

# Chalcones as Promising Antiproliferative Drug-A Review

Deepika.P<sup>1\*</sup>, D.Uma Maheswari<sup>2</sup>, Shiji Kumar P.S<sup>1</sup>

<sup>1</sup>Jamia Salafiya Pharmacy College, Pulikkal, Malappuram, Kerala, India

<sup>2</sup>Vinayaka Mission College of Pharmacy, Salem, Tamil Nadu, India

**Abstract:** - Cancer- a life threatening disease requires more molecular scaffolds for therapy. Chalcone and its different derivatives has found profound use as antiproliferative agents in various types of cancers. This review focus on novel derivatives of chalcones which has found to be active as cytotoxic agents.

**Key words:** Cancer, chalcones, cytotoxicity, cell lines, Claisen condensation

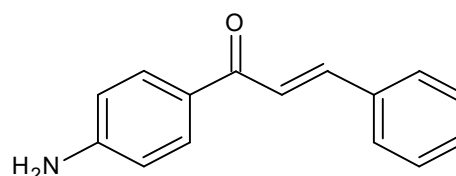
## I. INTRODUCTION

Cancer is the second most cause of death in US exceeded only by heart disease. As per American cancer society about 606880 Americans are expected to die of cancer in 2019 which translates to about 1660 deaths per day. In India the estimated number of people living with the disease is 2.25 million. The situation is worse in under developed countries due to lack of development and unavailability of drugs. Cancer is one of the health threat which require the development of newer and potent molecules for therapy. This scenario led to the design of cost-effective molecules by the medical chemist.

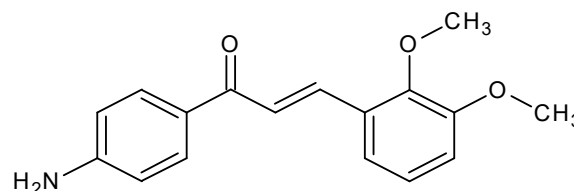
Chalcones are flavonoids of plant origin which is a precursor for flavonoid biosynthesis. About 2 dozen chalcones are known to occur in plants. It is a yellow pigment with open chain system for middle three fragments. Chemically it consist of two aromatic rings separated by  $\alpha$   $\beta$  unsaturated carbonyl group. The substitution pattern and type of substituent in chalcone give rise to wide structural diversity, for example hydroxylated, methylated, methoxylated prenylated and glycosylated chalcone and are attributed to enzyme catalysed modification dependent on endogenous and exogenous factors which regulate the enzymatic system of the plants. Synthetically it is prepared by Claisen Schmidt reaction by the condensation between benzaldehyde and acetophenone in the presence of sodium hydroxide. Chalcone possess a wide variety of pharmacological activities which include anticancer, antimicrobial, anti-inflammatory, antiprotozoal, antitubercular and antifungal. As anticancer agent it was found to be active against human colon cancer cell lines, MFC cell lines, human lung adenocarcinoma cell lines and human breast cancer cell lines, so the present literature focus on the molecular hybridisation of chalcones with other pharmacological scaffolds as potent antiproliferative agents.

Arina Novilla et al synthesized 7 methoxy amino chalcone derivatives and evaluated its cytotoxicity against human acute promyelocytic leukemia cell lines. Of all the synthesized

compounds 1-(4-amino phenyl)-3-phenyl prop-2-en-1-one showed highest cytotoxicity against K562 cell lines with IC<sub>50</sub> value of  $5.87 \pm 0.15 \mu\text{g/ml}$  whereas 1-(4-amino phenyl)-3-(2,4-dimethoxy phenyl)-prop-2-en-1-one showed maximum cytotoxicity against HL-60 cell lines with IC<sub>50</sub> value  $1.57 \pm 0.40 \mu\text{g/ml}$  as compared with the standard imitinib.

