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Review Article

CHALCONES AS A PRINCIPLE PHARMACOPHORE FOR DESIGN & DEVELOPMENT OF NOVEL ANTICANCER AGENTS

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ABSTRACT

Chalcones/1,3–diphenyl-2-propene-1-one/benzalacetophenone, are the name of structurally related same compound containing two aromatic rings conjunct via bridge system enveloping carbon and keto-ethylenic moiety, considered to be precursors of bioactive flavonoids and isoflavonoids. The molecule owing to presence of dual aromatic rings and keto-ethylenic functionalities act as a versatile and universally accepted lead for search of candidate drug molecule especially anticancer agents. Lower molecular weight, ease of synthetic modification, single step reaction, high yield of pure products are some of the advantages associated with chalcone making it an attractive target for search of better anticancer drug for future. The paper here, thus discuss some of the aspects of chalcone for development of next generation anticancer agents.

Keywords: Cancer, Chalcone, Claisen Schmidt reaction, Keto-ethylenic bridge, Pharmacophore design & Development, Novel Anticancer Agents.

INTRODUCTION

Cancer is a complex genomic disease responsible for sever ill-heath globally. The disease accounted 8.2 million deaths in 2012 & continues to swing worldwide with an estimate of 14-million new cases.[1] Clinically, the disease is characterized by cellular transformation, hyperproliferation, angiogenesis & metastasis. Despite of significance elucidation in carcinogenic molecular mechanism & intensive clinical trials cancer remains principal community problem worldwide with only three well defined, accepted & universally framed interventions *viz.* chemotherapy, radiotherapy, & surgery each with their own pros & cons. Chemotherapy although a versatile global affirmative with remarkable pharmacological appurtenance however suffers limitations of non-selective targeting, sever toxicity, and tumor acquired resistance thus need of novel anticancer agent with better therapeutic profile, selectivity, specificity, and "*reach by all*" is need of present era.[2] From "*clinigeographical*" prospective and in terms of global indices, India out of 184 countries singly contribute 7.8% burden of newer cancer cases & 8.33% of cancer mortality. Expansive treatment, unaffordable medicines, drastic adverse drug reactions, limited oncological clinician, poverty, ignorance, lack of knowledge, restricted resources are some of the major roadblock in fueling for better cancer treatment thus advancing the disease towards end-up progression.[3] Chalcones belongs to α-β-unsaturated carbonyl compound chemically known as 1,3-diaryl-2-propen-1-ones (figure-01) act as a core pharmacophore for synthetic manipulations yielding compounds responsible for numerous pharmacological activities[4]. Biphenylic bridged core structure of 1,3-diaryl-2-propen-1-ones provides firm backbone for generation of potential bioactive candidate molecule when derivatized yields multiple potent and highly

selective medicinal active compounds (*substituted carbocyclic & heterocyclic*) with differential biological activities.[5,15] In general 1,3-diaryl-2-propen-1-ones occurs naturally and are considered close conger (precursor) of bioactive flavonoid, isoflavonoids & their analogues but differ from them in having dual (instead of triple) ring system. Xanthohumol, Cardamonin, and Flavokawains A, B, C are the few bioactive naturally occurring chalcones derivatives possessing potent anticancer, vasorelaxant and anti-inflammatory properties.[16,17,18] Numerous methods are available for their synthesis however Claisen-Schmidt reaction holds extraordinarily advantages (figure-02), relay on base assisted condensation of equimolar quantities of arylmethlketone with arylaldehyde in the presence of absolute alcohol.

Chalcone Chemistry[19]

Chemically chalcones are 1,3–diphenyl-2-propene-1-one also known as benzalacetophenone or benzylidene acetophenone, containing two aromatic rings linked together via keto-ethylenic bridge (**–CO-CH=CH-)** fundamentally controlling overall chemical reactivity pattern of the molecule. Since the bridge envelops two different functionalities characteristically differ among each other in distribution of electrons not only towards adjacent phenyl rings, but also to neighboring atoms constituting α-β-unsaturated carbonyl chain.

