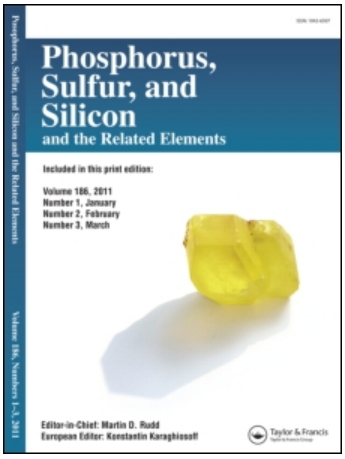

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Synthesis of New 4(3*H*)-Quinazolinone Derivatives by Reaction of 3-Amino-2(1*H*)-thioxo-4(3*H*)-quinazolinone with Selected Chloroformates: Ammonolysis of 3-Ethoxycarbonylamino-2-ethoxycarbonylthio-4(3*h*)-quinazolinone, Part 2[1]

Wanda P. Nawrocka[a]
[a] Wroclaw Medical University, Wroclaw, Poland

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Synthesis of New 4(3*H*)-Quinazolinone Derivatives by Reaction of 3-Amino-2(1*H*)-thioxo-4(3*H*)-quinazolinone with Selected Chloroformates: Ammonolysis of 3-Ethoxycarbonylamino-2-ethoxycarbonylthio-4(3*h*)-quinazolinone, Part 2[1]

Wanda P. Nawrocka
Wroclaw Medical University, Wroclaw, Poland

*A series of N- and S-alkylated 4(3H)-quinazolinone derivatives (**2–6**) have been synthesized by the reaction of 3-amino-2(1H)-thioxo-4(3H)-quinazolinone (**1**) with selected chloroformates. 3-Ethoxycarbonylamino-2-ethoxycarbonylthio-4(3H)-quinazolinone (**3**) was ammonolysed using ammonia, primary or secondary amines. Depending on the kind of substrates and conditions of ammonolysis, products of various chemical structures were obtained. The products %**2–17** were identified by the results of elemental analysis and by their IR, ^{1}H NMR, and mass spectra.*

Keywords 3-Amino-2(1*H*)-thioxo-4(3*H*)-quinazolinone derivatives; ammonolysis; 2,3-dialkoxycarbonyl-4(3*H*)-quinazolinone; IR, ^{1}H NMR; mass spectra; synthesis

INTRODUCTION

Numerous derivatives of 4(3*H*)-quinazoline exhibiting various biological and pharmacological activities have been obtained and studied in the last few years. They include compounds obtained synthetically and compounds isolated from natural materials.[2–6] 4(3*H*)-Quinazolinones showing anticancer activity are of special interest.[7–9a–c] Interest in this class of compounds increased after introduction of the so-called thymidylate synthetase inhibitors to therapeutic practice.[7,10,11] Tomudex™ from Astra Zeneca is used mainly in chemotherapy of colorectal cancer,[12] and Thymitaq™ from Zarix is used in lung cancer therapy.[13,14] The literature also presents 4(3*H*)-quinazolinones as having other mechanisms of anticancer action; for example, 8-hydroxy-2-methyl-4(3*H*)-quinazolinone (Nu 1025) is a PARP enzyme blocker and

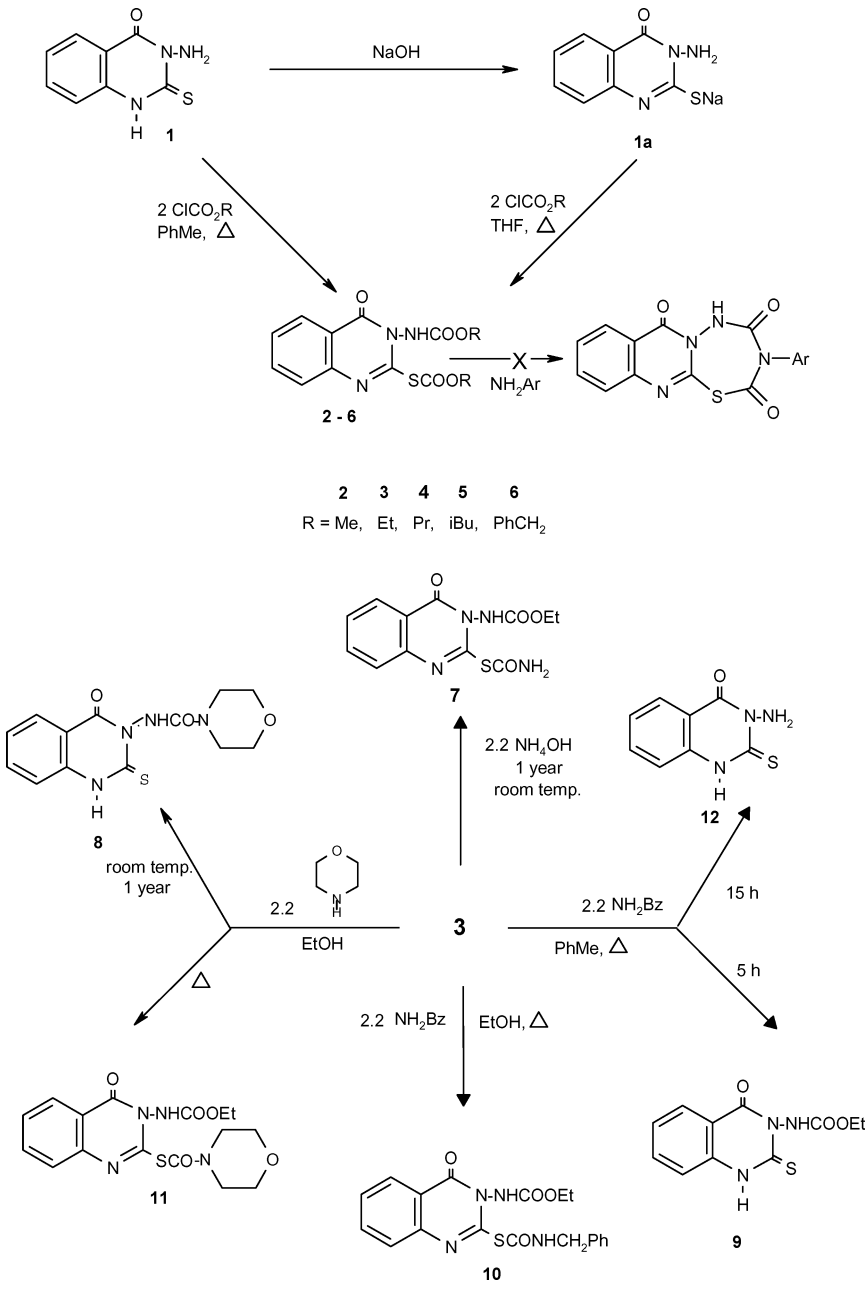
Received 26 January 2008; accepted 5 April 2008.
Address correspondence to Wanda P. Nawrocka, Department of Technology of Drugs, Wroclaw Medical University, 50-140 Wroclaw, Nankier Sq. 1, Poland. E-mail: paulina@ktl.am.wroc.pl

