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*Research Article*

# Synthesis, Characterization, and Photophysical Properties of 2-Quinolone-Based Compounds

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## ABSTRACT

2-Quinolone (1,2-dihydroquinoline) and 1-aza coumarin derivatives are quinoline class pharmacophore structures known for their versatile bioactive and stable photophysical properties. In the present study, *N*-amino (**2**) and *N*-acetamido (**3**) derivatives of 2-quinolone-based 1-aza Coumarin-3-carboxylic acid were synthesized. Structure characterizations of the synthesized compounds were performed using $^{1}$H NMR, IR, $^{13}$C NMR spectral techniques. The synthesized compounds are thought to be precursor structures for the development of new bioactive agents because of their structural similarity. The photophysical sensitivities of compounds (**2** and **3**), which have the 1-Aza coumarin skeleton, in different solvents were examined by ultraviolet−visible (UV−Vis) absorption spectroscopy and fluorescence spectroscopy methods. In addition, the compounds synthesized in this study could serve as fluorophores, fluorescently active and bioactive new Schiff base sensors in different fluorescence studies.

***Keywords:*** *1, 2-Dihydroquinoline, 2-Quinolone-3-carboxylic acid, 1-Azacoumarin, Photophysical properties*

# 2-Kinolon Temelli Bileşiklerin Sentezi, Karakterizasyonu ve Fotofiziksel Özellikleri

## ÖZ

2-Kinolon (1,2-dihidrokinolin) ve 1-aza kumarin türevleri çok yönlü biyoaktif ve kararlı fotofiziksel özellikleriyle bilinen kinolin sınıfı farmakofor yapılardır. Sunulan çalışmada 2-kinolon temelli 1-aza kumarin-3-karboksilik asit'in *N*-amino (**2**) ve *N*-asetamido (**3**) türevlerinin sentezi yapılmıştır. Sentezlenen bileşiklerin yapı karakterizasyonu $^{1}$H NMR, IR, $^{13}$C NMR spektral teknikleriyle gerçekleştirilmiştir. Sentezlenen bileşiklerin yapı benzerliğinden dolayı yeni biyoaktif ajanların geliştirilmesinde öncü yapılar olabileceği düşünülmektedir. 1-Aza kumarin iskeletine sahip bu bileşiklerin (**2** ve **3**) farklı çözücülerdeki fotofiziksel duyarlılıkları mor ötesi-görünür bölge (UV-GB) absorpsiyon spektroskopisi ve floresans spektroskopisi yöntemleriyle incelenmiştir. Ayrıca çalışmada sentezlenen bileşikler, farklı floresans çalışmalarda florofor, floresan aktif ve biyoaktif yeni Schiff bazı algılayıcı gibi görevler alabilir.

***Anahtar Kelimeler:*** *1,2-Dihidrokinolin, 2-Kinolon-3-karboksilik asit, 1-Azakumarin, Fotofiziksel özellikler*

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# I. INTRODUCTION

Quinolines belong to the class of heteroaromatic compounds with a two-ring structural skeleton consisting of pyridine bonded to benzene. Although they have names such as benzo[b]pyridine or 1-aza-naphthalene, these heterocyclic molecules are more commonly known as quinoline (Figure 1).

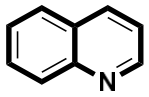


***Figure 1.*** *Quinoline*

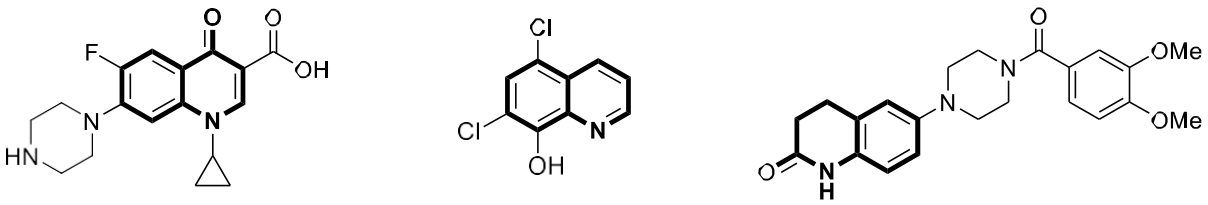


***Figure 2.*** *Some drugs containing a quinoline ring*

Quinolines, which are very popular in the field of pharmaceutical chemistry, have antibacterial, antifungal, antiviral, antituberculous, anti-inflammatory, anticonvulsant, analgesic or antimalarial, anticancer, etc. properties [1],[2]. They are representative of a privileged and superior class that attracts the attention of organic chemists because of their biological properties. Many drugs containing the quinoline ring are known to have the biological properties listed above (Figure 2). Therefore, the quinoline structural skeleton, in addition to being a natural product, is characterized as a highly potential, preferred, and versatile pharmacophore for drug discovery [1],[2].

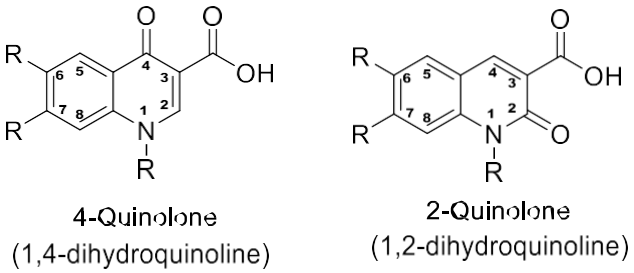



***Figure 3.*** *Quinolone scaffold*

In contrast, quinolones constitute a subclass of quinoline derivatives. The two-ring structure has ketone and carboxylic acid functional groups in the nitrogen-containing ring. These structures are called 4-quinolones or 2-quinolones depending on the position of the ketone group [3],[4]. The quinolone structures are also chemically referred to as 1,4-dihydroquinolines (4-quinolones) and 1,2-dihydroquinolines (2-quinolones) [3],[5]–[6] (Figure 3).

