ISSN No:-2456-2165

Synthesis and Biological Evaluation of Novel Flavones Derivatives, as Dual Anticancer Anti-Inflammatory Agents

Reshma Tendulkar [*a], Supriya Mahajan[b]
[a], Pharmaceutical Chemistry Department, H.K.College of Pharmacy, Mumbai University, Jogeshwari, India; [b] C.U.Shah college of Pharmacy, S.N.D.T University, Santacruz, India

Abstract

- ***Background:***

Numerous series of flavones (FL1- FL25) were designed and synthesized to screen dual anticancer and anti-inflammatory activities.

- ***Methods:***

The products were characterized by FTIR, 1 H NMR and Mass spectroscopy. In *vivo* carrageenan-induced rat paw-edema model was used to assess their anti-inflammatory activity. Their *in vitro* anticancer behavior were evaluated using MCF-7 (breast cancer) and HT-29 (colorectal) cell lines by SRB assay method.

- ***Results:***

For MCF-7 cell line, out of twenty five flavones, sixteen compounds showed total growth inhibition at drug concentrations of 69.7 to 98.7 µM and for the standard, Adriamycin, the concentration for the same was <0.1 Mm. In addition, out of twenty-five synthesized compounds, eleven compounds showed good anti-inflammatory activity and two compounds showed improved anti-inflammatory activity than that of Indomethacin (10 mg/Kg).

- ***Conclusion:***

It can be concluded that novel series of flavones, have the prospective to be developed into new anticancer and anti-inflammatory agents.

Keywords:- *Anti-Inflammatory, Anticancer, Flavones, MCF-7, Carrageenan*

I. INTRODUCTION

Cancer is defined as a malignant growth or tumor in different parts of the body that tends to multiply indefinitely and to replicate itself, as also to come back after removal. It eats away or corrodes the part in which it is located, and usually ends in death. Cancer is the second foremost cause of human death following cardiovascular diseases, worldwide, and more than 70 % of all cancer deaths occurred in developing and under-developed countries [1]. There is a incessant rise of deaths from various cancers globally and with an estimated 12 million deaths in 2030 [2]. In 2012, International Agency for Research on Cancer (IARC) statistics for global cancer burden estimates were 14.1 million new cases (being 12.7 million new cases as an estimate for the year 2008) and in the Indian scene, 1.1 million new cancer cases estimated signifying India as a single country contributing to 7.8 % of global cancer burden [3]. Various different therapeutic strategies are presently available for cancer treatments, including chemotherapy and radiotherapy. However, systemic toxicity of the chemotherapeutic agents and emergence of drug resistant tumors limit the successful outcomes in most cases. Among the cancers, breast cancer is the most widespread cancer, especially in women, and it is the second leading cause of death (after lung cancer) in women [4].

Inflammation is a significant component of tumor progression. Many cancers crop up from sites of infection, chronic irritation and inflammation. It is now becoming apparent that the tumor microenvironment, which is mainly orchestrated by inflammatory cells, is an indispensable participant in the neoplastic process, nurturing proliferation, survival and migration [5]. Non-steroidal anti-inflammatory drugs (NSAIDS) are most extensively used to decrease pain and swelling in the treatment of rheumatoid arthritis and other inflammatory diseases. They block the metabolism of arachidonic acid (AA) by inhibiting the enzyme cyclooxygenase (COX) [6]. Hence, long-term use of NSAIDs has been linked with gastrointestinal ulceration, bleeding and nephrotoxicity.

Flavones restrain a number of enzymes such as aldose reductase, xanthine oxidase, phosphodiesterase, Ca $^{(+2)}$ ATPase, lipoxygenase, cyclooxygenase, etc. They also have a regulatory function on different hormones like estrogens, androgens and thyroid hormone [7]. They have been found to have anti-inflammatory activity in both proliferative and exudative phases of inflammation [8]. Thus, anti-inflammatory activity of flavones can adjoin up to their anticancer activity.

Based on these result, the objective of this study was to synthesize newly designed flavones that have the potential to perform as a dual anticancer anti-inflammatory agent. In this study, twenty-five flavones derivatives were synthesized and their anti cancer and anti-inflammatory activities were tested.

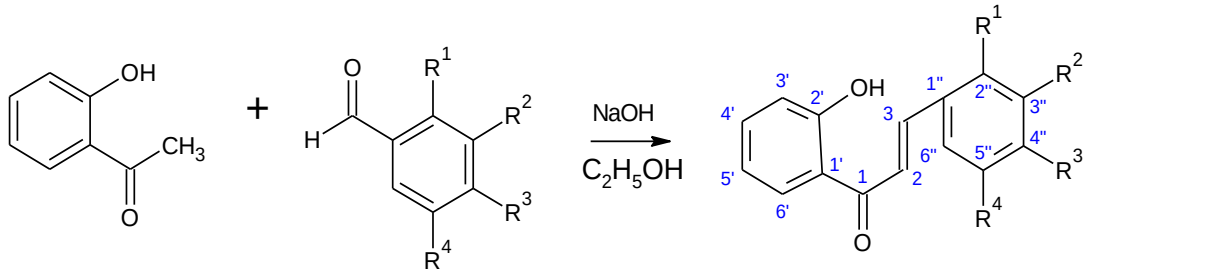
II. CHEMISTRY

Twenty five flavones (**FL1 to FL25**) were synthesized from chalcones on the laboratory level by the conventional and microwave irradiation techniques. The reactions concerned in the synthesis of chalcones and flavones are shown in **Scheme1.**

For the synthesis of chalcones **C1 to C25** by the conventional method, a solution of NaOH (2.5 mmol in 10 ml) in ethanol (20 ml) was added to a mixture of aromatic aldehydes and o-hydroxyacetophenone (1 mmol) in a conical flask. After heating on water bath for about 15 min, the reaction was quenched with ice and then concentrated HCl was added slowly with stirring till the reaction became acidic. A pale yellow solid which separated, was filtered and washed with ice cold water followed by recrystallization by means of absolute ethanol to afford 2^{l}-hydroxychalcone, which was monitored by thin layer chromatography (TLC) on silica gel G coated plates using a appropriate mobile phase.

The oxidative cyclization of chalcones to flavones was carried out by the conventional method [9] as follows-

A substituted chalcone (**C1 to C25**, 1 mmol) was oxidized by refluxing it with DMSO and the solution of iodine (0.02 mmol). The reaction was monitored by thin layer chromatography. The solid obtained after dilution with surplus amount of water was filtered and washed with aqueous sodium thiosulphate till the product became colourless. Flavones thus obtained was washed with water and recrystallized from a suitable solvent.



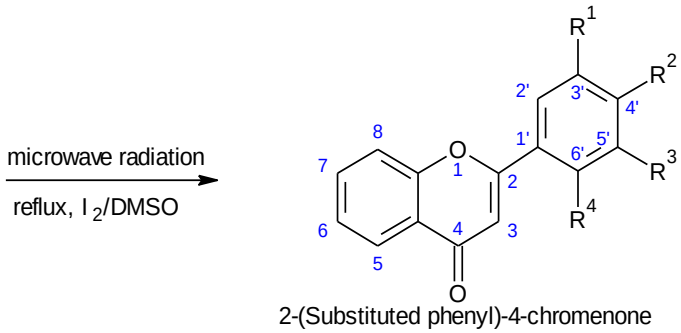


Fig 1:- Synthesis of chalcones (C1-C25) and flavones (FL1-FL25)

III. EXPERIMENTAL PROTOCOLS

A. Chemistry

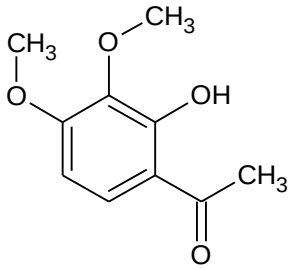
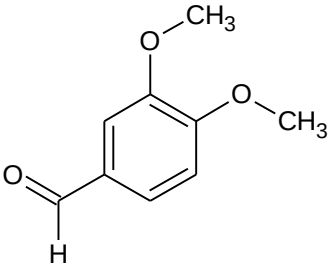
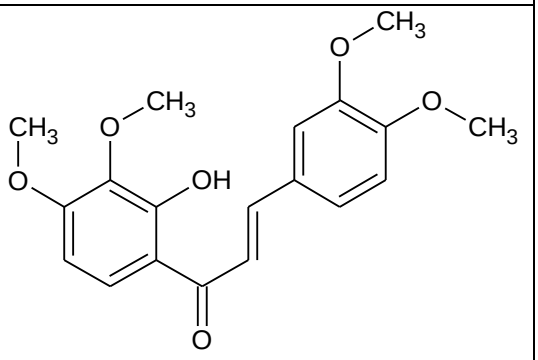
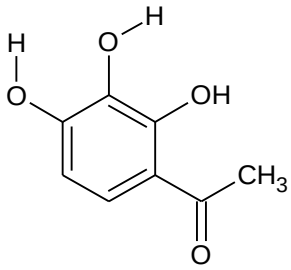
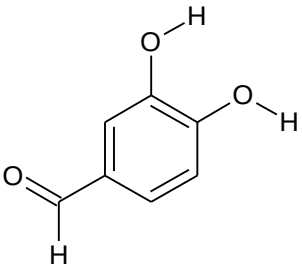
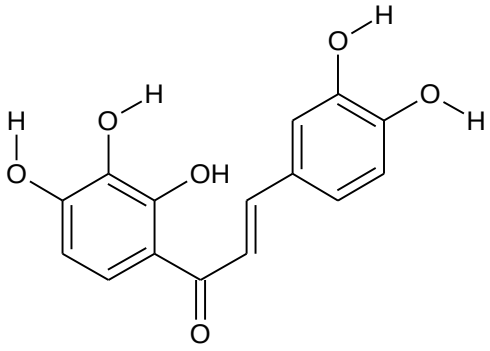
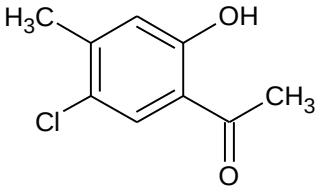
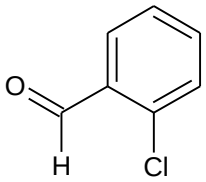
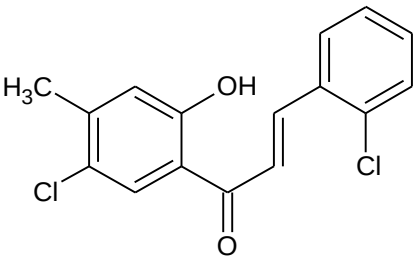
Melting points of the synthesized compounds were determined by open capillaries using Expo-Hi-tech melting point apparatus. The structures of the synthesized compounds were characterized by recording their IR spectra by means of KBr disc method. The structures were confirmed by recording their ^{1}H-NMR spectra using TMS as an internal reference. Chloroform and DMSO were used as solvents for recording ^{1}H NMR spectra. Mass spectroscopy was also carried out for confirming the structures of the synthesized compounds.

