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Review Article

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A REVIEW ON BIOLOGICAL ACTIVITY OF CHALCONE DERIVATIVES

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ABSTRACT

Chalcones are a class of organic compounds characterized by their simple versatile chemical structure, consisting of two aromatic rings connected by a three-carbon (α, β-unsaturated carbonyl system). These compounds have significant attention due to their diverse range of biological activities and potential applications in medicinal and agricultural fields. The distinctive structure of chalcones allows for modification leading to the synthesis of various derivatives with different properties. Chalcones exhibit a wide spectrum of biological effects, including antioxidant, anti-inflammatory, anticancer, antimicrobial, and antidiabetic activities. Their mechanisms of action often involve interactions with key cellular targets such as enzymes and receptors leading to modulation of various signaling pathways. These properties have prompted extensive research into developing chalcones as lead compounds for drug discovery and development. In the agricultural sector chalcones and their derivatives have demonstrated potential as natural pesticides and plant growth regulators. Their ability to disrupt insect growth and inhibit fungal pathogens makes them as eco-friendly pest management strategies. In conclusion chalcones represent a fascinating class of compounds with a myriad of biological activities and potential applications. And it is significance in both medicinal and agricultural area.

KEYWORDS: Chalcones, Biological activity, Anticancer, Antimicrobial activities, Drug discovery.

INTRODUCTION

The field of medicinal chemistry is the one area of research that directly affects the health, welfare, and development of people. Medicinal chemistry works at the boundary of synthetic organic chemistry and biology with principal focus on drug development. In particular, the study of heterocyclic chemistry is one of the most typical, but equally important branches of organic chemistry, constituting one of the wide areas of research for more than a century. In recent years, there has been a growing interest pertaining to the synthesis and biological progression of bioactive compounds in the field of organic chemistry.[1,2] Heterocyclic compounds are widespread in plant kingdom and animals in nature, as well as in various non-naturally occurring compounds also. Several heterocyclic compounds playing vital role in various metabolic processes and are very much essential to various compounds such as alkaloids, vitamins, hormones, antibiotics, hemoglobin, essential amino acids, dyes and a large number of drugs contain different heterocyclic ring systems as a part of their structures. Traditionally, naturally occurring low-molecular weight heterocyclic compounds have been used as medicinal drugs. Most of such natural products are difficult to isolate in large quantities. In recent years, however, it has become possible to synthesize low-molecular weight heterocyclic compounds which mimic natural products and show equal to or better medicinal properties. In the past few decades, almost all the new chemical entities, which have been approved for medicinal uses have been developed by drawing design from the structures of natural products.[3,4] Drug discovery is the process through which, potential new medicines are identified. It involves a wide range of scientific disciplines including biology, chemistry and pharmacology. In the past, most drugs were discovered through identifying the active ingredient from traditional remedies or by serendipitous discovery. Historically substances, whether crude extracts or purified chemicals were screened for biological activity without knowledge of the biological target. Only after an active substance was identified and efforts were made to identify the target. This approach is known as classical pharmacology or phenotypic drug discovery.[5,6] Developing a new drug from original idea to the launch of a finished product is a complex process which can take 12–15 years and cost in excess of one billion USD. The idea for a target can come from a variety of sources including academic and clinical research and from the commercial sector. It may take many years to build up a body of supporting evidence before selecting a target for a costly drug discovery programmed. Once a target has been chosen,

the pharmaceutical industry and more recently some academic centers have streamlined a number of early processes to identify molecules which possess suitable characteristics to make acceptable drugs. The outcome of this activity is the selection of a target which may require further validation prior to progression into the lead discovery phase in order to justify a drug discovery effort. During lead discovery, an intensive search ensues to find a drug-like small molecule or typically termed a development candidate, that will progress into preclinical, and if successful, then into clinical development and ultimately be a marketed medicine. Preclinical stages of the drug discovery processes are initial target identification and validation, through assay development, high throughput screening, hit identification, lead optimization and finally the selection of a candidate molecule for clinical development.[7]

