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Research Article

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An Efficient One-Pot Three-Component Synthesis of Novel Quinazoline-4 Carboxylic Acid and Its Ester and Amide Derivatives

Bir Etkili Tek Ortamda Üç Bileşenli Yeni Kinazolin-4-Karboksilik Asit ve Onun Ester ve Amit Türevlerinin Sentezi

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ABSTRACT

A series of novel quinazoline derivatives, which may be drug candidates, were synthesized, and their structures were characterized by IR, ^{1}H NMR, ^{13}C NMR and Q-TOF LC/MS spectrometry. First, 2-(4-chloro-phenyl)-quinazoline-4-carboxylic acid (2) was synthesized from a one-pot three-component condensation reaction of (2-amino-phenyl)-oxo-acetic acid sodium salt obtained from alkaline hydrolysis of isatin (indole-2,3-dione) with 4-chlorobenzaldehyde and ammonium acetate. The carboxylic acid compound 2 allowed the synthesis of the ester, acid chloride and amide derivatives. New quinazoline ester derivatives (3-6, 8) were synthesized by the reactions of compound 2 and various alcohols. Quinazoline amide derivatives (9-13) were then obtained from the reaction of different aliphatic and aromatic amines and 2-(4-chloro-phenyl)-quinazoline-4-carbonyl chloride (7) formed from the reaction of $SOCl_2$ and compound 2.

Key Words

Isatin, quinazoline-4-carboxylic acid, amide, ester.

ÖZ

İlaç adayları olabilecek bir dizi yeni kinazolin türevleri sentezlendi ve yapıları IR, ^{1}H NMR, ^{13}C NMR ve Q-TOF LC/MS spektrometresi ile karakterize edildi. Önce amonyum asetat ve 4-klorobenzaldehit ile isatinin (indol-2,3-dion) hidrolizinden elde edilen (2-amino-fenil)-okso-asetik asit sodyum tuzunun aynı ortamda üç bileşenli kondenzasyon reaksiyonundan 2-(4-kloro-fenil)-kinazolin-4-karboksilik asit (2) sentezlendi. Karboksilik asit bileşiği 2, ester, asit klorür ve amit türevlerinin sentezine izin verdi. Yeni kinazolin ester türevleri (3-6, 8), 2 bileşiği ve çeşitli alkollerin reaksiyonlarından sentezlendi. Daha sonra kinazolin amit türevleri (9-13), çeşitli alifatik ve aromatik aminlerin 2 bileşiği ve $SOCl_2$'ün reaksiyonundan oluşan 2-(4-kloro-fenil)-kinazolin-4-karbonil klorürün (7) reaksiyonundan elde edildi.

Anahtar Kelimeler

İsatin, kinazolin-4-karboksilik asit, amit, ester.

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INTRODUCTION

Quinazolines are one of the important classes of organic chemistry due to their presence in the structure of natural products and drugs. Also, they have an important place in medical chemistry because of the variety of biological and pharmacological activities exhibited by their natural and synthetic derivatives. The literature studies show that quinazolines have a wide range of biological activities such as antifungal [1], antitubercular [2, 3], anticancer [4], antiplasmodial [5], antiviral [6], anti-HIV [7], anti-malarial [8], anti-inflammatory [9], antihypertensive [10], anti-diabetic [11] etc. Furthermore, compounds containing quinazoline were found to inhibit dihydrofolate reductase [12], the epidermal growth factor receptor (EGFR) tyrosine kinase [13], and cellular phosphorylation [14]. It has also been reported that quinazolines are antagonists of some biological receptors [15].

In the structure of some drug molecules such as icotinib [16], prazosin [17] and lapatinib [18], the quinazoline ring forms the basic core structure (Fig. 1).

Dacomitinib and afatinib containing quinazoline scaffold are drugs confirmed for the treatment of patients with non-small-cell lung cancer (NSCLC) [19, 20] (Fig. 2).

As explained above, the fact that quinazolines have very important biological activities has led to the synthesis of their different derivatives. For this reason, it is very important to develop new, efficient and practical methods for the synthesis of N-heterocycles in organic chemistry. When literature sources are considered, it is seen that quinazoline derivatives are obtained by different methods such as condensation of aldehydes with 2-aminobenzylamines [21], copper-catalyzed condensation of amidine hydrochlorides with o-halobenzaldehydes [22], dehydrogenative coupling reaction of (2-aminophenyl) methanols with ammonia and aldehyde [23], tandem reactions from benzylic amines and 2-aminobenzophenones [24] and copper-catalyzed Ullmann N-arylation coupling reaction [25]. Most of these methods have certain limitations, such as difficult reaction conditions, long reaction times, use of expensive and toxic catalysts and reagents, low product yields and use of volatile organic solvents. Today, more stringent legislation and restrictions are applied to reduce the environmental impact of synthetic chemicals. Therefore, it becomes very important to meet environmental sustainability requirements when creating new reaction conditions.
One of the synthesis methods of quinazolines is the condensation reaction of 2-aminobenzophenones with ammonia and various aldehydes [26]. In this study, we