increases the activity of alkylating drugs.[15] In vitro studies showed that 6-chloro-2-ethyl-3-(3-phenylisoxazol-5-yl)-4(3*H*)-quinazolinone was active towards neoplastic cells of human leukemia, human lymphoma, and Burkitt's lymphoma.[16]3-Phenyl-6-iodo-4(3*H*)-quinazolinone was active towards Ehrich ascites tumor.[17] 2,2′-Thiobis[3-amino-4(3*H*)-quinazolinone][9*a,b*] exhibited the highest activity in vitro against melanoma cells. 3-Amino-2-methylthio-4(3*H*)-quinazolinone showed an antituberculostatic and antiproliferative activity in vitro towards human neoplastic cells CCRF/CEM (leukemia), SW707 (colorectal cancer), and Du145 (prostate cancer).[9*c*] In our latest article, we described the synthesis of new derivatives by the reaction of 3-amino-2(1*H*)-thioxo-4(3*H*)-quinazolinone (**1**) with selected substituted cinnamic acids and with halogenoketones.[1] The aim of this study was to synthesize new derivatives of 4(3*H*)-quinazolinone **1** by reaction with selected chloroformates. The presence of two chemically active groups, 3-amino and 2-thiocarbonyl, in the molecule of 4(3*H*)-quinazolinone **1**, allows us to obtain products of various chemical structures: *S*–, *N*–, *S*–, and *N*–substituted or tricyclic products derived from 3*H*-1,3,4-thiadiazol[2,3-*b*]quinazolin-2,5-dione. In the case of the substituted products obtained, their behavior towards nitrogen nucleophilic agents, such as ammonia and primary and secondary amines, was tested.

In our previous studies, we found that the presence of alkoxycarbonyl groups in 1,5-benzodiazepines is usually connected with high psychotropic activity.[18] The presence of such groups in pyrido[2,3-*b*]-[1,4]diazepine results in high antiproliferative activity in vitro against human neoplastic cells HL-60 (leukemia) and HCV29T (urinary bladder cancer) when *cis*-platinum is used as a reference.[19]

RESULTS AND DISCUSSION

3-Amino-2(1*H*)-thioxo-4(3*H*)-quinazolinone[20] (**1**) was added to selected chloroformates in a stoichiometric ratio. The reactions were carried out in boiling toluene in the presence of triethylamine (Scheme 1). Thin-layer chromatography (TLC) confirmed the presence of unreacted substrate—4(3*H*)-quinazolinone[20] **1**—in the solution, and the reaction products were obtained in the form of a precipitate. Prolonged heating did not cause any significant increase in the quantity of the products. The precipitate was collected by filtration and analyzed after recrystallization from ethanol. The results of elemental analysis and the mass spectra confirmed the formation of disubstituted derivatives. The reactions were repeated using 2.2-fold excess of the chlorofomates, giving the derivatives **2–6** with adequately higher yield. The same products



SCHEME 1

2–6 were obtained with similar yields, when the reactions were carried out using the sodium salt of 4(3*H*)-quinazolinone[20] **1a** in anhydrous boiling tetrahydrofurane with a 2.2-fold excess of the respective chloroformate.

Peaks of the molecular ions are present in the mass spectra of the products **2–5**, but they are not the base ions. In the mass spectrum of compound **6** there is no molecular ion peak, while a fragment ion peak is observed indicating the elimination of the benzyloxycarbonyl group. In the case of compounds **2** and **3**, the base ions are the quinazolinone cations, m/z = 146 (100), and in the case of compounds **4–6** the base ions are the cations propyl (m/z = 43), isobutyl (m/z = 57), and benzyl (m/z = 91), respectively. The further fragmentation of the compounds **2–6** is typical for 4(3*H*)-quinazolinones.[21] As a result, the cyclopropenyl ion m/z = 39 is present in the spectra, formed as the final product of the degradation of both aliphatic substituents and phenyl rings.

A single band at $\sim$ 3340 cm^{-1} was observed in the IR spectra of compounds **2–6**, and it was attributed to the stretching vibration of N-H belonging to the **NH**CO groups. In the region of 1760–1732 cm^{-1}, there are two absorption bands corresponding to the stretching vibration of C=O groups. Bands present in the region of $\sim$ 1760 cm^{-1} were attributed to C=O groups belonging to S**CO**OR moieties, and bands present at lower wave numbers $\sim$ 1740 cm^{-1} were attributed to C=O groups of NH**CO**OR fragments.

