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Original Article

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

F. Hassanzadeh[1], M. Rahmani Khajouei[1], G.H. Hakimelahi[1,2], E. Jafari[1] and G.A. Khodarahmi[1,*]

[1]Department of Medicinal Chemistry and Isfahan Pharmaceutical Sciences Research Center, School of Pharmacy and Pharmaceutical Science, Isfahan University of Medical Sciences, Isfahan, I.R.Iran.
[2]Institute 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)quinqzolinone 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, ^{1}HNMR 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 quinazolinone 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

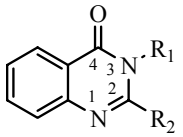
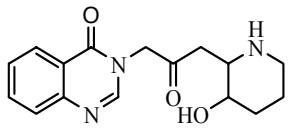
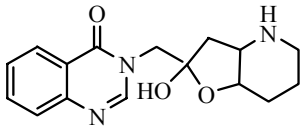


Fig. 1. 4(3H)-Quinazolinone chemical structure



Febrifugine



Isofebrifugine

Fig. 2. Representative examples of natural quiazolinones

*Corresponding author: Dr. G.A. Khodarahmi
Tel. 0098 311 7922561, Fax. 0098 311 6680011
Email: khodarahmi@pharm.mui.ac.ir

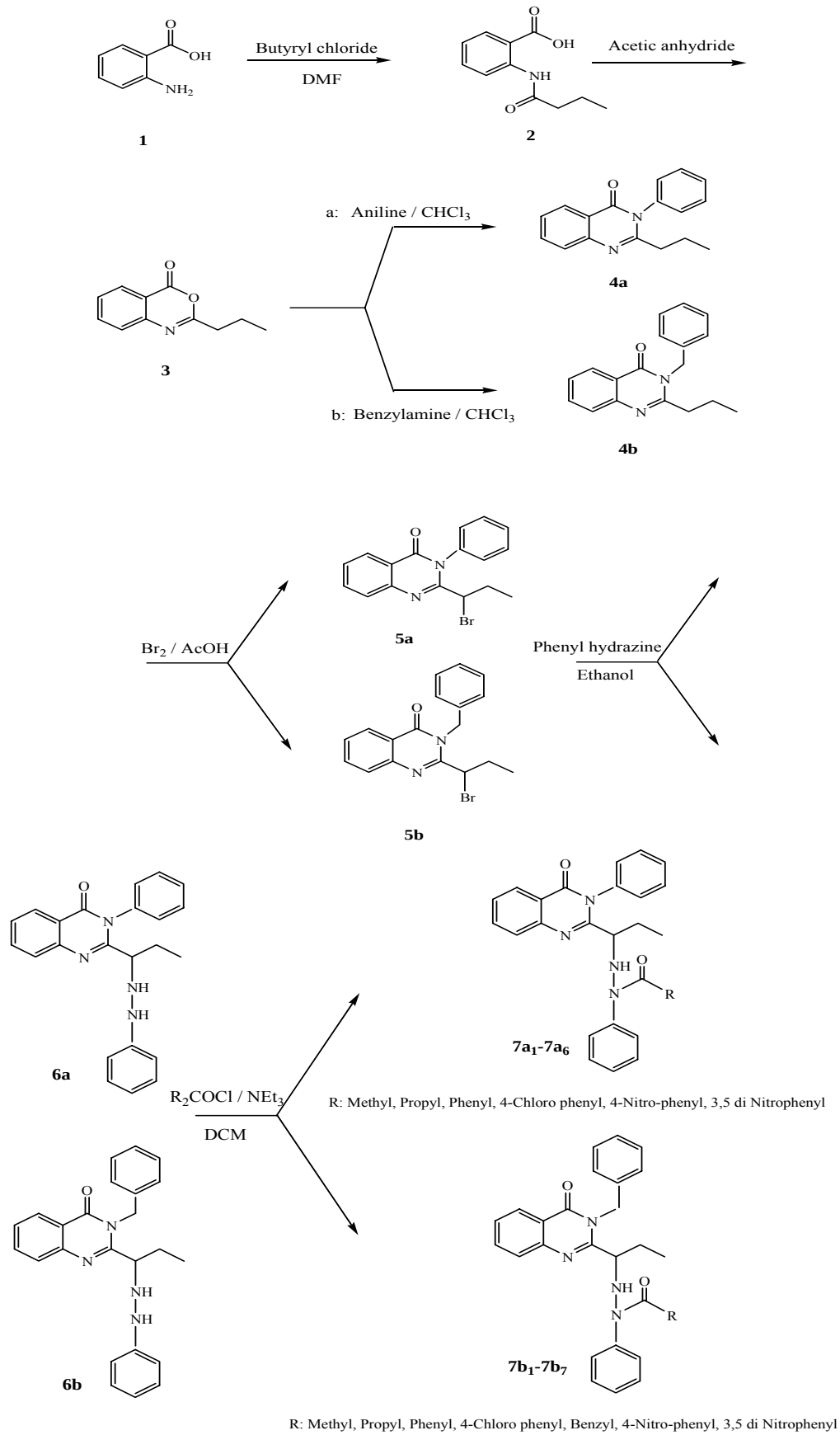
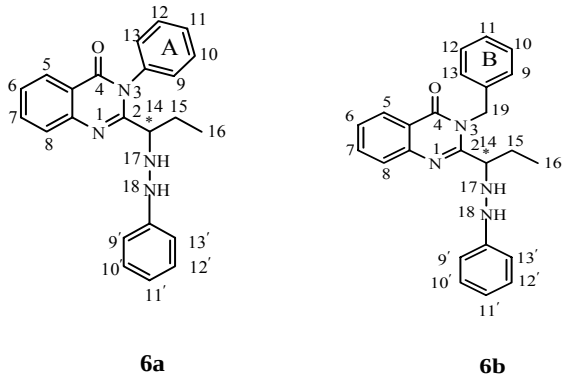
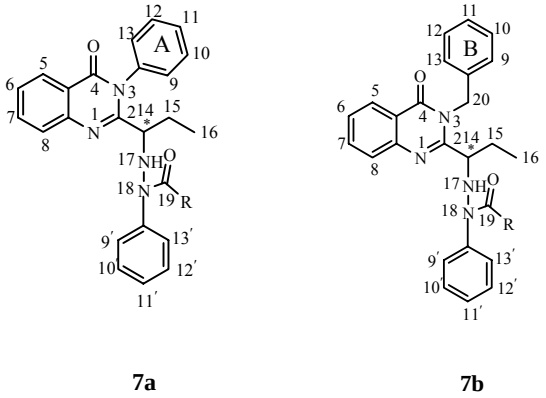


