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PREDICTION OF MOLECULAR PROPERTIES OF NOVEL COX-2 INHIBITORS UTILIZING ARTIFICIAL NEURAL NETWORK ANALYSIS

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ABSTRACT

Selective COX-2 inhibitors are a category of nonsteroidal anti-inflammatory drug (or NSAID) that directly and selectively targets cyclooxygenase-2 enzymes, which are responsible for pain and inflammation. The development of various NSAID type drugs to selectively inhibit COX-2 enzymes have been found to be very effective in suppressing certain serious pathological conditions such as neurodegenerative conditions, certain cancers, as well as pain. Neural networks are a nonlinear method of modeling extremely complex functions. This study shows the effectiveness of artificial neural network analysis (ANN) of the molecular properties of already proven COX-2 targeting NSAID's, to predict and model new drug structures. In this study, the molecular properties of seven known COX-2 inhibitors are utilized to produce a neural network model for determining molecular properties for new COX-2 drugs. Important properties such as Log P, polar surface area, molecular volume, etc. are input to the model to establish learning parameters for predicting new properties. The predicted molecular weight of new drugs are statistically alike to the molecular weights of the training parameters (F and t test: P=0.069). Properties of new COX-2 inhibitors with the range in value, include the following: Log P (from 0.706 to 4.4477); molecular weight (from 275.26 to 411.65); and molecular volume (from 260.0 Angstroms^3 to 317.01 Angstroms^3). The graphical comparison of ANN predicted properties for new COX-2 drugs are presented. ANN learning model is shown to be useful in the prediction of molecular properties for potential new COX-2 inhibitors.

KEYWORDS: ANN, artificial neural network, COX-2, TIBERIUS.

INTRODUCTION

The use of aspirin (acetylsalicylic acid) showed the efficacy of non-steroidal anti-inflammatory drugs (NSAID's) for the control of pain, inflammation, and anti-thrombotic activity.[1] The recognition of two cyclo-oxygenase isoforms encouraged the pursuit of a safer NSAID's, which this time focused on inhibition of the COX-2 isoform.[1] Over time, COX-2 inhibitors were found to be effective in inhibiting the inflammatory pathways is mental illness, having notable success in trial results for schizophrenia and major depressive disorder.[2] Furthermore, COX-2 inhibitors have been shown to reduce the occurrence of various cancers and pre-cancerous growths.[3]

COX-2 inhibitors are showing to be beneficial in breast cancer cases.[3]

NSAID's are among the widely used pharmaceutical therapeutics, having efficacy in the treatment of arthritis, rheumatisms, and general pain.[4] However, the use of NSAID's are associated with the side effects of renal toxicity and gastrointestinal toxicity.[4] The application of COX-2 inhibitors for patients having cancer, HIV, or AIDS, is being examined due to the antipyretic properties which may mask opportunistic infections.[5] Because COX-2 inhibitors block solely COX-2, they avoid the side-effects of blocking COX-1.[5] There has been promising results for the utilization of COX-2 inhibitors in the management of epilepsy, however, factors such as therapeutic dose, time of administration, treatment of duration, and selectivity of the COX-2 inhibitor must be determined, following close study.[6]

Studies have been accomplished concerning the potential cardiovascular risk of COX-2 inhibitors, showing that naproxen (a nonselective NSAID) has the lowest risk of cardiovascular events.[7] Nevertheless, other studies have shown that NSAID's selective for COX-2 have an enhanced risk for cardiovascular events.[8] Nevertheless, studies of the coxibs (celecoxib, rofecoxib, parecoxib, valdecoxib, and etoricoxib) showing their efficacy in the treatment of rheumatic conditions, malignant transformation, and Alzheimer disease, will assure their continued usage.[9] Further studies and development of COX-2 inhibitors are necessary for identification of new clinical applications and remediation of undesirable side effects.[10]

Neural networks are sophisticated modeling techniques for modeling extremely complex functions and are themselves non-linear.[11] Main categories of learning with neural networks include: supervised learning, reinforced learning, and unsupervised learning.[12,13] Neural network analysis (ANN) has previously been shown to possess substantial learning capabilities that are useful for data mining within large volumes of highly-dimensional data.[12,13] This study shows the efficacy of applying ANN for predicting molecular properties of potential new COX-2 inhibitors.

MATERIALS AND METHODS

Molecular Properties and Molecular Modeling

Numerical values of molecular properties (i.e. Log P, polar surface are, molecular weight) for all compounds were determined through heuristic calculation through Molinspiration Chemical Properties Service (Molinspiration Cheminformatics, Nova ulica 61, SK-900 26 Slovensky Grob, Slovak Republic). Identification of molecular structure was accomplished utilizing ACD.