Interpretation of the ^{1}H NMR spectra of compounds **2–6** is based on the comparison with the ^{1}H NMR spectrum of 3-amino-2(1*H*)-thioxo-4(3*H*)-quinazolinone (**1**). The most characteristic features for compound **1** are the chemical shifts of the protons in the N**H**$_2$ and N**H**-C=S groups. They are present as two- and one-proton singlets at $\delta \sim$ 6.30 ppm and $\delta \sim$ 14.50 ppm, respectively. Signals of these protons are absent in the ^{1}H NMR spectra of the synthesized compounds **2–6**. The lack of signals for the **NH**C=S proton indicates that substitution took place also at the position 2. However, the presence of one-proton singlet at $\delta \sim$ 9.50 ppm was observed for the compounds **2–5**, and in the case of the benzyl derivative **6**, this signal was observed at $\delta \sim$ 10.16 ppm. The signals were attributed to the NH proton of the **NH**CO group, present in the 3 position. Signals of the protons of the substituent connected with heteroatoms at positions 2 and 3 are clearly separated, and, therefore, can be identified. At lower δ values (shielding effect), the ^{1}H NMR signals of the alkoxy and benzyloxycarbonyl groups connected with nitrogen are observed, while the signals of groups attached to the sulphur atom appear at higher δ values (deshielding effect). For example, in the case of the compound **2**, the signals of the protons in

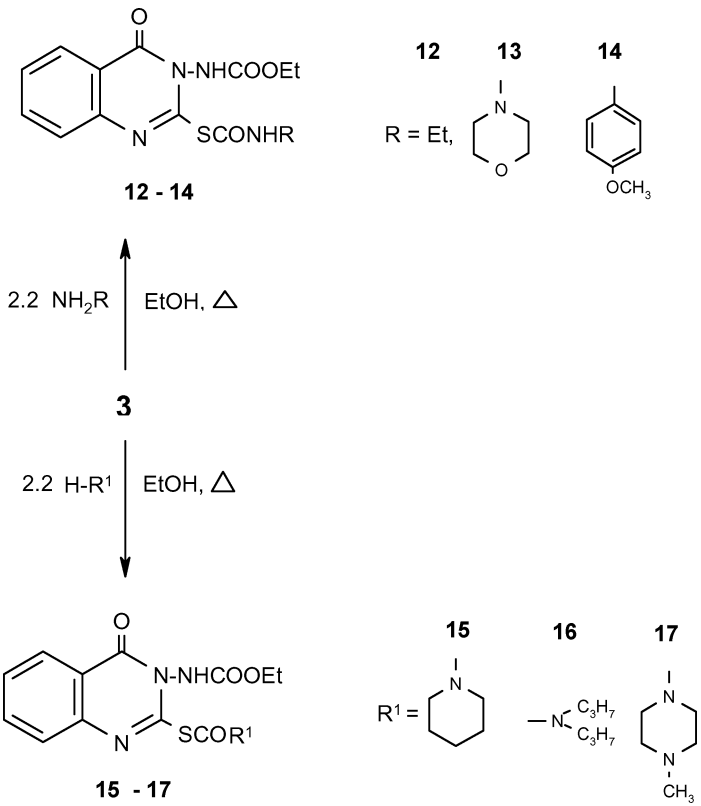
the methoxy groups NHCO**OCH**$_3$ and SCO**OCH**$_3$ appear at δ= 3.69 ppm and at δ= 4.02 ppm, respectively. Signals present in the range of δ 7.13–8.24 ppm confirm the presence of aromatic protons, and their number is consistent with the structures **2–6**.

The reactivity of 3-ethoxycarbonylamino-2-ethoxycarbonylthio-4(3*H*)-quinazolinone (**3**) towards an excess (2.2 mol) of a concentrated aqueous solution of ammonia, as well as towards primary and secondary amines under various conditions, was studied (Scheme 1). The reactions yielded tricyclic products derived from quinazolin[2,3-*b*][1,3,5,6]-thiatriazepin-2,4,7-trione, by ammonolysis at the position 2 or 3 or simultaneously at both positions 2 and 3. A long-lasting (1 week) reaction of compound **3** with concentrated aq. ammonia solution at room temperature resulted in the formation of 3-ethoxycarbonylamino-2-aminocarbonylthio-4(3*H*)-quinazolinone (**7**) (Scheme 1). Only the ethoxy group at position 2 underwent ammonolysis. In the IR spectrum of the compound **7**, there is no band of a carbonyl group at $\sim$ 1752 cm^{-1} indicating the presence of a –S**CO**NH$_2$ moiety, while the band of the second C=O group, originating from –NH**CO**OR, at $\sim$ 1738 cm^{-1} remained. The ^{1}H NMR spectrum provides good evidence for the product **7**. The spectrum contains the proton signals of a single ethyl group, and their chemical shifts at δ= 1.25 ppm (t, 3H) and δ= 4.15 ppm (q, 2H) confirm that they belong to a substituent NHCOOC**H**$_2$C**H**$_3$ at position 3.

Heating compound **3** with benzylamine or morpholine in ethanol yielded compounds **10** and **11,** while heating boiling **3** in toluene with an excess of benzylamine for 5 h gave 3-ethoxycarbonylamino-2(1*H*)-thioxo-4(3*H*)-quinazolinone **(9)**—a product of dealkylation at position 2. Long-term heating of the substrates led also to dealkylation at position 3, yielding 3-amino-2(1*H*)-thioxo-4(3*H*)-quinazolinone[20] (**1**). In a similar, long-term reaction of compound **3** with morpholine, compound **8** was obtained—a product of dealkylation at position 2 and ammonolysis at position 3.

3-Ethoxycarbonylamino-2-ethoxycarbonylthio-4(3*H*)-quinazolinone (**3**) was also ammonolysed with selected primary amines ethylamine, *p*-methoxyaniline, and aminomorpholine, as well as with secondary amines diisopropylamine, piperidine, and 4-methylpiperazine, in boiling ethanol (Scheme 2). Products of these reactions were the derivatives **12–17** having structures analogous to those of the ammonolysis products **10** and **11** obtained with benzylamine or morpholine in ethanol.

