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Synthesis of New 3-Substiuted Quinazolin-4(3H)-one Compounds

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Abstract: Quinazolin-4(3H)-one is a well-known heterocyclic compound with a unique place in medicinal chemistry, and it has drawn much attention due to its diversified biological activity. In this research we report the synthesis of some quinazolin-4-one derivatives containing acetylenic moiety. The quinazolin-4(3H)-one (1) was synthesized from the reaction of anthranilic acid with formamide under the conventional or microwave irradiation conditions. The quinazolin-4(3H)-one was converted to the corresponding 3-propargyl derivative (2) by its reaction with propargyl bromide in presence of potassium carbonate as a base and acetone as a solvent. The 3-propargyl quinazolin-4(3H)-one (2) was used as a precursor to synthesize new three series of heterocyclic compounds containing quinazolin-4(3H)-one moiety. Compound (2) was treated with ethyl magnesium bromide, then the resulted solution treated immediately with carbon disulfide and sublimed sulfur to synthesize 1,2-dithiol-3-thione compound (3). The 1,2,3-triazole compounds (5a-d) were synthesized by the reaction of compound (2) with alkyl azides (4a-d) according to Click reaction. The Mannich bases (6a-i) were synthesized *via* Mannich reaction by reaction of the acetylenic compound (2) with secondary amines in presence of paraformaldehyde in1,4-dioxane as a solvent. All the synthesized compounds were characterized by physical and spectral measurements.

Keywords: Quinazolin-4-one, 1,2-dithiol-3-thione, 1,2,3-triazole, Click reaction, Mannich reaction

Introduction

Quinazolin-4(3H)-one and its derivatives occupy a distinct position among the heterocyclic compounds and they considered as a building block for a huge number of synthetic and natural products such as alkaloids, agrochemicals, drugs, antibiotic and antimicrobial agents. These compounds have gained great attention owing to their wide and distinct biological and therapeutic activity. Many therapeutic activities were determined for the quinazolin-4(3H)-one derivatives, including anti-bacterial [Hess et al., 1968],[1] antifungal [Ghorab 2000; Bartroli et al., 1998] [2,3] anticancer [Dohle et al., 2018; Abdel-Hamid, 1997; EI-Brollosy et al., 2003; Shab et al., 1995] ,[4-7] anti-HIV [Khili et al, 1994],[8] anti-inflammatory [Shivaram et al, 1998],[9] anticonvulsant [Noureldin et al, 2017],[10] anti-oxidant [Saravanan et al, 2010],[11] anti-obesity [Sasmal et al, 2012].[12] The above facts encouraged us to synthesize several newer quinazolin-4(3H)-one derivatives by incorporating a set of biologically active moieties, such as acetylenic (oxotremorine analog), [Sjoqvist and Gilette, 1965; Leslie and Maxwell, 1904; Tang et al, 1993; Disingrini et al, 2006; Dallanoce et al, 1999],[13-17] 1,2,3-trizole [Xu et al, 2014; Saqlain et al, 2014],[18,19] and 1,2-dithiol-3-thione [Lee et al, 1986; Kensler et al, 1987][20,21] moieties at position-3 of quinazolinone nucleus, in order to improve the efficacy and biological activity of quinazolin-4(3H)-one.

Experimental

Melting points were determined with an open capillary tube by Stuard-SMP30 melting point apparatus, and were uncorrected. Microwave irradiation was performed by microwave oven with power output 900 W. Infrared spectra were recorded as neat on Alfa Bruker ATR- FT.IR Co. Germany, 2003, College of Pharmacy.

^{1}HNMR and ^{13}CNMR spectra were recorded on Bruker Bio Spin 400 MHz spectrometer, Turkey , using TMS as internal standard and (DMSO-d6) as a solvent.

Synthesis of Quinazolin-4(3H)-one (1):

This compound was synthesized *via* two synthetic methods, the conventional method and the green method *via* the free solvent, microwave irradiation.

The Conventional Method:

A mixture of anthranilic acid (0.1 mol, 13.7 g) and formamide (0.5 mol, 22.5 g) was heated on a sand bath at 150-160 ^{o}C for 8h, then left to cool. The resulted precipitate was filtered off, washed thoroughly with water, dried then recrystallized from methanol to afford shiny white powder in 61% yield, m.p. 214-216 ^{o}C.

