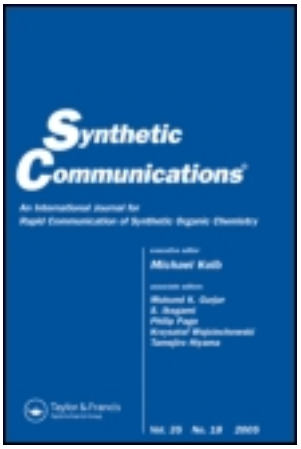

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One-Pot Synthesis of 2-Amino-5,10-dihydro-5,10-dioxo-4-phenyl-4H-benzo[g]chromene Derivatives Catalyzed by $ZnCl_2$

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ONE-POT SYNTHESIS OF 2-AMINO-5,10-DIHYDRO-5, 10-DIOXO-4-PHENYL-4*H*-BENZO[g]CHROMENE DERIVATIVES CATALYZED BY $ZnCl_2$

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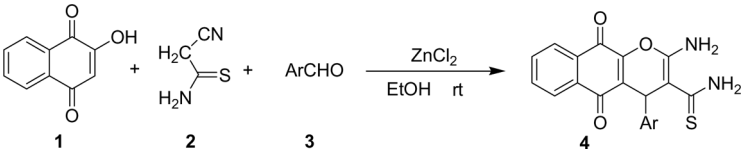
GRAPHICAL ABSTRACT



Abstract *An efficient one-pot synthesis of 2-amino-5,10-dihydro-5,10-dioxo-4-phenyl-4*H*-benzo[g]chromene derivatives has been achieved by the reaction of 2-hydroxynaphthalene-1, 4-dione, cyanothioacetamide, and aromaticaldehyde in EtOH at room temperature catalyzed by $ZnCl_2$. The structures of the products were characterized by infrared, ^1H NMR, mass, and elemental analysis.*

Keywords Benzo[g]chromene; cyanothioacetamide; lawsone; one-pot synthesis; $ZnCl_2$

INTRODUCTION

The chromene moiety often appears as an important structural component in both biologically active and natural compounds. Chromene fragments occur in alkaloids, flavonoids, tocopherols, and anthocyanins. Moreover, functionally substituted chromenes have played increasing roles in synthetic approaches to promising compounds in the field of medicinal chemistry.[1–4]

Recently, the synthesis of particular groups of naturally occurring pyranonaphthoquinones, such as pentalongin,[5–7] dehydroherbarin,[8] several 1,3-disubstituted-3,4-dehydropyranonaphthoquinones,[9] and 3-arylpyranonaphthoquinones[10,11] have been reported. The biological activities of these compounds were investigated too.[12] For example, pentalongin is a natural product, which is reported in Rwanda and Kenya for the treatment of malaria and skin diseases. These compounds have been synthesized via a multistep approach in the presence of transition-metal catalysts under sensitive conditions.[8,9] These compounds were semisynthetically obtained from lapachol.[13]

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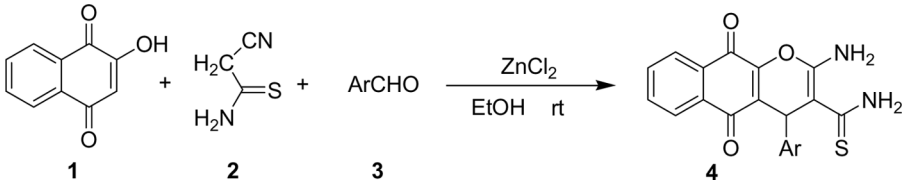


Scheme 1. Reaction of 2-hydroxynaphthalene-1,4-dione, cyanothioacetamide, and aromatic aldehydes.

Multicomponent reactions (MCRs), because of their productivity, simple procedures, convergence, and facile execution, are some of the best tools in combinatorial chemistry. Therefore, the design of novel MCRs has attracted great attention from research groups working in areas such as drug discovery, organic synthesis, and materials science.[14–20]

As part of our continuing interest in the development of new synthetic methods in heterocyclic chemistry and our interest in MCRs,[21,22] herein we describe an efficient synthesis of 4*H*-benzo[g]chromene **4** via a three-component reaction. 2-Hydroxynaphthalene-1,4-dione (**1**), cyanothioacetamide (**2**), and aromaticaldehyde (**3**) were treated with $ZnCl_2$ in ethyl alcohol at room temperature, which resulted in the formation of 2-amino-5,10-dihydro-5,10-dioxo-4-phenyl-4*H*-benzo[g] chromene derivatives (**4**) (Scheme 1). As shown in Table 1, we can see a series of **3** reacted with **1** and **2** to give the corresponding products **4** in good yields under the same reaction conditions.

