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Synthesis and spectroscopic studies of substituted 5,6,7,8-tetrahydroquinazolin-2-amine compounds via one-pot method

Fatma Tulay Tugcu*, Kadir Turhan

Yıldız Technical University, Faculty of Arts and Sciences, Department of Chemistry, Istanbul, Turkey

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ABSTRACT

5,6,7,8-Tetrahydro derivatives of quinazoline-2-amine have been synthesized and characterized. These reactions, which are carried out using one-pot multicomponent reactions (MCR's), proceed more easily than conventional multistep organic reactions. This method allows new organic molecules to be synthesized in a single step with minimum time and number of trials. Cyclocondensation of each of the previously substituted hetaryl carboxaldehydes with cyclic ketones and guanidine carbonate was achieved by the technique of MCR; and structures of all the synthesized compounds 6-methyl-4-(thiophen-2-yl)-8-(thiophen-2-ylmethylidene)-5,6,7,8-tetrahydroquinazolin-2-amine **(4f)**, 6-methyl-4-(3-methylthiophen-2-yl)-8-[(3-methylthiophen-2-yl)methylidene]-5,6,7,8-tetrahydroquinazolin-2-amine **(4g)**, 6-methyl-4-(5-methylthiophen-2-yl)-8-[(5-methylthiophen-2-yl)methylene]-5,6,7,8-tetrahydroquinazolin-2-amine **(4h)**, 4-(thiophen-2-yl)-8-(thiophen-2-ylmethylidene)-5,6,7,8-tetrahydroquinazolin-2-amine **(4i),** 4-(3-methylthiophen-2-yl)-8-[(3-methylthiophen-2-yl)methylidene]-5,6,7,8-tetrahydroquinazolin-2-amine **(4j)** and 4-(5-methylthiophen-2-yl)-8-[(5-methylthiophen-2-yl)methylidene]-5,6,7,8-tetrahydroquinazolin-2-amine **(4k)** have been determined and characterized by infrared, nuclear magnetic resonance, mass spectral data and elemental analysis. All the new synthesized compounds were evaluated for their antibacterial activity.

1. Introduction

Efficiency and sustainability in obtaining chemical compounds are objects of desire of many areas of chemistry, such as organic synthesis and medicinal chemistry, where the structural complexity of the molecules often requires multistep synthetic routes, diversified substrates and reagents, aggressive reaction media and difficulties in the isolation and purification of products, leading to extremely laborious and costly experimental procedures [1]. In this context, mulicomponent reactions (MCRs) are increasingly appreciated as efficient synthesis tools to rapidly access complex products. With MCRs, molecules can be assembled from three or more starting materials in a one-pot process. MCRs involve the inherent formation of several bonds in a single operation, without isolating the intermediates, changing the reaction conditions, and often without adding further reagents. Therefore, MCRs address sustainability by atom-, step-, and, thus, eco-efficiency, reducing the number of intermediate steps and functional group manipulations and avoiding protective group strategies. Syntheses involving MCRs save time and energy and proceed with process efficiency [2].

All these factors characterize what chemists call “ideal synthesis”. In the light of these explanations, the one-pot synthesis of a target molecule in the same reaction vessel is accepted as an effective approach in synthetic organic chemistry. One-pot reactions where several reaction sequences are conducted in the same reaction flask are one of the methods that can be used in order to conduct synthesis in a greener fashion.

Quinazolines, which have pyrimidine nucleus in their structures, represent the most interesting group of heterocycles that are used frequently in the medical field due to their biological activities. Quinazoline derivatives have been reported for their antibacterial [3], antifungal [4], anti-human immunodeficiency virus (HIV) [5,6], anthelmintic [7], anti-tubercular [8–10], hypotensive [11], anticonvulsant [12,13], antifibrillatory [14], diuretic [15], anti-inflammatory [16,17], anticancer activities [18–21], antiviral activities [22–25]. However, the development of new and efficient methods for the preparation of these important molecules still continues to be an important and attractive area of research in

* Corresponding author.
E-mail address: ftugcu@yildiz.edu.tr (F.T. Tugcu).

