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In Silico Approaches for the Design of Imidazolone Based Molecules as New Dual M-PGES-1/5-LO Inhibitors

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Abstract:

Inflammation is a local response to cellular injury, associated with many other diseases. NSAID's and selective inhibitors of COX-2 has been mainly used for the treatment as well as inhibition of various anti-inflammatory diseases. Although these drugs have several side-affects upon long term usage. Recently COX/5-LOX and other dual inhibitors have been developed, however these drugs did not enter into clinical trials owing to some drawbacks. Prostaglandin (PG)E_2 and leukotrienes (LTs) synthesized from microsomal prostaglandin E_2 synthase-1 (mPGES-1) and 5-lipoxygenase (5-LO) respectively are the pivotal players in inflammation. Therefore, microsomal prostaglandin E_2 synthase-1 (mPGES-1) and 5-lipoxygenase (5-LO) as the targets can be a classic approach sparing all other PGs of physiological importance for the design and development of a New Dual m-PGES-1/5-LO inhibitors. In this research, imidazolone based molecules (having various activities) have been subjected to structure based virtual screening and top lead molecules have been retrieved and molecular docking has been performed for hit molecules. By understanding their pharmacophoric interactions and incorporating these interactions in a single molecule a series of New Dual m-PGES-1/5-LO inhibitors have been designed and molecular properties plus toxicity profile had also been studied for the purpose of safety and efficacy by using Molinspiration, OSIRIS property explorer. Molecular docking using Dockthor and pharmacokinetic studies using SwissADME were also carried out for the designed compound. High docking scores was obtained and all the compounds showed high GI absorption.

Key words: Dual inhibition, Inflammation, Imidazolone, 5-LO, mPGES-1, molecular docking and virtual screening.

INTRODUCTION:

One of the cardinal medical discoveries of the last couple of decades has been that the inflammatory processes are mixed up with not just a few selected disorders, but with several physical and mental health conditions.[1] The most significant cause of death throughout the world is recognized due to chronic inflammatory diseases, about 50% of deaths occurred due to inflammation-related diseases such as diabetes mellitus, chronic kidney diseases, stroke, non-alcoholic fatty liver disease and neurodegenerative and autoimmune conditions.[2] Inflammation is an evolutionarily supportive process which is characterized by the stimulation of immune and non-immune cells that shield the host from various infections by eradicating pathogens and stimulating tissue repair and recovery. In order to preserve metabolic energy and apportion nutrients to activate immune system, neuroendocrine and metabolic changes occur on the basics of extent and degree of inflammatory response in conjunction with systemic or local. Cyclooxygenase and lipoxygenase pathways are the most important pathways related for the development of inflammatory responses.[3] The signs of inflammation are mainly rubor (redness), dolor (pain), calor(heat) and tumor(swelling).[4]

Prostaglandins:

Prostaglandins and thromboxane A_2 (TXA_2), combinedly referred as prostanoids, are the synthesised compounds of arachidonic acid (AA). There are four fundamental bioactive prostaglandins produced *in vivo* designated as prostaglandin (PG) E_2 (PGE_2), prostaglandin D_2 (PGD_2) prostacyclin (PGI_2), and prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$).[5] The most abundantly formed in the body is prostaglandin is PGE_2, and is mainly characterized in animal species.[6] Elevated prostaglandin levels indicate the tissue is inflamed and these prostaglandin can induce and develop the inflammatory responses.[7] PGE_2 among all the prostaglandins has the cardinal impact on the progression of inflammatory pain signals and also lead to classic signs of inflammation[8,9] PGE_2 is the product of PGH_2 formed by making use of any three different PGE_2 synthases that are mPGES-1, mPGES-2(membrane bound proteins) or cPGES enzymes. [10]Among all the three synthases, in response to various inflammatory stimuli mPGES-1 is up-regulated and mPGES-2 and cPGES are mainly expressed in various organs and tissues.[11,12,13]

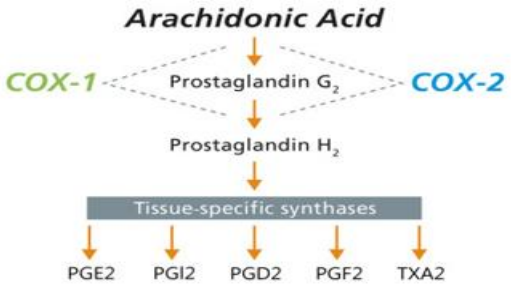


Figure:1 Prostaglandin biosynthesis pathway

Leukotrienes :

Leukotrienes which are the inflammatory mediators are biosynthesised through 5-lipoxygenase pathway of arachidonic acid metabolism. This metabolism occurs whenever there is any kind of inflammatory stimulation(both immunological and non-immunological stimuli) which calls leukotrienes production and it starts from the lysis of phospholipid membrane by the enzyme phospholipase A and is converted into arachidonic acid which is a twenty-member carbon fatty acid and further it is converted into LTA by the action of the enzyme 5-Lipoxygenase. As a substrate LTA is used for the

production of LTB through hydrolysis and through conjugation for the production of LTC, within the cell. Separate transport proteins are used to eliminate out LTB and LTA from the cell. LTC upon hydrolysis extracellularly produce different leukotrienes such as LTD, LTE.[14,15]