The same type of fragmentation and elimination is observed in the mass spectra of compounds **7**, **10–17**; molecular ions are not present.



SCHEME 2

The ion with the highest mass observed is a fragment ion with m/z = 265 [3-ethoxycarbonylamino-2(1*H*)-thioxo-4(3*H*)-quinazolinone]. It is formed from the parent molecules by elimination of carbamoyl groups of the substituent at position 2. Base ions for the majority of the compounds are quinazolinone ions with m/z = 146 (100), and for the compound **11** the morpholine ion with m/z = 87.

Depending on the kind of substrates and conditions of ammonolysis of compound **3**, products of various chemical structure were obtained, which are of interest for biological studies or which can be substrates 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 δ 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.

3-Amino-2(1*H*)-thioxo-4(3*H*)-quinazolinone (1)

The compounds **1** and **1a** were prepared exactly as described previously.[20]

General Procedure for the Synthesis of Compounds 2–6

To a mixture of compound **1** (1.93 g, 0.01 mol) and NEt_3 (3 mL) in anhydrous toluene (50 mL), methyl (**2**), ethyl (**3**), propyl (**4**), isobutyl (**5**), or benzyl (**6**) chloroformate (0.022 mol) was added dropwise with mechanical stirring. The mixture was refluxed for 10–15 h (TLC). The product was filtered off, washed with Et_2O (20 mL), 5% aq. $NaHCO_3$ solution (10 mL) and water (50 mL), dried and recrystallized from ethanol. The compounds **2–6** were obtained with similar yields from the reaction of the sodium salt **1a** with the respective chloroformate in boiling THF.

3-Methoxycarbonylamino-2-methoxycarbonylthio-4(3*H*)-quinazolinone (2)

Yield: 2.00 g (65%); white solid; m.p. 183–185°C. IR (KBr): ν (cm^{-1})= 3340 (NHCO), 2960 (CH_3), 1756 (S-COOR), 1732 (NHCOOR), 1620 (NHCO), 1548 (—NH, C—N), 1480 (C=N ring), 770 (arom.). ^{1}H NMR (DMSO-d_6, 300 MHz): δ = 3.69 (s, 3H), 4.02 (s, 3H), 7.29 (m, 1H), 7.65 (t, $J \sim$ 8.1 Hz, 1H), 7.77 (d, J = 7.8 Hz, 1H), 7.92 (d, J = 8.3 Hz, 1H), 9.50 (s, 1H). MS (70 eV) m/z = 311 (3), 310 (6), 309 (61), 217 (17), 193 (39), 178 (27), 147 (12), 146 (100), 91 (7), 90 (28), 59 (31), 39 (4). Analysis for $C_{12}H_{11}N_3O_5S$ (309.30): Calcd. C, 46.60; H, 3.58; N, 13.59%. Found: C, 46.66; H, 3.49; N, 13.70%.

3-Ethoxycarbonylamino-2-ethoxycarbonylthio-4(3*H*)-quinazolinone (3)

Yield: 2.32 g (69%); white solid; m.p. 175–178°C. IR (KBr): ν (cm^{-1})= 3336 (NHCO), 2984 (CH_3), 2912 (-CH_2-), 1752 (S-COOR), 1734 (NHCOOR), 1658 (NHCO), 1446 (-CH_2-), 775 (arom.). ^{1}H NMR (DMSO-d_6, 300 MHz): $\delta = 1.25$ (t, $J = 5.8$ Hz, 3H), 1.37 (t, $J = 7.1$ Hz, 3H), 4.14 (q, $J = 5.8$ Hz, 2H), 4.46 (q, $J = 7.1$ Hz, 2H), 7.13 (m, 1H), 7.65 (m, 1H), 7.77 (d, $J = 7.9$ Hz, 1H), 7.94 (d, $J = 8.3$ Hz, 1H), 9.57 (s, 1H). MS (70 eV) m/z = 339 (3), 338 (7), 337 (35), 293 (9), 147 (18), 146 (100), 145 (7), 120 (22), 119 (16), 92 (10), 91 (8), 90 (22), 77 (8), 69 (24), 44 (22), 43 (18), 39 (8). Analysis for $C_{14}H_{15}N_3O_5S$ (337.35): Calcd. C, 49.85; H, 4.48; N, 12.46. Found: C, 49.93; H, 4.46; N, 12.23%.

3-Propyloxycarbonylamino-2-propyloxycarbonylthio-4(3*H*)-quinazolinone (4)

Yield: 2.00 g (55%); white solid; m.p.132–133°C. IR (KBr): ν (cm^{-1})= 3336 (NHCO), 2964 (CH_3), 2912 (-CH_2-), 1752 (S-COOR), 1738 (NHCOOR), 1620 (NHCO), 1542 (N—H and C—N), 1448 (-CH_2-), 760 (arom.). ^{1}H NMR (DMSO-d_6, 300 MHz): δ= 0.92 (t, J= 5.9 Hz, 3H), 1.01 (t, J= 6.2 Hz, 3H), 1.64 (m, 2H), 1.75 (m, 2H), 4.06 (t, J= 6.8 Hz, 2H), 4.36 (m, 2H), 7.29 (t, $J \sim 7.7$ Hz, 1H), 7.65 (m, 1H), 7.87 (d, J= 7.9 Hz, 1H), 7.94 (d, J= 8.3 Hz, 1H), 9.49 (s, 1H). MS (70 eV) m/z = 367 (2), 366 (4), 365 (21), 281 (2), 280 (3), 279 (15), 220 (4), 206 (18), 164 (45), 146 (75), 120 (12), 66 (12), 57 (26), 55 (22), 43 (100), 39 (10). Analysis for $C_{16}H_{19}N_3O_5S$ (365.40): Calcd. C, 52.59; H, 5.24; N, 11.50. Found: C, 52.50; H, 5.29, N, 11.70%.

