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CELECOXIB–CHALCONE HYBRIDIZATION GENERATES DUAL COX-2/FACTOR XA INHIBITORS WITH ENHANCED COX-2 SELECTIVITY: AN *In-silico* DRUG DESIGN STUDY

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ABSTRACT

Anti-inflammatory selective cyclooxygenase-2 (COX-2) inhibitors have minimal gastrointestinal toxicity compared with non-selective NSAIDs; however, cardiovascular concerns associated with selective COX-2 inhibitors highlight the need for safer anti-inflammatory agents. This study aimed to design celecoxib-based chalcone derivatives with enhanced COX-2 selectivity and potential factor Xa inhibitory activity. Fifty derivatives were rationally designed by introducing an α,β-unsaturated carbonyl linker between the phenyl and pyrazole rings and subjected to in-silico evaluation using toxicity, physicochemical, ADME, and molecular docking studies against COX-2, COX-1, and anticoagulant factor (factor Xa). Of the 50 derivatives, 45 showed stronger predicted COX-2 binding than celecoxib, with reduced COX-1 interaction, while several exhibited favourable factor Xa affinity. The study has predicted lead molecules for the development of safer anti-inflammatory therapeutics with reduced cardiovascular risk. Thus, the present work contributes to the advancement of multitarget drug design strategies and supports United Nations Sustainable Development Goal (SDG) 3: Good Health and Well-being.

Keywords: Celecoxib Derivatives, Chalcone, COX-2 inhibitors, Factor Xa, Anticoagulant, Molecular Docking, Drug Design, Drug Discovery

INTRODUCTION

Inflammation is a complex biological response to tissue injury and infection, mediated by a network of cytokines, chemokines, and lipid-derived mediators. Among these, prostaglandins, which are biosynthesised by cyclooxygenase (COX) enzymes, play an important central role in inflammatory processes. Two major isoforms of cyclooxygenase have been characterised: COX-1, which is involved in physiological homeostasis such as gastric mucosal protection and platelet aggregation, and COX-2, an inducible isoform that is primarily responsible for the biosynthesis of pro-inflammatory prostaglandins.[1] Although selective COX-2 inhibitors such as celecoxib exhibit minimal gastrointestinal toxicity, the associated cardiovascular risk and thrombotic events restrict their long-term use.[2-4] Hence, the development of a new generation of safer COX-2 selective inhibitors having an additional virtue of anticoagulant activity represents an important unmet therapeutic need. Scientific studies have established that platelet aggregation and thromboxane A_2 synthesis are closely associated with COX activity and inflammatory pathways.[5] Recent advances in medicinal chemistry are now showing an inclination for the development of multi-target directed ligands (MTDLs) having the capability of modulating multiple disease-associated pathways, thereby improving therapeutic efficacy while minimising adverse effects.[6-9] Although numerous celecoxib analogues and chalcone derivatives have individually been reported as anti-inflammatory agents, and many chalcone analogues have demonstrated anticoagulant or factor Xa inhibitory activity, the systematic hybridisation of the celecoxib scaffold with a chalcone pharmacophore

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for the simultaneous optimization of COX-2 selectivity and factor Xa inhibition has remained largely unexplored.[10-17] Incorporation of a chalcone pharmacophore into bioactive scaffolds has been shown to enhance biological activity through synergistic or additive mechanisms.[18-21] Comprehensive studies integrating validated molecular docking, toxicity prediction, physicochemical characterisation, and SwissADME profiling to investigate such hybrid molecules are scarce. This constitutes an important research gap in the design of next-generation anti-inflammatory drugs.

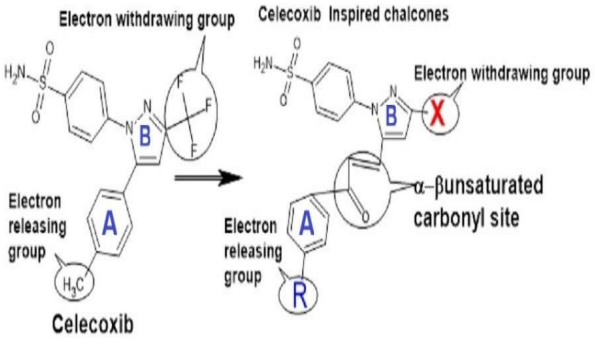


Fig.-1: Design of ligands

To address this gap, in the present study, celecoxib-based chalcones are rationally designed by inserting an α, β-unsaturated carbonyl linker between the phenyl ring (ring A) and the pyrazole ring (ring B) (Fig.-1) of the celecoxib core, followed by systematic electronic modulation through electron-releasing and electron withdrawing groups on ring A and on ring B. Fifty celecoxib–chalcone hybrid derivatives were designed and comprehensively evaluated using validated molecular docking against COX-2 (3LN1), COX-1 (1EQG), and coagulation factor Xa (1IQM), together with toxicity prediction, physicochemical characterization, and SwissADME analysis. The study further aimed to establish structure–activity relationships governing COX-2 selectivity and anticoagulant potential while identifying promising lead molecules for future synthesis and biological evaluation. The present investigation contributes to the growing field of multitarget drug discovery by providing a rational design strategy for dual COX-2/factor Xa inhibitors with favourable predicted pharmacokinetic and safety profiles. The findings are expected to facilitate future experimental validation and lead optimisation to develop anti-inflammatory therapeutics with reduced cardiovascular risk. In addition, the present research study supports the United Nations Sustainable Development Goal SDG-3: Good Health and Well-being, which emphasises the development of safer and more effective medicines through innovative pharmaceutical research.