Quinolones, unlike quinolines, are not natural products. The development and use of these compounds began after their first synthetic discovery in the 1960s and have attracted increasing clinical, and scientific attention [3],[7]. Since there are various drugs with quinolone rings that exhibit activities such as antituberculosis [8], anti-HIV [9], antimalarial [10], antibacterial [11], antibiotic [12], antitumor, antidepressant, antiulcer, antioxidant, and herbicide [4],[13], new modifications and bioactivities of dihydroquinoline derivatives have been intensively studied at the point of drug discovery [5],[8],[9],[13]–[19].

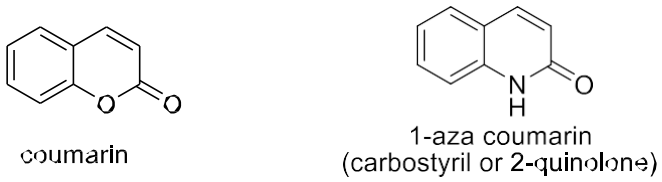



***Figure 4.*** *Coumarin and 1-azacoumarin*

In this regard, quinolones are structurally similar to coumarins. The nitrogen analog of coumarins, 1-azacoumarin compounds, are lactam class structures, also known as carbostyril [20]. 1-aza-coumarin molecules are also referred to as 2-quinolones [6],[21] (Figure 4). Coumarin and its derivatives are structures of great interest, especially in bioactivity and fluorescence studies, because they have a wide bioactivity spectrum and unequaled stable photophysical properties similar to those of quinolines [13],[20],[22]–[25].

Taking all these factors into consideration, the synthesis of 2-quinolone (dihydroquinoline or 1-azacumarin) derivative structures was presented within the scope of this study. Commercially available 2-oxo-coumarin-3-carboxylic acid (**1**), *N*-amino-2-quinolone-3-carboxylic acid (**2**), and *N*-acetamido-2-quinolone-3-carboxylic acid (**3**) compounds were respectively obtained (Scheme 1). Their structure characterization was performed using $^{1}$H- and $^{13}$H-NMR and IR spectral methods. These structures, which are quinoline derivatives, can form the structural unit of many pharmaceutical active agents in terms of structural similarity. The photophysical behaviors of the compounds (**2** and **3**) in the present study, which have a 1-aza coumarin skeleton, in different solvents were identified via ultraviolet−visible (UV−Vis) absorption and fluorescence spectroscopy techniques. In addition, based on the photophysical properties examined, it is evaluated that the structures synthesized in the study and their derivatives to be designed may be new and different probes with bioactive and fluorescent properties.

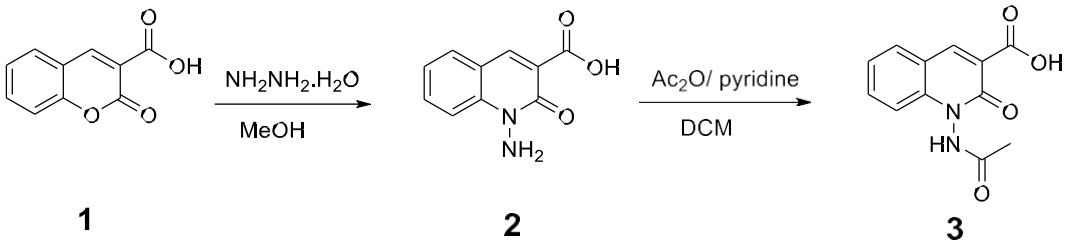
# II. MATERIAL AND METHOD

## A. CHEMICALS AND EQUIPMENT

The starting material coumarin-3-carboxylic acid, other chemical reagents (hydrazine monohydrate (98%), acetic anhydride, sodium sulphate anhydrous, and hydrochloric), and all solvents (Methanol, pyridine, and dichloromethane) used in the study were supplied by commercial companies and were used in the experiments without any purification unless otherwise stated. pH measurements were taken with a Thomas Scientific pH/conductivity meter. NMR, and IR spectra were obtained using Varian NMR, Magritek Spinsolve NMR spectrometer and Perkin Elmer Spectrum IR spectrometer devices, respectively. NMR spectra were obtained in chloroform-$d_3$. Chemical shift and splitting constant (*J*) values were recorded in ppm and in Hertz (Hz), respectively. FT−IR spectra are given in $cm^{-1}$. UV−Vis absorbance and fluorescence spectra were determined out with Varian Cary Eclipse fluorescence and Varian Cary 100 UV−visible spectrophotometer, individually.

### A.1. Syntheses and Characterization

The synthesis of compounds **2** and **3** is shown in Scheme 1.