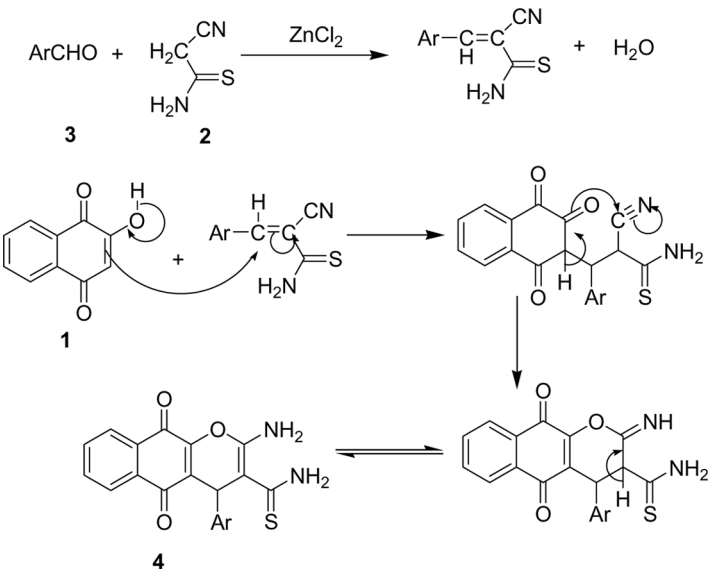
The structures of the products were deduced from their infrared (IR), ^{1}H NMR, and mass spectra. The mass spectra of these compounds displayed molecular ion peaks at the appropriate m/z values. The ^{1}H NMR spectrum of **4a** consists of a singlet for the NMe_2 ($\delta = 3.07$ ppm), a singlet for the CH of the pyran ring ($\delta = 8.05$ ppm), a multiplet for aromatic protons ($\delta = 7.85$–7.90 ppm), two multiplets for quinone aromatic protons ($\delta = 7.95$–7.98 and 8.00–8.05 ppm), a singlet for NH_2 ($\delta = 9.15$ ppm), and another singlet for thioamide NH_2 ($\delta = 9.70$ ppm) protons.

The plausible mechanism for the formation of **4** is proposed in Scheme 2.

In conclusion, we have demonstrated a novel, one-pot, three-component reaction that offers a facile and efficient route for the synthesis of 2-amino-5,10-dihydro-5,10-dioxo-4-phenyl-4*H*-benzo[g]chromene derivatives. This method has

Table 1. The products **4**

S. no.	Compound	Ar
1	**4a**	p-N,N-Dimethylaminophenyl
2	**4b**	Phenyl
3	**4c**	p-Tolyl
4	**4d**	4-Methoxyphenyl
5	**4e**	o-Hydroxyphenyl
6	**4f**	p-Hydroxyphenyl
7	**4g**	o-Hydroxy-m-methoxyphenyl
8	**4f**	3,4,5-Trimethoxyphenyl
9	**4h**	2-Hydroxynapththyl



Scheme 2. Mechanism of the reaction.

some advantages, such as milder conditions, simplicity of the reaction, easy workup procedure, and good product yields.

EXPERIMENTAL

Melting points were determined in open capillaries with a Cintex melting-point apparatus (Mumbai, India). Melting points are uncorrected, and CHNS analysis was done on a Carlo Erba EA 1108 automatic elemental analyzer. The purity of the compounds was checked by thin-layer chromotography (TLC) plates (E. Merek, Mumbai, India), and IR spectra (KBr) were recorded on a BrukerWM-4(X) spectrometer (577model). ^{1}H NMR spectra were recorded on a Bruker WM 400-MHz spectrometer in δ ppm using tetromethylsilane (TMS) as internal standard. The NH protons were exchanged with D_2O. Mass spectra (EI-MS) were determined on a Perkin-Elmer instrument (SCIEX API-2000, ESI) at 12.5 eV.