Chalcones consist of an aromatic ketone and an enone that form a variety of biological agents. Their skeleton is made up of two aromatic rings with an aliphatic three-carbon chain linking them to form a linear or planar skeleton structure. They are also interconnected by conjugated double bonds and possess a delocalized p-electron system on the aromatic rings.[8] Chalcones and their natural or synthetic derivatives (through some structural modifications of the chalcone rings) are known to have a wide range of numerous pharmacological actions comprising anti- inflammatory,[9] anti-oxidant,[10] antitumor,[11] anti-tubercular,[12] anti-viral,[13] anti-malarial, [14] anti-fungal[15] and antibacterial activities.[16] Several natural and synthetic or semi-synthetic chalcones have shown great medicinal bioactivity due to their actions against diverse target.[17] Their potential anti-viral activities have been well recognized via various targets including glyceraldehyde-3-phosphate dehydrogenase (GAPDH), topoisomerase-II, fumarate reductase, lactate dehydrogenase, several protein kinases, protein tyrosine phosphatase, human immunodeficiency virus (HIV integrase/protease), lactate/isocitrate dehydrogenase, etc.[18]

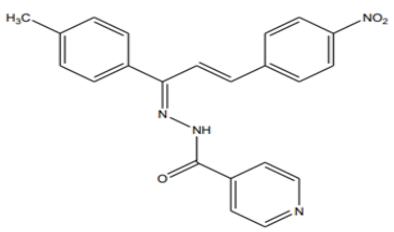
Review of literature

1. Antibacterial and Antifungal[19]

M.W. Bhade,[19] A new sequence of synthesized chalcone derivatives were synthesized and assessed for their *in-vitro* antibacterial and antifungal activity. The synthesized compounds underwent antimicrobial evaluations targeting both gram-positive bacteria *Staphylococcus aureus* and *Bacillus subtilis* and gram-negative bacteria namely, *Pseudomonas aeruginosa*, *Salmonella typhi*, and *Escherichia coli*. Furthermore, antifungal assays were conducted employing *Candida albicans*, *Aspergillus niger*, *Rhizopus stolonifera*, and *Penicillium notatum* as representative fungi. The antibacterial activity was ascertained via the pour plate method, while the antifungal activity was appraised using the surface plate method. Gentamycin served as the reference for antibacterial comparison, whereas Tioconazole was utilized for antifungal comparison. For solubilizing the tested compounds, Dimethylsulfoxide (DMSO) was used to create a 1 mg/ml solution. Inhibition zones, with an 8 mm diameter, were measured following an incubation period of 18-24 hours at 37°C for bacteria and 48 hours at 26-28°C for fungi. The basal media employed for bacterial and fungal testing encompassed Sterile Nutrient Agar and Sabouraud Dextrose Agar, respectively. Notably, compounds Ⅲ and Ⅳ exhibited remarkable antimicrobial efficacy in contrast to compounds Ⅰ and Ⅱ. Noteworthy among the tested bacterial cultures was the heightened susceptibility of *Staphylococcus aureus* to all four synthesized compounds. Moreover, among the tested fungal species, *Candida albicans* stood out, demonstrating substantial susceptibility to all synthesized compounds when compared to the other three fungal species.

2. Antibacterial and Antifungal[20]

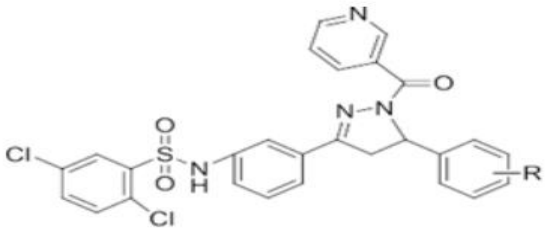
Amit Panaskar N[20] *et al.*, A new sequence of synthesized chalcone derivatives were synthesized and assessed for their anti-inflammatory activity. Dimethyl sulfoxide (DMSO) served as the solvent for preparing the test compounds. To establish a reference point, indomethacin was employed as the standard drug. Notably, after a 2-hour interval, the observed inhibition percentage reached 53.23%. These hydrazide derivatives of chalcones exhibited discernible anti-inflammatory properties. Particularly noteworthy was the compound designated as compound 2 (administered at 40mg/kg), which displayed a significant inhibitory effect on carrageenan-induced paw edema. This effect was attributed to the strategic positioning of functional groups on the compound's molecular structure an electron-donating group (-CH3) on ring A and an electron-withdrawing group (NO2) at the 4th position of ring B in the isonicotinyl hydrazide derivative.