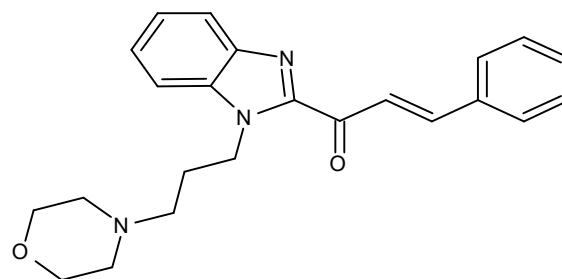


1-(4-amino phenyl)-3-phenyl prop-2-en-1-one



1-(4-amino phenyl)-3-(2,4-dimethoxy phenyl)-prop-2-en-1-one

Chang-Ying Hsieb et al carried out the cytotoxic activity of certain N-substituted benzimidazole containing chalcone group. The cytotoxic activity of synthesized compounds were performed using MTT assay method against A549, MCF-7, HEP-G2 and OVCAR cell lines. 1-(1-(3-morpholinopropyl)-1H-benzimidazol-2-yl)-3-phenyl-2-propen-1-one showed highest IC<sub>50</sub> value as compared with the standard drug cisplatin. The study concludes the presence of N containing 5 or 6 membered ring in N-substituted benzimidazole enhance anticancer activity against MCF and OVCAR cell lines.



1-(1-(3-morpholinopropyl)-1H-benzimidazol-2-yl)-3-phenyl-2-propen-1-one

Silvya marquina et al synthesized various 2-hydroxy 2-alkoxy chalcones and screened for antiproliferative activity against PC<sub>3</sub> (prostate), HF-6(colon), MCF-7 (breast), Caski (cervical) human cancer cell lines. The antiproliferative activity of synthesized 11 compound were compared and it was found that substitution by hydroxy group at 2<sup>1</sup> position and substitution by a methyl, ethyl and hydroxy group at 4<sup>1</sup> position gave compounds with highest activity. The compounds 2<sup>1</sup> hydroxy-4<sup>1</sup> methoxy chalcone, 2<sup>1</sup> hydroxy-4<sup>1</sup> ethoxy chalcone and 2<sup>1</sup>, 4<sup>1</sup> -dihydroxy chalcone showed anticancer activity against PC<sub>3</sub> cell lines as compared with the standard. The cell viability was checked by taking the absorbance at 450nm using ELISA reader. The synthesized compounds exhibited antiproliferative activity by G2 or M phase arrest.

S Satya et al synthesized chalcone derivatives by Claisen Schmidt condensation using substituted acetophenone and benzaldehyde. The 4 synthesized compounds include 3-(4-hydroxy-3-methoxy phenyl)-1-(4-hydroxy phenyl) prop-2-en-1-one, (2E)1-(4-hydroxy-3-methoxy phenyl)-3-(4-hydroxy phenyl)-prop-2-en-1-one, 4-((2E)-3-(4-methoxy phenyl)prop-2-enyl)phenyl benzoate, 3-(4-methoxy phenyl)-5-(4-benzyloxyphenyl)-6-methyl-2-cyclohexen-1-one. The compounds were screened for anticancer activity by MTT assay method against MCF-7 cell lines and its IC<sub>50</sub> value was determined. Compound 1 and 3 showed inhibition of viability at concentration less than 15.6µg/ml.

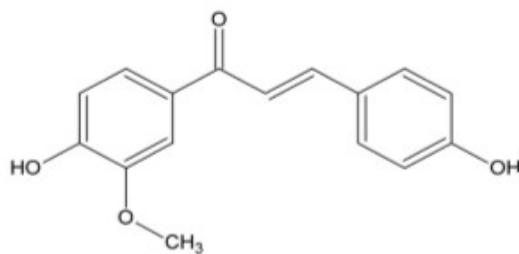


Fig: HMHP-I

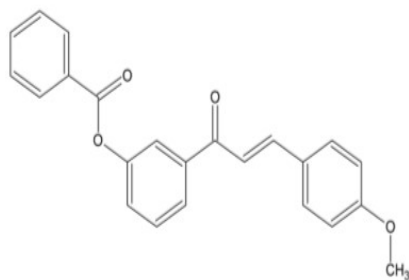


Fig: HMHP-II

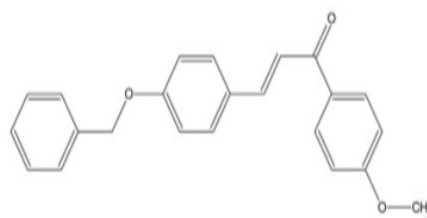


Fig: MPEB

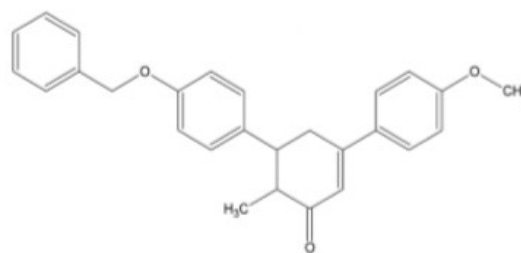
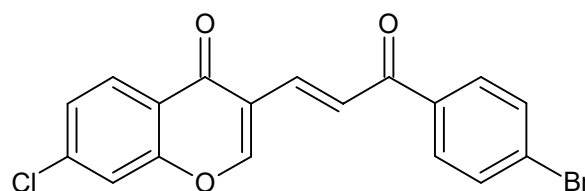


