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ARTICLE

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One-pot three-component synthesis of novel 2-(3-nitro-phenyl)-quinazoline-4-carboxylic acid derivatives

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Abstract

A simple and easy synthesis of 2-(3-nitro-phenyl)-quinazoline-4-carboxylic acid (**3**) has been successfully developed through a one-pot three-component condensation reaction of (2-amino-phenyl)-oxo-acetic acid sodium salt (**1**) obtained from the hydrolysis of isatin with ammonium acetate and 3-nitrobenzaldehyde. Some novel quinazoline-ester derivatives **4-7** were then obtained by the reaction between the new compound **3** and various alcohols. Then, quinazoline-amide derivatives **10-14** were synthesized from the reaction of various amines and 2-(3-nitro-phenyl)-quinazoline-4-carbonyl chloride (**8**), obtained by the reaction of compound **3** with $SOCl_2$. Finally, some novel quinazoline-azo derivatives **17-19** were synthesized by the coupling reaction between β-dicarbonyl compounds and the novel amino-quinazoline derivative compound **15**, obtained by reduction of nitro-quinazoline derivative compound **11**. Thus, a new series of quinazoline-4-carboxylic acid, ester, amide, and azo derivatives was synthesized and fully characterized by ^{1}H NMR, ^{13}C NMR, IR, and mass spectrometry analysis.

1 | INTRODUCTION

Among the various N-heterocyclic structures, quinazoline and its derivatives form a distinct class of compounds with different biological effects. In recent years, a number of different synthetic derivatives have been obtained because of their importance in medicinal quality. From the studies published every day, it turns out that these structures have different biological activities, such as antimicrobial,[1] antidiabetic,[2] anticancer,[3,4] anti-HIV,[5] antitubercular,[6] antileishmanial,[7] anti-inflammatory,[8] and antifungal[9] activities. Some compounds containing the quinazoline ring, such as gefitinib[10] and erlotinib,[11] are used as anticancer drugs (Figure 1).

Both of the compounds shown above are 4-anilinoquinazoline derivatives and chemotherapeutics used in the treatment of lung cancer.

Similarly, substances such as prazosin and doxazosin, which contain quinazoline skeleton, are used as alpha adrenergic receptor blockers[12,13] (Figure 2).

In addition, some derivatives containing the quinazolin-4-one structure are also important natural alkaloids. New alkaloids such as auranomides A and B (Figure 3) containing quinazolin-4-one structure were isolated from the marine-derived fungus *Penicillium aurantiogriseum*.[14]

As noted above, the biological activity of the quinazoline ring–containing structures has led to the development of various synthesis methods in their laboratory environment, such as photochemical methods,[15] copper-catalyzed syntheses,[16] a maltose-ammonium chloride-urea mixture as a solvent without any catalyst,[17] the use of microwave irradiation,[18] tandem reactions from 2-aminobenzophenones and benzylic amines,[19] and copper-catalyzed Ullmann N-arylation coupling.[20] In general, the disadvantages of these synthesis methods are the toxic and costly metal catalysts, the harmful and volatile solvents, laborious chromatographic methods, reactions at high temperatures, and low yields. For this reason, in the synthesis of such

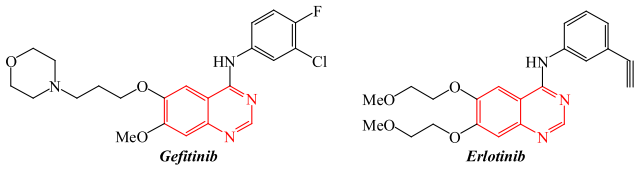


FIGURE 1 Structures of gefitinib and erlotinib [Color figure can be viewed at wileyonlinelibrary.com]

compounds, it is of great importance to develop new simple and practical methods that are not harmful to the environment. In this context, one-pot three-component reactions in the synthesis methods may be considered to facilitate the obtaining of the desired compounds.

In one study, Derabli et al[21] showed that 1,2-dihydroquinazolines can be obtained by 4-(*N*,*N*-dimethylamino)pyridine (DMAP)-catalyzed, one-pot three-component synthesis at low temperature (40°C) (Scheme 1).

For the above one-pot three-component reactions, two different reaction mechanisms were proposed.[22] In the first reaction mechanism (path a), an aldimine compound was formed by the condensation reaction of aromatic aldehyde and 2-aminobenzophenone compounds. Then, aldimine and ammonium acetate, the third component of the reaction, were again condensed to form a diimine compound. The proton transfer of diimine to catalyst and subsequent intramolecular cyclization reaction was converted to the corresponding 1,2-dihydroquinazoline compound, which can be aromatized by air to give the corresponding quinazoline. According to the other reaction mechanism (path b), the condensation reaction of aromatic aldehyde and ammonium acetate was first converted to the aldimine compound. Then the 1,2-dihydroquinazoline compound was formed from the cyclization reaction of aldimine with 2-aminobenzophenone. The proposed mechanisms are shown below (Scheme 2).

Quinazoline derivatives exhibit versatile biological activities as described above, which has stimulated the synthesis of these compounds. In this work, we aimed to show synthesis of new quinazoline derivatives containing carboxylic acid in 4-position. In the literature, we have noticed that there are no carboxylic acid–containing derivatives in the 4-position of the quinazoline ring and that our work is the first in this respect. We have obtained a series of quinazolines in the synthesis of the acid

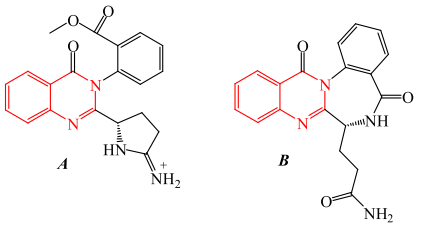
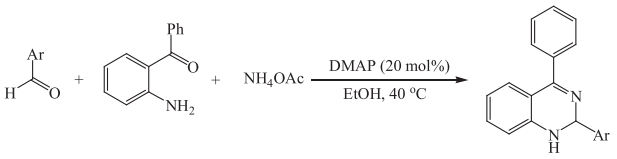


FIGURE 3 Structures of auranomides A and B [Color figure can be viewed at wileyonlinelibrary.com]



SCHEME 1 Synthesis of 1,2-dihydroquinazoline derivatives by Derabli et al

derivatives of our quinazoline compound containing a group of carboxylic acids, which we synthesized with different starting compounds.

The isatin compound was used as the starting compound in many reactions. It was also the starting compound of our reactions. It was hydrolyzed in alkaline medium to form (2-amino-phenyl)-oxo-acetic acid sodium salt (**1**). When we converted the alkaline medium to an acidic medium, it did not form (2-amino-phenyl)-oxo-acetic acid compound, and then it is recycled to the isatin compound by repeated cyclization and aromatization (Scheme 3). Thus, the presence of both the aromatic primary amine group and the ketone group in the hydrolysis isatin compound at certain positions allows the synthesis of quinazolines.

As the starting compound in this study, carboxylic acid salt-containing derivative of the quinazoline **2** was obtained through a one-pot three-component condensation reaction of 3-nitrobenzaldehyde, ammonium acetate, and (2-amino-phenyl)-oxo-acetic acid sodium salt (**1**) obtained from the hydrolysis of isatin. The interaction of **1** with $HCl_{(aq)}$ forms the quinazoline carboxylic acid derivative **3**. The presence of the carboxyl group bound to the quinazoline ring allows the synthesis of acid derivatives.