Fig. 3. General reaction scheme for preparation of the final compounds



6a **6b**

Fig. 4. Chemical structures of compounds **6a** and **6b**



7a **7b**

Fig. 5. Chemical structures of compounds **7a** and **7b**

containing appropriate substituents, by using benzoxazin-4(one) (benzoxazinone) or by modification of appropriate derivatives of other heterocyclic systems (13). Among various methods for quinazolinone synthesis, application of benzoxazinone has been repeatedly reported.

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. Replacement of oxygen in benzoxazinone ring system with primary amines resulted in production of 2,3-disubstituted quinazolinones. Synthesized quinazolinones have either phenyl or benzyl moiety at position 3 (Fig. 1) due to the application of aniline or benzyl amine as primary amines. Substitution of phenyl hydrazine on alkyl side chain at position 2 (Fig. 1) of quinazolinone backbone resulted in production of 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 quinazolinons 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 **1** 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(one) **3** as crystalline product.

The benzoxazinone was subsequently refluxed with two different amines to give the corresponding quinazolinones **4a** and **4b**. The quinazolinones were brominated (**5a, 5b**) and subsequent treatment with phenyl hydrazine afforded **6a** and **6b**. Finally **6a** and **6b** were reacted with different acid chlorides to obtain compounds **$7a_1$-$7a_6$** and **$7b_1$-$7b_7$**. 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 **2** and **3** were prepared as described by Eissa and coworkers (14). Compound **4a** was synthesized as reported by Kacker and coworkers (15) and compounds **4b**, **5a** and **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, $C_{23}H_{22}N_4O$ requires 370) ν_{max}, 3309, 3265 (NH), 3051 (Ar-H), 2931, 2870 (R-H), 1660 (C=O) cm^{-1}; ^{1}HNMR δ_H (400 MHz ; $CDCl_3$) 8.33 (1H, d, J=8.0 Hz, H-C^5 Ar), 7.83 (1H, t, J=8.0 Hz, H-C^7 Ar), 7.78 (1H, d, J=8.0 Hz, H-C^8 Ar), 7.55 (2H, t, J=6.8 Hz, H-C^{10}, H-C^{12} Ar), 7.46 (1H, t, J=7.2 Hz, H-C^6 Ar), 7.36 (1H, t, J=7.2 Hz, H-C^{11} Ar), 7.28(1H, d, J=7.6 Hz, H-C^9 Ar), 7.18 (2H, t, J=7.6 Hz, H-$C^{10'}$, H-$C^{12'}$ Ar), 7.00(1H ,d, J=7.6 Hz, H-C^{13} Ar), 6.88 (2H, d, J=8.0 Hz, H-$C^{9'}$, H-$C^{13'}$Ar), 6.79 (1H, t, J=7.2 Hz, H-$C^{11'}$ Ar), 5.53 (1H, s, H-N^{18}), 4.52 (1H, d, J=9.6 Hz, H-N^{17}), 3.65-3.75 (1H, m, H-C^{14}), 1.59-1.70(1H, m, H-C^{15}-H'), 1.40-1.53 (1H, m, H-C^{15}-H'), 0.87 (3H, t, J=7.2 Hz, H-C^{16}).