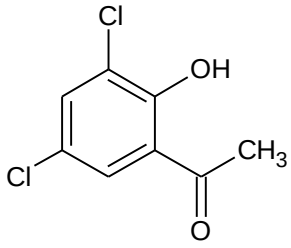
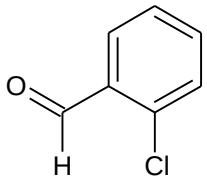
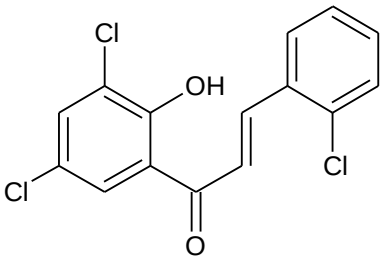
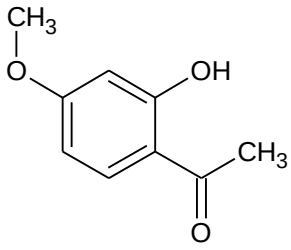
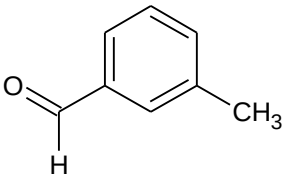
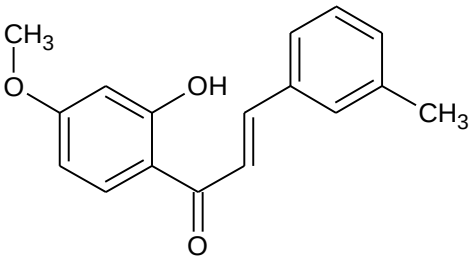
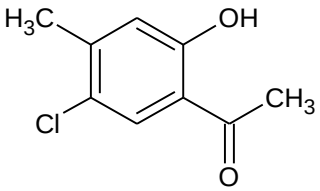
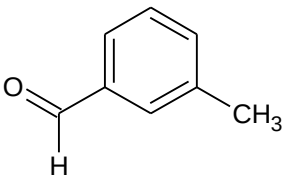
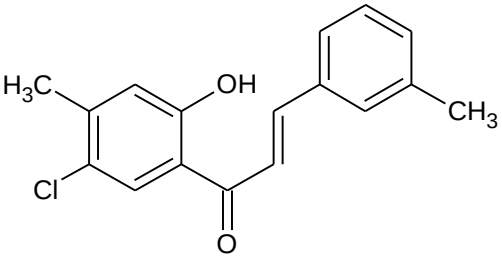
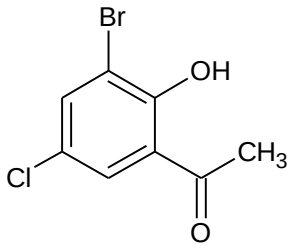
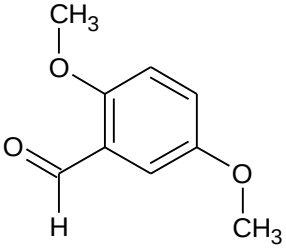
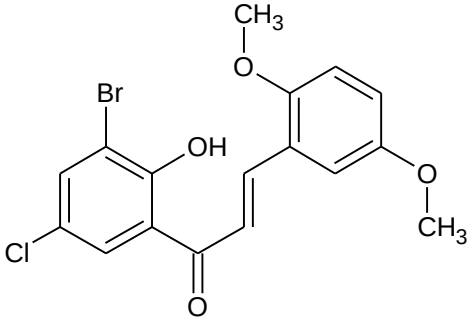
➢ *Synthesis of chalcones or 1-(2^{l}-Hydroxy phenyl)-3-(substituted phenyl)-2-propene 1-one (Compounds C1-C25)*

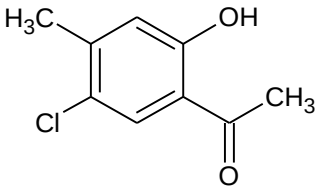
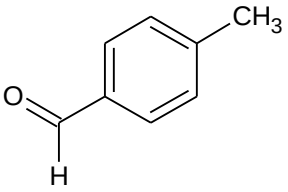
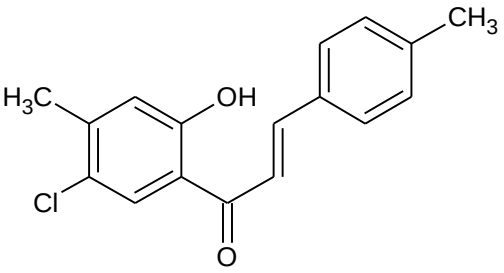
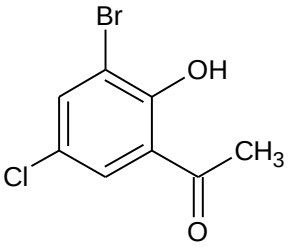
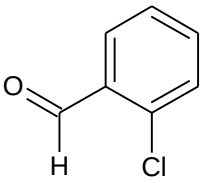
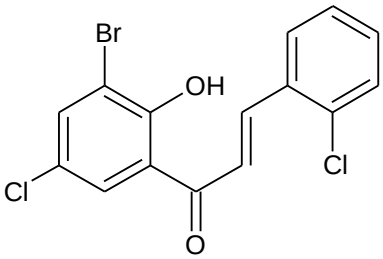
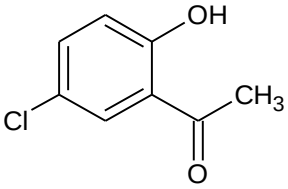
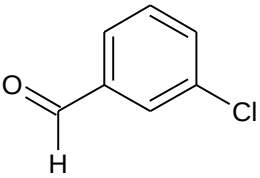
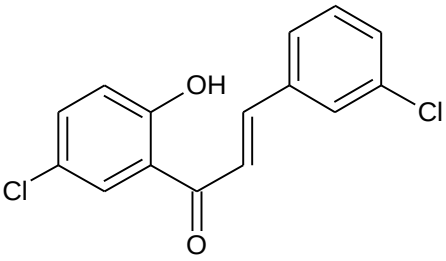
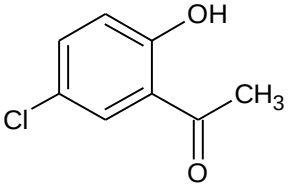
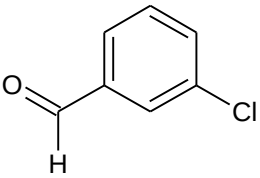
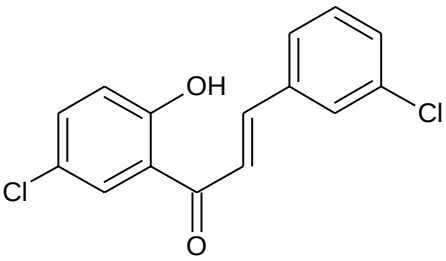
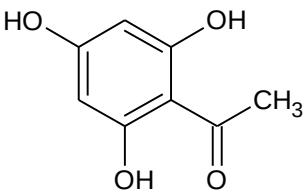
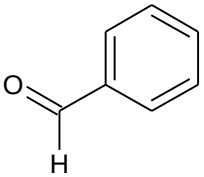
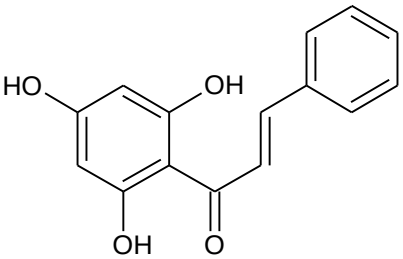
The reaction scheme for the synthesis of chalcones is shown in Scheme 1. All chalcones were synthesized by conventional method only.

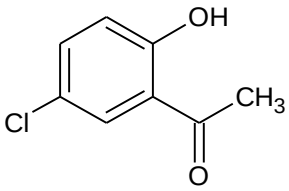
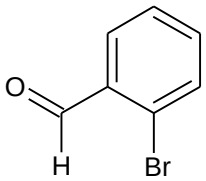
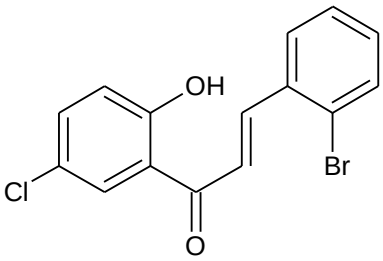
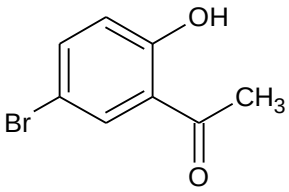
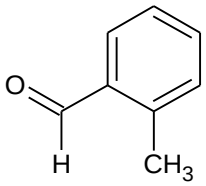
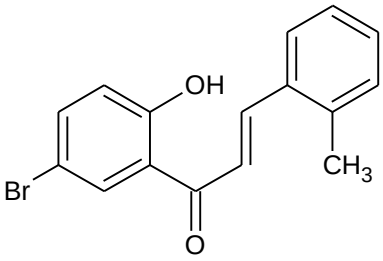
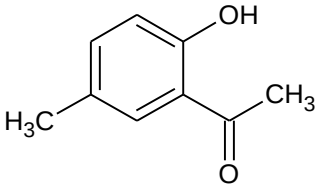
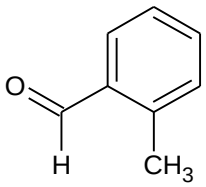
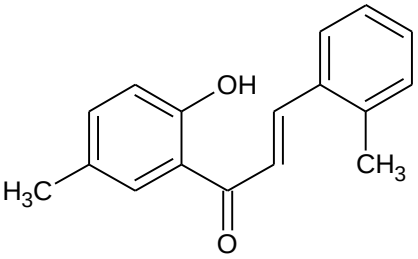
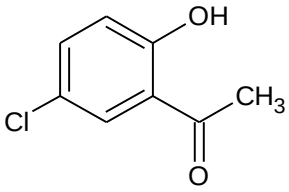
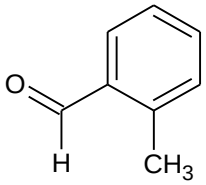
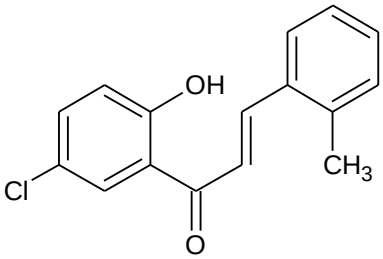
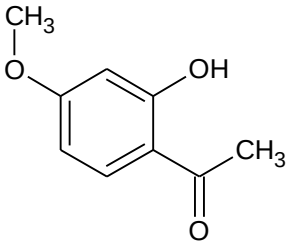
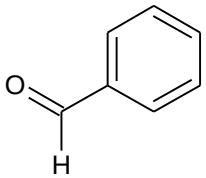
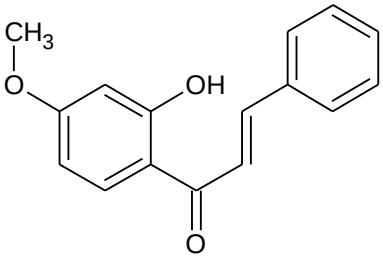
The general synthetic strategy employed to synthesize chalcones **C1 to C25** (reaction scheme was shown in Scheme 1) was based on Claisen-Schmidt condensation [11]. A solution of NaOH (2.5 mM in 10 ml) in ethanol (20 ml) was added to a mixture of substituted benzaldehyde (1 mm) and o-hydroxyacetophenone (1 mM) in a conical flask. After heating on water bath for about 15 min, the reaction was quenched with ice, and then conc. HCl was added slowly with stirring till the reaction became acidic. A