***Scheme 1.*** *Synthesis of N-amino 2-quinolone-3-carboxylic acid (**2**) and N-acetamido 2-quinolone-3-carboxylic acid (**3**)*

### *A.1.1. Synthesis of 1-amino-2-oxo-1,2-dihydroquinoline-3-carboxylic acid (2)*

To the solution of 2-oxo-coumarin-3-carboxylic acid (**1**) (190.16 mg, 1 mmol) in 5 mL absolute ethanol, hydrazine monohydrate (98%) (1.5 mL, 30 mmol) was added. The mixture was stirred under reflux for 1 h and then cooled to room temperature. After adding dilute HCl to the resulting mixture until the pH reached 4, 1-amino-2-quinolone-3-carboxylic acid (**2**) was obtained in 49% yield (101 mg) by washing the precipitate with plenty of water and drying it in the oven (Scheme 1). $^{1}$H NMR ($CDCI_3$) $\delta$ (ppm) 11.40 (s, 1H, $–CO_2H$), 8.70 (s, 1H, $–H_4$), 7.39 (dt, $J$ = 16.1, 7.2 Hz, 2H, –ArH), 7.01 (dt, $J$ = 23.8, 7.9 Hz, 2H, –ArH). $^{13}$C NMR ($CDCl_3$) $\delta$ (ppm) 164.96, 160.02, 133.69, 133.55, 132.81, 132.73, 119.98, 119.89, 117.51, 117.39. IR ($cm^{-1}$) 3072, 3044, 3018, 2974, 2917, 2846, 2754, 2711, 2639, 1618, 1571, 1486, 1447, 1386, 1331, 1316, 1269, 1197, 1115, 1032, 984, 893, 782, 747, 727, 682 (Figures 5,6 ve 7).

### *A.1.2. Synthesis of 1-acetamido-2-oxo-1,2-dihydroquinoline-3-carboxylic acid (3)*

Acetic anhydride (10 mmol, 0.95 mL) was added dropwise to an ice-bath stirred solution of 1-amino-2-quinolone -3-carboxylic acid (**2**) (205 mg, 1 mmol) in dichloromethane (20 mL) containing three drops of pyridine. After stirring the mixture at room temperature overnight, it was separated into phases by adding dichloromethane and water. The organic phase was washed sequentially with dilute HCl (3x25 mL) and brine (3x25 mL). The combined organic phases were then dried with $Na_2SO_4$, filtered, and concentrated under low vacuum to give 1-acetamido-2-quinolone-3-carboxylic acid (**3**) as a light brown solid in 99% yield (247 mg) (Scheme 1). $^{1}$H NMR ($CDCI_3$) δ (ppm) 8.67 (s, 1H, $–H_4$), 8.06 (dd, $J$ = 6.8, 2.7 Hz, 1H, –ArH), 7.58 – 6.87 (m, 3H, –ArH), 2.34 (s, 3H, $–NHCO\underline{CH_3}$). $^{13}$C NMR ($CDCl_3$) δ (ppm) 169.14, 157.19, 150.29, 132.16, 128.53, 126.32, 126.27, 123.09, 122.96, 122.51, 109.99, 21.02. IR ($cm^{-1}$) 3515, 3060, 3017, 2963, 2927, 2854, 1763, 1622, 1601, 1574, 1481, 1450, 1370, 1323, 1280, 1227, 1194, 1165, 1151, 1093, 1045, 1037, 1012, 967, 907, 855, 818, 765, 677 (Figures 8,9 ve 10).

# III. RESULTS AND DISCUSSION

## A. SYNTHESES

Within the scope of this study, two 2-quinolone-based compounds were synthesized from the coumarin compound, and their structures were elucidated using spectral techniques ($^{1}$H and $^{13}$C NMR, IR). First, *N*-amino-coumarin-3-carboxylic acid (**2**) was successfully synthesized by treating the compound coumarin-3-carboxylic acid (**1**) with hydrazine monohydrate under reflux conditions in absolute EtOH [12] (Scheme 1). $^{1}$H NMR, IR, and $^{13}$C NMR spectra of compound **2** are given in Figures 5, 6, and 7, respectively.