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.p188-189°C, (Found: M 384, $C_{24}H_{24}N_4O$ requires 384) ν_{max}, 3350, 3284 (NH), 3051 (Ar-H), 2933, 2871 (R-H), 1660 (C=O) cm^{-1}; ^{1}HNMR δ_H (400 MHz ; $CDCl_3$) 8.34 (1H, d, J=8.0 Hz, H-C^5 Ar), 7.80 (1H, t, J=8.0 Hz, H-C^7 Ar), 7.72 (1H, d, J=8.0 Hz, H-C^8 Ar), 7.52 (1H, t, J=7.2 Hz, H-C^6 Ar) , 7.08-7.23 (7H, m, C^{19}-C_6H$_5$, H-$C^{10'}$, H-$C^{12'}$ Ar), 6.83 (2H, d, J=8.0 Hz, H-$C^{9'}$, H-$C^{13'}$Ar), 6.77(1H, t, J=7.2 Hz, H-$C^{11'}$ Ar), 5.48(1H, d, J=16 Hz, H-C^{19}-H') , 5.34 (1H, s, H-N^{18}), 5.17(1H, d, J=15.6 Hz, H-C^{19}-H'), 4.62 (1H, d, J=9.2 Hz, H-N^{17}), 4.07-4.17 (1H, m, H-C^{14}), 1.48-1.70 (2H, m, H-C^{15}), 1.09 (3H, t, J=7.2 Hz, H-C^{16}).

General procedure for the preparation of final compounds **7a$_{1\text{-}6}$**

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 **7a$_{1\text{-}6}$** as white or yellow powders, yields: 25-30%.

N'-(1-(4-oxo-3-phenyl-3,4-dihydroquinazolin-2-yl)propyl)-N-phenylacetohydrazide (**7a$_1$**)

The compound was purified by PTLC (chloroform: methanol; 100:1), m.p 123-124°C (Found: M 412, $C_{25}H_{24}N_4O_2$ requires 412) ν_{max}, 3257(NH), 3064 (Ar-H), 2964, 2929 (R-H), 1689 (C=O) cm^{-1}; ^{1}HNMR δ_H (500 MHz ; $CDCl_3$) 8.29 (1H, d, J=5.0 Hz, H-C^5 Ar), 7.75-7.85 (2H, m, H-C^7, H-C^8 Ar), 7.44-7.55 (3H, m, H-C^{10}, H-C^{12}, H-C^6, Ar), 7.25-7.40 (4H, m, H-C^{11}, H-C^9, H-$C^{10'}$, H-$C^{12'}$ Ar), 7.10-7.25 (4H, m, H-C^{13}, H-$C^{11'}$, H-$C^{9'}$, H-$C^{13'}$ Ar), 3.4-3.6 (1H, brs, H-C^{14}), 1.8-2.1 (4H, m, C^{19}-C$\underline{H}_3$, $\underline{H}$-C^{15}-H'), 1.5-1.8 (1H, m, H-C^{15}-$\underline{H}$'), 0.6-0.8 (3H, brs, H-C^{16}).

N'-(1-(4-oxo-3-phenyl-3,4-dihydroquinazolin-2-yl)propyl)-N-phenylbutyrohydrazide (**7a$_2$**)

The compound was purified by PTLC (chloroform: methanol; 100:1), m.p 118-119°C (Found: M 440, $C_{27}H_{28}N_4O_2$ requires 440) ν_{max}, 3280 (NH), 3064 (Ar-H), 2929, 2871 (R-H), 1687 (C=O) cm^{-1}; ^{1}HNMR δ_H (500 MHz ; $CDCl_3$) 8.27 (1H, brs, H-C^5 Ar), 7.70-7.85 (2H, m, H-C^7, H-C^8 Ar), 7.40-7.55 (4H, m, H-C^{10}, H-C^{12}, H-C^6, H-C^{11} Ar), 7.22-7.40 (3H, m, H-C^9, H-$C^{10'}$, H-$C^{12'}$ Ar),7.10-7.22 (4H, m, H-C^{13}, H-$C^{11'}$, H-$C^{9'}$, H-$C^{13'}$ Ar), 6.55 (1H, brs, H-N^{17}), 3.4-3.5 (1H, brs, H-C^{14}), 2.0-2.15 (2H, brs, C^{19}-C$\underline{H}_2$), 1.85-1.95 (1H, m, $\underline{H}$-C^{15}-H'), 1.6-1.7 (3H, m, C^{19}-CH_2-C$\underline{H}_2$, H-C^{15}-$\underline{H}$'), 0.75-0.85 (3H, brs, C^{19}-CH_2-CH_2-C$\underline{H}_3$), 0.65-0.75 (3H, brs, H-C^{16})