EXPERIMENTAL

Material and Methods

Toxicity and physicochemical properties were predicted with Osiris Property Explorer. Pharmacokinetic parameters were evaluated using the Swiss-ADME online server. Chemical structures were drawn using ChemSketch, and energy minimisation was performed with Discovery Studio Visualizer. The target proteins cyclooxygenase-2 (3LN1), cyclooxygenase-1 (1EQG), and coagulation factor Xa (1IQM), co-crystallised with the ligands celecoxib, ibuprofen, and M54471, respectively, were obtained from the Protein Data Bank; the bond interactions of these ligands with their respective target proteins, as reported in the Protein Data Bank, are shown in Fig.- 2. Molecular docking studies were conducted using MGL Tools, including AutoGrid 4.0 and AutoDock 4.0, and the bond interactions between the ligand and protein were analysed using Discovery Studio software.

Molecular Docking

Protein Structure Preparation for Molecular Docking

The three-dimensional crystallographic structures of the target macromolecules were obtained in PDB format. Co-crystallised ligands and the entrapped water molecules were removed using Discovery Studio

Visualizer. Protein preparation for docking involved the addition of polar hydrogens, merging of non-polar hydrogens, and assignment of Kollman charges, followed by conversion of the processed structures from PDB to PDBQT format, using the AutoDock 4 platform.[22-25]

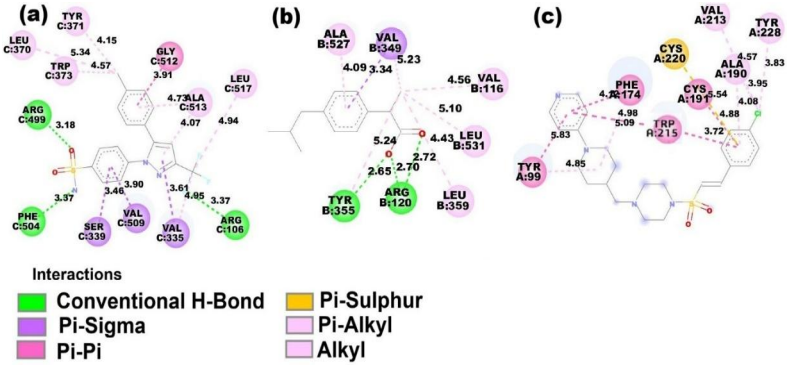


Fig.-2: Reported in Protein Data Bank, Interactions of Co-Crystallized Ligands (a) Celecoxib with 3LN1 (b) Ibuprofen with 1EQG (c) M54471-1IQM

Preparation of AutoDock Type Ligands

Ligand structures were drawn using ChemSketch and energy minimised with Discovery Studio Visualizer. The optimised three-dimensional ligand structures were saved in PDB format. Ligand preparation for docking was performed using AutoDock 4 by assigning AD4 atom types, merging non-polar hydrogens, and adding Gasteiger charges, after which the structures were converted to PDBQT format.[22-25]

Validation of Docking Protocol

The molecular docking process was validated by employing the re-docking approach. The ligands co-crystallised, namely celecoxib, ibuprofen, and M54471, were extracted from their respective protein–ligand complexes (PDB IDs: 3LN1, 1EQG, and 1IQM) using Discovery Studio software and saved in PDB file format. Each ligand was subsequently docked into the corresponding active site of its target protein using AutoDock 4 under varying grid box dimensions and grid centre coordinates. The accuracy of docking was evaluated by the root mean square deviation (RMSD) between the ligand's redocked pose and its experimentally determined co-crystallised pose. Grid parameters yielding the lowest RMSD values ($\leq$ 2.0 Å) were considered optimal and were selected for subsequent docking studies of the designed ligand library, thereby confirming the reliability of the docking methodology.[26]

Docking Setup for Macromolecule 3LN1, 1EQG, 1IQM

Molecular docking studies were performed for the macromolecules 3LN1, 1EQG, and 1IQM using AutoDock 4 implemented in the MGLTools suite. For 3LN1, a three-dimensional grid box comprising 100 × 90 × 90 grid points was defined with a 0.375 Å grid spacing and centered at x = 64.892, y = −45.465, and z = 54.542, whereas 1EQG was docked using a cubic grid of 64 × 64 × 64 points centered at x = 65.892, y = 28.216, and z = 182.438, and 1IQM employed a grid of 104 × 98 × 126 points centered at x = 13.227, y = 24.618, and z = 22.827, all maintaining the same grid spacing. Grid parameter files were generated for each macromolecule, and the corresponding grid maps were produced using AutoGrid 4. For each ligand, docking parameters were configured using the genetic algorithm, and an elitism value of 1 was applied during cluster analysis. Each docking experiment was conducted with 100 independent genetic algorithm runs, resulting in the generation of docking log files that were subsequently analysed to evaluate binding conformations and interactions. Docking outcomes, including binding free energy and inhibition constant, were obtained from the docking log files of the ligands. The optimal docked conformer–macromolecule complexes were saved in PDB format and subsequently visualised using Discovery Studio to analyze the binding interactions involved.[22-25]

