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Synthesis of novel substituted 4*H*-chromenes and their antioxidant screening

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ABSTRACT

Novel substituted 4H-chromenes were synthesized via O-alkylation of 2-amino-7-hydroxy-4-phenyl-4H-chromene-3-carbonitrile ***(1)*** *followed by hydrazinolysis to give the hydrazide* ***3.*** *This key intermediate* ***3*** *was reacted with aromatic aldehydes, arylmethylenemalononitriles and substituted isothiocyanates to yield compounds* ***4a&b*** *and* ***5a&b,*** *respectively. In addition, cyclization of* ***5a&b*** *in piperidine yielded the target thiazolo derivatives* ***6a&b****. All newly synthesized compounds were evaluated for their in vitro antioxidant activity. Compound* ***5a*** *was found to be the most potent antioxidant and the least active among the series being compound* ***1.***

Key Words: Heterocycles, substituted chromenes, thiazoles, Schiff bases, antioxidant activity.

INTRODUCTION

4*H*-Chromenes exhibit a remarkable array of biochemical and pharmacological activities. They constitute the basic structural back bone of many types of tannin and polyphenols widely present in plants e.g. green tea, fruits and vegetables [1]. The presence of the chromene-containing structure has been associated with the capability to prevent several diseases [2]. Synthetic analogues have attracted considerable attention due to their useful biological and pharmacological properties including antimicrobial [3-13], antioxidant [14,15], anticancer [16-19], hypotensive [20], local anesthetic [21] and central nervous system activities [12,22]. As well as treatment of Alzheimer's disease [23] and Schizophrenia disorder [24].

The aim of the present work is the synthesis of novel compounds bearing 4-aryl 4*H*-chromene and evaluation of their antioxidant activities.

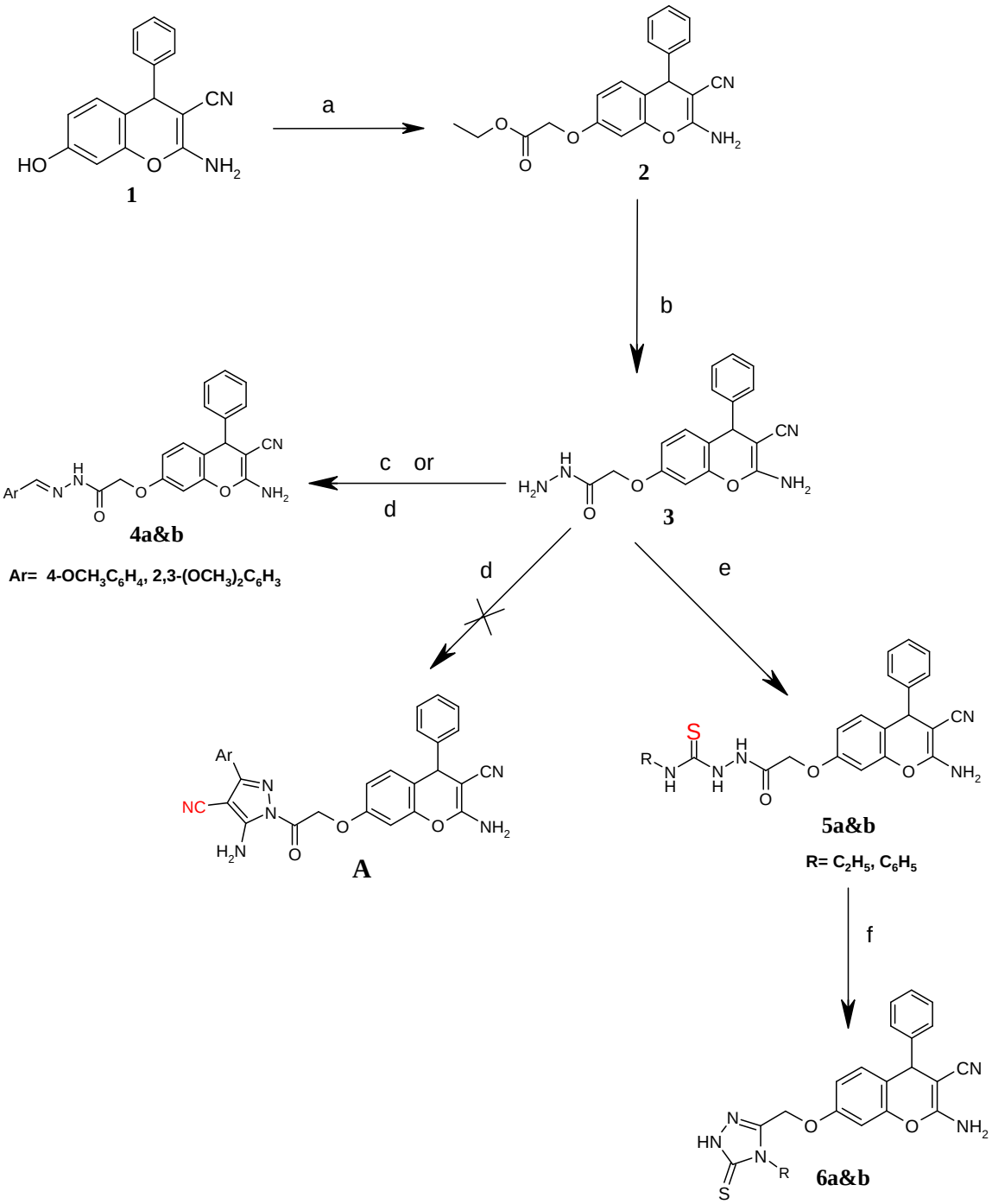
For this purpose the 2-amino-4-(4-phenyl)-7-hydroxy-4*H*-chromene-3-carbonitrile **1** [25], alongside with its ester and hydrazide derivatives **2&3** were synthesized (Scheme 1).

