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Research Article

SYNTHESIS, CHARACTERIZATION AND ANTIOXIDANT ACTIVITY OF NOVEL QUERCETIN DERIVATIVE

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Abstract

Reaction of Quercetin with thiourea in absolute ethanol give a novel Schiff base derivative (Z)-1-(2-(3',4'-dihydroxyphenyl)-3,5,7-trihydroxy-4 H -chromen-4-ylidene) thaiourea which coded (QTU) in good yield. The toxicity of QTU was assayed via the determination of its LD₅₀ value which obtained by using the graphical method of probit analysis and was found to have an LD₅₀ value of 250 mg/kg of body weight. The tested compound showed better antioxidant potential when compare to standard ascorbic acid by DPPH radicals scavenging method. The IC₅₀ value obtained were as 13 and 28 µg/ml for same ascorbic acid and tested compound respectively. It means that the tested compound at higher concentration captured more free radicals formed by DPPH resulting into decrease in absorbance and increase in IC₅₀ value. The antioxidant activity of the new compound was found higher than that of the quercetin itself. The QTU was characterized by elemental analysis, IR, ¹H-NMR and ¹³C-NMR spectroscopy which confirmed the proposed structure.

Article History

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Key words: Quercetin, QTU, IC₅₀ and Antioxidant activity.

1. Introduction

Flavonoids are polyphenolic substances that naturally occurring in plant kingdom (Amic *et al.*, 2007), they are mainly found in vegetables, fruits, cereals and foods (George *et al.*, 2017). Quercetin (3,5,7,3',4'-pentahydroxy flavone) is a type of a flavonoids called flavonols, from its chemical structure there are two aromatic rings linked by an oxygenated heterocyclic ring containing 3-carbon chain with hydroxyl group at

3-position and carbonyl group at 4-position and is mainly found in onions, tea, apples berries and red wines (Bukhari and Memoh Shahbudhin, 2008). There are many derivatives of quercetin; the main groups are glycosides, ethers, sulphates and prenyl substituent (Harbone, 1994; William and Grayer, 2004). Few examples involved Schiff base which synthesis from reaction of quercetin and quercetin-3-glyoxside with thiosemicarbazide in methanol and the resultant thiosemicarbazones derivatives react with some transition metals to form stable complexes (Subramanyham *et al.*, 2012). When Kaemferol treated with ethylene diamine and diethylene triamine, respectively, in 2:1 mole ratio

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gave new Schiff bases which in terms form stable metal complexes when treated with Copper (II) salts (Xin Bing Yang *et al.*, 2012). Quercetin are used widely in chemotherapy drugs (Mavel *et al.*, 2006; Balasubramaniyan *et al.*, 2007) and has several kinds of pharmacological activities involved scavenger of free radicals in the body (Ferry *et al.*, 1996), antioxidant activities (Zhang *et al.*, 2012) and other beneficial effects (Boyer *et al.*, 2004; Needs *et al.*, 2006; Gracia *et al.*, 2008; Spencer *et al.*, 2008; Jaramillo *et al.*, 2010; D'Archivic *et al.*, 2010; Juskiewicz *et al.*, 2011).

In the present work, we describe the synthesis of Schiff base derivative by reaction of Quercetin with thiourea to develop organic compound with high reactivity (the antioxidant activity of the new compound was found higher than that of the quercetin itself), low toxicity and low side effects which was characterized by spectroscopic data and elemental analysis, in addition to evaluation of the LD₅₀ value by using the graphical method of probit analysis, with the aim to develop a new drug which can be used in treatment of several animal diseases.

2. Materials and Methods

Physical measurements

FT-IR spectra were recorded, using Shimadzu FT-IR affinity spectrophotometer made in Japan, using KBr disc, and expressed in cm⁻¹. The melting point of the product compound was expressed in degree (°C) using melting point digital apparatus SMP31. Both measured in the department of pharmaceutical Chemistry College of Pharmacy University of Basrah Iraq. ¹H-NMR and ¹³C-NMR spectra of QTU was recorded using Bruker Ultra shield spectrophotometer (400 MHz), University of Isfahan, Isfahan, Iran. The Chemical shift was expressed as ppm. Using tetramethylsilane (TMS) as internal standard and DMSO-d₆ as a solvent. Elemental micro analysis of Carbon, Hydrogen, Nitrogen and Sulfur were carried out in Isfahan University, Isfahan, Iran, using Leco-932 Elemental microanalysis made in America.

Acute toxicity (LD₅₀)

Determination of medianlethal dose (LD₅₀) of QUA

Median lethal dose was determined according to the graphical method of Miller and Tainter (1944). Sixty adult male rats of about 4 months age, weighing 225±25 g were used for LD₅₀ determination. A pilot study was done in which small number of animals (2 animals for each dose) was used and increasing the doses of the drug to determine the range of doses used to estimate the LD₅₀. Rats were then divided into 6 groups of 8 rats each. Rats in control group were intraperitoneal a single dose of 0.5 ml DMSO, whereas those in groups 1, 2, 3, 4 and 5 were injected a single dose of 200, 225, 250, 275 and 300 mg/kg body weight of QUA which dissolved in 0.5 ml DMSO respectively. The animals were observed daily for acute toxicity signs. After 72 hours, the numbers of deceased rats were counted in each group and percentage of animals that had died at each dose level was transformed to probit units from probit table (Table - 1). The percentage of the dead for 0 and 100 are corrected before determination of probits as following:

Corrected % for 0 and 100 % mortality:

For 0% dead: 100 (0.25/n)

For 100% dead: 100 (n-0.25/n)

Where (8) is number of animal in each group.

