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Design and Synthesis of Flavonoid Derivatives as Anti-inflammatory Drug

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ABSTRACT

A series of 2-(3'-aminesubstituted)-7-hydroxyl-4H-1-benzopyran-4-one amine derivatives has been synthesized on the basis of molecular docking results. The novel derivatives prepared by condensation of 2,4-Dihydroxyacetophenonee (1.40 ml) and 3-chlorobenzaldehyde (0.01 mole) through Claisen-Schmidt condensation reaction. Novel flavone derivatives were access for anti-inflammatory activity by using carrageenan induced rat paw edema method. Among the synthesized compounds (t, v, w, k) shows good anti-inflammatory activity comparable to reference drug (Celecoxib).

Keywords: Molecular docking; Synthetic flavone; Claisen Schmidt condensation reaction; Anti-inflammatory; Celecoxib

INTRODUCTION

Flavonoids based on the backbone of 2-phenyl-4H-chromen-4-one (2-phenyl-1-benzopyran-4-one). The molecular formula of flavone molecule is $C_{15}H_{10}O_2$. It has three-ring skeletons, C_6-C_3-C_6 and the rings are referred to as A, C and B rings, respectively. They are found in seeds, citrus fruits, olive oil, tea and red wine, vegetables, nuts, stems and flowers, honey and are commonly consumed with the human diet. 2-(3'-aminesubstituted)-7-hydroxyl-4H-1-benzopyran-4-one derivatives these are Non-Steroidal Anti Inflammatory drugs (NSAIDs) exhibit their effect by inhibiting COX enzymes and by blocking the synthesis of prostaglandins [1-3].

In a literature, revealed that, flavone shows good to moderate anti-inflammatory activity. It is also observed that the flavone moiety should possess following characteristic pharmacophore pattern which is essential for binding to cyclooxygenase enzyme and their by its inhibition. Flavone possess following pharmacophoric pattern (Figure 1).

- The ligand should possess suitably positioned hetero atom, which strongly interact with heme iron.
- The ligand should have a hydrophobic spacer moiety between heme coordinating group and hydrogen bond acceptor moiety.
- Cyclooxygenase inhibitors need a chemical group that is able to accept H-bond from serine 478 present in active site.

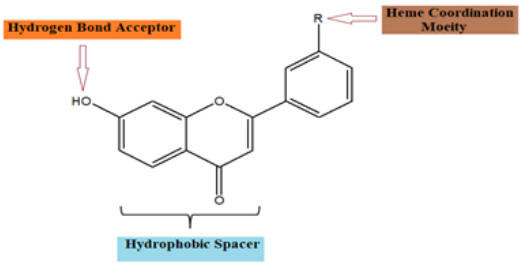

Figure 1: Pharmacophore pattern of cyclooxygenase inhibitors.

On the basis of literature and Pharmacophore pattern of non-steroidal aromatase inhibitors, the aim of present work is, to synthesize novel flavone derivatives, aliphatic/aromatic amines for anti-inflammatory screening *i.e.,* as a fundamental hetero-aliphatic/aromatic system with modification.

MATERIALS AND METHODS

Molecular docking of flavones studies on COX-2 enzyme

Molecular docking studies of all proposed flavones derivatives were carried using maestro 11.5 Schrodinger software. Glide score is the function, designed to calculate the free energy of binding for a protein ligand complex.

XPGlide score=$E_{coul}+E_{vdw}+E_{bind}+E_{penalty}$

Where, $E_{bind}=E_{hyd\text{-}enclosure}+E_{h\text{-}bond\ modif}+E_{h\text{-}bond\_cc\_modif}+E_{Pi\ interaction}+E_{h\text{-}bond\ pair}$

$E_{penalty}=E_{disolve}+E_{ligand\ strain}$

Hydrogen bonds provides stability to the protein-ligand complex, that means more the number of hydrogen bonding with protein, more will be the fitting of ligand molecule in the binding pocket and hence stay more bound or docked with the receptor. These provide stability to the complex [4-6].

RESULTS AND DISCUSSION

Total 8 molecules of flavones were designed and docked on COX-2 enzyme. Out of these, three molecules with good hydrogen bond interactions and glide score as compared to standard celecoxib are selected. Which includes (t,v,w,k) The Glide score (G-score) and the number of H bonds of all docked ligands and the standard SC-558, Celecoxib are shown in Table 1.

