Synthesis, Characterization and Evaluation Antimicrobial Activity of Some New substituted 2-Mercapto-3-Phenyl-4(3H)-Quinazolinone

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Abstract:
This work includes synthesis of new heterocyclic derivatives of 2-mercpto-3-phenyl-4(3H)-quinazolinone bearing 1, 2, 4-triazole and acetylenic amines moieties by using two ways. The first way includes reaction of 2-mercpto-3-phenyl-4(3H)-quinazolinone (1) with ethyl-2-bromopropanoate in methanol as solvent to gives ester derivative (2). Then, compound (2) was converted to (hydrazide, simecarbazid, phenylsimecarbazide and thiosimecarbazide) derivatives through its reactions with (hydrazine hydrate, simecarbazid, phenylsimecarbazide and thiosimecarbazide) respectively to give compounds (3-6). Finally, the cyclization of compounds (4-6) in alkaline media (4N-NaOH) gave the corresponding substituted triazole derivatives (7-9) respectively. While, compound (3) reacted with CS_2 in alkaline media (20%KOH) to gives compound (10) that reacted directly with hydrazine hydrate to gives compound (11). The second way includes reaction of compound (1) with propargylbromide to gives compound (12). Then, compound (12) reacted with different secondary amines (by Mannich reaction) to give compounds (13 a-m).
The structure of newly synthesized compounds were identified by spectral methods their [FTIR and some of them by ^{1}HNMR, ^{13}C-NMR] and measurements some of its physical properties and some specific reactions. Furthermore were studied the effects of the preparing compounds on some strains of bacteria and fungicidal.

Key words: substituted-1,2,4-triazole, acetylenic amines, antimicrobial.

تحضيرو تشخيص و تقدير الفعالية المضادة للميكروبات لعدد من المعوضات الجديدة لـ2-ميركبتو-3-فنيل-4(3H)-كوينازولينون

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الخلاصة
هذا العمل يتضمن تحضير مشتقات جديدة غير متجانسة الحلقة لـ 2-ميركبتو-3-فنيل-4(3H)-كوينزولينون من ضمنها وحدات من4,2,1-ترايازول واميدات استيلينية وتم ذلك بأستخدام مسارين. تضمن المسار الاول تفاعل لـ 2-ميركبتو-3-فنيل-4(3H)-كوينزولينون(1) مع اثيل -2-بروموبروبانويت في المثانول كمذيب ليعطي مشتق الاستر مركب (2). بعد ذلك المركب (2) حولَ الى مشتقات (هايدرازايد, سميكاربزايد, فنيل سميكاربزايد و ثايوسميكاربزايد) من خلال تفاعله مع (هيدرازين المائي, سمي كاربزايد, فنيل سميكاربزايد و ثايوسميكاربزايد)على التعاقب ليعطي المركبات (3-6). اخيراً, المركبات(4-6) حولقت في وسط قاعدي (4N-NaOH) واعطت مشتقات ترايزولات معوضة المقابلة (7-9). بينما المركب (3) تفاعل مع

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CS_2 في وسط قاعدي (20%KOH) واعطى المركب (10) الذي تفاعل مباشرتاً مع الهيدرازين المائي و اعطى المركب (11). تضمن المسار الثاني تفاعل المركب (1) مع بروبرجيل بروميد ليعطي المركب (12) الذي بدوره تفاعل مع امينات ثانوية مختلفة (بواسطة تفاعل مانخ) ليعطي المركبات (13a-m).

تم اثبات المركبات الجديدة المحضرة بواسطة الطرق الطيفية [FTIR وبعضها بواسطة ^{13}C-NMR, ^{1}H-NMR] وقياس لبعض خواصها الفيزياوية وكذلك بعض الكشوفات الخاصة. فضلا عن ذلك تمت دراسة تأثر المركبات المحضرة على بعض سلالات البكتيريا وفطر واحد.

Introduction:

The synthesis of high nitrogen-containing heterocyclic system has been attracting an increasing interest over the past decade due to their utility in various applications. In medicinal chemistry, the quinazolinone core and its derivatives form an important class of compounds, as they are present in a large family of products with broad biological activities [1]. They generally display useful therapeutic and pharmacological properties such as anti-inflammatory[2], anti-convulsant[3], anti-hypertensive[4] and anti-malarial activity [5]. It was reported that 3*H*-quinazolin-4-one derivatives have interesting antimicrobial activity against different species of Gram positive bacteria, Gram negative bacteria and pathogenic Fungi [6,7]. It was also reported that 2-substituted or 4-substituted thioquinazoline derivatives were identified as a possible pharmacophore for anti-tubercular activity [8,9].

For Triazoles, it has been reported to have pharmacological, insecticidal, fungicidal, and herbicidal activities [10-12]. In addition, it was reported that compounds having triazole moieties, such as Vorozole, Letrozole and Anastrozole, have been used as nonsteroidal aromatase inhibitors in medicine for treating breast cancer [13,14]. Moreover, 1, 2, 4-triazoles are a new class of antimicrobial and antiradical agents [15,16].