General Procedure for the Syntheses of 2-Amino-5,10-dihydro-5,10-dioxo-4-aryl-4*H*-benzo[g]chromene (4)

A dry 25-mL round-bottom flask was charged with 2-hydroxynaphthlene-1,4-dione **1** (1 mmol), cyanothioacetamide **2** (1 mmol), aromatic aldehyde **3** (1 mmol), $ZnCl_2$ (100 mg), and ethyl alcohol (10 mL). The mixture was stirred at room temperature for 5 h and then poured into 200 mL water. The solid was filtered off and washed with water. The crude product was purified by recrystallization from methanol to give **4**.

Data

2-Amino-4-(4-(dimethylamino)phenyl)-5,10-dihydro-5,10-dioxo-4H-benzo[g]chromene-3-carbothioamide (4a). Compound **4a** was obtained in 85% yield. Mp 204–205 °C; IR (KBr) ν: 3301 (NH_2 stretching of $CSNH_2$), 3158 (NH_2), 1641 (quinone C=O), 1280 (C=S) cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) (δ ppm): 3.07 (6H, s, NMe_2), 7.85–8.03 (8H, m, ArH), 8.05 (1H, s, CH of pyran ring), 9.15 (2H, s, NH_2), 9.70 (2H, s, NH_2). Anal. calcd. for $C_{22}H_{19}N_3O_3S$: C, 65.17; H, 4.72; N, 10.36; S, 7.91. Found: C, 65.12; H, 4.80; N, 10.39; S, 7.98.

2-Amino-5,10-dihydro-5,10-dioxo-4-phenyl-4H-benzo[g]chromene-3-carbothioamide (4b). Compound **4b** was obtained in 90% yield. Mp 174–175 °C; IR (KBr) ν: 3318 (NH_2 stretching of $CSNH_2$), 3202 (NH_2), 1624 (quinone C=O), 1277 (C=S) cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) (δ ppm): 7.65–8.03 (9H, m, ArH), 8.05 (1H, s, CH of pyran ring), 9.78 (2H, s, NH_2), 10.10 (2H, s, NH_2). Anal. calcd. for $C_{20}H_{14}N_2O_3S$: C, 66.28; H, 3.89; N, 7.73; S, 8.85. Found: C, 66.24; H, 3.84; N, 7.77; S, 8.89.

2-Amino-5,10-dihydro-5,10-dioxo-4-p-tolyl-4H-benzo[g]chromene-3-carbothioamide (4c). Compound **4c** was obtained in 89% yield. Mp 126–127 °C; IR (KBr) ν: 3356 (NH_2 stretching of $CSNH_2$), 3290 (NH_2), 1638 (quinone C=O), 1281 (C=S) cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) (δ ppm): 2.40 (3H, s, CH_3), 7.83–8.03 (8H, m, ArH), 8.05 (1H, s, CH of pyran ring), 9.58 (2H, s, NH_2), 10.10 (2H, s, NH_2). Anal. calcd. for $C_{21}H_{16}N_2O_3S$: C, 67.00; H, 4.28; N, 7.44; S, 8.52. Found: C, 67.10; H, 4.31; N, 7.48; S, 8.55.

2-Amino-5,10-dihydro-4-(4-methoxyphenyl)-5,10-dioxo-4H-benzo[g]-chromene-3-carbothioamide (4d). Compound **4d** was obtained in 90% yield. Mp 181–182 °C; IR (KBr) ν: 3396 (NH_2 stretching of $CSNH_2$), 3316 (NH_2), 1640 (quinone C=O), 1259 (C=S) cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) (δ ppm): 3.87 (3H, s, OCH_3), 7.17–8.03 (8H, m, ArH), 8.05 (1H, s, CH of pyran ring), 9.50 (2H, s, NH_2), 10.00 (2H, s, NH_2). Anal. calcd. for $C_{21}H_{16}N_2O_4S$: C, 64.27; H, 4.11; N, 7.14; S, 8.17. Found: C, 64.22; H, 4.15; N, 7.17; S, 8.19.

