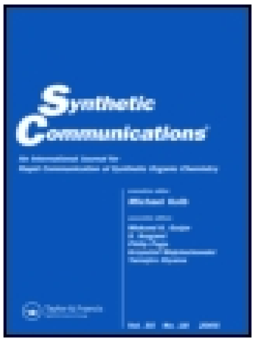

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Convenient synthesis of linear 2*H*,6*H*-pyrano[3,2-*g*] chromenes from natural occurring compound; visnagin

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ABSTRACT
A simple and convenient rout for the synthesis of linear 2-imino-2*H*,6*H*-pyrano[3,2-*g*] chromene-6-ones and 2*H*,6*H*-pyrano[3,2-*g*]chromene-2,6-diones has been described starting from natural occurring furochromone; visnagin (**1**). Ring opening of **1** yielded 6-formyl-7-hydroxy-5-methoxy-2-methylchromone (**2**), which underwent reaction with different acetonitrile derivatives furnished 2-imino-2*H*,6*H*-pyrano[3,2-*g*] chromene-6-ones (**5a–h**). Acid hydrolysis of **5a–h** led to the formation of 2*H*,6*H*- structures pyrano[3,2-*g*]chromene-2,6-diones (**6a–h**). Structures of the synthesized compounds were clarified based on their elemental analyses and spectral data. The entire target compounds were selected for *in vitro* anticancer activity against 60 human cancer cell lines at a single dose (10^{-5} M) by the National Cancer Institute (NCI, Bethesda, USA).

ARTICLE HISTORY
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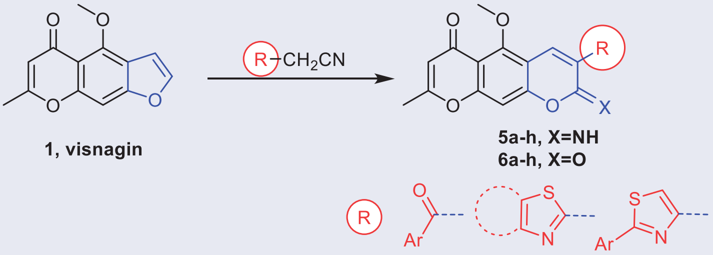
KEYWORDS
Anticancer activity; chromone; coumarine; 2H,6H-pyrano[3,2-g]chromene; visnagin

GRAPHICAL ABSTRACT



Introduction

It is well known that both chromones and coumarins possess pronounced biological activity.[1] Chromone and its derivatives are naturally occurring compounds everywhere exist in the plant kingdom, and therefore, present in representative amounts in the normal human diet.[2] The chromone and its derivatives possess numerous of biological activities such as anti-inflammatory,[3] antifungal,[4] antibacterial,[5] antiviral,[6]

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*These authors contributed equally to this work.
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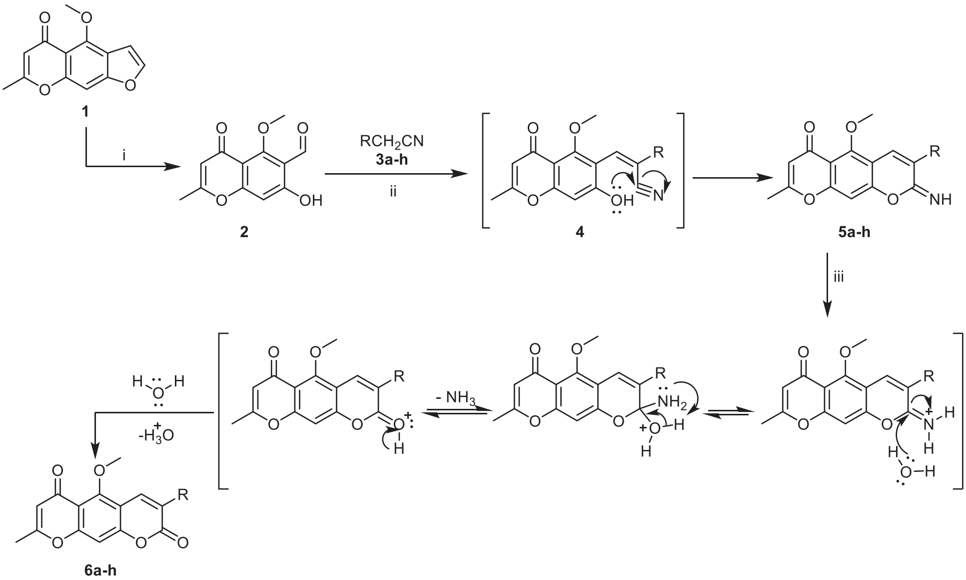