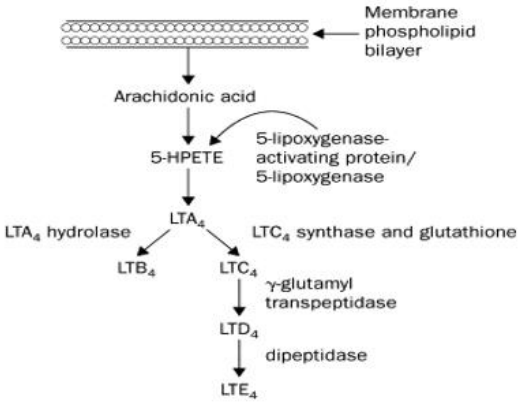


Figure:2 Leukotriene biosynthesis pathway

Imidazolone:

Imidazolone is a five-membered heterocycle compose of three carbon and two nitrogen atoms at the positions 1 and 3 with a carbonyl group at the fifth position. Various analogues of imidazolone were also found to be have different biological activities including analgesic and anti-inflammatory,[16-19]CNS depressant,[20] monoamine oxidase (MAO) inhibitory, anticonvulsant,[21,22] immunomodulator,[23] anthelmintic,[24] anticancer,[25] cardiovascular [26,27] and antimicrobial. [28,29] On the other hand coumarins also known to exhibit broad spectrum of biological activities for example antibacterial,[30] anti-coagulant,[31] antiviral,[32] anti-inflammatory activities,[33-35] and antitumor.[36,37] In the present study a new molecule that is imidazolone hybridized with coumarins has been designed in order to show Dual inhibition of mPGES-1/5-LO.

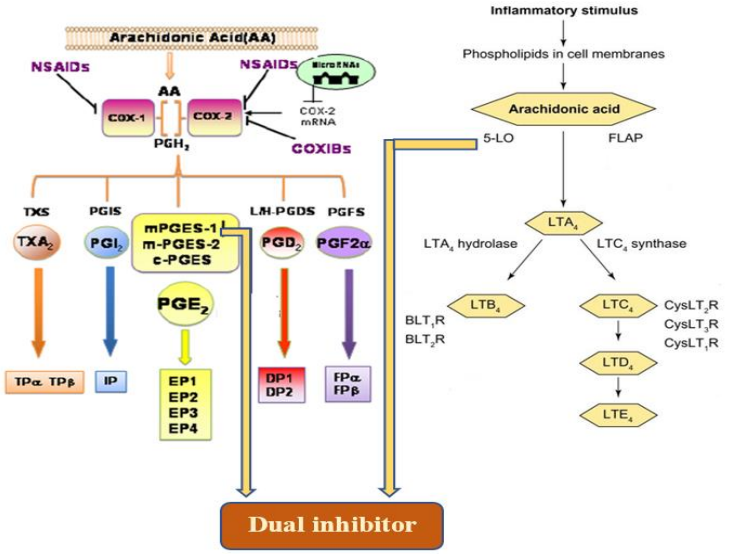


Figure:3 Our work simultaneous inhibition of mPGES-1/5-LO

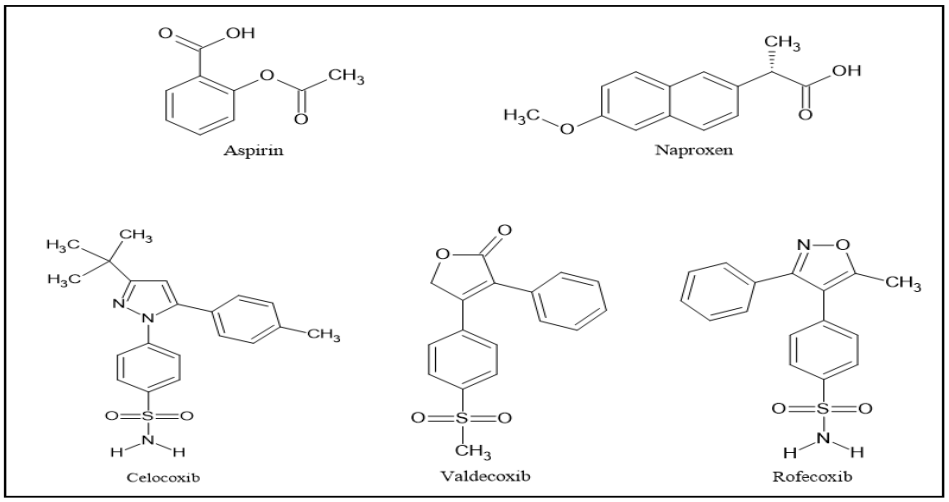


Figure:4 Existing drugs inhibiting cox-1 and cox-2

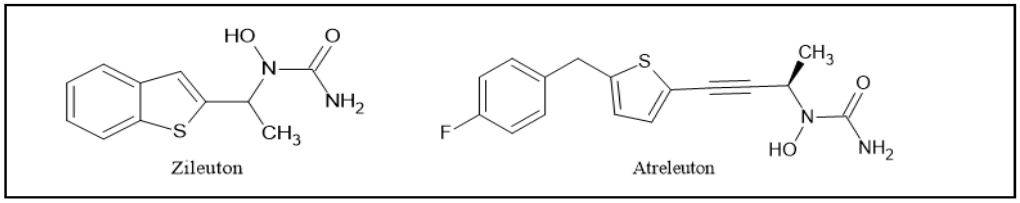


Figure:5 Existing drugs inhibiting 5-LO

MATERIALS AND METHODS

Computational methods:

Virtual screening: Virtual screening is performed using Pyrx virtual screening tool. To carry out this method first PDB ID from protein data base has to be downloaded. The ligands are required which can be downloaded from any database. Then open the tool and start the process.

Docking: Docking has been performed using Dockthor software which is a online software.

Molecular property prediction: Molecular property prediction studies were predicted through online software Molinsipiration which is an online tool for performing this studies slimes have to be uploaded.