EXPERIMENTAL SECTION

Chemistry

Reactions were routinely monitored by thin-layer chromatography (TLC) on silica gel sheets that precoated with UV fluorescent silica (MERCK 60 F 254) and spots were developed using I_2vapour / UV light as visualizing agents. Solvent system was chloroform: methanol (in different ratio). ^{1}H NMR spectra were determined in $CDCl_3$, or DMSO-d_6 solvent with Varian Gemini 300 MHZ Spectrometer. Peak positions were given in parts per million (δ) downfield the tetramethylsilane as internal standard. IR spectra were recorded on a Shimadzu 435 Spectrometer, using KBr discs and values were represented in cm^{-1}. GC Mass spectra were run on Shimadzu QP-2010 spectrometer and Mass spectra were run on Hewlett Packard 5988 spectrometer at the Microanalytical Center, Cairo University, Egypt. Melting points were determined on a Griffin instrument and are uncorrected. All reported products showed ^{1}H NMR spectra in agreement with the assigned structures. Elemental analyses were performed at

the Micro-analytical Center, Cairo University, Egypt. Compound **1** was prepared adopting a reported procedure [25].



Reagents & conditions: a: $ClCH_2COOC_2H_5$, K_2CO_3 / DMF, reflux 2h **b:** N_2H_4 / EtOH, reflux 4h

c: ArCHO, TEA/ EtOH, reflux 2-4h **d:** $ArCH=C(CN)_2$, piperidine/EtOH, reflux 2h