Fig: MBMC

Richa kaur Bhatia et al synthesized chalcone derivatives by reacting 6/7 substituted-3-formyl-4H-chromen-4-one with p-bromoacetophenone in the presence of glacial acetic acid and perchloric acid. The antiproliferative activity of the compound was observed using colon (HCT-116), leukemia (HTP-1) and lung (NCIH-322) cell lines. A chlorine substitution at the 7<sup>th</sup> position was found to increase the cytotoxic activity. The synthesized compound 7-chloro-3-(3-oxo-3-(4-bromo-phenyl) prop-1-enyl)-4H-chromen-4-one was found to be active against colon cancer cell lines with IC<sub>50</sub> value of 78.9µg/ml



7-chloro-3-(3-oxo-3-(4-bromo-phenyl) prop-1-enyl)-4H-chromen-4-one

Guangcheng Wang et al synthesized a series of chalcone derivatives containing indole and naphthalene moiety. Indole aldehyde was condensed with aromatic ketone in the presence of potassium hydroxide in methanol to afford chalcone derivatives. A series of N substituted chalcones were prepared by reacting these formed chalcones with alkyl halide so that the N position of indole was substituted with various groups. The anticancer activity was screened using MTT assay against human hepatocellular carcinoma (HepG2), human colon carcinoma (HCT116), and human breast adenocarcinoma (MCF-7). Cisplatin was taken as a standard drug to co-relate the activity. The compound in which the N-1 position of indole is substituted with benzyl or bulkier groups showed increase in activity (Fig:1). Substitution of N-1 of indole with

methyl group also showed good anticancer activity. The drug inhibited tubulin polymerisation by causing cell cycle arrest in G2/M phase with an  $IC_{50}$  value of  $3.9\mu M$ . Docking studies also revealed that the substitution at N-1 of indole with methyl gave best dock pose compared to other derivatives.

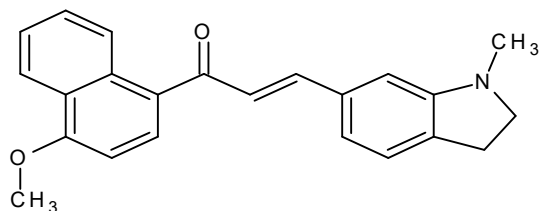
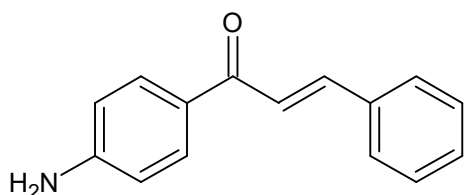


Fig: 1

Hery Su Wito et al synthesized a series of chalcone derivatives by condensing acetophenone derivatives with benzaldehyde derivatives in the presence of ethanol. The synthesized compounds were evaluated for anticancer activity using MTT assay method. Antiproliferative activity of synthesized compounds against human breast cancer cell lines (T47D) was performed taking doxorubicin as positive control. From the study it was found that methoxy-4-amino chalcone derivatives showed better antiproliferative activity than methoxy chalcone derivative which indicate the importance of amino group attached at 4<sup>th</sup> position towards growth inhibition of cancer cell lines. The compound (E)-1-(4-aminophenyl)-3-phenyl prop-2-en-1-one which does not have any methoxy group substituted on the ring showed highest antiproliferative activity which indicate that methoxy group has minor role in cytotoxic activity.



(E)-1-(4-aminophenyl)-3-phenyl prop-2-en-1-one

Ahmad Pesaran Seied et al synthesized various chalcone sulphonyl chloride derivatives by condensing cold chloro sulphonic acid with various chalcone derivatives. All the 5 synthesized compound was evaluated for anticancer activity using MTT assay method against MCF-7 cell lines. In the present study tamoxifen was used as a standard. Of all the synthesized derivatives compound (Fig:2) showed most potent anticancer activity as compared with standard.