In addition, compound **3** was easily converted to the new ester derivatives **4–7** by reacting with different alcohols in the sulfuric acid catalyst. The carbonyl group of

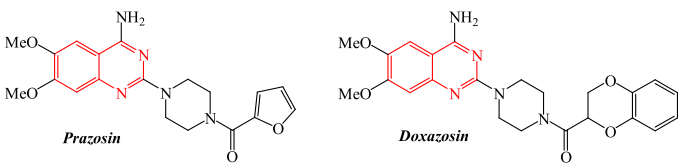
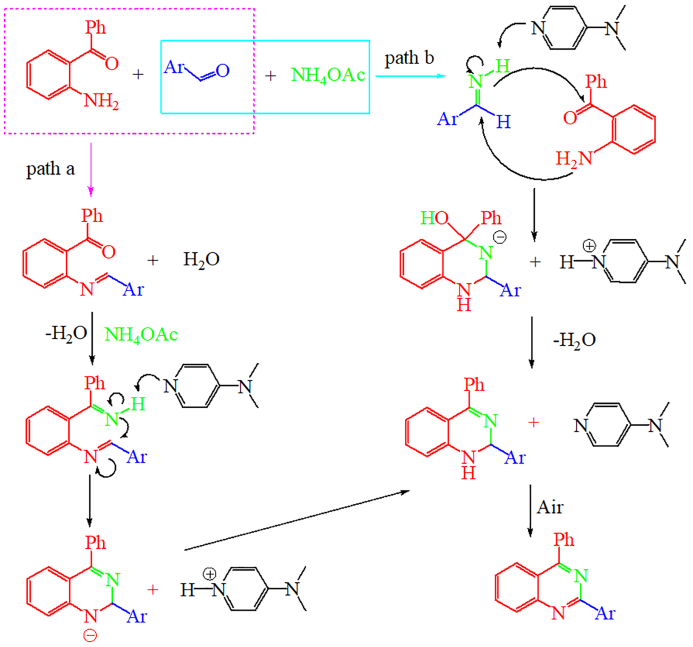
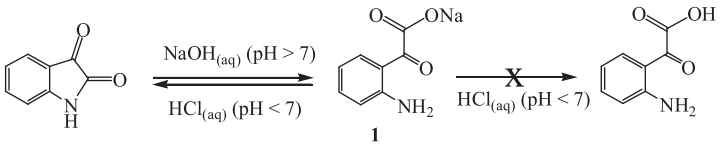


FIGURE 2 Structures of prazosin and doxazosin [Color figure can be viewed at wileyonlinelibrary.com]



SCHEME 2 Proposed mechanisms for the synthesis of 1,2-dihydroquinazolines [Color figure can be viewed at wileyonlinelibrary.com]



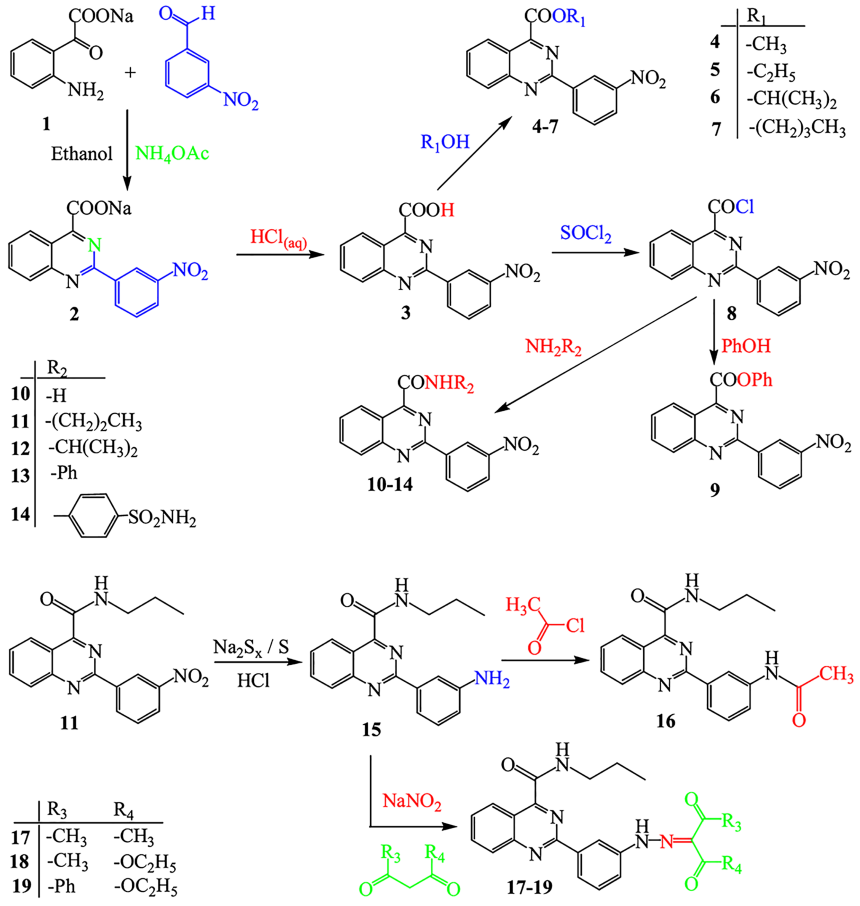
SCHEME 3 Hydrolysis of isatin in alkaline medium

compound **3** was then activated by treatment of $SOCl_2$ with compound **8**. New amide derivatives **10-14** were obtained by the reaction of the carbonyl group of compound **8** with various amines. The aromatic nitro group of compound **11** was then reduced with sodium polysulphur hydrogenation ($Na_2S/S/H_2O$) **15**. The presence of the aromatic amine group in compound **15** led us to the synthesis of the amide derivative. For this, a second amide group was bound to the compound containing the quinazoline ring by reaction of compound **15** with acetyl chloride **16**. As the last quinazoline derivative, compound **15** was first subjected to the diazoniation followed by coupling reactions with 1,3-dicarbonyl compounds to give the novel quinazoline derivatives **17-19**. The synthesis of compounds is shown in Scheme 4.

2 | RESULTS AND DISCUSSION

For the first time in this article, we have shown that by choosing different starting compounds, carboxylic acid derivatives bound to the quinazoline ring can be synthesized. Since quinazoline derivatives show very different biological activities, we hope that these synthesized compounds will contribute to medical chemistry.

In the quinazoline reaction (in the synthesis of compound **2**), since we do not use a catalyst in our reaction, it is believed that the catalytic function is the sodium salt of (2-amino-phenyl)-oxo-acetic acid (**1**) containing the aromatic amine group. That is, compound **1** acts as both a catalyst and a component of the reaction. At the same time, while compound **1** is insoluble in hot ethanol, it completely dissolves in warm ethanol in the same medium with ammonium acetate and 3-nitrobenzaldehyde. Since the resulting quinazoline compound **2** is an acid salt, it does not dissolve in hot ethanol again and forms a precipitate at the end of the reaction. This allowed compound **2** to be easily separated from both the byproducts and the starting compounds by filtration without the need for laborious processing such as chromatographic separation. This has greatly contributed to facilitating our work. However, when compound **2** was obtained, the yield of the reaction (31%) was very poor because of competitive side reactions and the three components. In addition, despite the reaction optimization studies (different reactant rates, different solvents, and different temperatures), the reaction time (24 hours) was very long. Despite these reaction difficulties, we were happy that the carboxylic acid derivatives bound to the quinazoline ring for the first time were obtained in this study.



