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Authors: Hülya Çelik Onar, Didem Erdoğan
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Synthesis of novel 8-formyl-7-hydroxy-4-methylcoumarin derivatives

Hülya Çelik Onar*[1], Didem Erdoğan

Abstract

This study was initiated by 7-hydroxy-4-methylcoumarin **1** synthesis according to the Peckmann reaction with resorcinol and ethylacetoacetate. This compound was converted into 8-formyl-7-hydroxy -4-methylcoumarin **2** by the Duff reaction. This aldehyde obtained was reacted with 6-amino-1,4-benzodioxane and 2-amino benzamide, which have their specific biological activities, to synthesize the original two novel compounds. While **3** (*7-Hydroxy-4-methyl-8-[(2,3-dihydro-1,4-benzodioxin-6-yl)iminomethyl]-2H-1-benzopyran-2-one*) is obtained as a coumarin schiff base, ring closure was observed at **4** (*2-(2'-Hydoxy-5-methyl coumarin-1-yl)-2,3-dihydro quinazoline-4(1H)-one*). Our compounds are thought to exhibit biological activity. Their structures were identified by IR, ^{1}H NMR, ^{13}C NMR, MS analysis.

Keywords: Schiff base, coumarin, Pechmann reaction, Duff reaction, 6-amino-1,4-benzodioxane and 2-amino benzamide.

1.INTRODUCTION

An important class of heterocyclic compounds, 2,3-dihydroquinazoline-4(1H) are derived from 2-aminobenzamide and affect many cellular processes. These compounds; antitumor, anticancer, antibiotic, antipyretic and analgesic drugs, diuretic activities such as the wide pharmacological properties have been proven [1]. Some quinazolines have been reported to be potent chemotherapeutic agents in the treatment of tuberculosis [2]. The pharmacological and biological activities of 4(3H)-quinazoline derivatives have a broad spectrum. Some of the clinical drugs are based on this scaffold. In particular 2-substituted quinazolines; cholecystokinin (released in the small intestine), angiotensin and cell holding receptors for peptidomimetik scaffolding is evaluated as. Therefore, simple methods for the 4- (3H) -quinazoline structure are investigated [3]. It has been reported that 4-oxo-4H-1-benzopyran-3-carboxaldehyde, synthesized from 3-formyl chromon and 6-amino-1,4-benzodioxane, has a strong effect in suppressing liver cancer cells in man as the anticancer agent [4]. The biological activities of the amines used in the reaction have been proven. This condition has been taken into account when choosing.

Schiff bases are used in paint industry, rubber production, pharmaceutical industry, electronics industry, plastic industry, liquid crystal technology, mineral oils, as oxygen carriers because they are prone to oxygen bonding, in the synthesis of K-amino acids which are important for the organism, struggling against pathogenic fungi causing diseases and crop losses in plants, in

[1] Corresponding Author: email:hcelikonar@gmail.com, ORCID: 0000-0003-2573-5751

the determination of arsenic with AAS, in the masking of copper, nickel, platinum and the like, in the enrichment of radioactive materials, in the production of polymers and pesticides [5-11]. Many studies have been carried out on the synthesis of complexes of metal cations by Schiff bases in many fields of chemistry. Schiff bases have an important place in the pharmaceutical industry because of their antibacterial, antifungal, antitumor and anticancer activities [12]. The complexation of these biologically active compounds has been observed to result in enhanced bacteriostatic and carcinostatic properties [13]. Modeling of Schiff's complexes in biological systems and their use as enzyme inhibitors in pharmacological applications has allowed them to develop in bioinorganic chemistry [14]. Multi-threaded Schiff base complexes containing electron donor atoms such as nitrogen, oxygen, sulfur are important for biological systems [15,16]. For example, copper chelates are similar to copper-containing metalloproteins such as "hemocyanin" and "tyrosinase".