Table 1: Docking score, Glide score (G-score) and number of H-bonds for the flavones and celecoxib.

Compound code	Docking score (Kcal/mole)	Glide score (Kcal/mole)	H-bonds
a	-8.253	-8.253	0
b	-9.077	-9.089	2
c	-8.06	-8.06	0
k	-8.331	-8.443	1
l	-8.574	-8.594	2
t	-10.916	-10.928	3
v	-11.086	-11.099	3
w	-10.525	-10.538	3
Celecoxib	-11.197	-11.198	3

Compound t, v, w possess 3 hydrogen bonding and having glide score of -10.928, -11.099 and -10.538 respectively, compound k has single hydrogen bonding and quiet good dock score. a and c have no hydrogen bonding with COX-2 enzyme [7-10]. It is reported in the literature that good bonding with Tyr355, Arg120, Leu531, Ser353, Ser530 and Tyr 385 is required for good affinity and also for good fitting of the compounds when docked into the enzyme pocket. Therefore from the docking result compound t, v, w, k are considered for the synthesis which may shows good anti-inflammatory activity (Table 2 and Figures 2-5) [11-15].

Table 2: Amino acids of 1CX2 enzyme making H-bonding interactions, π-π and π-cation interactions with celecoxib and novel flavones.

S. No.	Compound	Name of amino acids involved in interaction with ligands
1	Celecoxib	SER 353, LEU 352, ARG 513
2	t	TYR 355, MET 522
3	v	MET 522, TYR 385, TYR 355
4	w	MET 522, TYR 385, PHE 518

From above Table 2 it is clear that flavones showed good hydrogen bonding, π-π stacking and π-cation bonding with COX-2 enzyme.

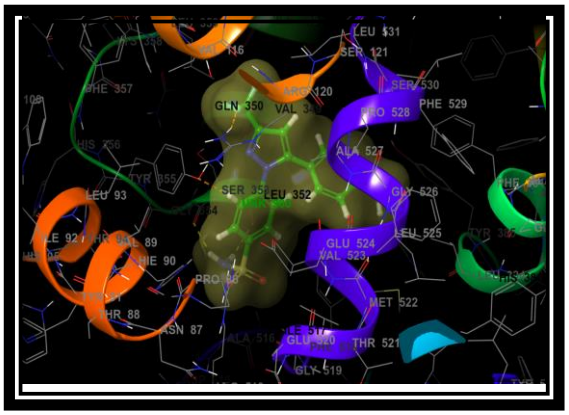

Figure 2: Ribbon structure of COX-2 enzyme with celecoxib.

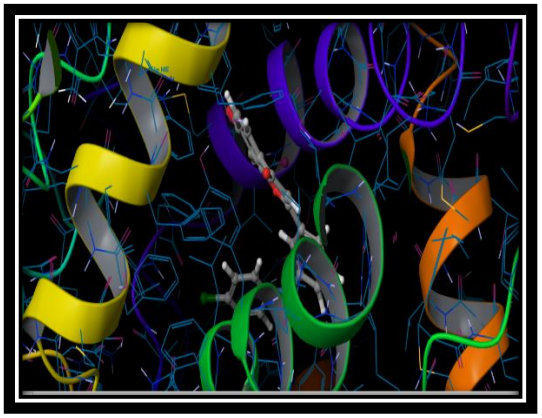

Figure 3: Ribbon structure of COX-2 enzyme with (v).

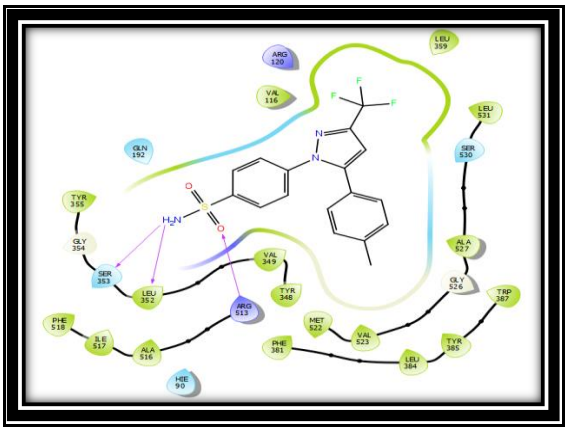

Figure 4: Amino acids of COX-2 enzyme showing hydrogen contacts with celecoxib.

