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Design, Molecular Docking and QSAR Study for New Propionic Acid Derivatives

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Abstract

A series of conformationally constrained new Propionic acid derivatives were subjected to a synergistic integration of docking and quantitative structure-activity relationship (QSAR) techniques to optimize non-steroidal anti-inflammatory agents (NSAIDs). The study was aimed to examine the particular conditions for COX-2 inhibition selectivity among these congeners as selective cyclooxygenase-2 (COX-2) inhibitors. Key findings include the successful identification of several potent COX-2 inhibitors with improved selectivity and efficacy. Notably, certain derivatives exhibited significantly lower IC50 values and stronger binding affinities compared to existing NSAIDs. The combination of these methodologies accelerates the identification and optimization of lead compounds, facilitating efficient prediction and screening of compound libraries. This integrated approach not only expedites drug discovery but also provides a rational foundation for the design of novel molecules with desired pharmacological activities and selectivity, offering promising avenues for future therapeutic developments.

Keywords: Cyclooxygenase-2, Propionic Acid Derivative, QSAR, Non-Steroidal Anti-Inflammatory Agents (Nsaids), Molecular Docking.

Introduction

Cyclooxygenase (COX), also known as prostaglandin endoperoxide synthase, plays a crucial role in the formation of prostanoids. Among its subtypes, Cyclooxygenase-2 (COX-2) has been implicated in various diseases, including inflammation and several types of cancers[1]. Numerous successful selective COX-2 inhibitors, categorized as new-generation NSAIDs, have been created and introduced to the market. Examples include Celecoxib[2], Rofecoxib[3], Valdecoxib[4], and Parecoxib[4]. While nonsteroidal anti-inflammatory drugs (NSAIDs) that selectively inhibit COX-2 may offer a reduction in gastrointestinal side effects, they pose potential cardiovascular risks such as heart failure, myocardial infarction, and stroke[5,6]. However, the withdrawal of Rofecoxib (Vioxx™) and Valdecoxib (Bextra™) due to elevated cardiovascular side effects underscores the importance of careful development. Over the past year, there has been a big effort to enhance the search for effective lead compounds in drug development. Ligand-Based Drug Design (LBDD) and Structure-Based Drug Design (SBDD) have been pivotal in this pursuit [7]. LBDD, relying on pharmacophore and Quantitative Structure/Activity Relationship (QSAR) models, leverages knowledge for a more targeted approach to developing safer and more effective COX-2 inhibitors. The use of from established inhibitors binding to the target [8]. QSAR models establish quantitative associations between compound structures and biological activities, forming predictive models. The digital representation of QSAR, using molecular descriptors, connects molecular structure, physicochemical properties, and quantity[7,8]. SBDD, on the other hand, focuses on crafting inhibitors based on the structural attributes of the drug target. Molecular docking, a key aspect of SBDD, aids in anticipating optimal ligand binding within the target's active site[9]. Virtual screening, an integral computational methodology in drug discovery, systematically assesses chemical libraries using machine-learning algorithms and molecular descriptors to identify potential structures impacting drug targets significantly[10–12].This study's innovative combina-tion of docking and QSAR techniques accelerates the identification and optimization of lead compounds, enabling efficient prediction and screening of compound libraries. Unlike traditional methods, this integrated approach not only speeds up drug discovery but also provides a rational basis for designing novel molecules with desired pharmacological activities. This is particularly groundbreaking for NSAIDs, allowing conformational constraints in propionic acid derivatives further enhances selectivity and potency,

representing a significant advancement over existing research[13].

Strategic Development of Novel COX-2 Inhibitors: A Rational Design Approach

Through an analysis utilizing X-ray crystallography, it has been elucidated that a crucial determinant of selectivity in most Cyclooxygenase-2 (COX-2) inhibitors is a single amino acid variation, where COX-1 features isoleucine, and COX-2 contains valine[14]. This variance, specifically the smaller size of valine in COX-2 compared to isoleucine in COX-1, allows for enhanced accessibility to a side pocket within the binding site—a characteristic exploited by numerous selective COX-2 inhibitors. Notably, COX-2 possesses a hydrophobic pocket that interacts with lipophilic groups in inhibitors[15].Moreover, COX-2 inhibitors, frequently derivatives of aryl propionic acids, exhibit sensitivity to substituents at the para position of the phenyl ring, influencing both selectivity and potency[16]. Achieving an optimal size and shape for accommodation within the COX-2 binding site is critical for their activity[17].A noteworthy example, Ibuprofen (IBP), a widely available non-prescription drug globally, demonstrates distinct efficacy in alleviating inflammation and providing pain relief. The primary mechanism of action is attributed to its inhibition of COX-2 rather than COX-1. This is supported by the structural analysis of Ibuprofen bound to cyclooxygenase-2, revealing insights into its binding interactions[18]. These scientific findings contribute to the rational design of COX-2 inhibitors, emphasizing the importance of structural considerations and molecular interactions for enhanced selectivity and therapeutic efficacy. Henceforth, our continuous research endeavors are directed towards exploring the physicochemical and structurally significant fused heterocyclic ring systems, particularly focusing on conformationally restricted 1,5-diaryl pyrazoles[14,19] These compounds have demonstrated notable selective inhibition of Cyclooxygenase-2 (COX-2), a characteristic that motivates our investigation through Quantitative Structure/Activity Relationship (QSAR) analysis. The chemical library scaffold under investigation involves a central carbocyclic core with two adjacent heterocyclic rings, strategically designed for selective inhibition of COX-2. A key element for achieving this selectivity is the substitution of one aromatic ring with specific functional groups, including methoxy, methyl, dimethylamine, bromide, or nitro. This substitution pattern is crucial for imparting unique properties to the compounds and influencing their selectivity for COX-2.The presence of heterocyclic rings is essential for ensuring the proper orientation of the aromatic rings within the COX binding site, contributing to the overall pharmacological activity. Pyrrole, furan, and thiophene are commonly employed as heterocycles for this central core. For instance, **Ketorolac** is an NSAID that contains a pyrrole ring [20], **Tiaprofenic acid** contains a thiophene ring, [21]and **Tenoxicam** is an oxicam-class NSAID that contains a thienopyridine ring, a sulfur analog of a furan ring[22]. These examples highlight how the inclusion of such heterocyclic rings plays a critical role in the structural design and effectiveness of NSAIDs targeting COX-2.