Coumarin (2H-1-benzopyran-2-one) derivatives, which have lactone structure, are common in plants alone or in combination. Antioxidant, anti-inflammatory, anti-tuberculosis, anti-tumor and anti-HIV activities of the coumarin derivatives have been proven. Coumarin based antibiotics such as Novobiocin and Cloribocin are commercially available. The presence of hydroxy and carboxy substituents in coumarin structure has been shown to increase antimicrobial activity. It is known that coumarin's Schiff bases and their metal complexes also have biological activity [17, 18]. In this study, two new coumarin derivatives, **3** (*7-Hydroxy-4-methyl-8-[(2,3-dihydro-1,4-benzodioxin-6-yl)imino methyl]-2H-1-benzopyran-2-one*) and **4** (*2-(2'-Hydoxy-5-methyl coumarin-1-yl)-2,3-dihydro quinazoline-4(1H)-one*), which we think have biological activities have been synthesized.

2. EXPERIMENTAL

2.1. Instruments

^{1}H NMR spectras were recorded in $CDCl_3$ on a BRUKER 500 MHz. ^{13}C NMR spectras were recorded in $CDCl_3$ or DMSO-d_6 on a VARIAN 125 MHz. Chemical shifts were reported in parts per million (ppm) using tetramethylsilane (TMS) as an internal standard. Infrared spectras were recorded in KBr on a Mattson 1000 FT-IR spectrophotometer in the 4000-400 cm^{-1} region. Melting points were detected on BUCHI B-540.

2.2. Synthesis of 7-hydroxy-4-methyl coumarin (1)

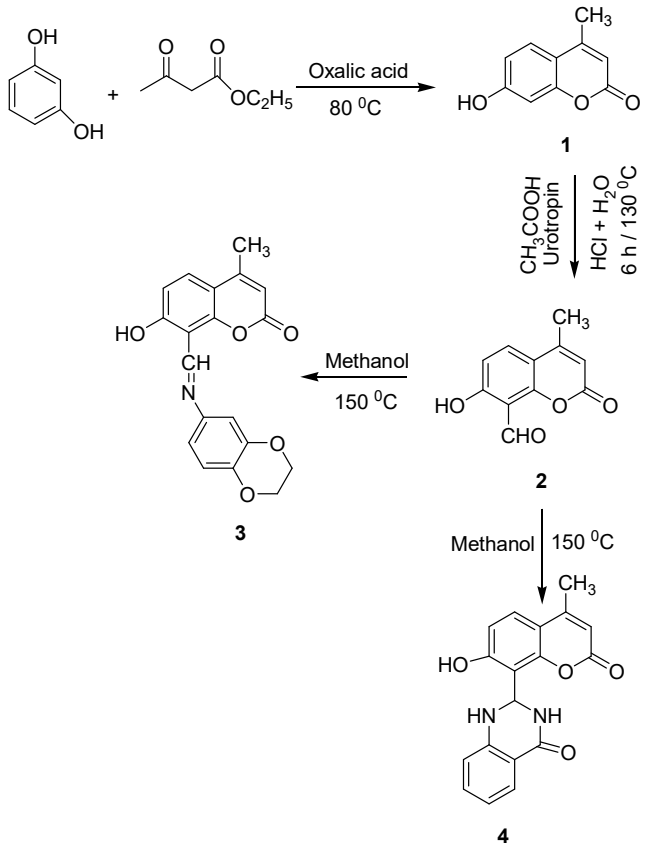
7-hydroxy-4-methylcoumarin was synthesized by reacting resorcinol (10 mmol, 1.1 g), ethylacetoacetate (20 mmol, 2.54 mL) and oxalic acid (1 mmol, 0.09 g) in a round bottom flask according to Pechmann reaction. Reaction mixture was refluxed at 80 ^{0}C until completion. Reaction was controlled by TLC. The product was filtered on a Buchner funnel. The solid was purified by recrystallization from ethanol. white solid, mp. 189.0-189.9 ^{0}C. yield: 85 % IR(KBr, cm^{-1}): 3500, 1669, 1615, 1284 ^{1}H-NMR (DMSO-d_6): 2.4 (s, -C<u>H</u>$_3$, 3H), 6.1 (s, Ar-H, 1H), 6.7 (s, Ar-H, 1H), 6.78-6.8 (dd, Ar-H, 1H, J_1= 2.44 J_2= 6.34), 7.56-7.6 (d, Ar-H, 1H, J=8.79), 10.5 (s, -O<u>H</u>, 1H).