Furthermore, Mannich reaction [17,18] is an interesting approach to the synthesis of propargylamines, which have found broad application as precursors of different nitrogen-containing compounds, as well as intermediates in the synthesis of different natural products including dynemicins, pharmaceuticals, herbicides and fungicides. Some of them have even been tested in the treatment of Parkinson's [19] and Alzheimer's [20] diseases.

Experimental

Materials and Instruments

Chemicals used in this work are supplied from Merck, BDH, Sigma Aldrich and Fluka companies and are used without further purification. Melting points were recorded using digital Stuart scientific SMP3 melting point apparatus and are uncorrected. FTIR spectra were recorded on SHIMAZU FTIR-8400 Fourier transform Infrared spectrophotometer using KBr discs in the (500-4000) cm^{-1} spectral range. ^{1}HNMR and ^{13}CNMR spectra were recorded on Burker 300MHzistrument using DMSO-d_6 as solvent and TMS as internal reference. Thin layer chromatography (TLC) was carried out using Fertigfollen precoated sheets type polygram Silg, and the plates were developed with iodine vapor.

Preparation of 2-mercpto-3-phenyl-4(3H)-quinazolinone (1). [21]

A mixture of anthranilic acid (4.114g, 0.03mol), phenylisothiocyanate (3.61ml, 0.03mol) and triethylamine (3ml) in (60ml) absolute ethanol was reflexed for (3 hrs.). The reaction mixture was cooled at room temperature, then, poured on ice-cold water, stirred and filtered; the precipitate was recrystallized from methanol to give crystals. Physical properties are listed in table-1.

Preparation of Ethyl 2-(3-phenyl-4-oxo-3,4-dihydroquinazolin-2-ylthio)propanoate (2). [22]

To mixture of 2-mercpto-3-phenyl-4(3H)-quinazolinone (1) (2g, 0.007mol) dissolved in (30ml) methanol and KOH (0.39g, 0.007mol) dissolved in (10 ml) methanol; Ethyl-2-bromopropanoate (0.9 ml, 0.007mol) was added and refluxed for (6 hrs.). The reaction mixture was cooled at room temperature, then poured on ice-cold water and filtered. The white precipitate was recrystallized from ethanol to give crystals. Physical properties are listed in table-1.

Preparation of 2-(3-phenyl-4-oxo-3,4-dihydroquinazolinone -2-ylthio) propanoyl [semicarbazide(4), phenylsemicarbazide(5), and thiosemicarbazide(6). [23]

A mixture of compound (2) (1 g, 0.0028mol) with (semicarbazide, phenylsemicarbazide, thiosemi-carbazide) respectively (0.0028mol) and sodium acetate (0.23g, 0.0028mol) in dimethylformamide (DMF) (15ml) was refluxed for (18-20 hrs.). The reaction mixture was filtered and poured on ice-cold

water; the precipitate was filtered and recrystallized from suitable solvents to give crystals. Physical properties are listed in table-1.

Preparation of 3-[1-(3-phenyl-4-oxo-3,4-dihydroquinazolin-2-yl-thio)ethyl]-4*H*-1,2,4 -triazole-5-ol (7),4-phenyl-1,2,4-triazole-5-ol(8), and 4H-1,2,4-triazole-5-thiol(9). [23]

(0.001mol) of compounds (4- 6) was refluxed with 20% aqueous sodium hydroxide solution (25ml) for (10-12 hrs.) , cooled, poured on ice-cooled water , stirred and neutralized by gradual addition of (1:1) hydrochloric acid. The formed precipitate was filtered and recrystallized from suitable solvents to give crystals. Physical properties are listed in table-1.

Preparation of 2-(4-oxo-3-phenyl-3,4-dihydroquinazolin-2-ylthio)propanehydrazide (3). [24]

Compound (2) (2 g, 0.0058mol) in (20 ml) dimethylformamide (DMF) as solvent; excess of hydrazine hydrate 98% was added to the reaction mixture and reflexed for (8 hrs.). Finally, the reaction mixture cooled at room temperature and poured on ice-cold water, stirred and filtered; the precipitate was recrystallized from ethanol and water to give crystals. Physical properties are listed in table-1.

Preparation of potassium 2-[(3-phenyl-3,4-dihydroquinazolinone-2-yl-thio) propanoyl] dithiocarbazate(10). [24]

To a stirred ethanolic solution of KOH (0.16g, 0.0029mol) in (20ml), hydrazide derivative (3) (1g, 0.0029mol) then CS_2 (0.24ml, 0.0058mol) were added slowly. The reaction mixture was stirred overnight. Dry ether (20ml) was added and the yellow ppt. was filtered, washed with ether and vacuum dried. The salt (10) was obtained in almost quantitative yield and was employed in the next step without further purification. Physical properties are listed in table-1.

Preparation of 3-[1-(3-phenyl-4-oxo-3,4-dihydroquinazolin-2-yl-thio)ethyl]-4-amino-1,2,4-triazole-5-thiol (11). [24]

A suspension of potassium salt (10) (0.45g, 0.001mol) in excess hydrazine hydrate 98% (5ml) was refluxed until the evolution of H_2S was ceased; during reflux the color of the reaction mixture changed to green and a homogenous solution resulted. After cooling, the reaction mixture was acidified with 10%HCl to yield a Grey precipitate. The precipitate was recrystallized from ethanol to give crystals. Physical properties are listed in table-1.

