Zinc Chloride-Catalyzed One-Pot, Three-Component Synthesis of 5,8-Dihydro-5,8-dioxo-4*H*-chromene Derivatives

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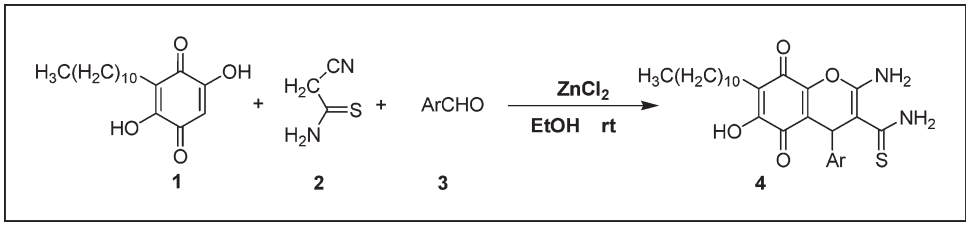

An efficient zinc chloride-catalyzed one-pot synthesis of 5,8-dihydro-5,8-dioxo-4*H*-chromene derivatives have been achieved by the reaction of 2,5-dihydroxy-6-undecyl-1,4-bezoquinone, cyanothioacetamide, and aromaticaldehyde, in EtOH at room temperature. The structures of the products were characterized by IR, ^{1}H-NMR, mass spectra, and elemental analyses.

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INTRODUCTION

Mass screening program of natural product by the National Cancer Institute has been identified the quinone moiety as an important pharmacophoric element for cytotoxic activity [1,2]. Compounds containing the quinone group represent an important class of biologically active molecules that are widespread in nature [3]. The chemistry of quinones is largely dependent on the substituent being either on the quinonic or on adjacent rings. This is reflected in their chemical reactivity, especially in heterocyclic quinones [4]. The efficiency of the quinonic compounds in inhibiting cancer cell growth is believed to stem from their participation in key cellular redox mechanisms with consequent generation of highly reactive oxygen species (ROS). The ROS turn out to modify and degrade nucleic acids and proteins within the cells [5,6].

One of the most simple 1,4-benzoquinonic compound isolated from natural sources is embelin (**1**). Compound **1** shows a diversity of relevant biological activities such as chemopreventive effect against DENA/PB-induced hepatocarcinogenesis in Wistar rats [7], antifertility effects [8], and *in vitro* cytotoxic activity against B16 and XC cell lines [9]. In addition, recent studies have shown that embelin is a fairly potent, nonpeptidic, cell-permeable inhibitor of XIAP (X-linked inhibitor of apoptosis protein), and it represents a promising lead compound for designing an entirely new class of anticancer agents that target the BIR3 domain of XIAP [10,11].

From the above facts, we are interested in developing newer synthetic methods for the construction of embelin derivatives. As a part of our continuing interest in the development of new synthetic methods in heterocyclic chemistry and multicomponent reactions [12,13], herein we describe an efficient synthesis of 5,8-dihydro-5,8-dioxo-4*H*-chromene derivatives *via* a three-component reaction.

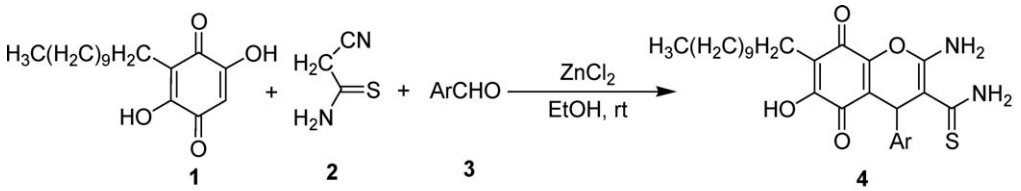
RESULTS AND DISCUSSION

The one-pot, three-component condensation reactions of embelin (**1**) with cyanothioacetamide (**2**) and aromatic aldehydes (**3**) in the presence of $ZnCl_2$ in EtOH at room temperature afforded corresponding 2-amino-4-(substitutedphenyl)-5,8-dihydro-6-hydroxy-5,8-dioxo-7-undecyl-4*H*-chromene-3-carbothioamides (**4**) in good yields (Scheme 1).

The mechanism of the reaction can be explained by the fact that in the presence of Lewis acid, cyanothioacetamide **2** reacts with aldehyde **3** to afford intermediate **5** (Scheme 2). The intermediate **5** on reaction with embelin can form another intermediate **6**. Compound **6** on cyclization will give the product **4**.