N'-(1-(4-oxo-3-phenyl-3,4-dihydroquinazolin-2-yl)propyl)-N-phenylbenzohydrazide (**7a$_3$**)

The compound was purified by column chromatography (petroleum ether: ethyl acetate; gradient), m.p 110-111°C (Found: M 474, $C_{30}H_{26}N_4O_2$ requires 474) ν_{max}, 3270 (NH), 3064 (Ar-H), 2966, 2927 (R-H), 1685(C=O) cm^{-1}; ^{1}HNMR δ_H (400 MHz ; $CDCl_3$) 8.31(1H, d, J=8.0 Hz, H-C^5 Ar) , 7.75-7.85 (2H, brs, H-C^7, H-C^8 Ar), 7.35-7.55 (4H,

m, H-C^{10}, H-C^{12}, H-C^{6} , H-C^{11} Ar), 7.29 (1H, d, J=7.6 Hz , H-C^{9} Ar), 7.04-7.27 (9H, m, C^{19}-$C_6\underline{H}_5$, H-$C^{10'}$, H-$C^{12'}$, H-C^{13}, H-$C^{11'}$Ar), 6.99 (2H, d, J=7.2 Hz, H-$C^{9'}$, H-$C^{13'}$ Ar), 6.50-6.65 (1H, brs, H-N^{17}), 3.56 (1H, t, J=6.4 Hz, H-C^{14}), 1.80-1.95 (1H, m, $\underline{H}$-C^{15}-H′), 1.60-1.75 (1H, m, H-C^{15}-$\underline{H}$′), 0.68 (3H, t, J=7.2 Hz, H-C^{16}).

4- chloro-N'- (1- (4-oxo-3- phenyl-3, 4-dihydro quinazolin -2 -yl) propyl) -N- phenylbenzo hydraide (**7a$_4$**)

The compound was purified by column chromatography (petroleum ether: ethyl acetate; gradient), m.p 127-128°C (Found: M 509, $C_{30}H_{25}ClN_4O_2$ requires 509) ν_{max}, 3251 (NH), 3070 (Ar-H), 2962,2873 (R-H), 1680 (C=O) cm^{-1}; ^{1}HNMR δ_H (400 MHz ; $CDCl_3$) 8.31 (1H, d, J=8.0 Hz, H-C^5 Ar), 7.77-7.90 (2H, m, H-C^7, H-C^8 Ar), 7.51 (2H, t, J=8.0 Hz, H-C^{10}, H-C^{12} Ar), 7.47(1H, t, J=7.2 Hz, H-C^6 Ar), 7.4(1H, t, J=7.6 Hz, H-C^{11} Ar), 7.05-7.33(9H, m, H-C^9, C^{19}-$C_6\underline{H}_4$Cl, H-$C^{10'}$, H-$C^{12'}$, H-C^{13}, H-$C^{11'}$ Ar), 7.0 (2H, d, J=7.6 Hz, H-$C^{9'}$, H-$C^{13'}$ Ar), 3.55(1H, t, J=6.4 Hz, H-C^{14}), 1.80-1.92 (1H, m, $\underline{H}$-C^{15}-H′), 1.65-1.80 (1H, m, H-C^{15}-$\underline{H}$′), 0.69 (3H, t, J=7.2 Hz, H-C^{16}).

4- nitro-N'- (1- (4-oxo-3- phenyl-3, 4-dihydro quinazolin -2- yl) propyl) -N- phenylbenzo hydrazide(**7a$_5$**)

The compound was purified by column chromatography (petroleum ether: ethyl acetate; gradient), m.p 191-192°C (Found: M 519, $C_{30}H_{25}N_5O_4$ requires 519) ν_{max}, 3288 (NH), 3064 (Ar-H), 2966, 2925 (R-H), 1685 (C=O), 1522, 1344 (NO_2) cm^{-1}; ^{1}HNMR δ_H (500 MHz ; $CDCl_3$) 8.34 (1H, d, J=7.9 Hz, H-C^5 Ar), 8.02 (2H, d, J=8.3 Hz, C^{19}-C-CH-C$\underline{H}$ Ar), 7.8-7.9 (2H, m, H-C^7, H-C^8 Ar), 7.5-7.6 (2H, m, H-C^{10}, H-C^{12} Ar), 7.48 (1H, t, J=7.2 Hz, H-C^6 Ar), 7.43 (1H, t, J=7.5 Hz, H-C^{11} Ar), 7.15-7.35 (7H, m, C^{19}-C-C$\underline{H}$,H-C^9 ,H-$C^{10'}$, H-$C^{12'}$ H-C^{13}, H-$C^{11'}$ Ar), 7.05 (2H, d, J=5.5 Hz, H-$C^{9'}$, H-$C^{13'}$ Ar), 3.55-3.62 (1H, m, $\underline{H}$-C^{14}), 1.85-1.97 (1H, m, $\underline{H}$-C^{15}-H′), 1.65-1.75 (1H, m, H-C^{15}-$\underline{H}$′), 0.69 (3H,t, J=5.0 Hz, H-C^{16}).

