Synthesis and reactions of methyl 2-[3-(2-phenylquinazolin-4-yl)thioureido]alkanoates

Walid Fathalla[a]* and Pavel Pazdera[b]

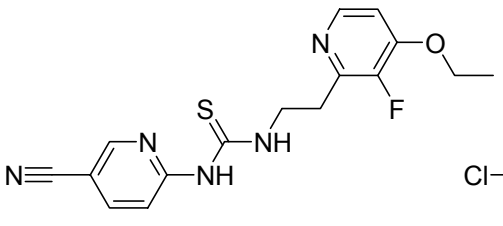
[a]Department of Mathematical and Physical Sciences, Faculty of Engineering, Suez Canal University, Port-Said, Egypt
[b]Department of Organic Chemistry, Faculty of Science, Masaryk University, Brno, Czech Republic
E-mail: walid399@yahoo.com

Abstract
Quinazoline thioureas **5** bearing an amino acid ester residue were prepared by a novel three step sequential reaction of *N*-(2-cyanophenyl)benzimidoyl isothioyanate with amino acid methyl ester hydrochlorides. Some chemoselective reactions of **5a** with alkyl halides were studied.

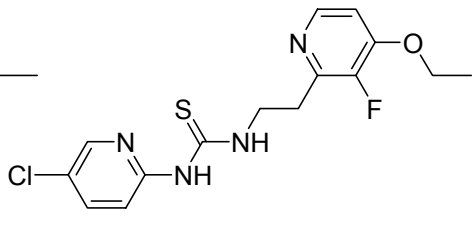
Keywords: Non-nucleoside RT inhibitors, quinazoline, thioureas, amino acids, imidoyl isothiocyanate

Introduction

Considerable attention has been directed to the design and synthesis of new AIDS therapies. Inhibition of the viral enzyme reverse transcriptase (RT) represents particularly attractive strategy for the anti AIDS drug design. Several heterocyclic thioureas have been reported as a new class of potent non-nucleoside inhibitors of human immunodeficiency virus type 1 reverse transcriptase (NNRTIs) such phenethylthiazolyl-thiourea (PETT) derivatives.[1-4]



PETT1



PETT2

Uckun *et al.*[5-7] described the synthesis of a number of heterocyclic thioureas having an amino acid ester or aryl side chain as NNRTIs.

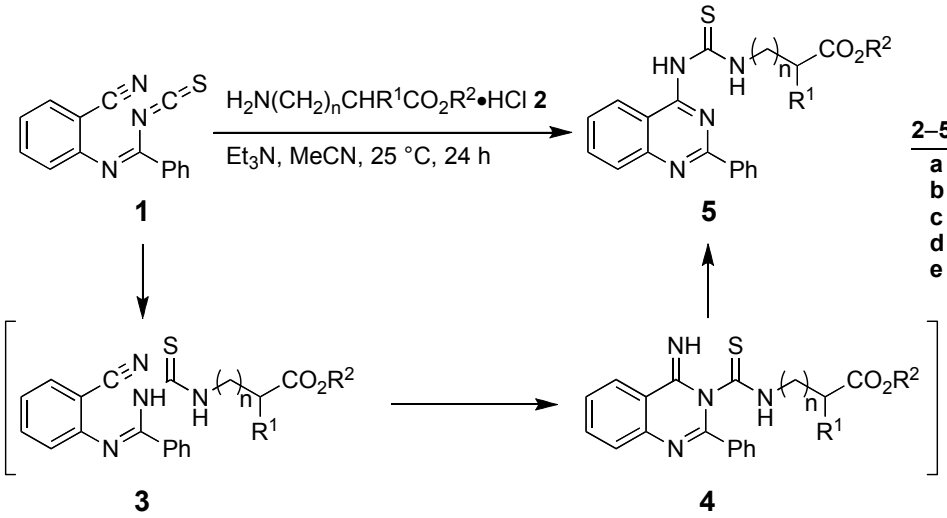
Result and Discussion

Recently, we have reported convenient one-pot syntheses of quinazolin-4-ylidenethioureas[8] and quinazolin-4-ylthioureas[9,10] from *N*-(2-cyanophenyl)benzimidoyl isothiocyanate with amines. *N*-(2-cyanophenyl)benzimidoyl isothiocyanate (**1**)[8,9] is a highly reactive compound featuring two electrophilic sites, the nitrile and isothiocyanate functional groups in a conjugated system.