ChemSketch Modeling v. 12.01 (Advanced Chemistry Development, 110 Yonge Street, Toronto Ontario, M5C 1T4 Canada, http://www.molinspiration.com/services/search.html). Molinspiration Cheminformatics (http://www.molinspiration.com/cgibin/properties) determined molecular properties of Log P, polar surface area (Angstroms2), molecular weight, number of atoms, molecular volume (Angstroms3), number of nitrogen, oxygen, amine groups, and hydroxyl groups.

Statistical Analysis and Prediction

Prediction by ANN analysis for various molecular properties of new and novel COX-2 inhibitors was accomplished by utilizing TIBERIUS v. 7.0.7 (http://www.tiberius.biz/, copyright 2001, Copyright © Tiberius Data Mining, and Copyright © 1999-2007 NeuSolutions).

TIBERIUS trial version can be obtained at http://www.tiberius.biz/download.html.

Statistical analysis of numerical data to include molecular properties of the compounds in this study was accomplished by Microsoft EXCEL v.14.0.6112.5000 (EXCEL Professional plus 2010). Other statistical tests F and T test, was accomplished utilizing PAST version 2.06 (copyright Oyvind Hammer, D.A.T. Harper, 2011). Numerical outliers were identified, where

stated, by utilizing Grubb's analysis for outliers with the online GraphPad quick calcs (http://www.graphpad.com/quickcalcs/). Box plots were accomplished utilizing Smith's Statistical Package v. 2.5 (copyright © 1995-2001, Gary Smith).

RESULTS AND DISCUSSION

Therefore, COX-2 inhibitors have been shown to useful in the treatment of pathological conditions that include pain, fever, and inflammation.[4] Studies have also shown that their potential for clinical application for treatment of various cancers and mental illness warrants additional study and development.[2,3]

There are a group of seven known and successful COX-2 inhibitors that are well characterized and will be utilized in this study (see Figure 1). The molecular structures of celecoxib, rofecoxib, valdecoxib, parecoxib, lumiracoxib, etoricoxib, and firocoxib are presented in Figure 1.

Similarities in molecular structure for these seven COX-2 inhibitors are noticeable immediately;
1) All have aromatic rings; 2) All have nitrogen and/or oxygen atoms; 3) All have multiple rings. Other studies of these coxibs (celecoxib, rofecoxib, parecoxib, valdecoxib, and etoricoxib) have already shown their efficacy in the treatment of rheumatic conditions, malignant transformation, and Alzheimer disease.[9]

All seven of these coxibs were selected for training of ANN modeling with TIBERIUS software program. By choosing already known and characterized COX-2 inhibitors is intended to maximize the potential utility of all predicted outcomes of ANN analysis. The judicious choice of training examples will focus on previously studied successful drugs. Spurious examples are avoided and the best training of the ANN model is anticipated. Hence, the predicted properties will be "constructed" around the best potential training parameters.