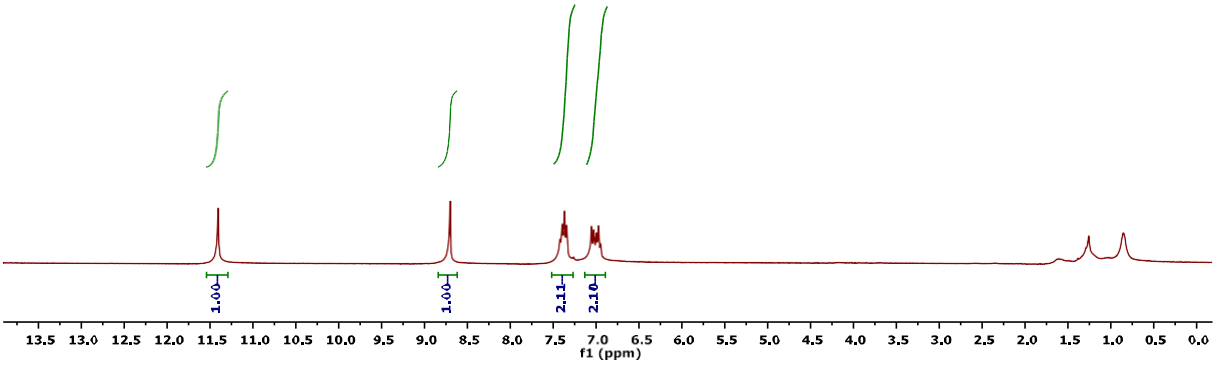



***Figure 5.*** *$^{1}$H NMR spectrum of compound **2***

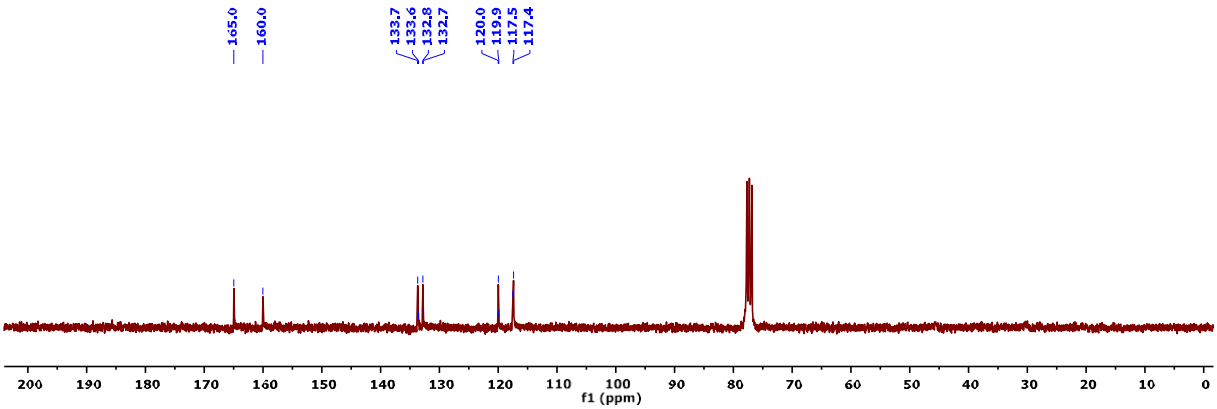



***Figure 6.*** *$^{13}$C NMR spectrum of compound **2***

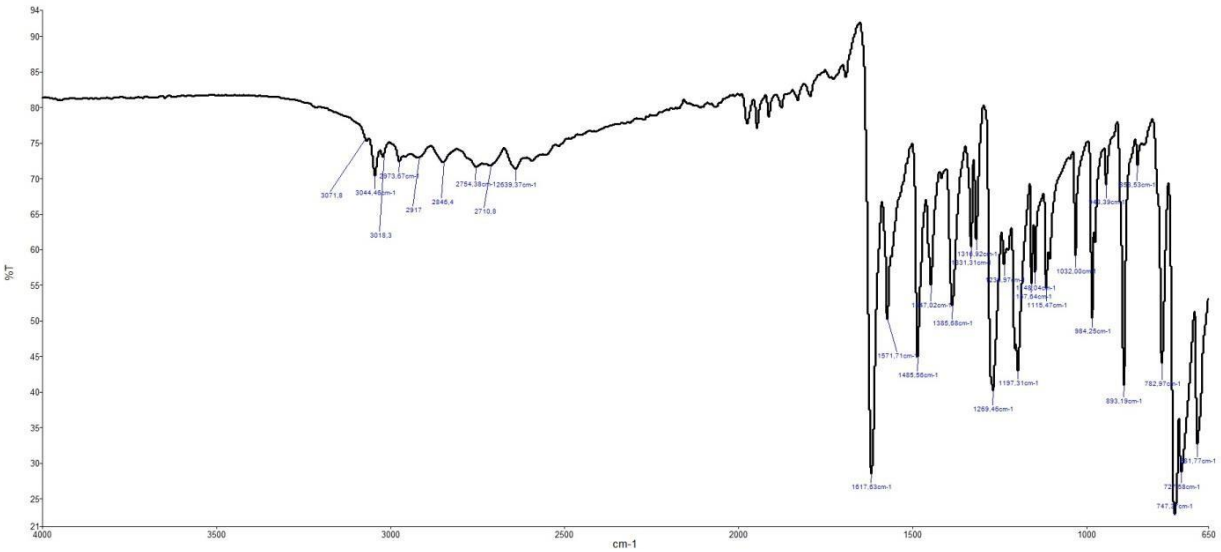



***Figure 7.*** *IR spectrum of compound **2***

Moreover, because amide groups have very stable and neutral properties, they are generally located in the backbones of many natural and synthetic bioactive substances [6]. Based on this, 1-amino-2-quinolne-3-carboxylic acid (**2**) was reacted with pyridine-catalyzed $Ac_2O$ in DCM and subjected to the amidation reaction of the amino group in the quinolone ring, resulting in an *N*-acetamido-substituted *N*-(*N*-acyl)-coumarin-3-carboxylic acid (**3**) (Scheme 1). $^{1}H$, $^{13}C$ NMR, and IR spectra of compound **3** are depicted in Figures 8, 9, and 10, respectively.