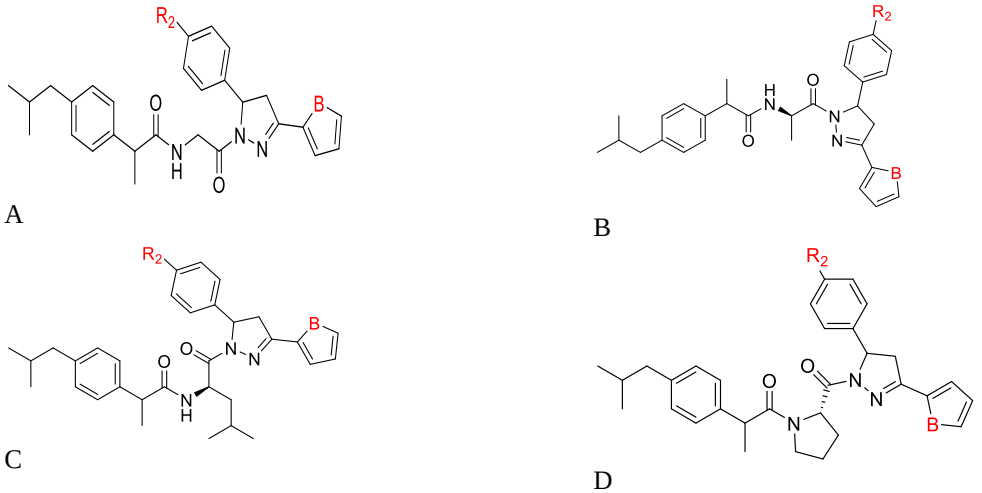
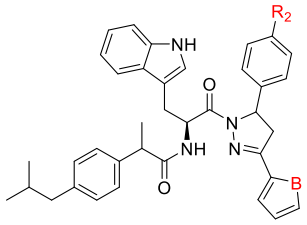


Figure 1. Scaffold chemical structure



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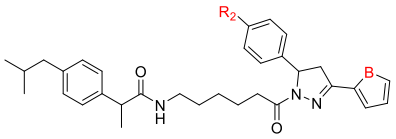

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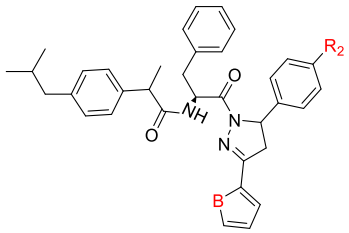

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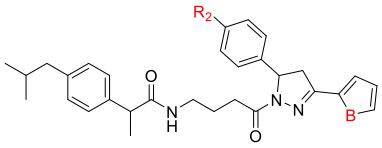

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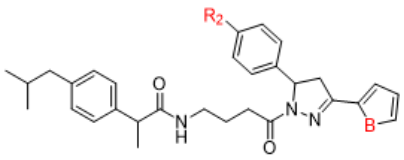

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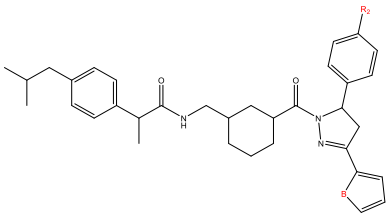

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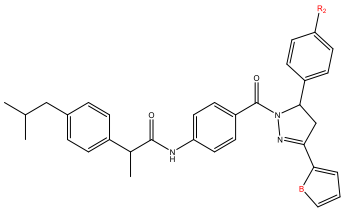

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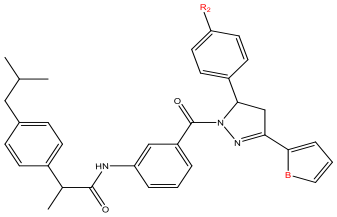

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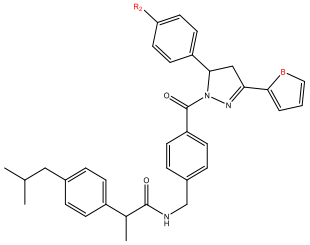

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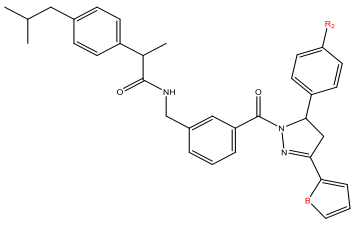

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Continued figure 1.

Materials and Methods

A synergistic methodology was applied, integrating docking and Quantitative Structure-Activity Relationship (QSAR) techniques to comprehensively analyze and optimize derivatives. All computational analyses were executed utilizing the molecular operating environment software version 2015.10, developed by the Chemical Computing Group in Montreal, Canada[23]. The construction of the final compounds was facilitated by the MOE builder module, and energy minimization was carried out employing the Merck Molecular force field (MMFF94x, with an RMSD gradient of 0.05 kcal $mol^{-1}Å^{-1}$)[24].