The probit values are plotted against log-doses and the dose corresponding to probit 5, i.e., 50% is found out and its antilog represents the LD₅₀ of QUA was calculated (Randhawa, 2009).

Synthesis of Schiff-base of Quercetin derivative

Reaction of Quercetin with thiourea

In 250 ml round bottom flask, 10 gm, (3.31 mmol) of quercetin, 0.1 gm of p-toluene sulphonic acid was added to 150 ml of absolute ethanol and stirring with heating until all components were completely dissolved to this solution, 2.5 gm, (3.31 mmol.) of thiourea was added. The reaction mixture were heating under reflux overnight and the reaction were monitoring under TLC, filtered hot and stand until cooling to room temperature orange-red precipitate were collected by filtration,

re-crystallization from absolute ethanol gave orange-red crystals wt. = 7.64 gm, 64 % yield with m.p. (116 - 118 C⁰). Elemental analysis: Found (Calculated) = C: 53.47 (53.33), H: 3.65 (3.34), N: 7.72 (7.78), S: 8.67 (8.89).

The FT-IR spectra for both Quercetin and QTU shows identical spectra in all resonance pattern except the strong bands at 1710 cm⁻¹ which attributed to C=O stretching was disappeared and new bands were appeared (Figure – 1). ¹H-NMR (400 MHz, DMSO-d₆, ppm vs TMS); spectrum of prepared new compound shows singlet band at 12.5 ppm due to 5H(OH) and two broad band at 10.8 ppm (s,b) due to 1H(NH₂), and 9.6 ppm (s,b) due to other 1H(NH₂), 6.4 ppm(d) due to 1H(H-8), 6.2 ppm(d) due to 1H(H-6), 7.56 ppm (dd) due to 1H(H-6'), 7.7 ppm (d) due to 1H (H-2') and 6.9 ppm (d) due to 1H (H-5') (Figure - 2 and 3). ¹³C-NMR (400 MHz, DMSO-d₆); spectrum of new QTU shows bands at 93.971 ppm (C8), 103.609 ppm (C10), 156.730 ppm (C9), 164.498 ppm (C5), 98.803 ppm (C6), 162.308 ppm (C7), 148.209 ppm (C2), 128.868 ppm (C3), 176.427 ppm (C4), 122.568 ppm (C1'), 115.658 ppm (C2'), 145.647 ppm (C3'), 147.380 ppm (C4'), 116.222 ppm (C5'), 120.596 ppm (C6'), 184.397 ppm (C=S) bond (Figure - 4 and 5).

3. Results and Discussion

In the present study equimolar amount of quercetin and thiourea in the presence of small amount of p-toluenesulphonic acid in 150 ml of absolute ethanol as a solvent were refluxed overnight, the color of solution was turned to red - orange but the yield was very low, increase the molar amount of thiourea to about tenfold give good yield percent about 64 %. The clear solution was filtered hot and the solution left to cool at room temperature red-orange precipitate was collected by filtration, twice re-crystallization from absolute ethanol gave red-orange crystals of the final product in good yield.

In general, the product was solid with high melting point, stable in air and dissolved in

common organic solvents. The carbon, hydrogen, nitrogen and Sulphur analyses for the prepared compound QTU were agreed well with calculated values. The QTU prepared in this study was characterized by FT-IR which show the characteristic broad band at 3298 cm⁻¹ due to overlap of OH groups of Quercetin with the -NH₂ group of Thiourea. The shoulder band at 3433 cm⁻¹ may attributed to symmetrical stretching of NH₂, while the shoulder band at 3217 cm⁻¹ may attributed to asymmetrical stretching of -NH₂ (Amgoth Srinivas Nayak and Neerati Venu Madhav, 2014). Weak band at 3045 cm⁻¹ due to C-H Aromatic, strong band at 1662 cm⁻¹ may attributed to N-H bending, Strong band at 1612 cm⁻¹ due to C=N bond (Moayad S. Al-Gwady, 2009) and strong band at 1246 cm⁻¹ attributed to C=S bond (Abdel Sattar *et al.*, 2012) (Figure - 1). Strong band at 1554 cm⁻¹ and 1512 cm⁻¹ due to symmetrical and asymmetrical C=C bond (Sangita *et al.*, 2015).