3-Isobutyloxycarbonylamino-2-isobutyloxycarbonylthio-4(3*H*)-quinazolinone (5)

Yield: 1.90 g (48%); white solid; 129–133 °C. IR (KBr): ν (cm^{-1})= 3332 (NHCO), 3052 (CH), 2960 (CH_3), 2888 (CH), 1756 (S-COOR), 1740 (NHCOOR), 1620 (NHCO), 1612 (ring), 1536 (N—H, C—N), 1168 ($C(CH_3)_2$), 760 (arom.). ^{1}H NMR (DMSO-d_6, 300 MHz): δ= 0.92 (d, J = 6.5 Hz, 6H), 1.00 (d, J= 6.7 Hz, 6H), 1.90 (m, 1H), 2.07 (m, 1H), 3.89 (d, J= 6.4 Hz, 2H), 4.22 (d, J= 6.7 Hz, 2H), 7.28 (m, 1H), 7.64 (m, 1H), 7.78 (d, J= 7.9 Hz, 1H), 8.11 (d, J= 8.1 Hz, 1H), 9.47 (s, 1H). MS (70 eV) m/z = 395 (1), 394 (2), 393 (11), 293 (10), 228 (5), 227 (18), 194 (4), 193 (19), 177 (16), 165 (5), 164 (74), 146 (74), 145(2), 91 (2), 90 (6), 57

(100), 56 (4), 41 (57), 39 (6). Analysis for $C_{18}H_{23}N_3O_5S$ (393.46): Calcd. C, 54.95; H, 5.89; N, 10.69. Found: C, 54.63; H, 5.68; N, 10.49%.

3-Benzyloxycarbonylamino-2-benzyloxycarbonylthio-4(3*H*)-quinazolinone (6)

Yield: 2.80 g (61%); white solid; m.p. 89–93 °C. IR (KBr): ν (cm^{-1})= 3340 (NHCO), 3030 (CH), 1750 (S-COOR), 1732 (NHCOOR), 1656, 1552 (N—H, C—N), 1484 (-CH_2-), 1424 (N—C—S—N), 772 (arom.). ^{1}H NMR (DMSO-d_6, 300 MHz): δ= 4.58 (s, 2H), 5.20 (s, 2H), 7.35 (m, 11H), 7.59 (m, 1H), 7.84 (d, *J*= 7.5 Hz, 1H), 8.24 (d, *J*= 8.4 Hz, 1H), 10.16 (s, 1H). MS (70 eV) m/z = 326 (3), 266 (2), 194 (2), 193 (8), 147 (10), 146 (9), 132 (8), 120 (7), 92 (17), 91 (100), 77 (6), 65 (14), 57 (4), 39 (7). Analysis for $C_{24}H_{19}N_3O_5S$ (461.49): Calcd. C, 62.46; H, 4.15; N, 9.11. Found: C, 62.80; H, 4.17; N, 9.23%.

General Procedure for the Synthesis of Compounds 7–17

To compound **3** (3.37 g, 0.01 mol) in ethanol (50 mL) the following reactants were added:

- 25% aq. ammonia (0.022 mol), and the reaction mixture was left at room temperature for 1 week (**7**).
- Primary amines: benzylamine (**10**), ethylamine (**12**), 4-aminomorpholine (**13**), 4-methoxyaniline (**14**), or secondary amines: morpholine (**11**), piperidine (**15**), diisopropylamine (**16**), 4-methylpiperazine (**17**), and the reaction mixture was refluxed for ca. 10 h (TLC).

To compound **3** in toluene (50 mL), benzylamine (0.022 mol) or morpholine (0.022 mol) was added, and the reaction mixture was refluxed for 5 h (**9**)–15 h (**8, 1**).

At the end of the reaction, the solvent was partially evaporated under reduced pressure. The residue was left for crystallization, and the precipitate was filtered, washed with Et_2O (10 mL), and recrystallized from ethanol.

3-Ethoxycarbonylamino-2-carbamoylthio-4(3*H*)-quinazolinone (7)

Yield: 1.37 g (45%); white solid; m.p. 200–202°C. IR (KBr): ν (cm^{-1})= 3388, 3348 ($CONH_2$), 3124 (NHCO), 2952 (CH_3), 1738 (NHCOOR), 1700

($SCONH_2$), 1642 (CON=, $CONH_2$), 1570 (C—N, N—H), 1470 (-CH_2-), 770 (arom.). ^{1}H NMR (DMSO-d_6, 300 MHz): δ= 1.25 (t, J= 5.8 Hz, 3H), 4.15 (q, J= 5.8 Hz, 2H), 7.18 (m, 3H), 7.49 (m, 1H), 7.73 (d, J= 6.9 Hz, 1H), 8.16 (d, J= 8.3 Hz, 1H), 10.20 (s, 1H). MS (70 eV) m/z = 265 (61), 220 (3), 205 (10), 147 (7), 146 (100), 120 (9), 92 (7), 91 (5), 90 (10), 77 (8), 65 (3), 39 (2). Analysis for $C_{12}H_{12}N_4O_4S$ (308.31): Calcd. C, 46.75; H, 3.92; N, 18.17. Found: C, 46.63; H, 4.07; N, 18.43%.