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synthetic organic chemistry. In continuation of our interest in heterocyclic molecules, we herein report the one-pot synthesis, characterization, and evaluation for antibacterial activities of substituted 5,6,7,8-tetrahydroquinazolin-2-amine derivatives.

2. Experimental

2.1. Instruments

Fourier Transform Infrared (FTIR) spectra of the starting materials and the obtained products were taken on the "Perkin Elmer Spectrum One" FTIR spectrophotometer by ATR technique. Nuclear magnetic resonance (^{1}H NMR) spectra were obtained from a "Bruker 400 MHz" spectrophotometer in chloroform-D ($CDCl_3$) using the tetramethylsilane (TMS) standard according to the solubility of the materials. Mass (MS) spectra were obtained with 70 eV "Hewlett Packard GC/MS 6890/5973".

Molecular models of the new compounds obtained were plotted in the computer program (C: black, H: light blue, N: dark blue, S: yellow) in the "ACD/Labs 12.00 (3D Viewer)" computer program (Table 1).

2.2. General procedure for the synthesis of compounds (4f-4k)

A mixture of 2.0 mmol of thiophene-2-carboxaldehyde (0.224 g) **(1a)** or 3-methylthiophene-2-carboxaldehyde (0.256 g) **(1b)** or 5-methylthiophene-2-carboxaldehyde (0.256 g) **(1c)**, 1.0 mmol of cyclopentanone (0.084 g) **(2d)** or 1.0 mmol of 4-methyl cyclopentanone (0.112 g) **(2e)** and 1.0 mmol of guanidine carbonate (0.180 g) **(3)** were placed in a round-bottom flask was subjected to TLC control at regular intervals using a magnetic stirrer in the presence of 0.2 g NaOH was stirred at 70 °C for 2 h (Scheme 1). After completion of the reaction (TLC control at regular intervals) the dark solid mixture which was left to cool was washed with water and then purified by column chromatography (chloroform) to obtain the product in pure form.

2.2.1. 4-(Thiophen-2-yl)-8-(thiophen-2-ylmethylidene)-5,6,7,8-tetrahydroquinazolin-2-amine (4f)

Yellow solid; mp 155–6 °C; yield 72%; FTIR (ATR) (ν cm^{-1}) 3329 and 3213 (NH_2), 3096 (aromatic ring, =C–H), 2928–2850 (cyclic ring, C–H), 1609 (heteroaromatic ring, C=N), 1531 (heteroaromatic ring, C=C), 1437 (C–N), 710 (C–S); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.97 (1H, m, cyclohexyl-CH_2), 2.55 (2H, m, cyclohexyl-CH_2), 2.94 (2H, m, cyclohexyl-CH_2), 5.15 (2H, s, NH_2), 7.15 (1H, dd, J = 5.0; 4.1 Hz, Ar–H), 7.20 (1H, dd, J = 4.6; 4.0 Hz, Ar–H), 7.38 (1H, brd, J = 5.0 Hz, Ar–H), 7.45 (1H, d, J = 5.1 Hz, Ar–H), 7.50 (1H, brd, J = 5.0 Hz, Ar–H), 7.54 (1H, brd, J = 5.1 Hz, Ar–H),7.99 (1H, s, vinyl H); MS: m/z $[M+H]^+$ calcd. for $C_{17}H_{15}N_3S_2$ (325.451 g/mol); found: 326 (M+1), 325 (M^+), 324 (M-1), 292, 282, 207, 97, 45. Anal. calcd.: C, 62.74; H, 4.65; N, 12.91; S, 19.70. Found: C, 62.77; H, 4.70; N, 12.95; S, 19.58.