The reaction of imidoyl isothiocyanate **1** with one equivalent of amino acid ester hydrochlorides **2** in the presence of triethyl amine furnished the desired quinazolinethioureas **5** in good yields. The reaction is assumed to proceed via three steps (Scheme 1).

The amino acid ester **2** adds to the isothiocyanate function of **1** to give the open chain thiourea intermediate **3**, which in turn, cyclizes by intramolecular addition of NH to the nitrile group giving rise to the 4-iminoquinazoline intermediate **4**; a Dimroth rearrangement furnishes the isolated product, methyl 2-[3-(2-phenylquinazolin-4-yl)thioureido]alkanoate **5** (Scheme 1).

This method has the advantage of a one pot reaction with an overall moderate to good yield of **5** at room temperature to minimize the degree of racemization in amino acid coupling. The alternative thiocarbonyldiimidazole method[5-7] requires a higher temperature and longer reaction time (100 °C, 30 h) for attaching the amino acid residue at heterocyclic ring moieties.



2–5	n	R^1	R^2
a	0	H	Me
b	0	Me	Me
c	0	CH_2CO_2Et	Et
d	0	Ph	Et
e	1	H	Et

Scheme 1

The structure assignment of the amino acid derivatives **5a**–**e** is based on spectroscopic methods and on the correlation with a fully analyzed reference, 1-benzyl-3-(2-phenylquinazolin-4-yl)thiourea[9] (Figure 1). The ^{1}H NMR spectrum of **5a** exhibits two signals at δ 12.35 and 8.98 corresponding to 1-NH and 3-NH of the thiourea moiety, respectively. The ^{13}C NMR spectrum of **5a** reveals quaternary carbon signals at δ 180.65, 169.19, 159.11 and 155.90 assigned to C=S, C=O, C2 and C4, respectively.

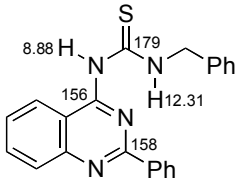
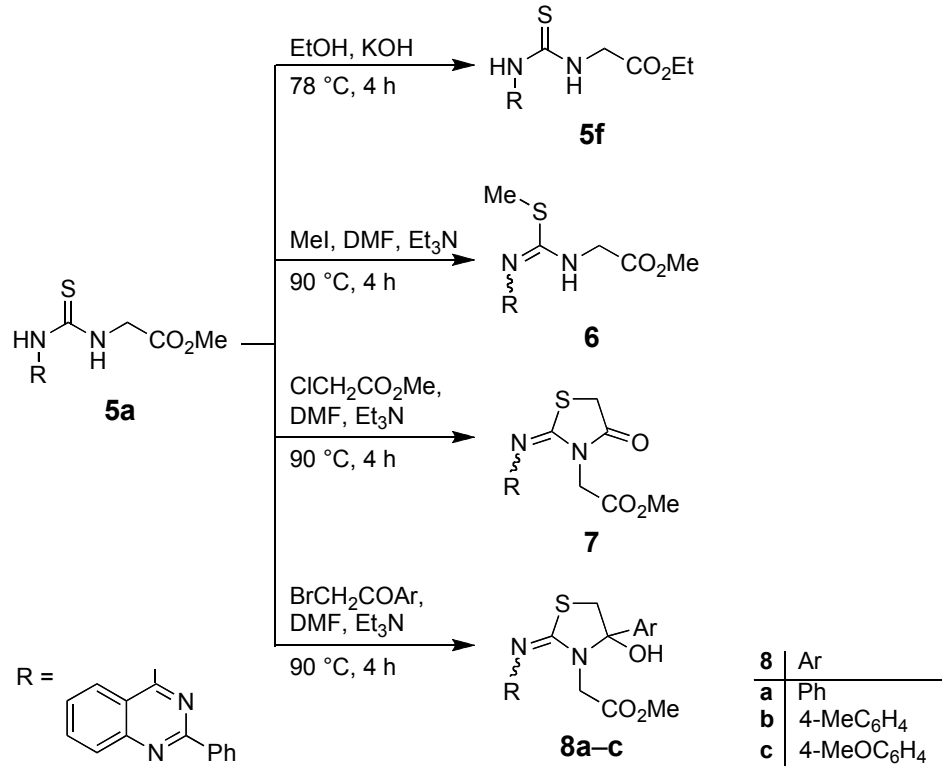