Preparation of 1-(3-phenyl-4-oxo-3,4-dihydro quinazolin-2-yl-thio)prop-2-yne (12). [25]

To mixture of 2-mercpto-3-phenyl-4(3H)-quinazolinone(1) (2g, 0.007mol) dissolved in (30ml) methanol and KOH (0.39g, 0.007mol) dissolved in (10 ml) methanol; propargyl bromide (0,55ml, 0.007mol) was added and refluxed for (1 hr.). The reaction mixture was cooled at room temperature, poured on ice-cold water and filtered; the white precipitate was recrystallized from ethanol and water to give crystals. Physical properties are listed in table-2.

Preparation of 1-(3-phenyl -4-oxo-3,4- dihydroquinazolin -2-yl-thio) but-2-yne-4-amino (13a-m). [25]

(0.5 g, 0.0018 mol) of the compound (12) in 6 ml of Dioxane peroxide-free as solvent, (0.05 g, 0.0018 mol) of paraformaldehyde and (0.16 g, 0.0018 mol) of cuprous chloride added to the reaction mixture, respectively. Then heated reaction mixture up to 50-60 C^{o} and then added an amine (0.0018 mol) for (2-3hrs). The reaction mixture was filtered and poured the filtrate on 20 ml of ice-cold water to form precipitate. The precipitate was filtered and recrystallized from suitable solvents to give crystals. Physical properties are listed in table-2.

Anti-microbial activity test

The test was performed according to the disk diffusion method [26]. Some of prepared compounds were tested against two strain gram +ve (*Staphylococcus aura* and *Bacilles*) and two strain gram –ve bacteria (*Escherichia coli* and *pseudoman acruginosa*). Also they tested against one strain of yeast (*Candidan*). Whattman no.1 filter paper disk of 5mm diameter were sterilized by autoclaving for 15 min. at 121C^{o}. The sterile disks were impregnated with different compounds (800µg/disk). Agar plates were surface inoculated uniformly with 100 ^{o} µL from both culture of tested microorganism. The impregnated disk were placed on the medium suitably spaced a part and the plates incubated at 5 C^{o} for 1 hr. to permit good diffusion and then transferred to an incubator at 37C^{o} for 24 hrs. . The inhibition zones caused by various compounds on the microorganisms were examined.

Table 1- Physical properties and FTIR spectral data cm^{-1} of compounds (1-11).