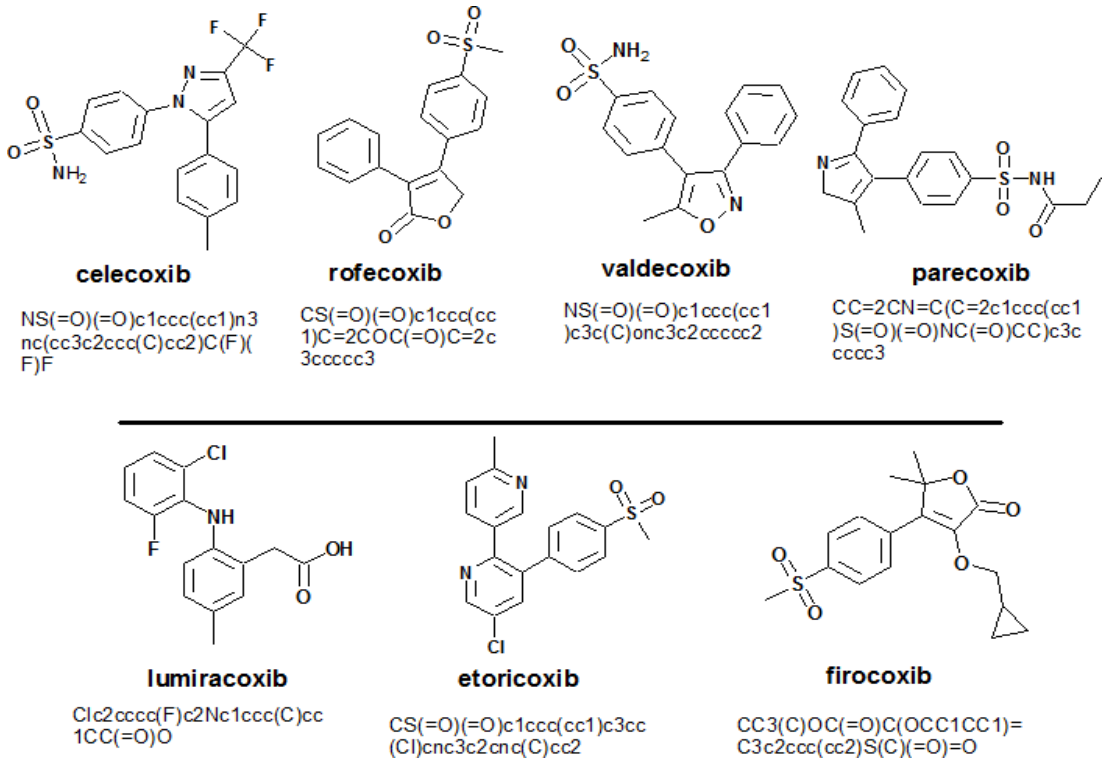


Figure 1: Molecular structures of known COX-2 inhibitors utilized for ANN training in TIBERIUS. The SMILES notation is presented with each structure.

The molecular properties of the seven training COX-2 inhibitors are shown in Table 1. Among the molecular properties presented are the parameters useful for screening potential drug candidates based on favorable drug-likeness for absorption or permeability.[14] Deemed the Rule of 5, these parameters are useful for identifying drug candidates from their properties that enhance drug permeation. The Rule of 5 states that, in general, an orally active drug has no more than one violation of the following criteria: 1) No more than 5 hydrogen bond donors (the total number of nitrogen–hydrogen and oxygen–hydrogen bonds); 2) No more than 10 hydrogen bond acceptors (all nitrogen or oxygen atoms); 3) A molecular mass less than 500 daltons; and 4) An octanol-water partition coefficient (log P) that does not exceed 5.[14] Notably, all seven of the training COX-2 inhibitors pass this criteria and have zero violations of the Rule of 5. Also, previous studies have shown that drugs having polar surface area less than 90 Angstroms^2 can effectively permeate into the brain, a criteria all seven drugs fulfill.[15,16,17]

Interestingly, there exist broad ranges in some the of ANN training properties. For example, the Log P values range from 0.706 to 4.477. However, none of these Log P values is an outlier after evaluation with Grubb's test. Among the properties of these seven training drugs,

there are very high correlations (Pearson r > 0.9000) for: 1) Number of atoms (nAtoms) to molecular weight (MW) and molecular volume (MV); 2) Polar surface area (PSA) to number of oxygen and nitrogen atoms (nON).

Table 1: Molecular Properties for Training ANN Analysis to Predict New COX-2 Drugs.

DRUG	Log P	Polar Surface Area (Angstroms^2)	Number Of Atoms	Molecular Weight	Number of Oxygen & Nitrogen Atoms	Number of -OH & NH_n	Number Of Rotatable Bonds	Volume (Angstroms^3)
celecoxib	3.611	77.991	26	381.379	5	2	4	298.65
rofecoxib	0.706	60.447	22	314.362	4	0	3	264.79
valdecoxib	2.734	86.197	22	314.366	5	2	3	263.553
parecoxib	3.38	75.6	26	368.46	5	1	5	324.83
lumiracoxib	4.477	49.326	20	293.75	3	2	4	246.686
etoricoxib	3.01	59.926	24	358.85	4	0	3	296.637
firocoxib	2.724	69.681	23	336.409	5	0	5	291.581

From Table 1, is derived the training properties for ANN analysis/modeling. In Figure 2, is a succinct view of the window seen for TIBERIUS selection of training properties. After location of data (i.e. in the form of EXCEL spreadsheet), the available variables are displayed (see Figure 2). The desired properties can be selected or deselected for input to ANN analysis. Note that in the "Select Mode" box, properties chosen are Log P, PSA (polar surface area), nOHNH (number of $–NH_n$ and –OH), nrotb (number of rotational bonds), and molecular volume (volume). Note that the desired output is molecular weight (MW), which will be used for comparing and determination new COX-2 drugs (see "Output box", Figure 2).