Osiris Property Explorer: This software is used to predict the toxicity of the compounds.

Pharmacokinetic studies: Pharmacokinetics studies can be studied using SwissADME online software.

RESULTS AND DISCUSSION:

Virtual screening of different heterocyclic molecules has been performed for anti-inflammatory activity. Among all the heterocyclic molecules imidazolones were found to have mPGES-1 inhibitory activity and coumarins were found to have 5-LO inhibitory activity. Virtual screening of 100 molecules has been performed by retrieving the imidazolones molecules from PubChem database for anti-mPGES-1 activity. Virtual screening of 100 molecules has been performed by retrieving the coumarin molecules from PubChem database for anti-5-LO activity.

Table:1 Virtual screening results of imidazolone derivatives for possible mPGES-1 inhibition

S.No	PubChem ID	PYRX RESULTS
1.	PubChem57003299	-12.8
2.	PubChem11002343	-9.1
3.	PubChem46919707	-9.2
4.	PubChem54613179	-9.5
5.	PubChem49862080	-9.4
6.	PubChem15454649	-11.1

Table:2 Virtual screening results of coumarin derivatives for possible 5-LO inhibition.

S.No	PubChem ID	PYRX RESULTS
1.	PubChem28916	-9.0
2.	PubChem62249	-9.0
3.	PubChem100335	-9.3
4.	PubChem28919	-9.3
5.	PubChem989328	-9.5
6.	PubChem20474272	-9.4

From the results obtained, it is understood that the above molecules could have possible anti-inflammatory activity i.e., inhibition of mPGES-1 and 5-LO . The below 12 molecules are considered as HITS, out of which 6 are the derivatives of imidazolone and the rest belongs to coumarins.

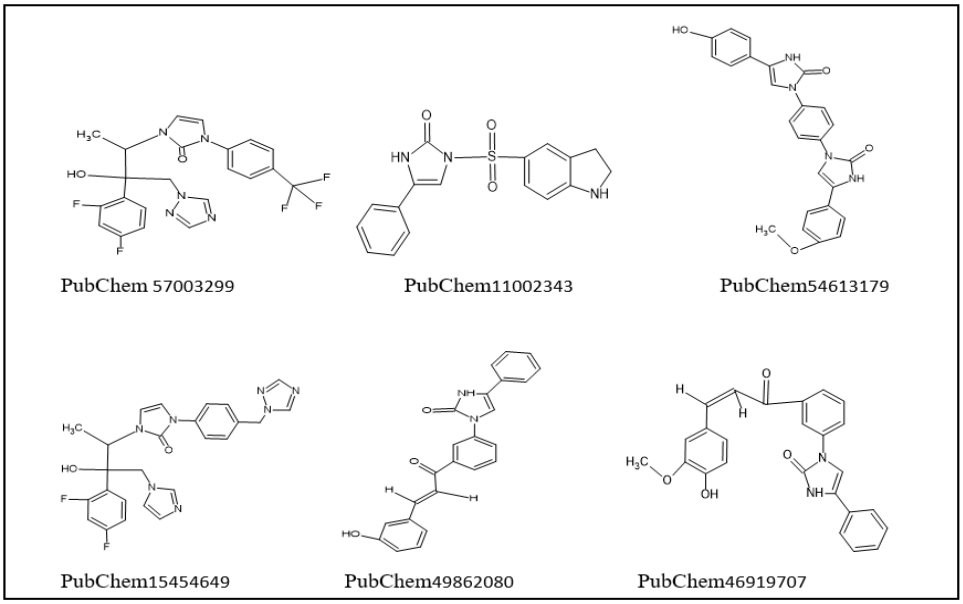


Figure:6 Structures of 6 potent HITS resulted from virtual screening process of mPGES-1

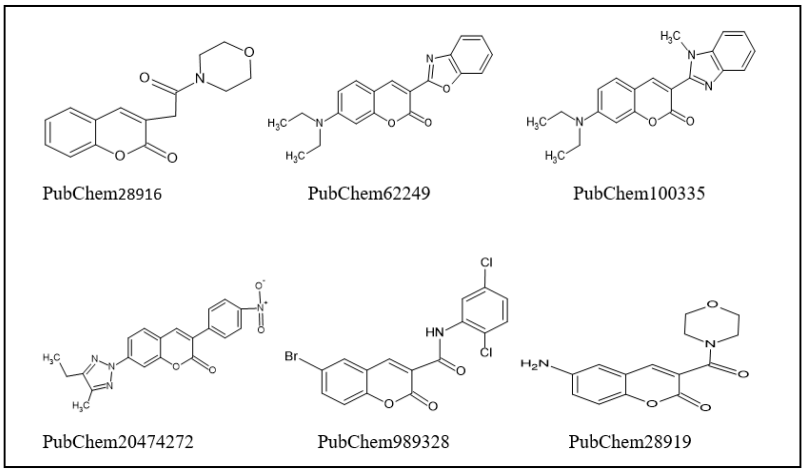


Figure:7 Structures of 6 potent HITS resulted from virtual screening process 5-LO

Molecular docking:

Structures and molecular docking interactions of HIT molecules with PGES-1 (PDB ID 3DWW) acquire from virtual screening results

The greater docking score is required for optimum binding with the desire environment and the compound will exhibit good activity against the targeted macromolecules. A hit compounds with a fit score ranging from -9.0 to -12.8 were selected from virtual screening and molecular docking has been performed for those molecules.

