Chem-Bio Informatics Journal, Vol.22, pp.63-87 (2022)

Multiple Logistic Regression Modeling of Compound Class as Active or Inactive Against COX-2 and Prediction on Designed Coxib Derivatives and Similar Compounds

Liza T. Billones*, Alex C. Gonzaga

Department of Physical Sciences and Mathematics
College of Arts and Sciences University of the Philippines Manila
Padre Faura, Ermita, Manila, 1000 Philippines

Email: ltbillones@up.edu.ph

(Received July 05, 2022; accepted September 29, 2022; published online October 31, 2022)

Abstract

The development of next generation non-steroidal anti-inflammatory drugs (NSAIDs) is one active area of research as inflammatory diseases continue to afflict over 1.5 billion people worldwide. The publicly available and computationally accessible chemical and biological data provide a wellspring of information for any research pursuit that could expedite the discovery of new anti-inflammatory drugs. Computational statistics is a handy tool in establishing quantitative relationship between the anti-inflammatory activity and the key molecular features that determine the compound's medicinal property. In this work, Multiple Logistic Regression (MLogR) was employed to develop a mathematical model of the inhibitory activity of a compound on cyclooxygenase-2 (COX-2), an enzyme that facilitates the production of inflammatory prostanoids. The best model with hit ratio of 94% and 91% on the train and test set, respectively, was used to predict the classification (*i.e. active* or *inactive*) of newly designed coxib Derivatives and Similars obtained through similarity search. The predicted actives were further screened based on their quantitative estimate of druglikeness (QED), synthetic accessibility, and ADMETox properties. The selected top 15 hits have superior confidence as actives, are highly druglike and easy to synthesize, and generally possess outstanding drug profile.

Keywords: Molecular descriptors, NSAID, COX-2 inhibitors, and multiple logistic regression

Area of Interest: *In silico* drug discovery

1. Introduction

Over 1.5 billion people suffer from chronic pain [1, 2]. Rheumatoid arthritis alone, an inflammatory disorder, has affected 17.6 million people worldwide, and this can occur at any age [2]. The typical signs of inflammation are heat, pain, redness, swelling, and loss of function [3]. The causes of inflammation can be physical (e.g. burns, injury, trauma, etc.), biological

(i.e. infection by pathogens, immune reaction due to hypersensitivity, stress), chemical (e.g. chemical irritants, toxins, alcohol, etc.), and psychological (e.g. excitement) [4–6]. Chronic inflammation can be a contributing factor in the pathology of many chronic diseases including cardiovascular diseases, respiratory diseases, autoimmune diseases, diabetes, and cancer [7–10]. Aside from societal and economic burdens, these adverse conditions have consequential effects on the quality of life as chronic pain has profound impact on the mood, sleep, ability to work, and overall enjoyment of life of 60% of sufferers [11, 12].

While there are different mechanisms of action for the anti-inflammatory therapies, this work focused on one of the anti-inflammatory drug targets that control the mechanism of arachidonic acid metabolism. In particular, it deals with compounds that act on cyclooxygenase-2 (COX-2), an enzyme responsible for the conversion of arachidonic acid to prostanoids including thromboxanes and prostaglandins [13]. COX has three isoforms namely COX-1, COX-2, and COX-3 [14, 15]. Unlike COX-2 that is only found in cells where there is inflammation, COX-1 is expressed in many tissues and is responsible for the production of natural mucus lining, which protects the inner stomach and controls acid secretion and pepsin content [16, 17]. Inhibition of COX-1 reduces the production of cytoprotective prostaglandins in the stomach that may result in gastric ulceration. Thus, those drugs that would spare COX-1 and target only COX-2 are expected to show fewer side effects associated with COX-1 inhibition [18]. Meanwhile, COX-3 is a splice variant of COX-1 and has no apparent role in prostaglandin-mediated processes [15, 16].

Non-steroidal anti-inflammatory drugs (NSAIDs) are a class of drugs that work by inhibiting the activity of cyclooxygenase (COX-1 and/or COX-2) enzymes thereby reducing pain, fever, and inflammation. Newer NSAIDs are mostly selective COX-2 inhibitors belonging to a class of molecules called “coxibs” such as Celecoxib (Celebrex®) [19], Etoricoxib (Arcoxia®) [20], Parecoxib (Dynastat®) [21], Valdecoxib (Bextra®) [22], and Rofecoxib (Vioxx®) [23]. Like the last two of the coxibs that were later withdrawn from the market due to serious adverse side effects [24], a range of other anti-inflammatory compounds available for diverse inflammatory conditions cause a wide array of unfavorable side effects including increased risk of gastrointestinal ulcers, bleeding, cardiovascular, and kidney diseases [25, 26]. Thus, despite the scores of NSAIDs that are available in the market, the discovery of new classes of anti-inflammatory compounds with safer drug profile is still an active area of research.

A practical approach in drug discovery is designing new chemical structures based on existing medicinal compounds and involves development of mathematical models that establish the quantitative relationship of the biological activity and the molecular properties. In this work, quantitative models that relate COX-2 inhibitory activity with structure-based molecular properties called descriptors were generated. Specifically, Multiple Logistic Regression (MLogR) models were developed to predict the COX-2 inhibitory activity (i.e. *active* or *inactive*) of a compound. MLogR uses a logit function to model a categorical response variable alongside the identification of the explanatory variables that are important in the prediction of the outcome [27, 28]. This is a technique suitable for this work as this has also already been used in various fields including drug discovery [29–31]. The best model was validated on experimentally tested compounds and then applied to a set of newly designed compounds called Derivatives (of coxibs) and to another set of structurally related compounds called Similars obtained through similarity search.

2. Materials and Methods

Sample Collection and Preparation, and Descriptor Calculations

The compounds included in the study were obtained from articles published during the period from 1997 to 2019 at the websites of leading journal publishers (ACS, Elsevier, and RSC). The articles were found using search keywords such as "COX inhibitors", "cyclooxygenase inhibitors", "COX1/COX2 compounds", and the like. However, only those that used the same methods of experimental measurement [32] of COX-2 activity were considered.

The collected compounds were grouped as COX-2 inactive labeled "0", and COX-2 active labeled "1", based on their experimental bioactivity, i.e., IC_{50}, the concentration of the compound that reduces the enzyme activity to half. Those with IC_{50} values $\leq$ 10 μM were classified as active while those with IC_{50} > 10 μM were classified as inactive.

The chemical structures of the compounds were generated and then the molecular properties calculated using a personal computer running on Microsoft Windows 7 Professional 64-bit Operating System with a 3.50-GHz Intel® Core™ i7-4770K processor, and 8.00-GB random access memory (RAM). ChemDraw Professional 16.0 (www.cambridgesoft.com) was used to draw the 2D chemical structures, which were individually saved as structure-data files (.sdf). The files were combined as a single file, which served as input in descriptor calculations in Discovery Studio (DS) version 4.5 (Biovia, Inc.) and Spartan 16 (Wavefunction, Inc.), which are both available in our laboratory. In DS, the 2D structures were converted into 3D and optimized at molecular mechanics level using the Dreiding force field [33]. In Spartan, the best conformer of each compound was obtained first by performing a conformational search, and then followed by geometry optimization using MMFF94 [34] forcefield. The structures were further optimized at semi-empirical level using the PM3 [35] method. All molecular descriptors were subsequently calculated based on the optimized molecular structures.

Data Management and Preprocessing

The data management and preprocessing were performed in a machine with MacOS Catalina operating system, 3.1-GHz Dual-Core Intel Core i7 processor, and 16-GB RAM using the application software MS Excel and SPSS (www.ibm.com). The dataset was cleaned by removing molecular properties that have numerous *NAN* (not a number) or predominantly invariant entries, and checked for multivariate outliers [36]. The final dataset included 184 molecular descriptors on 1381 compounds of which 930 (67%) are actives and 451 (33%) are inactives.

Model Building and Validation

The data was partitioned into train and test sets applying 80–20 split, i.e., 1105 compounds were randomly assigned to the train set (Actives = 74 and Inactives = 361) and the remaining 276 compounds (Actives=186 and Inactives=90) comprised the test set. Multiple Logistic Regression (MLogR) in SPSS and RapidMiner Studio 9.7.001 (www.rapidminer.com) was implemented on the train set to construct the models. The test set was used to validate the identified best model.

The following model goodness-of-fit and performance metrics were used: 1) Accuracy, the percentage of correctly classified compounds; 2) Specificity, the proportion of correctly predicted inactive compounds; 3) Positive Predictive Value (PPV) [37], the percentage of

predicted actives that are true active compounds; 4) Nagelkerke pseudo-R^2 [38], the proportion of the variance of the dependent variable that is explained by the model; 5) Hosmer-Lemeshow Test (HLT) [39], a measure of agreement between the observed and the expected frequencies of the compound classes at the different parts of the data; and 6) Matthews Correlation Coefficient (MCC) [40], a measure of agreement between the observed and the predicted frequencies of all the cells in the classification table. MCC summarizes the confusion matrix, that together with Accuracy, provides a measure of the overall prediction accuracy or how well the models predict the compound classes. Specificity, which shows the ability of the models in identifying inactive compounds, and PPV, which reflects how likely correct the model is in indicating that a compound is active, together show the meticulousness of the model in screening out false positives. HLT and R^2 provide measures of how well the models fit the data.

Derivatives and Similars

The MLogR model was applied to two sets of as yet untested compounds, i.e. Derivatives and Similars. The Derivatives consists of 1100 newly designed compounds generated by performing substitutions with bioisosteric groups [41] at three crucial positions in each of the 5 selected scaffolds representing the 5 families with the most number of compounds in the dataset. The Similars of 600 compounds is the collection of the top 10 most similar compounds, obtained through SwissSimilarity (www.swisssimilarity.ch), for each of the 60 families of known COX-2 actives, using as query molecule, the most active compound of each family. The duplicates that appeared in the top 10 were omitted and only unique compounds down the list in every search were taken so that each family was represented by 10 unique SwissSimilar compounds. The library of bioactive compounds (i.e. ChEMBL) was the primary search space. The ZINC (Druglike) database was explored only when there were no hits from ChEMBL. The chemical structures of these compounds were generated and their molecular properties calculated as described above.

Druglikeness Prediction

The final model was applied to the Derivatives and the Similars to predict their classification, active or inactive. For the predicted active compounds, the ADMET (absorption, distribution, metabolism, excretion, toxicity) properties were predicted using the *ADMET and TOPKAT* protocols and the QED (Quantitative Estimate of Druglikeness) scores were calculated with the *Calculate Molecular Properties* protocol in DS. In addition, the Synthetic Accessibility scores were obtained from SwissADME (http://www.swissadme.ch). The output is the set of top 15 hits that are considered potential leads against COX-2.

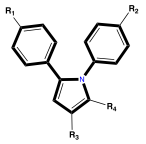
The top hits were then optimized at the semi-empirical PM3 level and each structure was saved as pdb file. The COX-2 enzyme target (PDB ID: 5IKR) was subjected to 100-ns Molecular Dynamics simulations [42] and the equilibrated structure was used in subsequent Molecular Docking studies involving the top hits with the use of Autodock Vina [43] in PyRx (www.pyrx.sourceforge.io).