SCHEME 4 Synthesis of quinazoline-4-carboxylic acid derivatives (**2-19**) [Color figure can be viewed at wileyonlinelibrary.com]

One of the two best known methods for ester synthesis is the Fischer esterification method, which is based on the direct esterification of acids and alcohols. In this method, ester products were obtained from separate reactions of the quinazoline-derived carboxylic acid compound with methanol, ethanol, isopropanol, and butanol. However, the ester product could not be obtained when the phenol and the acid were directly interacted. The phenol ester product was obtained by reacting the quinazoline acid chloride compound **8** with phenol. This can be explained by the fact that the acid chlorides are more active than the carboxylic acids and the phenyl groups decrease while the alkyl groups increase the electron density on the hydroxyl group of the alcohol. Similarly, compound **8** was readily converted to the amide derivatives from the reactions of various aromatic and aliphatic amines.

Furthermore, the aromatic nitro group of the quinazoline derivative compound was readily reduced with sodium polysulphur hydrogenation. After the reduction, the obtained aromatic amine compound **15** underwent diazoniation and final reactions with 1,3-dicarbonyl compounds to yield novel quinazoline hydrazo derivatives **17-19**. In these compounds, the resulting products may have as enol-azo or keto-hydrazo tautomeric structures.[23] In our work, ^{1}H NMR and ^{13}C NMR results showed that compound **18** show tautomeric structures, while compound **17** prefer enol-azo form and compound **19** prefer keto-hydrazo form, as shown below (Figure 4).

The peaks of C═C—OH and N—H are used to distinguish between possible tautomeric structures. According to the ^{1}H NMR spectra of the compounds **17-19**, compound **17** shows that the C═C—OH peak at δ = 14.86 ppm is only in the enol form. Compound **18** shows that the C═C—OH peak at δ = 14.93 ppm is in the enol form and the N—H peak at δ = 12.95 ppm is in the keto form. Compound **19** shows that the slight peak at δ = 13.77 ppm is not in enol form and the N—H peak at δ = 12.90 ppm is only in keto form. Also, since the relative integral

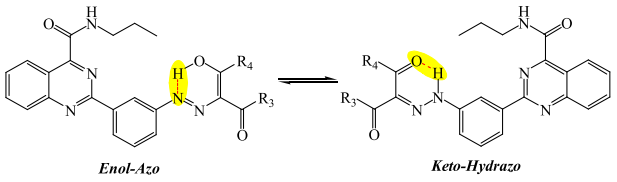


FIGURE 4 Tautomeric structures of keto-hydrazo and enol-azo for compounds **17-19** [Color figure can be viewed at wileyonlinelibrary.com]

of the enol and keto peaks of compound **18** is 1.00:1.08, it has almost equally probable tautomeric structures. A molecule may exhibit different tautomeric structures depending on the presence of alkyl and phenyl groups. This can be explained by the tendency of the −R moiety to attract or repel electrons. In addition, the phenyl group contributes to the molecule, keeping only one form rather than keeping tautomeric structures.

In summary, we have successfully synthesized ester, amide, and azo derivatives of quinazoline-4-carboxylic acid, which are very important for medicinal chemistry in this work.

3 | EXPERIMENTAL

3.1 | General

The chemicals used in the synthesis of all new compounds were purchased from Merck and Aldrich Chemical Company. All chemicals and solvents were of spectroscopic reagent grade. The reactions were monitored by thin-layer chromatography (TLC) using aluminum sheets coated with silica gel 60_{F254} (Merck). Purity of the synthesized compounds was confirmed by TLC in the same way. Spots were detected by their absorption under UV light (λ = 254 nm). Melting points were measured on a Stuart SMP30 apparatus. The IR data (Agilent Technologies Inc., Santa Clara, CA) were recorded on a Bruker Vertex 70 Sample compartment spectrometer using potassium bromide pellets. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker AVANS 300 MHz spectrometer operating at 300 and 75 MHz for ^{1}H and ^{13}C nuclei, respectively, in deuterochloroform and dimethyl sulphoxide-d_6 with tetramethylsilane as internal standard. Shifts were given in ppm, coupling constant (J) values were presented in hertz (Hz), and the abbreviations were as follows: 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 and 7890B GC/MS at the advanced technology research center of Dumlupınar University (ILTEM).

3.2 | (2-Amino-phenyl)-oxo-acetic acid sodium salt (1)

Isatin (1H-indole-2,3-dione) (0.147 g, 1 mmol) was added at room temperature to a stirred solution of NaOH (0.048 g, 1.2 mmol) in distilled water (10 mL). The mixture was stirred at room temperature for 1 hour. The obtained solution was neutralized with 2N $HCl_{(aq)}$ till reaching pH 7. The solvents were removed on a rotary evaporator at 80°C. Then, the precipitate was crystallized from DMF-ethyl acetate mixture and dried in vacuo at 70°C. Yield: 0.14 g (75%); mp 278°C-279°C; IR (ν, cm^{-1}): 3350 (NH_2), 3021 (Ar CH), 1613 (C═O), 1582-1454 (C═C); ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 7.50 (d, J = 7.97 Hz, 1H, H-6), 7.16 (t, J = 7.66 Hz, 1H, H-4), 7.00 (br, s, 2H, NH_2), 6.67 (d, J = 8.33 Hz, 1H, H-3), 6.46 (t, J = 7.46 Hz, 1H, H-5); ^{13}C NMR (75 MHz, DMSO-d_6) δ (ppm): 200.65 (C═O, ketone), 171.13 (COONa), 152.18 (C-NH_2), 134.54, 134.07, 116.79, 114.42, 114.27; HRMS (QTOF-ESI): m/z calcd for $C_8H_6NNaO_3$: 187.0245; found: 186.0169 $[M-1]^+$.

3.3 | 2-(3-Nitro-phenyl)-quinazoline-4-carboxylic acid sodium salt (2)

A mixture of ammonium acetate (0.154 g, 2 mmol) and 3-nitrobenzaldehyde (0.151 g, 1 mmol) were added to a solution of compound **1** (0.187 g, 1 mmol) in ethanol (10 mL) at room temperature. The mixture was stirred and heated to reflux for 24 hours. The formed precipitate was filtered while it was still hot. The product was crystallized from DMF and dried in vacuo at 70°C. Yield: 0.10 g (31%); mp over 345°C; IR (ν, cm^{-1}): 3108 (Ar CH), 1665 (C═O), 1586-1480 (C═C and C═N), 1541 (NO_2 asym.), 1348 (NO_2 sym.); ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 9.29 (s, 1H, phenyl H-2), 8.94 (d, J = 7.98 Hz, 1H, phenyl H-4), 8.39 (d, J = 8.17 Hz, 1H, quinazoline H-8), 8.17 (d, J = 8.23 Hz, 1H, quinazoline H-5), 8.04 (d, J = 8.02 Hz, 1H, phenyl H-6), 7.96 (t, J = 7.61, 1H, quinazoline H-7), 7.87 (t, J = 8.00, 1H, quinazoline H-6), 7.67 (t, J = 7.49, 1H, phenyl H-5); ^{13}C NMR (75 MHz, DMSO-d_6) δ (ppm): 171.18 (COONa), 168.80, 157.72, 150.70, 148.78, 140.10, 134.64, 134.48, 130.85, 128.44, 128.35, 127.95, 125.44, 122.77, 119.90; HRMS (QTOF-ESI): m/z calcd for $C_{15}H_8N_3NaO_4$: 317.0412; found: 316.9457 $[M-1]^+$.