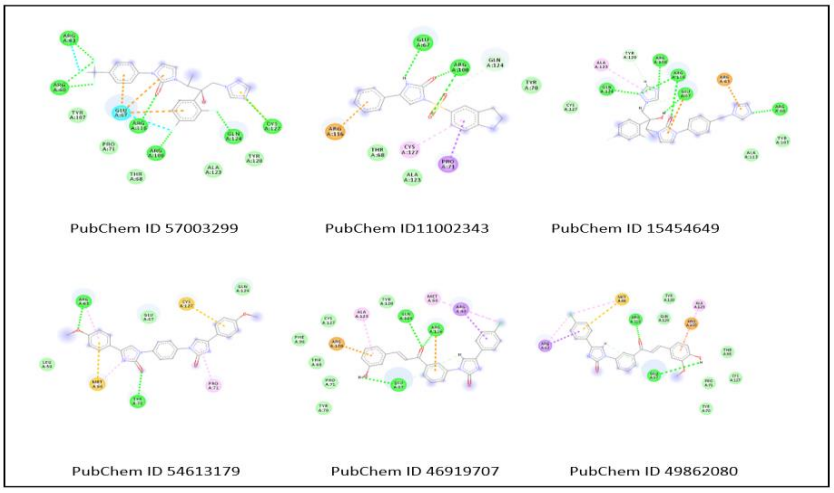


Figure:8 Binding interactions of six potent HIT molecules with mPGES-1 (PDB ID :3DWW) green dotted line showing hydrogen bond interaction and pink hydrophobic interactions.

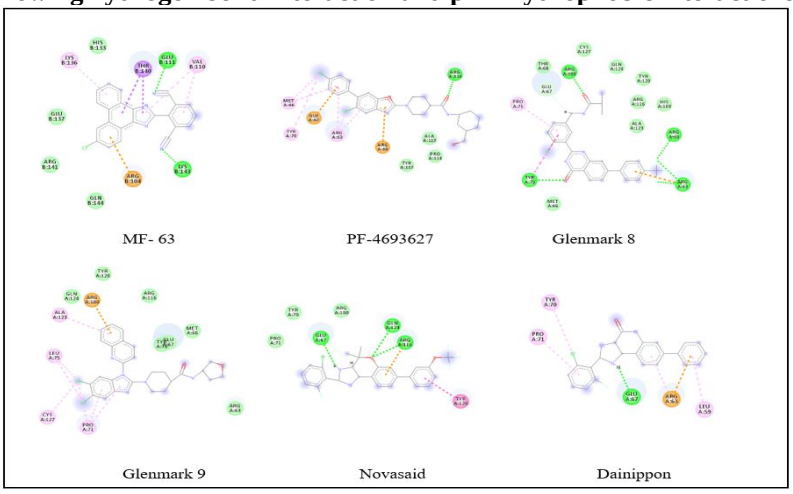


Figure:9 Binding interactions of six patent drugs with mPGES-1 (PDB ID :3DWW) green dotted line showing hydrogen bond interaction and pink hydrophobic interactions.

After performing molecular docking of hits of mPGES-1 molecules docking of the patent molecules of mPGES-1 has been performed in order to find any similar interaction and it has been noticed that GLU:A 67, ARG:A 116, GLN:A 124 etc are showing common interaction both in patents and hits.

And in the similar way molecular docking of hits and patents/marketed drugs of 5-LO has been performed and the common interaction observed were GLU:B 111, ARG:B 104, ARG:B 71, LYS:B 136 etc and their pictorial representation of docking interactions are shown below.