3,5-dinitro-N'- (1-(4-oxo-3-phenyl-3,4-dihydro quinazolin -2 -yl) propyl) -N- phenylbenzo hydrazide (**7a$_6$**)

The compound was purified by column chromatography (petroleum ether: ethyl acetate; gradient), m.p 208-209°C (Found: M 564, $C_{30}H_{24}N_6O_6$ requires 564) ν_{max}, 3240 (NH), 3095 (Ar-H), 2968, 2927 (R-H), 1684 (C=O), 1541, 1344 (NO_2) cm^{-1}; ^{1}HNMR δ_H (500 MHz; $CDCl_3$) 8.94 (1H, s, C^{19}-C-CH-CNO_2-C$\underline{H}$-CNO_2 Ar), 8.2-8.4 (3H, m, H-C^5, C^{19}-C-C$\underline{H}$ Ar), 7.8-7.9 (2H, m, H-C^7, H-C^8 Ar), 7.50-7.64 (3H, m, H-C^{10}, H-C^{12}, H-C^6, Ar), 7.47(1H, t, J=7.5 Hz, H-C^{11} Ar), 7.05-7.40 (7H, m, H-C^9, H-$C^{10'}$, H-$C^{12'}$, H-C^{13}, H-$C^{11'}$, H-$C^{9'}$, H-$C^{13'}$ Ar), 3.5-3.64 (1H,m, H-C^{14}), 1.8-2.0 (1H, m, $\underline{H}$-C^{15}-H), 1.60-1.75 (1H, m, H-C^{15}-$\underline{H}$′), 0.6-0.8 (3H, brs, H-C^{16}).

***General procedure for the preparation of final compounds* 7b$_{1-7}$**

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 **7b$_{1-7}$** as white or yellow powders, yields: 25-30%.

N'- (1- (3-benzyl-4-oxo-3,4-dihydroquinazolin-2-yl)propyl)-N-phenylacetohydrazide (**7b$_1$**)

The compound was purified by PTLC (chloroform: methanol; 100:1) m.p 149-150°C (Found: M 426, $C_{26}H_{26}N_4O_2$ requires 426) ν_{max}, 3244 (NH), 3064 (Ar-H), 2968, 2870 (R-H), 1674 (C=O) cm^{-1}; ^{1}HNMR δ_H (400 MHz ; $CDCl_3$) 8.29 (1H, d, J=7.6 Hz, H-C^5 Ar), 7.65-7.78 (2H, m, H-C^7, H-C^8 Ar), 7.48(1H, t, J=7.6 Hz, H-C^6 Ar), 7.17-7.40 (6H, m, H-$C^{10'}$, H-$C^{11'}$, H-$C^{12'}$, H-C^{10}, H-C^{11}, H-C^{12} Ar) , 7.12 (2H, d, J=5.6 Hz, H-$C^{9'}$, H-$C^{13'}$ Ar), 6.75-6.85 (2H, m, H-C^9, H-C^{13} Ar), 6.57 (1H, d, J=5.6 Hz, H-N^{17}), 5.57 (1H, d, J=16 Hz, $\underline{H}$-C^{20}-H′), 4.92 (1H, d, J=15.2 Hz, H-C^{20}-$\underline{H}$′), 3.85 (1H, dd, J=7.6 Hz, J=6.8 Hz, H-C^{14}), 1.90-2.05 (1H, m, $\underline{H}$-C^{15}-H′), 1.8-1.9 (3H, m, C^{19}-C$\underline{H}_3$) 1.6-1.8 (1H, m, H-C^{15}-$\underline{H}$′), 0.5-0.6 (3H, brs, H-C^{16}).

N'- (1- (3-benzyl-4-oxo-3,4-dihydroquinazolin-2-yl)propyl)-N-phenylbutyrohydrazide (**7b$_2$**)

The compound was purified by PTLC (chloroform: methanol; 100:1), m.p 168-169°C (Found: M 454, $C_{28}H_{30}N_4O_2$ requires 454) ν_{max}, 3246 (NH), 3055 (Ar-H), 2964, 2927

(R-H), 1668 (C=O) cm^{-1}; ^{1}HNMR δ_H (500 MHz ; $CDCl_3$) 8.29 (1H, d, J=7.5 Hz, H-C^5 Ar), 7.6-7.8 (2H, m, H-C^7, H-C^8 Ar), 7.48 (1H, t, J=7.5 Hz, H-C^6 Ar),7.2-7.4 (6H, m, H-$C^{10'}$, H-$C^{11'}$, H-$C^{12'}$, H-C^{10}, H-C^{11}, H-C^{12} Ar), 7.05-7.2 (2H, brs, H-$C^{9'}$, H-$C^{13'}$ Ar), 6.75-6.90 (2H, brs, H-C^9, H-C^{13} Ar),6.5-6.7(1H. brs, H-N^{17}), 5.62 (1H, d, J=17.0 Hz, H-C^{20}-H′),4.88 (1H, d, J=14.0 Hz, H-C^{20}-H′), 3.80-3.95 (1H, m, H-C^{14}), 1.9-2.2 (3H, m, C^{19}-CH_2, H-C^{15}-H′), 1.5-1.8 (3H, m, H-C^{15}-H′, C^{19}-CH_2-CH_2), 0.75-0.90 (3H, brs, C^{19}-CH_2-CH_2-CH_3), 0.5-0.7 (3H, brs, H-C^{16}).

