Antioxidant studies of thiazole ring bearing chalcone derivatives

Abstract

Oxidative stress is one of the common problems seen in a variety of diseases. Chalcones and in particular heteroaryl chalcones had reported with promising antioxidant activities. Hence, in the present work, we reported the antioxidant activity of twenty thiazole ring bearing chalcone derivatives (**1-20**). Among the tested compounds, compounds 17, 19 and 20 containing 2-pyridinyl, 3-pyridinyl and 2-thiazolyl scaffolds showed superior antioxidant activity than the standard with their IC_{50} values 4±1µg/mL, 3±1 µg/mL and 5±1µg/mL respectively. The compound 19 is an interesting lead for the development of newer antioxidant agents.

Key Words: Oxidative stress; Chalcones; Heteroaryl chalcones; Antioxidant activity.

1. Introduction

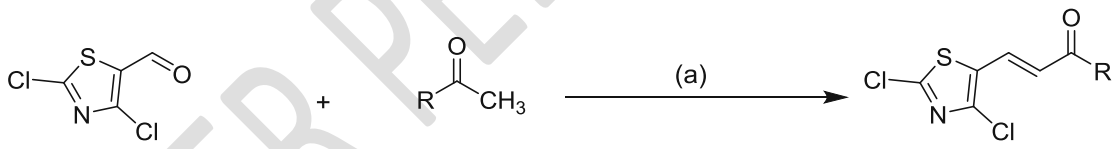
Chalcones are a type of natural products containing two aryl rings connected through a three-carbon linkage i.e., ketovinyl group. Chalcones were found to possess broad spectrum of pharmacological activities and many authors have reviewed the same [1-4]. The activity of chalcones is attributed mainly due to the ketovinyl chain and the level or the intensity of the activity is due to the nature of aryl rings [5]. Medicinal chemists had manipulated the basic chalcone core by replacing the phenyl ring with a variety of substituted aryl or heteroaryl rings. It was observed that the presence of heteroaryl ring had improved the intensity of bioactivity over the trivial phenyl or the substituted phenyl rings [6-7]. This improved activity may be due to the excellent biological properties of the heteroaryl scaffolds including good pharmacokinetics, metabolic stability and effective binding with the target receptors [8]. Due to these properties scientists had prepared and reported a large number of heteroaryl chalcones with potential anticancer, antimicrobial, antitubercular activities [9-16]. Among the other bioactivities, the antioxidant activity of small molecules had been well studied as oxidative stress play a vital role in the infectious diseases, cardiovascular (CVS) and neurological disorders, infectious diseases and different forms of cancers. Chalcones were reported with significant antioxidant activity [17-18] and some of their biological profiles are due to their antioxidant effect [19]. Many reports had clearly revealed that the heteroaryl

chalcones comprise excellent antioxidant potential and these compounds are good starting points for the successful development of new drug candidates[20-25].Chalcones display antioxidant action either by scavenging the highly reactive free radicals or the reactive oxygen species (ROS) or by antagonizing the enzyme aldose reductase [26].By considering the aforementioned facts we herein report the antioxidant activity of 20 previously synthesized chalcones bearing thiazole scaffold [27].

2. Materials and methods

2.1. Chemistry

Method for the synthesis of target thiazole ring bearing chalcone derivatives (1-20): The preparation and characterization of the target compounds was reported [27] wherein 1 mmol of the heteroaryl aldehyde i.e., 2,4-dichloro-5-carboxaldehyde was dissolved in glacial acetic acid and hydrochloric acid and to this mixture aryl/heteroaryl ketone (1 mmol) previously dissolved in ethanol was added and refluxed for a period of 4-6 h. At the end of the reaction, the precipitate that is formed was filtered and washed with 100 mL of cold water and dried. Further, the dry precipitate was purified by column chromatography to isolate the pure compounds (Scheme 1).



2,4-Dichlorothiazole-5-carboxaldehyde Aromatic ketones Thiazole-chalcone hybrids (**1-20**) (75-91% Yield)

R

1. 2-chlorophenyl; 2.3-chlorophenyl; 3. 4-chlorophenyl; 4. 2,3-dichlorophenyl; 5. 2,6-dichlorophenyl; 6. 2,5-dichlorophenyl; 7. 2,4-dichlorophenyl; 8. 3,4-dichlorophenyl; 9. 2-fluorophenyl; 10. 3-fluorophenyl; 11. 4-fluorophenyl; 12. 2,4-difluorophenyl; 13. 2,5-difluorophenyl; 14. 2,6-difluorophenyl; 15. 3,4-difluorophenyl; 16. 3,5-difluorophenyl; 17. 2-pyridinyl; 18. 3-pyridinyl; 19. 4-pyridinyl; 20. 2-thiazolyl

Scheme 1: Synthesis of target thiazole bearing chalcone derivatives (**1-20**)

2.2. In vitroAntioxidant activity

The DPPH assay is a rapid and simple spectrophotometric method for assessing antioxidants, and it may be used to analyse a large number of samples at once. The goal of this study was to use the DPPH free radical assay to assess the antioxidant activity (AA percent) of the target chalcones (**1-20**). The activity of DPPH radical scavenging was measured using the Brand-Williams et al. procedure [28]. In ethanol, the samples were treated with the stable