Figure 1. Selected ^{1}H and ^{13}C NMR data of 1-benzyl-3-(2-phenylquinazolin-4-yl)thiourea.[9]

Thioureas **5** were the only tautomers isolated, in good agreement with previous results with quinazolinethioureas bearing alkyl, aryl and heterocyclic substituents,[9,10] and those reported for phenethylthiazolylthioureas.[5–7] The reaction of methyl 2-[3-(2-phenylquinazolin-4-yl)thioureido]acetate (**5a**) with absolute ethanol in the presence of potassium hydroxide furnished the transesterification product **5f** (Scheme 2).

With methyl iodide, **5a** underwent chemoselective *S*-alkylation to form isothiourea **6**[13] (Scheme 2). The ^{1}H NMR spectrum of isothiourea derivative **6** shows signals at δ 3.5 and 12.6, characteristic for SCH_3 and C=N3···HN, respectively. According to ^{1}H NMR data, isothiourea **6** is formed as a single tautomer due to hydrogen bonding.



Scheme 2

Similarly, the reaction of methyl 2-[3-(2-phenylquinazolin-4-yl)thioureido]acetate (**5a**) with methyl chloroacetate resulted in the formation of thiazolidine **7**. The ^{1}H NMR spectrum of **7**

shows a singlet at δ 3.99, the ^{13}C NMR displays a signal at δ 34.19, typically associated with an SCH_2CO moiety.

Following the classical Hantzsch thiazole synthesis[14] the reaction of the glycinethioamide derivative **5a** with phenacyl halides afforded 4-hydroxythiazolidines **8a**–**c**. The ^{1}H NMR spectrum of compound **8a** shows two doublets at δ 4.38 and δ 3.60 for the A parts of the AB quartets of NCH_2 and SCH_2, respectively. In addition, an apparent doublet is displayed at δ 3.49 resulting from superimposed B doublets of both AB spectra of the NCH_2 and SCH_2 groups. Similarly, **8b** gives rise to superimposed B doublets of the NCH_2 and SCH_2 groups. On the other hand, the AB doublets of NCH_2 and SCH_2 in **8c** are well separated at δ 4.39, 3.58 and δ 3.82, 3.49, respectively.

Conclusions

The reaction of *N*-(2-cyanophenyl)benzimidoyl isothiocyanate (**1**) with amino acid esters **2** afforded methyl 2-[3-(2-phenylquinazolin-4-yl)thioureido]alkanoates (**5**) *via* a three step sequential reaction. Compound **5a** underwent alkylation reactions with methyl chloroacetate and phenacyl halides to afford thiazolidine derivatives **7** and **8a**–**c**, respectively.

Experimental Section

General Procedures. Melting points were measured on a Boetius Rapido PHMK 79/2106 (Wägetechnik) instrument. Elemental analysis were carried out with an Erba 1102 instrument. ^{1}H and ^{13}C NMR spectra were recorded at 300 MHz and 75.5 MHz, respectively (DRX 500 Avance Bruker) in $CDCl_3$ solution with tetramethylsilane as an internal standard.

Methyl 2-[3-(2-phenylquinazolin-4-yl)thioureido]alkanoates (5). General Method. To a solution of amino acid ester hydrochloride **2** (5 mmol) in acetonitrile (10 mL) was added triethyl amine (0.7 mL, 5 mmol). This solution was stirred at 5 °C for 30 min, filtered and subsequently added in portions to a previously prepared solution of imidoyl isothiocyanate **1** (1.32 g, 5 mmol) in acetonitrile (30 mL).[8,9] The reaction mixture was stirred at room temperature for 24 h. The solvent was evaporated under reduced pressure, and the residue was crystallized from ethanol.