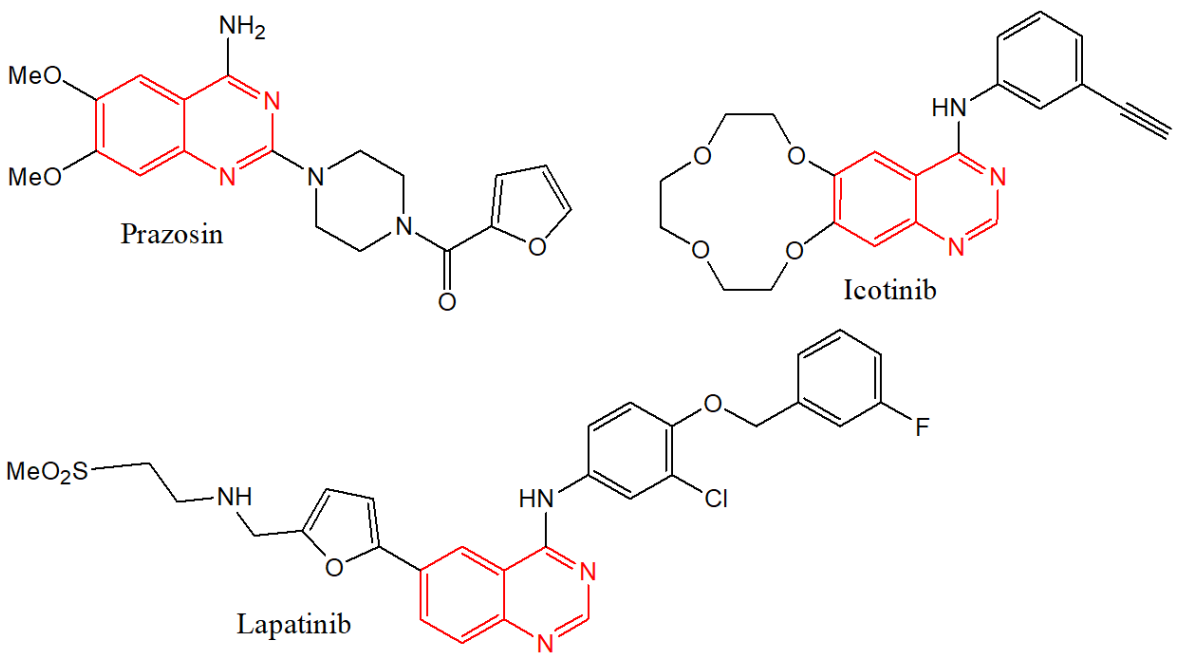


Figure 1. Chemical structure of prazosin, icotinib and lapatinib.

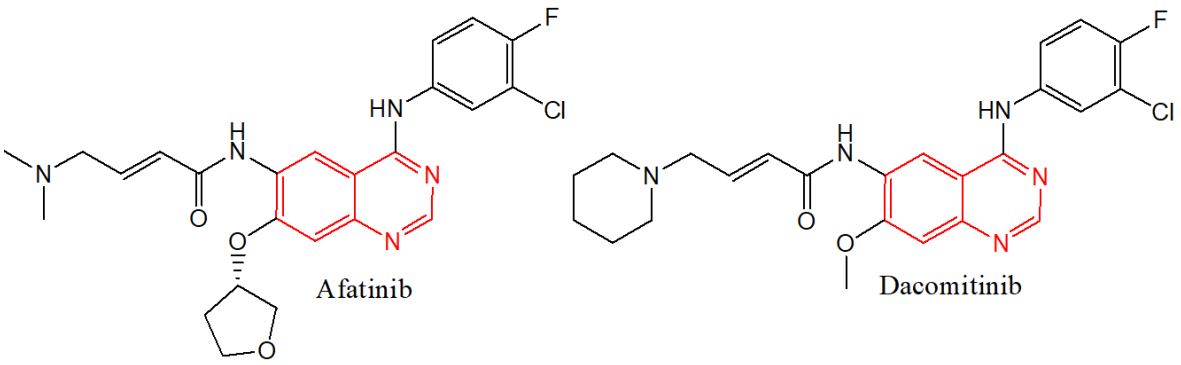
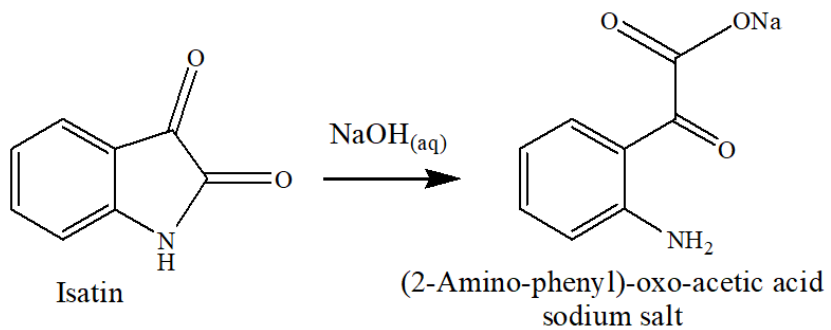


Figure 2. Chemical structure of afatinib and dacomitinib.