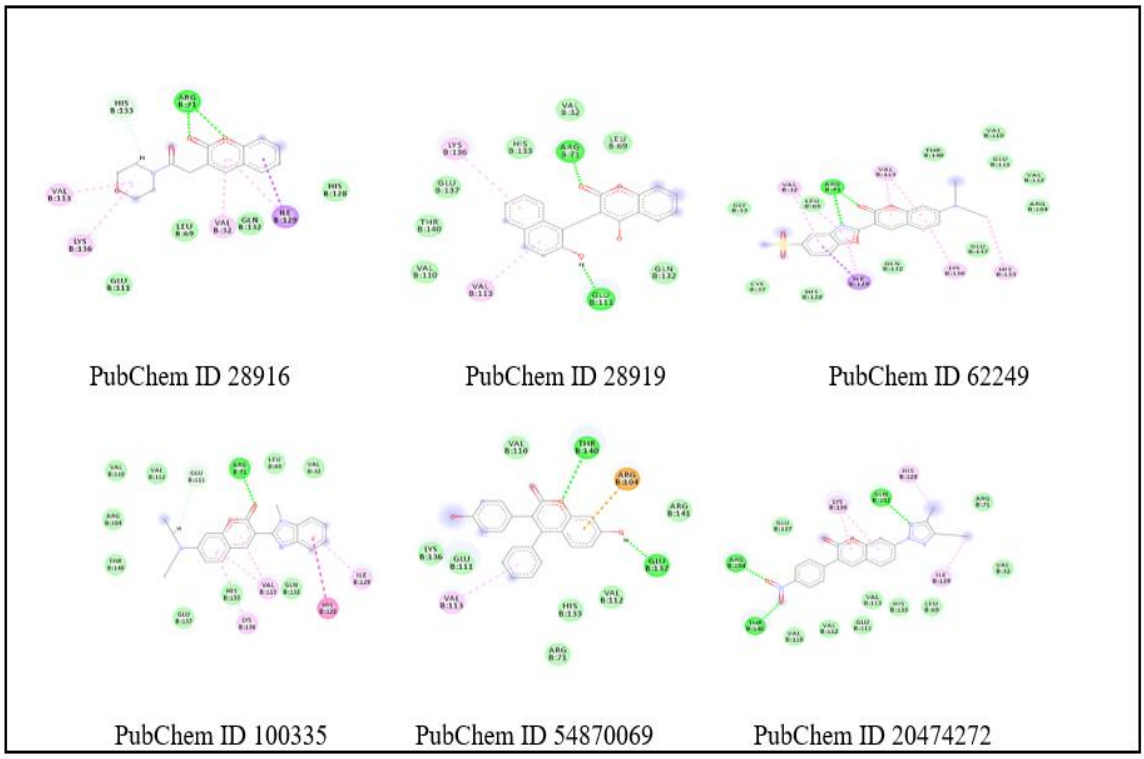


Figure:10 Binding interactions of six potent HIT molecules with 5-LO (PDB ID :6NFC) green dotted line showing hydrogen bond interaction and pink hydrophobic interactions.

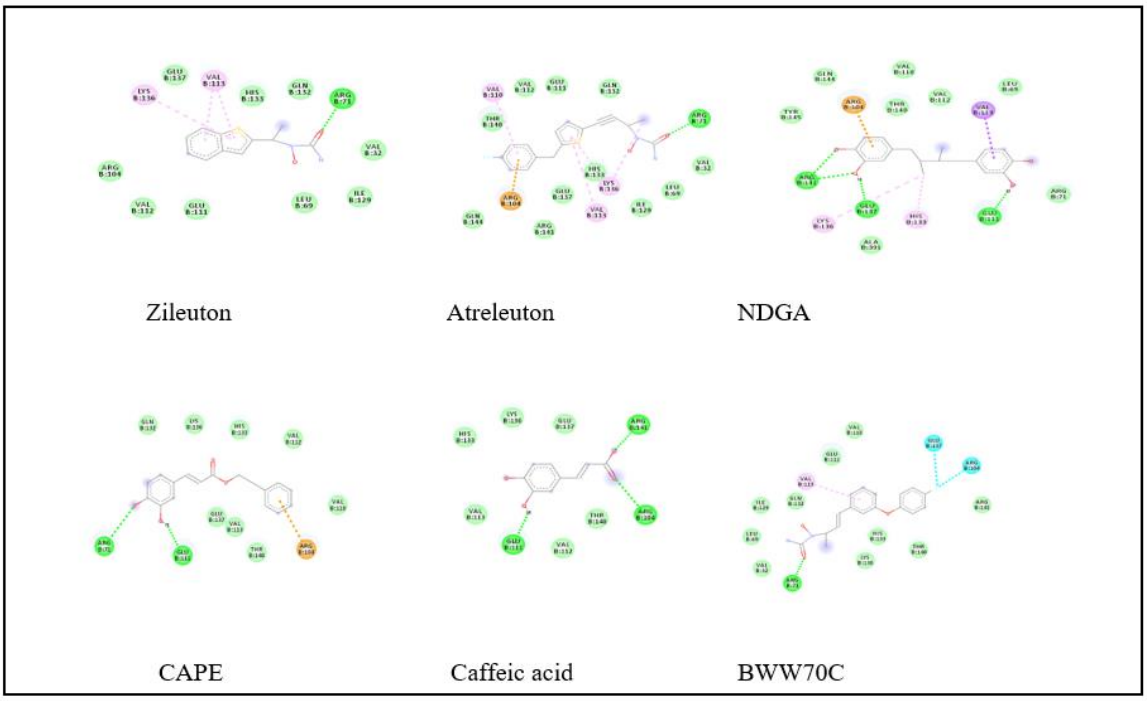


Figure:11 Binding interactions of six marketed/patent drugs with 5-LO (PDB ID :6NFC) green dotted line showing hydrogen bond interaction and pink hydrophobic interactions.

Design of the lead molecule from similar structural molecules, patent/marketed drugs and their pharmacophoric features

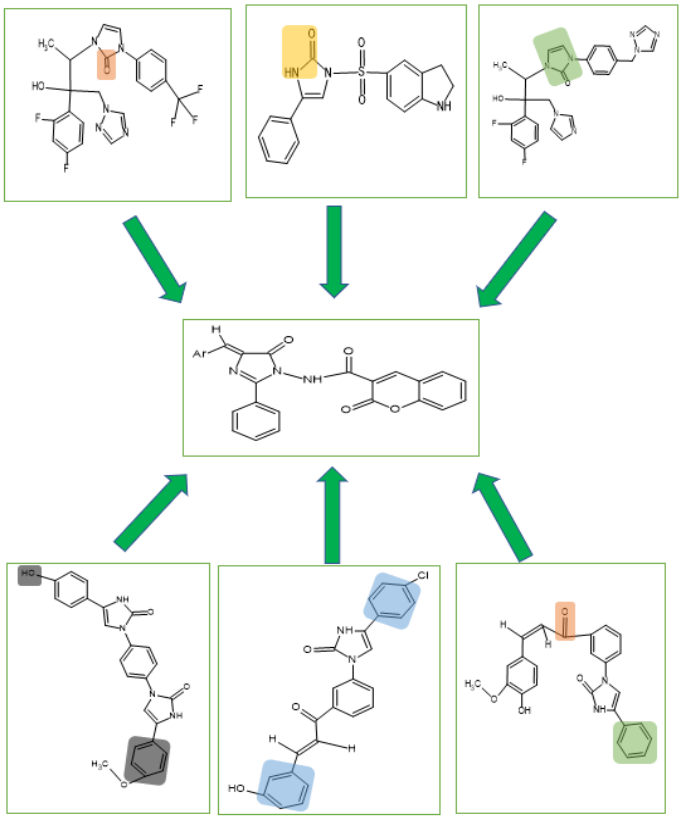


Figure:12 Design of Lead molecule from imidazolone hits.