RESULTS AND DISCUSSION

Selective inhibition of cyclooxygenase-2 (COX-2) remains a major strategy for developing safer anti-inflammatory agents with reduced gastrointestinal toxicity compared to non-selective NSAIDs[2]. However, the cardiovascular and thrombotic concerns associated with selective COX-2 inhibition have stimulated

interest in alternative or multitarget strategies capable of simultaneously modulating inflammatory and coagulation pathways.[1-5] In this context, the present study investigated whether molecular hybridisation of the celecoxib scaffold with a chalcone pharmacophore could improve COX-2 selectivity while introducing additional factor Xa inhibitory potential. The results obtained from toxicity prediction, ADME profiling, and validated molecular docking provide complementary evidence supporting the potential of this hybridisation strategy.

In silico Toxicity Prediction

According to the OSIRIS assessment (Table-1), all compounds exhibited a favourable predicted toxicity profile, with no mutagenic, tumorigenic, or irritant alerts. The limited reproductive-toxicity alerts observed for the acetyl-substituted members also suggest that substituent selection may influence the overall toxicity profile and therefore requires consideration during subsequent lead optimization. This observation supports the suitability of the chalcone moiety as a molecular-hybridisation element in the present series (Fig.-1), although experimental validation is required.[27]

Table-1: *In-silico* Toxicity Profile

S. No.	Derivative	X =	Mutagenicity[a]	Tumorigenicity[a]	Irritation potential[a]	Reproductive toxicity[a]
			R= Methyl (4-Methyl Series)			
1	C1	Triflоromethyl	N	N	N	N
2	C2	Floro	N	N	N	N
3	C3	Chloro	N	N	N	N
4	C4	Acetyl	N	N	N	Y
5	C5	Carbamoyl	N	N	N	N
6	C6	Amino-imino	N	N	N	N
7	C7	Cyano	N	N	N	N
8	C8	Ethynyl	N	N	N	N
9	C9	1-Methylene-ethyl	N	N	N	N
10	C10	Methyl-imino	N	N	N	N
		X =	R= Ethyl (4-Ethyl Series)			
11	C11	Triflоromethyl	N	N	N	N
12	C12	Floro	N	N	N	N
13	C13	Chloro	N	N	N	N
14	C14	Acetyl	N	N	N	Y
15	C15	Carbamoyl	N	N	N	N
16	C16	Amino-imino	N	N	N	N
17	C17	Cyano	N	N	N	N
18	C18	Ethynyl	N	N	N	N
19	C19	1-Methylene-ethyl	N	N	N	N
20	C20	Methyl-imino	N	N	N	N
		X =	R= Propyl (4-Propyl Series)			
21	C21	Triflоromethyl	N	N	N	N
22	C22	Floro	N	N	N	N
23	C23	Chloro	N	N	N	N
24	C24	Acetyl	N	N	N	Y
25	C25	Carbamoyl	N	N	N	N
26	C26	Amino-imino	N	N	N	N
27	C27	Cyano	N	N	N	N
28	C28	Ethynyl	N	N	N	N
29	C29	1-Methylene-ethyl	N	N	N	N
30	C30	Methyl-imino	N	N	N	N
		X=	R= Isopropyl (4-Isopropyl Series)			
31	C31	Triflоromethyl	N	N	N	N
32	C32	Floro	N	N	N	N

33	C33	Chloro	N	N	N	N
34	C34	Acetyl	N	N	N	Y
35	C35	Carbamoyl	N	N	N	N
36	C36	Amino-imino	N	N	N	N
37	C37	Cyano	N	N	N	N
38	C38	Ethynyl	N	N	N	N
39	C39	1-Methylene-ethyl	N	N	N	N
40	C40	Methyl-imino	N	N	N	N
		X=	R = 4-Methoxy(4-Methoxy Series)			
41	C41	Triflоromethyl	N	N	N	N
42	C42	Floro	N	N	N	N
43	C43	Chloro	N	N	N	N
44	C44	Acetyl	N	N	N	Y
45	C45	Carbamoyl	N	N	N	N
46	C46	Amino-imino	N	N	N	N
47	C47	Cyano	N	N	N	N
48	C48	Ethynyl	N	N	N	N
49	C49	1-Methylene-ethyl	N	N	N	N
50	C50	Methyl-imino	N	N	N	N
Celecoxib (Reference)			N	N	N	N

[a] N = No; Y = Yes

Among the 50 designed ligands, 48 have shown higher drug score values in comparison to the reference celecoxib (Table-2), whereas C21 and C31 have equal drug scores to that of celecoxib, indicating overall favorable drug-likeness in the designed ligand library.