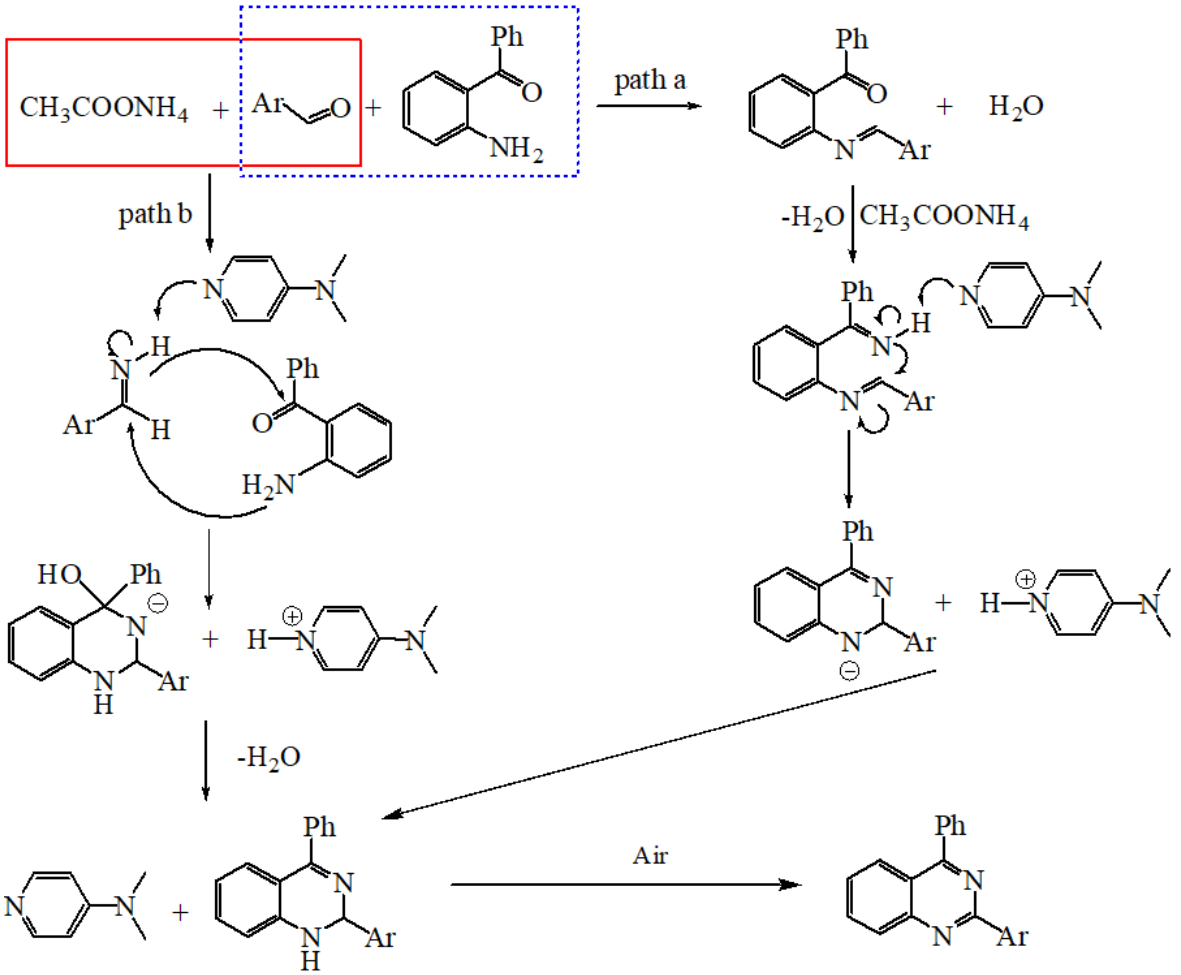
synthesized quinazoline derivatives according to this method. We used 4-chlorobenzaldehyde as the aldehyde. We added ammonium acetate as the ammonia source in the reaction. We used hydrolysis isatin as an alternative to the 2-aminobenzophenone compound. When isatin is hydrolysed with $NaOH_{(aq)}$ in alkaline medium, it turns into (2-amino-phenyl)-oxo-acetic acid sodium salt (Scheme 1).

While the aromatic primary amine group on the hydrolysis isatin compound reacts with 4-chlorobenzaldehyde, the ketone group reacts with ammonia. Thus, the synthesis of 2-(4-chloro-phenyl)-quinazoline-4-carboxylic acid sodium salt (1), a quinazoline derivative, was carried out by a one-pot three-component condensation reaction of hydrolysis isatin, 4-chlorobenzaldehyde and ammonium acetate. The quinazoline ring with a carboxyl group in the 4-position was synthesized for the first time by us in our previous study [27].

Two routes have been proposed for the mechanism of the synthesis of dihydroquinazoline and quinazoline by condensation reactions between aldehyde, 2-aminobenzophenone and ammonium acetate. In one of these routes (path a), firstly, the aldimine compound is obtained from the reaction of the 2-aminobenophenone and aldehyde compounds, and the reaction of the obtained aldimine and ammonium acetate compounds is converted to the diimine compound. Finally, it is converted to the 1,2-dihydroquinazoline compound by intramolecular cyclization of the diimine compound, which is then converted to the quinazoline compound upon aromatization by interacting with air. In the second route (path b), the reaction of ammonium acetate and aldehyde compounds is first converted to aldimine, the reaction of the obtained aldimine compound with 2-aminobenzophenone is then converted to 1,2-dihydroquinazoline and quinazoline as in the first route (Scheme 2) [28].



Sheme 1. Hydrolysis of isatin in basic medium.



