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Evaluation of DPPH Radical Scavenging Activity of 2-(Furan-2'-yl)-3-hydroxy-4*H*-chromen-4-one and Their Derivatives

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The 2-(furan-2'-yl)-3-hydroxy-4*H*-chromen-4-one and their substituted derivatives with electron donating and electron withdrawing groups have been synthesized. Free radical scavenging activity has been studied using 2,2'-diphenyl-1-picrylhydrazine (DPPH). The kinetic studies and co-relation of excited state intramolecular proton transfer (ESIPT) with electron donating and electron withdrawing group explains the effect of these groups on percentage scavenging activity.

Keywords: 2-(Furan-2'-yl)-3-hydroxy-4*H*-chromen-4-one, Free radical scavenging activity, Kinetic studies, DPPH.

INTRODUCTION

Flavonoids are a group of naturally occurring compounds, widely distributed as secondary metabolites in the plant kingdom. They have been well documented as having interesting medicinal properties, such as anti-inflammatory, antiviral, antibacterial and anti-tumor activities [1,2]. Flavonoids have also been reported to possess antioxidant and antiradical properties [3-5]. Antioxidants are the free radical scavengers which inhibits the activity of the free radicals generated in the body, which cause damage to all organs, muscles, *etc*. Phytochemicals like flavonoids are widely accepted class of naturally occurring plants compounds which are intensively been used as anti-oxidants [6-8]. Further, out of wide range of flavonoids 3-hydroxyflavones have attracted many researchers due to its antioxidant activity.

In this family, polyhydroxyflavones such as quercetin, morin, myricetin and kempferol are a subgroup of well-known natural antioxidant molecules [9]. Quercetin is most exclusively studied 3-hydroxy flavones. Its electron donating hydroxyl groups at position 3,5,7,3',4' may play a crucial role in increased antioxidant activity as compared to 3-hydroxy flavone [10].

Antioxidant activity can be evaluated using DPPH *in vitro*. DPPH is a stable free radical that can accept an electron or hydrogen radical to become a stable diamagnetic molecule. Due to its odd electron, the methanolic solution of DPPH shows a strong absorption band at 517 nm. DPPH radical react with various electron donating molecules (antioxidants). When electrons become paired off, bleaching of DPPH solution is the result. This results in the formation of the colourless 2,2'-diphenyl-1-picrylhydrazine. Reduction of the DPPH radicals can be estimated quantitatively by measuring the decrease in the absorption at 517 nm. Percentage scavenging has been calculated from the following equation [11]:

$$\text{Scavenging (\%)} = \frac{\text{Absorption of blank–Absorption of test}}{\text{Absorption of blank}} \times 100$$

The aim of present work to evaluate the percentage free radical scavenging activity using 2,2'-diphenyl-1-picryl-hydrazine (DPPH).

EXPERIMENTAL

Methanol of spectroscopic grade was purchased from S.D. Fine chemicals. 3-Hydroxyflavone, DPPH and the reagents used for the preparation of 2-furyl-3-hydroxychromone derivatives were purchased from Sigma Aldrich (USA).

Melting points of the synthesized compounds were determined in open capillary. IR spectra were recorded with FTIR Spectrophotometer (Perkin Elmer, RZX) and ^{1}H NMR on Bruker Avance 400 NMR Spectrophotometer with TMS as an internal standard. Double beam UV-visible spectrophotometer (UV-1800 Shimadzu) equipped with UV-probe software has been employed for recording the UV-visible spectra.