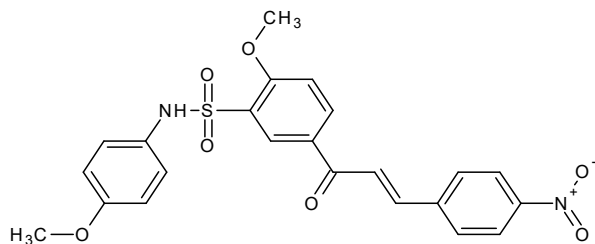


Fig:2

Sapavat Madhavi et al synthesized a series of chalcone incorporated quinazoline derivatives by condensing 4-(quinazolin-4-ylamino)-benzaldehyde with various acetophenone derivatives. The cytotoxic activity of synthesized compounds was determined using MTT assay method against human cancer cell lines such as A549 (Human alveolar adenocarcinoma cell lines), HT-29 (Human colorectal adenocarcinoma cell lines), A375 (Melanoma cancer cell lines) and MCF-7 (Human breast adenocarcinoma cell lines). The  $IC_{50}$  value was determined by taking combretastatin as standard drug. Compound (Fig: 11g) showed most potent activity against HT-29, MCF-7 and A549 cell lines with  $IC_{50}$  value  $0.13\mu M$ ,  $0.17\mu M$ ,  $0.10\mu M$  than the standard. The compound (Fig: 11f) showed highest cytotoxic activity against human colorectal adenocarcinoma cell lines with  $IC_{50}$  value of  $0.18\mu M$ . Compound (Fig: 11i) exhibited maximum cytotoxic activity on A549, MCF and A375 with  $IC_{50}$  value of  $0.10\mu M$ ,  $0.14\mu M$ ,  $0.19\mu M$  than the control

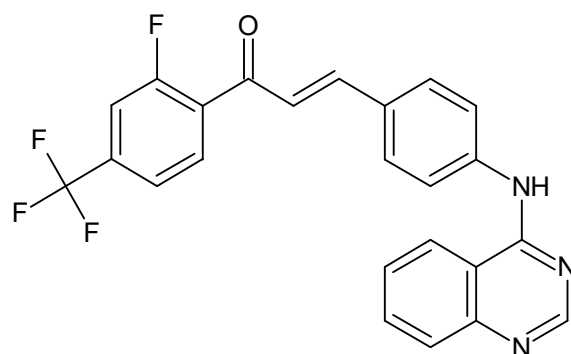


Fig:11f

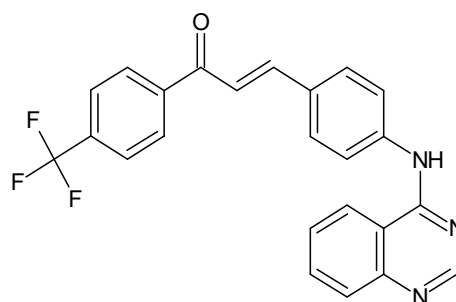


Fig:11g

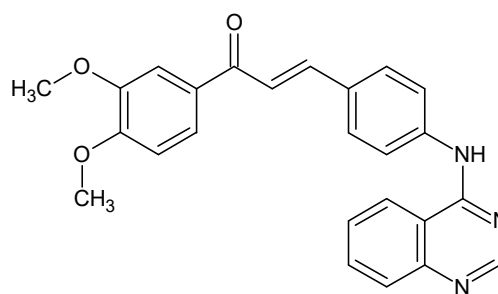


Fig:11i

Mellado Garcia M synthesized eight chalcone derivatives by Claisen Schmidt condensation. Antiproliferative activity was evaluated against MCF-7 and CaCo-2 cell lines. The activity was evaluated based on reduction of resazurin by viable cells to resorufin. In the present study position of methoxy group plays an important role in the activity. The monosubstituted chalcone with 3<sup>1</sup> methoxy group (Fig:3) was found to be 6 times more active than the one with methoxy group at 2<sup>1</sup> and 4<sup>1</sup> position which shows similar activity. Trisubstituted derivative was found to be less active than monosubstituted one. 3<sup>1</sup>,4<sup>1</sup>(OCH<sub>2</sub>O) group was also found to increase cytotoxic activity.