Compound 2

3. Antibacterial and Anti inflammatory[21]

Geeta Lodhi[21] ***et al.***, A new synthesized chalcone derivatives were synthesized and assessed for their *in-vitro* antibacterial and anti-inflammatory potential against Bacillus pumilis, Bacillus subtilis (gram-positive), and Escherichia coli, Proteus vulgaris (gram-negative). Chloramphenicol was employed as the reference drug for antibacterial evaluation. Notably, certain derivatives exhibited significant inhibitory effects, particularly against B. pumilis, B. subtilis, and E. coli, while displaying mild inhibitory action against P. vulgaris. Among the synthesized compounds, **Compound $3a_1$** displayed remarkable antibacterial activity against the tested bacterial species. Moreover, the chalcone derivatives were evaluated for anti-inflammatory efficacy using the carrageenan-induced rat paw edema method, with the standard and sample solutions administered at 100 mg/kg body weight. **Compound $3a_2$** exhibited potent anti-inflammatory activity, with indomethacin serving as the standard reference drug.

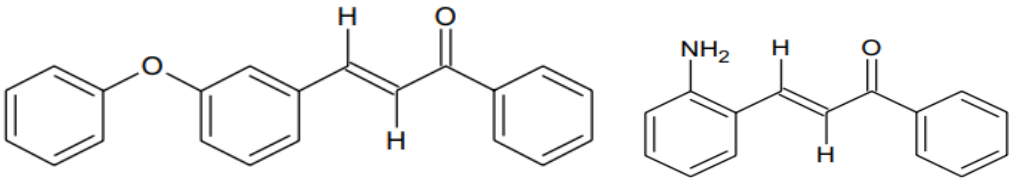


Compound $3a_1$ R= Pyridin-3-yl
Compound $3a_2$ R= 3,4,5-trimethoxy

Compound 3

4. Antimicrobial and Antioxidant[22]

Emelda Okolo N[22] ***et al.***, A new sequence of synthesized chalcones derivatives were synthesized and assessed for their *in-vitro* antimicrobial and antioxidant activity. The antimicrobial efficacy of the synthesized compounds was investigated against a range of microorganisms, including gram-positive bacteria such as Staphylococcus aureus and Bacillus subtilis, gram-negative bacteria including Pseudomonas aeruginosa, Salmonella typhi, Escherichia coli, as well as fungi such as Candida albicans and Aspergillus niger. As reference standards for antibacterial and antifungal comparisons, Ofloxacin, Ciprofloxacin, and Fluconazole were employed. Among the synthesized derivatives, **Compound $4a_1$** exhibited notable antibacterial activity specifically against Pseudomonas aeruginosa. Furthermore, **Compound $4a_2$** demonstrated remarkable antioxidant activity. Ethylenediaminetetraacetic acid (EDTA) was used as the standard reference drug for assessing antioxidant potential.

