Synthesis of new 5-alkyl substituted 4-thiazolidinones utilising condensation with ethyl 2-bromo alkanoates

Nalan Terzioğlu Klip*, Özlen Güzel and Aysel Gürsoy

Istanbul University, Faculty of Pharmacy, Department of Pharmaceutical Chemistry, Beyazıt, 34116 Istanbul, Turkey

2-[(3-Ethyl-4-oxo-3,4-dihydroquinazolin-2-yl)mercaptoacetylhydrazono]-3-alkyl/aralkyl-5-ethyl/propylthiazolidin-4-ones were synthesised by the cyclisation of 1-[(3-ethyl-4-oxo-3,4-dihydroquinazolin-2-yl)mercaptoacetyl]-4-alkyl/aralkyl thiosemicarbazides with ethyl 2-bromobutanoate or ethyl 2-bromopentanoate in the presence of anhydrous sodium acetate in anhydrous ethanolic medium. The regioisomer 2-alkyl/aralkyl 3-[(3-ethyl-4-oxo-3,4-dihydroquinazolin-2-yl)mercaptoacetylamino]-5-ethyl/propylthiazolidin-4-ones were not formed.

Keywords: 5-alkyl substituted 4-thiazolidinones, ethyl 2-bromo alkanoates

Quinazoline derivatives possess remarkable anti-inflammatory activity:[1-3] Primarily, a non-steroidal anti-inflammatory drug (NSAID) such as acetylsalicylic acid was identified as a first generation drug in the treatment of pain and inflammation. Phenylbutazone was considered a second generation NSAID and showed a significant improvement. Subsequently proquazone and fluproquazone[4] emerged as third generation NSAIDs and are superior in safety and efficacy, and are comparable with indomethacin.

In addition, quinazoline derivatives also have a therapeutic benefit as an anti-invasive agent with potential for activity in early and advanced solid tumors, metastatic bone disease and leukaemias.[5-7] Based on the importance of these molecules, our attention was attracted towards synthesis of novel quinazoline derivatives and evaluation of their anticancer properties.

In the present work, we synthesised some novel 1-[(3-ethyl-4-oxo-3,4-dihydroquinazolin-2-yl)mercaptoacetyl]-4-benzylthiosemicarbazide (**2c**) and 2-[(3-ethyl-4-oxo-3,4-dihydroquinazolin-2-yl)mercaptoacetylhydrazono]-3-alkyl/aralkyl-5-ethyl/propylthiazolidin-4-ones (**3**). The synthesis of the target compounds was carried out as outlined in Scheme 1. 1-[(3-Ethyl-4-oxo-3,4-dihydroquinazolin-2-yl) mercaptoacetyl]-4-alkyl/aralkyl thiosemicarbazides (**2**) were obtained by the procedures described in our previous work.[8,9] Condensation of **2** with ethyl 2-bromobutanoate or ethyl 2-bromopentanoate in boiling ethanol containing anhydrous sodium acetate afforded only one regioisomer, 2-[(3-ethyl-4-oxo-3,4-dihydroquinazolin-2-yl)mercaptoacetylhydrazono]-3-alkyl/aralkyl-5-ethyl/propylthiazolidin-4-ones (**3**). In the cyclisation, the key intermediate enethiol form of thiosemicarbazides is responsible for the formation of thiazolidinones (**3** and **4**). The structure of which was established to be **3** or **4** based on spectroscopic and analytical data.