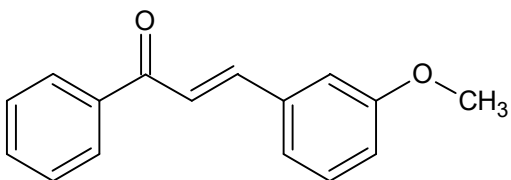


Fig:3

Aditya Narayan Pande synthesized a series of 2<sup>1</sup> hydroxy chalcone derivatives by Claisen Schmidt condensation. Cytotoxic activity of synthesized derivatives were determined using MTT assay method against human colorectal carcinoma and African green monkey kidney epithelial cells. 5-Flouro uracil was taken as a reference compound. Compound c1 was found to be highly potent against colon cancer cell lines with an IC<sub>50</sub> value of 37.07 $\mu$ M. Compound C1, C2 and C3 was found to be active against vero cell lines.

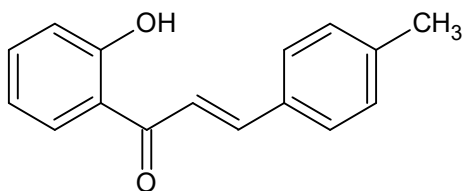


Fig:C1

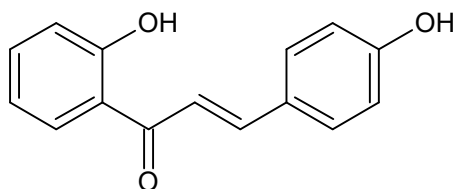


Fig:C2

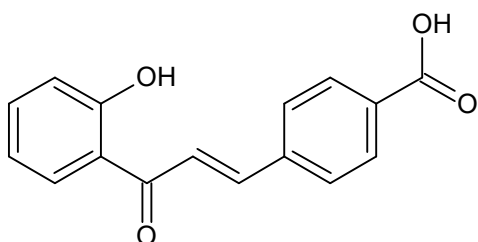


Fig:C3

Upendra. K. Jain et al performed the docking studies of certain novel halogenated chalcones. The docked poses were scored using dockscore (Accelrys) to find better dockpose. Highest dockscore was reported for compound 7b. Eight docked compounds were synthesized by Claisen schmidt condensation using acetophenone and benzaldehyde in ethanol. Invitro cytotoxicity of synthesized compounds were measured against five human cancer cell lines. The optical density was measured using ELISA reader at 540nm and the IC<sub>50</sub> value was determined. The compound 7b showed highest antiproliferative activity against colon cancer cell lines with an IC<sub>50</sub> value of 49.9 $\mu$ M. The compound 7d showed highest activity against ovarian cancer cell lines with an IC<sub>50</sub> value of 66.6 $\mu$ M. Both these compounds showed maximum inhibition against liver cell lines.

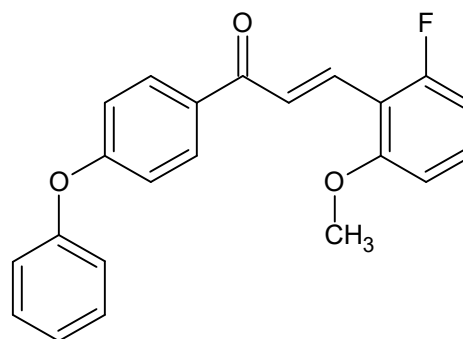


Fig:7b

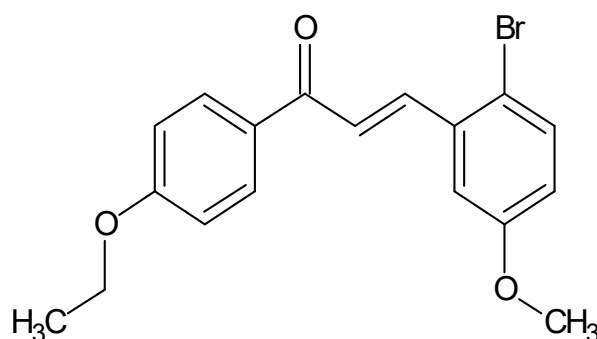


Fig:7d

Shima. H M E Ketabforoosh et al synthesized a series of dimethoxylated chalcone by Claisen Schmidt condensation using benzaldehyde derivatives and acetophenone in sodium hydroxide. The antiproliferative activity of synthesized compounds were evaluated using MTT assay method against MCF-7, MDA-MB-231 and SK-N-MC cell lines. Of all the synthesized compounds bromo chalcone 1d was found to be 8 times more potent against all the cell lines as compared with the standard compound etoposide. It was found that introduction of a chlorine and bromine atom on 3,4-dimethoxy phenyl part of the molecule was found to enhance the cytotoxicity. The compound was also found to be more selective towards cancer cell lines than normal human cell lines. The IC<sub>50</sub> value of the compound 1d on normal human

cell lines was  $31 \pm 3.1 \mu\text{M}$  whereas for human cancer cell lines was  $1-1.3 \mu\text{M}$ .