e: RCNS/EtOH, reflux 4h **f:** piperidine/H_2O, reflux 6h

Scheme 1

***(RS)*-Ethyl 2-(2-amino-3-cyano-4-(phenyl)-4*H*-chromen-7-yloxy) acetate (2)**

To a well-stirred mixture of **1** (2.64 g, 0.01 mol) and anhydrous potassium carbonate (5.52 g, 0.04 mol) in dry dimethylformamide (30 ml), ethyl chloroacetate (1.22 g, 0.01 mol) was added dropwise. After completion of the addition, the reaction mixture was heated under reflux for 2 h then cooled and poured into ice-cold water. The precipitated solid was filtered, washed with water, dried and crystallized from absolute ethanol to afford compound **2** in 3.25 g (93%) yield. mp 130-132 ^{o}C, IR (KBr): 3428.81, 3343.96 (forked, NH_2), 2983.34 (CH aliph.), 2184.95 (C≡N), 1747.19 (C=O) cm^{-1}; ^{1}H NMR (DMSO-d6): δ 1.20 (t, J_{value} = 7.2 Hz, 3H, $CH_2C\underline{H}_3$); 4.15 (q, J_{value} = 7.2 Hz, 2H, $C\underline{H}_2CH_3$); 4.66 (s, 1H, C4H); 4.77 (s, OCH_2); 6.55 (s, 1H, ArH), 6.67-7.33 (m, 7 H, Ar H and 2H, NH_2, D_2O exchangeable) ppm; EIMS: m/z (%) = 350 (M^+, 13.61%), 273 (100%); Anal. Calcd. for $C_{20}H_{18}N_2O_4$ (350.40): C 68.56, H 5.18, N 8.0; Found: C 68.30, H 5.10, N, 8.20% .

***(RS)*-2-(2-Amino-3-cyano-4-(phenyl)-4*H*-chromen-7-yloxy)acetohydrazide (3)**

A mixture of compound **2** (3.50 g, 0.01 mol) and hydrazine hydrate (0.055 g, 0.011 mol) in absolute ethanol (30 ml) was heated under reflux for 4 h. The solid formed while hot was filtered and crystallized from absolute ethanol to give 3.02 g (90%) of compound **3**. mp 215-217 ^{o}C, IR (KBr): 3323.71, 3180.04 (2NH_2, NH), 2922.59 (CH aliph.), 2185.92 (C≡N), 1662.34 (C=O); ^{1}H-NMR (DMSO-d6): δ 4.30 (s, 2H, NH$\underline{NH}_2$ D_2O exchangeable); 4.47 (s, 1H, C4H); 4.68 (s, 2H, OCH_2); 6.58-7.33 (m, 8 H, Ar H and 2H, NH_2, D_2O exchangeable); 9.36 (s, 1H, $\underline{NH}NH_2$, D_2O exchangeable) ppm; EIMS: m/z (%) = 336 (M^+, 16.07%), 259 (100%); Anal. Calcd. for $C_{18}H_{16}N_4O_3$(336.37): C 64.28, H 4.79, N 16.66; Found: C 64.40, H 4.60, N 16.80%**.**

General procedures for synthesis of compounds 4a&b

A mixture of compound **3** (1.68 g, 0.005 mol) and the appropriate aromatic aldehyde (0.005 mol) in absolute ethanol (25 mL) was treated with triethyl amine (2-3 drops) and heated under reflux for 2-4 h. The solid formed on hot was filtered, dried and crystallized from the absolute ethanol to give compounds **4 a&b**.

(2-Amino-4-(phenyl)-3-cyano-4*H*-chromen-7-yloxy)-*N'*-*(ZE)*-4-methoxy benzylideneacetohydrazides (4a)

Yield: 70%, mp 213-215 ^{o}C. IR (KBr): 3430.74, 3343.01, 3211.86 (NH, NH_2), 3083.62 (CH arom.), 2926.45(CH aliph.), 2185.92 ((C≡N), 1698.16 (C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 3.79 (s, 3H, OCH_3); 4.66 (d, 2H, OCH_2); 5.10 (s, 1H, C4H); 6.52-7.65 (m, 12H, ArH and 2 , NH_2, D_2O exchangeable); 7.94 (s, 1H, CH=N); 11.42 (d, 1H, NH, D_2O exchangeable**)** ppm; EIMS: m/z (%) = 455 (M+1 $^{\cdot\ddagger}$, 14.57%), 454 (M $^{\cdot\ddagger}$, 86.14 %), 133.1 (100%); Anal.Calcd. for $C_{26}H_{22}N_4O_4$ (454.49): C 68.71, H 4.88, N 12.33; Found: C 68.60, H 4.70, N 12.30%.