The ¹H-NMR spectrum of new Schiff-base compound shows that the resonances of the aromatic rings were observed at the range of 6.2 - 7.7 ppm, while the signal of hydroxyl proton appear as a singlet at 12.5 ppm and that may attributed to strong hydrogen bond (Donald *et al.*, 2005; Subrhamanyam Naidu and Prakash, 2012). The ¹H-NMR spectrum of the prepared compound exhibits two resonances for NH₂ protons at 10.8 ppm and 9.6 ppm a result explained in terms of hindered rotation about C(S)-NH₂ bond due to its partial double bond character (Clarke and Croode, 2003). The quercetin spectrum can be characterized by coupling of proton 8-H and 6-H through Meta coupled to appear as doublet at 6.2 and 6.4 ppm respectively (ring A). On (ring B), the protons on 6'-H(7.56) ppm and 5'-H (6.9) ppm appear as doublet-doublet due to Ortho -coupling of these protons, moreover, 6'-H proton signal was appear as doublet of doublet due to long range coupling with 2'-H proton; for that reason 2'-H proton appear as doublet at 7.7 ppm (Figure - 2 and 3).

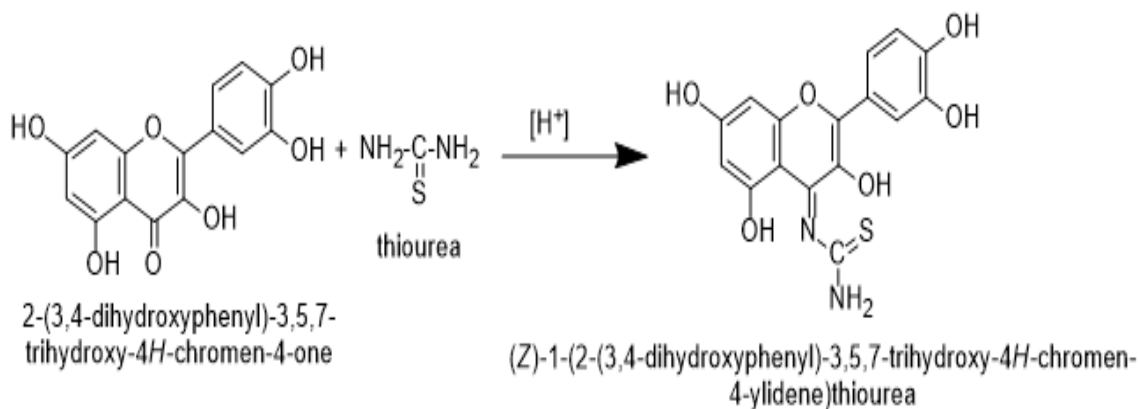


Table - 1: Transformation of percentage mortalities to probits

%	0	1	2	3	4	5	6	7	8	9
0	-	2.67	2.95	3.12	3.25	3.36	3.45	3.52	3.59	3.66
10	3.72	3.77	3.82	3.87	3.92	3.96	4.01	4.05	4.08	4.12
20	4.16	4.19	4.23	4.26	4.29	4.33	4.36	4.39	4.42	4.45
30	4.48	4.50	4.53	4.53	4.59	4.59	4.64	4.67	4.69	4.72
40	4.75	4.77	4.80	4.82	4.85	4.87	4.90	4.92	4.95	4.97
50	5.00	5.03	5.05	5.08	5.10	5.13	5.15	5.18	5.20	5.23
60	5.25	5.28	5.31	5.33	5.36	5.39	5.41	5.44	5.47	5.50
70	5.52	5.55	5.58	5.61	5.64	5.67	5.71	5.74	5.77	5.81
80	5.84	5.88	5.92	5.95	5.99	6.04	6.08	6.13	6.18	6.23
90	6.28	6.34	6.41	6.48	6.55	6.64	6.75	6.88	7.05	7.33

The SE of LD₅₀ was calculated from the following formula (Ghosh, 1984)

$$SE\ of\ LD_{50} = \frac{LD_{84} - LD_{16}}{\sqrt{2N}} \quad (N = \text{number of rats in each group})$$