Molecular docking

In this study, a molecular docking approach employing in silico methods is utilized to computationally predict the binding interactions between COX-2 inhibitors and the target COX-2 protein (PDB ID: 5F1A). X-ray crystal structures of COX-2 (5F1A) from the Protein Data Bank guide the study[25-27]. The target protein's binding site is identified with MOE Sitefinder, and docking dummies are generated. The MOE-Dock program is then employed to dock the optimized compound geometry into the binding site. Initial scoring is based on the London dG method, while the final scoring method is the Rigid Receptor. This comprehensive computational approach enhances

our understanding of the binding interactions, aiding in the rational design of potential COX-2 inhibitors[26-28].

Quantitative structure - activity relationship (QSAR)modeling

In this study, a robust QSAR model employing the Partial Least Squares (PLS) method was successfully developed using the data set, compounds with known COX2 inhibitory activities, was extracted from a previous study, The study found significant correlations between COX-2 inhibitory potency and certain physicochemical and topological descriptors, particularly std_dim3 and PEOE_VSA-1 [29]. The Balaban J descriptor was key in determining both COX-1 potency and COX-2 selectivity. The results indicated that molecular size, shape, and polarizability are important for selective inhibition, corroborated by previous X-ray crystallographic studies. These insights are valuable for designing new COX-2 inhibitors [14]. The dataset was randomly divided into training and test sets at a ratio of 75:25 using MOE's RAND or Diverse subset tool. The half minimum inhibitory concentration (IC50) values were converted to the logarithmic scale (pIC50) and utilized as the dependent variable. Molecular modeling and descriptor calculation involved a meticulous selection of descriptors representing essential molecular properties and structural features for predicting COX-2 inhibitory activities and selectivity over COX-1 [25,26]. The process included converting structures to Simplified Molecular Input Line Entry System (SMILES) notation and utilizing the Contingency tool in MOE, along with employing BestFirst with CfsSubsetEval in Weka 3.8.1, contributing to the identification of significant descriptors. This advanced approach enhances the reliability of the QSAR model for predicting the inhibitory activities of the studied compounds[27]

Table 1. Name, type, and meaning of descriptors with their Significance to the model[14].

Name	Type of descriptors	Meaning of descriptors	Significance in the Models
std_dim3	Standard Dimension 3	It is an external 3D descriptor, representing the square root of the third largest eigenvalue of the covariance matrix of atomic coordinates.	A negative coefficient suggests that an increased value of std_dim3 is associated with steric hindrance of ligands toward the COX-2 enzyme.
a_Ns	Number of Sulfur Atoms	It is a descriptor related to the number of sulfur atoms in the molecule.	A positive contribution implies that a higher number of sulfur atoms is correlated with enhanced COX-2 inhibitory potency.
PEOE_VSA-1	Partial Equalization of Orbital Electronegativities Van der Waals Surface Area 1	It denotes the sum of the van der Waals surface areas of the atoms whose partial equalization of orbital electronegativities (PEOE) is in a specific range.	A negative coefficient suggests that a decrease in PEOE_VSA-1 is associated with enhanced COX-2 inhibitory activity.
Balaban J	Balaban Connectivity Index	It is a topological descriptor related to the shape of the molecules.	A negative contribution suggests that COX-1 inhibitory activity increases with a decrease in the magnitude of this highly discriminating descriptor. Conversely, a positive correlation with the COX-2 selectivity index implies that an increase in the magnitude of Balaban J improves selective inhibition of COX-2 over COX-1.
MR COX-2 inhibition.	Molecular Refractivity	It is a measure of volume and polarizability.	If MR had a positive contribution, it implies that highly polar or bulkier substituents are crucial for enhancing selective activity.
chi1V	Valence Connectivity Index of Order 1	It is a topological descriptor related to the valence connectivity of atoms.	A positive contribution suggests that an increase in the value of chi1V is linked to enhanced COX-2 selectivity.

Results and Discussion

The study aimed to enhance the COX-2 inhibitors binding affinity and selectivity for COX-2 protein. This research contributes to the development of novel COX-2 inhibitors with improved potency and selectivity against COX-2 protein.

Molecular docking

Docking Analysis Results provide as supplementary file, including the binding affinity score and key interacting residues, analyze the obtained results and draw conclusions regarding the potential effectiveness of the newly designed COX-2 inhibitors, and visualize the binding mode of the COX-2 inhibitors within the active site of the COX-2 (5F1A) protein through molecular graphics.