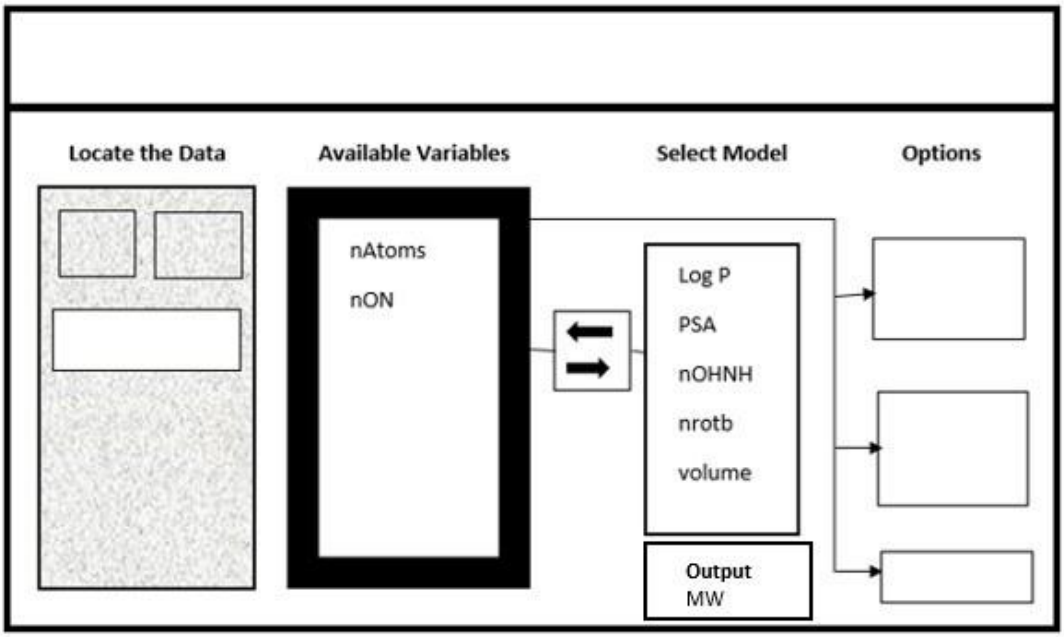


Figure 2: Input window for TIBERIUS ANN analysis of training COX-2 properties. Note that training inputs are found under "Select Model" and are Log P, PSA, nOHNH, nrotb, and volume. The user can select and deselect properties for training of ANN, with "Select Model". The "output' will be numerical values of predicted molecular weight of new drugs.

After completion of the "Select Model" and "Output", which is molecular weight (MW) for this study the actual training cycles can be accomplished. An example layout for the training cycle is presented in Figure 3, where is observed the training molecular properties (Volume, nrotb, nOHNH, PSA, and Log P). The "Output" is MW or molecular weight. For this study, the learning rate of 0.7000 with 65108 Epochs was found to be optimal. That is, no advantages in minimizing prediction error was achieved with lower or higher selections of Epochs or learning rate. Both learning rate and number of Epochs is determined by the user, but assumed to have minimal prediction error as the goal.