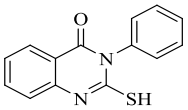
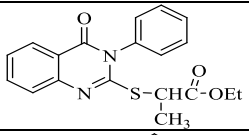
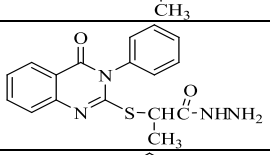
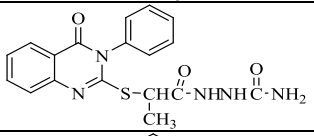
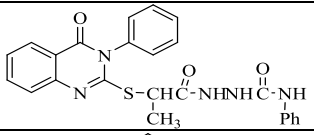
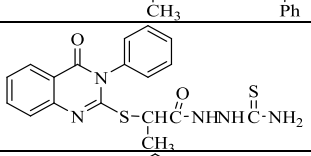
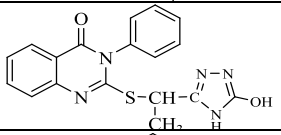
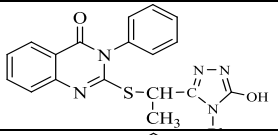
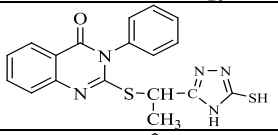
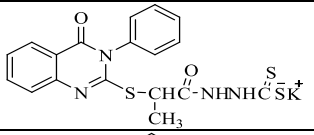
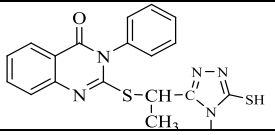
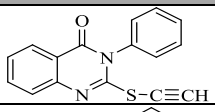
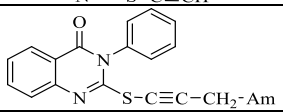
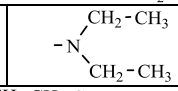
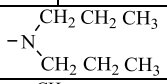
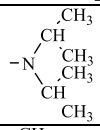
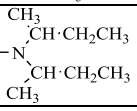
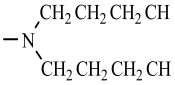
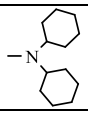
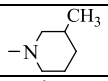
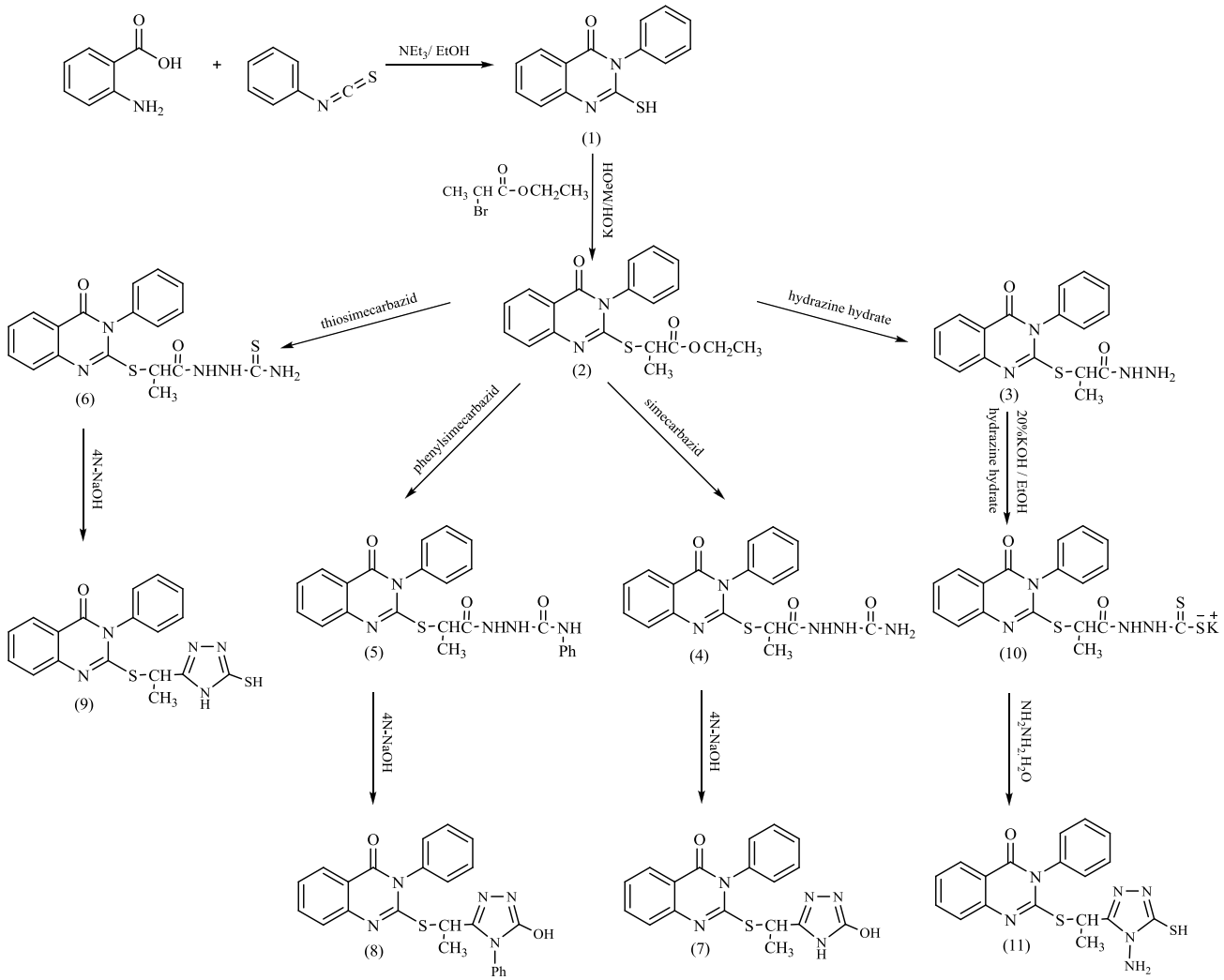
Com.No.	Physical Properties				Major FTIR Absorption cm^{-1}				
	Structures	Melting Point C°	Yield%	Color	ν(N-H)	ν(C-H) aliph.	ν(C=O) Amid	ν(C=O) sub. Amid	Others
1		298-296	89	Off white	3244	-	-	1691	2650 (S-H) 1226 (C=S)
2		184-182	92	White	-	2989	-	1687	1733 ν(C=O) Ester
3		270-273	62	Grey	3218	2923	1686	Overlap with ν(C=O) Amid	$\nu(NH_2)$ asym. 3453-Sym. 3363
4		160-162	78	White	3218	2983	1683	Overlap with ν(C=O) Amid	$\nu(NH_2)$ Asym. 3447 Sym.3364 ν(C=O)
5		148-151	74	Brown	3244	2931	1687	Overlap with ν(C=O) Amid	ν(C=O) Carbazide 1650
6		220-223	70	Brown	3247	2983	1691	Overlap with ν(C=O) Amid	$\nu(NH_2)$ Asym. 3448 Sym. 3365 ν(C=S)
7		215-213	76	Green	3377	2921	-	1685	ν(O-H) 3444 ν(C=N) 1635
8		204-201	72	Brown	3418	2923	-	1684	ν(O-H) 3467 ν(C=N) 1635
9		225	71	Green	3423	2923	-	1683	ν(S-H) 2650 ν(C=N) 1639
10		304-306	70	Green	3432	2975	1683	Overlap with ν(C=O) Amid	-
11		240-243	86	Grey	3281	2981	-	1679	$\nu(NH_2)$ Asym. 3483 Sym. 3326 ν(S-H)

Table 2- Physical properties and FTIR spectral data cm-1 of compounds (12-13a-m).

