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Wanda P. Nawrocka^a; Jan J. Staśko^a; Hanna Liszkiewicz^a

^a Wrocław Medical University, Wrocław, Poland

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Synthesis of New 4(3H)-Quinazolinone Derivatives by Reaction of 3-Amino-2(1H)-thioxo-4(3H)-quinazolinone with Selected Substituted Cinnamic Acids and Halogenoketones

Wanda P. Nawrocka, Jan J. Staśko, and
Hanna Liszkiewicz

Wroclaw Medical University, Wroclaw, Poland

Two series of N-acylated (2–6) and S-alkylated (7–13) 4(3H)-quinazolinone derivatives have been synthesized by reaction of 3-amino-2(1H)-thioxo-4(3H)-quinazolinone (1) with selected substituted cinnamic acids and halogenoketones, respectively. The structures of the compounds obtained result from the IR, ¹H NMR, and mass spectra.

Keywords ¹H NMR; 2-phenacylthio-; 3-amino-2(1H)-thioxo-4(3H)-quinazolinone derivatives; 3-cinnamoylamino-; IR; mass spectra; synthesis

INTRODUCTION

4(3H)-Quinazolinone derivatives show different biological and pharmacological activities. Approximately 30 medicines based on 4(3H)-quinazolinone derivatives are used worldwide. Methaqualone, ketanserin, and quinetazone are used on a large scale¹ and recently, raltitrexid and nolatrexed have been introduced as cytostatic drugs.² Alkaloids of antibiotics and toxins isolated from plants and fungi incorporating the 4(3H)-quinazolinone moiety were also described. Some of them like asperlicine and ruteacarpine³ became objects of detailed pharmacological research.

In recent years the synthesis and biological studies of 4(3H)-quinazolinone derivatives were described.^{4–8}

We have described the synthesis of 3-amino-2(1H)-thioxo-4(3H)-quinazolinone (1)⁹. It is a universal starting material for the preparation of substituted and annulated compounds based on the reactivity of the 3-amino and 2-thiocarbonyl group. We have reported the reaction

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Address correspondence to Wanda P. Nawrocka, Department of Drugs Technology, Wroclaw Medical University, Nankiera 1 Sq, 50-140 Wroclaw, Poland. E-mail:

of **1** with chloroacetic acid and its derivatives,⁹ cyanogen bromide,¹⁰ halocarbonyl compounds, and α,β -unsaturated carbonyl compounds, as well as the immunotropic properties of the resulting products.¹¹

Here, we describe the synthesis of new derivatives by reaction of 4(3*H*)-quinazolinone **1** with selected substituted cinnamic acids and with haloketones (Scheme 1), which are intended to be used for biological research.