3.4 | 2-(3-Nitro-phenyl)-quinazoline-4-carboxylic acid (3)

Compound **2** (0.317 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 × 15 mL). The product was crystallized from toluene and dried in vacuo at 70°C. Yield: 0.27 g (91%); mp 178°C-179°C; IR (ν, cm^{-1}): 3300-2500 (COOH), 3084 (Ar CH), 1752 (C═O, acid), 1616-1456 (C═C and C═N), 1522 (NO_2 asym.), 1349 (NO_2 sym.); ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 11.52 (br, s, 1H, COOH), 9.47-9.43 (m, 2H, phenyl H-2,4), 8.93 (d, J = 7.82 Hz, 1H, quinazoline H-8), 8.43 (d, J = 8.09 Hz,

1H, quinazoline H-5), 8.27 (d, J = 8.55 Hz, 1H, phenyl H-6), 8.11 (t, J = 7.65, 1H, quinazoline H-7), 7.88-7.76 (m, 2H, quinazoline H-6 and phenyl H-5); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 162.91 (C═O, acid), 156.31, 153.71, 151.70, 149.01, 137.91, 136.12, 133.93, 130.64, 130.00, 129.26, 127.33, 125.84, 123.35, 121.21; HRMS (QTOF-ESI): m/z calcd for $C_{15}H_9N_3O_4$: 295.0593; found: 294.0615 $[M - 1]^+$.

3.5 | General procedure for the syntheses of compounds 4-7

H_2SO_4 (95% to 97%, 0.5 mL) was added to a solution of 2-(3-nitro-phenyl)-quinazoline-4-carboxylic acid (**3**) (0.295 g, 1 mmol) in alcohol (25 mL) at room temperature, and the mixture was stirred and heated to reflux for 5 hours. The resulting mixture was filtered while it was still hot. The obtained solution was kept at 25°C overnight. Then, the precipitate was filtered off, washed with ether (3 × 15 mL), dried, and recrystallized from an appropriate solvent.

3.6 | 2-(3-Nitro-phenyl)-quinazoline-4-carboxylic acid methyl ester (4)

Synthesized from compound **3** and methanol according to the general procedure. The product was recrystallized from methanol and dried in vacuo at 70°C. Yield: 0.20 g (65%); mp 187°C-189°C; IR (ν, cm^{-1}): 3110 (Ar CH), 2957 (aliphatic CH), 1724 (C═O, ester), 1614-1457 (C═C and C═N), 1528 (NO_2 asym.), 1345 (NO_2 sym.); ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 9.52 (s, 1H, phenyl H-2), 9.03 (d, J = 7.82 Hz, 1H, phenyl H-4), 8.57 (d, J = 8.49 Hz, 1H, quinazoline H-8), 8.40 (d, J = 8.18 Hz, 1H, quinazoline H-5), 8.23 (d, J = 8.52 Hz, 1H, phenyl H-6), 8.04 (t, J = 7.69, 1H, quinazoline H-7), 7.79-7.72 (m, 2H, quinazoline H-6 and phenyl H-5), 4.20 (s, 3H, $OC\underline{H}_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 165.29 (C═O, ester), 157.84, 157.43, 152.34, 148.88, 139.16, 134.97, 134.37, 129.95, 129.62, 129.34, 126.05, 125.34, 123.65, 120.82, 53.42 (OCH_3); GC-MS (ESI): m/z calcd for $C_{16}H_{11}N_3O_4$: 309.1; found: 309.1 $[M]^+$.

3.7 | 2-(3-Nitro-phenyl)-quinazoline-4-carboxylic acid ethyl ester (5)

Synthesized from compound **3** and ethanol according to the general procedure. The product was recrystallized from ethanol and dried in vacuo at 70°C. Yield: 0.23 g (71%); mp 145°C-147°C; IR (ν, cm^{-1}): 3113 (Ar CH), 2982 (aliphatic CH), 1727 (C═O, ester), 1614-1455 (C═C and C═N), 1521 (NO_2 asym.), 1342 (NO_2 sym.); ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 9.53 (s, 1H, phenyl H-2), 9.03 (d, J = 7.85 Hz, 1H, phenyl H-4), 8.52 (d, J = 7.93 Hz, 1H, quinazoline H-8), 8.39 (d, J = 8.15 Hz, 1H, quinazoline H-5), 8.22 (d, J = 8.40 Hz, 1H, phenyl H-6), 8.02 (t, J = 7.69, 1H, quinazoline H-7), 7.78-7.71 (m, 2H, quinazoline H-6 and phenyl H-5), 4.67 (q, J = 7.15 Hz, 2H, $OC\underline{H}_2$), 1.58 (t, J = 7.14 Hz, 3H, $C\underline{H}_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 164.91 (C═O, ester), 158.05, 157.80, 152.22, 148.84, 139.17, 134.89, 134.37, 129.57, 129.31, 129.03, 125.97, 125.28, 123.64, 120.69, 62.81 (OCH_2), 14.30 (CH_3); HRMS (QTOF-ESI): m/z calcd for $C_{17}H_{13}N_3O_4$: 323.0906; found: 324.0992 $[M + 1]^+$.

3.8 | 2-(3-Nitro-phenyl)-quinazoline-4-carboxylic acid isopropyl ester (6)

Synthesized from compound **3** and isopropanol according to the general procedure. The product was recrystallized from isopropanol and dried in vacuo at 70°C. Yield: 0.23 g (68%); mp 120°C-122°C; IR (ν, cm^{-1}): 3091 (Ar CH), 2985 (aliphatic CH), 1726 (C═O, ester), 1613-1459 (C═C and C═N), 1523 (NO_2 asym.), 1341 (NO_2 sym.); ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 9.53 (s, 1H, phenyl H-2), 9.03 (d, J = 7.81 Hz, 1H, phenyl H-4), 8.45 (d, J = 8.47 Hz, 1H, quinazoline H-8), 8.40 (d, J = 8.17 Hz, 1H, quinazoline H-5), 8.22 (d, J = 8.49 Hz, 1H, phenyl H-6), 8.02 (t, J = 7.69, 1H, quinazoline H-7), 7.77-7.71 (m, 2H, quinazoline H-6 and phenyl H-5), 5.55 (heptet, J = 6.28 Hz, 1H, $OC\underline{H}$), 1.56 (d, J = 6.29 Hz, 6H, $2C\underline{H}_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 164.55 (C═O, ester), 158.68, 157.83, 152.13, 148.84, 139.20, 134.83, 134.39, 129.55, 129.32, 129.20, 125.73, 125.27, 123.65, 120.58, 70.99 (OCH), 21.92 (CH_3); HRMS (QTOF-ESI): m/z calcd for $C_{18}H_{15}N_3O_4$: 337.1063; found: 338.1148 $[M + 1]^+$.