Methyl 2-[3-(2-phenylquinazolin-4-yl)thioureido]acetate (5a). From $GlyOCH_3$·HCl **2a** (0.63 g). Colorless crystals (1.23 g, 69%); mp 197–198 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 12.35 (1H, s, N<u>H</u>CH_2), 8.98 (1H, s, 4-NH), 8.54–8.51 (2H, m, ArH), 8.04–8.01 (1H, m, ArH), 7.93–7.88 (2H, m, ArH), 7.64–7.56 (4H, m, ArH), 4.68 (2H, d, J = 4.66 Hz, NHC<u>H</u>$_2$) 4.7 Hz), 3.85 (3H, s, OCH_3); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 180.65 (C=S), 169.19 (C=O), 159.11 (C=N, C2), 155.90 (C=N, C4), 151.54 (C_{qAr}), 137.31 (C_{qAr}), 134.58 (CH_{Ar}), 131.12 (CH_{Ar}), 129.84 (CH_{Ar}), 128.68 (CH_{Ar}), 127.79 (CH_{Ar}), 120.60 (CH_{Ar}), 112.58 (C_{qAr}), 52.75 (OCH_3), 48.27 (NCH_2).

Anal. Calcd. for $C_{18}H_{16}N_4O_2S$ (352.4): C, 61.35; H, 4.58; N, 15.90; S, 9.10. Found: C, 61.23; H, 4.49; N, 15.88; S, 8.96.

Methyl 2-[3-(2-phenylquinazolin-4-yl)thioureido]propanoate (**5b**). From L-AlaOCH$_3$·HCl **2b** (0.7 g). White crystals (0.89 g, 49%); mp 182–183 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 12.34 (1H, s, N<u>H</u>CH$_2$), 8.87 (1H, s, 4-NH), 8.53–8.51 (2H, m, ArH), 8.03–7.98 (1H, m, ArH), 7.93–7.89 (2H, m, ArH), 7.64–7.55 (4H, m, ArH), 5.45–5.39 (1H, m, CH), 3.87 (3H, s, OCH$_3$), 1.35 (3H, d, *J* = 6.9 Hz CHC<u>H</u>$_3$); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 180.13 (C=S), 172.58 (C=O), 159.01 (C=N, C2), 155.98 (C=N, C4), 151.58 (C_{qAr}), 137.45 (C_{qAr}), 134.59 (CH_{Ar}), 131.17 (CH_{Ar}), 129.85 (CH_{Ar}), 128.89 (CH_{Ar}), 128.67 (CH_{Ar}), 127.83 (CH_{Ar}), 120.61 (CH_{Ar}), 112.63 (C_{qAr}), 54.84 (OCH$_3$), 52.81 (<u>C</u>HCH$_3$), 18.37 (CH<u>C</u>H$_3$). Anal. Calcd. For $C_{19}H_{18}N_4O_2S$ (366.4): C, 62.28; H, 4.95; N, 15.29; S, 8.75. Found: C, 62.27; H, 4.95; N, 15.24; S, 8.73.

Diethyl 2-[3-(2-phenylquinazolin-4-yl)thioureido]succinate (**5c**). From DL-AspOC$_2$H$_5$·HCl **2c** (1.13 g). White crystals (1.61 g, 71%); mp 148–149 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 12.68 (1H, d, *J* = 4.8 Hz, N<u>H</u>CH$_2$), 8.90 (1H, s, 4-NH), 8.59–8.57 (2H, m, ArH), 8.07–8.04 (1H, m, ArH), 7.95–7.90 (2H, m, ArH), 7.67–7.53 (4H, m, ArH), 5.54–5.67 (1H, m, CH), 4.34–4.21(2H, m, OCH$_2$), 4.17–4.04 (2H, m, OCH$_2$), 3.26–3.12 (2H, m, CHC<u>H</u>$_2$), 1.32–0.98 (6H, m, 2CH$_3$); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 180.01 (C=S), 170.63 (C=O), 169.97 (C=O), 159.35 (C=N, C2), 155.92 (C=N, C4) , 151.60 (C_{qAr}), 137.12 (C_{qAr}), 134.53 (CH_{Ar}), 131.10 (CH_{Ar}), 129.85 (CH_{Ar}), 129.20 (CH_{Ar}), 128.75 (CH_{Ar}), 127.72 (CH_{Ar}), 120.53 (CH_{Ar}), 112.62 (C_{qAr}), 62.34 (OCH$_2$), 61.19 (OCH$_2$), 55.87 (<u>C</u>HCH$_2$), 36.10 (CH<u>C</u>H$_2$), 14.30 (CH$_3$), 14.12 (CH$_3$). Anal. Calcd. for $C_{23}H_{24}N_4O_4S$ (452.5): C, 61.05; H, 5.35; N, 12.38; S, 7.09. Found: C, 61.05; H, 5.33; N, 12.36; S, 7.05.