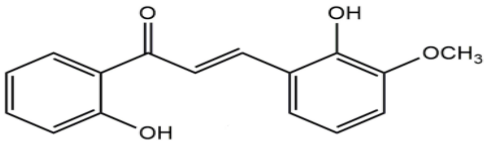


Compound $4a_1$ Compound $4a_2$

Compound 4

5. Antidiabetic activity[23]

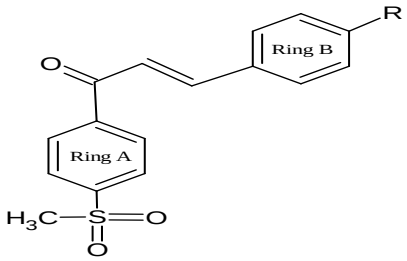
Semere Welday Kahssay[23] ***et al.***, A new series of synthesized chalcone derivatives was developed and evaluated for their *in-vitro* antidiabetic potential. Dimethyl sulfoxide (DMSO) was employed as the solvent vehicle. The first group (Group 1) was administered the vehicle alone (5% DMSO), serving as the diabetic control reference. The second group (Group 2) was treated with the standard antidiabetic drug, glibenclamide, serving as the positive control. Groups 3 to 7 received treatment with the synthesized compounds, dissolved in the solvent vehicle. For assessing the in vivo antidiabetic efficacy of the synthesized compounds, glibenclamide was used as the reference standard. Both the test compounds and glibenclamide demonstrated significant reductions in blood glucose levels (BGL) on days 7, 14, and 21 in comparison to the diabetic control group. Across each assessment day, all test compounds exhibited comparable reductions in fasting BGL similar to the standard drug (glibenclamide). Notably, among the synthesized derivatives, **Compound 5** exhibited the highest antidiabetic activity, with the most pronounced effect observed on day 21



Compound 5

6. Analgesic and Anti- inflammatory activity[24]

Lakshminarayanan B[24] *et al.*, A new sequence of synthesized chalcone derivatives were synthesized and assessed for their *in-vitro* analgesic and anti-inflammatory activity. Indomethacin, (10mg/kg b.w.IP) used as a standard. Sulfur-based chalcones containing various substituting groups at the para position of the benzene ring was synthesized and assessed for their anti-inflammatory activities. Among the synthesized derivatives, **Compound 6** showed potent anti-inflammatory activity.



R=4F

Compound 6

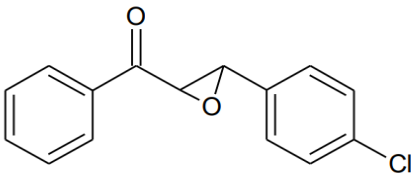
7. Antimicrobial activity[25]

Kalaiselvi E[25] *et al.*, A new sequence of synthesized chalcone derivatives were synthesized and assessed for their *in-vitro* antimirobial activity. The study encompassed a spectrum of microorganisms, including Gram-positive bacterium Staphylococcus aureus, Gram-negative bacterium Escherichia coli, as well as the fungi Candida albicans and Mucor spp, for assessing their antimicrobial activity. Ciprofloxacin was used as reference for antibacterial agent, and the agar well diffusion method was utilized. with DMSO serving as the solvent control. Inhibition zones were quantified in millimeters after incubating the plates at 37°C for 18 hours in the case of bacteria, and at room temperature for fungi, specifically against Staphylococcus aureus. For antifungal assessment, Amphotericin B was employed as the reference standard, and the disc diffusion method was employed. The results highlighted a notably higher inhibition zone against Mucor spp compared to the standard drug.

their *in-vitro* antifungal activity the test organisms including *Candida albicans*, *Escherichia coli*, *Pseudomonas aeruginosa*, and *Staphylococcus aureus.* The diameter of inhibition zones was measured in millimeters and compared with control standards. Antibiotic susceptibility testing was conducted using a modified Kirby-Bauer diffusion technique. This method involved swabbing Mueller–Hinton agar plates with a saline suspension of each strain. Six wells, created aseptically with a 6mm cork borer, were then made on the agar surfaces already seeded with the test organisms. For the extraction, a concentration of 100000 mcg/ml in Dimethylsulfoxide (DMSO) was used. The inhibition zones were measured after an incubation period of 24 hours at 37°C. Notably, among the synthesized derivatives, compound 8 exhibited significant inhibition against both *Staphylococcus aureus* and *Candida albicans*, surpassing the effectiveness of the standard antifungal agent Ketoconazole.