N'- (1- (3-benzyl-4-oxo-3,4-dihydroquinazolin-2-yl)propyl) -N-phenylbenzohydrazide (**7b$_3$**)

The compound was purified by column chromatography (petroleum ether: ethyl acetate; gradient), m.p 166-167°C (Found: M 488, $C_{31}H_{28}N_4O_2$ requires 488) ν_{max}, 3242 (NH), 3057 (Ar-H), 2931, 2873 (R-H) cm^{-1}; ^{1}HNMR δ_H (400MHz ; $CDCl_3$) 8.31 (1H, d, J=8.0 Hz, H-C^5 Ar), 7.70-7.80 (2H, m, H-C^7, H-C^8 Ar), 7.48 (1H, t, J=7.6 Hz, H-C^6 Ar), 7.1-7.3 (11H, m, C^{19}-C_6H_5 , H-$C^{10'}$, H-$C^{11'}$, H-$C^{12'}$, H-C^{10}, H-C^{11}, H-C^{12} Ar), 7.01 (2H, d, J=7.6 Hz, H-$C^{9'}$, H-$C^{13'}$ Ar), 6.9 (2H, d, J=6.4 Hz, H-C^9, H-C^{13} Ar), 6.5-6.7 (1H, brs, H-N^{17}), 5.67 (1H, d, J=16.4 Hz, H-C^{20}-H′) ,4.96 (1H, d, J=16 Hz, H-C^{20}-H′), 4.05 (1H, t, J=6.4 Hz, H-C^{14}), 1.9-2.2 (1H, m, H-C^{15}-H′), 1.70-1.82 (1H, m, H-C^{15}-H′), 0.53 (3H, t, J=7.2 Hz, H-C^{16}).

N'- (1- (3-benzyl-4-oxo-3,4-dihydroquinazolin-2-yl)propyl)-4-chloro-N-phenylbenzohydrazide (**7b$_4$**)

The compound was purified by column chromatography (petroleum ether: ethyl acetate; gradient), m.p 130-131°C (Found: M 523, $C_{31}H_{27}ClN_4O_2$ requires 523) ν_{max}, 3249 (NH), 3068 (Ar-H), 2962, 2873 (R-H), 1680 (C=O) cm^{-1}; ^{1}HNMR δ_H (400 MHz ; $CDCl_3$) 8.32 (1H, d, J=8.0 Hz, H-C^5 Ar), 7.67-7.80 (2H, m, H-C^7, H-C^8 Ar), 7.5 (1H, t, J=6.8 Hz, H-C^6 Ar), 7.08-7.30 (10H, m, C^{19}-C_6H_4Cl, H-$C^{10'}$, H-$C^{11'}$, H-$C^{12'}$, H-C^{10}, H-C^{11}, H-C^{12} Ar), 6.97 (2H, d, J=7.2 Hz, H-$C^{9'}$, H-$C^{13'}$ Ar), 6.91 (2H, d, J=6.0 Hz, H-C^9, H-C^{13} Ar), 6.59 (1H, d, J=7.2 Hz, H-N^{17}), 5.58 (1H, d, J=16.4 Hz, H-C^{20}-H′), 5.0 (1H,d, J=15.6 Hz, H-C^{20}-H′), 3.97-4.1 (1H, m, H-C^{14}), 1.85-2.0 (1H, m, H-C^{15}-H′) ,1.65-1.80 (1H, m, H-C^{15}-H′), 0.55 (3H, t, J=7.2 Hz, H-C^{16}).