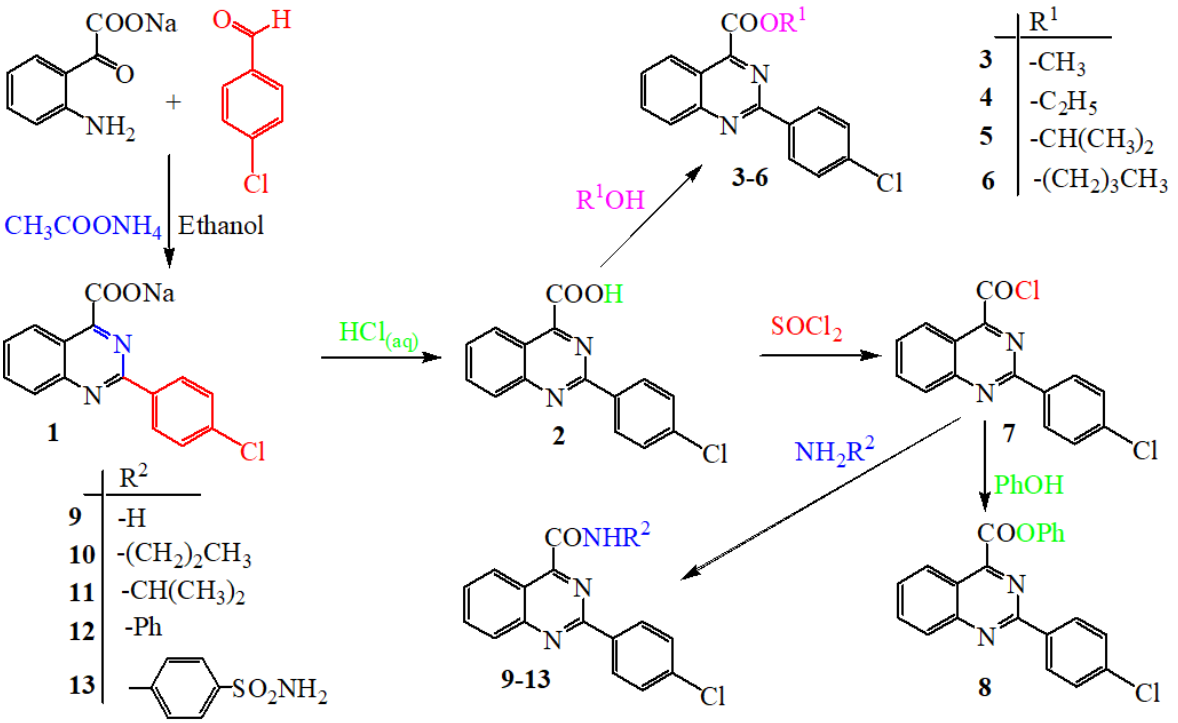
Sheme 2. Proposed mechanisms for the synthesis of quinazolines and 1,2-dihydroquinazolines with DMAP-catalyzed.

Compound 1, which is the acid salt, was converted to the quinazoline carboxylic acid derivative 2 by dissolving in water and acidifying the medium with HCl. The carboxyl group attached to the 4-position of the quinazoline ring allowed the synthesis of ester and amide derivatives. For this, new ester derivatives 3–6 of 2-(4-chloro-phenyl)-quinazoline-4-carboxylic acid (2) in various alcohols were easily synthesized under the catalysis of sulfuric acid. The carbonyl group of compound 2 was then activated by its interaction with $SOCl_2$ to give the 2-(4-chloro-phenyl)-quinazoline-4-carbonyl chloride (7) compound. Finally, new amide derivatives 9–13 were synthesized from the reaction of compound 7 with various aliphatic and aromatic amines. The synthesis of compounds is shown in scheme 3.

MATERIALS and METHODS

Chemicals and Instruments

The chemicals used in the synthesis and solvents were purchased from Merck (Darmstadt, Germany) and Sigma Aldrich (Steinheim, Germany) Chemical Company. Solvents were used without further purification. Reaction progress was monitored using thin layer chromatography (TLC) with an aluminium plate coated with silica gel $60F_{254}$ (Merck Millipore, Billerica, MA, USA). The Melting points were determined on a Stuart SMP30 apparatus. IR spectra were recorded as KBr pellets on a Bruker Vertex 70 Sample compartment spectrometer. ^{1}H-NMR and ^{13}C-NMR were recorded on a Bruker AVANS 300 MHz spectrometer with tetramethylsilane



Sheme 3. Synthesis of quinazoline-4-carboxylic acid derivatives (1-13).

(TMS) as internal standard. ^{1}H-NMR data are reported as follows chemical shift (s=singlet, d=doublet, t=triplet, and m=multiplet). The mass analyses were performed on an Agilent Technologies 6530 Accurate-Mass Q-TOF LC/MS. High resolution mass spectra were recorded on an Agilent Technologies 6530 Accurate-Mass Q-TOF LC/MS using ESI mode.

Synthesis

2-(4-Chloro-phenyl)-quinazoline-4-carboxylic acid sodium salt (1). A mixture of ammonium acetate (0.154 g, 2 mmol) and 4-chlorobenzaldehyde (0.140 g, 1 mmol) were added to a solution of (2-amino-phenyl)-oxo-acetic acid sodium salt (0.187 g, 1 mmol) in ethanol (10 mL) at room temperature. The mixture was stirred and heated to reflux for 24 h. The formed precipitate was filtered while it was still hot. The product was crystallized from toluene. Yield: 0.10 g (33%); M.P.: above 350 °C; IR (*v*, cm^{-1}): 3074 (Ar CH), 1611 (C=O), 1566-1450 (C=C and C=N), 778 (C-Cl); ^{1}H NMR (300 MHz, DMSO-d$_6$) δ (ppm): 8.54 (d, *J*=8.5 Hz, 2H, Ar-H), 8.14 (d, *J*=8.2 Hz, 1H, Ar-H), 7.98-7.89 (m, 2H, Ar-H), 7.65-7.60 (m, 3H, other Ar-H); ^{13}C NMR (75 MHz, DMSO-d$_6$) δ (ppm): 170.79 (COONa), 169.17, 158.82, 150.78, 137.29, 135.79, 134.36, 130.24, 129.11, 128.29, 127.41, 119.65; HRMS (QTOF-ESI): *m/z* calcd for $C_{15}H_8ClN_2NaO_2$: 306.0172; found: 284.0353 [M-Na]$^+$.