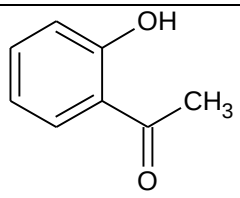
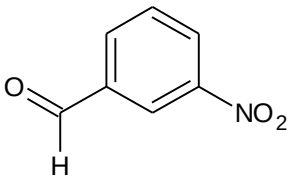
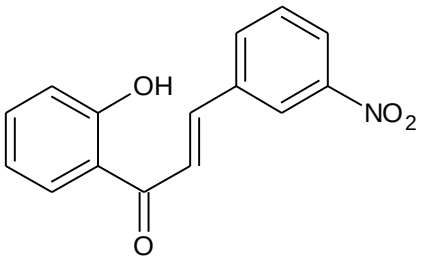
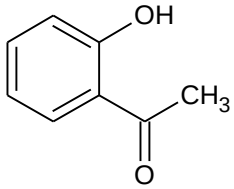
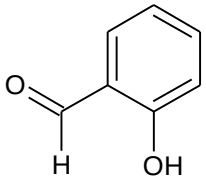
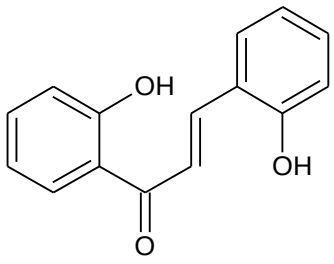
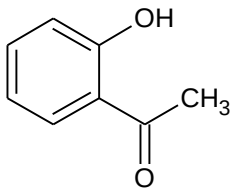
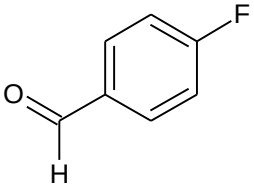
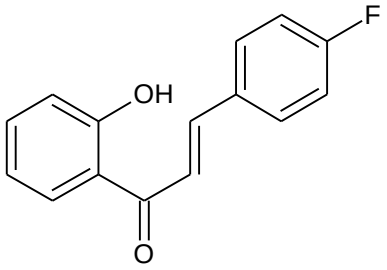
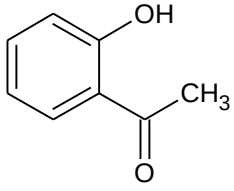
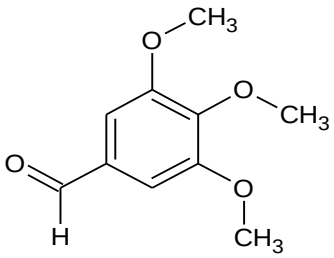
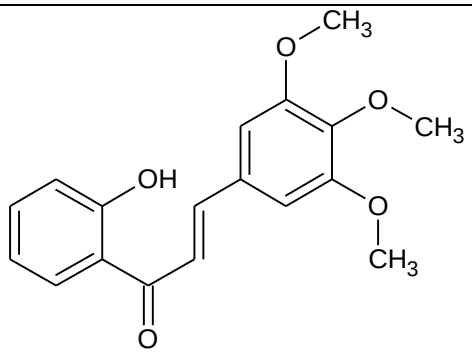
pale yellow solid which separated, was filtered and washed with ice cold water, followed by recrystallization using absolute ethanol, to acquire 2^{I}-hydroxy chalcone, which was monitored by thin layer chromatography (TLC) on silica gel G coated plates, using a proper mobile phase.

Compound no.	Ketone used	Aldehyde used	Structure of chalcones
C1	 2-Hydroxy-3,4-dimethoxyacetophenone	 3,4-Dimethoxybenzalehyde	 1-(2^{I}-Hydroxy-3^{I},4^{I}-dimethoxyphenyl)-3-(3^{II},4^{II}-dimethoxyphenyl)-2-propene-1-one
C2	 2,3,4-Trihydroxyacetophenone	 4,5-Dihydroxybenzalehyde	 1-(2^{I}-Hydroxy-3^{I},4^{I}-hydroxyphenyl)-3-(3^{II},4^{II}-dihydroxyphenyl)-2-propene-1-one
C3	 5-Chloro-2-hydroxy-4-methylacetophenone	 2-Chlorobenzalehyde	 1-(4^{I}-Chloro-2^{I}-hydroxy-3^{I}-methylphenyl)-3-(6^{II}-chlorophenyl)-2-propene-1-one

C4	 3,5-Dichloro-2-hydroxyacetophenone	 2-Chlorobenzalehyde	 1-(3^{I},5^{I}-Dichloro-2^{I}-hydroxyphenyl)-3-(6^{II}-chlorophenyl)-2-propene-1-one
C5	 2-Hydroxy-4-methoxyacetophenone	 3-Methylbenzalehyde	 1-(2^{I}-Hydroxy-4^{I}-methoxyphenyl)-3-(5^{II}-methylphenyl)-2-propene-1-one
C6	 5-Chloro-2-hydroxy-4-methylacetophenone	 3-Methylbenzalehyde	 1-(5^{I}-Chloro-2^{I}-hydroxy-4^{I}-methylphenyl)-3-(5^{II}-methylphenyl)-2-propene-1-one
C7	 3-Bromo-5-chloro-2-hydroxyacetophenone	 3,6-Dimethoxybenzalehyde	 1-(3^{I}-Bromo-5^{I}-chloro-2^{I}-hydroxyphenyl)-3-(2^{II},5^{II}-dimethoxyphenyl)-2-propene-1-one

C8	 5-Chloro-2-hydroxy-5-methylacetophenone	 4-Methylbenzalehyde	 1-(5^{I}-Chloro-2^{I}-hydroxy-4^{I}-methylphenyl)-3-(4^{II}-methylphenyl)-2-propene-1-one
C9	 3-Bromo-5-chloro-2-hydroxyacetophenone	 2-Chlorobenzalehyde	 1-(3^{I}-Bromo-5^{I}-chloro-2^{I}-hydroxyphenyl)-3-(6^{II}-chlorophenyl)-2-propene-1-one
C10	 5-Chloro-2-hydroxyacetophenone	 3-Chlorobenzalehyde	 1-(5^{I}-Chloro-2^{I}-hydroxyphenyl)-3-(5^{II}-chlorophenyl)-2-propene-1-one
C11	 5-Chloro-2-hydroxyacetophenone	 3-Chlorobenzalehyde	 1-(5^{I}-Chloro-2^{I}-hydroxyphenyl)-3-(5^{II}-chlorophenyl)-2-propene-1-one
C12	 2,4,6-Trihydroxyacetophenone	 Benzaldehyde	 1-(2^{I},4^{I},6^{I}-Trihydroxyphenyl)-3-(phenyl)-2-propene-1-one

C13	 5-Chloro-2-hydroxyacetophenone	 2-Bromobenzalehyde	 1-(5^{I}-Chloro-2^{I}-hydroxyphenyl)-3-(6^{II}-bromophenyl)-2-propene-1-one
C14	 5-Bromo-2-hydroxyacetophenone	 2-Methylbenzalehyde	 1-(5^{I}-Bromo-2^{I}-hydroxyphenyl)-3-(6^{II}-methylphenyl)-2-propene-1-one
C15	 2-Hydroxy-5-methylacetophenone	 2-Methylbenzalehyde	 1-(2^{I}-Hydroxy-5^{I}-methylphenyl)-3-(6^{II}-methylphenyl)-2-propene-1-one
C16	 5-Chloro-2-hydroxyacetophenone	 2-Methylbenzalehyde	 1-(5^{I}-Chloro-2^{I}-hydroxyphenyl)-3-(6^{II}-methylphenyl)-2-propene-1-one
C17	 2-Hydroxy-4-methoxyacetophenone	 Benzaldehyde	 1-(2^{I}-Hydroxy^{I},4^{I}-methoxyphenyl)-3-(phenyl)-2-propene-1-one

C18	 2-Hydroxyacetophenone	 3-Nitrobenzalehyde	 1-(2^{I}-Hydroxyphenyl)-3-(5^{II}-nitrophenyl)-2-propene-1-one
C19	 2-Hydroxyacetophenone	 2-Hydroxybenzalehyde	 1-(2^{I}-Hydroxyphenyl)-3-(6^{II}-hydroxyphenyl)-2-propene-1-one
C20	 2-Hydroxyacetophenone	 4-Fluorobenzalehyde	 1-(2^{I}-Hydroxyphenyl)-3-(4^{II}-fluorophenyl)-2-propene-1-one
C21	 2-Hydroxyacetophenone	 3,4,5-Trimethoxybenzalehyde	 1-(2^{I}-Hydroxyphenyl)-3-(3^{II},4^{II},5^{II}-trimethoxyphenyl)-2-propene-1-one

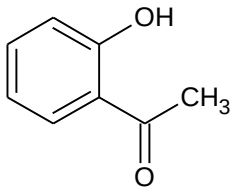
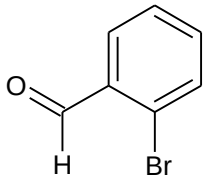
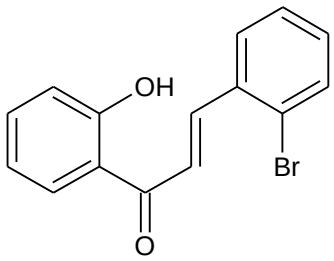
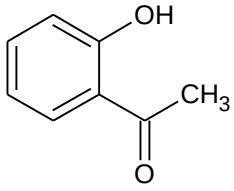
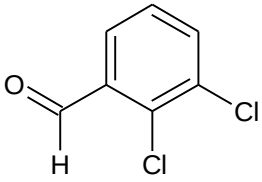
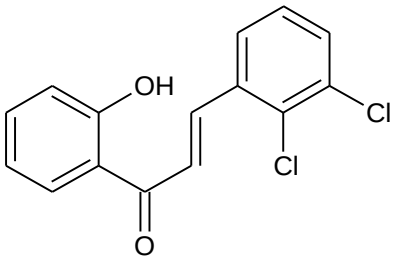
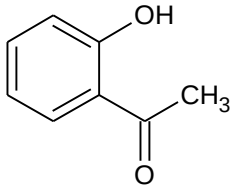
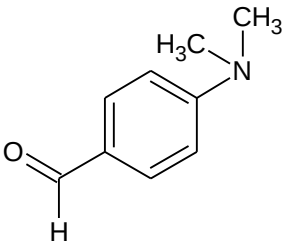
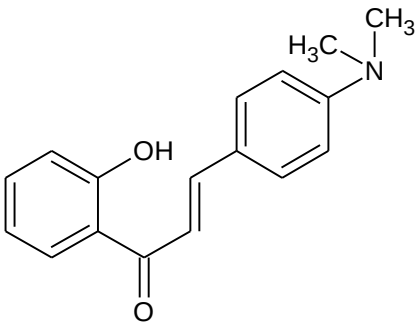
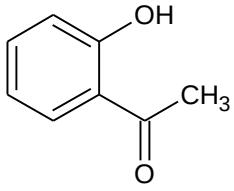
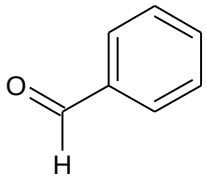
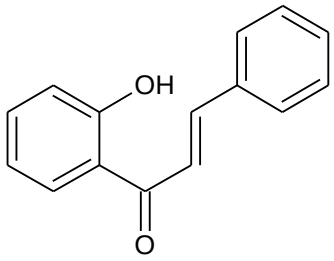
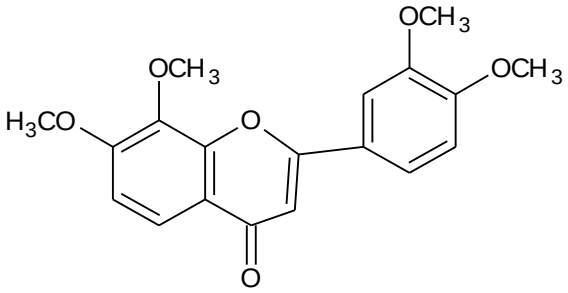
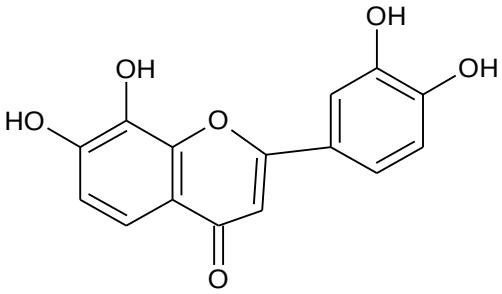
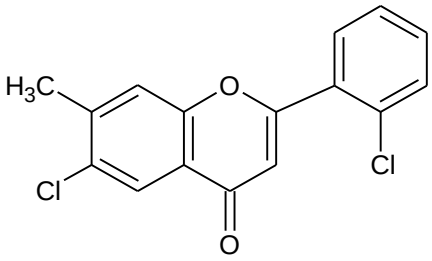
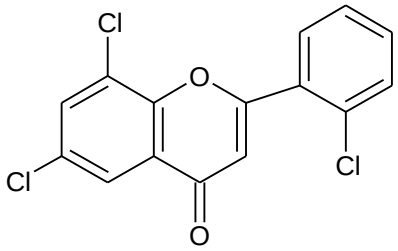
C22	 2-Hydroxyacetophenone	 2-Bromobenzalehyde	 1-(2^{I}-Hydroxy-3^{I},4^{I}-dimethoxyphenyl)-3-(2^{II},3^{II}-dimethoxy)-2-propene-1-one
C23	 2-Hydroxyacetophenone	 2,3-Dichlorobenzalehyde	 1-(2^{I}-Hydroxy-3^{I},4^{I}-dimethoxyphenyl)-3-(2^{II},3^{II}-dimethoxy)-2-propene-1-one
C24	 2-Hydroxyacetophenone	 4-Dimethylaminobenzalehyde	 1-(2^{I}-Hydroxy-3^{I},4^{I}-dimethoxyphenyl)-3-(2^{II},3^{II}-dimethoxy)-2-propene-1-one
C25	 2-Hydroxyacetophenone	 Benzaldehyde	 1-(2^{I}-Hydroxy-3^{I},4^{I}-dimethoxyphenyl)-3-(2^{II},3^{II}-dimethoxy)-2-propene-1-one