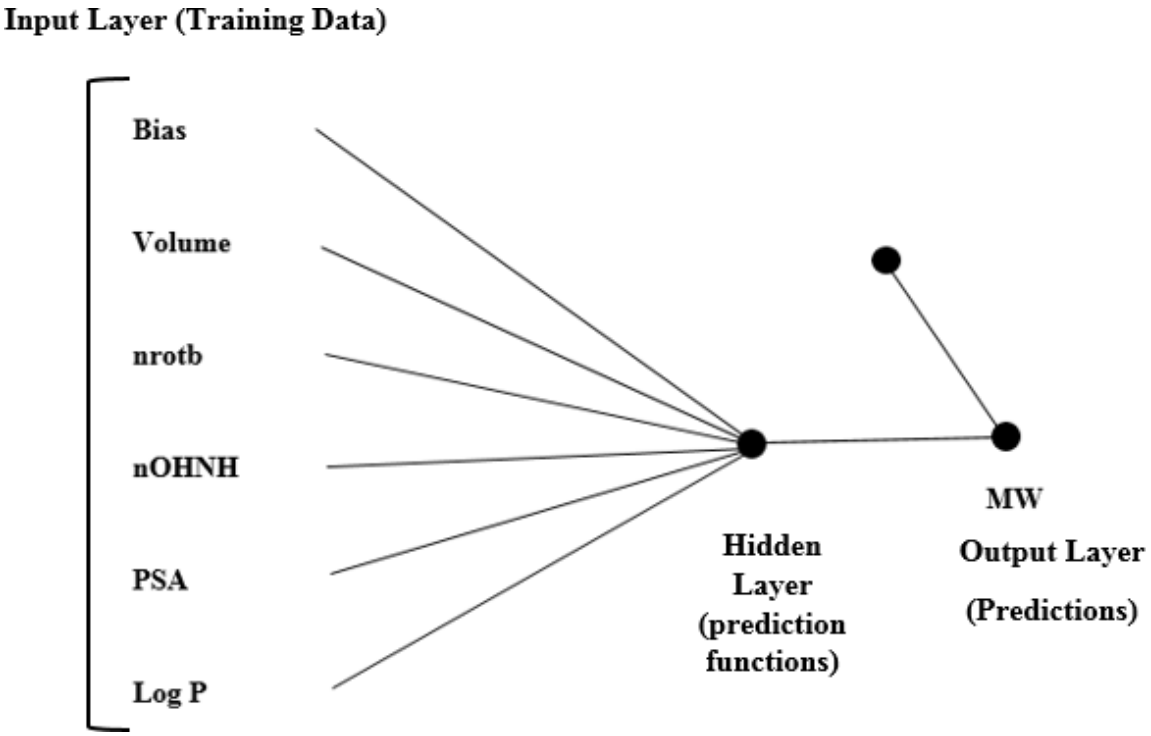


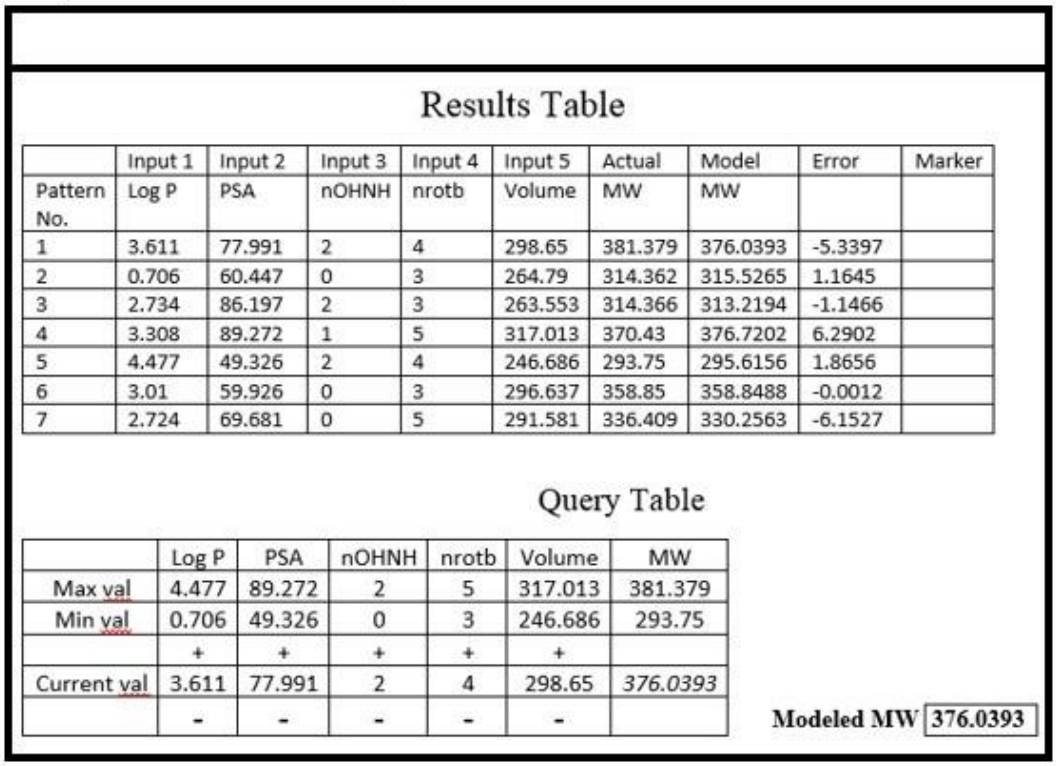
Figure 3: Training cycle. Number of Epochs for training can be monitored and assigned by the user. The greater the number of Epochs the longer time is required for training. For this study a conservative training time of less than five minutes was efficient, with longer training times not showing any advantages. Input layer is properties, followed by hidden layer, and output layer (predictions of molecular weight).

Next, the training result window is provided so that the user can visually observe which of the training properties carried the most influence on constructing the ANN model (see Figure 4). The training result window shows a table of data that included each of the training properties, their rank, and their relative importance for constructing the ANN model (see Figure 4). For this study the training properties with rank/relative importance shown, are as follow: (a) Volume (molecular volume) rank is 1 with relative importance of 1; (b) nOHNH (number of –OH & - NH) rank is 2 with relative importance of 0.646; (c) PSA (polar surface area) rank is 3 with relative importance of 0.215; (d) Log P rank is 4 with relative importance of 0.123; (e) Nrotb (number of rotatable bonds) rank is 5 with relative importance of 0.080. The ratings of the relative importance by "variable", assist the user to understand the contribution of each property to the model and providing insight into the properties having greater influence on the prediction of new COX-2 drugs. For this study, the molecular volume (1.00), number of –OH and $–NH_n$ (0.646), and polar surface area (0.215) contribute the greatest weight to prediction of new COX-2 drugs.