2-(4-Chloro-phenyl)-quinazoline-4-carboxylic acid (2). Compound 1 (0.306 g, 1 mmol) was added to distilled water (10 mL). The obtained solution was heated to 90 °C and slowly acidified with 2N $HCl_{(aq)}$ till reaching pH 1. The resulting mixture was kept at 5 °C overnight. Then, the precipitate was filtered off and washed with water (3 x 15 mL). The product was crystallized from toluene. Yield: 0.26 g (91%); M.P.: 172-173 °C; IR (*v*, cm^{-1}): 3500-2500 (COOH), 3119 (Ar CH), 1776 (C=O, acid), 1614-1455 (C=C and C=N), 778 (C-Cl); ^{1}H NMR (300 MHz, DMSO-d$_6$) δ (ppm): 14.55 (br, s, 1H, COOH), 8.58 (d, *J*=8.6 Hz, 2H, Ar-H), 8.43 (d, *J*=8.4 Hz, 1H, Ar-H), 8.18-8.09 (m, 2H, Ar-H), 7.83 (t, *J*=8.2, 1H, Ar-H), 7.67 (d, *J*=8.6 Hz, 2H, other Ar-H); ^{13}C NMR (75 MHz, DMSO-d$_6$) δ (ppm): 166.64 (C=O, acid), 159.85, 158.45, 151.78, 136.53, 136.01, 135.82, 130.35, 129.37, 129.07, 126.49, 119.83; HRMS (QTOF-ESI): *m/z* calcd for $C_{15}H_9ClN_2O_2$: 284.0353; found: 284.0357 [M]$^+$.

2-(4-Chloro-phenyl)-quinazoline-4-carboxylic acid methyl ester (3). H_2SO_4 (95-97%, 0.3 mL) was added to a solution of 2 (0.284 g, 1 mmol) in methanol (20 mL) at room temperature, and the mixture was stirred and heated to reflux for 6 h. The resulting mixture was filtered while it was still hot. The solution was kept at 5 °C overnight. Then, the obtained crystals were filtered. The product was recrystallized from methanol. Yield:

0.23 g (77%); M.P.: 154-155 °C; IR (*v*, cm^{-1}): 2999 (Ar CH), 2952 (aliphatic CH), 1728 (C=O, ester), 1611-1445 (C=C and C=N), 1212 (C-O, ester), 781 (C-Cl); ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 8.58 (d, *J*=8.7 Hz, 2H, Ar-H), 8.50 (d, *J*=7.3 Hz, 1H, Ar-H), 8.12 (d, *J*=8.5 Hz, 1H, Ar-H), 7.94 (t, *J*=7.7, 1H, Ar-H), 7.66 (t, *J*=7.8, 1H, Ar-H), 7.49 (d, *J*=8.7 Hz, 2H, other Ar-H), 4.15 (s, 3H, OCH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 165.48 (C=O, ester), 159.14, 157.07, 152.39, 137.18, 135.78, 134.58, 130.01, 129.17, 128.86, 128.47, 125.93, 120.47, 53.28 (OCH_3); HRMS (QTOF-ESI): *m/z* calcd for $C_{16}H_{11}ClN_2O_2$: 298.0509; found: 298.0513 $[M]^+$.

2-(4-Chloro-phenyl)-quinazoline-4-carboxylic acid ethyl ester (4). H_2SO_4 (95-97%, 0.3 mL) was added to a solution of 2 (0.284 g, 1 mmol) in ethanol (20 mL) at room temperature, and the mixture was stirred and heated to reflux for 6 h. The resulting mixture was filtered while it was still hot. The solution was kept at 5 °C overnight. Then, the obtained crystals were filtered. The product was recrystallized from ethanol. Yield: 0.24 g (77%); M.P.: 124-125 °C; IR (*v*, cm^{-1}): 3071 (Ar CH), 2989 (aliphatic CH), 1734 (C=O, ester), 1615-1451 (C=C and C=N), 1231 (C-O, ester), 765 (C-Cl); ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 8.60 (d, *J*=8.7 Hz, 2H, Ar-H), 8.45 (d, *J*=8.5 Hz, 1H, Ar-H), 8.13 (d, *J*=8.5 Hz, 1H, Ar-H), 7.94 (t, *J*=7.0, 1H, Ar-H), 7.66 (t, *J*=7.7, 1H, Ar-H), 7.50 (d, *J*=8.7 Hz, 2H, other Ar-H), 4.63 (q, *J*=7.1 Hz, 2H, OCH_2), 1.54 (t, *J*=7.1 Hz, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 165.09 (C=O, ester), 159.10, 157.67, 152.26, 137.12, 135.81, 134.48, 130.02, 129.13, 128.81, 128.34, 125.86, 120.35, 62.61 (OCH_2), 14.31 (CH_3); HRMS (QTOF-ESI): *m/z* calcd for $C_{17}H_{13}ClN_2O_2$: 312.0666; found: 312.0668 $[M]^+$.

2-(4-Chloro-phenyl)-quinazoline-4-carboxylic acid isopropyl ester (5). H_2SO_4 (95-97%, 0.3 mL) was added to a solution of 2 (0.284 g, 1 mmol) in isopropanol (20 mL) at room temperature, and the mixture was stirred and heated to reflux for 6 h. The resulting mixture was filtered while it was still hot. The solution was kept at 5 °C overnight. Then, the obtained crystals were filtered. The product was recrystallized from isopropanol. Yield: 0.20 g (61%); M.P.: 102-103 °C; IR (*v*, cm^{-1}): 3071 (Ar CH), 2983 (aliphatic CH), 1734 (C=O, ester), 1615-1448 (C=C and C=N), 1222 (C-O, ester), 773 (C-Cl); ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 8.60 (d, *J*=8.6 Hz, 2H, Ar-H), 8.38 (d, *J*=7.9 Hz, 1H, Ar-H), 8.12 (d, *J*=8.5 Hz, 1H, Ar-H), 7.93 (t, *J*=7.0, 1H, Ar-H), 7.65 (t, *J*=7.7, 1H, Ar-H), 7.49 (d, *J*=8.6 Hz, 2H, other Ar-H), 5.51 (heptet, *J*=6.2 Hz, 1H, OCH), 1.53 (d, *J*=6.3 Hz, 6H, $2CH_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 164.72 (C=O, ester), 159.07, 158.28, 152.15, 137.07, 135.84, 134.39, 130.03, 129.13, 128.76, 128.22, 125.75, 120.22, 70.68 (OCH), 21.93 (CH_3); HRMS (QTOF-ESI): *m/z* calcd for $C_{18}H_{15}ClN_2O_2$: 326.0822; found: 326.0825 $[M]^+$.

