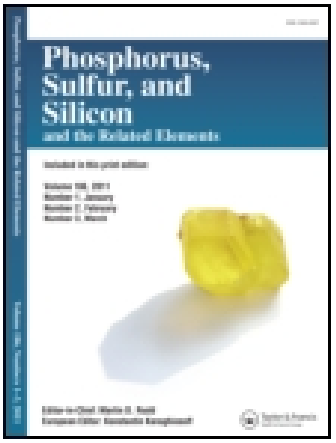

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Synthesis of Novel 3-Amino-2-(1H)-Thioxo-4(3H)-Quinazolinone Derivatives. Part 3

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SYNTHESIS OF NOVEL 3-AMINO-2-(1H)-THIOXO-4(3H)-*QUINAZOLINONE DERIVATIVES. PART 3*

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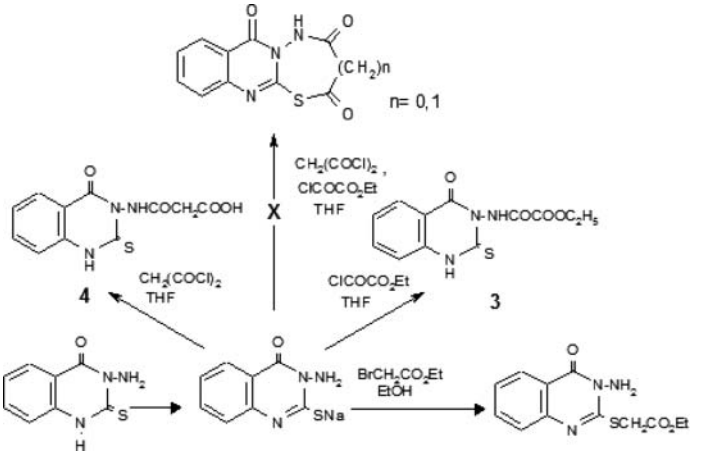
GRAPHICAL ABSTRACT



Abstract *The synthesis of novel derivatives containing the quinazolinone-4 moiety is described. 3-Amino-2(1H)-tioxo-4(3H)-quinazolinone (**1**) forms a sodium salt **2**, which was subjected to reaction with dicarboxylic acid chlorides such as chloroformyl ethyl formate and malonyl chloride, leading to the corresponding ester **3** and acid **4**, respectively. 3-Amino-2-ethoxycarbonylmethylthio-4(3H)-quinazolinone (**5**) was acylated or ammonolyzed and products of various chemical structure were obtained. The chemical structures **3**, **4**, **6–12**, and **14–18** were identified by the results of elemental analysis and their IR, ^{1}H NMR, and mass spectra.*

Keywords Acylation; ammonolysis; 3-amino-2(1*H*)-thioxo-4(3*H*)-quinazolinone; 3-amino-2-ethoxy-carbo-nylmethylthio-4(3*H*)-quinazolinone derivatives; synthesis

INTRODUCTION

Quinazolinone-4 derivatives have been found to be biologically and pharmacologically versatile compounds, having antimalarial, hypnotic, anticonvulsant, antitubercular,