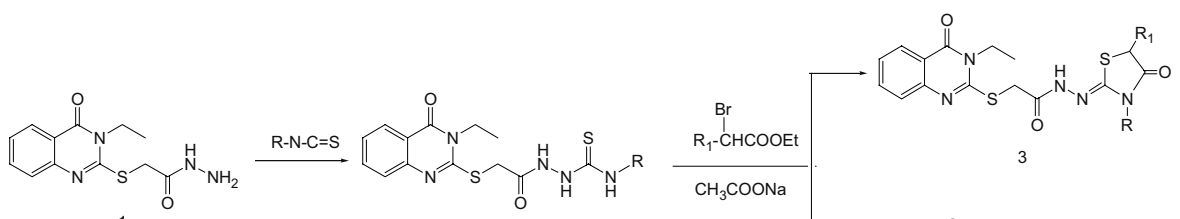
In the IR spectra of compounds, the lactam C=O stretching of the quinazolinone ring and amide C=O stretching were observed in the 1698–1661 cm^{-1} and 1660–1637 cm^{-1} regions, respectively.[8-10] In addition to these bands, observation of a third C=O stretching band in the 1716–1708 cm^{-1} region was diagnostic for the thiazolidinone ring (**3**). ^1H NMR spectra of all the compounds showed the protons of the quinazolinone ring and ethyl protons in the expected regions with splitting patterns in accordance with the literature.[8,9] In the ^1H NMR spectra of thiazolidin-4-one derivatives (**3**), the absence of the N^2–H and N^4–H of thiosemicarbazides **2** and the presence of new resonances attributed to the endocyclic SCH proton provided further evidence for 4-thiazolidinone formation. The thiazolidinone C_5–H resonances of 3 were observed at about δ 4.35–4.47 ppm as a quartet. The signals of N–CH_3, N–CH_2–CH=CH_2 and N–CH_2-Ph on thiazolidinone ring were easily assignable. The appearence of these signals at 3.05–3.06, 4.21–4.22 and 4.80 ppm, respectively ruled out the presence of the other regioisomer **4** which was expected to exhibit signals at upfield when compared to **3**.

Experimental

M.p., open capillaries, Büchi 530 apparatus: uncorrected. IR, Perkin-Elmer 1600 for KBr pellets; cm^{-1}. ^1H NMR: Bruker AC 200 and Bruker DPX 400 using DMSO-d_6; δ in ppm rel. to $SiMe_4$ (= 0 ppm) as internal Standard (thia. = thiazolidinone, quin. = quinazolinone). The structure of **3b** was confirmed also by ^{13}C NMR spectrum and HSQC. EI-MS: VG Zab Spec (70 eV); *m/z* (rel.%). Elemental analysis: Carlo Erba 1106.

1, 2a and **2b** were prepared as described in previous works.[8,9]

1-[(3-Ethyl-4-oxo-3,4-dihydroquinazolin-2-yl)mercaptoacetyl]-4-benzylthiosemicarbazide **(2c):** A mixture of **1** (10 mmol) and benzyl isothiocyanate (10 mmol) in absolute ethanol (50 ml) was refluxed



compound 3	a	b	c	d	e	f
R	CH_3	C_3H_5	$CH_2C_6H_5$	CH_3	C_3H_5	$CH_2C_6H_5$
R1	C_2H_5	C_2H_5	C_2H_5	C_3H_7	C_3H_7	C_3H_7

Scheme 1

* Correspondent. Email: nalant@istanbul.edu.tr

for 5 h. The crude product thus obtained on cooling was filtered and recrystallised from ethanol or washed with ethanol. Yield, 100%. m.p. 115–118°C. IR: 3156, 1698, 1652. ^{1}H NMR (400 MHz, DMSO-d_6): 1.24 (3H, t, J = 7.0 Hz, $NCH_2C\underline{H}_3$), 4.02–4.07 (2H, m, $NC\underline{H}_2CH_3$), 4.05 (2H, s, SCH_2), 4.59 (2H, d, J = 6.0 Hz, $NC\underline{H}_2Ph$), 7.08 (2H, d, J = 7.2 Hz, phenyl $C_{2,6}$–H), 7.14–7.21 (3H, m, phenyl $C_{3,4,5}$–H), 7.41 (1H, t, J = 7.4 Hz, quin. C_6–H), 7.52 (1H, d, J = 8.0 Hz, quin. C_8–H), 7.74 (1H, t, J = 7.6 Hz, quin. C_7–H), 7.99 (1H, d, J = 8.0 Hz, quin. C_5–H), 8.18 (1H, br.s, CONHN$\underline{H}$), 9.58 (1H, s, N$\underline{H}CH_2$), 10.34 (1H, s, CONH). EIMS *m/z*: 428 (M + 1). *Anal.* Calcd for $C_{20}H_{21}N_5O_2S_2$: C, 56.2; H, 4.95; N, 16.4; S, 15.0. Found: C, 55.6; H, 5.7; N, 14.9; S, 10.8.