(2-Amino-4-(phenyl)-3-cyano-4*H*-chromen-7-yloxy)-*N'*-*(ZE)*-2,3-dimethoxybenzylideneacetohydrazides (4b)

Yield: 60%, mp 203-205 ^{o}C. IR (KBr): 3430.74, 3317.93, 3231.15 (NH, NH_2), 3066.26 (CH arom.), 2936.09 (CH aliph.), 2187.85 ((C≡N), 1685.48 (C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 3.77 (s, 3H, OCH_3); 3.78 (s, 3H, OCH_3); 4.66 (d, 2H, OCH_2); 5.13 (s, 1H, C4H); 6.52-7.45 (m, 11H, ArH and 2 NH_2, D_2O exchangeable); 8,29 (s, 1H, CH=N); 11.57 (d**,** 1H, NH, D_2O exchangeable**)** ppm; EIMS: m/z (%) = 485 (M+1 $^{\cdot\ddagger}$, 5.13%), 484 (M $^{\cdot\ddagger}$, 13.76 %), 259.05 (100%); Anal.Calcd. for $C_{27}H_{24}N_4O_5$ (484.52): C 66.93, H 4.99, N 11.56; Found: C, 66.80, H 4.90, N 11.50%.

General procedure for the preparation of compounds 5a&b

To a solution of the acid hydrazide **3** (1.68 g, 0.005 mol) in absolute ethanol (20 mL), was added the appropriate isothiocyanate (0.005 mol). The reaction mixture was heated under reflux for 4 h; the solid formed while hot was collected by filtration, washed with ethanol and crystallized from the suitable solvent to afford **5a&b**

***(RS)*-2-(2-(2-Amino-3-cyano-4-phenyl-4*H*-chromen-7-yloxy) acetyl) -*N*-ethylhydrazinecarbothioamides (5a)**

Crystallized from methanol, Yield: 70%, mp 175-177 ^{o}C. IR (KBr): 3430.74, 3323.71, 3191.61 (3NH, NH_2), 3051.8 (CH arom.), 2929.34 (CH aliph.), 2186.88 ((C≡N), 1651.73 (C=O), 1285.23, 1232.11 (C=S) cm^{-1}; ^{1}H NMR (DMSO-d6): δ 1.23 (t, J_{value} = 7.2 Hz, 3H, $CH_2C\underline{H}_3$); 3.98 (q, J_{value} = 7.2 Hz, 2H, $C\underline{H}_2CH_3$); 4,69 (s, 1H, C4H); 5.22 (s, 2H, OCH_2) ; 6.75-7.33 (m, 8H, ArH and 2H, NH_2 D_2O exchangeable) ppm; but 3NH not observed; EIMS: m/z (%) = 425 (M+2 $^{\cdot\ddagger}$, 0.55%), 424 (M+1 $^{\cdot\ddagger}$, 0.79 %), 423 (M+ $^{\cdot\ddagger}$, 2,94 %), 187 (100%); Anal.Calcd. for $C_{21}H_{21}N_5O_3S$ (423.51): C 59.56 , H 5.00, N 16.54; Found: C 56.50, H 4.90, N 16.50%.

