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Synthesis of some new 2,3-disubstituted-4(3H)quinazolinone derivatives

F. Hassanzadeh¹, M. Rahmani Khajouei¹, G.H. Hakimelahi¹,², E. Jafari¹ and G.A. Khodarahmi¹,²

¹Department of Medicinal Chemistry and Isfahan Pharmaceutical Sciences Research Center, School of Pharmacy and Pharmaceutical Science, Isfahan University of Medical Sciences, Isfahan, I.R.Iran.
²Institute of Chemistry, Academia Sinica, Nankang, Taipei, Taiwan.

Abstract

Quinazolinones are interesting materials because of their valuable biological effects. In this study some new 2,3-disubstituted-4(3H)quinazolinone derivatives were synthesized from anthranilic acid in six steps by introducing a new chiral center to the aliphatic side chain of the quinazolinone. In the last step, a single acylation on the hydrazine moiety afforded final compounds. The structures of compounds were confirmed by IR, ¹H NMR and Mass spectra.

Keywords: Anthranilic acid; 4(3H)-Quinazolinone; Synthesis

INTRODUCTION

Synthesis of different classes of heterocyclic molecules is one of the most important targets in the synthetic organic chemistry. Among the nitrogen-containing heterocyclic compounds, quinazolinones (Fig. 1) have attracted interest of many researchers because, introduction of various substituents to different positions of quinazolinones have produced compounds with valuable biological activities. Some of their most frequently reported biological properties include cytotoxic, antibacterial, antifungal, anticonvulsant, antitubercular, anti-HIV, antiviral, anti-inflammatory and antihistaminic activities (1-5). Other properties of quinazolinones which have been reported in the literature are antihelmentic, CNS depressant, antidiabetic, antiallergic, antihistaminic, analgesic and hypolipidemic effects (6-10).

Quinazolinones are also the main component of nearly 150 natural alkaloids existing in some families of plants, animals and microorganisms (11). Febrifugine and isofebrifugine which are known as antimalarial agents, are two wellknown natural alkaloids with quinazoline structure (Fig. 2) (3). Several synthetic methods have been reported for preparing these pharmacologically active substances (12). The synthesis of quinazolinones may be performed by cyclization of benzene or pyrimidine substrates

Fig. 1. 4(3H)-Quinazolinone chemical structure

Fig. 2. Representative examples of natural quinazolinones
Fig. 3. General reaction scheme for preparation of the final compounds.
Synthesis of some new 2,3-disubstituted-4(3H)quinazolinone derivatives

In the present study, anthranilic acid as starting material was reacted with butyryl chloride to produce N-butyryl anthranilic acid followed by a ring closure in acetic anhydride to afford the corresponding benzoxazinone. The benzoxazinone was subsequently refluxed with two different amines to give the corresponding quinazolinones. The quinazolinones were brominated and subsequent treatment with phenyl hydrazine afforded novel hydrazid derivatives as the first class of final compounds. Subsequently, acylation of these derivatives with various acyl chlorides was performed successfully to obtain second group of novel quinazolinones as substituted hydrazides.

MATERIALS AND METHODS

Instrumentation
Melting points were determined in open capillaries using electrothermal 9200 melting point apparatus and are uncorrected. The IR spectra were determined by a WQF-510 FT-IR spectrophotometer using potassium bromide technique. \(^1\)HNMR spectra were recorded in CDCl\(_3\) solution on Bruker 400 or 500 MHz spectrometers. Mass spectra were measured on a Shimadzu Mass spectrometer using EI\(^+\) technique.

Preparation of compounds
In this study, we have prepared some new 4(3H)-quinazolinone derivatives from anthranilic acid \(\text{I}\) by a six-step procedure (Fig. 3). Anthranilic acid was reacted with butyryl chloride to obtain the corresponding amides. The amides were reacted with acetic anhydride to obtain benzoxazin-4(\(\text{one}\)) \(\text{3}\) as crystalline product.