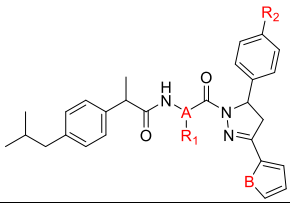
QSAR

Utilizing regression analysis for QSAR correlation, PLS was used to establish a relationship between biological activities as (dependent variable) and molecular descriptors as (independent variable). Strong correlations were found between COX-2 inhibitory potency and 2D (PEOE_VSA-1) and 3D (std_dim3) descriptors. Balaban J influenced COX-2 inhibitory regulation, emphasizing the significance of the molecule's size, shape, and polarizability. The predictive equation for COX-2 inhibition was derived based on selected descriptors.

$$PIC50(cox\_2) = 12.46355 + 0.50801 \times anS - 1.07893 \times std\_dim3 - 1.37101 \times balabanJ - 0.79672 \times chi1v - 0.46077 \times mr - 0.00054 \times PEOE\_VSA - 1.$$

- **anS:** Descriptor representing a number of sulfur atoms in the molecule.
- **std_dim3:** Descriptor related to the standard deviation of the three-dimensional dimensions, reflecting spatial distribution.
- **balabanJ:** Balaban index, a topological descriptor that quantifies the molecular connectivity.
- **chi1v:** Chi index, representing the distribution of molecular vertices and their connectivity.
- **mr:** Molecular refractivity, indicating the overall polarizability of the molecule.
- **PEOE_VSA:** Partial equalization of orbital electronegativity (PEOE) on van der Waals surface area, reflecting electronic distribution on the surface.The model's performance metrics underscore its aptitude for predicting activities of newly designed COX2 inhibitors. Notably, the elevated R^2 value at 0.745, coupled with a minimal standard error (RMSE = 0.166), and a robust predictive ability reflected in R^2_pred at 0.9554 for the test set, collectively affirm the model's suitability and effectiveness in this regard. The ranking of descriptors based on importance revealed balaban J, chi1v, and MR as key contributors.In the following table, each analog is characterized by its scaffold chemical structure and associated radical group. The Energy of Binding, expressed in Kcal/mol, is provided as a quantitative measure of the binding strength between the analogs and a specific target. Concurrently, Predicted Activity is reported, offering insights into the anticipated biological effects of each analog. The knowledge gained from the studies presented below offers structural details that are useful in directing the creation of new COX-2 inhibitors.

Table 2. Structure, Activity of Analogs

No.	chemical Scaffold	Radical group				Energy of Binding (Kcal/mol)	Predicted activity (pIC50)
							
		R1	R2	A	B		
1	a,1	-	H	CH_2	NH	-8.6	-6.64
2	a,2	-	H	CH_2	O	-8.4	-6.67
3	a,3	-	H	CH_2	S	-8.9	-7.64
4	a,4	-	OCH_3	CH_2	NH	-8.9	-7.50
5	a,5	-	OCH_3	CH_2	O	-9.8	-7.36
6	a,6	-	OCH_3	CH_2	S	-9.0	-8.28
7	a,7	-	CH_3	CH_2	NH	-9.1	-7.27
8	a,8	-	CH_3	CH_2	O	-8.8	-7.18
9	a,9	-	CH_3	CH_2	S	-9.0	-8.20
10	a,10	-	$-N(CH_3)_2$	CH_2	NH	-9.2	-8.13
11	a,11	-	$-N(CH_3)_2$	CH_2	O	-9.0	-8.01
12	a,12	-	$-N(CH_3)_2$	CH_2	S	-8.6	-8.98
13	a,13	-	Br	CH_2	NH	-9.3	-7.86

14	a,14	-	Br	CH_2	O	-9.3	-7.70
15	a,15	-	Br	CH_2	S	-8.5	-8.71
16	a,16	-	NO_2	CH_2	NH	-9.0	-7.37
17	a,17	-	NO_2	CH_2	O	-9.3	-7.32
18	a,18	-	NO_2	CH_2	S	-8.9	-8.39
19	b,1	CH_3	H	CH_2	NH	-8.6	-7.37
20	b,2	CH_3	H	CH_2	O	-8.5	-7.25
21	b,3	CH_3	H	CH_2	S	-8.4	-8.23
22	b,4	CH_3	OCH_3	CH_2	NH	-8.9	-8.11
23	b,5	CH_3	OCH_3	CH_2	O	-8.6	-7.99
24	b,6	CH_3	OCH_3	CH_2	S	-8.5	-8.89
25	b,7	CH_3	CH_3	CH_2	NH	-8.9	-7.94
26	b,8	CH_3	CH_3	CH_2	O	-8.4	-7.29
27	b,9	CH_3	CH_3	CH_2	S	-8.6	-8.80
28	b,10	CH_3	$-N(CH_3)_2$	CH_2	NH	-8.6	-8.77
29	b,11	CH_3	$-N(CH_3)_2$	CH_2	O	-9.0	-8.64
30	b,12	CH_3	$-N(CH_3)_2$	CH_2	S	-9.5	-9.65
31	b,13	CH_3	Br	CH_2	NH	-9.1	-8.46
32	b,14	CH_3	Br	CH_2	O	-8.7	-8.35
33	b,15	CH_3	Br	CH_2	S	-8.3	-8.13
34	b,16	CH_3	NO_2	CH_2	NH	-9.4	-7.84
35	b,17	CH_3	NO_2	CH_2	O	-8.8	-8.95
36	b,18	CH_3	NO_2	CH_2	S	-8.8	-9.33
37	c,1	C_4H_9	H	CH_2	NH	-7.8	-9.61
38	c,2	C_4H_9	H	CH_2	O	-6.2	-9.30
39	c,3	C_4H_9	H	CH_2	S	-7.1	-10.35
40	c,4	C_4H_9	OCH_3	CH_2	NH	-9.5	-9.91
41	c,5	C_4H_9	OCH_3	CH_2	O	-7.7	-10.40
42	c,6	C_4H_9	OCH_3	CH_2	S	-7.2	-11.02
43	c,7	C_4H_9	CH_3	CH_2	NH	-8.4	-9.83
44	c,8	C_4H_9	CH_3	CH_2	O	-6.9	-10.49
45	c,9	C_4H_9	CH_3	CH_2	S	-7.4	-11.13
46	c,10	C_4H_9	$-N(CH_3)_2$	CH_2	NH	-7.9	-10.88
47	c,11	C_4H_9	$-N(CH_3)_2$	CH_2	O	-8.2	-10.70
48	c,12	C_4H_9	$-N(CH_3)_2$	CH_2	S	-7.6	-12.03
49	c,13	C_4H_9	Br	CH_2	NH	-7.6	-10.57
50	c,14	C_4H_9	Br	CH_2	O	-8.2	-10.26
51	c,15	C_4H_9	Br	CH_2	S	-9.1	-11.63
52	c,16	C_4H_9	NO_2	CH_2	NH	-8.2	-9.92
53	c,17	C_4H_9	NO_2	CH_2	O	-7.7	-9.92
54	c,18	C_4H_9	NO_2	CH_2	S	-9.7	-10.96
55	d,1	-	H	C_4H_7	NH	-8.0	-8.29
56	d,2	-	H	C_4H_7	O	-7.2	-8.61
57	d,3	-	H	C_4H_7	S	-6.8	-9,59
58	d,4	-	OCH_3	C_4H_7	NH	-7.6	-9.48
59	d,5	-	OCH_3	C_4H_7	O	-7.5	-9,37
60	d,6	-	OCH_3	C_4H_7	S	-7.5	-10.35