8. Antifungal activity[26]

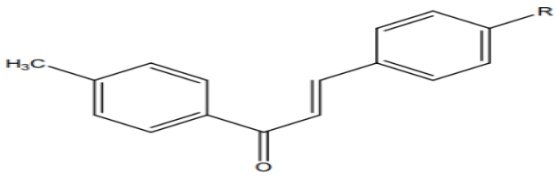
Jacob BS[26] *et al.*, A new sequence of synthesized chalcone derivatives were synthesized and assessed for



Compound 8

9. Analgesic and Antioxidant activities[27]

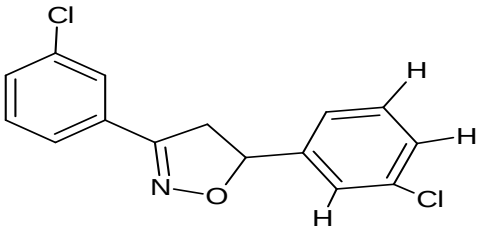
Padma R[27] *et al.,* A new sequence of synthesized chalcone derivatives were synthesized chalcone derivative were synthesized and assessed for their *in-vitro* analgesic and antioxidant activities. Acetylsalicylic acid and acetaminophen were used as standard drugs for comparison. Among the synthesized derivatives, **Compound 9a$_1$** exhibited noteworthy analgesic activity attributed to the substitution of a methyl group on the aromatic ring at the 4th position. The compounds underwent a comprehensive evaluation for antioxidant potential, encompassing assays such as DPPH stable free radical reduction, nitric oxide scavenging, inhibition of lipid peroxidation, hydroxyl radical and superoxide scavenging, as well as ABTS+ scavenging and reducing power determination. Notably, derivatives bearing functionalities like 4-dimethylamino, 2-hydroxy, 4-hydroxy-3,5-dimethoxy, 5-bromovanillinyl, and 5-iodovanillinyl derivatives **compound 9a$_2$** exhibited robust antioxidant activity across all in-vitro models at a concentration of 125µM.



Compound 9a$_1$ R=4-CH3
Compound 9a$_2$ R=4-N(CH$_3$)$_2$
Compound 9

10. Anthelmintic activity[28]

Anitha Kumari V[28] *et al.,* A new sequence of synthesized chalcone derivatives were synthesized and assessed for their to in-vitro antioxidant activity assessment. Solutions were prepared using 5% dimethylformamide (DMF) and saline solution. Both test solutions and standard drug solutions were freshly prepared prior to the commencement of the experiment. Earthworms were categorized into six groups of approximately uniform size and exposed to 25 ml solutions of varying concentrations (20, 40, 80 mg/ml) within petri dishes, each containing a 5% DMF solution. The time of paralysis and time of death of the earthworms were recorded as part of the evaluation. Piperazine citrate served as the reference standard for comparison. Notably, among the synthesized derivatives, compound 10 exhibited superior outcomes.

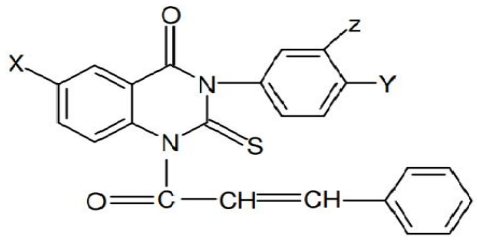


Compound 10

11. Antimirobial and Antihelmintic activity[29]

Lakshmi K[29] *et al.,* A new sequence of synthesized chalcone derivatives were synthesized and assessed for their *in-vitro* evaluations for both antifungal and antihelminthic activities. The antifungal effectiveness of these compounds was assessed against Gram-positive bacterial genera including *Streptococcus* and *Staphylococcu*s. The fungal strains used for antimicrobial and anthelmintic assays encompassed *Cryptococcus*, *Candida*, and *Aspergillus*. Among the synthesized derivatives, **compound 11a$_1$** was singled out for in vitro antibacterial screening. It was tested against nonpathogenic bacteria like *Bacillus subtilis* MTCC 441 and *Bacillus cereus* MTCC 430, as well as pathogenic bacteria like *Staphylococcus aureus* MTCC 737, *Staphylococcus epidermidis* MTCC 3086 (Gram-positive), *Pseudomonas aeruginosa* MTCC 1035, and *Escherichia coli* MTCC 1687 (Gram-negative). The paper disc diffusion method was employed, and the zone of inhibition was gauged in millimeters following 18-24 hours of incubation at 37±1°C using a digital antibiotic zone reader. The activity of test compounds was benchmarked against the standard Ciprofloxacin at a concentration of 100 µg/disc. Additionally, **compound 11a$_2$**, another derivative from the synthesis, was evaluated for *in vitro* antifungal activity against various pathogenic fungi such as *Aspergillus niger* MTCC 2638, *Aspergillus foetidus* MTCC 2737, *Candida albicans* MTCC 301, *Candida glabrata* MTCC 3019, and the nonpathogenic fungus *Saccharomyces cerevisiae* MTCC 170. The paper disc diffusion method was again used, and the zone of inhibition was determined in millimeters after 72 hours of incubation at 25±1°C using a digital antibiotic zone reader. The activity was then compared to