Preparation, purification and characterization of variously substituted 2-(furan-2'-yl)-3-hydroxy-4*H*-chromen-4-one: 2-(Furan-2'-yl)-3-hydroxy-4*H*-chromen-4-one (FHC) and its derivatives have been synthesized by two step synthesis scheme already reported [12]. First step is preparation of chalcone

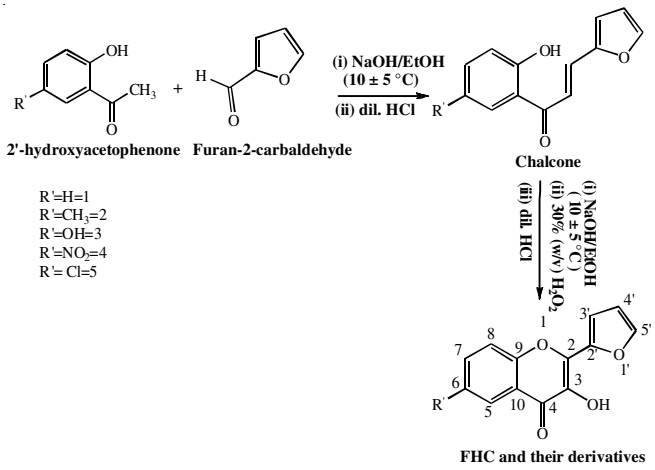
from 0.03 mole of furan-2-carboxaldehyde and 0.03 mol of 2'-hydroxyacetophenone in the presence of 0.09 mol of sodium hydroxide in ethanol at 10 ± 0.5 °C.

The chalcone obtained was subjected to Algar-Flynn-Oymada (A.F.O.) reaction conditions in sodium hydroxide and ethanol at 10 ± 0.5 °C with dropwise addition of 30 % (w/v) H_2O_2 over 1 h. The compounds were crystallized and characterized by IR and ^{1}H NMR spectral data are given in Table-1.

TABLE-1
CHARACTERIZATION DATA OF VARIOUSLY SUBSTITUTED 2-(FURAN-2-YL)-3-HYDROXY-4*H*-CHROMEN-4-ONE

Compd.	m.p. (°C)	IR (KBr, ν_{max}, cm^{-1})	^{1}H NMR
1	178	1616 (C=O), 3258 (OH)	Ar 7H (m, 7.64-7.35), OH, 1H, 6.88
2	198	1601 (C=O), 3225 (OH)	Ar 1H (d, 9.54), Ar 5H (m, 8-7) OH, 1H (s, 6.68), CH_3, 3H (s, 2.55)
3	202	1620 (C=O), 3324 (OH)	Ar 5H (m, 7.83-7.21), 6-OH, 1H (s, 9.70), 3-OH, (s, 6.67)
4	112	1618 (C=O), 3227 (OH), 1344 (NO_2)	Ar 7H (m, 7.0-8.55), OH, 1H (s, 6.98)
5	167	1628 (C=O), 3452 (OH)	Ar 6H (m, 8.32-7.13), OH, 1H, (s, 6.88)

For evaluation of percentage scavenging activity equal volume of 50 µM solution of DPPH and 20 µM solution of 3-hydroxyflavone and variously substituted 2-(furan-2'-yl)-3-hydroxy-4*H*-chromen-4-one (**1-5**) as shown in **Scheme-I** was prepared in methanol:water (80:20) and absor-bance at 517 nm was measured after different time intervals.



Scheme-I: Synthetic scheme for the preparation of FHC and their derivatives

RESULTS AND DISCUSSION

As already been discussed 3-hydroxy flavone shows low antioxidant activity as compared to quercetin. In order to resolve the problem that whether electron donating substitution plays a role in increasing the antioxidant activity. We have replaced the 6-membered ring (phenyl) with 5-membered ring (furan) at the 2-position of 3-hydroxy flavone. The representative polynomial (Fig. 1) with regression factor (R^2) 0.998 and 0.991 for 3-hydroxy flavone and FHC respectively shows decrease at 517 nm. The decrease in the absorbance shows that both