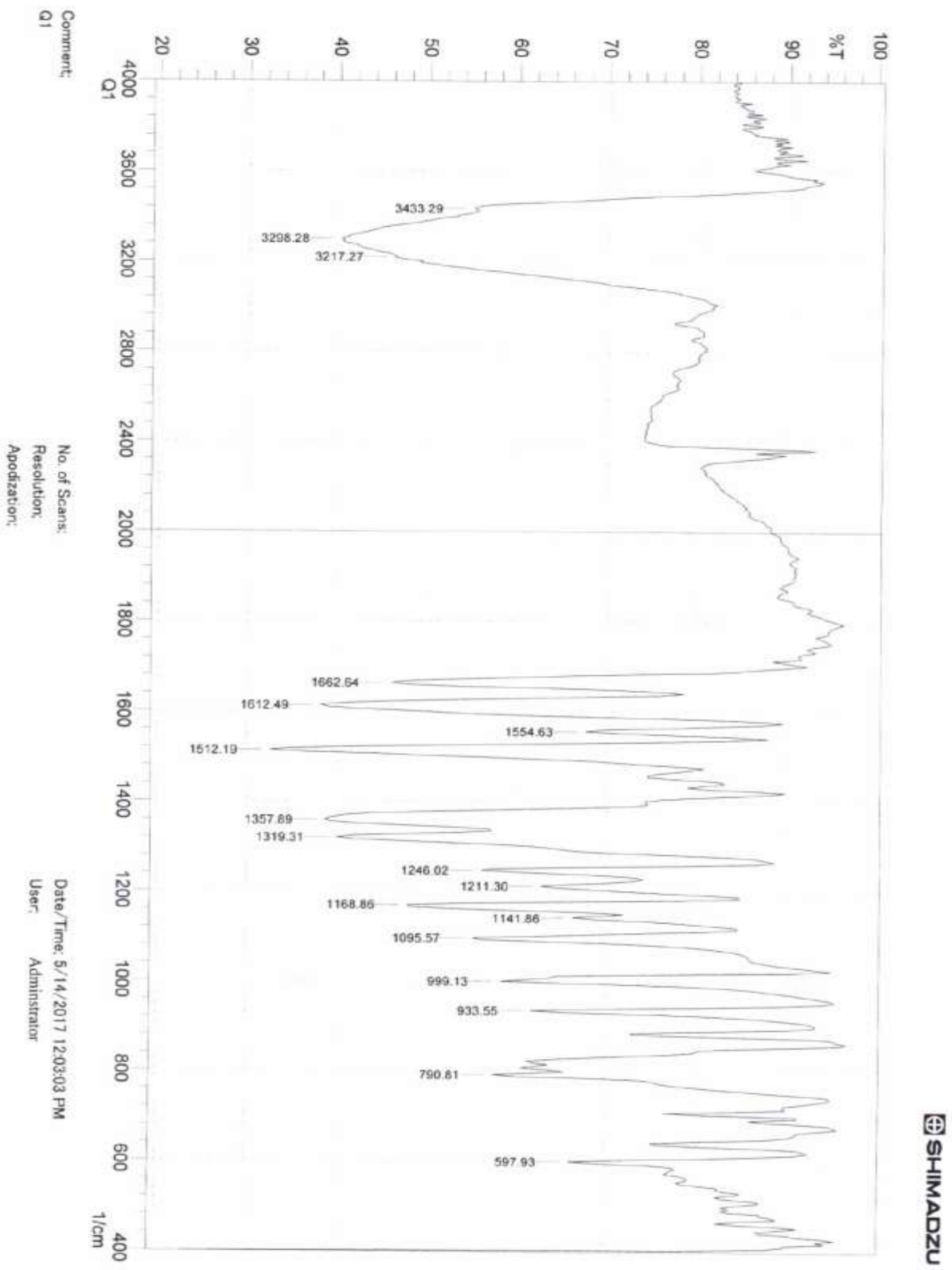


Figure – 1: FT-IR Spectrum for QTU

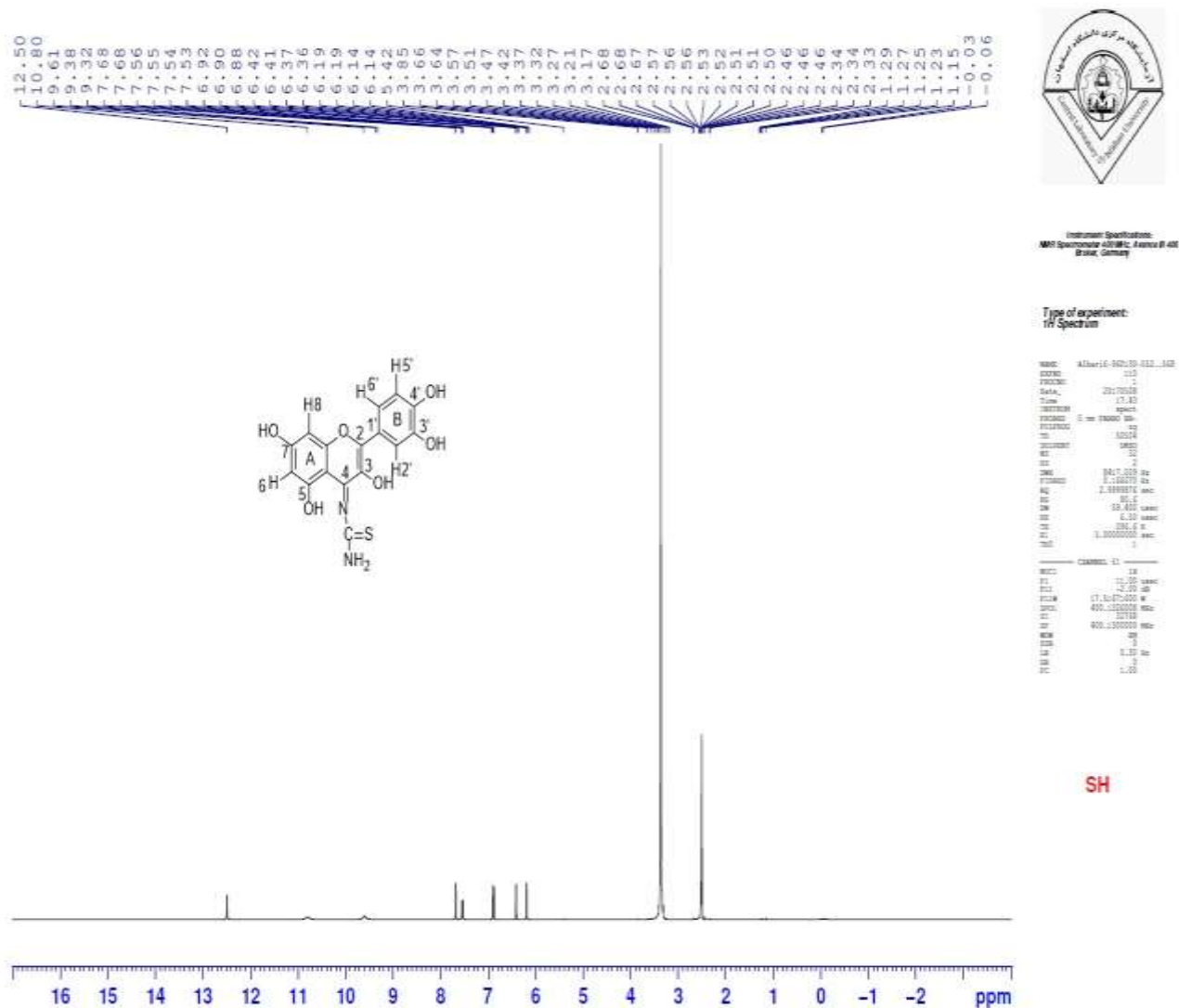


Figure – 2: The ¹H-NMR spectrum for Qtu using DMSO-d₆ as a solvent