3. Results and Discussion

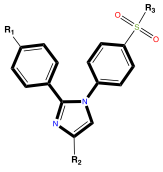
Sample Collection and Preparation, and Descriptor Calculations

The molecular structures used in this study were gathered from 66 papers [19, 22, 44−107] from over a hundred articles published in 7 scientific journals. Figure 1 shows the collected

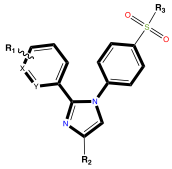
structures grouped into 60 families of organic compounds. Of the 1381 compounds, 930 (67%) were classified as COX-2 active and 451 (33%) were labeled inactive based on their IC_{50} values.



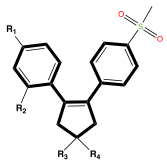
1,2-Diarylpyrroles [44]
Actives = 23 (**1**–**23**)
Inactives = 17 (**931**–**947**)



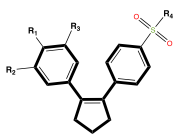
1,2-Diarylimidazoles [45]
Actives = 82 (**24**–**105**)
Inactives = 13 (**948**–**960**)



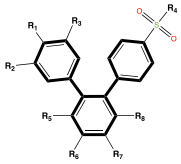
1,2-Arylhetero-arylimidazoles [46]
Actives = 37 (**106**–**142**)
Inactives = 11 (**961**–**971**)



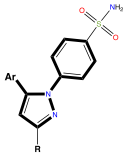
1,2-Diarylcyclopentenes [47]
Actives* = 17 (**143**–**159**)
Inactives = 2 (**972**–**973**)
*2 are standards; not cyclopentenes



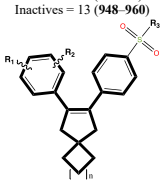
1,2-Diarylcyclopentenes [48]
Actives = 27 (**160**–**186**)
Inactives = 2 (**974**–**975**)



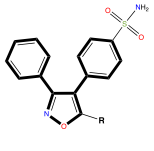
Terphenyls [49]
Actives = 42 (**187**–**228**)
Inactives = 7 (**976**–**982**)



1,5-Diarylpyrazoles [19]
Actives = 78 (**229**–**305**)
Inactives = 31 (**983**–**1013**)

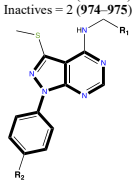


Diarylspiro[2.4]alkenes [50]
Actives = 33 (**306**–**338**)
Inactive = 1 (**1014**)

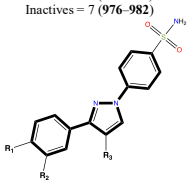


4,5-Diarylisoxazoles [22,51]
Actives = 3 (**339**–**341**)
Inactives = 0

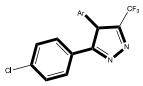
Pyrazoles [52]
Actives = 12 (**342**–**353**)
Inactives = 0



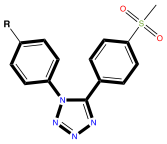
Pyrazolopyrimidine [53]
Actives = 18 (**354**–**371**)
Inactives = 0



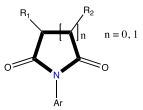
Celecoxib-Tolmetin hybrids [54]
Actives = 11 (**372**–**382**)
Inactives = 0



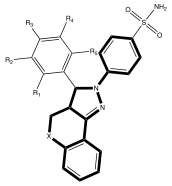
Pyrazole Derivatives [55]
Actives = 11 (**383**–**393**)
Inactives = 9 (**1015**–**1023**)



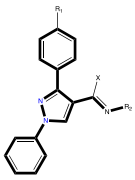
Tetrazoles [56,57]
Actives = 4 (**394**–**397**)
Inactives = 17 (**1024**–**1040**)



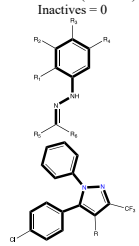
Cyclic imides [58,59]
Actives = 16 (**398**–**413**)
Inactives = 45 (**1041**–**1085**)



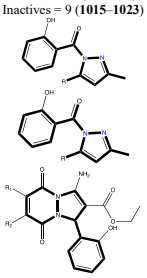
Dihydropyrazoles [60]
Actives =20 (**414**–**433**)
Inactives = 7 (**1086**–**1092**)



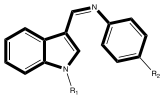
Pyrazole-Thiadiazole hybrids [61]
Actives =12 (**434**–**445**)
Inactives = 6 (**1093**–**1098**)



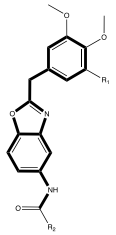
Hydrazones, Pyrazoles [62]
Actives =11 (**446**–**456**)
Inactives = 8 (**1099**–**1106**)



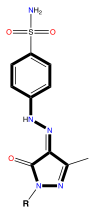
Pyrazoles, Salicylamides, Pyrazolo[1,2-a]pyridazines [63]
Actives =6 (**457**–**462**)
Inactives = 5 (**1107**–**1111**)



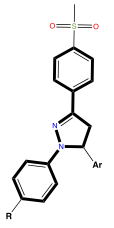
Indoles [64]
Actives = 5 (**463**–**467**)
Inactives = 5 (**1112**–**1116**)



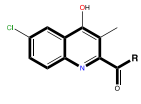
Benzoxazole benzamides [65,66]
Actives = 27 (**468**–**494**)
Inactives = 3 (**1117**–**1119**)



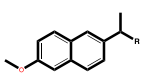
Pyrazolones [67]
Actives = 11 (**495**–**505**)
Inactives = 0



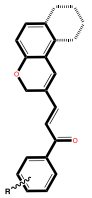
Triarylpyrazolines [68]
Actives = 16 (**506**–**521**)
Inactives = 0



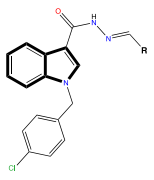
Quinoline-2-carboxamides [69]
Actives = 14 (**522**–**535**)
Inactives = 0



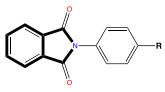
Naproxene derivatives [70]
Actives = 14 (**536**–**549**)
Inactives = 0



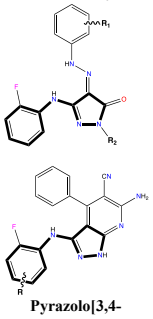
Chalcones [71]
Actives = 12 (**550**–**561**)
Inactives = 0



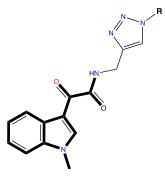
Indoles, standards [72]
Actives = 5 (**562**–**566**)
Inactives = 1 (**1120**)



Isoindolines [73]
Actives = 12 (**567**–**578**)
Inactives = 0



Pyrazolo[3,4-b]pyridines [74]
Actives = 24 (**579**–**602**)
Inactives = 0



Indole-3-glyoxamides [75]
Actives = 21 (**603**–**623**)
Inactives = 0

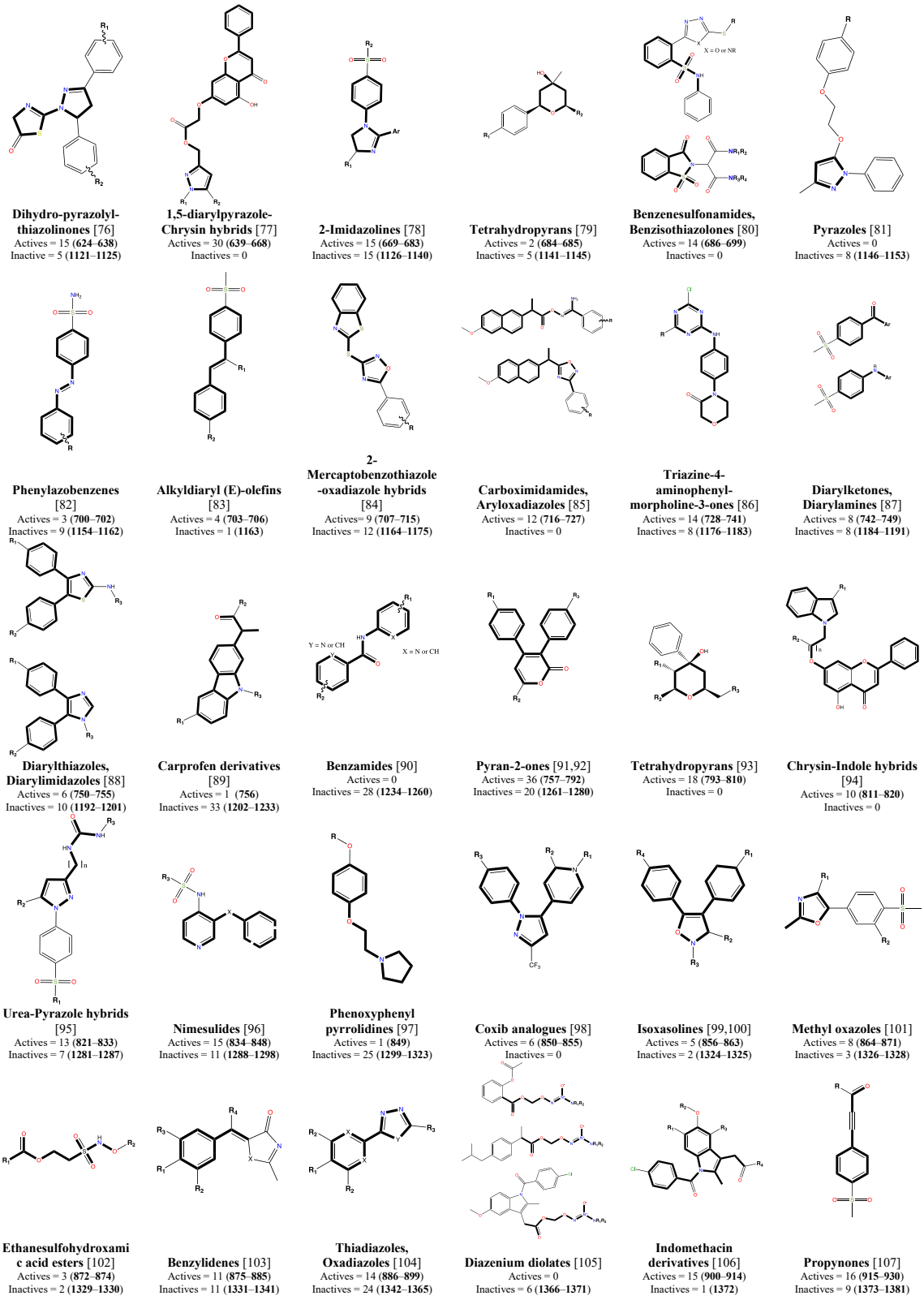


Figure 1. Compounds with experimental COX-2 inhibitory activity, grouped by structural motif, collected from literature published from 1997–2019
Total actives=930. Total inactives=451.

Although compounds for which IC_{50} values have been determined are in principle "active", in this work only those with $IC_{50} \leq 10$ μM were considered active. This arbitrary cut-off value

for classification was based on a common practice in drug discovery wherein only hits with IC_{50} values lower than 10 μM are further pursued [108].

Data Management and Preprocessing

As shown in Table 1, there were 425 molecular descriptors calculated for each of the compound structures using Spartan and Discovery Studio. But the dataset used in the subsequent analyses included only 184 molecular descriptors as a result of data cleaning, i.e., after removing those with numerous NAN or predominantly invariant entries.