The Green Method:

In a Pyrex beaker, anthranilic acid (0.1 mol, 13.7 g) and formamide (0.5 mol, 22.5 g) were mixed well. The beaker was covered with a turned over funnel, then placed in the microwave oven and irradiated at two stages: in the first stage the content of the beaker was irradiated with a power of 30% (270 W) for 5 min. then left for 15 min. In the second stage the beaker was subjected to microwave for further 5 min. at a power at a level 50% (450 W), then left to cool to room temperature. The resulted residue was washed thoroughly with water, dried then recrystallize from methanol to give shiny honey crystal in 86.4% yield, m.p. 216-2017 ^{o}C.

Synthesis of 3-Propargylquinazolin-4(3H)-one (2):

A mixture of quinazolin-4(3H)-one (1) (0.005 mol, 0.73 g), propargyl bromide (0.005 mol, 0.59 g) and potassium carbonate (1 g) in dry acetone (15 ml) was refluxed with stirring for 6h, then cooled and poured on 25 ml of an ice-water. The resulted precipitate was filtered off, washed thoroughly with water, dried and recrystallized from ethanol : water (90%) to give hazel shiny needle crystals in 76% yield, mp. 115-117 ^{o}C.

Synthesis of 4-Mercapto-5-[(4'-oxoquinazolin-3'-yl)methyl]-1,2-dithiol-3-thione (3):

Synthesis of Ethyl Magnesium bromide:

To dry magnesium turning (0.008 mol, 0.87 g) in dry diethyl ether (25 ml), a solution of ethyl bromide (0.008 mol, 0.87 g) in 10 ml of dry diethyl ether was dropwise added. The reaction was worked up according to the conventional method for preparation of Grignard reagent [Furniss et al, 1989].[22] After consuming of all magnesium, the mixture was cooled, and a solution of the acetylenic compound (2) (0.008 mol, 1.47 g) in 15 ml of dry diethyl ether was dropwise added with stirring. The stirring was continued for further 0.5h at room temperature to form the solution of magnesium acetylide, which is used immediately to synthesize 4-mercapto-5-[(4'-oxoquinazolin-3'-yl)methyl]-1,2-dithiol-3-thione (3).

Synthesize 4-Mercapto-5-[(4'-oxoquinazolin-3'-yl)methyl]-1,2-dithiol-3-thione (3):

The resulted solution from the previous step was cooled to (0-5 ^{o}C) in an ice-bath, then carbon disulfide (0.008 mol, 0.5 ml) and excess of sulfur (0.026 mol, 0.86 g) were added with stirring. The stirring was continued for further 1h in an ice-bath, and 6h at room temperature. The reaction mixture was filtered and the filtrate acidified with 10% hydrochloric acid. The ether layer was separated and the aqueous layer extracted with (2 * 20 ml) diethyl ether. The ether fractions were collected, dried with magnesium sulfate, filtered and the ether was evaporated to afford the crude 1,2-dithiol-3-thione compound (3) which recrystallized from ethanol to give faint yellow crystals in 65% yield, m.p. 199-200 ^{o}C.

Synthesis of 1-Alkyl-4-[(4'-quinazilin-3-yl)methyl]-1,2,3-triazoles (5a-d):

Synthesis of Alkyl azides (4a-d):

An alkyl halide (0.01mol) was added with stirring to a mixture of sodium azide (0.01 mol, 0.71 g) in (22 ml) of dimethyl sulfoxide (DMSO). The stirring was continued overnight at room temperature. The resulted reaction mixture was added to an ice-water (50 ml), then extracted with (2 *30 ml) diethyl ether. The collected ether fractions were washed with water, then with brine, dried with magnesium sulfated, then evaporated under reduced pressure at room temperature to give an oily product in ~ 90% yield. Their meting points are not measured because the azides classified as explosive materials. The IR spectral data of compounds (4a-d) were shown in Table 1.

Synthesis of 1,2,3-Triazole Derivatives (5a-d) (Click Reaction).