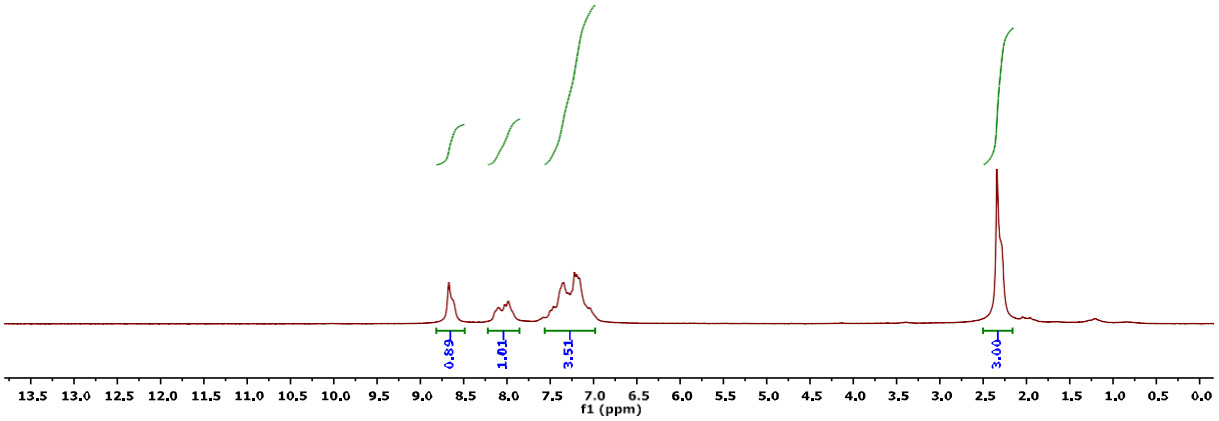



***Figure 8.*** *$^{1}H$ NMR spectrum of compound **3***

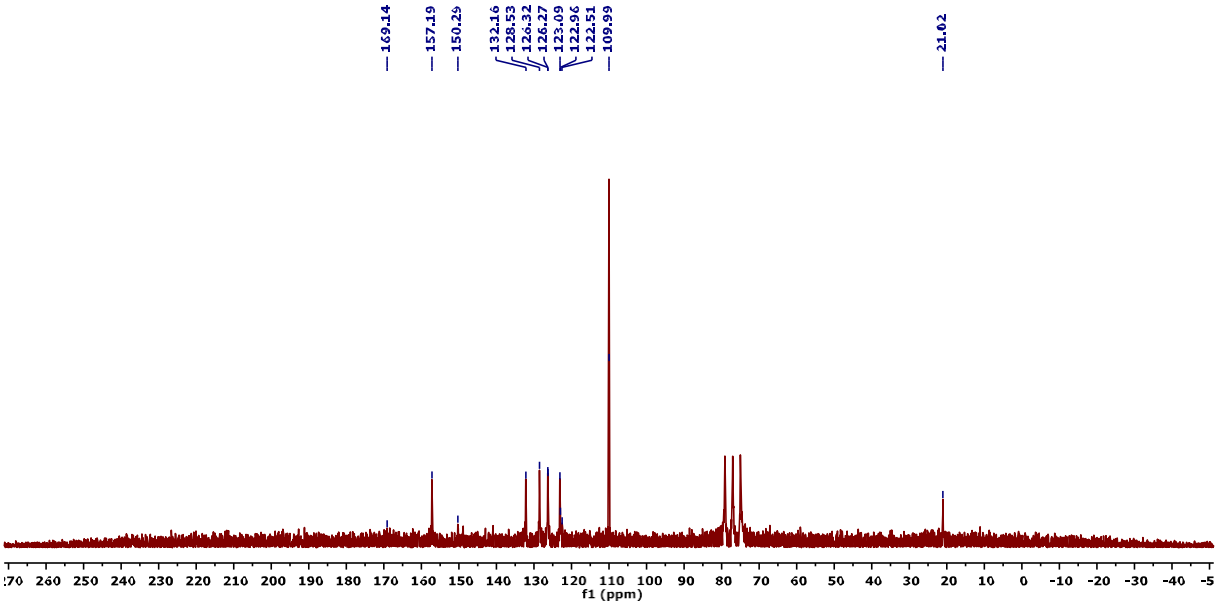



***Figure 9.*** *$^{13}C$ NMR spectrum of compound **3***

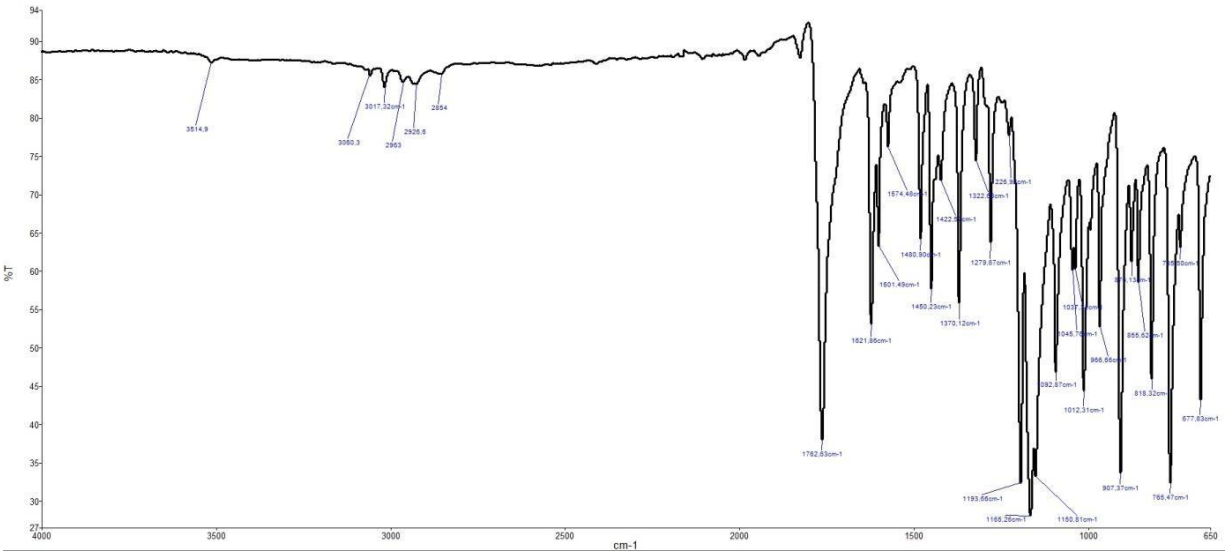



***Figure 10.*** *IR spectrum of compound **3***

## B. CHARACTERIZATION

When the $^{1}$H NMR spectrum of 1-amino-2-quinolone-3-carboxylic acid (**2**) was examined, the singlet peak monitored at 11.40 ppm was the proton signal belonging to the –$CO_2$H group located in the position 3 of the structure. In addition, the beta proton (*β*-H) at position 4 of the structure resonated with the singlet peak at 8.70 ppm, while the signals of aromatic protons were observed as the doublet of the triplet at 7.39 ppm and 7.01 ppm, respectively. The integration values on the spectrum were consistent with the proton numbers of compound **2** (Figure 5). The –$NH_2$ protons of compound **2** were not observed because of intramolecular hydrogen bonds, resonance formations, and conjugation, [26] (Figure 5 and 11). In the $^{13}$C NMR spectrum of compound **2**, the –C=O peak in the carboxylic acid and lactam ring resonated at 165 and 160 ppm, respectively. Signals of other aromatic carbons, quaternary carbons, and beta carbon (*β*-C) were observed in the range of 110–140 ppm (Figure 6). In the IR spectrum of the structure, the stretching vibrations of –$NH_2$ protons gave weak and broad peaks below 3200 cm$^{-1}$ due to intra- and intermolecular hydrogen bond interactions [26],[27] (Figure 7 and 11). Similarly, because of intermolecular hydrogen bond interactions, the frequency of the –$CO_2$H group in compounds (**2** and **3**) was seen as a broad peak in the range of 2500-3200 cm$^{-1}$ [26] (Figure 7, 10, and 11).

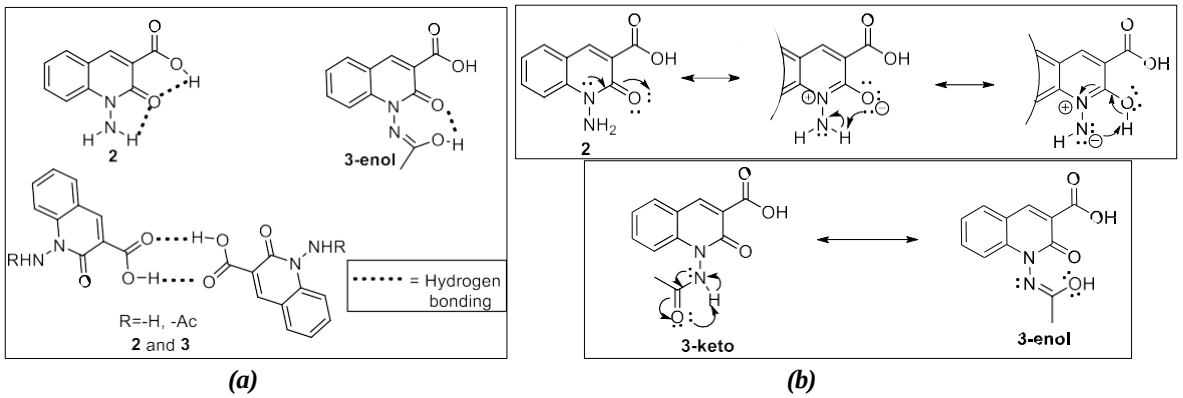



***Figure 11. (a)*** *Intramolecular and intermolecular hydrogen bonding for compounds **2** and **3** **(b)** resonance formation for compounds **2** and **3***

In the IR spectra of the starting compounds (**1** and **2**), the –C=O vibration peaks of –$CO_2$H, lactone (for **1**), and lactam (for **2**) shifted to low frequencies. In other words, the peak at 1736 cm$^{-1}$ belonging to the –C=O of compound **1** –$CO_2$H shifted to 1618 cm$^{-1}$ and was seen as the peak belonging to the –C=O of

compound **2** –$CO_2H$. Additionally, the peak at 1670 $cm^{-1}$ belonging to the –C=O of lactone **1** was observed at 1572 $cm^{-1}$ as the –C=O peak of lactam **2**, indicating that compound **2** was formed (Figure 12).