Table 1. Spartan- and Discovery Studio-Derived Molecular Descriptors*

Types of Descriptors	Number
I. Spartan-derived descriptors	**28**
Molecule	9
QSAR	14
Thermodynamics	5
II. Discovery Studio-derived descriptors	**397**
2D	*333*
AlogP	1
E-State Indices	163
Molecular Properties	34
Molecular Property Counts	85
Surface Area and Volume	7
Topological Descriptors	43
3D	*64*
Dipole	4
Jurs Descriptors	30
Molecular Properties	12
Principal Moments of Inertia	4
Shadow Indices	10
Surface Area and Volume	4
TOTAL	**425**

* Descriptors of compounds with experimental COX-2 inhibitory activity collected from literature published from 1997-2019.

Model Building and Validation

The forward stepwise automatic procedure of variable selection combined with methodical examination of the descriptors for key predictors of the model was performed on the train set. This generated several competing models of which the best three are shown in Table 2 for careful comparison of their fit indices and performance scores.

Table 2. Performance and Goodness-of-fit Indices of the Three Best MLogR Models* of Compound Classification as COX-2 Active or Inactive

Model	Specificity	PPV	Accuracy	MCC	HLT P-value	Nagelkerke R-Square	
Train Set							
Model 1	73.7	87.7	85.2	0.657	0.002	0.648	
Model 2	77.6	89.4	87.3	0.708	0.087	0.737	
Model 3	89.2	94.8	93.8	0.859	0.946	0.858	
Test Set							
Model 3	85.6	93.1	91.3	0.801			

* Predictors based on Spartan- and Discovery Studio-Derived molecular descriptors of compounds with experimental COX-2 inhibitory activity collected from literature published from 1997-2019.
Train Set (80%): n=1105; 744 actives, 361 inactives
Test Set (20%): n=276; 186 actives, 90 inactives
Model 1 variables: sz, sxz, dz, abl, neb, pmix
Model 2 vaiables: sz, sxz, dz, abl, noa, pmix, nac, jx, rpcg, elu, wpsa1, sx
Model 3 variables: sz, sxz, dz, dene, minlip, chiv2, rpcg, nac, pmiz, sx, sxy, 3dsav, elu, cpka, acca, cddsss, sdssc, saasc, nr6, chi1, jx, vdiste, dx, pnsa1, wpsa1

The object of this work has been to generate a model that would predict compound class, i.e., active or inactive, using the molecular properties as explanatory variables. The model is intended to serve as a mathematical filter of compounds so that those that would more likely be COX-2 inactive will be sifted out of the pool and so avoiding the high attrition rate in the advance stages of the drug discovery process, and thereby conserving resources. Thus, a model that will have a small false positive error rate is desired, or one that is able to effectively identify the inactives. Consequently, the models were first compared based on their Specificity and Positive Predictive Value (PPV). Model 1 with only 6 predictor variables already has good performance scores, only that it has not passed the HLT criterion (p-value < 0.01). Model 2, having 12 variables, not only bettered the performance scores, but also passed the HLT (p-value > 0.05) and increased the R^2 value. Model 3 emerged superior with Specificity of almost 90% and PPV of 95%. On top of that, the model has a matchless Hit Ratio of 94% that is confirmed with equally high MCC of 0.859. Furthermore, Model 3 also has the finest fit indices, i.e., very high values on both HLT p-value (0.946) and the Nagelkerke-R^2 (85.8%), signifying that the model is excellently suitable for the data. The score of variables in the model worked out favorably in the train dataset of 1105 observations, which is large enough to meet the 10:1 (i.e., 10 samples per variable) rule-of-thumb in model building. With upper-level Specificity and PPV, Model 3 would be successful in minimizing the false positive error rate and thus, in screening out the inactive compounds. When the model was validated in the test set, its performance scores were still impressively high at 93.1% PPV, 91.3% Hit Ratio, and 85.6% Specificity; only lowered by a minimal 2-3 percentage points in these three metrics. Its MCC is still high at 0.80 showing an outstanding overall accuracy of the model in classifying compounds. Having the hallmark of an excellent classifier, Model 3 was chosen for the final multiple logistic regression model of compound classification as COX-2 active or inactive . Table 3 shows the 25 predictors of the model that are all significant (p-value < 0.05) contributors to compound classification.

Table 3. Multiple Logistic Regression Model* of Compound Classification as COX-2 Active or Inactive

No.	Variables	B	S.E.	P-value	No.	Variables	B	S.E.	P-value
1	sz	-2.141	0.427	<.001	14	cpka	0.192	0.036	<.001
2	sxz	-0.415	0.080	<.001	15	acca	-0.204	0.024	<.001
3	dz	-0.584	0.066	<.001	16	cddsss	-2.220	0.835	0.008
4	dene	0.065	0.018	<.001	17	sdssc	1.247	0.210	<.001
5	minlip	-0.284	0.058	<.001	18	saasc	0.449	0.142	0.002
6	chiv2	0.868	0.345	0.012	19	nr6	-0.771	0.369	0.037
7	rpcg	12.501	2.326	<.001	20	chi1	4.144	0.91	<.001
8	nac	0.357	0.091	<.001	21	jx	4.540	1.383	0.001
9	pmiz	0.01	0.002	<.001	22	vdiste	-0.007	0.001	<.001
10	sx	0.866	0.282	0.002	23	dx	0.126	0.048	0.009
11	sxy	0.242	0.076	0.002	24	pnsa1	-0.050	0.015	0.001
12	3dsav	-0.105	0.022	<.001	25	wpsa1	-0.057	0.019	0.003
13	elu	1.194	0.507	0.019		Constant	9.753	6.678	0.144

* Predictors based on Spartan- and Discovery Studio-Derived molecular descriptors of compounds with experimental COX-2 inhibitory activity collected from literature published from 1997-2019.
Train Set: n=1105; 744 actives, 361 inactives *Test Set: n=276; 186 actives, 90 inactives*
HLT p-value=0.946(ns), Nagelkerke R^2=0.858 *PPV=93.1%, MCC=0.801, Accuracy=91.3%*
PPV=94.8%, MCC=0.859, Accuracy=93.8%

Table 4 gives the description of the variables, the first in the list *sz* (*shadow_zlength)* is the length of the molecular shadow that is projected along the z axis [109], which is the one that has the highest correlation with *compound class* (r_s = -0.48). This variable has inverse relationship with *logit P* as indicated by its negative coefficient consistent with its negative correlation with compound class. Thus, compounds with shorter shadow projected along the z axis have better chances of being active against COX-2. This relationship holds true to *sxz* (area of molecular shadow projected onto the xz plane) and *dz* (z component of dipole moment). *Dene* (or Dreiding Energy), the fourth descriptor in the list, is directly related with *logit P* so that a higher potential energy makes a compound more likely COX-2 active.

Table 4. Predictors* in the Multiple Logistic Regression Model for Compound Classification as COX-2 Active or Inactive

No.	Variable	Name	Description
1	*sz*	*Shadow_Zlength*	length of the molecular shadow along the z axis
2	*sxz*	*Shadow_XZ*	area of the molecular shadow that is projected onto the xz plane
3	*dz*	*Dipole_Z*	z component of the dipole moment
4	*dene*	*Dreiding_Energy*	calculated energy using the Dreiding force field
5	*minlip*	*Min_Loc_Ion_Pot*	minimum local ionization potential
6	*chiv2*	*Chi_V_2*	valence chi connectivity index of order 2
7	*rpcg*	*Jurs RPCG*	Jurs relative positive charge
8	*nac*	*Num_AtomClasses*	number of atom classes
9	*pmiz*	*PMI_Z*	principal moment of inertia based on z rotational axis
10	*sx*	*Shadow_Xlength*	length of the molecular shadow along the x axis
11	*sxy*	*Shadow_XY*	area of the molecular shadow that is projected onto the xy plane
12	*3dsav*	*Molecular_3D_SAVol*	molecular 3D solvent accessible volume
13	*elu*	*E_LUMO*	energy of the lowest unoccupied molecular orbital in electronvolt (eV)
14	*cpka*	*CPKArea*	Corey-Pauling-Koltun area
15	*acca*	*AccArea*	accessible area of the molecule
16	*cddsss*	*ES_Count_ddssS*	count of ddssS E-state
17	*sdssc*	*ES_Sum_dssC*	sum of dssC E-states
18	*saasc*	*ES_Sum_aasC*	sum of assC E-states
19	*nr6*	*Num_Rings_6*	number of 6-membered rings
20	*chi1*	*Chi_V_1*	chi molecular connectivity index of order 1
21	*jx*	*JX*	Balaban modified distance connectivity index based on atomic electronegativities
22	*vdiste*	*V_DIST_equ*	total information content on the distance equality
23	*dx*	*Dipole_X*	x component of dipole moment
24	*pnsa1*	*Jurs_PNSA1*	Jurs partial negative surface area
25	*wpsa1*	*Jurs_WPSA1*	Jurs surface weighted charged partial positive surface area

* Spartan and Discovery Studio-derived molecular descriptors of compounds with experimental COX-2 inhibitory activity collected from literature published from 1997-2019.

Model Application

The MLogR model was applied on the two sets, the Derivatives and the Similars. As shown in Figure 2, the set of Derivatives was comprised of 5 families: A (300 cyclopentenes), B (200 imidazolyls), C (200 difluorobenzenes), D (200 furanyl/thiophenyls), and E (200 isoxazoles). The Similars consisted of 600 compounds obtained from a library of bioactive molecules (*i.e.* ChEMBL) and from a database of druglike compounds (*i.e.* ZINC Drug-like) with the use of the SwissSimilarity tool.

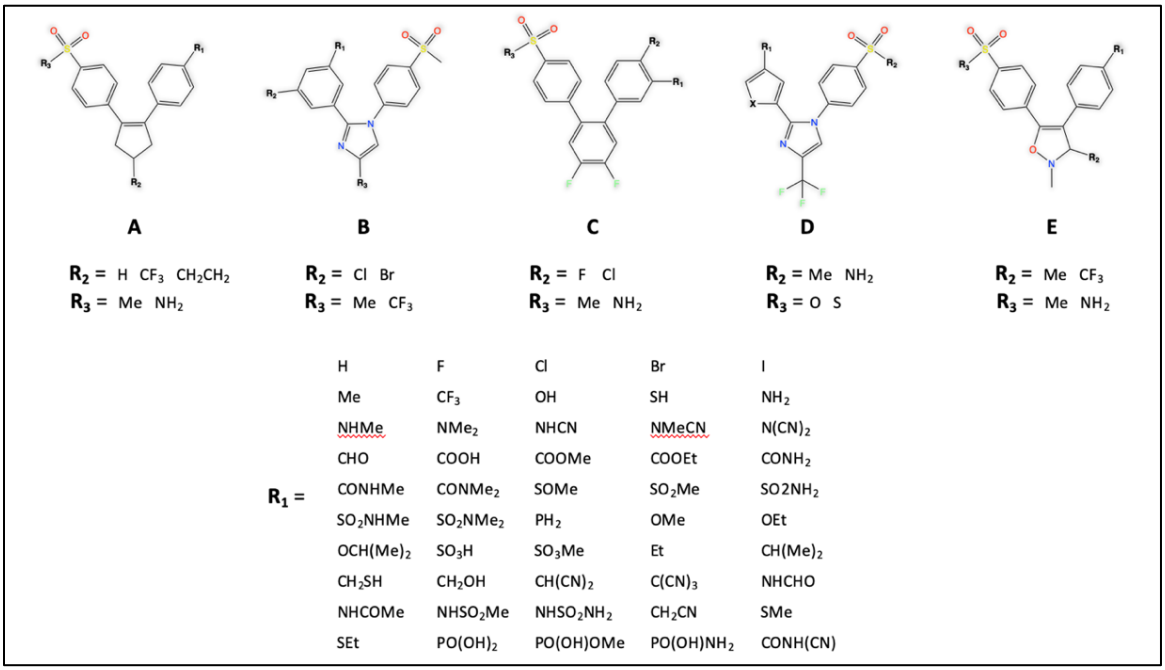


Figure 2. Derivatives of representative compounds from the 5 selected families with experimental COX-2 inhibitory activity collected from literature published from 1997–2019

Upon its implementation, the model identified as inactives a good number of Derivatives (mostly difluorobenzenes) and Similars (approximately half), as Figure 3 exhibits. Consistent with its high PPV of 95% and 93% in the train and test set, respectively, this model brought out a much greater number of supposed false positives compared to the other models. Henceforth, the model would serve as an excellent virtual screen for the identification of novel compounds with potential inhibitory activity against COX-2, and thus, in the creation of a pool of candidates as next generation NSAIDs.