Comp. No.	Physical Properties				Major FTIR Absorption cm-1			
	Compounds structures	Melting Point C°	Yield%	Color	ν(C-H) aliph.	ν(C≡C)	ν(C=O) amid	Others
12		170-172	9	White	2972	2361	1679	ν(≡C-H) 3228
13		-	-	-	-	-	-	-
13-a	Am= 	101-103	70	Deep Brown	2992; 2958; 2870	2352	1691	-
13-b		90-92	72	Brown	2960; 2931; 2869	2348	1687	-
13-c		84-85	68	Brown	2995; 2954; 2829	2347	1695	-
13-d		128-130	65	Brown	2952; 2927; 2864	2343	1674	-
13-e		72-73	75	Deep Brown	2954; 2931; 2860	2331	1686	-
13-f		92-94	70	Deep Brown	2931; 2852	2344	1691	-
13-g		105-107	60	Yellow	2960; 2854; 2810	2351	1674	ν(C-O-C) 1061
13-h		127-129	77	Brown	2970; 2931; 2871	2341	1674	-
13-i		113-115	73	Brown	2971; 2927; 2852	2338	1679	-
13-j		123-125	79	Light Brown	2965; 2927; 2906	2343	1674	-
13-k		146-148	52	Green	2962; 2927	2343	1670	-
13-l		128-130	75	Brown	2965; 2934; 2830	2357	1688	-
13-m		130-133	57	Off white	2945; 2904	2335	1672	-

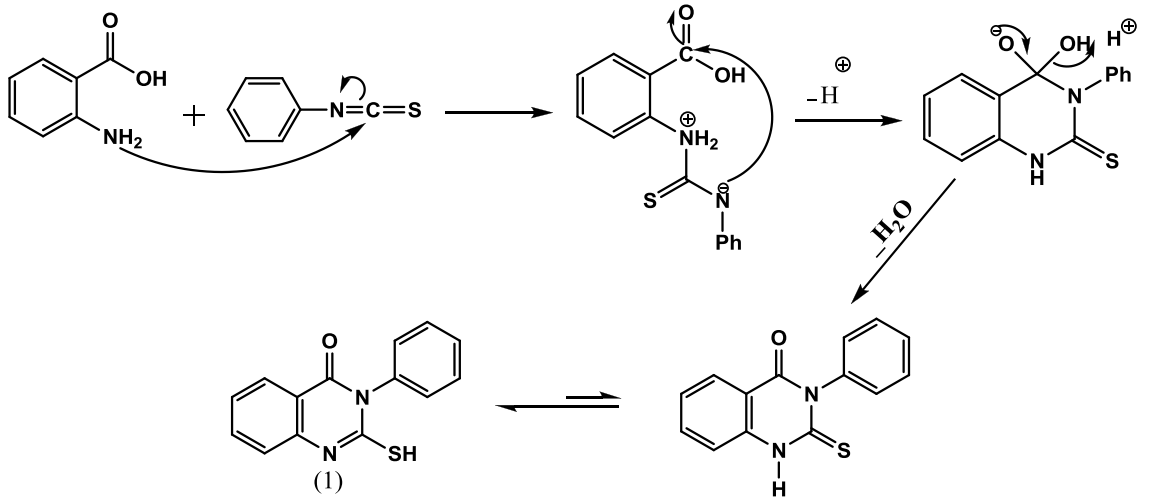
Results and Discussion:

The synthetic sequences for preparation of series of new 2-mercapto-3-phenyl-4(3*H*) quinazolinone, 1,2,4-triazoles as in schemes (1).



Scheme 1- Preparation of series of new 2-mercapto-3-phenyl-4(3H) quinazolinone, 1,2,4-triazoles

Compound (1) was prepared by condensing anthranilic acid with phenylisothiocyanate as the following mechanism [21]:-



Mechanism of prepared compound (1)

The FTIR spectrum indicated the presence of a ν(N-H) (3244 cm^{-1}) and ν(C=O) (1691 cm^{-1}) of substituted amid [27]. Compound (2) was prepared by reaction of compound (1) with Ethyl-2-bromo propanoate. The FTIR spectrum indicated that ν(S-H) (2650 cm^{-1}) was disappeared from the spectrum

while ν(C-H) aliphatic at (2989 cm^{-1}) and ν(C=O) ester at (1733 cm^{-1}) were appeared, table-1. ^{1}HNMR spectrum showed triplet signal at δ= (0.82) ppm due to (-CH_2-$\underline{CH_3}$) protons, doublet signal at δ= (1.19) ppm due to (-CH-$\underline{CH_3}$) protons, quartate signal at δ= (2.73) ppm due to (CH) protons, quartate signal at δ= (3.32) ppm due to (-O-CH_2) protons, and signals at δ= (7.15-8.10) ppm due to aromatic rings protons as shown in figure-1. and listed in table-3. ^{13}C-NMR spectrum data of this compound (2) were shown in figure-2, and listed in table-4. Also, hydroxamic acid test improved the presence of ester group [28].

