18.26|
|44   | H  | H  | CF₃| H  | H  | 32.26|
|45   | Cl | H  | Cl | H  | H  | 3.66|
|46   | Cl | H  | H  | H  | F  | 0.46|

| X=O |   |   |   |   |   |

3
|   |   |   |   |   |   |   |
|---|---|---|---|---|---|---|
| 47 | 47 | CH₃ | H | H | H | H | 0.33 |
| 48 | 48 | OCH₃ | H | H | H | H | 1.02 |
| 49 | 49 | H | H | OCH₃ | H | H | 7.24 |
| 50 | 50 | F | H | H | H | H | 2.28 |
| 51 | 51 | Cl | H | H | Cl | H | H | 8.24 |
| 52 | 52 | H | H | Br | H | H | 1.26 |
| 53 | 53 | Br | H | H | Cl | H | H | 6.88 |
| 54 | 54 | H | H | Br | H | H | 2.74 |
| 55 | 55 | Cl | H | Cl | H | H | 16.27 |
| 56 | 56 | Cl | H | H | F | 4.13 |

![Chemical Structure](image)

|   |   |   |
|---|---|---|
| 57 | A1 | 0.10 |
| 58 | A2 | 14.58 |
| 59 | A3 | 0.008 |
| 60 | A4 | 0.015 |
| 61 | A5 | 0.059 |
| 62 | A6 | 0.051 |
|   |   |   |
|---|---|---|
| 63 | B1 | 0.11 |
| 64 | B2 | 17.81 |
| 65 | B3 | 0.24 |
| 66 | B4 | 0.14 |
| 67 | B5 | 0.21 |
| 68 | B6 | 0.041 |

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|   |   |   |
|---|---|---|
| 69 | C1 | 67.13 |
| 70 | C2 | 173.6 |
| 71 | C3 | 1.97 |
| 72 | C4 | 5.65 |
| 73 | C5 | 27.09 |
| 74 | C6 | 60.98 |
2.4 Influential Parameters

Eleven parameters which represent physico-chemical properties of chemical compounds which should obey drug likeness parameters based on Lipinski rule of 5, such as molecular weight, hydrogen bond acceptors, hydrogen bond donors, log P, number of rotatable bonds and other parameters such as Dipole, lipole, number of halogen atoms, 6-membered aromatic rings, molecular surface area, and molecular volume are considered. Molecular weight, Hydrogen bond donors, acceptors, logP and number of freely rotatable bonds were selected based on Lipinski rule of 5 [17].

Table 2. Description of parameters used in the study

| Type       | Descriptors                                         |
|------------|-----------------------------------------------------|
| Structural | Molecular weight, number of rotatable bonds, number of hydrogen-bond acceptors, number of hydrogen-bond donors |
| Electronic | Dipole moments                                      |
| Lipophilicity | logP, Lipole moments                          |
| Geometrical | Molecular volume                                    |

2.5 Correlation

The Correlation of the dependent and independent variables measures the strength of the relationship between the two. In general, a positive correlation indicates a strong positive relationship, where an increase in one variable implies an increase in the other variable. A negative correlation indicates that an increase in the first variable implies a decrease in the second variable. A correlation of zero does not necessarily imply there is no relationship between the variables, if the data is non-linear. Often, the Pearson Correlation Coefficient is used to measure correlation, as denoted r.
2.6 Estimating the Predictive capability of regression equation

Predictive ability of the generated model was estimated externally by predicting the activities of validation set. This criterion may not be sufficient for a regression model to be truly predictive [18]. An additional condition for high predictive ability of regression model is based on external set cross-validation $R^2$, ($R^2_{cv,ext}$) and the regression of observed activities against predicted activities and vice versa for validation set, if the following conditions are satisfied [19].

$$R^2_{cv,ext} > 0.5$$  \hspace{1cm} (Eq. 2)

$$R^2 > 0.6$$ \hspace{1cm} (Eq. 3)

$$\frac{R^2 - R^2_0}{R^2} < 0.1 \text{ or } \frac{R^2 - R^2_0'}{R^2} < 0.1$$  \hspace{1cm} (Eq. 4)

$$0.85 \leq k \leq 1.15 \text{ or } 0.85 \leq k' \leq 1.15$$ \hspace{1cm} (Eq. 5)

Calculations relating to $R^2_{cv,ext}$, $R^2_0$ and the slopes, $k$ and $k'$ are based on regression of observed values against predicted values and vice versa. They were discussed in detail in ref [20].