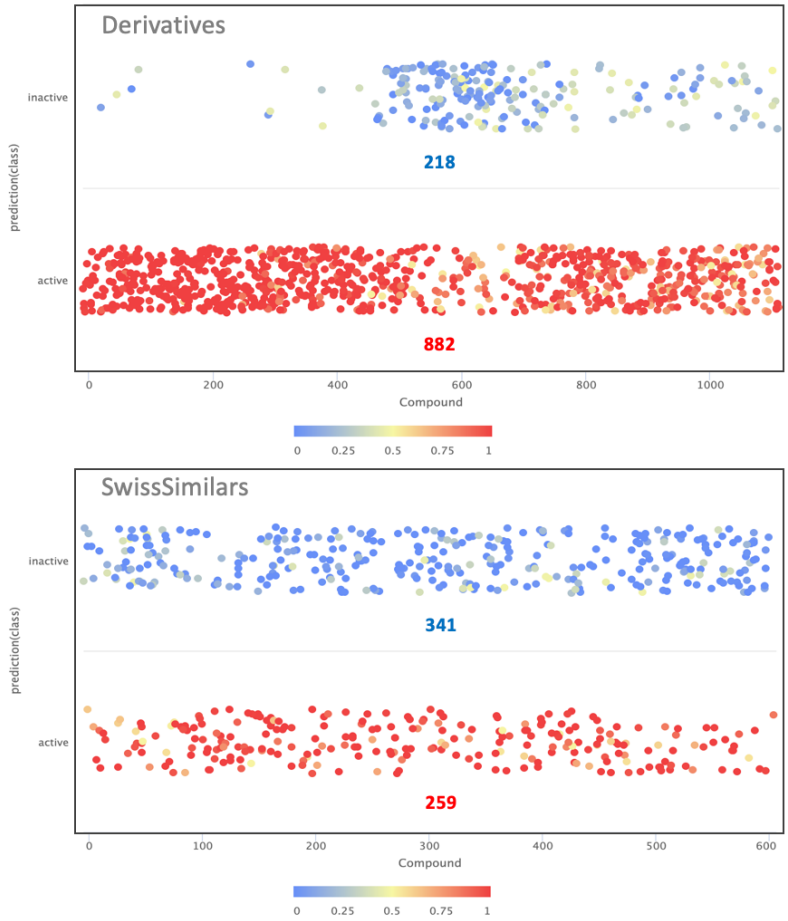


Figure 3. Multiple logistic regression model compound class prediction of the Derivatives (n = 1100) and Similars (n = 600) of compounds with experimental COX-2 inhibitory activity collected from literature published in 1997-2019
The 25 predictors of the model are sz, sxz, dz, dene, minlip, chiv2, rpcg, nac, pmiz, sx, sxy, 3dsav, elu, cpka, acca, cddsss, sdssc, saasc, nr6, chi1, jx, vdiste, dx, pnsa1, and wpsa.

The predicted active Derivatives and Similars were further evaluated by calculating certain measures of druglikeness. Figures 4 and 5 show that nearly all have Quantitative Estimate of Druglikeness or QED score [110] above 0.5 (i.e., druglike); all have synthetic accessibility score within the 1–6 (blue to red) acceptable range (i.e., relatively easy to synthesize) [111]; mostly have low to optimal aqueous solubility or within 2-4 range (orange to red), have good to moderate intestinal absorption or within 0–1 range (blue), and are non-carcinogens; although majority are hepatotoxic (blue), just like more than half (53%) of drugs in the market [112]. All in the Derivatives group and most of the Similars are non-mutagens (blue) and CYP2D6 non-inhibitors, and some in both sets are plasma protein non-binders.

Figure 4. Druglikeness profile and synthetic accessibility of MLogR-predicted active Derivatives of compounds with experimental COX-2 inhibitory activity collected from literature published from 1997–2019

Probability (Active)=1, most likely active against COX-2 Intestinal Absorption: 0=Good absorption, 1=Moderate absorption, 2=Low absorption, 3=Very low absorption. Aqueous Solubility: 0=extremely low, 1=very low but possible, 2=Yes but low, 3=Yes and good, 4=Yes and optimal, 5=too soluble. QED: 0 = least druglike … 1 = most druglike. SA Score: 1 = very easy to synthesize … 10 = very difficult to synthesize. The x-axis of the figures represents the compounds used in this study.

Figure 5. Druglikeness profile and synthetic accessibility of MLogR-predicted active Similars of compounds with experimental COX-2 inhibitory activity collected from literature published from 1997–2019.
Probability (Active)=1, most likely active against COX-2. Intestinal Absorption: 0=Good absorption, 1=Moderate absorption, 2=Low absorption, 3=Very low absorption. Aqueous Solubility: 0=extremely low, 1=very low but possible, 2=Yes but low, 3=Yes and good, 4=Yes and optimal, 5=too soluble. QED: 0 = least druglike … 1 = most druglike. SA Score: 1 = very easy to synthesize … 10 = very difficult to synthesize. The x-axis of the figures represents the compounds used in this study.

From the predicted active compounds, the top hits were determined based on the following criteria: (a) PA ≥ 0.7, (b) QED ≥ 0.9, (c) 1 ≤ SAS ≤ 6, (d) 2 ≤ AS ≤ 4, (e) 0 ≤ IA ≤ 1, (f) Non-Carcinogen, (g) Non-Mutagen, (h) CYP2D6 Non-inhibitor, and (i) DTP Non-Toxic. At this stage, compounds with probability of being active less than 0.7 were eliminated, thus further reducing the false positive error rate. Those that remained were sorted according to QED score and compounds with lower than 0.9 were removed, and so forth. All compounds that passed the 9 criteria were again sorted according to QED score, and then the top 10 were identified. Incidentally all came from the group of Derivatives. To include some Similars in the top hit list, the QED score criterion was lowered to 0.8 for this group of compounds. Subsequently, the top 5 Similars were picked out and are listed in Table 5 as top 11–15 for the Top 15 Hits, i.e., top 10 Derivatives and top 5 Similars. The top Derivatives and top Similars have QED scores greater than 0.91 and greater than 0.86, respectively, i.e., close to 1, and thus are very highly likely to possess the desirable properties of a drug [110]. These hits are relatively easy to prepare in an organic synthetic laboratory, have low to optimal aqueous solubility, and have good intestinal absorption. They are all non-carcinogens, non-mutagens, non-CYP2D6 inhibitors (i.e., can be taken with other drugs), and non-toxic to a developing fetus (i.e., can be administered to pregnant women).

Table 5. Druglikeness Profile of the Top 15 Hits from the Predicted* Active Derivatives and Similars**

No.	ID	PA	QED	SAS	AS	IA	CG	MG	CI	DTP	PPB	HT
1	D51	1.0	0.94	4	2	0	Non-C	Non-M	Non-I	Non-T	Binder	Hepatotoxic
2	D251	1.0	0.94	4	2	0	Non-C	Non-M	Non-I	Non-T	Binder	Hepatotoxic
3	D56	1.0	0.93	3	2	0	Non-C	Non-M	Non-I	Non-T	Binder	Hepatotoxic
4	D94	1.0	0.93	3	2	0	Non-C	Non-M	Non-I	Non-T	Binder	Hepatotoxic
5	D62	1.0	0.92	3	2	0	Non-C	Non-M	Non-I	Non-T	Binder	Hepatotoxic
6	D53	1.0	0.92	3	2	0	Non-C	Non-M	Non-I	Non-T	Binder	Hepatotoxic
7	D256	1.0	0.92	4	2	0	Non-C	Non-M	Non-I	Non-T	Binder	Hepatotoxic
8	D17	1.0	0.91	3	2	0	Non-C	Non-M	Non-I	Non-T	Binder	Hepatotoxic
9	D58	1.0	0.91	3	2	0	Non-C	Non-M	Non-I	Non-T	Binder	Hepatotoxic
10	D73	1.0	0.91	3	2	0	Non-C	Non-M	Non-I	Non-T	Binder	Hepatotoxic
11	S265	1.0	0.88	2	2	0	Non-C	Non-M	Non-I	Non-T	Binder	Hepatotoxic
12	S269	1.0	0.88	2	2	0	Non-C	Non-M	Non-I	Non-T	Binder	Hepatotoxic
13	S568	0.9	0.88	4	2	0	Non-C	Non-M	Non-I	Non-T	Binder	Hepatotoxic
14	S35	1.0	0.86	3	2	0	Non-C	Non-M	Non-I	Non-T	Binder	Hepatotoxic
15	S499	1.0	0.86	3	2	0	Non-C	Non-M	Non-I	Non-T	Binder	Hepatotoxic

ID=Compound Identification: D=Derivative, S=Similar.
PA=Probability(Active): 1=most likely active.
QED=Quantitative Estimate of Druglikeness: 1=most druglike.
SAS=Synthetic Accessibility Score:1=very easy to synthesize … 10=very difficult to synthesize; acceptable values=[1,6].
AS=Aqueous Solubility: 0=extremely low … 5=too soluble; acceptable values={2, 3, 4}.
IA=Intestinal Absorption: 0=good, 1=moderate, 2=low, 3=very low absorption; acceptable values={0, 1}.
CG=Carcinogenicity: Non-C=Non-Carcinogen.
MG=Mutagenicity: Non-M=Non-Mutagen.
DTP=Developmental Toxicity Potential: Non-T=Non-Toxic.
CI=CYP2D6 Inhibition: Non-I=Non-inhibitor.
PPB=Plasma Protein Binding.
HT=Hepatotoxicity.
* Predicted active by the MLogR model with the 25 molecular descriptors: sz, sxz, dz, dene, minlip, chiv2, rpcg, nac, pmiz, sx, sxy, 3dsav, elu, cpka, acca, cddsss, sdssc, saasc, nr6, chi1, jx, vdiste, dx, pnsa1, and wpsa.).
** Derivatives and Similars of compounds with experimental COX-2 inhibitory activity collected from literature published from 1997-2019.

The molecular structures of these top 15 hits are given in Figure 6. The top 10 hits are derivatives of cyclopentenes, although the two of which are actually spiro[2.4]hept-5-enes (**D251** and **D256**). For the top 5 Similars, three of the compounds are variants of diphenylamine (**S265, S269, S499**), while the other two (**S568** and **S35)** are derivatives of phenylthiadiazole and diphenylcyclobutene, respectively. These different structural motifs may lead to new classes of COX-2 acting drugs.