Scheme 1. Synthesis of 2*H*,6*H*-pyrano[3,2-*g*]chromene derivatives; reagents and conditions: (i) 10% H_2SO_4, 10% $K_2Cr_2O_7$, 70–80 °C; (ii) EtOH, piperidine (2 drops), stirring, 15 min and/or piperidine (2 drops), grinding, 5 min; (iii) 10% HCl, stirring, 1–2 min.

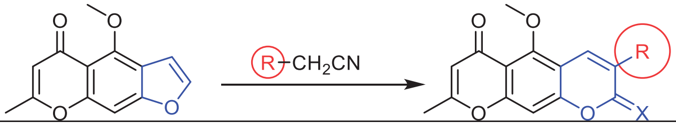
antitumour and anticancer.[7] On the other hand, coumarin the basic molecule of the simplest natural occurring phenolic substance that possessing fused benzene and α-pyrone rings.[8] The coumarins occur in a diversity of forms, due to the numerous substitutions possible in their basic structure, which alter their biological activity.[9] Coumarins possess anti-inflammatory,[10] antioxidant,[11] hepatoprotective,[12] antiviral,[13] antimicrobial[14] and anti-carcinogenic effects.[15] Some coumarins can be obtained based on chromone derivatives.[16] Starting from 6-formyl-7-hydroxy-5-methoxy-2-methylchromone a new coumarin derivative, namely 3-acetyl-5-hydroxy-8-methyl-2,6-dioxo-2*H*,6*H*-benzo[l,2-*b*:5,4-*b*′]dipyran has been created.[16] We are, therefore, searching for such heterocyclic systems that combine chromone and coumarin moieties namely 2*H*,6*H*-pyrano[3,2-*g*]chromene starting from natural occurring furochromone; visnagin to be exploited for further diversification and screened for anticancer activity.

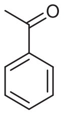
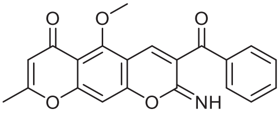
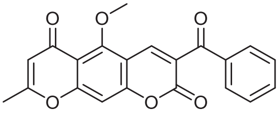
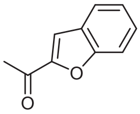
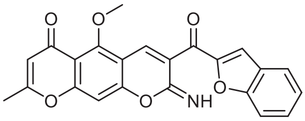
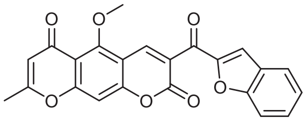
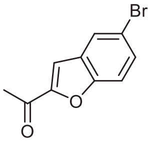
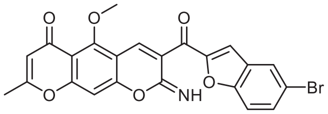
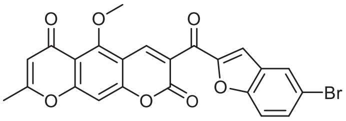
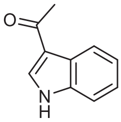
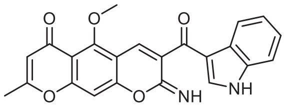
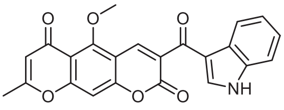
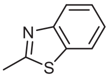
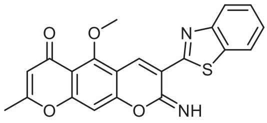
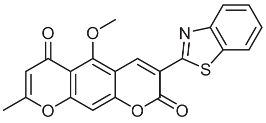
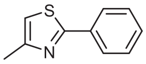
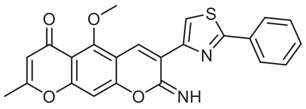
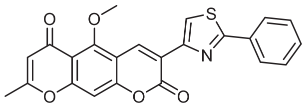
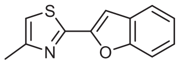
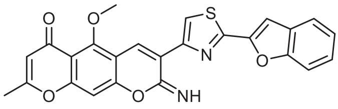
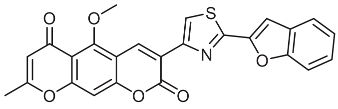
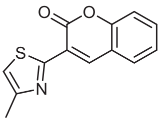
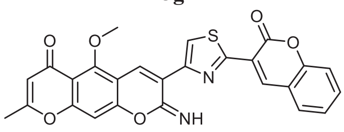
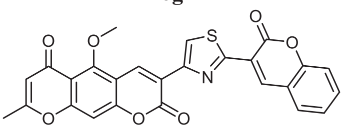
Results and discussion