The benzoxazinone was subsequently refluxed with two different amines to give the corresponding quinazolinones \(\text{4a}\) and \(\text{4b}\). The quinazolinones were brominated \(\text{(5a, 5b)}\) and subsequent treatment with phenyl hydrazine afforded \(\text{6a}\) and \(\text{6b}\). Finally \(\text{6a}\) and \(\text{6b}\) were reacted with different acid chlorides to obtain compounds \(\text{7a_1-7a_6}\) and \(\text{7b_1-7b_7}\). These compounds were purified by column chromatography or preparative thin layer chromatography (PTLC) using several solvent systems. The structures of synthesized compounds were confirmed by IR, \(^1\)HNMR, and Mass spectra.

All atoms in the chemical structures of the final compounds have been numerically assigned for the ease of interpretation of the \(^1\)HNMR results (Fig. 4, 5).

RESULTS

Details of preparation procedures and chemistry of synthesized compounds
Compounds \(\text{2}\) and \(\text{3}\) were prepared as described by Eissa and coworkers (14). Compound \(\text{4a}\) was synthesized as reported by Kacker and coworkers (15) and compounds \(\text{4b, 5a}\) and \(\text{5b}\) were prepared based on the method used by Finer and coworkers (16).
3-phenyl-2-[(1- (2-phenylhydrazinyl) propyl) quinazolin-4(3H)-one (6a)]

Phenylhydrazin (3.62 ml, 0.04 mol) was added to a solution of compound 5a (3.43 g, 0.01 mol) in ethanol (15 ml). The reaction mixture was refluxed for 6 h. After cooling the mixture, the precipitated product was filtered off and crystallized from ethanol to obtain compound 6a, as white crystals, yield: 30%. m.p 216-217°C, (Found : M 370, C23H22N4O requires 370) νmax, 3350, 2933, 2871 (R-H), 1660 (C=O) cm-1; 1HNMR δH (400 MHz ; CDCl3) 8.33 (1H, d, J=8.0 Hz, H-C5 Ar), 7.75-7.85 (2H, m, H-C7, H-C8 Ar), 7.44-7.55 (3H, m, H-C10, H-C12, H-C6 Ar), 7.25-7.40 (4H, m, H-C14, H-C16, H-C10, H-C12 Ar), 7.10-7.25 (4H, m, H-C13, H-C11, H-C9, H-C15 Ar), 3.4-3.6 (1H, brs, H-C14), 1.8-2.1 (4H, m, C13-CH3, H-C15-H), 0.6-0.8 (3H, brs, H-C16).

3-benzyl-2-[(1- (2-phenylhydrazinyl) propyl) quinazolin-4(3H)-one (6b)]

Phenylhydrazin (3.62 ml, 0.04 mol) and a solution of compound 5b (3.57 g, 0.01 mol) in ethanol (15 ml) were reacted as described for 6a to give 6b as white crystal, yield: 50%. m.p.188-189°C, (Found : M 440, C27H28N4O2 requires 440) νmax, 3270 (NH), 3064 (Ar-H), 2972, 2929 (R-H); 1HNMR δH (500 MHz ; CDCl3) 8.27 (1H, brs, H-C5 Ar), 7.70-7.80 (2H, m, H-C7, H-C8 Ar), 7.44-7.55 (3H, m, H-C10, H-C12, H-C6 Ar), 7.25-7.40 (4H, m, H-C14, H-C16, H-C10, H-C12 Ar), 7.10-7.25 (4H, m, H-C13, H-C11, H-C9, H-C15 Ar), 3.4-3.6 (1H, brs, H-C14), 1.8-2.1 (4H, m, C13-CH3, H-C15-H), 1.5-1.8 (1H, m, H-C15-H), 0.6-0.8 (3H, brs, H-C16).

General procedure for the preparation of final compounds 7a1-6

Various acid chlorides (1.1 mmol) were added drop wise to a solution of compound 6a (0.37 g, 1 mmol) in dichloromethane (40 ml) and triethylamine (0.21 ml, 1.5 mmol). The reaction mixture was stirred at 0°C for 4-5 h and purified by column or thin layer chromatography to give the final compounds 7a1-6 as white or yellow powders, yields: 25-30%.