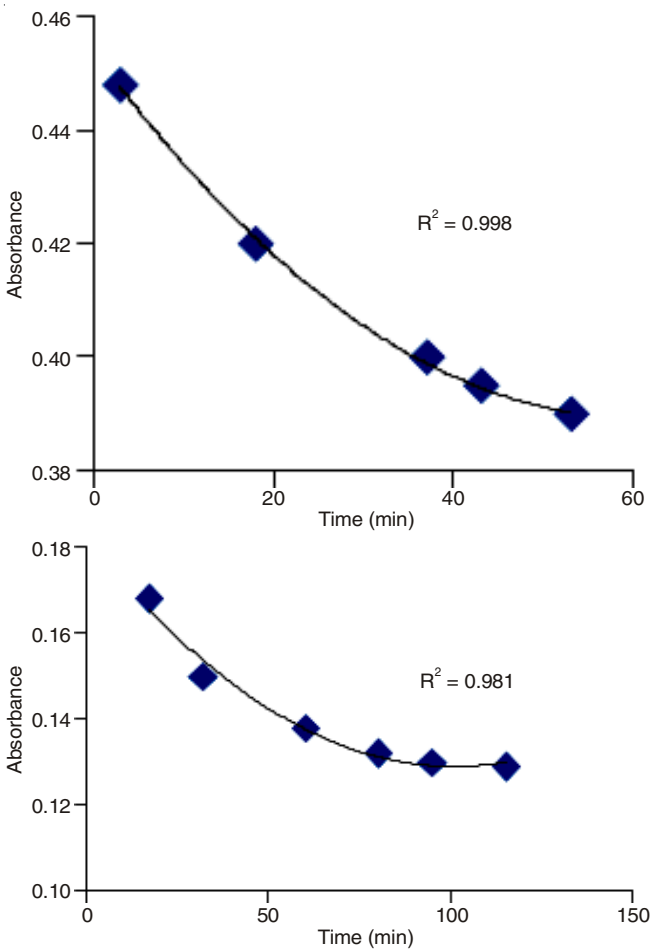


Fig. 1. Decrease in absorbance *versus* time for equal volumes of DPPH with 3-hydroxy flavone and FHC respectively

acts as antioxidants. The percentage scavenging activity was calculated using equation as given earlier.

Fig. 2 increase in percentage scavenging activity value with time for both 3-hydroxy flavone and FHC. From the value of percentage scavenging activity value, it was estimated that FHC is better antioxidant as compared to 3-hydroxy flavone.

2-(Furan-2'-yl)-3-hydroxy-4*H*-chromen-4-one is better antioxidant than 3-hydroxy flavone. As discussed in previous data [12] it was observed that in excited state intramolecular proton transfer (ESIPT), substitution at 2- position, in 3-hydroxy flavones plays a crucial role. In FHC the oxygen atom belonging to furan ring undergo conjugation to increase the electron density of 4-carbonyl group in addition to the only conjugation from oxygen atom of the benzopyran ring to 4-carbonyl in 3-hydroxy flavone. Proton transfer in excited state in such compounds depends upon number of factors like electron density, polarity, charge transfer, solvent polarity, *etc*. Out of these excited state intra-molecular charge transfer (ESICT) plays a vital role in increasing ESIPT interactions. The electron donor substitutents undergo conjugation to increase the charge density at 4-carbonyl group. So, in FHC better ESIPT is observed.

The contribution of phenyl ring at the 2- position to ESICT effect on 4-carbonyl, is little due to its non-planarity and non-conjugation [13,14]. In FHC, furyl, which replaces phenyl is the major contributor as electron donor in the molecule because planarity due to small size increases conjugation in the molecule

