SYNTHESIS AND ANTIOXIDANT ACTIVITY OF NAPHTHO [2,1-b] FURAN DERIVATIVES FOR THE SUPPRESSION OF PIMPLES

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Summary

The present study was undertaken to evaluate antioxidant activity of the synthesised naphtho [2,1- b] furan derivatives. 3-nitro-2-acetylnaphtho[2,1-b]furan, 3-nitro-2-acetylnaphtho[2,1-b] furanhydrazone, Ethyl-3-aminonaphtho[2,1b]furan-2-carboxylate, Ethyl-3-(2,5-dimethylpyrrole naphtho[2,1-b]furan-2-carboxylate, 3-(2,5-dimethylpyrrole naphtho[2,1b]furan-2-carboxyhydrazide were synthesised from 2-hydroxy-1- naphthaldehyde. The structure of these compounds was confirmed by analytical, IR and ^{1}H NMR spectral data. The above compounds were evaluated for their antioxidant activity by reducing power and DPPH methods. In reducing power the percentage of inhibition of naphtho [2,1- b] furan derivatives 1,2 and 3 were found 86.66%, 87.34% at 150 µg/ml and 85.18% at 125 µg/ml, similarly in DPPH 90.20%, 86.7% at 150 µg/ml and 84.4% at 125 µg/ml and respectively. These results suggest that the antioxidant effect of naphtho [2,1- b] furan derivatives as a powerful source used for suppression of pimples.

Key words: antioxidant, reducing power, DPPH, Naphtho [2,1- b] furan.

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Introduction

Naphthofurans possess a broad range of biological activities, the fact that Naphtho [2,1-b] furans are associated with wide spectrum of biological and pharmacological activities[1-3] which stimulated our interest to evaluate naphtho[2,1-b] furan derivatives for antioxidant activities[4-6].

Appearance of pimple is one of the symptoms of reaching adulthood in human beings. The formation of pimples occurs mainly on face. Hence, young people, especially young girls, feel shy having ugly appearance and try to avoid attending functions. A single pimple is more than enough to destroy the happiness of any special occasion. The most annoying thing is to see a bump on the nose in the morning when one had to go out for function in the evening. Hence, every young man and woman is worried about their skin and wants to look beautiful without any marks or scars on the face. Hence, nowadays, there is great demand for products, either natural or synthetic, which can prevent formation of pimples or at least reduce the after effects like leaving permanent scars on the face. The various free radicals that are released in to the body are superoxide anion ($O_2\bullet$), NO radical, $NOO^{\bullet}$, $OH^{\bullet}$ and H_2O_2 radical[7]. Thus released free radicals react with the membrane polyunsaturated lipids and oxidize them to lipid peroxides. This lipid peroxidation damage membrane protein as well as the lipids and thereby the integrity of membrane is lost. Therefore it is considered that the extent of lipid peroxidation is directly proportional to cell damage. In addition the free radicals may also attack DNA and causes tissue damage[8]. Hence, with a view to further assess the antioxidant profile of this class of compounds, it was thought worthwhile to synthesize some important naphtho[2,1-b]furan derivatives in a single molecular framework. The present work deals with

the synthesis of the title compounds starting from 2-hydroxy-1-naphthaldehyde followed by their antioxidant activity.

Experiments

Synthesis of 3-nitro-2-acetylnaphtho[2,1-b] furan.

A cooled nitrating mixture of concentrated nitric. acid and concentrated sulphuric acid in the ratio 1:2(6.5ml: 13ml) was added very slowly to a cooled solution of 2-acetylnaphtho [2,1-b] furan (2.1g.0.01mol) in glacial acetic acid(4ml) and the mixture was stirred for about 30 min at 0-5c.The stirring was continued for 3hrs at the same temperature and the reaction mixture was poured on to crushed ice. The product which was separated as solid was collected and dried. Recrystallised from aqueous ethanol. The structure of the compound was established by recording its IR, ^{1}H NMR and ^{13}C NMR and comparing it with an authentic sample.