2.3. Synthesis of 8-formyl-7-hydroxy-4-methylcoumarin (2)

8-formyl-7-hydroxy-4-methylcoumarin was synthesized by reacting 7-hydroxy-4-methylcoumarin **1** (0.56 mmol, 0.1 g), hexamethylenetetraamin (1.42 mmol,0.2 g) and 2 mL glacial acetic acid in a round bottom flask by Duff reaction. Reaction mixture was refluxed for 6 h at 130 ^{0}C. Then added 1.5 mL H_2O + 1.5 mL HCl, and refluxed for 1 h. The mixture was cooled and extracted with ether. Ether was evaporated. The solid was purified by recrystallization from ethanol. yellow solid, mp. 176.0-176.5 ^{0}C. yield: 22% IR (KBr, cm^{-1}): 3442(-OH), 1742 (-CO), 1644 (-CHO), 1594 (-C=C-) ^{1}H-NMR (DMSO-d_6): 2.44 (s, C<u>H</u>$_3$,3H), 6.22-7.66 (m, Ar-H, 3H), 10.63 (s, <u>H</u>CO, 1H), 12.28 (s, OH, 1H).

2.4. Synthesis of *(7-Hydroxy-4-methyl-8-[(2,3-dihydro-1,4-benzodioxin-6-yl)iminomethyl]-2H-1-benzopyran-2-one) and (2-(2'-Hydoxy-5-methyl coumarin-1-yl)-2,3-dihydro quinazoline-4(1H)-one*) (3-4)

2 mL methanol solution of 8-formyl-7-hydroxy-4-methylcoumarin **2** (10^{-4}mol, 0.02 g) was added slowly to 2 mL methanol solution of amine (10^{-4}mol, 0.015 g 6-amino-1,4-benzodioxan or 0.0136 g 2-aminobenzamid). Reaction mixture was acidified to pH 4-5 with HCl, then was refluxed at 150 ^{0}C. Obtained solid product **3** was purified by column chromatography with chloroform: methanol (8:0.5). **4** was purified by columnn chromatography with dichlormethan: methanol: triethylamine (9:1:0.1).



Scheme 1

3. RESULTS AND DISCUSSION

7-Hydroxy-4-methyl-8-[(2,3-dihydro-1,4-benzodioxin -6-yl) iminomethyl]-2H-1-benzopyran-2-one (**3**) was obtained as a schiff base. On the other hand, ring closure was observed at 2-(2'-Hydoxy-5-methyl coumarin-1-yl)-2,3-dihydro quinazoline-4(1H)-one (**4**). These compounds are originals. Their structures were identified by IR, ^{1}H NMR, ^{13}C NMR, MS analysis.

3.1. 7-Hydroxy-4-methyl-8-[(2,3-dihydro-1,4-benzodioxin-6-yl)iminomethyl]-2H-1-benzopyran-2-one (3)

Brown solid, m.p. 106.4-107℃. Yield: 90%. IR (KBr) spectrum of compound **3**; The OH group in the compound was observed at ν = 3423 cm^{-1} and azomethine ν = 1623 cm^{-1}, which is the determining group in the imine compounds. The signal of the carbonyl group in the coumarin ring was found at ν = 1600 cm^{-1} and the signal of the ether group (C-O-C) in the structure was found at ν = 1392 cm^{-1}.