2.2.2. 4-(3-Methylthiophen-2-yl)-8-[(3-methylthiophen-2-yl) methylidene]-5,6,7,8-tetra-hydroquinazolin-2-amine (4 g)

Yellow solid; mp 163–4 °C; yield 71%; FTIR (ATR) (ν cm^{-1}) 3308 and 3178 (NH_2), 3080 (aromatic ring, =C–H), 2970–2859 (cyclic ring, C–H), 1608 (heteroaromatic ring, C=N), 1531 (C=C), 1437 (C–N), 709 (C–S); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.82 (1H, m, cyclohexyl-CH_2), 2.20 (3H, s, thienyl-CH_3), 2.46 (3H, s, thienyl-CH_3), 2.56 (2H, m, cyclohexyl-CH_2), 2.89 (2H, m, cyclohexyl-CH_2), 5.30 (2H, s, NH_2), 6.92 (1H, d, J = 5.0 Hz, Ar–H), 6.97 (1H, d, J = 5.1 Hz, Ar–H), 7.34 (1H, d, J = 5.1 Hz, Ar–H), 7.38 (1H, d, J = 5.1 Hz, Ar–H), 8.36 (1H, s, vinyl H); MS: m/z $[M+H]^+$ calcd. for $C_{19}H_{19}N_3S_2$ (353.504 g/mol); found: 354 (M+1), 353 (M^+), 352 (M-1), 338, 320, 296, 255, 242, 177, 111, 45. Anal. calcd.: C, 64.55; H, 5.42; N, 11.89; S, 18.14. Found: C, 64.60; H, 5.48; N, 11.92; S, 18.00.

2.2.3. 4-(5-Methylthiophen-2-yl)-8-[(5-methylthiophen-2-yl) methylidene]-5,6,7,8-tetra-hydroquinazolin-2-amine (4 h)

Yellow solid; mp 156–8 °C; yield 75%; FTIR (ATR) (ν cm^{-1}) 3390 and 3307 (NH_2), 3095 (aromatic ring, =C–H), 2949 (cyclic ring, C–H), 1619 (heteroaromatic ring, C=N), 1532 (heteroaromatic ring, C=C), 1450 and 1434 (C–N), 715 and 699 (C–S); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.95 (1H, m, cyclohexyl-CH_2), 2.17 (3H, s, thienyl-CH_3), 2.48 (3H, s, thienyl-CH_3), 2.67 (2H, m, cyclohexyl-CH_2), 2.91 (2H, m, cyclohexyl-CH_2), 5.03 (2H, s, NH_2), 6.63 (1H, d, J = 5.0 Hz, Ar–H), 6.74 (1H, d, J = 5.0 Hz, Ar–H), 6.96 (1H, d, J = 5.1 Hz, Ar–H), 7.30 (1H, d, J = 5.0 Hz, Ar–H), 8.16 (1H, s, vinyl H); MS: m/z $[M+H]^+$ calcd. for $C_{19}H_{19}N_3S_2$ (353.504 g/mol); found: 354 (M+1), 353 (M^+), 352 (M-1), 338, 320, 296, 242, 111, 45. Anal. calcd.: C, 64.55; H, 5.42; N, 11.89; S, 18.14. Found: C, 64.58; H, 5.47; N, 11.93; S, 18.02.

2.2.4. 6-Methyl-4-(thiophen-2-yl)-8-(thiophen-2-ylmethylidene)-5,6,7,8-tetrahydroquin-azolin-2-amine (4i)

Yellow solid; mp 148–9 °C; yield 62%; FTIR (ATR) (ν cm^{-1}) 3307 and 3189 (NH_2), 3100 (aromatic ring, =C–H), 2948–2864 (cyclic ring, C–H), 1619 (heteroaromatic ring, C=N), 1531 (heteroaromatic ring, C=C), 1450 (C–N), 715 (C–S); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.21 (3H, d, J = 6.5 Hz, cyclohexyl-CH_3), 1.95 (1H, m, cyclohexyl-CH), 2.55 (2H, dd, J = 14.8; 12.7 Hz, cyclohexyl-CH_2), 3.20 (2H, brd, J = 14.3 Hz, cyclohexyl-CH_2), 5.00 (2H, s, NH_2), 7.15 (1H, t, J = 4.5; 4.1 Hz, Ar–H), 7.18 (1H, t, J = 4.6; 4.0 Hz, Ar–H), 7.34 (1H, brd, J = 5.0 Hz, Ar–H), 7.47 (1H, d, J = 5.1 Hz, Ar–H), 7.52 (1H, brd, J = 5.0 Hz, Ar–H), 7.56 (1H, brd, J = 5.0 Hz, Ar–H), 7.31 (1H, s, vinyl H); MS: m/z $[M+H]^+$ calcd. for $C_{18}H_{17}N_3S_2$ (339.478 g/mol); found: 339 (M+1), 338 (M^+), 306, 296, 207, 110, 45. Anal. calcd.: C, 63.68; H, 5.05; N, 12.38; S, 18.89. Found: C, 63.74; H, 5.11; N, 12.43; S, 18.72.