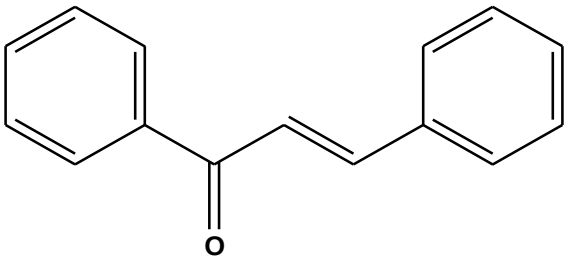


Figure 1: Chalcone

Owing to the presence of conjugated double bond and electron dense aromatic ring system, the molecule posses less redox potential; thus greater probability for undergoing characteristic electron transfer reactions. For this reason unsubstituted biarene ring system of this naturally occurring molecule act as an active site for electrophilic attack and overall extent of toxicity to pharmacological activity could be manipulated by differential ring substitutions. Furthermore ketonic-unsaturated bridge (*α,β-unsaturated bridge;* ***–CO-CH=CH-***) holding biphenylic ring systems itself responsible for anti-oxidant, antimicrobial activity, and chromogenic property any exploit in this part with synthetic modifications in phenyl ring/s may yield compounds with improved biological activity. Although, occurs naturally isolation of 1,3-diaryl-2-propen-1-ones (*due to enzyme chalcone synthase*) employ tedious, multi-step, time-consuming, complicated methodologies, which rarely compatible & comparable with synthetic procedures in terms of end product yield, purity, net time consumption, ease of procedure, & eco-handy technique.

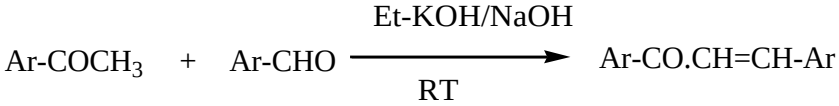


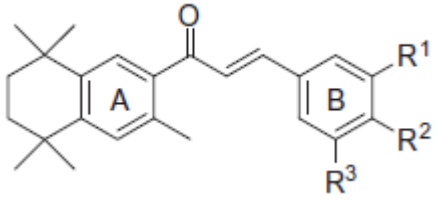
Figure 2: Claisen Schmidt scheme for chalcone synthesis

Problem Words & Future Scope

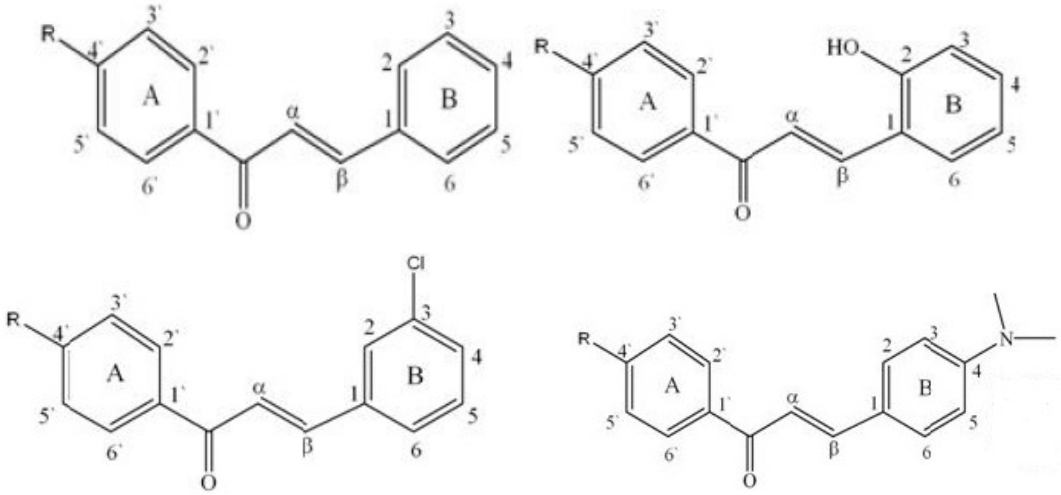
Oncological oriented chemotherapeutic agents (OCA), although shares larger proportion in cancer treatment, but their non-specific action imposes potential threat in maintaining physiological homeostasis. Over the last 50 years approximately 500,000 plus synthetic and natural molecules are screened against anticancer activity however only 25 are used commercially. Bulkier molecules, lengthy reaction time, multi-step synthetic procedures, continuous reaction monitoring, costlier reactants, potentially hazardous solvents, slow reaction rate, complex work-up procedure, uneconomic process, unpredictability & lower