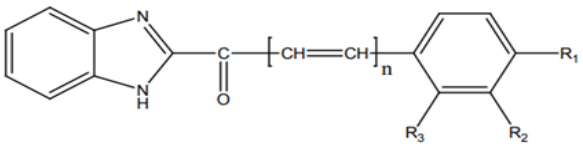
the standard Fluconazole at a concentration of 100 µg/disc. Furthermore, **compound 11a$_3$** underwent in vitro anthelmintic assessment using adult Indian earthworms Peritima posthuma, chosen for their anatomical and physiological similarity to human intestinal parasites. The synthesized compounds were prepared in 1% DMF in normal saline to achieve a concentration of 1 mg/ml in each 4-inch petri dish. Albendazole at a concentration of 10 mg/ml was utilized as the standard for comparing anthelmintic activity.



compound 11(a_1, a_2, a_3)

12. Antibacterial, Antifungal, Anthelmintic activity[30]

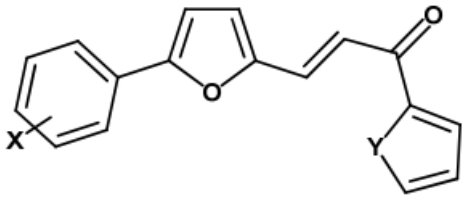
Selvakumar S[30] *et al.,* A new series of synthesized chalcone derivatives were synthesized and assessed for their *in vitro* assessment for their antifungal activity. The antimicrobial assay involved fungi species including *Aspergillus niger*, *Candida albicans* MTCC 183, and *Penicillium citrinum* MTCC 1256. Notably, all tested chalcones exhibited substantial zones of inhibition against the fungal species, and they also demonstrated potent activity against gram-positive microbial species. Among the synthesized derivatives, **compound 12a$_1$** displayed notable antimicrobial potential against *Candida albicans*. Ciprofloxacin and clotrimazole were employed as standard reference drugs. Furthermore, **compound 12a$_2$** showcased anthelmintic activity against Candida albicans, with albendazole serving as the standard reference drug**.**



Compound 12a$_1$ = R_1- F, R_2 – H, R_3 – H, n=1
Compound 12a$_2$ = R_1- F, R_2 – H, R_3 – H, n=1
Compound 12

13. Antibacterial activity[31]

Mutanabbi Abdula[31] *et al.,* A new sequence of synthesized chalcone derivatives were synthesized and assessed for their *in-vitro* antibacterial activity. The antibacterial effectiveness of the synthesized compounds was assessed against the following bacteria like *Escherichia coli* and *Klebsiella spp.* (gram-negative), as well as *Staphylococcus aureus* and *Enterococcus faecalis* (gram-positive). The well diffusion method was employed for evaluating antibacterial activity. The compounds were extracted using a 10 mg/ml concentration in Dimethylsulfoxide (DMSO). Tetracycline and amoxicillin served as the standard reference drugs. Among the synthesized derivatives, **Compound 13** exhibited a notable inhibition zone of mm when tested against *Staphylococcus aureus* at a concentration of 10 mg/ml.