Table-2: Drug Score Prediction

Derivative	cLogP	Solubility (LogS)	Mol.wt	Total polar surface area	Drug-likeness	Drug Score
C1	2.54	-4.64	435	103.4	-7.01	0.32
C2	2.09	-4.68	385	103.4	3.34	0.68
C3	2.34	-4.34	401	103.4	4.71	0.71
C4	1.56	-4.55	409	120.5	5.15	0.41
C5	0.78	-3.95	410	146.5	5.8	0.75
C6	0.38	-3.13	409	153.3	4.88	0.81
C7	1.52	-4.64	392	127.2	0.45	0.56
C8	1.79	-3.3	391	103.4	4.73	0.81
C9	2.61	-4.4	407	103.4	-6.34	0.35
C10	1.16	-3.73	408	127.2	4.96	0.77
C11	2.95	-4.8	449	103.4	-7.91	0.3
C12	2.5	-4.84	399	103.4	2.44	0.63
C13	2.75	-4.5	415	103.4	3.82	0.66
C14	1.98	-4.71	423	120.5	4.27	0.39
C15	1.19	-4.11	424	146.5	4.93	0.72
C16	0.79	-3.29	423	153.3	3.99	0.78
C17	1.94	-4.8	406	127.2	-0.45	0.46
C18	2.21	-3.46	405	103.4	3.83	0.77
C19	3.03	-4.56	421	103.4	-7.23	0.33
C20	1.58	-3.89	422	127.2	4.07	0.73
C21	3.41	-5.07	463	103.4	-9.81	0.27
C22	2.96	-5.11	413	103.4	0.54	0.49
C23	3.21	-4.77	429	103.4	1.93	0.58
C24	2.43	-4.98	437	120.5	2.39	0.35

Derivative	cLogP	Solubility (LogS)	Mol.wt	Total polar surface area	Drug-likeness	Drug Score
C25	1.65	-4.38	438	146.5	3.03	0.66
C26	1.25	-3.56	437	153.3	2.1	0.71
C27	2.39	-5.07	420	127.2	-2.34	0.34
C28	2.66	-3.73	419	103.4	1.94	0.69
C29	3.48	-4.83	435	103.4	-9.12	0.3
C30	2.03	-4.16	436	127.2	2.18	0.66
C31	3.38	-5.17	463	103.4	-10.04	0.27
C32	2.93	-5.21	413	103.4	0.31	0.47
C33	3.18	-4.87	429	103.4	1.7	0.56
C34	2.4	-5.08	437	120.5	2.08	0.34
C35	1.62	-4.48	438	146.5	2.8	0.65
C36	1.22	-3.66	437	153.3	1.87	0.69
C37	2.37	-5.17	420	127.2	-2.57	0.33
C38	2.63	-3.83	419	103.4	1.7	0.67
C39	3.45	-4.93	435	103.4	-9.43	0.29
C40	2	-4.26	436	127.2	1.87	0.64
C41	2.12	-4.32	451	112.6	-5.94	0.33
C42	1.67	-4.35	401	112.6	4.41	0.71
C43	1.92	-4.01	417	112.6	5.79	0.73
C44	1.15	-4.22	425	129.7	6.25	0.43
C45	0.36	-3.63	426	155.7	6.88	0.76
C46	-0.04	-2.81	425	162.5	5.96	0.81
C47	1.11	-4.31	408	136.4	1.52	0.66
C48	1.38	-2.97	407	112.6	5.8	0.81
C49	2.2	-4.07	423	112.6	-5.27	0.36
C50	0.75	-3.4	424	136.5	6.03	0.78
Celecoxib (Reference)	1.77	-6.87	317	73.23	-4.46	0.27

SwissADME Analysis

SwissADME predictions (Table-3) revealed that the designed ligands, being non- BBB permeant, would most probably be devoid of CNS-related adverse effects, a concern with some NSAIDs.[28] None of the designed ligands were predicted as P-gp substrates, suggesting that the ligands would not undergo transporter-mediated efflux, which would favour oral absorption and intracellular drug availability that may lead to enhanced anti-inflammatory activity.[29] All the compounds complied with "Lipinski's rule of five", indicating good bioavailability, and showed zero PAINS alerts, indicating the absence of problematic promiscuous substructures. CYP inhibition profiles showed predominant CYP2C9 inhibition, similar to celecoxib, aligning with known metabolic pathways of selective COX-2 inhibitors.[13] Overall, these findings support the drug-like and acceptable ADME characteristics of the designed compounds for further lead optimisation.

Molecular Docking Investigations

Docking Validation

The validity of the docking experiments was confirmed by comparing the co-crystallised and re-docked conformations of the reference ligands. Celecoxib exhibited an RMSD of 1.224 Å between its co-crystallised pose and the re-docked conformation within the 3LN1 binding site. Similarly, ibuprofen showed an RMSD of 1.365 Å upon re-docking into the active site of 1EQG, while the RMSD of 1.184 Å was observed between the ligand M54471 and its re-docked pose in 1IQM (Fig.-3).