N'- (1- (3-benzyl-4-oxo-3,4-dihydroquinazolin-2-yl)propyl)-N,2-diphenylacetohydrazide (**7b$_5$**)

The compound was purified by column chromatography (petroleum ether: ethyl acetate; gradient), m.p 165-166°C (Found: M 502, $C_{32}H_{30}N_4O_2$ requires 502) ν_{max}, 3290 (NH), 3055 (Ar-H), 2925, 2852 (R-H), 1676 (C=O) cm^{-1}; ^{1}HNMR δ_H (500 MHz ; $CDCl_3$) 8.2-8.4 (1H, brs, H-C^5 Ar), 7.6-7.8 (2H, m, H-C^7, H-C^8 Ar), 7.48 (1H, t, J=7.5 Hz, H-C^6 Ar), 7.10-7.45 (9H, m, H-$C^{10'}$, H-$C^{11'}$, H-$C^{12'}$, H-C^{10}, H-C^{11}, H-C^{12} , C^{19}-CH_2-C-CH-CH-CH Ar), 6.95-7.1 (4H, m, H-$C^{9'}$, H-$C^{13'}$, C^{19}-CH_2-C-CH Ar), 6.75-6.9 (2H, brs, H-C^9, H-C^{13} Ar), 5.61 (1H, d,J=17 Hz, H-C^{20}-H′) , 4.8 (1H, d, J=12.5 Hz, H-C^{20}-H′), 3.85-3.95 (1H, m, H-C^{14}), 3.4-3.6 (2H, brs, C^{19}-CH_2), 1.85-2.0 (1H, m, H-C^{15}-H′), 1.6-1.8 (1H, m, H-C^{15}-H′), 0.5-0.6 (3H, brs, H-C^{16}).

N'- (1- (3-benzyl-4-oxo-3,4-dihydroquinazolin-2-yl)propyl)-4-nitro-N-phenylbenzohydrazide (**7b$_6$**)

The compound was purified by column chromatography (petroleum ether: ethyl acetate; gradient), m.p 131-132°C (Found: M 533, $C_{31}H_{27}N_5O_4$ requires 533) ν_{max}, 3275 (NH), 3064 (Ar-H), 2928, 2871(R-H), 1674 (C=O), 1522, 1344 (NO_2) cm^{-1}; ^{1}HNMR δ_H (500 MHz ; $CDCl_3$) 8.35 (1H, d, J=7.5 Hz, H-C^5 Ar), 8.04 (2H, d, J=8.0 Hz, C^{19}-C-CH-CH-CNO_2 Ar), 7.75-7.85 (2H, m, H-C^7, H-C^8 Ar), 7.54 (1H, t, J=8.0 Hz H-C^6 Ar), 7.15-7.40 (8H, m, C^{19}-C-CH, H-$C^{10'}$, H-$C^{11'}$, H-$C^{12'}$, H-C^{10}, H-C^{11}, H-C^{12} Ar), 6.92-7.05(4H, m, H-$C^{9'}$, H-$C^{13'}$, H-C^9, H-C^{13} Ar), 5.5 (1H, d, J=15 Hz, H-C^{20}-H′), 5.12 (1H, d, J=15 Hz, H-C^{20}-H′), 4.0-4.1 (1H, brs, H-C^{14}), 1. 9-2.0 (1H, m, H-C^{15}-H′), 1.75-1.9 (1H, m, H-C^{15}-H′), 0.55-0.65 (3H, brs, H-C^{16}).

N'- (1- (3-benzyl-4-oxo-3,4-dihydroquinazolin-2- yl) propyl) -3, 5- dinitro -N- phenylbenzo hydrazide (**7b$_7$**)

The compound was purified by column chromatography (petroleum ether: ethyl acetate; gradient), m.p 120-121°C (Found: M 578, $C_{31}H_{26}N_6O_6$ requires 578) ν_{max}, 3267 (NH), 3095 (Ar-H), 2927, 2873 (R-H), 1666 (C=O), 1539, 1344 (NO_2) cm^{-1}; ^{1}HNMR δ_H (500 MHz ; $CDCl_3$) 8.94 (1H, s, C^{19}-C-CH-CNO_2-CH-CNO_2 Ar), 8.2-8.6 (3H, m, C^{19}-C-CH-NO_2, H-C^5 Ar), 7.80-7.92 (2H, m, H-C^7,