2-(4-Chloro-phenyl)-quinazoline-4-carboxylic acid butyl ester (6). H_2SO_4 (95-97%, 0.3 mL) was added to a solution of 2 (0.284 g, 1 mmol) in *n*-butanol (20 mL) at room temperature, and the mixture was stirred and heated to reflux for 6 h. The resulting mixture was filtered while it was still hot. The solution was kept at 5 °C overnight. Then, the obtained crystals were filtered. The product was recrystallized from *n*-butanol. Yield: 0.20 g (59%); M.P.: 83-84 °C; IR (*v*, cm^{-1}): 3073 (Ar CH), 2956 (aliphatic CH), 1726 (C=O, ester), 1615-1450 (C=C and C=N), 1216 (C-O, ester), 781 (C-Cl); ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 8.60 (d, *J*=8.7 Hz, 2H, Ar-H), 8.44 (d, *J*=8.1 Hz, 1H, Ar-H), 8.14 (d, *J*=8.5 Hz, 1H, Ar-H), 7.95 (t, *J*=7.7, 1H, Ar-H), 7.67 (t, *J*=7.7, 1H, Ar-H), 7.50 (d, *J*=8.7 Hz, 2H, other Ar-H), 4.57 (t, *J*=6.7 Hz, 2H, OCH_2), 1.89 (pentet, *J*=7.8 Hz, 2H, OCH_2CH_2), 1.56 (hextet, *J*=7.4 Hz, 2H, CH_2CH_3), 1.03 (t, *J*=7.4 Hz, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 165.21 (C=O, ester), 159.13, 157.84, 152.22, 137.18, 135.79, 134.53, 130.03, 129.11, 128.84, 128.37, 125.87, 120.37, 66.45 (OCH_2), 30.64 (OCH_2CH_2), 19.23 (CH_2CH_3), 13.76 (CH_3); HRMS (QTOF-ESI): *m/z* calcd for $C_{19}H_{17}ClN_2O_2$: 340.0979; found: 340.0978 $[M]^+$.

2-(4-Chloro-phenyl)-quinazoline-4-carbonyl chloride (7). A mixture of 2 (0.284 g, 1 mmol) and $SOCl_2$ (%95; 5 mL) were heated in an oil bath (80 °C) for 8 h. The solvent was removed on a rotary evaporator at 50 °C. The residue was washed with ether (3 x 5 mL). The product was crystallized from toluene. Yield: 0.27 g (89%); M.P.: 161-162 °C; IR (*v*, cm^{-1}): 1750 (C=O, carbonyl), 1588-1449 (C=C and C=N), 768 (C-Cl); ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 8.63 (d, *J*=8.7 Hz, 2H, Ar-H), 8.55 (d, *J*=8.1 Hz, 1H, Ar-H), 8.19 (d, *J*=8.5 Hz, 1H, Ar-H), 8.00 (t, *J*=7.7, 1H, Ar-H), 7.74 (t, *J*=7.7, 1H, Ar-H), 7.52 (d, *J*=8.7 Hz, 2H, other Ar-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 163.14 (C=O, carbonyl), 159.08, 155.57, 152.93, 137.94, 136.14, 135.26, 130.13, 129.91, 129.08, 127.18, 125.02, 119.30; HRMS (QTOF-ESI): *m/z* calcd for $C_{15}H_8Cl_2N_2O$: 302.0014; found: 302.0458 $[M]^+$.

2-(4-Chloro-phenyl)-quinazoline-4-carboxylic acid phenyl ester (8). A mixture of phenol (0.094 g, 1 mmol) and triethylamine (0.10 g, 1 mmol) were added to a solution of 4 (0.302 g, 1 mmol) in toluene (30 mL) at room temperature. The mixture was stirred and heated to

reflux for 7 h. The reaction mixture was filtered while it was still hot. The solution was kept at 5 °C overnight. Then, the obtained crystals were filtered. The product was recrystallized from toluene. Yield: 0.20 g (55%); M.P.: 172-173 °C; IR (*v*, cm^{-1}): 3093 (Ar CH), 1749 (C=O, ester), 1612-1450 (C=C and C=N), 1199 (C-O, ester), 782 (C-Cl); ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 8.67-8.61 (m, 3H, Ar-H), 8.17 (d, *J*=8.5 Hz, 1H, Ar-H), 7.97 (t, *J*=7.7, 1H, Ar-H), 7.69 (t, *J*=7.8, 1H, Ar-H), 7.54-7.49 (m, 4H, Ar-H), 7.41-7.33 (m, 3H, other Ar-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 163.50 (C=O, ester), 159.14, 156.24, 152.57, 150.62, 137.28, 135.69, 134.71, 130.06, 129.74, 129.30, 128.89, 128.75, 126.59, 125.74, 121.53, 120.70; HRMS (QTOF-ESI): *m/z* calcd for $C_{21}H_{13}ClN_2O_2$: 360.0666; found: 360.0658 $[M]^+$.