Reaction

Synthesis of 3-nitro-2-acetylnaphtho[2,1-b] furanhydrazone

A mixture of 3-nitro-2-acetylnaphtho[2,1-b]furan(2.5g,0.01mol),hydrazenehydrate (1ml,0.01mol),concentrated hydrochloric acid (3-4drops) in ethanol(30ml) was refluxed on water bath for 6hrs.The reaction mixture was poured in to ice water and neutralized with aqueous sodiumhydroxide (5%) Solid thus separated was collected by filtration, dried and recrystallised from ethanol

The structure of the compound was established by recording its IR, ^{1}HNMR spectra.

Synthesis of ^{ethyl} -3-aminonaphtho[2,1-b]furan-2-carboxylate

A mixture of 2-hydroxy-1-naphthaldoxime(0.93g,0.05mol),ethylchloro acetate(6.13g,0,05 mol) and anhydrous potassium carbonate(4.9g ,0.05mol)was heated under reflux in anhydrous

dimethyl formamide(60ml) for 12hrs.The reaction mixture was cooled ,potassium salts were filtered off and the filtrate was poured on to crushed ice to obtain the product as light brown coloured solid. It was collected by filtration and recrystallized from aqueous ethanol.

The structure of the compound was established by recording its IR, ^{1}HNMR and ^{13}C NMR and comparing it with an authentic sample.

Synthesis of ethyl 3-(2,5dimethylpyrrol)naphtho[2,1-b]furan-2-carboxylate,

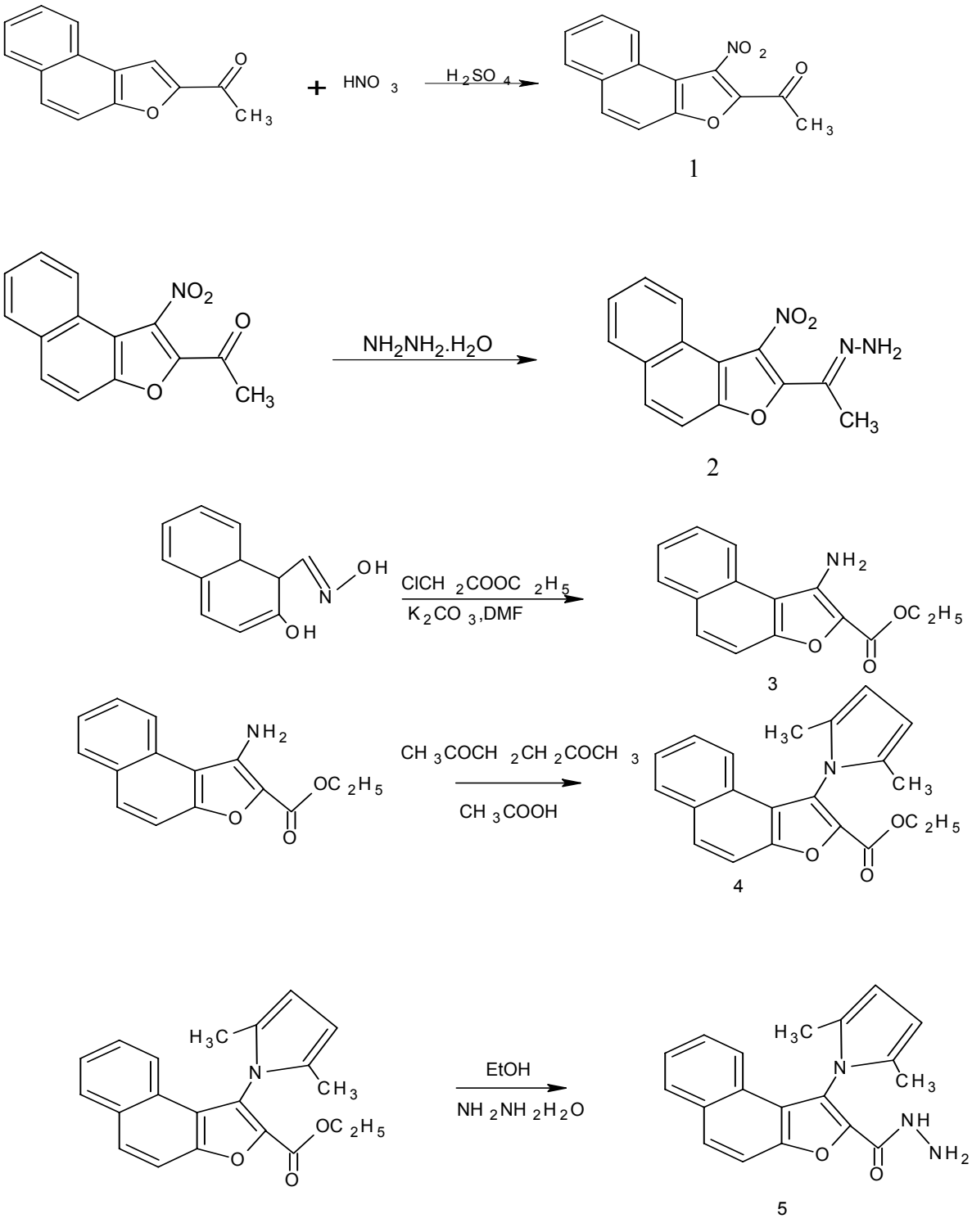
A mixture of ethyl 3-aminonaphtho[2,1-b]furan-2-carboxylate(25.5g,0.1mol) and acetonyl acetone(13.69g,0.12mol) in glacial acetic acid(100ml) was heated under reflux for 30mins.After removal of the solvent the product was filtered and recrystallized from ethanol. Acid catalyzed reaction of amino ester with acetonyl acetone resulted in the formation of ethyl 3-(2,5dimethylpyrrolnaphtho[2,1-b]furan-2-carboxylate.