Ethyl 2-phenyl-2-[3-(2-phenylquinazolin-4-yl)thioureido]acetate (5d). From *dl*-PhgOC$_2$H$_5$·HCl **2d** (1.08 g). White crystals (1.43 g, 67%); mp 157–158 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 12.65 (1H, d, *J* = 4.75 Hz, N<u>H</u>CH$_2$), 8.94 (1H, s, 4-NH), 8.27-8.25 (2H, m, ArH), 8.05–8.02 (1H, m, ArH), 7.92–7.87 (2H, m, ArH), 7.64–7.36 (9H, m, ArH), 6.25 (1H, d, *J* = 4.7 Hz, NHC<u>H</u>), 4.40–4.19 (2H, m, OCH$_2$), 1.27 (3H, t, *J* = 6.9 Hz, CH$_3$); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 180.11 (C=S), 170.00 (C=O), 158.91 (C=N, C2), 155.93 (C=N, C4), 151.43 (C_{qAr}), 135.57 (C_{qAr}), 134.59 (CH_{Ar}), 130.96 (CH_{Ar}), 129.81 (CH_{Ar}), 129.45 (CH_{Ar}), 129.16 (CH_{Ar}), 128.81 (CH_{Ar}), 128.62 (CH_{Ar}), 128.23 (CH_{Ar}), 127.80 (CH_{Ar}), 120.56 (CH_{Ar}), 112.62 (C_{qAr}), 63.33 (CH), 62.22 (OCH$_2$), 14.27 (CH$_2$<u>C</u>H$_3$). Anal. Calcd. for $C_{25}H_{22}N_4O_2S$ (442.5): C, 67.85; H, 5.01; N, 12.66; S, 7.24. Found: C, 67.83; H, 4.99; N, 12.54; S, 7.23.

Ethyl 3-[3-(2-phenylquinazolin-4-yl)thioureido]propanoate (5e). From β-AlaOC$_2$H$_5$·HCl **2e** (0.77 g). White crystals (1.65 g, 90%); mp 173–174 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 12.30 (1H, s, N<u>H</u>CH$_2$), 8.85 (1H, s, 4-NH), 8.53–8.51 (2H, m, ArH), 8.03–7.98 (1H, m, ArH), 7.93–7.89 (2H, m, ArH), 7.64–7.55 (4H, m, ArH), 4.16–4.10 (4H, m, NHC<u>H</u>$_2$, OCH$_2$), 2.90 (2H, t, *J* = 6.5 Hz, CH$_2$CO), 1.19 (3H, t, *J* = 7.0 Hz, CH$_3$); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 180.48 (C=S), 171.99 (C=O), 158.91 (C=N, C2), 155.95 (C=N, C4), 151.52 (C_{qAr}), 137.36 (C_{qAr}), 134.54 (CH_{Ar}), 131.14 (CH_{Ar}), 129.81 (CH_{Ar}), 128.98 (CH_{Ar}), 128.60 (CH_{Ar}), 127.73 (CH_{Ar}), 120.60 (CH_{Ar}), 112.58 (C_{qAr}), 61.01 (OCH$_2$), 41.871 (NCH$_2$), 33.27 (CO<u>C</u>H$_2$), 14.35 (CH$_3$). Anal.

Calcd. for $C_{20}H_{20}N_4O_2S$ (380.5): C, 63.14; H, 5.30; N, 14.73; S, 8.43. Found: 63.06; H, 5.27; N, 14.68; S, 8.41.