These low RMSD values (below 2 Å) indicate a high degree of concordance between the docked poses and their respective experimentally determined conformations, thereby validating the docking methodology employed.[26]

Table-3: ADME Profile Predictions

Derivative	Gastrointestinal absorption[b]	BBB permeability[b]	P-glycoprotein substrate[b]	Cytochrome-P450(CYP)enzyme- Type					Lipinski rule of five[b]	Bioavailability Score	PAINS alert
				1A2 inhibiton[b]	2C19 inhibiton[b]	2C9 inhibiton[b]	2D6 inhibiton[b]	3A4 inhibiton[b]			
C1	L	N	N	N	Y	Y	N	N	Y	0.55	0
C2	H	N	N	N	N	Y	N	N	Y	0.55	0
C3	H	N	N	N	Y	Y	N	Y	Y	0.55	0
C4	H	N	N	N	Y	Y	N	Y	Y	0.55	0
C5	L	N	N	N	N	Y	N	N	Y	0.55	0
C6	L	N	N	N	N	N	N	N	Y	0.55	0
C7	H	N	N	N	N	Y	N	Y	Y	0.55	0
C8	H	N	N	N	N	Y	N	Y	Y	0.55	0
C9	H	N	N	N	Y	Y	N	Y	Y	0.55	0
C10	L	N	N	N	N	Y	N	N	Y	0.55	0
C11	L	N	N	N	Y	Y	N	N	Y	0.55	0
C12	H	N	N	N	Y	Y	N	N	Y	0.55	0
C13	H	N	N	N	Y	Y	N	Y	Y	0.55	0
C14	H	N	N	N	Y	Y	N	Y	Y	0.55	0
C15	L	N	N	N	N	Y	N	N	Y	0.55	0
C16	L	N	N	N	N	Y	N	N	Y	0.55	0
C17	H	N	N	N	Y	Y	N	Y	Y	0.55	0
C18	H	N	N	N	Y	Y	N	Y	Y	0.55	0
C19	H	N	N	N	Y	Y	N	Y	Y	0.55	0
C20	L	N	N	N	Y	Y	N	Y	Y	0.55	0
C21	L	N	N	Y	Y	Y	N	Y	Y	0.55	0
C22	H	N	N	N	Y	Y	N	Y	Y	0.55	0
C23	H	N	N	N	Y	Y	N	Y	Y	0.55	0
C24	L	N	N	N	Y	Y	N	Y	Y	0.55	0
C25	L	N	N	N	N	Y	N	Y	Y	0.55	0
C26	L	N	N	N	N	Y	N	N	Y	0.55	
C27	L	N	N	N	Y	Y	N	Y	Y	0.55	0
C28	L	N	N	N	N	Y	N	N	Y	0.55	0
C29	H	N	N	N	Y	Y	N	Y	Y	0.55	0
C30	L	N	N	N	Y	Y	N	Y	Y	0.55	0
C31	L	N	N	N	Y	Y	N	N	Y	0.55	0
C32	H	N	N	N	Y	Y	N	Y	Y	0.55	0
C33	H	N	N	N	Y	Y	N	Y	Y	0.55	0
C34	L	N	N	N	Y	Y	N	Y	Y	0.55	0
C35	L	N	N	N	N	Y	N	N	Y	0.55	0
C36	L	N	N	N	N	Y	N	N	Y	0.55	0
C37	L	N	N	N	Y	Y	N	Y	Y	0.55	0
C38	H	N	N	N	Y	Y	N	Y	Y	0.55	0
C39	H	N	N	N	Y	Y	N	Y	Y	0.55	0
C40	L	N	N	N	Y	Y	N	Y	Y	0.55	0
C41	L	N	N	N	Y	Y	N	Y	Y	0.55	0
C42	H	N	N	N	N	Y	N	N	Y	0.55	0
C43	H	N	N	N	Y	Y	N	Y	Y	0.55	0
C44	H	N	N	N	Y	Y	N	Y	Y	0.55	0
C45	L	N	N	N	N	Y	N	N	Y	0.55	0
C46	L	N	N	N	N	Y	N	N	Y	0.55	0
C47	L	N	N	N	N	Y	N	Y	Y	0.55	0
C48	H	N	N	N	N	Y	N	Y	Y	0.55	0
C49	H	N	N	N	Y	Y	N	Y	Y	0.55	0
C50	L	N	N	N	N	Y	N	N	Y	0.55	0
Celecoxib (Reference)	H	N	N	Y	Y	Y	N	N	Y	0.55	0

[b]H = High; L = Low; Y= Yes; N = No.