General method for the synthesis of 2-[(3-ethyl-4-oxo-3,4-dihydroquinazolin-2-yl)mercaptoacetylhydrazono]-3-alkyl/aralkyl-5-ethyl/propylthiazolidin-4-ones **(3):** To a suspension of **2** (2.5 mmol) in 20 ml of absolute ethanol, were added anhydrous sodium acetate (10 mmol) and 2.5 mmol ethyl 2-bromobutanoate or ethyl 2-bromopentanoate. The reaction mixture was refluxed on a water-bath for 2 h, and after cooling it was poured onto ice-cold water and allowed to stand overnight. The precipitate was filtered, then washed with water, dried and purified by crystallisation from ethanol.

2-[(3-Ethyl-4-oxo-3,4-dihydroquinazolin-2-yl)mercaptoacetyl-hydrazono]-3-methyl-5-ethylthiazolidin-4-one **(3a):** Yield, 81%. m.p. 191–193°C. IR: 3170, 1711, 1681, 1643. ^{1}H NMR δ (ppm): 0.85 (3H, t, J = 7.4 Hz, thia. 5-$CH_2C\underline{H}_3$), 1.27 (3H, t, J = 7.0 Hz, quin. 3-$CH_2C\underline{H}_3$), 1.72–1.78 and 1.95–1.98 (2H, 2 m, thia. 5-$C\underline{H}_2CH_3$), 3.05 (3H, s, NCH_3), 4.05–4.12 (2H, m, quin. 3-$C\underline{H}_2CH_3$), 4.10 (2H, s, SCH_2), 4.35–4.37 (1H, m, thia. C_5–H), 7.42 (1H, t, J = 7.6 Hz, quin. C_6–H), 7.57 (1H, d, J = 8.0 Hz, quin. C_8–H), 7.75 (1H, t, J = 7.6 Hz, quin. C_7–H), 8.04 (1H, d, J = 7.6 Hz, quin. C_5–H), 10.56 (1H, s, CONH). Anal. Calcd for $C_{18}H_{21}N_5O_3S_2$ (419.52): C, 51.5; H, 5.05; N, 16.7. Found: C, 51.2; H, 4.8; N, 16.3.

2-[(3-Ethyl-4-oxo-3,4-dihydroquinazolin-2-yl)mercaptoacetyl-hydrazono]-3-allyl-5-ethylthiazolidin-4-one **(3b):** Yield, 82%. m.p. 160–162°C. IR: 3163, 1710, 1687, 1660. ^{1}H NMR δ (ppm): 0.85 (3H, t, J = 7.2 Hz, thia. 5-$CH_2C\underline{H}_3$), 1.27 (3H, t, J = 7.2 Hz, quin. 3-$CH_2C\underline{H}_3$), 1.73–1.81 and 1.93–1.99 (2H, 2 m, thia. 5-$C\underline{H}_2CH_3$), 4.06–4.15 (2H, m, quin. 3-CH_2CH_3), 4.09 (2H, s, SCH_2), 4.21 (2H, d, J = 4.0 Hz, $C\underline{H}_2CH{=}CH_2$), 4.43 (1H, q, J = 4.0 Hz, thia. C_5–H), 5.05–5.11 (2H, m, $CH_2CH{=}C\underline{H}_2$), 5.72–5.82 (1H, m, $CH_2C\underline{H}{=}CH_2$), 7.42 (1H, t, J = 7.6 Hz, quin. C_6–H), 7.56 (1H, d, J = 8.4 Hz, quin. C_8–H), 7.75 (1H, t, J = 7.6 Hz, quin. C_7–H), 8.04 (1H, d, J = 8.0 Hz, quin. C_5–H), 10.59 (1H, s, CONH). ^{13}C NMR (HSQC, 100 MHz): δ 10.70 (thia. 5-$CH_2\underline{C}H_3$), 13.19 (quin. 3-$CH_2\underline{C}H_3$), 26.51 (thia. 5-$\underline{C}H_2CH_3$), 33.62 (SCH_2), 40.25 (quin. 3-$\underline{C}H_2CH_3$), 45.12 ($\underline{C}H_2CH{=}CH_2$), 50.75 (thia. CH), 118.81 ($CH_2CH{=}\underline{C}H_2$), 125.95 (quin. C_{4a}), 126.44 (quin. C_8), 126.94 (quin. C_6), 127.28 (quin. C_5), 130.20 ($CH_2\underline{C}H{=}CH_2$), 134.30 (quin. C_7), 146.72 (quin. C_{8a}), 153.11 (thia. C_2), 157.31 (quin. C_2), 160.85 (quin. C_4), 164.97 (CONH), 172.60 (thia C_4). EIMS *m/z* 446 (M + 1). Anal. Calcd for $C_{20}H_{23}N_5O_3S_2$ (445.55): C, 53.9; H, 5.2; N, 15.7. Found. C, 53.1; H, 5.0; N, 15.3.