2-Amino-5,10-dihydro-4-(2-hydroxyphenyl)-5,10-dioxo-4H-benzo[g]-chromene-3-carbothioamide (4e). Compound **4e** was obtained in 88% yield. Mp 207–208 °C; IR (KBr) ν: 3422 (NH_2 stretching of $CSNH_2$), 1609 (quinone C=O), 1271 (C=S) cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) (δ ppm): 6.25 (1H, s, OH), 7.40–8.03 (8H, m, ArH), 9.00 (1H, s, CH of pyran ring), 9.80 (2H, s, NH_2), 10.35 (2H, s, NH_2). Anal. calcd. for $C_{20}H_{14}N_2O_4S$: C, 63.48; H, 3.73; N, 7.40; S, 8.47. Found: C, 63.44; H, 3.77; N, 7.45; S, 8.49.

2-Amino-5,10-dihydro-4-(4-hydroxyphenyl)-5,10-dioxo-4H-benzo[g]-chromene-3-carbothioamide (4f). Compound **4f** was obtained in 92% yield. Mp > 300 °C; IR (KBr) ν: 3326 (NH_2 stretching of $CSNH_2$), 1587 (quinone C=O), 1274 (C=S) cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) (δ ppm): 7.83–8.03 (8H, m, ArH), 8.05 (1H, s, CH of pyran ring), 8.98 (2H, s, NH_2), 10.10 (2H, s, NH_2), 10.60 (1H, s, OH). Anal. calcd. for $C_{20}H_{14}N_2O_4S$: C, 63.48; H, 3.73; N, 7.40; S, 8.47. Found: C, 63.50; H, 3.77; N, 7.44; S, 8.50.

2-Amino-5,10-dihydro-4-(2-hydroxy-3-methoxyphenyl)-5,10-dioxo-4H-benzo[g]chromene-3-carbothioamide (4g). Compound **4g** was obtained in 89% yield. Mp 110–111 °C; IR (KBr) ν: 3402 (NH_2 stretching of $CSNH_2$), 1587 (quinone C=O), 1274 (C=S) cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) (δ ppm): 3.98 (3H, s, OCH_3), 6.23 (1H, s, OH), 7.38–8.00 (7H, m, ArH), 8.98 (1H, s, CH of pyran ring), 8.80 (2H, s, NH_2), 10.38 (2H, s, NH_2). Anal. calcd. for $C_{21}H_{16}N_2O_5S$: C, 61.76; H, 3.95; N, 6.86; S, 7.85. Found: C, 61.71; H, 3.91; N, 6.89; S, 7.89.

2-Amino-5,10-dihydro-4-(3,4,5-trimethoxyphenyl)-5,10-dioxo-4H-benzo[g]chromene-3-carbothioamide (4h). Compound **4h** was obtained in 91% yield. Mp 192–193 °C; IR (KBr) ν: 3394 (NH_2 stretching of $CSNH_2$), 1577 (quinone C=O), 1271 (C=S) cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) (δ ppm): 3.82 (3H, s, OCH_3), 7.70–8.00 (6H, m, ArH), 8.08 (1H, s, CH of pyran ring), 9.56 (2H, s, NH_2), 10.08 (2H, s, NH_2). Anal. calcd. for $C_{23}H_{20}N_2O_6S$: C, 61.05; H, 4.46; N, 6.19; S, 7.09. Found: C, 61.12; H, 4.49; N, 6.15; S, 7.10.

2-Amino-5,10-dihydro-4-(2-hydroxynaphthalen-1-yl)-5,10-dioxo-4H-benzo[g]chromene-3-carbothioamide (4i). Compound **4i** was obtained in 90% yield. Mp 180–181 °C; IR (KBr) ν: 3429 (NH_2 stretching of $CSNH_2$), 1587 (quinone C=O), 1271 (C=S) cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) (δ ppm): 7.50–8.00 (10H, m, ArH), 8.10 (1H, s, CH of pyran ring), 9.40 (2H, s, NH_2), 10.72 (2H, s, NH_2), 10.80 (1H, s, OH). Anal. calcd. for $C_{24}H_{16}N_2O_4S$: C, 67.28; H, 3.76; N, 6.54; S, 7.48. Found: C, 67.23; H, 3.79; N, 6.59; S, 7.51.

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