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Review Article

The Synthesis and Pharmaceutical Profile of Chalcones and their Oxazine Compounds

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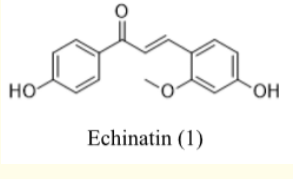
Abstract

The pharmacological value of heterocyclic compounds draw the synthesis of this kind of compounds due to the presence of hetero atoms within their structures which make these compounds active towards many diseases. According to the above, many routes were used for the synthesis of those heterocyclic compounds. Among the heterocyclic compounds having oxygen and Nitrogen heterocycles that showed a lot of pharmaceutical applications is the Oxazine compounds. In this study we will focus on the methods of synthesis especially the method which is the synthesis of the oxazine compounds from chalcone routes and their biological activities. All methods of oxazine synthesis in this review were starting from the synthesis of chalcone compounds. These chalcone compounds were synthesized using general method in which substituted aldehydes or ketones having alpha acidic hydrogen condensed together using Claisen-Schmidt condensation reaction. These chalcones were then interacted with urea or urea derivatives forming the corresponding oxazine compounds. These oxazine compounds have been studied for their anti microbial, anti fungal, antioxidant, cytotoxicity, anti platelet aggregation, anti diabetic and anti-inflammatory effects.

Keywords: Pharmaceutical; Profile; Oxazine; Chalcones; Derivatives

Introduction

Among the well-known natural chalcone compounds is Echinatin which was isolated from Licorice which is hydroxyl chalcone derivative called retro chalcone. This compound has divers therapeutic effects these effects including anti-oxidant and inflammatory effects which exhibited effects against I/R-induced myocardial on hearts due to this anti-inflammatory and oxidant bioactivities of Echinatin. And also it was found HAT active side 4-OH rather than 4-OH which both form the final RAF products [1].



Echinatin (1)

Figure 1

Chalcone compounds themselves have many medical and pharmaceutical applications including anti-cancer activity this was found in the work of Modo and his colleagues, they synthesized many chalcone derivatives among them are the compounds bellow [2].

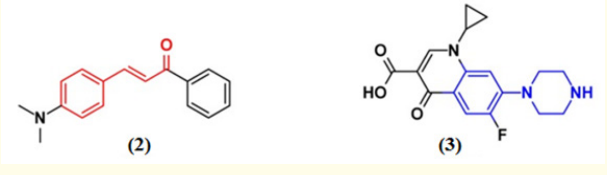


Figure 2

Marcelo N. and his colleagues have reviewed the investigation and the therapeutic drug design of many chalcone compounds as anti-cancer agent together with the well-known chalcone drugs

sealed in the market [3]. Gloria and his co-workers have studied the anti-oxidant activities of Coumarin chalcone hybrid as phenoxy radical scavengers using the density function and conventional transition state theory in polar solvents. They found that the scavenging ability is more than that for non-hybrid one. The study revealed that the molecules reacts faster than Trolox with the peroxy radical [4].