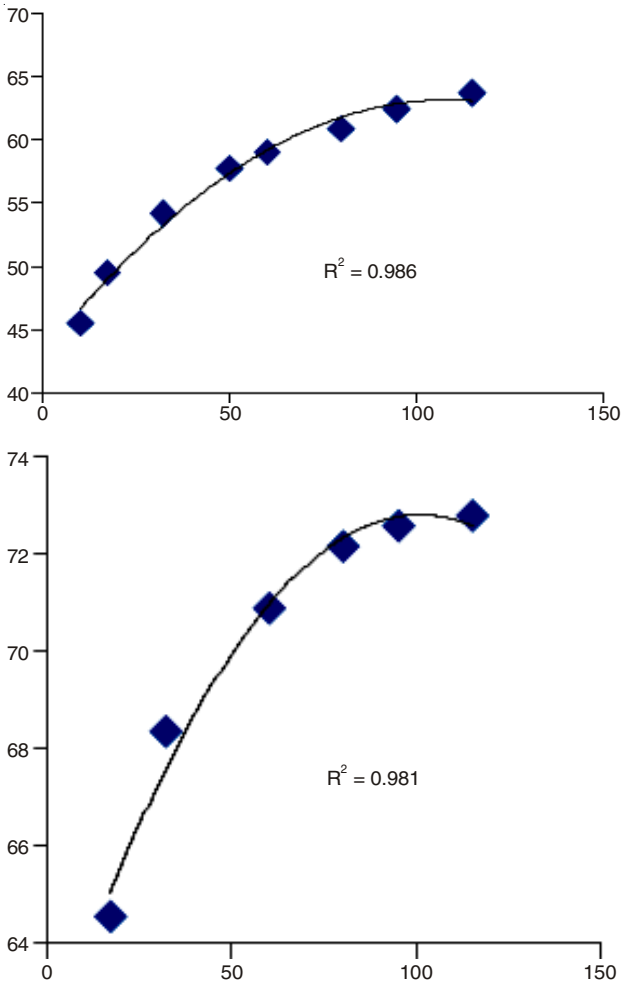


Fig. 2. Increase in % scavenging activity *versus* time for equal volumes of DPPH with 3-hydroxy flavone and FHC respectively

and is also richer in electron as compare to phenyl ring. Due to enhancement in electron density at the ring 'C' hydrogen radical for DPPH$^{\bullet}$ is easily available, which cause increase in antioxidant activity. When we compared the % scavenging activity approximately after 18 min the activity value is 11.39 for 3-hydroxy flavone and 64.55 for FHC, which is almost 6 times greater than 3-hydroxy flavone. More is the value of % scavenging better is the antioxidant. So, it shows that FHC is better antioxidant than 3-hydroxy flavone.

Substitution at the 6- position electron donor $–CH_3$, -OH, electron withdrawing $–NO_2$ and +M and –I effect –Cl group alter the antioxidant activity. The substitution at 6- position also effect the ESIPT process by changing the electron density and dipole moment of the molecule due to which change in overall polarity has been reported. Behaviour at 6-position is different from that of substitution at 2-position. The electromeric effect of this kind of substitution on 2-3 double bond in the 'C' ring is similar but the effect on the double bond of 4-carbonyl is opposite [15]. In case $–CH_3$ and –OH substitution at 6-position, % scavenging activity increases with time and the value is more as compare to 3-hydroxy flavone. After 2 h, % scavenging activity value is 59.07 for both 6-CH_3FHC and 6-OHFHC in Fig. 3. After 40 min, dramatic decrease was observed in % scaven-ging activity value behind which reason is not known yet.