3.9 | 2-(3-Nitro-phenyl)-quinazoline-4-carboxylic acid butyl ester (7)

Synthesized from compound **3** and n-butanol according to the general procedure. The product was recrystallized from n-butanol and dried in vacuo at 70°C. Yield: 0.23 g (65%); mp 106°C-107°C; IR (ν, cm^{-1}): 3088 (Ar CH), 2970 (aliphatic CH), 1727 (C═O, ester), 1615-1457 (C═C and C═N), 1521 (NO_2 asym.), 1341 (NO_2 sym.); ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 9.52 (s, 1H, phenyl H-2), 9.00 (d, J = 7.87 Hz, 1H, phenyl H-4), 8.49 (d, J = 8.45 Hz, 1H, quinazoline H-8), 8.37 (d, J = 8.16 Hz, 1H, quinazoline H-5), 8.20 (d, J = 8.43 Hz, 1H, phenyl H-6), 8.00 (t, J = 7.69, 1H, quinazoline H-7), 7.76-7.69 (m, 2H, quinazoline H-6 and phenyl H-5), 4.60 (t, J = 6.69 Hz,

2H, $OC\underline{H}_2$), 1.91 (pentet, J = 6.87 Hz, 2H, $OCH_2C\underline{H}_2$), 1.57 (hextet, J = 7.43 Hz, 2H, $C\underline{H}_2CH_3$), 1.06 (t, J = 7.37 Hz, 3H, $C\underline{H}_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 164.92 (C═O, ester), 157.91, 157.61, 152.12, 148.74, 139.05, 134.79, 134.21, 129.50, 129.24, 128.97, 125.91, 125.19, 123.52, 120.64, 66.55 (OCH_2), 30.63 ($OCH_2\underline{C}H_2$), 19.25 ($\underline{C}H_2CH_3$), 13.75 (CH_3); GC-MS (ESI): *m/z* calcd for $C_{19}H_{17}N_3O_4$: 351.1; found: 351.2 $[M]^+$.

3.10 | 2-(3-Nitro-phenyl)-quinazoline-4-carbonyl chloride (8)

A mixture of compound **3** (0.295 g, 1 mmol) and $SOCl_2$ (% 95; 5 mL) were heated in an oil bath (80°C) for 6 hours. The solvents were removed on a rotary evaporator at 50°C. The residue was washed with ether (3 × 15 mL). The product was crystallized from toluene-hexane mixture and dried in vacuo at 70°C. Yield: 0.24 g (76%); mp 135°C-136°C; IR (ν, cm^{-1}): 3093 (Ar CH), 1728 (C═O, carbonyl), 1613-1457 (C═C and C═N), 1522 (NO_2 asym.), 1342 (NO_2 sym.); ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 9.53 (s, 1H, phenyl H-2), 9.02 (d, J = 7.85 Hz, 1H, phenyl H-4), 8.51 (d, J = 7.91 Hz, 1H, quinazoline H-8), 8.39 (d, J = 8.17 Hz, 1H, quinazoline H-5), 8.22 (d, J = 8.48 Hz, 1H, phenyl H-6), 8.03 (t, J = 7.69, 1H, quinazoline H-7), 7.79-7.71 (m, 2H, quinazoline H-6 and phenyl H-5); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 164.95 (C═O, carbonyl), 158.09, 157.86, 152.26, 148.86, 139.20, 134.94, 134.42, 129.62, 129.34, 129.07, 126.00, 125.34, 123.69, 120.72; GC-MS (ESI): *m/z* calcd for $C_{15}H_8ClN_3O_3$: 313.0; found: 313.1 $[M]^+$.

3.11 | 2-(3-Nitro-phenyl)-quinazoline-4-carboxylic acid phenyl ester (9)

A mixture of phenol (0.094 g, 1 mmol) and triethylamine (0.10 g, 1 mmol) were added to a solution of compound **8** (0.313 g, 1 mmol) in toluene (30 mL) at room temperature. The mixture was stirred and heated to reflux for 5 hours. The reaction mixture was filtered while it was still hot. The obtained solution was kept at 25°C overnight. Then, the precipitate was filtered off and washed with ether (3 × 15 mL). The product was recrystallized from toluene and dried in vacuo at 70°C. Yield: 0.23 g (62%); mp 184°C-185°C; IR (ν, cm^{-1}): 3087 (Ar CH), 1757 (C═O, ester), 1612-1456 (C═C and C═N), 1525 (NO_2 asym.), 1345 (NO_2 sym.); ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 9.55 (s, 1H, nitrophenyl H-2), 9.06 (d, J = 7.84 Hz, 1H, nitrophenyl H-4), 8.66 (d, J = 8.47 Hz, 1H, quinazoline H-8), 8.38 (d, J = 8.16 Hz, 1H, quinazoline H-5), 8.25 (d, J = 8.48 Hz, 1H, nitrophenyl H-6), 8.04 (t, J = 7.68, 1H, quinazoline H-7), 7.80-7.71 (m, 2H, quinazoline H-6 and nitrophenyl H-5), 7.56-7.51 (t, J = 7.48, 2H, phenyl H-3), 7.44-7.35 (m, 3H, phenyl H-2,4); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 163.32 (C═O, ester), 157.89, 156.65, 152.56, 150.57, 148.93, 139.08, 135.10, 134.07, 129.79, 129.68, 129.51, 129.43, 126.68, 125.88, 125.44, 123.69, 121.51, 121.08; HRMS (QTOF-ESI): *m/z* calcd for $C_{21}H_{13}N_3O_4$: 371.0906; found: 372.0974 $[M + 1]^+$.

3.12 | 2-(3-Nitro-phenyl)-quinazoline-4-carboxylic acid amide (10)

A mixture of compound **8** (0.313 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 hours. The reaction mixture was continued and stirred at room temperature for an additional 2 hours. The obtained solution was filtered. The solvents were removed on a rotary evaporator at 40°C. The residue was washed with ether (3 × 15 mL). The product was crystallized from ethyl acetate and dried in vacuo at 70°C. Yield: 0.17 g (58%); mp 244°C-245°C; IR (ν, cm^{-1}): 3226 (NH), 3112 (Ar CH), 1645 (C═O, amide), 1611-1482 (C═C and C═N), 1526 (NO_2 asym.), 1344 (NO_2 sym.); ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 9.45 (s, 1H, phenyl H-2), 8.98 (d, J = 8.31 Hz, 1H, phenyl H-4), 8.41 (d, J = 9.04 Hz, 1H, quinazoline H-8), 8.20 (d, J = 8.59 Hz, 1H, quinazoline H-5), 8.05-7.99 (m, 2H, phenyl H-6 and quinazoline H-7), 7.79-7.73 (m, 2H, quinazoline H-6 and phenyl H-5), 5.85 (br, s, 2H, NH_2); ^{13}C NMR (75 MHz, DMSO-d_6) δ (ppm): 167.23 (C═O, amide), 160.56, 157.07, 151.94, 148.85, 138.93, 135.77, 134.97, 130.92, 129.57, 129.03, 127.36, 125.94, 122.96, 120.66; GC-MS (ESI): *m/z* calcd for $C_{15}H_{10}N_4O_3$: 294.1; found: 294.1 $[M]^+$.