In this investigation, we report the synthesis of linear 2-imino-2*H*,6*H*-pyrano[3,2-*g*]chromene-6-ones and 2*H*,6*H*-pyrano[3,2-*g*]chromene-2,6-diones as summed up in Scheme 1. 6-Formyl-7-hydroxy-5-methoxy-2-methylchromone (**2**) was used as the starting material, **2** was obtained by potassium dichromate oxidation of the naturally occurring furochromone; visnagin (**1**).[17]

Kenovenagel condensation of **2** with some prepared nitrile derivatives possessing an active methylene group **3a-h**, namely 3-oxo-3-phenylpropanenitrile (**3a**),[18] 3-(benzo-furan-2-yl)-3-oxopropanenitrile (**3b**),[19,20] 3-(5-bromobenzofuran-2-yl)-3-oxopropane-nitrile

Table 1. Linear 2*H*,6*H*-pyrano[3,2-*g*]chromenes **5a–h** and **6a–h**.



R	5a-h	6a-h
	 **5a**	 **6a**
	 **5b**	 **6b**
	 **5c**	 **6c**
	 **5d**	 **6d**
	 **5e**	 **6e**
	 **5f**	 **6f**
	 **5g**	 **6g**
	 **5h**	 **6h**

(**3c**),[21] 3-(1*H*-indol-3-yl)-3-oxopropanenitrile (**3d**),[22] 2-(benzo[*d*]thiazol-2-yl) acetonitrile (**3e**),[23] 2-(2-phenylthiazol-4-yl)acetonitrile (**3f**),[24] 2-(2-(benzo-furan-2-yl) thiazol-4-yl)acetonitrile (**3g**) and 2-(2-(2-oxo-2*H*-chromen-3-yl)thiazol-4-yl) acetonitrile (**3h**),[25] respectively, under stirring in presence of piperidine led to the formation of 3-substituted-2-imino-5-methoxy-8-methyl-2*H*,6*H*-pyrano[3,2-*g*] chromen-6-one (**5a–h**) (Table 1). Compounds **5a–h** were also formed when the reaction was carried out in presence of 2 drops of piperidine under grinding for 5 min; which gave products identical in all aspects (mp, admixed mp) with no difference in their yields.

It was difficult to dissolve most of the target compounds even in DMSO or TFA in order to elucidate their structures. Accordingly, the target compounds have ascertained based on their elemental analysis and IR spectra. A few of compounds were elucidated based on their ^{1}H NMR and ESI (LC-MS) spectra.

Compounds **5a–h** were subjected to hydrolysis via their reaction with 10% of hydrochloric acid under stirring to furnish 2*H*,6*H*-pyrano[3,2-*g*]chromene-2,6-diones **6a–h** (Scheme 1, Table 1). Most of compounds **6a–h** experiences the same behavior as the first compounds **5a–h**, where they're not dissolved even in DMSO or TFA. Accordingly, the target compounds were ascertained on the basis of their elemental analysis and IR spectra. A few of compounds have elucidated based on their ^{1}H NMR and ESI (LC-MS) spectra.