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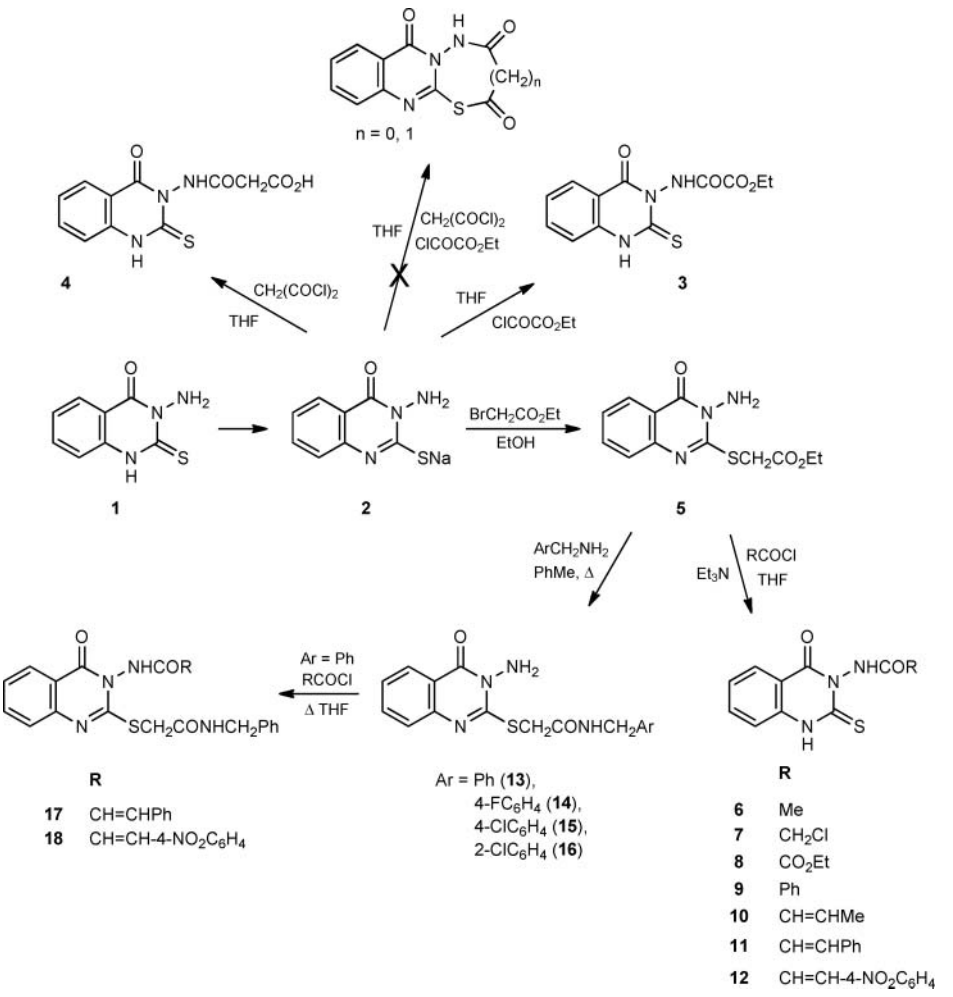
bronchodilator, immunotropic, anticancer, anti-inflammatory, analgesic and COX-2 inhibitor, and other diverse activities.[1–10] In our review papers, we have described the syntheses of various bioactive derivatives of quinazolinone-4,[11] of quinazolinone-4 derivatives occurring in alkaloids and fungi,[12] as well as of quinazolinone-4 derivatives showing antibacterial[13] and anticancer activity, together with novel mechanisms of action and strategies for their discovering.[14] 3-Amino-2(1*H*)-thioxo-4(3*H*)-quinazolinone (**1**)[15] is a universal substrate for syntheses of quinazolinone-4 derivatives. The reaction of 3-amino-2(1*H*)-thioxo-4(3*H*)-quinazolinone (**1**) with carbonyl compounds,[9] acetic acid derivatives,[15] cyanogen bromide,[16] halogenocinnamic acids, and halogenoketones,[17] as well as with selected chloroformates[18] has been described previously. The substituted derivatives or tricyclic compounds thus prepared show in vitro high antiproliferative,[19,20] antitubercular,[19,20] and immunotropic[9] activity. This study is a continuation of our previous investigations with the aim to synthesize new derivatives of 3-amino-2(1*H*)-thioxo-4(3*H*)-quinazolinone (**1**) for biological testing. The new compounds were obtained from the reactions of quinazolinone **1** with dicarboxylic acid chlorides, and also by modification of the chemical structure of previously obtained 3-amino-2-ethoxycarbonylmethylthio-4(3*H*)-quinazolinone (**5**). The presence of oxalyl (−COCO−) or malonyl (−$COCH_2CO$−) groups in heterocyclic compounds belonging to various chemical families is known to be related to psychotropic, antiaggregation, anti-inflammatory, anti-HIV, and antiproliferative activity of these compounds.[21–26] It is reasonable to assume that the presence of analogous units in derivatives of quinazolinone **1** yields bioactive compounds as well. Similar situation is assumed for the presence of pharmacophor substituents in the ester **5**.

RESULTS AND DISCUSSION

The sodium salt **2** of 3-amino-2(1*H*)-thioxo-4(3*H*)-quinazolinone (**1**) reacts with dicarboxylic acid chlorides, chloroformyl ethyl formate, and malonyl chloride (Scheme 1) to form substitution products or tricyclic compounds.

Most probably, in the first step of the reaction, acylation at the position 2 of the quinazolinone takes place, which is followed by acylation of the NH_2 group at the position 3 combined with cyclization. The reactions were carried out in boiling anhydrous THF. Homogenous products were obtained. Elemental analysis and analysis of the MS, IR, and ^{1}H NMR spectra confirmed the formation of monosubstituted derivatives and showed that substitution in the positions 2 or 3 had occurred. Substitution at the position 3 is confirmed by the IR spectra, where the 2 bands characteristic for the *NH*$_2$ group in compound **1** are missing.[15] There are bands at 3340 cm^{-1} characteristic for *NH*CO and bands characteristic for *C*=*O* groups. Correspondingly, in the ^{1}H NMR spectra, the singlet for the 2 protons of the *NH*$_2$ group at $\delta = 6.30$ ppm, which is present in the spectrum of compound **1**, is missing.[15] Instead, singlets corresponding to one proton are observed at $\delta = 11.16$ ppm (N*H*CO) and at $\delta = 14.73$ ppm (N*H*C=S) for compound **3**, and at $\delta = 10.09$, 11.54, and 14.82 ppm for compound **4**. In the last case they are attributed to the protons of COO*H*, N*H*CO, and N*H*CS, respectively. In the mass spectra of compounds **3** and **4**, peaks for the molecular ions at m/z = 293 and m/z = 279 as well as base peaks at m/z = 220 (M^+ − COOEt) and m/z = 146 (quinazolinone ion), respectively, are observed.