Compound (2) was converted to semicarbazide (4), phenylsemicarbazide (5) and thiosemicarbazide (6) derivatives by the reaction with (semicarbazide, phenylsemicarbazide and thiosemicarbazide) respectively (scheme 1). FTIR spectral data showed absorption at (3447cm^{-1}) asym. (3364cm^{-1}) sym. for ν-NH_2, (3218cm^{-1}) for ν-NH and (1683 cm^{-1}) νC=O in compound (4) .while in compound (5) showed absorption at (3244cm^{-1}) for ν-NH and (1687 cm^{-1}) for νC=O, and showed absorption at(3448 cm^{-1}) asym. (3365cm^{-1}) sym. for ν-NH_2, (3247 cm^{-1}) for ν-NH, (1691 cm^{-1}) νC=O and (1234 cm^{-1}) for νC=S in compound (6).

Treatment of compounds (4-6) with (4N.NaOH) solution afford intramolecular cyclization to give the hydroxytriazole (7), phenylhydroxytriazole (8) thiohydroxytriazole (9) were identified from FTIR spectra shows result in table-1. All the spectrum data showed the presence of absorption of (νC=N) group about (1636-1639 cm^{-1}).

On the other hand the compound (2) reacted with hydrazine hydrate and gave hydrazide compound (3). FTIR spectrum showed Absorption at (3453, 3363 and 3218 cm^{-1}) could be attributed to –NH_2 group asym. and sym., and –NH group stretching band respectively. Also showed shift in the νC=O band from (1733 cm^{-1}) of ester to (1686 cm^{-1}) of amide I . ^{1}HNMR spectrum showed doublet signal at δ= (1.56) ppm due to (-$\underline{CH_3}$) protons, quartate signal at δ= (2.83) ppm due to ($\underline{CH}$) protons, singlet signal at δ= (6.05) ppm due to (-$\underline{NH_2}$) protons, signals at δ= (7.41-8.34) ppm due to aromatic rings protons, and singlet signal at δ= (9.72) ppm due to (-$\underline{N\text{-}H}$) proton as shown in table-3. ^{13}C-NMR spectrum data of this compound (3) were listed in table-4.

Hoggarth's method[29] has been used for the preparation of compound (11) by reaction of hydrazide (3)with CS_2 in ethanolic KOH gave the dithiocarbazate salt (10) in excellent yield, which, was then cyclized by refluxing with 98% hydrazine hydrate to give a moderate yield of triazole derivative (11). FTIR spectrum showed absorptions at (3483 cm^{-1} Asym. and 3326cm^{-1} Sym.) for –NH_2 group and absorption at (3281 cm^{-1}) for N-H group, (1616 cm^{-1}) for νC=N group.

Compound (12) was prepared by the reaction of compound (1) with propargyl bromide. FTIR spectrum indicated the disappearance of ν(S-H) at (2650 cm^{-1}), while ν(≡C-H) at (3228cm^{-1}), ν(C-H) aliphatic at (2972 cm^{-1}) and ν(C≡C) at (2385 cm^{-1}) were appeared in the spectrum. ^{1}HNMR spectrum data showed triplet signal at δ= (3.17) ppm due to (≡C-H) proton, singlet signal at δ= (4.01) ppm due to (-CH_2-) protons and multi signals at δ= (7.27-8.11) ppm due to aromatic protons as showed in figure-3. ^{13}C-NMR spectrum data of this compound (12) were shown in figure-4.and listed in table-4.

Mannich bases (13a-m) were obtained in good yield through the reaction of compound (12) with different (aliphatic, aromatic, cyclic and hetero cyclic) secondary amine (scheme 2). The FTIR spectrum data of compounds (13a-m) are listed in table-2. All the spectrum data showed disappearance the absorption of ν(≡C-H) group.

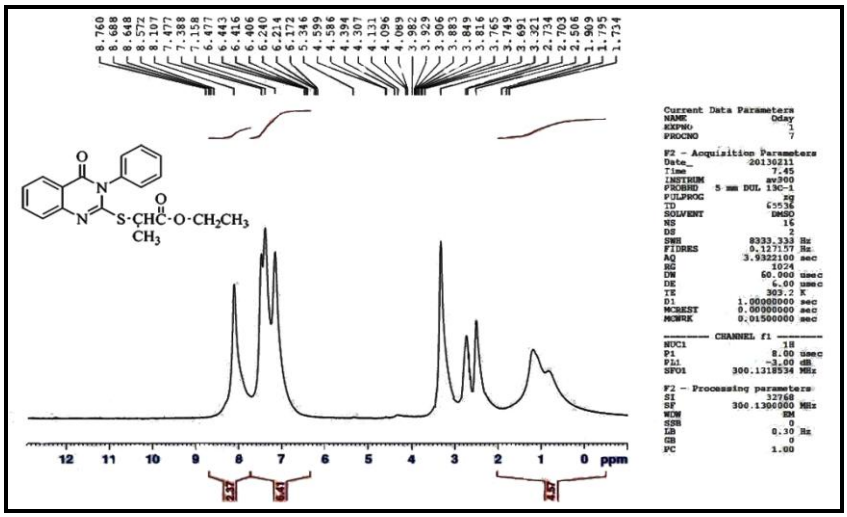
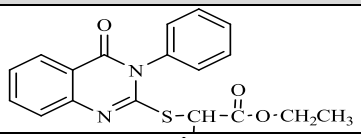
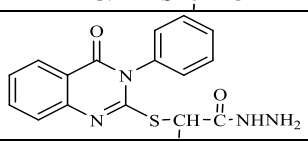
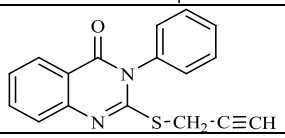


Figure-1- 1HNMR spectrum of compound (2).