Evaluation of *in vitro* anticancer activity

The newly synthesized compounds were selected by the National Cancer Institute, (NCI, Bethesda, Maryland, USA), to be evaluated *in vitro* towards a panel of the approximately 60 human tumors cell lines; derived from the nine different cancer types including leukemia, breast, ovarian, prostate, non-small cell lung, colon, CNS, melanoma and renal cancers at a single concentration of (10^{-5} M).[26–28] The results are summed up in Table S1 (Supporting Information) as growth inhibition percent (GIP) and delta values. The result indicate that, compounds **5d, 5e, 6e, 6c** and **6f** showed mild activity with growth inhibition (GI) of 28.90, 28.98, 27.29, 25.39 and 28.52%, respectively on the Renal Cancer UO-31; whereas **6b** showed moderate activity toward the same cancer cell with growth inhibition (GI) of 35.7%. Besides, compounds **5d** exerted moderate growth inhibition (GI) activity towards Non-Small Cell Lung Cancer (HOP-92) by 31.64%. In addition, compound **6e** showed moderate growth inhibition (GI) activity against Melanoma (UACC-62) by 32.28%. The rest of the tested compounds showed little to no effect on the human cancer cells under investigated.

Experimental

All reagents and solvents were of commercial grade. Visnagin **1** has been purchased from Chemical industries development CID, Giza (Egypt). Melting points were determined on the digital melting point apparatus (Electro thermal 9100, Electro thermal Engineering Ltd, serial No. 8694, Rochford, United Kingdom) and were uncorrected. Elemental analyses were performed on CHNS-O analyzer (Perkin-Elmer, USA) and were found within ±0.4% of the theoretical values.1H and 13C NMR spectra were measured with a Bruker Avance spectrometer (Bruker, Germany) at 400 and 101 MHz, respectively, using TMS as the internal standard. Hydrogen coupling patterns are described as (s) singlet, (d) doublet, (t) triplet, (q) quartet and (m) multiplet. The chemical shifts were defined as parts per million (ppm) relative to the solvent peak. The mass spectra (ESI) were measured with Liquid Chromatography Mass Spectrometry (LC-MS) using Multimode Source for 6100 Series Single Quad LC/MS. The reaction progress was checked by pre-coated TLC Silica gel 0.2 nm F_{254} nm [Fluka], visualized under UV lamp 254 and 365 nm.

General procedure for the preparation of 3-substituted-2-imino-5-methoxy-8-methyl-2*H*,6*H*-pyrano[3,2-*g*]chromen-6-one (5a–h)

Method 1

To a mixture of **2** (0.23 g, 1 mmol) and the appropriate acetonitrile derivatives **3a–h** (1 mmol) in ethanol (5 ml), was added two drops of piperidine under stirring at room temperature. After 10–15 min, the precipitate that formed was collected by filtration, then crystallized from *N,N*-dimethylformamide to obtain pure products.

Method 2

A mixture of **2** (0.23 g, 1 mmol) and the appropriate acetonitrile derivatives **3a–h** (1 mmol) containing two drops of piperidine was ground in a mortar with a pestle at room temperature for 2–3 min. After 5 min, a drop was taken out of the reaction mixture and dissolved in acetone to follow the progress of the reaction using TLC. After completion of the reaction, the mixture was transferred by ethanol then filtered off. The obtained solid was crystallized from *N,N*-dimethylformamide to obtain pure products.

2-Imino-5-methoxy-8-methyl-3-(2-phenylthiazol-4-yl)-2*H*, 6 *H*-pyrano[3,2-*g*]chromen-6-one (5 h)

Dark brown powder; yield 70%; mp 221-3 °C; FT-IR (KBr, ν cm^{-1}) 3262 (NH), 1714, 1667 (2C = O), 1618 (C = N), 1588 (C = C); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.90 (s, 1H, NH), 8.04 (s, 2H), 7.69 (s, 1H), 7.50 (t, J = 7.6 Hz, 2H), 7.40 (s, 1H), 7.28 (s, 1H), 6.94 (s, 1H), 6.09 (s, 1H), 4.10 (s, 3H, OCH_3), 2.37 (s, 3H, CH_3); **HRMS** (ESI): *m/z* $[M+Na]^+$ calcd for $C_{23}H_{16}N_2O_4S$ (416.45); found: 416.8; Anal Calcd for $C_{23}H_{16}N_2O_4S$: C, 66.34; H, 3.87; N, 6.73; S, 7.70; found: C, 66.30; H, 3.85; N, 6.69; S, 7.61.

Disclosure statement

No potential conflict of interest was reported by the authors.

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