In the next stage of our study, 3-amino-2-ethoxycarbonylmethylthio-4(3*H*)-quinazolinone (**5**) was allowed to react with selected acid chlorides like acetyl-, chloroacetyl-, ethyl chloroformyl formate, benzoyl-, crotonoyl-, cinnamoyl-, and *p*-nitrocinnamoyl chloride. Acylation reactions were carried out in boiling anhydrous THF,



Scheme 1

yielding the products **6–12**. The IR spectra of compounds **6–12** do not contain 2 absorption bands characteristic for NH_2 groups, present in compound **5**.[15] Bands characteristic for CO*NH* groups at approximately 3300 cm^{-1} are present, however. The IR spectra of derivatives **10–12** contain also bands for −CH=CH− groups at 3100–3080 cm^{-1} as well as bands at 1660–1635 cm^{-1} and at approximately 1620 cm^{-1}. In the ^1H NMR spectra of derivatives **6–12**, signals for NH_2 protons are missing; the signals at $\delta = 10.32$–11.92 ppm are attributed to N*H*CO protons. In the case of the derivatives **10–12**, the signal of the proton next to the carbonyl group −CH=C*H*−C=O is observed as a doublet at $\delta =$ 6.14, 6.89, and 7.12 ppm, respectively. The $^3J_{HH}$ coupling constants of 15–16 Hz indicate a *trans* configuration of the protons in the vinylic fragment. The signal of vinylic proton next to methyl, CH_3−C*H*=, or to aryl, Ar−C*H*=, appears among the signals of the aromatic protons. The mass spectra of the compounds **6–12** display the peaks of the molecular ions. The peaks of the base ions for compounds **6–8** result from the fragmentation and elimination of an acetyl (CH_3CO), a chloromethyl (CH_2Cl), and an ethoxycarbonyl

(COOEt) group, respectively. In the case of derivatives **9** and **10** the peaks of the base ions correspond to the benzoyl ion, m/z = 105 (100), and the crotonoyl ion, m/z = 69 (100), respectively. The base ions for derivatives **11** and **12** result from the elimination from the position 2 of ethoxycarbonylmethyl and ethoxy-carbonylomethylthio groups, respectively.

The other possibility for a chemical modification of ester **5** is the ammonolysis with equimolar amounts of *p*-fluoro-, *p*-chloro-, and *o*-chlorobenzylamine in boiling toluene. The reaction yields the products **14–16**. Two sharp bands characteristic for NH_2 groups are observed in the IR spectra of compounds **14–16**. Bands at approximately 3440 cm^{-1} correspond to NH vibrations of *NH*CO groups. In the ^{1}H NMR spectra of amides **14–16**, there are no signals for the protons of ethoxy groups, which are present in the ^{1}H NMR spectrum of ester **5**. However, singlets corresponding to two protons at $\delta = 4.16$, 4.19, and 4.20 ppm for SCH_2CO, and as doublets at $\delta = 4.29$, 4.33, and 4.38 ppm for CONHCH_2Ar, respectively, were observed. A broad signal for the NH proton of the CO*NH*CH_2Ar unit is found at $\delta = 8.87$, 8.87, and 8.85 ppm, respectively. The signal for the protons of the NH_2 group appears along with aromatic protons at $\delta = 6.64$, 6.42, and 6.65 ppm, respectively. The number of signals for the aromatic protons in the ^{1}H NMR spectra of compounds **14–16** is in good agreement with their structures. For compound **14** the peak for the molecular ion was observed at m/z = 358. Mass spectra of compounds **15** and **16** display peaks of the molecular ions at m/z = 374 and the isotope ions at m/z = 376. They additionally confirm the presence of chlorine in the parent molecules. For the *ortho*-derivative **16** elimination of Cl radical from the molecular ion is observed, which results in the formation of an ion with m/z = 339 (27). One of the observed routes of fragmentation of the compounds **14–16** is the elimination of the groups ArCH_2NHCOCH_2 from position 2. Peaks of *ortho*-iminobenzoyl ions are formed as base ions at m/z = 120 after fragmentation and degradation of the quinazolinone system.[9]

In the next stage, the previously obtained 3-amino-2-benzylcarbamylomethylthio-4(3*H*)-quinazolinone (**13**)[15] was subjected to acylation with cinnamoyl (**17**) and p-nitrocinamoyl (**18**) chloride. The reactions were carried out in a way similar to the synthesis of amides **6–12** yielding the corresponding 3-*N*-acyl derivatives.