When the ^{1}H-NMR ($CDCl_3$) spectrum of the **3** compound is examined, -CH_3 hydrogens at δ = 2.35 ppm (s), -CH hydrogens in the coumarin ring δ = 3.39 ppm (s), -CH_2-CH_2- hydrogens at δ=4.23 ppm (s), O-H hydrogens at δ = 6.06 ppm (s). The aromatic hydrogens in the structure were found to be multiplet at δ= 6.84-7.48 ppm and azomethine hydrogens at δ = 9.21 ppm (s), which is the determining group in imine compounds.

When the ^{13}C-NMR (DMSO-d_6) spectrum of compound **3** was examined, The -CH_3 signal and the carbon signals in the -CH_2-CH_2- were observed respectively, at 29.7 ppm and 64.6 ppm. The C signals in Aromatic CH were observed in the range of 106.9-115.5 ppm while the signal of coumarin CH was observed at 118.4 ppm. The aromatic carbon signals are in the range 130.8-134.0 ppm and the ether group (= C-O-C) is in the range 144.4-144.6 ppm. 154.4 ppm of the carbon to which the methyl group is bonded, 155.9 ppm of the carbon to which the oxygen in the coumarin ring is attached, 159.0 ppm of the carbon to which the OH group is attached, 159.9 ppm of the carbonyl carbon in the coumarin ring and 166.0 ppm of the azomethine carbon.

The molecular ion peak in the mass spectrum of compound **3** was observed at m/z +1 = 338.1 as expected. The compound **3** is original and was not found in the literature. When spectroscopic data were interpreted, it was found to be in agreement with the structure (Table 1).

3.2. 2-(2'-Hydoxy-5-methylcoumarin-1-yl)-2,3-dihydro quinazoline-4(1H)-one (4)

Pale green solid, mp. 340.1-340.5 ^{0}C. Yield: 18%. Ring closure was observed at **4.** In the IR (KBr) spectrum of compound **4**; the OH signal was found at ν = 3476 cm^{-1}, the -NH signal, the sharp lacton signal, azomethine signal and aromatic C=C signal

were observed respectively, at ν = 3338 cm^{-1}, ν = 1746 cm^{-1}, ν = 1623 cm^{-1}, ν = 1553 cm^{-1} and ν = 1296 cm^{-1}.

When the ^{1}H-NMR ($CDCl_3$) spectrum of compound **4** was examined, -CH_3 hydrogens δ = 2.47 ppm (s), CH in the coumarin ring adjacent to the carbonyl is singlet at δ = 3.51 ppm, the hydrogens of the hydroxyl group and CH hydrogens in the quinazoline ring δ = 6.19 ppm. The aromatic hydrogens in the structure were at δ = 7.04-7.1 ppm (d) and at δ = 7.5-7.85 ppm (m). The NH hydrogen in the quinazoline ring were found at δ = 7.95 ppm (d) and the other NH hydrogen adjacent to carbonyl were observed at δ = 11.43 ppm.

When the ^{13}C-NMR ($CDCl_3$) spectrum of compound **4** was examined, Aromatic CH signals in the range of 99.3-120.0 ppm, aromatic carbon signals in the range of 124.0-134.0 ppm, C=C signal at 143.0 ppm and the -CH_3 carbon at 18.4 ppm were observed. The signal of CH carbon in the coumarin ring at 152.7 ppm, the carbon to which the hydroxyl group in the coumarin ring was attached at 153.0 ppm, the -CH carbon at the quinazoline ring at 156.0 ppm, the carbonyl carbon in the coumarin ring at 160.1 ppm and in the quinazoline ring at 165.6 ppm which proves the validity of the construction of the signals given by carbonyl carbon.

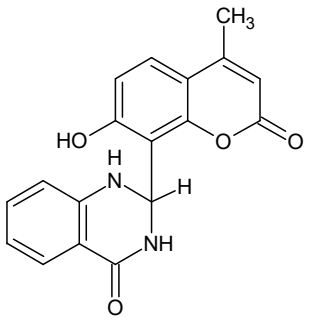
The molecular ion peak in the mass spectrum of compound **4** was observed at m/z +1 = 322.2 as expected. The compound **4** is original and was not found in the literature. When spectroscopic data were interpreted, it was found to be in agreement with the structure (Table 2).