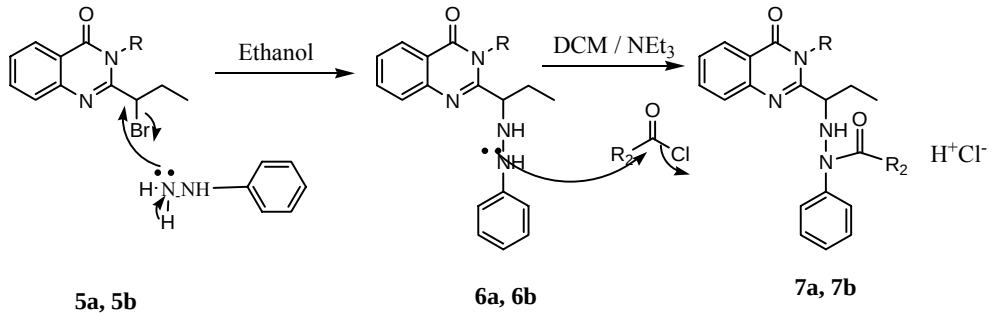


Fig. 6. The proposed mechanism for the production of final compounds

H-C[8] Ar), 7.58 (1H, t, J=7.4 Hz, H-C[6] Ar), 7.27-7.45(6H, m, H-C[10′], H-C[11′], H-C[12′], H-C[10], H-C[11], H-C[12] Ar), 7.2 (2H, d, J=6.0 Hz, H-C[9′], H-C[13′] Ar), 7.1 (2H, d, J=6.0 Hz, H-C[9], H-C[13] Ar), 5.4-5.6 (1H, brs, H-C[20]-H′), 5.1-5.3 (1H, brs, H-C[20]-H′), 4.0-4.2 (1H, brs, H-C[14]), 1.75-2.0 (1H, m, H-C[15]-H′), 1.5-1.7 (1H, m, H-C[15]-H′), 0.65-0.80 (3H, brs, H-C[16]).

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 ^{1}HNMR data, aromatic hydrogens at positions 9 and 13 of the phenyl ring (ring A) are seen as two separate doublets in ^{1}HNMR 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 CH_2 next to the ring B and the aliphatic CH_2 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 ^{1}HNMR. The singlet hydrogen's signal of phenyl-bonded NH has been disappeared 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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REFERENCES

1. Khosropour RA, Mohammadpoor-Baltork I, Ghorbankhani H. Bi (TFA) 3-[nbp] FeCl4: a new, efficient and reusable promoter system for the synthesis of 4 (3H)-quinazolinone derivatives. Tetrahedron Lett. 2006;47:3561-3564.
2. Raghavendra NM, Thampi P, Gurubasavarajaswamy PM, Sriram D. Synthesis and antimicrobial activity of some novel substituted 2-imidazolyl-N-(4-oxo-quinazolin-3(4H)-yl) acetamides. Chem Pharm Bull. 2007;55:1615-1619.
3. Philipova I, Dobrikov G, Krumova K, Kaneti J. Convenient synthesis of some 2 substituted 4 (3H) quinazolinone derivatives. J Heterocyclic Chem. 2006;43:1057-1063.
4. Laddha SS, Wadodkar SG, Meghal SK. Studies on some biologically active substituted 4 (3H)-quinazolinones. Part 1. Synthesis, characterization and anti-inflammatory-antimicrobial activity $ of 6, 8-disubstituted 2-phenyl-3-[substituted-benzothiazol-2-yl]-4 (3H)-quinazolinones. Arkivoc. 2006;11:1-20.
5. Zhou Y, Murphy DE, Sun Z, Gregor VE. Novel parallel synthesis of N- (4-oxo-2-substituted -4- H-quinazolin -3- yl) -substituted sulfonamides. Tetrahedron Lett. 2004;45:8049-8051.
6. Dinakaran M, Selvam P, DeClercq E, Sridhar SK. Synthesis, antiviral and cytotoxic activity of 6-bromo-2, 3-disubstituted-4 (3H)-quinazolinones. Biol Pharm Bull. 2003;26:1278-1282.
7. Nanda AK, Ganguli S, Chakraborty R. Antibacterial activity of some 3-(Arylideneamino)-2-phenyl quinazoline-4 (3H)-ones: synthesis and preliminary QSAR studies. Molecules. 2007;12:2413-2426.
8. Ghabrial SS, Gaber HM. Dipolar cycloaddition reactions with quinazolinones: A new route for the synthesis of several annelated pyrrolo and pyridazinoquinazoline derivatives. Molecules. 2003; 8:401-410.
9. Refaie FM, Esmat AY, Gawad SMA, Ibrahim AM, Mohamed MA. The antihyperlipidemic activities of 4 (3H) quinazolinone and two halogenated derivatives in rats. Lipids Health Dis. 2005;4:22.
10. Mourad AE, Aly AA, Farag HH, Beshr EA. Microwave assited synthesis of triazoloquinazolinones and benzimidazoqinazolinones. Beilstein J Org Chem. 2007;3:1-5.
11. Mhaske SB, Argade NP. The chemistry of recently isolated naturally occurring quinazolinone alkaloids. Tetrahedron. 2006;62:9787-9826.
12. Connolly DJ, Cusack D, O'Sullivan TP, Guiry PJ. Synthesis of quinazolinones and quinazolines. Tetrahedron. 2005;61:10153-10202.
13. Brown DJ. Quinazolines (Supplement I). New York: John Wiley & Sons; 1997. p. 1-5.
14. Eissa A, El-Mebvally A, El-Hashash M, El-Gohary A. Synthesis and biological evaluation of some new 2-propyl-4 (3H)-quinazolinone derivatives as antibacteria. J Korean Chem Soc. 2008;52:328-337.
15. Kacker IK, Zaheer SH. Potential analgesics. I. Synthesis of substituted 4-quinazolones. J Indian Chem Soc. 1951;28:344-346.
16. Finer JT, Bergnes G, Smith WW, Chabala JC, Feng B. Methods and Compositions utilizing quinazolinones. US Patents 6545004; 2003.