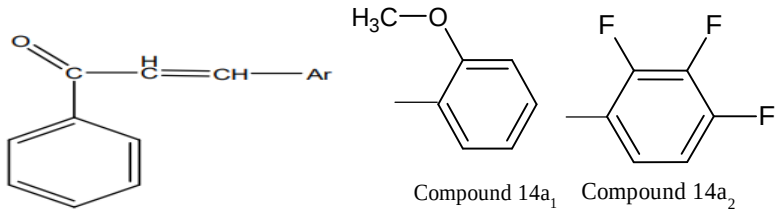


X= 4-Cl, Y = O
compound13

14. Antimicrobial Activity and Antioxidant activity[32]

Sandip Sen[32] *et al.,* A novel series of synthesized chalcone derivatives was generated and subsequently evaluated for their *in-vitro* antimicrobial and antioxidant activities. The synthesized compounds were tested against Gram-positive and Gram-negative bacteria, as

well as fungi, to determine their antimicrobial potential. Streptomycin was employed as a reference drug for comparison. The antimicrobial activity was assessed using the disk diffusion method, where sterile disks were positioned appropriately on the agar medium and then incubated at 50°C for 1 hour to facilitate diffusion. Following this, the plates were moved to an incubator set at 37°C for 24 hours (for bacteria) and 28°C for 72 hours (for fungi). Notably, **compound 14a$_1$** exhibited notable antimicrobial activity against Staphylococcus aureus and Candida albicans at a concentration of 150 mcg/ml. For antioxidant activity assessment, ascorbic acid was utilized as the standard drug. The test samples were introduced to a 3 ml solution containing 0.004% DPPH in ethanol. After 30 minutes, the absorbance at 517 nm was measured, and the IC50 (Inhibitory Concentration 50%) value was determined. The IC50 value signifies the concentration of the sample required to scavenge 50% of the DPPH free radicals. Among the synthesized derivatives, **compound 14a$_2$** demonstrated the highest potency in terms of antioxidant activity.

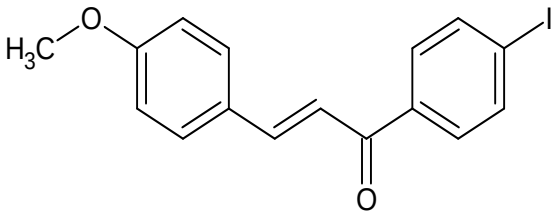


Compound 14a$_1$ Compound 14a$_2$

Compound 14

15. Antimicrobial activity[33]

Alka Choudhary N[33] ***et al.,*** A new sequence of synthesized chalcone derivatives were synthesized and assessed for their *in-vitro* antimicrobial activity assessment. The synthesized compounds were evaluated for their antimicrobial effectiveness against specific strains, including Gram-positive bacteria such as Staphylococcus aureus, and Gram-negative bacteria like Pseudomonas aeruginosa. To establish a baseline, chloramphenicol was employed as the reference standard. Remarkably, compound 15a exhibited significant activity against S. aureus at concentrations of 500 µg/ml and 1000 µg/ml, demonstrating its efficacy. The antimicrobial activity evaluation was carried out using the disc diffusion method. Dimethyl sulfoxide (DMSO) was used to achieve the concentrations of 500 µg/ml and 1000 µg/ml. The zones of inhibition produced by each compound were subsequently measured in millimeters.



Compound 15

CONCLUSION

Chalcones are noteworthy for their versatile synthetic methods and a broad spectrum of biological functions within the realm of medicine. The derivatives of chalcones display a diverse array of biological activities, spanning antitumor, anthelmintic, antitubercular, antimicrobial, antibacterial, antidiabetic, antioxidant, anti-inflammatory, antifungal properties, and more. The derivatives of chalcones have garnered considerable attention as a fertile ground for research in the pursuit of novel lead compounds, owing to their inherent range of activities. The extensive molecular targets this scaffold interacts with amplify its potential as a promising area of study. The insights presented in this review offer valuable pathways for further exploration of this chemical moiety, opening avenues to uncover its untapped biological potential and to facilitate the ongoing development of pharmacologically valuable therapeutic agents.

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