Table 1:- Structures of chalcones (C1-C25) and ketones and aldehydes used for their synthesis

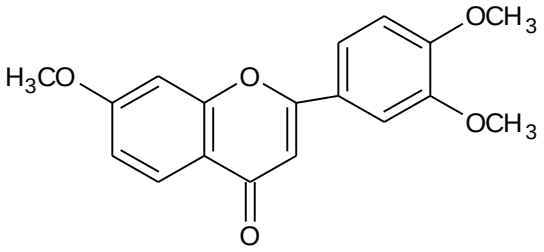
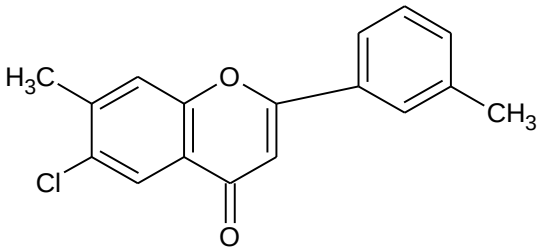
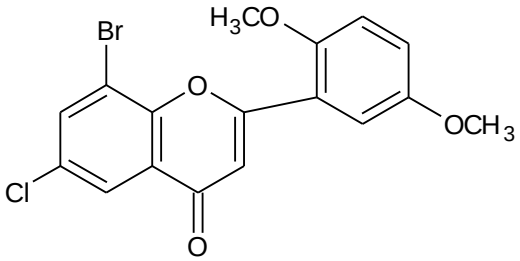
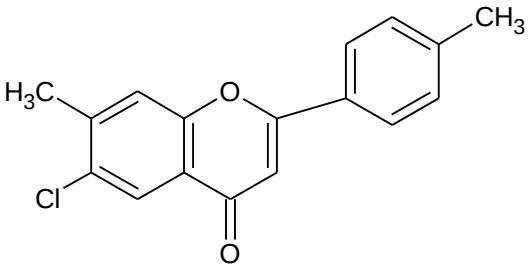
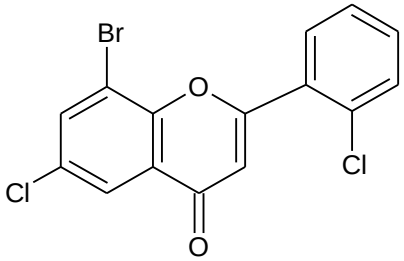
➢ *Synthesis of flavones or 2-(substituted phenyl)-4-chromenone (Compounds FL1- FL25)*

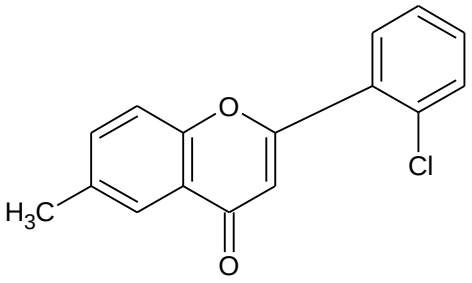
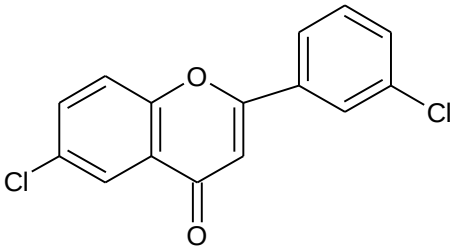
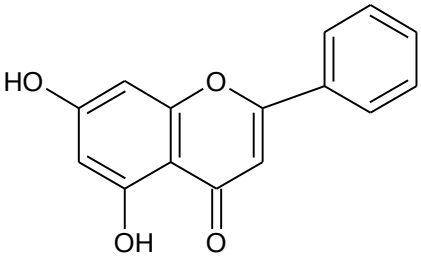
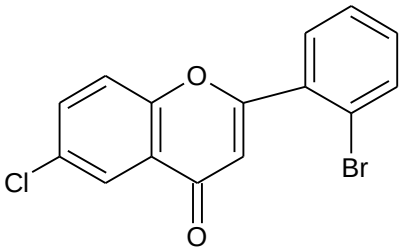
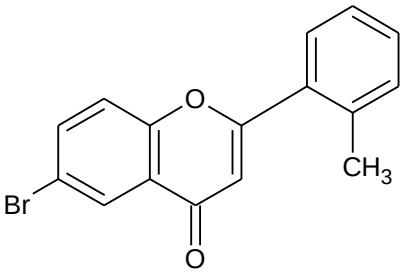
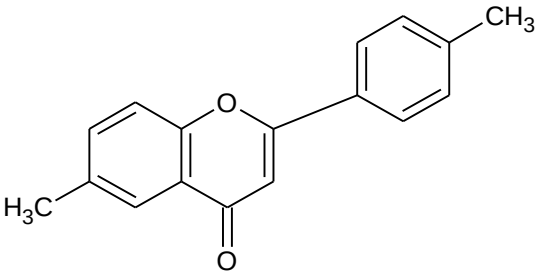
A substituted chalcone (**C1 to C25**, 1 mM) was oxidized by refluxing it with DMSO and the solution of iodine (0.02 mM). The reaction was monitored by thin layer chromatography. The solid obtained after dilution with excess of water was filtered, washed with aqueous sodium thiosulphate till the product became colourless. Flavone (**FL1 to FL25)** thus obtained was washed with water and recrystallized from a suitable solvent.

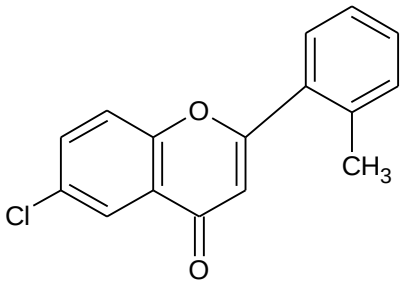
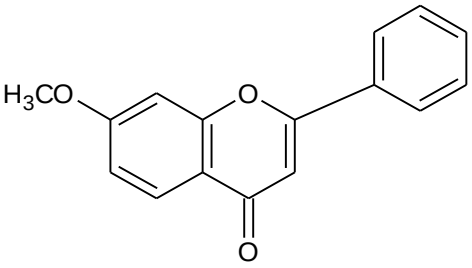
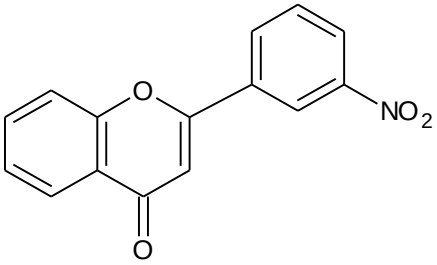
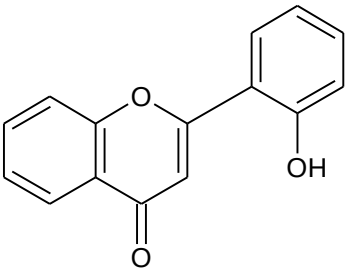
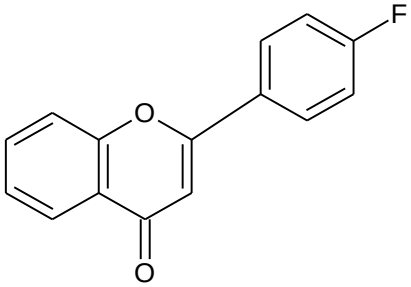
ISSN No:-2456-2165

Compd.	Chalcones used for synthesis (mentioned in Table 5.2, p-95)	Flavones
FL1	C1	 2-(3',4'-Dimethoxyphenyl) - 7,8-dimethoxy-4-chromenone
FL2	C2	 2-(3',4'-Dihydroxyphenyl)- 7,8-dihydroxy-4-chromenone
FL3	C3	 2-(6'-Chlorophenyl)- 6-chloro-7-methyl -4-chromenone
FL4	C4	 2-(6'-Chlorophenyl)- 6,8-dichloro-4-chromenone

ISSN No:-2456-2165

FL5	C5	 2-(4',5'- Dimethoxyphenyl)- 7-methoxy- 4-chromenone
FL6	C6	 2-(5'-Methylphenyl)- 6-chloro,7-methyl-4-chromenone
FL7	C7	 2-(2',5'-Dimethoxyphenyl)-8-bromo-6-chloro-4-chromenone
FL8	C8	 2-(4'-Methylphenyl)- 6-chloro-7-methyl-4-chromenone
FL9	C9	 2-(6'-Chlorophenyl)- 8-bromo-6-chloro -4-chromenone

FL10	C10	 2-(6'-Chlorophenyl)- 6-methyl-4-chromenone
FL11	C11	 2-(5'-Chlorophenyl)-6-chloro-4-chromenone
FL12	C12	 2-(Phenyl)- 5,7-dihydroxy-4-chromenone
FL13	C13	 2-(6'-Bromophenyl)- 6-chloro-4-chromenone
FL14	C14	 2-(6'-Methylphenyl)- 6-bromo-4-chromenone
FL15	C15	 2-(4'-Methylphenyl)- 6-methyl-4-chromenone

FL16	C16	 2-(6^{l}-Methylphenyl)- 6-chloro-4-chromenone
FL17	C17	 2-(phenyl)- 7-methoxy-4-chromenone
FL18	C18	 2-(5^{l}-Nitrophenyl)-4-chromenone
FL19	C19	 2-(6^{l}-Hydroxyphenyl)-4-chromenone
FL20	C20	 2-(4^{l}-Fluorophenyl)-4-chromenone

ISSN No:-2456-2165

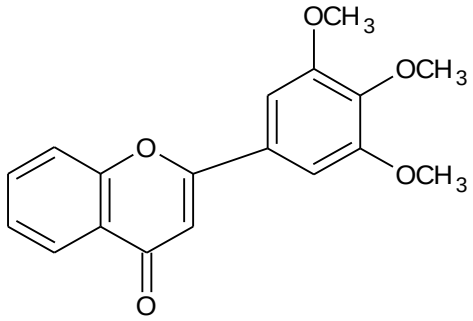
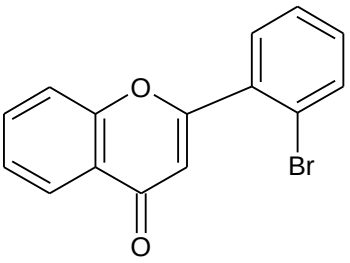
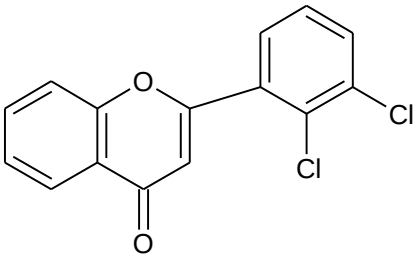
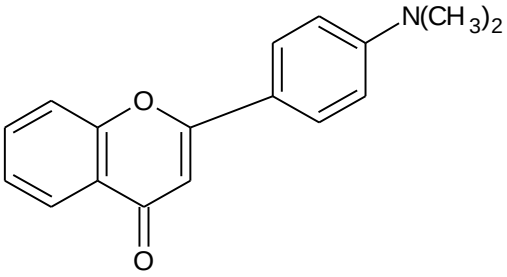
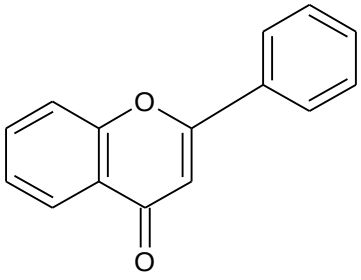
FL21	C21	 2-(3',4',5'-Trimethoxyphenyl)-4-chromenone
FL22	C22	 2-(6'-Bromophenyl)-4-chromenone
FL23	C23	 2-(5',6'-Dichlorophenyl)-4-chromenone
FL24	C24	 2-(4'-Dimethylaminophenyl)-4-chromenone
FL25	C25	 2-(Phenyl)-4-chromenone