Select	Rank	Variable	Scrambled Correlation	Relative Importance	
√	1	Volume	0.33897	1.00	
√	2	nOHNH	0.56691	0.646	
√	3	PSA	0.84423	0.215	
√	4	Log P	0.90364	0.123	
√	5	Nrotb	0.93165	0.080	
√	6	Full Model	0.98285	0.000	

Figure 4: Training results indicating relative importance of the contribution each training variable (molecular property) to the model. Note that the highest to lowest contribution to the model for each property are: Volume, nOHNH, PSA, Log P, and nrotb (i.e. see "Variable" and "Relative Importance").

The final window presenting the "Results Table" and "Query Table" is shown in Figure 5. It is from this final window that the measure of success of the ANN model and the determination of predicted properties of new COX-2 drugs can be accomplished. First, the "Results Table" is examined to find the initial training properties Log P, PSA, nOHNH, nrotb, volume, and actual molecular weight (MW) of all seven training COX-2 inhibitors (see Figure 5). The ANN model presents the predicted values of molecular weight based on the training properties. The TIBERIUS ANN also shows the numerical error of the predicted molecular weight from actual molecular weight. For this model, the error is quite small, ranging from -6.1527 to 6.2902 (only 1.8% to 1.7% error).



Results Table

Pattern No.	Input 1 Log P	Input 2 PSA	Input 3 nOHNH	Input 4 nrotb	Input 5 Volume	Actual MW	Model MW	Error	Marker
1	3.611	77.991	2	4	298.65	381.379	376.0393	-5.3397	
2	0.706	60.447	0	3	264.79	314.362	315.5265	1.1645	
3	2.734	86.197	2	3	263.553	314.366	313.2194	-1.1466	
4	3.308	89.272	1	5	317.013	370.43	376.7202	6.2902	
5	4.477	49.326	2	4	246.686	293.75	295.6156	1.8656	
6	3.01	59.926	0	3	296.637	358.85	358.8488	-0.0012	
7	2.724	69.681	0	5	291.581	336.409	330.2563	-6.1527	

Query Table

	Log P	PSA	nOHNH	nrotb	Volume	MW
Max val	4.477	89.272	2	5	317.013	381.379
Min val	0.706	49.326	0	3	246.686	293.75
	+	+	+	+	+	
Current val	3.611	77.991	2	4	298.65	*376.0393*
	-	-	-	-	-	

Modeled MW 376.0393

Figure 5: Results and prediction window. Note columns of "Actual MW" and "Model MW", followed by "Error" column for estimating efficacy of ANN prediction of molecular weight (see Results Table). Note that in the "Query Table", investigators can input variable numerical values and determine the outcome of molecular weight for new predicted COX-2 drugs.

At last, the "Query Table" (see Figure 5) allows the user to insert differing values of Log P, PSA, nOHNH, nrotb, and Volume to determine the predicted value of molecular weight (MW) for new predicted drugs. Note the molecular weight (MW) was selected for the "Output Variable" in the previous window (see Figure 2). Users can select other properties to serve as the "Output Variable". The user can input a variety of combinations of numerical values in each of the properties in the "Query Table" to obtain the predicted molecular weight (MW).

Another feature of TIBERIUS ANN, that is discussed next, is that the ANN model automatically constricts the numerical values that are inserted in the "Query Table", to the limits of the accuracy of the model. In other words, the model disqualifies input property numeric values that are "outside" the accuracy of the model itself. This is a tremendous advantage, which allows the user to constrain their predicted drugs to the actual strength of the ANN model. A very useful feature to appreciate, for legitimizing the predicted properties.

Therefore, for the training properties coming from seven actual COX-2 drugs, the ANN model allows the prediction of 22 new COX-2 inhibitors (see Table 2). These are derived from the "Query Table" and constrained to 22 potential drug candidates, based on the accuracy of the ANN model following the "training cycles" (Epochs, see Figure 3).

The predicted drugs are numbered 1 to 22 and the values of molecular properties (i.e. molecular weight, Log P, etc.), are derived completely from the "Query Table". Note, that in the first column of Table 2, the molecular property that is "varied" (i.e. changed) is listed, those numbers are varied within the constraint of the accuracy of the ANN model. All other properties are held constant except for molecular weight which is the "output" variable (see Table 2). The allowable range in Log P is 0.706 to 4.477. The allowable range for polar surface area is 60 A^2 to 89.272 A^2. The allowable range for molecular volume is 246.69 A^3 to 317.01 A^3, and so forth for the remaining varied property.

Table 2: Predicted Molecular Properties (New Drugs) Based on ANN Analysis.