Synthesis of 3-(2,5dimethylpyrrol)naphtho[2,1-b]furan-2-carboxamide

A mixture of ethyl 3-(2,5dimethylpyrrol)naphtho[2,1-b]furan-2-carboxylate(3.33g,0.01mol) and hydrazine hydrate(2.5ml,99%) in ethanol(10ml) was heated under reflux for 5hr,cooled to room temperature and the solid thus separated was filtered,washed with etanol and recrystallized from aqueous DMF to obtain the product as solid.

Melting paints were recorded in open capillaries and are uncorrected. The IR spectra were recorded on a FT-IR Research Spectrophotometer Schimadzu 8201 PC (4000-400 cm^{-1}) and NMR on Bruker DRX-300 (300MHz-FT-NMR with low and high temperature facility -90^{0} to +80^{0}). Standard chemical shifts are given in δ ppm values.All the reactions were monitored by Thin layer chromatographic method. TLC was run on silicon gel using ethyl acetate and petroleum ether (10:90) as eluent. The newly synthesized products are separated and purified by column chromatography using silica gel (60-120 mesh).

SCHEME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H2SO 4
NO 2
CH3
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NO2
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OH
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NH2
OC 2H5
3
CH 3COCH 2CH 2COCH 3
CH 3COOH
H3C
4
EtOH
NH 2NH 2H2O
NH
5

,

Antioxidant activities

1. Reducing Power:

The reducing power of synthesised naphtho [2,1- b] furan derivatives was determined according to the method of **Oyaizu (Oyaizu, 1986)**[9,10]**.** Different concentration of synthesized naphtho [2,1- b] furan derivatives, were mixed in 10 ml of DMF so as to get 25µg, 50µg, 75µg, 100µg, 125µg and 150µg concentration. This was mixed with phosphate buffer (2.5 ml, 0.2 M, pH 6.6) and potassium ferricyanide (2.5ml, 1%). The mixture was incubated at 50°C for 20 minutes. A portion (2.5 ml) of trichloroacetic acid (10%) was added to the mixture, which was then centrifuged at 3000 rpm for 10 minutes if precipitate occurs. The upper layer of the solution (2.5 ml) was mixed with distilled water (2.5 ml) and $FeCl_3$ (0.5 ml, 0.1%), and the absorbance (OD) was measured at 700nm.