The compound **4a** can also be prepared by alternative stepwise method (Scheme 3). Involving condensation of embelin with **5a** resulted in the formation of **4a**. The compound **5a** was prepared by following the literature procedure [14]. The yields of the products are good in a one-step process (85–93%). Compounds obtained by both the methods were found to be identical by mixed melting points measurements and co-TLC and spectral data. The product **4** was shown to have quinone moiety intact by its behavior toward Zn/AcOH in a reduction and re-aerial oxidation test. The structures of **4a–i** were

Scheme 1. One-pot reaction of 2,5-dihydroxy-6-undecyl-1,4-bezoquinone, cyanothioacetamide, and aromatic aldehydes.



1 **2** **3** **4**

4	Ar
a	p-N,N-Dimethylaminophenyl
b	Phenyl
c	p-Chlorophenyl
d	p-Methylphenyl
e	p-Methoxyphenyl
f	o-Hydroxyphenyl
g	p-Hydroxyphenyl
h	m,m,p-Trimethoxyphenyl
i	2-Hydroxynaphthyl

confirmed from their analytical, 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 triplet for the end CH_3 of alkyl group ($\delta = 0.87$ ppm), a multiplet for —$(CH_2)_9$— ($\delta = 1.20$–1.30 ppm), a triplet for allylic CH_2 ($\delta = 2.35$ ppm), a singlet for the NMe_2 ($\delta = 3.14$ ppm), two doublets for aromatic protons ($\delta = 6.71$ ppm and $\delta = 7.98$ ppm), a singlet for NH_2 ($\delta = 7.35$ ppm) and another singlet to thioamide NH_2 ($\delta = 7.45$ ppm) protons, and a singlet for the CH of pyran ring ($\delta = 8.68$ ppm).

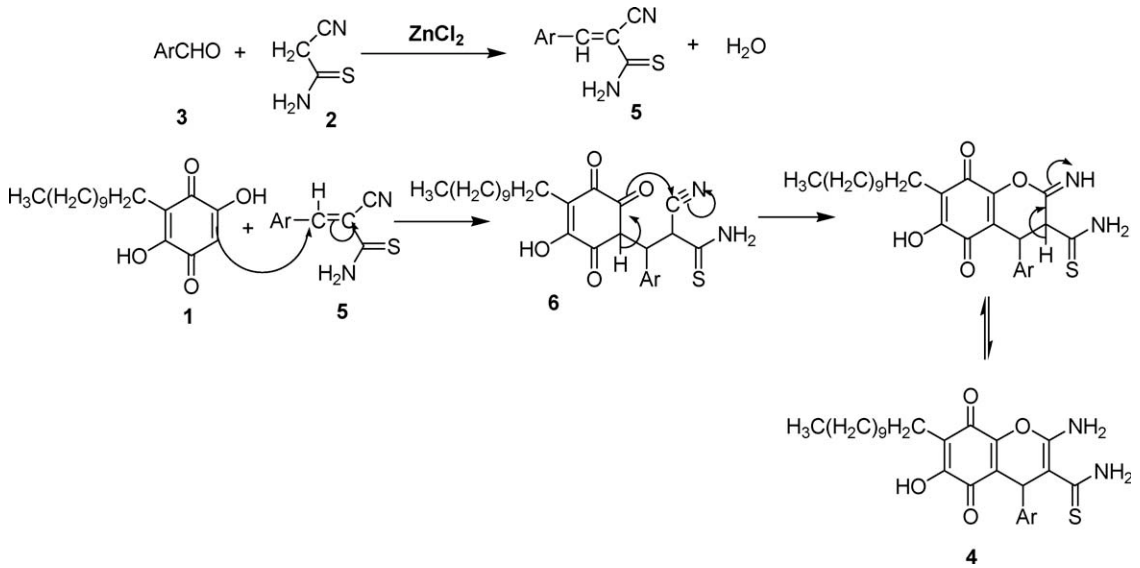
EXPERIMENTAL

Melting points were determined in open capillaries with a ''cintex'' melting point apparatus, Mumbai, India. Melting points were uncorrected, and CHNS analysis was done by Carlo Erba EA 1108 automatic elemental analyzer. The purity of the compounds was checked by TLC plates (E.Merek, Mumbai, India). 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 TMS as internal standard. The NH protons were exchanged with D_2O. Mass spectra (EI-MS) were determined on a Perkin Elmer (SCIEX API-2000, ESI) at 12.5 eV.