DPPH radical. A 0.1 mM solution of DPPH was prepared by dissolving it in methanol. The samples were treated with the stable DPPH radical in an ethanol solution. Methanol was used to create varied concentrations of test samples (5–100 g/mL) and standard (1.0, 2.5, and 5.0 g/mL). One millilitre of 0.1 mM DPPH solution was added separately to 3 mL of each concentration of test samples and standard. The absorbance of these combinations was measured at 517 nm after being kept in the dark for about 30 minutes [29]. The following formula was used to calculate the ability to scavenge the DPPH radical:

$$AA\% = 100 - \left[\frac{(\text{Absorbance of the sample} - \text{Absorbance of Control})}{\text{Absorbance of Control}}\right] X\ 100$$

After 100 minutes of DPPH reaction, a colour shift from deep violet to light yellow was measured using a UV-VIS spectrophotometer at 517 nm after reducing DPPH with antioxidant molecules.

3. Results and discussion

3.1. Chemistry

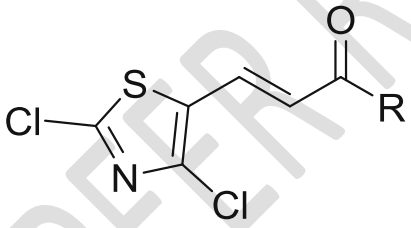
Thiazole bearing chalcone derivatives (1-20) were obtained in 75-91% yields and are characterized by spectral methods [27] (Reference???). In their FT-IR spectrum the compounds displayed absorption bands for C=O and HC=CH around the wave numbers 1651-1698 cm-1 and 1506-1520 cm-1 respectively whereas the 1H NMR revealed two diagnostic doublet peaks corresponding to the vinyl protons at chemical shift values 7.27-7.89 ppm and 7.66-8.16 ppm. For these doublets, the coupling constant value J was between 15 and 17 Hz indicating the trans geometry of the chalcone linkage. The synthesis of chalcones was further verified by the molecular ion peak in the mass spectrum. Furthermore, all of the compounds had an isotopic M+2 peak that was one-third intense as the molecular ion peak.

3.2. In vitroAntioxidant activity

The antioxidant activity of the target analogues was performed by DPPH assay using gallic acid as a standard and the results are summarized in Table 1. Th studied compounds had shown an interesting antioxidant activity with IC_{50} values ranging between 3-61 µg/mL. These values indicate that there is a difference in the level of the antioxidant activity

exhibited by the compounds. For instance, it was observed that compounds **17** and **19**containing heteroaryl 2-pyridinyl and 4-pyridinyl rings were more active than the standard gallic acid (IC_{50} =5 µg/mL) with IC_{50} values 4 µg/mLand 3 µg/mL respectively whereas compound **20** containing 2-thiazolyl motif was equipotent with gallic acid. The compound 18 bearing 3-pyridinyl ring was close in its activity to the standard with an IC_{50} value of8 µg/mL. The other compounds containing halogenated phenyl ring shown optimum antioxidant activity but is not equal or more than gallic acid. From the above results the structure activity relationships suggests that thiazole containing chalcone is optimal for activity and the nature of aryl or heteroaryl ring connected to the chalcone bridge is crucial in determining the antioxidant potency. The results indicate that the thiazole bearing chalcones containing heteroaromatic rings like pyridinyl or thiazolyl scaffolds are much useful for the antioxidant activity over the phenyl substituted rings.

Table 1. Antioxidant activities of thiazole ring bearing chalcone derivatives (1-20). (IC_{50}± SD, µg/mL)[a]



Entry	R	Antioxidant activity IC_{50} (µg/mL)
1	2-chlorophenyl	32±1
2	3-chlorophenyl	46±1
3	4-chlorophenyl	23±2
4	2,3-dichlorophenyl	39±1
5	2,6-dichlorophenyl	28±2
6	2,5-dichlorophenyl	33±2
7	2,4-dichlorophenyl	18±1
8	3,4-dichlorophenyl	30±2
9	2-fluorophenyl	36±1
10	3-fluorophenyl	61±2
11	4-fluorophenyl	12±1
12	2,4-difluorophenyl	14±1
13	2,5-difluorophenyl	31±2
14	2,6-difluorophenyl	35±1
15	3,4-difluorophenyl	28±1
16	3,5-difluorophenyl	49±2
17	2-pyridinyl	**4±1**
18	3-pyridinyl	8±1
19	4-pyridinyl	**3±1**
20	2-thiazolyl	**5±1**
Gallic acid	-	5±1

[a]IC_{50} are the mean values of three independent experiments

Conclusion

In the present study, we have assessed the antioxidant potential of 20 of the previously synthesized thiazole bearing chalcone derivatives containing different kinds of substituted aryl and heteroaryl rings. The compounds 17, 19 and 20 bearing pyridinyl and thiazolyl scaffolds elicited promising antioxidant activity that is more than the standard gallic acid. The most active compounds that have been identified by this study will be useful for the development of prospective antioxidant agents that will be of greater use in the treatment of different disorders.

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