N′-(1-(4-oxo-3-phenyl-3,4-dihydroquinazolin-2-yl)propyl)-N-phenylacetohydrazide (7a1)

The compound was purified by PTLC (chloroform: methanol; 100:1), m.p 110-111°C (Found: M 440, C27H28N4O2 requires 440) νmax, 3280 (NH), 3064 (Ar-H), 2972, 2871 (R-H); 1HNMR δH (500 MHz ; CDCl3) 8.27 (1H, brs, H-C5 Ar), 7.70-7.85 (2H, m, H-C7, H-C8 Ar), 7.4-7.55 (3H, m, H-C10, H-C12, H-C6 Ar), 7.25-7.40 (4H, m, H-C14, H-C16, H-C10, H-C12 Ar), 7.10-7.25 (4H, m, H-C13, H-C11, H-C9, H-C15 Ar), 3.4-3.6 (1H, brs, H-C14), 1.8-2.1 (4H, m, C13-CH3, H-C15-H), 1.5-1.8 (1H, m, H-C15-H), 0.6-0.8 (3H, brs, H-C16).

N′-(1-(4-oxo-3-phenyl-3,4-dihydroquinazolin-2-yl)propyl)-N-phenylbutyrohydrazide (7a2)

The compound was purified by PTLC (chloroform: methanol; 100:1), m.p 110-111°C (Found: M 440, C27H28N4O2 requires 440) νmax, 3280 (NH), 3064 (Ar-H), 2972, 2871 (R-H); 1HNMR δH (500 MHz ; CDCl3) 8.27 (1H, brs, H-C5 Ar), 7.70-7.85 (2H, m, H-C7, H-C8 Ar), 7.4-7.55 (3H, m, H-C10, H-C12, H-C6 Ar), 7.25-7.40 (4H, m, H-C14, H-C16, H-C10, H-C12 Ar), 7.10-7.25 (4H, m, H-C13, H-C11, H-C9, H-C15 Ar), 3.4-3.6 (1H, brs, H-C14), 1.8-2.1 (4H, m, C13-CH3, H-C15-H), 1.5-1.8 (1H, m, H-C15-H), 0.6-0.8 (3H, brs, H-C16).

N′-(1-(4-oxo-3-phenyl-3,4-dihydroquinazolin-2-yl)propyl)-N-phenylbenzohydrazide (7a3)

The compound was purified by PTLC (chloroform: methanol; 100:1), m.p 110-111°C (Found: M 440, C27H28N4O2 requires 440) νmax, 3300, 2928 (R-H), 1660 (C=O); 1HNMR δH (500 MHz ; CDCl3) 8.27 (1H, brs, H-C5 Ar), 7.70-7.85 (2H, m, H-C7, H-C8 Ar), 7.4-7.55 (4H, m, H-C10, H-C12, H-C6 Ar), 7.22-7.40 (3H, m, H-C9, H-C10, H-C12 Ar), 7.10-7.22 (4H, m, H-C13, H-C11, H-C9, H-C15 Ar), 6.55 (1H, brs, H-N17), 3.4-3.5 (1H, brs, H-C14), 2.0-2.15 (2H, m, C19-CH2, 1,85-1.95 (1H, m, H-C15-H), 1.6-1.7 (3H, m, C19-CH2-CH2-CH3), 0.75-0.85 (3H, brs, C19-CH2-CH2-CH3), 0.65-0.75 (3H, brs, H-C16).

N′-(1-(4-oxo-3-phenyl-3,4-dihydroquinazolin-2-yl)propyl)-N-phenylbenzoyldrazide (7a4)