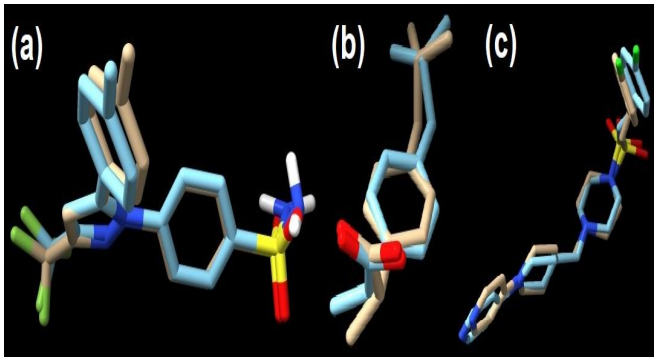


Fig.-3: Superimposition of the co-Crystallized Ligand Conformers (brown) with their Corresponding Redocked Poses (blue): (a) celecoxib (b) ibuprofen and (c) M54471

Docking Analysis (3LN1, 1EQG, and 1IQM)

The designed compounds (C1–C50) were subjected to molecular docking against COX-2 (3LN1), COX-1 (1EQG), and coagulation factor Xa (1IQM) to predict their binding and inhibitory potential. Binding energies (BE) and predicted inhibition constants (Ki) were used as key parameters to assess ligand–target

interactions and selectivity profiles. The investigated compounds were observed to bind within the catalytic sites of the target proteins**,** indicating favourable affinity toward the respective active sites.[30-32] The docking results are tabulated in Table-4.

Docking Results against COX-2 (3LN1)

Overall, 45 of the 50 tested compounds showed stronger predicted binding than celecoxib, and among them, the most potent derivative is C9, highlighting the structural suitability of the designed scaffold for COX-2 targeting.

Table-4: Docking Data

	3LN1 COX2		1EQG COX1		1IQM Coagulation factor Xa	
Derivative	Binding Energy Kcal/mol	Inhibition Constant Ki	Binding Energy Kcal/mol	Inhibition Constant Ki	Binding Energy Kcal/mol	Inhibition Constant Ki
C1	-9.07	225.61 nM	-6.01	39.46 µM	-6.87	9.14 µM
C2	-8.99	257.56 nM	-7.75	2.08 µM	-7.01	7.25 µM
C3	-9.47	115.19 nM	-7.52	3.05 µM	-7.26	4.79 µM
C4	-9.57	96.97 nM	-6.45	18.79 µM	-7.19	5.38 µM
C5	-9.22	175.23 nM	-6.54	16.01 µM	-7.74	2.12 µM
C6	-8.92	287.79 nM	-5.94	43.93 µM	-7.64	2.52 µM
C7	-9.51	106.80 nM	-6.92	8.48 µM	-7.7	2.26 µM
C8	-9.77	68.39 nM	-6.8	10.33 µM	-7.46	3.38 µM
C9	-9.9	55.8 nM	-5.72	64.43 µM	-7.38	3.87 µM
C10	-9.56	98.76 nM	-6.16	30.48 µM	-7.66	2.44 µM
C11	-7.67	2.37 µM	-6.34	22.47 µM	-6.88	9.10 µM
C12	-7.6	2.68 µM	-7.71	2.22 µM	-7.06	6.67 µM
C13	-8.1	1.15 µM	-7.63	2.55 µM	-7.49	3.25 µM
C14	-8.35	755.60 nM	-6.74	11.54 µM	-7.07	6.56 µM
C15	-8.46	629.62 nM	-7.13	5.95 µM	-7.27	4.67 µM
C16	-8.33	784.88 nM	-5.94	44.14 µM	-7.12	6.02 µM
C17	-8.13	1.10 µM	-6.89	8.94 µM	-7.53	3.02 µM
C18	-8.41	689.29 nM	-6.97	7.72 µM	-7.59	2.74 µM
C19	-8.62	476.88 nM	-5.66	70.82 µM	-7.47	3.36 µM
C20	-8.57	524.39 nM	-6.38	21.17 µM	-7.46	3.41 µM
C21	-7.95	1.50 µM	-6.85	9.47 µM	-6.55	15.91 µM
C22	-8.13	1.09 µM	-8.17	1.03 µM	-7.1	6.25 µM
C23	-8.17	1.03 µM	-7.67	2.40 µM	-5.41	108.37 µM
C24	-8.29	843.11 nM	-7.07	6.63 µM	-7.44	3.53 µM
C25	-8.55	543.34 nM	-6.79	10.57 µM	-7.53	3.04 µM
C26	-8.09	1.18 µM	-6.05	36.83 µM	-7.51	3.15 µM
C27	-8.3	818.30 nM	-6.9	8.71 µM	-7.56	2.86 µM
C28	-8.33	777.06 nM	-6.3	24.14 µM	-7.63	2.55 µM
C29	-8.63	469.14 nM	-6.11	33.01 µM	-7.14	5.83 µM
C30	-8.15	1.06 µM	-6.55	15.71 µM	-7.43	3.58 µM
C31	-7.49	3.26 µM	-7.26	4.74 µM	-7.29	4.52 µM
C32	-7.54	2.95 µM	-8.08	1.20 µM	-7.3	4.43 µM
C33	-8.08	1.19 µM	-7.88	1.68 µM	-7.79	1.96 µM
C34	-8.33	783.19 nM	-7.2	5.26 µM	-7.5	3.19 µM
C35	-8.1	1.16 µM	-7.06	6.63 µM	-7.81	1.89 µM
C36	-7.61	2.63 µM	-6.45	18.58 µM	-7.44	3.53 µM
C37	-8.31	809.08 nM	-7.54	2.99 µM	-7.72	2.18 µM