2.2.5. 6-Methyl-4-(3-methylthiophen-2-yl)-8-[(3-methylthiophen-2-yl)methylidene]-5,6,7,8-tetrahydroquinazolin-2-amine (4j)

Yellow solid; mp 160–1 °C; yield 69%; FTIR (ATR) (ν cm^{-1}) 3300 and 3183 (NH_2), 3060 (aromatic ring, =C–H), 2921–2864 (aliphatic ring, C–H), 1622 (heteroaromatic ring, C=N), 1531 (heteroaromatic ring, C=C), 1435 (C–N), 708 (C–S); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.09 (3H, d, J = 6.5 Hz, cyclohexyl-CH_3), 1.95 (1H, m, cyclohexyl-CH), 2.19 (3H, s, thienyl-CH_3), 2.22 (2H, dd, J = 15,7; 12.7 Hz, cyclohexyl-CH_2), 2.45 (3H, s, thienyl-CH_3), 3.17 (2H, brd, J = 16.4 Hz, cyclohexyl-CH_2), 4.96 (2H, s, NH_2), 6.93 (1H, d, J = 5.1 Hz, Ar–H), 6.97 (1H, d, J = 5.0 Hz, Ar–H), 7.33 (1H, d, J = 5.1 Hz, Ar–H), 7.37 (1H, d, J = 5.0 Hz, Ar–H), 8.35 (1H, s, vinyl H); MS: m/z $[M+H]^+$ calcd. for $C_{20}H_{21}N_3S_2$ (367.531 g/mol); found: 369(M+2), 368 (M+1), 367 (M^+), 352, 338, 310, 256, 239, 111, 97, 45. Anal. calcd.: C, 65.36; H, 5.76; N, 11.43; S, 17.45. Found: C, 65.40; H, 5.81; N, 11.48; S, 17.31.

2.2.6. 6-Methyl-4-(5-methylthiophen-2-yl)-8-[(5-methylthiophen-2-yl)methylene]-5,6,7,8-tetrahydroquinazolin-2-amine (4 k)

Yellow solid; mp 153–4 °C; yield 72%; FTIR (ATR) (ν cm^{-1}) 3320 and 3187 (NH_2), 3095 (aromatic ring, =C–H), 2956–2869 (aliphatic ring, C–H), 1621 (heteroaromatic ring, C=N stretch), 1532, C=C), 1452 (C–N), 719 (C–S); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.21 (3H, d, J = 6.5 Hz, cyclohexyl-CH_3), 1.95 (1H, m, cyclohexyl-CH), 2.22 (1H, dd, J = 15,7; 12.7 Hz, cyclohexyl-CH_2), 2.42 (3H, s, thienyl-CH_3), 2.55 (3H, s, thienyl-CH_3), 3.10 (2H, dd, J = 16.2; 14.1 Hz, cyclohexyl-CH_2), 5.33 (2H, s, NH_2), 6.80 (1H, d, J = 5.1 Hz, Ar–H), 6.87 (1H, d, J = 5.0 Hz, Ar–H), 7.20 (1H, d, J = 5.1 Hz, Ar–H), 7.47 (1H, d, J = 5.0 Hz, Ar–H), 7.99 (1H, s, vinyl H); $C_{20}H_{21}N_3S_2$ (367.531 g/mol); found: 369(M+2), 368 (M+1), 367 (M^+), 352, 338, 310, 256, 239,

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