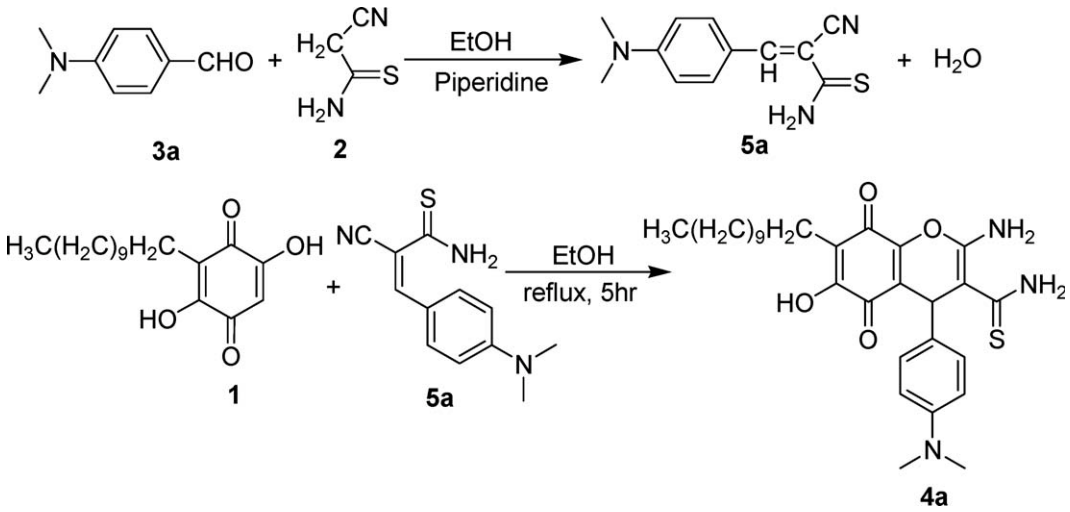
General procedure synthesis of 2-amino-5,8-dihydro-6-hydroxy-5,8-dioxo-4-ary-7-undecyl-4*H*-chromene-3-carbothioamide (4). A mixture of 2,5-dihydroxy-6-undecyl-1,4-bezoquinone (1 mmol), cyanothioacetamide (1 mmol) and aromatic aldehydes (1 mmol) and $ZnCl_2$ (100 mg) in ethyl alcohol (10 mL) was stirred at room temperature for 5 h. Then the reaction mixture was cooled and poured into cold water, and the solid separated was filtered off. The crude product was purified by recrystallization from ethanol to give **4**.

Synthesis of 2-amino-4-(4-(dimethylamino)phenyl)-5,8-dihydro-6-hydroxy-5,8-dioxo-7-undecyl-4*H*-chromene-3-carbothioamide (4a). An equimolar mixture of 2,5-dihydroxy-6-undecyl-1,4-bezoquinone (1 mmol) and 2-cyano-3-(4-

Scheme 2. Mechanism of the reaction.



Scheme 3. Stepwise synthesis of **4a**.



(dimethylamino)phenyl)prop-2-enethioamide (**5a**; 1 mmol) was refluxed in ethanol in the presence of piperidine for 3 h. The reaction mixture was cooled, and the solid separated was filtered and recrystallised from ethanol.

2-Amino-4-(4-(dimethylamino)phenyl)-5,8-dihydro-6-hydroxy-5,8-dioxo-7-undecyl-4H-chromene-3-carbothioamide (4a). Brown solid, yield 85%, m.p. 199–200°C; IR (KBr) ν: 3288 (NH_2 stretching of $CSNH_2$), 3152 (NH_2), 1612 (quinone C=O), 1376 (C=S) cm^{-1}; ^{1}H-NMR (400 MHz, DMSO-d_6) (δ ppm): 0.87 (t, 3H, end CH_3), 1.20–1.30 (m, 18H, —$(CH_2)_9$—), 2.35 (t, 2H, allylic CH_2), 3.14 (s, 6H, NMe_2), 6.71 (d, 2H, J = 6.9 Hz, ArH), 7.98 (d, 2H, J = 6.67Hz, ArH), 7.35 (bs, 2H, NH_2), 7.45 (bs, 2H, NH_2), 8.68 (s, 1H, CH of pyran ring). EI-MS m/z 525 (M^+); Anal. calcd. for $C_{29}H_{39}N_3O_4S$: C, 66.26; H, 7.48; N, 7.99; S, 6.10. Found: C, 66.29; H, 7.51; N, 7.94; S, 6.12%.