Table 3- 1HNMR spectral data (ppm) for selected compounds.

Comp. No.	Structures	^{1}HNMR Spectral data($^{\delta}$ppm)
2		0.82(b,3H,-CH_2-$\underline{CH_3}$); 1.19 (d,3H-CH-$\underline{CH_3}$); 2.73 (q,1H,CH) ; 3.32(q,2H-O-CH_2); 7.15-8.10 (m,9H,Ar-H)
3		1.56 (d,3H,CH_3); 2.83(q,1H,C-H); 6.05(s,2H,NH_2); 7.41-8.34 (m,9H,Ar-H); 9.72 (s,1H,N-H)
12		3.17(t,1H, ≡C-H);4.01(s,2H,-CH_2-);7.27-8.11 (m,9H,Ar-H)

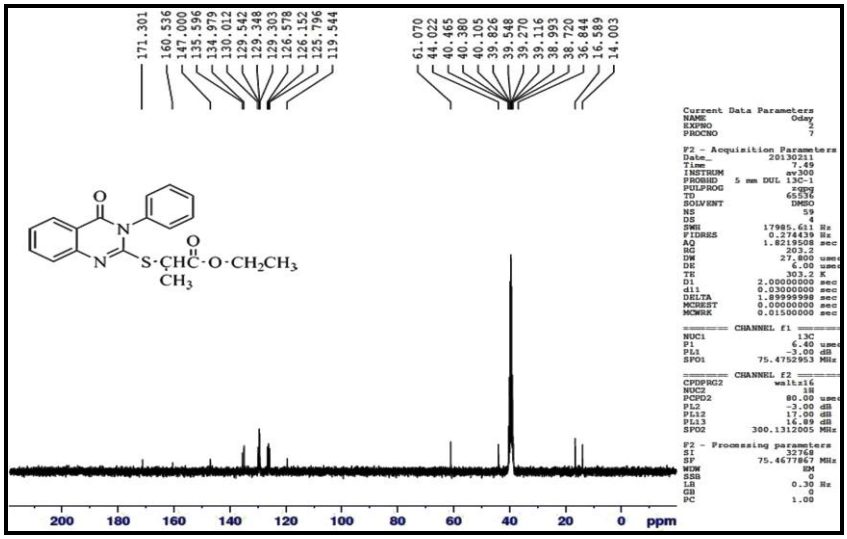
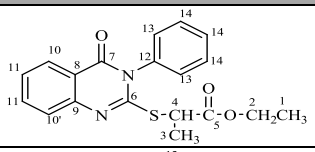
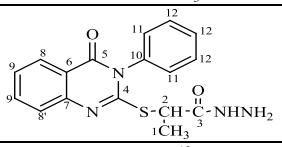
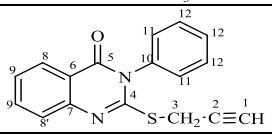


Figure 2- 13CNMR spectrum of compound (2).

Table 4- 13C-NMR spectral data (ppm) for selected compounds.

Com. No	structure	13CNMR Spectral data($^{\delta}$ppm)
2		14.00(C1); 16.58(C3); 44.02(C4); 61.07(C2); 119.54-135.59 (C-8, 9, 10, 10', 11, 12, 13, 14); 147.00 (C6), 160.53(C7), 171.30(C5).
3		11.19(C1); 28.98(C2); 116.63-149.07 (C- 6, 7, 8, 8', 9, 10, 11, 12), 155.43 (C4), 160.93(C5), 168.02(C3).
12		20.41(C1); 73.95(C3); 79.20(C2); 115.67-130.05(8, 8', 9, 11, 12); 134.94-147(C-6,7,10); 159.76(C4); 176.09(5).