3-Morpholinocarbonylamino-2(1H)-thioxo-4(3H)-quinazolinone (8)

Yield: 2.39 g (78%); white solid; m.p. 287–289°C. IR (KBr): ν (cm^{-1})= 3308 (NHCO), 3076 (CH), 1680 (NHCON), 1620 (=NCO), 1528 (C—N, NH), 1476 (CH_2), 768 (arom.). ^{1}H NMR (DMSO-d_6, 300 MHz): δ= 3.69 (m, 4H), 3.89 (m, 4H), 7.24 (m, 2H), 7.71 (t, J= 7.6 Hz, 1H), 7.94 (d, J= 7.8 Hz, 1H), 12.14 (br, 2H). MS (70 eV) m/z = 307 (1), 306 (7), 163 (31), 162 (100), 146 (29), 145 (6), 144 (22), 130 (17), 119 (98), 92 (42), 91 (11), 86 (69), 57 (20), 56 (12), 39 (8). Analysis for $C_{13}H_{14}N_4O_3S$ (306.34): Calcd. C, 50.97; H, 4.61; N, 18.29. Found: C, 50.72; H, 4.39; N, 18.27%.

3-Ethoxycarbonylamino-2(1H)-thioxo-4(3H)-quinazolinone (9)

Yield: 0.95 g (36%); white solid; m.p. 193–195 °C. IR (KBr): ν (cm^{-1})= 3280 (NHCO), 3060 (CH), 2900 (CH_2), 1740 (NHCOOR), 1660 (NHCO), 1450 (-CH_2-), 1350 (N—CS—N), 1200 (NH—CS), 760 (arom.), 708 (C—S). ^{1}H NMR (DMSO-d_6, 300 MHz): δ= 1.24 (t, J= 5.9 Hz, 3H), 4.14 (q, J= 5.9 Hz, 2H), 7.26 (m, 1H), 7.59 (t, J= 7.7 Hz, 1H), 7.76 (d, J= 7.9 Hz, 1H), 7.98 (d, J= 8.4 Hz, 1H), 9.45 (s, 1H), 12.79 (s, 1H). MS (70 eV) m/z = 267 (3), 266 (7), 265 (73), 220 (6), 193 (12), 146 (100), 120 (12), 118 (12), 107 (28), 106 (55), 91 (34), 90 (14), 77 (20), 57 (12), 44 (9), 39 (11). Analysis for $C_{11}H_{11}N_3O_3S$ (265.29): Calcd. C, 49.80; H, 4.18; N, 15.84. Found: C, 49.63; H, 4.39; N, 15.97%.

3-Ethoxycarbonylamino-2-benzylcarbamoylthio-4(3H)-quinazolinone (10)

Yield: 3.10 g (79%); white solid; m.p. 167–171 °C. IR (KBr): ν (cm^{-1})= 3240 (NHCO), 2976 (CH_3), 1730 (NHCOOR), 1658 (NHCO), 1620 (=NCO), 1570 (-NH, C-N), 1476 (-CH_2-), 758 (arom.). ^{1}H NMR (DMSO-d_6, 500 MHz): δ= 1.27 (t, J= 5.8 Hz, 3H), 4.05 (d, J= 5.4 Hz, 2H), 4.18 (q, J= 5.8 Hz, 2H), 7.13 (m, 2H), 7.41 (m, 5H), 7.70 (d, J= 8.1 Hz, 1H), 8.15 (br, 1H), 8.33 (d, J= 8.4 Hz, 1H), 10.89 (s, 1H). MS (70 eV) m/z = 267 (3), 266 (3), 265 (62), 220 (4), 205 (13), 147 (7), 146 (100), 145 (3), 104 (10), 91 (12), 77 (11), 39 (6). Analysis for $C_{19}H_{18}N_3O_4S$ (384.43): Calcd. C, 59.36; H, 4.72; N, 10.93. Found: C, 58.98; H, 4.77; N, 10.60%.

3-Ethoxycarbonylamino-2-morpholinocarbonylthio-4(3H)-quinazolinone (11)

Yield: 2.20 g (58%); white solid; m.p. 170–173°C. IR (KBr): ν (cm^{-1})= 3255 (NHCO), 2980 (CH_2), 2880 (CH_3), 2730 (=NCH_2), 1730 (NHCOOEt), 1615 (=NCO), 1560 (C=N), 1540 (C—O), 1470 (=N—CH_2, CH), 775 (arom.). ^{1}H NMR (DMSO-d_6, 500 MHz): δ= 1.27 (t, J= 5.9 Hz, 3H), 3.13 (m, 4H), 3.77 (m, 4H), 4.18 (q, J= 5.9 Hz, 2H), 7.14 (m, 1H), 7.42 (m, 1H), 7.71 (d, J= 7.8 Hz, 1H), 8.32 (d, J= 8.4 Hz, 1H), 10.88 (s, 1H). MS (70 eV): m/z = 267 (4), 266 (8), 265 (59), 146 (62), 119 (11), 118 (11), 91 (6), 90 (9), 87 (100), 86 (59), 57 (84), 56 (75), 39 (8). Analysis for $C_{16}H_{18}N_4O_5S$ (378.40): Calcd. C, 50.79; H, 4.79; N, 14.81. Found: C, 50.93; H, 5.11; N, 14.70%.

3-Ethoxycarbonylamino-2-ethoxycarbamoylthio-4(3H)-quinazolinone (12)

Yield: 1.78 g (53%); white solid; m.p. 146–150°C with benzene. IR (KBr): ν (cm^{-1})= 3400 (NHCO), 2984 (CH_3), 2845 (CH_2), 1740 (NHCOOR), 1700, 1658 (NHCO), 1570 (C—N, NH), 1464 (-CH_2-), 760 (arom.). ^{1}H NMR (300 MHz, DMSO-d_6,): δ= 1.23 (t, J= 5.9 Hz, 3H), 1.27 (t, J= 5.7 Hz, 3H), 2.84 (q, J= 5.9 Hz, 2H), 4.18 (q, J= 5.7 Hz, 2H), 7.13 (m, 1H), 7.42 (m, 1H), 7.71 (d, J= 7.9 Hz, 1H), 7.79 (br, 1H), 8.32 (d, J= 8.3, 1H), 10.89 (s, 1H). MS (70 eV) m/z = 267 (2), 266 (5), 265 (43), 220 (3), 219 (13), 148 (4), 147 (5), 146 (85), 107 (100), 106 (99), 104 (10), 91 (21), 90 (12), 79 (57), 78 (18), 77 (30), 76(5), 51(20), 39 (13). Analysis for $C_{14}H_{16}N_4O_4S$ (336.37): Calcd. C, 49.99; H, 4.79; N, 16.66. Found: C, 49.73; H, 4.92; N, 16.63%.