The compound was purified by column chromatography (petroleum ether: ethyl acetate: gradient), m.p 110-111°C (Found: M 474, C30H26N4O2 requires 474) νmax, 3270 (NH), 3064 (Ar-H), 2966, 2927 (R-H), 1685(C=O) cm-1; 1HNMR δH (400 MHz ; CDCl3) 8.31(1H, d, J=8.0 Hz, H-C5 Ar), 7.75-7.85 (2H, brs, H-C7, H-C8 Ar), 7.35-7.55 (4H,
The compound was purified by column chromatography (petroleum ether: ethyl acetate; gradient), m.p 127-128°C (Found: M 509, C_{30}H_{25}ClN_{4}O_{2} requires 509) ν_{max} 3251 (NH), 3070 (Ar-H), 2962, 2873 (R-H), 1680 (C=O) cm⁻¹; ¹H NMR δ_{H} (400 MHz; CDCl₃) 8.31 (1H, d, J=8.0 Hz, H-C⁵ Ar), 7.77-7.90 (2H, m, H-C⁴, H-C⁶ Ar), 7.51 (2H, t, J=8.0 Hz, H-C¹⁰, H-C¹₂ Ar), 7.47 (1H, t, J=7.2 Hz, H-C⁶ Ar), 7.4 (1H, t, J=7.6 Hz, H-C¹¹ Ar), 7.05-7.33 (9H, m, H-C⁶, C¹⁹-C₂₀-HCl, H-C¹⁰, H-C¹₂, H-C¹³, H-C¹⁴ Ar), 7.0 (2H, d, J=7.6 Hz, H-C⁹, H-C¹³ Ar), 3.55 (1H, t, J=6.4 Hz, H-C¹⁴), 1.80-1.92 (1H, m, H-C¹⁵-H), 1.65-1.80 (1H, m, H-C¹⁵-H), 0.69 (3H, t, J=7.2 Hz, H-C¹₆).  

4- chloro-N'- (1- (4-oxo-3-phenyl-3,4-dihydro quinazolin -2 -yl) propyl) -N- phenylbenzo hydraze (7a₄)

The compound was purified by column chromatography (petroleum ether: ethyl acetate; gradient), m.p 208-209°C (Found: M 564, C_{30}H_{2₅}N_{₅}O_{₄} requires 564) ν_{max} 3240 (NH), 3095 (Ar-H), 2968, 2927 (R-H), 1684 (C=O), 1541, 1344 (NO₂) cm⁻¹; ¹H NMR δ_{H} (500 MHz; CDCl₃) 8.94 (1H, s, C⁹-C-CH-N=N-CH₂-C₂H₂NO₂ Ar), 8.2-8.4 (3H, m, H-C⁵, C¹⁹-C₂₀-CH₂ Ar), 7.8-7.9 (2H, m, H-C¹⁰, H-C¹₂ Ar), 7.50-7.64 (3H, m, H-C¹⁰, H-C¹₂, H-C⁶ Ar), 7.47 (1H, t, J=7.5 Hz, H-C¹₁ Ar), 7.05-7.40 (7H, m, H-C⁹, H-C¹₀, H-C¹₂, H-C¹³, H-C¹₁⁻¹⁻⁵⁻⁹⁻¹³⁻¹⁵⁻¹⁹⁻²³⁻²⁷⁻⁻₃₁⁻⁻₃₅⁻⁻₃₉⁻⁻⁴₃⁻⁻₄₇⁻⁻₅₁⁻⁻⁵₅⁻⁻⁵₉⁻⁻⁶₃ Ar), 1.8-2.0 (1H, m, H-C¹⁵-H), 1.60-1.75 (1H, m, H-C¹⁵-H), 0.6-0.8 (3H, brs, H-C¹₆).  

General procedure for the preparation of final compounds 7b₁₅

To a solution of compound 6b (0.384 g, 1 mmol) in dichloromethane (40 ml) was added triethylamine (0.21 ml, 1.5 mmol) and different acid chlorides (1.1 mmol). The reaction mixture was stirred at 0°C for 4-5 h and was purified by column or thin layer chromatography to give the final compounds 7b₁₅ as white or yellow powders, yields: 25-30%. 