Derivatization reactions of 5a

Ethyl 2-(3-(2-phenylquinazolin-4-yl)thioureido)acetate (5f). To a stirred solution of **5a** (1.762 g, 5 mmol) in absolute ethanol was added KOH (0.28 g, 5 mmol). The reaction mixture was refluxed for 4 h, and then evaporated under reduced pressure. The residue was collected and crystallized from ethanol to give white crystals **5f** (1.23 g, 69%); mp 204–205 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 12.30 (1H, s, N<u>H</u>CH_2), 8.93 (1H, s, 4-NH), 8.54–8.51 (2H, m, ArH), 8.04–8.01 (1H, m, ArH), 7.93–7.88 (2H, m, ArH), 7.64–7.56 (4H, m, ArH), 4.68 (2H, d, *J* = 4.7 Hz, NHC<u>H</u>$_2$), 4.33 (2H, q, *J* = 6.8 Hz, OCH_2); 1.32 (3H, t, *J* = 6.9 Hz, CH_3). Anal. Calcd. for $C_{19}H_{18}N_4O_2S$ (366.4): C, 62.28; H, 4.95; N, 15.29; S, 8.75. Found: C, 62.11; H, 4.93; N, 15.18; S, 8.74.

Reactions with alkyl halides. To a stirred mixture of **5a** (1.762 g, 5 mmol) in DMF (20 mL) and triethyl amine (0.7 mL, 5 mmol) was added the appropriate alkyl halide (5 mmol). The reaction mixture was heated at 90 °C for 4 h, and was then evaporated under reduced pressure. The residue was recrystallized from ethanol.

Methyl 2-[2-methyl-1-(2-phenylquinazolin-4-yl)isothioureido]acetate (6). Using methyl iodide (0.30 mL). White crystals (1.27 g, 69%); mp 176–177 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 12.60 (1H, s, N<u>H</u>CH_2), 8.55–8.51 (2H, m, ArH), 7.93–7.88 (3H, m, ArH), 7.59–7.47 (4H, m, ArH), 4.34 (2H, s, NCH_2), 3.43 (3H, s, OCH_3), 2.74 (3H, s, SCH_3). Anal. Calcd. for $C_{19}H_{18}N_4O_2S$ (366.4): C, 62.28; H, 4.95; N, 15.29; S, 8.75. Found: C, 62.23; H, 4.91; N, 15.22; S, 8.70.

Methyl [4-oxo-2-(2-phenylquinazolin-4-ylimino)thiazolidin-3-yl]acetate (7). From methyl chloroacetate (0.45 mL): White crystals (1.32 g, 67%); mp 185–186 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.63 (2H, d, *J* = 7.7 Hz, ArH), 8.36 (1H, d, *J* = 8.0 Hz, ArH), 8.04 (1H, d, *J* = 8.4 Hz, ArH), 7.89–7.84 (1H, m, ArH), 7.55–7.53 (4H, m, ArH), 4.81 (2H, s, NCH_2), 3.99 (2H, s, SCH_2), 3.82 (3H, s, OCH_3); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 171.82 (C=O), 167.59 (C=O), 160.17 (C_{qAr}), 152.70 (C_{qAr}), 139.36 (C_{qAr}), 138.38 (CH_{Ar}), 137.31 (C_{qAr}), 134.10 (CH_{Ar}), 130.74 (CH_{Ar}), 128.75 (CH_{Ar}), 128.43 (CH_{Ar}), 126.92 (CH_{Ar}), 125.15 (CH_{Ar}), 119.26 (C_{qAr}), 52.95 (OCH_3), 44.50 (NCH_2), 34.19 (SCH_2). Anal. Calcd. for $C_{20}H_{16}N_4O_3S$ (392.4): C, 61.21; H, 4.11; N, 14.28; S, 8.17. Found: C, 61.16; H, 4.08; N, 14.15; S, 8.13.