***(RS)*-2-(2-(2-Amino--3-cyano-4-phenyl-4*H*-chromen-7-yloxy) acetyl)-*N*-substituted hydrazinecarbothioamides (5b)**

Crystallized from methanol:acetone (1:1), Yield: 60%, mp 200-202 ^{o}C. IR (KBr): 3479.92, 3379.64, 3164.61 (3NH, NH_2), 3059.51 (CH arom.), 2964.05 (CH aliph.), 2196.52 ((C≡N), 1646.91 (C=O), 1292.51, 1242.43 (C=S) cm^{-1}; ^{1}H NMR (DMSO-d6): δ 4.35 (s, 1H, NH, D_2O exchangeable); 4.64 (s, 1H, C4H); 4,82 (s, 2H, OCH_2); 6.53-7.42

(m, 13H, ArH and 2H, NH_2, D_2O exchangeable) ppm; but 2NH not observed ; EIMS: m/z (%) = 472 (M+1 $^{\cdot+}$, 1.19 %), 471 (M+ $^{\cdot+}$, 3,94 %), 235 (100%); Anal.Calcd. for $C_{25}H_{21}N_5O_3S$ (471.54): C 63.68, H 4.49, N 14.85; Found: C 63.70, H 4.40, N 14.90%.

General procedure for the preparation of compounds 6a&b

A mixture of the appropriate thiosemicarbazide derivative **5a&b** (0.005 mol) was heated under reflux for 6 h in a mixture of piperidine (2mL) and water (5mL). The reaction mixture was poured into ice-cold water and the mixture was adjusted to pH 7 with acetic acid (20%). The solid obtained was filtered, dried and crystallized from absolute ethanol to give **6a&b.**

***(RS)*-2-(2-Amino-3-cyano-4-phenyl-4*H*-chromen-7-yloxy)-*N'*-(4-oxo-3-ethylthiazolidin-*(ZE)*-2-ylidene) acetohydrazides (6a)**

Yield: 80%, mp 158-160 ^oC. IR (KBr): 3325.64, 3174.26 (NH, NH_2), 2936.09 (CH aliph.), 2186.88 (C≡N), 1646.64 (C=N), 1362.13, 1269.81 (C=S) cm^{-1}; ^1H NMR (DMSO-d6): δ 1.21 (t, J_{value} = 7.2 Hz, 3H, $CH_2C\underline{H}_3$); 3.97 (q, J_{value} = 7.2 Hz, 2H, $C\underline{H}_2CH_3$); 4.69 (s, 1H, C4H); 5.20 (s, 2H, OCH_2); 6.75-7.33 (m, 8H, ArH and 2H, NH_2, D_2O exchangeable) ppm; but NH not observed ; EIMS: m/z (%) = 405 (M+ $^{\cdot+}$, 1.04 %), 187 (100%); Anal. Calcd. for $C_{21}H_{19}N_5O_2S$ (405.48): C 62.21, H 4.72, N 17.27; Found: C 62.20, H 4.90, N 17.20%.

***(RS)*-2-(2-Amino-3-cyano-4-phenyl-4*H*-chromen-7-yloxy)-*N'*-(4-oxo-3-phenylthiazolidin-*(ZE)*-2-ylidene) aceto hydrazides (6b)**

Yield: 69%, mp: 174-176 ^oC. IR (KBr): 3436.53, 3163.65, 3108.69 (NH, NH_2), 2934.16 (CH aliph.), 2185.92 ((C≡N), 1647.66 (C=N), 1327.53, 1242.01 (C=S) cm^{-1}; ^1H NMR (DMSO-d6): δ 4.64 (s, 1H, C4H); 4.89 (s, 2H, OCH_2) ; 6.52-7.49 (m, 13H, ArH and 2H, NH_2 D_2O exchangeable) ppm; but NH not observed; EIMS: m/z (%) = 453 (M+ $^{\cdot+}$, 1.94 %), 235 (100%); Anal.Calcd. for $C_{25}H_{19}N_5O_2S$ (453.53): C 66.21, H 4.22, N 15.44; Found: C 66.30, H 4.10, N 15.50%.

Antioxidant activity

Materials and methods

2,2-diphenyl-1-picrylhydrazyl radical (DPPH) was purchased from Sigma–Aldrich (Missouri, USA). Ascorbic was purchased from Merck (New Jersey, USA). All the used chemicals and solvents were of analytical grade.