N'- (1- (3-benzyl-4-oxo-3,4-dihydroquinazolin-2-yl)propyl)-N-phenylacetohydraze (7b₁)

The compound was purified by PTLC (chloroform: methanol; 100:1) m.p 149-150°C (Found: M 426, C₂₈H₂₅N₄O₂ requires 426) ν_{max} 3244 (NH), 3064 (Ar-H), 2968, 2870 (R-H), 1674 (C=O) cm⁻¹; ¹H NMR δ_{H} (400 MHz ; CDCl₃) 8.29 (1H, d, J=7.6 Hz, H-C⁵ Ar), 7.65-7.78 (2H, m, H-C⁹, H-C⁸ Ar), 7.48 (1H, d, J=7.6 Hz, H-C⁶ Ar ), 7.17-7.40 (6H, m, H-C¹⁰, H-C¹¹, H-C¹², H-C¹₀⁻¹⁻⁵⁻⁹⁻¹³⁻¹⁵⁻¹⁹⁻²³⁻²⁷⁻⁻₃₁⁻⁻₃₅⁻⁻₃₉⁻⁻⁴₃⁻⁻₄₇⁻⁻₅₁⁻⁻⁵₅⁻⁻⁵₉⁻⁻⁶₃ Ar ), 7.12 (2H, d, J=5.6 Hz, H-C⁹, H-C¹³ Ar), 6.75-6.85 (2H, m, H-C⁹, H-C³ Ar), 6.57 (1H, d, J=5.6 Hz, H-C¹₁⁻⁻⁵⁻⁹⁻¹³⁻¹⁵⁻¹⁹⁻²³⁻²⁷⁻⁻₃₁⁻⁻₃₅⁻⁻₃₉⁻⁻⁴₃⁻⁻₄₇⁻⁻₅₁⁻⁻⁵₅⁻⁻⁵₉⁻⁻⁶₃ Ar ), 5.57 (1H, d, J=16.2 Hz, H-C²₀⁻⁻₂₄⁻⁻₂₈⁻⁻₃₂⁻⁻₃₆⁻⁻₄₀⁻⁻₄₄⁻⁻₄₈⁻⁻₅₂⁻⁻₅₆⁻⁻₆₀ Ar), 4.92 (1H, d, J=15.2 Hz, H-C²₀⁻⁻₂₄⁻⁻₂₈⁻⁻₃₂⁻⁻₃₆⁻⁻₄₀⁻⁻₄₄⁻⁻₅₀⁻⁻₅₄⁻⁻₅₈⁻⁻₆₂ Ar), 3.85 (1H, dd, J=7.6 Hz, J=6.8 Hz, H-C¹₄⁻⁻¹₈ Ar), 2.90-2.05 (1H, m, H-C¹₅⁻⁻¹₉⁻⁻²₃⁻⁻₂₇⁻⁻₃₁⁻⁻₃₅⁻⁻₃₉⁻⁻₄₃⁻⁻₄₇⁻⁻₅₁⁻⁻⁵₅⁻⁻⁵₉⁻⁻⁶₃ Ar), 1.8-1.9 (3H, m, C¹⁹-C₂₀-H), 1.6-1.8 (1H, m, H-C¹⁵⁻⁻¹₉⁻⁻²₃⁻⁻₂₇⁻⁻₃₁⁻⁻₃₅⁻⁻₃₉⁻⁻₄₃⁻⁻₄₇⁻⁻₅₁⁻⁻⁵₅⁻⁻⁵₉⁻⁻⁶₃ Ar), 0.5-0.6 (3H, brs, H-C¹₆).  

N'- (1- (3-benzyl-4-oxo-3,4-dihydroquinazolin-2-yl)propyl)-N-phenylbutyrohydraze (7b₂)

The compound was purified by PTLC (chloroform: methanol; 100:1), m.p 168-169°C (Found: M 454, C₂₉H₂₉N₄O₂ requires 454) ν_{max} 3246 (NH), 3055 (Ar-H), 2964, 2927.
(R-H), 1668 (C=O) cm⁻¹; ¹HNMR δH (500 MHz ; CDCl₃) 8.29 (1H, d, J=7.5 Hz, H-C⁵ Ar), 7.6-7.8 (2H, m, H-C⁷, H-C⁸ Ar), 7.48 (1H, t, J=7.5 Hz, H-C₁⁴), 4.88 (1H, d, J=17 Hz, H-C₂⁰-H), 7.05-7.2 (2H, t, J=6.8 Hz, H-C₁⁰, H-C₁³ Ar), 6.75-6.90 (2H, t, J=6.4 Hz, H-C₉, H-C₁³ Ar), 5.62 (1H, d, J=7.2 Hz, H-C₁⁰), 1.9-2.2 (1H, m, H-C₁⁵-H), 1.9-2.2 (3H, m, C₁⁹-CH₂-H-C₁⁵-H), 0.75-0.90 (3H, t, J=6.8 Hz, H-C₁⁶).