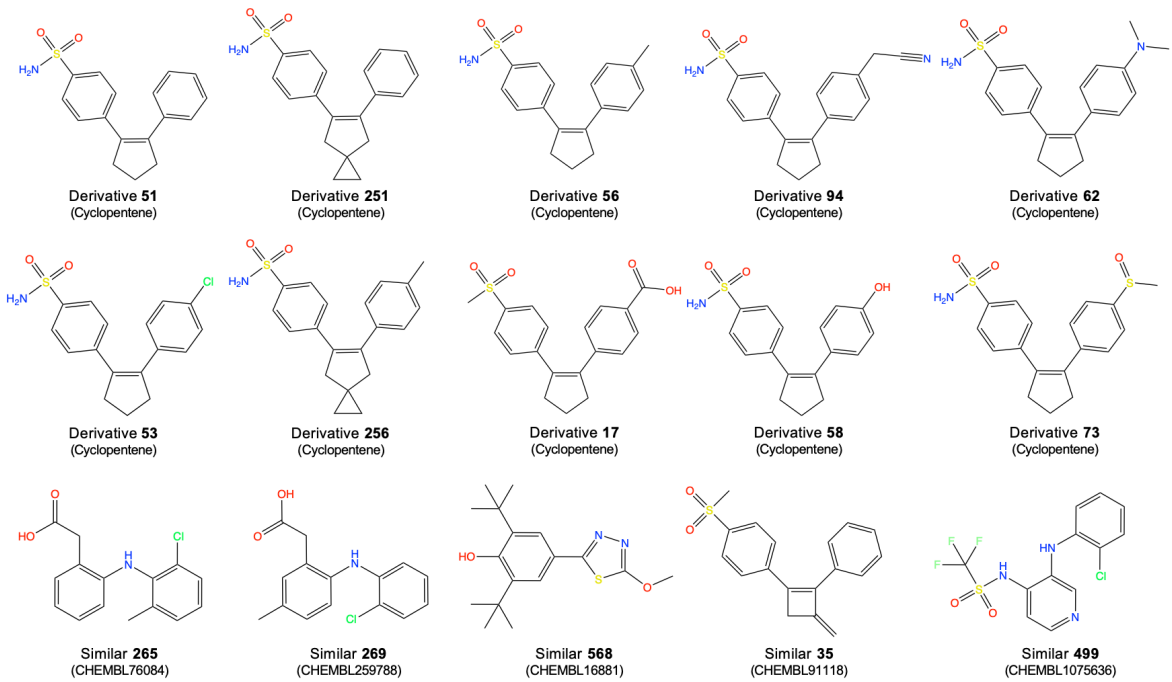
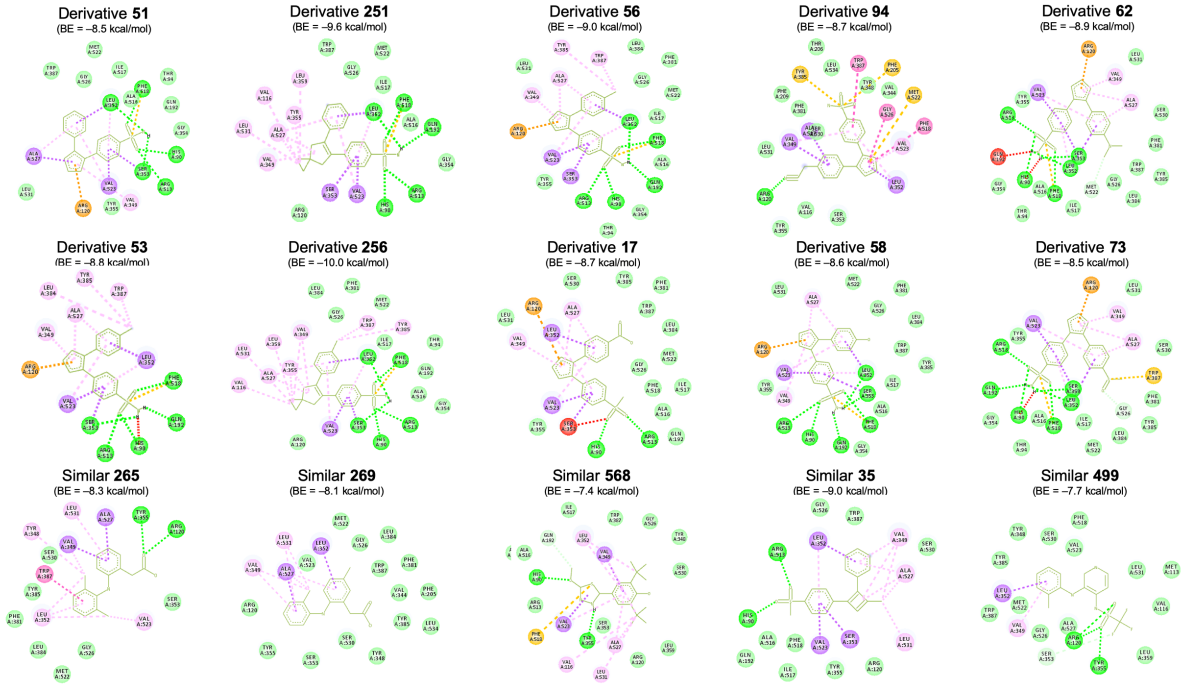


Figure 6. Molecular structures of the top 15 hits from the MLogR-predicted active Derivatives and Similars of compounds with experimental COX-2 inhibitory activity collected from literature published in 1997-2019

Docking studies on these hits were conducted with promising results displayed in Figure 7. It is encouraging to note that, compared to Etoricoxib (also known as Arcoxia), a COX-2 selective drug (BE = –7.8 kcal/mol), the top hits displayed greater binding affinity with the target, with the exception of only the 13th and 15th hits whose BE values are slightly smaller than that of the control. And compared to Mefenamic acid (BE = –8.6 kcal/mol), which was the co-crystallized ligand in complex with COX-2 [113], 9 out of the 15 hits have equal and even greater binding energy, topped by the spiroheptene **D256** (BE = –10.0 kcal/mol). Finally, among the top hits from *Similars*, the tricyclic **S35** displayed greater binding affinity compared to Etoricoxib and Mefenamic acid.



Control: Mefenamic acid (BE = –8.6 kcal/mol), Etoricoxib (BE = –7.8 kcal/mol); The crystal structure of the COX-2 target used was in complex with Mefenamic acid (PDB ID: 5IKR). After removing the ligands and the water molecules the enzyme was subjected to 100 ns Molecular Dynamics simulation and the final equilibrated structure was used in Molecular Docking calculations.

Figure 7. Binding energy and interaction map of the top 15 hits from the Model 3-predicted active Derivatives and Similars of compounds with experimental COX-2 inhibitory activity collected from literature published in 1997-2019

Conclusion

Multiple Logistic Regression was performed on a dataset consisting of 1381 compounds with experimental COX-2 activity and with 184 calculated molecular descriptors in order to establish a quantitative relationship between anti-inflammatory activity (active or inactive) against the COX-2 enzyme, and the key structural features of the molecules. Among the models generated in the train set, the 25-variable model showed superior performance scores and the finest fit indices. And upon model validation, it displayed outstanding prediction in the test set and thus, was subsequently utilized as a virtual filter of compounds for COX-2 inhibitory activity.

As an upshot of the model application, this work furnishes a new set of potential candidates of next generation COX-2 active anti-inflammatory agents with outstanding druglike profile. The top Derivatives are variants of cyclopentenes, two of which are actually spiroheptenes (**D251** and **D256**). For the top Similars, three are variants of diphenylamine (**S265, S269, S499**) and two (**S568** and **S35)** are derivatives of phenylthiadiazole and diphenylcyclobutene, respectively.

The molecular docking studies showed that the binding energy of the top 15 hits are comparable or even better than those of the control drugs.

These promising results may pave the way for a new generation of more potent and safer COX-2 acting NSAIDs.

Acknowledgement

This work was fully supported by the Office of the Vice President of Academic Affairs, University of the Philippines System through Faculty Reps Administrative Staff Development Program (FRASDP).

References

[1] Global Industry Analysts, Inc. Global Pain Management Market to Reach US$60 Billion by 2015. According to a New Report by Global Industry Analysts, Inc. *20*11.
[2] Centers for Disease Control and Prevention (CDC). Arthritis-Related Statistics. 2017. Retrieved from www.cdc.gov/arthritis/data_statistics/arthritis_related_stats.htm
[3] Ferrero-Miliani, L.; Nielsen, O. H.; Andersen, P. S.; Girardin, S. E. Chronic inflammation: importance of NOD2 and NALP3 in interleukin-1beta generation. *Clin. Exp. Immunol*. **2007**, *147*(2), 227–235. DOI: 10.1111/j.1365-2249.2006.03261.x
[4] Hall, J. E. Inflammation: Role of Neutrophils and Macrophages In Guyton and Hall textbook of medical physiology, 12th ; Philadelphia, PA: Saunders/Elsevier. 2011, pp 428.
[5] Neil, G. D.; Senchenkova, E. Leukocyte-endothelial cell. In Inflammation and the microcirculation. ; San Rafael, 2010.
[6] Piira, O.; Miettinen, J. A.; Hautala, A.; Huikuri, H. V.; Tulppo, M. P. Physiological responses to emotional excitement in healthy subjects and patients with coronary artery disease. *Auton. Neurosci*. **2013**, *177*(2): 280–285. DOI: 10.1016/j.autneu.2013.06.001
[7] Mallbris, L.; Akre, O.; Granath, F; Yin, L.; Lindelöf, B.; Ekbom, A.; *et al*. Increased risk for cardiovascular mortality in psoriasis inpatients but not in outpatients. *Eur. J. Epidemiol.* **2004**, *19*, 225–30. DOI: 10.1023/b:ejep.0000020447.59150.f9
[8] Kolb, H.; Mandrup-Poulsen, T. The global diabetes epidemic as a consequence of lifestyle-induced low-grade inflammation. *Diabetologia* **2010**, *53*(1), 10–20. DOI: 10.1007/s00125-009-1573-7
[9] Miller, A. H.; Malteic, V.; Raison, C. L. Inflammation and its discontents: the role of cytokines in the pathophysiology of major depression. *Biol. Psychiatry.* **2009**, *65*(9), 732–41. DOI:10.1016/j.biopsych.2008.11.029
[10] Grivennikov, S. I.; Greten, F. R.; Karin, M. Immunity, inflammation, and cancer. *Cell* **2010**, *140*(6), 883–899.
[11] National Fibromyalgia & Chronic Pain Association. Pain facts: An overview of American pain surveys, 2015. Available at: http://chronicpainaware.org/pain-101/pain-survey-results
[12] American Academy of Pain Association. Facts and figures on pain, 2016. Available at: http://www.painmed.org/files/facts-and-figures-on-pain.pdf
[13] Litalien, C.; Beaulieu, P. Molecular mechanisms of drug actions: From receptors to effectors. In Pediatric Critical Care (4th Ed.); Fuhrman, B.P., Zimmerman, J. J., Eds.; Philadelphia, PA: Elsevier Saunders. 2011, Chapter 117, pp1553–1568.
[14] Fu, J. Y.; Masferrer, J. L.; Siebert, K.; Raz, A.; Needleman, P. J. The induction of prostaglandin-H2 synthase (cyclooxygenase) in human monocytes. *J. Biol. Chem.* **1990**, *265*, 16737–16747.
[15] Botting, R. COX-1 and COX-3 inhibitors, *Thromb. Res*. **2003**, *110*(5–6), 269–272.
[16] Chandrasekharan, N. V.; Dai, H.; Roos, K. L.; Evanson, N. K.; Tomsik, J.; Elton, T. S.; Simmons, D. L. COX-3, a cyclooxygenase-1 variant inhibited by acetaminophen and

other analgesic/antipyretic drugs: cloning, structure, and expression. *Proc. Natl. Acad. Sci. U.S.A*. **2002**, *99*(21), 13926–13931.