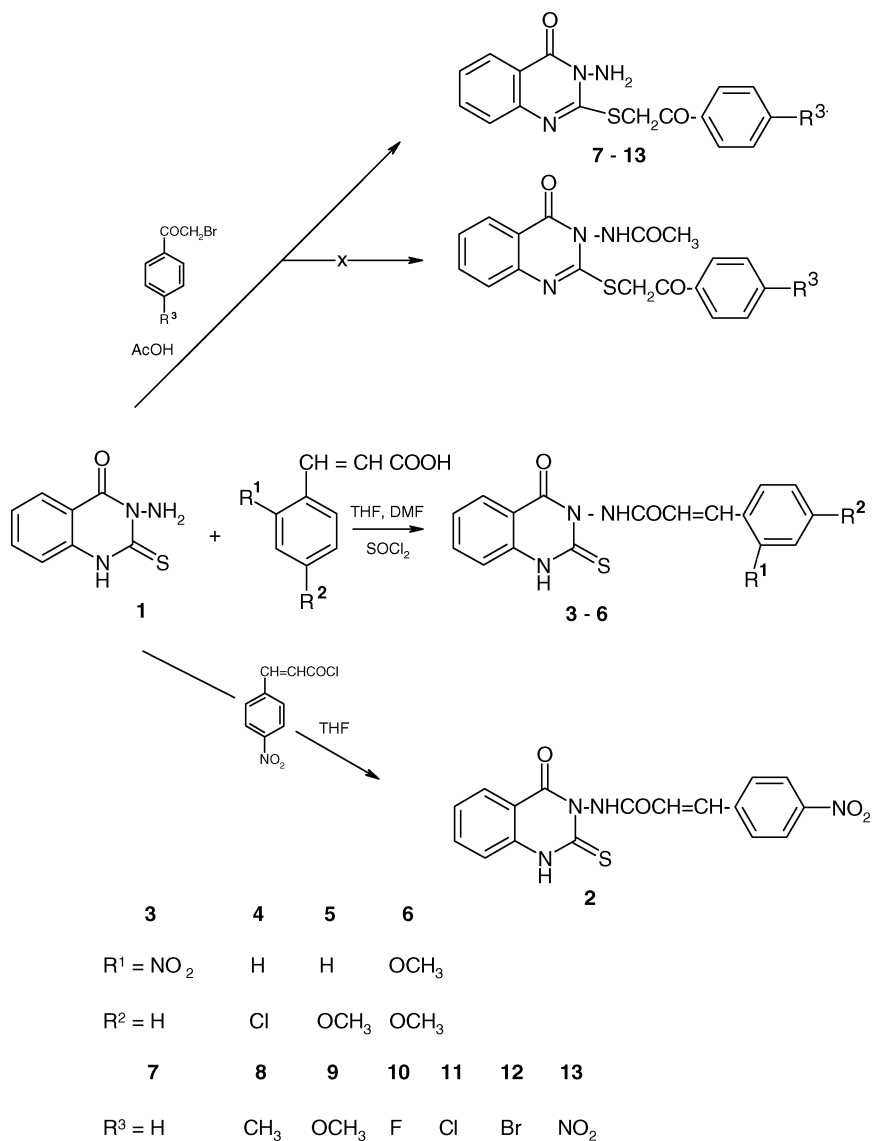
Polyphenolic acids including cinnamic acid and its substituted derivatives have been the subject of synthesis and biological research for several years. Curcumin and cinarine exhibit chologic activity, and some amides are inhibitors of 5-lipoxygenase (5-LO)¹². Cinnamic acid derivatives with antibacterial,¹³ anticancerous,¹⁴ and anti-UV radiation activity¹⁵ were also described. Cinnamoyl derivatives of 1,5-benzodiazepine synthesized in our group show psychotropic,¹⁶ high anticancerous,¹⁷ and immunotropic¹⁸ activity. Very high immunotropic activity with no toxicity is exhibited by 3-cinnamoylamino-2(1*H*)-thioxo- and 3-amino-2-cinnamoylthio-4(3*H*)-quinazolinone.¹¹ Anticancerous activity is shown by *S*-alkylated halo ketone derivatives of imidazo[4,5-*b*]pyridine.¹⁹

RESULTS AND DISCUSSION

Reaction of 4(3*H*)-quinazolinone **1** with *p*-nitrocinnamoyl chloride was carried out in anhydrous tetrahydrofuran at room temperature.¹¹ Acylation using substituted cinnamic acids was performed also in THF solution at room temperature in the presence of thionyl chloride and catalytic amounts of DMF.

The results of the elemental analysis of compounds **2–6**, and the mass spectrum of derivative **2** confirmed the addition of one cinnamoyl moiety to the 4(3*H*)-quinazolinone **1** molecule. There are no bands for a NH₂ group in the IR spectra of derivatives **2–6**, while they appear in the IR spectrum of 4(3*H*)-quinazolinone **1**⁹ at 3400, and 3320 cm⁻¹. Characteristic bands for an amide moiety are observed at 3340–3320 cm⁻¹ (NH) and at 1680 cm⁻¹ (CO). The (CH=CH) group shows bands at 1660 and 1290 cm⁻¹.

The formation of the amides **2–6** is also confirmed by the ¹H NMR spectra. Two signals are observed at 10.75–10.80 ppm and at 12.23–12.70 ppm, which are attributed to the protons of the NHCO and NHCS groups, respectively. The signals of the vinyl protons appear as doublets at 6.66–7.10 ppm (COCH=), and at $\delta \sim 7.15$ ppm (=CHAr). The coupling constants ³*J* = 15.7–16.0 Hz indicate the *trans* configuration at the –CH=CH– moiety.



SCHEME 1

In a previous study we have shown, that heating of 4(3H)-quinazolinone **1** in glacial acetic acid with chloroacetone or ω -bromoacetophenone results in the formation of tricyclic derivatives of 1,4,5-thiadiazin[2,3-b]quinazolin-6-one.¹¹

In continuation of these studies, reactions of 4(3*H*)-quinazolinone **1** with substituted haloketones in glacial acetic acid were carried out at room temperature for 7–14 days. Reaction of 4(3*H*)-quinazolinone **1** with ω -bromo-4'-nitroacetophenone was the fastest, that with ω -bromoacetophenone was the slowest reaction observed. All reactions led to the formation of homogenous products.

The structures of the compounds formed were confirmed unambiguously by the results of elemental analysis and by the IR, ^1H NMR, and mass spectra.