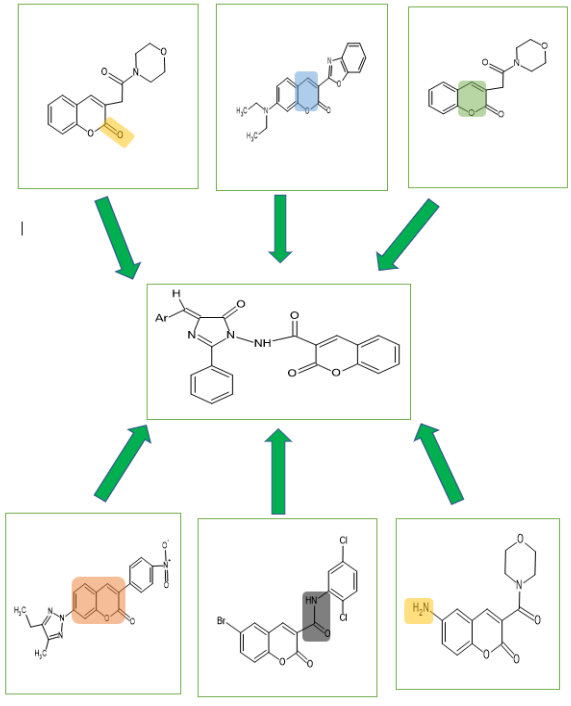


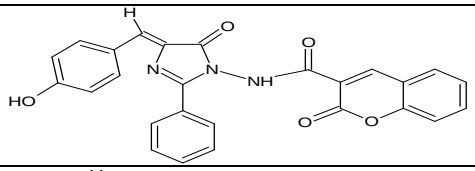
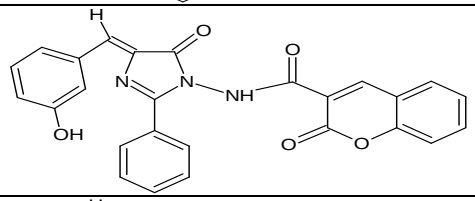
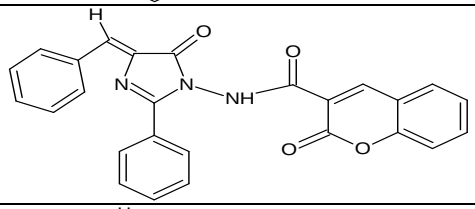
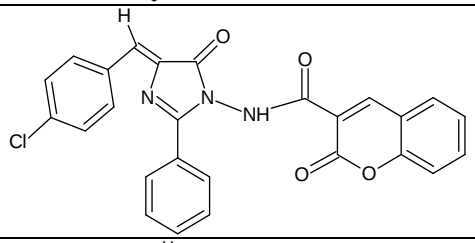
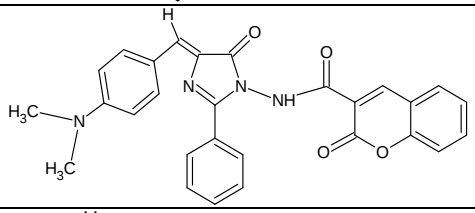
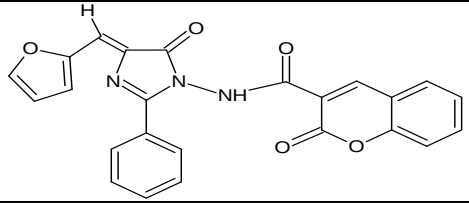
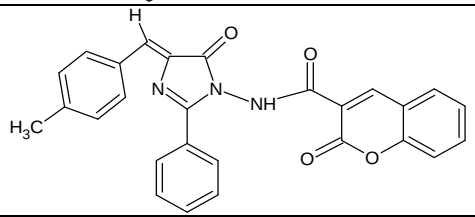
Figure:13 Design of Lead molecule from coumarin hits.

By understanding all these interaction of hits with the amino acids residues a hybridised molecule i.e. coumarin amido substituted imidazole-2-one derivatives were designed as a NEW DUAL INHIBITIORS OF PGES-1/5-LOX.

Molecular property and toxicity prediction of the coumarin amido substituted imidazole-2-one of derivatives using OSIRIS property Explorer

Based on the Druglikeness the compounds were predicted to be promising druggable candidates. One of the important factors is toxicity, at the clinical trial stage the adverse drug reactions generated due to the toxicity of the compound turn outs to be very expensive in the process of development of drug. *In silico* toxicity and Druglikeness prediction along with the prediction of other ADME property helps in speeding up the new targets discovery and eventually results in the formation of lead compound with the biological activity which has been predicted. The title compounds exhibited non-mutagenic, non-tumorigenic and non-reproductive effects which further substructure the drug features in the molecules. This *in silico* prediction prior to the synthesis of the compounds would help in the synthesis and also to select the compounds for animal study.