[17] Laine, L.; Takeuchi, K.; Tarnawski, A. Gastric mucosal defense and cytoprotection: bench to bedside. *Gastroenterology*. **2008**, *135*(1), 41–60.

[18] Fauci, A. S.; Braunwald, E.; Kasper, D. L.; Hauser, S. L.; Longo, D. L.; etc *In Harrison's Principles of Internal Medicine (17th Ed.)*; McGraw-Hill Medical: New York, 2008, Vol. 17, pp 661.

[19] Kurumbail, R. G.; Kiefer, J. R.; Marnett, L. J. Cyclooxygenase enzymes: catalysis and inhibition. *Curr. Opin. Struct. Biol*. **2001**, *11(6)*, 752–760. DOI: 10.1016/s0959-440x(01)00277-9

[20] Penning, T. D.; Talley, J. J.; Bertenshaw, S. R.; Carter, J. S.; Collins, P. W.; *et al*. Synthesis and biological evaluation of the 1,5-diarylpyrazole class of cyclooxygenase-2 inhibitors: identification of 4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide (SC-58635, celecoxib). *J. Med. Chem.* **1997**, *40(9)*, 1347–1365. DOI: 10.1021/jm960803q

[21] Riendeau, D.; Percival, M. D.; Brideau, C.; Charleson, S.; Dubé, D.; *et al.* Etoricoxib (MK-0663): Preclinical profile and comparison with other agents that selectively inhibit cyclooxygenase-2. *J. Pharmacol. Exp. Ther.* **2001**, *296*, 558–586.

[22] Talley, J.J.; Bertenshaw, S. R.; Brown, D. L.; Carter, J. S.; Graneto, M. J.; *et al*. N-[[(5-methyl-3-phenylisoxazol-4-yl)-phenyl]sulfonyl]propanamide, sodium salt, parecoxib sodium: A potent and selective inhibitor of COX-2 for parenteral administration. *J. Med. Chem.* **2000**, *43(9)*, 1661–1663.

[23] Talley, J. J.; Brown, D. L.; Carter, J. S.; Graneto, M. J.; Koboldt, C. M.; *et al*. 4-[5-Methyl-3-phenylisoxazol-4-yl]- benzenesulfonamide, valdecoxib: a potent and selective inhibitor of COX-2. *J. Med. Chem.* **2000**, *43(5)*, 775–777.

[24] Prasit, P.; Wang, Z.; Brideau, C.; Chan, C. C.; Charleson, S.; *et al*. The discovery of rofecoxib, [MK 966, Vioxx, 4-(4'-methylsulfonylphenyl)-3-phenyl-2(5H)-furanone], an orally active cyclooxygenase-2-inhibitor. *Bioorg. Med. Chem. Lett.* **1999**, *9(13)*, 1773–1778. DOI: 10.1016/s0960-894x(99)00288-7

[25] Merck Announces Voluntary Worldwide Withdrawal of VIOXX. Available at https://www.merck.com/newsroom/vioxx/pdf/vioxx_press_release_final.pdf.

[26] Bally, M.; Dendukuri, N.; Rich, B.; Nadeau, L.; Helin-Salmivaara, A.; *et al.* Risk of acute myocardial infarction with NSAIDs in real world use: Bayesian meta-analysis of individual patient data. *BMJ* (Clinical Research Ed.). **2017**, *357*, j1909. DOI: 10.1136/bmj.j1909

[27] Lanas, A.; Chan, F. K. Peptic ulcer disease. *Lancet* **2017**, *390(10094)*, 613–624. DOI: 10.1016/S0140-6736(16)32404-7

[28] Cramer, J. S. The origins of logistic (PDF) (Technical report). 119. Tinbergen Institute. 2002, pp 167–178.

[29] Cox, D. R. The regression analysis of binary sequences (with discussion). *J. R. Stat. Soc. B.* **1958**, *20(2)*, 215–242.

[30] Boyd, C. R.; Tolson, M. A.; Copes, W. S. Evaluating trauma care: The TRISS method. Trauma score and the injury severity score. *J. Trauma.* **1987**, *27(4)*, 370–378. DOI:10.1097/00005373-198704000-00005

[31] Palei, S. K.; Das, S. K. Logistic regression model for prediction of roof fall risks in bord and pillar workings in coal mines: an approach. *Saf. Sci*. **2009**, *47*, 88–96. DOI: 10.1016/j.ssci.2008.01.002

[32] Chen, C.; Wang, H. Logistic regression method for ligand discovery. *J. Comput. Biol.* **2020**, *27(6)*, 934–940. DOI: 10.1089/cmb.2019.0232

[33] Gierse, J. K.; Hauser, S. D.; Creely, D. P.; Koboldt, C.; Rangwala, S. H.; *et al.* Expression and selective inhibition of the constitutive and inducible forms of human cyclo-oxygenase. *Biochem. J.* **1995**, *305*, 479–484. DOI: 10.1042/bj3050479
[34] Mayo, S. L.; Olafson, B. D.; Goddard, W. A. DREIDING: A generic force field for molecular simulations. *J. Phys. Chem.* **1990**, *94*, 8897−8909. DOI:10.1021/J100389A010
[35] Halgren, T. A. Merck molecular force field. I. Basis, form, scope, parameterization, and performance of MMFF94. *J. Comput. Chem.* **1996**, *17*, 490–519. DOI:10.1002/(SICI)1096-987X(199604)17:5/6<490::AID-JCC1>3.0.CO;2-P
[36] Stewart. J. J. P. Optimization of parameters for semiempirical methods I. Method. *J. Comput. Chem*. **1989**, *10(2)*, 209–220. DOI:10.1002/jcc.540100208
[37] Ghorbani, H. (**2019**, October 4). Mahalanobis distance and its application for detecting multivariate outliers. *Facta Universitatis, Series: Mathematics and Informatics*, 583. DOI:10.22190/fumi1903583g
[38] Fletcher, R. H.; Suzanne, W. Clinical epidemiology: the essentials (4th Ed.) Baltimore, Md.: Lippincott Williams & Wilkins. 2005, pp. 45.
[39] Nagelkerke, N. J. D. Maximum likelihood estimation of functional relationships, Pays-Bas. *In Lecture Notes in Statistics*; Berger, J.; Fienberg, S.; Gani; K.; Krickeberg, I.; Olkin, I.; etc.; Springer-Verlag: 1992; Vol. 69.
[40] Hosmer, D. W.; Lemeshow, S. *Applied Logistic Regression* (2nd Ed.). Wiley, 2000.
[41] Matthews, B.W. Comparison of the predicted and observed secondary structure of T4 phage lysozyme. *Biochim. Biophys. Acta Protein Struct*. **1975**, *405(2)*, 442–451. DOI: 10.1016/0005-2795(75)90109-9
[42] Barillari, C.; Brown, N. Classical bioisosteres. *In Bioisosteres in medicinal chemistry*; Nathan, B. eds.; Wiley-VCH: Weinheim, 2012, pp15–29.
[43] Macalino, S. J. Y. Molecular dynamics simulation of COX-2. Unpublished work, **2021**.
[44] Trott, O.; Olson, A. J. AutoDock Vina: improving the speed and accuracy of docking with a new scoring function, efficient optimization, and multithreading. *J. Comput. Chem*. **2010**, *31(2)*, 455–61. DOI:10.1002/jcc.21334
[45] Khanna, I. K.; Weier, R. M.; Yu, Y.; Collins, P. W.; Miyashiro, J. M.; *et al*. 1,2-Diarylpyrroles as potent and selective inhibitors of cyclooxygenase-2. *J. Med. Chem.* **1997**, *40*, 1619–1633. DOI: 10.1021/jm970036a
[46] Khanna, I. K.; Weier, R. M.; Yu, Y.; Collins, P.W.; Miyashiro, J. M.; *et al*. 1,2-Diarylimidazoles as potent, cyclooxygenase-2 selective, and orally active antiinflammatory agents. *J. Med. Chem.* **1997**, *40*, 1634–1647.
[47] Khanna, I. K.; Yu, Y.; Huff, R. M.; Weier, R. M.; Xu, X.; *et al*. Selective cyclooxygenase-2 inhibitors: Heteroaryl modified 1,2-Diarylimidazoles are potent orally active antiinflammatory agents. *J. Med. Chem.* **2000**, *43*, 3168–3185.
[48] Reitz, D. B.; Li, J. J.; Norton, M. B.; Reinhard, E. J.; *et al*. Selective cyclooxygenase inhibitors: novel 1,2-diarylcyclopentenes are potent and orally active COX-2 inhibitors. *J. Med. Chem.* **1994**, *37*, 3878–3881. DOI:10.1021/jm00049a005
[49] Li, J. J.; Anderson, G. D.; Burton, E. G.; Cogburn, J. N.; Collins, J. T.*; et al.* 1,2-Diarylcyclopentenes as selective cyclooxygenase-2 inhibitors and orally active anti-inflammatory agents. *J. Med. Chem*. **1995**, *38*, 4570–4578.
[50] Li, J. J.; Norton, M. B.; Reinhard, E. J; Anderson, G. D.; Gregory, S. A.; *et al*. Novel terphenyls as selective cyclooxygenase-2 inhibitors and orally active anti-inflammatory agents. *J. Med. Chem*. **1996**, *39*, 1846–1856.
[51] Huang, H. C.; Li, J. J.; Garland, D. J.; Chamberlain, T. S.; Reinhard, E. J.; *et al.* Diarylspiro[2.4]heptenes as orally active highly selective cyclooxygenase-2 inhibitors: synthesis and structure-activity relationships. *J. Med. Chem*. **1996**, *39*, 253–266.

[52] Gans, K. R.; Galbraith, W.; Roman, R. J.; Haber, S. B.; Kerr, J. S.; *et al*. Antiinflammatory and safety profile of DuP 697, a novel orally effective prostaglandin synthesis inhibitor. *J. Pharmacol. Exp. Ther.* **1990**, *254*, 180–187.