Increased absorbance of the reaction mixture indicates increase in reducing power. The % reducing power was calculated by using following formula:

$$\% \text{ increase in absorbance} = \frac{\text{Test OD} - \text{Control OD}}{\text{Control OD}} \times 100$$

2) DPPH radical-scavenging activity[11]:

The stable 2,2-diphenly-1-picryl hydrazyl radical (DPPH) was used for determination of free radical-scavenging activity of the synthesised naphtho [2,1- b] furan derivatives to 1 ml of 0.135mM DPPH prepared in methanol was mixed with 1.0ml of synthesised naphtho [2,1- b] furan derivatives ranging from 25 - 150 µg /ml. The reaction mixture was vortexed thoroughly and left in dark at room temperature for 30 min. the absorbance was measured

spectrophotometrically at 517nm. The scavenging ability of the synthesised naphtho [2,1- b] furan derivatives was calculated using the standard equation.

$$\% \text{ inhibition} = \frac{\text{Control OD} - \text{Test OD}}{\text{Control OD}} \times 100$$

Results and Discussion

The structure of the synthesised compound was established by recording its IR, ^{1}HNMR and mass spectral data. The IR spectrum of 3-nitro-2 acetylnaphtho [2,1-b] furan exhibited characteristic absorbtion band at 1681 cm^{-1} due to C=O group and at 1548 cm^{-1} and 1353 cm^{-1} due to NO_2 group. The ^{1}HNMR spectrum showed a singlet at ∂ 2.6 integrating for three protons of CH_3 group and multiplet between ∂7.5 to8.2 for aromatic protons.Mass spectrum showed molecularion peak at m/Z 255, consistent with the molecular weight. **.** The IR spectrum of 3-nitro-2-acetylnaphtho[2,1-b]_furanhydrazone exhibited the absorption band at 1621cm^{-1}due to C=N group and at 3450 cm^{-1} due to NH_2 group.In the NMR spectrum singlet at ∂ 2.3,5.6 and multiplet at 7.2-8.0 due to CH_3, NH2 and aromatic protons. The IR spectrum of ethyl -3-aminonaphtho[2,1-b]furan-2-carboxylate exhibited characteristic absorption band at 1724 cm^{-1} due to ester carboxy group. The ^{1}H NMR specturm of ethyl 3-(2,5dimethylpyrrol)naphtho[2,1-b]furan-2-carboxylate exhibited a triplet at ∂ 1.47 (J=7.02 Hz) due to –CH_2,A singlet at ∂ 2.08 due to methyl protons, a quartet at ∂ 4.49 (J=7.43 Hz) due to –CH_3 ester protons and a multiplet at∂ 7.2-8.2 due to aromatic protons of signal due to –NH_2 The IR spectrum exhibited characteristic absorbtion band at 1720 cm^{-1} due to ester carboxy

group. The structure of ethyl (2,5dimethylpyrrolnaphtho[2,1-b]furan-2-carboxamide was established by its IR and ^{1}H NMR spectrum. The IR spectrum should absorption band at 3335 $cm^{-1}$and 3278 cm^{-1} due to amine/amide NH group and strong stretching band at 1650 cm^{-1} due to amide carbonyl. ^{1}H NMR spectrum showed a singlet at ∂ 4.51 and ∂ 9.81 (D_2O exchangeable), which were accounted for NH_2 and NH protons. In addition it also exhibited a singlet at ∂ 2.01 and multiplet at ∂ 7.2 – 8.2 which were attributed to methyl and aromatic protons respectively.