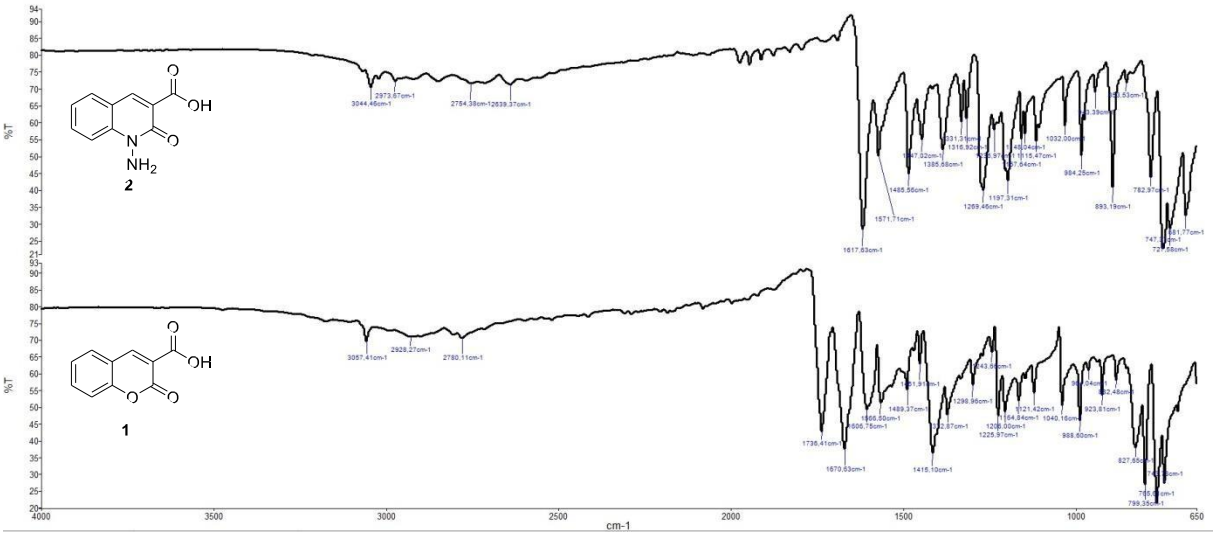



***Figure 12.*** *IR spectra of the starting compound (**1**) and the compound (**2**)*

Furthermore, when the $^1$H NMR spectrum of the other target compound 1-acetamido-2-quinolone-3-carboxylic acid (**3**) was elucidated, *β*-H of the compound with a singlet peak at 8.67 ppm, the aromatic proton at position 5 with a doublet of doublets peak at 8.06 ppm, other aromatic protons with multiplet peak in the range of 6-8 ppm were observed to resonate (Figure 8). When the $^{13}$C-NMR spectrum of compound **3** is interpreted that the –C=O peaks and other carbon peaks in the structure are compatible with the structure. In particular, the peak at 21 ppm belonging to the –$CH_3$ carbon of the –N-acyl group (–$NHCOCH_3$) attached to the nitrogen atom at position 1 confirmed that the compound was acetylated (Figure 9). The weak peak at 3513 $cm^{-1}$ in the IR spectrum of the compound belonged to –OH in the enol form, which was formed because of intramolecular tautomerization of the –NH stretching peak (Figure 11). In the IR spectrum of compound **3**, the peaks of –C=O group stretching vibrations belonging to carboxylic acid, lactam, and –$NHCOCH_3$ groups were observed at 1762 $cm^{-1}$, 1621 $cm^{-1}$ and 1601 $cm^{-1}$, respectively. In additional, the peaks in the 1300-1500 $cm^{-1}$ region belonged to the vibrations of Ar–H (Figure 10).

In terms of structural similarity, compounds (**2** and **3**) in the study could be described as 4-quinolone isomers and 2-quinolone derivative analogs [6],[12],[28]. Also, these compounds were similar to the coumarin derivative 1-azacoumarins [22]. When investigated under the framework of quinoline, both quinolone derivatives and 1-azacoumarin derivatives form the backbone of many pharmaceutical active compounds with a very wide bioactive spectrum [20]–[22]. In addition, amine, amide, and carboxylic acid functional groups can promote bioactivity [6],[14],[19],[28].

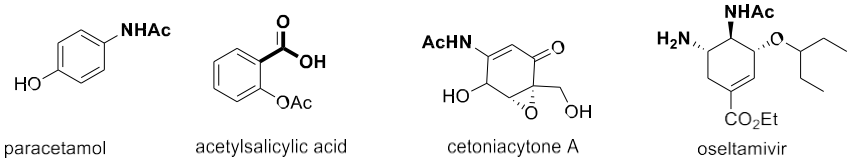



***Figure 13.*** *Effective bioactive agents with small molecular structures containing amino, acetamido, and carboxylic acid units.*

The structures of the analgesic and antipyretic paracetamol and acetylsalicylic acid used in daily life, the antibacterial and antitumor agent cetoniacyton A, and the antiviral drug oseltamivir are small and

highly effective and contain amino, acetamido, and carboxylic acid units [29],[30] (Figure 13). Therefore, the target molecules presented in this study were capable of leading to the synthesis of many new compounds that exhibit important bioactivities that can be used both drug-active agents and cures for various diseases. For this purpose, different approaches could be planned such as deriving these compounds from carboxylic acid and amino groups and including groups that will support bioactivity at positions 6 and 7 (such as -F, -piparizine, -$CF_3$) [14],[28]. Regarding the structures in the study as 1- aza coumarin and the very stable photophysical properties of coumarins, compounds **2** and **3** could serve as both a fluorophore, a fluorescent sensor, and a bioactive and fluorescent active Schiff base in fluorescence studies [4],[13],[24],[25].

## C. PHOTOPHYSICAL PROPERTIES

Considering the photophysical stability of the *N*-amino (**2**) and *N*-acetamido (**3**) substituted 3-carboxylic acid as quinolone derivatives synthesized in this study, their UV absorption and fluorescence behaviors were determined in equal concentrations ($10^{-5}$ M) and different solvents (hexane, dichloromethane, chloroform, acetonitrile, ethanol, methanol, *N*,*N*-dimethyl formamide, dimethyl sulfoxide and water).