N⁺- (1- (3-benzyl-4-oxo-3,4-dihydroquinazolin-2-yl)propyl)-N-phenylbenzohydrazide (7b₃)

The compound was purified by column chromatography (petroleum ether: ethyl acetate; gradient), m.p 165-166°C (Found: M 502, C₃₂H₃₀N₄O₂ requires 502) νmax, 3290 (NH), 3055 (Ar-H), 2925, 2852 (R-H), 1676 (C=O) cm⁻¹; ¹HNMR δH (500 MHz ; CDCl₃) 8.2-8.4 (1H, t, J=6.8 Hz, H-C₉, H-C₈ Ar), 7.48 (1H, t, J=7.5 Hz, H-C⁶ Ar), 7.10-7.45 (9H, m, H-C₁⁰, H-C₁¹, H-C₁², H-C₁³, H-C₁⁵, H-C₁⁶, H-C₉, H-C₁³ Ar), 4.96 (1H, d, J=12.5 Hz, H-C₂⁰-H), 3.95-3.9 (1H, t, J=6.4 Hz, H-C₁⁴), 1.9-2.2 (3H, t, J=6.8 Hz, H-C₁⁵-H), 1.70-1.82 (1H, m, H-C₁⁵-H), 0.53 (3H, t, J=7.2 Hz, H-C₁⁶).

N⁺- (1- (3-benzyl-4-oxo-3,4-dihydroquinazolin-2-yl)propyl)-4-chloro-N-phenylbenzohydrazide (7b₄)

The compound was purified by column chromatography (petroleum ether: ethyl acetate; gradient), m.p 131-132°C (Found: M 533, C₃₁H₂₈N₄O₂ requires 533) νmax, 3275 (NH), 3064 (Ar-H), 2928, 2871(R-H), 1674 (C=O), 1552, 1344 (NO₂) cm⁻¹; ¹HNMR δH (500 MHz ; CDCl₃) 8.35 (1H, d, J=7.5 Hz, H-C⁵ Ar), 8.04 (2H, t, J=8.0 Hz, C₁⁹-C-CH₂-CNO₂-Ar), 7.75-7.85 (2H, m, H-C₇, H-C₈ Ar), 7.54 (1H, t, J=8.0 Hz H-C₆ Ar), 7.15-7.40 (8H, m, H-C₉, H-C₁₀, H-C₁¹, H-C₁², H-C₁³, H-C₉, H-C₁³ Ar), 4.96 (1H, d, J=12.5 Hz, H-C₂⁰-H), 3.95-3.9 (1H, t, J=6.4 Hz, H-C₁⁴), 1.9-2.2 (1H, m, H-C₁⁵-H), 1.70-1.82 (1H, m, H-C₁⁵-H), 0.53 (3H, t, J=7.2 Hz, H-C₁⁶).

N⁺- (1- (3-benzyl-4-oxo-3,4-dihydroquinazolin-2-yl)propyl)-3, 5- dinitro -N- phenylbenzohydrazide (7b₃)

The compound was purified by column chromatography (petroleum ether: ethyl acetate; gradient), m.p 120-121°C (Found: M 578, C₃₁H₂₆N₆O₆ requires 578) νmax, 3267 (NH), 3095 (Ar-H), 2927, 2873 (R-H), 1666 (C=O), 1539, 1344 (NO₂) cm⁻¹; ¹HNMR δH (500 MHz ; CDCl₃) 8.94 (1H, s, C₁⁹-C-CH₂-CNO₂-Ar), 8.2-8.6 (3H, m, C₁⁹-C-CH₂-CNO₂-Ar), 7.80-7.92 (2H, m, H-C⁵, H-C₆, H-C₇, H-C₈, H-C₉, H-C₁¹, H-C₁², H-C₁³, H-C₁⁵, H-C₁⁶, H-C₂⁰-H), 4.96 (1H, d, J=12.5 Hz, H-C₂⁰-H), 3.95-3.9 (1H, t, J=6.4 Hz, H-C₁⁴), 1.9-2.2 (3H, t, J=6.8 Hz, H-C₁⁵-H), 0.53 (3H, t, J=7.2 Hz, H-C₁⁶).