Table 2:- Structures of synthesized flavones (FL1-FL25)

ISSN No:-2456-2165

➢ *Spectral data:*

- **2-(3', 4'-Dimethoxyphenyl) -7, 8-dimethoxy-4-chromenone (FL1):** IR cm-1 (KBr): 3430, 3186 (Ar-CH str), 1630(C=O str), 1094(COC str) ^{1}H NMR δ ppm (CDCl3): 7.94(s,1H),7.60(s,1H),7.43(s,1H),7.046.97(d,2H),6.70(s ,1H), 4.03-3.94(dd,4H).
- **2-(3', 4'-Dihydroxyphenyl) - 7, 8-dihydroxy-4-chromenone (FL2):** IR cm-1 (KBr): 3502(O-H str), 3482, 3189(Ar-CH str), 1897 (C=O str), 1071(COC str), ^{1}H NMR δ ppm (CDCl3): 7.47(s, 1H), 7.35-7.38(d, 2H), 6.88(t, 2H), 6.46(s, 1H)
- **2-(6'-Chlorophenyl) - 6-chloro-7-methyl -4-chromenone (FL3):** IR cm-1 (KBr): 3432 (Ar-CH str), 3065, 3037(C-H str), 1824(C=O str), 1071(COC str), 757(C-H bend), ^{1}H NMR δ ppm (CDCl3): 8.19(s,1H),7.62-7.26(m,5H),6.61(s,1H), 6.46(s,1H),2.50(s,3H).
- **2-(6'-Chlorophenyl) - 6, 8-dichloro-4-chromenone (FL4):** IR cm-1 (KBr): 3433, 3082 (Ar-CH str), 1660 (C=O str), 1073(COC str),^{1}H NMR δ ppm (CDCl3): 8.11(s,1H),7.73-7.70(m,2H),7.56-7.41 (m,3H), 6.77(s,1H).
- **2-(4', 5'- Dimethoxyphenyl) -7-methoxy-4-chromenone (FL5):** IR cm-1 (KBr): 3433 (Ar-CH str), 2836(O-CH_3 str), 1867 (C=O str), 1084(COC str), ^{1}H NMR δ ppm (CDCl3): 8.10(d,1H),7.52(d,1H),7.33(s,1H), 6.93-6.97(m,3H), 6.68(s,1H),3.91-3.96(t,9H).
- **2-(5'-Methylphenyl) - 6-chloro, 7-methyl-4-chromenone (FL6):** IR cm-1 (KBr): 3431, 3242(Ar-CH str), 3044(C-H str),1968 (C=O str), 1051(COC str),765(C-H bend), ^{1}H NMR δ ppm (CDCl3): 8.13(s,1H),7.67(d,2H),7.33-7.44(m,3H), 6.75(s,1H),2.49(d,6 H).
- **2-(2', 5'-Dimethoxyphenyl) - 8-bromo-6-chloro-4-chromenone (FL7):** IR cm-1 (KBr): 3433, 3083(Ar-CH str),2833(C-OCH_3 str) 1653 (C=O str), 1080(COC str), ^{1}H NMR δ ppm (CDCl3):8.11(s,1H),7.85(s,1H),7.68(s,1H),7.35(s,1H),7 .05(dd,1H),6.97(dd,1H),2.43-2.49 (S,6H)
- **2-(4'-Methylphenyl) - 6-chloro-7-methyl-4-chromenone (FL8):** IR cm-1(KBr): 3432 (Ar-CH str), 1638 (C=O str), 1048 (COC str),772(C-H bend), ^{1}H NMR δ ppm (CDCl3): 8.14(s,1H),7.76(d,2H),7.43(s,1H),7.26-7.31(d,2H),6.75(s,1H), 2.42-2.50(d,6H)
- **2-(6'-Chlorophenyl) -8-bromo- 6-chloro-4-chromenone (FL9):** IR cm-1(KBr): 3448, 3081(Ar-CH str), 1788 (C=O str), 1074(COC str), ^{1}H NMR δ ppm (CDCl3): 8.15(s,1H),7.90(s,1H),7.72-7.74(d,1H),7.41-7.56(m,3H),6.78(s,1H).
- **2-(6'-Chlorophenyl) - 6-methyl-4-chromenone (FL10):** IR cm-1(KBr): 3432, 3068 (Ar-CH str), 1915 (C=O str), 1069(COC str), 760(C-H bend), ^{1}H NMR δ ppm (CDCl3): 8.03(s, 1H), 7.423-7.63(m, 6H), 6.64(s, 1H).
- **2-(5'-Chlorophenyl)-6-chloro-4-chromenone (FL11):** IR cm-1(KBr): 3433, 3088, 3066, 3028(Ar-CH str), 1919 (C=O str), 1070(COC str), ^{1}H NMR δ ppm (CDCl3): 8.21(s, 1H), 7.26-7.65(m, 6H), 6.46(s, 1H).
- **2-(phenyl) -5, 7-dihydroxy-4-chromenone (FL12):** IR cm-1(KBr):3502 (O-H str), 3482, 3189(Ar-CH str), 1897 (C=O str), 1071(COC str) ^{1}H NMR δ ppm (CDCl3): 9.26-9.44(s,1H),7.22-7.04(m,5H), 6.15(s,1H), 6.00(s,1H), 4.45(s,1H), 3.04(dd,1H),2.79-2.84(d,1H).
- **2-(6'-Bromophenyl) - 6-chloro-4-chromenone (FL13):** IR cm-1(KBr): 3433,3088 (Ar-CH str), 1927,1650 (C=O str), 1064(COC str),^{1}H NMR δ ppm (CDCl3): 8.21(s,1H),7.25-7.74(m,6H),6.58(s,1H).
- **2-(6'-Methylphenyl)- 6-bromo-4-chromenone (FL14):** IR cm-1(KBr): 3270, 3062 (Ar-CH str), 1918,1641 (C=O str), 1069(COC str),756(C-H bend), ^{1}H NMR δ ppm (CDCl3):8.38(s,1H),7.26-7.78(m,6H), 6.46(s,1H), 2.47(s,3H).
- **2-(4'-Methylphenyl)-6-methyl-4-chromenone (FL15):** IR cm-1(KBr): 3214, 3065 (Ar-CH str),1643 (C=O str), 1085(COC str),792 (C-H bend), ^{1}H NMR δ ppm (CDCl3): 8.00(s,1H), 7.69(d,2H), 7.25-7.51(m,4H), 6.80(s,1H),2.45(d,6H).
- **2-(6'-Methylphenyl) - 6-chloro-4-chromenone (FL16):** IR cm-1(KBr): 3264, 3066 (Ar-CH str), 1640 (C=O str), 1028(COC str), 773(C-H bend), ^{1}H NMR δ ppm (CDCl3): 8.21(s,1H),7.26-7.64(m,6H),6.49 (s,1H), 3.35(s,3H).
- **2-(phenyl) -7-methoxy-4-chromenone (FL17):** IR cm-1(KBr): 3200, 3062(Ar-CH str), 2845(C-OCH_3str),1651 (C=O str), 1071(COC str), ^{1}H NMR δ ppm (CDCl3): 8.14(d,1H),7.91(m,2H),7.49-7.53(d,3H), 6.96-6.99(d,2H), 6.78(s,1H).
- **2-(5'-Nitrophenyl)-4-chromenone (FL18):** IR cm-1(KBr): 3431,3140 (Ar-CH str), 1633 (C=O str), 1565-1577 (C-N str),1051(COC str), ^{1}H NMR δ ppm (CDCl3): 8.21(s,1H),7.26-7.64(m,6H),6.49(s,1H), 3.35(s,3H).
- **2-(6'-Hydroxyphenyl)-4-chromenone (FL19):** IRcm-1(KBr): 3502 (O-H str), 3482, 3189 (Ar-CH str),1897 (C=O str), 1071(COC str), ^{1}H NMR δ ppm (CDCl3): 8.14(d,1H), 7.91(m,2H),7.49-7.53(d,3H), 6.96-6.99(d,2H), 6.78(s,1H).
- **2-(4'-Fluorophenyl)-4-chromenone (FL20):** IRcm-1(KBr): 3200, 3062(Ar-CH str), 1651 (C=O str), 1071(COC str), ^{1}H NMR δ ppm (CDCl3): 8.21(d,1H),7.38-7.89(m,5H),6.99-7.03(d,2H), 6.76(s,1H).
- **2-(3', 4', 5'-Trimethoxyphenyl)-4-chromenone (FL21):** IRcm-1(KBr): 3433 (Ar-CH str), 2836 (O-CH_3 str), 1867 (C=O str), 1084 (COC str), ^{1}H NMR δ ppm (CDCl3): 8.10(d,1H),7.52(d,1H),7.33(s,1H), 6.93-6.97(m,3H), 6.68(s,1H),3.91-3.96(t,9H).
- **2-(6'-Bromophenyl)-4-chromenone (FL22):** IRcm-1(KBr): 3200,3062(Ar-CH str),1651 (C=O str), 1071(COC str), ^{1}H NMR δ ppm (CDCl3):8.14(d,1H),7.91(m,2H),7.49-7.53 (d,3H) 6.96-6.99(d,2H), 6.78(s,1H).
- **2-(5', 6'-Dichlorophenyl)-4-chromenone (FL23):** IRcm-1(KBr): 3432(Ar-CH str), 3065, 3037(C-H str), 1824(C=O str), 1071(COC str), ^{1}H NMR δ ppm (CDCl3): 8.03(s, 1H), 7.423-7.63(m, 6H), 6.64(s, 1H).

- **2-(4'-Dimethylaminophenyl)-4-chromenone (FL24):** IRcm-1(KBr): 3200, 3062 (Ar-CH str), 2845(C-N str), 1651 (C=O str), 1071(COC str), ^{1}H NMR δ ppm (CDCl3): 8.14(d,1H),7.91(m,2H),7.49-7.53(d,3H), 6.96-6.99(d,2H), 6.78(s,1H).
- **2-(phenyl)-4-chromenone (FL25):** IRcm-1(KBr): 3264, 3066(Ar-CH str), 1640(C=O str), 1028(COC str),773(C-H bend), ^{1}H NMR δ ppm (CDCl3): 8.03(d,1H), 7.71(d,2H), 7.51(s,1H), 7.19-7.37 (m,5H), 6.63(s,1H).

B. Pharmacology:

➢ *Anticancer activity*

- *Sulforhodamine B (SRB) assay:*

National cancer institute protocol for the 48 h continuous drug exposure method, utilizing tumor cells (MCF 7 cell line and HT-29 cell line, grown in RPMI 1640 medium containing 10 % fetal bovine serum and 2 mM L-glutamine), were used to review antitumor activity of the synthesized compounds [10]. The cells were inoculated into a series of standard 96-well micro titer plates (5,000 cells/ well). After cell inoculation, the micro titer plates were incubated at 37 °C by maintaining 5 % CO_2, 95 % air and 100 % relative humidity for 24 h in the incubator, preceding to the addition of the experimental drugs. The test compounds were added after the pre-incubation period in four dilutions (10, 20, 30, 40 µg/ml). The cells were incubated for 48 h, then fixed with 10 % trichloroacetic acid (TCA) and washed numerous times with deionized water. The sulforhodamine B (SRB) was added to these cells and the cells were washed and dehydrated. The cell viability was resoluted by solubilizing the bound dye and determining the concentration spectrophotometrically at 540 nm.