Fourteen new compounds assigned for biological studies were obtained from the syntheses described here. These derivatives may also be used as starting materials for further syntheses.

EXPERIMENTAL

Melting points (uncorrected) were measured with a Boethius melting point apparatus. Analyses were performed with a Perkin Elmer 2400 analyzer and satisfactory results within ±0.4% of the calculated values were obtained for all new compounds. IR spectra (in KBr) were recorded with an IR 75 spectrophotometer. ^{1}H NMR spectra were obtained with a Bruker AVANCE DRX 300 and AVANCE 500 instrument using DMSO-d_6 as solvent at room temperature and chemical shifts are referred to the residual solvent signal at $\delta =$ 2.50 ppm. Mass spectra were obtained with a GCMS—LK 82091 spectrometer at ionization energy of 15 or 70 eV. The course of the reactions and the purity of the products were checked by TLC (Kieselgel G, Merck) in diethyl ether: ethanol = 5:1 as eluent. Compounds **1** and **2** were prepared as described previously.[15] 2-Amino-3-ethoxycarbonylmethylthio-4(3*H*)-quinazo-linone (**5**) was prepared as described.[15]

Synthesis of Compounds 3 and 4: General Procedure

Compound **2** (2.25 g, 0.01 mol) was suspended in anhydrous THF (50 mL) and 0.01 mol of the appropriate acid chloride (chloroformyl ethyl formate or malonyl chloride) in THF (20 mL) was added dropwise with mechanical stirring at room temperature. The mixture was refluxed for 10–20 h (TLC). The solid (NaCl + **1**) was filtered off. The filtrate was evaporated *in vacuo*, water was added (ca. 50 mL) and the mixture was neutralized with 5% of aq. $NaHCO_3$ (10 mL). The crude product was filtered off, washed with water (30 mL), dried, and crystallized from an appropriate solvent.

3-Ethoxalylamino-2-(1H)-Thioxo-4(3H)-Quinazolinone (3). Yield: 1.76 g (60%); yellow solid; mp 212 °C–214 °C, crystallized from ethanol. IR (KBr): ν (cm^{-1}) = 3400 (NHCO), 3010 (CH), 2900 (−CH_2−), 1750, 1700 (C=O), 1610, 1510 (arom.), 1360 (N−CS−N), 1260 (C=S), 760 (−CH−). ^{1}H NMR (DMSO-d_6, 300 MHz): δ = 1.33 (t, J = 7.4 Hz, 3H), 4.32 (q, J = 7.4 Hz, 2H), 7.37 (m, 1H), 7.62 (m, 1H), 7.84 (d, J = 7.8 Hz, 1H), 8.36 (d, J = 8.4 Hz, 1H), 11.16 (s, 1H), 14.73 (br, s, 1H). Analysis for $C_{12}H_{11}N_3O_4S$ (293.3): Calcd. C, 49.14; H, 3.78; N, 14.33; Found: C, 49.17; H, 3.39; N, 14.27%. MS (70 eV): m/z = 294 (5), 293 (41), 265 (40), 221 (9), 220 (100), 181 (7), 162 (19), 161 (15), 146 (40), 145 (12), 120 (17), 119 (61), 91 (6), 90 (17), 77 (10), 76 (6), 55 (11), 44 (16), 39 (9).

***β*-Oxo-3-[2(1H)-Thioxo 4(3H)-Oxo-Quinazolin-3-Ylamino]-Propionic Acid (4).** Yield: 0.78 g (28%); brown solid; mp 238 °C–240 °C crystallized from acetonitrile. IR (KBr): ν (cm^{-1}) = 3300 (NHCO), 3260 (OH), 3010 (CH), 2880 (−CH_2−), 1720 (*CO*OH), 1670 (NH*CO*), 1540 (NH, C−N), 1260 (C=S), 940 (-OH), 790 (arom.). ^{1}H NMR (DMSO-d_6, 500 MHz): δ = 4.12 (s, 2H), 7.35 (m, 1H), 7.53 (m, 1H), 7.83 (m, 1H), 8.14 (m, 1H), 10.09 (s, 1H), 11.54 (s, 1H), 14.82 (br s, 1H). Analysis for $C_{11}H_9N_3O_4S_1$ (279.27): Calcd. C, 47.31; H, 3.25; N, 15.05; Found: C, 47.59; H, 3.26; N, 15.00%. MS (70 eV): m/z = 279 (3), 234 (58), 192 (15), 160 (27), 146 (100), 133 (23), 133 (23), 115 (66), 96 (10), 91 (38), 65 (59), 43 (51), 42 (20), 41 (28), 39 (9).