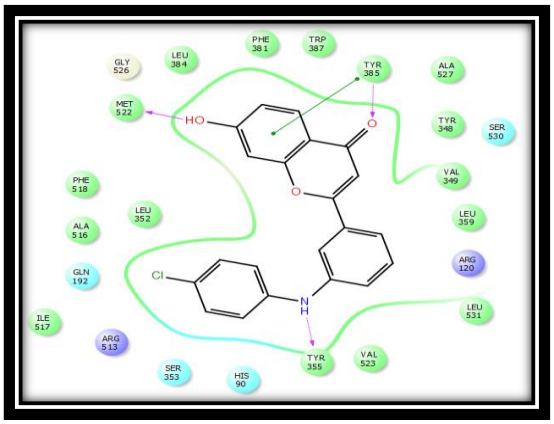

Figure 5: Amino acids of COX-2 enzyme showing hydrogen contacts with (v).

Synthetic work

In the present work, synthesis of novel flavone derivatives was carried out by reacting 2, 4-dihydroxyacetophenone with 3-chlorobenzakdehyde in basic medium in microwave for 3 min at level 5 to gives 3-(3'-chlorophenyl)-1-(2,4-dihydroxyphenyl)-prop-2-en-1-one shown in step: I. Further it is, cyclized in microwave for 2-3 min at level 5 to in the presence of DMSO/I2 or H_2O_2/ NaOH to form 2-(3'-chlorophenyl)-7- hydroxyl-4H-1-benzopyran-4-one step: II. Finally synthesis of all proposed novel flavone derivatives was carried out by adding a aliphatic or aromatic amines to a 2-(3'-chlorophenyl)-7- hydroxyl-4H-1-benzopyran-4-one in pyridine, then mixture was irradiated in microwave for 2-3 min at level 5 to achieve target derivatives step: III. Crude product was then crystallized from methanol (Figure 6) (Tables 3-5) [15-20].