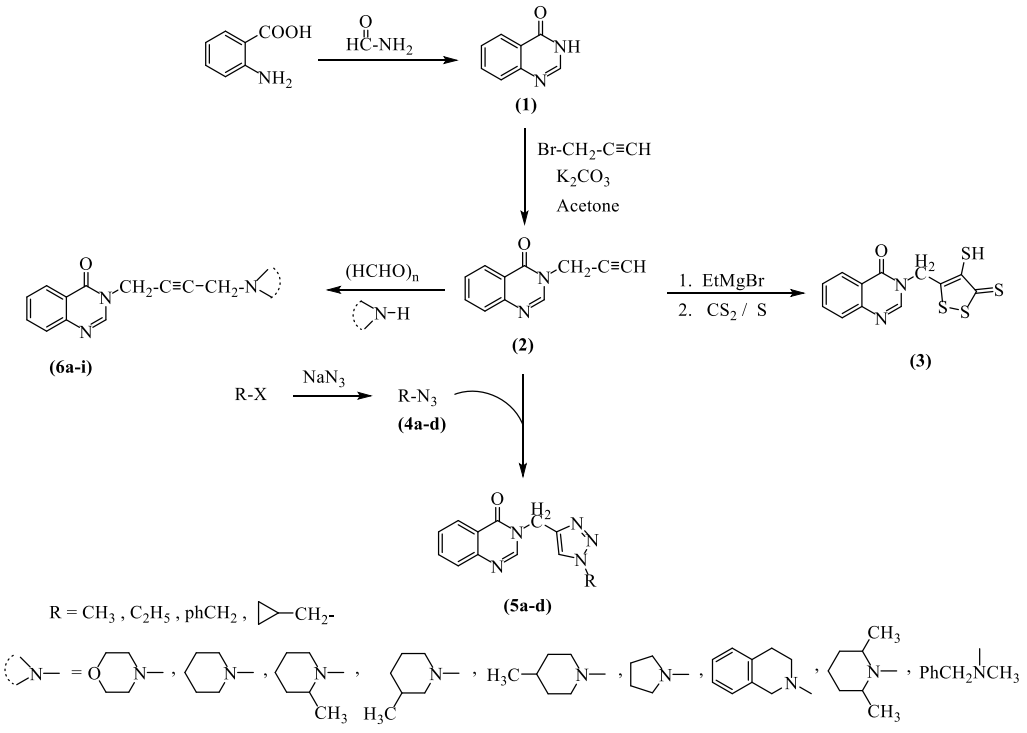
A mixture of acetylenic compound (2) (0.005 mol, 0.92 g), one of alkyl azides (4a-d) and catalytic amount (10 mg) of cuprous chloride in 15 ml of dry toluene was refluxed for 10h. The reaction mixture was filtered then the solvent evaporated and the residue was recrystallized from methanol to give 1,2,3-triazole derivatives (5a-d). The physical and IR spectral data are listed in table 2.

Synthesis of 1-(4'-Oxoquinazolin-3'-yl)-4-disubstituted amino-2-butyne (6a-i): General Procedure:

A mixture of the acetylenic compound (2) (0.03 mole, 0.69 g) and secondary amine (0.036 mole) was cooled to (0 ^{o}C). A solution of paraformaldehyde (0.036 mole, 0.13 g) in dry dioxane free peroxide (16 ml) was added dropwise slowly with stirring and finally catalytic amount of cuprous chloride (0.06 g) was added. After the completion of addition at (0 ^{o}C), 4.5 ml of glacial acetic acid was added in 5min period. The mixture was heated to 90 ^{o}C for 1.5h, then cooled and a cold water (100 ml) was added to the reaction mixture. The mixture was acidified with diluted hydrochloric acid (1:1) to pH=1 with continuous stirring. The mixture was extracted with (2*20 ml) diethyl ether, and the ether fractions were neglected and the aqueous layer was basified with sodium carbonate to pH=9 then extracted with five (20 ml) portion of chloroform. The collected chloroform was dried over magnesium sulfate, filtered and evaporated under reduced pressure to provide the acetylenic Mannich bases (6a-i). The physical and the spectral data were listed in Table 3.

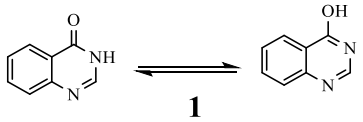
Result and Discussion

The synthetic strategy for this research to obtain the targeted compounds (1-6) is depicted in Scheme 1.