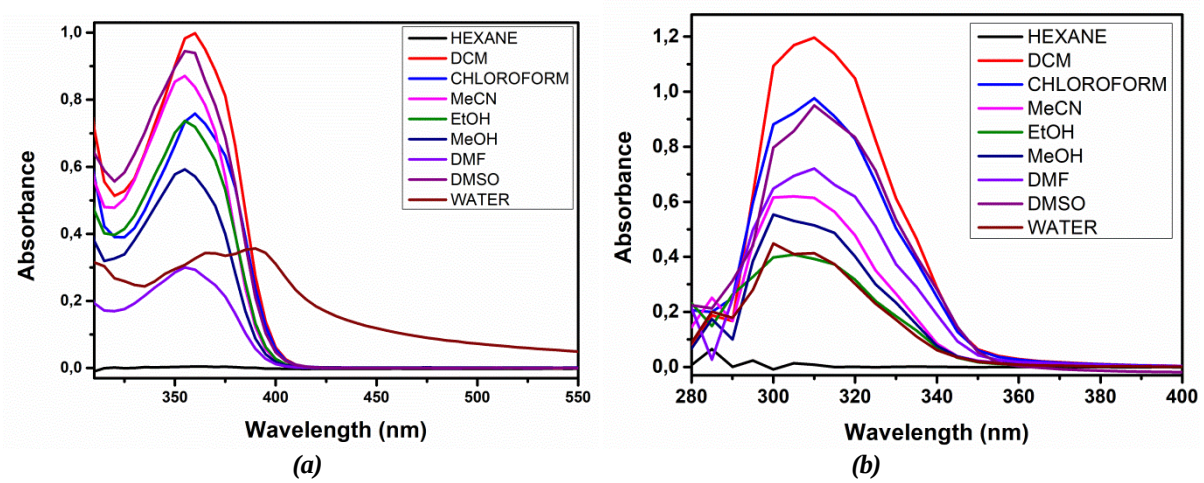



***Figure 14. (a)*** *Absorption spectra of compound (**2**) and* ***(b)*** *compound (**3**) in different solvents*

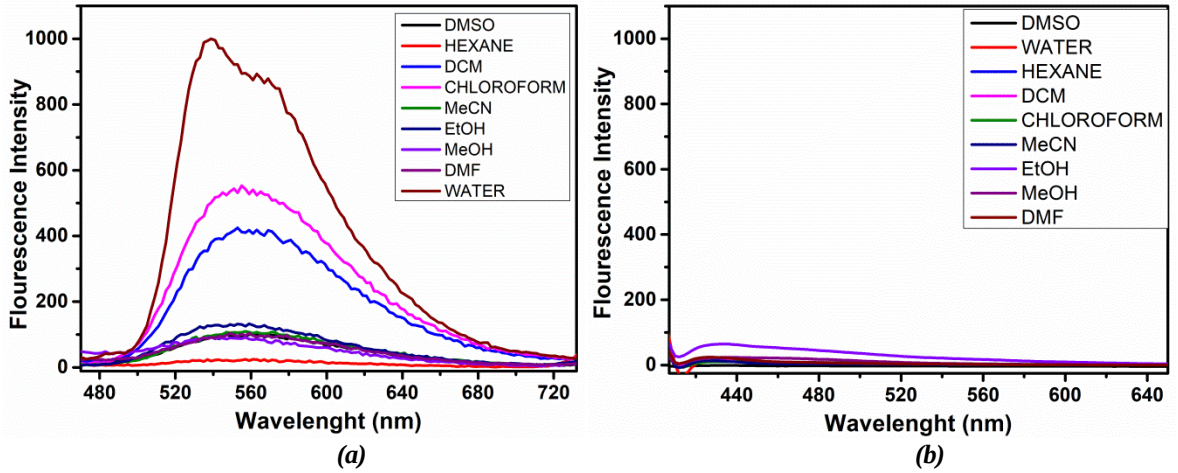



***Figure 15. (a)*** *Flourescence spectra of compound (**2**) and* ***(b)*** *compound (**3**) in different solvents*

When the UV−Vis absorption spectrum of compound **2** was examined, the wavelength signals of n−π* and π−π* transitions were observed in the 320-400 nm band (Figure). In the UV absorption spectrum of compound **3**, the wavelength values of the signals of n−π* and π−π* transitions were observed in the range of 280−360 nm (Figure 14). While both compounds did not give a signal in hexane due to the

intermolecular and intramolecular hydrogen bond effects due to the solvent effect, they gave a low intensity and broad signal in water [26] (Figure 15). While compound **2** showed a very high fluorescence intensity at 538 nm in water, compound **3** did not show an obvious fluorescence response under the same conditions (Figure 14). The high intensity fluorescence response of compound **2** in water is a promising development for intracellular imaging studies.

# IV. CONCLUSION

In this study, *N*-amino-2-quinolone-3-carboxylic acid (**2**) and *N*-acetamido-2-quinolone-3-carboxylic acid (**3**) compounds were synthesized from coumarin-3-carboxylic acid (**1**) and their structures were characterized by $^{1}$H-NMR, IR, and $^{13}$C-NMR spectrometry. The photophysical behaviors of the compounds were investigated using UV-visible and fluorescence Spectroscopy methods. It has been observed that the compounds absorb in the visible wavelength range in different solvents in the UV−Vis spectrum. Furthermore, in the fluorescence spectrum, compound **2** exhibited a strong fluorescence increment in the presence of water, whereas compound **3** did not show a significant fluorescence response in different solvents. Because of their isomeric similarities with active pharmaceutical agents containing quinolone rings, the compounds obtained in this study could be considered as precursors of new drugs to be developed within the framework of drug discovery. In this respect, it is possible to obtain compounds similar to the quinolone-3-carboxylic acids in the literature [19],[28] with the target molecules synthesized in the study. On the other hand, because these compounds are 1-azacoumarin derivatives, they could be used in the design and development of new fluorescent probes/fluorophores for the determination of critical species for living organisms and the environment in fluorescence spectroscopy studies. Besides, because the compounds in the study are 1-azacoumarin derivatives, they would be utilized in the design and development of new fluorescent probes/fluorophores to be used to identify critical species for living things and the environment in fluorescence spectroscopy studies. Further studies planned in this context are in progress.

ACKNOWLEDGEMENTS**:** This work was supported by the Karamanoglu Mehmetbey University.

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