[53] El-Shoukrofy, M. S.; Abd El Razik, H. A.; AboulWafa, O. M.; Bayad, A. E; El-Ashmawy, I. M. Pyrazoles containing thiophene, thienopyrimidine and thienotriazolopyrimidine as COX-2 selective inhibitors: Design, synthesis, in vivo anti-inflammatory activity, docking and in silico chemo-informatic studies. *Bioorg. Chem.* **2019**, *85*, 541–557. DOI: 10.1016/j.bioorg.2019.02.036

[54] Abdelall, E. K. A.; Lamie, P. F.; Ahmed, A. K. M.; EL-Nahass, E. S. COX-1/COX-2 inhibition assays and histopathological study of the new designed anti-inflammatory agent with a pyrazolopyrimidine core, *Bioorg. Chem*. **2019**, *86*, 235–253. DOI: 10.1016/j.bioorg.2019.01.031

[55] Abdellatif, K. R. A.; Abdelall, E. K. A.; Labib, M. B.; Fadaly, W. A. A.; Zidan, T. H. Design, synthesis of celecoxib-tolmetin drug hybrids as selective and potent COX-2 inhibitors. *Bioorg. Chem.* **2019**, *90*, 103029. DOI: 10.1016/j.bioorg.2019.103029

[56] El-Sayed, M. A. A.; Abdel-Aziz, N. I.; Abdel-Aziz, A. A. M.; El-Azab, A. S.; ElTahir, K. E. H. Synthesis, biological evaluation and molecular modeling study of pyrazole and pyrazoline derivatives as selective COX-2 inhibitors and anti-inflammatory agents. Part 2. *Bioorg. Med. Chem.* **2012**, *20*, 3306–3316. DOI: 10.3109/14756366.2015.1004059

[57] Al-Hourani, B. J.; Sharma, S. K.; Mane, J. Y.; Tuszynski, J.; Baracos. V.; *et al.* Synthesis and evaluation of 1,5-diaryl-substituted tetrazoles as novel selective cyclooxygenase-2 (COX-2) inhibitors. *Bioorg. Med. Chem*. *Lett.* **2011**, *21*, 1823–1826. DOI: 10.1016/j.bmcl.2011.01.057

[58] Al-Hourani, B. J.; Sharma, S. K.; Suresh, M.; Wuest, F. Novel 5-substituted 1H-tetrazoles as cyclooxygenase-2 (COX-2) inhibitors. *Bioorg. Med. Chem. Lett.* **2012**, *22*, 2235–2238. DOI: 10.1016/j.bmcl.2012.01.093

[59] Al-Suwaidan, I. A.; Alanazi, A. M.; El-Azab, A. S.; Al-Obaid, A. M.; ElTahir, K. E. H.; *et al*. Molecular design, synthesis and biological evaluation of cyclic imides bearing benzenesulfonamide fragment as potential COX-2 inhibitors. Part 2. *Bioorg. Med. Chem. Lett.* **2013**, *23*, 2601–2605. DOI:10.1016/j.bmcl.2013.02.107

[60] Alanazi, A. M.; El-Azab, A. S.; Al-Suwaidan, I. A.; ElTahir, K. E. H.; Asiri, Y. A.; *et al*. Structure-based design of phthalimide derivatives as potential cyclooxygenase-2 (COX-2) inhibitors: Anti-inflammatory and analgesic activities. *Eur. J. Med. Chem.* **2015**, *92*, 115–123.

[61] Chen, Z.; Wang, Z. C.; Yan, X. Q.; Wang, P. F.; Lu, X. Y.; *et al.* Design, synthesis, biological evaluation and molecular modeling of dihydropyrazole sulfonamide derivatives as potential COX-1/COX-2 inhibitors. *Bioorg. Med. Chem. Lett.* **2015**, *25*, 1947–1951.

[62] Alegaon, S. G.; Hirpara, M. B.; Alagawadi, K. R.; Hullatti, K. K.; Kashniyal, K. Synthesis of novel pyrazole-thiadiazole hybrid as potential potent and selective cyclooxygenase-2 (COX-2) inhibitors. *Bioorg. Med. Chem. Lett.* **2014**, *24(22)*, 5324–5329. DOI:10.1016/j.bmcl.2014.08.062

[63] El-Sayed, M. A. A.; Abdel-Aziz, N. I.; Abdel-Aziz, A. A. M.; El-Azab, A. S.; Asiri, Y. A.; *et al*. Design, synthesis, and biological evaluation of substituted hydrazone and pyrazole derivatives as selective COX-2 inhibitors: molecular docking study. *Bioorg. Med. Chem.* **2011**, *19*, 3416–3424.

[64] Ghareb, N.; Elshihawy, H. A.; Abdel-Daim, M. M.; Helal, M. A. Novel pyrazoles and pyrazolo[1,2-a]pyridazines as selective COX-2 inhibitors; ultrasound-assisted synthesis, biological evaluation, and DFT calculations. *Bioorg. Med. Chem. Lett.* **2017**, *27*, 2377–2383. DOI: 10.1016/j.bmcl.2017.04.020

[65] Kaur, J.; Bhardwaj, A.; Huang, Z.; Knaus, E. E. N-1 and C-3 substituted indole Schiff bases as selective COX-2 inhibitors: synthesis and biological evaluation. *Bioorg. Med. Chem. Lett.* **2012**, *22*, 2154–2159. DOI: 10.1016/j.bmcl.2012.01.130

[66] Kaur, A.; Pathak, D. P.; Sharma, V.; Narasimhan, B.; Sharma, P.; *et al*. Synthesis, biological evaluation and docking study of N-(2-(3,4,5- T trimethoxybenzyl)benzoxazole-5-yl) benzamide derivatives as selective COX-2 inhibitor and anti-inflammatory agents. *Bioorg. Chem*. **2018**, *81*, 191–202. DOI: 10.1016/j.bioorg.2018.07.007

[67] Kaur, A.; Pathak, D. P.; Sharma, V.; Wakode, S. Synthesis, biological evaluation and docking study of a new series of di-substituted benzoxazole derivatives as selective COX-2 inhibitors and anti-inflammatory agents. *Bioorg. Med. Chem*. **2018**, *26*, 891–902. DOI: 10.1016/j.bioorg.2018.07.007

[68] Abdelgawad, M. A.; Labib, M. B.; Ali, W. A. M.; Kamel, G.; Azouz, A. A.; *et al*. Design, synthesis, analgesic, anti-inflammatory activity of novel pyrazolones possessing aminosulfonyl pharmacophore as inhibitors of COX-2/5-LOX enzymes: histopathological and docking studies. *Bioorg. Chem*. **2018**, *78*, 103–114. DOI: 10.1016/j.bioorg.2018.03.011

[69] Abdellatif, K. R. A.; Abdelgawad, M. A.; Labib, M. B.; Zidan, T. H. Synthesis, cyclooxygenase inhibition, anti-inflammatory evaluation and ulcerogenic liability of novel triarylpyrazoline derivatives as selective COX-2 inhibitors, *Bioorg. Med. Chem. Lett.* **2015**, *25(24)*, 5787–5791. DOI: 10.1016/j.bmcl.2015.10.047

[70] Abdelrahman, M. H.; Youssif, B. G. M.; Abdelgawad, M. A.; Abdelazeem, A. H.; Ibrahim, H. M.; *et al.* Synthesis, biological evaluation, docking study and ulcerogenicity profiling of some novel quinoline-2-carboxamides as dual COXs/LOX inhibitors endowed with anti-inflammatory activity. *Eur. J. Med. Chem.* **2017**, *127*, 972–985. DOI: 10.1016/j.ejmech.2016.11.006

[71] El-Husseiny, W. M.; El-Sayed, M. A. A.; Abdel-Aziz, N. I.; El-Azab, A. S.; Asirig, Y. A.; *et al.* Structural alterations based on naproxen scaffold: synthesis, evaluation of antitumor activity and COX-2 inhibition, and molecular docking. *Eur. J. Med. Chem*. **2018**, *158*, 134–143. DOI: 10.1016/j.ejmech.2018.09.007

[72] Fu, Z. Y.; Jin, Q. H.; Qu, Y. L.; Guan, L. P. Chalcone derivatives bearing chromen or benzo[f]chromen moieties: design, synthesis, and evaluations of anti-inflammatory, analgesic, selective COX-2 inhibitory activities. *Bioorg. Med. Chem. Lett.* **2019**, *29*, 1909–1912. DOI: 10.1016/j.bmcl.2019.05.051

[73] Ju, Z.; Su, M.; Hong, J.; Kim, E. L.; Moon, H. R.; *et al.* Design of balanced COX inhibitors based on anti-inflammatory and/or COX-2 inhibitory ascidian metabolites. *Eur. J. Med. Chem*. **2019**, *180*, 86–98. DOI: 10.1016/j.ejmech.2019.07.016

[74] Labiba, M. B.; Sharkawib, S. M. Z.; El-Daly, M. Design, synthesis of novel isoindoline hybrids as COX-2 inhibitors: anti-inflammatory, analgesic activities and docking study. *Bioorg. Chem*. **2018**, *80*, 70–80. DOI: 10.1016/j.bioorg.2018.05.018

[75] Mohamed, L. W.; Shaaban, M. A.; Zaher, A. F.; Alhamaky, S. M.; Elsahar, A. M. Synthesis of new pyrazoles and pyrozolo [3,4-b] pyridines as anti-inflammatory agents by inhibition of COX-2 enzyme. *Bioorg. Chem*. **2019**, *3*, 47–54. DOI: 10.1016/j.bioorg.2018.10.014

[76] Naaz, F.; Pallavi, M. C. P.; Shafi, S.; Mulakayala, N.; Yar, M. S.; *et al.* 1,2,3-triazole tethered Indole-3-glyoxamide derivatives as multiple inhibitors of 5-LOX, COX-2 & tubulin: Their anti-proliferative & anti- inflammatory activity. *Bioorg. Chem*. **2018**, *81*, 1–20.