DPPH radical scavenging activity

DPPH (2,2-diphenyl-1-picrylhydrazyl) radical scavenging activity of each compound was determined as mentioned before [27-29]. Briefly, 2 mL of DPPH solution (0.2 mmol/L, in ethanol) was incubated with different concentrations of the test compounds. All reactions were performed in triplicates and the reaction mixtures were shaken and wrapped in aluminum foil and kept at room temperature for 30 min in dark. The Spectrophotometric measurements were done under dim light at 517 nm. All data are depicted as mean ± SD (n=3). The IC_{50} (the concentration of sample necessary to cause 50% inhibition of DPPH radical scavenging activity) was calculated for each compound. Ascorbate (Vitamin C), an antioxidant, was used as a positive control.

Yeast based antioxidant screening assay

The yeast based biological assay detects antioxidant activities of samples against physiologically relevant oxidants. Since DPPH radical scavenging activity method provides only an indication of the ability of a compound to scavenge oxidants we used yeast-based method which can also measure the ability of a compound to induce cellular resistance to the damaging effects of oxidants [30]. Antioxidant activity screening was done in a 96-well microplate high throughput assay using *Saccharomyces cerevisiae* as described before [31]. Briefly, *S. cerevisiae* (BY4743) were cultured overnight then diluted to an optical density of 0.2 at 600 nm (OD600) in the media. 180 µL of the diluted culture was added per well in a 96-well plate then 10 µL of test compound was added to a final concentration of 8 mM. H_2O_2 (10 µL) was added into each well to a final concentration of 4 mM. The OD600 reading as an indicator of yeast growth was taken using a microplate reader before and after the incubation at 30°C with shaking for 20 hours. Ascorbic acid was used as a positive control. The net growth of yeast after the treatment with H_2O_2 and test compounds was measured using the following equation:

$$P_{yeast\,growth} = \left(\frac{P_{Sample} - P_{Control}}{P_{Control}} \right) \times 100$$

"P yeast growth" = Net growth of yeast cells after treatment with test compounds.
"P Sample" = Observed optical density of yeast cells with the treatment with test compounds
"P Control" = Observed optical density of yeast cells with the treatment of negative control

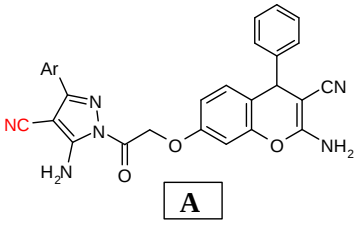
RESULTS AND DISCUSSION

Chemistry

One pot three-component reaction of resorcinol, malononitrile and benzaldehyde with few drops of piperidine base afforded aminocyanochromene **1** which upon alkylation using ethyl chloroacetate in dry dimethyl formamide in the presence of anhydrous potassium carbonate as a catalyst yielded the ester derivative **2** in an excellent yield (Scheme 1). There is no conflict of interest between both the hydroxyl group and the amino group during the alkylation process of compound **1** since; the amino group is very weak to an extent that could not undergo a simple condensation reaction with an aldehyde or benzene sulphonyl chloride [26]. The key intermediate **3** was achieved by refluxing both the substrate **2** and hydrazine hydrate in ethanol for 4 hours. The IR spectrum of **3** revealed band at 3323.71, 3180.04 cm^{-1} for (NH_2, NH) groups and at 1662.34 cm^{-1} for (amidic C=O) group. ^{1}H NMR spectrum of compound **3**, showed singlet signals derived from hydrazide structure appeared at δ 4.30 (NH_2) and δ 9.36 (NH) with the integration for two protons and one proton, respectively. Heating equimolar amounts of the hydrazide **3** with the corresponding aromatic aldehyde in absolute ethanol containing catalytic amount of triethyl amine yielded smoothly Schiff bases **4a&b** (Scheme 1).