Growth inhibition of 50 % (GI_{50}) and lethal concentration of 50 % (LC_{50}) were calculated for each test compound by the subsequent equations:

$$GI_{50} = \frac{Ti - Tz}{C - Tz} \times 100$$

$$LC_{50} = \frac{Ti - Tz}{Tz} \times 100$$

where Ti = cell growth in the presence of a test compound
Tz = cell growth at zero time
C = growth in the control

Growth inhibition of 50 % (GI_{50}) is the concentration of a compound resulting in a 50 % growth inhibition of cells. Lethal concentration of 50 % (LC_{50}) indicates the concentration of a compound which kills 50 % of cells.

➢ *Anti-inflammatory activity*

The anti-inflammatory activity was evaluated using carrageenan induced rat hind paw edema method [11]. The rats were fasted for 24 h and categorized into *control* (group 1), *standard* (group 2, indomethacin) and *test groups* (groups 3 to 27, compounds **FL1** to **FL25**), each consisting of six rats. The rats in group 1 were treated orally with a dose of 10 ml/kg body weight of a suspension of Na-CMC (1 % w/v). The rats in group 2 were administered orally a dose of 10 mg/kg body weight of indomethacin and groups 3 to 27 were treated orally with a dose of 160 mg/kg body mass of test compounds (compounds **FL1 to FL25**) suspended in 1 % Na-CMC. Thirty min after the administration of the standard and the test compounds, the animals were injected subcutaneously with 0.1 ml of freshly prepared suspension of carrageenan (1 % w/v) into the sub-plantar region of right hind paw of rats. The volume of rat hind paw was calculated using digital plethysmometer for all the animals in groups 1 to 27, at the time intervals of 0, 60, 120, 180 and 240 min after carrageenan injection. The initial volume of a paw was measured within thirty seconds of the injection of carrageenan. The anti-inflammatory activity was articulated as per cent inhibition of the inflammation in drug treated group in comparison with the untreated group.

The per cent inhibition of edema was calculated by using the following formula:

$$Per\ cent\ inhibition\ of\ edema = (1 - \frac{V_{test}}{V_{control}})$$

where, V_{test} = Mean relative change in the volume of paw edema in a treated group (Group 2 and groups 3 to 27),
$V_{control}$ = Mean relative change in the volume of paw edema in an untreated group (Group 1)

IV. RESULTS AND DISCUSSION

➢ *Twenty five flavones were synthesized by Claisen Schmidt condensation reaction from chalcones.*

Step-I : Synthesis of chalcones (C1 to C25)

All the chalcones **(C1 to C25)** were synthesized by Claisen-Schmidt condensation reaction. Melting points, R_f values and per cent yield of compounds obtained are illustrated in Table 3. The average yield obtained for all the compounds synthesized was in the range of 75 to 90 %.

ISSN No:-2456-2165

Compound code	Name of the compd	Melting point (°C)	R_f value*	% Yield
C1	1-(2^{I}-hydroxy-3^{I},4^{I}-dimethoxyphenyl)-3-(2^{II},3^{II}dimethoxyphenyl)- 2-propene-1-one	83-85	0.52	82
C2	1-(2^{I}-hydroxy-3^{I},4^{I}-dihydroxyphenyl)-3-(2^{II},3^{II}dihydroxyphenyl)- 2-propene-1-one	142-145	0.60	86
C3	1-(2^{I}-hydroxy-,5^{I}chloro-4^{I}-methylphenyl)-3-(5^{II}-chlorophenyl)-2-propene-1-one	54-57	0.41	89
C4	1-(2^{I}-hydroxy-3^{I},5^{I}dichloro-4^{I}-phenyl)-3-(5^{II}-chlorophenyl)-2-propene-1-one	154-158	0.56	75
C5	1-(2^{I}-hydroxy-4^{I}-methoxyphenyl)-3-(4^{II}-methylphenyl)-2-propene-1-one	121-124	0.66	76
C6	1-(2^{I}-hydroxy-5^{I}-chloro-4^{I}-methylphenyl)-3-(4^{II}-methylphenyl)-2-propene-1-one	89-92	0.71	88
C7	1-(2^{I}-hydroxy-5^{I}-chloro-3^{I}-bromophenyl)-3-(1^{II},4^{II}-dimethoxyphenyl)-2-propene-1-one	114-117	0.55	83
C8	1-(2^{I}-hydroxy-5^{I}-chloro-4^{I}-methylphenyl)-3-(3^{II}-methylphenyl)-2-propene-1-one	121-125	0.49	82
C9	1-(2^{I}-hydroxy-5^{I}-chloro-3^{I}-bromophenyl)-3-(5^{II}-chlorophenyl)-2-propene-1-one	75-78	0.42	81
C10	1-(2^{I}-hydroxy-5^{I}-chlorophenyl)-3-(4^{II}-chlorophenyl)-2-propene-1-one	52-58	0.58	77
C11	1-(2^{I}-hydroxy-5^{I}-chlorophenyl)-3-(4^{II}-chlorophenyl)-2-propene-1-one	159-163	0.63	90
C12	1-(2^{I}-hydroxy-4^{I},6^{I}-dihydroxyphenyl)-3-(phenyl)-2-propene-1-one	96-99	0.52	74
C13	1-(2^{I}-hydroxy-5'-chlorophenyl)-3-(5^{II}-bromophenyl)-2-propene-1-one	152-155	0.68	77
C14	1-(2^{I}-hydroxy-5^{I}-bromophenyl)-3-(5''-methylphenyl)-2-propene-1-one	174-178	0.72	80
C15	1-(2^{I}-hydroxy-5^{I}-methylphenyl)-3-(5^{II}-methylphenyl)-2-propene-1-one	180-183	0.61	83
C16	1-(2^{I}-hydroxy-5^{I}-chlorophenyl)-3-(5^{II}-methylphenyl)-2-propene-1-one	95-98	0.50	88
C17	1-(2^{I}-hydroxy-4^{I}-methoxyphenyl)-3-(phenyl)-2-propene-1-one	114-118	0.62	81
C18	1-(2^{I}-hydroxyphenyl)-3-(4^{II}-nitrophenyl)-2-propene-1-one	86-90	0.49	90
C19	1-(2^{I}-hydroxyphenyl)-3-(5^{II}-hydroxyphenyl)-2-propene-1-one	104-108	0.57	80
C20	1-(2^{I}-hydroxyphenyl)-3-(3^{II}-fluorophenyl)-2-propene-1-one	152-157	0.67	76
C21	1-(2^{I}-hydroxyphenyl)-3-(2^{II},3^{II},4^{II}-trimethoxyphenyl)-2-propene-1-one	195-200	0.63	73
C22	1-(2^{I}-hydroxyphenyl)-3-(4^{II}-bromophenyl)-2-propene-1-one	147-149	0.52	76
C23	1-(2^{I}-hydroxyphenyl)-3-(4^{II},5^{II}-dichlorophenyl)-2-propene-1-one	87-90	0.49	82
C24	1-(2^{I}-hydroxy-4^{I}-dimethylaminophenyl)-3-(phenyl)-2-propene-1-one	124-126	0.46	89
C25	1-(2^{I}-hydroxyphenyl)-3-(phenyl)-2-propene-1-one	111-115	0.57	82

*Mobile phase: Hexane:Ethyl acetate-6:4

Table 3:- Melting points, R_f values and per cent yield of chalcones

ISSN No:-2456-2165

Step II: Synthesis of flavones (FL1 to FL25)

All the flavones **(FL1 to FL25)** were synthesized by both the conventional and microwave irradiation methods. Melting points, R_f values, time essential for completion of the reaction and per cent yield of compounds obtained by both the methods are illustrated in Table 4. The average yield obtained for all the compounds synthesized by the conventional method was in the range of 48 to 68 % .When these compounds were synthesized by microwave (MW) irradiation method, the average yield was in the range of 71 to 91 %. Thus, the microwave irradiation method helped in increasing the yield of the compounds approximately by 23 %. The reaction time essential for the synthesis of the compounds by the conventional method was in the range of 2.5 to 4 h whereas, by the microwave irradiation method, it was notably reduced to 12 to 26 min. Thus,microwave irradiation method not only helped in reducing the reaction time but also helped in increasing the yield and improving the quality of the newly designed and synthesized flavones.

Comp code	Name of the compd.	Melting point (^OC)	R_f value*	Reaction time		% Yield	
				Conv (h)	MW (min)	Conv	MW
FL1	2-(3^l,4^l-dimethoxyphenyl) - 7,8-dimethoxy-4-chromenone	162-164	0.55	2.50	15	62.7	89.1
FL2	2-(3^l,4^l-dihydroxyphenyl)- 7,8-dihydroxy-4-chromenone	110-112	0.65	3.00	20	68.3	85.4
FL3	2-(6^l-chlorophenyl)- 6-chloro-7-methyl -4-chromenone	130-132	0.52	3.00	21	58.2	89.3
FL4	2-(6^l-chlorophenyl)- 6,8-dichloro-4-chromenone	145-148	0.51	3.50	26	52.8	80.2
FL5	2-(4^l,5^l-dimethoxyphenyl) - 7-dimethoxy-4-chromenone	163-165	0.59	3.00	24	55.4	85.1
FL6	2-(5^l-methylphenyl)-6-chloro,7-methyl-4-chromenone	152-155	0.58	3.75	21	62.2	81.0
FL7	2-(2^l,5^l-dimethoxyphenyl)-6-chloro-8-bromo-4-chromenone	165-168	0.59	4.00	22	59.7	85.2
FL8	2-(4^l-methylphenyl)-6-chloro-7-methyl-4-chromenone	141-143	0.55	3.75	15	65.1	86.8
FL9	2-(6^l-chlorophenyl)-6-chloro-8-bromo-4-chromenone	178-180	0.61	4.25	18	55.6	82.5
FL10	2-(6^l-chlorophenyl)-6-methyl-4-chromenone	141-144	0.68	4.00	20	57.0	83.6

FL11	2-(5^{l}-chlorophenyl)-6-chloro-4-chromenone	101-104	0.56	4.00	21	60.2	86.0
FL12	2-(Phenyl)-5,7-dihydroxy-4-chromenone	151-152	0.52	2.50	15	52.0	84.0
FL13	2-(6^{l}-bromophenyl)-6-chloro-4-chromenone	168-170	0.62	3.25	18	48.8	78.1
FL14	2-(6^{l}-methylphenyl)- 6-bromo-4-chromenone	189-191	0.61	2.5	15	51.5	82.8
FL15	2-(4^{l}-methylphenyl)- 6-methyl-4-chromenone	125-128	0.53	3.25	18	55.0	80.2
FL16	2-(6^{l}-methylphenyl)- 6-chloro-4-chromenone	122-124	0.55	3.00	16	60.2	86.6
FL17	2-(Phenyl)- 7-methoxy-4-chromenone	160-162	0.66	3.75	20	50.7	71.2
FL18	2-(5^{l}-nitrophenyl)-4-chromenone	159-161	0.53	3.00	12	68.2	88.9
FL19	2-(6^{l}-hydroxyphenyl)-4-chromenone	170-172	0.68	4.00	18	56.6	81.2
FL20	2-(4^{l}-fluorophenyl)-4-chromenone	91-93	0.52	2.50	15	62.1	86.0
FL21	2-(3^{l},4^{l},5^{l}-trimethoxyphenyl)-4-chromenone	96-100	0.59	2.75	22	59.4	91.2
FL22	2-(6^{l}-bromophenyl)-4-chromenone	183-185	0.68	3.00	17	50.0	82.1
FL23	2-(5^{l},6^{l}-dichlorophenyl)-4-chromenone	161-163	0.57	4.00	15	48.2	72.8
FL24	2(4^{l}-dimethyl amino phenyl)-4-chromenone	161-163	0.61	3.25	21	58.5	81.7
FL25	2-(Phenyl)-4-chromenone	130-131	0.58	2.50	18	68.3	86.7

*Mobile phase: Hexane: Ethyl acetate-8:2

Table 4:- Melting points and R_f values along with the comparison of the reaction time and yield of flavones synthesized by the coventional and mirowave irradiation techniques.