Table 1. Results of 7-Hydroxy-4-methyl-8-[(2,3-dihydro-1,4-benzodioxin-6-yl)iminomethyl]-2H-1-benzopyran-2-one (**3**)

	7-Hydroxy-4-methyl-8-[(2,3-dihydro-1,4-benzodioxin-6-yl)iminomethyl]-2H-1-benzopyran-2-one
Molecular formula	$[C_{19}H_{15}NO_5]$
Molecular weight	337 (g/mol^{-1})
Colour	Brown solid
Melting point (^{0}C)	106.4-107
Yield (%)	90
IR (KBr, cm^{-1})	3438, 1623, 1600, 1515, 1392
^{1}H-NMR ($CDCl_3$)	2.34 (s, -C<u>H</u>$_3$, 3H), 2.39 (s, -C<u>H</u>, 1H), 4.23 (s, -C<u>H</u>$_2$-C<u>H</u>$_2$-, 4H), 6.06 (s, O<u>H</u>, 1H), 6.84-7.48 (m, Ar-H, 5H), 9.21 (s, -C<u>H</u>=N, 1H)
^{13}C-NMR (DMSO-d_6)	166 (1C, -<u>C</u>H=N), 159.6 (1C, <u>C</u>-OH), 159.6 (1C, -<u>C</u>=O-), 155.9 (1C, coumarin =<u>C</u>-O), 154.6 (1C, <u>C</u>-CH_3), 144.6-144.4 (2C, C=<u>C</u>-O), 134-130.8 (3C, Ar-C), 118.4 (1C, -<u>C</u>H), 115.5-106.9 (5C, Ar-<u>C</u>H), 64.6 (2C, -<u>C</u>H$_2$-<u>C</u>H$_2$-), 29.7 (1C, <u>C</u>H$_3$)
MS (EI) m/z	338.1

Table 2. Results of 2-(2'-Hydoxy-5-methyl coumarin-1-yl)-2,3-dihydro quinazoline -4(1H)-one (**4**)

	2-(2'-Hydoxy-5-methyl coumarin-1-yl)-2,3-dihydro quinazoline-*4(1H)-one*

	
Molecular formula	$[C_{18}H_{14}N_2O_4]$
Molecular weight	322 (g/mol^{-1})
Colour	pale green solid
Melting point (^{0}C)	340.1-340.5
Yield (%)	18
IR (KBr, cm^{-1})	3476, 3338, 1746, 1553, 1296
^{1}H-NMR ($CDCl_3$)	2.47 (s, -C<u>H</u>$_3$, 3H), 3.51 (s, COC<u>H</u>, 1H), 6.19 (s, C<u>H</u>, 1H), 7.04-7.1 (d,J=8.95, Ar-H, 2H), 7.5-7.85 (m, Ar-H, 4H), 8.36 (d, J=7.95, N<u>H</u>, 1H), 11.43 (s, CON<u>H</u>, -O<u>H</u>, 2H)
^{13}C-NMR ($CDCl_3$)	165.6 (1C, <u>C</u>O), 160.1 (1C, <u>C</u>O), 156 (1C, -<u>C</u>H), 153 (1C, <u>C</u>-OH), 152.7 (1C, -<u>C</u>H), 143 (1C, -<u>C</u>=C), 134.1-124 (5C, Ar-C), 120-99.3 (6C, Ar-<u>C</u>H), 18.4 (1C, <u>C</u>H$_3$)
MS (EI) m/z	322.2

4. CONCLUSION

Synthesis of 2-(2'-Hydoxy-5-methyl coumarin-1-yl)-2,3-dihydro quinazoline-4(1H)-one and 7-Hydroxy-4-methyl-8-[(2,3-dihydro-1,4-benzodioxin-6-yl)iminomethyl]-2H-1-benzopyran-2-one are originals and synthesized for the first time. These compounds are also thought to exhibit biological activity.

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Conflict of interest statement: We declare that we have no conflict of interest.

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