The structure of the synthesized compounds was confirmed using microanalyses and spectral data. ^{1}H NMR spectra of compounds **4a&b** indicated the presence of the two isomers (*ZE*) in equimolar amounts, this is obviously showed by presence of two CH_2 groups as the peak is forked at its apex and a doublet signal which was D_2O exchangeable indicating NH proton (Scheme 1).

In the present work, hoping to synthesize *o*-Aminocyano pyrazoles **A** (Figure 1), the acid hydrazide **3** was allowed to react with arylidene malononitrile in ethanol. Actually, the products in hand were neither **A** nor the starting material **3**. Instead, the products were identified as Schiff bases **4a&b**.



A

Figure 1 Compound A

For the preparation of the thiosemicarbazides **5a&b;** the respective isothiocyanate was reacted with the acid hydrazide **3** in refluxing ethanol (Scheme 1). The ^{1}H NMR spectra of **5a** displayed the appearance of a triplet and a quartet signals at δ 1.20-1.25 and δ 3.95-4.01 due to ethyl group.

The triazolothione derivatives **6a&b** were prepared by refluxing the corresponding thiosemicarbazide derivatives **5a&b** in piperidine (Scheme 1). The structure of compounds **6a&b** was confirmed with the aid of spectroscopic data and element analysis.

Antioxidant activity

In the current study, the antioxidant activities of all newly synthesized compounds were evaluated using DPPH (2,2-diphenyl-1-picrylhydrazyl) radical scavenging method and yeast based antioxidant screening assay. Compound **5a** was found to be the most potent antioxidant with the least values of IC_{50} (inhibition concentration) and the least active compound among the series being compound **1** with the largest values of IC_{50} (Table 1 and Figure 2). Antioxidant activities of test compounds based on their ability to inhibit the H_2O_2 induced yeast oxidative stress are listed in Table 2 and illustrated in Figure 3.

Table 1 Free radical scavenging capacities of the test compounds measured by DPPH assay.
Values of IC_{50} are expressed as means ± SD (n= 3)

Compounds	Mean IC_{50} ±SD (mg/mL)
2	805.00 ± 26.63
3	701.67 ± 25.54
4a	432.33 ± 22.90
4b	404.67 ± 18.15
5a	55.67 ± 12.90
5b	267.33 ± 19.40
6a	199.00 ± 36.51
6b	85.33 ± 6.43

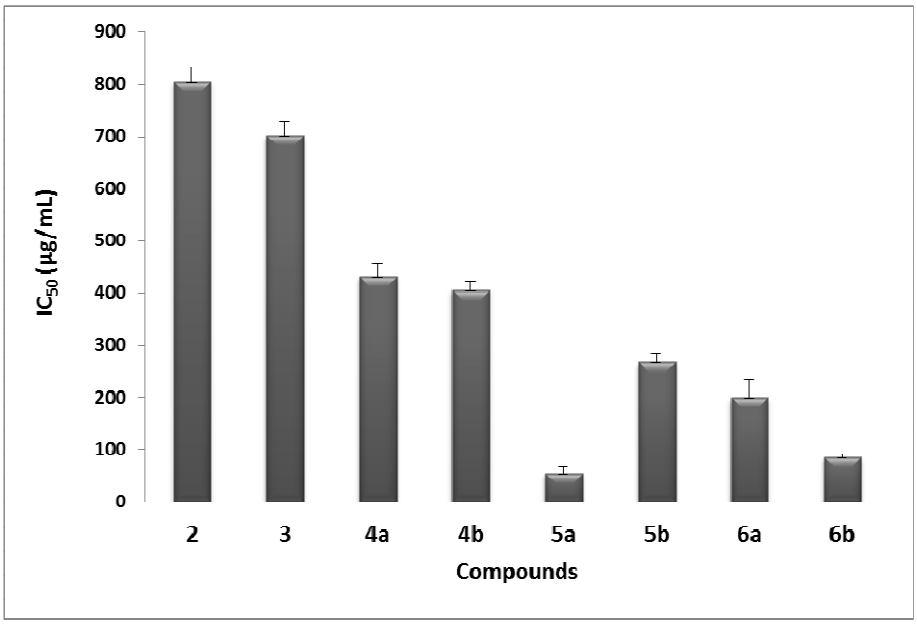


Figure 2 Free radical scavenging capacities of the test compounds measured by DPPH assay