2-[(3-Ethyl-4-oxo-3,4-dihydroquinazolin-2-yl)mercaptoacetyl-hydrazono]-3-benzyl-5-ethylthiazolidin-4-one **(3c):** Yield, 92%. m.p. 187–189°C. IR: 3168, 1708, 1661, 1637. ^{1}H NMR δ (ppm): 0.82 (3H, t, J = 7.4 Hz, thia. 5-$CH_2C\underline{H}_3$), 1.27 (3H, t, J = 7.2 Hz, quin. 3-$CH_2C\underline{H}_3$), 1.74–1.81 and 1.90–2.00 (2H, 2 m, thia. 5-$C\underline{H}_2CH_3$), 4.06–4.11 (2H, m, quin. 3-$C\underline{H}_2CH_3$), 4.09 (2H, s, SCH_2), 4.47 (1H, q, J = 4.0 Hz, thia. C_5–H), 4.80 (2H, d, J = 2.4 Hz, N-$C\underline{H}_2Ph$), 7.16–7.33 (5H, m, phenyl), 7.41 (1H, t, J = 7.0 Hz, quin. C_6–H), 7.55 (1H, d, J = 7.6 Hz, quin. C_8–H), 7.73 (1H, t, J = 7.6 Hz, quin. C_7–H), 8.04 (1H, d, J = 8.0 Hz, quin. C_5–H), 10.63 (1H, s, CONH). Anal. Calcd for $C_{24}H_{25}N_5O_3S_2$ (513.64): C, 56.1; H, 5.2; N, 13.6. Found. C, 56.1; H, 4.7; N, 13.9.

2-[(3-Ethyl-4-oxo-3,4-dihydroquinazolin-2-yl)mercaptoacetyl-hydrazono]-3-methyl-5-propylthiazolidin-4-one **(3d):** Yield, 84%. m.p. 204–205°C. IR: 3199, 1716, 1682, 1655. ^{1}H NMR δ (ppm): 0.85 (3H, t, J = 7.4 Hz, thia. 5-$CH_2CH_2C\underline{H}_3$), 1.12–1.26 (2H, m, thia. 5-$CH_2C\underline{H}_2CH_3$), 1.28 (3H, t, J = 7.2 Hz, quin. 3-$CH_2C\underline{H}_3$), 1.64–1.67 and 1.93–1.97 (2H, 2 m, thia. 5-$C\underline{H}_2CH_2CH_3$), 3.06 (3H, s, N-CH_3), 4.08–4.13 (2H, m, quin. 3-$C\underline{H}_2CH_3$), 4.11 (2H, s, SCH_2), 4.37 (1H, q, J = 4.4 Hz, thia. C_5–H), 7.45 (1H, t, J = 7.3 Hz, quin. C_6–H), 7.60 (1H, d, J = 7.8 Hz, quin. C_8–H), 7.76 (1H, t, J = 7.6 Hz, quin. C_7–H), 8.07 (1H, d, J = 7.8 Hz, quin. C_5–H), 10.55 (1H, s, CONH). EIMS *m/z*: 434 (M + 1). Anal. Calcd for $C_{19}H_{23}N_5O_3S_2$ (433.5): C, 52.6; H, 5.35; N, 16.15. Found. C, 52.2; H, 5.1; N, 16.1.