Scheme 1

The first route of this strategy involves the synthesis of the starting material, quinazolin-4(3H)-one (1), which was synthesized from the reaction of one equivalent of anthranilic acid and five equivalents of formamide, either by the conventional method or by the green method *via* the irradiation with microwave radiation. The second method is more favorable than first method because the green method performed in few minutes with high yield (87%), while the conventional method required at least 6h heating at 150-160 ^{o}C with a lower yield (61%). The IR spectrum of compound (1) showed a characteristic absorption bands at 1696 and 1604 Cm^{-1} for C=O bond stretching and C=N bond stretching respectively. The ^{1}HNMR spectrum [Crews et al, 1998][23] of compound (1) showed the following chemical shifts δ (ppm) at: 7.5 (t, 1H, H6) 7.65 (d, 1H, H5), 7.81(t, 1H, H7), 8.11(d, 1H, H8), 8.14 (s, 1H, H2), 12.26 (s, 1H, OH). The spectral data indicate that the compound present as quinazolin-4(3H)-one in the solution and as 4-hydroxyquinazoline in a solid state.



1

Quinazolin-4(3H)-one (1) was converted to its acetylenic derivative (2) *via* alkylation process with propargyl bromide in dry acetone in presence of potassium carbonate. Quinazolin-4(3H)-one (1) is known to be alkylated at either N-3 or oxygen depending on the reaction conditions. In this study, the alkylation of quinazolin-4(3H)-one (1) was occurred at the nitrogen in the 3-position to produce 3-propargyl quinazolin-4(3H)-one (2), on the dependence on the spectral data. The appearance of a characteristic absorption bands at 1657 Cm^{-1} in the IR spectrum for C=O bond stretching supported the alkylation at N-3 position. Moreover, the IR spectrum of compound (2) showed a characteristic absorption bands for the acetylenic moiety at 3214 and 2120 Cm^{-1} for the acetylenic ≡C-H and C≡C bond stretching respectively. The ^{1}HNMR spectrum of compound (2) showed the following chemical shifts, δ (ppm) at: 3.34 (s, 1H, ≡C-H), 4.84 (s, 2H, CH_2), 7.57 (t, 1H, H6), 7.7 (d, 1H, H5), 7.85 (t, 1H, H7), 8.17 (d, 1H, H8), 8.47 (s, 1H, H2). The ^{13}C NMR spectrum shows the following chemical shifts, δ (ppm) at: 35.59 (**C**H_2), 76.1(≡**C**-H), 78.99 (**C**≡C-H), 121.9 (C8), 126.56 (C6), 127.8 (C5), 127.88 (C10), 135.11 (C7), 147.5 (C2), 148.24 (C9), 159.96 (C5). The chemical shift of the C-13 of CH_2 gives a further support for the alkylation at the nitrogen-3. If the alkylation occurred at the oxygen, the spectrum must give a chemical shift at more than 50 ppm.

The acetylenic compound (2) was used as a precursor to synthesize new heterocyclic derivatives of quinazolin-4(3H)-one through three routes. The first route involves the synthesis of 4-mercapto-5-[(4-oxoquinazolin-3-yl)methyl]-1,2-dithiol-3-thione (3), which synthesized by conversion of the acetylenic compound (2) to the corresponding Grignard reagent (acetylide intermediate) by its reaction with ethyl magnesium bromide, then the resulted acetylide intermediate reacted with carbon disulfide in presence of elemental sulfur. The IR spectrum of compound (3) showed an absorption bands at 2447,1153 and 491Cm^{-1} for S-H, C=S and S-S bond stretching respectively, in addition to absorption band at 1645 Cm^{-1} for the C=O bond stretching of the quinazolinone moiety. Moreover, the absorption bands of ≡C-H and C≡C bonds stretching at 3214 and 2120 Cm^{-1} are disappeared from the spectrum, which indicates the acetylenic moiety was converted to the 1,2-dithiol-3-thione moiety. The ^{1}HNMR of compound (3) showed the following chemical shifts δ (ppm) at: 3.46 (s, 1H, SH), 4.85 (s, 2H, CH_2),), 7.63 (t, 1H, H6), 7.74 (d, 1H, H5), 7.89 (t, 1H, H7), 8.19 (d, 1H, H8), 8.7 (s, 1H, H2).

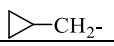
The second route involves the synthesis of 1-alkyl-4-[(4'-oxoquinazolin- 3'-yl)methyl]-1,2,3-triazole derivatives (5a-d) *via* the reaction of the acetylenic compound (2) with alkyl azides (4a-d). The azides (4a-d) were synthesized, as oily products, by the reaction of alkyl halide with sodium azide in DMSO as a solvent at room temperature. Their melting points are not measured owing to the azides are explosive materials. The characteristic absorption band for azide compounds is the bond stretching band of the N=N=N bonds which appeared at 2093-2099 Cm^{-1}.