3. Results and discussions

Using python program for multivariate regression analysis resulted in few influential parameters displayed significant positive and negative contribution towards biological activity of COX-2 inhibitors. A set of 79 COX-2 inhibitors were represented from Equation 6. The complete data set along with independent variables is presented in Table 3. A plot of actual values versus predicted values from Eq. 6 was given in Figure 1. In order to produce better predictive values, outliers should be analysed in data and should be removed from analysis. Therefore, leverages and outliers were calculated and data was presented.

$$\text{Log}(1/IC_{50}) = +0.064014 \times \text{DIPOLE} +0.072180 \times \text{LIPOLE} +0.142718 \times \text{MR} -0.289551 \times \text{KAPPA1} -0.845206 \times \text{KAPPA2} +0.931868 \times \text{KAPPA3} +0.415557 \times F -0.131285 \times CL -0.149720 \times 6AR -0.013773 \times MW +0.901670 \times HBA +0.626785 \times HBD -0.022891 \times \text{LOGP} -0.499466 \times \text{RB} +7.469486 \times \text{BALABAN} -14.125702$$
Table 3: Complete set data with predicted and residual values. Outliers calculated by leverages

```
| MOL | ACT  | DIP  | LIP  | MR  | KAPP A1  | KAPP A2  | KAPP A3  | F  | C  | H  | LO  | R  | BAL | P  | RED |
|-----|------|------|------|-----|----------|----------|----------|----|----|----|-----|----|-----|----|-----|
| 1_R | 0.20 | 4.24 | 11.6 | 155.4 | 23.168  | 9.868    | 5.907    | 0  | 0  | 3  | 420  | 5   | 1   | 4.8 | 1.28 |
| 1_R | 0.45332 | 7.23 | 12.3 | 115.66 | 24.135  | 10.992   | 5.742    | 1  | 0  | 3  | 438  | 5   | 1   | 4.9 | 1.27 |
| 1_R | 0.70 | 13.6 | 120.24 | 24.135  | 10.992   | 5.742    | 0  | 1  | 3  | 454  | 5   | 1   | 4.5 | 1.27 |
| 1_R | 0.09988 | 8   | 56  | 9    | 25.104  | 10.727   | 5.992    | 0  | 0  | 3  | 450  | 6   | 1   | 4.5 | 1.27 |
| 1_R | 0.67382 | 6   | 3   | 7    | 25.104  | 10.727   | 5.992    | 0  | 0  | 3  | 450  | 6   | 1   | 4.5 | 1.27 |
| 1_R | 0.35846 | 1   | 6   | 121.90  | 25.104 | 10.727   | 5.992    | 0  | 0  | 3  | 450  | 6   | 1   | 4.5 | 1.27 |
| 1_R | 0.599  | 7.86 | 128.37 | 27.046  | 11.899   | 6.297    | 0  | 0  | 3  | 480  | 7   | 1   | 4.3 | 1.29 |
| 1_B | 0.97287 | 5.97 | 7.89 | 134.83 | 28.994  | 12.458   | 6.405    | 0  | 0  | 3  | 510  | 6   | 1   | 4.8 | 1.33 |
| 1_R | 0.77379 | 2   | 6   | 3    | 121.06  | 25.104   | 9.932    | 1  | 0  | 3  | 473  | 5   | 1   | 3.7 | 1.28 |
| 1_R | 0.53 | 8.14 | 116.89 | 22.283  | 9.240    | 5.087    | 0  | 0  | 2  | 427  | 5   | 1   | 4.0 | 1.28 |
| 1_R | 0.06446 | 7   | 5   | 1    | 22.283  | 9.240    | 5.087    | 0  | 0  | 2  | 427  | 5   | 1   | 4.0 | 1.28 |
| 1_R | 0.41 | 9.93 | 120.84 | 24.135  | 9.704    | 5.742    | 0  | 0  | 3  | 455  | 5   | 1   | 5   | 1.27 |
| 1_B | 0.20935 | 3   | 3   | 25.104  | 10.727   | 5.992    | 1  | 0  | 3  | 438  | 6   | 1   | 4.5 | 1.27 |
| 1_B | 0.53275 | 7   | 0   | 121.06  | 25.104  | 9.932    | 5.992    | 1  | 0  | 3  | 473  | 5   | 1   | 3.7 | 1.28 |
| 1_R | 0.59 | 11.7 | 125.64 | 25.104  | 9.932    | 5.992    | 0  | 1  | 3  | 490  | 5   | 1   | 4.5 | 1.28 |
| 1_R | 0.42651 | 1   | 33  | 8    | 25.104  | 9.932    | 5.992    | 0  | 1  | 3  | 490  | 5   | 1   | 4.5 | 1.28 |
| 1_B | 0.34551 | 10.2 | 6.56 | 127.30  | 26.074  | 10.546   | 6.220    | 0  | 0  | 3  | 485  | 6   | 1   | 3.3 | 1.28 |
| 1_B | 0.32428 | 8.89 | 5.46 | 127.30  | 26.074  | 10.546   | 6.220    | 0  | 0  | 3  | 485  | 6   | 1   | 3.3 | 1.28 |
| 1_B | 0.38 | 5.28 | 133.77 | 28.019  | 11.396   | 6.533    | 0  | 0  | 3  | 515  | 7   | 1   | 3.1 | 1.30 |
| 1_B | 0.29467 | 5   | 8   | 0    | 28.019  | 11.396   | 6.533    | 0  | 0  | 3  | 515  | 7   | 1   | 3.1 | 1.30 |
| 1_B | 0.66952 | 6.23 | 3.27 | 140.23  | 29.970  | 12.250   | 6.840    | 0  | 0  | 3  | 545  | 8   | 1   | 2.8 | 1.34 |
| 1_B | 0.24534 | 5.02 | 5.29 | 122.29  | 23.168  | 9.894    | 5.333    | 0  | 0  | 2  | 492  | 5   | 1   | 2.8 | 1.26 |
| 1_B | 0.74 | 9.55 | 91.871 | 18.367  | 7.553    | 3.984    | 0  | 0  | 1  | 41   | 5   | 1   | 2.4 | 1.24 |
| 1_B | 0.61595 | 6   | 0   | 6    | 3.870   | 2.870    | 2.870    | 0  | 0  | 1  | 373  | 4   | 1   | 2.7 | 1.28 |
| 1_B | 0.7866 | 0.33 | 98.314 | 18.367  | 7.553    | 3.984    | 0  | 0  | 1  | 373  | 4   | 1   | 2.7 | 1.28 |
| 1_B | 0.56229 | 6   | 89  | 98.314 | 18.367  | 7.553    | 3.984    | 0  | 0  | 1  | 373  | 4   | 1   | 2.7 | 1.28 |
| 1_B | 0.7866 | 6.07 | 11.2 | 104.75  | 18.367  | 7.553    | 3.984    | 0  | 0  | 1  | 389  | 3   | 1   | 3.0 | 1.28 |
| 1_B | 0.7866 | 4   | 21  | 7    | 18.367  | 7.553    | 3.984    | 0  | 0  | 1  | 53   | 3   | 1   | 8   | 0.588 |
```