There are numerous antioxidant methods for evaluation of antioxidant activity. For *in vitro* antioxidant screening, DPPH, free radical scavenging, metal ion chelating, hydrogen peroxide scavenging, superoxide anion radical scavenging and ferric thiocyanate reducing activities are most commonly used. However, the total antioxidant activity of an antioxidant cannot be evaluated by using one single method, due to oxidative processes. Therefore, at least two methods should be employed in order to evaluate the total antioxidant activity[12]. Antioxidants are the chemical constituents, which are used for inhibiting the tissue damage by countering the free radicals. In addition there are reports that polyphenolic compounds like flavonoids and tannins are useful as antioxidants and organ protectants[13]. The naphtho[2,1-b]furan derivatives were subjected to screen antioxidant activity using *invitro* models like reducing power and DPPH. Figure 1 and 2 indicates noticeable effect of synthesised derivatives on scavenging of free radicals. These results revealed that the synthesised derivatives are free radical inhibitor or scavenger acting possibly as primary antioxidants. In reducing power the percentage of inhibition of naphtho [2,1- b] furan derivatives 1,2 and 3 were found 86.66%, 87.34% at 150 µg/ml and 85.18% at 125 µg/ml, similarly in DPPH 90.20%, 86.7% at 150 µg/ml and 84.4% at 125 µg/ml respectively as shown in table 1 and 2.

Reducing Power activity of naphtho [2,1- b] furan derivatives. Table 1

SL NO.	Conc.	Standard (Vit. C)		Compound No.1		Compound No.2		Compound No.3	
		Mean±SEM	% of inhibition	Mean±SEM	% of inhibition	Mean±SEM	% of inhibition	Mean±SEM	% of inhibition
1	Control	0.080±0.00	---	0.075±0.000	---	0.079±0.000	---	0.054±0.007	---
2	25µg/ml	0.090±0.020	12.5%	0.082±0.000	9.3%	0.075±0.001	13.9%	0.062±0.0016	14.81%
3	50µg/ml	0.145±0.000	81.25%	0.096±0.000	28%	0.111±0.001	40.5%	0.070±0.003	29.62%
4	75µg/ml	0.126±0.001	57.5%	0.114±0.000	52.0%	0.120±0.000	51.00%	0.082±0.002	51.85%
5	100µg/ml	0.132±0.000	65%	0.122±0.000	62.6%	0.132±0.000	67.08%	0.098±0.010	81.48%
6	125µg/ml	0.148±0.003	85%	0.138±0.000	84%	0.140±0.000	77.21%	0.102±0.001	85.18%
7	150µg/ml	0.154±0.000	92.5%	0.140±0.000	86.66%	0.148±0.000	87.34%	0.096±0.004	77.77%

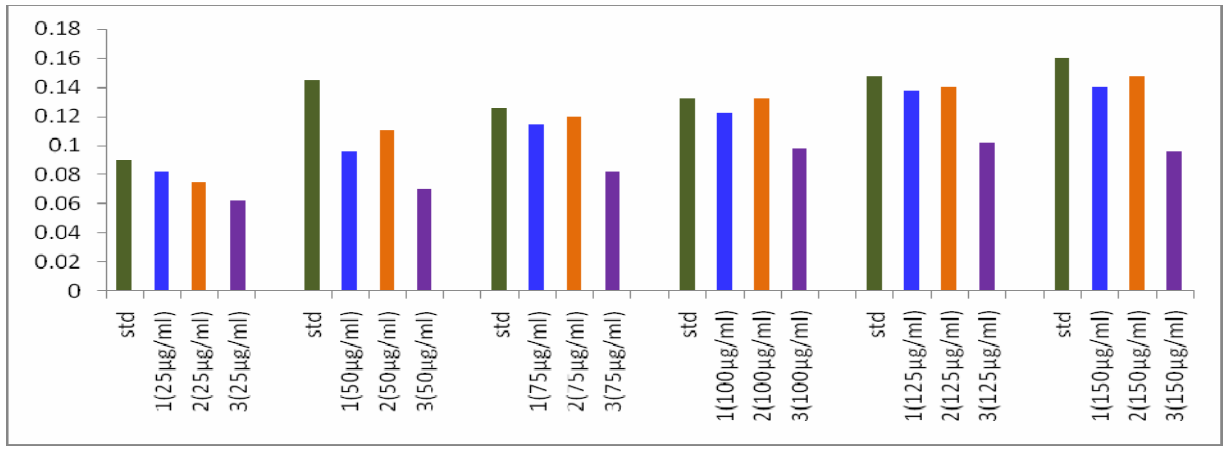
Values are the mean ± S.E.M., n=3, compared to control. Std: Vit.C