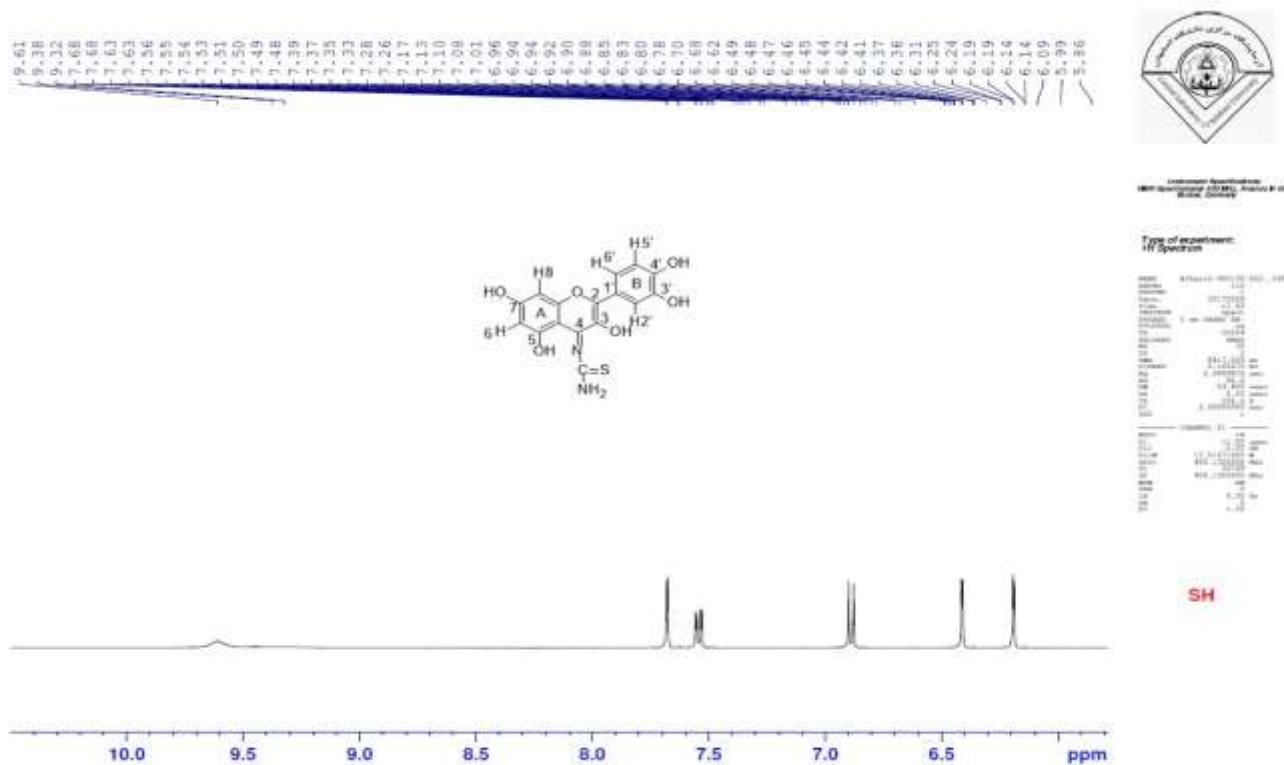


Figure - 3: Expansion of Fig2 1H-NMR for QTU

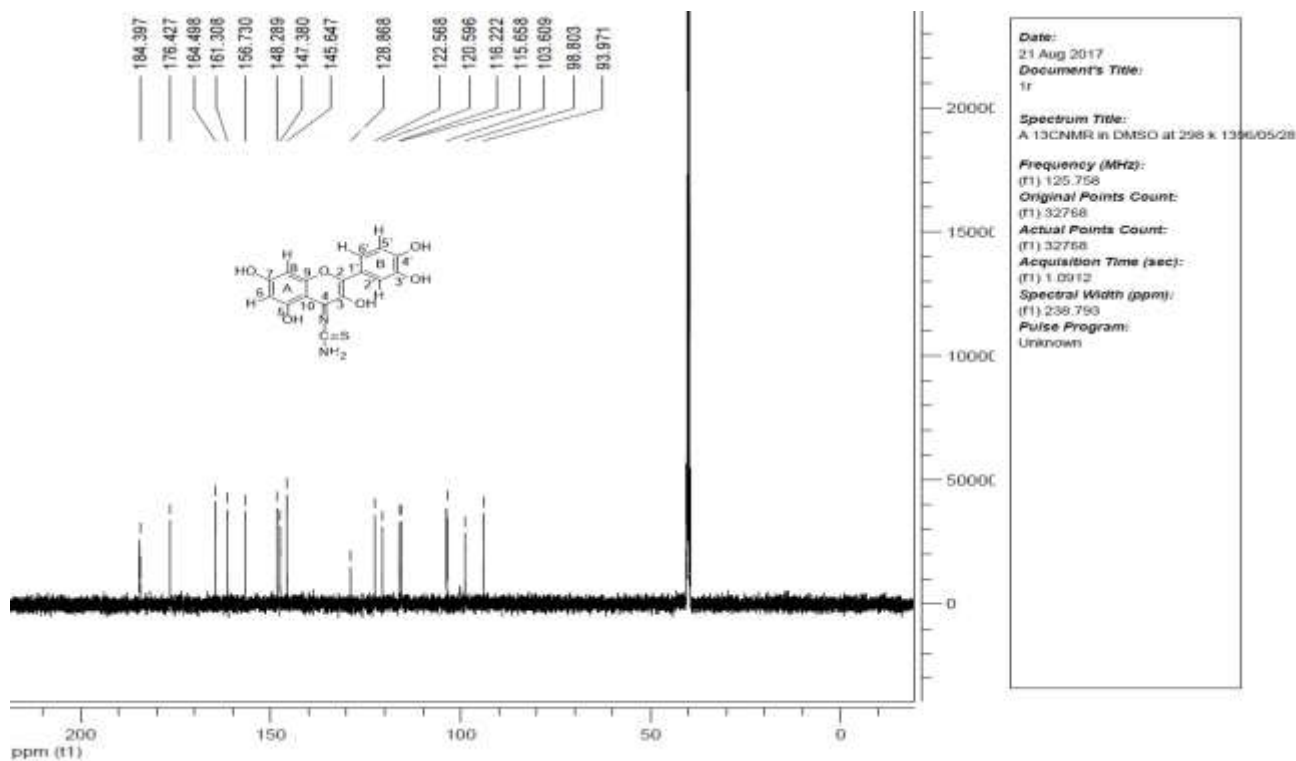


Figure - 4: ¹³C-NMR for Qtu using DMSO-d₆ as a solvent