3.13 | General procedure for the syntheses of compounds 11-13

Primary amine (2 mmol) was added to a solution of 2-(3-nitro-phenyl)-quinazoline-4-carbonyl chloride (**8**) (0.313 g, 1 mmol) in toluene (30 mL) at room temperature. The mixture was stirred and heated to reflux for 5 hours. The reaction mixture was filtered while it was still hot. The obtained solution was kept at 25°C overnight. The formed precipitate was filtered off, washed with water (3 × 20 mL) and ether (3 × 15 mL), dried, and recrystallized from an appropriate solvent.

3.14 | 2-(3-Nitro-phenyl)-quinazoline-4-carboxylic acid propylamide (11)

Synthesized from *n*-propylamine and compound **8** according to the general procedure. The product was recrystallized from toluene and dried in vacuo at 70°C. Yield: 0.21 g (62%); mp 185°C-186°C; IR (ν, cm^{-1}): 3298 (NH), 3088 (Ar CH), 2933 (aliphatic CH), 1656 (C═O, amide), 1611-1487 (C═C and C═N), 1523 (NO_2 asym.), 1338 (NO_2 sym.); ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 9.48-9.42 (m, 2H, phenyl H-2,4), 8.94 (d, J = 7.81 Hz, 1H, quinazoline H-8), 8.38 (d, J = 8.17 Hz, 1H, quinazoline H-5), 8.22 (br, s, 1H, NH), 8.16 (d, J = 8.52 Hz, 1H, phenyl H-6), 7.99 (t, J = 8.34 Hz, 1H, quinazoline H-7), 7.77-7.71 (m, 2H, quinazoline H-6 and phenyl H-5), 3.58 (q, J = 6.72, 2H, $NHC\underline{H}_2$), 1.79 (hextet, J = 7.20 Hz, 2H, $C\underline{H}_2CH_3$), 1.10 (t, J = 7.38 Hz, 3H, $C\underline{H}_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 164.48 (C═O, amide), 156.50, 156.35, 153.06, 148.84, 139.08, 134.97, 134.02, 129.71, 129.23, 128.90, 127.97, 125.28, 123.33, 121.48, 41.43 ($NHCH_2$), 22.88 ($\underline{C}H_2CH_3$), 11.52 ($CH_2\underline{C}H_3$); GC-MS (ESI): *m/z* calcd for $C_{18}H_{16}N_4O_3$: 336.1; found: 336.2 $[M]^+$.

3.15 | 2-(3-Nitro-phenyl)-quinazoline-4-carboxylic acid isopropylamide (12)

Synthesized from isopropylamine and compound **8** according to the general procedure. The product was recrystallized from toluene and dried in vacuo at 70°C. Yield: 0.20 g (59%); mp 215°C-216°C; IR (ν, cm^{-1}): 3302 (NH), 3089 (Ar CH), 2934 (aliphatic CH), 1650 (C═O, amide), 1612-1481 (C═C and C═N), 1523 (NO_2 asym.), 1339 (NO_2 sym.); ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 9.47-9.42 (m, 2H, phenyl H-2,4), 8.92 (d, J = 8.13 Hz, 1H, quinazoline H-8), 8.38 (d, J = 8.16 Hz, 1H, quinazoline H-5), 8.15 (d, J = 8.09 Hz, 1H, phenyl H-6), 8.01-7.96 (m, 2H, NH and quinazoline H-7), 7.77-7.72 (m, 2H, quinazoline H-6 and phenyl H-5), 4.39 (octet, J = 5.11, 1H, NHC$\underline{H}$), 1.42 (d, J = 6.57 Hz, 6H, $2C\underline{H}_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 163.68 (C═O, amide), 156.49, 156.43, 153.03, 148.85, 139.08, 134.93, 133.97, 129.70, 129.19, 128.91, 127.96, 125.25, 123.36, 121.48, 41.81 (CH), 22.69 (CH_3); HRMS (QTOF-ESI): *m/z* calcd for $C_{18}H_{16}N_4O_3$: 336.1222; found: 337.1306 $[M + 1]^+$.

3.16 | 2-(3-Nitro-phenyl)-quinazoline-4-carboxylic acid phenylamide (13)

Synthesized from aniline and compound **8** according to the general procedure. The product was crystallized from xylene and dried in vacuo at 70°C. Yield: 0.22 g (59%); mp 239°C-240°C; IR (ν, cm^{-1}): 3318 (NH), 3081 (Ar CH), 1665 (C═O, amide), 1612-1482 (C═C and C═N), 1527 (NO_2 asym.), 1339 (NO_2 sym.); ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 14.45 (br, s, 1H, NH), 9.21 (s, 1H, nitrophenyl H-2), 8.90 (d, J = 7.75 Hz, 1H, nitrophenyl H-4), 8.45-8.37 (m, 3H, quinazoline H-5,8 and nitrophenyl H-6), 8.18-8.08 (m, 4H, quinazoline H-6,7 and phenyl H-2), 7.87-7.82 (m, 4H, nitrophenyl H-5 and phenyl H-3,4); ^{13}C NMR (75 MHz, DMSO-d_6) δ (ppm): 163.67 (C═O, amide), 161.31, 157.30, 151.90, 148.94, 138.90, 138.65, 136.20, 135.07, 131.14, 129.95, 129.43, 129.22, 126.97, 126.15, 125.13, 123.08, 120.95, 120.51; HRMS (QTOF-ESI): *m/z* calcd for $C_{21}H_{14}N_4O_3$: 370.1066; found: 369.0986 $[M - 1]^+$.

3.17 | 2-(3-Nitro-phenyl)-quinazoline-4-carboxylic acid (4-sulfamoyl-phenyl)-amide (14)

4-aminobenzenesulfonamide (0.344 g, 2 mmol) was added to a solution of compound **8** (0.313 g, 1 mmol) in THF (30 mL) at room temperature. The mixture was stirred and heated to reflux for 6 hours. The reaction mixture was filtered while it was still hot. The solvents were removed on a rotary evaporator at 40°C. The residue was washed with ether (3 × 15 mL). The product was crystallized from THF-water mixture and dried in vacuo at 70°C. Yield: 0.23 g (51%); mp 291°C-292°C; IR (ν, cm^{-1}): 3326 (NH), 3096 (Ar CH), 1681 (C═O, amide), 1611-1486 (C═C and C═N), 1526 (NO_2 asym.), 1341 (NO_2 sym. and SO_2 asym.), 1158 (SO_2 sym.); ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 11.43 (s, 1H, NH), 9.39 (s, 1H, nitrophenyl H-2), 9.12 (d, J = 7.94 Hz, 1H, nitrophenyl H-4), 8.67 (d, J = 8.03 Hz, 1H, quinazoline H-8), 8.48 (d, J = 7.25 Hz, 1H, quinazoline H-5), 8.29 (d, J = 8.30 Hz, 1H, nitrophenyl H-6), 8.19 (t, J = 6.92 Hz, 1H, quinazoline H-7), 8.07 (d, J = 8.79 Hz, 2H, phenyl H-2), 7.97-7.86 (m, 4H, quinazoline H-6, nitrophenyl H-5 and phenyl H-3), 7.38 (s, 2H, $SO_2N\underline{H}_2$); ^{13}C NMR (75 MHz, DMSO-d_6) δ (ppm): 163.95 (C═O, amide), 160.32, 157.15, 151.97, 148.86, 141.47, 140.23, 138.74, 136.15, 135.04, 131.01, 129.97, 129.21, 127.24, 126.89, 126.09, 123.05, 120.74, 120.48; HRMS (QTOF-ESI): *m/z* calcd for $C_{21}H_{15}N_5O_5S$: 449.0794; found: 448.0602 $[M - 1]^+$.