Property Varied	Drug	Molecular Weight	Log P	Polar Surface Area (Angstroms^2)	Number of -OH & -NH_n	Number Rotatable Bonds	Volume (Angstroms^3)
Vary Log P	1	399.91	0.706	77.991	2	4	298.65
	2	397.49	1	77.991	2	4	298.65
	3	398.28	2	77.991	2	4	298.65
	4	368.92	4.477	77.991	2	4	298.65
	5	372.84	4	77.991	2	4	298.65
Vary Polar Surface Area	6	365.23	3.611	89.272	2	4	298.65
	7	374.11	3.611	80	2	4	298.65
	8	383.7	3.611	70	2	4	298.65
	9	393.28	3.611	60	2	4	298.65
Vary nOHNH	10	376.04	3.611	77.991	2	4	298.65
	11	355.32	3.611	77.991	1	4	298.65
	12	334.61	3.611	77.991	0	4	298.65
Vary nRotB	13	370.14	3.611	77.991	2	5	298.65
	14	376.04	3.611	77.991	2	4	298.65
	15	381.94	3.611	77.991	2	3	298.65
Vary Molecular Volume	16	368.96	3.611	77.991	2	4	295
	17	330.18	3.611	77.991	2	4	275
	18	275.26	3.611	77.991	2	4	246.69
	19	411.65	3.611	77.991	2	4	317.01
	20	378.66	3.611	77.991	2	4	300
	21	301.09	3.611	77.991	2	4	260
	22	359.26	3.611	77.991	2	4	290

A 2-way plot of predicted properties as dependent variables are presented using molecular weight as independent variable (see Figure 6). Here, the numerical values of predicted

molecular volume, polar surface area, Log P, number of –OH & -NH_n, and number of rotatable bonds are compared to one another. For molecular volume, the equation of line and coefficient of determination (R^2) are as follows: y=0.4136x + 142.04; R^2 = 0.8052. For polar surface area: y= - 0.0279x + 87.658; R^2 = 0.0334. For Log P: y = -0.0101x + 7.0558; R^2 = 0.1306. For number of rotatable bonds: y = -0.0005x + 4.1973; R^2 = 0.0032. For number of –OH and –NH_n: y = 0.0035x + 0.587; R^2 = 0.0578.

Here, the application of ANN analysis can produce sufficient data to obtain linear description in the form of equation of line. The coefficient of determination (R^2), allows a convenient means to evaluate the effectiveness of the linear model to describe the data. It would be possible to use the linear equations as a model for prediction of molecular weight (independent variable) based solely on the variation of the single dependent variable (molecular property). However, ANN analysis is known to be highly accurate and the TIBERIUS system allows for individual property variation in values followed by the expected molecular weight. After graphical plotting of the predicted values shown in Figure 6 of data presented in Table 2 (molecular weight is the independent variable), the data appears to be approximately linear.

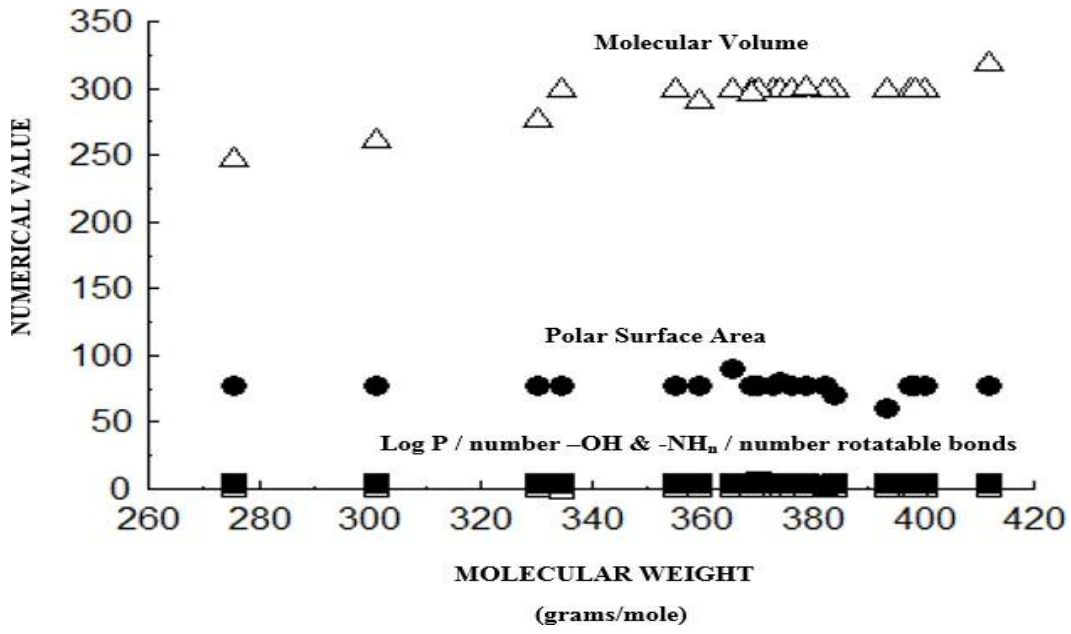


Figure 6: 2-way plot of predicted properties with molecular weight as the independent variable (X-axis), after TIBERIUS ANN analysis and use of Query Table found in the output window (see Figure 5). Note numerical values of properties are found on Y-axis (dependent variables) and are relative to molecular weight (independent variable).