3-Ethoxycarbonylamino-2-morpholincarbamoylthio-4(3H)-quinazolinone (13)

Yield: 2.60 g (66%); white solid; m.p. 159–163°C. IR (KBr): ν (cm^{-1})= 3248 (NHCO), 2980 (CH_3), 2852 (-CH_2-), 1732 (NHCOOR), 1656 (NH—CO—NH), 1636 (NHCO), 1570 (C=N ring), 1470 (-CH_2-), 756 (arom.). ^{1}H NMR (DMSO-d_6, 300 MHz): δ= 1.26 (t, J= 5.7 Hz, 3H), 3.13 (m, 4H), 3.76 (m, 4H), 4.16 (q, J= 5.7 Hz, 2H), 7.14 (m, 1H), 7.43 (t, J= 7.9 Hz, 1H), 7.79 (d, J= 7.8 Hz, 1H), 8.32 (d, J= 8.4 Hz, 1H), 8.77 (s, 1H), 10.81 (s, 1H). MS (70 eV) m/z = 266 (4), 265 (33), 220 (4), 219 (23), 177 (5), 163 (4), 162 (36), 147 (8), 146 (100), 120 (12), 119 (40), 92 (23), 91 (11), 90 (18), 87 (23), 86 (9), 77 (10), 76 (16), 39 (10). Analysis for $C_{16}H_{19}N_5O_5S$ (393.42): Calcd. C, 48.84; H, 4.89; N, 17.80. Found: C, 48.89; H, 4.62%; N, 17.98%.

3-Ethoxycarbonylamino-2-(p-methoxyphenylene)carbamoylthio-4(3H)-quinazolinone (14)

Yield: 1.41 g (34%); white solid; m.p. 155–159°C. IR (KBr): ν (cm^{-1})= 3256 (NHCO), 2880 (Ar—OCH_3), 1738 (NHCOOR), 1656 (NHCO), 1616 (C=N ring), 768 (arom.). ^{1}H NMR (DMSO-d_6, 300 MHz): δ= 1.27 (t, J= 5.8 Hz, 3H), 3.75 (s, 3H), 4.18 (q, J= 5.8 Hz, 2H), 6.97 (d, J= 8.5 Hz, 2H), 7.13 (t, J= 7.7 Hz, 1H), 7.45 (m, 3H), 7.71 (d, J= 7.7 Hz, 1H), 8.03 (br, 1H), 8.74 (d, J= 8.4 Hz, 1H), 10.89 (s, 1H). MS (70 eV) m/z = 267 (2), 266 (6), 265 (54), 192 (2), 146 (82), 138 (7), 137 (100), 136 (99), 122 (11), 121 (87), 120 (21), 109 (42), 108 (12), 106 (56), 94 (24), 93 (14), 92 (10), 91 (14), 90 (11), 65 (14), 39 (18). Analysis for $C_{19}H_{18}N_4O_5S$ (414.44): Calcd. C, 55.06; H, 4.38; N, 13.52. Found: C, 55.41; H, 4.73; N, 13.80%.

3-Ethoxycarbonylamino-2-piperidinocarbonylthio-4(3H)-quinazolinone (15)

Yield: 2.69 g (63%); white solid; m.p. 130–135°C. IR (KBr): ν (cm^{-1})= 3248 (NHCO), 2956 (CH_3), 2880 (CH_2), 1738 (NHCOOR), 1656 (NHCO), 1602 (C=N ring), 1570 (C-N, NH), 1480 (-CH_2-), 756 (arom.). ^{1}H NMR (DMSO-d_6, 500 MHz): δ= 1.27 (t, J= 5.8 Hz, 3H), 1.62 (m, 6H), 3.02 (m, 4H), 4.18 (q, J= 5.8 Hz, 2H), 7.13 (m, 1H), 7.42 (m, 1H), 7.70 (d, J= 7.9 Hz, 1H), 8.33 (d, J= 8.4 Hz, 1H), 10.89 (s, 1H). MS (70 eV) m/z = 267 (3), 266 (7), 265 (57), 205 (13), 193 (5), 162 (4), 147 (7), 146 (100), 145 (4), 120 (11), 119 (8), 118 (10), 104 (6), 91 (13), 77 (11), 39 (11). Analysis for $C_{17}H_{20}N_4O_4S$ (376.43): Calcd. C, 54.24; H, 5.36; N, 14.88. Found: C, 54.26; H, 5.39; N, 14.97%.

3-Ethoxycarbonylamino-2-diisopropylcarbamoylthio-4(3H)-quinazolinone (16)

Yield: 1.70 g (43%); white solid; m.p. 161–165 °C. IR (KBr): ν (cm^{-1})= 3240 (NHCO), 2984 (CH_3), 2844 (CH_2), 1730 (NHCOOR), 1656 (NHCO), 1600 (C=N ring), 1570 (C—N, N—H), 1474 (-CH_2-), 758 (arom.). ^{1}H NMR (DMSO-d_6, 500 MHz): δ = 1.20 (d, J = 6.5 Hz, 12H), 1.27 (t, J = 5.9 Hz, 3H), 3.36 (m, 2H), 4.18 (q, J = 5.9 Hz, 2H), 7.14 (m, 1H), 7.42 (m, 1H), 7.70 (d, J = 7.2 Hz, 1H), 8.33 (d, J = 8.4 Hz, 1H), 10.89 (s, 1H). MS (70 eV): m/z = 267 (3), 266 (7), 265 (64), 220 (3), 205 (14), 193 (4), 192 (3), 146 (100), 120 (10), 104 (12), 91 (5), 39 (6). Analysis for $C_{18}H_{24}N_4O_4S$ (392.47): Calcd. C, 55.09; H, 6.16; N, 14.28. Found: C, 55.38; H, 6.43; N, 14.26%.