Methyl [4-hydroxy-4-phenyl-2-(2-phenylquinazolin-4-ylimino)thiazolidin-3-yl]acetate (8a). From phenacyl bromide (1.0 g). White crystals (1.68 g, 71%); mp 208–209 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.59–8.51 (2H, m, ArH), 8.37 (1H, d, *J* = 8.1 Hz, ArH), 8.03 (1H, d, *J* = 8.2 Hz, ArH), 7.83–7.81 (1H, m, ArH), 7.71–7.68 (2H, m, ArH), 7.53–7.34 (7H, m, ArH), 5.85 (1H, bs, OH), 4.38 (1H, d, *J* = 16.8 Hz, NCH_A), 3.74 (3H, s, OCH_3), 3.60 (1H, d, *J* = 11.9 Hz, SCH_A), 3.49 (2H, d, *J* = 11.7 Hz, NCH_B, SCH_B); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 171.82 (C_{qAr}), 165.85 (C_{qAr}), 163.46 (C_{qAr}), 160.73 (C_{qAr}), 152.17 (C_{qAr}), 141.01 (C_{qAr}), 138.69 (C_{qAr}), 133.41 (CH_{Ar}), 130.53 (CH_{Ar}), 129.40 (CH_{Ar}), 129.13 (CH_{Ar}), 128.98 (CH_{Ar}), 128.55 (CH_{Ar}), 127.60 (CH_{Ar}), 126.91 (CH_{Ar}), 126.13 (CH_{Ar}), 125.69 (CH_{Ar}), 121.00 (C_{qAr}), 92.74 (COH), 52.68 (OCH_3), 47.16

(NCH_2), 45.54 (SCH_2). Anal. Calcd. for $C_{26}H_{22}N_4O_3S$ (470.5): C, 66.37; H, 4.71; N, 11.91; S, 6.81. Found: C, 66.29; H, 4.70; N, 11.88; S, 6.79.

Methyl [4-hydroxy-2-(2-phenylquinazolin-4-ylimino)-4-tolylthiazolidin-3-yl]acetate (8b). From 4-methylphenacyl bromide (1.07 g): White crystals (1.45 g, 60%); mp 194–195 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.60–8.53 (2H, m, ArH), 8.37 (1H, d, *J* = 8.0 Hz, ArH), 8.02 (1H, d, *J* = 8.0 Hz, ArH), 7.83–7.80 (1H, m, ArH), 7.68–7.59 (6H, m, ArH), 7.35–7.17 (2H, m, ArH), 5.70 (1H, bs, OH), 4.43 (1H, d, *J* = 16.9 Hz, NCH_A), 3.74 (3H, s, OCH_3), 3.59 (1H, d, *J* = 11.9 Hz, SCH_A), 3.52 (2H, d, *J* = 11.9 Hz, NCH_B, SCH_B), 2.41 (3H, s, CH_3); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 172.22 (C=O), 165.85 (C_{qAr}), 163.46 (C_{qAr}), 160.73 (C_{qAr}), 152.17 (C_{qAr}), 141.01 (C_{qAr}), 139.15 (C_{qAr}), 133.41 (CH_{Ar}), 130.50 (CH_{Ar}), 129.72 (CH_{Ar}), 129.25 (CH_{Ar}), 128.58 (CH_{Ar}), 127.82 (CH_{Ar}), 126.81 (CH_{Ar}), 126.13 (CH_{Ar}), 125.50 (CH_{Ar}), 120.89 (C_{qAr}), 92.83 (COH), 52.95 (OCH_3), 47.34 (NCH_2), 45.53 (SCH_2), 21.37 (CH_3). Anal. Calcd. for $C_{27}H_{24}N_4O_3S$ (484.6): C, 66.92; H, 4.99; N, 11.56; S, 6.62. Found: C, 66.87; H, 4.91; N, 11.43; S, 6.52.