C38	-8.44	649.21 nM	-6.04	37.43 µM	-7.54	2.97 µM
C39	-8.64	462.43 nM	-6.6	14.55 µM	-7.37	3.98 µM
C40	-8.08	1.19 µM	-6.93	8.34 µM	-7.51	3.12 µM
C41	-8.33	778.13 nM	-6.23	27.18 µM	-6.85	9.50 µM
C42	-8.23	921.47 nM	-7.2	5.26 µM	-7.03	7.06 µM
C43	-8.69	428.61 nM	-6.96	7.92 µM	-7.35	4.09 µM
C44	-8.76	376.65 nM	-6.33	22.75 µM	-7.4	3.74 µM
C45	-8.49	600.61 nM	-6.29	24.53 µM	-7.68	2.35 µM
C46	-7.97	1.45 µM	-5.09	185.38 µM	-7.14	5.87 µM
C47	-8.78	366.57 nM	-6.56	15.60 µM	-7.45	3.46 µM
C48	-9.05	232.98 nM	-6.53	16.42 µM	-7.53	3.01 µM
C49	-9.06	227.95 nM	-5.93	45.09 µM	-7.37	3.96 µM
C50	-8.58	517.34 nM	-5.83	53.55 µM	-7.23	5.05 µM
Celecoxib (Reference) BE = -7.91Kcal/mol Ki =1.59 µM			Ibuprofen (Reference) BE= -6.94 kcal/mol Ki = 8.13 µM		M54471 (Reference) BE = -7.64 kcal/mol Ki = 2.52 µM Celecoxib (Reference) BE = -6.86 kcal/mol Ki = 9.35 µM	

The Interactions of the Ligands C7 and C9 with 3LN1(COX2)

The docking studies (Fig.-4) revealed that the ligand's carbonyl "O" of the chalcone site and both the "O" atoms of the sulphonamide functional group act as H-bond acceptors with SER516, PHE504, and ARG499 amino acid residues, while the "NH2" site of the sulphonamide acts as an H-bond donor site for the GLN178 & LEU338 amino acids. The phenyl ring (attached to the pyrazole) forms Pi-Sigma interactions with VAL509 & SER339. Ring B makes Pi-Alkyl interactions with ALA513 and VAL335. The 4-methyl substituent on ring A makes alkyl interactions with MET508, TRP373, LEU370, and PHE504. In the ligand C9, the "methylene-ethyl" substituent on ring B makes alkyl interactions with VAL102, TYR341, LEU345 & LEU517.

Docking Results against COX-1 (1EQG)

Docking against COX-1 predicted comparatively weaker binding affinities of ligands for COX-1than COX-2 (Table-4). Such selectivity is essential to minimise gastrointestinal toxicity associated with COX-1 inhibition.[2]

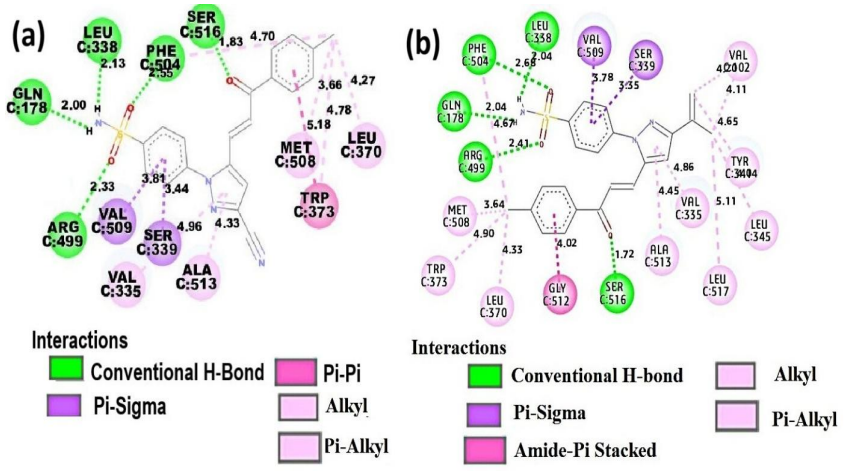


Fig.- 4: (a) C7-3LN1 Molecular Interactions (b) C9-3LN1 Molecular Interactions

Docking Results against Coagulation Factor Xa (1IQM)

Among the tested compounds, some derivatives showed promising binding affinity toward coagulation factor Xa, comparable or superior to M54471. Notably, these compounds are C35, C33, C5, and C7, suggesting potential anticoagulant activity. Among all the 50 designed ligand studies, 47 ligands showed superior predicted binding affinity to celecoxib (Table-4, Fig.-5).

The interactions of the ligands C7 and C35 with 1IQM (Coagulation factor Xa)

Docking analysis of C7 and C35 with factor Xa (1IQM) revealed several stabilising hydrogen-bond and Pi-interactions (Fig.-5). In both ligands, the sulphonamide oxygen acted as a hydrogen-bond acceptor with ILE175, while its NH_2 group donated hydrogen bonds to THR98 and ILE175. The phenyl ring of C7 formed a Pi–Pi interaction with PHE174, whereas C35 showed additional Pi–Pi interactions with PHE174, TRP215 and TYR99. The pyrazole ring interacted with TYR99 in C7 and PHE174 in C35. Furthermore, the cyano nitrogen of C7 and the carbamoyl groups of C35 formed hydrogen bonds with GLY216. The phenyl ring and 4-alkyl substituent of both the ligands contributed Pi-alkyl and alkyl interactions with LYS96, respectively.