61	d,7	-	CH_3	C_4H_7	NH	-8.4	-9,37
62	d,8	-	CH_3	C_4H_7	O	-7.6	-8.75
63	d,9	-	CH_3	C_4H_7	S	-9.1	-10.18
64	d,10	-	$-N(CH_3)_2$	C_4H_7	NH	-7.1	-10.17
65	d,11	-	$-N(CH_3)_2$	C_4H_7	O	-7.1	-10.07
66	d,12	-	$-N(CH_3)_2$	C_4H_7	S	-8.5	-11.02
67	d,13	-	Br	C_4H_7	NH	-7.5	-9,84
68	d,14	-	Br	C_4H_7	O	-7.1	-9.73
69	d,15	-	Br	C_4H_7	S	-7.6	-10.31
70	d,16	-	NO_2	C_4H_7	NH	-7.8	-9,.06
71	d,17	-	NO_2	C_4H_7	O	-7.7	-9,52
72	d,18	-	NO_2	C_4H_7	S	-7.8	-10,19
73	e,1	C_9H_7N	H	CH_2	NH	-7.9	-11,96
74	e,2	C_9H_7N	H	CH_2	O	-7.3	-12.15
75	e,3	C_9H_7N	H	CH_2	S	-8.0	-12.07
76	e,4	C_9H_7N	OCH_3	CH_2	NH	-7.0	-12.00
77	e,5	C_9H_7N	OCH_3	CH_2	O	-7.7	-12.59
78	e,6	C_9H_7N	OCH_3	CH_2	S	-8.2	-13.25
79	e,7	C_9H_7N	CH_3	CH_2	NH	-7.7	-12.25
80	e,8	C_9H_7N	CH_3	CH_2	O	-8.5	-12.62
81	e,9	C_9H_7N	CH_3	CH_2	S	-8.7	-13,11
82	e,10	C_9H_7N	$-N(CH_3)_2$	CH_2	NH	-8.1	-13.14
83	e,11	C_9H_7N	$-N(CH_3)_2$	CH_2	O	-7.3	-13.00
84	e,12	C_9H_7N	$-N(CH_3)_2$	CH_2	S	-7.9	-13.98
85	e,13	C_9H_7N	Br	CH_2	NH	-7.6	-12.68
86	e,14	C_9H_7N	Br	CH_2	O	-7.8	-12.98
87	e,15	C_9H_7N	Br	CH_2	S	-7.4	-13,50
88	e,16	C_9H_7N	NO_2	CH_2	NH	-7.4	-12.86
89	e,17	C_9H_7N	NO_2	CH_2	O	-8.5	-12.54
90	e,18	C_9H_7N	NO_2	CH_2	S	-8.2	-13.26
91	f,1	-	H	C_5H_{10}	NH	-9.0	-9,27
92	f,2	-	H	C_5H_{10}	O	-8.8	-9.05
93	f,3	-	H	C_5H_{10}	S	-9.5	-9,.86
94	f,4	-	OCH_3	C_5H_{10}	NH	-9.6	-9,39
95	f,5	-	OCH_3	C_5H_{10}	O	-9.6	-9,.69
96	f,6	-	OCH_3	C_5H_{10}	S	-9.5	-11.03
97	f,7	-	CH_3	C_5H_{10}	NH	-8.8	-9,82
98	f,8	-	CH_3	C_5H_{10}	O	-9.2	-9.71
99	f,9	-	CH_3	C_5H_{10}	S	-9.2	-10.69
100	f,10	-	$-N(CH_3)_2$	C_5H_{10}	NH	-9.3	-10.14
101	f,11	-	$-N(CH_3)_2$	C_5H_{10}	O	-9.2	-16.05
102	f,12	-	$-N(CH_3)_2$	C_5H_{10}	S	-10.3	-11.50
103	f,13	-	Br	C_5H_{10}	NH	-9.0	-10.32
104	f,14	-	Br	C_5H_{10}	O	-9.3	-10.20
105	f,15	-	Br	C_5H_{10}	S	-9.4	-11.17
106	f,16	-	NO_2	C_5H_{10}	NH	-9.7	-9,32
107	f,17	-	NO_2	C_5H_{10}	O	-10.0	-9,99