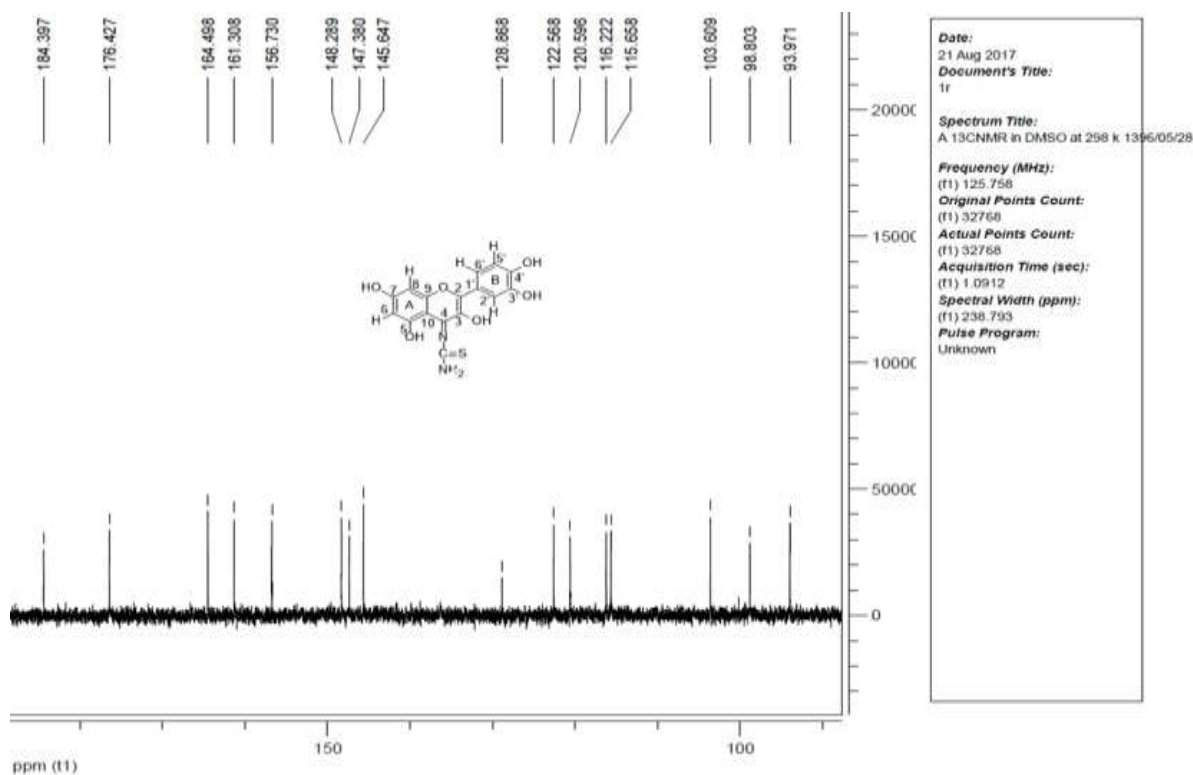


Figure - 5: Expansion for Fig – 4 ¹³C-NMR for QTU

All spectroscopic and elemental analysis confirm well with the proposed structure of new prepared compound.