3.18 | 2-(3-Amino-phenyl)-quinazoline-4-carboxylic acid propylamide (15)

$Na_2S{\cdot}9H_2O$ (0.240 g, 1 mmol) and sulfur (0.064 g, 2 mmol) were stirred and dissolved by boiling in 20 mL of water. This solution (sodium polysulfur) was then added

dropwise to a stirred solution of warm compound **11** (0.336 g, 1 mmol) in ethanol-THF. This mixture was refluxed for 1 hour, and then concentrated hydrochloric acid was added to this mixture, and the mixture was refluxed again for 1 hour. Precipitated solid was filtrated, and ammonia was added to the solution. The obtained solution was kept at 5°C overnight. The formed precipitate was filtered off and washed with water (3 × 20 mL). The product was crystallized from ethanol-water mixture and dried in vacuo at 70°C. Yield: 0.20 g (65%); mp 152°C-153°C; IR (ν, cm^{-1}): 3420 (NH_2, amine), 3302 (NH), 3075 (Ar CH), 2933 (aliphatic CH), 1650 (C═O, amide), 1614-1488 (C═C and C═N); ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 9.09 (t, J = 5.98 Hz, 1H, NH), 8.60 (d, J = 8.34 Hz, 1H, quinazoline H-8), 8.09-8.02 (m, 2H, quinazoline H-5,7), 7.88-7.83 (m, 2H, phenyl H-2,6), 7.74 (t, J = 7.29 Hz, 1H, quinazoline H-6), 7.23 (t, J = 7.80 Hz, 1H, phenyl H-5), 6.78 (d, J = 6.54 Hz, 1H, phenyl H-4), 5.43 (br, s, 2H, NH_2), 3.40 (q, J = 6.66, 2H, $NHC\underline{H}_2$), 1.64 (hextet, J = 7.11 Hz, 2H, $C\underline{H}_2CH_3$), 0.97 (t, J = 7.34 Hz, 3H, $CH_2C\underline{H}_3$); ^{13}C NMR (75 MHz, DMSO-d_6) δ (ppm): 165.46 (C═O, amide), 160.86, 159.87, 151.92, 149.23, 137.92, 135.29, 129.62, 128.81, 128.55, 126.97, 120.22, 117.37, 117.07, 114.11, 41.24 ($NHCH_2$), 22.77 ($\underline{C}H_2CH_3$), 11.93 (CH_3); HRMS (QTOF-ESI): m/z calcd for $C_{18}H_{18}N_4O$: 306.1481; found: 307.1641 $[M + 1]^+$.

3.19 | 2-(3-Acetylamino-phenyl)-quinazoline-4-carboxylic acid propylamide (16)

A mixture of acetyl chloride (0.078 g, 1 mmol) and triethylamine (0.10 g, 1 mmol) were added to a solution of compound **15** (0.306 g, 1 mmol) in THF (30 mL) at room temperature. The mixture was stirred and heated to reflux for 5 hours. The reaction mixture was filtered while it was still hot. The solvents were removed on a rotary evaporator at 40°C. The residue was washed with ether (3 × 15 mL). The product was crystallized from ethanol-water mixture and dried in vacuo at 70°C. Yield: 0.23 g (66%); mp 193°C-194°C; IR (ν, cm^{-1}): 3291 (NH), 3074 (Ar CH), 2933 (aliphatic CH), 1665 and 1653 (C═O, amide), 1616-1490 (C═C and C═N); ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 9.42 (d, J = 8.49 Hz, 1H, quinazoline H-8), 8.56 (s, 1H, phenyl H-2), 8.30-8.27 (m, 2H, Ph-N$\underline{H}$ and quinazoline H-5), 8.06 (d, J = 8.48 Hz, 1H, phenyl H-4), 7.93-7.85 (m, 2H, quinazoline H-7 and phenyl H-5), 7.65 (t, J = 7.58 Hz, 1H, quinazoline H-6), 7.53-7.47 (m, 2H, N$\underline{H}$ and phenyl H-6), 3.54 (q, J = 7.05, 2H, $NHC\underline{H}_2$), 2.24 (s, 3H, $COC\underline{H}_3$), 1.77 (hextet, J = 7.25 Hz, 2H, $C\underline{H}_2CH_3$), 1.07 (t, J = 7.35 Hz, 3H, $CH_2C\underline{H}_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 168.33 (C═O, amide), 164.82 (C═O, propylamide), 158.30, 155.86, 153.17, 138.44, 138.11, 134.50, 129.49, 128.77, 128.52, 127.84, 124.27, 122.40, 121.24, 119.48, 41.39 ($NHC\underline{H}_2$), 24.72 ($CO\underline{C}H_3$), 22.91 ($NHCH_2\underline{C}H_2$), 11.54 ($NHCH_2CH_2\underline{C}H_3$); HRMS (QTOF-ESI): m/z calcd for $C_{20}H_{20}N_4O_2$: 348.1586; found: 349.1665 $[M + 1]^+$.

3.20 | General procedure for the syntheses of compounds 17-19

2-(3-Amino-phenyl)-quinazoline-4-carboxylic acid propylamide (**15**) (0.306 g, 1 mmol) was dissolved in a mixture of ethanol (40 mL) and concentrated hydrochloric acid (2 mL). The solution was then cooled to 0°C to 5°C. Sodium nitrite (0.104 g, 1.5 mmol) in water (10 mL) was then added to this solution dropwise with vigorous stirring while keeping at 0°C to 5°C. After dissolving a β-dicarbonyl compound (1 mmol) in a sufficient amount of ethanol, the solution was cooled and added dropwise into the already prepared diazonium salt solution. The pH of the coupling mixture, in each case, was maintained at 7 and 8 through the coupling process by adding aqueous sodium acetate. Stirring was continued for 1 hour at 0°C to 5°C and 1 hour at room temperature. The precipitated products were filtered off, washed with water several times, dried, and recrystallized from an appropriate solvent.