yield of final product are some of the brusque in search & development of potential anticancer agents. In contrast 1,3-diaryl-2-propen-1-ones are extraordinarily free from above mentioned limitations. This study thus aims towards extensive search for small bioactive 1,3-diaryl-2-propen-1-ones based molecules with better, economical, potent, and lower side effect anticancer agent for tomorrow. Researchers around the world dynamically fuels towards development of novel anti-cancer agents by identification of newer biological targets and searching for versatile chemical entity however overall process for development of novel anticancer agent have to cross many hurdles and at each point of development process, emerging pitfalls have to be balanced against potential benefits at the end. It is perplexing to document round-the-globe natural product based novel 1,3-diaryl-2-propen-1-ones as surpass anticancer agent however a concise in-depth account is discussed here;

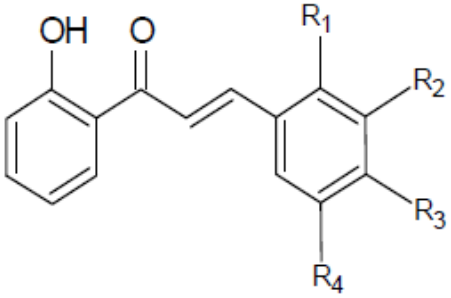
Mizuno *et. al.*[20] reported *in-vitro* anticancer activity of retinoid chalcone against colon cancer at concentration of 0.44µM.



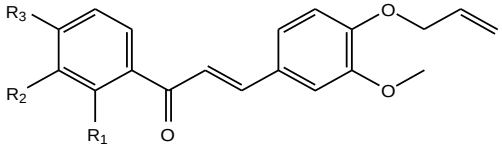
Syam *et. al.*[21] synthesize series of 25 biphenyl substituted chalcones derivative and evaluate their effect on MCF-7, A549, PC3, HT-29, & WRL-68 cell lines with positive orientation.



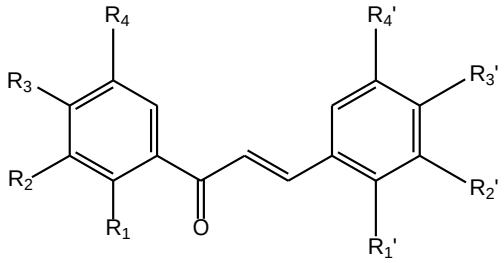
Selective structure activity relationship of substituents such as hydroxyl & methoxy group on phenyl ring system was well established by Echeverria *et. al* [22].



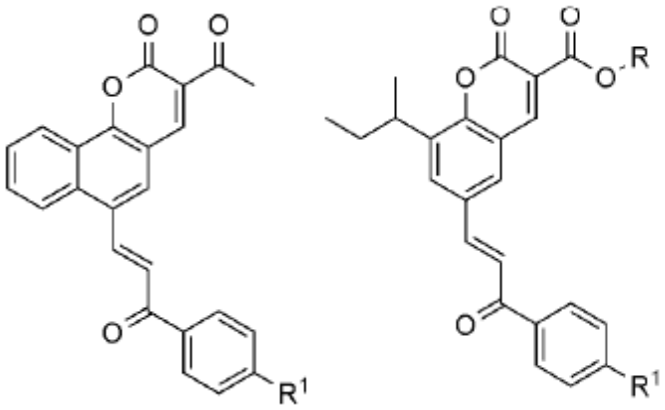
Ngameni *et. al.*[23] presented evaluation of O-allylchalcones as anticancer derivatives.