Median lethal dose (LD₅₀) QTU

The results of LD₅₀ determination showed 0 (0 %), 1 (12.5 %), 4 (50 %), 5 (62.5 %) and 8 (100 %) deaths in groups 1, 2, 3, 4 and 5 respectively within a period of 72 hours post-

administration of QTU (Table - 2). No mortality was recorded in control group which was given DMSO. LD₅₀ is obtained by using the graphical method of probit analysis. The log dose corresponding to probit 5, i.e., 50 % was found out from Figure - 7 and it was 3.1 and therefore the LD₅₀ was 250 mg/kg body weight

Table - 2: The results of the lethal doses of QTU for the determination of its LD₅₀ in rats after IP administration

Group	Dose (mg/kg)	Log dose	Total No.	No. Death	% mortality	*Corrected % mortality	Probit units
Control							
1	200	2.99	8	0	0	3.1	3.12
2	225	3.05	8	1	12.5	12.5	3.85
3	250	3.1	8	4	50	50	5
4	275	3.14	8	5	62.5	62.5	5.32
5	300	3.18	8	8	100	96.9	6.81

*Corrected formula for 0 and 100 % mortality are given previously in material and methods.

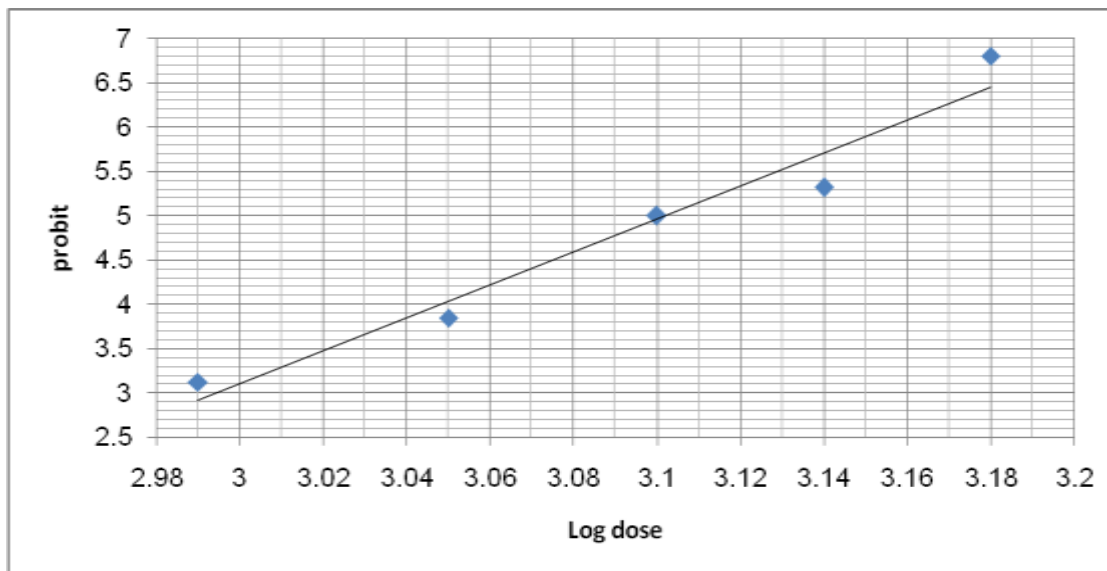


Figure - 2: Plot of probits versus log doses for calculation of oral LD₅₀ of QTU in male rats

The (Z) 1-(2-(3', 4'-dihydroxyphenyl) - 3, 5, 7-trihydroxy-4 H -chromen-4-ylidene) thiourea (QTU) is a novel compound and no data was available regarding its toxicity. Therefore, the experiment focused to determine its acute toxicity by measuring its LD₅₀ in adult's male rats. There are a number of methods for LD₅₀ determinations. The simpler ones are not very precise and often do not provide adequate information. Acute toxicity study was carried out by measuring the median lethal dose (LD₅₀) by using probit method. Although, this method requires large number of animals but it is less time consuming and gives more accurate result with a least degree error and does not require complex calculations (Donald *et al.*, 2005). Because QTU is poorly soluble in water, it was mixed in DMSO and intraperitoneal injection as suspension to abdominal cavity the rats for the determination of the LD₅₀. Intraperitoneal injection of QTU showed that no mortality recorded when rats are exposed to 200 mg/kg body weight, mortality increases as the dose of QUA increases and eventually reached to 100 % at 300 mg/kg (Table - 2). Mortality seems to depend on two factors: the dose and the apparent susceptibility to the compound, the larger the dose or the apparently less resistance of the rat, the greater mortality percentage. Lack of death of rats in control group showed that there was no factor that caused death in the test animals other than

QTU. According to Hodge and Sterner (2008) and WHO (2009), the estimated value of 250 mg/kg body weight of QTU was calculated as the LD₅₀ in our study rated the compound moderately toxic.