Table:3 Molecular property and toxicity prediction of the coumarin amido substituted imidazole-2-one of derivatives using OSIRIS property Explorer

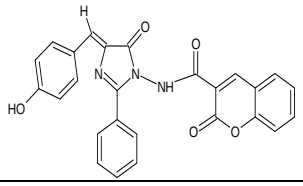
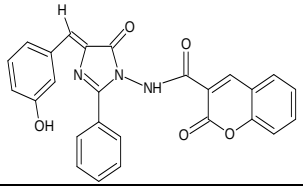
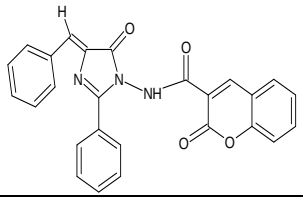
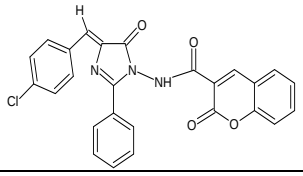
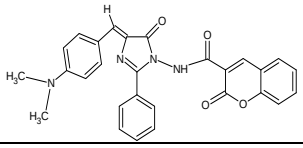
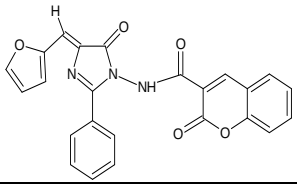
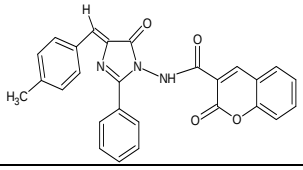
S.No	Molecule	Mol.wt.	cLogp	LogS	Druglikeness	Mutagenic	Reproductive effects
1.		451.0	1.75	-1.01	4.12	None	None
2.		451.0	1.75	-1.01	4.12	None	None
3.		435.0	1.79	-2.31	2.19	None	None
4.		469.0	1.66	-1.04	4.57	None	None
5.		478.0	1.65	-1.34	4.49	None	None
6.		425.0	1.52	-2.99	3.61	None	None
7.		449.0	1.44	-1.65	2.55	None	None

Bioactivity prediction studies coumarin amido substituted imidazole-2-one of derivatives using Molinspiration

The molecular properties of all the title compounds were calculated using Molinspiration cheminformatics and the data is present in the following table.

In order to predict the oral bioavailability of the drug or the potential lead molecule, Lipinski's rule of five is most commonly utilized by pharmaceutical chemists in the process of drug design and development. All the designed compounds have satisfied the Lipinski's rule of five and no compound has violated this rule. Thus, all the designed compounds were predicted to be therapeutic active compounds.

Table:4 Bioactivity prediction studies coumarin amido substituted imidazole-2-one of derivatives using Molinspiration

S.No	Molecules	miLogP	TSPA	natoms	MW	nOH	nOHN	nViolations	nrotb	Volume
		3.60	114.43	34	451.44	8	2	0	4	382.41
		3.57	114.43	34	451.44	8	2	0	4	382.41
		4.07	94.21	33	435.44	7	1	0	4	374.39
		4.75	94.21	34	469.88	7	1	0	4	387.93
		4.18	97.44	36	478.51	8	2	0	5	390.95
		3.33	107.35	32	425.40	8	2	0	4	355.96
		4.52	94.21	34	449.47	7	1	0	4	420.30

Molecular docking of title compounds

Molecular docking studies have been carried out based on the crystal structure of the desire mPGES-1 (PDB ID: 3DWW) and 5-LO (PDB ID: 6NFC) protein with the title compounds. As the protein pocket have different attachment site as well as shape for binding different ligands. And their binding scores were found to be between -8.2 to -9.5.

Three conventional hydrogen bonds were formed at GLN A:124,GLU A:67, ARG A:116. Two pi-alkyl bonds were formed, in some molecules bond was formed at PRO A:71(majority) and in some molecules bond was observed at ALA A:123. These binding sites are with respect to the PDB ID 3DWW.

One hydrogen bond was formed at ARG B:71 for all the molecules. And other hydrogen bond has also been observed at GLU B:111 and GLU B:137 in some molecules. Pi-alkyl bond was observed at VAL B:113 for every molecule. These binding interactions are with respect to PDB ID 6NFC.

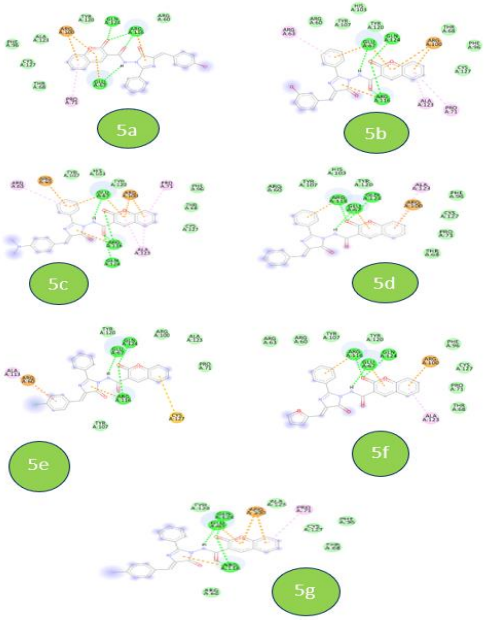


Figure:14 Binding interactions of the title compounds with PDB ID 3DWW

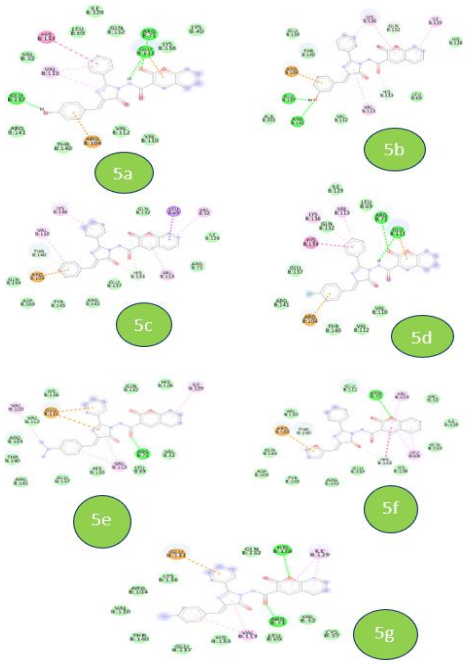


Figure:15 Binding interactions of the title compounds with PDB ID 6NCF

Pharmacokinetic property prediction of titled compounds

Pharmacokinetic property prediction of the title compounds has been performed using an online freeware SwissADME. Being highly bioactive and low toxic compound are not sufficient criteria for a drug to qualify the compound as a good drug candidate. It is exclusively important for a novel compound to have a better pharmacokinetic profile. Therefore, to avoid waste of time and resources it is necessary to evaluate ADMET profile.