ISSN No:-2456-2165

➢ *Anticancer activity*

Anticancer activity was carried out on the sensitive cell line by SRB assay. All the synthesized compounds were tested for *in vitro* anticancer activity against MCF-7 breast cancer cell line and HT 29 colon cancer cell line using sulforhodamine B assay. Lethal concentration (LC_{50}), total growth inhibition (TGI) and growth inhibition (GI_{50}) values for MCF-77 breast cancer cell line are mentioned in Table 5. Figure 1 shows concentration of flavones for 50% growth inhibition of MCF-7 breast cancer cell line.

Serial No.	Compound	Concentration of flavones (µm)		
		LC_{50}	TGI	GI_{50}
1	FL1	>100	93.3	42.6
2	FL2	>100	69.7	31.1
3	FL3	>100	>100	39.7
4	FL4	>100	>100	43.3
5	FL5	>100	>100	43.0
6	FL6	>100	85.5	39.1
7	FL7	>100	>100	41.3
8	FL8	>100	>100	41.1
9	FL9	>100	>100	46.1
10	FL10	>100	75.7	32.1
11	FL11	>100	94.7	40.1
12	FL12	>100	>100	41.6
13	FL13	>100	93.9	39.0
14	FL14	>100	87.3	35.1
15	FL15	>100	>100	54.1
16	FL16	>100	77.2	32.6
17	FL17	>100	98.5	40.2
18	FL18	>100	98.7	42.0
19	FL19	>100	86.5	**15.0**
20	FL20	>100	98.5	35.9
21	FL21	>100	87.3	38.7
22	FL22	>100	87.3	37.4
23	FL23	>100	88.3	**8.2**
24	FL24	>100	>100	**<0.1**
25	FL25	>100	95.5	37.4
26	Std. Adriamycin	78.6	<0.1	<0.1

Table 5:- Flavones LC_{50}, TGI and GI_{50} for MCF-7 breast cancer cell line

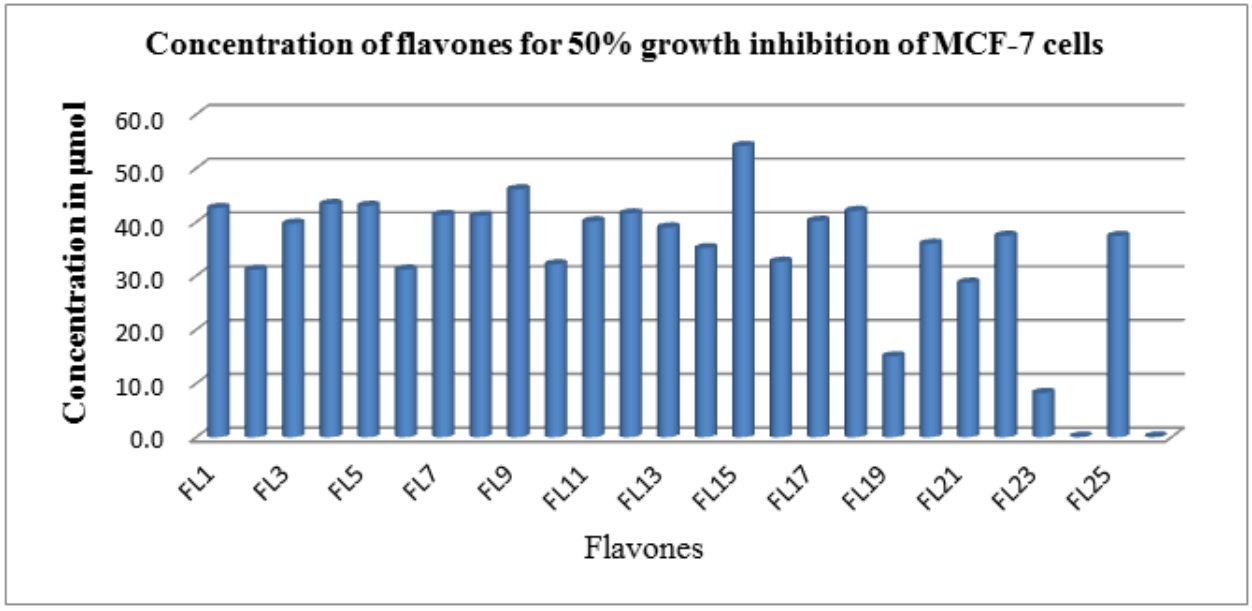


Fig 2:- Concentration of flavones for 50% growth inhibition of MCF-7 cells

ISSN No:-2456-2165

All synthesized compounds showed mild to moderate anticancer activity for MCF-7 cells as compared to standard Compound Adriamycin. Compound **FL15** showed mild activity (54.1) as compared to that of standard Adriamycin (<0.1). Compounds **FL19** and **FL23** showed total growth inhibition of MCF-7 cells at concentrations (8.2-15.0) which is good as compared to the standard Adriamycin (<0.1). Compound **FL24** showed 50 % growth inhibition of MCF-7 cells at concentration (<0.1) which is equivalent to that of Adriamycin (<0.1). The remaining compounds showed 50 % growth inhibition at concentration (31.1-46.1) which showed moderate anticancer activity as compared to Adriamycin. Thus, compounds **FL19, FL23** and **FL24** can prove to be better anticancer agents compared to Adriamycin.

All synthesized compounds showed mild to moderate anticancer activity for HT-29 cells as compared to standard Compound Adriamycin apart from compound **FL24.** Compound **FL24** showed no activity (>100) for HT-29 cells. Compounds **FL10, FL16** and **FL21** showed total growth inhibition of HT-29 cells at concentrations (32.5-36.3) which is moderate as compared to the standard Adriamycin (<0.1). The remaining compounds showed 50 % growth inhibition at concentration (37.4-84.7) which showed mild anticancer activity as compared to Adriamycin. Thus, compounds **FL10, FL16** and **FL21** can prove to be enhanced anticancer agents compared to Adriamycin. Lethal concentration (LC_{50}), total growth inhibition (TGI) and growth inhibition (GI_{50}) values for HT-29 colon cancer cell line are mentioned in Table 6. Figure 2 shows concentration of flavones for 50% growth reduction of HT29 colon cancer cell line.

Serial No.	**Compound**	**Concentration of flavones (µm)**		
		LC_{50}	**TGI**	**GI_{50}**
1	FL1	>100	>100	57.5
2	FL2	>100	>100	78.9
3	FL3	>100	>100	68.6
4	FL4	>100	>100	84.7
5	FL5	>100	>100	60.3
6	FL6	>100	>100	52.6
7	FL7	>100	97.9	48.5
8	FL8	>100	>100	49.0
9	FL9	>100	>100	58.2
10	FL10	>100	71.9	**34.3**
11	FL11	>100	94.0	45.5
12	FL12	>100	85.1	44.4
13	FL13	>100	91.1	46.9
14	FL14	>100	89.1	39.0
15	FL15	>100	>100	57.6
16	FL16	>100	80.7	**36.3**
17	FL17	>100	88.3	38.7
18	FL18	>100	92.2	38.5
19	FL19	>100	91.2	37.4
20	FL20	>100	94.2	37.5
21	FL21	>100	88.0	**32.5**
22	FL22	>100	88.0	45.0
23	FL23	>100	>100	57.2
24	FL24	>100	>100	>100
25	FL25	>100	>100	61.5
26	Std. Adriamycin	>100	38.2	<0.1

Table 6:- Flavones $LC_{50,}$ TGI and GI_{50} for HT-29 colon cancer cell line

ISSN No:-2456-2165

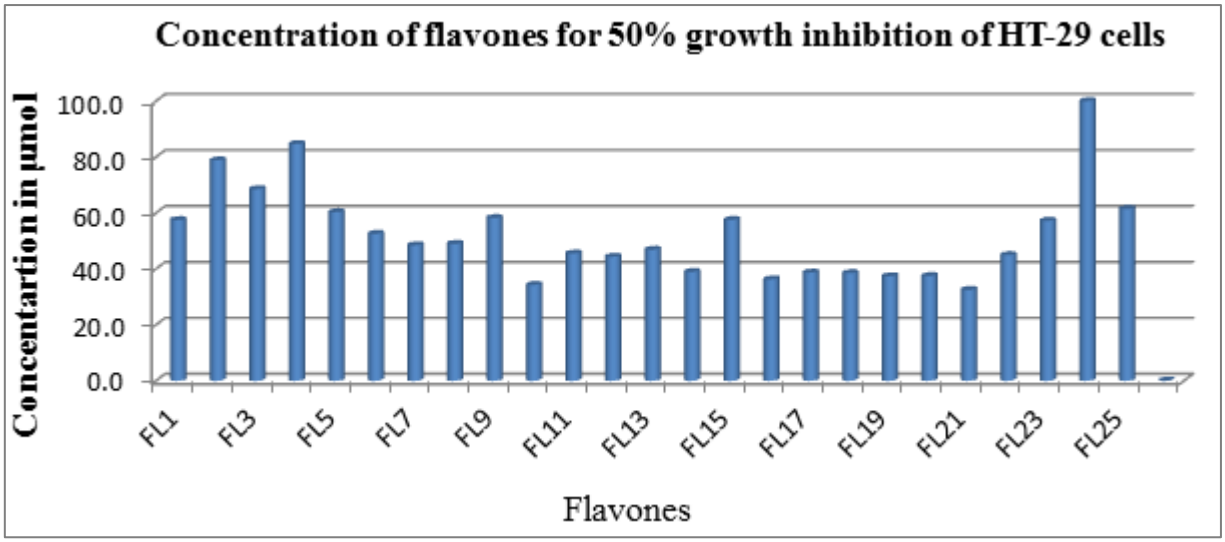


Fig 3:- Concentration of flavones for 50% growth inhibition of HT-29 cells

➢ *Anti-inflammatory activity*

The *in-vivo* anti-inflammatory activity of all the flavones and indomethacin was evaluated using the carrageenan induced rat paw edema model. The results were articulated as the (mean ± S.E.M) of the actual paw volume (mL) of rats after the treatment with flavones. The results were tested statistically by one way ANOVA method. The mean reduction in the paw volume (ml) after the treatment with the test and the standard compounds is shown in Table 7.