2-(4-Chloro-phenyl)-quinazoline-4-carboxylic acid amide (9). A mixture of 4 (0.302 g, 1 mmol) and THF (30 mL) were cooled to 0 °C. The obtained solution was slowly added to ammonium hydroxide solution (0.15 mL, 2 mmol) at 0 °C, stirred, and kept at this temperature for 2 h. The reaction mixture was continued and stirred at room temperature for an additional 6 h. The solvents were removed on a rotary evaporator at 40 °C. The residue was washed with water (3 x 10 mL) and ether (3 x 10 mL). The product was crystallized from THF. Yield: 0.18 g (63%); M.P.: 239-240 °C; IR (*v*, cm^{-1}): 3184 (NH), 3069 (Ar CH), 1703 (C=O, amide), 1612-1491 (C=C and C=N), 783 (C-Cl); ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 8.82 (d, *J*=8.5 Hz, 1H, Ar-H), 8.70-8.67 (m, 3H, Ar-H), 8.15-8.05 (m, 3H, Ar-H and NH_2), 7.79 (t, *J*=7.7, 1H, Ar-H), 7.66 (d, *J*=8.7 Hz, 2H, other Ar-H); ^{13}C NMR (75 MHz, DMSO-d_6) δ (ppm): 166.77 (C=O, amide), 159.63, 157.57, 151.49, 135.87, 135.53, 134.94, 130.61, 130.02, 129.27, 128.68, 126.76, 119.82; HRMS (QTOF-ESI): *m/z* calcd for $C_{15}H_{10}ClN_3O$: 283.0512; found: 283.0515 $[M]^+$.

2-(4-Chloro-phenyl)-quinazoline-4-carboxylic acid propylamide (10). *n*-Propylamine (0.118 g, 2 mmol) was added to a solution of 4 (0.302 g, 1 mmol) in toluene (30 mL) at room temperature. The mixture was stirred and heated to reflux for 6 h. The reaction mixture was filtered while it was still hot. The solution was kept at 5 °C overnight. Then, the obtained crystals were filtered. The product was recrystallized from toluene. Yield: 0.21 g (64%); M.P.: 165-166 °C; IR (*v*, cm^{-1}): 3321 (NH), 3068 (Ar CH), 2929 (aliphatic CH), 1653 (C=O, amide), 1616-1491 (C=C and C=N), 786 (C-Cl); ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 9.43 (d, *J*=8.0 Hz, 1H, Ar-H), 8.52 (d, *J*=8.6 Hz, 2H, Ar-H), 8.23 (br, s, 1H, NH), 8.09 (d, *J*=8.5 Hz, 1H, Ar-H), 7.93 (t, *J*=7.0, 1H, Ar-H), 7.67 (t, *J*=7.7, 1H, Ar-H), 7.52 (d, *J*=8.6 Hz, 2H, other Ar-H), 3.55 (q, *J*=7.4, 2H, $NHC\underline{H}_2$), 1.77 (hextet, *J*=7.2 Hz, 2H, $C\underline{H}_2CH_3$), 1.08 (t, *J*=7.3 Hz, 3H, $C\underline{H}_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 164.70 (C=O, amide), 157.75, 155.90, 153.07, 137.08, 135.68, 134.51, 129.62, 128.87, 128.70, 128.50, 127.79, 121.07, 41.35 ($NHCH_2$), 22.90 ($\underline{C}H_2CH_3$), 11.54 ($CH_2\underline{C}H_3$); HRMS (QTOF-ESI): *m/z* calcd for $C_{18}H_{16}ClN_3O$: 325.0982; found: 325.0981 $[M]^+$.

2-(4-Chloro-phenyl)-quinazoline-4-carboxylic acid isopropylamide (11). İsopropylamine (0.118 g, 2 mmol) was added to a solution of 4 (0.302 g, 1 mmol) in toluene (30 mL) at room temperature. The mixture was stirred and heated to reflux for 6 h. The reaction mixture was filtered while it was still hot. The solution was kept at 5 °C overnight. Then, the obtained crystals were filtered. The product was recrystallized from toluene. Yield: 0.20 g (61%); M.P.: 191-192 °C; IR (*v*, cm^{-1}): 3307 (NH), 3065 (Ar CH), 2933 (aliphatic CH), 1648 (C=O, amide), 1614-1491 (C=C and C=N), 787 (C-Cl); ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 9.43 (d, *J*=8.6 Hz, 1H, Ar-H), 8.52 (d, *J*=8.5 Hz, 2H, Ar-H), 8.09 (d, *J*=8.5 Hz, 1H, Ar-H), 8.00 (br, d, *J*=7.5 Hz, 1H, NH), 7.93 (t, *J*=7.7, 1H, Ar-H), 7.67 (t, *J*=7.7, 1H, Ar-H), 7.52 (d, *J*=8.5 Hz, 2H, other Ar-H), 4.37 (octet, *J*=7.9, 1H, NHC<u>H</u>), 1.39 (d, *J*=6.5 Hz, 6H, $2C\underline{H}_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 163.90 (C=O, amide), 157.74, 155.99, 153.04, 137.07, 135.69, 134.48, 129.63, 128.88, 128.70, 128.47, 127.79, 121.08, 41.76 (CH), 22.71 (CH_3); HRMS (QTOF-ESI): *m/z* calcd for $C_{18}H_{16}ClN_3O$: 325.0982; found: 325.0981 $[M]^+$.