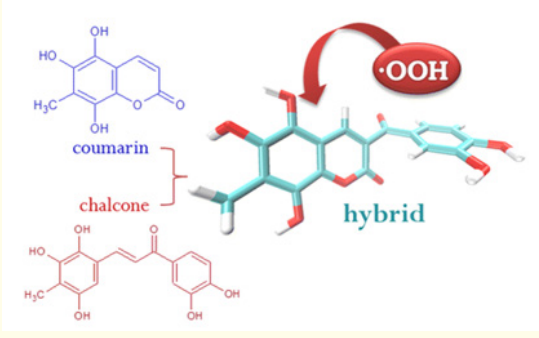


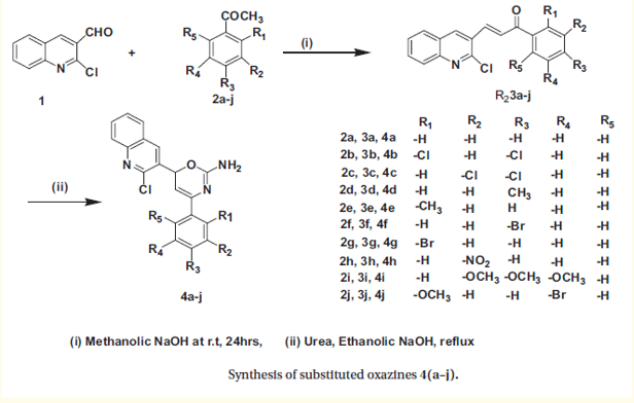
Figure 3

Yasameen K., *et al.* have reviewed the anti-microbial activity of many chalcones against different microorganism [5]. There are many papers in the literatures concerning the preparation of oxazine compounds, the most popular method is the cyclization of chalcone compound using urea derivatives [6-8].

R Kalirajan., *et al.* have synthesized some heterocyclic compounds including oxazines by the cyclization of chalcones using hydrazine and urea derivatives. The synthesized compound were evaluated for anti-microbial activities against both gram-ve and gram +ve which showed comparable activities toward the standard anti-biotics [9].

V. Tiwari., *et al*. have studied the synthesis of some oxazine compounds from chalcone derivatives and also studied the cytotoxicity and inhibition of *β* hematin formation in both *vitro* and *vivo* [10].

Sadhana and her co-workers in 2013 have prepared oxazine from chalcones and urea (Scheme 1). They studied the biological activities of these compounds including testing against gram +ve and -ve bacteria and some fungi [11].



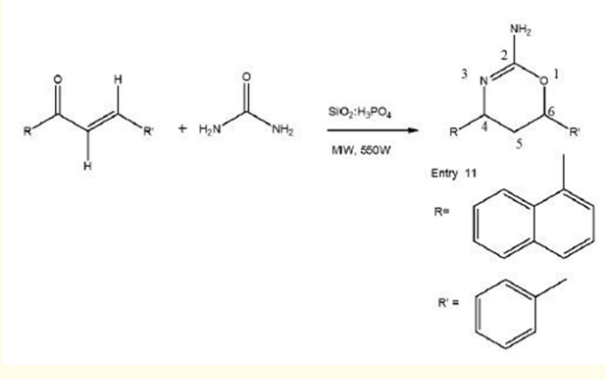
	R_1	R_2	R_3	R_4	R_5
2a, 3a, 4a	-H	-H	-H	-H	-H
2b, 3b, 4b	-Cl	-H	-Cl	-H	-H
2c, 3c, 4c	-H	-Cl	-Cl	-H	-H
2d, 3d, 4d	-H	-H	CH_3	-H	-H
2e, 3e, 4e	$-CH_3$	-H	H	-H	-H
2f, 3f, 4f	-H	-H	-Br	-H	-H
2g, 3g, 4g	-Br	-H	-H	-H	-H
2h, 3h, 4h	-H	$-NO_2$	-H	-H	-H
2i, 3i, 4i	-H	$-OCH_3$	$-OCH_3$	$-OCH_3$	-H
2j, 3j, 4j	$-OCH_3$	-H	-H	-Br	-H

Scheme 1

In the same year Thirunarayanan G. and his co-workers were also studied aryl chalcones as an efficient precursors for oxazine compounds, the oxazine compounds were also studied for anti-microbial activity against gram +ve and -ve bacteria [12].

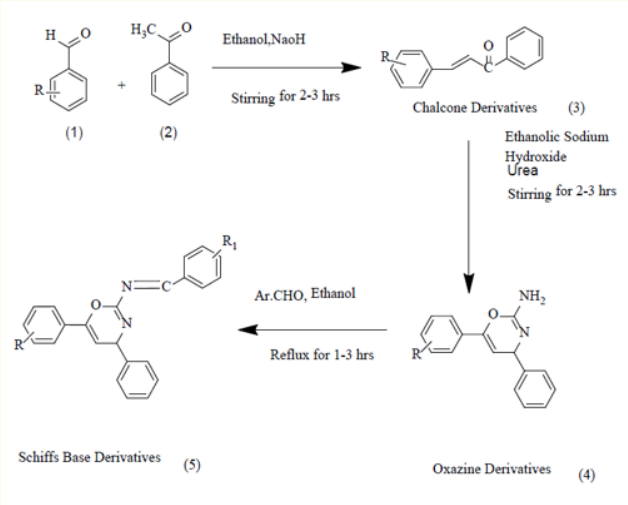
Girly and co-workers have synthesized some oxazine compounds from chalcone derivatives. These oxazine compounds were studded their anti-fungal activity by molecular docking using Argus lab. The *in vivo* study of anti-microbial assay revealed that the synthesized compounds have an inhibition of β-hematin inhibitory using DMSO as solvent [13].