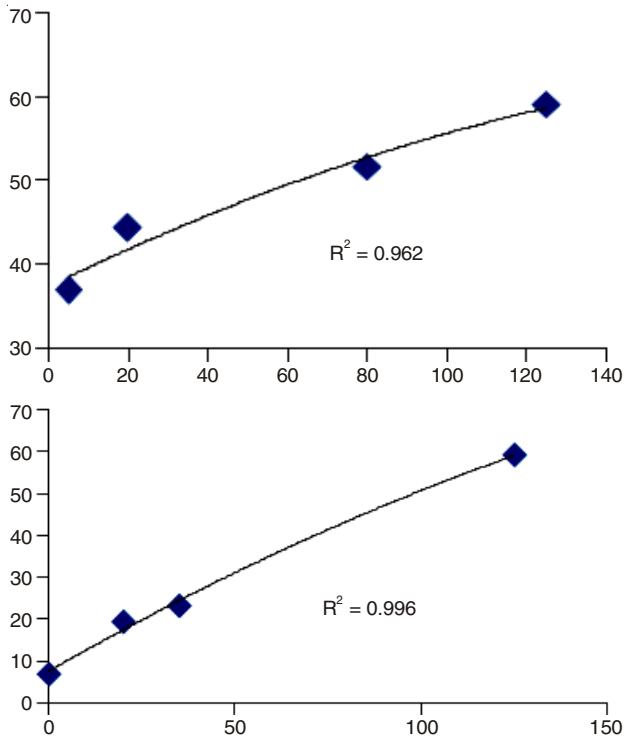


Fig. 3. Increase in % scavenging activity *versus* time for equal volumes of DPPH with 6-OHFHC and 6-CH_3FHC respectively

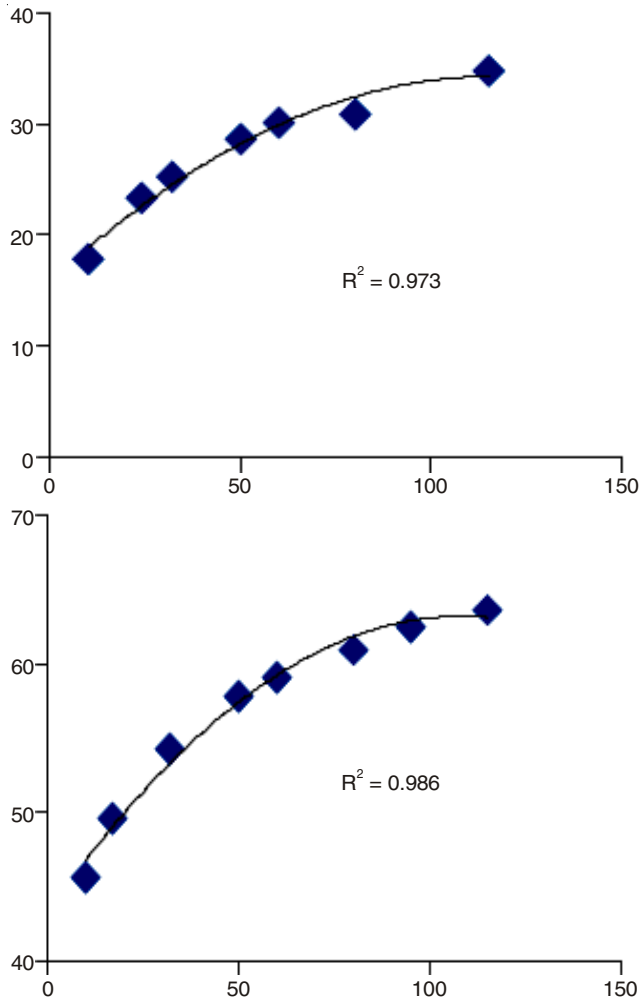


Fig. 4. Increase in % scavenging activity *versus* time for equal volumes of DPPH with 6-NO_2FHC and 6-ClFHC, respectively

In electron withdrawing group $–NO_2$ substitution cause decrease in electron density at ring 'C' due to which % scavenging value of 6-NO_2FHC is much lower than FHC and is almost nearly comparable with 3-hydroxy flavone. Fig. 4 represents the % scavenging activity of 6-NO_2FHC with time.

Whereas the % scavenging activity for 6-ClFHC after 125 min is 63.71, which is 72.18 for FHC. As –Cl group shows +M and –I effect due to which effect of electron donating group and electron withdrawing group almost get neutralize showing negligible electromeric effect. The value is 10 less than FHC which may be due to the reason that +M effect is more pronounced as compared to -I effect. Fig. 4 represents the polynomial fitting with regression factor (R^2=0.986) of % scaven-ging activity of 6-ClFHC with time.

Conclusion

The experimental studies show that the % scavenging activity depends upon number of factors. In this piece of work effect of time and substitution has been studied which alter the antioxidant activity. The substitution at 2- and 6-position effect the electron density and dipole moment of the molecule due to which ESIPT interactions and antioxidant activity varies. It is further required to study various parameters which effects both ESIPT and % scavenging together.

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