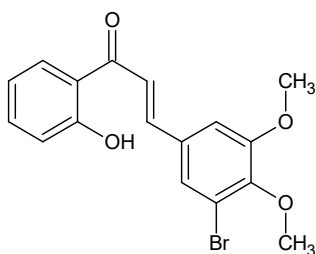


Fig:1d

#### REFERENCES

- [1] Aditya Narayan Pande, Subhankar Biswas, Neetin Kumar, D Reddy, B S Jayashree, Nitesh Kumar, C Mallikarjuna Rao. In vitro and in vivo anticancer studies of 2<sup>1</sup> hydroxy chalcone derivatives exhibit apoptosis in colon cancer cells by HDAC inhibition and cell cycle arrest. *EXCLI Journal*. 2017, 16:448-463
- [2] Mellado-Garcia M, Reyna M, Weinstein Oppenheimer C, Cuellar M, Aguilar L P. Preliminary evaluation of cytotoxicity for small chalcones on breast and colorectal cancer cell lines-Synthesis and structural activity relationship. *Journal of pharmacology and therapeutics forecast*. 2018, 1, 1
- [3] Hery Suwito, Jumina, Mustofa, Ni' matuzahroh, Ni Nyoman Tri Puspa Ningsih. Anticancer and antimicrobial activity of methoxy amino chalcone derivatives. *Der Pharma Chemica*. 2015, 7(3):89-94
- [4] Ahmad Pesaran Seied Bonakdar, Farzane Vafaei, Mahbobeh Farokh Pour, Mohammad Hossein Nasr Esfahani, Ahmad Reza Massah. Synthesis and anticancer activity assay of novel chalcone sulphonamide derivatives. *Iranian journal of pharmaceutical research*. 2017, 16(2):565-568
- [5] Sapavat Madhavi, Reddymasu Sreenivasalu, Jyothsna Pragathi Yazala, Rudraraju Ramesh Raju. Synthesis of chalcone incorporated quinazoline derivative as anticancer agent. *Saudi pharmaceutical journal*. 2016
- [6] Shima H M E Ketabforoosh, Asma Kheirollahi, Maliheh Safavi, Nasim Esmati, Sussan K Ardestani, Saeed Emami, Loghman Firoozpour Abbas Shafier, Alireza Foroumadi. Synthesis and anticancer activity evaluation of new dimethoxylated chalcone and flavanone analogs. *Arch. Pharm. Chem. LifeSci*. 2014, 347:1-8
- [7] Upendra K Jain, Richa K Bhatia, Akkinepally R Rao, Ranjit Singh, Ajit K Saxena, Irum Sechar. Design and development of halogenated chalcone derivatives as potential anticancer agents. *Tropical journal of pharmaceutical research*. 2014, 13(1):73-80
- [8] S. Satya, D. Reuben, Jonathan, S. Pandiammal, B. K. Revathi, G. Usha. Synthesis and screening of anticancer activity of a series of chalcone derivatives on MCF cell lines. *International journal of chem tech research*. 2017, 10(2):995-1005
- [9] Guangcheng Wang, Zhiyun Peng, Yongjun Li. Synthesis, Anticancer Activity and Molecular Modeling Studies of Novel Chalcone Derivatives Containing Indole and Naphthalene Moieties as Tubulin Polymerization Inhibitors. *Chem. Pharm. Bull*. 2019, 67(7):725-728
- [10] Richa Kaur Bhatia, Lakhwinder Singh, Ruchika Garg, Satyavathi Kancherla, Upendra K. Jain, Nitasha Suri, Anpurna Kaul, Ajit Kumar Saxena. Synthesis and anticancer evaluation of some chromenone derived chalcones. *European Journal of Pharmaceutical and medical research*. 2017, 4(11): 509-515
- [11] Arina Novilla, Mustofa, Indwiani Astuti, Jumina, Hery Suwit. Cytotoxic activity of methoxy 4-amino chalcone derivatives against leukemia cell lines. *Mol Cell Biomed Sci*. 2019, 3(1): 34-41