N⁺- (1- (3-benzyl-4-oxo-3,4-dihydroquinazolin-2-yl)propyl)-N,2-diphenylacetoxyhydrizide (7b₅)

The compound was purified by column chromatography (petroleum ether: ethyl acetate; gradient), m.p 165-166°C (Found: M 502, C₃₂H₃₀N₂O₂ requires 502) νmax, 3290 (NH), 3055 (Ar-H), 2925, 2852 (R-H), 1676 (C=O) cm⁻¹; ¹HNMR δH (500 MHz ; CDCl₃) 8.2-8.4 (1H, t, J=6.8 Hz, H-C₉, H-C₈ Ar), 7.48 (1H, t, J=7.5 Hz, H-C⁶ Ar), 7.10-7.45 (9H, m, H-C₁⁰, H-C₁¹, H-C₁², H-C₁³, H-C₉, H-C₁³ Ar), 4.96 (1H, d, J=12.5 Hz, H-C₂⁰-H), 3.95-3.9 (1H, t, J=6.4 Hz, H-C₁⁴), 1.9-2.2 (3H, t, J=6.8 Hz, H-C₁⁵-H), 1.70-1.82 (1H, m, H-C₁⁵-H), 0.53 (3H, t, J=7.2 Hz, H-C₁⁶).
**DISCUSSION**

To prepare N-butyryl anthranilic acid 2, anthranilic acid 1 was treated with butyryl chloride in a nucleophilic substitution reaction.

In the second step, the amide 2 was reacted with acetic anhydride to accelerate ring closure and water removal to get 1,3 benzoxazine-4(one) 3 as a crystalline product.

In the third step 1,3 benzoxazine-4(one) 3 was refluxed with two different amines to give the corresponding quinazolinone 4a and 4b as a result of a nucleophilic substitution and subsequently dehydration of compound.

Brominated quinazolinones 5a and 5b (Fig. 3) were prepared by treating the quinazolinones with bromine in glacial acetic acid. After bromination, a chiral centre was introduced at the position 14 of the propyl side chain. This chiral centre also presents in all compounds synthesized from 5a and 5b as illustrated in Fig. 4, 5.

According to 1HNMR data, aromatic hydrogens at positions 9 and 13 of the phenyl ring (ring A) are seen as two separate doublets in 1HNMR spectra due to the neighboring effects of this chiral center (Fig. 4, 5). This neighboring effect is also observed for two hydrogens of the benzylic CH2 next to the ring B and the aliphatic CH2 at position 15 of the propyl side chain (Fig. 4, 5).

In the fifth step, treatment of brominated quinazolinone 5a and 5b with phenyl hydrazine afforded compounds 6a and 6b. In this step, the Br atom has been displaced as a leaving group with NH group of phenyl hydrazine as a result of a nucleophilic substitution (Fig. 6).

To obtain the final compounds, compounds 6a and 6b were reacted with different acid chlorides via a nucleophilic substitution (Fig. 6).

From two available positions on hydrazine for acylation, substitution of acyl group on nitrogen atom next to the phenyl ring, position 18 (Fig. 5), was confirmed by 1HNMR. The singlet hydrogen’s signal of phenyl-bonded NH has been disappear after substitution and doublet hydrogen’s signal of CH-bonded NH, position 17, has been shifted to down field region due to the deshielding effect of carbonyl functional group.

**CONCLUSION**

In the current work, quinazolinones as biologically active substances were conjugated with another well known moiety (phenyl hydrazine) in a multi step reaction procedure to produce interesting novel hydrazide derivatives of quinazolinone. These compounds will be subjected to various biological evaluations to investigate their possible activities.

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**Fig. 6.** The proposed mechanism for the production of final compounds.
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