108	f,18	-	NO_2	C_5H_{10}	S	-9.5	-10.91
109	g,1	C_7H_7	H	CH_2	NH	-7.8	-10.12
110	g,2	C_7H_7	H	CH_2	O	-7.7	-10.92
111	g,3	C_7H_7	H	CH_2	S	-8.5	-10.57
112	g,4	C_7H_7	OCH_3	CH_2	NH	-8.5	-10.80
113	g,5	C_7H_7	OCH_3	CH_2	O	-8.2	-11.66
114	g,6	C_7H_7	OCH_3	CH_2	S	-7.5	-10.79
115	g,7	C_7H_7	CH_3	CH_2	NH	-9.3	-10.54
116	g,8	C_7H_7	CH_3	CH_2	O	-8.6	-11.67
117	g,9	C_7H_7	CH_3	CH_2	S	-8.9	-11.89
118	g,10	C_7H_7	$-N(CH_3)_2$	CH_2	NH	-7.8	-11.60
119	g,11	C_7H_7	$-N(CH_3)_2$	CH_2	O	-7.9	-12.72
120	g,12	C_7H_7	$-N(CH_3)_2$	CH_2	S	-8.5	-11.38
121	g,13	C_7H_7	Br	CH_2	NH	-7.7	-11.01
122	g,14	C_7H_7	Br	CH_2	O	-8.4	-12.25
123	g,15	C_7H_7	Br	CH_2	S	-7.5	-11.11
124	g,16	C_7H_7	NO_2	CH_2	NH	-8.2	-10.92
125	g,17	C_7H_7	NO_2	CH_2	O	-7.5	-11.70
126	g,18	C_7H_7	NO_2	CH_2	S	-8.7	-9.87
127	h,1	-	H	C_3H_6	NH	-8.6	-7.91
128	h,2	-	H	C_3H_6	O	-8.7	-7.88
129	h,3	-	H	$C3H_6$	S	-8.6	-8.80
130	h,4	-	OCH_3	C_3H_6	NH	-9.2	-8.27
131	h,5	-	OCH_3	C_3H_6	O	-8. 5	-8.11
132	h,6	-	OCH_3	C_3H_6	S	-8.9	-9.25
133	h,7	-	CH_3	C_3H_6	NH	-9.1	-8.61
134	h,8	-	CH_3	C_3H_6	O	-8.9	-8.56
135	h,9	-	CH_3	C_3H_6	S	-8.6	-9.50
136	h,10	-	$-N(CH_3)_2$	C_3H_6	NH	-8.8	-9.05
137	h,11	-	$-N(CH_3)_2$	C_3H_6	O	-9.4	-8.90
138	h,12	-	$-N(CH_3)_2$	C_3H_6	S	-9.3	-9.85
139	h,13	-	Br	C_3H_6	NH	-8.6	-9.04
140	h,14	-	Br	C_3H_6	O	-8.9	-8.97
141	h,15	-	Br	C_3H_6	S	-8.8	-9.01
142	h,16	-	NO_2	C_3H_6	NH	-8.5	-8.31
143	h,17	-	NO_2	C_3H_6	O	-9.2	-8.12
144	h,18	-	NO_2	C_3H_6	S	-9.7	-9.12
145	i,1	-	H	C_3H_6	NH	-9.4	-8.02
146	i,2	-	H	C_3H_6	O	-8.5	-7.81
147	i,3	-	H	C_3H_6	S	-8.2	-8.79
148	i,4	-	OCH_3	C_3H_6	NH	-9.3	-8.38
149	i,5	-	OCH_3	C_3H_6	O	-8.5	-8.09
150	i,6	-	OCH_3	C_3H_6	S	-9.4	-9.07
151	i,7	-	CH_3	C_3H_6	NH	-8.6	-8.54
152	i,8	-	CH_3	C_3H_6	O	-9.2	-8.46
153	i,9	-	CH_3	C_3H_6	S	-8.8	-9.32
154	i,10	-	$-N(CH_3)_2$	C_3H_6	NH	-9.7	-8.99