The IR spectra showed, that acylation of the amino group at position three did not occur: in the region of $3500\text{--}3300\text{ cm}^{-1}$ characteristic bands for a primary amino group were observed. The bands of the C=O group appeared in the region of $\sim 1690\text{ cm}^{-1}$.

Similar conclusions can be drawn from analysis of the ^1H NMR spectra. No signal was observed at $\delta \sim 14.5$ ppm, a region characteristic for the NH proton of the NH-C=S group. However, a singlet corresponding to two amino protons was observed at ~ 6.70 ppm. In the case of **10** and **12**, the signal for the NH₂ group overlaps with the signals of the aromatic protons. In the ^1H NMR spectra of compounds **7–13**, the signal for the methylene group is observed at 5.15–5.23 ppm at low field.

The mass spectra of compounds **7–13** display the respective molecular ion peaks. In the mass spectra of compounds **11** and **12** the expected isotopic pattern is observed, indicating the presence of chlorine and bromine in the molecules. Cleavage of the bond between the α carbon atom and the C=O group is the main fragmentation pathway. It leads to the formation of acyl ions, which yield the basic peaks for derivatives **7–11**. In the case of compound **12**, the *o*-iminobenzoyl ion $m/e = 118$ (100%), is preferably formed as the result of the fragmentation of 4(3*H*)-quinazolinone **1**. In the case of compound **13**, an ion with $m/e = 120$ (100%) yields the basic peak. It is formed as the result of the rearrangement of the *p*-nitrobenzoyl ion, $m/e = 150$, to the corresponding nitrite followed by NO \cdot radical elimination.

The synthesized compounds are intended for biological research and may act as suitable 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 analyser and satisfactory results within $\pm 0.4\%$ of the calculated values were obtained for all new compounds. IR spectra (in KBr) were recorded with an IR 75 spectrophotometer. ^1H NMR spectra were obtained with a Bruker AVANCE DRX 300 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.

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

Compound **1** was prepared exactly as described previously.⁹

3-(4-Nitrocinnamoylamino)-2(1H)-thioxo-4(3H)-quinazolinone (2)

Compound **2** was prepared exactly as described previously.¹¹

General Procedure for the Synthesis of Compounds 3–6

To a mixture of compound **1** (1.93 g, 0.01 mol) and the respective cinnamic acid (0.01 mol) was added dropwise with mechanical stirring at room temperature 3 drops of DMF, anhydrous THF (50 mL), and SOCl₂ (10 mL). Stirring was continued for 25–48 h. The product was filtered off, washed with Et₂O (20 mL), 5% aq NaHCO₃ (20 mL) solution and water (50 mL), dried, and recrystallized from ethanol (**3**, **5**) or *n*-butanol (**4**, **6**).

3-(2-Nitrocinnamoylamino)-2(1H)-thioxo-4(3H)-quinazolinone (3)

Yield: 51%; yellow solid from ethanol; m.p. 238–240°C. IR (KBr): ν [cm⁻¹] = 3320 (NHCO), 3080 (CH=), 3010 (CH), 1680 (NHCO), 1660 (CH=CH), 1620 (C=CHAr), 1530, 1330 (NO₂), 1290 (CH=CH), 740 (C-H arom.), 705 (CS). ¹H NMR (DMSO-d₆): δ = 6.68 (m, 2H), 6.90 (m, 1H), 7.10 (d, *J* = 15.8 Hz, 1H), 7.30 (m, 2H), 7.65 (m, 2H), 7.95 (d, *J* = 7.7 Hz, 1H), 8.10 (d, *J* = 8.0 Hz, 1H), 10.80 (s, 1H), 12.25 (s, 1H).

3-(4-Chlorocinnamoylamino)-2(1H)-thioxo-4(3H)-quinazolinone (4)

Yield: 57%; white solid from *n*-butanol; m.p. 265–268°C. IR (KBr): ν [cm⁻¹] = 3330 (NHCO), 3010 (CH=CH), 1680 (NHCO), 1660 (CH=CH), 1220, 760 (CH-arom.), 705 (CS). ¹H NMR (DMSO-d₆): δ = 6.79 (d, *J* = 16.0 Hz, 1H), 6.92 (m, 2H), 7.01 (d, *J* = 7.7 Hz, 1H), 7.28 (m, 3H), 7.60 (m, 2H), 8.09 (m, 1H), 10.80 (s, 1H), 12.23 (s, 1H).