A box plot is a means of summarizing a set of data measured on an interval scale and is often used in explanatory type data analysis. Box plots are used to show the shape of the distribution, its central value, and its variability Box plots are useful for visualizing and comparing numerical ranges of several to many variables in analysis.[18,19] The ranges for molecular weights of the seven training COX-2 inhibitors (Plot A) and for the 22 predicted examples (Plot B) are shown in Figure 7. The ranges of molecular weights of training and predicted examples overlap. Non-overlapping box plots show groups that are different. The broader the whiskers of the box plot, then the more the variability of the data.[18,19]

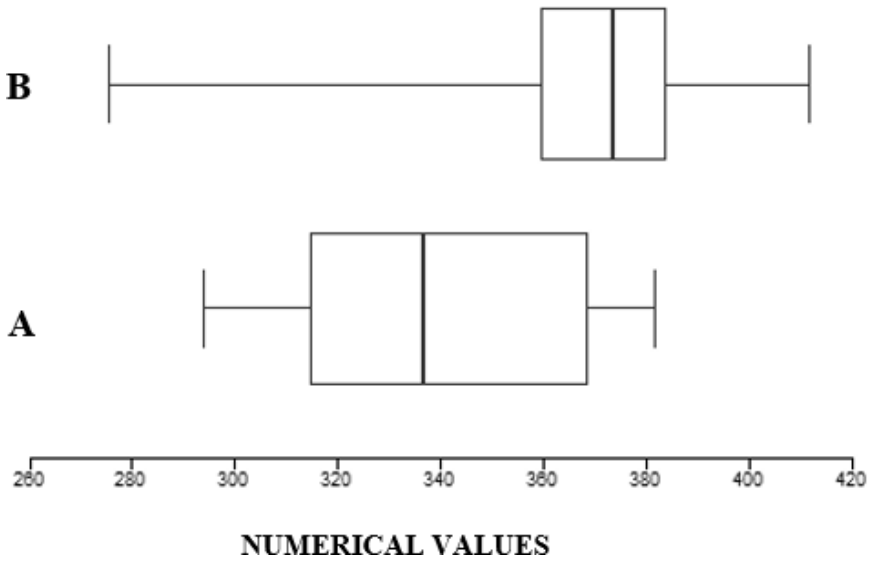


Figure 7: The box plot A are the actual molecular weight values of the known training COX-2 inhibitors for training of artificial neural network analysis by TIBERIUS. The box plot B represents the range of predicted values of molecular weight by varying molecular properties such as Log P, polar surface area, etc. (see Table 2).

An important feature of neural networks is the iterative learning process in which values are presented to the network one at a time, but the weights associated with the input values are adjusted each time. Then the process is repeated during this learning phase and the network trains by adjusting the weights. Two advantages of neural networks are their high tolerance to noisy data, and the ability to classify patterns on which they have not been trained. The most popular neural network is the backpropagation.[11,12,13] Neural networks generally have a high level of accuracy, even if the data has a significant amount of noise. In other words, when the hidden layer can still discern relationships in the data in spite of the noise, it may be possible to use this otherwise-unusable data.

CONCLUSION

Applying ANN analysis, after training with the molecular properties of seven successful COX- 2 inhibitors, is useful for the further prediction of the same properties for potential new drugs.

For demonstration, potential 22 drug structures were presented with molecular properties predicted by ANN. The molecular properties of new COX-2 inhibitors have the range in values shown to be: Log P (from 0.706 to 4.4477); molecular weight (from 275.26 to 411.65); and molecular volume (from 260.0 Angstroms^3 to 317.01 Angstroms^3). The molecular weight and molecular volume of the 22 examples were found to be very highly correlated (Pearson r > 0.9000). All 22 examples showed polar surface area and molecular weight suitable for penetration into the central nervous system. All 22 examples showed zero violations of the rule of 5, thus having favorable drug absorption. Numerical values of molecular weight for the 22 predicted examples were shown to overlap the values for seven training drugs by box plot and are the statistically the same by F and t test. The neural network modeling by TIBERIUS is shown to have potential for the prediction of new drug properties.

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