Solid SiO_2-H_3PO_4 was used for the cyclization of some chalcones using solvent free-condition for the preparation of some oxazine derivatives (Scheme 2). These derivatives (amino oxazine) was studded for anti-microbial activity some of these compounds have showed appreciable anti-microbial effects [14].



Scheme 2

P. Anusha and his co-workers have investigate the synthesis of Schiff bases oxazine compounds from chalcones and screened them for anti-bacterial activities. They found that these compounds possess good anti-bacterial activities against *Eschertia coli* and *Pseudomonas aeruginosa* [15]. As shown in the following scheme 3 below.



Scheme 3

Nadia S and her co-workers have synthesized some oxazine derivatives from some chalcone derivatives, these compounds were screened against different types of microorganisms they found that these compounds showed high effective towards these microorganisms even at low concentration and more effective than Ampicillin and Ciprofloxacin [16].

In 2020 Mohammad A. and Mohd have reviewed the pharmacological profile of oxazine and its derivatives including antimicrobial activity, antiplatelet aggregation, ant diabetic, antidepressant, enzyme inhibitory, anticoagulant and receptor agonist activities, just one of them was from chalcone precursors [17,18]. Chaitra and coworkers have prepared some oxazines from pyridyl chalcones and studied the *in-vitro* antioxidant activity and anti-inflammatory effects. The synthesized compounds exhibited good activity as compared to standard ascorbic acid [18]. Guhfran in her thesis studied anti -bacterial screening of some oxazines derived from oxazolone chalcones which showed good screening effects [19].

Results and Discussion

There were a lot of research concerning the pharmaceutical, biological and medical applications of oxazine from chalcones but are rarely found as a review in the literature. According to the wide applications of these compounds as it was mentioned in the introduction part of this review, which involved Bacterial screening effects which was found higher or comparable to the standard antibiotic and anti- oxidants especially for hybrid chalcones. The study was also revealed that oxazine compounds which were derived from chalcones having hetero atoms moieties makes the oxazine compounds more effective as antiplatelet aggregation, antidiabetic, antidepressant, enzyme inhibiting agents this was clear from the work of, Chaitra., *et al.* [18] in which the pyridine moiety of oxazine or nitrogen base moiety has higher effects than other studied substituents as antimalarial and anti -inflammatory effects than the alkyl substituent of phenyl one more over the works of, Vandana T., *et al.* [10], P. Anusha., *et al.* [15] and Gufhran [19] also support this fact in inhibition of β-hematin formation, anti- bacterial actions respectively. We are here provide a collections of many research works of authors whom they did these biological and pharmacological studies to introduce this work for other researchers in an aim to develop or extend the researchers study and find an appropriate way for application of the synthesized compounds as drug. We know that some microorganism becomes resistant to drug so it is important to timely improve the drugs commercially available in the market into more effective one. we hope to put the researcher efforts available to others pharmacologist or drug companies for further studies in a desire to make them commercially available in the market bringing researchers lab investigations into a batch production as drugs or co-drugs. That is the goal of our present study.

Conclusion

In conclusion to the above study we have collected the more studied pharmaceutical profile of chalcone compounds as it was mentioned in the introduction and the discussion part above using Claisen-Schmidt method in synthesizing chalcones, that hybrid chalcones were most effective than single chalcone compounds as anti oxidant. It was also clear from the study above that changing the oxazine moieties with hetero atoms makes these oxazine compounds most effective as antioxidant and anti- bacterial screening as well as anti -inflammatory compounds. According to the men-

tioned synthetic methodologies above. We found that these compounds have promising application in the area of drug and drug discovery programs and focusing on these types of compounds make them under consideration.

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