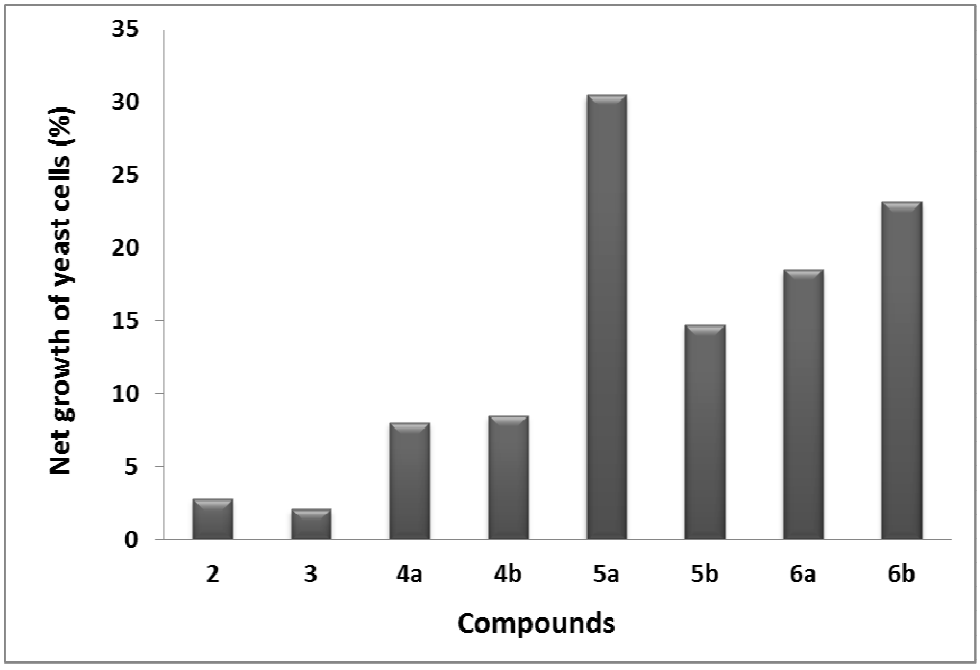


Figure 3 Antioxidant activity screening in a 96-well microplate high throughput assay using *Saccharomyces cerevisiae.*

Table 2 Antioxidant activity screening in a 96-well microplate high throughput assay using *Saccharomyces cerevisiae.*
Yeast oxidative stress was measured on the basis of survival of yeast cells (yeast growth) after treatment with H_2O_2.

Compounds	Net growth of yeast cells (%)
2	2.80
3	2.10
4a	8.03
4b	8.50
5a	30.50
5b	14.73
6a	18.50
6b	23.17

CONCLUSION

In conclusion, we have successfully reported the synthesis of some novel compounds bearing 4-aryl 4*H*-chromene and evaluation of their antioxidant activities. The antioxidant activities of the 8 newly prepared compounds were measured using DPPH radical scavenging method and yeast based antioxidant screening assay. The reactivity of the tested compounds as antioxidant was increased upon hydrazionlysis of **2** to give **3**. Also, conversion of **3** to **4a&b** was accompanied with increasing of activity which also increased significantly upon reaction of **3** with ethyl isothiocyanate to give the most potent compound **5a** but this activity was decreased upon cyclization of **5a** to **6a**. On contrast, the antioxidant activity was increased upon cyclization of **5b** to **6b**.

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