3.21 | 2-{3-[*N′*-(1-Acetyl-2-oxo-propylidene)-hydrazino]-phenyl}-quinazoline-4-carboxylic acid propylamide (17)

Synthesized from compound **15** (0.306 g, 1 mmol) and acetylacetone (0.100 g, 1 mmol) according to the general procedure. The crude product was purified by crystallization from ethanol-THF mixture and dried in vacuo at 70°C. Yield: 0.29 g (69%); mp 208°C-209°C; IR (ν, cm^{-1}): 3410 (NH), 3088 (Ar CH), 2932 (aliphatic CH), 1672 (C═O, ketone), 1629 (C═O, amide), 1612-1486 (C═C and C═N); ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 14.86 (s, 1H, C═C─OH), 9.46 (d, J = 8.57 Hz, 1H, quinazoline H-8), 8.58 (s, 1H, phenyl H-2), 8.43 (d, J = 7.18 Hz, 1H, quinazoline H-5), 8.26 (br, s, 1H, NH), 8.13 (d, J = 8.44 Hz, 1H, phenyl H-6), 7.97 (t, J = 8.40 Hz, 1H, quinazoline H-7), 7.73-7.61 (m, 3H, quinazoline H-6 and phenyl H-4,5), 3.57 (q, J = 7.33, 2H, $NHC\underline{H}_2$), 2.65 and 2.57 (s, 6H, 2COC$\underline{H}$3), 1.77 (hextet, J = 7.25 Hz, 2H, $C\underline{H}_2CH_3$), 1.08 (t, J = 7.35 Hz, 3H, $C\underline{H}_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 197.93 and 196.85 (C═O, ketone), 164.64 (C═O, amide), 157.53, 155.96, 152.90, 141.95, 138.66, 134.50, 133.24, 129.90, 128.74, 128.60, 127.75, 125.55, 121.17,

117.99, 116.01, 41.38 ($NHCH_2$), 31.68 and 26.55 ($COCH_3$), 22.95 ($NHCH_2CH_2$), 11.54 ($NHCH_2CH_2CH_3$); HRMS (QTOF-ESI): *m/z* calcd for $C_{23}H_{23}N_5O_3$: 417.1801; found: 418.1886 $[M + 1]^+$.

3.22 | 3-Oxo-2-{[3-(4-propylcarbamoyl-quinazolin-2-yl)-phenyl]-hydrazono}-butyric acid ethyl ester (18)

Synthesized from compound **15** (0.306 g, 1 mmol) and ethyl acetoacetate (0.130 g, 1 mmol) according to the general procedure. The crude product was purified by crystallization from ethanol and dried in vacuo at 70°C. Yield: 0.27 g (60%); mp 161°C-162°C; IR (ν, cm^{-1}): 3309 (NH), 3075 (Ar CH), 2931 (aliphatic CH), 1706 (C=O, ester), 1688 (C=O, ketone), 1650 (C=O, amide), 1613-1489 (C=C and C=N); ^1H NMR (300 MHz, $CDCl_3$) δ (ppm): 14.93 (s, 1H, C=C—OH enol tautomer), 12.95 (s, 1H, Ar-NH-N= keto tautomer), 9.46 (d, J = 8.55 Hz, 1H, quinazoline H-8), 8.53 (s, 1H, phenyl H-2), 8.39 (d, J = 7.77 Hz, 1H, quinazoline H-5), 8.27 (br, s, 1H, NH), 8.13 (d, J = 8.41 Hz, 1H, phenyl H-6), 7.96 (t, J = 7.75 Hz, 1H, quinazoline H-7), 7.74-7.57 (m, 3H, quinazoline H-6 and phenyl H-4,5), 4.40 (q, J = 7.00 Hz, 2H, OCH_2), 3.57 (q, J = 7.67, 2H, $NHCH_2$), 2.64 and 2.58 (s, 3H, $COCH_3$), 1.78 (hextet, J = 7.20 Hz, 2H, $CH_2CH_2CH_3$), 1.44 (t, J = 7.08, 3H, OCH_2CH_3), 1.08 (t, J = 7.39 Hz, 3H, $CH_2CH_2CH_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 197.08 (C=O, ketone), 194.33 (C=O, ester), 164.73 (C=O, amide), 157.84, 156.00, 153.04, 142.16, 138.72, 134.56, 129.95, 128.78, 128.63, 127.82, 125.52, 124.75, 121.25, 117.48, 115.40, 61.46 and 60.99 (OCH_2), 41.39 ($NHCH_2$), 30.81 and 26.85 ($COCH_3$), 22.96 ($NHCH_2CH_2$), 14.36 and 14.13 (OCH_2CH_3), 11.53 ($NHCH_2CH_2CH_3$); HRMS (QTOF-ESI): *m/z* calcd for $C_{24}H_{25}N_5O_4$: 447.1907; found: 448.1991 $[M + 1]^+$.

3.23 | 3-Oxo-3-phenyl-2-{[3-(4-propylcarbamoyl-quinazolin-2-yl)-phenyl]-hydrazono}-propionic acid ethyl ester (19)

Synthesized from compound **15** (0.306 g, 1 mmol) and ethylbenzoylacetate (0.192 g, 1 mmol) according to the general procedure. The crude product was purified by crystallization from ethanol and dried in vacuo at 70°C. Yield: 0.29 g (57%); mp 157°C-158°C; IR (ν, cm^{-1}): 3309 (NH), 3030 (Ar CH), 2934 (aliphatic CH), 1708 (C=O, ester), 1670 (C=O, ketone), 1650 (C=O, amide), 1614-1488 (C=C and C=N); ^1H NMR (300 MHz, $CDCl_3$) δ (ppm): 13.77 (s, 1H, C=C—OH enol tautomer), 12.90 (s, 1H, Ar—NH—N= keto tautomer), 9.45 (d, J = 8.60 Hz, 1H, quinazoline H-8), 8.40 (s, 1H, phenyl H-2), 8.30 (d, J = 7.68 Hz, 1H, quinazoline H-5), 8.20 (br, s, 1H, NH), 8.09 (d, J = 8.46 Hz, 1H, phenyl H-6), 8.00-7.93 (m, 3H, quinazoline H-6,7 and phenyl H-4), 7.72-7.38 (m, 6H, phenyl H-6 and benzoyl Ar—H), 4.41 (q, J = 7.12 Hz, 2H, OCH_2), 3.54 (q, J = 7.42, 2H, $NHCH_2$), 1.72 (hextet, J = 7.20 Hz, 2H, $CH_2CH_2CH_3$), 1.38 (t, J = 7.11, 3H, OCH_2CH_3), 1.05 (t, J = 7.43 Hz, 3H, $CH_2CH_2CH_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 189.46 (C=O, ketone), 185.00 (C=O, ester), 164.75 (C=O, amide), 158.06, 155.96, 153.15, 142.52, 138.73, 134.60, 132.49, 130.43, 130.01, 128.79, 128.67, 128.28, 128.04, 127.87, 126.87, 124.30, 121.30, 117.37, 115.37, 61.52 and 61.24 (OCH_2), 41.35 ($NHCH_2$), 22.88 ($NHCH_2CH_2$), 14.06 and 13.87 (OCH_2CH_3), 11.51 ($NHCH_2CH_2CH_3$); HRMS (QTOF-ESI): *m/z* calcd for $C_{29}H_{27}N_5O_4$: 509.2063; found: 510.2154 $[M + 1]^+$.

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