Table 1. The physical and IR spectral data of the azides (4a-d)

Compd. No.	R	Yield %	IR (neat) ν (Cm^{-1}) N=N=N str.
4a	CH_3-	82	2093
4b	C_2H_5-	90	2095
4c	$PhCH_2$-	91	2094
4d		92	2099

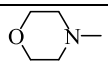
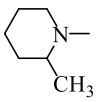
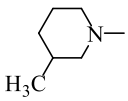
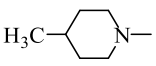
The synthesized alkyl azides (4a-d) were used to synthesize the 1-alkyl-4-[(4'-oxoquinazolin-3'-yl)methyl]-1,2,3-triazole derivatives (5a-d) *via* Click reaction by its reaction with the acetylenic compound (2) in presence of catalytic amount of cuprous chloride in dry toluene. The IR spectra of compounds (5a-d) showed a characteristic absorption bands at 1467-1468 $cm^{-1}$for N=N bonds stretching, and absorption bands at 1661-1672 Cm^{-1} for the C=O bond stretching for quinazolinone moiety. The absence of the absorption bands at 3214 and 2120 Cm^{-1} for ≡C-H and C≡C bonds stretching supported the conversion of the acetylenic moiety to the triazole moiety.

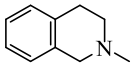
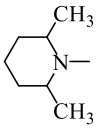
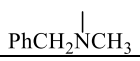
Table 2. The physical and IR spectral data of 1,2,3-triazoles (5a-d)

Compd. No.	R	Yield %	m.p. °C	Color	IR (neat) ν (Cm^{-1})		
					C=O	N=N	=C-H
5a	CH_3-	70	203-204	Light green	1672	1467	3055
5b	C_2H_5-	71	165-167	Brown	1668	1468	3055
5c	$PhCH_2$-	77	134-135	Brown	1661	1467	3058
5d		75	86-88	Light brown	1672	1467	3048

The third route in this research is the synthesis of acetylenic Mannich bases [1-(4'-oxoquinazolin-3'-yl)-4-disubstituted amino-4-butyne] (6a-i). The synthesis of the Mannich bases performed by reaction of the acetylenic compound (2) with secondary amines in presence of paraformaldehyde and catalytic amount of cuprous chloride in dioxane free peroxide. The IR spectra of the Mannich bases (6a-i) showed a characteristic absorption bands at 2124-2220 $cm^{-1}$for the C≡C bonds stretching, and absorption bands at 1660-1679 cm^{-1} for the C=O bond stretching of quinazolinone moiety. It is notice that the absorption bands of the ≡C-H bond stretching is absent, which indicates the formation of the titled Mannich bases. The ^{1}HNMR spectrum of compound (5d) showed the following chemical shifts (δ, ppm): 0.8 (d, 3H, CH_3), 1.69-2.83(m, 9H, piperidine-H), 3.49 (s, 2H, piperidine-CH_2-C≡), 4.9 (s, 2H, quin-CH_2-C≡), 7.53 (t, 1H, H6), 7.59 (d, 1H, H5), 7.85 (t, 1H, H7), 7.17 (d, 1H, H8), 8.5 (s, 1H, H2). Moreover, the ^{1}HNMR spectrum of compound (5f) showed the following chemical shifts (δ, ppm): 1.48-1.94 (m, 8H, pyrrolidine-H), 2.49 (s, 2H, pyrrolidine -CH_2-C≡), 4.87 (s, 2H, quin-CH_2-C≡), 7.57 (t, 1H, H6), 7.69 (d, 1H, H5), 7.84 (t, 1H, H7), 8.17 (d, 1H, H8), 8.48 (s, 1H, H2).

Table 3: The physical and IR spectral data of the acetylenic Mannich bases (6a-i):

Compd. No.		Yield %	m.p. °C	color	IR (neat) ν (Cm^{-1})		
					C=C	C≡ C	C=O
6a		50	51-53	Orang	1606	2203	1679
6b		64	60-62	Faint green	1606	2154	1673
6c		62	148-150	Faint brown	1606	2184	1670
6d		65	68-70	brown	1606	2175	1669
6e		69	88-89	brown	1606	2214	1669
6f		70	66-68	yellow	1602	2135	1666

6g		61	72-74	brown	1597	2168	1664
6h		52	73-75	brown	1636	2148	1660
6i		62	79-80	Faint brown	1603	2215	1667

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