Synthesis of Compounds 6–12, 17, and 18: General Procedure

To a mixture of compound **5** (2.51 g, 0.01 mol) or **13** (3.40 g, 0.01 mol) and NEt_3 (2.5 mol) in anhydrous THF (50 mL), 0.01 mol of the respective acid chloride (acetyl chloride for **6**, chloroacetyl chloride for **7**, chloroformyl ethyl formate for **8**, benzoyl chloride for **9**, crotonoyl chloride for **10**, cinnamoyl chloride for **11** and **17**, *p*-nitrocinnamoyl chloride for **12** and **18**) in THF (20 [mL]) was added dropwise with mechanical stirring at room temperature. The mixture was refluxed for 10–20 h (TLC). The solvent was evaporated in vacuo and water was added (50 mL). The crude product was filtered off, washed with water (30 mL), dried and crystallized from ethanol or *n*-butanol (for **10**, **12**).

3-Acetylamino-2-Ethoxycarbonylmethylthio-4(3H)-Quinazolinone (6). Yield: 2.05 g (64%); white solid; mp 137 °C–139 °C. IR (KBr): ν (cm^{-1}) = 3330 (NHCO), 2980 (CH_3), 2940 (CH_2), 1740, 1680, 1650 (C=O), 1480 (CH_2), 1305, 1260, 1195 (C−O), 740 (C−H arom.). ^{1}H NMR (DMSO-d_6, 300 MHz): δ = 1.20 (t, J = 7.20 Hz, 3H), 1.99 (s, 3H), 4.17 (q, J = 7.20 Hz, 2H), 4.31 (s, 2H), 7.29 (m, 1H), 7.59 (m, 1H), 7.87 (d, J = 8.0 Hz, 1H), 8.26 (d, J = 8.2 Hz, 1H), 10.32 (s, 1H). Analysis for $C_{14}H_{15}N_3O_4S$ (321.36): Calcd. C, 52.33; H, 4.70; N, 13.08; Found: C, 52.37; H, 5.01, N, 13.38%. MS (70 eV) m/z = 323 (3), 322 (6), 321 (34), 280 (13), 279 (100), 203 (5), 202 (40), 162 (20), 161 (3), 160 (18), 146 (11), 120 (85), 119 (11), 118 (45), 92 (16), 91 (8), 77 (7), 43 (49), 39 (5).

3-Chloroacetylamino-2-Ethoxycarbonylmethylthio-4(3H)-Quinazolinone (7). Yield: 1.88 g (53%); white solid; mp 139 °C–140 °C. IR (KBr): ν (cm^{-1}) = 3300 (NHCO), 2950 (CH_3), 2900 (CH_2), 1730, 1710, 1680 (C=O), 1470, 1440 (CH_2), 1310, 1250, 1180 (C−O), 750 (C−H arom.). ^{1}H NMR (DMSO-d_6, 300 MHz): δ = 1.19 (t, J = 7.2 Hz, 3H), 4.16 (q, J = 7.2 Hz, 2H), 4.31 (s, 2H), 4.45 (s, 2H), 7.36 (m, 1H), 7.64 (m, 1H), 7.91 (d, J = 7,2 Hz, 1H), 8.34 (d, J = 8.4 Hz, 1H), 10.91 (s, 1H). Analysis for $C_{14}H_{14}N_3O_4SCl$ (355.80): Calcd. C, 47.26; H, 3.97; N, 11.81; Found: C, 47.18; H, 4.15; N, 12.17%. MS (70 eV) m/z = 357 (11), 356 (5), 355 (30), 309 (2), 308 (11), 307 (100), 238 (9), 237 (5), 236 (30), 198 (9), 197 (3), 196 (44), 133 (9), 132 (11), 92 (15), 91 (22), 90 (23), 77 (17), 39 (6).

3-Ethoxalylamino-2-Ethoxycarbonylmethylthio-4(3H)-Quinazolinone (8). Yield: 2.46 g (65%); white solid; mp 127 °C–129 °C. IR (KBr): ν (cm^{-1}) = 3220 (NHCO), 2980 (CH_3), 2940 (CH_2), 2900 (CH_2), 1760, 1730, 1705 (C=O), 1470 (CH_2), 1310, 1270, 1180 (C−O), 770 (C−H arom.). ^{1}H NMR (DMSO-d_6, 300 MHz): δ = 1.21 (t, J = 7.2 Hz, 3H), 1.35 (t, J = 7.4 Hz, 3H), 4.16 (q, J = 7.2 Hz, 2H), 4.31 (s, 2H), 4.34 (q, J = 7.4 Hz, 2H), 7.39 (m, 2H), 7.95 (d, J = 7.0 Hz, 1H), 8.55 (d, J = 7.8 Hz, 1H), 11.92 (s, 1H). Analysis for $C_{16}H_{17}N_3O_6S$ (379.39): Calcd. C, 50.65; H, 4.52; N, 11.08; Found: C, 50.53; H, 4.78; N, 11.21%. MS (70 eV) m/z = 380 (11), 379 (7), 308 (13), 307 (100), 206 (6), 186 (13), 163 (4), 162 (4), 146 (97), 145 (16), 144 (4), 120 (10), 119 (16), 118 (11), 91(23), 90 (23), 90 (29), 65 (4), 39 (4).