2-Amino-5,8-dihydro-6-hydroxy-5,8-dioxo-4-phenyl-7-undecyl-4H-chromene-3-carbothioamide (4b). Black solid, yield 89%, m.p. 187–188°C; IR (KBr) ν: 3329 (NH_2 stretching of $CSNH_2$), 3210 (NH_2), 1620 (quinone C=O), 1370 (C=S) cm^{-1}; ^{1}H-NMR (400 MHz, DMSO-d_6) (δ ppm): 0.83 (t, 3H, end CH_3), 1.22–1.30 (m, 18H, —$(CH_2)_9$—), 2.35 (t, 2H, allylic CH_2), 7.30–7.55 (m, 5H, ArH), 8.18 (s, 1H, CH of pyran ring). Anal. calcd. for $C_{27}H_{34}N_2O_4S$: C, 67.19; H, 7.10; N, 5.80; S, 6.64. Found: C, 67.16; H, 7.14; N, 5.84; S, 6.61%.

2-Amino-4-(4-chlorophenyl)-5,8-dihydro-6-hydroxy-5,8-dioxo-7-undecyl-4H-chromene-3-carbothioamide (4c). Black solid, yield 90%, m.p. 208–209°C; IR (KBr) ν: 3330 (NH_2 stretching of $CSNH_2$), 3215 (NH_2), 1624 (quinone C=O), 1366 (C=S) cm^{-1}; ^{1}H-NMR (400 MHz, DMSO-d_6) (δ ppm): 0.83 (t, 3H, end CH_3), 1.22–1.30 (m, 18H, —$(CH_2)_9$—), 2.35 (t, 2H, allylic CH_2), 7.52–7.65 (m, 4H, ArH), 8.45 (s, 1H, CH of pyran ring). Anal. Calcd. for $C_{27}H_{33}ClN_2O_4S$: C, 62.72; H, 6.43; N, 5.42; S, 6.20. Found: C, 62.70; H, 6.47; N, 5.45; S, 6.24%.

2-Amino-5,8-dihydro-6-hydroxy-5,8-dioxo-4-p-tolyl-7-undecyl-4H-chromene-3-carbothioamide (4d). Green solid, yield 91%, m.p. 162–163°C; IR (KBr) ν: 3357 (NH_2 stretching of $CSNH_2$), 3288 (NH_2), 1640 (quinone C=O), 1291 (C=S) cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) (δ ppm): 0.83 (t, 3H, end CH_3), 1.22–1.30 (m, 18H, —$(CH_2)_9$—), 2.25 (t, 2H, allylic CH_2), 2.46 (s, 3H, p-CH_3), 7.24 (d, 2H, ArH), 7.78 (d, 2H, ArH), 8.05 (s, 1H, CH of pyran ring), 9.68 (bs, 2H, NH_2), 10.05 (bs, 2H, NH_2). Anal. calcd. for $C_{28}H_{36}N_2O_4S$: C, 67.71; H, 7.31; N, 5.64; S, 6.46. Found: C, 67.74; H, 7.34; N, 5.68; S, 6.48%.

2-Amino-5,8-dihydro-6-hydroxy-4-(4-methoxyphenyl)-5,8-dioxo-7-undecyl-4H-chromene-3-carbothioamide (4e). Light yellow solid, yield 85%, m.p. 176–177°C; IR (KBr) ν: 3396 (NH_2 stretching of $CSNH_2$), 3315 (NH_2), 1641 (quinone C=O), 1257 (C=S) cm^{-1}; ^{1}H-NMR (400 MHz, DMSO-d_6) (δ ppm): 0.84 (t, 3H, end CH_3), 1.22–1.30 (m, 18H, —$(CH_2)_9$—), 2.35 (t, 2H, allylic CH_2), 3.86 (s, 3H, p-OCH_3), 7.14 (d, 2H, J = 6.6Hz, ArH), 7.97 (d, 2H, J = 6.3Hz, ArH), 8.06 (s, 1H, CH of pyran ring), 9.48 (bs, 2H, NH_2), 9.98 (bs, 2H, NH_2). Anal. calcd. for $C_{28}H_{36}N_2O_5S$: C, 65.60; H, 7.08; N, 5.46; S, 6.25. Found: C, 65.63; H, 7.00; N, 5.44; S, 6.28%.