155	i,11	-	$-N(CH_3)_2$	C_3H_6	O	-8.6	-8.88
156	i,12	-	$-N(CH_3)_2$	C_3H_6	S	-8.5	-9.83
157	i,13	-	Br	C_3H_6	NH	-9.6	-8.96
158	i,14	-	Br	C_3H_6	O	-8.4	-8.94
159	i,15	-	Br	C_3H_6	S	-9.0	-9.81
160	i,16	-	NO_2	C_3H_6	NH	-8.6	-8.99
161	i,17	-	NO_2	C_3H_6	O	-8.5	-8.09
162	i,18	-	NO_2	C_3H_6	S	-9.5	-9.10
163	j,1	-	H	C_7H_{12}	NH	-8.5	-10.36
164	j,2	-	H	C_7H_{12}	O	-8.8	-10.15
165	j,3	-	H	C_7H1_2	S	-8.8	-10.76
166	j,4	-	OCH_3	C_7H_{12}	NH	-8.8	-10.88
167	j,5	-	OCH_3	C_7H_{12}	O	-9.3	-10.74
168	j,6	-	OCH_3	C_7H_{12}	S	-9.1	-11.69
169	j,7	-	CH_3	C_7H_{12}	NH	-10.0	-10.71
170	j,8	-	CH_3	C_7H_{12}	O	-7.9	-10.56
171	j,9	-	CH_3	C_7H_{12}	S	-8.4	-11.57
172	j,10	-	$-N(CH_3)_2$	C_7H_{12}	NH	-9.4	-11.50
173	j,11	-	$-N(CH_3)_2$	C_7H_{12}	O	-9.5	-11.35
174	j,12	-	$-N(CH_3)_2$	C_7H_{12}	S	-10.3	-12.30
175	j,13	-	Br	C_7H_{12}	NH	-9.1	-11.35
176	j,14	-	Br	C_7H_12	O	-8.9	-11.21
177	j,15	-	Br	C_7H_{12}	S	-8.9	-12.11
178	j,16	-	NO_2	C_7H_{12}	NH	-10.8	-10.80
179	j,17	-	NO_2	C_7H_{12}	O	-8.8	-10.41
180	j,18	-	NO_2	C_7H_{12}	S	-9.2	-11.67
181	k,1	-	H	C_6H_4	NH	-8.3	-8.75
182	k,2	-	H	C_6H_4	O	-8.6	-8.62
183	k,3	-	H	C_6H_4	S	-9.1	-9.60
184	k,4	-	OCH_3	C_6H_4	NH	-9.0	-10.00
185	k,5	-	OCH_3	C_6H_4	O	-8.5	-9.71
186	k,6	-	OCH_3	C_6H_4	S	-8.1	-11.03
187	k,7	-	CH_3	C_6H_4	NH	-10.4	-9.40
188	k,8	-	CH_3	C_6H_4	O	-8.9	-9.24
189	k,9	-	CH_3	$C6H_4$	S	-9.3	-10.31
190	k,10	-	$-N(CH_3)_2$	C_6H_4	NH	-8.8	-10.42
191	k,11	-	$-N(CH_3)_2$	C_6H_4	O	-8.4	-10.24
192	k,12	-	$-N(CH_3)_2$	C_6H_4	S	-9.2	-11.68
193	k,13	-	Br	C_6H_4	NH	-9.2	-9.49
194	k,14	-	Br	C_6H_4	O	-9.3	-9.77
195	k,15	-	Br	C_6H_4	S	-9.3	-10.72
196	k,16	-	NO_2	C_6H_4	NH	-8.3	-9.83
197	k,17	-	NO_2	C_6H_4	O	-8.4	-9.56
198	k,18	-	NO_2	C_6H_4	S	-8.6	-10.75
199	l,1	-	H	C_6H_4	NH	-9.6	-8.35
200	l,2	-	H	C_6H_4	O	-8.9	-8.22
201	l,3	-	H	C_6H_4	S	-9.4	-9.22

202	l,4	-	OCH_3	C_6H_4	NH	-9.6	-9.18
203	l,5	-	OCH_3	C_6H_4	O	-9.5	-9.21
204	l,6	-	OCH_3	C_6H_4	S	-9.8	-9.96
205	l,7	-	CH_3	C_6H_4	NH	-9.4	-8.95
206	l,8	-	CH_3	C_6H_4	O	-9.5	-8.79
207	l,9	-	CH_3	C_6H_4	S	-9.0	-9.76
208	l,10	-	$-N(CH_3)_2$	C_6H_4	NH	-9.1	-9.88
209	l,11	-	$-N(CH_3)_2$	C_6H_4	O	-9.6	-9.59
210	l,12	-	$-N(CH_3)_2$	C_6H_4	S	-9.0	-10.65
211	l,13	-	Br	C_6H_4	NH	-9.1	-9.50
212	l,14	-	Br	C_6H_4	O	-8.8	-9.25
213	l,15	-	Br	C_6H_4	S	-9.6	-9.18
214	l,16	-	NO_2	C_6H_4	NH	-9.9	-8.97
215	l,17	-	NO_2	C_6H_4	O	-9.7	-9.91
216	l,18	-	NO_2	C_6H_4	S	-9.1	-10.37
217	m,1	-	H	C_7H_6	NH	-8.7	-6.80
218	m,2	-	H	C_7H_6	O	-8.2	-6.67
219	m,3	-	H	C_7H_6	S	-8.3	-7.67
220	m,4	-	OCH_3	C_7H_6	NH	-8.0	-7.47
221	m,5	-	OCH_3	C_7H_6	O	-8.6	-7.38
222	m,6	-	OCH_3	C_7H_6	S	-8.9	-8.32
223	m,7	-	CH_3	C_7H_6	NH	-8.4	-7.29
224	m,8	-	CH_3	C_7H_6	O	-9.0	-7.08
225	m,9	-	CH_3	C_7H_6	S	-8.7	-8.13
226	m,10	-	$-N(CH_3)_2$	C_7H_6	NH	-8.5	-8.10
227	m,11	-	$-N(CH_3)_2$	C_7H_6	O	-9.0	-7.98
228	m,12	-	$-N(CH_3)_2$	C_7H_6	S	-9.9	-8.89
229	m,13	-	Br	C_7H_6	NH	-8.0	-7.67
230	m,14	-	Br	C_7H_6	O	-8.3	-7.77
231	m,15	-	Br	C_7H_6	S	-8.7	-8.65
232	m,16	-	NO_2	C_7H_6	NH	-9.0	-7.40
233	m,17	-	NO_2	C_7H_6	O	-8.8	-7.29
234	m,18	-	NO_2	C_7H_6	S	-8.5	-8.22
235	n,1	-	H	C_7H_6	NH	-9.2	-9.04
236	n,2	-	H	C_7H_6	O	-8.6	-8.92
237	n,3	-	H	C_7H_6	S	-8.9	-9.88
238	n,4	-	OCH_3	C_7H_6	NH	-9.8	-9.99
239	n,5	-	OCH_3	C_7H_6	O	-9.2	-9.77
240	n,6	-	OCH_3	C_7H_6	S	-8.6	-11.25
241	n,7	-	CH_3	C_7H_6	NH	-9.6	-9.74
242	n,8	-	CH_3	C_7H_6	O	-9.5	-9.60
243	n,9	-	CH_3	C_7H_6	S	-9.7	-10.59
244	n,10	-	$-N(CH_3)_2$	C_7H_6	NH	-10.2	-10.98
245	n,11	-	$-N(CH_3)_2$	C_7H_6	O	-10.3	-10.77
246	n,12	-	$-N(CH_3)_2$	C_7H_6	S	-10.0	-11.86
247	n,13	-	Br	C_7H_6	NH	-8.9	-10.16
248	n,14	-	Br	C_7H_6	O	-8.5	-10.27