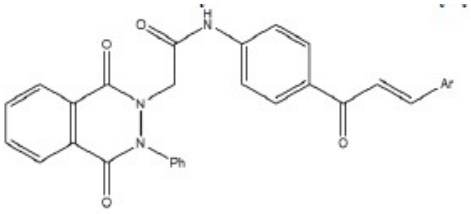
Sehar *et. al.*[24] developed halogenated chalcone based derivatives and evaluated their anticancer activity against prostrate (PC-3), colon (COLO-205), ovary (OVCAR-5), neuroblastoma (IMR-32), and liver (HEP-2) cancer cell lines against Paclitaxel, Adiramycin & 5-fluorouracil as standard.



A series of twenty-one coumarin-chalcone hybrid were synthesized by Sashidhara *et. al.*[25] and their cytotoxic activity was established against four human cancer cell lines with a best modulating activity of 3.59µm against cervical carcinoma.



El-Fekya *et. al.*[26] design synthesized & studied anticancer activity of several new phthalazine-1,4-diones and tested *in-vitro* on HCT-116 colon cancer and MCF-7 breast cancer cell lines.



Srinivasarao *et. al.*[27] established *in-vitro* cell viability assay of aromatic chalcones against T-lymphocyte leukemia and reported importance of hydroxyl or methoxy group as ring substituents for development potent anticancer agents.

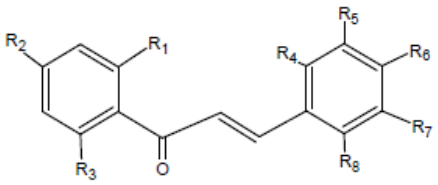


Table 1: Infrences on reported anticancer activity of chalcone

S.No.	Researcher/s/ Ref. Nos	In-vitro/In-vivo screening	Inferences
01.	Cassia S. Mizuno *et. al.* (20)	Colon cancer cell line (HT-29)	(E)-3-(3-oxo-3-(3,5,5,8,8-pentamethyl-5, 6, 7, 8 tetrahydronaphthalen-2-yl)prop-1-enyl) benzo-nitrile exhibit sub-micromolar activity at IC_{50} of 0.66 µm.
02.	Suvitha Syam *et. al.* (21)	Lung adenocarcinoma cell line (A549), breast adenocarcinoma cell line (MCF-7), , prostate cancer cell line (PC3), human adenocarcinoma cell line HT-29 (colorectal cancer) and human normal liver cell line WRL-68	Compounds apoptosis in cell line possible due to ROS.
03	Cesar Echeverria (22)	Hepatocellular carcinoma cell line-HepG2	Inhibition of cell proliferation and apoptosis is shown in HepG2 cell line by 2-hydroxy chalcones with methoxy group substitution.
04.	Bathelemy Ngameni *et. al.* (23)	Hepatocarcinoma Hep-G2, prostate carcinoma DU-145, breast carcinoma MCF-7, and monocytic leukemia THP-1 and HL-60 cell line	Some of the compounds exhibit activity at mico-molar level.
05	Irum Sehar *et. al.* (24)	Prostate cancer cell line (PC-3), colon cell line(COLO-205) ovarian cancer cell line (OVCAR-5), Neuroblastoma IMR-32, and Hepatocarcinoma Hep-G2.	Single compound shows activity at 49.9 micro-molar against colo-205.
06	Koneni V. Sashidhara *et. al.* (25)	Oral squamous cell carcinoma , cervical carcinoma, breast adenocarcinoma, lung cancer cell line and one normal human	Synthesized compounds shows activity
07.	Said A.H. El-Fekya *et. al.* (26)	Colon cancer breast cancer cell lines	Compounds are active against screened cell lines

08.	Vankadari Srinivasa rao *et. al.* (27)	Human tumour cell lines (Jurkat T-lymphocyte leukemia), human leukemia cells HL-60, and MTT assay	Chalcone with electron donating group are active.

CONCLUSION

In summary, chalcones act as an excellent pharmacophore for development and design of novel anticancer agents. Synthetic feasibility, on hand literature data, less time consumption, and excellent yield of product makes the same as an attractive backbone for future research.

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