3-Benzoylamino-2-Ethoxycarbonylmethylthio-4(3H)-Quinazolinone (9). Yield: 2.95 g (77%); white solid; mp 167 °C–169 °C. IR (KBr): ν (cm^{-1}) = 3320 (NHCO), 3000 (CH arom.), 2950 (CH_3), 2915 (CH_2), 1740, 1680 (C=O), 1480 (CH_2), 1310, 1260, 1190 (C−O), 1170, 770, 765 (C−H arom.). ^{1}H NMR (DMSO-d_6, 300 MHz): δ = 1.22 (t, J = 7.2 Hz, 3H), 4.17 (q, J = 7.2 Hz, 2H), 4.31 (s, 2H), 7.35 (m, 1H), 7.60 (m, 4H), 8.25 (m, 3H), 8.57 (d, J = 8.4 Hz, 1H), 11.17 (s, 1H). Analysis for $C_{19}H_{17}N_3O_4S$ (383.43): Calcd. C, 59.52; H, 4.47; N, 10.96; Found: C, 59.48; H, 4.43; N, 10.81%. MS (70 eV) m/z = 384 (2), 383 (8), 265 (9), 264 (51), 263 (11), 105 (100), 90 (3), 77 (66), 76 (3), 44 (12), 39 (2).

2-Ethoxycarbonylmethylthio-3-Crotonoylamino-4(3H)-Quinazolinone (10). Yield: 1.77 g (51%); white solid; mp 167 °C–169 °C. IR (KBr): ν (cm^{-1}) = 3330 (NHCO), 3100 (−CH=CH), 2950 (CH_3), 2880 (CH_2), 1740, 1700, 1680 (C=O), 1660 (CO−CH=CH), 1620 (−CH=CH), 1550 (NH, C−N), 1480 (CH_2), 1310, 1280, 1170 (C−O), 770, 750 (C−H arom.), 700 (C−S). ^{1}H NMR (DMSO-d_6, 300 MHz): δ = 1.20 (t, J = 7.2 Hz, 3H), 1.57 (d, J = 6.6 Hz, 3H), 4.17 (q, J = 7.2 Hz, 2H), 4.30 (s, 2H), 6.14 (d, J = 15.3 Hz, 1H), 6.86 (m, 1H), 7.29 (m, 2H), 7.88 (d, J = 7.9 Hz, 1H), 8.39 (d, J = 8.4 Hz, 1H), 10.41 (s, 1H). Analysis for $C_{16}H_{17}N_3O_4S$ (347.40): Calcd. C, 55.32; H, 4.93; N, 12.10; Found: C, 55.60; H, 5.17; N, 12.23%. MS (70 eV) m/z = 349 (2), 348 (4), 347 (23), 280 (7), 279 (52), 249 (11), 228 (90), 227 (15), 188 (11), 186 (3), 146 (17), 92 (8), 91 (5), 90 (8), 69 (100), 44 (40), 39 (18).

3-Cinnamoylamino-2-Ethoxycarbonylmethylthio-4(3H)-Quinazolinone (11). Yield: 2.30 g (56%); white precipitate; mp 155 °C–157 °C. IR (KBr): ν (cm^{-1}) = 3280 (NHCO), 3080 (−CH=), 2980 (CH_3), 1740, 1690 (C=O), 1640 (CO−CH=CH), 1620 (−CH=CH-Ar), 1540 (N−H, C−N), 1480 (CH_2), 1475, 1310, 1280 (C−O), 765, 745 (C−H arom.). ^{1}H NMR (DMSO-d_6, 300 MHz): δ = 1.19 (t, J = 7.2 Hz, 3H), 4.15 (q, J = 7.2 Hz, 2H), 4.31 (s, 2H), 6.89 (d, J = 15.7 Hz, 1H), 7.64 (m, 8H), 7.91 (d, J = 7.9 Hz, 1H), 8.40 (d, J = 8.5 Hz, 1H), 10.57 (s, 1H). Analysis for $C_{21}H_{19}N_3O_4S$ (409.47): Calcd. C, 61.60; H, 4.68; N, 10.26; Found: C, 61.43; H, 4.26; N, 10.11%. MS (70 eV) m/z =

410 (3), 323 (9), 322 (17), 321 (100), 236 (6), 235 (42), 202 (14), 178 (10), 163 (5), 162 (53), 160 (10), 145 (22), 144 (25), 134 (12), 131 (19), 130 (10), 103 (9), 102 (22), 91 (13), 76 (5), 57 (6), 44 (18), 39 (3).