249	n,15	-	Br	C_7H_6	S	-10.5	-11.87
250	n,16	-	NO_2	C_7H_6	NH	-9.2	-10.32
251	n,17	-	NO_2	C_7H_6	O	-7.7	-10.09
252	n,18	-	NO_2	C_7H_6	S	-9.4	-11.09
253	1std					-5.9	0.97

This comprehensive compilation facilitates a systematic assessment of the relationships between chemical structure, radical group variations, binding energetics, and predicted activities for the examined analogs.

The strategic substitution of specific groups and the choice of a suitable central heterocyclic core are crucial considerations in the design of compounds aimed at selectively inhibiting COX-2. In molecular docking studies, the Energy of Binding (Kcal/mol) represents the strength of interaction between a ligand (molecule) and its target. A lower energy of binding, indicated by more negative values, generally suggests a stronger binding affinity between the ligand and the target. In QSAR study negative pIC50 value as predicted activities for the examined analogs are generally associated with a more potent drug, as it implies a lower concentration needed to produce a biological effect[7,28]. These results are consistent with the previous X-ray crystallographic investigations into the binding mechanisms of these COX-2 inhibitors that are selective. The data suggests that the nature and combination of substituents at the R2, A, and B positions significantly influence the predicted radical scavenging activity of the analogs. Electron-withdrawing groups like Br and NO_2 tend to enhance activity, while electron-donating groups like CH_3 and $-N(CH_3)_2$ show varying effects depending on their specific interactions. The highest activity is observed with (compound no. 174) the combination of $-N(CH_3)_2$ at R2, C_7H_{12} at A, and S at B, while the lowest activity is seen with (compound no.1) H at R2, CH_2 at A, and NH at B. Thiophene derivatives have emerged as noteworthy candidates, emphasizing the importance of these structural features in the development of COX-2 inhibitors.

Conclusion

The investigation focused on the importance of specific structural features—such as conformational constraints and strategic substitutions (e.g., dimethylamine, bromide, and nitro groups)—in influencing the pharmacological profiles of the derivatives. By employing a synergistic integration of docking and QSAR techniques, the research aligns with current efforts to enhance COX-2 selectivity through advanced computational methods. It highlights a significant shift from traditional approaches, offering deeper insights into how these structural elements influence inhibitor efficacy. This integrated approach not only validates existing findings but also accelerates the discovery and optimization of selective COX-2 inhibitors, providing a systematic and rational framework for designing more effective and selective NSAIDs [29,30]. and paving the way for future therapeutic advancements.

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Conflicts of Interest

The authors declare no conflict of interest.

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Ethics Statements

It does not need ethical approval from an ethics committee

Author Contribution

All authors contribute for data collection, analysis and interpretation of results and approved the final version of the manuscript.

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التصميم والربط الجزيئي والعلاقة الكمية بين التركيب والفعالية الدوائية لمشتقات جديدة من حمض البروبيونيك

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[١،٢،٣] قسم الكيمياء الصيدلانية ،كلية الصيدلة ، جامعة بغداد ،بغداد ،العراق.

الخلاصة

تضمنت الدراسة سلسلة من المشتقات الجديدة المقيدة لحمض البروبيونيك، حيث تم تطبيق تكامل تآزري بين تقنيات الربط الجزيئي وتحليل العلاقة الكمية بين التركيب والفعالية الدوائية لتحسين فعالية هذه المركبات كمضادات للالتهابات غير الستيرويدية. كان الهدف الرئيسي للدراسة هو تقييم الظروف التي تؤثر على انتقائية تثبيط إنزيم السيكلوأوكسجيناز-٢ وتحديد مثبطات انتقائية لهذا الإنزيم. وتضمنت النتائج الرئيسية تحديد عدة مثبطات فعالة للإنزيم، أظهرت انتقائية وفعالية محسنة مقارنة بالمضادات الحالية. يساهم دمج هذه الطرق في تسريع عملية تحديد المركبات الفعالة وتحسينها، مما يعزز التنبؤ الفعّال وفحص مكتبة المركبات. ويوفر هذا النهج المتكامل أساسًا منطقيًا لتصميم جزيئات جديدة تتمتع بفعالية دوائية مرغوبة وانتقائية، مما يفتح آفاقًا واعدة للتطورات العلاجية المستقبلية.

الكلمات المفتاحية: إنزيم السيكلوأوكسيجينيز -٢، مشتقات حمض البروبيونيك ، العلاقة الكمية بين التركيب والفعالية الدوائية ،عوامل مضادات الالتهاب غير الستيرويدية ،الربط الجزيئي.