Figure 1: Actual Vs predicted activities of complete dataset (n=79).

```
Table 3: Complete set data with predicted and residual values. Outliers calculated by leverages

r = 0.827; r2 = 0.684; adj r2 = 0.609; F = 9.106;
p-value = 0.0009; f-value = 3.870; Chi^2 = 1.0676; n=79

(Eq. 6)
| 2.1 | a | 0.58995 | 7.60 | 11.8 | 99.80 | 19.322 | 8.163 | 4.380 | 0 | 0 | 2 | 367 | 4 | 1 | 3.4 | 1.28 | 0.999 |
| 2.1 | a | 0.7947 | 7.60 | 11.8 | 99.80 | 19.322 | 8.163 | 4.380 | 0 | 0 | 2 | 367 | 4 | 1 | 3.4 | 1.28 | 0.999 |
| 2.1 | a | 0.61349 | 7.60 | 11.8 | 99.80 | 19.322 | 8.163 | 4.380 | 0 | 0 | 2 | 367 | 4 | 1 | 3.4 | 1.28 | 0.999 |
| 2.1 | a | 0.18104 | 7.60 | 11.8 | 99.80 | 19.322 | 8.163 | 4.380 | 0 | 0 | 2 | 367 | 4 | 1 | 3.4 | 1.28 | 0.999 |
| 2.1 | a | 0.4216 | 7.60 | 11.8 | 99.80 | 19.322 | 8.163 | 4.380 | 0 | 0 | 2 | 367 | 4 | 1 | 3.4 | 1.28 | 0.999 |
| 2.1 | a | 0.29447 | 7.60 | 11.8 | 99.80 | 19.322 | 8.163 | 4.380 | 0 | 0 | 2 | 367 | 4 | 1 | 3.4 | 1.28 | 0.999 |

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A leverage graph was also plotted (Figure 2) to eliminate outlying data using python code, given below.

```python
fig = plot_leverage_resid2(results, ax = ax)
fig, ax = plt.subplots(figsize=(8,6))
from statsmodels.graphics.regressionplots import plot_leverage_resid2
```

from statsmodels.graphics.regressionplots import plot_leverage_resid2

fig = plot_leverage_resid2(results, ax = ax)
Figure 2: Leverages calculated from python program showing 5A2, 5B1, 5B2, 5B6, 5_C5 and 5_D6 compounds being displayed as having high leverage points.

Compounds 5A2, 5B1, 5B2, 5B6, 5_C5 and 5_D6 were excluded from the dataset and subjected to several regression trials. In all cases, either one or more of the following parameters failed to produce desired result, viz., correlation coefficient, F-statistic, p-value, chi2, AIC or BIC respectively. Hence, a method was employed to eliminate error causing data by calculating relative error and therefore nearly 9 data points were excluded from the dataset thereby achieving a dataset of 64 compounds. This is further selected to divide the dataset as training and validation sets.

4. Conclusion
An attempt has been made to study linear regression analysis on a dataset of COX-2 inhibitors. Multivariate regression analysis using python program resulted in H-bond acceptor and donors, number of Fluorine atoms, molecular weight, log p and rotatable bonds as well as dipole, Lipole and molar refractivity as influential parameters displayed significant positive and negative contribution towards activity of COX-2 inhibitors. The generated equations when applied on test set molecules resulted in better predictive values. Further, applying FIT Kubinyi function on the models resulted in model with 12 variables as the best model. Hence, designing or screening compound libraries for new compounds or analogs with possible H-bond acceptor and donor substitutions, and increase in number of Fluorine atoms and decrease in molecular weight, log p and rotatable bonds on the molecule with concomitant increase in dipole. Lipole and molar refractivity would enhance inhibitory activity against COX-2.

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