DPPH activity of naphtho [2,1- b] furan derivatives. Table 2

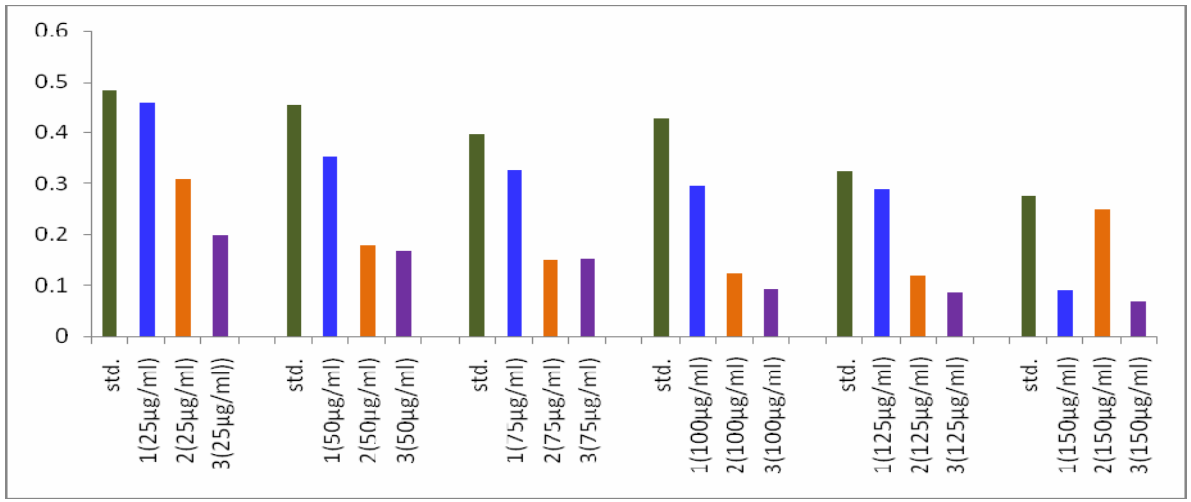
SL.NO	Conc.	Standard (Vit. C)		Compound No. 1		Compound No. 2		Compound No. 3	
		Mean±SEM	%inhibition	Mean±SEM	%inhibition	Mean±SEM	%inhibition	Mean±SEM	%inhibition
1.	control	0.689±0.00	---	0.689±0.00	---	0.689±0.00	---	0.689±0.00	---
2.	25 µg/ml	0.482±0.001	30.0%	0.458±0.00	33.5%	0.310±0.001	55.0%	0.199±0.002	71.1%
3.	50 µg/ml	0.454±0.002	34.10%	0.354±0.00	48.62%	0.178±0.010	74.1%	0.168±0.010	76.92%
4.	75 µg/ml	0.396±0.102	42.5%	0.328±0.00	52.39%	0.150±0.003	78.2%	0.154±0.09	75%
5.	100 µg/ml	0.428±0.00	37.8%	0.296±0.00	57.0%	0.126±0.00	81.7%	0.092±0.12	87 %
6.	125 µg/ml	0.324±0.00	52.9%	0.289±0.00	58.0%	0.121±0.100	84.4%	0.086±0.06	87.24%
7.	150 µg/ml	0.276±0.00	59.9%	0.091±0.000	86.7%	0.250±0.00	63.7%	0.069±0.087	90.2%

Values are the mean ± S.E.M., n=3, compared to control. Std: Vit.C

Reducing power activity of naphtho [2,1- b] furan derivatives. Figure 1



DPPH activity of naphtho [2,1- b] furan derivatives. Figure 2



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