2-Amino-5,8-dihydro-6-hydroxy-4-(2-hydroxyphenyl)-5,8-dioxo-7-undecyl-4H-chromene-3-carbothioamide (4f). Brown solid, yield 89%, m.p. 189–190°C; IR (KBr) ν: 3435 (NH_2 stretching of $CSNH_2$), 3291 (NH_2), 1611 (quinone C=O), 1359 (C=S) cm^{-1}; ^{1}H-NMR (400 MHz, DMSO-d_6) (δ ppm): 0.85 (t, 3H, end CH_3), 1.20–1.30 (m, 18H, —$(CH_2)_9$—), 2.35 (t, 2H, allylic CH_2), 7.40–7.48 (m, 2H, ArH), 7.78–7.80 (m, 1H, ArH), 7.98 (d, 1H, J = 6 Hz, ArH), 8.98 (s, 1H, CH of pyran ring), 9.80 (bs, 2H, NH_2), 10.30 (bs, 2H, NH_2). Anal. calcd. for $C_{27}H_{34}N_2O_5S$: C, 65.04; H, 6.87; N, 5.62; S, 6.43. Found: C, 65.00; H, 6.85; N, 5.65; S, 6.47%.

2-Amino-5,8-dihydro-6-hydroxy-4-(4-hydroxyphenyl)-5,8-dioxo-7-undecyl-4H-chromene-3-carbothioamide (4g). Green solid, yield 93%, m.p. 171–172°C; IR (KBr) ν: 3422 (NH_2 stretching of $CSNH_2$), 3242 (NH_2), 1612 (quinone C=O), 1369 (C=S) cm^{-1}; ^{1}H-NMR (400 MHz, DMSO-d_6) (δ ppm): 0.84 (t, 3H, end CH_3), 1.18–1.30 (m, 18H, —$(CH_2)_9$—), 2.28 (t, 2H, allylic CH_2), 6.96 (d, 2H, J = 6Hz, ArH), 7.95 (d, 2H, J = 6.6Hz, ArH), 8.10 (s, 1H, CH of pyran ring), 9.48 (bs, 2H, NH_2), 9.95 (bs, 2H, NH_2). Anal. calcd. for $C_{27}H_{34}N_2O_5S$: C, 65.04; H, 6.87; N, 5.62; S, 6.43. Found: C, 65.10; H, 6.89; N, 5.65; S, 6.40%.

2-Amino-5,8-dihydro-6-hydroxy-4-(3,4,5-trimethoxyphenyl)-5,8-dioxo-7-undecyl-4H-chromene-3-carbothioamide (4h). Yellow solid, yield 91%, m.p. 197–198°C; IR (KBr) ν: 3393 (NH_2

stretching of $CSNH_2$), 3260 (NH_2), 1633 (quinone C=O), 1335 (C=S) cm^{-1}; ^{1}H-NMR (400 MHz, DMSO-d_6) (δ ppm): 0.83 (t, 3H, end CH_3), 1.22–1.30 (m, 18H, —$(CH_2)_9$—), 2.35 (t, 2H, allylic CH_2), 3.85 (s, 3H, OCH_3), 3.91 (s, 6H, OCH_3), 7.44 (s, 2H, ArH), 8.15 (s, 1H, CH of pyran ring), 9.64 (bs, 2H, NH_2), 10.17 (bs, 2H, NH_2). Anal. calcd. for $C_{30}H_{40}N_2O_7S$: C, 62.91; H, 7.04; N, 4.89; S, 5.60. Found: C, 62.74; H, 7.00; N, 4.86; S, 5.64%.

2-Amino-5,8-dihydro-6-hydroxy-4-(2-hydroxynaphthalen-1-yl)-5,8-dioxo-7-undecyl-4H-chromene-3-carbothioamide (4i). Brown solid, yield 92%, m.p. 177–178°C; IR (KBr) ν: 3405 (NH_2 stretching of $CSNH_2$), 3306 (NH_2), 1689 (quinone C=O), 1343 (C=S) cm^{-1}; ^{1}H-NMR (400 MHz, DMSO-d_6) (δ ppm): 0.82 (t, 3H, end CH_3), 1.10–1.23 (m, 18H, —$(CH_2)_9$—), 2.31 (t, 2H, allylic CH_2), 7.74–7.80 (m, 2H, ArH), 7.85–7.90 (m, 1H, ArH), 8.13 (d, 1H, ArH), 8.32 (d, 1H, ArH), 8.60 (d, 1H, ArH), 9.81 (s, 1H, CH of pyran ring), 9.95 (bs, 2H, NH_2), 10.38 (bs, 2H, NH_2). Anal. calcd. for $C_{31}H_{36}N_2O_5S$: C, 67.86; H, 6.61; N, 5.11; S, 5.84. Found: C, 67.88; H, 6.58; N, 5.14; S, 5.82%.

CONCLUSIONS

We find a novel zinc chloride-catalyzed one-pot method for the synthesis of 5,8-dihydro-5,8-dioxo-4*H*-chromene derivatives. This method has an advantage of one-step, easy work-up, milder reaction conditions, and good yields.

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