Methyl [4-hydroxy-4-(4-methoxyphenyl)-2-(2-phenylquinazolin-4-ylimino)thiazolidin-3-yl]-acetate (8c). From 4-methoxyphenacyl bromide (1.15 g): Yellowish white crystals (1.54 g, 64%); mp 198–199 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.61–8.59 (2H, m, ArH), 8.36 (1H, d, *J* = 8.0 Hz, ArH), 8.01 (1H, d, *J* = 8.4 Hz, ArH), 7.84–7.80 (1H, m, ArH), 7.62 (2H, d, *J* = 8.8 Hz, ArH), 7.55–7.46 (4H, m, ArH), 6.97 (2H, d, *J* = 8.8 Hz, ArH), 5.76 (1H, bs, OH), 4.39 (1H, d, *J* = 16.9 Hz, NCH_A), 3.86 (3H, s, OCH_3), 3.82 (1H, d, *J* = 11.9 Hz, SCH_A), 3.74 (3H, s, OCH_3), 3.58 (1H, d, *J* = 16.8 Hz, NCH_B), 3.49 (1H, d, *J* = 12.1 Hz, SCH_B); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 171.89 (C=O), 166.06 (C_{qAr}), 163.46 (C_{qAr}), 161.15 (C_{qAr}), 152.14 (C_{qAr}), 139.15 (C_{qAr}), 132.85 (CH_{Ar}), 130.49 (CH_{Ar}), 129.69 (CH_{Ar}), 129.25 (CH_{Ar}), 128.27 (CH_{Ar}), 127.81 (CH_{Ar}), 126.14 (CH_{Ar}), 125.50 (CH_{Ar}), 120.55 (C_{qAr}), 92.97 (COH), 55.78 (OCH_3), 53.18 (OCH_3), 47.47 (NCH_2), 46.14 (SCH_2). Anal. Calcd. For $C_{27}H_{24}N_4O_4S$ (500.57): C, 64.78; H, 4.83; N, 11.19; S, 6.41. Found: C, 64.74; H, 4.78; N, 11.12; S, 6.41.

References

1. Ahgren, C.; Backro, K.; Bell, F.W.; Cantrell, A. S.; Clemens, M.; Colacino, J. ; Deeter, M. J. B.; Engelhardt, J. A.; Jaskunas, S. R.; Johansson, N. G.; Jordan, C L.; Kasher, J. S.; Kinnick, M. D.; Lind, P.; Lopez, C.; Morin, J. M.; Muesing, M. A.; Noreen, R.; Oberg, B.; Paget, C. J.; Palkowitz, J. A.; Parrish, C.; Pranc, P.; Rippy, M. K.; Rydergard, C.; Sahlberg, C.; Swanson, S.; Ternansky, R.; Unge, J.; Vasileff, T. R. T.; Vrang, L.; West, S. J.; Zhang, H.; Zhou, X. X. *Antimicrob. Agents Chemoth*. **1995**, *39*, 1329.
2. Heinisch, G.; Matuszczak, B.; Pachler, S.; Rakowitz, D. *Antivir. Chem. Chemother.* **1997**, *8*, 443.
3. Ren, J.; Diprose, J.; Warren, J.; Esnouf, R. M.; Bird, L. E.; Ikemizu, S.; Slater, M.; Milton, J.; Balzarini, J.; Stuart, D. I; Stammers, D. K. *J. Biol. Chem.* **2000,** *275*, 5633.

4. Ahgren, C.; Backro, K.; Bell, F. W.; Cantrell, S.; Clemens, M.; Colacino, J. M.; Deeter, M. J. B.; Engelhardt, J. A.; Hogberg, M.; Jaskunas, S. R. *Antimicrob. Agents Chemoth.* **1995**, *39,* 1329.
5. Venkatachalam, T. K.; Uckun, F. M. *Synth. Commun.* **2006***, 36*, 2103.
6. Venkatachalam, T. K.; Sudbeck, E.; Uckun, F. M. *J. Mol. Struc.* **2004**, *687*, 45.
7. Venkatachalam, T. K.; Qazi, B. S.; Samuel, P.; Uckun, F. M. *Bioorganic & Medicinal Chemistry* **2003**, *11*, 1095.
8. Fathalla, W.; Cajan, M.; Marek, J.; Pazdera, P. *Molecules* **2001**, *6*, 574.
9. Fathalla, W.; Cajan, M.; Marek, J.; Pazdera, P. *Molecules* **2001**, *6*, 588.
10. Fathalla, W.; Pazdera, P. *Arkivoc* **2002**, *1*, 7.
11. Szczepur, L. F.; Eilts, K. K.; Hermetet, A. K.; Ackerman, L. J.; Sweingen, J. K.; West, D. X. *J. Mol. Struc.* **2002**, *607*, 101.
12. West, D. X.; Swearingen, J. K.; Hermetet, A. K.; Ackerman, L. *J. Mol. Struc.* **2001**, *562*, 95.
13. Fathalla, W.; Cajan, M.; Pazdera, P. *Molecules* **2001**, *6,* 557.
14. Mohareb, R. M.; Sherif, M. *Heteroatom Chem.* **1997**, *8*, 77.