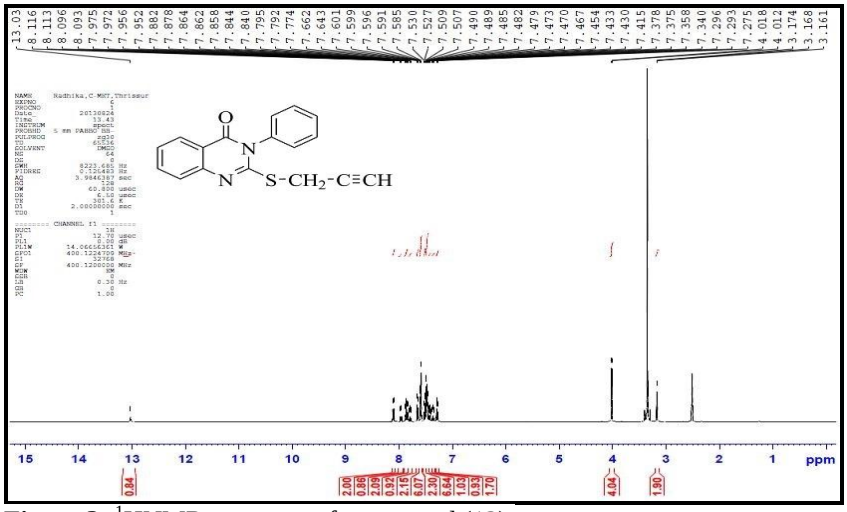


Figure 3- ^{1}HNMR spectrum of compound (12).

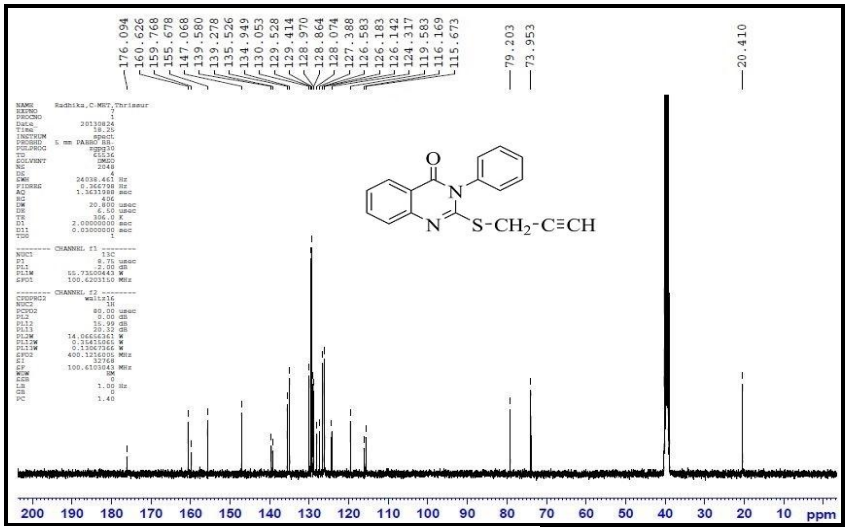
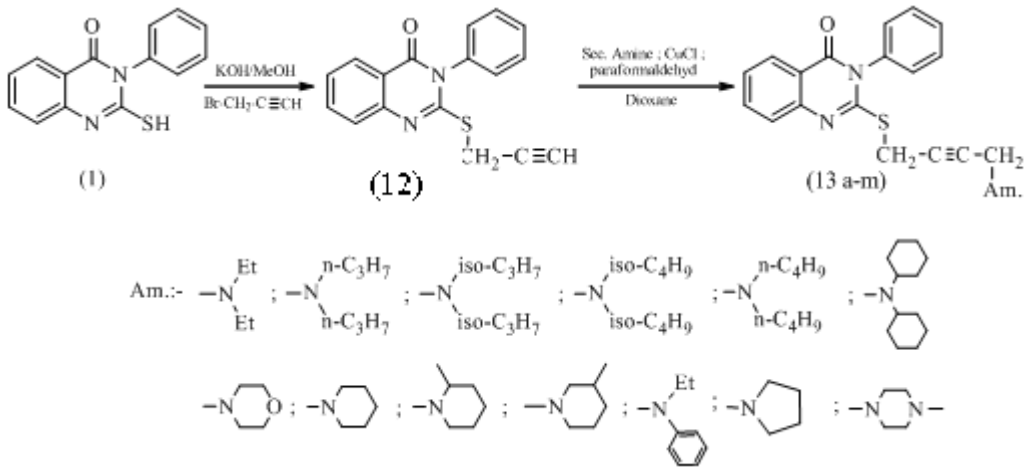


Figure 4- 13C-NMR spectrum of compound (12).



Scheme (2): preparation of Mannich bases derivatives for compounds (12-13a-m)

Anti-microbial study

The results of antimicrobial activity are listed in table 5. The results referred that all synthetic compounds possess moderate activity against certain types of bacteria and *Candidau*, while it did not possess any activity against others. While compounds (12 and 13h) possess strong activity against *Staphylococcus aureus* and compound (13e) also possess strong activity against *Bacillies*. As far as compound (13g) possess strong activity against *Candidau*.

Table 5- Anti-microbial activity of the tested prepared compounds

Comp. No.	*Staph. Aure*	*Bacillies*	*E. Coli*	*Pseu. Aure*	*Candida*
2	-	8	-	9	-
3	8	-	-	7	-
8	-	8	-	-	-
11	-	8	-	-	-
12	12	7	8	-	-
13e	7	10	8	-	9
13f	-	-	8	-	9
13g	8	-	-	-	11
13h	13	-	9	-	-

Solvent: DMSO; [C]: 800µg/ml.
Zone of inhibition: (-) no inhibition zone; (3-6) weak; (7-10) moderate; (11-15) strong.

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