2-Ethoxycarbonylmethylthio-3-(p-Nitrocinnamoyl)Amino-4(3H)-Quinazolinone (12). Yield: 3.22 g (71%); white solid; mp 209 °C–212 °C. IR (KBr): ν (cm^{-1}) = 3280 (NHCO), 3080 (−CH−), 2980 (CH_3), 2940 (CH_2), 1740, 1690 (C=O), 1635 (CO−CH=CH), 1625 (−CH=CH-Ar), 1530 (N−H, C−N), 1480 (CH_2), 1430, 1340 (NO_2), 1310, 980 (CH=CH trans), 770, 750 (C−H arom.). ^{1}H NMR (DMSO-d_6, 300 MHz): δ = 1.20 (t, J = 7.2 Hz, 3H), 4.15 (q, J = 7.2 Hz, 2H), 4.31 (s, 2H), 7.12 (d, J = 15.7 Hz, 1H), 7.36 (m, 1H), 7.66 (m, 1H), 7.75 (d, J = 7.7 Hz, 1H), 7.92 (d, J = 7.9 Hz, 1H), 8.00 (d, J = 8.8 Hz, 1H), 8.27 (d, J = 8.8 Hz, 2H), 8.38 (d, J = 8.4 Hz, 2H), 10.65 (s,1H). Analysis for $C_{21}H_{18}N_4O_6S$ (454.46): Calcd. C, 55.50; H, 3.99; N, 12.33; Found: C, 55.73; H, 4.18; N, 12.61%. MS (70 eV) m/z = 456 (3), 455 (9), 454 (33), 435 (1), 336 (17), 335 (100), 334 (20), 279 (41), 278 (4), 177 (8), 176 (68), 160 (8), 147 (4), 146 (22), 133 (6), 131 (7), 130 (31), 120 (29), 119 (11), 118 (19), 102 (0), 90 (14), 76 (8), 44 (21).

3-Amino-2-Benzylcarbamoylmethylthio-4(3H)-Quinazolinone (13). It was prepared similarly as described.[15]

Synthesis of Compounds 14–16: General Procedure

An equimolar (0.01 mol) mixture of the ester **5** and the substituted benzylamine (*p*-fluoro- **14**, p-chloro- **15**, *o*-chlorobenzylamine **16**) in toluene (50 mL) was refluxed for 4 h and subsequently cooled to ambient temperature. The solid obtained was filtrated, washed with diethyl ether and recrystallized from ethanol.

3-Amino-2-(p-Fluorobenzylcarbamoylmethylthio)-4(3H)-Quinazolinone (14). Yield: 1.50 g (42%); white solid; mp 172 °C–175 °C. IR (KBr): ν (cm^{-1}) = 3440, 3400, 3300 (NH, NH_2 + NHCO), 3080 (CH arom.), 2940 (−CH_2−), 1655 (NHCO), 1625 (NH), 1550 (NH, N−C), 1160, 850, 760, 740 (C−H arom.). ^{1}H NMR (DMSO-d_6, 500 MHz): δ = 4.16 (s, 2H), 4.29 (d, J = 5.0 Hz, 2H), 6.64 (m, 3H), 6.90 (d, J = 8.1 Hz, 1H), 7.85 (m, 2H), 7.74 (d, J = 6.2 Hz, 3H), 7.58 (d, J = 7.6 Hz, 1H), 8.85 (br, 1H). Analysis for $C_{17}H_{15}N_4O_2SF$ (358.39): Calcd. C, 56.97; H, 4.22; N, 15.63; Found: C, 57.19; H, 4.28; N, 16.00%. MS (70 eV) m/z = 360 (4), 359 (12), 358 (59), 195 (2), 194 (13), 193 (12), 166 (22), 165 (29), 164 (10), 137 (19), 122 (11), 121 (9), 120 (100), 118 (53), 110 (4), 109 (47), 92 (22), 91 (6), 90 (2), 77 (4), 65 (11), 39 (3).

3-Amino-2-(p-Chlorobenzylcarbamoylmethylthio)-4(3H)-Quinazolinone (15). Yield: 1.80 g (48%); white solid; mp 175 °C–176 °C. IR (KBr): ν (cm^{-1}) = 3450, 3410, 3320 (NH_2 + NHCO), 3080 (CH arom.), 2950 (−CH_2−), 1655 (NHCO), 1625 (NH), 1555 (NH, N−C), 1458 (−CH_2−), 1165, 840, 750 (C−H arom.). ^{1}H NMR (DMSO-d_6, 500 MHz) δ = 4.19 (s, 2H), 4.33 (d, J = 5.9 Hz, 2H), 6.42 (m, 3H), 6.99 (d, J = 8.4 Hz, 1H), 7.28 (m, 5H), 7.58 (m, 1H), 8.88 (br, 1H). Analysis for $C_{17}H_{15}N_4O_2SCl$ (374.84): Calcd. C, 54.47; H, 4.03; N, 14.95; Found: C, 54.12; H, 4.18; N, 15.17%. MS (70 eV) m/z = 376 (24), 375 (13), 374 (63), 194 (19), 193 (18), 184 (7), 183 (11), 182 (24), 181 (28), 160 (5), 146 (21), 125 (32), 120 (100), 119 (7), 118 (59), 92 (21), 65 (10), 39 (2).