[77] Qiu, K. M.; Yan, R.; Xing, M.; Wang, H. H.; Cui, H. E.; *et al.* Synthesis, biological evaluation and molecular modeling of dihydro-pyrazolyl-thiazolinone derivatives as potential COX-2 inhibitors. *Bioorg. Med. Chem.* **2012**, *20*, 6648–6654.
[78] Rena, S. Z.; Wang, Z. C.; Zhu, X. H.; Zhu, D.; Li, Z.; *et al*. Design and biological evaluation of novel hybrids of 1, 5-diarylpyrazole and Chrysin for selective COX-2 inhibition . *Bioorg. Med. Chem.* **2018**, *26*, 4264–4275. DOI: 10.1016/j.bmc.2018.07.022
[79] Sarnpitak, P.; Mujumdar, P.; Morisseau, C.; Hwang, S. H.; Hammock, B.; *et al*. Potent, orally available, selective COX-2 inhibitors based on 2-imidazoline core. *Eur. J. Med. Chem*. **2014**, *84*, 160–172. DOI: 10.1016/j.ejmech.2014.07.023
[80] Singh, P.; Bhardwaj, A.; Kaur, S.; Kumar, S. Design, synthesis and evaluation of tetrahydropyran based COX-1/-2 inhibitors. *Eur. J. Med. Chem.* **2014**, *44*, 1278–1287. DOI:10.1016/j.ejmech.2008.08.008
[81] Taher, E. S.; Ibrahim, T. S.; Fares, M.; AL-Mahmoudy, A. M. M.; Radwan, A. F.; *et al.* Novel benzenesulfonamide and 1,2-benzisothiazol-3(2H)-one-1,1- dioxide derivatives as potential selective COX-2 inhibitors. *Eur. J. Med. Chem.* **2019**, *171*, 372–382.
[82] Tewari, A. K.; Singh, V. P.; Yadav, P.; Gupta, G.; Singh, A.; *et al.* Synthesis, biological evaluation and molecular modeling study of pyrazole derivatives as selective COX-2 inhibitors and anti-inflammatory agents. *Bioorg. Chem*. **2014**, *56*, 8–15. DOI: 10.1016/j.bioorg.2014.05.004
[83] Tsai, W. J.; Shiao, Y. J.; Lin, S. J.; Chiou, W. F.; Lin, L. C.; *et al.* Selective COX-2 inhibitors. Part 1: Synthesis and biological evaluation of phenylazobenzenesulfonamides. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 4440–4443.
[84] Uddin, M. J.; Rao, P.; Rahim, A.; McDonald, R.; Knausa, E. E. A new class of acyclic 2-alkyl-1,2-diaryl (E)-olefins as selective cyclooxygenase-2 (COX-2) inhibitors. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 4911–4914. DOI:10.1016/j.bmcl.2004.07.027
[85] Yatam, S.; Gundla, R.; Jadav, S. S.; Pedavenkatagari, N.; Chimakurthy, J.; *et al*. Focused library design and synthesis of 2-mercapto benzothiazole linked 1,2,4-oxadiazoles as COX-2/5-LOX inhibitors, *J. Mol. Struc.* **2018**, *1159*, 193–204. DOI:10.1016/j.molstruc.2018.01.060
[86] Youssif, B. G. M.; Mohamed, M. F. A.; Al-Sanea, M. M.; Moustafa, A. H.; Abdelhamid, A. A; *et al.* Novel aryl carboximidamides and 3-aryl-1,2,4-oxadiazoles analogues of naproxen as dual selective COX-2 / 15-LOX inhibitors: Design, synthesis and Docking studies, *Bioorg. Chem*. **2019**, *85*, 577–584. DOI: 10.1016/j.bioorg.2019.02.043
[87] Singh, P.; Kaur, S.; Kumari, P.; Kaur, B.; Kaur, M.; *et al.* Tailoring the substitution pattern on 1,3,5-triazine for targeting cyclooxygenase-2: Discovery and structure−activity relationship of triazine−4-aminophenylmorpholin-3-one hybrids that reverse algesia and inflammation in swiss albino mice. *J. Med. Chem.* **2018**, *61*, 7929−7941. DOI: 10.1021/acs.jmedchem.8b00922
[88] Harrak, Y.; Casula, G.; Basset, J.; Rosell, G.; Plescia, S.; *et al.* Synthesis, anti-inflammatory activity, and in vitro antitumor effect of a novel class of cyclooxygenase inhibitors: 4-(Aryloyl)phenyl Methyl Sulfones. *J. Med. Chem.* **2010**, *53*, 6560–6571. DOI: 10.1021/jm100398z
[89] Abdelazeem, A. H.; El-Saadi, M. T.; Safi El-Din, A. G.; Omar, H. A.; El-Moghazy, S. M. Design, synthesis and analgesic/anti-inflammatory evaluation of novel diarylthiazole and diarylimidazole derivatives towards selective COX-1 inhibitors with better gastric profile. *Bioorg. Med. Chem.* **2017**, *25(2)*, 665–676. DOI: 10.1016/j.bmc.2016.11.037
[90] Favia, A. D.; Habrant, D.; Scarpelli, R.; Migliore, M.; Albani, C.; *et al*. Identification and characterization of carprofen as a multitarget fatty acid amide

hydrolase/cyclooxygenase inhibitor. *J. Med. Chem*. **2012**, *55(20)*, 8807–8826. DOI: 10.1021/jm3011146

[91] Kakuta, H.; Zheng, X.; Oda, H.; Harada, S.; Sugimoto, Y.; *et al*. Cyclooxygenase-1-selective inhibitors are attractive candidates for analgesics that do not cause gastric damage. Design and in vitro/in vivo evaluation of a benzamide-type cyclooxygenase-1 selective inhibitor. *J. Med. Chem.* **2008**, *51*, 2400–2411. DOI: 10.1021/jm701191z

[92] Rao, P. N. P.; Amini, M.; Li, H.; Habeeb, A. G.; Knaus, E. E. Design, synthesis, and biological evaluation of 6-substituted-3-(4-methanesulfonylphenyl)-4-phenylpyran-2-ones: A novel class of diarylheterocyclic selective cyclooxygenase-2 inhibitors. *J. Med. Chem.* **2003**, *46(23)*, 4872–4882. DOI: 10.1021/jm0302391

[93] Rao, P. N. P.; Uddin, J.; Knaus, E. E. Design, synthesis, and structure−activity relationship studies of 3,4,6-triphenylpyran-2-ones as selective cyclooxygenase-2 inhibitors. *J. Med. Chem*. **2003**, *47(16)*, 3972–3990. DOI: 10.1021/jm049939b

[94] Singh, P.; Bhardwaj, A. Mono-, di-, and triaryl substituted tetrahydropyrans as cyclooxygenase-2 and tumor growth inhibitors. Synthesis and biological evaluation. *J. Med. Chem.* **2010**, *53*, 3707–3717. DOI: 10.1021/jm1001327

[95] Singh, P.; Kaur, J.; Singh, G.; Bhatti, R. Triblock conjugates: Identification of a highly potent anti-inflammatory agent. *J. Med. Chem.* **2015**, *58(15)*, 5989–6001.

[96] Hwang, S. H.; Wagner, K. M.; Morisseau, C.; Liu, J. Y.; Dong, H.; *et al*. Synthesis and structure activity relationship studies of urea-containing pyrazoles as dual inhibitors of cyclooxygenase-2 and soluble epoxide hydrolase. *J. Med. Chem.* **2011**, *54*, 3037–3050.

[97] Julémont, F.; de Leval, X.; Michaux, C.; Renard, J.; Winum, J.; *et al.* Design, synthesis, and pharmacological evaluation of pyridinic analogues of nimesulide as cyclooxygenase-2 selective inhibitors. *J. Med. Chem.* **2004**, *47*, 6749–6759. DOI: 10.1021/jm049480l

[98] Chen, Z.; Wu, Y.; Liu, Y.; Yang, S.; Chen, Y.; *et al.* Discovery of dual target inhibitors against cyclooxygenases and leukotriene A4 hydrolyase. *J. Med. Chem.* **2011**, *54*, 3650–3660. DOI: 10.1021/jm200063s

[99] Chowdhury, M. A.; Abdellatif, K. R. A.; Dong, Y.; Das, D.; Suresh, M. R.*; et al.* Synthesis of celecoxib analogues possessing a N-difluoromethyl-1,2-dihydropyrid-2-one 5-lipoxygenase pharmacophore: Biological evaluation as dual inhibitors of cyclooxygenases and 5-lipoxygenase with anti-inflammatory activity. *J. Med. Chem.* **2009**, *52*, 1525–1529. DOI:10.1021/jm8015188

[100] Habeeb, A. G.; Rao, P. N. P.; Knaus, E. E. Design and synthesis of 4,5-diphenyl-4-isoxazolines: novel inhibitors of cyclooxygenase-2 with analgesic and antiinflammatory activity. *J. Med. Chem.* **2001**, *44(18)*, 2921–2927. DOI: 10.1021/jm0101287

[101] Habeeb, A. G.; Rao, P. N. P.; Knaus, E. E. Design and synthesis of celecoxib and rofecoxib analogues as selective cyclooxygenase-2 (COX-2) inhibitors: replacement of sulfonamide and methylsulfonyl pharmacophores by an azido bioisostere. *J. Med. Chem*. **2001**, *44(18)*, 3039–3042. DOI: 10.1021/jm010153c

[102] Hashimoto, H.; Imamura, K.; Haruta, J.; Wakitani, K. 4-(4-cycloalkyl/aryl-oxazol-5-yl)benzenesulfonamides as selective cyclooxygenase-2 inhibitors: enhancement of the selectivity by introduction of a fluorine atom and identification of a potent, highly selective, and orally active COX-2 inhibitor JTE-522(1). *J. Med. Chem.* **2002**, *45(7)*, 1511–1517. DOI: 10.1021/jm010484p

[103] Huang, Z.; Velázquez, C. A.; Abdellatif, K. R. A.; Chowdhury, M. A.; Reisz, J. A.; *et al*. Ethanesulfohydroxamic acid ester prodrugs of nonsteroidal anti- inflammatory drugs (NSAIDs): Synthesis, nitric oxide and nitroxyl release, cyclooxygenase inhibition, anti-inflammatory, and ulcerogenicity index studies. *J. Med. Chem.* **2011**, *54*, 1356–1364. DOI: 10.1021/jm101403g

[104] Song, Y.; Connor, D. T.; Doubleday, R.; Sorenson, R. J.; Sercel, A. D.; *et al*. Synthesis, structure-activity relationships, and in vivo evaluations of substituted di-tert-butylphenols as a novel class of potent, selective, and orally active cyclooxygenase-2 inhibitors. 1. Thiazolone and oxazolone series. *J. Med. Chem.* **1999**, *42(7)*, 1151–1160. DOI: 10.1021/jm9805081

[105] Song, Y.; Connor, D. T.; Sercel, A. D.; Sorenson, R. J.; Doubleday, R.; *et al.* Synthesis, structure-activity relationships, and in vivo evaluations of substituted di-tert-butylphenols as a novel class of potent, selective, and orally active cyclooxygenase-2 inhibitors. 2. 1,3,4- and 1,2,4-thiadiazole series. *J. Med. Chem.* **1999**, *42(7)*, 1161–1169. DOI: 10.1021/jm9805081

[106] Velázquez, C.; Rao, P. N. P.; Knaus, E. E. Novel nonsteroidal antiinflammatory drugs possessing a nitric oxide donor diazen-1-ium-1,2-diolate moiety: Design, synthesis, biological evaluation, and nitric oxide release studies. *J. Med. Chem.* **2005**, *48*, 4061–4067. DOI: 10.1021/jm050211k

[107] Wey, S.; Augustyniak, M. E.; Cochran, E. D.; Ellis, J. L.; Fang, X.; *et al*. Structure-based design, synthesis, and biological evaluation of indomethacin derivatives as cyclooxygenase-2 inhibiting nitric oxide donors. *J. Med. Chem.* **2007**, *50*, 6367–6382. DOI: 10.1021/jm0611861

[108] Rao, P. N. P.; Chen, Q.; Knaus, E. E. Synthesis and structure-activity relationship studies of 1,3-diarylprop-2-yn-1-ones: Dual inhibitors of cyclooxygenases and lipoxygenases. *J. Med. Chem.* **2006**, *49*, 1668–1683. DOI: 10.1021/jm0510474

[109] Rahman, A. U.; Choudhary, M.; Reitz, A. In *Frontiers in medicinal chemistry;* Rahman, A.U., Choudhary, M. I, Reitz, A. B., Eds.; Volume 8; Bentham Science Publishers: 2016.

[110] Todeschini, R.; Consonni, V. Handbook of molecular descriptors. In *methods and principles in medicinal chemistry*, Vol. 11, Wiley-VCH Verlag GmbH: Weinheim, Germany, 2000.

[111] Bickerton, G. R.; Paolini, G. V.; Besnard, J.; Muresan, S.; Hopkins, A. L. Quantifying the chemical beauty of drugs. *Nat. Chem*. **2012**, *4*, 90–98. DOI: 10.1038/nchem.1243

[112] Ertl, P.; Schuffenhauer, A. Estimation of synthetic accessibility score of drug-like molecules based on molecular complexity and fragment contributions. *J. Cheminform*. **2009**, *1*, 8. DOI: 10.1186/1758-2946-1-8

[113] Björnsson, E. S. Hepatotoxicity by drugs: The most common implicated agents. *Int. J. Mol. Mol. Sci.* **2016**, *17(2)*, 224. DOI: 10.3390/ijms17020224

[114] Orlando, B. J.; Malkowski, M. G. Substrate-selective inhibition of cyclooxygeanse-2 by fenamic acid derivatives is dependent on peroxide tone. *J. Biol. Chem.* **2016**, *291*, 15069–15081. DOI:10.1074/jbc.M116.725713