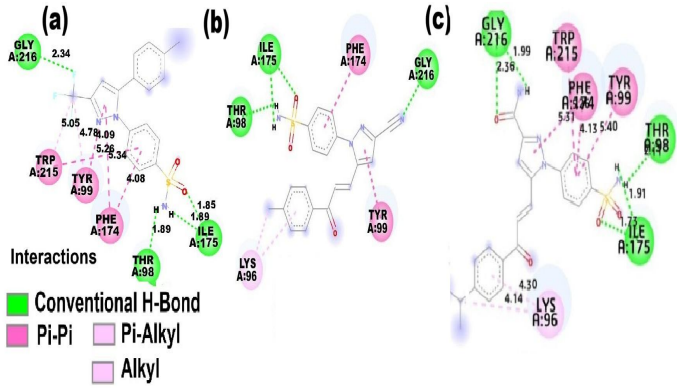


Fig.-5: Complex Interactions (a) Celecoxib-1IQM (b) C7-1IQM (c) C35-1IQM

SAR predictions (based on docking)

For COX-2 inhibition and selectivity

Effect of the α,β-unsaturated carbonyl linker: Its insertion between phenyl (ring A) and pyrazole (ring B) enhanced predicted COX-2 affinity compared with celecoxib, possibly due to hydrogen bonding involving the carbonyl oxygen (<2 Å) (Fig.-4). Increased spatial separation between rings A and B may also favor accommodation in the larger COX-2 catalytic pocket, resulting in greater predicted affinity for COX-2 than COX-1.[33] Effect of ring-A substituents: Methyl substitution generally favoured COX-2 binding over bulkier electron-releasing groups such as methoxy, ethyl, propyl, and isopropyl, suggesting that steric effects predominate. The methyl group showed hydrophobic interactions with MET508, TRP373 and LEU370. Effect of ring-B substituents: Bulkier electron-withdrawing substituents appeared favourable, as exemplified by C9, whose methylene-ethyl group showed hydrophobic interactions with VAL102, TYR341, LEU345, and LEU517 (Fig.-4). Ring A appears to favour smaller substituents, whereas the larger COX-2 side pocket may accommodate bulkier substituents on ring B (Table-4).

For Factor Xa binding

Role of the linker

The α,β-unsaturated carbonyl linker imparts conformational flexibility to attain an L-shaped (Fig.-5) conformation that facilitates occupancy of the S1 and S4 pockets.[34] Notably, 47 derivatives showed stronger predicted binding than celecoxib (BE = −6.86 kcal/mol; Ki = 2.52 μM).

Role of sulphonamide

The oxygen and amino group of sulphonamide participate as a hydrogen-bond acceptor and as a donor, respectively, interacting with key residues ILE175 and THR98.

Aromatic Interactions

The phenyl and pyrazole rings contribute hydrophobic, Pi–Pi and Pi-alkyl interactions with TYR99, PHE174, TRP215, LYS96, and ILE175, supporting complex stabilisation.

Substituent Effects

Polar groups on ring B, such as carbamoyl and cyano, form hydrogen bonds with GLY216 in the S1 pocket, whereas alkyl groups on ring A contribute hydrophobic interactions within S4. Dual COX-2/factor Xa targeting may provide a rational strategy to treat inflammatory conditions associated with thrombotic risk. In this study, celecoxib–chalcone hybridisation generated compounds with a predicted dual-target profile of simultaneous modulation of inflammatory and coagulation pathways. C7 and C9 emerged as promising candidates based on their favourable predicted binding to both biological targets. These key findings demonstrate the potential of molecular hybridisation to expand the pharmacological profile of established scaffolds and provide a basis for further lead optimisation. By identifying candidates for subsequent synthesis and biological validation, this work supports SDG 3 (Good Health and Well-being) through the development of potential multifunctional therapeutic agents.

CONCLUSION

The present study demonstrates that celecoxib–chalcone molecular hybridisation is a promising strategy for developing potential dual COX-2/factor Xa inhibitors. Among the 50 designed ligands, 45 showed stronger predicted COX-2 binding than celecoxib, while 47 showed stronger predicted factor Xa binding; eight compounds also showed stronger predicted factor Xa binding than the reference inhibitor M54471. C7 and C9 emerged as the most promiscuous leads based on their favourable predicted binding profiles and acceptable in-silico ADME and toxicity characteristics. These findings provide a rational basis for further lead optimization and experimental validation by enzymatic, in-vitro and in vivo studies. The study supports SDG-3 (Good Health and Well-being) by contributing to the early-stage development of potential multifunctional therapeutic candidates.

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CONFLICT OF INTERESTS

The authors declare that there is no conflict of interest.

AUTHOR CONTRIBUTIONS

The present work is related to *SDG-3: Good Health and Well-being*. All the authors contributed significantly to this manuscript, participated in reviewing/editing and approved the final draft for publication. The research profile of the authors can be verified from their ORCID ids, given below:

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