2-(4-Chloro-phenyl)-quinazoline-4-carboxylic acid phenylamide (12). Aniline (0.186 g, 2 mmol) was added to a solution of 4 (0.302 g, 1 mmol) in toluene (30 mL) at room temperature. The mixture was stirred and heated to reflux for 6 h. The reaction mixture was filtered while it was still hot. The solution was kept at 5 °C overnight. Then, the obtained crystals were filtered. The product was recrystallized from toluene. Yield: 0.21 g (58%); M.P.: 181-182 °C; IR (*v*, cm^{-1}): 3305 (NH), 3064 (Ar CH), 1658 (C=O, amide), 1597-1493 (C=C and C=N), 780 (C-Cl); ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 10.14 (br, s, 1H, NH), 9.48 (d, *J*=8.6 Hz, 1H, Ar-H), 8.52 (d, *J*=7.8 Hz, 2H, Ar-H), 8.09 (d, *J*=8.5 Hz, 1H, Ar-H), 7.94 (t, *J*=7.1, 1H, Ar-H), 7.83 (d, *J*=8.5 Hz, 2H, Ar-H), 7.68 (t, *J*=7.7, 1H, Ar-H), 7.53-7.42 (m, 4H, Ar-H), 7.24 (t, *J*=5.3 Hz, 1H, other Ar-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 162.32 (C=O, amide), 157.66, 155.22, 153.44, 137.32, 137.21, 135.50, 134.82, 129.66, 129.26, 129.04, 128.92, 128.89, 127.69, 125.09, 121.22,

120.15; HRMS (QTOF-ESI): *m/z* calcd for $C_{21}H_{14}ClN_3O$: 359.0825; found: 359.0825 $[M]^+$.

2-(4-Chloro-phenyl)-quinazoline-4-carboxylic acid (4-sulfamoyl-phenyl)-amide (13). 4-aminobenzenesulfonamide (0.344 g, 2 mmol) was added to a solution of 4 (0.302 g, 1 mmol) in THF (30 mL) at room temperature. The mixture was stirred and heated to reflux for 6 h. The reaction mixture was filtered while it was still hot. The resulting precipitate was washed with hot water and ether (3 x 5 mL). The product was crystallized from DMF-water mixture. Yield: 0.24 g (55%); M.P.: 323-324 °C; IR (*ν*, cm^{-1}): 3303 (NH), 3122 (Ar CH), 1675 (C=O, amide), 1614-1448 (C=C and C=N), 1336 (SO_2 asym.), 1156 (SO_2 sym.), 778 (C-Cl); ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 11.35 (s, 1H, NH), 8.71-8.63 (m, 3H, Ar-H), 8.21-8.05 (m, 4H, Ar-H), 7.92-7.81 (m, 3H, Ar-H), 7.69 (d, *J*=8.5 Hz, 2H, other Ar-H), 7.37 (s, 2H, $SO_2N\underline{H}_2$); ^{13}C NMR (75 MHz, DMSO-d_6) δ (ppm): 164.08 (C=O, amide), 159.91, 158.19, 152.07, 141.52, 140.16, 136.63, 135.92, 135.82, 130.65, 129.41, 129.31, 129.07, 127.23, 126.82, 120.73, 120.19; HRMS (QTOF-ESI): *m/z* calcd for $C_{21}H_{15}ClN_4O_3S$: 438.0553; found: 438.0546 $[M]^+$.

RESULTS and DISCUSSION

In this study, new quinazoline derivative compounds carrying carboxyl group in 4-position, which were synthesized by us for the first time, were synthesized. The hydrolysis isatin compound we used as the starting material was easily obtained from the alkaline hydrolysis of isatin. Quinazoline derivative, which is a salt of carboxylic acid, was synthesized from the one-pot three-component reaction of hydrolysis isatin, ammonium acetate and 4-chlorobenzaldehyde. Ammonium acetate, one of the starting materials, creates a nitrogen source with ammonia, while acetic acid makes the medium weakly acidic. This shows the importance of the role of ammonium acetate in the reactions.

In the reaction mechanism shown above, an aromatic amine compound (DMAP) is used as a catalyst in the synthesis of quinazoline. Because we do not use a catalyst in the reaction to obtain the quinazoline derivative, the catalytic function is presumed to be the hydrolysis isatin compound containing the aromatic primary amine group such as DMAP. Therefore, while the hydrolysis isatin compound is present as a reactant in the reaction, it also acts as a catalyst.

The quinazoline carboxylic acid salt 1, insoluble in hot ethanol, was easily separated from the reaction medium by filtration. In this way, the main product was easily separated from the reaction medium, where there were both starting materials and by-products such as dihydroquinazoline derivative. The quinazoline carboxylic acid salt containing the aromatic ring was dissolved in water and turned into a water-insoluble carboxylic acid derivative by acidifying the medium with HCl. Then, quinazoline carboxylic acid derivative 2, which is insoluble in acidic medium, was easily isolated from the medium by filtration. The fact that 1 and 2 products are easily obtained by the filtration method has facilitated and accelerated the chemical process.

The carboxyl group attached to the 4-position of the obtained quinazoline ring was easily converted to its esters by the Fischer esterification method with various alcohols under the catalysis of sulfuric acid. Quinazoline carboxylic acid compound (2) was activated to quinazoline acid chloride compound (7) with high yield (89%) by reacting with $SOCl_2$. The synthesis of amide derivatives was also carried out from the reaction of compound 7 with various aromatic and aliphatic amines.

As a result, we successfully obtained the ester and amide derivatives of the quinazoline, which we synthesized with a one pot three component reaction. Because quinazoline derivatives show a wide variety of biological activities in the literature, we hope that the compounds obtained from this study will contribute to medicinal chemistry.

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