3-Ethoxycarbonylamino-2-(4-methylpiperazinyl)carbonylthio-4(3H)-quinazolinone (17)

Yield: 2.00 g (51%); cream solid; m.p. 173–176 °C. IR (KBr): ν (cm^{-1})= 3252 (NHCO), 2976 (CH_3), 2880 (CH_2), 1736 (NHCOOR), 1656 (CON), 1616 (C—N ring), 1570 (—NH, C—N), 1480 (-CH_2-), 756 (arom.). ^{1}H NMR (DMSO-d_6, 500 MHz): δ = 1.27 (t, J = 5.9 Hz, 3H), 2.21 (s, 3H), 2.50 (m, 4H), 3.06 (m, 4H), 4.18 (q, J= 5.9 Hz, 2H), 7.14 (m, 1H), 7.42 (m, 1H), 7.71 (d, J = 7.9 Hz, 1H), 8.32 (d, J = 8.4 Hz, 1H), 10,87 (s, 1H). MS (70 eV) m/z = 267 (3), 266 (7), 265 (65), 205 (12), 165 (1), 147 (7), 146 (100), 104 (9), 100 (23), 91 (5), 90 (13), 77 (10), 58 (9), 51 (6), 44 (11), 43 (30), 42 (19), 41 (4), 39 (6). Analysis for $C_{17}H_{21}N_5O_4S$ (391.44): Calcd. C, 52.16; H, 5.41; N, 17.89. Found: C, 52.24; H, 5.33%; N, 17.72%.

REFERENCES

[1] W. Nawrocka, J. J. Staśko, and H. Liszkiewicz, *Phosphorus, Sulfur, and Silicon*, **183, 1379** (2008).

[2] A. H. Amin, D. R. Meta, and S. S. Samarth, *Arzneim. Forsch.*, **14,** 218 (1970).

[3] S. Hojne, *Pharmazie*, **36,** 583 (1981).

[4] W. Nawrocka and J. J. Staśko, *Boll. Chim. Farm.*, **137,** 35 (1998).

[5] (a) W. Nawrocka and J. J. Staśko, *Boll. Chim. Farm.*, **140,** 195 (2001); (b) W. Nawrocka and J. J. Staśko, *Boll. Chim. Farm.*, **141,** 84 (2002).

[6] S. B. Mhaske and N. P. Argade, *Tetrahedron*, **62,** 9787 (2006).

[7] W. Nawrocka and J. J. Staśko, *Farm. Pol.*, **60,** 603 (2004).

[8] T. Aono, S. Marui, and M. Yamaoka, *EP 733,633*, *Chem. Abstr.,* **125,** 328725u (1996).

[9] (a) W. Nawrocka and J. J. Staśko, *Pol. J. Chem*., **71,** 792 (1977); (b) W. Nawrocka, Sc. Thesis, Wroclaw University of Medicine, Wrocław (1999); (c) E. Huszcza, J. Dmochowska, and W. P. Nawrocka, *P 382856, Bulletin of Patent Office,* **7** (2007).

[10] P. R. Marsham, L. R. Hughes, A. L. Jackman, and D. L. Alison, *J. Med. Chem.,* **34,** 1594 (1991).

[11] S. E. Weber, T. M. Bleckman, J. Attard, J. G. Deal, V. Kathardekar, and K. M. Welsh, *J. Med. Chem.*, **36,** 733 (1993).

[12] J. K. Podlewski and A. K. Podlewska, The drugs of contemporary therapy (The State of Medical Issue, Warsaw, 2000).

[13] H. H. Backus, H. M. Pinedo, D. Wouters, C. M. Kuiper, G. Jansen, C. J. Groeningen, and G. J. Peters, *Oncol. Res.*, **12,** 231 (2000).

[14] T. S. Mok, T. W. Leung, S. D. Lee, Y. Chao, A. T. Chan, A. Huang, M. Lui, K. Chak, A. Johnston, and P. Johnson, *Cancer Chemother. Pharmacol.*, **44,** 307 (1999).

[15] K. J. Bowman, A. White, B. T. Golding, R. J. Griffin, and N. J. Curtin, *Brit. J. Canc.,* **78,** 1269 (1998).

[16] D. Raffa, G. Daidone, D. Schillaci, B. Magio, and F. Plescia, *Pharmazie,* **54,** 251 (1999).

[17] M. M. Ghorab, S. G. Abdel-Hamid, and S. M. El-Sayed, *Phosphorus, Sulfur, and Silicon*, **142,** 57 (1998).

[18] A. Nawojski, W. Nawrocka, and H. Liszkiewicz, *Pol. J. Pharmacol*., **43,** 69 (1985).

[19] H. Liszkiewicz, W. P. Nawrocka, A. Opolski, and J. Wietrzyk, *P 363207, Bulletin of Patent Office,* **9**, (2005).
[20] W. Nawrocka and B. Sztuba, *Pol. J. Chem.* **70,** 197 (1997).
[21] (a) W. Nawrocka and M. Zimecki, *Arch. Pharm. Pharm. Med. Chem*., **330,** 399 (1997); (b) S. El-Sayed Barakat, M. M. Ghorab, H. M. Saker, and M. M. Abd Rabo, *Phosphorus, Sulfur, and Silicon*, **182,** 65 (2007).