COMPOUND CODE	**Actual paw volume (mL) of rats after the treatment with flavones MEAN+S.E.M**				
	0 h	**1 h**	**2 h**	**3 h**	**4 h**
FL1	0.3466±0.009	0.4216±0.008	0.495±0.0079	0.526±0.01	0.551±0.009
FL2	0.2966±0.006	0.4966±0.012	0.5583±0.011	0.433±0.015	0.3914±0.012
FL3	0.3733±0.007	0.4566±0.013	0.615±0.008	0.52±0.0078	0.49±0.0012
FL4	0.34±0.013	0.406±0.008	0.44±0.0078	0.480±0.0075	0.46±0.0081
FL5	0.338±0.01	0.501±0.006	0.626±0.009	0.568±0.01	0.552±0.008
FL6	0.337±0.01	0.427±0.008	0.467±0.012	0.542±0.014	0.521±0.009
FL7	0.346±0.01	0.421±0.009	0.473±0.007	0.543±0.0078	0.499±0.0085
FL8	0.333±0.01	0.446±0.008	0.596±0.007	0.523±0.0012	0.519±0.0069
FL9	0.2466±0.006	0.4416±0.01	0.5633±0.009	0.3633±0.012	0.3514±0.008
FL10	0.441±0.009	0.531±0.012	0.651±0.014	0.576±0.009	0.589±0.01
FL11	0.2566±0.008	0.35±0.007	0.4933±0.009	0.3516±0.013	0.3696±0.004
FL12	0.25±0.008	0.395±0.007	0.543±0.006	0.4866±0.012	0.3289±0.005
FL13	0.2566±0.009	0.3566±0.01	0.4566±0.008	0.3412±0.01	0.3569±0.006
FL14	0.33±0.013	0.46±0.009	0.55±0.009	0.47±0.012	0.49±0.001
FL15	0.376±0.0012	0.448±0.008	0.554±0.009	0.6233±0.012	0.6123±0.006
FL16	0.3433±0.004	0.47±0.006	0.55±0.0132	0.62±0.004	0.51±0.01
FL17	0.354+0.005	0.48+0.014	0.63+0.009	0.6+0.008	0.59+0.014
FL18	0.338±0.008	0.466±0.01	0.672±.006	0.626±0.004	0.479±0.001
FL19	0.2566±0.013	0.3483±0.009	0.461±0.012	0.4833±0.005	0.3589±0.006
FL20	0.3483±0.009	0.4551±0.014	0.5716±0.006	0.5466±0.014	0.5214±0.006
FL21	0.251±0.01	0.355±0.005	0.526±0.008	0.413±0.016	0.409±0.003
FL22	0.37±0.008	0.46±0.004	0.63±0.001	0.5±0.012	0.48±0.006
FL23	0.3033±0.008	0.4383±0.005	0.545±0.012	0.446±0.002	0.451±0.005
FL24	0.3116±0.005	0.4183+0.015	0.598+0.009	0.535+0.004	0.524+0.008

FL25	0.204±0.008	0.3416±0.004	0.4716±0.015	0.421±0.005	0.3216±0.007
- ve control	0.387±0.009	0.589±0.006	0.661±0.014	0.719±0.008	0.793±0.004
Indomethacin (+ ve control)	0.2833±0.006	0.4783±0.01	0.4033±0.008	0.355±0.002	0.291±0.004

Table 7:- Actual paw volume (mL) of rats after the treatment with flavones

The per cent inhibition of inflammation in rats by the test compounds and the standard, after 1, 2, 3 and 4 h is shown in Table 8

	Anti-inflammatory activity (% inhibition)			
COMPOUND CODE	**1 h**	**2 h**	**3 h**	**4 h**
FL1	13.22	19.86	25.68	48.28*
FL2	65.42	41.29	**48.74**	**86.00***
FL3	35.69	39.87	**47.52**	**70.36***
FL4	32.58	45.85	**52.36**	**70.45***
FL5	15.34	19.85	25.65	48.12*
FL6	59.36	36.87	31.45	56.07*
FL7	61.58	28.65	24.39	66.69*
FL8	25.69	30.65	32.69	53.25*
FL9	56.98	54.74	**52.59**	**79.38***
FL10	7.96	22.58	35.98	63.01*
FL11	62.14	59.85	**55.58**	**73.26***
FL12	26.25	45.25	**74.12**	**82.45***

FL13	58.36	39.12	**52.74**	**75.69***
FL14	8.69	13.25	18.96	61.82 *
FL15	53.95	43.48	**39.38**	41.39 *
FL16	59.63	33.87	30.78	58.87 *
FL17	42.11	13.04	19.83	41.69 *
FL18	61.84	29.35	25.00	68.02 *
FL19	68.42	40.22	**44.83**	**78.15 ***
FL20	60.53	35.87	32.76	58.25 *
FL21	8.19	13.04	15.51	61.36 *
FL22	35.14	38.74	**48.25**	**73.56 ***
FL23	7.89	20.65	32.76	63.02*
FL24	14.47	18.48	24.14	48.14*
FL25	64.47	71.74	**65.52**	**70.25***
Indomethacin	**42.56**	**42.25**	**36.98**	**80.51***
- ve control	-	-	-	-

Data analyzed by one-way ANOVA, followed by Dunnett's test
*P<0.001 significant from control

Table 8:- The per cent inhibition of inflammation in rats by the test compounds and the standard, after 1, 2, 3 and 4 h

ISSN No:-2456-2165

Out of 25 synthesized compounds, compounds **FL2** and **FL12** showed per cent inhibition of edema as 86.0 % and 82.45 %, respectively, at the end of 4 h, which was higher than that of indomethacin (80.51 %). Eight compounds **FL3, FL4, FL9, FL11, FL13, FL19, FL22** and **FL25** showed % inhibition in the range of 70-79 % than that of indomethacin at the end of 4 h and compounds **FL7, FL10, FL14, FL18**, **FL21 and FL23** showed anti-inflammatory activity in the range of 61 - 68 %. Out of 25 compounds, 11 compounds showed considerably higher % inhibition, as compared to indomethacin, at the end of 4 h.
The graphical presentation of the per cent inhibition of inflammation by the test compounds and the standard, at the end of 4 h, is depicted in Figure 3

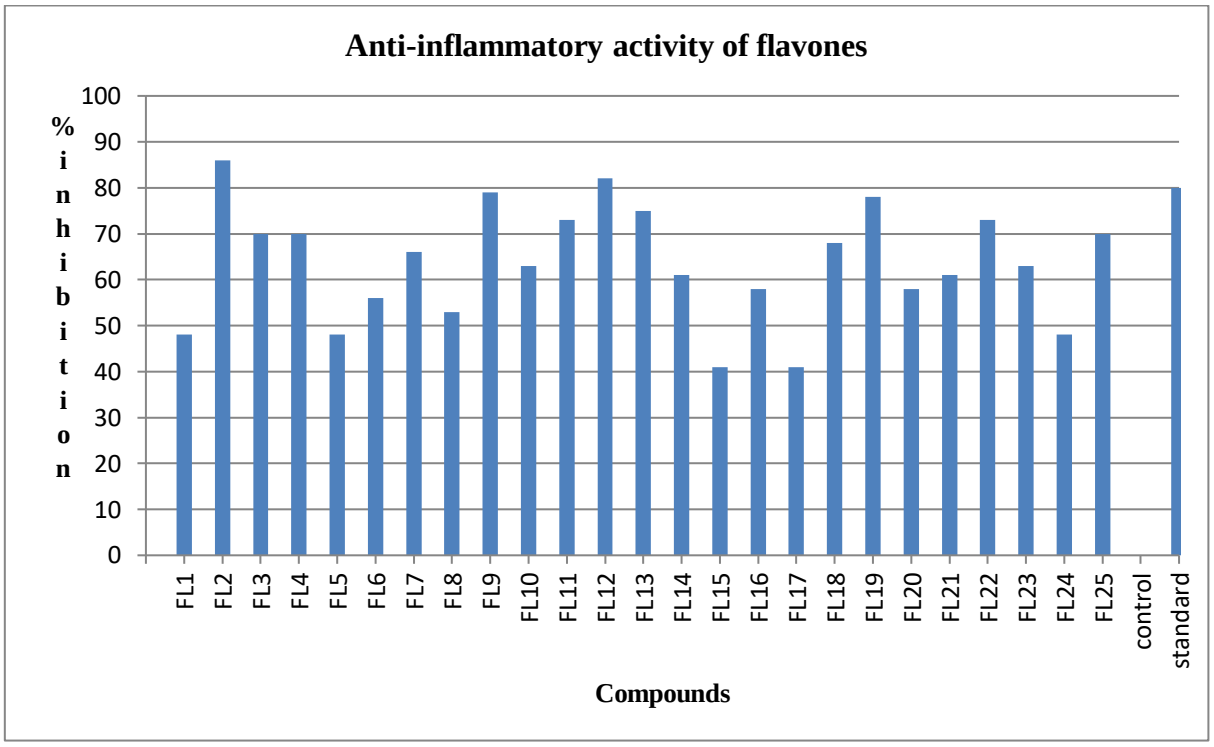


Fig 4:- Per cent inhibition of inflammation by flavones and Indomethacin at the end of 4 h

V. CONCLUSION

In *in vitro* anticancer activity against MCF-7 cell line, compounds **FL19** and **FL23** showed total growth inhibition of MCF-7 cells at concentration range of (8.2-15.0 µM) which is comparable to the standard Adriamycin. Compound FL24 showed 50 % growth inhibition of MCF-7 cells at concentration (<0.1 µM)) which is equivalent to that of Adriamycin. In *in vitro* anticancer activity against HT-29, Compounds **FL10, FL16** and **FL21** showed total growth inhibition of HT-29 cells at concentration range of (32.5-36.3 µM), which is fairly active as compared to the standard Adriamycin (<0.1 µM)).

The *in-vivo* anti-inflammatory activity of all the synthesized flavones and indomethacin was evaluated using carrageenan induced rat paw edema model. Out of 25 synthesized compounds, compounds **FL2** and **FL12** showed per cent inhibition of edema as 86.0 % and 82.45 %, respectively, at the end of 4 h, this was advanced than that of indomethacin (80.51 %). Eight compounds **FL3, FL4, FL9, FL11, FL13, FL19, FL22** and **FL25** showed % inhibition in the range of 70-79 % than that of indomethacin at the end of 4 h and compounds **FL7, FL10, FL14, FL18**, **FL21 and FL23** showed anti-inflammatory activity in the range of 61 - 68 %. Out of 25 compounds, 11 compounds showed significantly higher % inhibition, as compared to indomethacin, at the end of 4 h.

Flavones inhibit a number of enzymes such as aldose reductase, xanthine oxidase, phosphodiesterase, $Ca^{(+2)}$ ATPase, lipoxygenase, cyclooxygenase, etc. They have been found to have anti-inflammatory activity in both proliferative and exudative phases of inflammation. Thus, anti-inflammatory activity of flavones can add up to their anticancer activity.

- *Ethics Approval and Consent to Participate:*
  After analysis of the procedure and aim of this study, local ethical committee authorization was obtained.

- *Availability of Data and Materials:*
  The data that support the findings of this study are accessible from the corresponding author upon reasonable appeal**.**

- *Conflict of Interest:*
  The authors assert no conflict of interest, financial or otherwise.

- *Acknowledgements*
  Declared none.

REFERENCES

[1]. Haslam EA.; Chemistry and pharmacology of natural products, Cambridge University Press, Sydney, Australia, **1989**, 8-12.
[2]. Srivastava SD.; Srivastava SK.; Synthesis of a new flavone, *Indian journal of chemistry*, **2001**, 75,197-202.
[3]. Eisenberg L.; Distinctions between professional and popular ideas of sickness, *Culture Medicine and Psychiatry*, **1977,** 1, 9–23.
[4]. Saranath DV.; Khanna AV.; Current status of cancer burden: Global and Indian scenario, *Biomedical Research Journal***, 2014**, 1, 1-5.
[5]. Wulff HR.; The concept of disease: from Newton back to Aristotle, *Lancet*, **1999,** 354(Suppl):SIV50. N
[6]. Smith JB.; Willis AL.; Aspirin selectively inhibits prostaglandin production in human platelets, *Nature new biology*, **1971**, 231, 235-237.
[7]. Brenton JD.; Carey LA.; Ahmed AA.; Molecular classification and molecular forecasting of breast cancer, *Journal of Clinical Oncology*, **2005**, 23, 7350–7360.
[8]. American Cancer Society, Breast cancer facts and figures, *American Cancer Society*; **2011**.
[9]. Menezes MJ.; Manjrekar S.; Pai V.; Tilve SG.; A facile microwave assisted synthesis of flavones, *Indian Journal of Chemistry*, **2009**, 48B, 1311-1314.
[10]. Vanicha V.; Kanyawim K.; Sulforhodamine B colorimetric assay for cytotoxicity screening, *Nature protocols*, **2006**, 1, 1112 – 1116.
[11]. Winter CA.;,Risely EA.; Nuss GW.; Carrageenan induced edema in hind paw of the rats as an assay for anti-inflammatory drugs, *Proceedings of the society of experimental biology and medicines*, **1962**, 111, 541-552.