3-Amino-2-(o-Chlorobenzylcarbamoylmethylthio)-4(3H)-Quinazolinone (16). Yield: 1.99 g (53%); white solid; mp 149 °C–150 °C. IR (KBr): ν (cm^{-1}) = 3440, 3410, 3320 (NH_2 + NHCO), 3100 (CH arom.), 2960 (−CH_2−), 1660 (NHCO), 1630 (NH), 1560 (NH, N−C) 1170, 760, 740 (C−H arom.). ^{1}H NMR (DMSO-d_6, 500 MHz): δ = 4.20 (s, 2H), 4.38 (d, J = 5.8 Hz, 2H), 6.65 (m, 3H), 6.90 (d, J = 8.3 Hz, 1H), 7.26 (m,

3H), 7.36 (m, 1H), 7.42 (m, 1H), 7.60 (m, 1H), 8.87 (br, 1H). Analysis for $C_{17}H_{15}N_4O_2SCl$ (374.84): Calcd. C, 54.47; H, 4.03; N, 14.95; Found: C, 54.18; H, 4.12; N, 15.30%. MS (70 eV) m/z = 376 (22), 375 (12), 374 (58), 340 (6), 339 (27), 199 (6), 193 (7), 181 (15), 153 (12), 125 (29), 121 (8), 120 (100), 118 (53), 92 (20), 76 (10), 39 (2).

2-Benzylcarbamoylmethylthio-3-Cinnamoylamino-4(3H)-Quinazolinone (17). Yield: 2.73 g (58%); white solid; mp 147 °C–149 °C. IR (KBr): ν (cm^{-1}) = 3320 (NHCO), 3080 (CH=), 2880 (CH_2), 1690 (C=O), 1650 (C=O, C=C−C=O), 1620 (C=C−Ph), 1550 (N−H, C−N), 1490 (CH_2), 1290 (CH=CH trans), 770, 750 (C−H arom.), 700 (C−S). ^{1}H NMR (DMSO-d_6, 300 MHz): δ = 4.19 (s, 2H), 4.32 (d, J = 5.9 Hz, 2H), 6.88 (d, J = 15.7 Hz, 1H), 7.26 (m, 6H), 7.31 (m, 3H), 7.45 (m, 4H), 7.89 (m, 1H), 8.44 (d, J = 7.8 Hz, 1H), 8.85 (br, 1H), 10.64 (s, 1H). Analysis for $C_{26}H_{22}N_4O_3S$ (470.54): Calcd. C, 66.37; H, 4.71; N, 11.91; Found: C, 66.29; H, 4.37; N, 12.15%. MS (70 eV) m/z = 470 (8), 453 (13), 452 (42), 377 (37), 322 (14), 290 (32), 250 (41), 247 (25), 204 (23), 132 (12), 131 (100), 103 (48), 102 (12), 92 (8.), 91 (6), 77 (22), 65 (8), 51 (4).

2-Benzylcarbamoylmethylthio-3-(p-Nitrocinnamoyl)Amino-4(3H)-Quinazolinone (18). Yield: 3.15 g (61%); white solid; mp 221 °C–223 °C. IR (KBr): ν (cm^{-1}) = 3320, 3300 (NHCO), 3080 (CH=), 2880 (CH_2), 1690 (C=O), 1660 (C=O, C=C−C=O), 1620 (C=C−Ar), 1560 (N−H, C−N), 1530, 1340 (NO_2), 1480 (CH_2), 1290 (CH=CH trans), 760, 740 (C−H arom.). ^{1}H NMR (DMSO-d_6, 300 MHz): δ = 4.20 (s, 2H), 4.32 (d, J = 5.9 Hz, 2H), 7.11 (d, J = 15.7 Hz, 1H), 7.25 (m, 2H), 7.33 (m, 4H), 7.65 (m, 1H), 7.75 (d, J = 15.7 Hz, 1H), 7.91 (d, J = 7.9 Hz, 1H), 7.99 (d, J = 8.7 Hz, 2H), 8.26 (d, J = 8.7 Hz, 2H), 8.41 (d, J = 8.3 Hz, 1H), 8.84 (br, 1H), 10.71 (s, 1H). Analysis for $C_{26}H_{21}N_5O_5S$ (515.55): Calcd. C, 60.57; H, 4.11; N, 13.58; Found: C, 61.00; H, 4.28; N, 13.47%. MS (70 eV) m/z = 515 (31), 422 (5), 335 (73), 295 (31), 221 (21), 176 (81), 147 (58), 146 (41), 130 (37), 91 (100), 76 (14), 65 (9).

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