3-(4-Methoxycinnamoylamino)-2(1H)-thioxo-4(3H)-quinazolinone (5)

Yield: 34%; white solid from ethanol; m.p. 256 – 257°C. IR (KBr): ν [cm^{-1}] = 3330 (NHCO), 3010 (CH), 2840 (OCH_3), 1680 (NHCO), 1660 ($\text{CH}=\text{CH}$), 1290 ($\text{CH}=\text{CH}$), 1270 (N-H, C-N), 1225, 740 (C-H arom.), 705 (CS). ^1H NMR ($\text{DMSO}-d_6$): δ = 3.70 (s, 3H), 6.66 (d, J = 15.7, 1H), 6.82 (m, 2H), 7.01 (m, 2H), 7.15 (d, J = 15.7 Hz, 1H), 7.30 (m, 2H), 7.70 (m, 1H), 8.10 (m, 1H), 10.75 (s, 1H), 12.30 (s, 1H).

3-(2,4-Dimethoxycinnamoylamino)-2(1H)-thioxo-4(3H)-quinazolinone (6)

Yield: 60%; white solid from *n*-butanol; m.p. 260–262°C. IR (KBr): ν [cm^{-1}] = 3330 (NHCO), 3010 (CH), 2840 (OCH_3), 1675 (NHCO), 1660 ($\text{CH}=\text{CH}$), 1220, 1000, 760 (C-H arom.), 705 (CS). ^1H NMR ($\text{DMSO}-d_6$): δ = 3.69 (s, 3H), 3.78 (s, 3H), 6.72 (d, J = 15.7 Hz, 1H), 6.95 (m, 2H), 7.18 (m, 3H), 7.40 (m, 2H), 8.12 (m, 1H), 10.80 (s, 1H), 12.30 (s, 1H).

General Procedure for the Synthesis of Compounds 7–13

To a suspension of compound **1** (1.93 g, 0.01 mol) in 50 mL of glacial acetic acid was added at room temperature with stirring the appropriate phenacyl bromide (0.01 mol). After stirring for 7–14 days (TLC) the precipitate was collected by filtration and washed 5% solution (20 mL) of NaHCO_3 and water (100 mL), dried, and recrystallized from ethanol (**7–12**) or *n*-butanol (**13**).

3-Amino-2-phenacylthio-4(3H)-quinazolinone (7)

Yield: 50%; white solid; m.p. 158–160°C. IR (KBr): ν [cm^{-1}] = 3465, 3340 (NH), 3060 (CH), 2870 (CH_2), 1695, 1670 ($\text{C}=\text{O}$), 1620 (NH), 1480 ($\text{C}=\text{N}$), 1450 (CH_2), 760, 745 (CH arom.), 700 (CS). ^1H NMR ($\text{DMSO}-d_6$): δ = 5.17 (s, 2H), 6.62 (m, 2H), 6.63 (s, 2H), 7.21 (m, 3H), 7.62 (m, 2H), 8.09 (m, 2H). MS (70 eV): m/e [%] – 313 (4), 312 (13), 311 (73), 206 (3), 120 (50), 119 (4), 118 (77), 105 (100), 77 (26), 65 (10), 44 (20), 39 (9).

3-Amino-2-(4'-methylphenacylthio)-4(3H)-quinazolinone (8)

Yield: 60%; white solid; m.p. 171–172°C. IR (KBr): ν [cm^{-1}] = 3465, 3340 (NH), 2950 (CH_3), 2915 (CH_2), 1680 ($\text{C}=\text{O}$), 1625 (NH), 1490 (CH_2), 1475 ($\text{C}=\text{N}$), 1445 (CH_2), 760, 745 (CH arom.), 700 (CS). ^1H NMR ($\text{DMSO}-d_6$): δ = 2.20 (s, 3H), 5.17 (s, 2H), 6.62 (m, 2H), 6.73 (s, 2H), 6.92 (m, 3H), 7.92 (m, 1H), 8.10 (m, 2H). MS (70 eV): m/e [%] = 326 (4), 325 (12), 324 (65), 160 (2), 120 (58), 119 (100), 118 (23), 92 (16), 91 (29), 65 (12).

3-Amino-2-(4'-methoxyphenacylthio)-4(3H)-quinazolinone (9)

Yield: 61%; white solid; m.p. 182–184°C. IR (KBr): ν [cm^{-1}] = 3435, 3360 (NH), 2930 (CH_3), 2860 (Ar-O- CH_3), 1695 (C=O), 1625 (NH), 1490 (C=N), 1430 (CH_2), 1190, 770, 760 (CH arom.), 705 (CS). ^1H NMR (DMSO- d_6): δ = 3.87 (s, 3H), 5.16 (s, 2H), 6.43 (s, 2H), 7.10 (d, J = 8.0 Hz, 2H), 7.71 (m, 4H), 8.17 (m, 2H). MS (70 eV): m/e [%] = 342 (5), 341 (26), 136 (10), 135 (100), 120 (16), 119 (3), 118 (9), 92 (16), 77 (8), 65 (5).