According to the pharmacokinetic properties all the title compounds exhibited high rate of gastrointestinal absorption through which it is evident that all the compounds are efficacious. All the title compounds are non-toxic as they do not permeated BBB. Log K_p (skin permeation) ranges from -5.56 to -6.32 cm/s, which are under accepted ranges.

Table:5 Pharmacokinetics property prediction studies of the coumarin amido substituted imidazole-2-one of derivatives using SwissADME freeware

Molecules	5a	5b	5c	5d	5e	5f	5g
GI absorption	High	High	High	High	High	High	High
BBB permeation	No	No	No	No	No	No	No
P-gp permeation	No	No	No	No	No	No	No
CYP1A2 Inhibitor	No	No	No	No	No	No	No
CYP2C19 Inhibitor	Yes	Yes	Yes	Yes	Yes	Yes	Yes
CYP2C9 Inhibitor	Yes	Yes	Yes	Yes	Yes	Yes	Yes
CYP2D6 Inhibitor	No	No	No	No	No	No	No
CYP3A4 Inhibitor	No	No	No	No	No	No	No
Log K_p (skin permeation)	-6.09 cm/s	-6.09 cm/s	-5.74 cm/s	-5.50 cm/s	-5.91 cm/s	-6.32 cm/s	-5.56 cm/s

Discussion:

CADD plays a crucial role in drug discovery and development and it is essential tool in pharmaceutical industry. Computational medicinal chemist can grip the advantages of various software's for *in silico* approaches in drug design and development. In the present research investigation, different software's are used for studying different parameters. For virtual screening Pyrx virtual screening tool has been used, to carry out the docking studies Dockthor online tool was used. Virtual screening for various heterocyclic molecules has been carried out in order to predict anti-inflammatory activity. This technique predicted that among all the heterocyclic molecules imidazolones and coumarins possess excellent interaction profile with the targets mPGES-1 and 5-LO respectively. This screening has been performed by retrieving 100 molecules of imidazolones from PubChem database for anti-mPGES-1 activity. And also, by retrieving 100 molecules of coumarin from same database for anti-5-LO activity. Hence, from the above results achieve from virtual screening it is confirmed that the imidazolones as well as coumarins has the possible anti-inflammatory activity. The top HIT molecules were selected from both imidazolones and coumarin as well from the virtual screening results and docking studies has been performed in order to find out the accurate binding conformation of the ligand within a targeted protein. Docking studies was also carried out for some of the marketed as well as patent drugs. After observing the docking interactions of both the hit molecules and patent/marketed drugs with the amino acid residues and by understanding the basic pharmacophoric features a hybridized molecule i.e., coumarin amido substituted imidazole-2-one derivatives were designed as a NEW DUAL INHIBITIORS OF mPGES-1/5-LOX. To calculate the molecular properties of the compounds Molinspiration cheminformatics has been used and through that it is interpreted that all the compounds are druggable compound as none of the compound has violated Lipinski rule of five all the results were under the limits. OSIRIS property explorer was used to estimate toxicity profile all the designed compounds showed non-tumorigenic and non-reproductive effect. The prediction of toxicity profile prior biological evaluation would save the animals, time and investment as well. Molecular docking studies were performed to estimate the correct binding interactions of the title compounds with both the PDB ID's 3DWW and 6NCF and good binding scores were obtained. For the prediction of pharmacokinetic properties Swiss ADME online tool has been used. All the compounds showed high GI absorption and no BBB penetration was seen.

CONCLUSION

In the present research investigation, imidazolones, their derivatives and coumarins, their derivatives evince a wide range of biological activity including anti-inflammatory activity. Inflammation was inhibited with the inhibition of PGE_2 synthesis by targeting mPGES-1 (which is the terminal enzyme regulating inflammation) simultaneously with the inhibition of leukotrienes synthesis by targeting 5-LOX enzyme in order to achieve complete inhibition of inflammation without disturbing the normal gastroprotection function and other physiological activities. To carry out the work 100 molecules of imidazolone and 100 molecules of coumarin was retrieved from PubChem database and for those molecules virtual screening has been performed. 12 HITS were selected, 6 from imidazolone and other 6 from coumarins based on the highest scores and docking has been performed for selected molecules and by understanding their pharmacophoric features a hybridized molecule i.e., coumarin amido substituted imidazole-2-one derivatives were designed as a NEW DUAL INHIBITIORS OF mPGES-1/5-LOX, their molecular properties alongside toxicity studies have also been studied. Molecular docking was also carried out in order to find out the binding affinity and correct binding conformation with the intention to save time as well as huge investment. Pharmacokinetics profile reveal that the compounds are druggable. All the compounds were predicted as potential therapeutic agents.

Future Prospective

However, growing evidences suggest us that dual inhibitor such as mPGES-1/5-LO inhibitors might work effectively and all the designed title compounds can be synthesized however clinical trials will additionally validate this present novel concept in future. And mPGES-1 is not only a target for inflammation but is an attractive target for the cancer as well.

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