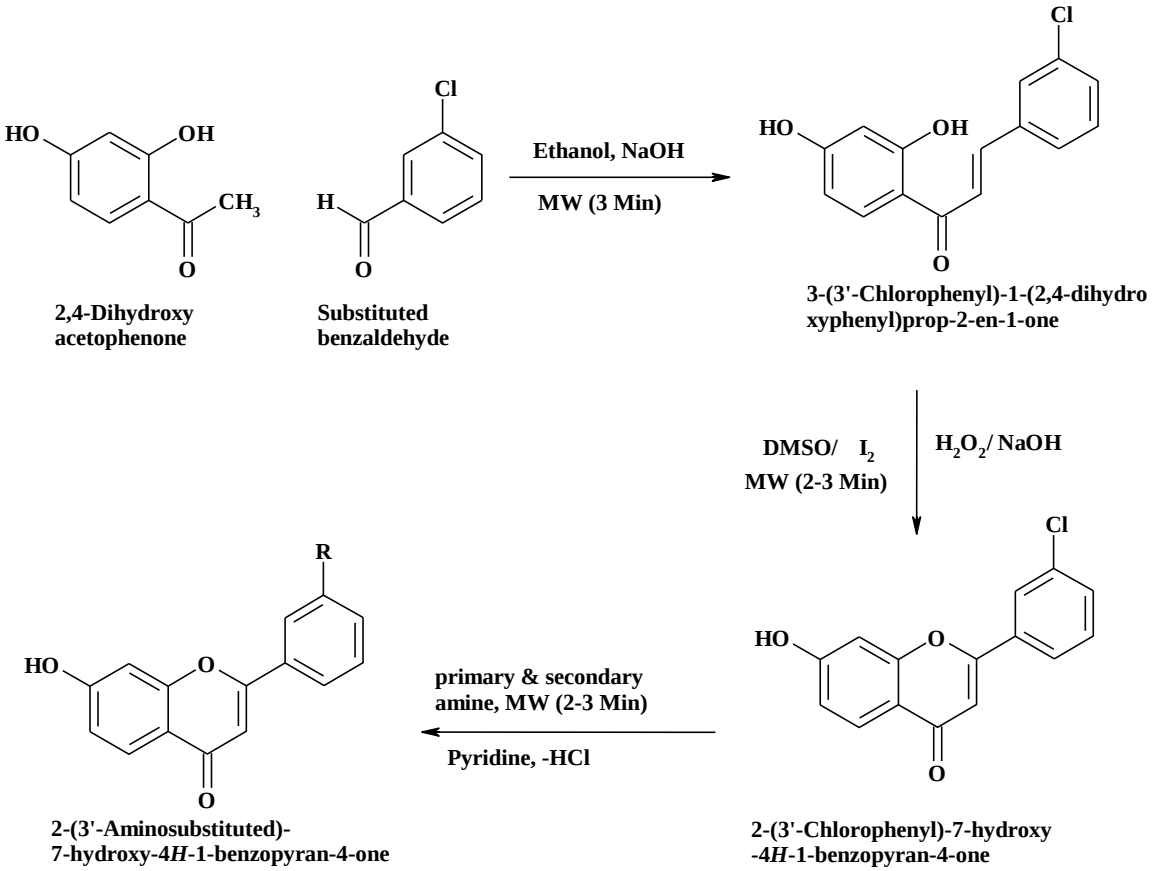

Figure 6: Synthesis of novel flavone derivatives.

Table 3: Derivatives of novel flavonoids.

Sr. no.	Compound	-R/Ar	S. No.	Compound	-R/Ar
1	A	Methylamino	5	l	Ethylmethylamino
2	B	Ethylamino	6	t	*p*-Methylaniline,
3	C	Propylamino	7	v	*p*-Chloroaniline
4	K	Diethylamino	8	w	*p*-Nitroaniline

Table 4: Characterization data for 2-(3'-aminesubstituted)-7- hydroxyl-4*H*-1-benzopyran-4-one derivatives.

Sr. No.	Code	Molecular formula	Mol. weight (g/mol)	Yield %	Melting point (°C)	Rf-value	U.V. λ_{max} (nm)
1	a	$C_{16}H_{13}NO_3$	267	63.12	178-180	0.6	241.6
2	b	$C_{17}H_{14}NO_3$	280	57	184-185	0.82	309.2
3	c	$C_{18}H_{17}NO_3$	295	57.86	187-190	0.84	297
4	k	$C_{19}H_{19}NO_3$	309	66.21	179-182	0.62	298
5	l	$C_{18}H_{17}NO_3$	295	59.09	181-183	0.47	319
6	t	$C_{22}H_{18}NO_3$	365	72.25	190-195	0.72	340

7	v	$C_{21}H_{15}NO_3CI$	375	69.24	192-196	0.82	290
8	w	$C_{21}H_{15}N_2O_5$	344	70.16	190-194	0.68	318

Table 5: Anti-inflammatory activity obtained by carrageenan induced rat paw edema method and comparative study of inhibition (%I) for anti-inflammatory activity by carrageenan induced rat paw edema method.

Sr. No.	Groups	Mean of paw volume (mL)				± SEM				% Inhibition of paw edema			
		0 h	1 h	2 h	3 h	0 h	1 h	2 h	3 h	0 h	1 h	2 h	3 h
1	Control	0.51	0.57	0.56	0.55	0.087	0.098	0.095	0.098	--	--	--	--
2	A	0.56	0.47	0.46	0.45	0.098	0.142	0.096	0.122	--	17.55	17.86	18.19
3	B	0.56	0.47	0.46	0.45	0.098	0.142	0.096	0.122	--	16.2	16.8	17.02
4	C	0.57	0.48	0.46	0.46	0.098	0.102	0.096	0.096	--	16.79	16.04	17.37
5	K	0.57	0.43	0.38	0.32	0.08	0.128	0.124	0.107	--	23.7	33.14	44.03
6	L	0.51	0.43	0.46	0.4	0.102	0.143	0.149	0.145	--	24.57	25	27.28
7	T	0.57	0.43	0.38	0.3	0.098	0.128	0.128	0.109	--	30.7	39.14	40.03
8	V	0.57	0.43	0.42	0.41	0.098	0.143	0.149	0.16	--	21.46	24	24.46
9	W	0.51	0.36	0.3	0.2	0.102	0.092	0.088	0.052	--	43.26	43.75	45.08
10	Celecoxib	0.54	0.38	0.38	0.27	0.096	0.104	0.104	0.087	--	33..34	32.15	45.91

CONCLUSION

From present work it is prove that novel series of 2-(3'-aminesubstituted)-7- hydroxyl-4H-1-benzopyran-4-one derivatives has been synthesized, physical characteristics followed by the anti-inflammatory screening occurs. Derivatives (t, v, w, k) shows the good anti-inflammatory activity when compared against vehicle treated control and standard celecoxib.

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