2-[(3-Ethyl-4-oxo-3,4-dihydroquinazolin-2-yl)mercaptoacetyl-hydrazono]-3-allyl-5-propylthiazolidin-4-one **(3e):** Yield, 74%. m.p. 164–165°C. IR: 3166, 1716, 1677, 1637. ^{1}H NMR δ (ppm): 0.85 (3H, t, J = 7.4 Hz, thia. 5-$CH_2CH_2C\underline{H}_3$), 1.14–1.26 (2H, m, thia. 5-$CH_2C\underline{H}_2CH_3$), 1.30 (3H, t, J = 7.4 Hz, quin. 3-$CH_2C\underline{H}_3$), 1.65–1.69 and 1.92–1.98 (2H, 2 m, thia. 5-$C\underline{H}_2CH_2CH_3$), 4.07–4.13 (2H, m, quin. 3-$C\underline{H}_2CH_2$), 4.09 (2H, s, SCH_2), 4.22 (2H, d, J = 4.4 Hz, $C\underline{H}_2CH{=}CH_2$), 4.44 (1H, q, J = 4.4 Hz, thia. C_5–H), 5.06–5.12 (2H, m, $CH_2CH{=}C\underline{H}_2$), 5.75–5.79 (1H, m, $CH_2C\underline{H}{=}CH_2$), 7.38–7.59 (1H, m, quin. C_6-H), 7.58 (1H, d, J = 8.4 Hz, quin. C_8–H), 7.75 (1H, t, J = 7.6 Hz, quin. C_7–H), 8.05 (1H, dd, J = 7.8, 1.4 Hz, quin. C_5–H), 10.60 (1H, s, CONH). Anal. Calcd for $C_{21}H_{25}N_5O_3S_2$ (459.6): C, 54.9; H, 5.5; N, 15.2. Found. C, 53.9; H, 5.5; N, 15.1.

2-[(3-Ethyl-4-oxo-3,4-dihydroquinazolin-2-yl)mercaptoacetyl-hydrazono]-3-benzyl-5-propylthiazolidin-4-one **(3f):** Yield, 89%. m.p. 192–194°C. IR: 3163, 1710, 1687, 1657. ^{1}H NMR δ (ppm): 0.83 (3H, t, J = 7.4 Hz, thia. 5-$CH_2CH_2C\underline{H}_3$), 1.24–1.33 (3H, m, quin. 3-$CH_2C\underline{H}_3$ and 5-$CH_2C\underline{H}_2CH_3$, 1.64–1.66 and 1.93–1.96 (2H, 2 m, thia. 5-$C\underline{H}_2CH_2CH_3$), 4.05–4.11 (2H, m, quin. 3-$C\underline{H}_2CH_3$), 4.08 (2H, s, SCH_2), 4.47 (1H, q, J = 4.0 Hz thia. C_5–H), 4.80 (2H, s, N-$C\underline{H}_2Ph$), 7.17–7.31 (5H, m, phenyl), 7.42 (1H, t, J = 7.2 Hz, quin. C_6–H), 7.55 (1H, d, J = 8.0 Hz, quin. C_8–H), 7.73 (1H, t, J = 7.4 Hz, quin. C_7–H), 8.04 (1H, d, J = 8.0 Hz, quin. C_5–H), 10.64 (1H, s, CONH). EIMS *m/z*: 510 (M + 1). Anal. Calcd for $C_{25}H_{27}N_5O_3S_2$ (509.6): C, 58.9; H, 5.3; N, 13.7. Found. C, 59.0; H, 5.6; N, 14.0.

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