3-Amino-2-(4'-fluorophenacylthio)-4(3H)-quinazolinone (10)

Yield: 52%; white solid; m.p. 182–184°C. IR (KBr): ν [cm^{-1}] = 3460, 3330 (NH), 3060 (CH), 2940 (CH_2), 1690, 1670 (C=O), 1620 (NH), 1480 (C=N), 1440 (CH_2), 1180, 760, 745 (CH arom.), 700 (CS). ^1H NMR (DMSO- d_6): δ = 5.16 (s, 2H), 6.62 (m, 3H), 6.87 (d, J = 7.7 Hz, 1H), 7.24 (m, 1H), 7.43 (m, 2H), 7.55 (m, 1H), 8.16 (m, 2H). MS (70 eV): m/e [%] = 331 (6), 330 (89), 206 (8), 160 (9), 124 (13), 123 (100), 121 (9), 120 (80), 108 (66), 95 (36), 92 (16), 92 (32), 91 (9), 77 (6), 75 (12), 65 (22), 39 (11).

3-Amino-2-(4'-chlorophenacylthio)-4(3H)-quinazolinone (11)

Yield: 62%; white solid; m.p. 180–182°C. IR (KBr): ν [cm^{-1}] = 3460, 3340 (NH), 3080 (CH), 2940 (CH_2), 1690 (C=O), 1620 (NH), 1490 (C=N), 1480 (CH_2), 1190, 760, 740 (CH arom.), 690 (CS). ^1H NMR (DMSO- d_6): δ = 5.15 (s, 2H), 6.61 (d, J = 7.2 Hz, 1H), 6.64 (s, 2H), 6.85 (d, J = 8.2 Hz, 1H), 7.25 (m, 3H), 7.54 (m, 1H), 7.67 (d, J = 8.9 Hz, 1H), 8.09 (d, J = 8.6 Hz, 1H). MS (70 eV): m/e [%] = 348 (4), 347 (25), 346 (12), 345 (71), 206 (7), 160 (9), 142 (3), 141 (38), 140 (9), 139 (100), 120 (98), 118 (58), 111 (22), 65 (21), 51 (9), 39 (9).

3-Amino-2-(4'-bromophenacylthio)-4(3H)-quinazolinone (12)

Yield: 53%; white solid; m.p. 191 – 193°C. IR (KBr): ν [cm^{-1}] = 3460, 3340 (NH), 3070 (CH), 2900 (CH_2), 1690, 1660 (C=O), 1610 (NH), 1490 (C=N), 1440 (CH_2), 1210, 760, 740 (CH arom.), 690 (CS). ^1H NMR (DMSO- d_6): δ = 5.15 (s, 2H), 6.62 (m, 3H), 6.87 (d, J = 8.4 Hz, 1H), 7.25 (m, 1H), 7.54 (d, J = 7.9 Hz, 1H), 7.80 (d, J = 7.8 Hz, 2H), 8.00 (d, J = 7.8 Hz, 1H). MS (70 eV): m/e [%] = 393 (5), 392 (16), 391 (81), 390 (15), 238 (86), 206 (12), 186 (8), 185 (80), 184 (9), 183 (97), 160 (15), 142 (3), 121 (13), 120 (81), 119 (10), 118 (100), 104 (8), 92 (49), 91 (14), 90 (13), 77 (10), 76 (23), 65 (34), 39 (13).

3-Amino-2-(4'-nitrophenacylthio)-4(3H)-quinazolinone (13)

Yield: 72%; white solid; m.p. 207–209°C. IR (KBr): ν [cm⁻¹] = 3460, 3360 (NH), 3080 (CH), 2900 (CH₂), 1685, 1660 (C=O), 1620 (NH), 1490 (C=N), 1440 (CH₂), 1545, 1340, 840 (NO₂), 760, 740 (CH arom.). ¹H NMR (DMSO-d₆): δ = 5.23 (s, 2H), 6.63 (s, 2H), 6.64 (m, 1H), 6.87 (d, J = 8.4 Hz, 1H), 7.25 (m, 1H), 7.56 (d, J = 7.8 Hz, 1H), 8.34 (m, 4H). MS (70 eV): m/e [%] = 358 (5), 357 (13), 356 (76), 206 (5), 160 (13), 150 (21), 121 (11), 120 (100), 118 (73), 104 (16), 92 (33), 91 (4), 65 (17), 39 (3).

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