Evaluation of antioxidant activity by DPPH radical scavenging method

Free radical scavenging activity of QTU measured by 1,1-diphenyl-2-picryl hydrazyl (DPPH). In brief, 0.1 mM (0.0392) solution of DPPH in ethanol was prepared. This solution (1 ml) was added to 3 ml in ethanol at different concentration (5, 10, 15, 20, 25, 30 µg/ml). Here, only those concentrations are used which are solubilize in ethanol and their various concentrations were prepared by Dilution method (Garg, 2000). The mixture was shaken vigorously and allowed to stand at room temperature for 30 min. Then, absorbance was measured at 517 nm by using Spectrophotometer (Goldstein, 1974). Reference standard compound being used was ascorbic acid and experiment was done in triplicate (WHO, 2009). The IC₅₀ value of the sample, which is the concentration of sample required to inhibit 50 % of the DPPH free radical was calculated using Log dose inhibition curve. Lower absorbance of the reaction mixture indicated higher free radical activity (Vaidyaratnam and Varier, 2002). The percent DPPH scavenging effect was calculated by using following equation:

DPPH scavenging effect (%) or Percent inhibition = $A_0 - A_1 / A_0 \times 100$

Where A_0 was the Absorbance of control reaction and A_1 was the Absorbance in presence of test or standard sample (Ahamed *et al.*, 2013).

Table – 3: Absorbance of different concentrations of unknown with standard ascorbic acid at 517 nm, where Absorbance of control $A_0 = 0.250$

Concentration (µg/ml)	Ascorbic acid (Abs)	QTU (Abs)
5	0.243	0.246
10	0.182	0.238
15	0.114	0.220
20	0.071	0.211
25	0.055	0.155
30	0.038	0.107

Table – 4: Percentage inhibition % of different concentrations of unknown with ascorbic acid

Concentration (µg/ml)	Ascorbic acid (% Inhibition)	QTU (% Inhibition)
5	2.8 %	1.6 %
10	27 %	4.8 %
15	54 %	12 %
20	71 %	15 %
25	78 %	38 %
30	84 %	57 %

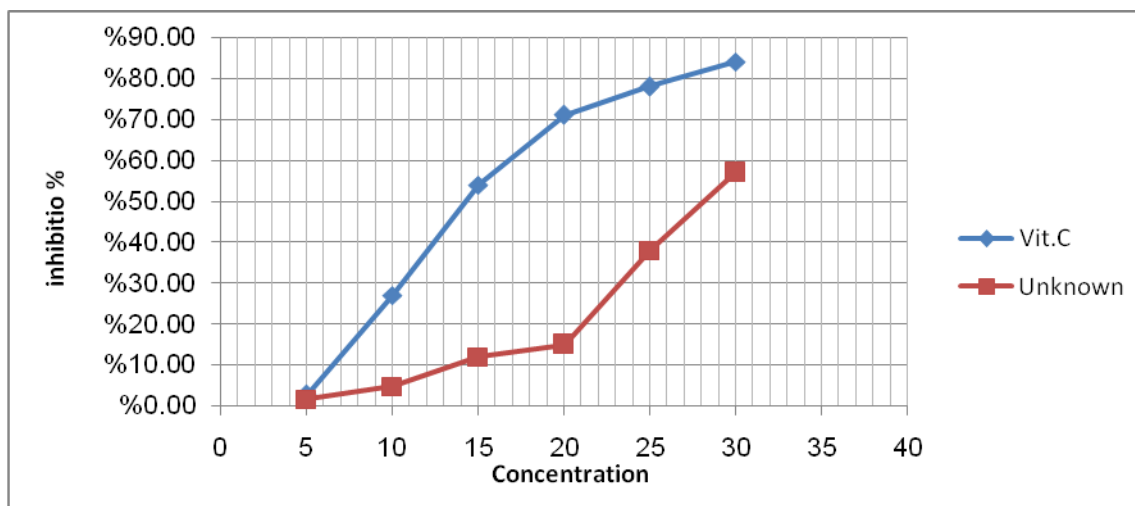


Figure - 2: % inhibition of Vit. C and tested compound in different concentration

The tested compound showed better antioxidant potential when compare to standard ascorbic acid by DPPH scavenging assay method. The IC₅₀ value obtained were as 13 and 28 µg/ml. for same ascorbic acid and tested compound respectively. It means the tested compound at higher concentration captured more free radicals formed by DPPH resulting to decrease in absorbance and increase in IC₅₀ value.

4. Conclusion

In conclusion, the present study reported the synthesis of (Z)-1-(2-(3,4-dihydroxyphenyl)-3,5,7-trihydroxy-4 H -chromen-4-ylidene) thiourea (QTU) which revealed moderate *in vivo* toxic effects by LD₅₀ measurement.

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